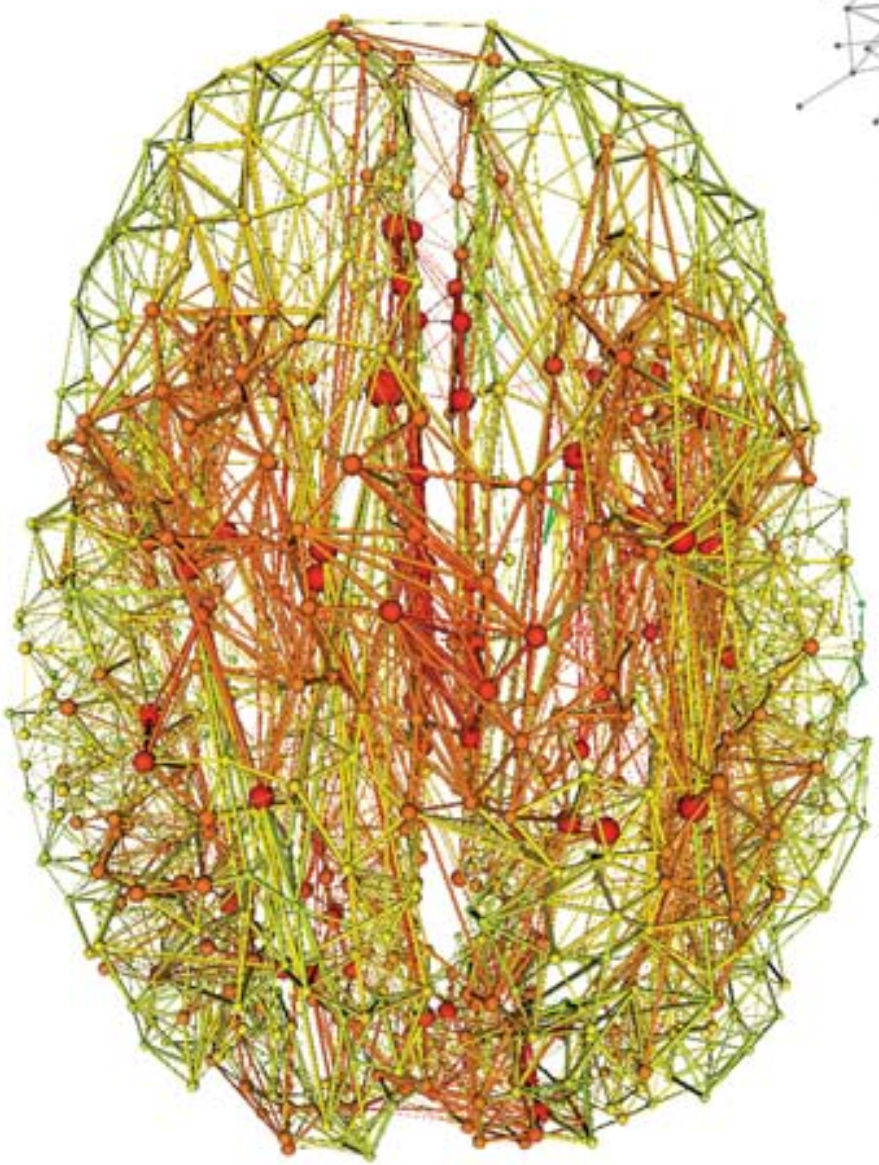
Olaf Sporns

Discovering the Human Connectome



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For Anita

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Preface

In the early summer of 2005 my colleagues Rolf Kötter, Giulio Tononi, and I put the finishing touches to a review article (really a position paper) somewhat ambitiously entitled "The Human Connectome: A Structural Description of the Human Brain" (Sporns et al., 2005). At the time, the connectome was just an idea, nothing more. The idea seemed simple enough. The human brain is a complex network whose operation depends on how its neurons are linked to each other. When attempting to understand the workings of a complex network, one must know how its elements are connected, and how these elements and connections cooperate to generate network function. The human connectome describes the complete set of all neural connections of the human brain. It thus constitutes a network map that is of fundamental importance for studies of brain dynamics and function. When I googled the term "connectome" (just to be sure no one else had thought of it earlier) I remember getting around 10 hits, none of them relevant to the brain. In fact, some of them were oddly irrelevant—I recall finding "connect-to-me" (a dating site, I believe) and "connect-home" among the search results. As of April 2012 the same Google search returns nearly a quarter million hits. What happened?

The simple idea of mapping the connections of the human brain in their entirety has captured the imagination of many, not only neuroscientists but also researchers in adjoining fields interested in human cognition, brain and mental disorders, and complex systems and networks, as well as members of the general public. I believe it is fair to say that the connectome and the nascent field of connectomics are beginning to influence the ways many neuroscientists collect, analyze, and think about their data. Connectomics is directed at integrative function—central to connectomics is the notion that the brain can be described and understood as a *network*, not just by way of a metaphor but in the precise

technical and mathematical sense of a connectivity graph. Adopting this view opens new horizons on brain function, and it allows the use of powerful analytic tools and concepts coming from the emerging science of complex networks. In my previous book *Networks of the Brain*, I made the case that neuroscience has much to gain from adopting this theoretical framework, and I attempted to sketch a first draft of an integrative theory of brain function that is based on network architectures and mechanisms. The present book builds on this theoretical framework to ask some very specific questions. What is the nature of the human connectome? Why is it important to pursue the connectome as a high-priority scientific goal, and what will the connectome tell us once we have discovered it? What are the most compelling empirical strategies for mapping the human connectome, and how can we make sense of the extraordinary amount of data they will deliver? What is the future promise and, equally importantly, what are the limitations of connectomics in neuroscience?

Today, the human connectome is known to us only in broad outline, and intensive research under way in many laboratories and research centers around the world will add substantially to our understanding of human brain connectivity over coming years. While future iterations of this book will undoubtedly deliver a much more refined and detailed picture of the connectome, some of the basic concepts and theoretical ideas that lie at the origin of connectomics will likely remain valid. Central among these ideas is the notion that the connectome is a complex network and that a detailed account of network structure and function can deliver a much needed new perspective on brain function. One of the biggest challenges will be to discover how these networks shape the integrated and dynamic activity of neurons and brain regions and how the network architecture of our brain relates to our behavioral and cognitive capacities. I suspect that meeting this challenge will take far longer than attaining the first goal of creating an accurate and detailed map of human brain connectivity. Connectomics as a comprehensive research effort directed at understanding the brain as a complex network will occupy us for some time to come. We are only at the very beginning of what promises to be an exciting new period of empirical investigation and theoretical inquiry.

The connectome might never have become a reality, at least not with a prominent focus on the human brain, without my longtime colleague and friend Rolf Kötter. Rolf and I first talked about a future project to map all of the connections of the human brain in November 2004 at a

meeting near Toronto, organized by Randy McIntosh and sponsored by the J.S. McDonnell Foundation. We continued to pursue our discussion via frequent e-mail and phone conversations and started to generate a draft of a "white paper" outlining a detailed proposal for mapping the human connectome. I fondly remember a long discussion on a cold morning in early March 2005, over breakfast in a café outside the National Science Foundation in Arlington (we were both members of a review panel). We had already sketched out the main rationale for the connectome, and we were pondering how we might gain broader support and acceptance for the concept in our field (perhaps even from funding agencies!). Both of us were unsure about the project's feasibility in the near term, but we convinced each other that, despite these uncertainties, it was important to make a public argument that laid out the motivation for the connectome as a foundational network model of the brain. We formulated a multistep plan for the project, including diffusion and functional magnetic resonance imaging as well as electromagnetic recordings across a large population to assess individual variability. Within a few weeks the article was written and submitted, and eventually published in the journal *PLoS Computational Biology*. Over the years, the idea of the connectome gathered momentum, driven by new techniques and the discoveries of many colleagues in the field. Rolf and I were tremendously excited when, in 2009, the Human Connectome Project finally moved forward under National Institutes of Health (NIH) sponsorship, something neither of us had envisioned even a few years earlier. I am deeply saddened that Rolf will not be with us on the journey toward discovering the human connectome. His untimely death after a long battle with a devastating disease was a profound and tragic loss to our research community. Rolf's vision and insight, his scholarly wisdom, and his warm collegiality (and dry sense of humor) will be missed dearly.

My own research described in this book has been generously sponsored by the J.S. McDonnell Foundation and, more recently, by the NIH under the auspices of the Human Connectome Project. I wrote the book with the support of a 2011 John Simon Guggenheim Memorial Fellowship and while on sabbatical leave at Indiana University. I owe thanks to many colleagues for the inspiration their work has given me. It is an extraordinary privilege to be one among many investigators collaborating on the NIH's Human Connectome Project, under the leadership of David Van Essen and Kamil Ugurbil. I have no doubt that the project will be a major milestone on the road toward understanding the workings of the human brain. While the ideas laid out in this book are entirely my

own, I do hope that some of them will be of use in ongoing and future connectome projects.

Many colleagues have encouraged me to write this book, and I thank them for their support and intellectual generosity in sharing ideas and opinions. Mika Rubinov graciously volunteered to read draft chapters, and his input has been extremely useful. I am grateful to Michael Breakspear, Kevin Briggman, Yoonsuck Choe, Patric Hagmann, Martijn van den Heuvel, Marc Joliot, Christoph Palm, Marc Raichle, and David Van Essen for generously providing figures and other materials. I thank Bob Prior at MIT Press for allowing me to become (in his words) a "repeat offender" by supporting my second book project in three years. Finally, I thank my wife, Anne Prieto, for her love and support—and I promise I won't do this again so soon!

1 Introduction

If I had to point to the single most important thing to know about how the brain works, my answer would be "connectivity." Of course, much else comes to mind—the interplay of ionic currents that generate neuronal membrane potentials, the variety of neurotransmitter systems involved in synaptic transmission and plasticity, the capacity of neurons to convert inputs into outputs, the endlessly rich patterns of cellular and synaptic morphology, and many other features of the brain at molecular, cellular, and systems scales. And yet, I believe it is fair to say that the brain's computational power depends critically (though certainly not entirely) on how individual processing elements are networked together. The human brain is a network of extraordinary complexity, an intricate web of billions of neurons connected by trillions of synapses and wiring that spans a distance halfway to the moon. How this network is connected is important for virtually all facets of the brain's integrative function (Sporns, 2011a). Brain connectivity allows neurons to exhibit an extraordinary range of physiological responses and enables them to generate and distribute information, to coordinate their activity over short and long distances, and to retain a structural record of past events.

The centerpiece of brain connectivity is the connectome—a comprehensive description of how neurons and brain regions are interconnected. Much of this book is about current efforts to chart these connections in the human brain and what the first maps created with a variety of techniques tell us about the brain's network architecture. To be sure, the insights we have gained so far are preliminary and incomplete, and there is much still to be discovered. However, the journey toward mapping the human connectome has begun, and significant progress is being made at an ever-accelerating pace. A growing number of empirical and theoretical studies of the brain's network architecture and dynamics are laying

the groundwork for the nascent field of connectomics. The main goal of this book is to describe the origins and prospects of the endeavor and to chart its main scientific and intellectual underpinnings.

The book is arranged in eight chapters. This first chapter positions the connectome within the wider context of biological systems by examining the role of structure for understanding biological function, the nature of complexity, and the importance of networks in making sense of brain connectivity. It also provides an introduction to basic concepts and terminology of graphs and network models. Chapter 2 offers a more detailed treatment of the conceptual foundations of the connectome, and chapter 3 focuses on some of the challenges posed by the connectome's multiscale architecture, the inherent variability of nervous systems, and the ongoing structural change that continually remodels neurons and connections. Chapters 4 and 5 survey current empirical strategies for mapping the connectome, covering the entire range of approaches from electron microscopy to magnetic resonance imaging (MRI). I will explore the merits of each technology and ask how these approaches may be integrated to yield a coherent map linking cellular connectivity to brain systems. Chapter 6 deals with how the connectome generates temporal structure in neuronal dynamics. I will also reflect on the important role of "functional connectomics" for linking brain networks to human behavior. Chapters 7 and 8 cover the significant impact of connectomics on computational studies of the nervous system, including the emerging picture of network organization delivered by graph analysis, the need for advanced neuroinformatics tools, and the progress made toward building comprehensive computational models of the human brain. I end by attempting to forecast some of the innovations that connectomics will bring to both basic and translational neuroscience.

Before squarely focusing on the brain, let us briefly look at how the notion of the connectome as a structural foundation for understanding brain function fits with related and more general ideas about the role of structure in the biological sciences. Two ideas are central to the endeavor, the importance of structure for shaping biological function and the role of networks for coordinating the actions of components into coherent system dynamics.

Structure and Complexity

The importance of structure for the functioning of biological systems can hardly be overstated. Examples are found everywhere, ranging from

macromolecules to whole organisms. Structure strongly determines the physicochemical attributes of biomolecules, including their locations within the cell and their interactions with other molecular species. The iconic double-helix structure of deoxyribonucleic acid (DNA), widely considered one of the most important scientific discoveries of the 20th century, "immediately suggests a possible copying mechanism for the genetic material" (Watson and Crick, 1953, p. 737). The chemical specificity of enzymes is largely determined by their shape and geometry, which permit interactions with substrates, inhibitors, and activators. Virtually all electrical properties of neuronal membranes depend on the actions of transmembrane protein channels that regulate the passage of specific ions across the cell surface (figure 1.1). Their stable placement within the membrane, the aggregation of protein subunits to form a nanometer scale pore, the selectivity of the channel for specific ions, and the gating of channels in response to chemical ligands or changes in the cell's

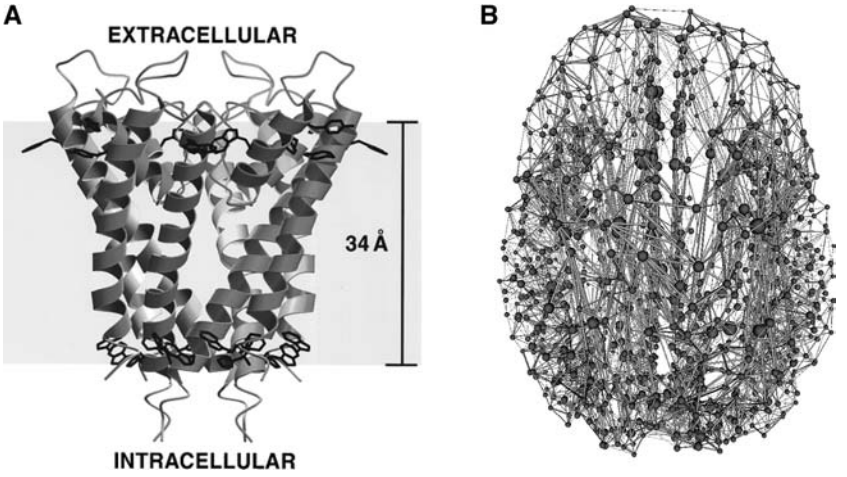

Figure 1.1
The importance of structure in biological function. (A) Schematic representation of the protein structure of the potassium channel. The diagram shows the folding pattern of the four channel subunits and its integration into the cell membrane, here shaded in gray. The channel forms a pore through which potassium ions can cross. Its structure enables the fundamental biological process of selective membrane conductance which underlies all electrical signaling among neurons. The image is reproduced with permission from Doyle et al. (1998). (B) Schematic representation of the network of fiber tracts coursing through the human brain's white matter. The nodes correspond to a set of cortical regions covering both cerebral hemispheres, and the edges between them correspond to neural connections. The structure of this network shapes neural activity across the brain and forms the anatomical basis of large-scale brain function. The image was kindly provided by Martijn van den Heuvel (University Medical Center Utrecht, The Netherlands).

membrane potential all depend on the spatial configuration of the channel's molecular components.

Relations between structure and function are also evident at larger scales, in the shape and form of organelles, cells, tissues, organs, and even in the biomechanics of the whole organism. An organism's behavioral repertoire is shaped by numerous structural and mechanical constraints, from the basic layout of the body's sensors and effectors to the articulation of limbs or wings and the couplings of muscles and connective tissues. As a whole, the anatomical organization of the musculoskeletal system supports the stability and adaptive control of bodily motion and behavior. The importance of structure and biological form extends to the nervous system, and how this structural organization shapes brain function is the central theme of this book. The brain's numerous anatomical components and their physical couplings are critically important for its functional activity, the flow of neural signals that underlies all mental experience. Structural linkages between elements of neuronal systems channel their dynamic interactions and constrain the paths across which neurons can communicate and share information (see figure 1.1). Just as the network of chemical bonds comprising a macromolecule determines which of its subdomains fold into spatial proximity,[1] the brain's network of synaptic connections determines the similarity and specificity of functional and physiological attributes among neuronal collectives.

The importance of structure does not imply that structure alone can fully predict all functional outcomes or that full knowledge of structure allows a keen observer to deduce all of the physiology and behavior of a biological system. For function to be properly expressed, structure has to be placed into a wider context. In the case of biomolecules, this context is supplied by the roughly 10^{12} molecules making up a cell—a function of a protein channel such as voltage-gating, while certainly dependent on its molecular configuration, requires a surrounding neuron and its membrane potential. In the case of the brain, context comes from internal as well as sensory signals, for example those caused by the behaviors of a social group—neuronal activity related to emotional constructs such as empathy, while caused by connectivity in the brain, also reflects interpersonal processes occurring in a social environment.

In addition to context, structure and function must also be viewed as engaging in a continuous dialogue. Just as structure shapes function, the emergence of new functions often depends on making structural changes. Heritable modification of the structural arrangement of molecules, cells, or tissues is one way by which selectional forces operating on an evolu-

tionary time scale can mold biological function. Selection based on function is ultimately responsible for the kinds of structures we find as part of organisms today. In the case of the brain, alterations in neural circuitry contribute to the emergence of new behaviors or cognitive capacities. Function itself leaves a structural record as is amply demonstrated by the many structural traces left as a result of neuronal activity.

This consideration of the centrality of structure–function relationships leads us to two important aspects shared by most, if not all, biological systems. They are *multiscale systems* that are organized as *complex networks*. Biological processes unfold on multiple scales that range from molecules to organisms and span 10 and 15 orders of magnitude in space and time, respectively (e.g., Hunter and Borg, 2003; figure 1.2). Importantly, these scales interact and are mutually interdependent. No scale is privileged over others in the sense that system behavior cannot be fully reduced to processes occurring at one scale only. At each scale, and across scales, biological systems are organized as networks, consisting of a large number of components that are connected in complex patterns. It is the coordinated action of networks that is responsible for global functional properties of cells and organisms.

Understanding the global functional properties of a biological system requires knowledge about the system's elements as well as a map of how these elements mutually interact. Significant research efforts in areas such as ecology and biodiversity, cancer biology, cellular signal transduction, metabolism and gene regulation, and, finally, neuroscience are directed toward mapping the structure of complex biological networks. As it turns out, the research program of connectomics closely parallels that of the relatively new field of "systems biology."

Connectomics and Systems Biology

A major aim of systems biology is the application of mathematical and computational models in areas such as population biology, enzyme kinetics, biochemical pathways, and genetic regulatory circuits. The inception of systems biology coincided with the arrival of large-scale genomics and proteomics data sets (Ideker et al., 2001; Kitano, 2001).[2] These data sets required concerted efforts to collect, store, visualize, and integrate large amounts of biological information. Building on data about genes and proteins, the overarching goal of systems biology is to account for the molecular origins of emergent biological phenomena: "Systems biology is a scientific discipline that endeavors to quantify all of the molecular

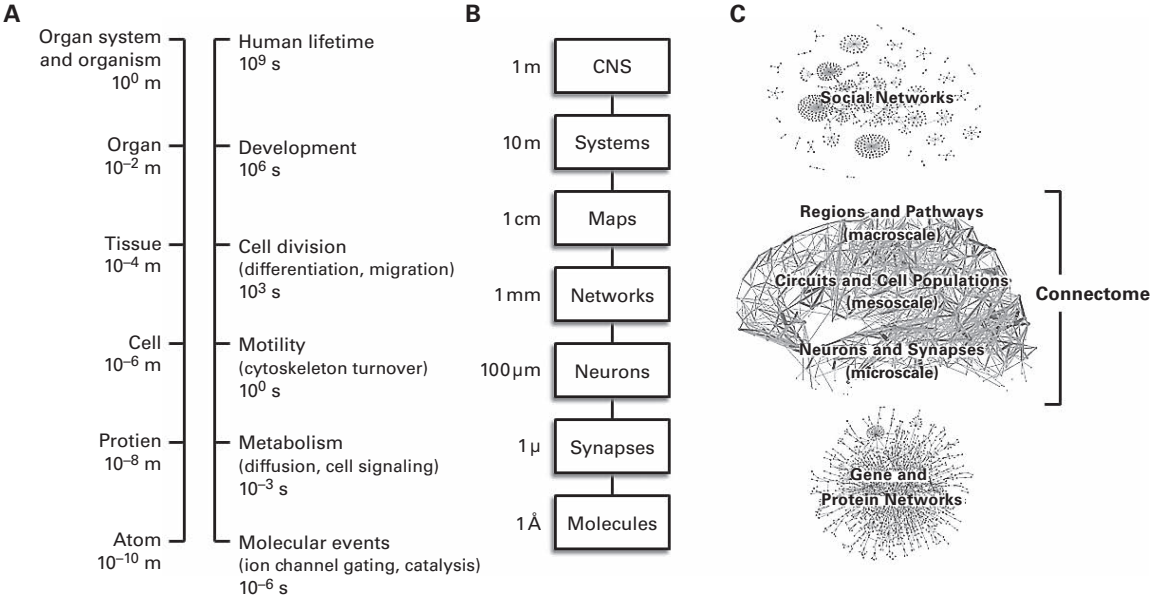

Figure 1.2
Levels of organization in biological systems and in the brain. (A) Spatial and temporal scales, spanning many orders of magnitudes. Similar diagrams can be found in Hunter and Borg (2003) and Dada and Mendes (2011). (B) Levels of organization in the nervous system. The diagram is adapted from a similar illustration in Churchland and Sejnowski (1992). CNS, central nervous system. (C) The nervous system as a hierarchy of networks. The multiscale networks of the connectome are interspersed between networks operating at cellular and social scales.

elements of a biological system to assess their interactions and to integrate that information into graphical network models that serve as predictive hypotheses to explain emergent behaviors" (Hood et al., 2004, p. 640). Hiroaki Kitano poignantly expressed the principal aim of systems biology as going beyond static descriptions of the inventory of genes and proteins. A biological system, in his words, "is not just an assembly of genes and proteins, [and] its properties cannot be fully understood merely by drawing diagrams of interconnections. Although such a diagram represents an important first step, it is analogous to a static roadmap, whereas what we really seek to know are the traffic patterns, why such traffic patterns emerge, and how we can control them" (Kitano, 2002, p. 1662).

Several aspects of systems biology set it apart from more traditional research approaches (Aitchison and Galitski, 2003). In addition to "hypothesis-driven" investigation, systems biology includes an important component of "discovery science." Discovery science involves the analy-

sis of large data sets with the explicit goals of identifying significant statistical patterns, which can then lead to the formulation of new hypotheses. By charting the elementary components of functional systems and their dynamic interactions, systems biology aims at discovering the network architecture of biological systems. To accomplish this aim and to effectively bridge system structure and function, systems biology must integrate data from disparate sources and across levels of organization. Finally, the overall research effort is directed at creating plausible models of biological systems that can be tested, as hypotheses, against empirical data (figure 1.3). These models are formulated within a quantitative mathematical modeling framework and allow researchers to examine the dependency of global state transitions on specific system variables or to predict global system responses to specific perturbations.

Systems biology draws on the creation of large-scale data sets that record comprehensive information about specific domains of biology and that lay the material foundations for entire subdisciplines. These data sets are often labeled with the suffix "ome," signifying that they comprise a complete set of elementary components within their respective domain of knowledge. The first was the genome, a term coined in 1920 by the geneticist Hans Winkler.[3] Other "omes" that have proven useful in molecular and cellular biology include the proteome (the complete set of proteins expressed by a specific cell or organism), the transcriptome (the set of RNA molecules), the metabolome (the set of metabolites), and the interactome (the set of molecular interactions, for example, between proteins, in a specific cell or organism).[4] Some "omes" primarily record molecular components while others (like the interactome) explicitly refer to networks of interactions (Giot et al., 2003; Li et al., 2004). While not all "omes," once coined, turn out to be viable additions to the biological repertoire, several "omes" such as the genome and interactome have unquestionable utility that derives from their universality (they apply to all living forms), their totality (each comprises a complete set of data), and their permanence (the genome of an organism, once determined, does not change with time).[5]

Beyond semantic similarities, there are several reasons why the connectome belongs in the family of complex biological systems and why connectomics represents an extension of systems biology into the realm of neuroscience.[6] Mirroring the approach of systems biology, connectomics draws on cumulative and foundational data about components and interactions. The connectome records structure in all organisms with a nervous system (universality), comprises a complete description of

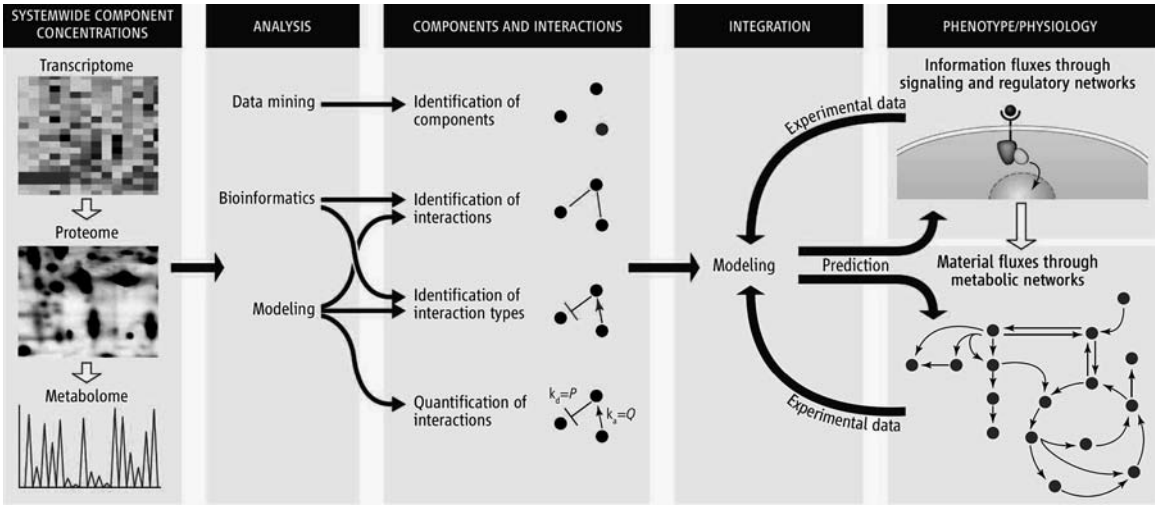

Figure 1.3
Models in systems biology. This schematic diagram illustrates the major data and modeling components of systems biology and how they relate to each other. On the left are comprehensive system-wide measurements of transcripts, proteins, and metabolites. Data analysis efforts identify system components and interactions, which feed into explicit computational models that lead to predictions of new data. Models are continually refined by feedback from experiments. Modified (converted to grayscale) and reproduced with permission from Sauer et al. (2007).

brain connectivity (totality), and, once determined, serves as a lasting resource and foundation for future research (permanence). Like systems biology, connectomics goes beyond static "wiring diagrams" to account for the rich dynamics that emerge from complex brain networks. The connectome's primary goal is the collection of information on structural brain networks comprised of neurons and synapses; however, the wider aim of connectomics includes an account of how this static network is transcribed into dynamic brain activity and behavior. Connectomics is a cumulative scientific effort, involving the collection of very large data sets on brain connectivity that are shared and made available across a broad research community. Finally, connectomics has a strong discovery-science component, and it relies on statistical and computational models for the interpretation and analysis of large data sets in order to generate new questions and hypotheses about brain function.[7]

The "omics" revolution, as it is sometimes called, brings with it the formidable challenge of representing and integrating large-scale foundational data sets to allow their interpretation in the context of the workings of the cell or organism (Joyce and Palsson, 2007). Computation and

modeling play an important part in meeting this challenge, and as a result the fields of bioinformatics and computational biology have experienced significant growth over recent years. Both fields have profited from the development of new modeling techniques and approaches. Computational models of biological systems need to capture phenomena on different temporal and spatial scales and thus require integration of physical and biological processes across different levels of organization (Coveney and Fowler, 2005; Southern et al., 2008; Dada and Mendes, 2011). In some areas of computational biology, multiscale models are by now quite well developed. For example, multiscale models of organ systems such as the human heart have successfully integrated information across micro- and macroscales (Noble, 2002). Based on an anatomically detailed structural description of the heart, these models simulate its mechanical and electrical dynamics. Components at the microscale include membrane currents and ion pumps to model voltage changes across cardiac muscle cell membranes, resulting in waves of excitation unfolding across the tissue. Models of current flow and muscle cell contraction are combined to create a description of the deformation dynamics of the myocardium through the cardiac cycle. The result is an integrative account of electrical activation, pulsation, and blood flow at the macroscale, based on microscale mechanisms simulated in conjunction with a structural model of heart tissue.

An important conceptual foundation for thinking about complex biological systems comes from the science of networks. Cataloguing system components and their relations is only a first step toward the ambitious goal of understanding how their dynamic interactions give rise to integrated functional states. Network analysis and modeling offers an attractive and by now widely adopted theoretical framework for translating components and relations into global system behavior. A full exploration of the many applications of network approaches in neuroscience is beyond the scope of this book (instead, see Sporns, 2011a). However, a brief survey of network methodology and terminology is needed to set the stage for much of what is to come. Let us turn to an overview of how brain networks can be described and analyzed with modern quantitative approaches.

Networks of the Brain

Network diagrams are ubiquitous in the neurobiological literature and have long served as useful devices to summarize anatomical and

physiological relationships among circuit elements (figure 1.4). The discovery of the cellular architecture of the brain in the 19th century first revealed the nervous system as a complex aggregate of seemingly innumerable nerve cells interconnected in ways that were anatomically organized and specific to each part of the brain. The "neuron theory" motivated early theoretical accounts directed at linking psychological phenomena to their anatomical and physiological substrates. Examples are Theodor Meynert's attempts at deciphering brain architectures (see chapter 5), Sigmund Freud's anticipation of changes in neuronal connections as the material basis of memory in his (then unpublished) 1895 manuscript entitled *A Project for a Scientific Psychology* (Freud, 1966), and Sigmund Exner's early network diagrams. In the opening passage of his treatise *Entwurf zu einer Physiologischen Erklärung der Psychischen Erscheinungen*, Exner expressed his central goal "to trace the most prominent psychological phenomena back to differential excitation of nerves and nerve centers, that is, to link the diversity of consciousness to quantitative relations and differences in the central connections of otherwise equivalent nerves and centers" (Exner, 1894, p. 3).[8]

However, the quantitative framework for describing those differences in connections of "nerves and centers" was missing. While the origins of graph theory extend back over 250 years, its prominence as a model for complex social and biological systems composed of numerous elements and interactions is a fairly recent phenomenon. Beginning in the 1930s with "sociograms," graphical descriptions of interpersonal relationships between members of a social group, the full power of network analysis as a quantitative model for sociological theory was realized only much later. In a seminal paper written almost 40 years ago, the sociologist Mark Granovetter proposed that network theory could address what he saw as the fundamental weakness in his field, "that it does not relate micro-level interactions to macro-level patterns in any convincing way" (Granovetter, 1973, p. 1360). He went on to suggest that "it is through […] networks that small-scale interaction becomes translated into large-scale patterns, and that these, in turn, feed back into small groups."[9] Network theory has since undergone enormous expansion in virtually all areas of the social and natural sciences. Most recently, it has become an integral part of sophisticated analysis and modeling of biological systems at cellular and organismic scales (Barabási and Oltvai, 2004; Zhu et al., 2007; Bascompte, 2007).

Networks or graphs are collections of nodes and edges, with edges representing relationships between pairs of nodes. In the case of the

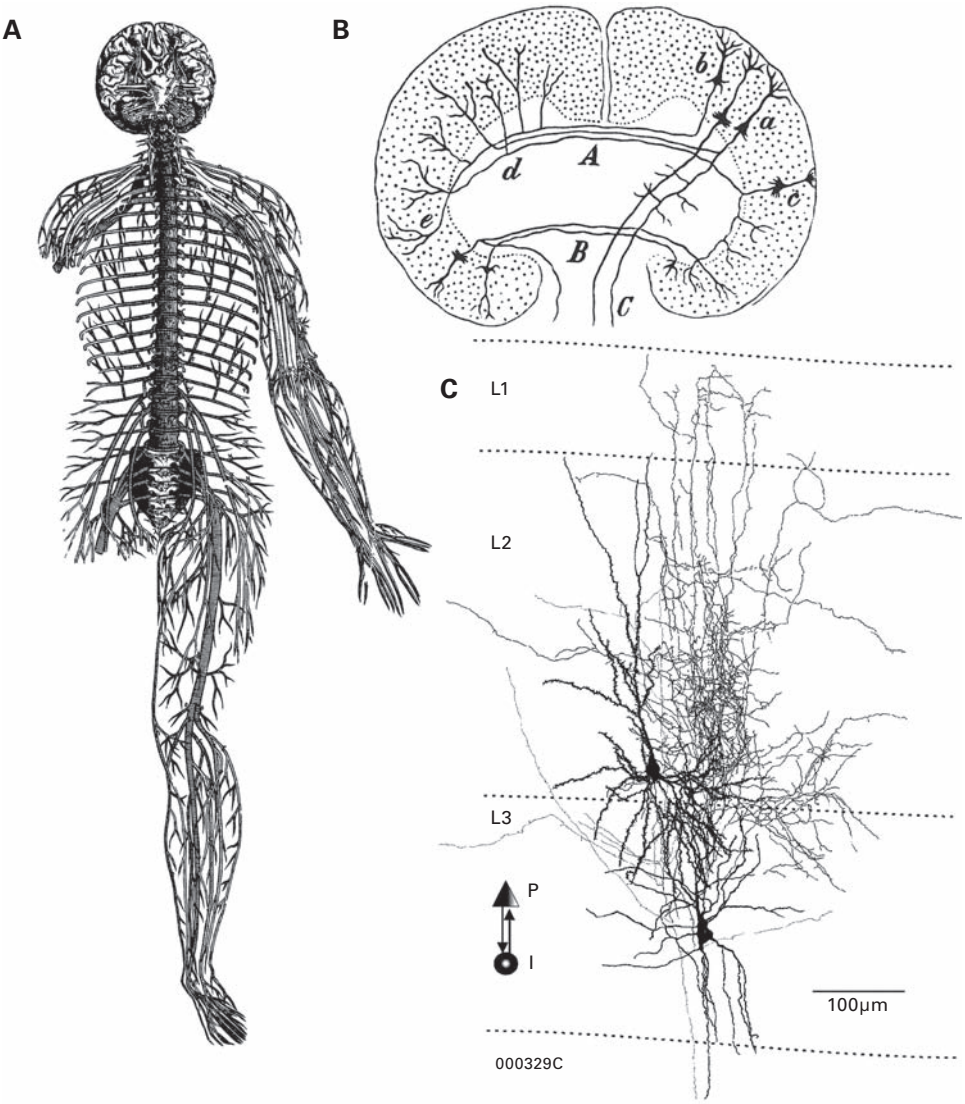

Figure 1.4
Examples of brain networks. (A) An illustration of the human central and peripheral nervous system, from Andreas Vesalius's 1555 edition of *De humani corporis fabrica*, reproduced from Swanson (2007) with permission. (B) A schematic diagram of the major connections of the cerebral cortex, including commissural fibers linking the cerebral hemispheres, association fibers linking cortical regions, and fibers linking cortical and subcortical regions. A, corpus callosum; B, anterior commissure; C, pyramical tract; a, b, c, cortical neurons; d, e, axonal branches. Reproduced from Exner (1894). (C) Dendritic and axonal arbors of a synaptically connected pair of neurons in cat cortex. At the bottom (dark gray) is an interneuron (I) located in L (layer) 3 whose axon innervates a L2 pyramidal cell (P). Scale bar: 100 μm. Reproduced with permission from Thomson et al. (2002).

nervous system, nodes most often refer to neurons or brain regions, while the edges between them can stand for a variety of measures of association, including the strength of a structural linkage (synapse, pathway) or an estimate of the dynamic flow of information. The variety of ways in which brain networks can be defined and measured is a somewhat unique feature compared to other fields—most applications of graph theory in social or natural systems so far have focused on fairly static representations without attempting to track dynamic network interactions. Dynamics, however, are an integral aspect of neural function, and thus dynamic networks represent a major branch of brain graph analyses. Broadly, brain networks can be classified as describing structural connectivity (anatomy), functional connectivity (statistical dependencies), and effective connectivity (causal relations) among collections of nodes (Jirsa and McIntosh, 2007; figure 1.5; table 1.1). Structural connectivity is the central objective of connectome-mapping studies while functional and effective connectivity describe the many facets of variable brain dynamics that accompany different aspects of sensorimotor function, behavior, and cognition.

Before observations of brain structure or function can be analyzed with the tools and metrics of graph theory, the empirical data must be represented in the form of a network (Bullmore and Sporns, 2009). Key steps in this process involve the definitions of nodes and edges. If the data come from neurophysiological recordings, network nodes might correspond to individual neurons, while neuroimaging studies require that the brain be divided into regions or parcels. This parcellation step is critical because many graph measures are sensitive to the way nodes (and thus edges) are initially defined. Parcellation strategies for the human brain are thus a central concern of current efforts to map the human connectome (see chapter 5). Once nodes are defined, their mutual pairwise association can be determined from measurements of structural, functional, or effective connectivity. These pairwise associations can be assembled in the form of a connection matrix, which, in turn, represents a graph or network. The edges between the nodes define the graph's adjacency structure, that is, they determine which nodes are immediate neighbors. Depending on the nature of the measure used to define the edges, graphs can be binary (edges are either present or absent), weighted (edges can take on graded values), undirected (edges express a symmetrical relationship), or directed (edges express an asymmetrical relationship). The graph adjacency makes no reference to the spatial position of the nodes and edges, instead capturing only the topology of the network.

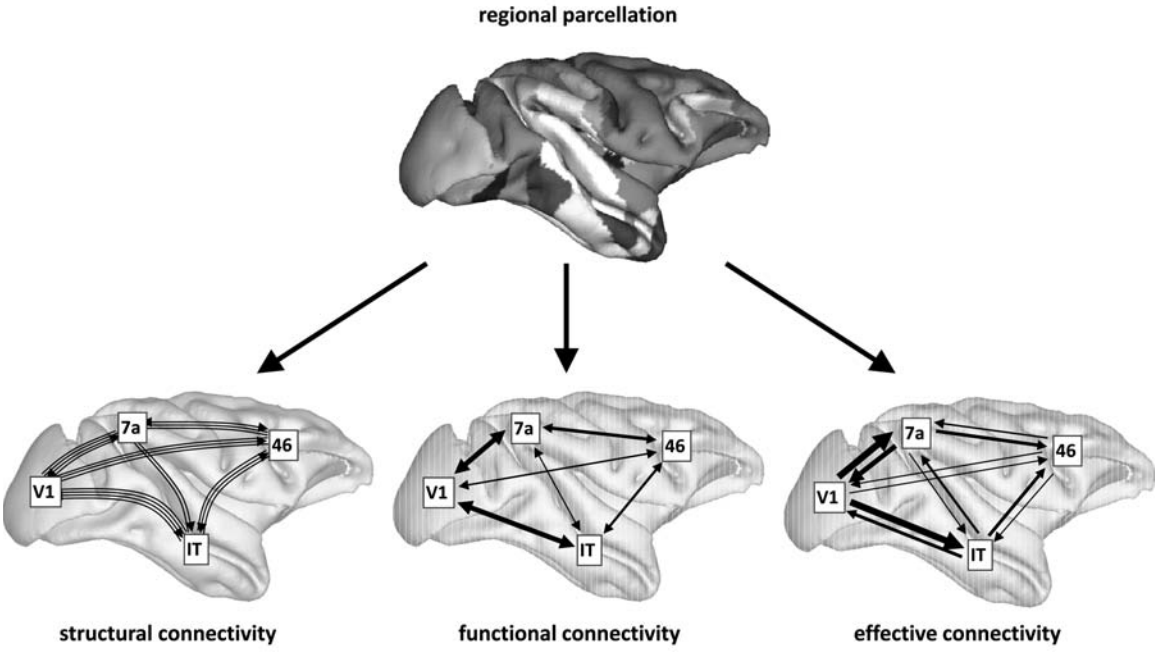

Figure 1.5
Structural, functional, and effective connectivity. This schematic illustration shows a lateral view of the macaque cortex and illustrates the different modes of brain connectivity through the relations between four cortical regions, V1 (visual area V1), 7a (parietal visual area 7a), 46 (prefrontal area 46), and IT (inferior temporal cortex). The diagram at the top shows a regional parcellation of the cortical surface, defining cortical areas and thus the nodes of the brain network. Structural connectivity (left) is shown as a collection of white matter fiber bundles, functional connectivity (middle) is shown as symmetrical statistical relationships (arrows), which can be extracted from regional time courses of activation, and effective connectivity (right) is shown as inferences of directed (causal) interregional interactions. See figure 2.3 for a related illustration of the dynamic aspect of functional connectivity.

As I will discuss later (in chapter 7), the spatial embedding of brain networks entails a close relationship between the location of network elements and their propensity for being topologically connected.

Graph theory offers a comprehensive set of quantitative measures that capture global (network-wide) or local (node or edge specific) aspects of connectivity (figure 1.6). Table 1.2 provides a glossary for a selection of some of the most important graph concepts and measures that will be referred to throughout the book. More in-depth and formal surveys of graph measures are available in the form of numerous review articles (e.g., Rubinov and Sporns, 2010; Kaiser, 2011). Applications of graph

Table 1.1
Major modalities of brain networks

Network Modality	Edge Representation	Empirical Techniques	Network Characteristics
Structural connectivity	Presence/absence of physical link (synapses, pathways), biophysical efficacy (synaptic weight), time delay (chapters 2, 3)	Microscopy: tissue volume reconstruction (chapter 4) Neuroanatomy: tract tracing (chapter 5) Neuroimaging: diffusion imaging/tractography (chapter 5)	Weighted or unweighted, sparse and directed (synapses, projections), sparse and undirected (diffusion MRI)
Functional connectivity	Statistical relationships between neural time courses (e.g., spikes, EEG, BOLD; chapter 6)	Neurophysiology: spike or field potential correlations EEG/MEG: correlation, synchronization, coherence, phase locking fMRI: BOLD signal cross-correlations, partial correlations (chapter 6)	Full and weighted, or sparse and weighted (or unweighted) after thresholding; undirected
Effective connectivity	Causality inference based on temporal precedence cues; causality inference based on generative model (chapter 6)	Spikes, EEG/MEG, fMRI: time series analysis (e.g., Granger causality, transfer entropy) or model inference (e.g., dynamic causal modeling)	Full or sparse; weighted (or unweighted) and directed

Structural connectivity is also referred to as anatomical or synaptic connectivity. The distinction between functional and effective connectivity is based on whether network edges are expressing directed influences. An alternative and more stringent definition of effective connectivity refers only to the explicit inference of a causal or generative model (e.g., Friston, 2011). MRI, magnetic resonance imaging; EEG, electroencephalography; BOLD, blood oxygen level dependent signal; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging.

theory to the brain are covered in some detail in Sporns et al. (2004), Bassett and Bullmore (2006), Stam and Reijneveld (2007), Bullmore and Sporns (2009), Guye et al. (2010), Wang et al. (2010), Bullmore and Bassett (2011), Telesford et al. (2011), Sporns (2011a), and Stam and van Straaten (2012). An open-source Matlab toolbox for computing all of the measures discussed in this book, including a number of brain connectivity data sets, is available at www.brain-connectivity-toolbox.net.

The most fundamental graph measure is the node degree. It refers to the number of connections that are attached to a specific node. Many other graph measures are derived from or correlated with node degree, and some of the local and global architectural features of a network can be gleaned from its degree distribution. A related measure is the "weighted degree," or node strength, which in a weighted network

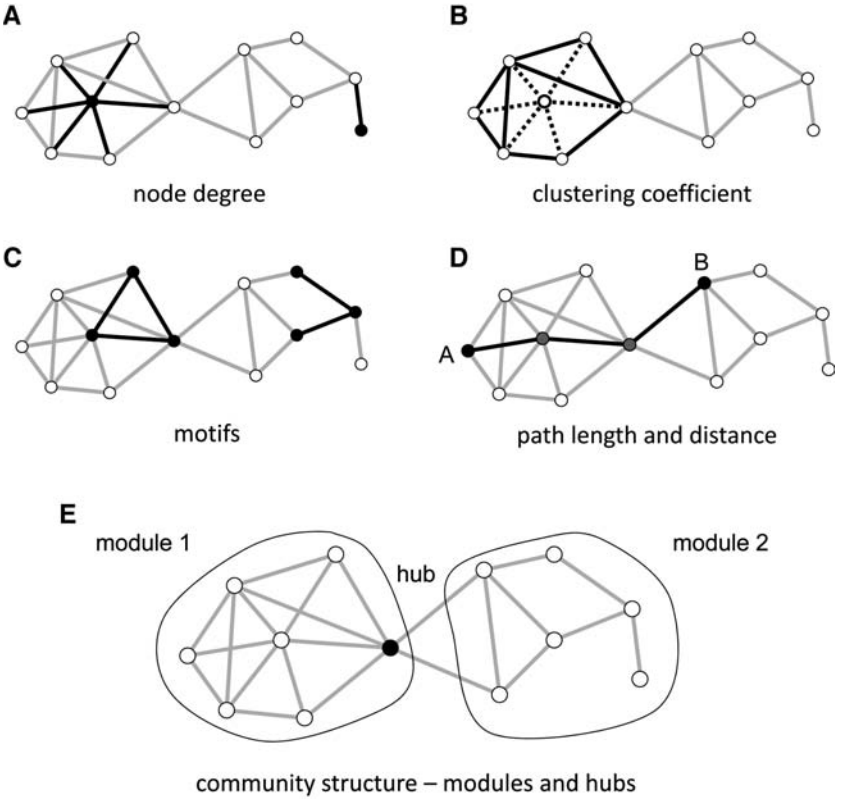

Figure 1.6
Network measures. This schematic diagram shows a selection of some measures that are among the most widely used in neuroscience. The measures are illustrated in a rendering of a simple undirected graph with 12 nodes and 23 edges. (A) The node degree corresponds to the number of edges attached to a given node, shown here for a highly connected node (left) and a peripheral node (right). (B) The clustering coefficient is shown here for a central node and its six connected neighbors. These neighbors maintain 8 out of 15 possible edges, yielding a clustering coefficient of 0.53. (C) The network can be decomposed into connected subgraphs, also called network motifs. The plot shows two examples of two different motifs composed of three nodes. (D) The distance between two nodes is the length of the shortest path. Nodes A and B connect in three steps, through two intermediate nodes (shown in gray). The average of the finite distances for all node pairs is also called the graph's path length. (E) The network forms two modules interconnected by a single hub node. Reproduced with permission from Sporns (2011b).

Table 1.2
Important graph concepts and measures that are widely used in the analysis of brain networks and are frequently referred to in this book

Graph Concept	Definition
Graph	A graph is a set of nodes and edges describing or representing a network.
Network	A network is a system composed of interconnected elements that can be mathematically represented as a graph. The terms "network" and "graph" are often used interchangeably.
Node	An element of a graph or network. In the case of a brain network, nodes may represent a neuron, a neuronal population, a brain region, a brain voxel, or a recording electrode. Nodes are sometimes also referred to as "vertices."
Edge	Nodes are linked by edges (also called links or connections). Edges may be directed or undirected, and they may be binary or have fractional weights.
Topology	The geometric relation between nodes defined by their connecting edges, irrespective of any metric distances or spatial embedding.
Binary graph	A binary graph contains only binary edges, that is, it records only whether a pair of nodes is connected or not. If a connection is present, the edge is set to 1; otherwise it is 0. Binary graphs can be directed or undirected. Binary graphs often result when a threshold is applied to continuous data matrices.
Weighted graph	A weighted graph contains edges that can take on any fractional value (including positive and negative values).
Undirected graph	All edges in an undirected graph represent a symmetrical relation between each pair of nodes—for example, a cross-correlation.
Directed graph	Edges represent asymmetrical (directed) relations between node pairs—for example, a synaptic link or a causal effect.
Path	A path is a set of unique edges that link one node to another. In directed graphs, paths consist of sets of directed edges that link a source node to a target node. In most graphs, a large number of paths exist between any pair of nodes.
Distance	The distance refers to the length of the shortest path between a given pair of nodes. If no path exists, the distance is infinite. Distance is recorded as the number of distinct edges (an integer) in binary graphs or as the combined lengths of the edges comprising the path in weighted networks. Distance refers only to the topology of the graph, not its metric or spatial embedding.
Connection matrix	The most basic representation of a graph or network in matrix format, with the entries a_{ij} of the matrix equal to the weight of the connection between node i and node j. The entries a_{ij} are zeros or ones for binary graphs. In binary graphs, the connection matrix is also referred to as the adjacency matrix.
Distance matrix	The entries of the distance matrix contain the distances between all pairs of nodes.
Module	A community of nodes, generally defined by the connection topology. Modules tend to comprise nodes that are more strongly interconnected within than between modules. In brain networks, modules may be defined on the basis of structural or functional connections.
Hub	A node that has high influence or importance to the integrity of the network and its global interconnectedness. Hubs can be detected on the basis of their high degree or high centrality.
Core	A network core is a coherent set of nodes that are highly and mutually interconnected. A core can be mapped by using a recursive procedure that prunes away weakly connected nodes (i.e., nodes with low degree).

Table 1.2
(continued)

Graph Concept	Definition
Rich club	Related to the core, a rich club is a set of high-degree nodes that are more strongly interconnected than expected by chance.
Random network	A network whose nodes are randomly interconnected. In the simplest case, a random network is generated by assigning edges to each node pair with a fixed and uniform probability. More complex random models can be constructed.
Small-world network	A network whose average clustering coefficient is similar to that of a regular lattice network and whose characteristic path length is similar to that of a random network.
Graph Measure	**Definition**
Degree	The most fundamental attribute of each node, referring to the number of edges (undirected or directed, i.e., incoming and outgoing) that are attached. Across the whole network, statistics on node degrees are often summarized in a degree distribution.
Strength	The sum of all edge weights (incoming and outgoing) for all edges attached to a given node.
Clustering coefficient	The fraction of edges (out of all possible) that connect the neighbors of a given node. The clustering coefficient of a node captures the degree to which its neighbors are also neighbors of each other (the "cliquishness" of a network neighborhood). The clustering coefficient can be averaged across an entire network. Different versions of the measure exist for undirected and directed, binary and weighted graphs.
Path length	Computed from the distance matrix, the path length (also called "characteristic path length") is the average of all finite distances in a network.
Modularity	The modularity score is computed relative to a partition of the network into modules. For a given partition, the modularity score records how many of the graph's edges are made within the modules, relative to what would be expected by chance. The modularity of a graph represents the optimal score that can be achieved under any partitioning scheme.
Global efficiency	The global efficiency is the average of the inverse distances across a graph. If two nodes are unconnected, their inverse distance is 0. In binary networks, the efficiency of an unconnected graph (no edges) is 0 and the efficiency of a fully connected graph is 1.
Centrality	In general, centrality expresses the importance or influence of a given node or edge. There are many measures of centrality. For example, the node betweenness centrality is computed as the function of short paths between all nodes of the network that pass through a given node. An equivalent measure can be computed for all edges.

These definitions are deliberately simplified and nonmathematical as they are meant to provide an intuitive idea and a first point of reference for the nonspecialist reader. For more in-depth treatment and mathematical background (including primary citations for all measures), see Rubinov and Sporns (2010).

records the sum of the weights of all connections maintained by a given node. The importance of node degree and strength derives from the fairly direct impact of degree on the dynamic "importance" of a given node. "Importance" captures the extent to which a network element has access to the rest of the network, influencing or affecting interactions elsewhere. Other measures of influence, such as various centrality measures (e.g., closeness centrality, betweenness centrality, eigenvector centrality) are often found to be correlated with node degree or strength.

Graph measures relevant to the brain can be divided into three categories by virtue of what they tell us about brain organization. Measures of segregation capture the degree to which the nodes of a network exhibit clustered connectivity, which arises, for example, when connected partners (neighbors) are also neighbors of each other. The clustering coefficient of the network, generally expressed as the mean of the clustering coefficient over all nodes, is high if many of its connected nodes have common partners. Of particular interest are networks that can be decomposed into distinct communities or modules, defined on the basis of the density of connections within and between modules. Measures of integration estimate how efficiently information can be exchanged among all nodes in the network. Commonly used metrics to express this capacity are the path length and the global efficiency. Measures of influence yield metrics for individual nodes and edges—for example, quantifying their contribution or participation in dynamic processes unfolding on the network. Examples are measures of centrality, which is an important indicator of hubs in the brain. Most network measures, once obtained from empirical data, must be compared to appropriate random models—for example, randomly rewired networks that have equal size, edge density, and node degrees—to assess their significance. In general, the full characterization of a given network in terms of its topology, the different network roles of nodes and edges, and its overall architecture requires the evaluation of a broad range of network measures. As it turns out, many empirical networks, including those found in the brain, express characteristic combinations of network attributes that are associated with specific topological families.

The modern era of network science began with the realization that virtually all real-world networks exhibit highly nonrandom properties of local and global patterns of network connectivity. A number of these properties were found to be universal in the sense that they could be

identified across a wide range of natural, social, and technological systems. Among these, the "small-world" property is of particular interest to neuroscience. The small-world phenomenon, long studied in the context of social networks (Travers and Milgram, 1969), refers to the surprising tendency of some very large networks to allow links between any two nodes via short paths, or sequences of a small number of unique edges. A large social network with thousands or millions of nodes (people) often contains a remarkable number of very short paths of acquaintanceship that link most people to each other.[10] Duncan Watts and Steven Strogatz, in a seminal paper published in 1998, noticed the joint occurrence of two topological attributes, short paths and high clustering, across a wide range of networks, from collaborations among movie actors, to the U.S. power grid, to the synaptic connectivity of the nematode *Caenorhabditis elegans* (Watts and Strogatz, 1998). Soon after, small-world architectures were also found in structural connectivity data recording large-scale projections among regions of mammalian cerebral cortex (Sporns et al., 2000; Hilgetag et al., 2000; Sporns and Zwi, 2004).

Closer examination reveals that small-world attributes like high clustering and short path length, despite their near-universal presence, do not identify a single coherent topological class. Rather, it is possible for networks to attain small-world connectivity in different ways. Structural and functional brain networks express small-world attributes through the existence of modules or communities of tightly interconnected nodes that are more weakly coupled among each other. In many cases, these modules are arranged hierarchically (as "modules within modules"), an architecture that may have important consequences for neural dynamics (see chapter 7). The detection of network modules or communities is of special importance for studies of brain networks as it allows the identification of closely coupled subnetworks and functional systems. We will encounter modules repeatedly throughout the book in various contexts, including when discussing the parcellation of the brain into coherent regions (chapter 5), the identification of functional networks supporting different cognitive capacities (chapter 6), and the definition of global network architecture (chapter 7).[11]

While most network approaches can, in principle, be applied to network data regardless of origin, careful distinctions have to be made in the interpretation of network metrics obtained from structural and functional brain networks (see chapter 6). Structural networks are considerably more straightforward to define and interpret because of the sparsity

and specificity of their links and their (relative) stability across time. Functional networks exhibit significantly greater temporal variability and comprise statistical relations between neurons or brain regions that may or may not be structurally linked. These specific characteristics of structural and functional networks entail differences in the way these networks are analyzed.

In summary, network theory offers an indispensable framework for the representation and analysis of connectome data sets. Extending a gradual shift in emphasis from functional localization to functional integration (Friston, 2009; figure 1.7), the growth of connectomics in systems neuroscience will be accompanied by an expansion of graph-based modeling and data analysis. Importantly, network theory offers an extremely broad theoretical framework that transcends the traditional boundaries of scientific disciplines and links neuroscience with the emerging science of complex systems.

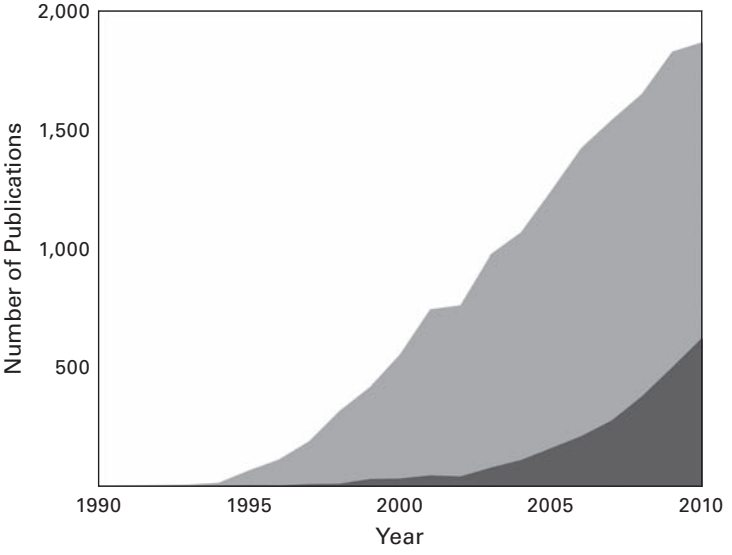

Figure 1.7
The shift from brain activation to brain connectivity. The graph shows an estimate of the number of neuroimaging publications per year that focus on activation (functional segregation, light gray) and connectivity (functional integration, dark gray), respectively. These estimates were derived from a search of the ISI Web of Knowledge with the search terms "((neuroimaging OR fMRI OR DTI) AND activation)" and "((neuroimaging OR fMRI OR DTI) AND connectivity)." The proportion of papers referring to aspects of functional integration has risen from less than 5 percent in 2000 to around 30 percent in 2011; their number has grown over 20-fold. Based on a similar figure first published in Friston (2009).

An "ome" for Neuroscience

The discovery of the human connectome will bring significant new opportunities to brain sciences. The connectome is a foundational neurobiological data set, a structural model of the brain that is indispensable for understanding brain function. Like other structural models in biology, the connectome provides a basic plan, a necessary ingredient for building mechanistic models of brain activity. However, while necessary, the connectome alone is not sufficient for understanding neural dynamics and behavior. The relation of structure to function, centrally important all across biology, is complex and nonlinear. The connectome is a key player in constraining and shaping neural activity, but, as we will see in later chapters, knowledge of the graphical layout of the connectome is only a first step toward a comprehensive account of brain function. Deep understanding of the connectome can only come from considering brain networks in the context of the whole organism and its behavior.

The connectome offers a common operational goal for a broad spectrum of neuroscientists working across different scales and systems. In the future, connectomics will likely foster increased collaboration and cooperation between researchers who previously worked in relative isolation from one another. Connectomics is an inherently transdisciplinary endeavor that brings together anatomists, neurophysiologists, radiologists, geneticists, and computer scientists. Like systems biology, connectomics employs a blend of hypothesis-driven and discovery-based research that involves the integration of multiple data types. Connectomics culminates in the construction of quantitative computational models that embody neurobiological mechanisms at multiple levels of organization. As connectomics gains ground in neuroscience, it supplements more conventional small-scale (single-laboratory) research with a model now commonly seen in the physical sciences: very large-scale projects that are driven by consortia of experts aiming for broad research objectives and clearly defined deliverables while building technologies and infrastructure that benefit entire research communities. This model naturally involves interdisciplinary collaborations, with greater dependence on specialized technical expertise and a complex management structure. In addition, it strongly relies on informatics resources with the explicit goal of cumulative data collection and data sharing (see chapter 8). Connectomics represents one of the first examples of this research model in neuroscience.

In 2012, several concerted research efforts directed at discovering the human connectome are under way. In the United States, the National Institutes of Health supports two large multi-institution research consortia through the Human Connectome Project (http://humanconnectome.org/consortia/). Awarded in September of 2010, one grant supports work led by Washington University and the University of Minnesota (in addition to seven other institutions) involving the study of structural and functional brain connectivity, as well as behavior and genetics, of 1,200 participants. Separately, a second grant supports the development of new imaging technology and analysis tools for structural brain connectivity, centered at the University of California (Los Angeles) and Massachusetts General Hospital. Other efforts, some of them in Europe and Asia, are rapidly gathering momentum.[12] In addition to human connectome projects, several large-scale efforts are under way to map the connectome of the mouse brain (e.g., http://www.mouseconnectome.org/; http://brainarchitecture.org/) and of the fruit fly *Drosophila* (e.g., http://www.flycircuit.tw/; http://research.janelia.org/Chklovskii/). Not surprisingly, a key focus of many of these projects is technology development, leading to methodological enhancement and validation. The science itself will accelerate as new methodologies are shared across laboratories and become more affordable and reliable. The inexorable rise of computation in the biological sciences further fuels progress in the acquisition and analysis of connectome data sets. Despite the many challenges that accompany efforts to map the connectome of any species, comprehensive network maps of the brains of several "model organisms" will become available at an accelerating rate and with ever-increasing resolution and accuracy.

Connectomics is an exciting new field, but a sober assessment of its future promise is in order.[13] I share the enthusiasm of many early practitioners in this emerging field, but I am also keenly aware of the significant difficulty of relating a structural map of the brain to neural dynamics, computation, cognition, and behavior. The project of mapping the connectome is sometimes referred to as tracing the brain's blueprint or wiring diagram, and the resulting map is widely viewed as central for making us who we are as a species and as individuals. The simplicity of this idea is, at first, rather appealing.[14] However, serious problems arise when the notion of "wiring diagram" is taken too literally. The brain is not a giant electrical appliance, or a powerful computer chip, whose wiring is engineered to carry out specific operations. I believe a different perspective is needed to make sense of the intricate web of

trillions of synaptic links that form a human brain. That perspective comes from viewing the brain as a network whose physical architecture enables *complex dynamic behavior* (Sporns, 2011a; Bassett and Gazzaniga, 2011). Brain networks operate as integrated systems where connectivity is laid out in the service of bringing about a wide range of global functional outcomes. The combined action of many individual elements and connections at small scales generates collective and coordinated states at large scales that are essential for cognition and behavior. In this dynamic sense, the network architecture of the connectome is critically important for enabling integrative processes in the nervous system.

Understanding integrative processes from the interactions of neural elements is a central research focus of connectomics, an extension of systems biology to the brain. A corollary of adopting this perspective is that brain function cannot be fully *reduced* to the connectome or wiring diagram, just as knowing an organism's genetic material does not furnish a complete account of its biological form and physiology. The connectome is not a blueprint of "who we are," no more so than the genome, which was supposed to deliver the "book of life" that explained "the chemical underpinnings of human existence" (Watson, 1990, p. 44).[15] Alas, despite the ever-increasing volume of genomic data, a principled understanding of how the genome underpins biological function is still in its infancy. Nevertheless, in ways that are subtle and complex, both genome and connectome carry important information about the natural history of the human species and the biological substrate of our individuality. Gaining access to the basic inventory of genetic components and a growing understanding of the complex networks they set in motion has transformed the biological sciences.[16] In a similar vein, discovering the human connectome will give us new insights and tools for asking better questions about how the structure of the brain gives rise to its functional operations, in both health and disease.

So far we have informally defined the connectome as a comprehensive description or map of the brain's connections. Now, let us explore the nature of the connectome in more detail—what do we mean by "connections," how are they mapped and described, and why does this description matter so much in neuroscience? What exactly is the human connectome?

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