DEC 13 1990

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LA-UR--90-3733

DE91 004824

TITLE: A Computational Model of the Cerebellum

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SUBMITTED TO: Analysis and Modeling of Neural Systems Workshop
Berkeley, CA, July 25-27, 1990

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A COMPUTATIONAL MODEL OF THE CEREBELLUM

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Abstract

A highly detailed computational model of mammalian cerebellum has been developed. It is being compared to physiological recordings for validation purposes. The model is also being used to study the relative contributions of each component to cerebellar processing.

INTRODUCTION

The concept of 'function follows structure' is both a long-enduring and fundamental precept of neuroscience. The notion that the layered structure of the cortex or the dendritic structure of a neuron are reflected in their physiological processing has been of prime importance in shaping the theoretical framework of neurobiology. Recent advances in recording from neurons and in staining techniques are revealing the details of a key structural level -- that of circuitry or microarchitecture. This is the level that is believed to hold the secret of how the brain performs such complex functions as vision and audition and motor control, and it is also the level at which computational models can make the greatest contribution.

The need for realistic computational models of neural microarchitecture is growing increasingly apparent. While traditional neural networks have made inroads on understanding cognitive functions, more realism (in the form of structural and connectivity constraints) is required to explain processes such as vision or motor control. In the past few years, a number of tools for simulating highly detailed architectural models of neural systems have been developed (e.g., Travis, 1986; Wilson and Bower, 1989). Rather than model a function or behavior itself, either mathematically or computationally, these models mimic the actual network architecture of a system in order to determine what contributions various aspects of structure -- including connectivity, synaptic weighting, and geometry -- make to function.

Models serve several purposes. They provide a mechanism for uniting in a single operation a great deal of diverse information about neural systems. In addition, they allow for testing the consistency of such data. Further, they allow us to determine the relative contributions of various pathways and processes, and to test theories about the relationship between function and structure. Finally, they can make predictions which can be tested experimentally and thereby guide as well as interpret experimental research.

Such models can improve our knowledge regarding how circuitries and synaptic weightings interact in real systems. Such questions are best studied for systems whose structures are very well characterized, for example, the cerebellum.

CEREBELLAR STRUCTURE

The cerebellum is an excellent subject for modeling because of its highly regular structure, the small number of neuron types (5, ie, Purkinje, Golgi, stellate, basket and granule cells) found there, the wealth of anatomical and physiological data available from it, and the ability to relate its neural activity to observable motor activity.

The basic architecture of the cerebellum is well established. Three layers are commonly designated: the upper, molecular layer (about 400 microns thick), the Purkinje cell body layer (about 50 microns thick), and the lower, granule-cell layer (about 250 microns thick). The molecular layer contains the stellate and basket cells, the dendrites of Purkinje and Golgi cells and the axons (parallel fibers) of granule cells. The parallel fibers excite all the other cell types; in turn, stellates inhibit dendritic regions of Purkinjes and Golgis, while basket cells inhibit at Purkinje cell bodies. Stellate cells are involved in limiting currents in dendrites of Purkinjes while basket cells can turn off an entire Purkinje cell. Purkinje cells inhibit each other and basket cells as well. Golgi cells add inhibitory input to glomeruli, where inputs to granule cells are collected. The granule layer contains the granule cells and the glomeruli, as well as axons of Purkinje and Golgi cells.

Perhaps the most notable feature of the cerebellum is the Purkinje cell, with its large and highly arborized dendritic tree filling the molecular layer. The Purkinje cells, despite their complex appearance, are essentially two-dimensional - their dendrites lie in a common plane (but their axons are not similarly restricted). Golgi cells have dimensions somewhat larger than Purkinjes and their dendrites are not restricted to a plane. The cerebellum is also characterized by the existence of a large number of parallel fibers that run individually for almost 2 mm or so along the long axis of the folium, perpendicular to the planes of the Purkinje cells. The parallel fibers are axonal projections of granule cells found in the granule cell layer. Detailed studies of cell types, numbers and ratios of each cell type, and their spatial distribution and organization within the cerebellum have been determined in a number of studies, e.g., Palkovits, Magyar and Szentagothai, (1971a, b, c; 1972), Palkovits, Mezey, Hamori and Szentagothai (1977), Llinas, (1975), Bishop (1982), King and Bishop (1982), Ito (1984). All of the cell types generate inhibitory responses except for the granule cells. Input fibers are excitatory.

Input to the cerebellar neural circuitry is effected through two cell types - climbing fibers and mossy fibers. Climbing fibers are incoming axonal fibers that contact Purkinje cells at the base of the dendritic tree and climb up the trunk of the tree and out along the various dendritic branches, making frequent strong excitatory synaptic contacts. The climbing fibers originate in the inferior olivary nucleus and possibly from other centers. Climbing fibers also send collaterals to cells in the immediate neighborhood of the target Purkinje (Albus, 1971). Climbing fibers maintain a one-to-one relationship with the Purkinjes. Innervation by mossy fibers is somewhat complicated. Mossy fibers originate in many parts of the brain. Mossy fibers entering the granular layer branch extensively there, each branch terminating in a candelabrum-shaped arborization of synaptic structures called mossy rosettes or glomeruli. The glomeruli (mossy rosettes) are sites which receive projections from Golgi and Purkinje cells.

Individual Purkinje cells exhibit two kinds of firing behavior. Excitation by a single parallel fiber can result in a single simple spike discharge. Activation of the climbing fiber to a Purkinje cell results in a complex response in that cell

(Bell and Grimm, 1969). Ca channel dynamics are responsible for multiple firing and bursting patterns. It appears that Ca^{++} channels occur in the dendritic tree, generally at discrete locations, mainly in the primary and secondary branches (Tank, Sugimori, Connor and Llinas, 1988). Several other studies have clarified aspects of Purkinje cell dynamics, e.g., Chan, Hounsgaard, and Nicholson, (1988), Hounsgaard and Midtgaard (1988). Detailed models of neurons containing Ca^{++} channels can be found, e.g., in Traub (1982).

The special nature of the interaction between Purkinje cells and basket cells has recently been made clearer in a series of experiments (O'Donoghue, King and Bishop, 1989). Intra-cellular recordings and staining techniques show a unitary Purkinje cell input to basket cells, i.e., any basket cell soma receives input from only one Purkinje cell via axon collaterals (see Fig. 1).

These studies provide data with which to calibrate the present computational model. Eventually, patterns of activity generated in the model when large numbers of these computational units are present will be compared with measurements made in cerebellar brain slices using voltage sensitive dyes. A further source of data on spatial activity in the cerebellum will come from neuromagnetic recordings. These will allow a calibration and test of the model on a larger scale.

Figure 1. Left. basket cells (open circles) innervate Purkinje cells (letter P) in narrow transverse strips. Right. Purkinje collaterals synapse on other Purkinjes and on basket cells. Only one collateral to a basket cell soma. Collaterals tend to run longer in the longitudinal direction than in the transverse.

MODEL SIMULATIONS

The present modeling effort is somewhat like that of Pellionisz, Llinas and Perkel (1977), and Pellionisz and Llinas (1977), who constructed a computational model of frog cerebellum, using a very detailed compartmental model for Purkinje cell dynamics. Frog cerebellum is simpler in structure than mammalian cerebellum. It has only Purkinje cells, granule cells and mossy fiber input. Missing are the inhibitory stellate and basket cells which can shape Purkinje cell activity, Golgi cells, which exert control over granule cells, and the climbing fiber input. The present model includes those components, and Ca^{++} channel dynamics in Purkinje dendrites as well, an important feature missing from the earlier studies.

The Hodgkin-Huxley equations are used to model the soma dynamics of all neurons except the Purkinje cells. The dendrites are considered passive cables. For the Purkinje cells, a compartmentalized model is used, with Traub dynamics in each active compartment (some dendritic compartments are passive). Ca channels are restricted to secondary and tertiary dendritic branches. All Purkinjes have the same dendritic structure in this model (see Fig. 2); however, locations of synapses will vary from neuron to neuron. The number of compartments in the canonical Purkinje cell is specified in the input control file; typically a hundred or so are used.

Figure 2. Typical model Purkinje cell showing dendritic tree compartments.

Typical responses of Purkinje cells to constant stimuli are shown in Figure 3. Fig. 3a shows response at a soma to a long duration, constant strong current. A long rapid firing pattern sets in for the duration of the stimulus. In contrast, Fig. 3b shows response in a dendrite to a low applied current. Potential gradually builds until action potentials are triggered. The response patterns that can be generated cover a wide spectrum, as shown in Hounsgaard and Midtgaard (1988), e.g., depending on sign, strength and duration of applied currents. The present model is being compared to actual recordings for many situations.

Another simulation presented here is similar to an experiment by Eccles, Sasaki and Strata (1966). A 600 micron wide band of parallel fibers are stimulated. As the signal passes along the parallel fibers in the sagittal direction, Purkinjes, stellates and basket cells are stimulated. Cells on the sides of the central stimulated region are inhibited temporarily for several hundred microns. Also, the inhibitory collaterals that Purkinjes send to one another restricts the active region to a moving block of cells, lagging behind the signal moving along the parallel fibers. After a short period of time, the pattern is repeated (see Fig. 4).

CONCLUSIONS

A highly detailed computational model of mammalian cerebellum has been developed. It is being validated against recordings from Purkinje and basket cells and various other experiments. With the level of detail in the present model, a number of theories for cerebellar functioning, including e.g., Marr (1969), Albus (1971), Mortimer (1970), and Keeler (1990), can be examined in detail to determine if they are consistent with the dynamics as well as the anatomy of the cerebellum. Also, recent promising motor control learning strategies such as those developed by Kawato (1988) and Sinkajer, Wu, Barto and Houk (1990) may be further improved through additional constraints which might be gleaned from the model described here.

This work has been supported by the U.S. Department of Energy.

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Figure 3. (a) Response in a model Purkinje cell soma to strong, long duration applied current. Dynamics are dominated by Na currents. (b) Response in a model dendrite to weak applied current. Dynamics are dominated by Ca currents.

Figure 4. (a) Purkinje cell response 3 msec after initiation of parallel fiber volley. Open circles are Purkinjes that have not produced an action potential in the soma during the previous 1.0 msec, while filled circles have fired. (b) Pattern of activation 1.0 msec later. Center of the active region has moved several hundred microns down-stream. (c) After another msec, the active region has reached the far end of the simulation region and a new pattern is just beginning at the front (bottom). Width of region is 3000 microns, length is 1200 microns.

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