Towards embodied brain emulations: A *Drosophila* connectome-constrained brain model accurately predicts neural activity and controls behavior in a virtual environment

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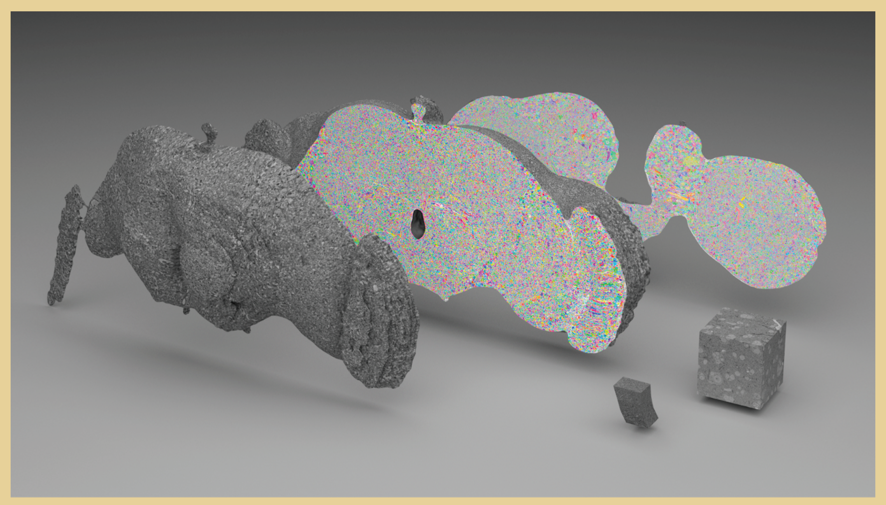
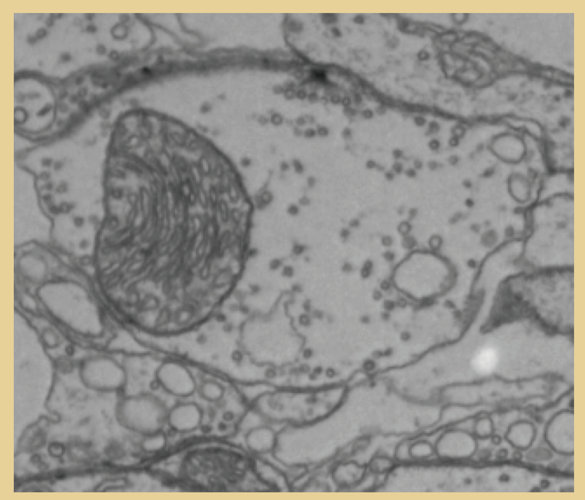
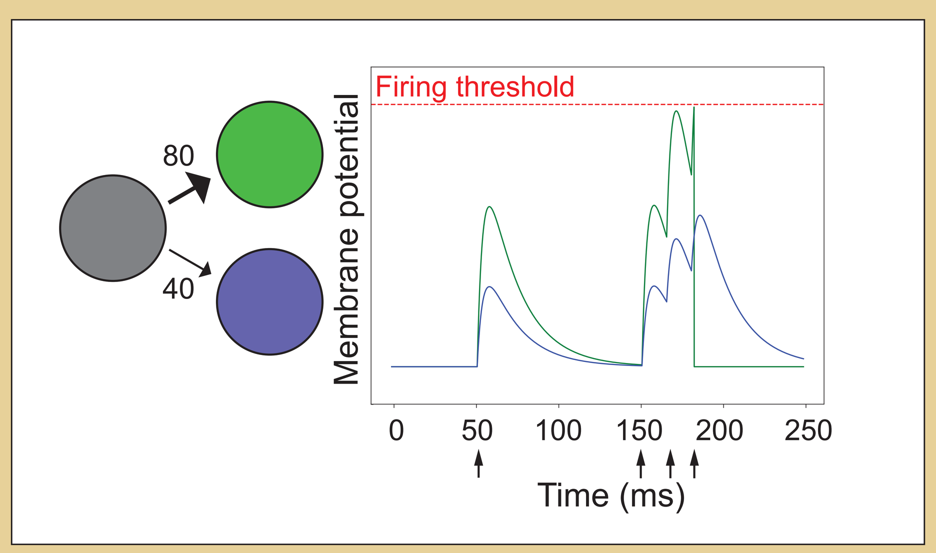
A whole-brain computational model

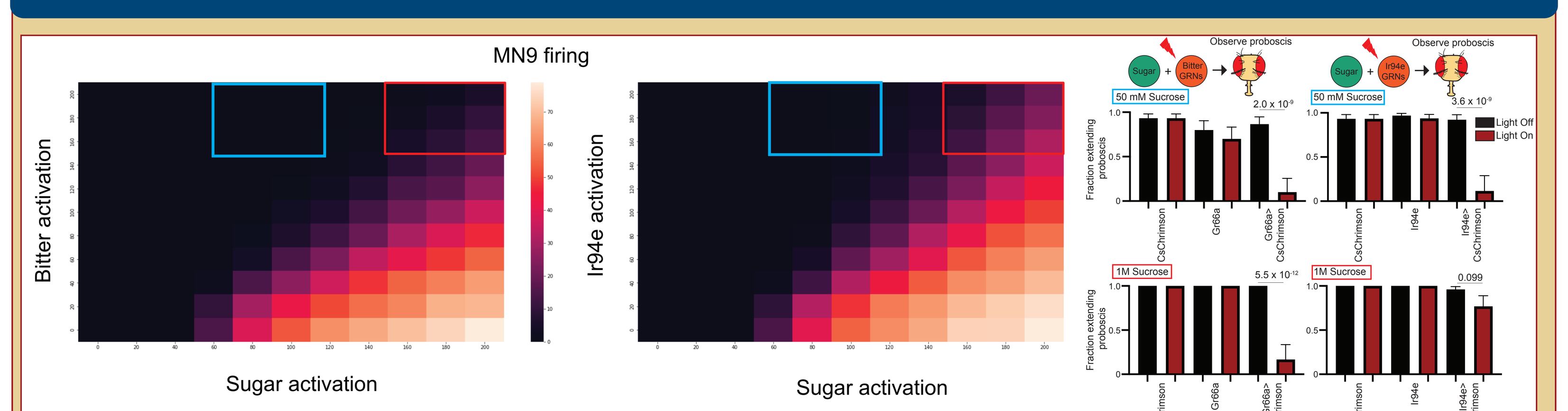



We use data from an electron microscopy volume of the *Drosophila* brain. Our model draws whole-brain connectome data of segmented and proofread neurons on the Flywire platform (Dorkenwald et al., 2024). The number of synapses each neuron makes onto each other neuron has been determined. Further, using machine learning tools, the neurotransmitter each neuron expresses can be accurately predicted (Eckstein et al., 2024).



We have built a leaky integrate-and-fire (LIF) model of the brain. In this model, when a neuron fires, downstream neurons respond in proportion to the connectivity from this neuron. A neuron's membrane potential decays back to its resting potential, unless it hits the firing threshold; in this case, it will alter the membrane potential of downstream neurons in proportion to its connectivity.

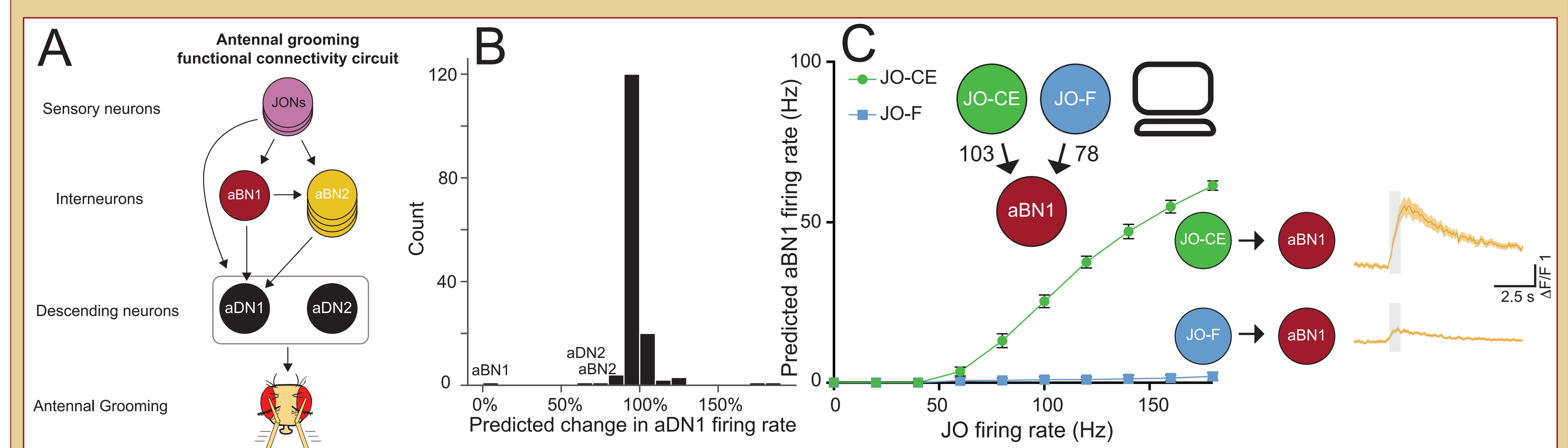
The model makes accurate predictions



The model predicts that bitter and Ir94e neurons will inhibit feeding, but strong sugar activation will override Ir94e activation. Shiu et al., 2024, *Nature*

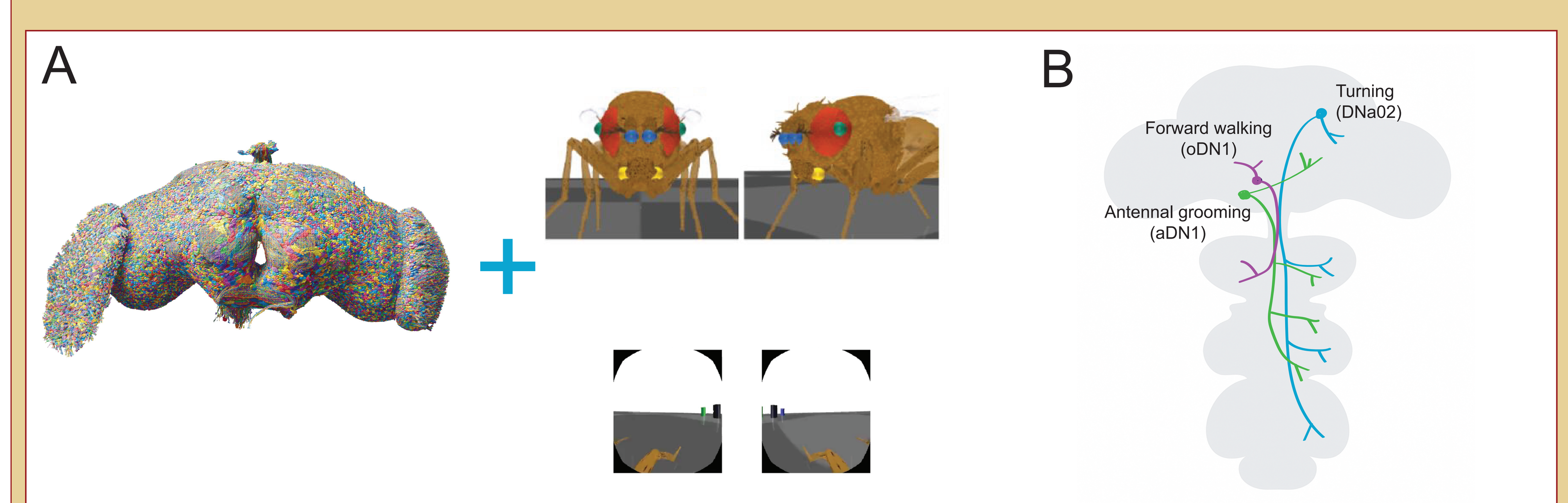
The computational model correctly predicts activation phenotypes at greater than 90% accuracy. Top, computational activation predictions. Bottom, optogenetic activation phenotypes.

Antennal grooming predictions



The computational model recapitulates the activation and silencing phenotypes of the antennal grooming circuit (Hampel et al., 2015). A. A schematic of the antennal grooming circuit. Dust or other irritants activate mechanosensory neurons that result in activation of descending neurons (DNs) that elicit grooming. B. Computational silencing experiments accurately predict the known neurons required for antennal grooming. C. The computational model accurately predicts that one population of mechanosensory neurons, JO-CE will strongly activate aBN1, but not the JO-F population, despite direct connectivity from both populations.

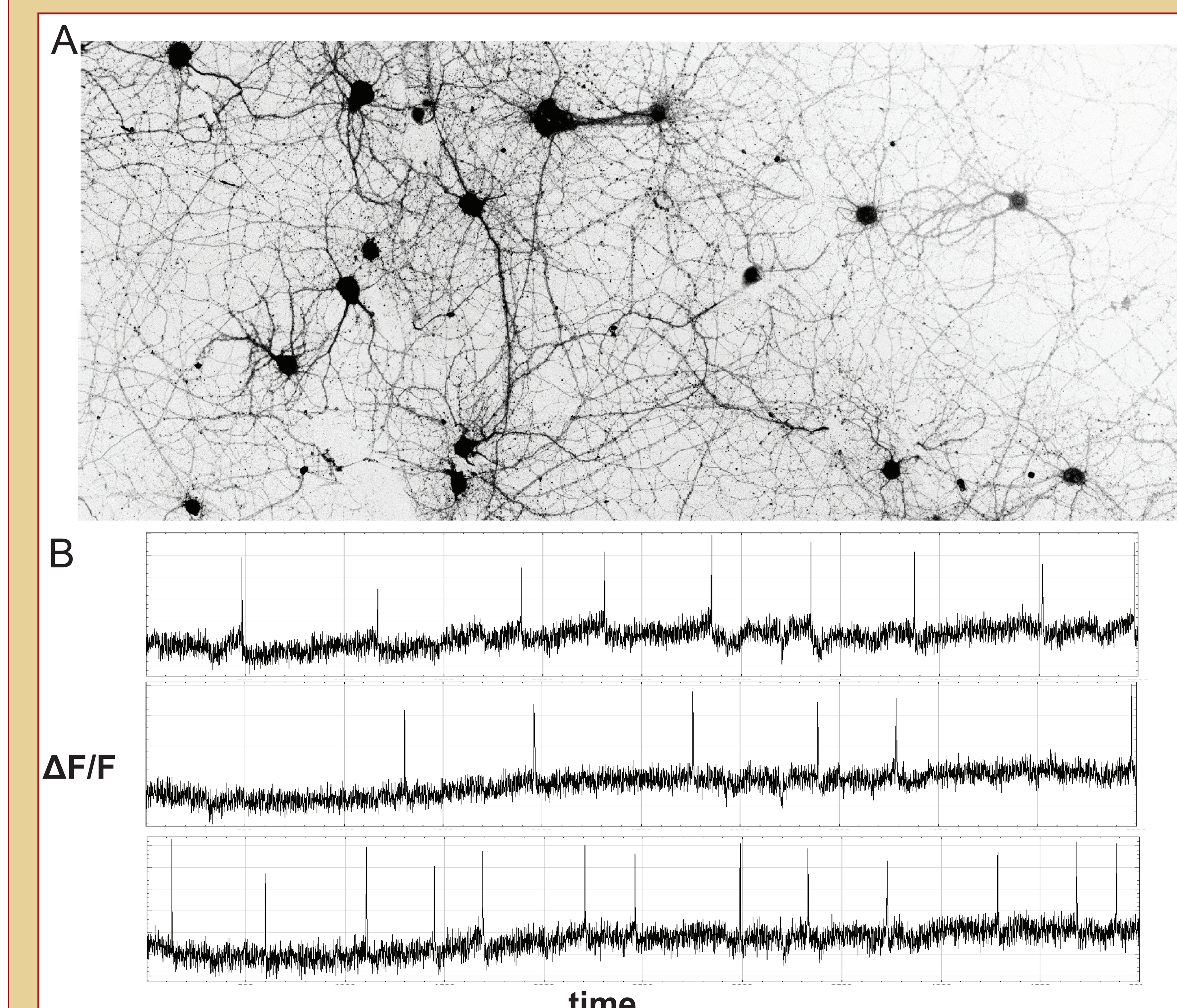
Generating embodied brains



We embodied our brain models in the NeuroMechFly virtual fly that runs in the physics simulator MuJoCo (Wang-Chen et al., 2024). We provided virtual sensory input to our brain model using the sensory input modules provided in NeuroMechFly, e.g., virtual visual stimuli and odor stimulation. Next, we controlled the behavior of the fly by using the output of known descending neurons known to control particular behaviors, for example, aDN1 causes antennal grooming while DNa02 is one of several neurons controling turning. (Simpson, 2024; see also Braun et al., 2024). One challenge is the exact input/output relation between firing rates and behavioral inputs or sensory stimuli and activations of sensory neurons.

Taste and olfaction based navigation. Virtual embodied flies can use taste information to navigate towards vitual food and olfaction to avoid aversive odors (Or56 activation).

Structure to function in mammalian tissue



Paired structure-function data in cultured mammalian cells. A. We have cultured rat hippocampal neurons in "microislands" of roughly 25 neurons per microisland (Walker et al., 2021). The structural connectivity of these neurons can be determined with expansion microscopy (NHS pan-protein stain shown here), while the distribution of other proteins (e.g., synaptic proteins or cell type markers) can also be determined. B. Voltage imaging is performed with the BeRST voltage dye, allowing paired structure-function data, and subsequent structure-function predictions.

Conclusions

1. A leaky integrate-and-fire model can accurately predict what neurons will respond to sensory stimulation, as well as what neurons are necessary for behavior.

2. Embodying this brain model results in a virtual animal that "out of the box" performs some realistic behaviors.

3. Structure to function modeling and similiar brain and body models likely will permit similar virtual brain-body models in other animals.

Citations:

Shiu et al., 2024 Nature, "A Drosophila computational brain model reveals sensorimotor processing"
Dorkenwald et al., 2024, Nature, "Neuronal wiring diagram of an adult brain"
Lappaleinen et al., 2024, Nature, "Connectome-constrained networks predict neural activity across the fly visual system"
Vaxenburg et al., 2025, Nature "Whole-body physics simulation of fruit fly locomotion"
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Wang-Chen et al., 2024 Nature Methods, "
NeuroMechFly v2, simulating embodied sensorimotor control in adult Drosophila."
Braun et al., 2024, Nature "Descending networks transform command signals into population motor control."
Simpson, 2024, "Descending control of motor sequences in Drosophila"
Hampel et al., 2015, eLife, "A neural command circuit for grooming movement control"
Walker et al., 2024, Front Neurosci. "Imaging Voltage in Complete Neuronal Networks Within Patterned Microislands Reveals Preferential Wiring of Excitatory Hippocampal Neurons"