Brain structure–function relationships: advances from neuroinformatics

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THE ROYAL SOCIETY

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1. STRUCTURE–FUNCTION RELATIONSHIPS

One of the sustaining assumptions in biology is that structure and function are everywhere closely linked. This assumption reproduces itself in studies aimed at every level of the nervous system. At the smallest scales, the conformation of membrane proteins is assumed to be a key determinant in their functions in the cell's electrodynamics; at a larger scale, the morphology of dendrites and distribution of channels are intimately related to the biophysical function of the neuron; and at a still more molar level, computation by local cortical circuits is assumed to be a function of the pattern and properties of local and distant synapses. At the level of whole neural systems, too, it is widely assumed that information processing is closely determined by the inputs, internal connectivity and outputs of the network of areas and nuclei that make up the brain.

Some assumptions about neural structure–function relationships are better substantiated than others, and at many levels of organization the relationships have remained opaque and elusive. Part of the difficulty arises from the fact that both structure and function are often very complex, so that demonstrating a compelling relationship between them requires that both structure and function are characterized in considerable detail. There is, for example, a well-known mismatch between the anatomical complexity and extent of cortical neurons and the localized physiological properties reported by neurophysiologists (Douglas & Martin 1991) that is only now starting to give way through very detailed anatomical and physiological study (e.g. Douglas *et al.* 1996). Similarly, at the systems level, the extent and complexity of corticocortical and thalamo-cortical networks has proven difficult to relate clearly to the functional properties of the network or of its constituent structures (Young 1995). Given the startling complexity in the pattern of connections between different brain areas, and the complexity in the response properties of single neurons, it is encouraging that this latter difficulty has also begun to give way. Collations and analyses of the corticocortical and thalamocortical networks revealed by neuroanatomists' experiments have recently predicted successfully the location of cells with specific physiological properties (e.g. Scannell *et al.* 1996, 1997; cf. Merabet *et al.* 1998). The same analyses have also started to account for the distribution of particular kinds of selectivity by reference to the structure of part of the network (Burns & Young, this issue; Hilgetag *et al.* 1996; Hilgetag, O'Neill & Young, this issue), and to account for the spatial distribution of activity across the areas of the cortex after localized experimental disinhibition (Kötter & Sommer, this issue; Stephan *et al.*, this issue).

2. NEUROINFORMATICS: DATA COLLATION AND ANALYSIS

These advances share a common feature. They were all revealed by a strategy that involved systematic collation and formal analysis of neuroscientific data. This approach echoes similar problems and solutions elsewhere in biology. Many successful empirical programmes in biology face a difficulty generated by the great quantity and complexity of the data they produce. This problem is particularly evident in genome mapping and taxonomy, where data are so numerous and complex that computational and mathematical methods have become indispensable tools for understanding. To deal with this problem, these disciplines have developed computer-based information collation, management and data analysis—an approach often called 'bioinformatics'. This approach has made the complex data more tractable, leading to the development and appropriate testing of better-informed hypotheses. The success of experimental neuroscience has brought with it a problem very similar to that faced by these other biological disciplines. The quantity and complexity of relevant data, and their dispersion through an extensive literature, make it very difficult to derive reliable conclusions about the information they collectively bear about the nervous system. An example of the scale of the problem is provided by the fact that more than 14 000 reports of connections between the different gross structures of the rat brain have been reported in the past 20 years (Burns & Young, this issue). Data so numerous and complex provide ample opportunity for the derivation of false hypotheses if treated informally, simply through the ease with which inconvenient data can be overlooked or forgotten. These complex and numerous data plainly require analysis in order to develop and substantiate hypotheses about the organization of the rat brain. Similarly, possible structure–function relationships in the brain cannot be demonstrated in a rigorous and compelling way while the structural aspects of the system specified by the data are left undefined. Before analysis can begin, however, relevant data must be brought together into an empirically faithful but tractable form. Hence, as in other areas of biology, computer-based collation, management and analysis of neurobiological data—by direct analogy 'neuroinformatics'—is a necessary step towards understanding in several areas of neuroscience.

Neuroinformatics is presently in its infancy, and is underdeveloped in most potential applications. The greatest progress has been made in areas in which very similar kinds of data have been collected experimentally over long periods. Although work is in progress in many laboratories to develop neuroinformatic tools for both anatomical and physiological data, the most developed examples of a neuroinformatic approach are databases and analyses of neuroanatomical connectivity (e.g. Felleman & Van Essen 1991; Young 1992, 1993; Young *et al.* 1994; Scannell & Young 1993; Scannell *et al.* 1995, this issue; Stephan, Zilles & Kötter, this issue), and of patterns of cortical activation in neuronographic experiments (Stephan, Hilgetag, Burns, O'Neill, Young & Kötter, this issue).

3. NEUROINFORMATICS IS DISTINCT FROM NETWORK MODELLING

Neuroinformatics can be discriminated from other applications of computational methods in neuroscience, as for example in neural network modelling. Indeed there are two largely distinct computational approaches in neuroscience. In neuroinformatics, modelling begins with experimentally derived data and employs computational methods as methods of data analysis to try to understand what the data mean. In the other approach, modelling begins with ideas or hypotheses and proceeds by implementing these ideas in a computer simulation, very often in the form of a neural network. Both the analytic approach represented by neuroinformatics and the latter, synthetic, approach attempt to bring mathematical and computational rigour to the areas of neuroscience to which they are applied. The analytic approach brings rigour by enforcing the same standards of statistical propriety in the interpretation of data as are observed in other areas of the subject where data analysis is routine. The synthetic approach brings rigour by evaluating the consequences of hypotheses and other premises in an unforgiving manner, so that if the simulation differs in principled ways from what is observed in the brain, these hypotheses can be ruled out or refined. The present collection of studies concerns results from the analytic approach as it has been applied to data from experimental neuroscience, and it is therefore primarily concerned with data analysis rather than modelling, in the sense in which that term is usually applied.

4. STATISTICAL RIGOUR

Most areas of neuroscience already employ methods of statistical data analysis to substantiate experimenters' interpretations of their data. No study in neurophysiology, for example, could be published without detailed analysis of the data, the results of which rigorously constrain the conclusions that can reliably be drawn from them. Those areas that have not routinely employed data analysis methods have most often not done so because the experimentally derived data have not appeared to be data analytically tractable, or because the benefits of data analysis have not been clear. Both these considerations have previously applied, for example, to the application of data analysis methods to data on connectional neuroanatomy. However, as regards tractability, Maunsell & Van Essen (1983), Nicolelis *et al.* (1990) and Young (1992) demonstrated that different types of experimentally derived neuroanatomical data could be analysed in different ways to inform the organization of neural systems. Maunsell & Van Essen (1983) examined data on the laminar origin and termination patterns of corticocortical connections to develop an idea of the hierarchical organization of the primate visual system. Nicolelis and colleagues examined the connectivity of a presumed cardiovascular control circuit to investigate the number of steps between processing stations (Nicolelis *et al.* 1990). Young (1992) analysed the area-to-area connection pattern of areas of visual cortex to reveal the topology of the system. These studies presaged a new approach to the computational analysis of neuroanatomical data in which several types of connectivity data from several different species have now been analysed by many different analytical methods to demonstrate aspects of the organization of the neural systems in these brains (e.g. Young 1992, 1993, 1995; Scannell & Young 1993; Young *et al.* 1995; Scannell *et al.* 1995; Hilgetag *et al.* 1996, both papers this issue).

5. NEUROINFORMATICS AND EMPIRICAL NEUROANATOMY ARE COMPLEMENTARY

Neuroinformatics and experimental neuroscience are allied, interdependent and interacting approaches, rather than in any sense alternatives. However, while computational analysis of neurophysiological data is widely undertaken and acknowledged, computational analysis of neuroanatomical data is less well known (Young 1995). Indeed, the benefits of systematic analysis of neuroanatomical data have not been clear to all. To clarify the complementary nature of empirical connection tracing and systematic collation and analysis, it is beneficial to consider the kinds of issue that unanalysed data can inform, and the kinds of issue that can only be informed by the results of analyses. If, for example, an experimental study revealed the carriage of retrograde label from V4 to MT, this datum would be sufficient (assuming no transneuronal labelling) to conclude that MT is connected to V4. A problem arises, however, when conclusions about the organization of the system are made on the basis of individual data. For example, it has been argued that there cannot be two streams in visual cortex because V4, the prototypical ventral stream area, and MT, the prototypical dorsal stream area, are reciprocally connected (Young 1995). In this case, a conclusion about the organization of the system—that it is not organized into two streams—is based on replicable, uncontentious data. The problem is that the organization of the system is defined by many hundreds of connections (e.g. Felleman & Van Essen 1991; Young 1992), of which the connections mentioned are only two. It is plainly not possible to draw reliable conclusions about something defined by hundreds of data on the basis of only two data. In the same way, a few spikes fired to null stimuli could not be used to argue that a neuron is not directionally tuned. Because large numbers of connections define neural systems, conclusions about their organization require the support of analysis (Young 1995). In the case of laminar data, the limitations on interpreting individual data are even more poignant. Even in the case that area A sends a projection that terminates in layer IV of area B, it cannot reliably be concluded that B is 'higher than' A. This is because hierarchical relationships are properties of the organization of the system and are determined by global connectivity (see Hilgetag *et al.* 1996; Hilgetag, O'Neill & Young, this issue). Area A's 'ascending' projection to B might, for example, be a rare hierarchical anomaly between stations that are specified by hundreds of other connections to have the relationship B 'lower than' A. For these reasons, both analysis of neuroanatomical data and neuroanatomical experiments are necessary before reliable conclusions about the organization of neural systems can be drawn. Also, both experimental and data analytic work is required to further refine knowledge about neural organization. Computational analysis of neuroanatomical data is in no sense a replacement for, or undertaken instead of, experimental neuroanatomy. It is clearly entirely dependent on high-quality primary data. In the same way, computational analysis of spike trains is best promoted by analysts encouraging the collection of high-quality spike data in well-designed neurophysiological experiments.

6. A NEW APPROACH

The approach presented in this volume offers a number of benefits over less formal methods for analysing connection data. First, it allows theories of neuroanatomical organization to be tested with the statistical rigour that is common in other fields of neuroscience. Second, the approach has had some success in helping to anticipate anatomical and physiological features of areas that have not yet been studied in detail. For example, in the cortical visual system there was significant correlation between the positions taken by areas on a peripheral-to-central axis and the laminar origin and termination patterns of projections between these areas (Young 1992). If this relationship holds for other neural systems, areas would be expected to make projections terminating mainly in layer IV to less peripheral areas, and projections avoiding layer IV to more peripheral areas. Third, the approach has started to help anticipate the physiological properties of brain regions that have not yet received extensive experimental attention. This is because the positions taken by particular cortical areas in the configuration derived for the cortical visual system correspond remarkably well with the physiological properties of neurons in these areas (Young 1992). This correspondence may reflect the possibility that the local connectivity and membrane biophysics of cortical cells may vary relatively little across the cortex (Douglas & Martin 1991; Mountcastle 1982), so that the pattern of external inputs, determining the 'place' of an area in the cortical macro-circuitry, specify in large part the area's functional properties. Fourth, the approach has allowed us to begin to see the 'big picture' of brain organization in a relatively understandable yet reasonably accurate manner. The large-scale organization of the brain is not often emphasized in contemporary neuroscience, and this may in part be because there have not been the tools to provide enquiry into such matters with quantitative rigour.

7. MAPS OF THE BRAIN

Neuroinformatics is thus beginning to provide an approximate route map of brain systems in a small number of well-studied species. As represented in this collection, this route map is not so approximate that it cannot demonstrate, for the first time at the level of neural systems, quantitative relationships between structure and function in the brain. The present collection reflects almost all of the current growth points in neuroinformatics. In this issue, Hilgetag & Grant and Scannell *et al.* reflect mathematically on issues that arise in the analysis of quantitative neuroanatomical data. Quantitative data and their analysis hold the key to the refinement of understanding of structure–function relationships at the level of local circuits and above. Stephan, Zilles & Kötter present a new computational approach to the collation of neuroanatomical data, which makes translation between the different parcellation schemes employed by experimenters tractable by computational means. Burns & Young treat data from the most comprehensive database yet derived for a mammalian species' connectivity in order to explore structure–function relationships in systems associated with the hippocampus. Hilgetag, O'Neill & Young re-examine the issue of hierarchical organization of brain systems from the perspective of computational analysis, and explore aspects of aspects of structure–function relationships in the primate visual system, such as the apparent contradiction between hierarchically organized neuroanatomy and non-hierarchical neurophysiology in dorsal stream structures. Hilgetag, Burns, O'Neill, Scannell & Young develop and apply a new and explicit computational analysis, optimal set analysis, to describe optimal clusters, systems and streams in both cat and macaque cortex. Stephan, Hilgetag, Burns, O'Neill, Young & Kötter employ this new data analytic approach in the different context of clusters of cortical areas defined by their co-activation in neuronographic experiments. Kötter & Sommer employ dynamic computer modelling to demonstrate a link between the structural description of the cat cortex derived by Scannell & Young (1993) and the patterns of co-activation of cortical areas by neuronographic disinhibition. Friston *et al*. also explore questions of brain dynamics, by developing nonlinear factor analytic methods capable of treating electro- and magnetoencephalographic data. Finally, Young *et al*. explore the link between the connectional patterns of neural systems and the distributed and complex effects of making lesions in such elaborate networks in order to clarify what can be reliably inferred from the behavioural effects of brain lesions. In summary, the many structure–function relationships demonstrated in this issue are a powerful evocation of the truth that, in seeking to understand how something works, it is often helpful to know how it is organized.

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