EMERGING PRINCIPLES GOVERNING THE OPERATION OF NEURAL NETWORKS

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INTRODUCTION

A basic tenet of neuroscience is that the ability of the brain to produce complex behaviors such as sensory perception or motor control arises from the interconnection of neurons into networks or circuits. Finding out how neural networks are organized and understanding what computational principles underlie their operation remain challenges to modern neuroscience. Advances in anatomical, biochemical, electrophysiological, and computational techniques have provided the tools to begin uncovering concepts underlying neural network function. This review is a summary of insights into the organization and operation of neural circuits acquired through application of these techniques to invertebrate and vertebrate systems. This review is not a survey of the vast variety of known neural networks but rather concentrates on emerging concepts applicable to networks in general. The first section provides a brief historical perspective. The second and third sections summarize two emerging concepts about the operation and modulation of neural circuits. The first concept is that the operation of a neural network depends upon interactions among multiple nonlinear processes at the cellular, synaptic, and network levels. The second concept is that modulation of these underlying processes can alter network operation. The final section suggests potentially profitable research directions for the future.

HISTORICAL PERSPECTIVE

By the late 1960s, the basic principles of excitability and synaptic transmission were fairly well understood. Ideas about how central neurons and

185

synapses might operate were based upon a rather simple picture provided by the squid axon (Hodgkin & Huxley 1952), the neuromuscular junction (Katz 1966), and the spinal motor neuron (Eccles 1964). Based upon these views, the abilities of a network arose from the interconnection of simple elements into complex networks, thus, from connectivity emerged function. Neural networks were viewed largely as "hard wired" (Bentley & Konishi 1978) and could therefore be defined by their anatomical or monosynaptic connectivity. Activity coming into a network would be operated upon by that network in accordance with the pattern of synaptic connectivity, much like data fed to a digital computer is processed by a preset program. Over the time span it took for a network to process incoming signals and generate an output, circuitry was considered fixed, thus, the operation of a network did not involve the making or breaking of synaptic connections or altering cellular and synaptic properties.

The challenge of uncovering the secrets to brain function lay in the unravelling of neural connectivity. Toward this end, major experimental effort has been expended to identify relevant neurons involved in various behaviors and to characterize their interconnection. Early success with invertebrate systems (Zucker et al 1971) signaled the onslaught of neural network "cracking." These studies were approached with several expectations in mind: First, a knowledge of the connectivity would explain how neural networks operated. Second, it was hoped that for each function (e.g. visual processing or generation of rhythmic motor patterns) we would find only a limited number of ways to implement that function in neural circuitry. Third, it was hoped that circuitry would be conserved, thus, similar functions might be subserved by similar neural networks. After nearly two decades of neural circuit analysis, it is reasonable to ask how well these expectations have fared.

What we found should not have been unexpected but was nonetheless surprising. First, neural networks turned out to be extremely complex and diverse. Even networks underlying simple behaviors in the small neural systems of invertebrates are remarkably complicated (Selverston 1985). Networks that initially appeared relatively straightforward and simple (e.g. crayfish tailflip, Zucker et al 1971; *Tritonia* swimming, Willows 1973) turn out to involve multiple levels of feedforward and feedback pathways imbedded in complicated arrays of connections and cells (Krasne & Wine 1984, Getting 1983c). Second, networks subserving similar functions do not appear to be conserved. This point has become particularly clear in the study of rhythmic motor systems (Getting 1988). In general, these systems produce an alternating pattern of activity between antagonistic motor elements, yet the underlying networks for generating these patterns appear to be unique for each system. Networks with similar connectivity

can produce dramatically different motor patterns and, conversely, similar motor patterns can be produced by dramatically different networks (Getting 1988). These observations illustrate a third general finding. Knowledge of connectivity alone is not sufficient to account for the operation and capabilities of neural networks. For example, detailed knowledge of cerebellar circuitry has not provided a clear understanding of its operation (Llinas 1981).

If a knowledge of connectivity is not enough, what does it take to understand how a neural network operates? A debate often arises about what is meant by the term "to understand" how a neural network operates, for understanding can occur at many levels. For example, one can understand how an internal combustion engine works from the principles of thermodynamics without a detailed knowledge of pistons, crankshafts, and fuel injectors. If one's car engine should stall, however, such an understanding will be of little value because the failure was probably not caused by a breakdown in the laws of thermodynamics but a failure in the implementation of these principles. To understand how nervous systems operate, and therefore how they might fail due to disease or injury, requires (*a*) a knowledge of the overriding principles of neural network organization and function (equivalent to the rules of thermodynamics), and (*b*) how those principles are implemented by cells and synapses (the "nuts and bolts" of network operation). In an effort to acquire these two levels of understanding, much of the experimental work on neural networks has been guided by a reductionist approach in which a system is successively pared down to its constituent pieces or "building blocks" with the hope of uncovering general principles and how they are implemented.

THE BUILDING BLOCK BASIS FOR NETWORK OPERATION

A major contribution of the reductionist approach has been the delineation of properties crucial to the operation of neural networks. Although knowledge of connectivity is essential, network operation depends upon the "cooperative interaction" (Selverston et al 1983) among multiple network, synaptic, and cellular properties, many of which are inherently nonlinear. No longer can neural networks be viewed as the interconnection of many like elements by simple excitatory or inhibitory synapses. Neurons not only sum synaptic inputs but are endowed with a diverse set of intrinsic properties that allow them to generate complex activity patterns. Likewise synapses are not just excitatory or inhibitory but possess an equally diverse set of properties. The operation of a neural network must be considered as the parallel action of neurons or classes of neurons, each with potentially different input/output relationships and intrinsic capabilities inter-

connected by synapses with a host of complex properties. What are the cellular, synaptic, and network properties that constitute the building blocks of network operation, and how do they contribute to network operation? Table 1 summarizes a partial list of cellular, synaptic, and network properties important to neural network operation.

Cellular Properties

The application of voltage clamp and pharmacological techniques to CNS neurons has uncovered a lengthy and diverse catalog of ionic conductances (Adams et al 1980, Llinas 1984, Jahnsen 1986). These individual conductances can be found mixed and matched in nearly any combination, but more importantly, each combination endows the host neuron with a different set of response properties. For the purposes of this review the natures of the individual conductances are not as important as the properties that they impart, for these response properties will have a direct impact on network operation.

Most CNS neurons fire spikes repetitively when depolarized. The relationship between firing frequency (F) and input (I), generally injected current, is expressed as an F-I plot. Two properties of the F-I plot are important. First is the threshold below which the cell does not fire. Second, above threshold, firing frequency is a monotonically increasing, but not necessarily linear, function of input. On theoretical grounds, nonlinear input/output relationships have been implicated as computationally important characteristics of neurons (McCulloch & Pitts 1943, Hopfield & Tank 1986). A seminal observation is that the F-I plots for different cell types are distinct. For example, the repetitive firing properties of tectal neurons (Lopez-Barnes & Llinas 1988), cerebellar Purkinje neurons (Llinas & Sugimori 1980a,b), hippocampal neurons (Kandel & Spencer 1961),

Table 1 Building blocks

Cellular	Synaptic	Connectivity
Threshold	Sign	Mutual
F-I relationship	Strength	or recurrent inhibition
Spike frequency adapt.	Time course	Reciprocal
Post-burst hyperpol.	Transmission	or lateral inhibition
Delayed excitation	Electrical	Recurrent inhibition
Post-inhibitory rebound	Chemical	Recurrent cyclic inhibition
Plateau potentials	Release mechanism	Parallel excit./inhib.
Bursting	Graded	
Endogenous	Spike	
Conditional	Multicomponent PSP	

thalamic neurons (Deschenes et al 1984), neocortical neurons (Connors & Gutnick 1984), brainstem bulbospinal neurons (Dekin & Getting 1987a), olivary neurons (Llinas & Yarom 1981, 1986), and spinal motoneurons (Schwindt & Crill 1984) all differ. Even within a restricted network subserving a single behavior, each interneuron type may display a different F-I relationship (Getting 1983a).

Input/output relationships are not fixed but may undergo a variety of modifications depending upon the recent firing history of the cell. Spike frequency adaptation is a decrease in firing rate during a maintained input. Its effect is to decrease the slope of the F-I plot in time. The mechanism of adaptation appears to be the activation of slow outward potassium currents (Brown & Adams 1979, Meech 1978, Partridge & Stevens 1976, Dekin & Getting 1987b). The degree and time course of adaptation can vary dramatically from one cell type to another and give rise to different temporal firing patterns to the same input (Hume & Getting 1982a). Following a period of activity, many neurons display a transient hyperpolarization and cessation of firing that may last from milliseconds to seconds. This post-burst hyperpolarization appears to be a manifestation of mechanisms similar to those responsible for spike frequency adaptation.

Upon depolarization, many neurons begin firing almost immediately in accord with the charging of their membrane capacitance. Other neurons show a prolonged delay between the onset of depolarization and the beginning of firing. This delay in firing has been termed *delayed excitation* and may range from hundreds of milliseconds in vertebrate neurons (Dekin & Getting 1984, 1987a) to several seconds in molluscan neurons (Byrne 1980a, Getting 1983b). The delay is caused by the activation of a transient potassium current called A-current (Connor & Stevens 1971). This current is ubiquitous (Rogawski 1985) but appears to be expressed as delayed excitation only in cells that are maintained within the proper voltage range for its activation (Dekin & Getting 1987a,b). Delayed excitation provides an intrinsic mechanism for producing long delays and has been implicated in the neural networks controlling inking behavior in *Aplysia* (Byrne 1980b) and swimming in *Tritonia* (Getting 1983b).

Following a hyperpolarization, membrane potential may rebound above resting level to produce a transient depolarization called post-inhibitory rebound (PIR). If sufficiently strong, PIR can lead to a burst of spikes. The mechanism for PIR is not well understood, but it has been implicated in the production of several rhythmic motor patterns (Mulloney & Selverston 1974, Satterlie 1985) and is found in numerous cell types such as tectal neurons (Lopez-Barneo & Llinas 1988), thalamic neurons (Deschenes et al 1984), and brainstem neurons (Johnson & Getting 1987).

Plateau potentials are expressed as two membrane potential states: a

resting state and a depolarized state (Russell & Hartline 1978). Small or transient depolarizations can cause transition from the resting state to the depolarized state, where the potential may remain for considerable lengths of time (tens to hundreds of milliseconds) before it either spontaneously reverts or is actively converted by a short hyperpolarizing input back to the resting state. The ability to produce plateau potentials provides a mechanism for translating a transient input into sustained firing, or a prolonged burst. Such mechanisms have been implicated in the generation of rhythmic motor patterns (Dickinson & Nagy 1983, Arshavsky et al 1985), and are seen in the responses of olivary neurons (Llinas & Yarom 1981, 1986), cerebellar Purkinje neurons (Llinas & Sugimori 1980a,b), and spinal motoneurons (Hounsgaard et al 1986).

Many neurons are autoactive and fire continuously in the absence of synaptic input. Pacemaker neurons produce a continuous train of spikes at regular intervals. Other autoactive neurons produce patterned bursts. Endogenous bursting neurons fire bursts of spikes independent of synaptic activation (Alving 1968), while conditional bursters express bursting only upon appropriate synaptic or neurohumoral activation (Anderson & Barker 1981, Miller & Selverston 1982a). The ability to burst arises from particular combinations of intrinsic membrane currents (Adams 1985, Adams & Levitan 1985) and may be expressed in many different forms (Alving 1968, Marder & Eisen 1984, Flamm & Harris-Warrick 1986, Hatton 1984, Dekin et al 1985).

Synaptic Properties

Synaptic properties also impact directly on network operation. Two properties of obvious importance are the sign (excitation or inhibition) and the strength of synaptic connections. Although determination of the sign of a connection may be relatively straightforward, assessment of synaptic strength is not always clear. Two measures of strength are (a) the amplitude of the post-synaptic potential (PSP), and (b) the degree to which activation of a particular synapse influences the activity of the post-synaptic cell. These two measures may not always covary. For example, an inhibitory synapse with a reversal potential close to rest potential may produce only a small IPSP, but the associated conductance change can have a powerful inhibitory effect by shunting excitatory currents. The relative placement of excitatory and inhibitory synapses on the dendritic structure, therefore, plays an important role in regulating integration (Rall 1981).

Temporal properties of synapses also play an important role in network operation. Individual PSPs may have dramatically different time courses, and thus operate over different time scales. For example, within the network of interneurons that generates the escape swimming motor program

of *Tritonia*, the fastest and slowest PSPs differ by a factor of 30 (Getting 1981). Also included under temporal properties are characteristics such as facilitation, depression, and potentiation that modulate the strength of connections in a history dependent manner.

A single synaptic connection may mediate several actions, each with different time courses. For multicomponent synapses, an initial action (either excitation or inhibition) is followed by a second action of either the same or opposite sign (Kehoe 1972). Multicomponent synapses can have a number of interesting integrative properties, including maximal expression *after* the end of a presynaptic burst (Getting 1983a). Complex connections having three and even four different components have been observed (Hume & Getting 1982b).

Mechanisms of synaptic transmission fall into two broad categories—electrical and chemical. Within each category, however, a wide diversity of mechanisms have been described, including both rectifying and non-rectifying electronic synapses, as well as conductance-increase and conductance-decrease chemical connections. The mechanism of transmission influences not only the character of the individual synaptic event but also how the PSPs from various sources will interact. For example, non-rectifying electrotonic synapses can have profound effects upon integrative properties, making a network selectively responsive to distributed afferent input (Getting 1974). Conductance-increase chemical PSPs may shunt whereas conductance-decrease PSPs may potentiate other inputs (Rall 1981). The action of each connection, therefore, cannot be considered in isolation but must be integrated with the actions of all other active synapses.

Mechanisms of transmitter release also influence the nature of the information transmitted at a synapse. Although transmitter release is a continuous function of presynaptic voltage (Graubard 1978), the threshold for detectable release may vary. Some terminals release transmitter only when invaded by a spike, while others release transmitter to graded presynaptic voltages. Graded release transmits information about absolute voltage of the presynaptic cell, whereas spike-mediated release transmits information only after the presynaptic signal has been processed into spike-frequency. Different release mechanisms, therefore, have a profound influence upon the nature of the information being conveyed at a particular connection.

Network Connectivity Patterns

Network connectivity includes patterns of interconnection between neurons within a network. The number of possible pathways between N neurons grows rapidly as $N!/(N-2)!$. Therefore, it is not reasonable to

summarize all possible combinations even for relatively small networks. A few patterns, however, are commonly encountered (Figure 1). Mutual or recurrent excitation (Figure 1A) promotes synchrony in firing and is usually found among synergists. Reciprocal inhibition and its cousin lateral inhibition are two forms of mutual inhibition (Figure 1B). Recurrent inhibition occurs when one cell excites a second neuron, which then inhibits the first cell or its synergists (Figure 1C). This pattern of connectivity can serve to regulate excitability (e.g. Renshaw cells) or, under appropriate conditions, can produce patterned output (Friesen & Stent 1978). Recurrent cyclic inhibition is characterized by a ring of neurons interconnected by inhibition (Figure 1D) and can, in theory, produce an oscillatory burst pattern with as many phases as number of cells in the ring (Szekely 1965, Friesen & Stent 1978). In many circuits a single cell may mediate more than one action on its targets. Parallel excitation and inhibition can be mediated by separate pathways (Figure 1E, *left*) or by a single multi-component synapse (Figure 1E, *right*). If the time course of either the excitation or inhibition is longer, then this connectivity scheme can lead to a delayed reversal in the sign of synaptic action (Getting 1983a).

Calling these patterns of connectivity *building blocks* is not meant to imply that all neural networks can be either constructed from, or reduced to, these few connection schemes. For some small systems, relatively com-
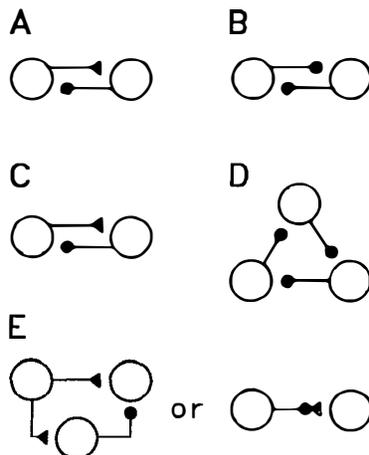
Figure 1 Simple patterns of connectivity. *A*. Mutual or recurrent excitation. *B*. Reciprocal or lateral inhibition. *C*. Recurrent inhibition. *D*. Recurrent cyclic inhibition. *E*. Parallel excitation/inhibition. Symbols: *triangles*, excitation; *dots*, inhibition.

plex networks can be simplified in terms of these more restricted connection schemes (Getting & Dekin 1985, Miller & Selverston 1982b), but for larger networks, additional pathways may preclude such reduction. Nor should it be construed that network function, particularly in large networks, can be considered as the simple summation of the action of these components. The properties of these simple schemes may become modified when embedded in larger networks. In addition, large networks may give rise to properties not found in these restricted smaller sets. These simple patterns of connectivity are, however, commonly encountered and appear to form a basis for network function in many diverse systems.

This list of cellular, synaptic, and network properties includes only the more commonly encountered features. It serves, however, to illustrate the vast diversity in properties employed within neural networks. No doubt additional properties will be added as more networks are analyzed. Despite the possible incompleteness of the list, several generalities can be drawn about the use of these properties in neural circuits. First, many of these building blocks are inherently nonlinear, thus the capabilities of neural networks emerge from a complex spatial and temporal interaction of multiple, nonlinear processes at the cellular, synaptic, and network levels. Second similar building block mechanisms have been identified throughout a wide variety of animals, thus suggesting that these constituent building blocks may be conserved. Third, if neural networks acquire their abilities by combining a set of conserved building blocks, then the ability of nervous systems to perform or control diverse behaviors reflects the multitude of ways that these building blocks can be combined. Finally, because of the large number of possible building block mechanisms and ways in which they could be combined, there may be many ways of implementing the same or similar function. For example, many rhythmic motor patterns share features in common, yet the central pattern generator networks underlying the production of these rhythms are disparate (Getting 1988). This disparity suggests that there are numerous ways of combining the building blocks to produce oscillatory, antiphasic patterns, each suited to the particular constraints of the behavior being controlled.

NETWORKS CAN BE MULTIFUNCTIONAL

If the ability of a neural circuit to perform a function derives from the collective action of the constituent network, synaptic, and cellular building blocks, then altering the properties of building blocks can change the operation of that network. Thus, a single network could subserve several different functions. An important finding in the past decade is that all three classes of building block mechanisms can be controlled by a host of

modulatory mechanisms. The implications of these observations for the operation of neural networks are profound. By changing the properties of selected synapses, cells, or pathways, the operation of a network can be dramatically altered. A single network could be multifunctional, participating in or generating more than one behavior. This is not to say that an auditory system can be made into a visual system, but, within the confines of the anatomical substrate, the functional organization of many neural networks appears to be under dynamic control, changing in accordance with the conditions at the moment.

Definitions of Network Organization and Operation

The idea that the functional organization within a network may be under dynamic control is not new (Sherrington 1906). What is new is an appreciation for the pervasiveness of this principle for neural networks in general (Baldissera et al 1981, Edgerton et al 1976, Getting & Dekin 1985). To provide a framework for discussing the concept of modulation in network operation, the following definitions may prove helpful. One level of network organization is the *anatomical organization*, which is defined by the monosynaptic or anatomical connectivity between neurons. Anatomical organization is specified by the distribution of afferent fibers, the synaptic connectivity within the network, and the projection of efferents. In essence, anatomical organization defines the limits of the network and who talks to whom within the network, but does not give rise to function. The ability of a network to perform a task depends upon what building block mechanisms (network, synaptic, and cellular) are being expressed at a given moment. If these network, synaptic, and cellular mechanisms are under modulatory control, then an anatomical network may be configured into any one of several *modes*, depending upon the particular combination of currently active mechanisms. A *mode* is defined by the distribution and properties of the network, synaptic, and cellular building blocks within the anatomical network. The term *mode* is intended to imply a manner in which a network processes information or generates an output pattern, thus each mode represents the functional organization of the network that gives rise to a function or task. Transitions between modes may occur when afferent or modulatory inputs alter the properties of the constituent building blocks.

To understand how a network operates, the flow of activity within the network must be described quantitatively. One method for quantification is to define *states* of activity within the network. A *state* is defined as the spatial distribution of activity at a given moment in time. If a neuron is considered to either fire an action potential (state 1) or not (state 0), then a network of two neurons has four possible states: both cells firing (1,1),

one or the other cell firing (1,0 or 0,1), or neither cell firing (0,0). In this two-cell network, transition between states occurs when either cell starts or terminates an action potential. The temporal sequence of states yields the output pattern of the network. Using the occurrence of individual spikes in every neuron can result in a large number of possible states (2^N where N is the number of neurons in the network), and thus may not be the best criterion to distinguish states. Other criteria such as membrane potential, firing frequency, the onset and termination of bursts, or even the integrated activity across a population may provide better insight into the operation of a particular system. For example, Lennard et al (1980) used a combination of membrane potential and burst times to quantify the temporal sequence of network states underlying swimming in *Tritonia*. This analysis provided important insight into mechanisms for pattern generation in this system (Getting 1983c). When a network is configured into a mode of operation, it expresses a subset of all possible states. The mode, by setting the network, synaptic, and cellular properties, provides an algorithm to produce a temporal sequence of states.

Modulation of Building Blocks Can Alter Network Operation

Modulation of the network, synaptic, and cellular building blocks can serve to adapt the output pattern to ongoing needs or may dramatically reorganize a network into an entirely new mode mediating a different behavior. The next section deals with mechanisms for modulating each of the three classes of building blocks.

In order to understand how connectivity within a network can be modulated it is necessary to make a distinction between anatomical and functional connectivity. *Anatomical connectivity* refers to the pattern of monosynaptic connections among a group of neurons. *Functional connectivity* refers to the effect of one cell upon another by whatever pathways, monosynaptic or polysynaptic, interconnect the two cells. Anatomical connectivity defines the constraints of a network but functional connectivity determines the activity pattern.

The difference between anatomical and functional connectivity can be illustrated by the network controlling escape swimming in *Tritonia*. Swimming consists of a series of alternating dorsal and ventral flexion movements and is generated by a group of interneurons interconnected by a complex pattern of monosynaptic connections that define the anatomical network (Figure 2A). Within this network, the three dorsal swim interneurons (DSI) excite each other via monosynaptic connections, but this monosynaptic excitation is paralleled by polysynaptic inhibition mediated by the I-cell. From the anatomical connectivity alone, one can not predict
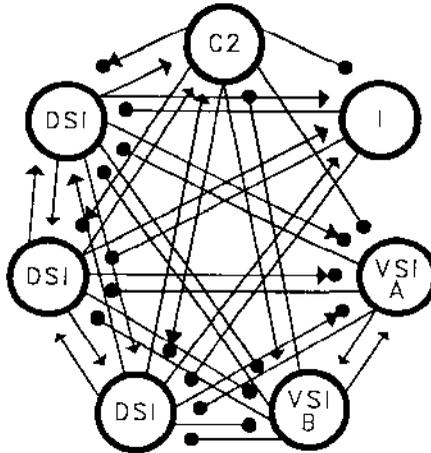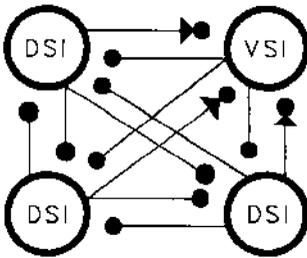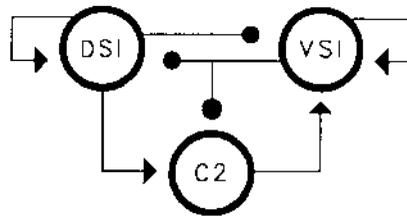
Figure 2 *A*. Network diagram showing the monosynaptic connectivity between interneurons of the *Tritonia* escape swim system. *B*. Network configuration reflecting the functional connectivity when C2 is silent. In this configuration (mode), the network contributes to reflexive withdrawals. *C*. Network configuration when C2 is active. In this mode the network generates an alternating burst pattern between DSI and VSI which in turn activates motoneurons for each flexion movement. Pathways with more than one symbol indicate multi-component synapses.

what the effect of driving one DSI would be on another DSI. If the monosynaptic excitation was stronger than the polysynaptic inhibition, then the net effect would be excitatory. In fact, driving one DSI leads to inhibition of another DSI (Getting & Dekin 1985). The polysynaptic inhibitory pathway dominates, thus the functional connectivity between

DSI is inhibitory even though the DSI connect monosynaptically by excitatory synapses.

Functional connectivity reflects the relative strengths of the synaptic connections and the excitability of each neuron along all pathways from one cell to another. Functional connectivity can, therefore, be modulated by alteration in synaptic strengths or in the excitability of neurons along the pathways. The circuit of Figure 2 provides an example of modulation in functional connectivity. When *Tritonia* is not swimming, the C2 neuron is silent and the three DSI functionally inhibit each other via the polysynaptic pathway through the I-cell. During swimming, however, C2 fires in bursts coactive with DSI. Under these conditions, the I-cell is inhibited by C2 and the functional connection among DSI becomes excitatory, mediated by the monosynaptic connections. The functional connection among the DSI can be switched from mutual inhibition to mutual excitation depending upon whether C2 is active.

The consequences of modulation in the functional connectivity within the network of Figure 2A are profound. The anatomical network of Figure 2A can be redrawn to reflect functional connectivity when C2 is silent (Figure 2B) and when C2 is active (Figure 2C). When C2 is silent (Figure 2B), the network is dominated by inhibitory interactions. In this configuration, or mode, each interneuron can be activated independently by afferent input and can contribute to the routing of activity to motor neurons mediating directed reflexive withdrawals (Getting & Dekin 1985). When the animal is stimulated to swim, C2 becomes active, the functional connectivity among DSI becomes excitatory, and the network is reorganized to form the pattern generator circuit shown in Figure 2C. The three DSI have been lumped together because in this configuration they excite each other and act as a single population. In the pattern generator mode, the network produces a sequence of alternating bursts between the DSI and VSI that in turn drives the dorsal and ventral flexion motoneurons. The circuit remains in this mode until the excitation to C2 wanes, the I-cell is disinhibited, and the network reverts to the reflexive withdrawal mode of Figure 2B.

The concept of reordering functional connectivity has been applied to spinal circuitry for some time (Baldissera et al 1981). Many descending pathways to the spinal cord share the same interneurons as peripheral inputs, but the association of these interneurons into functional groups apparently depends upon the task being performed (H. Jankowska, personnal communication). Task-dependent modulation of reflexes has also been observed during different modes of locomotion (Capaday & Stein 1986) and during different phases of the step cycle (Forssberg et al 1975).

Descending influences presumably reorganize the functional connectivity within the spinal cord to fit the task at hand. Reordering of functional connectivity has also been observed in the auditory cortex in response to different sounds (G. L. Gerstein, personal communication). In these cases input may not only *activate* a network but may also *configure* it into an appropriate mode to process that input. Descending commands and afferent inputs should be considered as both instructive and permissive in that they may organize the functional interactions within a network to be appropriate for the task at hand as well as activate the network to perform the task.

Alterations in synaptic properties fall into two general categories: homosynaptic and heterosynaptic. *Homosynaptic* influences depend upon the recent activity of a single synapse, and include such phenomena as facilitation, depression, or potentiation. For *heterosynaptic* modulation, the synaptic efficacy in one pathway can be altered (either increased or decreased) by activity in a second pathway. Heterosynaptic influences can be mediated by direct contact between the two pathways as in presynaptic inhibition or can be mediated by more distant neurohumoral interactions (Shain & Carpenter 1981). The lobster stomatogastric system provides a clear example of application of dopamine selectively altering one IPSP, thus resulting in a phase change in the motor pattern (Eisen & Marder 1984).

Modulation of intrinsic cellular properties also takes many forms (Kaczmarek & Levitan 1987). Since repetitive firing properties reflect the expression of the underlying ionic conductances, modulation of the ionic conductances will alter the input/output relationship of a cell. Many ionic conductances are voltage dependent in the region of resting potential; thus, biasing a neuron more depolarized or hyperpolarized than rest can modulate the expression of these conductances. For example, delayed excitation mediated by A-current can be potentiated by hyperpolarization or nearly abolished by subthreshold depolarization (Getting 1983b, Dekin & Getting 1984). A second mechanism for modulation of intrinsic properties is through receptor-mediated action of neuromodulators. Modulatory substances bind to surface receptors and alter the kinetics of ion channels either directly or by the production of a second messenger (Kaczmarek & Levitan 1987). The effects of modulatory substances can be so profound that cells acquire entirely new properties not seen in the absence of the modulator. The effects of modulators covers the range of intrinsic properties, including increased or decreased excitability, the modulation of spike frequency adaptation, the enhancement of post-inhibitory rebound, the induction of plateau potentials, and the expression of intrinsic bursting.

PROSPECTS FOR THE FUTURE

The comparative study of neural networks has led to a picture of neural networks as dynamic entities, constrained by their anatomical connectivity but, within these constraints, able to be organized and configured into several operational modes each depending upon the expression and modulation of the constituent cellular, synaptic, and network building blocks. This view has two components: (a) neural networks are assembled from a set of cellular, synaptic, and network building blocks, and (b) these building blocks can be modulated, thereby altering the operation of the network. These concepts are attractive from several perspectives. First, these organizational principles indicate that a separate neural network is not needed for each behavior or for each modification thereof. A single anatomical set of neurons may perform multiple tasks. Second, these concepts help to reconcile the apparent diversity in neural networks, even those subserving similar functions, since the constituent building block mechanisms appear to be conserved, but not the particular combination. Finally, these concepts provide a framework for approaching neural networks experimentally. In order to understand how a function is implemented one must identify the underlying cellular, synaptic, and network building blocks and how they interact.

These concepts present some formidable problems, however, To understand how a network operates, it will be necessary to analyze the appropriate building blocks while the network is performing the task of interest, otherwise the requisite combination of building block mechanisms may not be operative. This is less of a problem for some invertebrate preparations in which large portions of the nervous system can be isolated while preserving function (Selverston 1985). For vertebrate systems, the situation may be more difficult. Isolation by cell culture or brain slice techniques, although allowing access to and experimental manipulation of individual cells, commonly disrupts the networks sufficiently so that network operation is lost. These preparations can serve an important role, however, in characterizing possible cellular and synaptic mechanisms, but it will be necessary to show how these properties are used within operational networks. For this purpose new methods for gaining access to the relevant building block mechanisms in operational networks will be required. In this regard the advent of a number of in vitro methods for maintaining large portions of the vertebrate CNS hold particular promise (McClellan 1987, O'Donovan 1987, Fulton & Walton 1986, Smith & Feldman 1987, Llinas et al 1981, Richerson & Getting 1987).

Now that some of the building blocks of network operation have been identified, rules for their assembly into neural networks need to be sought.

Further reductionism to the single channel or molecular levels will be important in providing information about mechanisms underlying the building block properties, but these approaches are unlikely to provide insight into principles of network operation. For this purpose we need synthesis, not further reductionism. Do particular combinations of building blocks underlie certain tasks? Are all combinations of building blocks possible or only restricted subsets? What are the processing capabilities of the various building blocks and what do they contribute to network operation? Are there rules governing the assembly of the building blocks into networks?

Answering these questions will require a multidisciplinary approach. In particular, comparative studies will be important to delineate "successful" or useful combinations and may provide insights into rules for network assembly. In this regard, comparative analysis of rhythmic motor pattern generator networks has begun to yield general hypotheses about the assembly and modulation of pattern generator networks (Getting 1988, Harris-Warrick 1988). Ways of manipulating the various building blocks need to be found so that the ways they contribute to network operation can be investigated. In small systems, single cells or small groups of cells can be controlled or deleted (Lennard et al 1980, Miller & Selverston 1979) to allow assessment of their role. In larger systems other methods for altering the constituent building blocks, including possible genetic (Herrup & Sunter 1986, Thomas & Wyman 1984), pharmacologic (Harris-Warrick 1988), and developmental (O'Donovan 1987) manipulations, will be required.

Finally, methods for assessing rules for network assembly and operation must be developed. Biologically realistic computer models should be useful for this purpose. Crude network models based upon the interaction of nonlinear elements are revealing the underpinnings of cognitive function, including content addressable memory and simple pattern recognition (Rumelhart & McClelland 1986, Hopfield & Tank 1986). In terms of the properties of the elements and the complexity of the networks, these models are still barren in comparison with biological systems. What will happen to the emergent properties of these networks when biological reality is incorporated is as yet unclear. The hope is that the capabilities of the networks will increase to approximate that of the CNS, but this remains to be seen. Recent successes such as computer simulation of the establishment and modification of cortical somatosensory maps hold particular promise (Pearson et al 1987). Biologically realistic simulations offer an additional advantage in that individual building blocks or rules governing their assembly must be explicitly stated and therefore can be tested by systematic variation. The ability to manipulate all aspects of model net-

works should provide a powerful window into the importance of various building blocks and the ways they contribute to overall network function. Computer simulations, however, will be no more useful than the degree of their biological reality. Close interplay between experimentation and simulation must be maintained to ensure the validity of any model of the nervous system.

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