Spatial Contrastive Learning for Anchoring Histological Human Brain Sections Within a Reference 3D Model

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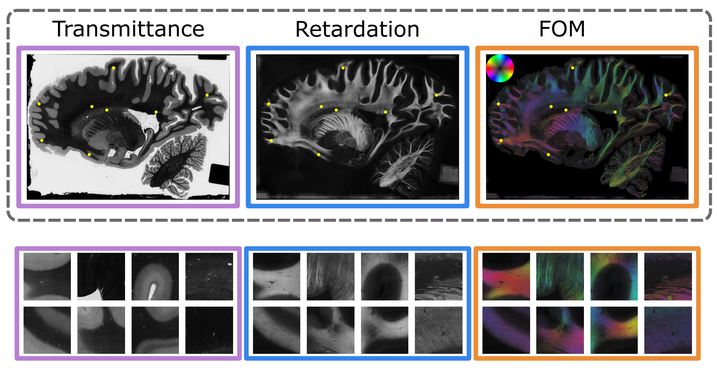
Introduction

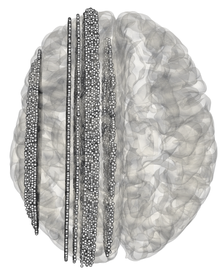
Brain atlases serve as a spatial framework for **comparing brain structures** across individuals and imaging modalities. Histological techniques like **Nissl staining** and **3D-PLI** offer complementary insights into cytoarchitecture and fiber architecture, respectively. To enable integrative analysis, these sections must be aligned to a standard 3D reference space. Traditional image registration methods rely on estimating transformations from image features or landmarks, but they often require manual handling, are sensitive to modality differences, and scale poorly to large datasets.

We propose an alternative, **learning-based approach** that anchors image patches from histological sections into a 3D reference brain using spatial contrastive learning. By training on high-resolution image patches, we learn embeddings that capture local microstructural patterns. We hypothesize that these representations support coarse **spatial anchoring** via cosine similarity in latent space, yielding patch correspondences that define point pairs for estimating 3D transformations.

Human Brain Sections



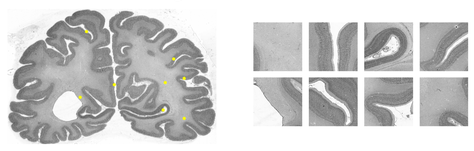
3D-PLI: Enables the visualization of single nerve fibers and fiber bundles with a resolution of 1.33µm/px.



MNI-Colin27 [4] space, visualized with low opacity: Coordinates sampled from available sections are projected onto the reference space, represented by dots.

Dataset:
- Left hemisphere of a single brain
- Cutting results in 1260 brain slices (sagittal plane)
- Number of sections scanned with the microscope is lower
- After filtering: 26 sections were used for training
- Section thickness: 50 µm

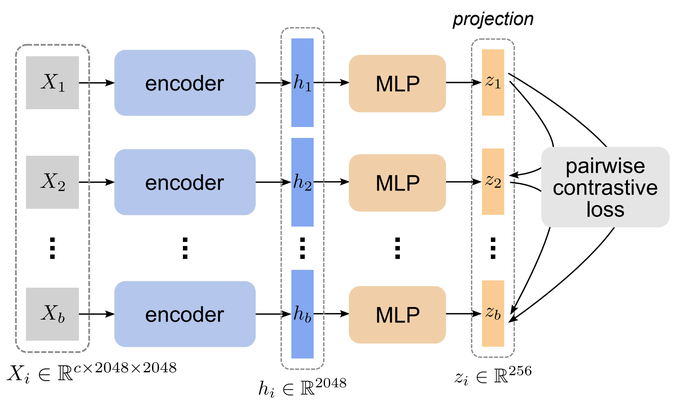
Nissl staining



Dataset:
- Eleven brains, each having ~450 coronal sections
- Microscopic scans of cell-body stained sections
- Reveals cytoarchitectonic organization
- Every 15th section is digitized
- Section thickness: 20 µm
- Each brain is registered into MNI-Colin27

Data sampling:
- Identical sampling strategy applied to both cytoarchitectonic and 3D-PLI modalities.
- Sample locations selected at regular 500 µm intervals in the 2D tissue plane.
- Image patches of size 2048 x 2048 px at ~2 µm/px resolution
- *Nissl-stained sections*: 10 brains used for contrastive pre-training, 1 brain held out for evaluation
- 3D-*PLI sections*: 4-fold cross-validation over available sections - each fold: 21 sections for training
- Sampling ensures uniform spatial coverage

Self-Supervised 3D Contrastive Learning



Assumption: Image patches sampled from *spatially close* locations are more similar than those extracted from distant locations.

Idea: Learn latent space so that representations of similar inputs are closer than those of negative pairs

Prerequisite: Registration of brain sections in an anatomical reference space to obtain canonical spatial coordinates.

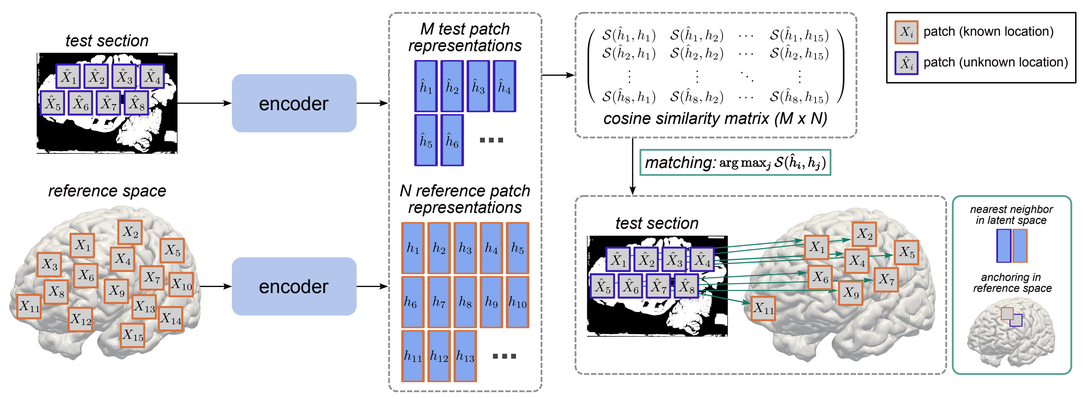
Number of samples in a batch — Scalar product — Temperature

$$\ell_{dist}(i) = -\frac{1}{\sum_{j=1}^{b} \mathbb{I}_{i\neq j}\,\omega_{ij}} \sum_{j=1}^{b} \mathbb{I}_{i\neq j}\,\omega_{ij} \log \frac{\exp(\langle \boldsymbol{z_i}, \boldsymbol{z_j} \rangle / \tau)}{\sum_{k=1}^{b} \mathbb{I}_{k\neq i} \exp(\langle \boldsymbol{z_i}, \boldsymbol{z_k} \rangle / \tau)}$$

Sample in the batch at index i — Weighting of pairs using RBF kernel — L2 normalized feature vector computed by the neural network

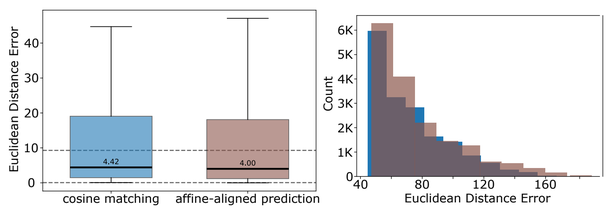
- Pre-training independently on each data modality
- Employ spatial contrastive learning to learn representations of local microstructural patterns from high-resolution image patches extracted from large tissue sections

Spatial Anchoring Within a 3D Reference Model



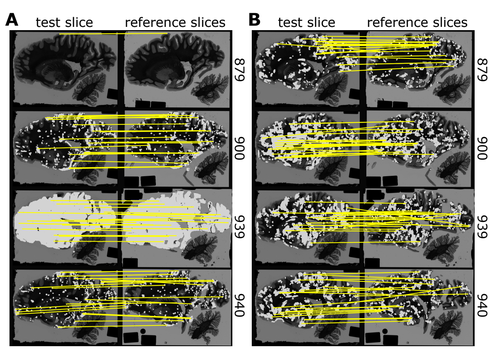
Pipeline:
- Sample image patches from the test section and the reference sections, and then encode them.
- Determine the most similar reference patch in latent space for each test patch.
- Similarity is defined by the cosine similarity between the representations of any two patches.
- Matched image patches then give rise to corresponding point pairs between the image coordinate system and the 3D model.

Evaluation: 3D-PLI Sections



Euclidean distance error distributions

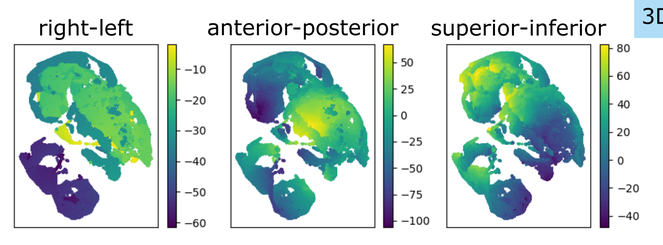
- Left: Whiskers up to the 90th percentile
- Right: Error distribution of outliers
- Outliers: wrong point correspondences
- Concentration of preds at low values
- Aggregated across the test sections of all cross-validation folds



Matched points between an example section #920 and selected reference sections.

- Yellow lines: matching correspondences
- Lightgray dots: sampled points in test slice that are matched to each respective section on the right

- Geometric matching: matches to four sections, provides a lower bound on the error
- Feature-based matching: in most cases accurate correspondences

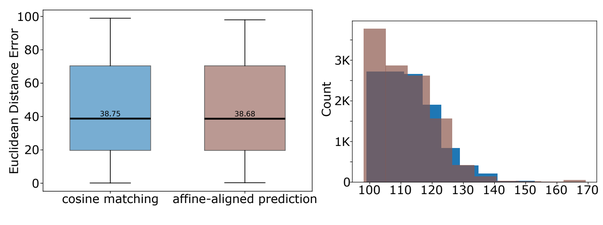


3D spatial points projected onto U-MAP

- A-P and S-I spatial encoding are represented smoothly across the latent space

- Sharp transitions in the R-L axes
- More fragmented due to local discontinuities

Evaluation: Nissl-Stained Sections



Euclidean distance error distributions

- Left: Whiskers up to the 90th percentile
- Right: Error distribution of outliers
- Concentration of preds at low values
- 1 reference 3D brain (#9) is used to anchor test sections
- Higher mean compared to PLI data

Conclusion

- We train a neural network using a distance-based contrastive learning approach to analyze how the learned features relate to anatomical structures.
- We evaluate our approach on two complementary datasets: (1) multi-subject dataset of densely sampled, high-resolution microscopic scans of cell-body-stained histological sections, and (2) a single-subject dataset of sparsely sampled high-resolution 3D-PLI sections.
- Analyses show that features in the U-MAP latent space reveal clusters related to cytoarchitecture or fiber architecture using the "Julich Brain Atlas" [1] and the "Deep White Matter Fibre Bundles Atlas" [5].
- We demonstrate the feasibility of aligning PLI brain sections into a 3D reference model based on similarity of latent texture representations.
- PLI sections in our training data are unevenly distributed, creating spatial gaps that may prevent direct continuity between early and mid sections due to missing intermediate sections.

REFERENCES
[1] K. Amunts, K. Zilles (2020). "Julich-Brain: A 3D Probabilistic Atlas of the Human Brain's Cytoarchitecture", Science, 369, no. 6506, 988, 2020.
[2] Axer, M. (2011). "High-Resolution Fiber Tract Reconstruction in the Human Brain by Means of Three-Dimensional Polarized Light Imaging", Frontiers in Neuroinformatics, vol. 5, 2011, doi: 10.3389/fninf.2011.00034.
[3] C. Schiffer (2021). "Contrastive Representation Learning For Whole Brain Cytoarchitectonic Mapping In Histological Human Brain Sections", 2021 IEEE 18th International Symposium on Biomedical Imaging (ISBI 2021), pp. 603–606.
[4] Holmes, C. J., R. Hoge, L. Collins, R. Woods, A. W. Toga, and A. C. Evans (Mar.– Apr. 1998). "Enhancement of MR Images Using Registration for Signal Averaging". In: Journal of Computer Assisted Tomography 22.2, pp. 324–333.
[5] Guevara, P., Duclap, D., Poupon, C., Marrakchi-Kacem, L., Fillard, P., Le Bihan, D., Leboyer, M., & Mangin, J. F. (2019). Maximum probability map of deep white matter fibre bundles (atlas of deep white matter fibre bundles, version 2018) [Data set]. Human Brain Project Neuroinformatics Platform. https://doi.org/10.25493/V5BH-P7P

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