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Title: Notes on “A cautionary note on the use of SIFT in pathological connectomes”

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BODY

Following comments made in Sarwar et al¹ regarding the potential introduction of erroneous differences into structural connectome measurements by the Spherical-deconvolution Informed Filtering of Tractograms (SIFT) method², we published a Letter To The Editor³ demonstrating that the claims made were the consequence of inappropriate application of this method (the “Letter”). A response to this Letter has now been published⁴ (the “Response”); there the authors suggest that they revisit their example and:

“... show that these two modifications [which we had mentioned in our Letter] do not alleviate the paradoxical conclusions that result when SIFT is used”,

despite our prior demonstration that their erroneous inference of a 50% decrease in the healthy bundle is alleviated to 5% with appropriate usage of the method, to 0.5% if a greater number of streamlines are used, and to 0% if the SIFT2 method⁵ is instead used. The authors present a novel set of experiments and arguments to attempt to back up their claim with further criticisms of SIFT. However, while there is one important observation made (which we clarify in the Conclusion section), their reporting of such is distorted by errors in experimental design, application of the SIFT method, presentation of experimental results, and specificity of attribution; these are disentangled in the various sections below.

1. Raw streamline count

In their formulation (Figure 1A), Zalesky and colleagues define the probability p of a streamline tracking within a pathological bundle succeeding in fully reconstructing the entire bundle length to be directly proportional to the FOD integral v_f within a solitary affected voxel:

“We denote the total number of streamlines traversing the normal fiber with N . The total number of streamlines traversing the full length of the pathological fiber is, therefore, Np .”

“Setting $v_f = p$ ensures that the pathological FOD integral is commensurate with the number of streamlines traversing the pathological fiber.”

- a. *This is a completely erroneous premise given how streamlines tractography algorithms operate.* It is well-established^{6,7} that the number of generated streamlines that pass through a voxel is *not* directly related to the voxel's FOD amplitude: as long as the latter exceeds the threshold used for tracking, then streamlines will *not* terminate prematurely in the voxel concerned (for erroneous trajectories due to erroneous fibre orientations see point 2 below). This perfect correlation between FOD amplitude and raw streamline count is therefore wholly inconsistent with the empirical behavior of actual streamlines tractography experiments (even in this simple phantom).
- b. This, in combination with raw streamline count being presented in the figure within the Response directly alongside the results of SIFT (and with identical visual formatting), may misleadingly imply to readers that raw streamline count is in fact the ideal metric for sensitivity to such pathology. In this phantom, the data for raw streamline counts are *not* experimental results, but part of the experimental *construction*, and so warrant corresponding interpretation (see Figure 1C).

This formulation is particularly ironic given it is the very *lack* of correlation between raw streamline count and FOD magnitude that *motivated the development* of SIFT and related methods, the intention of which is achieving exactly that goal.

2. Removal of streamlines prior to applying SIFT

"This reduction, in addition to a possible rotation of the FOD orientation due to pathology, can partially or fully obstruct streamline propagation at the site of pathology, resulting in fewer streamlines traversing the full length of the pathological fiber, ..."

Even if some streamlines were to terminate prematurely in the affected bundle (Figure 1B), and/or follow an erroneous orientation somewhere along its length, the authors have still applied the SIFT method erroneously given their own presupposition. The model underlying the SIFT methods cannot be applied to extracted bundles: it must be applied to a whole-brain tractogram; only after application of an optimization algorithm can those streamlines corresponding to any bundle of interest be extracted and the connectivity of that bundle quantified. In other words: those streamlines failing to traverse the full length of the bundle of interest should have still been included in the tractogram provided as input to SIFT, with the quantified bundle connectivity

following SIFT being proportional to the number of remaining streamlines traversing the entire bundle length.

As shown in Figure 1B, if all generated streamlines are appropriately included in the model, both streamline removal (SIFT) and streamline weighting (SIFT2) algorithms yield endpoint-to-endpoint connectivity estimates that match the severity of pathology (derivations in Supporting Information). Importantly, this result emerges through enforcing consistency between the image data and streamlines reconstruction data, unlike the artificial experimental control of raw streamline count (point 1).

3. *Streamline count quantization*

Zalesky and colleagues state, following derivation of an exact solution to their algebraic analogue of SIFT:

*“Given that n^*_1 is not necessarily an integer in the above equation, we apply the integer remapping...”*

Here, the analytic expression of the optimal “number” of streamlines n^*_1 to remove from the lower bundle that achieves the best possible correspondence between streamlines and fibre densities is mapped to the most appropriate neighbouring integer, in order to mimic the removal of quantised streamlines by the SIFT algorithm. This leads to the following observations:

“The hypothetical patient’s normal fiber shows paradoxical decreases in connectivity, which are often equal in percentage change to the pathological fiber.”

“The percentage change in connectivity is erratic and not monotonic in N_p .”

- a. These behaviours are not intrinsic properties of the SIFT method, but are entirely the result of streamline count being an integer measure. This is demonstrated in Figure 1D-E (shaded areas), which echoes results presented in the Response but additionally highlights how both of these supposedly paradoxical effects are exceeded by the uncertainty associated with this discretisation. This was also addressed in our previous Letter:

“This occurs only because resolving a very small difference in bundle density using streamlines counts requires an adequate number of streamlines to numerically represent that difference”.

- b. Discretisation effects do not manifest in the plot for raw streamline count (Figure 1C) due to Zalesky and colleagues experimentally setting v_f based on p . Instead choosing p for a

given v_f – which would be more faithful to reality since streamlines are generated from FODs – would incur a similar integer rounding effect (see also point 1b).

- c. This non-monotonic behaviour arises principally when the effect size in the pathological voxel is exceptionally large (note logarithmic x -axes in Figure 1C-E), where fibre density estimates in real data would either have comparably large uncertainty due to the diffusion signal noise floor, or prevent streamlines propagation entirely due to tracking thresholds, making the nuanced behaviour of this exact algebraic solution irrelevant.
- d. Increasing the number of streamlines can be predicted *a priori* to reduce the prevalence of such discretisation effects, and was explicitly demonstrated in our Letter. While this is evident for $N=1000$, bundle lengths 10mm and 20mm (Figure 1E, highlighted rectangle) - particularly for the more realistic scenarios of $p \geq 0.1$ - these specific results were not included in the Response; specifically for $N=1000$, results for a bundle length of 80mm only were shown, which exhibits a comparable oscillation effect because the simulated pathology represents just 2.5% of the bundle at this length (more in point 4 below).
- e. In the Letter, we highlighted that application of the SIFT2 method⁵ to this phantom overcomes the discrete nature of streamline counting, and provides accurate bundle connectivity strength estimation with fewer reconstructed streamlines. This method is akin to the exact analytic solution derived in the Response prior to integer rounding; we show results of the latter in Figure 1D-E (dashed lines). Despite SIFT2 having been created as a *tailored solution* to such numerical issues, being *universally recommended* for neuroscientific applications over the original SIFT method, and having been demonstrated in our Letter as a preferable pre-existing solution *in this very phantom*, in their Response to that Letter, Zalesky and colleagues chose to exclude consideration of such, focusing only on the superseded SIFT method for their criticisms:

“Alternative streamline postprocessing methods based on continuous weighting schemes might, therefore, furnish connectivity measures that alleviate the first two paradoxical behaviors listed above. We limit this note to the SIFT method.”

4. Focal pathologies

In the “Interpretation” section of their Response letter, Zalesky et al. imply that SIFT and related methods are inappropriate for use due to the problems associated with quantifying fibre bundle

connectivity in the presence of a focal lesion (the “weakest link”), and suggest that sampling of voxel-wise diffusion model metrics is a preferable alternative for connectome construction.

- a. We never made any claim to SIFT’s sensitivity to focal pathologies. In fact, limited sensitivity to focal pathologies is a property not specifically of SIFT, but of any reasonable approach that collapses the “connectivity” of any given pathway to a scalar value - which is a *prerequisite for connectome construction* – as we explicitly stated in our previous Letter:

“Any method that derives quantitative values from endpoint-to-endpoint connectivity will intrinsically be less sensitive to spatially localised white matter lesions (such as that envisaged in this phantom) than analysis methods that are tailored to provide spatial sensitivity and specificity.”

[Note that our statement intrinsically included the authors’ subsequent suggestion of “*specific markers of brain tissue microstructure*”; in this case Fixel-Based Analysis⁸, which we chose to refer to since it provides fibre-specific metrics and analysis, whereas the alternatives referred to in this context by Zalesky et al. are voxel-based metrics.]

- b. *“... the percentage change decreases with fiber length, suggesting a bias toward detection of pathology in short fibers.”*

This effect is not specific to SIFT. Calculating the mean value of a voxel-wise diffusion model metric within each bundle - as is regularly performed in the field (including using those metrics suggested by Zalesky et al.) - *exhibits an identical dependence* of bundle percentage change on single-voxel pathology magnitude and bundle length as that for which SIFT was criticised (Figure 1F).

5. **Conclusion**

Where the authors of the Response are correct is: in the specific case where neuronal fibres are truncated within the white matter, but streamlines manifesting such truncation are not present in the tractogram (point 2; Figure 1B) (whether due to lack of reconstruction of such, or erroneous removal of such prior to applying SIFT), the endpoint-to-endpoint connectivity of the relevant bundle quantified by SIFT will be an over-estimate relative to the underlying biological endpoint-to-endpoint connectivity. This observation could however have been made without being predicated on misleading or erroneous experimental design (points 1a and 2) or reported

results (points 1b and 3), and should not have been attributed to SIFT with such specificity (point 4). Readers are urged to not be dissuaded from the demonstrable quantitative benefits of such methods due to:

- a. The raw streamline count metric having been artificially given more desirable quantitative attributes than SIFT in the experiment presented in the Response (point 1; Figure 1C), which is contrary to the empirical behaviour of such^{2,6,7};
- b. The original SIFT method possessing numerical precision limitations that have already been overcome by the SIFT2 method (point 3);
- c. These methods failing to overcome one specific limitation that is in fact ubiquitous in connectome construction (point 4; Figure 1F) and for which no robust solution is yet available (see point 5d below).

While these methods do not solve all limitations and inaccuracies of structural connectome construction (e.g. false positives / negatives), and are themselves dependent on the spherical deconvolution model (including in the presence of pathology), they have nevertheless been shown to provide demonstrable benefits to connectome biological accuracy⁹.

We will demonstrate in coming work:

- d. How endpoint-to-endpoint connectivity estimates can in fact be modulated within this model in a physically-motivated way to reflect such pathologies¹⁰, and thus make these approaches more accurate in such scenarios;
- e. The complex interactions between white matter pathology, premature streamlines termination, and connectome construction¹¹, and how these can be managed using capabilities already available within the Anatomically-Constrained Tractography (ACT) framework^{12,13}.

Scripts and requisite data for digitally replicating these experiments are available at <https://github.com/Lestropie/Zalesky2020/>, which include utilisation of the SIFT and SIFT2 methods provided as part the *MRtrix3* software package (www.mrtrix.org)¹⁴.

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FIGURE LEGENDS

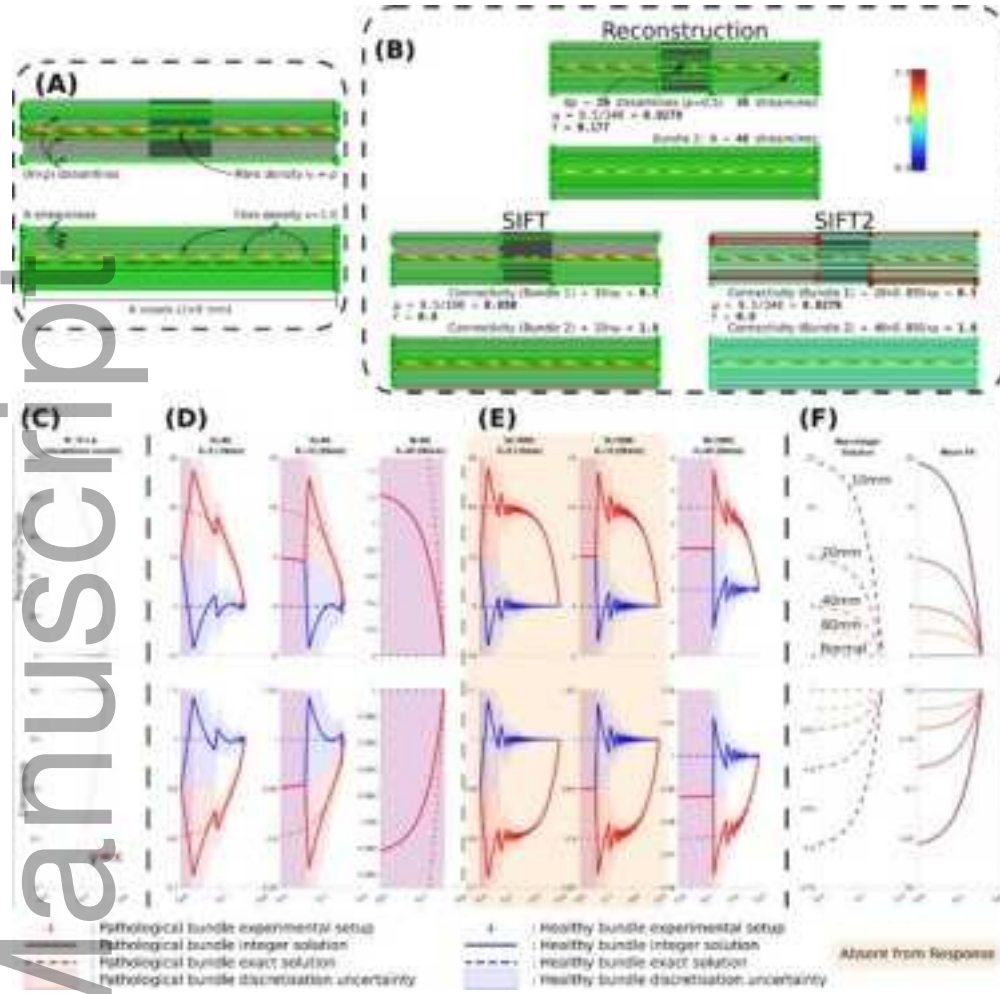
Figure 1: Re-evaluation of the SIFT method in the presence of focal pathology. A. The phantom structure under consideration, with relevant parameters highlighted. B. Results of the SIFT and SIFT2 methods for the phantom structure with $N=40$, $p=0.5$, length 5 voxels, if those streamlines purported to terminate prematurely are not erroneously discarded prior to optimization. C. The streamline counts that were synthesized as part of the phantom construction. D-E. Results of experimental analysis of analytic solution akin to SIFT method as presented in the Response, but including additional information: uncertainty associated with discretization of streamline counts (blue / red shaded areas); exact analytic solution (dashed lines); results for $N=1000$, $K=5$ and $N=1000$, $K=10$ (highlighted rectangle). F. Quantification of bundle connectivity as a function of bundle length and pathology magnitude for: SIFT analytic solution; bundle mean FA (FA=0.8 in unaffected voxels).

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