Simulation of Double Pulsed Field Gradient Experiments

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Introduction The assessment of local diffusion anisotropy in tissue using diffusion tensor imaging (DTI) is known to be problematic in regions that contain an admixture of tissue types or multiple fiber orientations. One approach to ameliorating this problem is to acquire high angular resolution *q*-space data, augmented with more sophisticated analysis schemes using higher order tensor models. However, this approach is still ultimately limited to tissues like white matter that exhibit highly anisotropic diffusion on both microscopic and voxel length scales. Recently, the ability to detect microscopic anisotropythrough the use of "multiple scattering" [1] that applies multiple *q*-space encoding gradients between successive refocusing pulses so that the net signal is sensitive to local variations in diffusion. The double pulsed field gradient (DPFG) is one such method of particular interest because it is sensitive to restricted diffusion at diffusion wavelengths long compared to the dimensions of the restrictions (and thus requires only modest diffusion gradients). Because the pulse sequence is simple it can be included in standard imaging sequences. Recently, a theory has been developed to quantify the effects of restricted diffusion in the general DPFG experiment [2]. Here we present an independent validation of this theory by simulating two key DPFG experiments for a cylindrical pore in [2] using a recently developed diffusion simulation environment DIFSIM [3]. We then extend the simulation to a physiologically more realistic model of packed cylinders in a water bath for which analytical models are more difficult to obtain.

Theory The general theory of the NMR signal in restricted diffusion in a multiple PFG is presented in [2] and is an extension of the multiple correlation function method of Grebenkov [4] to arbitrary angular variations between the gradients, a critical feature for applications to diffusion weighted MRI. The method is applied to the general DPFG pulse sequence (Fig 1). Two important special cases are evaluated: (1) collinear gradients for a range of mixing times (the diffraction problem), and (2) angular variations between the two gradients for a fixed mixing time, both in a cylindrical pore. For the cylindrical pore and equal gradient widths ($\delta_1=\delta_2$), the signal attenuation is given by $E=\langle 0|e^{-\mathbf{\Lambda}\delta+i2\pi(\mathbf{q}_1+\mathbf{q}_2)\cdot\mathbf{A}}|0\rangle$ where $\mathbf{\Lambda}(D_0,r_0)$ is an operator that depends on the diffusion coefficient D_0 and the cylinder radius r_0, and $\mathbf{A}=(X,Y)^T$, X is an operator that depends on r_0, and Y is a rotated version of X [2]. The theoretical curves for these two cases are shown as lines in Figs 3 and 4, respectively. In Fig 3, dashed lines represent negative values.

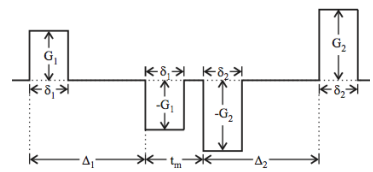

Fig 1. DPFG pulse sequence.

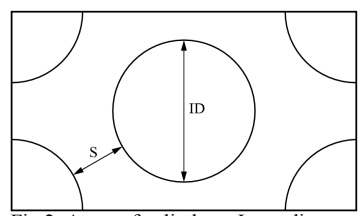

Fig 2. Array of cylinders. Inner diameter (ID), distance between cylinder boundaries (S).

Simulation Three different types of simulations were run: **(1)** The diffraction problem (different mixing times, t_m) We used: D_0 = 2.0e-3 mm^2/s, Δ = 150 ms, δ = 2 ms, ID = 28.64 µm, t_m = (6, 30, 100) ms. We ran simulations with 31 values of *q*, from *q* = 0 to *q* = 60 mm^{-1}. We used 2.5e6 diffusing particles for *q* < 30 and 1.0e7 particles for *q* ≥ 30. We needed many particles to get results accurate to 1.0e-3. Smaller values of E show significant noise. Results fit very well with theory. **(2)** Two gradient directions We used: D_0 = 2.0e-3 mm^2/s, Δ = 40 ms, δ = 2 ms, ID = 8 µm, T_m = 0 ms. We ran simulations with 3 values of *q*: (30, 45, 60) mm^{-1}, and 24 values of the azimuthal angle from 0˚ to 345˚. We used 9e5 to 3.6e6 diffusing particles (more for higher *q* values). Not as many particles were necessary for these simulations since not as much accuracy was necessary. **(3)** Angular simulations with arrays of hexagonally packed impermeable cylinders with internal and external water and varying spacing between the cylinders. The array of cylinders was simulated using periodic boundary conditions (as shown in Fig 2). Simulation parameters were the same as in **(2)**, with these changes: Only one *q* value of 45 mm^{-1} and only 12 values of azimuthal angle from 0˚ to 330˚. Spacing between the cylinders was set to 0, 2, and 8 µm.

Results Points derived from simulation are overlaid on the theoretical curves for the **(1)** diffraction problem (Fig 3) and the **(2)** gradient angular variations (Fig 4). Very close agreement with theory is evident. In Fig 5 is shown the simulation results for **(3)** angular variations in the hexagonally packed impermeable cylinders in a water bath. Results deviate significantly from the single cylinder problem. For large spacing, where more signal is from free diffusion, the curves are lowered and flattened. For zero spacing, where smaller pores are created between the cylinders, the curves are slightly raised. Further tests with varying cylinder permeability are planned to model the effects of demyelinating and dysmyelinating diseases.

Conclusion This Monte Carlo simulation method provides a flexible way to explore multiple PFG experiments that are increasingly being used to elucidate tissue microstructure. It provides a means to include important parameters such as different T_1s and T_2s in different compartments, wall relaxation, partial reflection or membrane permeability, whose effects on the MR signal are all difficult to model analytically, but potentially easy to include in a simulation.

References [1] Ozarslan & Basser, J. Chem. Phys. 128:(2008), [2] Ozarslan, et al., J. Chem. Phys. 130:(2009), [3] Balls & Frank, MRM 62:2009, [4] Grebenkov, Rev. Mod. Phys 79: (2007).

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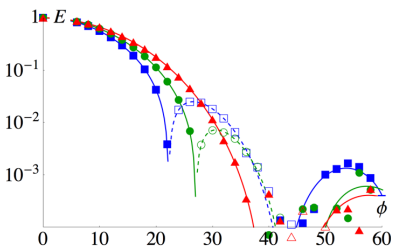

Fig 3. Variations in t_m for fixed collinear G.

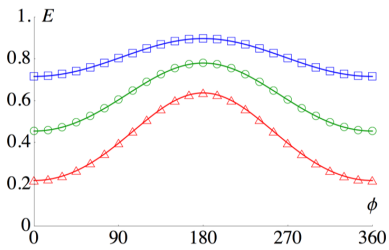

Fig 4. Variations of angle for fixed t_m=0.

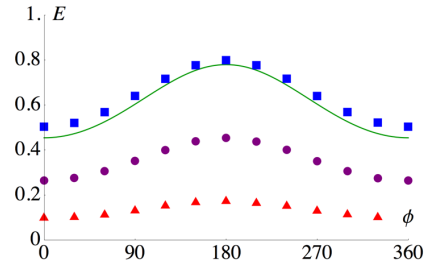

Fig 5. Variations of angle in arrays of hexagonally packed impermeable cylinders in a water bath. Spacing (sq.) 0, (cir.) 2, (tri.) 8 µm.