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Connectomics: Relating synaptic connectivity to physiology

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Synaptic wiring diagrams, or connectomes, promise constraints for highly detailed neural circuit models, but relating the connectivity information they provide to physiological properties is challenging. A new study describes this relationship for a fruit fly neural pathway, suggesting a path forward for future models.

In the past few years, the scale of datasets containing the wiring of neural systems — 'connectomes' — obtained from electron microscopy has increased by orders of magnitude. While a complete map of the relatively small nervous system (~300 neurons) of the nematode *Caenorhabditis elegans* has existed for decades[1], there are now near-complete connectomes of the central brains of *Drosophila* fruit fly larvae[2] (~2000 neurons) and adults[3,4] (~30,000 neurons), a volume of human cerebral cortex containing ~60,000 neurons[5], and datasets from several other species[6]. These datasets have great potential for building models of neural circuits with realistic connectivity, but basic questions, such as how synaptic connectivity in a connectome relates to physiology, remain unanswered. In this issue of *Current Biology*, Liu *et al.*[7] report a step toward answering this question in a well-characterized *Drosophila* neural pathway.

The availability of connectomic data has led to a large number of recent modeling studies in which the presence or absence of a connection between neuron pairs is determined by electron microscopy. These include models of associative learning[8], motor pattern generation[9], visual processing[10], and decorrelation[11]. However, these and other studies face issues of model parameters that are unconstrained or must be inferred indirectly[12], requiring simplifying modeling choices to be made. One such choice relates to the issue of spatial scale. At one extreme, a modeler might construct a network of 'point neurons', in which each neuron is represented by a single electrical compartment that linearly integrates synaptic input and produces a nonlinear output in response (Figure 1A). Such simplified models form the foundation of many theoretical studies, in particular those using artificial neural networks

popular in the fields of machine learning and artificial intelligence. At the other extreme, three-dimensional morphology and synapse locations obtained by electron microscopy may be used to construct extremely detailed multi-compartment models (Figure 1B). These allow for the possibility of complex computations within, for instance, nonlinear dendrites[13].

Another modeling choice is the relationship between connection strength and synaptic connectivity as assayed by electron microscopy. In mammals, the size of postsynaptic densities is linearly related to the magnitude of excitatory postsynaptic potentials[14]. In fruit flies, synapse sizes are less variable but an individual presynaptic neuron can form anywhere from one to hundreds of synaptic connections onto a single postsynaptic neuron[4]. This has led to an assumption, common in the *Drosophila* modeling literature, of a linear relationship between synapse count and size of postsynaptic potentials. In support of this, studies have found that models initialized with connectome-determined weights fit neural data better than those initialized with random weights[15]. Another study found that an artificial neural network model of the early stages of the fly visual system that was optimized to track objects in natural scenes only elicited neuronal response properties consistent with experiment when network weights were initialized with synapse counts from the connectome[10].

Given these issues, quantitative characterizations of how anatomical factors such as the number and locations of presynaptic inputs affect connection strength are a valuable resource. Liu *et al.*[7] provide such a characterization by relating connectivity from a recent comprehensive *Drosophila* 'hemibrain' connectome dataset[4] to existing whole-cell recordings of neurons whose presynaptic partners were activated optogenetically[16]. Specifically, the authors considered a cholinergic synaptic pathway implicated in innate olfactory behaviors, between olfactory projection neurons in the antennal lobe and lateral horn neurons[17]. Projection neurons form the output units of spatially stereotyped antennal lobe glomeruli, where information from olfactory receptor neurons is processed. The lateral horn contains an anatomically diverse but stereotyped set of cell types that receive input from projection neurons, allowing the authors to align hemibrain connectome neurons to those previously identified with light microscopy.

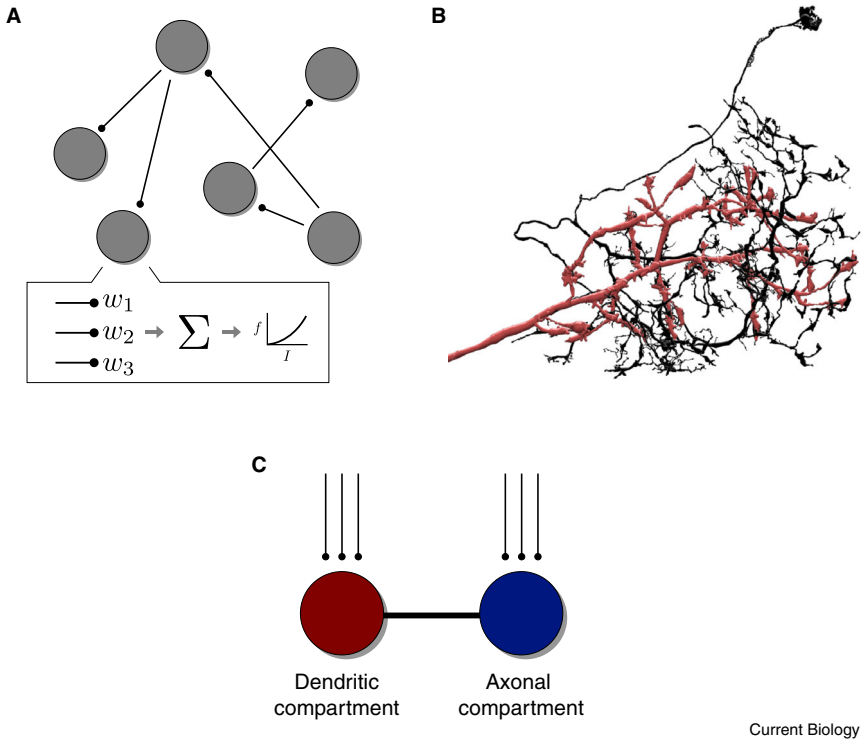

Figure 1. Levels of abstraction for connectome-constrained models.
(A) A network of 'point neurons', in which it is assumed that synaptic inputs sum linearly according to weights w_i and a nonlinear response is produced according to each neuron's f–I curve (the mapping from input current to a neuron's output firing rate). (B) Illustration of the morphologies of a projection neuron (VA6, red) and a postsynaptic lateral horn neuron (AV2m1, black), reconstructed from the *Drosophila* hemibrain dataset[4] and visualized using neuPrint (neuprint.janelia.org). (C) The abstraction proposed by Liu *et al.*[7], in which neurons are modeled with distinct dendritic and axonal compartments that each linearly integrate their synaptic inputs.

Liu *et al.*[7] examined the magnitude of unitary evoked postynaptic potentials (uEPSPs) in lateral horn neuron membrane voltage in response to two-photon optogenetic activation of projection neurons, recorded in an *ex vivo* preparation[16]. Importantly, they focused only on glomeruli with single projection neurons, ensuring uEPSPs from single presynaptic partners could be resolved. They found that these magnitudes indeed exhibit an approximately linear relationship with synapse density (synapse count of a lateral horn neuron normalized by its surface area), as would be expected from a passive model in which membrane resistance is inversely proportional to surface area.

Despite this significant relationship, however, Liu *et al.*[7] identified a subset of outliers in the data. Notably, these outliers appeared to be associated with connections involving projection neurons that preferentially synapse onto the axonal, rather than dendritic, arbor of the postsynaptic lateral horn neuron. Given this observation, the authors predicted that two-compartment models that treat integration in the dendritic and axonal arbors separately would better account for the data, which was indeed the case. On the other hand, distance from synapse to soma had no systematic effect on measured uEPSP amplitude, pointing to a form of 'synaptic democracy'[18] in which passive attenuation *en route* to the spike initiation zone equalizes synaptic efficacies. Multi-compartment simulations of lateral horn neurons in which the authors stimulated and recorded from different locations supported this approximation, though a modest distance dependence was present in these models.

Further studies are required to determine the consequences and generality of these results. How the results extend to the *in vivo* state and different neuromodulatory or internal motivational states[12] will require additional calibration experiments. Although the set of lateral horn neurons that Liu *et al.*[7] study are morphologically diverse, other cell types may behave differently. Similar calibration experiments for non-cholinergic synaptic connections are also needed. A characterization of inter-individual connectome variability would permit an estimation of whether deviations from the linear relationships the authors observed could be accounted for by individual differences.

Nonetheless, Liu *et al.*[7] provide a crucial guide for future modeling studies constrained by the *Drosophila* connectome. Their findings of synaptic democracy within but independence across axonal and dendritic arbors suggest a potential intermediate abstraction between point neuron and detailed multi-compartmental models in which dendritic and axonal integration are modeled separately (Figure 1C). Such models are reminiscent of 'gated' models of artificial neural network units, in which two sources of input interact multiplicatively[19]. Understanding the logic and interaction of these two sources of inputs may reveal new computational principles for network function but at a level of abstraction still amenable to theoretical analysis.

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Paleobiogeography: Why some sauropods liked it hot

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Dinosaurs dominated terrestrial ecosystems for over 150 million years, and while most groups spread globally, giant, long-necked sauropods never managed to reach polar regions. A new study documents dinosaur biogeographic patterns and examines the role climate played in shaping their distribution and dispersal.

Dinosaurs are perhaps the most easily recognisable and widely studied fossil organisms. They reigned over terrestrial ecosystems for over 150 million years, diversifying into a spectacular variety of shapes, sizes, and life-styles. Decades of study have illuminated many details of this diversity, including important insights into dinosaur morphology, locomotion, evolutionary trends, diets