



Review

From simple graphs to the connectome: Networks in neuroimaging

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ABSTRACT

Connectivity is fundamental for understanding the nature of brain function. The intricate web of synaptic connections among neurons is critically important for shaping neural responses, representing statistical features of the sensory environment, coordinating distributed resources for brain-wide processing, and retaining a structural record of the past in order to anticipate future events and infer their relations. The importance of brain connectivity naturally leads to the adoption of the theoretical framework of networks and graphs. Network science approaches have been productively deployed in other domains of science and technology and are now beginning to make contributions across many areas of neuroscience. This article offers a personal perspective on the confluence of networks and neuroimaging, charting the origins of some of its major intellectual themes.

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Introduction

Many of the most daunting unfulfilled challenges for science in the 21st century involve understanding, forecasting and manipulating the behavior of complex systems — ranging from social systems and economics, the earth's climate and biosphere, to the molecular interactions that drive the functioning of cells and organisms. What makes these systems “complex” is not only that they consist of many components or elements (people, cells, proteins). Importantly, these elements engage in dynamic interactions that give rise to new phenomena at global scales whose properties cannot be trivially reduced to or predicted from properties of the elements themselves. The totality of these interactions among elements can be described as a network or, more formally, a graph composed of nodes and edges. The global behavior of a complex system often sensitively depends on the structure of this network. The study of networks has undergone significant expansion over the past decade (Boccaletti et al., 2006; Newman et al., 2006; Newman, 2010). Today, modern network science has become an important contributor

to a diverse range of scientific disciplines, from the social sciences (Watts, 2004) to cell biology (Barabási and Oltvai, 2004).

Until recently, complex systems and network approaches have had relatively little impact on brain science. This may seem surprising, since the brain is a complex network *par excellence*, an intricate web of interconnected elements, “an enchanted loom where millions of flashing shuttles weave a dissolving pattern” (Sherrington, 1940). Today, network approaches are rapidly gaining ground, across cellular and systems neuroscience, and also in many applications of neuroimaging. As a result we find ourselves in the middle of an important transition, a paradigm shift that will usher in a new way of thinking about brain function. Networks and graph models are core concepts driving this transition. At an ever accelerating pace, network approaches are beginning to make significant contributions towards understanding integrative aspects of brain function.

This paper is not intended to be a scholarly review of the state of the field (instead see Bullmore and Sporns, 2009; Sporns, 2011; Bressler and Menon, 2010). Rather, in keeping with the spirit of this Special Issue the article should be read as a personal perspective on how network theory has influenced human neuroimaging and cognitive neuroscience over the past twenty years.

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Early explorations of graphs and networks

Around 1990, when I completed my PhD and embarked on my postdoctoral research, no one in neuroscience was interested in graph theory. To be sure, the term “network” was used informally to describe neural circuits, but quantitative and theoretically driven applications of networks and graphs were virtually non-existent. This stood in sharp contrast to the analytic rigor and rich methodology that had sprung up surrounding graph models of social systems (e.g. Wasserman and Faust, 1994). Social scientists had long been in the lead in applying graphical models to empirical questions. By the end of the 1980s, numerous seminal papers had already been written (e.g. Moreno and Jennings, 1938; Granovetter, 1973), many of the key concepts that are still in use today had been developed (including the “small world”; Travers and Milgram, 1969), and data-driven applications to real-world problems were flourishing.

What prevented the early use and adoption of network approaches, apart from the skeptical attitude of most neuroscientists against anything “theoretical”, was the lack of suitable network data sets, as well as a strong preference for characterizing neural function in terms of distinctive response properties of individual units. My first exposure to more dynamic and integrative views of brain function came through the theoretical ideas of my PhD advisor, Gerald Edelman (Edelman, 1987) and early work on computational brain models carried out by my colleagues Leif Finkel and George Reeke at the Neurosciences Institute in New York. These models attempted to simulate the responses of large populations of neurons involved in visual perception (Finkel and Edelman, 1989) and sensorimotor behavior (Reeke et al., 1990). A key lesson coming from these efforts was that the pattern of anatomical connections put into the model was crucial for generating realistic neural responses. For example, building on Edelman's notion of “dynamic reentry”, the recursive exchange of signals between cell populations and brain regions, we were able to link observed patterns of stimulus-

dependent cross-correlations in the visual system to known patterns of anatomical connections between neurons (Sporns et al., 1991).

When entering connectivity data into a simulation, the connections were encoded as lists of directed edges, specifying the source and target of each anatomical link. Such a list is easily summarized in a “connection matrix” and we often used this format to display the connections supplied to a specific computer model. While working with Giulio Tononi on various simulations of visual circuits I came across the anatomical connection matrix for the interregional projections of the macaque visual cortex, published in table form in a seminal paper by Dan Felleman and David Van Essen (Felleman and Van Essen, 1991). Two ideas occurred to us almost immediately. First, we could use this matrix to build a comprehensive model of the neural responses of different regions in the visual brain (Tononi et al., 1992). Second, this matrix could be subjected to graph-theoretical analysis, a mathematical framework I had encountered earlier through the work of Joel Cohen, a professor at Rockefeller University and member of my PhD advisory committee. The latter idea was also grasped independently by Malcolm Young whose graph analysis of the similarity structure of regional connectivity in the macaque visual cortex provided important insight into the global organization of this network (Young, 1992, 1993).

Our computational explorations of visual circuits had given us an appreciation of the importance of anatomical connection patterns for dynamic responses. Giulio and I set out to explore this relationship more formally, drawing links between graph theory on the one hand and information theory on the other. Over many long discussions (and lunches at the “Silver Spoon”, a diner on New York's First Avenue; Fig. 1) some basic ideas took shape. We developed and adapted a set of network metrics to quantify the connection topology of graphs, and then characterized the distribution and flow of information on these graphs using statistical measures coming from information theory. Our goal was to capture the global organization of how

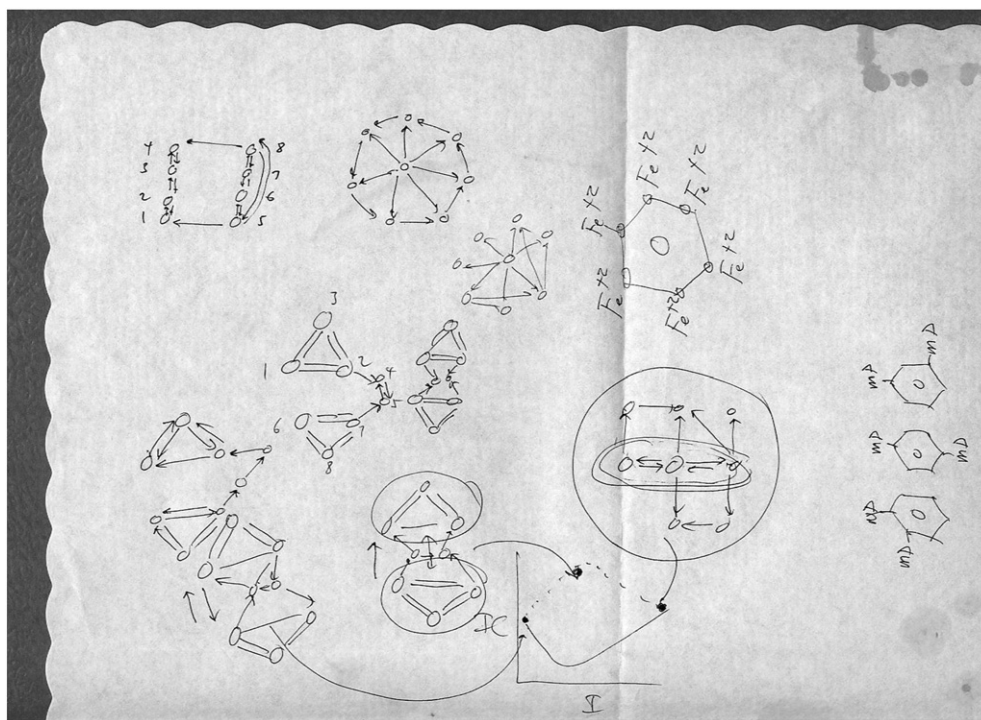


Fig. 1. Early discussions over graphs and simple network motifs, recorded on a paper napkin (circa 1993) — the diagram at the bottom later appeared as Fig. 3 in Tononi et al. (1994). Note the appearance of network motifs and various modular network architectures, as well as sketches of chemical isomers. The latter is fitting since the very term “graph” originated from the early graphical notation for molecules introduced by James Joseph Sylvester in 1878.

information was distributed across a network and how this organization depended on the underlying structural couplings. From the beginning, we approached the graph structure of the brain as a “causal skeleton” from which neural dynamics and distributed information emerged.

The “Van Essen matrix” (as we called it) became a key test case in these graphical explorations. Early on, we became particularly interested in paths (sequences of unique edges linking pairs of nodes) because they formed the structural basis for inter-neuronal communication and information flow. We considered not only the matrix of shortest path lengths (also called the distance matrix) but in addition a number of other path-based metrics, for example the number of edge-disjoint paths between pairs of nodes. Two paths are edge-disjoint (or edge-independent) if they have no edges in common, and they are an important concept for characterizing network flows. We attempted to characterize optimal flow patterns across cortical networks by applying the max-flow min-cut theorem, which stated (roughly) that maximal flow between two nodes is equal to the minimal number of edges that, when cut, disconnect these nodes from each other. We recognized that, due to noisy signal transmission, shorter paths were likely to be more influential and that most paths in cortical networks were short in length. Quoting from an unpublished early draft of a manuscript (Tononi et al., 1994), “the activity of short paths is likely to dominate the dynamic behavior of the system. In this context, it is interesting that the graph-theoretical analysis of the connectivity of the primate visual system shows that most paths between areas are shorter than 6 synaptic steps in length”.

This line of work resulted in the construction of several multivariate measures of information in networks, including integration, complexity, matching and degeneracy, introduced in a series of papers (Tononi et al., 1994, 1996, 1999). Integration is essentially a multivariate extension of mutual information and, unbeknownst to us at the time, had been formulated decades earlier, called “multi-information” by McGill (1954). Complexity, on the other hand, turned out to be a novel measure that showed interesting and meaningful variations across different neural systems. Deeply intrigued by optical recordings of neural activity and their relation to anatomical circuits in visual cortex carried out by Malach et al. (1993); Arieli et al., 1996), we began to study spontaneous noise-driven (or in today’s terminology, “resting-state”) activity in network models of visual circuits. We found that different wiring patterns generated different patterns of covariance (functional connectivity) whose structure could be captured by global information measures such as integration and complexity (Tononi et al., 1994). Complexity was driven by the coexistence of local and global structure in neuronal interactions and appeared to be maximal for biologically realistic wiring patterns. The crucial insight was that the information dynamics of the network depended on how its elements were structurally coupled. At the time, most of our explorations were guided by experimental data from neurophysiology – regrettably, we remained unaware of Bharat Biswal’s discovery of ongoing fluctuations and patterns of correlations in functional MRI (Biswal et al., 1995) until much later.

Neuroimaging and the rise of brain connectivity

The inception of fMRI in 1992 opened up an unprecedented opportunity for observing the dynamic activation of the human brain. Preceding the fMRI revolution, Barry Horwitz had pioneered the application of network modeling approaches to PET data (e.g. Horwitz et al., 1984, 1992). I met Barry while attending one of the first meetings on “Functional Neuroimaging” at NIH in 1992 and we developed an idea for a workshop on “Neuroimaging and Neural Modeling”. The Neurosciences Institute graciously provided financial support as well as the meeting venue, and so, in late 1992, we found ourselves organizing a meeting on a topic that didn’t exist yet. We somehow managed to bring together a creative group of participants (among them

Ad Aertsen, Dan Felleman, Karl Friston, Peter Fox, Scott Grafton, Mike Hasselmo, and Randy McIntosh) and in free-ranging discussions we explored the value of models for analyzing neuroimaging data sets. A review article based on the meeting (Horwitz and Sporns, 1994) identified several key areas where we predicted models would soon make a difference, including the identification of the neural basis of signals measured with neuroimaging technology, the creation of large-scale system-level models of neuronal responses, and the realization of multimodal integration, particularly across electromagnetic and hemodynamic data.

The worlds of neuroimaging and graph theory remained apart from each other for most of the 1990s. While functional and effective connectivity had been introduced by Friston (1994), the dominant mode of fMRI experimentation and analysis was “brain mapping”, with a focus on localizing task-evoked brain activations that could be used to assign functional roles to specific brain regions. Nevertheless, the notion of functional connectivity started to gather momentum, particularly due to the work of Randy McIntosh and colleagues on mechanisms of memory encoding and retrieval (McIntosh et al., 1997) as well as awareness (McIntosh et al., 1999). The work clearly demonstrated that differences in cognitive state were accompanied not only by changing patterns of brain activation but also by changes in co-activation and connectivity. This led to the important notion that the functionality of brain regions was determined at least in part by neural context (McIntosh, 1999, 2000, 2004), the pattern of activation and coactivation across the whole network. But despite these promising beginnings for connectivity-based approaches to brain function, the link to network theory remained tenuous. By the end of the 1990s, in the eyes of most biologists and neuroscientists graph theory was little more than an arcane subfield of mathematics. The appeal of graph theory was not yet widely felt outside of the social sciences – but all that was about to change.

In 1998, an elegant paper by Duncan Watts and Steven Strogatz appeared in the journal *Nature* (Watts and Strogatz, 1998). In less than two thousand words the authors presented a simple explanation for the puzzling phenomenon of “small-world behavior”, the tendency of many networks to allow a surprising number of short communication paths, despite large size and sparse connectivity. The explanation was based on a network model that interpolated between complete randomness and complete regularity of connections. Watts and Strogatz proposed that many different real-world networks, including collaborations among film actors, the U.S. power grid, and the neural wiring of the nematode *Caenorhabditis elegans*, consisted of a mixture of regular and random features, and it was this mixture that gave rise to their propensity for small-world behavior. I remember immediately being struck by the correspondence between the small-world regime for networks, created by the co-existence of random and regular connectivity, and our measure of dynamic complexity, characterized by the co-existence of functional segregation and integration. A natural next step was to look for small-world features in some of the networks we found to be capable of high complexity. Indeed, there was compelling evidence that the two sets of measures were associated. We developed network selection algorithms for deriving connectivity patterns that gave rise to high complexity and we found that they all, without exception, contained small-world attributes. Optimizing for other information measures instead yielded very different networks. Furthermore, upon examining the “Van Essen matrix”, we again found prominent small-world organization, and dynamics unfolding on this matrix generated high complexity. We postulated that the anatomical organization of the brain reflected an environmentally driven demand for highly complex neural activity, i.e. activity that simultaneously expressed functional specialization and integration (Sporns et al., 2000).

Around the same time, other colleagues in the field, notably Claus Hilgetag and Rolf Kötter, began developing network algorithms and approaches in the area of primate neuroanatomy. Claus developed a

clustering algorithm based on connectivity to derive anatomical modules (Hilgetag et al., 2000) while Rolf drew direct links between neuroanatomy and functional connectivity through large-scale modeling of structural connections and neural dynamics in the cat neocortex (Kötter and Sommer 2000). Rolf also co-authored an influential review article that discussed the unique patterns of structural connections of primate brain regions and their relation to functional specialization (Passingham et al., 2002). Rolf's later studies introduced the use of "connectional fingerprints" to characterize neural elements on the basis of graph theory metrics (Kötter and Stephan, 2003) and the decomposition of brain networks into subgraphs or motifs (Sporns and Kötter, 2004). Notably, virtually all of these early explorations of the brain network architecture were carried out on (relatively small) anatomical data sets, most of them coming from collations of connectivity data acquired through anatomical tract tracing (e.g. Felleman and Van Essen, 1991; Scannell et al., 1995; Stephan et al., 2001).

The broadening appeal of graph-based analysis was catalyzed by a series of workshops with an explicit focus on brain connectivity. In 2001, Randy McIntosh organized a small meeting on integrative brain function at the University of Toronto, supported by the JS McDonnell Foundation. The workshop introduced a rather unconventional way of delivering presentations – no slides were allowed, just a blackboard, and 15 minutes of time, followed by 30 minutes of interactive discussion. The event was so productive that Rolf Kötter and Karl Friston decided to adopt this format for a workshop on "Functional Brain Connectivity" that convened the following year in Düsseldorf, Germany. Now an annual event called the "Brain Connectivity Workshop", the meeting routinely attracts hundreds of participants and has become the prime venue for cutting-edge research and modeling of brain networks. Early meetings in the series stimulated discussion about the different modes and scales of connectivity in the brain (Horwitz, 2003; Lee et al., 2003), and later meetings continually expanded the range of connectivity-based approaches in new directions, from resting-state fMRI to multiscale computational modeling (Stephan et al., 2008).

It was at the 2005 Brain Connectivity Workshop that I first became aware of direct applications of graph theory to fMRI data. Ed Bullmore presented work in progress that examined a network of fMRI functional connections obtained during the brain's resting-state. The network exhibited robust small-world features, contained a specific set of highly connected hub regions, and was highly resilient to structural damage (Achard et al., 2006). The study demonstrated the generality of the graph-theoretic approach, as well as its analytic power. Since then a large number of fMRI studies have used graph methods to compare patterns of functional connectivity across individuals (e.g. Buckner et al., 2009), over developmental stages (e.g. Fair et al., 2009), in clinical conditions (e.g. van den Heuvel et al., 2010), or directly in relation to behavior (e.g. Bassett et al., 2011). A growing number of studies have used network models and graphs to characterize spontaneous BOLD fluctuations occurring during resting brain dynamics. Identification of coherently fluctuating brain systems led to the discovery of the brain's "default mode" (Raichle et al., 2001), associated with a network of functionally coupled regions in frontal and parietal cortex (Greicius et al., 2003). Since then, resting-state fMRI has turned out to deliver extraordinarily detailed insights into brain organization (Fox and Raichle, 2007; Buckner et al., 2008), particularly by revealing distinct resting-state networks that become engaged in different task or stimulus conditions (Smith et al., 2009; Raichle, 2011). The energetic demands imposed by spontaneous brain activity are significant (Raichle and Mintun, 2006) and strongly suggest that this mode of activity is of great importance to brain function in general.

The consistency with which resting-state fMRI patterns could be mapped across individuals suggested an anatomical basis. For me, given earlier work on models of intrinsically driven neural dynamics

and the role of networks in shaping it (e.g. Tononi et al., 1994), a natural next step was to attempt to simulate spontaneous BOLD fluctuations observed in the resting-state and trace their dynamics to the underlying structural connectivity. I was lucky to convince an extraordinarily gifted graduate student, Chris Honey, to take on this project. Combining basic biophysical equations for membrane currents and voltage-time series with structural connection matrices, we simulated spontaneous neural activity and synthetic BOLD signals first in macaque cortex (Honey et al., 2007) and then in human cortex (Honey et al., 2009). We found that the models were able to reproduce a number of characteristic spatiotemporal features of the empirical resting-state, including the slow time course of BOLD fluctuations and the topology of functional connectivity, both in monkey (Adachi et al., in press) and human (Honey et al., 2009). The models made several key predictions, including the dependence of BOLD fluctuations on changes in fast neural activity (see Schölvinck et al., 2010) as well as the occurrence of non-stationarities in cross-correlations revealed by computing them on overlapping time windows (see Chang and Glover, 2010).

As documented in a recent review (Friston, 2009), the balance between neuroimaging studies focused on functional localization (brain activation) and those focused on functional integration (brain connectivity) has shifted in recent years. This shift is partly driven by the growth of studies employing task-free resting-state fMRI in neuroimaging. I suspect another reason is the success of graphical models in revealing important aspects of brain organization across individuals and subject groups. Modern graph theory offers a virtually unlimited range of analytic tools, with continual innovations across an extraordinarily wide range of applications in science and technology. Graphical tools naturally fit the organization of the brain (the brain is a network, after all), and they provide a coherent theoretical framework that links networks across scales (neurons, populations, brain regions) and modes (structural, functional, effective). Different sets of graph metrics highlight local or segregated versus global or integrated aspects of network architectures, as well as the "influence" or centrality of specific network elements (Rubinov and Sporns, 2010). Increasingly important is the detection of community structure or modularity, as modules often correspond to functional units that exhibit coherent fluctuations in the resting-state or become engaged in specific task conditions (Meunier et al., 2010). The power of graph models makes them indispensable as functional neuroimaging focuses more and more on brain networks. This brings us to the final chapter of this historical perspective, the human connectome.

Discovering the human connectome

Over two decades of work with computational network models of the brain have given me a strong appreciation for the role of connectivity in shaping dynamic neural responses. Structural connections define what's possible (and impossible) in a given circuit – which neurons or brain regions can influence each other, and how strongly and directly that influence can be conveyed. Beyond determining the causal flow of information between pairs of network elements, the network topology as a whole organizes and coordinates global states of the brain, enabling coherent dynamic states and temporal fluctuations on multiple scales of space and time. Knowledge of structural connectivity greatly facilitates building "forward models" of neural dynamics as well as carrying out "model inversion" for inferring the causes of observed neural responses. Connectivity is thus an important ingredient in any causal analysis of observed brain data (Valdes-Sosa et al., 2011).

A decade ago, as we began to discern some of the architectural principles of mammalian cortex, it became clear that understanding the functioning of the human brain required a map of its structural connectivity. Discussions with Giulio Tononi and Rolf Kötter led to the formulation of a plan for mapping human brain connectivity

with noninvasive neuroimaging technology. I managed to convince my colleagues that because of the foundational and invariant nature of such a data set the term “connectome” would be appropriate. Back then, a google search of the term gave virtually no hits — I remember coming across a dating site (as in “connect-to-me”) but nothing relevant to the brain. We drafted an article outlining our proposal and discussing the importance and implications of a future project to map the human connectome (Sporns et al., 2005). In the article, we recognized some of the challenges that needed to be addressed, for example those posed by the inherent multiscale aspect of synaptic connectivity, its variability over time and across individuals, and the important role of development and experience in shaping the connection topology.

Despite these challenges, we felt it was important to proceed in this direction. As I discovered some time later, we had not been the only ones thinking in this way. Patric Hagmann had formulated a very similar set of ideas in his PhD thesis (Hagmann, 2005), and we soon established contact and embarked on a collaborative study of the network topology of the human connectome as derived from diffusion imaging and tractography. Our study (Hagmann et al., 2008), carried out on a small cohort of healthy participants, clearly demonstrated robust small-world attributes, modules and hubs in the human brain. One of the most conspicuous features was a highly connected structural core centered on medial parietal regions of cortex. When first submitted, the study exclusively reported human diffusion imaging data but reviewers rightly demanded that the connection pattern we reported be cross-validated. We decided to include two additional empirical components, one involving diffusion imaging and tractography of a portion of the macaque brain and the comparison of the resulting connectivity pattern with tract tracing data, and the other using resting-state fMRI to establish a relationship between structural and functional connectivity.

The latter comparison was particularly productive in that it showed not only a strong and reliable statistical relationship between structural and functional connectivity, but also pointed to some crucial differences in these two types of brain networks (Honey et al., 2009). Functional connectivity is significantly denser, with many strong functional links between nodes that are found to be structurally unconnected. This means that simple thresholding of functional connectivity to retain only the strongest links does not allow the reliable inference of structural connections. Conversely, structural connections can be quite successful in predicting and modeling resting-state functional connectivity in the human brain. This underscores their central causal role in shaping neural time series and the resulting topology of functional brain networks. This was of course precisely the rationale for mapping the connectome of the human brain.

In 2009, the U.S. National Institutes of Health formulated a strategy for creating such a map by combining different neuroimaging modalities, electromagnetic recordings, and comprehensive behavioral, cognitive and genomic information, initially collected from a large cohort of healthy adults. The Human Connectome Project, now underway in two parallel consortia (<http://humanconnectome.org/consortia/>), will provide an unprecedented amount of publicly available data on human brain connectivity. Much of these data will be rendered in the form of networks or graphs, thus allowing users to perform their own analysis and modeling studies. In parallel, other connectome mapping efforts are underway, some of them embracing open-access data repositories and data sharing across sites, e.g. the “1000 Functional Connectomes Project” (Biswal et al., 2010). Large-scale data collection projects demand the development of capable neuroinformatics platforms that allow users to access and mine large volumes of data (Akil et al., 2011). It will be interesting to see how these new developments change neuroimaging in the future. My hope is that connectomics will not only drive large-scale data collection and sharing but also, through the adoption of network approaches, greatly increase our understanding of the network basis of the human brain and mind.

Outlook

Over the past twenty years, we have come a long way in this journey from simple graphs to the full complexity of the human connectome. Network approaches have gained considerable ground and have greatly expanded across cognitive and systems neuroscience. Their success derives from the natural fit between graph models and the network architecture of the brain. Regardless of where the ever increasing sophistication of neuroimaging technology will take us, graph theory will become indispensable along the way. The common theoretical framework it provides will continue to advance our fundamental understanding of how brain networks give rise to behavior and cognition.

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