

Investigating human neocortical architecture in 3D

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Propositions accompanying the PhD thesis

Investigating human neocortical architecture in 3D: New approaches for clearing, labelling and imaging large samples

Sven Hildebrand, Maastricht, 14th December 2021

1. The combination of optical tissue clearing with light-sheet microscopy has become an important tool for the investigation of brain architecture in 3D and its importance will likely grow in the near future with respect to both fundamental and clinical questions.
2. The application of MASH tissue clearing to the human brain enables the visualisation of cortical cytoarchitecture in up to 5 mm thick transparent samples, at a quality and resolution that allows for single cell segmentation, while obtaining volumes that can be co-registered and re-identified in lower resolution *post mortem* MRI scans.
3. The dual imaging of blood vessels and brain cells with *angioMASH* makes it possible to study *angio-* and *cytoarchitecture* in the same tissue sample.
4. The current state of optical tissue clearing allows for the affordable processing of organ slices, arbitrarily large in the lateral dimension, and custom-made, 3D-printed labware offers an economic way for smaller labs to build up their own large scale tissue-processing pipelines.
5. The conventional light-sheet microscope geometry is not suitable for the increasing tissue volumes rendered transparent with new optical clearing protocols. It is expected that oblique geometries will become more popular and wide-spread, as they offer advantages in terms of sample size with little disadvantages compared to the standard geometry.
6. Despite all the technical progress, one should rein in ones expectations regarding the achievable imaging depths, especially with multiple labels. Even the highest transparency cannot overcome the physical limitations when relying on wavelengths below the red spectrum.
7. Tolerance to frustration and failure are invaluable personality traits in the development of (histological) methods.
8. It is remarkable what anatomical and histological knowledge can be gained from decades-old publications relying on techniques more than a hundred years old. Usually the trouble of some literary gold digging is worth it.
9. Raw data of the highest possible quality saves you a lot of trouble down the data-processing road.
10. *"The real virtue of science is that it changes our perspective of our place in the cosmos like, art, music, and literature."*
-Lawrence Krauss