Q-space and Microstructure

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Diffusion MRI gives us a unique non-invasive probe into the microstructure of materials. For restricted diffusion, the diffusion MR signal depends on the size of the restricting pore: large pores admit greater displacements than small ones so lead to greater signal attenuation. This dependence supports the estimation of pore sizes from diffusion MR measurements, as well as a range of other useful microstructure features such as pore density, shape and permeability. In biomedical imaging, this sensitivity is useful for providing estimates of features of the cellular architecture of tissue. To illustrate the idea, the rest of this document concentrates on the use of diffusion MRI for mapping axon diameters in white matter. However, the same ideas extend for applications in grey matter in the brain, or other tissue, such as liver, lung, muscle, prostate, breast, and pathological tissue such as cancer tumours.

In white matter, axons have largely impermeable boundaries so act as pores with approximately cylindrical geometry. This makes them amenable to pore-size estimation with diffusion MR and underpins the idea of axon diameter mapping through diffusion MRI.

Axons in the mammalian brain have diameters in the range 0.2 to 20 microns [1] and, in white matter, often pack tightly into bundles of approximately parallel fibres. Fibre bundles pack axons with a distribution of diameters to a density of around 10^5 mm^{-2}. However, the distribution of axon diameters varies among fibre bundles and depends on the trade off between signal conduction speed (larger fibres transmit signals more quickly [2]) and volume of information (smaller fibres pack more densely so can transmit more diverse information simultaneously). Mapping axon diameters thus offers insight into brain functionality, by informing on the conduction speed of different fibre pathways, potentially provides biomarkers for neurological diseases such as multiple sclerosis, which preferentially attacks smaller axons [3], and may help resolve ambiguities in tractography and connectivity mapping, such as crossing versus kissing fibres [4].

Q-space imaging provides one candidate approach for estimating the pore size. For restricted diffusion, the diffusion MR signal as a function of gradient strength shows a diffraction pattern with frequency that depends on the pore size [5]. Several researchers use the frequency of the diffraction pattern to measure the pore size in simple systems, such as water-filled glass capillaries; see for example [6]. For measuring axon diameters, this approach has several limitations. First, the approach does not account for extra-axonal signal, which can mask any potential diffraction pattern significantly. Second, observation of the diffraction pattern requires high gradient strength and signal to noise that are not achievable on current human imaging systems. Third, the diffraction pattern

requires a single pore size and rapidly disappears as the distribution of pore sizes departs from a delta distribution. Q-space imaging can also inform on pore size by reconstructing the displacement density and using the full-width half-maximum as an estimate of mean diameter; Ong et al [7,8] use this approach to estimate axon diameters in the spinal cord.

Model-based approaches use a simple geometric picture of the restricting geometry of the tissue to predict the diffusion MR signal as a function of parameters describing the axon density and diameter distribution. They then solve an inverse problem fitting the model to measurements to find the best estimate of the parameters. These approaches have several advantages over the q-space approach for measuring axon diameters. First, the models can incorporate distributions of pore sizes and other tissue compartments naturally. Second, the acquisition demands are more modest, as measurements show sensitivity to model parameters at gradient strengths lower than where the diffraction pattern begins and where the signal to noise ratio is higher. For these reasons, the model-based approach dominates current axon diameter mapping techniques.

Models for white matter generally assume compartmentation of several water populations giving rise to independent signals: water trapped inside axons exhibiting restricted diffusion; water in the extra-cellular space outside but in amongst the axons; water in other cellular compartments, such as glial cells; free water from partial volume with cerebro-spinal fluid. For example, Stanisz et al [9] proposed a three-compartment model of nervous tissue: one population of water inside elongated ellipsoidal axons, another inside spherical glial cells, and a third in the extracellular space. Each compartment has its own dimensions, volume fraction, membrane permeability, and internal diffusivity and relaxation constants. The AxCaliber technique [10] uses a two-compartment model consisting of impermeable cylindrical axons with a gamma distribution of diameters and a homogeneous extra-axonal space with anisotropic but unrestricted diffusion. The model is similar to that of [9], but simpler, because it assumes impermeable membranes and no glial cell compartment. Later work [11] adds a free-water compartment for in-vivo experiments.

The early in vitro work [9,10] demonstrates feasibility of estimating axon diameters from diffusion MR experiments by fitting to rich data sets from excised tissue samples on high-field scanners with low noise and a wide range of measurements with different diffusion times and b-values. Experiments show good agreement between the axon diameter distribution estimated from diffusion MR and those measured on histology images. Later work [11] adapts AxCaliber to map the axon diameter distribution over the corpus callosum of a live rat. The recovered distributions match axon diameter histograms from histology of different regions of the corpus callosum and reflect the known trend in the mammalian brain of low diameter axons at the two ends of the corpus callosum (genu towards the front of the brain and splenium at the back) and high diameters in the mid-body [1,12,13].

The ActiveAx technique [14,15,16] aims to map fibre composition parameters, including the axon diameter, over the whole brain and, potentially, on live human volunteers. Two limitations of the earlier techniques prevent widespread usage in brain mapping. First, the acquisition requires high gradient strengths and long acquisition times that are not feasible on human imaging systems. Second, they assume a particular and known fibre orientation and cannot map fibre properties over the whole brain where the fibre orientation varies. The original version of ActiveAx [14] addresses the limitations by combining optimised high angular resolution diffusion imaging (HARDI) [17] with a simplified model designed to minimise complexity while capturing the dependence of the data on acquisition parameters (diffusion time, b-value, etc). The model assumes a single axon diameter in each voxel rather than the gamma-distribution model in AxCaliber and includes both a free-water contribution, as in [11], and an isotropically restricted compartment similar to the glial cell component of Stanisz's model [9]. Experiments with fixed monkey brains recover the low-high-low trend in axon diameter across the mid-sagittal corpus callosum with high reproducibility, and preliminary results from human volunteers, showing similar trends albeit more weakly.

A later generation of ActiveAx [15] includes a fibre dispersion parameter. Although the assumption of straight parallel fibres may be reasonable in major pathways such as the corpus callosum and cortico spinal tracts, more peripheral pathways have less directional coherence. In such regions, an assumption of straight parallel fibres causes overestimation of the axon diameter, because some are oblique to the assumed orientation so appear to have larger cross section. Zhang et al [15] use a Watson distribution of fibre orientations and demonstrate good separation of the effects of axon diameter and dispersion through parameter estimation using similar data to the original ActiveAx [14]. The addition of the fibre dispersion parameter, first extends the portion of white matter over which the technique gives sensible results, but also provides a useful new parameter, the orientation dispersion index. Fibre crossings still pose some difficulties for the model [18].

These various techniques show compelling results in spectroscopic studies of tissue samples [9,10], and for animal brains imaged using small-bore high-field high-gradient-strength scanners [11,14]. However, the performance with in-vivo human brain data is more questionable [14,15]. Simulations [14,15,16] demonstrate that even under idealized conditions where the models are very close to reality, measurements from current state-of-the-art human imaging systems are sensitive to size differences only in the largest axons with diameters greater than 5 microns or more. Such axons represent only a small proportion of the axon diameter distribution in human white matter. The histograms in [1] suggest that even in the mid-body of the corpus callosum where axons are largest, only 5% of axons are in this range. However, allowing for tissue shrinkage during histological preparation by a factor between 1.5 and 2, that proportion increases to around 10%. Moreover, considering that the contribution to the signal is proportional to the square of the axon diameter, around 25% of the intra-axonal signal comes from water contained in these large axons (about 50% accounting for tissue shrinkage). So it is reasonable to expect

to observe contrast based on axon diameter distribution even at clinical gradient strengths. However, extending the lower bound on the range of diameters we can distinguish would increase that contrast and its utility significantly.

In practice, the characteristic axon diameter estimated from diffusion MRI often overestimates those measured from histology even taking tissue shrinkage, weighting of signal to larger axons, and fibre dispersion into account [14,15,16]. One contributing effect might be microscopic fibre dispersion: undulation of individual fibres, rather than varying orientation of multiple straight fibres, can appear as straight fibres with larger diameter [19]. Permeability of axons causing exchange between the intra and extra-axonal spaces may also contribute. Differences in myelination, compartmental relaxation constants, glial cell or blood vessel density are other possible contributing factors.

Three avenues potentially provide improvements to current axon diameter mapping techniques: better models, better pulse sequences, and better hardware.

Better mathematical models potentially incorporate sensitivities of the signal to axon diameter that current models do not. For example, all the wide range of candidate white matter models in [20,21], which include most of those in the literature, currently assume that the extra-cellular signal is entirely insensitive to the axon diameter distribution and rely entirely on the intra-cellular signal to inform on the axon diameter distribution. Exploring and exploiting dependence of the extra-cellular signal to the axon diameter distribution may increase sensitivity. Incorporating other effects, such as fibre undulation, exchange, relaxation etc, may increase accuracy of parameter estimates, but must be handled with care to keep models simple enough to obtain reasonable parameter estimates.

All the axon diameter estimation and mapping techniques discussed so far rely on single pulsed-field gradient (sPFG) spin echo or stimulated echo sequences. However, a range of alternative pulse sequences are available that may increase the sensitivity to axon diameters particularly in the smaller diameter range. Oscillating gradient spin echo (OGSE) sequences [22,23] probe shorter timescales than standard sPFG sequences so potentially provide additional sensitivity to small axon diameters. Multiple-pulsed field gradient (mPFG) [24,25,26,27] sequences probe the correlations of displacements over separate time intervals, which provides sensitivity to pore-shape anisotropy inaccessible to sPFG and may lead to additional sensitivity to pore size.

For axon diameter mapping, preliminary work by Siow et al demonstrates advantages of OGSE over sPFG for recovering diameters of glass capillaries [28] and for mapping axon diameters in the rat corpus callosum [29]. A body of work by Koch, Finsterbusch and colleagues [30,31] and Shemesh, Ozarslan and colleagues [6] explores the use of double PFG sequences for estimating pore-size motivated both by stronger diffraction patterns at clinically achievable gradient strengths than sPFG can achieve [26] and the distinctive pattern of signal variation as the angle between the pulse pairs varies [25]. Later work

demonstrates the technique for mapping axon diameters in tissue samples [32] and in the human brain [33]. Numerical pulse-sequence optimization experiments in [34,35] suggest that angular mPFG offers no advantage over OGSE at least using simple models representing axons as straight impermeable fibres. Multiple PFG sequences however may well offer advantages for more sophisticated future models that incorporate exchange and fibre undulation effects [19,36,37].

A key hardware enhancement for improving axon diameter mapping is higher gradient strength. Dyrby et al [16] demonstrate the effect of increasing maximum gradient strength on axon diameter maps empirically using a fixed monkey brain and high-field small-bore scanner with maximum gradient strength 300mT/m rather than the 40-80 mT/m typically available on clinical systems. Increasing gradient strength from around 60mT/m to 300mT/m moves the lower bound on axon diameter sensitivity down from about 5 microns to about 2.5 microns [16], which increases the proportion of the intra-axonal signal that comes from measurable axons from 25-50% in the mid-body of the corpus callosum (according to the data in [1]) to around 60-80%. The differences in contrast and quality of the maps are striking.

The importance of gradient strength for probing white matter composition is one key motivation for the construction of the one-off connectome scanner at Massachusetts General Hospital, which has 300mT/m gradients unique among human systems (at the time of writing). One of the early applications of the machine is to map axon diameter distributions across the mid-sagittal corpus callosum of live human volunteers using the AxCaliber technique and [38] shows promising early results.

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Pre/Post Questions

1. Considering a simple model of white matter with impermeable cylindrical axons in a homogeneous extra-cellular space, what is the effect on the mean diffusivity and diffusion anisotropy if the mean axon diameter increases with all other histological features staying the same?

    a) diffusivity increases, anisotropy increases
    b) diffusivity increases, anisotropy unaffected
    c) diffusivity unaffected, anisotropy unaffected
    d) diffusivity increases, anisotropy decreases
    e) diffusivity unaffected, anisotropy decreases

Answer (d)

2. What is the effect if the fibre dispersion increases?

    a) diffusivity increases, anisotropy increases
    b) diffusivity increases, anisotropy unaffected
    c) diffusivity unaffected, anisotropy unaffected
    d) diffusivity increases, anisotropy decreases
    e) diffusivity unaffected, anisotropy decreases

Answer (e)

3. What is the effect if the fibre permeability increases?

    a) diffusivity increases, anisotropy increases
    b) diffusivity increases, anisotropy unaffected
    c) diffusivity unaffected, anisotropy unaffected
    d) diffusivity increases, anisotropy decreases
    e) diffusivity unaffected, anisotropy decreases

Answer (d)