Toolbox Graph Theory

> **IS THIS TOOLBOX FOR ME?**
>
> In this toolbox, we review the basic terminology used to describe the structure of networks. The concepts covered in this toolbox are instrumental in quantifying both structural and functional neuronal networks. If you have studied graph theory, you can safely skip this toolbox.

Understanding the structure of how neurons are connected to each other is fundamental for explaining the signaling of neuronal networks. Networks are not unique to neuroscience. There is an entire mathematical theory dedicated to describing and analyzing networks, often referred to as *graph theory*. In this toolbox, we will introduce the basic terminology in preparation for the application of graph theory to microscopic (individual neurons) and macroscopic (entire brain areas) structural networks, as well as functional networks, which describe "connectivity" based on the relative coupling of activity in different network locations (chapter: Network Interactions).

DEFINING GRAPHS

Graphs describe pairwise relationships between discrete entities. Each entity is called a *node* (in our case, nodes are individual neurons or brain areas), and nodes are connected by *vertices* or *edges*. Edges are *directed* if we are able to define the direction of the interaction, or *undirected* in cases where the interaction between the two nodes has no direction (Fig. A9.1). For example, a network of two neurons is drawn as a directed graph, because synaptic

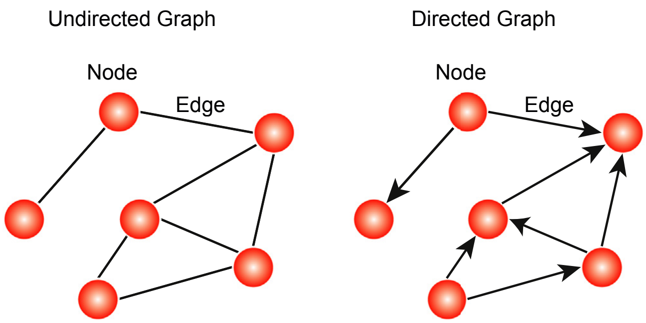

FIGURE A9.1 Undirected (*left*) and directed (*right*) graph.

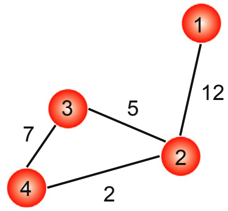

FIGURE A9.2 Graph with nodes numbered and weights assigned to edges.

TABLE A9.1 Adjacency Matrix for the Undirected Graph in Fig. A9.2

	Node 1	Node 2	Node 3	Node 4
Node 1	0	12	0	0
Node 2	12	0	5	2
Node 3	0	5	0	7
Node 4	0	2	7	0

connectivity has a direction caused by the unidirectional nature of chemical synapses (ignoring retrograde transmission). In addition, the edges can be of different strengths, which are referred to as *weights* (Fig. A9.2).

A graph can be either drawn with nodes (eg, circles) and edges (eg, arrows or lines), or it can be represented as a table that lists all connections. In such a table, called an *adjacency matrix*, there is a row and a corresponding column for each node. In this n-by-n matrix (where n is the number of nodes), row i lists the nodes that node i connects to ("targets"). The values in Table A9.1 denote the strength of each connection for the example graph in Fig. A9.2. For example, if node 1 is connected with node 2 with strength 12, the value where the first row and second column meet is 12. Since the example graph is undirected, the adjacency matrix is symmetrical, since no distinction could be made between the connection from node A to B and the connection from node B to A.

ANALYZING GRAPHS

Neighbors are nodes connected by an edge (and therefore have a nonzero entry in the corresponding location of the adjacency matrix). The *degree of a node* quantifies to what extent a node is connected to the remainder of the network. In an undirected graph, the degree of a node corresponds to the number of connections formed by that particular node. In a directed graph, the distinction between the number of incoming edges (*indegree*) and outgoing edges (*outdegree*) is made (Fig. A9.3).

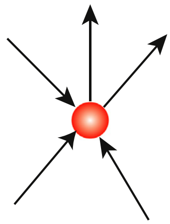

FIGURE A9.3 Node with three incoming (*indegree* = 3) and two outgoing (*outdegree* = 2) connections.

For any given graph, the degree of all nodes can be determined and subsequently represented by a distribution called *degree distribution*. The correlation between degrees of connected nodes is referred to as *assortativity*. Positive assortativity indicates that nodes with high degrees are likely to connect to each other. If nodes are not neighbors, they can be indirectly connected by paths, defined as an ordered sequence of nodes and edges. If the edges do not have different strengths, meaning if the only information provided is the absence (indicated by 0) or presence (indicated by 1) of an edge for all entries in the connectivity matrix (*binary graph*), the length of a path is defined as the number of edges it contains. For every pair of nodes, the length of the shortest path can be determined and represented in a distance matrix comprised of rows and columns, similar to an adjacency matrix. The *path length* denotes the average of all the values represented in the distance matrix.

With these definitions in hand, we can now describe both microscopic (local) and macroscopic (global) properties of graphs. First, we look for local organization of nodes that are highly interconnected. Groups of nodes with high connectivity among their members are referred to as *neighborhoods* or *clusters*. For every node, we can compute a *clustering coefficient* that describes the connectivity of all neighbors of the node. First, the total number of possible connections between the neighbors is a function of the number of neighbors k_i of node i, since in principle each node can connect with all of other nodes, but not itself.

$$k_i(k_i - 1) \tag{A9.1}$$

In the case of an undirected graph, Eq. (A9.1) is divided by 2, since every pair of directed edges between two nodes is replaced with a single, undirected edge.

$$\frac{k_i(k_i - 1)}{2} \tag{A9.2}$$

Second, we count the number of actual connections in the cluster and divide it by the total number of possible connections to determine the cluster coefficient. At the scale of an entire graph, there can be clusters (groups of nodes with high clustering coefficients) that are connected by few edges that connect nodes from different clusters. This property of the

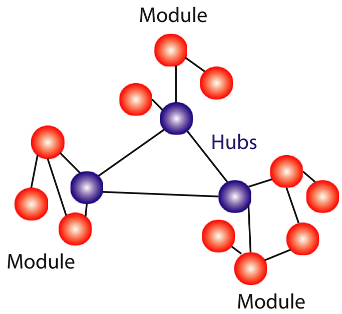

FIGURE A9.4 Network with three modules. Hubs (*blue*) have a higher node degree and are part of the shortest path between any pairs of nodes, as long as the two nodes are part of different modules.

network being divided into interconnected clusters (so-called *modules*) is referred to as *modularity*. The relative importance of a node can be defined by considering its role within a network. Nodes that are "centers" of the network are called *hubs*. For example, nodes with high degrees are often considered hubs (Fig. A9.4). Alternatively, if a graph is partitioned into modules, hubs can also be defined by the number of connections that connect different modules (*participation index*). Furthermore, *centrality* can be determined by the number of shortest paths (between any two nodes in the network) a node participates in (*betweenness centrality*).

SMALL-WORLD NETWORKS

With this technical vocabulary in place, we can now discuss different types of graphs and their structure (*topology*). Random graphs are constructed by randomly assigning connections between nodes. The key characteristics of a random graph are a normal degree distribution, short path lengths, and low levels of clustering. In a certain sense, the opposite of a random graph is a lattice graph, in which nodes connect to their neighbors. Such graphs have longer paths but higher clustering than random graphs. One of the most important concepts in network science is so-called small-world connectivity [1]. Mathematically, a small-world network is generated by starting with a lattice network (only local connections) and replacing a certain fraction of those local connections with random connections that originate from the same node but target a randomly chosen node. The fraction of connections subject to this process is called the *rewiring probability*. If the rewiring probability is zero, we are left with a lattice graph. If the rewiring probability is one, we have transformed the graph into a random graph. For very small rewiring probability values, the graphs combine short path lengths and high clustering, the two features of small-world networks (Fig. A9.5). Notably, this is not the only algorithm that can be used to generate small-world networks. Small-world networks are prevalent in the brain. There are multiple advantages for brain networks to exhibit small-world structure, such as the comparably small number of long-range connections needed to synchronize networks and the ability for local processing by means of the local connections.

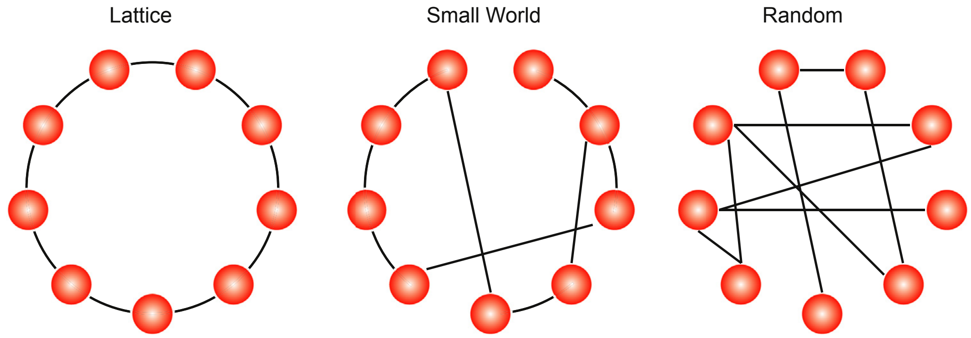

FIGURE A9.5 Transformation of a lattice network (*left*) into a small-world network (*middle*) and ultimately into a random network (*right*). The number of paths remains constant between graphs. But the average path length and clustering coefficients of the graphs are different. *Adapted from Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. Nature 1998;393(6684):440–442.*

POWER LAWS

In reality, few networks exhibit the structure of a random network, which has a normal degree distribution. Rather, networks often have a *power law* as their degree distribution, such that the probability of a node to have degree x is

$$p(x) = \frac{c}{x^k} = cx^{-k} \tag{A9.3}$$

where k is an integer number, c is a constant, and x needs to be at least as large as $x_{\min}$ (to avoid a division by zero):

$$x \geq x_{\min} \tag{A9.4}$$

Unlike most other distributions typically considered, random variables that follow a power distribution do not cluster around a "typical value" (Fig. A9.6). Instead, power distributions are referred to as *heavy-tailed distributions*, because they are much more likely to produce values that are orders of magnitude larger than others. As a result, the mean of the distribution is infinite for distributions where $1 < k < 2$. For $2 < k < 3$, the mean exists, but the standard deviation is infinite. The power law is referred to as *scale-free* since the probability of a small event occurrence and a large event occurrence always has a constant ratio. Mathematically, we can show this by comparing the likelihood of a random process to generate values x and mx, with m being a constant:

$$\Pr(mx) = (cmx)^{-k} = cm^{-k}x^{-k} \sim cx^{-k} = \Pr(x) \tag{A9.5}$$

One way to generate graphs that have a power-law degree distribution is to use the rule of *preferential attachment*. This growth rule (referred to as a *generative model* by mathematicians) starts with a single node. Then, nodes with outdegree 1 are added. With probability $\alpha < 1$, this one outbound connection of the newly added node is formed with a randomly chosen

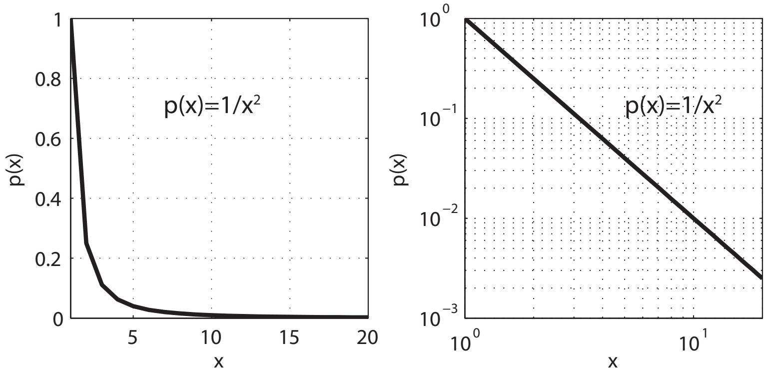

FIGURE A9.6 Power law distribution (*left*) corresponds to a straight line when plotted in a log–log plot (*right*). In such a plot, the logarithm of the values is plotted on both axes.

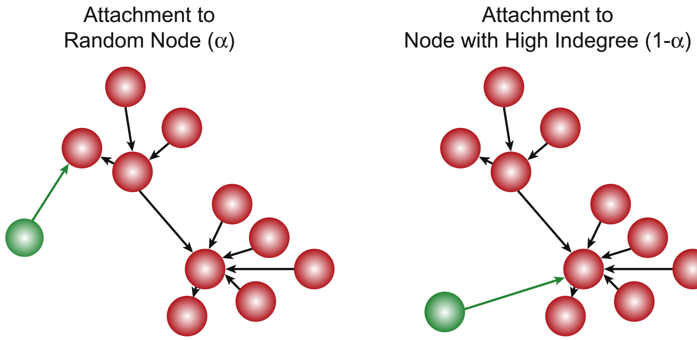

FIGURE A9.7 (*Left*) Attachment of a new node (*green*) to a random existing node (*red*), here a node with an indegree of 1. (*Right*) Attachment to an existing node with high indegree, here a node with an indegree of 6.

node in the already existing network. With probability $1-\alpha$, the new node connects to a node that is not randomly chosen but is selected by a rule that favors nodes with high indegree (Fig. A9.7). This way, nodes that are already highly connected are bound to receive even more connections. Mathematically, in approximation, the indegree distribution then follows a power law with exponent $k = 1/(1-\alpha)$.

SUMMARY AND OUTLOOK

Graph theory provides a conceptual framework to describe the structure of networks. In this toolbox, we introduced the basic concepts we will encounter throughout the book. For example, the "chapter Imaging Structural Networks With MRI" describes how noninvasive imaging of white matter can be used to determine how different brain areas are connected to each other. This structural connectivity can be represented and quantified by using the graph theoretical approaches discussed here. Similar analysis strategies can be applied to functional networks, as described in the "chapter Imaging Functional Networks With MRI." Similarly, the methods discussed in the "chapter Network Interactions" are used to determine network graphs based on functional interactions between different measurement locations.

NOTES

- The book *Networks of the Brain* by Olaf Sporns provides a highly readable and comprehensive introduction to the use of graph theory in network neuroscience [2].

References

[1] Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature* 1998;**393**(6684):440–2.
[2] Sporns O. *Networks of the brain*. Cambridge, Mass: MIT Press; 2011. xi, 412 p., 8 p. of plates.