

3D Modelling, Finite Element Analysis, and Artificial Neural Network Analysis of a Complex Nonlinear Structure: A Study on a Long Bone

by

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Abstract

The bodies of humans and animals act like a mechanical system, in which bones are the major link for withstanding compressive loads. The extraordinarily hierarchical essence of the structure and mechanical properties of bones makes bone a difficult material to fully comprehend. It would be difficult to find another material that possesses such multivariable and exceptional mechanical properties. The horse has been identified as a useful model to investigate the effects of mechanical loading and induced deformations on tissues and structures in humans. Also, the equine distal forelimb is the source of most career-ending injuries to sport horses in all disciplines, and as such understanding how the materials in this part of the body respond to loads is key to understanding how and why they break down. The equine third metacarpal (MC3) is a large bone that shows a relatively restricted and simple range of normal movements in-vivo, has minimal muscle attachments (lacking any muscle or ligamentous attachments for a range around 6-8 cm along its midshaft), forms an essential part of the lower forelimb in withstanding loads, is vulnerable to failure during the majority of disastrous injuries occurring in racing horses worldwide, is well-adapted (well-engineered) for exercise at high speeds, and can withstand substantial compressive load as much as 22.5 kN in-vivo. To compare this huge force that MC3 is capable of withstanding in a normal daily basis, a large SUV car weighs 20.6 kN to 23.3 kN. Furthermore, this anatomical region provides a potential insight into how complex biological materials like bone and ligament respond to loading in all species and what parameters are vital to retain their integrity during normal use.

Despite recent enormous advancement in techniques, gaining deep knowledge to find correlations between whole bone shape and material, mechanical, and overall physical responses as well as properties is a daunting task due to both complexity of the material itself and the convoluted shapes that this complex material forms. Moreover, many uncertainties and ambiguities exist concerning the use of computational techniques that unfortunately triggers a growing tendency for the misapplication of these computational tools. This thesis presents novel computational modelling frameworks and algorithms to build reliable 3D models of MC3 long bones and to replicate data recorded via ex-vivo experiments undertaken on MC3 bones. The major endeavor was to sufficiently establish precise and accurate computational models employing novel techniques (computer-aided design, finite element analysis, and machine learning algorithms using artificial neural networks) to predict the mechanical responses (for example, cyclic mechanical loading, displacement, and strains recorded experimentally) of a

highly nonlinear well-engineered structure (MC3 long bone). This thesis reports the: (1) establishment of a reliable finite element analysis (FEA) and computer-aided design (CAD) model with reduced errors, (2) investigation of the significance of shape and geometry variations in the bone midshaft (where the strains are typically read) versus age and maturation, and (3) employment of novel machine learning algorithms with predominant use of feedforward back-propagation neural networks to tackle the enormous challenges in comprehending mechanical responses in long bones and equine forelimb mechanics. Otherwise conventional tools fail to provide a satisfactory outcome due to the availability of limited data and the extreme complexity of anticipating mechanical properties and discovering performance attributes in this highly interdisciplinary domain.

Bones have remarkable properties and, as such, offer intriguing opportunities for investigation by researchers and engineers. The use of equine MC3 long bones in performing mechanical experiments and then in establishing the computational techniques in this thesis is motivational for engineers who are dealing with less complicated structures and less complex materials. The encouraging outcomes also exhibit the exceptional ability of artificial neural networks in capturing the mechanical characteristics of complex structures and will assist researchers and engineers as well as biologists in discerning mechanical features of complex engineering structures that exhibit exotic and peculiar nonlinear mechanical properties. These models and frameworks would potentially assist in improving clinical assessments, avoiding and/or minimizing injuries that inhibit performance of humans and animals, and encourage the early detection of associated injuries and failures.

Declaration of Authorship

I, Saeed Mouloudi, declare that this PhD thesis entitled, “3D Modelling, Finite Element Analysis, and Artificial Neural Network Analysis of a Complex Nonlinear Structure: A Study on a Long Bone” and the work presented in it are my own original work.

I confirm that:

- the thesis comprises my original work;
- the co-authors of published/submitted papers contained in this thesis have granted permission that the articles be included in this thesis;
- the co-authors of published/submitted papers contained in this thesis have completed “Declaration for a thesis with publication” and “Co-author authorisation” forms as required by The University of Melbourne;
- the thesis contains no materials that have been submitted previously, in whole or in part, for the award of any other academic degree or diploma;
- due acknowledgement has been made in the text to all other material used; and
- the thesis is fewer than the maximum word limit in length, exclusive of tables, figures, and bibliographies as approved by the Research Higher Degrees Committee.

Saeed Mouloudi
October 2020

Preface

This thesis presents original work conducted by Saeed Mouloudi during his PhD candidature and was financially supported by a Melbourne Research Scholarship. The majority of the contributions during the course of the PhD are presented as manuscripts which have been published in five scholarly journals (a sixth paper has been submitted for publication). Saeed Mouloudi performed the majority of the work (substantially more than 50% as also outlined in the “Declaration for a thesis with publication” and “Co-author authorisation” forms).

- Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Accuracy quantification of the reverse engineering and high-order finite element analysis of equine MC3 forelimb, *Journal of Equine Veterinary Science* (IF: 1.1 as of 2020), 78 (2019) 94-106, <https://doi.org/10.1016/j.jevs.2019.04.004>.
- Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design, *Comparative Exercise Physiology* (IF: 0.8 as of 2020), 15 (2019) 349-358, <https://doi.org/10.3920/CEP190010>.
- Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm, *Biocybernetics and Biomedical Engineering* (IF: 2.537 as of 2020), 40 (2020) 849-863, <https://doi.org/10.1016/j.bbe.2019.09.001>.
- Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Prediction of load in a long bone using an artificial neural network prediction algorithm, *Journal of the Mechanical Behavior of Biomedical Materials* (IF: 3.372 as of 2020), 102 (2020) 103527, <https://doi.org/10.1016/j.jmbbm.2019.103527>.
- Hadi Rahmanpanah, Saeed Mouloudi, Colin Burvill, Soheil Gohari, Helen M S Davies, Prediction of load-displacement curve in a complex structure using artificial neural networks: A study on a long bone, *International Journal of Engineering Science* (IF: 9.219 as of 2020), 154 (2020) 103319, <https://doi.org/10.1016/j.ijengsci.2020.103319>.
- Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Soheil Gohari, Helen M S Davies, Feedforward backpropagation artificial neural networks for predicting mechanical responses in complex nonlinear structures: A study on a long bone, Submitted to the *International Journal of Mechanical Sciences* (IF: 4.631 as of 2020).

The author has also presented at international refereed conferences, as follows:

- S. Mouloudi, H. Rahmanpanah, C. Burvill, H. M. S. Davies, ‘Prediction of Cyclic Load from Strain Measurement in a Long Bone using an Artificial Neural Network Algorithm’, The American Society for Bone and Mineral Research (ASBMR 2020), September. 11-15 2020, Virtual Event.
- S. Mouloudi, H. Rahmanpanah, C. Burvill, H. M. S. Davies, ‘Artificial neural network algorithm for prediction of displacement in equine third metacarpal bone’, International Society of Biomechanics (ISB 2019), August. 1-4 2019, Calgary, Canada.
- H. Rahmanpanah, S. Mouloudi, C. Burvill, H. M. S. Davies, ‘Prediction of load in the equine third metacarpal forelimb through neural network prediction algorithm’, International Society of Biomechanics (ISB 2019), August. 1-4 2019, Calgary, Canada.
- S. Mouloudi, H. Rahmanpanah, C. Burvill, H. M. S. Davies, ‘Accuracy quantification of finite element stress analysis in long bones’, International Society of Biomechanics (ISB 2019), August. 1-4 2019, Calgary, Canada.
- S. Mouloudi, C. Burvill, H. M. S. Davies, ‘Converging-Diverging shape configuration of the diaphysis of equine third metacarpal midshaft bone through computer-aided design’, International Conference on Equine Exercise Physiology, November. 12-16 2018, Lorne, Australia.
- S. Mouloudi, H.M.S. Davies, C. Burvill, ‘Is the modulus of elasticity of bones force-dependent?’, 8th World Congress of Biomechanics, July. 8-12 2018, Dublin, Ireland.
- S. Mouloudi, C. Burvill, H. M. S. Davies, ‘Reverse engineering and reconstruction of bones by employing two different methods, new measurement possibilities’, 8th World Congress of Biomechanics, July. 8-12 2018, Dublin, Ireland.

The author has been the recipient of the following awards during his PhD candidature:

- Distinguished Talent Visa (permanent residency), Australian Government, June 2020.
- Sunshine Foundation Scholarship for 2020, The University of Melbourne, Valued at \$1,600, May 2020.
- Dr Robert McCarthy Scholarship for 2019, The University of Melbourne, Valued at \$5,000. June 2019.
- Student Travel Award Scheme (STAS), The University of Melbourne, Valued at \$1,500. April 2019.
- Financial Support from Supervisors, The University of Melbourne, Valued at \$3,000, May 2018.

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I thank my trusted and best friend as well as colleague, Mr. Hadi Rahmanpanah, who has always been such a great friend assisted me tremendously to tackle challenges and to handle upheavals that I have encountered during my life. I am also thankful to Dr. Soheil Gohari for his generous help, support, and excellent advice during my PhD candidature.

Doing a PhD at one of the best universities in the world and contributing to its academia and research, as well as its teaching programme, are an immensely exciting, yet very challenging, experience. I appreciate The University of Melbourne for offering me a Melbourne Research Scholarship and providing me with a stimulating and nurturing environment for me to develop my research skills. I am grateful to the McCarthy family for endowing the Dr Robert McCarthy Scholarship. I am also thankful to the donors of the Sunshine Foundation Scholarship. I hope that, when the opportunity arises, I will be as generous as these people have been.

Thanks to all my wonderful friends and colleagues from FABLab (Department of Veterinary Biosciences) and E310 Lab (Department of Mechanical Engineering) for making our offices a charming environment that never lack smiles.

The last year of this PhD was conducted when the world was experiencing a dreadful and unprecedented COVID-19 pandemic. While I pay tribute to, and express my sympathy to, all people who have lost loved ones and who have been affected by this virus, I sincerely thank

the University of Melbourne for providing strong continued support to RHD students. I particularly thank Mrs. Jan May (Department of Mechanical Engineering Administrator) and Prof. Jason Monty (Head of Department of Mechanical Engineering) for their generous support, in particular, providing me with funds to purchase a work-from-home workstation that enabled me to continue my research work from home since March 2020 when the entire state of Victoria went into a COVID-19 lockdown.

Last, but certainly not the least, I am incredibly thankful to my amazing parents, Shahla and Hassan. I would not be in this position without their love, care and support. They have absolutely been the best teachers in my entire life and have assisted me tremendously in shaping me as a person, and supporting and encouraging my educational career. Although they have been 12,000 km away from me during my PhD program, they have always been but a few seconds away to remotely talk with me and support me. I appreciate my siblings Hamid (and his wife Hiwa), Chonoor (and her husband Peyman and my cute little nephew Artin), and Farid who always being there for me. I have been so lucky to be the last child of this wonderful family who always provided me with invaluable experiences, considerable support and insightful advice. No words can adequately describe how greatly they have inspired me throughout my life to achieve higher goals and to become a better person in the first place.

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Chapter 1

Introduction

This thesis reports on research completed by the author on 3D Modelling, Finite Element Analysis (FEA), and Artificial Neural Network (ANN) analysis of a complex nonlinear structure, to wit, a long bone. This introduction chapter outlines the contributions of this thesis, presents overall research motivations (i.e. the anecdotal starting point regarding the significance of this field of research), and describes an outline of the thesis structure and salient outcomes of the research undertaken, in particular, in the published contributions associated with subsequent chapters.

The author has successfully published original research in 5 refereed journal papers (a 6th paper has been submitted for publication) and 7 international conference presentations. As such, this PhD thesis is presented according to the University of Melbourne guidelines for Thesis with Publication¹.

All chapters containing original contributions are based on papers either published or submitted for review. The author has sought to offer a logical narrative flow in this thesis. Chapter contributions and incorporated research papers are as follows:

Chapter 2: Literature Review.

Chapter 3: Published Paper: Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Accuracy quantification of the reverse engineering and high-order finite element analysis of equine MC3 forelimb, Journal of Equine Veterinary Science (IF: 1.1 as of 2020), 78 (2019) 94-106, <https://doi.org/10.1016/j.jevs.2019.04.004>.

Chapter 4: Published Paper: Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design, Comparative Exercise Physiology (IF: 0.8 as of 2020), 15 (2019) 349-358, <https://doi.org/10.3920/CEP190010>.

¹ Thesis with publication: <https://gradresearch.unimelb.edu.au/preparing-my-thesis/thesis-with-publication>

Chapter 5: Published Paper: Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm, Biocybernetics and Biomedical Engineering (IF: 2.537 as of 2020), 40 (2020) 849-863, <https://doi.org/10.1016/j.bbe.2019.09.001>.

Chapter 6: Published Paper: Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Prediction of load in a long bone using an artificial neural network prediction algorithm, Journal of the Mechanical Behavior of Biomedical Materials (IF: 3.372 as of 2020), 102 (2020) 103527, <https://doi.org/10.1016/j.jmbbm.2019.103527>.

Chapter 7: Published Paper: Hadi Rahmanpanah, Saeed Mouloudi, Colin Burvill, Soheil Gohari, Helen M S Davies, Prediction of load-displacement curve in a complex structure using artificial neural networks: A study on a long bone, International Journal of Engineering Science (IF: 9.219 as of 2020), 154 (2020) 103319, <https://doi.org/10.1016/j.ijengsci.2020.103319>.

Chapter 8: Submitted Paper: Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Soheil Gohari, Helen M S Davies, Feedforward backpropagation artificial neural networks for predicting mechanical responses in complex nonlinear structures: A study on a long bone, Submitted to the International Journal of Mechanical Sciences (IF: 4.631 as of 2020).

Chapter 9: Conclusion and Future Work.

1.1. Research Motivations

The primary motivation of the research reported in this thesis was to present novel computational modelling frameworks and algorithms to build reliable 3D models of the equine third metacarpal bone (MC3) and to replicate data recorded via ex-vivo experiments undertaken on a long bone (MC3). The major endeavor was to sufficiently establish precise and accurate computational models using novel techniques to predict the mechanical responses (e.g. mechanical loading, displacement, and strains recorded experimentally) of a highly nonlinear well-engineered structure (a long bone) where traditional methods and conventional techniques may present limitations. To achieve this, it is required to: (1) establish reliable and efficient computer-aided design (CAD) models and finite element analysis (FEA) with reduced errors, (2) investigate the significance of shape and geometry variations in the bone midshaft (where the strains are typically read) versus age and maturation, and (3) to offer novel machine learning algorithms to tackle the enormous challenges in comprehending mechanical responses in long bones and equine forelimb mechanics. Otherwise conventional tools fail to provide a satisfactory outcome due to the availability of limited data and the extreme complexity of anticipating mechanical properties and discovering performance attributes in this highly interdisciplinary domain. Three major emphases that underpin the author's novel contributions are introduced in the Research Focus sections to follow.

1.1.1. Research Focus 1

Performing reverse engineering to construct a 3D model of MC3 midshaft bones and to calculate error analysis of the reconstructed MC3 bones obtained through the extrapolation process. Also, employing analytical displacement-based error estimation and offering adaptive mesh refinement processes to present a framework for minimizing stress and strain errors in finite element analysis of equine third metacarpal bones. The proposed model, which presents an accurate FEA (error of 0.12%) in the smallest number of iterations possible, will assist future investigators to maximize FEA accuracy performed on all different sorts of bones in general. Furthermore, the accuracy of models can be enhanced if experienced engineers incorporate carefully-selected parameters using CAD tools such as ANSYS and CATIA to achieve reliable FEA. A critical issue for rapid product development is to efficiently create and modify a CAD model from the existing components of a desired object. While others have attempted to employ FEA on equine MC3 long bone and surrounding areas ([Collins et al., 2009](#); [Harrison et al., 2014](#); [Hinterhofer et al., 2001](#); [Jansová et al., 2015](#); [Les et al., 1997](#); [Liley et al., 2017](#);

McCarty et al., 2016a; MERRITT et al., 2006; O'Hare et al., 2013), data was lacking to quantify the accuracy of generated models and to address sources and magnitudes of errors in both CAD and FEA (Mouloudi et al., 2019c) (Page 43 of this thesis). Chapter 3 presents accuracy quantification via reverse engineering using computer-aided design to construct the diaphysis of MC3 long bones. It also outlines analytical and numerical displacement-based error estimation methods to minimize stress and strain errors in finite element analysis of equine MC3 bones. The major objectives of Chapter 3 (Figure 1) were to provide the following salient points:

- The modelling of equine third metacarpal bones with limited available geometric data was investigated.
- Reverse engineering (CAD-based) through an extrapolation process of slices was undertaken to reconstruct MC3 long bones. 3D CAD software assists in generating 3D models of the bones and provides engineers with opportunities to manipulate and alter the shape configuration of bones.
- The error map of the reconstructed geometries was plotted.
- Anatomical features causing noticeable errors were identified and discussed.
- A displacement-based error estimation and the relationship to finite element convergence analysis were developed to assist future investigators to maximize the accuracy of their models.
- The significance of performing mesh refinement and mesh convergence procedure was stressed.
- FEA errors of 3-5% have been shown to be acceptable in previously published papers, while the proposed model offers an accurate FEA (error of 0.12%) in the smallest number of iterations possible.
- Quantifying errors of the finite element analysis presented in this study are essential prior to treatment of bone diseases when using FEA models to guide treatment.

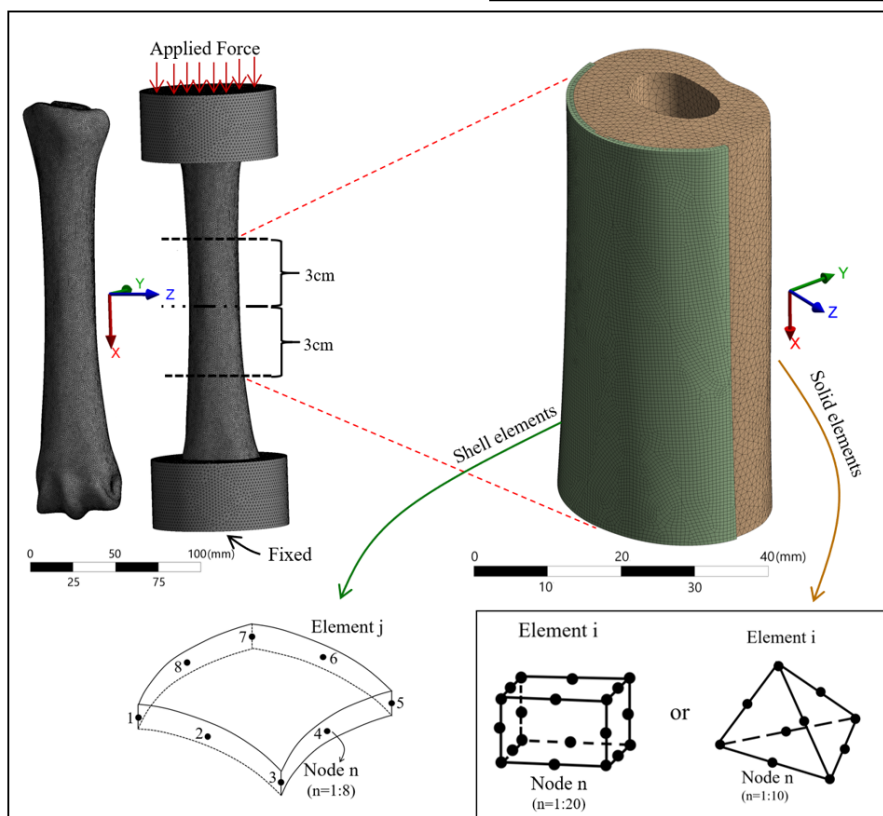
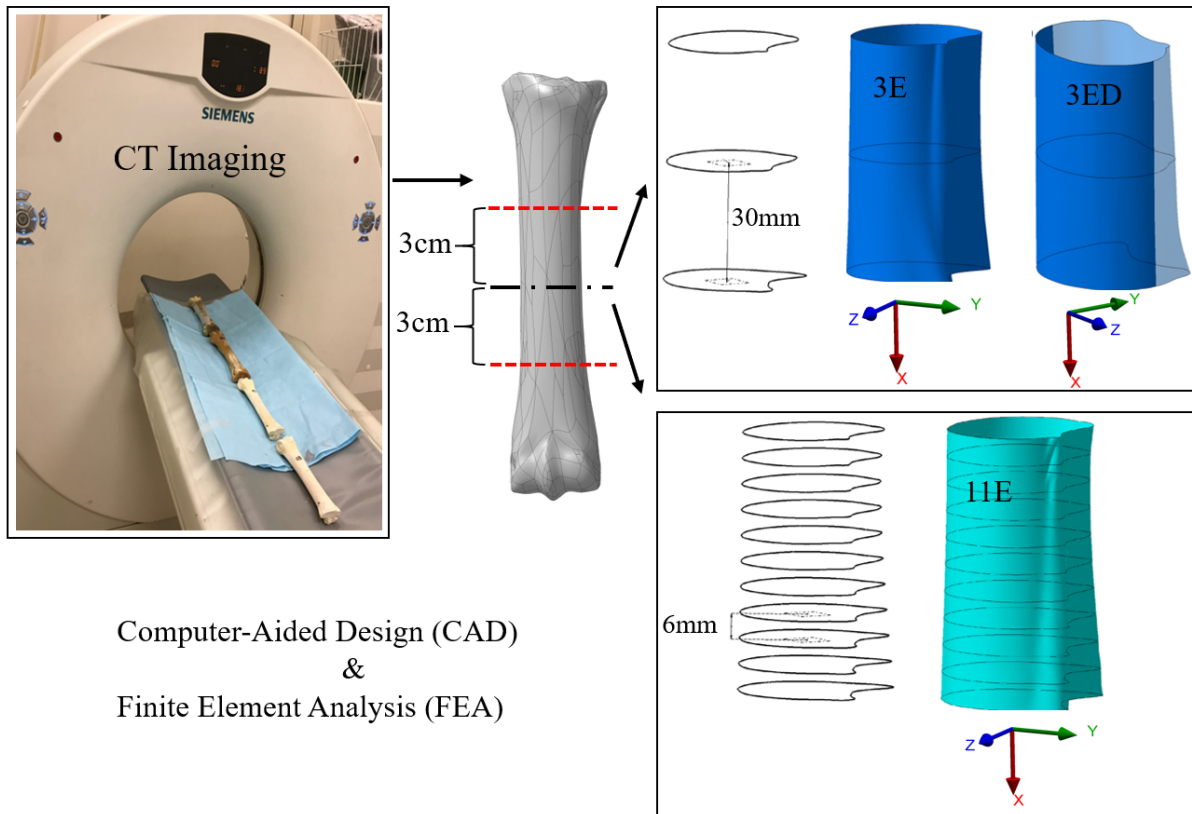


Figure 1. A graphical abstract that outlines the contribution reported in Chapter 3.

1.1.2. Research Focus 2

Investigations of shape and a variety of geometrical parameters within the midshaft of MC3 long bones and their variation versus individual age and maturation. Such studies are essential because bones repair themselves (self-repairing) and adapt to changing mechanical demands by altering their shape and mechanical properties (self-adapting) (Rahmanpanah et al., 2020). Therefore, statistical analysis, proper comprehension of shape and geometrical parameters, and discovering the connection between bone shape and bone adaptive responses are likely to be useful in forecasting the response of MC3 to a training program as well as predicting its internal loading (Mouloudi et al., 2019a) (Page 58 of this thesis). The mechanical properties of a bone (stiffness and strength, for example) are dependent on the overall anatomical geometry and the bone size and shape. The strains recorded on the dorsal surface of MC3 during exercise were shown to be linearly related to exercise speed and differed between individual horses (Davies, 2002). The differences in strains were further demonstrated to be significantly related to bone size at the midshaft of MC3 (Davies, 2001). The MC3 midshaft (a region in its diaphysis) is a region where strain measurements are normally recorded from. Previous research showed that bone as a complex biological material is stimulated to change shape when the individual ages. Yet, it is not exactly clear which geometrical parameters in a cross section of the MC3 are subjected to change during maturation. Neither is the degree by which they change properly explained. Therefore, it is of essential importance to investigate the variations of geometrical parameters of MC3 cross sections versus different age groups and exercise history and to assess their significant changes employing statistical tools. Chapter 4 is presented to address this and primarily aims to provide measurements of a variety of geometrical parameters in three main cross sections (slices) within the diaphysis of MC3 bones and then compare the values to assess their significant changes employing ANOVA and *t*-tests. The major contributions of Chapter 4 (Figure 2) are summarized as follows:

- A variety of geometrical parameters including cortical area (A), width of dorsal cortex (D), palmar cortex (P), medial cortex (M), lateral cortex (L), medulla in dorsopalmar plane (M_d), and medulla in lateromedial plane (M_l) in three main cross sections (slices) within the diaphysis of MC3 long bones were measured using computer-aided-design.
- Shape indices ($[D/P] \times [(D+P)/M_d]$), H ($D+M_d+P$), and V ($M+M_l+L$) were also calculated.
- Horse age, metacarpus length, and a summary of training history of horses were recorded.

- MC3 long bones belonging to 27 Thoroughbred horses aged from 12 hours to 15 years were categorized into five groups (foals, yearlings, two-year-olds, three-year-olds, and adults).
- The geometrical parameters were analysed using t -tests and ANOVA tests (conducted on the aforementioned three cross sections for the five groups) to compare the geometrical measurements among different groups and to assess their significant changes among different groups.
- Variations in the geometrical parameters should be considered in designing equine training programs in attempts to predict and prevent bone damage.
- Data, methodologies, and insights provided in this study will assist in finding an optimized and desirable shape configuration of long bone beams within their midshaft.

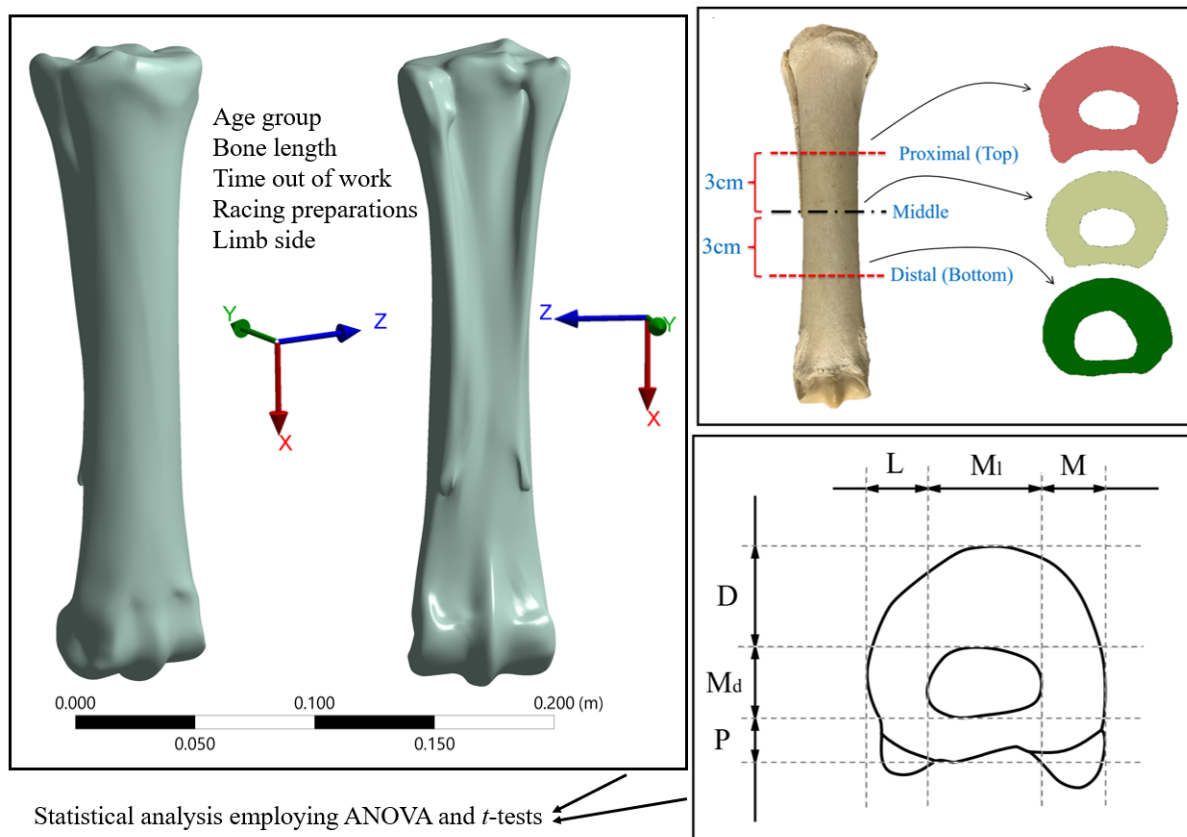


Figure 2. A graphical abstract that outlines the contribution reported in Chapter 4.

1.1.3. Research Focus 3

The use of artificial intelligence (AI) employing artificial neural network (ANN) algorithms was investigated, discussed, and thoroughly elaborated in the prediction of the mechanical response and behaviour of an advanced complex material (MC3 long bones). Implementation of neural networks as a constitutive approach to model engineering structures is a novel research area ([Mouloudi et al., 2020b](#); [Rahmanpanah et al., 2020](#)) (Pages 93 and 107 of this thesis). This anatomical region (i.e. MC3 bones) provides a potential insight into how complex biological materials like bone and ligament respond to loading in all species and what parameters are vital to retain their integrity during normal use. The ability to learn from examples (patterns inherent in observations) and to generalize this learning to a wider population in foreseeing unknown parameters makes data-driven tools such as ANNs exceptional tools in the field of bone mechanics. This is the first study in which the mechanical responses of an advanced biological material with exotic mechanical properties (a long bone) has been quantified using an expert system (artificial neural network) from measurements recorded experimentally. The remaining chapters of this thesis (Chapter 5 to Chapter 8, inclusive) delve into the use of artificial neural network expert systems on equine MC3 long bones with the development of appropriate ANN structures that are well-designed to fulfil the required tasks. Training of machine learning algorithms such as ANNs with inadequate datasets will lead to poorly developed ANNs exhibiting poor performances in their applicability and generalization. To mitigate this concern more than three years of ex-vivo experiments and data collection were used to establish, train, test, validate, and generalize ANNs to gain the favourable outcomes. Chapter 5 (Figure 3) elaborates the following key points:

- Artificial neural network algorithms were used for the prediction of displacement in the equine third metacarpal bones.
- The entire hydrated bone samples were loaded in compression in an MTS machine.
- Experimental data of load exposure time, loading, displacement, and strains was recorded and was introduced to the ANN.
- The ANN model which was trained using 3,250 noisy data points from two bone samples successfully predicted the displacement of the third bone ($R^2 \geq 0.98$) within a couple of seconds.

- An FEA required more than 160 times as long to merely predict one cycle of load-displacement curve, emphasizing the real-time ability of ANNs in computational mechanics of complex nonlinear structures.
- Artificial neural networks provide a promising approach to quantify mechanical features of complex structures without the current runtime penalty.

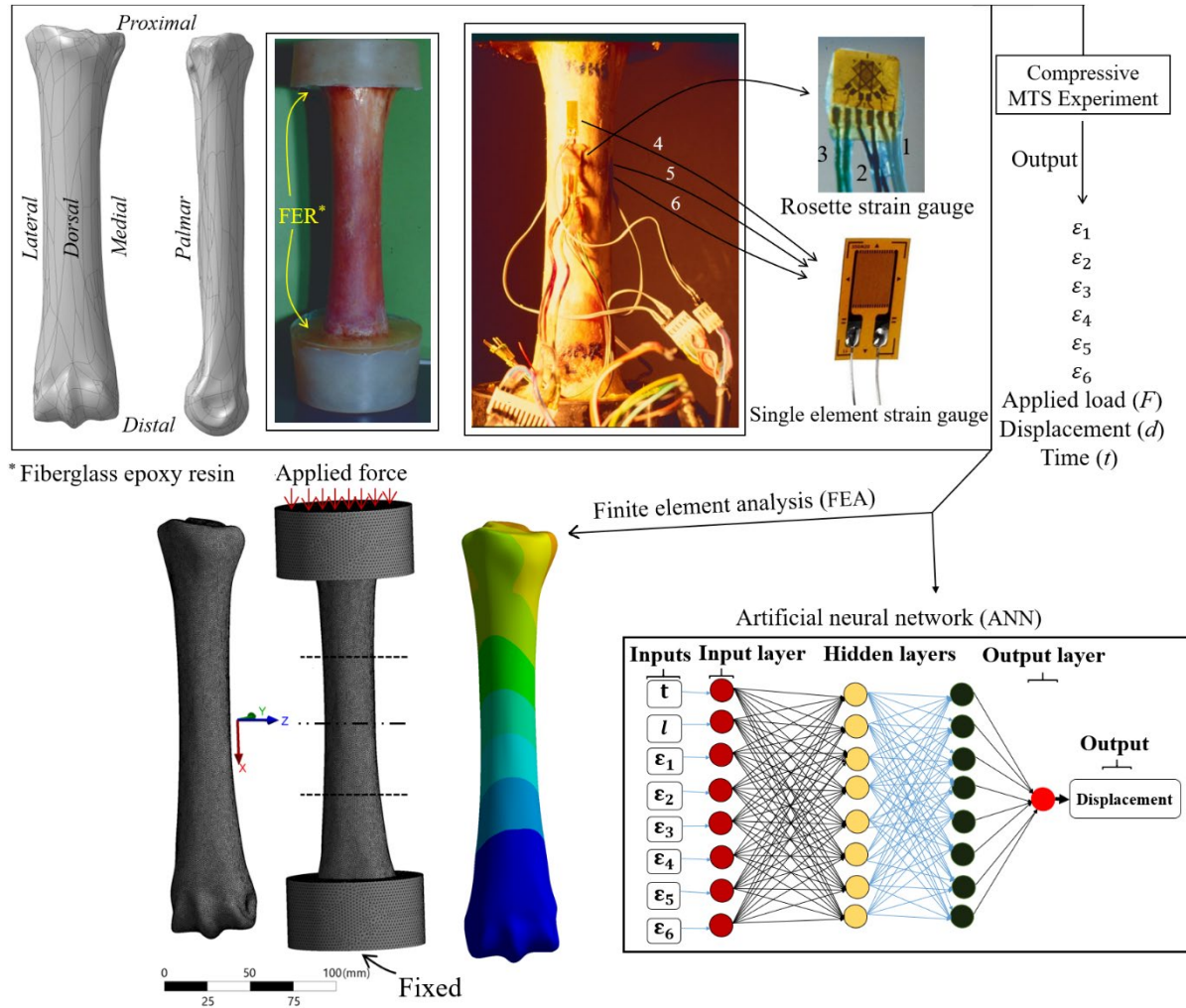


Figure 3. A graphical abstract that outlines the contribution reported in Chapter 5.

Chapter 6 provides the reader with the following summarized highlights (Figure 4):

- An artificial neural network expert system was used to quantify loading of equine third metacarpal bones.
- The entire hydrated bone samples were loaded in compression in an MTS machine.
- Experimental data of strains, associated displacement, and load exposure time were introduced to the ANN.
- The ANN offered excellent prediction ability for the prediction of load in the MC3 long bones.
- ANN expert systems provide promising outcomes to predict loading of an advanced material with exotic mechanical properties.
- A categorizing approach employing pattern recognition algorithms was adopted to elucidate age-dependent attributes of experimental measurements through identification of a confusion matrix (three classes of ages associated with different individual samples).

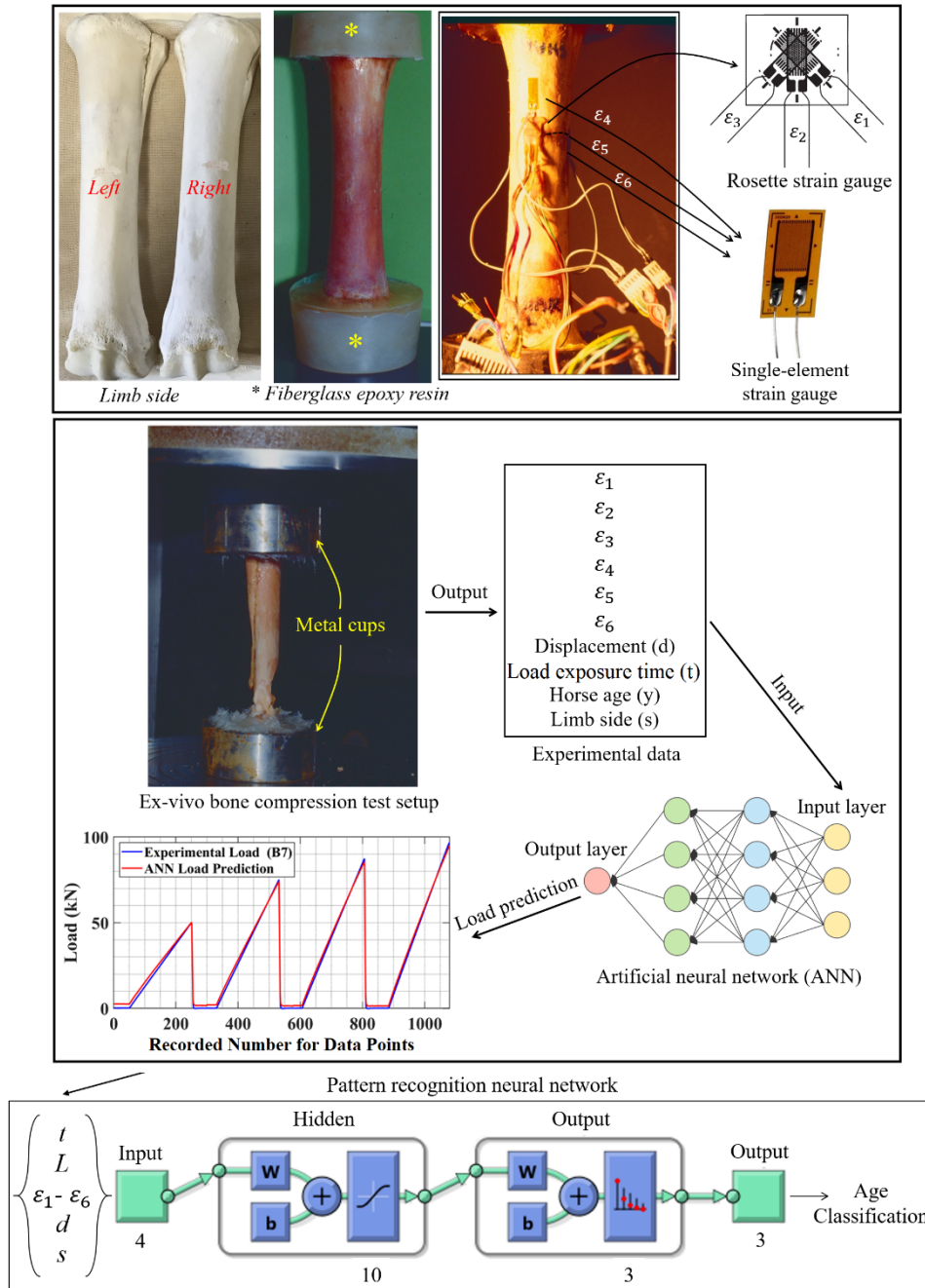


Figure 4. A graphical abstract that outlines the contribution reported in Chapter 6.

Chapter 7 investigated the following key parameters (Figure 5):

- Two in-series feedforward back-propagation artificial neural networks were employed to offer strategies to predict a cyclic load-displacement curve and cyclic stiffness of a complex structure possessing exotic mechanical properties.
- Recordings of ex-vivo experiments, including six kinds of strains measured at different locations on the MC3 midshaft, load exposure time, horse age, and bone side (left or right limb) from thirteen hydrated MC3 bones shaped ANNs input variables.
- ANNs with overall two outputs (unknown variables) offered predictions of both applied load and exposed displacement (and subsequently stiffness).
- The results of predictions made by ANNs were plotted versus experimental counterparts.

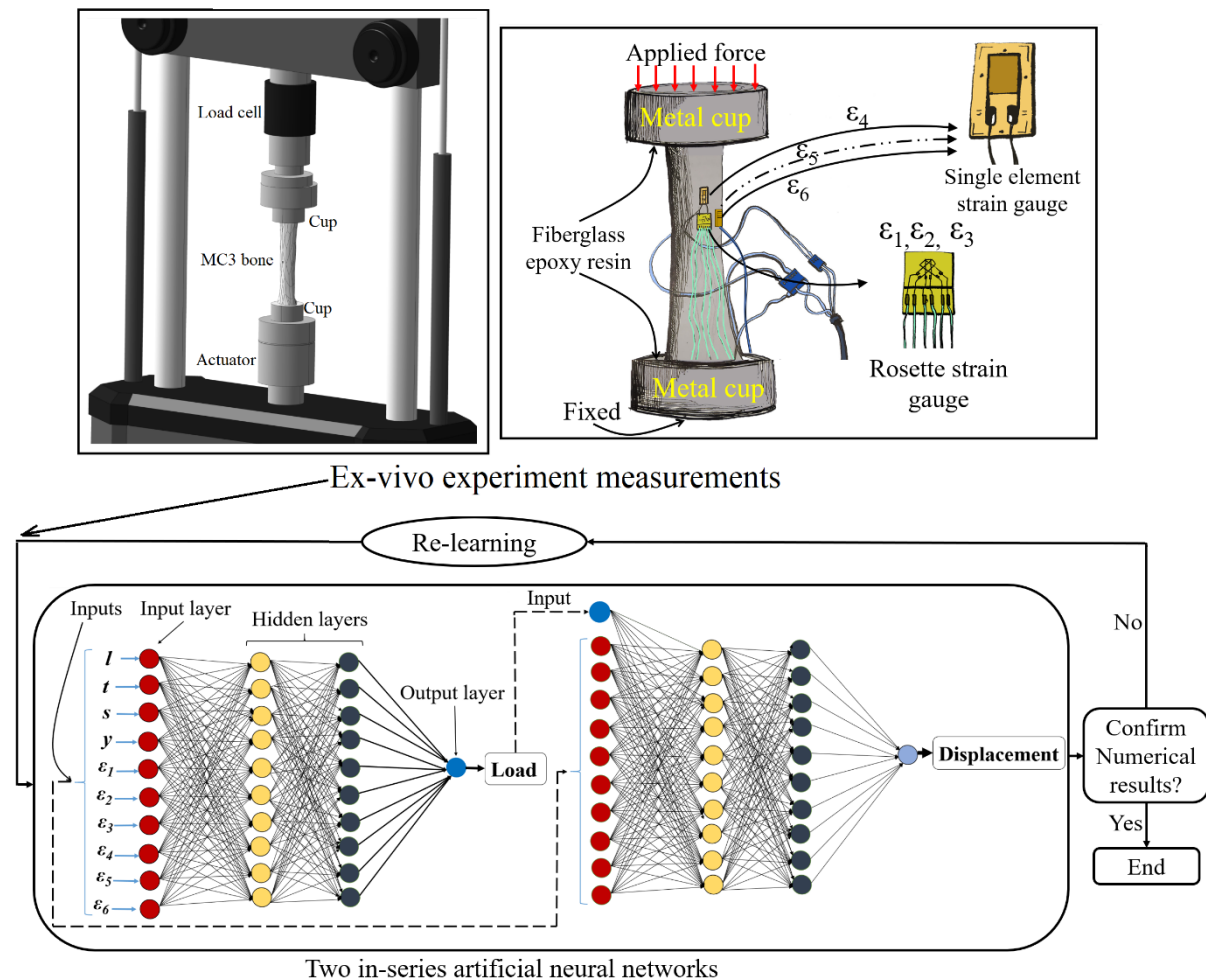
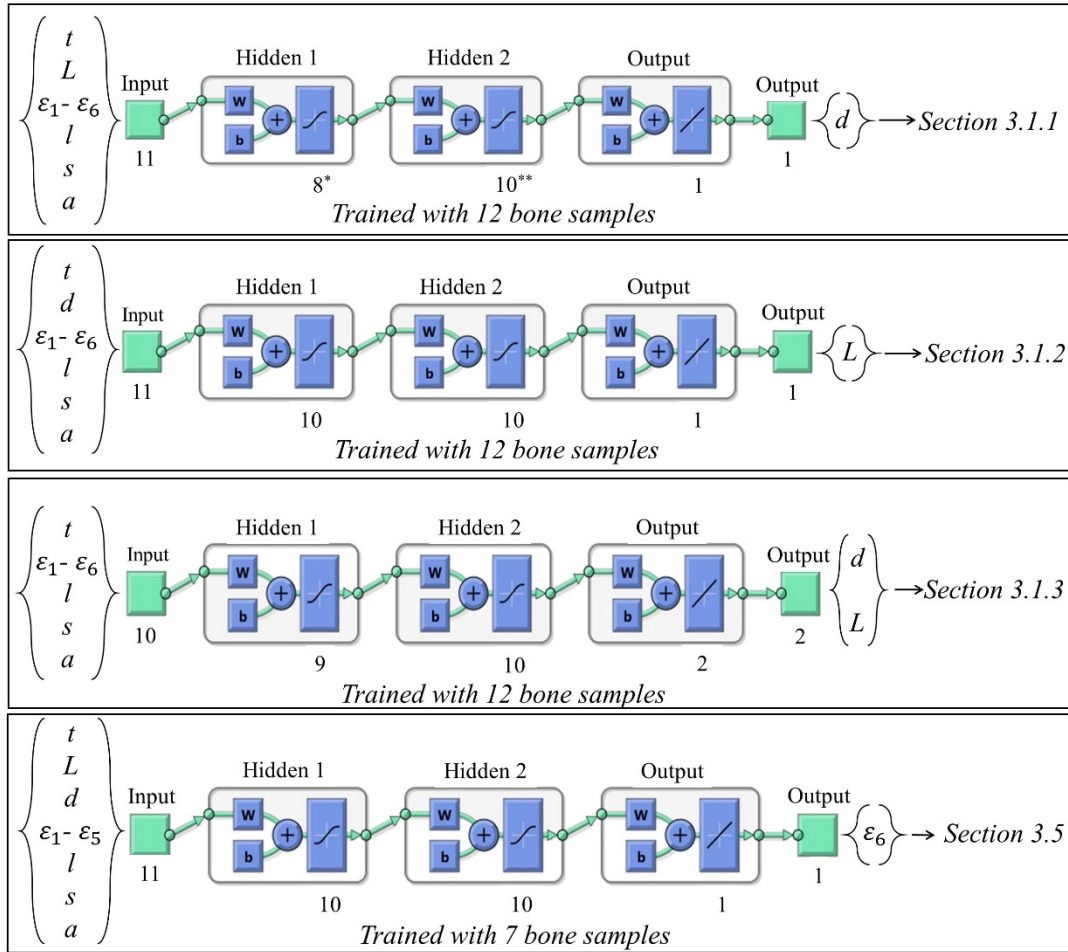
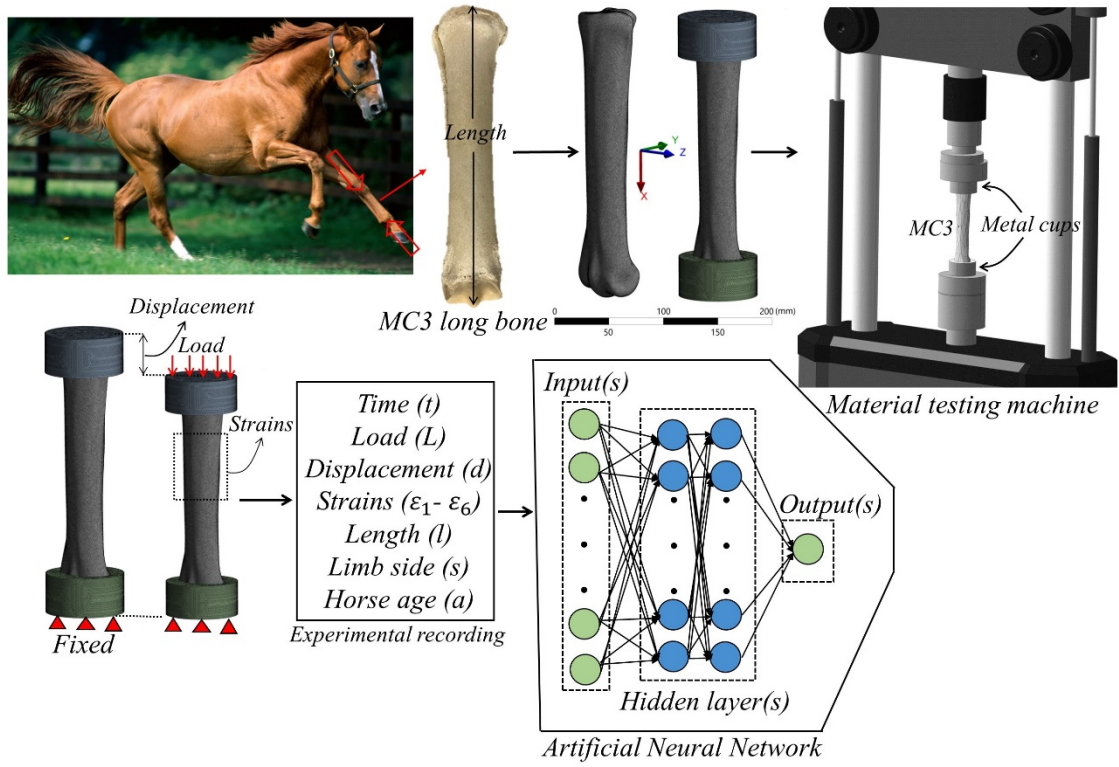


Figure 5. A graphical abstract that outlines the contribution reported in Chapter 7.

Chapter 8 presents (Figure 6):

- The use of feedforward back-propagation artificial neural networks (FF-BP-ANNs) was elaborated to improve the performance and generalization of trained ANNs in predicting mechanical responses of complex nonlinear engineering structures.
- Three years of experimental data collections were used to establish the neural networks.
- Loading, displacement, cyclic load and displacement (stiffness), and strains were predicted in a long bone representing an advanced biological material with exotic mechanical properties.
- A growing technique was employed to tackle the challenge of selecting an optimum ANN structure (architecture).
- A major emphasis was placed on the analyses conducted on the new specimens that ANNs had not seen before, which offers an unbiased measure of the performance of the model on unseen data different from those used for training.
- The generalization ability of ANNs in making predictions on unseen samples was assessed when the ANNs were trained with and without injected noise.
- Strategies to select an appropriate range for the values of injected noise were offered.
- The reduction in generalization error was recorded when the ANNs were trained with and without normalized input data.
- The influence of network training algorithm on reliable predictions and generalization performance of ANNs was investigated and discussed.
- Essential parameters influencing decision making in identifying well-trained and well-generalized ANNs were elaborated.



* Number of neurons in the first hidden layer

** Number of neurons in the second hidden layer

Figure 6. A graphical abstract that outlines the contribution reported in Chapter 8.

Chapter 2

Literature Review

2.1. Introduction

Each of chapters 3 to 8 correspond to a published/submitted peer-reviewed journal paper. As such, each chapter includes a review of the foundation literature relevant to the novel contribution reported. This chapter offers an overview of the current literature and seeks to integrate the literature reviews contained in chapters 3 to 8 to assist the overall narrative of this thesis.

The equine distal forelimb is the source of most career-ending injuries to sport horses in all disciplines, and as such understanding how the materials in this part of the body respond to loads is key to understanding how and why they break down ([Davies, 1995](#)). Fractures of the equine forelimb (in particular, the distal limb) in racehorses are typically catastrophic, and the injuries associated with the equine forelimb place an enormous burden on both equine welfare and the economics pertaining to the equine industry. The third metacarpal (MC3) long bone is a typical site for damage in the bones of racing Thoroughbreds and is exposed to strains far larger than appears to be the limit that other mammalian bones can tolerate without damage ([Davies, 2006](#)). Hence, it is important to reduce disastrous incidents associated with the equine distal forelimb. The anatomical region of MC3 also offers potential insights into how complex biological materials like bone and ligament respond to loading in all species, and what parameters are vital to retain their integrity during normal function. The exceptional mechanical properties and responses exhibited by MC3 long bones encourage researchers and engineers to dive into understanding this advanced material using novel techniques, simultaneously facilitating our comprehension of less complex materials (such as composites, nanomaterials, and alloys). Many external and internal parameters in the equine forelimb are measured such as: kinematics and motion of the limbs, ground reaction forces, and tendon and bones strains, some are quantified non-invasively while obtaining others are invasive and far more problematic. A growing body of research offers solutions to relate these external and internal quantities as well as general characteristics of individuals to one another, and to

validate the accuracy and reliability of measurements (Davies, 2009; Grassi and Isaksson, 2015; Merritt et al., 2010).

Despite recent advances in measurement techniques, gaining deep knowledge to then distil correlations among whole bone shape; material, mechanical, and overall physical responses; and, associated properties suitable for subsequent computer modeling, is a daunting task due to the complexity of both geometry and material (Shahar and Weiner, 2007; Sharir et al., 2008). Nonetheless, the complicated nonlinear, inhomogeneous and anisotropic properties of long bones offer researchers intriguing comprehension opportunities. Nonlinear relationships exist among stress, strains, applied loads, deformation, and the mechanical properties in these biological materials. Biological system factors such as race, sex, level of activity of a living animal and the possible state of pathological degradation of any of its structures, as well as the preservation conditions of the specimens taken from the animal until it is used for experimentation, lead to an irregular distribution of mechanical properties and consequently considerable challenges in the prediction of responses of bones. Bones are mainly responsible for withstanding and absorbing applied loads. To predict bone fracture and failure, and to investigate reasons for such incidents, comprehensive insight into the responses of bones to loading is crucial. Identifying the strains and stresses to which bones are exposed will assist in elucidating the reasons for fractures and locating their most likely sites. The mechanical properties and responses of these advanced engineering structures have been shown to be density-dependent (Carter and Hayes, 1977; Gačnik et al., 2014; Rice et al., 1988), site- and length-dependent (Asgari et al., 2019; Fradinho et al., 2015; Nobakhti et al., 2017), force- and loading-rate-dependent (Bagherian et al., 2019; Edwards et al., 1987; Kulin et al., 2011; Rostedt et al., 1998), time-dependent (viscoelasticity) (Manda et al., 2017; Mouloudi et al., 2019d; Xie et al., 2017), strain-rate-dependent (exhibiting both viscoelastic and viscoplastic behaviour) (Johnson et al., 2010), size- and scale-dependent (Frame et al., 2017; Mirzaali et al., 2016), shape-dependent (Davies, 2001; Mouloudi et al., 2019a), age-dependent (Berlin et al., 2019; Kulin et al., 2011; Mouloudi et al., 2020b; Patton et al., 2019), sex-dependent (Patton et al., 2019) and so forth. It would be difficult to find another material that possesses such multivariable and exceptional mechanical properties (Mouloudi et al., 2020b). Integration of novel and efficient computational tools, with collection of trustworthy experimental data, using intelligent systems, for example, hybrid models coupling computer-aided design (CAD) and finite element analysis (FEA) as well as artificial intelligence (AI), is motivational due to the excessive demand in the field of biomechanics for the development of rapid multiscale

approaches (Hambli and Hattab, 2013). Achieving this requires accurate CAD and FEA of bones and successful application of such expert systems to the field, and this thesis reports on the research that has been conducted in this area.

This chapter includes the following sections to expand the reviews of literature contained in each of the novel contribution chapters in this thesis: Section 2.2 offers a brief introduction and explanation to CAD and FEA in solid mechanics of structures with a primary emphasis on their scientific application to equine MC3 long bones. Section 2.3 introduces artificial intelligence (AI) and machine learning (ML) algorithms with reference their general application to the mechanical engineering practices concerning modeling of materials and structures. Section 2.4 introduces artificial neural networks (ANNs) and their practical applications in comprehending and predicting the mechanical responses and behaviors of structures. Section 2.5 reports on the studies investigating the application of ANNs in bone mechanics. Very few research studies have been published on the application of ANNs to the equine discipline (with no published research, in the available published literature, on the equine forelimb other than those presented in this thesis). Finally, Section 2.6 outlines a concluding remark identifying the knowledge gaps in the published literature, and introduces research questions and hypotheses associated with the original contributions reported in chapters 3 to 8 of this thesis.

2.2. Computer-Aided Design and Finite Element Analysis

Stress and strain analyses are the hallmark of engineering mechanics where the responses of complex structures under load and specific sets of boundary conditions are quantified using numerical techniques such as finite element analysis (FEA) and computational fluid mechanics (CFD), for which basic constitutive equations are required to be derived or defined including the characteristics of the materials such as linear elasticity, plasticity, viscoelasticity, viscoplasticity, hyperelasticity, and moreover, combinations of these features since some advanced materials exhibit behaviors that can only be estimated using a combination of different models. Undertaking stress and strain analysis is one of the major applications of FEA in solid mechanics, biomedical engineering and biomechanics of bones ([Anderson et al., 2010](#); [Chand et al., 1976](#); [Gohari et al., 2019b](#); [Imai, 2015](#); [Mouloudi et al., 2014a](#); [Mouloudi et al., 2014b](#); [Naceur et al., 2015](#); [Parashar and Sharma, 2016](#); [Park et al., 2017](#); [Ural et al., 2011](#)). As an advanced computer simulation technique to solve problems concerning structural analysis, the finite element method (FEM) was first developed in engineering mechanics, and then it was employed to analyze mechanical behavior and responses of human bones (skeletal parts) in 1972 ([Breklemans et al., 1972](#); [Huiskes and Chao, 1983](#)). Due to the complex shape, very irregular structure, and peculiar properties of bones, classical theoretical and mathematical tools are not suitable to obtain accurate mechanical responses of bones, emphasizing an essential need to implement computational techniques. As such, FEA is currently an indispensable tool in the analysis of bone mechanics and has been applied to a diverse range of bones across different species. Creating a three-dimensional geometry is the initial, and an essential, step for successfully establishing and performing an FEA ([Gföhler and Peham, 2013](#); [Mouloudi et al., 2019c](#)) (Page 43 of this thesis). Thus, CAD and FEA are intimately tied together and are becoming necessary tools in attempts to model and analyse bones, optimize complicated soft and hard tissues, design implants, and offer novel design strategies for manufacturing processes such as employing 3D printing, provide communication tools among biologists and engineers, identify regions with highest strains and stresses, predict areas of potential fracture and failure, and provide a way to replicate experimental data ([Colombo et al., 2006](#); [Mouloudi et al., 2019c](#); [Parthasarathy et al., 2011](#); [Starly et al., 2005](#); [Sun et al., 2004](#); [Sun and Lal, 2002](#); [Wehmöller et al., 2005](#); [Yoshihara et al., 2012](#)). Establishment of a CAD model is one of the major pre-processing steps prior to undertaking FEA, in which the geometry and mechanical properties of the investigated bone can be extracted from different sources of

data such as imaging techniques (for example, computed tomography, CT). Then, CT and MRI (magnetic resonance imaging) based software such as *Mimics* (Materialise Medical Software, Leuven, BE), *ScanIP* (Simpleware Ltd., Exeter, UK), and *Amira* (Visage Imaging, Inc., Carlsbad, CA, USA) enable engineers to control and modify the segmentation of CT and/or MRI images, accurately define 3D models (the software allows creation of 3D surface models from stacks of 2D image data), perform CAD, assign material properties, and apply finite element meshes. Since there is a direct correlation between the intensity of the images and the density of bone and because grey values in the grayscale images from the CT scan represent material density, the CT data are also used as an input for assigning material properties to the elements of finite meshes (volume meshes). The modulus of elasticity (also referred to as Young's modulus) and Poisson's ratio are then defined as power functions of density. More advanced software (for example, *SolidWorks*, *Inventor*, *CATIA*) that are dedicated to creating complex 3D models for structural and mechanical practices, can also be used to create implants, and their subcomponents, and to link them to the bone models already generated. Employing different CAD methodologies in biomedical and tissue engineering practices demands considerable effort and diligence to appreciate the value and significance of different methods (Davidoff and Freivalds, 1993; Starly et al., 2005; Sun et al., 2005). FEA may still be unfamiliar to the readers of equine-related journals, yet it has the potential to provide tremendous benefits (Gföhler and Peham, 2013). It is not the intention of this thesis to explain the basics of CAD and FEA and their underlying features and analysis functionality (there is plentiful material in the literature for the interested reader). Rather, as an engineer with a background in the solid mechanics of structures and expertise in successful application of CAD and FEA in different areas of mechanical engineering (Gohari et al., 2019b; Moulloodi et al., 2014a; Moulloodi et al., 2014b), the author sought to address limitations in frequently employed FEA and to establish a framework to identify important features that are required to be followed to increase the accuracy of FEA and CAD-related studies undertaken on the equine MC3 long bones (the performed study in Chapter 3). This is also a requirement to: (1) ascertain the sources of errors while investigating MC3 bones, (2) minimize the errors to enhance the accuracy of the results, and (3) ensure the suitability and precision of the models when the study is further expanded in the subsequent chapters.

Several studies have been conducted on 3D modelling and stress distribution in the equine MC3 bone and surrounding structures. To refine previously conducted FEA of an equine stifle joint in the evaluation of bone stresses (Frazer et al., 2017) and to enhance the comprehension of the equine stifle joint, FEA was performed from CT images of a stifle of a yearling horse

(Frazer et al., 2019). The model was then loaded to 8 kN and the stresses were quantified in the medial femoral condyle. A subject-specific FEA of an equine metacarpophalangeal joint was developed where deformable cartilage, elastic ligaments, muscle forces, and rigid representation of MC3 bone were included to determine loading of joint contact and cartilage stresses (Harrison et al., 2014). CT and MRI imaging was used to extract a 3D model of the bone, muscle, and cartilage geometries, ex-vivo mechanical testing was performed to extract bone kinematics and tendon and ligament properties, in-vivo gait analysis experiments were conducted to obtain ground reaction forces and joint kinematics. Then, musculoskeletal, inverse kinematics, inverse dynamic, and finite element models were adopted to build the equine metacarpophalangeal joint model. With inclusion of all the relevant tissues (such as distal phalanx, navicular bone, and middle phalanx) that were missing in the previously existing studies, an FEA of an equine hoof was completed to emphasize the mechanical responses of all the relevant structures, and the model was only validated in terms of measured displacement (Jansová et al., 2015). To tackle the problems involved in the analysis of bones due to their irregular geometry and nonhomogeneous material properties, 3D finite element stress analysis was shown to be an essential tool to understand bone remodelling, and this automated method of generating patient-specific 3D FEA of bones was presented by Keyak et al. (Keyak et al., 1990) in which CT scan data was used to predict the geometry and material properties of the bones representing a new and relatively rapid method. Using this algorithm, 3D FEA of equine MC3 from five adult horses was completed using CT imaging data. The bones also had 12 rosette strain gauges attached ex-vivo, and were then mechanically loaded in compression (Les et al., 1997). Maximum and minimum principal strains obtained via 3D FEA were compared against the experimental results. The validation study suggested that the 3D FEA computer simulation was capable of predicting surface strains. Owing to the power of finite element models to be a valid predictor of experimentally measured strains, automated FEA was suggested to provide a suitable tool for routine assessment of fracture risks of bones in clinical problems (Keyak et al., 1993). Verification of surface strains in that study with the output of FEA was inspiring enough to expand the studies in this area of research. Inspired by such perspectives and since bone stresses cannot be noninvasively measured in-vivo, similar FEA studies were carried out to evaluate the accuracy of FEA of long bones with ex-vivo and in-vivo experiments, for example (Den Hartog et al., 2009; Knowles et al., 2016; Lescun et al., 2020; Mirzaei et al., 2014; Taddei et al., 2006). To understand mechanical loading and stress of the equine metacarpophalangeal joint (fetlock joint), two fetlock joints were scanned using micro-CT images with subsequent segmentation of the images, generation of 10-node quadratic

tetrahedral finite element meshes, assignment of bone-density-dependent material properties, and then impact and static loading were applied to the models (McCarty et al., 2016b). Contact pressure and stress distribution were then calculated, identifying high stresses associated with impact loading and some in the surrounding areas due to midstance (high mass) loading.

FEA studies reviewed by the author often included limitations such as a “lack of evidence in terms of quantifying dimensional error of reconstructed geometries, performing mesh quality assessment, determining the error of FEA, or assigning linear tetrahedron meshes to the models, which would all potentially lead to misleading stress and strain results” (Mouloudi et al., 2019c). In addition, CT-based FEA is time consuming. For example, irrespective of implementing innovative computational techniques (Keyak, 2001; Koivumäki et al., 2012; Mirzaei et al., 2012), a minimum of 8-10 hours of runtime are required to complete a nonlinear FEA of a human proximal femur constructed from a typical CT-based framework (Mirzaei et al., 2014). It is therefore important to ensure appropriateness and accuracy of CAD and FEA predictions by identifying and addressing the effect of uncertainties, necessitating uncertainty management methods to enable robust decision making and to develop appropriate method to address them. Efficient and reliable models of this advanced complex material, at the whole bone level, whose mechanical properties exhibit dependency on multiple factors will also assist in understanding how different surfaces of this complex structure are responding under loads, which would enable a better comprehension of MC3 fatigue analysis (Malekipour et al., 2020b) and subchondral bone damage in the joints of both humans and animals (Malekipour et al., 2020a; Martig et al., 2013).

2.3. Artificial Intelligence and Machine Learning Algorithms

Artificial intelligence (AI), also referred to as cognitive simulation or information processing psychology (Simon, 1983), is an interdisciplinary science where machines, algorithms, and expert systems are endowed with the human intelligence to learn from existing experience and real-world examples, decipher meanings, languages, images, and patterns (as humans do), to then anticipate future trends associated with the learned precedent. Hence, AI is regarded as human intelligence exhibited by machines (Jones et al., 2018). Challenging and appealing goals of machine learning algorithms in the study of AI predominantly involve the acquisition of knowledge through observation and experimentation, making predictions, proposing new theories, taking rational decisions, enhancing performance of a variety of tasks, and performing certain averaging over realizations (Mitchell et al., 2013; Rahmanpanah et al., 2020). Several methodologies and approaches using AI have been devised and proposed to replace integral and constitutive equations (learning through examples is replaced with physical modelling) by data-driven methods such as artificial neural networks (Bock et al., 2019; Oeser and Freitag, 2009). Herbert A. Simon elaborates on the inquiry that, “why should machines learn?”, where tediousness of human learning, lack of the ability to copy human learning, agonizingly slow rates of human learning and its associated inefficiency were among his reasons and explanations (Simon, 1983). Machine learning holds the promise of accelerating of research procedures and expediting the comprehension of materials through establishing principles from observations (datasets that AI and machine learning are being trained on), thereby facilitating building models enabling reliable and efficient predictions to be made to advance material design and performance.

The emergence of AI with the rapid development of machine learning algorithms offers new possibilities in the advancement of material science, striving to map nonlinear relationships among multiple variables involved in the definition and understanding of materials such as: their properties, structure, and application. These data-driven machine learning algorithms require data to train the algorithm (to complete the learning process), with the algorithm then tasked with elucidating insight and meaning from the data. Machine learning is primarily divided into four steps: data collection (through observations, online data sources, experiments, simulations such as FEA and CFD), data representation (pre-processing and initial analysis of the input data to make data appropriate for the algorithm thereby expediting and improving its learning), algorithm selection (supervised learning such as regression and pattern recognition

or unsupervised learning such as clustering and associations), and model optimization (to select the appropriate degree for the fitted mathematical function using regularization and cross-validation techniques to minimize the likelihood of overfitting and to reduce any unnecessary complexity of the model) (Rajan, 2005; Sha et al., 2020).

There are many AI algorithms, for example, fuzzy logic, artificial neural network, neuro-fuzzy (combining both ANN and fuzzy logic), and logistic regression. Likewise, there are numerous machine learning algorithms such as: linear regression, decision tree, support vector machines, random forest, among others. Each of these AI and machine learning algorithms excels in a specific area that seeks inherent patterns among various time and length scales, attempts to offer the best fitting idea to a problem, and strives to find appropriate nonlinear mappings from the space of input(s) to that of output(s), thus providing the most precise correlation among variables (input and output data). Despite their remarkable development and enormous success, AI and machine learning are in their infancy and still undergoing continuous changes (Bock et al., 2019). Interested readers are directed to the extensive review papers on the application of artificial intelligence and different machine learning algorithms, for example, ANNs in computational mechanics (Yagawa and Okuda, 1996), clinical biomechanics (Schöllhorn, 2004), continuum materials mechanics (Bock et al., 2019), computational science and engineering (Frank et al., 2020), materials science and engineering (Sha et al., 2020).

FEA and CFD are two computational techniques that assist in solving problems of mechanical and biomedical engineering, in which the investigated system or problem is subdivided into simpler and far finer parts (called finite meshes). As the mesh density (the number of nodes and elements) increases, so does the accuracy, however at the expense of computational time. Time is a precious commodity, particularly in clinical practice where rapid patient-specific simulations are critical. Moreover, computer-aided engineering products developed for FEA (e.g. commercial products such as ANSYS and Abaqus, which are widely used in engineering mechanics), without manipulating their underlying algebraic formulae and hence developing cumbersome finite element coding that is frequently performed in MATLAB (Gohari et al., 2019a; Mouloudi et al., 2014a; Mouloudi et al., 2014b), lack the ability to tackle the inverse problem and fail to conduct reverse-engineered problems (Mouloudi et al., 2020b; Rahmanpanah et al., 2020) (Pages 93 and 107 of this thesis). Machine learning and artificial neural network algorithms are worth investigating as alternative tools to assess their aptness and relative performance in these engineering applications. Concerns associated with machine learning algorithms traditionally focus on the requirement of comprehensive and extensive data

for their training, testing and validation, as well as the necessities of calculating and optimizing millions of parameters (Lipton et al., 2015). These concerns have been alleviated thanks to: (1) the availability, affordability, and ease of access to enormous data storage; (2) extensive experimental measurements performed and recorded in recent years (with high precision offered by the current experimental setups and techniques) that enormously grow the volume of datasets; and (3) considerable advancement in parallel computing systems and the development of large computational capacity offered by rapidly growing powerful computers, among others, have expedited developing new algorithms and optimization techniques and have accelerated the use of diverse methodologies for interpretation and prediction of highly nonlinear datasets in classification, pattern recognition, and regression problems (Kim, 2010).

The behaviour of concrete (exhibiting properties that significantly alter with respect to the properties of its constituents) under different loading conditions were predicted using backpropagation neural networks to comprehend stress-strain relationship and to analyze cracking behaviour of materials using machine learning algorithms (Ghaboussi et al., 1991; Ramanauskas et al., 2020). The application of these networks has also been explained and discussed concerning the bending analysis of beams: damage detection in steel beams, elastoplastic beams, applied load prediction on elastoplastic beams (Waszczyszyn and Ziemiański, 2001). In that study machine learning techniques were found to be numerically efficient to be implemented in hybrid modeling, to process experimentally recorded datasets in the analysis of mechanics problems, and moreover, to effectively solve the problems for which: (1) noisy data are prevalent, (2) the underlying mathematical identification is lacking, (3) incomplete and limited data are available, and (4) merging machine learning techniques with traditional simulations (such as FEA) is advantageous. Aimed at developing predictive models to enhance forecasting in clinical applications using structural and morphological characteristics of bones, machine learning can be used as either linear regression (apprehending correlations among input and output variables) or regression classifier (discriminating the pattern in data into different classes) (Sohail et al., 2019). A deep learning model using machine learning techniques was developed and proposed which was trained from the output of FEA (stress distributions under applied pressure were quantified using Abaqus), and then a machine learning model took patient features and image data (aorta shape) (Liang et al., 2018). The model then estimated the stress distribution of the aorta (output of the model). That study attempted to promptly and accurately predict the FEA results via machine learning (an alternative model tool to FEA). This assists in time-sensitive clinical applications where using

traditional FEA requires long computing times to obtain final simulation results (Mouloudi et al., 2020a, b) (Pages 76 and 93 of this thesis). Concluded to be a major improvement over empirical and analytical solutions that can extensively alter the way in which engineering problems are solved, machine learning algorithms using ANNs and regression trees were adopted to measure fracture toughness (Liu et al., 2020). Mechanical tests measuring fracture toughness associated with mode-I, and results of FEA shaped the data for the purpose of their machine learning training session. Computational solid mechanics is gaining considerable benefits from inclusion of deep learning and a variety of machine learning algorithms in stress analysis of structures (Nie et al., 2020) for which FEA is a conventional and widely employed computational tool. This is partly due to the high demand for accurate, yet rapid, structural analysis of advanced engineering components, which enables engineers to broaden the scope of traditional computational mechanics such as finite element and boundary element methods by incorporation of strong capabilities exhibited by deep learning such as regression and classification (Oishi and Yagawa, 2017).

Comprehension of bone mechanics and gaining comprehensive knowledge on equine MC3 long bones (an advanced and complex engineering structure) offers exciting research challenges. Disciplines with large datasets and complex interactions among multiple input parameters, such as the MC3, simpler linear models (such as conventional simple regression analysis) tend to under-fit to the investigated dataset, and thus exhibit poor performance. Nonetheless, neural network models are well-suited computational techniques, provided meticulous consideration is taken into account in the design and application of neural networks to avoid or minimize their misapplications (Sha and Edwards, 2007). The most frequently encountered type of machine learning in material mechanics is an artificial neural network, to the extent that the term ANN sometimes is interchangeably used with machine learning (Bock et al., 2019). ANNs are explained in the next sections and their successful applications to this exciting and challenging area of research (equine MC3 long bones) are elaborated throughout this thesis.

2.4. Artificial Neural Networks

Artificial neural networks (ANNs) are a group of algorithms used for machine learning, which can interpret the nature of many qualitative and quantitative problems as humans do, learn from real-world examples and experiences by being exposed to rich and comprehensive data enabling them to classify and predict inherent patterns and correlations that exist in datasets. Inspired by the structure of biological neural networks in the human brain (Hertz, 2018; McCulloch and Pitts, 1943), ANNs are comprised of three main features: transmission, processing, and storage of information (Hornik, 1991). ANNs are advanced computational learning algorithms that are capable of considering and learning from examples (Van Gerven and Bohte, 2017), and enable scientists to take full advantage of the computational capacity offered by recent powerful computers, thus allowing researchers to process datasets encompassing enormous sizes thanks to availability of huge data storage (Jones et al., 2018). ANN models are massively parallel computing systems consisting of a parallel processing architecture, composed of a large number of highly interconnected processing neurons capable of diving into high-dimensional data to learn their amazingly intricate patterns (Jones et al., 2018). They strive to mimic the way by which humans learn and decipher meanings through examples and experience, demonstrate exceptional flexibility to changing situations, and are configured for a specific application (such as classification, optimization, data prediction, and pattern recognition) to comprehend convoluted nonlinear input-output relationships (Olden and Jackson, 2002). As it was also stressed in Section 2.3, ANNs are very powerful computational techniques to complete reliable solutions to a wide range of supervised and unsupervised problems. Dependent on the learning process, ANNs can also be categorized into three main classes: supervised learning (hypothesis verifying), unsupervised learning (hypothesis generating), and hybrid learning combining the two aforementioned learning methods (Jain et al., 1996). Supervised ANNs generate a relationship between the input and output data to verify prescribed hypotheses, where each of the network inputs is already being provided with a correct answer, target, or output (Mouloudi et al., 2019d, 2020b) (Pages 76 and 93 of this thesis). Then the trained and tested ANNs can be generalized to make reliable predictions on a wider population (samples or individuals that were not involved in the ANNs training session). In the unsupervised ANNs, on the other hand, only the criteria for classification (inputs) are given and the output classifications are expected to generate hypotheses in response to the inputs of the network only (i.e. there are no target outputs available) (Demuth et al., 2014).

Feedforward ANNs (Jain et al., 1996) using supervised learning algorithm are commonly employed in the majority of regression and classification problems in mechanical engineering practices concerning materials and structures design and optimization (Mandal, 2017; Mouloudi et al., 2020a; Stoffel et al., 2018). The impressive success of feedforward ANNs is obvious from their numerous successful applications in addressing and solving real-world problems (Ojha et al., 2017). Backpropagation algorithms, which follow the gradient descent optimization principle and was introduced by (Rumelhart et al., 1986), is widely employed to train feedforward ANNs and is a typical learning rule adopted for most supervised learning algorithms (Riedmiller, 1994). Weights and biases in the neural network are repeatedly adjusted in this method in order to minimize the network error, i.e. to minimize the difference between output of the ANN and the desired target value.

Traditional approaches found desired solutions to several problems concerning pattern recognition, optimization, regression, prediction, and control analyses. These approaches fail to demonstrate sufficient flexibility outside the studied domain, despite their successful application in specific well-constrained environments (Jain et al., 1996). ANNs have proved immensely useful alternative tools in several research domains and have been considered to be a universal approximator (Hornik, 1991). Applications of ANNs in capturing the mechanical characteristics of complex structures and predicting behavior of engineering structures are substantially growing and the body of research is gaining considerable attention in many spheres of life such as medical science, engineering, and education (Abiodun et al., 2018). Some of these studies relevant to solid mechanics of engineering structures are briefly reviewed herein. Backpropagation ANNs constructed in MATLAB were used to predict the compressive strength and load-displacement curve of composite fibre reinforced concrete using fiber percentage and mix proportions (to train and test the networks) measured during mechanical testing of the studied samples. Different ANNs were trained and tested in that study to minimize the error (convergence of mean squared error to a marginal band), and then the optimum topology for the ANN was determined. It is evident that similar processes must be performed based on the investigated problem to investigate the structure, architecture, and/or topology of the ANN. Ashrafi and colleagues argued that, based on the investigated datasets, a completely new neural network should be designed and its suitability be confirmed in making reliable predictions on a wider population. The influence of other parameters such as learning algorithm and normalization methods (pre-processing of data prior to ANNs training) was also investigated and addressed (Ashrafi et al., 2010). Although the authors asserted that the trends of network output in prediction were similar to the experimental counterpart, no specific

graphical results were provided to compare the ANNs outputs with experimental data. This needs to be thoroughly delineated in the application of ANNs to engineering practices. Many parameters such as the number of data points with which the ANN is trained and tested, error analysis on the testing datasets, and not merely error of training datasets, (because the error for the former is much larger than the error for the latter), the effectiveness and reasons for using a complex ANN rather than a conventional statistical tool (for example, a simple trend line function using Microsoft Excel can be more effective than an ANN), and so forth, must be discussed and demonstrated in such studies (Sha and Edwards, 2007). Assisting engineers to design and simulate confined concretes components under compressive loading, (Ahmad and Raza, 2020) proposed ANN, FEA, and empirical models to evaluate axial strength of concrete cylinders with carbon fibre reinforced polymers. Experimental datasets served for the training purpose of the multilayer backpropagation neural network, and commonly adopted trial and error procedures were followed to discover an optimum ANN architecture. To investigate the effects of geometrical and material parameters of annealed copper and to construct a link between indentation response and the mentioned parameters, a feedforward backpropagation ANN model encompassing two hidden layers was presented followed by numerical results obtained for 2D and 3D FEA (Muliana et al., 2002). The results were obtained from the loading portion of nanoindentation tests, and the outcomes of FEA were compared against experimental measurements on the annealed copper. Geometrical parameters and material properties (stiffness) constructed the input layer of the ANN (trained with the datasets generated from conducting FEA), and it outputs the indentation force which was compared against other FEA results that were not employed in the training sessions. The outcome identifies the intellectual predictive capability of ANNs in such nonlinear practices. Similar studies were undertaken using data from loading-unloading portions of an indentation curve in which ANNs were employed to predict the stress-strain behaviour of thin metallic films on substrates produced during indentation tests (Huber et al., 2002; Huber et al., 2000). ANNs also enabled the prediction of damage evolution in forged aluminium matrix composites as a function of forging parameters (Roberts et al., 1998) where multilayer feedforward neural networks were trained using a combination of FEA results and experimental measurements (mostly associated with deformation parameters such as strain, strain rate, stress, and temperature). Similarly, micromechanical numerical investigations of fibre reinforced ceramic composites were performed using FEA, experiments, and ANN, the training of which was performed using the results of micromechanical FEA, and then ANN predicted the mechanical behaviour of these composites, such as stress-strain responses (Rao and Mukherjee, 1996). The requirement of

minimal computational time and effort accentuates the suitability of these intelligent systems in the efficient and rapid investigation of problems involved in the mechanics of materials. Such noteworthy features of ANNs have also been illustrated in this thesis (Page 76 of this thesis) and in the recent literature ([Mouloudi et al., 2020a](#)). Implementing feedforward backpropagation ANNs trained with experimental data (covering a variety of parameters such as geometrical variables, mechanical properties being the modulus of elasticity and Poisson's ratio, and manufacturing process type), buckling load of thin-walled cylindrical shells was predicted including subsequent comparison with: (1) the experimental data, and (2) buckling loads recommended by standards in the relevant field ([Mandal, 2017](#)). This research also emphasized the successful application of ANNs in capturing mechanical responses of complex structures, enabling researchers to perform ANNs alongside other simulation techniques such as FEA to increase the accuracy of analysis, and simultaneously, to reduce computational time and endeavor. Detailed and thorough explanations were offered in that paper to further delineate the influential parameters in defining a suitable ANN architecture (using growing technique) and in properly interpreting the results produced by an ANN during and post training such as network performance, regression, and error histogram. Studies like this are encouraging in the development of hybrid models, in which AI approaches using ANNs are coupled with finite element methods, to investigate problems pertaining to nonlinear engineering applications of structures ([Ly et al., 2019](#); [Stoffel et al., 2018](#)). Reliability analysis of engineering structures using ANNs has also been the focus of researchers, for example a review paper was presented to pinpoint the different types of ANNs, several techniques employed for ANNs training, and their applications to the design and analysis of steel structures ([Chojaczyk et al., 2015](#)). Size and surface effects appear in the mechanical properties and responses of nanostructures when the ratio of surface to the volume is incredibly high ([Ansari and Sahmani, 2011](#); [Mouloudi et al., 2014a](#); [Mouloudi et al., 2014b](#)). In such scenarios where mechanical features of structures in nanoscale dimension are peculiar, classical theories cannot capture the responses of the structure (such as critical buckling loading, mechanical properties, etc.). Papadopoulos et al via characterization of the behavior of carbon nanotubes at the nanoscale dimension demonstrated that ANNs are powerful tools which can efficiently assist in such scenarios with incorporation of several geometries, different loading conditions and boundary conditions to produce the desired results in a timely manner ([Papadopoulos et al., 2018](#)). To predict mechanical properties using ANNs, as an example, a feedforward neural network was trained from the measurements recorded from dynamic mechanical testing (temperature, frequency, and elastic modulus) to investigate the dynamic properties of

graphene reinforced epoxy matrix composites at several frequencies and temperatures (Xu and Gupta, 2019). Besides this investigation, the effects of network architecture (the number of neurons) and regularization factor to improve generalization, thereby minimizing the likelihood of overfitting, were also considered and discussed. Such characterizations of viscoelastic materials versus strain rate and temperature are important in the development of better models to expand our knowledge of viscoelastic materials (Omari et al., 2020). Inspired by the great ability of ANNs in establishing a framework to represent nonlinear mapping among several input and output variables, and moreover, benefitting from flexible learning and generalization capabilities that have been demonstrated so far, ANNs were employed to predict fatigue life of different composite materials (Al-Assadi et al., 2011), metallic materials (Barbosa et al., 2020), and steels (Maleki et al., 2018; Pujol and Pinto, 2011).

2.5. Application of Artificial Neural Networks to Bone Mechanics

Dramatic advancements in interdisciplinary research, especially the implementation of computer science, nourish the potential for artificial intelligence and machine learning algorithms being applied to mechanical and biomedical engineering. Being at the forefront of machine learning algorithms, ANNs are providing considerable impetus for advancing knowledge in the field of bone mechanics and for addressing many of largely open forward and inverse problems associated with bone adaptation modelling. These investigations are gaining advantage from the spectacular advances in imaging techniques, computers, and enhanced precision as well as the increased power of mechanical testing and our improved realization of previously ignored features associated with testing methods (Currey, 2009). The receipt of meticulous and significant attention in computational modelling of bones (Zadpoor, 2013) stems from such breakthroughs in these fundamental features. Research on bone adaptation commenced and inspired since the time when Wolff observed and stated that bones grow according to the forces exposed to them representing an inherent relationship between bone loading and their shape and morphology (Wolff, 1892, 2012). Function of the bone and the types of loads it is exposed to dictate its shape, because the shape of a bone is intimately correlated to its function. Investigations on the long bones adaptations to loading are intriguing because long bones (such as humerus, radius, ulna, femur, tibia, and metacarpals) possess a relatively simple shape, and furthermore, what they have generally to do under loads is reasonably straightforward to understand (Currey, 2006, 2014). A deeper understanding of extremely well-engineered, if not optimised, structures such as long bones offers generalised opportunities for researchers. Long bones have engineering features such as being thick-walled hollow tubes, expanded at the ends, and being built in a way to have a minimized mass while performing their particular function (Currey, 2010).

Extensive experimental recordings are available in the literature which can be imported into ANN algorithms for computer simulation analysis to predict responses of bones (Currey, 2009). Each ANN input data point represents recorded in-vivo or ex-vivo measurements, such as loading, load exposure time, individual age, displacement, strains, stiffness, modulus of elasticity (Young's modulus), density distribution, shape and geometrical parameters, kinematic parameters, etc. Several types of ANNs will be employed to find the optimum ANN in gaining desirable outcomes (i.e. completing a solution to either an inverse problem or a forward problem). Furthermore, different architecture types and learning methods, feedforward

or recurrent ANNs (based on ANNs connection pattern), single layer or multilayer (based on the number of hidden layer), and fixed or adaptive (based on the nature of weights adjustment during ANNs training), will be examined to present a reliable and efficient model for bone tissue adaptation. Sensitivity and error analysis will also be performed using different training algorithms for neural networks, such as Levenberg-Marquardt backpropagation, Bayesian regularization backpropagation, and scaled conjugate backpropagation ([Mandal, 2017](#)). Backpropagation neural network (BPNN) is a well-suited network for predicting mechanical responses of bones and tissues. BPNN is an artificial neural network that employs a supervised learning method ([Deng et al., 2008](#)), possesses feedforward architecture, accommodates complex and nonlinear data relationships, and hence is well-suited for regression and pattern recognition analysis and also practical application ([Mandal, 2017](#)).

The connection weights approach, which uses raw input-hidden and hidden-output connection weights in the neural network ([Mandal et al., 2009](#); [Olden et al., 2004](#)), can be employed to quantify the relative importance of ANNs input variables. The connection weights approach calculates the product of the raw input-hidden and hidden-output connection weights between the neuron of input and the neuron of output and then sums these products across all hidden layers. This approach defines the influential input variables (e.g. strains, load, displacement, shape) that have considerable influence on the prediction of the ANN (output). For example, in a recent study it was observed that strains measured experimentally on the several surfaces of equine MC3 long bones significantly affect the load predicted by ANNs, exhibiting the profound effects of bone midshaft strains measurement on the estimation of loads ([Mouloudi et al., 2020b](#)) (Page 93 of this thesis). Remaining parameters, though important, revealed a relatively moderate effect on load prediction.

Machine learning approaches are also used to develop a deep learning model to promptly and accurately estimate stress and strain distribution in bones. The deep learning model is designed and trained to take its input information from finite element analysis (FEA) and then directly output the stress and strain distributions (bypassing the FEA calculation process). Bone shapes are generated from a statistical shape model, then FEA is performed to obtain stress and strain distribution of each shape. The deep learning model takes shape as an input and it will output the stress and strain distributions. To do so, three main steps are performed ([Liang et al., 2018](#)): encode the input shape as a set of scalar values (shape code), conduct a nonlinear mapping of the shape code to the stress code represented by a set of scalar values, and finally decode the

stress code into bone stress and strain distributions. Supervised and unsupervised ANNs offer considerable benefits to clinical biomechanics in general. For instance, they can be employed to classify gait and running data, classify different movement tasks (such as classifying the relationship between pain and vertebral motion ([Dickey et al., 2002](#))), and analysing muscle activities through classification of EMG data. Because mechanical properties and responses of bones and tissues are multivariable and depend to a great extent on multiple factors, in order to model the elusive relationship among loading, strains, kinematic and dynamic parameters, EMG and so forth, employing ANNs are attractive and provide encouraging outcomes in biomedical engineering. Furthermore, future finite element studies will benefit from employing hybrid modelling, also referred to as intelligent finite element method, in which neural networks algorithms are integrated with a finite element framework (facilitating bypassing the FEA calculation process). This assists in time-sensitive clinical applications where using traditional FEA requires long computing times to obtain a final simulation result ([Liang et al., 2018](#); [Zadpoor, 2013](#)). In such scenarios, neural networks are incorporated in an FEA as an alternative to the constitutive model of a bone. ANNs are then trained using raw in-vivo experimental measurements representing the mechanical response of the bone to applied loads. The trained network is then used in the FEA to predict different types of stress and strain ([Javadi et al., 2003](#)). Supervised and unsupervised ANNs using radiographs of lower limb long bones belonging to children (femur, tibia, and fibula) were employed to investigate lower limb fractures and to classify healing time ([Malek et al., 2016](#); [Malek et al., 2018](#)). Age of the children, displacement, angulation, type, contact area of the fracture were used as the ANNs input variables to classify fracture healing time and to evaluate accuracies exhibited by two different ANN models: self-organizing maps (SOM) and multilayer perceptron (MLP) neural networks. Feedforward ANNs were adopted to estimate musculoskeletal loading of the proximal femur that have resulted in the bone density distribution measured via CT imaging ([Campoli et al., 2012](#)). 1,581 different combinations of loading parameters (including various loading magnitude and load angles) via solving forward tissue adaptation model were established in that study to form the ANNs training dataset. The angle and the magnitude of contact force constructed two ANNs outputs. ANNs were also employed as a nonlinear system identification approach to solve an inverse problem, i.e. to predict loading of trabecular bone from its density distribution ([Zadpoor et al., 2013](#)). The use of ANNs was demonstrated in that study enabling mapping nonlinear relationship from the space of bone density distribution (serving as ANNs input parameters) to the space of applied loads (ANNs outputs). This is called a backward mapping (finding a solution to an inverse problem) for which there are no

straightforward approaches using traditional tools such as FEA, and moreover, differential equations representing such inverse models are typically not known ([Zadpoor, 2013](#); [Zadpoor et al., 2013](#)). The development of investigations on other bones, and not merely the femur, has also been recommended in the literature. Garijo et al. also offered a general methodology using machine learning techniques (ANN and support vector machines) and a linear statistical technique (linear regression) to make predictions on the likely loads supported by the proximal femur ([Garijo et al., 2014](#)). Different loading conditions with a wide variation were simulated using bone remodelling problems through FEA to obtain corresponding bone density distribution, thereby input data were formed to establish linear regression, ANN, and support vector machines. Such methodologies elucidate patient-specific musculoskeletal loads and assist in finding effective remedies for musculoskeletal treatments in a timely manner, because it is critically important to determine physiological loading that a bone has been exposed to from continuous changes that have occurred in the bone morphology (geometry, shape, and density distribution) ([Christen et al., 2012](#)). Knee adduction moment was predicted using a simple method where a multilayer ANN was employed from some measurements including force plate recordings, and the extracted results demonstrated a significant correlation with those achieved from inverse dynamics ([Favre et al., 2012](#)). ANNs have been further employed in other areas of bone mechanics to elucidate mechanical responses exhibited by bones substantiating our knowledge of this advanced well-engineered biological structure. Several artificial intelligent expert systems and linear regression were fused to assess resistance of cortical bone fracture (quantification of bone fracture toughness) where R-curve slope, toughness threshold, and stress intensity factor were estimated from patients age and crack length as the input variables of the algorithms, while stress intensity factor that is a critical factor related to crack, shaped the ANN output ([Vukicevic et al., 2018](#)). These input parameters are frequently available during clinical examinations, and thus, such studies are of profound significance to tackle the challenges of establishing cost-effective and competent management tools for the associated bone fracture risks. Inspired by the importance of bone age, relevant studies have been undertaken in the application of machine learning algorithms such as ANNs and convolutional neural networks (CNNs) to complete significant assessments of bone age from different perspectives ([Dallora et al., 2019a](#); [Dallora et al., 2019b](#); [Liu et al., 2019](#)). In order to offer potential insights into the enhancement of bone repair analyses, an ANN was developed using measurements such as apparent modulus of elasticity, bone volume fraction, and bone ash density as ANN input variables to make reliable and quick prediction of apparent damage at specific bone sites (ANN outputs the failure and fatigue damage of trabecular bone)

(Hambli, 2011). That study, incorporating ANN expert systems and FEA, also revealed a superior ability of the ANN in terms of considerable reduction in computational time versus FEA, which accentuated the development of a rapid computational technique using ANNs to simulate fatigue analysis of bones (rapid prediction of damage accumulation in a bone). Similar approaches were carried out by Hambli and colleagues to further investigate fracture and fatigue analysis of bone tissues using FEA and neural networks as well as a combination of both which represents hybrid multiscale modelling (Barkaoui et al., 2016; Hambli, 2014; Hambli et al., 2016; Hambli and Hattab, 2013). In-vivo measurements of applied forces on different parts of humans and animal skeleton are extremely challenging, and sometimes, impossible. For example, knee contact force that is highly affected by gait patterns is not always straightforward to be quantified through in-vivo measurements, and moreover, widely employed computational techniques to calculate this force such as inverse dynamics analysis has its own drawbacks (Ardestani et al., 2014). In that research a feedforward ANN was proposed and was trained on pre-rehabilitation gait patterns including ground reaction forces and marker trajectories (since knee contact force is significantly affected by gait patterns and knee joint alignment (Fregly et al., 2009; Shelburne et al., 2008)), and then the ANN predicted knee contact force related to rehabilitation gait pattern. Another noteworthy feature of that study, which is often overlooked in literature concerning applications of ANN, is assessing: (1) the generalization ability of the already trained and tested ANN to demonstrate its feasibility to be employed to a wider population, and (2) the validation of ANNs predictions against a reliable source such as experimental data. Proven to offer valuable potentials in bone engineering enabling monitoring and predicting the solutions associated with clinical practices, a multilayer feedforward ANN was applied to undertake multidimensional data analysis associated with physical and mechanical properties of trabecular bone emphasizing a major demand to develop stand-alone ANN models that integrate a variety of mechanobiological parameters and their correlations with clinical parameters, which eventually accelerates clinical diagnosis with prevention of bone disorders (Khovanova et al., 2015). Age of the patients was predicted in that study from the mechanobiological parameters of bones: porosity, gender, morphology, level of interconnectivity, and compressive strength. A surrogate model using ANN was developed to predict femoral strains and fracture loads to fulfil clinical purposes in real time from clinically obtainable measurements including body weight, femoral neck bone mass, and femoral neck length (Taylor et al., 2017). To detect essential input variables, prior to their injection to the ANNs, that make a significant contribution to the strain prediction (ANN output), a multivariate linear regression was adopted in that study. Due to the fact that

the ANNs were trained from the previously developed population based FEA (requiring 300 CPU seconds per femur, 150,000 in total for 500 femurs, accounting for the bones image segmentation, mesh generation, and definition of appropriate load and boundary conditions), the computational cost involved was considered as a drawback. However, as it was also accentuated by the authors that the preparation of these population-based data is performed only once, and then the already trained and tested ANN is able to be fed with input variables of a new patient in the clinic to produce satisfactory results in real time (enabling prediction of strains and fracture loads on a new patient in 0.002 seconds). It has also been shown that feedforward backpropagation ANNs, trained with the results of finite difference time domain simulations, are successful at estimating micro-architectural parameters of human cortical bones (pore diameter, pore density, and porosity) (Mohanty et al., 2019).

Besides peculiar and exceptional mechanical properties and responses exhibited by bones in general that make them intriguing engineering materials (as emphasized in previous paragraphs), the use of equine MC3 long bones in performing mechanical experiments and then in establishing the ANN in this study is motivational for engineers who are dealing with less complicated structures and less complex materials. MC3 is a large bone (in Thoroughbred type horses, its length varied in the range 25-29 cm and the area of its cross section in the midshaft varied in the range 250-1050 mm² excluding the marrow area inside the bone (Mouloudi et al., 2019a)), and shows a relatively restricted and simple range of normal movements (Mouloudi et al., 2019c), has minimal muscle attachments (lacking any muscle or ligamentous attachments for a range around 6-8 cm along its midshaft), forms an essential part of the lower forelimb in withstanding loads, is vulnerable to failure during the majority of disastrous injuries occurring in racing horses worldwide, is well-adapted (well-engineered) for exercise at high speeds (Davies, 2005), and can withstand substantial compressive dynamic load as much as 22.5 kN in-vivo (Merritt et al., 2010). To compare this huge force that MC3 is capable of withstanding in a normal daily basis, a large SUV car weighs 20.6 kN to 23.3 kN. Moreover, enormous compressive loads (parallel to, and aligned with, the long axis of the bone) exceeding 110 kN ex-vivo without bone failure were recorded and reported in MC3 long bones (Mouloudi et al., 2020b), Page 93 of this thesis). Such a unique well-engineered structure (resembling and categorized as a cylindrical long beam or column in the engineering context) which is functioning well in a living biological system provides the best chance to develop a model to investigate the normal mechanical responses of an advanced structure to loading.

Also, many investigations into human bone fatigue, for example, are heavily reliant on the outcome of equine bone research ([Couch and Nielsen, 2017](#)).

Development of reliable qualitative and quantitative methods are also of essential importance to evaluate patterns in equine gait analysis to gain improved accuracies in diagnosis of equine lameness enabling diagnosis with the aid of neural networks only ([Schobesberger and Peham, 2002](#)), avoiding biases that otherwise will very likely be exhibited in traditional subjective analyses ([Clayton and Schamhardt, 2013](#); [Kajima, 2005](#)). For example, the applicable ability of conventional analytical tools to discover precise relationship among ground reaction forces and wall strains that equine hoof is experiencing is diminished, due to the inherent nonlinear complex relationships that exist among variables. However, using hoof wall deformation of a horse (with acquisition of strain data measured experimentally on the dorsal, lateral, and medial part of the hoof), an ANN was trained and tested to quantify ground reaction forces (ANN output) and then the results were compared against recordings from a force plate, affirming the suitability and accuracy of ANN algorithms (with ease of use) in the determination of ground reaction forces, facilitating practical applications ([Savelberg et al., 1997](#)). ANN expert systems were similarly adopted to investigate their appropriate and effective uses as primary modelling work to predict cracking of equine hoof material for which ANNs were tested to be trained on the data which can be obtained relatively effortlessly without allocating significant cost ([Suchorski-Tremblay et al., 2001](#)). Using machine learning tools and intelligent finite element methods, it is aimed to solve bone adaptation models both in the forward direction (i.e. determining responses of bone to a given set of loads) and the inverse direction (i.e. quantifying loads that have resulted in a given state of bone) ([Mouloudi et al., 2019b](#); [Mouloudi et al., 2019c, d, 2020b](#)) (Pages 76, 93, 107, and 126 of this thesis). The current state of research on mechanical interpretation of long bones demands more comprehensive models integrating ANN expert systems with various biological, mechanical, and structural features of long bones, and yet to be more dominantly based on the actual experimental and clinical data.

2.6. Concluding Remarks and Research Questions

Despite the applications of CAD and FEA in the stress and strain analysis of equine MC3 bone (and similar long bones), research is lacking to determine the accuracy of the generated CAD models and errors associated with FEA. A limitation of published studies is a lack of evidence associated with quantifying dimensional error of reconstructed geometries, performing mesh quality assessment, determining the error of FEA, or assigning linear tetrahedron meshes to the models, all of which would potentially lead to misleading stress and strain results. Prior to investigating the responses of MC3 under load and comprehending its shape-dependent mechanical behavior (particularly in the MC3 midshaft), reliable 3D models and accurate FEA are essential.

The published literature is limited to investigate the geometrical parameters of cross sections in equine MC3 bones with different ages and exercise history ([Lawrence et al., 1994](#); [Nunamaker et al., 1989](#); [Thomason, 1985](#)). The author measured the geometrical parameters in three main cross sections (slices) within the diaphysis of MC3 bones and then compare the values to assess their significant changes employing statistical tools. Specifically, the following geometrical parameters were investigated by the author: cortical area (A), width of dorsal cortex (D), palmar cortex (P), medial cortex (M), lateral cortex (L), medulla in dorsopalmar plane (M_d), and medulla in lateromedial plane (M_l).

Alternative approaches are required to be considered and addressed in the literature to predict the mechanical behaviour of these complex biological materials. This is partially due to the many limitations that are associated with the use of prevalently employed tools such as FEA. For example, subject-specific usefulness of FEA, requirement of huge computational time to conduct an FEA, many simplifying assumptions for a successful application of an FEA, and its lack of applicability when some underlying data is lacking or missing. Neither are commercially available FEA packages (e.g. ANSYS and Abaqus) capable of completing a solution to an inverse problem, i.e. quantifying cyclic mechanical loading that has resulted in the induced deformation and strains. Machine learning using artificial neural network algorithms can be a valuable alternative method to quantify loading, strains, displacement, and material properties of such advanced structures. Introducing elaborate mathematical expressions to quantify the mechanical features of these exotic materials (long bones) is not straightforward, yet ANNs provide a promising approach to quantify mechanical features of complex structures without the current runtime penalty. To the best knowledge of the author,

the experimental procedure and ANN algorithms investigated in this thesis have never been discussed in the publicly available literature (other than those published by the author and collaborators) to predict cyclic load, displacement, load-displacement and stiffness, as well as strains of this advanced biological material from the data recorded during ex-vivo experiments. Furthermore, notwithstanding the extensive applications of feedforward backpropagation ANNs in many engineering practices concerning materials modeling, how to achieve successfully trained and tested ANNs is not thoroughly explained in the literature, nor are there lucid discussions to delineate influential parameters obtained from analyses.

As such, the main research questions of the current research and the associated research hypotheses can be summarized as follows.

2.6.1. Research Questions and Hypotheses for Chapter 3

Research Questions:

Q.1. How to employ analytical and numerical displacement-based error estimation and convergence analysis to present a framework for minimizing stress and strain errors in the finite element analysis of MC3 bones? How accurate will the results become?

Q.2. Is it possible to perform reverse engineering procedure to reconstruct a 3D model of MC3 through extrapolating cross-sectional slices within the MC3 bone midshaft? How accurate are the results when compared with the CT-based model?

Hypotheses:

H.1. The adopted design rules can reduce the FEA error to a mean value of less than 1% for both stress and strain analysis, which maximizes the accuracy of FEA.

H.2. The errors of reconstructed surfaces (normal distance between the reference geometry and its reconstructed counterpart) can be reduced to less than ± 0.5 mm. Splint bones (MC2 and MC4 sometimes fused to the main MC3 bone) will cause noticeable error.

2.6.2. Research Questions and Hypotheses for Chapter 4

Research Questions:

Q.3. Is there a wide diversity in the geometrical parameters of cross sections (within the diaphysis of MC3 bones) in horses with different ages and exercise history? Which of these

geometrical parameters exhibit significant differences using ANOVA and t-tests when the values are compared between five groups (foals, yearlings, two-year-olds, three-year-olds, and adults) and between two groups (foals compared to the rest of the samples as a single group)?

Q.4. Is there a way to define a qualitative parameter by which converging-diverging shape parameters could be inferred within the midshaft of MC3 bones?

Hypotheses:

H.3. Significant differences ($p < 0.05$) for the geometrical parameters will be observed for the proximal and middle cross-sectional area when foals are compared with the rest of the bone samples.

H.4. The least geometrical magnitude for area, dorsal cortex, palmar cortex, medial cortex, lateral cortex, and shape index of cross sections in the bone midshaft for the foal samples will reveal a converging-diverging shape from the proximal cross-sectional slice to the distal one.

H.5. A two-degree polynomial function can be fitted to the plots and then the curvature (k) of these fitted plots can be compared to assess its significant changes among the groups (the level of significance was set at $p = 0.05$).

H.6. The width of the dorsal cortex (D), palmar cortex (P), and lateral cortex (L) will change significantly ($p < 0.05$) with maturation (comparison between foals and the rest of the samples).

2.6.3. Research Questions and Hypotheses for Chapter 5 to Chapter 7

Research Questions:

Q.5. Is it possible to implement feedforward backpropagation neural networks for the prediction of displacement in third metacarpal long bones followed by ex-vivo experiments to reduce the computational cost (as compared with the results produced by a finite element analysis) and to enhance the accuracy of simulations?

Q.6. How is the performance of the trained and tested ANNs altered in response to changes in the number of input data points and then by assuming a lack of input strain data?

Q.7. How can an inverse problem be solved to quantify mechanical loading from the measurements of strains, displacement, and load exposure time? Is it possible to employ an artificial neural network to quantify the load required to produce the MC3 displacement and surface strains determined experimentally on nine bone samples?

Q.8. What is the relative importance of ANNs input variables using the connection weights approach? Does the employment of a categorizing approach using pattern recognition algorithms elucidate age-dependent attributes of experimental measurements?

Q.9. How can two connected in-series feedforward backpropagation artificial neural networks be implemented to simultaneously solve forward and inverse problems in the computational mechanics of a complex structure possessing exotic mechanical properties (a long bone) to predict stiffness and cyclic load-displacement curves?

Q.10. What are the performance and error characteristics of the trained and tested neural networks (compared against the experimental counterparts) when their generalization abilities are assessed to make predictions on independent datasets from new samples (not used for either training or testing)?

Hypotheses:

H.7. Feedforward backpropagation artificial neural networks are suitable techniques to be adopted for solving both a forward problem (Chapter 5) and an inverse problem (Chapter 6) as well as a combination of both problems simultaneously (Chapter 7) in the computational mechanics of equine third metacarpal long bones.

H.8. ANNs substantially reduce the computational time as compared with performing a finite element analysis.

H.9. For the different scenarios (ANNs with different outputs), the ANN models enable successful prediction of the mechanical responses and behavior of MC3 long bones with coefficient of correlation (R) or coefficient of determination (R^2) higher than 0.95 for training and testing datasets as well as for datasets associated with unseen samples (new datasets that ANNs have not seen before).

H.10. The relative importance analysis will reveal that strains significantly affect the ANN output in load prediction.

H.11. Pattern recognition algorithms will show that there is an inherent difference between group of foals and that of two- and three-year-olds at least in terms of the measured experimental data.

2.6.4. Research Questions and Hypotheses for Chapter 8

Research Questions:

Q.11. How can several influential elements such as a network training algorithm, injecting noise to datasets prior to training, the level of injected noise which directly affects model fitting and regularization as well as data normalization prior to training, affect the ANNs performance and the associated errors?

Q.12. Is it possible to implement the growing technique to find optimum network structures (architectures) that encompass the best prediction ability? What are the essential parameters influencing decision making in identifying well-trained and well-generalized ANNs?

Hypotheses:

H.12. Selecting an optimum feedforward ANN structure (architecture) depends on the complexity of the problem, number of specimens, number of datasets (observations through experiments, for example), number of input(s) and output(s).

H.13. For different scenarios (ANNs with different outputs), ANNs performance was oversensitive to both the number of hidden layers and number of neurons in the hidden layer. The same ANN with the same datasets can produce completely different results when it is trained each time (training each ANN multiple times and averaging their outputs are recommended).

H.14. To exhibit the generalization ability of an ANN model, a major emphasis must be placed on the regression and performance analyses conducted on the new specimens (unseen samples that ANNs have not seen before).

H.15. The neural networks trained with injected noise drastically reduce the generalization error (substantial improvement in the generalization ability). Likewise, the error of ANNs in generalization (RMSE) is drastically decreased when data is normalized prior to commencement of training.

Chapter 3

Accuracy quantification of the reverse engineering and high-order finite element analysis of equine MC3 forelimb

This chapter reports on a paper published by the author and collaborators that investigated the following hypotheses (as discussed in Section 2.6.1):

- **H.1.** The adopted design rules can reduce the FEA error to a mean value of less than 1% for both stress and strain analysis, which considerably maximizes the accuracy of performed FEA.
- **H.2.** The errors of reconstructed surfaces (normal distance between the reference geometry and its reconstructed counterpart) can be reduced to less than ± 0.5 mm. Splint bones (MC2 and MC4 sometimes fused to the main MC3 bone) cause noticeable error.

This chapter also provides the background and the procedures by which strategies are implemented to increase the accuracy of FEA conducted in subsequent chapters of this thesis (in particular Chapter 5).

3.1. Published Journal Paper

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Original Research

Accuracy Quantification of the Reverse Engineering and High-Order Finite Element Analysis of Equine MC3 Forelimb

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ABSTRACT

Shape is a key factor in influencing mechanical responses of bones. Considered to be smart viscoelastic and inhomogeneous materials, bones are stimulated to change shape (model and remodel) when they experience changes in the compressive strain distribution. Using reverse engineering techniques via computer-aided design (CAD) is crucial to create a virtual environment to investigate the significance of shape in biomechanical engineering. Nonetheless, data are lacking to quantify the accuracy of generated models and to address errors in finite element analysis (FEA). In the present study, reverse engineering through extrapolating cross-sectional slices was used to reconstruct the diaphysis of 15 equine third metacarpal bones (MC3). The reconstructed geometry was aligned with, and compared against, computed tomography–based models (reference models) of these bones and then the error map of the generated surfaces was plotted. The minimum error of reconstructed geometry was found to be $+0.135$ mm and -0.185 mm (0.407 mm $\pm$ 0.235 , $P > .05$ and -0.563 mm $\pm$ 0.369 , $P > .05$ for outside [convex] and inside [concave] surface position, respectively). Minor reconstructed surface error was observed on the dorsal cortex (0.216 mm $\pm$ 0.07 , $P > .05$) for the outside surface and -0.185 mm $\pm$ 0.13 , $P > .05$ for the inside surface. In addition, a displacement-based error estimation was used on 10 MC3 to identify poorly shaped elements in FEA, and the relations of finite element convergence analysis were used to present a framework for minimizing stress and strain errors in FEA. Finite element analysis errors of 3%–5% provided in the literature are unfortunate. Our proposed model, which presents an accurate FEA (error of 0.12%) in the smallest number of iterations possible, will assist future investigators to maximize FEA accuracy without the current runtime penalty.

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1. Introduction

Bones are mainly responsible for withstanding and absorbing applied loads. To predict bone fracture and failure, and to investigate reasons for such incidents, comprehensive insight into the responses of bones to loading is crucial. Identifying the strains and stresses to which bones are exposed will assist in elucidating the reasons for fractures and locating their most likely sites. Bones are complex both in their material characteristics and their shape but

respond in similar ways to external loads throughout the animal kingdom [1]. Clearly, a large bone that shows a relatively restricted range of normal movements would provide the best chance to develop a model to investigate the normal responses of bones to loading. Horses are large animals with large, elongated, and simplified forelimb bones that are apparently well-adapted for exercise at high speeds. Hence, considerable forces can be exerted on their forelimb bones. These forces are believed to be involved in different kinds of injuries and incidents, and most disastrous injuries in racing horses worldwide are associated with forelimb injuries, especially failures of the third metacarpal bone (MC3) [2–8]. The third metacarpal bone forms an essential part of the lower forelimb in withstanding loads [9]. Furthermore, due to its large size, minimal muscle attachments, and relatively simple movements, the MC3 is a unique long bone that can assist in investigating the responses of bones when they are exposed to forces.

Animal welfare/ethical statement: No ethical permission was sought as no animal was euthanised for the purposes of this study.

Conflict of interest statement: The authors have no conflict of interest to declare.

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Table 1

Summary of the mesh quality assessment, FEA error analysis, and the percentage of FEA error reported in the literature.

Author	Studied Bone	Mesh Quality Assessment	FEA Error Analysis	FEA Error
Yosibash et al. [51]	Human femur	No	Yes	2%
Edwards et al. [52]	Human radius	No	No	—
Les et al. [47]	Equine MC3	No	No	—
Harrison et al. [45]	Equine fetlock joint	Yes	No	—
Malekipour et al. [48]	Equine stifle joint	Yes	No	—
Merritt et al. [53]	Equine MC3	No	No	—
Helgason et al. [54]	Human femur	Yes	Yes	1%
O'hare et al. [49]	Equine proximal phalanx	No	No	—
McCarty et al. [46]	Equine fetlock joint	Yes	Yes	5%
Biswas et al. [55]	Human lumbar	Yes	Yes	3%
Jansová et al. [50]	Equine hoof	No	No	—

Abbreviations: FEA, finite element analysis; MC3, third metacarpal bone.

Surface strains on the MC3 midshaft bone can be related to exercise speed [10], locomotion type [11,12], and, more significantly, the shape of the bone [13,14]. The shape of the midshaft dorsal cortex (DC) of MC3 alters (expands and thickens) when it

undergoes increasing applied forces during racing and training [15,16]. Many investigations into human bone fatigue, for example, are heavily reliant on the outcome of equine bone research [9].

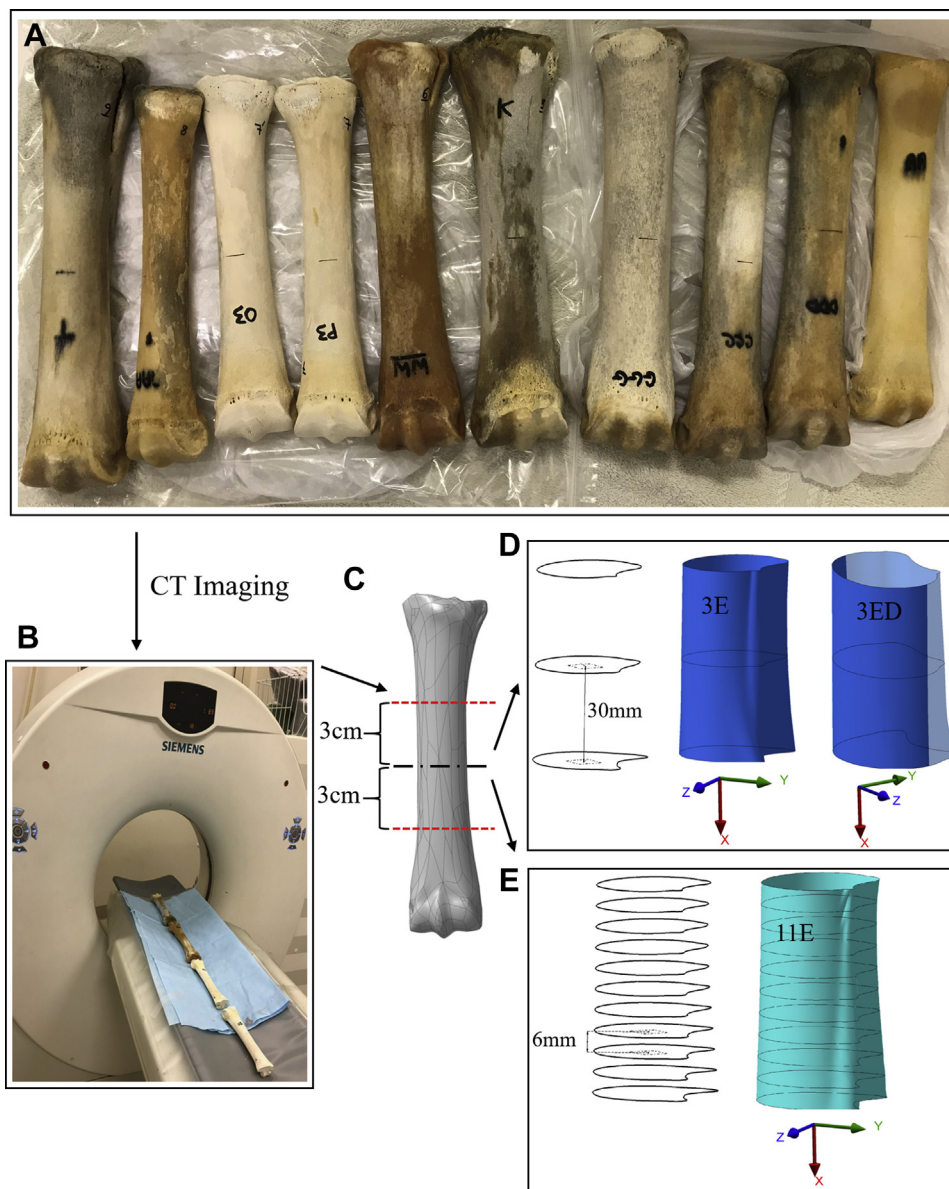


Fig. 1. An illustration of the process taken for reconstructing the MC3 and its diaphysis. (A) MC3. (B) CT imaging of the bones. (C) A 3D model of the bones. (D) Reconstructing the diaphysis by extrapolating three slices (3E) and generating the dorsal surface only (3ED). (E) Reconstructing the diaphysis by extrapolating eleven slices (11E). CT, computed tomography; MC3, third metacarpal bone.

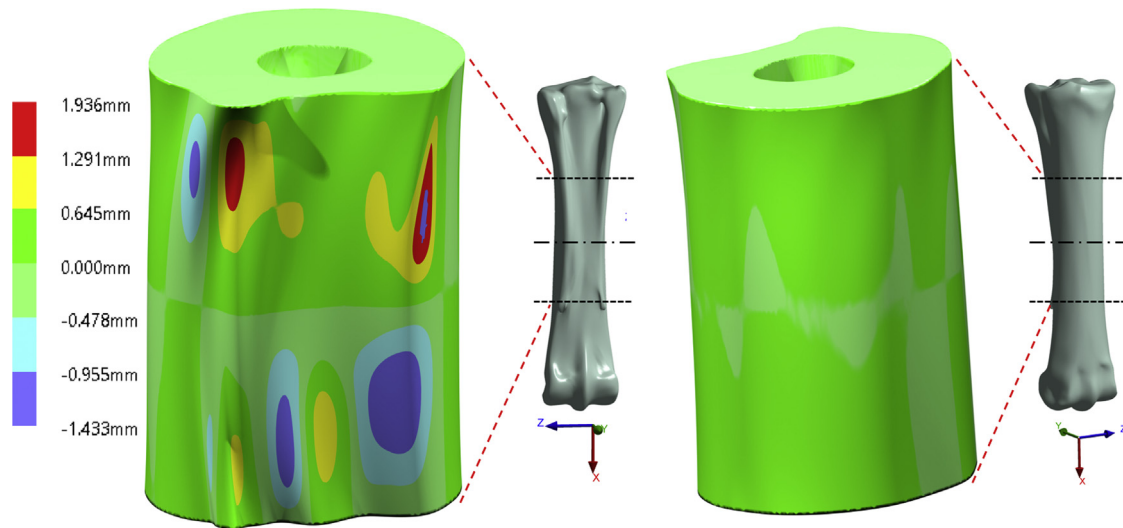


Fig. 2. The error analysis commenced with computing the normal distance between the reference geometry and its reconstructed counterpart. This process ended with finding the maximum and minimum values. Positive values (Max) show regions where reference geometry comparatively expanded (convex shape, outside surface), whereas negative values (Min) demonstrate regions for which reference geometry comparatively contracted (concave shape, inside surface).

Computer-aided design (CAD) and finite element analysis (FEA) are indispensable tools in attempts to model and analyze bones and to replicate experimental data. Using different CAD methodologies in biomedical and tissue engineering practices demands considerable effort and diligence to appreciate the value and significance of different methods [17,18]. Finite element analysis may still be unfamiliar to the readers of equine-related journals, yet it has the potential to provide tremendous benefits [19]. As Erdemir et al. reported, “There has been a 6,000% increase in the number of finite element articles published between 1980 and 2009” [20]. However, mesh quality, model validation, and appropriate energy balance have not been adequately addressed in these studies [21]. Generating a three-dimensional model, which has been done by various methods such as geometry-based and voxel-based [22–25], is an initial step before performing FEA. In many biomechanical engineering activities [26–28], alternative methods such as reverse engineering via CAD are frequently required to produce the 3D models of bones. Examples of times when alternative methods are required include when computed tomography (CT)/magnetic resonance imaging (MRI) images are not available, if the images possess poor or bad quality, if bones are shattered, or when modifications are required to the 3D model of bones before implant design or conducting FEA. Furthermore, CT/MRI imaging has drawbacks, being expensive and difficult to perform on live animals [29], and causing a relatively high radiation exposure [30–32], so CT scanning may not be ethically justified [25]. Neither is it advisable for it to be regularly used in scanning healthy bone volunteers [33]. Reverse engineering techniques can be used either to reconstruct an incomplete or damaged bone or to make a duplicate model from an existing one [34]. In addition, 3D voxel-based surface extraction (CT/MRI-based modeling) requires a substantial computational power, and although they can describe anatomical morphology, a CAD-based solid modeling (vector-based) environment is needed to design, analyze, and simulate anatomical models [25]. This emphasizes the utility of CAD-based solid modeling. Irrespective of many influential factors that alter the mechanical behavior of bones, the importance of shape has been overly neglected in the literature. However, the significance of shape variation in the diaphysis of MC3 has been highlighted in some research [15,29]. The DC of MC3 midshaft enlarges when the horses are exposed to fast exercise speed [10,13,35,36], and compressive

strains exceeding 3000 and 5670 microstrains have been recorded in this region [37,38]. These findings define bone as a smart material that is able to adjust its mass and structure according to the loads it experiences [39]. The midshaft of MC3 is a region of considerable interest to investigate its response under load and to comprehend the shape-dependent mechanical behavior of bones. To commence addressing such inquiries, reverse engineering and determining accuracy of the 3D models are required to shape the fundamental grounding. Afterward, investigating the relationship among size, shape, and mechanical properties is feasible. The 6 cm segment of the MC3 midshaft which was investigated in this study has thick cortical bone, and this bone material redistributes toward either ends to become predominantly trabecular. The MC3 has variable directions of loads at either ends, which need to focus onto the central shaft (the segment being studied here). Not only does the elliptical cross-sectional shape of MC3 prevent and equalize directional loading but also it serves to enhance the sagittal bending once a horse is racing [9,40]. In addition, having unique length and cross-sectional properties, MC3 can support relatively large compressive loads without experiencing substantial strains [41]. The objective is to comprehend the importance of different sizes and shapes in this piece of MC3 and to investigate how those shapes change with loads and strains. To accomplish this, reliable 3D models of the MC3 in this region and accurate FEA are essential.

Nonetheless, there is no current evidence of reverse engineering (CAD-based) through an extrapolation process of slices in the literature for reconstructing MC3. Neither has dimensional error analysis been performed in most of the previous studies to verify and assess the accuracy of reconstructed models [29,42–44]. In CT imaging (voxel-based representation), a 3D model of an object is reconstructed from a 3D region growing from a series of cross-sectional slices (2D segmentations). In extrapolation via CAD systems, on the other hand, inner and outer cortices (contours) of slices are detected independently for each slice. A multisection surface will then be generated by sweeping the contours (cortex or curves) of each slice along an automatically defined long axis of the bone. This process is separately performed to generate internal and external surfaces. A similar process was discussed as an application of reverse engineering methods to reconstruct the human femur [26].

Several studies have been conducted on 3D modeling and stress distribution in the equine MC3 and surrounding structures

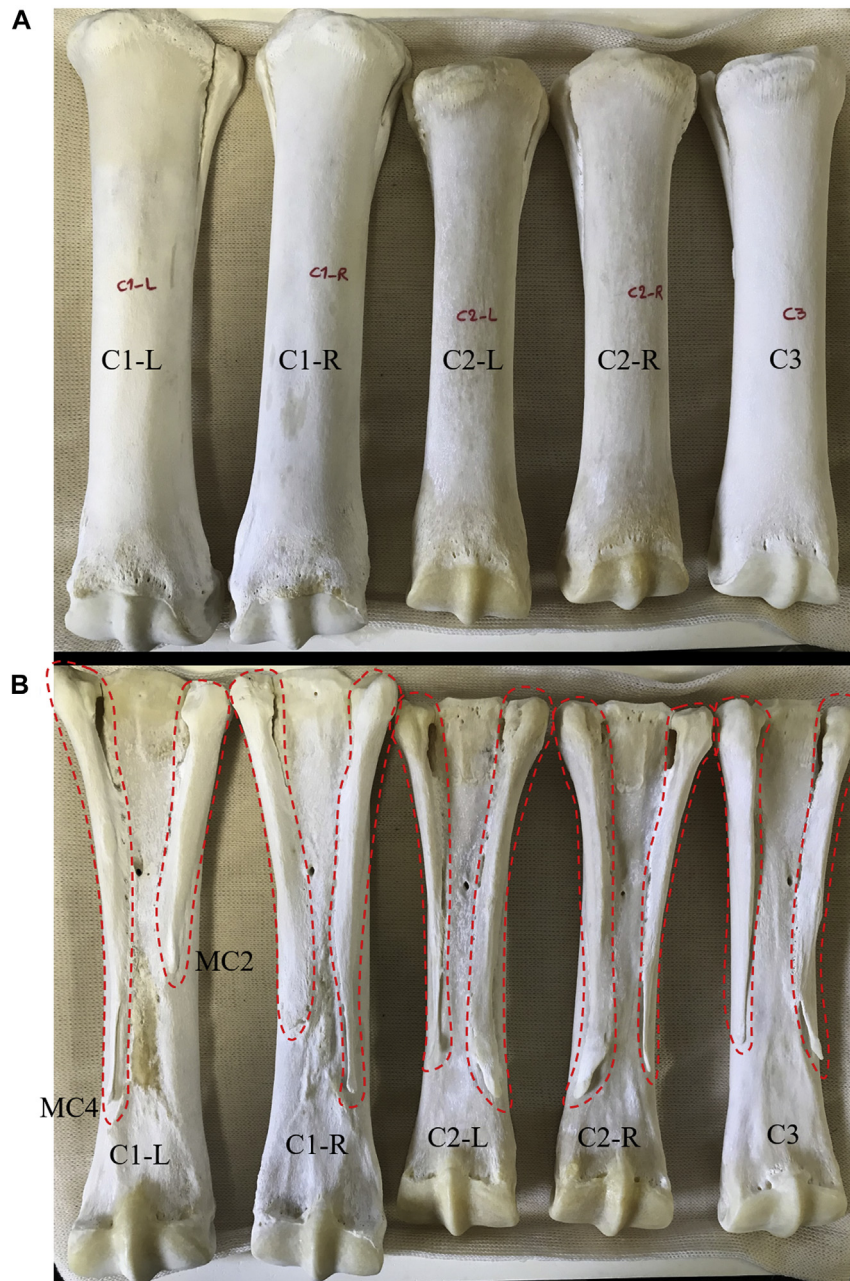


Fig. 3. More samples, having comparatively bigger splint bones than the previous ones, were analyzed to further investigate the error of reconstructed geometries. Significant errors occurred because of the existence of splint bones (MC2 and MC4). The splint bones are identified by red dashed lines.

[45–50]. An essential part of an FEA should be dedicated to convergence and error analysis before publishing the results. A limitation to most of these previous studies is the lack of evidence in terms of quantifying dimensional error of reconstructed geometries, performing mesh quality assessment, determining the error of FEA, or assigning linear tetrahedron meshes to the models, which would all potentially lead to misleading stress and strain results. A summary of considerations in FEA error analysis reported in the literature is presented in Table 1. In addition, orthotropic material identification is one of the most crucial contributions toward a reliable FEA. To the best knowledge of the authors, finite element error analysis, as conducted in the present study, has never been discussed in the equine literature. Even in human studies, literature similar to what has formerly been conducted on the computer

simulations of human feet [56] is limited in determining proper elements and methods for FEA. The purpose of this study is to present dimensional error analysis of reverse engineering through an extrapolation process of cross-sectional slices. In addition, the relations of stress and strain convergence and the displacement-based error estimation are presented that can be used to evaluate the accuracy of FEA and to minimize the associated errors.

2. Materials and Methods

2.1. Reconstructed Surface Error Analysis

Fifteen equine MC3 bones were extracted from forelimbs of cadavers of Thoroughbred and Standardbred horses that were more

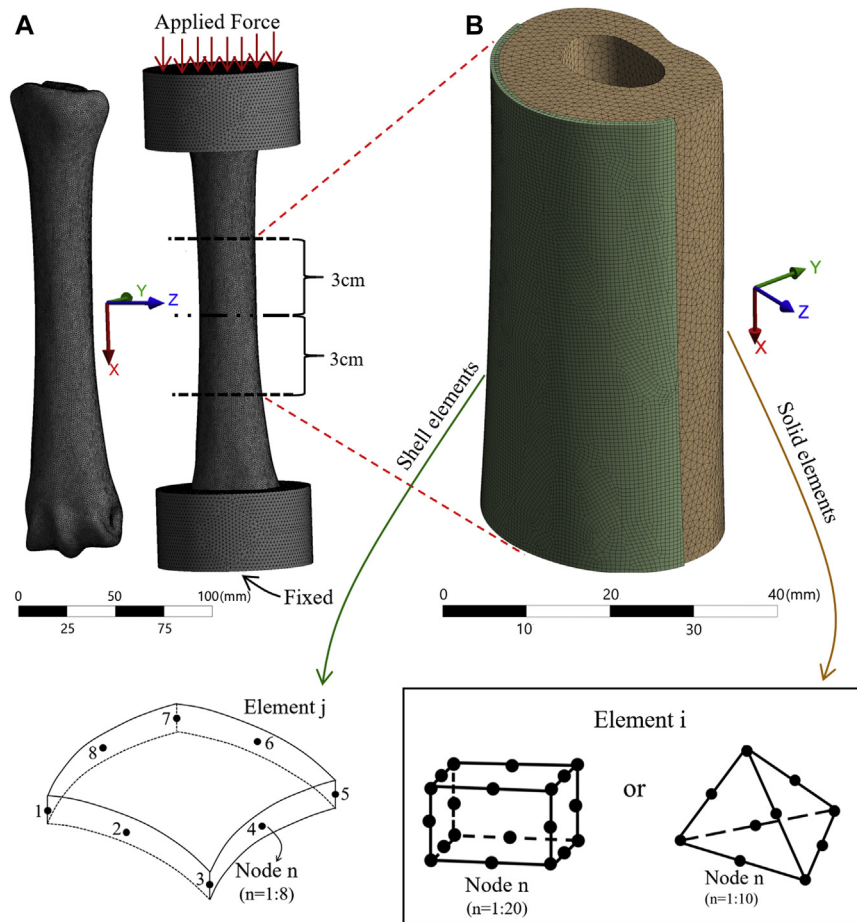


Fig. 4. Preparation of bone samples for computer simulation and FEA. (A) 2.38 million nodes and 1.69 million elements in an analysis of an MC3. (B) The diaphysis of the MC3. Higher order (quadratic) tetrahedron and hexahedron elements were used in the analysis, which are accurate and well suited for stress and strain analysis. FEA, finite element analysis; MC3, third metacarpal bone.

than 2 years old. The horses died for reasons unrelated to the locomotory system or this study and cadavers were sourced from a local slaughterhouse or specifically donated for use in teaching and research. The bones were taken for CT imaging using a SIEMENS CT scanner machine (Fig. 1). The DICOM images (slice thickness of 0.75 mm) were imported into 3D slicer software and segmented to generate surface meshes of the samples. Then they were imported into a CAD to generate a 3D model of the bones, which was then used for reference geometry. Afterward, reverse engineering was used to reconstruct the diaphysis of the MC3. This was first performed by extrapolating three slices (span of 30 mm) across the midshaft of MC3 (Fig. 1D), and then by extrapolating eleven slices of cross-sections (span of 6 mm, Fig. 1E).

The reconstructed geometries were then aligned with and compared against CT-based models (reference models). The distance between the reconstructed surface from extrapolated cross-sectional spline curves and the surface constructed from CT images was considered the error source. This was calculated by computing the normal distance between two sets of elements throughout the surfaces. The surfaces reconstructed via different extrapolation processes (Fig. 1) had the same coordinate system and hence were precisely aligned with the reference model. This enabled the errors to be readily calculated and identified. Because surfaces represent an orientation in three-dimensional space, both negative and positive values were expressed when analyzing the distance between surfaces. As illustrated in Fig. 2, positive values

for error demonstrated a convex CT-based surface, whereas negative values illustrated a concave CT-based surface as compared with the surface reconstructed through the extrapolation process. To strengthen the finding that splint bones cause noticeable error, the 5 MC3 bones with large associated splint bones when compared to the remaining 10 MC3 bones were used in the error analysis (Fig. 3).

2.2. Model Preparation in FEA

Computed tomography-based models were used in performing FEA. Solid meshes were generated on the bulk of the bones, whereas shell elements were used to mesh the dorsal surface of MC3 (Fig. 4). Two cups covering the bones' epiphyses were modeled at either ends of the bone samples to facilitate the loading of the bones in FEA and to reduce the stress singularity that would otherwise occur because of the application of point loads. The stiffness of the cups was chosen to be as high as possible for better transformation of the loads to the bone samples, while causing only a minor displacement in the cups. Because the geometry of the bones is more complex than ordinary engineering objects and because the major part of each bone is not suitable for regular sweeping, and to achieve a better mesh quality, both 10-node nonlinear quadratic tetrahedron and 20-node nonlinear quadratic hexahedron elements were assigned to the finite element models. It is important to apply higher order (quadratic) elements for three-dimensional stress and strain analysis rather than using linear ones,

Table 2
Mechanical properties used in the finite element models [57,58].

Mechanical Properties	Formula	Value
E_x	(None)	12.25 GPa
E_y	$0.45 \times E_x$	5.512 GPa
G_{xy}	$0.16 \times E_x$	1.96 GPa
$\nu_{yz} = \nu_{xz}$	(None)	0.36
ν_{xy}	$(E_y/E_x) \times \nu_{yz}$	0.16

which are mostly appropriate for deformation analysis. An automated process was performed in FEA which adaptively refined the meshes in regions where maximum stress and strain occurs and automatically recalculated the results until the values of stress and strain converged to show an error of no more than $\pm 1\%$. This will be discussed further in the next section. In vivo compression force which a horse experiences during walking [53] was used to test the finite element models. A maximum compression force (80 kN) which an MC3 from an adult horse can withstand before fracture in an ex vivo experiment [57] was considered in the FEA while obtaining the results. Orthotropic mechanical properties which were assigned to the meshes in FEA (Table 2) were based on the findings of an experimental protocol of the previous study [58]. ANSYS (Mechanical APDL 19.0 and Workbench 19.0, academic research, The University of Melbourne, Australia) and MATLAB (R2017a, academic use, The University of Melbourne, Australia) were used to obtain the results, conduct error analyses, and to compare the results. All the simulations were performed on 8 cores of an Intel Xeon Gold 3.00 GHz virtual machine with 96 GB RAM.

2.2.1. Stress and Strain Convergence and Error Analysis

Adaptive mesh refinement requires a user-specified accuracy (expected value), which will be achieved through the refinement process on a region of the model geometry [59]. Therefore, in this study, the following formula needs to be satisfied for convergence analysis:

$$\left(\frac{\sigma_{i+1}^R - \sigma_i^R}{\text{mean}(\sigma_{i+1}^R, \sigma_i^R)} \right) \times 100 < 1\% \quad (1)$$

$$\left(\frac{\varepsilon_{i+1}^R - \varepsilon_i^R}{\text{mean}(\varepsilon_{i+1}^R, \varepsilon_i^R)} \right) \times 100 < 1\% \quad (2)$$

where σ and ε indicate stress and strain tensor, respectively, and i is the node or element identification number counted on a region of interest (region R), which in this study is specified as the dorsal

surface of MC3 samples (region Ω). In addition to the error calculation discussed previously, a displacement-based error was used to identify poorly shaped elements causing error or inaccuracy in the results of structural analysis [59–61]. According to the theory of continuum mechanics which has been shown to be applicable in numerous disciplines of solid mechanics [62,63], the total potential energy of the bone samples comprises three terms,

$$\Pi = U^b + U^s - W \quad (3)$$

where U^b is the potential energy of the bulk of the bone samples, U^s is the potential energy of the dorsal surface, and W expresses the work done by external forces.

The error analysis is going to be applied for both the shell and the solid elements, and therefore, the potential energy of the dorsal surface is considered separately in Equation (3). The potential energies are expressed as follows:

$$U^b = \frac{1}{2} \int_V \{ \sigma^b \}^T \{ \varepsilon^b \} dV = \frac{1}{2} \int_V \{ \sigma^b \}^T [D]^{-1} \{ \sigma^b \} dV \quad (4)$$

$$U^s = \frac{1}{2} \int_{\Omega} \{ \sigma^s \}^T \{ \varepsilon^s \} t d\Omega = \frac{t}{2} \int_{\Omega} \{ \sigma^s \}^T [D]^{-1} \{ \sigma^s \} d\Omega \quad (5)$$

The thickness of shell elements (t) is constant and is selected to be as small as possible to gain accurate aspect ratios for the shell elements. As a consequence, the integration in Equation (5) is applied over an area (Ω). $[D]$ denotes the stiffness matrix of the solid or surface elements (stress-strain matrix).

The difference between the average nodal stress and the element nodal stress is the elemental stress error:

$$\{ \Delta \sigma_n^i \} = \frac{\sum_{i=1}^N \{ \sigma_n^i \}}{N} - \{ \sigma_n^i \} \quad (6)$$

in which $\Delta \sigma_n^i$ is stress error at node n of element i (Fig. 4), σ_n^i is nodal stress at node n of element i , and N is the number of adjacent elements, which are connected to node n . Depending on the body for which the error needs to be calculated, this stress error is integrated either over the element volume (V) or over the shell element surface (Ω), to achieve the energy error [similar to Equations (4) and (5)]:

$$E_i^b = \frac{1}{2} \int_V \{ \Delta \sigma_n^i \}^T [D]^{-1} \{ \Delta \sigma_n^i \} dV \quad (7)$$

Table 3

The error analysis when the reference CAD model of an MC3 (Fig. 1) was compared against, first, the extrapolated CAD model from 3 spline curves of cross-sections (Fig. 1D), second, the extrapolated CAD model from 11 spline curves of cross-sections (Fig. 1E), and third, the dorsal surface generated from the extrapolated CAD model from 3 spline curves of cross-sections.

Rebuilt surfaces (Fig. 1)	B1		B2		B3		B4		B5	
	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)
3E	0.305	−0.225	0.244	−0.185	0.319	−0.257	0.278	−0.396	0.946	−1.228
11E	0.101	−0.028	0.016	−0.024	0.011	−0.009	0.069	−0.024	0.330	−0.223
3ED	0.223	−0.106	0.114	−0.102	0.249	−0.244	0.176	−0.083	0.350	−0.135
Rebuilt surfaces (Fig. 1)	B6		B7		B8		B9		B10	
	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)
3E	0.417	−1.080	0.312	−0.529	0.135	−0.853	0.475	−0.322	0.647	−0.557
11E	0.106	−0.071	0.1080	−0.310	0.059	−0.035	0.032	−0.017	0.159	−0.041
3ED	0.209	−0.120	0.3050	−0.529	0.132	−0.194	0.196	−0.190	0.207	−0.147

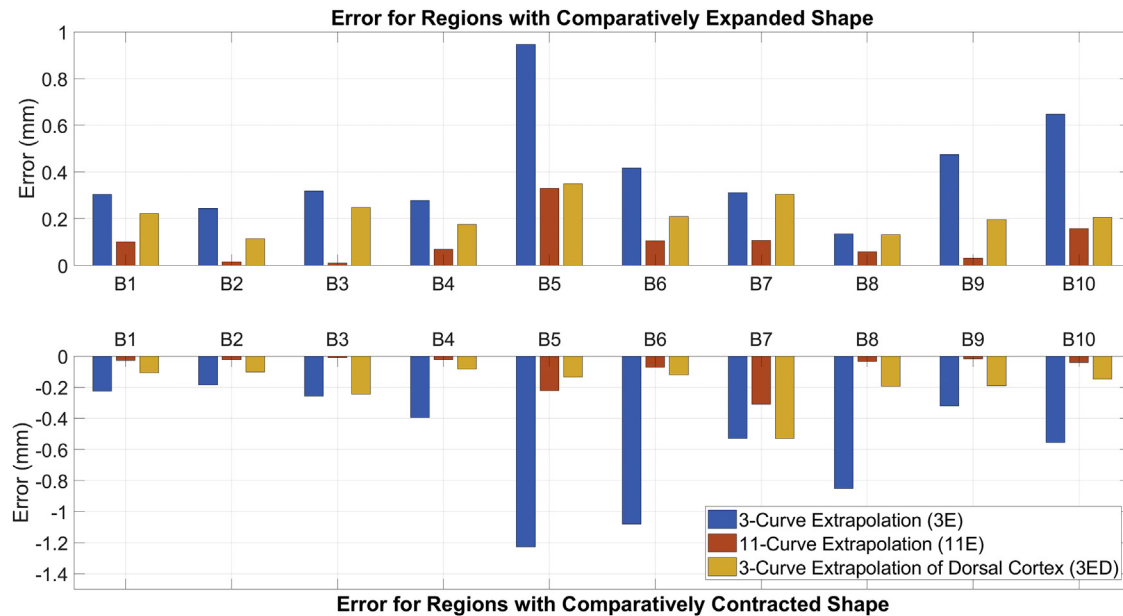


Fig. 5. Errors associated with surface reconstructions are inevitable in reverse engineering of bones. Errors associated with models which were constructed by extrapolating more curves were significantly less than those constructed from fewer curves. Shape is highly influential in determining the biomedical behavior of bones, and even when the same methodology was performed, the outcome was shown to be strongly shape dependent.

$$E^b = \sum_{i=1}^{N^b} E_i^b \quad (8)$$

$$E_j^s = \frac{t}{2} \iint_{\Omega} \{ \Delta \sigma_n^j \}^T [D]^{-1} \{ \Delta \sigma_n^j \} d\Omega \quad (9)$$

$$E^s = \sum_{j=1}^{N^s} E_j^s \quad (10)$$

where E_i^b and E_j^s are the energy error for element i of the bulk and the energy error for element j of the dorsal surface, respectively. The energy error over the bulk (E^b) or over the surface (E^s) is then calculated by summing up the respected elemental energy errors. N^b and N^s are the number of solid bulk elements and the number of surface shell elements.

3. Results

3.1. Reconstructed Bone Samples

Table 3 and Fig. 5 present the calculated error analysis of the reconstructed MC3 obtained through the extrapolation process. Design rules could be implemented that enabled the extrapolated CAD model (3E) to achieve a minimum error of +0.135 and −0.185 mm when compared with the equivalent CT-based CAD

model (reference model). These minimum errors were further reduced to +0.01 and −0.009 mm when more cross-sectional slices (11E) within the diaphysis of the bones were included. By eliminating the splint bones in the reconstructed models and performing reverse engineering on the DC (3ED), the extrapolation process via three curves achieved a minimum error of 0.114 and −0.083 mm. For the all samples and for both positive and negative errors (comparatively expanded and contracted shapes), reconstructing the dorsal surface through extrapolating three curves led to a lower error than reconstructing the entire segment through extrapolating the same curves. Significant errors (e.g., B5 in Fig. 5) occurred on the sharp edges of the splint bones (MC2 and MC4), both of which might be fused to the main MC3 or may slightly slide along its main shaft if unfused.

Table 4 presents the values of error analysis for 5 MC3 bones which had bigger splint bones than the other 10 (Fig. 3). The errors are noticeably higher than those previously reported in Table 3 and Fig. 5 for the first 10 bones. MC2 and MC4 splint bones are highlighted in Fig. 3B. The outcome of error analysis demonstrates that the absolute maximum error occurs on the surface, or in the vicinity of, the splint bones (Fig. 6).

The advantage which makes 3D CAD software a good solution in biomechanical studies is that it provides engineers with opportunities to manipulate and alter the shape configuration of bones. For instance, engineers can add or remove extraartificial spline curves in attempts to separate bones which have grown or fused together. The proposed method allows accurate modeling of bony structures, although its main interest is to make it possible to

Table 4
The error analysis was repeated on five more samples to highlight that a long bone with bigger splint bones engenders a greater error in the reverse engineering process.

Rebuilt surfaces	C1-L		C1-R		C2-L		C2-R		C3	
	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)	Max (mm)	Min (mm)
3E	1.936	−1.433	2.964	−2.579	1.371	−0.757	1.506	−0.902	1.559	−1.870
11E	0.197	−0.138	1.549	−1.720	1.422	−1.220	0.342	−0.357	0.108	−0.266
3ED	0.486	−0.164	0.366	−0.204	0.211	−0.076	0.170	−0.097	0.224	−0.868

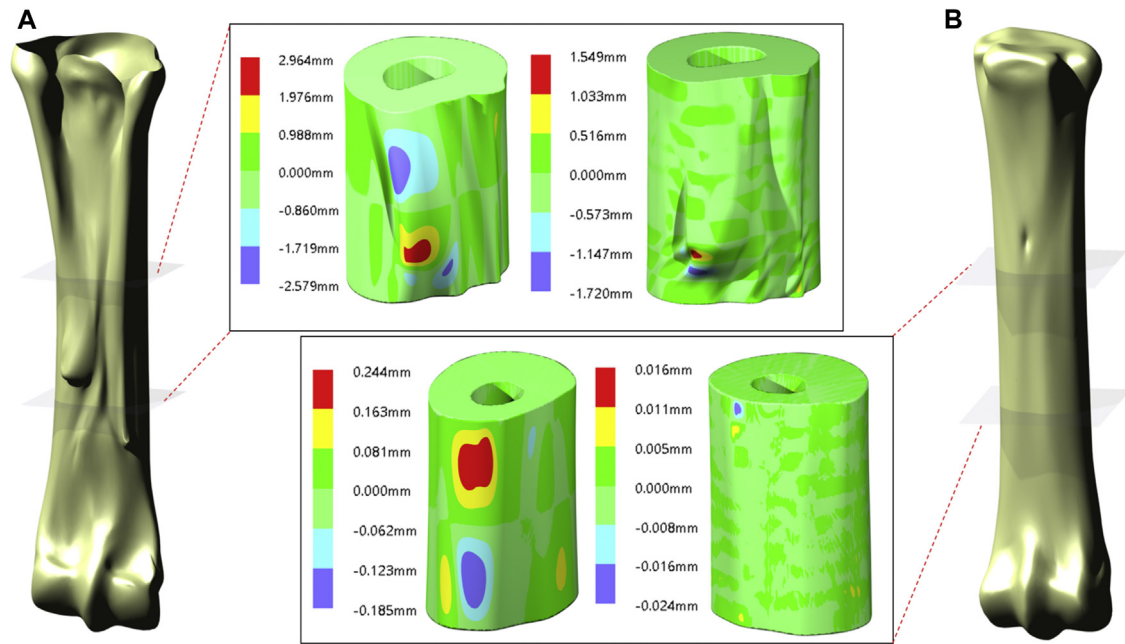


Fig. 6. Modeling of two samples (A) C1-R and (B) B2 from the group with large splint bones and the initial group, respectively. The reconstructed surface error associated with bones having bigger splint bones (more complex geometry) was conspicuously higher than those models for which splint bones were eliminated (the shape becomes far simpler).

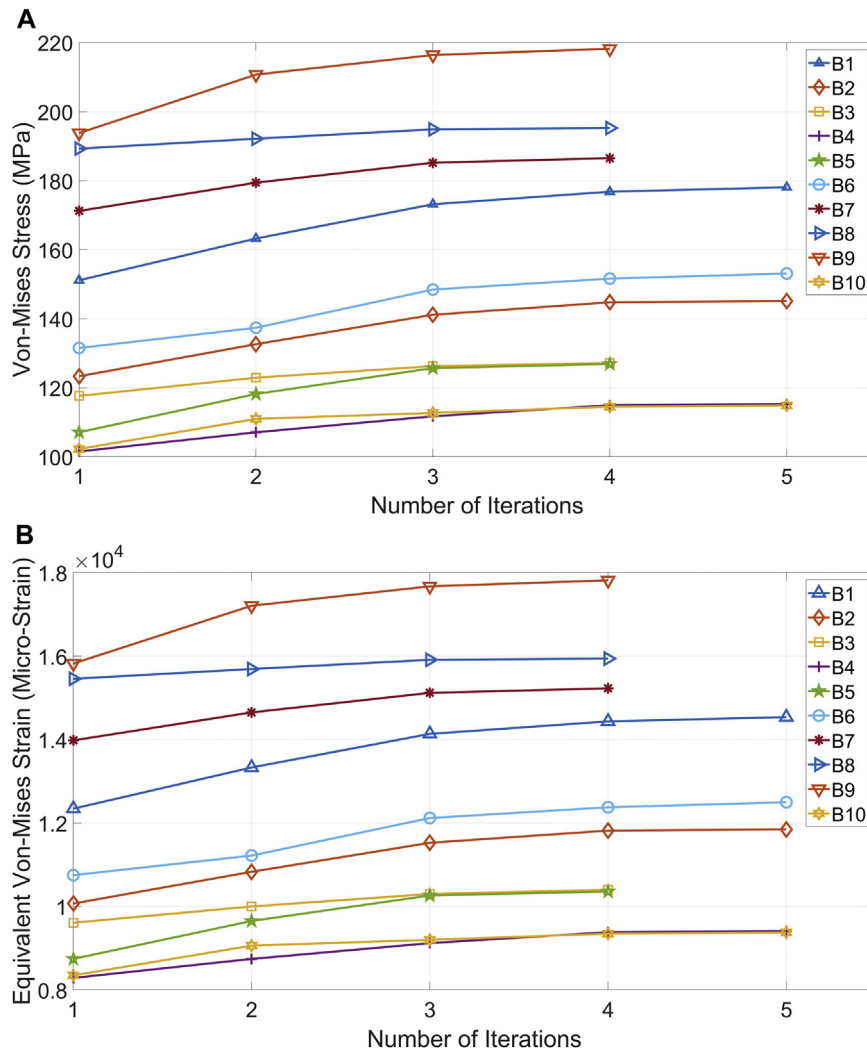


Fig. 7. The results of finite element convergence analysis for (A) von Mises stress and (B) von Mises strain imposed on the dorsal cortex of MC3 bone samples. MC3, third metacarpal bone.

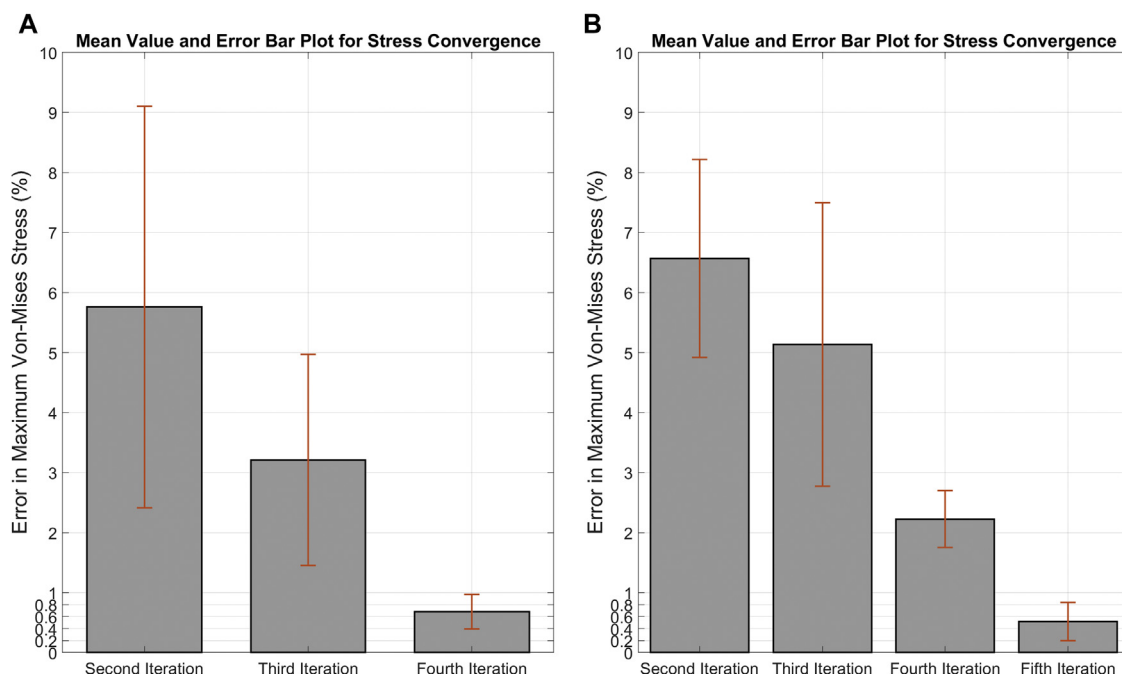


Fig. 8. In an initial step to identify poorly shaped finite element meshes, Equation (1) was computed for all the bone samples. Error bars show the standard deviation. In some bone samples, an error of less than 1% was achieved at the fourth iteration (A), whereas others required five iterations to achieve the same accuracy (B).

separate bones which have grown together. In the equine metacarpal bone, for example, between the main bone (MC3) and the small splint bones (MC2 and MC4), there may or may not be fusion. If there is no fusion, then these bones will slide very slightly against the main bone because of the fibrous tissue between them. Including MC2 and MC4 in the analysis of the entire system changes the computed stresses and the area properties of the metacarpal bone [64].

3.2. Finite Element Convergence and Error Analysis

Convergence analysis of stress and strain was completed on the CT-based models, and a major accomplishment was to present a model with an error of no more than 1%. Regarding Equations (1), (2), (8), and (10) presented in the preceding sections, the results of convergence and those of error analysis are computed and demonstrated in Figs. 7–9. Design rules used in this study reduced

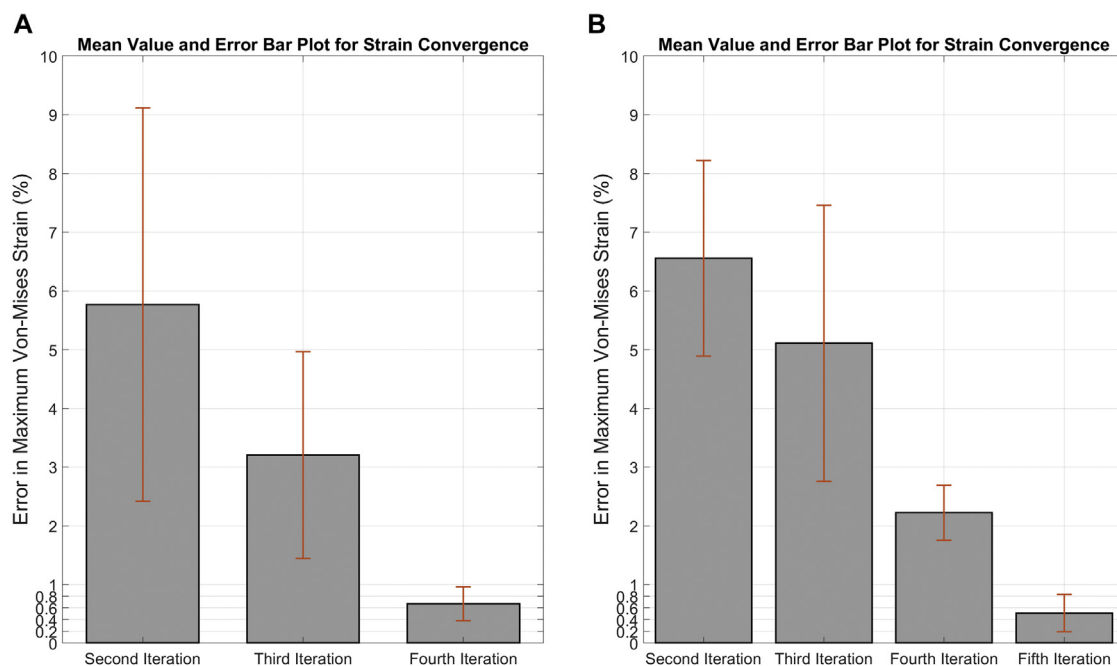


Fig. 9. In an initial step to identify poorly shaped finite element meshes, Equation (2) was computed for all the bone samples. Error bars show the standard deviation. In some bone samples, an error of less than 1% was achieved at the fourth iteration (A), whereas others required five iterations to achieve the same accuracy (B).

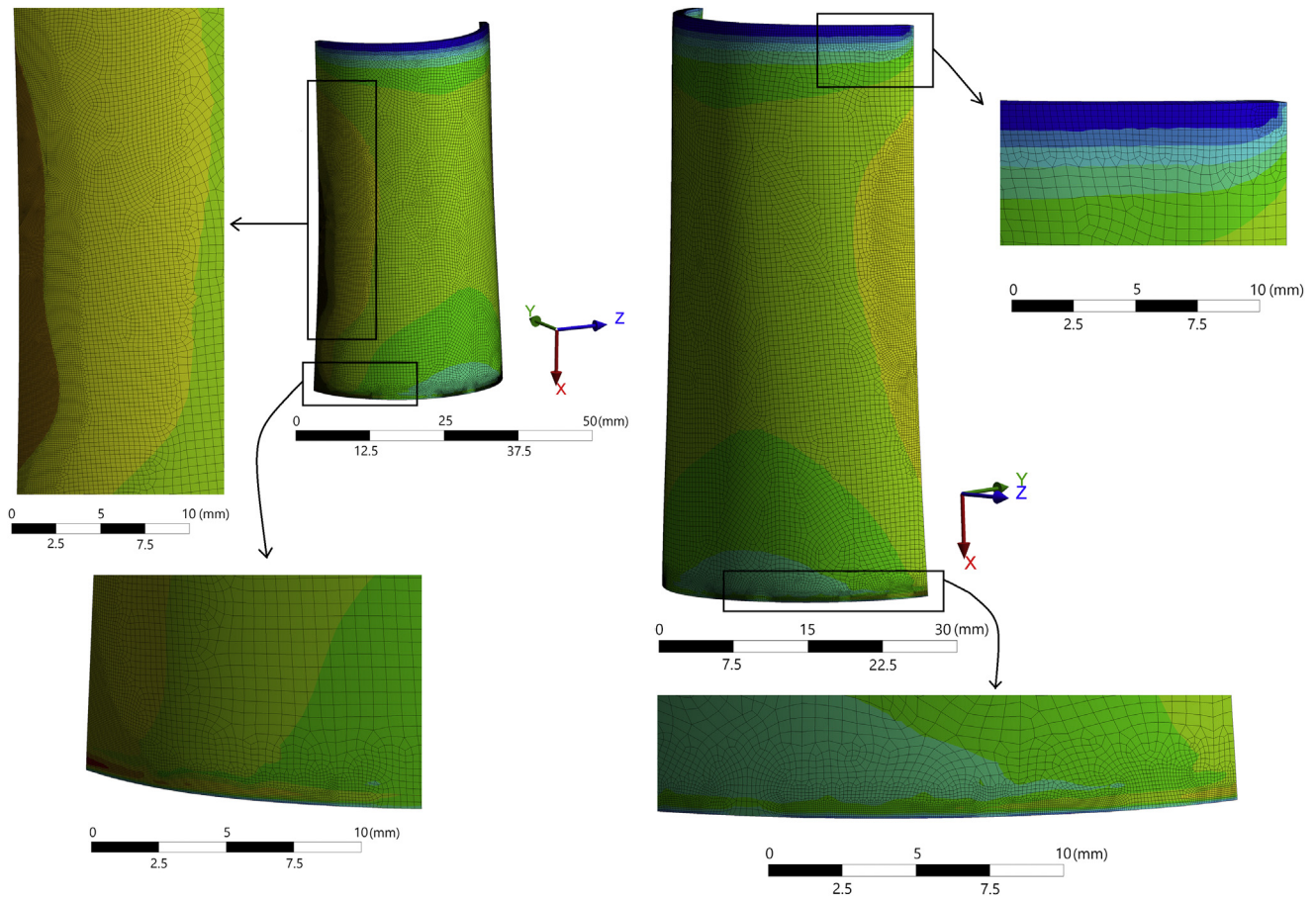


Fig. 10. The refined configuration of a bone surface was generally similar to this figure when the last solution was conducted (Fig. 8). The element size should be sufficiently small to gain stress and strain convergence. Automated mesh refinement was performed on the regions indicated with the boxes and was completed when the desired accuracy (an error of no more than $\pm 1\%$) was satisfied.

the error analysis to a mean value of 0.52% ($\pm$ SD 0.32%) for stress (Fig. 8) and 0.51% ($\pm$ SD 0.32%) for strain (Fig. 9). Although the analysis for all the bone samples was commenced by assigning fine meshes on the finite element models, a considerable error existed in the outcome of simulation (roughly 6% with respect to Figs. 8 and 9). Finally, by using the methods discussed in this study, the error of analysis substantially decreased to an acceptable value. In each solution iteration, the bone samples underwent a precise mesh refinement process (Fig. 10) and the solution completed when the desired accuracy (an error of no more than $\pm 1\%$) was satisfied.

Fig. 11 shows how demanding the mesh refinement process of the bone models would be in terms of the skill and experience of the researcher and the solution time. The number of nodes and elements in the original model (Fig. 11A) was 604,138 and 418,009, respectively, which then reached 787,215 and 478,876 (Fig. 11B), followed by 4 iterations in the refinement process. To save substantial time and effort for such models (like B3), it is recommended that finer meshes be assigned (with a smaller mesh size) at the beginning and before sending the model to mesh refinement and the solving processes. A similar process was repeated by manually assigning finer meshes with a size of no more than 0.3 mm, and by so doing, the model converged to the specified accuracy with only two iterations in the refinement process. The minimum mesh size which needs to be defined beforehand varies from sample to sample and, as such, requires consideration to decide on suitable solution parameters. This further highlighted the significance of shape in the responses of bones to loading, as has been discussed in the recent literature [29,65].

4. Discussion

Reverse engineering is an approach for constructing a CAD model from a physical part through surface modeling and 3D measurements. A critical issue for rapid product development is to efficiently create and modify a CAD model from the existing components of a desired object. Apart from the wide applications of CAD in mechanical engineering, it has been receiving considerable attention in medical engineering to gain a successful design. This requires a detailed knowledge of surrounding areas of the desired object in biomedical practices, so this demands an accurate and robust CAD model.

Reverse engineering via extrapolation of cross-sectional slices was used to reconstruct the MC3 midshaft. In addition, a fully automatic adaptive mesh refinement process and its associated finite element formulation were used to minimize the errors caused by features of finite element meshes. The accuracy of simulation is significantly affected by the quality, type, and statistics of meshes generated in FEA. To make the process reliable, errors associated with the results of stress and strain were computed in this study. This is an exhaustive method to create a fully automatic and integrated process that takes advantage of many of the mesh refinement and mesh optimization algorithms. The incorporated methodology can produce numerical results with an error of less than 1% (Figs. 8 and 9). This provides the user with the desired accuracy in the smallest number of iterations possible. Because the primary objective of FEA in biomechanics is generally related to human health and animal welfare (injury risk assessment, healing

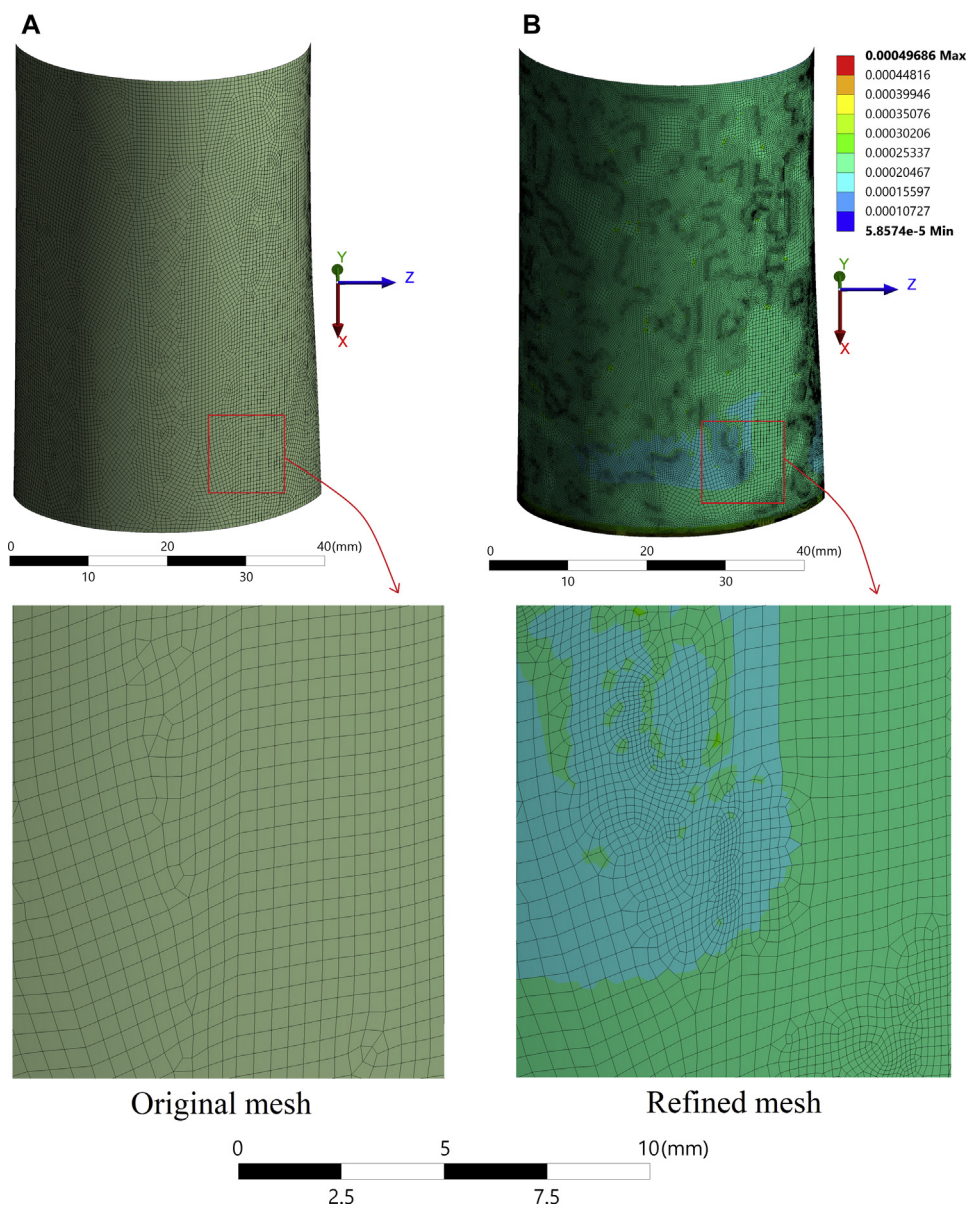


Fig. 11. The manual meshing and the automatic mesh refinement having been performed on B3. (A) The dorsal cortex of B3 was manually meshed using elements with a size of no more than 0.5 mm. (B) The mesh refinement (mesh quality assessment) was automatically conducted and finalized once the results of maximum von Mises strain approached an accuracy of 99.88% (Fig. 9).

prognosis, implant failure), it is imperative that the finite element models be presented with as much accuracy as possible. Fig. 8 shows an error of 9.85% in the result of FEA for the second attempt of the iteration process of a bone sample (mean 5.76% for the all samples studied). This step is where most of the FEA results are reported in publicly available literature. This is due to the fact that mesh sensitivity and mesh quality assessment which cause considerable error in the analysis have been overlooked in most articles [21]. Table 1 presents a summary of considerations in FEA error analysis reported in the literature. By incorporating the methods presented in our study, the error reduced to a mean value of 0.68%.

Unpredictable stresses with noticeable error occurred because of assigning an overly coarse mesh to the models. The results of displacement are less sensitive to mesh quality and density than those of stress and strains. This is where the significance of

performing several simulation iterations becomes apparent in ensuring the reliability of the results (Figs. 7 and 10). The smaller the elements, the higher the element statistics, and the more stress and strain levels increase. However, it should not be concluded that assigning higher numbers of nodes and elements necessarily results in a reliable finite element outcome. Instead, the meshing process should be optimized until further optimizing of mesh qualities has a diminishing effect on the results. This process predominantly involves identifying poorly shaped elements and refining them (Figs. 10 and 11), and then, the process of simulation is stopped when the changes in the result of stress between two consecutive iterations become insignificant (less than 1%). In the calculation of von Mises stress and von Mises strain, principal and axial components of stress and strain are inherently incorporated and as such only these results were presented in this study. The axial and principal components of stress and strain will meet the

same condition reported in Equations (1)–(10), and hence, the presented method is applicable for the error estimation of any type of stress and strain.

The researcher can save substantial time and effort before completing an FEA of a model (e.g., B3 in Fig. 11). It is recommended to assign finer meshes (with a smaller mesh size) at the beginning and before sending the model to the mesh refinement and solving processes. The process of mesh refinement was repeated by manually assigning finer meshes with a size of no more than 0.3 mm. By so doing, the model was converged to the specified accuracy with only two iterations in the refinement process. Therefore, the minimum mesh size, which needs to be defined beforehand varies from sample to sample and, as such, requires an informed decision on suitable solution parameters. This further emphasizes the significance of shape in the responses of bones to loading, as has been discussed in the recent literature [29,65]. New algorithms for generating a CAD model from CT data and, more significantly, smoothing of contours will improve 3D modeling of bones [66]. Modifications and smoothing of models alter the geometry (if only slightly), and hence it contributes to changing finite element meshing of the object. As such, investigations of error caused in FEA are needed before conducting stress and strain simulation (as shown in Figs. 8 and 10). The accuracy of models can be enhanced if experienced engineers incorporate carefully selected parameters using CAD tools such as ANSYS and CATIA to achieve reliable FEA [67].

Intuitively introducing more spline curves during extrapolation should result in a smaller error. However, the reverse was found in reverse engineering of C1-R via extrapolation of 11 spline curves (Fig. 6 and Table 4). This was due to the sharp edge and fused material of the splint bones at the distal diaphysis of C1-R. Therefore, introducing more spline curves in the reverse engineering process does not necessarily result in a smaller error. This further highlights the importance of investigating shape variation and quantifying the error map of reconstructed geometries. Even when the same engineering methods were applied, the results were shown to be highly shape-dependent. Hence, care should be taken when engineers attempt to segment, volume render, and reconstruct bones. The results presented in Table 4 suggest that generating the dorsal surface of the MC3 from an extrapolation of three spline curves introduces minor errors. This indicates that when the entire MC3 segment is generated from extrapolating three slices, splint bones are the major contributing factor in causing dimensional error. The significance of such error analysis has been demonstrated in ten legs of human cadavers [68].

Generating the models from the extrapolation process via CAD occasionally creates additional nonuniform rational B-spline and guide curves. These curves appear in the solid object of the model and, mostly, remain in data transfer to STP (STandard for the exchange of Product model data, sometimes referred to as STEP). Therefore, finite element packages (such as ANSYS) recognize these spline curves and change the mesh attributes of the model (e.g., the statistics of the meshes). This has been shown to occur in reconstructed models from more cross-sectional slices (e.g., 11E in Fig. 1). As a result, convergence error analysis on such models, as presented in this study, is critical before publishing the results. This fact and assigning proper mesh types (not using linear elements in stress and strain analysis) must be addressed in FEA performed on equine forelimb and human bones [19,46,47,49,54,69].

The load that a horse experiences during walking was applied in the FEA to test the finite element models. The presented results were based on a maximum compression force that an MC3 can withstand without a fracture in an ex vivo experiment. It is worth considering loads being applied during trotting and galloping in the FEA. Several studies have been conducted on the stress, strain, and

force calculations of the MC3, which indicates that the dominant loading at various gaits and speeds is compression. Therefore, in this study, only compression load was applied. Performing a sensitivity study for varying the direction of loading and also for incorporating bending and torsion might be useful. The MC3 of donated cadaver limbs were collected based on availability, timing, and storage space and as such either the left or right limb was used for most of the samples.

5. Conclusion

This article presented a consideration of reverse engineering through extrapolated cross-sectional slices and an FEA study with a focus on solid mechanics of long bones. A basic explanation of the mesh discretization error has been provided, and ANSYS error estimation tools were used to evaluate the accuracy of the finite element solution. Although FEA errors of 3%–5% have been shown to be acceptable in previously published articles, design rules presented in our study reduced the FEA error to a mean value of 0.52% ($\pm$ SD 0.32%) for stress and 0.51% ($\pm$ SD 0.32%) for strain. Geometric representation of bones relies on their anatomical features, and the associated errors must be reported in the reverse engineering process. Although this has been mostly overlooked in the literature, the errors of reconstructed surfaces in our study reduced to +0.135 and –0.185 mm. Addressing and minimizing such errors establish confidence in the reproducibility of such models.

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References

- [1] Currey JD. *Bones: structure and mechanics*. Princeton, NJ: Oxford: Princeton university press; 2013.
- [2] McKee SL. An update on racing fatalities in the UK. *Equine Vet Educ* 1995;7: 202–4.
- [3] Parkin T, Clegg P, French N, Proudman C, Riggs C, Singer E, Webbon P, Morgan K. Horse-level risk factors for fatal distal limb fracture in racing Thoroughbreds in the UK. *Equine Vet J* 2004;36:513–9.
- [4] Boden L, Anderson G, Charles J, Morgan K, Morton J, Parkin T, Slocumbe R, Clarke A. Risk of fatality and causes of death of Thoroughbred horses associated with racing in Victoria, Australia: 1989–2004. *Equine Vet J* 2006;38: 312–8.
- [5] Johnson B, Ardans A, Stover S, Daft B, Kinde H, Read D, Barr B, Moore J, Woods L, Anderson M. California racehorse postmortem program: a 4-year overview. In: *Proc. Am. Ass. Equine Practns*; 1994. p. 167–9.
- [6] Maeda Y, Hanada M, Oikawa M-a. Epidemiology of racing injuries in Thoroughbred racehorses with special reference to bone fractures: Japanese experience from the 1980s to 2000s. *J Equine Sci* 2016;27:81–97.
- [7] Liley H, Davies H, Firth E, Besier T, Fernandez J. The effect of the sagittal ridge angle on cartilage stress in the equine metacarpo-phalangeal (fetlock) joint. *Comput Methods Biomech Biomed Engin* 2017;20:1140–9.
- [8] Loughridge A, Hess A, Parkin T, Kawcak C. Qualitative assessment of bone density at the distal articulating surface of the third metacarpal in Thoroughbred racehorses with and without condylar fracture. *Equine Vet J* 2017;49:172–7.
- [9] Couch S, Nielsen B. A review of dorsal metacarpal disease (bucked shins) in the flat racing horse: prevalence, diagnosis, pathogenesis, and associated factors. *J Dairy Vet Anim Res* 2017;5:228–36.
- [10] Davies H. The timing and distribution of strains around the surface of the midshaft of the third metacarpal bone during treadmill exercise in one Thoroughbred racehorse. *Aust Vet J* 2005;83:157–62.
- [11] Davies HM, Merritt JS. Surface strains around the midshaft of the third metacarpal bone during turning. *Equine Vet J* 2004;36:689–92.
- [12] Murray RC, Branch MV, Dyson SJ, Parkin TDH, Goodship AE. How does exercise intensity and type affect equine distal tarsal subchondral bone thickness? *J Appl Physiol* 2007;102:2194–200.
- [13] Davies HM. Relationships between third metacarpal bone parameters and surface strains. *Equine Vet J Suppl* 2001;33:16–20.
- [14] Davies HM. Estimating peak strains associated with fast exercise in Thoroughbred racehorses. *Equine Vet J Suppl* 2006;38:383–6.

- [15] Davies H, Watson K. Third metacarpal bone laterality asymmetry and mid-shaft dimensions in Thoroughbred racehorses. *Aust Vet J Suppl* 2005;83: 224–6.
- [16] Rubio-Martínez LM, Cruz AM, Gordon K, Hurtig MB. Mechanical properties of subchondral bone in the distal aspect of third metacarpal bones from Thoroughbred racehorses. *Am J Vet Res* 2008;69:1423–33.
- [17] Sun W, Starly B, Nam J, Darling A. Bio-CAD modeling and its applications in computer-aided tissue engineering. *Comput Aided Des* 2005;37:1097–114.
- [18] Starly B, Fang Z, Sun W, Shokoufandeh A, Regli W. Three-dimensional reconstruction for medical-CAD modeling. *Comput Aided Des Appl* 2005;2:431–8.
- [19] Gföhler M, Peham C. What can finite element analysis tell us? *Equine Vet J* 2013;45:265–6.
- [20] Erdemir A, Guess TM, Halloran J, Tadepalli SC, Morrison TM. Considerations for reporting finite element analysis studies in biomechanics. *J Biomech* 2012;45:625–33.
- [21] Burkhart TA, Andrews DM, Dunning CE. Finite element modeling mesh quality, energy balance and validation methods: a review with recommendations associated with the modeling of bone tissue. *J Biomech* 2013;46:1477–88.
- [22] Lengsfeld M, Schmitt J, Alter P, Kaminsky J, Leppke R. Comparison of geometry-based and CT voxel-based finite element modelling and experimental validation. *Med Eng Phys* 1998;20:515–22.
- [23] Caon M. Voxel-based computational models of real human anatomy: a review. *Radiat Environ Biophys* 2004;42:229–35.
- [24] Yosibash Z, Padan R, Joskowicz L, Milgrom C. A CT-based high-order finite element analysis of the human proximal femur compared to in-vitro experiments. *J Biomech Eng* 2006;129:297–309.
- [25] Sun W, Lal P. Recent development on computer aided tissue engineering — a review. *Comput Methods Programs Biomed* 2002;67:85–103.
- [26] Viceconti M, Zannoni C, Pierotti L. TRI2SOLID: an application of reverse engineering methods to the creation of CAD models of bone segments. *Comput Methods Programs Biomed* 1998;56:211–20.
- [27] Yoo D-J. Three-dimensional surface reconstruction of human bone using a B-spline based interpolation approach. *Comput Aided Des* 2011;43:934–47.
- [28] van Eijnatten M, van Dijk R, Dobbe J, Streekstra G, Koivisto J, Wolff J. CT image segmentation methods for bone used in medical additive manufacturing. *Med Eng Phys* 2017;51:6–16.
- [29] Liley H, Zhang J, Firth E, Fernandez J, Besier T. Using partial least squares regression as a predictive tool in describing equine third metacarpal bone shape. *Comput Methods Biomech Biomed Engin* 2017;20:1609–12.
- [30] Koivisto J, Kiljunen T, Kadesjö N, Shi XQ, Wolff J. Effective radiation dose of a MSCT, two CBCT and one conventional radiography device in the ankle region. *J Foot Ankle Res* 2015;8:8.
- [31] Semelka RC, Armao DM, Elias J, Huda W. Imaging strategies to reduce the risk of radiation in CT studies, including selective substitution with MRI. *J Magn Reson Imaging* 2007;25:900–9.
- [32] Fujita H, Hatanaka Y. In: Computer-aided diagnosis with retinal fundus images, in: medical image analysis and informatics. CRC Press; 2017. p. 59–86.
- [33] Rathnayaka K, Momot KI, Noser H, Volp A, Schuetz MA, Sahama T, Schmutz B. Quantification of the accuracy of MRI generated 3D models of long bones compared to CT generated 3D models. *Med Eng Phys* 2012;34:357–63.
- [34] Ma W, Kruth J-P. NURBS curve and surface fitting for reverse engineering. *Int J Adv Manuf Technol* 1998;14:918–27.
- [35] McCarthy R, Jeffcott L. Effects of treadmill exercise on cortical bone in the third metacarpus of young horses. *Res Vet Sci* 1992;52:28–37.
- [36] Sherman K, Miller G, Wronski T, Colahan P, Brown M, Wilson W. The effect of training on equine metacarpal bone breaking strength. *Equine Vet J* 1995;27: 135–9.
- [37] Davies H, McCarthy R. Strain in the yearling equine metacarpus during locomotion. *Equine Vet J Suppl* 1994;17:25–8.
- [38] Nunamaker D. In: On bucked shins, in: annual convention of American association of equine practitioners; 2002. p. 76–89.
- [39] Pivonka P, Park A, Forwood MR. Functional adaptation of bone: the mechanostat and beyond. In: Pivonka P, editor. Multiscale mechanobiology of bone remodeling and adaptation. Cham: Springer International Publishing; 2018. p. 1–60.
- [40] Les CM, Stover S, Keyak J, Taylor K, Willits N. The distribution of material properties in the equine third metacarpal bone serves to enhance sagittal bending. *J Biomech* 1997;30:355–61.
- [41] Merritt JS, Davies HM. Metacarpal geometry changes during Thoroughbred race training are compatible with sagittal-plane cantilever bending. *Equine Vet J Suppl* 2010;42:407–11.
- [42] Xu L, Lin MX, Li JQ, Wang ZL, Chirende B. Three-dimensional geometrical modelling of wild boar head by reverse engineering technology. *J Bionic Eng* 2008;5:85–90.
- [43] Sun L, Tian H, Wu D, Du Z. In: Three-dimensional geometric modeling of the spine based on reverse engineering technology, in: biomedical Engineering and Informatics (BMEI), 2010 3rd International Conference on, IEEE; 2010. p. 1292–5.
- [44] Zhang J, Besier TF. Accuracy of femur reconstruction from sparse geometric data using a statistical shape model. *Comput Methods Biomech Biomed Engin* 2017;20:566–76.
- [45] Harrison SM, Whitton RC, Kawcak CE, Stover SM, Pandey MG. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. *J Biomech* 2014;47:65–73.
- [46] McCarty CA, Thomason JJ, Gordon KD, Burkhart TA, Milner JS, Holdsworth DW. Finite-element analysis of bone stresses on primary impact in a large-animal model: the distal end of the equine third metacarpal. *PLoS One* 2016;11: e0159541.
- [47] Les C, Keyak J, Stover S, Taylor K. Development and validation of a series of three-dimensional finite element models of the equine metacarpus. *J Biomech* 1997;30:737–42.
- [48] Malekipour F, Oetomo D, Lee PVS. Equine subchondral bone failure threshold under impact compression applied through articular cartilage. *J Biomech* 2016;49:2053–9.
- [49] O'Hare LMS, Cox PG, Jeffery N, Singer ER. Finite element analysis of stress in the equine proximal phalanx. *Equine Vet J* 2012;45:273–7.
- [50] Jansová M, Ondoková L, Vychytil J, Kochová P, Witter K, Tonar Z. A finite element model of an equine hoof. *J Equine Vet Sci* 2015;35:60–9.
- [51] Yosibash Z, Tal D, Trabelsi N. Predicting the yield of the proximal femur using high-order finite-element analysis with inhomogeneous orthotropic material properties. *Philos TransA Math Phys Eng Sci* 2010;368:2707–23.
- [52] Edwards WB, Troy KL. Finite element prediction of surface strain and fracture strength at the distal radius. *Med Eng Phys* 2012;34:290–8.
- [53] Merritt JS, Pandey MG, Brown NAT, Burvill CR, Kawcak CE, McIlwraith CW, Davies HMS. Mechanical loading of the distal end of the third metacarpal bone in horses during walking and trotting. *Am J Vet Res* 2010;71:508–14.
- [54] Helgason B, Taddei F, Pålsson H, Schileo E, Cristofolini L, Viceconti M, Brynjólfsson S. A modified method for assigning material properties to FE models of bones. *Med Eng Phys* 2008;30:444–53.
- [55] Biswas JK, Sahu TP, Rana M, Roy S, Karmakar SK, Majumder S, Roychowdhury A. Design factors of lumbar pedicle screws under bending load: a finite element analysis. *Biocybernetics Biomed Eng* 2019;39:52–62.
- [56] Tadepalli SC, Erdemir A, Cavanagh PR. Comparison of hexahedral and tetrahedral elements in finite element analysis of the foot and footwear. *J Biomech* 2011;44:2337–43.
- [57] Mouloudi S, Burvill CR, Rahmanpanah H, Davies HM. Nonlinear force-dependent mechanical characteristics of bones, a novel investigation into modulus of elasticity, Biocybernetics and Biomedical Engineering. Submitted for Publication; 2019. <https://www.journals.elsevier.com/biocybernetics-and-biomedical-engineering>.
- [58] Merritt JS, Burvill CR, Pandey MG, Davies HM. Determination of mechanical loading components of the equine metacarpus from measurements of strain during walking. *Equine Vet J Suppl* 2006;38:440–4.
- [59] Tristano JR, Chen Z, Hancq DA, Kwok W. Fully automatic adaptive mesh refinement integrated into the solution process. Conference paper published at the 12th International Meshing Roundtable (IMR) in 2003, Santa Fe, New Mexico, USA. IMR; 2003. p. 307–14. <https://imr.sandia.gov/papers/imr12/tristano03.pdf>.
- [60] Zienkiewicz OC, Zhu JZ. A simple error estimator and adaptive procedure for practical engineering analysis. *Int J Numer Meth Eng* 1987;24:337–57.
- [61] ANSYS®, Academic research mechanical, release 19.0, help system, Chapter 17: Postprocessing, ANSYS, Inc: Canonsburg, PA.
- [62] Mouloudi S, Khojasteh J, Salehi M, Mohebbi S. Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region. *Int J Mech Sci* 2014;85:160–7.
- [63] Mouloudi S, Mohebbi S, Khojasteh J, Salehi M. Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects. *Int J Mech Sci* 2014;79:162–7.
- [64] Piotrowski G, Sullivan M, Colahan PT. Geometric properties of equine metacarpus. *J Biomech* 1983;16:129–39.
- [65] Liley H, Zhang J, Firth EC, Fernandez JW, Besier TF. Statistical modeling of the equine third metacarpal bone incorporating morphology and bone mineral density. *PLoS One* 2018;13:1–11.
- [66] Ryu JH, Kim HS, Lee KH. Contour-based algorithms for generating 3D CAD models from medical images. *Int J Adv Manuf Technol* 2004;24:112–9.
- [67] Relvas C, Ramos A, Completo A, Simões JA. Accuracy control of complex surfaces in reverse engineering. *Int J Precision Eng Manufacturing* 2011;12: 1035–42.
- [68] Van den Broeck J, Vereecke E, Wirix-Speetjens R, Vander Sloten J. Segmentation accuracy of long bones. *Med Eng Phys* 2014;36:949–53.
- [69] Marr C. Equine Veterinary Journal: recent and future directions. *Equine Vet J* 2014;46:1–3.

3.2. Summary and Concluding Remarks

This chapter presented underlying formulae to quantify elemental energy errors (for both solid bulk elements and surface shell elements) for successful completion of finite element convergence and error analysis with an aim to maximize the accuracy of finite element analysis performed on equine third metacarpal bones. This emphasized conducting mesh sensitivity analysis and assigning proper mesh types (not employing linear elements) for stress and strain analysis of this complex biological structure. Higher-order (quadratic) tetrahedron and hexahedron elements were used in the analysis, which are accurate and well-suited for stress and strain analysis. These strategies will be followed and implemented in the finite element analysis performed in Chapter 5 to maximize the accuracy prior to comparison of the results with experimental and artificial neural network counterparts. Reverse engineering (CAD-based) through an extrapolation process of slices within the MC3 bone midshaft was undertaken to reconstruct a 3D model of the MC3 bone midshaft. The error map of the reconstructed geometries (as compared with the CT-based models) was plotted to determine the accuracy of the generated surfaces and to identify anatomical features causing noticeable errors. 3D CAD software assists in generating 3D models of the bones and provides engineers with opportunities to manipulate and alter the shape configuration of bones. This enhances confidence in the employment of CAD and the measurement of geometrical parameters completed in the next chapter (Chapter 4).

Chapter 4

Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design

This chapter reports on a paper published by the author and collaborators that investigated the following hypotheses (as discussed in Section 2.6.2):

- **H.3.** Significant differences ($p < 0.05$) for the geometrical parameters were observed for the proximal and middle cross-sectional area when foals were compared with the rest of the bone samples.
- **H.4.** The least area, dorsal cortex, palmar cortex, medial cortex, lateral cortex, and shape index of cross sections in the bone midshaft for the foal samples were observed, which revealed a converging-diverging shape from the proximal slice to the distal one.
- **H.5.** A two-degree polynomial function can be fitted to the plots and then the curvature (k) of these fitted plots can be compared to assess its significant changes among the groups (the level of significance was set at $p = 0.05$).
- **H.6.** The width of the dorsal cortex (D), palmar cortex (P), and lateral cortex (L) will change significantly ($p < 0.05$) with maturation (comparison between foals and the rest of the samples).

This chapter also provides the background information to understand age-dependent mechanical attributes and geometrical parameters of equine MC3 long bone. Age will be considered further as an input of the artificial neural networks employed in the subsequent chapters (Chapter 6 to Chapter 8, inclusive).

4.1. Published Journal Paper

Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design, *Comparative Exercise Physiology* (IF: 0.8 as of 2020), 15 (2019) 349-358, <https://doi.org/10.3920/CEP190010>

(<https://www.ingentaconnect.com/content/wagac/cep/2019/00000015/00000005/art00007>)



Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design

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RESEARCH ARTICLE

Abstract

The shape of the diaphysis of the equine third metacarpal bone (MC3) has a substantial influence on its mechanical properties. The connection between bone shape and bone adaptive responses is likely to be useful in forecasting the response of MC3 to a training program as well as predicting its internal loading. A variety of geometrical parameters including cortical area (A), width of dorsal cortex (D), palmar cortex (P), medial cortex (M), lateral cortex (L), medulla in dorsopalmar plane (M_d), and medulla in lateromedial plane (M_l) in three main cross sections (slices) within the diaphysis of 27 Thoroughbred horses aged from 12 hours to 15 years were measured using computer-aided-design and were analysed using *t*-tests and ANOVA test (performed in statistical MATLAB codes). Shape indices $[(D/P) \times [(D+P)/M_d]]$, $H (D+M_d+P)$, and $V (M+M_l+L)$ were also calculated. For all the samples, the values were plotted for a slice taken from around the mid-point of the shaft, and from two others taken at 3 cm proximally and distally from the middle slice. Cortical area decreased from proximal to distal slices in the majority of the specimens, except for all the foal samples where the area fluctuated and showed a converging-diverging shape. A similar trend was observed for one of the adult horses. To investigate converging-diverging shape configuration, a two-degree polynomial function was fitted to the plots of geometrical parameters and then the curvature (*k*) of these fitted curves was quantified and compared to assess the significant changes. Previous research showed that 0.5 mm differences in thickness of the midshaft dorsal cortex have a significant effect on local strain *in vivo*. Variations in the geometrical parameters of the midshaft metacarpus have a dramatic impact on the internal loading of the MC3 and should be considered in designing equine training programs in attempts to predict and prevent bone damage.

Keywords: equine metacarpus, equine third metacarpal bone (mc3), area of cross sections, shape, exercise

1. Introduction

The shape of a bone is tied to its function. Geometric properties are crucial in comprehending the demands placed on the bone during normal activities. Employing engineering principles such as beam theory and conducting numerical simulations, such as finite element analysis (FEA) in long bones are useful in understanding failure mechanisms, discovering regions of failure, and designing treatments for pathological conditions. The majority of disastrous injuries in racing horses worldwide are associated with forelimb injuries, especially failures of the third metacarpal bone (MC3) (Boden *et al.*, 2006; Johnson *et*

al., 1994; Liley *et al.*, 2017a; Loughridge *et al.*, 2017; Maeda *et al.*, 2016; McKee, 1995; Parkin *et al.*, 2004). MC3 forms an essential part of the lower forelimb in withstanding loads (Couch and Nielsen, 2017). Compressive strains exceeding 3,000 microstrains have been recorded on the MC3 midshaft surface during horse locomotion (Davies and McCarthy, 1994; Nunamaker, 2002). These strains can be related to the shape of the bone (Davies, 2001b; 2006), as well as exercise speed (Davies, 2005) and locomotion type (Davies and Merritt, 2004; Murray *et al.*, 2007). The shape of the midshaft dorsal cortex (DC) of MC3 alters (expands and thickens) when it undergoes increasing applied forces during racing and training (Davies and Watson, 2005;

Rubio-Martínez *et al.*, 2008). High strains occurring at the dorsal cortex of MC3 may be the stimulus for remodelling in this area to withstand the applied stresses. However, only limited data is available in the literature associated with investigation into the geometrical parameters of cross sections in horses with different ages and exercise history. Therefore, the main objective of this study was to measure a variety of geometrical parameters in three main cross sections (slices) within the diaphysis of MC3 bones and then compare the values to assess their significant changes employing ANOVA and *t*-tests.

2. Materials and method

MC3 bones and measurement of geometries

Bones were harvested post-mortem from Thoroughbred horses that died for reasons not associated with this study. The bone samples were categorised into five groups based on their age, the details of which are given in Table 1. Besides age group, Table 1 depicts the measured length of

the bones and a summary of the training history of horses. The mean ($\pm$ standard deviation (SD)) bone lengths for each group were 26.32 (± 1) for foals, yearlings 26.98 (± 1.09), two-year-olds 27.6 (± 0.94), three-year-olds 27.47 (± 0.45), and adults 27.73 (± 0.49). The length of the MC3 is a critical parameter to be considered for buckling analysis.

Scans of three thin cross sections of the shaft of the equine third metacarpal bone were imported into a computer-aided design (CAD using ANSYS Mechanical APDL 19.0 and ANSYS Workbench 19.0; ANSYS Inc., Canonsburg, PA, USA). Continuous spline-curves were then created on the inner and outer edges of the cortex, and a surface was created for each slice (Figure 1). Construction elements (parallel dashed lines illustrated in Figure 1) were then sketched on each cross-sectional slice to assist in measuring geometrical parameters (Figure 1). These slices were taken from around the mid-point of the bone shaft (middle slice), and the two others from 3cm proximally (proximal slice) and distally (distal slice) to the middle cross section. Width of dorsal cortex (D), palmar cortex (P), medial cortex (M),

Table 1. The number, age, metacarpus length, and a summary of training history of horses used in this study.

Age group	Horse number/age	Bone length (cm)	Time out of work	Number of racing preparations	Limb side
Foal (<6 months)	F1 (4 weeks)	26	untrained	0	right
	F2 (12 hours)	25.2	untrained	0	left
	F3 (2 months)	26.5	untrained	0	left
	F4 (6 months)	27.6	untrained	0	left
Yearling (16-19 months)	Y1 (19 months)	26.6	untrained	0	right
	Y2 (17 months)	28.7	untrained	0	left
	Y3 (18 months)	27.2	untrained	0	right
	Y4 (16 months)	25.7	untrained	0	left
	Y5 (18 months)	26.1	untrained	0	right
	Y6 (19 months)	27.6	untrained	0	right
Two-year-old ¹	2Y1	28.8	-	-	left
	2Y2	27	-	-	left
	2Y3	27.6	-	-	left
	2Y4	28.2	-	-	right
	2Y5	26.4	-	-	right
Three-year-old ¹	3Y1	27.7	-	-	right
	3Y2	27.7	-	-	right
	3Y3	27.7	-	-	left
	3Y4	26.8	-	-	left
Adult (≥ 4 years)	A1 (4 years)	28	8 weeks	2	left
	A2 (15 years)	27.5	never raced trained for eventing	0	right
	A3 (6 years)	27.5	3 years	1	left
	A4 (5 years)	27	8 weeks	3	right
	A5 (8 years)	28.4	2 years	many	left
	A6 (5 years)	28	4 weeks	>4	left

¹ The previous training history for two-year-old and three-year-old horses was unknown, but they were all racehorses, mostly in training. The yearling horses were all previously untrained and then were exercised for up to seven days prior to euthanasia for another project.

lateral cortex (L), medulla in dorsopalmar plane (M_d), and medulla in lateromedial plane (M_l) were measured for each cross section. Cortical area and a shape index ($[D/P] \times [(D+P)/M_d]$) were also quantified for these three cross sections. The index ratio reflects the tendency of the MC3 bone to be deposited preferentially onto the dorsal cortex and is a reflection of MC3 bone shape in the dorsopalmar plane (Davies, 2001b, 2002). The bone porosity was not considered in the calculation of these parameters. These geometrical parameters were then plotted versus proximal, middle, and distal slices. In addition, to have a qualitative parameter by which converging-diverging shape parameters could be inferred within the midshaft of MC3 bones, a two-degree polynomial function was fitted to the plots and then the curvature (k) of these fitted plots was compared to assess its significant changes among the groups. The following formula was used to calculate the curvature (the reciprocal of the radius of an oscillating circle) (Thomas and Finney, 1984):

$$k = \frac{\ddot{y}}{(1 + \dot{y}^2)^{3/2}} \quad (1)$$

where, y indicates a two-degree polynomial function fitted to each plot, $\dot{y}$ and $\ddot{y}$ represent the first and the second derivative of function y .

Statistical analysis

Mean $\pm$ SD values of geometrical parameters were measured for each group. The differences of these parameters within each group were tested for significance using t -tests in MATLAB (R2019a; Mathworks, Natick, MA, USA). The level of significance was set at $P=0.05$. To compare the geometrical measurements among different groups, and since there are more than 2 groups in our study, ANOVA test was performed (Kitchen, 2009). The t -tests and ANOVA analyses were conducted on the aforementioned three cross sections for the five groups (foals, yearlings, two-year-olds, three-year-olds, and adults).

3. Results

Figures 2, 3, and 4 demonstrate the area of middle, proximal, and distal slices (respectively) within the diaphysis of the metacarpus for all of the samples. These figures showed a similar decreasing trend in the measured area from proximal to distal, except for all the foal samples (Figure 2) in which the area fluctuated and showed a converging-diverging shape within the midshaft of the bone. A similar trend was observed for one adult sample (A2) where the value of area also fluctuated in the right limb but not the left (Figure 4). The trends for the area of cross sections of A3 were also somewhat different between the right and left limbs (Figure 4).

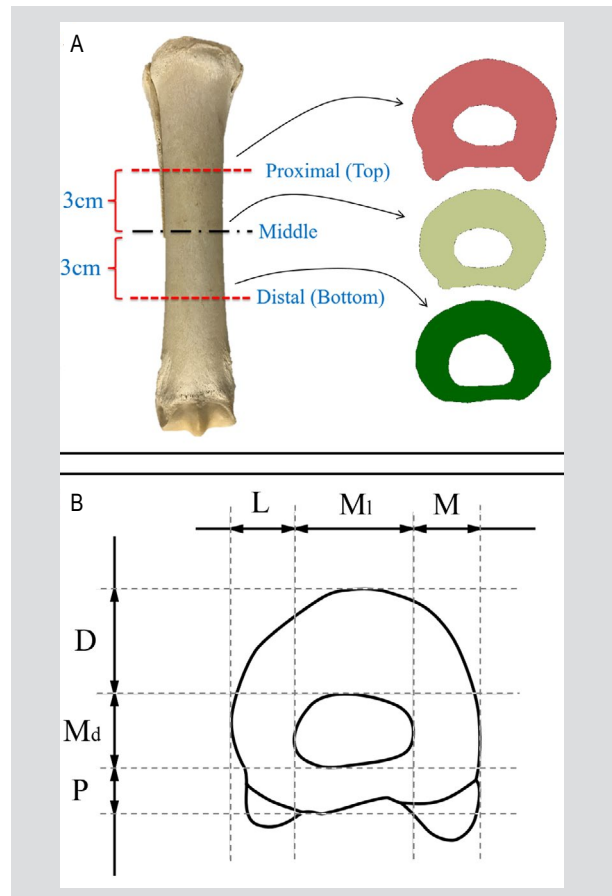


Figure 1. The three thin cross sections of the shaft of the equine metacarpus used in the measurement of geometrical parameters. (A) A slice taken from around the mid-point of the shaft, and the two others from 3 cm proximally and distally to the middle cross section (slice). (B) A range of different geometrical parameters were measured using CAD for each slice.

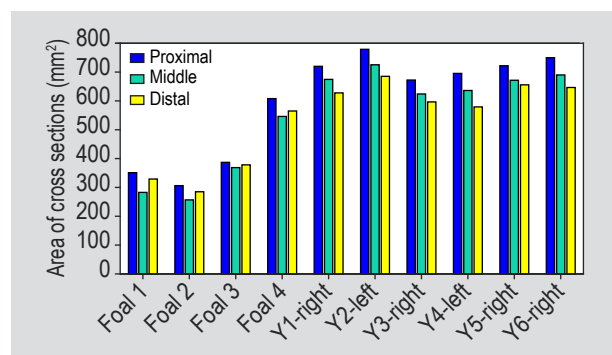


Figure 2. The area of three cross sections proximal, middle, and distal (as shown in Figure 1). The horizontal axis identifies the samples from individual foals and yearlings.

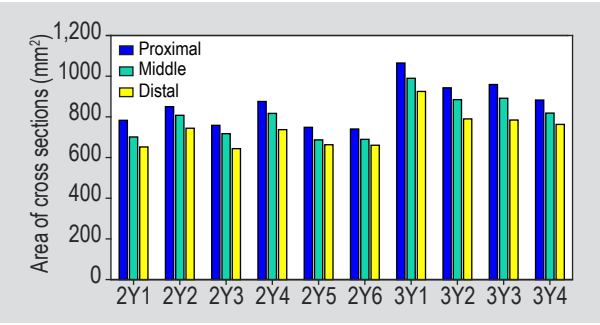


Figure 3. The area of three cross sections proximal, middle, and distal (as shown in Figure 1). The horizontal axis identifies the samples from individual two-year-olds and three-year-olds.

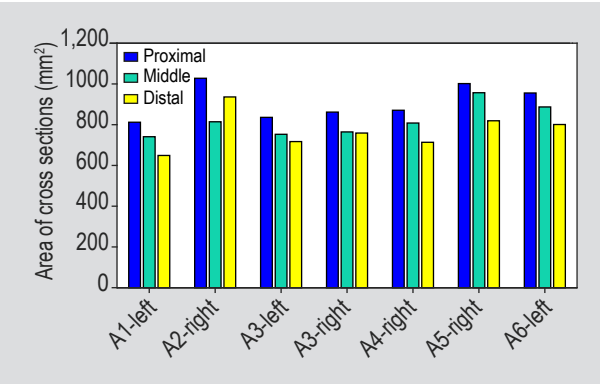


Figure 4. The area of three cross sections proximal, middle, and distal (as shown in Figure 1). The horizontal axis identifies the samples from individual adults.

The variations of the width of the dorsal cortex (Supplementary Figure S1), palmar cortex (Supplementary Figure S2), and medulla in the dorsopalmar plane (Supplementary Figure S3); medial cortex (Supplementary Figure S4), lateral cortex (Supplementary Figure S5), and medulla in the lateromedial plane (Supplementary Figure S6) of the third metacarpal bones are presented for proximal, middle, and distal cross sections. Table 2 shows the mean ($\pm$ SD) of various geometrical measurements of the middle (mid-MC3), proximal, and distal cross sections (Figure 1) for the five groups of horses that were reported in Table 1. The data contained in Table 2 has a large number of significant figures due to the requirements of the statistical tests.

The ANOVA tests produced thirty plots that were then used for comparisons between the foals and the rest of the samples as a single group. Figure 5 shows a plot obtained from the ANOVA test on the measured value of M (width of medial cortex) for the proximal slice. For the rest of the parameters from the different cross sections, the P-values are reported in Table 3. The second ANOVA tests also produced thirty plots that were then used for comparison among the five different groups (i.e. foals, yearlings, two-year-olds, three-year-olds, and adults). As an example,

Figure 6 shows a plot obtained from that ANOVA test on the measured value of P (width of palmar cortex) for the middle slice. For the rest of analysis in this case, the P-values are reported in Table 4.

Table 3 reports the outcome of the ANOVA tests for the geometrical parameters of three cross sections (Figure 1) when the data is compared between two groups (i.e. foals as one group and the rest of the samples as a second group). A significant difference ($P < 0.05$) was observed in Table 3 with the proximal slice for the all geometrical parameters except for M_d and M_l . As such, for those parameters, differences between foals and the rest of the bones are significant. The reported P-values for the distal slice (column three in Table 3) are mostly higher than those reported for the proximal and middle slices. This indicates that significant differences for the geometrical parameters are generally observed for the proximal and middle cross-sectional area when foals are compared with the rest of the bone samples. k presents a measure of converging-diverging shape configuration for the measured geometrical parameters. The reported P-values for k in Table 3 indicate a significant converging-diverging shape configuration for D, H, and cortical area when the foals are compared with the rest of the bones. However, no significant change was observed for the measured values of P, M_d , L, M_l and V.

To investigate whether there was a wide diversity in the measured geometrical parameters within the studied group of ages, another ANOVA test was performed. Table 4 reports the outcome of the ANOVA tests for the geometrical parameters of three cross sections when the data is compared between five groups (i.e. foals, yearlings, two-year-olds, three-year-olds, and adults). A significant difference ($P < 0.05$) was observed in Table 4 with the proximal and middle slices for the all geometrical parameters except for M_d , M_l and Index. The reported P-values for k in Table 4 indicate a significant converging-diverging shape configuration for H, and cortical area when the five groups are compared.

Overall, the calculated least square means for the P-values presented in Table 3 (0.27) are less than those reported in Table 4 (0.38). This indicates slightly larger changes in the measured parameters when foals are compared against the rest of the group.

4. Discussion

The mechanical properties of a bone (stiffness and strength, for example) are dependent on the overall anatomical geometry and the bone size and shape. The strains recorded on the dorsal surface of MC3 during exercise were shown to be linearly related to exercise speed and differed between individual horses (Davies, 2002). The differences in strains were further demonstrated to be significantly related to

Table 2. Mean ($\pm$ standard deviation) measurements of a range of different geometrical parameters taken from three cross sections (i.e. proximal, middle, and distal slices) of the third metacarpal bones of horses.¹

	Age groups	Proximal slice	Middle slice	Distal slice
D (mm)	Foal	7.011 $\pm$ 2.021	5.8557 $\pm$ 1.3341	5.8670 $\pm$ 1.6276
	Yearling	10.9247 $\pm$ 0.9137	10.1460 $\pm$ 1.1078	7.8770 $\pm$ 1.0505
	Two-year-old	12.4964 $\pm$ 2.0255	11.1474 $\pm$ 1.6741	8.4820 $\pm$ 1.6243
	Three-year-old	13.9142 $\pm$ 4.3463	12.9560 $\pm$ 5.01061	11.0697 $\pm$ 5.5142
	Adult	12.7025 $\pm$ 1.1725	11.3458 $\pm$ 1.3552	9.6128 $\pm$ 0.5937
P (mm)	Foal	4.258 $\pm$ 1.305	3.8087 $\pm$ 1.066	4.0407 $\pm$ 1.4410
	Yearling	6.0465 $\pm$ 1.1888	5.9265 $\pm$ 1.0437	5.1851 $\pm$ 0.8072
	Two-year-old	7.3024 $\pm$ 0.6365	6.5026 $\pm$ 0.8514	5.5296 $\pm$ 0.8243
	Three-year-old	7.0562 $\pm$ 0.7941	7.0330 $\pm$ 0.7162	5.7125 $\pm$ 0.9609
	Adult	8.2946 $\pm$ 1.0891	7.1611 $\pm$ 1.0865	5.7771 $\pm$ 1.4142
M _d (mm)	Foal	11.841 $\pm$ 0.588	13.3972 $\pm$ 0.782	13.8935 $\pm$ 1.5913
	Yearling	11.0711 $\pm$ 1.2050	12.1526 $\pm$ 0.8158	15.2343 $\pm$ 1.4200
	Two-year-old	11.1392 $\pm$ 1.2616	12.1782 $\pm$ 1.3470	15.0120 $\pm$ 1.5939
	Three-year-old	12.1327 $\pm$ 1.8781	13.0737 $\pm$ 1.9827	15.6762 $\pm$ 2.8732
	Adult	10.6388 $\pm$ 1.695	12.9541 $\pm$ 2.8023	14.3095 $\pm$ 1.1621
M (mm)	Foal	6.776 $\pm$ 3.601	5.8560 $\pm$ 1.6448	6.7815 $\pm$ 3.14769
	Yearling	9.6318 $\pm$ 1.6394	9.5273 $\pm$ 1.5706	9.0573 $\pm$ 1.4268
	Two-year-old	11.3064 $\pm$ 1.4647	10.2988 $\pm$ 0.5637	9.6654 $\pm$ 0.8896
	Three-year-old	13.4822 $\pm$ 0.3395	13.1372 $\pm$ 0.9947	12.7810 $\pm$ 0.6238
	Adult	12.2231 $\pm$ 0.6497	12.4505 $\pm$ 0.7239	11.3871 $\pm$ 0.9127
L (mm)	Foal	6.502 $\pm$ 1.757	5.9850 $\pm$ 2.8877	5.8230 $\pm$ 1.3227
	Yearling	11.0841 $\pm$ 1.4924	11.1346 $\pm$ 2.0299	10.8101 $\pm$ 2.1996
	Two-year-old	10.5372 $\pm$ 1.3414	10.9818 $\pm$ 1.7169	10.1752 $\pm$ 1.1363
	Three-year-old	11.7075 $\pm$ 1.8276	11.14225 $\pm$ 2.1676	10.0737 $\pm$ 1.7680
	Adult	12.6858 $\pm$ 2.5054	11.2210 $\pm$ 1.6281	11.6178 $\pm$ 2.6653
M _l (mm)	Foal	14.626 $\pm$ 2.196	16.1000 $\pm$ 1.4423	16.7130 $\pm$ 1.8902
	Yearling	15.2233 $\pm$ 1.9768	15.0360 $\pm$ 1.9864	17.4668 $\pm$ 2.3030
	Two-year-old	14.6348 $\pm$ 2.4398	15.3338 $\pm$ 2.4145	18.6506 $\pm$ 2.7751
	Three-year-old	15.1915 $\pm$ 3.4831	15.9280 $\pm$ 3.1808	18.9172 $\pm$ 3.7021
	Adult	14.0371 $\pm$ 1.7358	14.9283 $\pm$ 3.5339	16.9511 $\pm$ 0.5147
H (mm)	Foal	23.111 $\pm$ 2.725	23.0617 $\pm$ 2.3182	23.8012 $\pm$ 1.4892
	Yearling	28.0423 $\pm$ 1.2730	28.2251 $\pm$ 0.8709	28.2965 $\pm$ 1.1200
	Two-year-old	30.9380 $\pm$ 1.7557	29.8282 $\pm$ 1.3109	29.0236 $\pm$ 1.0830
	Three-year-old	33.1032 $\pm$ 2.7891	33.0627 $\pm$ 3.0343	32.4585 $\pm$ 3.3173
	Adult	31.6360 $\pm$ 0.5006	31.4611 $\pm$ 0.7458	29.6995 $\pm$ 1.5929
V (mm)	Foal	27.905 $\pm$ 3.487	27.9410 $\pm$ 4.7095	29.3175 $\pm$ 2.5883
	Yearling	35.9393 $\pm$ 1.3898	35.6980 $\pm$ 1.4840	37.3343 $\pm$ 1.6480
	Two-year-old	36.4784 $\pm$ 1.0684	36.6144 $\pm$ 1.6307	38.4912 $\pm$ 2.3542
	Three-year-old	40.3812 $\pm$ 2.1268	40.2075 $\pm$ 2.6292	41.7720 $\pm$ 2.7986
	Adult	38.9461 $\pm$ 2.9075	38.5998 $\pm$ 2.4789	39.9561 $\pm$ 1.7864
Index	Foal	1.594 $\pm$ 0.54	1.1366 $\pm$ 0.3553	1.0763 $\pm$ 0.3961
	Yearling	2.8431 $\pm$ 0.4855	2.3442 $\pm$ 0.5705	1.3308 $\pm$ 0.2878
	Two-year-old	3.1341 $\pm$ 0.9469	2.5490 $\pm$ 0.6699	1.4975 $\pm$ 0.4910
	Three-year-old	3.8565 $\pm$ 2.7115	3.4181 $\pm$ 2.9931	2.6762 $\pm$ 2.8106
	Adult	3.1333 $\pm$ 0.6877	2.3857 $\pm$ 0.6058	1.8282 $\pm$ 0.1506
Area (mm ²)	Foal	413.047 $\pm$ 134.09	363.5850 $\pm$ 130.7902	389.3175 $\pm$ 123.18046
	Yearling	723.0433 $\pm$ 37.914	670.2833 $\pm$ 36.7173	631.8233 $\pm$ 39.1536
	Two-year-old	803.1220 $\pm$ 56.636	746.0560 $\pm$ 61.5855	688.0360 $\pm$ 48.5710
	Three-year-old	962.3350 $\pm$ 75.799	896.1000 $\pm$ 70.4939	815.5950 $\pm$ 73.8670
	Adult	901.7233 $\pm$ 90.342	806.2850 $\pm$ 79.51404	765.7100 $\pm$ 100.6643

¹ The individual horses are specified in Table 1.

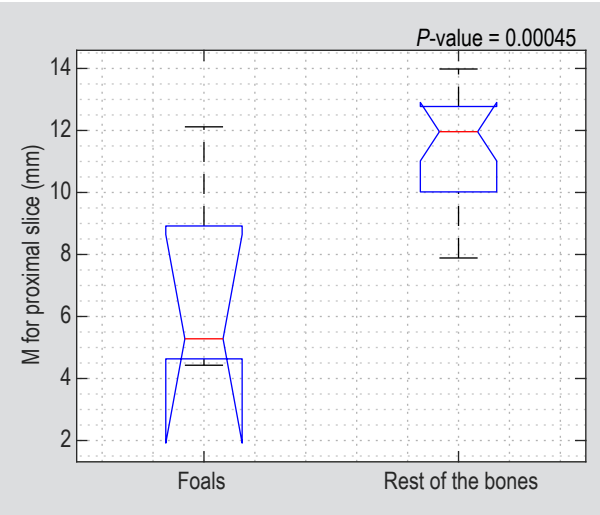


Figure 5. Output of the ANOVA test to compare the measured width of the medial cortex (M for the proximal slice) between foal bones and the rest of the MC3 bones. The *P*-values for the rest of the parameters are reported in Table 3.

bone size at the midshaft of MC3 (Davies, 2001a). The midshaft of MC3 is a region of considerable interest to comprehend shape-dependent mechanical responses of bones. A recent study in our research group has discussed creating reliable 3D models and performing accurate finite element analysis of the MC3 (Mouloudi *et al.*, 2019). The width of the dorsal cortex (D), palmar cortex (P), and lateral cortex (L) significantly changed with maturation (comparison between foals and the rest of the samples, Table 3). This was true for the all cross sections that were considered in this study (i.e. proximal, middle, and middle slices). It is worth introducing the exercise history of horses as a factor in ANOVA tests for future studies to investigate changes in the geometrical parameters due

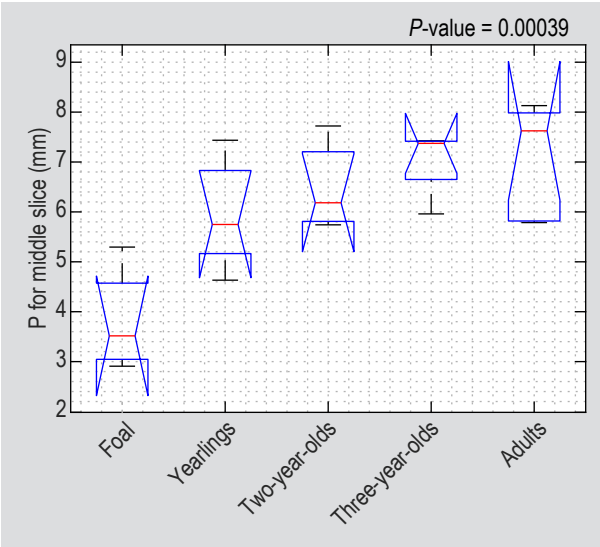


Figure 6. Output of the ANOVA test to compare the measured width of the palmar cortex (for the middle slice) between five different groups. The *P*-values for the rest of the parameters are reported in Table 4.

to exercise history. The mean values of D, P, M, and L (Supplementary Figures S1, S2, S4, S5) for all three cross sections of foals were lower than those for the other four groups (i.e. yearlings, two-year-olds, three-year-olds, and adults). These values for the foals also demonstrated a converging-diverging shape configuration. This trend was also observed for the values of cortical area in the foal samples (Figure 2) where they were lower than those for the rest of the group samples. The significance of these changes is presented in Tables 3 and 4. Similarly, the mean values of the index for foals were lower than those reported for the other samples (Table 2).

Table 3. The *P*-values were obtained from the ANOVA test (comparison between two groups, i.e. foals compared to the rest of the samples as a single group) for the geometrical parameters of three cross sections (i.e. proximal, middle, and distal slices).¹

Parameter	Proximal slice	Middle slice	Distal slice	k	Least square mean
D	0.0003*	0.0003*	0.0261*	0.0095*	0.0139*
P	0.0003*	0.0000*	0.0171*	0.1745	0.0877
M _d	0.3856	0.3803	0.2372	0.1924	0.3109
M	0.0005*	0.0000*	0.0018*	0.0650	0.0325*
L	0.0001*	0.0001*	0.0001*	0.8763	0.4382
M _l	0.9275	0.5389	0.3674	0.1111	0.5696
H	0.0000*	0.0000*	0.0001*	0.0213*	0.0107*
V	0.0000*	0.0000*	0.0000*	0.5653	0.2827
Index	0.0221*	0.0413*	0.2816	–	0.1648
Cortical area	0.0000*	0.0000*	0.0000*	0.0001*	0.0001*
					0.27

¹ Significant differences (*P*<0.05) between the two groups are indicated with an asterisk.

Table 4. The *P*-values were obtained from ANOVA tests (comparison between five groups, i.e. foals, yearlings, two-year-olds, three-year-olds, and adults) for the geometrical parameters from three cross sections (i.e. proximal, middle, and distal slices).¹

Parameter	Proximal slice	Middle slice	Distal slice	k	Least square mean
D	0.0021*	0.0038*	0.0588	0.0816	0.0503
P	0.0001*	0.0004*	0.1791	0.5554	0.2918
M _d	0.4918	0.7526	0.5573	0.2207	0.5403
M	0.0002*	0.0000*	0.0002*	0.2922	0.1461
L	0.0009*	0.0047*	0.0033*	0.7247	0.3624
M _l	0.9114	0.9441	0.5300	0.5410	0.7576
H	0.0000*	0.0000*	0.0000*	0.0005*	0.0003*
V	0.0000*	0.0000*	0.0000*	0.9855	0.4928
Index	0.1605	0.2041	0.3199	–	0.2379
Cortical area	0.0000*	0.0000*	0.0000*	0.0002*	0.0001*
					0.38

¹ Significant differences (*P*<0.05) between the two groups are indicated with an asterisk.

MC2 and MC4 (the splint bones) occur along the long axis of MC3 in equine forelimbs (Figure 7). These bones have a strong fibrous union with the MC3 that frequently becomes ossified (Dyce *et al.*, 1987). If MC2 and MC4 fuse with MC3, the bending strength and rigidity are significantly increased (Piotrowski *et al.*, 1983). If there is no fusion, then these bones will slide very slightly against the MC3 bone due to the fibrous tissue between them. Thus, including MC2 and MC4 in the analysis changes the computed stresses and area properties of the metacarpal bone. These bones substantially affect the properties of the section. This further emphasises the significance of

shape in the responses of bones to loading, and this has been discussed in the recent literature (Liley *et al.*, 2017b, 2018). However, the geometric influence of MC2 and MC4 was not examined in previous studies (Nunamaker *et al.*, 1989; Rubin *et al.*, 2013). Investigations of the force on MC3 indicate that the dominant loading at various gaits and speeds is compression (Merritt *et al.*, 2010). With structures loaded in compression (like MC3), buckling is of concern. For a column simply supported at both ends, the fundamental buckling formula for calculating critical buckling load is given by:

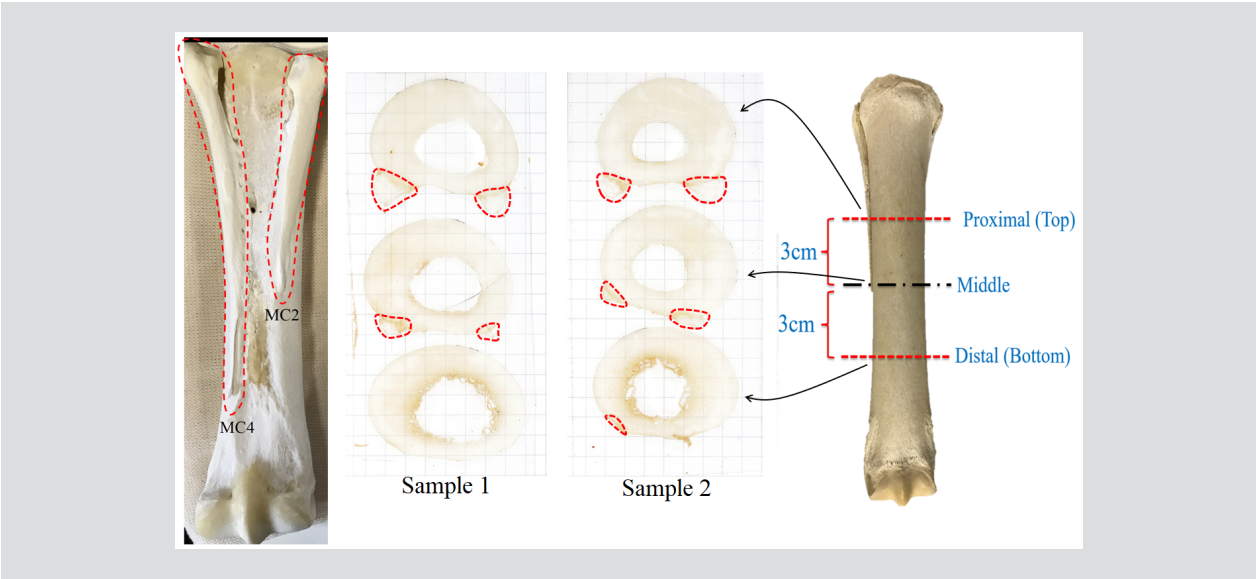


Figure 7. Fusion of the second and fourth metacarpal bone (MC2 and MC4) with the MC3 will alter the geometric properties of the third metacarpal bone. In the two samples, the left dashed line regions correspond to MC4 and the right dashed line regions correspond to MC2.

$$P_{\text{Critical}} = \frac{\pi^2 EI}{L^2} \quad (2)$$

where, E is the modulus of elasticity, I is area moment of inertia, and L is the length of the MC3. In order to quantify the area moment of inertia in this equation, the values of geometrical parameters investigated in this study are essential parameters and have substantial influence on the critical loading predictions for the MC3. The mechanical properties of materials are substantially influenced by size and shape (Mouloudi *et al.*, 2014a,b) and performing accurate 3D models of the MC3 is critically important prior to publishing outcomes (Mouloudi *et al.*, 2019). Increased exercise appears to increase the bone midshaft cross sectional size rather than alter its material quality (Davies, 1995). The peak locomotory strains on the dorsal surface of MC3 have been shown to be dependent on the bone shape and size (Davies, 2001a; Liley *et al.*, 2017b). The amount of bone modelling response to a specific level of exercise should therefore be related to the bone size and shape.

Although more sophisticated tools, such as finite element method, are widely employed for the stress and strain analysis of complex structures (Gohari *et al.*, 2019), beam models are often used since they provide valuable insight into the behaviour of structures. As Budynas *et al.* (2015) reported, 'Many structures must often be treated as beams in the design and analysis of mechanical structures and systems'. Normal and shear stresses act over cross sections of a beam. The dominant loading on the MC3 at various gaits and speeds is compression (Mouloudi *et al.*, 2019) which can cause bending stresses at the midshaft of MC3. The longitudinal strain in a beam is given by (Bauchau and Craig, 2009; Budynas and Nisbett, 2008):

$$\epsilon = \frac{-y}{R} \quad (3)$$

where R is the radius of curvature (1/R represents the curvature of a beam subjected to bending moment). The relation for calculating 1/R (which is equal to k) was given in Equation 1. y is the distance of a point on the cross section from the neutral axis. Equation 3 implies that a small R (a large curvature) is related to a large strain and subsequently a large stress. An existing curvature (a converging-diverging shape for parameter V in the midshaft of the MC3) would decrease the resistance of MC3 to bending because the radius of curvature increases more easily within the deflected MC3 beam when it is loaded. Additionally, MC3 beams with smaller cross-sections (specifically smaller second moment of area for the middle slice) experience more stresses and will fail at lower bending loads. Data presented in this study will assist in finding an optimised and desirable shape configuration of the MC3 beam within its midshaft. Minimising the curvature and avoiding a

converging-diverging shape of cross sections might be a reasonable starting point as long as various types of MC3 loads on different orthogonal planes are considered. Lack of exercise for foal samples in this study illustrated the least area, dorsal cortex, palmar cortex, medial cortex, lateral cortex, and shape index of cross sections in the bone midshaft, which revealed a converging-diverging shape from the proximal slice to the distal one. However, for horses with a regular training background, remodelling caused a different trend. The previous training history for two-year-old and three-year-old horses was unknown, yet none of the yearling horses (Y1 to Y6) had been specifically exercised or trained except for the few days to a week immediately before death which should be before such constrained exercise would have had any substantial effects on the bone shape. The current study aimed to provide equine population-based data of bone size and shape, age, and exercise history, since the details of exercise regimen prior to assessments are usually unknown in the literature (Firth, 2004). Measurements of bone quality, shape and size across the mid shaft of MC3 are crucial in comprehending the bone modelling responses to loading.

5. Conclusions

Previous research showed that bone as a complex biological material is stimulated to change shape when the individual ages. Yet, it is not exactly clear which geometrical parameters in a cross section of the MC3 are subjected to change during maturation. Neither is the degree by which they change properly explained. In this study, a significant difference was observed among five groups (foals, yearlings, two-year-olds, three-year-olds, and adults) for the values of cortical area, the width of the dorsal cortex, palmar cortex, medial cortex, and lateral cortex. However, no significant change was observed for the measured values of the width of the medulla in dorsopalmar plane and that of the medulla in lateromedial plane. Second, the curvature of the two-degree polynomial functions that were fitted to the plots of geometrical parameters (a measure of converging-diverging shape configuration) was different between foals and the rest of the bones, and it had significant changes for the cortical area, the width of the dorsal cortex, and H (i.e. the summation of the widths of the dorsal cortex, the medulla in dorsopalmar plane, and the palmar cortex). Third, the mean values of cortical area, shape index, the width of the dorsal cortex, palmar cortex, medial cortex, and lateral cortex for all three cross sections of foals were lower than those reported for the other four groups. These geometrical parameters for the foals (except the shape index) demonstrated a converging-diverging shape configuration. Insight into the changes of the studied geometrical parameters will assist in determining the effects of maturation and exercise history on bone modelling around the midshaft of the MC3.

Supplementary material

Supplementary material can be found online at <https://doi.org/10.3920/CEP190010>.

Figure S1. Variations of the width of the dorsal cortex of the MC3 bones from proximal slice to the distal one.

Figure S2. Variations of the width of the palmar cortex of the MC3 bones from the proximal slice to the distal one.

Figure S3. Variations of the width of the medulla in the dorsopalmar plane of the MC3 bones from the proximal slice to the distal one.

Figure S4. Variations of the width of the medial cortex of the MC3 bones from the proximal slice to the distal one.

Figure S5. Variations of the width of the lateral cortex of the MC3 bones from the proximal slice to the distal one.

Figure S6. Variations of the width of the medulla in the lateromedial plane of the MC3 bones from the proximal slice to the distal one.

References

- Bauchau, O.A. and Craig, J.I., 2009. Euler-Bernoulli beam theory. In: Bauchau, O.A. and Craig J.I. (eds.) *Structural analysis*. Springer Netherlands, Dordrecht, the Netherlands, pp. 173-221. https://doi.org/10.1007/978-90-481-2516-6_5
- Boden, L., Anderson, G., Charles, J., Morgan, K., Morton, J., Parkin, T., Slocombe, R. and Clarke, A., 2006. Risk of fatality and causes of death of Thoroughbred horses associated with racing in Victoria, Australia: 1989-2004. *Equine Veterinary Journal* 38: 312-318.
- Budynas, R.G. and Nisbett, J.K., 2008. *Shigley's mechanical engineering design*, 8. McGraw-Hill, New York, NY, USA.
- Budynas, R.G., Nisbett, J.K. and Shigley, J.E., 2015. *Shigley's mechanical engineering design*. McGraw-Hill, New York, NY, USA.
- Couch, S. and Nielsen, B., 2017. A review of dorsal metacarpal disease (bucked shins) in the flat racing horse: prevalence, diagnosis, pathogenesis, and associated factors. *Journal of Dairy, Veterinary and Animal Research* 5: 228-236.
- Davies, H., 2001a. The relationship between surface strain and measurements of bone quality, quantity and shape. *Equine Veterinary Journal Suppl.* 33: 16-20.
- Davies, H., 2001b. Relationships between third metacarpal bone parameters and surface strains. *Equine Veterinary Journal* 33: 16-20.
- Davies, H., 2002. Dorsal metacarpal cortex ultrasound speed and bone size and shape. *Equine Veterinary Journal* 34: 337-339.
- Davies, H., 2005. The timing and distribution of strains around the surface of the midshaft of the third metacarpal bone during treadmill exercise in one Thoroughbred racehorse. *Australian Veterinary Journal* 83: 157-162.
- Davies, H., 2006. Estimating peak strains associated with fast exercise in Thoroughbred racehorses. *Equine Veterinary Journal* 38: 383-386.
- Davies, H. and McCarthy, R., 1994. Strain in the yearling equine metacarpus during locomotion. *Equine Veterinary Journal Suppl.* 17: 25-28.
- Davies, H. and Watson, K., 2005. Third metacarpal bone laterality asymmetry and midshaft dimensions in Thoroughbred racehorses. *Australian Veterinary Journal* 83: 224-226.
- Davies, H.M.S., 1995. The adaptive response of the equine metacarpus to locomotory stress. PhD-thesis, University of Melbourne, Melbourne, Australia.
- Davies, H.M.S. and Merritt, J.S., 2004. Surface strains around the midshaft of the third metacarpal bone during turning. *Equine Veterinary Journal* 36: 689-692. <https://doi.org/10.2746/0425164044848109>
- Dyce, K., Sack, W. and Wensing, G., 1987. *Veterinary anatomy*. W.B. Saunders Co., Philadelphia, PA, USA.
- Firth, E., 2004. Problems in quantifying bone response to exercise in horses: a review. *New Zealand Veterinary Journal* 52: 216-229.
- Gohari, S., Sharifi, S., Burvill, C., Mouloudi, S., Izadifar, M. and Thissen, P., 2019. Localized failure analysis of internally pressurized laminated ellipsoidal woven GFRP composite domes: analytical, numerical, and experimental studies. *Archives of Civil and Mechanical Engineering* 19: 1235-1250.
- Johnson, B., Ardans, A., Stover, S., Daft, B., Kinde, H., Read, D., Barr, B., Moore, J., Woods, L. and Anderson, M., 1994. California racehorse postmortem program: a 4-year overview. In: *Proceedings of the 40th Annual Conference of the American Association of Equine Practitioners*. December 4-7, 1994. Vancouver, British Columbia, Canada, pp. 167-169.
- Kitchen, C.M., 2009. Nonparametric vs parametric tests of location in biomedical research. *American Journal of Ophthalmology* 147: 571-572.
- Liley, H., Davies, H., Firth, E., Besier, T. and Fernandez, J., 2017a. The effect of the sagittal ridge angle on cartilage stress in the equine metacarpo-phalangeal (fetlock) joint. *Computer Methods in Biomechanics and Biomedical Engineering* 20: 1140-1149.
- Liley, H., Zhang, J., Firth, E., Fernandez, J. and Besier, T., 2017b. Using partial least squares regression as a predictive tool in describing equine third metacarpal bone shape. *Computer Methods in Biomechanics and Biomedical Engineering* 20: 1609-1612.
- Liley, H., Zhang, J., Firth, E.C., Fernandez, J.W. and Besier, T.F., 2018. Statistical modeling of the equine third metacarpal bone incorporating morphology and bone mineral density. *PLoS ONE* 13: 1-11. <https://doi.org/10.1371/journal.pone.0194406>
- Loughridge, A., Hess, A., Parkin, T. and Kawcak, C., 2017. Qualitative assessment of bone density at the distal articulating surface of the third metacarpal in Thoroughbred racehorses with and without condylar fracture. *Equine Veterinary Journal* 49: 172-177.
- Maeda, Y., Hanada, M. and Oikawa, M.-A., 2016. Epidemiology of racing injuries in Thoroughbred racehorses with special reference to bone fractures: Japanese experience from the 1980s to 2000s. *Journal of Equine Science* 27: 81-97.
- McKee, S.L., 1995. An update on racing fatalities in the UK. *Equine Veterinary Education* 7: 202-204.

- Merritt, J.S., Pandey, M.G., Brown, N.A., Burvill, C.R., Kawcak, C.E., McIlwraith, C.W. and Davies, H.M., 2010. Mechanical loading of the distal end of the third metacarpal bone in horses during walking and trotting. *American Journal of Veterinary Research* 71: 508-514.
- Mouloudi, S., Khojasteh, J., Salehi, M. and Mohebbi, S., 2014a. Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region. *International Journal of Mechanical Sciences* 85: 160-167. <https://doi.org/10.1016/j.ijmecsci.2014.05.023>
- Mouloudi, S., Mohebbi, S., Khojasteh, J. and Salehi, M., 2014b. Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects. *International Journal of Mechanical Sciences* 79: 162-167. <https://doi.org/10.1016/j.ijmecsci.2013.12.011>
- Mouloudi, S., Rahmanpanah, H., Burvill, C. and Davies, H.M., 2019. Accuracy quantification of the reverse engineering and high-order finite element analysis of equine MC3 forelimb. *Journal of Equine Veterinary Science* 78: 94-106.
- Murray, R.C., Branch, M.V., Dyson, S.J., Parkin, T.D.H. and Goodship, A.E., 2007. How does exercise intensity and type affect equine distal tarsal subchondral bone thickness? *Journal of Applied Physiology* 102: 2194-2200. <https://doi.org/10.1152/jappphysiol.00709.2006>
- Nunamaker, D., 2002. On bucked shins. *Proceedings of the Annual Convention of American Association of Equine Practitioners* 48: 76-89.
- Nunamaker, D., Butterweck, D. and Provost, M., 1989. Some geometric properties of the third metacarpal bone: a comparison between the thoroughbred and standardbred racehorse. *Journal of Biomechanics* 22: 129-134.
- Parkin, T., Clegg, P., French, N., Proudman, C., Riggs, C., Singer, E., Webbon, P. and Morgan, K., 2004. Horse-level risk factors for fatal distal limb fracture in racing Thoroughbreds in the UK. *Equine Veterinary Journal* 36: 513-519.
- Piotrowski, G., Sullivan, M. and Colahan, P., 1983. Geometric properties of equine metacarpi. *Journal of Biomechanics* 16: 129-139.
- Rubin, C.T., Seeherman, H., Qin, Y.-X. and Gross, T.S., 2013. The mechanical consequences of load bearing in the equine third metacarpal across speed and gait: the nonuniform distributions of normal strain, shear strain, and strain energy density. *FASEB Journal* 27: 1887-1894. <https://doi.org/10.1096/fj.12-216804>
- Rubio-Martínez, L.M., Cruz, A.M., Gordon, K. and Hurtig, M.B., 2008. Mechanical properties of subchondral bone in the distal aspect of third metacarpal bones from Thoroughbred racehorses. *American Journal of Veterinary Research* 69: 1423-1433.
- Thomas, G.B. and Finney, R.L., 1984. *Calculus and analytic geometry*. Addison Wesley Publishing Company, Boston, MA, USA.

Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design

S. Mouloudi, H. Rahmanpanah, C. Burvill and H.M.S. Davies

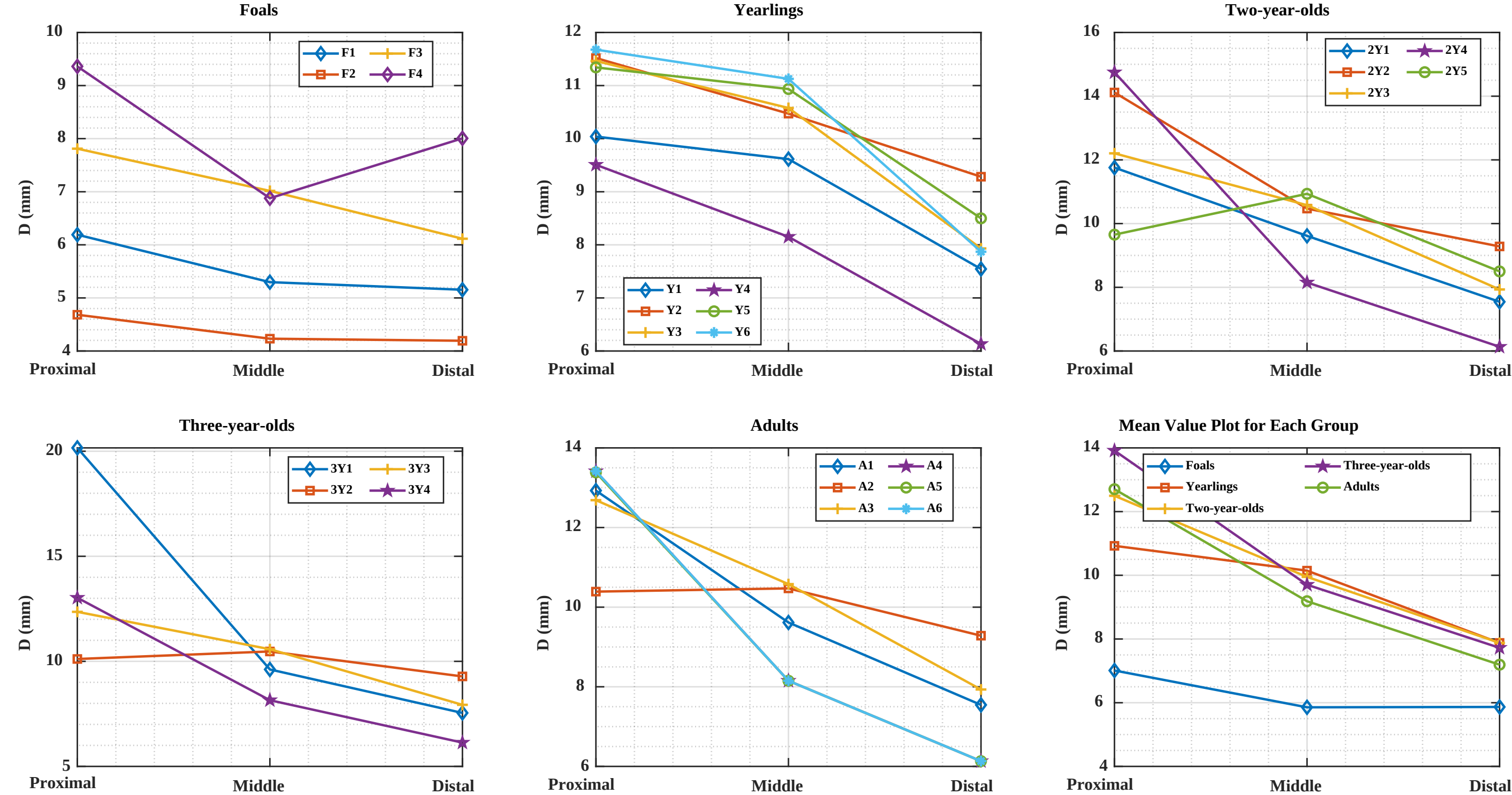


Figure S1. Variations of the width of the dorsal cortex of the MC3 bones from proximal slice to the distal one. Both individual group plots and the plot of mean values are presented. Legend acronyms defined in Table 1.

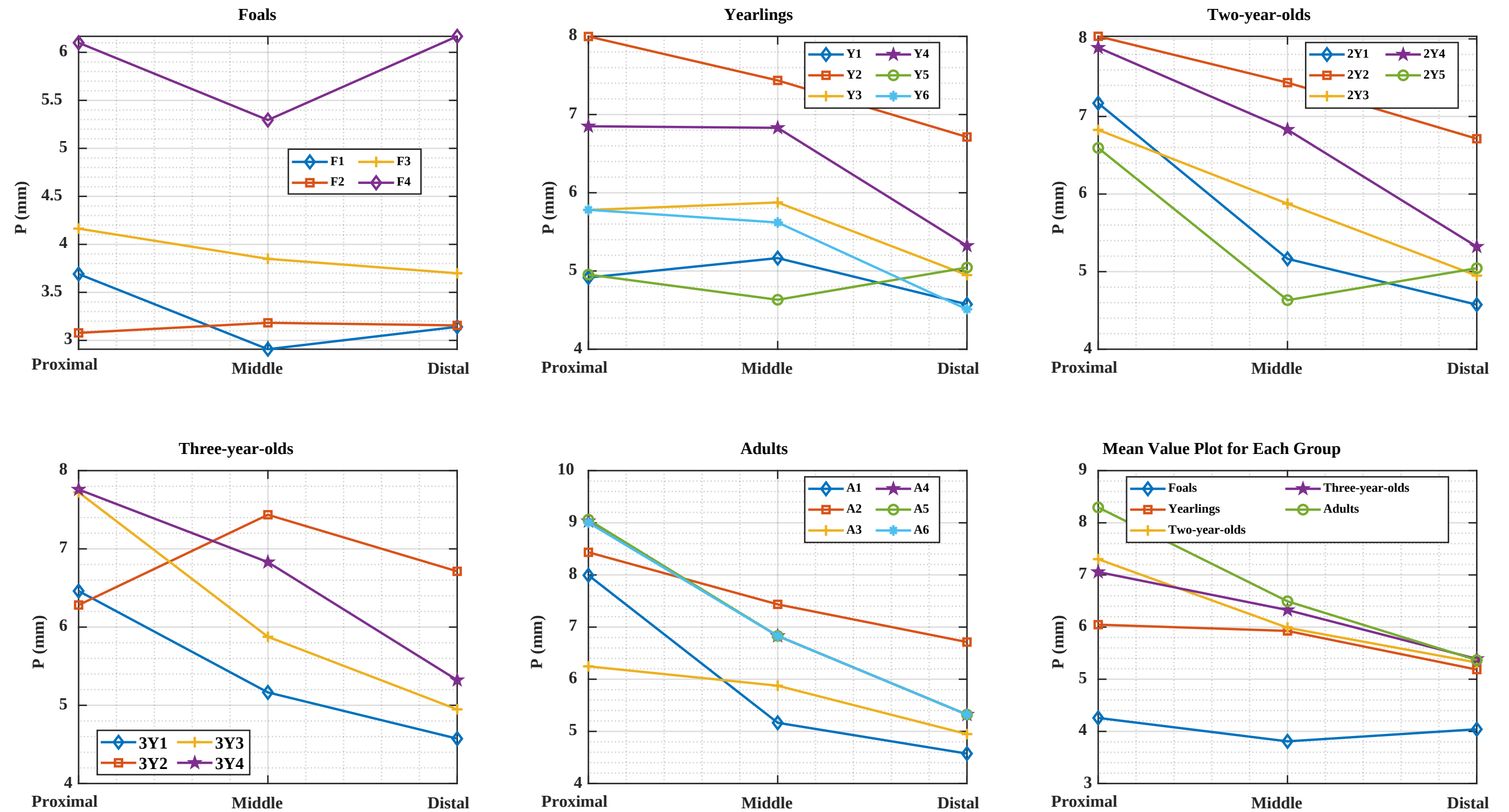


Figure S2. Variations of the width of the palmar cortex of the MC3 bones from the proximal slice to the distal one. Both individual group plots and the plot of mean values are presented. Legend acronyms defined in Table 1.

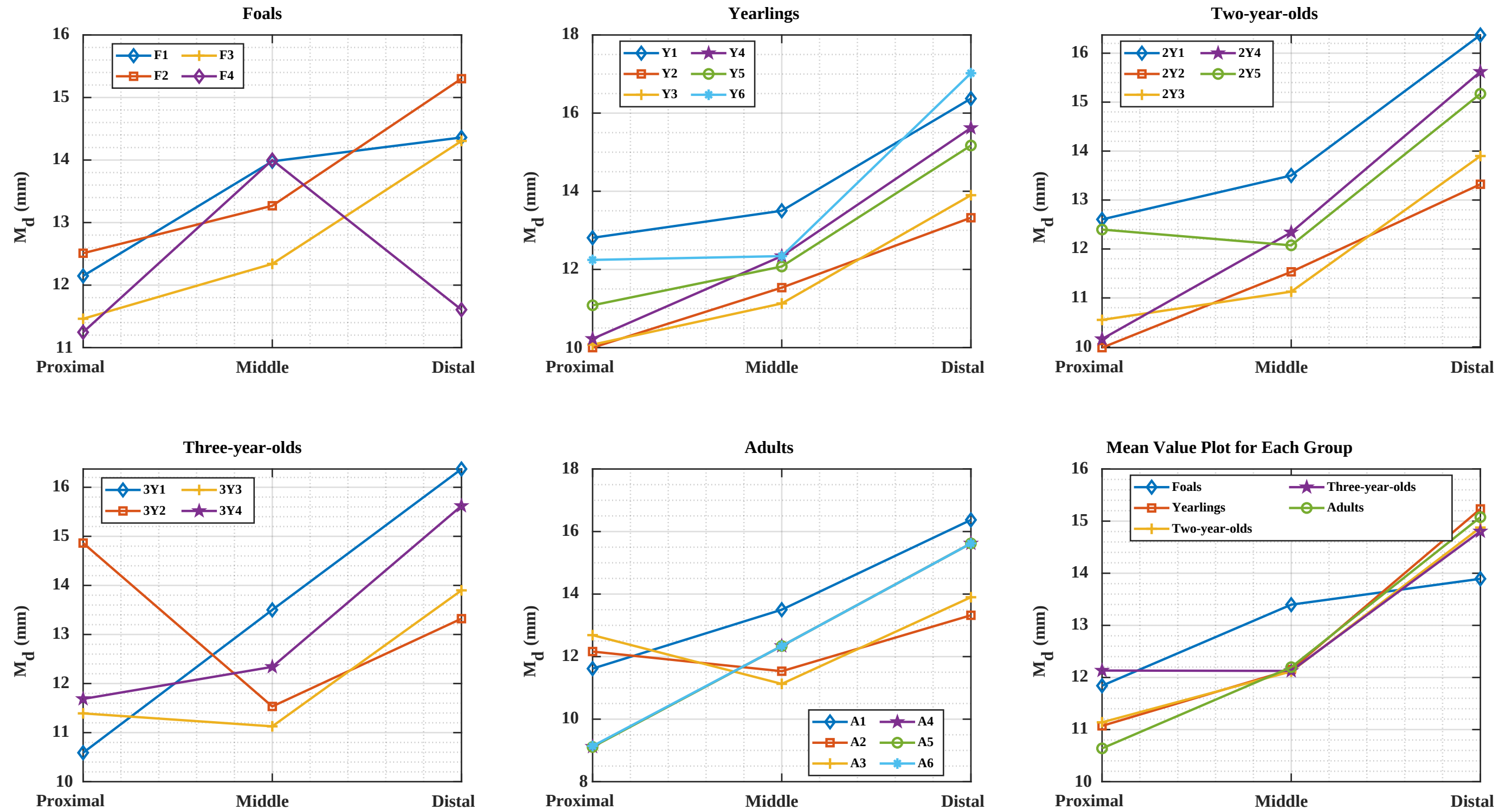


Figure S3. Variations of the width of the medulla in the dorsopalmar plane of the MC3 bones from the proximal slice to the distal one. Both individual group plots and the plot of mean values are presented. Legend acronyms defined in Table 1.

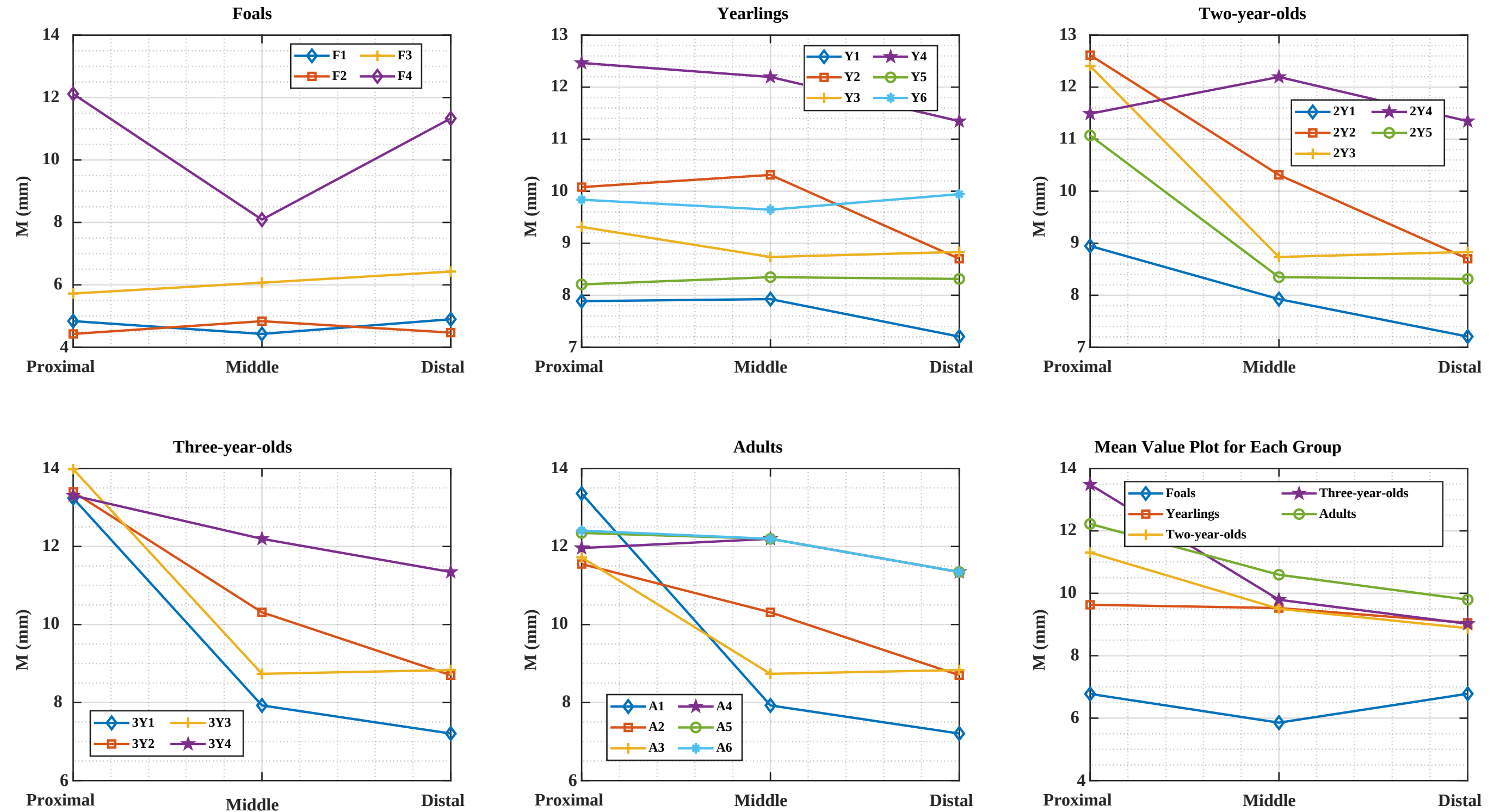


Figure S4. Variations of the width of the medial cortex of the MC3 bones from the proximal slice to the distal one. Both individual group plots and the plot of mean values are presented. Legend acronyms defined in Table 1.

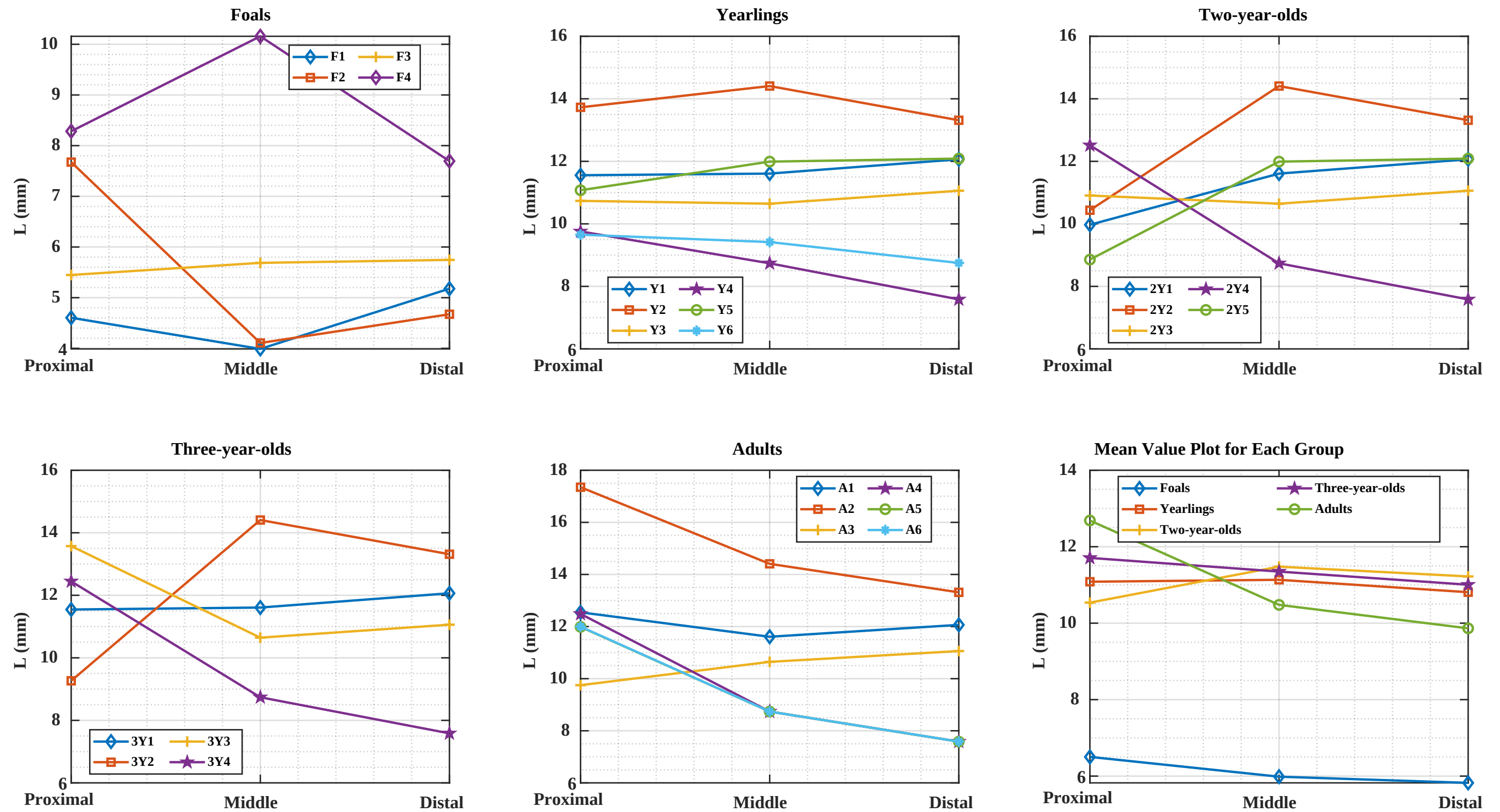


Figure S5. Variations of the width of the lateral cortex of the MC3 bones from the proximal slice to the distal one. Both individual group plots and the plot of mean values are presented. Legend acronyms defined in Table 1.

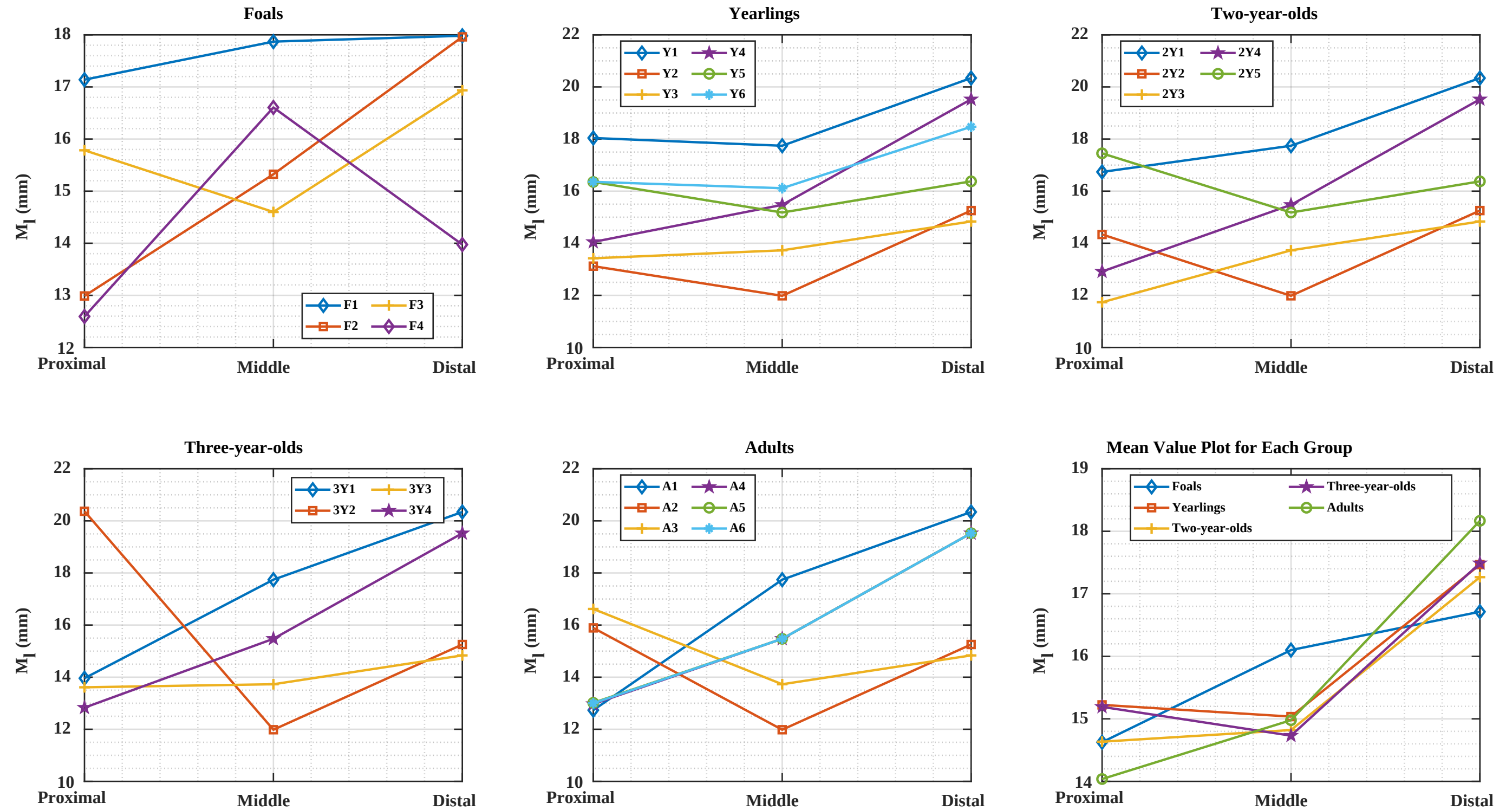


Figure S6. Variations of the width of the medulla in the lateromedial plane of the MC3 bones from the proximal slice to the distal one. Both individual group plots and the plot of mean values are presented. Legend acronyms defined in Table 1.

4.2. Summary and Concluding Remarks

This chapter presented the measurement of a variety of geometrical parameters (using computer-aided-design) in three main cross sections (slices) within the diaphysis of MC3 long bones: cortical area, width of dorsal cortex, palmar cortex, medial cortex, lateral cortex, medulla in dorsopalmar plane, medulla in lateromedial plane, and Shape indices. Then, statistical tools (using ANOVA and t-tests) were used to investigate significant differences of shape and geometrical parameters versus horse age and maturation. Converging-diverging shape configuration of the diaphysis of the equine third metacarpal bone was also investigated. The degree by which these geometrical parameters exhibit significant differences was discussed when the values were compared between five groups (foals, yearlings, two-year-olds, three-year-olds, and adults) and between two groups (foals compared to the rest of the samples as a single group). The midshaft of MC3 is a region to which the strain gauges were attached to record six kinds of strains during ex-vivo experiments and that shaped some of the input variables for the artificial neural networks performed in the subsequent chapters in this thesis (Chapter 5 to Chapter 8, inclusive). Horse age was considered as an input for the artificial neural networks, and this assisted the comprehension of shape- and age-dependent mechanical responses of bones. The study reported in this chapter assisted the author determine optimized shape configurations of the midshaft of long bones. Geometric parameter variation has the potential to inform improved equine training programs where bone damage is better predicted and prevented.

Chapter 5

Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm

The use of a data-driven approach using artificial neural networks is elaborated in this chapter to quantify the displacement occurring on the equine third metacarpal bones (at the whole bone level) and to compare the results with the experimental counterparts. As such, This Chapter reports on a published paper completed by the author and collaborators that investigated the following hypotheses (as discussed in Section 2.6.3):

- **H.7.** Feedforward backpropagation artificial neural networks are suitable techniques to be adopted for solving a forward problem in computational mechanics of equine third metacarpal long bones.
- **H.8.** ANNs substantially reduce the computational time as compared with performing a finite element analysis.
- **H.9.** The ANN models exhibit successful ability in capturing the underlying data (for nonlinear mapping between the space of inputs and output) to predict the displacement of MC3 long bones recorded via ex-vivo experiments, i.e. with coefficient of correlation ($R > 0.99$) for ANNs training and testing as well as $R^2 > 0.98$ when the trained ANNs are employed to make prediction on unseen samples (new datasets that ANNs have not seen before).

5.1. Published Journal Paper

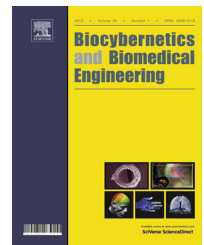
Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Helen M S Davies, Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm, Biocybernetics and Biomedical Engineering (IF: 2.537 as of 2020), 40 (2020) 849-863, <https://doi.org/10.1016/j.bbe.2019.09.001>
(<https://www.sciencedirect.com/science/article/pii/S0208521619301366>)



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Original Research Article

Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm



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ABSTRACT

Bone is a nonlinear, inhomogeneous and anisotropic material. To predict the behavior of bones expert systems are employed to reduce the computational cost and to enhance the accuracy of simulations. In this study, an artificial neural network (ANN) was used for the prediction of displacement in long bones followed by ex-vivo experiments. Three hydrated third metacarpal bones (MC3) from 3 thoroughbred horses were used in the experiments. A set of strain gauges were distributed around the midshaft of the bones. These bones were then loaded in compression in an MTS machine. The recordings of strains, load, load exposure time, and displacement were used as ANN input parameters. The ANN which was trained using 3,250 experimental data points from two bones predicted the displacement of the third bone ($R^2 \geq 0.98$). It was suggested that the ANN should be trained using noisy data points. The proposed modification in the training algorithm makes the ANN very robust against noisy inputs measurements. The performance of the ANN was evaluated in response to changes in the number of input data points and then by assuming a lack of strain data. A finite element analysis (FEA) was conducted to replicate one cycle of force-displacement experimental data (to gain the same accuracy produced by the ANN). The comparison of FEA and ANN displacement predictions indicates that the ANN produced a satisfactory outcome within a couple of seconds, while FEA required more than 160 times as long to solve the same model (CPU time: 5 h and 30 min).

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1. Introduction

Research in the material modelling of expert systems aims to introduce mathematical models and to describe relationships between variable parameters and material properties. Bone as a complex biological material is stimulated to change shape when it experiences changes in the compressive strain distribution. Modelling the behaviour of this multi-variable advanced material is a daunting task. Nonetheless, a proper prediction of bones responses under load is crucial to understand their behavior, avoid incidents that otherwise result in failures, and to develop strategies for injury prevention [1]. Using novel techniques to fulfil such predictions will rapidly and accurately [2] elucidate bone adaptation [3], fracture load [4], and micromorphological parameters in bones [5]. Due to high clinical demands, the prevention of failure, and the prediction of fractures in bones, subject-specific models are becoming increasingly important [6–9]. In order to facilitate the creation of such realistic computational-based models, employing advanced technologies and tools such as computed tomography (CT), magnetic resonance imaging (MRI), finite element analysis (FEA), and artificial neural networks (ANNs) are essential. As John Curry reported, “The advancement in bone mechanics was driven not by deep theoretical insights, but by advances in techniques” [10].

ANNs have been used to estimate loading conditions in joint contact models [11], simulate damage accumulation in bones [12], investigate trabecular bone adaptation and multi-scale bone remodelling [13,14], and predict load from the bone density distribution [15]. However, to date ANNs have not been used for the prediction of load, displacement, and strains in the equine forelimb, which represents an expert system. New tools such as FEA and ANNs may still be unfamiliar to readers interested in the biological systems [16,17], yet they provide extremely valuable information in quantifying the mechanical properties of structures [18,19] and in the prediction of areas of potential failure. ANNs are worth employing as techniques for systems where complex attribute relationships exist among their variables [20]. A long bone, as a multivariable viscoelastic and complex structure, demonstrates highly nonlinear behavior. As such, ANNs are a gold standard method to be employed for the prediction of displacement, load, and mechanical properties in this complex structure. It has also been demonstrated that ANNs are quicker and easier to perform, and as such, have advantageous as computational tools compared with FEA [2,4,21]. This is due to the fact that a considerable time is required to construct stiffness matrices of finite element meshes and to find a solution to the FEA, particularly for models with substantial numbers of nodes and elements, for nonlinear dynamics and contact analysis [21], and for cases where several loading conditions must be examined [22]. In such scenarios, employing an ANN has the merit of reducing computational time, and then the trained ANN provides a reasonable outcome in the prediction of outputs. In addition, it has been shown that an ANN gives a better simulation outcome as compared with an FEA in several engineering practices [23,24]. Most FEA involving the human skeleton and the equine MC3 are subject-specific or rely on

very few samples [25–28]. Thus, alternative approaches are required to be considered and addressed in the literature for predicting the mechanical behaviour of these complex structures. The major advantage of ANNs over conventional methods is that there is no need to comprehend the intrinsic theory of the problem [29], nor is it required to analyse the relationships that are not fully known amongst the variables involved in the models.

ANN or connectionist systems are computing systems vaguely inspired by the biological neural networks that constitute animal brains [30]. This is an information processing paradigm that is inspired by the way biological nervous systems, such as the brain, process information. The key element of this paradigm is the novel structure of the information processing system. An ANN is composed of a large number of highly interconnected processing elements (neurons) working in parallel to solve specific problems. ANNs, like people, learn by example. An ANN is configured for a specific application, such as pattern recognition or data classification, through a learning process.

Currently, the most commonly used type of ANNs is a multilayer feed-forward back-propagation ANN (FF-BP-ANN) due to its structural simplicity, enhanced learning ability, and high predictive performance [31]. In this study, ANNs are trained by applying the Bayesian regularization backpropagation. This method is commonly used in the different disciplines of engineering practice [32–34]. However, to the best knowledge of the authors, the experimental procedure and ANN algorithms investigated in our study have never been discussed in the publicly available literature to predict load-displacement of this advanced biological material.

2. Materials and methods

2.1. Experimental data

This experiment used materials collected from donated cadavers of horses that died for reasons unrelated to this experiment. In this study, 3 third metacarpal bones (B1, B2, and B3) from 3 thoroughbred racehorses with no history of bone disease were used in the *in-vitro* experiments. The horses were all in race training at the time of death. B1 and B2 were 2.4 and 2.5 year old females; B3 was a 1.9 year old gelding. The skins and all soft tissue were removed from the bones except for the periosteum. In order to minimize dehydration, the bones were wrapped separately in a clear plastic wrap and were stored at -9°C until used. The light plastic wrapping was kept throughout the test to maintain hydration and to reduce evaporative loss during the test. Each end of the cleaned bones was embedded in fiberglass impregnated epoxy resin contained in a metal cup, which facilitated a smooth surface onto which the forces could be applied more evenly. Furthermore, to record strains around the midshaft of the MC3 samples, a set of strain gauges, including one rosette strain gauge and three single-element strain gauges, were attached to the lateral, dorsal, and palmar cortices of the bone samples (Fig. 1). A 250 kN load frame with an MTS 430 controller was used to apply compressive loads parallel to the anatomical axis of the bones. The change in the length of the whole bone (displace-

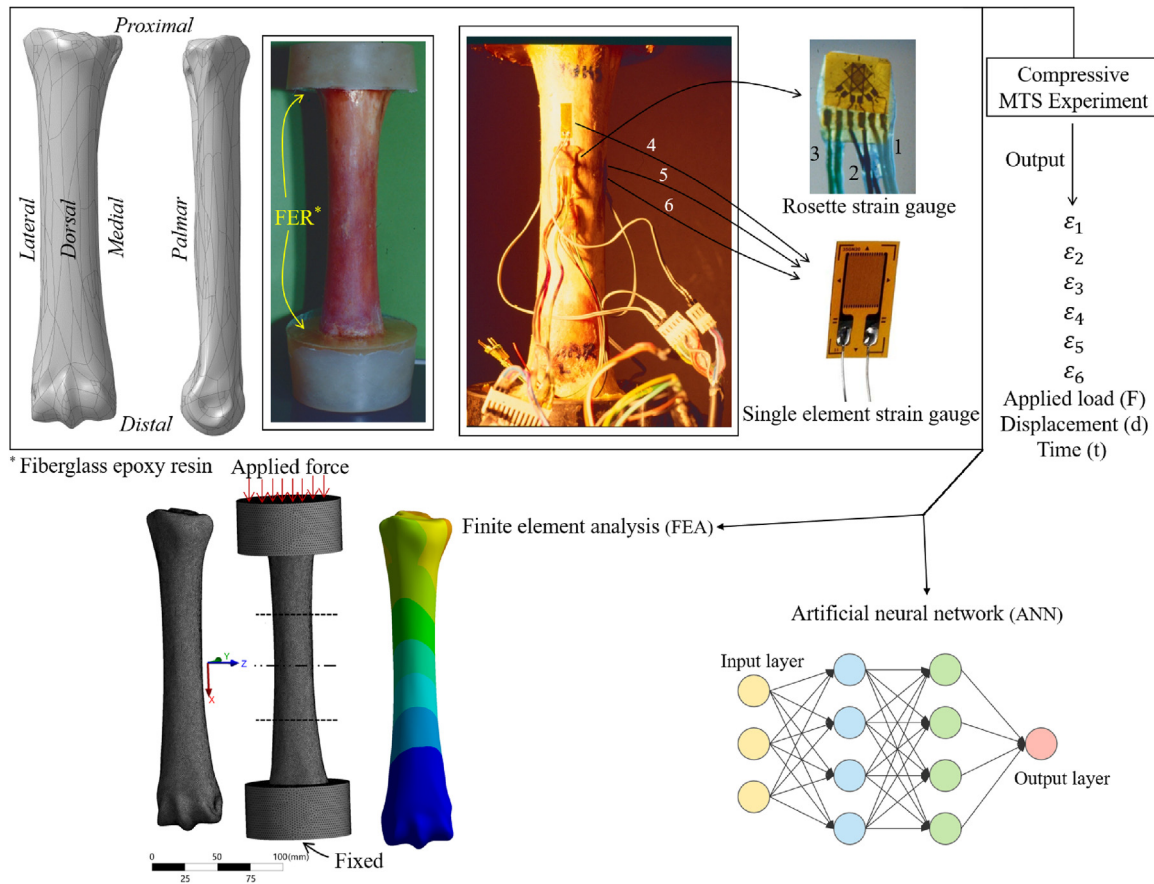


Fig. 1 – The process of bone preparation for the experiments. The output of experiments was imported into MATLAB to train the neural networks and to develop the finite element analysis. The distal and proximal ends of the MC3 bones were surrounded by metal cups into which slow-curing fiberglass resin was poured. An apparatus with the parallel edges exactly perpendicular to the base was designed to ensure maintenance of the vertical position of the bones while the resin was curing. Due to the resin, both ends of the bones became flat parallel surfaces and were perpendicular to the shaft of the bones.

ment of the machine ends), the values of strains, the load being applied onto the samples, and the load exposure time were recorded. The pieces of data obtained from the experimental process were imported into both the ANN and FEA for computer simulation analyses.

2.2. Artificial neural networks

The predominant type of artificial neural network consists of three groups or layers of units. A layer of input units (neurons or nodes) is connected to a layer of hidden units, which is connected to a layer of output units. The number of ANN inputs and outputs determines the numbers of neurons in the input and output layer (Fig. 2). The number of neurons in the hidden layers varies and an optimal number of hidden nodes is found during the training procedure [20].

Each piece of input information has an associated weight, also known as the synaptic weight, which mathematically represents its degree of significance for that neuron. The input signals of the neurons are multiplied by their synaptic weight, and the summation of this result, which is added to the bias,

forms the input information of the neuron. A single neuron model is shown in Fig. 2b. The output y_i^m of the neuron i in a layer m is calculated as:

$$v_i^m = \sum_{j=1}^L w_{ji}^{m-1} y_j^{m-1} + b_i^m \quad (1)$$

$$y_i^m = f(v_i^m) \quad (2)$$

where f is the activation function, L is the number of connections to the previous layer, w_{ji}^{m-1} corresponds to the weights of each connection, and b_i^m is the bias, which represents the constant part in the activation function. The activation function of a node defines the output of that neuron, given an input or set of inputs. This output is then used as an input for the next neuron and so forth until a desired solution to the original problem is found. Amongst activation functions, the sigmoid (logistic) function is the most usually employed in ANN applications. This mathematically is presented as [35]:

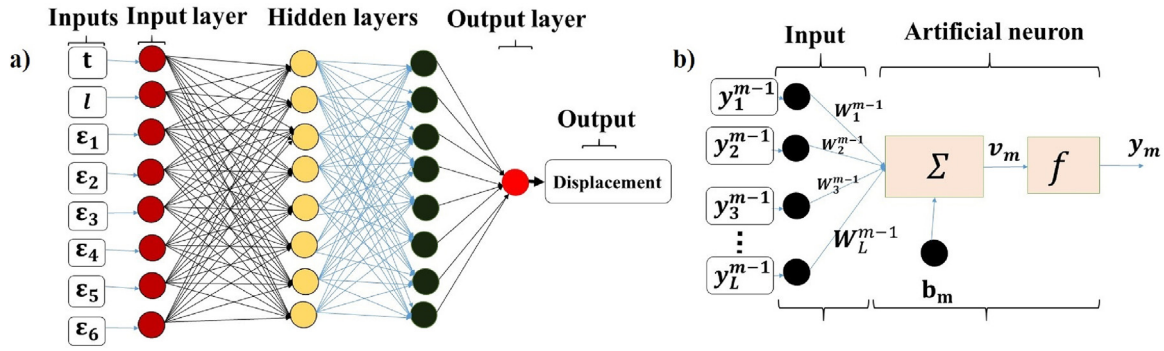


Fig. 2 – (a) Structure of artificial neurons to introduce the feed forward neural network; (b) Architecture of an artificial neuron being tested.

$$f(u_i^m) = \frac{1}{1 + e^{(-\theta u_i^m)}} \quad (3)$$

Training error of the network or the mean squared error (MSE) is defined between the actual output and the value of target and is explained as:

$$E = \frac{1}{2} \sum (t_k - y_k)^2 \quad (4)$$

where t_k and y_k are the target and actual outputs of the k^{th} neuron of the output layer. In order to optimize the performance of the ANN models, a performance factor of the back-propagation neural network is required. Eventually, the MSE between the output of the network and the desired target is calculated as follows:

$$MSE = \frac{1}{m_1 q_{out}} \sum_{m=1}^{m_1} \sum_{k=1}^{q_{out}} e_k^2(m) \quad (5)$$

where q_{out} is the number of neurons of the output layer, and $e_k^2(m)$ is the error of the k^{th} output neuron for the m^{th} weight. To maximize the performance, MSE was minimized with respect to weights and according to the training algorithms in batch or incremental styles.

During the training phase of the ANN, an appropriate knowledge is accumulated using several pieces of input and output data, principles are inserted and introduced to the ANN structure, and the weights and the biases are adapted and tuned (according to the previously determined algorithm) such that the ANN learns to interpret the inputs and to produce desired outputs [36]. Training data is presented to the network during the training step, and the network is adjusted according to its errors. The data split into training, and test data points were performed on a random basis. The test dataset was never used in the training process. Hence, it can be used to assess how the ANN performs for data points other than the ones used for its training.

The input sector had 8 variables, including time, load being applied onto the sample, and strains (Fig. 1). The output of the simulation was the displacement of the bones as a function of the measured inputs:

$$Displacement = f(time, load, \epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5, \epsilon_6) \quad (6)$$

The input and target of the proposed FF-BP-ANN were stored in the matrix of inputs and targets, and then they were inserted into two matrices in the form as follows:

$$Input = [t \quad l \quad \epsilon] \quad (7)$$

$$Target = [d] \quad (8)$$

The inputs matrix was comprised of column vector of time (t), loads (l), and strains (ϵ), while the outputs column was the displacement vector of the samples (d).

$$Inputs = \begin{bmatrix} t_{11} & l_{12} & \epsilon_{13} & \cdots & \epsilon_{16} \\ t_{21} & l_{22} & \epsilon_{23} & \cdots & \epsilon_{26} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ t_{n1} & l_{n2} & \epsilon_{n3} & \cdots & \epsilon_{n6} \end{bmatrix} \quad (9)$$

$$Outputs = \begin{bmatrix} d_1 \\ \vdots \\ d_n \end{bmatrix} \quad (10)$$

where n represents the number of data points. The inputs matrix was comprised of $n \times 8$ pieces of data, representing the ex-vivo measurements. Target is a matrix with the dimension of $n \times 1$. This matrix represents the displacement of the bones which was used for the next sets of training. Afterwards, the ANNs were trained using a training dataset. For this training dataset, both the output and the input were known. The input data was normalized and was introduced to the ANN as a vector. The training of the ANNs was mostly carried out using 80% of the data points. In the ANNs, some regularization techniques were used with the backpropagation training algorithm to obtain a smaller error. This causes the responses of the network to be smoother and less likely to overfit to training patterns [37,38]. To do so, the Bayesian regularization back-propagation was employed. Bayesian regularized artificial neural networks (BRANNs) are more robust than standard back-propagation nets, and as such, can reduce or eliminate the need for a process of cross-validation [39]. However, the Bayesian regularization is a training algorithm which typically requires a considerable solution time. Nonetheless, it is well-

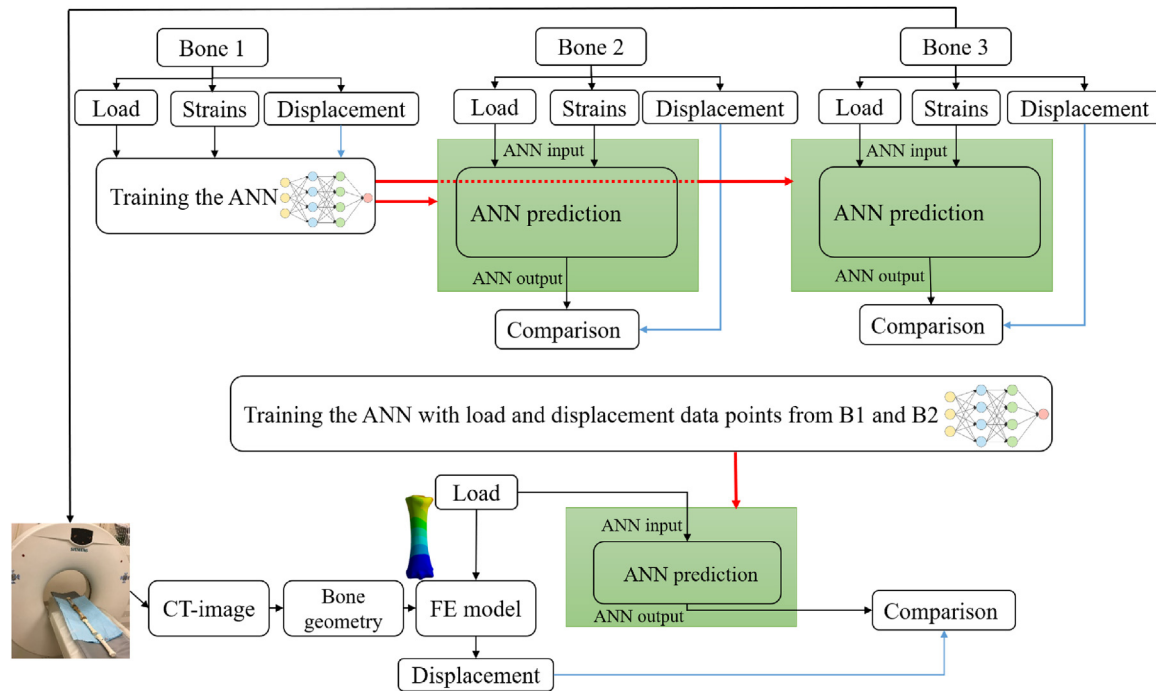


Fig. 3 – Schematic flow chart of the steps involved in the prediction of displacement.

suiting for complex systems or noisy data points. The training stops according to adaptive weight minimization regularization. The remaining 20% of the data points were used to test the trained ANN. The number of neurons in the hidden layers equals the number of the ANN inputs. The ANNs were selected to have 4 hidden layers. The performance of the ANNs were not oversensitive to the number of hidden layers. Neural networks usually do not allow a calculation of standard statistical parameters that are commonly used for the evaluation of a regression analysis of experimental data [40]. Therefore, other methods were used to assess the suitability of the ANN models, namely performance, training state, regression, model error plots, and ANN error histogram.

Fig. 3 schematically presents a flow chart indicating the steps involved in the prediction of displacement via the discussed methods. The ANN was trained using the experimental data points obtained for B1, and then the trained version of the ANN was employed and tested to predict the displacement of B2 and B3. The same process was then completed to predict the displacement of B3 using an ANN that was trained with B1 and B2.

Furthermore, in order to investigate the effects of strains data points on the performance of the ANN, an ANN was trained using B1 and B2 without introducing strains data to the ANN. The trained ANN was then used to predict the displacement of B3. To improve the accuracy of the ANN model the effects of different parameters such as the number of data points, introducing noise to the data, were explored and discussed.

2.3. Finite element analysis (FEA)

An FEA was conducted on B3 to replicate the experimental force-displacement data. B3 was taken for CT imaging using

a SIEMENS CT scanner machine. The DICOM images (slice thickness of 0.75 mm) were imported into 3D slicer software and were segmented to generate volumetric meshes. Eventually, a 3D model of B3 with cups at either end was generated in CAD to replicate the experimental scenario (Fig. 1). The model was imported into ANSYS (Mechanical APDL 19.0 and Workbench 19.0, academic research, The University of Melbourne, Australia) to perform the FEA. Both 10-node quadratic tetrahedron and 20-node quadratic hexahedron elements were assigned to the model. Finite element convergence analysis and a fully automatic adaptive mesh refinement process were completed according to the methods presented in a recent publication by the authors [41] to perform mesh sensitivity and mesh quality assessment and to evaluate the accuracy of the FEA. This minimized FEA error to 0.12% in the smallest number of iterations possible [41]. The MC3 model comprised 3.99 million and 2.84 million of nodes and elements, respectively. Orthotropic mechanical properties were assumed in the FEA (from findings of previous experimental studies), and their values were set to $E_x = 8.92$ GPa, $E_y = 0.45 \times E_x$, $G_{xy} = 0.16 \times E_x$, $\nu_{xy} = 0.36$, and $\nu_{yx} = 0.16$ [26,41, 42]. The results of FEA agreed with those of the experiments (rmse = 0.032 mm). All the simulations were performed using ANSYS 19.0 on 8 cores of an Intel Xeon Gold 3.00 GHz virtual machine with 96 GB RAM.

3. Results and discussion

The results and the associated discussions are presented in four subsections. First, the trained ANN is presented. Second, the outcome of the ANN model in predicting displacement is

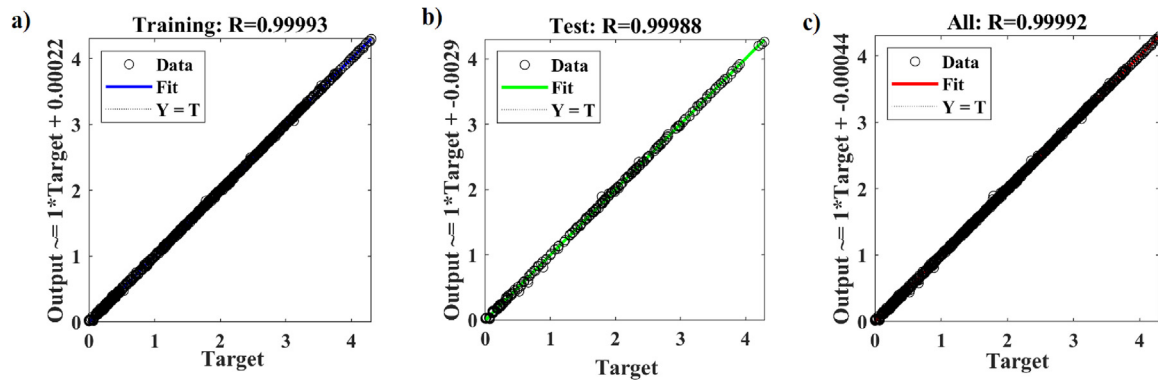


Fig. 4 – The three scatter plots represent: (a) training, (b) testing, and (c) all data points from B1. The dashed line in each plot represents the perfect result which is outputs = targets. The solid line represents the best linear regression fit between outputs of the ANN and its targets (the experimental data points). The value of R is approximately 1, which indicates that there is a perfect linear relationship between the outputs and the targets. The test results show a higher R value as compared with the training data. The scatter plot is helpful in showing that certain data points have poor fits.

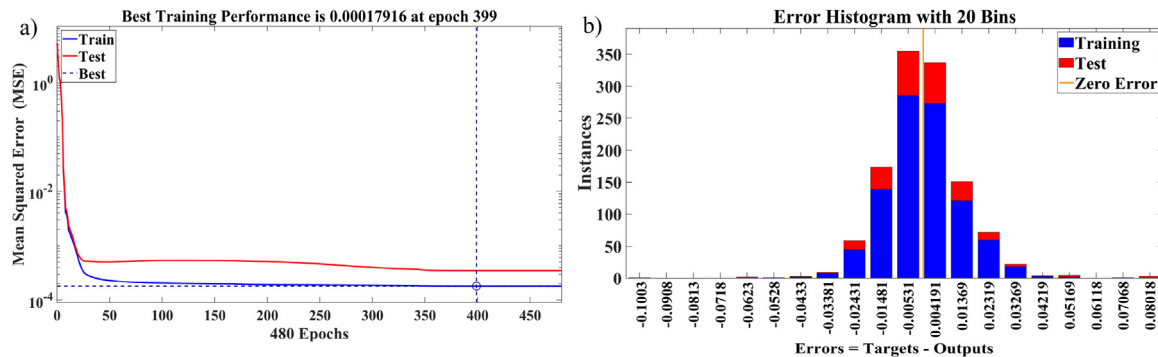


Fig. 5 – (a) The training curve of the ANN when a total of 1,540 training data points from B1 were used; (b) The absolute identification errors for the test dataset are presented in the histogram. Minor errors between the output of the ANN model and the target were observed. This confirms the suitability of the proposed model.

compared with the experimental results which were recorded for B2 and B3. The strategies as to how to overcome overfitting are then explored. Third, the behaviour of the trained ANN is examined in response to changes in the numbers of input data points and then by assuming a lack of strain data. Fourth, the ANN model is compared with the FEA results.

3.1. Training the ANN

Fig. 4 presents the results of training and testing of the ANN when 1,540 training data points from B1 were employed (80% of the entire data points, the rest was used for ANN testing). These pieces of information include 8 parameters (time, load, and the values of strains on different surfaces of the bones). The values of coefficients (R) are shown at the top of the linear regression or fitness plots. The linear fit function is also demonstrated in Fig. 4. These sets of linear regression plots indicate that all the data falls directly on a 45° line with the associated R value (slope) of 1. This emphasizes the precise agreement between the output of ANN (computed) and its target (experimental data).

Fig. 5 shows the performance and the error histogram of the ANN when 1,540 data points were used for training. Fig. 5a

shows mean squared error that is the average squared difference between the output and the target. The lower the value of mean squared error, the better the estimation of the model. The value of zero indicates no error. For a training dataset composed of 1,540 data points, the error of displacement estimation decreased enormously. This indicates a desired outcome since less than 400 training iterations were performed in the model. The absolute identification errors for the test dataset are presented in a histogram in Fig. 5b. The histogram explains that the all errors of the ANN model are almost symmetrically distributed around the zero value, and more significantly, they fall into a relatively narrow interval. A few minor outliers were observed in the left and right parts of the histogram (Fig. 5b). This corresponds to the data scattering at the beginning of the linear regression process. This figure further confirms the suitability of our proposed model both in obtaining the results and in prediction of the experimental results. An advantage of the generation of training data points to predict displacement is that the whole process can be easily parallelized. This provides the ability to perform several simultaneous simulations on the different cores of a single CPU. This offers exceptional merit over typical simulation tools such as FEA

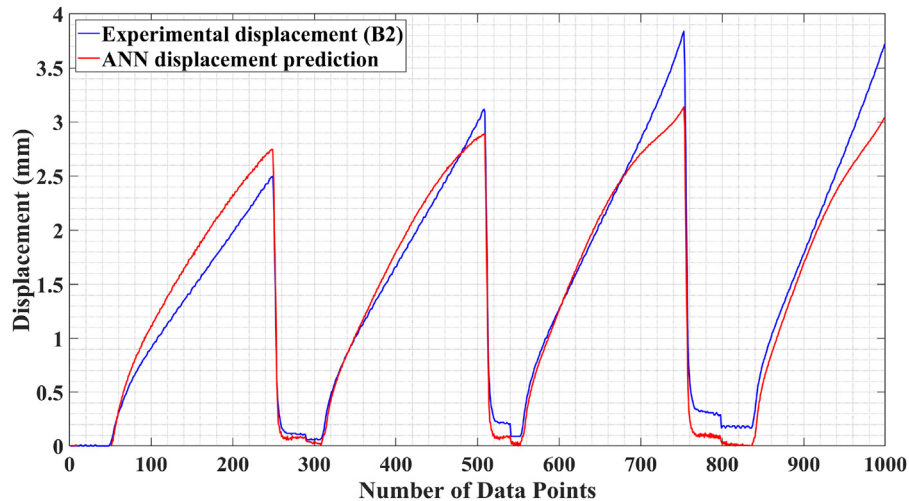


Fig. 6 – The ANN model was trained using 1,540 sample data points from B1, and then it was employed to predict the responses of B2 under load. Comparison of the experimental recordings with the prediction of the ANN model is depicted herein.

that requires substantial solution time or powerful computers to complete a solution to similar complex nonlinear problems. Moreover, the entire simulation in this study was performed on a highly nonlinear expert system whose peculiar mechanical properties are not only site-dependent [43], but also are density-dependent [44]. Minor computational resources are required in the ANN models, and therefore the process can easily be conducted on typical systems. Hence, the methods presented in this study can easily be performed in attempts to predict the mechanical behaviour of regular engineering structures whose mechanical properties are mainly isotropic or occasionally anisotropic.

3.2. Prediction of displacement from the ANN model

The ANN model was successfully trained, and its suitability in the prediction of the results was addressed in the previous subsection. In this subsection, the attempt was to predict the displacement of B2 and B3 from the previously trained ANN model. As explained previously, the ANN model was trained using the ex-vivo measurements from B1. The knowledge of the trained network was then stored in terms of weights and biases. Comparison of the results of ex-vivo experiments and those of the ANN model is demonstrated in Fig. 6 for B2 and Fig. 7 for B3. These figures demonstrate the displacement response of B2 and B3 to the cyclic loads applied to the bones. The trend of the ANN in predicting the displacement is consistent with that of the experimental data. This highlights the significant performance of the ANN algorithm for both identifying the trends of the results and predicting the displacement data. This model is currently unable to perfectly identify the maximum value of displacement in some cycles. Investigations are needed as to how to address this issue which will be discussed in the upcoming subsections. Force-displacement curves recorded during the experimental process and that obtained via the ANN model for both B2 and B3 are demonstrated in Fig. 8.

Since experimental data points of merely one bone sample (B1) were considered in the analysis presented in Fig. 8, less precise ANN results were observed for the higher loads ($F > 50$ kN). A remedy for this would be the introduction of new bone samples to the analysis, so that the ANN perfectly captures the behavior of MC3 bones under higher loads and improves its displacement prediction capability. Introducing a noise source to the ANN inputs would also overcome the impaired ability of the ANN in the displacement estimation for the higher loads exhibited in Fig. 8. These hypotheses will be examined and discussed in the following sections.

Fig. 9 demonstrates the regression model for both B2 and B3. The scatter data points represent the values of displacement for both recorded experimental data and the ANN prediction. R^2 is 0.9585 for B2, while it represents the value of 0.9788 for B3 (Fig. 9 and Table 1). The more of the variance that is accounted for by the regression model, the closer the data points will meet the fitted regression line. The similarity between the values of displacement predicted by the ANN models (vertical axis in Fig. 9) and the actual displacement that was recorded experimentally (horizontal axis in Fig. 9) can be deduced from the simple linear regression model. The type of the simple linear function which was fitted is $y = ax + b$. The line angular coefficient (the value of “a” in the fitted function) was observed to be 0.9599 for B2 and 0.9116 for B3. The determination coefficient (R^2) was approximately 1, indicating that the ANN model is capable of estimating displacement in this advanced biological material.

Recently, it has been shown that both the accuracy of the model and the training performance will be enhanced when some levels of noise are added to the trained neural network algorithms [45,46]. Neural network algorithms are capable of learning and anticipating the functions of output when they are modified with minor changes in the inputs [15]. In order to investigate the robustness of the ANN model employed in this study, it was trained with noisy data (introducing noise to the training data points of B1). Afterwards, the trained model was again investigated by anticipating data points of B2 and B3. The noise introduced to the input variables is:

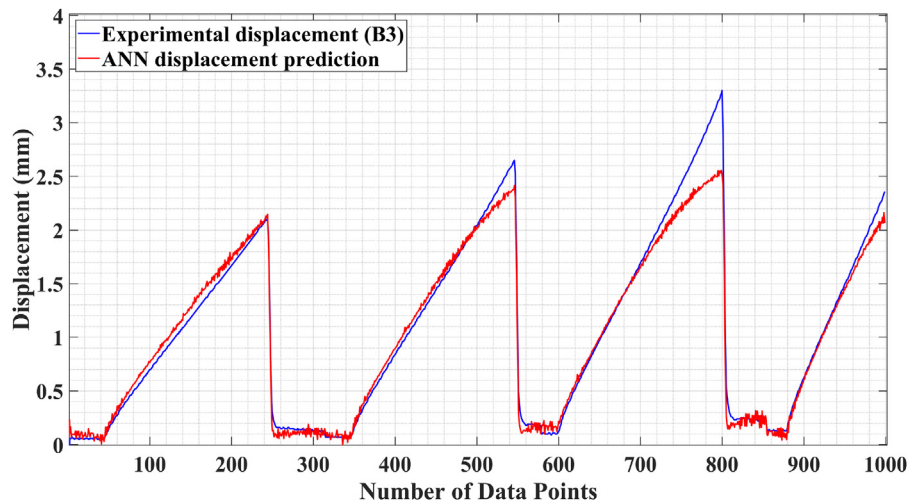


Fig. 7 – The ANN model was trained using 1,540 sample data points from B1, and then it was employed to predict the responses of B3 under load. Comparison of the experimental recordings with the prediction of the ANN model is depicted herein.

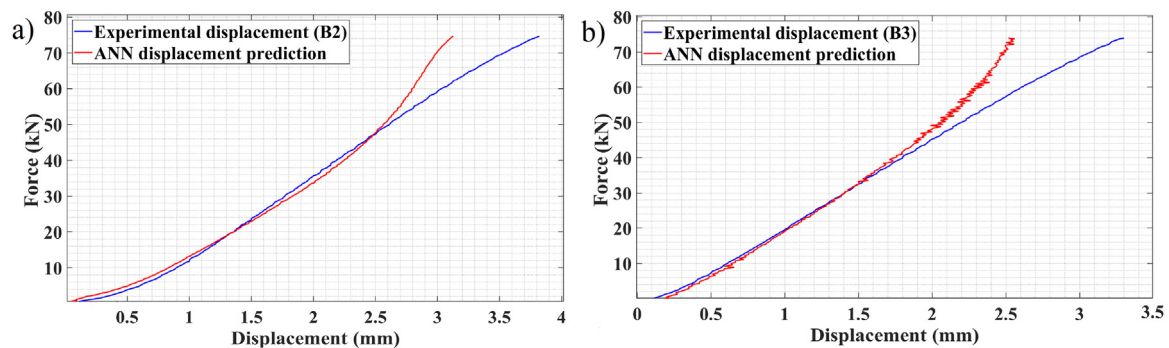


Fig. 8 – Force-displacement curves were plotted for only: (a) the third cycle of loading which includes sample data points 516 to 752 for B2; (b) the third cycle of loading which includes data points 555 to 800 for B3. The ANN model was originally trained using 1,540 sample data points from B1.

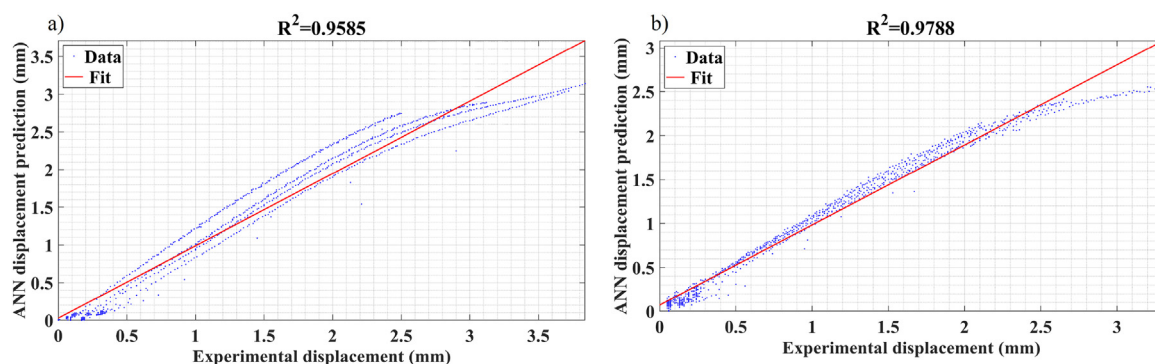


Fig. 9 – The regression model, the experimental, and the ANN model which was trained using 1,540 sample data points from B1. The ANN model was then used to predict the displacement of (a) B2 and (b) B3.

Table 1 – A summary of the correlation analyses performed in this study.

Trained ANN	λ	Figure	Number of inputs	Predicting	Linear model Poly1: $f(x) = ax + b$ Coefficients (with 95% confidence bounds)		R^2
					a	b	
1,540 data points (B1)	noise free	Fig. 9a	8	B2	0.9599	0.0004	0.9585
1,540 data points (B1)	noise free	Fig. 9b	8	B3	0.9116	0.0016	0.9788
1,540 data points (B1)	100	Fig. 11c	8	B2	1.0110	0.0006	0.9852
1,540 data points (B1)	100	Fig. 11d	8	B3	0.9870	0.0005	0.9805
3,250 data points (B1 & B2)	200	Fig. 13	2	B3	0.8835	0.0015	0.9874
1,000 data points (B1)	100	Fig. 14b	8	B3	0.8694	0.0002	0.9818
3,250 data points (B1 & B2)	100	Fig. 15b	8	B3	0.9938	0	0.9970
3,250 data points (B1 & B2)	200	Fig. 16	8	FEA output	0.9920	0.001	0.9960

$$Input' = Input + N\left(0, \frac{Input}{\lambda}\right)$$

where $N(\mu, \sigma)$ stands for a Gaussian distribution with the mean (μ) and standard deviation (σ). In most situations an appropriate range for the value of noise is difficult to decide. Gaussian distribution assists in finding the most appropriate values of noise. λ represents a signal to noise ratio. The ANN was then trained, validated, and tested using noisy data points with

signal to noise ratios (λ values) between 10 and 200. The accuracy of the displacement prediction clearly decreased with substantial decreases in λ . The optimum value for λ for the best prediction model was found to be 100.

Fig. 10 depicts the results of experiments and those obtained from the ANN model of B2 and B3. The ANN model in this analysis was trained using 1,540 noisy data points from B1 ($\lambda = 100$). The comparison between the force-displacement and the regression plots (Figs. 10 and 11) and those presented

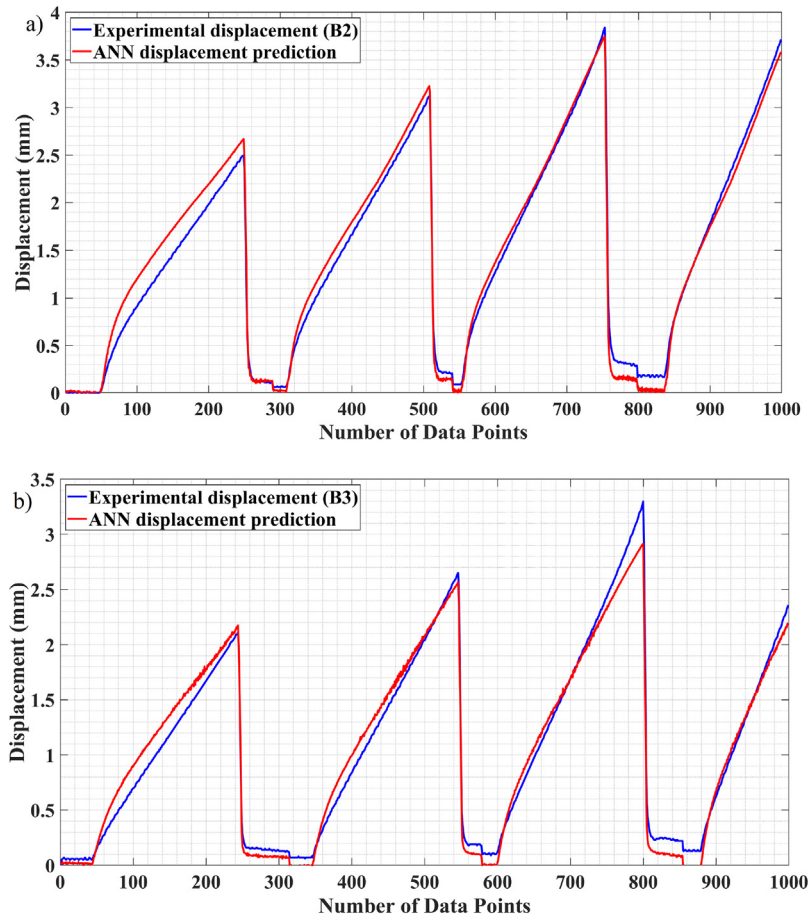


Fig. 10 – The ANN model was trained using 1,540 noisy data points from B1 ($\lambda = 100$), and then it was employed to predict the cyclic displacement of (a) B2 and (b) B3.

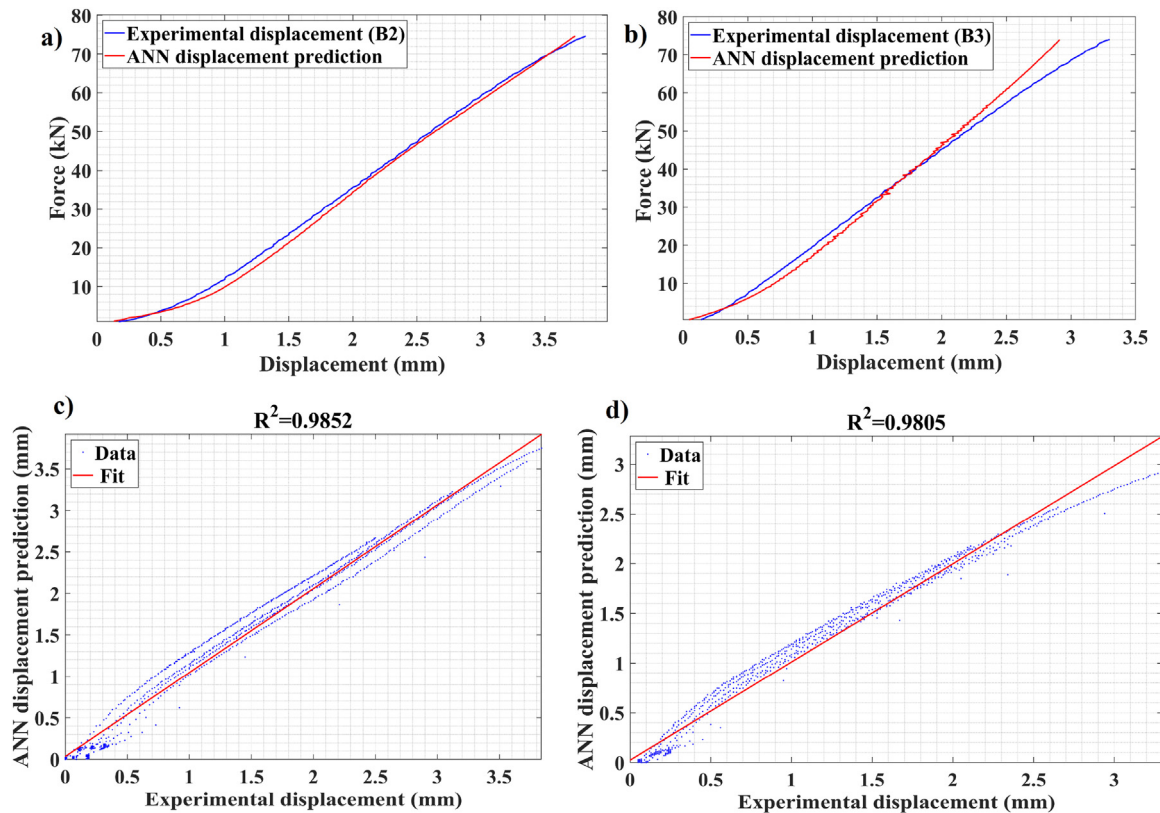


Fig. 11 – The ANN model was trained using 1,540 noisy data points from B1 ($\lambda = 100$), and then it was employed to predict the first cycle of loading for (a) B2 and (b) B3. The regression model, the experimental data, and the results of the ANN model are demonstrated for (c) B2 and (d) B3.

with lack of introduced noise in the model (Figures 6, 7, 8 and 9) indicates that using noisy data points will significantly improve the prediction performance of the ANN model. It was demonstrated that when ANNs are trained while employing noisy data points ($\lambda = 100$), they become robust and perform very well in predicting the results as compared with

training the ANN model via noise-free data points. Furthermore, applying noisy data points to the ANN model assists in identifying the pick values of the displacements. In contrast, as can be deduced from the Figures 6, 7 and 8, the noise-free ANN model was noticeably weak in predicting the pick values of the displacement. In this modified ANN, the value of R^2

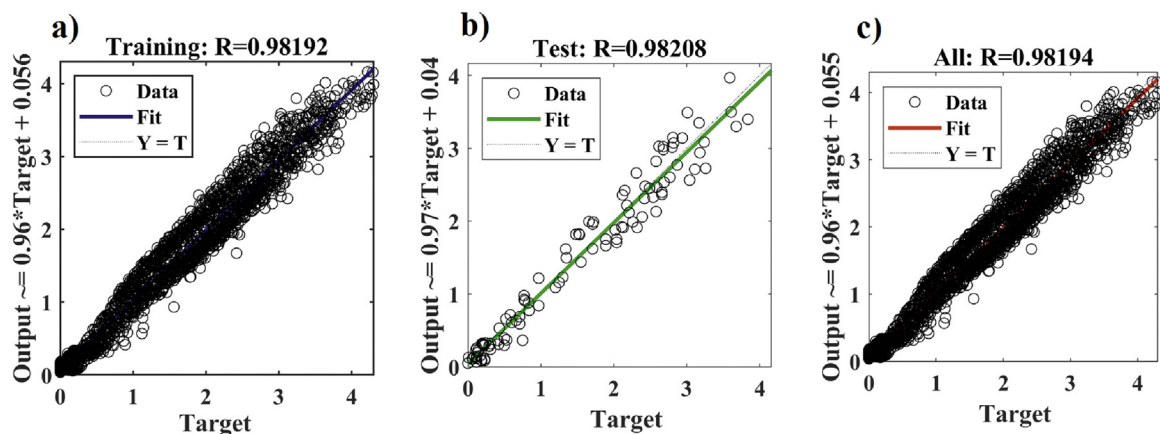


Fig. 12 – The three scatter plots represent: (a) the training; (b) testing; (c) and the all data points from B1 and B2. In this model, only the data of load and time was introduced as the inputs ($\lambda = 200$). The dashed line in each plot represents the perfect result which is outputs = targets. The solid line represents the best linear regression fit line between the outputs of the ANN and its targets (the experimental data points).

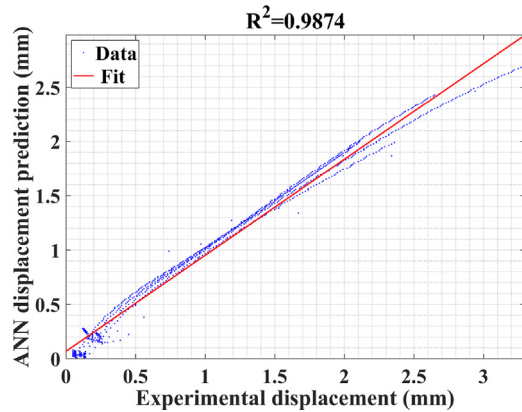


Fig. 13 – The regression model, correlation of the ANN prediction, and experimental displacement for B3. The ANN model was trained using 3,250 noisy data points from B1 and B2 ($\lambda = 200$), where merely two inputs (load and time) were defined as the inputs. The model was then employed to predict the displacement of B3.

increased from 0.9585 to 0.9852 for B2 and from 0.9788 to 0.9805 for B3 (Table 1). The values of R are also getting closer to 1 (Table 1).

3.3. The effects of strains and the number of data points

First, the effects on the performance of the ANN model of including several strains measured on the different surfaces of the bones were investigated. An ANN was trained using 3,250 data points from B1 and B2. In this model, only the data of load and time were employed for the training step. Since limited input data was employed, a higher value for λ was introduced to the ANN model and set to $\lambda = 200$ (a decrease in the noise). Fig. 12 shows the correlation between displacement for the training and the testing data points. The ANN was employed to predict the displacement of B3. The outcome of the ANN is depicted in Fig. 13. This indicates that the ANN is still capable of predicting the trends of displacement.

Finally, the effects of the number of training data points on the performance of the ANN were investigated. A slight

difference was observed between the performance of the ANN in estimating the displacement and those that were used in its training. Fig. 14 depicts the results of experiments and those obtained from the ANN model for the displacement prediction of B3. The ANN model in this analysis was trained using 1,000 noisy data points ($\lambda = 100$) from only one sample (B1). The structure of the ANN was the same as the previous one. Fig. 14 indicates that for a training dataset which is merely composed of 1,000 data points from one bone, the prediction of the ANN model is precise. The regression model for this analysis is depicted in Fig. 14b. This presents the correlation of the ANN in predicting the displacement of B3 as compared with the real-world data from experiments. The value of R^2 is 0.9818 (Table 1) which does not have a significant difference with $R^2 = 0.9805$ calculated in the previous section (Fig. 11). The slope of the fitted curve is 0.8694. This highlights an important assertion. When the size of the training dataset (sample data points) is large enough, there is no noticeable difference between the accuracy of the ANN in the estimation of displacement. However, it is obvious that with a decreasing number of data points the accuracy of the predictions decreases.

An ANN that is trained with data points from one bone has a limited ability to predict the displacement of other bones. Therefore, it is worthwhile to train the ANN with B1 and B2, and then predict the deformation of B3. As such, the ANN model was trained using 3,250 noisy data points from B1 and B2, and then it was employed to predict the displacement of B3 (Fig. 15). The accuracy of the ANN model in predicting the results of displacement ($R^2 = 0.997$) is significantly better than that presented in Fig. 14. B1 and B2 were a similar age, the same sex, and with a similar training background. B3 was 6 months younger and a castrated male so the successful test of data from that subject against the trained ANN from the B1 and B2 data suggests that the method may be useful in specimens beyond those from the ages and sexes that it is trained on.

3.4. Finite element analysis

Fig. 16 presents the comparison of the finite element analysis and the ANN model (trained with the data points from B1 and B2) with the experimental force-displacement data. The

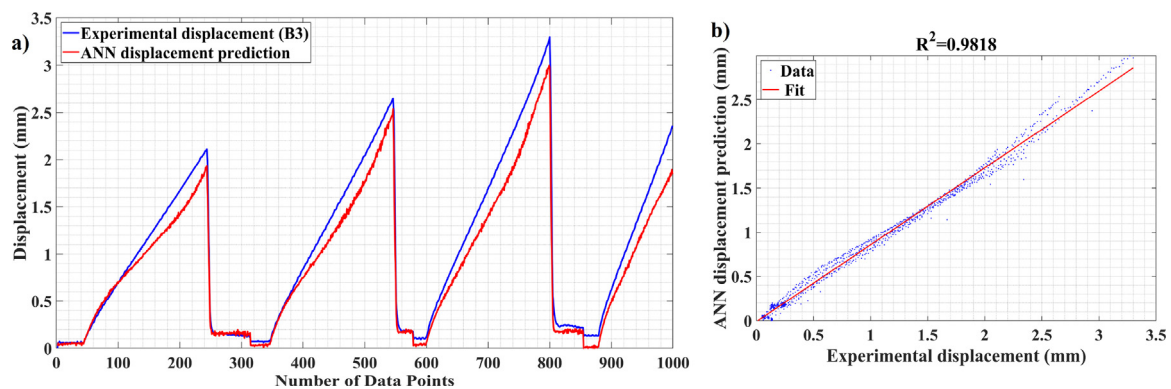


Fig. 14 – (a) The ANN model was trained using 1,000 noisy data points from B1 ($\lambda = 100$), and then it was employed to predict the cyclic displacement of B3; (b) The regression model, correlation of the ANN prediction, and the experimental displacement of B3.

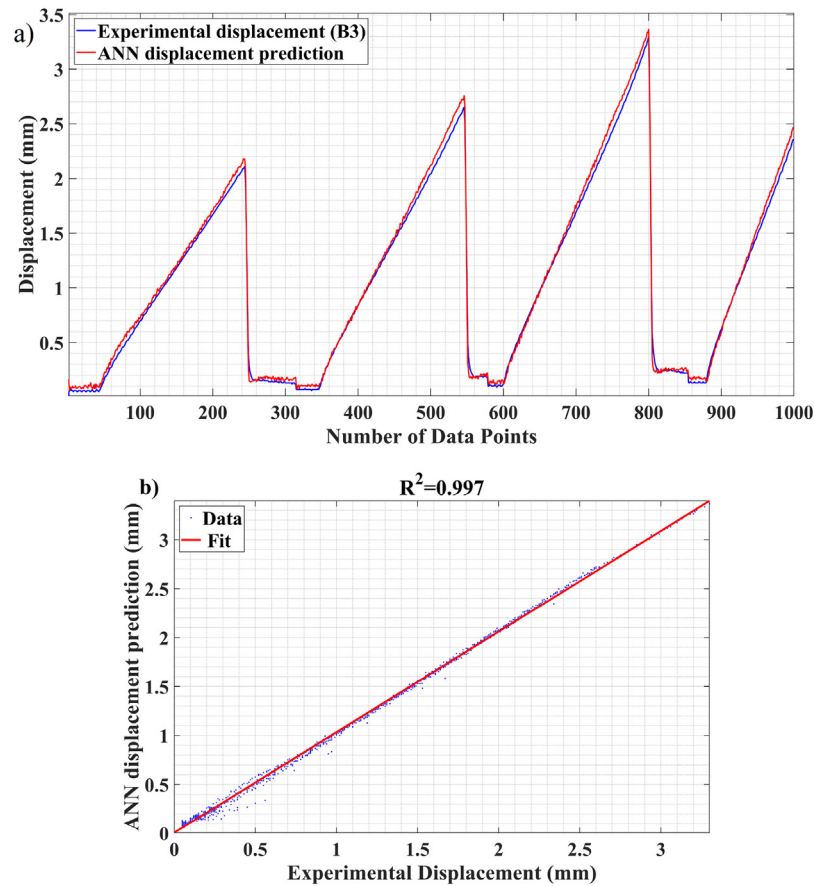


Fig. 15 – (a) The ANN model was trained using 3,250 noisy data points from B1 and B2 ($\lambda = 100$), and then it was employed to predict the cyclic displacement of B3; (b) The regression model, correlation of the ANN prediction, and the experimental displacement of B3.

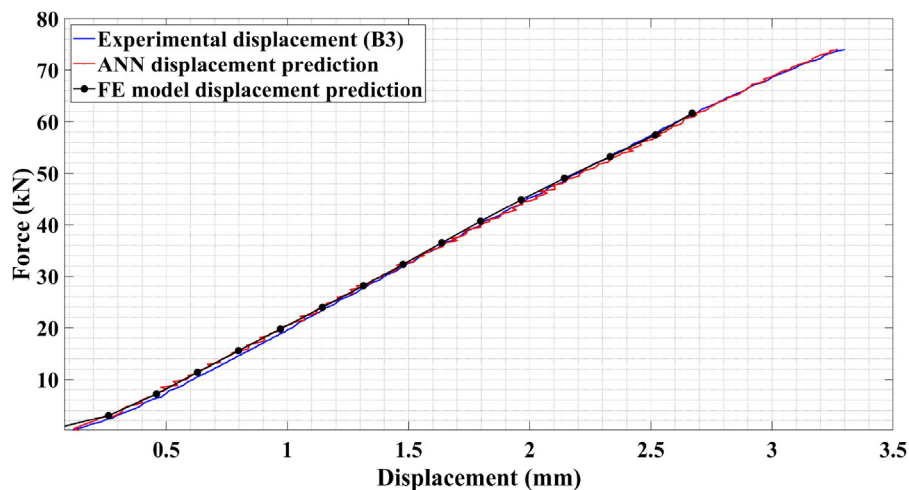


Fig. 16 – Comparison of the finite element and the ANN model to data obtained from the ex-vivo measurements of B3. Nonlinear FEA was conducted and the force-displacement data was presented.

prediction of the ANN model and the experimental value of displacement for B3 was originally presented in Fig. 15.

CT/MRI-based pieces of software such as Mimics (Materialise Medical Software, Leuven, BE), ScanIP™ (Simpleware Ltd.,

Exeter, UK), and Amira (Visage Imaging, Inc., Carlsbad, CA, USA) enable engineers to control and modify the segmentation of CT/MRI images, accurately define 3D models, perform CAD, assign material properties, and apply finite element meshes.

However, CT/MRI imaging have some limitations in FEA. For instance, an assumption of quasi-static loading must be made when using density-dependent mechanical properties in FEA. In addition, alternative approaches are required when CT/MRI images are not available, when images possess poor quality, or when bones are shattered. Furthermore, CT/MRI images are expensive and can be difficult to perform on live animals [47]. In addition, due to the radiation exposure [48–50], CT scanning may not be ethically justified [51] nor advisable for regular use in scanning volunteers with healthy bones [52]. Moreover, most FEA involving the human skeleton and the equine MC3 are subject-specific or rely on very few samples [25,26,28,53]. However, the ANN model presented in this study employed a substantial amount of data to obtain the results, which would have taken a significant amount of time using regular tools such as FEA. The outcome of the FEA presented in Fig. 16 further strengthens the suitability of the ANN model in predicting the displacement of this advanced biological material. While the FEA required a huge amount of time to merely predict a single cycle of force-displacement, the ANN model predicted the entire cycles of force-displacement 160 times quicker.

A Summary of correlation analyses performed in our study is presented in Table 1. Unlike the model-driven approach of classical mathematical models, ANN models belong to the class of data-driven approaches. The data-driven approach can directly cover all the complicating effects of the problem under investigation. This method simplifies the problems by excluding the need to understand their physical nature and the relationships amongst variables, because a data-driven approach learns from representative experimental data. The ability to learn complex relationships among supplied data sets and then to apply this knowledge to a fresh dataset is a major advantage of an ANN over purely analytical and empirical models. As explained above and since information regarding the physical parameters of the system is not required, an ANN does not rely upon the physical laws of the system from which it is nurtured. In addition, the ANN model presented in this study is a non-destructive tool, and therefore can be a valuable alternative method to quantify loading, strains, displacement, and material properties of advanced structures [54]. A lack of substantial progress in predicting the mechanical features of expert systems (such as biological structures) is due to the multiple variables involved in the definition of their characteristics. Introducing elaborate mathematical expressions to quantify the mechanical features of these exotic materials is not straightforward, yet artificial neural network provides a promising approach to quantify mechanical features of complex structures without the current runtime penalty.

4. Conclusion

The remarkably hierarchical nature of bones makes it a difficult material to comprehend properly. This is the first study in which an expert system (artificial neural network) is used for the prediction of displacement in a highly anisotropic material (long bone) from the ex-vivo measurements of load, load exposure time, and strains. Solving this problem using

typical tools such as FEA is highly complex and sometimes impossible. To obtain accurate results, particularly for a better prediction of the peak values of cyclic displacement, it was suggested that a Gaussian noise component be introduced to the data points. The proposed model made the ANN very robust against noisy strain data. The ANN model which was trained using 3,250 noisy data points ($\lambda = 100$) from two bone samples successfully predicted the displacement of the third bone ($R^2 \geq 0.98$). An FEA required more than 160 times as long to merely predict one cycle of displacement, while the ANN model predicted the entire cycles of displacement within a couple of seconds.

Competing interests

None declared

Funding

None

Ethical approval

This experiment was approved by the Animal Experimentation Ethics Committee of the University of Melbourne.

REFERENCES

- [1] Whitton RC, Ayodele BA, Hitchens PL, Mackie EJ. Subchondral bone microdamage accumulation in distal metacarpus of Thoroughbred racehorses. *Equine Vet J* 2018;50:766–73.
- [2] Ziaei-poor H, Martelli S, Pandey M, Taylor M. Efficacy and efficiency of multivariate linear regression for rapid prediction of femoral strain fields during activity. *Med Eng Phys* 2019;63:88–92.
- [3] Gerdle DM, Modenese L, Phillips ATM. Consideration of multiple load cases is critical in modelling orthotropic bone adaptation in the femur. *Biomech Model Mechanobiol* 2016;15:1029–42.
- [4] Taylor M, Perilli E, Martelli S. Development of a surrogate model based on patient weight, bone mass and geometry to predict femoral neck strains and fracture loads. *J Biomech* 2017;55:121–7.
- [5] Martig S, Hitchens PL, Stevenson MA, Whitton RC. Subchondral bone morphology in the metacarpus of racehorses in training changes with distance from the articular surface but not with age. *J Anat* 2018;232:919–30.
- [6] Zadpoor AA, Weinans H. Patient-specific bone modeling and analysis: the role of integration and automation in clinical adoption. *J Biomech* 2015;48:750–60.
- [7] Lekadir K, Noble C, Hazrati-Marangalou J, Hoogendoorn C, van Rietbergen B, Taylor ZA, et al. Patient-specific biomechanical modeling of bone strength using statistically-derived fabric tensors. *Ann Biomed Eng* 2016;44:234–46.
- [8] Taddei F, Cristofolini L, Martelli S, Gill HS, Viceconti M. Subject-specific finite element models of long bones: an in vitro evaluation of the overall accuracy. *J Biomech* 2006;39:2457–67.

- [9] Harrison SM, Chris Whitton R, Kawcak CE, Stover SM, Pandey MG. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. *J Biomech* 2014;47:65–73.
- [10] Currey J. Measurement of the mechanical properties of bone: a recent history. *Clin Orthop Relat Res* 2009;467:1948–54.
- [11] Eskinazi I, Fregly BJ. Surrogate modeling of deformable joint contact using artificial neural networks. *Med Eng Phys* 2015;37:885–91.
- [12] Hambli R. Apparent damage accumulation in cancellous bone using neural networks. *J Mech Behav Biomed Mater* 2011;4:868–78.
- [13] Hambli R. Numerical procedure for multiscale bone adaptation prediction based on neural networks and finite element simulation. *Finite Elem Anal Des* 2011;47:835–42.
- [14] Hambli R. Application of neural networks and finite element computation for multiscale simulation of bone remodeling. *J Biomech Eng* 2010;132:114502.
- [15] Zadpoor AA, Campoli G, Weinans H. Neural network prediction of load from the morphology of trabecular bone. *Appl Math Model* 2013;37:5260–76.
- [16] Gföhler M, Peham C. What can finite element analysis tell us? *Equine Vet J* 2013;45:265–6.
- [17] Marr C. *Equine Veterinary Journal: recent and future directions*. *Equine Vet J* 2014;46:1–3.
- [18] Mouloudi S, Khojasteh J, Salehi M, Mohebbi S. Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region. *Int J Mech Sci* 2014;85:160–7.
- [19] Mouloudi S, Mohebbi S, Khojasteh J, Salehi M. Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects. *Int J Mech Sci* 2014;79:162–7.
- [20] Shanmuganathan S. Artificial neural network modelling: an introduction. In: Shanmuganathan S, Samarasinghe S, editors. *Artificial neural network modelling*. Cham: Springer International Publishing; 2016. p. 1–14.
- [21] Hambli R, Chamekh A, Bel Hadj Salah H. Real-time deformation of structure using finite element and neural networks in virtual reality applications. *Finite Elem Anal Des* 2006;42:985–91.
- [22] Ziaei-poor H, Taylor M, Pandey M, Martelli S. A novel training-free method for real-time prediction of femoral strain. *J Biomech* 2019;86:110–6.
- [23] Vasundara M, Padmanaban K, Sabareeswaran M, RajGanesh M. Machining fixture layout design for milling operation using FEA, ANN and RSM. *Procedia Eng* 2012;38:1693–703.
- [24] Javadi A, Tan T, Zhang M. Neural network for constitutive modelling in finite element analysis. *Comput Assisted Mech Eng Sci* 2003;10:523–30.
- [25] Harrison SM, Whitton RC, Kawcak CE, Stover SM, Pandey MG. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. *J Biomech* 2014;47:65–73.
- [26] Merritt J, Burvill C, Pandey M, Davies H. Determination of mechanical loading components of the equine metacarpus from measurements of strain during walking. *Equine Vet J* 2006;38:440–4.
- [27] Merritt JS, Davies H, Burvill C, Pandey MG. Influence of muscle-tendon wrapping on calculations of joint reaction forces in the equine distal forelimb. *Biomed Res Int* 2008;2008.
- [28] McCarty CA, Thomason JJ, Gordon KD, Burkhart TA, Milner JS, Holdsworth DW. Finite-element analysis of bone stresses on primary impact in a large-animal model: the distal end of the equine third metacarpal. *PLoS One* 2016;11:e0159541.
- [29] Sousa WdS, de Sousa FdA. Rede neural artificial aplicada à previsão de vazão da Bacia Hidrográfica do Rio Piancó. *Revista Brasileira de Engenharia Agrícola e Ambiental-Agriambi* 2010;14.
- [30] Barron AR. Universal approximation bounds for superpositions of a sigmoidal function. *IEEE Trans Inf Theory* 1993;39:930–45.
- [31] Jin D, Lin S. *Advances in computer science, intelligent systems and environment*. Springer Science & Business Media; 2011.
- [32] Liang G, Chandrashekhara K. Neural network based constitutive model for elastomeric foams. *Eng Struct* 2008;30:2002–11.
- [33] Kopal I, Harnicárová M, Valíček J, Kušnerová M. Modeling the temperature dependence of dynamic mechanical properties and visco-elastic behavior of thermoplastic polyurethane using artificial neural network. *Polymers* 2017;9:519.
- [34] Yang X, Behrooz M, Olatunbosun OA. A neural network approach to predicting car tyre micro-scale and macro-scale behaviour. *J Intell Learn Syst Appl* 2014;6:11.
- [35] Hornik K. Approximation capabilities of multilayer feedforward networks. *Neural Networks* 1991;4:251–7.
- [36] Schöllhorn WI. Applications of artificial neural nets in clinical biomechanics. *Clin Biomech* 2004;19:876–98.
- [37] Saini LM. Peak load forecasting using Bayesian regularization, Resilient and adaptive backpropagation learning based artificial neural networks. *Electr Power Syst Res* 2008;78:1302–10.
- [38] Demuth H, Beale M. *Matlab neural network toolbox user's guide version 6*. The MathWorks Inc; 2009.
- [39] MacKay DJ. Bayesian interpolation. *Neural Comput* 1992;4:415–47.
- [40] Fausett LV. *Fundamentals of neural networks: architectures, algorithms, and applications*. Prentice-Hall Englewood Cliffs; 1994.
- [41] Mouloudi S, Rahmanpanah H, Burvill C, Davies HM. Accuracy quantification of the reverse engineering and high-order finite element analysis of equine MC3 forelimb. *J Equine Vet Sci* 2019.
- [42] Mouloudi S, Rahmanpanah H, Burvill CR, Davies HMS. Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design. *Comparative Exercise Physiology* 2019. Accepted for Publication.
- [43] Nobakhti S, Katsamenis OL, Zaarour N, Limbert G, Thurner PJ. Elastic modulus varies along the bovine femur. *J Mech Behav Biomed Mater* 2017;71:279–85.
- [44] Nobakhti S, Shefelbine SJ. On the relation of bone mineral density and the elastic Modulus in healthy and pathologic bone. *Curr Osteoporos Rep* 2018;1–7.
- [45] Noh H, You T, Mun J, Han B. Regularizing deep neural networks by noise: its interpretation and optimization. *Adv Neural Inf Process Syst* 2017;5109–18.
- [46] Zur RM, Jiang Y, Pesce LL, Drukker K. Noise injection for training artificial neural networks: a comparison with weight decay and early stopping. *Med Phys* 2009;36:4810–8.
- [47] Liley H, Zhang J, Firth E, Fernandez J, Besier T. Using partial least squares regression as a predictive tool in describing equine third metacarpal bone shape. *Comput Methods Biomech Biomed Engin* 2017;20:1609–12.
- [48] Koivisto J, Kiljunen T, Kadesjö N, Shi X-Q, Wolff J. Effective radiation dose of a MSCT, two CBCT and one conventional radiography device in the ankle region. *J Foot Ankle Res* 2015;8:8.
- [49] Semelka RC, Armao DM, Elias J, Huda W. Imaging strategies to reduce the risk of radiation in CT studies, including selective substitution with MRI. *J Magn Reson Imaging* 2007;25:900–9.

- [50] Fujita H, Hatanaka Y. Computer-aided diagnosis with retinal fundus images. *Medical image analysis and informatics*. CRC Press; 2017. p. 59–86.
- [51] Sun W, Lal P. Recent development on computer aided tissue engineering — a review. *Comput Methods Programs Biomed* 2002;67:85–103.
- [52] Rathnayaka K, Momot KI, Noser H, Volp A, Schuetz MA, Sahama T, et al. Quantification of the accuracy of MRI generated 3D models of long bones compared to CT generated 3D models. *Med Eng Phys* 2012;34:357–63.
- [53] Merritt JS, Davies HMS, Burvill C, Pandy MG. Influence of muscle-tendon wrapping on calculations of joint reaction forces in the equine distal forelimb. *J Biomed Biotechnol* 2008.
- [54] Mouloudi S, Rahmanpanah H, Burvill C, Davies H. Prediction of load in a long bone using an artificial neural network prediction algorithm. *J Mech Behav Biomed* 2019;103527.

5.2. Summary and Concluding Remarks

This chapter reported on the adoption of feedforward artificial neural networks trained with experimental measurements to predict the displacement of equine third metacarpal bones subjected to cyclic mechanical load. This aimed to replace constitutive equations by data-driven methods using artificial intelligence methodologies. The results associated with regression, performance, and error histogram analyses demonstrated the potent ability of ANNs to successfully map the space of inputs to that of output, highlighting the significant performance of the ANN algorithms for both identifying the trends of the results as well as predicting the displacement data. Besides injecting a noise source to the ANN inputs, the introduction of new bone samples to the ANNs (availability of more relevant data that the ANNs can be trained on) was shown to improve the accuracy of the results, i.e. ANNs output as compared with experimental displacement particularly for the higher loads ($F > 50$ kN). The strategies as to how to overcome overfitting were also explored, such as introduction of a noise source to the input data prior to ANNs training. This will be investigated further in the next chapters. The behaviour of the trained ANN was examined in response to changes in the numbers of input data points and by assuming a lack of strain data. Finite element analysis was also performed, followed by a fully automatic adaptive mesh refinement process (Chapter 3) to replicate one cycle of force-displacement experimental data (RMSE=0.032mm). The FEA required more than 160 times as long to merely predict one cycle of the load-displacement curve while the ANN produced a satisfactory outcome within a couple of seconds. This emphasized the real-time computational efficiency of ANNs when applied to computational mechanics of complex nonlinear structures. The generalization ability of all the trained and tested ANNs was assessed to investigate as to whether the already trained ANNs were able to predict the displacement of a specific bone sample that had not been involved in the ANNs training session (i.e. to extrapolate beyond trained data sets). The ANN model which was trained using 3,250 noisy data points from two bone samples successfully predicted the displacement of the third bone ($R^2 \geq 0.98$) with computational efficiency. Chapters 6 to 8 of this thesis explore the performance of ANNs in predicting cyclic mechanical loading, stiffness, and strains of MC3 long bones.

Chapter 6

Prediction of load in a long bone using an artificial neural network prediction algorithm

The use of a data-driven approach using artificial neural networks is explored in this Chapter. The author sought to solve an inverse problem in computational mechanics of a complex biological structure (MC3 bones).

This Chapter reports on a published paper completed by the author and collaborators that investigated the following hypotheses (as discussed in Section 2.6.3):

- **H.7.** Feedforward backpropagation artificial neural networks are suitable techniques to be adopted for solving an inverse problem (cyclic mechanical loading from measurements of strains and displacement) in computational mechanics of equine third metacarpal long bones.
- **H.9.** The ANN models exhibit successful ability in capturing the underlying data to predict the loading of MC3 long bones recorded via ex-vivo experiments, i.e. with coefficient of correlation ($R > 0.99$) for ANNs training and testing as well as $R^2 > 0.98$ when the trained ANNs are employed to make prediction on unseen samples (new datasets that ANNs have not seen before).
- **H.10.** The relative importance analysis will reveal that strains significantly affect the ANN output in load prediction.
- **H.11.** Pattern recognition algorithms explain that there is an inherent difference between group of foals and that of two- and three-year-olds at least in terms of the measured experimental data.

6.1. Published Journal paper

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Prediction of load in a long bone using an artificial neural network prediction algorithm

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ABSTRACT

The hierarchical nature of bone makes it a difficult material to fully comprehend. The equine third metacarpal (MC3) bone experiences nonuniform surface strains, which are a measure of displacement induced by loads. This paper investigates the use of an artificial neural network expert system to quantify MC3 bone loading. Previous studies focused on determining the response of bone using load, bone geometry, mechanical properties, and constraints as input parameters. This is referred to as a forward problem and is generally solved using numerical techniques such as finite element analysis (FEA). Conversely, an inverse problem has to be solved to quantify load from the measurements of strain and displacement. Commercially available FEA packages, without manipulating their underlying algebraic formulae, are incapable of completing a solution to the inverse problem. In this study, an artificial neural network (ANN) was employed to quantify the load required to produce the MC3 displacement and surface strains determined experimentally. Nine hydrated MC3 bones from thoroughbred horses were loaded in compression in an MTS machine. Ex-vivo experiments measured strain readings from one three-gauge rosette and three distinct single-element gauges at different locations on the MC3 midshaft, associated displacement, and load exposure time. Horse age and bone side (left or right limb) were also recorded for each MC3 bone. This information was used to construct input variables for the ANN model. The ability of this expert system to predict the MC3 loading was investigated. The ANN prediction offered excellent reliability for the prediction of load in the MC3 bones investigated, i.e. $R^2 \geq 0.98$.

1. Introduction

Prediction of load in complex structures such as bone is challenging because bone is capable of modifying and altering its microstructure by mechanisms called modelling and remodelling. Modelling is needed to adapt the microarchitecture to external influences such as changes in mechanical loading (Frost, 1990a). Remodelling ensures the maintenance of the bone structure to cope with daily physical activities. It is generally accepted that the relationship between bone morphology (density and its micro-architecture) and loading is the result of a local load-adaptive remodelling process. This process is regulated and carried out by bone cells in such a way that bone tissue is added to regions which undergo high loads, and is removed from those regions experiencing lower loads (Wolff's law) (Frost, 1990a, b; Schulte et al., 2011). Since there is a relationship between bone loading history and its morphology, it might be feasible to quantify the loading history from the density and micro-architecture of bones (Christen et al., 2012). In addition, bones

exhibit a wide variety of architectures and their shape is intimately related to their function (Currey, 2006). It has been asserted that a high magnitude of loading in bones results in a dense plate-like architecture, whereas lower loads are likely to produce low-density rod-like structures (Ding et al., 2002). Therefore, quantifying mechanical loads is essential when determining and predicting the shape of bone, and when investigating the geometric response of bone.

Mechanical overload, which has been shown to be a significant contributing factor in horse injuries (Martig et al., 2018; Muir et al., 2008; Norrдин et al., 1998; Santschi, 2008), may be acute or chronic, resulting from a single event or cumulative damage over an extended period of time (Merritt et al., 2010). However, despite the clear relationship between mechanical loading and the occurrence of injuries, little is known about employing novel and efficient approaches for load prediction in this complex material. Several studies involving strain gauge methods (Merritt et al., 2006) or limb dynamics procedures (Merritt et al., 2008) have been conducted for force calculations in the

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MC3. These studies indicated that MC3 is predominantly exposed to compression forces at various gaits and speeds (Biewener et al., 1983; Merritt et al., 2010). Since this loading regime is believed to have a considerable impact on bone damage and modelling (Davies et al., 1993; Nunamaker et al., 1990; Turner et al., 1975), it is essential to predict axial force through measurements of strains and displacement (Mouloudi et al., 2019b).

The artificial neural network (ANN) algorithm has been receiving considerable attention in a range of engineering disciplines, with an associated growth in the literature (Shanmuganathan, 2016). This expert system has been treated as a standard nonlinear alternative to traditional models for pattern classification (Wang et al., 2018), time series analysis (Che et al., 2018), and regression problems (Asiltürk and Çunkaş, 2011). The popularity of ANNs, to a large extent, is due to their powerful modelling, their prediction ability, and their generalization capability while allowing the exclusion of many unrealistic assumptions in the problem (Chou et al., 2004). The process of modelling is highly adaptive, and the model is largely determined by the features that the ANN algorithm learned from the existing data during the learning process. This data-driven approach is applicable for any real-world situation where theory on the underlying relationships is scarce or complex to prescribe, but data is plentiful or is easier to collect. In addition, the mathematical property of the neural network to accurately approximate or represent various complex relationships has been established and supported theoretically (Castro et al., 2000). For example, ANN methodologies were developed to predict and model the static load applied on a wing rib of an airplane (Amali et al., 2014) and the operational loads experienced by a fixed-wing aircraft structure (Reed and Cole, 2003).

It is therefore intriguing to investigate whether it is possible using an ANN (an expert system) to predict the musculoskeletal loads in the equine MC3 (an advanced biological material) that resulted in certain measured displacement and strains. An ANN has been employed to predict loading of the human femur associated with bone density distribution variations (Campoli et al., 2012). However, published literature is still lacking to quantify load from measured strains and displacement of long bones.

In FEA packages, boundary conditions, material properties, and applied loads are known and considered as inputs, and the requirement is to derive deformation and strains. However, an inverse problem has to be solved in FEA in order to derive musculoskeletal loads from given measurements of displacement and strains. Due to the complexities involved in the solution of nonlinear inverse problems, quantifying mechanical loads from experimental measurements of bones has not been extensively investigated. Even when the shape of the bone, density distribution, and all of its material quality parameters are known, it is complicated to solve the problem of estimation of load (Zadpoor, 2013). Nor is there an assurance that a unique solution exists for the inverse problem (Nicholson, 2012). Commercially available FEA packages (ANSYS, Abaqus, etc.) are incapable of performing inverse analysis to obtain loads, and as such, a series of finite element algebraic manipulations (Dennis et al., 2011), reconstructing finite element formulae, minimizing derived criterion functions (Song and Gu, 2012), and developing cumbersome finite element coding (frequently performed in MATLAB (Gohari et al., 2019; Mouloudi et al., 2014a)) are required. Pursuing this path demands extensive use of parametric design language and a comprehensive understanding of finite element subroutines in these FEA packages. This path was followed and explained in inverse problems of mechanical properties quantification of multicrystalline nanoplates (Mouloudi et al., 2014a, 2014b). For highly nonlinear complex structures such as bones, developing this sort of programmed codes is extremely challenging and frequently impossible. In this paper, we employed artificial neural networks (expert systems) to solve the forward problem for the estimation of applied load from the ex-vivo measurements. Most of the previous studies used the human femur as their case study, however investigation is required for load estimation in

bones other than the femur (Zadpoor et al., 2013). Furthermore, MC3 provides a unique environment without the interference of muscle attachments throughout the midshaft, so these results may reflect the mechanical properties of mammalian long bones in general. To the best knowledge of the authors, employing an expert system (artificial neural network) to predict loads in an advanced biological material (equine MC3) from the ex-vivo measurements of displacement and strains has never been discussed in publicly available literature. If this approach is practical in determining loads, it would be worthwhile exploring and developing in several applications. For instance, it would enable investigators to estimate the history of bone loading in cases where the bone morphology can be assessed but no loading conditions can be measured (in CT/MRI-based computer simulation). Additionally, mechanical loading, overall strength, and structural features of long bones are required to be quantified throughout human evolution (Ruff, 2005) where data such as geometric information is lacking or missing.

The aim of our study was to investigate the ability of the ANN algorithm to solve a forward problem to predict axial mechanical loading of the equine MC3 using experimental data. The methods presented in this paper will assist future investigators to determine mechanical loading of advanced materials with exotic mechanical properties in general.

2. Materials and methods

2.1. Experimental data

In this study, nine equine third metacarpal bones from nine thoroughbred horses with no history of bone disease were used in the ex-vivo experiments. The samples were collected from donated cadavers of horses that died for reasons unrelated to this experiment (Table 1). To minimize dehydration the bones were wrapped separately in a clear plastic wrap and stored at -9°C until used. The defrosted bones were wrapped lightly in plastic to reduce evaporative loss during the test and hydration was maintained with normal saline when necessary. Each end of the bones was embedded in fiberglass impregnated epoxy resin contained in a metal cup, which provided a smooth surface onto which the forces could be applied more evenly (Fig. 1). To record strains around the midshaft of the MC3 samples a set of strain gauges, including one rosette strain gauge and three single-element strain gauges, were attached to the lateral, dorsal, and palmar cortices of the bone samples (Fig. 1). A 250 kN load frame with an MTS 430 controller was used to apply compressive loads parallel to the anatomical axis of the bones. The change in the length of the whole bone (displacement of the machine ends), the values of strains, the load being applied onto the samples, and the load exposure time were recorded. For each bone sample the magnitudes of strains, displacement, and applied load increased gradually (during loading) and decreased (during unloading) depending on the response of the individual bones, but load exposure time (t) increased continuously until bones failed. The strain range ($\mu\epsilon$) for the strain

Table 1

The sample number, age group, and the length of the third metacarpal bones used in this study. The total number of recorded experimental data points (maximum value of n in the Equations (6) and (7)) was also reported herein.

Age group	Horse number	limb	Bone length (cm)	Total number for recorded data points
Two-year-old	B1	Left	27	1926
	B2	Left	27.6	1324
	B3	Right	26.4	1365
Three-year-old	B4	Right	27.7	1845
	B5	Right	27.7	2708
	B6	Left	27.7	1806
	B7	Left	26.8	1156
Foal (<6 months)	B8 (12 h)	Left	25.2	569
	B9 (2 months)	Left	26.5	1093

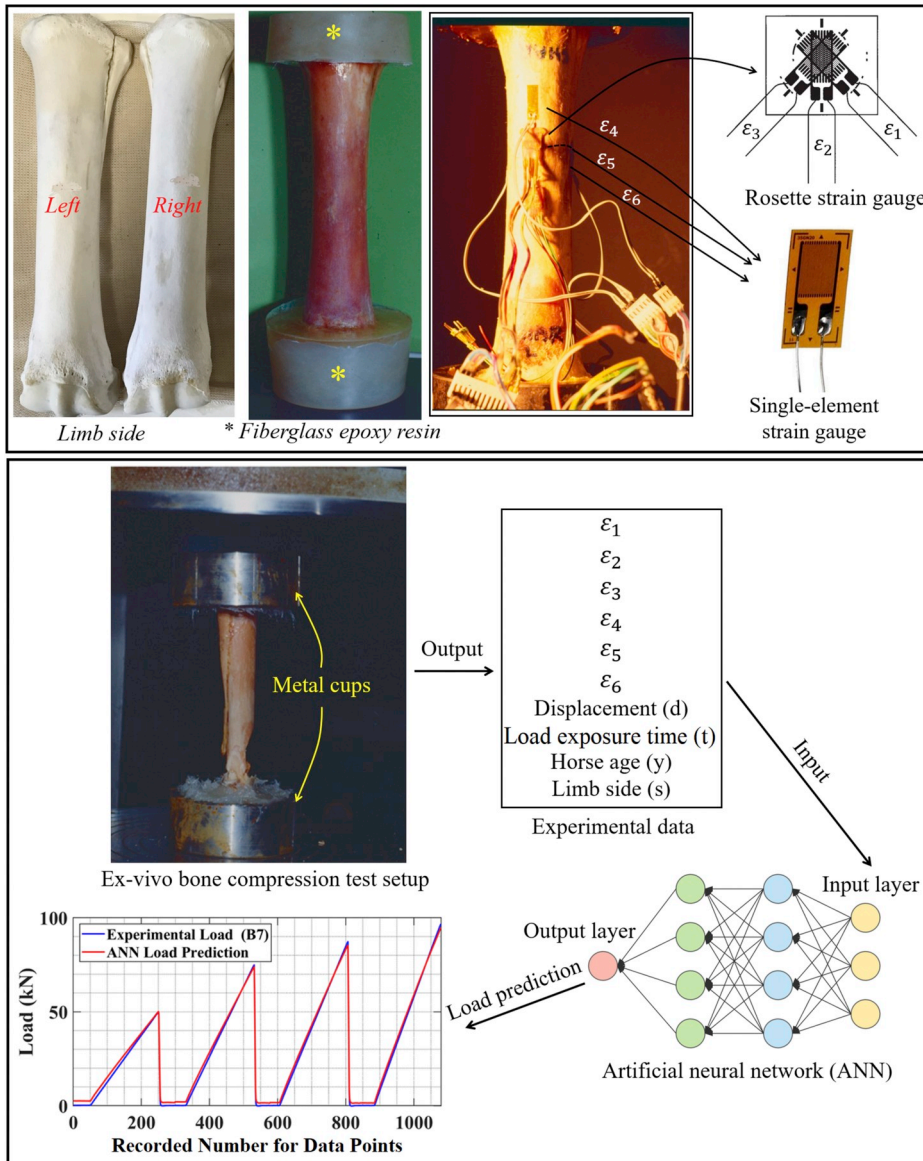


Fig. 1. The process of bone preparation for the experiment. The output of the experiment was imported into MATLAB to train neural networks and to develop the cyclic load prediction algorithm. The distal and proximal ends of the MC3 bones were surrounded by metal cups into which slow-curing fiberglass resin was poured. Due to the resin, both ends of the bones became flat parallel surfaces and were perpendicular to the shaft of the bones. Recorded number for data points represents n in Equation (7).

gauges as pool data was $[-11,600$ to $+1190]$. The range of other experimental variables was $[0-112.38$ kN] for load, $[0-10.2$ mm] for displacement, and $[0-162$ s] for time. The mean ($\pm$ S.D.) values were -1198.2 (± 1626.8) for strains ($\mu\epsilon$), 28.19 (± 28.31) for load (kN), 1.4 (± 1.7) for displacement (mm), and 6.8 (± 4) for load exposure time (seconds). The data obtained from the experimental process was imported into the ANN algorithm for computer simulation analysis. Each data point represents the recorded ex-vivo measurements, i.e. applied load (L), time (t), limb side (s), horse age (y), displacement (d), and strains ($\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5, \epsilon_6$) during loading and unloading. A substantial number of data points were recorded for each variable (load, time, displacement, and strains) during experimental data acquisition. Each of these variables, after data acquisition, was expressed as an $n \times 1$ column matrix. In this paper, n is referred to as recorded number for data points and is introduced to Equations (6) and (7). The displacement data was then normalized, and the absolute values were introduced to the ANN as a vector.

2.2. Artificial neural networks

An artificial neural network is a computational learning algorithm that employs a network of functions to comprehend and translate series of input data into a desired output. The concept of the artificial neural network was originally inspired by human biology, and the way human brain neurons function collaboratively to understand inputs from human senses. These systems learn to perform tasks by considering and learning from examples, generally without being programmed with any task-specific rules (Van Gerven and Bohte, 2017). Artificial neural networks (ANNs) are comprised of highly interconnected neurons (nodes) and typically are modelled into one input layer, one or several hidden layers, and one output layer. The number of input variables and output variables equals the number of neurons in the input layer and the number of neurons in the output layer, respectively. The structure of artificial neurons and the architecture of a neuron are shown in Fig. 2. Input data has an associated weight (w_i), also known as the synaptic

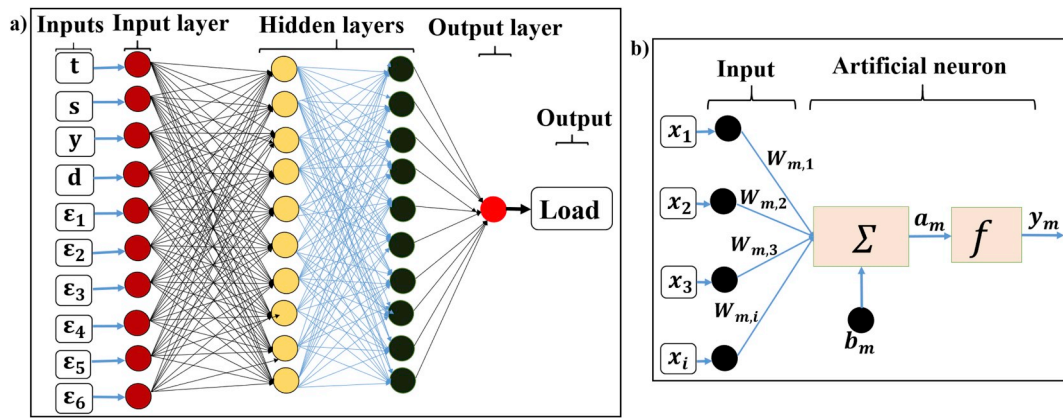


Fig. 2. a) The structure of artificial neurons developed for this study to introduce the feed forward neural network. b) The architecture of an artificial neuron being tested. x_i is an introduced input to each neuron, $w_{m,i}$ is the weight assigned to the corresponding neuron, $a_m = \sum(x_i \times w_{m,i}) + b_m$, and $y_m = f(a_m)$, where f is the activation function.

weight, which mathematically represents a degree of significance for that neuron. The input signals of the neurons are multiplied by their synaptic weight, and the summation of this result, which is added to the bias (b), forms the input information of the neuron (Fig. 2b). Each neuron has an activation function (f). Weights (w_i) are assigned to the signals (x_i) by the neurons. The weighted signals are then summed up and biased. The outcome is eventually introduced to the activation function. The activation function is used to transform the output into a desired range (usually 0–1 with Sigmoid function), to introduce nonlinearity to the data where needed, and finally to achieve the desired ANN output. Sigmoid (logistic) activation function, hyperbolic (Tanh) activation function, and rectified linear unit (ReLU) activation function are some of the commonly used activation functions for artificial neurons.

Besides different architecture types and learning methods, artificial neural networks can be classified into different categories such as feedforward or recurrent (based on ANNs connection pattern), single layer or multilayer (based on the number of hidden layer), and fixed or adaptive (based on the nature of weights adjustment during ANNs training). Levenberg-Marquardt backpropagation, Bayesian regularization backpropagation, and scaled conjugate backpropagation are some of the training algorithms for neural networks (Mandal, 2017). Back-propagation neural network (BPNN) is an artificial neural network that employs a supervised learning method (Deng et al., 2008), possesses feed-forward architecture, accommodates complex and nonlinear data relationships, and hence is well-suited for regression analysis and practical application (Mandal, 2017). This network was employed in this study. BPNN architecture comprises one input layer, one output layer, and one or several hidden layers, which determine the mapping relationship between input and output layers. The number of hidden layers and the number of neurons in the hidden layers vary and an optimal number for each is estimated by the complexity of the problem and is found during the training procedure (Mouloudi et al., 2019b). The BPNN was selected to have two hidden layers, one input layer with ten inputs, and a single output. The neurons have a sigmoid transfer function within the hidden layers, whereas the neuron of output layer has a linear transfer function (used as default by the Bayesian regularizations backpropagation training function, referred to as trainbr in MATLAB).

The mean squared error (MSE), as an indication of the training error of the network, is defined between the actual output and the target value and is explained as:

$$E = \frac{1}{2} \sum (t_k - y_k)^2 \quad (1)$$

where t_k and y_k are the target and actual outputs of the k th neuron of the output layer. The MSE between the output of network and the desired

target is then calculated as:

$$MSE = \frac{1}{m_1 q_{out}} \sum_{m=1}^{m_1} \sum_{k=1}^{q_{out}} e_k^2(m) \quad (2)$$

where q_{out} is the number of neurons of the output layer, and $e_k^2(m)$ is the error of the k th output neuron for the m th weight. To maximize the performance of the model, MSE was back propagated to the neural network to adjust the weights and bias according to the Bayesian regularization backpropagation training algorithm that employs Levenberg-Marquardt optimization in batch or incremental styles, thereby minimizing MSE between the ANN prediction (output) and the target output (experiments). Finally, a neural network that is well-generalized to the target is produced.

The experimental measurements collected from the MC3 bone samples (B1–B9) were employed to train, test, and then to confirm the accuracy of the ANNs. The input sector has 10 variables, including time, s (1 indicating a left and 0 indicating a right limb), age, displacement, and strains (Fig. 1). The output of the ANN (MC3 bone load) is a function of the ANN input variables:

$$Load = f(\text{time}, s, \text{age}, \text{displacement}, \epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5, \epsilon_6) \quad (3)$$

The input and the target of the proposed ANN were stored in the matrix of inputs and the matrix of targets, respectively.

$$Input = [tsyde] \quad (4)$$

$$Output = [Load] \quad (5)$$

The matrix of inputs is comprised of a column vector of time (t), right or left limb (s), age (y), displacements (d), and strains (ϵ), while the matrix of outputs is a column vector of loads (L).

$$Inputs = \begin{bmatrix} t_{11} & s_{11} & y_{11} & d_{11} & \epsilon_{11} & \cdots & \epsilon_{16} \\ t_{21} & s_{21} & y_{21} & d_{21} & \epsilon_{21} & \cdots & \epsilon_{26} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ t_{n1} & s_{n1} & y_{n1} & d_{n1} & \epsilon_{n1} & \cdots & \epsilon_{n6} \end{bmatrix} \quad (6)$$

and

$$Output = \begin{bmatrix} L_1 \\ \vdots \\ L_n \end{bmatrix} \quad (7)$$

where n represents recorded number for data points. The matrix of input is comprised of $n \times 10$ pieces of data, which were used for training. The target is a matrix with a dimension of $n \times 1$. The input data was normalized and was introduced to the ANN as a vector. The performance of the ANN was not oversensitive to the number of hidden neurons.

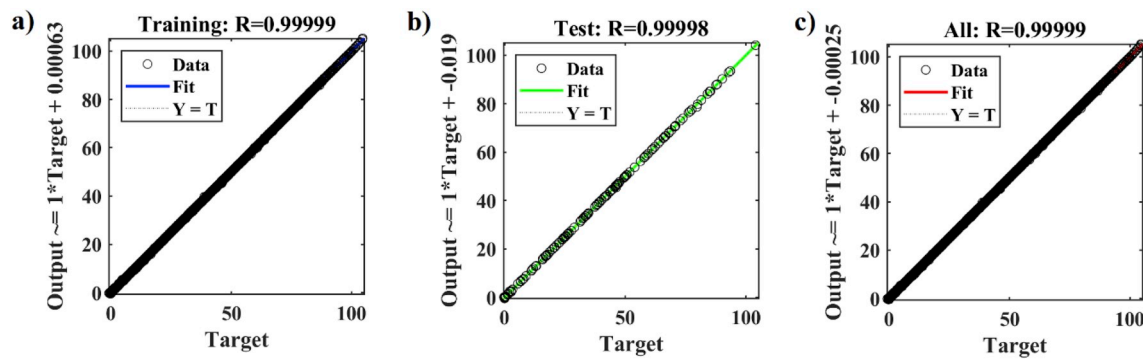


Fig. 3. The three scatter plots represent a) the training, b) testing, c) all data points. The ANN was trained with data points from B1 and B3. The dashed line in each plot represents the perfect result which is outputs = targets. The solid line represents the best fit linear regression line between the outputs of ANN and targets (the experimental data points). The value of R (coefficient of correlation) is approximately 1, which indicates that there is an exact linear relationship between outputs and targets. As such, the fitted curve in each sub-plot overlaps the dashed line contributing to the invisibility of the dashed lines in these sub-plots. The training data indicates a good fit. The test results also show a high value for R .

In this study, 90% of the recorded data points for each variable were used for the ANN training, and the remaining 10% were used to test the trained ANN. The ANN randomly divides the data into the training and testing categories. Regularization techniques were used with the back-propagation training algorithm to obtain a smaller error (Mouloudi et al., 2019b). This causes the responses of the network to be smoother and less likely to overfit to training patterns (Demuth and Beale, 2009; Saini, 2008). This was performed by applying the Bayesian regularization backpropagation. Bayesian regularized artificial neural networks (BRANNs) are more robust than standard back-propagation nets, and as such can reduce or eliminate the need for a process of cross-validation (MacKay, 1992). Bayesian regularization is a mathematical process that converts a nonlinear regression into a well-suited statistical problem in the manner of ridge regression. It is a training algorithm which typically requires considerable time. Nonetheless, it results in a good generation for difficult or noisy data points. The process of training stops according to adaptive weight minimization regularization (this was explained before).

A pattern recognition neural network was also developed to investigate the impact of horse age on the recorded experimental parameters. It succeeded in classifying data by age group using the data points of load, displacement, side of the limbs, time, and strains. This model was selected to be a two-layer feed-forward network, with sigmoid function for hidden neurons and softmax function for output neurons. The network was trained by scaled conjugate backpropagation. For a more detailed discussion, we refer interested readers to the book by Haykin (1994) and the paper by Lu (John Lu, 2010).

3. Results and discussion

Three distinct ANN models were trained, tested, and their accuracy was confirmed using different bone samples. The bone samples that were used to train these ANNs were: B1 and B3 for the first ANN; B1, B3, and B4 for the second ANN; and lastly, B1–B6 inclusive for the third ANN. Each ANN was then employed to predict the loading of specific bone samples that were not used in the ANN training. This offers a robust procedure whereby the accuracy of the ANNs are checked and confirmed in predicting real-world data that ANNs have not seen before.

The ANN was first trained using experimental data points from B1 and B3. These bones are representative of the two-year-old group (Table 1). There is a very good agreement between the output and target for both training ($R = 0.9999$) and testing ($R = 0.9999$) (Fig. 3). The regression plot (R) depicts the relevance between the target (the desired output) and the ANN output (the actual output). $R = 0.9999$ shows that the output of ANN in load prediction is in a good agreement with the ex-vivo measurements. In general, when R approaches 1, this indicates a precise linear relevance between the targets and the desired outputs. On the contrary, when R approaches zero, only a slight linear relevance between the targets and the outputs exists. Since the values of R are promising, the response of the network is favourable (Fig. 3). Hence, the ANN model can be employed to import new inputs.

The post-processing plots that demonstrate the performance of the ANN are shown in Fig. 4 where mean squared error training performance for successive training epochs and an error histogram are shown. An initial factor to be considered in the analysis is the performance plots which display the evolution of loss-functions per iteration for the

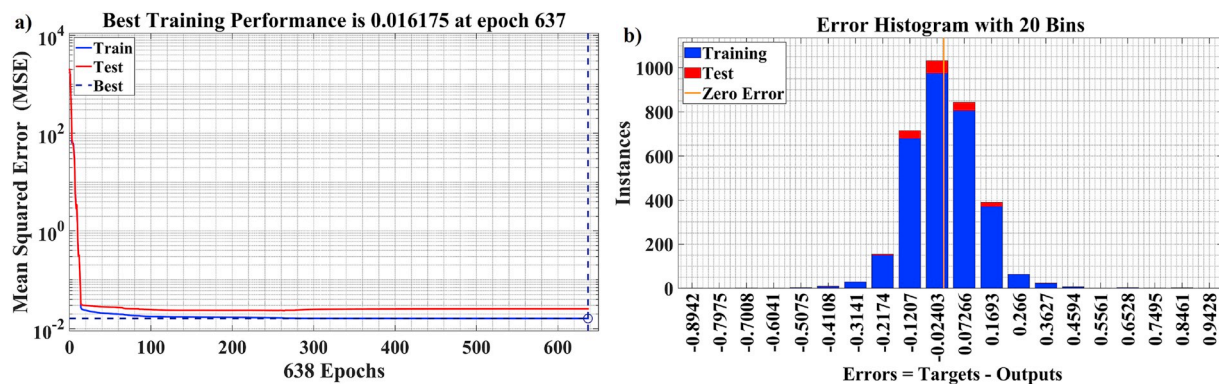


Fig. 4. The ANN was trained with data points from B1 and B3. a) The training curve of the ANN. b) The identification errors for the train and test datasets are presented in the histogram.

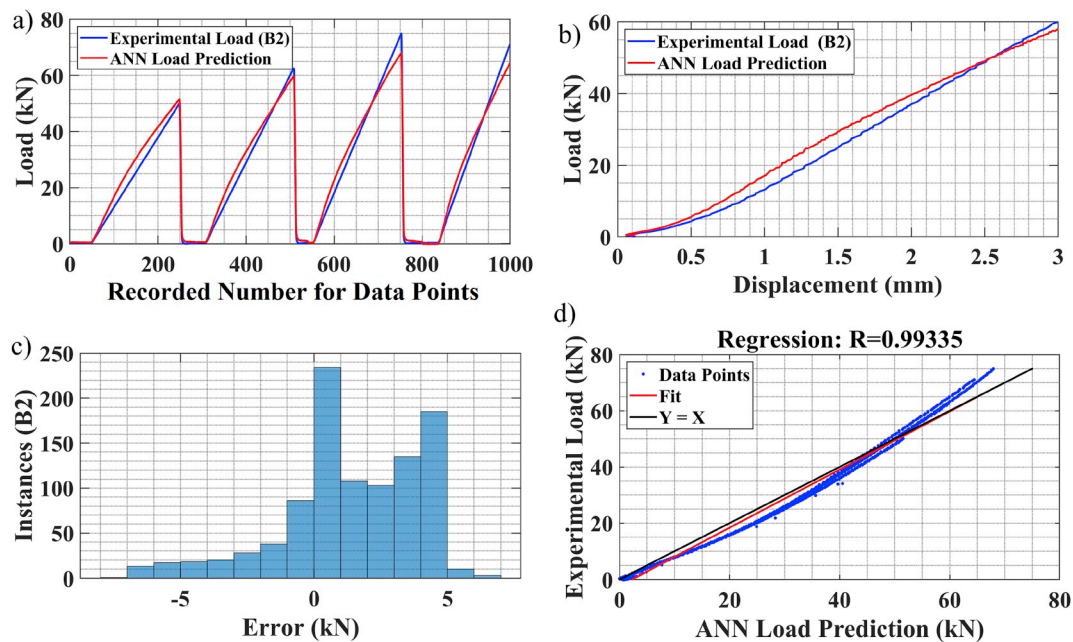


Fig. 5. The ANN model was trained using data points from B1 and B3, and then it was employed in order to investigate the load prediction for B2. a) Comparison of the experimental force with the prediction of the ANN model where recorded number for data points represents n expressed in Equation (7). b) Comparison of the second cycle of the force-displacement curve for both the experiment and the ANN model. c) Histogram of errors between experimental load and the load predicted by ANN model. d) The regression model, the experimental results, and the prediction of the ANN model.

training dataset. The main objective is to continue training the ANN model until the decrease in the test error stops. A single presentation of the entire data set is referred to as an epoch. Fig. 4a shows the variations of MSE during both the training and testing process. The error in the estimation of load decreased enormously by increasing the number of epochs. The best training performance occurs at epoch 637. The identification errors for the test data points are presented in a histogram in Fig. 4b. The histogram explains that all the errors of the ANN model are almost symmetrically distributed around the zero value and, more significantly, they fall into a relatively narrow interval.

The ANN model was successfully trained using ex-vivo measurements of B1 and B3. The knowledge of the trained network was stored in terms of weights and biases. The ANN model was then employed to predict the responses of B2 (that was not used in ANN training). Fig. 5a presents the values of the ex-vivo experiments and the load estimation produced by the ANN. The trend of the experimental results is consistent with those quantified by the ANN model. The value of load varies during loading/unloading and thus varies versus the recorded number for data points. The force-displacement curve that was recorded during the ex-vivo experiments and that obtained via the ANN model for B2 are demonstrated in Fig. 5b. The histogram of errors between the ex-vivo load experiment and the prediction of the ANN is presented in Fig. 5c. The outcome of regression analysis between experimental results and the prediction of the ANN model is illustrated in Fig. 5d. The more the value of variance that is accounted for by the regression model, the closer the data points will fall towards the fitted regression line. Agreement was found between the values of load predicted by the ANN model (horizontal axis in Fig. 5d) and the values that were recorded through ex-vivo experiments (vertical axis in Fig. 5d). The value of R is shown to be 0.9933. In a nutshell, Fig. 5 highlights the significant performance of the ANN model for the prediction of cyclic load recorded in the ex-vivo experiments for B2.

A hypothesis was now tested as to whether the ANN model, which was trained using samples from two-year-old horses, possessed the ability to predict the loading of samples from three-year-old horses. The ANN model which was described in Fig. 3 was employed to predict the loading of a sample from the three-year-old group (B7). Fig. 6a presents

the comparison of ex-vivo experiments and that of the ANN model for B7. The second cycle of the force-displacement curve recorded during the ex-vivo experiments and that which was obtained via the ANN model for B7 are demonstrated in Fig. 6b. The histogram of errors between the results of experiments and the ANN model is presented in Fig. 6c. The regression analysis for B7 demonstrates that the ANN is still capable of estimating load, testifying to the predictive quality of the model (Fig. 6d), and as such the hypothesis was confirmed. The deviation between the results became more noticeable with increasing load. This might be due to the different response of samples from two-year-olds and three-year-olds in absorbing maximum loads prior to failure. A remedy for this would be the introduction of bone samples from three-year-olds to the training session of a new ANN model, so that the ANN could perfectly capture the behavior of long bones under higher loads and could improve its load prediction capability (to reduce error of analysis).

To address the aforementioned comment, besides using B1 and B3 on which the ANN was initially trained and validated (Figs. 3 and 6), experimental data points from B4 and B5 (samples from three-year-olds) were also introduced into a new ANN model in order to investigate the outcome of load prediction for B7. Fig. 7 shows the outcome of the ANN model in the load prediction for B7 compared with the ex-vivo measurements and shows an improvement in the accuracy of ANN load prediction, mostly for the higher load magnitudes, when compared to the previous analysis (Fig. 6).

The ANN model was trained using data points from two-year-olds and three-year-olds (B1, B2, B3, B4, B5 and B6) and then it was employed to predict the responses of B7 (a sample from three-year-olds), and B9 (another sample from foals) (Fig. 8). The ANN was capable of predicting the load for B7, however, it failed to precisely predict the loading of a sample from the foals (Fig. 8). This indicates that an ANN which was trained using samples from two-year-olds and three-year-olds had a limited ability in load prediction of a bone from individual foals. Immaturity and lack of exercise might be responsible for the peculiar loading conditions of the foal samples, which would have impaired the ability of the ANN model to estimate their loading. Furthermore, the range of loading that MC3 bones from foals could withstand prior to

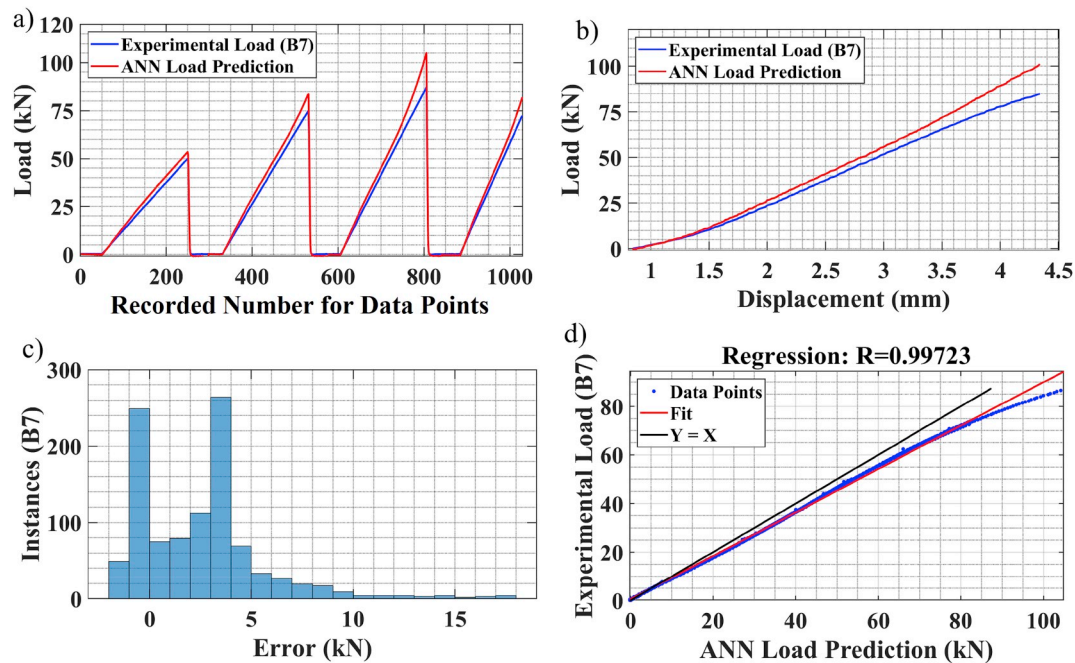


Fig. 6. The ANN model was trained using data points from B1 and B3, and then it was employed in order to investigate the load prediction for B7. a) Comparison of the experimental forces with the prediction of the ANN model where recorded number for data points represents n expressed in Equation (7). b) Comparison of the second cycle of the force-displacement curve for both the experiment and the ANN model. c) Histogram of errors between experimental load and the ANN model. d) The regression model, the experimental results, and the prediction of the ANN model.

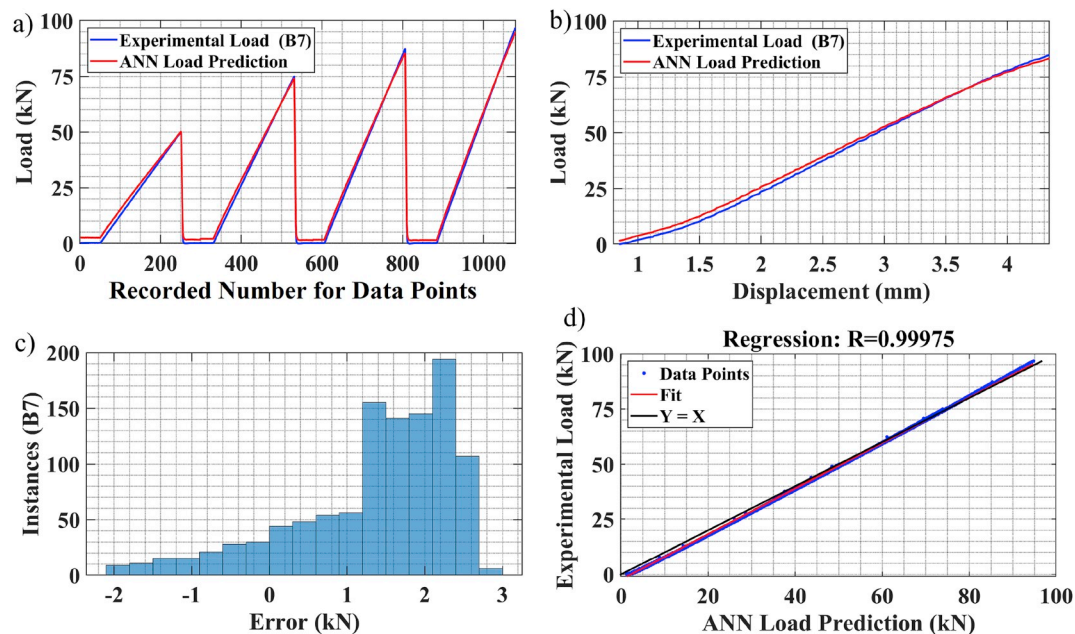


Fig. 7. The ANN model was trained using data points from B1, B3, B4 and B5, and then it was employed to investigate the load prediction for B7. a) Comparison of the experimental forces with the prediction of the ANN model where recorded number for data points represents n expressed in Equation (7). b) Comparison of the second cycle of the force-displacement curve for both the experiment and the ANN model. c) Histogram of errors between experimental load and the ANN model. d) The regression model, the experimental results, and the prediction of the ANN model. A major improvement in the accuracy of the ANN model was found with consideration of more samples from both two and three-year-old age groups.

fracture was less than that observed for two-year-olds and three-year-olds. This was dictated by a monitored process while loading all bones, including the foal bones, to minimize the risk of bones shattering. These facts along with the lower numbers of cyclic loads prior to failure contributed to the smaller number of experimental data points that could be recorded for the foal samples (Table 1). Also, in a recent study

by the authors converging-diverging shape configuration of the diaphysis of MC3 bones was discussed where a significant change in the width of the dorsal cortex (D), palmar cortex (P), and lateral cortex (L) was observed with maturation (a comparison between foals and the rest of the samples) (Mouloudi et al., 2019c). A variety of geometrical parameters within the midshaft of MC3 bones was measured and compared in

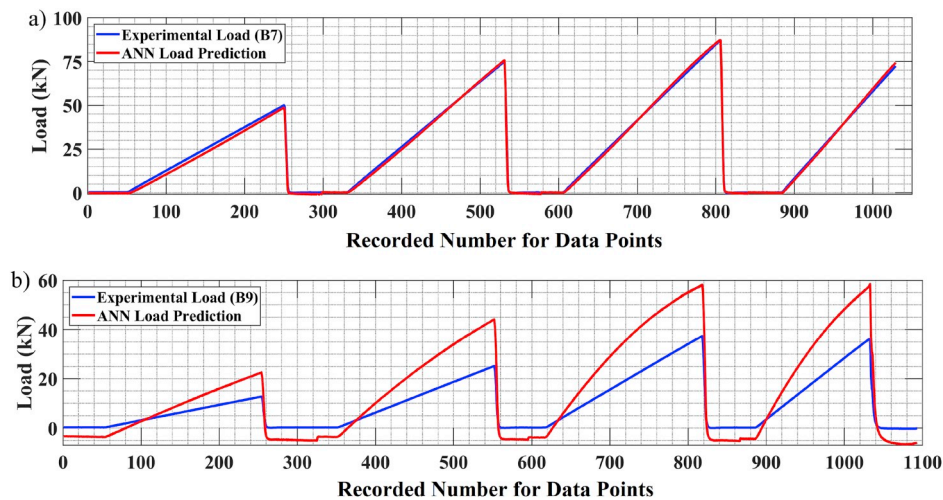


Fig. 8. The ANN model was trained using data points from two and three-year-olds (B1, B2, B3, B4, B5 and B6) and then it was employed to predict the responses of a) B7 which belongs to a three-year-old horse and b) B9 from a two-month-old foal. Recorded number for data points represents n in Equation (7).

that study. Immaturity, horse training history, lack of exercise, and bone shape are all closely tied to bone function (and its response under load that we recorded in this study). These factors, along with a decrease in quasi-static fracture toughness with age (Kulin et al., 2011), contribute to the lower magnitudes and cycles of loads that bones (at the whole level) from foals can tolerate prior to failure. Increasing the sample size and range of ages of foals in the experiments to acquire more data is recommended, so that the ANN is trained using more data points during loading/unloading of foal samples. The majority of growth in length of the MC3 in horses occurs in the first 6 weeks of life while the majority of the overall growth of body height and weight continues to around 15–18 months of age and complete maturity in body size is reached between the ages of 5–8 years. Hence it might be expected that immaturity would have a large and complex effect on the responses of the MC3 to loading, especially in horses less than 18 months of age.

Training multiple times will generate different results due to different initial conditions and sampling, nonetheless, this is not a remedy to enhance the ability of ANN in making reliable predictions on foal datasets. Overfitting is inevitable because the data used for training may not be completely representative to reflect the behaviour of all the samples. This may be explained by a lack of generality in the recorded data.

A potential reason for inaccuracy in the results presented in Fig. 8 was investigated by a categorizing approach. To categorize the data points of samples from two-year-olds, three-year-olds and foals by their age, a classification method was employed. Fig. 9a depicts a confusion matrix obtained using the measurements including t , s , d , ϵ , l , and age. Class one, class two, and class three indicate samples from two-year-olds, three-year-olds, and foals, respectively (Fig. 9). The ANN was trained using data points of the above-mentioned parameters from B1, B3, B5, B6, B7, and B9 (six bones from the three classes). The objective was to classify data points associated with B2, B4, and B8 (which were not involved in the trained ANN). The rows in Fig. 9a correspond to the predicted class (Output Class) and the columns indicate the true class (Target Class). The confusion matrix consists of two regions (i.e. the inner and the outer region, which include the last column and the bottom row of the matrix). These regions are shaded in grey in Fig. 9a. The diagonal cells (shaded in green) contain the number of correct matches (top digit) and their associated percentage (bottom digit). The percentages are relative to the number of inputs. Similarly, the off-diagonal cells (shaded in red) contain mismatches. The last column of the confusion matrix identifies a true positive rate (top digit) and a true negative rate (bottom digit) for the categorization of individual results. The true positive rate is the probability that an input which was

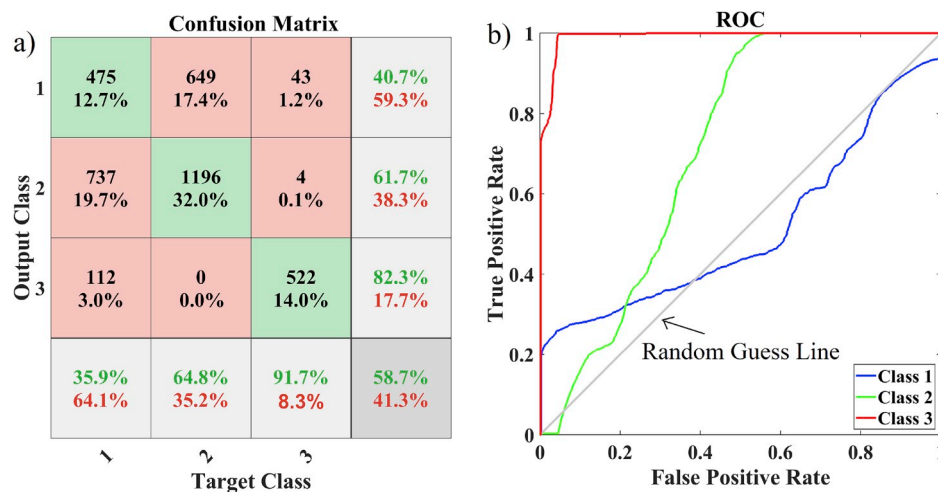


Fig. 9. a) Confusion Matrices for age Prediction: the ANN trained using all input features from B1, B3, B5, B6, B7, and B9 then the ANN model was employed to classify data points including time, displacement, and strains from B2, B4, and B8. The bottom right corner cells contain the overall accuracy of the results. b) Receiver operating characteristic (ROC) curve.

classified by the neural network belongs to the true category. While, the true negative rate is the probability that the prediction of the neural network for classification of the input data was incorrect. The bottom right cell (shaded in dark grey) identifies the overall accuracy of the ANN in categorizing data, where the top figure is the percentage of correct data classification, whereas, the bottom figure shows the percentage of misclassified data.

True positive rate (TPR), false positive rate (FPR), and receiver operating characteristic (ROC) are depicted in Fig. 9b. TPR defines the number of correct positive results that exists amongst all the available positive samples. FPR, on the other hand, defines the number of incorrect positive results that exist among all the negative samples. The space of ROC is defined by FPR and TPR on the x and y axes respectively. This space depicts relative trade-offs between true positive (benefits) and false positive (costs) values. The (0, 1) coordinate is called a perfect classification point. A completely random guess would give a point along a diagonal line (a line of no-discrimination). This line is drawn from the left bottom to the top right corner of the Fig. 9b. Fig. 9b shows that the outcome of the classifier for class three is clearly associated with the best predictive power amongst all the classes. The outcome of the classifier for class one and class two is relatively close to the random guess line (the diagonal line). This indicates a good ability of the proposed model to distinguish the data points between class three and other classes. However, the ability of the model to classify the data points associated with class one and class two diminishes. This explains that there is an inherent difference between class three and other classes at least in terms of the measured experimental data. This further highlights that the data points of class one and class two are closely tied and correlated. This connection, however, is lacking with the data points of class three. While the ANN trained with data points of class one and class two could not precisely predict the data points from class three, it was able to predict the overall trends. Through feeding more data points and including more samples from each class, the accuracy of the ANN in data classification will be improved.

It was observed that the ANN which was trained with samples from class one can predict the loading of samples from class two, and vice versa. Nonetheless, a trained ANN with data points of samples from class one and class two cannot accurately predict the loading of samples from class three. The data-driven methods such as ANN tend to adapt to any poorly-designed pieces of data. ANNs do not make a priori assumptions about the type of model being investigated. Therefore, when the ANN is trained with appropriate and relevant data, the model is capable of precisely estimating the values of load.

The connection weights approach, which uses raw input-hidden and hidden-output connection weights in the neural network (Mandal et al., 2009; Olden et al., 2004), was employed to quantify the relative importance of input variables. The connection weights approach calculates the product of the raw input-hidden and hidden-output connection weights between the neuron of input and the neuron of output and then sums these products across all hidden layers. Table 2

Table 2
The percentage of relative importance for the individual input variables using the connection weight approach. The ANN input variables were defined in the Equations (4) and (5).

Input number	ANN input variable	Importance (%)
1	t	2.58
2	s	9.16
3	y	4.86
4	d	2.14
5	ε_1	4.29
6	ε_2	9.16
7	ε_3	9.32
8	ε_4	32.98
9	ε_5	10.97
10	ε_6	14.54

reports on the relative importance of input variables on the ANN load prediction investigated in this study. Overall, strains significantly affect the load prediction, which demonstrates the profound effect of midshaft strains measurement on the load estimation. The rest of the parameters, though important, revealed a moderate effect on load prediction. As stated by Olden et al., the “connection weight approach provides the best methodology for accurately quantifying variable importance” (Olden et al., 2004), yet future studies are expected to employ different algorithms (such as Garson’s algorithm, partial derivatives, backward stepwise elimination, and input perturbation) along with the connection weights approach to carefully investigate different techniques using several ANNs (with different training algorithms) to elucidate the importance of ANN input variables in biomechanical engineering and to connect this importance to the underlying physics of long bones.

The fundamental advantage of artificial neural networks is that they are able to automatically map a relationship from the supplied input and output parameters. Hence, complicated relationships between various parameters can be found out by an ANN. ANN is a model-free estimator, as such, parameters that are difficult to be measured experimentally can be estimated via the ANN model. ANNs are particularly useful in cases where solving a forward finite element model is time consuming (Hambli et al., 2006; Mouloudi et al., 2019b; Unger and Könke, 2008), particularly when the model is comprised of a high number of nodes and elements (Mouloudi et al., 2019a), or when the loading condition on a model is not straightforward. In such cases, ANNs bring enormous benefits in reducing the time required for predicting the load, because the generation of the training dataset which involves solving the forward finite element problem needs to be performed just once. Afterwards, the trained ANN can be employed to predict the load without any need to solve the forward problem again. Solving inverse problems often involves a solution of several forward problems. Therefore, it is generally more computationally expensive to solve an inverse problem than to solve a forward one. The main advantage of artificial neural networks is that they are more efficient than the methods (such as direct optimization) where the results of previously solved forward problems cannot be used (Sung, 1998). These are the merits of using ANNs in predicting loading of complex engineering structures with exotic mechanical properties.

The ANN models developed for this study have demonstrated several advantages when compared to other approaches. Computer-aided-design (CAD) and finite element analysis (FEA) have been used extensively to model and analyse bones and to replicate experimental data. For example, there has been a 6000% increase in the number of finite element papers published between 1980 and 2009 (Erdemir et al., 2012). However, mesh quality, model validation, and appropriate energy balance have not been adequately addressed in these studies (Burkhart et al., 2013; Mouloudi et al., 2019a). Many assumptions are required to be made in FEA of highly complex structures like bones to produce desired results. Although such assumptions simplify the solution, they have a deleterious impact on the reliability of the outcomes and change the underlying physics of the bone. For example, FEA literature involving the human skeleton and the equine MC3 are subject-specific or rely on very few samples (Harrison et al., 2014; McCarty et al., 2016; Merritt et al., 2006, 2008). In addition, homogeneous bone material (Rubin et al., 2013) and linear isotropic mechanical properties (Gross et al., 1992; Skedros et al., 2006) have been assumed in several studies. The majority of published FEA studies lack substantial details to enable reproducibility, verification and validation procedures (Erdemir et al., 2012; Mouloudi et al., 2019a, 2019b). In reporting the results of FEA, it is necessary to gain confidence in the adequacy of the mesh statistics. Mesh quality assessment has not been adequately addressed in the literature (Burkhart et al., 2013). These inadequate assumptions in the previous FEA studies result in potentially misleading and inaccurate outcomes. Strategies to maximize FEA accuracy without the current runtime penalty were discussed by the authors in a recent study (Mouloudi et al., 2019a). Since complex attribute relationships

exist in bones, it is difficult to precisely quantify their responses using traditional analytical models. The limitations of reported FEA studies demonstrate why ANNs are becoming a valuable tool (Shanmugathan, 2016), for example, in biomechanical engineering, ANNs are providing a means of determining load responses of long bones. Sometimes, however, the enormous advantage of ANNs becomes a potential weakness. Lack of control over the learning process may lead to overfitting, a situation when the neural network is closely fitted to the training data points yet demonstrates impaired ability in making predictions for new datasets (data that ANN was not trained on). An indication of overfitting is when the accuracy of a testing session is considerably worse than a training dataset. The performance of ANNs performed in this study was rigorously monitored via regression analysis for both training and testing datasets (Fig. 3). Numerous ANNs with different structures were trained and tested, and subsequently to avoid overfitting an optimum number of neurons in the hidden layers was found to be five. A neural network having too many numbers of neurons causes overfitting (Mandal, 2017). With data acquisition on nine long bones and collecting more experimental data points for each bone (to feed into ANNs), the authors were aware of the size of the dataset recorded for each variable and the bone sample size, hence reliable decisions were made in data split into training and testing to further avoid overfitting. Moreover, to validate the already trained and tested ANNs, new datasets (that the ANNs have not seen before) were introduced to the ANNs inputs, and then the load predicted by the ANNs (referred to as output) was compared against experimental data (Figs. 5–8 inclusive). Using fully new datasets (that were not used in the training) offers an unbiased information on how well the algorithm performs, reduces both the error of analysis and the likelihood of overfitting, and ensures the reliability of developed ANNs (Mouloudi et al., 2019b). This is a novel contribution of the current study that is mostly overlooked in ANN studies where merely outcome of regression for testing and validation during ANN training is reported.

The current study reported in this paper has used ANN in a novel fashion to quantify cyclic load of bones from the experimental strains and displacement data. The ANN can be used to predict any type of load in any form of tissue adaptation including both long bones (whole scale) and trabecular bone with a given density distribution (Zadpoor et al., 2013) and will assist in affirming fatigue data available in the literature (Shaktivish et al., 2019). The experimental protocol performed in this study was promising in considering the entire geometry of the intact bone and in maintaining bone hydration during the experiment as well as the approach by which the bones were loaded. Advancement in bone mechanics has been driven by advances in techniques (Currey, 2009), as such employing artificial neural network expert systems to predict mechanical features of bone will assist future investigators to obtain a better understanding of bone mechanics. Much remains to be done at the micro and nanolevels to obtain a full comprehension of bone mechanics (Currey, 2009). Future research will combine the expertise of the authors in ANN, FEA, nanomechanics, and bone (Mouloudi et al., 2014a, 2019b; Mouloudi et al., 2019a, 2019b, 2019c). Since the ANN expert system was successful at predicting loading of an advanced material with exotic mechanical properties (whole bone), it will provide promising outcomes for predicting features of engineering structures in general.

4. Conclusion

A back-propagation neural network (BPNN) was used to predict the compressive loading of the equine third metacarpal bone. This is the first study in which the loading of an advanced biological material with exotic mechanical properties (a long bone) is quantified using an expert system (artificial neural network) from the experimental measurements of displacement and strains. The proposed model successfully predicted the load from the measurements of displacement and surface strains ($R^2 \geq 0.98$). Artificial neural networks provide a promising approach to

quantify mechanical features of complex structures without the current runtime penalty.

Funding

None.

Ethical approval

This experiment was approved by the Animal Experimentation Ethics Committee of the University of Melbourne.

Declaration of competing interest

We have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jmbbm.2019.103527>.

References

- Amali, R., Cooper, S., Noroozi, S., 2014. Application of Artificial Neural Network to Predict Static Loads on an Aircraft Rib, IFIP International Conference on Artificial Intelligence Applications and Innovations. Springer, pp. 576–584.
- Asiltürk, I., Çunkaş, M., 2011. Modeling and prediction of surface roughness in turning operations using artificial neural network and multiple regression method. *Expert Syst. Appl.* 38, 5826–5832.
- Biewener, A., Thomason, J., Goodship, A., Lanyon, L., 1983. Bone stress in the horse forelimb during locomotion at different gaits: a comparison of two experimental methods. *J. Biomech.* 16, 565–576.
- Burkhart, T.A., Andrews, D.M., Dunning, C.E., 2013. Finite element modeling mesh quality, energy balance and validation methods: a review with recommendations associated with the modeling of bone tissue. *J. Biomech.* 46, 1477–1488.
- Campoli, G., Weinans, H., Zadpoor, A.A., 2012. Computational load estimation of the femur. *J. Mech. Behav. Biomed. Mater.* 10, 108–119.
- Castro, J.L., Mantas, C.J., Benitez, J., 2000. Neural networks with a continuous squashing function in the output are universal approximators. *Neural Netw.* 13, 561–563.
- Che, Z., Purushotham, S., Cho, K., Sontag, D., Liu, Y., 2018. Recurrent neural networks for multivariate time series with missing values. *Sci. Rep.* 8, 6085.
- Chou, S.-M., Lee, T.-S., Shao, Y.E., Chen, I.-F., 2004. Mining the breast cancer pattern using artificial neural networks and multivariate adaptive regression splines. *Expert Syst. Appl.* 27, 133–142.
- Christen, P., van Rietbergen, B., Lambers, F.M., Müller, R., Ito, K., 2012. Bone morphology allows estimation of loading history in a murine model of bone adaptation. *Biomechanics Model. Mechanobiol.* 11, 483–492.
- Currey, J., 2009. Measurement of the mechanical properties of bone: a recent history. *Clin. Orthop. Relat. Res.* 467, 1948–1954.
- Currey, J.D., 2006. *Bones: Structure and Mechanics*. Princeton university press.
- Davies, H., McCarthy, R., Jeffcott, L., 1993. Surface strain on the dorsal metacarpus of thoroughbreds at different speeds and gaits. *Acta Anatomica.* 146, 148–153.
- Demuth, H., Beale, M., 2009. *Matlab Neural Network Toolbox User's Guide Version 6*. The MathWorks Inc.
- Deng, W.-J., Chen, W.-C., Pei, W., 2008. Back-propagation neural network based importance-performance analysis for determining critical service attributes. *Expert Syst. Appl.* 34, 1115–1125.
- Dennis, B.H., Jin, W., Dulikravich, G.S., Jaric, J., 2011. Application of the finite element method to inverse problems in solid mechanics. *Int. J. Struct. Chang. Solids* 3, 11–21.
- Ding, M., Odgaard, A., Danielsen, C.C., Hvid, I., 2002. Mutual associations among microstructural, physical and mechanical properties of human cancellous bone. *J. Bone Joint Surg. Br. Vol.* 84, 900–907.
- Erdemir, A., Guess, T.M., Halloran, J., Tadepalli, S.C., Morrison, T.M., 2012. Considerations for reporting finite element analysis studies in biomechanics. *J. Biomech.* 45, 625–633.
- Frost, H.M., 1990a. Skeletal structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's law: the bone modeling problem. *Anat. Rec.* 226, 403–413.
- Frost, H.M., 1990b. Skeletal structural adaptations to mechanical usage (SATMU): 2. Redefining Wolff's law: the remodeling problem. *Anat. Rec.* 226, 414–422.
- Gohari, S., Sharifi, S., Burvill, C., Mouloudi, S., Izadifar, M., Thissen, P., 2019. Localized failure analysis of internally pressurized laminated ellipsoidal woven GFRP composite domes: analytical, numerical, and experimental studies. *Arch. Civ. Mech. Eng.* 19, 1235–1250.
- Gross, T., McLeod, K.J., Rubin, C.T., 1992. Characterizing bone strain distributions in vivo using three triple rosette strain gages. *J. Biomech.* 25, 1081–1087.
- Hamblil, R., Chamekh, A., Salah, H.B.H., 2006. Real-time deformation of structure using finite element and neural networks in virtual reality applications. *Finite Elem. Anal. Des.* 42, 985–991.

- Harrison, S.M., Whitton, R.C., Kawcak, C.E., Stover, S.M., Pandey, M.G., 2014. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. *J. Biomech.* 47, 65–73.
- Haykin, S., 1994. *Neural Networks: a Comprehensive Foundation*. Prentice Hall PTR.
- John Lu, Z., 2010. The elements of statistical learning: data mining, inference, and prediction. *J. R. Stat. Soc. Ser. A* 173, 693–694.
- Kulin, R.M., Jiang, F., Vecchio, K.S., 2011. Effects of age and loading rate on equine cortical bone failure. *J. Mech. Behav. Biomed. Mater.* 4, 57–75.
- MacKay, D.J., 1992. Bayesian interpolation. *Neural Comput.* 4, 415–447.
- Mandal, P., 2017. Artificial neural network prediction of buckling load of thin cylindrical shells under axial compression. *Eng. Struct.* 152, 843–855.
- Mandal, S., Sivaprasad, P., Venugopal, S., Murthy, K., 2009. Artificial neural network modeling to evaluate and predict the deformation behavior of stainless steel type AISI 304L during hot torsion. *Appl. Soft Comput.* 9, 237–244.
- Martig, S., Hitchens, P.L., Stevenson, M.A., Whitton, R.C., 2018. Subchondral bone morphology in the metacarpus of racehorses in training changes with distance from the articular surface but not with age. *J. Anat.* 232, 919–930.
- McCarty, C.A., Thomason, J.J., Gordon, K.D., Burkhart, T.A., Milner, J.S., Holdsworth, D. W., 2016. Finite-element analysis of bone stresses on primary impact in a large-animal model: the distal end of the equine third metacarpal. *PLoS One* 11, e0159541.
- Merritt, J., Burvill, C., Pandey, M., Davies, H., 2006. Determination of mechanical loading components of the equine metacarpus from measurements of strain during walking. *Equine Vet. J.* 38, 440–444.
- Merritt, J.S., Davies, H., Burvill, C., Pandey, M.G., 2008. Influence of muscle-tendon wrapping on calculations of joint reaction forces in the equine distal forelimb. *BioMed Res. Int.* 2008.
- Merritt, J.S., Pandey, M.G., Brown, N.A., Burvill, C.R., Kawcak, C.E., McIlwraith, C.W., Davies, H.M., 2010. Mechanical loading of the distal end of the third metacarpal bone in horses during walking and trotting. *Am. J. Vet. Res.* 71, 508–514.
- Mouloudi, S., Khojasteh, J., Salehi, M., Mohebbi, S., 2014a. Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region. *Int. J. Mech. Sci.* 85, 160–167.
- Mouloudi, S., Mohebbi, S., Khojasteh, J., Salehi, M., 2014b. Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects. *Int. J. Mech. Sci.* 79, 162–167.
- Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H.M., 2019a. Accuracy quantification of the reverse engineering and high-order finite element analysis of equine MC3 forelimb. *J. Equine Vet. Sci.* 78, 94–106.
- Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H.M., 2019b. Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm. *Biocybernetics and Biomedical Engineering*. <https://doi.org/10.1016/j.bbe.2019.09.001>.
- Mouloudi, S., Rahmanpanah, H., Burvill, C.R., Davies, H.M.S., 2019c. Converging-diverging Shape Configuration of the Diaphysis of Equine Third Metacarpal Bone through Computer-Aided Design. *Comparative Exercise Physiology* Accepted for Publication.
- Muir, P., Peterson, A., Sample, S., Scollay, M., Markel, M., Kalscheur, V., 2008. Exercise-induced metacarpophalangeal joint adaptation in the Thoroughbred racehorse. *J. Anat.* 213, 706–717.
- Nicholson, D.W., 2012. On finite element analysis of an inverse problem in elasticity. *Inverse Probl. Sci. Eng.* 20, 735–748.
- Norrdin, R., Kawcak, C., Capwell, B., McIlwraith, C., 1998. Subchondral bone failure in an equine model of overload arthrosis. *Bone* 22, 133–139.
- Nunamaker, D., Butterweck, D., Provost, M., 1990. Fatigue fractures in thoroughbred racehorses: relationships with age, peak bone strain, and training. *J. Orthop. Res.* 8, 604–611.
- Olden, J.D., Joy, M.K., Death, R.G., 2004. An accurate comparison of methods for quantifying variable importance in artificial neural networks using simulated data. *Ecol. Model.* 178, 389–397.
- Reed, S., Cole, D., 2003. Development of a parametric aircraft fatigue monitoring system using artificial neural networks. In: *Proceedings of the 22nd Symposium of the International Committee on Aeronautical Fatigue*. International Committee on Aeronautical Fatigue (ICAF) Ottawa, p. 73.
- Rubin, C.T., Seeherman, H., Qin, Y.-X., Gross, T.S., 2013. The mechanical consequences of load bearing in the equine third metacarpal across speed and gait: the nonuniform distributions of normal strain, shear strain, and strain energy density. *FASEB J.* 27, 1887–1894.
- Ruff, C.B., 2005. Mechanical determinants of bone form: insights from skeletal remains. *J. Musculoskelet. Neuronal Interact.* 5, 202.
- Saini, L.M., 2008. Peak load forecasting using Bayesian regularization, Resilient and adaptive backpropagation learning based artificial neural networks. *Electr. Power Syst. Res.* 78, 1302–1310.
- Santschi, E.M., 2008. Articular fetlock injuries in exercising horses. *Vet. Clin. N. Am. Equine Pract.* 24, 117–132.
- Schulte, F.A., Lambers, F.M., Kuhn, G., Müller, R., 2011. In vivo micro-computed tomography allows direct three-dimensional quantification of both bone formation and bone resorption parameters using time-lapsed imaging. *Bone* 48, 433–442.
- Shaktivesh, Malekipour, F., Whitton, C., Lee, P., 2019. A method for fatigue testing of equine MCIII subchondral bone under a simulated fast workout training programme. *Equine Vet. J.*
- Shanmuganathan, S., 2016. Artificial neural network modelling: an introduction. In: Shanmuganathan, S., Samarasinghe, S. (Eds.), *Artificial Neural Network Modelling*. Springer International Publishing, Cham, pp. 1–14.
- Skedros, J.G., Dayton, M.R., Sybrowsky, C.L., Bloebaum, R.D., Bachus, K.N., 2006. The influence of collagen fiber orientation and other histocompositional characteristics on the mechanical properties of equine cortical bone. *J. Exp. Biol.* 209, 3025–3042.
- Song, J., Gu, R.J., 2012. A finite element-based methodology for inverse problem of determining contact forces using measured displacements. *Inverse Probl. Sci. Eng.* 20, 769–783.
- Sung, A., 1998. Ranking importance of input parameters of neural networks. *Expert Syst. Appl.* 15, 405–411.
- Turner, A.S., Mills, E., Gabel, A., 1975. In vivo measurement of bone strain in the horse. *Am. J. Vet. Res.* 36, 1573–1579.
- Unger, J.F., Könke, C., 2008. Coupling of scales in a multiscale simulation using neural networks. *Comput. Struct.* 86, 1994–2003.
- Van Gerven, M., Bohte, S., 2017. Artificial neural networks as models of neural information processing. *Front. Comput. Neurosci.* 11, 114.
- Wang, Z., Joshi, S., Savel'ev, S., Song, W., Midya, R., Li, Y., Rao, M., Yan, P., Asapu, S., Zhuo, Y., 2018. Fully memristive neural networks for pattern classification with unsupervised learning. *Nat. Electron.* 1, 137.
- Zadpoor, A.A., 2013. Open forward and inverse problems in theoretical modeling of bone tissue adaptation. *J. Mech. Behav. Biomed. Mater.* 27, 249–261.
- Zadpoor, A.A., Campoli, G., Weinans, H., 2013. Neural network prediction of load from the morphology of trabecular bone. *Appl. Math. Model.* 37, 5260–5276.

6.2. Summary and Concluding Remarks

In commercially available FEA packages (e.g. ANSYS, Abaqus), boundary conditions, material properties and applied loads are known inputs, and FEA algorithm produces sought outcomes such as stress, deformation and strain. Nonetheless, an inverse problem has to be solved to derive musculoskeletal loads from experimental displacement and strain measurements. Due to the complexities involved in the solution of nonlinear inverse problems, quantifying mechanical loads from experimental measurements of bones has not been extensively investigated and reported in the available literature. Nor is there an assurance that a unique solution exists for the inverse problem.

This Chapter reported on the adoption of feedforward artificial neural networks trained with experimental measurements to predict the cyclic mechanical loading of equine third metacarpal bones from experimental recording of strains, displacement, load exposure time, horse age and limb side (left or right). In other words, the author used ANN to find a solution for an inverse problem.

Training of the ANNs was found to be very successful, displaying a very good agreement between the output (load predicted by the ANNs) and target (experimental load) for both training ($R=0.9999$) and testing ($R=0.9999$). The results associated with regression, performance, and error histogram analyses demonstrated the potent ability of ANNs to successfully map the space of inputs to that of output, highlighting the significant performance of the ANN algorithms to determine mechanical loading of advanced materials with exotic mechanical properties in general. Because this approach was effective and practical in determining loads of this advanced biological material, it would be worthwhile exploring and developing in several other applications to determine mechanical loading of less complex structures. To explore the relative importance of ANNs input variables, a connection weights approach was also employed which identified that strains significantly affect the ANN output in prediction of load. The employment of a categorizing approach using pattern recognition algorithms elucidated age-dependent attributes of experimental measurements (supporting the findings of the study performed in Chapter 4).

Pattern recognition algorithms explained that there was an inherent difference between the bones from a group of foals and those from two- and three-year-olds at least in terms of the measured experimental data. This might be a reason for a relatively diminished ability of the

ANNs to predict mechanical loading of foal samples. The generalization ability of all the trained and tested ANNs was also assessed to investigate as to whether the already trained ANNs were able to make reliable predictions on bone samples that had not been involved in the ANNs training session.

Chapter 7

Prediction of load-displacement curve in a complex structure using artificial neural networks: A study on a long bone

Chapters 5 and 6 reported on the use of feedforward backpropagation neural networks to complete specific tasks. The ANNs encompassed one output and predicted either load or displacement. To explore the feasibility of neural networks to make reliable predictions of mechanical properties (stiffness in this chapter), both load and displacement were required to be quantified simultaneously and in a timely manner. This chapter reports on a published paper by the author and collaborators that investigated the following hypotheses (as discussed in Section 2.6.3):

- **H.7.** It is practical to implement two connected in-series feedforward backpropagation artificial neural networks to simultaneously solve forward and inverse problems in the computational mechanics of a complex structure possessing exotic mechanical properties (a long bone) to predict stiffness and cyclic load-displacement curves.
- **H.9.** The ANN models enable successful prediction of the mechanical responses and behavior of MC3 log bones ($R > 0.99$ for training and testing datasets of both ANN models) and are generalized very well to new datasets that ANNs had not seen before, i.e. $R > 0.99$, RMSE < 2.5 kN for load prediction, $R > 0.94$, RMSE < 0.33 mm for displacement prediction, and $R > 0.98$, RMSE < 1.2 kN/mm for stiffness prediction.

7.1. Published Journal Paper

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Prediction of load-displacement curve in a complex structure using artificial neural networks: A study on a long bone



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ABSTRACT

Long bones are composite materials possessing nonhomogeneous and anisotropic properties. They repair themselves (self-repairing) and adapt to changing mechanical demands by altering their shape and mechanical properties (self-adapting). Such exceptional features make long bones intriguing materials to comprehend properly. This also expands our knowledge of engineering materials and motivates researchers to employ novel techniques where conventional approaches may present limitations. This paper delves into the use of artificial neural network (ANN) expert systems to predict load-displacement curves of a long bone. Thirteen hydrated third metacarpal (MC3) bones from thoroughbred horses aged from twelve hours to three years were loaded in compression in an MTS machine. Strain readings from one three-gauge rosette and three distinct single-element gauges at different locations on the MC3 midshaft, displacement, load, load exposure time, horse age and bone side (left or right limb) were recorded for each bone. This information shaped ANNs input variables. Two in-series feedforward back-propagation ANNs were employed where the experimental recordings except for load were fed into the first ANN to predict load. Then, the predicted load along with the rest of experimental recordings were fed into the second ANN to predict displacement. Cyclic load-displacement and stiffness predicted by ANNs were plotted versus experimental counterparts. ANNs regression analyses showed $R > 0.95$ for training and testing datasets. To confirm their accuracy, ANNs were used to predict responses of specific bone samples that were not used in ANNs training. The ANNs trained using 17,718 experimental data points from twelve bones predicted the load ($R = 0.997$, RMSE = 2.44 kN), displacement ($R = 0.948$, RMSE = 0.321 mm), and stiffness ($R = 0.982$, RMSE = 1.197 kN/mm) of the thirteenth bone. The encouraging outcomes exhibit the exceptional ability of artificial neural networks in capturing the mechanical characteristics of complex structures.

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1. Introduction

Proper comprehension of the behaviour of nonlinear materials is essential in a variety of engineering applications. Non-linear relations exist among stress, strain, applied loads and deformation in these materials. To explain the behaviour of

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these materials (such as soil, rock, concrete, masonry, and composites) theoretical or empirical constitutive models were developed (Shin & Pande, 2000). For linear materials two essential mechanical properties are required to be defined: the modulus of elasticity (referred to as the elastic modulus or Young's modulus) and Poisson's ratio. In contrast, in nonlinear materials constitutive models involve the determination of several material parameters, which are scalar functions of induced deformation (Mihai & Goriely, 2017) and many of them do not convey a physical meaning (Shin & Pande, 2000). The intricacy of capturing these relationships stems from the complexity and variety of directions in defining strains and stresses in nonlinear materials (Mihai & Goriely, 2017). Developing such relationships depends on how a particular experiment is conducted and how the experimental data is processed (Evans, 2017). There are many approaches that can be used to determine the material parameters of complex materials. For instance, an inverse finite element method (FEM) is employed when geometries and responses of an investigated object are complex (Jamal & Morgan, 2019). In addition, the choice of constitutive models associated with one set of computed parameters versus another remains unclear (Destrade, Gilchrist, Motherway, & Murphy, 2012). Prevalent isotropic materials deform uniquely under load, yet this does not occur for nonlinear anisotropic materials that have peculiar shapes and geometry, such as bone. In a recent study by the authors a converging-diverging shape configuration of this complex structure was delineated in which a variety of geometrical parameters within the midshaft of MC3 long bones was explored to elucidate linkages between the shape of these expert biological materials and maturation (Mouloudi, Rahmanpanah, Burvill, & Davies, 2019a). Advancement in bone mechanics is driven by advances in techniques (Currey, 2009), and hence employing novel approaches are required to more efficiently predict the behaviour of nonlinear materials (Mouloudi et al., 2019c). Several approaches and methodologies using artificial intelligence (AI) have been suggested and devised to replace constitutive equations by data-driven methods such as artificial neural networks (Bock et al., 2019; Oeser & Freitag, 2009). There is an ample variety of AI algorithms such as fuzzy logic, artificial neural network, neuro-fuzzy (combining both ANN and fuzzy logic), and logistic regression; each excels in a specific area that aims to offer the best fitting idea to a problem and strives to provide the most precise correlation among variables (input and output data).

Predicting load-displacement curves of bones categorized as nonlinear materials at the whole bone level is a daunting task. Because many assumptions are required to be made while obtaining mechanical properties of bone tissues (Mouloudi et al., 2020). Also, mechanical properties of bones are multivariable, depend to a great extent on multiple factors (Currey, 2010), and change as a result of loads placed upon them. An equine bone, for example, adapts to the increase in body weight and exercise loading from birth and throughout the horse's life (Lawrence, 2005). The modulus of elasticity and stiffness of bones have been shown to be density-dependent (Carter & Hayes, 1977), anatomic-site-dependent (Keaveny, Morgan, Niebur, & Yeh, 2001), length-dependent (Nobakhti, Katsamenis, Zaarour, Limbert, & Thurner, 2017), and time-dependent (viscoelasticity) (Manda, Wallace, Xie, Levrero-Florencio, & Pankaj, 2017; Xie et al., 2017). Hence, the mechanical properties of bones change during life and thus are not fixed even in a single individual. These peculiar mechanical responses make bones intriguing materials for researchers and engineers, and if a proper comprehension of these advanced materials using novel techniques is achieved, our understanding of less complex materials (such as composites, nanomaterials and alloys) will be enhanced.

Moreover, predicting the mechanical responses of bone under load has a practical value in the design and post-operative analysis of orthopaedic implants (Council, 2001; Currey, 2009; Sharir, Barak, & Shahar, 2008), is critically important when determining the optimal shape of bones, and is essential to avoid mechanical overload that has been exhibited to be a significant contributing factor in horse injuries (Martig, Hitchens, Stevenson, & Whitton, 2018; Muir et al., 2008; Norrdin, Kawcak, Capwell, & McIlwraith, 1998; Santschi, 2008). Such injuries may be acute or chronic and stem from a single impact event or cumulative damage during time (Merritt et al., 2010). Still, little is available in the literature to describe the employment of novel and efficient approaches in a timely manner for load and deformation prediction in this complex material, except for recent studies by the authors where displacement (Mouloudi et al., 2019c) and loading (Mouloudi et al., 2020) were individually investigated using finite element analysis and a single artificial neural network to process the experimental data.

Elongated and simplified forelimb bones of horses are apparently well-adapted for exercise at high speeds (Davies, 2005). The third metacarpal bone (MC3) forms an essential part of the lower forelimb in withstanding loads, and many investigations into human bones are heavily reliant on the outcome of equine bone research (Couch & Nielsen, 2017). Clearly, a large bone that shows a relatively restricted range of normal movements would provide the best chance to develop a model to investigate the normal responses of bones to loading (Mouloudi, Rahmanpanah, Burvill, & Davies, 2019b). Conventional methods involving strain gauge methods (Merritt, Burvill, Pandey, & Davies, 2006) or limb dynamics procedures (Merritt, Davies, Burvill, & Pandey, 2008) have been proposed to quantify loading of MC3 and have stated that compression is the predominant loading exposed on MC3 at various horse gaits and speeds. This loading regime and the associated displacement are believed to have a considerable impact on bone damage (Davies, McCarthy, & Jeffcott, 1993; Turner, Mills, & Gabel, 1975) and its noteworthy self-repairing and self-adapting features. Engineers and biologists are increasingly interested in gaining deep biological insights to enable development of self-repairing materials (Speck & Speck, 2019). Quantification of mechanical load and associated displacement is also a vital step in determining stiffness (and finally the modulus of elasticity), comprehending the underlying physics of complex structures, and offering strategies to avoid disastrous incidents. Strength is also derived from, and is strongly correlated to, stiffness estimations because both these mechanical properties depend on similar morphological and material properties (Kontulainen et al., 2008). Proper estimations of whole bone strength and

stiffness as well as evaluating stiffness-strength correlation are also important to identify individuals that may benefit from prophylactic treatments aimed at reducing fracture risk (Patton et al., 2019).

Artificial intelligence (AI, human intelligence exhibited by machines (Jones, Golan, Hanna, & Ramachandran, 2018)) models can perceive the world, decipher meanings as humans do, and learn from real-world examples (certain averaging over realization). Considered as one group of algorithms employed for machine learning, artificial neural networks (ANNs) are advanced fitting and pattern recognition algorithms that allow users to extract complex relationships among nonlinear variables (Mouloudi et al., 2020; Somers & Casal, 2009). ANNs considerably simplify the methodology of modelling in a problem and are potent modelling tools, particularly for cases where establishing relationships among variables (load, stress, displacement and strains) is not a straightforward task due to the complexity of the problem and exotic properties of the material. In ANN models learning through examples replaces physical modelling. This makes ANN computational tools very appealing in engineering applications where there is little or incomplete understanding of the problem, yet experimental measurements are readily available, or when geometrical data is missing or unavailable. Finite element analysis (FEA) is being extensively employed in mechanical and biomechanical engineering. Applied loads, geometry, the manner in which elements are connected, mechanical properties of the elements, boundary conditions (or constraints), and the type of analysis to be performed are normally introduced as input parameters. The computer then uses these pieces of input information to generate and solve the equations necessary to carry out the analysis (Logan, 2011) and to quantify induced stresses, displacement, and strains (regarded as output information). This process is referred to as completing a solution to a forward problem in FEA. A partial or total lack of one of these input parameters impairs the ability of FEA to solve the problem. ANNs are superior techniques to be employed in such circumstances. Engineers are obliged to make many simplifying assumptions in their FEA models, which engender inaccurate and misleading results. Neither is there consensus regarding an optimal constitutive model nor the bone mechanical properties to be implemented in these FEA models. The proposed ANN models in the current study do not require the inclusion of these simplifying assumptions.

Completing a solution to an inverse problem (and not the aforementioned forward problem) is required to quantify applied loads that induce deformations and strains in a system (Tarokh, 2017). When the input information such as geometric data, density distribution, constraints (boundary conditions) and strain measurements are known, it is still complicated to solve an inverse problem (Zadpoor, 2013) and requires the development of sophisticated optimization algorithms (Nocedal & Wright, 2006). FEA packages (such as Abaqus and Ansys), frequently employed in the biomechanical studies, are incapable of completing a solution to the inverse problem. Hence, alternative methods are required to quantify loads in a highly nonlinear advanced material (such as a bone) from strain recordings. This was investigated and discussed in a recent study by the authors where back-propagation neural networks (BPNN) were employed to predict the compressive loading of MC3 bones from the experimental measurements of displacement and strains (Mouloudi et al., 2020). In that study displacement of the bones was also used as an input of the ANN. In this study, both displacement and applied load are to be quantified using ANNs.

Empirical elasticity-density relationships are commonly employed in CT/MRI-based FEA to define and assign mechanical properties to the elements of finite meshes. There are considerable differences among the proposed relationships in the literature, nor is it clear whether such differences in elasticity-density relationships can be entirely explainable in terms of methodological discrepancies among studies (Helgason et al., 2008). Also, an assumption of quasi-static loading must be made in FEA when using density-dependent mechanical properties, which impairs the ability to conduct a dynamic analysis of bone tissues. This is one instance where employing alternative approaches such as ANN are advantageous. ANNs are also useful in scenarios where performing an FEA is cumbersome and time-consuming (Hambli, Chamekh, & Salah, 2006; Unger & Könke, 2008). In several engineering practices, it was shown that ANN gives better simulation as compared with FEA (Javadi, Tan, & Zhang, 2003; Vasundara, Padmanaban, Sabareeswaran, & RajGanesh, 2012).

ANNs were shown to be able to predict the load-displacement relationship of composite fibre reinforced concrete (Ashrafi, Jalal, & Garmsiri, 2010) and that of annealed copper obtained from the loading portion of nanoindentation tests (Muliana, Haj-Ali, Steward, & Saxena, 2002). Using data from loading-unloading portions of an indentation curve ANNs were employed to predict the stress-strain behaviour of thin metallic films on substrates produced during indentation tests (Huber, Nix, & Gao, 2002, 2000). ANNs also enabled the prediction of damage evolution in forged aluminium matrix composites as a function of forging parameters (Roberts, Kusiak, Liu, Forcellese, & Withers, 1998) and to model the mechanical behaviour of ceramic-matrix-composites (Rao & Mukherjee, 1996). Given the complex shape and geometry of long bones and their intricate mechanical characteristics, a successful prediction of their load-displacement curve will greatly assist researchers in predicting the responses of such engineering materials.

Multilayer feed-forward back-propagation artificial neural network (FF-BP-ANN) is the prevalent type of ANN performed in several engineering practices (Jin & Lin, 2011; Mouloudi et al., 2019c). In the current study, two connected in series FF-BP-ANNs were trained and employed using Bayesian regularization backpropagation to predict load-displacement curves of an advanced biological material (equine MC3 bone) from recorded ex-vivo surface strains measurement, exposure time, limb side, bone length, and horse age. Considered to be expert systems, ANNs developed in this study are encouraging and will assist researchers in predicting mechanical characteristics of engineering structures that exhibit exotic and peculiar mechanical properties.

Table 1

The sample number and age group of the third metacarpal bones used in this study. The total number of recorded experimental data points (maximum value of n in the Eqs. (7)–(10)) was also reported herein.

	Foal (< 6 months)				Two-year-old					Three-year-old			
	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13
n	1375	569	1093	1026	1266	1926	1324	1415	1365	1845	2708	1806	1156
s	Right	Left	Left	Left	Left	Left	Left	Right	Right	Right	Right	Left	Left

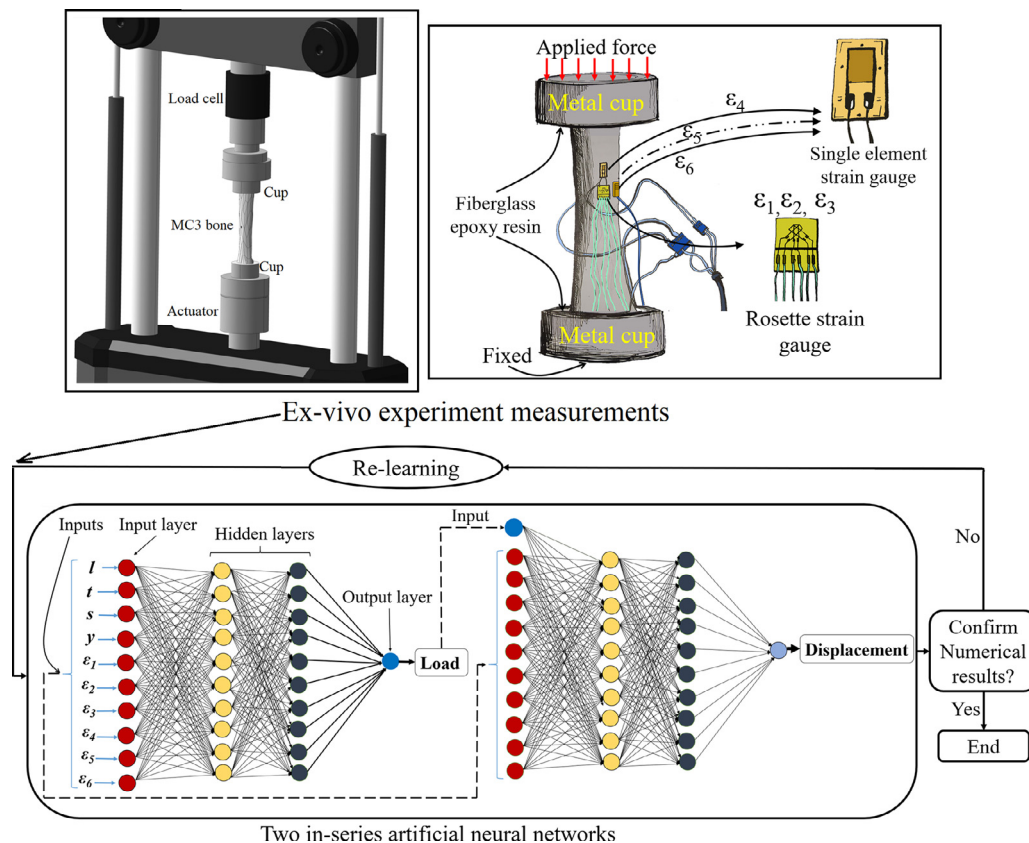


Fig. 1. The process of bone preparation for the experiment. The distal and proximal ends of the MC3 bones were surrounded by metal cups into which slow-curing fiberglass impregnated resin was poured. Due to the resin, both ends of the bones became flat parallel surfaces and were perpendicular to the shaft of the bones. The output of the experiment was imported into MATLAB to train neural networks and to develop the load-displacement prediction algorithms.

2. Materials and methods

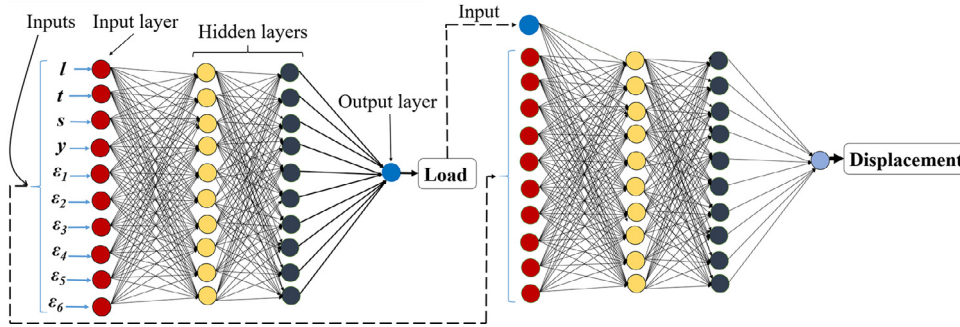
2.1. Experimental data

The experiment in this study used materials collected from donated cadavers of horses that died for reasons unrelated to this experiment. Thirteen third metacarpal bones (B1 to B13) from thirteen thoroughbred racehorses aged from twelve hours to three years and with no history of bone disease were used in the *ex-vivo* experiments. The details of the bone samples are presented in Table 1. Detailed processes from which the experimental data was measured and collected were delineated in the recent studies by the authors (Mouloudi et al., 2019c, Mouloudi et al., 2020). Briefly, each cleaned MC3 bone with strain gauges in place was loaded in a material testing system (MTS) and strains were recorded during loading/unloading (Fig. 1). This was followed by embedding both ends of the MC3 bones in fibreglass-impregnated resin. Strain gauges remain a reliable means of measuring and recording strains repeatably, and are recommended for accurate and discrete measurements in specific bone locations (Grassi & Isaksson, 2015). A 250 kN load frame and an MTS 430 controller loaded the bones *ex-vivo* in compression. Peak loads were increased incrementally to failure. To minimize dehydration, the bones were wrapped separately in a clear plastic wrap that was kept throughout the test to maintain hydration and to reduce evaporative loss during the test. The range and examination of the experimental data are reported in Table 2 to better

Table 2

Ranges, mean, and standard deviation of the original data recorded during ex-vivo experiments.

	Strains ($\mu\epsilon$)	Load (kN)	Displacement (mm)	Load exposure time (seconds)
Range	-11,600 to +1190	0 to 112.38	0 to 10.2	0 to 162
Mean ($\pm$ S.D.)	-1198.2 ($\pm$ 1626.8)	28.19 ($\pm$ 28.31)	1.4 ($\pm$ 1.7)	6.8 ($\pm$ 4)

**Fig. 2.** Structure of two neural networks which were performed in this study for prediction of load and displacement.

comprehend the distribution of experimental variables. These experimental data were imported into the ANN algorithms for computer simulation analysis.

2.2. Artificial neural networks

Artificial neural network (ANN) algorithms are inspired by the structure of neural networks in the human brain (Hertz, 2018). Like biological neurons, the information processing system of ANNs comprises three main aspects: transmission, processing and storage of information (Hornik, 1991). Data preparations that serve for ANNs training and testing along with the development of appropriate ANNs are comprised of several essential steps as follows:

Step 1. Identifying the training datasets and specification of the ANNs input and output variables.

The selection of appropriate input variables that allows an ANN to capture desired outputs is essential. Deep comprehension of the biomechanics of the studied bones is critically important for successful ANN training. This assists both in avoiding the loss of information when key input variables are inadvertently omitted and in preventing inclusion of spurious inputs that hinder the ANNs training. The test data was used to check and affirm the accuracy of the trained ANNs. To achieve the objective of this study (predicting load-displacement curve of the studied bones) many networks were trained and tested, from which the configuration of the network, the optimal number for the hidden layers, and the optimal number for the neurons in each hidden layer were selected. Two in-series feed-forward back-propagation neural networks (FF-BP-NN) were employed in the current study where the networks comprised one input layer (with multiple variables), two hidden layers (comprised of ten neurons each), and one output layer (encompassing one variable). The first neural network was used for load prediction, then the predicted load along with the other input variables were fed into the second neural network through which the displacement of the bones was quantified (Fig. 2). This figure schematically presents a flow chart indicating the steps involved in the prediction of a load-displacement curve via the discussed methods. The recording of experiments conducted on the bone samples constructed the input variables and was employed for the ANNs training. The input layer of the first ANN comprises 10 neurons (indicating 10 variables): bone length (l), load exposure time (t), limb side (s), horse age (y) and six kinds of strain. These variables, along with the applied load that was predicted by the first ANN, comprised the input variables of the second ANN (the input layer of the second ANN comprises 11 neurons) (Fig. 2). Hence, these two ANNs aim to predict both load (L) and displacement (D) of MC3 long bones:

$$\text{Load} = \text{ANN}_1(\text{length, time, } s, \text{ age, } \epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5, \epsilon_6) \quad (1)$$

$$\text{Displacement} = \text{ANN}_2(\text{load, length, time, } s, \text{ age, } \epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \epsilon_5, \epsilon_6) \quad (2)$$

The input and the target of the proposed ANNs were stored in the matrix of inputs and the matrix of outputs, respectively:

$$\text{Input}_1 = [l \ t \ s \ y \ \epsilon] \quad (3)$$

$$\text{Output}_1 = [L] \quad (4)$$

$$Input_2 = [L t s y \varepsilon] \quad (5)$$

$$Output_2 = [D] \quad (6)$$

Each of the matrices in Eqs. (3)-(6) is comprised of a column vector of the variables, and as such the breakdown representation of these matrices is conveyed as:

$$Input_1 = \begin{bmatrix} l_1 t_1 s_1 y_1 \varepsilon_{1.1} \cdots \varepsilon_{1.6} \\ l_2 t_2 s_2 y_2 \varepsilon_{2.1} \cdots \varepsilon_{2.6} \\ \vdots \\ l_n t_n s_n y_n \varepsilon_{n.1} \cdots \varepsilon_{n.6} \end{bmatrix} \quad (7)$$

$$Output_1 = \begin{bmatrix} L_1 \\ \vdots \\ L_n \end{bmatrix} \quad (8)$$

$$Input_2 = \begin{bmatrix} L_1 l_1 t_1 s_1 y_1 \varepsilon_{1.1} \cdots \varepsilon_{1.6} \\ L_2 l_2 t_2 s_2 y_2 \varepsilon_{2.1} \cdots \varepsilon_{2.6} \\ \vdots \\ L_n l_n t_n s_n y_n \varepsilon_{n.1} \cdots \varepsilon_{n.6} \end{bmatrix} \quad (9)$$

$$Output_2 = \begin{bmatrix} D_1 \\ \vdots \\ D_n \end{bmatrix} \quad (10)$$

where n represents the total number of observations recorded for each variable.

Step 2. Employing selected normalization principles to normalize the training datasets and adding uncertainties to the training datasets in order to improve the ANNs performance.

Since the value of different raw datasets varies across a wide range, objective functions in some machine learning practices will not perform properly unless data normalization is included. Normalization of the input variables to the same range is a recommended practice that improves the performance of artificial neural networks (Ceylan, 2003). The ANNs input variables in the current study possess distinct features encompassing a dissimilar range of magnitudes. To investigate the influence of normalization, each ANN was trained and tested using two normalization methods: min-max (minimum and maximum) and mean-std (in which std stands for standard deviation).

The outcome of pilot studies revealed that using the mean-std method was associated with a lower error in quantifying the targets, and hence, the mean-std normalization method was employed in this study. This method commenced with obtaining the mean and standard deviation for each of the input variables recorded for each individual bone. Then each of these variables was normalized using the following formula:

$$x' = \frac{x - \bar{x}}{\sigma} \quad (11)$$

where x is the original (intact) recorded input variable for a specific bone, $\bar{x}$ is the mean value of that variable, and σ is its standard deviation. The ANNs input parameters are normalized prior to their exposure to the neural networks. It has also been shown that the accuracy of the model and the training performance will be enhanced when some levels of inaccuracy are added to the trained neural networks (Noh, You, Mun, & Han, 2017; Zur, Jiang, Pesce, & Drukker, 2009).

Neural network algorithms are capable of learning and anticipating the trends of outputs when they change with slight changes in the inputs. Experimental measurements involving *in-vivo* or *ex-vivo* recordings of strains, loads and time are not free of noise. Neural networks perfectly learn output functions in scenarios where the magnitude and trend of outputs are super sensitive to small changes in the inputs. Adding noise is similar to teaching the network to not change the output in a range around your exact input. This dictates that the ANN should not substantially change the outcome prediction should there are some minor fluctuations in the input variables. Gaussian noise (also referred to as white noise) is a common noise source introduced to ANN input variables during training (Zadpoor, Campoli, & Weinans, 2013). Gaussian noise has a mean value of zero and a standard deviation of one and can be generated using a random number generator. The amount of introduced noise (e.g. the spread or standard deviation) plays a critical role. Little noise has no effect, while too much noise makes the mapping function too challenging to learn. The standard deviation of the noise source controls the amount of

Table 3

Design parameters of the two ANNs.

Design parameters	First ANN	Second ANN
Type	Feed-forward	Feed-forward
Number of neurons in input layer	10	11
Number of hidden layers	2	2
Number of neurons in each hidden layer	10	10
Number of neurons in output layer	1	1
Data division	Random	Random
Learning algorithm	Bayesian regularization back-propagation	Bayesian regularization back-propagation
Activation function for hidden layers	Sigmoid transfer function	Sigmoid transfer function
Activation function for output layers	Linear transfer function	Linear transfer function
Performance function	Mean squared error (MSE)	Mean squared error (MSE)

spread and can be adjusted based on the scale of each input variable. The authors recommend performing data normalization first prior to introducing noise source to the data. The noise introduced to the input variables is (Mouloudi et al., 2019c; Zadpoor et al., 2013):

$$Input' = Input + N\left(0, \frac{Input}{\lambda}\right)$$

where $N(\mu, \sigma)$ stands for a Gaussian distribution with the mean (μ) and standard deviation (σ). In most situations it is difficult to decide on an appropriate range for the value of introduced noise. Gaussian distribution assists in finding the most appropriate values of noise. λ represents a signal to noise ratio. The ANNs were then trained and tested using noisy data points where the influence of different signal to noise ratios (λ values) was checked. An optimum value for λ , for which the ANNs demonstrated very good prediction ability, was found to be 100.

Step 3. Defining design parameters for the ANNs.

In designing an artificial neural network, there are a series of parameters that need to be selected. The choice of these parameters considerably influences the performance of networks. A traditional method of selecting these parameters is to adopt a trial and error approach. ANNs are typically modelled into one input layer, one or several hidden layers, and one output layer. The input layer comprises several nodes (neurons) each of which receives input information from an independent variable. The total number of nodes in the input layer equals the number of input variables. Likewise, the number of nodes in the output layer equals the number of output variables. The number of hidden layers and that of nodes in each hidden layer are influential factors in the design of an ANN. Nor are there absolute rules to determine the statics involved for the features of hidden layers. Suggestions, nonetheless, are offered that aid in concluding the optimum number of neurons and layers in the hidden part (Hajela & Berke, 1991). An ANN shaped from merely one hidden layer might not be well-suited to capture nonlinear relationships in datasets involved in complex practices (Ripley & Hjort, 1996). On the other hand, a neural network comprising too many hidden layers and hidden neurons causes overfitting and should be avoided. To ensure a robust generalization, an ANN must perform well not only on the data used for its training but also on new data that it has not seen before. The details of parameters used for ANNs design are presented in Table 3.

Synaptic weights store all information learnt by the ANNs from input variables. These weights include the magnitudes of the connections between pairs of neurons corresponding to two different layers: either the input-hidden layer; or, the hidden-output layer. Synaptic weights are coefficients that are progressively optimized by the learning algorithm during a training session, and the objective of the learning algorithm is to find the best collection of weights. Learning algorithms normally initialize a random value for synaptic weights, and then during many iterations the weights are adjusted according to the training algorithm and its optimization method. The aim is to reduce the error between the ANN prediction (output) and the target (experiments).

Step 4. Defining training and learning algorithm for neural networks.

Among different learning algorithms, back-propagation is a predominant algorithm used prevalently in engineering applications. This algorithm is used to find a local minimum of the error function. The ANN is initialized with random weights, then the gradient of the error function is calculated and used to optimize the initial weights (MacKay, 1992). Employing a backpropagation algorithm was also promising in this study to predict the required response of the MC3 long bones. Some regularization techniques are used in ANNs with the backpropagation training algorithm to obtain a smaller error. This causes the response of networks to be smoother and less likely to overfit to training patterns (Demuth & Beale, 2009; Saini, 2008). Some of the ANN training algorithms are Bayesian regularization backpropagation, Levenberg-Marquardt back-propagation, and scaled conjugate backpropagation. Bayesian regularized artificial neural networks (BR-ANNs) can reduce or eliminate the need for cross-validation processes because they are more robust than standard back-propagation networks (MacKay, 1992). A single presentation of the entire dataset (completing both training and testing sessions) is called an epoch. Hence, an epoch describes the number of times the algorithm sees the entire dataset. At each epoch the dataset is divided randomly, and examples in the training set are used to update and modify the connection weights and biases of the neural

networks. Upon completion of ANN training and once the error between output and target is minimized; so that it lies within an acceptable range; the bias and connection weights of the neural networks are fixed. Then the testing datasets are introduced to the network whereby the accuracy of the trained ANN is checked.

Step 5. Determining the training parameter required for ANN convergence (MSE).

Training error of the ANN or the mean squared error (MSE) is defined between the actual output (ANN prediction) and the target (experiments) and is explained as:

$$E = \frac{1}{2} \sum (t_k - y_k)^2 \quad (12)$$

where t_k and y_k are the target and actual outputs of the k^{th} neuron of the output layer. To optimize the performance of the ANNs, a performance factor associated with the back-propagation neural network is used. The MSE between the output of the network and the desired target is calculated as follows:

$$MSE = \frac{1}{m_1 q_{out}} \sum_{m=1}^{m_1} \sum_{k=1}^{q_{out}} e_k^2(m) \quad (13)$$

where q_{out} is the number of neurons of the output layer, and $e_k^2(m)$ is the error of the k^{th} output neuron for the m^{th} weight. MSE was back propagated to the network to adjust the weights and bias (as per the explanations of Step 4). By so doing, MSE is minimized between the ANN prediction and experiments. Finally, a neural network that is well-generalized to the target is produced. A well-trained network should have an MSE of the testing dataset less than, or equal to, the training dataset (Mandal, 2017).

Step 6. Plotting the output of ANNs prediction versus the target datasets.

This is highly recommended to evaluate the ANNs training efficiency.

Step 7. Validating the already trained and tested ANN models.

Validation is the process of determining the degree to which a model is an accurate representation of the real world from the perspective of the intended uses of the model. Fresh unseen data of new bone samples was introduced to the ANN models (input), and their prediction ability (output) was compared against the experiment. This offers a robust procedure whereby the accuracy of the ANNs are checked and confirmed in predicting real-world data that ANNs have not been trained on.

3. Results

3.1. Training the ANN and its performance

The progress of an artificial neural network during training is monitored by a learning curve. Fig. 3 depicts a learning curve for the first ANN (from the two in-series ANNs) that was trained using data points from B1 to B13, excluding B9. The learning curve shows the change in mean squared error (MSE) for the training and testing data sets throughout the training session. At the end of each epoch, which is the number of times the algorithm sees the entire data set, MSE for the training and testing data is calculated and plotted versus elapsed epochs. This facilitates monitoring the rate of ANN learning, diminishing associated errors, and the convergence of errors to a certain and acceptable value. Generally, it starts with a sharp decrease in the training and testing errors and then gradually reaches a plateau where the artificial neural network is regarded as a converged ANN.

Once the ANN is converged, its predictions are tested by a line of equality (i.e. $y = x$ plot) where x and y axes represent target values and the corresponding ANN predictions, respectively. Each scatter point is a target-output pair at the final epoch of a training session. Scatter points appear on the line of equality for a perfect match, and hence, the closer these points to the equality line, the more precise ANN predictions would be. Fig. 3 contains the scatter points and also the line of equality for training, testing, and all the studied data. Similar accuracy is observed for training and testing data points, which indicates that the trained ANN offers a reliable prediction. This is an important point because the dataset employed for testing was not involved in the training session.

3.2. ANN prediction of load, displacement, load-displacement and stiffness

The first ANN model was successfully trained using ex-vivo measurements of B1 to B13 excluding B9. The knowledge of the trained network was stored in terms of weights and biases. The second ANN model was trained using applied load (the output of the first ANN) and the mentioned ex-vivo measurements. Both ANN models were then employed to predict the load and displacement of B9. Fig. 4a presents the results of experimental load variation versus the cyclic load estimation produced by the first ANN. The trend of the experimental results is consistent with those quantified by the ANN model. The histogram of errors between the ex-vivo load measurement and the prediction of the first ANN is presented in Fig. 4b. The

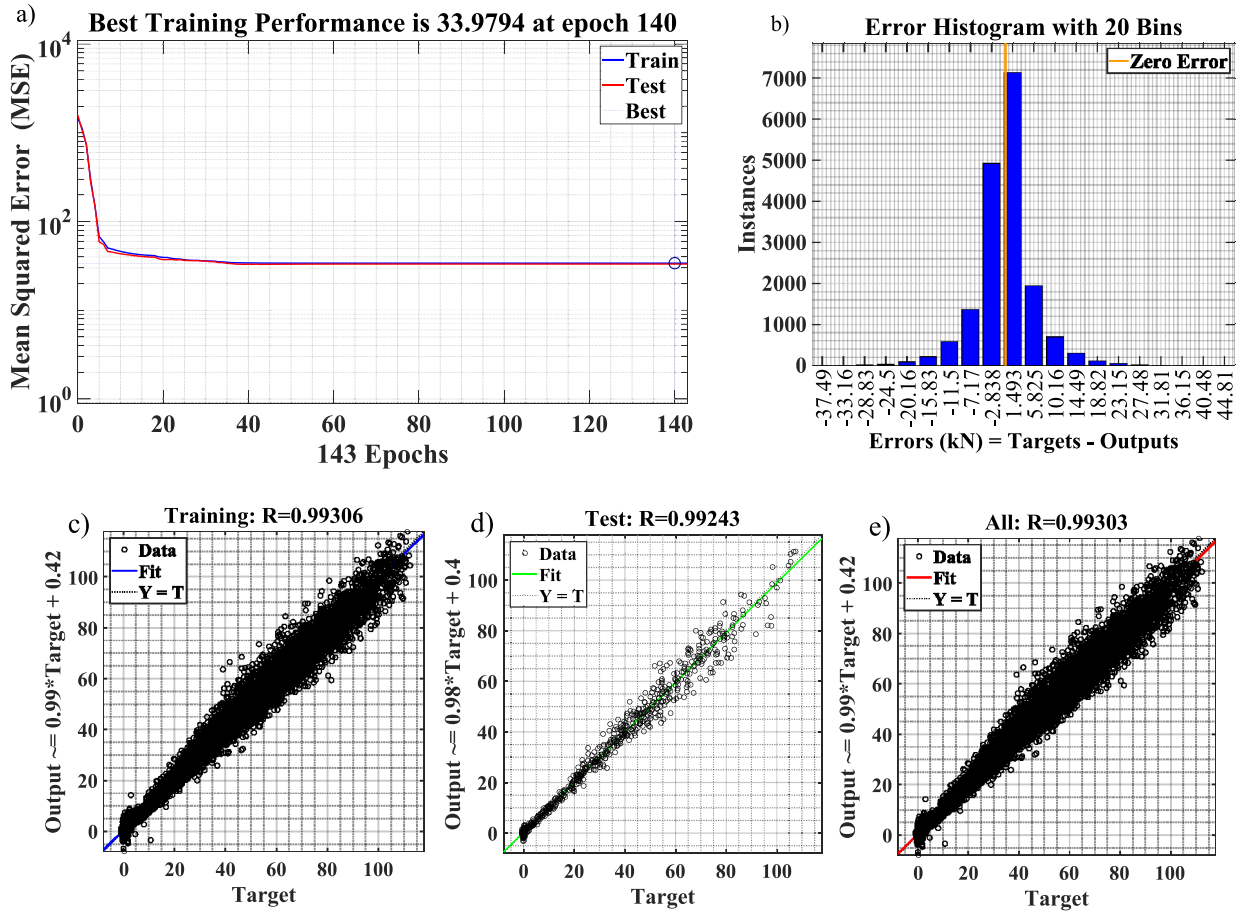


Fig. 3. The first ANN was trained with data points from B1 to B13 excluding B9. a) The training curve of the ANN. b) The absolute identification errors for the test dataset are presented in the histogram. This confirms the suitability of the proposed model. The three scatter plots represent c) training, d) testing, and e) all data points. The dashed line in each plot represents the perfect result which is outputs = targets. The solid line represents the best fit linear regression line between the outputs of ANN and targets (the experimental data points). The value of R is close to 1, which indicates an approximate linear relationship between outputs and targets.

outcome of regression analysis (a measure of comparison between experiments and ANN prediction) is shown in Fig. 4c. The results of the regression model ($R = 0.98$) also emphasize that there is a good agreement between the load predicted by ANN and the associated values recorded through ex-vivo experiments. This offers a value of 0.98 for R that indicates a convincing performance of the first ANN model for identifying the trends of the cyclic applied load and its magnitudes.

The second ANN model was employed to quantify cyclic displacement of the studied MC3 bones and to compare its outcome with the values recorded during the ex-vivo experiments (Fig. 5a). The histogram of errors that is an indication of the distribution of error between the prediction (output) of ANN and the displacement recorded during ex-vivo experiments is shown in Fig. 5b. This reveals that the distribution of the identification error for the output of ANN was close to a normal distribution. The coefficient of correlation (R) that measures the strength of a linear relationship between the ANN prediction and the displacement recorded experimentally is shown to be 0.95 (Fig. 5c).

The load-displacement response which was generated during the ex-vivo experiments and that obtained via the ANN models are demonstrated in Fig. 6. This plots a load-displacement curve of B9 for each of the four cycles of loading and unloading individually.

Identification of load-displacement is essential in predicting stiffness of a material and in comprehending its underlying physics. The relationship between force and response is the dynamic stiffness of a system, which is defined as the ratio of the applied force to the response (displacement) of the system (MC3 bones studied here):

$$\text{Stiffness} = \frac{\text{Load}}{\text{Displacement}} \quad (14)$$

Stiffness was calculated (from the estimation of both ANN models and employing Eqn (14)) and was plotted against the experimental recordings for B9 (Fig. 7).

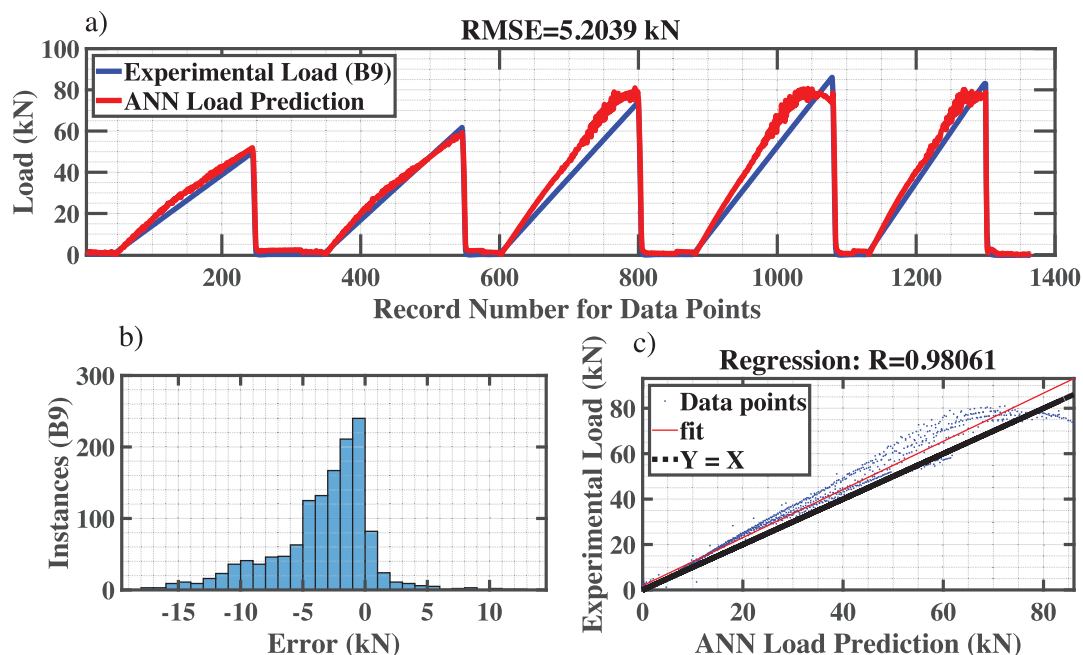


Fig. 4. The first ANN model was trained using data points from B1 to B13 except for B9, and then it was employed to quantify loading of B9. a) Comparison of the experimental load with the prediction of the first ANN model. b) Histogram of errors between experiments and the prediction of the first ANN model. c) The regression model, the experimental results, and the prediction of the first ANN.

Table 4

A summary of the ANN regression analyses conducted in this study. The correlation coefficient (R) and RMSE were obtained when the outputs of ANNs were compared against the recordings of ex-vivo experiments, which were not involved in the ANNs training sessions. This offers a reliable performance indicator of the ANNs.

Trained ANN	Number of Data Points	Bone Predicted	Load Prediction		Displacement Prediction		Stiffness Prediction	
			RMSE (kN)	R	RMSE (mm)	R	RMSE (kN/mm)	R
B1 to B13 except for B9	17,509	B9	5.2039	0.9806	0.3385	0.9512	2.8712	0.9514
B1 to B13 except for B12	17,068	B12	2.1845	0.9959	0.2235	0.9790	2.1845	0.9847
B1 to B12	17,718	B13	2.4418	0.9975	0.3211	0.9481	1.1979	0.9826
Average	17,431	—	3.2767	0.9913	0.2944	0.9728	2.084	0.9729

Similar processes were completed to predict cyclic load, displacement, and stiffness of B12 (Figs. 8 and 9) and B13 (Figs. 10 and 11) that belong to a different age group to B9, which was investigated before (Figs. 4–7 inclusive).

Table 4 summarizes the parameters that were involved in the regression analyses preparation of the ANNs. Table 4 also reports on the root mean square error (RMSE) and the correlation coefficient (R , the degree of relationship between ANNs outputs and the corresponding experimental values). These parameters assist in assessing the suitability of the performed ANNs in predicting the real-world data that was not used in their training session.

4. Discussion

The ideal way of modelling materials when their governing rules and equations are perfectly known is to employ traditional computing solutions. This provides a clear definition of the problem and is well-suited to determine the behaviour of prevalent engineering structures. Nonetheless, for advanced complex materials (such as long bones) whose mechanical properties exhibit dependency on multiple factors, applying alternative potent approaches are essential to capture such multivariable dependencies and to reduce the complexity of problem definition and its solution. The proposed method in this study predicted the load-displacement curve and was also capable of individually determining load (via the first ANN model) and displacement (the second ANN). Although existing non-linear relationships between the applied load/displacement and the surface strains make the prediction difficult, the system always converges and the MSE is in the range of an acceptable error. The latter was depicted in Figs. 4, 8a and 10a, and the former was demonstrated in Figs. 5, 8b, and 10b. The ANN was less accurate in load prediction when load approached its peak values, and the reverse trend was observed in displacement prediction where the ANN was shown to be less accurate in replicating low values of displacement recorded experimentally. Introducing a noise source to the ANN inputs and also using more bone samples during ANN training was suggested and

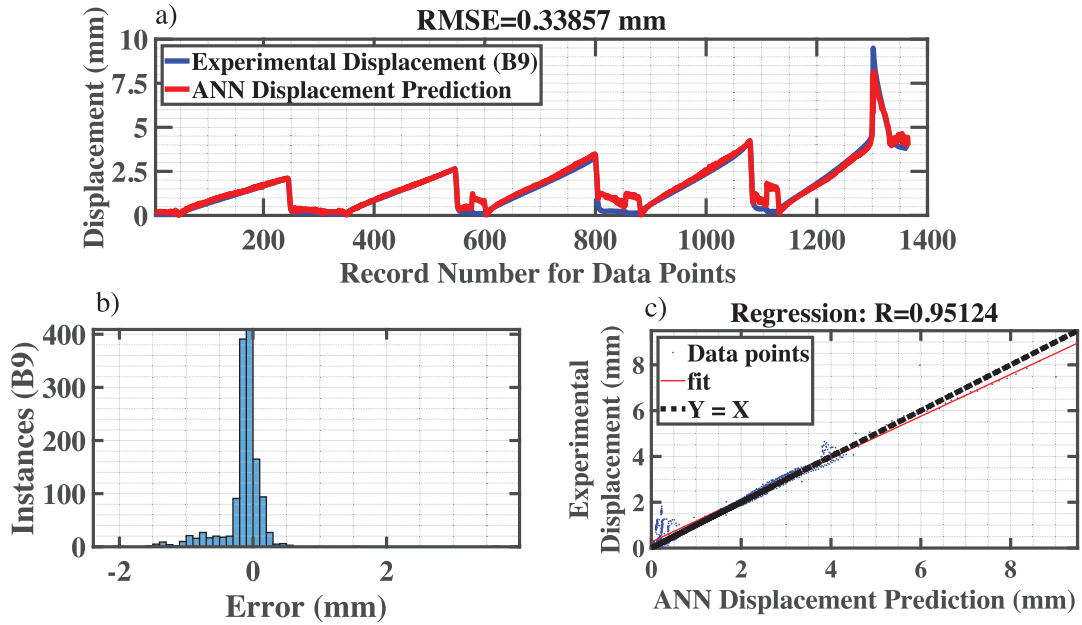


Fig. 5. The second ANN model was trained using data points from B1 to B13 except for B9. Besides experimental recordings, the output of the first ANN model (predicted load) was used as an input to the second ANN model. Then this ANN was employed to quantify displacement of B9. a) Comparison of the experimental displacement with the prediction of the second ANN model. b) Histogram of errors between experiments and the ANN prediction. c) The regression model, the experimental results, and the prediction of the second ANN.

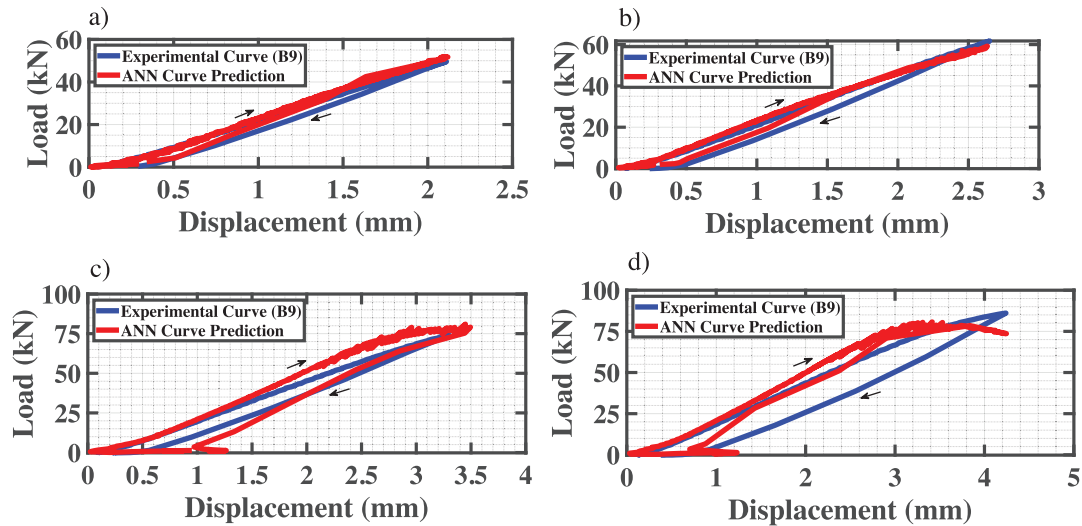


Fig. 6. The output of both ANN models was plotted against, and was compared to, experiment recordings. a) The first b) second c) third and d) fourth cycle of load-displacement response during loading/unloading of B9.

explained in the recent studies as remedies for enhancing ANN performance (Mouloudi et al., 2019c, Mouloudi et al., 2020). It was also recommended to conduct more experiments to capture more data for the low and high values of loads (within a range for which ANN exhibited diminished accuracy), so that there are more pieces of data available for this range of loading which ANN can benefit from during training sessions. An increase in stiffness with increasing applied load during loading was observed (Figs. 7, 8c, and 10c). This is not surprising and in the atomistic modelling of mechanical properties of biological materials an increase in dynamic stiffness for the higher loading rates and magnitudes was observed (Buehler, 2006). Stiffness predicted by ANNs agreed with the experiments, which demonstrates the ability of ANN models to obtain stiffness of advanced complex materials. Neural networks have, therefore, the merit of further investigation to estimate behaviour of widely applicable engineering materials (Ashrafi et al., 2010). The load-displacement hysteresis loops obtained for the axially loaded long bones were presented in Figs. 6, 9, and 11. The area enclosed by the loading and unloading path (hys-

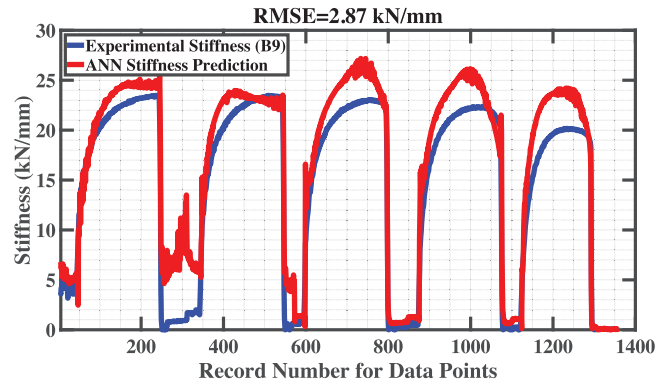


Fig. 7. The output of both in-series ANN models (Figs. 4 and 5) was used to quantify stiffness of B9 during loading/unloading.

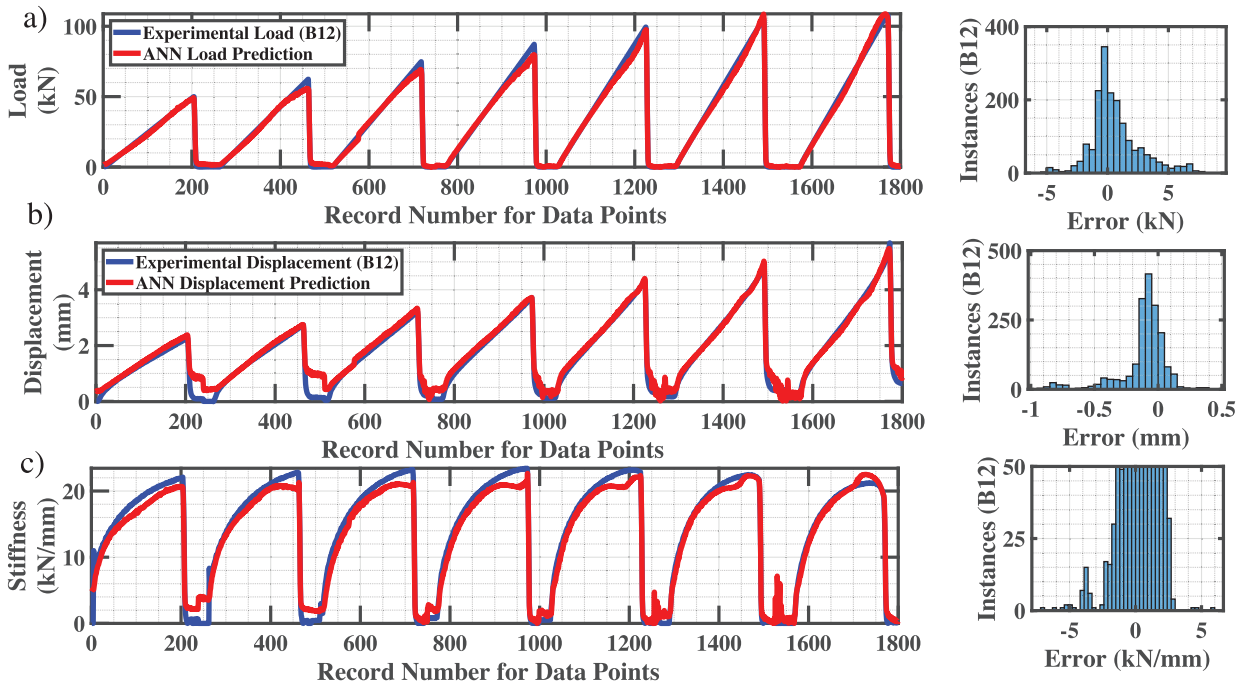


Fig. 8. Both ANN models were trained using data points from B1 to B13 except for B12, and then they were employed to quantify a) load b) displacement, and c) stiffness of B12 during loading/unloading. Histogram of errors between experiments and the ANNs predictions is depicted beside each relevant plot.

teresis loop) is a representative of heat dissipated and its presence for a viscoelastic material (long bone) is an indication of increase in the bone temperature for the continuous loading/unloading (Özkaya, Leger, Goldsheyder, & Nordin, 2017). It can be seen that the curves produced by ANNs almost envelop the corresponding hysteresis loop recorded experimentally. Hysteresis prediction was shown to be more precise for the initial loading/unloading cycles than the final cycle (Figs. 6 and 11). This might be an indication of the peculiar behaviour of some bone samples prior to complete fracture. Conducting proper fatigue experimentation and subsequent analysis at the whole bone level, improving data acquisition for the final cycles prior to fracture, and collecting sufficient data points for the higher applied load would all potentially improve ANNs prediction ability. These hypotheses need to be confirmed, since ANNs predicted the final hysteresis loop of B12 (Fig. 9) very well. Also, the performance of ANN in replicating experimental data points collected during loading is better than those gathered during unloading. The minor fluctuations were observed in the outcome of the ANNs, which probably are related to the introduction of noise to the input variables.

Investigations into whether the ANN prediction is affected by excluding some input variables were also conducted. Excluding time from the input matrices contributes to a significant decrease in the accuracy of the ANN outputs. This is a valid conclusion because the strain-rate dependency of the mechanical properties of the bone is quite well known. Also, excluding *s* (indicating the side of the limb, i.e. left or right) has a moderate effect on the results and contributes to a noticeable error. This observation suggests that the mechanical behaviour of the right and left limbs differ in a way that is discernible to the

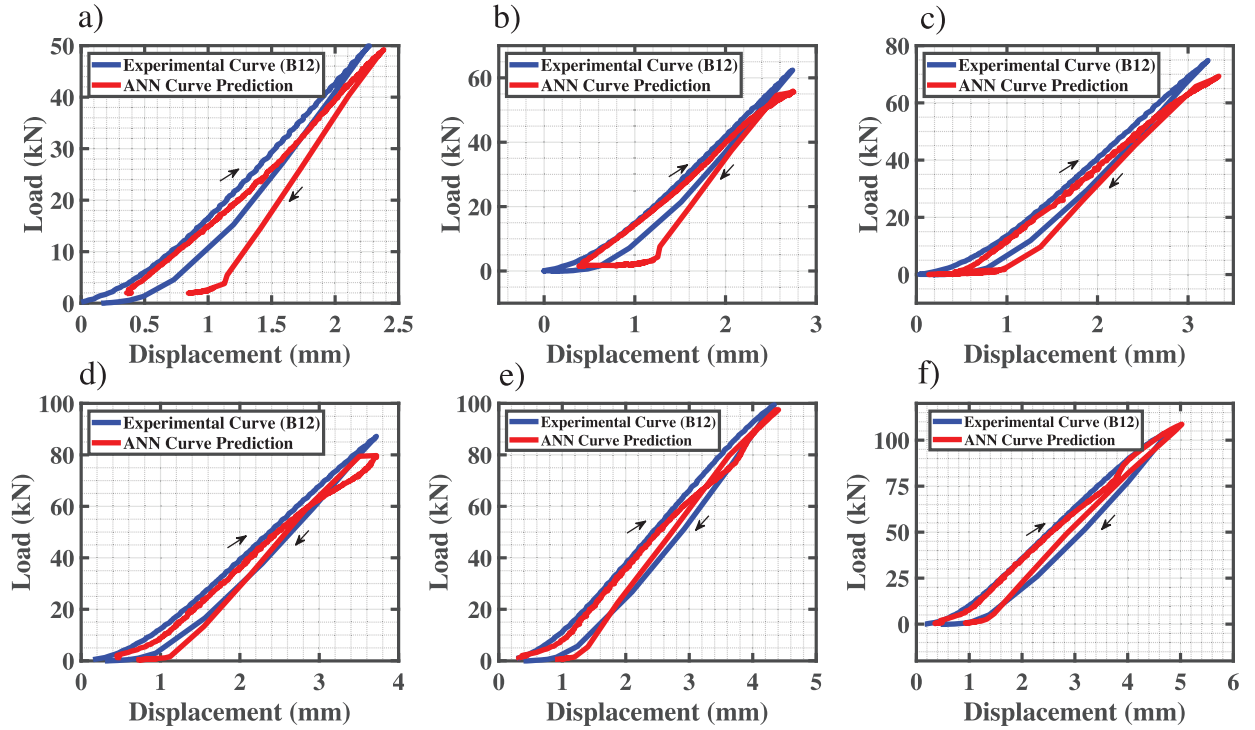


Fig. 9. The output of both ANN models was plotted against, and was compared to, experiment recordings. a) The first b) second c) third d) fourth e) fifth and f) sixth cycle of load-displacement response during loading/unloading of B12.

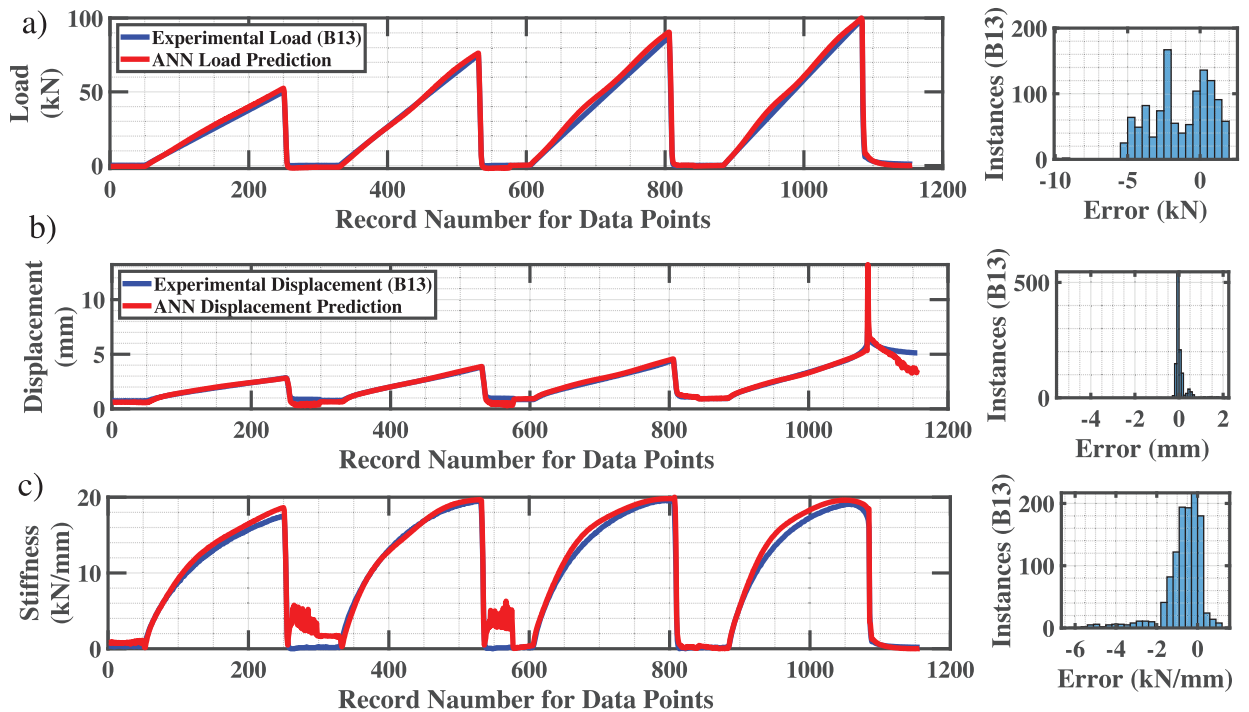


Fig. 10. Both ANN models were trained using data points from B1 to B12, and then they were employed to quantify a) load b) displacement, and c) stiffness of B13 during loading/unloading. Histogram of errors between experiments and the ANNs predictions is depicted beside each relevant plot.

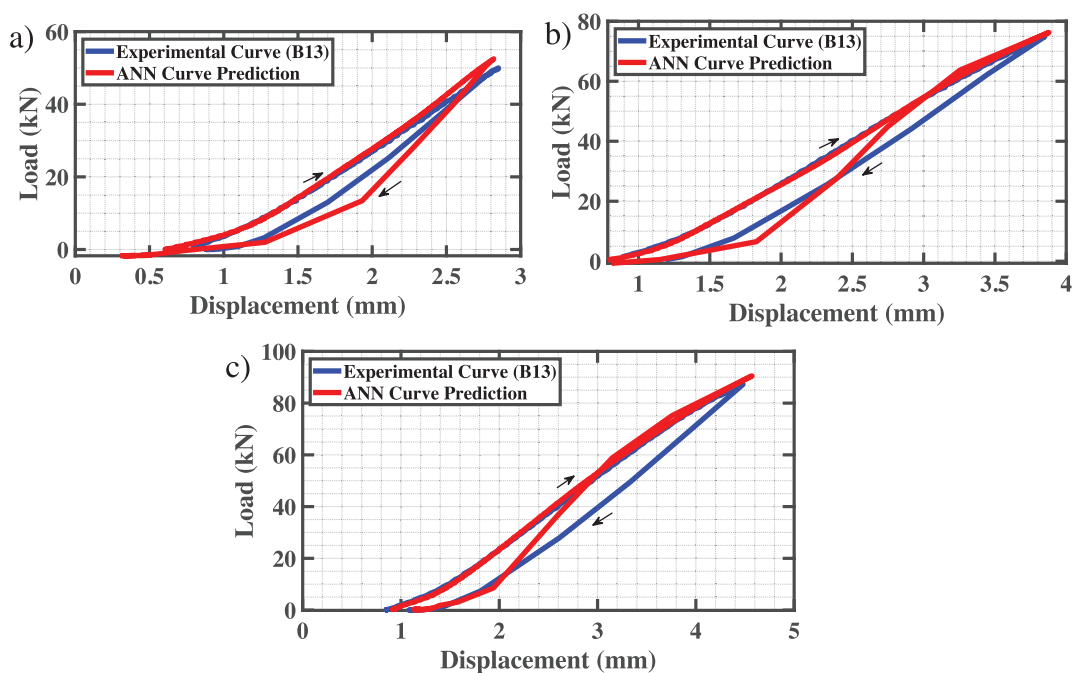


Fig. 11. The output of both ANN models was plotted against, and was compared to, experiment recordings. a) The first b) second and c) third cycle of load-displacement response during loading/unloading of B13.

ANN. The slight differences in shape of the bone shaft where the left is a mirror image of the right might explain this effect. Strains that are directed away from the bone axis for example might be expected to create an increase in error when the left and right are not identified to the ANN.

Success in accurately predicting the load-displacement curve of an advanced material with exotic mechanical properties lies in the adoption of an appropriate constitutive model including appropriate definition of material parameters. There is not a general mathematical solution for the stress-strain behaviour of nonlinear elastic materials such as long bones. Doing so; using traditional numerical simulation such as FEA, requires a series of finite element algebraic manipulations (Dennis, Jin, Dulikravich, & Jaric, 2011), reconstructing finite element formulae, minimizing derived criterion functions (Song & Gu, 2012), and developing cumbersome finite element coding (frequently performed in MATLAB (Gohari et al., 2019; Mouloudi, Khojasteh, Salehi, & Mohebbi, 2014a, 2014b)). Conversely, all aspects of material behaviour can be implemented in the ANN environment without a need to identify material parameters, nor is there a need to define complicated mathematical relationships (Javadi et al., 2003). The ANN approach, which is well-suited to capture the complex stress-strain behaviour of long bones by comparatively simple algorithms, is a suitable alternative to these intricate FEA subroutines (whose successful achievement demands multiple simplifying assumptions). Despite lack of an appropriate constitutive model in FEA, a partial or total lack of information regarding bone geometry and boundary conditions hinders the ability of FEA to offer reliable outcomes. In contrast, the ANNs are potent tools in making reliable predictions when some underlying data is lacking or missing. Furthermore, future finite element studies benefit from employing hybrid modelling, also referred to as intelligent finite element method, in which neural network algorithms are integrated with a finite element framework (facilitating bypassing the FEA calculation process). This assists in time-sensitive clinical applications where using traditional FEA requires long computing times to obtain a final simulation result (Liang, Liu, Martin, & Sun, 2018). In such scenarios, neural networks are incorporated in an FEA as an alternative to the constitutive model of a bone. ANNs are then trained using raw in-vivo experimental measurements representing the mechanical response of the bone to applied loads. The trained network is then used in the FEA to predict different types of stress and strain (Javadi et al., 2003). Finding a solution to the inverse problems in advanced materials (encompassing nonlinear governing equations) is more challenging than solving a forward problem. Commercially available FEA packages, without manipulating their underlying algebraic formulae, are incapable of completing a solution to the inverse problem, for example, to quantify the load required to produce displacement and strains in a structure (Mouloudi et al., 2020). The ability to learn complex relationships among readily available datasets and then to apply this knowledge to a new dataset is an exceptional merit of ANNs (which could serve as an alternative method) over traditional computational tools such as FEA. The first ANN employed in this study is an inverse problem solver (quantifying applied load) and the second one is a forward problem solver (quantifying induced displacement).

When many experimental data for a complex engineering structure is available, the productivity and suitability of conventional methods and standard statistical analyses reduce, because they are not capable of capturing the complexity of such multivariable problems. Consequently such traditional approaches fail to make proper predictions on datasets associ-

ated with new samples. In contrast, when additional experimental data becomes available, artificial neural networks can be adopted via relearning a new pattern within the new dataset in a time efficient manner (Mouloudi et al., 2019c, Mouloudi et al., 2020). Another merit of ANNs employed in this study is that the predictions are based on experimental data, and thus, these estimations are likely to be more realistic than those achieved from the finite element method which strongly depends on FEA input variables including imperfections (Mandal, 2017). ANNs are also able to deal with incomplete and noisy datasets, which are prevalent in engineering applications.

However, artificial neural networks also have drawbacks. Artificial intelligence using different machine learning models predominantly involve making predictions, taking rational decisions, and performing certain averaging over realizations. Uncertainty in, for instance, which AI model is appropriate given the data, plays a fundamental role in all of this (Ghahramani, 2015). Nonuniqueness in selecting different AI methods is a contributing factor to such uncertainties (Nadiri, Chitsazan, Tsai, & Moghaddam, 2014). Small datasets and insufficient data observations are also problematic when training large neural networks. The first problem is that the network may instead of learning a general mapping from inputs to outputs, will learn from specific input examples and their associated outputs. This results in a model that performs well on the training dataset, yet performs poorly on new data, such as a holdout dataset. In this study, nonetheless, fresh datasets belonging to new bone samples, which the ANNs had neither trained on nor tested on, were used to examine and to confirm the accuracy of the neural network models. A small dataset also provides less opportunity to fully describe the structure of the input space and its relationship to the output. More training data provides a richer description of the problem from which the model learns and that could be generalized to a wider population. Despite immense benefits exhibited by AI models in replacing physical modelling via learning through examples, the so called “black box” feature of machine learning algorithms (such as ANNs) makes it challenging to gain insight into the investigated problem (Sargent, 2001). Therefore, human expertise and proper knowledge of the investigated domain are required to eliminate some sources of errors and uncertainties and to offer the best fitting idea.

Several influential factors within biological systems lead to an irregular distribution of mechanical properties and consequently considerable challenges in the prediction of load-displacement curves, including: race, sex, level of activity of a living bone; the state of pathological degradation of the bone; and, the preservation conditions of the specimen until it is used for experimentation. Further investigations are required to explore the reliability of the model by extending database with inclusion of several bones at different bone scale level. Also, the experimental data in this study was recorded during ex-vivo measurements, while in-vivo data will be more useful and realistic in finding solutions to complex biological problems in which monitoring exposed loads are essential. For instance, estimation of the load history of a live horse, which is one of the challenging problems throughout equine studies, is achievable employing the proposed artificial neural network methods by importing in-vivo measurements. The authors aim to fully address this in future studies.

5. Conclusion

Implementation of neural networks as a constitutive approach to model engineering structures is a novel research area. The ability of artificial intelligent expert systems (using feedforward back-propagation neural networks) was examined to predict cyclic load-displacement and stiffness of a complex structure possessing exotic mechanical properties. The systematic ANN analyses revealed its excellent performance in quantifying cyclic load, displacement, stiffness, and load-displacement curves of long bones. This emphasized that ANNs are suitable for solving complex inverse problems in computational mechanics. Artificial intelligent expert systems could be potent alternative computational tools over conventional counterparts like finite element methods, providing proper knowledge of the investigated problem is gained through experience. To affirm the accuracy of the trained ANNs, independent datasets from new samples (not used for either training or testing) were imported to the ANNs, and their predicted outcomes were compared against experimental recordings. This affirmed an excellent generalization of the proposed model. The results were encouraging enough to merit further investigations into complex nonlinear materials in general.

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Ethical approval

This experiment was approved by the Animal Experimentation Ethics Committee of the University of Melbourne.

Declaration of Competing Interest

None declared.

References

- Ashrafi, H. R., Jalal, M., & Garmsiri, K. (2010). Prediction of load-displacement curve of concrete reinforced by composite fibers (steel and polymeric) using artificial neural network. *Expert Systems with Applications*, 37, 7663–7668.

- Bock, F. E., Aydin, R. C., Cyron, C. J., Huber, N., Kalidindi, S. R., & Klusemann, B. (2019). A review of the application of machine learning and data mining approaches in continuum materials mechanics. *Frontiers in Materials*, 6, 110.
- Buehler, M. J. (2006). Atomistic and continuum modeling of mechanical properties of collagen: Elasticity, fracture, and self-assembly. *Journal of Materials Research*, 21, 1947–1961.
- Carter, D. R., & Hayes, W. C. (1977). The compressive behavior of bone as a two-phase porous structure. *The Journal of Bone and Joint Surgery American*, 59, 954–962.
- Ceylan, H. (2003). Analysis and design of concrete pavement systems using artificial neural networks.
- Couch, S., & Nielsen, B. (2017). A review of dorsal metacarpal disease (bucked shins) in the flat racing horse: Prevalence, diagnosis, pathogenesis, and associated factors. *Journal of Dairy Veteriner Animal Research*, 5, 228–236.
- Council, N. R. (2001). *Musculoskeletal disorders and the workplace: Low back and upper extremities*. National Academies Press.
- Currey, J. (2009). Measurement of the mechanical properties of bone: A recent history. *Clinical Orthopaedics and Related Research*, 467, 1948–1954.
- Currey, J. (2010). Mechanical properties and adaptations of some less familiar bony tissues. *Journal of Mechanical Behaviour Biomedical Materials*, 3, 357–372.
- Davies, H. (2005). The timing and distribution of strains around the surface of the midshaft of the third metacarpal bone during treadmill exercise in one Thoroughbred racehorse. *Australian Veterinary Journal*, 83, 157–162.
- Davies, H., McCarthy, R., & Jeffcott, L. (1993). Surface strain on the dorsal metacarpus of thoroughbreds at different speeds and gaits. *Cells Tissues Organs*, 146, 148–153.
- Demuth, H., & Beale, M. (2009). *Matlab neural network toolbox user's guide version 6*. The MathWorks Inc.
- Dennis, B. H., Jin, W., Dulikravich, G. S., & Jaric, J. (2011). Application of the finite element method to inverse problems in solid mechanics. *The International Journal of Structural Changes in Solids*, 3, 11–21.
- Destraide, M., Gilchrist, M. D., Motherway, J., & Murphy, J. G. (2012). Slight compressibility and sensitivity to changes in Poisson's ratio. *International Journal for Numerical Methods in Engineering*, 90, 403–411.
- Evans, S. (2017). How Can We Measure the Mechanical Properties of Soft Tissues? In *Material parameter identification and inverse problems in soft tissue biomechanics* (pp. 67–83). Springer.
- Ghahramani, Z. (2015). Probabilistic machine learning and artificial intelligence. *Nature*, 521, 452–459.
- Gohari, S., Sharifi, S., Burvill, C., Mouloudi, S., Izadifar, M., & Thissen, P. (2019). Localized failure analysis of internally pressurized laminated ellipsoidal woven GFRP composite domes: Analytical, numerical, and experimental studies. *Archives of Civil and Mechanical Engineering*, 19, 1235–1250.
- Grassi, L., & Isaksson, H. (2015). Extracting accurate strain measurements in bone mechanics: a critical review of current methods. *Journal of Mechanical Behaviour Biomedical Materials*, 50, 43–54.
- Hajela, P., & Berke, L. (1991). Neurobiological computational models in structural analysis and design. *Computers & Structures*, 41, 657–667.
- Hambli, R., Chamekh, A., & Salah, H. B. H. (2006). Real-time deformation of structure using finite element and neural networks in virtual reality applications. *Finite Elements in Analysis and Design*, 42, 985–991.
- Helgason, B., Perilli, E., Schileo, E., Taddei, F., Brynjólfsson, S., & Viceconti, M. (2008). Mathematical relationships between bone density and mechanical properties: A literature review. *Clinical Biomechanics*, 23, 135–146.
- Hertz, J.A. (2018). *Introduction to the theory of neural computation*. CRC Press.
- Hornik, K. (1991). Approximation capabilities of multilayer feedforward networks. *Neural Networks*, 4, 251–257.
- Huber, N., Nix, W., & Gao, H. (2002). Identification of elastic-plastic material parameters from pyramidal indentation of thin films. In *Proceedings of the Royal Society of London. Series A: Mathematical, Physical and Engineering Sciences*: 458 (pp. 1593–1620).
- Huber, N., Tsagrakis, I., & Tsakmakis, C. (2000). Determination of constitutive properties of thin metallic films on substrates by spherical indentation using neural networks. *International Journal of Solids and Structures*, 37, 6499–6516.
- Jamal, M., & Morgan, M. N. (2019). Characterization of material properties based on inverse finite element modelling. *Inventions*, 4, 40.
- Javadi, A., Tan, T., & Zhang, M. (2003). Neural network for constitutive modelling in finite element analysis. *Computer Assisted Mechanics and Engineering Sciences*, 10, 523–530.
- Jin, D., & Lin, S. (2011). Advances in Computer Science. *Intelligent systems and environment*. Springer Science & Business Media.
- Jones, L., Golan, D., Hanna, S., & Ramachandran, M. (2018). Artificial intelligence, machine learning and the evolution of healthcare: A bright future or cause for concern? *Bone & Joint Research*, 7, 223–225.
- Keaveny, T. M., Morgan, E. F., Niebur, G. L., & Yeh, O. C. (2001). Biomechanics of trabecular bone. *Annual Review Biomedical Engineering*, 3, 307–333.
- Kontulainen, S., Johnston, J., Liu, D., Leung, C., Oxland, T., & McKay, H. (2008). Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. *Journal of Musculoskeletal Neuronal Interact.*, 8, 401–409.
- Lawrence, L. A. (2005). Effects of exercise and training on skeletal development in horses. *Advances in Equine Nutrition*, (Nottingham University Press. Nottingham, United Kingdom), 219–226.
- Liang, L., Liu, M., Martin, C., & Sun, W. (2018). A deep learning approach to estimate stress distribution: A fast and accurate surrogate of finite-element analysis. *Journal of The Royal Society Interface*, 15, 20170844.
- Logan, D. L. (2011). *A first course in the finite element method*. Cengage Learning.
- MacKay, D. J. (1992). Bayesian interpolation. *Neural Computer*, 4, 415–447.
- Manda, K., Wallace, R. J., Xie, S., Leviero-Florencio, F., & Pankaj, P. (2017). Nonlinear viscoelastic characterization of bovine trabecular bone. *Biomechanics and Modeling in Mechanobiology*, 16, 173–189.
- Mandal, P. (2017). Artificial neural network prediction of buckling load of thin cylindrical shells under axial compression. *Engineering Structure*, 152, 843–855.
- Martig, S., Hitchens, P. L., Stevenson, M. A., & Whitton, R. C. (2018). Subchondral bone morphology in the metacarpus of racehorses in training changes with distance from the articular surface but not with age. *Journal of Anatomists*, 232, 919–930.
- Merritt, J., Burvill, C., Pandey, M., & Davies, H. (2006). Determination of mechanical loading components of the equine metacarpus from measurements of strain during walking. *Equine Veterinaria Journal*, 38, 440–444.
- Merritt, J. S., Davies, H., Burvill, C., & Pandey, M. G. (2008). Influence of muscle-tendon wrapping on calculations of joint reaction forces in the equine distal forelimb. *BioMed Research International* 2008.
- Merritt, J. S., Pandey, M. G., Brown, N. A., Burvill, C. R., Kawcak, C. E., McIlwraith, C. W., & Davies, H. M. (2010). Mechanical loading of the distal end of the third metacarpal bone in horses during walking and trotting. *American Journal of Veterinaria Research*, 71, 508–514.
- Mihai, L. A., & Goriely, A. (2017). How to characterize a nonlinear elastic material? A review on nonlinear constitutive parameters in isotropic finite elasticity. In *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*: 473.
- Mouloudi, S., Khojasteh, J., Salehi, M., & Mohebbi, S. (2014a). Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region. *International Journal of Mechanical Sciences*, 85, 160–167.
- Mouloudi, S., Mohebbi, S., Khojasteh, J., & Salehi, M. (2014b). Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects. *International Journal of Mechanical Sciences*, 79, 162–167.
- Mouloudi, S., Rahmanpanah, H., Burvill, C., & Davies, H. M. (2019c). Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm. *Biocybernetics and Biomedical Engineering*.
- Mouloudi, S., Rahmanpanah, H., Burvill, C., & Davies, H. (2019a). Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design. *Comparative Exercise Physiology*, 15, 349–358.
- Mouloudi, S., Rahmanpanah, H., Burvill, C., & Davies, H. M. (2019b). Accuracy Quantification of the Reverse Engineering and High-Order Finite Element Analysis of Equine MC3 Forelimb. *Journal of Equine Veterinaria Science*, 78, 94–106.
- Mouloudi, S., Rahmanpanah, H., Burvill, C., & Davies, H. M. (2020). Prediction of load in a long bone using an artificial neural network prediction algorithm. *Journal of Mechanical Behaviour and Biomedical Materials*, 102, 103527. doi:10.1016/j.jmbbm.2019.103527.

- Muir, P., Peterson, A., Sample, S., Scollay, M., Markel, M., & Kalscheur, V. (2008). Exercise-induced metacarpophalangeal joint adaptation in the Thoroughbred racehorse. *Journal of Anatomy*, 213, 706–717.
- Muliana, A., Haj-Ali, R. M., Steward, R., & Saxena, A. (2002). Artificial neural network and finite element modeling of nanoindentation tests. *Metallurgical and Materials Transactions A*, 33, 1939–1947.
- Nadiri, A. A., Chitsazan, N., Tsai, F. T.-C., & Moghaddam, A. A. (2014). Bayesian artificial intelligence model averaging for hydraulic conductivity estimation. *Journal of Hydrologic Engineering*, 19, 520–532.
- Nobakhti, S., Katsamenis, O. L., Zaarour, N., Limbert, G., & Thurner, P. J. (2017). Elastic modulus varies along the bovine femur. *Journal of Mechanical Behaviour and Biomedical Materials*, 71, 279–285.
- Nocedal, J., & Wright, S. (2006). Numerical optimization. Springer Science & Business Media.
- Noh, H., You, T., Mun, J., & Han, B. (2017). Regularizing deep neural networks by noise: its interpretation and optimization. *Advance Neural Information and Processing System* (pp. 5109–5118). Springer Link, Part of the Springer Series in Operations Research and Financial Engineering book series (ORFE).
- Norrdin, R., Kawcak, C., Capwell, B., & McIlwraith, C. (1998). Subchondral bone failure in an equine model of overload arthrosis. *Bone*, 22, 133–139.
- Oeser, M., & Freitag, S. (2009). Modeling of materials with fading memory using neural networks. *International Journal for Numerical Methods in Engineering*, 78, 843–862.
- Özkaya, N., Leger, D., Goldsheyder, D., & Nordin, M. (2017). *Mechanical properties of biological tissues, fundamentals of biomechanics: Equilibrium, motion, and deformation* (pp. 361–387). Cham: Springer International Publishing.
- Patton, D. M., Bigelow, E. M., Schlecht, S. H., Kohn, D. H., Bredbenner, T. L., & Jepsen, K. J. (2019). The relationship between whole bone stiffness and strength is age and sex dependent. *Journal of Biomechanics*, 83, 125–133.
- Rao, H., & Mukherjee, A. (1996). Artificial neural networks for predicting the macromechanical behaviour of ceramic-matrix composites. *Computational Materials Science*, 5, 307–322.
- Ripley, B.D., & Hjort, N. (1996). Pattern recognition and neural networks. Cambridge University Press.
- Roberts, S., Kusiak, J., Liu, Y., Forcellese, A., & Withers, P. (1998). Prediction of damage evolution in forged aluminium metal matrix composites using a neural network approach. *Journal of Materials Processing Technology*, 80, 507–512.
- Saini, L. M. (2008). Peak load forecasting using bayesian regularization, resilient and adaptive backpropagation learning based artificial neural networks. *Electric Power Systems Research*, 78, 1302–1310.
- Santschi, E. M. (2008). Articular fetlock injuries in exercising horses. *Veterinarian Clinical North America. Equine Practice*, 24, 117–132.
- Sargent, D. J. (2001). Comparison of artificial neural networks with other statistical approaches. *Cancer*, 91, 1636–1642.
- Sharir, A., Barak, M. M., & Shahar, R. (2008). Whole bone mechanics and mechanical testing. *The Veterinary Journal*, 177, 8–17.
- Shin, H., & Pande, G. (2000). On self-learning finite element codes based on monitored response of structures. *Computers and Geotechnics*, 27, 161–178.
- Somers, M. J., & Casal, J. C. (2009). Using artificial neural networks to model nonlinearity: The case of the job satisfaction–job performance relationship. *Organizational Research Methods*, 12, 403–417.
- Song, J., & Gu, R. J. (2012). A finite element-based methodology for inverse problem of determining contact forces using measured displacements. *Inverse Problems in Science and Engineering*, 20, 769–783.
- Speck, O., & Speck, T. (2019). An overview of bioinspired and biomimetic self-repairing materials. *Biomimetics*, 4, 1–34. doi:10.3390/biomimetics4010026.
- Tarokh, M. (2017). Solving a Class of Nonlinear Inverse Problems Using a Feedback Control Approach. *Mathematical Problems in Engineering*, 2017, 1–11 2017. doi:10.1155/2017/6843614.
- Turner, A. S., Mills, E., & Gabel, A. (1975). In vivo measurement of bone strain in the horse. *American Journal of Veterinaria Research*, 36, 1573–1579.
- Unger, J. F., & Könke, C. (2008). Coupling of scales in a multiscale simulation using neural networks. *Computers & Structures*, 86, 1994–2003.
- Vasundara, M., Padmanaban, K., Sabareeswaran, M., & RajGanesh, M. (2012). Machining fixture layout design for milling operation using FEA, ANN and RSM. *Procedia Engineering*, 38, 1693–1703.
- Xie, S., Manda, K., Wallace, R. J., Levrero-Florencio, F., Simpson, A. H. R., & Pankaj, P. (2017). Time dependent behaviour of trabecular bone at multiple load levels. *Annual Biomedical Engineering*, 45, 1219–1226.
- Zadpoor, A. A. (2013). Open forward and inverse problems in theoretical modeling of bone tissue adaptation. *Journal of Mechanism Behaviour Biomedical Materials*, 27, 249–261.
- Zadpoor, A. A., Campoli, G., & Weinans, H. (2013). Neural network prediction of load from the morphology of trabecular bone. *Applied Mathematical Modeling*, 37, 5260–5276.
- Zur, R. M., Jiang, Y., Pesce, L. L., & Drukker, K. (2009). Noise injection for training artificial neural networks: A comparison with weight decay and early stopping. *Medical Physics*, 36, 4810–4818.

7.2. Summary and Concluding Remarks

The feasibility and efficacy of employing two in-series feedforward backpropagation artificial neural networks was examined and relevant strategies (for example, injecting noise source and data normalization prior to training) were elaborated and illustrated to predict cyclic load-displacement curves and stiffness of a complex structure possessing exotic mechanical properties. More bone samples from foals, two-year-olds, and three-year-olds were tested in the ex-vivo experiments, enabling more datapoints from several bone samples to be used in the training sessions of the ANNs employed in this chapter.

The ability of ANN models to learn through examples, and thus replacing physical modelling, was demonstrated to establish relationships among variables (load, displacement, strains, and time as well as bone features such as length, age, and left or right side). This is not a straightforward task using traditional techniques due to the complexity of the problem and exotic properties of the material. ANN computational tools were shown to be appealing in engineering applications where there is little or incomplete understanding of the problem, yet experimental measurements are readily available, or when geometrical data is missing or unavailable. Machine learning techniques might entirely replace traditional computational techniques such as FEA that are being extensively employed in biomedical and mechanical engineering concerning materials modelling and design.

Several ANNs using different combinations of bone samples were trained and tested to predict load, displacement, and stiffness with subsequent evaluation of each trained ANN enabling generalization (successful prediction on new datasets from new bone samples that were not used in the ANN training session). Specifically, it was exhibited that: the ANNs were able to make effective prediction on the mechanical responses and behavior of MC3 long bones ($R > 0.99$ for training and testing datasets of both ANN models) and were generalized very well to new datasets that ANNs had not seen before, i.e. $R > 0.99$, $RMSE < 2.5$ kN for load prediction, $R > 0.94$, $RMSE < 0.33$ mm for displacement prediction, and $R > 0.98$, $RMSE < 1.2$ kN/mm for stiffness prediction. Certainty over nonlinear material performance is essential in a variety of engineering applications. The peculiar mechanical responses exhibited by the MC3 long bone makes it an intriguing nonlinear material for researchers and engineers. The successful application of neural networks (data-driven tools) in computational mechanics of advanced materials such as bone offers the potential for deeper understanding of less complex materials, for example, composites, nanomaterials, and alloys.

Chapter 8

Feedforward backpropagation artificial neural networks for predicting mechanical responses in complex nonlinear structures: A study on a long bone

Comprehensive explanations of results produced by feedforward neural networks using a backpropagation algorithm, post training, can assist the researcher determine which parameters are of critical influence. A repeatable and objective means of identifying well-trained and well-generalized feedforward neural networks provides the researcher with the opportunity to more quickly assess the degree of success of a specific ANN.

This chapter reports on a submitted journal paper by the author and collaborators that investigated the following hypotheses (as discussed in Section 2.6.4):

- **H.12.** Selecting an optimum ANN structure (architecture) depends on the complexity of the problem, number of specimens, number of datasets (observations through experiments, for example), number of input(s) and output(s).
- **H.13.** For different scenarios (ANNs with different outputs), ANNs performance was oversensitive to both the number of hidden layers and number of neurons in the hidden layer. The same ANN with the same datasets can produce completely different results when it is trained each time (training each ANN multiple times and averaging their outputs are recommended).
- **H.14.** To exhibit the generalization ability of an ANN model, a major emphasis must be placed on the regression and performance analyses conducted on the new specimens (unseen samples that ANNs have not seen before).
- **H.15.** The neural networks trained with injected noise drastically reduce the generalization error (substantial improvement in the generalization ability). Likewise, the error of ANNs in generalization (RMSE) is drastically decreased when data is normalized prior to commencement of training.

8.1. Submitted Journal Paper

The following journal paper was submitted to the International Journal of Mechanical Sciences on 2020-08-30:

Saeed Mouloudi, Hadi Rahmanpanah, Colin Burvill, Soheil Gohari, Helen M S Davies, Feedforward backpropagation artificial neural networks for predicting mechanical responses in complex nonlinear structures: A study on a long bone, Submitted to the International Journal of Mechanical Sciences (IF: 4.631 as of 2020).

Feedforward backpropagation artificial neural networks for predicting mechanical responses in complex nonlinear structures: A study on a long bone

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Abstract

Feedforward backpropagation artificial neural networks (ANNs) have been increasingly employed in many engineering practices concerning materials modeling. Despite their extensive applications, how to achieve successfully trained ANNs is not thoroughly explained in the literature, nor are there lucid discussions to delineate influential parameters obtained from analyses. Long bones are composite materials possessing nonhomogeneous and anisotropic properties, and their mechanical responses exhibit dependency on numerous variables. Material complexity hinders researchers from arriving at a consensus in implementing an optimal constitutive model or encourages them to adopt a simple constitutive model including many simplifying assumptions. However, such exceptional features and engineering challenges make long bones materials worth investigating, enriching our comprehension of complex engineering structures using novel techniques where traditional methods may present limitations. This paper reports on the prediction of loading, displacement, load and displacement simultaneously, and strains using feedforward backpropagation ANNs trained with experimental recordings. The technique was used to find optimum network structures (architectures) that encompass the best prediction ability. To enhance predictions, the influence of several elements such as a network training algorithm, injecting noise to datasets prior to training, the level of injected noise which directly affects model fitting and regularization, and data normalization prior to training were investigated and discussed. Essential parameters influencing decision making in identifying well-trained and well-generalized ANNs were elaborated. A considerable emphasis in this study was placed on examining the generalization ability of the already trained and tested ANNs, thus guaranteeing unbiased models that avoided overfitting. Gaining favourable outcomes in this study required three years of performing experiments and data collection before establishing the networks. The subsequent training, testing, and determination of the generalization of more than 60,000 ANNs are promising and will assist researchers in comprehending mechanical responses of complicated engineering structures that exhibit peculiar nonlinear properties.

Keywords: Artificial neural network (ANN); prediction of mechanical properties; complex engineering structures; long bones; strains; load & displacement

1. Introduction

A primary motivation for applying artificial neural network (ANN) algorithms in engineering practices is the prospect of expediting, simplifying, or even enabling a proper comprehension of features of advanced and novel materials. An enormous challenge in fully understanding material performance in biomechanical engineering is the extreme complexity of anticipating mechanical properties and discovering performance attributes. The ability to learn from examples (patterns inherent in observations) and to generalize this learning to a wider population in foreseeing unknown parameters makes ANNs exceptional tools in a highly interdisciplinary domain, such as biomedical engineering that encompasses engineering, medicine, biology, physics and psychology disciplines [1, 2]. These expert systems, thanks to the availability of enormous experimental measurements and huge data storage as well as increasing precision and power of the physical mechanical tests [3], are becoming intriguing computational tools in several areas of engineering science [4]. Stress and strain analyses are the hallmark of engineering mechanics where the responses of complex structures under load and specific sets of boundary conditions are quantified using numerical techniques such as finite element analysis (FEA) and computational fluid mechanics (CFD), for which basic constitutive equations are required to be derived including the characteristics of the materials such as linear elasticity, plasticity, viscoelasticity, viscoplasticity and hyperelasticity, and moreover, combinations of these features since some advanced materials exhibit behaviors that can only be estimated using a combination of different models.

Bones are highly complex biological materials that possess exotic mechanical properties, and therefore are characterized as complex engineering structures [5] and are also categorized as nanocomposite and anisotropic solids [4, 6]. The mechanical properties and responses of these advanced engineering structures have been shown, for example, to be density-dependent [7, 8], site- and length-dependent [9, 10], force- and loading-rate-dependent [11-13], time-dependent (viscoelasticity) [14-16], strain-rate-dependent (exhibiting both viscoelastic and viscoplastic behavior) [17], size- and scale-dependent [18, 19], shape-dependent [20, 21], age-dependent [5, 13, 22], sex-dependent [22]. It would be difficult to find another material that possesses such multivariable and exceptional mechanical properties. Such an extraordinarily hierarchical essence of its structures and mechanical properties makes bone a difficult material to fully comprehend, hinders the development of universally accepted theoretical or empirical constitutive models incorporating all the mentioned-above influential parameters, and prevents researchers from: (1) arriving at a consensus over implementing an optimal constitutive model in numerical-based simulation packages (such as FEA and CFD); or (2) encouraging them to adopt a simple constitutive model with inclusion of many simplifying assumptions in these packages, which ignores the multi-factorial nature of bone. Nonetheless, such remarkable properties and tackling these challenges in the realm of engineering makes bones intriguing materials for researchers and engineers for further investigation, and if a proper comprehension of these sophisticated materials using novel techniques and innovative tools is achieved, our understanding of less complex and prevalent engineering structures (such as composites, nanomaterials, and alloys) will be enhanced. This greatly assists with the establishment of a general framework that enables importing and inclusion of all the parameters or variables influencing responses and behavior of such intricate engineering materials and that eventually concludes with integrating or replacing the conventional constitutive models. Employing machine learning techniques using different algorithms such as ANN is a key to establishing this general framework and to tackling the previously mentioned challenges in the engineering

discipline. As Currey stated, “The study of bone mechanics has been driven by advances in techniques, and although considerable enlightenment has come from the transfer of ideas from the physical sciences, most increases have come from the vastly increased power and resolution of the observational and mechanical techniques available” [3]. ANN algorithms are advanced tools gaining a dramatic and impressive advantage from these observational and mechanical techniques to further advance our knowledge of complex engineering materials.

ANN algorithms have been successfully implemented in several areas of engineering research, and literature on ANNs and their application to a wide variety of engineering practices has grown intractably vast during the last few years. The following studies have contributed to a deeper understanding of advanced and novel materials within mechanical engineering sciences. For instance, ANNs were used in predicting buckling load of thin cylindrical shells under axial compression [23], designing steel structures [24], characterizing the behavior of carbon nanotubes at the nanoscale [25], predicting deformations in complex structural mechanics [26, 27], predicting the load-displacement relationship of composite fibre reinforced concrete [28] and that of a complex structure possessing exotic mechanical properties (a long bone) [4], modelling the mechanical behavior of ceramic-matrix-composites [29], predicting fatigue life of a variety of materials [30-32], predicting tensile force during suturing of a kidney [33], assessing cortical bone fracture with estimation of toughness threshold, R-curve slope, and stress intensity factor [34], predicting knee loading [35, 36], predicting musculoskeletal loads and displacement that have resulted in a certain recorded bone density and strain distribution [5, 16, 37, 38], and simulating multilevel fatigue of bone [39].

Assisting engineers to design and simulate confined concretes components under compressive loading, Ahmad and colleagues proposed ANN, FEA and empirical models to evaluate axial strength of concrete cylinders with carbon fibre reinforced polymers [40] to assist in the engineering design and simulation of confined concrete components under compressive loading. To investigate the effects of geometrical and material parameters of annealed copper, and to construct a link between indentation response and the material parameters, Muliana and colleagues developed a feedforward backpropagation ANN model encompassing two hidden layers, and their paper also presented numerical results obtained for 2D and 3D FEA [41]. Geometrical parameters and material properties (stiffness) constructed the input layer of the ANN (trained with the datasets generated from FEA results), and the ANN outputs the indentation force, which was then compared against other FEA results not employed in the training sessions. These outcomes identified the intellectual predictive capability of ANNs for nonlinear applications. Roberts and colleagues employed ANNs to predict damage evolution in forged aluminium matrix composites as a function of forging parameters [42] where multilayer feedforward neural networks were trained using a combination of FEA results and experimental measurements (mostly associated with deformation parameters such as strain, strain rate, stress, and temperature). Hambli employed feedforward (multilayer perceptron) neural networks using a backpropagation training algorithm to predict burr height formation during sheet metal blanking processes [43]. The method was reported to be a very fast and accurate method that combines FEA with ANN. Xu and Gupt predicted mechanical properties using a feedforward neural network trained from the measurements recorded from dynamic mechanical testing (temperature, frequency, and elastic modulus) to investigate the dynamic properties of graphene reinforced epoxy matrix composites at several frequencies and temperatures [44]. Besides this investigation, the effects of network architecture (the number of neurons) and regularization factor to improve generalization, thereby minimizing the likelihood of overfitting, were also considered and discussed. Such characterizations of

viscoelastic materials versus strain rate and temperature are important in the development of better models to expand our knowledge of viscoelastic materials [45]. The major contributions in the mechanical sciences are to provide scientific and practical insights into the use of analytical, experimental, and computational techniques (FEA, boundary element method, mesh free methods, among others) to advance our knowledge in rigid-body mechanics (such as dynamics and vibration modeling), structural mechanics, responses and applications of advanced materials (for example, metals, composites, bio-inspired materials, and metamaterials), impact mechanics, large deflections and plasticity, among others. The mechanical engineering research community continues to take advantage of the advancement in machine learning tools, and the above-mentioned literature are some examples illustrating how researchers are striving to implement machine learning algorithms with predominantly the use of feedforward neural networks to advance our comprehension in such spheres of mechanical sciences. With such increased use there is unfortunately a growing tendency for the misapplication of artificial neural networks [46]. Therefore, it is essential to critically review and investigate in detail the use of feedforward neural network algorithms, to bring it to the attention of the mechanical and materials research community to assist them to gain successful and reliable outcomes as well as prevent potentially new research from misapplication of ANNs. It is hoped that that this article can be used as a reference guide for researchers designing new feedforward backpropagation artificial neural networks for predicting mechanical responses and properties of complex engineering structures.

The selection of neural network architecture (number of hidden layers and number of neurons in each layer), determination of influential parameters in the design of the network (regression, performance, error analyses), the use of a suitable training algorithm that fulfils the demands of the investigated task, and identification of input-output pairs and how they should span the intended domain require experimentation and experience. Also, pre-processing of the data (experimental measurements in the current study) is frequently required before presenting the data to the neural network for training. A noise injection method that improves the generalization ability of ANNs [47] and that reduces their likelihood of overfitting [48] was considered and investigated in this study. The penalty terms that are introduced by injected noise are related to, yet distinct from, those found in the other regularization approaches (such as Bayesian neural networks and early stopping). Besides noise injection, data normalization was adopted on the data prior to training the ANNs [49, 50]. It was investigated whether data normalization and noise injection in feedforward backpropagation neural networks make input variables more suitable for network training, expedite the learning of the ANN, enhance its prediction precision, and more significantly, improve the generalization ability of ANNs in making prediction on unseen samples (new datasets that ANNs have not seen before). These important factors were not fully addressed in the application of ANNs to the engineering problems available in the literature.

Moreover, a considerable emphasis in this study was placed on investigating the generalization ability of the trained ANN models. This guarantees a correct and unbiased generalization of the already trained neural networks which have avoided overfitting to the training datasets and provides a robust verification of the networks post-training. The ability of an ANN to generalize, i.e. to properly respond to previously unseen input data, is critically important. This has been neglected or ignored in neural network studies performed in the literature, where merely coefficient of correlation (R -value) and performance (errors such as MSE) of ANNs for training, testing, and validation were presented. Although engineers, as mentioned in the previous paragraphs, successfully applied ANNs to find impressive solutions to their

engineering problems, the details of how to construct such successful neural networks are not thoroughly explained, nor are there lucid discussions in the literature in this regard or in explaining the influential parameters obtained from the ANNs analyses. These essential factors are going to be delineated in this study for the feedforward backpropagation artificial neural networks in predicting mechanical responses of a complex structure (a long bone). A major benefit of our study is that the prediction of ANNs is based on the experimental measurements that were collected within our research group, hence the estimations are likely to be more realistic than merely using a hybrid system integrating ANNs and FEA, where inputs of ANNs are obtained from performing multiple FEA. In contrast to much of the published work, the problem considered in the current study is three-dimensional and is encouraging in considering the whole geometry of the intact bones (performing the experiment on the whole bone level) and in maintaining bone hydration during the ex-vivo experiments. Besides peculiar and exceptional mechanical properties and responses exhibited by bones in general that make them intriguing engineering materials (as emphasized in previous paragraphs), the use of equine MC3 long bones in performing mechanical experiments and then in establishing the ANN in this study is motivational for engineers who are dealing with less complicated structures and less complex materials. MC3 is a large bone (in Thoroughbred type horses, its length varied in the range 25-29 cm and the area of its cross section in the midshaft varied in the range 250-1050 mm² excluding the marrow area inside the bone [21]), and shows a relatively restricted and simple range of normal movements [51], has minimal muscle attachments (lacking any muscle or ligamentous attachments for a range around 6-8 cm along its midshaft), forms an essential part of the lower forelimb in withstanding loads, is vulnerable to failure during the majority of disastrous injuries occurring in racing horses worldwide, is well-adapted (well-engineered) for exercise at high speeds [52], and can withstand substantial compressive load as much as 22.5 kN in-vivo [53]. Moreover, enormous compressive loads (parallel to, and aligned with, the long axis of the bone) exceeding 110 kN ex-vivo without bone failure was recorded and reported on MC3 long bones (outcomes from the current study and from a previous study [5]). Obviously, such a unique well-engineered structure (resembling and categorized as a cylindrical long beam or column in the engineering context) which is functioning well in a living biological system provides the best chance to develop a model to investigate the normal mechanical responses of an advanced structure to loading. Also, many investigations into human bone fatigue, for example, are heavily reliant on the outcome of equine bone research [54].

We employed feedforward backpropagation artificial neural networks (expert systems) to find solutions for both the forward problem (estimating and predicting displacement and strains) and the inverse problem, which is predicting loading history that has resulted in the given morphology and responses of bones. Employing traditional numerical simulation techniques (such as FEA and CFD) to tackle the forward problem is cumbersome and time-consuming, and furthermore the comparison of FEA and ANN displacement predictions in a recent study indicates that employing ANN substantially reduces the computational time (160 times) compared to the use of FEA [16]. Computer-aided engineering products developed for FEA (e.g. ANSYS and Abaqus, which are widely used in engineering mechanics), without manipulating their underlying algebraic formulae and hence developing cumbersome finite element coding (frequently performed in MATLAB [55-57]), lack the ability to tackle the inverse problem and fail to conduct reverse-engineered problems [5]. Three years of conducting experiments and data collection that were used to establish the networks as well as more than 60,000 feedforward backpropagation ANNs trained, tested, validated, and

228 generalized in this study are encouraging and will assist researchers/engineers/biologists in
229 discerning mechanical features of complex engineering structures that exhibit exotic and
230 peculiar nonlinear mechanical properties.

2. Materials and Methods

The following steps summarize the application of the proposed ANN algorithms employed in this study:

- Step-1 Data collection for training ANNs via conducting ex-vivo experiments on thirteen third metacarpal bones (at the whole bone level) belonging to donated cadavers of thoroughbred racehorses aged from twelve hours to three years and with no history of bone disease. In this study, three years of experimental data collections were used to establish the neural networks [5, 16]. Briefly, both ends of bone samples were embedded in a solid mixture by pouring a combination of slow-curing resin (to reduce heating of the bone ends) and fiberglass into two metal cups until it covered the joint surfaces and extended about 1 cm up the bone shaft. This produced smooth and level surfaces onto which the forces could be applied more evenly (Figure 1). To ensure the exact parallelism of the top and bottom surfaces of the embedded bones, the bone orientation was checked with two spirit levels one placed on the base of the upper cup and one on the edge of the lower cup. Several strain gauges, including one rosette strain gauge and three single-element strain gauges, were attached to different surfaces of the bone samples to record six kinds of strain around the midshaft of the MC3 samples. To reduce evaporative loss and to maintain hydration, the bones were wrapped lightly in a clear plastic wrap during the tests. Each MC3 bone was then loaded in compression parallel to, and aligned with, the long axis of the bone using a material testing system (MTS). The experimental recordings include bone length, load, displacement, load exposure time (loading/unloading time in seconds which specimens were exposed to), limb side (left or right), horse age, and six kinds of strain (from reading of strain gauges adhered to different locations on the midshaft of the bones).
- Step-2 Preparation and pre-processing a proper set of datasets (from recording of experiments) to construct input variables of neural networks and then creating a neural network.
- Step-3 Predicting different features of bone specimens using different ANNs, i.e. displacement individually (an ANN with one output), load individually (an ANN with one output), load and displacement simultaneously (an ANN with two outputs), and normal strain (an ANN with one output).
- Step-4 Training the artificial neural networks based on the input-output data specified in the previous steps.
- Step-5 Application of the previously trained and tested neural network as a predictive tool to rapidly estimate the outcome of new bone specimens that were not used in Steps 2, 3, and 4. Using fully new datasets (that were not used in ANNs training) offers an unbiased information on how well the neural network performs, reduces the likelihood of overfitting, and ensures the validity of previously trained ANNs. This critically important approach is mostly overlooked in ANN studies where merely the outcome of ANN regression for testing and validation is reported.
- Step-6 Selecting an optimum ANN structure (architecture) that encompasses the best prediction ability (through monitoring the outcome of regression and performance analyses performed in Step 4) and that generalizes well to the unseen specimens (via monitoring the outcome of regression and performance analyses performed in Step 5). To achieve this, a substantial number of ANNs encompassing distinct structures was

trained and tested. The number of hidden layers was set to one and two. Growing technique was used to find the optimum number of neurons changing from one to fifteen (for ANNs with one hidden layer) and changing from one to ten (for ANNs with two hidden layers). The former represents fifteen distinct ANNs comprising one hidden layer, and the latter presents one hundred distinct ANNs comprising two hidden layers. Hence, 115 unique ANNs were constructed from which an optimum structure would finally be selected. To ensure that an ANN with good accuracy has been found and to improve the generalization of ANNs [23], it is recommended to train each ANN multiple times and average their outputs. Therefore, each 115 unique ANNs was trained, tested, and validated ten times (completing Steps 2 to 5 ten times) and then the average of the outputs for each of these networks was taken. For each feature prediction (Step 3), an ANN which demonstrated the best performance among these 1150 trained networks was selected, and its architecture was employed for the ensuing predictions.

The present study was divided into multiple subsections to investigate and address the following influential factors and to assess the ANNs prediction ability:

Section 2.1. Description of ANNs

Section 2.2. Injecting noise to the training dataset prior to the ANNs training

Section 2.3. Data normalization prior to commencing the ANNs training

Section 2.4. How to assess and then confirm a suitable ANN

2.1. Description of Artificial Neural Network Method

ANNs are a group of algorithms used for machine learning, which can interpret the nature of many problems as humans do and learn from real-world examples. ANNs are advanced computational tools that enable scientists to take full advantage of the computational capacity offered by GPUs (graphics processing units), allowing them to process datasets encompassing enormous sizes thanks to current enormous data storage [58]. An ANN model is a parallel processing architecture, is composed of a large number of highly interconnected processing neurons (nodes), learns through examples or experience (like humans do) and adapts to changing situations, is configured for a specific application (such as classification, data prediction, and pattern recognition), and typically is modelled into one input layer, one or several hidden layers (also referred to as intermediate layers), and one output layer. The number of an ANN inputs equals the number of neurons in the input layer. Inputs are then directly transmitted to the subsequent neurons of the hidden layers [5, 39] and then the accumulated knowledge is proceeded to the output layer via hidden layer(s). The number of neurons in the output layer equals the ANN output variables. The neurons interact with one another via weighted connections.

A synaptic weight (w_i), known as associated weight or simply weight, is assigned to each signal by the neurons and mathematically represents a degree of importance for that neuron. It actually determines the strength and nature of the influence between neurons. The signals are processing lines that connect neurons in different layers. A representative model of an artificial neural network is shown in Figure 1. The individual inputs are each weighted (multiplied) by their corresponding synaptic weight matrix and then are added to the bias (b) of each neuron. The outcome is then passed through an activation function (f). This output is then used as an input

for the next neuron and so forth. Hence, the output y_i^m of a neuron i in a layer m is calculated as:

$$y_i^m = f(v_i^m) \quad (1)$$

$$v_i^m = \sum_{j=1}^L w_{ji}^{m-1} y_j^{m-1} + b_i^m \quad (2)$$

where L is the number of connections to the previous layer, w_{ji}^{m-1} corresponds to the weights of each connection, and b_i^m is the bias. Transfer function and offset are interchangeably used by some authors rather than activation function and bias, respectively. Some of the commonly used activation functions for artificial neurons are sigmoid (logistic or log-sigmoid), hyperbolic (Tanh), and rectified linear unit (ReLU) activation/transfer function. Partially because it is differentiable [59], log-sigmoid transfer function is widely used in ANN studies. This function takes the inputs encompassing any value between $\pm \infty$ (infinity) and squashes the output onto the range (0,1), and is given by:

$$f(x) = \frac{1}{1 + e^{(-\theta x)}} \quad (3)$$

where θ is a parameter defining the slope of the function, which in neural network training influences the learning speed and is dependent upon the investigated problem. Nevertheless, a constant value ($\theta=1$) is generally applied [60]. Substituting Equations 1 and 2 into Equation 3 yields the output of each neuron:

$$f(v_i^m) = \frac{1}{1 + e^{(-v_i^m)}} = \frac{1}{1 + e^{-\left(\sum_{j=1}^L w_{ji}^{m-1} y_j^{m-1} + b_i^m\right)}} \quad (4)$$

The training of ANNs commences with introducing input and output variables to the network, which it then strives to map as nonlinear relationships between inputs and outputs and finally makes satisfactory prediction on outputs. A sufficiently large and representative dataset to form input and output variables is required to train an ANN. Based on the requirement of ANN training algorithm, the dataset is typically divided (split) into either two (training and testing) or three (training, testing, and validation) subsets. The training dataset, which the ANN is trained with, is used by the neural network to learn relationships among input and output datasets, and therefore encompasses the largest in volume; whereas the testing and validation datasets aim to provide a measure of how well the already trained network performs on fully new datasets (assessing generalization and performance of the neural network model). There is no fixed rule in how to divide or split the data into these subsets rather than with gaining experience or performing trial and error. A common practice is to employ a division of 80% or 90% for training and 20% or 10% for testing [50]. The data split into training, testing, and validation was performed on a random basis, and the training of the ANNs was mostly carried out using 80% of the data points. At the onset of training, the assigned weights to each neuron's connection (w_{ji}^{m-1}) and also bias (b_i^m) are chosen haphazardly, using random magnitudes, and then they are adjusted via the network (employing a desired training algorithm that can be achieved using a number of different optimization strategies) during the training session until the errors between the neural network prediction (network output) and target (actual output that

was already available) are minimized to a marginal value range. The training phase of an ANN is analogous to a simple curve-fitting process using a polynomial function, in which mapping from a single input parameter to a single output variable is performed where the polynomial coefficients play the same role as the weights and biases do in an ANN [45]. A single presentation of the entire data set to the network along with adjusting or updating the weights and bias is called an epoch or a cycle. Training of the neural network is carried out by repeatedly completing several epochs and it is stopped, according to adaptive weight minimization regularization through conducting the gradient descent methods, when either the error between ANN output and target is small enough or the learning iteration reaches its higher level without a considerable decrease in the error (default is normally 1000 iterations or epochs). This is when it is stated that the errors are minimal, and that convergence occurs. The corresponding weights and bias are then stored, which makes the trained ANN prepared to be fed with a separate and fully new dataset (that belongs to the same knowledge domain) from a fresh sample that the ANN has not seen before. This quite critical testing phase where the prediction capability of the neural network is assessed as compared with the target values (experimental measurements for example) is mostly neglected in the engineering applications of artificial neural network. In this study, on the other hand, the major emphasis is placed on investigating this generalization ability of the ANN models. This guarantees a correct and unbiased generalization of the trained neural network model which has avoided overfitting to the training datasets.

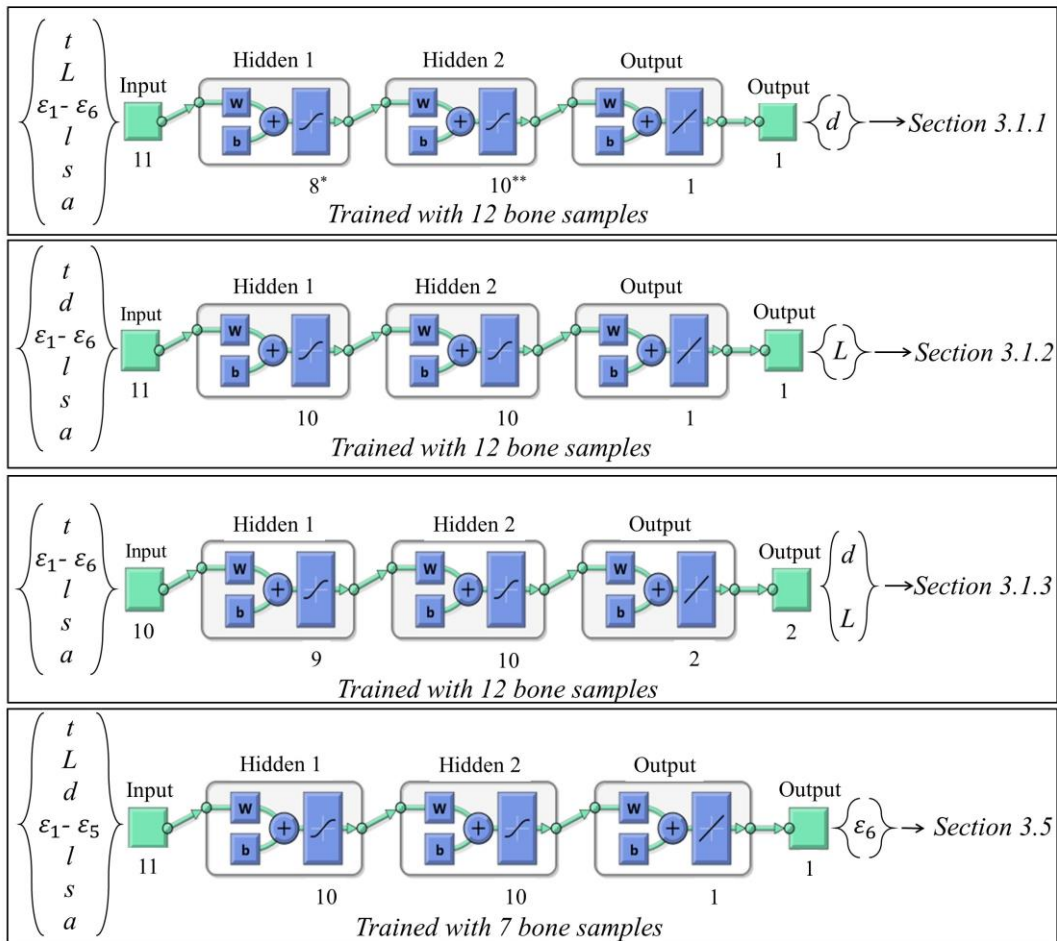
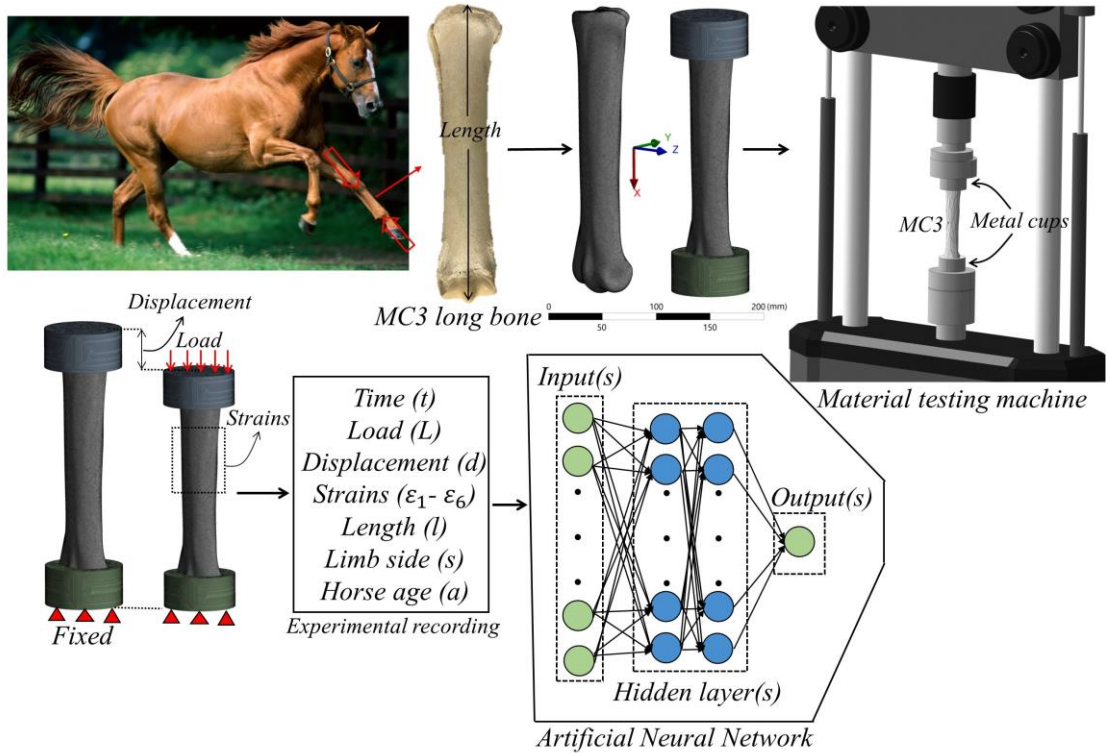
A number of training algorithms are employed in ANNs such as Bayesian regularization backpropagation, Levenberg-Marquardt backpropagation, and scaled conjugate backpropagation. The process of adapting and tuning the weights and the biases as well as minimizing the error using one of the mentioned training algorithms is referred to as optimising the performance function. Mean squared error (MSE), an indication of the training, testing, and validation error of the neural network, is the default performance function for a feed forward neural network and is calculated by the network as follows:

$$E = \frac{1}{2} \sum_{i=1}^k (t_i - y_i)^2 \quad (5)$$

where t_i is the target value (desired output e.g. an experimental one) of the i^{th} neuron of the output layer, y_i is the corresponding actual output (the predicted value from the ANN), and k represents the number of outputs (i.e. number of neurons in the output layer). A back-propagation artificial neural network (BPANN) possesses feed-forward architecture, employs a supervised learning method, learns from examples given to it; and therefore, lacks a need for specifying mathematical relationships among variables, and accommodates complex data relationships. Using one of the above-mentioned training algorithms, these types of ANNs are trained by gradient descent methods in which the error propagates in a backward manner through the network. BPNN architecture comprises one input layer, one output layer, and one or several hidden layers, which enable the neural network to calculate and estimate complicated associations between patterns that establish the nonlinear mapping relationship among multiple variables. The information in this type of ANN flows in a feedforward way. These ANNs are also called either Multilayer feedforward or multilayer perceptron (MLP).

Besides methodically monitoring the ANNs past training session, it must be emphasized that the results and conclusions presented in this paper are mainly focused on the regression and performance analyses conducted on the new specimens (new bone samples that were not used

399 in the ANNs training). This gives an unbiased and potent measure of performance of the model
400 on unseen data different from those used for training.



* Number of neurons in the first hidden layer

** Number of neurons in the second hidden layer

Figure 1. An illustration of several stages involved in conducting this study. The experimental recording shaped ANNs input variables to process data and finally to predict mechanical loading, displacement, and strains.

2.2. Noise Injection prior to ANNs Training

The effect of a noise injection method to improve the generalization of ANNs prediction ability and to reduce their likelihood of overfitting was investigated. Besides Bayesian neural networks and early stopping, noise injection is another method of regularization, which attempts to avoid overfitting of ANNs and indirectly penalizes complex neural network models by adding noise to the training dataset (input variables) [48]. The penalty terms that are introduced by injected noise are related to, yet distinct from, those found in the mentioned regularization approaches. Noise injection method (introducing noise to the inputs) refers to artificially adding noise to each ANN input variables during training sessions. This challenges ANNs to find a solution that precisely fits to the original training datasets, and thereby, reduces the likelihood of overfitting of the ANNs. This also encourages the output of ANNs to be a smooth function of the input [47]. In a nutshell, a smoother neural network function avoids overfitting the training dataset and leads to a better generalization (giving more satisfactory results when the ANN is applied to new data). The effects of including the noise source (ANNs trained with noisy inputs) or excluding it (ANNs trained without noisy inputs) on the performance of neural networks were investigated through both evaluating R -values and errors produced during ANNs training (Step 4 in Section 2) and observing the ability of trained ANNs in making reliable predictions on the unseen specimens (Step 5 in Section 2). Furthermore, through training multiple ANNs for each predicted feature (Step 3 in Section 2), we changed the magnitude of injected noise within a range, and then the performance of ANNs was observed and finally the best magnitude for the injected noise was selected and reported for each scenario. These processes were consistently repeated with inclusion of several new specimens (new datasets that ANNs have not seen before).

The noise vector added to neural networks is typically drawn from some probability density function [48]. The noise injected to the ANNs performed in our study was sampled from Gaussian distribution (a certain probability distribution, also referred to as white noise), which is a common noise source with which ANN input variables can be successfully trained and generalized [5, 16, 38]. Gaussian noise has a mean value of zero and a standard deviation of one and can be generated using a random number generator. It generates normally distributed random variables. The amount of introduced noise (e.g. the spread or standard deviation) plays a critical role. Little noise has no effect, whereas too much noise makes the mapping function too challenging for the ANN to learn.

2.3. Data Normalization prior to ANNs Training

Pre-processing of the data (Step 2 in Section 2) is frequently required before presenting the data to the neural network for training. Besides noise injection that was explained in the previous section, data normalization is commonly adopted in artificial neural network applications [49, 50]. Data normalization in backpropagation neural networks makes input variables more suitable for network training, expedites the learning of the ANN, and enhances its prediction precision. Having a uniform scale among the input variables, since they are related to different measurements and vary across a wide range and units, helps in enhancing the performance of neural networks. When an input variable is significantly larger or smaller than others (such as strains and displacement measurements in this study), using non-normalized datasets might dominate the process of optimization, thereby avoiding proper

convergence. Also, data normalization assists in subsiding the biases which otherwise occur due to variations in dimension, units, and the range of different input datasets. Steps 2 through 5 (Section 2) were conducted using three normalization techniques as follows:

$$\text{Normalized Data} = \left| \frac{x_i - \text{Min}(x)}{\text{Max}(x) - \text{Min}(x)} \right| \quad (6)$$

$$\text{Normalized Data} = \frac{x_i - \bar{x}}{\text{std}(x)} \quad (7)$$

$$\text{Normalized Data} = \sqrt{\frac{x_i^2}{\sum_{i=1}^n x_i^2}} \quad (8)$$

where x is an $n \times 1$ column matrix representing the original recorded input variable for a specific bone, $\text{Min}(x)$ and $\text{Max}(x)$ represent the minimum and maximum value of the raw matrix respectively, $\bar{x}$ is the mean value of that variable, and $\text{std}(x)$ is its standard deviation. Within the timeframe of conducting each experiment on individual bones, each variable was recorded consistently over time and therefore there were many observations (changed with experiment timeframe) for each of these variables. n in the above Equations explains total recorded number for each variable and x_i denotes the value of an observed recorded variable. The outcome of pilot studies revealed that using the third normalization technique (Equation (8)) was associated with a lower error in quantifying the targets, and hence, this normalization method was employed and elaborated in the current study.

2.4. Assessing and then confirming a suitable ANN: Influential parameters

Two major steps are required to be monitored to affirm the suitability of an ANN: (A) the performance of the trained neural network; and (B) the performance of the trained network in making reliable predictions on new datasets (datasets that the ANN has not been trained on, i.e. a generalization of the ANN). The influential parameters upon which the decisions were made to select an acceptable ANN, to fulfil steps A and B, are as follows:

Step A:

- The network regression analysis to obtain the R -value (linear correlation coefficient) and linear function ($f(x) = mx + b$) between ANN output and target (experimental recording). The regression plots of training, testing, and all datasets display the output of ANN (prediction) versus the target value. The coefficient of correlation (R) measures the strength of a linear relationship between the ANN prediction and the experimental counterpart. For a perfect ANN prediction, the fitted line should fall along the 45-degree line for the training, testing, and all datasets. In such a perfect scenario, the value of R , m , and b would become 1, 1, and 0, respectively. Hence, R , m , and b were calculated, monitored, and reported for the all ANNs trained in this study.
- Mean squared error (MSE) for the training, testing, and validation datasets.
- The network training, testing, and validation error histogram as an additional check of the neural network performance. This also assists in indicating the outliers where the ANN predicted values are significantly worse than the majority of target values.

485 Step B:

- 486 • R -value and collecting the value of m and b appeared in the linear function ($f(x) = mx$
487 $+ b$).
- 488 • Root mean squared error (RMSE) achieved from a comparison between the output of
489 ANN on a new unseen sample and the recordings of ex-vivo experiments.

3. Results and Discussions

3.1. Selection of Optimum ANN Structures

This subsection aims to present the outcome for the methods described in Section 2 (to complete Steps 3 to 6). A substantial number of ANNs encompassing distinct structures were trained, tested, and finally validated with new datasets to find an optimum ANN structure (architecture) for each prediction of bones features (Step 3 in Section 2). Besides R -values and performance of ANNs during training sessions, the R -values and RMSE of trained ANNs on a new bone sample (unseen sample) were monitored in selection of an optimum ANN structure. Load exposure time (time during which the bone samples went through loading/unloading), six kinds of strains recorded on the midshaft of bones, applied load, displacement, horse age, bones limb side (left or right), and the length of the bones from 13 distinct horses were among the input variables of the ANNs. Constructing the ANN with too few neurons for both one hidden layer and two hidden layers impairs the ability of ANNs to map a correct pattern of inputs to outputs. In some cases, using too many neurons impedes the ability of ANNs to generalize as was observed for the regression and performance analyses on the unseen samples. Each ANN was trained ten times and the average of the results was reported in this study.

3.1.1. ANN with One Output (Prediction of Displacement)

Figures S1 and S2 ([supplementary material](#)) demonstrate the result of regression and performance analyses for ANNs in displacement prediction (one output). The results present R -values and MSE for the training of ANNs as well as R -values and RMSE for the generalization of ANNs (i.e. validation of the trained and tested ANNs when a new specimen that ANNs have not seen before is introduced to the ANNs). The results obtained from the last 100 trained ANNs to complete the sensitivity analysis of ANNs to the number of hidden layer(s) and number of neuron(s) are presented in Figure 2 (for regression analysis) and Figure 3 (for performance analysis). Figure S1 ([supplementary material](#)) shows the outcome for ANNs with one hidden layer (number of neurons changes from 1 to 15), while Figure S2 ([supplementary material](#)) and Figure 3 depict the results for the ANNs with two hidden layers (number of neurons changes from 1 to 10 in each hidden layer). For ANN [15] (i.e. an ANN comprising one hidden layer with 15 neurons), R -values for training, testing and combined data are high enough. Also, R -value for the unseen sample is more than 0.99, and RMSE is also within an acceptable range. ANN [10] could also be a potential candidate to be selected as an optimum ANN structure, however, R -values for training of the ANN and for the unseen sample are not high enough. With consideration of two hidden layers (Figure S2 ([supplementary material](#))), ANN [8,10], ANN [9,10], and ANN [10,10] are potential candidates. In addition to R -values and MSE for ANN training session and R -value and RMSE for the unseen sample, the values of m and b in the linear function ($f(x) = mx + b$) were monitored for selection of the optimum ANN architecture (Section 2.4). ANN [8,10], i.e. an ANN comprising two hidden layers with 8 and 10 neurons in the first and second hidden layer respectively (Figure 4), was selected for the displacement prediction since R -Values for training, testing and combined data during ANN training sessions were all higher than 0.99, and the R -value on the unseen sample ($R=0.9907$) exhibits a promising prediction ability of this ANN structure. These values along with the rest of the influential factors in selection of the optimum ANN structure are reported in Table 1. It is worth repeating that each ANN was trained 10 times and the average of values is reported.

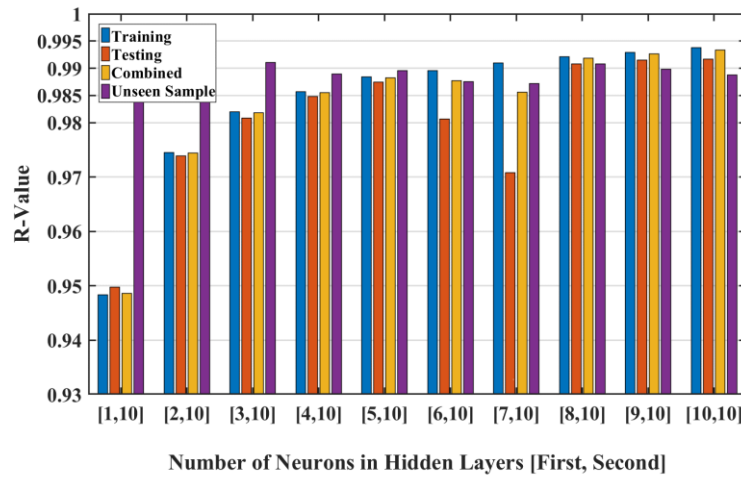


Figure 2. Regression analysis of ANNs (comprising two hidden layers) for prediction of displacement. Each ANN was trained ten times and the average of R-values was plotted herein. R-values of training, testing, and all datasets for training of ANNs were presented. Also, R-values between output of already trained ANNs and experiment when a new specimen (unseen sample) was introduced to the ANNs were reported. The number of neurons in the first hidden layer changes from 1 to 10, and the number of neurons in the second hidden layer was set to 10. A complete set of figures is presented in Figure S2 (supplementary material).

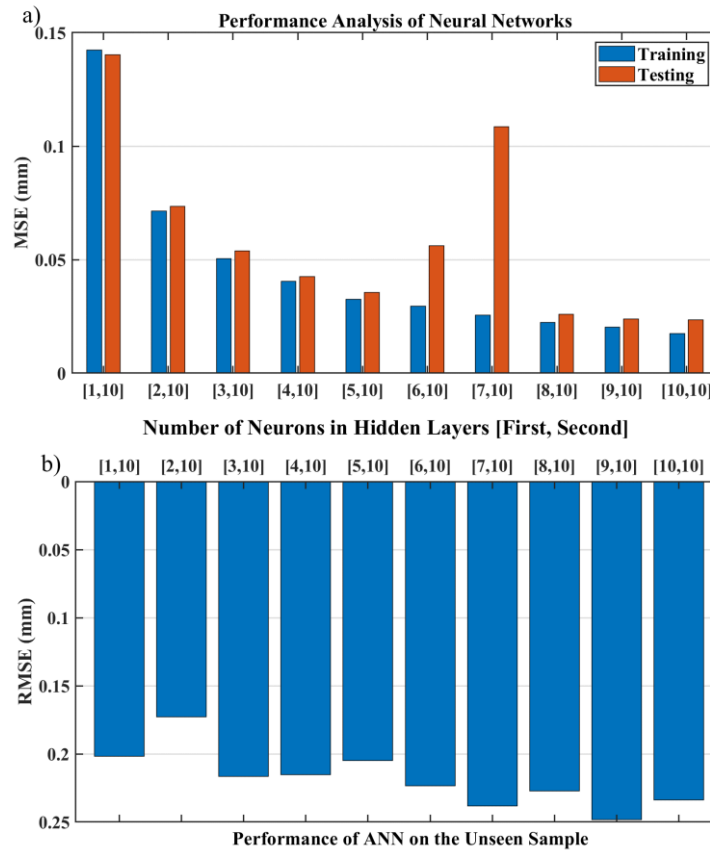


Figure 3. Performance (error) analysis for the prediction of displacement was conducted on the all ANNs comprising two hidden layers (Figure S2). Only representative plots are reported herein, which are for the ANNs having 10 neurons in the second hidden layer, and neurons changing from 1 to 10 in the first hidden layer. a) MSE of training and testing datasets for training of ANNs versus number of neurons in the hidden layers. b) RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layers when a new specimen (unseen sample) that ANNs had not seen before was introduced to the ANNs.

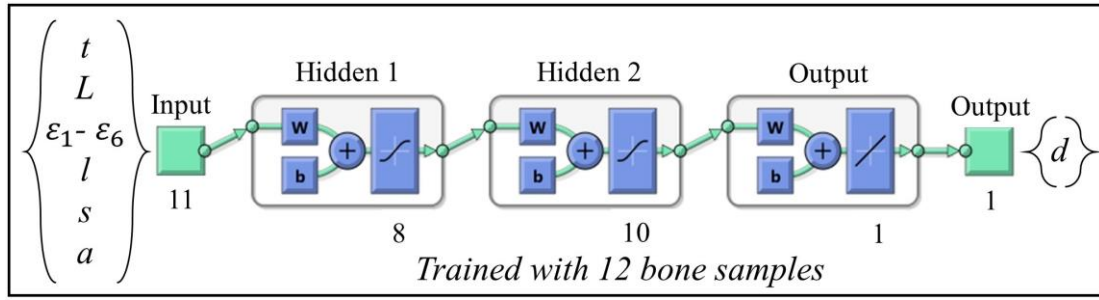


Figure 4. The topology and details of the optimum ANN structure (ANN [8,10]) that was selected to predict displacement. This ANN structure was found from training, testing, and assessing the generalization of 1150 ANNs.

Figure 5 shows the outcome of different performed analyses during training of the ANN with selected optimum structure (i.e. ANN [8,10], Figure 4) for the prediction of displacement. 17,000 training data points (from recording of experiments) were employed to train the ANN, among which 80% were used for training and the rest were used for testing the ANN. The values of the linear correlation coefficient (R -value) are depicted above each subplot (Figure 5a-c). Also, the values of m and b in the linear function ($Output = m(Target) + b$) can be drawn from each subplot. The average of these values, since the ANN was trained ten times, is reported in Table 1. The performance of the neural network (ANN [8,10]) in terms of MSE for 555 epochs (the number of times the algorithm sees the entire dataset) is presented in Figure 5d, in which the log of MSE is plotted versus the number of epochs. There was a similar trend in the error reduction for both training and testing datasets and a small difference in both errors was observed. This indicates a well-trained ANN which is well-suited for generalization to predict real-world data that the ANN has not seen before. For a convincing performance, the ultimate value of MSE should be small, the error of training and testing datasets should have similar characteristics, and there should be no significant overfitting. The network training error histogram is shown in Figure 5e, which indicates that the error is normally distributed, for more than 62% of data points (instances) the ANN has an absolute error less than 0.075 mm, and for more than 95% of data points the network has an absolute error less than 0.307 mm.

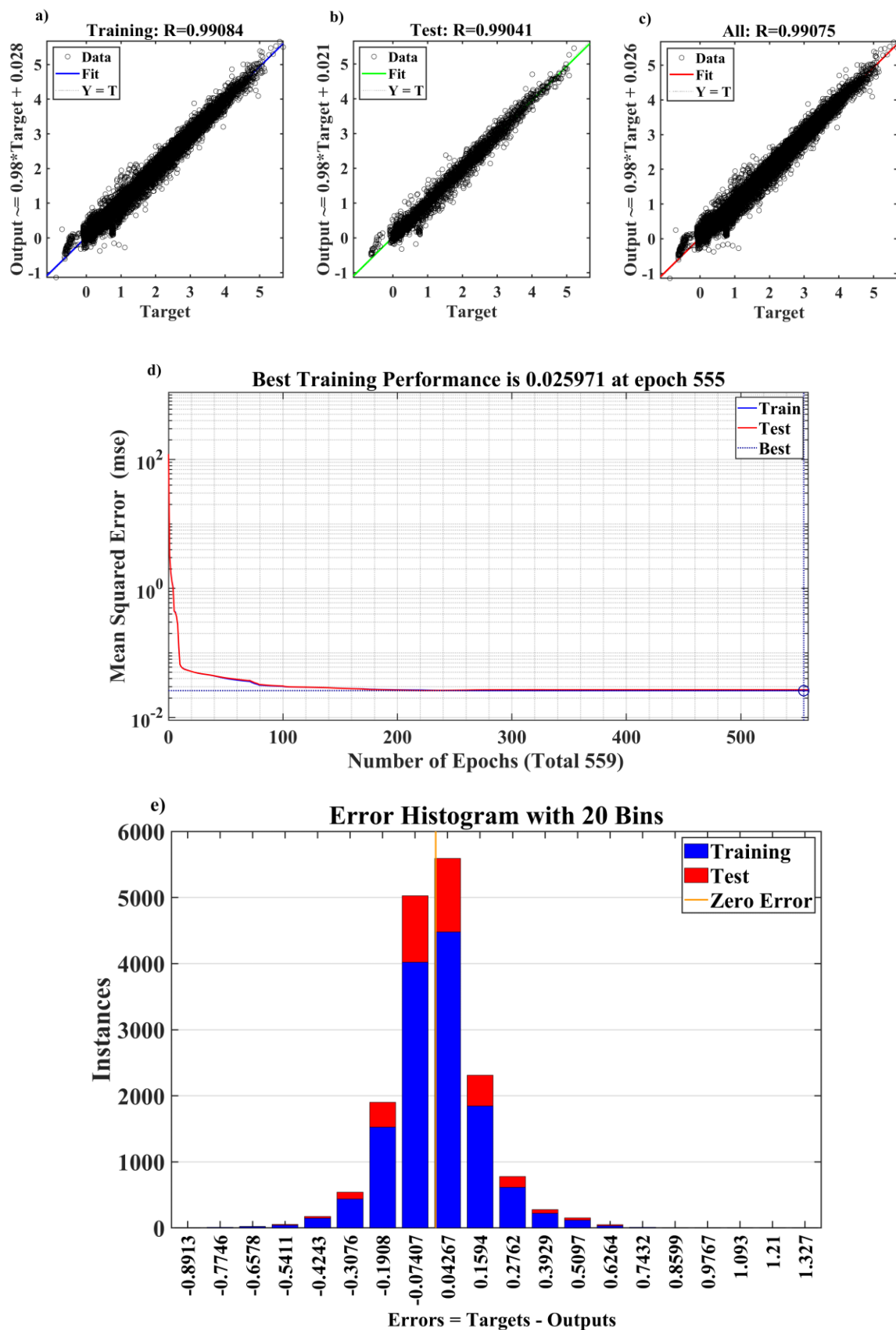


Figure 5. The outcome of regression, performance, and error histogram analyses when an ANN with the optimum structure (ANN [8,10], Figure 4) was trained to predict displacement of MC3 long bones. Three scatter plots represent the outcome of regression analysis for a) training, b) testing, and c) all data. d) Performance analysis of the neural network during training. e) Error histogram of the neural network during training.

To offer a robust model in which the accuracy of the trained ANNs are assessed and checked in predicting real-world data, the inputs of the trained and tested ANNs (mentioned above) were fed with unseen data of new specimens (new bone samples), and the output of the ANN (its prediction ability) was compared against the experiment (target value). Figure 6 shows the outcome of regression analysis as a comparison of ex-vivo experiments and that of the ANN model for a new bone sample that was not involved in the ANN training. Similar to training sessions, the process of validating ANN through introduction of a new specimen was conducted ten times and then the average of the outputs is reported in Table 1. Figure 6 is a typical plot produced by the ANN.

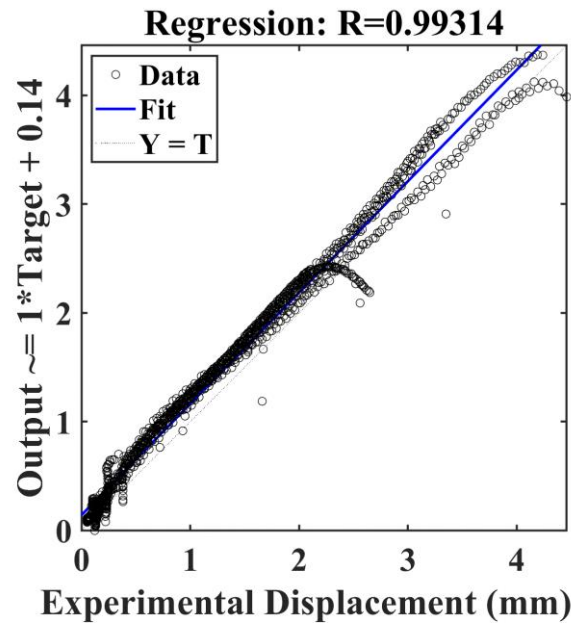


Figure 6. The already trained and tested ANN (Figure 5) was employed in order to investigate the displacement prediction on a new specimen (an unseen sample) that was not used in ANN training. A representative plot indicating the outcome of the regression model between ANN output and target (experiment) is displayed herein.

3.1.2. ANN with One Output (Prediction of Load)

Figures S3 and S4 ([supplementary material](#)) demonstrate the result of regression and performance analyses for ANNs in prediction of load (ANN with one output). The results present R -values and MSE for the training of ANNs as well as R -values and RMSE for the generalization of ANNs (i.e. validation of the trained and tested ANNs when a new specimen that ANNs have not seen before is introduced to the ANNs). The results obtained from the last 100 trained ANNs to complete the sensitivity analysis of ANNs to the number of hidden layer(s) and number of neuron(s) are presented in Figure 7 (for regression analysis) and Figure 8 (for performance analysis). Figure S3 ([supplementary material](#)) shows the outcome for ANNs with one hidden layer (number of neurons changes from 1 to 15), while Figure S4 ([supplementary material](#)) and Figure 8 depict the results for the ANNs with two hidden layers (number of neurons changes from 1 to 10 in each hidden layer).

ANN [14] and ANN [15], i.e. ANNs comprising one hidden layer with 14 and 15 neurons respectively, produce similar encouraging results. However, R -values for training, testing, and combined data produced by ANN [14] are slightly more than those exhibited by ANN [15]. Although ANN [15] produced a marginally higher R -value on the unseen sample than that offered by ANN [14], the latter revealed lower errors for both training and testing as well as on the unseen sample (Figure S3b and d ([supplementary material](#))). With consideration of two hidden layers for load prediction there are several potential structures (ANN architectures) for which ANNs exhibited strong ability in predicting load. For instance, ANN [9,2], ANN [9,3], ANN [8,5], ANN [9,6], ANN [6,8], and ANN [10,10] revealed high magnitudes of R -values for training, testing, and all datasets as well as high magnitudes of R -values for the unseen sample. Among these ANN structures, ANN [10,10] was selected for the aim of load prediction (Figure 9). The average R -value (from the ten times trained ANNs) for the training, testing, and all datasets for ANN [10,10] approaches 1 (higher than that displayed by other ANNs). Moreover, its prediction outcome on the unseen sample exhibits a potent capability of this ANN structure in load prediction ($R=0.997$). Furthermore, performance analysis performed by the network ANN [10,10] indicates trivial MSE for both training (i.e. 1.62 kN) and testing (i.e. 1.95 kN) datasets as well as minor RMSE (i.e. 2 kN) in making load prediction on a new bone sample that ANNs have not seen before in their training session (Figure 8). Besides R -values for the regression plots and MSE (performance) for training of ANNs; and R -value and RMSE when the trained ANN was validated using an unseen-to-ANN sample (new specimen), the values of m and b in the linear function ($f(x) = mx + b$) were monitored for selection of the optimum ANN architecture (Section 2.4). $f(x)$ identifies the prediction of ANNs and x represents targets (i.e. experimental recordings). In line with the recommendation of MATLAB to train each neural network multiple times and average their outputs and as delineated before, the magnitudes of the above-mentioned parameters were recorded once each network training was completed, with the average for each variable reported in Table 1.

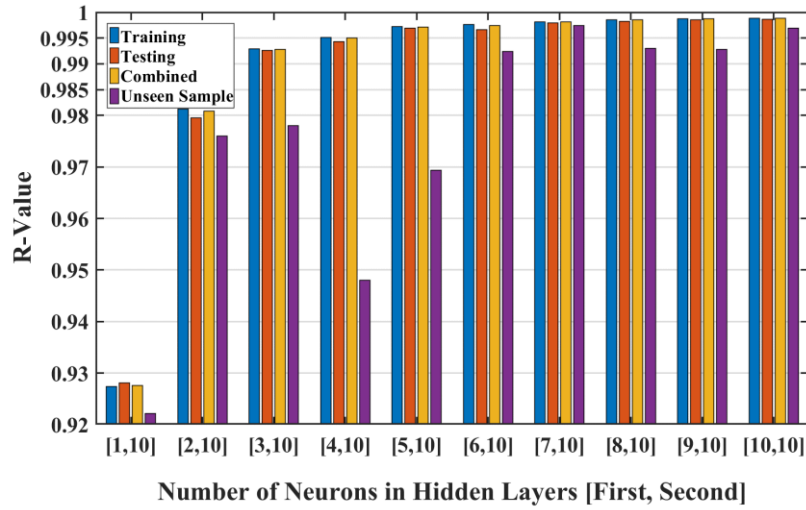


Figure 7. Regression analysis of ANNs (comprising two hidden layers) for prediction of load. Each ANN was trained ten times and the average of R-values was plotted herein. R-values of training, testing, and all datasets for training of ANNs were presented. Also, R-values between output of already trained ANNs and experiment when a new specimen (unseen sample) was introduced to the ANNs were reported. In the all subfigures the number of neurons in the first hidden layer changes from 1 to 10, and the number of neurons in the second hidden layer was set to 10. A complete set of figures is presented in Figure S4 (supplementary material).

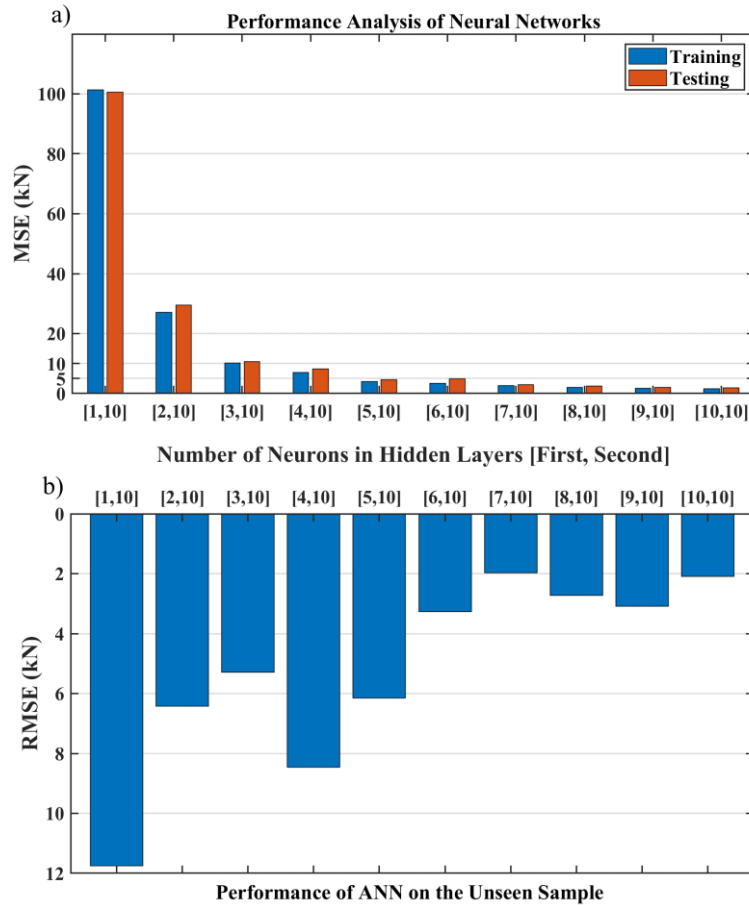


Figure 8. Performance (error) analysis for the prediction of load was conducted on the all ANNs comprising two hidden layers (Figure S6). Only representative plots are reported herein which are for the ANNs having 10 neurons in the second hidden layer and neurons changing from 1 to 10 in the first hidden layer. a) MSE of training and testing datasets for training of ANNs versus number of neurons in the hidden layers. b) RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layers when a new specimen (unseen sample) that ANNs had not seen before was introduced to the ANNs. Compressive load is represented with positive values in this study.

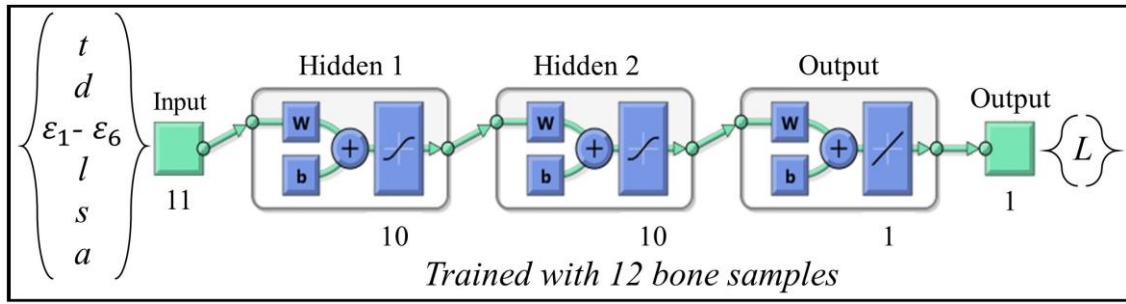


Figure 9. The topology and details of the optimum ANN structure (ANN [10,10]) that was selected to predict mechanical loading. This ANN structure was found from training, testing, and assessing the generalization of 1150 ANNs.

Figure 10 shows the outcome of regression, performance, and error histogram analyses obtained during and post training of the ANN with the selected optimum structure (i.e. ANN [10,10]) for the prediction of load. Similar to the latest scenario (Section 3.1.1) in which displacement was predicted, 17000 training data points from recording of ex-vivo experiments on 12 bone samples were also employed here to train the ANN to accomplish the objective of load prediction. The plots of network regression analysis for training, testing, and all data are shown in Figure 10a-c, all of which demonstrate R -values greater than 0.998, $m=1$ and $b=0.064$ in the linear function derived from the comparison between output of the ANN and target ($Output = m \times Target + b$). Figure 10d shows the performance of the network (ANN [10,10]) identifying MSE versus 1000 epochs for both training and testing. The best training performance (lowest training error) occurred at 1000 epochs (iterations). This is where the training of the ANN is stopped according to adaptive weight minimization regularization through conducting the gradient descent methods, when either the error between ANN output and target is small enough or the learning iteration reaches its higher level without a considerable decrease in the error (default is normally 1000 iterations/epochs). The average values obtained on different parameters for both the trained ANN and its prediction on an unseen sample (new specimen that ANN has not seen before) are summarized in Table 1. Upon completion of the neural network training, an error histogram is produced which is depicted in Figure 10e. This plot pinpoints that the error is almost normally distributed with the error of the majority of the data points (instances) close to zero. This figure also reveals that for more than 44% of data points the neural network (ANN [10,10]) has an absolute error less than 0.46 kN, for more than 76% of data points the network exhibits an absolute error less than 0.86 kN, and for more than 93% of data points the neural network has an absolute error less than 2.17 kN.

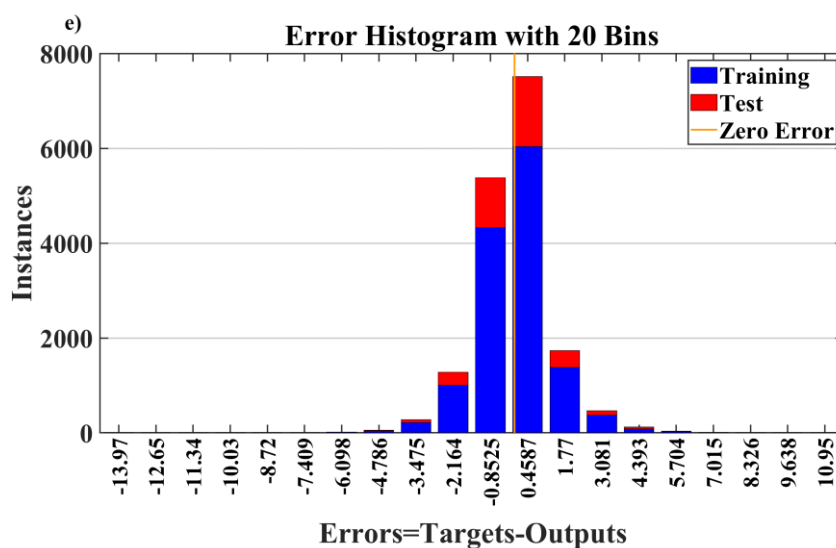
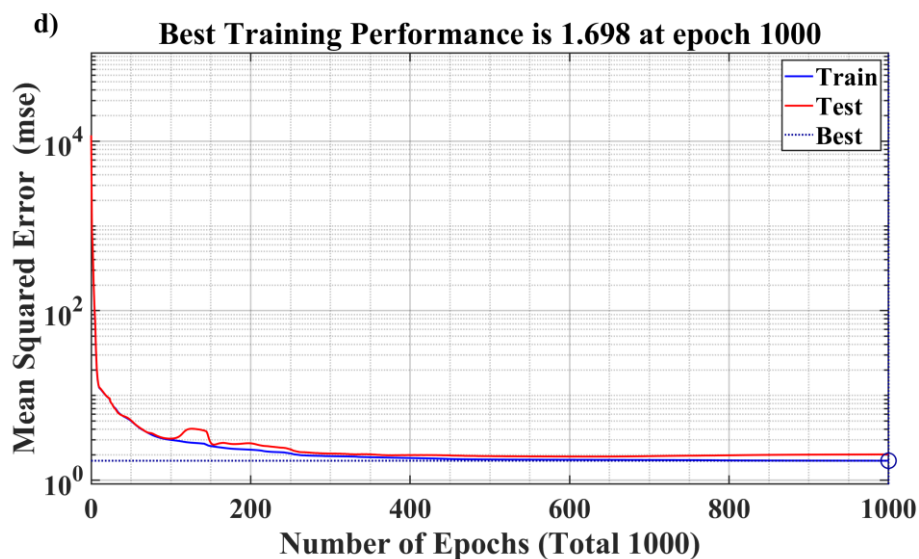
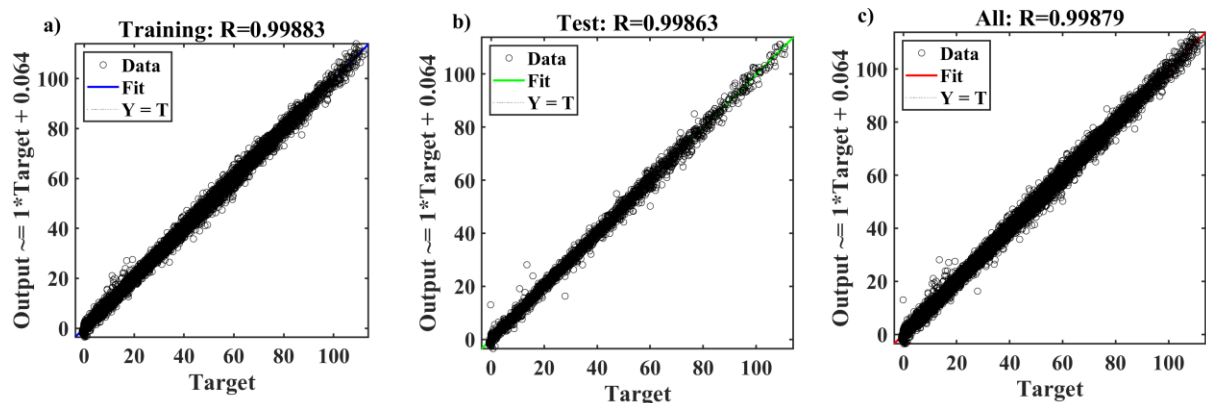


Figure 10. The outcome of regression, performance, and error histogram analyses when an ANN with the optimum structure (ANN [10,10], Figure 9) was trained to predict loading of MC3 long bones. Three scatter plots represent the outcome of regression analysis for a) training, b) testing, and c) all data. d) Performance analysis of the neural network during training. e) Error histogram of the neural network during training.

To confirm the accuracy of the already trained and tested ANN mentioned above (Figures 9 & 10), the ANN was employed to predict the loading of new specimens (new bone samples) that were not used in the ANN training. Afterwards, the output of the ANN (its prediction ability) was compared against the experiment (target value). The outcome of regression analysis as a comparison between load recorded via experiments (target) and the load predicted by the ANN model is illustrated in Figure 11. This process (to validate an already trained ANN through introduction of new specimens) was conducted ten times and then the average of the outputs was reported in Table 1. Figure 11 is a typical plot produced by the ANN.

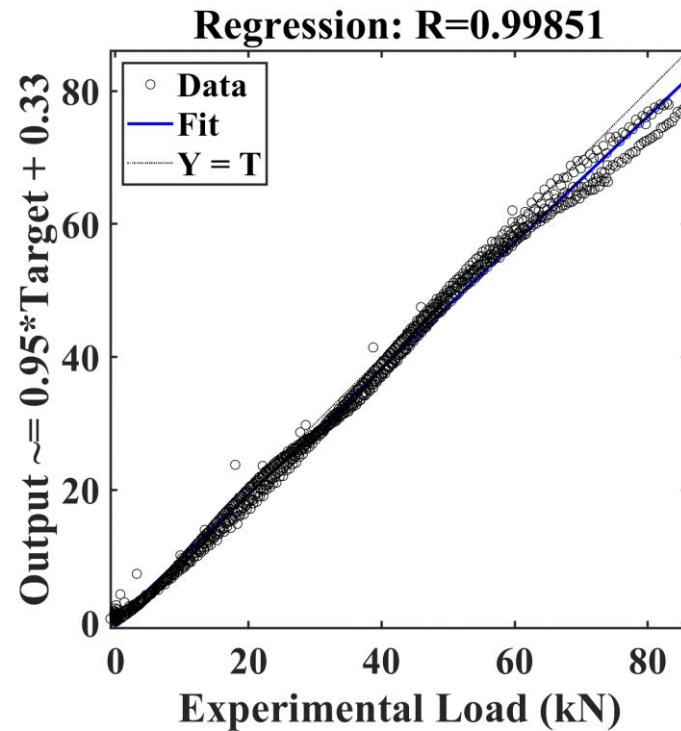


Figure 11. The already trained and tested ANN (Figure 10) was employed in order to investigate the load prediction on a new specimen (an unseen sample) that was not used in ANN training. A representative plot indicating the outcome of regression model between ANN output and target (experiment) is displayed herein.

3.1.3. ANN with Two Outputs (Prediction of Both Load and Displacement)

The output of this neural network comprises two outputs and aims to predict both load and displacement simultaneously. This reveals the significance of using artificial neural networks to predict stiffness (and then other mechanical properties) in structures and nonlinear materials possessing exotic mechanical properties. Neither load nor displacement was considered as the ANN input variables in this scenario. The selection of an optimum ANN structure should be based on successful and reliable prediction of both load and displacement. Hence, the outcome of multiple regression and performance analyses was plotted individually for each of these output variables. In Sections 3.1.1 and 3.1.2, when load and displacement were individually predicted using distinct ANNs, it was observed that ANNs comprising two hidden layers are superior in producing favorable results than ANNs comprising only one hidden layer. Hence, in this scenario where both load and displacement are to be predicted (outputs of ANN) only ANNs comprising two hidden layers were employed, considered, and tested.

Similar to the scenarios presented in Sections 3.1.1 and 3.1.2, the number of neurons in each hidden layer (two hidden layers in total) changes from 1 to 10, and thus 100 distinct ANNs were constructed, and then each of these ANNs was trained, tested and validated ten times. Afterwards, the average of outcomes was monitored and considered. *R*-values associated with train, test, and combined displacement prediction datasets (Output 1) that were accumulated for the initial 400 trained neural networks lie within the range of 0.91 (for ANNs comprising 1 neurons in the second hidden layer) and gradually increased to 0.93 (for ANNs comprising 4 neurons in the second hidden layer). For the next 400 trained ANNs, where the number of neurons in the second hidden layer increased from 5 to 8, *R*-values hardly reached 0.95 and for just a few ANN structures went beyond 0.95. Among these structures that have been discussed so far and with inclusion of more ANN structures (the next 200 trained ANNs for which the number of neurons in the second hidden layer was set to either 9 or 10), both ANN [9,10] and ANN [10,10] displayed a good performance. The performance (error) analysis of these neural networks also exhibited favorable mean square error for both training and testing datasets as compared with other ANN structures. To avoid superabundance of figures that were obtained during 1000 times of training, testing, and validating ANNs, only the plots for the outcome of ANNs having 10 neurons in the second hidden layer and neurons changing from 1 to 10 in the first hidden layer are presented (Figure S5 ([supplementary material](#))). A similar process of monitoring the ANNs regression and performance analyses, which was thoroughly delineated before, was followed to determine the best structures for which the outcome of load prediction was also encouraging. In this case ANN [9,10] displayed a better performance. In conclusion, to ensure that both outputs of the ANN fulfill the requirements of desirable regression and performance analyses as well as enhanced accuracy in predictions, ANN [9,10] was selected as the optimum structure in this scenario (Figure 12 and Table 1).

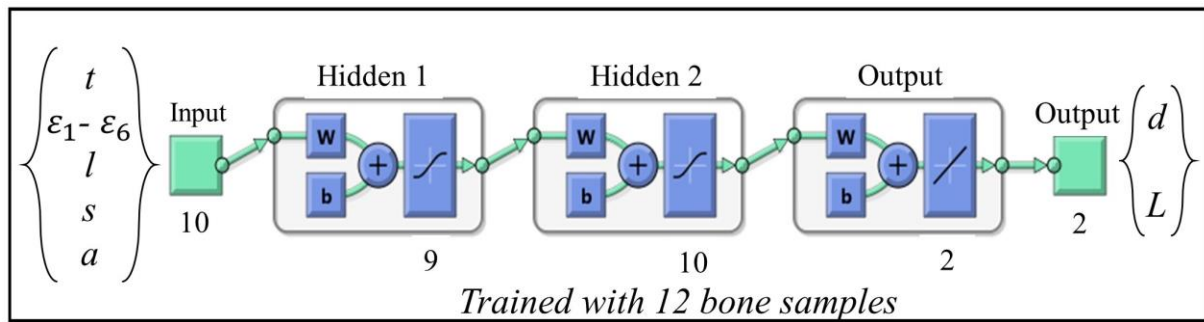
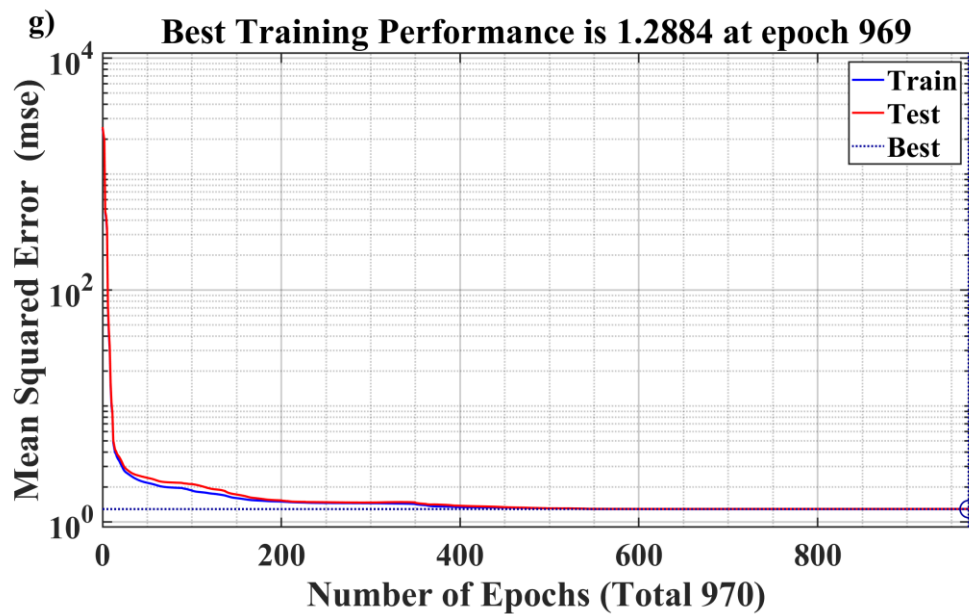
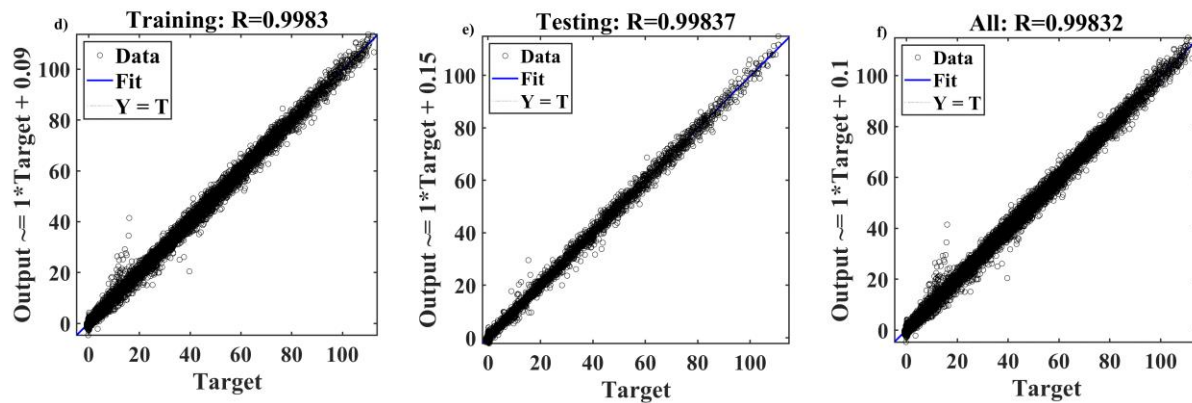
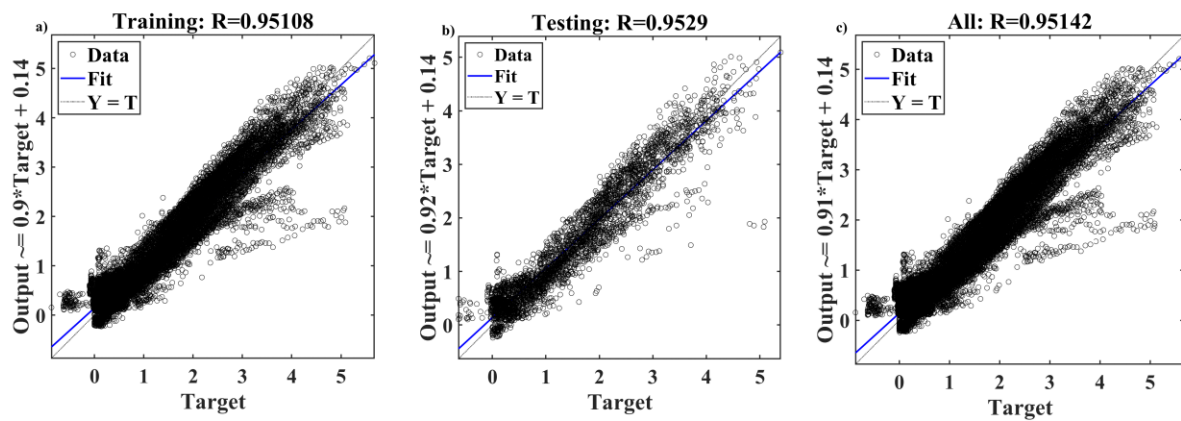


Figure 12. The topology and details of the optimum ANN structure (ANN [9,10]) that was selected to predict both mechanical loading and displacement. This ANN structure was found from training, testing, and assessing the generalization of 1000 ANNs.

Figure 13 shows the outcome of regression, performance, and error histogram analyses obtained during and post training of the ANN with the selected optimum structure (i.e. ANN [9,10]) comprising two outputs for the prediction of displacement and load. Figure 13a-c displays the outcome of regression analysis for training, testing, and all data points in predicting displacement (Output 1), while Figure 13d-f represents the outcome of regression analysis for training, testing, and all data points in predicting load (Output 2). The ideal scenario is when both output and target are exactly equal in which case the scatter data points lie on the dotted line shown in the regression plots (i.e. a representation of the perfect result which is $Y=T$). The solid blue line represents the best linear regression fit line between outputs (predictions of ANN) and targets (experiments). It is observed from Figure S10 that more scatter data points in the displacement prediction plots deviate from the dotted line ($Y=T$) than those in the load prediction plots. Hence, R -values associated with training, testing, and all data points for load prediction are higher than those for displacement prediction. This was also already concluded while observing Figure S5 a and b ([supplementary material](#)). Furthermore, the scatter plot is helpful in showing that certain data points have poor fits. For example, there are data points in the test set (Figure 13b) whose network outputs lie within the range 1.8-2.0 mm, whereas the corresponding target values are within the range 4.8-5.2 mm. In scenarios in which a majority of the data is behaving like this (which is not the case here), it is worth investigating such deviated data to determine if they represent extrapolation (i.e. they are outside of the training data set). If so, it is recommended that they be included in the training dataset and that additional data should be collected to be employed in the testing dataset. Figure 13h shows the error histogram for predicted load and predicted displacement both combined in a plot. This plot is automatically produced by MATLAB once the training is completed. To enable observation of errors for each output individually, a script was developed in MATLAB to split the plots of error histogram. Figure 13 i and j display individual error histogram plots for displacement and load prediction, respectively. A comparison of these two plots reveals that more data points in the predicted displacement deviated from the expected target values than those in the predicted load. This indicates that more data points in load prediction are closer to the zero-error line (i.e. vertical orange line), whereas the same data points deviated relatively more from the zero-error line in displacement prediction. Bins are the number of vertical bars that one can observe on an error histogram plot. As an example and to further explain such plots, the total error from the neural network for output 1 (displacement prediction) ranges from -1.116 (leftmost bin) to 3.128 mm (rightmost bin), Figure 13i. This error range is then divided into 20 smaller bins, from which the width of each bin is calculated. Each vertical bar represents the number of data points (instances) which lie in a specific bin, and from the width of each bin the range of error for each bar is then easily calculated.



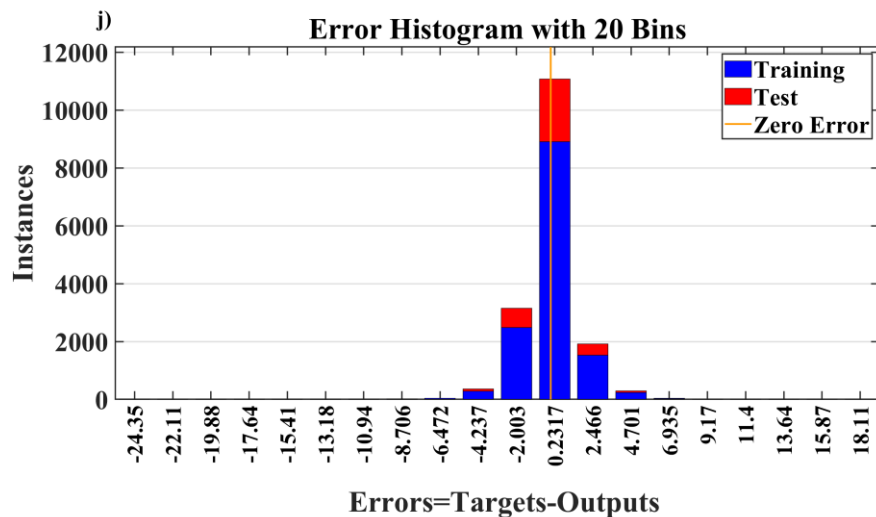
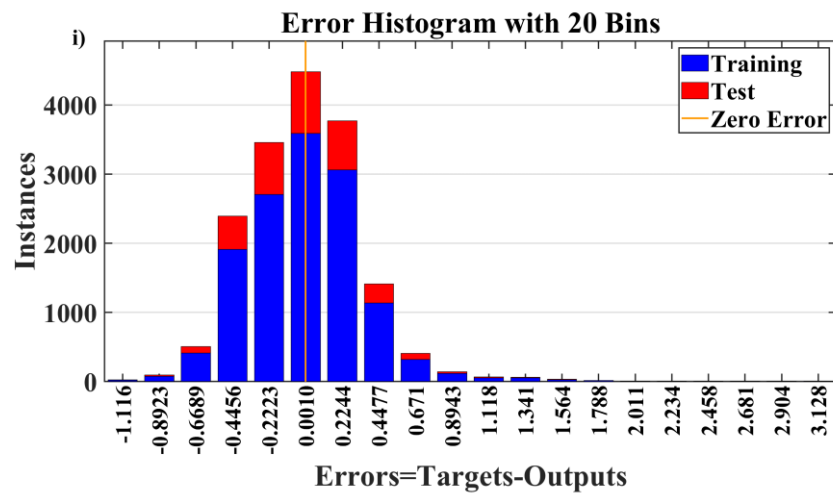
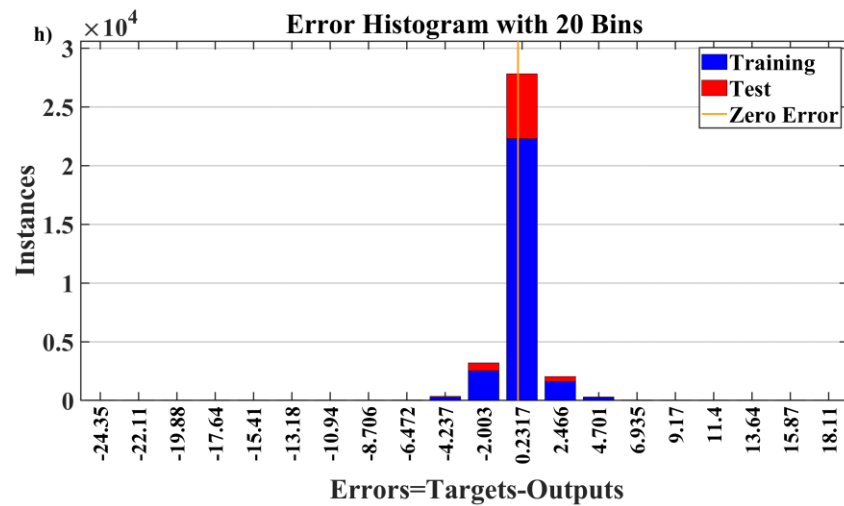


Figure 13. The outcome of regression, performance, and error histogram analyses when an ANN with the optimum structure (ANN [9,10], Figure 12) comprising two outputs was trained to predict both displacement and loading of MC3 long bones. The first three scatter plots represent the outcome of regression analysis for a) training, b) testing, and c) all data in predicting displacement (Output 1), while the second three scatter plots represent the outcome of regression analysis for d) training, e) testing, and f) all data in predicting load (Output 2). g) Performance analysis of the neural network during training. h) The overall error histogram of the neural network during training. Also, the plots of error histogram are individually represented for i) displacement prediction (Output 1) and for j) load prediction (Output 2).

To assess as to whether the already trained and tested ANN could generalize well to real-world data, the ANN was used to produce the two outputs of new specimens (new bone samples) that were used neither in the ANN training nor in its testing. The outcome of regression analysis as a comparison between ANN predictions (outputs) and experimental counterparts is depicted in Figure 14a for the first output of the ANN (predicted displacement) and Figure 14b for the second output of the ANN (predicted load).

The quality of the ANNs was oversensitive to both the number of hidden layers and number of neurons in the hidden layer(s). This was observed for the all predictions made in this study using ANNs. Conversely, in a study on prediction of load from the density distribution of trabecular bone it was observed that the quality of the ANNs was not oversensitive to the number of hidden neurons [38]. It is critical to keep in mind that our study was conducted on long (whole) bones, while that study was performed on trabecular bone samples. Therefore, even though ANNs can accurately represent any sufficiently smooth nonlinear mapping in different tissue scales in the engineering practices, such differences must be delineated to make proper use of ANNs. MSE in a training step is decreased when the number of neurons in the hidden layer(s) is increased, whereas this is not true for the testing step and RMSE on the unseen samples (Figures S1, S3, and S5 (supplementary material) as well as Figure 3 and Figure 8). This indicates that low error (MSE or RMSE) in the training datasets does not confirm low error in the testing datasets. Despite the errors being oversensitive to the network structures, this finding accentuates the significant importance of affirming the accuracy of the already trained ANNs with the use of independent datasets from new samples (not used for either training or testing) in the applications of neural networks in the engineering practices.

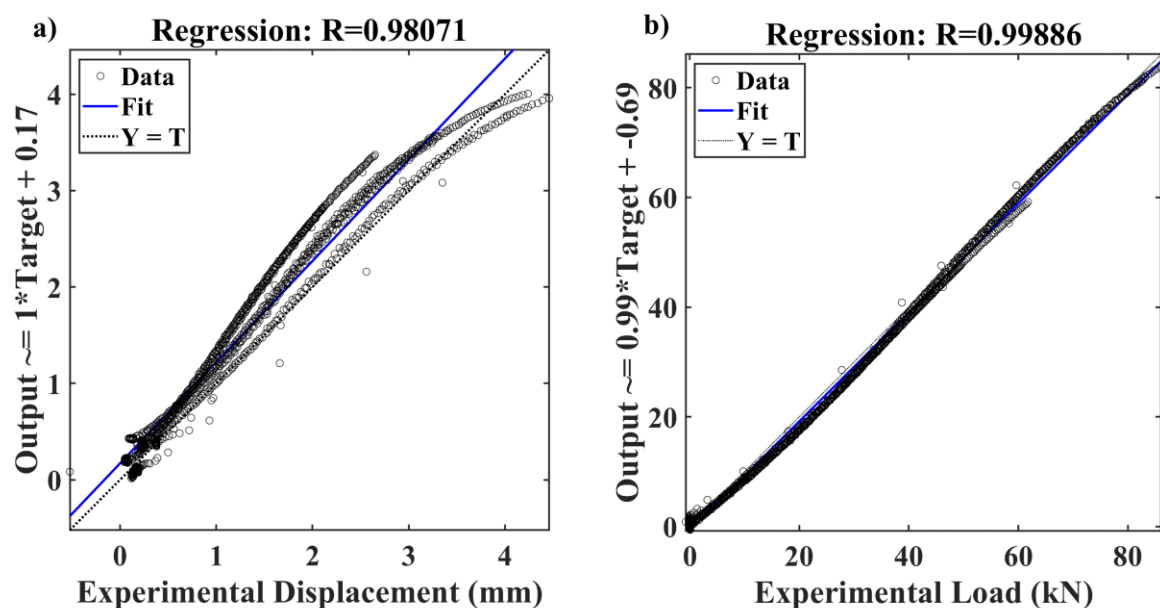


Figure 14. The already trained and tested ANN comprising two outputs (Figure 13) was employed in order to investigate the displacement and load prediction on a new specimen (an unseen sample) that was not used in ANN training. A representative plot indicating the outcome of a regression model between ANN output and target (experiment) is displayed herein for a) Output 1 (predicted displacement) and b) Output 2 (predicted load).

Table 1. More than 340 ANNs with distinct structures were trained, tested, and validated, each 10 times, to find the optimum ANN structure (architecture) that best predicts displacement (D), load (L), and both together (D & L). The outcome of regression analyses (R-value and linear model) and performance analyses (MSE) for the training session of ANNs is reported. Furthermore, to assess the ability of the trained ANNs in generalization, the outcome of regression analyses (R-value and linear model) and performance analyses (RMSE) is reported when the trained ANNs were employed to make predictions on new specimens (unseen samples). $f(x)$ identifies the ANN output (prediction) and x expresses the target (experimental) value. To improve the generalization of ANNs, each ANN was trained 10 times, and hence the average of the obtained results is reported herein.

ANN output	Optimum ANN structure		Trained ANN				Prediction on unseen sample			
			R-Value	MSE	Linear model $f(x) = mx + b$		R-Value	RM SE	Linear model $f(x) = mx + b$	
					m	b			m	b
D	[8,10]	Train Test All	0.9921 0.9908 0.9919	0.0223 0.0258 -	0.9843 0.9833 0.9841	0.0238 0.0250 0.0241	0.9907	0.2 272	1.0598	0.0390
L	[10,10]	Train Test All	0.9989 0.9987 0.9988	1.6247 1.9489 -	0.9977 0.9982 0.9978	0.0604 0.0676 0.0619	0.997	2.0 929	1.0126	-0.748
D & L	[9,10]	Train Test All	Output 1: D							
			0.9554	0.1234	0.9127	0.1327	0.9789	0.2 328	0.9948	0.0514
			0.9556	0.1239	0.9138	0.1332				
			0.9555	-	0.9129	0.1329				
		Train Test All	Output 2: L							
			0.9982	2.5464	0.9965	0.0941	0.9976	2.0 235	1.0145	-0.582
			0.9980	2.9707	0.9963	0.1065				
			0.9982	-	0.9964	0.0966				

3.2. Network Training Algorithm

The results that have been obtained and presented so far are based on ANNs trained with a Bayesian regularization backpropagation algorithm. To investigate the influence of the training algorithm on the prediction of ANNs, more than 2300 ANNs were retrained using Levenberg-Marquardt backpropagation and Scaled conjugate backpropagation training algorithms, and then the outcomes of predictions were compared against those presented in Section 3.1.

3.2.1. Levenberg-Marquardt Backpropagation

Levenberg-Marquardt backpropagation demonstrated a quicker training time and hence the algorithm stopped network training in a smaller number of epochs. This means that when the networks are trained using Levenberg-Marquardt backpropagation algorithm, the required number of times that the network sees the entire dataset is smaller than those required by a Bayesian regularization backpropagation training algorithm. Nonetheless, the regression analyses revealed comparatively lower R -values (for both prediction of load and displacement) when Levenberg-Marquardt backpropagation was employed as the ANN training algorithm. This was true for R -values recorded on ANN training datasets, and with more noticeable influence on R -values associated with unseen samples (Figures S6 and S7 ([supplementary material](#))). Furthermore, error analysis showed higher MSE values in the training, validation, and testing datasets as compared with MSE values achieved from ANNs where a Bayesian regularization backpropagation training algorithm was employed. The prediction of ANNs on unseen sample using these two different training algorithms demonstrate a smaller value of RMSE when the ANN was trained using a Bayesian regularization backpropagation training algorithm. This is extremely valid in prediction of load where values of RMSE on the unseen samples (validation of already trained ANNs using new samples) were substantially higher when ANNs were trained using a Levenberg-Marquardt backpropagation training algorithm (comparison Figure S7 ([supplementary material](#)) Figure 8). As an example, RMSE observed from using the ANN with the optimum structure (ANN [10,10]) in predicting load is approximately 8 kN (Figure S7d ([supplementary material](#))), whereas Figure 8b reveals RMSE with the value around 2 kN, which indicates a 75% reduction in error (RMSE) when the Bayesian regularization backpropagation algorithm is used in the network training algorithm for prediction of load. As it was repeatedly emphasized in this study, a vital factor that needs to be considered in selecting a suitable neural network among hundreds of trained ANNs is the robustness of that ANN in making reliable predictions on new (unseen) sample datasets (Assessing and then confirming the generalization performance of trained ANNs). The results of regression analyses performed on training more than 2300 networks exhibit that employing a Levenberg-Marquardt backpropagation training algorithm does not reveal relatively higher R -values in the prediction of mechanical responses for the unseen samples (i.e. inferior ability in generalization).

The outcome of regression, performance, and error histogram analyses obtained during and post training of the ANN with selected optimum structures (i.e. ANN [8,10] for displacement prediction and ANN [10,10] for load prediction) trained using a Levenberg-Marquardt backpropagation training algorithm is demonstrated in Figure S8 ([supplementary material](#)) for prediction of displacement and in Figure S9 ([supplementary material](#)) for prediction of load. The best validation performance occurs at epoch 65 and at epoch 40 in the prediction of displacement and in the prediction of load, respectively (Figures S8e and S9e ([supplementary material](#))). These indicate the iterations at which the validation performance reached a

minimum. The training continued for six more iterations before the training stopped. Generally speaking, if the test curve increases significantly before the validation curve does, then it is possible that some overfitting might occur. Hence, in a well-trained network the performance plot should reveal similar characteristics and trends for the training and validation datasets. Despite expediting the training process and stopping the training at smaller iterations (epochs), the error analyses both for the trained ANNs and for the unseen sample showed higher MSE and RMSE when the Levenberg-Marquardt backpropagation training algorithm was used for the prediction of load (Figures S7 and S9 ([supplementary material](#))). This was also observed, with relatively less significant deviation in errors, for the displacement prediction (Figures S6 and S8 ([supplementary material](#))). As it was already explained, each ANN was trained and then was used to make prediction on new specimens that the ANN had not seen before. These processes were completed 10 times, in each of which the outcomes of analyses were obtained and recorded, and finally the average of each value was stored. This process minimizes biased decisions in interpreting the data and making the decisions. The outcome of regression analysis on unseen samples (average value for R -value) when ANN was trained using the Levenberg-Marquardt backpropagation training algorithm showed $R = 0.9908$ in predicting MC3 long bone loading. The error analysis, following a similar procedure, revealed $RMSE = 7.62$ kN. Comparing these values with their counterparts when ANNs were trained using the Bayesian regularization backpropagation algorithm (Table 1, $R = 0.997$ and $RMSE = 2.09$ kN) shows that employing this training algorithm reduces the generalization error for this problem by as much as 73%. Also, the linear model ($f(x) = mx + b$) in that case provided a better estimation produced by ANN as compared with the target (experimental) values.

3.2.2. Scaled Conjugate Backpropagation

All the processes mentioned in the previous subsection were conducted, and the results were achieved using another algorithm for the training of ANNs, which is a scaled conjugate backpropagation training algorithm. The observed remarks and conclusions using this training algorithm are almost identical to those exhibited using the Levenberg-Marquardt backpropagation algorithm. Similar to the Levenberg-Marquardt backpropagation algorithm, the error histogram for the scaled conjugate backpropagation training algorithm indicated more outliers and consequently was associated with lower R -values in the regression analyses. These error histograms give an indication of outliers, which are data points where the fit produced by the ANN is significantly worse than the majority of the data. It also shows a quicker response in terms of training time and as such completed training, testing, and validation processes in a smaller number of epochs (iterations). The comparatively worse regression results obtained using scaled conjugate backpropagation and Levenberg-Marquardt backpropagation training algorithms do not however mean that these algorithms should be totally rejected in future studies. It is sometimes the case that training time (how quickly we can obtain the results) is a critically essential parameter rather than achieving absolutely precise results (if the error range is acceptable in that specific case).

Employing the Bayesian regularization backpropagation as the neural network training algorithm demonstrated a superior ability in making reliable load and displacement predictions (mostly in using the ANN in making predictions on new datasets, i.e. its generalization). This emphasizes the comparatively inferior capability of ANNs trained with Levenberg-Marquardt and scaled conjugate backpropagation algorithms in generalization to new (unseen) samples.

3.3. Injecting Noise prior to ANNs Training

A major concern and one of the most critical challenges in training artificial neural networks and their application to fully new datasets is the likelihood of overfitting. It is expected that injecting noise to the inputs of feedforward ANNs during backpropagation training be effective in improving the generalization performance for the regression analysis conducted in this study. In this section, it is investigated whether injecting noise to the datasets prior to neural networks training constrains the ANN function to be smooth, and therefore, to enhance generalization on fully new datasets that the ANNs have not seen before.

For each of three distinct problems (first displacement prediction, second load prediction, and third prediction of both simultaneously), two scenarios were considered: first training each ANN with injected noise to the datasets and second training each ANN without injected noise. For each scenario, each ANN was trained and then was used to make predictions on new specimens that the ANN had not seen before. These processes were completed ten times and then the average of the outcomes was reported in Table S1 ([supplementary material](#)). The entire processes were conducted on three distinct (new/unseen) bone specimens that ANNs have not seen before in their training session. In this table, training error indicates mean squared error (MSE) of ANNs for the training session. Generalization error presents root mean squared error (RMSE) when the trained ANN was employed to predict output(s) of a new specimen (not involved in ANNs training). As such, generalization error is calculated between the output of this ANN in predicting the specific bone feature and the experimental counterparts. Likewise, generalization R -value in this table delineates the value of R (linear correlation coefficient) that measures the strength of a linear relationship between the output(s) of the ANN and experimental counterparts (either load, displacement, or both). The results are presented when both injected noise and no noise are introduced to the datasets. A hypothesis is investigated here, which is injecting noise prior to ANNs training substantially reduces error in the generalization performance of ANNs. Therefore, a noteworthy element of Table S1 ([supplementary material](#)) is the measurement of reduction in the generalization error when the neural networks were trained with or without injected noise.

For the ANNs comprising one output (prediction of displacement) without injected noise, the regression values of training and all datasets were increased as compared with ANNs where datasets were noisy. Likewise, the error (MSE) of training datasets was observed to be higher when ANNs were trained using noisy input variables (Table S1 ([supplementary material](#))). For the ANNs used in prediction of load, the regression values for train, test, and all datasets increased when no noise was introduced to the ANN training session ($R=1$). However, for both problems noise injection substantially reduces the error of ANN generalization (RMSE) and thus increases the performance of the ANN to generalize well to new datasets. For example, the regression value on the unseen sample reduced by 28% (0.9881 versus 0.7686 as observed for specimen #3) for displacement prediction and RMSE increased by 84% (1.4208 versus 8.9281) for load prediction when no noise was introduced. Reduction in generalization error (a critically essential parameter) is reported for all the different scenarios in Table S1 ([supplementary material](#)). This obviously highlights the significant influence of introducing noise to the datasets for improving the prediction ability on the unseen samples. For the third scenario where the ANN comprises two outputs and simultaneously predicts both load and displacement, we found that training with injected noise reduces the generalization error by as much as 58% in predicting displacement (Output 1) and by as much as 93% in predicting load (Output 2). Therefore, the neural networks trained with injected noise drastically reduces the

generalization error, substantially improves the generalization ability of ANNs in making predictions on unseen samples, and hence they generalize far better than those trained without noise.

3.4. Data Normalization prior to ANNs Training

For each of three distinct problems (first displacement prediction, second load prediction, and third prediction of both simultaneously), two scenarios were considered: first training each ANN when the input variables were normalized and second training each ANN without prior data normalization. As in the explanations in Section 2.3, three different normalization techniques were employed in this study, among which employing the third technique (Equation (8)) demonstrated lower errors in predicting the targets, and hence was associated with relatively superior ability in generalizing the ANNs. Each ANN was trained and then was used to make predictions on new specimens that the ANN had not seen before. These processes were completed ten times and then the average of the outcomes was reported in Table S2 ([supplementary material](#)). The entire processes were conducted on three distinct (new/unseen) bone specimens that the ANNs had not seen before in their training session. In this table, training error indicates MSE of ANNs for training session, and generalization error presents RMSE when the trained ANN was employed to predict output(s) of a new specimen (not involved in ANNs training). As such, generalization error is calculated between the output(s) of this ANN and the experimental counterparts. Likewise, generalization *R*-value (linear correlation coefficient) measures the strength of a linear relationship between the output(s) of ANN and experimental counterparts (either load, displacement, or both). The results are presented when ANNs are trained both with data normalization and without data normalization. A hypothesis is investigated here, which is data normalization prior to ANNs training considerably reduces error in the generalization performance of ANNs. Therefore, a noteworthy element of Table S2 ([supplementary material](#)) is the measurement of reduction in generalization error when the neural networks are trained with or without normalized data.

For the all three problems (displacement prediction, load prediction, and both), the error (MSE) of training datasets was observed to be higher when input data is normalized prior to training ANNs (Table S1 ([supplementary material](#))). This slight increase in the training error makes ANNs robust for generalization, and hence as this table also expresses, the error of ANN in generalization (RMSE) is drastically decreased when data is normalized prior to commencement of training. This indicates enhancement in the performance of the ANNs to generalize well to new datasets that were not involved in training. Reduction in generalization error (a critically essential parameter) is reported for the all different scenarios in Table S2 ([supplementary material](#)). This obviously highlights the significant influence of data normalization in advance of the ANNs training for improving the prediction performance on the unseen samples. For instance, we observed that training with normalized data reduces error in generalization of ANN for displacement prediction by as much as 68% (for an unseen data, i.e. specimen #1) and by 96% (specimen #3). Data normalization also exhibits marked reduction in generalization error of ANNs for load prediction: 85% reduction in error for specimen #1 and 98% for specimen #3. For the third scenario where the ANN comprises two outputs and simultaneously predicts both load and displacement, we found that training with normalized data reduces the ANN generalization error by as much as 43% in predicting displacement (Output 1) and by as much as 83% in predicting load (Output 2).

3.5. Strain Prediction

New neural networks were developed and subsequently employed to predict the normal strain ($\mu\epsilon$) exposed on the dorsal cortex recorded experimentally around the mid-point of the bone shaft (Figure S10 ([supplementary material](#))). The dorsal cortex of MC3 midshaft has thick cortical bone that enlarges during fast exercise speed [52, 61]. Compressive strains exceeding 3000 and 5670 microstrains ($\mu\epsilon$) have been recorded in this region [62, 63], and it is a region of growing interest to discern shape-dependent (geometry-dependent) mechanical responses of smart engineering materials [51]. These findings encapsulate that this smart nonlinear material is able to adjust its mass, structure, and properties according to the loads it withstands, and hence it is worth considering as a structure to investigate the application of neural networks (expert systems) in the prediction of strains in this region. The preliminary outcomes of this investigation revealed that the ANNs are potent tools to provide satisfactory results on the training, testing, and all datasets. However, these well-trained and tested ANNs exhibited diminished ability to generalize well to new datasets that ANNs have not seen before (for prediction of the normal strain). This critically significant step (assessing and confirming the generalization ability of the trained ANNs) has been overly overlooked in the literature and strong emphasis was placed only on the performance of ANNs during training in those studies.

Nonetheless, further analyses in this regard demonstrated that if we confine strain prediction to be established within a specific age group (age of individual horses), an evidently enhanced generalization ability of the ANNs in making reliable strain prediction is observed. This also emphasizes the importance of age-dependent mechanical properties in these complex structures [21, 22]. Firstly, three bone specimens from two-year-olds were used to address this problem, two of which were used for training an ANN and the third one was employed for assessing and confirming the generalization ability of the trained ANN. Secondly, four bone specimens from three-year-olds were used, three of which were used for training an ANN and the fourth one was employed for assessing and confirming the generalization ability of the trained ANN. Since limited input data was employed (with lower number of bone specimens), a higher value of noise was injected into the ANN models in these scenarios, which greatly enhanced the generalization ability of the trained ANNs for strain prediction (similar to the conclusion drawn in Section 3.3). The results obtained for both trained ANNs and their prediction on unseen samples are summarized in Table S3 ([supplementary material](#)) for two-year-old samples and in Table S4 ([supplementary material](#)) for three-year-old samples. Figures S11-S14 ([supplementary material](#)) inclusive display the correlation between midshaft normal strain predicted via ANNs and their target (experimental) counterparts. These Figures indicate that neural networks are capable of predicting strain in this complex nonlinear structure. It is also worth mentioning that predicting strains in this nonlinear exotic structure possessing peculiar mechanical properties are more challenging than predicting load, displacement (and both simultaneously) which were quantified and discussed in Sections 3.1.1 to 3.1.3. Hence it might be expected that immaturity (for example age and exercise history [21]) would have a large and complex effect on the responses of the MC3 to loading, especially in horses less than 18 months of age [5]. It is recommended to increase the sample size (conducting experiments on more bone samples) and broaden the range of ages in the experiments to acquire more data, so that neural networks are trained with more gathered data from the studied knowledge during loading and unloading, and therefore, the domain from which the ANNs can learn more effectively gets wider, thus accommodating for learning unexpected and more peculiar patterns in the exposed strains.

3.6. Selection of Appropriate Values for Injected Noise

The importance of introducing a source of noise to input variables prior to ANNs training was already explained and discussed in Sections 2.2 and 3.3. The noise vector added to neural networks is typically drawn from some probability density function (MATLAB returned a random scalar drawn from the standard normal distribution which was sampled from Gaussian distribution). These normally distributed random vectors were generated in MATLAB and were introduced to the ANNs inputs as follows:

$$[X] = [x] \times [1 + N(0, \frac{1}{\lambda})]$$

where $[X]$ is the matrix of an input variable to which noise was injected, $[x]$ is the matrix of original (intact) input variable, and $N(\mu, \sigma^2)$ means normally distributed generated vector with mean μ and variance σ^2 (standard deviation, σ). The amount of introduced noise ($1/\lambda$, the spread or standard deviation) plays a critical role, its selection demands a proper knowledge of the training and generalization datasets, and is found through training multiple ANNs and monitoring ANNs performance. Several ANNs were trained and tested using noisy input variables with the values of the injected noise ($1/\lambda$) changing between 0 and 1. Afterwards, each ANN was used to assess its generalization performance (the ability to make reliable prediction on new specimens that the ANN has not seen before). R -values for training, testing, combined data, and R -value on the unseen samples were gathered versus the changes to injected noise. Also, the values of m and b that appeared in the linear function ($f(x) = mx + b$) were collected, which determines the strength of ANN predictions versus target (experimental) counterparts (Section 2.4). The outcomes for a representative problem (i.e. for displacement prediction) are demonstrated in Figure S15 ([supplementary material](#)). Similar procedures were repeated for the all prediction problems presented in this study to judge the influence of injected noise and to decide upon a range of acceptable values for injected noise. The generalization performance of the ANNs are enhanced (as observed from the results presented for the unseen samples, Figure S15 ([supplementary material](#)) and Figure 15) when ANNs are trained using noisy datasets. Nonetheless, care must be taken in selecting an appropriate range for the values of injected noise because, as is evident from these Figures, adding too much noise has detrimental effects in making reliable predictions. The outcome for ANNs training (R -values, m and b for training and testing datasets) shows a perfectly precisely trained ANN when there is no noise (i.e. noise=0), however the generalization ability is substantially reduced in this case (as already concluded in Section 3.3). A proper range of values for noise ($1/\lambda$) is achieved with an aim that the value of R , m , and b becomes 1, 1, and 0, respectively. These could also be deduced from monitoring the plots achieved from training regression analyses and from the regression plots for the unseen samples (Figure 15). It was found that the ANN is extremely sensitive to noise and gives inaccurate predictions when a high value of noise is injected into the inputs. An acceptable value for the injected noise for this problem (and also for the problem of load prediction) was found to be in the range (0.03-0.08). A drastic reduction in the R -values and a steep deviation from 1 for m and from zero for b were observed with an increasing level of noise. This should be avoided in the neural network studies performed in the literature (Figure S15 ([supplementary material](#)) and Figure 15). Both noise-free ANNs and ANNs with noticeable/excessive injected noise were noticeably weak in predicting the output(s) and failed to generalize well to the new datasets that ANNs have not seen before. Guozhong also found the effectiveness of input noise in improving the generalization performance for both regression and classification problems [47]. Hence, injecting noise to various parts of an ANN

1099 during backpropagation training can remarkably improve the generalization performance
1100 (reduce overfitting). The level of injected noise ($1/\lambda$) directly affects two terms, i.e. model
1101 fitting and regularization, as such it is desirable to maintain proper noise level (following the
1102 proposed methodologies) during networks training in the engineering practices.

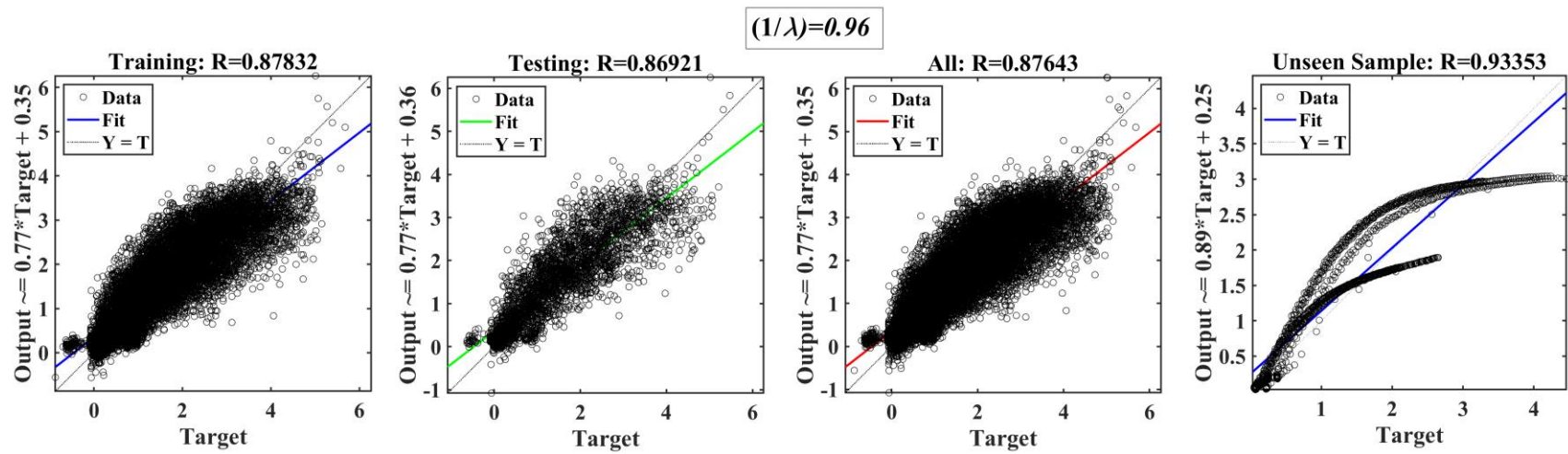
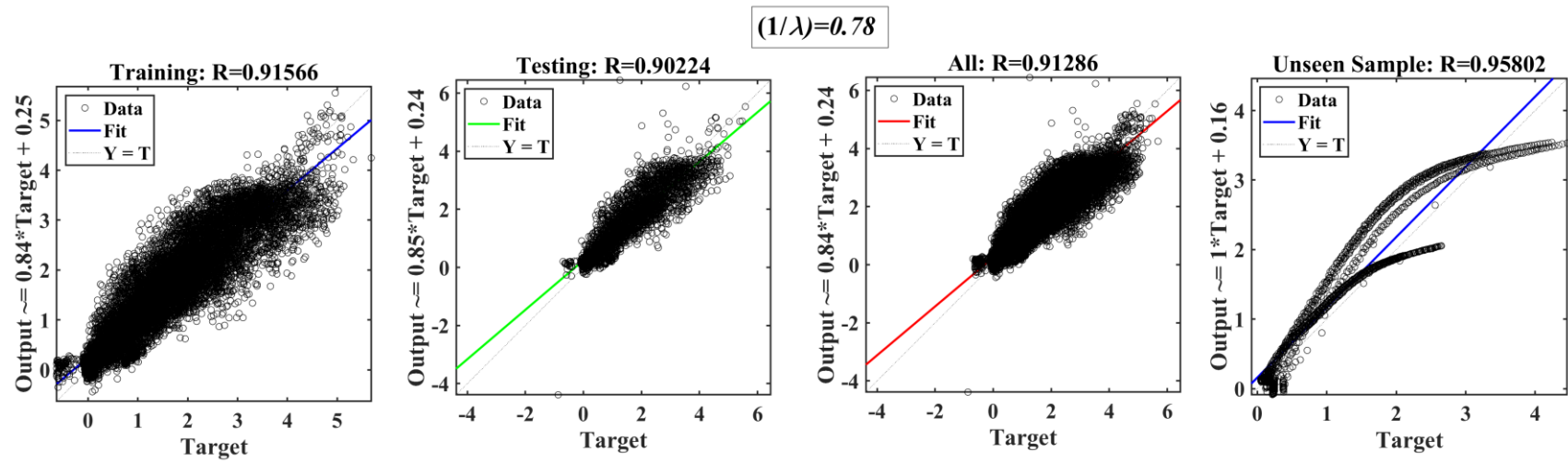
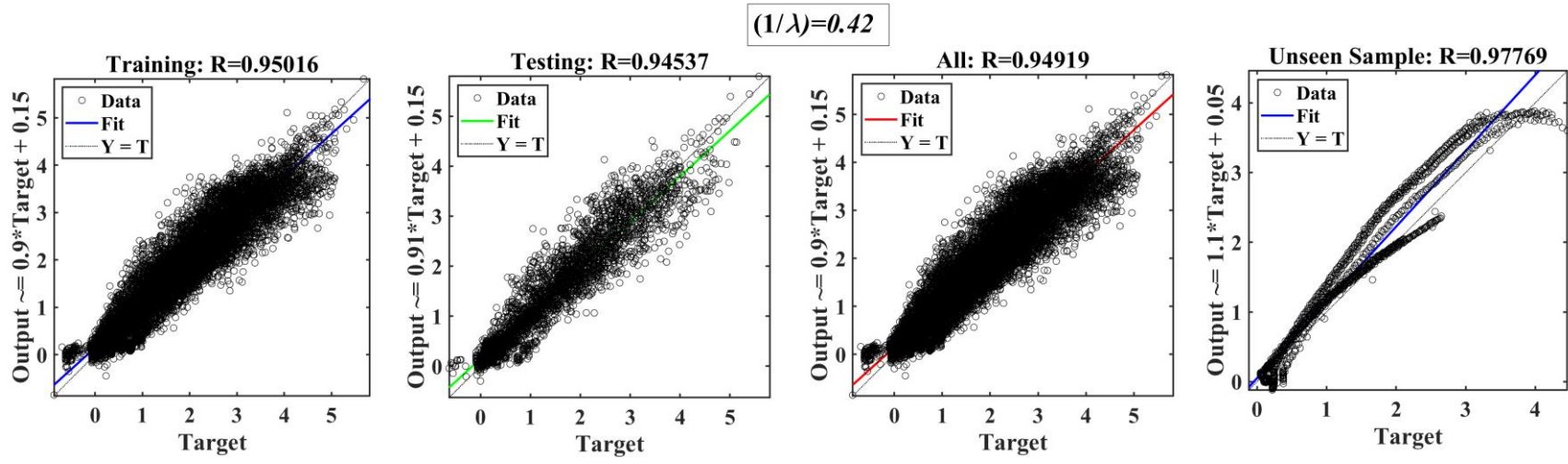
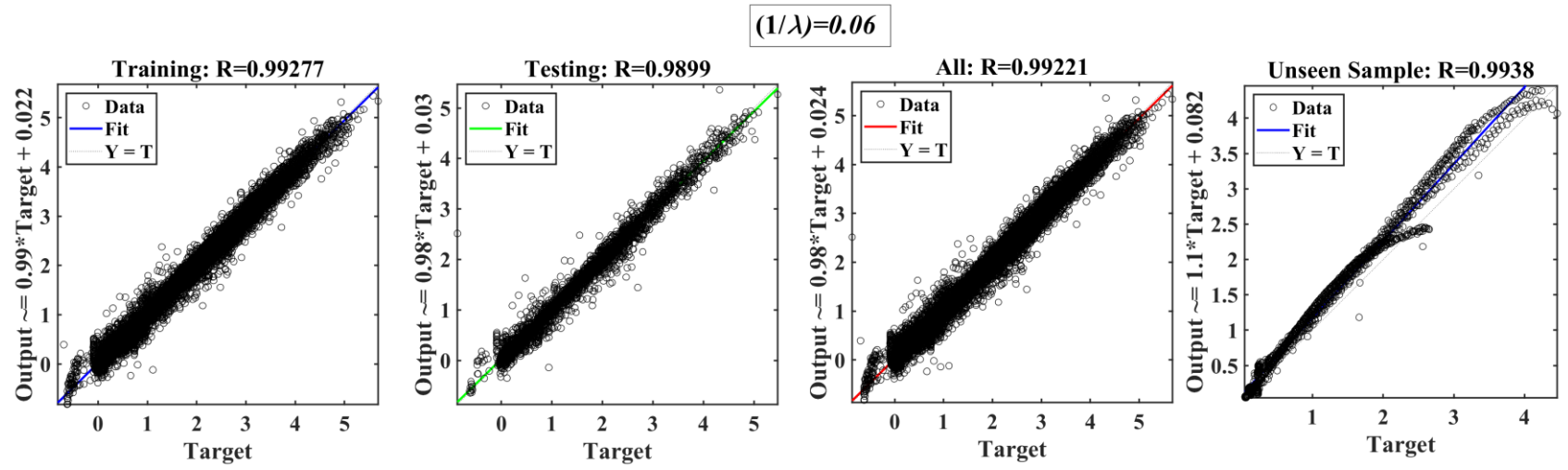
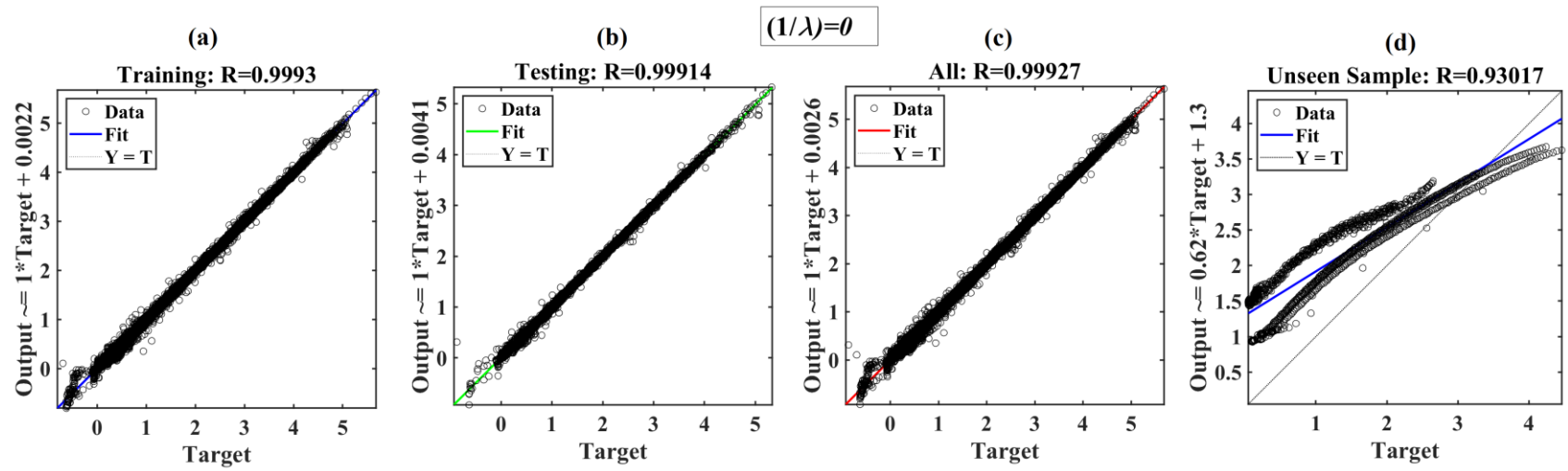


Figure 15. Regression analysis for a) training, b) testing, c) all data, and d) the unseen sample when the neural networks were trained using noisy datasets (injected noise to the ANNs inputs) with increasing levels of noise.

4. Significance to Mechanical and Biomedical Sciences

Avoiding and/or reducing the likelihood of failure and fracture of structures are the ongoing goals of experts dealing with engineering structures. An essential key for anticipating the fracture of bones, as a highly complex and advanced engineering structure, depends on not only the level and magnitudes of applied loads but also on appropriate comprehension of their mechanical properties and responses. Therefore, it is critical to derive meaning, extract patterns, and capture nonlinear relationships that exist in advanced and convoluted multivariable engineering materials/systems/structures [4]. The phenomenal success of artificial neural network applications in recent years lead us to draft this article to assist researchers in efficiently applying ANN algorithms to their engineering practices.

The use of feedforward backpropagation artificial neural networks in this study covers all the complicating effects of the engineering problems, streamlines the problems by learning from examples (such as experimental measurements, results of finite element analyses, etc) which otherwise is almost impossible to be attained through developing a constitutive model incorporating all the influential parameters. The ANNs developed and employed in our study enabled the capture of the complex nonlinear relationship existing among variables and successfully made reliable predictions of load, displacement, load and displacement simultaneously, and strains. The details and the processes by which these promising results were obtained were thoroughly delineated. It is hoped that that this article be used as a reference guide for researchers designing new feedforward backpropagation artificial neural networks for predicting mechanical responses and properties of complex engineering structures. Some prevalent challenges in quantifying the mechanical responses of a long bone (a well-engineered material exhibiting peculiar and exceptional properties) were successfully addressed using expert systems (ANNs). A more efficient and proper perception of several problems in the engineering applications such as static, dynamic, vibration, and fatigue analyses of different structures (for example, beams, columns, shells, plates, bones) possessing distinct properties/construction (for example, composites, nanomaterials, alloys) will be augmented using these successfully trained and generalized neural networks. This paper has emphasized the critical importance of careful ANN design, training and testing when developing hybrid models, where ANN-based artificial intelligence is coupled with FEA-based methods to investigate problems associated with nonlinear applications of mechanical structures. Introducing elaborate mathematical expressions to quantify the mechanical features of these exotic materials is not straightforward, yet it is noteworthy to employ methodologies presented in this study, providing appropriate data is available belonging to the same knowledge domain. Much remains to be done at the macro, micro, and nanolevels to obtain a full comprehension of these complex structures. Future research will combine the expertise of the authors in machine learning and artificial neural networks, FEA, nanomechanics, solidmechanics, and biomechanics [4, 5, 16, 21, 51, 55-57].

1148 Conclusion

1149 To estimate engineering properties and fully comprehend responses of complex engineering
1150 structures (e.g. a long bone representing an advanced biological material with exotic
1151 mechanical properties) nonlinear empirical relationships are often employed. Development of
1152 these mathematical formulae using traditional techniques is a formidable task demanding
1153 sophisticated, and frequently unavailable, models as well as human experience and inspiration.
1154 Thanks to their extraordinary ability to decipher meaning from complex, imprecise or limited
1155 data, ANNs can be employed to capture relationships and to detect patterns between
1156 accumulated data which are too complicated to be comprehended by humans, conventional
1157 tools or computer techniques. This paper delved into the use of feedforward back-propagation
1158 artificial neural networks, the most popular neural network model, to alleviate this problem and
1159 to establish a framework to improve the performance and generalization of trained ANNs in
1160 predicting mechanical responses of complex nonlinear engineering structures. These
1161 investigations included more than three years of conducting ex-vivo experiments and data
1162 collection that were then used to establish, train, test, validate, and generalize more than 60,000
1163 feedforward backpropagation artificial neural networks. These investigations were
1164 exhaustively discussed to identify correlations and to provide confidence in the following
1165 conclusions:

- 1166 • Selecting an optimum ANN structure (architecture) is an arduous task requiring gradual
1167 changes in both the number of hidden layer(s) and that of neurons(s) until the best
1168 prediction ability is observed from the network. This depends on the complexity of the
1169 problem, number of specimens, number of datasets (observations through experiments,
1170 for example), number of input(s) and output(s).
- 1171 • The quality of the ANNs was oversensitive to both the number of hidden layers and
1172 number of neurons in the hidden layer. This was observed for the all predictions made
1173 in this study using ANNs.
- 1174 • To ensure that an ANN with good accuracy is found and to improve the generalization
1175 of ANNs, it is recommended to train each ANN multiple times and average their
1176 outputs. The same ANN with the same datasets can produce completely different results
1177 when it is trained each time.
- 1178 • The ability of an ANN to generalize (i.e. to properly respond to previously unseen
1179 datasets) is critically important. ANNs normally can produce satisfactory outcomes
1180 (high R -values and low errors) once they are trained. However, the performance of the
1181 already trained network must be assessed in making reliable predictions on new datasets
1182 (confirming the generalization of the already trained ANNs). A major emphasis in this
1183 study was placed on the regression and performance analyses conducted on the new
1184 specimens (unseen samples that ANNs have not seen before). This gives an unbiased
1185 and potent performance of the model on unseen data different from those used for
1186 training.
- 1187 • The coefficient of correlation (R -Value) measures the strength of a linear relationship
1188 between the ANN predictions and targets (experimental recordings). A high R -value
1189 does not necessarily demonstrate precise predictions made by the ANN versus targets,
1190 as it merely measures the strength of a linear relationship among predictions and targets.
1191 Hence, besides the R -value, the values of ' m ' and ' b ' in the linear function ($f(x) = mx$
1192 $+ b$) between ANN outputs and targets should be presented or regression plots for the
1193 successfully trained ANNs are required to be presented.

- Employing Bayesian regularization backpropagation as the neural network training algorithm demonstrated superior ability in making reliable load, displacement, and strains prediction over using Levenberg-Marquardt and scaled conjugate backpropagation algorithms. Despite requiring relatively more computational time for training, ANNs trained with a Bayesian regularization backpropagation training algorithm exhibited greater ability in making predictions on new datasets (i.e. superior ability in generalization). For instance, employing a Bayesian regularization backpropagation training algorithm in a load prediction problem in this study reduced the generalization error by as much as 73%.
- The neural networks trained with injected noise drastically reduced the generalization error, and therefore substantially improves the generalization ability of ANNs in making prediction on unseen samples. For example, training with injected noise reduced the generalization error by as much as 74% in predicting displacement of a specimen and by as much as 84% in predicting load.
- Care must be taken in selecting an appropriate range for the values of injected noise. Both noise-free ANNs and ANNs with noticeable/excessive injected noise were noticeably weak in predicting the output(s) and failed to generalize well to the new datasets that ANNs have not seen before. A proper range of values for the noise ($1/\lambda$) is achieved with an aim that the value of R , m , and b becomes 1, 1, and 0, respectively.
- The methods for normalization influence the predictive performance of ANNs. The error of ANNs in generalization (RMSE) is drastically decreased when data is normalized prior to commencement of training. This reduction in generalization error (a critically essential parameter) indicates enhancement in the performance of the ANNs to generalize well to new datasets that were not involved in their training.

1218 **References**

- 1219 [1] R. Nayak, L. Jain, B. Ting, Artificial neural networks in biomedical engineering: a review,
1220 in: *Computational mechanics–New Frontiers for the New Millennium*, Elsevier, 2001, pp. 887-
1221 892.
- 1222 [2] W. Schöllhorn, Applications of artificial neural nets in clinical biomechanics, *Clin.*
1223 *Biomech.*, 19 (2004) 876-898.
- 1224 [3] J. Currey, Measurement of the Mechanical Properties of Bone: A Recent History, *Clinical*
1225 *Orthopaedics and Related Research®*, 467 (2009) 1948-1954.
- 1226 [4] H. Rahmanpanah, S. Mouloudi, C. Burvill, S. Gohari, H.M. Davies, Prediction of load-
1227 displacement curve in a complex structure using artificial neural networks: A study on a long
1228 bone, *International Journal of Engineering Science*, 154 (2020) 103319.
- 1229 [5] S. Mouloudi, H. Rahmanpanah, C. Burvill, H.M. Davies, Prediction of load in a long bone
1230 using an artificial neural network prediction algorithm, *J. Mech. Behav. Biomed. Mater.*, 102
1231 (2020) 103527.
- 1232 [6] T.M. Keaveny, E.F. Morgan, G.L. Niebur, O.C. Yeh, Biomechanics of trabecular bone, in:
1233 *Annu. Rev. Biomed. Eng.*, 2001, pp. 307-333.
- 1234 [7] D.R. Carter, W.C. Hayes, The compressive behavior of bone as a two-phase porous
1235 structure, *JBJS*, 59 (1977) 954-962.
- 1236 [8] J.C. Rice, S.C. Cowin, J.A. Bowman, On the dependence of the elasticity and strength of
1237 cancellous bone on apparent density, *J. Biomech.*, 21 (1988) 155-168.
- 1238 [9] M.J. Fradinho, A.C. Vale, N. Bernardes, R.M. Caldeira, M.F. Vaz, G. Ferreira-Dias,
1239 Biomechanical properties of the equine third metacarpal bone: In vivo quantitative
1240 ultrasonography versus ex vivo compression and bending techniques, *J. Equine Vet. Sci.*, 35
1241 (2015) 198-205.
- 1242 [10] S. Nobakhti, O.L. Katsamenis, N. Zaarour, G. Limbert, P.J. Thurner, Elastic modulus
1243 varies along the bovine femur, *J. Mech. Behav. Biomed. Mater.*, 71 (2017) 279-285.
- 1244 [11] M. Rostedt, L. Ekström, H. Broman, T. Hansson, Axial stiffness of human lumbar motion
1245 segments, force dependence, *J. Biomech.*, 31 (1998) 503-509.
- 1246 [12] W.T. Edwards, W.C. Hayes, I. Posner, I.A.A. White, R.W. Mann, Variation of Lumbar
1247 Spine Stiffness With Load, *J. Biomech. Eng.*, 109 (1987) 35-42.
- 1248 [13] R.M. Kulin, F. Jiang, K.S. Vecchio, Effects of age and loading rate on equine cortical
1249 bone failure, *J. Mech. Behav. Biomed. Mater.*, 4 (2011) 57-75.
- 1250 [14] S. Xie, K. Manda, R.J. Wallace, F. Levrero-Florencio, A.H.R.W. Simpson, P. Pankaj,
1251 Time Dependent Behaviour of Trabecular Bone at Multiple Load Levels, *Ann. Biomed. Eng.*,
1252 45 (2017) 1219-1226.
- 1253 [15] K. Manda, R.J. Wallace, S. Xie, F. Levrero-Florencio, P. Pankaj, Nonlinear viscoelastic
1254 characterization of bovine trabecular bone, *Biomech. Model. Mechanobiol.*, 16 (2017) 173-
1255 189.
- 1256 [16] S. Mouloudi, H. Rahmanpanah, C. Burvill, H.M. Davies, Prediction of displacement in
1257 the equine third metacarpal bone using a neural network prediction algorithm, *Biocybernetics*
1258 *and Biomedical Engineering*, 40 (2020) 849-863.
- 1259 [17] T. Johnson, S. Socrate, M. Boyce, A viscoelastic, viscoplastic model of cortical bone valid
1260 at low and high strain rates, *Acta Biomater.*, 6 (2010) 4073-4080.
- 1261 [18] M.J. Mirzaali, J.J. Schwiedrzik, S. Thaiwichai, J.P. Best, J. Michler, P.K. Zysset, U.
1262 Wolfram, Mechanical properties of cortical bone and their relationships with age, gender,
1263 composition and microindentation properties in the elderly, *Bone*, 93 (2016) 196-211.
- 1264 [19] J. Frame, M. Wheel, P. Riches, A numerical investigation and experimental verification
1265 of size effects in loaded bovine cortical bone, *Int. J. Numer. Method. Biomed. Eng.*, (2017).
- 1266 [20] H. Davies, The relationship between surface strain and measurements of bone quality,
1267 quantity and shape, *Equine vet. J., Suppl*, 33 (2001) 16-20.

- [21] S. Mouloudi, H. Rahmanpanah, C. Burvill, H. Davies, Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design, *Comparative Exercise Physiology*, 15 (2019) 349-358.
- [22] D.M. Patton, E.M. Bigelow, S.H. Schlecht, D.H. Kohn, T.L. Bredbenner, K.J. Jepsen, The relationship between whole bone stiffness and strength is age and sex dependent, *J. Biomech.*, 83 (2019) 125-133.
- [23] P. Mandal, Artificial neural network prediction of buckling load of thin cylindrical shells under axial compression, *Eng. Struct.*, 152 (2017) 843-855.
- [24] A.A. Chojaczyk, A.P. Teixeira, L.C. Neves, J.B. Cardoso, C. Guedes Soares, Review and application of Artificial Neural Networks models in reliability analysis of steel structures, *Struct. Saf.*, 52 (2015) 78-89.
- [25] V. Papadopoulos, G. Soimiris, D.G. Giovanis, M. Papadrakakis, A neural network-based surrogate model for carbon nanotubes with geometric nonlinearities, *Computer Methods in Applied Mechanics and Engineering*, 328 (2018) 411-430.
- [26] M. Stoffel, F. Bamer, B. Markert, Artificial neural networks and intelligent finite elements in non-linear structural mechanics, *Thin-Walled Structures*, 131 (2018) 102-106.
- [27] M. Stoffel, R. Gulakala, F. Bamer, B. Markert, Artificial neural networks in structural dynamics: A new modular radial basis function approach vs. convolutional and feedforward topologies, *Computer Methods in Applied Mechanics and Engineering*, 364 (2020) 112989.
- [28] H.R. Ashrafi, M. Jalal, K. Garmsiri, Prediction of load-displacement curve of concrete reinforced by composite fibers (steel and polymeric) using artificial neural network, *Expert Systems with Applications*, 37 (2010) 7663-7668.
- [29] H. Rao, A. Mukherjee, Artificial neural networks for predicting the macromechanical behaviour of ceramic-matrix composites, *Computational materials science*, 5 (1996) 307-322.
- [30] J.F. Barbosa, J.A. Correia, R.F. Júnior, A.M. De Jesus, Fatigue life prediction of metallic materials considering mean stress effects by means of an artificial neural network, *Int. J. Fatigue*, 135 (2020) 105527.
- [31] J.C.F. Pujol, J.M.A. Pinto, A neural network approach to fatigue life prediction, *Int. J. Fatigue*, 33 (2011) 313-322.
- [32] M. Al-Assadi, H.A. El Kadi, I.M. Deiab, Using artificial neural networks to predict the fatigue life of different composite materials including the stress ratio effect, *Applied Composite Materials*, 18 (2011) 297-309.
- [33] D. Yu, Y. Qing, Z. Jianxun, D. Jun, An artificial neural network approach to the predictive modeling of tensile force during renal suturing, *Ann. Biomed. Eng.*, 41 (2013) 786-794.
- [34] A.M. Vukicevic, G.R. Jovicic, M.N. Jovicic, V.L. Milicevic, N.D. Filipovic, Assessment of cortical bone fracture resistance curves by fusing artificial neural networks and linear regression, *Comput. Methods Biomech. Biomed. Eng.*, 21 (2018) 169-176.
- [35] Y. Liu, S.-M. Shih, S.-L. Tian, Y.-J. Zhong, L. Li, Lower extremity joint torque predicted by using artificial neural network during vertical jump, *J. Biomech.*, 42 (2009) 906-911.
- [36] J. Favre, M. Hayoz, J.C. Erhart-Hledik, T.P. Andriacchi, A neural network model to predict knee adduction moment during walking based on ground reaction force and anthropometric measurements, *J. Biomech.*, 45 (2012) 692-698.
- [37] G. Campoli, H. Weinans, A.A. Zadpoor, Computational load estimation of the femur, *J. Mech. Behav. Biomed. Mater.*, 10 (2012) 108-119.
- [38] A.A. Zadpoor, G. Campoli, H. Weinans, Neural network prediction of load from the morphology of trabecular bone, *Appl. Math. Model.*, 37 (2013) 5260-5276.
- [39] R. Hambli, Apparent damage accumulation in cancellous bone using neural networks, *J. Mech. Behav. Biomed. Mater.*, 4 (2011) 868-878.
- [40] A. Ahmad, A. Raza, Reliability analysis of strength models for CFRP-confined concrete cylinders, *Composite Structures*, (2020) 112312.

- [41] A. Muliana, R.M. Haj-Ali, R. Steward, A. Saxena, Artificial neural network and finite element modeling of nanoindentation tests, *Metallurgical and Materials Transactions A*, 33 (2002) 1939-1947.
- [42] S. Roberts, J. Kusiak, Y. Liu, A. Forcellese, P. Withers, Prediction of damage evolution in forged aluminium metal matrix composites using a neural network approach, *Journal of Materials Processing Technology*, 80 (1998) 507-512.
- [43] R. Hambli, Prediction of burr height formation in blanking processes using neural network, *International Journal of Mechanical Sciences*, 44 (2002) 2089-2102.
- [44] X. Xu, N. Gupta, Artificial neural network approach to predict the elastic modulus from dynamic mechanical analysis results, *Advanced Theory and Simulations*, 2 (2019) 1800131.
- [45] M.A. Omari, A. Almagableh, I. Sevostianov, M.d.S. Ashhab, A.B. Yaseen, Modeling of the viscoelastic properties of thermoset vinyl ester nanocomposite using artificial neural network, *International Journal of Engineering Science*, 150 (2020) 103242.
- [46] W. Sha, K. Edwards, The use of artificial neural networks in materials science based research, *Materials & design*, 28 (2007) 1747-1752.
- [47] G. An, The effects of adding noise during backpropagation training on a generalization performance, *Neural Comput.*, 8 (1996) 643-674.
- [48] R.M. Zur, Y. Jiang, L.L. Pesce, K. Drukker, Noise injection for training artificial neural networks: A comparison with weight decay and early stopping, *Med. Phys.*, 36 (2009) 4810-4818.
- [49] D. Kim, Normalization methods for input and output vectors in backpropagation neural networks, *International journal of computer mathematics*, 71 (1999) 161-171.
- [50] T. Gulikers, An Integrated Machine Learning and Finite Element Analysis Framework, Applied to Composite Substructures including Damage, (2018).
- [51] S. Mouloudi, H. Rahmanpanah, C. Burvill, H.M. Davies, Accuracy Quantification of the Reverse Engineering and High-Order Finite Element Analysis of Equine MC3 Forelimb, *J. Equine Vet. Sci.*, 78 (2019) 94-106.
- [52] H. Davies, The timing and distribution of strains around the surface of the midshaft of the third metacarpal bone during treadmill exercise in one Thoroughbred racehorse, *Aust. Vet. J.*, 83 (2005) 157-162.
- [53] J.S. Merritt, M.G. Pandy, N.A. Brown, C.R. Burvill, C.E. Kawcak, C.W. McIlwraith, H.M. Davies, Mechanical loading of the distal end of the third metacarpal bone in horses during walking and trotting, *Am. J. Vet. Res.*, 71 (2010) 508-514.
- [54] S. Couch, B. Nielsen, A Review of Dorsal Metacarpal Disease (Bucked Shins) in the Flat Racing Horse: Prevalence, Diagnosis, Pathogenesis, and Associated Factors, *J Dairy Vet Anim Res*, 5 (2017) 228-236.
- [55] S. Mouloudi, J. Khojasteh, M. Salehi, S. Mohebbi, Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region, *International Journal of Mechanical Sciences*, 85 (2014) 160-167.
- [56] S. Gohari, S. Sharifi, C. Burvill, S. Mouloudi, M. Izadifar, P. Thissen, Localized failure analysis of internally pressurized laminated ellipsoidal woven GFRP composite domes: Analytical, numerical, and experimental studies, *Archives of Civil and Mechanical Engineering*, 19 (2019) 1235-1250.
- [57] S. Mouloudi, S. Mohebbi, J. Khojasteh, M. Salehi, Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects, *International Journal of Mechanical Sciences*, 79 (2014) 162-167.
- [58] L. Jones, D. Golan, S. Hanna, M. Ramachandran, Artificial intelligence, machine learning and the evolution of healthcare: A bright future or cause for concern?, *Bone & joint research*, 7 (2018) 223-225.
- [59] H.D. Beale, H.B. Demuth, M. Hagan, *Neural network design*, Pws, Boston, (1996).

- 1368 [60] R. Hambli, Statistical damage analysis of extrusion processes using finite element method
1369 and neural networks simulation, *Finite Elements in Analysis and Design*, 45 (2009) 640-649.
1370 [61] H. Davies, Relationships between third metacarpal bone parameters and surface strains,
1371 *Equine Vet. J.*, 33 (2001) 16-20.
1372 [62] H. Davies, R. McCarthy, Strain in the yearling equine metacarpus during locomotion,
1373 *Equine vet. J., Suppl*, 17 (1994) 25-28.
1374 [63] D. Nunamaker, On bucked shins, in: *Annual Convention of American Association of*
1375 *Equine Practitioners*, 2002, pp. 76-89.

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Feedforward backpropagation artificial neural networks for predicting mechanical responses in complex nonlinear structures: A study on a long bone

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Nomenclature	
ANN	Artificial neural network
R	Coefficient of correlation (R -Value)
MSE	Mean squared error
RMSE	Root mean squared error
ANN [x]	An ANN comprising one hidden layer with x neuron(s)
ANN [x,y]	An ANN comprising two hidden layers with x and y neuron(s) in the first and second hidden layer respectively
MC3	Third metacarpal bone
Y	ANN prediction (output)
T	Target (experiment)
D	Displacement
L	Load
m	Slope of the linear model ($f(x) = mx + b$) between ANN output(s) and target(s)
b	Y-intercept of the linear model ($f(x) = mx + b$) between ANN output(s) and target(s)
ε	Strain
I/λ	Injected noise
t	Loading/unloading time in seconds which specimens were exposed to (load exposure time)
l	Bone length

5. Prediction of Displacement (ANN with One Output)

1.1. Sensitivity Analysis of ANNs to the Number of Hidden Layer(s) and Number of Neuron(s)

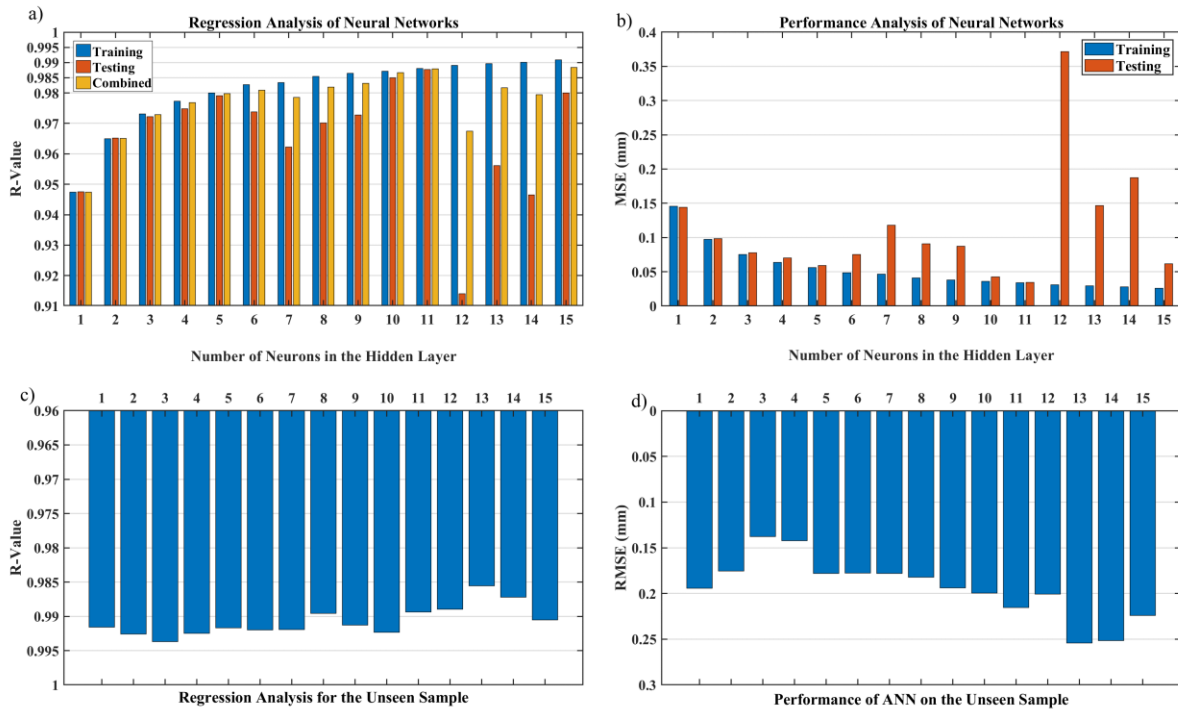
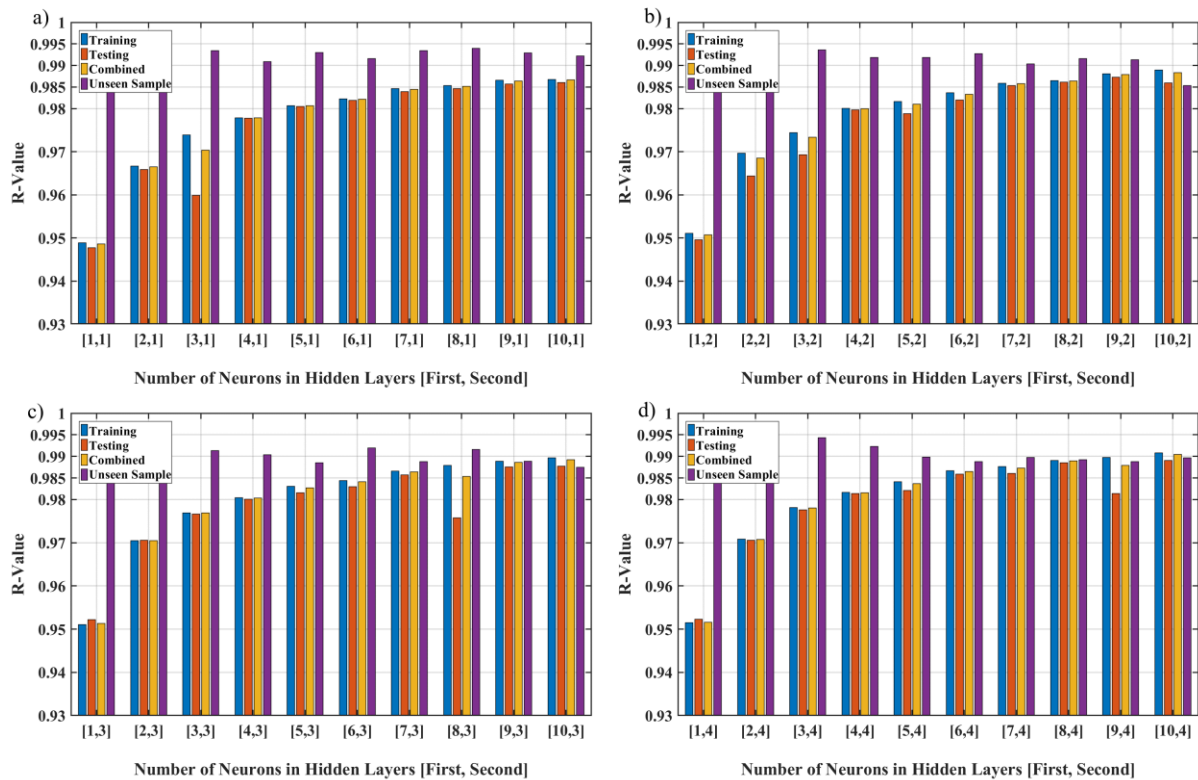


Figure S1. Regression and performance analysis of ANNs (comprising one hidden layer) for prediction of displacement. Each ANN was trained ten times and the average of R-values and errors of these networks was plotted herein. a) R-values of training, testing, and all datasets for training of ANNs versus number of neurons in the hidden layer. b) MSE of training and testing datasets for training of ANNs versus number of neurons in the hidden layer. c) R-values and d) RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layer when a new specimen (unseen sample) that the ANNs had not seen before was introduced to the ANNs.



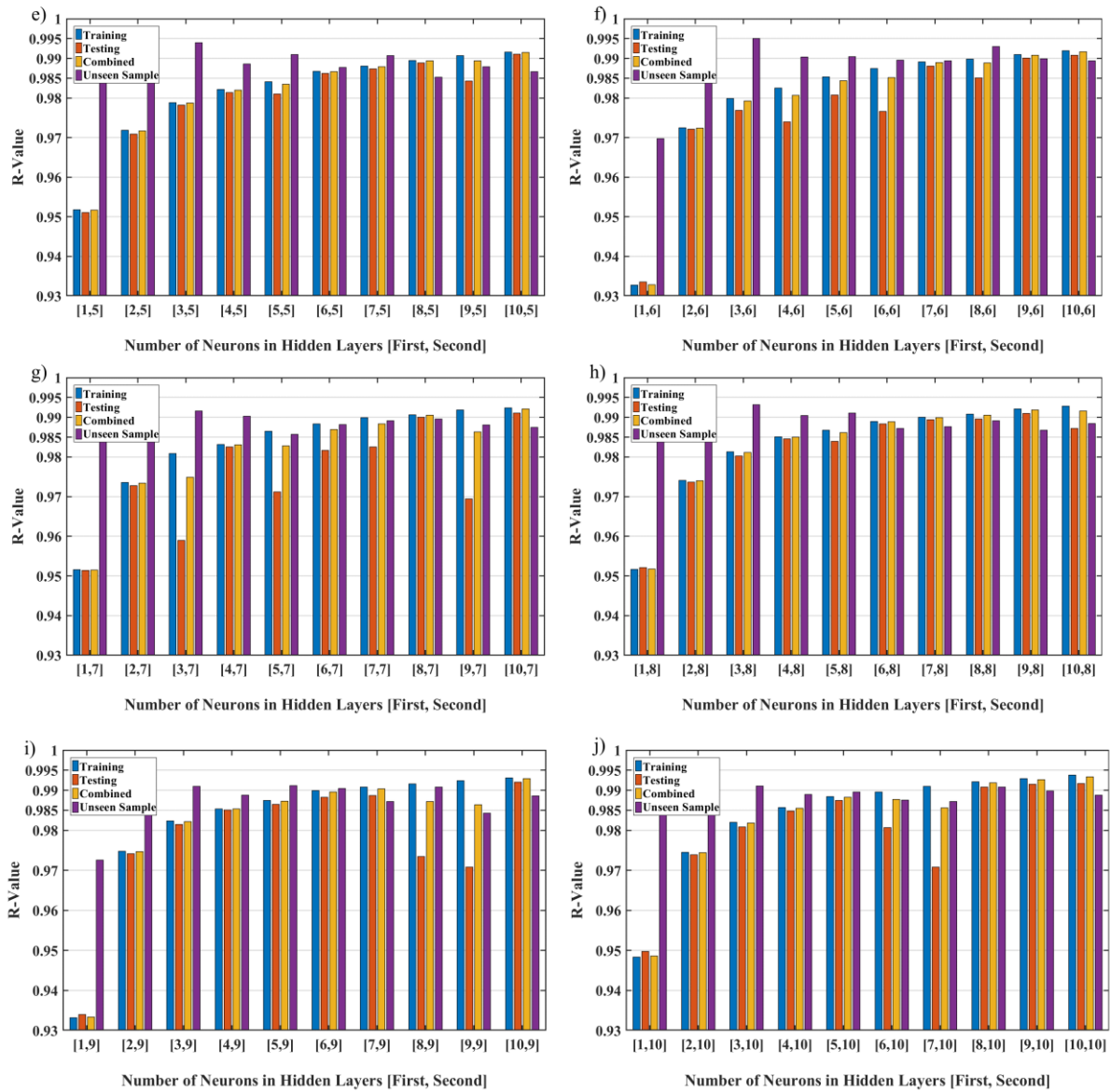


Figure S2. Regression analysis of ANNs (comprising two hidden layers) for prediction of displacement. Each ANN was trained ten times and the average of R-values was plotted herein. R-values of training, testing, and all datasets for training of ANNs were presented. Also, R-values between output of already trained ANNs and experiment when a new specimen (unseen sample) was introduced to the ANNs were reported. In the all subfigures the number of neurons in the first hidden layer changes from 1 to 10, and the number of neurons in the second hidden layer was set to 1 in a), 2 in b), 3 in c), 4 in d), 5 in e), 6 in f), 7 in g), 8 in h), 9 in i), and 10 in j).

6. Prediction of Load (ANN with One Output)

2.1. Sensitivity Analysis of ANNs to the Number of Hidden Layer(s) and Number of Neuron(s)

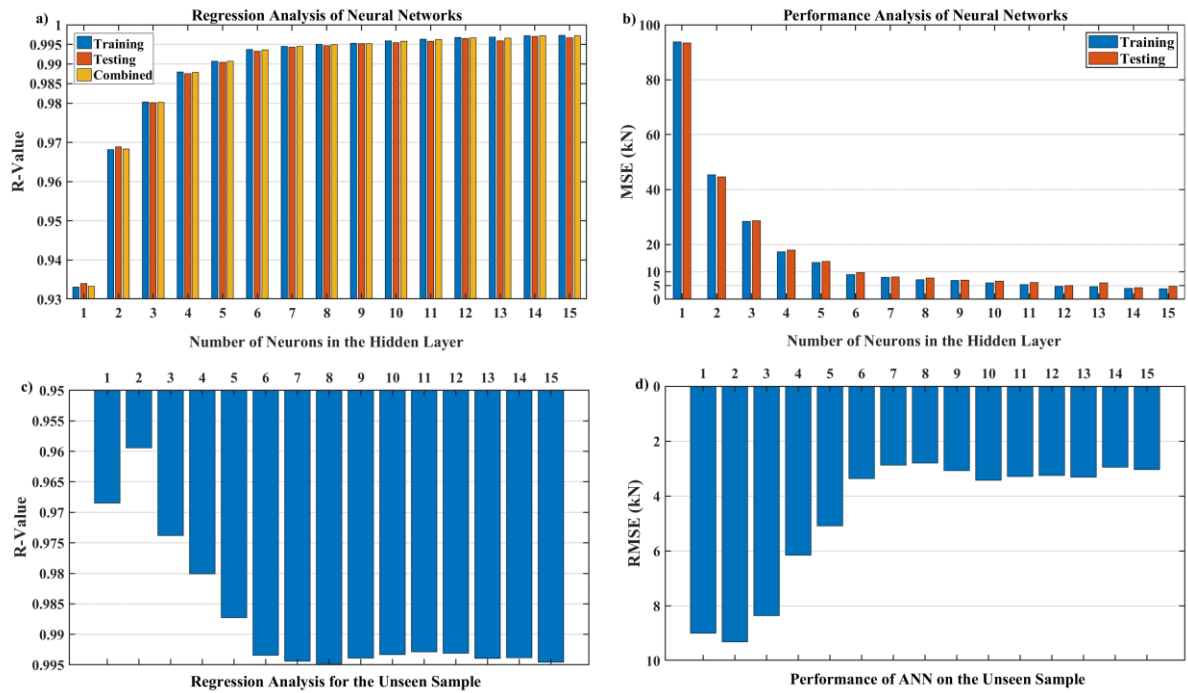
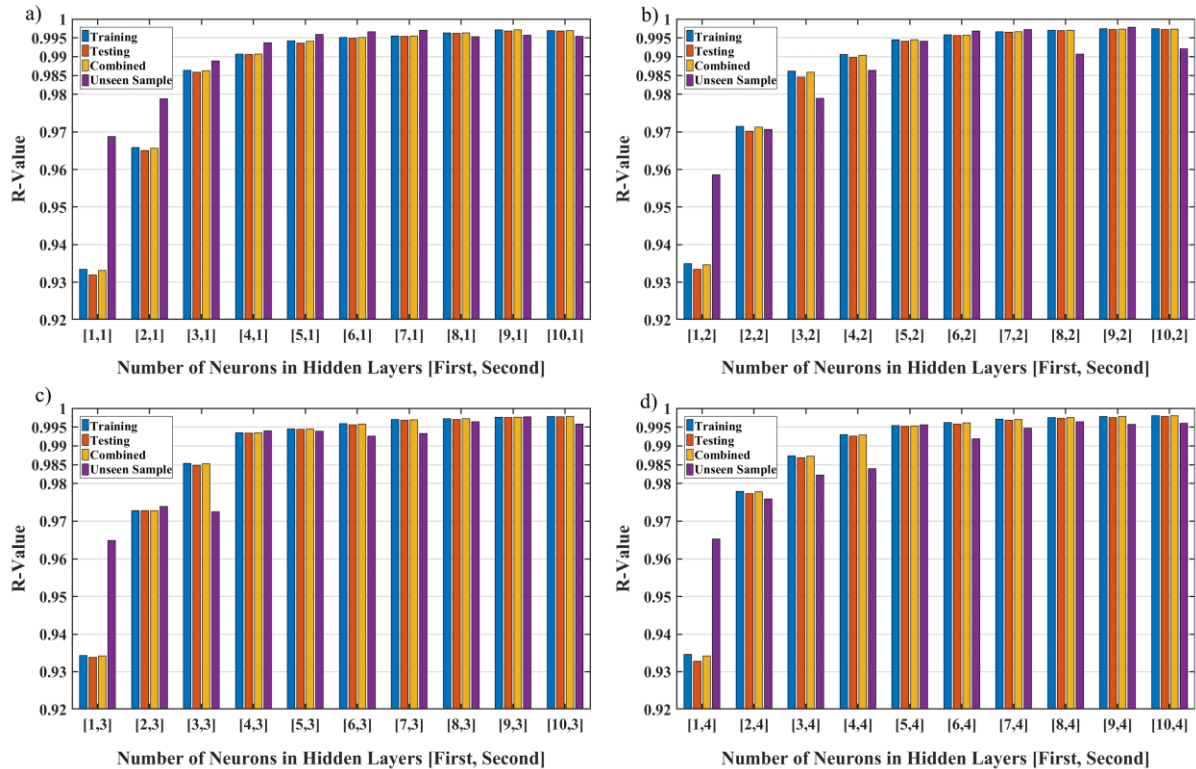


Figure S3. Regression and performance analysis of ANNs (comprising one hidden layer) for prediction of load. Each ANN was trained ten times and the average of R-values and errors of these networks was plotted herein. a) R-values of training, testing, and all datasets for training of ANNs versus number of neurons in the hidden layer. b) MSE of training and testing datasets for training of ANNs versus number of neurons in the hidden layer. c) R-values and d) RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layer when a new specimen (unseen sample) that ANNs had not seen before was introduced to the ANNs. Compressive load is represented with positive values in this study.



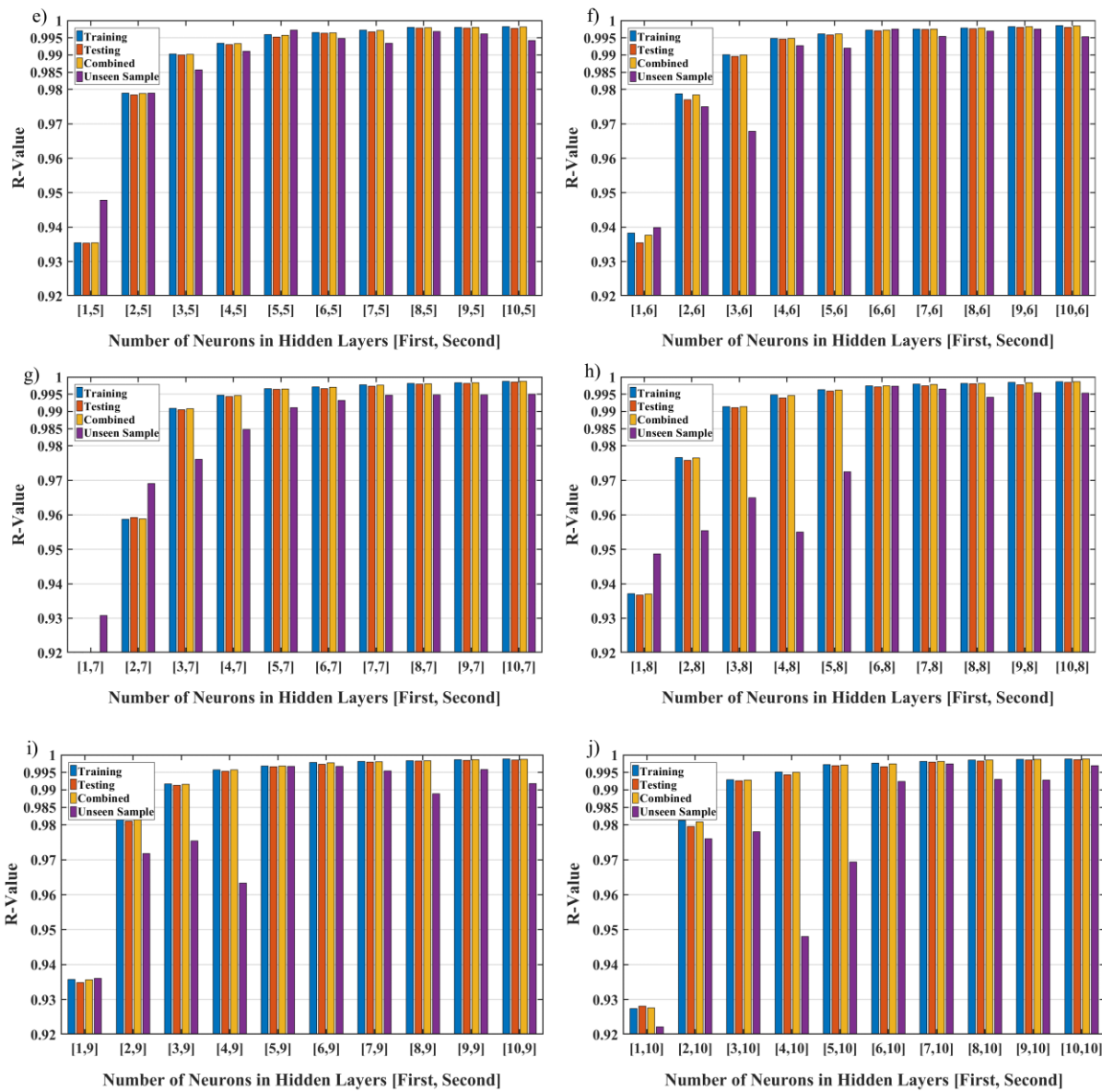


Figure S4. Regression analysis of ANNs (comprising two hidden layers) for prediction of load. Each ANN was trained ten times and the average of R -values was plotted herein. R -values of training, testing, and all datasets for training of ANNs were presented. Also, R -values between output of already trained ANNs and experiment when a new specimen (unseen sample) was introduced to the ANNs were reported. In the all subfigures the number of neurons in the first hidden layer changes from 1 to 10, and the number of neurons in the second hidden layer was set to 1 in a), 2 in b), 3 in c), 4 in d), 5 in e), 6 in f), 7 in g), 8 in h), 9 in i), and 10 in j).

7. Prediction of both Load and Displacement (ANN with Two Outputs)

3.1. Sensitivity Analysis of ANNs to the Number of Hidden Layer(s) and Number of Neuron(s)

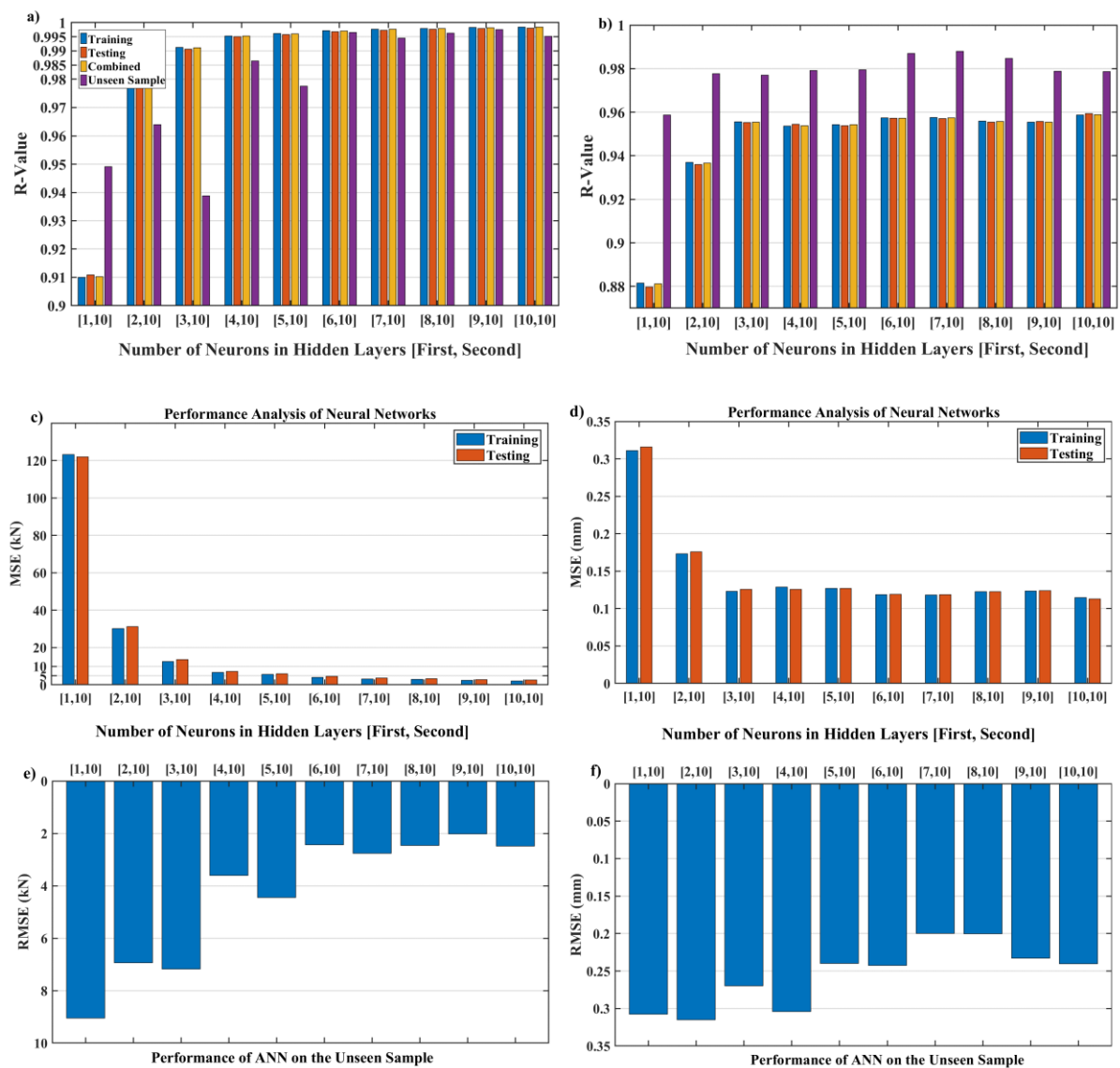


Figure S5. The results obtained when the ANNs were employed to predict both load and displacement (i.e. ANNs with two outputs). Among 100 distinct ANN structures that were trained, tested, and validated (each ten times), only the results for the last 10 distinct ANN structures were presented herein. R-values obtained from the regression analyses of the ANNs are indicated for a) load prediction and b) displacement prediction. MSE of training and testing datasets for training of ANNs versus number of neurons in the hidden layers for c) load prediction and d) displacement prediction. RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layers when a new specimen (unseen sample) that ANNs had not seen before was introduced to the ANNs for e) load prediction and f) displacement prediction. Compressive load is represented with positive values in this study.

8. Network Training Algorithm

4.1. Displacement Prediction & Sensitivity Analysis

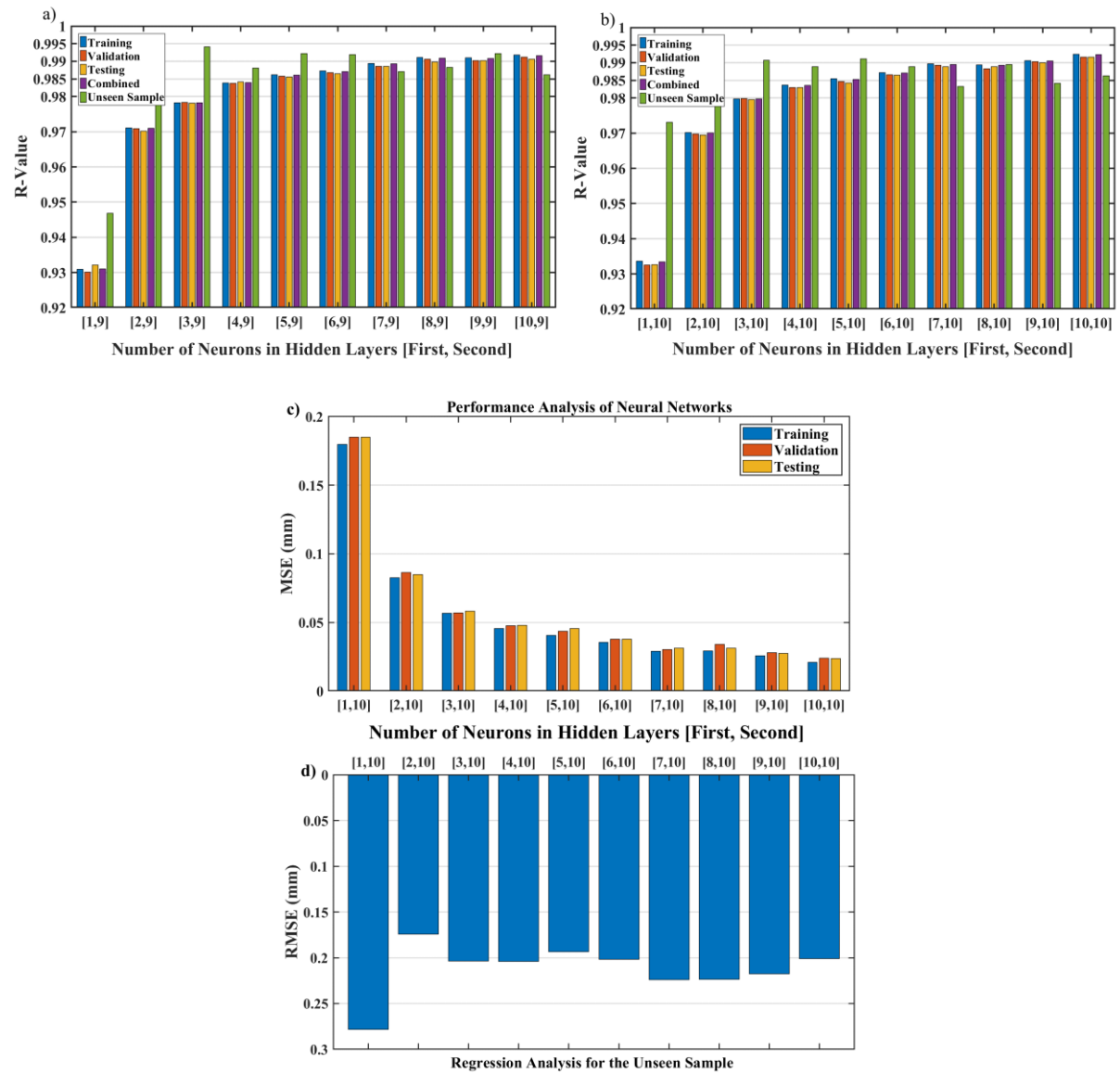


Figure S6. ANNs were trained to investigate the use of Levenberg-Marquardt backpropagation as the training algorithm in prediction of displacement. Among more than 100 distinct ANN structures that were trained, tested, and validated (each ten times), only some representative plots are provided herein. R-values of training, testing, and all datasets for training of ANNs were presented. Also, R-values between output of already trained ANNs and experiment when a new specimen (unseen sample) was introduced to the ANNs were reported. The number of neurons in the second hidden layer was set to 9 in a) and 10 in b). Some representative results indicating performance (error) analysis are also reported: c) MSE of training, validation, and testing datasets for training of ANNs versus number of neurons in the hidden layers. d) RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layers when a new specimen (unseen sample) that ANNs had not seen before was introduced to the ANNs.

4.2. Load Prediction & Sensitivity Analysis

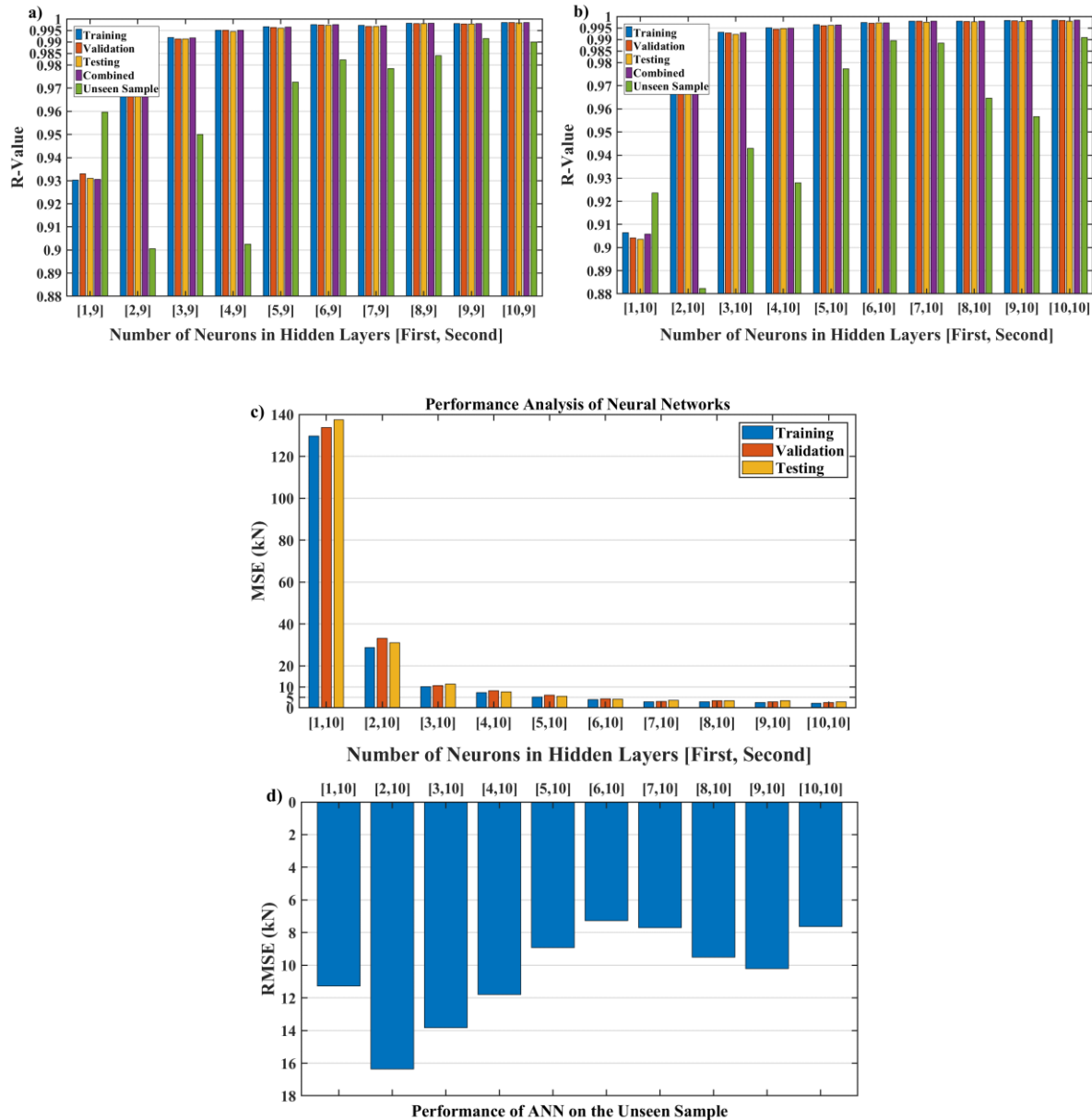


Figure S7. ANNs were trained to investigate the use of Levenberg-Marquardt backpropagation as the training algorithm in prediction of load. Among more than 100 distinct ANN structures that were trained, tested, and validated (each ten times), only some representative plots are provided herein. R-values of training, testing, and all datasets for training of ANNs were presented. Also, R-values between output of already trained ANNs and experiment when a new specimen (unseen sample) was introduced to the ANNs were reported. The number of neurons in the second hidden layer was set to 9 in a) and 10 in b). Some representative results indicating performance (error) analysis are also reported: c) MSE of training, validation, and testing datasets for training of ANNs versus number of neurons in the hidden layers. d) RMSE between output of already trained ANNs and experiment versus number of neurons in the hidden layers when a new specimen (unseen sample) that ANNs had not seen before was introduced to the ANNs. Compressive load is represented with positive values in this study.

4.3. Optimum ANN Structure (Displacement Prediction)

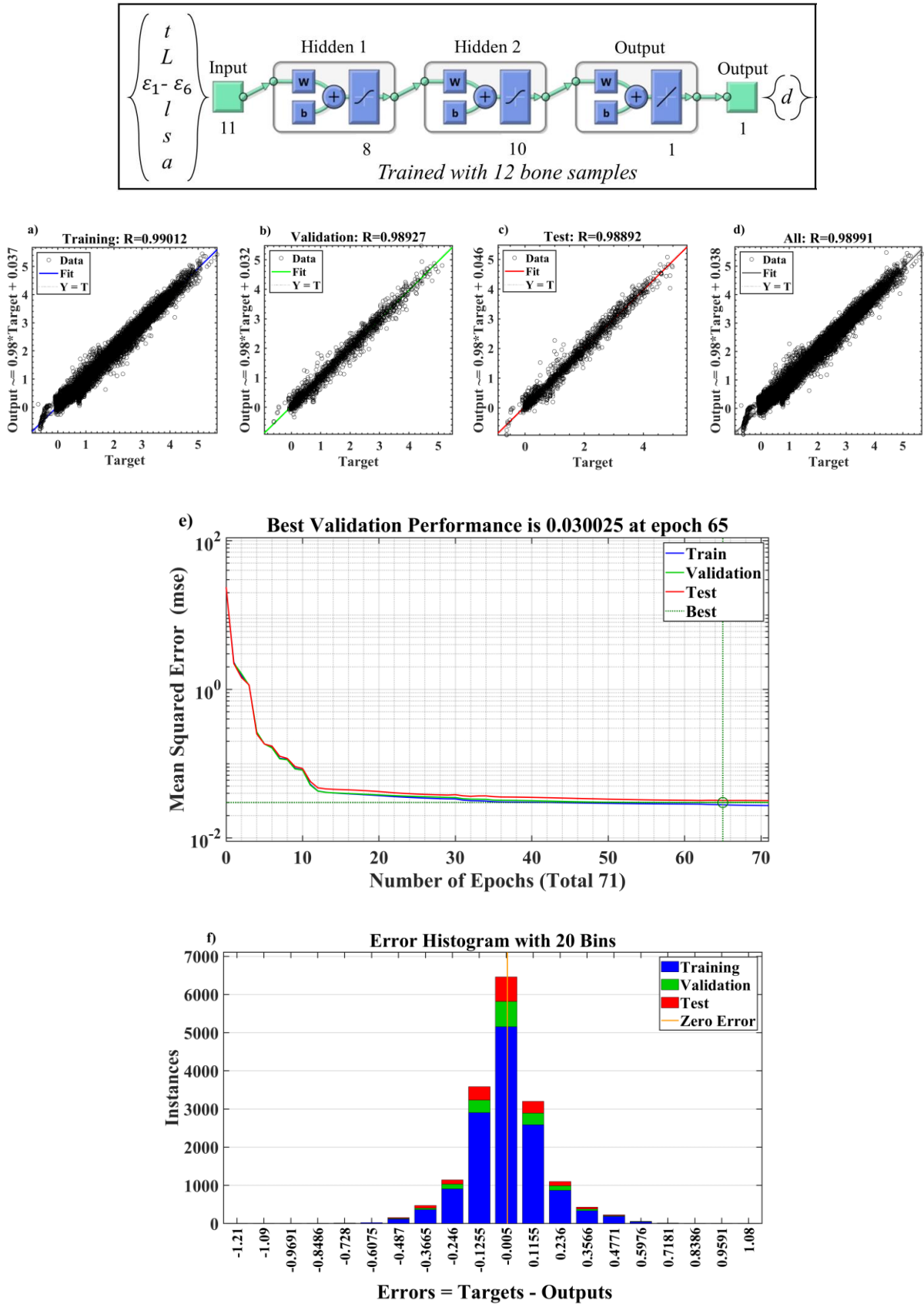


Figure S8. To investigate the use of Levenberg-Marquardt backpropagation as the training algorithm, an ANN with the optimum structure (ANN [8,10]) was trained to predict displacement. Regression analysis for a) training, b) validation, c) testing, and d) all data. e) Performance analysis and f) error histogram of the neural network during training.

4.4. Optimum ANN Structure (Load Prediction)

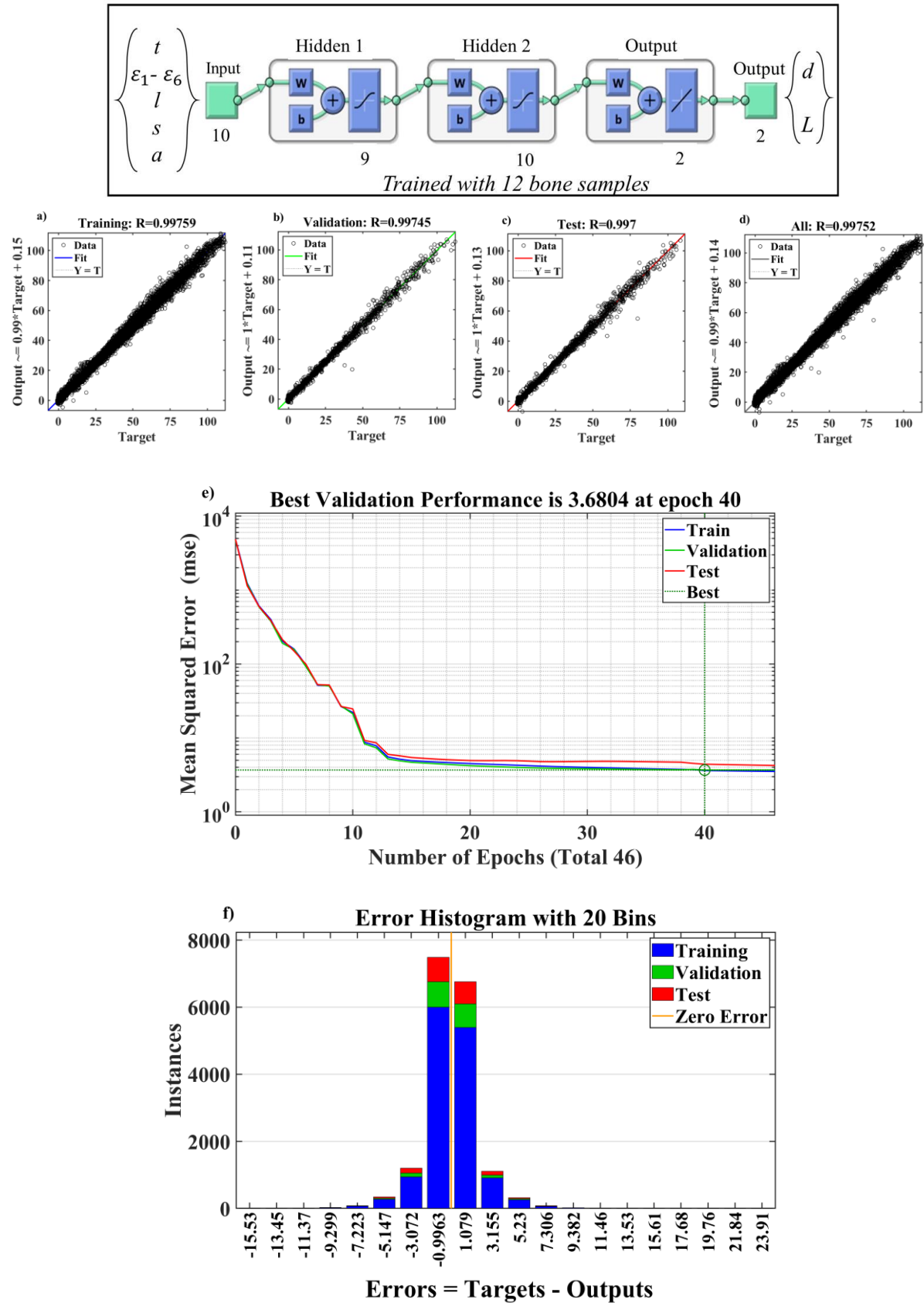


Figure S9. To investigate the use of Levenberg-Marquardt backpropagation as the training algorithm, an ANN with the optimum structure (ANN [10,10]) was trained to predict load. Regression analysis for a) training, b) validation, c) testing, and d) all data. e) Performance analysis and f) error histogram of the neural network during training.

9. Noise Injection

Table S2. Generalization performance of training artificial neural networks with and without injecting noise to the datasets for the regression analysis conducted in this study. The unit of errors is “mm” for displacement and “kN” for load.

ANN output(s)	New data	Injected noise	Training error (MSE)	Generalization error (RMSE)	Reduction in generalization error (%)	Generalization <i>R</i> -Value (ANN versus experiment)
D	Specimen #1	No noise	0.0025 mm	0.7065 mm	68	0.9347
		Input noise	0.0223 mm	0.2272 mm		0.9907
	Specimen #2	No noise	0.0016 mm	1.2233 mm	39	0.9754
		Input noise	0.0126 mm	0.7504 mm		0.9864
	Specimen #3	No noise	0.0020 mm	1.6751 mm	74	0.7686
		Input noise	0.0178 mm	0.4359 mm		0.9881
L	Specimen #1	No noise	0.0355 kN	3.3020 kN	37	0.992
		Input noise	1.6247 kN	2.0929 kN		0.997
	Specimen #2	No noise	0.0202 kN	20.288 kN	63	0.9415
		Input noise	1.1573 kN	7.5043 kN		0.9684
	Specimen #3	No noise	0.0270 kN	8.9281 kN	84	0.9880
		Input noise	1.4206 kN	1.4208 kN		0.9988
D & L	Output 1: D					
	Specimen #1	No noise	0.0354 mm	0.5491 mm	58	0.9495
		Input noise	0.1234 mm	0.2328 mm		0.9789
	Specimen #2	No noise	0.0231 mm	1.1745 mm	43	0.9608
		Input noise	0.0999 mm	0.6723 mm		0.9687
	Specimen #3	No noise	0.0319 mm	0.9592 mm	58	0.8797
		Input noise	0.1152 mm	0.4063 mm		0.9917
	Output 2: L					
	Specimen #1	No noise	0.0438 kN	15.123 kN	87	0.9447
		Input noise	2.5464 kN	2.0235 kN		0.9976
	Specimen #2	No noise	0.0326 kN	22.5863 kN	61	0.8858
		Input noise	1.5868 kN	8.7339 kN		0.9699
	Specimen #3	No noise	0.0441 kN	26.80 kN	93	0.8401
		Input noise	2.5676 kN	1.9305 kN		0.9974

10. Data Normalization

Table S3. Generalization performance of training artificial neural networks with and without data normalization prior to ANNs training. The units of errors are “mm” for displacement and “kN” for load.

ANN output(s)	New data	Normalized dataset	Training error (MSE)	Generalization error (RMSE)	Reduction in generalization error (%)	Generalization R-Value (ANN versus experiment)
D	Specimen #1	No	0.0076 mm	0.7181 mm	68	0.9834
		Yes	0.0223 mm	0.2272 mm		0.9907
	Specimen #2	No	0.0062 mm	0.6645 mm	-7	0.9905
		Yes	0.0126 mm	0.7504 mm		0.9864
	Specimen #3	No	0.0013 mm	10.3347 mm	96	0.5081
		Yes	0.0178 mm	0.4359 mm		0.9881
L	Specimen #1	No	0.4709 kN	14.4072 kN	85	0.9413
		Yes	1.6247 kN	2.0929 kN		0.997
	Specimen #2	No	0.4853 kN	9.7290 kN	23	0.9929
		Yes	1.1573 kN	7.5043 kN		0.9684
	Specimen #3	No	0.0113 kN	62.045 kN	98	0.6672
		Yes	1.4206 kN	1.4208 kN		0.9988
D & L	Output 1: D					
	Specimen #1	No	0.0675 mm	0.4090 mm	43	0.9847
		Yes	0.1234 mm	0.2328 mm		0.9789
	Specimen #2	No	0.0578 mm	0.6671 mm	-0.78	0.9695
		Yes	0.0999 mm	0.6723 mm		0.9687
	Specimen #3	No	0.0679 mm	0.4594 mm	12	0.9920
		Yes	0.1152 mm	0.4063 mm		0.9917
	Output 2: L					
	Specimen #1	No	0.6155 kN	11.8844 kN	83	0.9754
		Yes	2.5464 kN	2.0235 kN		0.9976
	Specimen #2	No	0.6217 kN	9.2259 kN	5	0.9299
		Yes	1.5868 kN	8.7339 kN		0.9699
	Specimen #3	No	0.6211 kN	4.6299 kN	58	0.9924
		Yes	2.5676 kN	1.9305 kN		0.9974

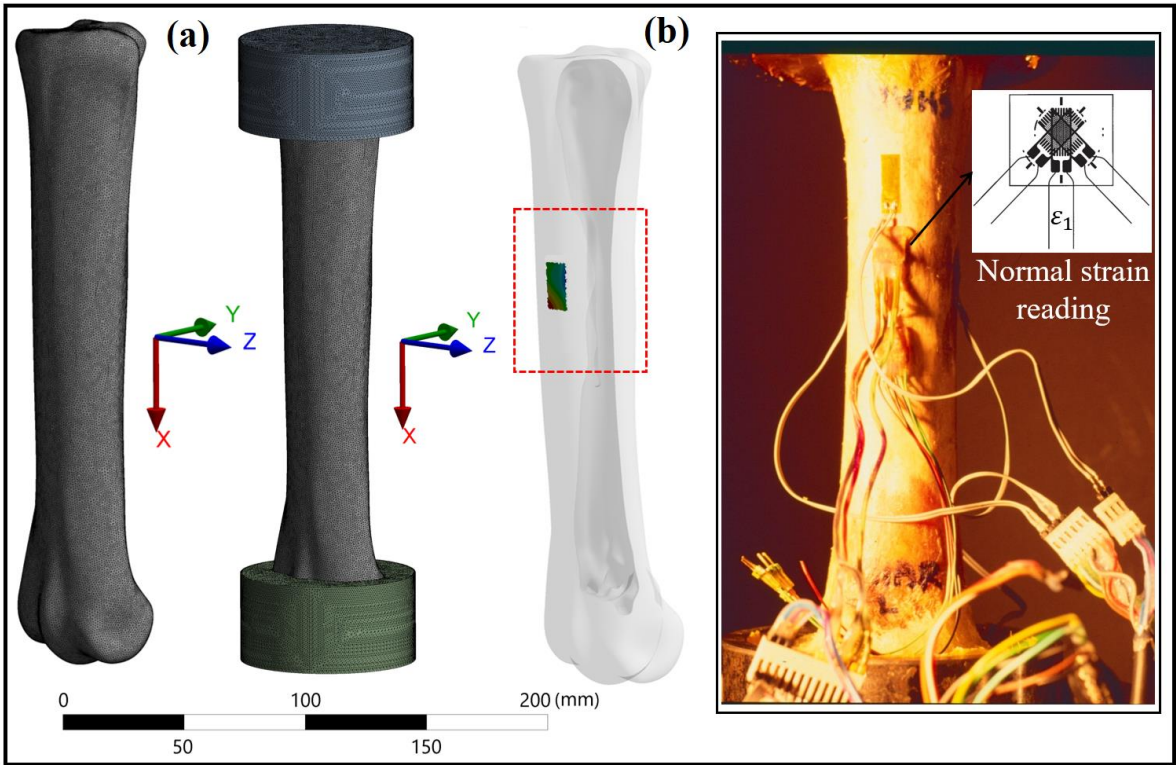


Figure S10. a) Both ends of the MC3 bones were surrounded by metal cups into which slow-curing fiberglass reinforced epoxy resin was poured. b) A confined area on the dorsal surface of MC3 long bones to represent a region where the midshaft normal strain readings were measured experimentally and then were predicted using artificial neural networks. Compressive strains are represented with positive values in this study.

Table S4. The outcome of regression and performance analyses for the training session of ANNs is reported for prediction of normal strains ($\mu\epsilon$) (samples from two-year-olds). To assess the ability of the trained ANNs in generalization, the outcomes of regression and performance analyses were reported when the trained ANNs were used to make strain prediction on new specimens (unseen samples). To improve the generalization of ANNs, each ANN was trained 10 times, and the average of those results is reported herein.

ANN output		Trained ANN			Prediction on unseen sample		
		R-Value	Linear model $f(x) = mx + b$		R-Value	Linear model $f(x) = mx + b$	
			m	b		m	b
Strain ($\mu\epsilon$)	Train	0.9630	0.9260	108.74	0.9592	0.7519	90.29
	Test	0.9080	0.8837	173.05			
	All	0.9520	0.9177	121.46			

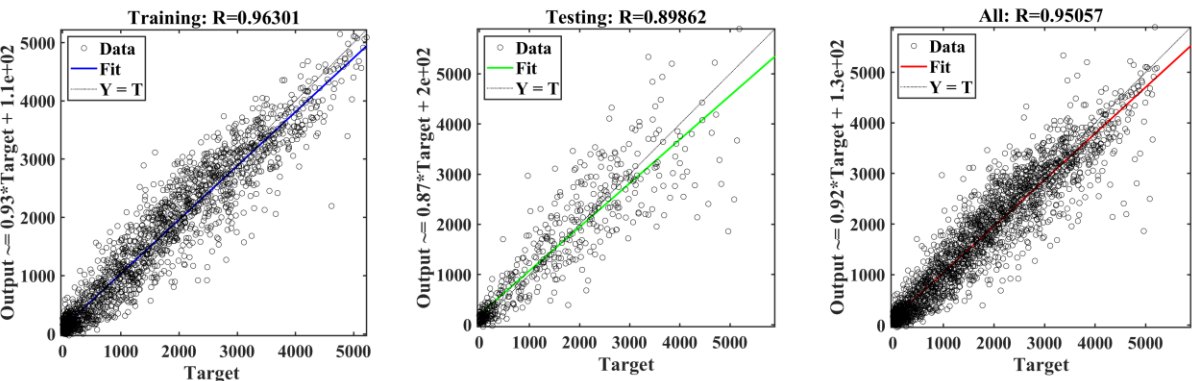


Figure S11. The outcome of regression analysis when the neural networks were trained to predict normal strain on the dorsal surface of samples from two-year-old horses.

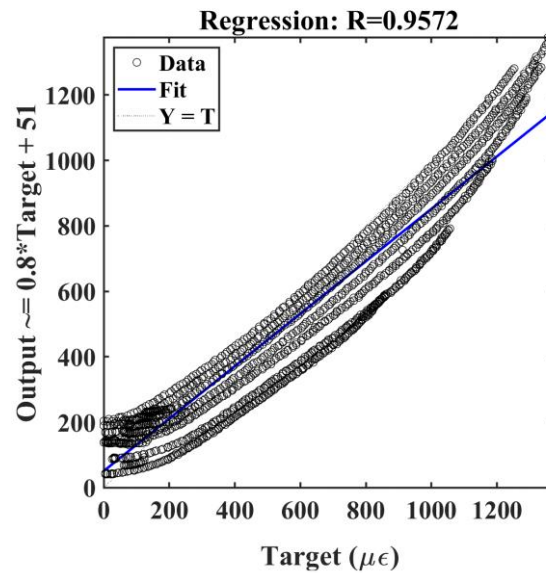


Figure S12. The already trained and tested ANN (Figure S16) was employed to investigate the strain prediction on a new specimen (an unseen sample) that was not used in the ANN training. A representative plot indicating the outcome of the regression model between ANN output and target (experiment) is displayed herein.

Table S5. The outcome of regression and performance analyses for the training session of ANNs is reported for prediction of normal strains ($\mu\epsilon$) (samples from three-year-olds). To assess the ability of the trained ANNs in generalization, the outcomes of regression and performance analyses were reported when the trained ANNs were used to make strain predictions on new specimens (unseen sample). To improve the generalization of ANNs, each ANN was trained 10 times, and the average of those results is reported herein.

ANN output		Trained ANN			Prediction on unseen sample		
		R-Value	Linear model $f(x) = mx + b$		R-Value	Linear model $f(x) = mx + b$	
			m	b		m	b
Strain ($\mu\epsilon$)	Train	0.9511	0.9037	91.60	0.9736	0.8652	44.97
	Test	0.9185	0.8747	112.97			
	All	0.9446	0.8979	95.92			

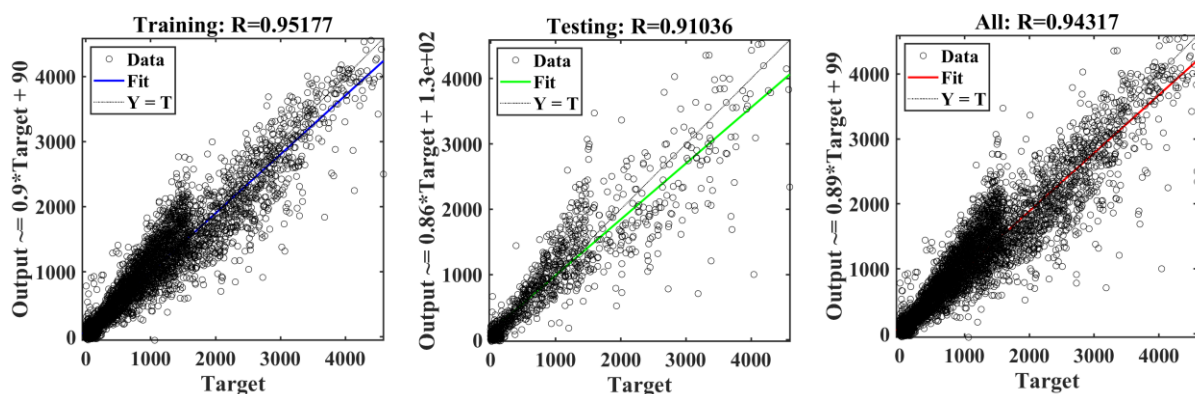


Figure S13. The outcome of regression analysis when the neural networks were trained to predict normal strain on the dorsal surface of samples from three-year-old horses.

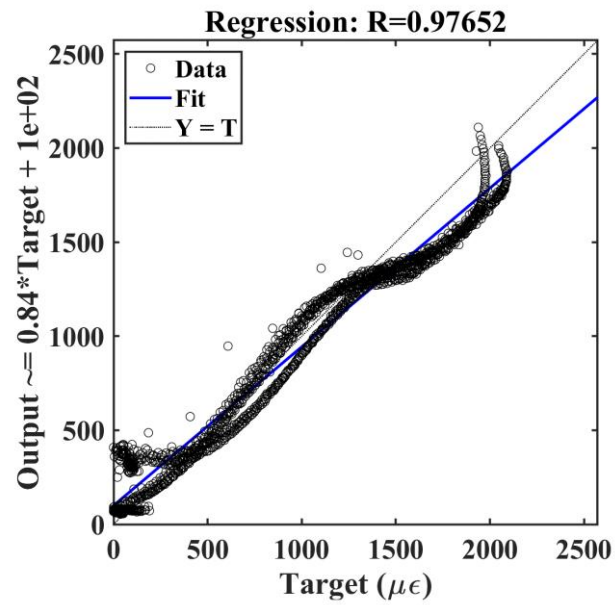


Figure S14. The already trained and tested ANN (Figure S18) was employed to investigate the strain prediction on a new specimen (an unseen sample) that was not used in the ANN training. A representative plot indicating the outcome of regression model between ANN output and target (experiment) is displayed herein.

12. The Level of Injected Noise (Appropriate Values)

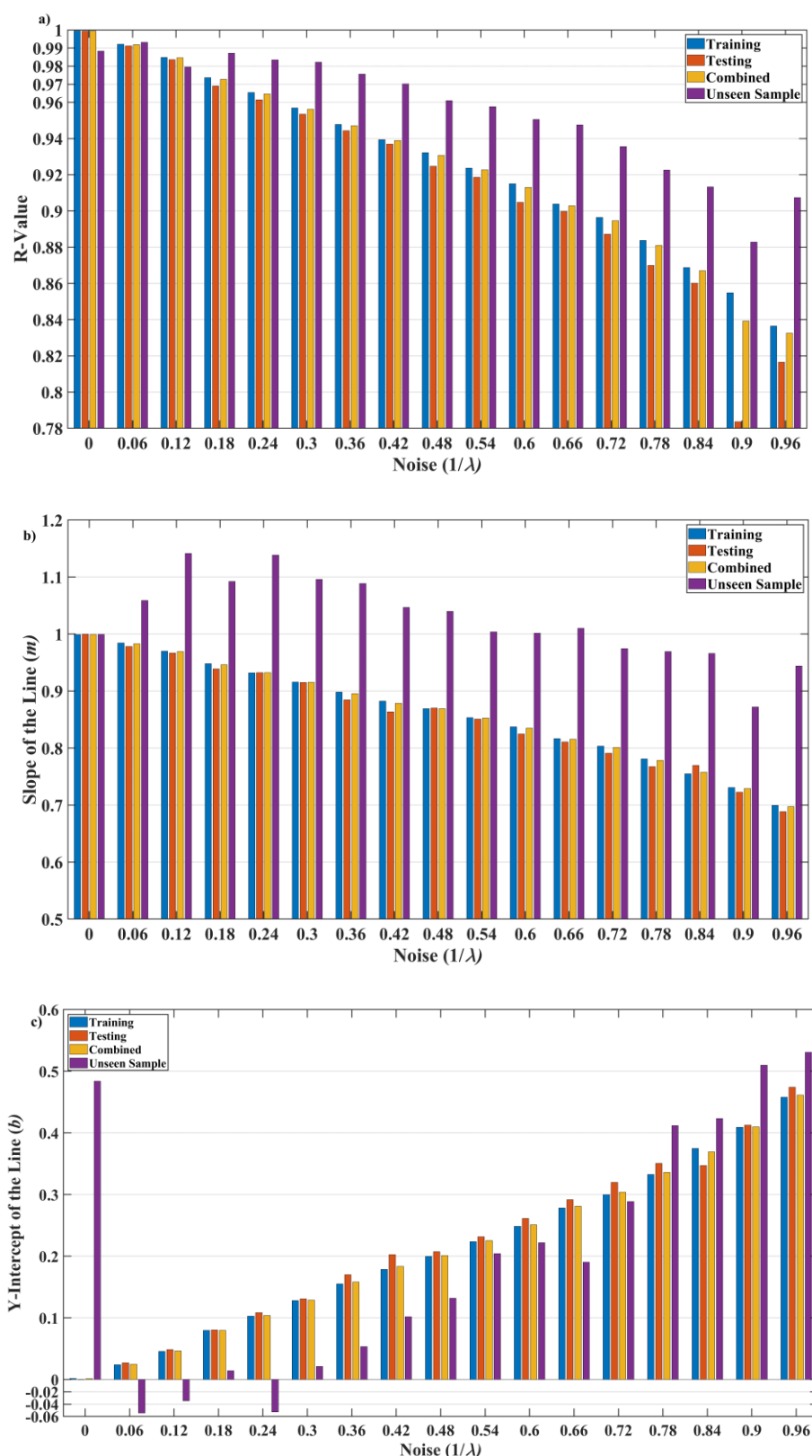


Figure S15. Influential parameters with which an optimum range of values for the injected noise ($1/\lambda$) was found. a) R-values, b) slope of the linear model, c) y-intercept of the linear model for training, testing, all datasets, and the unseen sample when the neural networks were trained using noisy datasets with increasing levels of noise. The linear model is represented as " $f(x) = mx + b$ " where $f(x)$ identifies the ANN output (prediction) and x expresses the target (experimental) value.

8.2. Summary and Concluding Remarks

Feedforward backpropagation artificial neural networks (ANNs) have been widely applied to engineering related problems, as reported in the available literature. How to achieve successfully trained ANNs, and how to delineate influential output parameters from ANN analyses, have not been thoroughly explained in the literature.

To explore the changes in ANN performance, this chapter investigated the effects of several influential elements: a network training algorithm using Bayesian regularization backpropagation, Levenberg-Marquardt backpropagation and Scaled conjugate backpropagation training algorithms; injecting noise to datasets prior to training, with the level of injected noise correlated with model fitting and regularization effects; and, data normalization to make input data more suitable for training.

The author sought to identify optimum network algorithm structures (architectures) that were both repeatable and objective. This involved analysing the essential parameters; such as R -values, RMSE and linear function parameters; that best enabled the identification of well-trained and well-generalized ANNs. For each scenario, the results of regression, performance and error analyses were explored to assess the ability of ANNs to predict known output parameters for a variety of bone samples. Analyses were conducted on new specimens that the ANNs had not seen before, and this offered an unbiased measure of the performance of each ANN architecture on unseen data that differed from the data used for ANN training.

The generalization ability of ANNs in making predictions on unseen bone samples was assessed when the ANNs were trained with and without injected noise. Similar processes were completed when the ANNs were trained with and without normalized input data. Each ANN was trained multiple times and their outputs were averaged. The same ANN with the same datasets produced completely different results each time it was trained. Using Bayesian regularization backpropagation as the neural network training algorithm resulted in the most reliable predictions. The error of ANNs in generalization (RMSE) was drastically decreased when data was normalized prior to the commencement of training and also when the ANNs were trained with injected noise. ANNs with noise-free inputs and ANNs with noticeable/excessive injected noise were less able to predict the output(s) and generalized poorly in response to the new (previously unseen) datasets.

Chapter 9

Conclusions and Future Work

9.1. Concluding Remarks

Avoiding and/or reducing the likelihood of failure and fracture of structures is a significant goal of both researchers and engineers. Anticipating the fracture of bone, as an example of a highly complex engineering structure, depends on the level and magnitudes of applied loads and on appropriate comprehension of the bone's mechanical properties and responses under load. Therefore, it is critical to derive meaning and extract patterns from the associated nonlinear relationships.

This thesis reported on the use of computer-aided design, finite element analysis and feedforward artificial neural networks to complete original research on shape and the mechanical responses of the equine third metacarpal (MC3) bone. The MC3 long bone is a unique well-engineered structure, functioning as a cylindrical long Euler column within a living biological system. The MC3 is ideal for bioengineering research to investigate the normal mechanical responses of a complex structure with highly nonlinear mechanical properties.

Chapter 1 offered an introduction to the overall contributions of this thesis and described an outline of the thesis structure and salient outcomes of the research undertaken. In particular, Chapter 1 identified the published contributions associated with Chapters 3 to 8.

Chapter 2 provided an overview of salient published literature and identified gaps in the current literature that were investigated by the author and reported in this thesis.

Chapter 3 presented underlying formulae to quantify elemental energy errors (for both solid bulk elements and surface shell elements) for successful completion of finite element convergence and error analysis with an aim to maximize the accuracy of finite element analysis performed on equine third metacarpal bones. This emphasized conducting mesh sensitivity analysis and assigning proper mesh types (not employing linear elements) for stress and strain analysis of this complex biological structure. These strategies were followed and implemented in the FEA performed in Chapter 5 to maximize the accuracy prior to comparison of the results with experimental and artificial neural network counterparts. Quantifying the errors generated

from the use of 3D CAD software was shown to enhance confidence in the employment of CAD and the measurement of MC3 geometrical parameters.

Chapter 4 presented the measurement of a variety of geometrical parameters (using CAD) in three main cross sections (slices) within the diaphysis of MC3 long bones. The chapter then reported on the use of statistical tools (using ANOVA and t-tests) to identify significant differences of shape and geometrical parameters versus horse age and maturation and to investigate converging-diverging shape configuration of the diaphysis of the equine third metacarpal bone. The midshaft of MC3 is a region to which the strain gauges were attached to record six kinds of strains during ex-vivo experiments. This data was used as the input variables for the artificial neural networks reported in Chapter 5 to Chapter 8, inclusive. Chapter 4 also provided the background information to further explore shape- and age-dependent mechanical responses of MC3 long bones.

Aimed to replace constitutive equations by data-driven methods using artificial intelligence methodologies, Chapter 5 to Chapter 8 delved into the use of feedforward artificial neural networks trained with experimental measurements to predict the cyclic mechanical loading, displacement, stiffness, and strains of equine third metacarpal bones subjected to cyclic mechanical load. Training of machine learning algorithms such as ANNs with inadequate datasets will lead to poorly developed ANNs exhibiting poor performances in their applicability and generalization. To mitigate this concern more than three years of ex-vivo experiments and data collection were used to establish, train, test, validate, and generalize ANNs to gain the favourable outcomes. The results associated with regression, performance, and error histogram analyses demonstrated the potent ability of ANNs to successfully map the space of inputs to that of output, highlighting the significant performance of the ANN algorithms for both identifying the trends of the results as well as predicting the experimental data. The ability of ANN models in learning through examples, and thus replacing physical modelling, was demonstrated to establish relationships among variables (load, displacement, strains, and load exposure time as well as bone features such as length, age, and side) which is not a straightforward task to be tackled using traditional techniques due to the complexity of the problem and exotic properties of the material. The strategies as to how to overcome overfitting were also explored, such as introduction of a noise source to the input data prior to ANNs training. Similar processes were completed when the ANNs were trained with and without normalized input data. Besides injecting a noise source to the ANN inputs, the introduction of new bone samples to the ANNs (availability of more relevant data that the

ANNs can be trained on) was shown to improve the accuracy of the predictions. A major emphasis in this thesis concerning the use of ANNs, was placed on the analyses conducted on the new specimens that ANNs had not seen before, which offered an unbiased measure of the performance of the model on unseen data different from those used for training. This assessed the generalization ability of all the trained and tested ANNs to investigate as to whether the already trained ANNs were able to make reliable predictions as compared with the experimental measurements. The ANNs produced a satisfactory outcome within a couple of seconds, emphasizing the real-time ability of ANNs in the computational mechanics of complex nonlinear structures. The connection weights approach exploring the relative importance of ANNs input variables identified that strains significantly affected the ANN output in the prediction of mechanical loading. Pattern recognition algorithms explained that there was an inherent difference between the bones from a group of foals and those from two- and three-year-olds at least in terms of the measured experimental data. The effects of several influential elements such as a network training algorithm (using Bayesian regularization backpropagation, Levenberg-Marquardt backpropagation, and Scaled conjugate backpropagation training algorithms), injecting noise to datasets prior to training, the level of injected noise which directly affects model fitting and regularization, and data normalization prior to the commencement of training were explored and discussed.

9.2. Future Research Opportunities

Artificial neural network developments have enabled researchers to efficiently applying ANN algorithms to complex engineering problems. In the research reported in this thesis, ANNs were found to be effective in determining loads in bone, an advanced biological material. Exploring less complex structures may enable machine learning techniques to entirely replace traditional computational techniques, such as FEA.

Recommendations for further research are summarized as follows:

- Implementation of artificial neural networks as a constitutive approach to investigating the biomechanics of the equine forelimb to fully comprehend advanced biomaterials (with an emphasis on bones). Presenting efficient models of bone tissue adaptation using machine learning approaches to make reliable predictions in biomedical engineering that will allow the identification of individual structures at increased risk of failure and may provide insight into how and why they fail.

- Predicting an optimized and desirable shape configuration (anatomy) of equine long bones to maximize their well-being during maturation and aging.
- Developing hybrid modelling, also referred to as intelligent finite element method, in which neural network algorithms are integrated with a finite element framework (facilitating bypassing the FEA calculation process). This assists in time-sensitive clinical applications where using traditional FEA requires long computing times to obtain final simulation results and provide information into exactly how the tissue will respond to specific clinical or surgical interventions.
- Developing a deep learning model to promptly and accurately estimate stress and strain distribution in long bones (and other complex engineering structures) and to determine the loading environment that causes bones to fail.
- Developing reliable methods to evaluate patterns in equine gait analysis. This has the potential to improve the diagnosis of equine lameness in an objective manner, that could avoid the subjective biases that can occur in traditional analyses.
- Establishment of a universal framework (using already collected in-vivo and ex-vivo experimental data, FEA, and artificial intelligence) to solve bone adaptation models both in the forward direction (i.e. determining responses of equine forelimb to a given set of loads) and the inverse direction (i.e. quantifying loads and materials that have resulted in a given state of a bone).

References

- Abiodun, O.I., Jantan, A., Omolara, A.E., Dada, K.V., Mohamed, N.A., Arshad, H., 2018. State-of-the-art in artificial neural network applications: A survey. *Heliyon* 4, e00938.
- Ahmad, A., Raza, A., 2020. Reliability analysis of strength models for CFRP-confined concrete cylinders. *Composite Structures*, 112312.
- Al-Assadi, M., El Kadi, H.A., Deiab, I.M., 2011. Using artificial neural networks to predict the fatigue life of different composite materials including the stress ratio effect. *Applied Composite Materials* 18, 297-309.
- Anderson, A.E., Ellis, B.J., Maas, S.A., Weiss, J.A., 2010. Effects of idealized joint geometry on finite element predictions of cartilage contact stresses in the hip. *J Biomech* 43, 1351-1357.
- Ansari, R., Sahmani, S., 2011. Surface stress effects on the free vibration behavior of nanoplates. *International Journal of Engineering Science* 49, 1204-1215.
- Ardestani, M.M., Chen, Z., Wang, L., Lian, Q., Liu, Y., He, J., Li, D., Jin, Z., 2014. Feed forward artificial neural network to predict contact force at medial knee joint: Application to gait modification. *Neurocomputing* 139, 114-129.
- Asgari, M., Abi-Rafeh, J., Hendy, G.N., Pasini, D., 2019. Material anisotropy and elasticity of cortical and trabecular bone in the adult mouse femur via AFM indentation. *Journal of the mechanical behavior of biomedical materials* 93, 81-92.
- Ashrafi, H.R., Jalal, M., Garmsiri, K., 2010. Prediction of load–displacement curve of concrete reinforced by composite fibers (steel and polymeric) using artificial neural network. *Expert Systems with Applications* 37, 7663-7668.
- Bagherian, A., Baghani, M., George, D., Rémond, Y., Chappard, C., Patlazhan, S., Baniassadi, M., 2019. A novel numerical model for the prediction of patient-dependent bone density loss in microgravity based on micro-CT images. *Continuum Mechanics and Thermodynamics*, 1-17.
- Barbosa, J.F., Correia, J.A., Júnior, R.F., De Jesus, A.M., 2020. Fatigue life prediction of metallic materials considering mean stress effects by means of an artificial neural network. *International Journal of Fatigue* 135, 105527.
- Barkaoui, A., Tlili, B., Vercher-Martínez, A., Hambli, R., 2016. A multiscale modelling of bone ultrastructure elastic proprieties using finite elements simulation and neural network method. *Computer methods and programs in biomedicine* 134, 69-78.
- Berlin, A., Simon, D., Tascilar, K., Figueiredo, C., Bayat, S., Finzel, S., Klaus, E., Rech, J., Hueber, A., Kleyer, A., 2019. The ageing joint-standard age-and sex-related values of bone erosions and osteophytes in the hand joints of healthy individuals. *Osteoarthr Cartilage* 27, 1043-1047.
- Bock, F.E., Aydin, R.C., Cyron, C.J., Huber, N., Kalidindi, S.R., Klusemann, B., 2019. A review of the application of machine learning and data mining approaches in continuum materials mechanics. *Frontiers in Materials* 6, 110.
- Brekelmans, W., Poort, H., Slooff, T., 1972. A new method to analyse the mechanical behaviour of skeletal parts. *Acta Orthopaedica Scandinavica* 43, 301-317.
- Campoli, G., Weinans, H., Zadpoor, A.A., 2012. Computational load estimation of the femur. *Journal of the mechanical behavior of biomedical materials* 10, 108-119.
- Carter, D.R., Hayes, W.C., 1977. The compressive behavior of bone as a two-phase porous structure. *JBJS* 59, 954-962.
- Chand, R., Haug, E., Rim, K., 1976. Stresses in the human knee joint. *J Biomech* 9, 417-IN415.
- Chojaczyk, A.A., Teixeira, A.P., Neves, L.C., Cardoso, J.B., Guedes Soares, C., 2015. Review and application of Artificial Neural Networks models in reliability analysis of steel structures. *Structural Safety* 52, 78-89.

- Christen, P., van Rietbergen, B., Lambers, F.M., Müller, R., Ito, K., 2012. Bone morphology allows estimation of loading history in a murine model of bone adaptation. *Biomechanics and Modeling in Mechanobiology* 11, 483-492.
- Clayton, H.M., Schamhardt, H.C., 2013. Measurement techniques for gait analysis. *Equine locomotion* 2, 31-60.
- Collins, S., Murray, R., Kneissl, S., Stanek, C., Hinterhofer, C., 2009. Thirty-two component finite element models of a horse and donkey digit. *Equine veterinary journal* 41, 219-224.
- Colombo, G., Bertetti, M., Bonacini, D., Magrassi, G., Year Reverse engineering and rapid prototyping techniques to innovate prosthesis socket design. In *Three-Dimensional Image Capture and Applications VII*.
- Couch, S., Nielsen, B., 2017. A Review of Dorsal Metacarpal Disease (Bucked Shins) in the Flat Racing Horse: Prevalence, Diagnosis, Pathogenesis, and Associated Factors. *Journal of Dairy Veterinary Animal Research* 5, 228-236.
- Currey, J., 2009. Measurement of the Mechanical Properties of Bone: A Recent History. *Clinical Orthopaedics and Related Research®* 467, 1948-1954.
- Currey, J., 2010. Mechanical properties and adaptations of some less familiar bony tissues. *Journal of the Mechanical Behavior of Biomedical Materials* 3, 357-372.
- Currey, J.D., 2006. *Bones: structure and mechanics*. Princeton university press.
- Currey, J.D., 2014. *The mechanical adaptations of bones*. Princeton University Press.
- Dallora, A.L., Anderberg, P., Kvist, O., Mendes, E., Diaz Ruiz, S., Sanmartin Berglund, J., 2019a. Bone age assessment with various machine learning techniques: A systematic literature review and meta-analysis. *Plos One* 14, e0220242.
- Dallora, A.L., Berglund, J.S., Brogren, M., Kvist, O., Ruiz, S.D., Dübbel, A., Anderberg, P., 2019b. Age Assessment of Youth and Young Adults Using Magnetic Resonance Imaging of the Knee: A Deep Learning Approach. *JMIR Medical Informatics* 7, e16291.
- Davidoff, N.A., Freivalds, A., 1993. A graphic model of the human hand using CATIA. *International Journal of Industrial Ergonomics* 12, 255-264.
- Davies, H., 2001. The relationship between surface strain and measurements of bone quality, quantity and shape. *Equine veterinary Journal, Suppl* 33, 16-20.
- Davies, H., 2002. Dorsal metacarpal cortex ultrasound speed and bone size and shape. *Equine Veterinary Journal* 34, 337-339.
- Davies, H., 2005. The timing and distribution of strains around the surface of the midshaft of the third metacarpal bone during treadmill exercise in one Thoroughbred racehorse. *Australian Veterinary Journal* 83, 157-162.
- Davies, H., 2006. Estimating peak strains associated with fast exercise in Thoroughbred racehorses. *Equine Veterinary Journal* 38, 383-386.
- Davies, H., 2009. Ex vivo calibration and validation of in vivo equine bone strain measures. *Equine veterinary journal* 41, 225-228.
- Davies, H.M.S., 1995. The adaptive response of the equine metacarpus to locomotory stress.
- Demuth, H.B., Beale, M.H., De Jess, O., Hagan, M.T., 2014. *Neural network design*. Martin Hagan.
- Den Hartog, S., Back, W., Brommer, H., Van Weeren, P., 2009. In vitro evaluation of metacarpophalangeal joint loading during simulated walk. *Equine veterinary journal* 41, 214-217.
- Deng, W.-J., Chen, W.-C., Pei, W., 2008. Back-propagation neural network based importance-performance analysis for determining critical service attributes. *Expert Systems with Applications* 34, 1115-1125.
- Dickey, J.P., Pierrynowski, M.R., Bednar, D.A., Yang, S.X., 2002. Relationship between pain and vertebral motion in chronic low-back pain subjects. *Clinical Biomechanics* 17, 345-352.

Edwards, W.T., Hayes, W.C., Posner, I., White, I.A.A., Mann, R.W., 1987. Variation of Lumbar Spine Stiffness With Load. *Journal of Biomechanical Engineering* 109, 35-42.

Favre, J., Hayoz, M., Erhart-Hledik, J.C., Andriacchi, T.P., 2012. A neural network model to predict knee adduction moment during walking based on ground reaction force and anthropometric measurements. *Journal of Biomechanics* 45, 692-698.

Fradinho, M.J., Vale, A.C., Bernardes, N., Caldeira, R.M., Vaz, M.F., Ferreira-Dias, G., 2015. Biomechanical properties of the equine third metacarpal bone: In vivo quantitative ultrasonography versus ex vivo compression and bending techniques. *Journal of Equine Veterinary Science* 35, 198-205.

Frame, J., Wheel, M., Riches, P., 2017. A numerical investigation and experimental verification of size effects in loaded bovine cortical bone. *International Journal for Numerical Methods in Biomedical Engineering*.

Frank, M., Drikakis, D., Charissis, V., 2020. Machine-learning methods for computational science and engineering. *Computation* 8, 15.

Frazer, L.L., Santschi, E.M., Fischer, K.J., 2017. The impact of subchondral bone cysts on local bone stresses in the medial femoral condyle of the equine stifle joint. *Medical engineering & physics* 48, 158-167.

Frazer, L.L., Santschi, E.M., Fischer, K.J., 2019. Impact of a void in the equine medial femoral condyle on bone stresses and peak contact pressures in a finite element model. *Veterinary Surgery* 48, 237-246.

Fregly, B.J., D'Lima, D.D., Colwell Jr, C.W., 2009. Effective gait patterns for offloading the medial compartment of the knee. *J Orthop Res* 27, 1016-1021.

Gačnik, F., Ren, Z., Hren, N.I., 2014. Modified bone density-dependent orthotropic material model of human mandibular bone. *Medical engineering & physics* 36, 1684-1692.

Garijo, N., Martínez, J., García-Aznar, J., Pérez, M., 2014. Computational evaluation of different numerical tools for the prediction of proximal femur loads from bone morphology. *Computer Methods in Applied Mechanics and Engineering* 268, 437-450.

Gföhler, M., Peham, C., 2013. What can finite element analysis tell us? *Equine Veterinary Journal* 45, 265-266.

Ghaboussi, J., Garrett Jr, J., Wu, X., 1991. Knowledge-based modeling of material behavior with neural networks. *Journal of engineering mechanics* 117, 132-153.

Gohari, S., Sharifi, S., Burvill, C., Mouloudi, S., Izadifar, M., Thissen, P., 2019a. Localized failure analysis of internally pressurized laminated ellipsoidal woven GFRP composite domes: Analytical, numerical, and experimental studies. *Archives of Civil and Mechanical Engineering* 19, 1235-1250.

Gohari, S., Sharifi, S., Burvill, C., Mouloudi, S., Izadifar, M., Thissen, P., 2019b. Localized failure analysis of internally pressurized laminated ellipsoidal woven GFRP composite domes: Analytical, numerical, and experimental studies. *Archives of Civil and Mechanical Engineering* 19, 1235-1250.

Grassi, L., Isaksson, H., 2015. Extracting accurate strain measurements in bone mechanics: A critical review of current methods. *Journal of the mechanical behavior of biomedical materials* 50, 43-54.

Hambli, R., 2011. Apparent damage accumulation in cancellous bone using neural networks. *Journal of the mechanical behavior of biomedical materials* 4, 868-878.

Hambli, R., 2014. 3D finite element simulation of human proximal femoral fracture under quasi-static load. *Advances in Biomechanics & Applications* 1, 1.

Hambli, R., Frikha, S., Toumi, H., Tavares, J.M.R., 2016. Finite element prediction of fatigue damage growth in cancellous bone. *Computer methods in biomechanics and biomedical engineering* 19, 563-570.

Hambli, R., Hattab, N., 2013. Application of neural network and finite element method for multiscale prediction of bone fatigue crack growth in cancellous bone, *Multiscale Computer Modeling in Biomechanics and Biomedical Engineering*. Springer, pp. 3-30.

Harrison, S.M., Whitton, R.C., Kawcak, C.E., Stover, S.M., Pandy, M.G., 2014. Evaluation of a subject-specific finite-element model of the equine metacarpophalangeal joint under physiological load. *Journal of Biomechanics* 47, 65-73.

Hertz, J.A., 2018. *Introduction to the theory of neural computation*. CRC Press.

Hinterhofer, C., Stanek, C., Haider, H., 2001. Finite element analysis (FEA) as a model to predict effects of farriery on the equine hoof. *Equine Veterinary Journal* 33, 58-62.

Hornik, K., 1991. Approximation capabilities of multilayer feedforward networks. *Neural networks* 4, 251-257.

Huber, N., Nix, W., Gao, H., 2002. Identification of elastic-plastic material parameters from pyramidal indentation of thin films. *Proceedings of the Royal Society of London. Series A: Mathematical, Physical and Engineering Sciences* 458, 1593-1620.

Huber, N., Tsagrakis, I., Tsakmakis, C., 2000. Determination of constitutive properties of thin metallic films on substrates by spherical indentation using neural networks. *International Journal of solids and structures* 37, 6499-6516.

Huiskes, R., Chao, E., 1983. A survey of finite element analysis in orthopedic biomechanics: the first decade. *Journal of Biomechanics* 16, 385-409.

Imai, K., 2015. Analysis of vertebral bone strength, fracture pattern, and fracture location: a validation study using a computed tomography-based nonlinear finite element analysis. *Aging and disease* 6, 180.

Jain, A.K., Mao, J., Mohiuddin, K.M., 1996. Artificial neural networks: A tutorial. *Computer* 29, 31-44.

Jansová, M., Ondoková, L., Vychytil, J., Kochová, P., Witter, K., Tonar, Z., 2015. A finite element model of an equine hoof. *Journal of Equine Veterinary Science* 35, 60-69.

Javadi, A., Tan, T., Zhang, M., 2003. Neural network for constitutive modelling in finite element analysis. *Computer Assisted Mechanics and Engineering Sciences* 10, 523-530.

Johnson, T., Socrate, S., Boyce, M., 2010. A viscoelastic, viscoplastic model of cortical bone valid at low and high strain rates. *Acta biomaterialia* 6, 4073-4080.

Jones, L., Golan, D., Hanna, S., Ramachandran, M., 2018. Artificial intelligence, machine learning and the evolution of healthcare: A bright future or cause for concern? *Bone & joint research* 7, 223-225.

Kaijima, M., 2005. *Canine gait analysis and diagnosis using artificial neural networks and ground reaction force*. University of Georgia.

Keyak, J., Fourkas, M., Meagher, J., Skinner, H., 1993. Validation of an automated method of three-dimensional finite element modelling of bone. *Journal of biomedical engineering* 15, 505-509.

Keyak, J., Meagher, J., Skinner, H., Mote Jr, C., 1990. Automated three-dimensional finite element modelling of bone: a new method. *Journal of biomedical engineering* 12, 389-397.

Keyak, J.H., 2001. Improved prediction of proximal femoral fracture load using nonlinear finite element models. *Medical engineering & physics* 23, 165-173.

Khovanova, N.A., Shaikhina, T., Mallick, K.K., 2015. Neural networks for analysis of trabecular bone in osteoarthritis. *Bioinspired, Biomimetic and Nanobiomaterials* 4, 90-100.

Kim, T.-h., Year Pattern recognition using artificial neural network: a review. In *International Conference on Information Security and Assurance*.

Knowles, N.K., Reeves, J.M., Ferreira, L.M., 2016. Quantitative computed tomography (QCT) derived bone mineral density (BMD) in finite element studies: a review of the literature. *Journal of experimental orthopaedics* 3, 36.

- Koivumäki, J.E., Thevenot, J., Pulkkinen, P., Kuhn, V., Link, T.M., Eckstein, F., Jämsä, T., 2012. Ct-based finite element models can be used to estimate experimentally measured failure loads in the proximal femur. *Bone* 50, 824-829.
- Kulin, R.M., Jiang, F., Vecchio, K.S., 2011. Effects of age and loading rate on equine cortical bone failure. *Journal of the Mechanical Behaviour of Biomedical Materials*. 4, 57-75.
- Lawrence, L., Ott, E., Miller, G., Poulos, P., Piotrowski, G., Asquith, R., 1994. The mechanical properties of equine third metacarpals as affected by age. *Journal of animal science* 72, 2617-2623.
- Les, C., Keyak, J., Stover, S.M., Taylor, K., 1997. Development and validation of a series of three-dimensional finite element models of the equine metacarpus. *Journal of Biomechanics* 30, 737-742.
- Lescun, T.B., Adams, S.B., Main, R.P., Nauman, E.A., Breur, G.J., 2020. Finite Element Analysis of Six Transcortical Pin Parameters and Their Effect on Bone-Pin Interface Stresses in the Equine Third Metacarpal Bone. *Vet Comp Orthopaed* 33, 121-129.
- Liang, L., Liu, M., Martin, C., Sun, W., 2018. A deep learning approach to estimate stress distribution: a fast and accurate surrogate of finite-element analysis. *Journal of The Royal Society Interface* 15, 20170844.
- Liley, H., Davies, H., Firth, E., Besier, T., Fernandez, J., 2017. The effect of the sagittal ridge angle on cartilage stress in the equine metacarpo-phalangeal (fetlock) joint. *Computer Methods in Biomechanics and Biomedical Engineering* 20, 1140-1149.
- Lipton, Z.C., Berkowitz, J., Elkan, C., 2015. A critical review of recurrent neural networks for sequence learning. *arXiv preprint arXiv:1506.00019*.
- Liu, X., Athanasiou, C.E., Padture, N.P., Sheldon, B.W., Gao, H., 2020. A machine learning approach to fracture mechanics problems. *Acta Materialia*.
- Liu, Y., Zhang, C., Cheng, J., Chen, X., Wang, Z.J., 2019. A multi-scale data fusion framework for bone age assessment with convolutional neural networks. *Computers in biology and medicine* 108, 161-173.
- Ly, H.-B., Le, L.M., Duong, H.T., Nguyen, T.C., Pham, T.A., Le, T.-T., Le, V.M., Nguyen-Ngoc, L., Pham, B.T., 2019. Hybrid artificial intelligence approaches for predicting critical buckling load of structural members under compression considering the influence of initial geometric imperfections. *Applied Sciences* 9, 2258.
- Malek, S., Gunalan, R., Kedija, S., Lau, C., Mosleh, M.A., Milow, P., Amber, H., Saw, A., Year A primary study on application of artificial neural network in classification of pediatric fracture healing time of the lower limb. In *International Conference on Practical Applications of Computational Biology & Bioinformatics*.
- Malek, S., Gunalan, R., Kedija, S., Lau, C., Mosleh, M.A., Milow, P., Lee, S., Saw, A., 2018. Random forest and Self Organizing Maps application for analysis of pediatric fracture healing time of the lower limb. *Neurocomputing* 272, 55-62.
- Maleki, E., Unal, O., Kashyzadeh, K.R., 2018. Fatigue behavior prediction and analysis of shot peened mild carbon steels. *International Journal of Fatigue* 116, 48-67.
- Malekipour, F., Hitchens, P.L., Whitton, R.C., Lee, P.V.-S., 2020a. Effects of in vivo fatigue-induced subchondral bone microdamage on the mechanical response of cartilage-bone under a single impact compression. *Journal of Biomechanics* 100, 109594.
- Malekipour, F., Whitton, R.C., Hitchens, P.L., Lee, P.V., 2020b. Fatigue behavior of subchondral bone under simulated physiological loads of equine athletic training. *Journal of the Mechanical Behavior of Biomedical Materials*, 103920.
- Manda, K., Wallace, R.J., Xie, S., Levrero-Florencio, F., Pankaj, P., 2017. Nonlinear viscoelastic characterization of bovine trabecular bone. *Biomechanics and Modeling in Mechanobiology* 16, 173-189.

Mandal, P., 2017. Artificial neural network prediction of buckling load of thin cylindrical shells under axial compression. *Engineering Structures* 152, 843-855.

Mandal, S., Sivaprasad, P., Venugopal, S., Murthy, K., 2009. Artificial neural network modeling to evaluate and predict the deformation behavior of stainless steel type AISI 304L during hot torsion. *Applied Soft Computing* 9, 237-244.

Martig, S., Lee, P.V., Anderson, G.A., Whitton, R.C., 2013. Compressive fatigue life of subchondral bone of the metacarpal condyle in thoroughbred racehorses. *Bone* 57, 392-398.

McCarty, C.A., Thomason, J.J., Gordon, K.D., Burkhart, T.A., Milner, J.S., Holdsworth, D.W., 2016a. Finite-element analysis of bone stresses on primary impact in a large-animal model: the distal end of the equine third metacarpal. *PLoS One* 11.

McCarty, C.A., Thomason, J.J., Gordon, K.D., Burkhart, T.A., Milner, J.S., Holdsworth, D.W., 2016b. Finite-element analysis of bone stresses on primary impact in a large-animal model: the distal end of the equine third metacarpal. *PLoS One* 11, e0159541.

McCulloch, W.S., Pitts, W., 1943. A logical calculus of the ideas immanent in nervous activity. *The bulletin of mathematical biophysics* 5, 115-133.

MERRITT, J.S., BURVILL, C.R., PANDY, M.G., DAVIES, H.M.S., 2006. Determination of mechanical loading components of the equine metacarpus from measurements of strain during walking. *Equine Veterinary Journal* 38, 440-444.

Merritt, J.S., Pandy, M.G., Brown, N.A., Burvill, C.R., Kawcak, C.E., McIlwraith, C.W., Davies, H.M., 2010. Mechanical loading of the distal end of the third metacarpal bone in horses during walking and trotting. *American journal of veterinary research* 71, 508-514.

Mirzaali, M.J., Schwiedrzik, J.J., Thaiwichai, S., Best, J.P., Michler, J., Zysset, P.K., Wolfram, U., 2016. Mechanical properties of cortical bone and their relationships with age, gender, composition and microindentation properties in the elderly. *Bone* 93, 196-211.

Mirzaei, M., Keshavarzian, M., Naeini, V., 2014. Analysis of strength and failure pattern of human proximal femur using quantitative computed tomography (QCT)-based finite element method. *Bone* 64, 108-114.

Mirzaei, M., Samiezadeh, S., Khodadadi, A., Ghazavi, M.R., Year Finite element prediction and experimental verification of the failure pattern of proximal femur using quantitative computed tomography images. In *Proceedings of the International Conference on Biomechanics and Biomedical Engineering*.

Mitchell, R., Michalski, J., Carbonell, T., 2013. *An artificial intelligence approach*. Springer.

Mohanty, K., Yousefian, O., Karbalaeisadegh, Y., Ulrich, M., Grimal, Q., Muller, M., 2019. Artificial neural network to estimate micro-architectural properties of cortical bone using ultrasonic attenuation: A 2-D numerical study. *Computers in biology and medicine* 114, 103457.

Mouloudi, S., Khojasteh, J., Salehi, M., Mohebbi, S., 2014a. Size dependent free vibration analysis of multicrystalline nanoplates by considering surface effects as well as interface region. *International Journal of Mechanical Sciences* 85, 160-167.

Mouloudi, S., Mohebbi, S., Khojasteh, J., Salehi, M., 2014b. Size-dependent static characteristics of multicrystalline nanoplates by considering surface effects. *International Journal of Mechanical Sciences* 79, 162-167.

Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H., 2019a. Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design. *Comparative Exercise Physiology* 15, 349-358.

Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H., 2019b. Converging-diverging shape configuration of the diaphysis of equine third metacarpal bone through computer-aided design. *Comparative Exercise Physiology*, 1-10.

Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H.M., 2019c. Accuracy Quantification of the Reverse Engineering and High-Order Finite Element Analysis of Equine MC3 Forelimb. *Journal of equine veterinary science* 78, 94-106.

Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H.M., 2019d. Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm. *Biocybernetics and Biomedical Engineering*.

Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H.M., 2020a. Prediction of displacement in the equine third metacarpal bone using a neural network prediction algorithm. *Biocybernetics and Biomedical Engineering* 40, 849-863.

Mouloudi, S., Rahmanpanah, H., Burvill, C., Davies, H.M., 2020b. Prediction of load in a long bone using an artificial neural network prediction algorithm. *Journal of the Mechanical Behavior of Biomedical Materials* 102, 103527.

Muliana, A., Haj-Ali, R.M., Steward, R., Saxena, A., 2002. Artificial neural network and finite element modeling of nanoindentation tests. *Metallurgical and Materials Transactions A* 33, 1939-1947.

Naceur, H., Rahmoun, J., Halgrin, J., Chabrand, P., 2015. Multiscale finite element modelling of ductile damage behaviour of the human femur under dynamic loading. *International Journal of Damage Mechanics* 24, 418-445.

Nie, Z., Jiang, H., Kara, L.B., 2020. Stress field prediction in cantilevered structures using convolutional neural networks. *Journal of Computing and Information Science in Engineering* 20.

Nobakhti, S., Katsamenis, O.L., Zaarour, N., Limbert, G., Thurner, P.J., 2017. Elastic modulus varies along the bovine femur. *Journal of the Mechanical Behavior of Biomedical Materials* 71, 279-285.

Nunamaker, D., Butterweck, D., Provost, M., 1989. Some geometric properties of the third metacarpal bone: a comparison between the thoroughbred and standardbred racehorse. *Journal of Biomechanics* 22, 129-134.

O'Hare, L., Cox, P., Jeffery, N., Singer, E., 2013. Finite element analysis of stress in the equine proximal phalanx. *Equine Veterinary Journal*. 45, 273-277.

Oeser, M., Freitag, S., 2009. Modeling of materials with fading memory using neural networks. *International Journal for Numerical Methods in Engineering* 78, 843-862.

Oishi, A., Yagawa, G., 2017. Computational mechanics enhanced by deep learning. *Computer Methods in Applied Mechanics and Engineering* 327, 327-351.

Ojha, V.K., Abraham, A., Snášel, V., 2017. Metaheuristic design of feedforward neural networks: A review of two decades of research. *Engineering Applications of Artificial Intelligence* 60, 97-116.

Olden, J.D., Jackson, D.A., 2002. Illuminating the “black box”: a randomization approach for understanding variable contributions in artificial neural networks. *Ecological modelling* 154, 135-150.

Olden, J.D., Joy, M.K., Death, R.G., 2004. An accurate comparison of methods for quantifying variable importance in artificial neural networks using simulated data. *Ecological Modelling* 178, 389-397.

Omari, M.A., Almagableh, A., Sevostianov, I., Ashhab, M.d.S., Yaseen, A.B., 2020. Modeling of the viscoelastic properties of thermoset vinyl ester nanocomposite using artificial neural network. *International Journal of Engineering Science* 150, 103242.

Papadopoulos, V., Soimiris, G., Giovanis, D.G., Papadrakakis, M., 2018. A neural network-based surrogate model for carbon nanotubes with geometric nonlinearities. *Computer Methods in Applied Mechanics and Engineering* 328, 411-430.

Parashar, S.K., Sharma, J.K., 2016. A review on application of finite element modelling in bone biomechanics. *Perspectives in Science* 8, 696-698.

Park, G., Kim, T., Forman, J., Panzer, M.B., Crandall, J.R., 2017. Prediction of the structural response of the femoral shaft under dynamic loading using subject-specific finite element models. *Computer Methods in Biomechanics and Biomedical Engineering* 20, 1151-1166.

Parthasarathy, J., Starly, B., Raman, S., 2011. A design for the additive manufacture of functionally graded porous structures with tailored mechanical properties for biomedical applications. *Journal of Manufacturing Processes* 13, 160-170.

Patton, D.M., Bigelow, E.M., Schlecht, S.H., Kohn, D.H., Bredbenner, T.L., Jepsen, K.J., 2019. The relationship between whole bone stiffness and strength is age and sex dependent. *Journal of Biomechanics* 83, 125-133.

Pujol, J.C.F., Pinto, J.M.A., 2011. A neural network approach to fatigue life prediction. *International Journal of Fatigue* 33, 313-322.

Rahmanpanah, H., Mouloudi, S., Burvill, C., Gohari, S., Davies, H.M., 2020. Prediction of load-displacement curve in a complex structure using artificial neural networks: A study on a long bone. *International Journal of Engineering Science* 154, 103319.

Rajan, K., 2005. Materials informatics. *Materials Today* 8, 38-45.

Ramanauskas, R., Kaklauskas, G., Sokolov, A., 2020. Estimating the primary crack spacing of reinforced concrete structures: Predictions by neural network versus the innovative strain compliance approach. *Mechanics of Advanced Materials and Structures*, 1-17.

Rao, H., Mukherjee, A., 1996. Artificial neural networks for predicting the macromechanical behaviour of ceramic-matrix composites. *Computational materials science* 5, 307-322.

Rice, J.C., Cowin, S.C., Bowman, J.A., 1988. On the dependence of the elasticity and strength of cancellous bone on apparent density. *Journal of Biomechanics* 21, 155-168.

Riedmiller, M., 1994. Advanced supervised learning in multi-layer perceptrons—from backpropagation to adaptive learning algorithms. *Computer Standards & Interfaces* 16, 265-278.

Roberts, S., Kusiak, J., Liu, Y., Forcellese, A., Withers, P., 1998. Prediction of damage evolution in forged aluminium metal matrix composites using a neural network approach. *Journal of Materials Processing Technology* 80, 507-512.

Rostedt, M., Ekström, L., Broman, H., Hansson, T., 1998. Axial stiffness of human lumbar motion segments, force dependence. *Journal of Biomechanics* 31, 503-509.

Rumelhart, D.E., Hinton, G.E., Williams, R.J., 1986. Learning representations by back-propagating errors. *nature* 323, 533-536.

Savelberg, H., Van Loon, T., Schamhardt, H., 1997. Ground reaction forces in horses, assessed from hoof wall deformation using artificial neural networks. *Equine Veterinary Journal* 29, 6-8.

Schobesberger, H., Peham, C., 2002. Computerized detection of supporting forelimb lameness in the horse using an artificial neural network. *The Veterinary Journal* 163, 77-84.

Schöllhorn, W., 2004. Applications of artificial neural nets in clinical biomechanics. *Clinical Biomechanics* 19, 876-898.

Sha, W., Edwards, K., 2007. The use of artificial neural networks in materials science based research. *Materials & design* 28, 1747-1752.

Sha, W., Guo, Y., Yuan, Q., Tang, S., Zhang, X., Lu, S., Guo, X., Cao, Y.-C., Cheng, S., 2020. Artificial Intelligence to Power the Future of Materials Science and Engineering. *Advanced Intelligent Systems* 2, 1900143.

Shahar, R., Weiner, S., 2007. Insights into whole bone and tooth function using optical metrology. *Journal of Materials Science* 42, 8919-8933.

Sharir, A., Barak, M.M., Shahar, R., 2008. Whole bone mechanics and mechanical testing. *The Veterinary Journal* 177, 8-17.

Shelburne, K.B., Torry, M.R., Steadman, J.R., Pandy, M.G., 2008. Effects of foot orthoses and valgus bracing on the knee adduction moment and medial joint load during gait. *Clinical biomechanics* 23, 814-821.

Simon, H.A., 1983. Why should machines learn?, *Machine learning*. Elsevier, pp. 25-37.

Sohail, A., Younas, M., Bhatti, Y., Li, Z., Tunç, S., Abid, M., 2019. Analysis of trabecular bone mechanics using machine learning. *Evolutionary Bioinformatics* 15, 1176934318825084.

Starly, B., Fang, Z., Sun, W., Shokoufandeh, A., Regli, W., 2005. Three-dimensional reconstruction for medical-CAD modeling. *Computer-Aided Design and Applications* 2, 431-438.

Stoffel, M., Bamer, F., Markert, B., 2018. Artificial neural networks and intelligent finite elements in non-linear structural mechanics. *Thin-Walled Structures* 131, 102-106.

Suchorski-Tremblay, A., Kok, R., Thomason, J., 2001. Modelling horse hoof cracking with artificial neural networks. *Canadian Biosystems Engineering* 43, 7.15-17.22.

Sun, W., Darling, A., Starly, B., Nam, J., 2004. Computer-aided tissue engineering: overview, scope and challenges. *Biotechnology and applied biochemistry* 39, 29-47.

Sun, W., Lal, P., 2002. Recent development on computer aided tissue engineering—a review. *Computer methods and programs in biomedicine* 67, 85-103.

Sun, W., Starly, B., Nam, J., Darling, A., 2005. Bio-CAD modeling and its applications in computer-aided tissue engineering. *Computer-Aided Design* 37, 1097-1114.

Taddei, F., Cristofolini, L., Martelli, S., Gill, H., Viceconti, M., 2006. Subject-specific finite element models of long bones: an in vitro evaluation of the overall accuracy. *Journal of Biomechanics* 39, 2457-2467.

Taylor, M., Perilli, E., Martelli, S., 2017. Development of a surrogate model based on patient weight, bone mass and geometry to predict femoral neck strains and fracture loads. *Journal of Biomechanics* 55, 121-127.

Thomason, J.J., 1985. The relationship of structure to mechanical function in the third metacarpal bone of the horse, *Equus caballus*. *Canadian Journal of Zoology* 63, 1420-1428.

Ural, A., Zioupos, P., Buchanan, D., Vashishth, D., 2011. The effect of strain rate on fracture toughness of human cortical bone: a finite element study. *Journal of the mechanical behavior of biomedical materials* 4, 1021-1032.

Van Gerven, M., Bohte, S., 2017. Artificial neural networks as models of neural information processing. *Frontiers in Computational Neuroscience* 11, 114.

Vukicevic, A.M., Jovicic, G.R., Jovicic, M.N., Milicevic, V.L., Filipovic, N.D., 2018. Assessment of cortical bone fracture resistance curves by fusing artificial neural networks and linear regression. *Computer methods in biomechanics and biomedical engineering* 21, 169-176.

Waszczyszyn, Z., Ziemiański, L., 2001. Neural networks in mechanics of structures and materials—new results and prospects of applications. *Computers & Structures* 79, 2261-2276.

Wehmöller, M., Warnke, P., Zilian, C., Eufinger, H., Year Implant design and production—a new approach by selective laser melting. In *International Congress Series*.

Wolff, J., 1892. Das gesetz der transformation der knochen. *A Hirshwald* 1, 1-152.

Wolff, J., 2012. The law of bone remodelling. *Springer Science & Business Media*.

Xie, S., Manda, K., Wallace, R.J., Levrero-Florencio, F., Simpson, A.H.R.W., Pankaj, P., 2017. Time Dependent Behaviour of Trabecular Bone at Multiple Load Levels. *Annals of Biomedical Engineering* 45, 1219-1226.

Xu, X., Gupta, N., 2019. Artificial neural network approach to predict the elastic modulus from dynamic mechanical analysis results. *Advanced Theory and Simulations* 2, 1800131.

Yagawa, G., Okuda, H., 1996. Neural networks in computational mechanics. *Archives of Computational Methods in Engineering* 3, 435.

Yoshihara, H., Yoshii, T., Shibutani, T., Maekawa, T., 2012. Topologically robust B-spline surface reconstruction from point clouds using level set methods and iterative geometric fitting algorithms. *Computer Aided Geometric Design* 29, 422-434.

Zadpoor, A.A., 2013. Open forward and inverse problems in theoretical modeling of bone tissue adaptation. *Journal of the mechanical behavior of biomedical materials* 27, 249-261.

Zadpoor, A.A., Campoli, G., Weinans, H., 2013. Neural network prediction of load from the morphology of trabecular bone. *Applied Mathematical Modelling* 37, 5260-5276.

Appendix

This appendix responds to points raised by an external examiner of this thesis, and this appendix addendum is the approach suggested by the external examiner. Chapter subheadings identify the specific chapter associated with the points raised.

Chapter 3

Large population analysis, such as principal component analysis (PCA), is recommended for future studies. This will allow a quantification of the variation of the bone shape population, and the PCA models could be used to help re-create 3D geometries with limited input data. This was not the approach of the study presented in this thesis but could be used in future studies, and could benefit from comparisons with the methodologies developed and used in this thesis.

Chapters 5 to 8

Two bones with a substantial number of data points were used. The bone samples that were used in Chapter 5 was sufficient to successfully predict displacement of the third bone (Chapter 5: Table 1, Figures 14 and 15). The data split into training and testing datasets was done randomly via the ANN. Chapter 8 considered inclusion of more bone samples from different groups of ages to predict displacement among other mechanical variables that were predicted.

Future studies will employ different machine learning approaches, such as multivariable regression, partial least squares, support vector machines, and convolutional neural network to compare the results with the algorithms that were implemented in this thesis.

As stated in this thesis, MC3 long bones have minimal muscle attachments (lacking any muscle or ligamentous attachments for a range around 6-8 cm along its midshaft). However, other long bones have many soft tissues that are attached to the main bone. A comprehensive investigation into the interaction between muscle attachments and the bone is extremely challenging. Similar machine learning algorithms developed in this thesis have the potential to be implemented on ex-vivo and in-vivo experimental data collected on other long bones. However, rich datasets are required to be gathered: when soft tissues are attached to the main bone, and when these soft tissues are removed from the bone. This approach allows the algorithm to discover the patterns and to make reliable distinctions between these two scenarios.

The noise injected to the ANNs performed in this study was sampled from Gaussian distribution (a certain probability distribution, also referred to as white noise), which is a common noise source with which ANN input variables can be successfully trained and generalized. Little noise has no effect, whereas too much noise makes the mapping function too challenging for the ANN to learn (Chapter 8, Figure 15).

Data pre-processing completed in this thesis (for example, data normalization) did not adversely impact the practical usefulness of the implemented ANN models. The research reported in the thesis found that machine learning approaches that use more raw data are easier

to translate to practice. However, in some practices the gathered data are related to different measurements and thus vary across a wide range of values and units. In such scenarios having a uniform scale among the input variables and hence data-normalization helps in enhancing the performance of neural networks.

The experimental setup measured mechanical responses of MC3 bones (including vertical displacement of MC3 long bones along its anatomical axis) under compression loading. As such, this component of displacement was obtained using FEA. This was introduced and discussed in Chapter 5.