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PROF. ANDREW ZALESKY (Orcid ID : 0000-0003-2298-9908)

MS. TABINDA SARWAR (Orcid ID : 0000-0001-7313-5350)

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SIFT in pathological connectomes: Follow-up response to Smith and colleagues

Andrew Zalesky[1,2], Tabinda Sarwar[3], Ramamohanarao Kotagiri[3]

1. Department of Biomedical Engineering, The University of Melbourne, Victoria, 3010, Australia
2. Melbourne Neuropsychiatry Centre, The University of Melbourne, Victoria, 3010, Australia
3. Department of Computing and Information Systems, The University of Melbourne, Victoria 3010, Australia

Corresponding author:

Dr Andrew Zalesky
Melbourne Neuropsychiatry Centre
Level 3, Alan Gilbert Building
The University of Melbourne
Victoria 3010, AUSTRALIA

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Email: azalesky@unimelb.edu.au

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Background and Context

SIFT is a method that was developed with the objective of improving the biological plausibility of connectomes. Its utility has been queried by us (1) and others (2). We recently published a hypothetical example demonstrating paradoxical behavior of SIFT in the presence of pathology (1). In short, we demonstrated that SIFT can potentially cause healthy fiber bundles to appear pathological in case-control comparison studies, leading to erroneous inference. Smith and colleagues recently responded that the problem can be remedied with two simple modifications (3). Responding to their Letter to the Editor, we mathematically analyzed the two proposed modifications in detail, finding that they did not resolve or alleviate the problem (4).

In a recently published preprint (5), Smith and colleagues proposed a new approach to remedy the concerns raised, which is based on partial tissue segmentation. Although mandating *a priori* knowledge about the anatomical location of pathology, the new approach appears to perform quite well at alleviating the over-estimation problem of SIFT. This work empirically corroborated some of the concerns raised by our hypothetical example (1), and more importantly, provides a viable solution to the over-estimation problem.

More recently, in a second Letter to the Editor (6), Smith and colleagues contend that the application of SIFT to our original hypothetical example was flawed. We dispute this new contention, as explained in the below response. While we are happy to respond again, we do query the utility of raising new concerns about our original hypothetical example at this time, given that the over-estimation problem that was pointed out with our example appears to have been acknowledged and addressed by the authors (5).

Response Details

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In our hypothetical example (4), we discarded all streamlines that terminated prematurely in white matter at the site of the pathology. Smith and colleagues now contend that we should have instead included the prematurely terminating streamlines (PTSs) as input to SIFT. *First*, we show that including the PTSs does not necessarily resolve the paradoxical behavior of SIFT. We provide multiple examples in Figure 1. *Second*, unless anatomical priors on the location of pathology are prescribed, the anatomically-constrained tractography framework advocated by the authors would presumably discard the PTSs. This is because the PTSs could potentially represent invalid streamline terminations in white matter. Crucially, the precise locations of pathology are often unknown *a priori*, particularly for neuropsychiatric conditions, and thus delineating anatomical priors on the locations of pathology is not always feasible. As remarked by the anonymous reviewer, gross white matter lesions may potentially be classified as gray matter, in which case PTSs terminating in these lesions would not be discarded due to invalid terminations. *Third*, we note that the authors themselves discarded the PTSs in their first Letter to the Editor (3). It is unclear why this supposed error was not pointed out from the outset. We do, however, agree that retaining the PTSs can be beneficial, since these streamlines can convey useful information about pathology. But doing so does not resolve the concerns about SIFT (Figure 1).

Smith and colleagues contend that FOD amplitudes and streamline counts are not directly related and criticize the relation that we assumed between these two quantities. While this is a fair criticism, assuming a relation between FOD amplitudes and streamline counts is not needed to demonstrate the paradoxical behavior of SIFT. For instance, consider a scenario in which a traumatic shear force causes focal neurofilament misalignment (7), resulting in a slight rotation of the pathological FOD's orientation. This orientational misalignment would partially or fully obstruct streamline propagation in the pathological fiber bundle, resulting in the same hypothetical example, but without any dependence on the FOD amplitude. We provide an example in Figure 1. Similar scenarios can arise when the pathological FOD's amplitude falls below the tracking threshold.

The authors also assert that SIFT must be applied to whole-brain tractograms, rather than extracted sets of fiber bundles. We agree and never suggested using SIFT contrary to this assertion. Indeed, the fiber bundles comprising our example constitute the whole tractogram in our model and we never apply SIFT to each bundle independently. However, we recognize that a tractogram of two fiber bundles is exceptionally small, and thus we scaled up the model to eight fibers and were able to reproduce all of the paradoxical behaviors of SIFT (4).

Next, the authors seek to explain why connectivity differences under SIFT can paradoxically decrease following an increase in pathology severity, referred to as the *oscillatory effect* or *non-*

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monotonicity. They remark that the oscillatory effect only emerges for relatively severe focal pathologies, where a majority of streamlines are obstructed. While we agree with this remark, we suggest that complete or near-complete streamline obstruction between a pair of cortical regions (i.e. p=0) is not necessarily an unrealistic scenario. For example, consider the effect of a deep white matter lesion, or agenesis of the corpus callosum, resulting in absence of trancallosal fibers. Indeed, we first recognized the shortcomings of SIFT while studying the connectome of a patient with Kallmann syndrome (8). Furthermore, although the oscillatory effect only emerges for relatively severe pathology, the more problematic paradoxical connectivity changes in the healthy fiber are evident for mild obstructions (i.e. p>0.8). The authors also argue that the oscillatory effect resides within the uncertainty of streamline discretization. This is an interesting point but does not alleviate the practical difficulties of interpreting between-group connectivity differences that have been confounded by the oscillatory effect, which is partly due the fact that streamline counts are whole numbers.

Smith and colleagues once again highlight a newer version of SIFT. We agree that alternative streamline filters, such as SIFT2, LiFE, ReAI-LiFE and COMMIT, can potentially address some of the paradoxical behaviors of SIFT. Indeed, we agree that SIFT2 alleviates the oscillatory effect, although the authors have demonstrated that the more problematic over-estimation issue persists under SIFT2, unless tissue segmentations of pathology are available (5). Further work is needed to numerically compare the performance of these various streamline filters. Recent work by Schiavi and colleagues (9,10) using COMMIT is relevant in this context.

Notably, several clinical studies aiming to identify case-control connectivity differences in the presence of both focal and non-focal pathologies have used SIFT. The point of our example is to raise awareness about the potential for SIFT to result in paradoxical inferences in these pathological scenarios and motivate the development of viable solutions.

Finally, we recently applied SIFT to the connectome phantoms developed in our original paper (1). Consistent with Sinke and colleagues (2), we found that SIFT did not appreciably improve connectome accuracy under both deterministic (raw: F = 0.40 ± 0.06, SIFT: F = 0.40 ± 0.05) and probabilistic (raw: F = 0.19 ± 0.02, SIFT: F = 0.22 ± 0.04) tractography (mean ± standard deviation in F-measure, no thresholding).

Conclusion

We believe that the remarks in the second Letter to the Editor do not abrogate our concerns about the use of SIFT in the presence of pathology. Based on the above response, we dispute the assertion that our experimental design was erroneous. Moreover, the authors did not address

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our core contention of whether the fundamental premise of SIFT breaks down in diseased connectomes, as we analogized with the adage *a chain is only as strong as its weakest link* (4).

Smith and colleagues first dismissed the problem that we raised on the basis of an insufficient number of streamlines and lack of normalization (3). They then proposed that the problem can be overcome with appropriate segmentation of pathological tissue and the use of a density ratio (5). Now they suggest that the problem is due to the elimination of streamlines that prematurely terminate at the site of pathology (6). We suggest that such inconsistency of advice is likely to cause confusion among researchers.

Our position remains the same: SIFT should be used cautiously when applied to pathological connectomes because it can potentially lead to erroneous inference. A newer version of the method (SIFT2) does not appear to resolve the core concern, although further investigation using *in vivo* diffusion-weighted MRI data is warranted.

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Figure Legend

Figure 1. Further examples demonstrating the paradoxical behavior of SIFT in the presence of pathology. ***Example I:*** SIFT suggests that the connectivity in Fiber B is 14% greater in the patient compared to the healthy control. However, Fiber B comprises exactly the same number of streamlines in both the patient and control. SIFT therefore results in erroneous inference on the healthy fiber. The pathology in this example comprises multifocal lesions, which is characteristic of diffuse axonal injury (7). ***Example II:*** SIFT fails to detect the pathology in Fiber A. While connectivity in Fiber A is 40% lower in the patient compared to the control, SIFT does not detect any patient-control difference. The pathology in this example models a traumatic shear force resulting in neurofilament misalignment. As such, the orientation of the pathological FOD is slightly rotated, resulting in partial obstruction of streamline propagation (p=0.6). The FOD integral is however unaltered, providing an example without the assumption that was criticized by Smith and colleagues. This scenario is consistent with previous studies reporting patient-control differences in the principal diffusion direction, which are not accompanied by differences in anisotropy (11,12). In both examples, prematurely terminating

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streamlines (PTSs) are indicated with solid blue lines. All PTSs are included in the SIFT calculation. End-to-end streamlines are indicated with solid black lines. The raw streamline count and the number of streamlines discarded by SIFT (parenthesized) are indicated above each group of streamlines. The FOD integral is indicated below each FOD (oval). In both examples, 20 streamlines were initiated from each of the two ends of each fiber. The percentage change in connectivity between the patient and control is defined as (control − patient) / control × 100%. We only show the exact (non-integer) solutions here, which are analogous to SIFT2; see (4) for details about integer and non-integer solutions. We found that the integer and non-integer solutions for both examples are similar. Note that while we model complete obstruction (p=0) in Example I for simplicity, the paradoxical behavoir of SIFT is also evident for partial obstruction (e.g. p=0.1). *FOD*: fiber orientation distribution. *SIFT*: spherical-deconvolution informed filtering of tractogram.

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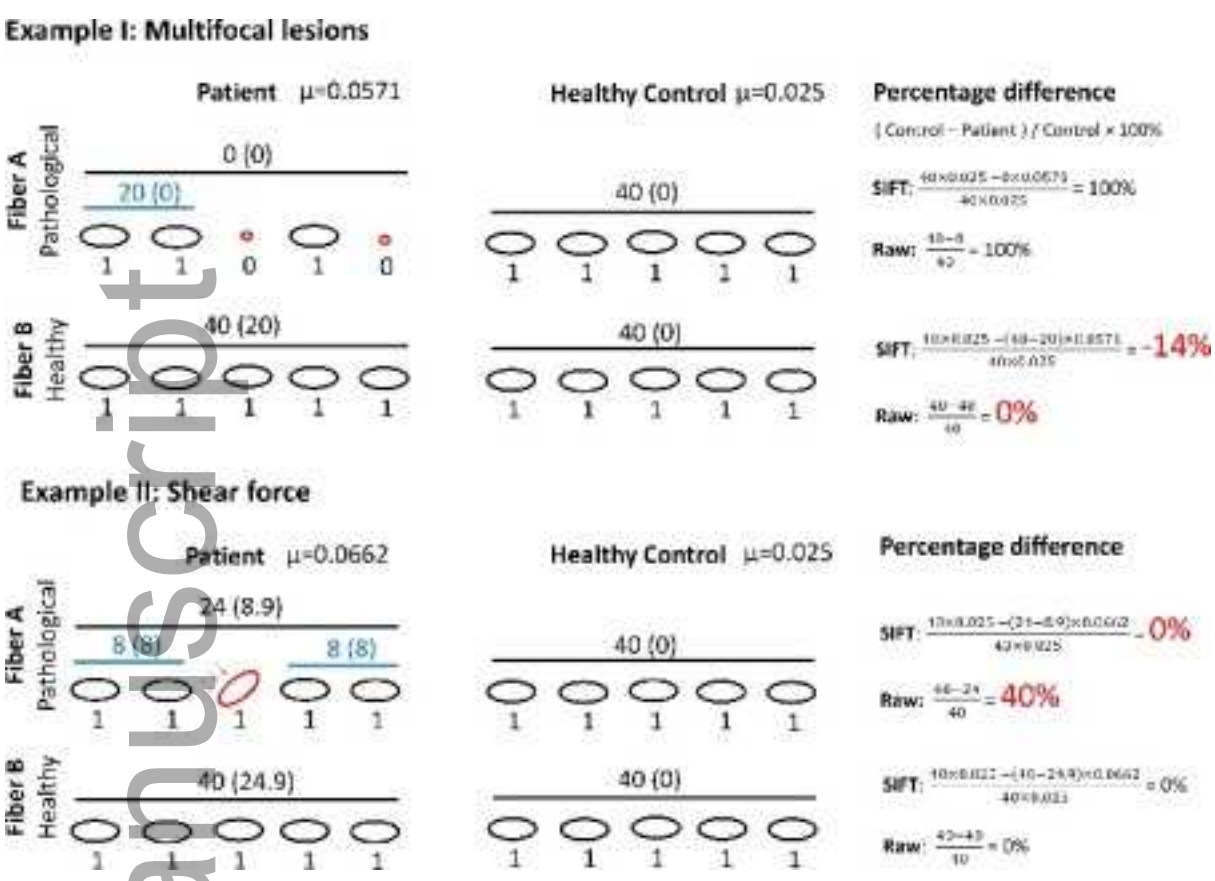
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