THE UNIVERSITY OF MICHIGAN
COLLEGE OF LITERATURE, SCIENCE, AND THE ARTS
Computer and Communication Sciences Department

Technical Report

A COMPUTER-SIMULATED MODEL OF MAMMALIAN CEREBELLAR CORTEX

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ABSTRACT

An automata-theoretic model of mammalian cerebellar cortex was developed to investigate the role of the four principal neuronal populations in determining the spatio-temporal response of the cortex to natural and electrical stimuli. Results obtained by digital computer simulation of the model are in substantial agreement with the physiological data of Eccles et al. (1,5,6,7,8,9,10,11,12) and suggest that the observed time course of activity in the cerebellar cortex of an anesthetized cat may be explained without postulating nonlinear properties for synaptic transmission.

The role of Purkinje recurrent collaterals is examined and their possible functional significance discussed. A transfer function for the cortex is obtained by simulating natural inputs along the mossy fiber pathway and observing changes in Purkinje cell activity. The results are discussed in the context of information processing properties of the cortex.

INTRODUCTION

Among large structures in the vertebrate central nervous system, the cerebellar cortex is perhaps the most well-understood with regard to its morphology and electrophysiology. The work of Eccles et al. (1,5,6,7,8,9,10,11,12) has led to a new understanding of neural function by relating the stereotyped circuitry of the cortex to its response to electrical stimuli. However, despite the extent of our knowledge of this structure, there is still no adequate hypothesis for its overall function or explanation as to how the arrangement of neuronal machinery serves that function.

This report summarizes the development and computer simulation of a model of mammalian cerebellar cortex. Although the objectives of this study are limited to an examination of the role played by the four principal populations of neurons in the cortex in determining the overall spatio-temporal output, a number of important functional questions are considered:

1. Is the presently available information about the patterns of neuronal connectivity and the time course of unit events in the cortex sufficient to explain the overall spatio-temporal activity observed in the cerebellum of the anesthetized cat?

2. What is the functional significance of the recurrent collaterals of Purkinje cell axons?

3. What kind of transfer function is provided by the cortex to natural inputs along the mossy fiber pathway?

In order to answer these questions, a model was developed which permitted a wide variety of neurophysiological experiments to be

simulated. Before presenting the model, it is appropriate to describe briefly the morphological basis of our present knowledge of cerebellar circuitry.

MAMMALIAN CEREBELLAR CORTEX CIRCUITRY (Figure 1)

As indicated by Llinás (22), the cerebellar cortex of all vertebrates is organized around Purkinje cells, whose axons form the only output from the cortex. Substantial physiological evidence has been collected which shows that these neurons have an inhibitory effect on all cells which they contact (19,20, 23).

Of the two principal afferent systems which project to the cortex, the climbing fiber system appears to be more primitive, differing little from species to species. In all cerebella which have been studied, the monosynaptic contact of a single climbing fiber upon each Purkinje cell has been observed (14,16). The other input to the cortex occurs through the mossy fibers. These fibers make contact with a population of excitatory interneurons (granule cells), which, in turn, project to the Purkinje cells and to two populations of inhibitory interneurons. In contrast to the one-for-one projection of climbing fibers onto Purkinje cells, there is a great deal of divergence in the mossy fiber system. Through the granule cells and the inhibitory interneurons, one mossy fiber can affect the state of excitation of several thousand Purkinje cells. (21)

Of the two populations of inhibitory interneurons, one is found only in the molecular layer. These neurons are excited by the axons of the granule cells (the parallel fibers) and have axons which terminate

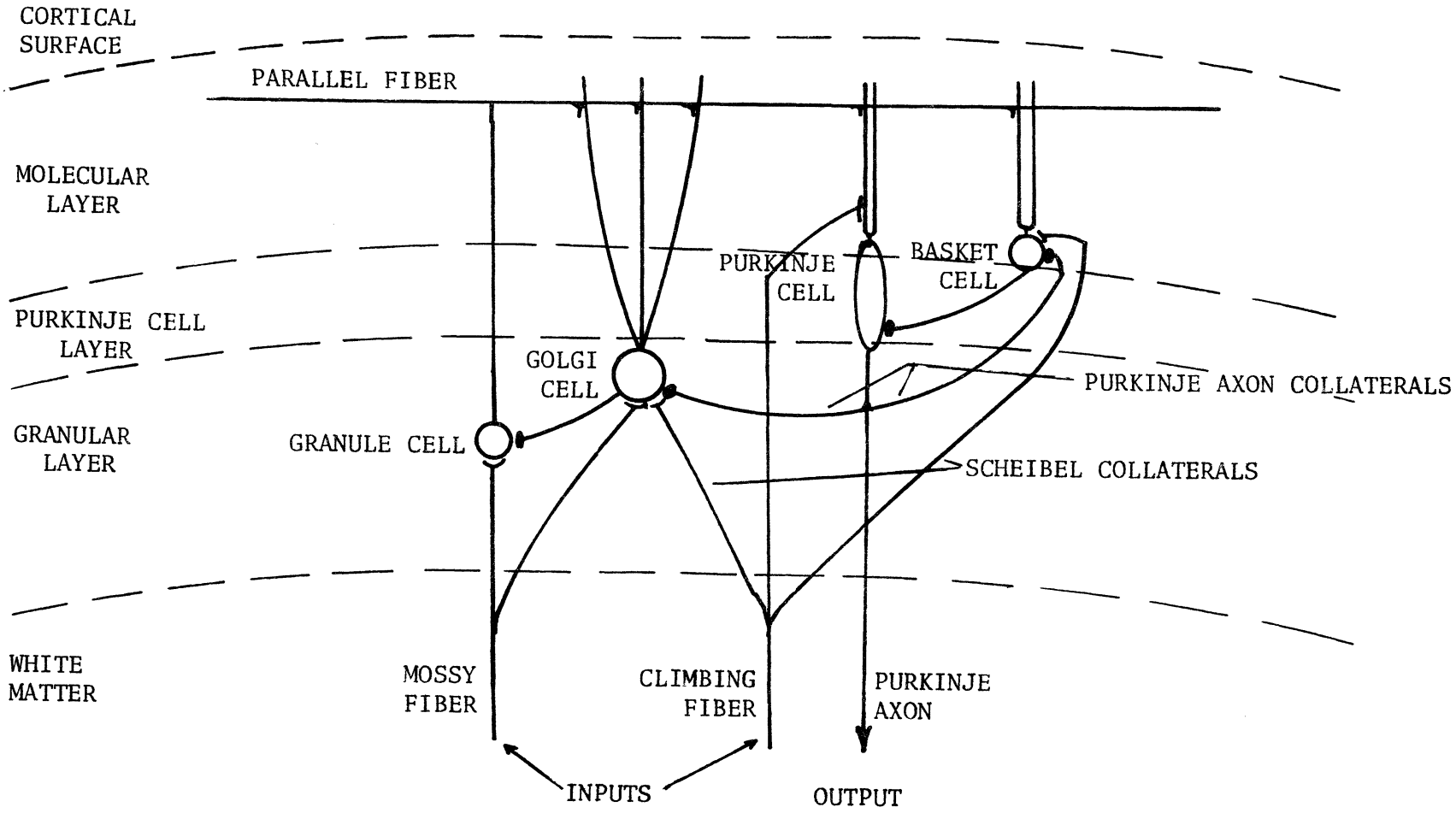

FIGURE 1. Mammalian Cerebellar Cortex Circuitry

upon the soma and dendrites of Purkinje cells, forming inhibitory synapses. In the cerebellar cortex of the cat, this population has been divided into two subpopulations: the outer stellate and basket cells (4). However, because both of these subpopulations receive their input from the same set of fibers and project to the same group of cells, for purposes of the model they will be considered as a single population (hereafter referred to as basket cells).

In the granular layer, situated below the layer of Purkinje cells, are the cell bodies of a second population of inhibitory interneurons, the Golgi cells. While Golgi cells are also excited by parallel fiber input, they have been shown to receive direct excitatory input from mossy fibers as well (17). The axons of these cells form a dense plexus and terminate on the dendrites of granule cells in inhibitory synapses. They are therefore capable of reducing their own excitatory input and can act as a negative feedback, regulating the amount of parallel fiber activity.

Coincident with the phylogenetic development of these two populations of inhibitory interneurons, two prominent axonal plexuses appeared. These plexuses, situated directly above and below the layer of Purkinje cell bodies, have been identified as the recurrent collaterals of Purkinje cell axons (25). On the basis of light and electron microscopical evidence it has been established that these recurrent collaterals terminate on the somata and dendrites of Golgi and basket cells, where they form inhibitory synapses (23). Some physiological evidence has been presented (9) for the termination of Purkinje recurrent collaterals onto the Purkinje cells themselves, but this connection has not been demonstrated in EM studies.

THE MODEL

Restriction to the Mossy Fiber System

The apparent independence of climbing and mossy fiber inputs to a single Purkinje cell has led Llinás to postulate that these two inputs use the cortex in a time-sharing fashion (22). A complete understanding of cortical function requires that the response of the cortex to each of these inputs be investigated. The present model deals with the more phylogenetically-advanced mossy fiber system in an attempt to determine the significance of the spatial arrangement of elements within the cortex. It, therefore, provides a basis from which a more complete model (including both mossy and climbing fibers) can be constructed.

Block Diagram of Circuitry

Figure 2 summarizes the circuitry examined in the model in a block diagram. Unfortunately, the information presented in this form can be misleading if it is interpreted as the wiring diagram for a specific set of four neurons. The projection of Purkinje recurrent collaterals (to basket cells in the longitudinal direction of the folium) and the transverse orientation of the axons of basket cells make reciprocal connections between Purkinje and basket cells unlikely (2). In order to take into account the effect of this spatial pattern of connectivity on the electrophysiological activity of the cortex, information about the spatial distribution of axonal plexuses must be included in the model.

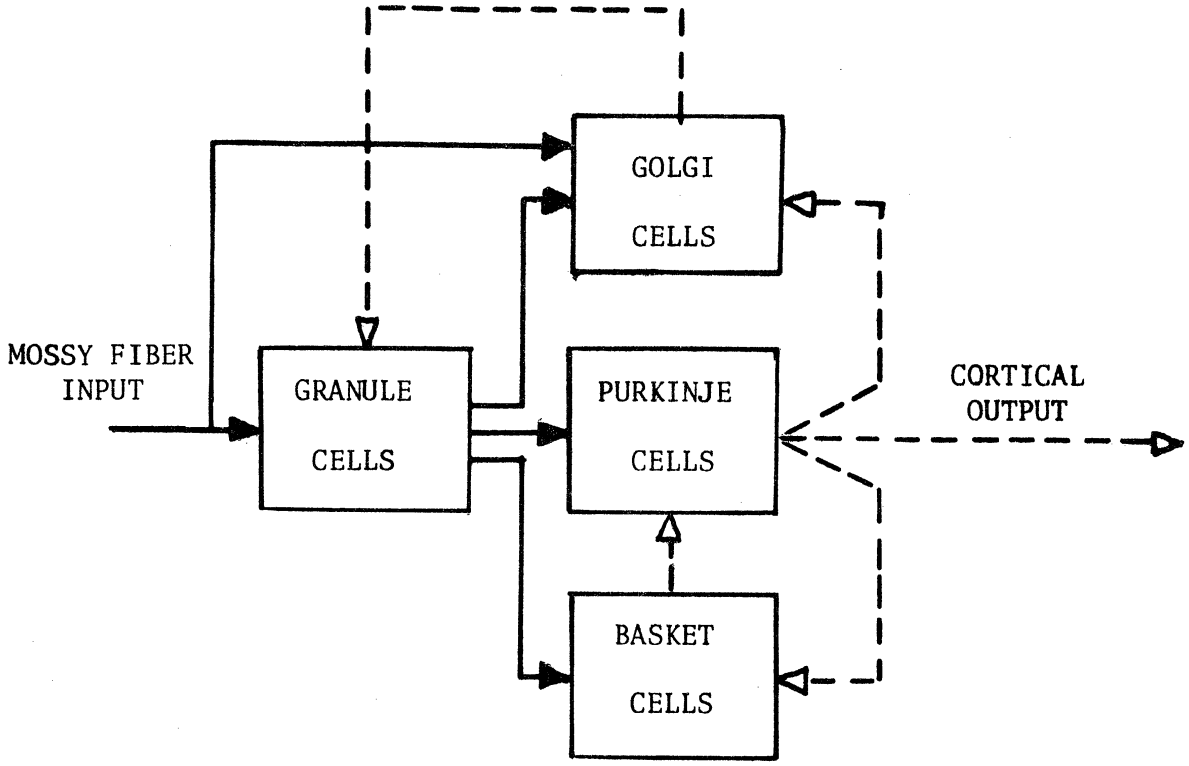

FIGURE 2. Block Diagram of Cortical Circuitry. Excitatory connections are shown by solid lines; inhibitory connections by broken lines.

Mathematical Description

The formulation of a mathematical model of the cortex could be approached from various directions. For example, because of the homogeneity of the microanatomical structure and the great density of the cells, it might be possible to describe the electrophysiological behavior of the cortex by a set of partial, nonlinear differential equations. The solution of such a set of equations in closed form would be unbounded in space, allowing the examination of any size

piece of cortex. However, except for some special cases, such a solution would be extremely difficult to obtain. A much more tractable approach, used in this study, is to obtain an approximate solution by digital computer simulation.

Simulation of a model on a digital computer requires that the model be bounded in space and that time and space be discretized in some way. Because of the extent of anatomical connections in the cortex, it was determined that the smallest piece of cortex that it would be possible to simulate without introducing discontinuities in spatial connectivity would have a 6 mm. square surface area. Figure 3 illustrates how such an area might appear within a single folium.

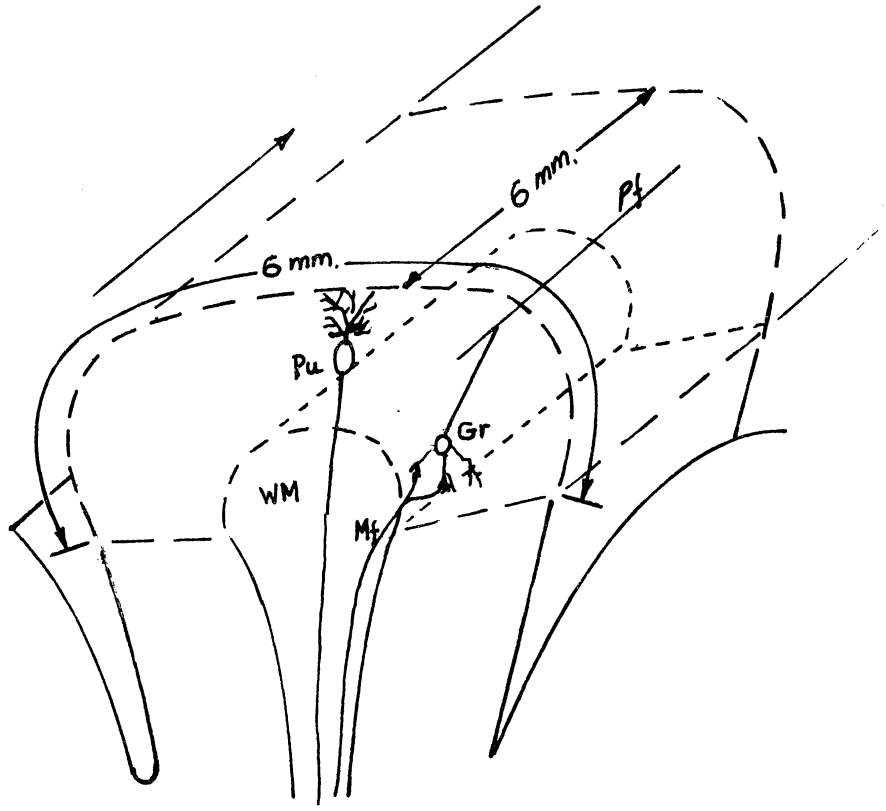

FIGURE 3. Three-dimensional View of a Folium Showing 6 mm. Square Surface Area. Simulated piece of cortex is outlined in dashed lines. Purkinje cell (Pu), granule cell (Gr), parallel fiber (Pf), mossy fiber (Mf) and white matter (WM) are indicated.

In order to investigate interactions among the four populations of cortical neurons in space, an embedding into an automata-theoretic cellular space was defined, in which each *cell** of the cellular space was associated with a small region within the 6 mm. square (Figure 4). Such an automata-theoretic model is especially appropriate for systems in which the interactions among populations are spatially homogeneous, in which case a fixed neighborhood relationship and local transition function may be assumed.**

Since it was clearly impossible to simulate the activity of every neuron within the 6 mm. square area, the primitive unit or *cell* in the cellular space had to be larger than a single neuron. A unit region size of 300μ square was selected. Each such region defines a pseudofunctional unit, the state of which is specified by a measure of the average activity of each of the four neuronal populations within that region.

It is well known that all four populations of neurons in the cortex are spontaneously active in both anesthetized and unanesthetized preparations (2,3,5). Therefore, an obvious measure for the state of a unit region would be the set of average firing frequencies of the four neuronal populations within that region. However, the cellular automaton model requires that from the current state, the state at any time in the future be derivable. Since a neuron continues to have a significant effect upon its target cells for a period of time equal to the duration

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* *Cell* refers to the primitive unit of a cellular automaton and is to be distinguished from cell, which has been used synonomously with neuron.

** The concept of a cellular automaton is discussed in more detail below.

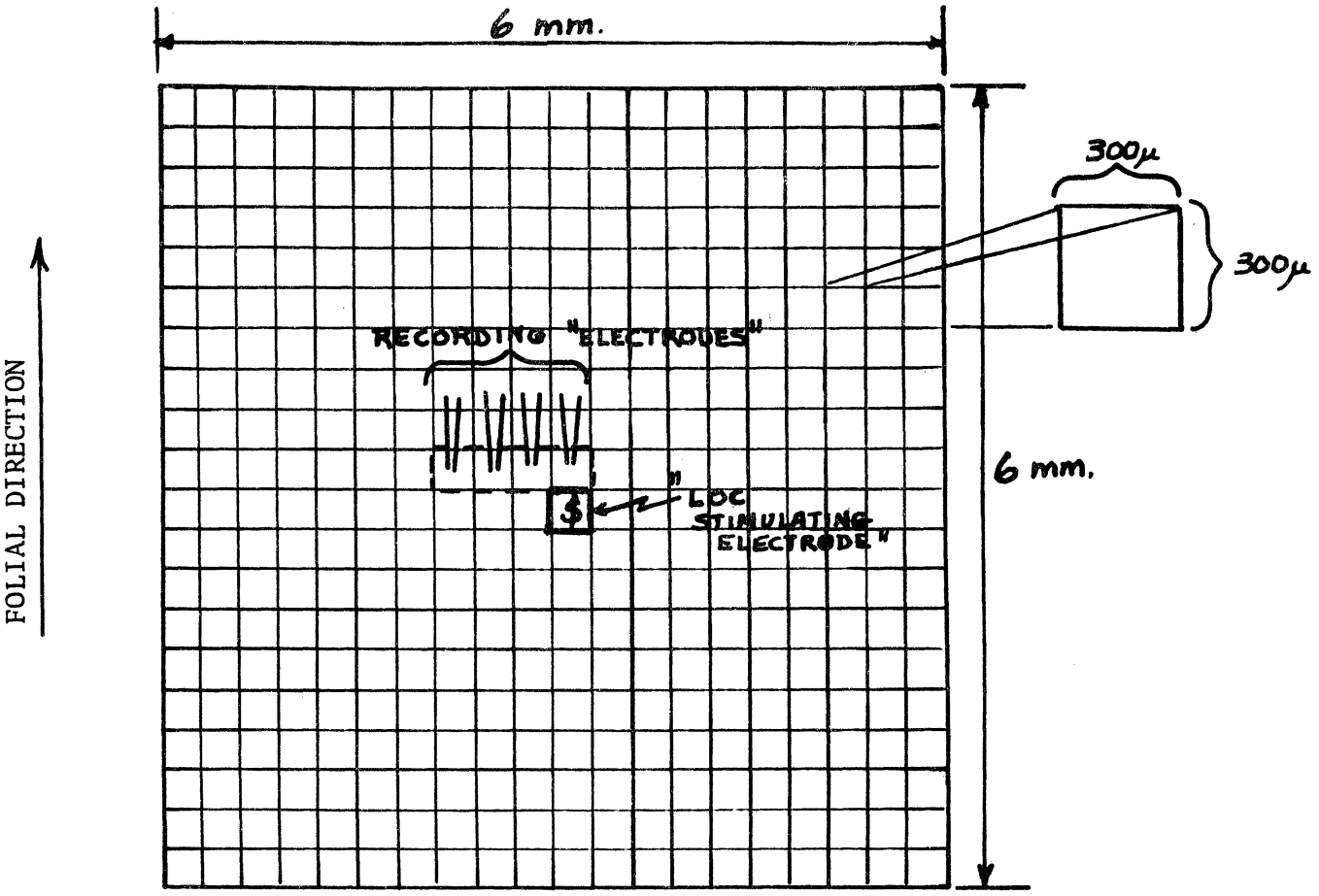

FIGURE 4. The Cellular Space. Unit region size shown at right is 300 μ square. A typical configuration of electrodes is illustrated.

of the post-synaptic potential it induces in those cells, the firing state of a neuron depends upon not only the most recent firing state, but also upon an extensive state history of all neurons which synapse upon it. Because it was impractical to keep such a state history for every region in the space, the state of a unit region was defined by the "compound amplitude" of the EPSP's and IPSP's induced by neurons of this region in the neurons of the same or other regions of the space. With this definition it is possible to determine any future

state, knowing only the present state and the transition function. Furthermore, the average excitation or firing frequency of a population of cells within a particular region of the space can be obtained easily from the states of those populations of neurons which excite and inhibit cells within that region.

Time was discretized in the customary way by allowing changes in state to take place at regularly spaced intervals or time steps. From the sampling theorem of communication theory (24), it is clear that in order to preserve information about a change in state, it is necessary to sample or update the state of the model at twice the rate of occurrence of that change. In order to preserve information about changes of state occurring over 6 msec., a time step of 3 msec. was selected for the simulation.

The discretization of space and time reduces the set of partial differential equations for the continuous case to a set of difference equations (Figure 5) suitable for computer simulation. In order to completely define these equations, some additional information about the spatial connectivity and time course of unit events in the cortex is required.

Spatial Connectivity

Since the earliest anatomical studies of the cerebellum, the parallel fibers have been known to run strictly parallel with the axis of the folium. Estimates of their length in cat cerebellar cortex indicate that they probably have a maximum length of around 3 mm. and

$$F_{1i}(t) = R_1\, S_{0i}(t-T) - \sum_h R_6\, S_{2h}(t-T) - T_1$$

$$F_{2i}(t) = \sum_k R_2\, S_{0k}(t-T) + \sum_j R_3\, S_{1j}(t-T) - \sum_l R_8\, S_{3l}(t-T) - T_2$$

$$F_{3i}(t) = \sum_j R_4\, S_{1j}(t-T) - \sum_m R_7\, S_{4m}(t-T) - T_3$$

$$F_{4i}(t) = \sum_j R_5\, S_{1j}(t-T) - \sum_n R_9\, S_{3n}(t-T) - T_4$$

where

$$S_{1i}(t) = A_1\, S_{1i}(t-T) + B_1\, F_{1i}(t-T)$$

$$S_{2i}(t) = A_2\, S_{2i}(t-T) + B_2\, F_{2i}(t-T)$$

$$S_{3i}(t) = A_3\, S_{3i}(t-T) + B_3\, F_{3i}(t-T)$$

$$S_{4i}(t) = A_4\, S_{4i}(t-T) + B_4\, F_{4i}(t-T)$$

FIGURE 5. Difference Equations for Simulation. F_{pi} is the average firing frequency of neuronal population p in region i of the cellular space; S_{pi}, the state of population p in *cell* i. Synaptic gains are specified by constants $R_1,\ldots,R_9$. All summations over neighborhoods of *cell* i. See text.

a mean length somewhat shorter (15). It has been assumed in the model that their lengths from the point of bifurcation are normally distributed around 1.5 mm. Figure 6 shows the resulting relationship between probability of synapse and distance from the granule cell of origin. The probability of synapse remains relatively constant until around 1 mm. and then decreases, becoming effectively zero at a distance of 1.8 mm. This distribution is in good agreement with physiological data collected from cat cerebellar cortex (6).

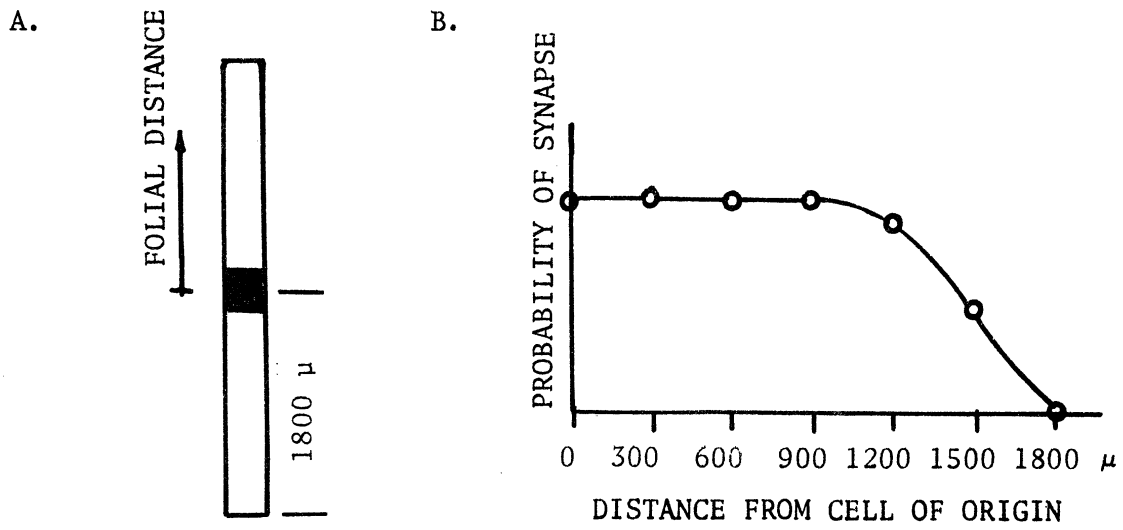

FIGURE 6. Spatial Distribution of Parallel Fibers. A. Set of *cells* reached by the parallel fibers originating in the filled square. B. Relationship between probability of synapse and distance from the granule cell of origin.

The spatial distribution of the two Purkinje axonal plexuses is illustrated in Figure 7. The plexus situated above the layer of Purkinje cells (the supraganglionic plexus) is oriented in the same direction as the parallel fibers, while the other plexus (the infraganglionic plexus) is distributed more transversely (4). In the absence of quantitative data for the length distribution of the recurrent collaterals, the assumption has been made that the probability of termination decreases exponentially with distance from the Purkinje cell of origin.

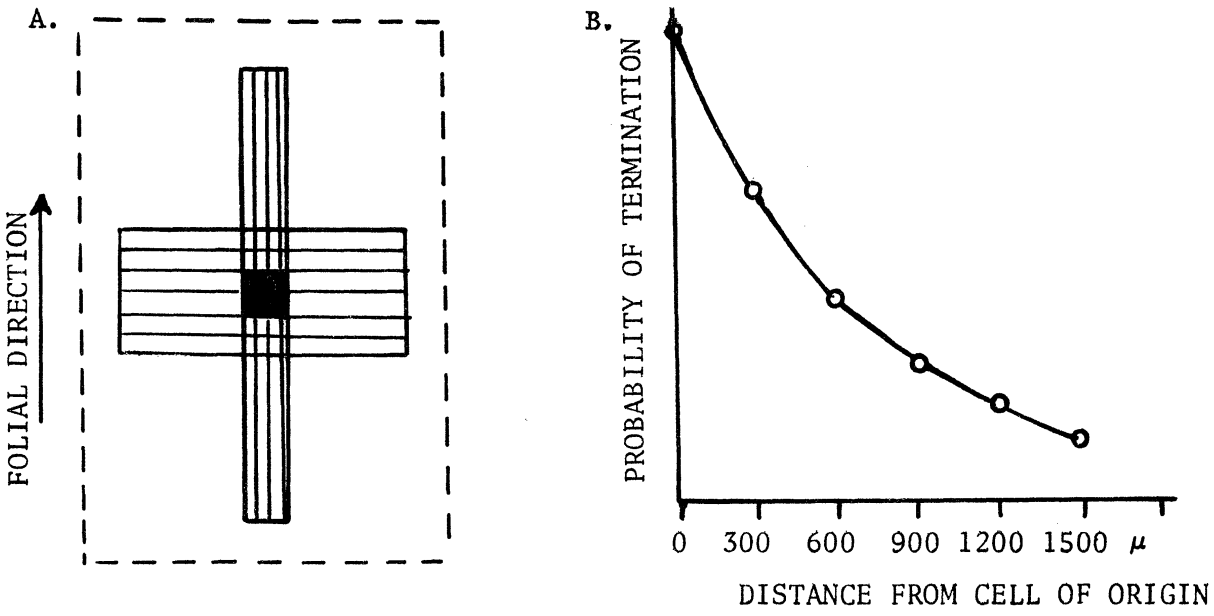

FIGURE 7. Spatial Distribution of Purkinje Axonal Plexuses. A. Set of *cells* reached by infraganglionic plexus (horizontal stripes) and by supraganglionic plexus (vertical stripes). B. Relationship between probability of termination and distance from Purkinje cell of origin (supraganglionic plexus).

The axonal plexus of a single basket cell has been assumed to have a potential matrix of termination extending 1 mm. transversely and 350μ in both longitudinal directions, in agreement with Golgi studies of isolated folia (26). Because basket and outer stellate cells are considered to be part of the same neural population, the area that can be reached by the terminals of basket and outer stellate cells of one unit region extends 1 mm. in each transverse direction and 350μ in each longitudinal direction. (Figure 8A). As with the Purkinje recurrent collaterals, the assumption has been made that the probability of synaptic termination decreases exponentially with distance from the basket cell of origin (Figure 8B).

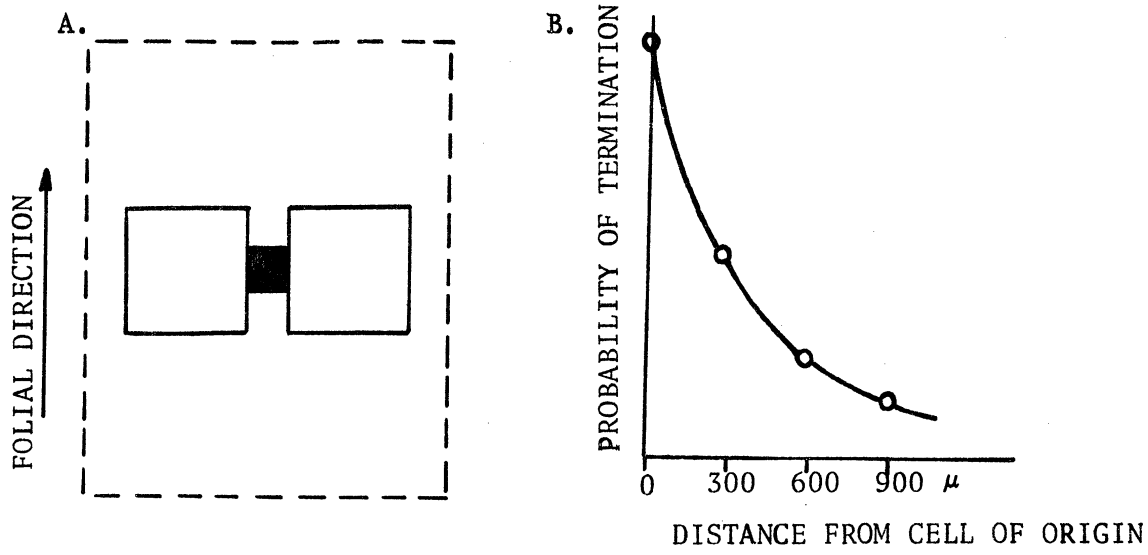

FIGURE 8. Potential Matrix of Termination of Basket Cell Axons. A. Set of cells reached by basket cell axons originating in filled square (includes filled square). B. Relationship between probability of synaptic termination and distance from basket cell of origin.

Time Course of Single Post-Synaptic Potentials

Although the time course of compound post-synaptic potentials may exceed 100 msec., single or miniature IPSP's and EPSP's have a much shorter duration. Inversion of IPSP's of intracellularly recorded Purkinje cells by chloride diffusion (Figure 9) indicates that the total duration of these spontaneously occurring miniature IPSP's does not exceed 60 msec. (7). A good fit to the time course of one of these IPSP's was obtained with the exponential function assumed in the model (Figure 10). Similarly, it was found that the time course of single EPSP's was fitted well by another exponential function.

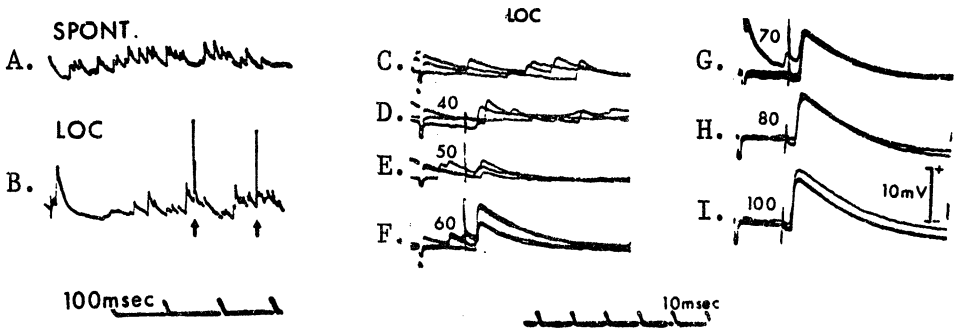

FIGURE 9. Inhibitory Synaptic Noise and Inverted IPSP's. A. Background inhibitory synaptic noise in Purkinje cell inverted by Cl^- injection. B. Suppression of background noise by LOC stimulus. C. Inhibitory synaptic noise in 3 superimposed traces. D - I. Progressive increase in strength of LOC stimulus. Time scales as indicated. (Eccles, Llinas and Sasaki (7,8)).

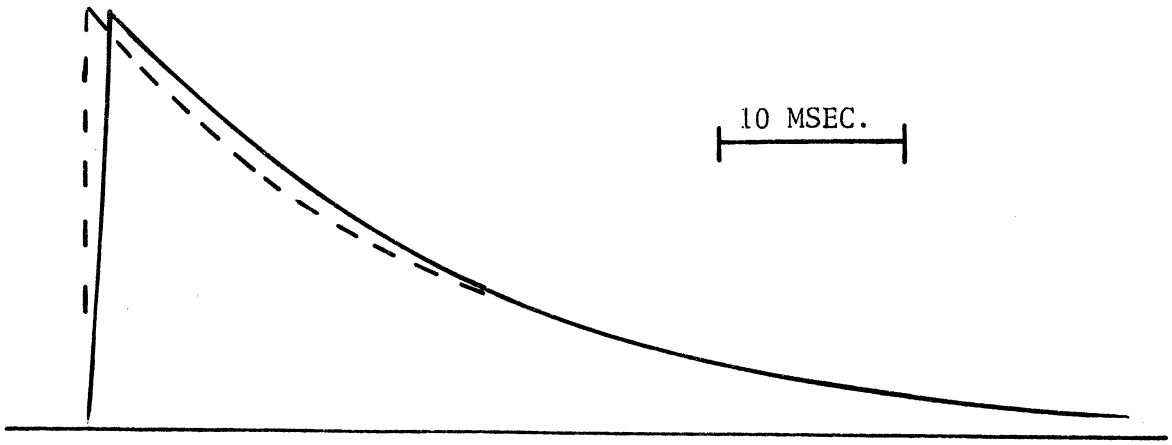

FIGURE 10. Time Course of Single IPSP's in Purkinje Cells. Exponential time course assumed in model (dashed lines) is compared to the time course of a spontaneous IPSP (Eccles, Llinas and Sasaki (7)). Amplitude in arbitrary units; time calibration as illustrated.

COMPUTER IMPLEMENTATION OF THE MODEL

The simulation program was run on an IBM 1800 with 16 K of core storage and associated disk memory. A DEC 338 display under the control of a PDP-7 provided the investigator at run time with a spatial representation of the current state of the model and permitted interaction with the program by means of a light pen. Additional input could be entered through the keyboard of the PDP-7, which was connected with the IBM 1800 through a specially-designed high speed interface.

The programming of the model was facilitated by the development and implementation of a simulation system for cellular spaces. This system, which consists of a set of assembly language programs written for the IBM 1800 and PDP-7, offers a great deal of flexibility in the initial specification of such parameters as the geometry and connectivity of the space, as well as permitting changes in these and other characteristics at run time.

The concept of a cellular automaton, introduced by von Neumann (28) to present a proof of machine self-reproduction, has proven to be a valuable model for the representation of biological systems in which a large number of primitive elements interact in a stereotyped relationship to one another. In this model, each square of a two dimensional array contains a copy of the same finite automaton. Each of these automata is assigned an initial state and a set of "neighbors" or squares with which it can communicate. From the initial state, subsequent states are computed by means of a transition function, which maps the current state of a square and that of its neighbors into the state of that square

one time step later. Since the same automaton occupies every square of the array, the same local transition function is defined at every point within the space.

Within this abstract framework a rather natural definition of the cerebellar cortex model is possible. Because of the assumed structural homogeneity of the cortex, the same transition function can be used at every point within the 6 mm. square area. Interactions among neurons are assumed to occur only through synapses. Thus, specification of the set of unit regions which contain neurons whose axons terminate within a particular unit region of the space defines the set of neighbors of that *cell* in the space. Structural homogeneity guarantees that the neighborhood relations will be invariant throughout the 6 mm. square region.

The next state of the model, in addition to depending upon the current state, is determined by the input to the cortex. Mossy fiber input to the model consists of a diffuse, randomly-generated background activity upon which is superimposed a nonrandom component specified by the investigator. Specification of this component as well as input to the parallel fibers and antidromic Purkinje stimulation is accomplished in two steps. First, a spatial map presented on the visual display allows the investigator to select with a light pen the set of *cells* which are to receive a nonrandom input (e.g., a sharply-defined surface stimulus or a relatively diffuse mossy fiber input to a large area of cortex). Then, through the PDP-7 keyboard, the amplitude and time course of the spatially-defined inputs can be specified.

A typical run of the simulation begins with the specification of nine parameters, giving the strengths of the various synaptic connections within the cortex. [A strength of zero indicates that a particular connection, e.g., the Purkinje recurrent collateral termination on Golgi cells, does not exist.] Once this parameter set has been given, an experiment is defined by means of a command language macroprogramming facility developed by the author. Any sequence of commands constitutes an experiment. Therefore, the input to the cortex is not limited to a single stimulus, but may consist of a number of different stimuli interacting in time and space. After an "experiment" has been so defined, all further investigator interaction is optional. The output in terms of the average firing frequencies of all four populations of neurons at every point in the space is either saved on movie film or stored on the disk for later processing. However, especially during the early stages of exploration of a parameter set, interaction with the program is necessary while the simulation is in progress. This interaction is particularly useful for determining a set of parameters which gives stable firing behavior in the appropriate range for the four neuronal populations, when the only input is the diffuse mossy fiber background activity.

RESULTS

Time Course of Inhibition in Purkinje Cells After Single LOC Stimuli

In Purkinje cells of the anesthetized cat a single stimulus given

through a small concentric electrode to the surface of the cortex causes a prolonged period of inhibition* (8). A typical response is shown in the intracellular record of Figure 11A. The hyperpolarization following the stimulus has been attributed to the IPSP induced by activation of basket cells by the excited parallel fibers (4), whereas its long rise time (15-18 msec.) has been explained by special anatomical properties of the basket cell synapse with Purkinje cells. For example, it has been suggested that the large separation between presynaptic terminals and the presumed receptor sites on the Purkinje cell soma and pre-axon region may contribute to the slow onset and long duration of the IPSP by causing a gradual buildup of transmitter at the receptor site (4). Another explanation for the time course of the IPSP attributes the long rise time to the glial encapsulation which surrounds the synapse, thereby preventing the rapid dissipation of transmitter (4).

An examination of the simulated Purkinje response of a cell 300μ off-beam to a single LOC stimulus (Figure 11B) demonstrates that the time course of inhibition in Purkinje cells can be explained without postulating special properties for this synapse. As in the intracellular record, there is a slow build-up to a maximum, followed by a slow recovery to the baseline. However, since in the model no special assumption was made for the basket cell synapse, the time course must be a result of a spatio-temporal summation of inhibitory and excitatory post-synaptic

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* A local stimulus to the surface of the cortex (LOC) excites a "beam" of parallel fibers. The terms "on-beam" and "off-beam" used in reference to a cell indicate whether that cell is situated so as to receive direct excitation (on-beam) or is positioned off the excited beam of parallel fibers (off-beam).

potentials, all of which have a very brief rising phase.

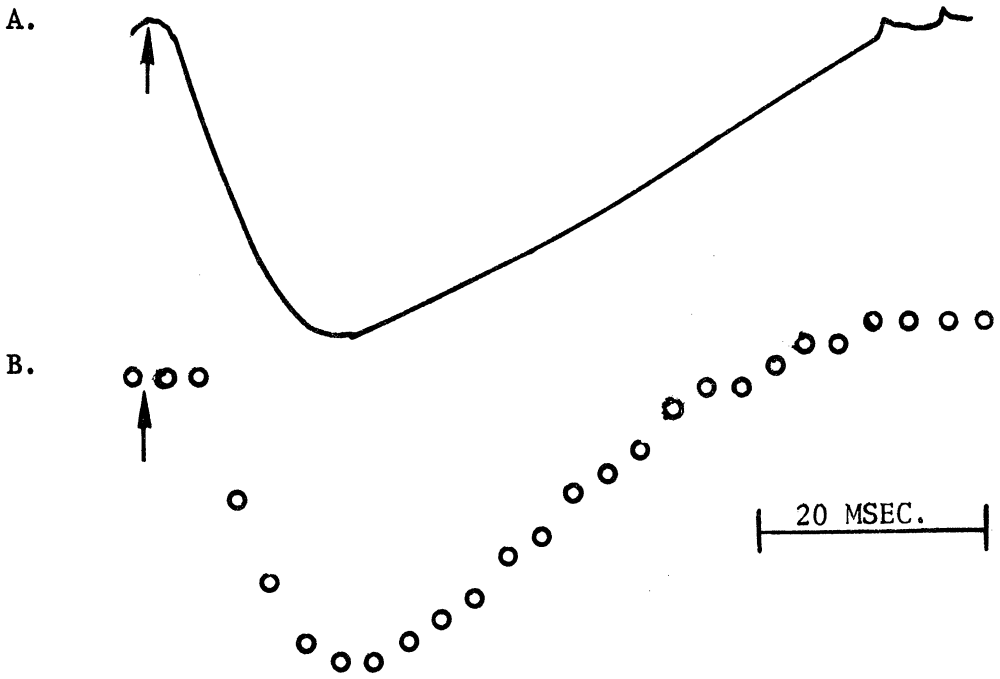

FIGURE 11. Time Course of Inhibition in Purkinje Cells Following Single LOC Stimulus. A. Intracellular record from cat Purkinje cell (Eccles, Llinas and Sasaki, 1966 (8)). B. Simulated Purkinje cell response, 300 μ off-beam. Time calibration as illustrated.

Further evidence is provided by Figure 12, in which the time course of inhibition in Purkinje cells after a LOC stimulus is compared with the simulated time course of an on-beam cell. In this case, the time course of inhibition was determined by measuring the amplitude of the antidromic Purkinje spike potential evoked by deep white matter stimulation at different time intervals after the surface stimulus (9).

The agreement in rise time (30 msec. to peak amplitude) and in total duration (105 msec.) is excellent.

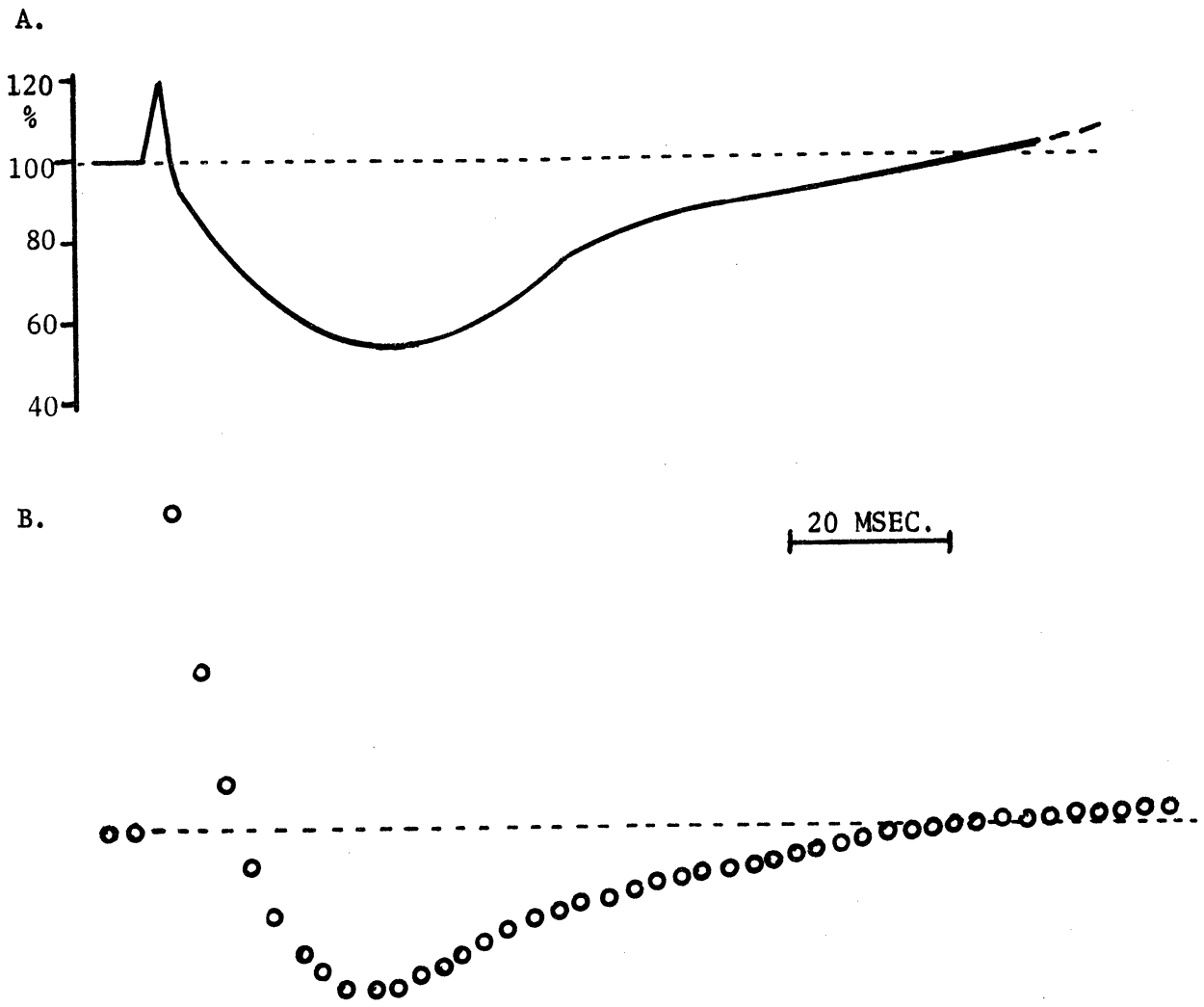

FIGURE 12. Time Course of Inhibition in Purkinje Cells Following a Single LOC Stimulus. A. Time course of the action exerted by a parallel fiber volley on the antidromic spike potential. Ordinate gives percentage of mean control response amplitude. Abscissa is the stimulus interval between surface (LOC) and antidromic(JF) stimuli. (Redrawn from Eccles, Llinas and Sasaki (9)). B. Simulated Purkinje potential on-beam following single LOC stimulus. Abscissal scaling same as in A.

Effect of Stimulus Strength on the Duration of Inhibition

An investigation of the effect of stimulus strength on the duration of inhibition in Purkinje cells reveals an approximately linear increase in the duration of inhibition with stimulus strength over a range roughly corresponding to that employed in physiological experiments (Figure 13). The 15 msec. difference between the duration of inhibition on-beam and 900μ off-beam in the simulated output is probably due to the reduction of background granule cell discharge on-beam caused by activation of Golgi cells. For comparison, a series from Eccles, Llinás and Sasaki (8) is plotted with the simulated results.

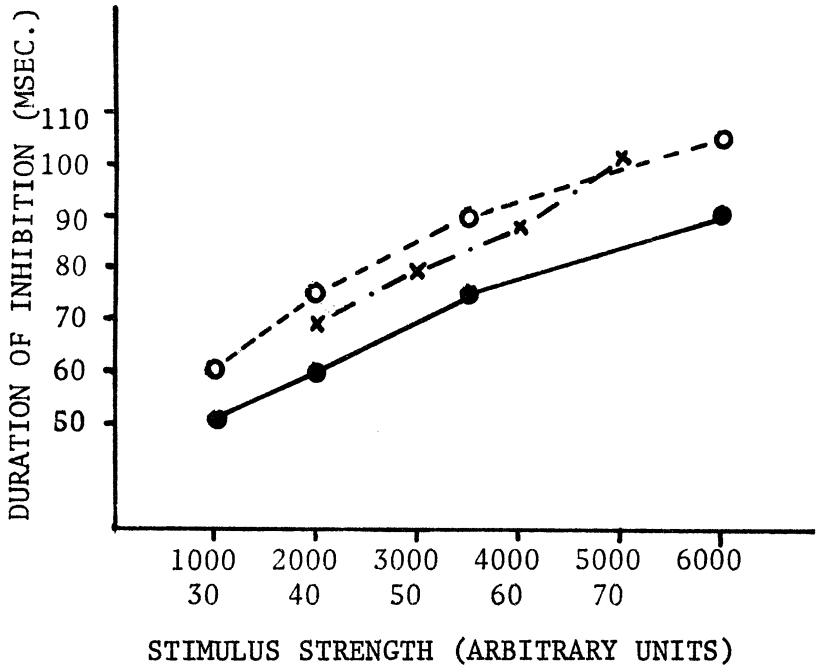

FIGURE 13. Effect of Stimulus Strength on the Duration of Inhibition in Purkinje Cells After Single LOC Stimulus. Simulated duration on-beam (open circles) is approximately 15 msec. longer than that 900 μ off-beam (filled circles). For comparison, a series from Eccles, Llinas and Sasaki (8) is plotted on the same axes (crosses). Top stimulus strength scale is for simulated results, bottom scale for physiological data.

Response of Cerebellar Neurons to Double LOC Stimuli

The response of cerebellar neurons to a pair of LOC stimuli delivered sequentially through the same electrode has been examined by Eccles et al. (5,8). When the interval separating the conditioning and test stimuli was less than 45 msec., a significant facilitation was observed in the response of Golgi and basket cells to the test stimulus (5). In Figure 14, the simulated extracellular response of an on-beam basket cell to a test stimulus alone (A) and to the test stimulus preceded 30 msec. before by a conditioning stimulus (B) are given. As in the physiological experiment, the response to the test stimulus is facilitated by a preceding conditioning volley, the number of spikes increasing from four to five.

Intracellular recording from a Purkinje cell during the same double pulse stimulation, however, produced an unexpected finding. The IPSP induced by the test stimulus was found by Eccles et al. (8) to be markedly depressed despite considerable potentiation of the basket cell response presumably responsible for the IPSP. Three possible explanations were given for this depression: depletion of transmitter in basket cell terminals, desensitization of the post-synaptic membrane, and approximation of the membrane potential to the equilibrium potential of the inhibitory synaptic current (4).

Figure 15 shows the simulated Purkinje potential to the test stimulus alone (A) and to the test stimulus preceded by the conditioning volley (B). It is apparent at this interval between the two stimuli that the inhibition resulting from the second stimulus does not exceed appreciably the

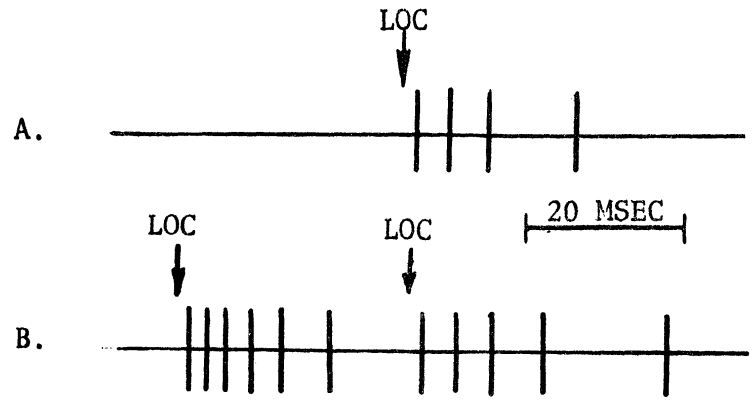

FIGURE 14. Simulated Extracellular Potential In On-beam Basket Cell Evoked By Two Parallel Fiber Volleys. A. Response to test stimulus. B. Response to conditioning and test stimuli. Strength of conditioning stimulus is approximately double that of test stimulus. Interval between stimuli: 30 msec.

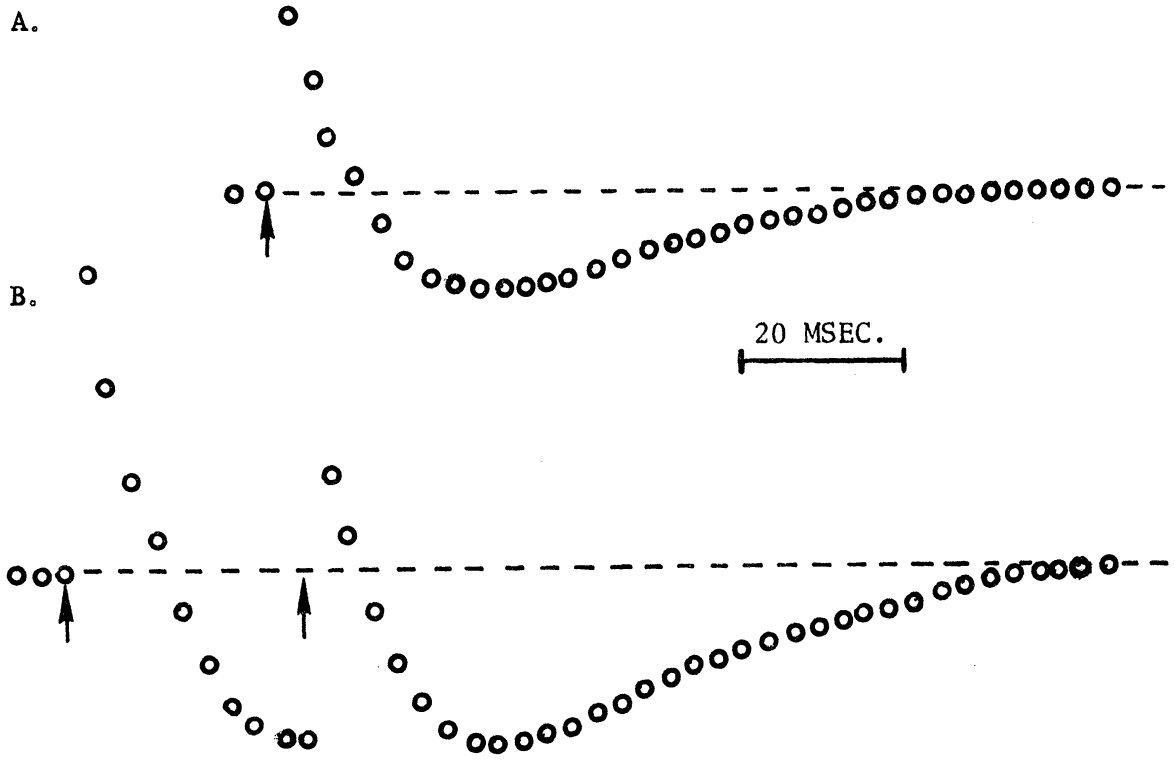

FIGURE 15. Simulated Purkinje Potential During Two Parallel Fiber Volleys. (LOC→LOC). A. Response to test stimulus. B. Response to conditioning and test stimuli. Stimulus parameters same as in FIGURE 14.

peak level of inhibition caused by the conditioning stimulus. Since no assumption of nonlinearity in the synaptic process was made, the resulting depression in the amplitude of the inhibition induced by the test stimulus must be a result of spatio-temporal activity of the neuronal populations responsible for this inhibition.

Because of the demonstrable facilitation in the evoked basket cell response, it is unlikely that this depression is caused by a change in the basket cell activity. An alternative hypothesis is generated by a consideration of the effect of the strong conditioning volley on the activity of Golgi cells. The excitation of Golgi cells by this volley would have the effect of reducing the background excitatory input to Purkinje cells, thereby adding to the observed inhibition. As shown in Figure 13, the reduction in background granule cell discharge by activation of Golgi cells can increase the duration of inhibition by as much as 15 msec. Therefore, a possible explanation for the depression might be that the contribution of Golgi cells to the observed inhibition generated by the test stimulus was reduced by the conditioning volley. This would be the case if, for example, the Golgi cell spike train evoked by the conditioning volley were able to completely suppress the granule cell background discharge. The second stimulus would then have little additional effect. The nonlinearity introduced would be the inherent one of a threshold element, rather than a special property of synaptic transmission.

The Role of the Purkinje Cell Recurrent Collaterals

The functional importance of a weak Purkinje recurrent collateral system has been questioned by Eccles and his colleagues (4). Physiological

evidence has been presented which indicates that antidromic stimulation of Purkinje cell axons has only a small inhibitory effect on the activity of inhibitory interneurons and Purkinje cells (5,9). Because of the ease with which various neuronal components can be eliminated from the model, it was decided to investigate the effect of Purkinje recurrent collaterals on the overall response of the cortex using this technique.

In Figure 16 the transverse profile of inhibition in Purkinje cells after a single LOC stimulus is illustrated by the simulated Purkinje potential on-beam, and 300, 600 and 900μ off-beam. The time course and overall duration of inhibition are similar at all four locations, except that the inhibition on-beam is preceded by an EPSP resulting from direct parallel fiber excitation of Purkinje cells.

In order to examine the influence of Purkinje recurrent collaterals on this spatio-temporal pattern of inhibition, various parameters of the response have been investigated. It seemed likely that the peak amplitude of inhibition might be affected by the presence of recurrent collaterals to basket and Golgi cells. However, an examination of Figure 17 shows little difference in the amplitude of inhibition at distances of 0, 300, 600 and 900μ off-beam between the model with a weak recurrent collateral system and with this system eliminated.

When the duration of inhibition is examined, however, (Figure 18) a significant difference is seen between these two cases. While the variance in duration is small with recurrent collaterals present, elimination of this system produces increased variation in this parameter of the response. Selective elimination of the recurrent collaterals to basket cells leads to a marked reduction in the duration of inhibition

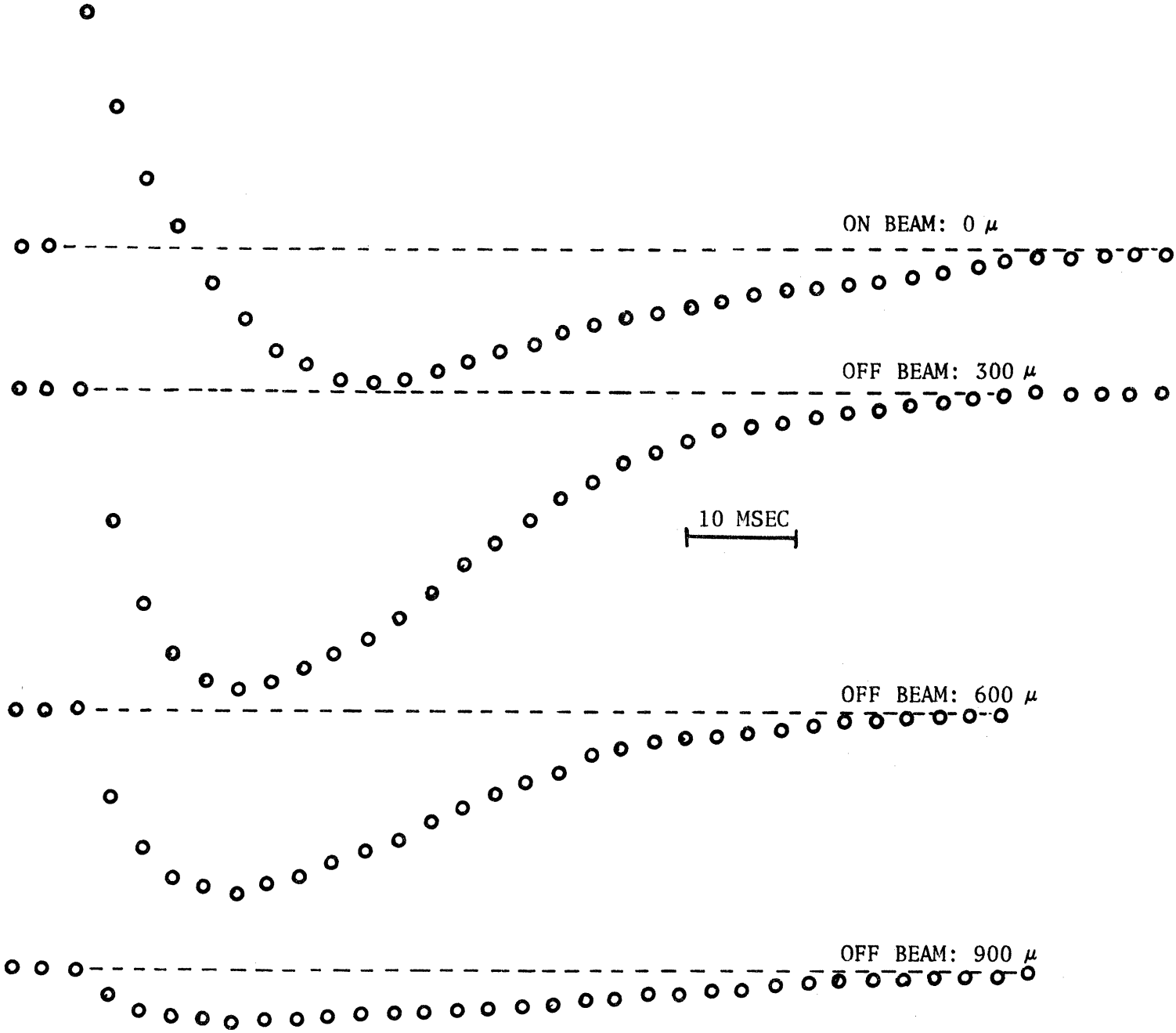

FIGURE 16. Transverse Profile of Inhibition in Purkinje Cells Following Single LOC Stimulus.

at all locations without affecting its variance appreciably, whereas removal of the Purkinje collaterals to Golgi cells (not shown) leads to a locally-unstable condition in which the duration of inhibition becomes infinite.

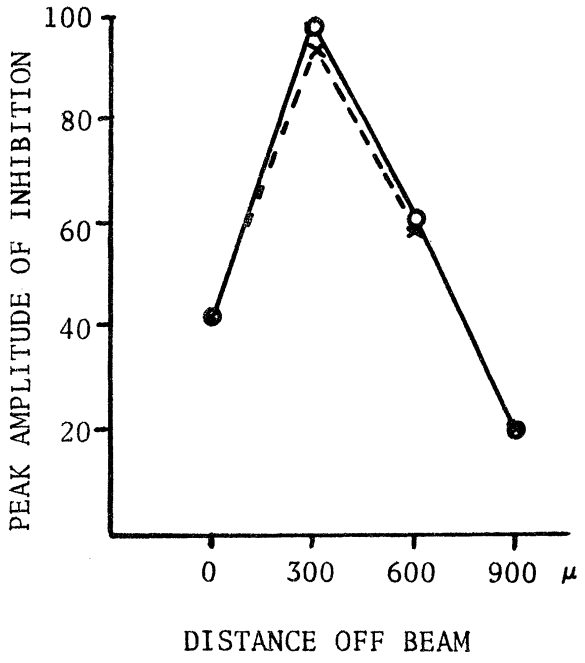

FIGURE 17. Spatial Distribution of the Peak Amplitude of Inhibition in Purkinje Cells After Single LOC Stimulus. The distribution with Purkinje recurrent collaterals (dashed lines) is compared to that without recurrent collaterals (solid lines).

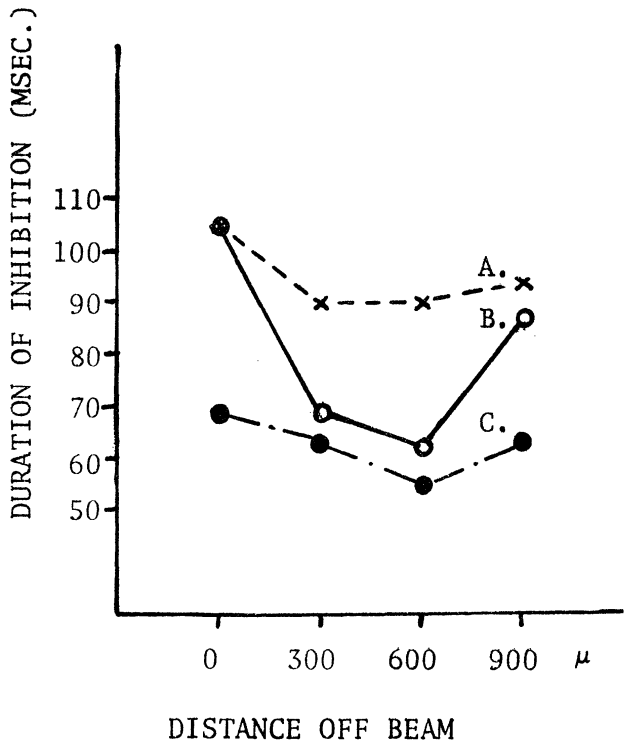

FIGURE 18. Spatial Distribution of the Duration of Inhibition in Purkinje Cells After Single LOC Stimulus. A. With recurrent collaterals (crosses). B. With no recurrent collaterals (open circles). C. Without recurrent collaterals to basket cells (filled circles).

These results suggest that the Purkinje recurrent collaterals to basket cells affect the overall duration of inhibition in Purkinje cells following a LOC stimulus, while the recurrent collaterals to Golgi cells reduce the variance in the duration of inhibition of Purkinje cells situated in a plane transverse to the excited beam of parallel fibers. If, as has been suggested (4), the inhibition of Purkinje cells is an important output of the cortex, the recurrent collateral plexuses could have important functional significance. The set of Purkinje cells projecting to a single cerebellar nuclear neuron has been shown to be distributed over a wide region of cortex (18). The synchron-

ization of the activity of these Purkinje cells achieved by reducing the variance in the period of inhibition may serve to sharpen the response of the cerebellum to mossy fiber input. While any hypothesis relating to the specific function of the recurrent collaterals requires further investigation, it is clear that a weak collateral system cannot be ignored.

Response to Mossy Fiber Input

The response of the cortex to natural inputs along the mossy fiber pathway was investigated by superimposing upon the randomly distributed background input, a ramp increase in the firing frequencies of mossy fibers in a 900μ by 1500μ elliptical focus (See Figure 19A).

The simulated Purkinje potential produced on-beam to this stimulus (Figure 19B) shows little increase in amplitude, slowly becoming more and more inhibited and only very gradually returning to the baseline after termination of the ramp input. Shortly after the beginning of this period of inhibition (indicated by arrow), Purkinje cell firing is completely suppressed. After this time all further information about the time course of the input would be completely lost, unless it was recoverable by some device such as the postulated climbing fiber read-out mechanism (4).

An on-beam basket cell, on the other hand, responds to this input by increasing its firing rate in an approximately linear manner (Figure 19C), preserving information about the time course of the ramp increase in mossy fiber firing frequency. Although the functional significance

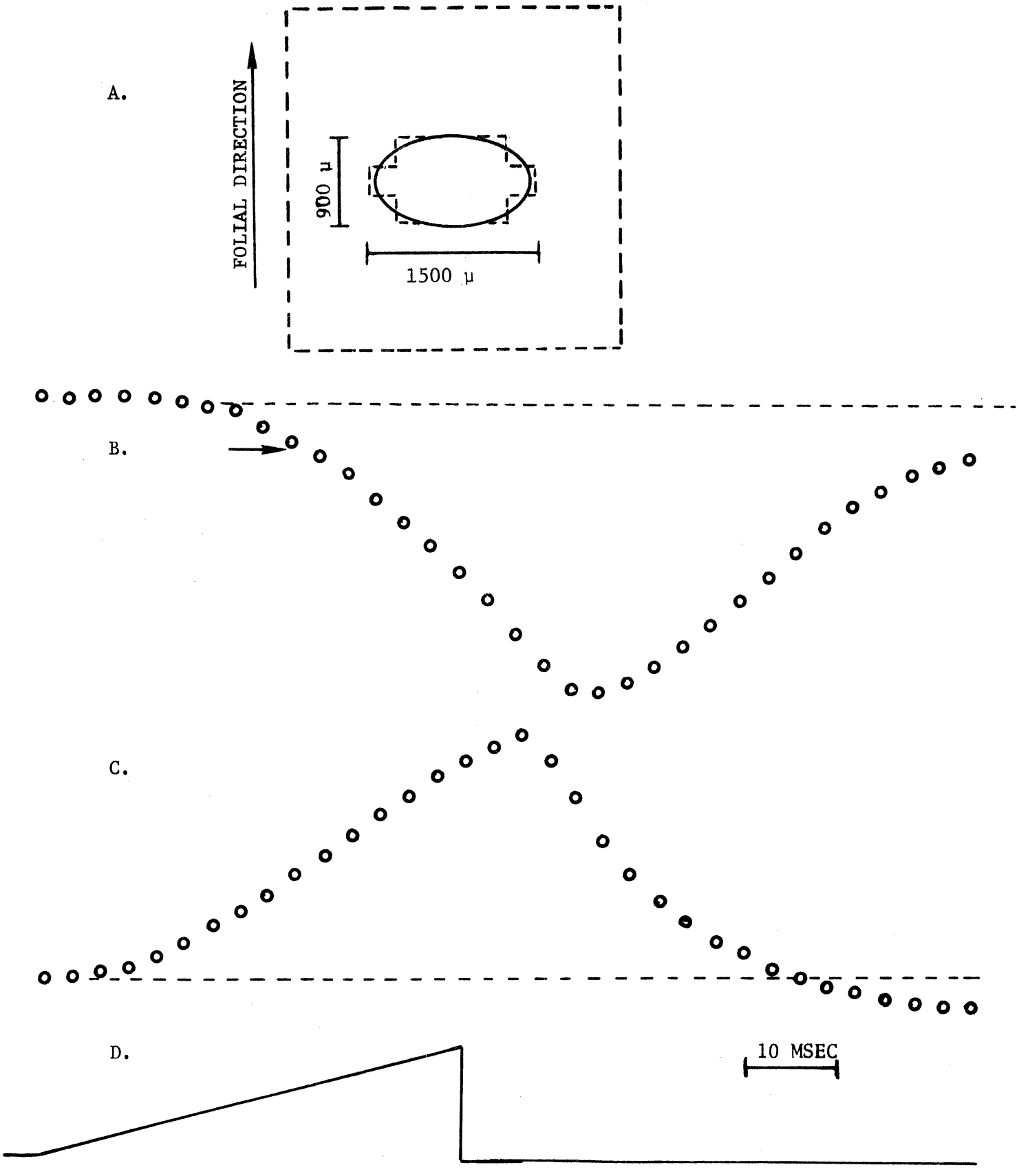

FIGURE 19. Response of On-beam Purkinje and Basket Cells to Ramp Mossy Fiber Input. A. Elliptical focus of mossy fiber input. B. On-beam Purkinje potential. Arrow indicates zero firing rate. C. On-beam basket potential. D. Time course of mossy fiber input. Time calibration as indicated. Ordinate of B and C: firing rate of Purkinje and basket cells. Upward direction indicates increase.

of this transfer function is unknown, it seems unlikely that information about the time course of mossy fiber inputs would be preserved only in the firing pattern of an interneuron which has no axon leaving the cortex.

Several explanations can be given for the apparently disfunctional transfer function of the cortex:

1. Information is preserved in the amplitude of the compound IPSP induced in Purkinje cells, which is "read-out" by climbing fibers.

2. Through a temporal-to-spatial transformation, information about the time course of the mossy fiber input is preserved in Purkinje cell activity. However, this information is distributed throughout a large ensemble of Purkinje cells, so that the firing pattern of any one gives little information about the time course of the input.

3. The model parameters, selected to give reasonable values of spontaneous activity in anesthetized cats, are not appropriate for representation of neuronal activity in the awake, unanesthetized animal.

Since it has not been demonstrated explicitly that a climbing fiber response generates more than one conducted spike (13), the first explanation must be regarded as tentative. Even assuming that all climbing fiber-evoked spikes are conducted, it is doubtful that the number of spikes evoked in a climbing fiber response can be distinguished from mossy fiber-induced activity by the cerebellar nuclear neurons.

The demonstrable relationship between the firing of single Purkinje cells and the time course of natural stimuli seems to indicate

that single Purkinje cells preserve much of the information about the time course of mossy fiber input. In an experiment in which Purkinje cells were recorded in the awake monkey during rapidly alternating arm movements, many Purkinje cells were found to have firing patterns displaying consistent temporal relationships to the movement (27). While such results cannot be taken as evidence against a temporal-to-spatial transformation, it is clear that the firing pattern of single Purkinje cells carries a significant amount of information about the time course of natural inputs.

A recent study of the effect of anesthesia on the activity of Purkinje cells in the cerebellum of a cat (2) lends some support to the third explanation. The strong off-beam inhibition of Purkinje cells seen in the anesthetized cat after a single LOC stimulus was replaced by facilitation in the unanesthetized preparation. A series of trials carried out at different levels of anesthesia showed this reversal of inhibition to be graded phenomenon. It seems likely from these results that the level of spontaneous activity of the four neuronal populations can have an important effect on the cortical response to electrical stimuli. It is not unreasonable therefore, to suppose that the transfer function of the cortex for the unanesthetized preparation differs greatly from that for the anesthetized cat. A new series of computer experiments is currently being run to investigate this possibility.

CONCLUSIONS

Three questions were posed in the introduction to this report. Although they were physiological in nature, it was clear, due to the

complexity of the system being investigated and the difficulty in carrying out experiments, that the only feasible approach to these questions was through modeling and computer simulation.

Through abstraction from the real system, it has been possible to demonstrate that many of the heretofore unexplained characteristics of cortical activity are the natural result of spatio-temporal interaction of the four neuronal populations. While there are probably aspects of cortical activity which cannot be explained by the model, it appears that the presently available information about the patterns of neuronal connectivity and the time course of unit events in the cortex is sufficient to explain at least the major features of the cortical response of anesthetized cats.

The importance of the Purkinje recurrent collateral system has been established. While the functional significance of these collaterals is still not entirely clear, it is now possible to suggest what parameters of the cortical response they influence.

The transfer function of the cortex to natural inputs along the mossy fiber pathway raises still more fundamental questions about the function of the cerebellar cortex: Is the important output of the cortex the inhibition of background Purkinje cell activity or an increase in Purkinje cell firing frequency? Or both? What is the functional significance of the difference in cortical response between anesthetized and unanesthetized animals? The investigation of these questions will require a coordinated program of neurophysiological experiment and modeling.

SUMMARY

1. An automata-theoretic model of the mossy fiber system of mammalian cerebellar cortex was developed to investigate the role of the four neural populations in determining the spatio-temporal response of the cortex to natural and electrical stimuli.

2. A set of difference equations suitable for computer simulation was defined by restricting the model to a 6 mm. square region of cortex and discretizing space and time. Current anatomical and physiological information about cerebellar circuitry, the distribution of dendritic and axonal plexuses, and the time course of post-synaptic potentials was used to determine initial parameter values.

3. Simulation results are in substantial agreement with the physiological data of Eccles et al. (1,5,6,7,8,9,10,11,12)and suggest that the observed time course of activity in the cerebellar cortex of an anesthetized cat following electrical stimulation may be explained by a relatively simple model.

    a. The simulated time course of inhibition in Purkinje cells following a single stimulus to the surface of the cortex (LOC) demonstrates that the slow onset and prolonged time course of inhibition recorded from cat cerebellar cortex can be explained by a spatio-temporal summation of post-synaptic potentials with exponential time courses, without postulating nonlinear properties for synaptic transmission.

    b. An approximately linear relationship between the strength

of the LOC stimulus and the duration of inhibition in Purkinje cells which is predicted by the model is substantiated by physiological data.

c. The time course of facilitation and inhibition in the cortex is explored by simulating the cortical response to two stimuli given through the same surface electrode (LOC → LOC). As in the published experimental results (5), facilitation in the simulated extracellular response of on-beam basket cells is evident when the test stimulus is preceded by a conditioning stimulus. The facilitation is accompanied by a depression in the amplitude of inhibition of Purkinje cells. This depression, which had been attributed to nonlinearities in synaptic transmission, is given an alternative explanation.

d. Investigation of the role of Purkinje recurrent collaterals shows that a weak collateral system has little effect on the peak amplitude of inhibition in Purkinje cells, but exerts an important influence on its duration. The possible functional significance of this relationship is discussed.

e. The electrophysiological response of the cortex to natural inputs along the mossy fiber pathway is examined by simulating a ramp increase in mossy fiber activity to a broad elliptical area. An approximately linear increase in basket cell firing frequency is observed, whereas Purkinje cell firing is completely suppressed throughout the period of stimulation. Several explanations for this transfer function are discussed and evaluated.

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