30 Modeling of Neurons and Neuronal Networks

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ABSTRACT Neuronal systems have been investigated at the molecular, membrane, cellular, network, and system levels, and a multitude of experimental techniques have been used at each level. Due to the complexity of neuronal systems, however, it is often impossible to account for holistic properties at any level on the basis of detailed components. The task of synthesizing all essential data into a self-consistent framework is made harder by the fact that data are often obtained from different levels and with different methodologies.

Using the cerebellum as an example, it is shown that neuronal modeling, as a conceptual representation of data, can be an effective tool to bridge these gaps, especially if the quantitative methodology is aided by computers. A computer model of the cerebellum is presented, based on current morphological and physiological data. It accounts for structurofunctional properties of single neurons (e.g., the so-called complex spike of Purkinje cells) and of the entire cerebellar cortex (e.g., gross spatial distribution and individual dynamical properties of activated cells within the structure of 1.68 million neurons). Finally, the expanded model also encompasses global cerebellar systems (e.g., fundamental characteristics of vestibulocerebellum and the cerebellar coordination of locomotion).

Introduction

NEUROSCIENCE, in its relatively short history, has amassed such a formidable body of data that unifying approaches are becoming necessary to assess the functional implications of new results. The problem is twofold. First, as the body of data grows it is increasingly difficult, due to sheer volume, to establish the relative significance of a given datum. Furthermore, it is not uncommon to have some knowledge of the overall properties of a system and some particular details of the system, with large gaps between the two sets of information. Second, because experimental observations are sometimes obtained in the absence of a general concept, their ultimate use is often quite limited. These problems threaten the continuing synthesis of experimental findings into general concepts.

It is clear that to overcome these problems a quantitative methodology is needed that can provide a self-consistent framework for the handling of complex data. One such methodology is neuronal modeling, which has become a powerful tool with the advent of computers. This has the additional merit of bridging the gap between experimentalists and theoreticians and thus promoting dialogue.

This paper will outline some aspects of neuronal modeling. Then, with the cerebellum as an example, computer modeling of individual neurons and neuronal networks will be discussed.

Outline of neuronal modeling

Although the word *model* from the Latin *modulus* (small measure) is usually taken to mean an "illustration," "prototype," or "standard," in this paper the term *neuronal model* refers to a conceptual representation of data concerning neurons or neuronal systems. If the underlying principle is hypothetical, then the model provides the methodology by which it may be determined whether the hypothesis is consistent with the available data in a systematic quantitative manner. As a body of data grows in complexity, confirmation or falsification of hypotheses becomes increasingly crucial, and thus modeling becomes an indispensable tool.

Models have three important characteristics. First, they are powerful in organizing and simplifying the body of data, since they dictate, by definition, the class of data to be included. Second, modeling is an important heuristic tool that helps us gain insight into how the data are related to underlying concepts. Such insights and the deeper understanding that the modeling yields often lead to new hypotheses. Third, properly designed models are predictive, that is, they reveal previously unseen conclusions that are often testable experimentally.

Neuronal modeling is used in neurobiology as well

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as in artificial-intelligence research, but it is used for different purposes in each discipline. In artificial intelligence the aim is the design of machines capable of performing particular brainlike functions, even though their working principle may be totally different from that of brain. Consequently the role of neuronal modeling in artificial intelligence is limited to the representation of data that fit into a scheme (often biologically unrealistic) of a particular brain function such as pattern recognition.

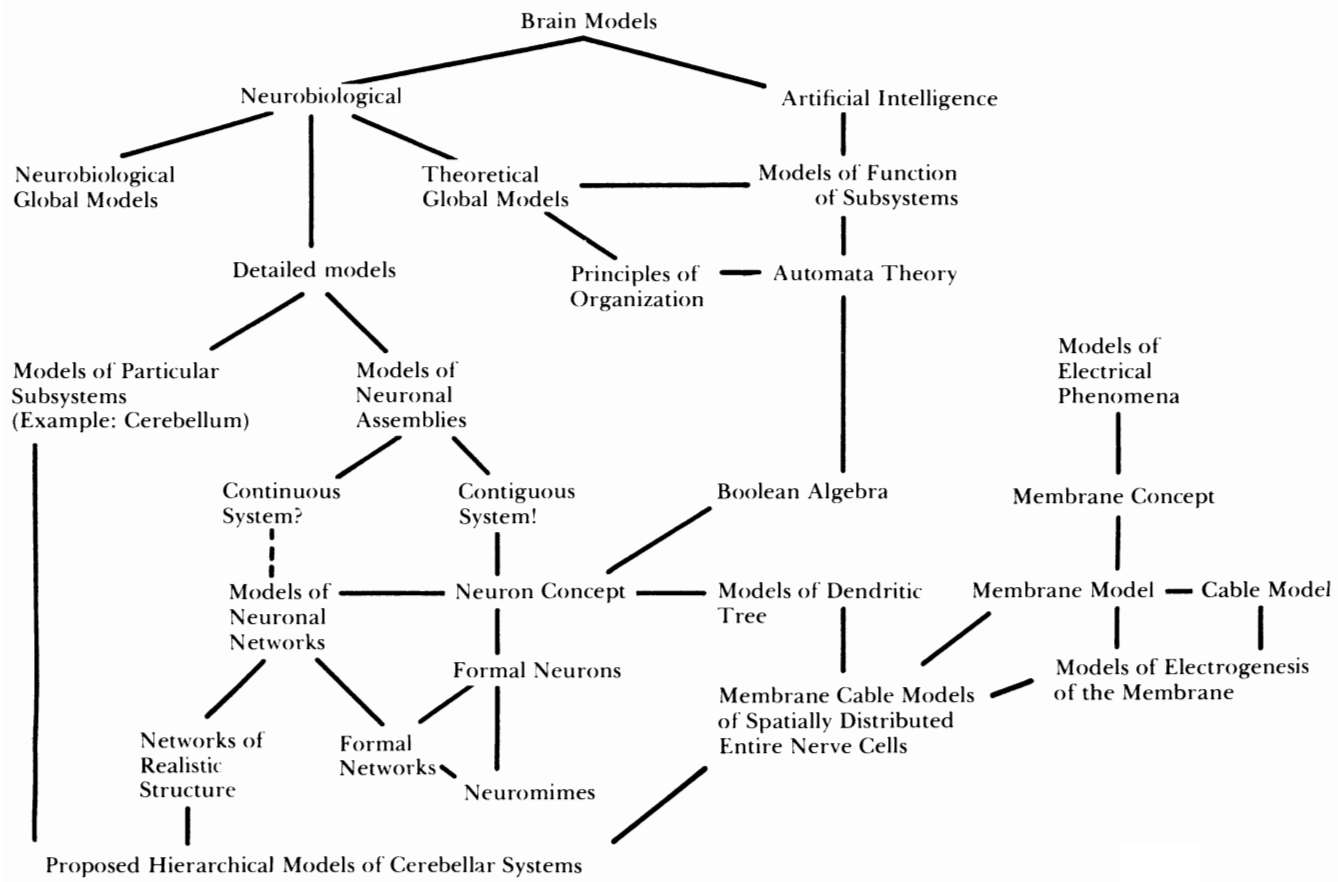
In contrast, neurobiology seeks to understand how the nervous system itself works. Since there can be no a priori decision concerning which particular function or functional unit is the key to understanding the basic principles of its operation, neuroscience adopted an all-out strategy: the nervous system has been studied stimultaneously at *all* levels of complexity and by *all* available experimental techniques. As a result, the body of available data is as unwieldy as its interpretation is diverse. In neurobiology, modeling should therefore serve as a tool for synthesis. This crystallization of data starts at several points simultaneously, by a cementing together of smaller groups of experimental evidence. Accordingly, neuronal modeling has developed along several lines that were at times independent of one another, and at times quite intertwined. The main evolutionary lines in neuronal modeling are illustrated in Table I. A rough chronology also gives perspective, although sometimes a digression in time may be necessary to reconstruct a particular line of models from its conception.

For the early history of neuronal modeling the reader is referred to the excellent reviews of Harmon and Lewis (1966) and Cole (1972). Modern neuronal modeling stems from three roots: efforts were made (1) to interpret the nervous electrical phenomena, (2) to abstract the principles of functional organization of neuronal assemblies, and (3) to relate morphology to function in the central nervous system.

Electrophysiology began its development with Helmholtz (1853), who realized that some fundamental electrical properties of the nerve, such as its slow conduction velocity, could not be interpreted in terms

TABLE I

Main evolutionary lines in the modeling of neurons and neuronal networks.



of the electrical properties of known conductors. Equally important was Bernstein's hypothesis that neurons are encompassed by a membrane that governs the different ionic milieus across the cell (Bernstein, 1902).

Although "global" concepts for brain function such as the reflex-schools of Sherrington (1906) and Pavlov (1927) gave great impetus to neurobiology, only recently has this kind of global approach been developed into a theoretical model of the organization of the brain. The best-known examples of these efforts are those of Ashby (1952), Young (1964), and, in a different light, von Neumann (1959), who pointed out the fundamental differences between brains and computers. Von Neumann's essay had a most salutory effect since the prevailing neuron model gave a misleading impression that the two systems (computers and brains) had a common basis in Boolean algebra (see below).

The idea that the morphology of neuronal assemblies reflects their function prompted a "mapping" of circuitries, resulting in a vast amount of detail (see Ramón y Cajal, 1911). The pursuit of the meaning of neuronal form not only diversified the body of data but also led to controversies. For example, did the neuronal assemblies constitute a continuous net or a set of contiguous units? This question was first answered with the help of light-microscopic methods, and the consequent neuron concept blossomed in the classical work of Ramón y Cajal (1911). Final consolidation of the neuron doctrine was later achieved with the help of electron-microscopic techniques (see Szentágothai, 1975).

Another open question was whether understanding the properties of single neurons and neuronal networks was a sequential task. One may contend that in order to understand circuits, the function of their elements must first be known. Then again, it may be impossible to understand the properties of elements without first knowing the principles by which they are organized into networks. Neurobiologists adopted the only practical strategy—simultaneous exploration of both the properties of networks and single neurons. As a result, neuronal modeling has been plagued by an obvious ambivalence, pursuing networks and single neurons, sometimes separately, sometimes jointly, with varying degrees of emphasis on one or the other. [Recently new considerations have influenced this matter: (1) Results showing that assemblies of neurons can be directly affected through the interneuronal ionic medium (see Nicholson, this volume) lessen the emphasis on the axonal "wiring" among neurons of a network. (2) The dominance of axonal wiring in the organization of a circuit is seriously brought into question by the existence of dendritic interactions via local circuit neurons (see Shepherd, this volume).]

Abstract Functional Models: Formal Neurons

Once the neuron doctrine was accepted, the morphological investigation of different kinds of neurons and neuronal networks rapidly became a major field of research. From a functional viewpoint, the mechanisms underlying the working of single neurons was tackled rather early. McCulloch and Pitts (1943) proposed the so-called formal-neuron model, which equates a neuron to a decision-making unit that performs logical threshold functions on its inputs and, as a result, generates a binary output. Boolean algebra was thus applicable to formal neurons, so that the function of even networks of neurons could be handled, although the structures of the circuits studied were largely arbitrary. The formal-neuron model was of interest because it linked single neurons to neuronal networks, but the main reason for the popularity of the McCulloch-Pitts view was that it tied brain theories to the rapidly developing field of computer science. By equating neurons to electronic flip-flops and neuronal networks to finite-state automata and to computers, the misconception was established that the success by brain research and that of computer science were directly coupled. In spite of the disillusionment of von Neumann (1959), the field of formal-neuron modeling expanded rapidly, and some of its adherents are still to be found making analogies between computers and brains or representing a single neuron as a set of several decision-making elements.

Formal-neuron modeling diverged in three directions. One direction was the exploration of events occurring in arbitrary neuronal nets. Discrete computer models of networks by Rochester et al. (1956) and Farley and Clarke (1961) and continuous mathematical models by Beurle (1956) are prominent examples of this approach. Boolean algebra provided a second avenue for handling assemblies of formal neurons and interpreting their potential function. This theoretical approach overlapped with abstract automata theory (and this field therefore linked neuronal modeling to artificial intelligence and to computer science). The works of Turing (1950), Kleene (1956), Uttley (1959), Arbib (1969), and the school of Caianello (1968) are typical of this approach (see also Griffith, 1971, and Reiss, 1964). The third approach was the physical representation of highly simplified neurons by small electrical circuits (so-called neuro-

mimes: see Harmon, 1959; McGrogan, 1961; Jenik, 1962; Lewis, 1964). Although this approach received a great impetus from the widespread acceptance of the McCulloch-Pitts concept, it is actually rooted in an idea of Schmitt (1937), who created the binary-output electrical circuit that realizes threshold function (the Schmitt trigger).

These artificial neurons were meant to be used for analysis of the salient properties of simple networks. For example, this approach was combined with a simple arrangement of spinal motoneurons to provide a cyclic firing pattern similar to the spinal pattern generator for locomotion in *Urodela* (Székely, 1965) and led to the use of mathematical methods to describe abstract properties of cyclic nets of formal neurons (Ádám, 1968). This latter approach represented a departure from arbitrary networks of highly simplified neurons and moved toward a more realistic representation of neuronal activity. Moving in the opposite direction (toward abstraction via automata theory), the formal-neuron concept was implicitly utilized to interpret the overall function of subsystems of the nervous system (Rosenblatt, 1962).

DIVERSITY IN MODELING: CEREBELLAR MODELS Research on the cerebellum can be divided into two main lines. The first seeks a theoretical explanation of overall function based on a single hypothesis with little concern for other functional details. One example is the model of Braitenberg (1961), which suggests that the cerebellar cortex is a timing device that utilizes the delays provided by the conduction time in parallel fibers. Another example shows rather clearly how an abstract idea can develop into a "theory": The hypothesis of modifiable synapses by Hebb (1949) was gradually turned into a theory for motor learning in the cerebellum (Brindley, 1964) and was further elaborated by Marr (1969) and Albus (1971) but failed to gain experimental support (see Eccles, 1973).

The second line provides a complementary approach: the generation of realistic models of detailed functioning. These phenomenological models can be further grouped into two categories according to whether they bypass or follow the neuron concept. If the representation of single neurons is bypassed in a cerebellar model, the system can be significantly simplified and treated linearly (Calvert and Meno, 1972). Similarly it may be viewed from a system-theoretical point of view without taking into consideration details of cerebellar structure and function (Arbib, Franklin, and Nilsson, 1968). Other approaches treat larger assemblies of neurons as units (Mortimer, 1970) or emphasize the dynamics of the operation of circuitry (Boylls, 1975). In the second category of phenomenological models, the integral components of neural assemblies are single neurons. As mentioned before, neuronal networks have proved not to be continuous in structure. Still the idea held that the structure of the networks bears direct relevance to their function. In the special case of the cerebellum, this structuro-functional approach to neuronal networks was firmly established by Szentágothai (1963, 1968, 1975). The idea of deducing the basic functional properties of a system from morphological structure required systematic quantitative morphological models of circuitry (Palkovits, Magyar, and Szentágothai, 1971a,b,c, 1972). On this basis, phenomenological models containing McCulloch-Pitts-type neurons were constructed (Pellionisz, 1970). Later single units featuring some aspects of dendritic neuronal models were used (Pellionisz and Szentágothai, 1973, 1974). A similar approach to cerebellar modeling has been used by Mittenthal (1974).

The above approach has been applied to the visual cortex by von der Malsburg (1973). A review of current conceptual models of neuronal organizations (including the cerebellum) is provided by Szentágothai and Arbib (1974).

MODELING OF NEURONAL ELECTRICAL PHENOMENA The first significant theories developed to explain electrophysiological phenomena focused on the role of the cellular membrane and were based on the concepts of Bernstein (1902). Rashevsky (1933) and Hill (1936) used differential equations to develop an empirical description of the membrane potential in an active nerve, based on the idea that two opposing forces lie behind the dynamism of the rising and falling phases of an action potential. The pursuit of the phenomena underlying the genesis of action potential was greatly advanced by the development of sophisticated electrophysiological techniques, especially the powerful method of voltage clamping (see reviews by Katz, 1966, and Cole, 1972).

Probably the single most important development in the modeling of neuronal electrical phenomena was that of Hodgkin and Huxley (1952). They provided an empirical description of the electrogenesis of regenerative membrane discharge. In this model, the constants for a set of differential equations were established by fitting theoretical curves to the data obtained by voltage clamping the squid giant axon. This model is based on the notion that the sodium and potassium ion channels of the membrane have a time- and voltage-dependent permeability. That is,

the dynamics of the permeability is responsible for the characteristic shape of the observed action potentials. The strength of this model is that it is a quantitative elaboration of Bernstein's ionic membrane theory. Thus the solution of the Hodgkin-Huxley equations could be related directly to a variety of electrophysiological recordings. The predictive power of the model has provided a stimulus for a vast array of investigations (for reviews see Cole, 1972; Adelman, 1971; Jack, Noble, and Tsien, 1975).

Despite its obvious strengths, the model has several conceptual limitations. For example, the only question the Hodgkin-Huxley model asks is, "How does the dynamics of ion permeabilities explain the shape of the active membrane potential?" Also, the relevance of the original model was limited to a spatially homogeneous segment of an axon.

The Hodgkin-Huxley model has proven to be very flexible since it was formulated a quarter of a century ago. For example, the parameters of equations have been adapted to preparations other than the squid giant axon (for the sciatic nerve of frog see Frankenhaeuser and Huxley, 1964).

The differential equations made the quantitative handling of the Hodgkin-Huxley model cumbersome before the advent of digital computers. In fact, digital computers were probably the most important determinant in the widespread applications of this model (FitzHugh, 1955; FitzHugh and Antosiewicz, 1959; Cooley and Dodge, 1966; Adelman and Fitzhugh, 1975). As stated above, by combining the original Hodgkin-Huxley equations with the cable equations, (which were originally applied to transatlantic telegraph lines by Lord Kelvin (1855) and then to excitable cells by Weber (1873), the Hodgkin-Huxley model is capable of explaining spatially distributed electrical phenomena. This allows mathematical treatment of the propagation of a spike along the axon (Joyner, Moore, and Ramon, 1975; Hardy, 1973). Recent techniques permit the computation of action-potential propagation even along spatially inhomogeneous axons (see Parnas, this volume).

The differences between the fully developed formal-neuron models and the Hodgkin-Huxley cable models are clear. Formal-neuron models address themselves to the ultimate function of neurons. The Hodgkin-Huxley model is concerned with the precise description of the shape of the output signal. It follows from this fundamental difference that for formal-neuron models the "wiring" of axonal connections is crucial, whereas for the Hodgkin-Huxley model only the membrane properties of the axon are important.

Such basic theoretical questions as the nature of neuronal coding or of neuronal information processing are not directly addressed by the Hodgkin-Huxley model, but they are amenable to study by successors of formal-neuron models (von Neumann, 1956; Perkel, 1970; Bullock, 1970). As for neuronal integration, formal neurons provided a simple abstraction stating that integration is a threshold function. The unsatisfactory character of such a solution to this basic question became increasingly evident through the years as a result of morphological and electrophysiological findings and theoretical studies. If nothing else, the impressive polymorphic appearance of dendritic trees made a simple threshold function unlikely, even from a teleological point of view. Further, detailed studies of the electroresponsiveness of dendritic trees strongly suggested that the concept of neurons being simple decision-making units was at best an oversimplification (see Llinás and Nicholson, 1971).

The question of how synaptic inputs arriving at various locations on a passive dendritic tree might propagate electrotonically to the soma has been studied in great detail by Rall (1959, 1962, 1964; for review see Rall, 1977). The idealization of dendritic trees into uniform equivalent cylinders simplified the analysis of the contribution of dispersed inputs to the passive steady-state membrane potential in the dendrites. Although this technique provided an excellent approach to relating dendritic electrotonic phenomena to cable properties (Calvin, 1969; for review see Jack, Noble, and Tsien, 1975), it was only recently combined with the Hodgkin-Huxley equations to model a motoneuron (Dodge and Cooley, 1973). This modeling technique was carried one step further in order to treat neurons with complex morphologies. This was accomplished through multicompartmental Hodgkin-Huxley cable models in which each spatial compartment quantitatively represents both the particular structural properties of the neuron and the electrical parameters of its membrane. The model incorporated functional inhomogeneities throughout the entire neuron. Such a mathematical model (Pellionisz and Llinás, 1975, 1977a) was shown to be capable of synthesizing a single-unit morphology with detailed electrophysiological findings and of providing a means for the analysis of complex membrane properties, such as the role of multiple sites of spike initiation in the integrative properties of single neurons. A similar model for the motoneuron was recently developed by Traub and Llinás (1978), and by Dodge (this volume).

It is conceivable that by including the dynamics of

calcium ion membrane conductance in the Hodgkin-Huxley model (see Llinás, this volume), it will become possible to analyze the role played by calcium currents in the integrative properties (and eventually in the neuronal coding mechanism) of nerve cells.

Neuronal modeling in cerebellar research

The most striking feature of diversity of cerebellar research is the multitude of simultaneous levels of approach. This is due in part to the limits of applicability of the various methods. For example, electron-microscopic techniques are most suitable for studying spatial relationships between synaptic structures, while microelectrode techniques are well suited to single-unit analysis. The pluralistic approach is also a result of the divergent basic considerations that guide this research. For example, the network approach led to investigations of neuronal assemblies, while the membrane theory stressed the importance of investigations at the membrane level.

In this section, cerebellar research will be used as an example of the role of modeling in bringing apparently divergent data together. It will be shown that within a hierarchy of complexities on several levels there are data available concerning both the details of the machinery and the overall properties that emerge from the details. Still, the complexity of the unit under investigation masks the relationship between the parts and the whole. By creating a common basis, a model allows the data to be synthesized and allows us to establish how the complex system is more than the simple sum of its components.

Modeling Single Cerebellar Neurons

As in other areas of neurobiology, the main thrust of cerebellar research is at the level of single cells. These investigations are especially fruitful because at this level there is a convergence of several basic considerations: (1) neuronal form reflects function; (2) the neuron is the unit of activity; and (3) networks of single cells should be studied from a structurofunctional viewpoint. Further, several experimental methods, including light and electron microscopy and intra- and extracellular electrophysiology, are applicable at single-neuron level.

This section presents a computer model of the Purkinje cell (Pellionisz and Llinás, 1975, 1977a). The goal of this model is to account for the functional properties of the total neuron from its morphological and functional details. This will enable us to synthesize electrophysiological recordings (which reflect the electrogenesis of the whole, spatially distributed cell) from details of morphological structure and membrane properties. Explanations will thus be given for different characteristic intracellular recordings, such as the hitherto ambiguously interpreted "complex spike" of Purkinje cells.

Why should we concentrate our efforts on this particular type of neuron of the cerebellar cortex? There are two reasons. First, the cerebellar cortex is of special interest because it is morphologically unique. Its regular, almost crystalline cytoarchitecture is constructed from only a handful of types of neurons. It has but two input systems: the mossy-fiber/granule-cell/parallel-fiber path and the climbing-fiber input. These afferents converge on the only output elements, the Purkinje cells (for details see Eccles, Ito, and Szentágothai, 1967; Llinás, 1969; Palay and Chan-Palay, 1974). Moreover, it apparently lacks internal loops that could perpetuate reverberations; the interneuron systems (comprised of Golgi, basket, and stellate cells) are not only entirely inhibitory but are a superposition onto the so-called "basic circuit" of lower species such as amphibians (see Llinás, 1969).

Second, the single Purkinje cell is a center of interest because (1) it is the sole output neuron, (2) the two input systems converge on it, and (3) the convergence is extreme (as many as 400,000 parallel fibers may contact one Purkinje cell in the cat: see Palkovits, Magyar, and Szentágothai 1971a). On the other hand, there is one and only one climbing fiber per Purkinje cell, but they form a large number of contacts (in frog, 200–300 synapses; see Hillman, 1969a). Finally, (4) the Purkinje cell is remarkable in both its size and its anisotropic dimensions: it has an almost planar dendritic tree (measuring about 250 × 250 × 8 microns; see Figure 5A).

There is a wealth of morphological data available for cerebellar Purkinje cells (see Hillman, 1969a; Llinás, 1969). Moreover, using quantitative three-dimensional stereological methods (especially computer-aided methods) the morphological features of this cell can be established to an unprecedented degree of precision and completeness (Hillman, Chujo, and Llinás, 1974; Somogyi and Hámori, 1976).

The details of the generation of electrical signals in this cell are also well understood, especially since all of our basic knowledge of membranes (the Hodgkin-Huxley model, cable theory, and methods for modeling electrotonic signal propagation) should be applicable to this kind of neuron. In addition to a wealth of morphological and physiological details concerning the machinery of the Purkinje cell, considerable information is available on the overall properties emerging from the entire cell. This latter

knowledge is provided largely through single-unit electrophysiology, for which the Purkinje cell is an ideal target since it has a large soma (about 15 μm in diameter even in the frog: Hillman, 1969a) and it can be activated in three distinctly different ways: (1) orthodromically by parallel fibers, both naturally and by artificial electrical stimulation (Eccles, Llinás, and Sasaki, 1966a), (2) antidromically by artificially evoking a backward invasion of the neuron via stimulation of the outgoing axon in the white matter of the cerebellar cortex (Llinás, Bloedel, and Roberts, 1969), and (3) orthodromically by the climbing fiber of the Purkinje cell (Eccles, Llinás, and Sasaki, 1966b; Martinez, Crill, and Kennedy, 1971). While all three activations result in markedly different waveforms of the action potential, the climbing-fiber-evoked response (CFR) stands out with its complicated pattern of wavelets; it is appropriately called a "complex spike" (see Figure 5).

Details and overall properties of the Purkinje cell are shown in Figure 1. An intracellular recording of an antidromically evoked spike in frog cerebellum is shown in Figure 1B. Coupling the information available on both the structural and functional details (electroresponsive properties of membrane) would, in theory, allow one to account directly for such overall properties as the characteristic waveform of antidromic response (note the prolonged afterdepolarization in Figure 1B). However, the complexity of even one cell is too great to be penetrated by intuitive reasoning. Therefore, while such a rather simple response as the antidromically evoked action-potential waveform can be speculated about with relative ease and with some confidence, for the interpretation of more complex phenomena such as the climbing-fiber response of Purkinje cells, a systematic methodology is needed. Elaborating such a technique for Purkinje cells offers an advantageous opportunity since the threefold challenge of markedly different responses to parallel-fiber-evoked orthodromic, artificial antidromic, and climbing-fiber-evoked orthodromic stimulations provides a reasonable guarantee that if the model produces all these different responses accurately, then it must represent the Purkinje cell realistically.

In order to synthesize the morphological, membrane biophysical, and electrophysiological data into a meaningful whole, a model of the Purkinje cell was developed (Pellionisz and Llinás, 1975, 1977a; see Figure 2). This model combines the Hodgkin-Huxley membrane model and cable theory with the electrotonic propagation of dendritic signals. Specifically, morphological knowledge of a particular dendritic

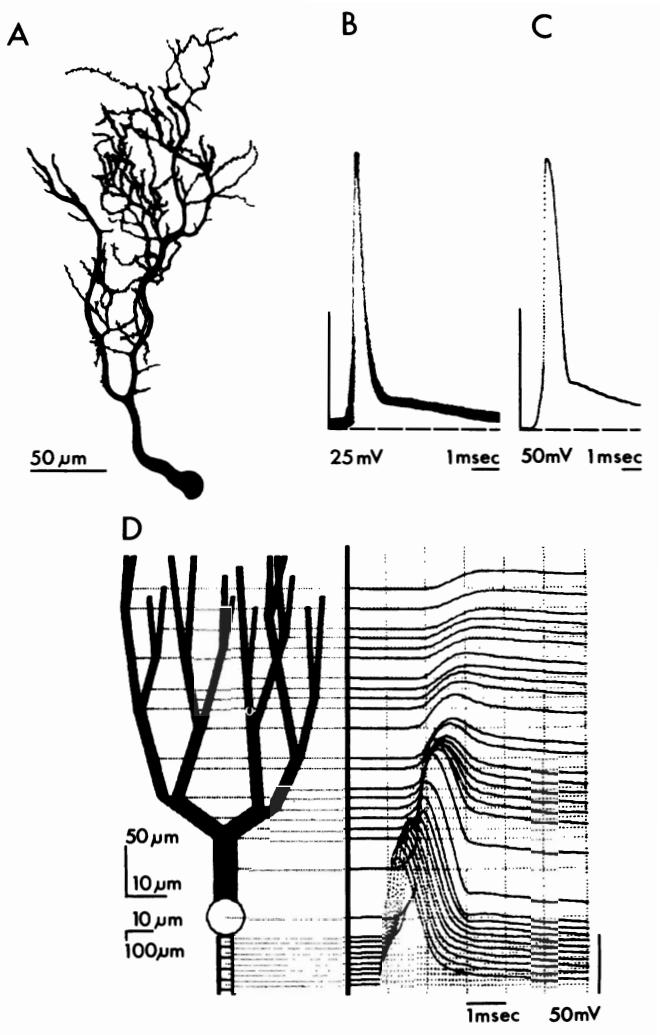


FIGURE 1 Structurofunctional model of the Purkinje cell. A: Golgi-impregnated Purkinje cell of the frog (after Hillman, 1969a). B: Intracellular recording of the Purkinje cell response to antidromic stimulation (courtesy of Llinás and Sugimori). C: Comparable output of the computer model: somatic membrane potential response to antidromic stimulation (from D). D: Computer model synthesizing morphological and electrophysiological data to provide an explanation for the electrogenesis of antidromic response throughout the model Purkinje cell. To the left is the model neuron composed of 62 compartments with individual morphological and physiological variables. All dendritic compartments are passive. To the right are the membrane potential waveforms at different compartments. (From Pellionisz and Llinás, 1975, 1977a.)

tree and the somatoaxonal area is merged with electrophysiological data. The model directly relates the two sets of information and could provide the needed explanation for the waveform of the antidromically evoked action potential (as shown in Figure 1C, D). An outline of this modeling method is given below.

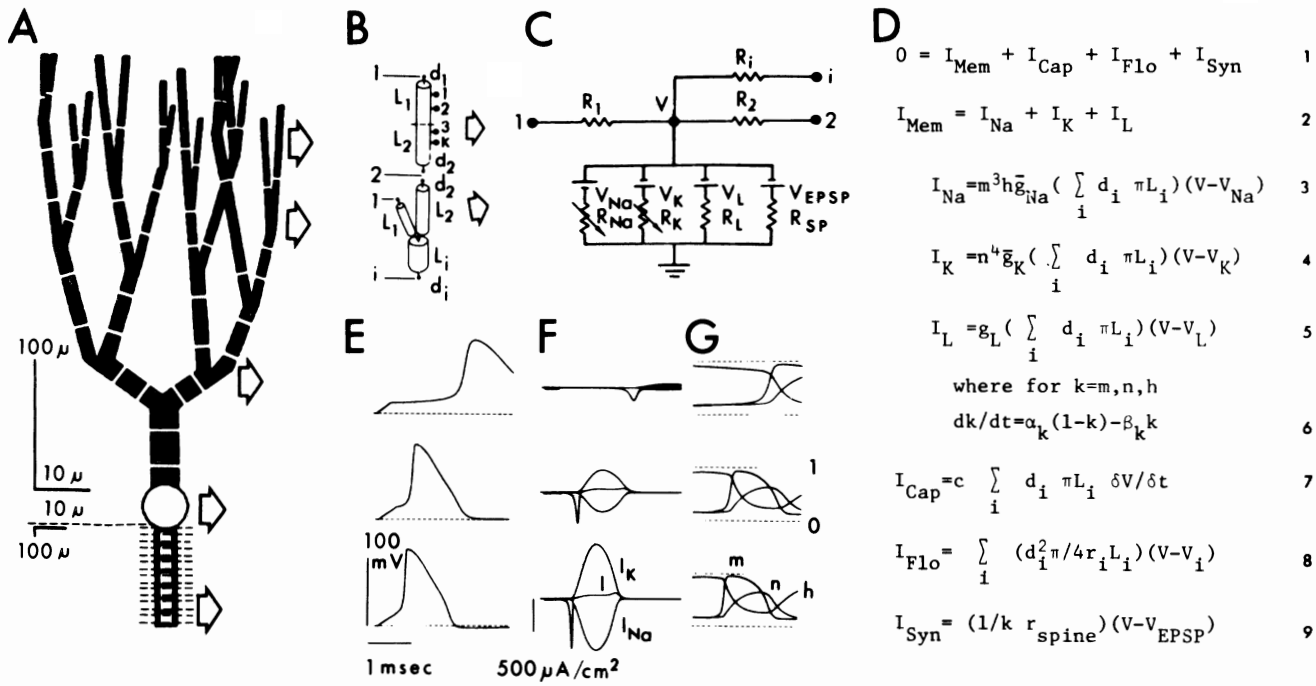


FIGURE 2 Scheme of the model of Purkinje cell with particular setting of structural and functional parameters of each compartment. A: Structure of compartmentalization (62 compartments: 31 dendritic branches, 15 bifurcation points, soma, initial segment, and 7 nodes with 7 myelinated segments). B: Single compartment with individual values for length (L_i) and diameter (d_i). C: Equivalent circuit for one compartment. All functional parameters (including Na and K excitability) are individually set. D: Equations governing the membrane electrogenesis for each compartment. The membrane potential (V) is determined by four currents: transmembrane (eq. 2; as described by the Hodgkin-Huxley equations 3–6), capacitive (eq. 7), longitudinal (eq. 8), and synaptic (eq. 9). E–G: Solutions by numerical integration of the Hodgkin-Huxley equations (as a function of time following a brief current injection) for three compartments. *Upper row*: Dendritic branching (low excitability). *Middle row*: Soma. *Lower row*: Node of Ranvier (high excitability). E: Membrane potential. F: Transmembrane currents. G: Hodgkin-Huxley *m*, *n*, *h* variables. (After Pellionisz and Llinás, 1975, 1977a.)

In this approach the entire neuron (dendritic tree, soma, initial segment, and axon) is constructed of cylindrical segments of specific lengths and diameters. The ability to assign values to each segment individually is especially important because the abstraction of real dendritic trees into equivalent cylinders is permitted only for trees following the 3/2 constraint of branching power (Rall, 1959, 1962, 1964); apparently, Purkinje cells do not obey this rule (Hillman, this volume). Another important advantage of modeling particular cells is that the electrical properties of each compartment are also determined individually. Therefore, each compartment can be set to conform electrically with either a passive (resistor-capacitor) or an active equivalent circuit (with individualized setting of Hodgkin-Huxley excitability parameters). In this way the model can be used to investigate the functional implications of a partially or totally active dendritic tree, even one that elicits dendritic spikes (Purpura, 1967; Nicholson and Llinás, 1971; Czéh, 1972; Llinás and Hess, 1976).

In modeling the antidromically evoked response of Purkinje cell the dendritic compartments were initially assumed to be passive resistor-capacitor cables. Application of a brief (<0.05 msec) current injection of 10 nA to the lowermost axonal compartment evoked an antidromically propagated axonal spike and a response at the soma level comparable to electrophysiological recordings (Figure 1B, C). The display of the intracellular voltage across the different dendritic segments reveals a rapid reduction of membrane potential with distance from the soma. For dendritic trees, reduced to equivalent cylinders, the attenuation of the electrotonic invasion in response to a given spike waveform could also be described by the theory of passive cables (see Jack, this volume). This attenuation in the Purkinje-cell dendritic tree is in good agreement with conclusions drawn from

field-potential analysis (Llinás, Bloedel, and Roberts, 1969; Freeman and Nicholson, 1975).

Orthodromic activation of Purkinje cells by parallel-fiber stimulation via surface electrodes has been thoroughly investigated (Eccles, Llinás, and Sasaki, 1966a), and theoretical consideration has also been given to the possible implications of differences in integration as a result of different spatial patterns of parallel-fiber input (Llinás, 1970). This type of Purkinje-cell activity was modeled by current injections into dendritic spines distributed over the dendritic arborization (Pellionisz and Llinás, 1975, 1977a; see Figure 2B).

Spatially different orthodromic activations, assuming a passive dendritic tree, are modeled as shown in Figure 3. If the tree is stimulated through parallel fibers in a horizontal strip along the uppermost dendritic branches via a brief (0.5 msec) current pulse, the depolarization propagates electrotonically in much the same way as expected from Rall's studies (1964), and the stimulus remains subthreshold (Figure 3B). However, if the current injection is applied 0.05 msec longer, then after a delay of 2 msec a spike is generated which propagates along the axon and produces an attenuated electrotonic invasion of the upper dendrites.

By comparison, vertical application of a synaptic input of equal strength and duration as in Figure 3C results in a markedly different response (Figure 3D, E). Thus vertical integration produces an amply suprathreshold depolarization, resulting in a short "burst" of two propagating spikes.

Beyond the analysis of passive cable properties of particular arborizations, this model also yields a powerful method with which to explore effects of different variables of the machinery on the overall electrogenesis. Perhaps its most important use is in analyzing the significance of partially active dendritic trees in the integrative properties of the whole cell. This work has just begun for the Purkinje cell (Pellionisz and Llinás, 1975) and motoneurons (Traub and Llinás, 1978; Dodge, this volume). Since in the model presented here all structural and functional properties of the compartments are set individually, it is easy to experiment with "mosaic patterns" of ion permeabilities over the dendrites.

Orthodromic activation of the Purkinje-cell model, capable of firing dendritic spikes, is studied in close connection with electrophysiological recordings (Llinás, this volume). In the case shown in Figure 4, the branching compartments of the tree were considered active; sodium and potassium conductance values

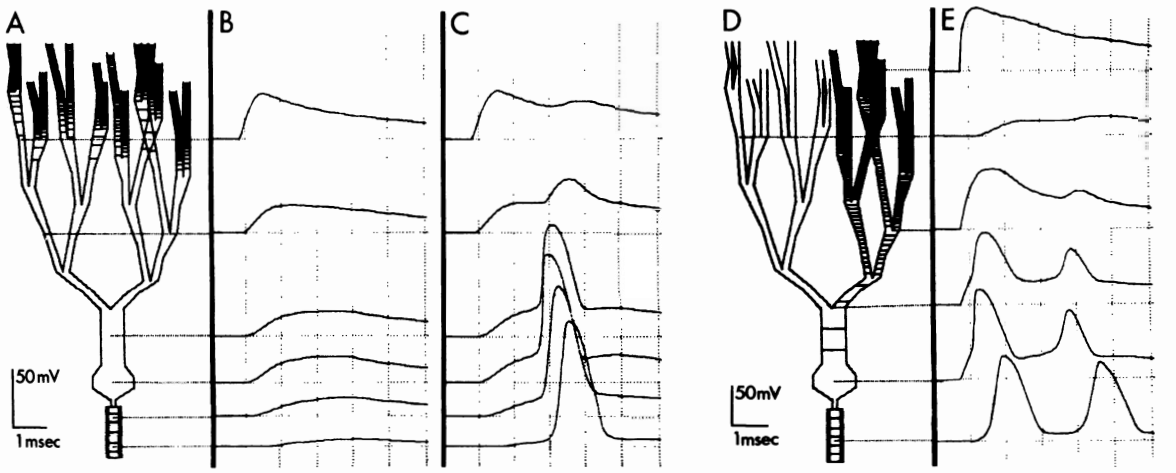


FIGURE 3 Numerical solutions for membrane potential responses to spatially different orthodromic stimulation in a passive dendritic tree (after Pellionisz and Llinás, 1975, 1977a). A: Orthodromic activation of the model Purkinje cell by injecting a square pulse of synaptic current into the uppermost dendritic branches. Hatching is proportional to the depolarization at 0.5 msec after the onset of input. B: Five representative recordings from the computed responses of 62 compartments. The current pulse is just subthreshold; therefore the dendritic compartments show only a passive electrotonic propagation of the depolarization, and no spike is generated at the soma. C: Same as B, but the stimulus is suprathreshold. D: Model of vertical integration. Synaptic current pulse (identical in overall strength and duration to the case in C) was applied to the right half of the dendritic tree. The hatching shows the membrane depolarization computed at 3.0 msec. Note that in case of vertical integration the input evokes a burst of two spikes starting at only 0.3 msec latency. The somatic action potentials electrotonically invade the left side of dendritic tree, which was not stimulated by current injection.

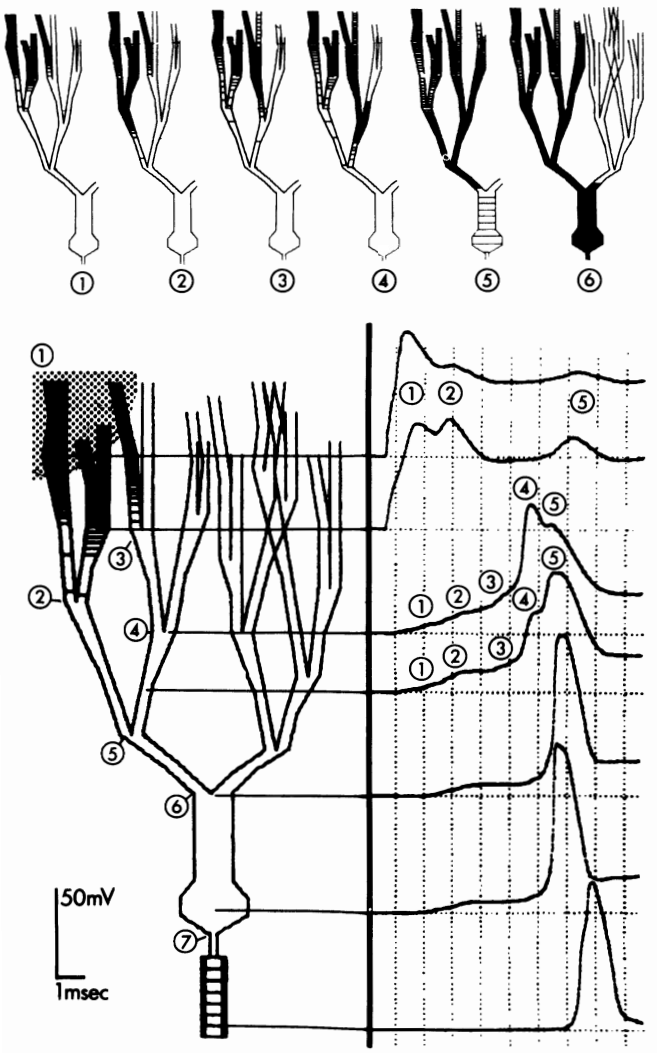


FIGURE 4 Numerical solution of orthodromically evoked action potential in a Purkinje-cell model capable of firing dendritic spikes. Dendritic branching compartments are active. Upper row of schematic dendritic trees provides a phase diagram of the sequence of dendritic spikes. (Hatching is proportional to the computed membrane depolarizations.) Lower part of the figure is a spatiotemporal display of the computed response. To the left, the spatial scheme of the Purkinje cell is shown. The dendritic tree was stimulated by synaptic current injection at the dotted area. This triggers a sequence of the firing of bifurcation zones (follow the numbering). To the right, a temporal display is given of seven representative membrane potential waveforms of the computed responses of 62 compartments.

were 10–30% of those of the initial segment and decreased with the distance between the soma and branching compartment. Also, a higher longitudinal resistance of the dendritic branches was assumed (the branching power was taken as 2.0; see Hillman, this volume). For other details see the model in Pellionisz and Llinás (1977a). A brief (<0.3 msec) current pulse was applied to the upper dendritic branches at the left (see dotted area in Figure 4) and evoked dendritic spikes at the uppermost branching regions. The sequence of six dendritic spikes and the seventh firing (of the soma) can be followed by the numbering in Figure 4. Dendritic spikes 1 and 2 produce a prolonged depolarization at somatic level but do not bring it to firing. However, the even weaker corollary stimulation of the neighboring branch (at 3) triggers another sequence (3 and 4) which provides a late contribution to the somatic depolarization. Thus a propagated firing emerges (5, 6, and 7). At midlevel of the dendritic tree the ortho- and antidromically propagating dendritic and generalized spikes produce a characteristic cascaded waveform of membrane potential (see, e.g., 4 in Figure 4; see also Llinás, this volume).

The most stringent test of the accuracy of the Purkinje-cell model is that it ought to yield not only realistic antidromic and orthodromic responses but also the complicated, but still highly stereotyped, "complex-spike" response (or CFR). This response is evoked by the climbing fiber that injects currents through its numerous synapses over most of the dendritic tree of the Purkinje cell (see the classical figure of Ramón y Cajal, reproduced in Figure 5A). The overall response of the whole neuron to this massive electrotonic event is known by intracellular recordings from several different preparations (see Figure 5B, C). Precisely because the entire neuron is involved in this response, however, speculations as to how this characteristic waveform is generated have remained obscure and ambiguous. Two basic and equally compelling suggestions were that the wavelets in CFR emerge either from the dendrites or from the axon (Eccles, Llinás, and Sasaki, 1966b; Martinez, Crill, and Kennedy, 1971). A clarification of this point was required, not only to resolve this dilemma, but also because it was expected that a deeper understanding of the electrogenesis of CFR could provide important insights into the operation of the cerebellar cortex itself.

First, using an entirely passive dendritic tree, it was asked whether the model would yield a realistic CFR without including the possibility of dendritic spikes. As shown in Figure 5D, E, the output of the model to brief but massive current injection into the dendrites (which simulates climbing-fiber activation) is comparable to the electrophysiological recordings. Note that not only is the overall pattern of the prolonged waveform reproduced, but the intriguing double twin wavelets are also present.

It is noteworthy that, at least in this particular case, by putting already known details into the model we can generate information that was not known before; that is, we can determine where the multiple wavelets are generated. From Figure 5E it is apparent that the twin wavelets recorded at the soma are generated by the repetitive firing of the axon initial segment. Figure 5E also suggests that the repetitive firing of the initial segment is caused by a basically rather simple chain of events: The climbing-fiber synapses inject a large amount of current into the entire dendritic tree, resulting in a virtually homogeneous, massive depolarization. Repolarization of the dendritic compartments is impeded because the neighboring compartments, being similarly depolarized, cannot drain charges away rapidly enough. Repolarization therefore depends largely on the leakiness of the dendritic cable. During this prolonged process the highly active somatic and axonal compartments not only repolarize, but fire repetitively.

Some corollary results of the modeling of CFR are also worth mentioning. First, it was considered a promising initial result that the model could reproduce a CFR with a passive dendritic tree. The next problem was to determine how robust this response was, that is, to establish if the characteristic waveform was consistent with a partially active dendritic tree. Using the active dendritic tree shown in Figure 4, the repolarization of dendrities during CFR was faster, but the active compartments at branching points boosted the repeated action of the initial segment. As a result of these balancing differences, the pattern of CFR was remarkably retained. (The main difference was that because of the increased firing rate the last two spikes of the initial segment merged into one propagated spike. This may explain the variation in propagating spikes of a CFR found by Ito and Simpson (1971).) The studies described above suggest that the proven existence of dendritic spikes in Purkinje cells of several species is immaterial, as regards the CFR waveform.

Second, the robustness of modeled CFR to other variations of structural and functional parameters was also found satisfactory. For example, it was demonstrated that, in very good agreement with electrophysiological recordings (Llinás and Volkind, 1972;

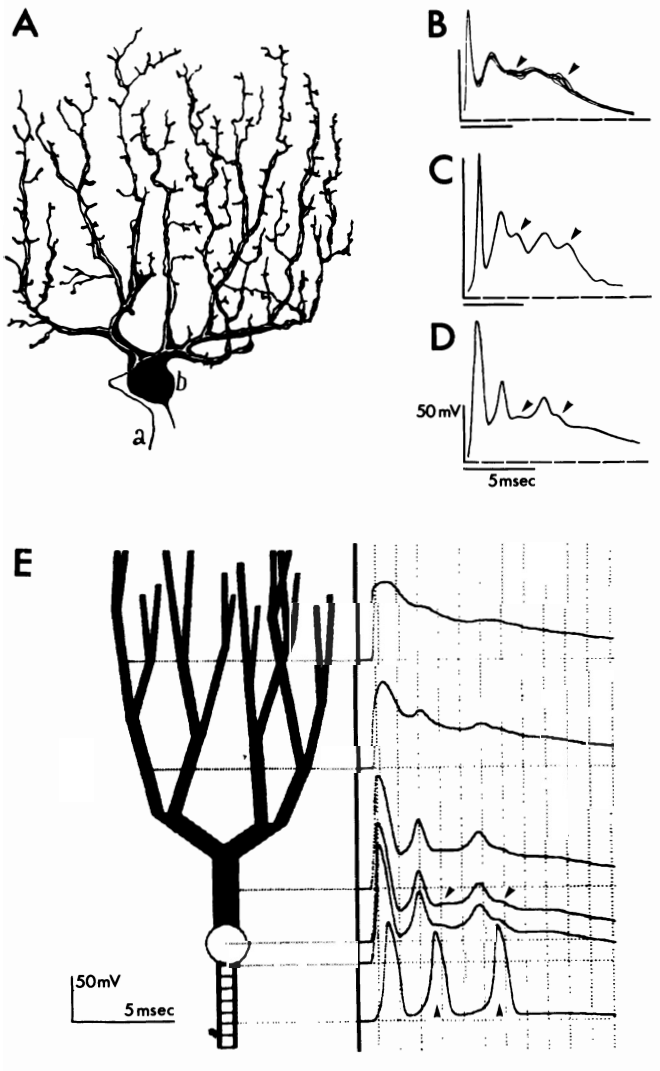


FIGURE 5 An explanation by computer modeling of the climbing-fiber-evoked complex spike (CFR) of the Purkinje cell. A: Golgi-impregnated Purkinje cell (b) and its climbing fiber (a) in cat (after Ramón y Cajal, 1911, Fig. 47). B: Six superimposed intracellular recordings of the Purkinje-cell response to climbing-fiber stimulation (CFR, as recorded in the soma), in cat. Arrows point to the two most delicate wavelets of the largely stereotypic response. (After Llinás and Volkind, 1972.) C: Intracellular recording of CFR in frog. Note the remarkable similarity of the double twin wavelets of CFR in frog and cat, although the structural features of the Purkinje cell are different in these species (compare Figures 5A and 1A). (After Llinás, Bloedel, and Hillman, 1969.) D: Output of the computer model of Purkinje cell of frog (compare with E). Note that the model provides a comparable somatic membrane potential waveform of CFR, including the double twin wavelets (arrows). E: Computer model that synthesizes morphological and electrophysiological data to provide an explanation for the electrogenesis of the CFR. To the left is a model neuron composed of 62 compartments with passive dendritic tree. To the right are six representative recordings from the computed responses of 62 compartments. Note that the double twin wavelets in CFR are produced by the repetitive firing of the axon initial segment, each spike followed by an antidromic invasion (arrows) evoked by the propagating axonal spike (arrows). (After Pellionisz and Llinás, 1975, 1977a.)

see Figure 5B), it is the last wavelet of the CFR that is most vulnerable to variations. Reversal of the climbing-fiber-evoked EPSP by depolarizing the soma was modeled in accordance with the data as well. (For the detailed studies see Pellionisz and Llinás, 1977a.)

Third, beyond providing an explanation for a complex phenomenon, this model also led to a novel, though rather speculative, line of thought that may be worth mentioning to illustrate its heuristic power. The idea concerns the possible role of climbing-fiber activation of Purkinje cells. In view of the massive overall depolarization of even the uppermost regions of dendritic tree during the CFR (see Figure 5E), it is conceivable that the primary function of climbing-fiber activation is not to elicit a burst of spikes, but to generate this deep and prolonged depolarization of the entire dendritic tree. It has been hypothesized that the CFR modifies ("shapes") the dynamism of the Purkinje-cell spike-producing membrane mechanism (Pellionisz, 1976). This notion of physiological tuning (Pellionisz, 1976, 1978), which is in contrast to the modification of synaptic efficacy (Marr, 1969), may shed new light on the operation of the cerebellar cortex. (It has also been pointed out that the basic functioning of neurons, in general, may be based on the plasticity of their spike-generating properties: see Pellionisz, 1976; Traub and Llinás, 1977.)

The described single-unit model illustrates that, if hitherto isolated fields of research (in this case single-cell morphology and electrophysiology) are integrated by computer modeling, even highly complex phenomena such as the CFR may be explained on the basis of already known details. Such modeling of particular neurons may therefore become a fruitful area in the future since there are many sets of corresponding electrophysiological and morphological data available for specific neurons that await mutual explanation by such synthesis.

It should be stressed that the approach of investigating the cerebellum at the single-neuron level is a rather "close view" of the cerebellar system. Although without the help of computers even one Purkinje cell is much too complex to allow us to directly interrelate morphological and physiological details, it is inevitable that we proceed to consider single cells from a broader, "more general" perspective, that is, from the point of view of the role they might play in the cerebellar cortex. In making this attempt, the obvious problem is that even an "overall" phenomenon of a single neuron (e.g., the CFR) is only an element in the functioning of the circuitry of cerebellar cortex. However, at this higher level in the hierarchy of complexities, the situation that was seen at the single-neuron level repeats itself: we know many of the overall features and also various details of the cerebellar cortex, but the two need to be interrelated in some systematic way. It is therefore reasonable to turn to the already proven method of computer modeling at this higher level of complexity.

MODELING LOCAL CEREBELLAR NETWORKS The cytoarchitecture and electrophysiology of the elements of the cerebellar cortex are well known (Eccles, Ito, and Szentágothai, 1967; Llinás, 1969; Palay and Chan-Palay, 1974; Palkovits, Magyar, and Szentágothai, 1971a,b,c, 1972). Combining these separate sets of information concerning the individual elements in order to achieve an understanding of the function of this cortex has only just begun. Early attempts to synthesize data concerning both single cells and large networks of cerebellar circuits (not the entire cortex) met with many difficulties (see, e.g., Szentágothai, 1963; Eccles, Ito, and Szentágothai, 1967; Eccles, 1973). This was due mainly to a lack of adequate techniques to handle the complex body of data that it takes to describe tens of thousands of neurons. Computer methods have since been introduced that can provide phenomenological models for the possible events of a "functional block" (i.e., a small piece of cerebellar cortex that can be interpreted as an unbroken self-contained network). The first cerebellar computer models (Pellionisz, 1970) treated the neurons as either excitatory or inhibitory McCulloch-Pitts-type elements, connected as the elements are known to be in the real circuit. Subsequent computer simulation (Pellionisz and Szentágothai, 1973, 1974) studied the patterns of excitation and inhibition that emerged from these neuronal assemblies. These models suggest, for example, that the original assumption (Szentágothai, 1963) that the activity of Purkinje cells is characterized by simultaneous excitation of rows of Purkinje cells along a parallel-fiber beam may, in fact, need to be modified to include the isolated firings of single Purkinje cells. This modeling led to a newly established functional interpretation of the individual character of firing (see Pellionisz and Llinás, 1978, 1979).

In problems concerning the whole cerebellar cortex, the contribution of such studies on restricted segments of circuitry is limited. For example, activity following vestibular stimulation is a good example of a feature that emerges from the *entire* circuitry of cerebellar cortex. Activity in the frog cerebellum following angular acceleration is characterized by a marked spatial distribution of Purkinje-cell activities involving the whole cerebellar cortex. Precht and Lli-

nás (1969) showed that Purkinje cells with type I and type III firing patterns (see below and Figure 9) are distributed in different areas of the cerebellum. These features of the total cerebellar cortex are obviously related both to the structural organization of the entire cerebellum ("how an input to the cerebellar cortex is conducted through the circuitry to reach certain Purkinje cells") and to single-unit activity ("how the single Purkinje neuron processes that information"). Thus our knowledge of morphology and single-cell activity offers no direct explanation for the spatial distribution of the firing patterns in the model *unless* the two are interpreted within a single, self-consistent framework. This dictates that the hierarchy of models be extended to include modeling of the entire cerebellar cortex.

MODELING THE ENTIRE CEREBELLAR CORTEX In an attempt to bridge the described gap in our understanding, a computer model based on morphological structure was developed (Pellionisz, Llinás, and Perkel, 1977). The model simulates the morphogenesis of the entire frog cerebellar cortex. What makes this approach possible is the relative simplicity of the amphibian cerebellum. It is a good model of the "basic cerebellar circuit": it has practically no inhibitory interneurons, its overall structure is limited to only one transverse folium, and the total number of neurons is only on the order of 1–2 million (Hillman, 1969a,b; Llinás, 1969, 1977).

The model "grows" the circuitry; that is, it generates mossy fibers, Purkinje cells, and parallel fibers by simulating the ontogenetic development. The same programs that generate these neuronal elements can be used to set up any particular configuration of activated neuronal elements of the circuitry. Thus, although the programs are capable of generating the total circuitry of the cerebellar cortex, the computer must deal with only those sections that are actually activated (Pellionisz, Llinás, and Perkel, 1977). This appeared to be the only reasonable approach for handling a circuit containing over a million neurons.

The morphogenesis programs are based on the assumption that the growth of neuronal elements is probabilistic. Thus probability distributions were set up for the key parameters of different cells from the available morphological data. Then the actual parameter values for every neuron were drawn at random from these probability distributions. The morphological structure of the computer model of frog cerebellum is shown in Figure 6. The overall body of the cerebellum is represented by a curved three-layered lattice structure containing 1.68 million cell locations. Mossy fibers project into the granular layer through the two peduncles. A straight trunk of mossy fibers forms the basis for a triangular "fan" on which the endings lie. (The fan takes off from the trunk by pitch, roll, and yaw angles that are drawn from standard distributions.) It is assumed that a spatiotemporally coincident excitation of mossy-fiber endings is required for activation of a granule cell. Granule cells are located at three-dimensional lattice points in the granular layer. Their axons, the parallel fibers, ascend into the molecular layer where they make a T-shaped bifurcation. The parallel fibers run transversely through the planar dendritic trees of Purkinje cells, whose bodies lie on the middle Purkinje-cell layer (each dot of the Purkinje layer in Figure 6C represents one of 8,285 cell body locations). Dendritic trees are generated with different arborization patterns in order to provide a variance in their parallel-fiber input. This comprehensive model enables us to tackle questions relating to the functioning of the entire cerebellar cortex.

Partial activation of the circuitry was used to analyze such problems as the spatial distribution of excitation in populations of granule and Purkinje cells. Such localized activation of mossy-fiber inputs is triggered, for example, by vestibular input evoked by angular acceleration. (See the schematic diagram in Figure 7.) This activation has been thoroughly investigated by both anatomical (Hillman, 1977) and physiological (Llinás and Precht, 1972) methods. The model simulates this case as shown in Figures 6 and 7. A cluster of such incoming mossy fibers activates a "spindle" of granule cells that, in turn, excites a rather tight bundle of parallel fibers. Accordingly, a column of Purkinje cells select their inputs from a basically identical set of activated parallel fibers (although Purkinje cells are not totally "in register"; in the cat they show a staggered arrangement: see Palkovits, Magyar, and Szentágothai, 1971a).

One striking structural feature of the model cerebellum is a tendency to form spindles of activated parallel fibers (see Figure 6). This property of the model of the frog's cerebellum was shown to be a very robust feature, in two ways. First, even with a large variance (more than doubling the standard deviation) of pitch, yaw, and roll angles between the trunk and the fan of mossy fibers, the "beams" of activated granule cells were retained (Pellionisz, Llinás, and Perkel, 1977). Second, it was expected that separated mossy-fiber systems, when they project into the cerebellum, would give a combined action on certain Purkinje cells that are in the spatial overlap

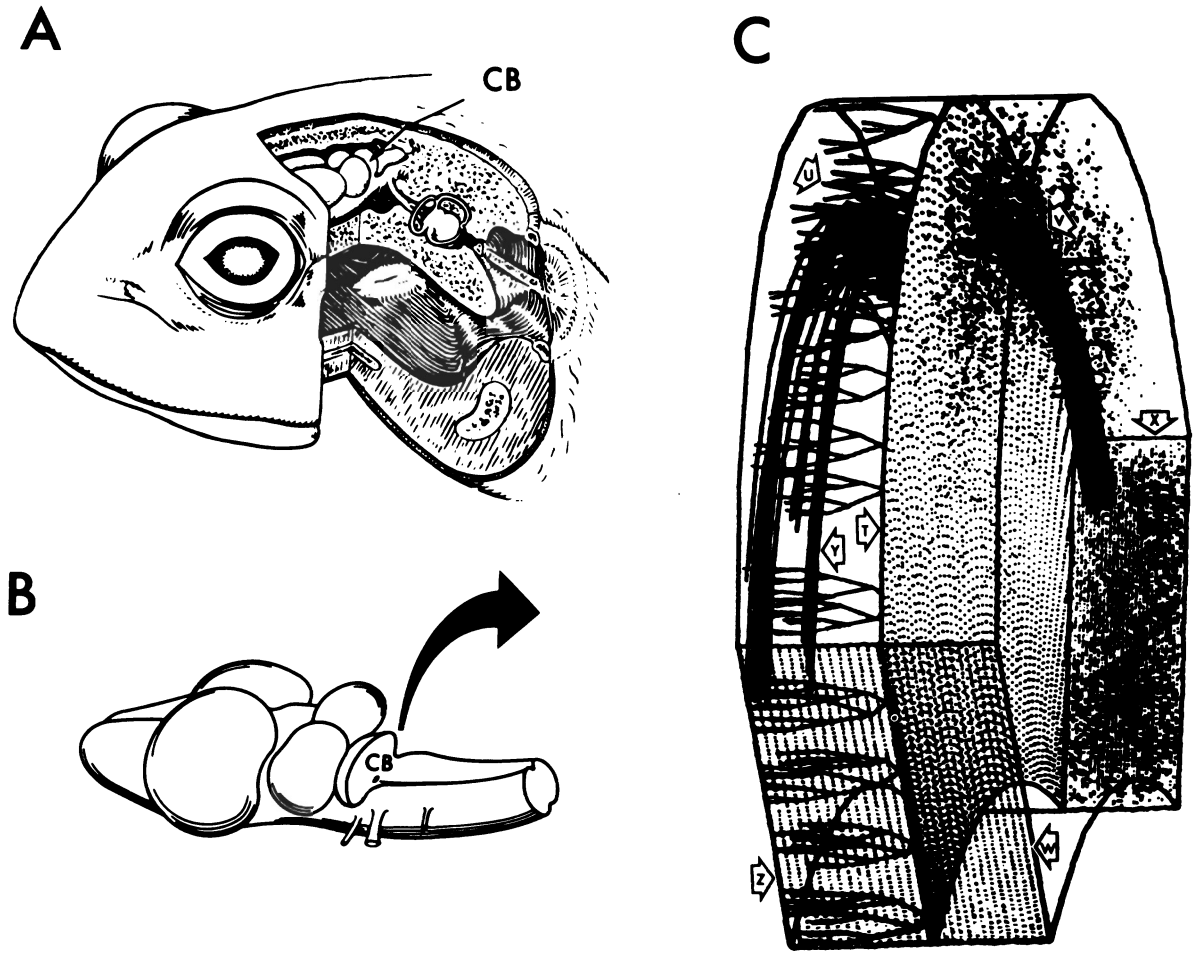


FIGURE 6 The morphological basis of the computer model of the frog cerebellar cortex. A: Cutaway illustration of a frog head showing the cerebellum (CB) and its connection with left vestibular labyrinth (after Precht, Llinás, and Clarke, 1971). B: Diagram of a frog brain with the single-folium cerebellum (after Hillman, 1969). C: Structure of the model. The mossy fibers entering the cerebellar peduncle are indicated only by their entry points (X), except for a cluster of 100 vestibular mossy fibers. These are illustrated by their trunks and 2% of their endings (V). This cluster triggers granule cells (depending on their threshold to mossy-fiber stimulation). For illustrative purposes the threshold is high (6) and only 56 granule cells are activated. The parallel fibers (Y) arising from these granule cells protrude from the granule layer (W) into the molecular layer (Z). This activated "beam" of parallel fibers traverses the Purkinje cells (U) whose somata are found in the Purkinje-cell layer (T). For a fuller description see Pellionisz, Llinás, and Perkel (1977).

of the two populations of excited mossy-fiber terminals. These neurons would then "integrate" the information coming from separate inputs. This assumption was tested by the model. Figure 8 shows the effect of the spatial localization of incoming mossy fibers on the spatial distribution pattern of activated granule cells. In the first case, two separated clusters of mossy fibers enter the peduncle (upper part of Figure 8A). In the second, the activated mossy fibers (which may be coming from different sources) are scattered at random over a quarter of the peduncle (lower part of Figure 8B). In both cases, the activated mossy-fiber endings cover almost the entire granular layer (Figure 8B). Thus, in terms of mossy fiber endings, the model seems to support the expectation that Purkinje cells over the center of the activated region would be of the integrative type. However, as shown in Figure 8, in spite of the apparent loss of spatial specificity of mossy fibers, the activated granule cells form spindles. In the first case, these appear in the form of remarkably separated clusters (upper part of Figure 8C), each carrying information that comes from one or the other mossy-fiber input. More interestingly, the other, similarly massive "cloud" of activity created by the scattered input forms three small spindles (lower part of Figure 8C). In the latter case,

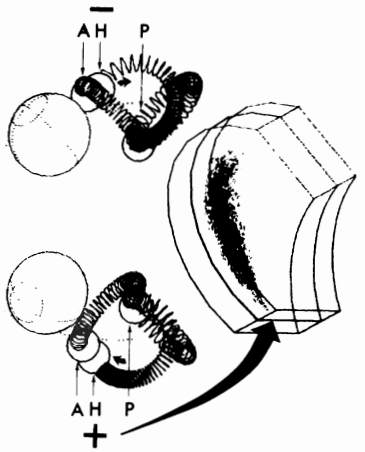


FIGURE 7 Schematic diagram of the asymmetrical spatial input to the cerebellum in the case of angular acceleration in yaw (horizontal rotation counterclockwise). The two sets of semicircular canals of the labyrinth are shown magnified. The horizontal (H), anterior (A), and posterior (P) semicircular canals are represented in the form of "coil springs" to visualize the "pushing and pulling" inertial forces in response to angular acceleration. In horizontal accelerating rotation only the horizontal semicircular canals are activated. In the left labyrinth the inertia exerts a force towards the ampulla (see small arrow) that evokes excitation (+). At the right labyrinth the inertia is "pulling away" from the ampulla (see small arrow) and reduces the spontaneous firing (−). The resulting asymmetrical input to cerebellum (from left labyrinth, see big arrow) is shown by the inset, indicating the "spindle" of activated granule cells.

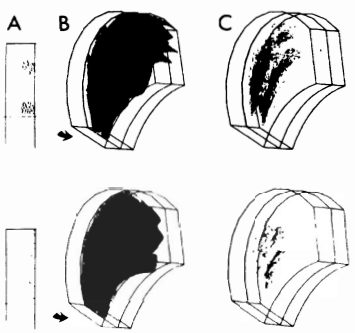


FIGURE 8 The spatial distribution over the cerebellar cortex of clusters of activated mossy fibers. A: A cross section of the cerebellar peduncle. The entry points of mossy fibers are shown by dots. In the upper row two clusters of 100 mossy fibers project into the cerebellum. In the lower row 100 mossy fibers are scattered randomly over one-quarter of the peduncle. B: Spatial distribution in the cortex of these mossy fibers and their endings. In both cases the activated mossy fiber endings cover most of the cortex. C: The spatial distribution of activated granule cells. Note the remarkable separation of the activated granule cells into two spindles (upper row) and the three smaller but separated spindles of granule cells that emerge as a result of the scattered mossy-fiber activation. (After Pellionisz, Llinás, and Perkel, 1977.)

the granule cells in one spindle receive mossy-fiber information from both mossy-fiber inputs. In either case, the result of activation is a bombardment of a set of Purkinje cells by basically the same parallel-fiber spindle.

This feature of the model suggests that the anuran cerebellum has a natural ability to extract transverse spindles of granule-cell activities with a strikingly limited dorsoventral integration. This, in fact, may be a general property that is further refined in high vertebrates by the lateral inhibition produced by the basket cells.

With the help of the model we can now attempt to explain the spatial distribution of type I and type III Purkinje cells (those that are activated by only one direction of rotation or by both, respectively), as observed in experimental vestibular stimulation (Figure 9A). Since these cells differ in their individual spike pattern response (and their spatial distribution covers the entire cortex), it is obvious that the above experimental results cannot be accounted for without combining the structural model of the entire cerebellar cortex with functional models of single Purkinje cells. In the case of ipsi- and contralateral horizontal angular acceleration, mossy fibers from the horizontal semicircular canal are carried in the eighth nerve and project into the cerebellum through the peduncle (Hillman, 1969b; Precht, Llinás, and Clarke, 1971; Hillman, 1977). Ipsi- and contralateral angular acceleration is modeled, therefore, by the activation of a cluster of mossy fibers, projecting from either the ipsi- or contralateral side (compare Figure 7). This activation creates a beam of excited mossy-fiber terminals (as shown in Figure 6).

A map of Purkinje cells receiving a suprathreshold (>30) number of activated parallel fibers is shown in Figure 9C–E. By varying this arbitrary threshold the spatial distributions of type I and type III cells are revealed. Type I cells are shown for ipsilateral (Figure 7C) and contralateral (Figure 9D) activation. Type III cells are also shown (Figure 9E). By a tenfold increase in the threshold one may localize those areas in which the input to Purkinje cells is maximal (i.e., those areas having the highest probability of containing type I cells). The model predicts that these regions are not directly at the peduncles, as one might expect intuitively, but are about one-third of the folium away from the peduncle transversely along the parallel fibers. Recent experimental observations confirm this prediction (Amat, personal communication).

At this level of modeling, it is possible to relate electrophysiological recordings for single Purkinje cells to the microstructure of the entire cerebellar

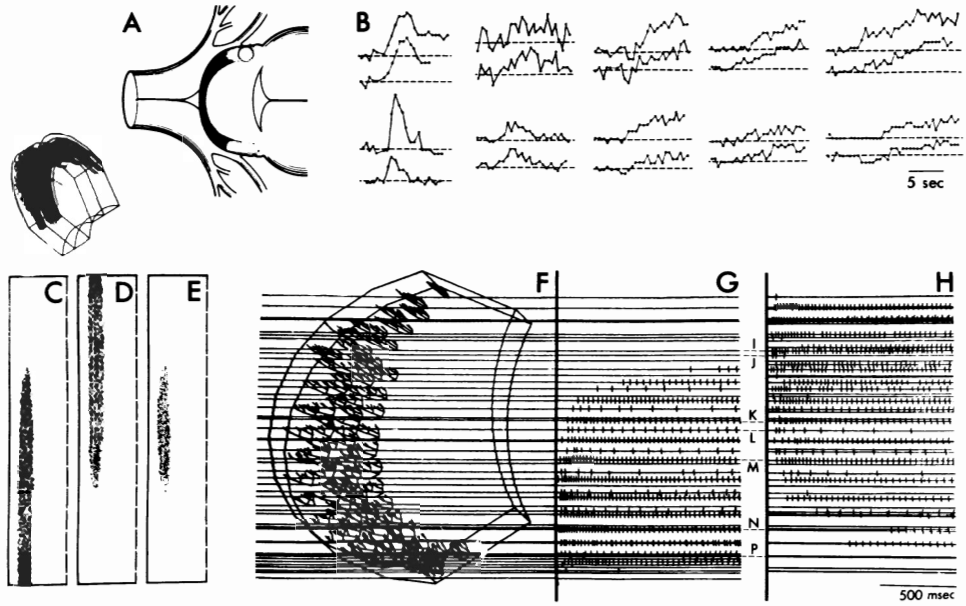


FIGURE 9 Comparison of experimental and modeled spatial distribution of single-unit activities of Purkinje cells in response to vestibular input. Parts A and B show experimental data; C–H show output from the model. A: Schematic diagram of frog brain stem and cerebellum (top view). Type III Purkinje cells are found on the dorsal rim of the cerebellum (dark area). Type I cells are found in the two lateral dotted areas. B: Frequency responses of ten type III cells, following a ramp increase of horizontal angular acceleration. Although each cell shows individual dynamism, the twin sets of recordings in both rows are almost identical pairs of responses of the cell to ipsi- and contralateral rotation. Note the wide spectrum of phasic-to-tonic dynamism of individual Purkinje cells. These rotations correspond in the model to the activation of clusters of mossy fibers (see insert at left and Figures 4 and 5). Purkinje cells receiving a suprathreshold number of activated parallel fibers (>30) are shown for ipsilateral (C) and contralateral (D) rotation. Their spatial overlap (E) contains cells responding to both directions of rotation (type III). F, G and H show spike trains of randomly selected Purkinje cells at different locations, responding to the modeled asymmetrical mossy-fiber input. Cells I, J, and P are type I cells; K, L, M, and N are type III. Note the variety of firing patterns. (Part A after Precht and Llinás, 1969; part B after Llinás, Precht, and Clarke, 1971; parts C–E from Pellionisz, Llinás, and Perkel, 1977; parts F–H from Pellionisz and Llinás, 1977b.)

cortex. This is done by combining the single-Purkinje-cell model with that of the whole circuit in the following way. The morphogenesis provides the spatial distribution of activated Purkinje cells for a given mossy-fiber input, and the resulting parallel-fiber activation is then applied to single Purkinje cells (Pellionisz and Llinás, 1977b).

One intriguing finding that has to be accounted for by this approach is the extreme variance of dynamical properties of type III Purkinje cells recorded at various locations over the cortex. Different Purkinje cells exhibit a remarkably wide spectrum of phasic-to-tonic dynamics of spike-train responses to identical vestibular input (Figure 9B). Moreover, the phasic or tonic character of the dynamics of one cell is maintained for both ipsi- and contralateral angular acceleration. This finding was accounted for in the model as follows. In order to simulate the microelectrode penetration of cells at various loci over the cerebellar cortex, the parallel-fiber beam that is activated by ipsi- or contralateral mossy-fiber cluster input was applied to quasi-randomly selected Purkinje cells (Figure 9F). At all "probed" locations the activated or nonactivated parallel fibers represent two-dimensional matrices. Purkinje cells, by their modeled dendritic arborization pattern, contact a sample of the total number of encountered parallel fibers. These samples vary, since Purkinje cells are staggered and also differ in their dendritic patterns (some having partially overlapping dendritic trees). This difference is most significant for Purkinje cells at different dorsoventral positions. Some will be "on-line" and others "off-line" with regard to the parallel-fiber beam.

The model shown in Figure 9 involves the activity of several Purkinje cells over many tens of milliseconds. For this reason a simplified single-unit model of the Purkinje cells was used instead of the full multicompartmental Hodgkin-Huxley model. It was assumed that the threshold of Purkinje cells increases after every spike and then returns exponentially to its

original resting value. This is necessary to provide a phasic-to-tonic firing response following an input that increases linearly and then saturates. In order to study the variance that is provided solely by the difference in parallel-fiber input to Purkinje cells, the algorithm of firing was held strictly identical for all Purkinje cells (i.e., no individuality was allowed). Then the parallel-fiber beam generated by the ipsi- and then contralateral mossy-fiber cluster was applied to a sample of Purkinje cells selected at random from the entire body of cerebellar cortex. The spatial distribution of overall activation and the individual dynamic properties arising from the spatial dispersion of parallel-fiber activation emerges from the model as shown in Figures 9G and H. This result illustrates the extent to which the observed phenomena can be explained on the basis of a knowledge of the structure of circuitry. The network provides a spatial variance in transmitting mossy-fiber inputs through parallel fibers to Purkinje cells. As seen in Figure 9G and H, the overall spatial distributions of the type I and type III activities are adequately explained. Also, it can be concluded that a wide variety of dynamic patterns of Purkinje cells may arise solely from the variance of the parallel-fiber input. However, the consistent characteristic of phasic or tonic firing for both ipsi- and contralateral rotation does not emerge from this model because it excludes individuality. The model thus suggests that the individual character of the activity of Purkinje cells is more likely to originate from individual differences of the electroresponsive properties of Purkinje cells than from their varied parallel-fiber inputs.

This conclusion is important when considering that these sets of Purkinje-cell output patterns do not merely represent an envelope of spike trains with various dynamics but probably reflect some fundamental principles regarding the organization of the functional output of the cerebellar cortex (for a recent hypothesis utilizing this individual Purkinje-cell dynamics see Pellionisz, 1976, 1978). Presently completed models (Pellionisz and Llinás, 1978, 1979) have provided a meaningful functional interpretation of such varied Purkinje-cell activities: they act as a spatially distributed Taylor series expansion, yielding prediction. Tackling such questions requires that the cerebellar output (in the form of Purkinje-cell activities) be put in the context of a total cerebellar control system. Thus a still higher level of complexity needs to be considered.

MODELING THE CEREBELLAR CONTROL SYSTEM It is generally accepted that it may be impossible to understand the function of the cerebellum without considering the cerebellar control system as a whole. Beyond this consideration, it is on the *system level* that some global functions of the cerebellum present themselves in the form of the coordination of motor activities. Skilled locomotion, balanced posture, and coordinated head and eye movements are a few prominent final results to which the cerebellar control system contributes (see Dow and Moruzzi, 1958). These functions can be directly observed and have been studied at the phenomenological level in great detail (for a review on locomotion and posture see Stein et al., 1973; on head and eye coordination see Bach-y-Rita, Collins, and Hyde, 1971).

It is important to realize that in order to meet the ultimate challenge of explaining such emergent properties as, for example, a coordinated gait, a methodology must be prepared that can handle such complex phenomena on the basis of known details of the functioning of the underlying neuronal machinery. From the perspective of this highest level of complexity, even the overall spatial distribution of the Purkinje-cell output of the cerebellar cortex represents only a small detail. A number of other isolated experimental findings also appear as details: the structural and functional features of the peripheral vestibular apparatus, vestibular and cerebellar nuclei, olivary system, or skeletal and eye musculature. The degree of complexity of any of the above systems is high, and the amount of factual information abundant. It is essential, therefore, to generate realistic conceptual representations that both synthesize these data and penetrate the complexity of the system. Within the hierarchy of computer models of the cerebellum, spanning several levels of complexity, techniques are being developed for representing the overall outputs of the system, such as locomotion and eye and head movements.

As a first step in putting this hierarchical modeling in perspective, a computer representation of the skeleton of bullfrog was established (Figure 10). Lengths and three-dimensional angles of the major elements of the skeleton are handled in the model as vectors in successive three-dimensional polar coordinate systems. For example, the radio-ulna bone is oriented in its own polar coordinate system fixed to the humerus. As long as the elbow joint is not moved, the radio-ulna moves with the humerus, keeping its own θ and ϕ coordinates representing the flexion and rotation, respectively. The frog's head and eyes are also shown schematically. The three-dimensional positions and movements of all these elements are handled by the computer and displayed graphically (Fig-

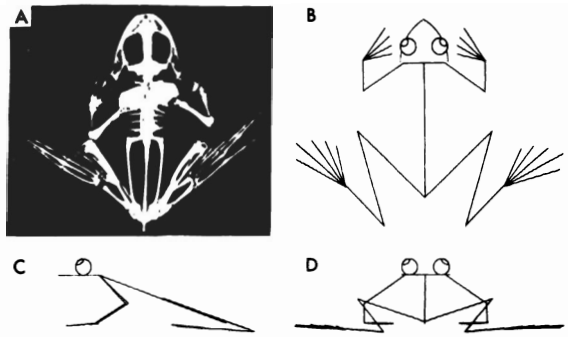


FIGURE 10 Computer representation of the skeleton of bullfrog. A: Top view of skeleton. B: Top view of the model, showing major skeletal bones and schematic head and eyes. C: Side view. D: Front view.

ures 10 and 11). Further, eye and head movements can be analyzed in relation to each other, as well as to the body. Since all joints of the skeleton model are movable, by varying the θ and ϕ angles, the model can display movements such as uncoordinated or coordinated locomotion. Thus the basic characteristics of eye, head, and limb movements can be displayed and analyzed separately as well as simultaneously. The graphic display enables direct observation of their combined result and makes it easier to relate this to the experimental findings. This ability to represent overall emergent phenomena ends the hierarchy of interconnected computer models spanning the range from membranes to the overall input-output function of angular accelerations and correlated body movements. It is therefore expected that with the help of this framework accommodating both the details and the overall features of the system, it will become possible to account for emergent phenomena on the basis of details (as the model of a single Purkinje cell made it possible to explain the waveform of a complex spike).

The methodology offered by these models might be used, for example, to study the following problem. Vestibular stimulation of a frog in the dark results largely in head nystagmus, while optokinetic input without vestibular stimuli evokes eye nystagmus (Grüsser and Grüsser-Cornehls, 1977; Precht, 1977). In the case of combined vestibular and optokinetic stimulation, the response of the total system is a combined response of head and eye movements. However, these two systems are far from being independent (they are coupled both physically and through the visual field) and are both under cerebellar control (Grüsser and Grüsser-Cornehls, 1977). It is important, therefore, to be equipped to study them together and in connection with the cerebellar model.

Although locomotor movements of the limbs themselves raise many questions that await explanation, our particular interest is in how coordination of locomotion is achieved. Coordination is both intrinsic and extrinsic. In an intrinsic sense it concerns how the activations of different major muscles are related to one another. This coordination results in an overall

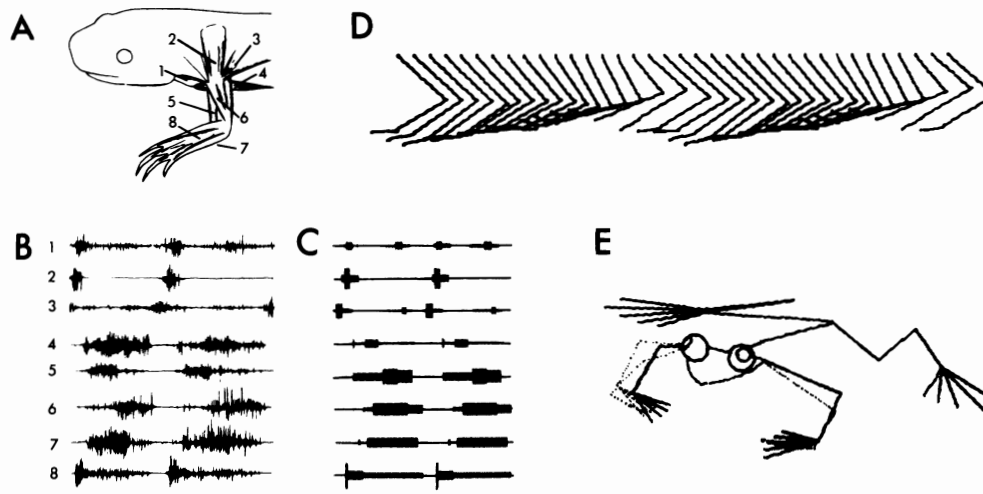


FIGURE 11 Computer techniques for the representation of locomotor movements. A: Anatomical positions of eight major forelimb muscles used for electromyogram recordings during locomotion: 1, acromialis; 2, dorsalis scapulae; 3, latissimus; 4, pectoralis; 5, brachialis; 6, extensor ulnae; 7, (hidden) flexor digitorum; 8, extensor digitorum. (Modified from Székely, Czéh, and Vörös, 1969.) B: Myochronograms recorded from the forelimb of an intact *Triturus* (modified from Székely and Czéh, 1977). C: Computer representation of myochronograms. D: Phase diagram of two step cycles of the left forelimb (side view), as reconstructed from C by the computer model. E: Diagram of the computer model of frog skeleton to illustrate the display of reconstructed locomotor movements of forelimbs.

locomotor activity that is functionally superior to the simple sum of the elementary muscle contractions. In an extrinsic sense, it is important to be able to analyze how locomotor movements are coordinated to resist external disturbances of the total system (such as, for example, angular acceleration during locomotion). An understanding of the principles of these extrinsic and intrinsic aspects of motor coordination (and of the role of cerebellum) is needed to account for such extremely complex emergent properties as walking. (For a newly developed tensorial interpretation of coordination as a distributed property, see Pellionisz and Llinás, 1978, 1979.)

As a first approach to the development of a methodology for handling these complex phenomena, the computer model of the frog skeleton was used to directly observe the overall effects of elementary locomotor muscle contractions. Electromyograms recorded from freely moving salamanders are available in the form of "electromyocronograms" (Czéh and Székely, 1971; Székely and Czéh, 1977; see Figure 11A). The amplitude and time sequence of the activation of eight major forelimb muscles was deduced from these recordings (Figure 11B). These data were used to alter the three-dimensional angles of the joint vectors (representing skeletal bones). By computer display and cinematographic animation of the skeletal model, these data emerge as a crude pattern of locomotor limb movements (see Figure 11C).

In order to coordinate this crude form of locomotor movements, to allow the model to accommodate external disturbances (such as angular acceleration), the outputs of Purkinje cells of the cerebellar cortex have to be incorporated into the full model of motor control. This requires further information, especially about the structural and functional features of the cerebellar nuclei and of the olivary system. While important new anatomical findings (Palkovits et al., 1977; Chan-Palay, 1977), overall functional observations (Llinás et al., 1975), and basical electrophysiological knowledge (Ito et al., 1970) are available for these systems, it is crucial that, for further advancement of this modeling, a concept be developed for the role of these systems in cerebellar coordination. Any such proposal is the more useful if it can interpret single-neuron events as well as phenomena at the system level; but it is very difficult to envisage the evolution of a new scheme capable of integrating such an enormous span of details without the working tool of hierarchical computer modeling such as described in this paper.

This goal of promoting a dialogue between concepts and data on any and all levels is the ultimate reason for modeling. If interconnected computer models within a coherent framework succeed in encompassing the data on neuronal membranes, single neurons, populations of cells in the cerebellar cortex, the structure of the cerebellum, the spatial distribution properties of single-unit activities in the cerebellar cortex, and overall emergent phenomena, we hope it will help to achieve a breakthrough in the understanding of the function of the cerebellum.

Computer modeling of cerebellar neurons and networks is only one example of efforts in recent years to develop methods that can bring together, in a supradisciplinary manner, a heterogeneous and diffuse body of data. Since this trend must counterbalance spontaneous "centrifugal" tendencies (that the empirical basis of scientific fields scatters and proliferates into increasingly unwieldy agglomerations of data), it is expected that computer modeling will become indispensable in the coming years not only in neuroscience, but in all fields requiring the handling and interpreting complex systems.

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