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Next-Generation BigBrain: Building a 3D model of the human brain at cellular precision

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Background
The first 3D reconstruction of an entire human brain from histological sections, "BigBrain", was provided at 20μm resolution (Amunts et al. 2013). Advances in brightfield microscopy enabled rescanning the histological sections at 1μm isotropic resolution. The enhanced resolution allows visualization of individual cells, thereby supporting more detailed insights into the structural organization of the human brain.

However, it remains challenging to reconstruct 1μm images into a 3D volume with cellular level precision. Conventional intensity-based registration methods, as used for the original BigBrain dataset, do not achieve such high precision. Therefore, we aimed to develop an improved reconstruction method for the next generation 1μm BigBrain.

Method
300 cell-body-stained sections from BigBrain were used to develop and evaluate our reconstruction method. Each section was rescanned with an in-plane resolution of 1μm.

Our reconstruction strategy involves a three step process: (i) identifying and matching bisected cells between adjacent images, (ii) optimizing the positions of bisected cells in 3D space and (iii) applying a non-linear transformation to each image, which aligns the image to the cellular distribution computed in step (ii).

First, we segmented neuronal cell bodies (Upschulte et al. 2022) and matched corresponding pairs of bisected cells between adjacent histological images based on their centroid positions. Next, we minimized a cost function comprising multiple anatomical regularization constraints to optimally align bisected cells in 3D space. The computed distribution aims to capture the most likely distribution of cells in the undistorted brain. Notably, this procedure allows for non-iterative registration, helping to avoid propagation errors that manifest in iterative approaches. Finally, we used the optimized cell positions to define poly-affine transformations that transform each image into the 3D reconstructed space.

Results
Our results show that bisected cells can be used to reconstruct a stack of histological sections to a high level of precision. We found that the reconstruction strategy was critical to achieve anatomically reasonable results. Iterative approaches resulted in scaling artefacts, artificial straightening and anatomically implausible surfaces. In contrast, the non-iterative method did not suffer from such propagation errors and resulted in an anatomically accurate 3D reconstruction, with smooth cortical layers and cell-on-cell alignment (Figure 1).

Discussion
Iterative registration combined with linear transformations was previously used to reconstruct small volumes of interest at cellular precision (Huysegoms et al. 2022). This work shows that a non-iterative strategy with poly-affine transformations enables reconstruction of whole brain sections, paving the way for cellular level reconstructions of an entire brain.

Typically, a reference volume (e.g. blockface or MRI) is used to reconstruct histological sections into 3D. Such volumes, which have lower resolution and contrast than histology, are primarily informative for macroscale structures, with limited utility for cellular alignments. Instead, the present approach uses the intrinsic distribution of cells and anatomical regularization to achieve an accurate reconstruction, without depending on a reference volume. Nevertheless, a reference volume (if available) can be integrated into the pipeline to provide additional anatomical constraints.

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