

Networks of the Brain: Quantitative Analysis and Modeling

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From Graph Theory to Modern Network Science

Over the past decade, the study of networks has rapidly expanded across a number of scientific disciplines, from social sciences to economics, systems biology, and, most recently, neuroscience. The principal reason for this expansion is the realization that a wide range of complex interconnected and dynamic systems can be described and analyzed using a set of mathematical and statistical techniques originally developed in graph theory. Graph theory is a branch of mathematics that originated with Leonhard Euler's famous 1736 treatment of the Königsberg bridge problem. Today, its applications are extremely broad, ranging from urban planning and traffic control to epidemiology, financial planning, internet search engines, and the analysis of complex biological systems from ecological to molecular scales (Barabási and Oltvai, 2004). Numerous surveys (Strogatz, 2001; Watts, 2004; Boccaletti et al., 2006; Barabási, 2009) have documented different classes of network architectures, dynamics, and growth processes. While much of classical graph theory has dealt with the analysis of random graphs, modern network science, with its renewed focus on real-world systems, has revealed that most, if not all, such systems have a distinctly nonrandom organization. This organization reflects the fundamental processes underlying their growth and functionality.

Understanding the organization of a complex network like the brain is a necessary first step to understanding its functions as an integrated system (Sporns, 2010). The arrival of modern brain mapping and recording techniques, together with renewed and concerted efforts to collect comprehensive brain connectivity data sets (for example, the human connectome) (Sporns et al., 2005), necessitates the development of novel quantitative analysis and modeling tools to reveal features of brain network organization. Collectively, the chapters compiled for this short course provide an overview of how network approaches can be brought to bear on the anatomy and function of large-scale brain networks, particularly those of the human brain. The present chapter will briefly outline some of the relevant theoretical and methodological foundations that motivate and enable the analysis of brain networks. More detailed and formal treatments can be found elsewhere (Reijneveld et al., 2007; Bullmore and Sporns, 2009; Rubinov and Sporns, 2010).

Brain Networks and Relevant Network Metrics

Given the variety of methods for observing the brain's anatomy and physiology, it is not surprising that

there are also a number of different ways to define and record brain connectivity (Horwitz, 2003; Jirsa and McIntosh, 2007). There are three main types of brain connectivity, describing structural, functional, and effective modes of interaction, respectively:

- Structural connectivity refers to a set of physical connections linking neuronal elements, such as synaptic links or fiber pathways;
- Functional connectivity describes patterns of dynamic interactions, usually computed from neural time series data (e.g., cross-correlation, mutual information, or coherence); and
- Effective connectivity captures a network of causal effects between neural elements, often inferred on the basis of temporal precedence cues in time series or on the basis of experimental perturbations.

While structural connectivity (at least on time scales of seconds to minutes) remains fairly stable, functional and effective connectivity can undergo rapid reconfigurations on the order of hundreds of milliseconds in the course of spontaneous or task-evoked neural activity. Common to all modes of brain connectivity is that they can be represented and analyzed as a network or graph.

Graphs are mathematical descriptions of a system that is composed of interconnected elements, comprising a set of nodes and edges. The nodes are the fundamental functional units of the system; in the brain, nodes may correspond to individual neurons, neuronal populations, or brain regions. The edges are connections or links that relate the nodes to each other; in the brain, edges can be synapses, fiber pathways, or statistical or causal relationships that describe functional association or similarity. The complete set of nodes and edges can be represented in a connection matrix, also called the "adjacency matrix" because it records which pairs of nodes are "adjacent" (i.e., directly connected by an edge).

Another fundamental concept is that of neural paths: sequences of edges that indirectly connect nodes to one another. The length of the shortest path between two nodes is also called the distance, defined as the minimal number of edges that lead from one node to the other. Note that, in graphs, distance refers to a topological separation of two nodes, not to their separation in a metric space. Most graph measures described in this brief survey derive either from the adjacency or the distance matrix, i.e., the direct connections (edges) or indirect connections (paths) between neural nodes.

Brain networks can be extracted in a number of different ways, depending on the recording method or

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experimental system employed in a given empirical study. A few basic steps are common to most approaches (Fig. 1). First, network nodes and edges must be defined. This is an extremely important step in any graph-based analysis of a brain network because all statistical analyses depend on the way the biological system is partitioned into a set of nodes and edges. At the level of large-scale brain systems, node definition involves partitioning the brain into coherent regions on the basis of histological or imaging data. Objective, data-driven parcellation methods are an active area of investigation and still face a number of serious challenges. Significant progress has been made by using clustering techniques that assess the similarity profile of structural (Johansen-Berg et al., 2004) or functional (Cohen et al., 2008) connections to derive boundaries between coherent brain regions.

Once nodes are defined, the definition of edges typically involves estimating pairwise associations between nodes. Structural networks are constructed on the basis of measured fiber tracts or pathways, whereas functional and effective edges are often based on statistical associations estimated from time series data. A wealth of possible measures is available for representing functional coupling. While most studies of functional connectivity still utilize simple measures such as correlation or coherence, more complex strategies involving partial correlations or estimates of directed (“causal”) interactions are beginning to gain ground.

Once a brain network has been constructed, it can be analyzed with quantitative tools from graph theory. Many such tools and measures are available, and at the time of writing only a small subset has been adapted and applied in the context of neuroscience. Before graph-theoretical approaches become more widely used, several important methodological issues need to be addressed. For example, recent studies have focused on the impact parcellation schemes and spatial scales make on the robustness of graph metrics (Zalesky et al., 2009) and on their test-retest reproducibility (Deuker et al., 2009). So far, these

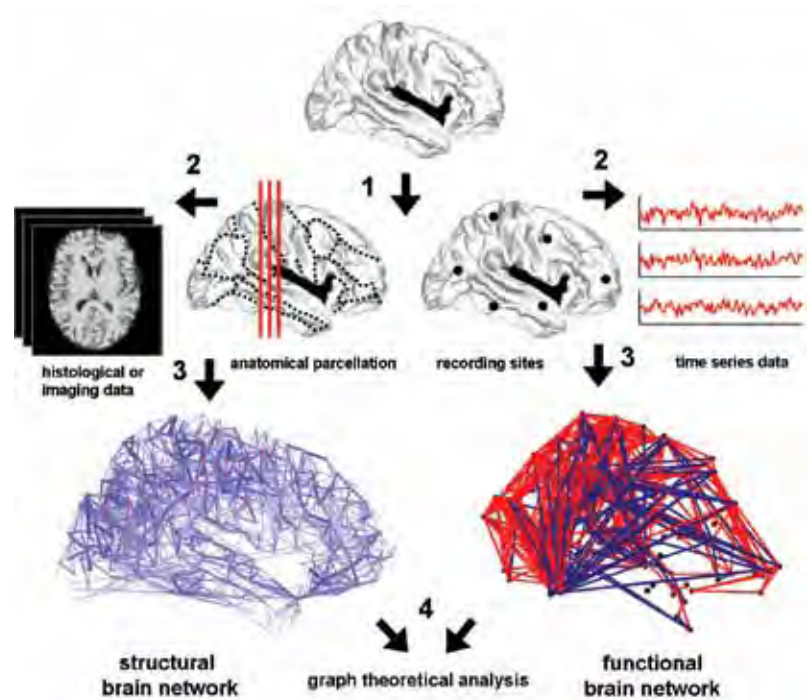


Figure 1. Recording structural and functional brain networks. The diagram illustrates four major steps: definition of network nodes (step 1), estimation of a suitable association measure (step 2), generation of an association matrix (step 3), and graph theoretical analysis of the resulting network (step 4). Modified with permission from Bullmore and Sporns (2009), their Figure 1.

methodological studies suggest that graph metrics report key features of network organization with high reliability and robustness.

In the remainder of the chapter, we will distinguish three broad classes of graph metrics that capture distinct aspects of brain network organization:

- The existence of specialized communities or modules (“functional segregation”);
- The pattern of global interactions between communities (“functional integration”); and
- The functional impact of individual network elements (“functional influence”).

Functional Segregation: Clustering and Modularity

Of particular importance for a neural node’s processing characteristics and functional contribution are its interactions with its immediate neighbors. These are defined as the collection of nodes to which it is directly connected. Numerous studies of large-scale brain networks have shown that neural regions are arranged in clusters or “communities,” with individual nodes communicating in densely and mutually interconnected “neighborhoods.”

The clustering coefficient (Watts and Strogatz, 1998) is one of the most elementary measures for capturing the degree to which nodes in a network form local communities. Clustering of a node is high if the node's neighbors are also neighbors of each other. In neural terms, a region has a high clustering coefficient if the regions to which it is connected are also connected to each other. Averaged over the entire network, the clustering coefficient reports the degree to which the network as a whole consists of nodes that share local connectivity. Because clustering varies greatly depending on the size and density of any given network, it is important to conduct statistical comparisons within populations of appropriately constructed random networks.

In many (but not all) cases, high clustering indicates the existence of multiple segregated communities of nodes. Such communities or modules can be identified by using algorithms that search for partitioning schemes. These schemes optimally subdivide the network, given a modularity measure: for example, one that is based on the relative density of within-module to between-module connections (Newman, 2006). Numerous studies of structural and functional brain networks have identified modules in large-scale brain networks whose placement and boundaries often coincide with either known cognitive networks (Dosenbach et al., 2008) or functional subdivisions of the human brain. By extending analytic approaches to modularity, investigators have recently demonstrated that modules in brain networks are arranged hierarchically (Meunier et al., 2009). This architectural feature promotes economical physical embedding (Bassett et al., 2010) and may have significant implications for brain dynamics (Kaiser et al., 2007).

Functional Integration: Path Length and Efficiency

While clustering and modularity provide information about the network's local community structure, a complementary set of measures captures the network's capacity to engage in more global interactions that bind together and integrate its dynamic activity. Several of these measures are based on paths: specifically, the lengths of the shortest paths linking pairs of nodes. Generally, shorter paths are thought to be more effective in passing information. Thus, the average path length for a network can provide an indication of its capacity for global information exchange. A related measure (essentially an inverse of the average path length but less disrupted by the presence of disconnected nodes) is the global efficiency (Latora and Marchiori, 2001). As is the

case for clustering, path length should be quantified in relation to a null population of random graphs, controlling for the size and density of the network.

Because of the importance of communication and information flow in large-scale brain networks, these measures of functional integration have fairly straightforward neurobiological implications. In a network with high efficiency, short communication paths can be identified between most or all pairs of nodes. Since clustering and path length are capturing complementary aspects of a network's functional organization, they are often measured in conjunction. Also, these measures can be combined to assess the degree to which the network balances the existence of local and segregated communities with global, systemwide integration. High clustering and a short path length are the defining characteristics of a universal class of network architectures found in social, technological, and biological systems, including the brain (Sporns and Zwi, 2004). These are referred to as small-world networks (Watts and Strogatz, 1998). The modular small-world networks encountered in the brain not only allow for efficient information processing but are economical with respect to their wiring and metabolic cost (Bassett and Bullmore, 2006).

Functional Influence: Centrality and Hubs

Real-world networks deviate from randomness; in many cases, this entails specialization among nodes. Different classes of network elements can be distinguished by the way they participate in the network, i.e., by the way they are connected to the rest of the system. An important distinction can be made based on their "influence": that is, their potential impact on the system as a whole and their capacity to transfer or process information. Highly influential nodes are often referred to as "hubs," and identifying such hubs in brain networks can help one to map regions of the brain that are critical for coordinating functional interactions and for generating coherent system states. Hubs can be identified either on the basis of the number of interactions they engage in or by the degree to which they participate in short paths across the network. The latter measure, called "betweenness centrality" (Freeman, 1977), is particularly salient for structural networks, and it can be computed for edges as well.

Once an optimal modularity partition has been identified (Fig. 2A), the diversity of a node's connections with respect to individual modules can be assessed in the form of a participation coefficient

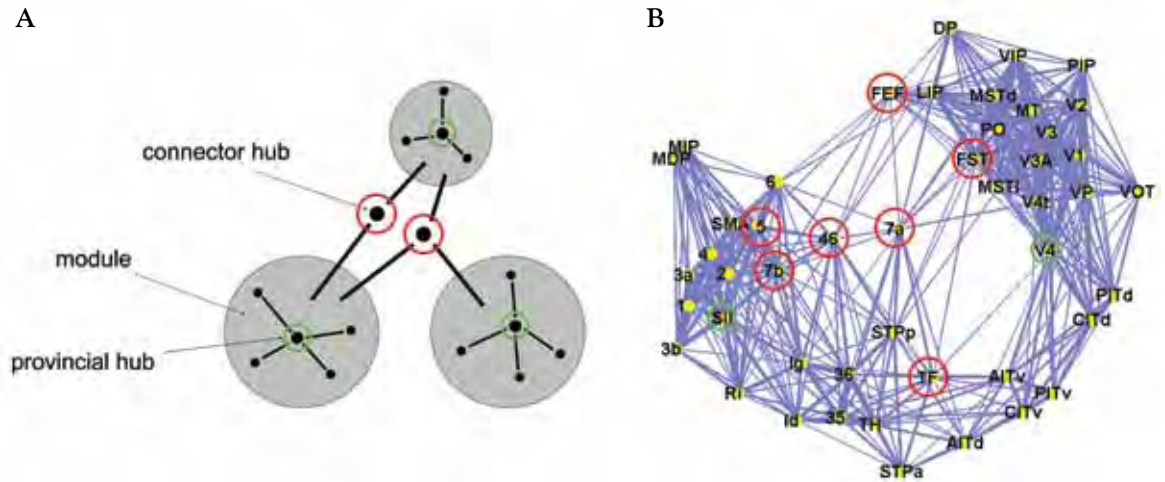


Figure 2. Modularity and classification of hubs. The schematic diagram **A** shows three modules (gray circles) linked by provincial (green) and connector hubs (red). Provincial hubs link nodes within a single module, while connector hubs link modules to each other. The diagram **B** shows a visualization of the community structure of the functional connectivity estimated from simulated blood oxygenation level–dependent (BOLD) responses of 47 regions of the macaque cortex (Honey et al., 2007). Two modules consisting mostly of visual and somatomotor regions are linked by multiple connector hubs located predominantly in parietal and frontal cortex.

(Guimerà et al., 2007) (Fig. 2B). Of particular interest are highly connected nodes with a high participation coefficient: the so-called “connector hubs.” These maintain a diverse set of between-module connections and thus facilitate global intermodule communication. On the other hand, high-degree nodes with few or less diverse between-module connections have a low participation index. Consequently, these so-called “provincial hubs” participate mostly in interactions within their own module.

Hubs are of special interest in large-scale brain networks. Their high degree of centrality and, in the case of connectors, high level of participation in multiple functional communities predict that they will play a crucial role in integrative processes and information flow. The association of at least some hubs in the human brain with regions that engage in a high rate of metabolism (Hagmann et al., 2008), as well as with neuropathological changes in degenerative brain disease (Buckner et al., 2009), suggests intriguing hypotheses that may link brain network topology to function. Furthermore, the assessment of centrality or influence is a crucial component for predicting functional disturbances that will occur upon node or edge deletion. In a neurobiological context, the loss of more highly central nodes or edges owing to trauma or disease

should result in more widespread disruptions of information flow and dynamics in the remaining brain (Alstott et al., 2009).

Future Applications

Graph methods and their application to large-scale networks have begun to provide significant insights into the organization and function of the human brain. The remaining contributions to this short course illuminate various approaches, ranging from anatomical networks to functional connectivity in the resting brain, task-evoked activity, individual differences, and clinical populations. As the applications of graph theory continue to expand, important methodological and interpretational questions will need to be addressed. For example, objective methods for comparing networks within individual subjects or across subject populations will be needed to facilitate longitudinal studies of brain development and disease progression.

Many aspects of brain networks await future investigation. Network approaches have already revealed significant between-subject variability in structural and functional connectivity, so the role of variations in networks for variable cognition and behavior will likely be an intense area of future research. Other promising avenues will lead to the areas of translational neuroscience and in discovering relations between genetic and brain networks.

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