Forecasting connectomics - a naive Kurzweilian approach

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The connectome of an organism is a map of all neurons and their connections. This may be thought of as a graph with the neurons as nodes and synaptic connections as edges. However, to successfully simulate an organism's brain using a connectome, more information will be needed. Here we take the term 'connectome' to refer to the graph and the underlying electron microscopy images of the neurons, which contain much more information.

The complete connectome of the nematode worm (*Caenorhabditis Elegans*) was published in 1986. A complete set of images of the fruit fly (*Drosophila melanogaster*) was published in 2018. However, all of the neurons and their connections have not yet been segmented or traced. In January 2020 researchers published the connectome of the central brain of the fruit fly, containing 25,000 neurons, which to my knowledge is the largest connectomics dataset published to date.

I thought it would be fun/interesting to plot the progress of connectomics over time and try to extrapolate out any trend observed. So, I did a literature search for all studies to date which either traced or segmented neurons and marked out synapses in electron microscopy data:

tissue	date	# neurons	# synapses	method	ref.
Mouse visual cortex	03-2011	14	250	skeletons	[1]
Mouse retina	09-2011	30	831	skeletons	[2]
Nematode pharyngeal nervous system (2x)	01-2013	40		skeletons	[3]
Fruit fly protocerebral bridge	05-2013	526		skeletons	[4]
Fruit fly visual system motion detection subcircuits	08-2013	379	637	segmentations	[5]
Mouse retina	08-2013	950			[6]
Mouse somatosensory cortex 0.13 mm volume	07-2015	≈ 4	700		[7]
Zebrafish olfactory bulb interglomerular projectome	11-2016	1022		skeletons	[8]
Ciona intestinalis tadpole larva	12-2016	177	6618		[9]
Fruit fly learning and memory center	07-2017	983	$> 61{,}000$	segmentations	[10, 11]
Fruit fly central brain	01-2020	$\approx 25{,}000$	20M	segmentations	[12, 13]
fruit fly motor and sensory neurons	02-2021	$\approx 1{,}000$		segmentations	[14]

[1] D. D. Bock, et al. "Network anatomy and in vivo physiology of visual cortical neurons", *Nature* **471** (7337) (2011) 177–182. doi:10.1038/nature09802.

[2] K. L. Briggman, M. Helmstaedter, W. Denk, Wiring specificity in the direction-selectivity circuit of the retina, *Nature* **471** (7337) (2011) 183–188.

[3] D. J. Bumbarger, M. Riebesell, C. Rodelsperger, R. J. Sommer, System-wide rewiring underlies behavioral differences in predatory and bacterial-feeding nematodes, *Cell* **152** (1-2) (2013) 109–119.

[4] C.-Y. Lin, et al., A comprehensive wiring diagram of the protocerebral bridge for visual information processing in the drosophila brain, *Cell Reports* **3** (5) (2013) 1739–1753. [link]

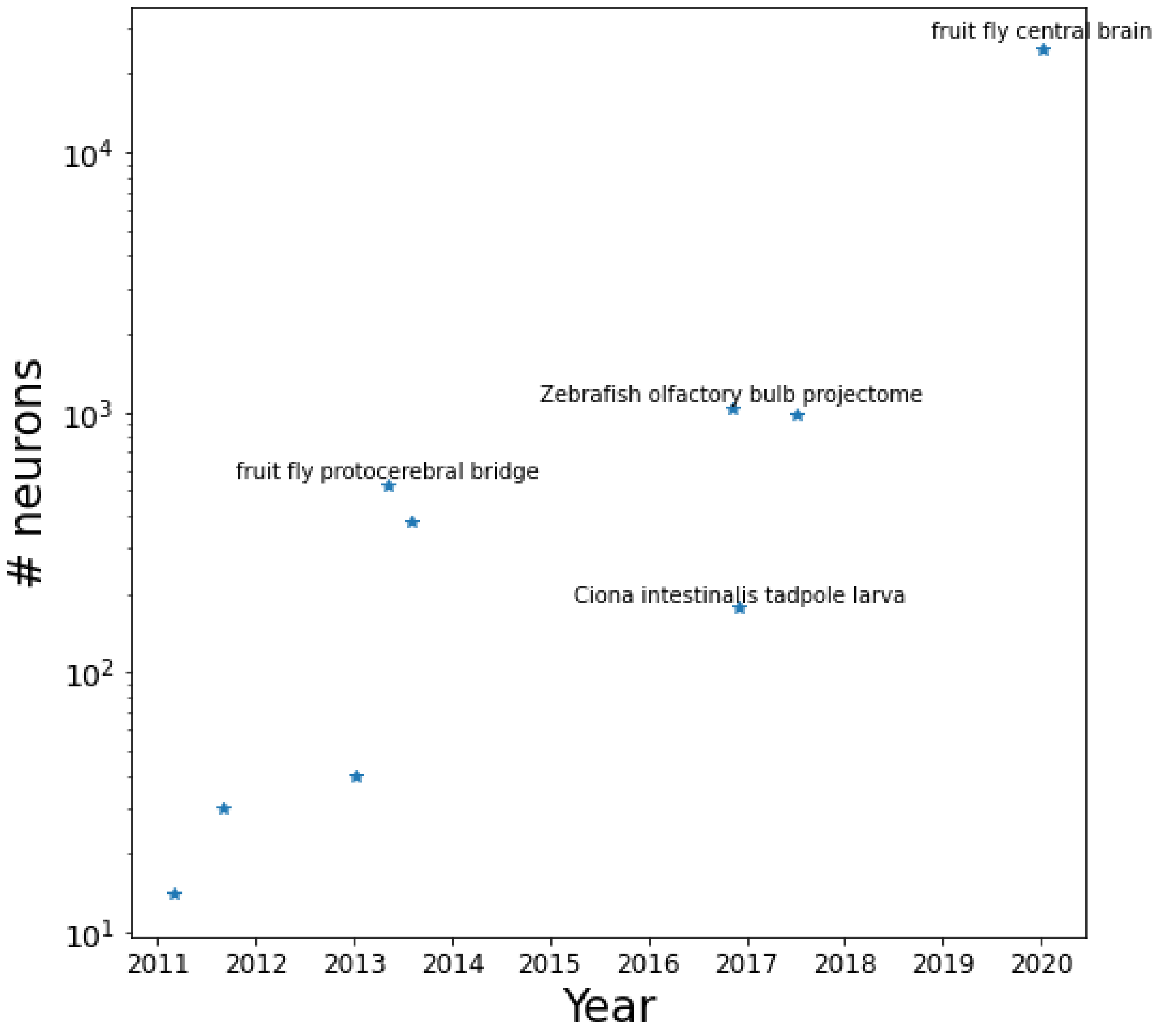
[5] S. ya Takemura, et al., A visual motion detection circuit suggested by drosophila connectomics, *Nature* **500** (7461) (2013) 175–181. [link]

[6] M. Helmstaedter, K. L. Briggman, S. C. Turaga, V. Jain, H. S. Seung, W. Denk, Connectomic reconstruction of the inner plexiform layer in the mouse retina, *Nature* **500** (7461) (2013) 168–174. [link]

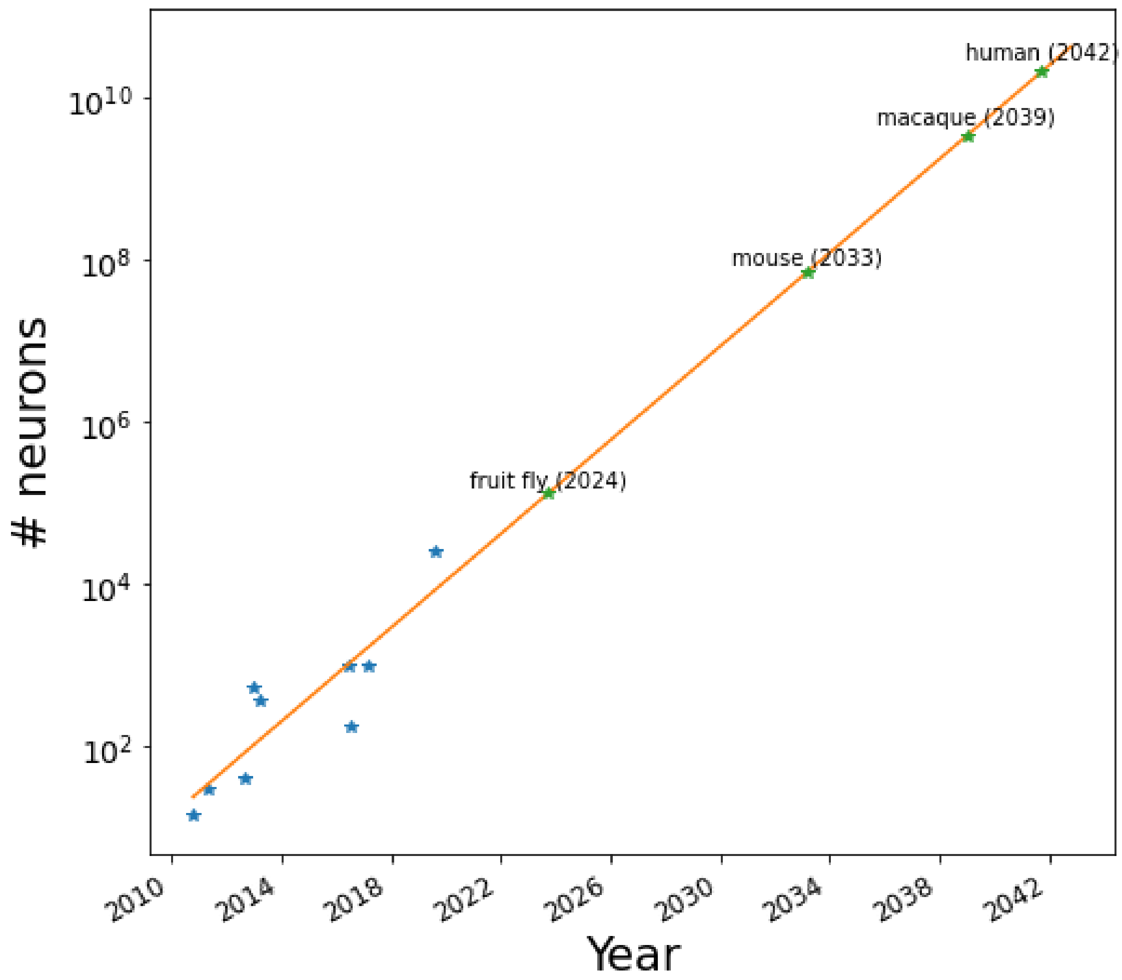
[7] N. Kasthuri, et al., Saturated reconstruction of a volume of neocortex, *Cell* **162** (3) (2015) 648–661. [link]

[8] A. A. Wanner et al., 3-dimensional electron microscopic imaging of the zebrafish olfactory bulb and dense reconstruction of neurons, *Scientific Data* **3** (1). [link]
[9] K. Ryan, Z. Lu, I. A. Meinertzhagen, The CNS connectome of a tadpole larva of Ciona intestinalis (l.) highlights sidedness in the brain of a chordate sibling, *eLife* **5** (2016) [link]
[10] S.-y. Takemura, et al., A connectome of a learning and memory center in the adult Drosophila brain, *eLife* **6** (2017). [link]
[11] K. Eichler, et al., The complete connectome of a learning and memory centre in an insect brain, *Nature* **548** (7666) (2017) 175–182. [link]
[12] C. S. Xu, et al., A connectome of the adult drosophila central brain (preprint) [link]
[13] L. K. Scheffer, et al., A connectome and analysis of the adult drosophila central brain, *eLife* **9** (2020). [link]
[14] J. S. Phelps, et al., Reconstruction of motor control circuits in adult drosophila using automated transmission electron microscopy, *Cell* **184** (3) (2021) 759–774.e18. [link]

Next I plotted most of the # neurons data vs the date of publication:



Next I did linear regression on the (year, log(# neurons)) data which is equivalent to fitting an exponential function to the data. (The reason for fitting the data in this way was to avoid the bias that occurs when fitting an exponential function with least squares regression that leads to the y larger values being fit more accurately than smaller ones.) After doing the linear regression I extrapolated it forward in time.



The projection for the fruit fly connectome (2024) seems about right. If anything, we may see it slightly sooner. It will be interesting to see how much longer it will take before we have physically realistic models of the fruit fly and fruit fly behavior, something my friend Logan T. Collins has advocated for. A project to produce the mouse brain connectome is underway, and again, the date extrapolated to — 2033 — seems plausible. Beyond that though, I have very little idea how plausible the projections are!

Here's some numbers that show the challenges just with scanning the entire brain (not to mention segmenting/tracing all the neurons accurately!):

Assuming an isotropic voxel size of 20 nm, it is estimated that storing the images of an entire human brain would require 175 exabytes of storage. It seems we are approaching hard drives which cost about 1.5 cents per gigabyte. Even at those exorbitantly low prices, it would still cost $2.6 billion to store all those images!

The volume of the human brain is about 1.2x10^6 cubic millimeters. The Zeiss MultiSEM contains either 61 or even 91 electron beams which scan a sample in parallel. According to a Zeiss video presentation from April 8th, 2020, it can scan a 1x1mm area at 4nm resolution in 6.5 minutes. Assuming a slice thickness of 20 nn, a single such machine would require 742,009 years to scan the entire brain!

X-ray holographic nano-tomography might be the path forward …

Write a comment…

TheGodfatherBaritone Dec 9, 2021

This might be a dumb question but what do you do once you’ve mapped out these edges and nodes?

Reply

1 reply by Dan Elton

David Martuscello Mar 31, 2021

Isn't it reasonable to assume that we would only need to scan parts of the brain and then extrapolate to model a full brain? Especially as AI improves this seems reasonable. Have there been any generative connectomics models that generate plausible brains?

Also, do we currently have "physically realistic models" of nematode worm behaviour? Seems like that would be a first step.

Reply

1 reply by Dan Elton

2 more comments...