Theoretical Neuroanatomy: Analyzing the Structure, Dynamics, and Function of Neuronal Networks

Anil K. Seth and Gerald M. Edelman

The Neurosciences Institute, 10640 John Jay Hopkins Drive, San Diego, CA 92121
USA

Abstract. The mammalian brain is an extraordinary object: its networks give rise to our conscious experiences as well as to the generation of adaptive behavior for the organism within its environment. Progress in understanding the structure, dynamics and function of the brain faces many challenges. Biological neural networks change over time, their detailed structure is difficult to elucidate, and they are highly heterogeneous both in their neuronal units and synaptic connections. In facing these challenges, graph-theoretic and information-theoretic approaches have yielded a number of useful insights and promise many more.

1 Introduction

The human cerebral cortex contains a network consisting of approximately 30 billion neurons and about 1×10^{15} connections. The state of each neuron varies in complex ways over time, and neurons are diverse in their intrinsic properties and in the number of connections they make. Moreover, the structure of the brain continuously changes as a result of ongoing interactions among neural substrates, neural activity, and the embodied action of the organism within an environment [1–3].

The aim of this chapter is to describe some recent developments in understanding structural, dynamical and functional aspects of neural networks from the perspective of network theory. We focus our analysis on vertebrate cortical networks (the cortex is the heavily folded outer layer of the brain). Given this focus, our coverage is not intended to be comprehensive, and we present a mixture of previous results and new modeling data.

The structure of a neural network is reflected by the set of synaptic connections among neurons at a given time. These synapses have different strengths (weights) which may vary over time as a result of plasticity processes. Dynamics here refers to the neural firing patterns that a neural network supports. This is the level of effective connectivity in the brain [4], and there is now substantial evidence that cognitive and perceptual states are closely related to dynamical patterns of neural activity [5–7]. Finally, we use the term ‘function’ to refer to the role of these firing patterns within the context of a larger system [8], in this case the generation of adaptive behavior for the organism within its environment.

Structural and neuroanatomical analyses are most directly related to current network theory. Representing neural networks as directed graphs allows the ap-

plication of a broad range of analytical tools from graph theory and statistical cluster analysis [9–14]. At present, much less is known about the detailed connectivity of the vertebrate cortex in comparison to artificial networks such as the internet (see, for example, [15]). However, the topology of biological neural networks can be described at many different spatial scales, and graph-theoretic analysis at the level of interconnected brain regions has revealed distinctive features of structural organization including so-called ‘small-world’ characteristics [16].

Network structure is particularly important inasmuch as it provides a substrate for dynamic processes [17,18]. Most dynamical data recorded from neural tissue consist of sequences of discrete action potentials — or ‘spikes’ — with varying inter-spike-intervals, and there is increasing evidence that precise spike timing is significant for normal neural operations [19,20]. Statistical information theory provides a very general means of characterizing these dynamics, and while there is a growing literature concerning the measurement of the information content of single neural spike trains [21–24], we focus here on the dynamics generated by *networks* of neuronal elements. We describe several information-theoretic measures appropriate for this task, including entropy, ‘integration’ and ‘neural complexity’ [25,14]. Theoretical models show that networks optimized to generate each kind of dynamics possess distinctive structural motifs [14]. Of particular interest is neural complexity [25], which is maximized for networks that show an even balance between dynamical segregation and dynamical integration. Networks that generate high complexity contain dense local clusters that are linked by reciprocal bridges. Intriguingly, cortical connection matrices have very similar structural properties, suggesting that they may be near-optimal for generating complex dynamics [14].

To be useful, a network-theoretic approach to neuroscience must take *function* into account. Since biological neural networks are embodied in organisms which are themselves embedded within environments, the most general function of a biological neural network is to generate action for the organism that is adaptive within the current environment. It has been suggested [14] that adaptation to rich sensory environments and motor demands may require complex neural dynamics. In this chapter we describe results that support this hypothesis, based on a model of target fixation by a simulated agent that is controlled by an artificial neural network [26].

While neuroscience has its specific explanatory targets and sources of data, the problem of understanding interactions among network structure, dynamics, and function is a very general one. Some aspects of the analyses presented in this chapter will prove useful for elucidating these interactions in network systems of many different kinds.

2 Structure

The anatomical or structural connectivity of a neuronal system is determined by the network of connections linking its elements at a given time. This network can be described at a variety of spatial scales, from synaptic connections

among individual neurons, to fiber bundles linking local neuronal groups, to the massively parallel pathways connecting distributed areas of the brain.

In the vertebrate (and especially the human) cortex, global connectivity patterns at the level of individual neurons remain largely unknown [27]. Most recent analyses of brain connectivity have made use of datasets such as those describing connectivity at the level of segregated brain regions in the macaque monkey visual cortex [28,29] and the cat cortex [30,31]. While these datasets have proven very useful, they are far from complete. Recent efforts to combine results across many anatomical studies are improving this situation and have resulted in the development of online databases with increasingly detailed connectivity information [32]. For example, as of December 5, 2003 the CoCoMac database (accessible at www.cocomac.org) contained details of 33,850 connections among 6,466 distinct sites in the macaque brain [33]. Future analyses using this database, and others like it, may reveal many presently unknown features of neuroanatomical organization.

2.1 Graph Theoretic Analysis

Neural networks can be described as directed graphs (digraphs) G_{NK} with N vertices (nodes) and K edges. The connection matrix $\mathbf{C}_{ij}(G)$ of G contains elements c_{ij} holding the connection strength between node j (source) and node i (target). If no information is available about relative connection strengths, as is often the case, then $\mathbf{C}_{ij}(G)$ is written as a binary matrix, with entries 1 (connection present) and 0 (connection not present). Paths within G_{NK} refer to any ordered sequence of distinct nodes linking a source j to a target i with the condition that no node is visited more than once, unless $i = j$, in which case the path is a cycle.

Given G_{NK} and the corresponding $\mathbf{C}_{ij}(G)$ matrix, many standard tools of graph theory can be applied to yield insights into the structure of a neural network system [9–14].

The average connectivity of a digraph is the total number of connections present divided by the total number of connections possible. For the human cerebral cortex, this value appears to be very small, perhaps as low as 9.7×10^{-7} [34]. However, most synapses in the brain are between neurons that share the same local neighborhood, so that locally defined average connectivity values are much higher. For example, Nicoll and Blakemore estimate that neurons located within $300\mu\text{m}$ of each other in rat visual cortex are connected with a probability of 0.09 [35]. Average connectivity also increases at larger spatial scales; at the level of cortical areas, connection densities may be as high as 0.36 [28].

Average connectivity by itself does not give much insight into the structural organization of the brain. More useful are local measures such as the ‘matching index’ which gives the proportion of connections shared by two nodes i and j , normalized by the total number of connections belonging to both nodes [36]. A high matching index between two nodes suggests a possible functional overlap. For example, primate cortical areas FST and MSTd have a matching index of

0.71 [12], and electrophysiological studies indicate that cells in these areas do indeed have similar response properties [37].¹

Another useful local measure is the cluster index f_{clust} , which is defined for a node i as the number of connections present among i and its immediate neighbors divided by the maximal number of connections possible among this subset [16]. The (global) cluster index for a graph G is the mean of f_{clust} for all nodes. A high global cluster index indicates a ‘cliquish’ graph in which neighboring nodes connect mainly among each other. Since most synaptic connections are made locally, neural networks may be expected to have high cluster indices, and indeed the macaque visual cortex has a cluster index $f_{clust} = 0.57$, much higher than the value for a randomly connected network with equivalent N and K ($f_{clust} \simeq 0.36$) [12].

The cluster index f_{clust} is often measured in conjunction with the ‘characteristic path length’ of a graph, l_{path} , which is a measure of the mean separation between any two nodes [16]. Formally, $l_{path}(G)$ is the global average of the distance matrix $\mathbf{D}_{ij}(G)$ whose elements d_{ij} hold the shortest path between nodes j and i . Highly clustered networks usually have high values for l_{path} , whereas random networks have low f_{clust} and low l_{path} . In a widely cited paper, Watts & Strogatz [16] identified a class of networks which combine high clustering with short characteristic path lengths; these ‘small-world’ networks consist mainly of local connections with a small proportion of randomly rewired edges. Small-world characteristics are present in networks of many different kinds [16,39], and analysis of cortical connection matrices also reveals high cluster indices in combination with comparatively short path lengths [14,12]; for example, the macaque visual cortex has $f_{clust} = 0.57$ (see above) and $l_{path} = 1.64$ (l_{path} for an equivalent random network $\simeq 1.60$).

‘Scale-free’ networks have the property that the probability $P(k)$ that a node connects to k other nodes follows a power law, i.e. $P(k) = k^{-\gamma}$, where typically $2 < \gamma < 3$. Such power-law degree distributions contrast with randomly connected networks which have Poissonian distributions with a characteristic average degree [40]. As with small-world networks, scale-free characteristics have been found in a wide variety of networks, including the internet, the world-wide web, and biological systems such as metabolic reaction networks [41,42]. As yet, however, no data have been found to indicate the existence of scale-free networks in the brain [12], although of course this does not rule out their discovery in the future.

It has been suggested that a distinctive feature of neurobiological structure and dynamics is *reentry*; the ongoing recurrent exchange of signals along massively parallel reciprocal pathways among neural areas [43–47]. The possibility of reentrant activity in a network can be estimated to a first approximation by the fraction of reciprocal connectivity among areas, i.e. the relative abundance

¹ Areas FST (floor of the superior temporal sulcus) and MSTd (dorsomedial superior temporal cortex) are visual areas whose cells show selective responses to the correlations in visual input that result from movement through a visual environment (optic flow) [38,37].

of cycles of length two. This quantity, designated as f_{recip} , is high for most cortical connection matrices [14]. For example, the macaque visual cortex has $f_{recip} = 0.77$, a fraction much higher than the expected value of 0.3 for equivalent random networks [28,12].

A more general measure of reentry is provided by the quantity $p_{cyc}(q)$, which captures the relative abundance of cycles of length q in a network (note that $p_{cyc}(2)$ is equivalent to f_{recip}) [14]. Both macaque visual cortex and cat cortex have values for $p_{cyc}(q)$, for cycles of lengths up to at least $q = 5$, that are significantly above those obtained for equivalent random networks [14].

2.2 Optimal Wiring

None of the measures presented so far take into account the physical separations among neurons. Yet biological neural networks exist within the three-dimensional confines of the skull. Moreover, neural material is metabolically expensive, both to develop and to sustain in operation. These considerations have led some researchers to propose that neuroanatomical structure is arranged in such a way as to minimize the total wiring length among neural structures [48–51].

While some evidence exists in support of these ideas from studies of invertebrate nervous systems [49], analyses of cortical connection matrices are less convincing. Both the macaque visual cortex and the cat cortex have minimal wiring lengths that are significantly shorter than those of equivalent random networks; however there exist many other networks with equivalent N and K that have even shorter wiring lengths [14]. In any case, it seems improbable that the sole selection pressure during brain evolution was minimization of wiring length. More likely, anatomical arrangements evolved primarily to support dynamical activity patterns that contributed to the generation of adaptive behavior by the organism, with metabolic and developmental constraints playing a secondary role.

2.3 Statistical Analysis

Statistical techniques complement graph-theoretic analyses by detecting consistent patterns in complex data sets, usually by some form of dimensionality reduction. A constellation of techniques is currently available; here we briefly mention only one: non-metric multidimensional scaling (NMDS) [52,53,12]. NMDS rearranges objects in a low dimensional space (usually 2D or 3D) so that the rank-ordering of the original (high-dimensional) distances among them are best preserved. Proximity in a NMDS diagram indicates that two nodes are strongly interconnected and/or share a relatively large proportion of their connections.

Young et al. [54] applied NMDS to the connection matrix of the macaque visual system. They found that the resulting 2D configuration showed a clear separation between two distinct groups of nodes. This separation corresponds to the commonly accepted distinction between ‘dorsal’ and ‘ventral’ streams of

visual processing [55].² Alternative methods, which give results that are largely consistent with the NMDS analysis, are reviewed by Hilgetag et al. [56,12].

3 Dynamics

The networks of the brain support the exchange of signals among neurons. There is now substantial evidence that the resulting activity patterns are closely related to our cognitive and perceptual states [5–7]. A central challenge for a network-theoretic approach to neuroscience is to relate structural descriptions to dynamical patterns of activity at different spatial and temporal scales. In this section we focus on the application of statistical information theory as a means of characterizing neural network dynamics [25,14].

3.1 Information-Theoretic Analysis

The dynamical – or effective – connectivity of a neuronal system consists of the pattern of temporal correlations, or deviations from statistical independence, in the activities of neuronal elements that are generated by their interactions [4]. It has been suggested that cortical networks exhibit a balance between two main principles of dynamical organization, segregation and integration [25,14,57, 58]. Cortical networks contain many kinds of specialized neuronal units that are anatomically segregated from each other; for example, cells in different regions of visual cortex are specialized to respond to color, orientation, motion and so forth [59,60]. At the same time, in order to support globally coherent cognitive and perceptual states, the activity of these segregated elements has to be integrated across space and over time.

Global Dynamical Measures. A useful description of the effective connectivity of a neural system is the joint probability distribution function of the activities of its neuronal elements. Assuming that this function is Gaussian, this is equivalent to the covariance matrix of the system. Importantly, the covariance matrix captures the *total* effect of all (anatomical) connections within a system on deviations from statistical independence of the activities of a pair of elements, not just the effect of any direct anatomical connection linking them [61].

Covariance matrices can be numerically estimated by direct observation of system activity over time. Alternatively, if linear dynamics are assumed, the covariance matrix of a system X can be derived analytically from the anatomical connectivity matrix $\mathbf{C}_{ij}(X)$:

$$\mathbf{COV}(X) = \mathbf{Q}^T * \mathbf{Q}, \quad \mathbf{Q} = [\mathbf{I} - \mathbf{C}_{ij}(X)]^{-1}, \quad (1)$$

where T indicates matrix transpose [25].

² The dorsal visual stream is also called the ‘where’ stream and is usually associated with object location, whereas the ventral stream – the ‘what’ stream – is usually associated with object identification.

Once the covariance matrix is obtained, a number of global dynamical measures can be calculated. Three such measures, which are based on the foundations of statistical information theory, are entropy $H(X)$, ‘integration’ $I(X)$ and ‘neural complexity’ $C_n(X)$ [25,14].

For a system X , the entropy $H(X)$ measures the system’s overall degree of statistical independence. Assuming stationarity, $H(X)$ can be calculated using the standard formula

$$H(X) = 0.5\ln((2\pi e)^N |\mathbf{COV}(X)|), \quad (2)$$

where $\mathbf{COV}(X)$ is the $N \times N$ covariance matrix of X , and $|\cdot|$ denotes the matrix determinant [25,62].

The integration $I(X)$ measures the system’s overall *deviation* from statistical independence. All elements in a highly integrated neural system are tightly coupled in their activity. With x_i denoting the i ’th element, $I(X)$ can be calculated using

$$I(X) = \sum_{i=1}^N H(x_i) - H(X). \quad (3)$$

Perhaps the most interesting global dynamical measure is neural complexity $C_n(X)$, which measures the extent to which a system balances dynamical segregation and dynamical integration [25]. The component parts of a neurally complex system are differentiated; however, as larger and larger subsets of elements are considered they become increasingly integrated (see Fig. 1). The term ‘complexity’ may be considered appropriate for such systems since they are intermediate between the two relatively simple extremes of disorder (maximal statistical independence) and order (maximal statistical dependence).

The neural complexity $C_n(X)$ of a system X is calculated by summing the average Mutual Information (MI) between subsets of different sizes, for all possible bipartitions of the system:

$$C_n(X) = \sum_{k=1}^{n_t/2} \langle MI(X_j^k; X - X_j^k) \rangle, \quad (4)$$

where n_t is the total number of ways of bipartitioning X , X_j^k is the j ’th bipartition of size k , and $\langle \cdot \rangle$ is the average across index j . The MI between two subsets (A and B) measures the uncertainty about A that is accounted for by the state of B , and is defined as $MI(A; B) = H(A) + H(B) - H(AB)$ [63] (see Fig. 1).

Another, closely related measure of complexity expresses the portion of entropy that is accounted for by interactions among all the elements of a system [58]:

$$C(X) = H(X) - \sum_{k=1}^N H(x_i | X - x_i). \quad (5)$$

Fig. 1. Neural complexity is defined as the ensemble average MI between subsets of a given size and their complement, summed over all subset sizes (adapted from Fig. 2 in [64]). Small circles represent neuronal elements and bold arrows indicate MI between subsets and the remainder of the system. Shown in the figure are a selection of subsets of size 1 ($S=1$), size 2 ($S=2$), and size $N/2$ for system size N ($S=N/2$). A neurally complex system is one in which small subsets of the system show high statistical independence, but large subsets show low statistical independence.

This measure takes on high values if single elements are highly informative about the system to which they belong, without being overly alike. It has the advantage of being easier to compute than the first formulation $C_n(X)$, and all results described in this chapter use this formulation.

Dynamical Cluster Analysis. In Sect. 2.3 we described how statistical techniques such as NMDS could be used to identify clusters of highly interconnected nodes from high dimensional connectivity data. Cluster analysis can also be performed at the level of network dynamics, where a dynamical cluster corresponds to a strongly interactive subset of elements. Note that dynamically identified clusters need not correspond to structurally identified clusters, although in many cases they may do so.

A dynamical cluster is characterized by a high level of statistical dependence among its elements and, at the same time, a low level of statistical dependence with elements outside the cluster. Clusters can be identified by calculating the cluster index $Cl(X_i^k)$, which is defined as follows [65]:

$$Cl(X_i^k) = I(X_i^k) / MI((X_i^k); X - (X_i^k)), \quad (6)$$

where X_i^k denotes the i 'th subset of size k , $I(X_i^k)$ indicates its integration, and $MI((X_i^k); X - (X_i^k))$ denotes its mutual information with the rest of the system.

Note that Tononi et al. [65] describe this cluster index as a measure of *functional* clustering rather than dynamical clustering. However, as we remarked in the introduction, function here refers to the role of a particular pattern of dynamics in the context of the behavior of the organism.

Graph Selection. To explore the relationship between network structure and network dynamics, Sporns et al. [14] applied an evolutionary search procedure to look for distinct anatomical motifs associated with different measures of effective connectivity. This procedure uses a global dynamical measure as a fitness (or cost) function, and it is implemented as follows. First, an initial population of U random graphs is created, each with N nodes and K edges with fixed identical positive weights w_{ij} . The 'fitness' of each graph is then assessed by deriving the corresponding covariance matrix and calculating the global dynamical measure, either $H(X)$, $I(X)$ or $C(X)$. After all members of U have been assessed, the graph with highest fitness is selected and all others are discarded. The selected graph is then replicated $U - 1$ times to create the next generation. Each replication introduces a small amount of variation by randomly rewiring r edges of the selected graph. After a sufficient number of generations (these authors typically used 3,000 generations, a population size $U = 10$ and a rewiring rate $r = 1$) the members of U should have near-optimal structures for generating the particular dynamical measure used as the selection criterion.³

Sporns et al. selected separately for graphs with high entropy $H(X)$, high integration $I(X)$, and high neural complexity $C(X)$. In each case they found that the resulting graphs ($N = 32$, $K = 256$) had distinctive structural features, as revealed both by simple visual inspection and by analysis using the graph-theoretic measures described in Sect. 2.1. Graphs optimized for high entropy contained mostly reciprocal connections without any apparent local clustering; they had high f_{recip} , low f_{clust} , as well as a short diameter ($diam_G$) and a short characteristic path length (l_{path}). Graphs optimized for integration, by contrast, were highly clustered (high f_{clust}), had low values for f_{recip} , large diameters and large characteristic path lengths. Visual inspection of these graphs revealed a very large central cluster loosely connected to an outlying mesh of nodes. Graphs optimized for neural complexity were the most similar to the 'small-world' class of networks. These graphs usually are comprised of a number of dense groups of nodes linked by a relatively small number of reciprocal bridges; they had high values for f_{recip} and f_{clust} , as well as low values for l_{path} and $diam_G$.

³ Sporns et al. [14] applied three neurobiologically motivated constraints during graph selection. First, the number of incoming edges to each node was kept constant (8). Second, all graphs were required to be 'strongly connected' such that at least one path exists between all pairs $\{i, j\}$ of nodes. Third, small self-inhibitory weights w_{ii} were applied to each graph such that the total variance – given by the sum of the diagonal terms in $\mathbf{COV}(X)$ – remained constant.

3.2 Dynamical Properties of Cortical Networks

To relate these theoretical observations to empirical data, Sporns et al. [14] analyzed the complexity of the connection matrices of the macaque visual cortex and the cat cortex. They assumed linear dynamics, equal connection strengths, and used equation (1) to derive covariance matrices corresponding to the respective connection matrices. They found that both connection matrices gave rise to effective connectivity with high neural complexity $C(X)$ as compared to random networks with equivalent N and K . Indeed, the matrices seemed to be near-optimal for generating highly complex dynamics. Random rewiring of edges, in virtually all cases, led to a reduction in the complexity of the corresponding effective connectivity.

To identify the sets of anatomical areas responsible for these complex dynamics, these authors applied dynamical cluster analysis (see Sect. 3.1) to the macaque visual cortex connection matrix. This analysis revealed an hierarchical organization which separated into two distinct streams corresponding to the ‘dorsal’ and ‘ventral’ visual processing streams [55], together with a small subset of areas which were strongly interactive with both streams (these authors suggest that these areas are strong candidates for mediating inter-stream interactions). Overall, this dynamical analysis was highly consistent with the structural cluster analyses of Young et al. [54] and Hilgetag et al. [56].

Another application of dynamical cluster analysis compared PET⁴ data obtained from normal and schizophrenic subjects performing a set of cognitive tasks [65]. This study found significant differences in cluster profiles between these two groups, despite the absence of differences in overall levels of activity. Future application of this analysis using imaging methods with higher temporal resolution (for example magnetoencephalography, see [67]) may be extremely revealing.

3.3 Matching Complexity and Degeneracy

While entropy, integration and neural complexity provide measures of the intrinsic dynamics of a neural system, it is also of interest to characterize the dynamics of neural systems as they interact with a surrounding environment. Measures of ‘matching complexity’ [68] and ‘degeneracy’ [69,70] fulfil this role respectively for systems connected to an input or to an output.

The matching complexity between system X and input S is defined as the total complexity when the input is present $C(X)^T$ minus the intrinsic complexity $C(X)^I$ and the complexity $C(X)^S$ that is directly attributable to the input S [68]:

$$M(X; S) = C(X)^T - C(X)^I - C(X)^S. \quad (7)$$

A high level of matching complexity indicates that there is strong match between the statistical structure of the system and that of the input. A low value indicates statistical ‘novelty’.

⁴ Positron Emission Tomography: A brain imaging technique based on measurement of metabolic activity [66].

Degeneracy refers to the ability of elements (or sets of elements) that are structurally different to perform the same function or yield the same output [69, 70]. Degeneracy can be expressed as the mutual information between the various subsets of a system and the system's output [69]:

$$D(X; O) = MI^P(X, O) - \sum MI^P(x_i; O | X - x_i; O), \quad (8)$$

where $MI^P(x_i; O | X - x_i; O)$ refers to the conditional mutual information between each element and O , given the mutual information between the rest of the system and O . Degeneracy is high for systems in which many different elements affect the output in a similar ways but at the same time can have independent effects. This property contributes to the robustness of a system [70].

Sporns et al. [14] extended their graph selection method (see Sect. 3.1) to select for graphs that exhibited high matching complexity with respect to an input, and, separately, high degeneracy with respect to an output. In the former case, a subset of 8 nodes was connected to an 8-node sensory sheet S that had a particular input pattern described by a covariance matrix $\mathbf{COVs}$. In the latter case, a subset of nodes was chosen as a representation of output, and selection was carried out based on the global measure of degeneracy with respect to a particular output pattern.

In all cases, selection for matching or degeneracy resulted in graphs with high neural complexity $C(X)$ [14]. This suggests that high $C(X)$ may reflect not only an intrinsic balance between dynamical integration and segregation, but may also correspond to the ability of a network rapidly to distribute input signals and robustly generate output signals.

4 Function

As we remarked in the introduction, the most general function of a biological neural network is to generate adaptive behavior for the organism within its environment [71]. The analysis of graphs with high degeneracy and high matching complexity begins to address this issue of function. However, in the studies described above, there is no *behavior* as such: networks are coupled either to a static input or a static output, and there is no sense in which the output at a given time affects the input at a subsequent time.

In this section, we tackle these concerns by describing a relatively simple model of target fixation by a simulated head/eye system that is controlled by an artificial neural network. This model explicitly involves behavior, and its analysis provides support for the hypothesis that complex neural dynamics facilitate adaptation to rich sensory environments and motor demands [14]. An extended analysis of this model is given in Seth & Edelman [26].

As in the studies described above, the present model makes use of the technique of evolutionary graph selection. However, instead of using a global dynamical measure as a fitness function, in this case the fitness of a network is

Fig. 2. Simulation model of target fixation, depicting projections onto a plane ($100u \times 100u$, where u denotes an arbitrary spatial unit), of head direction H and gaze direction G . Also shown are target position T , and maximum offset of G from H (circle, radius $35u$). The position of G is calculated as a vector sum of H and an eye direction (E , not shown).

determined by its ability to support adaptive behavior when employed as a control mechanism for a simulated head/eye system engaged in a target fixation task. To explore how network structure, dynamics, and function interact, we select networks for their target fixation ability in a variety of conditions that differ in the (qualitative) complexity of the environment and the phenotype (the head/eye system). Networks which evolved in different conditions are then analyzed in terms of their behavioral properties, their structural properties, and their dynamical properties.

4.1 Methods

Model Outline. This section describes basic properties of the model; specifics are provided in Appendix A. The simulated environment is a simple planar area, 100×100 arbitrary units u , within which a target (T) can appear. The simulated head/eye system, or phenotype, is represented by the projection onto the plane of a head direction (H) and a gaze direction (G), which is the combination of the head direction (H) and an eye direction (E) relative to the head (Fig. 2).

The velocities of H and E in the x, y plane, and thus the position of G , are controlled by a neural network ($N = 32$, $K = 256$). The edges of this network have real-valued weights, and certain nodes are specified as sensory inputs and others as motor outputs (see below). The remainder are ‘interneurons’ mediating the transformation of input signals into output signals. Evolutionary algorithms are used to specify the connectivity and weight distribution of networks so that they give rise to adaptive behavior, which in this case consists of maximizing the time for which G and T are aligned (i.e. keeping the target fixated) while simultaneously minimizing the offset between H and G (i.e. keeping the head

Table 1. Phenotype parameters in the four conditions (E_S , E_T , E_H , and E_C). V_{maxH} , V_{maxE} : maximum velocity of head and eye, A_H , A_E : motor gain of head and eye, m_H , m_E : momentum of head and eye, lag : the time-lag between head motor node output and head movement.

Condition	V_{maxH}	V_{maxE}	A_H	A_E	m_H	m_E	lag
E_S	7.0	7.0	1.0	1.0	0.0	0.0	0
E_T	7.0	7.0	1.0	1.0	0.0	0.0	0
E_H	5.0	10.0	0.33	1.0	0.75	0.05	10
E_C	5.0	10.0	0.33	1.0	0.75	0.05	10

and eye aligned). A constraint on the system is that G must remain within $35u$ of H, as indicated by the circle in Fig. 2.

Environment/Phenotype Conditions. We specify four conditions which are distinguished by properties of the target and the head/eye phenotype. The phenotype is defined by seven parameters: V_{maxE} specifies the maximum velocity of H, V_{maxH} specifies the maximum velocity of E with respect to H; motor gain parameters A_H and A_E specify scaling factors relating motor node output to H and E velocity; momentum parameters m_H and m_E specify the inertial resistance of H and E, and lag specifies a time-lag between head motor node output and head movement. These parameters constrain the movements of H, E and G as described in Appendix A (which also describes how T is updated).

The values taken by the parameters in the four conditions are shown in Table 1. In condition E_S (for ‘simple’) both the head and eye have the same maximum velocity, identical motor gains, and zero momentum; the target is stationary. Condition E_T (for ‘tracking’) presents a more complex environment in which the target may occasionally jump to a different random location and/or drift at a slow speed in a random direction; the phenotype is the same in condition E_S . Condition E_H (for ‘head’) keeps the simple environment of condition E_S but introduces a more complex phenotype in which E can move twice as fast as H, has a higher motor gain, a much lower momentum, and in which there is a non-zero time-lag. Finally, condition E_C (for ‘complex’) combines the properties of both conditions E_T and E_H and is therefore the richest of the four.

Network Implementation. Each behavioral trial begins with the head and eye aligned and pointing to the center of the plane. The target position is initialized at a randomly selected location within $20u$ of this point. All trials last for 600 time steps, each of which involves updating the state of the network controller (X) as well as the positions of E, G, H, and, in conditions E_T and E_C only, T. The network is updated using, for all nodes j ,

$$s_j(t) = f \left(s_{in}(j, t) + \sum_{i=1}^K \mathbf{C}_{ij}(\mathbf{X}) s_i(t-1) \right), \quad s_j(0) = 0.0, \quad (9)$$

where $s_j(t)$ is the output of node j at time t , $s_{in}(j, t)$ denotes the sensory input to node j at time t (if any), f is a sigmoid function with input range ± 10.0 and output range ± 1.0 , and $\mathbf{C}_{ij}(\mathbf{X})$ is the connection matrix of $\mathbf{X}$.

Six nodes are specified as ‘sensory’ inputs, two responding to the x, y displacement of G from T (with a maximum range of $\pm 50.0u$), and four delivering ‘proprioceptive’ information, two of which reflect the displacement of H from the center of the plane (range $\pm 50.0u$), and two of which reflect the displacement of G from H (range $\pm 35.0u$). In all cases, input values are linearly scaled to the range ± 1.0 . Four nodes are specified as output nodes, two influencing H velocity in the x, y plane, and two influencing the velocity of E. Appendix A describes how the activities of these nodes, along with the values in Table 1, are used to update the positions of E, G, and H.

Network Structure. Evolutionary algorithms (EAs) were used to specify the connectivity and weight distribution of networks so that they supported target fixation behavior.⁵ We ran a total of 40 separate EAs: 10 replications of the selection process for each of the four environment/phenotype conditions.

Each EA evolved a population of 64 networks over 2000 generations, with each network initialized (generation 0) by randomly allocating K connections (each connection strength assigned randomly in the range ± 1.0), subject to the constraint that each node had 8 incoming connections. Each generation involved evaluating the fitness of each network, as described below, and then using stochastic rank-based selection to replace low-fitness networks with mutated versions of high-fitness networks. Each mutation of a network involved randomly rewiring 1 connection (preserving in-degree) and also modifying the strength of each connection (probability 0.05 per connection) in the range ± 0.1 .

The fitness of a network was calculated as the mean of four separate behavioral trials, with the fitness of each trial (ϕ) given by

$$\phi = \frac{t_f}{t_{tot}} + c_0(1.0 - c_1\bar{d}), \quad (10)$$

where t_f denotes the number of time steps for which the target was fixated (within a tolerance of $3u$), t_{tot} the total number of time steps in the trial (600), and $\bar{d}$ the mean offset for the trial between H and G. The constants c_0 and c_1 were selected in order to balance the fitness contributions due to target fixation and those due to minimizing the offset between H and G ($c_0 = \frac{1}{4}$, $c_1 = \frac{1}{35}$).

⁵ We used a distributed evolutionary algorithm [72]: Each EA was initialized by arranging the population on an 8x8 toroidal grid and evaluating the fitness of each network. Each subsequent generation involved 64 repeats of the following: A random grid position was chosen determining a 3x3 sub-grid. Stochastic rank-based selection was then used to select a weak member of this sub-grid for replacement, and a strong member as the ‘parent’. A mutated copy of the parent then replaced the weak member and was evaluated (the parent was also re-evaluated with probability 0.75).

Table 2. Summary of target fixation performance. Shown are mean percentage of each behavioral trial for which T was fixated (within a tolerance of $3u$), and mean displacement of G from H, for each network type. Average values were calculated from 10 behavioral trials of each evolved network in the corresponding environment/phenotype condition. Standard errors are given in parentheses.

Network type	fixation %	$ G-H $ (u)
S-network	98.81 (0.01)	0.28 (0.07)
T-network	92.43 (0.51)	0.92 (0.08)
H-network	96.15 (0.79)	1.94 (0.19)
C-network	84.76 (1.23)	15.41 (0.50)

4.2 Results

For convenience, networks which evolved in condition E_S will be referred to as S-networks, with the same nomenclature for conditions E_T (T-networks), E_H (H-networks) and E_C (C-networks).

Behavioral Analysis. The target fixation behavior of evolved networks was assessed by measuring the percentage of each behavioral trial for which the target was fixated (i.e. the fraction of time steps for which the displacement between H and G was less than $3u$). Table 2 shows that average fixation performance was very high for S-networks, T-networks, and H-networks, and slightly lower for C-networks.

Figure 3 shows representative examples of successful fixation behavior for S-networks and C-networks in the corresponding conditions (E_S and E_C respectively). Inspection of the trajectories of the head and the eye indicates that the behavioral dynamics for C-networks were qualitatively more complex than for S-networks. A non-trivial coordination of head and eye is needed in E_C conditions in order to maintain consistent fixation of the target. Table 2 affirms

Fig. 3. Typical successful fixation behavior for S-networks in condition E_S (left) and for C-networks in condition E_C (right), showing trajectories of G (solid line), H (dotted line) and T (dashed line, E_C only), gray circle indicates initial positions of G and H, gray arrows indicate initial positions of T. Successful target tracking by C-networks is indicated by the overlap of the trajectories of G and T.

Fig. 4. Robustness of S-networks and C-networks to a novel perturbation: (a) Mean displacement of G from T during enforced H movement, calculated over the 20 time steps of enforced movement and the 10 time steps following for 10 S-networks and 10 C-networks. Asterisk indicates statistical significance ($p < 0.001$, two-tailed t test). (b,c) trajectories generated by a typical (b) S-network and (c) C-network during this operation (solid line G, dotted line H, gray circles indicates initial positions of G and H, gray arrows indicate positions of T). For the S-network, fixation is lost (both H and G are displaced from the target), whereas for the C-network, fixation is maintained (G remains close to the target even though H is displaced).

that the average displacements between H and G were considerably larger in for C-networks than for all other network types, while target fixation was achieved reliably in all cases.

To better compare the behavioral properties of S-networks and C-networks, they were reevaluated in a novel condition involving unexpected perturbations. As in condition E_S , the environment was initialized with a stationary target T. An evolved S-network or C-network was then introduced and allowed to fixate. After 100 time steps, a head velocity (V_{hx}, V_{hy}) of between 1.0 and 3.0 (u per time step) was induced for 20 time steps in a random direction. Importantly, neither network type had been selected to respond adaptively to this perturbation. Nevertheless, Fig. 4 illustrates that C-networks were generally able to maintain fixation, whereas S-networks were not. These results show that network optimization in a rich environmental/phenotypic context can facilitate the emergence of robust behavior.

Structural Analysis. To assay reliable structural differences between network types, connectivity matrices were transformed into binary adjacency matrices $\mathbf{A}_{ij}(X)$ by replacing all non-zero elements in $\mathbf{C}_{ij}(X)$ with the value 1 (we also tried various thresholds, see below). We calculated four graph-theoretic quantities from each $\mathbf{A}_{ij}(X)$: f_{recip} , $diam_G$, l_{path} , and f_{clust} (see Sect. 2.1).

Table 3 shows the results of applying these metrics to the fittest networks from each EA in each condition. Values were also calculated for an additional 64 random networks (R-networks) with equivalent N and K (and a per-node in-degree of 8). The table indicates that there are no significant differences between network types (including random) in any of the metrics.

Table 3. Structural analysis of network types showing values for f_{recip} , $diam_G$, l_{path} and f_{clust} . Each entry in the table shows mean and standard error (in parentheses) calculated from 10 networks of each type (64 for R-networks).

Network type	f_{recip}	$diam_G$	l_{path}	f_{clust}
S-network	0.27 (0.028)	3.1 (0.32)	1.82 (0.01)	0.25 (0.001)
T-network	0.26 (0.006)	3.2 (0.42)	1.83 (0.02)	0.25 (0.001)
H-network	0.26 (0.019)	3.3 (0.67)	1.83 (0.03)	0.25 (0.001)
C-network	0.27 (0.023)	3.0 (0.01)	1.82 (0.01)	0.24 (0.001)
R-network	0.27 (0.042)	3.0 (0.01)	1.82 (0.01)	0.25 (0.001)

Why are no differences observed? It may be that the transformation of $\mathbf{C}_{ij}(\mathbf{X})$ into $\mathbf{A}_{ij}(\mathbf{X})$ overemphasizes the importance of weak connections. We tested this possibility by recalculating values after thresholding adjacency matrices to include only relatively strong connections. We tested a variety of thresholds, but in no case did we observe differences in structural measures among conditions. This suggests that specific connection strengths may be critical for the behavioral properties of the networks. Importantly, this is *not* to say that network anatomy is irrelevant to the behavioral differences among the network types; rather, it emphasizes the need for graph-theoretic measures which can be usefully applied to weighted networks as well as to binary networks [73,74].

4.3 Dynamical Analysis

Intrinsic Dynamics. As a first approach to describing the dynamical properties of evolved networks, we treated the evolved $\mathbf{C}_{ij}(\mathbf{X})$ matrices as in Sect. 3.1, i.e., assuming linear dynamics and activation by Gaussian noise, we applied equation (1) to derive the corresponding covariance matrices. An important property of this method is that $\mathbf{COV}(\mathbf{X})$, and therefore also the resulting values of $C(\mathbf{X})$, $I(\mathbf{X})$, and $H(\mathbf{X})$, are *independent of behavioral context*. This method is therefore best described as characterizing the *intrinsic* dynamical properties of a network.

For each EA, the fittest member of the final generation was used to generate a covariance matrix, which in turn was used to calculate the intrinsic neural complexity $C(\mathbf{X})$, integration $I(\mathbf{X})$, and entropy $H(\mathbf{X})$ of the network dynamics. Values were also calculated for 64 R-networks.

Figure 5 shows mean and standard deviations of intrinsic $C(\mathbf{X})$, $I(\mathbf{X})$, and $-H(\mathbf{X})$, for each network type. In contrast to the structural analysis (see above), clear differences are evident: Random R-networks scored lowest on all three dynamical measures, and C-networks scored highest. Differences between C-networks and all other networks were significant at the $p < 0.01$ level by two-tailed t test for $C(\mathbf{X})$, $I(\mathbf{X})$, and $H(\mathbf{X})$. These observations indicate that adaptation to comparatively complex environmental/phenotypic conditions (E_C) endows C-networks with above random neural complexity and integration, and below random entropy. Furthermore, only networks with these dynamical characteristics displayed the behavioral robustness and flexibility as described above.

Fig. 5. Mean and standard error intrinsic $C(X)$, $I(X)$, and $-H(X)$ for S-networks (S), T-networks (T), H-networks (H), C-networks (C), and R-networks (R). Asterisks indicate that the value for C-networks is significantly higher than for all other network types ($p < 0.01$, two-tailed t tests). Values of $C(X)$, $I(X)$ and $-H(X)$ for S-networks, T-networks, and H-networks are significantly lower than the corresponding values for C-networks, and significantly higher than the corresponding values for R-networks ($p < 0.01$, two-tailed t tests). There are no significant differences in $C(X)$, $I(X)$ or $-H(X)$ among S-networks, T-networks, and H-networks. All distributions are normal ($p < 0.05$, Bera-Jarques test).

Figure 5 also shows that S-networks, H-networks, and T-networks scored at intermediate levels on all measures. Values of $C(X)$, $I(X)$ and $-H(X)$ for these networks are significantly lower than the corresponding values for C-networks, and significantly higher than the corresponding values for R-networks ($p < 0.01$, two-tailed t tests); there are no significant differences in $C(X)$, $I(X)$ or $-H(X)$ among S-networks, T-networks, and H-networks. Changes in intrinsic dynamics, therefore, depend both on properties of the environment (condition E_T) and on properties of the phenotype (condition E_H).

While these results show that neurally complex network dynamics can accompany adaptive behavior in rich environmental/phenotypic conditions, intrinsic neural complexity is not unique in this respect, since similar patterns of results are apparent for both intrinsic integration $I(X)$ and entropy $H(X)$.

Interactive Dynamics. An alternative approach to characterizing network dynamics is to derive covariance matrices directly from recordings of node activities during behavior, i.e. while the network is actively transforming input signals into output signals. We define the resulting dynamics as ‘interactive’ since they are relative to a particular behavior, environment, and phenotype. One important property of interactive dynamics, as compared to intrinsic dynamics, is that they enable comparison of dynamics generated by the same network in different behavioral regimes or in different environments/phenotypes.

Each behavioral trial yields a ($N \times 600$) matrix $\mathbf{F}$ which contains the individual activity records of each node for all 600 time steps. This matrix can be used to generate a covariance matrix according to:

Fig. 6. Representative behavior for various network-environment/phenotype combinations, showing trajectories of G (solid line), H (dotted line) and T (dashed line), gray circles indicate initial positions of G and H, gray arrows indicate initial positions of T. RC: R-network in condition E_C , RS: R-network in condition E_S , SC: S-network in condition E_C , CS: C-network in condition E_S . Trajectories of a C-network in condition E_C and an S-network in condition E_S are shown in Fig. 3.

$$\mathbf{COV}(X) = cov(\dot{\mathbf{F}}), \quad (11)$$

where $\dot{\mathbf{F}}$ is the first derivative (with respect to time) of the activity matrix and $cov()$ is a standard covariance function. This approach was chosen because rates of change of node activities are more likely to reflect interactions between the network and its phenotype and environment, than are absolute activity levels. $\mathbf{COV}(X)$ can then be used to calculate corresponding values of interactive $C(X)$, $I(X)$ and $H(X)$ in just the same way as for the calculation of intrinsic dynamics. Note that calculation of interactive dynamics does not require equation (1) and so does not assume linear system dynamics.

We compared interactive dynamics for C-networks, S-networks, and random R-networks evaluated in both E_C and E_S conditions, recording both network activities and behavioral trajectories. Figure 6 shows representative trajectories from the various combinations (trajectories of a C-network in condition E_C and an S-network in condition E_S are shown in Fig. 3). R-networks in E_C and E_S conditions never achieve fixation, and their behavior is highly variable. S-networks in E_C conditions are unable to achieve or maintain fixation despite a general tendency to track towards the target, and C-networks in E_S conditions rapidly achieve fixation despite some persistent oscillation in the head direction. Notice that in all except the last of these cases, the behavioral dynamics are rich, even though the behavior itself is not adaptive.

Fig. 7. Interactive $C(X)$, $I(X)$, and $-H(X)$ calculated from covariance matrices derived from recorded neural activity during behavior. CC: C-network in condition E_C , SC: S-network in condition E_C , CS: C-network in condition E_S , SS: S-network in condition E_S , RS: R-network in condition E_S , RC: R-network in condition E_C . Each column shows mean and standard error calculated from 10 repetitions of each combination of network and condition. There is a significant correlation between the rank ordering of combination (from ‘CC’ to ‘RC’) and mean $C(X)$ ($r = 0.97$, $p < 0.01$; Spearman’s rank correlation). No significant correlations exist for $I(X)$ or $-H(X)$ ($p > 0.1$). Asterisks indicate statistically significant differences between combinations ((*) $p < 0.01$, (**) $p < 0.05$, two-tailed t tests; only adjacent combinations were tested). All distributions are normal ($p < 0.05$, Bera-Jarques test).

Figure 7 shows the interactive dynamics generated in each combination of network and condition. The top row shows a clear gradient in interactive $C(X)$ proceeding from C-networks in condition E_C (‘CC’; high), to R-networks in conditions E_S and E_C (‘RS’, ‘RC’; low). Intermediate values of $C(X)$ were observed for simple networks in rich environmental/phenotypic conditions (‘SC’), and for complex networks in simple conditions (‘CS’). C-networks in condition E_C (‘CC’) have significantly higher $C(X)$ than all other combinations. The remaining significant differences among combinations are also consistent with the steady gradient in interactive $C(X)$.

Strikingly, only $C(X)$ shows a pattern of values reflecting rich adaptive behavior. Neither $I(X)$ (Fig. 7, middle row) nor $H(X)$ (bottom row) show any

such sensitivity. This is in contrast to the intrinsic analysis, in which all three dynamical measures behaved in a similar way (Fig. 5).

It is also notable that R-networks evoke low interactive $C(X)$ despite displaying the rich behavioral patterns shown in Fig. 6. The contrast between R-networks and C-networks, together with the steady gradient in interactive $C(X)$ across combinations (Fig. 7, top row), suggests that $C(X)$ is indeed selectively sensitive to the dynamics of rich *adaptive* behavior. Figure 7 also suggests that high interactive $C(X)$ depends on a combination of environmental and phenotypic properties. The intermediate values of $C(X)$ in Fig. 7 ('SC' and 'CS') are consistent with the intermediate values of intrinsic $C(X)$ associated with rich environments (condition E_T) and complex phenotypes (condition E_H) shown in Fig. 5.

4.4 Summary

In this model, evolutionary algorithms were used to generate neural networks able to support target fixation in environment/phenotype combinations of qualitatively different levels of complexity. Not surprisingly for a selectional system, we found that those networks which evolved under rich environmental/phenotypic conditions exhibited (qualitatively) more complex behavior than networks which evolved in comparatively simple conditions (Fig. 3). When compared in a condition involving a novel perturbation, networks which evolved in rich conditions showed greater robustness than networks which evolved in simple conditions (Fig. 4).

This robustness was reflected by significantly higher neural complexity $C(X)$ for networks which evolved in rich conditions, than for networks which evolved in relatively simple conditions, or for equivalent random networks (figs. 5 and 7). This was true for both intrinsic and interactive methods of calculating dynamics, where the former are derived analytically from network connectivity, and the latter are computed from observed network activity during behavior. However, while intrinsic dynamics did not differentiate between neural complexity $C(X)$, integration $I(X)$ or entropy $H(X)$ (Fig. 5), interactive dynamics revealed that only $C(X)$ consistently associated with adaptive behavior in rich environmental/phenotypic conditions (Fig. 7).

Both types of dynamical analysis indicate that the magnitude of neural complexity depended on a combination of environmental, phenotypic, and mechanistic properties. Networks evolved in conditions of intermediate richness (E_T and E_H) generated intermediate values of intrinsic $C(X)$ (Fig. 5). Networks evolved in rich environmental/phenotypic conditions, and tested in simple conditions, and *vice-versa*, generated intermediate values of interactive $C(X)$ (Fig. 7). Taken together these results show that, in the present target fixation task, neural complexity is selectively sensitive to the dynamics of adaptive behavior in rich environmental and phenotypic conditions.

5 General Discussion

This chapter has surveyed a network-theoretic approach to neuroscience at the levels of structure, dynamics and function. While the coverage has not been comprehensive, we have described some key results and techniques that can be applied not just to vertebrate cortical networks but to the analysis of complex network systems of many different kinds. For example, the new results described in the previous section show the importance of drawing a sharp distinction between the dynamical patterns a network may support, and the functional applications that these patterns may serve.

5.1 Structure

Structure provides the most basic level of analysis of cortical networks. Many interesting features are revealed by the application of graph-theoretic and statistical analytical tools, most notably the presence of small-world characteristics as well as the prevalence of reentrant connectivity [14].

However, current structural analysis has certain important limitations. Detailed structural information is hard to obtain, especially at the microscopic level of neuron-to-neuron connectivity, especially with regard to the human brain. Moreover, this fine structure is continually changing as a result of a host of activity-dependent plasticity processes. Also, most methods of structural analysis assume unweighted, binary networks (although see [73–75]) and also assume that all nodes are essentially identical. Neither assumption is remotely satisfied in the case of the brain, and it is certain that both neuronal diversity and differences among synaptic strengths are essential for normal brain function.

Nonetheless, the rapid development of novel graph-theoretic methods [41,18], together with the accelerating accumulation of detailed neuroscientific data sets [32,33], promises that future structural analyses will reveal further important features of the structural organization of neural systems.

5.2 Dynamics

Anatomical structure gives rise to neural dynamics. The tools of statistical information theory are well suited to the analysis of these dynamics. It bears emphasizing that the global dynamical measures described in this chapter apply equally well to dynamics generated by both binary and weighted networks; in this sense, at least, dynamical analysis may be more generally applicable than structural analysis.

However, some assumptions have to be made in the application of these measures. For example, the analytical derivation of a covariance matrix from a connectivity matrix requires that linear dynamics be assumed. At least in some cases, linear and non-linear systems behave similarly with respect to effective connectivity [58], and it has also been argued that large-scale dynamics of interacting brain areas are accurately represented by linear systems [76,77]. Also,

one may drop assumptions of linear dynamics by deriving covariances directly from recorded activity (see Sect. 4.3).

Calculation of entropy from covariance further assumes that network activity can be described as a stationary Gaussian process. This condition is by definition satisfied for calculation of intrinsic dynamics (see Sect. 3.1), but may not be strictly satisfied in the calculation of interactive dynamics from network activity during behavior. Indeed, it is a fact that many natural processes are not well modeled as stationary. Information-theoretic treatment of non-stationary signals has been widely discussed [78,79,62], and as long as deviations from stationarity are not too extreme, such techniques remain well placed to provide insight into the structure of dynamical interactions that a network produces.

More generally, the present methods are cross-sectional: Covariance matrices are derived from observations of network activity at successive time slices, so that correlations over time exhibited in the activity profiles of *single nodes* are overlooked (by definition, the analytical calculation of intrinsic dynamics assumes that there are no such correlations). A contrasting approach, which focuses on these correlations, is provided by a growing literature concerned with measuring the information content of single spike trains [21–24]. Integrating these two approaches stands out as an important challenge for theoretical neuroscience.

Notably absent from this chapter has been any mention of neural synchrony. Some of the most obvious features of human brain dynamics are the prominent oscillations in different frequency bands known as the delta (3–5Hz), alpha (8–13Hz), beta (10–20Hz) and gamma (35–80Hz) rhythms. Different functional roles have been proposed (but not proven) for these rhythms; for example, delta oscillations have been associated with the maintenance of items in short-term memory [80], and alpha oscillations are strongest during sleep and relaxed wakefulness [81], and may represent an ‘idling state’ of the brain.

Gamma oscillations have a controversial interpretation: it has been suggested that gamma oscillations serve to ‘bind’ together disparate neural processes into globally integrated activity patterns [45,82,83]. In support of this idea, detailed computer simulations of visual cortical areas have shown that reentrant interactions can synchronize the activity of anatomically segregated neural areas, leading to coherent perceptual performance and behavior in visually complex environments [44,47]. Computer simulations have also suggested that small-world architectures may be particularly suitable for facilitating neural synchrony [84].

5.3 Function

Linking dynamic patterns to functional roles is perhaps the least visited of the tasks facing a science of networks. However, it is at least as important as understanding structural and dynamical features by themselves. Many structural and dynamical features of brains have been selected by evolution precisely because of the adaptive functions they provide for the organism. Functional criteria can also be described for networks of many other kinds, for example power grids (the transmission of power from source to consumer) and telephone networks (the maintenance of uninterrupted service for clients).

As for the brain, we remarked above that neural synchrony may play an essential role in binding disparate neural processes to a common purpose. More generally, the results described in this chapter support the view that the brain is a selectional system [43], in which complex neural dynamics may facilitate adaptation to rich sensory environments and motor demands by providing a special kind of flexibility in the balance between dynamical integration and dynamical segregation. It has even been suggested that neurally complex dynamics in the thalamocortical system constitute the neural correlates of conscious states in humans and other animals [64,46,85]. Further empirical research and theoretical analysis of the interactions between dynamics and function are therefore likely to be valuable for neuroscience in the broader context of modeling the situated organism [86].

5.4 Summary

While important insights can be, and have been gained by analyses at the levels of structure, dynamics, and function separately, it must be recognized that in biological systems these levels are in complex and continuous interaction. Structure is continually changing as a result of activity-dependent plasticity processes. These structural changes evoke dynamical changes which shape the behavior of the organism, and behavior itself determines the correlations in the sensory signals that impinge on these networks, triggering further dynamical changes and structural alterations. Finding a language in which to articulate these complex couplings is the major challenge for a network-theoretic approach to neuroscience. Success in this task will advance not just neuroscience, but also our understanding of many other network systems in which interactions among structure, dynamics, and function are important.

Acknowledgements

This research was supported by the Neurosciences Research Foundation. Special thanks to Bruno van Swinderen for Fig. 2, and to George Reeke and our anonymous reviewers for helpful comments.

Address correspondence to Anil K. Seth (seth@nsi.edu).

Appendix A: Implementation Details

Motor node outputs ($s_{hx}, s_{hy}, s_{ex}, s_{ey}$) are used to update E, H and G according to:

$$V_{hx}(t) = m_H V_{hx}(t-1) + A_H(1 - m_h)s_{hx}(t - lag), \quad (12)$$

$$V_{hy}(t) = m_H V_{hy}(t-1) + A_H(1 - m_h)s_{hy}(t - lag), \quad (13)$$

$$V_{ex}(t) = m_E V_{ex}(t-1) + A_E(1 - m_E)s_{ex}(t), \quad (14)$$

$$V_{ey}(t) = m_E V_{ey}(t-1) + A_E(1 - m_E)s_{ey}(t), \quad (15)$$

where $V_{hx}(t), V_{hy}(t)$ represent the velocity of H in the x, y directions respectively at time t , and $V_{ex}(t), V_{ey}(t)$ represent the velocity of E. In all cases, $V(t)$ is bounded by

the corresponding value of V_{max} . These values, as well as those of A_H , A_E , m_H , m_E , and lag , are specified for each condition in the text. The positions of E, H and G in the x, y plane are then updated using:

$$H(t) = H(t-1) + V_{hx}(t) + V_{hy}(t), \quad (16)$$

$$E(t) = E(t-1) + V_{ex}(t) + V_{ey}(t), \quad (17)$$

$$G(t) = H(t) + E(t), \quad (18)$$

where $H(t)$ and $G(t)$ represent the positions of H and G on the x, y plane at time t , and $E(t)$ represents the position of the eye relative to H. If the distance between G and H exceeds $35.0u$ then G is not updated at that time step. In conditions E_C and E_T the target position (T) is also updated at each time step, alternating between 50 time steps of drift and 50 time steps without drift. Each period of drift is in a random direction at a random speed in the range 0.5 to 1.5 (u per time step). During the intervening periods T is stationary except for occasional jumps (with a probability of 0.025 per time step), each to a randomly chosen location within a radius of $25u$ to $31u$ of its previous location. The target cannot leave the 100^2u^2 area: If drift is leading it out of bounds the appropriate velocity component is reversed at the boundary.

References

1. G.M. Edelman. *The remembered present*. Basic Books, Inc., New York, NY, 1989.
2. A. Clark. *Being there: Putting brain, body, and world together again*. MIT Press, Cambridge, MA, 1997.
3. D. Buonomano and M. Merzenich. Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience*, 21:149–186, 1998.
4. K. Friston. Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, 2:56–78, 1994.
5. S.L. Bressler. Large-scale cortical networks and cognition. *Brain Research Reviews*, 20:288–304, 1995.
6. R.S.J. Frackowiak, K.J. Friston, C.D. Frith, R.J. Dolan, and J.C. Mazziotta. *Human brain function*. Academic Press, San Diego, CA, 1997.
7. F. Varela, J.-P. Lachaux, E. Rodriguez, and J. Martinerie. The brainweb: Phase synchronization and large-scale integration. *Nature Reviews Neuroscience*, 2:229–239, 2001.
8. R. Cummins. Functional analysis. *Journal of Philosophy*, 72:741–764, 1975.
9. F. Harary. *Graph theory*. Addison-Wesley, Reading, MA, 1969.
10. B. Bollobás. *Random graphs*. Academic Press, London, 1985.
11. B. Jouve, P. Rosentiehl, and M. Imbert. A mathematical approach to the connectivity between the cortical visual areas of the macaque monkey. *Cerebral Cortex*, 8:28–39, 1998.
12. C.C. Hilgetag, R. Kötter, K.E. Stephan, and O. Sporns. Computational methods for the analysis of brain connectivity. In G.A. Ascoli, editor, *Computational neuroanatomy: Principles and methods*, pages 295–331. Humana Press, Totowa, NJ, 2002.
13. O. Sporns. Graph theory methods for the analysis of neural connectivity patterns. In R. Kötter, editor, *Neuroscience Databases. A Practical Guide*, pages 169–183. Kluwer Publishers, Boston, MA, 2002.

14. O. Sporns, G. Tononi, and G.M. Edelman. Theoretical neuroanatomy: Relating anatomical and functional connectivity in graphs and cortical connection matrices. *Cerebral Cortex*, 10:127–141, 2000.
15. R. Albert, H. Jeong, and A.-L. Barabási. Diameter of the world wide web. *Nature*, 401:130–131, 1999.
16. D.J. Watts and S.H. Strogatz. Collective dynamics of ‘small world’ networks. *Nature*, 393:440–442, 1998.
17. S.H. Strogatz. Exploring complex networks. *Nature*, 410:268–276, 2001.
18. M.E.J. Newman. The structure and function of complex networks. *SIAM Review*, 45(2):167–256, 2003.
19. G.Q. Bi and M.M. Poo. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *Journal of Neuroscience*, 18:10464–10472, 1998.
20. Y.X. Fu, K. Djupsund, H. Gao B. Hayden, K. Shen, and Y. Dan. Temporal specificity in the cortical plasticity of visual space representation. *Science*, 296:1999–2003, 2002.
21. W. Bialek, I. Nemenman, and N. Tishby. Predictability, complexity, and learning. *Neural Computation*, 13:2409–2463, 2001.
22. M. Costa, A.L. Goldberger, and C.K. Peng. Multiscale entropy analysis of complex physiological time series. *Physical Review Letters*, 89:681–682, 2002.
23. L. Paninski. Estimation of entropy and mutual information. *Neural Computation*, 15:1191–1253, 2003.
24. G.N. Reeke and A.D. Coop. Estimating the temporal interval entropy of neuronal discharge. *Neural Computation*, in press.
25. G. Tononi, O. Sporns, and G.M. Edelman. A measure for brain complexity: Relating functional segregation and integration in the nervous system. *Proceedings of the National Academy of Science (USA)*, 91:5033–5037, 1994.
26. A.K. Seth and G.M. Edelman. Environment and behavior influence the complexity of evolved neural networks. *Adaptive Behavior*, in press.
27. F. Crick and E. Jones. Backwardness of human neuroanatomy. *Nature*, 361:109–110, 1993.
28. D.J. Felleman and D.C. Van Essen. Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex*, 1:1–47, 1991.
29. M.P. Young. The organization of neural systems in the primate cerebral cortex. *Philosophical Transactions of the Royal Society of London: Series B*, 252:13–18, 1993.
30. J.W. Scannell, C. Blakemore, and M.P. Young. Analysis of connectivity in the cat cerebral cortex. *Journal of Neuroscience*, 15, 1995.
31. J.W. Scannell, G.A.P.C. Burns, C.C. Hilgetag, M.A. O’Neil, and M.P. Young. The connectional organization of the cortico-thalamic system of the cat. *Cerebral Cortex*, 9:277–299, 1999.
32. R. Kötter. Neuroscience databases: Tools for exploring brain structure-function relationships. *Philosophical Transactions of the Royal Society of London: Series B*, 356:1111–1120, 2001.
33. K.E. Stephan, L. Kamper, A. Bokzurt, G.A.P.C. Burns, M.P. Young, and R. Kötter. Advances in database methodology for the collation of connectivity data on the macaque brain (CoCoMac). *Philosophical Transactions of the Royal Society of London: Series B*, 356:1159–1186, 2001.
34. J.M.J. Murre and D.P.F. Sturdy. The connectivity of the brain: Multi-level quantitative analysis. *Biological Cybernetics*, 73:529–545, 1995.

35. A. Nicoll and C. Blakemore. Patterns of local connectivity in the neocortex. *Neural Computation*, 5:665–680, 1993.
36. C.C. Hilgetag. *Mathematical approaches to the analysis of neural connectivity in the mammalian brain*. PhD thesis, Faculty of Medicine, University of Newcastle upon Tyne, 1999.
37. L. Lagae, D.K. Xiao, S. Raquel, H. Maes, and G.A. Orban. Position invariance of optic flow component selectivity differentiates monkey MST and FST cells from MT cells. *Invest. Ophthalmol. Vis. Sci.*, 32:823, 1991.
38. J.J. Gibson. *The ecological approach to visual perception*. Houghton-Mifflin, Boston, 1979.
39. D.J. Watts. *Small worlds*. Princeton University Press, Princeton, NJ, 1999.
40. P. Erdős and A. Rényi. On random graphs. *Publicationes Mathematicae*, 6:290–297, 1959.
41. R. Albert and A.-L. Barábasi. Statistical mechanics of complex networks. *Reviews of Modern Physics*, 74:47–97, 2002.
42. H. Jeong, B. Tombor, R. Albert, Z. Oltvai, and A.-L. Barábasi. The large-scale organization of metabolic networks. *Nature*, 407:651–654, 2000.
43. G.M. Edelman. *Neural Darwinism*. Basic Books, New York, 1987.
44. G. Tononi, O. Sporns, and G.M. Edelman. Reentry and the problem of integrating multiple cortical areas: Simulation of dynamic integration in the visual system. *Cerebral Cortex*, 2(4):31–35, 1992.
45. G.M. Edelman. Selection and reentrant signaling in higher brain function. *Neuron*, 10:115–125, 1993.
46. G.M. Edelman and G. Tononi. *A universe of consciousness: How matter becomes imagination*. Basic Books, New York, 2000.
47. A.K. Seth, J.L. McKinstry, G.M. Edelman, and J.L. Krichmar. Visual binding through reentrant connectivity and dynamic synchronization in a brain-based device. *Cerebral Cortex*, in press.
48. G. Mitchison. Neuronal branching patterns and the economy of cortical wiring. *Proceedings of the Royal Society of London: Series B. Biological Sciences.*, 245:151–158, 1991.
49. C. Cherniak. Component placement optimization in the brain. *Journal of Neuroscience*, 14:2418–2427, 1994.
50. C. Cherniak. Optimal-wiring models of neuroanatomy. In G.A. Ascoli, editor, *Computational neuroanatomy: Principles and methods*, pages 71–83. Humana Press, Totowa, NJ, 2002.
51. C. Cherniak, Z. Mokhtarzada, R. Rodriguez-Esteban, and K. Changizi. Global optimization of cerebral cortex layout. *Proceedings of the National Academy of Sciences, USA*, 101(4):1081–1086, 2004.
52. J.B. Kruskal. Nonmetric multidimensional scaling: A numerical method. *Psychometrika*, 29:115–129, 1964.
53. J.B. Kruskal. Multidimensional scaling by optimizing goodness of fit to a nonmetric hypothesis. *Psychometrika*, 29:1–27, 1964.
54. M.P. Young, J.W. Scannell, M.A. O'Neill, C.C. Hilgetag, G.A.P.C. Burns, and C. Blakemore. Non-metric multidimensional scaling in the analysis of neuroanatomical connection data and the organization of the primate visual system. *Philosophical Transactions of the Royal Society of London: Series B*, 348:281–308, 1995.
55. L.G. Ungerleider and J.V. Haxby. 'what' and 'where' in the human brain. *Current Opinion in Neurobiology*, 4:157–165, 1994.

56. C.C. Hilgetag, G.A.P.C. Burns, M.A. O'Neill, and M.P. Young. Cluster structure of cortical systems in mammalian brains. In J.M. Bower, editor, *Computational neuroscience*, pages 41–46. Plenum Press, New York, 1998.
57. G. Tononi, G.M. Edelman, and O. Sporns. Complexity and coherency: Integrating information in the brain. *Trends in Cognitive Science*, 2:474–484, 1998.
58. O. Sporns and G. Tononi. Classes of network connectivity and dynamics. *Complexity*, 7(1):28–38, 2002.
59. S. Zeki. Functional specialization in the visual cortex of the Rhesus monkey. *Nature*, 274:423–428, 1978.
60. S. Zeki. *A vision of the brain*. Blackwell, Oxford, 1993.
61. W. Vanduffel, B.R. Payne, S.G. Lomber, and G.A. Orban. Functional impact of cerebral connections. *Proceedings of the National Academy of Science (USA)*, 94:7617–7620, 1997.
62. A. Papoulis and S.U. Pillai. *Probability, random variables, and stochastic processes*. McGraw-Hill, New York, NY, 2002. 4th edition.
63. D.S. Jones. *Elementary information theory*. Clarendon Press, 1979.
64. G. Tononi and G.M. Edelman. Consciousness and complexity. *Science*, 282:1846–1851, 1998.
65. G. Tononi, A.R. McIntosh, D.P. Russell, and G.M. Edelman. Functional clustering: identifying strongly interactive brain regions in neuroimaging data. *Neuroimage*, 7:133–149, 1998.
66. S.E. Petersen, P.T. Fox, M.I. Posner, M. Mintun, and M. Raichle. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*, 331:585–589, 1988.
67. R. Hari, S. Levänen, and T. Raij. Timing of human cortical functions during cognition: role of MEG. *Trends in Cognitive Science*, 4(12):455–461, 2000.
68. G. Tononi, O. Sporns, and G.M. Edelman. A complexity measure for selective matching of signals by the brain. *Proceedings of the National Academy of Science (USA)*, 93:3422–3427, 1996.
69. G. Tononi, O. Sporns, and G.M. Edelman. Measures of degeneracy and redundancy in biological networks. *Proceedings of the National Academy of Science (USA)*, 96:3257–3262, 1999.
70. G.M. Edelman and J. Gally. Degeneracy and complexity in biological systems. *Proceedings of the National Academy of Sciences, USA*, 98(24):13763–13768, 2001.
71. A.K. Seth. *On the relations between behaviour, mechanism, and environment: Explorations in artificial evolution*. PhD thesis, University of Sussex, 2000.
72. M. Mitchell. *An introduction to genetic algorithms*. MIT Press, Cambridge, MA, 1997.
73. V. Latora and M. Marchiori. Efficient behavior of small-world networks. *Physical Review Letters*, 87(19):198701–4, 2001.
74. C. Cannings and C. Penman. Random graphs. In C.R. Rao and D.N. Shanbhag, editors, *Stochastic processes: Modelling and simulation*, Vol. 21. Handbook of Statistics series. Elsevier, 2002.
75. M. E. J. Newman. Who is the best connected scientist? A study of scientific coauthorship networks. *Physical Review E*, 64:016131, 2001.
76. A.R. McIntosh and F. Gonzalez-Lima. Structural equation modeling and its application to network analysis in functional brain imaging. *Human Brain Mapping*, 2:2–22, 1994.
77. A.R. McIntosh, C.L. Grady, L.G. Ungerleider, J.V. Haxby, S.I. Rapoport, and B. Horwitz. Network analysis of cortical visual pathways mapped with PET. *Journal of Neuroscience*, 14:655–666, 1994.

78. M.S. Pinsker. *Information and information stability of random variables and processes*. Holden-Day, San Francisco, 1964.
79. R.M. Gray. *Probability, random processes, and ergodic properties*. Springer-Verlag, Berlin, 1988.
80. M. Doppelmayr, W. Klimesch, J. Schwaiger, and T. Winkler. Theta synchronization in human EEG and episodic retrieval. *Neuroscience Letters*, 257(1):41–4, 1998.
81. J.L. Cantero, M. Atienza, and R.M. Salas. Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: different electroencephalographic phenomena within the alpha band. *Neurophysiol. Clin.*, 32(1):54–71, 2002.
82. W. Singer and C. Gray. Visual feature integration and the temporal correlation hypothesis. *Annual Review of Neuroscience*, 18:555–586, 1995.
83. C. Gray. The temporal correlation hypothesis: still alive and well. *Neuron*, 24:31–47, 1999.
84. L.F. Lago-Fernandez, R. Huerta, F. Corbacho, and J. Siguenza. Fast response and temporal coherent oscillations in small-world networks. *Physical Review Letters*, 84:2758–2761, 2000.
85. G.M. Edelman. Naturalizing consciousness: A theoretical framework. *Proceedings of the National Academy of Sciences, USA*, 100(9):5520–5524, 2003.
86. J.L. Krichmar and G.M. Edelman. Machine psychology: Autonomous behavior, perceptual categorization and conditioning in a brain-based device. *Cerebral Cortex*, 12(8):818–30, 2002.