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Monte Carlo Simulation of Multiparameter Effects in Double Diffusion Encoding MRI

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Synopsis

Keywords: Microstructure, Microstructure

Motivation: Double Diffusion Encoding (DDE) MRI presents a promising approach for probing tissue microstructure, yet its clinical utility is challenged by the complexity of multiparameter optimization.

Goal(s): This study aims to investigate the effects of DDE encoding parameters and tissue microstructure and geometry on the diffusion signal.

Approach: Monte Carlo simulations using DifSim were conducted, varying τ_m and Δ across three fiber geometries: coherent, tilted, and crossing fibers.

Results: The pore sizes of coherent were extracted from diffusion signal. Sin(2θ) modulation was observed in both tilted and crossing fibers, allowing differentiation based on the ratio of their signal amplitudes.

Impact: Monte Carlo simulations demonstrate a promising method for studying the effects of parameters in DDE, aiding in the optimization of pulse sequences to obtain specific microstructural information and facilitating the translation to MRI scanners.

Introduction

Diffusion-weighted imaging (DWI) provides critical insights into cellular structures by estimation of water molecule displacement. The standard Single Diffusion Encoding (SDE) acquisition is limited in its ability to resolve microstructural details. Double Diffusion Encoding (DDE) MRI has been proposed[1] as an alternative. DDE involves two pairs of diffusion gradient pulses separated by a mixing time (τ_m), allowing for more nuanced interrogation of cellular environments.
Previous studies[2,3] have primarily applied DDE to simple or geometrically undefined structures. Applying DDE to more complex, well-defined geometries remains challenging due to the need to balance multiple encoding parameters, making numerical simulations that can accommodate three-dimensional tissue geometry essential for optimizing specificity to tissue microstructure in DDE frameworks.
The objective of this study is to assess the impact of multiparameter optimization in DDE MRI using Monte Carlo simulations across three fiber geometries with known diameters: coherent, tilted, and crossing fibers.

Method

Monte Carlo simulations for DDE were performed using DifSim[4] , with three-dimensional cellular microstructures created in Blender 2.93. The simulations targeted only the intra-axonal compartment, simulating with diffusion coefficient (D) of 2 $\mu m^2/ms$ and 200,000 particles within three primary geometries: coherent, tilted, and crossing fibers.
For the DDE gradient parameters, we set the gradient pulse duration (δ) to 1 ms, mixing times (τ_m) ranged from 0 to 100 ms, diffusion times (Δ) between 5 and 100 ms and gradient strength (G) was 60 G/cm. Gradients were applied perpendicular to the axonal axis, with the second gradient rotated in 30-degree increments from 0° to 360° relative to the first, placing both gradients within the xy plane of the axon fibers.
In the coherent axon geometry, we created cylindrical structures with diameters ranging from 0.5 to 5 microns aligned along the x-axis. We examined the effects of τ_m and Δ on the diffusion signal, fitting DDE signals to the Mitra equation[5] to estimate axon diameters. For tilted axons, we modeled 5-micron-diameter cylinders tilted at angles between 15° and 90°, while for crossing fibers, cylinders intersected at the same angle range. In both cases, we assessed signal changes in response to variations in τ_m.

Results and Discussion

In the coherent axon geometry, a sin(θ) modulation in the diffusion signal was observed at τ_m 0 ms. As τ_m increased, the sine-shaped signal modulation gradually decreased, vanishing at τ_m = 20 ms. Axon diameter estimates were calculated using the Mitra equation, yielding the most accurate estimate of 2.5 μm at τ_m = 0 ms (which corresponds to theory) and Δ = 100 ms. The limitation of τ_m = 0 ms is a specific case and although it can be implemented on MRI scanners, the signal dependence over a range of τ_m values is important for developing DDE frameworks that are specific to the length scales and angular distributions of cellular features in tissue. Additionally, we interpret the dependence of axon diameter accuracy in this experiment as related to the independence of signal from Δ in the Mitra equation.
Importantly, the signal retained a sine curve shape even as Δ increased. While larger axons (3-5 μm) tended to show underestimated diameters shown by R/R_0 (estimated/real radius) at low Δ (< 30 ms), smaller axons (0.5–2.0 μm) consistently showed underestimation across all Δ showed underestimation.
For tilted and crossing fibers, similar sin(2θ) modulation shapes were observed representing characteristics of eccentric compartments. With longer mixing times ($\tau_m \geq 50$ ms), a sin(2θ) modulation pattern emerged. Increasing tilt or crossing angles resulted in decreased signal amplitude due to enhanced microstructural anisotropy. In crossing fibers, within-voxel gradient averaging further reduced signal amplitudes relative to tilted fibers, enabling differentiation between the two. Notably, the signal ratio at 90° versus 0° was higher for tilted fibers, as crossing fiber signals reflected an average across multiple orientations.

Conclusion

DDE experiments offer valuable insights into feature size and shape although the large parameter space and paucity of three-dimensional signal frameworks limit its use. This study examined multiparameter effects in DDE, demonstrating accurate pore size estimation for 2.5 μm and differentiating diffusion signals in tilted versus crossing fibers. Simulation using 3D tissue models both recapitulated expected signal behavior in theoretically described simple geometries and extended to more complex geometries for which theoretical relationships do not exist. While this analysis used limited fiber diameter and configurations, real tissue contains a range of feature sizes and fiber geometries. Future studies using DifSim can explore more complex tissue environments with multiple compartments and geometric features to optimize parameters and develop frameworks with greater specificity to tissue microstructural features, paving the way for applications in biological and clinical research.

Acknowledgements

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References

Figures

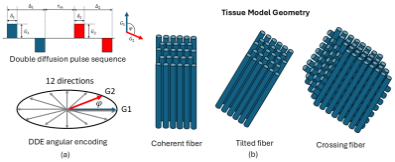

Figure 1: (a) Schematic of the double diffusion encoding (DDE) pulse sequence, illustrating angular encoding between two pairs of diffusion gradients separated by a mixing time (τ_m). (b) Fiber geometries used in the study include coherent, tilted, and crossing fibers.

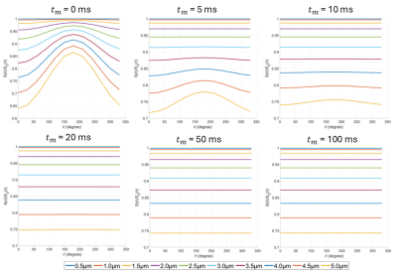

Figure 2: DDE signal from simulation for coherent fiber geometry with radii ranging from 0.5 to 5.0 μm. Simulations were conducted across a range of mixing times (τ_m) from 0 to 100 ms to examine the impact on signal modulation patterns.

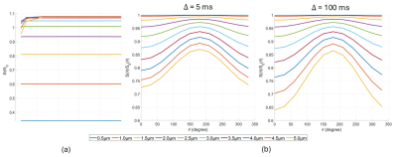

Figure 3: (a) DDE signal from simulation for coherent fiber geometry with radii from 0.5 to 5.0 μm. Plot of R/R_0, the estimated radius (R) compared to the actual fiber radius (R_0), across different diameters. (b) Signal response variation across diffusion times (Δ) of 0 and 100 ms.

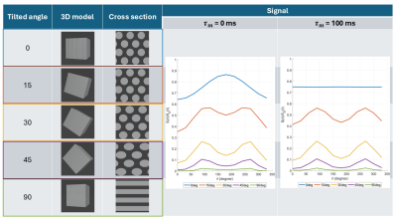

Figure 4: 3D model representation of tilted fiber geometry with cross-sectional view. Simulated diffusion signal responses are shown for short mixing time (τ_m = 0 ms) and long mixing time (τ_m = 100 ms).

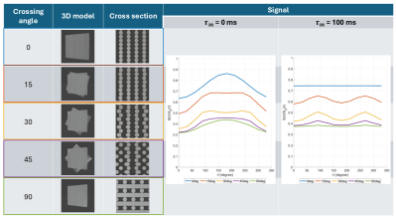

Figure 5: 3D model representation of crossing fiber geometry with cross-sectional view. Simulated diffusion signal responses are shown for short mixing time (τ_m = 0 ms)

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and long mixing time (τ_m = 100 ms).