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# Extracting Brain Connectivity from Diffusion MRI

Diffusion magnetic resonance imaging (dMRI) is an MRI modality that has gained tremendous popularity the past five years and is especially promising for imaging the white matter in the brain. The white matter is the tissue through which signals are passed between different areas of gray matter in the brain, analogous to the cables between processing units in a computer.

Diffusion imaging is one of the first methods that made it possible to visualize and quantify the organization of white matter in the human brain in vivo. It has the potential to aid in the diagnosis and subsequent treatment of disorders of the central nervous system and is likely to have a major impact on assessment of white matter pathologies (e.g., schizophrenia, multiple sclerosis), quantification of abnormal white matter development, detection of stroke and trauma including traumatic brain swelling, diffuse axonal injury, and spinal trauma, as well as a large variety of brain tumors. In addition to direct clinical impact, dMRI has the potential to contribute to basic neurosciences, improving our understanding of physiological white matter development, aging, and connectivity. Extracting connectivity information from dMRI, termed "tractography," is an especially active area of research as it promises to model the pathways of white matter tracts in the brain by connecting local diffusion measurements into global trace lines.

This article gives a short introduction to dMRI tractography methods but is not a comprehensive review due to space limitations. It is intended as an introduction to the field; the interested reader may study the cited papers and references therein.

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## DIFFUSION

Diffusion is the process by which matter is transported from one part of a system to another due to random molecular motions. The transfer of heat by conduction is also due to random molecular motion. The analogous nature of the two processes was first recognized by Fick (1855) [1], who described diffusion quantitatively by adopting the mathematical equation for heat conduction derived some years earlier by Fourier (1822). Fick's law states that a local difference in the concentration of a solution gives rise to a net flux of molecules from high to low concentration regions. The net amount of material diffusing across a unit cross section that is perpendicular to a direction is proportional to the concentration gradient. Thus, the phenomenon of diffusion was described scientifically before any systematic developments of thermodynamics. This phenomenon, known as Brownian motion, is named after the botanist Robert Brown, who observed the movement of plant spores floating in water in 1827. The first satisfactory theoretical treatment of Brownian motion, however, was not made until much later by Albert Einstein (1905) [2]. Einstein's interest in explaining the erratic movement of pollen in water was not directly motivated by specific interest in diffusion but by the general interest in proving the existence of the atom.

Depending on the media, diffusion can be restricted in different ways. For example, anisotropic media such as crystals, textile fibers, and polymer films have different diffusion properties depending on direction. Tissue in general also has anisotropic properties, and in neural tissue the major direction of diffusion is along the direction of the myelinated axons. Diffusion is often described by an ellipsoid where the distance to the center defines the diffusion in a particular direction.

## DIFFUSION MRI

Diffusion tensor MRI (DT-MRI) is an MR imaging modality used for relating image intensities to the relative mobility of endogenous tissue water molecules [3]. In DT-MRI, a tensor describing local water diffusion is calculated for each voxel from measurements of diffusion in several directions. To measure diffusion, the Stejskal-Tanner imaging sequence is used [4]. This sequence uses two strong gradient pulses, symmetrically positioned around a 180° refocusing pulse, allowing for controlled diffusion weighting. The first gradient pulse induces a phase shift for all spins; the second gradient pulse will invert this phase shift, thus canceling the phase shift for static spins. Spins having completed a change of location due to Brownian motion during the time period will experience different phase shifts by the two gradient pulses, which means they are not completely refocused and consequently will result in a signal loss. To eliminate the dependence on MRI parameters such as spin density, spin-lattice relaxation (T1), and transvere relaxation (T2) we must take at least two measurements of diffusion-weighted images that are differently sensitized to diffusion but remain identical in all other respects. The tensor model of diffusion is not the only one, and there is a growing interest in more general models [5], which motivates the more general term diffusion MRI, or dMRI.

The dMRI technique has raised hopes in the neuroscience community for a better understanding of the fiber tract anatomy of the human brain. Various methods have been proposed to visualize the anatomy of fiber pathways and to derive connectivity between different parts of the brain in vivo [6].

## DIFFUSION MRI TRACTOGRAPHY

### *THE PDD METHOD*

A simple and effective method for tracking nerve fibers using DT-MRI is to follow the direction of the principal diffusion (direction of maximal diffusion) in small steps, producing long fiber tracts that connect anatomically distant brain regions [6], [7]. The principal diffusion direction is equivalent to the direction of the main eigenvector in each tensor. This method is usually referred to as tracking using the principal diffusion direction (PDD).

For accurate solution of the PDD tracking problem, stated as a differential equation, both Euler and Runge-Kutta methods have been used [6]. These tractographic paths are commonly referred to as fibers, though the data resolution is too low to measure any individual fibers or axons; instead, the paths represent large-scale features of the diffusion data (the size of a voxel in the dMRI imaging data is in the order of mm, compared to the diameter of axons, which is in the order of $\mu$m). A result from dMRI tractography is shown in Figure 1. Note that although the result represents large-scale features, there is an intriguing similarity of tractography results to drawings of white matter in anatomy textbooks [8].

### *A STOCHASTIC METHOD*

Although the PDD method is widely used, it suffers from some major disadvantages. The connectivity is restricted to a one-to-one mapping between points, not allowing the branching that real fiber tracts may undergo. It also gives the impression of being precise, not taking the uncertainty of fiber paths into account in the tracking procedure. In practice there are several factors that introduce uncertainty in the tracking procedure. Noise, splitting and crossing fibers, head motion, and image artifacts are all examples of factors that cause variability in the estimated fibers. To quantify this uncertainty, several stochastic tractography methods have been developed [9]–[12].

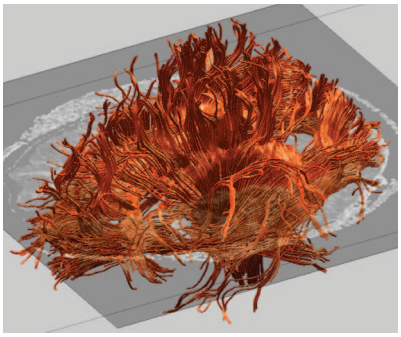
In such a framework, the tracking procedure is regarded as a stochastic process. Instead of following only the PDD, the tracking proceeds in a given direction with a probability derived from the tensor field. The result is a distribution of fiber traces emanating from the seed point where the procedure was initiated and from this distribution a certain measure of connectivity, from the seed-point to all other voxels in the volume, may be derived. In Friman et al. [12], this is achieved by modeling the fiber as a finite length path described by a train of vectors $\mathbf{v}_{1:n} = \{\mathbf{v}_1, \ldots, \mathbf{v}_n\}$. Let $\Omega_A^n$ denote the set of all possible paths of length $n$ that originate in a point $A$, and assuming that we can assign a probability $p(n)$ to each path in this space, and by further introducing a discrete probability function $p(n)$ for the path length, we have

$$\int_{\Omega_A^n} p(\mathbf{v}_{1:n}) = 1 \quad \text{and}$$
$$\sum_{n=1}^{\infty} \int_{\Omega_A^n} p(n) p(\mathbf{v}_{1:n}) = 1. \qquad (1)$$

We can then find the probability $p(A \to B \,|\, \mathcal{D})$ of a fiber going from $A$ to $B$, given the diffusion data $\mathcal{D}$, by summing the probabilities for all paths of all lengths between theses areas

$$p(A \to B \,|\, \mathcal{D}) = \sum_{n=1}^{\infty} \int_{\Omega_{AB}^n} p(n) p(\mathbf{v}_{1:n} | \mathcal{D}) \qquad (2)$$

The integrals in (2) are defined over complicated path spaces $\Omega_{AB}^n$, and we cannot hope to find analytical solutions. For solving these integrals we have to resort to numerical integration, and it is only possible by applying Monte Carlo methods to estimate such high-dimensional integrals. A technique called rejection sampling is well suited for this problem. In [12], the probability distribution of the underlying fiber orientation is derived in a Bayesian framework. Based on such probability functions, using a sequential importance sampling technique [9], [13], one can generate thousands of fibers starting in the same point by sequentially drawing random step directions. This gives a very rich model of the fiber distribution, which should be contrasted with the single fibers that are produced by conventional tractography methods.



[FIG1] Result from dMRI tractography.

## GROUPING FIBERS IN BUNDLES

In neurological studies of white matter using tractography, it is often important to identify anatomically meaningful fiber bundles. However, as shown in Figure 1, the result of tractography is a large number of unorganized traced pathways, which need to be organized according to connectivity or anatomy to be used in a study. One way is to group fibers that have "similar" connections. The idea behind clustering is shown in Figure 2(a), where traced fibers are mapped into points in a high-dimensional embedded space and segmented into groups. Similar fibers form clusters of points, where each cluster is identified as a "fiber bundle."

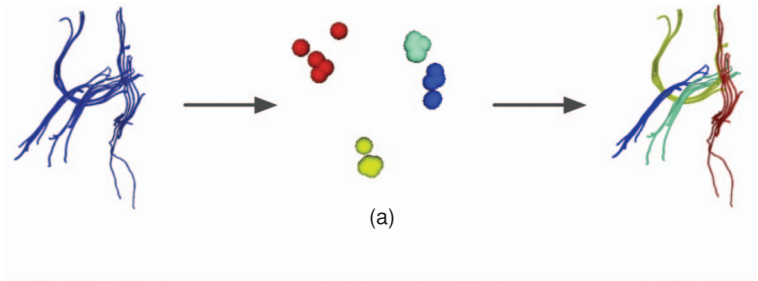
To perform clustering, first a mathematical definition of fiber similarity must be specifed. Then, pairwise fiber distances may be calculated and used as input to a clustering algorithm. In [14], a method was proposed that aims to segment fibers into bundles based

on spectral graph analysis using a graph partitioning method called normalized cuts. The proposed method recursively divides clusters into two parts until a satisfactory segmentation has been obtained. A fiber grouping result using this method is shown in Figure 2(b).

The above work was extended in [15], where a method for finding white matter fiber correspondences and clusters across a population of brains was presented. The clustering methods generally involve an eigendecomposition of a matrix with size equal to the number of input fibers. Since thousands of fibers are drawn in each brain, this matrix quickly becomes very large. In [15] a technique known as the Nystrom method was used to address this problem. The Nystrom method calculates the basis vectors defining the embedding space using a random sample of the input data. This technique allows us to use fibers from multiple brains as input, and thereby obtain a simultaneous clustering and matching of the bundles in all brains. In addition, this automatically provides correspondence of bundles across brains; by selecting one or several paths of interest in one brain, the most similar paths in all brains are obtained as the nearest points in the high-dimensional space. An interesting feature of this method is that the embedded cluster space created from a set of subjects can generalize to new subjects, and thus can be used to create a high-dimensional atlas describing the major white matter fiber tracts in the human brain.

## CONCLUSIONS

We have highlighted some dMRI tractography methods and described how the modality has opened a new window into the white matter of the human brain. While there are strong indications that DT-MRI reveals information about the fiber pathways in the brain, it is important to stress that the explicit measurements are of water diffusion, and not of the axons themselves. As dMRI is a fairly new field of research, many studies are yet to be made to compare the measured diffusion tensors to detailed tissue properties important for fiber path inference.





[FIG2] **(a) Overview of the clustering procedure, figure adapted from [16]: input fibers (left) are transformed to points in a cluster space based on their pairwise similarity (middle) where clusters are identified and used for labeling the tracts (right). (b) Result from automated clustering. The colors represents groups of tracts that connect to similar gray matter areas in the brain.**

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The tractography results in Figure 1 were generated by Dr. Hae-Jeong Park, Dr. Martha Shenton, and Dr. Marek Kubicki, and the tractography visualization in Figure 2(b) was generated together with Dr. David C. Banks, Dr. Lauren O'Donnell, and Dr. Martha Shenton, using a fast global illumination rendering technique.

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**S.C. Draper:** In my view, usability is most affected by sensor design and can also be impacted by the selection of algorithms. For example, being able to segment and extract features of an iris at long range (one to a few meters) and in real time would improve the acceptability of iris biometrics. However, such developments would also raise privacy concerns.

Improved matching algorithms can lead to better overall matching accuracy and, often more significantly, can improve performance for users with more challenging biometrics (e.g., those whose finger prints do not register well on many devices). Faster algorithms and intelligent search techniques can yield massive speed-ups when searching large databases for a match with an unlabeled probe data (i.e., a probe without an associated user identification number). Such developments would increase the acceptability of a biometric system.

**Moderator: If you were to summarize one last thought or outlook on what comes next for biometrics, what would that be?**

**P.J. Phillips:** I would mention the development of personal biometric information systems (PBIS) for mobile Web-enabled cell phones. In a mobile Web PBIS, facial images or fingerprints acquired by a cell phone (using included sensors) could be sent via the mobile Web to a personal biometric information system's provider for matching against a personal biometric database. The results of the search could then be transmitted to the originating cell phone. This would provide a capability to identify people on an extensive business contact list.

**R. Chellappa:** My thought is that next, biometric systems may be employed for keyless access to office rooms, homes, cars, and other devices. They may also be used to personalize settings in a given space, e.g., to adjust car seats, temperature control, positions of mirrors, etc.

**A.K. Jain:** With a wider perspective in mind, any system for reliable person recognition must contain a biometric component. Because of the unique person recognition potential provided by biometrics, they have and will continue to provide useful societal value by deterring crime, identifying criminals, securing our borders, and eliminating fraud. At the same time, the success and acceptance of their deployment will depend on our ability to create systems that are cost effective, usable, and that do not threaten basic rights to privacy and anonymity.

## PANELISTS

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