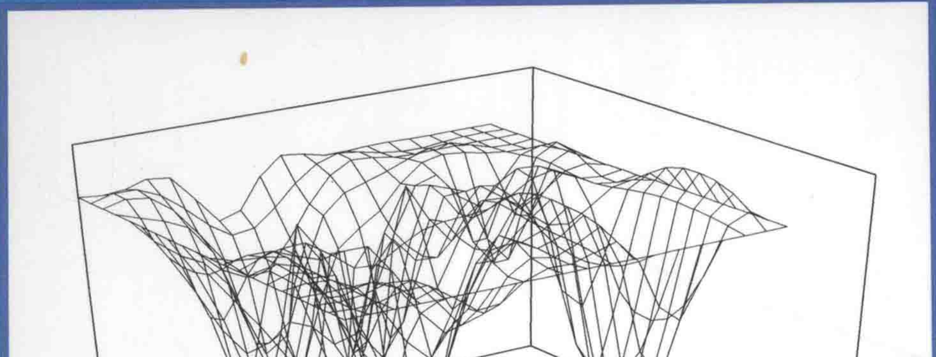
NERVOUS SYSTEM ACTIONS AND INTERACTIONS

CONCEPTS IN NEUROPHYSIOLOGY



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Preface

Science and art are arguably the most intrinsically human of all of our activities. The English word "science" derives from the Latin word *scire*, meaning to know. A host of other English words concerning knowledge springs from this root: conscious, from sharing knowledge; innocent, from not knowing; and omniscient, from all-knowing. Perhaps only in humans, and certainly to the highest degree in humans, do we encounter the native curiosity necessary to acquire knowledge about nature purely for the sake of that knowledge. The directing of this curiosity toward ourselves, and in particular toward the function of our brains, has always held a special place in the quest for knowledge.

Much of our approach to understanding nature derives from the philosophy of Sir Francis Bacon, who in 1620 wrote in the *Novum Organum* that "Man, as the minister and interpreter of nature, does and understands as much as his observations on the order of nature, either with regard to things or the mind, permit him, and neither knows nor is capable of more." We have built elaborate scientific systems of hypotheses and laws using this empirical approach, and most people today accept this method as valid.

A book on the science of neurophysiology might be expected to serve as a compendium of refined empirical observations about the function of the nervous system. There is definitely a role for such compendiums and many such books are available. There are inherent risks, however in describing the current state of knowledge in any field of science that is as dynamic as neurophysiology. First, the written word has a subtle effect that nudges observations from the realm of hypotheses to the realm of laws. Second, an active research effort continually provides new empirical observations and the basis for reinterpreting older observations. Third, publication removes the author from any subsequent discourse, and the reader lacks recourse for question or discussion. Perhaps this is why Galileo favored expressing his most controversial ideas as dialogues.

Scientific method is a cycle consisting of empirical observations, hypothesis formation, and hypothesis testing through further observation. We would like, in this book, to insert the reader into this cycle. The book is organized around a series of concepts supported by descriptions of empirical data, open-ended questions, and proposed further experiments. We have used the word "concept" in the hope that it conveys neither the tentativeness of a hypothesis nor the finality of a law. If we succeed in this presentation, it is because we have established a dialogue in which the reader amplifies these concepts into his or her own framework of understanding of the function of the nervous system. We hope to entice the reader to test some of these concepts and in places we have suggested demonstrations or experiments that might lead to provocative empirical observations. Sometimes we have suggested that the reader form hypotheses from his or her existing observations. At other times we leave it to the curiosity that derives from a questioning and discerning mind to lead the reader to make observations and to form working hypotheses. The reader should never accept a purely passive position, but rather should be like Luigi Galvani, the premier electrophysiologist, who performed experiments because "I was fired with incredible zeal and desire of having the same experience, and of bringing to light whatever might be concealed in the phenomenon" (*De viribus electricitatis in motu musculari Commentarius*).

Part of the philosophical legacy that we have inherited from Aristotle is the separation of biological science into function and form. Carried to its extreme, the logical extension of this thinking would be that the unique connectivity of each neuron imparts on that neuron its unique function. We are accepting a very different premise in this book, namely that many functions exist independent of structural localization. Rather than an emphasis on location, we shall emphasize the classes of information processing that support a variety of nervous system functions.

We have organized the concepts of neurophysiology in a somewhat non-traditional manner that perhaps deserves comment. We begin, in the first 6 chapters, with a discussion of information and the means by which information that is relevant to an individual is made accessible to the nervous system. In chapters 7 through 9, we consider the outputs available to the nervous system for this information and how information is interpreted and stored. It is then essential to delve into the cellular mechanisms by which the nervous system manipulates information, so chapters 10 through 14 are directed toward concepts in cellular electrophysiology. Finally, the last 3 chapters are directed toward the network interactions that are central to much of nervous system function, leading ultimately to the generation of the mind.

We hope to establish an active dialogue with our readers and to provoke some interaction in the communication of observations and hypotheses about nervous system function. To initiate this dialogue, we will begin here with a concept that surfaces in many guises throughout the various topics of this book.

1. ***While the functions of cells and subcellular structures are essential to nervous system function, additional essential properties emerge from the interactions of neurons in networks.***

Do you agree with this concept?

Acknowledgements

This writing adventure has been possible because of the skepticism, ideas, and support of many individuals. Our view of the nervous system has grown through hundreds of discussions at scientific meetings, in classrooms, and in university hallways. We are indebted to our colleagues and especially our students who have challenged us with the provocative and insightful questions that ultimately led us to write this book. We especially thank, Mike Yen and Michael Newman for support during revision, Buz Tyler for unfailing guidance through computer dilemmas, Daniella and Jeff Smart for help in producing the CD and Susan Patrick for insightful proof reading.

Contents

Chapter #1

Introduction

1. The human nervous system, with more than 10^{14} neurons, each unique by virtue of its connectivity, is structurally the most complex object that humans have tried to understand.

STRUCTURE	LOG n
Central Neurons	14
Sensory Receptors	9
Neurons in Enteric Nervous System	8
Rods and Cones in Retina	8
Sensory Fibers	7
Retinal Ganglion Cells	6
Synapses per Neuron	<6
Motor Units	5
Muscle Fibers per Motor Unit	1 – 4

Table 1.1 Number of certain structures in the human nervous system expressed as logs of the number. (This scale is in keeping with the limited accuracy of the numbers.)

Table 1.1 gives approximate numbers of a few of the components of the human nervous system. These numbers alone are impressively large, but the true complexity of the nervous system must also take into account the interactions among these components. If we attempt to understand the function of the nervous system in a reductionist way by identifying the function and interaction of each component as the basis upon which to build an understanding of the whole, we will have little hope of success. On the other hand, we can accept the premise that evolution designs conservatively so that functions tend to be reused to solve similar problems. This gives us an incentive to seek and to understand prototypical operators that occur in multiple locations and species. We can concentrate, then, on similarity of function without having to catalogue each occurrence separately.

A. Question:* What information about neural function can be surmised from the numbers of the different types of components listed in Table 1.1?

(N.B.: Questions and problems marked with an asterisk are further discussed in the Notes section.)

2. The historical context provides an important perspective for our current understanding of nervous system function.

The initial understanding of the brain was largely structural and was based on divisions that are easily identified in gross dissection. These structures were given Latin names stemming from their resemblance to familiar objects. With the development of more formal study, additional structures were named for the investigators who described them. When it was demonstrated that nerves activated muscles, peripheral nerves were named for the muscle served. By the beginning of the 20^{th} century, considerable information had accumulated about the pathways and loci involved in particular functions, and the responses to volley stimulation of peripheral nerves had been well explored, but little was known about how inputs were combined in the central nervous system. By this time, Cajal had shown that the central nervous system was made up of discrete units (neurons) and that multiple synaptic connections converged on central neurons. At the same time, Charles Sherrington had begun a half century of study of the differences between nerve impulse signals and reflexes and Ivan Pavlov had used gastrointestinal reflexes in his classic experiment that combined auditory inputs with food presentation. (See Appendix II.)

By the middle of the 20^{th} century, evidence had accumulated that supported a dynamic basis of neural signaling rather than one based on a strictly Boolean approach to these signals. After years of acceptance that synaptic transmission was the electrical transfer of impulses, it became clear that impulses caused the release of chemical transmitters that lead to the generation, with dynamic lag, of new impulses. Engineering tools for dynamic system analysis made it possible to predict the effect of the sequential combination of dynamic operators on neural signals. One of these tools, control theory, provided new insights into reflex feedback and added a new terminology to the discussion of nervous system function. By the end of the 20^{th} century, new tools had become available to study such discrete aspects of nervous system function as ion fluxes through single ion channels and to identify the genetic specification of critical molecules in neurons. (Appendix III further discusses some of these topics.)

Some of the references for this chapter provide a sampling of these important historical turning points in the development of our current understanding of the function of the nervous system. These articles are still very worthwhile reading for a student of neuroscience.

3. The nervous system has a special controlling or modifying action over most body functions and is the home of the unique personalities of higher animals. Its cells, however, depend on the same metabolic processes as do other animal cells.

The nervous system subserves a broad range of functions, some more apparent than others: it gives to an animal the ability to relate to its environment by moving through it in a purposeful manner; it carries an influence of past experience into its current responses; it controls constriction of the pupil in bright light; it modifies pituitary activity; it coordinates the thousands of muscle units that produce an individual speech phoneme; it reports that a finger is in a position so hot that tissue damage is imminent; it speeds the heart rate during exercise; it holds the urinary sphincter closed for hours; it contracts tiny muscles that increase the insulating effectiveness of fur and cause "goose bumps;" and it processes information that leads to a scientific discovery or a musical composition. With a moment's reflection, you should be able to add many more items to this list. The breadth of this list makes it obvious why a neurologist, physical therapist, ophthalmologist, psychologist, bioengineer, neurosurgeon, or psychiatrist needs to understand nervous system function. Nervous system function plays a less obvious but important role in most other medical and paramedical fields. This is true even without the more subtle consideration that both a patient's complaints and a clinician's responses are products of the function of their respective nervous systems. As an example, our current understanding of internal medicine problems such as those resulting from loss of ions with sweating, vomiting, or diarrhea is closely tied to information about cell membranes that was originally acquired in the study of giant nerve fibers of the squid. We will devote chapters 11 and 12 to discussions of the interactions between certain ions and specialized large molecules in cell membranes that have common characteristics in as diverse tissues as nerve fibers, cardiac muscle, or kidney tubules.

4. Sensory receptors provide the nervous system with information about environmental conditions – information that is especially important when those conditions are changing.

The evolution of a species provides the successful survivors with adaptive functions that are optimized for the particular environment in which they evolved. If environmental conditions are maintained, the adaptive functions do not require new sensory information. However, variation in environmental conditions typically does occur, and this calls for ongoing sensory input to optimize the functions. Even rather simple reflexes have evolved to be capable of adjusting to sensed deviations of environmental conditions. Since the reflex compensation is subject to delay and lag, by the time that reflex compensation occurs, the sensory information upon which it is based is already aging. Consequently, unless the correction is based on a prediction of the expected conditions at the time of the correction, the response will be based on outdated information. Such prediction can be observed in some reflexes. Learning provides a means by which the nervous system can retain an adjustment of functions for long-term changes of conditions such as occur during seasonal changes.

The response of the nervous system to current world conditions contributes to the physical welfare of the animal by acting through an effector that in turn modifies some relationship of the animal to that environment. These effectors may further process the nerve signals, and ultimately, they transduce them into physical responses. For example, muscle contributes more to compensation of the load encountered during a motor action than does the nervous system, so muscle is as much a computer as a physical effector.

5. All functions that have been retained by evolution presumably had direct importance to survival or were fortuitously associated with functions that did.

Most biological functions contribute to the probability that those individuals with the genetic basis for that function will survive and successfully reproduce their genes. As a matter of fact, in a continually changing environment, organisms must continually evolve just to maintain a constant level of fitness, much as Lewis Carroll has the Red Queen advise Alice that "it takes all the running you can do to keep in the same place." The overriding benefit that supports the retention of a metabolically expensive vertebrate nervous system is its contribution to adjusting the relationship of the individual to changing environmental conditions, thereby removing some of the pressure for evolutionary change. Such adjustment originates in information about the changing conditions and is completed with the modification of some action that affects the relationship of the individual to those conditions. On the other hand, many functions have no obvious survival advantage but are associated with other selected functions that do. For example, many birds will nurture anything that is within their nest, including not only their own eggs and nestlings, but also other egg-like objects and other unrelated young birds. The cuckoo takes advantage of this by laying its eggs in the nests of other birds, who then expend considerable energy as foster parents to raise the young cuckoos.

B. Problem:* Make a list of functions that appear to have no survival value of their own, but rather depend on other functions with recognizable survival value.

6. Excitability, the foundation for nervous system function, uses membrane properties, some of which evolved at the time of the transition from prokaryotic to eukaryotic cells.

Crucial to the function of nerve cells are large molecules in the cell membranes that allow the selective passage of specific (charged) ions across the membrane. Very similar molecules have been the basis of signaling since the very simplest single-celled organisms. Excitation is the process by which a cell, in response to a change of some external variable, allows a selective flux of ions across its membrane, thereby changing its internal potential. There are four important characteristics of excitation: (1) it occurs following a considerably smaller environmental change than would be necessary to damage the cell; (2) it is reversible, allowing the cell to return to its unexcited state upon cessation of the environmental change; (3) it is usually graded, with a greater magnitude when the environmental change is of greater magnitude; and (4) it always involves an exchange of energy between the environment and the excited cell, but the response exceeds the simple passive effects of the external energy. The function of sensory receptors, nerve fibers, and neurons depends on their excitability, so that, when stimulated, they generate a pattern of one or more nerve impulses that represent the stimulus pattern. Figure 1.1 presents a vastly oversimplified scheme of the transfer of information through the excitable cells of the nervous system.

Figure1.1 Simplified linear representation of the successive transduction processes and intervening transmission of information from a sensory input to an effector action.

An important advance in the understanding of nervous system function was the demonstration by Edgar Adrian and Yngve Zotterman that the signals carried by nerve fibers consist of sequences of nerve impulses that repeat at a rate proportional to the momentary signal magnitude. Although pulses are similarly used for signaling in electronic applications, the use of pulses in the nervous system involves a very different form of signaling. An impulse on a nerve fiber excites the adjacent region of that fiber to generate a new local impulse, resulting in a traveling wave that reliably moves an impulse pattern from the site of generation to the point of utilization. Similar to the electronic application of pulsatile signals, nerve fibers suppress the effect of background noise by using all-or-nothing impulses whose thresholds and amplitudes are orders of magnitude greater than the interfering noise.

In 1850 Hermann von Helmholtz demonstrated that, although nerve impulse transmission is rapid, it is sufficiently slow that its velocity could be measured in a few centimeters of nerve. Actually, the vertebrate nerve, which he used, consists of many individual fibers that conduct at different velocities, the fastest of which he measured. Except in some instances in invertebrates, those structures that we identify in dissection as nerves are bundles of 10^3 to 10^6 independent fibers. In fact, most peripheral nerves are composed of both motor and sensory fibers carrying signals simultaneously in opposite directions. When one of these fibers branches, impulses that are delivered by the parent fiber travel to the end of each division.

C. Problem: Identify a non biological process with similarities to biological excitability. Now refine the definition of excitability in such a way that it separates the two cases.

7. An individual's sensory receptors reduce ongoing information about the world to a set of about 10^9 details of magnitude. This information is then transduced into impulse signals each of which informs the nervous system about one sample of environmental conditions.

At every moment, only a small fraction of the multitude of properties of an object that might lead to excitation of a sensory receptor actually stimulates that receptor, and a particular object stimulates a different pattern of receptor activity when sensed from different perspectives. Most of the other properties of that object do not stimulate or modify the exchange of energy with any receptor. Thus, at every moment, the total input of nerve impulses from sensory receptors represents only a small part of the information about the environment. Sensory information is further modified by signals generated by neurons in the sensory transmission pathway. As nerve fibers deliver these impulse signals to synapses, the electrical impulse code is transduced into a chemical signal. Consequently, all processing of information within the nervous system is reduced to the manipulation of electrical or chemical codes. In either form, those internal signals do not directly modify the way in which the animal interacts with the world until those signals affect neurons that act on effectors, which in turn produce physical responses in the internal or external world. The fragment of information about conditions in the environment that is delivered to the nervous system originates in many different physical dimensions, but the processing of the resultant electrical and chemical signals becomes the common denominator of all nervous system functions.

8. While sensory sampling changes with the sensing perspective, objects are usually perceived as unchanging from one moment to another, producing what is called perceptual constancy.

Many of the details of the total visual input generated by a moving object change continuously, yet the object is accurately perceived as being a constant. Loosely stated, this is the nervous system's representation of the law of conservation of mass. This effect, called perceptual constancy, is involved in a variety of changing relations such as lighting, distance, occlusions, and orientation. This constancy spans even sensory modalities, so that the perception of an object is constant despite considerable variation in sensory inputs from that object. Perceptual constancy must involve learning, since infants generally fail to recognize continuity in objects once they are removed from the infant's visual field. Although the phenomenon is well documented under diverse conditions of changing stimulus, the underlying neuronal mechanism remains obscure.

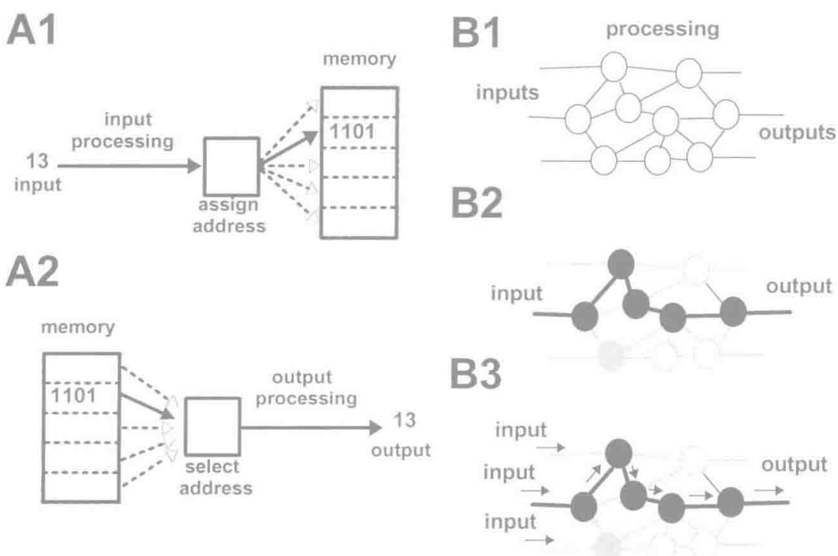

Figure 1.2 Comparison of computer (A) and biological memory (B). **A1.** Storage in a computer memory selects a specific storage register for one item of information following appropriate input processing. **A2.** Retrieval requires that the correct storage register is chosen, and then the information is extracted and processed. **B1.** A biological circuit consists of input units, processing units, output units, and interconnections. **B2.** Under appropriate conditions an input will reinforce a specific set of interconnections (including feedback elements). **B3.** At a later time, another input with some of the same characteristics as the previous input will excite the same circuit and elicit the previous output.

D. Problem:* Identify examples in which very different sensory inputs all lead to the perception of a common source object.

9. An important function of both nervous systems and electronic computers is memory, although the form of storage involved is quite different in these two cases.

In a computer, memory takes the form of a static, but exactly retrievable, representation of the signal pattern. The information stored in a computer can be retrieved repeatedly without incidental modification or it can be replaced completely. On the other hand, memory in the nervous system takes the form of a modification of the responsiveness of those structures involved in the handling of signals. Neural memories adjust future processing of signals in the pathways used by the original signal, but they do not depend on the replication of the signal itself. These memories then may be further modified by reuse of the pathway. Plasticity of the synapses in a network of synaptically interconnected neurons, which were active in the original response, may increase the probability of a new signal retracing the pathway taken by the previous excitation. Thus the network maintains a memory of past excitation. Figure 1.2 provides a very simplistic contrast of these two forms of memory. Some examples of the neural type of memory that are rather different from computer memories are: recall of many complex details of an object when presented with one detail of that object; modification of "simple" spinal reflexes in response to sensory information about the previous results of that reflex action; hypertrophy of a muscle with exercise, which results in an increase in the mechanical response to a repetition of the original motor neuron signal.

10. The mind is a function that emerges from interactions of the multiple operators of the nervous system with the influence of past and present actions of the environment.

The brain is an extremely sparsely interconnected network of 10^{14} nodes that have functionally modifiable interconnections. No individual neuron can be directly informed about the activity of more than a minuscule portion of the brain's other neurons. Thus there is no anatomical basis for the brain to operate with a monarchical organization. Instead, it is likely that the brain operates more as a commonwealth of co-operating, but separately organized, constituent operators. Neural functions often drive external processes that act back on sensory receptors, so that the overall function is in part extra-neural. Likewise, the mind is a function and not a structure and thus is not subject to the conservation of mass law that would restrict it to spatial and temporal boundaries. Functions of the mind both produce and are affected by conditions in the environment, including actions of other individuals. As emphasized by Konrad Lorenz, individuals operate in a vaguely bounded set of nested environments. For some functions, particular external links have more influence on the mind than do the internal links between brain operators. Functions usually ascribed to the mind might properly include