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Constraining computational models using electron microscopy wiring diagrams

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Numerous efforts to generate "connectomes," or synaptic wiring diagrams, of large neural circuits or entire nervous systems are currently underway. These efforts promise an abundance of data to guide theoretical models of neural computation and test their predictions. However, there is not yet a standard set of tools for incorporating the connectivity constraints that these datasets provide into the models typically studied in theoretical neuroscience. This article surveys recent approaches to building models with constrained wiring diagrams and the insights they have provided. It also describes challenges and the need for new techniques to scale these approaches to ever more complex datasets.

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Introduction

Theoretical models in neuroscience often make assumptions about synaptic connectivity that lead to predictions about neural activity and behavior. These assumptions range from specifying the parameters of a statistical distribution that characterizes the wiring of many neurons (for example, populations of pyramidal cells in a volume of neocortex [1]) to specifying the properties of connections among individual neurons with prescribed functions (for example, specific connections among motion-selective retinal neurons [2••]). Except for systems with sufficiently few neurons, these assumptions are often informed by incomplete knowledge of connectivity obtained from electrophysiological measurements of a subset of connections.

Electron microscopy (EM) reconstruction techniques promise a more complete picture of neuronal interconnectivity, obtained by tracing the processes and identifying the synaptic connections of all neurons in an imaged volume of brain tissue [3]. An EM wiring diagram has existed for the nematode *C. elegans* since the mid-1980s [4], and for the larva of the ascidian *Ciona intestinalis* since 2016 [5]. Efforts are underway to map the full nervous systems of the adult [6] and larval [7,8,9,10•] *Drosophila melanogaster* fruit fly, larval zebrafish [11], volumes of rodent brains including retinal [12] and cortical areas [13–15], and other systems [16,17].

These efforts suggest the possibility of inferring the connectivity of models directly from EM data, rather than assuming it. Such an approach may lead to better models whose activity and interactions can be more readily compared to experiments. We survey recent studies that build models based on synaptic wiring diagrams, highlighting results that have been obtained and the assumptions that are required to build the models. We argue that new quantitative techniques must be developed to exploit EM data as a meaningful constraint in models with many uncertain parameters.

EM wiring diagrams and the information they provide

EM reconstructions of neuronal connectivity are based on images obtained from thin sections of a volume of brain tissue [3]. These images are analyzed to identify structures of interest, typically 3-d reconstructions of neurons, their processes, and their synaptic connections. While this is often done manually, advances in automated image segmentation methods are accelerating the speed at which analyses can be performed [18]. EM reconstructions are effective at identifying neurons and the presence of chemical synapses between them, but many quantities of interest for modeling remain unconstrained (Figure 1). The first source of uncertainty involves the connectivity itself. In addition to tracing errors, EM datasets often provide reconstruction of only a subset of a complete neural circuit. Such "partial" connectomes do not provide knowledge of interactions between neurons that involve unreconstructed synapses. Such "hidden" neurons can make it substantially more difficult to infer accurate models [19,20].

As has been discussed before [21], even knowledge of a "complete" connectome leaves many parameters relevant for modeling unknown. Neurotransmitter identities

Figure 1

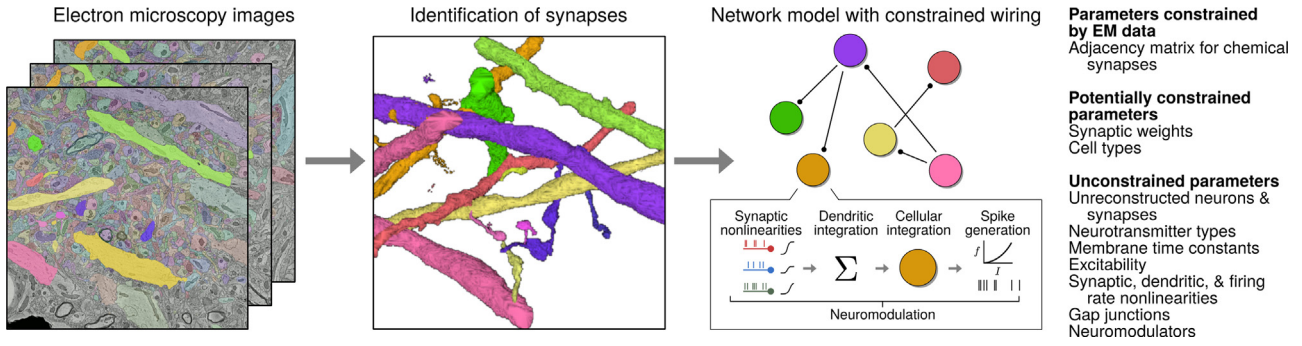

Illustration of the use of EM data to constrain the wiring of a network model. While such data can be used to determine the presence or absence of chemical synapses between neurons, only incomplete information about synaptic weights and cell types may be available, and many biophysical parameters remain unconstrained. EM images illustrate a volume of mouse somatosensory cortex [14] (available under the Open Data Common Attribution License) and are visualized using the NeuroGlancer software (https://github.com/google/neuroglancer).

for each synapse are not revealed and must be identified by other means, for example by antibody staining or transcriptomic profiling [22,23]. This can make it difficult to identify excitatory or inhibitory interactions unless morphology clearly identifies excitatory or inhibitory cell types. Size and number of synaptic contacts likely correlate with the size of evoked postsynaptic potentials, but the precise relationship has not been quantitatively measured [24]. Gap junctions may be difficult to identify, depending on the staining protocol used. The effects of neuromodulators cannot be inferred [21]. Many other cellular and synaptic properties, such as membrane time constants, excitability, and plasticity, are also unconstrained and must be characterized by non-EM means [25•,26•]. What can we infer from a neural circuit's connectivity alone in the face of this uncertainty? An instructive account comes from modeling studies that focus on the stomatogastric ganglion (STG), a collection of about 30 neurons in crustaceans that reliably produces a periodic rhythm [27]. The limited number of neurons has permitted a relatively complete characterization of this system's wiring diagram using electrophysiological methods. This wiring diagram has guided many important studies of the STG's dynamics, but does not fully constrain them. Researchers have found that there is a space of distinct models that differ in their cellular and synaptic properties but are consistent with both the observed rhythm that the STG produces and its connectivity [28]. Modelers must therefore contend with the challenge that any dynamical model they build will contain unknown parameters and dynamics that are not a perfect match to real neurons, raising the concern that knowledge of a wiring diagram will be unable to sufficiently constrain the space of models consistent with available data.

Graph theoretic approaches

One approach to this challenge is to develop methods that draw conclusions based only on the graph of connections defined by a synaptic wiring diagram and independent of unknown quantities. Methods have been developed to extract structure such as the presence of distinct cell types from combined connectivity and anatomical data [29••], or to infer latent variables that characterize neurons and their connectivity based on a graph of connections [30]. Studies of *C. elegans* have quantified the statistics of network *motifs* [31]—patterns of connections among small groups of neurons—which may be over- or underrepresented compared to an Erdös–Rényi random graph in which all connections are drawn independently. However, relating these graphical properties to neural dynamics is challenging. Theoretical progress has been made relating motif statistics to correlations between the spike trains of neuron pairs [32], but these approaches require assumptions such as homogeneity of cellular properties, linearized synaptic interactions, and knowledge of the correlation structure of external inputs. Mathematical progress has also been made in understanding how the dynamics of inhibitory threshold-linear recurrent networks depend on network motifs [33•]. Models of associative learning make testable predictions about motif statistics under the assumption that wiring is optimized to maximize the number of stable patterns, or "attractors," of neural activity [1]. EM reconstructions will quantify these graph statistics with greater accuracy and scope than has been previously possible with electrophysiology [34].

The nervous system of *C. elegans* exhibits global coordinated activity during movement [35]. An account of such dynamics likely requires analyses beyond average graph properties or small circuit motifs. A recent study approached this subject by focusing on the notion of *network controllability*, defined as follows [36]: if a time-varying input to a subset of N neurons (the controlling neurons) can be chosen such that the output of another subset of M neurons (the outputs) can be driven to an

arbitrary point in M-dimensional space, then the outputs are said to be controllable by the controlling neurons. The authors identified classes of neurons in the graph of the *C. elegans* connectome, that, if ablated, reduce the number of controllable muscles, and compared their results to experiments. This network control theory approach is attractive because it connects global structure to function using only a graph of connections. However, like other approaches that focus on graph-theoretic properties, it requires strong assumptions on neuronal dynamics. Interactions between neurons are modeled as a linear dynamical system with identical time constants for each neuron, and the strengths or signs of interactions do not come into play. Complete controllability may also be too strong a requirement to ask of a biological system. Future studies may relax some of these assumptions.

Models constrained by function

Among the first results provided by the wiring diagram of *C. elegans* was a characterization of its circuitry for detecting touch [37]. Systems close to the periphery are attractive targets for modeling based on EM wiring diagrams. For many of these systems, inputs and outputs can often easily be identified and relatively complete circuits can be reconstructed, leading to readily-formed hypotheses about function that can be tested even if certain system parameters are unknown.

A major target of EM reconstruction efforts in mice and *Drosophila* has been the visual system, which has the advantages of well-characterized cell types and inputs. Since the 1960s, researchers have known that subtypes of mammalian retinal neurons exhibit selectivity to the direction of visual motion [38], but the mechanisms of this selectivity have been a matter of debate. EM reconstruction of mouse retina permitted, for the first time, testing of models that predicted specific connectivity motifs, such as direction selectivity of connections from starburst amacrine cells onto retinal ganglion cells [39], or differential dendritic targeting of connections from bipolar cells onto starburst amacrine cells [2••]. Such direct model evaluation was only possible once EM reconstructions were available. In *Drosophila*, the early visual system has also been the target of reconstruction efforts. A reconstruction of of the optic medulla made predictions about the circuit underlying motion selectivity of neurons in this area [40,41]. Connectivity constraints from these data combined with activity measurements have led to models of *Drosophila* motion processing that are being continually refined [42–46].

EM reconstructions of the olfactory system have also been performed, including maps of the *Drosophila* antennal lobe [47] and zebrafish olfactory bulb [48], which receive input from olfactory receptor neurons. A recurrent network model of the zebrafish olfactory bulb, using threshold-linear neurons with connectivity constrained by EM data, demonstrated that its wiring is consistent with a role in decorrelating odor responses [49••]. In *Drosophila*, several studies have focused on the mushroom body (MB), an associative learning center that receives input from the antennal lobe [50,10•,6]. Previous experiments in adult *Drosophila* found that the wiring of Kenyon cells (KCs) in the MB is consistent with random formation of synapses [51], an idea with theoretical support [52,53]. An EM reconstruction of the larval MB found KC connectivity largely consistent with this hypothesis [10•]. Modeling KCs as threshold-linear neurons, the study argued that these wiring statistics were optimal based on the ability of a readout of KC responses to discriminate odors. A more recent analysis of an adult *Drosophila* EM volume suggests that there may be additional structure in PN-to-KC wiring that has yet to be characterized, and future models will investigate the consequences of this structure [6].

Other studies have focused on the motor periphery, modeling the generation of locomotor activity and escape responses in *Drosophila* larvae [7,8,54••] and visual navigation in *Platynereis* larvae [17]. Frequent themes in the above studies are largely feedforward architectures, limited numbers of input channels that convey information with well-characterized statistics, and sufficient knowledge of the properties of cell types of interest to model their responses (Table 1). For many systems, not all of these features may be present. In the next section, we discuss the possibility of constraining neural network models to infer task-relevant neural activity in the face of uncertainty in biophysical parameters.

Constrained optimization of neural network models

For many complex neural circuits, it may not be possible to manually infer or tune unknown model parameters in order to produce a desired function, even with knowledge of the circuit's connectivity. In recent years, artificial neural networks (ANNs), optimized using stochastic gradient descent, have proven effective at performing tasks such as object classification and at predicting neural responses in higher visual cortical areas [55]. Can such optimization approaches benefit from knowledge of a neural system's wiring diagram? This question is not easy to answer because, in typical ANN approaches, the activity of model units is generally not compared directly with individual recorded neurons. Instead, projections of population activity (obtained by algorithms like principal components analysis) in the model and the recordings are compared, or a linear mapping is found that relates the two.

If the wiring of an ANN model is constrained by EM data, however, a one-to-one correspondence between model units and biological neurons is introduced. In certain cases, knowledge of a task and this correspondence may be sufficient to predict features of neural activity,

Table 1

Examples of published modeling approaches that infer properties of a neural system from knowledge of its connectivity. With the exception of the first entry, we focus on approaches that use connectivity as a constraint for models of neural dynamics.

Modeling approach	Data used	Assumptions on dynamics	Assumptions on function	Prediction
Graphical approaches [31,29••])	Adjacency matrix, potentially other anatomical information [29••]	None	None	Motifs, community structure, cell types, etc.
Motif expansion (reviewed in [32])	Motifs of weighted adjacency matrix	Linearized interactions, homogeneous neurons, knowledge of external input correlations	None	Spike train cross-correlations
Competitive threshold-linear networks [33•]	Adjacency matrix	Homogeneous threshold-linear neurons, purely inhibitory interactions	None	Qualitative behavior (e.g. fixed points, limit cycles)
Network control theory [36]	Adjacency matrix	Linear dynamical system with identical time constants for each neuron	Full control of output neurons	Necessity of each neuron for full controllability
Decorrelation [49••]	Weighted adjacency matrix	Threshold-linear neurons, known membrane and synaptic properties	Decorrelation of inputs	Correlations between neurons
Dimensionality [10•]	Weighted adjacency matrix	Feedforward network, threshold-linear neurons, known membrane and synaptic properties	Maximization of dimension of neural representation	Dimension and linear separability
Constrained neural network optimization (e.g. [56••])	Weighted adjacency matrix	Known external inputs and parameterized firing rate response functions	Determined by cost function	Activity of modeled neurons

even if neurons are modeled with simplified dynamics. A recent study used this approach to analyze the early *Drosophila* visual system [56••]. A convolutional neural network model with threshold linear dynamics, whose lower layers were constrained by EM connectivity data, was trained to track objects in videos of natural scenes. The authors observed that the model reproduced the experimentally measured motion selectivity of specific neuron classes, but only when the connections in the model were initialized using the synapse counts obtained from EM (a proxy for connection strength). A similar approach has also been applied to the premotor circuitry of the *Drosophila* larva by training the model to reproduce the measured pattern of muscle activity during forward and backward crawling [54••].

Future work must determine how much of a limitation mismatches between model and neural dynamics pose for predicting neuronal activity. To potentially reduce this mismatch, studies should aim to parameterize uncertainty in neural response properties (e.g. gains, thresholds, and time constants) and infer these unknown parameters during optimization, rather than connection strengths which may be inferred from synapse counts or sizes. Under the assumption that these parameters can be inferred by optimizing for the system's function, this approach reduces the number of unconstrained parameters from $O(N^2)$ synaptic weights to $O(N)$ biophysical parameters, where N is the number of neurons. Theoretical work has demonstrated that modulating single-neuron properties rather than connections can substantially reorganize network activity [57], supporting the feasibility of such an approach.

Incorporating other sources of knowledge

Constraints in addition to connectivity and optimization for task performance are likely necessary to achieve a good match between model and recordings. Many of the above studies relied on knowledge of neuronal response properties or neurotransmitter identities, which can be used to infer the signs of weights corresponding to excitatory or inhibitory synapses. Future work should also aim to infer, for distinct neurotransmitter types, distinct mappings from synapse count or size to effective synaptic strength.

The identification and recording of many neurons simultaneously using calcium imaging has made combined EM and electrophysiological datasets possible [58,39]. If a subset of neurons' activities during a task or behavior is known, a model may be optimized subject to constraints on these activity profiles. Such approaches trade off between optimizing for function and producing realistic neural activity. These neural activity constraints will likely be particularly important for systems for which only partial wiring diagrams are available, or for systems in which neurons do not have stereotyped functions (for example, reconstructions of cortical columns; [14]).

Partial wiring diagrams

The strength of EM reconstructions comes from the comprehensiveness of connectivity data that they

provide, but so far the only "complete" connectomes to have been annotated are those of *C. elegans* [4] and *Ciona intestinalis* [5], and only recently at the level of detail needed to assess variability across individuals or sexes [59]. While a relatively complete wiring diagram of the *Drosophila* adult and larva will likely be available soon, for larger organisms such completeness is still far away. It is therefore important to assess what information can be inferred from partial wiring diagrams.

For structures with specific functions and well-characterized input and output pathways, such as sensory or motor systems, a limited wiring diagram containing the structure of interest may be sufficient to construct models of the function of individual neurons (e.g. [39,2••,56••]). On the other hand, this may be difficult in the case of a reconstruction of a portion of a highly recurrent network, such as mammalian neocortex [14]. In these cases, EM data may provide a statistical characterization of properties such as cell-type-specific connectivity [29••], motifs [34] or preferential connectivity among functionally similar neurons [15]. These properties may be used to generate realistic simulated wiring diagrams for modeling studies focused on statistical descriptions of population activity rather than individual neurons.

Conclusions

Future theoretical work focused on EM datasets should attempt to develop techniques for identifying features of interest in connectivity graphs independent of assumptions on neural dynamics. Techniques to automatically cluster neuronal types [29••], identify latent connectivity structure [30], and visualize wiring diagrams are needed to facilitate the discovery of connectivity patterns that suggest further experimental or modeling study. Such techniques must be robust to reconstruction errors and account for heterogeneity within and across individuals if and when multiple reconstructions of individuals of the same species are available [59].

Studies that use wiring diagrams to infer neural dynamics should focus on leveraging multiple sources of information – from biophysics to neural activity to function – to guide modeling. Regarding biophysics, an understanding of the variables that determine effective synaptic weights, whether they can be determined from EM images using synapse counts, postsynaptic density sizes, and spine sizes, and how these vary across neurotransmitter and cell types, would lead to better parameterizations of unknown model variables. An understanding of when standard assumptions such as additive synaptic interactions and simple neuronal input/output functions apply, and when circuit elements should be simulated as point neurons (as is done in most theoretical models; Table 1) or as multi-compartmental models, would outline regimes in which modeling efforts are likely to be well-constrained. Expanding these regimes by relaxing assumptions – for example, by generalizing approaches that require linear input/output functions to restricted forms of nonlinearities – would also bring models closer to biology. Calibration experiments are crucial to the development of these new classes of models of single neurons and synapses. It would be particularly useful to be able to correlate detailed EM measurements of neuronal morphology and connectivity [24] to measurements of neural activity under perturbations [60,61] in the same circuit.

Approaches should be able to incorporate constraints on subsets of the network to predict unknown quantities – for example, using recordings of a subset of neurons along with a connectivity graph to predict the activity of unrecorded neurons. They should be able to trade off between constraints of different types, including connectivity, activity, and function. Theoretical work should also focus on an understanding of the solution spaces of models consistent with these constraints [28]. Such an understanding would help determine analyses and experiments that would be most effective at reducing uncertainty in model parameters, permitting an iterative refinement of models based on experimental data.

Conflicts of interest

The authors report no conflicts of interest.

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