Validation of Multi-Compartmental Diffusion MRI Models for Peripheral Nerve Trauma

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PURPOSE / OBJECTIVES

Traumatic Peripheral Nerve Injury (TPNI):

- Partial or complete transection of peripheral nerves results in catastrophic loss of sensorimotor function, leading to a life-long disability, paralysis, muscle weakness, and chronic pain[1].
- For higher-degree injuries, surgical intervention is required to regain function.
- Depending on the neuron's regenerative capability and the distance from the target tissue, the surgical repair failure rate is approximately 40%[2].
- Current tools for monitoring nerve regeneration and assessing injury severity are limited[3-4].
  - Electrodiagnostics requires many months after surgery to determine whether the axon regeneration is successful.
  - The resulting “wait and watch” approaches delay clinical decision-making and increase the likelihood of permanent muscle atrophy and sensory loss following the injuries.
- Sensitive biomarkers are needed to monitor axon regeneration and repair response through the nerve recovery process.

Multi-compartmental diffusion: spherical mean technique (SMT)[5]:

- Diffusion MRI metrics yield insights into microstructural integrity in peripheral nerves following trauma and surgical repair.
  - Fractional anisotropy (FA) reports on surgical success and injury severity.
  - However, DTI is limited due to its inability to discriminate signals from other pathologies, such as demyelination, edema, and inflammation.
- SMT has been used to specifically evaluate axonal loss in the brain of multiple sclerosis patients and similarly holds promise as a biomarker of peripheral nerve regeneration following injury and surgical repair.
  - Estimates of intra-axonal axial diffusivity (D_{ax}) and axonal volume fractions (V_{ax})
  - V_{ax} may specifically report on axonal de/regeneration
- The SMT method has yet to be validated for peripheral nerve trauma, which is challenging due to the various pathologies (axonal regeneration, incoherent fiber growth in neuromas, Wallerian degeneration, edema) that often present concurrently after trauma.
- **In this work, the SMT model was validated via computational modeling studies based on light microscopy data from rat models of sciatic nerve trauma.**

MATERIAL & METHODS

Image Segmentation (Figure 1):

Images derived from histology sections in adult rat sciatic nerves (following crush, cut and surgically repaired, and sham surgeries) served as the basis of these simulations. Samples were taken at 1, 2, 4, and 12 weeks after surgery distal to the injury site. The resulting Toluidine blue stained sections were then segmented using CellProfiler into distinct and non-overlapping compartments of the axon, myelin, and extracellular spaces. Post hoc manual corrections of axon and myelin masks were done using GIMP for misclassified regions of interest. The segmented images were then cropped prior to the signal simulation steps.

Computational Simulation:

A finite difference simulation method[6] was used to simulate multi-compartment diffusion-weighted signals in nerves based on the morphometry of intra-axonal, myelin, and extra-axonal compartments. Signals were simulated for each section over 24 diffusion directions and a range of b-values [0-4000 s/mm^2]. The resulting simulated data were fitted with the SMT model to estimate V_{ax} and D_{ax} values.

$$\bar{S} = v_{ax}\overline{S_{ax}} + (1 - v_{ax})\overline{S_{ex}},$$

$$\begin{cases} \overline{S_{ax}} = \dfrac{S_0\left[\sqrt{\pi}\,\mathrm{erf}\left(\sqrt{bD_{ax}}\right)\right]}{\left[2\sqrt{bD_{ax}}\right]} \\ \overline{S_{ex}} = \dfrac{S_0\,\exp(-bD_{ex})\left[\sqrt{\pi}\,\mathrm{erf}\left(\sqrt{b(D_{ax}-D_{ex})}\right)\right]}{\left[2\sqrt{b(D_{ax}-D_{ex})}\right]} \end{cases}$$

Statistical Analysis:

SMT-derived V_{ax} values were compared to ground-truth axonal volume fractions derived from the same section for validation purposes using Bland-Altman analysis and Pearson’s correlations. The simulation results were also compared to previously acquired DTI data of the corresponding adult rat sciatic nerve samples using Spearman’s rank correlations.

RESULTS

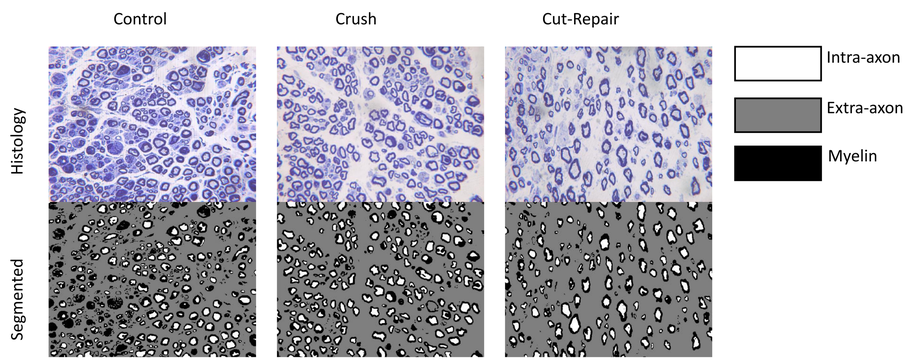

Figure 1: Representative histological sections (top row) from rat sciatic nerve (control and following trauma/repair). The histology images were segmented (bottom row) into distinct, non-overlapping compartments of axon (intra-axon), extracellular (extra-axon), and myelin.

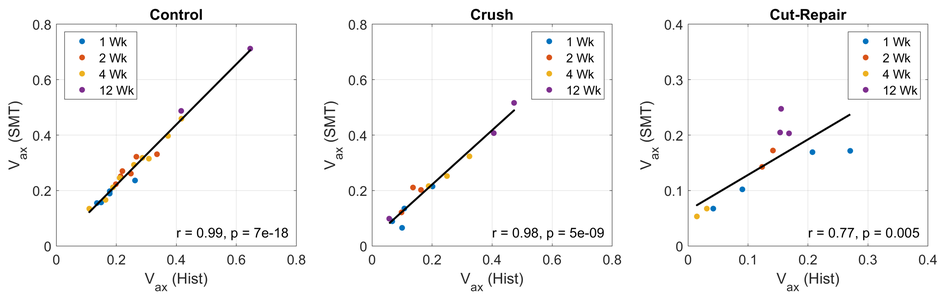

Figure 2: Correlations between V_{ax} derived from histology and the SMT method for three treatment groups (control, crush, and cut/repair) at four different time points (1, 2, 4, and 12 weeks after injuries). The relationships were significant for all treatment groups, indicating the consistency of the SMT-derived V_{ax} values relative to ground truth histologically-derived values. 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.

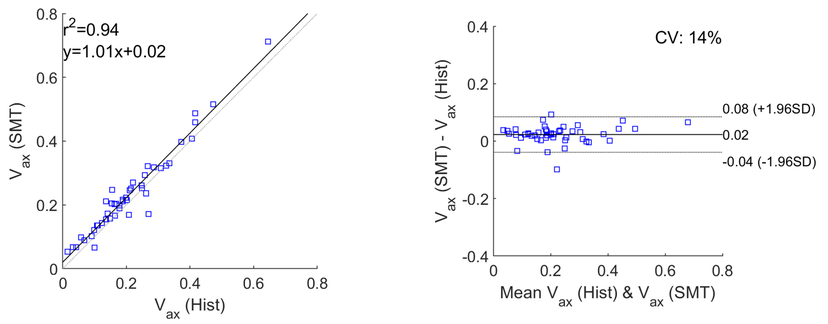

Figure 3: Correlation plots between axonal volume fractions derived from histology and SMT method for all samples, and the corresponding Bland-Altman plot. The histologically- and SMT-derived V_{ax} values were not significantly different ($p < 0.01$) and showed a strong correlation for all injuries and time points. The coefficient of determination across all samples is 0.94 and the coefficient of variation (CV) was 14%. This indicates the accuracy of SMT for quantifying axonal volume changes associated with regeneration.

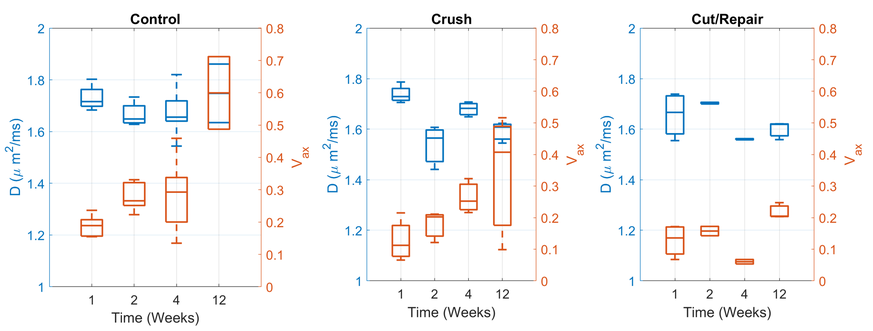

Figure 4: SMT–derived diffusivity (blue boxes) and axonal volume fractions (orange boxes) of nerve trauma over 12 weeks after injury from the simulations above. These trajectories of estimated V_{ax} for control (sham), crushed, and cut/repaired nerves over 12 weeks are consistent with published experimental results and indicate that SMT assays axonal pathologies after trauma and/or repair.

RESULTS (cont.)

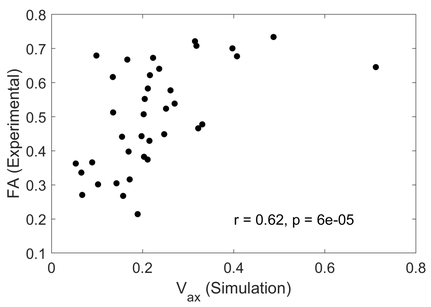

Figure 5: Relationship between the simulation-derived V_{ax} estimates (from the SMT model) and experimentally-derived fractional anisotropy (FA) values from the same samples. Note the moderate, but significant (p??), correlation between FA and SMT-derived V_{ax} values. This indicates SMT may provide complementary (and potentially more specific) information on axonal pathologies compared to DTI.

CONCLUSION

SMT is a specific axonal biomarker following TPNI, which may be valuable in guiding surgical decision-making (when surgery is warranted and if it is successful). The numerical simulations demonstrated that SMT can assay regeneration in the presence of other potentially confounding features (e.g., edema, Wallerian degeneration).

Limitations & Future Directions:

- Large axon diameters in peripheral nerves and the heterogeneous compartmental T_2s may violate certain SMT assumptions, which will be evaluated in future studies.
- The SMT acquisition (b-values, directions) need to be optimized for clinical nerve imaging, which will be the focus of our future computational studies.

Acknowledgments

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