Theoretical and experimental challenges in understanding the brain

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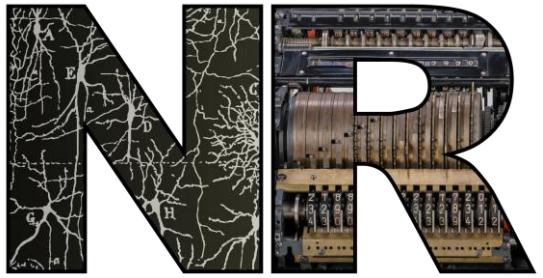


neural-reckoning.org

Outline

I'm introducing the panel discussion on "Will we ever understand the whole brain?"

So I have to say something at least moderately controversial...

💡 TLDR: **yes, but not if we keep doing neuroscience the way we are now**.

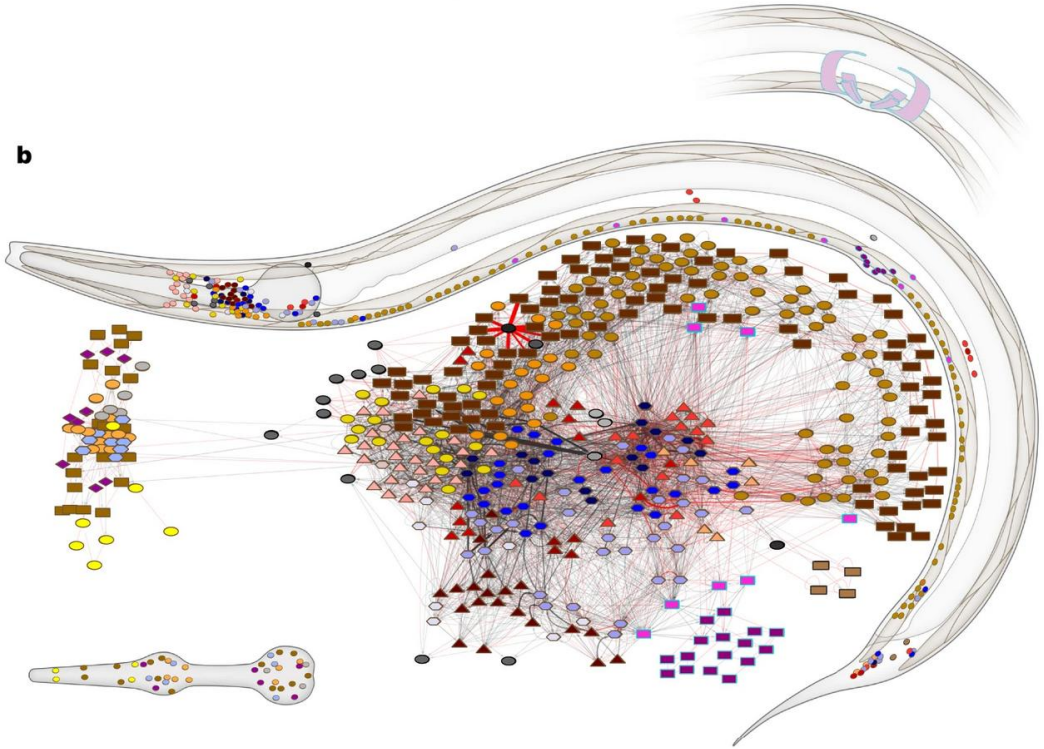
Specifically:

Challenges in understanding whole brains

Why current methods may not meet these challenges

Can I dig myself out of this hole? Let's see. 😅

Uncontroversial (?): we're not there yet



C. elegans
302 neurons

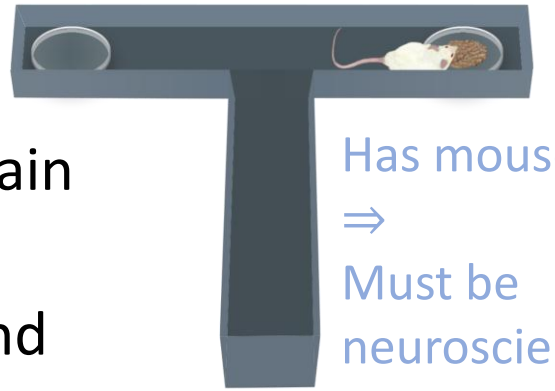
Paramecium, the "swimming neuron"
$\leq$ 1 neuron

Challenge 1: we take on problems that are too easy

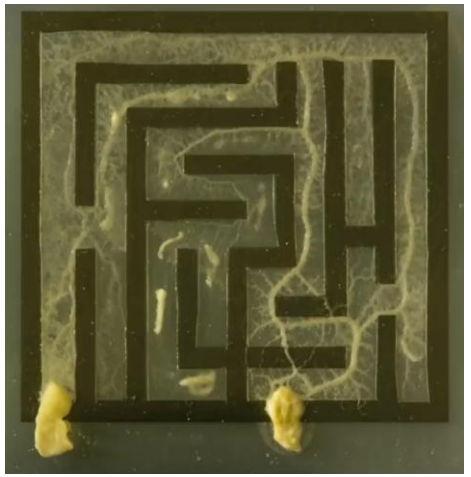
Aim: understand the brain

So we should study the unique property of the brain
(⚠️ let's call this "intelligence" ⚠️)

This means solving challenging tasks in realistic and dynamic environments



Has mouse
⇒
Must be neuroscience



Slime mould ⇒ not neuroscience

But that's not what we do

Experimental tasks that require ≤ 1 neurons

In theory work too!

- Yang et al. (2019) dataset of 20 cognitive tasks can be solved by a handful of disconnected neurons (Khona et al. 2023).
- Binz et al. (2025) used a 70 bn parameter model to solve text-based psychophysics

Classic "multimodal" tasks can be solved without a multimodal area (Ghosh et al. 2024)

Recommended: "To understand decision-making, we need to truly challenge lab animals" (Chandrasekaran, The Transmitter)

Challenge 2: our concepts don't scale

An old favourite: "What I cannot create, I do not understand." (Feynman)

Two main routes at the moment towards understanding "intelligence":

1. Machine learning / artificial intelligence
2. Neuroscience

Can these achieve Feynman's criteria?

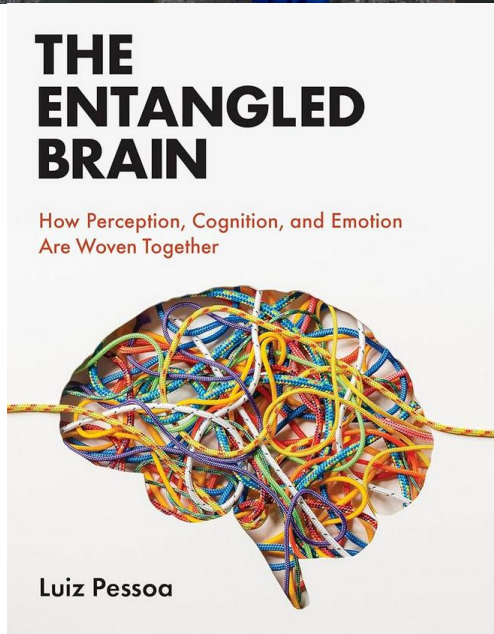
1. Current ML requires too much data, compute, energy
   This limits scaling in terms of performance *and* understanding
2. More "brain-like" models don't scale in terms of performance

If the brain were modular, that would give us a route

But these modules appear to be entangled

Disentangling is challenging (Béna and Goodman 2025)

And maybe misguided ("Everything is everywhere" Hayden et al. 2025)

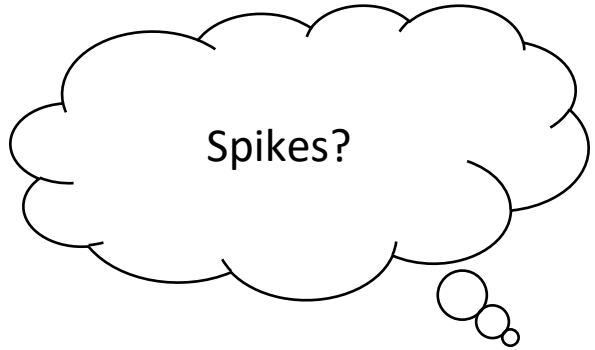


Challenge 3: our understanding is unstable

To build understanding of a whole brain, we need solid foundations.

Our basic understanding keeps getting challenged:

- Synaptic turnover (many papers)
- Representational drift (many papers)
- "mRNA trafficking in the nervous system" (Fila et al. 2021)



I'm not complaining, this makes neuroscience fun!

On a more personal note:

- When I started in neuroscience (~2007) I was drawn into the question of whether or not the brain used spike times or only rates
- This question was already old then
- We are no closer to an answer to this question now

Challenge 4: doing theory and experiment together

Claim: we can't understand the brain by doing just experiments or just theory

In principle not controversial, but in practice: (here goes)

Most experimental and computational studies do not engage with the complexities of the other one

Experiments based on intuitive computational thinking

Computational studies that don't explore parameter spaces

Why do we do this?

Causal reasoning with complex nonlinear models is hard!

Career incentives to not engage with this: simple stories sell

Advert: Come to our Crick/Imperial seminar series and help us figure this out! (free food! 🥳🎉🦙)

So why the optimism? (note: last slide!)

The challenges I've raised can be addressed and they are being addressed

What does it mean to "understand" the brain?

- Prediction?
- Treat medical conditions?
- Build AI?
- Read / write thoughts from the brain?

My take: we will find answers to this question and this is part of neuroscience.

I'll finish by sticking my neck out and providing my probably wrong answer

Aim: a step towards "understanding" that respects these challenges

My approach: deeply explore theoretical models[3] to show what biological mechanisms can contribute to[2] relevant hard computational functions[1] under what conditions

Current: neuromodulation, energy supply, heterogeneity - biological questions not AI[4]

Conclusion: we can understand the brain, but we need to think about what that understanding could look like, take on the hard challenges and address career incentives