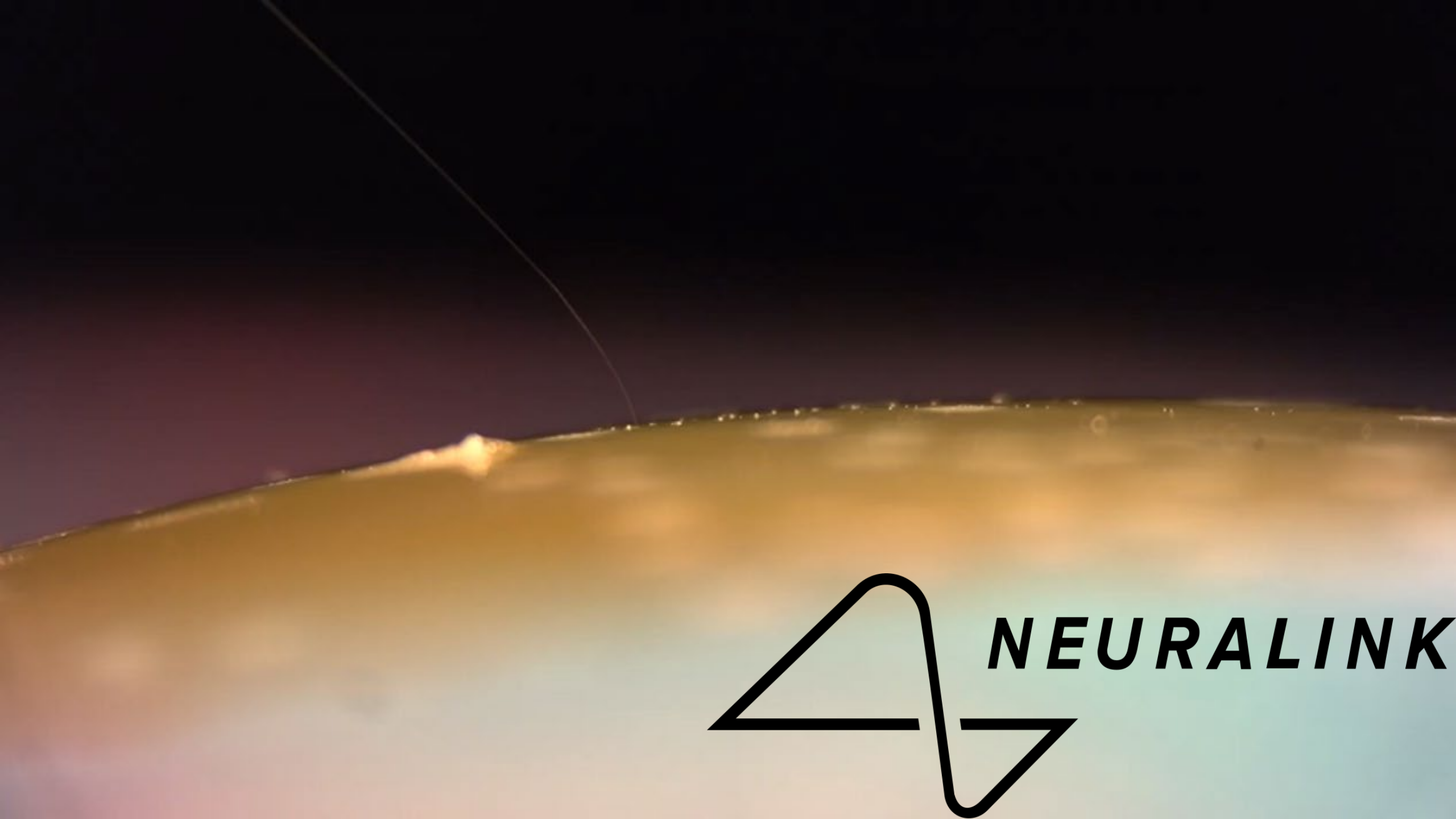
Technology is Overcoming Reductionism in Neuroscience

Timothy Wiggin

HHMI Interfaces Scholar Award Lecture

QB Bootcamp 2020


NEURALINK

What would it mean if Neuralink succeeds?

Animal models are at the beginning of a high-volume data revolution - what lessons can we learn?

The usual assumption:

Detail and scope are mutually exclusive goals in data collection

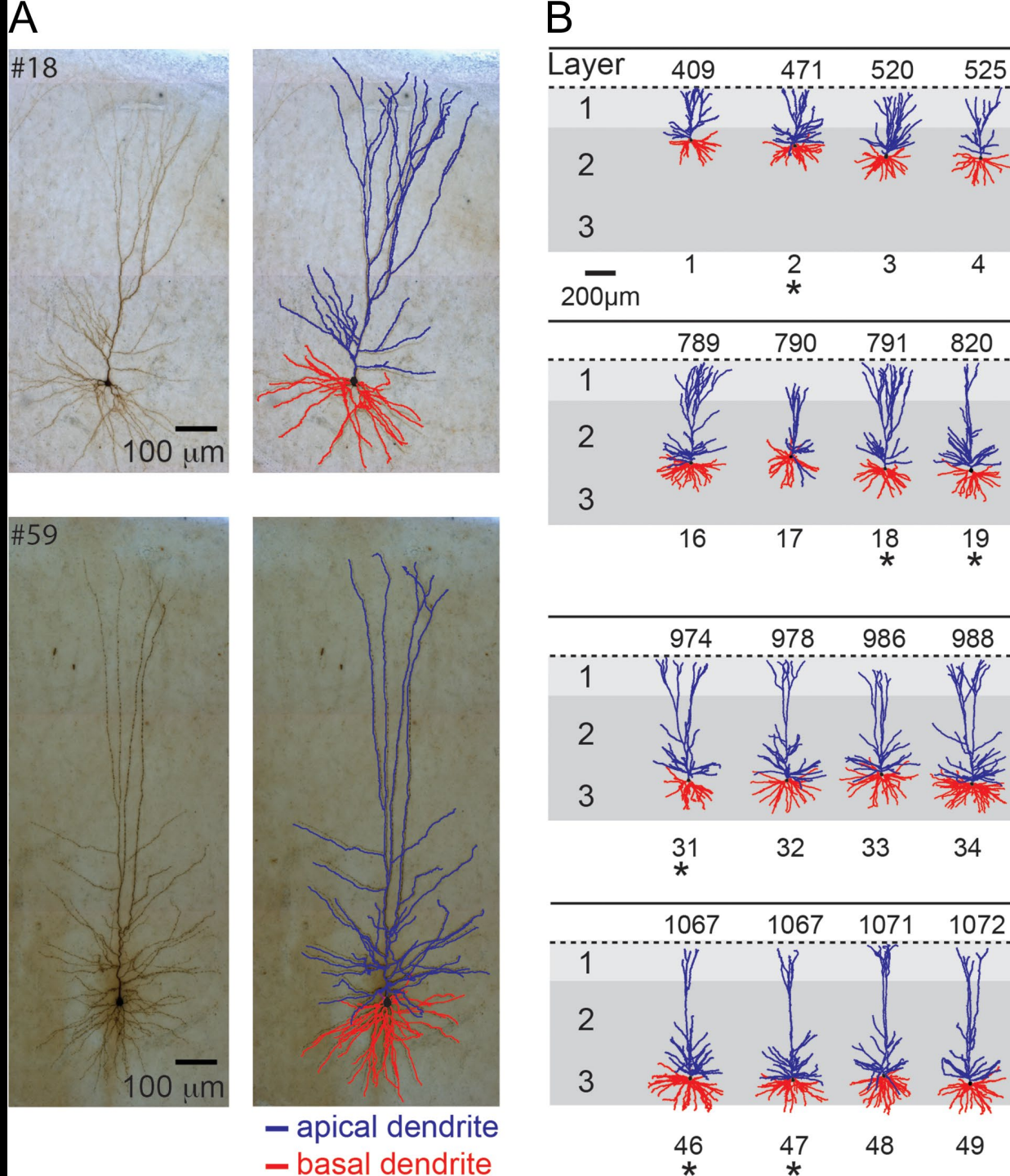
Reductionist Neuroscience

Get a good parts list for the brain, assemble the parts at the end

Reductionist Neuroscience

Deitcher Y, *et al*. *Cereb Cortex.* (2017)

An inventory of 60 cells in human cortex



What's wrong with Reductionism?

Human :
- 1011 neurons

Mouse :
- 108 neurons

Larval Zebrafish :
- 105 neurons

Larval *Drosophila* :
- 104 neurons

C. Elegans :
- 102 neurons

The previous study :
- 60 neurons

Reductionist Neuroscience

Get a good parts list for the brain, assemble the parts at the end

Pablo Picasso, *Buste de femme (Dora Maar)*

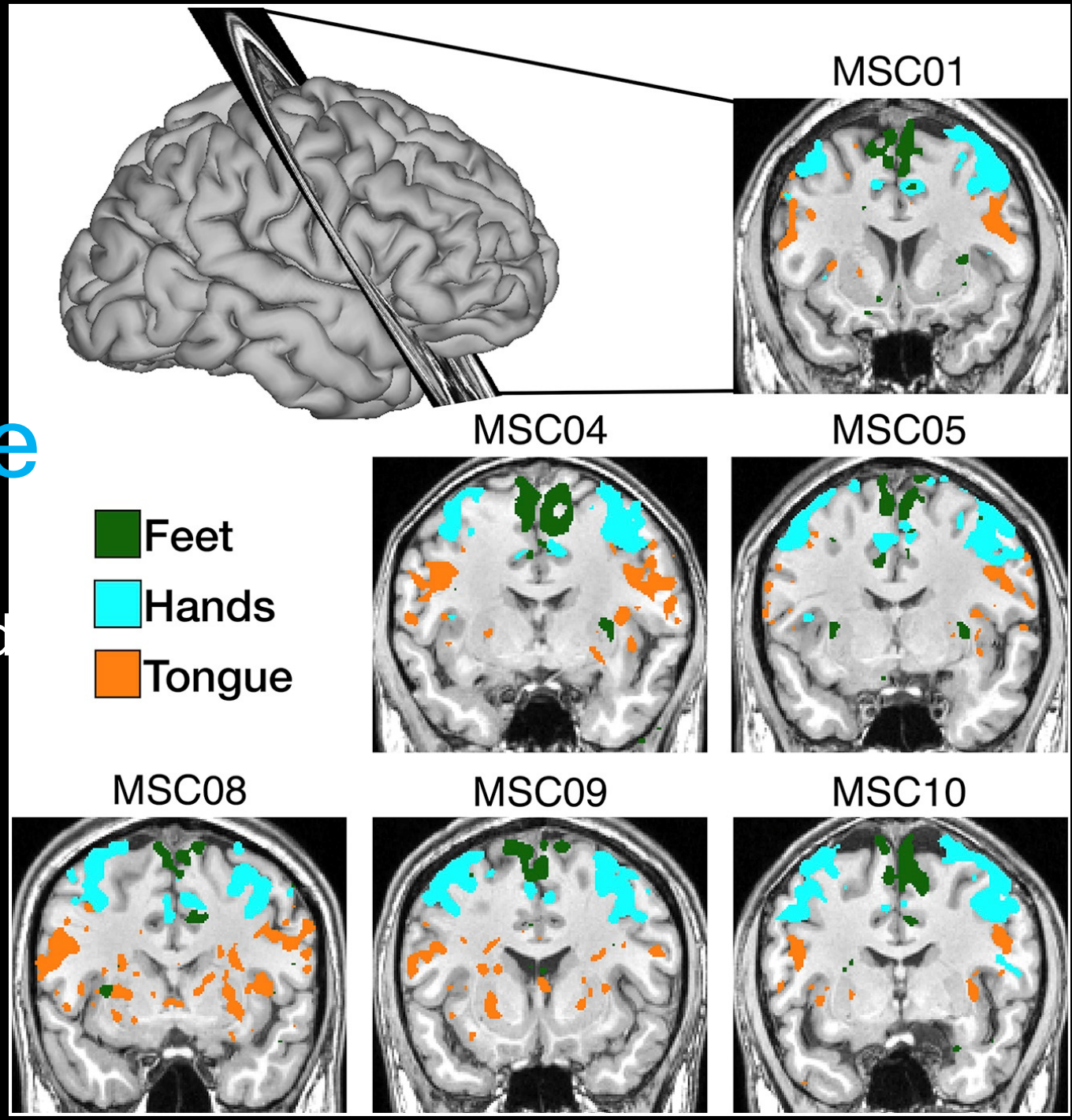
Holistic Neuroscience

Get the overall model right at low resolution, focus in when possible

Holistic Neuroscience

Gordon EM, *et al*. *Neuron* (2017)

A map of brain use in several individ
people during a motor task



What's wrong with Holism?

- Human Cerebral Cortex:
- 1010 cortex neurons
- ÷
- 103 cm3 cortex volume
- ×
- 10-2 cm3 max resolution
- =
- Approx. 100,000 neurons in the smallest resolvable voxel

Holistic Neuroscience

Get the overall model right at low resolution, focus in when possible

Chuck Close, *Paul* (1994)

Hyper-Realism

Every feature is represented at every scale

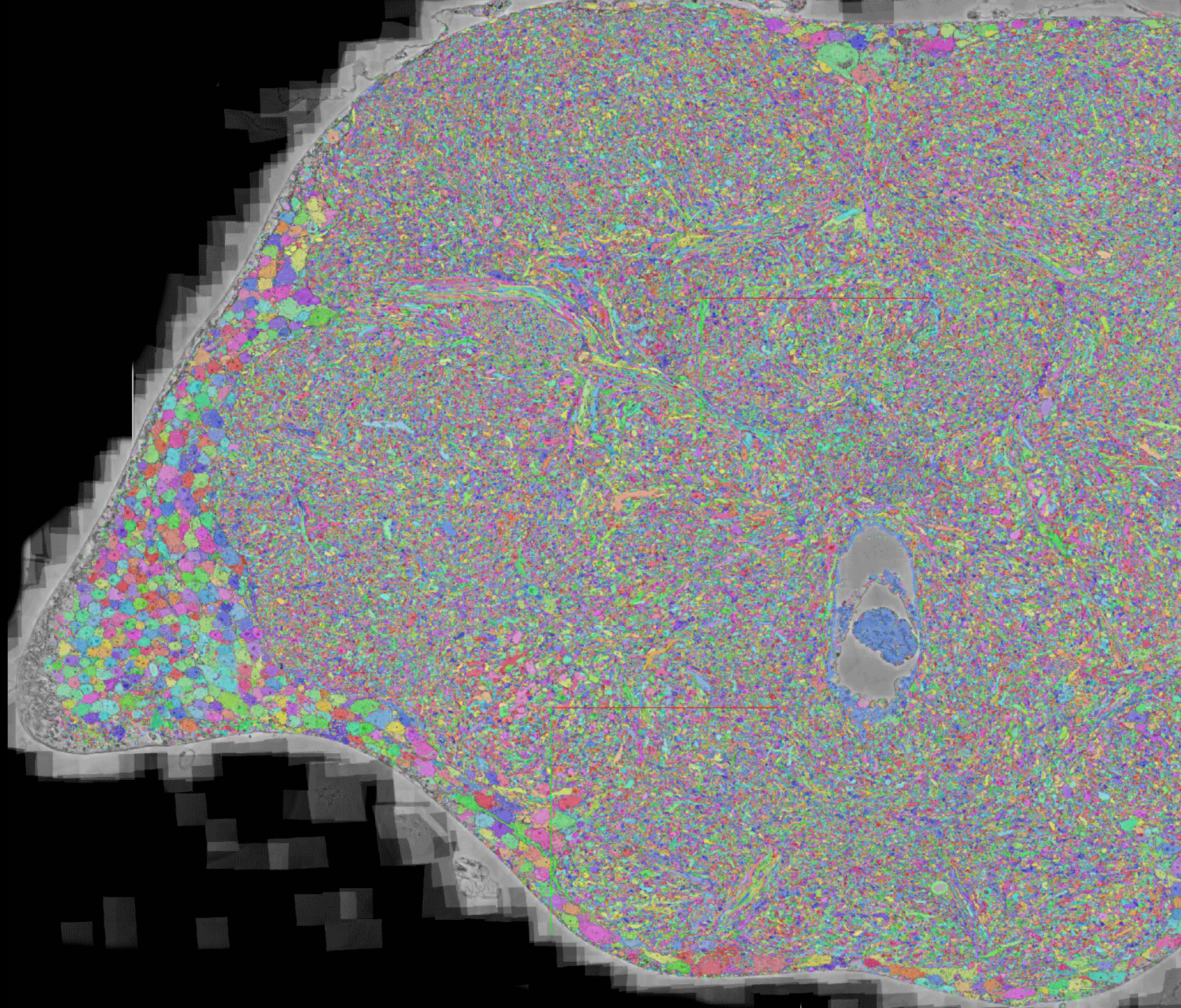
Evan Penny, *(Old) No One - in Particular #6,*

Challenges to Hyper-Realism:

1. Resolution
2. Storage *(solved by money)*
3. Analysis

Hyper-Realism Neuroscience

NeuroGlancer, HHMI



Talk Outline

1. Introduction
2. Ion-beam milling electron microscopy
3. Super-resolution light microscopy
4. How do we navigate a 1:1 scale map?

Why use electrons in a microscope?

Abbe's Equation:

$$d = \frac{\lambda}{n \sin a}$$

- λ: wavelength
- $n \sin a$: Good microscope?
- d: Resolution

(*i.e.* $d \propto \lambda$)

De Broglie equation:

$$\lambda = \frac{h}{p}$$

- p: momentum
- h: Planck's Constant

It's easier to give an electron lots of momentum than it is to build a good microscope for X-Rays

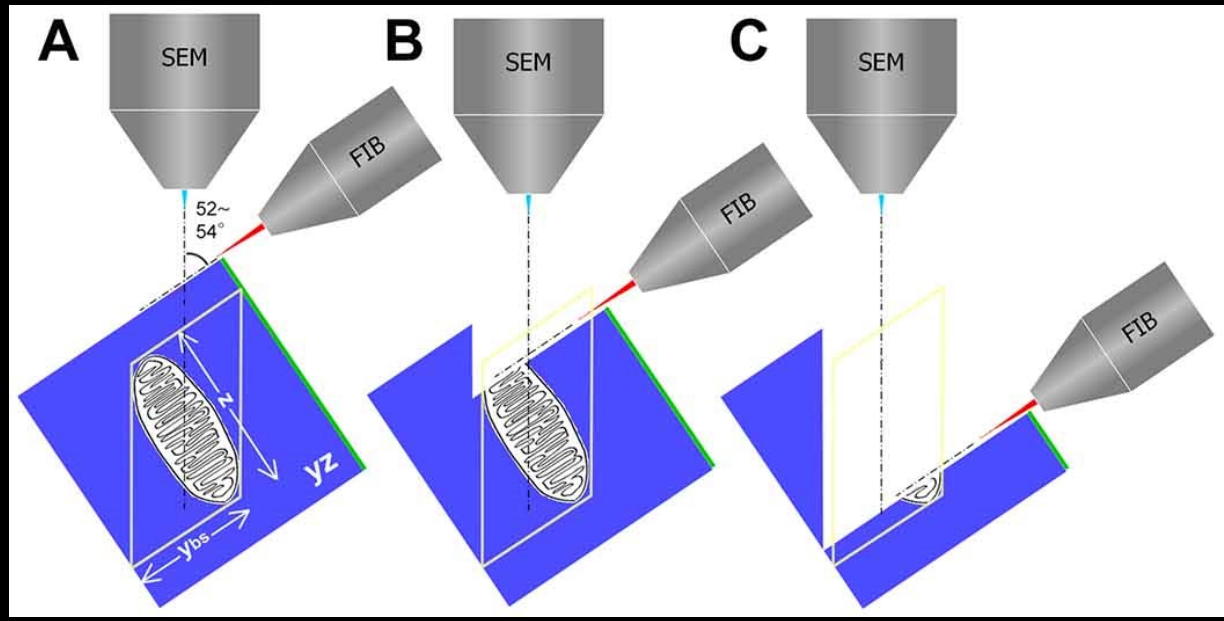
Challenges for electron microscopy:

1. How do you collect data in 3D?

2. How can you turn the image data into a network?

Focused Ion Beam Milling

Use Ions to slice tissue instead of a knife

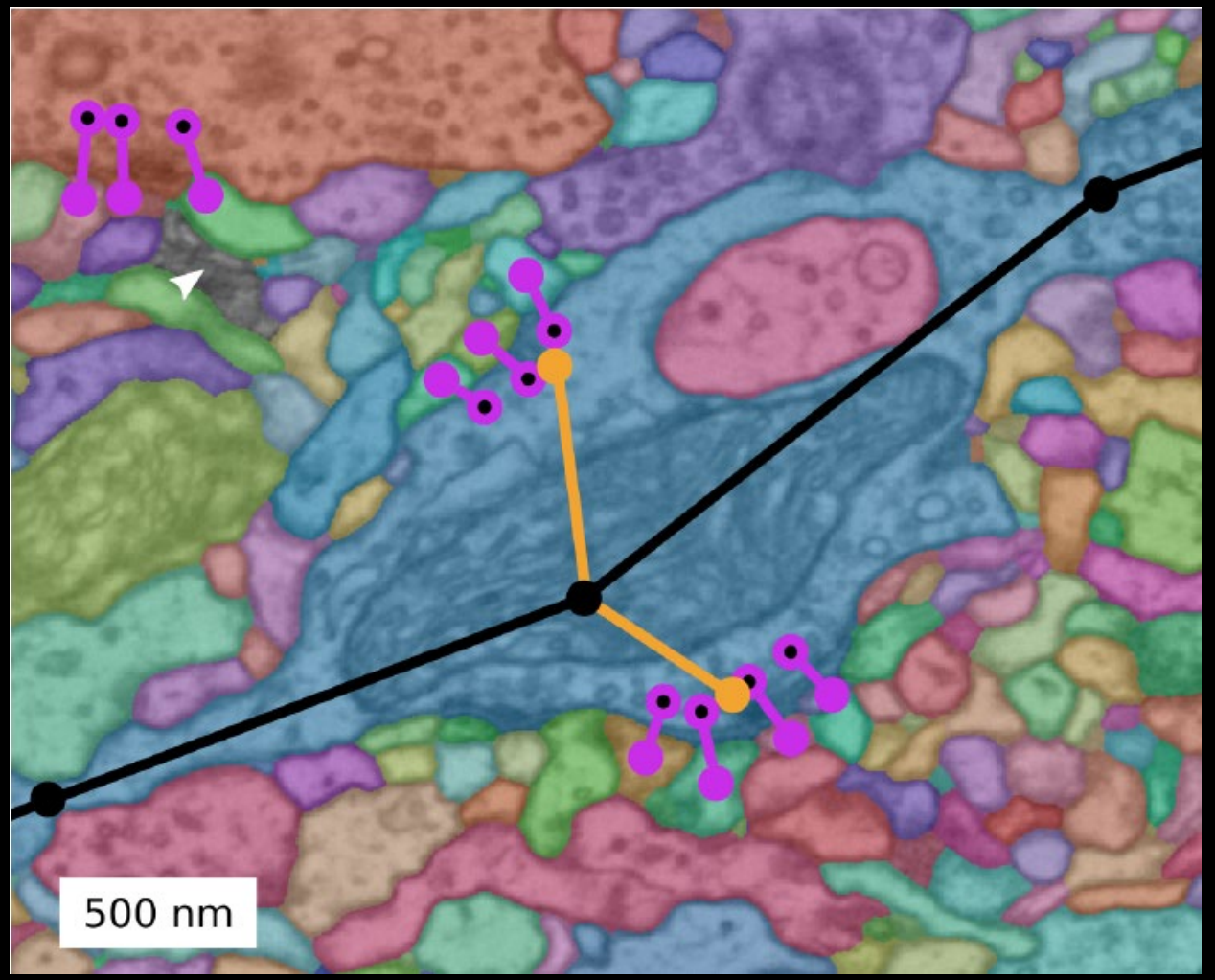


Kubota Y, et al. *Front. Neural Circuits* (2018)

Xu CS, et al. *eLife* (2017)

Semi-automated annotation

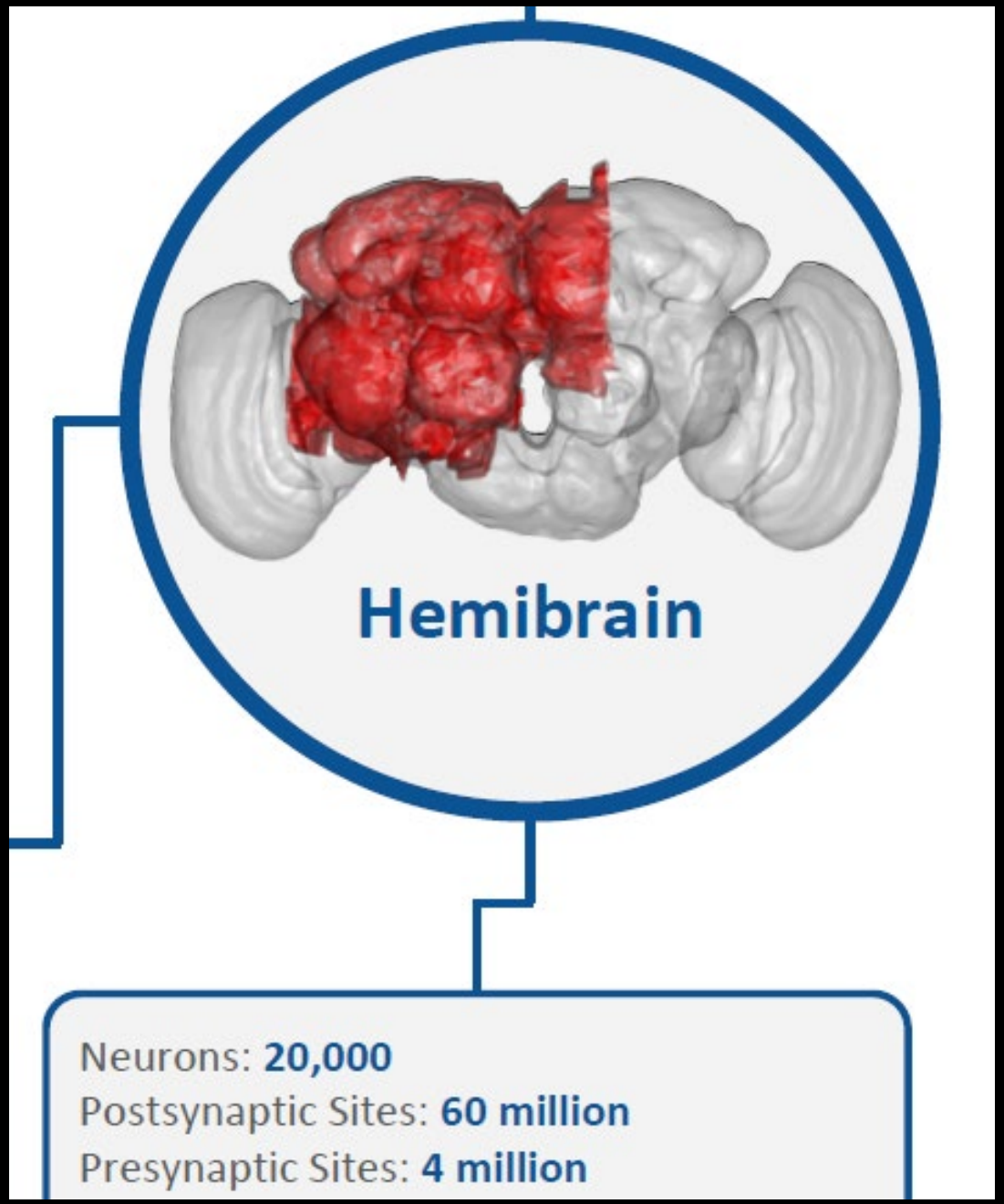
Turn a lifetime of manual labor into a person-computer partnership



Buhmann J, et al. *bioRxiv 874172*

Breakthrough result

Hemi-brain connectome coming later this month



Talk Outline

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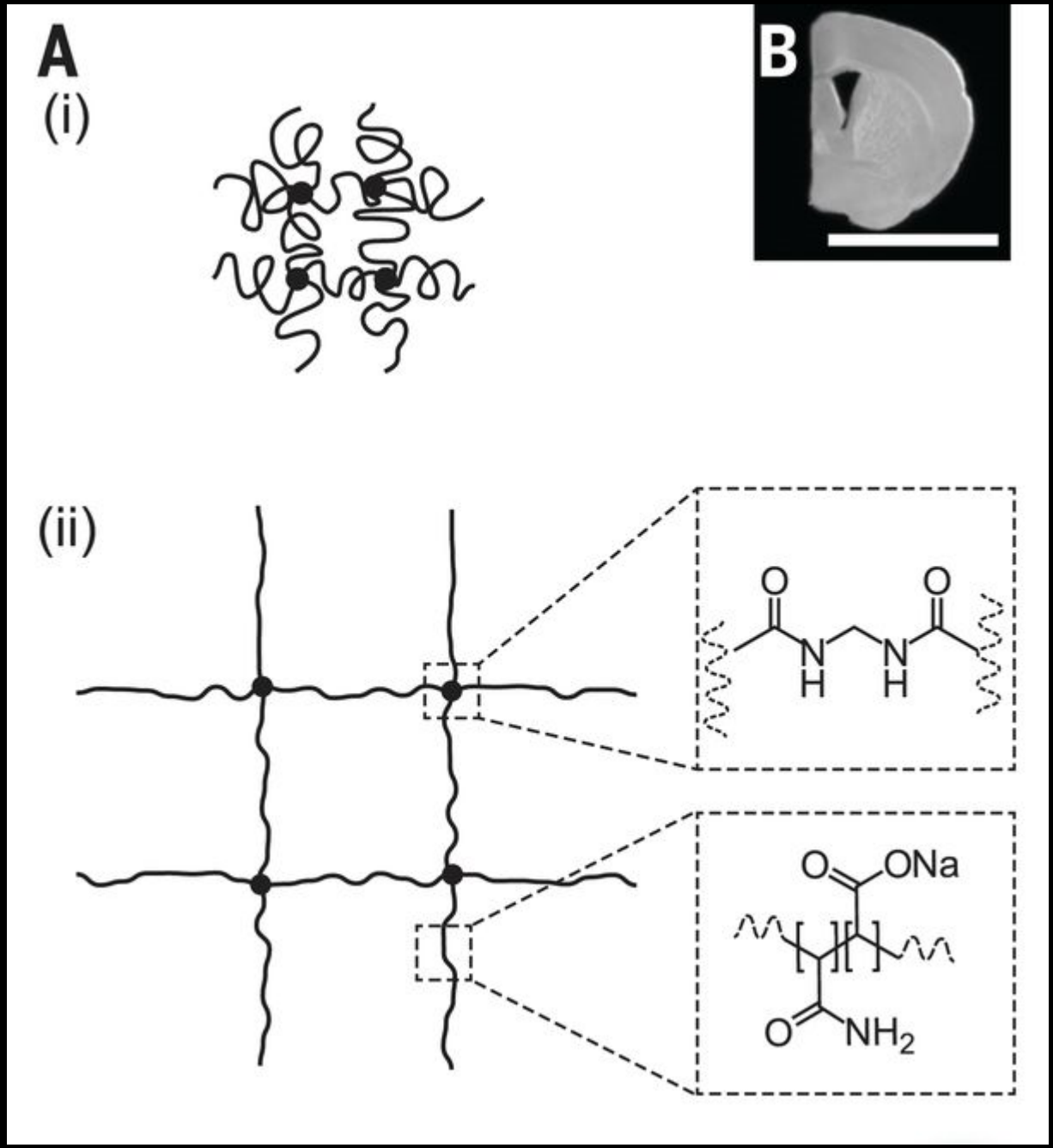
The challenge:

If FIB-SEM is a moonshot, how do you get a sample size of 2?

Expansion Microscopy

Make little things big



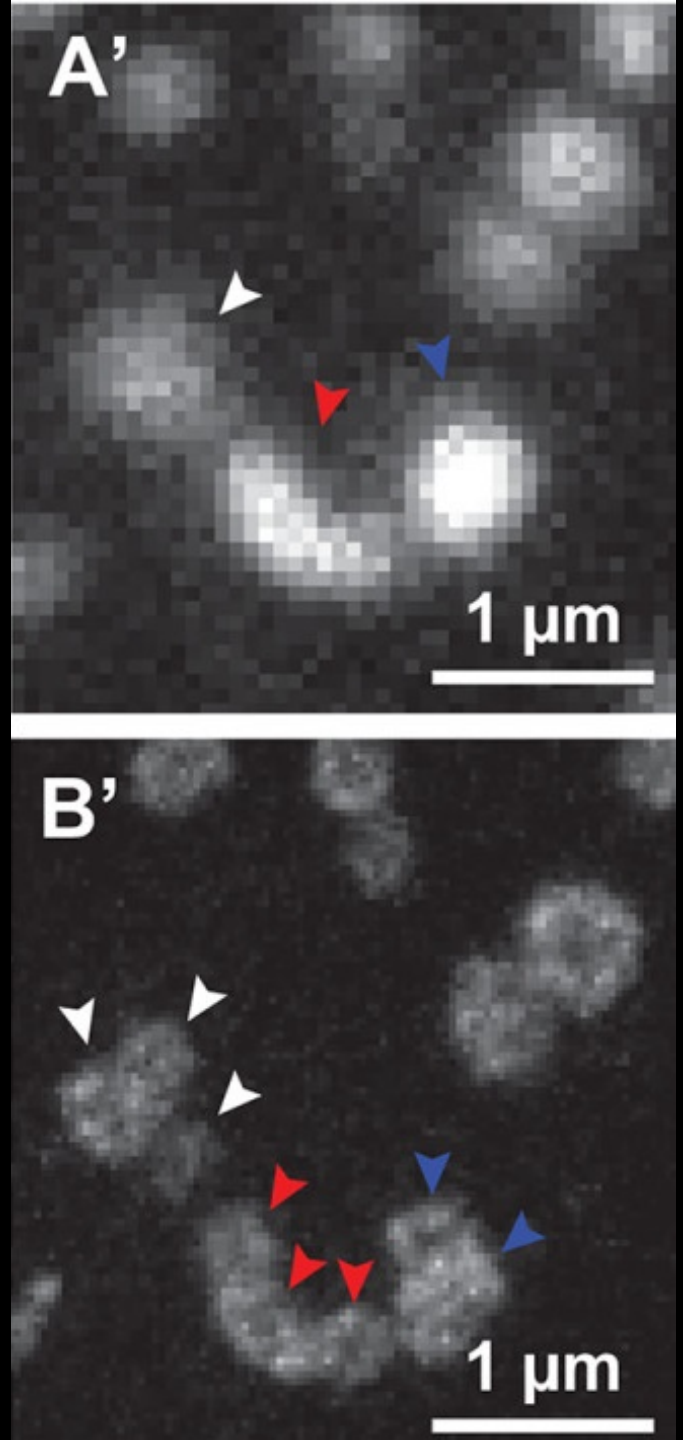
Chen F, et al. *Science* (2015)

Expansion Microscopy

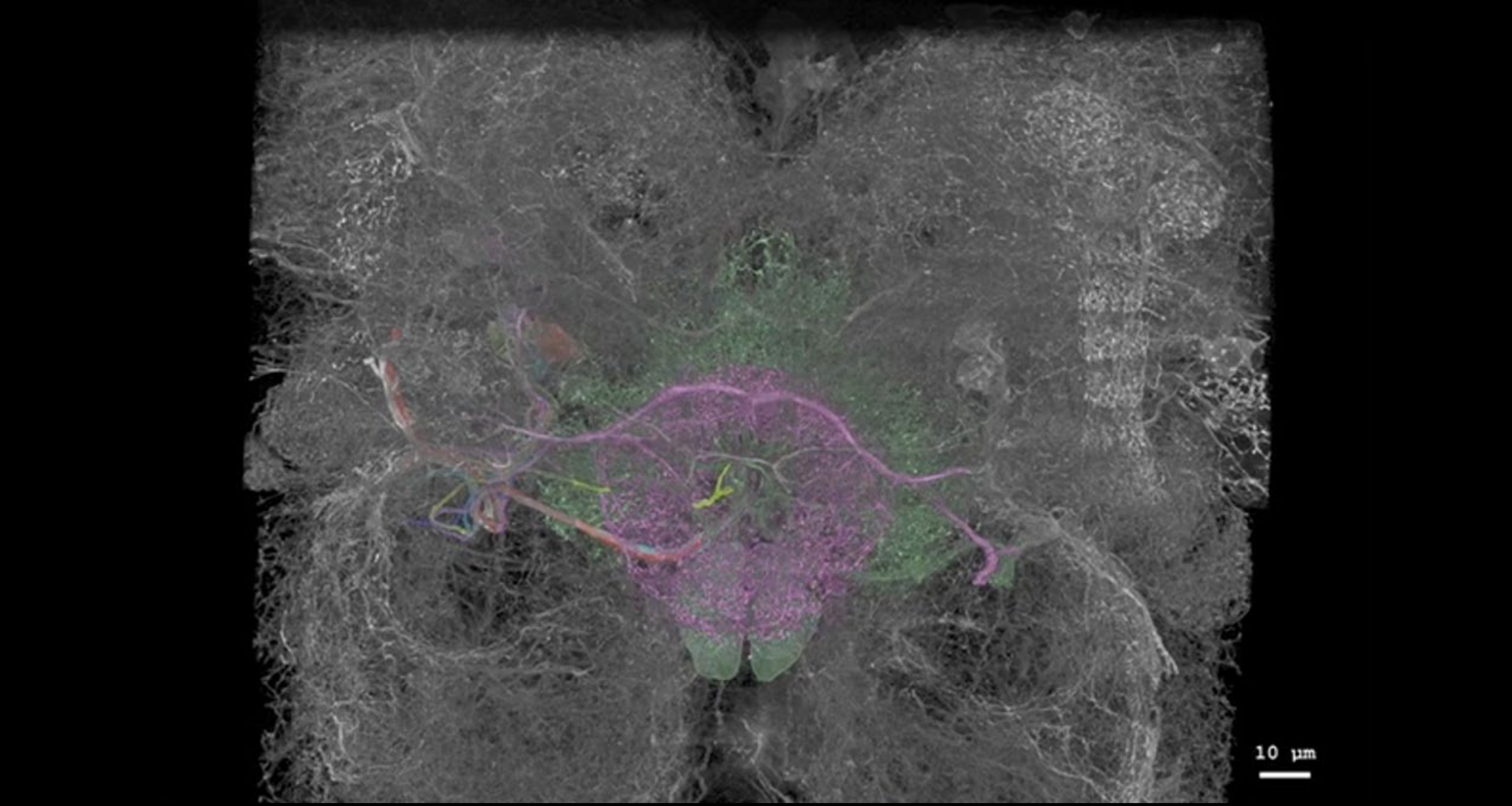
Make little things big

Before:

After:



Jiang N, et al. *Mol Biol Cell* (2018)



Gao R, et al. *Science* (2019)

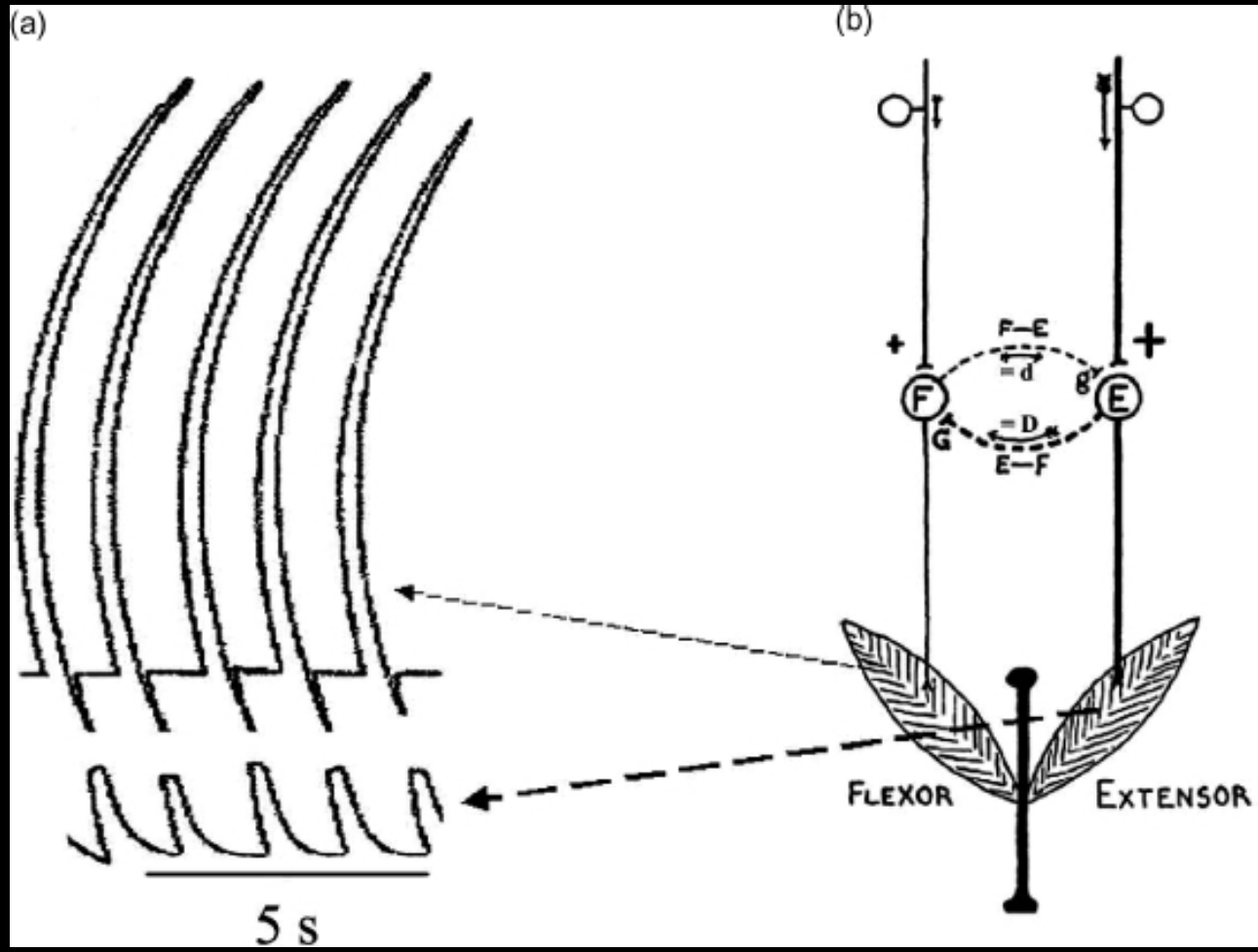
What can we do with a comprehensive map of the brain?

The scientific toolkit:

- Reasoning and dialog
- Math and human-directed computation
- Artificial Intelligence *(In progress)*

T. Graham Brown

1. Observe
2. Reason
3. Report
4. Repeat



Jones JG, et al. *J Hist Neurosci.* (2011)

The scientific toolkit:

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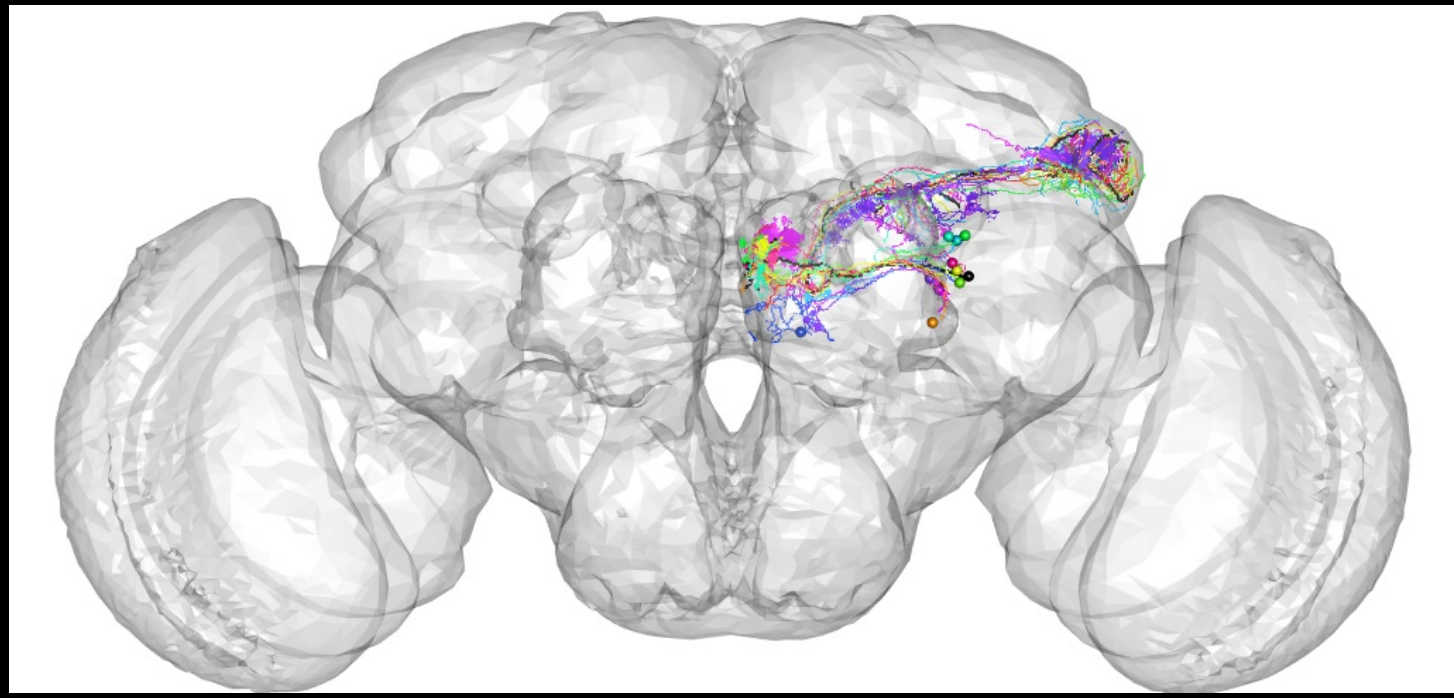
- Artificial Intelligence *(In progress)*

Clustering and dimensionality reduction

Reduce the scope to human scale



NBLAST, FlyLight

The scientific toolkit:

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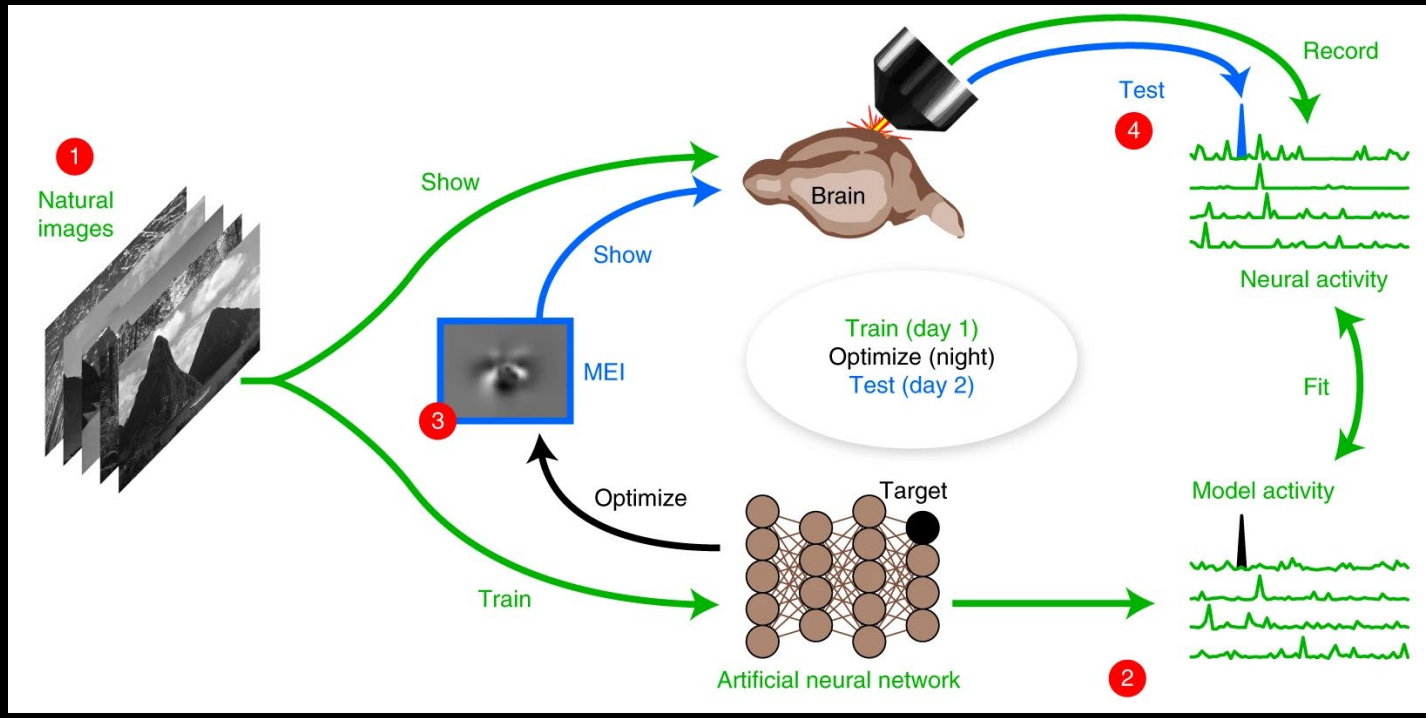
Neuronal Inception

Use the brain to train a naive artificial neural network



Walker EY, et al. *Nature* (2019)

The problem is bigger than biology

An interdisciplinary approach is a necessity, not a luxury