

Relating network connectivity to dynamics: opportunities and challenges for theoretical neuroscience

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We review recent work relating network connectivity to the dynamics of neural activity. While concepts stemming from network science provide a valuable starting point, the interpretation of graph-theoretic structures and measures can be highly dependent on the dynamics associated to the network. Properties that are quite meaningful for linear dynamics, such as random walk and network flow models, may be of limited relevance in the neuroscience setting. Theoretical and computational neuroscience are playing a vital role in understanding the relationship between network connectivity and the nonlinear dynamics associated to neural networks.

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Introduction

Unlike other cellular networks, neural networks possess intricate and precise patterns of connectivity, whose rules are complex and difficult to ascertain. Another striking feature of neural networks is their repertoire of rich and varied dynamics. These two properties go hand in hand, as the structure of connectivity plays an important role in shaping neural activity. Connectomics, and related efforts that aim to describe the structure of brain networks, promises to deliver a vastly improved and detailed understanding of how networks of neurons are connected in the brain [53,2,44,73,12,35,80,49,19,69*,20,36,83]. A typical output of such research is a graph, with each vertex representing a neuron and each (directed) edge representing a connection, or synapse, between cells. The vertices may be further differentiated by location or cell

type, and edges may be weighted to carry information about connection strengths. Suppose we are handed such a graph. What does the connectivity structure tell us about a circuit's function? How does the graph of a network shape its dynamics? On the flip side, we may also ask how this particular pattern of connectivity came about. Can we explain it via simple rules of learning and development?

While much experimental work remains to be done, many of the central questions relating network connectivity to dynamics are theoretical in nature. Abstractly, a network can be thought of as a graph together with a prescription for the dynamics. The main dynamic variables are the activity levels of each neuron, $x_i(t)$, and the synaptic weights W_{ij} . When we try to relate network connectivity to dynamics, the main goal is to understand how the structure of the graph affects the dynamics of the neurons. This poses enormous challenges, because our current understanding of the problem is limited by much more than a lack of experimental data. Mathematically, inferring properties of the dynamics from the underlying network architecture is hard — even in idealized settings where the dynamics are simple, the model is deterministic, and every detail of the connectivity graph is known. Mathematical theories relating network structure to dynamics are notoriously difficult to develop, except when the dynamics are linear. In the nonlinear setting, the easiest cases are the extremes of either a completely random or geometrically structured network architecture [79]. For more intricate patterns of connectivity, as we see in neuroscience, even the simplest nonlinearities are sufficient to introduce serious complexities in the relationship between graph structure and dynamics [57,56**].

In light of these challenges, how do we decide which features of a connectivity graph are meaningful for a network's dynamics? A common approach has been to look for structures in the zoo of graph features given to us by network science. These structures typically arise in two ways: first, they have been shown to be meaningful in highly simplified network models (usually not neuroscience-related); and second, they have been identified as common or overrepresented across a variety of 'natural' networks. For the first way, examples of simplified network models include a random walk model or a network flow model. On the second way, an alternative approach is to look for non-random features across a database of real neural networks, such as those coming out of connectomics. In both cases, the resulting graph properties may

be difficult to interpret in a neuroscience context. In particular, when the properties are motivated by *linear* dynamics, as in random walk and network flow models, the selected features may not be relevant for networks whose dynamics are fundamentally nonlinear. On the other hand, adding too many biological details can quickly make a network model intractable to both mathematical and computational analysis. Finding a good balance between biological relevance and interpretability of graph structures is both a challenge and an opportunity for theoretical and computational neuroscience.

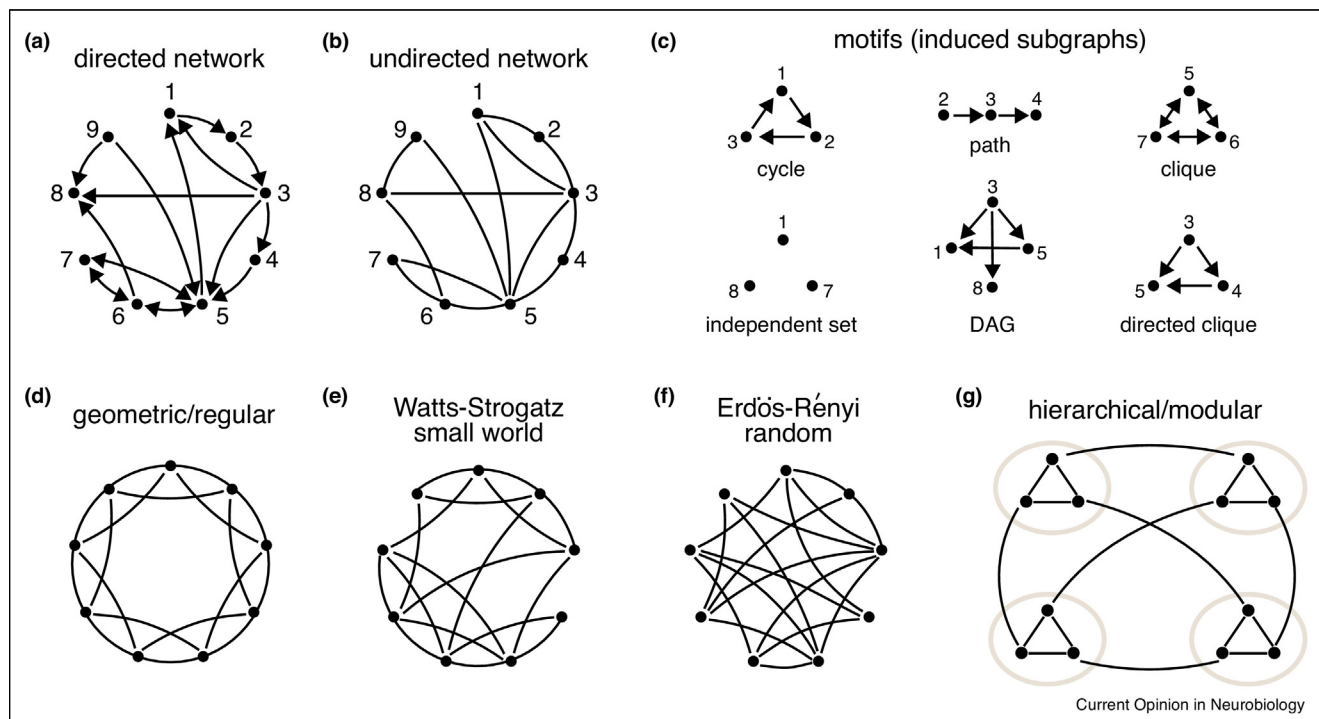
Graph-theoretic concepts and terminology

We begin by reviewing some useful graph theory concepts and terminology, with the aid of Figure 1. In neuroscience we care primarily about directed networks, but many of the graph-theoretic measures available to us are more naturally defined on undirected graphs. An important property of single nodes is the *degree*, which simply counts the number of edges incident to a vertex. In directed graphs, this is further refined into the *in-degree*

and *out-degree*. A vertex is called a *source* if it has in-degree zero, and a *sink* if it has out-degree zero. The *path length* from one node to another is the length of the shortest (directed) path. For example, in Figure 1a node 9 is a source, while 8 is a sink. The path length from node 2 to node 5 is 2, assuming each edge is assigned a distance of 1. In general, if different distances (e.g. coming from weights) are assigned to edges, we add these distances in order to obtain the (shortest) path length.

We are also interested in understanding the organization of graphical *motifs*, as these subnetworks could provide the basic units, or building blocks, of neural computation. Figure 1c depicts three different kinds of motifs, all as induced subgraphs of the directed graph in (a). While cycles and cliques are associated with recurrent network dynamics, a directed acyclic graph (DAG) has a feedforward structure. Specifically, the nodes in a DAG may be ordered in such a way that there can only be an edge from earlier to later nodes in the order. For example, the DAG motif in Figure 1c has such an ordering: 3,5,1,8.

Figure 1



Graph-theoretic concepts for directed and undirected networks. **(a)** A directed network is one in which each edge of the graph has a direction $i \rightarrow j$. Bidirectional edges, such as $5 \leftrightarrow 6$, reflect the presence of both the $i \rightarrow j$ and $j \rightarrow i$ edges. **(b)** The undirected graph corresponding to the network in (a). **(c)** Motifs are induced subgraphs, obtained by selecting a subset of nodes and keeping all edges between them. The graph in (a) has a variety of motifs, depicted here with matching vertex labels. **(d)** A geometric graph consists of vertices embedded in a metric space, with (typically undirected) edges between nodes obeying rules based on the distance between them. **(e)** A small world network has an underlying geometric organization, but also randomly selected long-range connections. **(f)** An Erdős-Rényi random graph assigns undirected edges with probability p , independently for each pair of vertices. **(g)** A hierarchical, or modular, network consists of local modules with long-range connections between them.

The global network organizations that are most often discussed in the literature range from Erdős–Rényi random graphs (Figure 1f) to geometric ones (Figure 1d), whose connectivity rules (or probabilities) are dictated by a spatial organization of the nodes. In between these extremes are the so-called ‘small world’ networks, such as the Watts–Strogatz small world network depicted in Figure 1e, which have a mix of geometric organization together with random long-range connections [84]. Finally, networks can have a hierarchical or modular structure, combining local motifs into larger networks with multiple scales of organization [10] (see Figure 1g).

Graph measures from network science

There are several common graph structures that routinely come up in network analyses [10,11,81,67,71,29]. Perhaps the most obvious feature to study is the degree distribution of the connectivity graph. The degree distribution is the set of all degrees, with multiplicity, and viewed as a histogram or probability distribution. Although many features of graphs are not captured by the degree distribution, certain types of graph structures lead to stereotyped degree distributions, which can serve as coarse signatures. In the case of an Erdős–Rényi random graph, the degrees are Poisson distributed, while *scale-free* networks are characterized by degree distributions that follow a power law [5].

In some cases, different types of degree distributions may be associated to the same network structure. For example, *small world* networks [84] are graphs characterized by a different set of measures called the *characteristic path length*, L , and the *clustering coefficient*, C :

$$L = \frac{1}{n(n-1)} \sum_{i \neq j} d_{ij} \quad \text{and} \quad C = \frac{1}{n} \sum_i C_i,$$

where d_{ij} denotes the length of the shortest path from node i to j , and C_i is the fraction of all possible connections that is present in the neighborhood of i . A network with a short characteristic path length, comparable to that of an Erdős–Rényi random network, and a large clustering coefficient, significantly higher than that of a random network (and comparable to a geometric network), is considered to be *small world* [84]. This can be achieved in various ways. In the original Watts–Strogatz formulation [84], small world networks were created by interpolating between a completely regular geometric network and one that is Erdős–Rényi random (see Figure 1d–f). These networks have exponentially decaying degree distributions. On the other hand, many scale-free networks are also small world, but have power law degree distributions. Modularity can also give a network small world characteristics, with very different degree distributions [37]. In particular, one could have a small world

network with uniform degree (that is, a delta function degree distribution) as in Figure 1g.

The reason the small world structure is considered meaningful for dynamics comes from thinking about simple linear models, such as random walks, network flow, or disease transmission. For example, in the case of infectious disease spreading dynamics, Watts and Strogatz showed that the time to global infection scales with the characteristic path length. With coupled oscillator dynamics, small world networks synchronize much more quickly than expected given the (small) number of edges [84]. More generally, having a small characteristic path length, and related measures of *centrality* [9], are interpreted as facilitating the fast flow of information [10]. This notion of information flow along shortest paths, however, does not have a straightforward interpretation for neural networks.

Finally, it is worth noting that spectral properties of the *graph Laplacian* (a modified version of the adjacency matrix) can capture various measures of graph structure such as number of connected components, bounds on min/max degree, bipartiteness, and community structure [3,50]. The graph Laplacian is also highly relevant for diffusion-based dynamics [3] and chip-firing dynamics [46]. It has been used to study macroscopic anatomical neuronal networks of the macaque and cat, and the microscopic network of *C. elegans* [17]. Here they also found spectral signatures for particular motifs in the network (see [4] for more details).

Relevance of graph measures to neural dynamics

Figure 2 (top) summarizes various graph structures in terms of degree distribution, geometric organization, and modularity. Several studies have looked for signatures of these graph properties in a variety of neural networks, such as microscale connectomes like *C. elegans* [54,17,82], mesoscale connectomes [34,17,75,70], functional connectivity networks in cortex and hippocampus [76,63,23,66,21], and synthetic biological networks such as the Blue Brain [77,30,24]. Figure 2 also lists a variety of dynamic models that are often considered when studying networks (bottom left), and which are often used to ascribe meaning to various graph properties. Although there is a considerable literature applying network science measures to neural networks [10,11,81,67,71,29], in order to fully understand the meaning and appropriateness of these measures we must consider dynamics that are more relevant to neuroscience, including nonlinearities and spiking.

Dynamic properties of interest for neural networks are also distinct, and often richer, than what is considered in traditional network science models. They include things like oscillations, state transitions, attractor structure, and

Figure 2

<p>Graph Structures</p> <p>Degree distribution</p> <ul style="list-style-type: none"> • Erdős-Rényi random (Poisson distribution) • Scale-free (power law distribution) • Exponential • Truncated log normal • Sparsity <p>Geometric/regular organization</p> <ul style="list-style-type: none"> • Ring or lattice connectivity • Probability of connection drops off with distance • Watts-Strogatz small world: locally geometric with random long range connections <p>Characteristic path length, Clustering coefficient</p> <p>Centrality measures</p>	<p>Hubs, Rich Clubs, Modularity</p> <p>Clusters & Communities (structural vs. functional)</p> <p>Spectral properties of</p> <ul style="list-style-type: none"> • Adjacency matrix • Weighted connectivity matrix • Graph Laplacian <p>Connectivity statistics</p> <ul style="list-style-type: none"> • Probability of unidirectional vs. bidirectional connections • Probability of connection between cell types • Distribution of synaptic weights <p>Motif statistics</p> <ul style="list-style-type: none"> • Overrepresentation with respect to null model • Motifs within/across cell types
<p>Dynamic Models</p> <p>Linear/Network flow models</p> <ul style="list-style-type: none"> • Random walk • Percolation • Diffusion • Disease transmission • Markov chain • Information flow -- broadcast vs. routing • Transport network • Electric network flow <p>Nonlinear/Neuro-inspired models</p> <ul style="list-style-type: none"> • Spiking models, e.g., LIF, Hodgkin-Huxley • Morris-Lecar, Fitzhugh-Nagumo, Izhikevich • Coupled oscillators • Firing rate models, e.g. Threshold-linear • Discrete networks, e.g. Hopfield, SER models • Linear conductance-based models 	<p>Dynamic Properties</p> <p>Global population activity</p> <ul style="list-style-type: none"> • Average/mean field activity • Synchronization vs. asynchronous firing • Spontaneous activity • UP/DOWN states • State transitions • Criticality/edge of chaos • Oscillations and rhythmicity • Traveling waves <p>Specific patterns of neural activity</p> <ul style="list-style-type: none"> • Attractor structure -- number and type • Cell assembly structure • Persistent activity • Sequence generation <p>Spiking properties</p> <ul style="list-style-type: none"> • Correlation structure/variance of spike trains • Bursting • Neural avalanches, cascades

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Graph structures, dynamic models, and dynamic properties of interest. Many of the graph structures we look for in neural networks are motivated by their relevance in very simple dynamic models [10,6**]. These models are often linear, and may be poor predictors of nonlinear behavior that is more typical of neural activity.

detailed correlation structure (see Figure 2, bottom right). Much recent research in computational neuroscience aims to connect graph structure to these kinds of dynamic phenomena [48,22,43,27,64,67,85,47,68,78,7,13,45,26,74,1,31,40,18,52*,58**,62**,61**,86]. Here we summarize a few examples where graph structures, such as clusters or hubs, have been shown to be relevant to neural network dynamics, and also some measures where the dynamic relevance is far more questionable.

Recent experimental studies have shown that network hubs significantly shape neural dynamics. Specifically, functional connectivity was mapped in hippocampus [8] and entorhinal cortex [55**], and a subset of the neurons with high in-degree were shown to drive network synchronization and/or slow down network oscillations when optogenetically stimulated. Hubs have been shown to have dynamic relevance in neuro-inspired modeling work as well. For example, in [72] it is shown that the

presence of ‘weight hubs,’ neurons with strong incoming edges, induces regular and irregular slow oscillations similar to UP/DOWN state transitions in a generalized integrate-and-fire neuron model. In a 3-state automaton model of susceptible-excited-refractory (SER) dynamics, hubs were shown to have a significant impact on directing co-activation patterns within a network [25]. Additionally, these co-activation patterns are highly correlated with modular structure, or clusters, in the network. Litwin-Kumar and Doiron also show that the presence of clusters of highly connected excitatory neurons significantly changes the dynamics of balanced networks [51]. These clusters appear to support attractor-like dynamics during which a cluster transiently increases the neural firing rates while other clusters have decreased firing rates, suppressed by inhibition, consistent with experimental findings from cortex.

In contrast, small world measures have shown little dynamic relevance. In [32], the authors considered a laminar model of cortical connectivity generated from experimental connectivity statistics and investigated the computational power of such a network with Hodgkin–Huxley dynamics in contrast to a matched random network and a network with matched small world measures of clustering coefficient and average shortest path length. The matched networks showed dramatically lower performance on a variety of neuro-inspired computational tasks. In [42] it was also found that characteristic path length and average betweenness centrality alone do not predict the emergence of population synchronization of bursting neurons, and only when degree distribution is also taken into account can this property be understood. Finally, Govan *et al.* [28] considered dynamics similar to those of Boolean networks on the *C. elegans* connectome and compared the network activity to that of Erdős–Rényi random and Watts–Strogatz small world networks that were matched according to average degree, average shortest path

length and clustering coefficient. They found dramatically different likelihoods of regular network oscillations across these networks, despite matching parameters, indicating the lack of dynamic relevance of these measures.

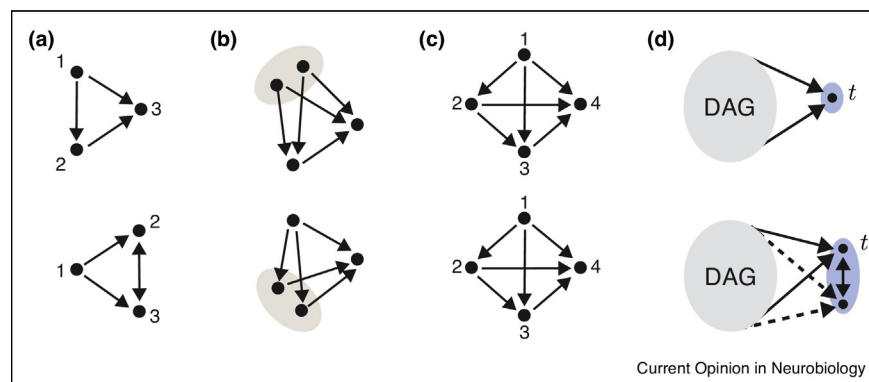
Furthermore, even in the case of linear models of network flow, the relevance of a network measure is highly dependent on the characteristics of the flow model for which it was designed. Borgatti [9] nicely summarizes the relevant features of numerous network flow models and highlights how these features relate to different measures of node centrality. Simulations of different flow dynamics on the same network topology show that different centrality statistics make dramatically different predictions for these dynamics that are not informative when the features of the dynamic flow do not match those for which the measure was designed.

Graph motifs

To get a sense of the challenges involved in studying graph motifs in neural networks, consider this: the number of directed graphs of sizes $n = 1, \dots, 5$ are 1, 3, 16, 218, and 9608. These have been enumerated, and are available in databases like the one in SageMath (www.sagemath.org). For $n = 6$, on the other hand, there are roughly 1.5 million directed graphs. Studying the dynamic properties associated to these structures by brute force methods appears intractable, even for the simplest dynamics. When one introduces additional variations, such as different node types (for cell types) or different edge types (for synapse types), the combinatorial complexity rises even higher.

Because of these challenges, most analyses looking for overrepresented motifs in network graphs such as connectomes have focused on the very smallest motifs, of size $n = 2, 3, 4$ [54,76,33,63,82,66,24^{*}]. The two motifs in Figure 3a were identified as overrepresented in at least

Figure 3



Overrepresented motifs and robust motifs. **(a)** Two motifs that were overrepresented in several distinct connectome studies [76,63,82]. **(b)** Generalized motifs obtained by doubling one of the nodes in the top graph of (a). These have also been found to be overrepresented in the *C. elegans* connectome [41]. **(c)** Directed cliques have an ordering of the nodes for which $i \rightarrow j$ if $i < j$. Note that bidirectional edges are also allowed. **(d)** Robust motifs of TLNs.

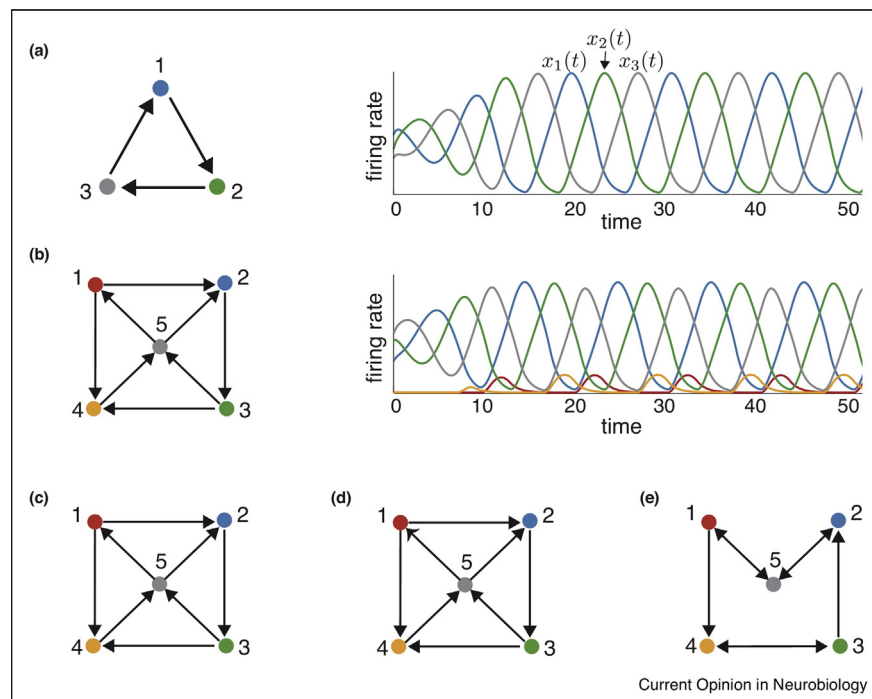
three different studies, ranging from connectivity data in *C. elegans* to mammalian cortex [76,63,82]. Interestingly, some simple generalizations of these small motifs have also been found to be overrepresented [41]. For example, the two graphs in Figure 3b were created from the top graph in panel (a) by doubling one of the nodes (shaded), and copying the same edge pattern to the rest of the graph. In [41], these graphs were also found to be overrepresented in the *C. elegans* connectome. In a separate study [65**], it was found that *directed cliques* are greatly overrepresented in the Blue Brain's cortical networks, whose connections are devised to be biologically realistic. Directed cliques are graphs with the following property: there exists an ordering of the nodes $1, \dots, n$ such that $i \rightarrow j$ if $i < j$. In particular, there is at least one edge between any pair of nodes, and an overall sense of direction to the graph (see Figure 3c).

Once motifs have been found to be overrepresented, the next question is to interpret them in the context of neural dynamics. Two natural questions arise: how did these motifs emerge through developmental and plasticity rules? and how do they affect the network's dynamics? A number of studies have addressed the question of how motifs affect dynamics in neural networks

[85,39,40,62**,38], and also how network dynamics produce emergent motifs via plasticity rules [60,59*]. While some studies have shown a large effect of motif structure [85,25,14,40], others have concluded that motifs without knowledge of weights and other local parameters tell us very little about a network's dynamics [47]. Furthermore, it has been suggested that only local properties, like the degree distribution, matter [61**,62**]. For example, in [33] it was found that motif structure was not important for certain dynamic properties if one controlled for its effects on the degree distribution.

Another approach to studying motifs is to look for specific subfamilies of graphs that have been pre-identified, by theoretical work, as being relevant to neural network dynamics. In a recent study of threshold-linear networks (TLNs), it was found that certain motifs are 'robust' in the following sense: once the graph associated to the network is fixed, the structure of (stable and unstable) fixed points of the network is invariant across all allowed choices of the synaptic weights [16**]. In other words, robust motifs have highly constrained dynamics with qualitative features that remain the same in the presence of synaptic plasticity. Nearly all robust motifs up to size $n = 5$ fit into two infinite families, depicted in Figure 3d,

Figure 4



Motif embedding matters. **(a)** A simple 3-cycle motif produces a sequential limit cycle attractor in an inhibition-dominated TLN. **(b)** The attractor associated to a 3-cycle may or may not survive as an attractor of a larger network. In the 5-neuron network (left), there are two 3-cycles but only one of them, 235, has an associated limit cycle (right). **(c–e)** Three additional networks have identical connectivity statistics as the graph in (b). However, they all exhibit qualitatively distinct dynamics. The network in (c) has two limit cycles, corresponding to the 3-cycles 125 and 253, but no attractor for 145. In contrast, the network in (d) has four chaotic attractors, while the one in (e) has three fixed point attractors, one for each 2-clique [56**].

corresponding to graphs that can be decomposed as a DAG together with a target node, t , that receives edges from all the other nodes [16^{••}]. Interestingly, the over-represented motifs in Figure 3a–c all fit into the robust motif families shown in (d), so it may be that robust motifs are more generally overrepresented in neural networks.

Motif embeddings and local connectivity

In addition to identifying new classes of motifs that may be of interest, theoretical work can also give us hints on the effects of motif embedding in larger networks. In other words, the dynamic relevance of a given motif may be highly dependent on how it interacts with other neurons. As an example, consider the case of simple threshold-linear network dynamics on graph motifs with binary synapses (see [57,15[•],56^{••}] for more details). In these networks, cyclic motifs give rise to periodic (limit cycle) attractors, where the neurons fire in a repeated sequence (see Figure 4a). These dynamics can be significantly altered, however, depending on how the motif is embedded in a larger network. In Figure 4b, there are two 3-cycle motifs, given by neurons 145 and 235. However, in the associated TLN dynamics only one of these, 235, produces a limit cycle. While the two motifs are identical, their embedding in the larger network of 5 neurons is different: the 235 cycle only sends one outgoing edge to each external node, while 145 sends two edges to node 2. This produces large differences in their effect on the network's dynamics: only one has a surviving attractor. Properties of the embedding can also affect the basins of attraction for a motif's associated attractor(s).

More generally, theoretical studies can alert us to the fact that local connectivity statistics may be misleading. In particular, networks with identical degree sequences can have very different dynamics. For example, the four networks in Figure 4b–e have identical degree sequences, given by in/out degrees (1,2), (1,2), (2,1), (2,1) and (2,2). Nevertheless, they all display qualitatively different dynamics, ranging from one or two limit cycles (b,c) to multiple chaotic attractors (d) or multiple stable fixed points (e). This illustrates a situation in which the global network structure has a strong effect on the dynamics, while local connectivity statistics tells us very little.

Conclusions

The problem of relating network connectivity to dynamics will continue to pose a serious challenge for theoretical and computational neuroscience. Theory is essential for identifying and interpreting important graph structures in neural networks, while computational studies allow us to analyze existing networks, and to test our ideas as to how various graph structures can impact neural dynamics. Although the tools of network science provide a valuable starting point, it is important to keep in mind where these measures come from. In particular, we should not assume that because a measure is meaningful in the context of

simple (and linear) dynamic models that its relevance will automatically translate to the more complicated (and nonlinear) neuroscience setting. It also seems likely that graph motifs will play an important role in understanding the structure and function of neural circuits. Here, too, is an area where new developments in theoretical and computational neuroscience will be needed.

Conflict of interest statement

Nothing declared.

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