# FlyBrainLab: a Complete Programming Environment for Discovering the Functional Logic of the Fruit Fly Brain

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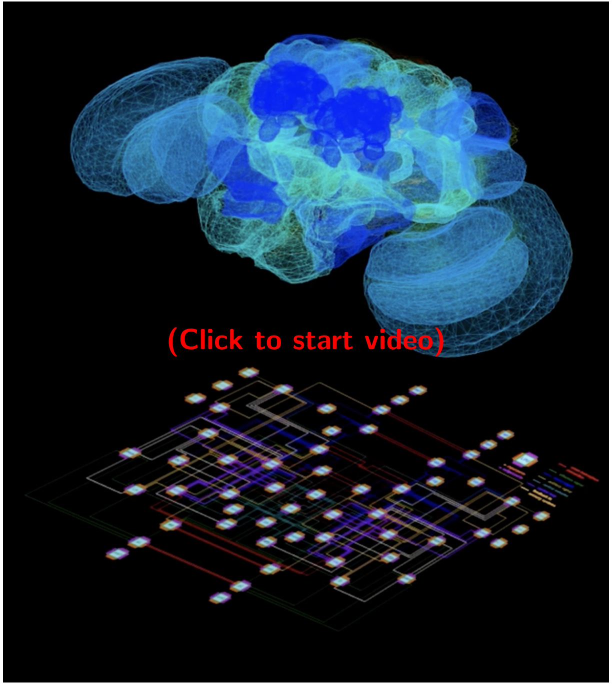
Part I

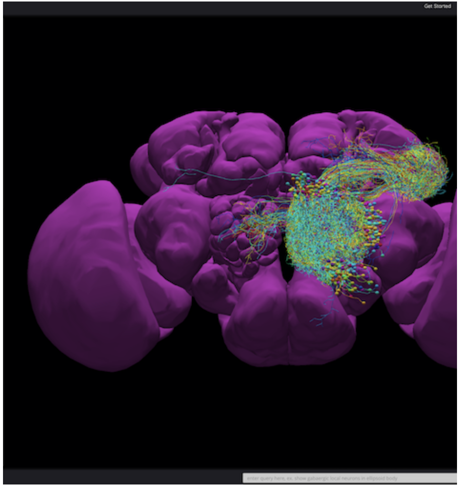
# The Fruit Fly Brain Observatory




3D view of the neuropils of the fruit fly brain. Central question: What is the functional logic of the fruit fly brain?

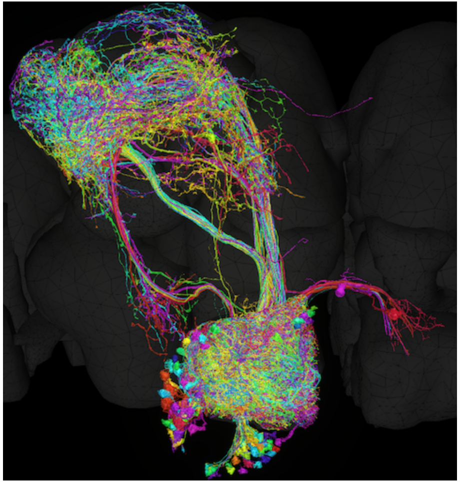
3D circuit diagram depicting a hypothesized systems level architecture of the "local processing units" modeling the neuropils.

FlyCircuit Dataset



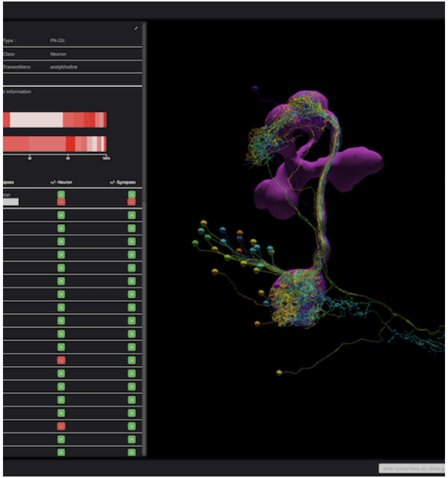
Ann-Shyn Chiang et al., Current Biology 2011, 21(1), pp.1-11.

Hemibrain Dataset

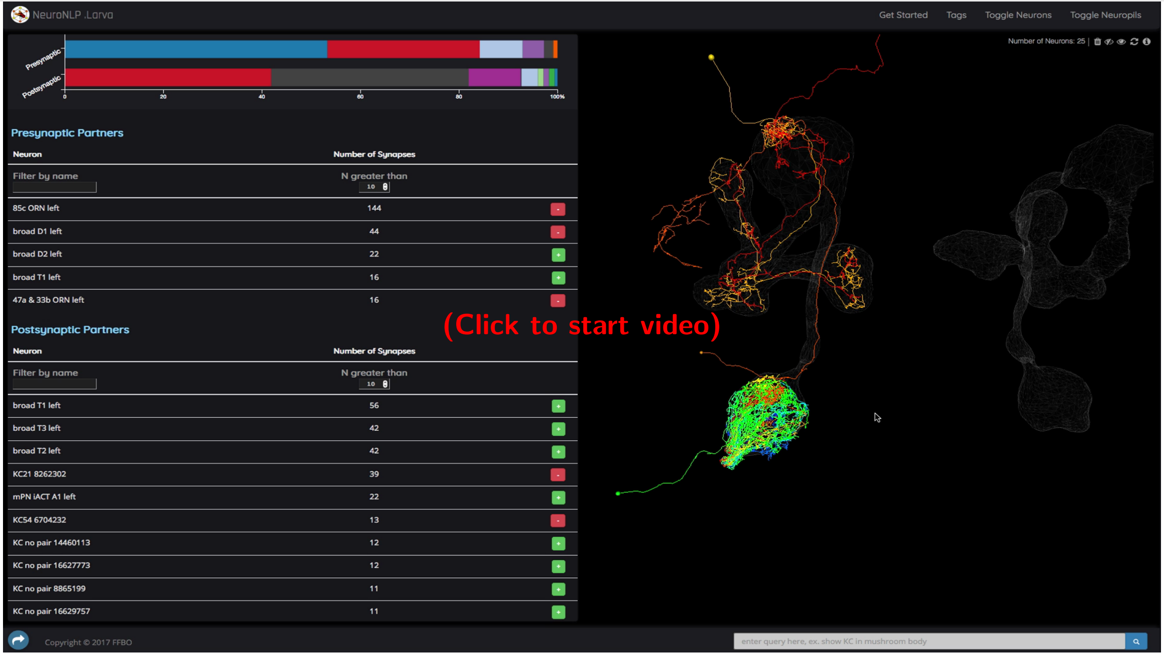


C. Shan Xu et al., A Connectome of the Adult Drosophila Central Brain. bioRxiv 2020.

Larva Datasset



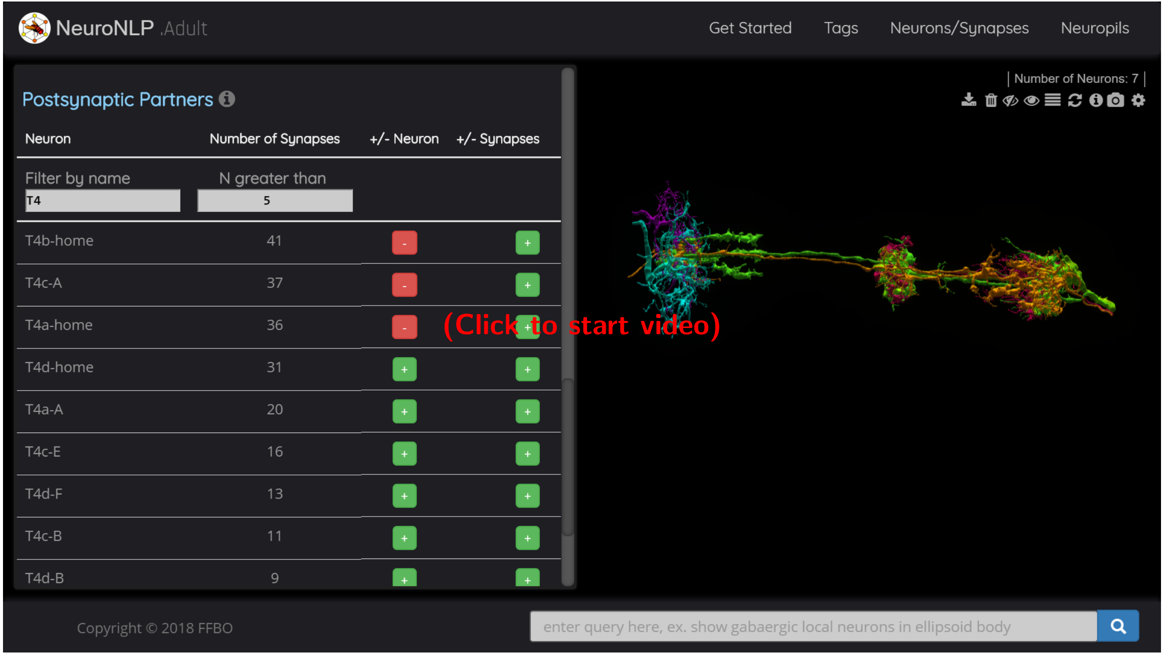
Berck et al., ELife 5 (2016):1-21.
Eichler et al., Nature 548, 175-182 (2017).




NeuroNLP at https://neuronlp.larva.fruitflybrain.org

# Visualizing the Adult Early Vision System

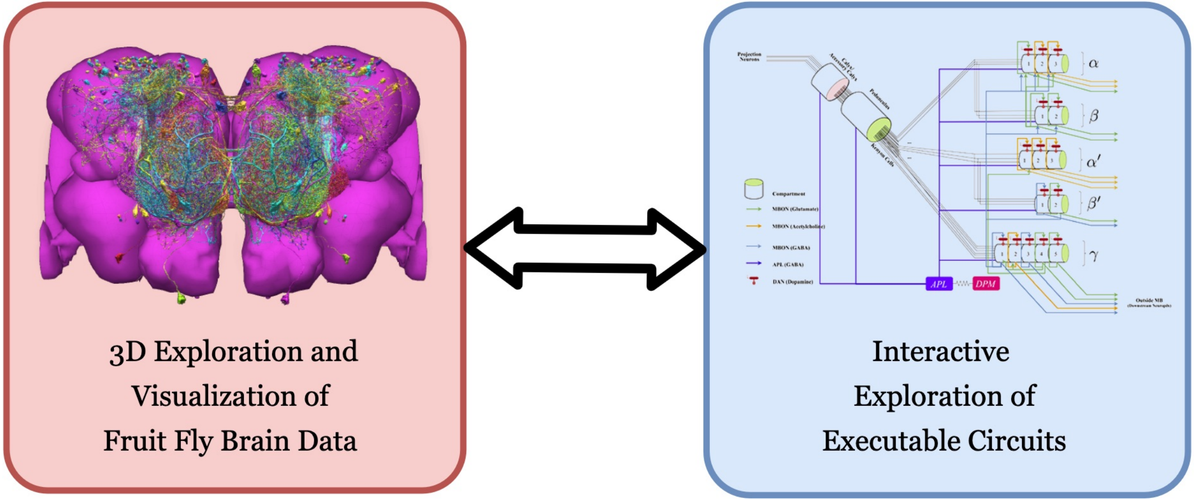
## Exploring Lamina Cartridge > Medulla Column Neuronal Pathways




NeuroNLP at https://neuronlp.adult.fruitflybrain.org

Part II

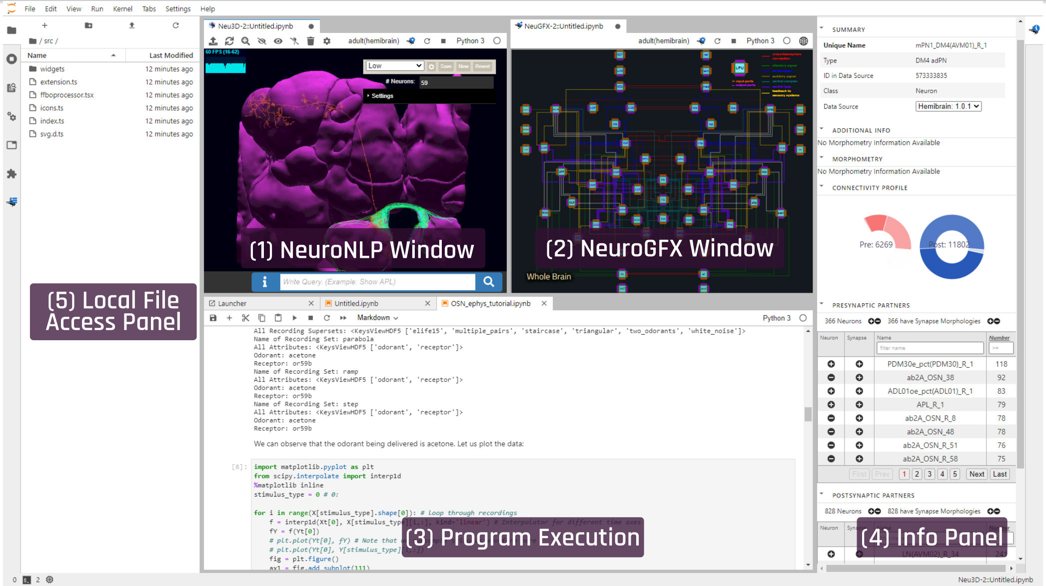
# The FlyBrainLab Interactive Computing Platform



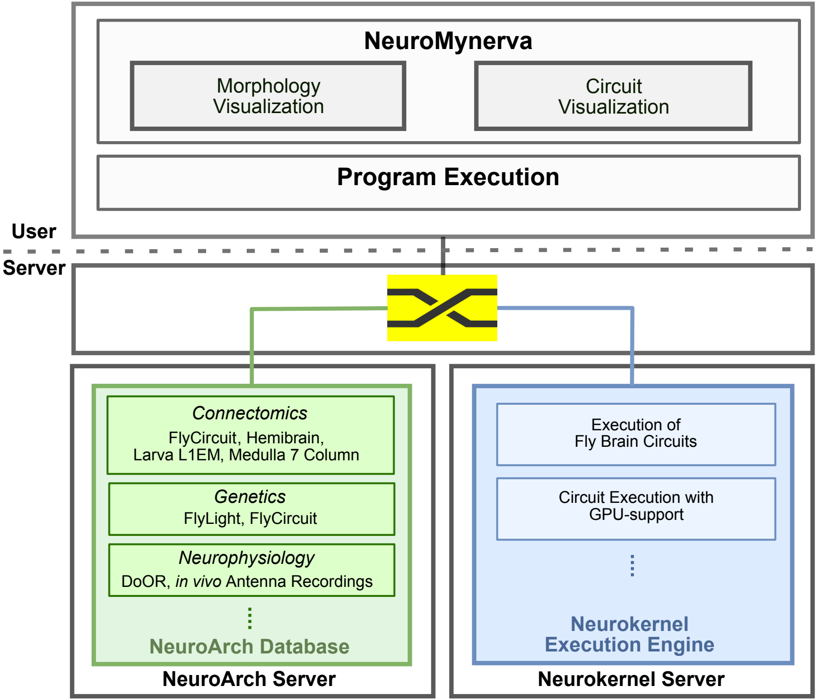

FlyBrainLab is designed with three main capabilities in mind:

- 3D exploration and visualization of fruit fly brain data,
- creation of executable circuits directly from the explored and visualized fly brain data,
- interactive exploration of the functional logic of the devised executable circuits.

# The FlyBrainLab User Interface (NeuroMynerva)




(**top left**) NeuroNLP 3D visualization window. (**top right**) NeuroGFX executable circuits window.
(**bottom**) Program Execution Window with a built-in Jupyter notebook.
(**far left**) Local File Access with Jupyter FileBrowser widget.
(**far right**) Information Panel for individual neurons/synapses.

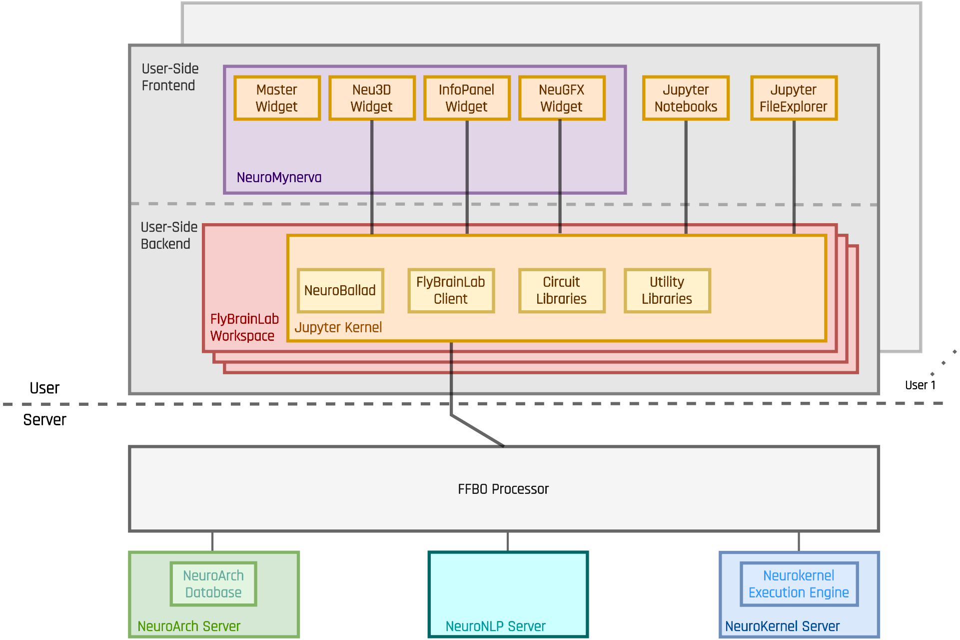



In addition to the NeuroMynerva front-end, the main FlyBrainLab back-end components include the:

**NeuroArch Database**
that integrates and stores anatomical, genetic, and neurophysiology datasets, and the associated circuit models.

**Neurokernel Execution Engine**
that supports the execution of fruit fly brain circuits on GPUs.

(Lazar et al., eLife 2021)




The **user-side architecture** provides the local execution environment as well as an easy-to-use GUI for multi-user access to the services provided by the server-side.

The **Utility Libraries and Circuit Libraries** can be loaded into the workspace of the user-side backend.

The **server-side architecture** consists of the NeuroNLP Server, the NeuroArch Server and the Neurokernel Server.

# FlyBrainLab Utility and Circuit Libraries

The FlyBrainLab Utility Library of the Fruit Fly Connectome/Synaptome include:

- **NeuroEmbed**: Cell Classification and Cell Type Discovery,
- **NeuroSynapsis**: High Level Queries and Analysis of Connectomic and Synaptomic Data,
- **NeuroGraph**: Connectivity Pattern Discovery and Circuit Visualization Algorithms,
- **NeuroWatch**: 3D Fruit Fly Data Visualization in Jupyter Notebooks,
- **NeuroMetry**: Morphometric Measurements of Neurons.

The FlyBrainLab Circuit Library for Analyzing, Evaluating and Comparing Fruit Fly Brain Circuits

- **CXcircuits**: Library for Central Complex Circuits,
- **EOScircuits**: Library for Larva and Adult Early Olfactory Circuits,
- **MolTrans** Library for Molecular Transduction in Sensory Encoding.

Part III

# Analyzing, Evaluating and Comparing *Drosophila* Circuit Models

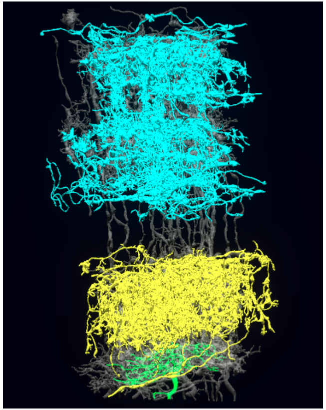
# Creating Executable Circuit Models from Fly Brain Data

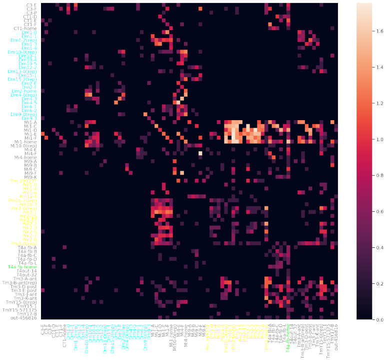
## Building Fly Brain Circuits with English Queries

The NeuroNLP natural language query interface is designed to accommodate users with widely different expertise. A layperson can perform sophisticated database queries with only knowledge of fly brain neuroanatomy. For example, to query the neuron circuit involved in visual motion detection:

1) “`show T4a in column home`”
2) “`color lime`”
3) “`add presynaptic neurons`”
4) “`color grey`”
5) “`add presynaptic $Dm$ neurons with more than 5 synapses`”
6) “`color cyan`”
7) “`add presynaptic $Pm$ neurons with more than 5 synapses`”
8) “`color yellow`”

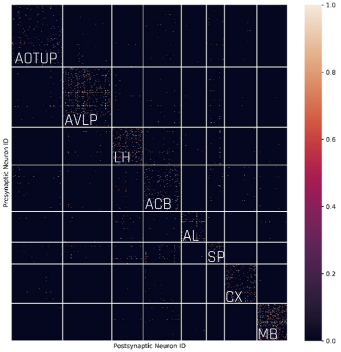
The resulting circuit is visualized (left), and the connectivity matrix of the queried circuit can be easily retrieved (right).



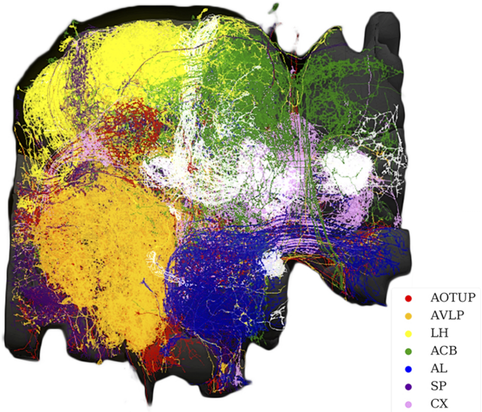


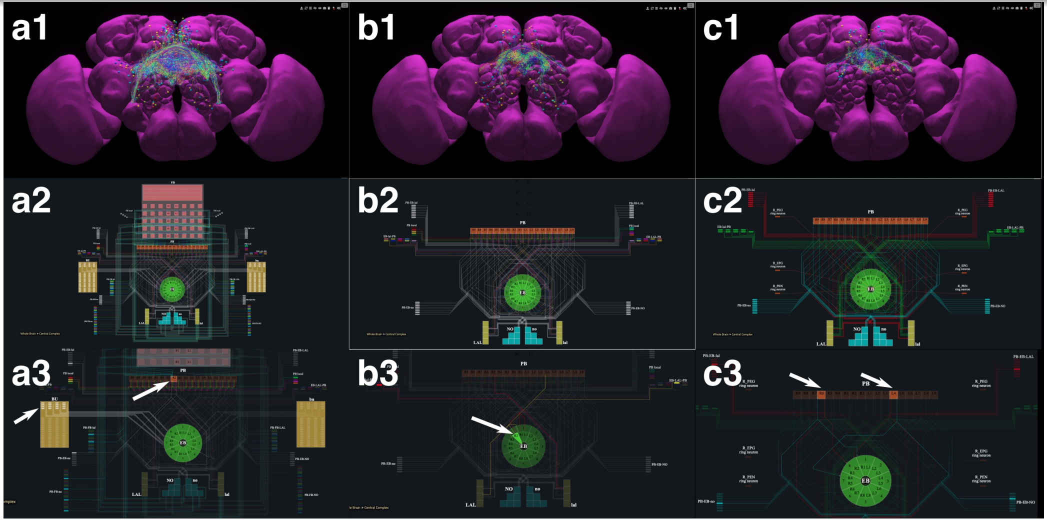
FlyBrainLab provides a set of utilities for exploring the structure of fly brain circuits.

To explore the structure of densely-connected brain circuit at the whole-brain level, we invoke an algorithm provided in the utilities library to extract 8 densely connected neuron groups (left), and pseudo-color the neurons of each group (right).

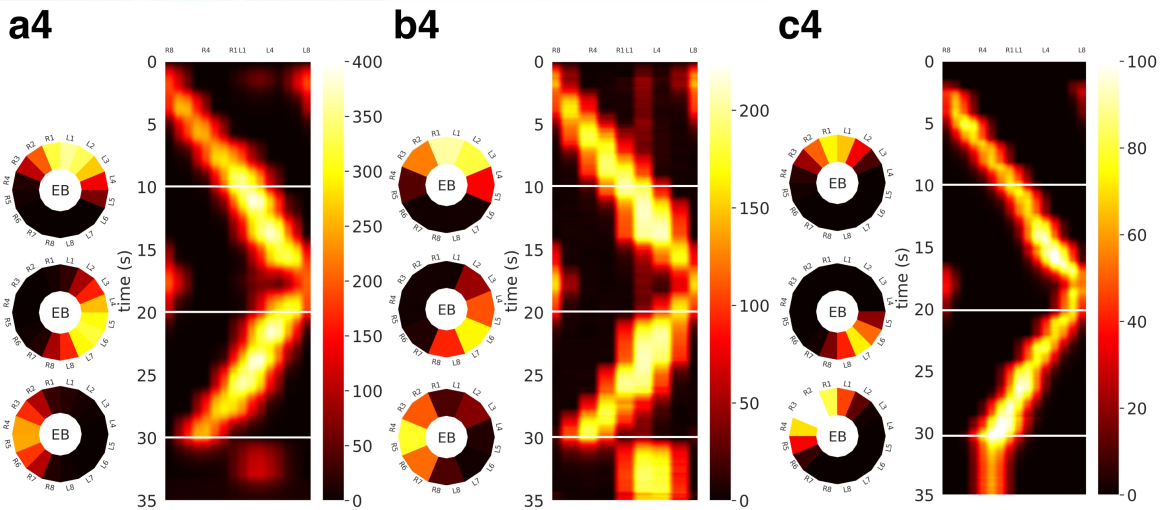



Zoom in for details





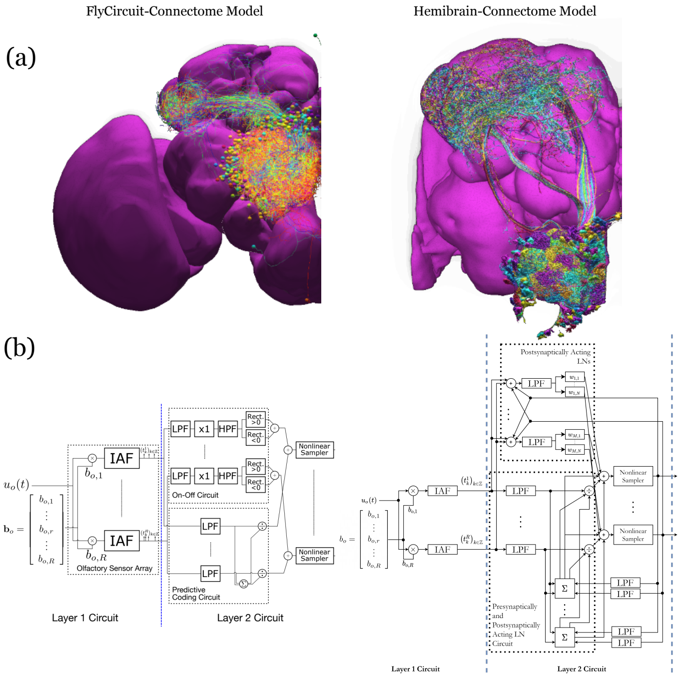

- (a1, b1, c1) Morphology of the neurons visualized in the NeuroNLP window.
- (a2, b2, c2) Neurons in the NeuroNLP window depicted in the NeuroGFX window as abstract interactive circuit diagrams.
- (a3, b3, c3) When a single vertical bar is presented in the visual field, different sets of neurons/ subregions receive either current injections or external spike inputs for each of the models, respectively.




- (a4, b4, c4) Mean firing rate of neurons in each of the EB subregions. Insets show the rates at 10, 20, and 30 seconds, respectively.

# Analyzing, Evaluating and Comparing 3 Circuit Models of the CX (cont'd)

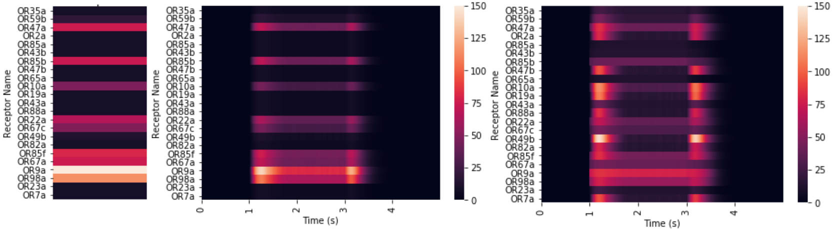
## FlyCircuit Dataset



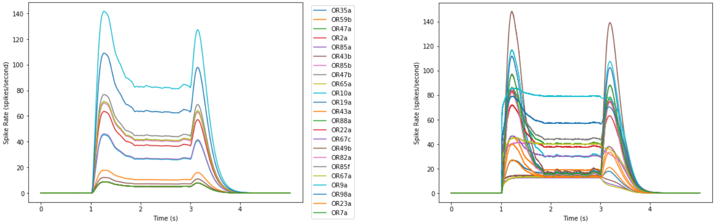

(a) Morphology of olfactory sensory neurons, local neurons and projection neurons in the antennal lobe for the FlyCircuit and Hemibrain datasets.

(b) Circuit diagrams depicting the antenna and antennal lobe circuit motifs derived from the two datasets.

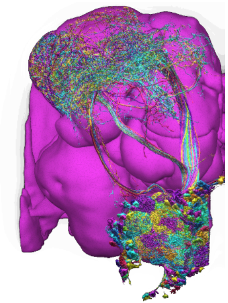
(Lazar et al., eLife 2021)

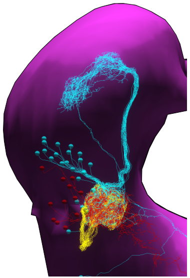



(d)

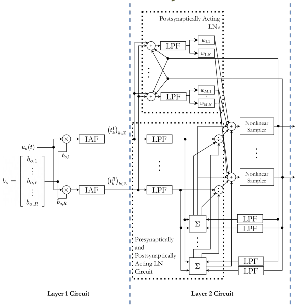


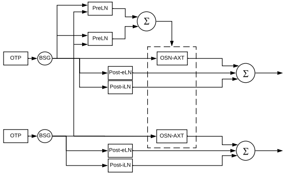

(**top**) Response of the antenna/antennal lobe circuit to a constant ammonium hydroxide step input;
(**left**) interaction between the odorant and 23 olfactory receptors captured as the vector of affinity values;
(**middle and right**) a heatmap of the uniglomerular PN PSTH values (spikes/second) grouped by glomerulus for the 2 circuit models.
(**d**) The PN response transients of the 2 circuit models for uniform noise input with a minimum of 0ppm and a maximum of 100ppm preprocessed with a 30Hz low-pass filter and delivered between 1s and 3s.





Morphology of Olfactory Sensory Neurons (OSNs) in the Antenna (ANT), Local Neurons (LNs) in the Antennal Lobe (AL) and Projection Neurons in the AL of the adult (left) and larva (right).

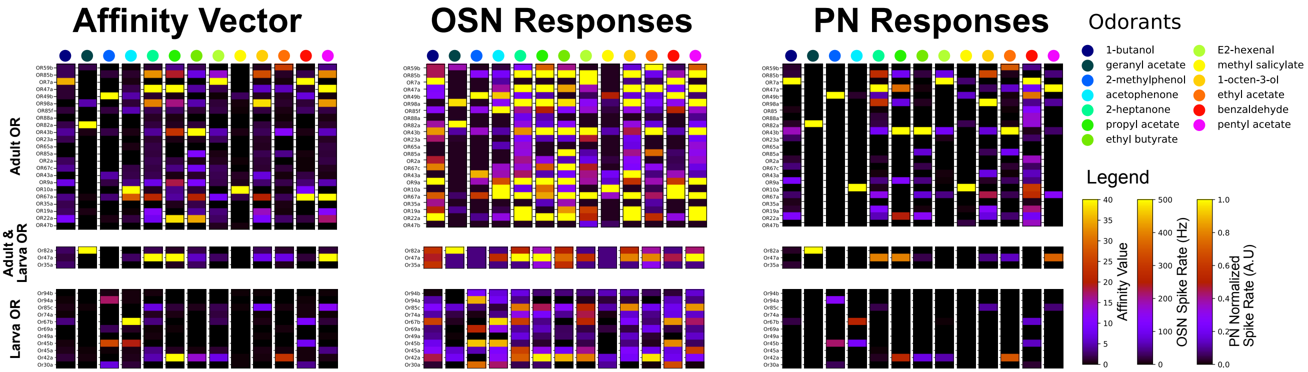



Circuit diagrams depicting the Antenna and Antennal Lobe circuit motifs of the adult (left) and larva (right).

# Evaluating and Comparing 2 *Drosophila* Early Olfactory System (EOS) Models (cont'd)

## Adult (*left*, Developed Based Hemibrain Dataset) and Larval (*right*, Developed Based on LarvaEM Dataset) Circuits




(**left**) Interaction between 13 odorants and 37 odorant receptors (ORs) characterized by affinity values. The ORs expressed only in the adult fruit flies are grouped in the top panel; the ones that are expressed in both the adult and the larva are grouped in the middle panel; and those expressed only in the larva are shown in the bottom panel.

(**middle and right**) Steady-state outputs of the EOS models to a step concentration waveform of 100 ppm are used to characterize combinatorial codes of odorant identities at the OSN level (**middle**) and the PN level (**right**).