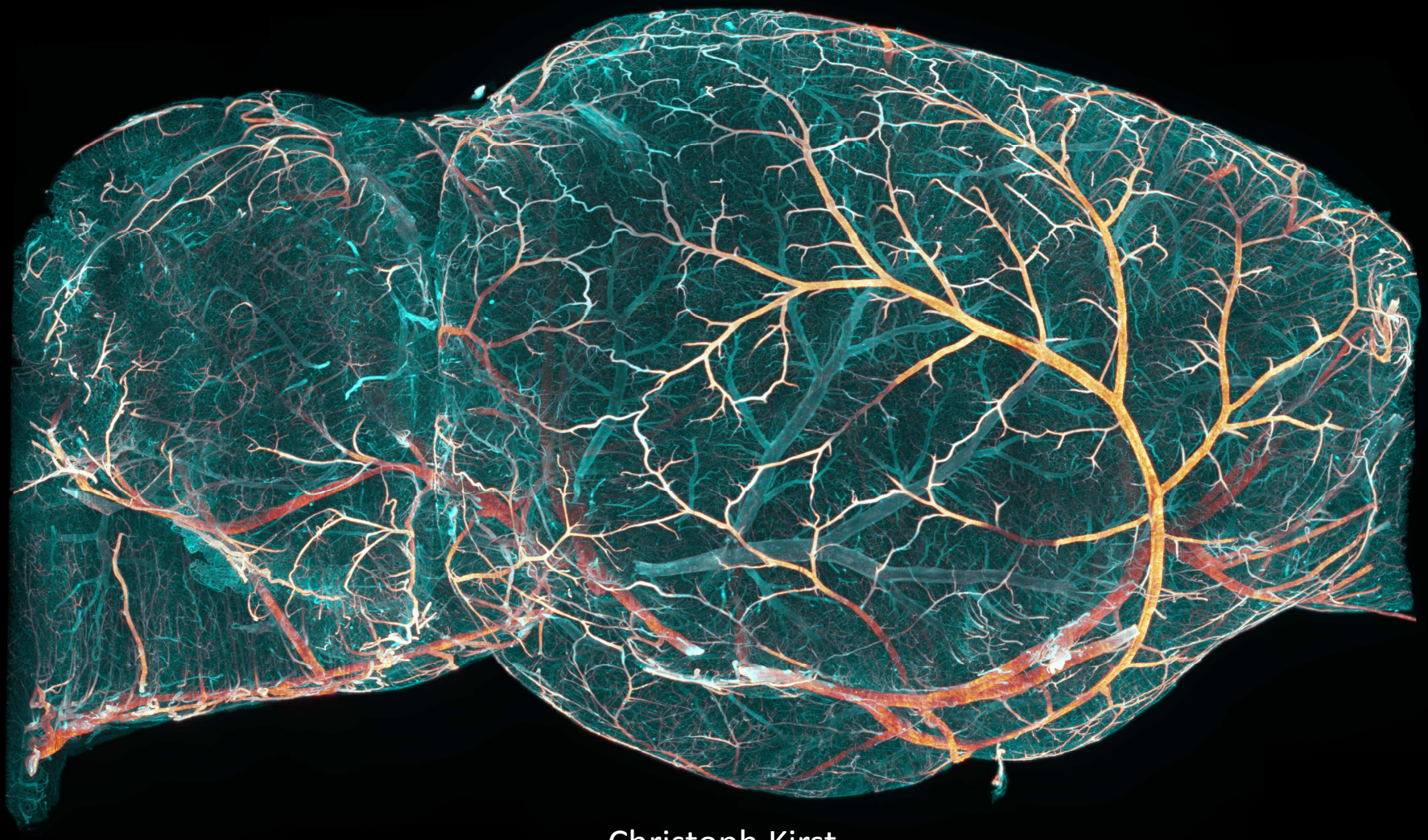
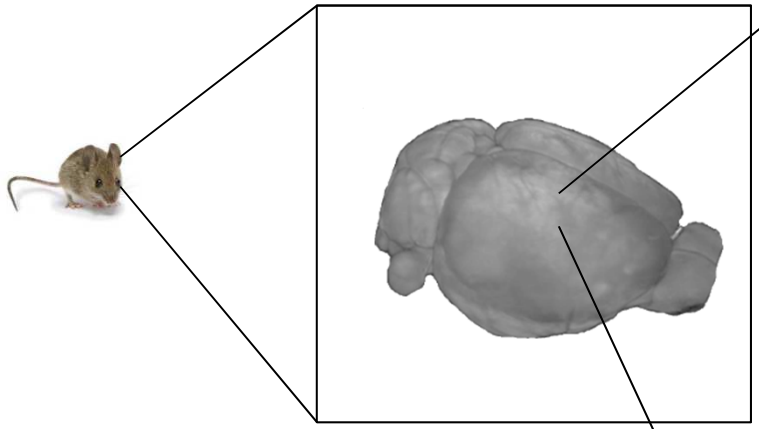
Mapping brain activity and structure: iDISCO+ and ClearMap

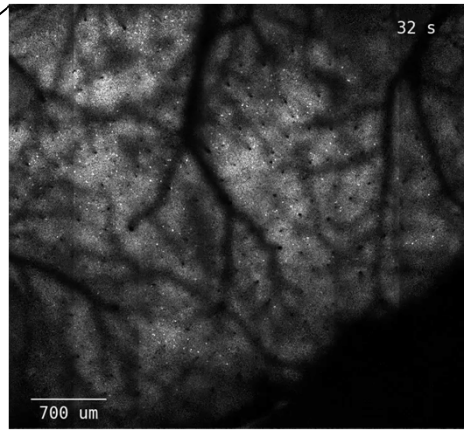


Christoph Kirst
University of California, San Francisco and Lawrence Berkeley National Laboratory

Complex system brain



Brain activity



[Sofroniew, …, Svoboda, 2016]

Brain structure

[Renier*, Adams*, Kirst*, Wu*, et al. 2016]

How do brain networks compute, enable cognition and generate intelligent behavior ?

How is brain activity and structure altered in diseases, by genetics, or via drugs ?

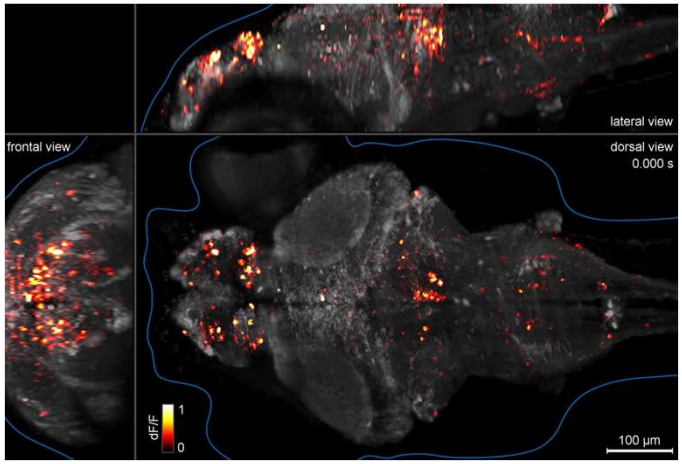
Neuroscience and large data

+ microscopy and method development

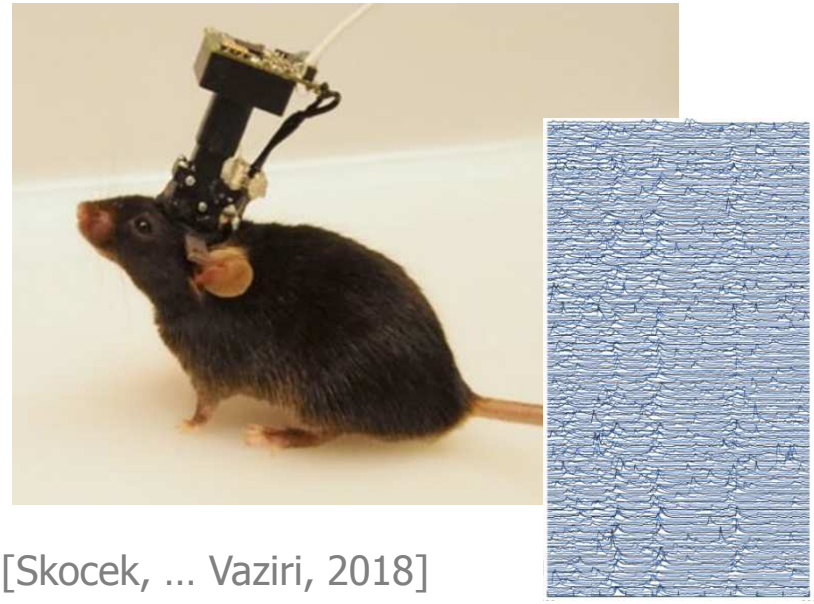
+ Morse law for computational power

= boost in scale and data size

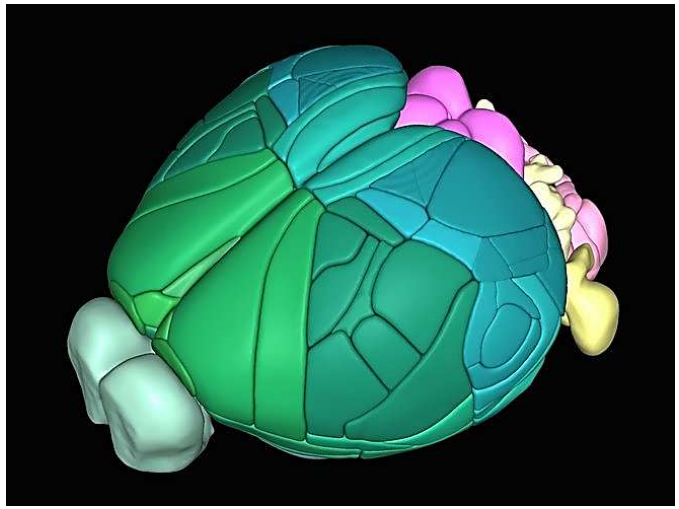
→ understand circuit function
on the brain-wide level



[Vladimirov, …, Ahrens, 2014]



[Skocek, … Vaziri, 2018]



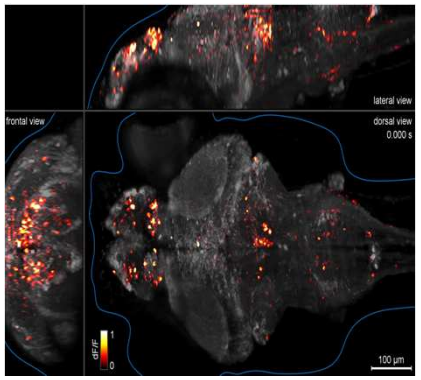
[Allen Brain Atlas]

Brain wide activity mapping

-EEG, MEG, fMRI
- \+ fast, non-invasive
- \- low spatial resolution

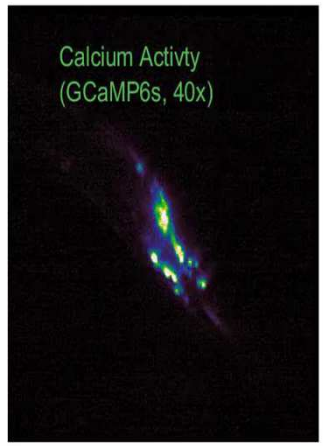
-multi-channel silicon probes
- \+ fast
- \- limited number of channels

- opto-genetics
- \+ larger populations & dynamics
- \- challenging for deeper structures / limited field of view



[Vladimirov, …, Ahrens, Nat Meth 2014]

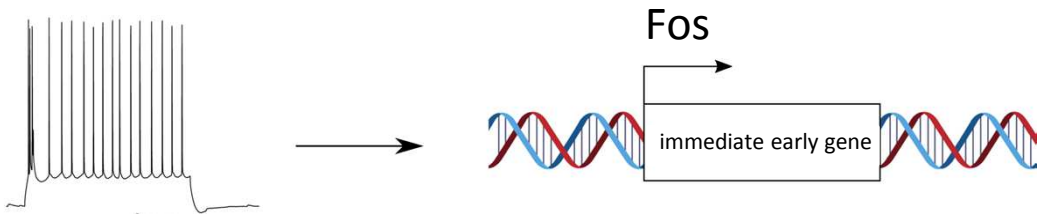
⇒ not achieved in mammalian brain



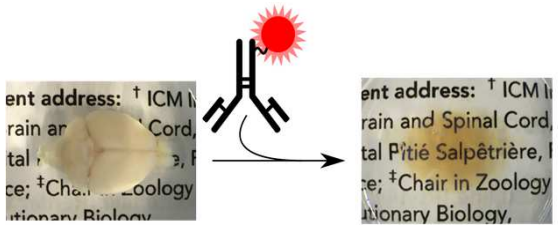
[Nguyen, …, Leifer, PNAS 2014]

Mapping whole brain activity at cellular resolution

- neuronal activity drives Fos expression



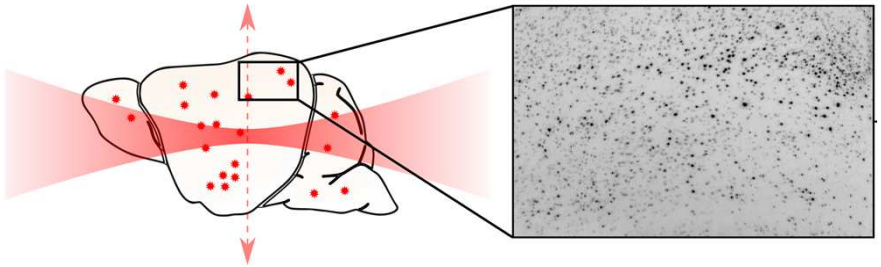
- vascutissue clearing



iDISCO+ ✓

- light sheet imaging and data analysis

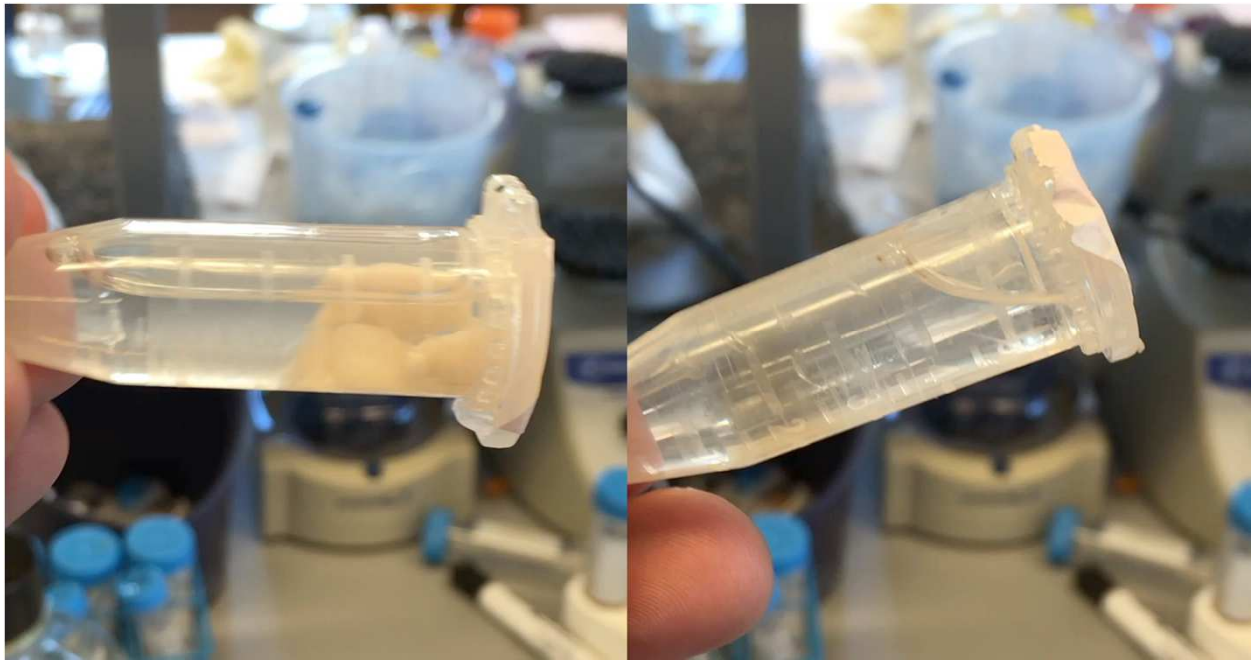
raw data (~ TB)

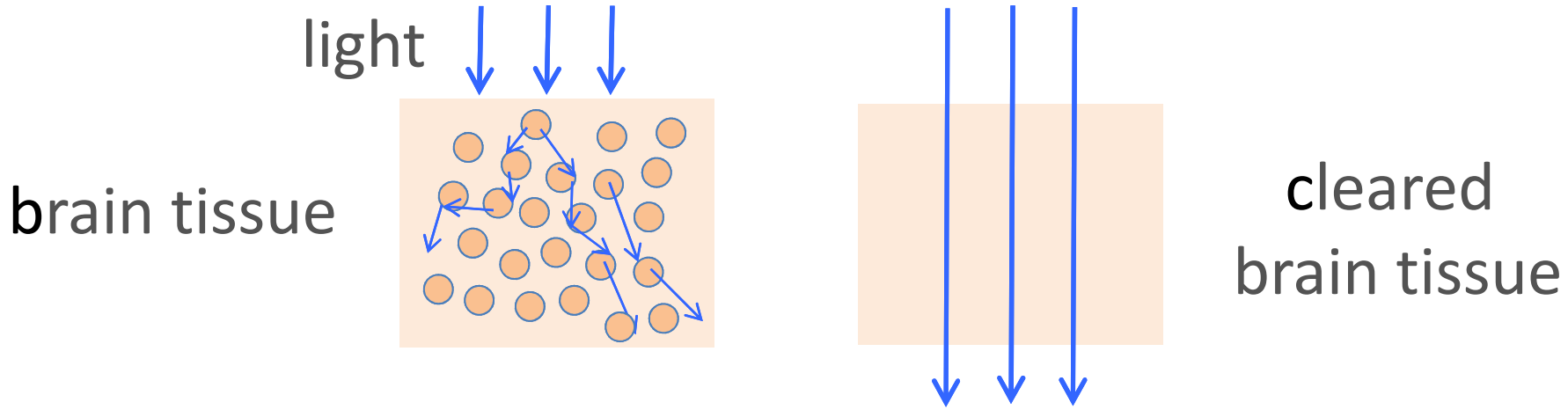


ClearMap ✓

Renier*, Adams*, Kirst*, Wu* et al. Cell 2016

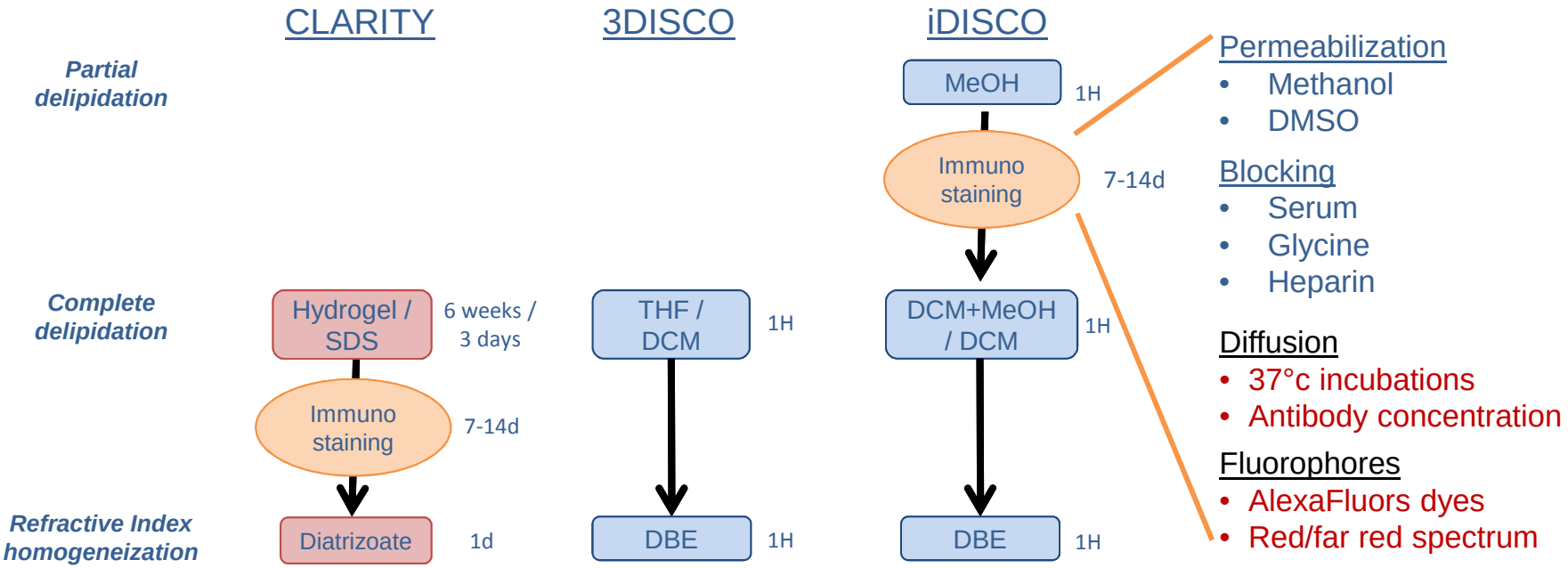
iDISCO+ tissue clearing





Renier et al. Cell 2014
Renier*, Adams*, Kirst*, Wu* et al. Cell 2016

Tissue clearing: iDISCO



Enhanced whole-mount labeling protocol + 3DISCO clearing =

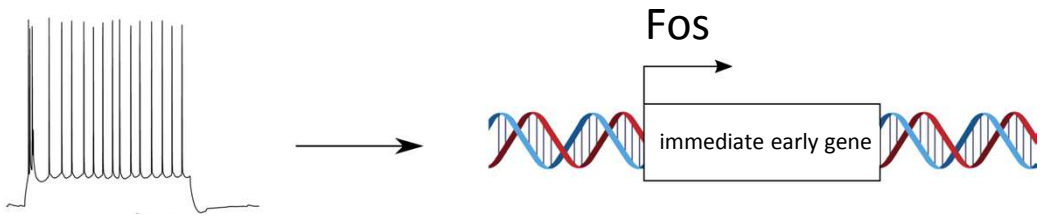
iDISCO: immunolabeling-enabled 3 dimensional clearing of solvent cleared organs

Aqueous | Organic

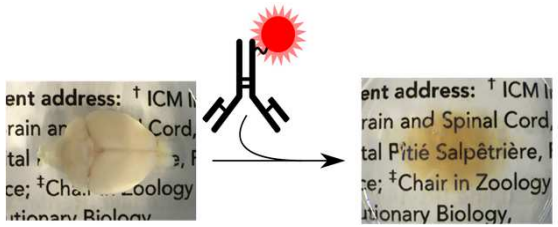
Renier et al. Cell 2014
Renier*, Adams*, Kirst*, Wu* et al. Cell 2016

Mapping whole brain activity at cellular resolution

- neuronal activity drives Fos expression



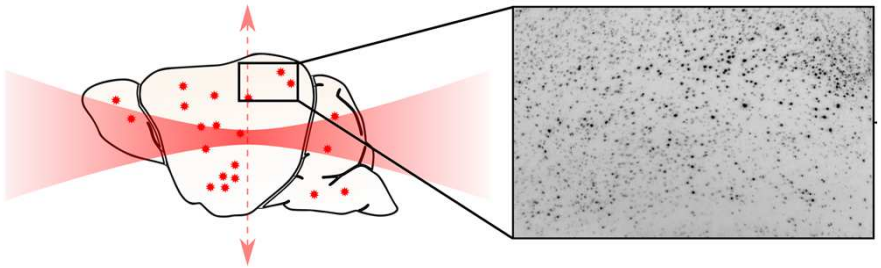
- vascutissue clearing



iDISCO+ ✓

- light sheet imaging and data analysis

raw data (~ TB)



Renier*, Adams*, Kirst*, Wu* et al. Cell 2016

ClearMap: A pipeline to detect and register cells in 3D

3D image registration
- Elastix
- ITK
- ABA annotation

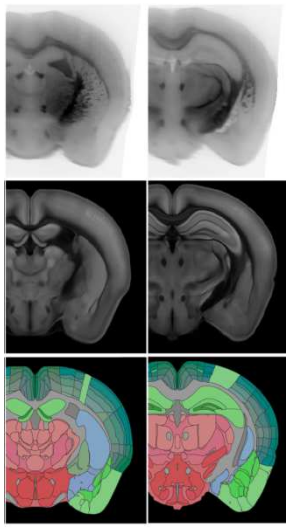
3D object detection
- DoG filtering
- Watershed
- Ilastik
- …

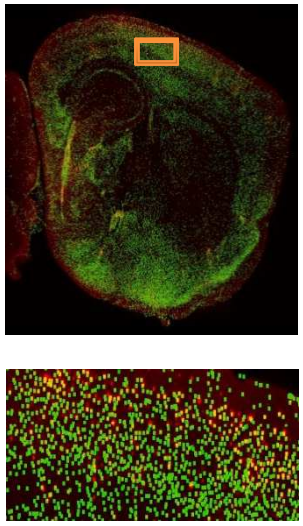
Analysis and statistics
- heat maps
- regional statistics
- P-value maps
- …

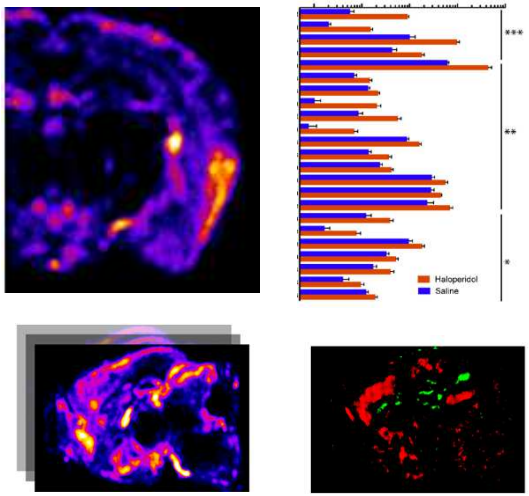
Auto-flourescence

Reference

Annotation







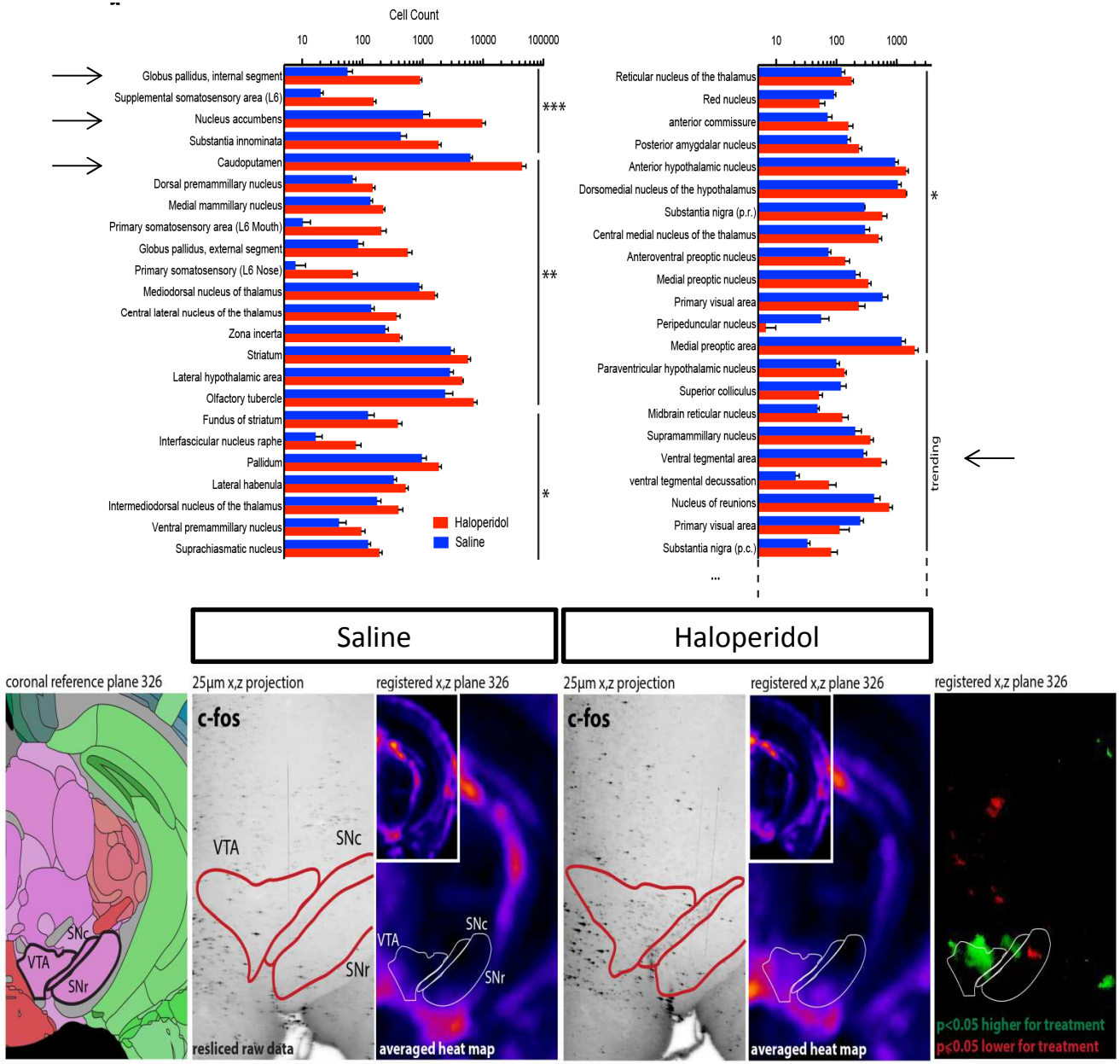
- 20k+ lines pyhton & c++
- open source

- widely used (Harvard, MIT, Princeton, Stanford, Yale, Columbia, CalTech, IMP Vienna, Rockefeller, CNRS, …)

https://www.github.com/ChristophKirst/ClearMap

[Renier*, Adams*, Kirst*, Wu* et al. **Cell** 2016]

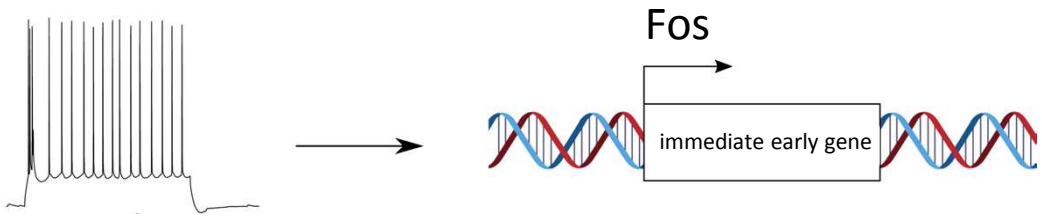
Mapping the effects of psychoactive drugs



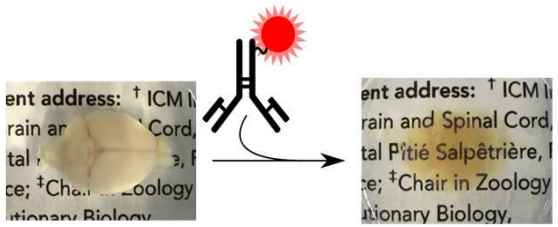
Renier*, Adams*, Kirst*, Wu* et al. Cell 2016

Mapping whole brain activity at cellular resolution

- neuronal activity drives Fos expression



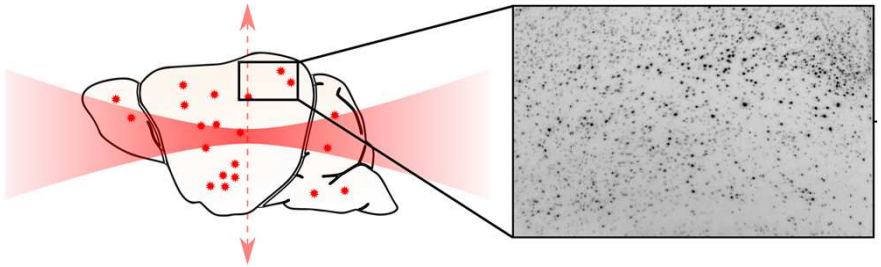
- vascutissue clearing



iDISCO+ ✓

- light sheet imaging and data analysis

raw data (~ TB)

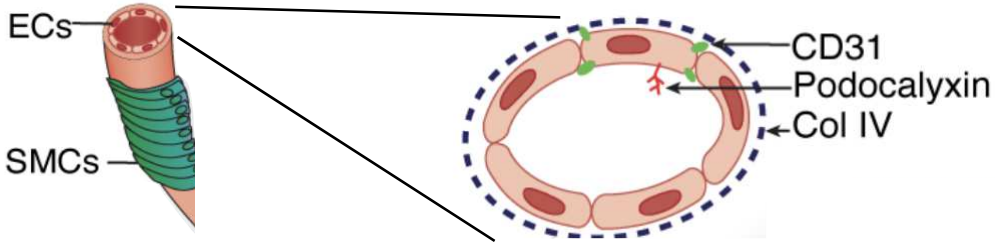


ClearMap ✓

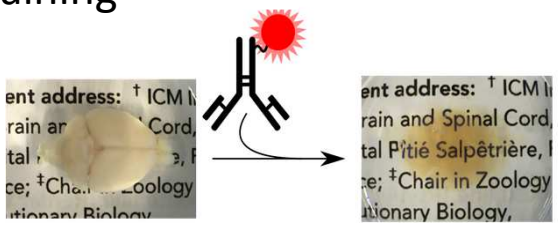
Renier*, Adams*, Kirst*, Wu* et al. Cell 2016

Mapping whole brain structure at cellular resolution

- vasculature network via tissue markers



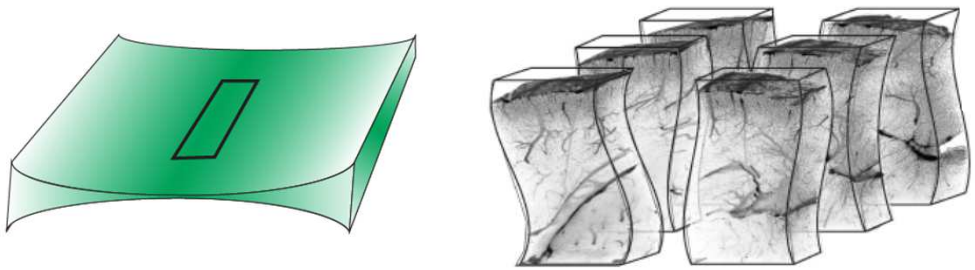
- tissue clearing & immunostaining



iDISCO+ ✓

- light sheet imaging and data analysis

raw data (~ TB)



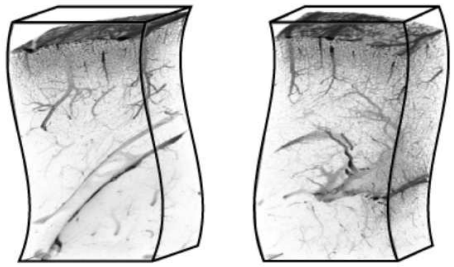
ClearMap 2.0

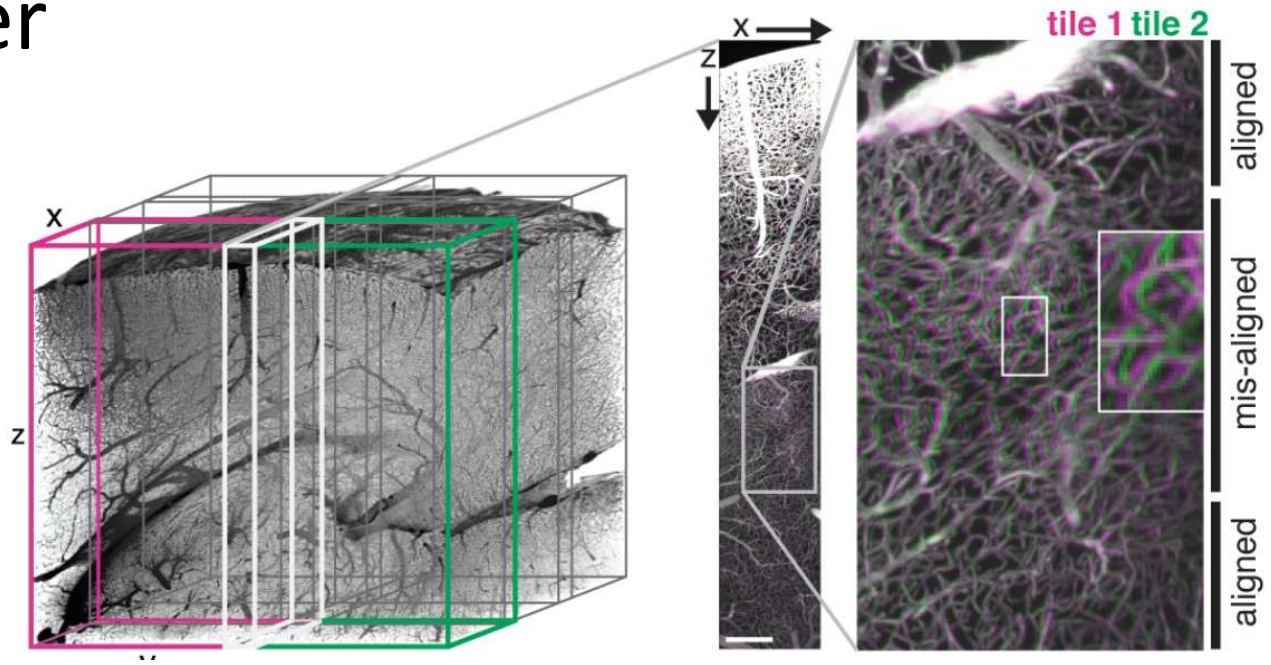
[Renier*, Adams*, Kirst*, Wu* et al. Cell 2016] [Kirst et al. Cell 2020]

Wobbly Stitcher

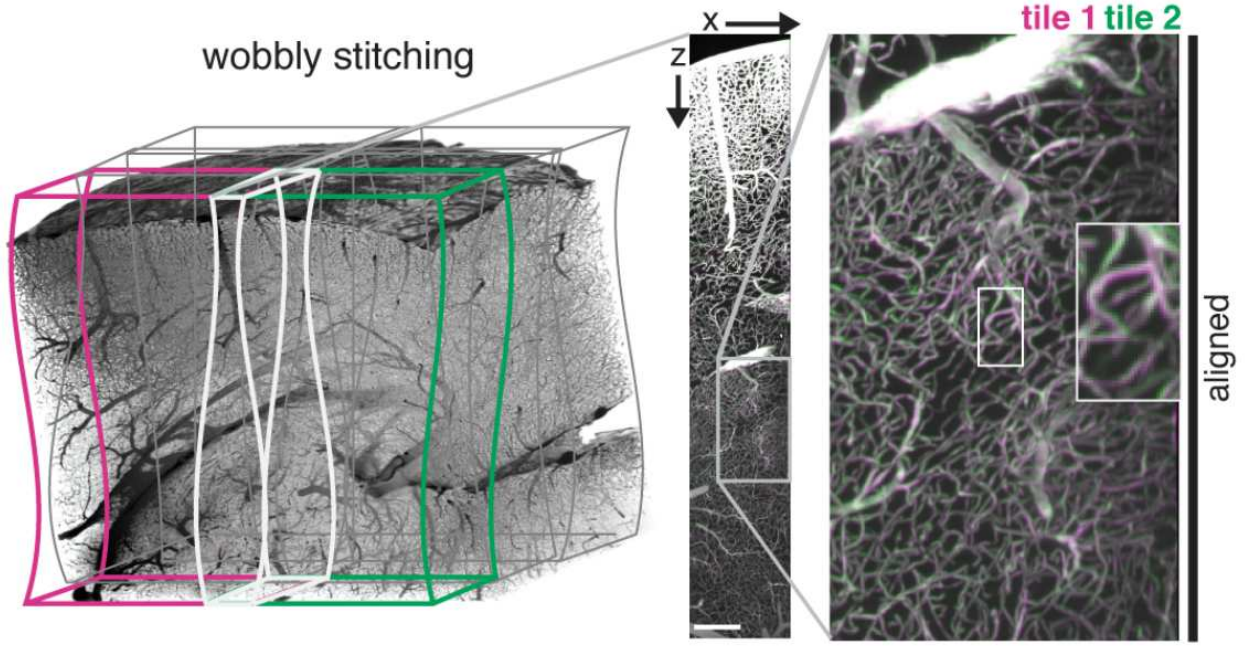
- rigid stitching fails

'wobbly' image stacks
(oscillations along stack axis)





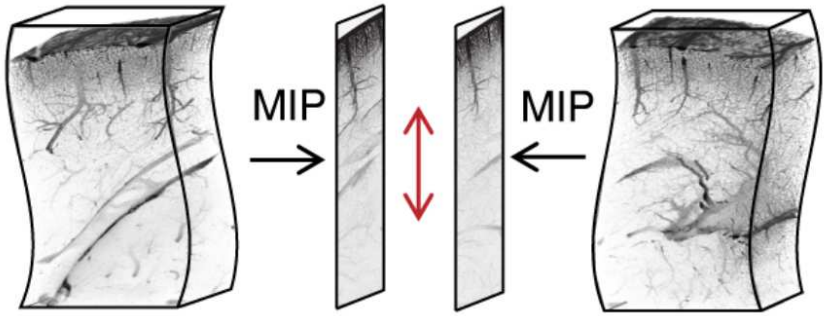
- wobbly stitching



[Kirst et al. **Cell** 2020]

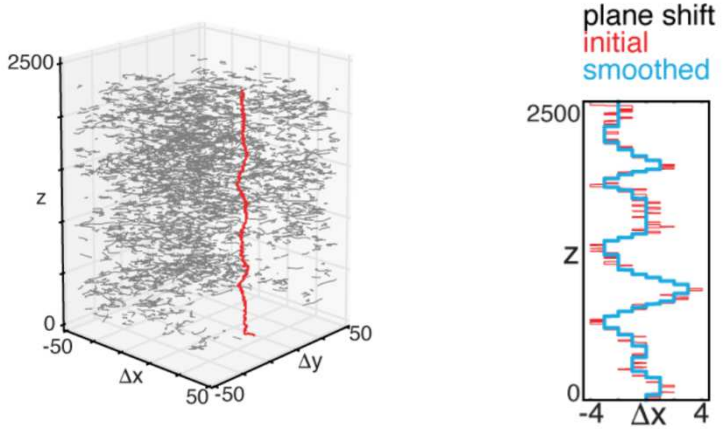
Wobbly Stitcher

1. z-alignment via MIP projections

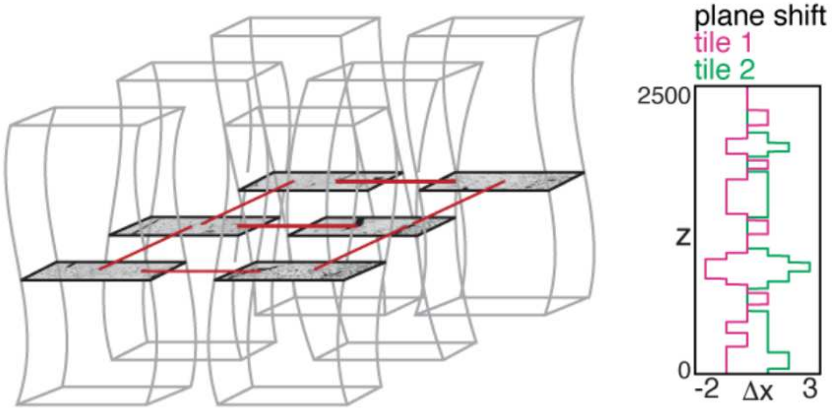


2. plane-wise x-y alignment

3. alignment tracking

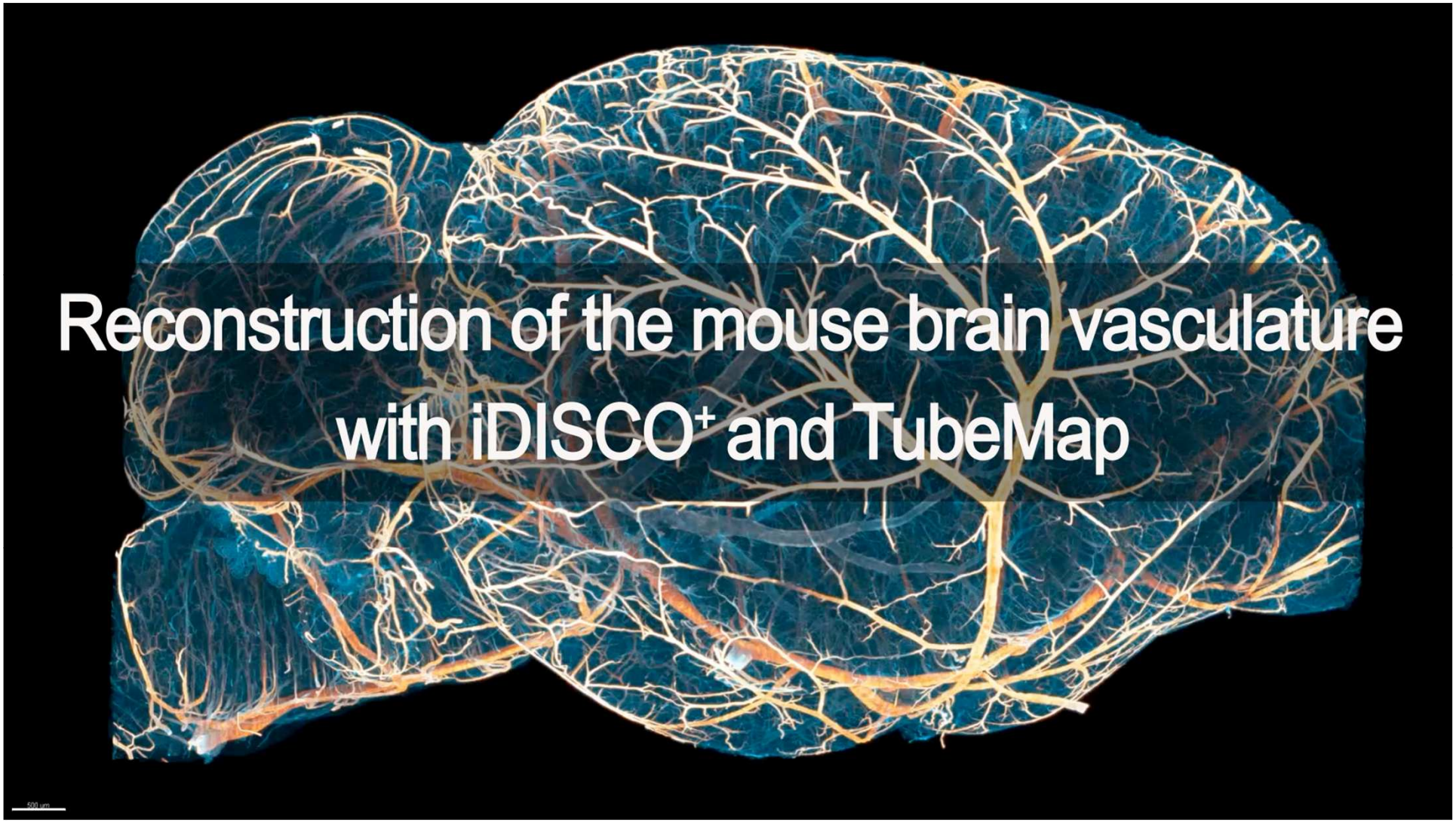


4. global optimial placement



⇒ ~15min for 100 giga pixel volume (~ 3000 planes, ~100 individual stacks)

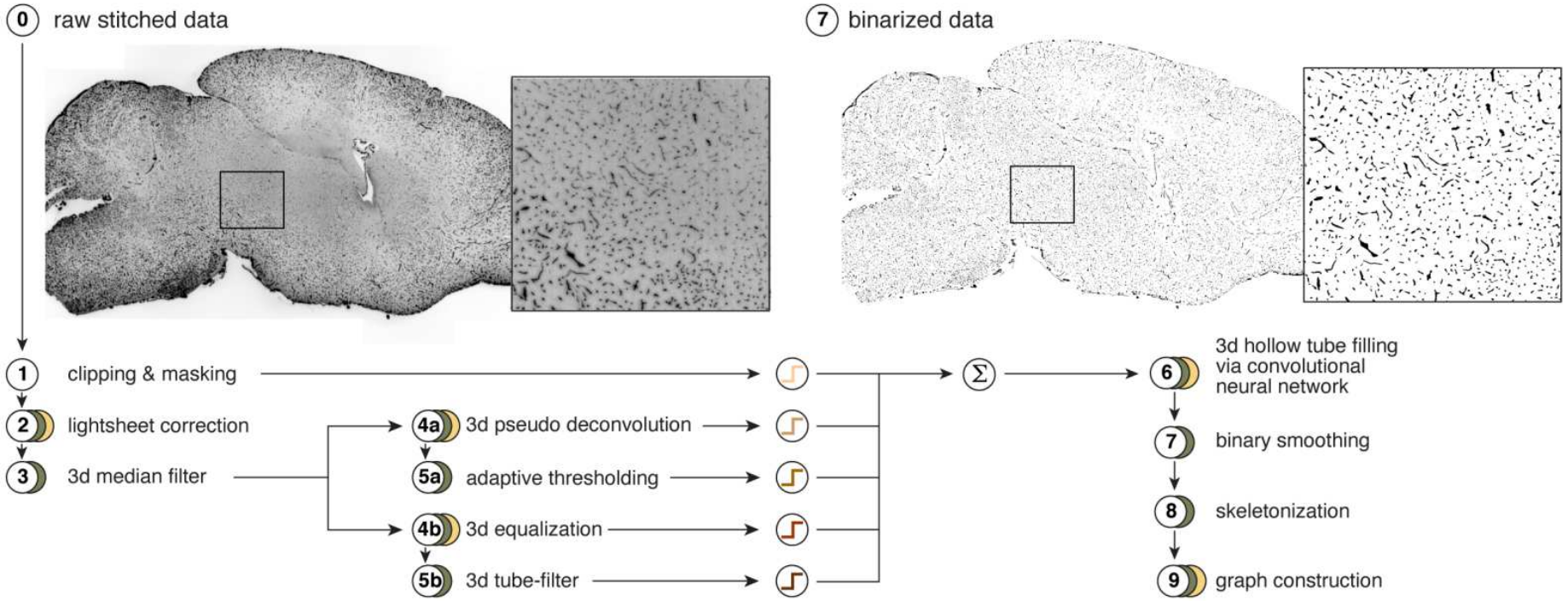
[Kirst et al. **Cell** 2020]



[Kirst et al. **Cell** 2020]

ClearMap 2.0: A toolbox for 3d image processing

- Toolbox for fast 3d image processing methods of TB sized light sheet microscopy data.
- TubeMap: full vasculature network reconstruction



[Kirst et al. **Cell** 2020]

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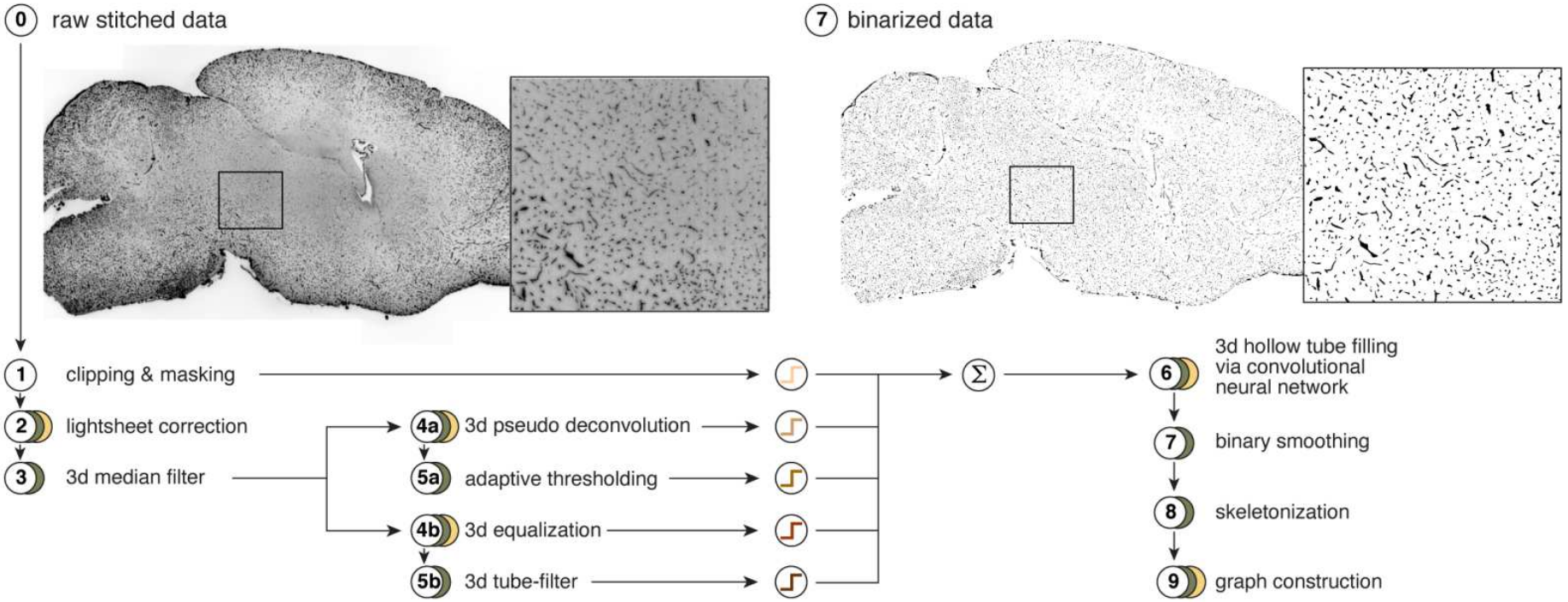
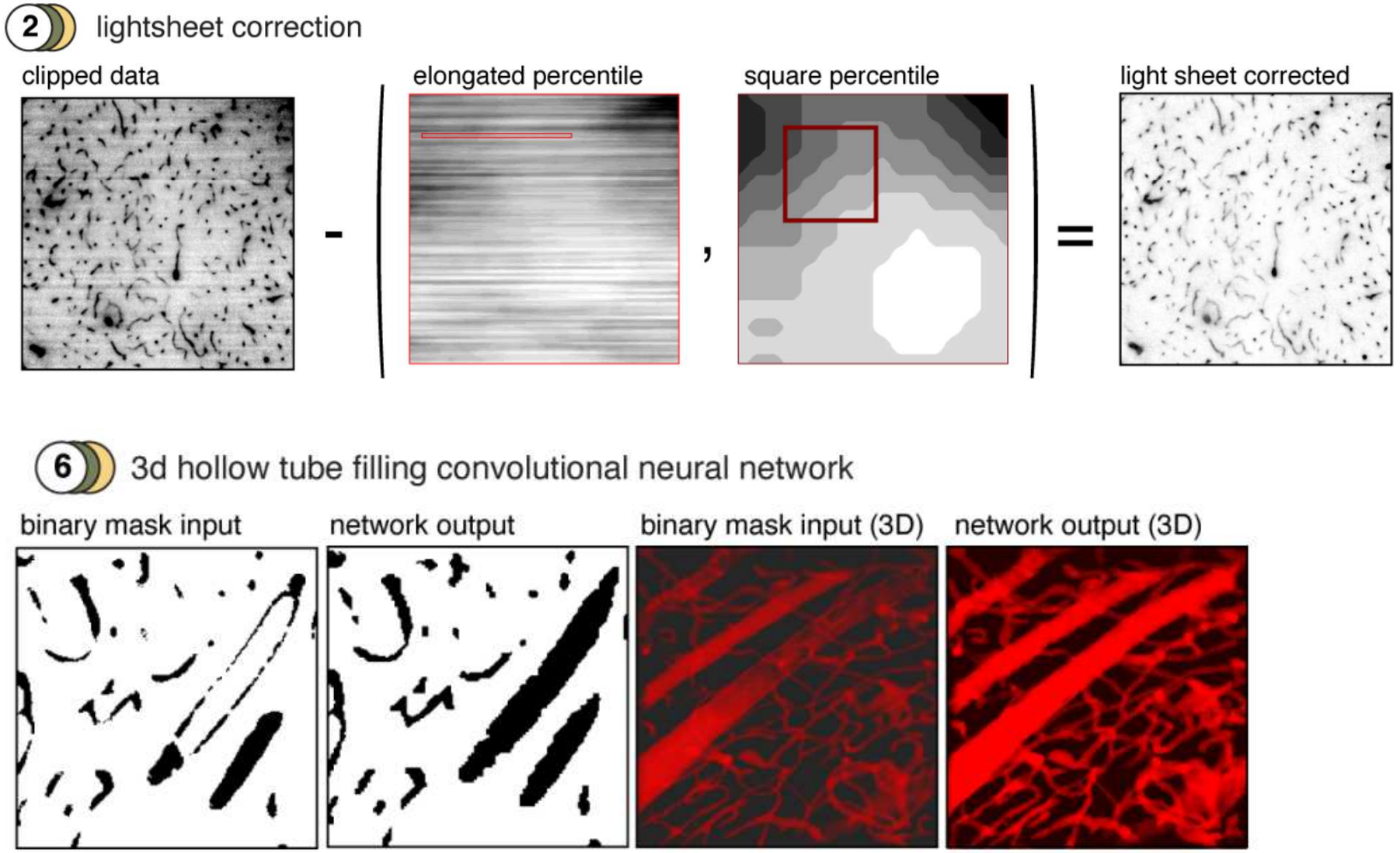


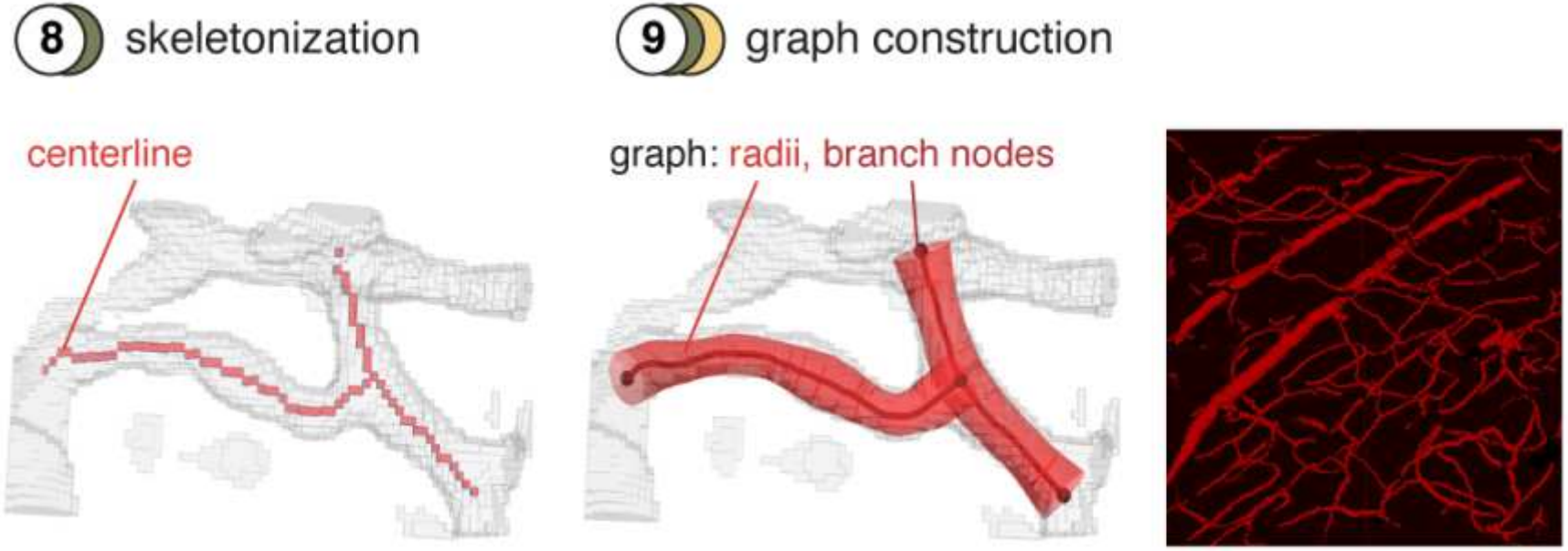
[Kirst et al. **Cell** 2020]

ClearMap 2.0: a toolbox for 3d image processing



[Kirst et al. **Cell** 2020]

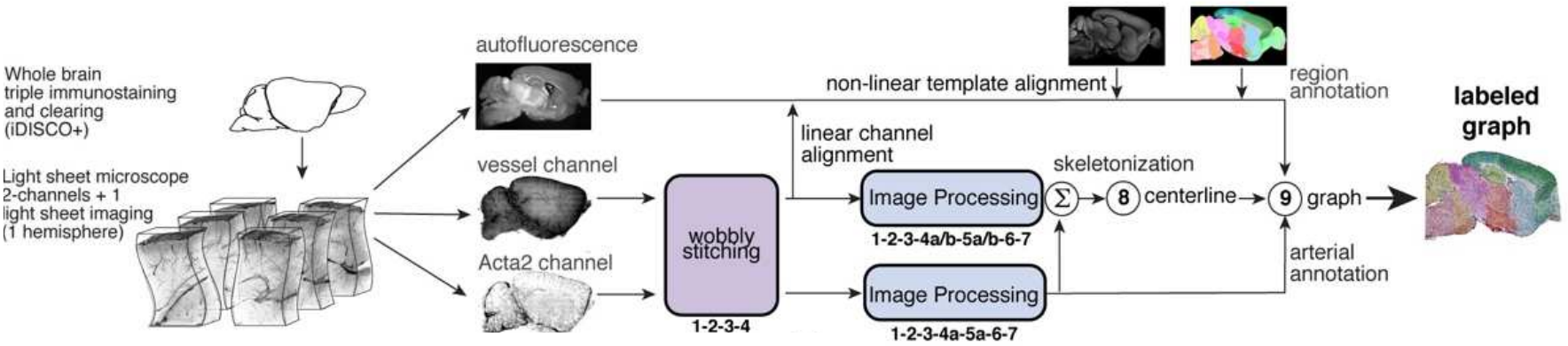
ClearMap 2.0: a toolbox for 3d image processing



[Kirst et al. **Cell** 2020]

ClearMap 2.0: a toolbox for 3d image processing

TubeMap pipeline:



[Kirst et al. **Cell** 2020]

ClearMap 2.0: a toolbox for 3d image processing

Alignment methods:

- 3d resampling
- 3d alignment to reference atlases
- wobbly stitching (see above)
- Allen Brain Atlas modules

Image processing methods:

- clipping and normalization
- binary filling
- discrete topology based binary smoothing
- 3d local gradients and Hessian matrices
- 3d tube filter and tubeness measures
- 3d rank filter library (>30 filters)
- skeletonization via parallel thinning
- 3d tracing
- fast calculation of 3d local image statistics
- equalization methods
- hysteresis and seeded thresholding
- 3d adaptive and local image statistics based thresholding
- light-sheet artifact removal
- fast pseudo deconvolution
- deep convolutional neuronal network based image processing
- expert processing pipelines for specific applications

Graph analysis:

- graph preprocessing and cleanup
- graph branch reduction
- graph annotation
- graphs embedded 3d space
- 3d graphs with 3d edge geometry
- graph processing
  - morphological operations on edges and vertices
  - sub-graph extraction and spatial slicing
  - network analysis

Visualization tools for 3d images:

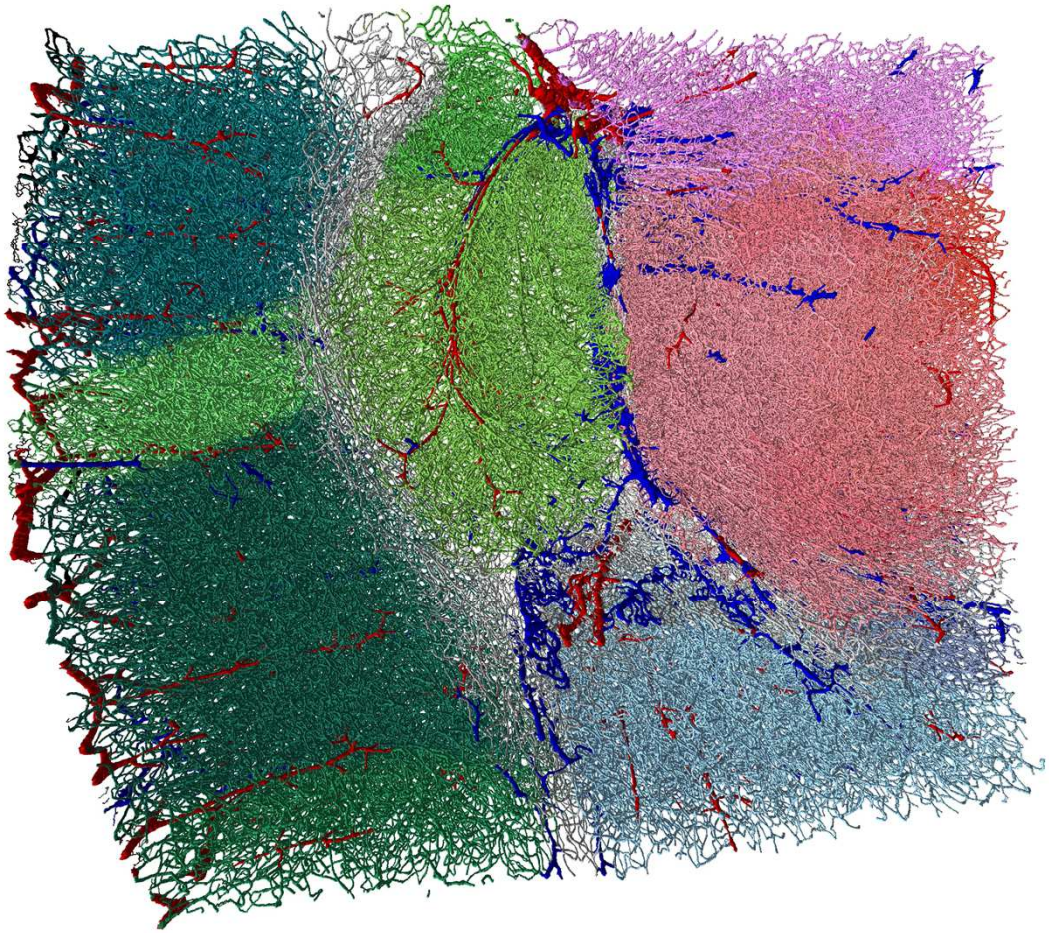
- fast interactive 2d slice plotting of 3d TB data sets
- overlays and/or synchronized window display
- interactive image processing pipeline
- 3d volume rendering
- 3d list and line plots

Visualization tools for 3d graphs:

- 3d line plots of 3d graphs
- 3d mesh plots of 3d vasculature graphs

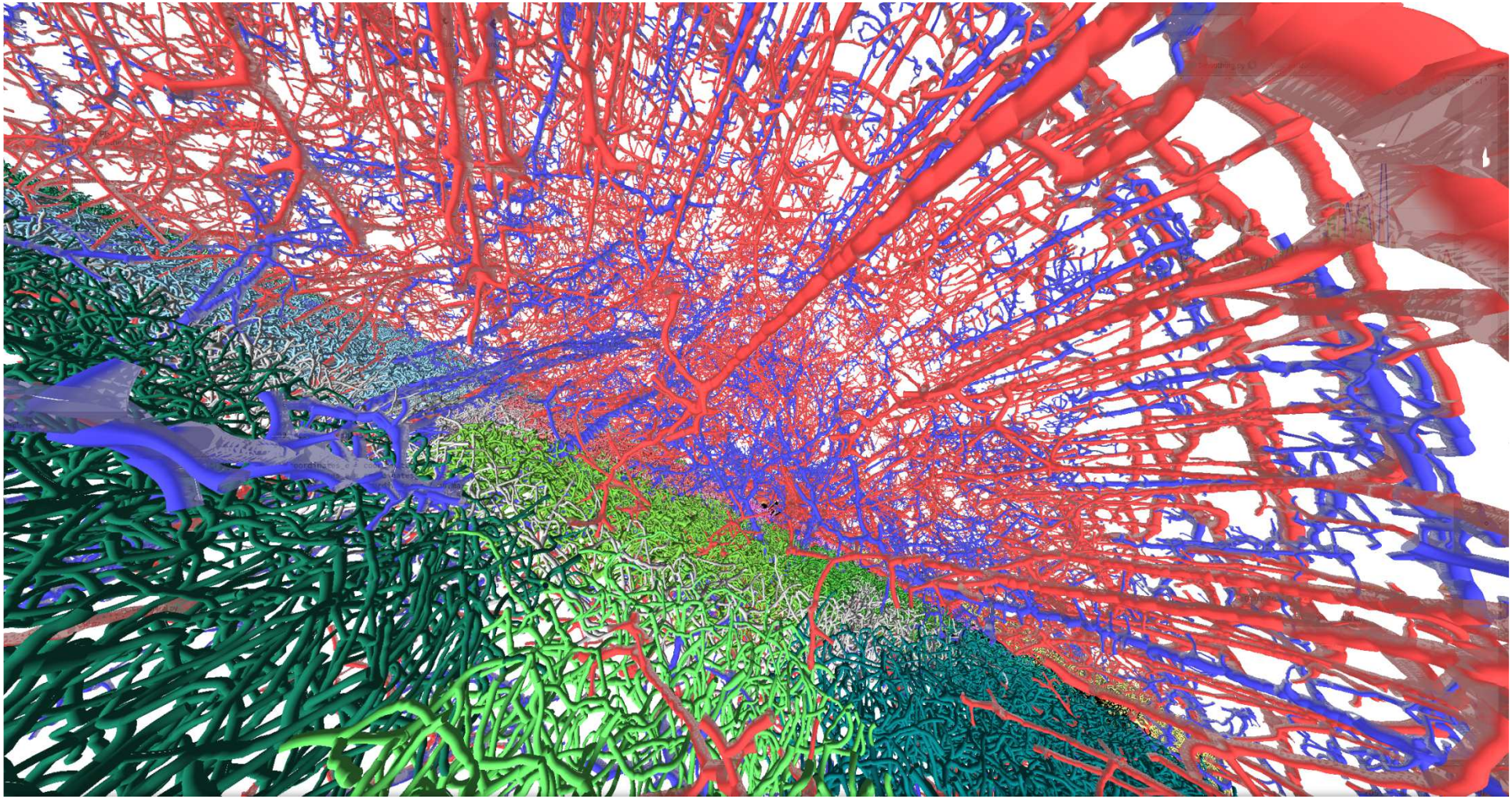
[Kirst et al. **Cell** 2020]

Vasculature graph reconstruction

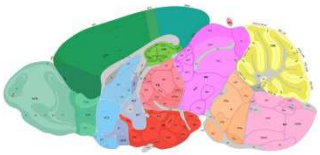


[Kirst et al. **Cell** 2020]

Vasculature graph reconstruction

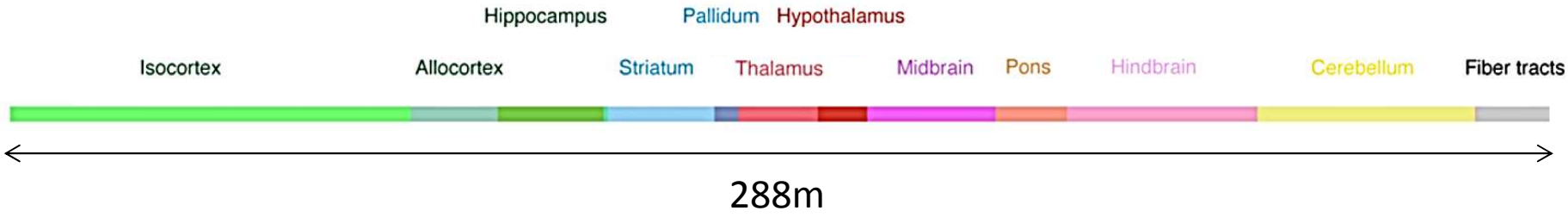


Vasculature Features

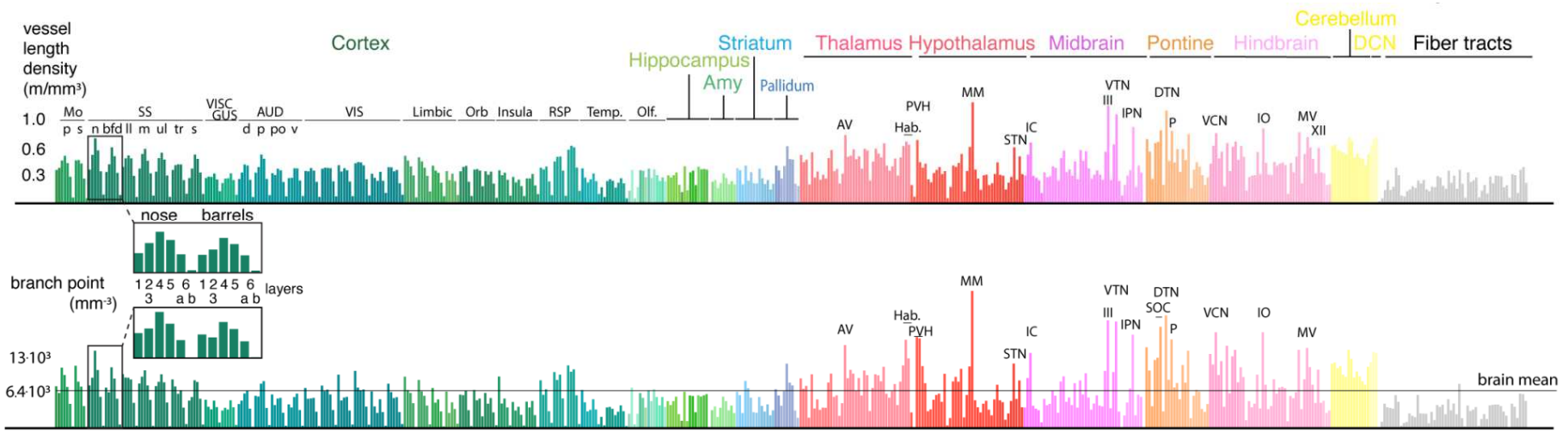


1cm

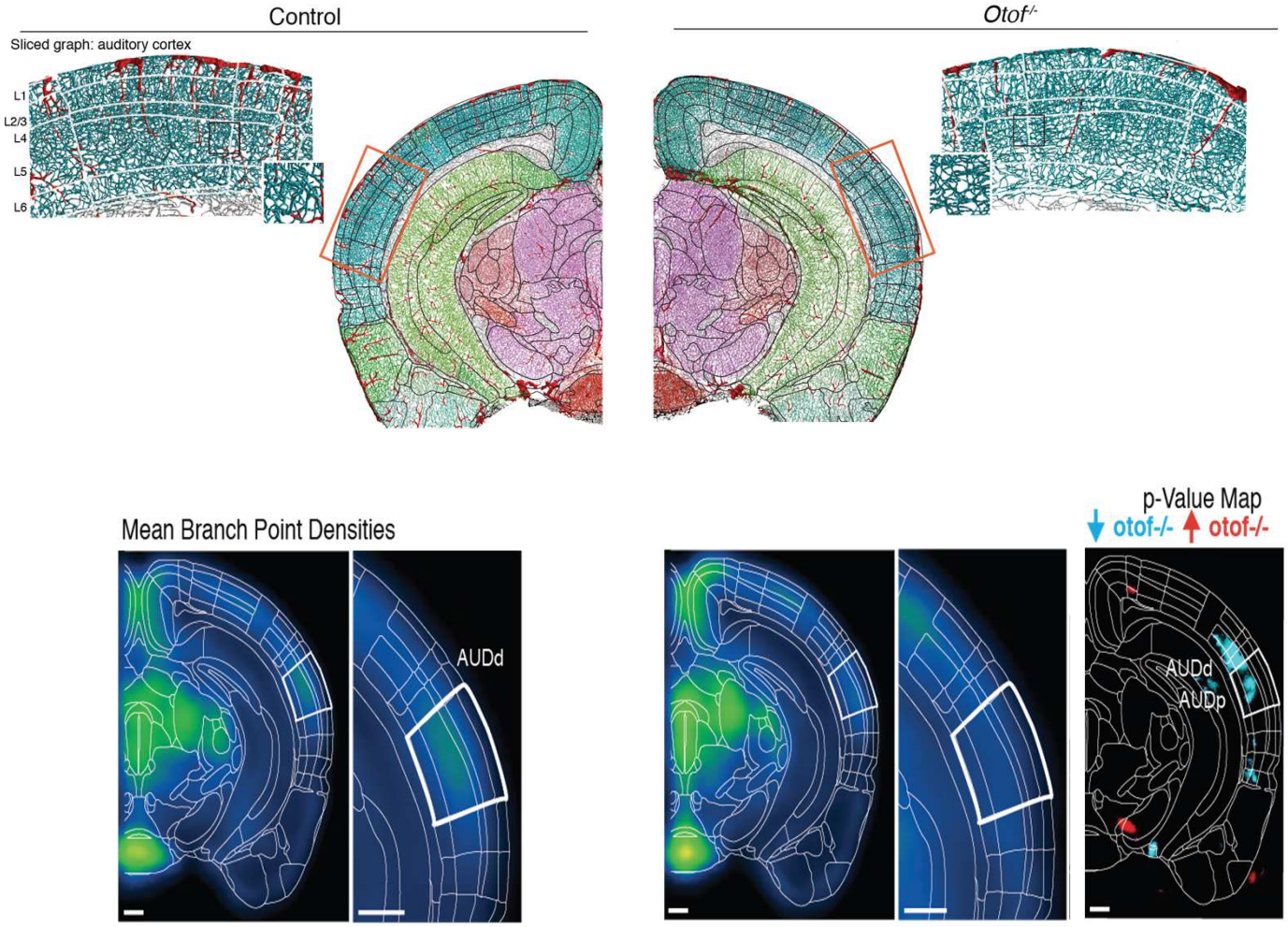
total vasculature vessel length



Vessel length density



Brain wide alterations to the vasculature in congenitally deaf mice



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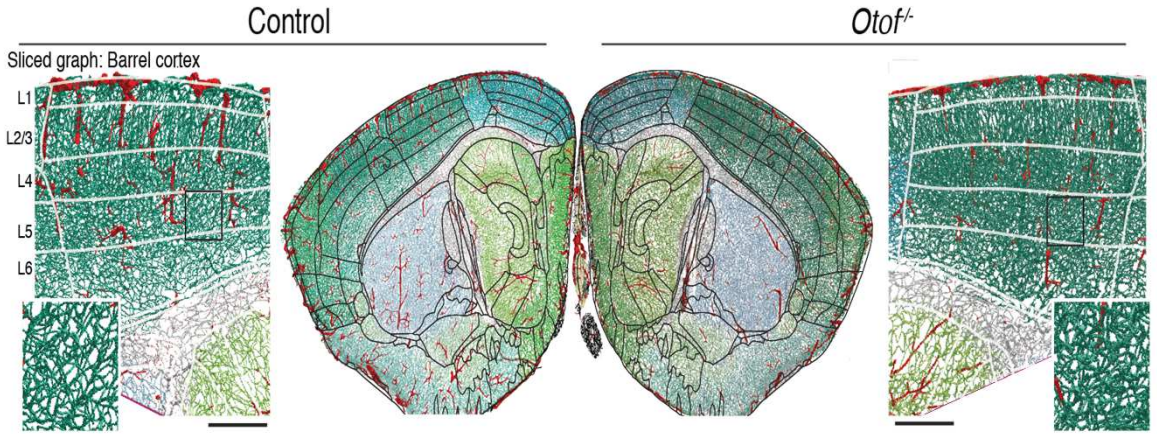
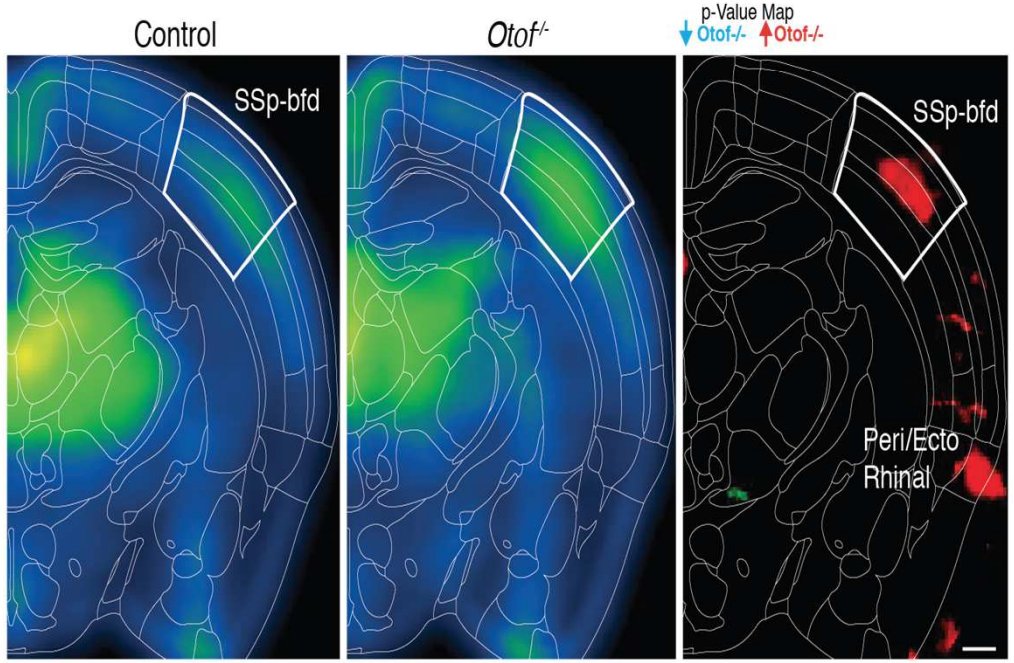




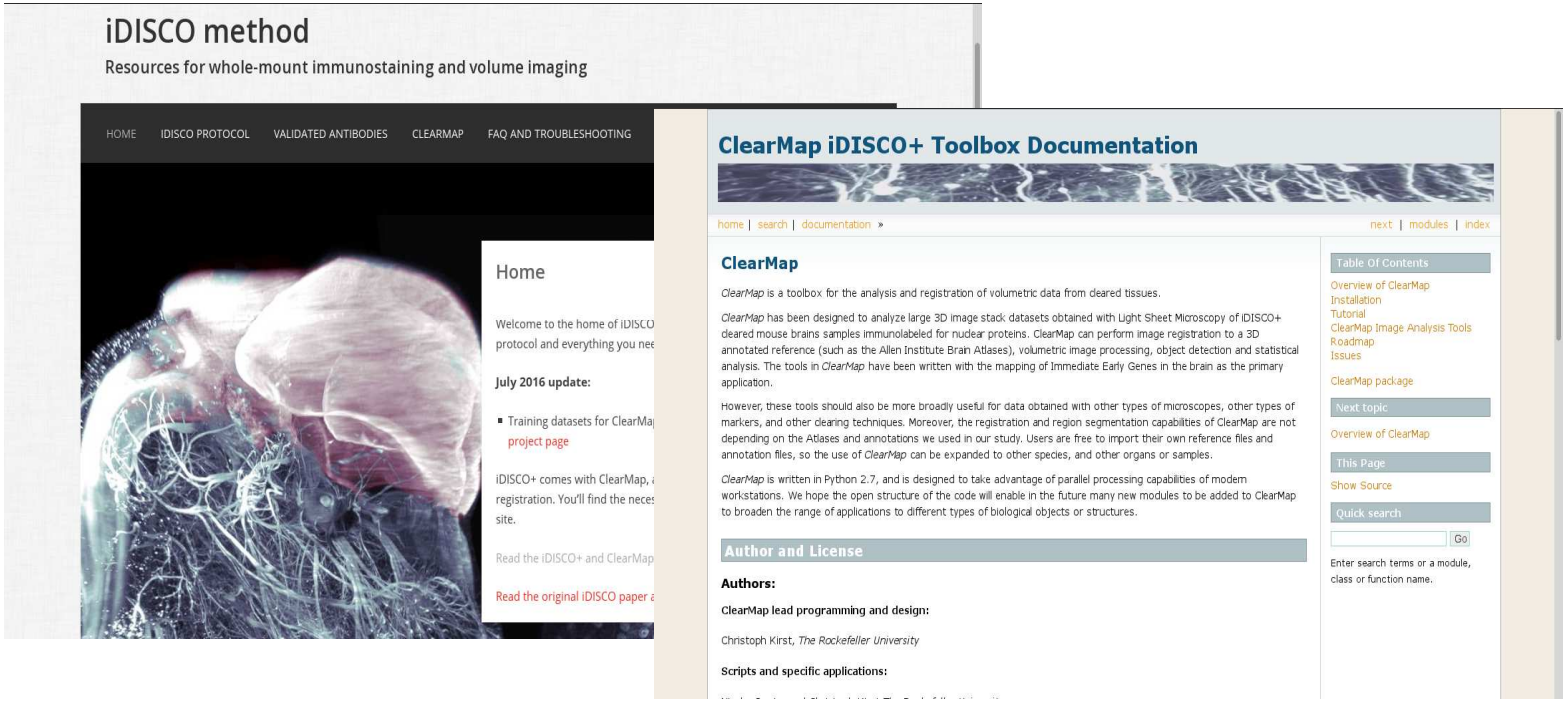
iDISCO+ and ClearMap 1.0 Resources

- iDISCO+

  www.idisco.info
- Brain activity mapping:

  www.github.com/ChristophKirst/ClearMap
- Structure mapping:

  www.github.com/ChristophKirst/ClearMap2



[Renier*,. Adams*, Kirst*, Wu*, et al., **Cell** 2016]

[Kirst et al. **Cell** 2020]

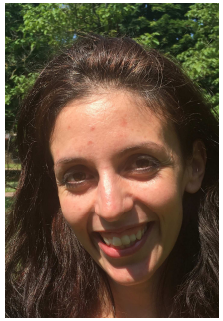
Acknowledgments

- Laboratory of Structural Plasticity, ICM Paris

Nicola Renier

histological development:

Thomas Topilko



Alba Vieites Prado

pipeline development:

Sophie Skriabine

Paul Bertin

- Funding

UCSF

THE KAVLI FOUNDATION

SCIENTIA PRO BONO HUMANI GENERIS
The Rockefeller University
1901