Numerical Validation of Multi-Compartment Diffusion Biomarkers of Peripheral Nerve Trauma

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Synopsis

Keywords: Simulation/Validation, Diffusion Modeling, biomarkers,volume fraction, spherical mean technique

Motivation: The spherical mean technique (SMT) is a multi-compartmental diffusion model that has been used to evaluate axonal loss in the brain. This method holds promise as a biomarker of peripheral nerve regeneration following injury and surgical repair but has yet to be validated.

Goal(s): This study aims to validate the use of the multi-compartmental diffusion MRI in peripheral nerve imaging.

Approach: The SMT technique was validated via computational modeling studies based on light microscopy data of rats' sciatic nerves.

Results: We found that the SMT specifically assays axonal regeneration after trauma, even in the presence of other potentially confounding features.

Impact: The spherical mean technique (SMT), a multi-compartmental diffusion MRI model, demonstrated potential as a biomarker of peripheral nerve regeneration following injury and surgical repair.

Introduction

Traumatic Peripheral Nerve Injury (TPNI) often leads to a catastrophic loss of sensorimotor function and life-long disabilities if not treated in a timely fashion[1]. Higher-degree injuries typically require surgical intervention with surgical repair failure rate depending on several factors, including the regenerative capability of neurons and distance from the target tissue[2]. Unfortunately, current tools for monitoring nerve regeneration are limited, resulting in delayed decision-making and poor outcomes[3-4]. Given these limitations, new biomarkers are needed to monitor the nerve recovery process for peripheral nerve injuries.
Diffusion MRI has shown promise in filling this gap by providing insights into microstructural properties of peripheral nerves following trauma and surgical repair; however, conventional DTI-based metrics may lack pathological specificity. Multi-compartmental diffusion MRI models, such as the spherical mean technique (SMT), have shown increased specificity to axonal loss in the brain[1]. However, this method has yet to be validated for peripheral nerve trauma, which poses unique challenges due to the various pathologies (axonal regeneration, incoherent fiber growth, Wallerian degeneration, and edema) that often present concurrently after trauma. As a result, this work attempts to numerically validate the use of the SMT model in peripheral nerves via computational modeling studies based on light microscopy data from rat models of sciatic nerve trauma.

Methods

A finite difference simulation[5-6] method was used to simulate diffusion-weighted signals in peripheral nerves. Images derived from histology sections in rat sciatic nerves (following crush, cut and surgically repaired, and sham surgeries) served as the basis of these simulations[7]. Samples were taken 1, 2, 4, and 12 weeks after surgery distal to the injury site. The resulting Toluidine blue stained sections were then segmented into distinct and non-overlapping compartments of the axon, myelin, and extracellular spaces. Signals were simulated for the cropped segment (150x150 matrix to reduce computation time) of each sample over 36 diffusion directions (Ng) in a range of b-values [0-4000 s/mm^2]. The SMT model was then used to estimate axonal volume fractions (V_{ax}) and intra-axonal axial diffusivity (D_{ax}) values, the former of which has been reported to indicate axonal de/regeneration in the brain. Finally, SMT-derived V_{ax} values were compared to ground truth axonal volume fractions from the same section. Furthermore, the effects of Rician noise and imaging parameters (b-values and Ng) on the accuracy of SMT-derived estimates were investigated.

Results and Discussion

Figure 1 shows the representative histological sections from the rat sciatic nerve (sham and cut/repair). The images were segmented into distinct, non-overlapping axon, extracellular, and myelin compartments. The histologically- and SMT-derived V_{ax} values showed a significant correlation with Spearman's correlation coefficient (*r*) of 0.94 and Lin's concordance correlation coefficient (CCC) of 0.95 (0.91-0.97 confidence interval) (Figure 2). Significant correlations were also observed for each treatment group (sham, crush, and cut/repair) (r = 0.97/0.95/0.84, and p-value = 2.3e-6/0/2.6e-3, respectively). In addition, a strong correlation was observed between the V_{ax} of full and cropped images, indicating that the cropped regions were representative of the larger nerve structure. The largest deviation between SMT and ground-truth values was from the 12-week cut-repair data, which may be related to scar tissue in these samples that affected segmentation results.
Figure 3 shows SMT-derived D_{ax} and V_{ax} of nerve trauma over 12 weeks after injury from the simulations. The increase in V_{ax} and the decrease in D_{ax} were observed over 12 weeks at a more consistent and faster rate in the crush group compared to the cut-repair group. These trajectories of estimated V_{ax} demonstrated the potential of SMT in evaluating peripheral nerve regeneration and differentiating self-resolving crush injuries from cut-repair injuries. The plots in Figure 4 show the variation of SMT-estimated V_{ax} in the presence of Rician noise (assuming SNR of 50 for the b=0 image) and the changes in root mean square error (RMSE) of V_{ax} across ranges of Ng and maximum b-values (using two evenly spaced b-shells and b=0). RMSE decreases as the Ng and the b-value increase. The observed optimal Ng and b-values were 20 and 3 ms/ m^2, respectively. However, further investigation is needed to explore the impact of other parameters (e.g., trade-offs between TE and max b-value, efficiency).

Conclusion

Diffusion MRI with SMT technique is a specific axonal biomarker following TPNI, which may be valuable in guiding surgical decision-making. The numerical simulations demonstrated the validity of SMT in evaluating peripheral nerve regeneration in the presence of other potentially confounding features. Thermal noise and imaging parameters, including b-values and the number of gradient directions, could affect the SMT-derived parameter's precision, and the optimal parameters will be further investigated.

Acknowledgements

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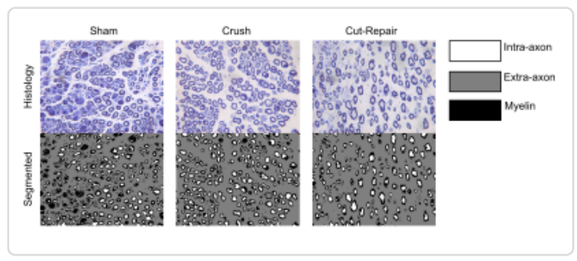
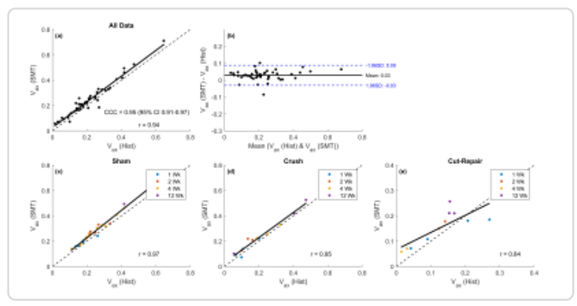
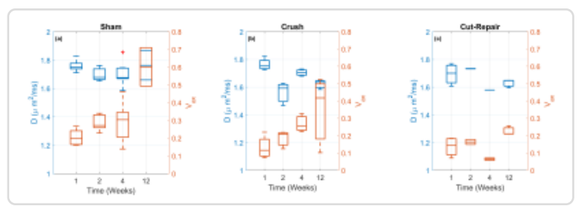
Figures



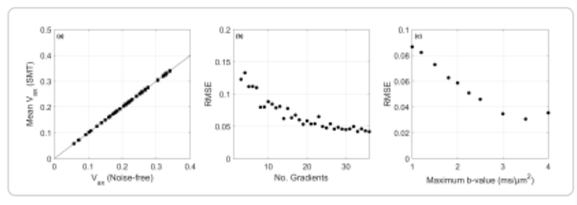
Representative histological sections (top row) from rat sciatic nerve (sham and following trauma/repair). The histology images were segmented (bottom row) into distinct, non-overlapping compartments of the axon (intra-axon), extracellular (extra-axon), and myelin.



Correlation plots between V_{ax} derived from histology and the SMT method for all data sets (a) and three separate treatment groups [sham (c), crush (d), and cut/repair (e)] at four different time points (1, 2, 4, and 12 weeks after injuries). The variable '*r*' indicates the Spearman's correlation coefficient. Bland-Altmann plot for all data is also shown in (b).



Box plots of SMT–derived diffusivity (blue boxes) and axonal volume fractions (orange boxes) of nerve trauma over 1-12 weeks after injury from the diffusion MRI signal simulations for sham (a), crush (b), and cut/repair (c) treatment groups.



Error plot of SMT-derived V_{ax} (with Rician noise, assuming SNR of 50 for the b=0 image) for all data compared to Noise-free V_{ax} (a). The changes in root mean square error (RMSE) of SMT-derived V_{ax} across ranges of gradient direction numbers (with constant b-values) (b) and maximum b-values (with 36 gradient directions) (c).