

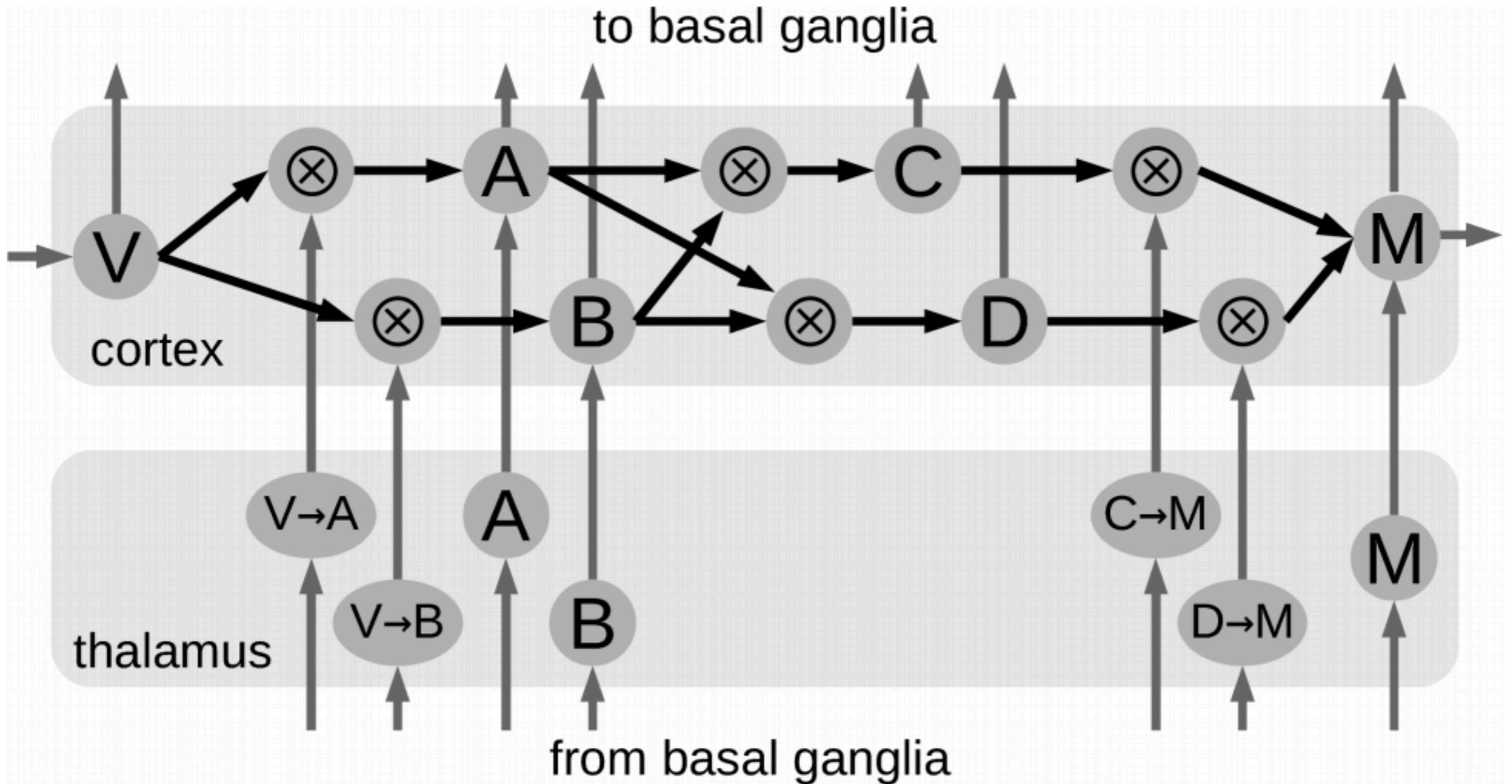
Digital encoding for scalable brain mapping?

Adam Marblestone

Bits ↔ **Bio**

2014

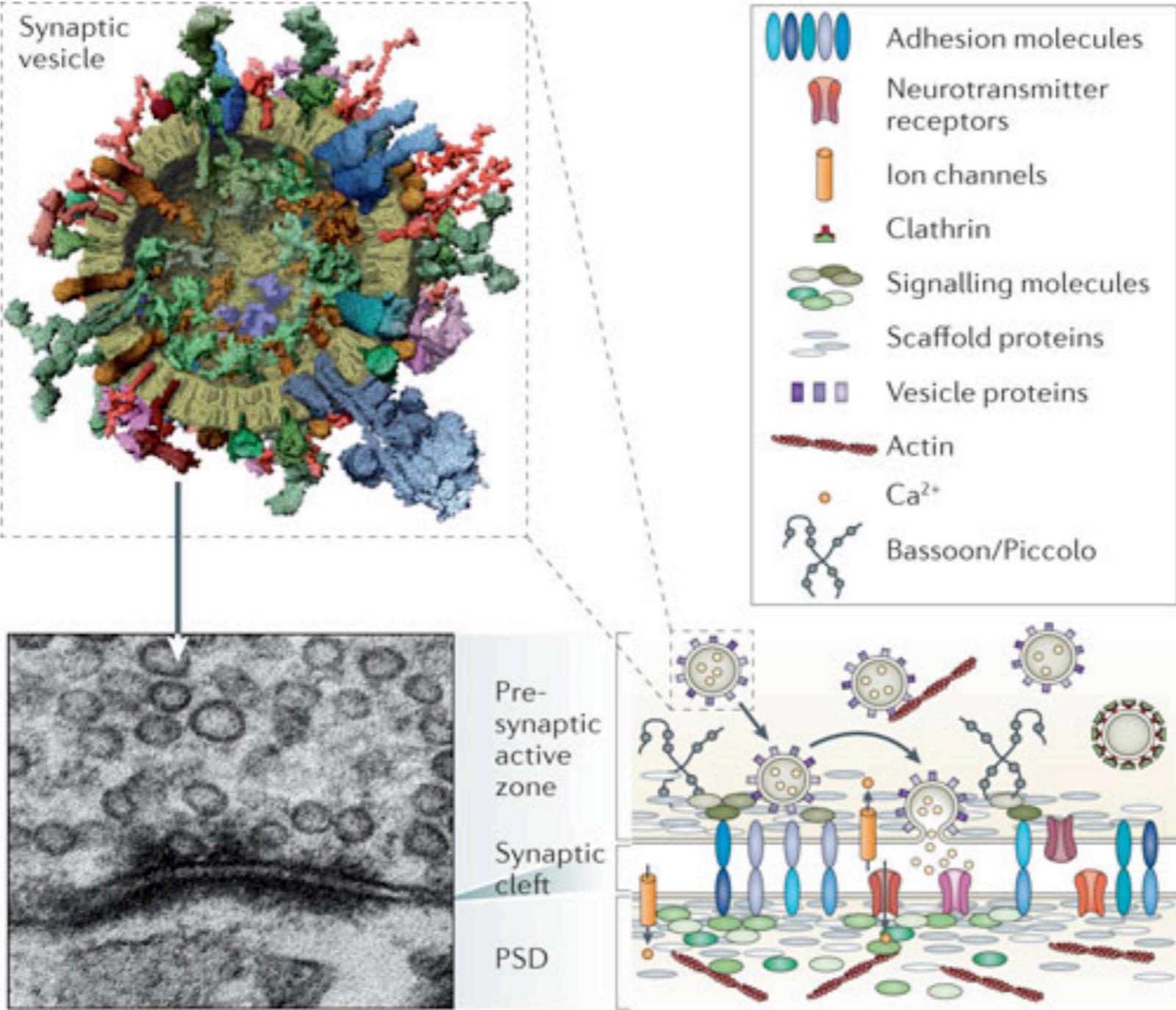
Coarse-grained brain *maps* give un-testable *models*



?? thalamic gating of “copy and paste” operations between cortical working memory buffers, executing a sequence of steps controlled by the basal ganglia ???

Computationally-relevant molecular complexity?

Example: hundreds of proteins in each synaptic vesicle



Nature Reviews | Neuroscience

Deep molecular diversity of mammalian synapses: why it matters and how to measure it

Nancy A. O'Rourke, Nicholas C. Weiler, Kristina D. Micheva and Stephen J. Smith

How to cope with the brain's complexity?

Activity history

Behavior

Connectivity (circuit diagram)

Development (cell lineage tree)

Expression (epigenetic cell types,
+ single-synapse proteomes)

Need: a technology to cheaply / rapidly
measure all these variables in a single brain.

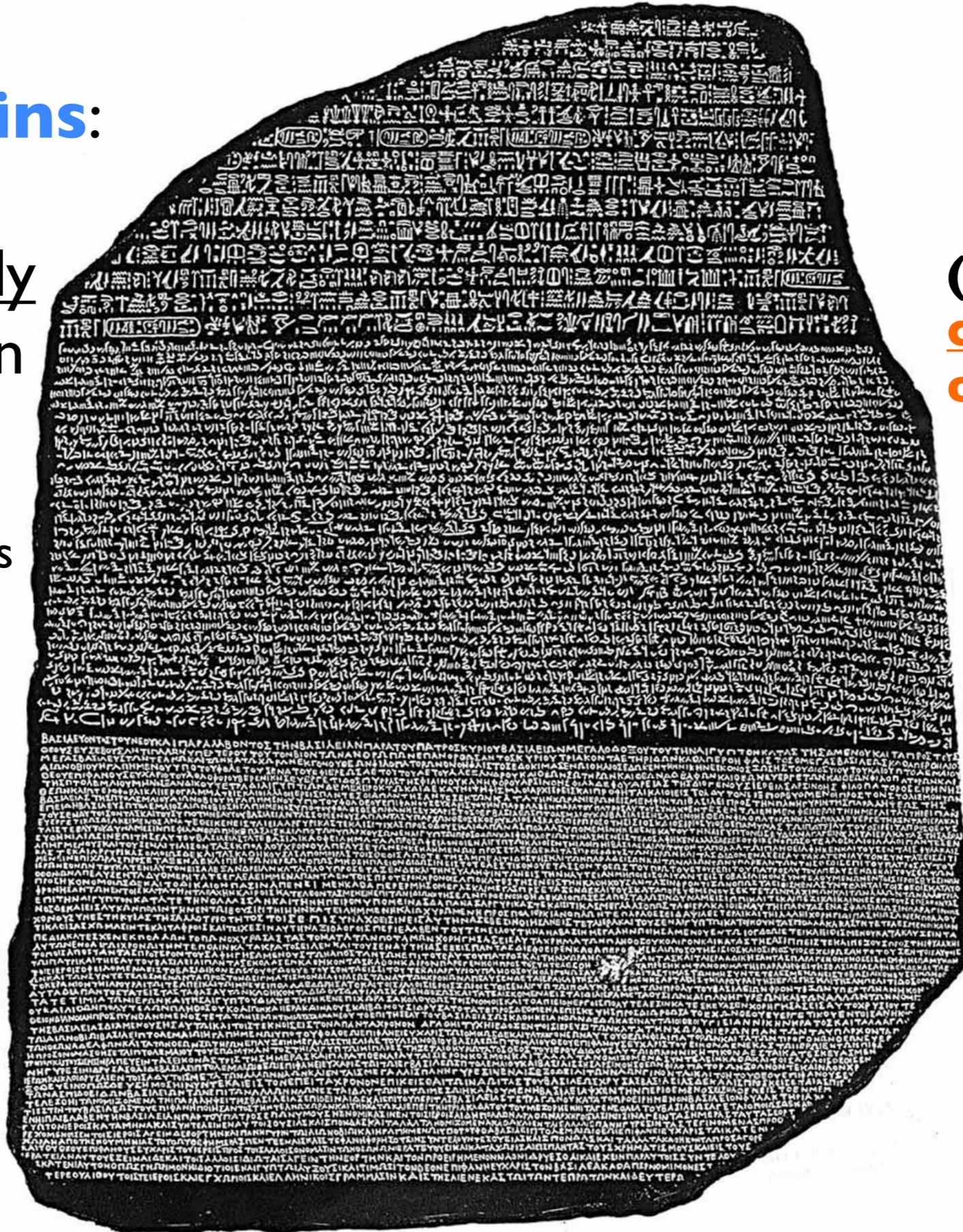
Need: (sub)cellular resolution + whole brain scope.

How to cope with the brain's complexity?

Rosetta Brains:

A, B, C, D & E
comprehensively
on a single brain

allows correlations
across variables/levels



(sub)cell-level
co-registration
of variables

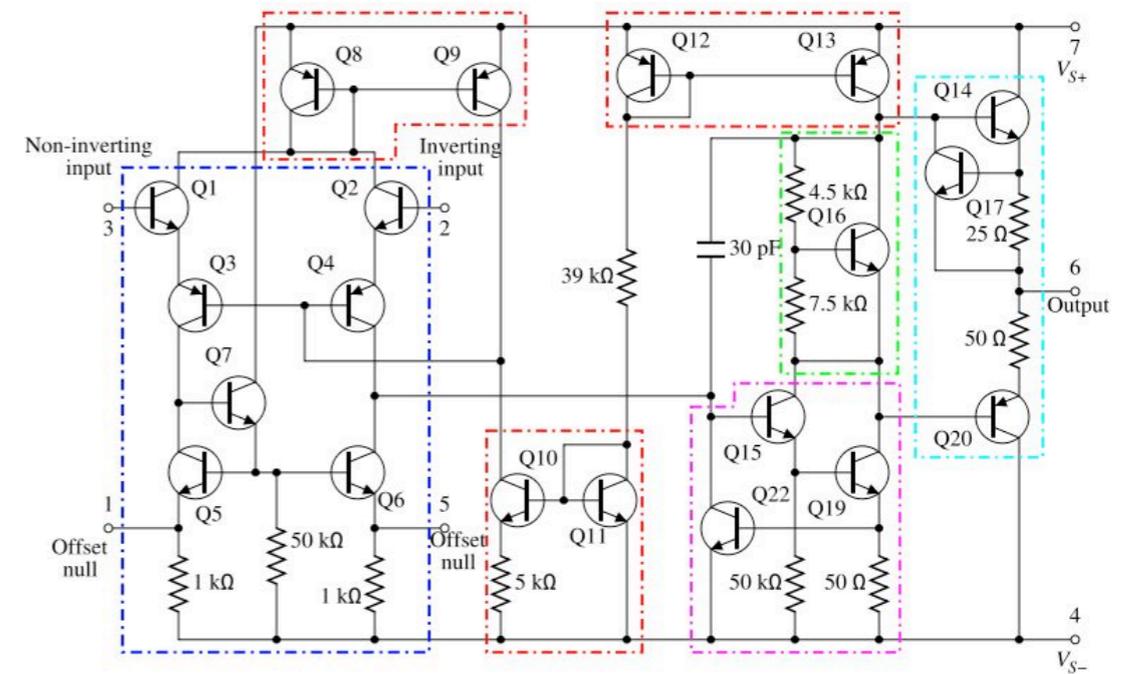
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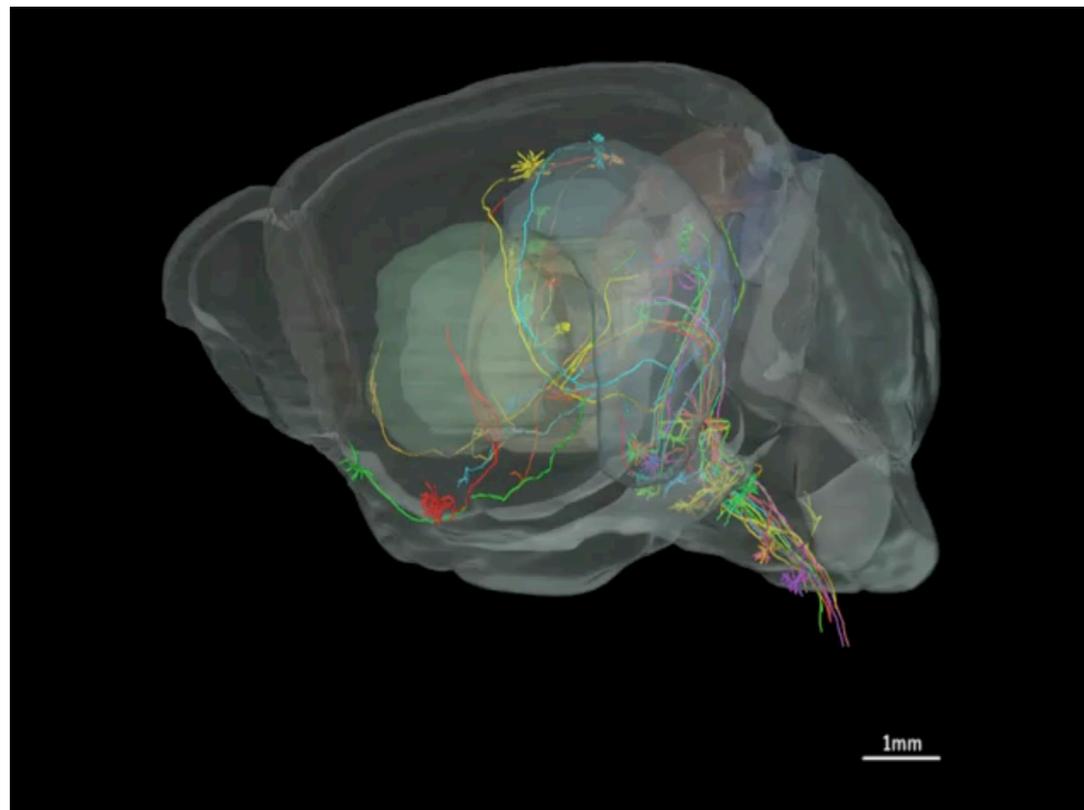
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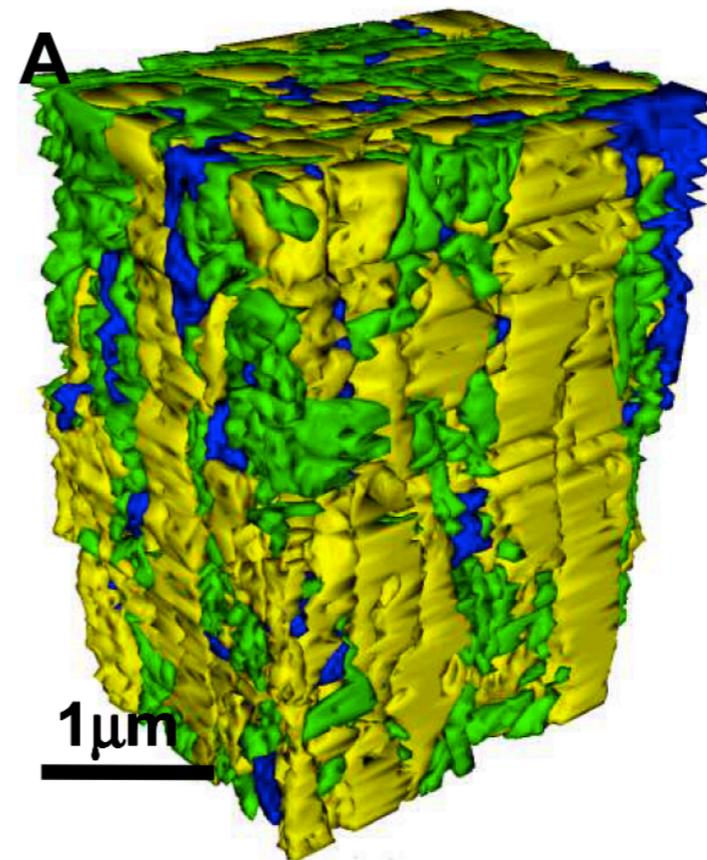
Need: (sub)cellular resolution + whole brain scope.

long-range connections

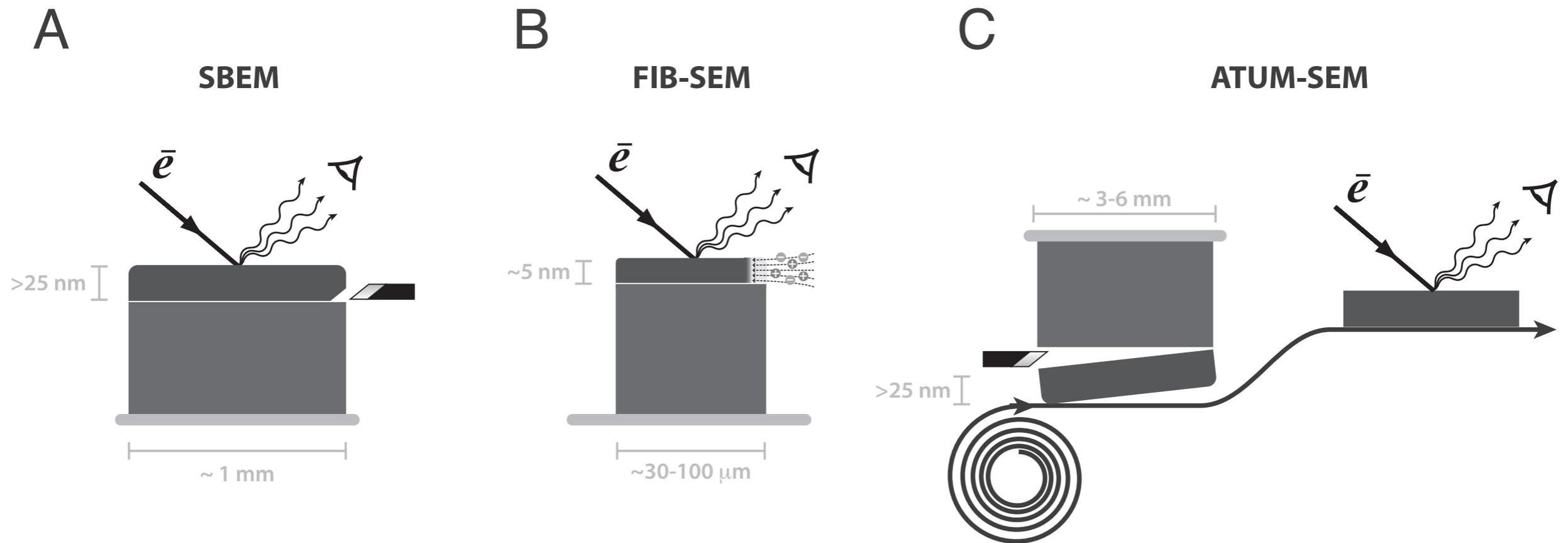


[Gong et al, 2013]

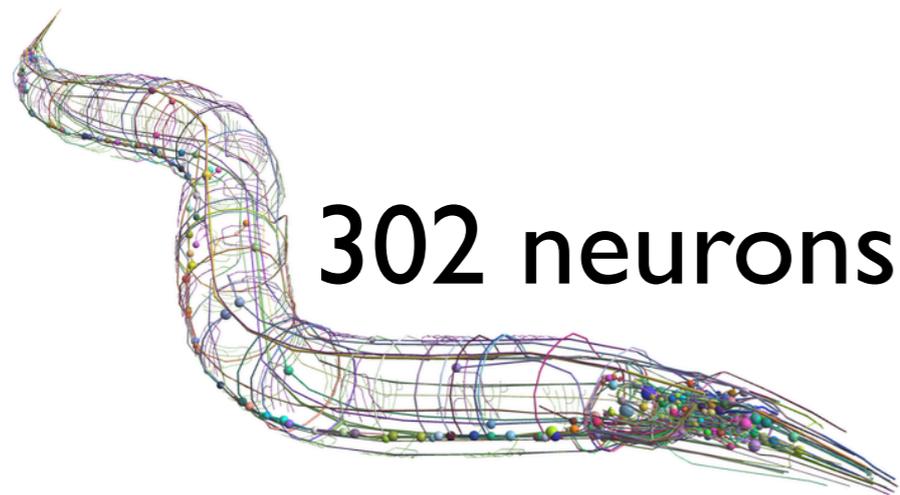
dense 3D circuitry:
> 1 synapse (connection) per μm



[Mischenko, 2010]



Current practice: widely believed that electron microscopy (EM) is the **only** viable method for cellular-resolution connectomics



302 neurons: 50 person-years for *C. elegans*

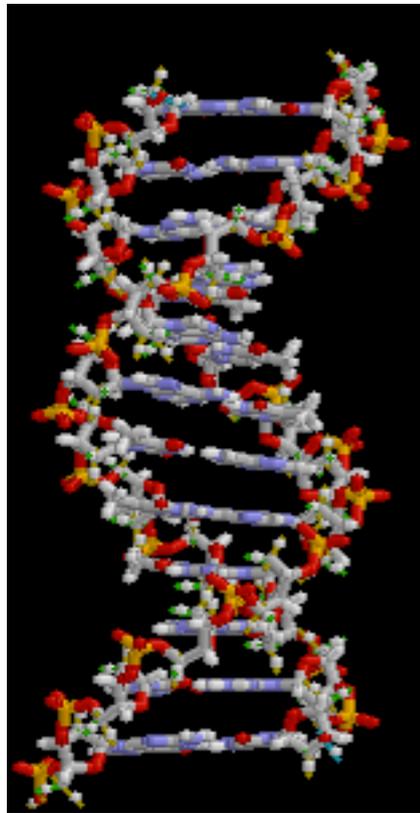


\$\$\$\$ for mouse w/ **no molecular info**



Can't run a simulation?

4^N possible DNA sequences of length N “letters”



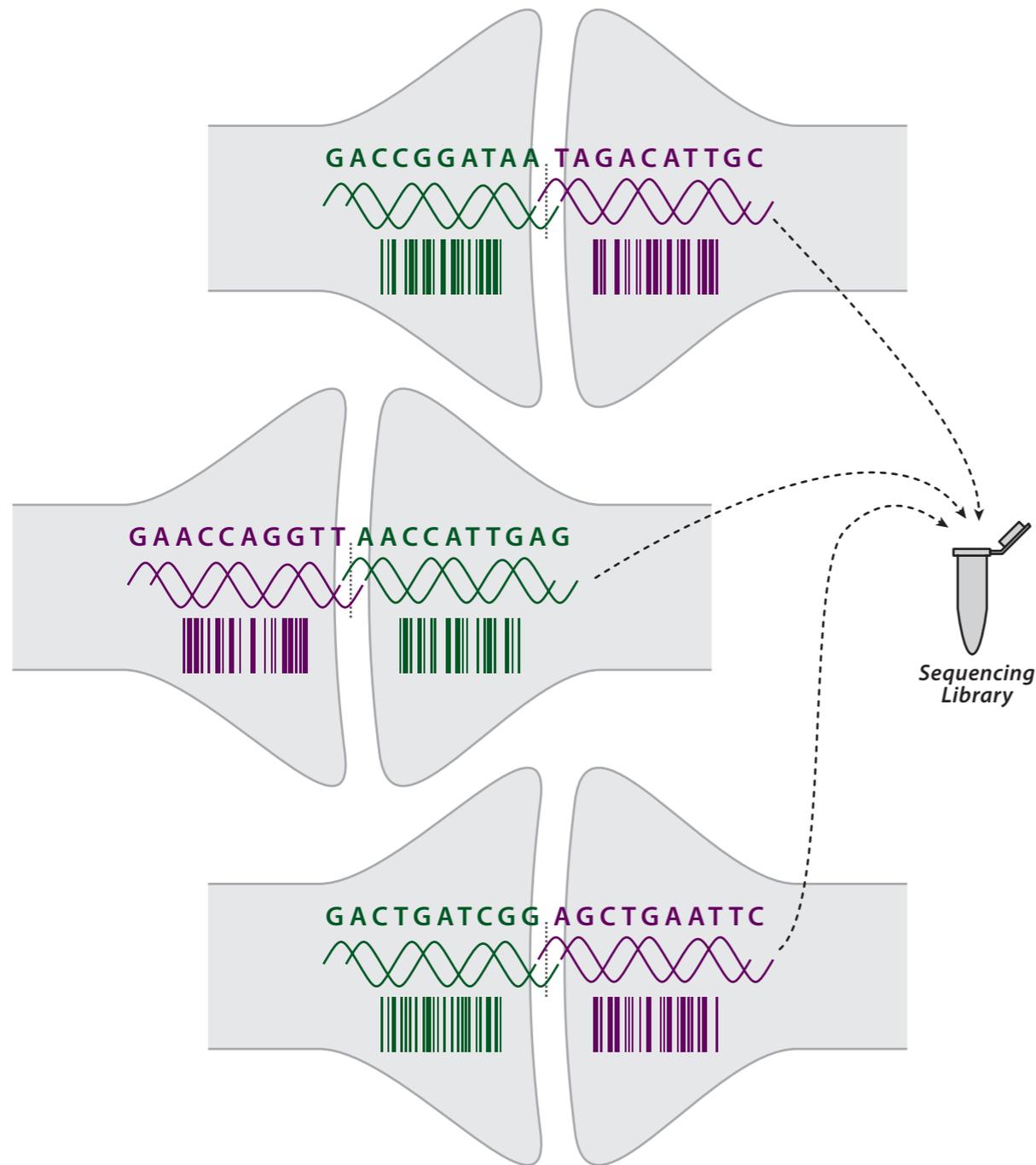
=
0101001010101010010101
0101010101001010110111
0010110101010111010011
=



Zador, Cepko, Tabin, Walsh, Church et al:
can give every neuron a uniquely-identifiable DNA “barcode”

Zador: Pair barcodes of connected cells, then sequence

potential for extremely low cost due to cheap sequencing



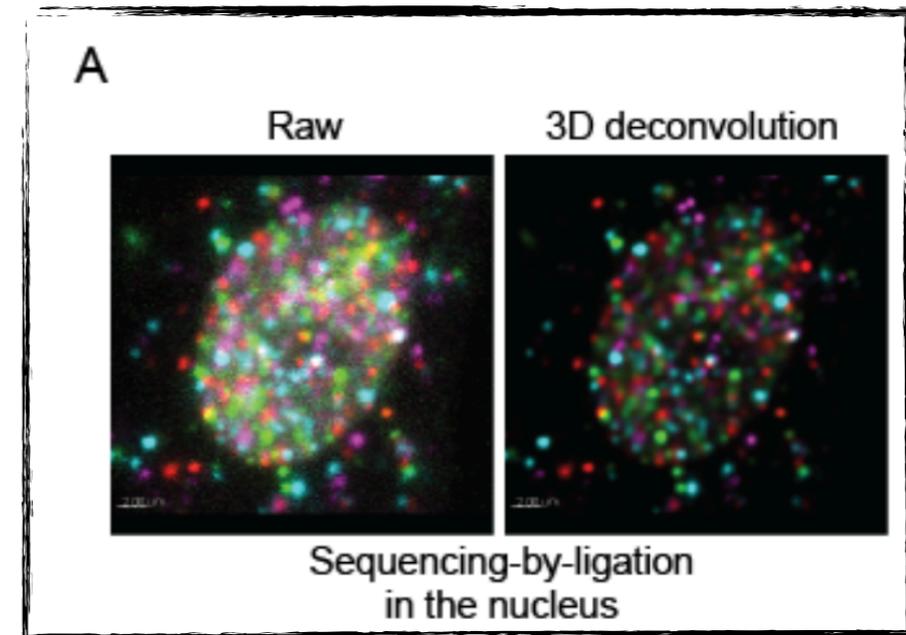
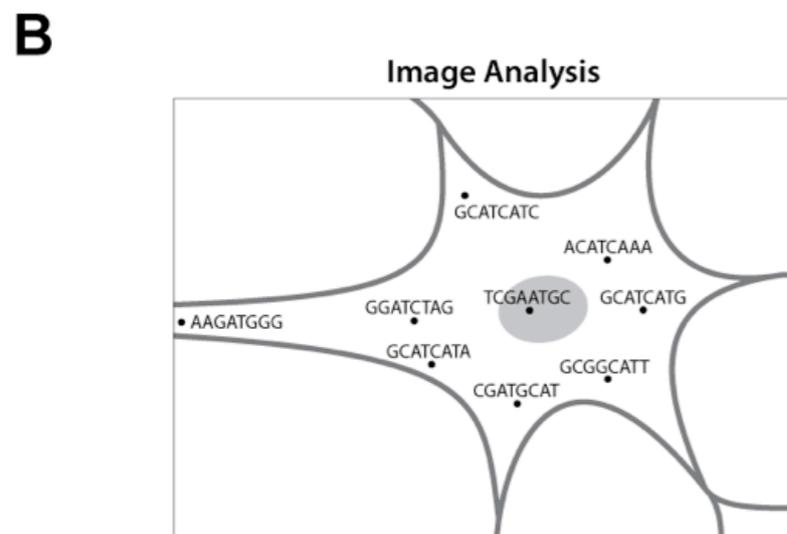
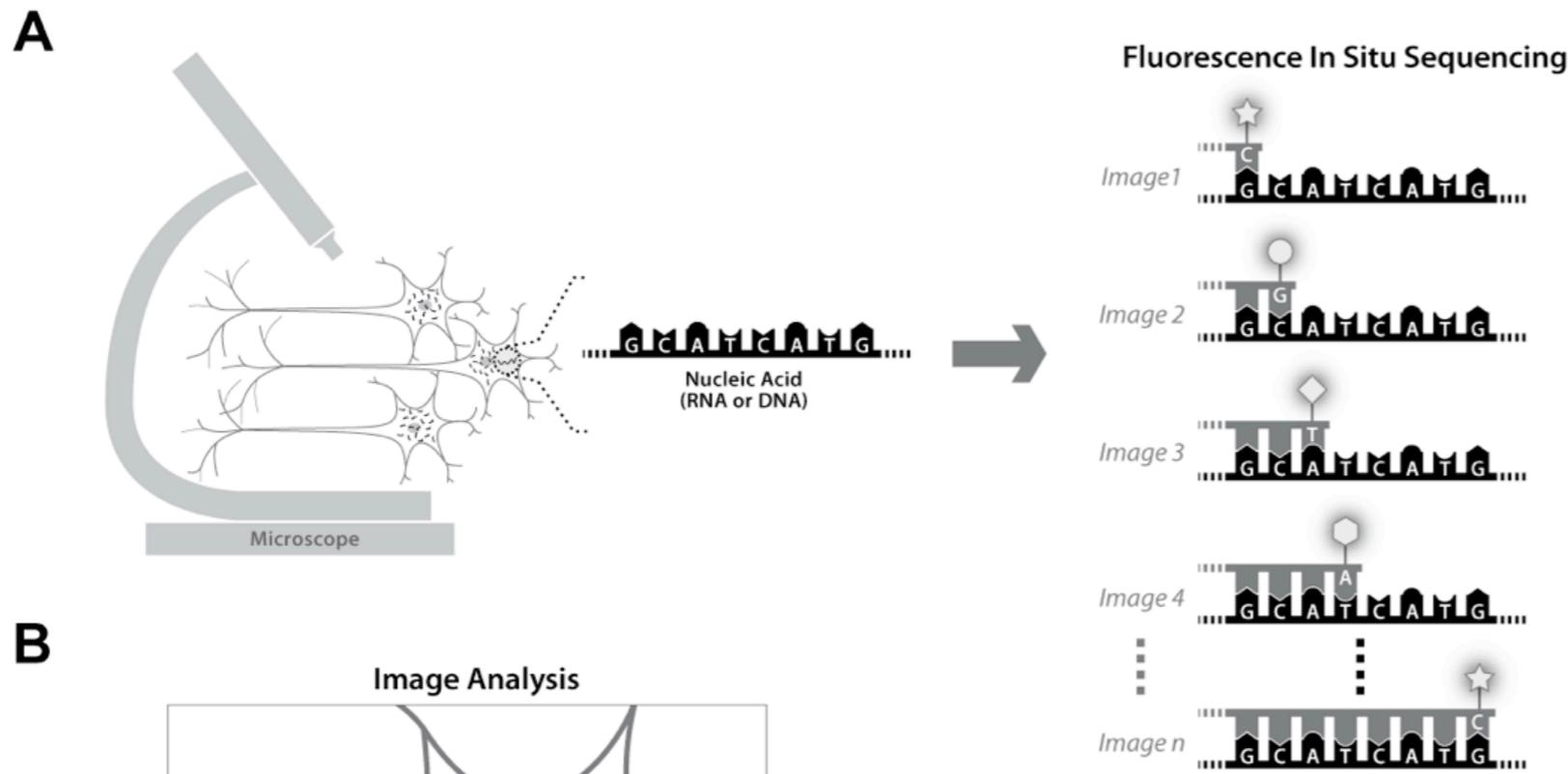
extracts connectivity

but

- 1) scrambles the precise positions of cells + synapses**
- 2) nontrivial to integrate w/ molecular “*annotations*” (e.g., gene expression)**

digital 4^N color microscopy

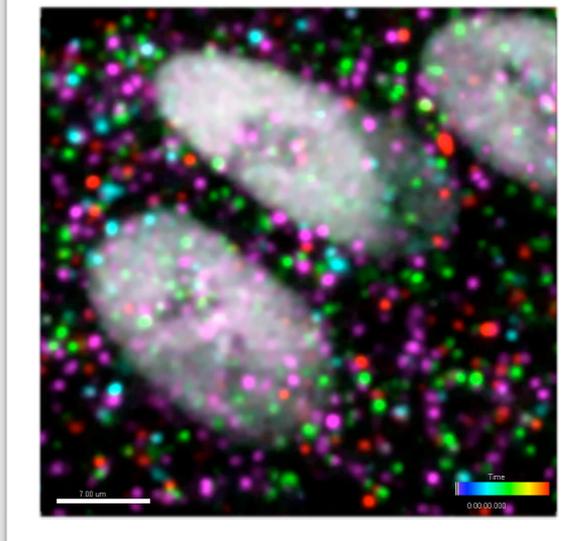
Fluorescent In-Situ DNA Sequencing (FISSEQ):



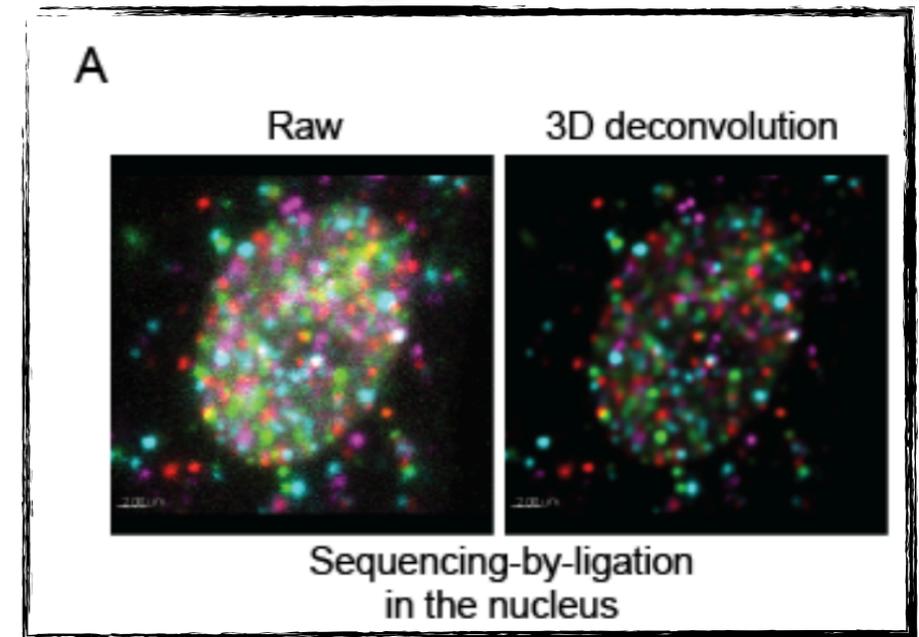
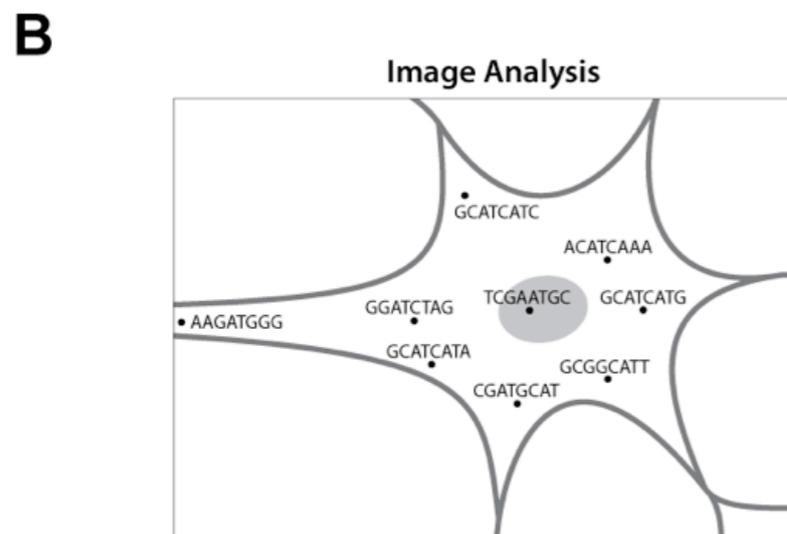
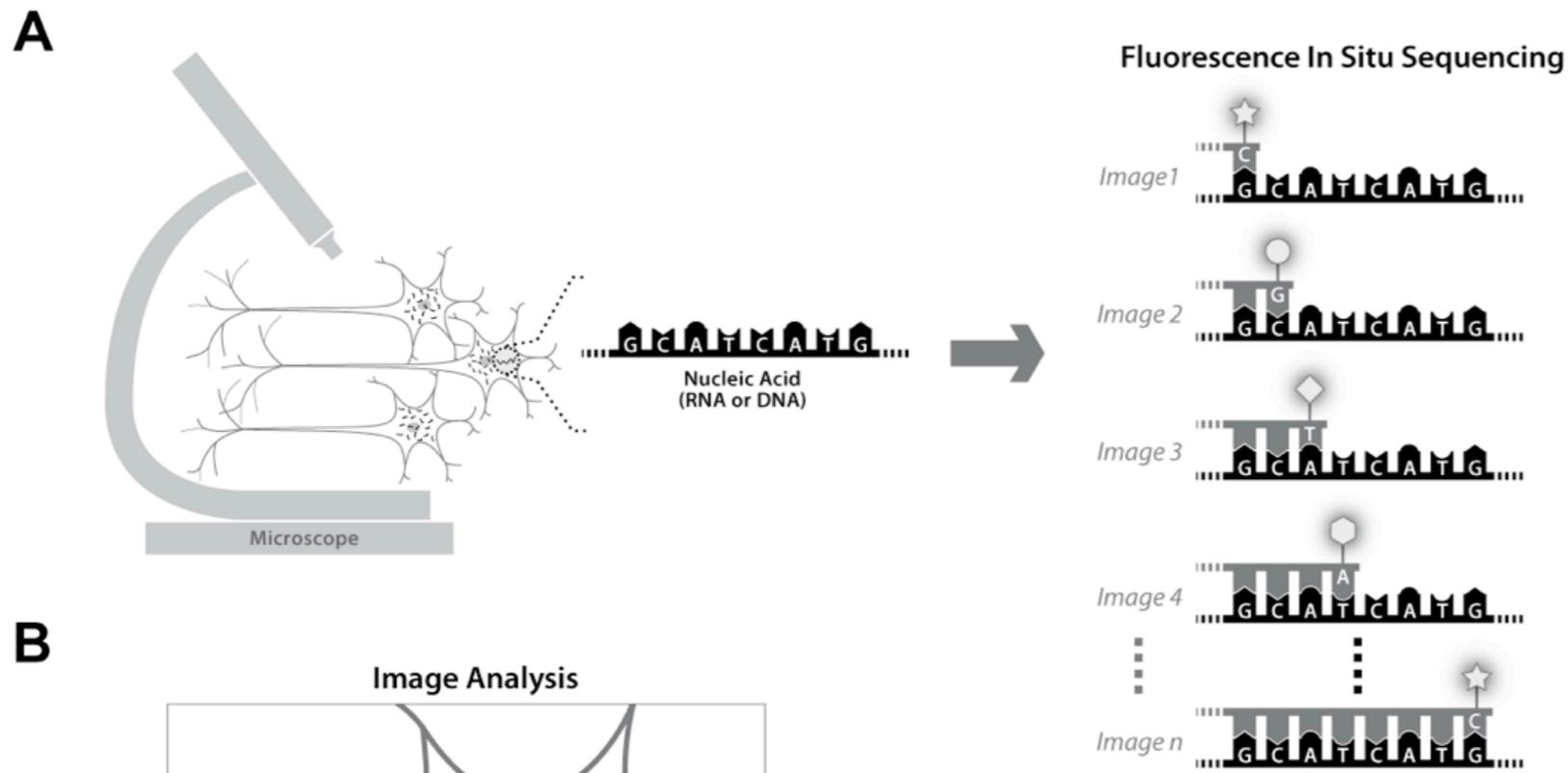
Highly Multiplexed Subcellular RNA Sequencing in Situ

Je Hyuk Lee,^{1,2*†} Evan R. Daugharthy,^{1,2,4*} Jonathan Scheiman,^{1,2} Reza Kalhor,² Joyce L. Yang,² Thomas C. Ferrante,¹ Richard Terry,¹ Sauveur S. F. Jeanty,¹ Chao Li,¹ Ryoji Amamoto,³ Derek T. Peters,³ Brian M. Turczyk,¹ Adam H. Marblestone,^{1,2} Samuel A. Inverso,¹ Amy Bernard,⁵ Prashant Mali,² Xavier Rios,² John Aach,² George M. Church^{1,2†}

digital 4^N color microscopy



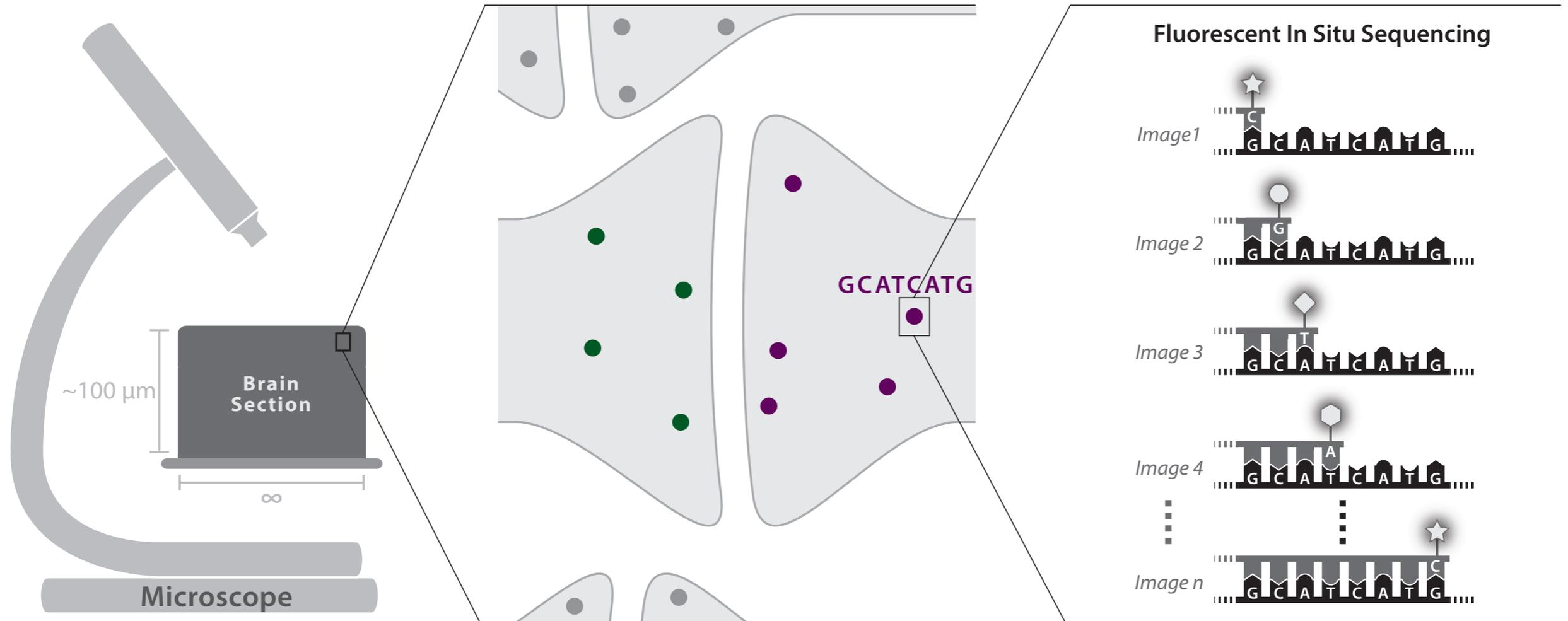
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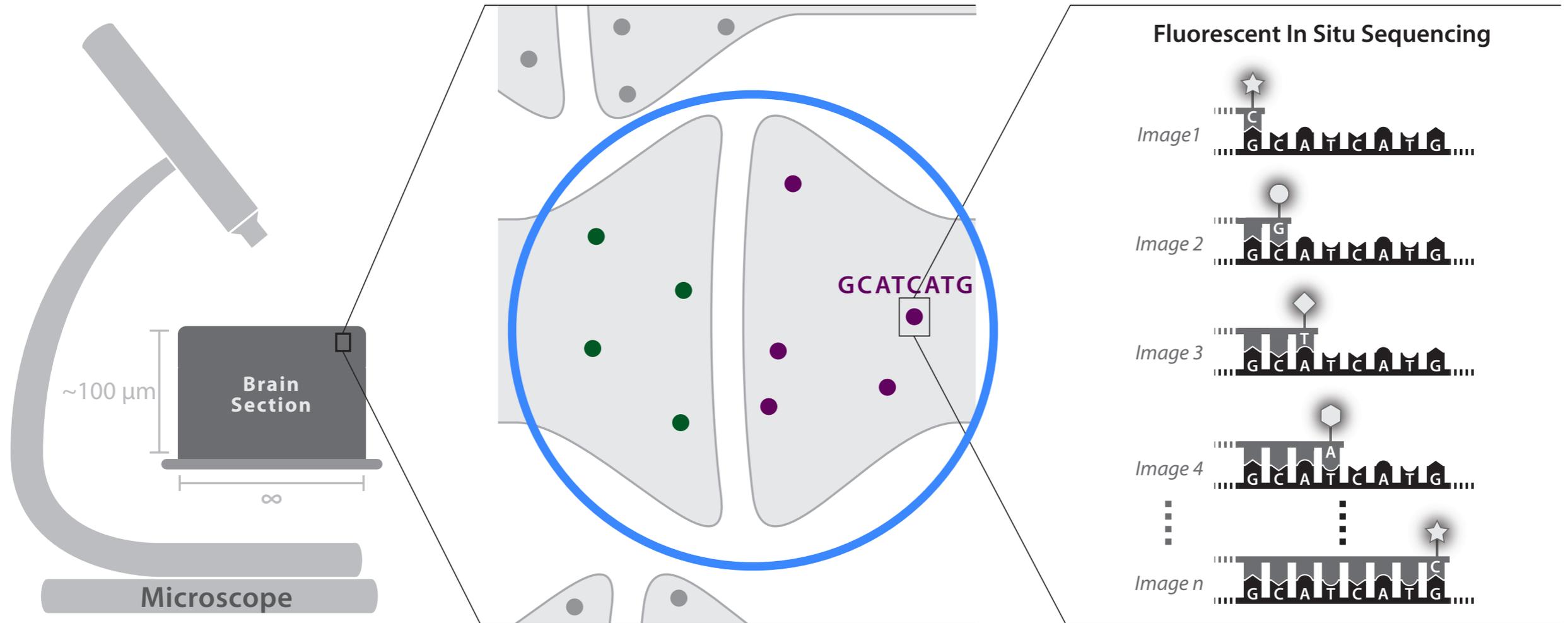
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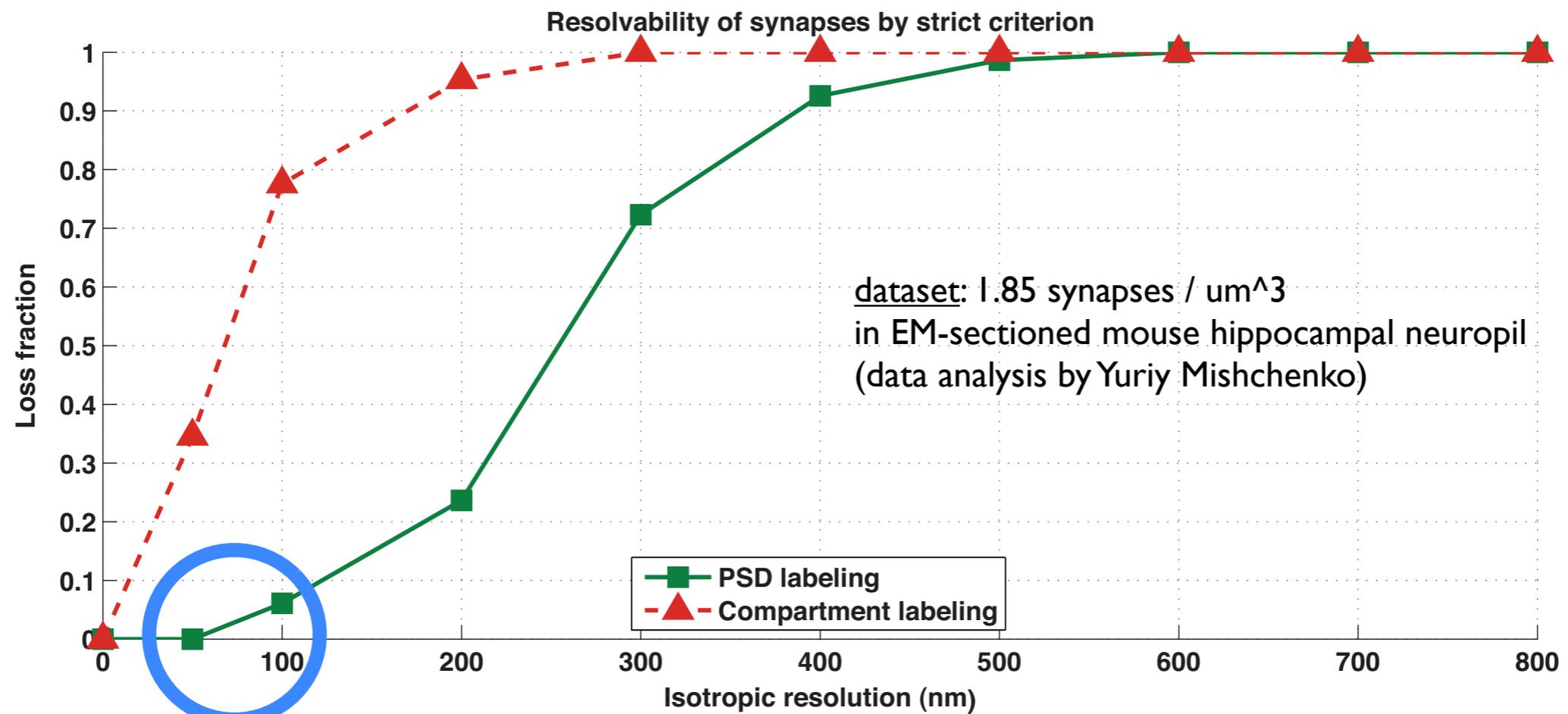
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digital 4^N color microscopy

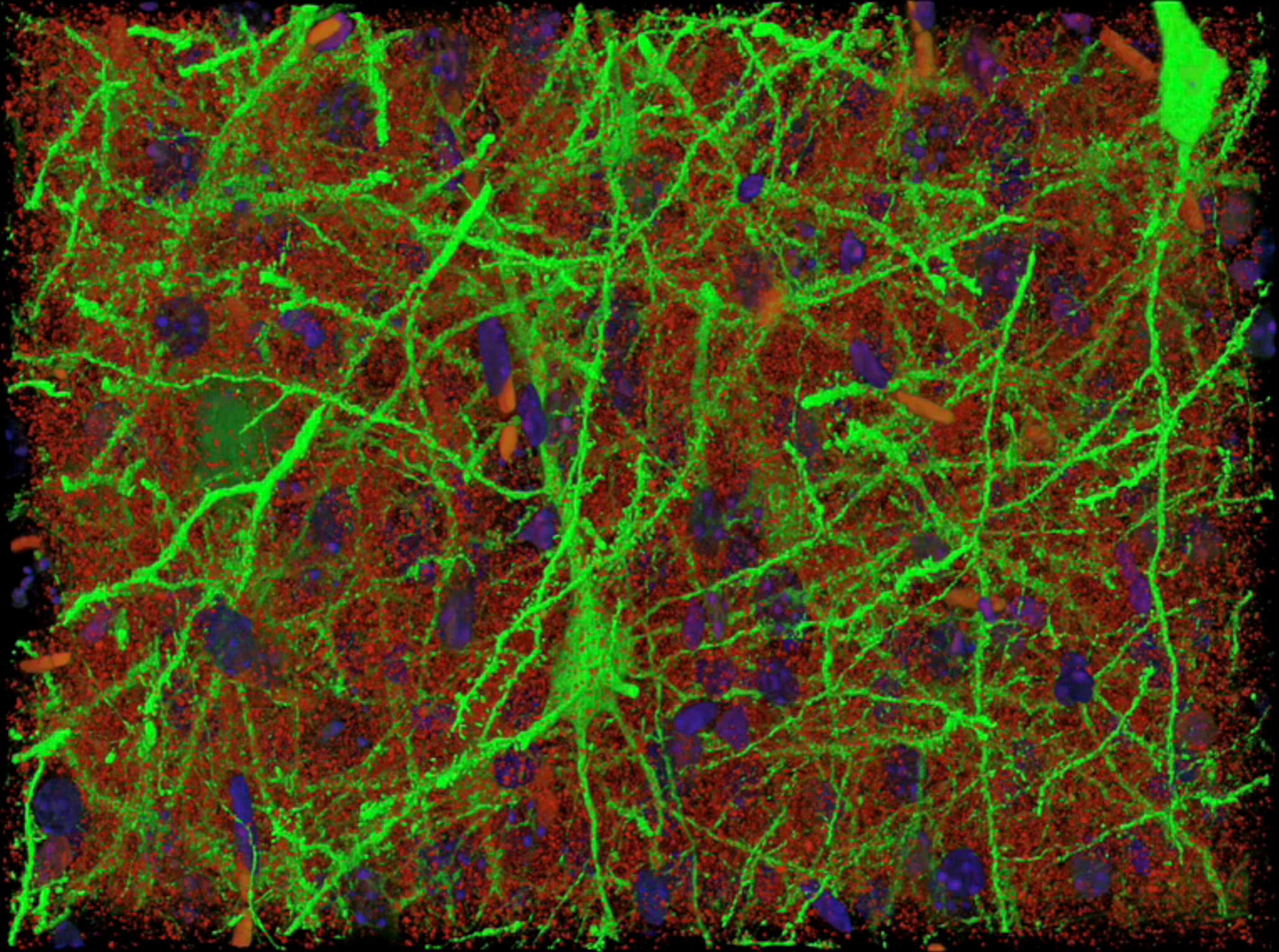


digital 4^N color microscopy



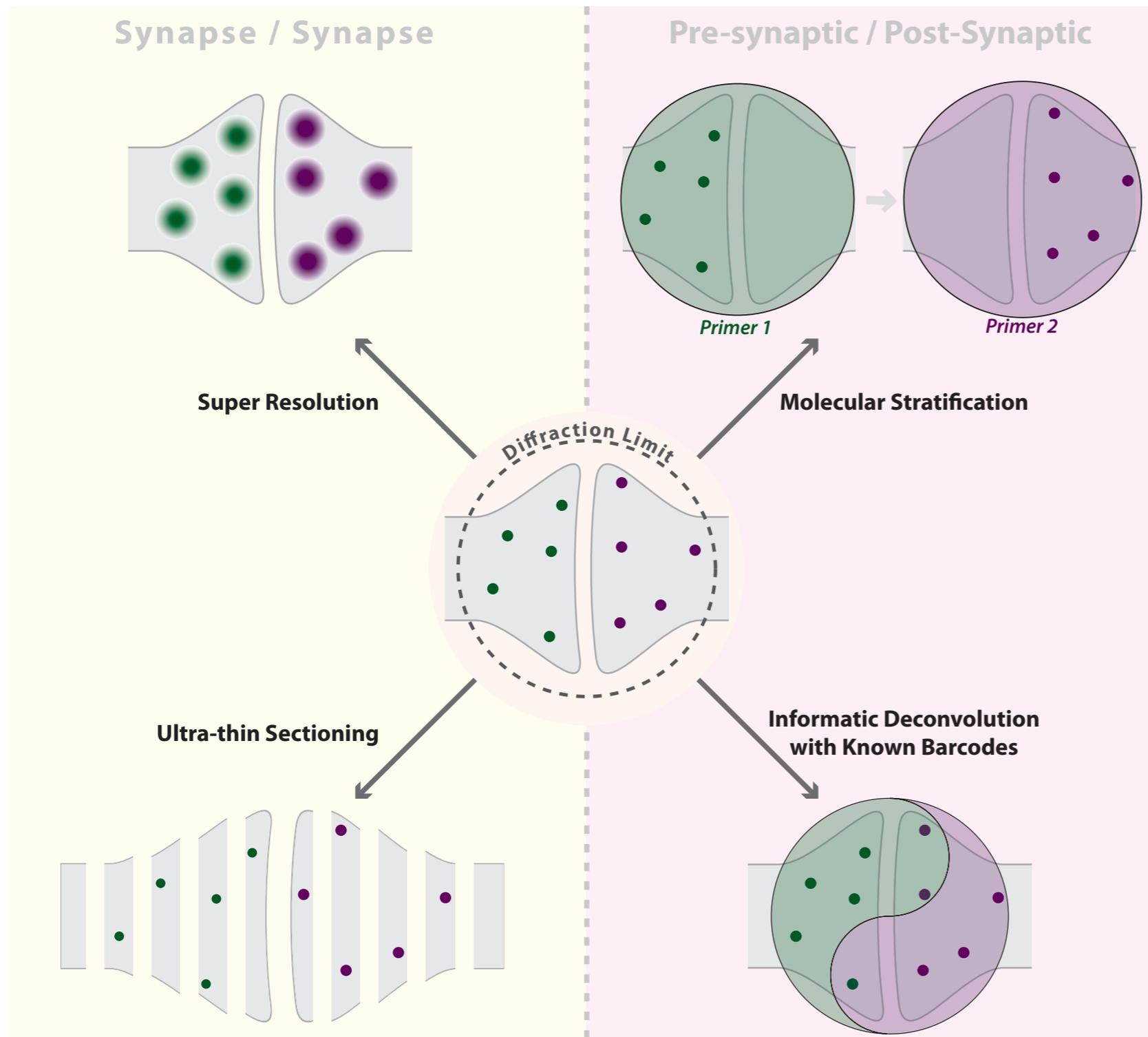
A much easier problem than whole-brain electron microscopy!

Red dots are synapses, resolved w/ diff. limited optics via thin-sectioning



Smith lab, Stanford

digital 4^N color microscopy

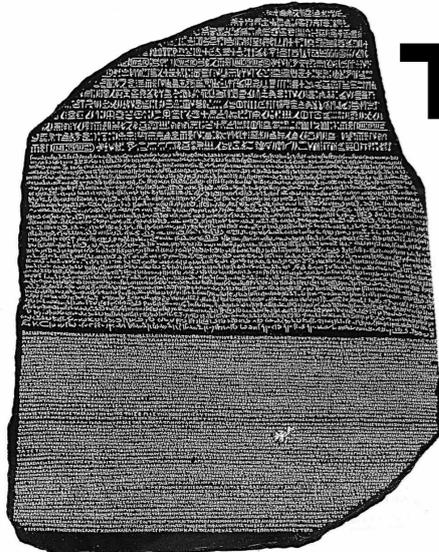


Enhance effective resolution by “stratifying” molecules into different image frames:

$S^{(1/3)}$ xyz improvement where S is slowdown factor

Use prior information about entire pool of barcodes to de-mix multiple signals from a single resolution voxel:

35-base barcodes suffice for no deconvolution ambiguities in mouse



The Rosetta Brain integration project

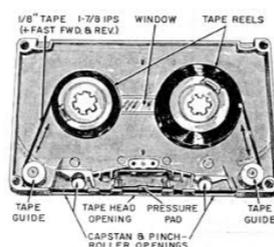
Activity

Behavior

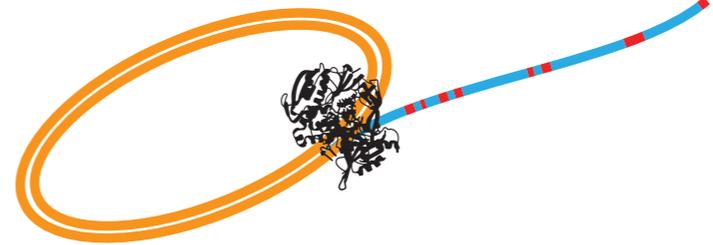
Connectivity

Development

Expression



Molecular recordings

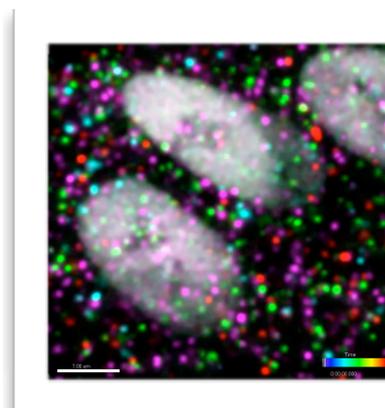


Preliminary Exp'ts:
Zamft*,
Marblestone*,
Glaser,
Kording et al
PLoS ONE / CB (2012)



In-vivo-generated cell barcodes
(update 1x per division)

Transcripts + DNA-barcoded antibodies



FISSEQ
(Lee et al 2014)

Further reading: roadmaps for BRAIN map strategy

frontiers in
COMPUTATIONAL NEUROSCIENCE

HYPOTHESIS AND THEORY ARTICLE
published: 21 October 2013
doi: 10.3389/fncom.2013.00137



Physical principles for scalable neural recording

Adam H. Marblestone^{1,2*}, Bradley M. Zamft^{3†}, Yael G. Maguire^{3,4}, Mikhail G. Shapiro⁵,
Thaddeus R. Cybulski⁶, Joshua I. Glaser⁶, Dario Amodei⁷, P. Benjamin Stranges³, Reza Kalhor³,
David A. Dalrymple^{1,8,9}, Dongjin Seo¹⁰, Elad Alon¹⁰, Michel M. Maharbiz¹⁰, Jose M. Carmena^{10,11},
Jan M. Rabaey¹⁰, Edward S. Boyden^{9,12‡}, George M. Church^{1,2,3‡} and Konrad P. Kording^{13,14‡}



Rosetta Brains: A Strategy for Molecularly-Annotated Connectomics

Adam H Marblestone, Evan R Daugharthy, Reza Kalhor, Ian D Peikon, Justus M Kecsichull, Seth L Shipman, Yuriy Mishchenko, Je Hyuk Lee, Konrad P Kording, Edward S Boyden, Anthony M Zador, George M Church

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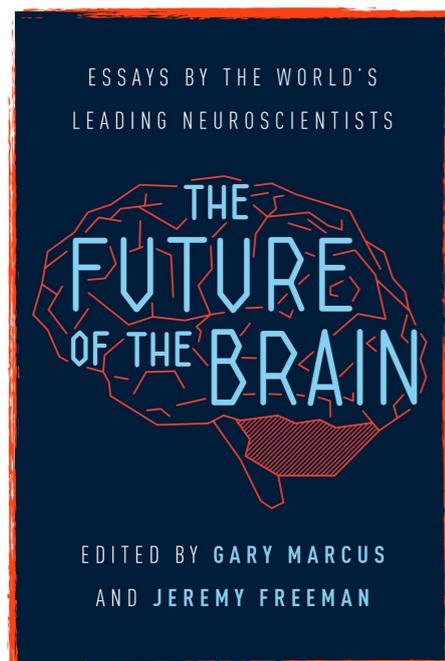
PLOS ONE

Measuring Cation Dependent DNA Polymerase Fidelity Landscapes by Deep Sequencing

Bradley Michael Zamft^{1‡}, Adam H. Marblestone^{2,9‡}, Konrad Kording^{3,8}, Daniel Schmidt^{4,5,7},
Daniel Martin-Alarcon^{4,5,7}, Keith Tyo⁶, Edward S. Boyden^{4,5,7}, George Church^{1,2*}

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PLOS COMPUTATIONAL BIOLOGY

Statistical Analysis of Molecular Signal Recording

Joshua I. Glaser^{1*}, Bradley M. Zamft^{2‡}, Adam H. Marblestone^{3,4‡}, Jeffrey R. Moffitt⁵, Keith Tyo⁶,
Edward S. Boyden^{7,8,9}, George Church^{2,3,4}, Konrad P. Kording^{1,10,11}

Conneconomics: The Economics of Dense, Large-Scale, High-Resolution Neural Connectomics

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doi: 10.1101/001214