how to simulate a connectome

how to predict neural activity from neural connectivity

with advice from

Nathan Klapoetke
Lou Scheffer
Michael Reiser
James Fitzgerald
Axel Borst
Damon Clark

Janne Lappalainen

Fabian Tschopp
Mason McGill
Sridhama Prakhya

Jakob Macke

Shin-ya Takemura
Kazunori Shinomiya
Aljoscha Nern
Eyal Gruntman

Join us!

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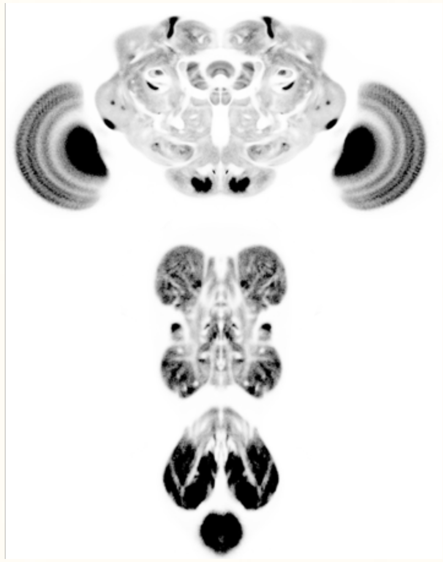
Drosophila melanogaster
2.5 mm
40-50 day lifespan

160,000 neurons

brain

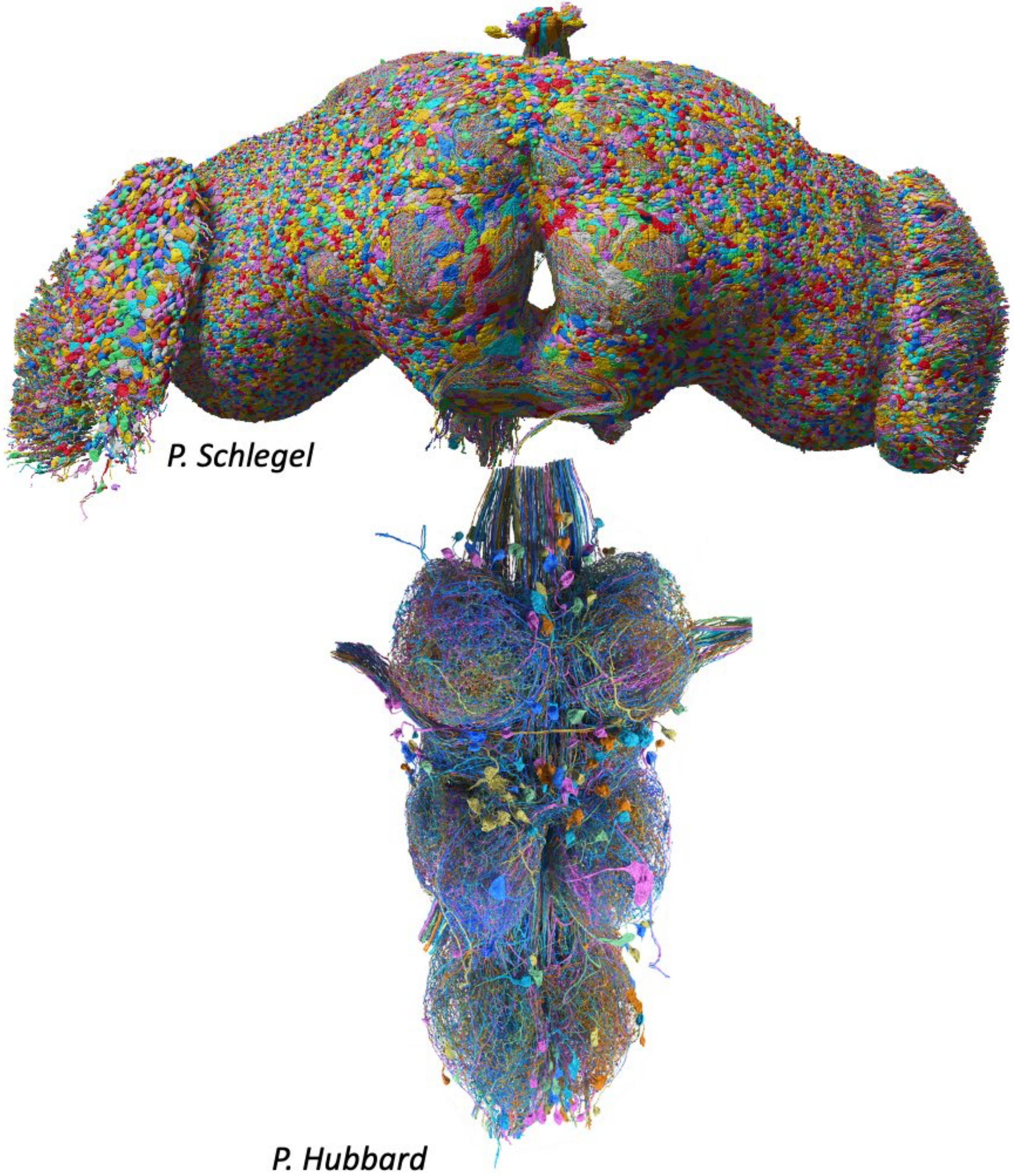
ventral
nerve
cord



largely conserved
across individuals

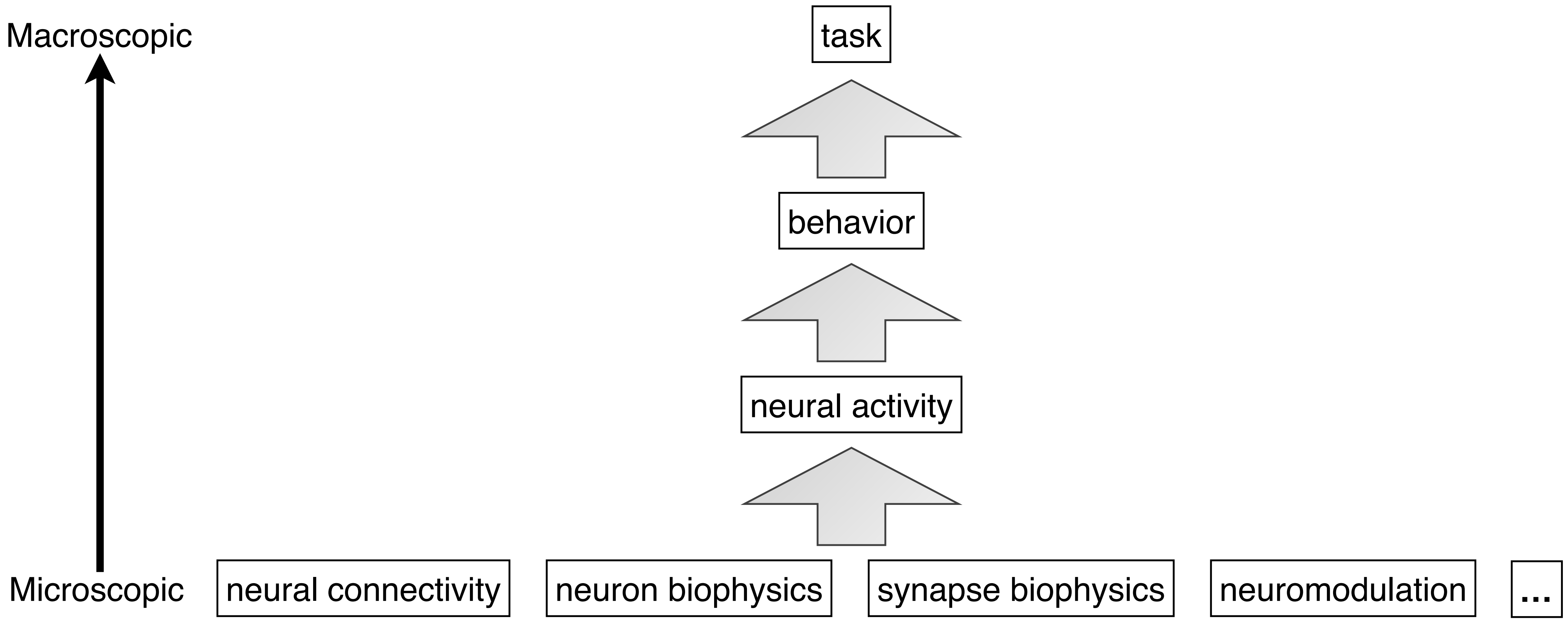
brain

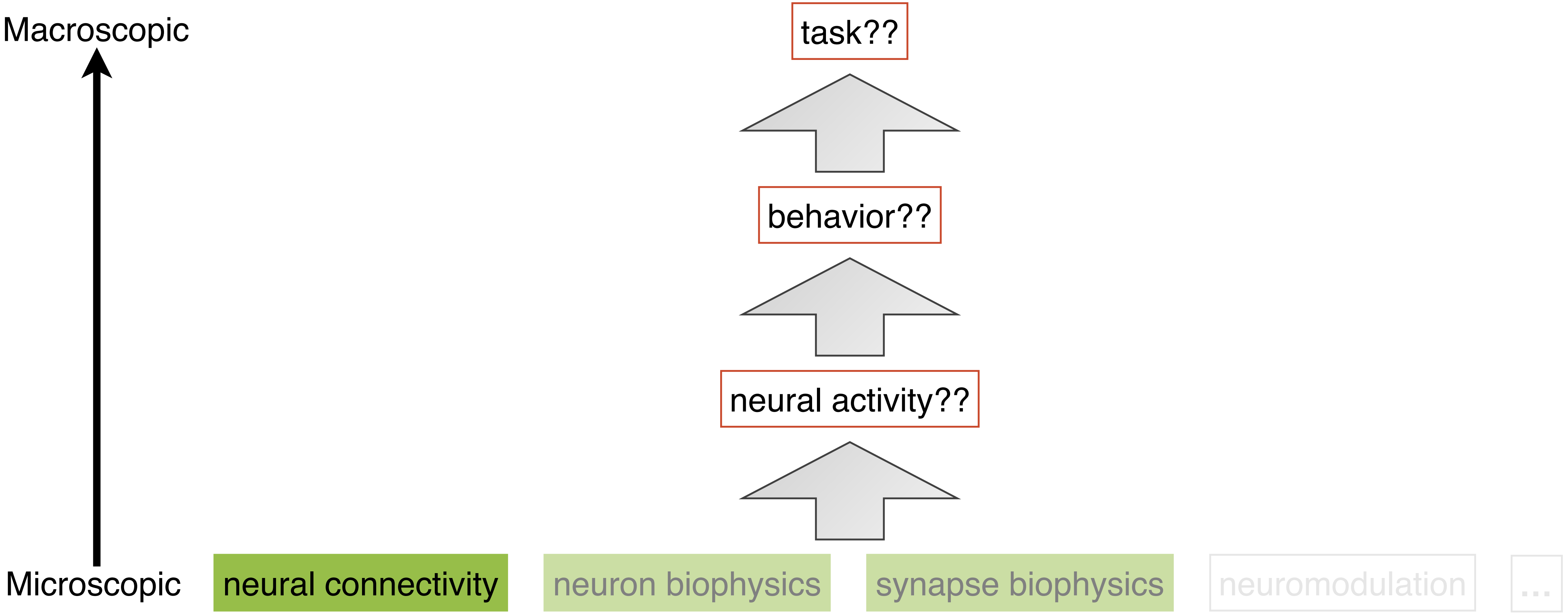
ventral
nerve
cord



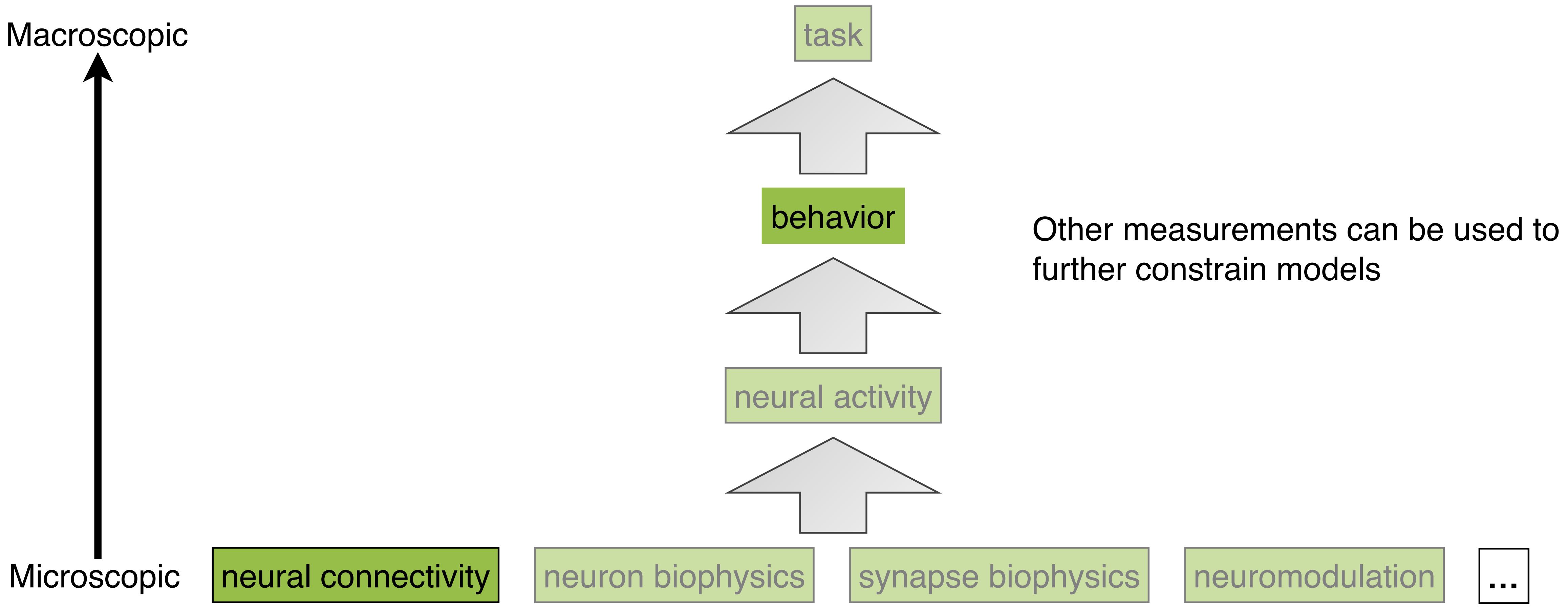
FAFB-FlyWire
Female
~130,000 neurons
~150m cable
Princeton, Cambridge et al
Dorkenwald et al 2023
Schlegel et al 2023

MANC
Male
~23,000 neurons
~45m cable
Janelia, Cambridge, Google
Takemura et al 2023
Marin et al 2023
Cheong et al 2023


Macroscopic
task
behavior
neural activity
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


Macroscopic
Microscopic
task
behavior
neural activity
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neuron biophysics
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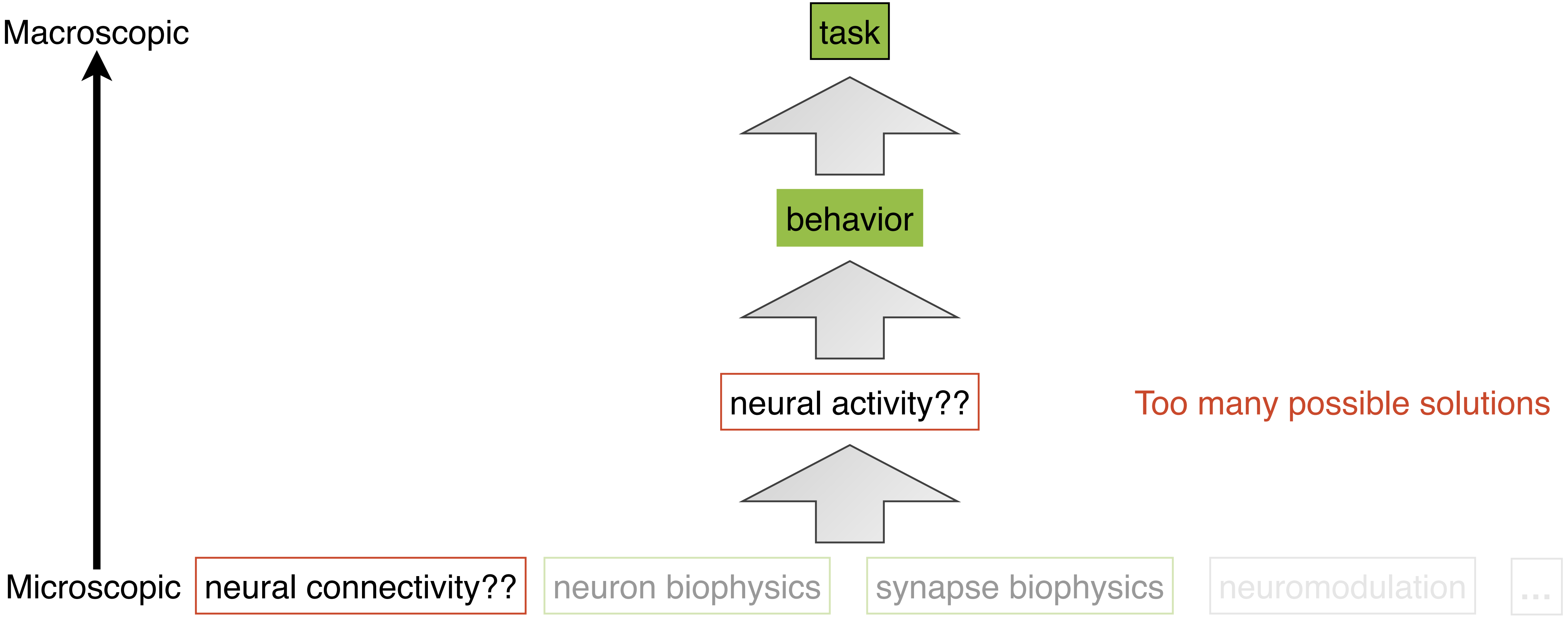
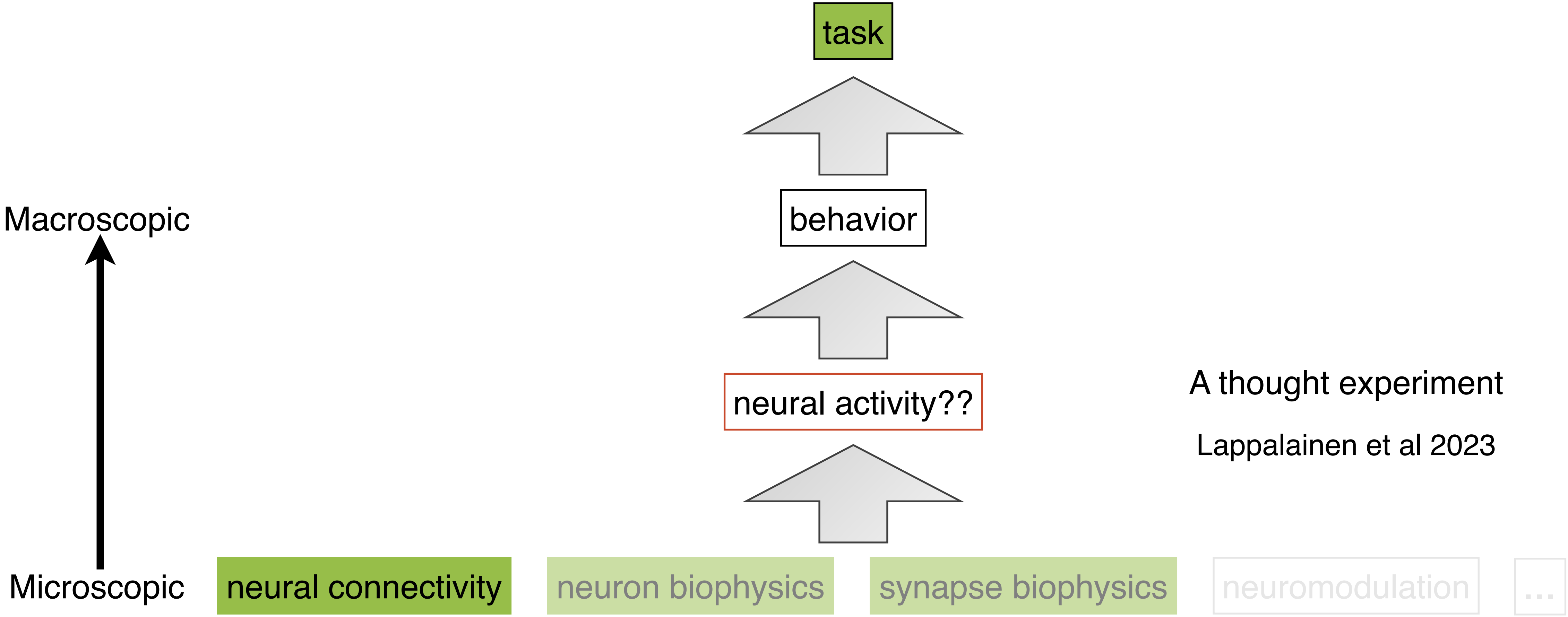
...
Other measurements can be used to further constrain models

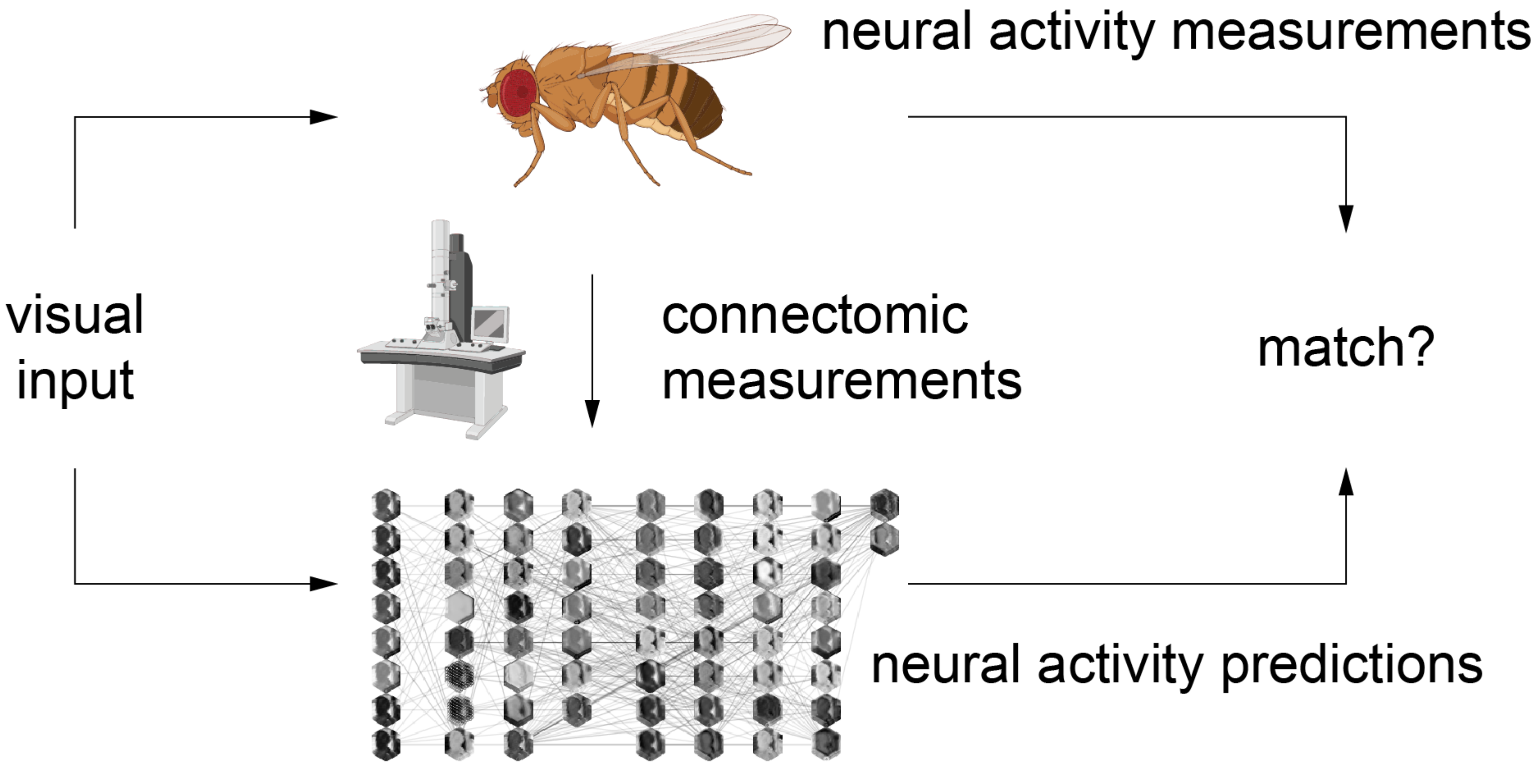


Yamins, DiCarlo, …
Mante, Sussillo, Shenoy, …
Banino, Fiete, …
Yang, …



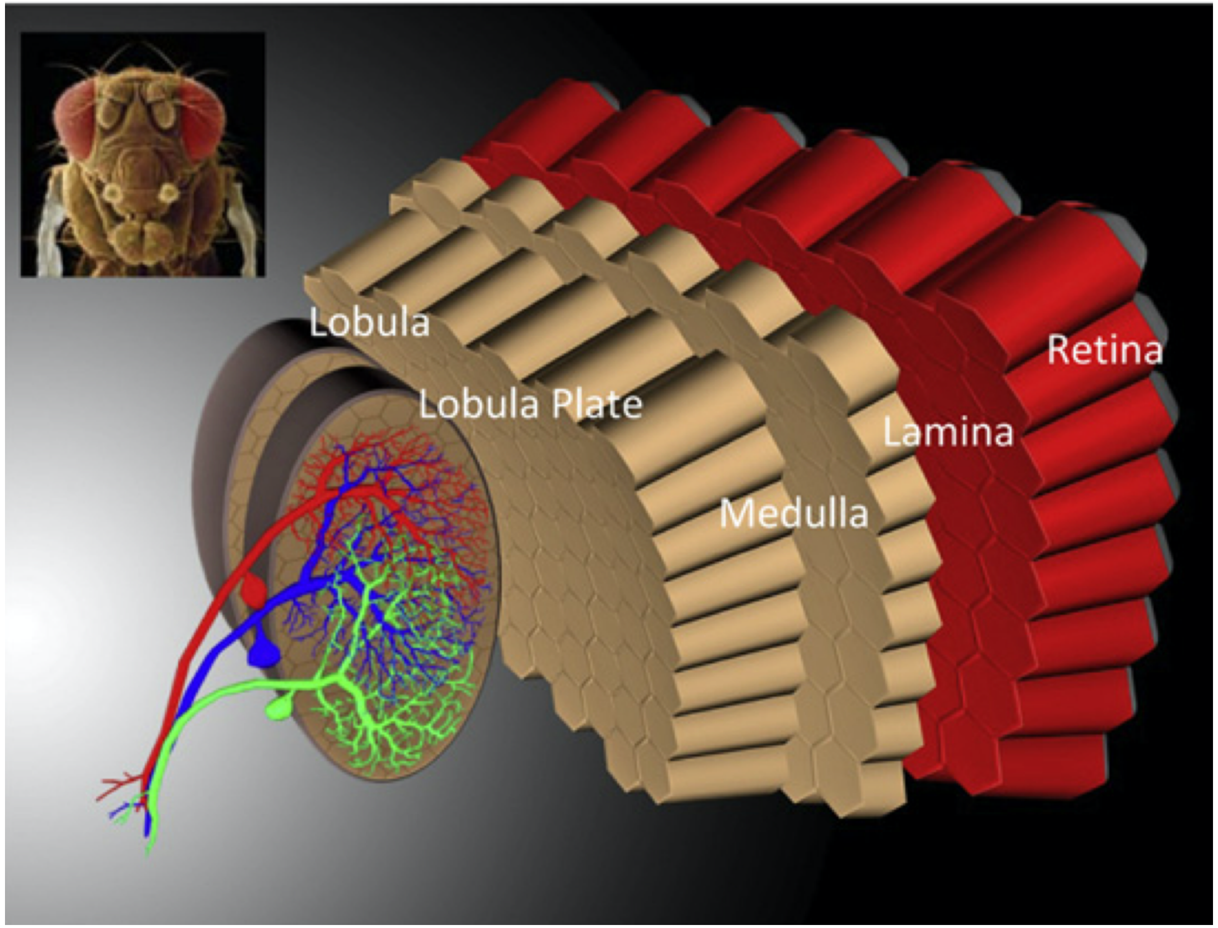
A thought experiment

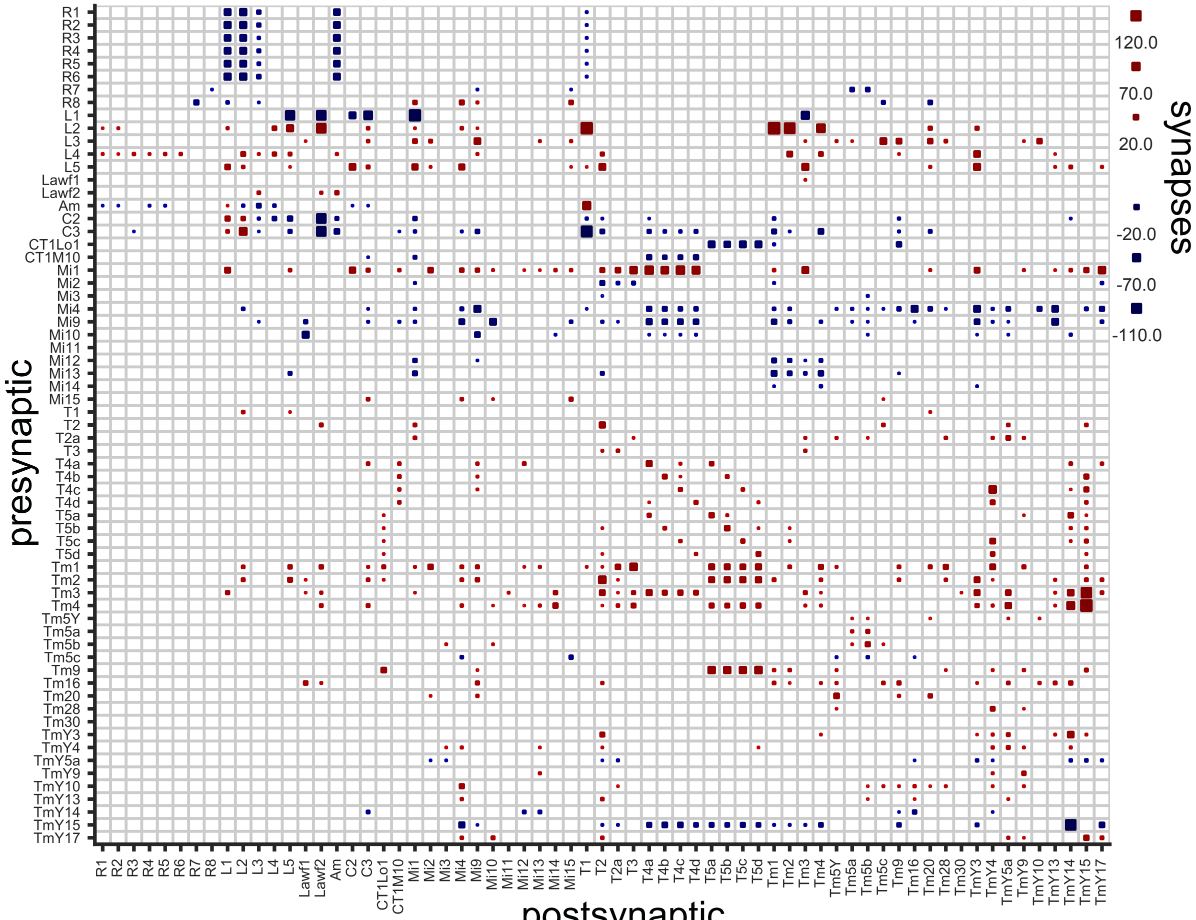
Lappalainen et al 2023



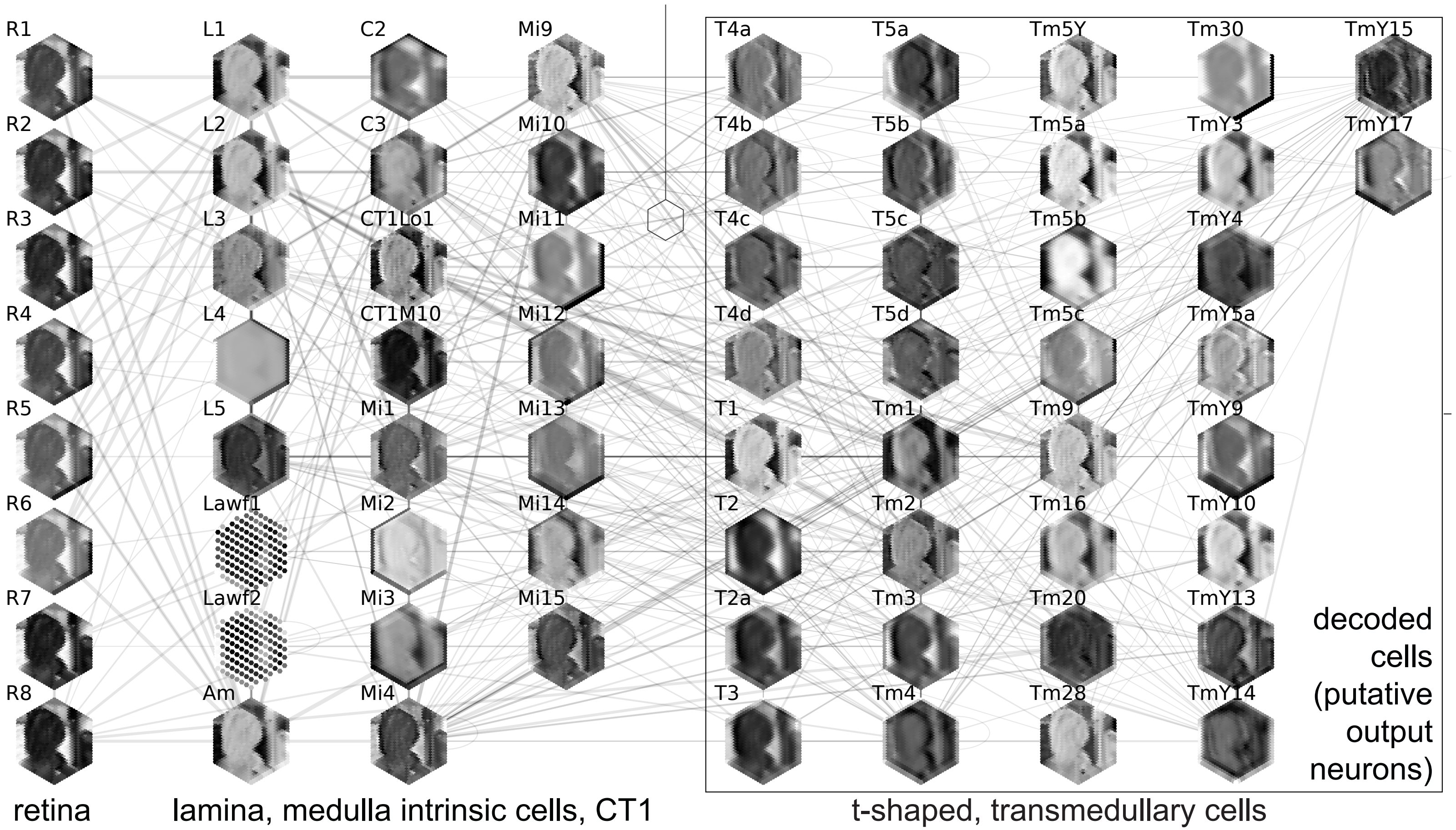
Lappalainen et al. 2023

connectome + neurotransmitters





Janelia FlyEM, Rivera-Alba et al. 2011, Takemura et al. 2013, 2015, 2017, Shinomiya et al. 2019, Davis et al. 2020



Lappalainen et al 2023

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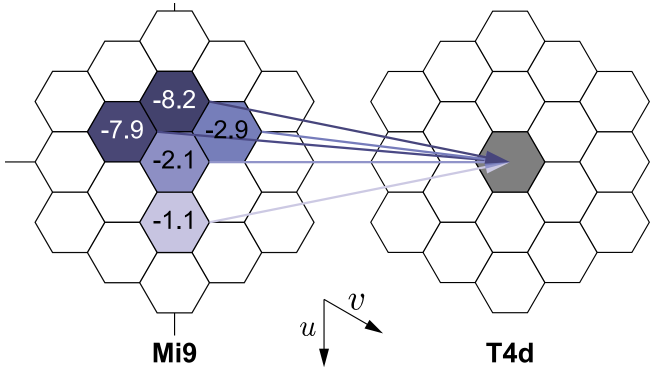

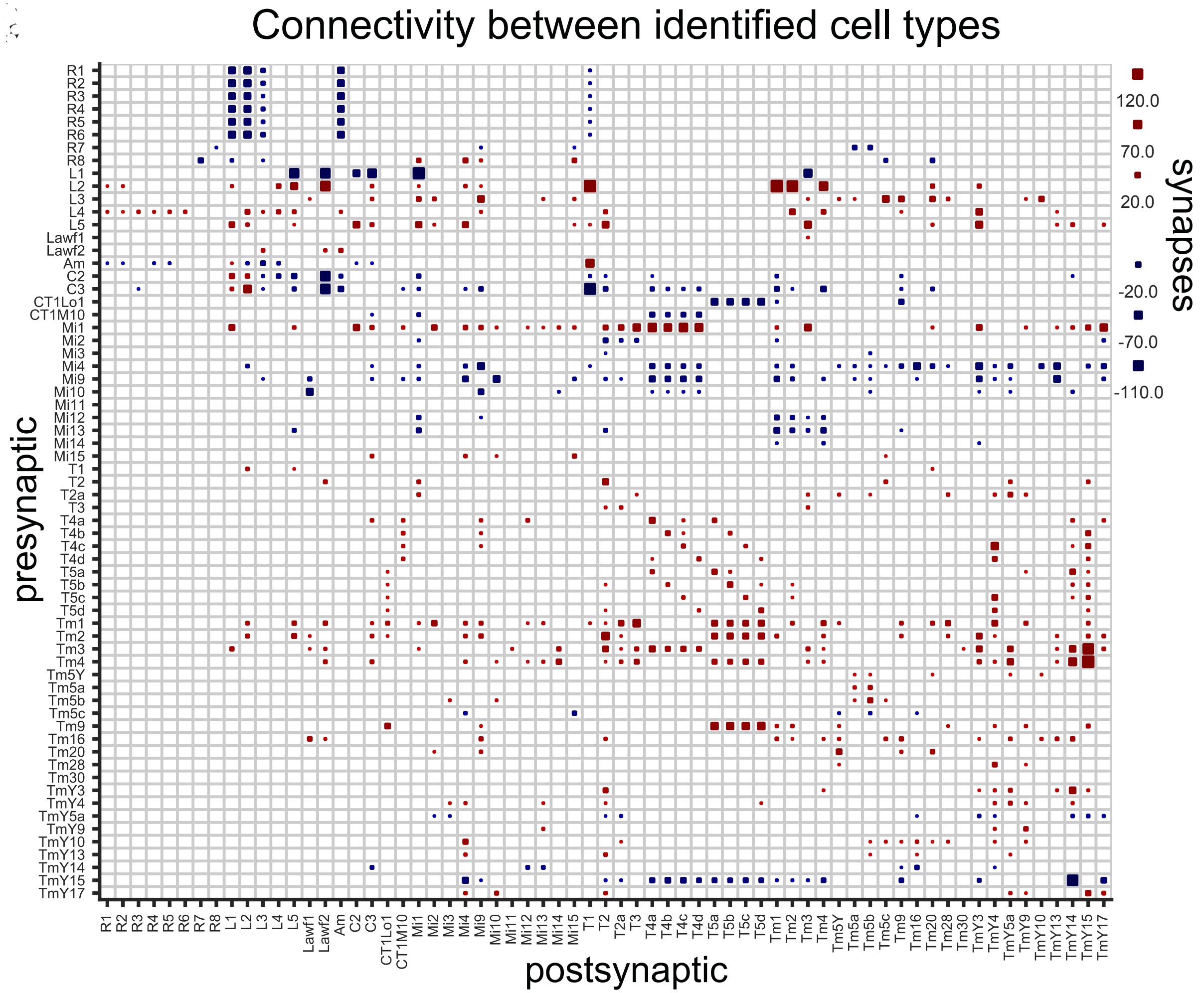

Janelia FlyEM, Rivera-Alba et al. 2011, Takemura et al. 2013, 2015, 2017, Shinomiya et al. 2019, Davis et al. 2020

Passive point neuron

time constant

$$\tau_{t_i} \dot{V}_i = -V_i + \Sigma_j s_{ij} + V_{t_i}^{\text{rest}}$$

resting membrane potential

Lappalainen et al. 2023

Passive point neuron

time constant

$$\tau_{t_i} \dot{V}_i = -V_i + \Sigma_j s_{ij} + V_{t_i}^{\text{rest}}$$

resting membrane potential

Current-based synapse

$$s_{ij} = w_{ij} f(V_j)$$

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

Lappalainen et al. 2023

Passive point neuron — time constant

$$\tau_{t_i}\dot{V}_i = -V_i + \Sigma_j s_{ij} + V_{t_i}^{\text{rest}}$$

resting membrane potential

Current-based synapse

$$s_{ij} = w_{ij} f(V_j)$$

Connectome-constrained weight

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

unitary synaptic strength

sign of connection
number of synapses

t_i cell type of neuron i

u_i v_i retinotopic coordinates of neuron i (hexagonal lattice)

Lappalainen et al. 2023

Passive point neuron — time constant

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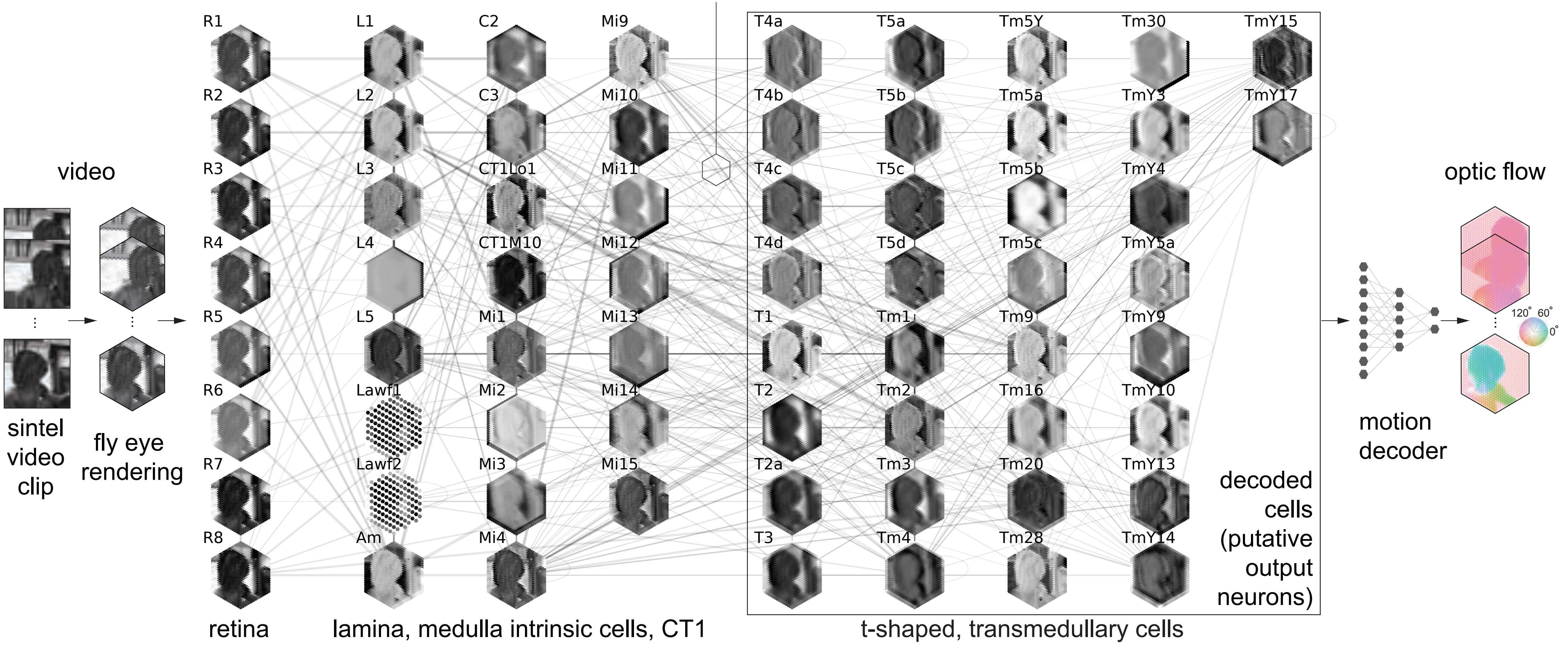
with connectome, just 734 free parameters
without connectome, ~400,000 parameters

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



Lappalainen et al 2023

Not this

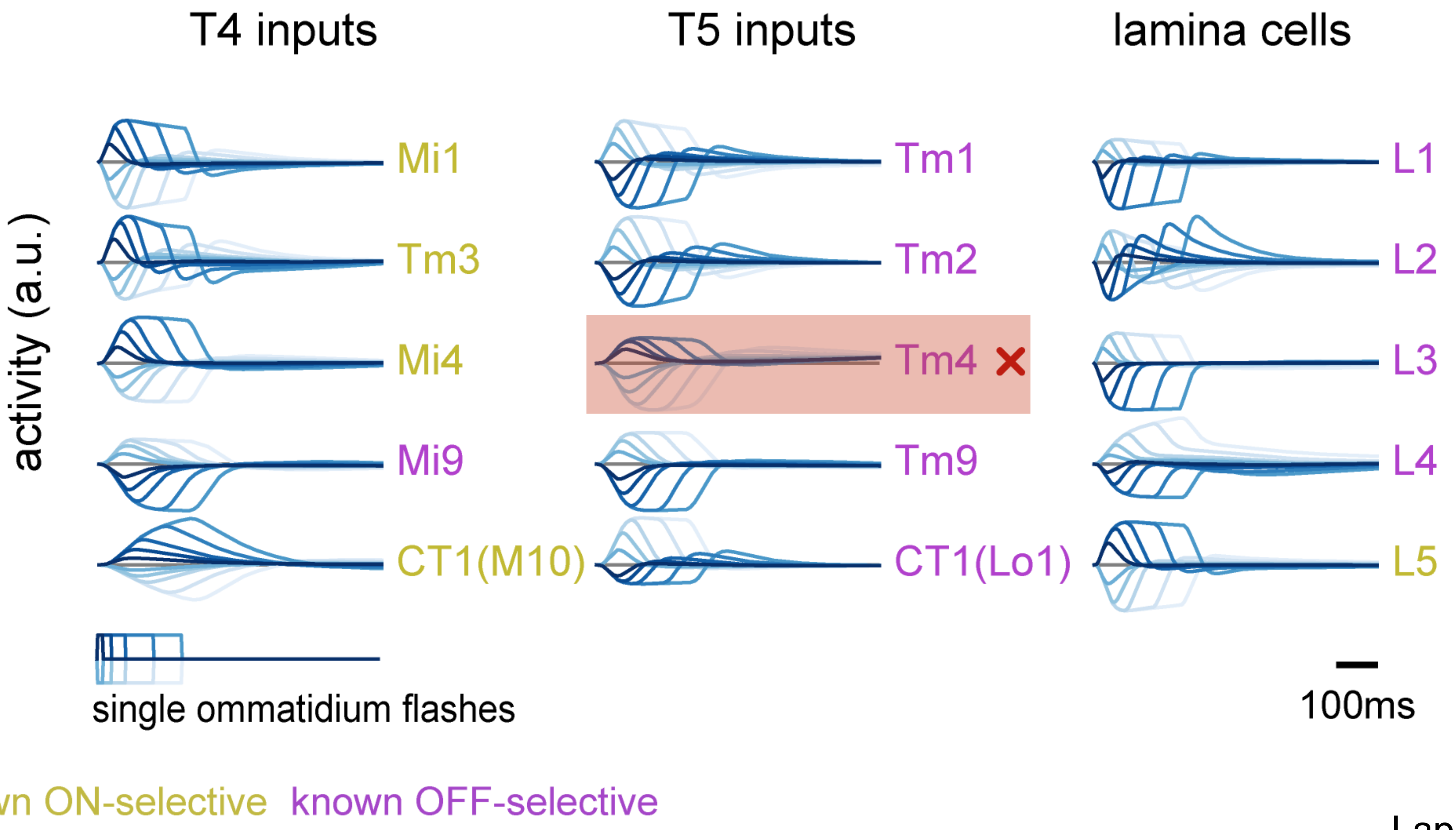
But this

https://readv3.com/2019/12/frank-murphy-marble-hero/

https://www.cnn.com/style/article/sphinx-shrine-discovery-egypt-scn-scli-intl/index.html

- connectome + biophysics + task optimization = neural activity?

Responses to single ommatidium flashes broadly recapitulate known ON vs OFF contrast preference of most cell types



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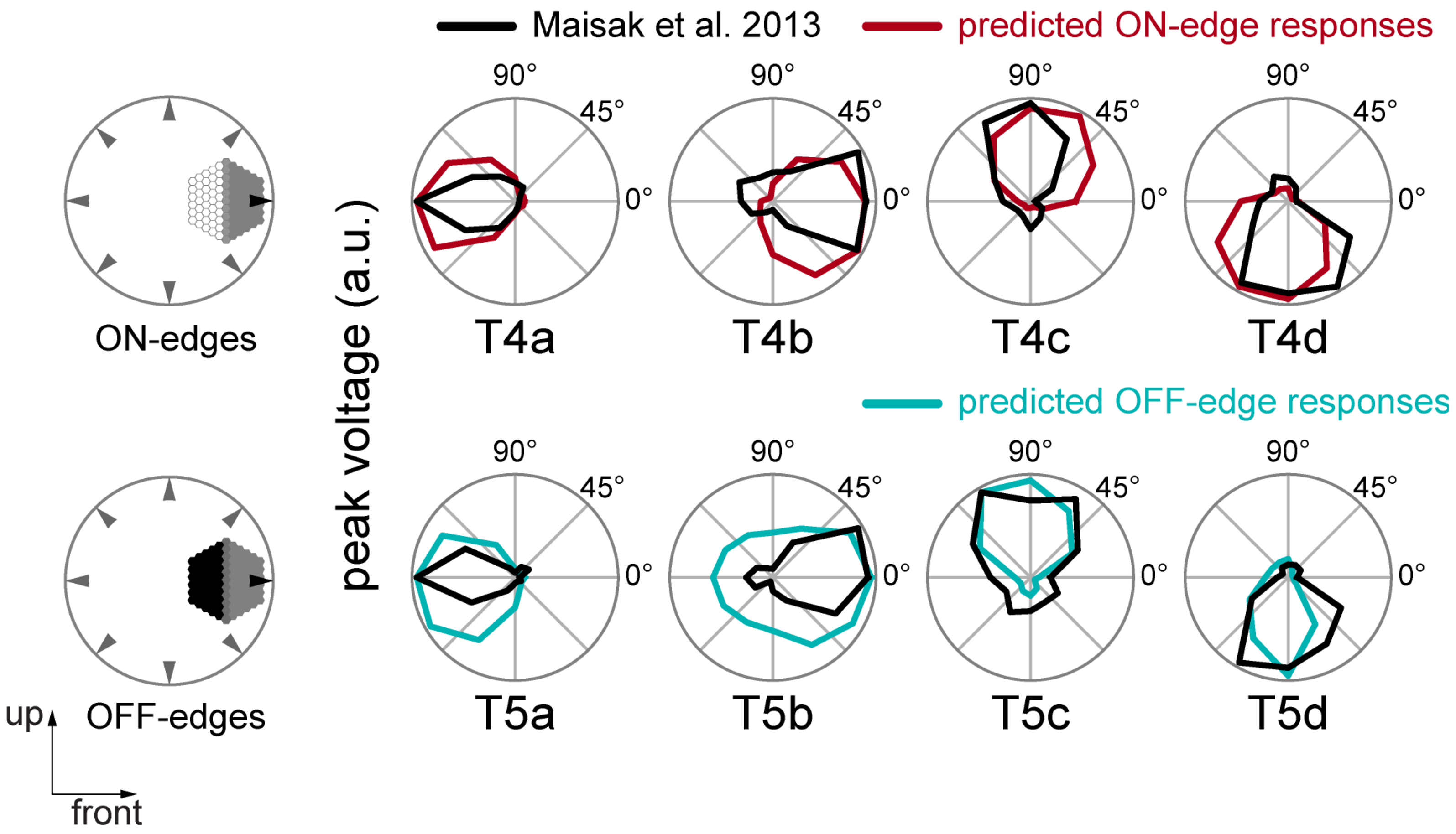
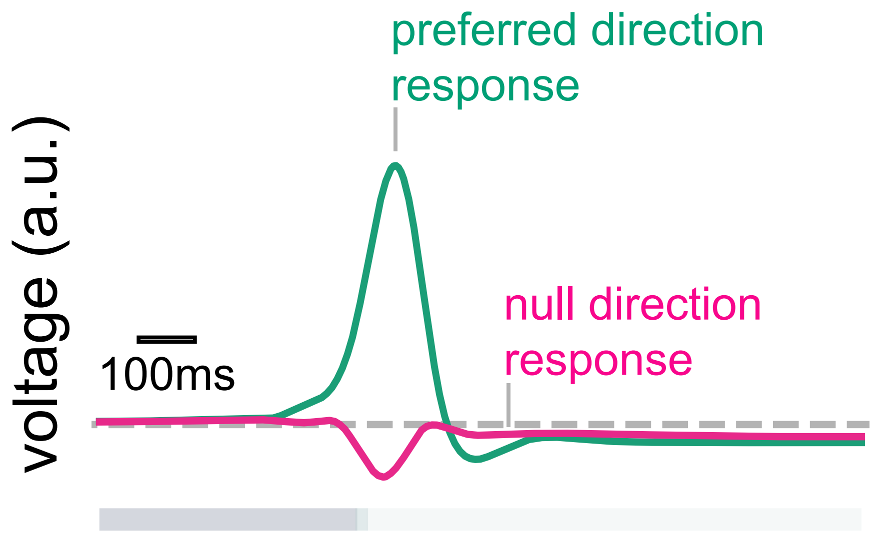
best model correctly recapitulates experimentally known direction selectivity of T4 and T5 sub types to 4 cardinal directions

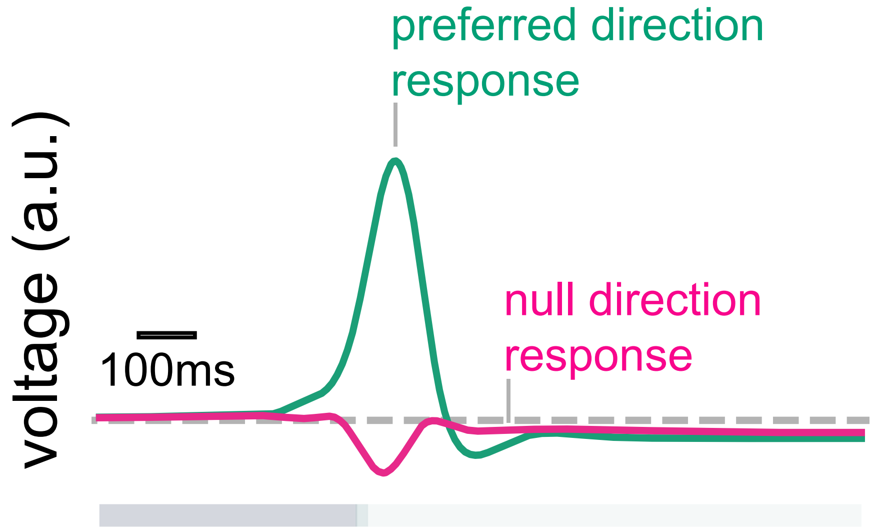


Lappalainen et al. 2023



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

Lappalainen et al. 2023



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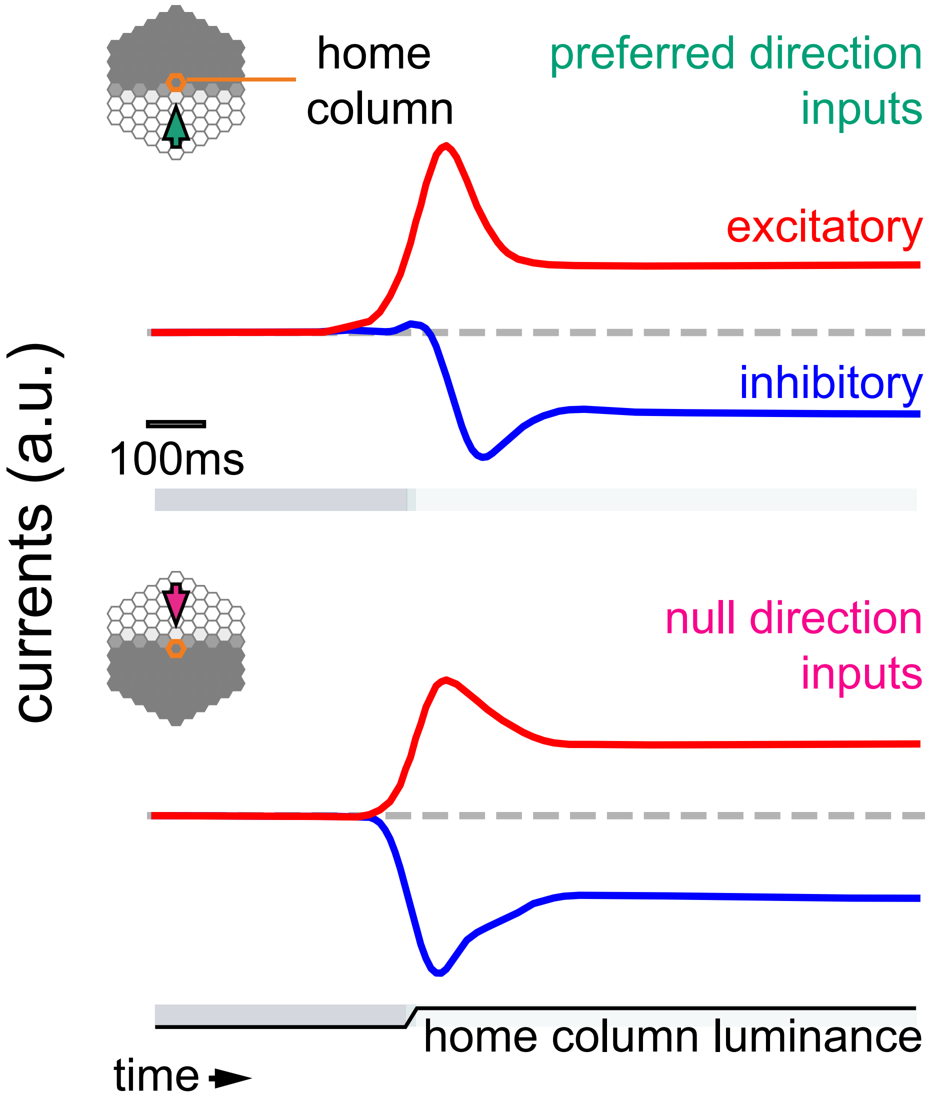
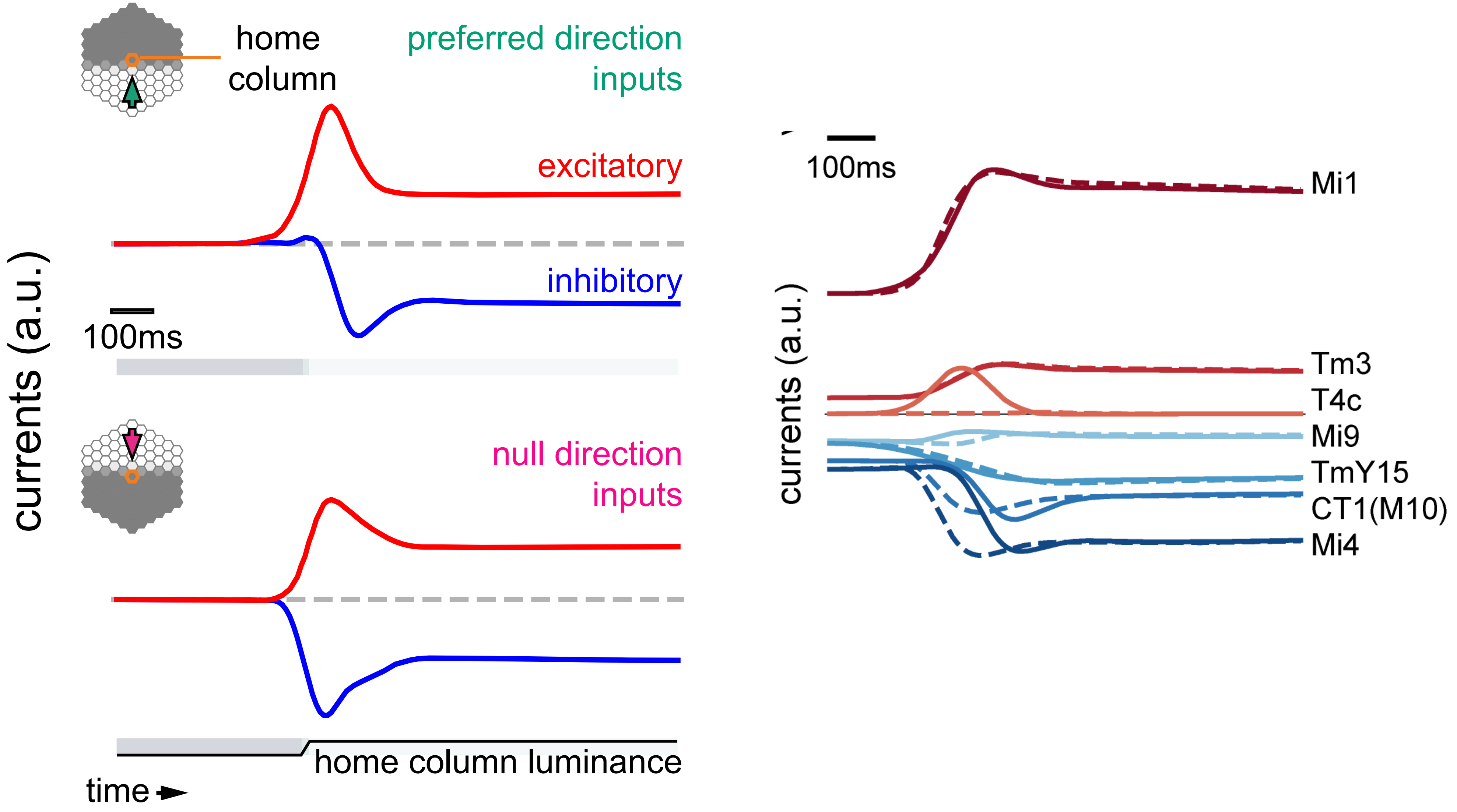
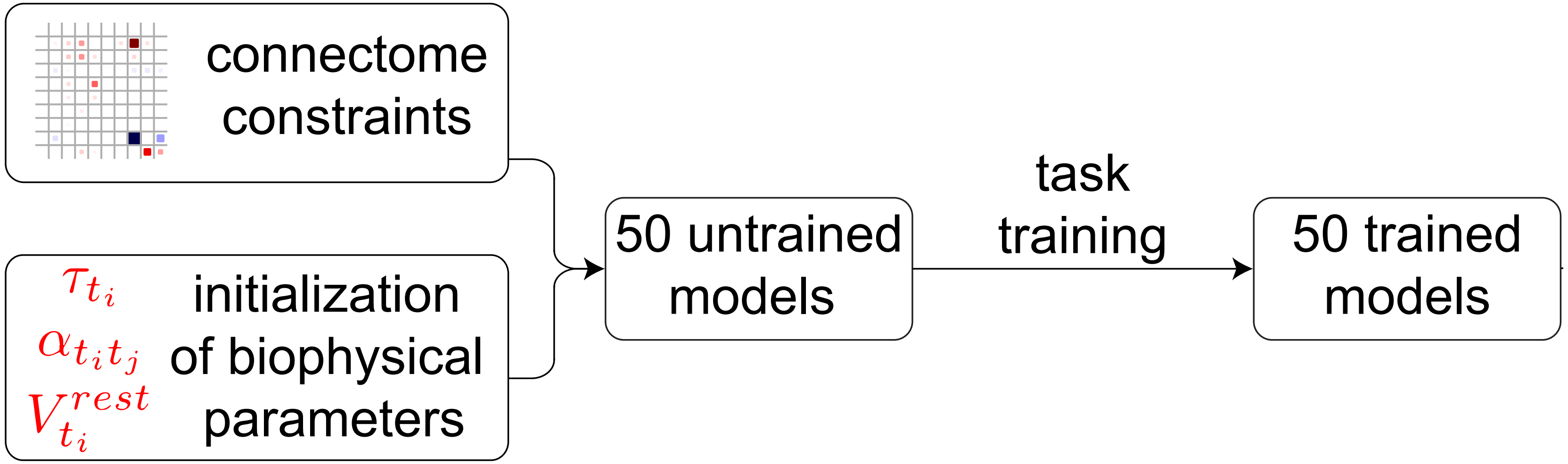


Lappalainen et al. 2023


home
column
preferred direction
inputs
excitatory
inhibitory
100ms
null direction
inputs
home column luminance
time
currents (a.u.)
100ms
Mi1
currents (a.u.)
Tm3
T4c
Mi9
TmY15
CT1(M10)
Mi4



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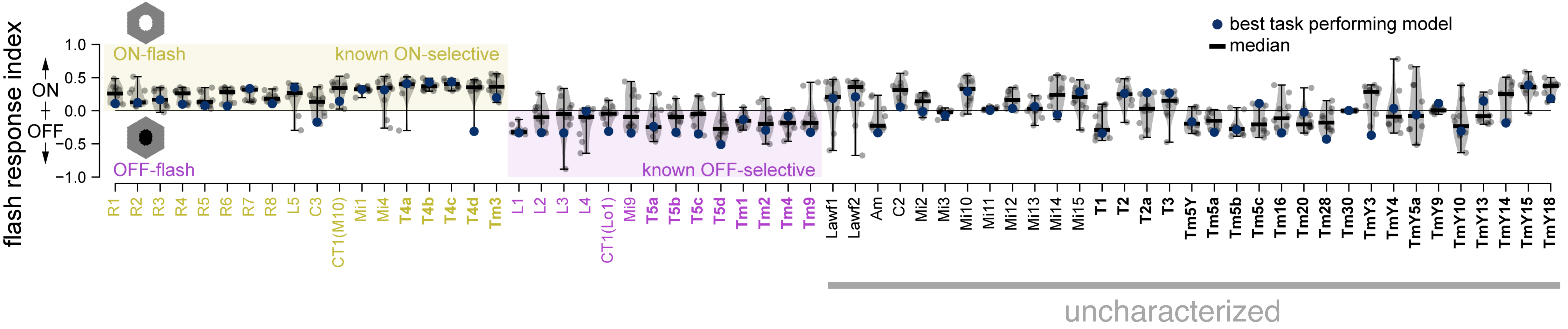
Segregation into ON and OFF pathways well predicted



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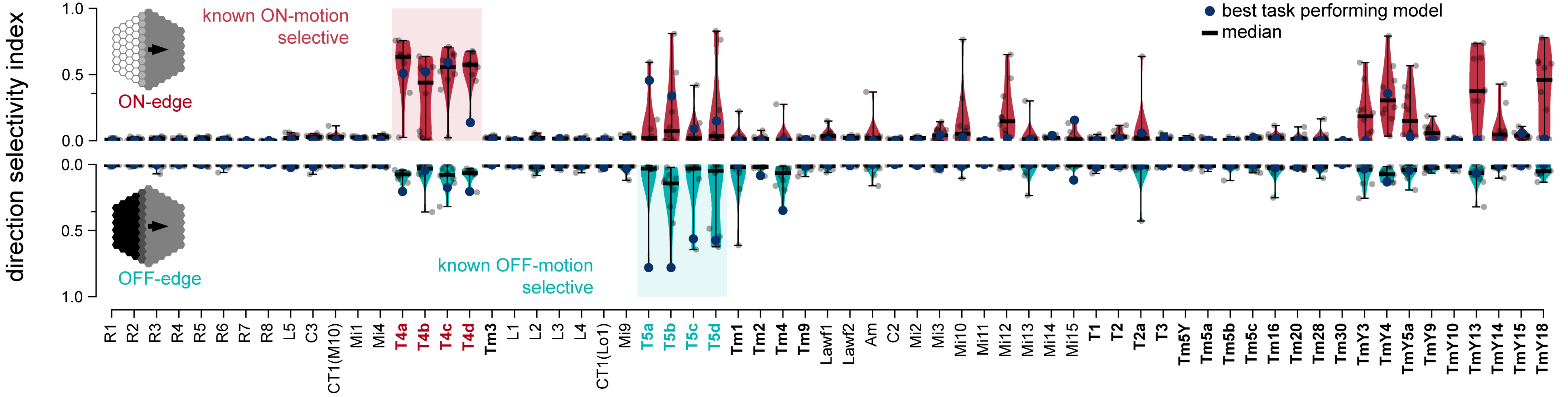
models predict known motion selectivity in T4 + T5 neurons



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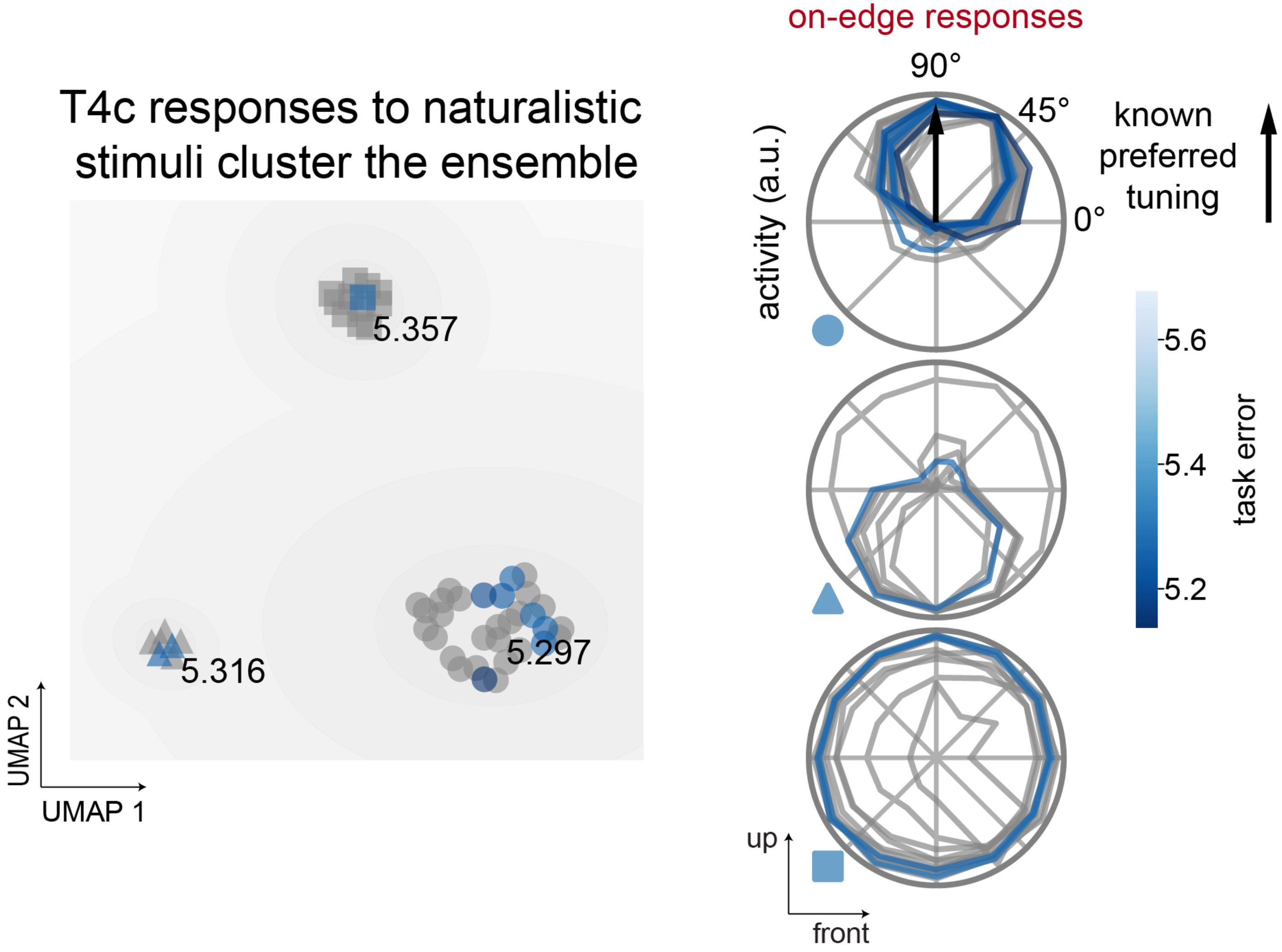
exploring the solution space



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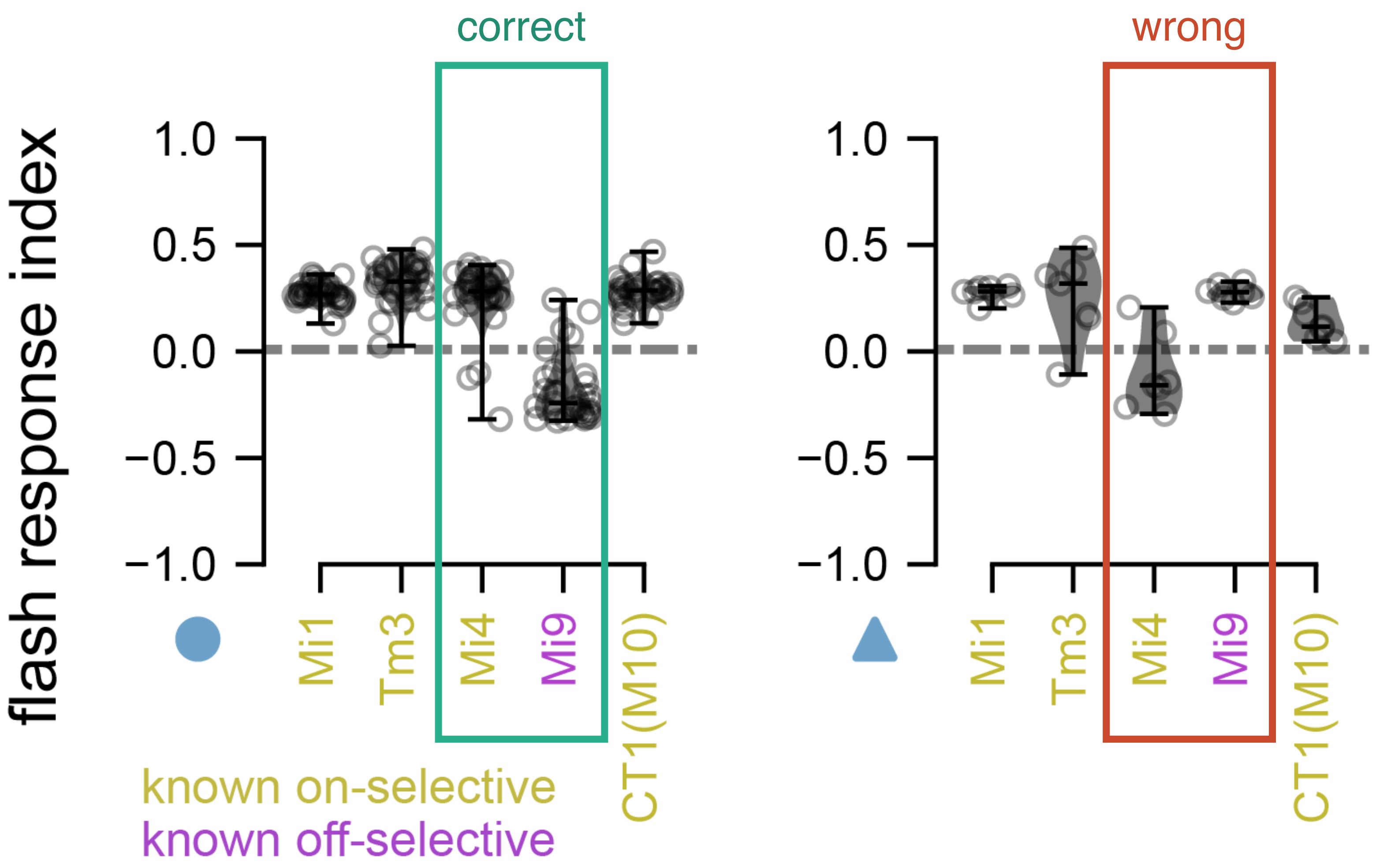
Switching Mi4 and Mi preferred contrasts leads to directionally opposite motion tuning in T4



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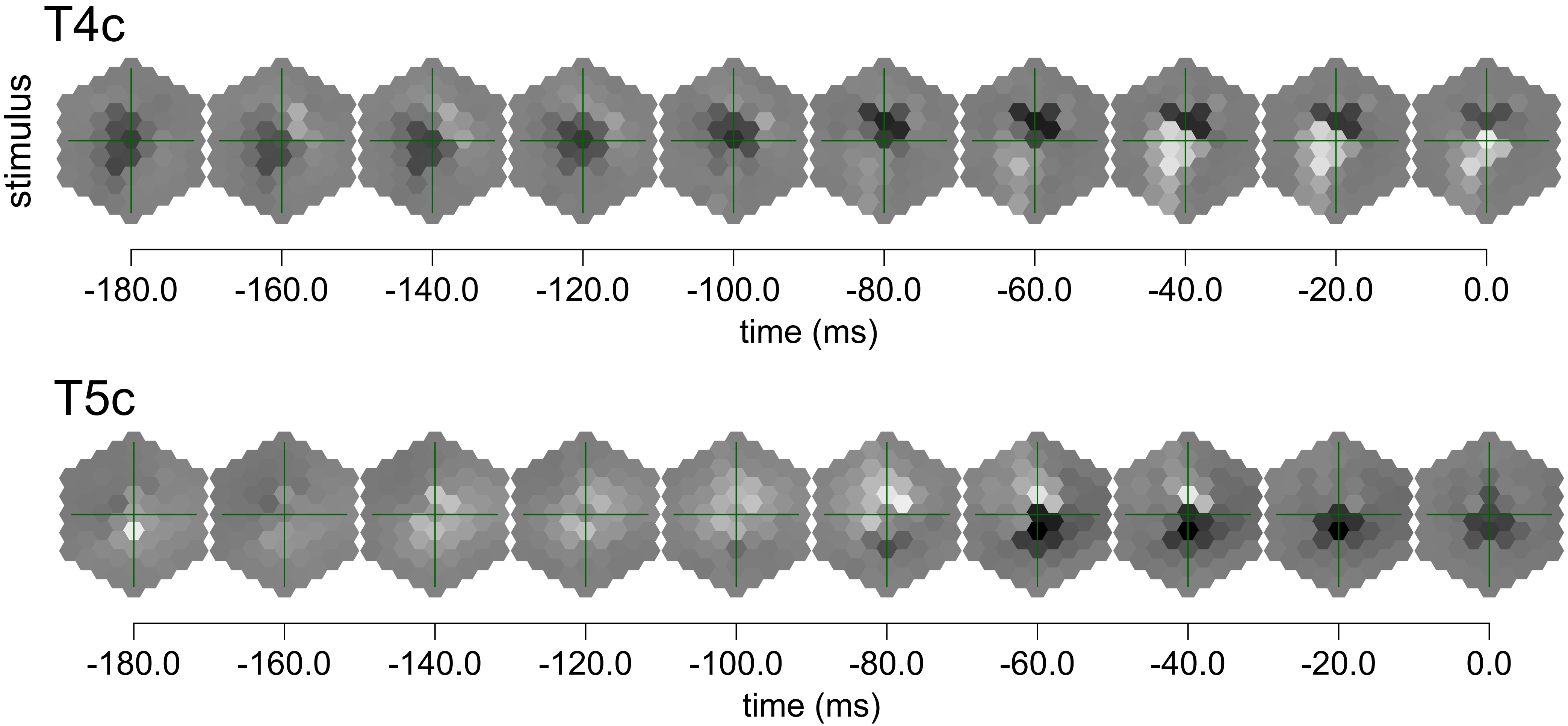
can use model to discover optimal stimuli for all neuron types



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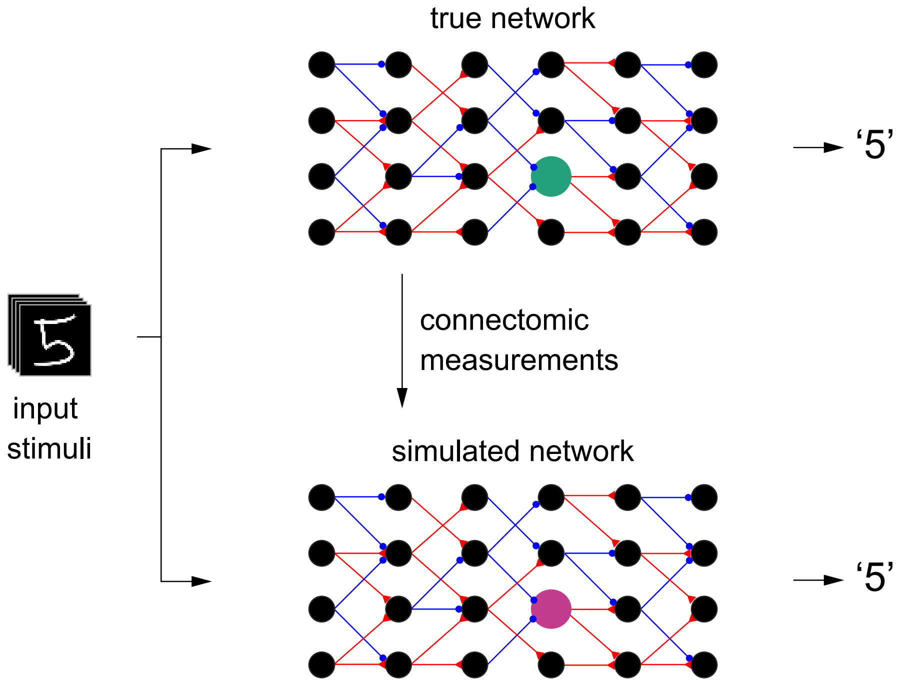
when are connectomic constraints sufficiently strong?



Sridhama Prakhya

Lappalainen et al. 2023

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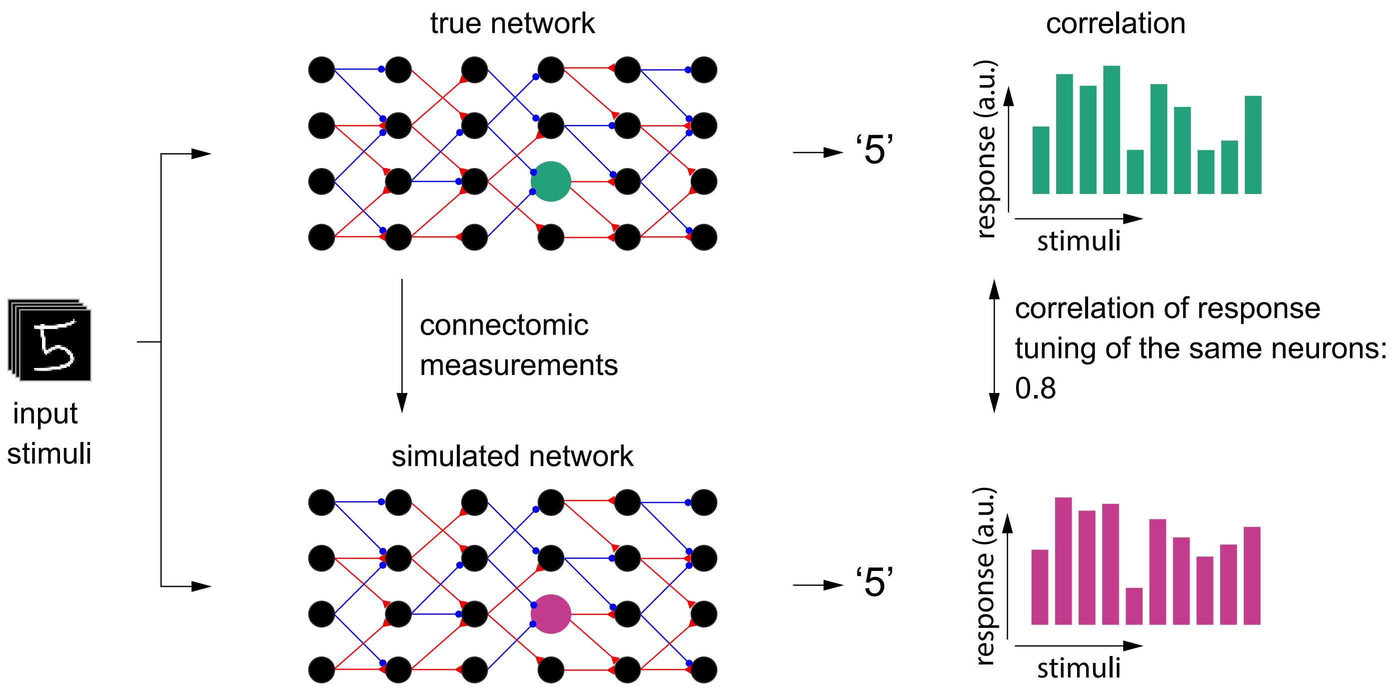

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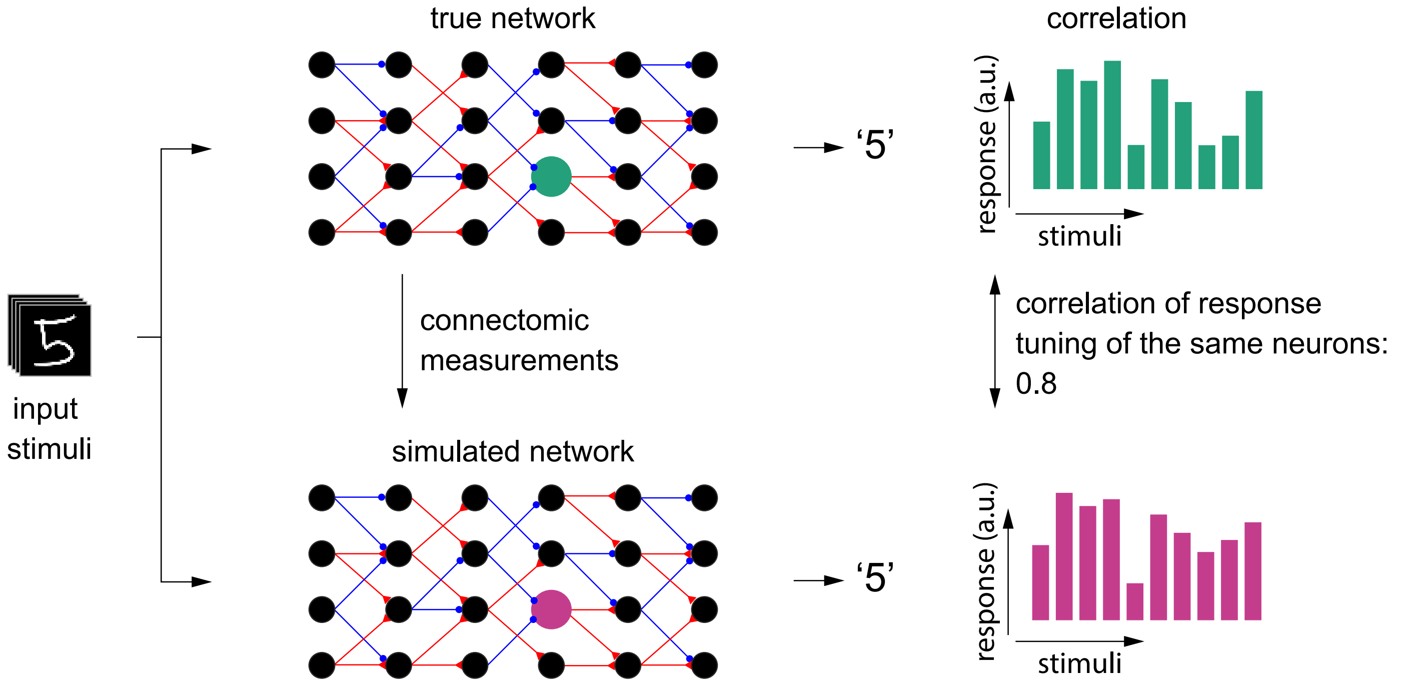

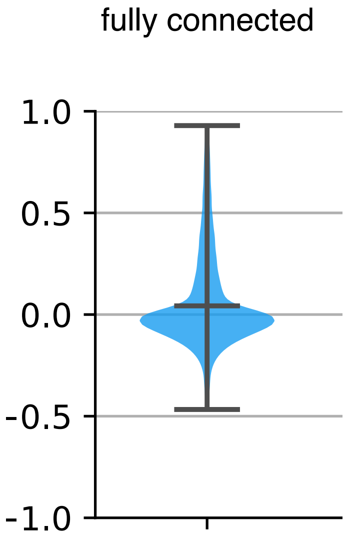

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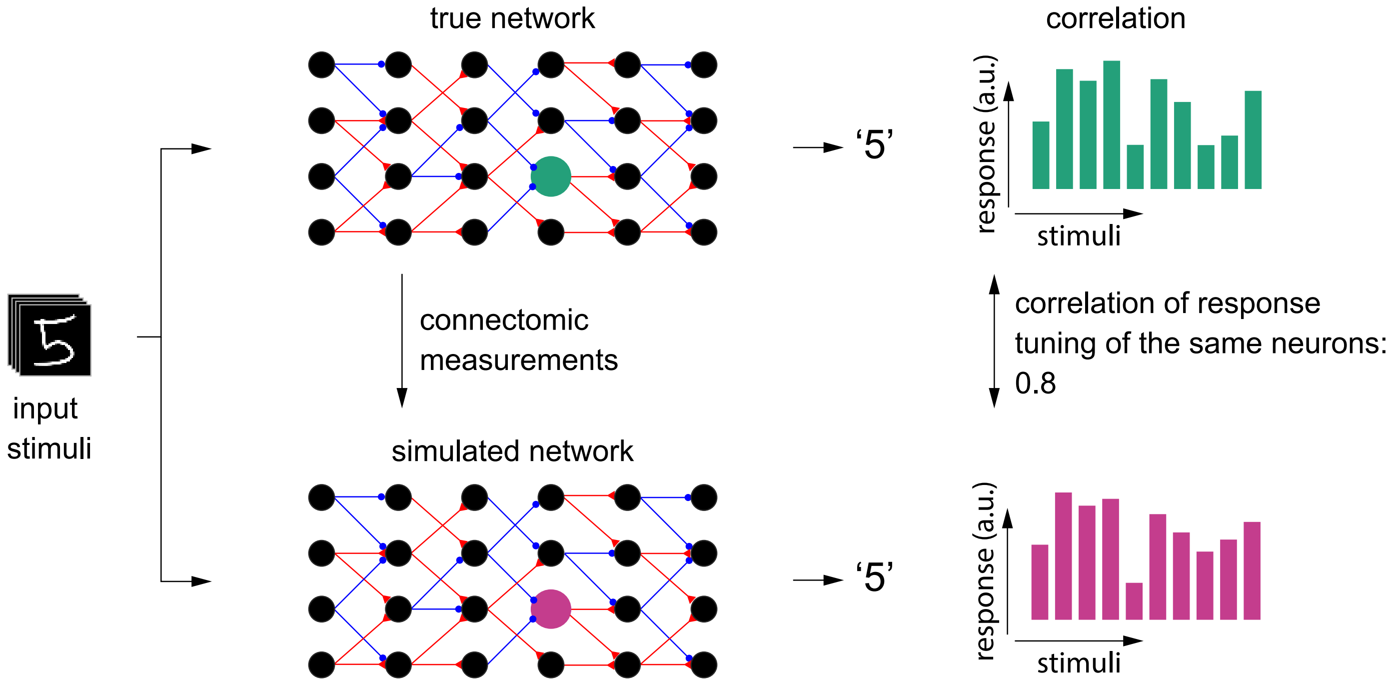

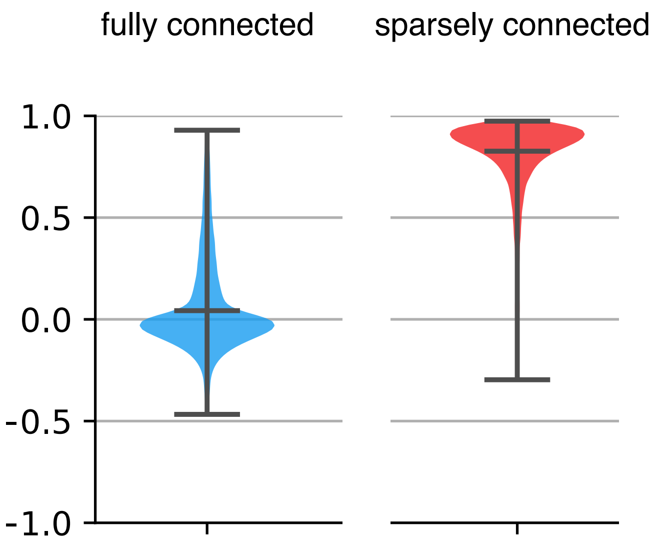

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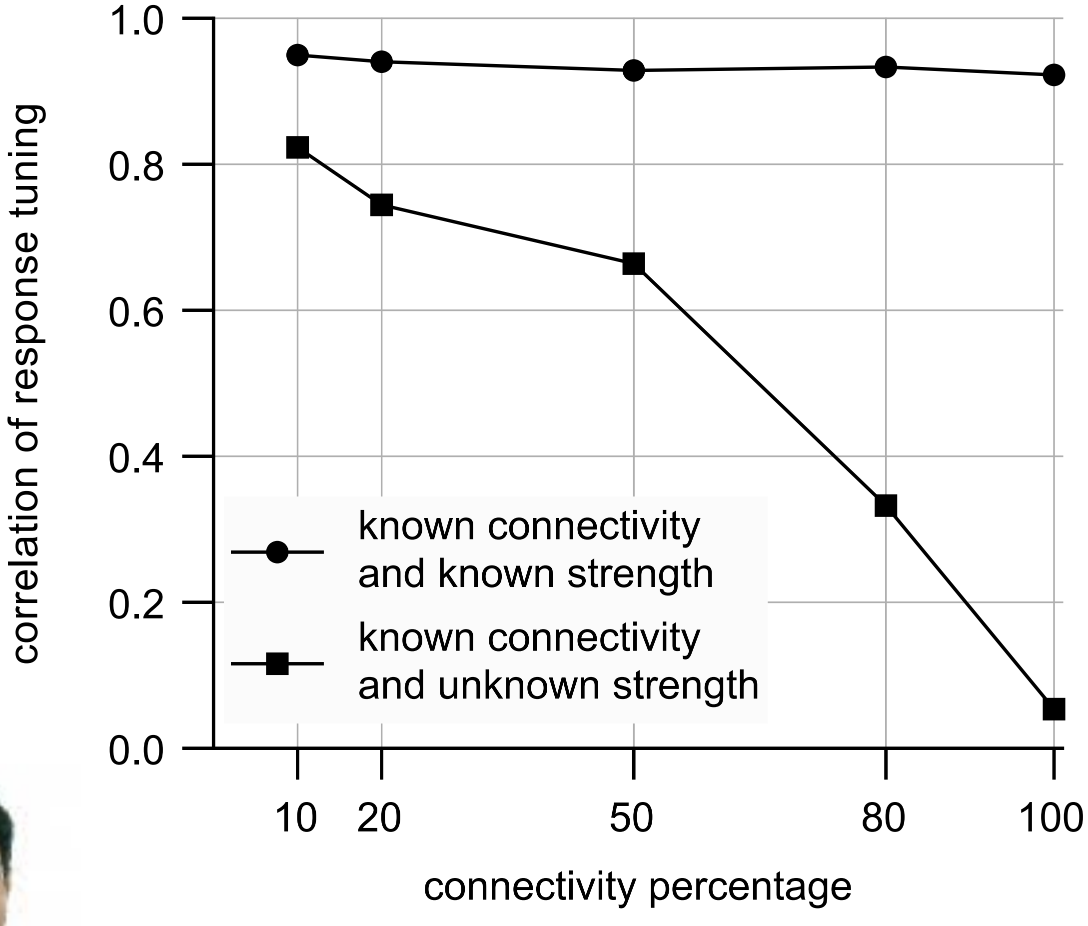

sparse + structured connectivity in the connectome constrains models strongly

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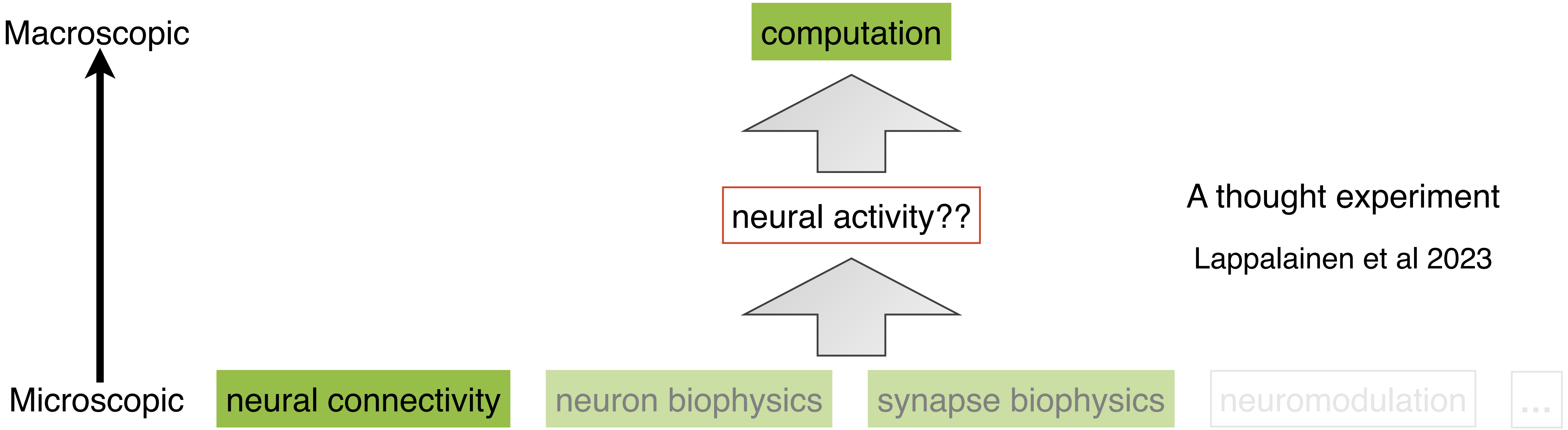
A thought experiment

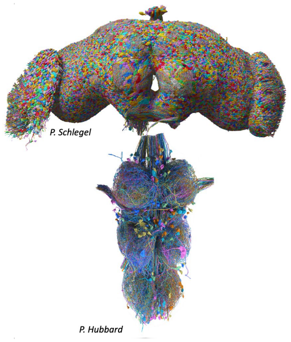
Lappalainen et al 2023



Connectome + Circuit-level function —-> neural activity
Other possible constraints: neural activity, behavior.

Whole brain
(big model)

Behavior
(big data)



Neural activity

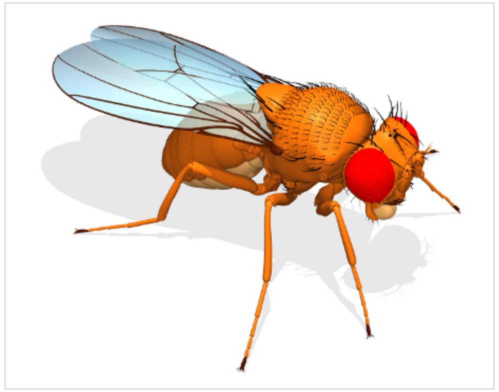
Connectome
(big data)

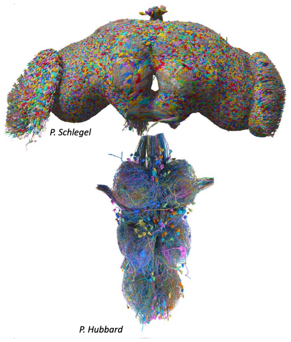
Biophysics

Whole body
(big model)

Whole brain
(big model)

Behavior
(big data)





Neural activity

Connectome
(big data)

Biophysics

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DeepMind

Yuval Tassa | Guido Novati | Josh Merel | Matt Botvinick

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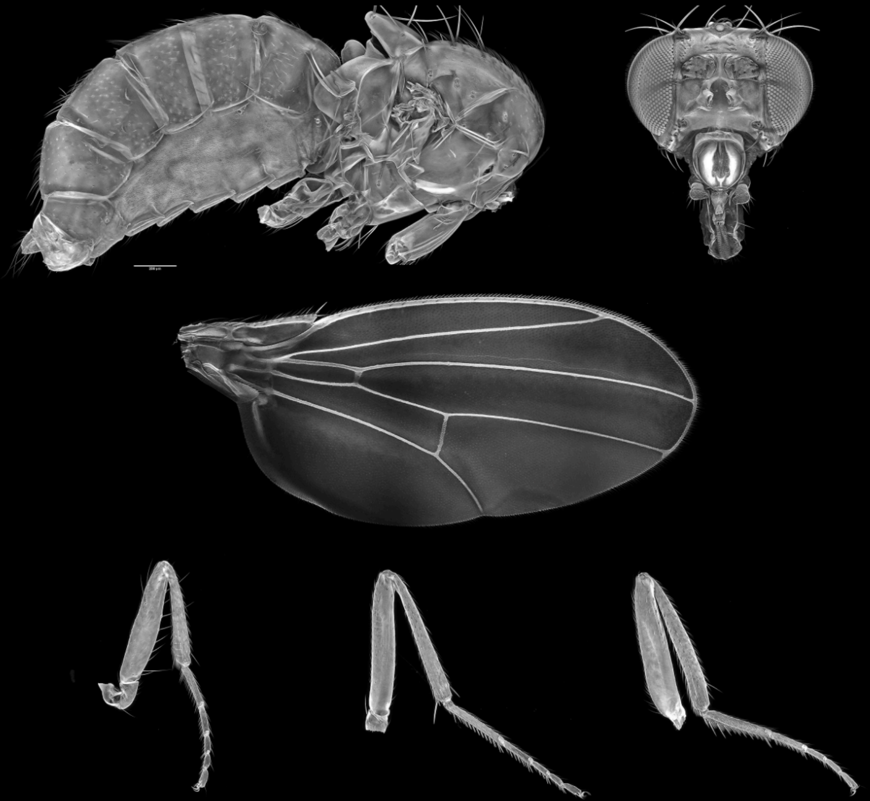

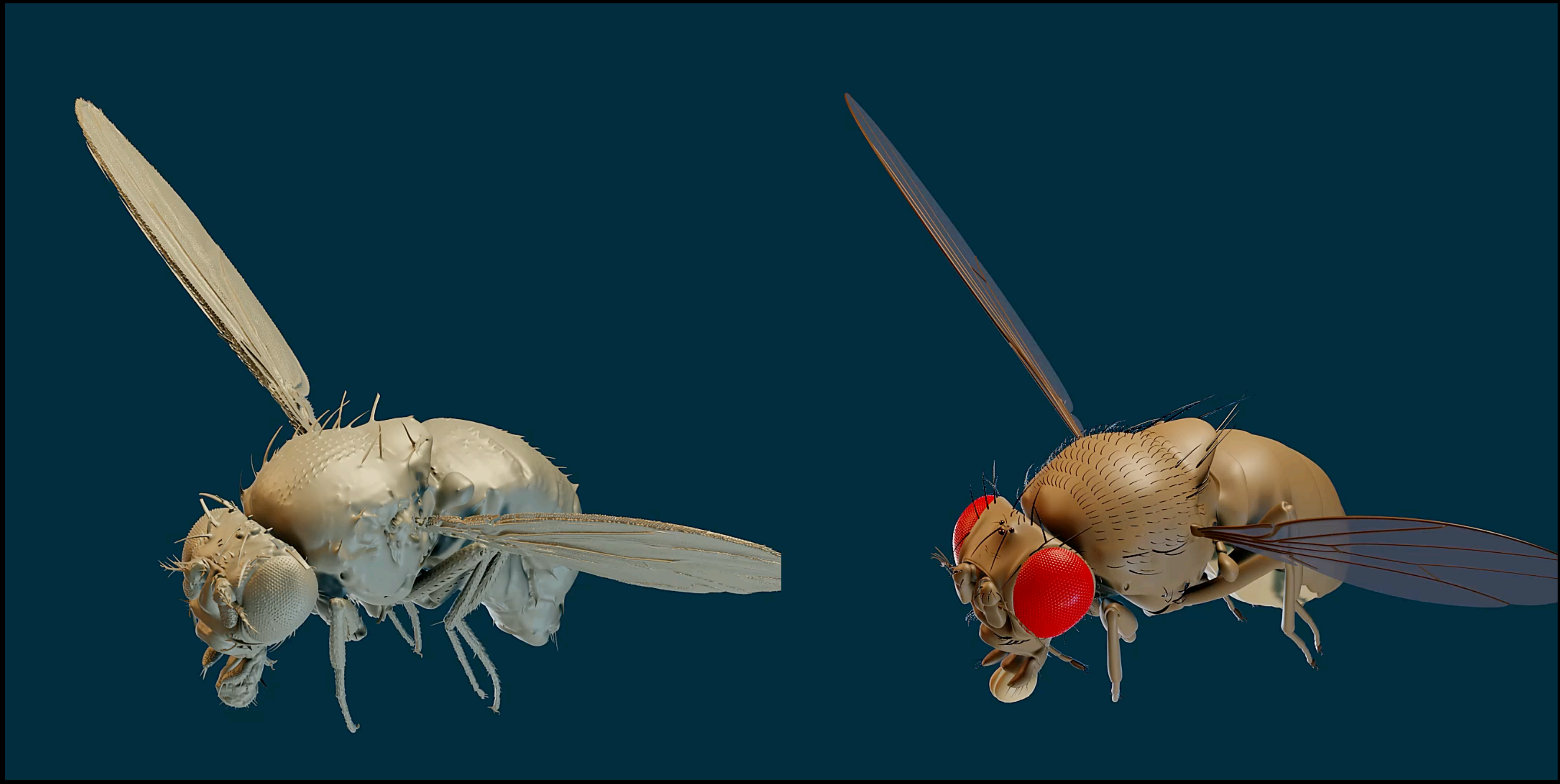

Vaxenburg et al (in prep)

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Roman Vaxenburg, Igor Siwanowicz, Alice Robie, Carmen Morrow, Zina Stefanidi, Kristin Branson, Gwyneth Card, Michael Reiser, Srini Turaga

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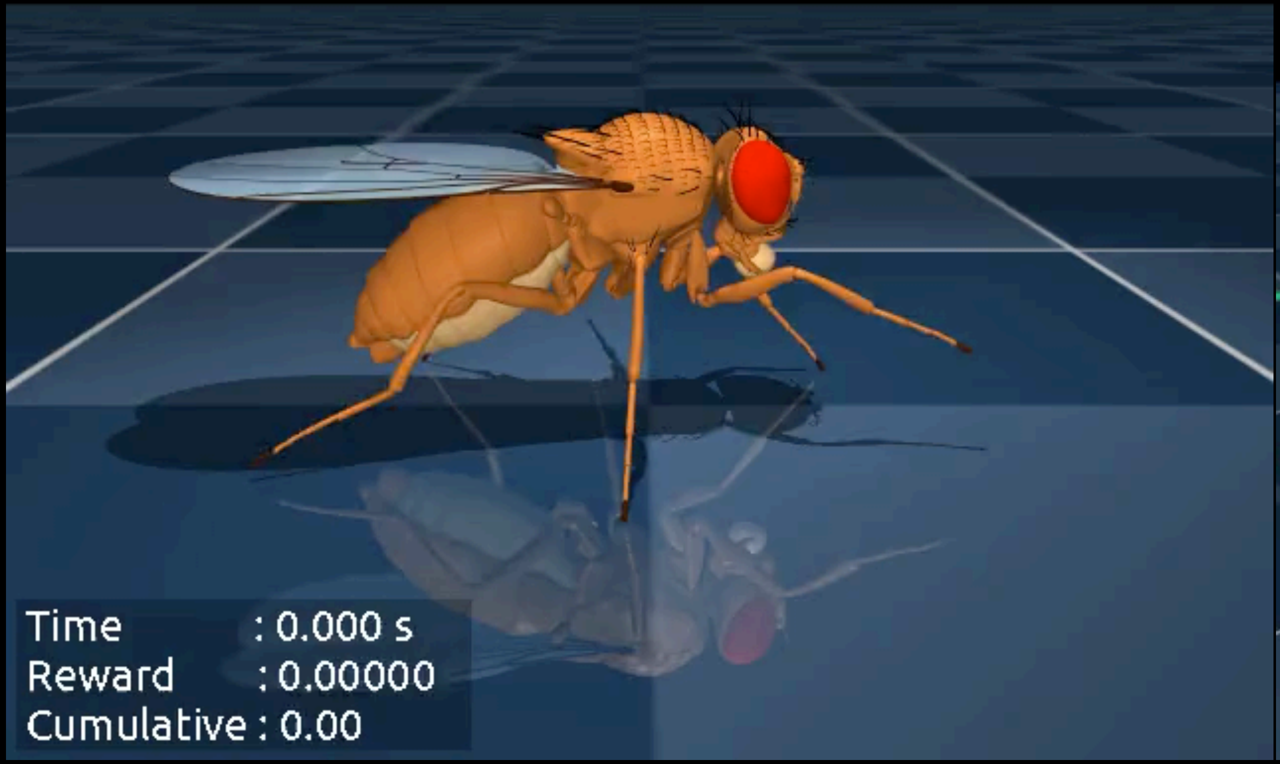
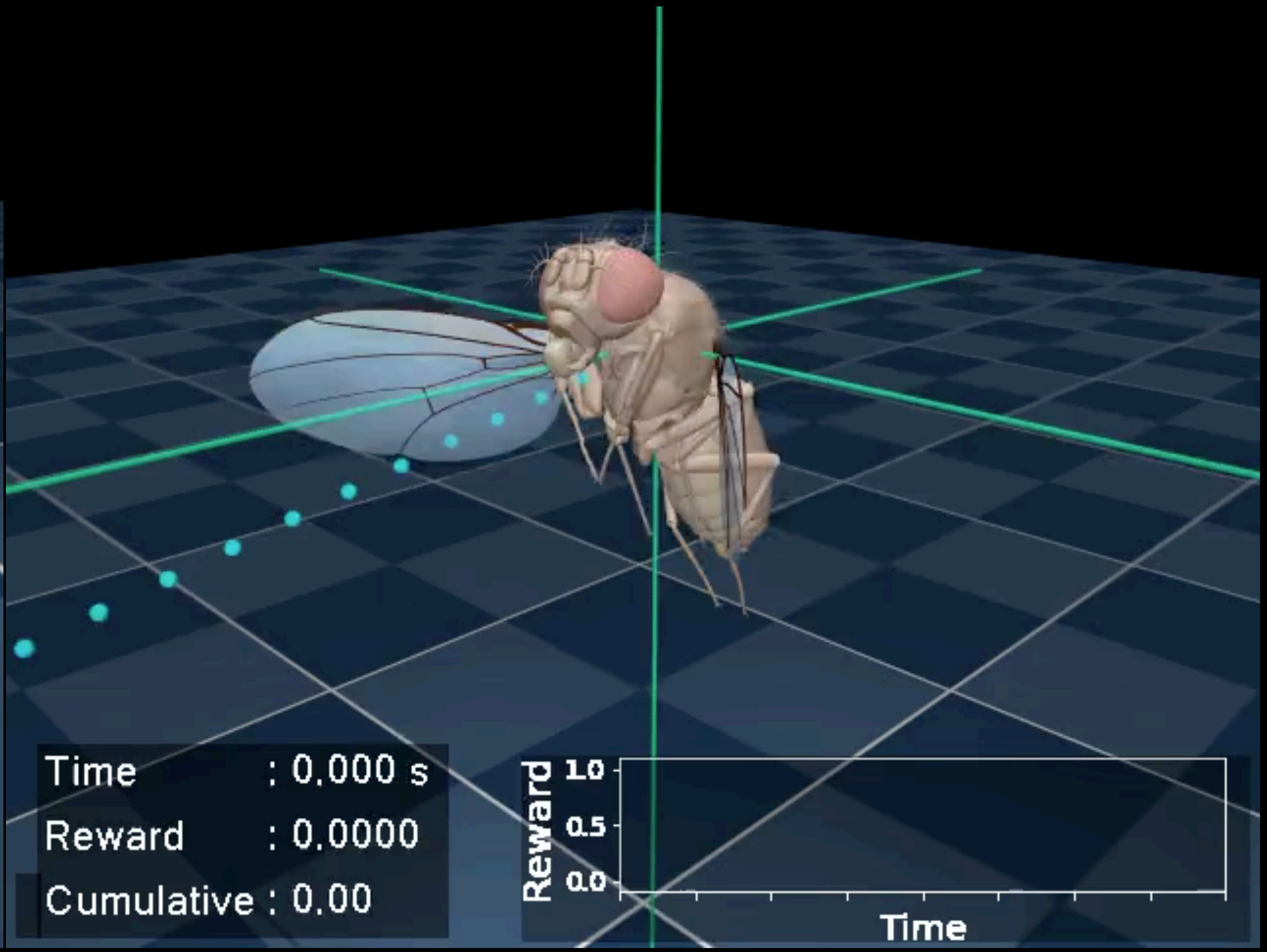
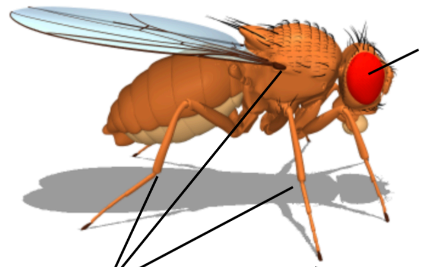




Vaxenburg et al (in prep)

Roman
Vaxenburg

sensory system



Vision

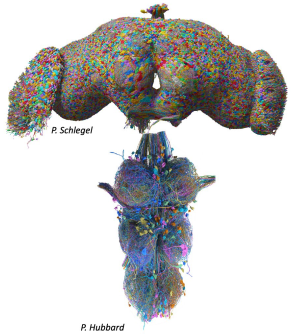
Vestibular:
Velocity
Acceleration
Gyro
Orientation in space

Proprioception:
Body/leg/wing posture
Actuator activation

Contact

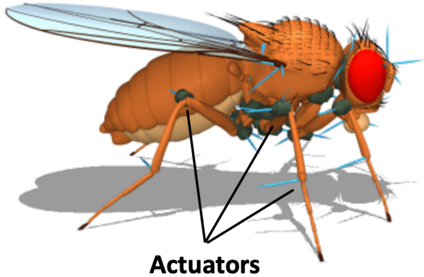
sensory in

“brain”



motor
commands out

actuation system

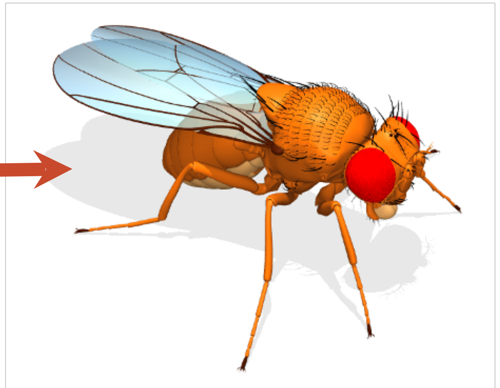


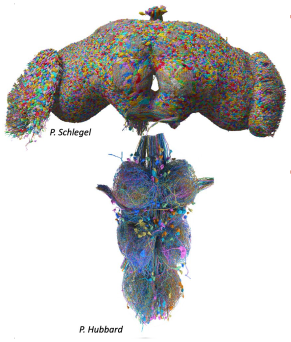
Actuators

Whole body
(big model)

Whole brain
(big model)

Behavior
(big data)





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

Join us!

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