Measuring Cell Permeability with Diffusion-Weighted Simultaneous Spin-Echo and Stimulated Echo EPI

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Introduction:

In the white matter of the brain the myelin sheath is the effective barrier separating the intra-axonal space from the continuous extracellular space surrounding the fibers (for myelinated axons). It is considered to be the main cause of the high water diffusion anisotropy observed in mature white matter. The exchange rate across this barrier is determined by its physicochemical properties. The lengthy diffusive exchange delay times possible when using the stimulated-echo (STE) diffusion MRI method, as opposed to the standard spin-echo (SE) method, make it sensitive to exchange rates. **Thus, it is proposed that a comparison of the SE and STE signals may yield an in vivo biomarker reflecting the permeability and/or thickness of the myelin sheath.** Fortunately, the SE and the STE NMR signals can both be measured after a single excitation, as suggested for diffusion-weighted MRI in Refs. [1-3]. The acquisition of both echoes in separate EPI readouts after a single excitation allows a fast, self-calibrating, direct comparison of two signals differing from one another in the length of the diffusion exchange delay time – the effect of which can then be isolated.

Method:

A realistic embodiment of a simultaneous spin-echo and stimulated-echo DW-EPI pulse sequence was simulated using the Monte Carlo framework from Ref. [4]. The permeability (κ) was defined as the percent of particles hitting the wall that are allowed to exchange in each time interval. The diffusion gradient length, δ, was 20ms; the diffusion exchange time for the spin-echo, Δ_{SE}, was also 20 ms and that of the stimulated echo was either Δ_{STE}=50ms or 100ms. The *b*-value for the spin-echo signal was 596 mm^2/s, and the stimulated echo signals had *b*=1935 mm^2/s and 4168 mm^2/s respectively.

Results:

Figure 1 shows the signal, measured with diffusion weighting perpendicular to the simulated axon axis, as a function of the myelin sheath permeability in the case of short and long Δ_{STE}. The spin-echo signal, shown in black, varies very little with permeability. The signal from the longer diffusing time, Δ_{STE}=100ms shown in green, is highly sensitive to permeability. The explanation for this is that at higher permeability the diffusion is freer, resulting in a greater difference between the SE and STE signals.

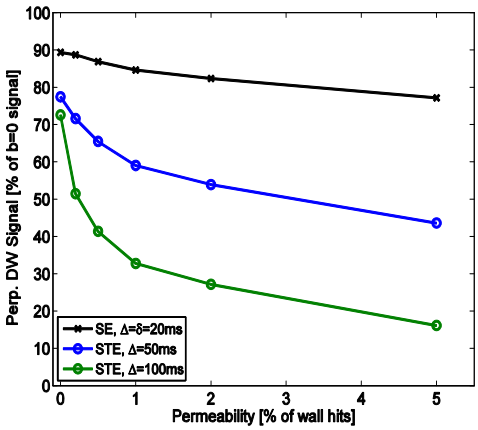

Fig. 1: Simulated DW-MRI signal perpendicular to fiber direction for the simultaneous spin-echo (SE) and stimulated-echo (STE) pulse sequence. Permeability was varied (see Table 1) and the diffusion delay of the stimulated echo was either 50 ms (blue line) or 100 ms (green line). Note the high sensitivity of the STE signal to permeability at low permeabilities.

Note that the permeability values used in the simulations cover the range of exchange times in white matter hypothesized in the literature [5-7] - the calculated intracellular (IC) residence times for the simulation are shown in Table 1.

The higher the permeability, the closer the STE signal is to the monoexponential extrapolation of the SE curve. As a result of this observation, a new parameter is suggested – a restriction index (RI). An empirical formula can be defined as follows:

$$RI = (S_{STE} - S'_{STE})/\lambda_{3,SE} \quad ,$$

here S_{STE} is the normalized perpendicular STE signal, $S'_{STE} = e^{-b_{STE}\lambda_{3,SE}}$ represents the extrapolated perpendicular signal at high b-value b_{STE} , and $\lambda_{3,SE}$ is the smallest eigenvector (perpendicular diffusivity) of the SE tensor. Table 1 shows this new "restriction index", RI, calculated from the simulations. For a large range of permeabilities, RI appears to reflect this characteristic very sensitively, particularly at low permeabilities..

Summary:

By taking advantage of the increased sensitivity to cellular barriers afforded by the stimulated echo diffusion technique, this method may have the potential to recognize and quantify areas of subtle myelin damage if it affects water permeability.

References: [1] Sotak CH, Li L. *MRM.* 1992 Jul;26(1):174-83. [2] Börnert P, Jensen D. *MRI.* 1994;12(7):1033-8. [3] Franconi F, et al. *MRI* 1994. 12(4):605-11. [4] Peled S. *IEEE TMI* 2007 Nov;26(11):1448-55. [5] J. Pfeuffer, et al. *MRI* vol. 16, no. 9, pp. 1023-32, 1998.[6] J. D. Quirk et al. *MRM.* vol. 50, no. 3, pp. 493-9, 2003. [7] P. van Gelderen et al. *MRM.,* vol. 31, no. 2, pp. 154-63, 1994.

κ	0	0.2%	0.5%	1%
Restriction Index (RI)	143	41	7	5.0
IC residence time [ms]	∞	59	25	12

Table 1. The mean intracellular (IC) residence time of a water molecule in the simulations as a function of the permeability (κ), and a corresponding index calculated from the simulated MRI signal.