From wing to wiring- a short introduction to *Drosophila* brain connectomics.

Did you know that a fruit fly brain has about 140,000 neurons? It sounds like a lot until you consider that the human brain has over 86 billion neurons. Fruit flies can perform impressive tasks such as navigation, learning from surroundings and constantly updating the memory and foraging for food. How do they manage all this? That's where connectomics comes in to explain all of this.

What is a connectome?

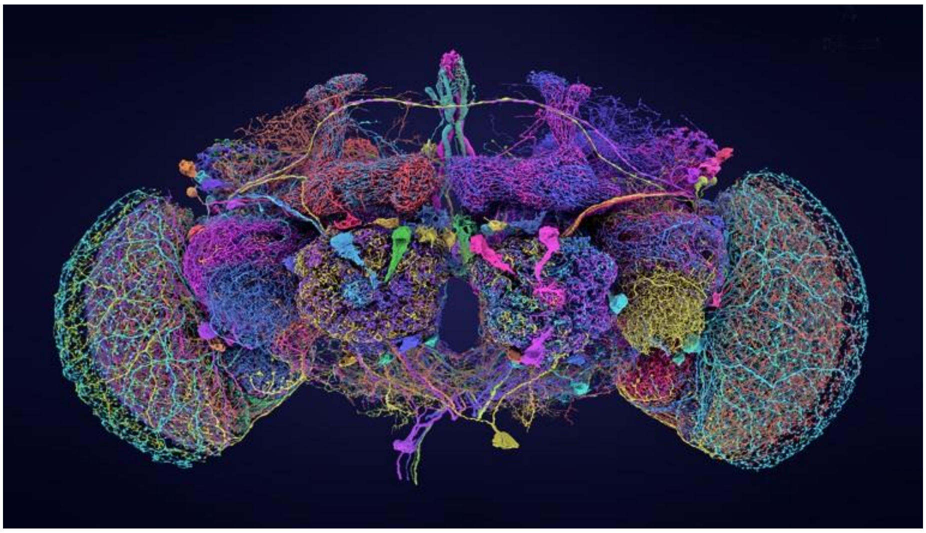

Figure 1: Depicting nearly 140,000 mapped neurons in the fruit-fly brain. This version shows the 50 largest. Credit: Tyler Sloan and Amy Sterling for Flywire, Princeton University.

Connectome is the brain's wiring diagram. It's the detailed map of neural connections and a blueprint for connectivity of neurons and synapses. Getting this detailed map can help us study how information is processed and how different brain regions communicate with each other and in turn help us study behaviour and many neurological conditions. It includes all the information about which neurons are connected to each other.

Information flow starts with sensory neurons called upstream neurons or presynaptic neurons which receive input from sensory receptor, picking up signals like sweet smell from the environment and they pass it down to the other neurons called downstream neurons or postsynaptic neurons which process it further to the other parts of the nervous system for initiating specific behavioural response like a fruit fly extending its proboscis to taste something sweet.

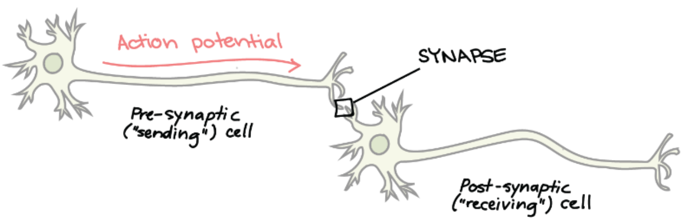

Figure 2 : Neural signal transmits from pre-synaptic neuron to post synaptic neuron via synapse. Source : https://www.khanacademy.org/science/biology/human-biology/neuron-nervous-system/a/the-synapse

Now this signal is carried via chemical messengers called neurotransmitters, these are present across the tiny gaps between the neurons called synapses. There are two types of neurotransmitters: 1. Excitatory: they promote signal to the next (downstream) neuron to fire and 2. Inhibitory: they decrease the likelihood of next (downstream) neuron firing which can inhibit neural activity and these messengers make sure the brain doesn't get overwhelmed.

The connectome has all this information, and it is enriched with other data such as single transcriptomics data which reveals the genes that neurons express and predictions about the neurotransmitter types using machine learning. This data helps researchers link the structure of neural circuits to their functions, helping to understand behaviour and neurological conditions.

Why *Drosophila?*

Model organisms are small non-human organisms that are generally used in research, they are easy to work with, have small life cycles and can be tailored to study any disease condition via mutations. *Drosophila melanogaster* commonly known as the fruit fly is one of the model organisms used in neuroscience studies. Despite its small size it has 140,000 neurons, allowing researchers to study the neural circuits and behavioural questions that involve sensory processing, learning, memory and decision making. For instance, a fruit fly can learn to associate a specific smell with a reward or punishment, just like how we remember good and bad experiences, making it a good model to study associative and reinforcement learning.

Drosophila brain is organised into distinct functional modules such as olfactory (smell), visual, and auditory processing units. This enables segregated processing of different types of information while also allowing for integration across modules. The similarity in the brain connectivity patterns between *Drosophila* and higher order mammals suggest that fundamental principles of brain organisation have been conserved throughout evolution despite the differences in size and complexity among species. This conservation implies that findings from *Drosophila* can explain human neural circuits. The parallels of brain architecture and function allow for meaningful studies in neurological diseases. These studies can be extrapolated to larger brains such as mammals.

How do scientists map the *Drosophila* connectome?

The process of mapping this connectome involves advanced imaging techniques like electron microscopy which takes incredibly detailed images of thinly sliced brain tissue and then later on these slices are put together to create the entire 3D brain map which is called reconstruction using a tool called Neuroglancer, this allows the scientists to visualise the neurons in detail and collaborative projects- Flywire (https://flywire.ai/) have been pivotal in this research. Automated segmentation is used to automate the segmentation process which involves using machine learning algorithms to identify individual neurons with synaptic connections and after this, manual proofreading is done to correct neurons such as false merges between neurons or missed branches to ensure the accuracy.

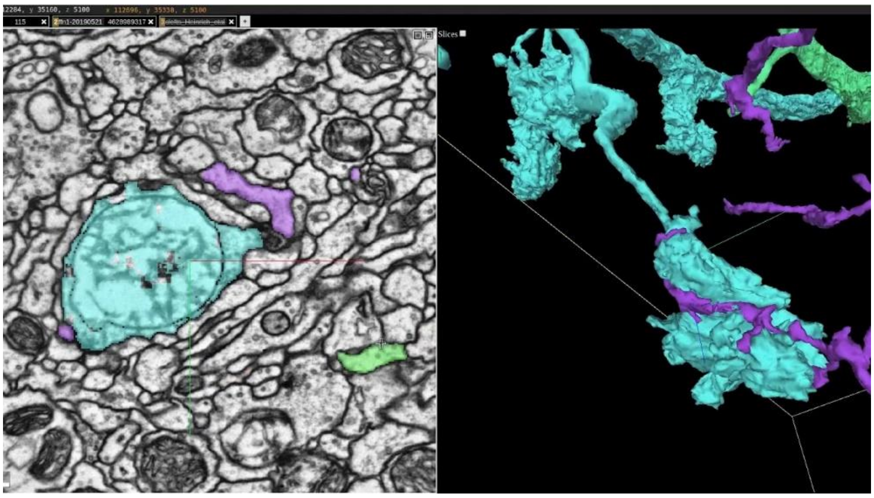

Figure 3 : 3D image reconstruction using Neuroglancer.

Source: https://research.google/blog/an-interactive-automated-3d-reconstruction-of-a-fly-brain/

How is this connectome utilised?

The flow of information within the *Drosophila* neural circuits can be studied using computational simulation approaches. Computational models can act like a virtual brain on computers, integrating vast amounts of data from connectome, which includes information about neurons and neurotransmitters. This integration allows researchers to stimulate brain activity on computers and study how the neurons fire and interact with each other, leading to specific actions such as fruit fly's response to tasting sugar. How cool is that? by generating testable hypotheses, researchers can now identify which neurons are involved in certain behaviours and these are then validated via experimental approaches.

The paper titled "A *Drosophila* computational brain model reveals sensorimotor processing" by Philip K. Shiu et al. presents a comprehensive computational model of the *Drosophila melanogaster* brain, focusing on how sensory inputs are processed to generate specific behaviours, particularly in feeding and grooming.

Features of the Model:

1.Mathematical Frameworks: Computational models use mathematical equations to describe how neurons work. Differential equations are used to simulate how a neuron's membrane potential (its electrical charge) changes over time. What's a Membrane Potential? Think of a neuron like a battery: it has an electrical charge that changes based on inputs. If the charge hits a certain level (the threshold), the neuron fires a signal.

Differential equations are mathematical tools that describe how things change over time. In this study, they model how a neuron's membrane potential changes as it receives input. The leaky integrate-and-fire (LIF) model used in the *Drosophila* study is a prime example, where the change in membrane potential:

$$\tau_m \frac{dV(t)}{dt} = -(V(t) - V_{\text{rest}}) + R_m I(t)$$

This equation captures how a neuron's potential leaks over time while integrating incoming signals, ultimately leading to spiking behaviour when a threshold is reached.

2. Behavioural Replication: One of the model's main goals is to replicate the behaviour of the fly's neural circuits. By simulating how neurons interact based on their connections and properties, researchers can predict how specific sensory inputs, like sugar detection, lead to motor outputs, such as feeding movements. How Does the Model Work? Imagine a chain reaction: when one neuron fires (due to sugar detection), it sends signals to other neurons based on their connection strengths. If these downstream neurons reach their firing threshold, they also fire, creating a cascade of activity that drives behaviour.

By simulating neural circuits in simpler organisms, researchers can uncover universal principles that apply to more complex systems, including human brains.

References and further reading:

Galili, D. S., Jefferis, G. S., and Costa, M. 2022. Connectomics and the neural basis of behaviour. *Current Opinion in Insect Science* 54:100968. Available at: https://doi.org/10.1016/j.cois.2022.100968.

Shiu, P. K., Sterne, G. R., Spiller, N., Franconville, R., Sandoval, A., Zhou, J., Simha, N., Kang, C. H., Yu, S., Kim, J. S., et al. 2024b. A Drosophila computational brain model reveals sensorimotor processing. *Nature* 634:210–219. Available at: https://www.nature.com/articles/s41586-024-07763-9.