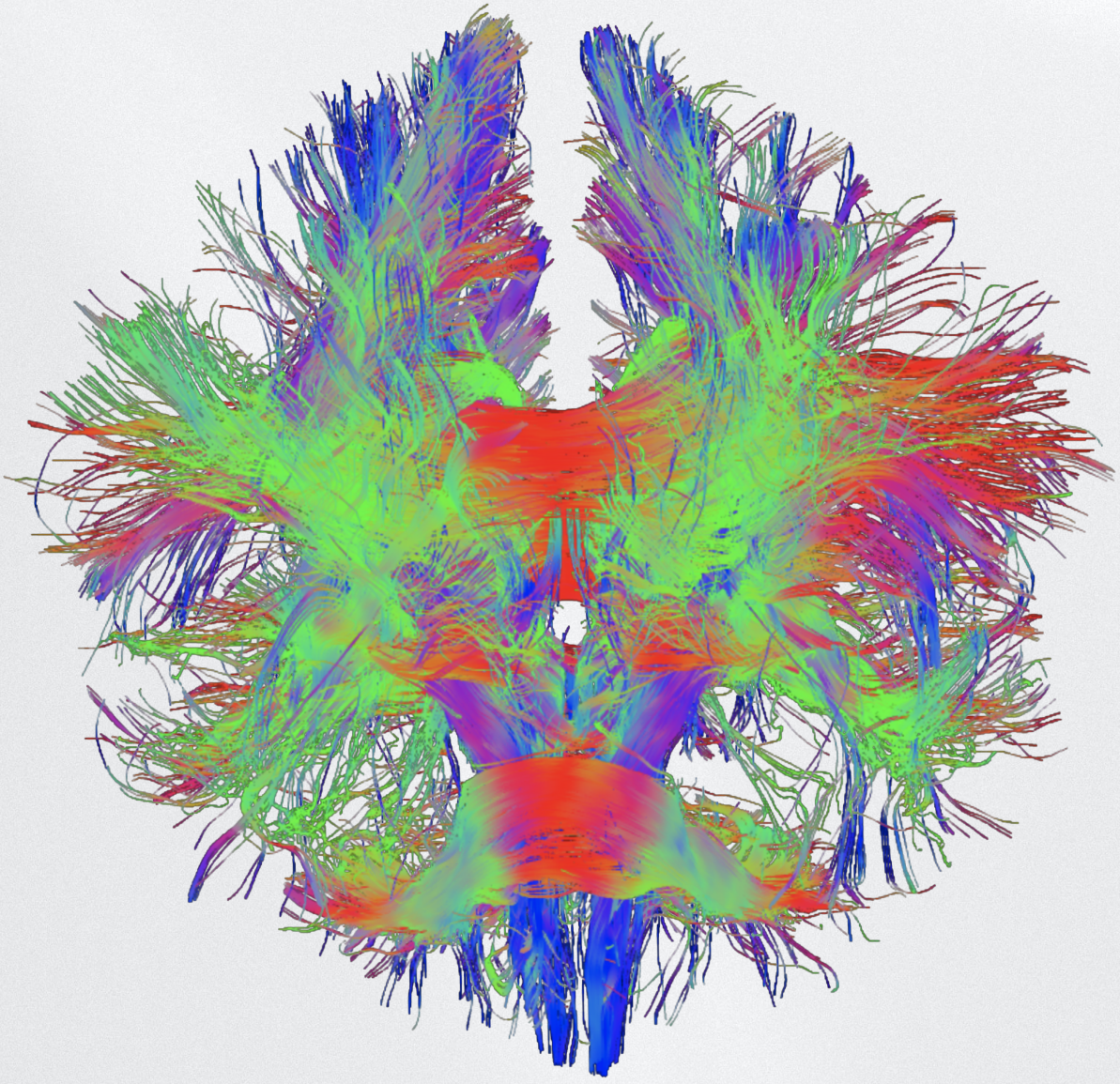
Constrained spherical deconvolution–based (CSD) tractography



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1.0. OVERVIEW

Diffusion weighted imaging captures the orientation of white matter fibers in the brain and can offer insight into human brain connectivity and function. Constrained Spherical Deconvolution (CSD) is a methodology used for estimating the distribution of fiber orientations using diffusion weighted imaging. CSD offers key advantages over the traditional diffusion tensor (DTI) model because CSD can additionally represent regions with multiple fiber orientations whilst DTI can only accurately represent a fiber bundle with a single orientation. This has implications in the ability to recreate white matter structures in regions of multiple fiber orientations. CSD can generate all the main tractographic structures that DTI can generate but has additional support for non-primary crossing fibers.

CSD is typically used for fiber tracking algorithms to generate full brain tractography. In this process, a fiber tracking algorithm tracks white matter fibers from seed points throughout the brain along the fiber directions calculated in CSD.

2.0. GENERAL BACKGROUND IN METHODS FOR GENERATING WHITE MATTER TRACTOGRAPHY

2.1. DIFFUSION OF WATER MOLECULES IN THE HUMAN BRAIN

White matter tracts in the brain are highly structured tissue. White matter is composed of bundles of long myelinated axons called tracts. The myelin sheaths that encircle neurons give white matter a unique diffusion profile. This can be seen in **Figure 1** which demonstrates how water molecules can diffuse quickly along an axon but more slowly across it.

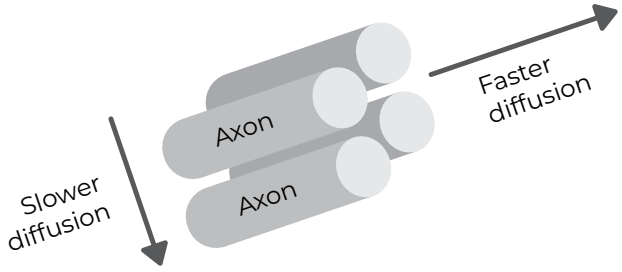

Figure 1 - The difference in diffusion speed along a white matter fiber axon as opposed to across an axon. Water molecules can diffuse quickly along the length of the white matter axons but diffuse slowly in a perpendicular direction because of the myelin sheath[13]

Because water diffusion is so drastically different along the white matter axon as opposed to across it, white matter has a very heterogeneous water diffusion profile. Situations where water molecules can diffuse freely in all directions is called **isotropic** whilst situations where there is a strong directionality to the diffusion of water molecules is called **anisotropic** as is illustrated in **Figure 2**.

In this framework the diffusion of water in white matter fibers can be described by its anisotropic component as there is a strong directionality along the axon of the fiber. The ability to measure the diffusivity of water in diffusion weighted imaging thus gives important information about the underlying structure of the white matter in the brain.

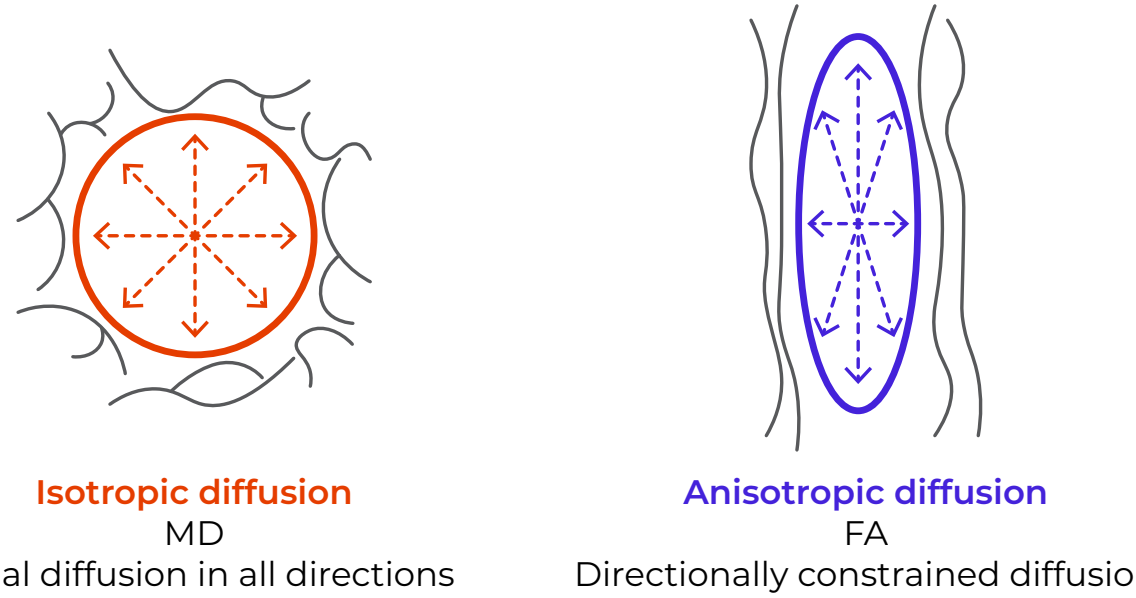

Figure 2 - The difference between isotropic and anisotropic diffusion. The quick diffusion of water along white matter axons and slow diffusion of water across white matter axons is called anisotropic because diffusion has a strong directionality to it. This is in contrast to equal diffusion in all directions which is called isotropic diffusion[12]

2.2. DIFFUSION WEIGHTED IMAGING

Diffusion weighted images capture the diffusivity of water molecules throughout the brain. Generally, this involves stimulating water molecules in different directions and measuring how easily water can diffuse. This category of MRI acquisition is called **diffusion weighted** because it aims to measure the diffusion

profile of the underlying brain tissue. Because white matter is anisotropic, careful measurement and interpretation of this diffusion weighted signal can offer insight into the white matter fibers of the brain.

Diffusion weighted imaging sequences typically comprise of a series of acquisitions in different gradient directions and at least one baseline B0 scan. Gradient direction acquisitions involve sensitizing water molecules in different directions and measuring the degree of diffusion. There are different MRI pulse sequences that can stimulate and measure this effect. In its simplest form this involves dephasing and rephasing MR pulses where phase dispersion from diffusing molecules will lead to signal attenuation. In contrast if the water molecules are stationary and do not diffuse then signal attenuation will be minimal[13].

Given that water diffuses faster along the length of a white matter fiber axon, a high degree of signal attenuation in a particular direction indicates that this is the length of a white matter fiber. Conversely, low signal attenuation in a particular direction implies that this is the wall of a white matter fiber myelin sheath. Thus a typical sequence of diffusion weighted imaging provides a measure for the diffusivity of water in different directions. The B0 baseline scan captures the tissue signals and contrasts in the absence of diffusion gradient. Using these two acquisitions forms a model for how freely water can move in different directions and an initial representation of the underlying white matter fiber structures.

2.3. DIFFUSION TENSOR MODEL AND THE ISSUE OF CROSSING FIBERS

To interpret and analyze the diffusion weighted signal it is important to build a representation of the diffusion process within each voxel. The traditional methodology of doing this is **diffusion tensor imaging (DTI).** While DTI offers valuable additional information from DWI, it has known limitations when representing complex fiber orientations.

In contrast, **constrained spherical deconvolution (CSD)** iterates upon DTI with a more advanced method that models the same fibers as DTI as well as additional and and more complex areas of multiple fiber orientations.

2.3.1. BACKGROUND TO DTI

The traditional diffusion tensor imaging (DTI) model represents the orientation of fibers in each voxel by a *single* primary direction.

It involves fitting the diffusion weighted signal to a Gaussian model of water molecule displacement[13]. The “diffusion tensor” in this context is the 3x3 covariance matrix of the Gaussian distribution. Here the major eigenvector points in the direction of the highest diffusion. In white matter this is akin to the direction of the axon bundle. One of the drawbacks of this system is that it assumes that there is a unique orientation of fibers in each voxel[7].

2.3.2. LIMITATIONS OF DTI IN COMPLEX FIBER ORIENTATIONS

The DTI model of fiber orientation is built on the assumption that a single fiber orientation in each voxel is sufficient. The presence of an additional fiber orientation is instead absorbed in calculating a single dominant orientation.

Unforunately, many regions of the brain are better represented by a “crossing fibers” model, that is, situations where white matter fibers pass by and cross over each other. This detail is not captured in the traditional DTI model.

Figure 3 illustrates the scenarios in which complex fiber orientations arise in the brain including crossing, bottlenecks, branching, fanning, and kissing situations. These are all situations in which DTI is challenged.

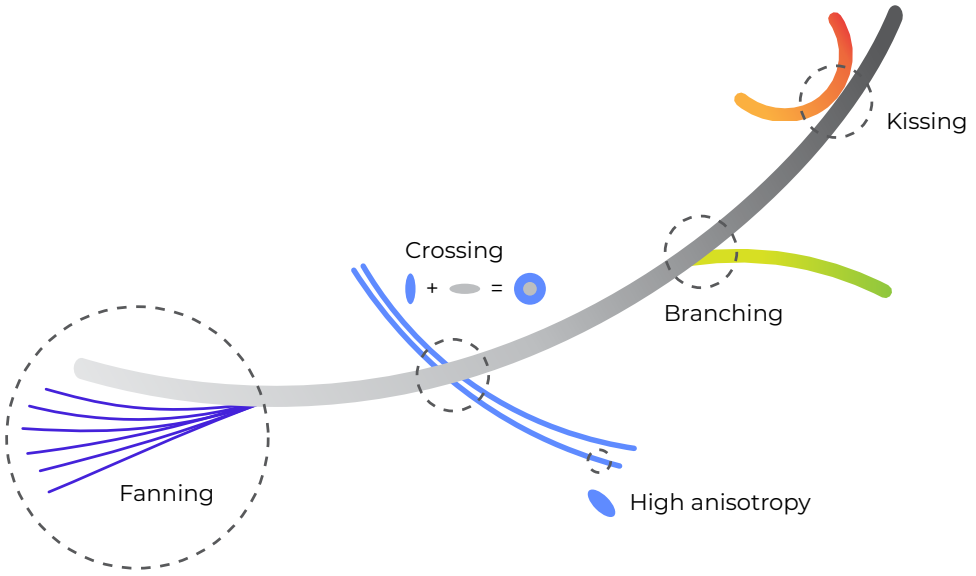

Figure 3 - The many situations in which complex fiber orientations arise in the brain[11]. Situations such as crossing fibers, branching, and fanning require a more robust fiber orientation model to accurately represent and construct tractography with.

2.3.3. CONSEQUENCES OF DTI'S LIMITATIONS WITH COMPLEX FIBER ORIENTATIONS

The inability of DTI to accurately model complex fiber orientations limits its applicability. In circumstances where the underlying fiber orientation is complex such as in the branching, fanning, or crossing scenarios portrayed in **Figure 3**, the resulting DTI tensor cannot accurately represent the data and results in a tensor which is an ellipsoid with an ill-defined peak that doesn't accurately correspond to any of the fiber populations. That is- not only is the presence of a non-primary fiber orientation missed, but the primary fiber orientation is also erroneously skewed.

Estimates place the proportion of white matter voxels that contain multiple fiber orientations at roughly 70%[8]. This is the case, for instance, in areas such as the corticospinal tract (CST), which critically challenges the DTI model because the crossing of the superior longitudinal fasciculus (SLF) leads to fibers that the model cannot generate[6]. This implies that, whilst DTI offers an additional layer of information over DWI which proves to be useful for functional structures[9], it remains unable to properly distinguish between crossing fibers and those in a fanning pattern, a limitation that the CSD algorithm solves.

2.3.4. CSD AS AN ALTERNATIVE TO DTI

An alternative model to DTI which accommodates the issue of 'crossing fibers' is the **fiber orientation distribution (fODF)** model that is supported by CSD. CSD calculates multiple tensors in heterogeneous regions and is thus able to support crossing fibers and areas of multiple fiber orientations[1]. It captures the primary eigenvector signal that is generated in the DTI model but can additionally differentiate with and capture the presence of non-primary crossing fibers. This enables CSD to accurately reconstruct white matter structures in regions such as the aformentioned CST. **Figure 4** displays the difference between DTI and CSD in the fiber response model and how this leads to different outcomes in deeper analytics such as tractography.

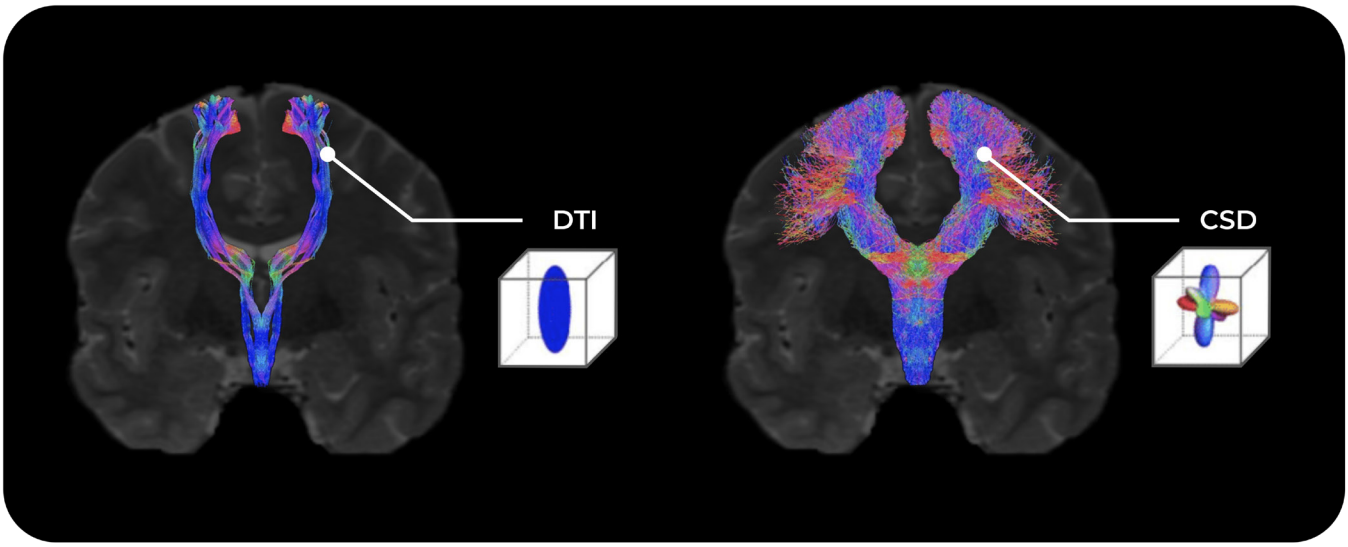

Figure 4 - A comparison of outputs between DTI (on the left) and CSD (on the right) in modelling the fiber response and reconstructing the Corticospinal Tract. The DTI model only assumes one direction per model by extracting its eigenvector while the CSD algorithm handles multiple crossing fibers per voxel.

3.0. TECHNICAL INFORMATION ON CSD TRACTOGRAPHY

In addition to summarizing the mathematical methodology behind CSD, the following section describes a technical workflow to utilize CSD for whole brain tractography; in particular, the workflow used in Omniscient software.

3.1. PREPROCESSING

Prior to undergoing CSD transformation, images pass through a standard pre-processing pipeline consistent with DTI including motion correction and generation of a brain mask[15].

3.2. FRACTIONAL ANISOTROPY (FA) MAP

The **fractional anisotropy (FA hereafter)** map is a measure for the amount of diffusion asymmetry in each of the voxels. It is obtained by measurement from a tensor fit on the diffusion data. Therefore, areas with high FA values are those where there is relatively unrestricted diffusion in one particular direction. This is typically associated with areas where there is a dense packing of fibers in a single direction. **Figure 5** depicts a typical FA map of the brain where areas of highly directional dense white matter are whiter than the grey matter on the edge of the brain.

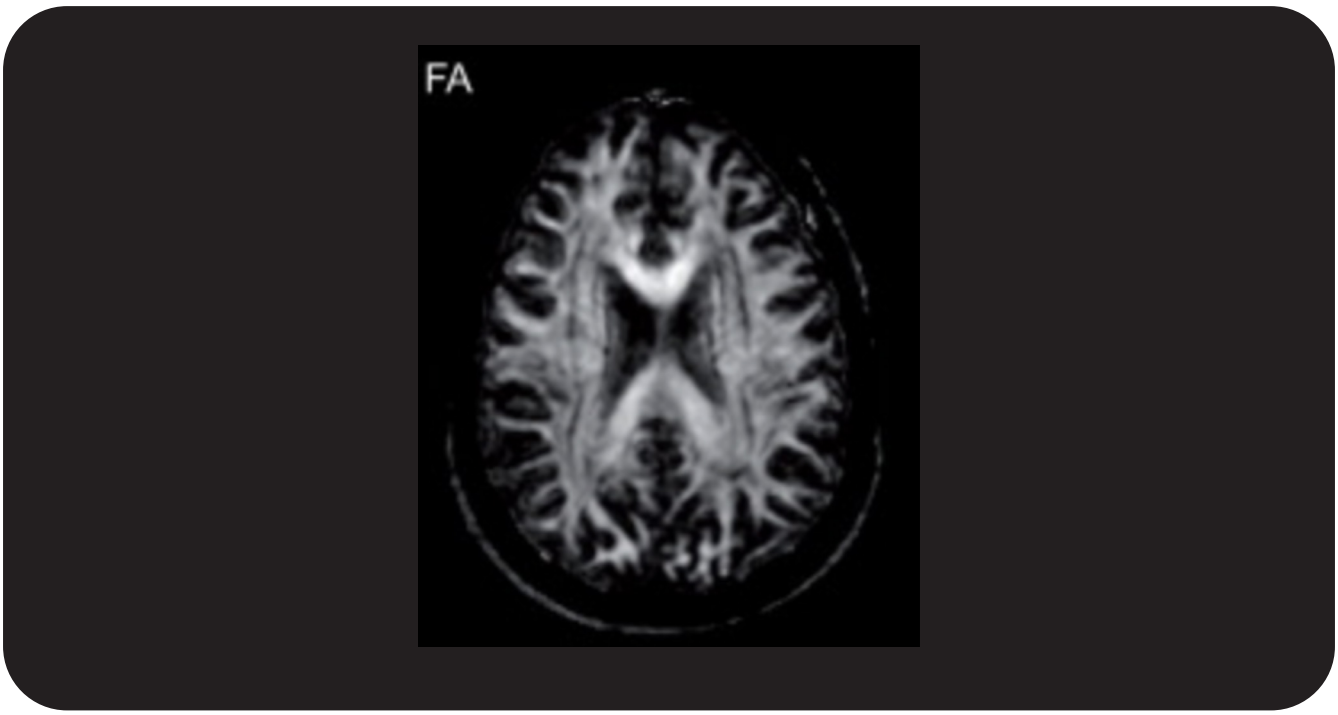

Figure 5 - An illustration of a FA map of the brain. Voxels with high diffusion directionality (those that are highly anisotropic) are whiter (corresponding to a higher fractional anisotropy value)

3.3. CSD ALGORITHM

The CSD algorithm calculates the white matter fiber orientation distribution function (fODF) using diffusion weighted imaging data. This process involves 1) estimating the fiber response function and 2) using the fiber response function in the context of constrained spherical deconvolution to determine the fODF.

3.3.1. ESTIMATING THE FIBER RESPONSE FUNCTION

The first step in the CSD fODF calculation is the estimate of the **fiber response function**. The fiber response function is the expected signal in a voxel that contains a single and coherently oriented bundle of axons. Accordingly, it is helpful to look towards regions of the brain where it is known that there are single coherent fiber populations. The FA map is used here to identify regions where unrestricted diffusion implies a dense fiber bundle which are used to calculate the response function.

3.3.2 RECONSTRUCTING OF THE FODF

The CSD model then estimates the fiber orientation distribution (fODF) by assuming that the diffusion weighted signal captured can be adequately described by the fiber response function[4]. The assumption is that the diffusion weighted signal in each voxel is a summative *combination* of the fiber response from the multiple fibers in each voxel. This is mathematically described as a **"convolution"** of the response function over the fODF as shown in **Figure 6**.

Hence, the goal of CSD is to seperate each fiber response out by **"deconvoluting"** the fODF from the DW signal using the fiber response function described above.

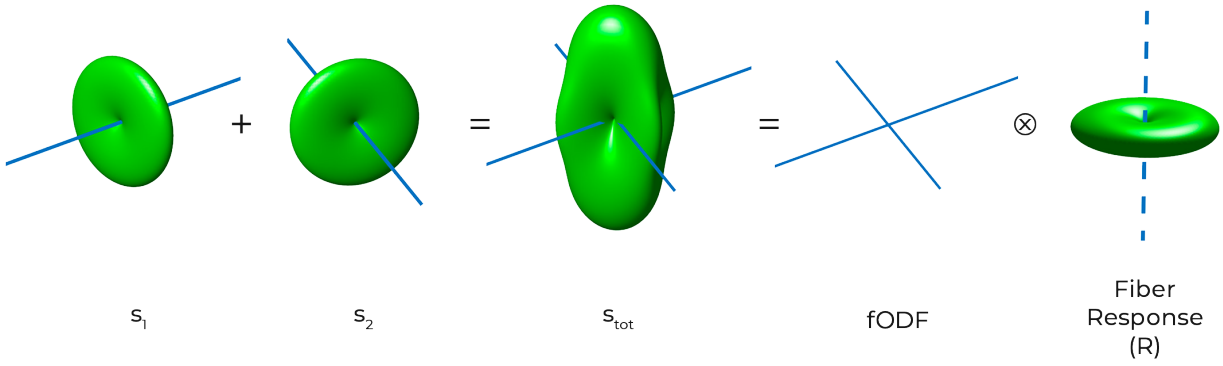

Figure 6 - The CSD model of fiber response equates the summation of diffusion weighted signals against the convolution of the fiber orientation diffusion function with the fiber response[16]

To achieve this, the process of CSD involves representing the fODF in a **spherical harmonic basis** which can take the form of both a positive or negative solution. A negative solution to fODF, however, is physically impossible and is purely a result of noise contamination as there is no such thing as negative white matter orientation[4]. One of the innovations of CSD is therefore to penalize negative amplitudes through a soft regularizer in the least-squares fit of the coefficients of the fODF to the diffusion weighted signal. This soft regularizer penalises negative amplitudes in the fODF coefficients which does not guarantee a non-negative solution but prefers one. Herein lies the **"constrained"** nature of constrained spherical deconvolution which vastly increases efficiency and robustness to noise, and enables the resolution of complex fiber orientations where fibers are separated by small angles.

Completing this, the fODF generated through CSD contains all the primary eigenvector directions that are calculated via DTI but with additional tensor peaks representing the non-primary fibers.

3.4. FIBER TRACKING

Once the fODF has been calculated, **whole brain tractography** can be conducted by pairing fiber direction data with a set of seed points to define start points and stopping criteria in the process of fiber tracking. With these criteria and input parameters defined a deterministic fiber tracking algorithm can generate individual white matter fiber bundles called **streamlines**. The extension of individual streamlines to the entire brain is called whole brain tractography.

3.4.1. OVERVIEW OF FIBER TRACKING

Whole brain tractography is the cumulative and iterative process of tracking streamlines from seed points along the primary tensor directions until they reach a stopping point. **Figure 7** depicts the flow of streamline accumulation and the iterative process of repeatedly tracking a streamline from one voxel to the next until it meets the stopping criteria.

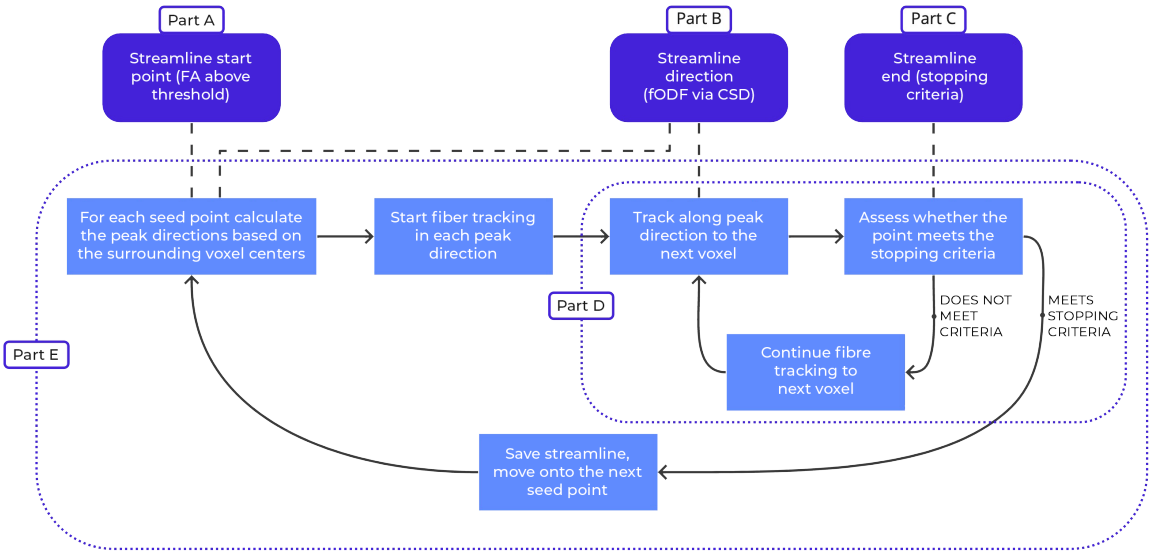

Figure 7 - The iterative process of fiber tracking. This flow chart describes the procedure through which each seed point is used to start a streamline, the streamline is tracked along peak tensor directions until it meets each stopping criteria. The collection of streamlines across all the seed points culminates in whole brain tractography.

3.4.2. PART A – SEED POINTS

Seeding points are the start points of the fiber tracking. Voxels in which there is sufficiently high FA (set in line with field standards[1,2]) are retained as ideal voxels to set seed points and used as such. Multiple seeds are distributed uniformly through each eligible voxel. The use of FA threshold to determine seed points alleviates the risk of missing any potential streamlines and creating any erroneous streamlines. Voxels with high FA values are those that have a strong directionality to the diffusion of water. This is a feature of white matter fiber bundles. Hence using the FA map to determine seed points gives assurance that streamlines are being traced from all eligible white matter bundle points.

3.4.3. PART B – STOPPING CRITERIA

A set of criteria for which fiber tracking should stop is used to enforce the end points of white matter fibers. One criterion is that fibers are only tracked through voxels in which the FA value is above the threshold sufficient for white matter. A second criterion is that the distance between other fibers is above a minimum threshold for separation (set in accordance with field standards[1,2]). This ensures that individual fibers are tracked throughout the white matter areas of the brain.

3.4.4. PART C – CSD TENSOR DIRECTIONS

Fibers are tracked from seed voxel points along the peak directions from the fiber orientation distribution function (fODF). The fODF is the outcome of CSD applied to a diffusion weighted signal. Each voxel will have multiple CSD peaks representing the different fiber orientations of the complex underlying white matter structure.

3.4.5. PART D – ITERATIVE FIBER TRACKING

For each iteration, this algorithm tracks a fiber from a seeded voxel point using

stopping criteria. Fibers are tracked along the peak direction in both directions, linking one voxel to another via a streamline in 3D space until the stopping criteria is met[3]. The peak direction for initiating a track from a seed, and for propagating a track throughout the brain is based on a combination of the tensor peaks of the surrounding voxel centers from that point.

Figure 8 shows the fiber tracking process from seed points along the peak directions and how this constructs the streamlines (shown on the left side of the figure). When the stopping criteria is met this streamline is saved and the next seed point is used for tracking.

Figure 9 shows the fiber tracking process from seed points in an area of crossing fibers. Here there are multiple peaks in the voxels surrounding the seed point so the fiber tracking algorithm propagates tracks in each peak direction.

This algorithm gives completely deterministic results from the same seed points. That is to say, since the seed points are fixed, then repeating the fiber tracking process will generate the same set of streamlines.

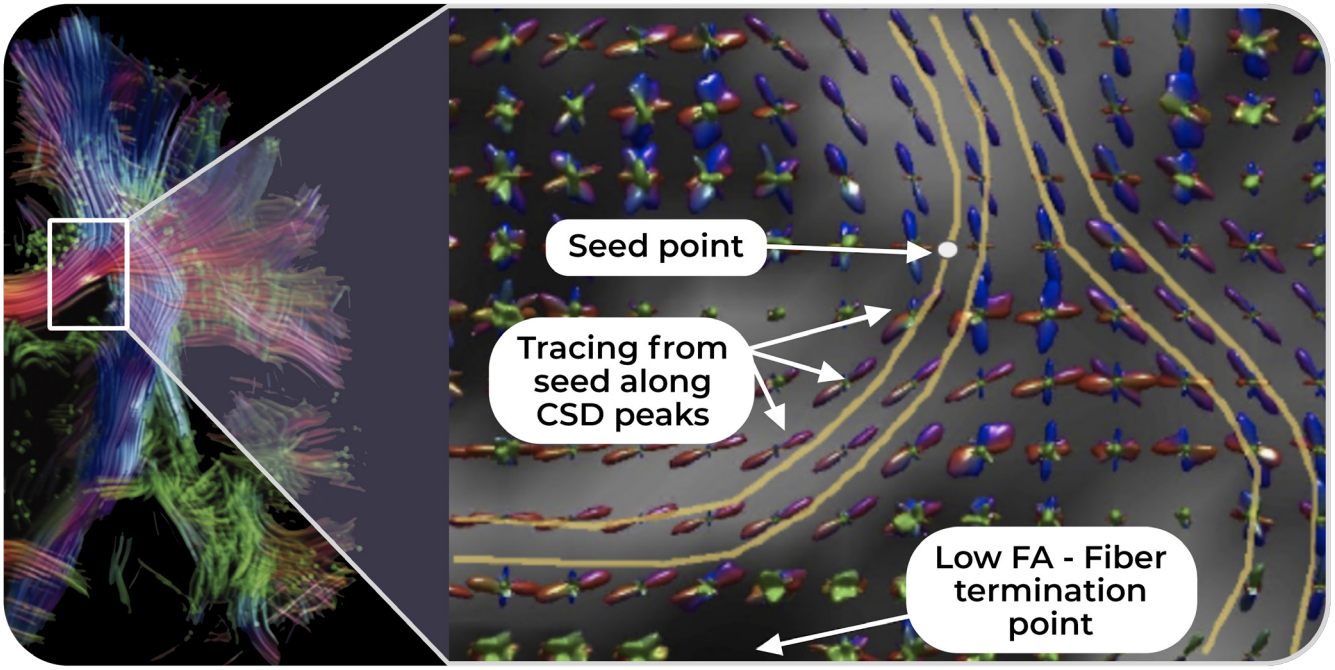

Figure 8 - The fiber tracking process from seed points along the peak direction from voxel to voxel. Fiber tracking begins at the seed points and continues in the direction of each of the CSD peaks until it reaches any of the stopping criteria. Low FA is a termination point.

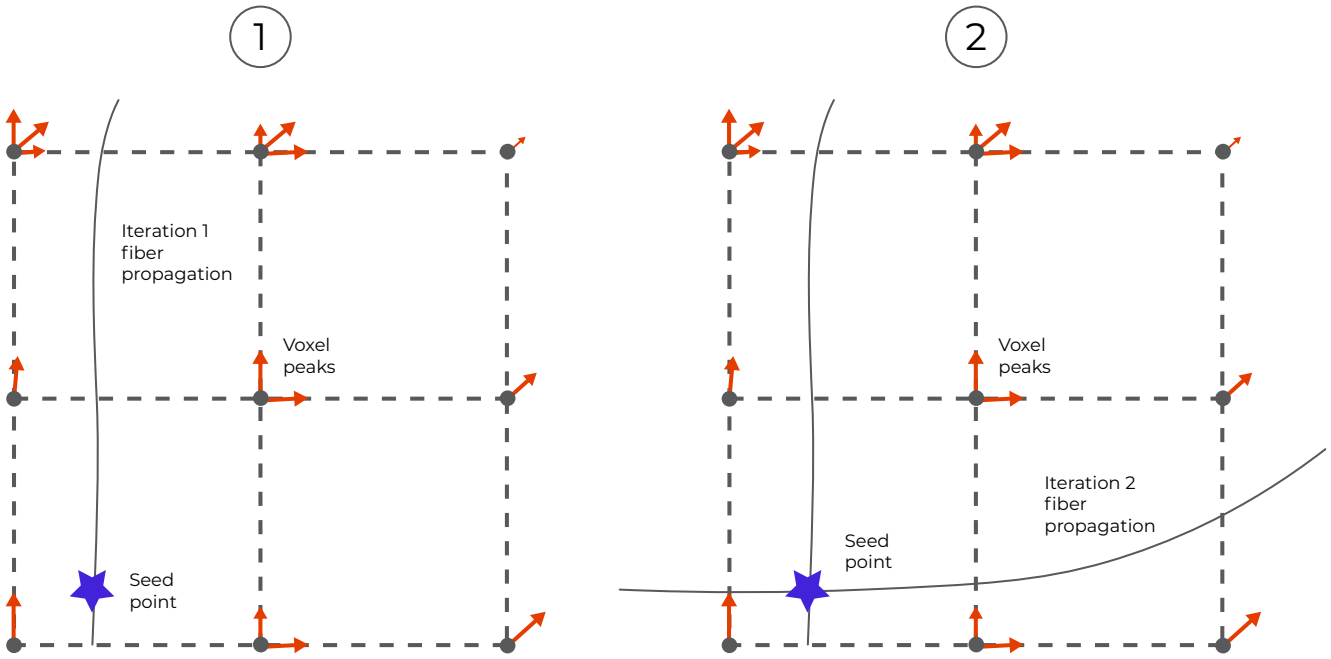

Figure 9 - Fiber tracking from a seed in an area of crossing fibers. Black dots represent voxel centers and the red vector arrows represent tensor peaks. A seed point (the blue star) is within a crossing region, identifiable because there are multiple peaks in the voxels surrounding the point. The fiber tracking algorithm propagates tracks in each peak direction. After a first pass on the primary peak the fiber track in (1) is generated. A second pass occurs on the secondary peak resulting in the fiber track (2) being generated 3.

3.4.6. PART E – BUILDING UP TO WHOLE BRAIN TRACTOGRAPHY FROM STREAMLINES

This algorithm is run until all the seeds have been utilized as starting points. Each seed point will generate multiple fibers as the fiber is tracked in each of the peak directions. Iterating over each seed point forms a collection of streamlines. Once seed points throughout all eligible voxels have been completed the resulting set of streamlines forms a whole brain tractography.

4.0. REFERENCES

1. A.M. Auriat, M.R. Borich, N.J. Snow, K.P. Wadden, L.A. Boyd, *Comparing a diffusion tensor and non-tensor approach to white matter fiber tractography in chronic stroke*, NeuroImage: Clinical, Volume 7, 2015, Pages 771-781, ISSN 2213-1582, https://doi.org/10.1016/j.nicl.2015.03.007.
2. Tournier, J. D., Calamante, F., and Connelly, A. (2007). Robust determination of the fiber orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *Neuroimage 35*, 1459–1472. doi: 10.1016/j.neuroimage.2007.02.016
3. Garyfallidis, E. (2012). Towards an Accurate Brain Tractography. Ph.D. thesis, University of Cambridge, Cambridge
4. Smith, R. E., Tournier, J.-D., Calamante, F., & Connelly, A. Anatomically-constrained tractography: Improved diffusion MRI streamlines tractography through effective use of anatomical information. NeuroImage, 63(3), 1924-1938, 2012
5. Girard, G., Whittingstall, K., Deriche, R., & Descoteaux, M. Towards quantitative connectivity analysis: reducing tractography biases. NeuroImage, 98, 266-278, 2014.
6. Lee et al. Have You Ever Seen the Impact of Crossing Fiber in DTI?: Demonstration of the Corticospinal Tract Pathway. PLoS ONE 2015, 10.
7. Basser PJ, Mattielo J, LeBihan (1994). MR diffusion tensor spectroscopy and imaging.
8. Jeurissen et al. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum. Brain Mapp. 2013, 34: 2747–2766.
9. Kinoshita et al. Fiber-tracking does not accurately estimate size of fiber bundle in pathological condition: initial neurosurgical experience using neuronavigation and subcortical white matter stimulation. NeuroImage 2005, 25: 424–429.

10. Jbabdi S, Johansen-Berg H. Tractography: where do we go from here? *Brain Connect*. (2011) 1:169–83. doi: 10.1089/brain.2011.0033

11. Siless, V.. “Multi-modal registration of T1 brain image and geometric descriptors of white matter tracts. (Recalage Multi-modal des image du cerveau T1 et les descripteurs de trajectoires de la matière blanche).” (2014).

12. Katherine H. Karlsgodt, ‘*White Matter Microstructure across the Psychosis Spectrum*’, Published: April 26, 2020, DOI:https://doi.org/10.1016/j.tins.2020.03.014

13. O’Donnell LJ, Westin CF. An introduction to diffusion tensor image analysis. *Neurosurg Clin N Am*. 2011;22(2):185-viii. doi:10.1016/j.nec.2010.12.004

14. Alexander, A.L., Lee, J.E., Lazar, M. et al. Diffusion tensor imaging of the brain. *Neurotherapeutics* 4, 316–329 (2007). https://doi.org/10.1016/j.nurt.2007.05.011

15. Haddad SMH, Scott CJM, Ozzoude M, Holmes MF, Arnott SR, et al. (2019) Comparison of quality control methods for automated diffusion tensor imaging analysis pipelines. PLOS ONE 14(12): e0226715. https://doi.org/10.1371/journal.pone.0226715

16. Dell’Acqua, F, Tournier, JD. Modelling white matter with spherical deconvolution: How and why? *NMR in Biomedicine*. 2019; 32:e3945. https://doi.org/10.1002/nbm.3945