

# A Digital Pathology Pipeline for Automatic Detection of Tangle-bearing Neurons

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## Introduction

Neurofibrillary tau tangles are a hallmark pathological feature of Alzheimer's disease (AD), yet their quantification remains challenging due to reliance on subjective manual annotation and the lack of standardized automated methods for assessing tau burden. As large-scale studies increasingly rely on digital neuropathology, there is a critical need for scalable, interpretable, and standardized approaches to tangle quantification. We developed a two-stage, foundation model-based digital pathology pipeline for automatic detection of tangle-bearing neurons, mirroring expert annotation workflows.

## Data/Processing

Whole-slide images (WSI; NDPI format) from three AD donor brains (one WSI per donor) were processed using a grid-based patch extraction strategy to enable segmentation at full resolution across entire tissue sections. For each patch, a tissue-detection step excluded background regions (patches with <10% non-background pixel content) prior to model inference, reducing unnecessary computation on empty slide area.

Across the three donors, tangle-positive neurons represented a minority class (7.8% overall), with substantial inter-donor variation in prevalence.

| Donor   | Total neurons | Tangle-positive (n; %) |
|---------|---------------|------------------------|
| Donor 1 | 7,605         | 232 (3.1%)             |
| Donor 2 | 8,604         | 532 (6.2%)             |
| Donor 3 | 11,989        | 1556 (13.0%)           |
| Total   | 29,558        | 2,320 (7.8%)           |

**Table 1.** Neuron counts and tangle-bearing proportions by donor.

## Model Architecture

### Stage 1: Neuronal Segmentation

*Input.* HuD-stained immunohistochemistry whole-slide images, where HuD labels neuronal cell bodies and neurites.

*Model.* We fine-tuned CellPose-SAM, a hybrid segmentation model combining cellular morphology expertise with the Segment Anything Model architecture (SAM), for neuronal morphology.

*Output.* The fine-tuned model produces instance-level neuron masks.

### Stage 2: Tangle-Bearing Status Classification

*Input.* Single-neuron crops from AT8-stained sections, derived from Stage 1 masks. Crops were resized and intensity-normalized prior to feature extraction.

*Model.* Neuron crops are encoded into high-dimensional feature representations using Virchow2, a vision foundation model pre-trained on histopathology slides. These embeddings are input to a multi-layer perceptron (MLP) classifier.

*Output.* For each neuron, the classifier outputs a binary tangle-bearing prediction (positive/negative), which can be aggregated to donor- or region-level tangle burden estimates.

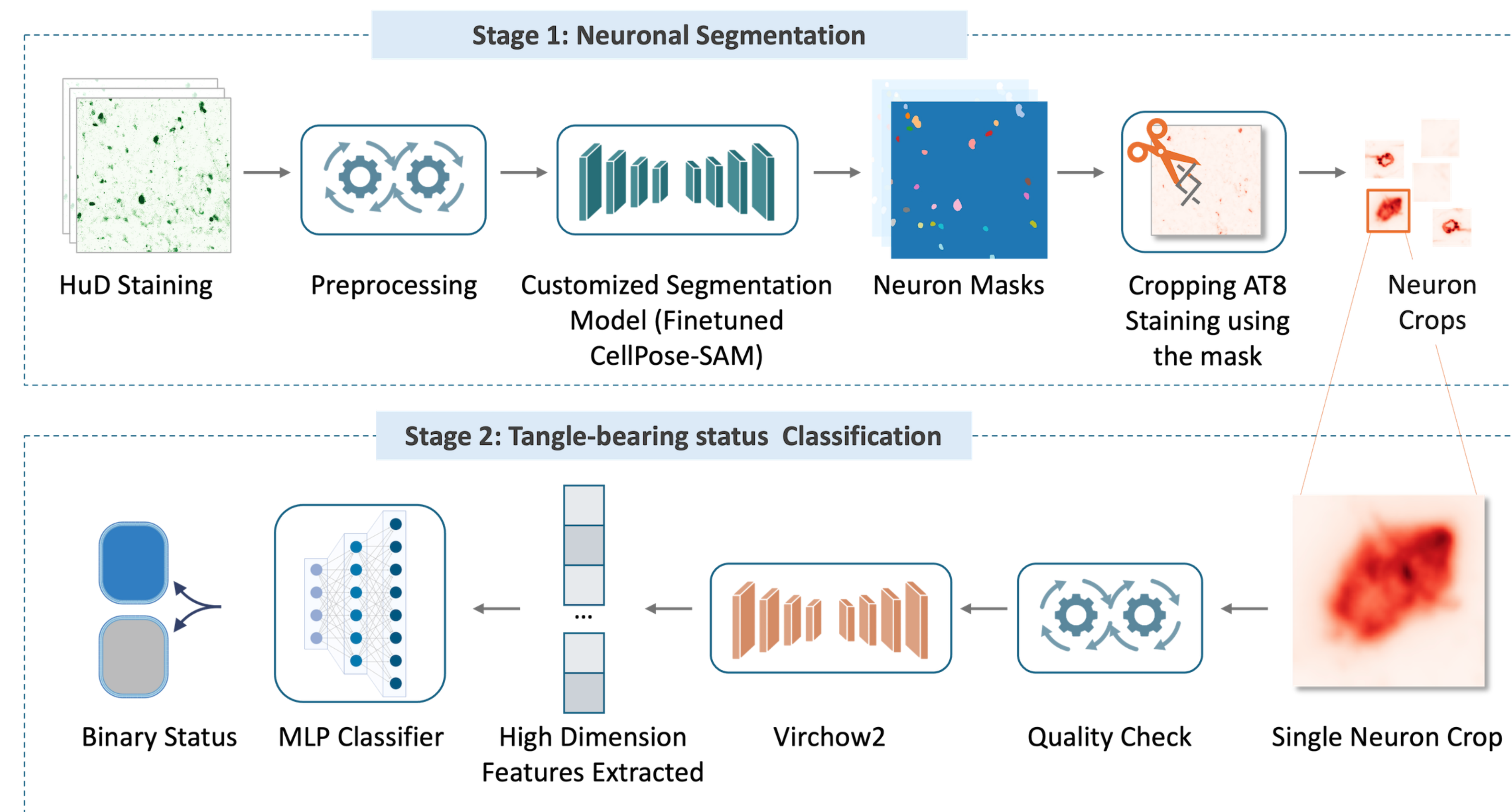


**Figure 1.** Overview of the two-stage digital pathology pipeline for automated detection of tangle-bearing neurons.

## Results

To assess generalizability and avoid donor-level information leakage, we employed leave-one-donor-out (LODO) cross-validation strategy, in which tissue from one donor was held out for testing while models were trained and validated exclusively on the remaining donors.

Class imbalance in the training data was addressed through balanced sample weighting during MLP training. Across three AD donor brains (29,558 annotated neurons), the pipeline showed robust cross-donor generalization in LODO evaluation, with PR-AUC ranging from 0.92–0.98 and F1-scores from 0.86–0.93 (Figure 2).

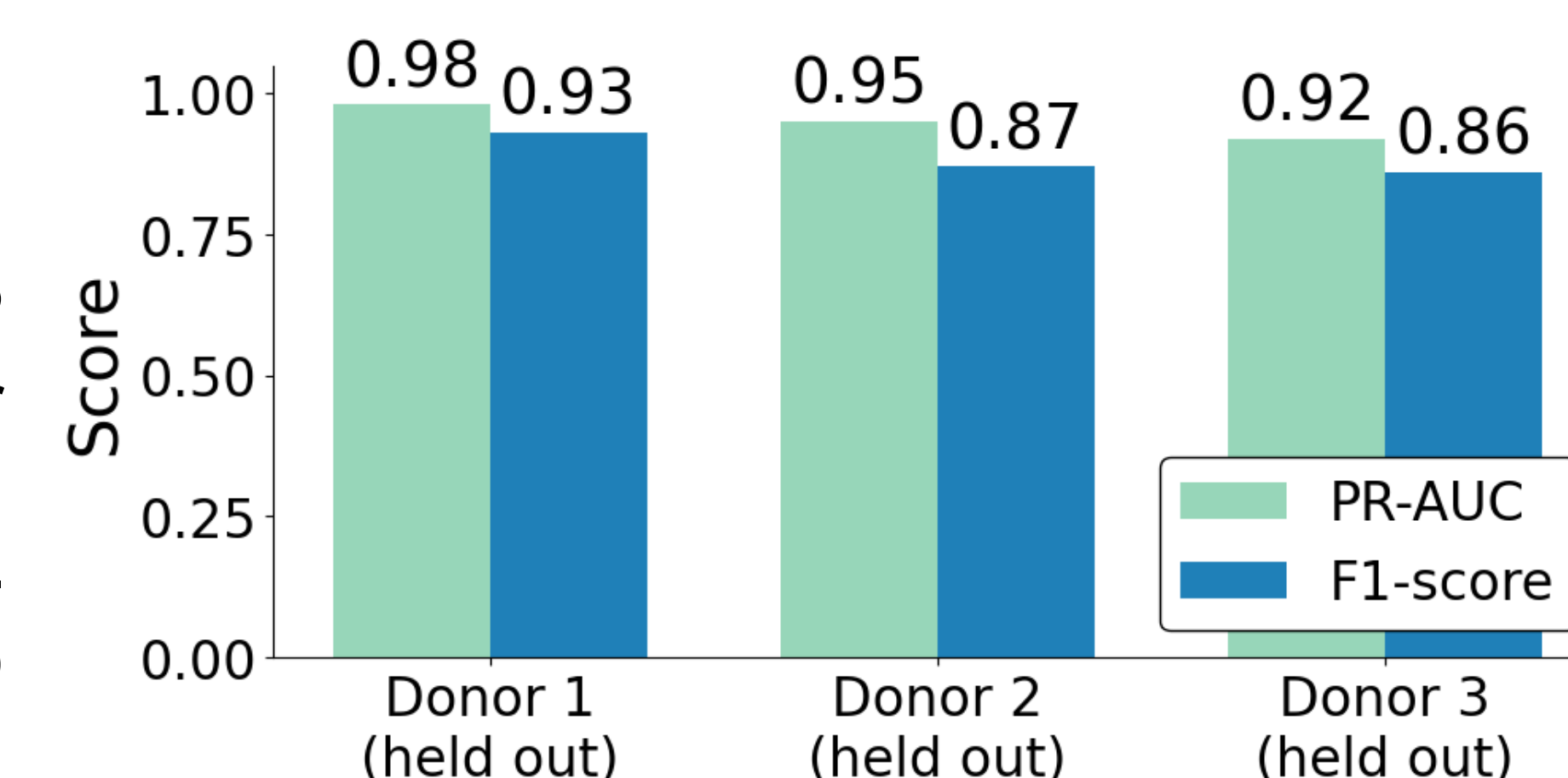


**Figure 2.** Cross-donor classification performance under LODO evaluation

## Conclusions

Our foundation model-based pipeline demonstrates strong performance in automatic tangle-bearing neuron detection, reflecting the potential for automated tau pathology quantification in AD research. However, substantial validation work remains, including assessment of generalizability across laboratories, staining protocols, and donor characteristics. In the future, integrating validated models with digital pathology software such as QuPath to apply to unlabeled slides may reduce manual annotation effort and enable scalable, standardized tau burden assessment in Alzheimer's research.