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A probabilistic approach for modelling bone fracture healing under Ilizarov circular fixator

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Abstract

Bone fracture treatments using Ilizarov circular fixator (ICF) involve dealing with uncertainties about a range of critical factors that control the mechanical microenvironment of the fracture site such as ICF configuration, fracture gap size, physiological loading etc. To date, the effects of the uncertainties about these critical factors on the mechanical microenvironment of the fracture site have not been fully understood. The purpose of this study is to tackle this challenge by using computational modelling in conjunction with engineering reliability analysis. Particularly, the effects of uncertainties in fracture gap size (GS), level of weight-bearing (P), ICF wire pretension (T) and wire diameter (WD) on the fracture site mechanical microenvironment at the beginning of the reparative phase of healing was investigated in this study. The results show that the mechanical microenvironment of fracture site stabilised with ICF is very sensitive to the uncertainties in P and GS. For example, an increase in the coefficient of variation of P (COV_P) from 0.1 to 0.9 (i.e. an increase in the uncertainty in P) could reduce the probability of achieving a favourable mechanical microenvironment within the fracture site (i.e. Probability of Success, PoS) by more than 50%, while an increase in the coefficient of variation of GS (COV_{GS}) from 0.1 to 0.9 could decrease PoS by around 30%. In contrast, an increase in the uncertainties in T and WD (COV increase from 0.1 to 0.9) has little influence on the fracture site mechanical microenvironment (PoS changes < 5 %).

Keywords: Biomechanics; engineering reliability; deviatoric tissue strain; mechanical microenvironment, porous media theory, treatment planning

1. Introduction

Treating bone fractures involves dealing with uncertainties in biological factors [1, 2], fracture geometry [3, 4], fixation configuration [2] and loading conditions [1, 5] that affect the healing process [2, 3, 6-9]. Such uncertainties could significantly influence the healing progression and ultimately affect the healing outcome. While it may be preferable to minimize the uncertainties associated with such factors, doing so may not always be possible. Therefore, it is essential to consider the uncertainties associated with such factors to determine the reliability of fracture treatment strategies. As fracture treatments usually focus on maintaining a suitable mechanical microenvironment at the fracture site to best utilize the intrinsic biological healing capacity of bones [10, 11], it is of prime importance to consider the uncertainties associated with mechanical factors in fracture treatments.

The objective of fracture treatment is restoring functionality (e.g. weight-bearing in lower extremities) of the fractured bone as early as possible. Traditionally, most fractures are treated with plaster casts by stabilizing fractures and minimizing disturbance to the fracture site [12]. However, plaster casts may not always be suitable to treat all types of fractures. With the advancements in orthopaedic surgery, several internal and external bone fixation devices have come into existence [13, 14]. Internal fixation devices (e.g. locking compression plates) usually require complex surgical procedures as they are mounted inside patients' bodies. Besides, they are less flexible in terms of post-surgical alterations. External fixation devices are advantageous in this regard as they are minimally invasive and adjustable post-surgically depending on the progress of healing.

Ilizarov circular fixator (ICF) (Fig. 1) is one such external device that has been used by orthopaedic surgeons in treating a variety of bone defects [15]. It is a modular fixation device which provides flexibility to surgeons in tailoring the fixation configuration on a case-by-case basis. However, when treating fractures using ICF, it may be necessary to deal with a higher degree of uncertainty about the mechanical microenvironment at the fracture site due to several reasons. Firstly, ICFs are affixed to bones using fine pre-tensioned wires which exhibit nonlinear stiffness behaviour [16] and ICF stiffness could be influenced by the level of weight-bearing which itself is an uncertain factor. Secondly, pretension loss and loosening of wires is a common problem associated with ICFs which leads to uncertainties in fixation rigidity [16, 17]. Moreover, being a modular external fixation could potentially lead to uncertainties in the configuration of ICF. These uncertainties in turn lead to uncertainties in predicting the

mechanical behaviour of ICFs and the mechanical microenvironment of fracture sites stabilised with ICFs.

To understand the effects of such uncertainties on fracture healing, it is necessary to have a deeper understanding of the fracture healing process. In general, most fractures heal by secondary healing which involves the formation of fracture callus [18, 19]. It follows a characteristic course which involves three phases: inflammation, repair and remodelling [20]. Secondary healing begins with the formation of a haematoma at the fracture site as a result of rupture of blood vessels which initiates the inflammation phase. Hypoxic conditions within the fracture site due to lack of blood supply leads to bone death and release of angiogenic factors that induce the formation of new blood vessels from existing ones [20]. Subsequently, the haematoma is transformed into granulation tissue which forms the early callus. This callus acts as an early scaffold at the fracture site and provides a suitable environment for cell migration, proliferation, differentiation and tissue synthesis to facilitate the fracture repair process [19]. During the repair phase, various types of tissues are formed within the callus depending on the local mechanical and biological microenvironments. In regions with adequate blood supply and higher local tissue strains, fibrous tissue prevails [21]. Bone tissue is directly formed in regions with adequate blood supply and lower tissue strains [21]. Whereas cartilage tissue is formed in avascular regions with low blood supply and subsequently transformed into bone tissue as the conditions become favourable for bone tissue formation [21]. The latter is the predominant form of bone formation in secondary healing [18]. In the remodelling phase, the immature bone tissue formed during the repair process is transformed into lamellar bone to restore the shape and strength of the bone [20].

Clearly, the local tissue strain and the level of blood supply influence the tissue differentiation process during bone repair. Therefore, it is essential to ensure that both these factors remain favourable for timely fracture repair. It should be noted that local tissue strain does not just directly influence the tissue differentiation process. It can also influence the tissue differentiation process indirectly by affecting angiogenesis (i.e. formation of new blood vessels) during the repair process. Relatively higher tissue strains lead to rupture of blood vessels and hinder the angiogenesis process [21]. Therefore, the local tissue strains should be small enough not to inhibit angiogenesis. Moreover, relatively smaller tissue strains are beneficial for bone tissue synthesis as well [22, 23]. However, tissue strains that are too low could lead to bone resorption, compromised bone quality and delayed healing [21-23].

Therefore, the tissue strains should be neither too low nor too high to have a favourable mechanical microenvironment within the fracture site.

The local tissue strains within the callus resulting from weight-bearing must be maintained within this range for timely fracture repair. Since the fracture callus goes through changes during the healing process, it will be necessary that the weight-bearing protocols are chosen such that the mechanical microenvironment within the fracture callus remains favourable for healing throughout the healing process. This requires a deeper understanding of the temporal changes that take place within the callus as healing moves through inflammation, repair and remodelling phases.

Vetter et al. [24], demonstrated that secondary healing goes through six different stages (stage I-VI) based on the tissue distribution patterns observed within the callus in an experimental study on sheep long bone osteotomies (Fig. 2). As per Vetter et al. [24], stage I of secondary healing represents the late inflammatory phase where remnants of haematoma are present in callus. Stage II corresponds to the early reparative phase of healing where neither remnants of haematoma nor cartilage tissues are observed within the callus. By the end of stage II, the internal callus (i.e. cortical and endosteal callus) and the region at the level of osteotomy gap in the external callus (periosteal callus) are filled fully with remnants of haematoma indicating no repair within these regions. Stage III marks the reparative phase where bone formation within the fracture gap, cartilage formation and subsequent periosteal bridging occurs. This is also the stage when endochondral ossification begins. In stage IV, periosteal bony bridging between the proximal and distal parts of the fracture callus occurs and in stage V endosteal bony bridging between medial and lateral parts of the callus occurs. Finally, stage VI corresponds to the remodelling phase where the newly formed bone is transformed into lamellar bone.

In each of these stages, maintaining a favourable mechanical microenvironment within the fracture site requires careful controlling of the interfragmentary strain (IFS). IFS results from interfragmentary movement (IFM) and influences the local mechanical microenvironment within the fracture site [12]. Thus, the mechanobiology of bone healing is sensitive to IFS. IFS depends on several factors including fracture gap size, external loading (e.g. weight-bearing), type and mechanical properties of the fixation used, fixation configuration and bone quality [6, 25-28]. Any of these factors could influence IFS and change the fate of bone healing. Among these factors, IFS is highly sensitive to fracture gap size and external loading [6, 25].

Uncertainties in these mechanical variables could have profound effects on the mechanical microenvironment of the fracture site. Notably, these are also variables that are subjected to significant levels of uncertainty [6]. These uncertainties combined with the inherent uncertainties in ICFs make it difficult to predict if fractures treated with ICFs result in favourable mechanical microenvironments within the fracture site or not.

It is possible to quantitatively estimate the level of uncertainties in ICF treatments in achieving favourable mechanical microenvironments within the fracture site. This requires systematic parametric investigations into fracture healing under controlled environments which can be achieved using validated computational models. However, most of the existing computational studies on fracture healing [8, 25, 29-34] including those relevant to ICFs [35-37] have neglected the uncertainties associated with such factors and taken deterministic approaches.

This study takes a probabilistic approach to address this problem. Probabilistic methods have been used in several engineering applications (e.g. structural reliability of infrastructure facilities) in the past [38, 39]. Recently, probabilistic approaches have been used in the field of orthopaedics to design new orthopaedic components and assess the structural reliability of orthopaedic constructs [40-43]. However, no studies so far have incorporated probabilistic methods to investigate the effects of uncertainties in mechanical variables on the mechanical microenvironment of the fracture sites stabilised with ICFs.

In this study, a sheep fracture model is taken as an example and the uncertainties associated with fracture gap size (GS), axial loading resulting from weight-bearing (P) and ICF configuration are considered. It should be noted that GS in this study refers to the fracture gap size under unloaded condition (i.e. non-weight-bearing condition) which is intended to be achieved by the fracture reduction surgery. Therefore, GS will have a fixed target value (e.g. 3 mm) at the time of surgery. However, there could be deviations from this target value due to reasons such as imperfect fracture reduction [6]. In other words, uncertainties exist in achieving the target GS. On the other hand, uncertainties regarding loading (P) may arise from patients' noncompliance to the post-surgical clinical weight-bearing instructions [44]. This may be partially due to patients' difficulties in controlling the loading exerted on the injured limb.

Regarding ICF configuration, wire pretension level (T) and wire diameter (WD) were considered in this study as these are important sources of uncertainty in ICF. It should be noted that T and WD refer to the wire pre-tension that is intended to be achieved and the wire diameter that is intended to be used, respectively at the time of surgery. Therefore, both T and WD will

have a fixed target value (e.g. $T = 1275$ N and $WD = 1.8$ mm) at the time of surgery. However, there could be deviations from these target values due to various reasons such as loss of pretension, wire manufacturers tolerances, stretching of wires etc. In other words, uncertainties exist in achieving the target T and WD .

This study investigates how the probability of achieving favourable mechanical microenvironment for fracture healing (i.e. Probability of Success, PoS) within the fracture site (i.e. callus) changes with the level uncertainties in GS , P , T and WD . It should be noted that weight-bearing could have inhibitory effects on angiogenesis and fracture healing during the very early stages of healing when the callus is filled with haematoma and/or very soft tissue [6, 45, 46]. In the subsequent stages, weight-bearing could commence depending on the progress of healing. Since this study considers axial loading resulting from weight-bearing (P), the focus was on the stages of healing where partial weight-bearing is allowed (post-early stages). According to the healing stages of Vetter et al. [24], angiogenesis and bone formation are critically important in stage III. It is essential to promote angiogenesis while minimizing bone resorption during this stage. To achieve this, partial weight-bearing in a controlled manner is necessary at this stage. If the mechanical microenvironment at the fracture site is unfavourable during this stage, the fracture repair process and the weight-bearing capacity could be hindered. Besides, it could delay the subsequent stages of healing (stage IV-VI) as well. Therefore, how PoS within the callus changes with the uncertainties in GS , P , T and WD , was investigated at the beginning of stage III (reparative phase) in this study.

2. Materials and Methods

The time point at which stage III (reparative phase) of healing begins depends on several subject-specific factors [24]. In this study, GS , T and WD are variables that are fixed at the time of surgery as described before. These variables could affect the rate of healing progression and the time taken to reach stage III. For example, a fracture with a smaller gap size may reach stage III of healing faster than that with a larger gap size when other conditions are identical. Besides, differences in healing rates could even result from differences in subject-specific factors which is evident from the sheep experiment of Vetter et al. [24]. Therefore, this analysis focuses on a specific point in the healing pathway rather than a specific point in time during healing. The inherent assumption in this analysis is that the 'healing pathway' as defined by the succession of healing stages remains unchanged and the differences in variables (i.e. GS , P , T and WD) only alter the speed at which the healing path is followed [24].

2.1 Computational simulations

A 3-D computational model was used in conjunction with the principles of engineering reliability analysis as shown in Fig. 3 to carry out the investigation. The model represents the beginning of stage III of healing of a transverse mid diaphyseal metatarsal sheep fracture of 3 mm gap size stabilized with a four ring ICF (Fig. 1). This model was developed by modifying our previous model which was developed to simulate fracture healing under various configurations of ICF and validated with experimental data [35-37]. The ICF construct used in the present study consisted of four identical rings of 80 mm internal diameter (two rings per fragment), eight stainless steel pretension wires (two mutually perpendicular wires per ring) and four 4.69 mm diameter rods connecting the rings as shown in Fig. 1. The metatarsal bone fragments were modelled as hollow cylinders with 12 and 16 mm inner and outer diameters, respectively and the fracture callus was assumed to have a maximum diameter of 32 mm (Fig.1). All the ICF components were assumed to be made of stainless steel and modelled as linear elastic material while the tissues including callus were modelled as poroelastic materials. The bone-ICF contact interfaces were modelled using continuous solid-to-solid connections.

Based on the theory of porous media, the stress tensor of the tissue, momentum equation and continuity of solid and fluid phases can be expressed by Eq.1, Eq.2 and Eq.3, respectively [47-51].

$$\boldsymbol{\sigma} = -p\mathbf{I} + \boldsymbol{\sigma}^e \quad (1)$$

$$\nabla \cdot \boldsymbol{\sigma} = -\nabla p + \nabla \cdot \boldsymbol{\sigma}^e = \mathbf{0} \quad (2)$$

$$\nabla \cdot (\mathbf{v}^s - \mathbf{k}\nabla p) = 0 \quad (3)$$

In the above equations, $\boldsymbol{\sigma}$ is the stress tensor of the tissue, p is the incremental interstitial fluid pressure, $\mathbf{I}$ is an identity matrix, $\boldsymbol{\sigma}^e$ is the elastic stress of solid matrix, $\mathbf{v}^s$ is the velocity of the solid phase and $\mathbf{k}$ is the tissue permeability tensor.

The external boundaries of the poroelastic tissues were assumed to be impermeable to fluid flow in the model. The pretension in the wires was applied as initial stress along their axial direction and weight-bearing was simulated by applying axial compression on the top end of the proximal fragment while keeping the bottom end of the distal fragment fixed (Fig.1). The

entire geometry was meshed using second-order tetrahedral elements to numerically solve the model. All the simulations in this study were carried out using the finite element software package COMSOL Multiphysics v 5.3a (COMSOL AB, Stockholm, Sweden). Further details about the model are available in our previous works [35-37].

Most of the material properties used the model were directly obtained from the literature. However, the Young's Modulus of the callus at the beginning of stage III was not readily available in the literature; hence it had to be estimated. Vetter et al. [24] reported that 3 mm sheep osteotomies stabilized using external fixations of various rigidities marked the beginning of stage III on average on the fourth-week post osteotomy. Therefore, it was assumed that stage III of healing for 3 mm sheep fractures stabilized with external fixators begin on the fourth-week post-fracture as reported in Vetter et al. [24]. In an experimental study, Claes et al. [6] reported temporal IFM changes at transverse mid diaphyseal metatarsal sheep osteotomies of 3 mm gap size stabilized with an external ring fixator. We obtained the IFM measured on the fourth week (beginning of stage III) from Claes et al. [6] and used our model to estimate the average Young's modulus of the callus at the beginning of stage III based on this IFM. This approach has been used by computational studies on fracture healing elsewhere [52, 53]. On a trial and error basis, we varied Young's modulus of the callus until the model produced the same IFM (week 4) reported by Claes et al. [6] under conditions similar to their experiment (e.g. loading, geometry etc.). Thus, we estimated an indicative value of the average Young's modulus of the callus at the beginning of stage III. In the absence of experimental data for Young's modulus of the callus at the beginning of stage III, we assumed that it is reasonable to use our estimate in this study. The material properties used in the model are summarised in Table 1.

2.2 Reliability analysis

Reliability analysis was carried out to investigate how the PoS changes within different zones of fracture callus. In structural engineering, reliability analysis is a common technique used to investigate the structural reliability of infrastructure facilities. The principle behind this approach is that there are uncertainties regarding the load acting on a structure and the resistance of it. The probability of failure of a structure is defined as the probability of loading exceeding its resistance (i.e. the probability of achieving inadequate resistance). This could be calculated by plotting the probability density functions of both loading and resistance and calculating the area of overlap.

In the context of this study, the probability of failure at a given location in the callus can be defined as the probability of the callus zone failing to achieve a favourable mechanical microenvironment at that location. This can result from inadequate or excessive deviatoric tissue strains which can lead to bone resorption and angiogenesis inhibition, respectively. Since the local deviatoric tissue strain distribution could be inhomogeneous within the callus, the present investigation was conducted within the periosteal, cortical and endosteal zones of the callus separately considering their average tissue strains. Therefore, the probability of failure (PoF) in a callus zone in this study is defined as the probability of the average deviatoric tissue strain (ε) within the callus zone falling outside the deviatoric tissue strain limits for bone resorption (lower bound) and angiogenesis inhibition (upper bound).

On the other hand, The ‘Probability of Success (PoS)’ or in other words, ‘the probability of achieving favourable mechanical microenvironment for fracture healing’ within a callus zone was defined as the probability of average deviatoric tissue strain (ε) within the callus zone lying between the deviatoric tissue strain limits for bone resorption (lower bound) and angiogenesis inhibition (upper bound). The deviatoric tissue threshold for bone resorption (ε_{res}) and the deviatoric tissue strain threshold for angiogenesis inhibition (ε_{ang}) were taken as 0.005 % and 6 %, respectively based on the mechanobiological model of Burke and Kelly [21]. Therefore, $PoF = P(\varepsilon < 0.005 \%) + P(\varepsilon > 6 \%)$ and $PoS = P(0.005 \% \leq \varepsilon \leq 6 \%)$ in any callus zone.

To calculate the PoS in each callus zone, the probability density function (PDF) of average deviatoric tissue strain (ε) in each callus zone is required. As the average tissue strain (ε) depends on GS, P, T and WD, it could be described as follows:

$$\varepsilon = f(GS, P, T, WD) \quad (4)$$

In this function, it is reasonable to assume that GS, P, T and WD are independent variables as their values are not correlated. For example, there is no correlation between the load exerted by patient post-surgery and the gap size (GS) or fixation configuration (T,WD) which were set at the time of surgery as described before. Furthermore, GS, P, T and WD were assumed to be normally distributed with their means equal to their target values [9]. This assumption was based on the idea that treatments strive to achieve the target values of the variables, but the achieved values may differ from the target values and be lower or higher than the target values. Since most fractures heal without complications, it is reasonable to say that the achieved values of the variables are closer to the target values most of the time and relatively larger deviations

are not very common. Considering these aspects, it is reasonable to assume the distribution of the variables to be normal [9]. To approach this problem, let's consider a dependent variable X defined as follows:

$$X = g(X_1, X_2, X_3, \dots, X_n) \quad (5)$$

where, $X_1, X_2, X_3, \dots, X_n$ are random variables. By Taylor series expansion, the mean and standard deviation of X (i.e. μ_X and σ_X) could be expressed as

$$\mu_X \approx g(\mu_{X1}, \mu_{X2}, \mu_{X3}, \dots, \mu_{Xn}) \quad (6)$$

$$\sigma_X \approx \sqrt{\sum_{i=1}^n \sum_{j=1}^n \frac{\partial g}{\partial X_i} \frac{\partial g}{\partial X_j} Cov(X_i, X_j)} \quad (7)$$

where, $\mu_{X1}, \mu_{X2}, \mu_{X3}, \dots, \mu_{Xn}$ are means of $X_1, X_2, X_3, \dots, X_n$, respectively and $Cov(X_i, X_j)$ is the covariance of X_i and X_j . If X is linearly related to $X_1, X_2, X_3, \dots, X_n$, this relationship could be expressed by Eq. 8 and μ_X could be expressed by Eq. 9.

$$X = a_0 + a_1X_1 + a_2X_2 + a_3X_3, \dots + a_nX_n \quad (8)$$

$$\mu_X = a_0 + a_1\mu_{X1} + a_2\mu_{X2} + a_3\mu_{X3} + \dots + a_n\mu_{Xn} \quad (9)$$

In Eqs. 8 and 9, $a_0, a_1, a_2, \dots, a_n$ are constants. If the variables $X_1, X_2, X_3, \dots, X_n$ are independent, σ_X could be expressed as

$$\sigma_X = \sqrt{(a_1\sigma_{X1})^2 + (a_2\sigma_{X2})^2 + (a_3\sigma_{X3})^2 + \dots + (a_n\sigma_{Xn})^2} \quad (10)$$

The unknown constants $a_0, a_1, a_2, \dots, a_n$ could be determined from a regression analysis. Once μ_X and σ_X are known the probability of different ranges of X could be calculated by considering the PDF of X . For a given set of values for the independent variables $X_1, X_2, X_3, \dots, X_n$, the effect of uncertainty (variability) in any specific variable (say $X_i ; i \leq n$) on the probability of X falling within a specific range could be studied by considering the variability of only that variable (X_i) while keeping others constant at their given values. In such

cases, if the variable considered (i.e. X_i) is normally distributed, the distribution of X will also be normal.

2.3 Parametric studies

In the investigation, first, the model was used to determine a combination GS, P, T and WD that would result in favourable mechanical microenvironments within all three zones of the callus. In other words, the model was used to identify a combination of GS, P, T and WD that would cause average deviatoric tissue strains in each callus zone to fall between the deviatoric tissue strain limits for bone resorption (lower bound) and angiogenesis inhibition (upper bound). We used a GS of 3 mm and the fixation configurations parameters T and WD were set to be 130 kg and 1.8 mm, respectively based on commonly used clinical configurations [54]. Under these values of GS, T and WD, we found from the model that $P = 150$ N would result in favourable mechanical microenvironments within all three zones of the callus. Hence, this combination (i.e. GS = 3 mm; $P = 150$ N; T = 130 kg; WD = 1.8 mm) would give a PoS of 100 % in the analysis. These values were assumed as the target values of the variables in the analysis. Therefore, as mentioned before, the variables (GS, P, T and WD) were assumed to be normally distributed with their means equal to their target values.

Starting with all four variables (GS, P, T and WD) set to their mean (i.e. target) values, we considered one variable at a time and solved the model under various values of the variable while keeping the remaining three variables at their mean values. In each case, the average deviatoric tissue strains (ε) within the periosteal, endosteal and cortical zones were calculated separately. Based on the simulation results, the average deviatoric tissue strain vs GS, average deviatoric tissue strain vs P, average deviatoric tissue strain vs T and average deviatoric tissue strain vs WD in each callus zone were plotted separately. A regression analysis was carried out based on the plots to determine the unknown constants (in Eq.8) using Microsoft Excel 365 (Microsoft Corp., Washington, USA). Subsequently, reliability analysis was carried out.

We could say that the mean value of GS (μ_{GS}) is 3 mm and the standard deviation of GS (σ_{GS}) is equal to $COV_{GS} \times \mu_{GS}$, where COV_{GS} is the coefficient of variation of GS. Similarly, the mean value of P (μ_P) = 150 N, the mean value of T (μ_T) = 130 kg and the mean value of WD (μ_{WD}) = 1.8 mm. The standard deviation of P (σ_P) = $COV_P \times \mu_P$, the standard deviation of T (σ_T) = $COV_T \times \mu_T$ and the standard deviation of WD (σ_{WD}) = $COV_{WD} \times \mu_{WD}$, where COV_P , COV_T and COV_{WD} are the coefficients of variation of P, T and WD, respectively. Therefore, if a coefficient of variation (COV) is assumed for a variable, the standard deviation of the variable

can be calculated and the normal distribution curve of the variable can be established. We can then work out the PoS based on these distributions. Thus, the level of uncertainty of each variable was accounted for in the analysis by their respective coefficient of variations. The means and the coefficient of variation used for each variable in this study are summarised in Table 2.

3. Results

3.1 Regression analysis

Figure 4 shows how the average deviatoric tissue strains predicted within periosteal, cortical and endosteal callus zones vary with each variable while the others are set to their mean values. Then the least square curve fitting was used to determine the relationship between average tissue strain and the independent variables within each callus zone (Table 3). As we can observe from the model results (Fig. 4), all four variables exhibited a linear relationship with the average deviatoric tissue strain within all three regions. This is interesting as ICFs tend to exhibit non-linear stiffness behaviour due to pretension wires. However, as reported in several studies elsewhere [55-58], ICFs usually behave linearly under relatively smaller loading ranges and non-linear behaviour becomes observable when relatively larger loads are applied. Since the present study deals with relatively smaller loading levels due to partial weight-bearing, it is reasonable that ICF exhibited a more linear stiffness behaviour.

It was noted that the average tissue strain within the cortical zone was always the highest and that of the periosteal zone was always the lowest under all cases. Out of the four variables, the axial load resulting from weight-bearing (P) was the most influential parameter at the beginning of stage III (reparative phase) of secondary healing. This is evident from the relatively steeper slopes of lines seen in Fig.4b. Particularly, a relatively strong positive correlation between the average tissue strain and P was predicted within the cortical zone. Furthermore, positive correlations between P and average tissue strain were seen within the endosteal and periosteal zones as well.

The correlation between average tissue strain and GS was predicted to be negative within the cortical zone but positive in the other two regions. On the other hand, a weak negative correlation between the average tissue strain and the ICF configuration parameters (i.e. T and WD) was predicted within the cortical zone. However, no significant changes (very weak negative correlation) were predicted in average tissue strains in response to variabilities in T or

WD within the periosteal or endosteal zones of the callus. As the correlations between the average tissue strain and independent variables (i.e. GS, P, T and WD) in all three regions of the callus are linear, the average tissue strain ε could be expressed as

$$\varepsilon = a_0 + a_{GS} \times GS + a_P \times P + a_T \times T + a_{WD} \times WD \quad (11)$$

Based on the results (Fig. 4), the unknowns a_0 , a_{GS} , a_P , a_T and a_{WD} were determined by regression analysis and the equations for ε in each callus zone were obtained as follows:

Periosteal zone:

$$\varepsilon = -0.1588 + 0.1204 \times GS + 0.0053 \times P - 0.0006 \times T - 0.0691 \times WD \quad (12)$$

Cortical zone:

$$\varepsilon = 3.2218 - 0.7000 \times GS + 0.0329 \times P - 0.0039 \times T - 0.3118 \times WD \quad (13)$$

Endosteal zone:

$$\varepsilon = 0.0069 + 0.1071 \times GS + 0.0091 \times P - 0.0011 \times T - 0.1068 \times WD \quad (14)$$

3.2 Reliability analysis

The PoS within each callus zone was calculated by considering the probability density function of the average deviatoric tissue strain (ε) based on Eqs. 12-14. Since each variable was assumed to be normally distributed and considered one by one in the analysis, ε will also be normally distributed. Therefore, the PoS in each callus zone can be calculated as

$$\text{PoS} = P(0.005\% \leq \varepsilon \leq 6\%) = \phi(6\%) - \phi(0.005\%) \quad (15)$$

where ϕ is the standard normal cumulative density function (CDF) of ε .

Taking weight-bearing (P) as an example, the process of calculating the PoS within the periosteal, cortical and endosteal zones of the callus under different COV_P values are shown in Fig. 5, Fig. 6 and Fig. 7, respectively. For the mean (μ_P) and each value of COV_P , the corresponding mean (μ_ε) and standard deviation (σ_ε) of ε are calculated using Eq. 9 and Eq. 10, respectively and the PoS is calculated using Eq. 15. It can be seen that PoS within each

callus zone changes differently as the level of uncertainty in P changes. Similarly, PoS within each callus zone were calculated under different values of COV_{GS} , COV_T and COV_{WD} . Subsequently, the variation of PoS with COV for each variable were plotted as shown in Fig.8.

It can be seen from Fig.8 that PoS within all callus zones tends to fall with the increase of the degree of uncertainty in variables. However, the changes within the periosteal and endosteal zones are not significant except due to uncertainties in axial load (P) where the PoS decreased from 100 % to 86 % as COV_P increased from 0.1 to 0.9. The PoS within periosteal and endosteal zones were insensitive to variabilities in GS, T and WD. The changes in PoS were most significant within the cortical zone of the callus where the PoS decreased from 100 % to 46 %, 100 % to 70 % and 100 % to 95 % in response to COV increase from 0.1 to 0.9 for P, GS and WD, respectively. However, no noticeable changes in PoS were predicted due to uncertainties in T.

4 Discussion

In this study, computational modelling was used in conjunction with engineering reliability techniques to investigate how the level of uncertainties in mechanical variables affect the mechanical microenvironment of fracture sites stabilised with ICFs. Unlike most of the existing computational studies on fracture healing which have taken deterministic approaches, this study has taken a probabilistic approach to solve the problem in hand.

IFS plays an important role in the mechanobiology of fracture healing by influencing callus development, angiogenesis and tissue differentiation [20]. It is known that angiogenesis is a prerequisite for successful healing and inhibition to this process could lead to unfavourable healing conditions [59]. Therefore, the fracture site needs to be prevented from excessive IFS which can cause rupture of vessels and inhibition of angiogenesis [20]. On the other hand, relatively smaller IFSs are conducive to direct bone formation but too little IFS at the fracture site can give rise to bone resorption and compromise the quality of bone [22]. Therefore, the success of healing relies on achieving a balance between these two extremities. Accordingly, favourable mechanical microenvironment for fracture healing was assumed to occur when the deviatoric tissue strains within the callus are between the limits for bone resorption (lower bound) and angiogenesis inhibition (upper bound). This assumption was used to calculate the Probability of Success (PoS) under different levels of uncertainties associated with mechanical variables. Although there are a plethora of uncertain variables that could influence fracture

healing under ICF, only some of the most uncertain and influential variables (i.e. GS, P, T and WD) were considered in this study.

Considering the ICF configuration-specific variables, T and WD were chosen in this study for two reasons. Firstly, wires are the invasive elements of ICF which connect the bone fragments to ICF and controls IFS at the fracture site. Secondly, a higher degree of uncertainty exists regarding T and WD. It has been reported that wires could lose pretension due to several reasons such as slippage, yielding etc. [17]. Besides, the accuracy of wire tensioners is also a source of uncertainty as errors as high as 37 % have been reported with commercially available wire tensioners [60]. Furthermore, there is uncertainty about the effective diameter of wires used due to manufacturing tolerances and stretching (tensioning) of wires. Also, there is a chance of using different diameter wires than those intended due to the unavailability of specific diameter wires. Since there are wires of several diameters within the small range of 0.7 – 2.0 mm [61, 62], it is also possible to inadvertently use a different diameter wire as the differences in their diameters are difficult to perceive without high precision measurement.

The present investigation was conducted at the beginning of stage III (reparative phase) which refers to the stage when bone formation within the fracture gap, periosteal bridging and endochondral ossification begins [24]. However, there is uncertainty about the time at which this stage is reached as the rate of healing depends on numerous subject-specific factors. In this study, this problem was tackled by focusing on a specific point in the healing pathway rather than a specific point in time. Thus, this analysis inherently assumes that the healing pathway remains the same for all cases and the differences in subject-specific variables only alter the rate at which the pathway is followed, which is reasonable [24].

Several mechanobiological models that describe fracture healing have been proposed so far [21, 23, 25]. Mechanobiological models generally involve one or more mechanical stimuli (e.g. deviatoric tissue strain, IFS etc.) and specify threshold values of them for differentiation and/or degradation of the various tissues involved in fracture healing. In this study, the threshold deviatoric tissue strains were obtained from the model of Burke and Kelly [21]. These thresholds specify the deviatoric tissue strain interval in which the mechanical microenvironment becomes favourable for healing. It should however be noted that some deviatoric strains within this interval might be more favourable and lead to faster healing than the others. It should also be noted that changes in the threshold tissue strain values could significantly change the results. A sensitivity analysis on the effect of changing various

threshold values including the deviatoric tissue strain threshold for angiogenesis inhibition (ϵ_{ang}) on healing is presented in the study of Burke and Kelly [21].

Previous studies focusing on the very early stage of healing under ICF [36, 37] have suggested that the fracture site mechanical microenvironment is more sensitive to fracture gap size (GS) than axial loading (P). Interestingly, the findings of this study suggest that the fracture site is more sensitive to P than GS at the beginning of stage III of secondary healing. In fact, out of the four variables considered in this study (i.e. GS, P, T and WD), PoS at the beginning of stage III was most sensitive to axial loading (P). This suggests that the sensitivity of the fracture site mechanical microenvironment to mechanical variables could vary as healing progresses from one stage to the other. GS is regarded as the most critical mechanical variable in the early stages of healing under ICF when the callus is very soft [6, 25, 36, 37]; whereas, P could become the most critical variable as callus stiffens and starts to attract more load.

This phenomenon could be explained by the study of Prat et al. [63], which investigated into load transmission in fracture sites stabilized with circular external fixators during different stages of healing. The study [63] involved both theoretical and experimental investigations using a rabbit model. Their study demonstrated that when healing moves from early stages to subsequent stages and callus achieves some nominal mechanical stiffness, drastic change in the load share between the fixator and callus would occur (under fixed loading). In the early stages of healing, almost all the applied load is supported by the fixation. This condition reverses to callus taking nearly 85 % of the applied load as callus stiffness increases to just below 1 % of that of intact bone which can occur relatively early during healing [63]. This explains why the fracture site becomes more sensitive to axial loading (P) as healing moves from early-stage to subsequent stages. This has an important clinical implication as post-operative weight-bearing exercises need to be carefully designed considering this fact and patients need to strictly adhere to clinical recommendations as PoS is most sensitive to P during the reparative phase.

An important challenge here is that the degree of uncertainty about the level of weight-bearing is relatively high as patients cannot precisely control how much weight is borne by the fractured bone. For example, in sheep, up to 110 % of the body weight may be borne by metatarsal bones during normal walking [64]. However, the recommended level of weight-bearing at the beginning of the reparative phase could be around 20 % of the bodyweight [27]. The results of this study showed a relatively strong positive correlation between P and average deviatoric tissue strains within callus zones (Fig. 4b). PoS decreased from 100 % to 46 % within the

cortical zone with COV_P increased from 0 to 0.9 (Fig. 8b) and it could reduce further if the degree of uncertainty about P increased further, which is suggestive of potential failure of healing.

Gap size (GS) was predicted to be negatively correlated to the average deviatoric tissue strain within the cortical zone (Fig. 4a). This prediction is consistent with Perren [12] who explained that cells within smaller fracture gaps are subjected to increased mechanical stimuli when compared to those within larger fracture gap sizes. However, this does not suggest that larger gap sizes are preferable over smaller gap sizes as larger gap sizes could lead to relatively high IFSs in the early stages and delay the healing process [6]. It could be noticed from Fig. 4a that GS is positively correlated to the average deviatoric tissue strain within the periosteal zone. Although periosteal callus is not very sensitive to GS at the beginning of stage III, it will be very sensitive to GS in the early stages of healing as reported by Ganadhepan et al. [37]. Since secondary healing relies on periosteal stabilization of the fracture site, conducive mechanical environments to healing must be maintained within the periosteal callus during the early stages. Therefore, larger gap sizes which give rise to higher tissue strains within the periosteal region in the early stages could lead to delays in healing. Furthermore, the intrinsic healing capacity of bones may not be utilized if the gap size is more than a critical size limit [10]. Nevertheless, clinical studies suggest that very small fracture gaps lead to very high mechanical stimuli and result in unfavourable healing conditions [65]. This emphasizes the need for careful preplanning and execution of surgical reduction of fractures considering all the patient-specific factors.

The results showed that the uncertainties in ICF configuration parameters (T and WD) have very little effect on the mechanical microenvironment and PoS at the beginning of reparative phase (beginning of stage III) of healing. Fig. 4c, d show no significant changes in tissue strains in response to changes in T or WD. Also, Fig. 8c, d show insignificant changes in PoS in response to uncertainties in T or WD. This could also be explained by the findings of Prat et al. [63]. As described before, when healing moves from the early stages to subsequent stages and the fracture callus begins to harden, a little increase in callus stiffness is enough to attract a major fraction of the applied load. As most of the load is transferred via fracture callus, the fixator becomes less effective. Thus, changes made to the fixator will not significantly alter the mechanical microenvironment of the fracture site. This suggests that although there is a significant level of uncertainty about ICF configuration, it may not affect the PoS significantly during the reparative phase.

This is further supported by the finding of Prat et al. [63], which reported no significant changes in the mechanical behaviour of fractures stabilized with external ring fixations due to differences in fixation rigidities once callus achieves some nominal mechanical properties. In their study, rigid and dynamized fixation systems were compared and noticeable differences in mechanical behaviours were only identified in the very early stages of healing. Once the elastic modulus of the callus reached around 0.7 % of that of intact bone, no noticeable differences in load transmission were seen between the two fixation types [63]. This is further corroborated by the findings of Terjesen and Svenningsen [66] and Aro et al. [67]. Therefore, the influence of ICF configuration appears to be important only in the early stages of healing to achieve fracture stability. Once callus achieves a nominal stiffness (e.g. around 1 % of intact bone or even less), differences in ICF configuration may not significantly influence the fracture site - ICF interaction (i.e. load transmission) [63] and hence not significantly affect the PoS.

The results also indicate that the mechanical microenvironments in the periosteal and endosteal zones of the callus are not significantly altered by the mechanical variables at the beginning of stage III of secondary healing (i.e. beginning of reparative phase) which is in contrast to the predictions made for the early stages of healing [27, 36, 37]. This is due to the increase in callus stiffness by stage III which would lead to a concentration of stresses closer to the bone ends (i.e. cortical zone) in response to loading.

In summary, the results of the present study emphasize the need for careful surgical reduction of the bone fragment and design of post-operative partial weight-bearing exercises. Studies elsewhere [6, 25] have highlighted the profound influence of GS and P on IFS and the mechanical microenvironment of the fracture site during the early stages (e.g. stage I and II) of healing which suggests that uncertainties in GS and P in the early stages could have significant effects on the early mechanical microenvironment of the fracture site. The present study shows that uncertainties associated with GS and P could have significant effects on the mechanical microenvironment of the fracture site during subsequent stages of healing (e.g. stage III) as well. At the beginning of the reparative phase (stage III), P is the most dominant parameter influencing the mechanical environment of the fracture site. Thus, careful controlling of weight-bearing is highly recommended during this stage to minimize the uncertainties associated with P. Use of instrumented insoles which allows accurate measurements of weight-bearing is a possible way of achieving this [9]. Furthermore, this study suggests that ICF configuration does not significantly affect the PoS once callus reaches stage III secondary

healing (reparative phase). Moreover, the cortical zone of the callus was predicted to be the most sensitive zone to uncertainties in mechanical parameters.

4.1 Limitations and future directions

This study has several limitations that need to be stated. Firstly, simplifications were made to the fracture geometry and loading conditions. The bone fragments were assumed to be cylindrical and only axial compression was considered in this study. It is possible to extend this study to include realistic bone geometries and loading conditions which would lead to inhomogeneous strains within the callus due to bending and torsion effects. In such cases, it would be ideal focus on the anterior/posterior and medial/lateral regions of the callus separately. Also, it was assumed that fracture healing pathway remains the same for all the cases considered in this study and the differences in parameters only affect the rate at which the healing path is followed [24]. Moreover, only some of the most important mechanical variables that affect fracture healing under ICF were considered in this study. It should also be noted that the input variables were assumed to be independent and normally distributed which needs to be verified. Future studies need to address these limitations. Nevertheless, this study provides useful insights into how uncertainties associated with mechanical variables affect the mechanical microenvironment of fracture sites stabilised with ICFs. However, more clinical and experimental data are needed to further corroborate the findings of this study.

Since the fracture callus is too soft in the early stages, early weight-bearing under the relatively flexible ICF configurations could negatively affect the mechanical microenvironment of the fracture callus. Therefore, the present investigations were carried out at a stage in the healing pathway (beginning of stage III) where partial weight-bearing is allowable. However, delaying weight-bearing is unfavourable as it makes patients immobile for long periods and may even lead to impaired healing [68]. Therefore, it would be interesting to consider more rigid ICF configurations (e.g. with half pins) or fixation types which can allow early weight bearing without negatively affecting the fracture site. Future studies could further extend the developed model to investigate the influence of early weight-bearing under a variety of fixations and ICF configurations. Since this study focuses on a specific timepoint of healing and achieving favourable mechanical microenvironment within the fracture callus (based on a previous model [21]), the mechanobiological rules for tissue differentiation was not explicitly modelled in this study. If investigations are to be carried out at various timepoints throughout the course of healing, it would be ideal to incorporate the mechanobiological rules for tissue differentiation

based on tissue strains and angiogenesis in the model as done elsewhere [69]. Also, future studies may consider the mechanical variables that were not considered in the present study.

5 Conclusions

This study uses computational models in conjunction with probabilistic methods based on engineering reliability analysis to investigate how fracture healing under ICF is affected by the uncertainties associated with GS, P, T and WD. The probabilities of achieving favourable mechanical microenvironment for fracture healing (i.e. Probability of Success, PoS) were calculated under different levels of uncertainties associated with these variables. The main findings of this study are as follows:

- The cortical callus is very sensitive to uncertainties in mechanical variables at the beginning of stage III (reparative phase). PoS in the cortical callus dropped from 100 % to as low as 46 % with the increase of COV of variables (i.e. uncertainty) from 0.1 to 0.9. However, periosteal and endosteal callus zones appear to be relatively insensitive to the mechanical variables with PoS dropping from 100% to just 86% for the same increase in COV .
- Axial loading due to weight-bearing (P) is the most critical mechanical variable that affects the PoS at the beginning of stage III (reparative phase). PoS drop from 100 % to as low as 46 % was predicted as COV_P increased from 0.1 to 0.9 (cortical zone). Since loading is the most uncertain and easily changeable variable post-surgery, careful controlling of weight-bearing is highly recommended (e.g. via the use of instrumented insoles).
- PoS is also sensitive to fracture gap size (GS) at the beginning of stage III healing (reparative phase). The greatest change in the PoS predicted due to uncertainty in GS was from 100 % to 70 % as COV_{GS} increased from 0.1 to 0.9 (cortical zone).
- The uncertainties in ICF wire pretension (T) and wire diameter (WD) do not significantly affect PoS at the beginning of the reparative phase of healing. The greatest PoS change predicted due to uncertainties in T or WD was from 100 % to just 95 % as COV_T or COV_{WD} increased from 0.1 to 0.9. This suggests that the effectiveness of ICF is reduced significantly as the healing reaches stage III.

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Conflict of Interest

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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Table 1 Material properties of poroelastic tissues (at the beginning of stage III of healing) and linear elastic ICF components (stainless steel) used in this study

Material	E (MPa)	ν	Φ	k (m⁴ N⁻¹ s⁻¹)	K_s (MPa)	K_f (MPa)
Cortical bone	20000 ^a	0.3 ^a	0.04 ^a	10 ⁻¹⁷ ^a	13920 ^a	2300 ^a
Fracture callus	12 ^b	0.167 ^{a,b}	0.8 ^{a,b}	10 ⁻¹⁴ ^{a,b}	2300 ^{a,b}	2300 ^{a,b}
Stainless steel	197000 ^c	0.29 ^c	-----	-----	-----	-----
E – Young’s modulus ν - Poisson’s Ratio Φ – Porosity k –Permeability K_s – Solid compression modulus K_f – Fluid compression modulus						

^a Lacroix and Prendergast [25] ^b Estimated based on the results of Claes et al [6] and Vetter et al. [24]

^c Watson et al. [57]

Table 2 Mean (μ) and coefficient of variation (COV) of the mechanical variables used in this study.

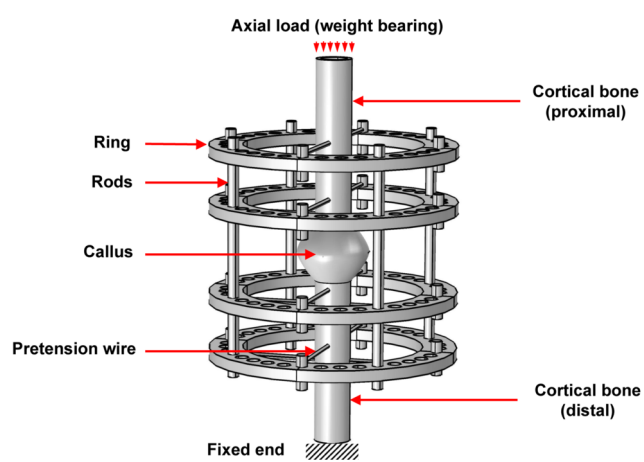
Variable	Mean (μ)	Coefficient of variation (COV)
Fracture gap size (GS)	3 mm ^a	0.1 – 0.9 ^d
Weight bearing loading (P)	150 N ^b	0.1 – 0.9 ^d
Wire pretension (T)	130 kg (1275 N) ^c	0.1 – 0.9 ^d
Wire diameter (WD)	1.8 mm ^c	0.1 – 0.9 ^d

^a Claes et al. [6] ^b Estimated from the model to produce favourable mechanical microenvironment within all zones of the callus ^c Fleming et al.[54] ^d The effect of varying these parameters were studied (see results)

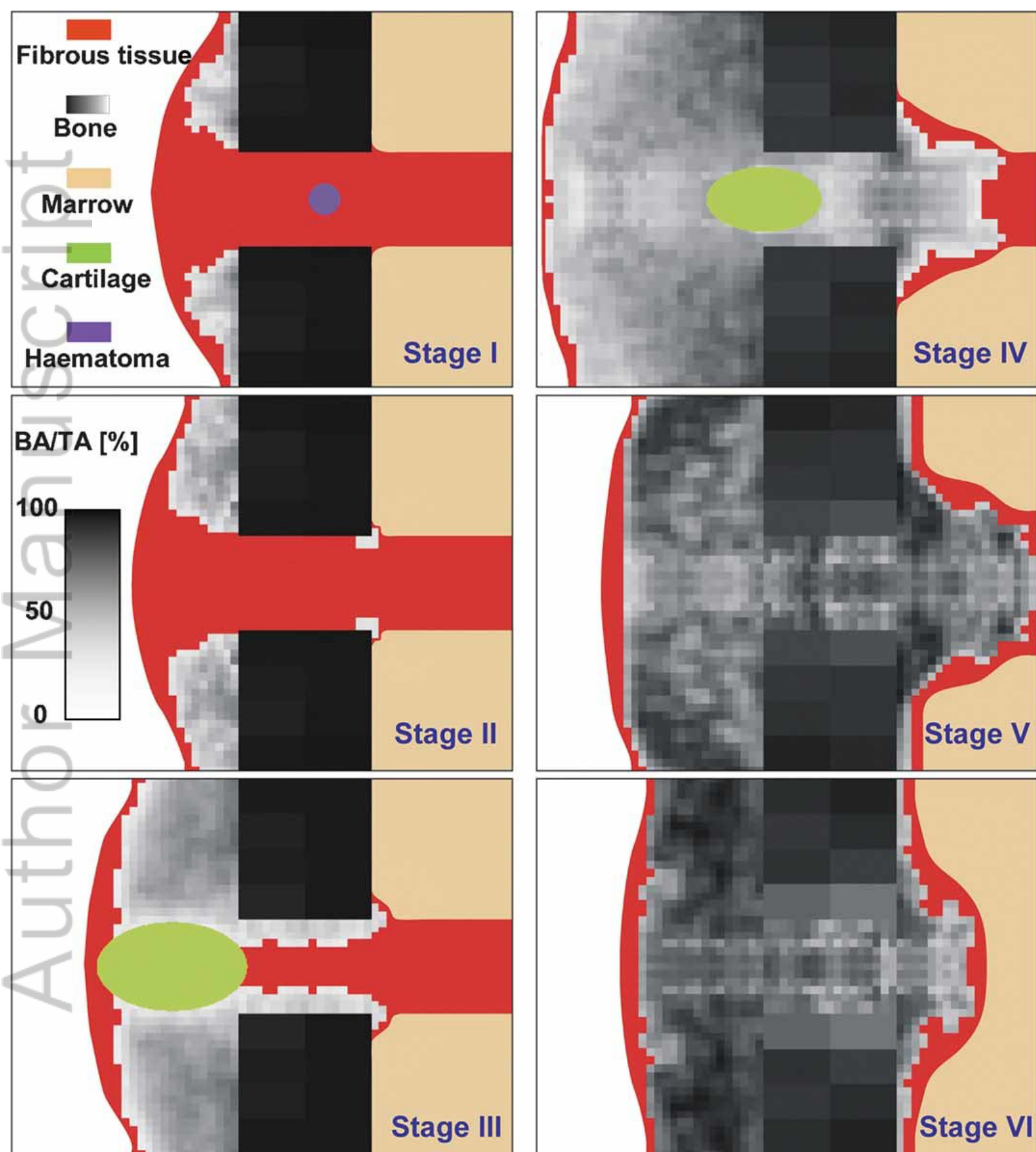
Table 3 Relationships between independent variables and average tissue strains within the periosteal, cortical and endosteal callus

X_n	Periosteal	Cortical	Endosteal
GS	$\varepsilon = 0.1204 \times \text{GS} + 0.4198$	$\varepsilon = -0.7000 \times \text{GS} + 7.1800$	$\varepsilon = 0.1071 \times \text{GS} + 1.0300$
P	$\varepsilon = 0.0053 \times \text{P} + 0.0017$	$\varepsilon = 0.0329 \times \text{P} - 0.0014$	$\varepsilon = 0.0091 \times \text{P} + 0.0029$
T	$\varepsilon = -0.0006 \times \text{T} + 0.8877$	$\varepsilon = -0.0039 \times \text{T} + 5.4588$	$\varepsilon = -0.0011 \times \text{T} + 1.5082$
WD	$\varepsilon = -0.0637 \times \text{WD} + 0.9137$	$\varepsilon = -0.3867 \times \text{WD} + 5.618$	$\varepsilon = -0.1067 \times \text{WD} + 1.552$

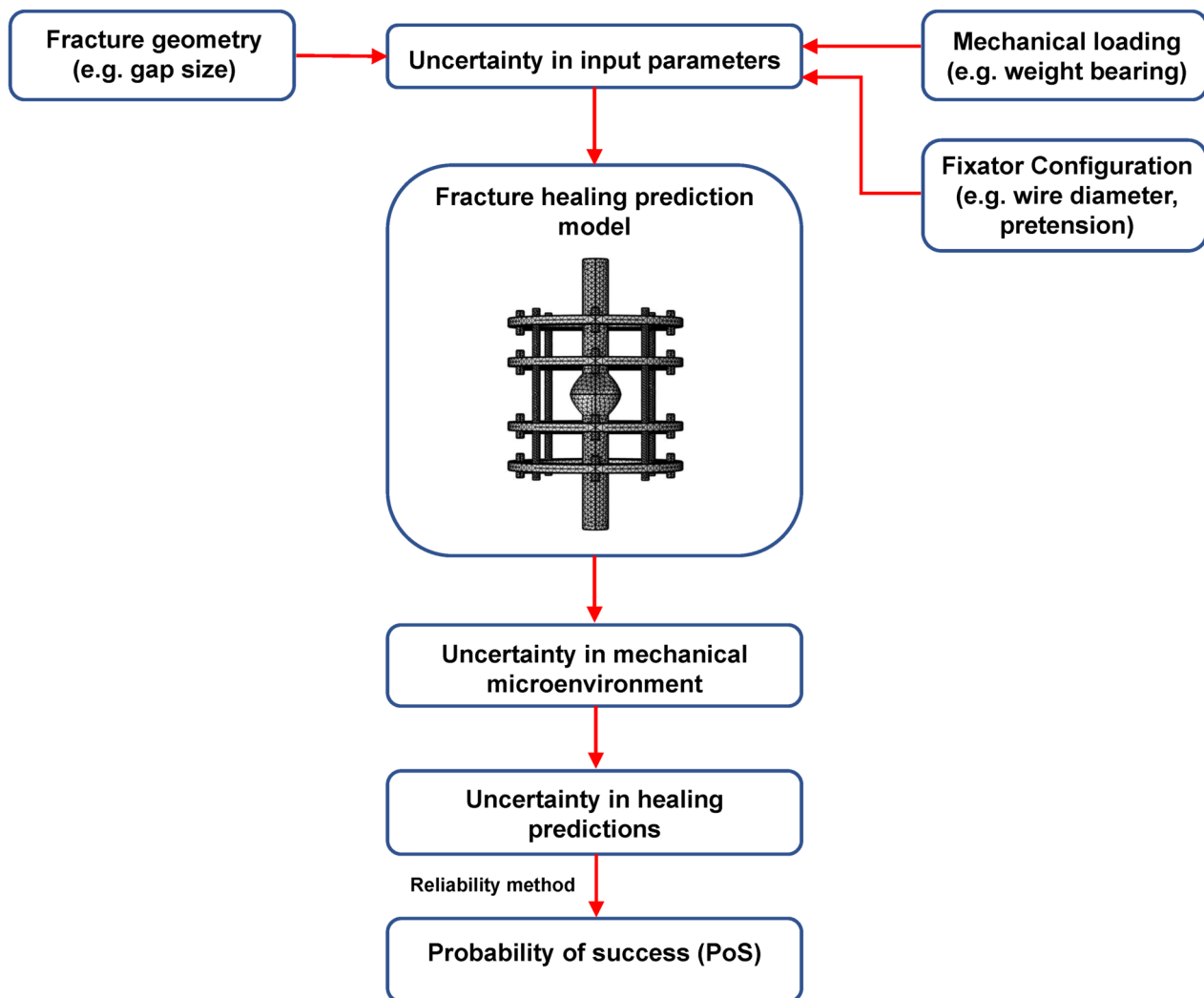
Notes: The units of GS, P, T and WD are mm, N, kg and mm, respectively.
The means of variables are GS = 3 mm, P = 150 N, T = 130 kg and WD = 1.8 mm
When a variable is considered, the other three variables are set to their means.



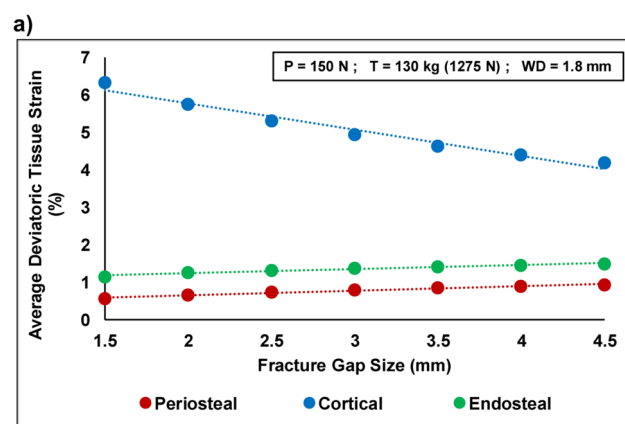
CNM_3466_Fig1.tif



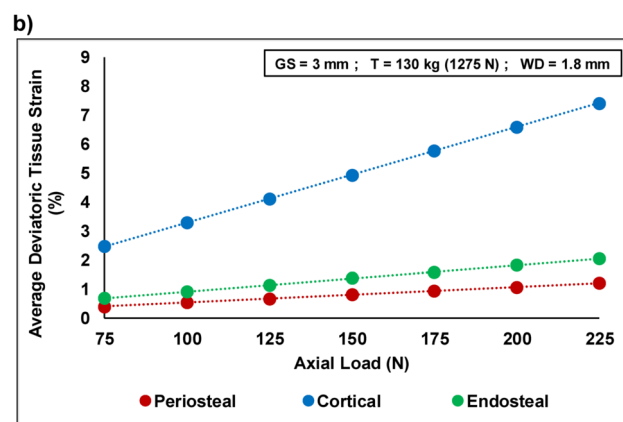
CNM_3466_Fig2.tif



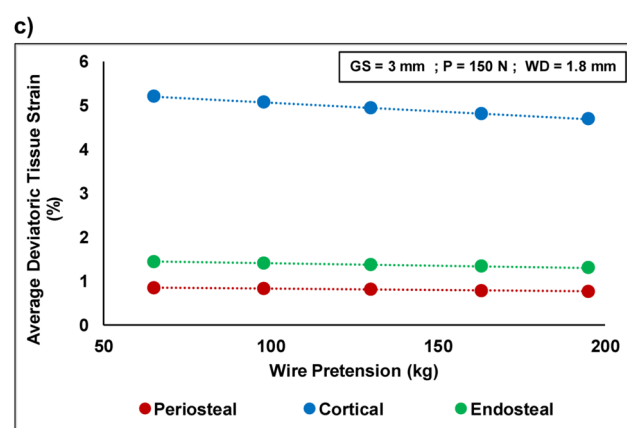
CNM_3466_Fig3_.tif



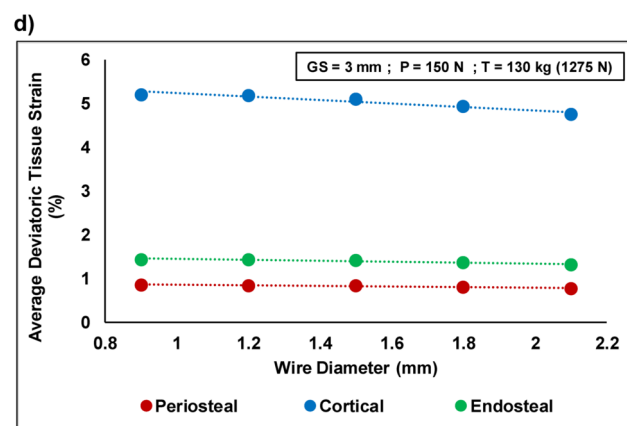
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CNM_3466_Fig4b.tif

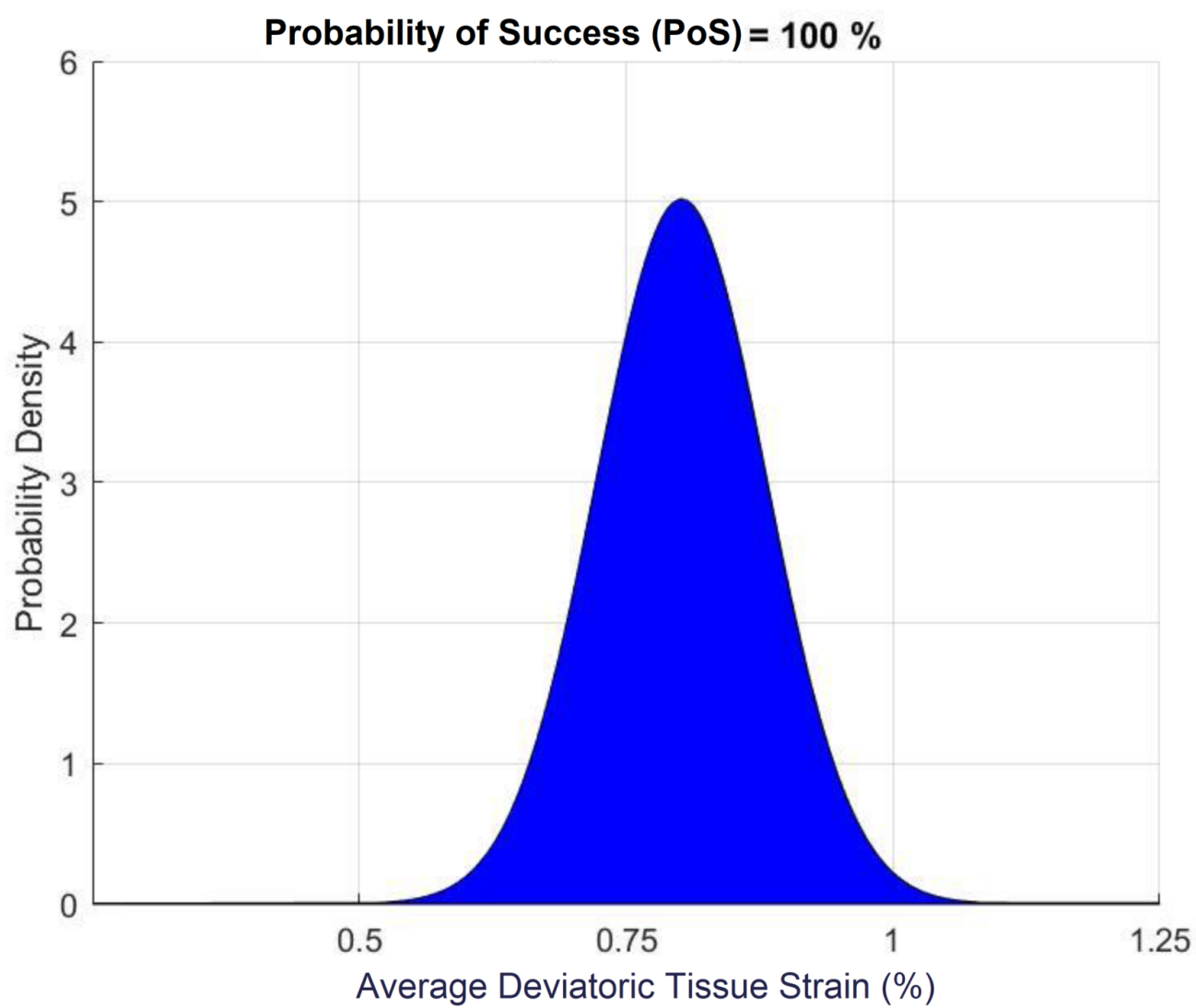


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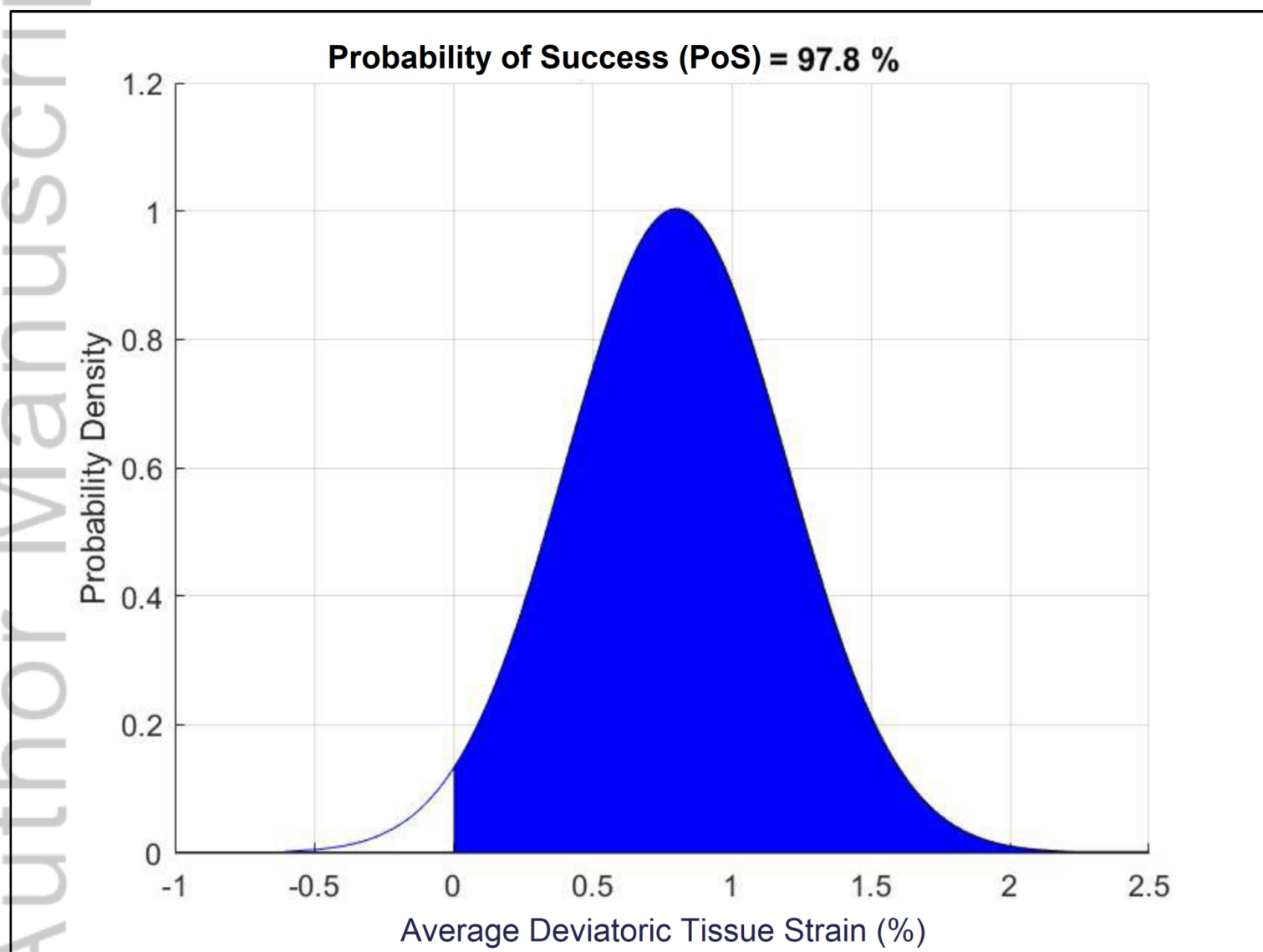


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a) COV = 0.1

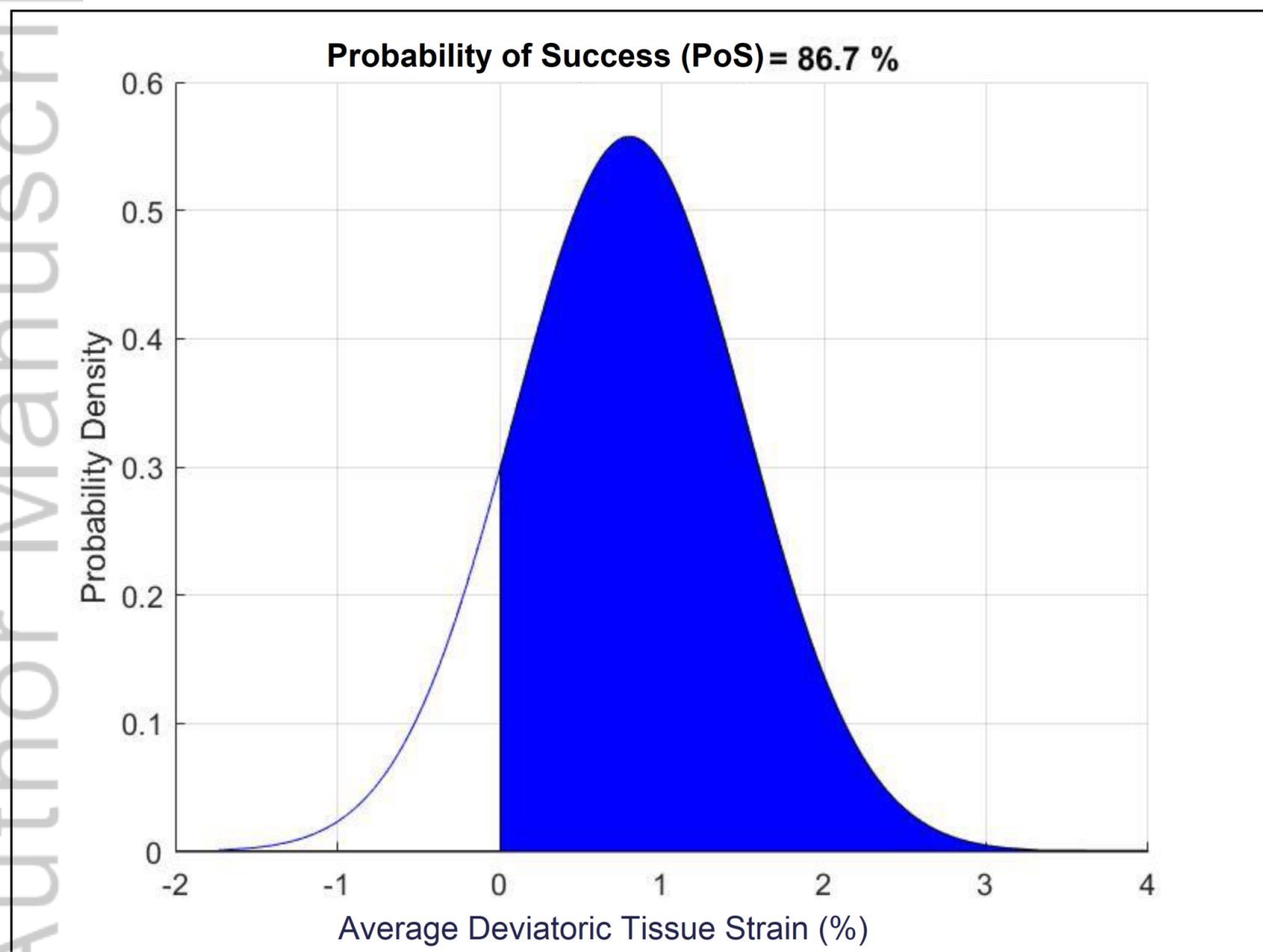


b) COV = 0.5



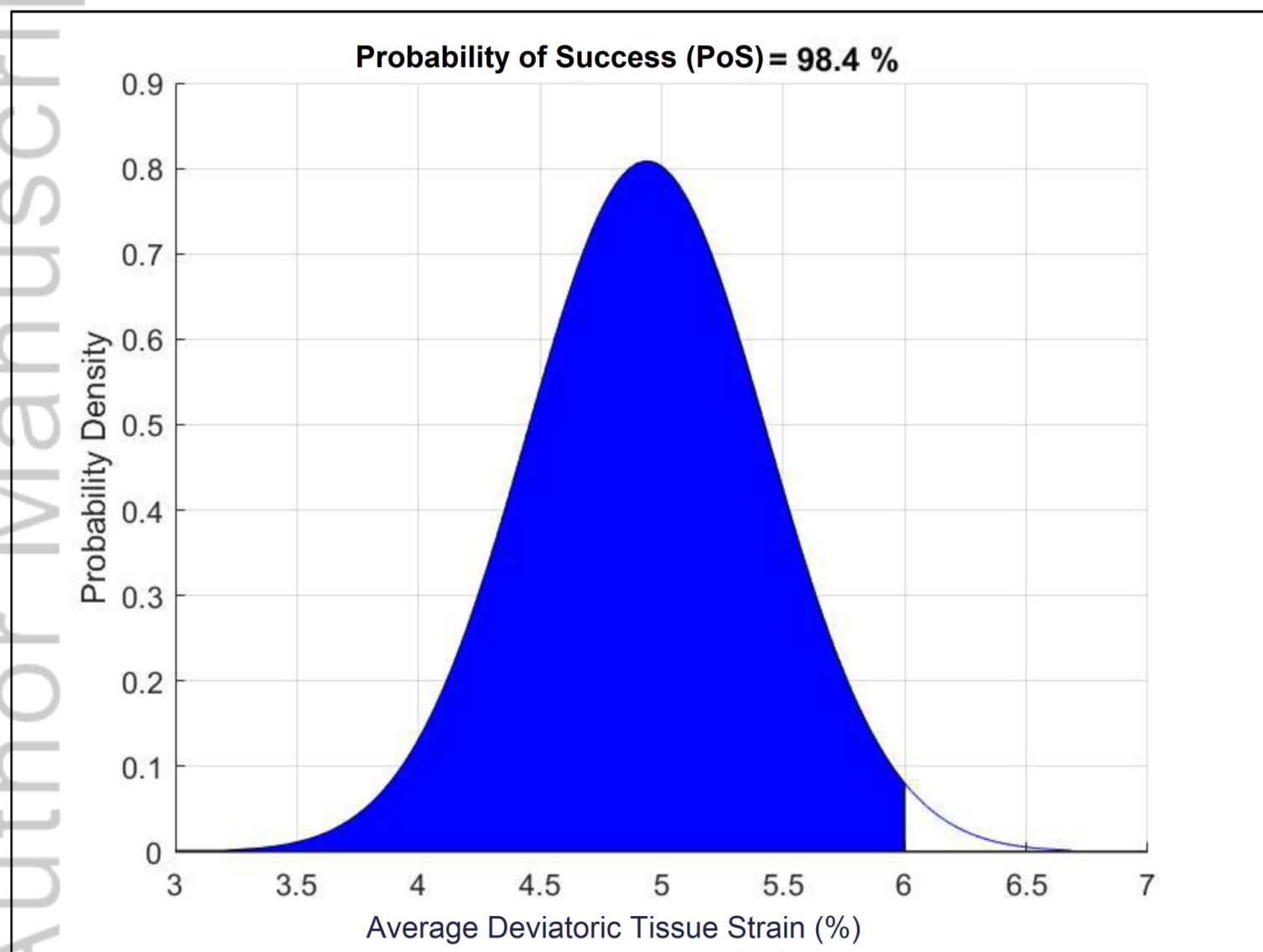
CNM_3466_Fig5b.tif

c) COV = 0.9



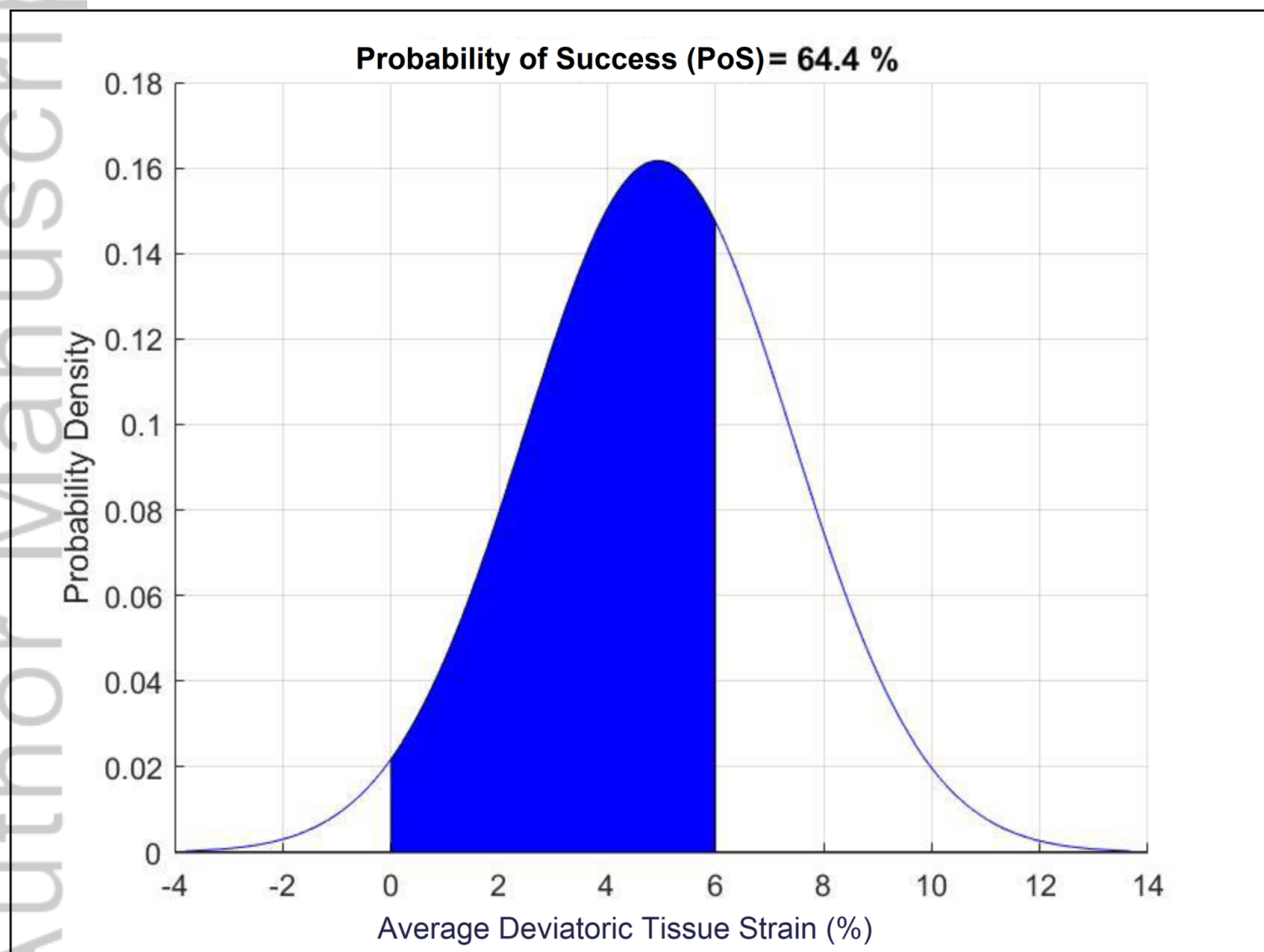
CNM_3466_Fig5c.tif

a) COV = 0.1



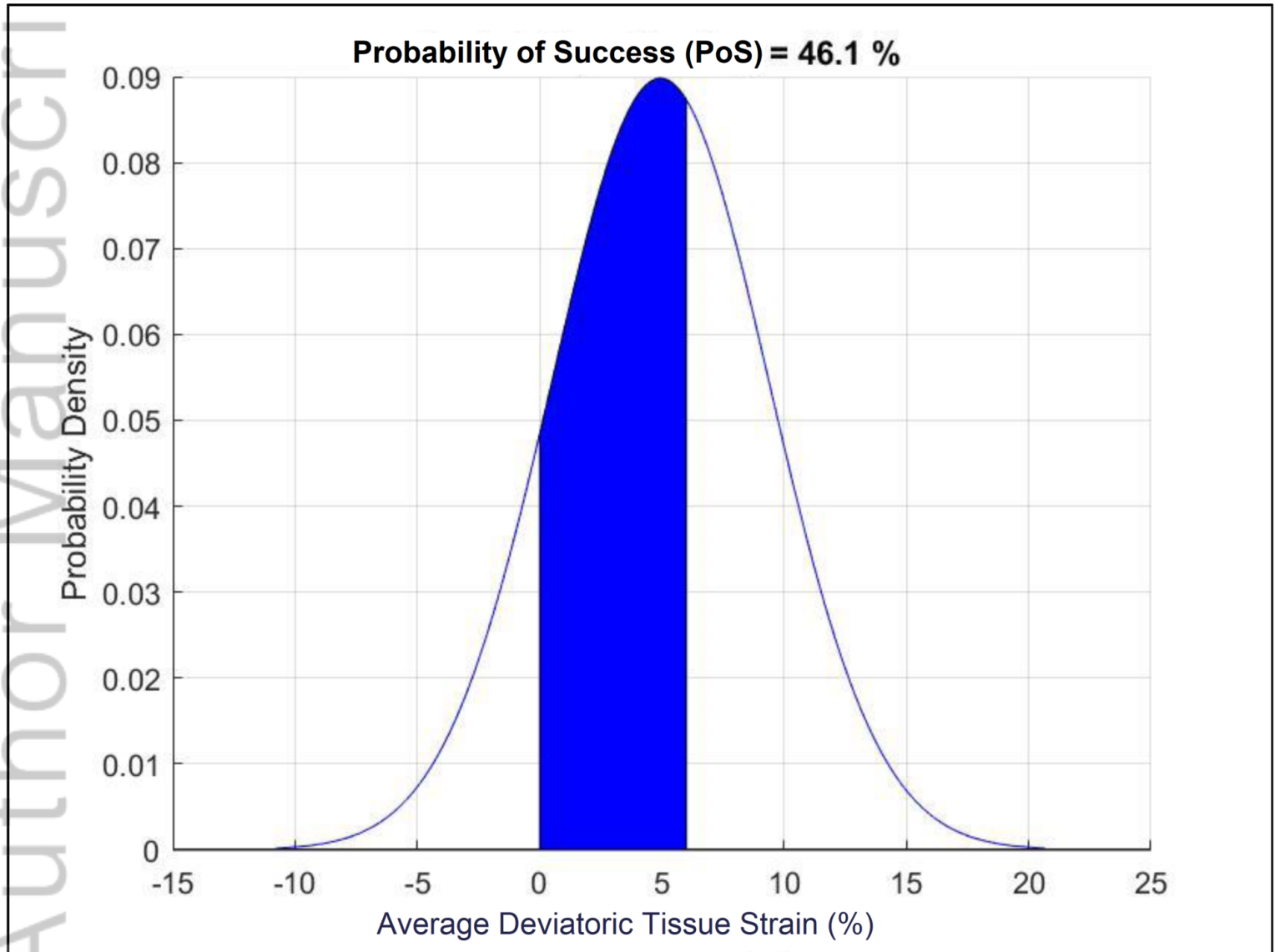
CNM_3466_Fig6a.tif

b) COV = 0.5



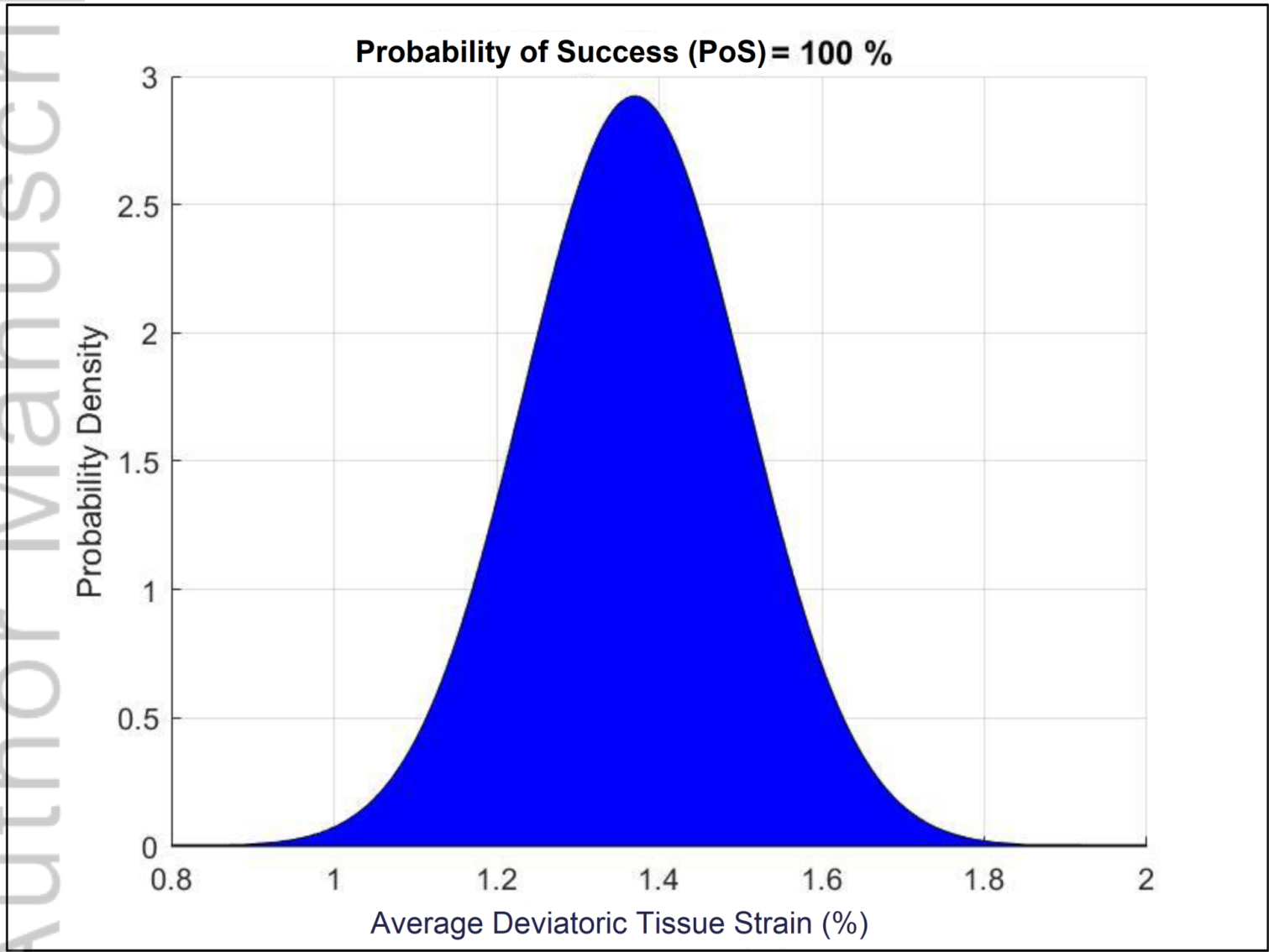
CNM_3466_Fig6b.tif

c) COV = 0.9



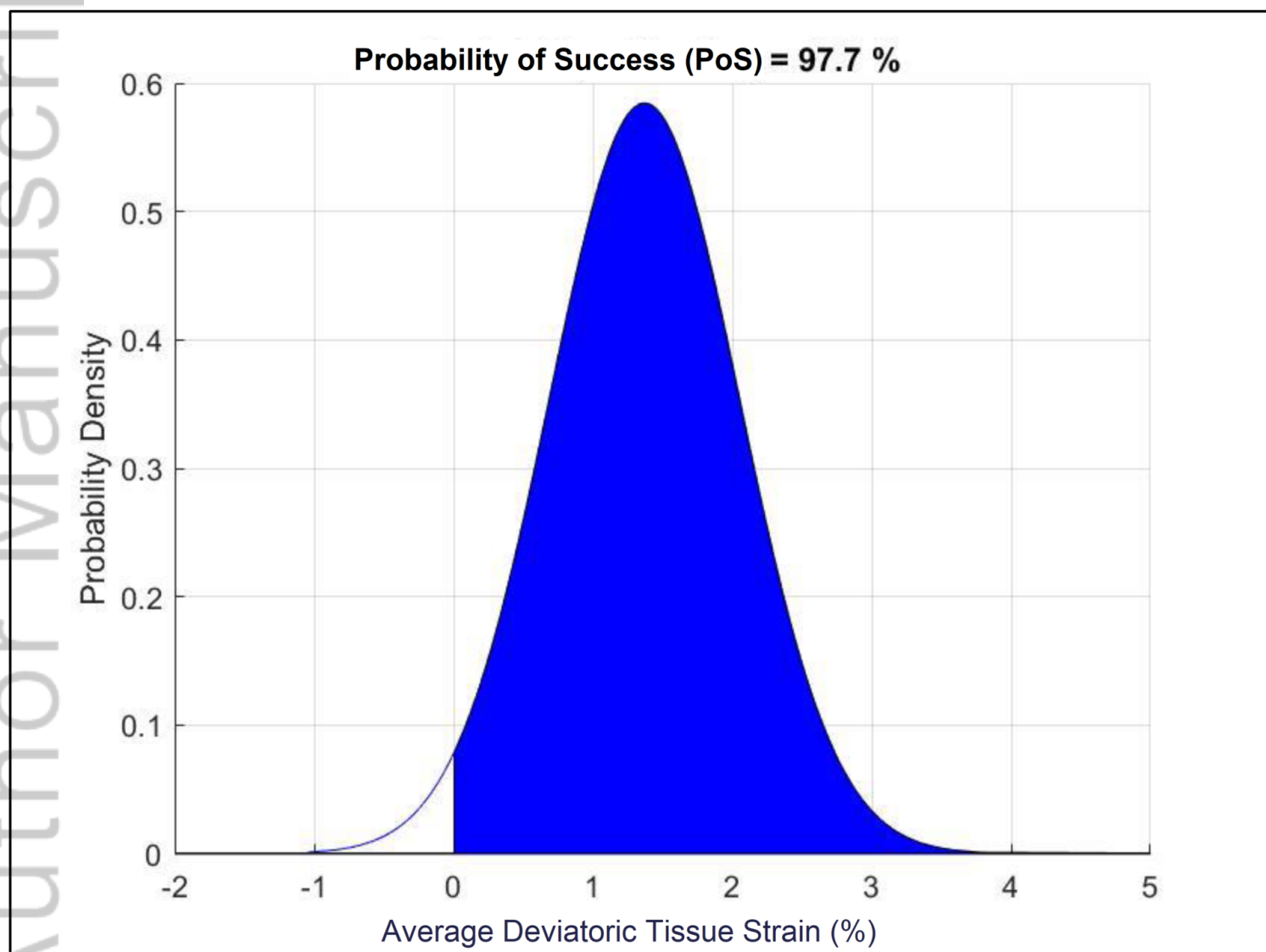
CNM_3466_Fig6c.tif

a) COV = 0.1

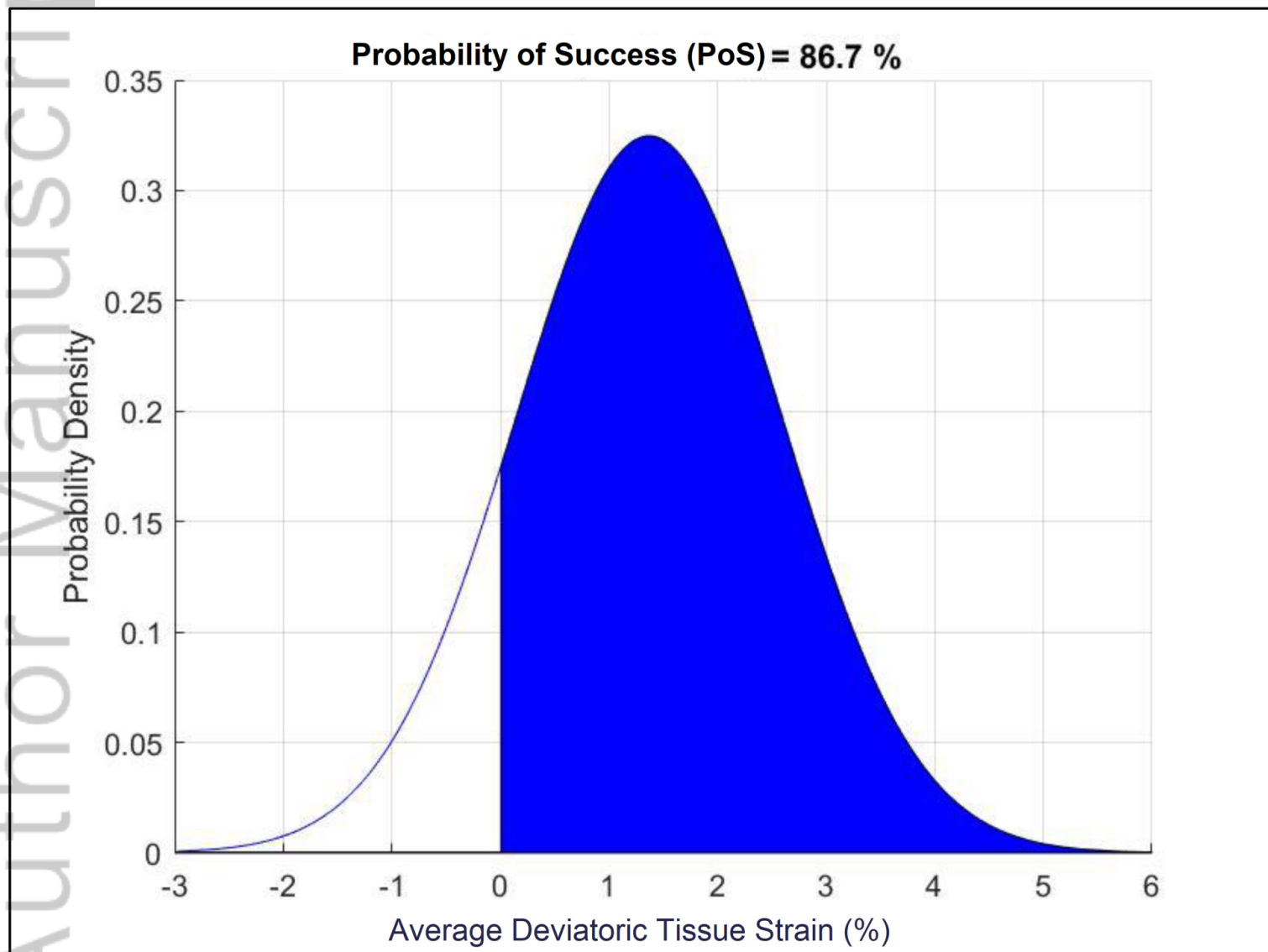


CNM_3466_Fig7a.tif

b) COV = 0.5

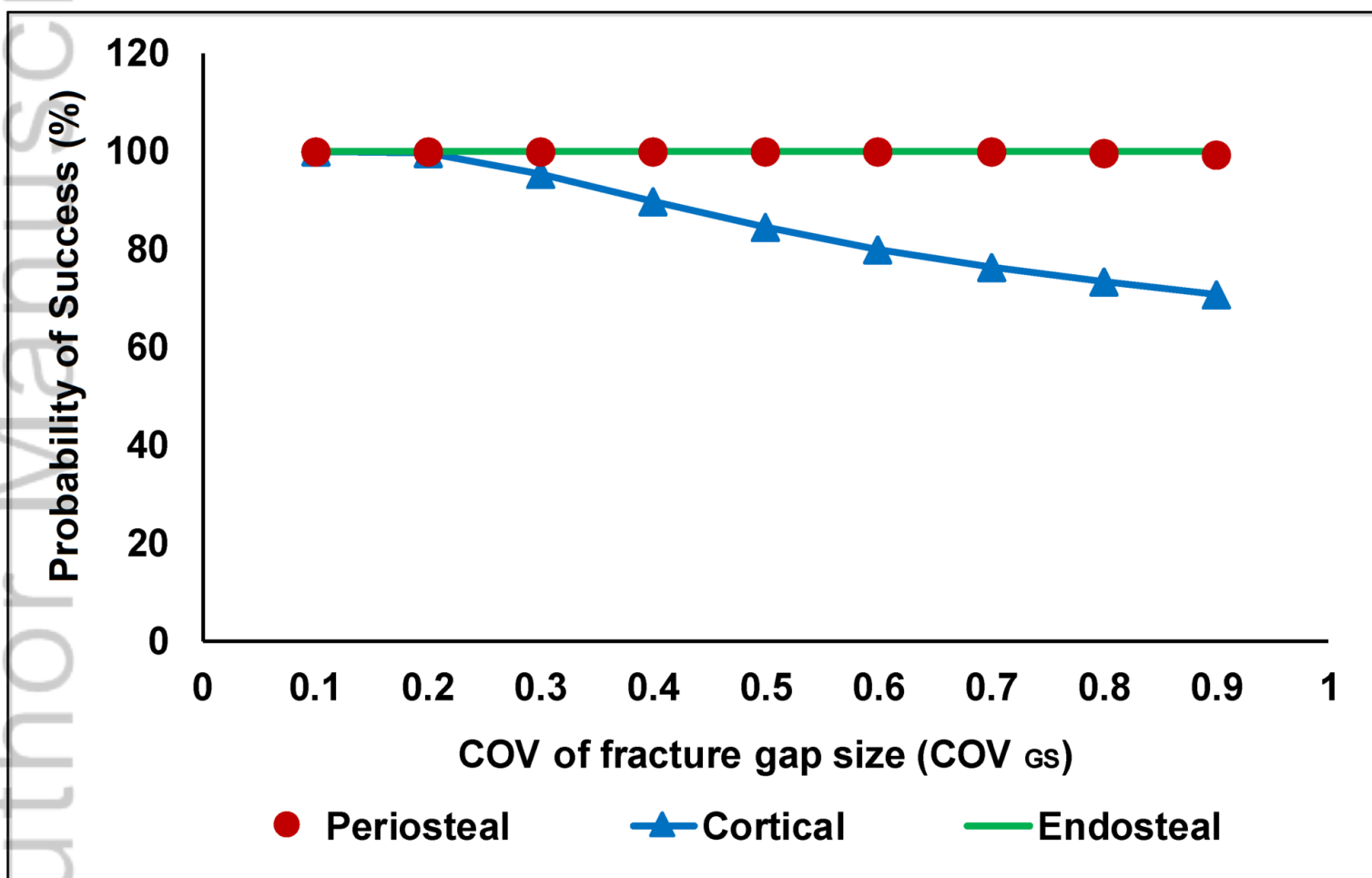


c) COV = 0.9

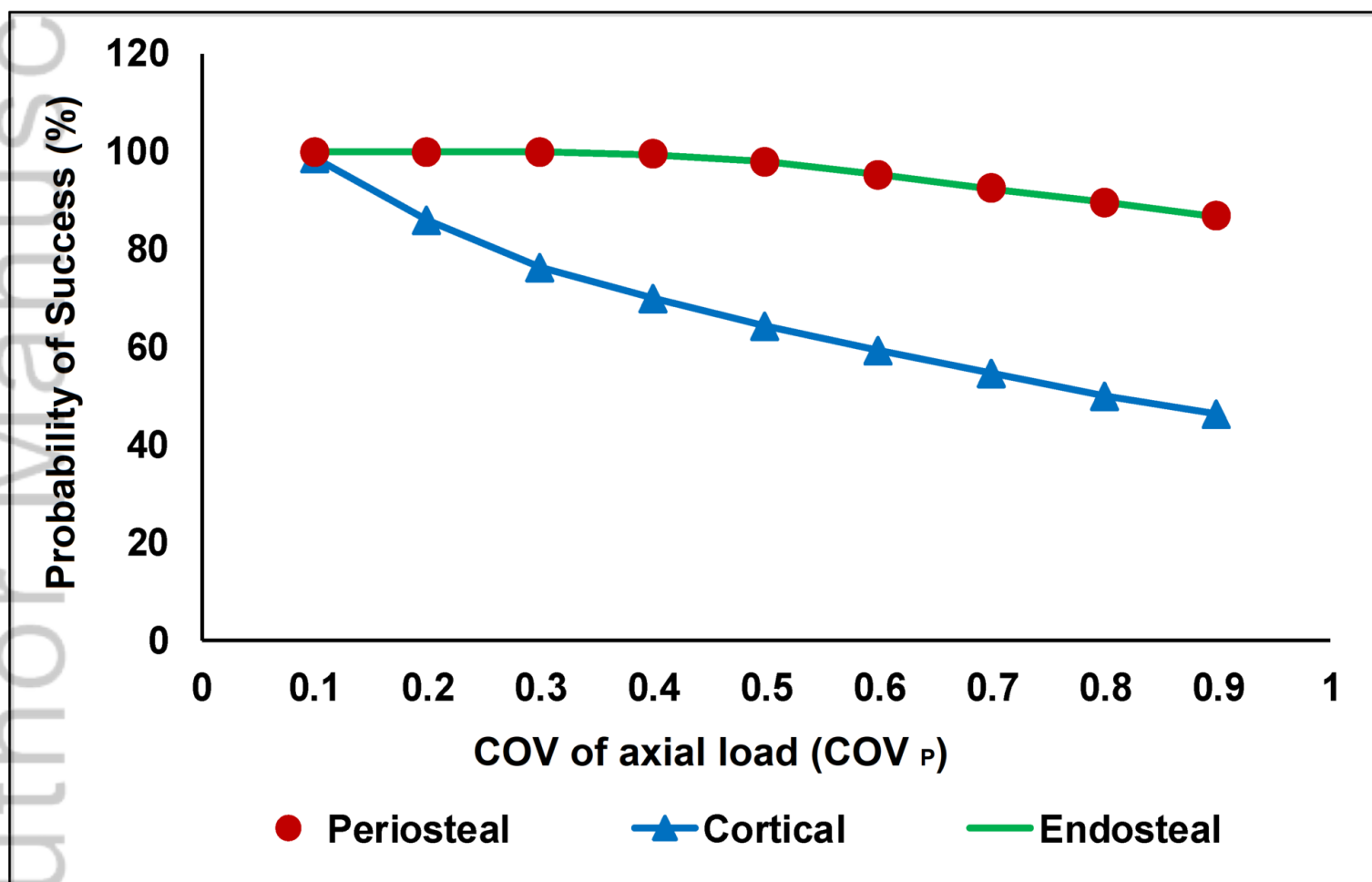


CNM_3466_Fig7c.tif

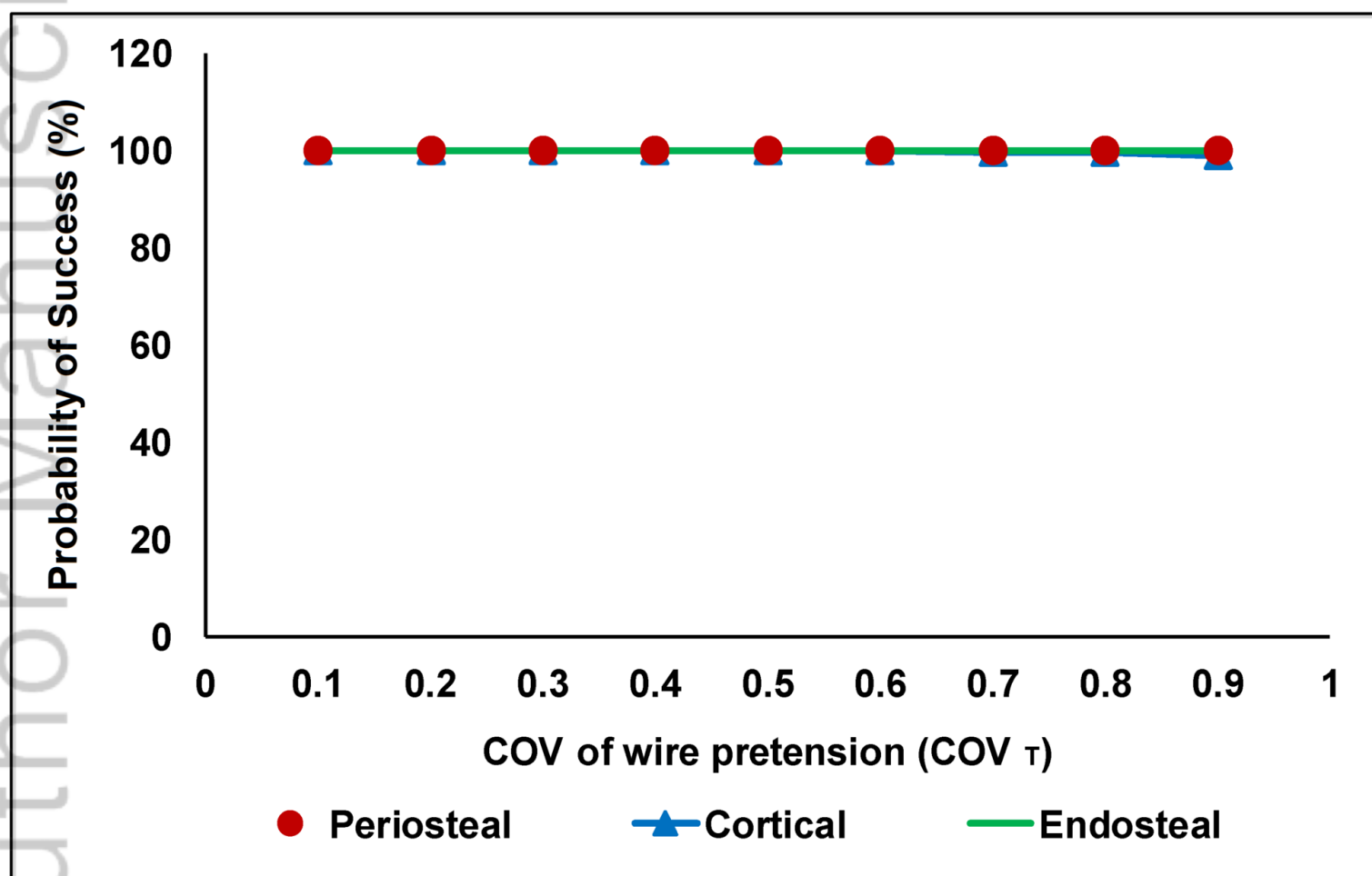
a)



b)

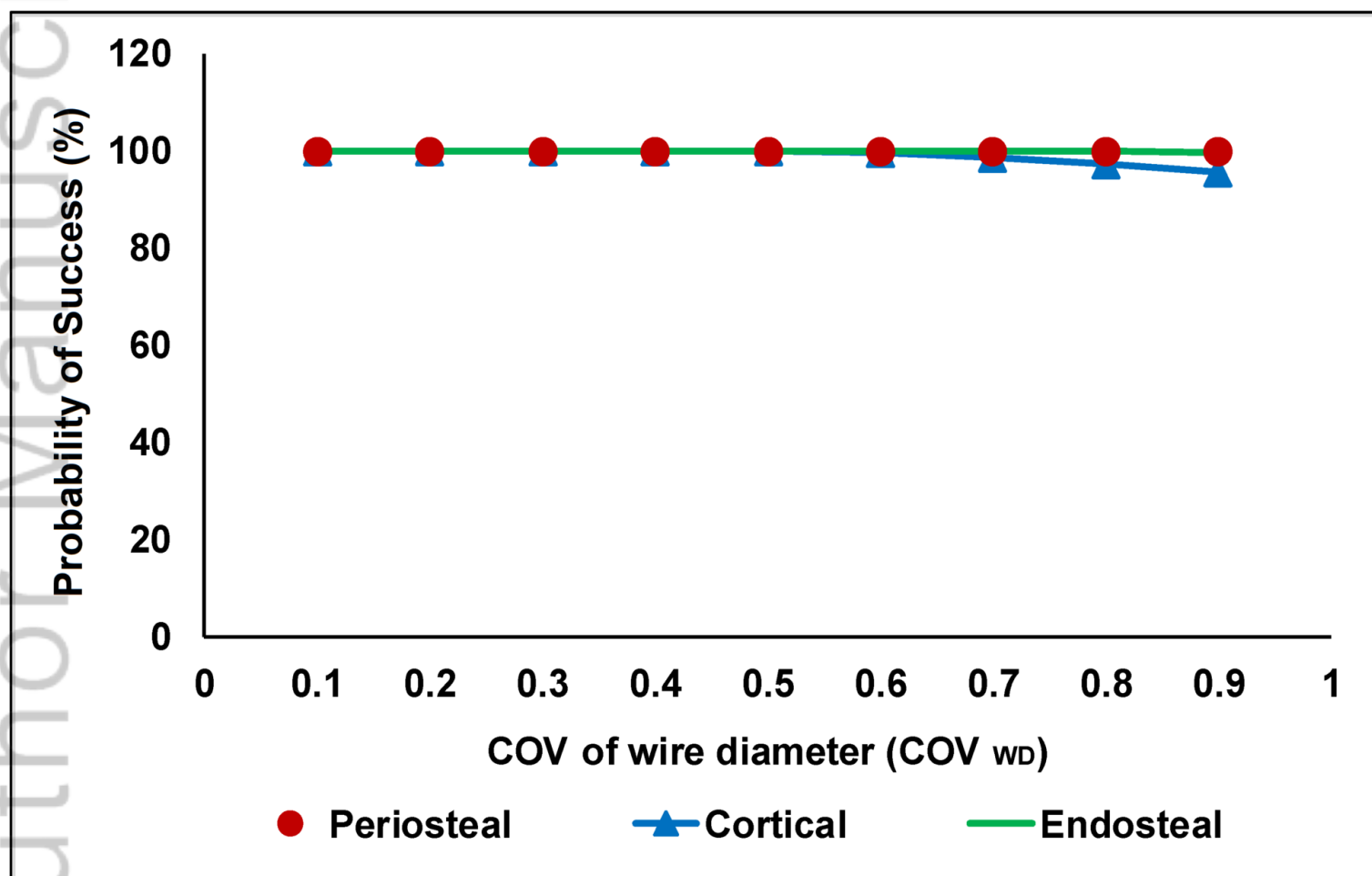


c)



CNM_3466_Fig8c.tif

d)



A probabilistic approach for modelling bone fracture healing under Ilizarov circular fixator

Ganesharajah Ganadhepan, Saeed Miramini, Priyan Mendis, Minoo Patel and Lihai Zhang*

Using the engineering reliability method in conjunction with computational modelling, this study aims to enhance the understanding of the effect of uncertainties in Ilizarov circular fixator configuration, fracture gap size and weight-bearing on the fracture site mechanical microenvironment during fracture repair. The uncertainties in weight-bearing and gap size have a prominent effect while the uncertainties in fixator configuration have only little effect on the fracture site mechanical microenvironment. These findings have potential applications in assessing treatment reliability.

