Chapter 12

Graph Theory Methods For The Analysis Of Neural Connectivity Patterns

Olaf Sporns

Department of Psychology, Indiana University, Bloomington, IN 47405, osporns@indiana.edu

Abstract: This paper summarizes a set of graph theory methods that are of special relevance to the computational analysis of neural connectivity patterns. Methods characterizing average measures of connectivity, similarity of connection patterns, connectedness and components, paths, walks and cycles, distances, cluster indices, ranges and shortcuts, and node and edge cut sets are introduced and discussed in a neurobiological context. A set of Matlab functions implementing these methods is available for download at http://php.indiana.edu/~osporns/graphmeasures.htm.

Key words: networks, neuroanatomy, cortex, correlation, complexity

1.   INTRODUCTION

As is evident from many of the other contributions in this volume, recent advances in neuroscience and neuroinformatics are bringing about fundamental changes in the collection, access, and computational analysis of neuroscience data sets (Kötter, 2001).   An increasing number of neuroscience databases are being developed and are made available online. Specifically, significant progress has been made in the collation and representation of neuroanatomical connection patterns.   These efforts provide researchers with comprehensive data sets of connectional relationships between individual neurons or brain areas. The availability of such data sets necessitates the development of appropriate computational tools for their principled and comprehensive analysis. One avenue for such an analysis is provided by graph theory, a branch of mathematics and combinatorics with many applications in diverse fields, ranging from

physics, communication science and electrical engineering to genetics, linguistics, and sociology.

   All graph theory methods are based on a network's connection (adjacency) matrix, which can be derived from several different sources:
–   Databases of cortico-cortical and cortico-thalamic pathways yield connection matrices representing the large-scale connectional organization of cortical networks. Several such matrices have been published (e.g. Felleman and Van Essen, 1991; Young, 1993; Scannell et al., 1999) and computationally analysed.
–   Studies of individual neurons and local circuits provide statistical estimates of connection densities and indications of spatial patterns (e.g. Braitenberg and Schüz, 1998), which can be used to compile probabilistic connection matrices.
–   In computational neuroscience, network models incorporate often highly specific patterns of connections, which can be represented as artificial connection matrices.

   Supplementing this chapter is a set of Matlab (The Mathworks, Inc., Natick, MA, http://www.mathworks.com/) functions designed to allow the computational exploration of specific neuroanatomical connection data sets. The functions have been developed and tested with Matlab version 6.0 and are available at: http://php.indiana.edu/~osporns/graphmeasures.htm. This web resource will be continually updated. All Matlab functions contain extensive comments on their usage and limitations. The information in this chapter is designed to provide some mathematical background and a rationale for the potential use of these functions in neurobiology. All corrections, suggestions for expansion or modification of the software, additional neurobiological applications, or additional functions are welcome (contact osporns@indiana.edu).

   This chapter is not intended to be a general review of graph theory, or a review of cortical networks or of computational neuroanatomy. Rather, the chapter summarizes a set of graph theory methods of particular relevance for neuroscience applications, specifically the computational analysis of neural connectivity data. Other computational methods, such as multivariate statistical approaches used to display and organize connection data sets, are not covered (instead, see Hilgetag et al., 2002, for a comprehensive overview). The methods reviewed here represent only a small selection of graph theory tools, collected from a variety of textbooks and papers. The main criterion for their inclusion in this chapter is their potential usefulness for computational analyses of neural connection patterns. Individual methods focus on characterizing average measures of connectivity and degree distributions (3.1, 3.2), within-network similarity of connection patterns (3.3), paths and cycles (3.4, 3.5, 3.6), connectedness and components (3.7), distances (3.8), cluster indices (3.9), shortcuts (3.10) and

vulnerability measures such as node and edge cut sets (3.11).   Other methods, not included in this chapter, may be implemented in the future and will be made available at the website listed above.

2.   REPRESENTING NETWORKS AS GRAPHS

To allow mathematical analysis, we represent neuronal connectivity patterns (networks) as graphs.   All graphs are composed exclusively of vertices (nodes, points, units) and edges (arcs, connections). While much of classical graph theory (covered in numerous textbooks, e.g. Harary, 1969; Chartrand and Lesniak, 1996) is dealing with un-directed (random) graphs, graphs that represent neural connectivity patterns contain directed edges and are thus called directed graphs, or digraphs. A digraph $G_{n,k}$ consists of a set $\{v_l\}$ of n vertices and a set $\{e_{ij}\}$ of k directed edges, each linking a source vertex v_j to a target vertex v_i. Excluding self-connections, the number of edges ranges between 0 and n^2-n. The structure of the graph is described by the graph's <u>adjacency matrix</u> $A(G)$ (also called the connection matrix), with binary entries a_{ij} ($a_{ij} = 1$ if the connection from j to i is present, and $a_{ij} = 0$ if the connection is absent) and an all-zero main diagonal.   An important concept in graph theory is the path.   <u>Paths</u> are all ordered sequences of *distinct* edges and vertices, linking a source vertex j to a target vertex i. If $j = i$, the corresponding paths link the source vertex to itself and are called <u>cycles</u>.

The Matlab functions provided with this chapter are designed for graphs with these characteristics:
– directed edges,
– unweighted edges (i.e. all-positive, binary adjacency matrix),
– simple edges (no multiple connections between j and i), and
– edges e_{ii} (self-connections) are not allowed.

For most Matlab functions, there are no constraints (other than CPU time or memory) on size (n, k), sparseness or connectedness of the graph. No distinction is made between connections that are absent or presumed absent (i.e. for which no empirical information is available). This distinction (a measure of "confidence" in the existence or non-existence of individual pathways) is sometimes taken into account in the analysis of large-scale connection matrices assembled from individual neuroanatomical studies.

3.   GRAPH THEORY METHODS

3.1   Average Connection Density (*density.m*)

The <u>average connection density</u> k_{den} of an adjacency matrix *A(G)* is the number of all its non-zero entries, divided by the maximal possible number of connections (n^2-n for a directed graph, excluding self-connections). Thus, we have $0 \le k_{den} \le 1$. The sparser a graph, the lower its k_{den}.

Average connection densities can vary widely, depending on the particular neural structure, on the level of analysis (i.e. populations or single cells), and on the spatial extent of the neural network (e.g. entire brain versus local circuit). While the average connection density between cells across the entire cerebral cortex is approximately 10^{-6}-10^{-7}, local connection densities are significantly higher within single cortical columns (10^{-1}-10^{-3}). Matrices of connection pathways linking cortical areas tend to have $k_{den} \sim 0.2$-0.4. Connection matrices of patches of local cortical circuits comprising multiple columns would likely have very low $k_{den} \sim 0.01$-0.001.

3.2   Indegree and Outdegree (*degrees.m*)

The <u>indegree</u> *id(v)* and <u>outdegree</u> *od(v)* of a vertex is defined as the number of incoming (afferent) or outgoing (efferent) edges, respectively. The degree of a vertex *deg(v)* is the sum of its *id(v)* and *od(v)*. Note that the sum of *id(v)* over all vertices equals the sum of *od(v)* (and both are equal to *k*). Individual vertices may show imbalances in their indegree and outdegree. These imbalances are recorded in the joint degree distribution matrix of the graph *J(G)*, whose entries J_{tu} correspond to the number of vertices with an indegree *id(v) = u* and an outdegree *od(v) = t*. Entries of J_{tu} far away from the main diagonal correspond to vertices with a high imbalance in incoming and outgoing edges. Vertices above the main diagonal have an excess of outgoing edges, while vertices below the main diagonal have an excess of incoming edges.

Indegrees and outdegrees have obvious functional interpretations. A high indegree indicates that a neural unit is influenced by a large number of other units, while a high outdegree indicates a large number of potential functional targets. For most neural structures, indegrees and outdegrees of neural units are subject to constraints due to growth, tissue volume or metabolic limitations. Connections cannot be attached or emitted beyond the limits imposed by these constraints. The distribution of *deg(v)* (or *id(v)*, *od(v)*) over the entire graph may be inspected for scale-free attributes such as power laws (Albert and Barabási, 2002). The joint degree distribution matrix *J(G)* may be compared to corresponding matrices obtained from

same-sized random graphs (Newman et al., 2001), to identify significant deviations from balanced or symmetrical degree distributions.

3.3   Connectivity Matching Index (*compare.m*)

The connectivity matching index m_{ij} between two vertices i and j ($i \neq j$) can be defined as the amount of overlap in their connection patterns (Hilgetag et al., 2000). For example, $m_{ij,in}$ for afferent connections refers to the proportion of existing identical connections, divided by the total number of connection pairs for which at least one connection exists (excluding connections between i and j). Analogously, m_{ij} can be defined for efferent connections ($m_{ij,out}$) or for all connections ($m_{ij,all}$, afferent and efferent). Note that $m_{ij} = m_{ji}$, and $m_{ii} = 1$. All entries m_{ij} form the connectivity matching matrix $M(G)$. We distinguish between $M_{in}(G)$, $M_{out}(G)$, and $M_{all}(G)$. In some computational schemes (not implemented here, but see Hilgetag et al., 2000; Kötter et al., 2001; Stephan et al., 2001), connections that have been shown to be absent in anatomical studies have been distinguished from connections for which no evidence has been collected.

This measure provides an indication of the extent to which the connectivity patterns (afferent, efferent or both) of two neuronal units coincide or correlate and has been applied in several previous studies of neural connection patterns. High m_{ij} indicates that both units maintain similar anatomical and functional connections with other units within the system. Strong overlap in the structural relationships of two units within a network may be predictive of an overall similarity in their functional contributions. Matching indices have been used in developing optimal clustering schemes for systems of cortical areas (Hilgetag et al., 2000). Interestingly, these anatomical clustering approaches yield results that are very similar to functional clustering methods based on covariance matrices capturing the pattern of statistical deviations between dynamically interacting brain areas (functional connectivity, see Sporns et al., 2000; Sporns and Tononi, 2002). Thus $M(G)$ may be interpreted as a simple representation of expected baseline correlation in functional activity across a network.

3.4   Reciprocal Connections (*reciprocal.m*)

Reciprocal connections are pairs of edges that reciprocally link two vertices. Thus, in $G_{n,k}$, a reciprocal connection is found if both e_{ij} and e_{ji} exist. Edges that participate in reciprocal connections can be labeled and

counted; their number divided by k results in $\rho(G)$, the <u>fraction of reciprocal connections</u> for the graph.

In the brain, reciprocal connections are found in many systems and at many levels of scale, from local circuits to pathways between brain areas (where they are very abundant). Evaluating $\rho(G)$ provides a first-order estimate of the extent of reciprocal dynamical coupling present within the entire network. Typical large-scale cortical connection matrices have $\rho(G)$ of around 0.7-0.8 (perhaps higher, given that reciprocity of connection pathways may be underestimated due to missing anatomical information). This is much higher than the $\rho(G)$ of random networks of corresponding size (n,k) (Sporns et al., 2000). We note that the existence of reciprocal connections does not, in general, imply a symmetrical functional relationship between the linked neural units. For example, connection pathways in the cortex show characteristic laminar termination patterns that differ for feedforward and feedback connections (Felleman and Van Essen, 1991) and that may have different functional impact on their neuronal targets.

3.5   Paths and Walks (*findpaths.m, findwalks.m*)

As defined above, <u>paths</u> are ordered sequences of *distinct* edges and vertices, linking a source vertex j to a target vertex i. Distinctness means that no vertex or edge may be visited twice along a path from j to i. If $j = i$, the corresponding path links a source vertex to itself and is called a <u>cycle</u>. The length of a path or a cycle is defined as the number of distinct edges. The number of unique paths of length q from vertex j to i are recorded as entries in the path matrix of the graph, $P_q(G)$. Entries on the main diagonal of $P_q(G)$ indicate the number of cycles of length q. While all paths between j and i are unique sets of edges and vertices, they are usually not edge- or vertex-disjoint (see below). The path length distribution $pl(q)$ plots the total number of paths found within the graph for each path length q and t_{path} indicates the total number of paths of all lengths. Finding and recording all existing paths within even modest sized graphs is a significant computational challenge. The supplied Matlab function 'findpaths.m' uses a breadth-first approach to "grow" paths from source vertices to target vertices. <u>Walks</u> are defined as any sequence of vertices and edges leading from j to i, without the condition of distinctness. Walks are easily obtained from the powers of $A(G)$ (Buckley and Harary, 1990), yielding the walk matrix of the graph, $W_q(G)$. The walk length distribution $wl(q)$ contains the total number of walks of given length q, and t_{walk} records the total number of walks of all lengths for the graph.

The number of paths of different lengths linking two neuronal units is an important measure of the number of ways through which signals can travel

between them. A large number of paths from j to i implies a potentially high degree of redundancy in their interconnections and interactions. However, the number of paths alone is not a good measure of the vulnerability of the interaction (see discussion on disjoint paths in 3.11). Paths provide a more selective and specific view of a graphs's structural connectivity and are widely preferred over walks as the principal basis for the evaluation of reachability and distance (see 3.7, 3.8). Most of the discussion in this chapter will therefore focus on paths. Clearly the length of a path (or a walk) has a dramatic influence on its potential impact on real neuronal interactions. We must assume that potential interactions between two neuronal units, be they neurons or brain areas, rapidly decrease as the length of paths between them increases. In other words, neurons will tend not to influence each other through paths that are highly indirect, i.e. more than a few synaptic steps in length. It is unlikely that even large numbers of weak indirect interactions occurring in parallel (through large numbers of long, indirect paths) would have a significant cumulative functional impact in neuronal networks. Thus, we may assume that $P_q(G)$ and $W_q(G)$ with $q > 3$ or 4 are of relatively little functional significance in the brain. If this assumption is correct, then a complete derivation of $P_q(G)$ or $W_q(G)$ for all path lengths may be rather unnecessary and computational analyses should focus on entries of these matrices for small values of q.

3.6   Cycles and Cycle Probability (*cycprob.m*)

Cycles are paths that link a given source vertex j to itself, with otherwise distinct vertices and edges. The main diagonals of $P_q(G)$ record the number of cycles of a given length q. A measure of the overall probability of continuing a given non-cyclic path as a cycle can be defined, called cycle probability (Sporns et al., 2000). This measure, $p_{cyc}(q)$, estimates the probability that a non-cyclic path of length $q-1$ can be continued as a cycle of length q (i.e. by the addition of one edge), obtained from the ratio between the total number of non-cyclic paths of length $q-1$ and the total number of cycles of length q. If all non-cyclic paths of length $q-1$ can be continued as cycles of length q, then $p_{cyc}(q) = 1$, if none of them can be continued as a cycle, $p_{cyc}(q) = 0$. Computationally, $p_{cyc}(q)$ is calculated from the path matrix, as the ratio between the sum of all entries of $P_q(G)$ on the main diagonal and the sum of all off-diagonal entries of $P_{q-1}(G)$. Note that $p_{cyc}(1) = 0$ and $p_{cyc}(2) = \rho(G)$ (see 3.4). Another measure, the cycle frequency $f_{cyc}(q)$, captures the overall abundance of cycles as a fraction of all paths for a given path length q. Both p_{cyc} and f_{cyc} range between 0 and 1.

Frequencies and probabilities of cycles within a graph are important indicators of the graph's local connectivity, and are often associated with the

amount of clustered connections within the graph (see 3.9). Just as high proportions of reciprocal connections (high $p_{cyc}(2) = f_{recip}$) indicate high levels of dynamic coupling between pairs of vertices, high values for $p_{cyc}(3)$ indicate an abundance of triads of edges (forming cycles of length 3). Important reference points for comparison are random graphs of equivalent n and k. Distributions of $p_{cyc}(q)$ and $f_{cyc}(q)$ for a given neuronal connection matrix should be compared to averaged distributions for such random graphs, to determine if cycles of varying length are more or less abundant than expected based on a random model.

3.7   Reachability Matrix, Connectedness, and Components (*reachdist.m, components.m*)

The <u>reachability</u> matrix $R(G)$ records whether or not at least one path (of any length) exists between j and i (Harary, 1969). Its entries are $r_{ij} = 1$ if i is reachable from j ($r_{ij} = 0$ otherwise). Note that (deviating from Buckley and Harary, 1990) we set $r_{ii} = 1$ only if at least one cycle linking vertex i to itself exists. Computationally, the reachability matrix can be obtained using a variety of algorithms. Following Buckley and Harary (1990), the Matlab function 'reachdist.m' uses the powers of $A(G)$ to derive $R(G)$, together with the distance matrix (see below). The reachability matrix allows the assessment of <u>connectedness</u>, which, in digraphs, is a subtle concept, with gradations from strong, to unilateral, weak, and trivial. Most importantly, if all entries of $r_{ij} = 1$, then all vertices can be reached from all other vertices within the graph and the graph is strongly connected. If $R(G)$ contains multiple (mutually exclusive) subsets of vertices that are strongly connected within each subset, but are not connected between subsets, then the graph contains multiple (strong) <u>components</u>. If there are vertices whose entries r_{ij} are zero for either an entire row or a column, they cannot be reached from any other vertex or no other vertex can be reached from them (their $id(v)$ and $od(v)$ would also be zero, respectively).

Reachability is a fundamental and insurmountable prerequisite for the transmission of functional effects. If reachability is lost, for example by disconnection of areas after brain injury, functional interactions are abolished. Thus, the reachability matrix (and the distance matrix) is a good candidate for monitoring and measuring the vulnerability of neuronal circuits to functional dissociation (see 3.11). Studies of the connection patterns of extended cortical systems in the primate and the cat have shown that (at the level of segregated areas) the cortex is a strongly connected graph (Sporns et al., 2000).

3.8 Distance Matrix, Eccentricity, Radius, Diameter, and Characteristic Path Length (*reachdist.m, breadthdist.m, charpath.m*)

The <u>distance</u> matrix $D(G)$ records the distances between j and i, defined as the length of the shortest path between them (Harary, 1969). If no path exists, d_{ij} = Inf. Thus, d_{ij} = Inf if r_{ij} = 0. Note that (deviating from Buckley and Harary, 1990) d_{ii} = Inf, unless at least one cycle linking vertex i to itself exists (in which case d_{ii} is the length of that cycle). Computationally, $D(G)$ is derived together with $R(G)$ from the powers of $A(G)$ (see Buckley and Harary, 1990). Aternatively, distances can be determined using Floyd's algorithm, Dijkstra's algorithm, or through breadth-first search (implemented in 'breadthdist.m'). The <u>eccentricity</u> of a vertex j is the maximum of its finite distances to all other vertices, i.e. $ecc(j) = \max(d_{ij})$. Computationally, $ecc(j)$ is the maximum of each row of $D(G)$. If all other vertices can be reached from j, then $ecc(j)$ is the maximum number of steps needed to reach all of them. The <u>radius</u> of a digraph is the minimum eccentricity of all its vertices, $radius(G) = \min(ecc(j))$. The <u>diameter</u> of a digraph is the maximum eccentricity, $diameter(G) = \max(ecc(j))$. Following Watts and Strogatz (1998; see also Watts, 1999), we define the <u>characteristic path length</u> $\lambda(G)$ of a graph as the global mean of the finite entries of its distance matrix. Thus, the characteristic path length constitutes a measure of central tendency of $D(G)$.

The distance matrix provides information about the "directness" with which two units in a network can interact. For example, if d_{ij} = 2, then j can influence i through just one intermediate unit. In general, the length of the shortest path is indicative of the potential strength of functional interactions. Note that another factor determining this strength may be how many different short paths exist. The entries of the path matrix $P_q(G)$ for $q = d_{ij}$ give the total number of paths between j and i that have shortest possible length. Distance *per se* in graphs makes no reference to the physical distances between neuronal units located in metric space. It is possible for one pair of neuronal units to be separated by d_{ij} = 3 and be 200 μm apart, while another pair is directly connected (d_{ij} = 1), but separated by a metric distance of 20 mm. It seems reasonable to assume that, in many cases, graph distance is a better predictor of the degree and strength of functional interactions than metric distance. However, as a result of developmental and volumetric factors, metric distance may constrain the probability that a connection between two neuronal units actually exists.

3.9   Cluster Index (*clustind.m*)

Introduced by Watts and Strogatz (1998), the <u>cluster index</u> of a vertex $\gamma_v(v)$ indicates how many connections are maintained between a vertex's neighbours.   For digraphs, neighbours are all those vertices that are connected, either through an incoming or an outgoing connection, to the central vertex v. The number of neighbours per vertex is b_v. The vertex's cluster index is defined as the ratio of actually existing connections between the b_v neighbours and the maximal number of such connections possible $(b_v^2 - b_v)$.   If $b_v = 0$, $\gamma_v(v) = 0$. The average of the cluster indices for each individual vertex is the cluster index of the graph $\gamma(G)$.

The cluster index for a network expresses the extent to which the units within the network share common neighbours that "talk" among each other, an attribute that has been called the "cliquishness" of the network. A high cluster index $\gamma(G)$ points to a global organizational pattern consisting of groups of units that mutually share structural connections and can thus be surmised to be functionally closely related. However, the cluster index does not provide information about the number or size of these groups and only captures local connectivity patterns involving the direct neighbours of the central vertex. Watts and Strogatz (1998) used the cluster index as well as the characteristic path length as attributes defining "small-world" network architectures, characterized by an abundance of surprisingly short paths linking units within a very large and sparsely connected network. The small-world model has had a tremendous impact for studies of a wide range of networks, from social and communications networks to the brain.

3.10   Ranges and Shortcuts (*range.m*)

The <u>range</u> g_{ij} of an edge e_{ij} is the length of the shortest path from j to i, after the edge e_{ij} has been removed from the graph (Watts, 1999). If removal of e_{ij} results in disconnecting j from i, $g_{ij} = $ Inf. Before removal of e_{ij}, there is a direct link (formed by e_{ij}) from j to i ($d_{ij} = 1$). Thus, g_{ij} must be 2 or greater. The average range $\eta(G)$ for the entire graph is the sum of the ranges of all edges for which $g_{ij} \neq $ Inf, divided by their number. If $g_{ij} > 2$, then the removed edge forms a <u>shortcut</u> from j to i (Watts, 1999). The fraction of shortcuts f_s averaged over the entire graph is the number of edges with $r_{ij} > 2$, divided by k. Note that high values for cycle probabilities and cluster indices will generally be associated with low incidences of shortcuts resulting in $\eta(G)$ just slightly higher than 2.

In a neural context, removal of edges corresponds to cutting or lesioning of connections or pathways. The range of an edge provides information about its role in linking vertices. If the edge is a shortcut, its presence may

be crucial in functionally connecting two vertices that would otherwise be separated by a longer (and thus functionally ineffectual) distance. The fraction of shortcuts f_s is related to the prevalence of densely clustered (triadic) local connection patterns throughout the graph. A low value of f_s indicates a high number of short paths linking all pairs of vertices and is found in many graphs with high k_{den}, or in graphs with locally clustered connections (see 3.9).

3.11   Disjoint Paths, Cut-Vertices and Bridges, Vertex Cut Sets and Edge Cut Sets (*vertexcutsets.m*, *edgecutsets.m*)

Two paths linking vertex j to vertex i are <u>vertex- (edge-) disjoint</u>, if they have no vertices (edges) in common (apart from source j and target i). Disjoint paths may be of equal or unequal lengths. The maximum number of vertex- (edge-) disjoint paths (of any length) between j and i is equal to the minimum number of vertices (edges) that need to be removed in order to disconnect j from i (a version of Menger's theorem; see Harary, 1969; Buckley and Harary, 1990). A <u>cut-vertex</u> is a vertex whose removal from the graph increases the number of the graph's components. For example, the number of components of a graph would increase, if removal of a vertex from a connected graph would result in a disconnected graph (with multiple components). Correspondingly, a <u>bridge</u> is an edge whose removal increases the number of components. A <u>vertex cut set</u> (<u>edge cut set</u>) is a set of vertices (edges) whose removal results in a disconnected graph (White and Harary, 2001). The vertex- and edge-connectivity of a graph G are defined as the smallest number of vertices (edges) that, upon removal, result in a disconnected graph, and are denoted as $\kappa_v(G)$ and $\kappa_e(G)$, respectively. For example, if a graph contains at least one cut-vertex or one bridge, its $\kappa_v(G)$ or $\kappa_e(G)$ are equal to one.

The number of disjoint paths between two neuronal units provides a strong indication of the amount of (structural) redundancy in their mutual interconnectivity. For example, if two edge-disjoint paths exist between two units j and i, removal of only one edge cannot disconnect j from i; at least two edges must be removed. The vertex- or edge-connectivity of a neuronal network may be interpreted as a measure of its internal cohesiveness, vulnerability, or resistance to disintegration upon damage. The higher $\kappa_v(G)$ or $\kappa_e(G)$, the more vertices or edges need minimally to be removed in order to bring about the disconnection (disintegration or dissociation) of the original network. Of particular interest are cut-vertices or bridges that result in the disconnection of a strongly connected graph. Such cut-vertices and

bridges correspond to single neuronal units or pathways whose removal abolishes functional interactions between two separate components of the network.

4.   EXAMPLES

As an example of a structural analysis of a neuronal network using the methods and Matlab functions outlined in this chapter we select a connection matrix of cortico-cortical pathways of the macaque cortex, originally published by Young (1993) (an electronic copy of the matrix was kindly provided by Claus Hilgetag). For the present analysis, the amygdala and area A14 (which has an indegree of 0 in the original matrix) are omitted. In many cases, it is useful to compare actual neurobiological connection data sets to other connection matrices whose main organizational features (i.e. randomness, clusters, defined degree distributions) are known. Here, the macaque connection matrix is compared to equivalent random matrices and highly ordered ring lattice matrices (Watts, 1999), both with $n = 71$, $k = 755$.

The adjacency matrix (with reciprocal connections highlighted), the connectivity matching matrix, the joint degree distribution, and the distance matrix of the macaque cortex are shown in Figure 1. For $n = 71$, $k = 755$ we obtain $k_{den} = 0.152$. Macaque cortex contains a high proportion of reciprocal connections, with $\rho(G) = 0.824$ (random: 0.117; ring lattice: 0.940). The joint degree distribution is balanced, with 27 units having a higher $id(v)$ than $od(v)$ and 25 units *vice versa*. We find $p_{cyc}(2) = 0.824$, $p_{cyc}(3) = 0.386$, and $p_{cyc}(4) = 0.311$ (random: 0.117, 0.152, 0.150; ring lattice: 0.940, 0.674, 0.539). The characteristic path length $\lambda(G)$ is 2.312 (random: 2.022; ring lattice: 3.772), with radius = 3 and diameter = 5 (random: 3, 3; ring lattice: 7, 7). The cluster index $\gamma(G)$ is 0.461 (random: 0.151; ring lattice: 0.656). The average range $\eta(G)$ is 2.019 (random: 2.109; ring lattice: 2.000), with only 14 connections serving as shortcuts (random: 143; ring lattice: 0). The vertex connectivity is at least $\kappa_v = 3$ and the edge connectivity is at least $\kappa_e = 2$, as no cut sets are found up to these levels.

Having derived these structural measures, it is now possible to inspect the adjacency matrix in detail and derive explicit information about the structural contributions and relationships of identified cortical areas. For example, identified shortcuts in the graph can be traced to specific pathways leading to hypotheses about their role in facilitating direct interactions between specific areas. Another possibility is the use of the connectivity matching matrix to derive hypotheses about functional overlap between sets of areas and their cluster structure (Hilgetag et al., 2000). Other, more global comparisons, such as those between macaque cortex and

corresponding random and ring lattice matrices are possible (see Sporns et al., 2000) allowing insight into the potential "small-world" architecture of the cortex.
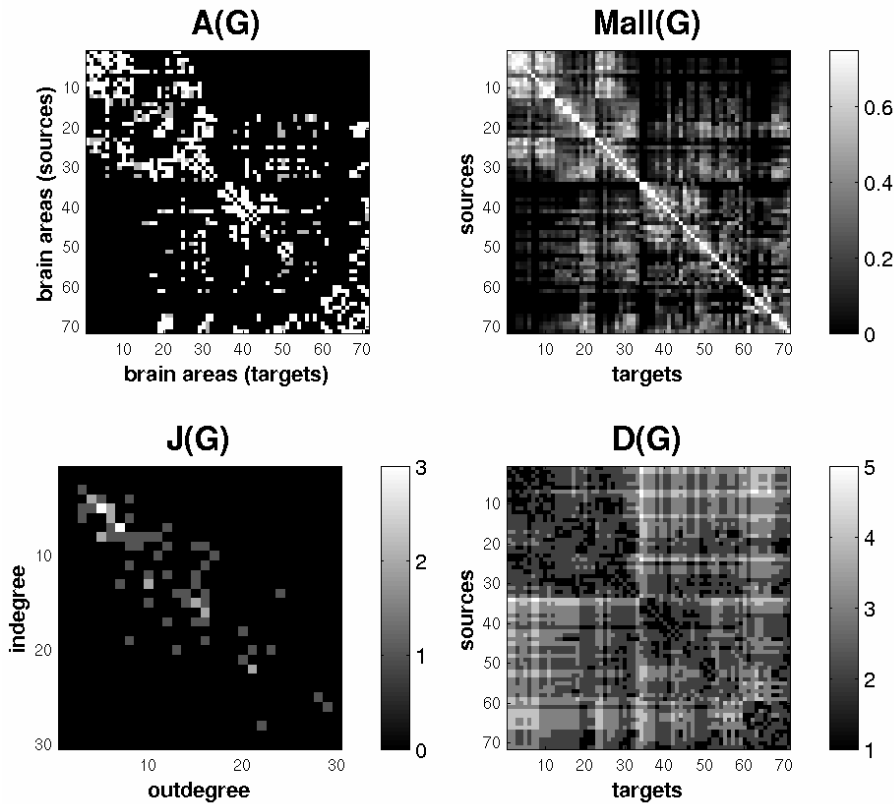

Figure 1: Adjacency matrix $A(G)$, connectivity matching matrix $M_{all}(G)$, joint degree distribution $J(G)$ and distance matrix $D(G)$ for the connectivity matrix of the macaque cortex (Young, 1993). $A(G)$ shows reciprocal connections in white and unidirectional connections in light gray. Brain areas are V1, V2, V3, VP, V3A, V4, VOT, V4T, MT, MSTD, MSTL, FST, PITD, PITV, CITD, CITV, AITD, AITV, STPP, STPA, TF, TH, PO, PIP, LIP, VIP, DP, A7A, FEF, A46, TGV, ER, HIPP, A3A, A3B, A1, A2, A5, R1, S2, A7B, IG, ID, A35, A4, A6, SMA, A3, A23, A24, A9, A32, A25, A10, A45, A12, A11, A13, G, PAAR, PAAL, PAAC, KA, PAL, PROA, REIT, TGD, TS1, TS2, TS3, TPT (1-71); the connection matrix can be found at the website http://php.indiana.edu/~osporns/graphmeasures.htm.

5.   DISCUSSION

Sparked by an increasing need in science and technology for understanding complex interwoven systems as diverse as the world wide web, cellular metabolism and human social interactions, there has been an explosion of interest in "network dynamics", the computational analysis of the structure and function of large physical and virtual networks (Strogatz, 2001; Albert and Barabási, 2002). Brain networks are of central interest to neuroscience, as their structural patterns are of fundamental importance for all neuronal information processing and, ultimately, for the emergence of coherent perceptual and cognitive states (Tononi et al., 1998; Sporns and Tononi, 2002).

The methods outlined in this chapter represent only one approach to the computational analysis of brain connectivity patterns. Additional methods are needed, including methods that take into account the sign and weight of connections, the density of projection pathways, or their physiological effects on their targets. The computational analysis of neural connection patterns is still in its infancy and future applications and studies will almost certainly utilize additional methods, likely including some that are not yet developed or even envisioned. Of particular significance are multivariate methods designed to display and extract significant structural features of connection or other matrix representations, such a multidimensional scaling or clustering approaches (reviewed in Hilgetag et al., 2002).

The structure of brain networks is a key for understanding the brain's functional dynamics. Therefore, structural analyses of neuronal connectivity patterns are best interpreted in a functional context. This can be done by making explicit reference to the specific physiological and cognitive contributions of identified sets of neurons or brain areas. Another avenue includes the simultaneous evaluation and analysis of functional connectivity patterns (Sporns and Tononi, 2002), empirically derived through neuroimaging or obtained from computer simulation of a structurally based neuronal model. In the nervous system, structural and functional connectivity are strongly interdependent, with structural connections shaping statistical and informational patterns across large-scale networks, while such dynamical interactions in turn lead to alterations in the structural substrate. These and other considerations lead us to expect that the computational analysis of structural and functional connectivity patterns will be a main contributor to our understanding of brain dynamics and its role in perception and cognition.

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