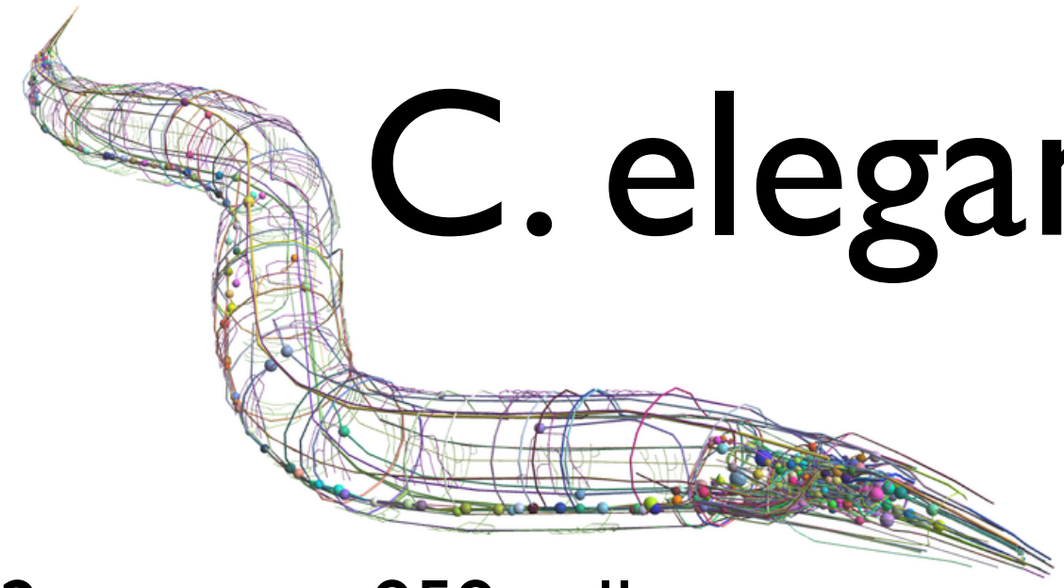
Towards a "complete" activity map for the smallest brain

Adam Marblestone

w/ Semon Rezchikov, Young-Gyu Yoon, Nikita Pak and Ed Boyden

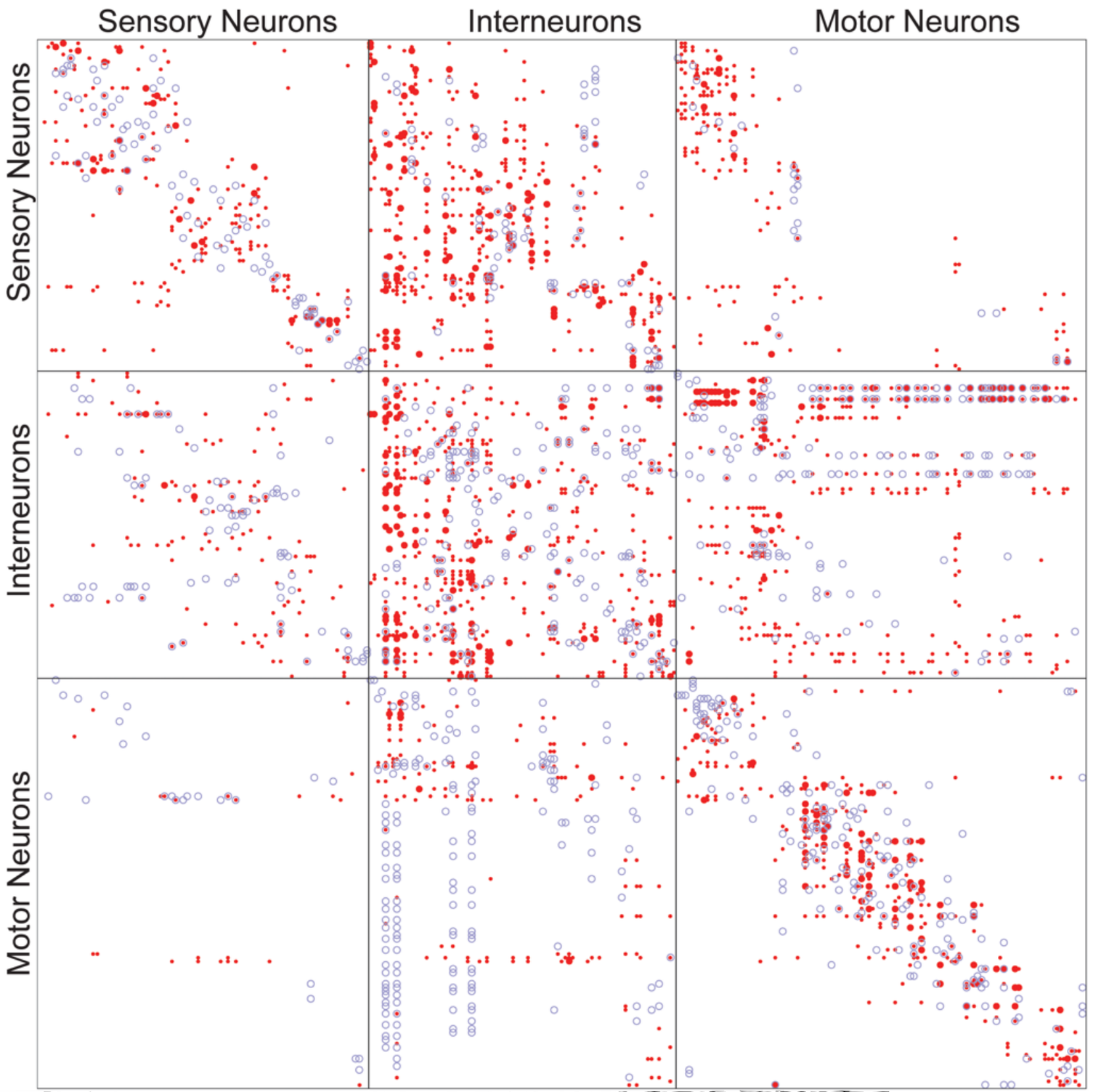
2014-08-06



C. elegans

- 302 neurons, 959 cells
- Some neurons have known functions
    - Example: “egg laying neuron”
- The only organism with a “completely known” neural connectome
    - Obtained via electron microscopy circuit tracing in the late 1980s
    - Includes both chemical synapses and electrical “gap junctions”

Connectome

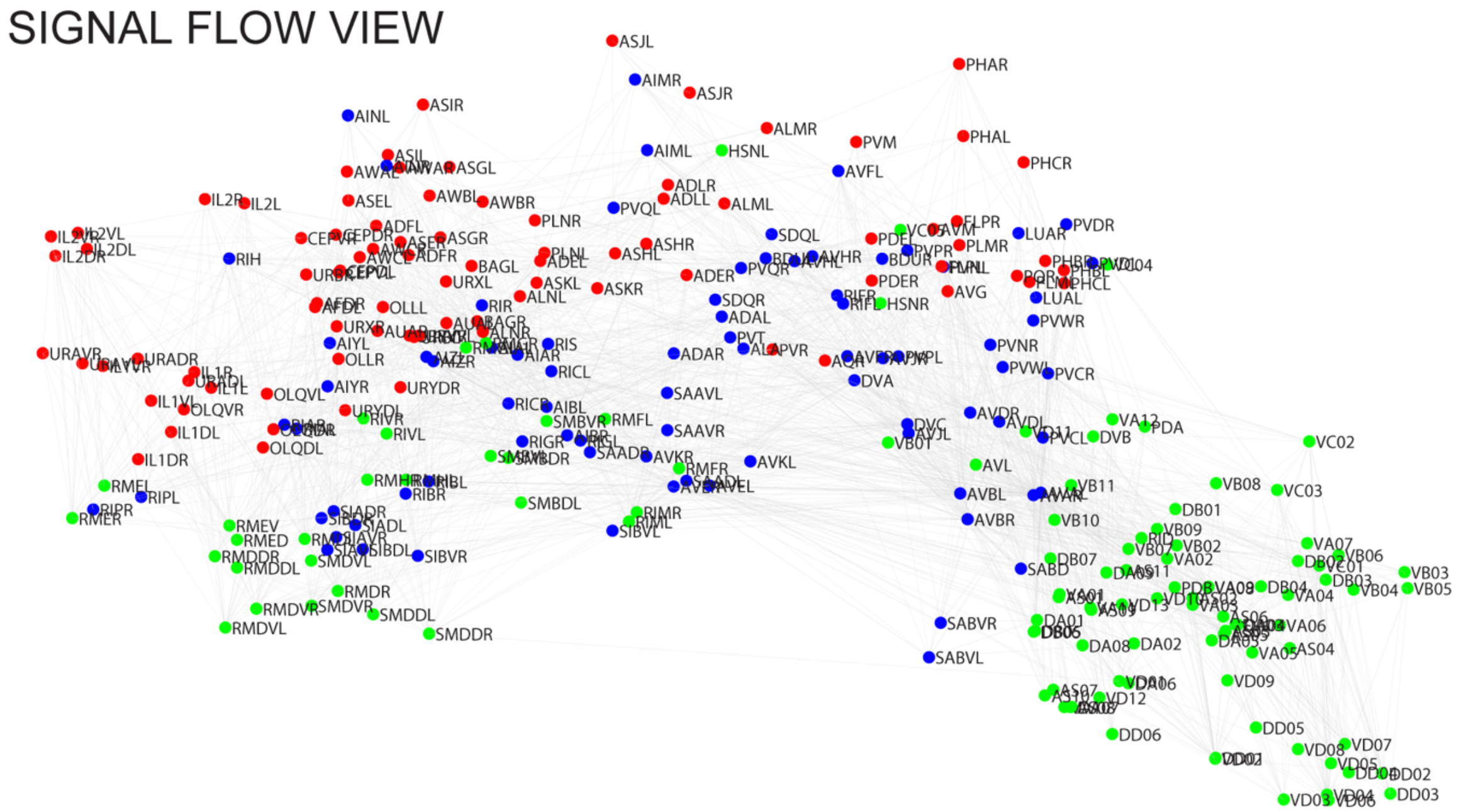


Structural Properties of the *Caenorhabditis elegans* Neuronal Network

Lav R. Varshney, Beth L. Chen, Eric Paniagua, David H. Hall, Dmitri B. Chklovskii

Published: February 03, 2011 • DOI: 10.1371/journal.pcbi.1001066

Connectome



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So why can’t we just run a simulation?

So why can't we just run a simulation?

- Unknown "**polarities**": excitatory vs. inhibitory
- Unknown roles for **neuro-modulators**
- Unknown **dynamical laws** of neurons & networks

Synapse polarities

Approach #1: brute-force optimization to match limited activity or behavior datasets (including in the presence of "ablations")

Simulate "tap reversal reflex"

$$\text{Propensity to Reverse} \propto \int V_{\text{AVB}} - V_{\text{AVA}} dt.$$

Compare with experimental reversal propensity

Repeat as a function of various "ablations" to the circuit

A Dynamic Network Simulation of the Nematode Tap Withdrawal Circuit: Predictions Concerning Synaptic Function Using Behavioral Criteria

Stephen R. Wicks,[1] Chris J. Roehrig,[1] and Catharine H. Rankin[2]

Synapse polarities

Approach #1: brute-force optimization to match limited activity or behavior datasets (including in the presence of "ablations")

	ALM	PLM	PVD	AVB	PVC	AVA	AVD	AVM	DVA		ALM	PLM	PVD	AVB	PVC	AVA	AVD	AVM	DVA
1	1	-1	-1	-1	1	1	1	-1		26	1	-1	1	-1	1	1	-1	-1	
2	-1	-1	-1	1	-1	-1	1	-1		27	-1	-1	-1	1	1	1	-1	-1	
3	-1	-1	-1	1	-1	1	1	-1		28	1	1	-1	-1	1	-1	-1	-1	
4	1	-1	-1	-1	1	-1	1	-1		29	-1	1	-1	1	1	-1	1	1	
5	1	-1	-1	-1	1	1	-1	-1		30	1	-1	1	-1	1	-1	1	-1	
6	1	-1	-1	1	1	-1	1	-1		31	-1	-1	-1	-1	1	-1	-1	-1	
7	-1	-1	-1	1	1	-1	-1	-1		32	-1	1	-1	-1	1	-1	-1	-1	
8	-1	-1	-1	1	1	-1	1	-1		33	1	-1	1	1	1	1	-1	-1	
9	1	-1	1	1	1	1	1	-1		34	-1	-1	-1	-1	-1	1	1	-1	
10	-1	-1	-1	-1	1	-1	1	-1		35	1	-1	-1	1	1	-1	-1	-1	
11	-1	-1	-1	-1	1	1	-1	-1		36	1	-1	-1	-1	1	-1	-1	-1	
12	1	-1	1	-1	1	1	1	-1		37	-1	1	1	-1	1	-1	1	-1	
13	-1	-1	-1	1	1	1	1	-1		38	1	1	1	-1	1	-1	1	-1	
14	-1	-1	1	1	1	1	1	-1		39	-1	1	-1	-1	1	1	1	1	
15	-1	-1	1	1	1	-1	1	-1		40	-1	-1	1	1	-1	-1	1	-1	
16	-1	-1	-1	-1	1	1	1	-1		41	1	1	1	-1	1	1	-1	-1	
17	-1	-1	1	-1	1	1	1	-1		42	-1	1	1	-1	1	1	-1	-1	
18	1	-1	1	1	1	-1	1	-1		43	-1	-1	1	1	1	-1	-1	-1	
19	1	-1	-1	1	1	1	1	-1		44	-1	1	1	1	1	-1	1	-1	
20	-1	-1	1	-1	1	1	-1	-1		45	-1	1	1	-1	1	1	1	-1	
21	-1	-1	1	1	1	1	-1	-1		46	-1	1	-1	1	1	1	1	-1	
22	1	-1	-1	1	1	1	-1	-1		47	-1	-1	1	-1	1	-1	-1	-1	
23	-1	-1	-1	-1	-1	-1	1	-1		48	-1	1	1	1	1	1	1	-1	
24	-1	1	-1	-1	1	-1	1	1		49	1	1	1	1	1	-1	1	-1	
25	-1	-1	1	-1	1	-1	1	-1		50	-1	-1	1	-1	-1	1	1	-1	

Figure 4. Sample polarity configurations. The top 50 polarity configurations sorted according to error from experiment 1 are shown. This circuit did not include the DVA interneuron, and hence there were 256 possible configurations (2^6) in the complete sorted list. Thus, the top 10% of the list reported in Table 3A consists of the top 26 polarity configurations shown in this figure. The PVD sensory neuron class was not externally stimulated during this run. A polarity consistent with that which resulted from statistical considerations is shown as a *lightly shaded box*; a polarity that is not consistent is shown in an *unshaded box*. No polarity predictions were made for the AVA or DVA neurons. These columns are *darkly shaded*. In this experiment, the tenth and sixteenth configurations are entirely consistent with the consensus configuration predicted in this report.

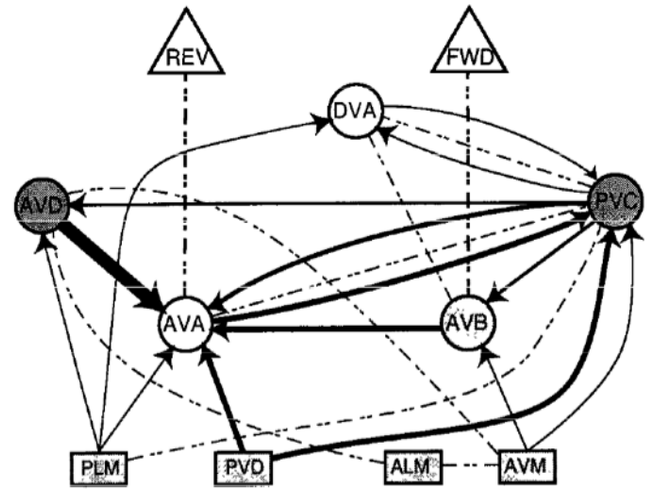


Figure 6. Simplified circuit with predicted polarities. The circuit that mediates the nematode tap withdrawal reflex consists of seven sensory neurons (*squares*), nine interneurons (*circles*), and two motorneuron pools (not shown), which produce forward and backward locomotion (*triangles*). All cells represent bilateral classes of cells except AVM and DVA, which are single cells. Chemical connections are indicated by *arrows*, with the number of synaptic contacts proportional to the width of the *arrow*. Gap junctions are indicated by *dotted lines*. This circuit has been simplified for ease of presentation in two ways: the bilateral symmetry of the circuit has been collapsed, and only classes of connections with an average of greater than five synaptic contacts are shown. The consensus polarities of the neurons in this circuit, which were derived from four experiments, are also shown. Neurons that are predicted to make excitatory connections are *darkly shaded*, whereas neurons that are predicted to make inhibitory connections are *lightly shaded*. Two neurons (AVA and DVA) did not possess polarities that clustered at above chance levels in any of the experiments presented in this report.

A Dynamic Network Simulation of the Nematode Tap Withdrawal Circuit: Predictions Concerning Synaptic Function Using Behavioral Criteria

Stephen R. Wicks,[1] Chris J. Roehrig,[1] and Catharine H. Rankin[2]

Synapse polarities

Approach #1: brute-force optimization to match limited activity or behavior datasets (including in the presence of "ablations")

Only works for small circuits

Combinatorial explosion

Not "ground truth"

Synapse polarities

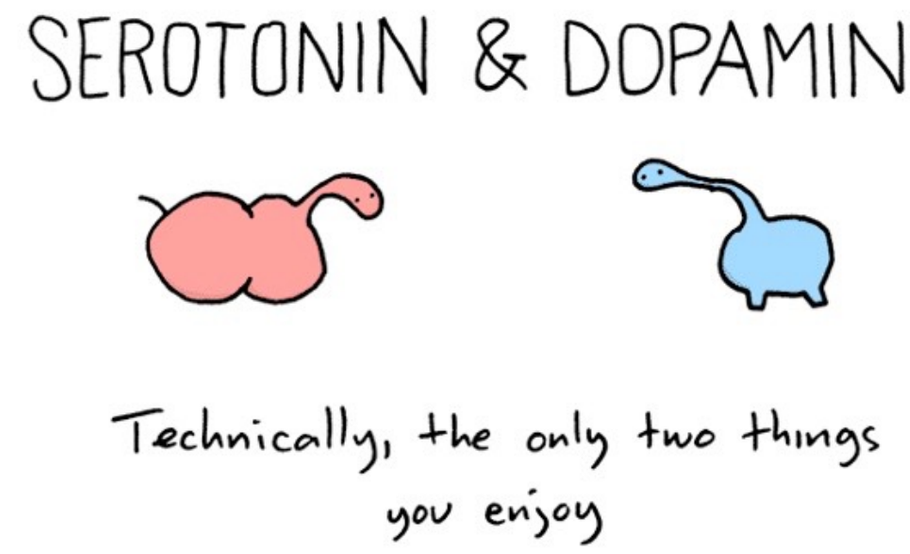
Approach #2: use neurotransmitter gene expression data

The neurons which are taken to be **inhibitory** are those that express GABA:

DVB, AVL, RIS,
DD01–DD06,
VD01–VD13,
and the four RME neurons

Neuromodulators

Many results, however, suggest that anatomically-defined connections between brain areas are necessary but not sufficient to define patterns of brain activity. The ultrastructural synapses between neurons will encode the precise, millisecond-speed information flow that is essential to sensory perception, complex motor outputs, and cognition. These synapses will not represent the modulators that alter circuit dynamics and circuit composition, because most neuromodulatory inputs are extrasynaptic and many derive from diffuse long-range projections that will be invisible or uninformative in the first level of connectome analysis. In the simplest formulation, modulators will select a subset of the anatomically-defined synapses for activity under a given set of conditions. Through their effects on neuronal excitability and presynaptic efficacy, they will sculpt information flow on the seconds-to-minutes timescale of GPCRs and second messengers.



Beyond the connectome: How neuromodulators shape neural circuits

Cornelia I. Bargmann

Let's just give it a try anyway

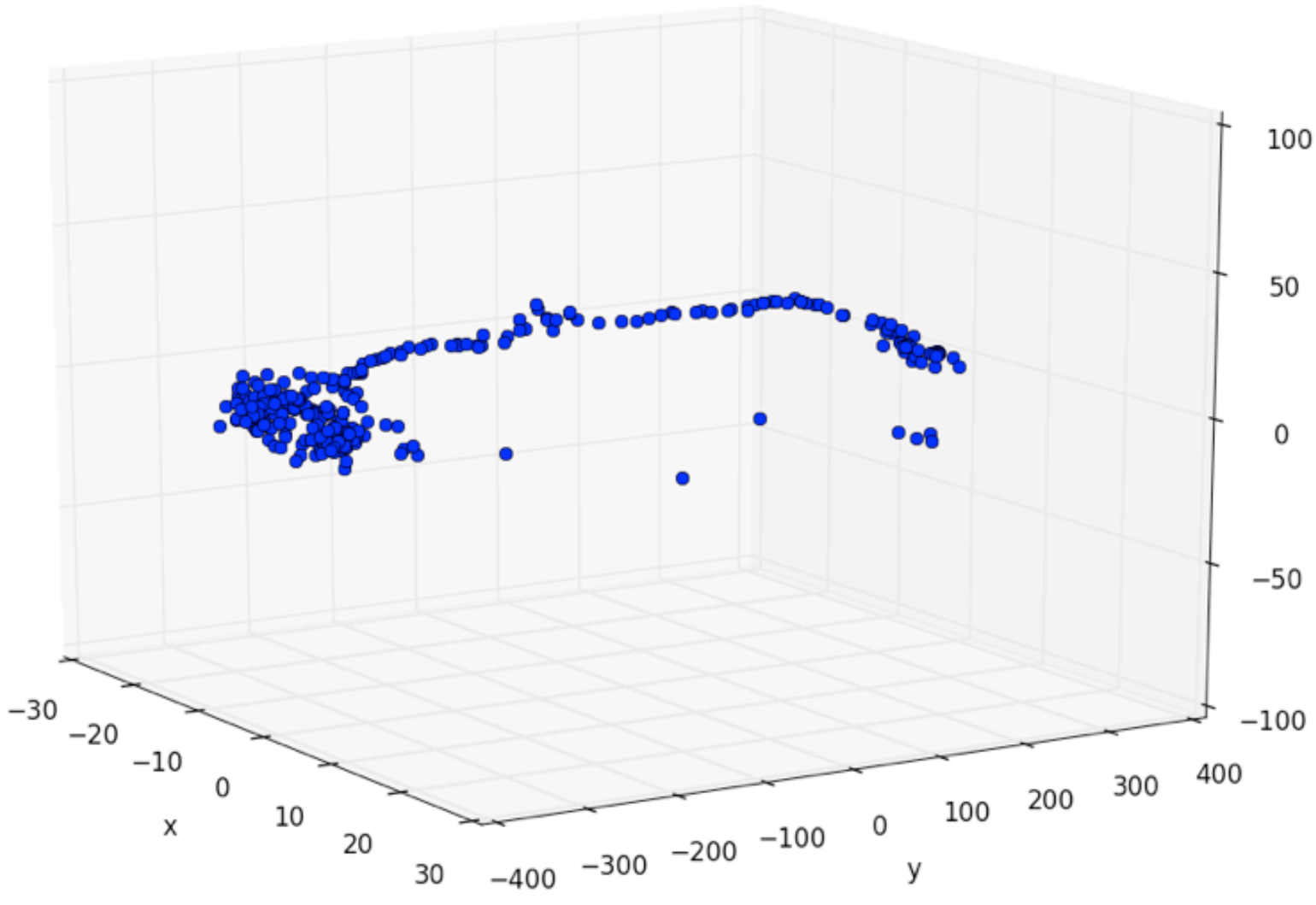
- Assume each neuron's membrane voltage is iso-potential
  - One variable per cell
- Capacitive charging of membrane, leak conductance of membrane
- Gap junction as a resistor between cells
- Synapse as a dynamic nonlinear resistor + battery (reversal potential)
  - Inhibitory synapses have a negative reversal potential

$$I_i^{\mathrm{Syn}} = \Sigma_j G_{ij}^s s_j (V_i - E_j) \qquad \frac{ds_j}{dt} = \frac{a_r(1-s_j)}{1+e^{-\beta(V_j - V_{\mathrm{th}})}} - a_d s_j$$

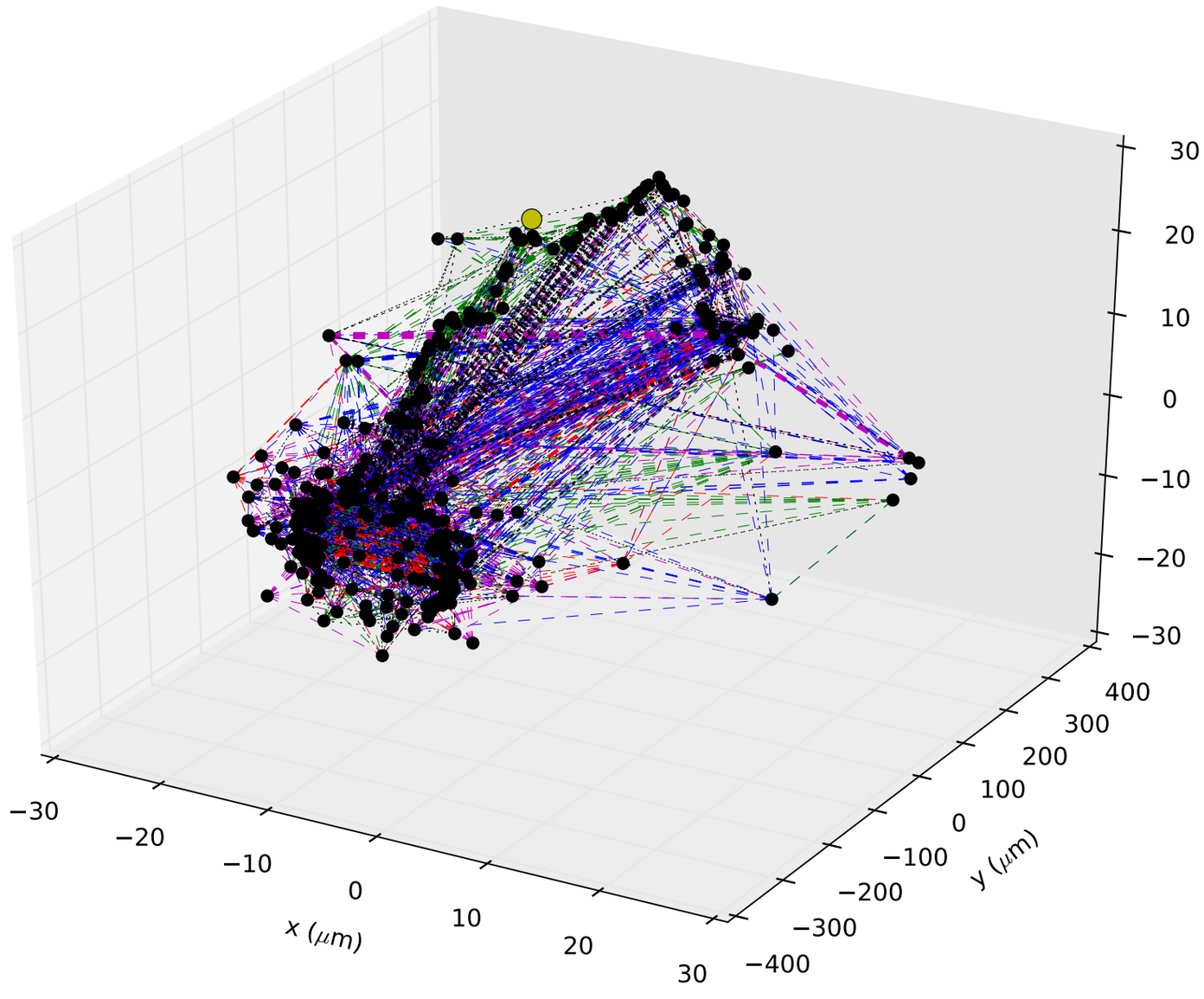
Low-dimensional functionality of complex network dynamics: Neuro-sensory integration in the Caenorhabditis elegans connectome

James Kunert[1], Eli Shlizerman[2] and J. Nathan Kutz[2]
[1] *Department of Physics, University of Washington, Seattle, WA. 98195 and*
[2] *Department of Applied Mathematics, University of Washington, Seattle, WA. 98195-2420*
(Dated: February 19, 2014)

Let’s just give it a try anyway

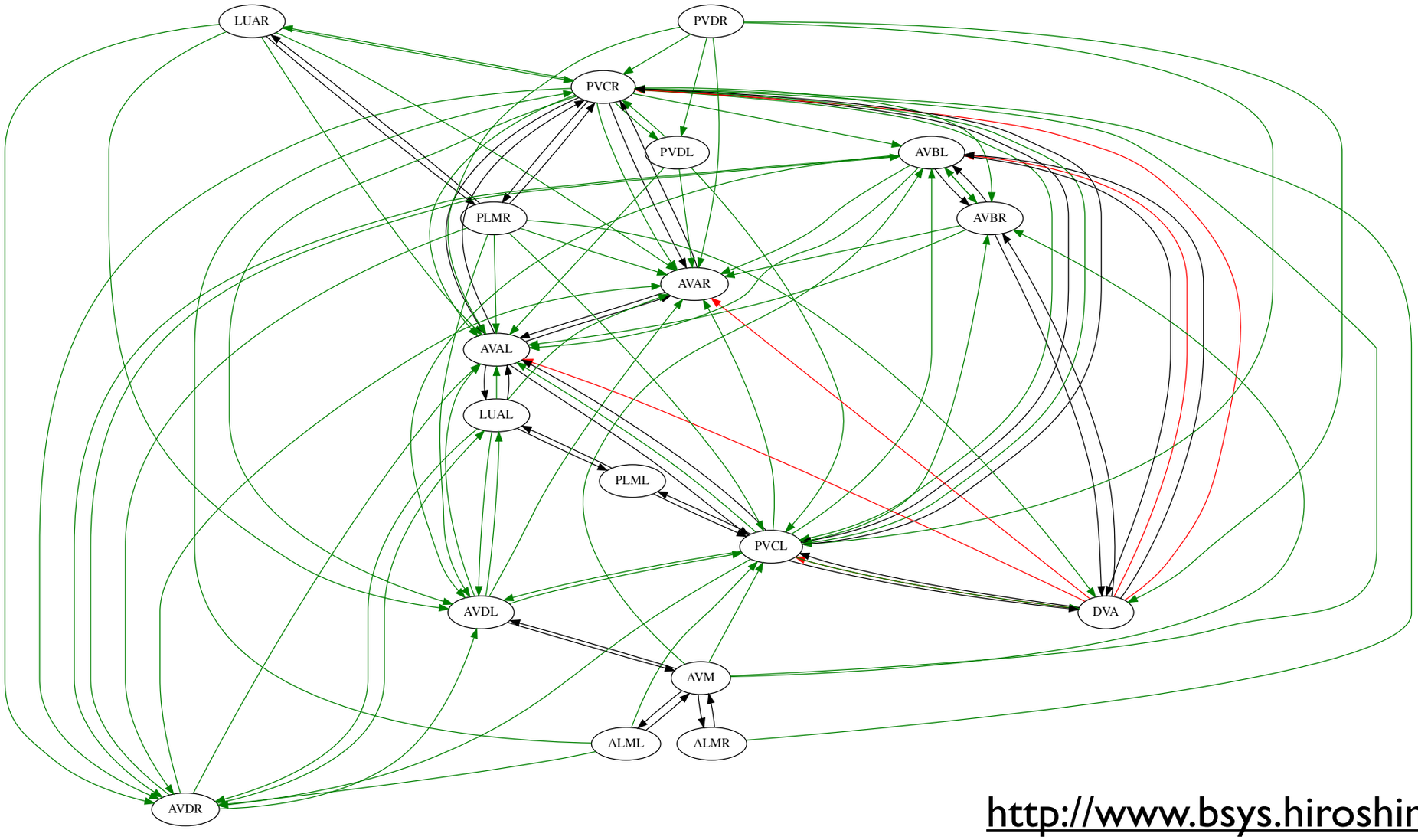


Let’s just give it a try anyway



Let's just give it a try anyway

reduce to a "classical" small sub-circuit relevant for tap-response



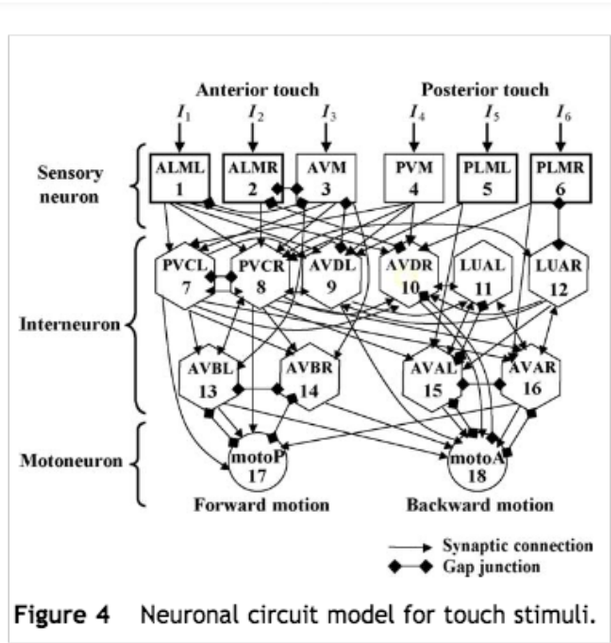
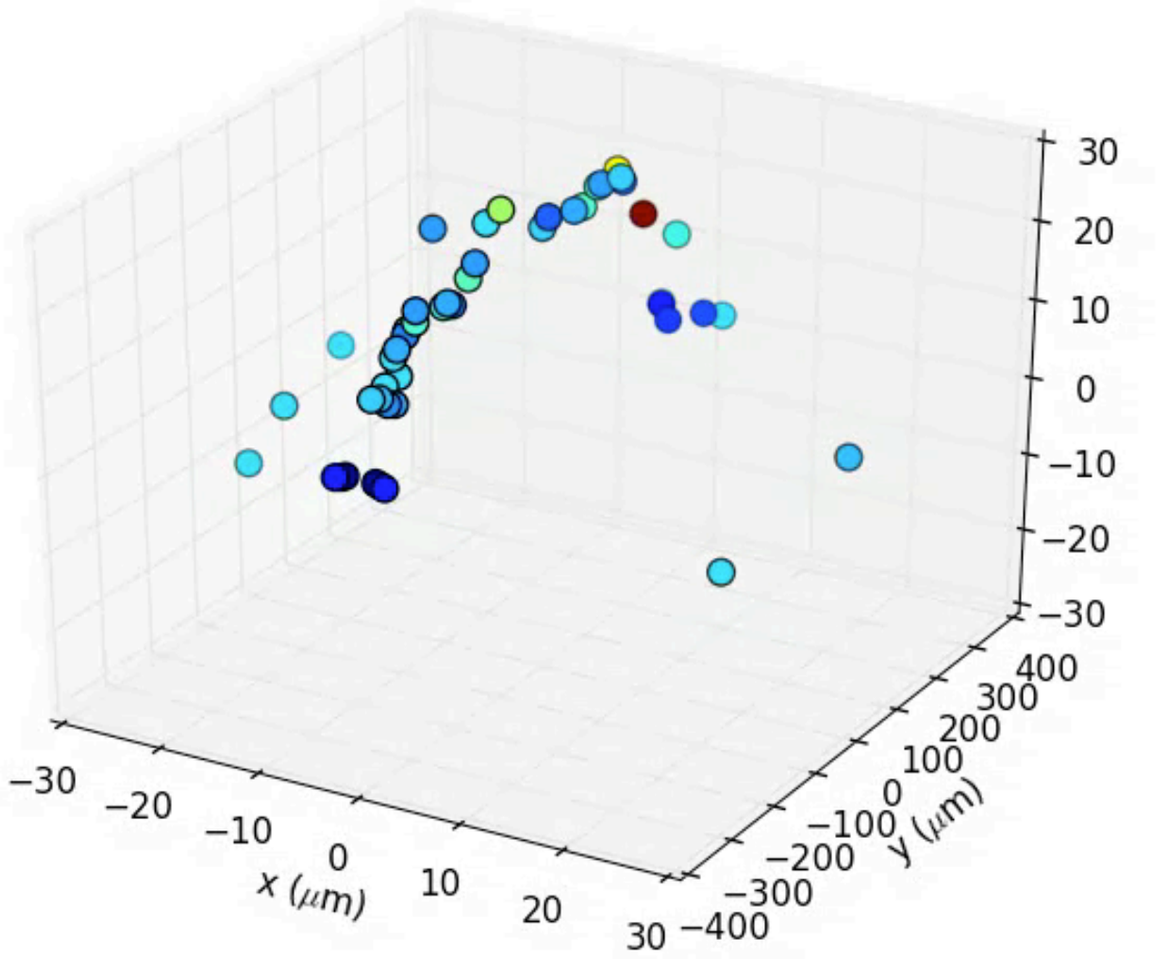


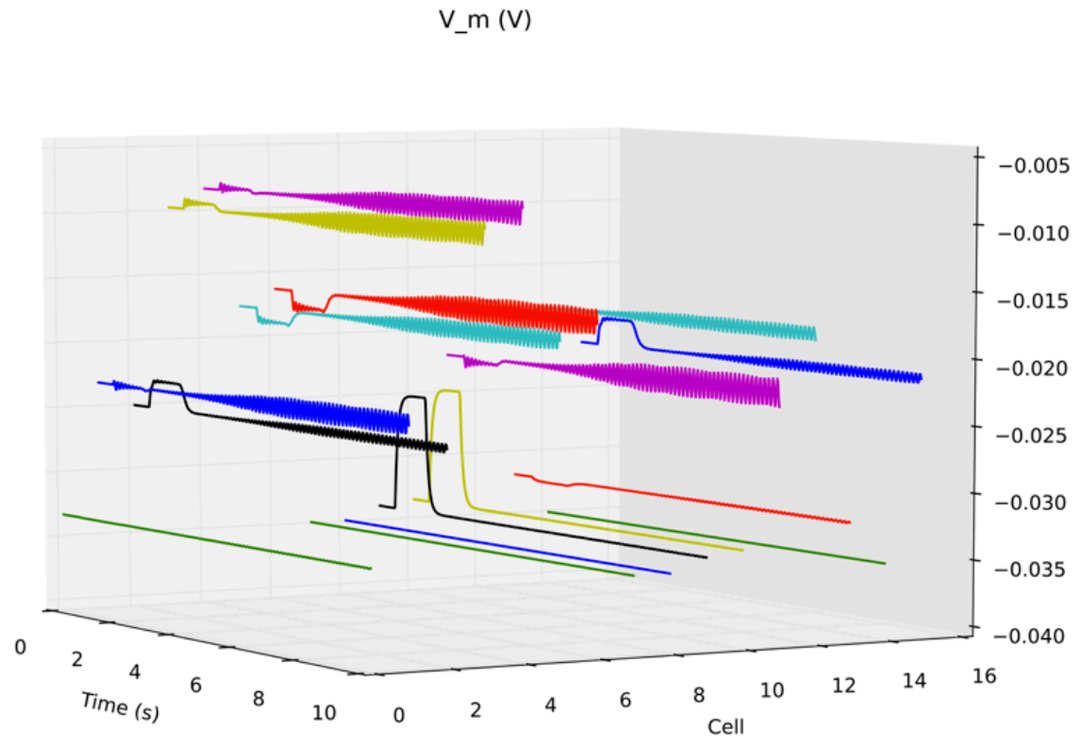
Figure 4 Neuronal circuit model for touch stimuli.

http://www.bsys.hiroshima-u.ac.jp/pub/pdf/J/J_153.pdf

Let's just give it a try anyway

Python code based on Kunert 2014 and OpenWorm





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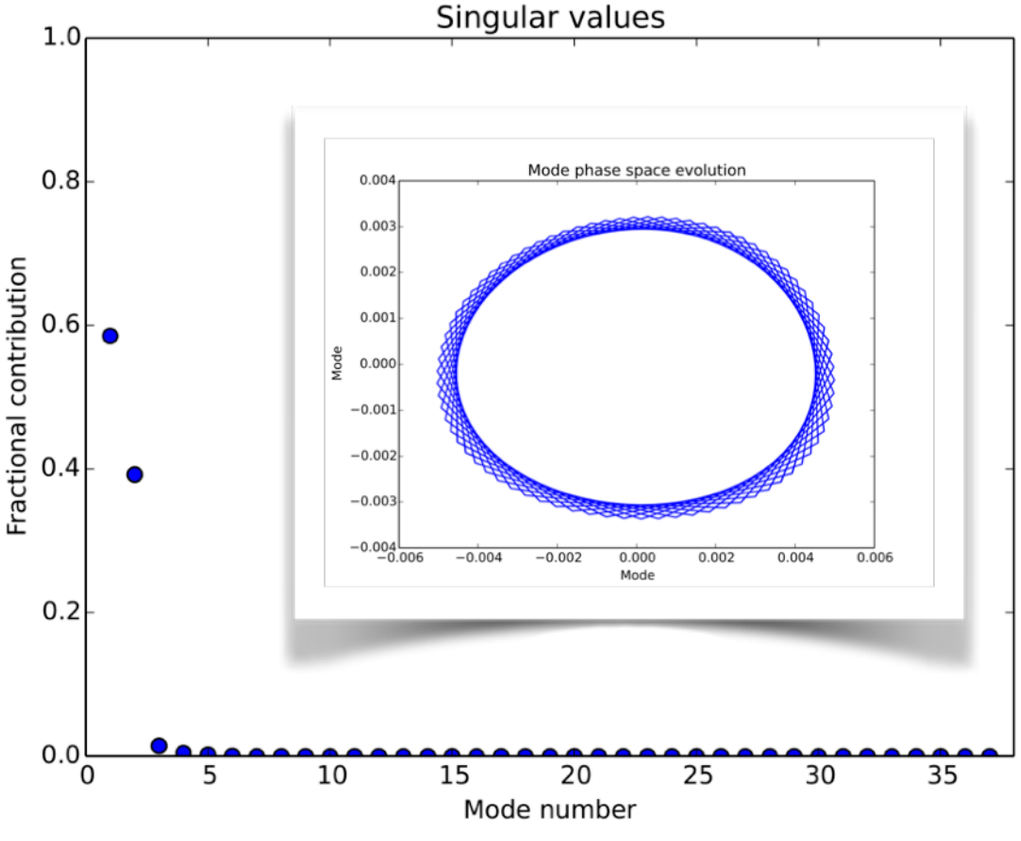
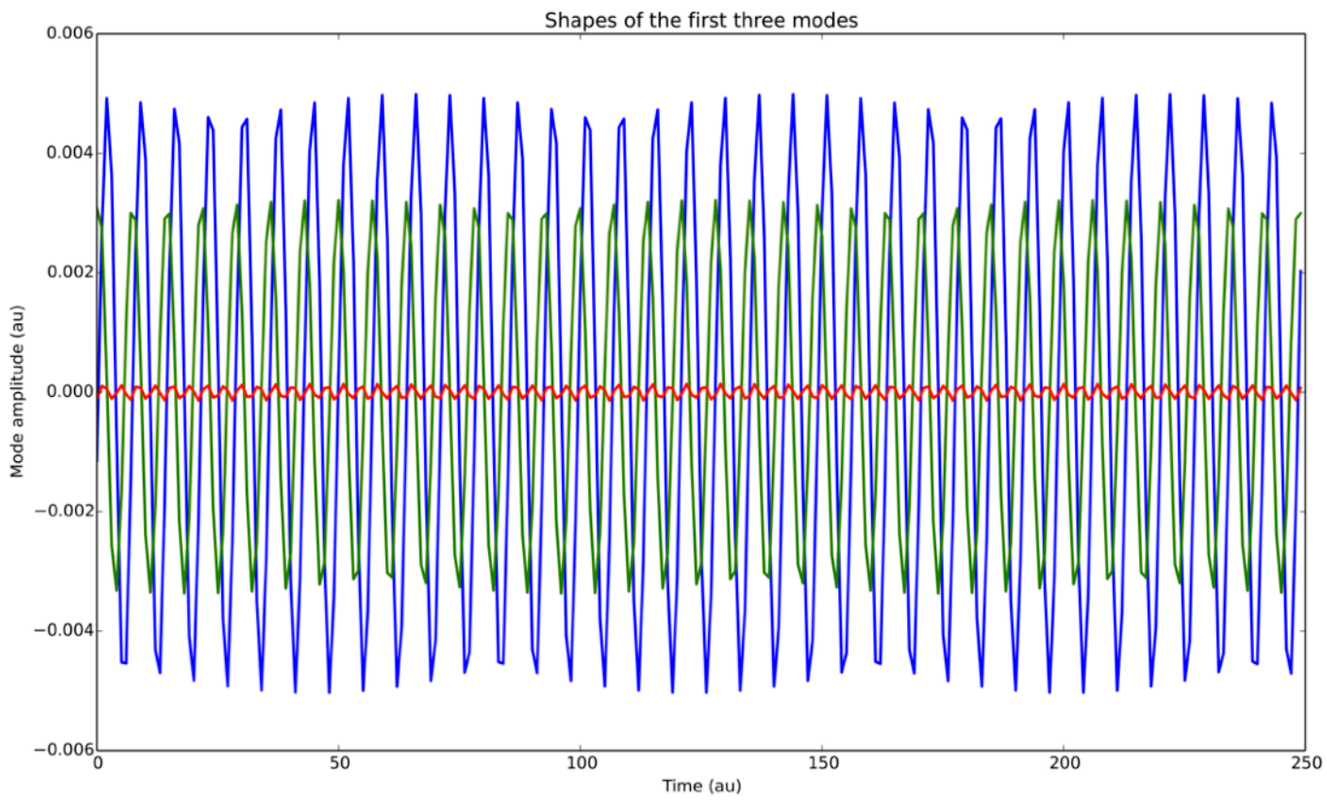




Let's just give it a try anyway

Python code based on Kunert 2014 and OpenWorm

Kunert's claim: this 2-mode oscillation is biologically significant

Behaviorally, crawling is known to be dominated by a two-mode stroke motion [2], i.e. the so-called eigenworm motion. Thus the motor-neuron response to PLM stimulation should produce a two-mode dominance in accordance with the eigenworm behavior given that the motor responses control muscle contraction [10]. We therefore intuitively anticipate that a constant input of sufficient strength, corresponding to sensory stimulus, should be able to drive two-mode oscillatory behavior in the forward motion motorneurons. To test if this is qualitatively

Let's just give it a try anyway

Python code based on Kunert 2014 and OpenWorm

Kunert's claim: this 2-mode oscillation is biologically significant

HOWEVER:

A very wide class of systems can exhibit a bifurcation leading to 2-mode oscillation: is this due to a particular feature of the connectome?

I find that the properties of this oscillation are
quite parameter-sensitive (e.g., 2-mode vs. 3-mode)

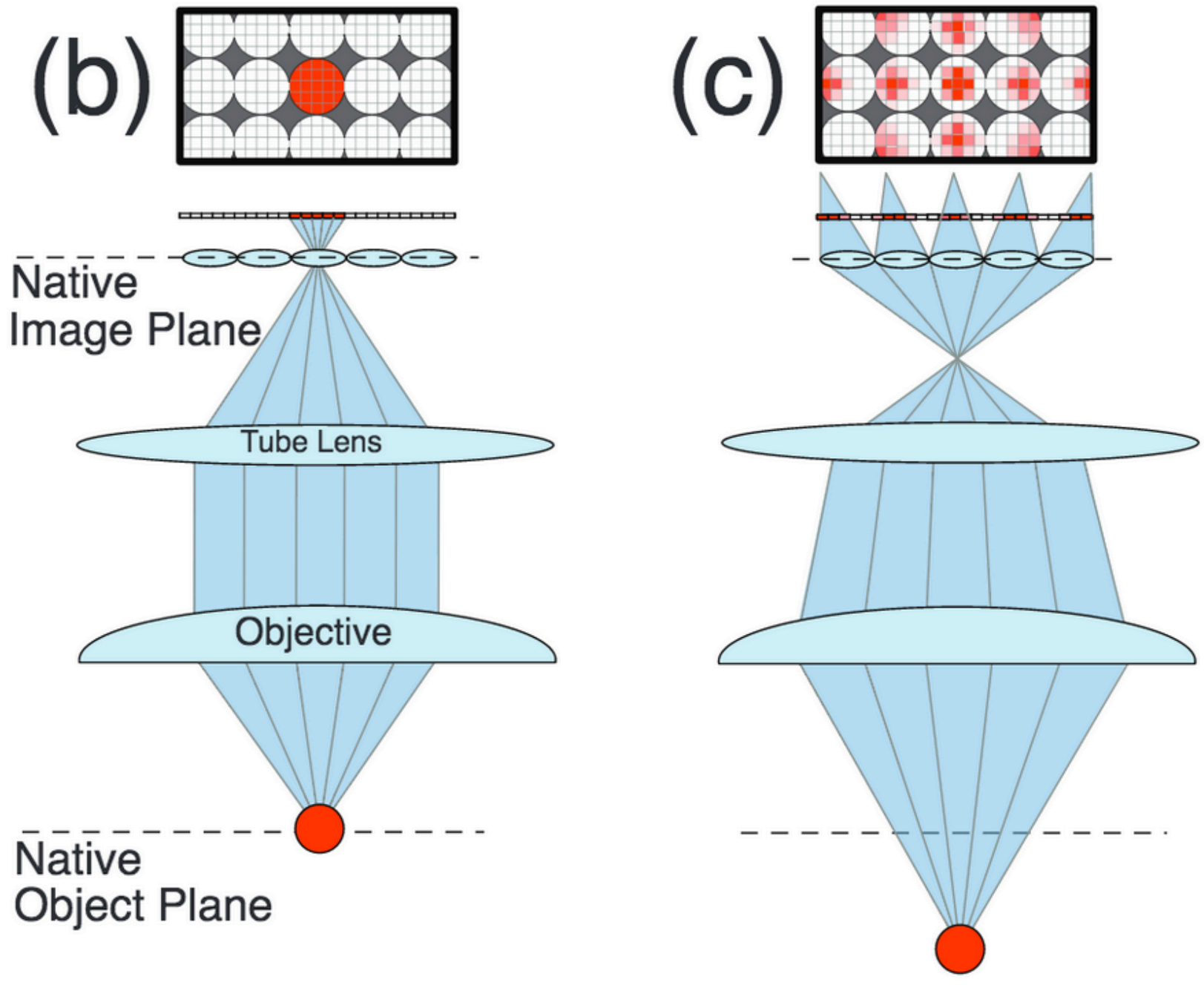
It is not clear the parameters used are realistic

I see this even in the reduced circuit: not a "whole network" property but rather a sub-circuit property?

How to obtain “ground-truth” dynamics?

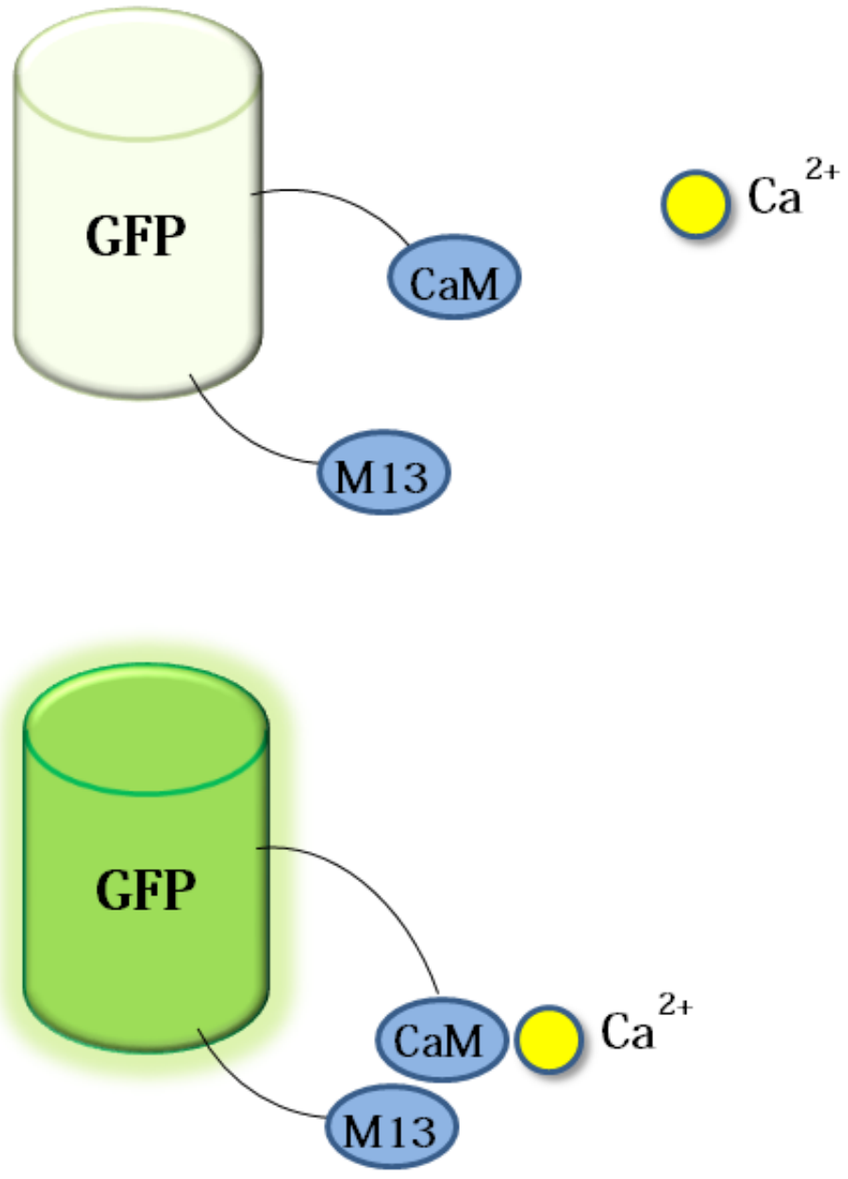
How to obtain "ground-truth" dynamics?

Light-field microscopy: 3D picture in a single 2D snapshot

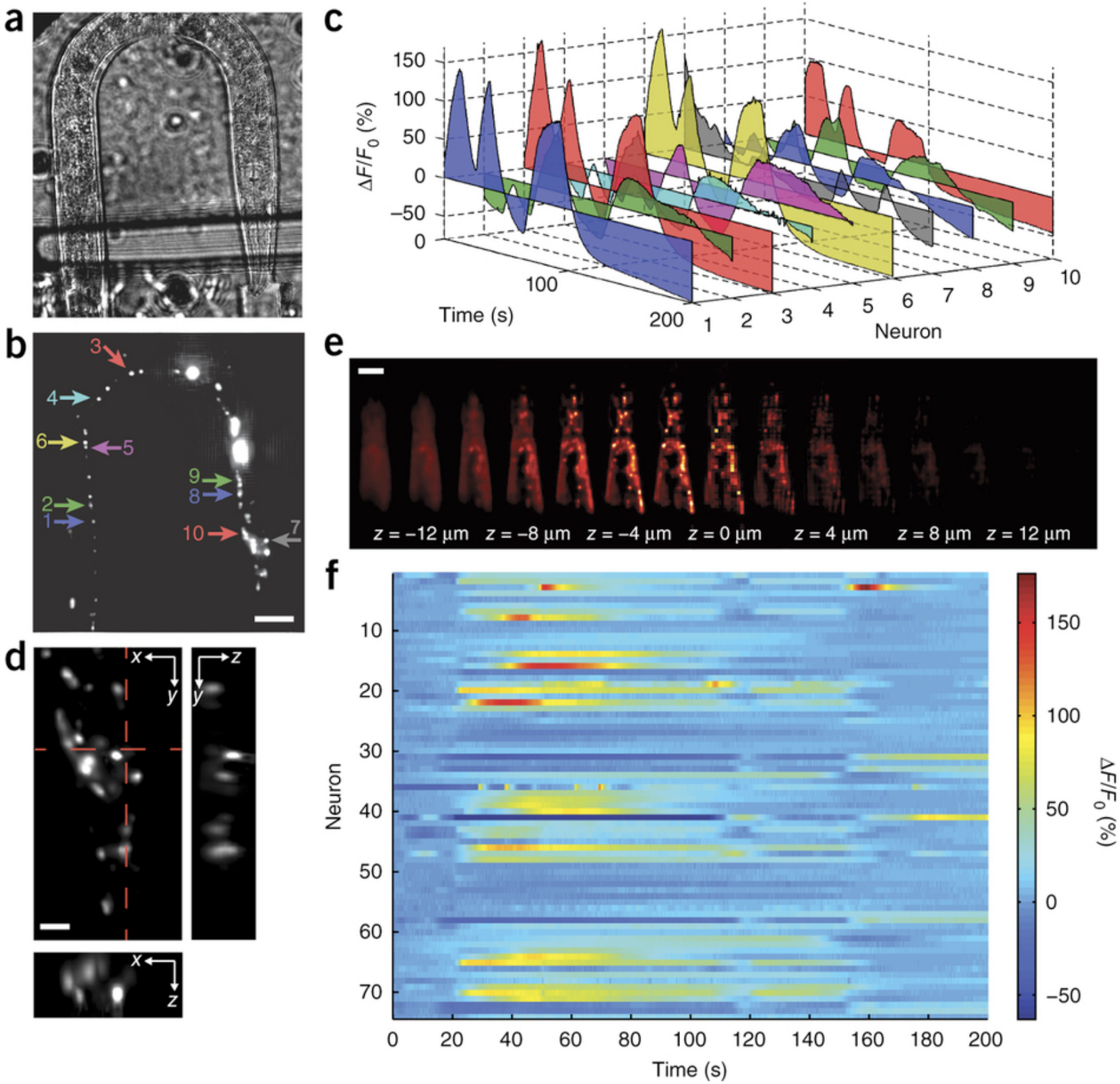


How to obtain "ground-truth" dynamics?

Genetically encoded calcium indicators (nucleus-localized)



How to obtain “ground-truth” dynamics?

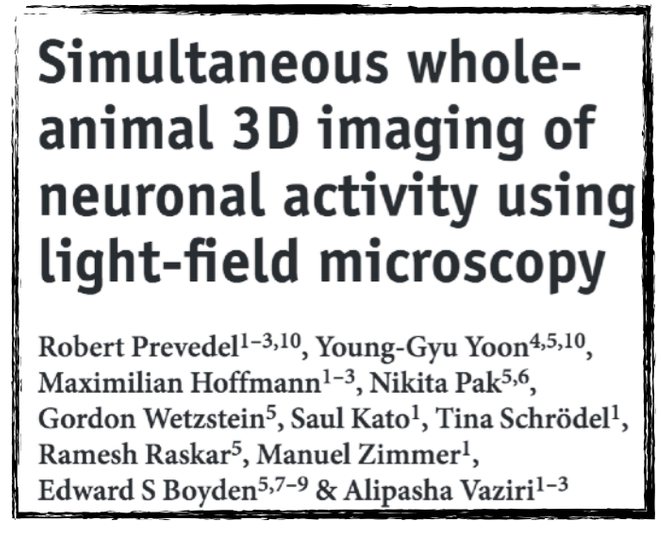


Simultaneous whole-animal 3D imaging of neuronal activity using light-field microscopy

Robert Prevedel[1–3,10], Young-Gyu Yoon[4,5,10], Maximilian Hoffmann[1–3], Nikita Pak[5,6], Gordon Wetzstein[5], Saul Kato[1], Tina Schrödel[1], Ramesh Raskar[5], Manuel Zimmer[1], Edward S Boyden[5,7–9] & Alipasha Vaziri[1–3]

How to obtain "ground-truth" dynamics?

[Switch to movie]



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How to obtain "ground-truth" dynamics?

Current targets:

Resolution improvement

Cell segmentation currently manual:

fully automatic segmentation likely needs a slight resolution boost

automatically co-register observed cells with known cell positions

Field of view improvement:

to allow imaging the *freely moving* worm

Where we want to go

Activity maps in the context of behavior:

automatically co-registered w/ known connectome

Behavior as an “index” for “meaningful” patterns

Constrain the forms of the dynamical equations:

what are the “conservation laws” of neural dynamics?