how to simulate a connectome
how to predict neural activity from neural connectivity

with advice from
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Research Campus
*Drosophila melanogaster*

- 2.5 mm
- 40-50 day lifespan
- 160,000 neurons

- brain
- ventral nerve cord

largely conserved across individuals
FAFB-FlyWire
Female
~130,000 neurons
~150m cable
Princeton, Cambridge et al
Dorkenwald et al 2023
Schlegel et al 2023

MANC
Male
~23,000 neurons
~45m cable
Janelia, Cambridge, Google
Takemura et al 2023
Marin et al 2023
Cheong et al 2023
neural activity
neural connectivity
neuron biophysics
synapse biophysics
neuromodulation

behavior

task

Macroscopic

Microscopic

neural connectivity
neuron biophysics
synapse biophysics
neuromodulation...

...
• connectomes are not sufficient
• a lot of detail
  • precise neuronal morphology
  • synapse counts, shape, size, neurotransmitter
• a lot of missing data
  • neuron biophysics, F-I curves
  • synapse biophysics, how to translate measurements (synapse counts) to synaptic strengths and time constants
Other measurements can be used to further constrain models.
Yamins, DiCarlo, …
Mante, Sussillo, Shenoy, …
Banino, Fiete, …
Yang, …
A thought experiment
Lappalainen et al 2023
Connectome + neurotransmitters

Connectivity between identified cell types

Connectivity between identified cell types in the optic lobe of the Drosophila fruit fly visual system. 

- Identified cell types: 
  - R1-R8 (retina) 
  - L1-L5, C2 (lamina, medulla intrinsic cells, CT1) 
  - Lawf, Mi1-Mi15 (t-shaped, transmedullary cells) 

- Decoded cells (putative output neurons): T4a, T5a, Tm5a, TmV15, TmV17 

- Constraints: Connectome, task, and biophysics constrained model of the fruit fly visual system.

- Lappalainen et al. 2023
Connectome, task, and single-neuron dynamics constrained DMN of the fruit fly visual system.

Connectivity between identified cell types:

- Lamina, medulla intrinsic cells, CT1
- Postsynaptic
- Presynaptic

Visual video rendering of the fly eye retinal field.

Constraints:
- Connectome + neurotransmitters
- Task optimization
- Match?

Passive point neuron

\[ \tau_{t_i} \dot{V}_i = -V_i + \sum_j s_{ij} + V_{rest} \]

resting membrane potential

Lappalainen et al. 2023
Passive point neuron

\[ \tau_{ti} \frac{d V_i}{dt} = -V_i + \sum_j s_{ij} + V_{i_{\text{rest}}} \]

Current-based synapse

\[ s_{ij} = \omega_{ij} f(V_j) \]

with connectome, just 734 free parameters

without connectome, \( \sim 400,000 \) parameters

Lappalainen et al. 2023
Passive point neuron

\[ \tau_{t_i} \dot{V}_i = -V_i + \sum_j s_{ij} + V^\text{rest}_{t_i} \]

Current-based synapse

\[ s_{ij} = w_{ij} f(V_j) \]

Connectome-constrained weight

\[ w_{ij} = \alpha_{t_i t_j} \sigma_{t_i t_j} N_{t_i t_j, u_i - u_j, v_i - v_j} \]

| \( t_i \) | cell type of neuron \( i \) |
| \( u_i, v_i \) | retinotopic coordinates of neuron \( i \) (hexagonal lattice) |

unitary synaptic strength

sign of connection

number of synapses
Passive point neuron
\[ \tau_{ti} \dot{V}_i = -V_i + \sum_j s_{ij} + V_{i \text{rest}} \]

Current-based synapse
\[ s_{ij} = \omega_{ij} f(V_j) \]

Connectome-constrained weight
\[ \omega_{ij} = \alpha_{ti} \sigma_{t_i t_j} N_{t_i t_j, u_i - u_j, v_i - v_j} \]

with connectome, just 734 free parameters
without connectome, ~400,000 parameters

<table>
<thead>
<tr>
<th>time constant</th>
<th>resting membrane potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>unitary synaptic strength</td>
<td>sign of connection number of synapses</td>
</tr>
<tr>
<td>( t_i ) cell type of neuron ( i )</td>
<td></td>
</tr>
<tr>
<td>( u_i, v_i ) retinotopic coordinates of neuron ( i ) (hexagonal lattice)</td>
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</tr>
</tbody>
</table>

Lappalainen et al. 2023
• Deep mechanistic network model of the motion pathways of the fruit fly visual system
• Every simulated neuron and synapse corresponds to a real neuron and synapse
• 64 cell types, 45K neurons, unknown biophysical parameters
Not this

But this
• connectome + biophysics + task optimization = neural activity?
Responses to single ommatidium flashes broadly recapitulate known ON vs OFF contrast preference of most cell types.

<table>
<thead>
<tr>
<th>T4 inputs</th>
<th>T5 inputs</th>
<th>lamina cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mi1</td>
<td>Tm1</td>
<td>L1</td>
</tr>
<tr>
<td>Tm3</td>
<td>Tm2</td>
<td>L2</td>
</tr>
<tr>
<td>Mi4</td>
<td>Mi9</td>
<td>L3</td>
</tr>
<tr>
<td>CT1(M10)</td>
<td>CT1(Lo1)</td>
<td>L4</td>
</tr>
</tbody>
</table>

The graph illustrates the activity (a.u.) of different cell types in response to single ommatidium flashes. The colors (blue and red) indicate known ON-selective and OFF-selective cell types, respectively. The time scale is 100ms.
best model correctly recapitulates experimentally known direction selectivity of T4 and T5 sub types to 4 cardinal directions

Lappalainen et al. 2023
preferred direction enhancement and null direction suppression in agreement with Gruntman et al 2018
preferred direction enhancement and null direction suppression in agreement with Gruntman et al 2018

Lappalainen et al. 2023
Predicted on-motion and off-motion tuning across best task-performing models of retina lamina, medulla intrinsic cells, CT1 known off-motion selective cells and on-motion t-shaped, transmedullary cells.

Ensemble statistics and clustering to assess finite predictions of neural tuning.

Clustering of natural stimuli responses discovers performance related tuning motifs.

Quantify statistics with UMAP and cluster models of synthetic stimuli and natural stimuli responses.

Initial parameters of biophysical models include\[ \tau_{t_i}, \alpha_{t_i,t_j}, V_{t_i}^{rest} \].

Connectome constraints.

50 untrained models task training 50 trained models.
Segregation into ON and OFF pathways well predicted
models predict known motion selectivity in T4 + T5 neurons
exploring the solution space

T4c responses to naturalistic stimuli cluster the ensemble

Lappalainen et al. 2023
Switching Mi4 and Mi preferred contrasts leads to directionally opposite motion tuning in T4
can use model to discover optimal stimuli for all neuron types
when are connectomic constraints sufficiently strong?

A true-network and simulated-network framework to investigate the role of sparse connectivity. True network and simulated network recover function better.

Sridhama Prakhya

Lappalainen et al. 2023
when are connectomic constraints sufficiently strong?

A true-network and simulated-network framework to investigate the role of sparse connectivity and unknown strength. Lappalainen et al. 2023
when are connectomic constraints sufficiently strong?

A true-network and simulated-network framework to investigate the role of sparse connectivity measurements. The correlation of response tuning of the same neurons for stimuli response (a.u.) correlation of response tuning of the same neurons: 0.8. Input stimuli '5'

Sridhama Prakhya

Lappalainen et al. 2023
when are connectomic constraints sufficiently strong?

A true-network and simulated-network framework to investigate the role of sparse connectivity measurements. The correlation of response tuning of the same neurons: 0.8.

Sridhama Prakhya

Lappalainen et al. 2023
correlation of response tuning

connectivity percentage

0.0
0.2
0.4
0.6
0.8
1.0
10 20 50 80 100

known connectivity and known strength

known connectivity and unknown strength

sparse + structured connectivity in the connectome constrains models strongly
Connectome + Circuit-level function —> neural activity
Other possible constraints: neural activity, behavior.
Whole brain (big model)

Behavior (big data)

Neural activity

Connectome (big data)

Biophysics
sensory system

- Vision
- Vestibular: Velocity, Acceleration, Gyro, Orientation in space
- Proprioception: Body/leg/wing posture, Actuator activation
- Contact

“brain”

motor commands out

actuation system

- Actuators

Roman Vaxenburg
Whole body (big model)

Behavior (big data)

Whole brain (big model)

Neural activity

Connectome (big data)

Biophysics

Speiser et al 2017
Aitchison et al 2017
Tschopp et al 2018
Mi et al 2021
Lappalainen et al 2023
Vaxenburg et al (in prep)
thanks

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Connectivity between identified cell types
Optic lobe of the Drosophila retinotopic hexagonal lattice columnar organization
Convolutional filters (anatomical connectivity)
Constraints
Connectome, task, and biophysics constrained model of the fruit fly visual system

motion decoder
decoded cells (putative output neurons)
fly eye rendering

0° 60° 120° -110.0 -70.0 -20.0 20.0 70.0 120.0

synapses
pre
post
home column
L1-L5
R1-R8
Lawf
T1
T2
T3
T4
tm
Mi

light

retina
lamina
t

medulla
lobula
lobula plate
central brain

10μm

...