Accelerating Whole-Brain Axonal Mapping With FastRandomForest and Proof of Concept in a Familial Alzheimer’s Disease Mouse Model

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Mapping long - range axonal projections is critical for understanding neural circuit dysfunction in neurodegenerative diseases. While machine learning (ML) tools have advanced volumetric cell mapping, manual axonal segmentation remains the standard for generating ground truth datasets. This process is time - consuming and depends heavily on expert annotators. Familial Alzheimer's disease (fAD) leads to progressive and region - specific axonal degeneration. However, current mapping strategies are limited in throughput, hindering comprehensive studies of circuit - and region - specific vulnerability. To address this, we integrated supervised ML (SML) into the early 2D segmentation stage traditionally performed manually by experts, with the goal of accelerating and scaling training data generation for downstream 3D U - Net modeling. We imaged noradrenergic projections in fAD and wild - type (WT) mouse brains, trained SML models to segment axons in 2D across distinct regions, and used these outputs to generate training datasets for 3D segmentation using TrailMap. In parallel, we quantified axonal density changes in key brain regions using ImageJ to measure fAD progression. Our approach enabled segmentation of over 382k usable images within one month, reducing human data preparation by 98.9% compared to the traditional manual annotation. The resulting 3D U - Net model achieved an F1 score of 0.75 and is projected to match the accuracy of manually trained models once the training completes. Regionally, we observed pronounced axonal loss in the frontal pole and ventral CA1 of fAD brains, while the periaqueductal gray (PAG) and mammillary bodies (MBO) were relatively preserved.

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