A biomimetic phantom of white matter for application in diffusion MRI

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Introduction Within diffusion MRI, there is a need for a physical biomimetic phantom to act as a gold standard to allow a full characterisation and validation of the different diffusion acquisition methods, models, tracking algorithms, and microstructure measures. Such validation is necessary in order to fully characterise the capabilities of diffusion MRI in neuroscience and in clinical use. However, the dissimilarity between the microscopic geometry and permeability characteristics of the existing phantoms and that of brain tissue sets a limit on the degree of validation that they can provide. Here we introduce the use of co-electrospinning [1], as a technique that allows the deposition of hollow, aligned, micron-sized fibres for the development of phantoms which mimic the microstructural and bulk characteristics of white matter tracts.

Methods *Phantom construction* A co-axial spinneret, with two concentric needles, was filled with a solution of polycaprolactone (PCL; outer needle) and polyethelene oxide (PEO; inner needle). The outer needle was connected to the positive electrode from the DC high voltage power supply, whereas the fibre collector, which was placed 5 cm from the tip of the concentric needles, was connected to the negative electrode (ground). A voltage of 9 kV was applied and the flow rate of the outer solution was fixed at 3 ml/hr, whilst the inner solution was varied (0.1, 0.4, 0.8 ml/hr) to modulate the inner diameter of the fibres [2]. A rotating disk was used as a collector to align the fibres, which were deposited with micron-scale diameters via the electrospinning process. The inner core solution evaporates, leaving a solidified outer sheath. The diameter of the fibres was characterised using scanning electron microscopy, and the average diameter of the three phantoms found to be 3.3 ± 1.0, 5.1 ± 0.8, and 5.7 ± 1.2 µm.

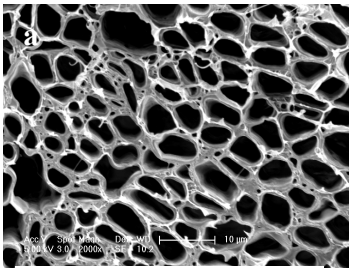

Figure 1 SEM image of co-electrospun phantom

MR imaging Layers of electrospun fibres, with varying inner diameter, were packed into 8 mm NMR tubes using a plastic rod to ensure good packing, with the fibres aligned along the axis of the tubes. The tubes were filled with cyclohexane; a proton rich solvent capable of infusing into the hydrophobic polymer, with a suitable T_1 and apparent diffusion coefficient (ADC) to mimic the free liquid in axonal bodies [3]. Diffusion tensor imaging with 30 gradient directions, b=800 s mm^{-2} (plus a b=0 s mm^{-2}), δ = 4 ms, Δ = 10 ms, G_{max} = 302.8 mT m^{-1}) was carried out on a Bruker 7 T horizontal bore magnet (Bruker Biospin, Germany). Other sequence parameters were; axial FOV 2 cm x 2 cm, 128 x 128 matrix, 1 mm thick slices, TR = 8 s, TE = 18.2 ms.

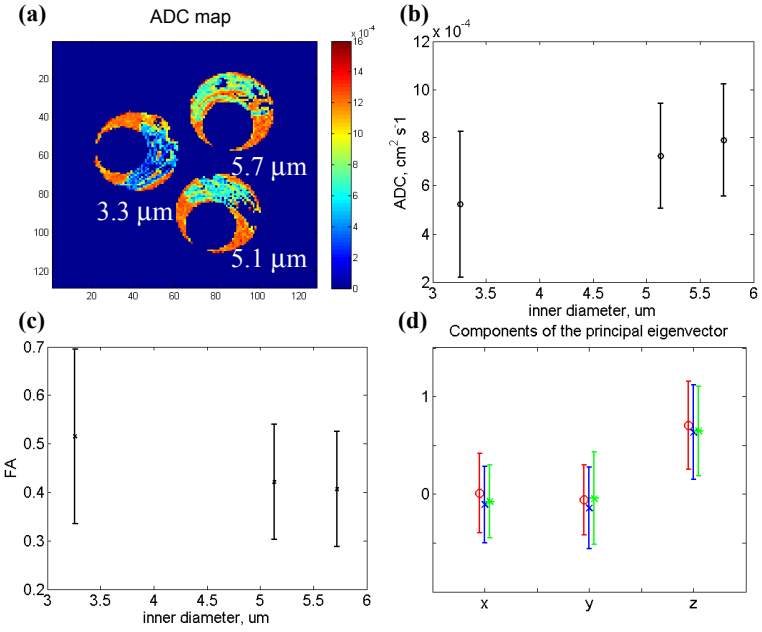

Figure 2 (a) MD maps of three phantoms; **(b)** MD v inner diameter; **(c)** FA v inner diameter; **(d)** eigenvectors for each phantom; red circles 3.3 µm, blue cross 5.1 µm, green asterisks 5.7 µm.

Analysis All three tubes were positioned in the FOV (Figure 1a). Mean diffusivity (MD), fractional anisotropy (FA) and the components of the principal eigenvector (Figures 1 b, c, d, respectively) were calculated for each of the tubes in a total of 7 slices, where the phantom could be observed. All maps were masked to regions where FA > 0.2, to allow differentiation from the free solvent diffusion.

Results Preliminary diffusion experiments on three co-electrospun hollow cylindrical phantoms of increasing inner diameter have shown an increase in ADC from 5.2 ± 0.3 to 7.9 ± 2.3 x 10^{-4} cm^2 s^{-1} (Figures 1a and 1b), coupled with a decrease in FA from 0.49 ±0.20 to 0.36 ± 0.13 (Figure 1c). The fibres are aligned along the axis of the tube (ie along the z-axis), leading to a markedly higher measured diffusivity in this orientation. The perpendicular diffusivities are approximately equal, consistent with radially symmetrical microstructure.

Discussion Co-electrospinning shows great promise as a technique for the manufacture of hollow, aligned fibres that can mimic the cellular barriers imposed by axonal cell membranes and myelin. We have demonstrated that the measured diffusivity is within the approximate range of biological tissues [4] and that different diameter electrospun hollow fibres lead to different diffusivities and anisotropies. Alignment of the fibres according to the diffusion measurements is as expected from the deposition method. This process allows the microstructure of the tissue to be mirrored and the size and density of the fibres to varied in an efficient, scalable, one-step synthesis from various solution combinations.

References **[1]** Loscertales, I.G, *J. Am. Chem. Soc.*2004,126(17),5376–5377; **[2]** Zhou F-L, *Polymer* 52(16),3603–3610; **[3]** Tofts. P.*MRM* 2000,43(3),368–374; **[4]** Lebel C. *NeuroImage* 2008,40,1044–1055.

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