Exploring the Flywire Connectome

College Neuroscience
Lesson #2

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Section 1: Connectivity

1. Brains can be thought of as collections of neurons which are wired together to form circuits which are capable of performing computations and controlling the body. Similarly, man-made computers are built by wiring electrical components together, and are similarly capable of computations and hardware control.

    a. Brainstorm as a group to identify a function both brains and computers are capable of performing.

    b. Identify a function computers are capable of which brains are poor at.

    c. Identify a function brains are capable of which computers are poor at.

2. One significant difference between computers and brains is in the wiring of their components. While artificial computers tend to be feedforward in their connectivity, brains have a highly parallel circuit architecture with many recurrent and reciprocal connections. *To search for neurons with a certain connectivity feature, use the command "connectivity tag == [name]."*

    a. Neurons A and B are **reciprocally connected** if neuron A makes a connection with neuron B and neuron B also makes a connection back to neuron A. What purpose could such a feedback loop serve?

    b. How many neurons in the brain are reciprocal? What fraction of all neurons does this represent? *Use "connectivity tag == reciprocal."*

    c. How do the fractions of each neurotransmitter amongst the reciprocal neuron population compare to the fractions of each neurotransmitter across the whole brain?

Section 2: reciprocal and recurrent motifs

1. Let us examine in greater detail a specific neuron with reciprocal connections. Find one of the cM15 neurons (*Use "cell type == cM15"*).

    a. Sketch this neuron, identify its neurotransmitter, and use both the 3D Render with Synapse Markers and the input and output neuropils to identify where its incoming and outgoing synapses are.

    b. To find the neurons reciprocal to cM15, click on "reciprocal cells" in the Connected Cells box. How many reciprocal partners does cM15 have? Note the cell type, number of connected synapses, and neurotransmitter identities of each of the three largest reciprocal partners.

    c. One of the neurons reciprocal to cM15 is MeLp1. Click on this neuron and identify where its incoming and outgoing synapses are. How do their locations compare with those of cM15?

    d. Examine the network graph of the reciprocal connections made by cM15 by navigating to the Network tool. *Use a query of the format "[cM15 root ID#] {or} {reciprocal} [cM15 root ID#] ". Note that you can adjust network visualization parameters using the Settings button.*
        i. Are cM15's reciprocal partners independent, or do they also connect with each other?

        ii. Based on this network diagram, are excitatory-inhibitory (E-I), excitatory-excitatory (E-E), or inhibitory-inhibitory (I-I) reciprocal connections more common? Speculate on why this may be. *(In the fly brain, ach is excitatory and GABA and glut are inhibitory)*

    e. Based on the information available in the connectome, including synapse locations, neurotransmitter expression, and its partners (reciprocal and otherwise), hypothesize on the role of the cM15 neuron.

2. Neurons A, B, and C form a structure called a **3-cycle** if neuron A makes a connection with neuron B, neuron B makes a connection with neuron C, and neuron C makes a connection back to neuron A.

    a. How many neurons in the brain are 3-cycle participants? What fraction of all neurons does this represent? *Use "connectivity tag == 3_cycle_participant."*

    b. How do the fractions of each neurotransmitter amongst the 3-cycle neuron population compare to the fractions of each neurotransmitter across the whole brain?

    c. A 3-cycle is the simplest form of indirect feedback loop. Why might a circuit require indirect feedback, rather than the direct feedback of a reciprocal connection?

3. Let us examine in greater detail a specific neuron which participates in 3-cycles. Find one of the CB1078 neurons (*Use "cell type == CB1078"*). These neurons, also called AMMC-B1, are part of the fly's auditory circuit.

    a. Sketch this neuron, identify its neurotransmitter, and use both the 3D Render with Synapse Markers and the input and output neuropils to identify where its incoming and outgoing synapses are.

    b. While we're here, let's check out the neurons reciprocal to CB1078. How many reciprocal partners does it have, and what neurotransmitters do they express? Does this make these reciprocal connections E-E or E-I?

    c. To access the 3-cycle motifs involving CB1078: *pull up the Motif Search tool by clicking on "3_cycle_participant" under Connectivity Tags*.

        i. How many different 3-cycles does CB1078 participate in?

        ii. Are the synapses which make up these connections localized to a small part of the brain?

iii. Based on the neurotransmitters expressed by the neurons, how many E-E-E, E-E-I, E-I-I, and I-I-I 3-cycles do you find? Are any compositions rare?

d. Speculate about why a neuron like CB1078 is part of both direct (reciprocal) and indirect (3-cycle) feedback loops. How might multiple sources and types of feedback interact to influence the activity of a neuron or a circuit?

Section 3: Large-scale connectivity features

The fly brain exhibits a mathematical network property known as **rich club organization**, in which nodes (neurons) that have high degree are preferentially connected to other high-degree nodes. This means that neurons with large numbers of partners are more likely than chance to share connections with other neurons with large numbers of partners. Rich club organization has been observed in other networks, such as the internet and air transport, and is hypothesized to be a hallmark of efficient integration and dissemination of information.

1. To examine the population of rich club neurons in the fly brain, search using: "*connectivity tag == rich_club*", and examine the statistics of this population.

    a. How many rich club neurons are there in the brain? What fraction of the total neurons does this represent?

    b. Using the number of internal connections and the number of rich club neurons, compute the average connection probability within the rich club regime. How does this connection probability compare to that of the entire brain?

    c. Compute the prevalence of each neurotransmitter among the rich club population and compare with the neurotransmitter fractions of the entire brain. Why might these fractions differ?

2. Some neurons receive inputs from many partners, but have only a small number of outputs. Such neurons likely integrate information from many sources. Within Codex, we define an **integrator neuron** to be an intrinsic rich club neuron which has at least 5 times as many incoming connections as outgoing connections.

    a. Pick and sketch 3 integrator neurons.

    b. What is the neurotransmitter composition of the integrator population?

    c. Dopaminergic neurons have often been implicated in learning and memory processes. How does the fraction of dopaminergic integrators compare to the overall prevalence of dopaminergic neurons in the brain? Why might integrator neurons be involved in learning circuits?

    d. What is the super class breakdown of the integrators?

3. We can likewise find neurons which have a small number of inputs but a large number of outputs. Within Codex, we define a **broadcaster neuron** to be an intrinsic rich club neuron which has at least 5 times as many outgoing connections as incoming connections.

    a. Pick and sketch 3 broadcaster neurons.

    b. What is the neurotransmitter composition of the broadcaster population?

c. What is the super class breakdown of the broadcasters?

d. Compare the neurotransmitter and super class frequencies between integrators and broadcasters. Can you identify any salient differences?

Interested in doing more with connectomics? Contact flywire@princeton.edu for the latest opportunities to join our scientific community, or check out the latest data challenges on Codex!