Diffusion MRI on undulating versus straight axons: Reduced fractional anisotropy and increased apparent axonal diameter

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Introduction

The axonal diameter distribution may be estimated using diffusion MRI [1], but the result can be influenced by a number of biophysical mechanisms. Axons in fiber tracts may not be straight and can have an undulating, approximately sinusoidal course. Axonal undulations are present in the peripheral nervous system and in those parts of the central nervous system that are subjected to strain during locomotion, for example, the extra cranial course of the cranial nerves [2], the spinal cord [3] and the optic nerve [4]. However, the presence of axonal undulations has hitherto not been included in estimations of axonal diameter obtained using diffusion NMR or MRI data with high diffusion sensitisation (*b*-value). In this study, we use three-dimensional (3D) Monte Carlo simulations to investigate the implication of axonal undulations on the signal-versus-*b* curves and the fractional anisotropy (*FA*).

Method

3D Monte Carlo simulations of pulsed gradient measurements of water diffusion were performed using a previously described simulation framework [5]. The simulation geometry is shown in Fig. 1. The simulated axons have walls that are non-permeable to water, and exhibit sinusoidal shaped undulations in one direction, i.e. fiber wall position oscillates according to $A \cdot \sin(2\pi l/L)$, where A is the amplitude of the undulations, l is the position in the direction parallel to the fibers and L is the wavelength of the undulations. The water diffusion coefficient was assumed to be 2.0 $\mu m^2/ms$.

Signal-versus-*b* curves (simulated echo attenuations) for *b*-values up to 25 $ms/\mu m^2$ were generated by simulation of diffusion measurements in the direction perpendicular to the fiber direction and parallel to the plane of the undulations. The simulated diffusion encoding duration was $\delta = 10$ ms and the diffusion time was $T_D = 30$ ms. Signal-versus-*b* curves were generated in two different simulations, one assuming undulating axons and another assuming straight axons, i.e. $A = 0$ µm. These simulations included only intracellular particles.

In another set of simulations, DTI measurements were simulated using 15 diffusion encoding directions and a single *b*-value of 1 $ms/\mu m^2$, with simulated particles both in the intra- and extracellular space. The undulation amplitude A and wavelength L was varied in different simulations, using $\delta = 20$ ms and $T_D = 30$ ms. The fractional anisotropy (*FA*) was evaluated by fitting the apparent diffusion tensor to the obtained simulation data [6].

Results

The signal-versus-*b* curves obtained by simulated diffusion measurements in undulating axons with diameter d_U were similar to those obtained from non-undulating axons having diameters of approximately $d_S = d_U + 2A$, where d_S and d_U are the diameters of the straight and undulating fiber geometries, respectively (Fig 2). For undulating axons with small d_U (smaller than approximately 3 µm), the apparent diameter was slightly larger than $d_U + 2A$. Hence, the presence of axonal undulations, if not accounted for in the data analysis, results in an overestimation of fiber diameters. The DTI simulations showed that *FA* decreased with increasing undulation amplitude and frequency (Fig 3). The cause of the *FA* reduction was that the apparent diffusion coefficient (*ADC*) perpendicular to the axons was increased and the *ADC* in the parallel direction reduced, as compared to corresponding straight fibers.

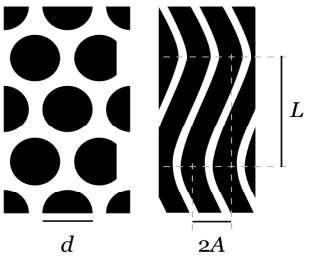

Fig. 1. Transversal and sagittal slices through the 3D simulation geometry, where the undulating axons are shown in black. The intracellular space in shown in black and the extracellular space in white.

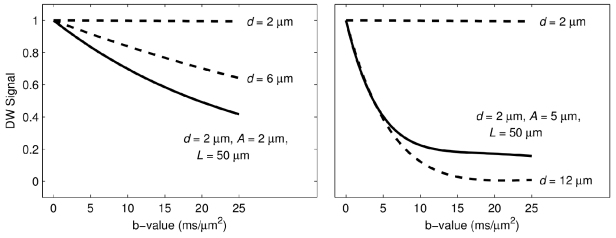

Fig. 2. Intracellular signal-versus-*b* curves for simulations in the direction perpendicular to the fiber direction and parallel to the plane of the undulations for two different amplitudes of the undulations, i.e. $A = 2$ µm (left) and $A = 5$ µm (right). The curves from undulating and straight fibers are shown as solid and dashed lines, respectively. The evaluated diameter of undulating axons will be overestimated if axonal undulations are not taken into account in the data analysis.

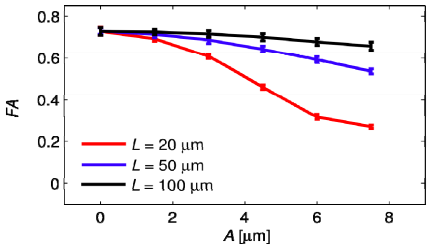

Fig. 3. The *FA* value versus the undulation amplitude A for different undulation wavelengths L. The error bars represent one standard deviation between simulations performed with d_U = 2, 5, 8 and 11 µm. Undulating axons results in a reduced *FA* value, as compared to straight axons.

Discussion and conclusion

Our simulations show that diffusion MRI/NMR data obtained on tissue comprising undulating axons and on tissue composed of straight fibers, exhibit markedly different characteristics. This aspect is important when interpreting data estimated using compartmental models [1,5]. For instance, the evaluated diameter of undulating axons is markedly overestimated, unless the effects of axonal undulations are taken into account in the data analysis (Fig. 2). Moreover, the *FA* value in tissue comprised of undulating axons is reduced as compared to tissue composed of straight fibers, as shown in Fig 3. In conclusion, axonal undulations are important to consider when interpreting diffusion MRI/NMR data.

References

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