Abstract Title

"Noise" in diffusion tractography connectomes is not additive

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Synopsis

With the increasing popularity of diffusion MRI tractography-based connectomes in the literature, a better analysis of their reproducibility is crucial. Studying connectome differences across a test-retest dataset allows us to investigate their variance. In this work we highlight the non-additive nature of tractography based connectome "noise". This observation holds even when accounting for some of the biggest tractography biases such as seeding density, seeding region, tract volume and fiber length.

Purpose

To raise awareness to all researchers tempted to post-process structural connectomes from diffusion tractography with "standard" algorithms that often implicitly assume an additive noise model (for example least-squares fit).

Methods

We acquired a T1-weighted image (1 mm^3 isotropic) and 64+2b0 diffusion weighted images (2 mm^3 isotropic) at b=1000 s/mm^2 for 11 healthy volunteers on a 1.5T Siemens Magnetom. The acquisitions were repeated 3 times (with 1 month intervals) for each subjects to obtain a test-retest database. The images were corrected using FSL/TOPUP. The DWI were upsampled to 1 mm^3 isotropic using tri-linear interpolation. The T1 images were registered linearly to the upsampled DWI using FSL/FLIRT, then non-linearly using ANTs. The Destrieux atlas[1] was registered to each diffusion warped T1 image using Freesurfer[2]. We computed Fiber Orientation Distribution Functions from spherical deconvolution[3]. We performed probabilistic streamline tractography using Particle Filtering Tractography[4], seeding from the WM (5 seeds by voxel) and from the WM-GM interface (10 seeds by voxel), resulting in ~2M fibers by tractogram. DWI connectome were computed by intersecting the resulting streamlines with dilated version of the 150 cortical regions from the registered atlas (total of 11325 possible pairwise connections). We produced several connectomes by using fiber count and average inverse fiber length similarly to [5,6] and normalizing the connections values by different combinations of tract volume, GM parcel volume/area and seeding density. We averaged the 3 repeated connectomes for each metric and each subject to obtain gold standard

connectomes. From these connectomes, we compute the deviation with respect to each acquisitions and estimate the variance connections by connections (grouped in bins of equal connection strength) by fitting zero-mean normal distributions.

Results

For all connectivity metrics, the resulting connectomes are fairly similar (fig.1). The overlaps between the set of the 500 biggest bundles from any two metrics is at least 54% (fig.2). The distribution of the connections weight is also similar between acquisitions and subjects with correlation of at least 60% (fig.3). The computed connectome noise standard deviation exhibits strong correlation to the connection values for all subjects and all metrics, suggesting a noise model closer to multiplicative noise than additive noise (fig.4). Surprisingly, the deviation from additive Gaussian noise is comparable across very different connection weight metrics.

Discussion

In this work we treated the connectomes as if they were some measurable quantity subject to acquisition noise rather than the cumulation of many sub-steps, each with their own errors and biases. This approach is a useful abstraction that attempts to relate the tractography based connectomes to some underlying (unknown) notion of connection strength (i.e. $$Connection_{measured}=Connection_{Ground-Truth}+Noise$$ with $$Noise$$ potentially a function of $$Connection_{Ground-Truth}$$ leading to multiplicative-like behavior). Claiming that the "connectomic noise" behave multiplicatively is akin to saying that a larger fiber bundle should have a much greater variance in term of number of streamlines (for a certain set of tractography parameters) than a small bundle when repeating measurements, which seems reasonable considering known tractography biases. However, we have used both WM and GM-WM interface seeding, which have different tract volume/length biases. The tractography algorithm used is also resistant to high curvature and partial volume effects[4] which could be argued to affect smaller tract more than larger (other tractography algorithm were studied and the same "noise" behavior was present). Finally, we have accounted for fiber length and/or tract volume and/or GM parcel size through our multiple connectome metrics and the multiplicative-like nature of the noise persist, opening new questions about the nature of this unknown definition of diffusion based connectivity strength.

Conclusion

Various flavors of tractography based connectomes are present in the literature[5,7]. This new tool offers great promise as a complement to scalar map group comparisons. It is however crucial to have a good understanding of the mathematical properties and limitations of this object before we can be confident in our statistics derived from it. For instance, in diffusion MRI, it is often implicitly assumed in algorithm that noise is gaussian additive while it is truly closer to Rician or non-central chi^2 additive noise, which leads to biases somewhat proportional to the noise variance that can be accounted for. However, in the case of connectivity matrices, the noise seems to exhibit multiplicative behavior which needs to be treated with more restraint. Future research will look into different definition of connection strength such as fiber weights extracted from COMMIT[8].

Acknowledgements

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Figure 1: Connectome examples for four metrics on the same DWI. WM_VOL is normalization by tract volume and GM_VOL is normalization by GM parcel volume. The upper triangles are computed from the GM-WM interface seeding and the lower triangle are computed from WM seeding.
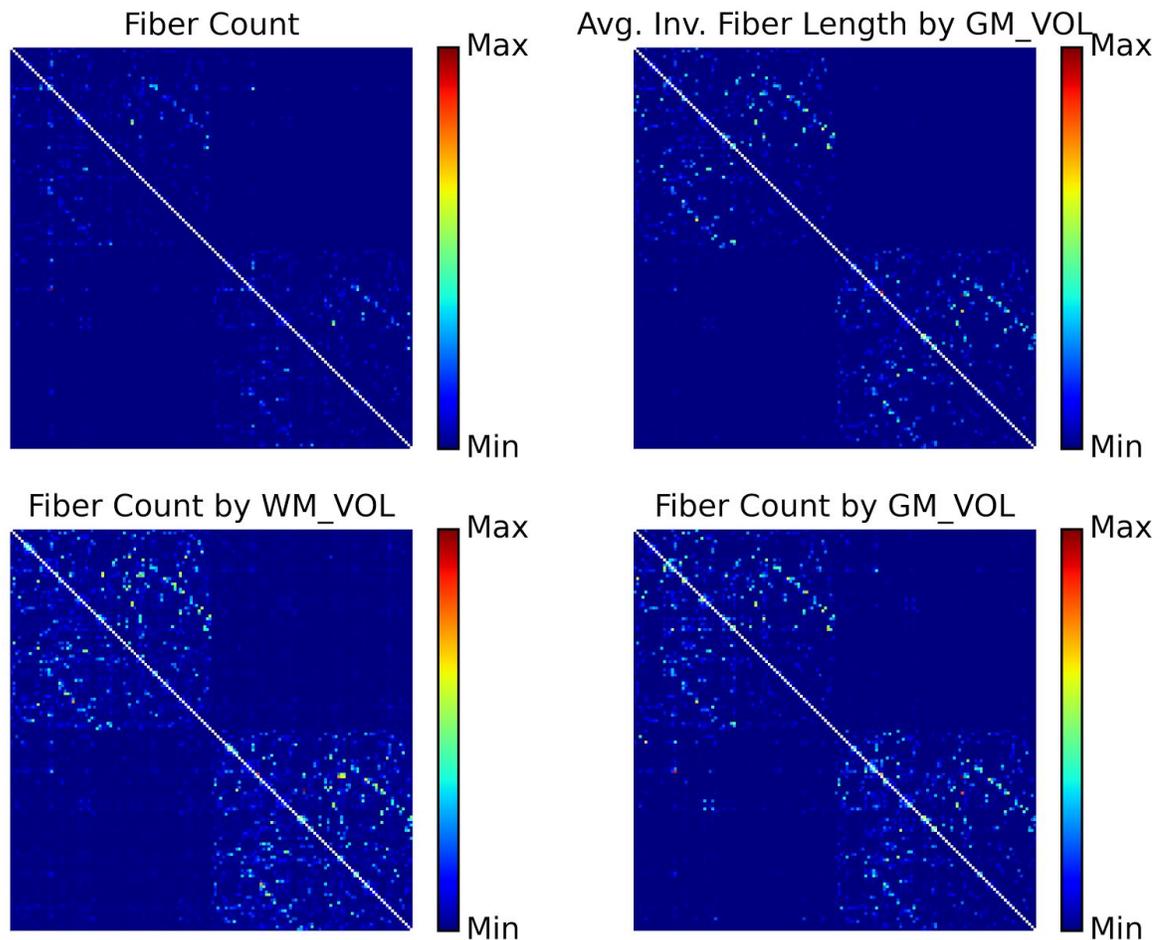
Figure 2: Overlap between the 500 biggest bundles between different metrics and seeding strategy, averaged over all subjects and acquisitions. M is fiber count and L is average inverse fiber length. WM and INT are the seeding strategy. GM_VOL and WM_VOL are the volume normalization.
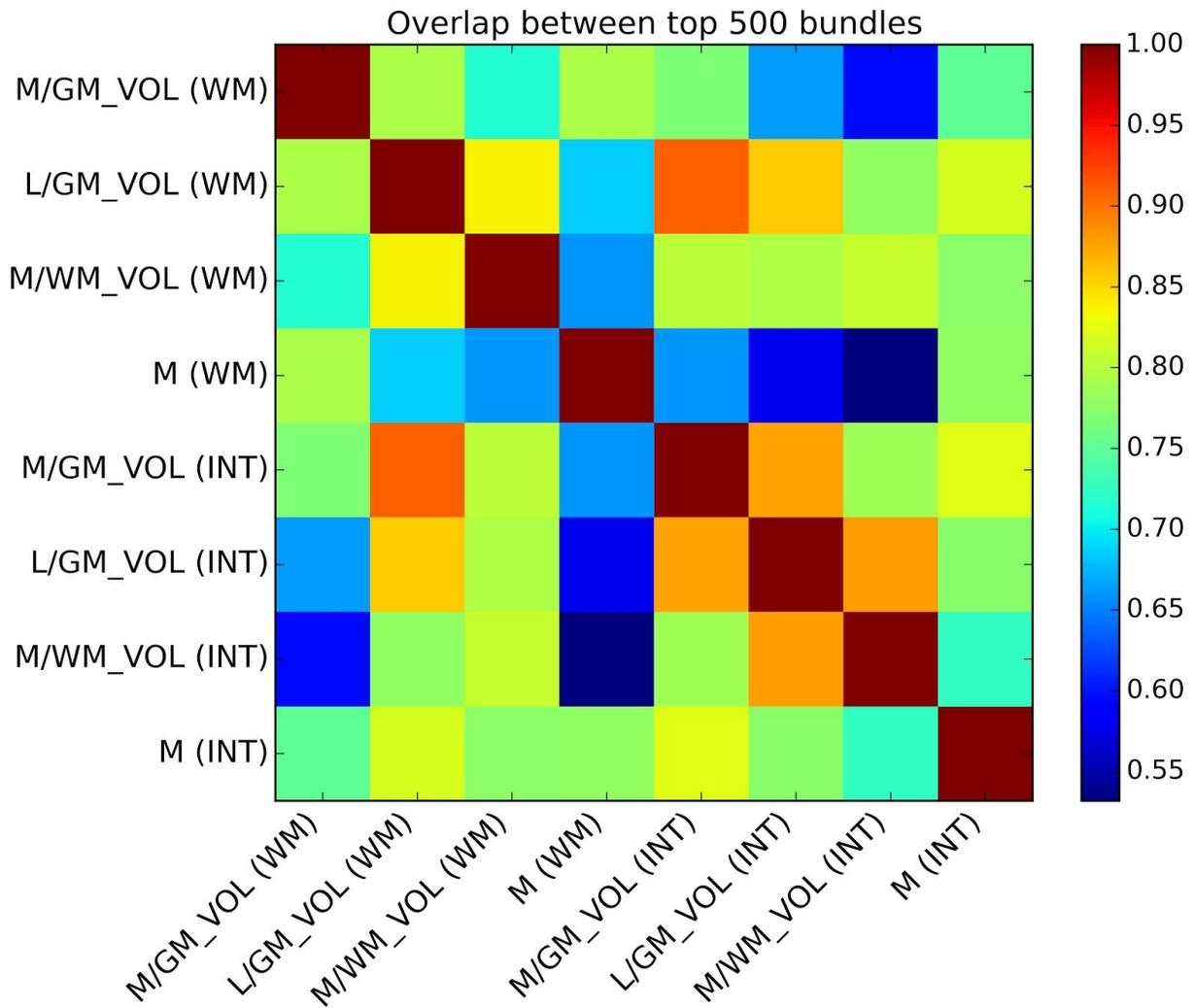
Figure 3: Correlation coefficient between connectomes for fiber count. Every 3 consecutive line block are the different acquisitions of a specific subject. The first half of the graph are from WM seeding, second half from GM-WM interface seeding.
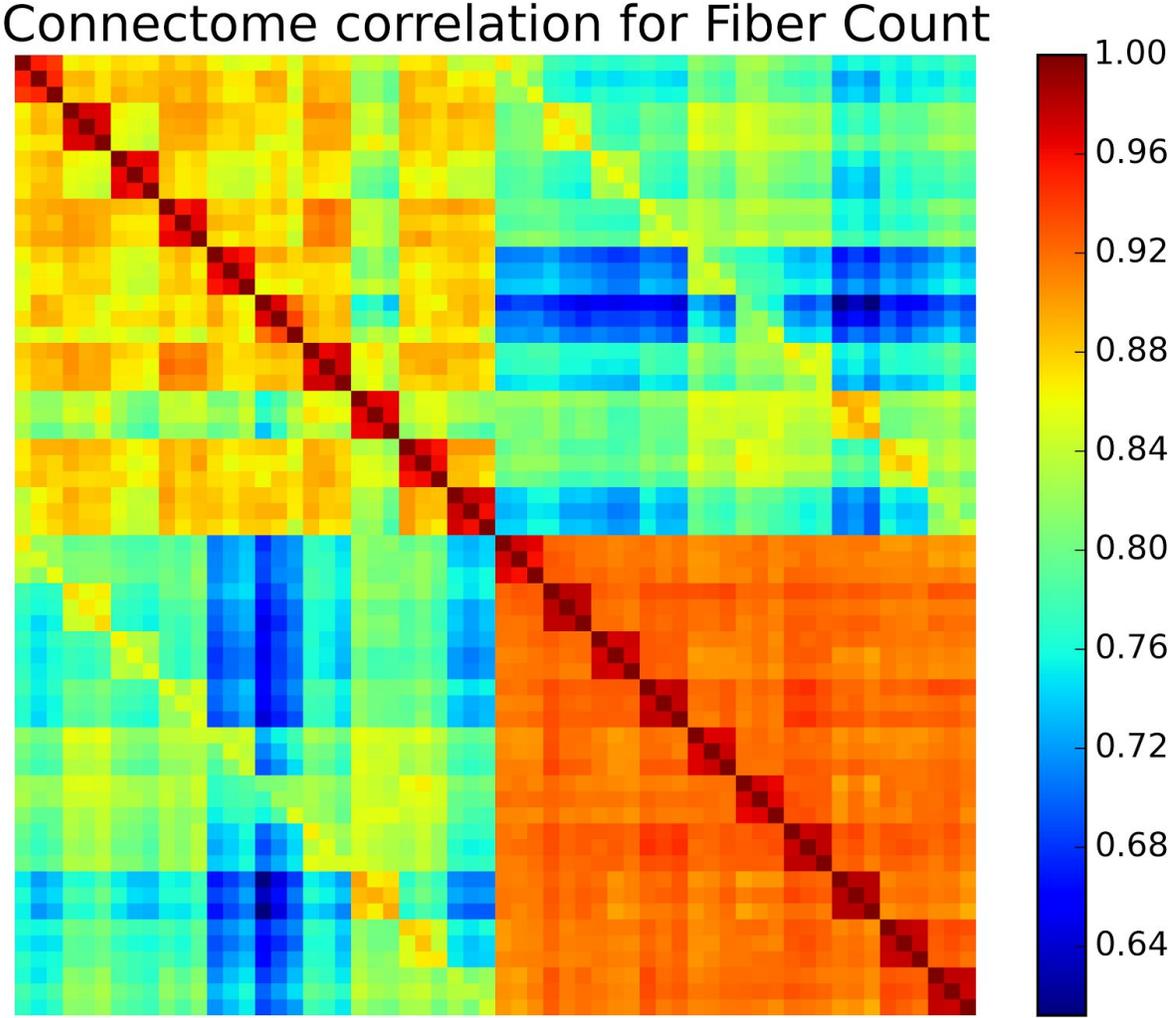

Connectome correlation for Fiber Count

Figure 4: Comparison of the connectomes gold standard and estimated noise std for different metrics (introduced before). The values are sorted and normalized to be aligned for better appreciation of the noise intensity correlation with the connections strength.