



# Geometry-Informed Multi-Compartmental Diffusion MRI Modeling of Injured Peripheral Nerves

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## ABSTRACT

Diffusion MRI metrics yield insights into microstructural integrity in peripheral nerves following trauma and surgical repair. However, the relationship between diffusion-based metrics and the underlying axonal loss and demyelination following traumatic peripheral nerve injuries (TPNIs) has yet to be systematically validated. Here we developed methods to automatically segment histological sections from rat models of peripheral nerve trauma to estimate axonal volume fractions ( $V_{ax}$ ). Based on these segmentations, we found that conventional DTI-derived metrics exhibited significant linear associations against histologically derived  $V_{ax}$ . Yet interestingly, a relationship was not observed for a more advanced multi-compartment model based on the spherical mean technique (SMT), which suggested practical limitations of SMT model assumptions for peripheral nerve applications. Moving forward, the segmented geometries from this study, which accurately captured the heterogenous nature of TPNI pathologies, will be used in finite difference (FD) computer simulations to better understand the impact of these model assumptions on MRI-derived  $V_{ax}$  for the evaluation of successful or failed nerve repairs in TPNI.

## INTRODUCTION

TPNI is characterized by a partial or complete transection of peripheral nerves, which results in distal Wallerian degeneration and, if untreated, permanent axonal loss and sensorimotor deficits.<sup>1</sup> Surgical interventions are constrained as a result of diagnostic uncertainties. Spontaneous axonal regeneration during post-surgery requires extensive time ( $\sim 1$  mm/day) with a failure rate up to  $\sim 40\%$ , notably for higher-grade TPNIs.<sup>1, 2</sup> Current methods cannot monitor regeneration during this prolonged process; ergo, there is a clear need for tools to monitor nerve regeneration after surgery to guide revisional surgeries when repairs fail.

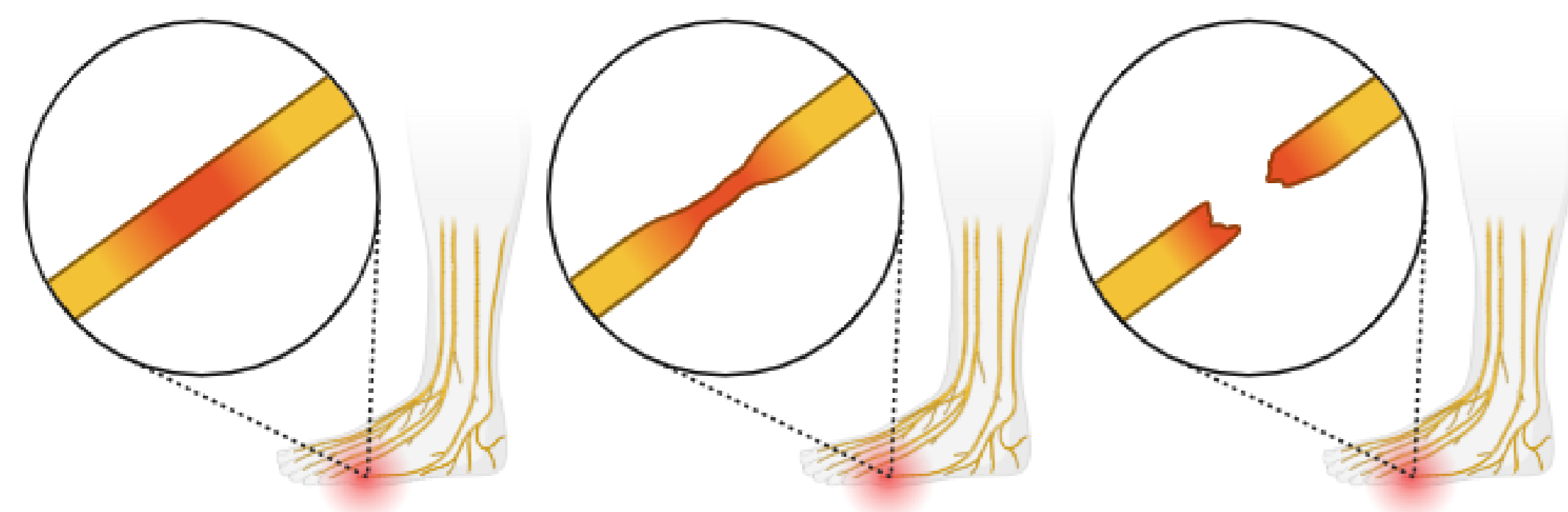


Figure 1. Seddon/Sunderland classifications of peripheral nerve injury as neuropraxia, degree I (left), axonotmesis, degrees II-IV (middle), and neurotmesis, degree V (right).

SMT can provide  $V_{ax}$  estimates based on the powder averaged MRI diffusion signals arising from intra- and extra-axonal compartments.<sup>3</sup> Signal contributions from myelin are assumed to be negligible due to rapid  $T_2$ -relaxation.<sup>3</sup> SMT-derived  $V_{ax}$  may act as an effective imaging biomarker of axonal de/regeneration in the presence of heterogeneous pathophysiological processes in TPNI for distinguishing axonal sprouting at injury sites from random neuroma-induced fiber growth relative to conventional orientation-dependent DTI-derived metrics (fractional anisotropy, FA; axial/radial diffusivity, AD/RD).<sup>4</sup>

## METHODS

**Tissue Samples.** A total of 111 cross-sections of injured sciatic nerves 1, 2, 4, and 12 weeks post-surgery from adult rats were acquired in preclinical models of nerve trauma and divided into three treatment groups by injury type (Sham = 57, Cut/Repair = 27, Crush = 27).

**Image Segmentation.** Pixel-wise automated segmentation was performed on distal toluidine blue stained cross-sections using CellProfiler. Post hoc manual corrections of axon/myelin masks were done using GIMP for misclassified regions of interest.

**Numerical Simulation.** MRI Diffusion signals were simulated via FD based on the morphometry of intra-axonal, myelin, and extra-axonal compartments, serving as the geometric basis for DTI/SMT-derived metrics using the corresponding diffusion MRI data.

**Statistical Analysis.** DTI/SMT-derived metrics were correlated against histologically derived  $V_{ax}$  and quantified with the Pearson correlation coefficient. Outliers were excluded from the analysis with respect to unrealistic samples (i.e.,  $RD > 1 \mu\text{m}^2/\text{ms}$  and  $V_{ax} = 1$ ).

## RESULTS

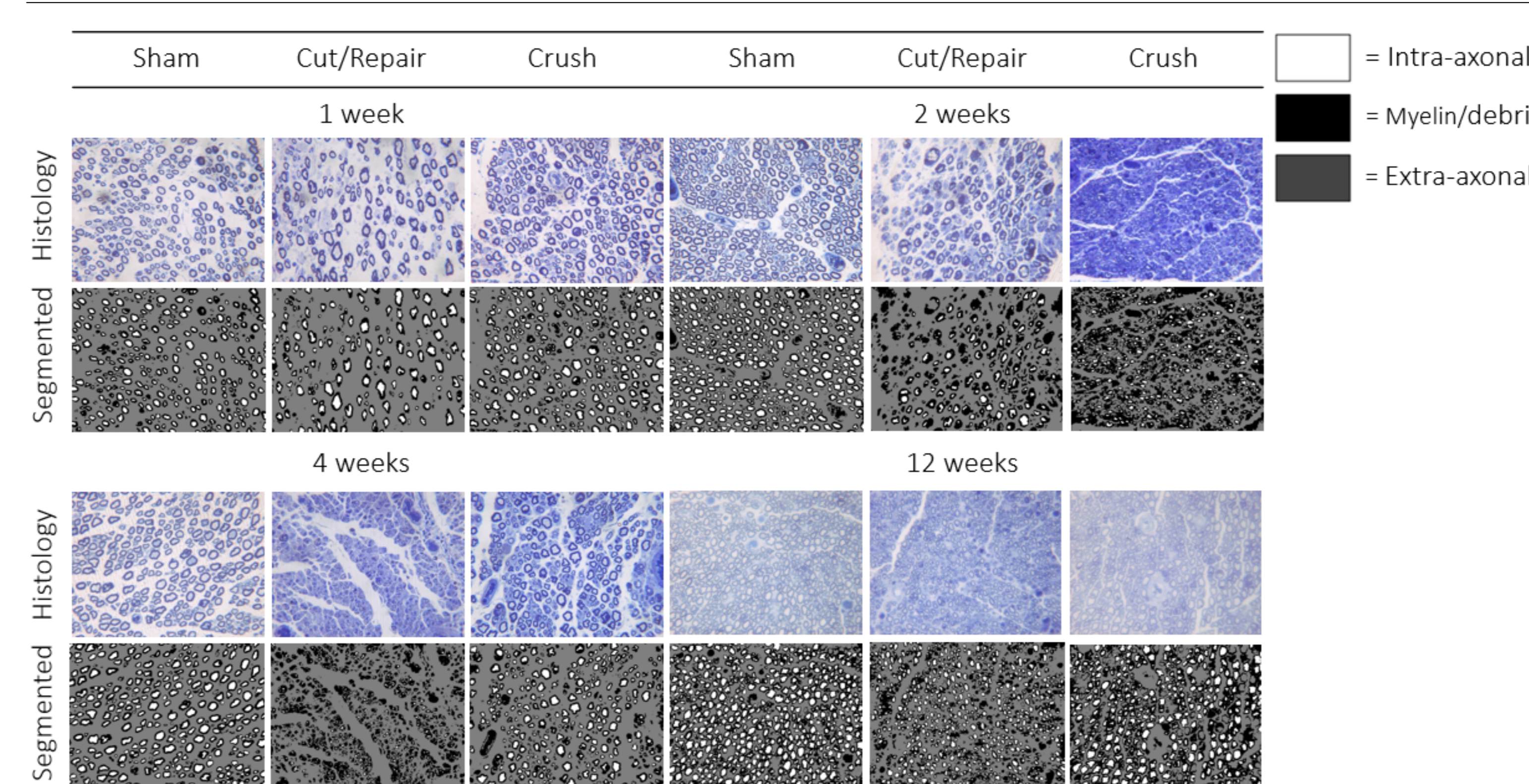


Figure 2. Representative images of distal peripheral nerve cross-sections from histology. The tissues were segmented into distinct, non-overlapping compartments quantified by axonal, myelin, and extracellular volume fractions which sum up to 1. The volume fraction for a compartment is based on the ratio of the volume fraction of interest to the total volume fraction of the given space.

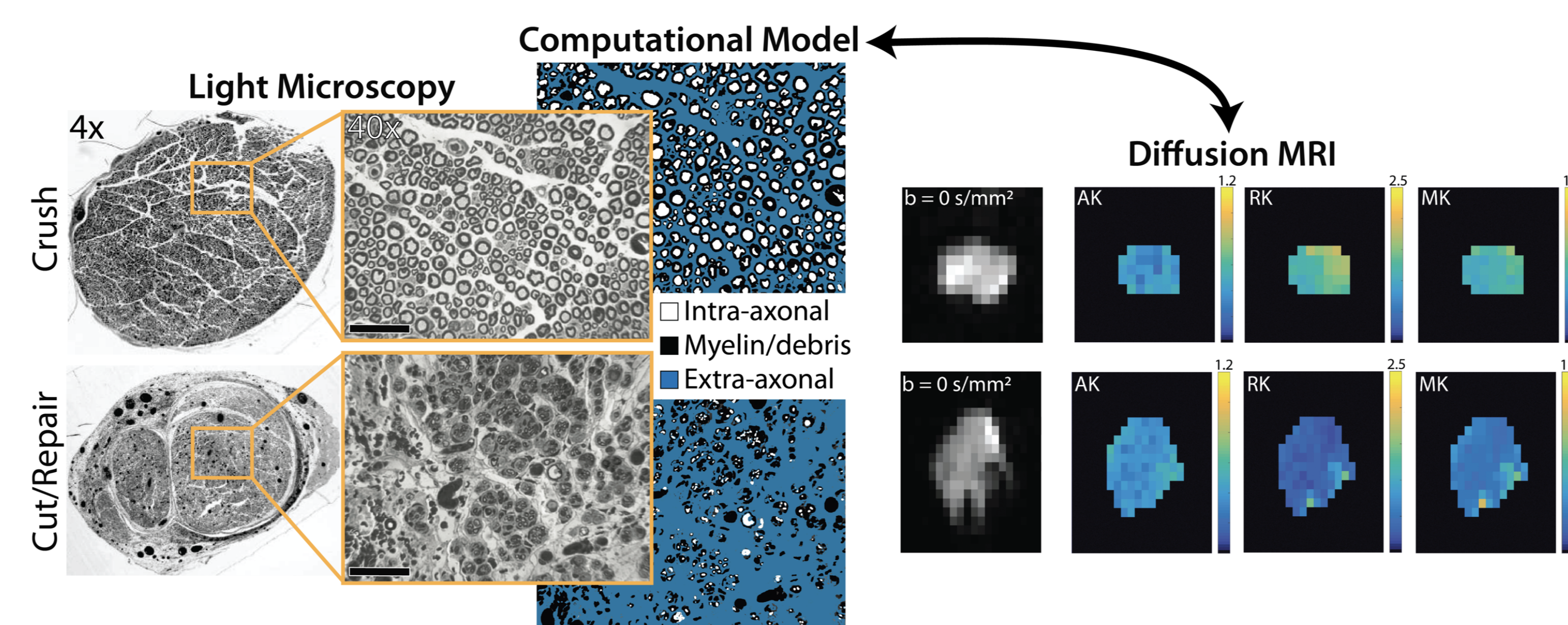


Figure 3. Proposed computational framework based on light microscopy. Shown are distal sections 4 weeks after crush and cut/repair injuries. The resulting geometry will serve as the basis for the FD computational modeling studies using corresponding diffusion MRI data to constrain model parameters (e.g., intrinsic intra/extra-axonal diffusivities) and numerically solve the Bloch-Torrey equation.<sup>5</sup>

$$\frac{\partial \mathbf{M}}{\partial t} = \gamma \mathbf{M} \times \mathbf{B} - \left( \frac{M_x \mathbf{i} + M_y \mathbf{j}}{T_2} \right) - \left( \frac{M_z - M_0}{T_1} \right) \mathbf{k} - \nabla \cdot (D \nabla \mathbf{M}) \quad (1)$$

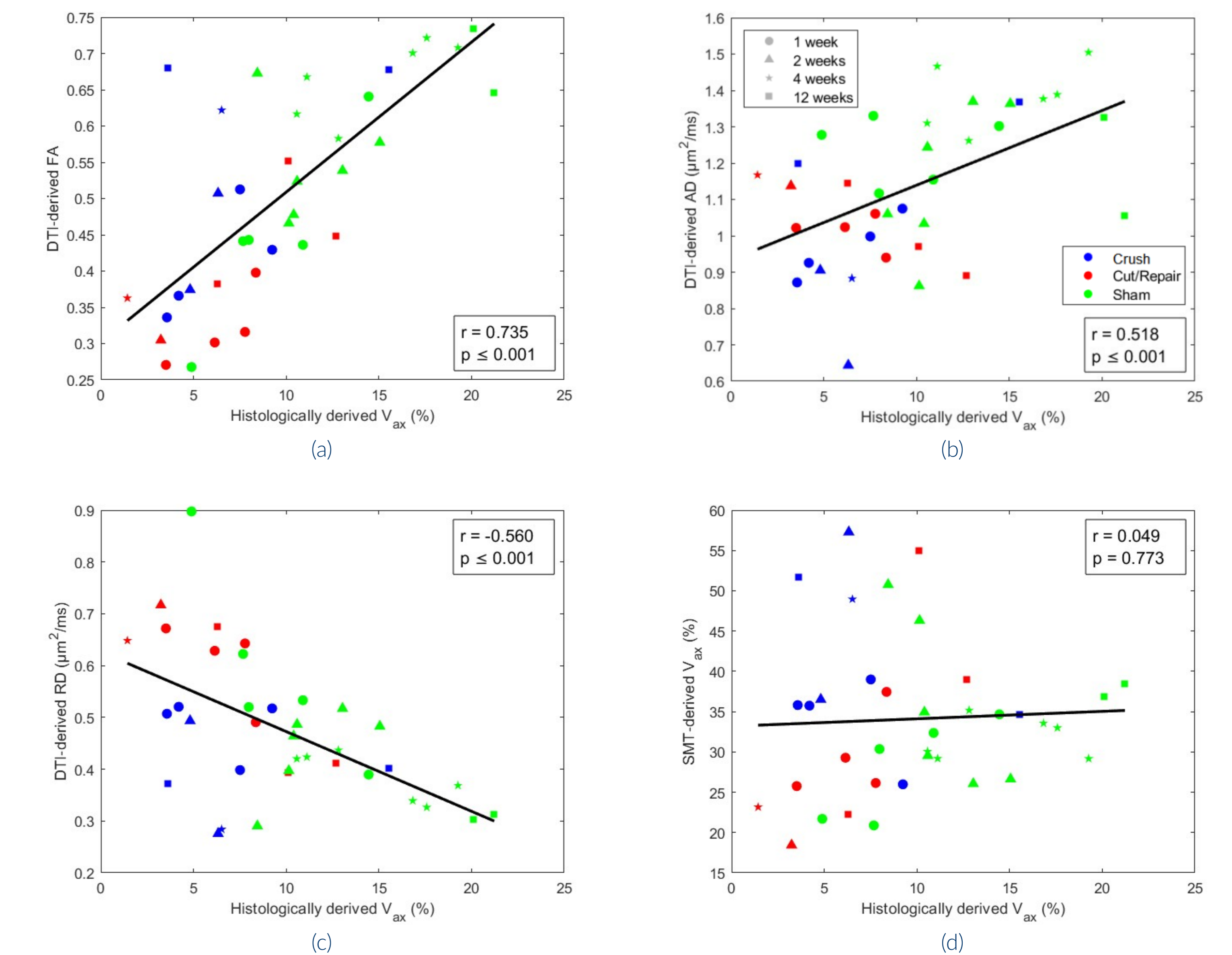


Figure 4. Linear correlations between DTI/SMT-derived metrics and histologically derived  $V_{ax}$  for all treatment groups across every timepoint. The relationship of DTI-derived metrics (a, b, c) against  $V_{ax}$  was significant with FA showing the strongest relationship. The relationship of SMT-derived metric (d) against  $V_{ax}$  did not demonstrate a significant correlation.

## DISCUSSION

SMT-derived  $V_{ax}$  has the potential to be utilized for predictive and prognostic purposes in TPNI, as they pertain to histological measurements of  $V_{ax}$  in peripheral nerves following injury and repair.

**Limitations & Future Directions.** SMT-derived metrics are biased due to large axon diameters and heterogenous compartmental  $T_2$ s in peripheral nerves, unlike tissues in the central nervous system, thus violating SMT model assumptions, including the impact of undetected myelin signals. Future work will deploy FD models to understand the impact of these assumptions and derive peripheral nerve-specific models for improved accuracy.

## ACKNOWLEDGEMENTS

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