A THEORY OF CEREBELLAR FUNCTION WITH APPLICATIONS TO LOCOMOTION. I. THE PHYSIOLOGICAL ROLE OF CLIMBING FIBER INPUTS IN ANTERIOR LOBE OPERATION[†]

C. Curtis Boylls, Jr.
Neurological Sciences Institute
of
Good Samaritan Hospital and Medical Center
Portland, Oregon

COINS Technical Report 75C-6

(August 1975)

Abstract

The cat anterior lobe cerebellum appears to be subdivided into sagittal compartments, each influencing a specific class of muscles. This report proposes that the spino-olivocerebellar, climbing fiber system, which terminates cortically in the sagittal strip zones of Oscarsson, effects redistributions of activity among those compartments. The spino-olivocerebellar system thus becomes one means whereby intrinsic spinal locomotor circuits bias cerebellar outflow to accord with muscle usage in different gaits.

[†]This work was supported in part by NIH Grant No. 5 R01 NS09755-3 COM awarded to M. A. Arbib, Computer and Information Sciences, University of Massachusetts, Amherst, Mass., and by NIH grants NS-06728-06 to C. C. Bell and NS-02289-16 to D. S. Rushmer of the Neurological Sciences Institute of Good Samaritan Hospital and Medical Center, Portland, Oregon.

A THEORY OF CEREBELLAR FUNCTION WITH APPLICATIONS TO LOCOMOTION. I. THE PHYSIOLOGICAL ROLE OF CLIMBING FIBER INPUTS IN ANTERIOR LOBE OPERATION[†]

C. Curtis Boylls, Jr.
Neurological Sciences Institute
of
Good Samaritan Hospital and Medical Center
Portland, Oregon

COINS Technical Report 75C-6

(August 1975)

Abstract

The cat anterior lobe cerebellum appears to be subdivided into sagittal compartments, each influencing a specific class of muscles. This report proposes that the spino-olivocerebellar, climbing fiber system, which terminates cortically in the sagittal strip zones of Oscarsson, effects redistributions of activity among those compartments. The spino-olivocerebellar system thus becomes one means whereby intrinsic spinal locomotor circuits bias cerebellar outflow to accord with muscle usage in different gaits.

[†]This work was supported in part by NIH Grant No. 5 R01 NS09755-3 COM awarded to M. A. Arbib, Computer and Information Sciences, University of Massachusetts, Amherst, Mass., and by NIH grants NS-06728-06 to C. C. Bell and NS-02289-16 to D. S. Rushmer of the Neurological Sciences Institute of Good Samaritan Hospital and Medical Center, Portland, Oregon.

A mathematical model of the anterior lobe cerebellar cortex, underlying cerebellar nuclei, and certain pre-cerebellar reticular nuclei is constructed and its responses to climbing fiber strip inputs ascertained. It is shown that such inputs leave intact the cerebellar nuclear excitation within the sagittal compartment where they are received, but cause nuclear regions in neighboring compartments to become suppressed. The agency of such suppression is lateral recurrent inhibition achieved primarily through parallel fiber diffusion of reticulocerebellar recurrent excitation arriving on slow mossy fibers. This excitation is also found to cause retention of compartmental activity distributions for substantial periods of time (perhaps seconds). The cerebellar anterior lobe complex may thus possess a dynamic (as distinct from plastic) short-term memory capacity.

Anatomical and physiological features of the anterior lobe leading to the above phenomena are treated in detail in the discussion. Experimental tests are proposed and speculations advanced on the spino-olivocerebellar encoding of gait information from spinal locomotor circuits. It is suggested that the short-term reprogramming of anterior lobe outflow by the climbing fiber system implies that activity in the latter may be interpretable only in the slowly changing context of holistic motor acts, rather than in the immediate modulation of movements comprising such acts.

Acknowledgments

The author wishes to express his sincere gratitude to Dr. M. A. Arbib for guidance in all aspects of this research, to Drs. W. L. Kilmer and P. H. Greene for their insight into many of the problems, to Drs. P. Dev, J. D. Cowan, W. T. Thach, E. Bizzi, W. A. Spencer, C. C. Bell, W. J. Roberts, R. J. Grimm, and L. T. Robertson for numerous useful discussions, and to Ms. Marilyn C. Donner for ably typing the manuscript.

A THEORY OF CEREBELLAR FUNCTION WITH APPLICATIONS TO LOCOMOTION. I. THE PHYSIOLOGICAL ROLE OF CLIMBING FIBER INPUTS IN ANTERIOR LOBE OPERATION

1. Introduction

The locomoting mesencephalic (or thalamic) cat preparation described by Shik, Orlovskii, and their coworkers[198,239,240] supplies forms of motor behavior akin to those of the intact animal. Removal of the cerebellum adversely affects mesencephalic locomotor coordination[200], indicating that the organ may still be fulfilling portions of its normal locomotor role. The absence of the cerebral hemispheres dictates that the so-called vestibular and spinal divisions of the cerebellum, the anterior lobe in particular, must also account for most of cerebellar computation during mesencephalic locomotion. In the mesencephalic cat, then, one has the opportunity to explore anterior lobe function using the wide literature available on its spinal relationships, without the complications introduced by cerebral inputs present in intact animals. This report describes the specification, mathematical treatment, and computer simulation of the physiology of cat anterior lobe cortex and of several cerebellar and brainstem nuclei intimately related to it. Each of these centers appears to be critically involved in synthesizing the cerebellar locomotor contribution. The work aims at discovering, at least in theory, just what sort of physiological impact cerebellar climbing fibers have upon the anterior lobe. Given this, an attempt will be made to deduce, in an abstract fashion, the type of information

transmitted to the cerebellum on the spino-olivocerebellar pathways. Application of the findings specifically to the mesencephalic cat are reported elsewhere[36]. Conjectures on generalization of the anterior lobe theory to other cerebellar regions and behaviors have also been developed[37]. Portions of the results have appeared in brief[8,247].

As will be described in various subsequent sections, the cerebellar climbing fiber system is phylogenetically as old as the organ itself. And in one sense, climbing fibers have a very straightforward physiological function. Each contacts a single cortical Purkinje cell (and gives off a modest number of excitatory collaterals to cerebellar nuclear cells); when it fires, it causes the Purkinje cell to emit a brief burst of spikes at very high frequency, usually followed by a short pause of variable duration (nuclear cells, of course, are momentarily excited by the collaterals). In another sense, the physiological role of climbing fiber inputs is almost completely opaque. Save under very special (and sometimes questionable) circumstances, climbing fibers show little or no activity correlation with ongoing movement or with sensory events in behaving animals. Physiologists have almost come to expect them to be "doing nothing" in behavioral experiments. Yet when their seemingly random firings are interrupted, as after a lesion of the inferior olive, "cerebellar" motor deficits appear. Current theories of climbing fiber function range from near-restatements of experimental observations, with no attempt at behavioral correlation, to direct identifications of climbing fiber action with attributes of motor behavior (starting and stopping movements, acquisition of skill or motor learning), but with little attempt at physiological correlation. The

present report attempts to construct a theory of what climbing fibers do which has both a sound physiological and behavioral basis. To begin that work requires that working hypotheses be developed on the organization of cerebellar motor modulation. These hypotheses will be drawn from the example of locomotion:

Locomotor control from the standpoint of spinal mechanisms has recently received thorough review by Grillner[127], while the author has surveyed the descending influences upon those mechanisms[36]. It is evident from the two studies that cerebellar outflow likely only modulates locomotor performance. Fundamental algorithms for stepping patterns in the paired hindlimbs have been shown to reside spinally in low spinal cats both chronically[124] and following DOPA or chlonidine injections acutely[109,124]. Indeed it would seem that the effect of brainstem "locomotor region" stimulation in the mesencephalic cat is precisely to facilitate noradrenergic reticulospinal paths[128]. That a basic program for cat locomotion be spinally localized is not surprising in the light of results on lower forms[125,126,144,148,245]. Anomalies involving lateral stability and limb extension do occur in chlonidine[109] or chronic spinal[124] cats, demonstrating that the spinal locomotory prescription but defines global movement contraints.

The aforementioned ataxia of the decerebellate, mesencephalic cat speaks for cerebellar involvement in the supraspinal tuning of spinal locomotor programs. In fact, using autoradiography, Edwards[102] has now traced substantial descending projections from the cat locomotor region (cuneiform nucleus) to the nucleus reticularis tegmenti pontis, lateral reticular nucleus, various reticulospinal nuclei, locus coeruleus, and medila accessory olive, all of which are immediately

pre- or postsynaptic to the spinocerebellum. Thus, the noradrenergic potentiation of spinal locomotor circuits by cuneiform nucleus stimulation simultaneously will potentiate the cerebellar system required for locomotor modulation (for details, see ref. 36). What must be the format of this modulation, and how is it constructed?

In the mesencephalic cat cerebellar locomotor intervention should necessarily be revealed in activities of the Deiters and (magnocellular) red nuclei and of the pontine and medullary reticular formation. These are the only spinally-projecting centers not supremely dependent upon inflow from the cerebral hemispheres. Thus, many reticular[200] and most rubral[204] and Deiters[203] neurons show cyclic variation of activity with phases of limb step cycles, alterable by perturbations to the limbs and abolished by cerebellectomy. Neurons of the cerebellar nuclei[202] and cortical Purkinje cells[201] display similar locking to locomotion. Now (as will be discussed below) electrical stimulation of different regions in the red and Deiters nuclei leads to potentiation of particular muscle groups according to a somatotopic pattern. The anatomical substrate for this somatotopy is documented. The somatotopic organization is retained in the interpositus and fastigial nuclei that respectively excite red and Deiters. It follows that anterior lobe modulation of specific muscles at a given moment in time may well be encoded as a spatially differentiated distribution of neural activity within a cerebellar nucleus. On a broader scale, the findings of Voogt and others (to be described) indicate that the cerebellar cortex may also orchestrate activity among cerebellar and brainstem nuclei as well as within each. Thus, one should note that each brainstem target of the cerebellar nuclei seems to be characterized by a

functional specificity in terms of the muscles--that is, a propensity for selectively affecting either the physiological flexors or extensors, irrespective of somatotopy. Deiters nucleus and pontine reticular centers can, for example, be associated with extensors, and the red nucleus and medullary reticular regions with flexors. So given that distinct sectors of the fastigial and interpositus nuclei are connected with these functionally specific brainstem regions, it follows that a functionotopic, as well as somatotopic, organization obtains within the anterior lobe complex. Moreover, functionotopy exists even when somatotopy does not, as in the reticulospinal nuclei (below). From these considerations is drawn the first working hypothesis of this investigation:

> The format of anterior lobe locomotor modulation is one of changing spatial patterns of neuronal activity in the cerebellar nuclei. Each such pattern has an interpretation in terms of various functionally (and often somatotopically) defined groups of muscles.

In the studies of locomotion in spinal cats mentioned above, it was found that the gait (walk, trot, gallop) adopted by the animal was in part a function of locomotor speed (dictated by a treadmill). That is, on the basis of afferent information spinal mechanisms "decide" upon the gait. Now the utilization of muscles differs in different gaits, but not only in terms of obvious changes in EMG timing and in interlimb coordination[36,127]. The relative amplitudes of activity among muscles and sometimes actual muscles deployed, depend upon the gait. For instance, trunkal muscles become relatively more active in the gallops[122], where they are used to extend the stride[127] and

store elastic energy[119,131]. In certain animals (not cats) high-speed locomotion requires a shift from plantar- to digigrade stepping, requiring a restructuring of activity in distal extensors[127]. By the above hypothesis, one must then expect that qualitatively different cerebellar spatial activity patterns arise with different types of gait. Since the mesencephalic locomoting cat also retains the gait/speed dependency of the spinal cat (when locomotor region stimulation remains constant)[240], it is probable that cord mechanisms continue to decide on the gait even with the cerebellum in place. These observations lead to a second hypothesis:

> The cerebellar anterior lobe and associated nuclei must be informed of the choice of gait made by spinal locomotor mechanisms. The receipt of this information results in alterations of the spatial distribution of cerebellar neuronal activity so as to agree with the muscular usage within that gait.

It seems reasonable to assume that the cerebellum is informed of gait choices either by direct afferent information (in which instance it must largely duplicate the spinal decision-making process) and/or by monitoring activity in spinal locomotor circuitry generating various gaits. Grillner and Zangger[129] have recently shown that hindlimb deafferentation in mesencephalic cats has only a modest effect upon stepping EMG patterns in hindlimb muscles. This suggests that the cerebellum may receive its gait-choice data largely from internal spinal locomotor circuits. Arshavskii and coworkers[18,20,21] have directly demonstrated that one subset of so-called "fast" spinocerebellar tracts (VSCT and,

likely, RSCT; terminology of Eccles[90]) does transmit activity in locomotor generators to the anterior lobe via mossy fibers. Periodic activity within the VSCT in phase with stepping continues after deafferentation and cerebellectomy (the latter preventing fluctuations in descending pathways). However, this class of mossy inputs is probably not the only source of cerebellar information on spinal gait choices: Oscarsson has suggested that spino-reticulocerebellar, "slow" mossy fiber tracts[64,66] and spino-olivocerebellar climbing fiber pathways[207,208] are no doubt also related to spinal motor mechanisms. Unfortunately, recordings from spinal interneurons originating slow mossy or climbing fiber tracts during locomotion (or other behaviors) are not available. Still, drawing from earlier discussion, one arrives at a third hypothesis:

> One or more of the VSCT-RSCT, the spino-reticulocerebellar, or the spino-olivocerebellar pathways alters the spatial distribution of cerebellar neuronal activity to accord with muscle usage in spinally-selected locomotor gaits.

The present report examines the proposition that the spino-olivocerebellar system--the climbing fiber system of the anterior lobe--may have much to do with this spatial restructuring of cerebellar activity pursuant to different gaits. As mentioned earlier, it has been notoriously difficult to correlate climbing fiber activity with any attribute of immediate movement[172,252,253,254] (Grimm and Robertson, in preparation), save in the operation of the vestibulo-ocular reflex and the cerebellar flocculus (reviewed in ref. 37). Explicit studies

of anterior lobe climbing fibers during locomotion are still unavailable (observations on 3 Purkinje cells are reported by Orlovskii[201]). Lesions of the cat inferior olive, however, do appear to result in serious gait disturbances approximating those seen after cerebellectomy (for review, see refs. 9, 36). Therefore, despite the notion that the climbing fiber is related only to some sort of long-term plastic change in the cerebellar cortex[37], the evidence suggests that it also has an immediate impact upon cerebellar function, albeit one unrelated to the "on-line" control of movement.

The results to be reported here indicate that, in theory, the climbing fiber system is well suited to the production of distinct spatial patterns of neuronal activity within the cerebellar nuclei--or in other words, that the spino-olivocerebellar system may serve to redistribute activity among the various brainstem targets of cerebellar outflow in accordance with muscle usage in spinally-selected gait programs. It is shown that the anterior lobe may in fact be sharply tuned to the spatial properties of the strip-like climbing fiber projections onto the cerebellar cortex that have been described by Oscarsson, Armstrong, and others (below). Moreover, it is found that neuronal activity patterns set up by climbing fibers may be maintained for prolonged periods (perhaps seconds) by the reticulocerebellar recurrent excitation studied by Tsukahara. This dynamic (as distinct from plastic), short-term memory capacity has many implications both for the interpretation of climbing fiber properties and for the more abstract understanding of cerebellar motor modulation (addressed in refs. 36, 37). In particular, it reinforces the association of climbing fiber activity with classes of action (the gaits) rather than with ongoing acts within a

class (the kinematic events of a particular step).

The model of climbing fiber operation given below arises from a straightforward application of known cerebellar anatomy and physiology. Plasticity and other unproved and experimentally distant conjectures are avoided. The possibility that the VSCT-RSCT and spino-reticulocerebellar pathways could be responsible for like effects on the anterior lobe is not ruled out. Yet once the nature of the results is clear, it should become heuristically evident that these pathways may be better suited to other functions. Some speculations on those functions are given at the conclusion, along with methods of experimental test.

2. Architecture of the Anterior Lobe Model

2.1 Cerebellar Module

From the anatomies subserving cerebellar outflow through the red, Deiters, and reticulospinal nuclei in cats may be abstracted circuitry duplicated in each system. This replicated schema is herein termed the cerebellar module and is illustrated in figure 1. Names of certain specific structures have been replaced by generic labels: The "brainstem 'output' nucleus" thus may become the red, Deiters, or a reticulospinal nucleus in a specific situation. "Cerebellar nucleus" will then denote the appropriate portion of the interpositus or fastigial nucleus (the Deiters nucleus also shares some of the hallmarks of a "cerebellar nucleus;" see sections 2.2, 2.3). The hatching in figure 1 is intended as a reminder that some (not all) of the interconnections between the cerebellar and brainstem output nuclei are somatotopically organized. By "reticular nucleus" is meant any of

several pre-cerebellar nuclei (described below) receiving spinal inputs. As to other features of the module, the "fast" mossy fibers refer to components of the direct spinocerebellar pathways (VSCT, RSCT, DSCT, CCT) preferentially affecting the cerebellar cortex, while the "slow" emanate from pre-cerebellar reticular nuclei and reach both cortex and cerebellar nuclei. Only reticulocerebellar mossy fibers will be treated here. In addition, the physiological effects of climbing fibers and their nuclear collaterals are incorporated into the model, but the inferior olive per se is not. Evidence for possible extensions of the cerebellar module to areas outside the anterior lobe is given elsewhere[37].

Each component of figure 1 will now be examined in detail to the end of creating reasonable mathematical analogues for computer simulation. General assumptions embedded within that process are as follows:

1. All cerebellar nuclei are taken without proof to be topologically transformable into two-dimensional sheets in conformation with the cerebellar cortex. Specifically, two principal curvilinear "planes"-- one containing the parallel fibers ("mediolateral") and the other orthogonal to it ("sagittal")-- will also be used to localize corresponding underlying nuclear regions.

2. All pre-cerebellar reticular nuclei are also assumed warpable into sheets conforming with the cerebellar nuclei. Thus, the entire modular structure becomes unified by a single coordinate system based upon the cerebellar cortex.

3. Neuronal interconnections among sheets of the module are presumed representable in "template" fashion--that is, by diagrams showing

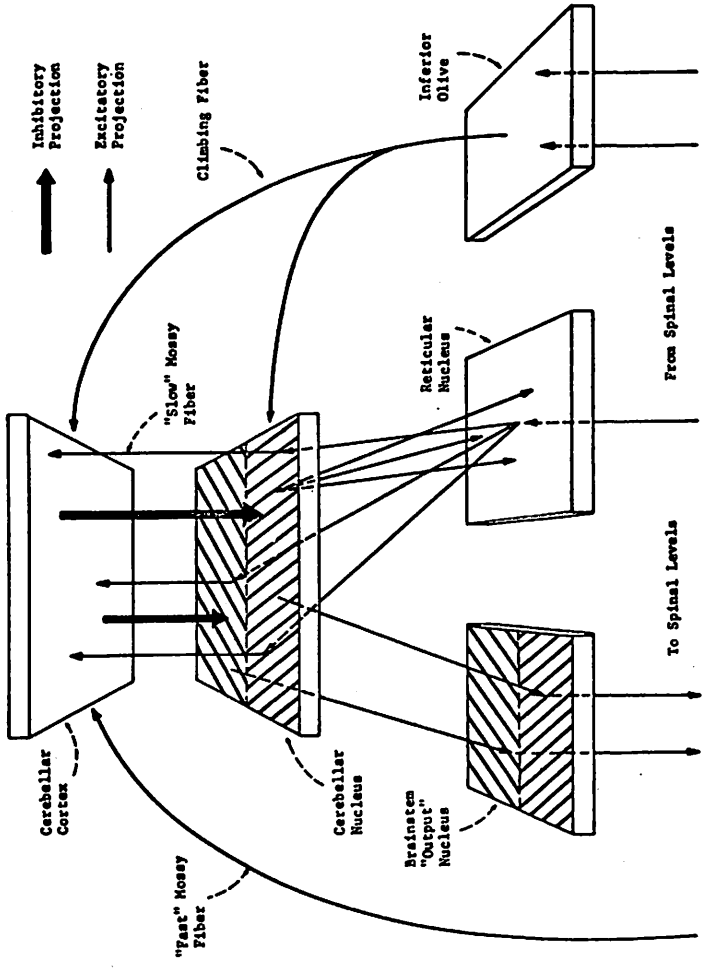

FIGURE 1

Components of the cerebellar module and their interconnections.

the field of influence in one structure of a typical neuron (or fiber) at an arbitrary location in the other. Template diagrams, then, are simply the complements of traditional receptive field mappings, with the important, additional assumption of spatial homogeneity.

2.2 Brainstem Output Nucleus and Cerebellar Nucleus

Each of the red and Deiters nuclei enjoys a gross somatotopic relation with bodily musculature. So likewise do their associated cerebellar nuclei. Thus, in particular, the anterior interpositus nucleus is known to project somatotopically to the (magnocellular) red nucleus in cat[69] and monkey[108] which in turn originates the somatotopic rubrospinal tract to the cord[196,222,225]. The facilitatory action of this pathway on the flexor musculature[134,220,236] has been mentioned above. Detailed monosynaptic effects may be stronger on distal, rather than proximal, flexor motoneurons[235,237,238] with a greater affinity for the forelimbs[38]. Likewise, the anterior fastigial nucleus affects Deiters nucleus[44,267] and thence the cord through the lateral vestibulospinal tract[169,196,221], all topographically; it appears that the proximal[235], extensor[135,170,220] muscles are most effectively aroused. Orlovskii has recorded from the red[204] and Deiters[203] nuclei during mesencephalic locomotion, finding their activities well correlated with the flexion and extension phases of the step cycle, respectively. In intact cats trained to flex and extend their elbows, Burton and Onoda (in press) have also demonstrated a correlation of interpositus activity with control of elbow flexors.

The reticulospinal projections influenced by the cerebellum, which arise principally from the nucleus reticularis pontis caudalis (NRPC) and the more caudal gigantocellularis (NRG), show little evidence

of somatotopic organization[256]. Nonetheless, anatomical considerations (see ref. 196 for review) suggest that NRPC has a functional specificity for extensors and NRG for flexors. Recordings from the vicinity of the NRG during mesencephalic walking show peaks of neural activity locked to the flexion phase of the ipsilateral hindlimb[202]. Cerebellectomy extinguishes this modulation[200]. The two reticulospinal nuclei probably receive much of their excitation from the fastigial nucleus, although the connections and their physiology are quite complex and are reviewed elsewhere[36]. The evidence indicates that the fastigial nucleus may be subdivided into a medial portion which excites the ipsilateral flexor and contralateral extensor reticular regions, and a lateral area projecting to the ipsilateral Deiters nucleus. This is somewhat contrary to the more traditional concept that the entire fastigial nucleus has its prime influence upon Deiters. Actual recordings from fastigial units[202], however, reveal many which are poorly related to Deiters activity, but are well in phase with reticulospinal neurons. This observation also indirectly emphasizes the well known direct Purkinje cell control of Deiters. Perhaps that nucleus at times should be considered "cerebellar" in the sense of figure 1. Deiters does also share some of the interrelations with pre-cerebellar reticular nuclei that are characteristic of the fastigial and interpositus nuclei (see section 2.3).

For modeling purposes, activity in the red, Deiters, and reticulospinal nuclei is taken to replicate events in their source cerebellar nuclei during mesencephalic locomotion. Thus, only the cerebellar nuclei will be explicitly represented in the analysis. The cessation of activity modulation in all these centers following

cerebellectomy (mentioned earlier) demonstrates that the direct spinal and labyrinthine inputs received by some of these regions contribute only secondarily to their operation. In fact, during locomotion some of these pathways may be suppressed, as are the labyrinthine inputs to Deiters nucleus[205].

2.3 Reticulocerebellar Interactions: Recurrent Excitation

It has become increasingly apparent that along with their classical projections to brainstem motor centers, the cerebellar nuclei also originate significant collateral outflow to particular pre-cerebellar reticular nuclei in cats. The latter in turn give rise to "slow" mossy fiber pathways which return excitatory collaterals to the cerebellar nuclei while continuing to the cortex (figure 1). The potential for regenerative effects or "reverberation" in these excitatory loops was pointed out in the past by Ito[138] and Tsukahara[260]. Physiological investigation of one such loop (between the nucleus reticularis tegmenti pontis (NRTP) and interpositus nucleus), in the absence of cerebellar cortical inhibition, has in fact revealed a potent reverberatory propensity[259,261].

The "rubral" cerebellar module embraces not only the above disynaptic, mutually-excitatory loop between interpositus and NRTP[47,90], but also a possible interpositus liaison with the red nucleus itself [70,71]. More roundabout loops involving the lateral reticular nucleus are possible[68,146]. As for Deiters nucleus, it originates a projection to one area of NRTP (a reciprocal return awaits documentation) as does the fastigial nucleus[47]. Fastigial exchanges with the lateral[48,73] and paramedian[43] reticular nuclei and with the descending vestibular nucleus[49] have also been described.

The physiological demonstration of recurrent excitation between the NRTP and the cerebellum has been complemented by anatomical studies of NRTP loops by Brodal and coworkers[47,51]. The interconnections, described as substantial[45,47], appear to be rather diffusely organized. Regions of the anterior interpositus and fastigial nuclei do project to somewhat circumscribed areas of NRTP, but considerable overlap exists (a greater topographic organization may be present in cerebral cortical afferents to NRTP[45]). The NRTP return projection seems diffusely to affect most of the organ[47], although this requires more study to establish. In any event, this description was used in the simulation of anterior lobe reticulocerebellar loops, along with two further assumptions:

1. All pre-cerebellar reticular nuclei involved in recurrently exciting the anterior lobe give rise to slow mossy fibers exclusively (figure 1).

2. Loop interconnections between each small area of a cerebellar nucleus and its associated reticular region(s) are truly reciprocal[50].

Based upon these assumptions, the simulation template diagram of figure 2 is constructed. It illustrates a tendency to localization in the cerebello-reticular projection, with greater diffuseness in the return path. The quantifying of spatial extent of the projections is left to section 4.3.

Considering that the lateral reticular nucleus is usually considered to be the chief "spinal" pre-cerebellar reticular nucleus, one might wish that more information about that nucleus (rather than the NRTP) could have gone into the above description. Such data, aside

from being unavailable, could prove to be less relevant in the light of several recent findings: Autoradiographic study of the lateral reticular nucleus projection to the anterior lobe has been unable to demonstrate significant mossy fiber collaterals to the cerebellar nuclei[151] (although a rich cortical arborization was evident). Direct stimulation of the lateral reticular nucleus does excite fastigial nucleus neurons, but with surprisingly long and variable latencies[92]--suggesting the possible antidromic activation of lateral reticular afferents and subsequent cerebellar excitation via another route. Lateral reticular stimulation is reported to have little effect whatever upon interpositus neurons, despite the presence of "slow" mossy activation of these units by peripheral stimuli[97]. These observations tend to place the lateral reticular nucleus in the same category as the pontine nuclei: The latter originate an apparently "diffuse" projection primarily to the cerebellar cortex and not the nuclei[6]. On the other hand, the heaviest descending projection of the cuneiform locomotor region in the cat was found to be in the contralateral NRTP[102]; only a weak contribution of cuneiform fibers was seen in the lateral reticular nucleus. It seems clear, then, that when locomotion is pursued, reticulocerebellar recurrent excitation mediated by the NRTP must be a telling force.

The spinal inputs received in greater or lesser numbers by the pre-cerebellar reticular nuclei (figure 1) are not treated explicitly in this report, except insofar as they provide "background" excitation to the cerebellar module (section 3.3). As mentioned in the Introduction, the function of the spino-reticulocerebellar system may

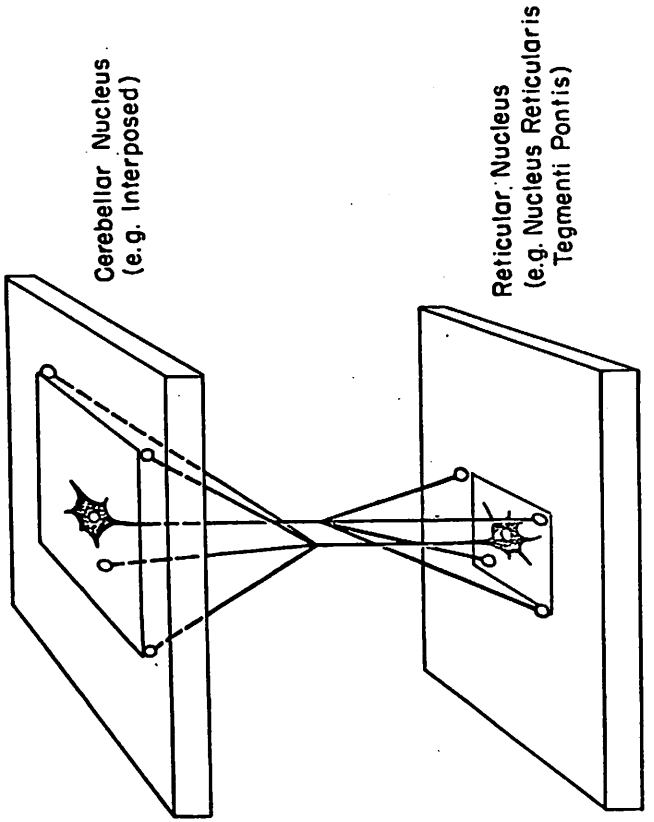

FIGURE 2
Template diagram of a reticulocerebellar loop.

not be to provoke changes in the spatial distribution of cerebellar activity. Its role in the temporal aspects of cerebellar processing during ongoing movement is currently under investigation (Boylls, in preparation).

Lastly, recurrent facilitation may come to the cerebellar nuclei through intrinsic factors such as recurrent axon collaterals [58,60,138,181], interneurons[58,60] (Grimm and Rushmer, in preparation), and internuclear connections[78,79]. None of these features is known to give rise to mossy fibers and so receives no representation here. However, some of this possible recurrent excitation may have a beneficial effect upon the operation of the cerebellar module (see section 9.1.1).

2.4 Geometry of Cerebellar Cortex and of Cortical Afferents and Efferents

Within the cerebellar nuclei the action of cortical inhibition has often been described as spatiotemporal "sculpting"[96,139]. Such sculpting will be considered largely responsible for creating the spatially differentiated nuclear activity patterns of locomotion (see Introduction). To deduce these patterns' topologic properties one surely must attend carefully to the extraordinary neuronal geometry both within the cortex and in the terminal patterns of its afferents and efferents. The "sagittal" and "mediolateral" coordinate planes defined above will now be employed to unify that geometry throughout the cerebellar module.

2.4.1 Intrinsic Cortical Geometry

Llinás[157,158,162,167] has extracted a "basic cerebellar

circuit," consisting of granule and Purkinje cells and mossy, parallel, and climbing fibers, which seems phylogenetically invariant (and may also be mimicked early in ontogeny[157]). The orthogonal relation of parallel fibers (mediolateral plane) with the Purkinje dendritic tree (sagittal plane) is likewise preserved. This basic circuit, shorn of elaborate interneuronal networks, comprised the cortex in the initial computer simulations of the cerebellar module (section 6). Such a cortical model hews more closely to the frog[31,133] than to the cat (the frog cortex has already been suggested as a simulation candidate[159]). No attempt was made to capture the staggered arrangement of Purkinje cells described in the cat[210,242], nor any supposed intermittency of single parallel fiber synapses over successive dendritic trees[212,242], nor observations of multiple synapses of a fiber on one tree[209]. The spatial scaling of the simulation (one simulated Purkinje cell representing a neighborhood group of about 10; section 5.3) is such that these local anomalies are unrepresentable. Other authors consider some of them insignificant[218]. Various reported peculiarities of parallel fibers, notably occasional myelination[189] or variations in length or diameter with depth[111,242] were also not dealt with.

There can be little doubt that the interneurons of the cerebellar cortex play a significant role in its operation, even in the most primitive instances[158,230]. Thus, in concert with an hypothesis on the function of the cortical granular layer (section 7), certain properties of Golgi interneurons were introduced in later simulations. These properties are described in section 8. The effect of Golgi interneurons does not radically alter the results from the case of the "basic cerebellar circuit," but does alleviate certain of the latter's

shortcomings. Simulation of stellate and basket cell influences was not carried out owing to technical limitations; however, their contributions are considered in the final discussion (sections 9.2, 9.3).

2.4.2 Organization of Slow Mossy Fibers and of Mossy-Granule Interface

"Slow" mossy fibers from the reticular nuclei are taken to branch predominantly in the sagittal plane upon reaching the cerebellar cortex. This proclivity has been documented within single folia[213] and over a number of folia, even entire lobules[130,194,197,264]. Sagittal branching at the cortical level is not to be construed as precluding prior mediolateral (and further sagittal) arborization of slow mossy fibers before the cerebellar cortex is reached; mediolateral branching has been clearly demonstrated[65,151,232,246].

Recent investigations of the slow mossy projection from the lateral reticular nucleus to the spinocerebellum have hinted that some degree of topographic organization may be present. Clendenin, et al.,[65,66] find a crude somatotopic mapping electrophysiologically, while Künzle[151] sees mossy fiber concentrations in sagittal strips within the cortex (reminiscent of the climbing fiber and corticonuclear projections; sections 2.4.3, 2.4.4) using autoradiography. A purely "diffuse" slow mossy projection was employed in the present computer simulations, which may or may not have some bearing upon the quantitative accuracy of the results.

The mossy-granule interface, through which mossy fibers transmit excitation to parallel fibers, has inspired considerable theoretical speculation[176,184,215,216,217]. In this investigation the granular

layer is assumed subdividable, purely figuratively, into close-packed cylinders ("columns") with principal axis normal to the cortical sheet. The nominal dimensions of the smallest such column may be taken as follows:

a. Height: The thickness of the granular layer (which varies widely), minimally 100 μ[89].

b. Radius: That of the granule cell (3 μ[189]) plus an "average" dendritic span (13 μ[213]) or 16 μ, representing the net synaptic field of a granule cell.

Given a granule cell density of $2.8 \cdot 10^6/mm^3$ for cat[211], each column contains perhaps 225 cells minimally.

The imaginary granule columns act in the simulation as nodal points for the interaction of mossy inputs at each spatial locus in the granular layer. An "aggregate mossy fiber input" to each column may be defined, with an "aggregate parallel fiber output" leaving the column upon a bundle of parallel fibers aimed at the molecular layer. A "columnar transfer function" relates input to output. Mathematical definitions of these terms are found in sections 3.5 and 7.1.

Two ways of viewing the processing in the columns were examined in simulations: In the first, a column merely relays to Purkinje cells the aggregate mossy activity entering it (sections 3.5, 6). In the second, recruitment (analogous to the well known recruitment of spinal motoneurons) was assumed to take place among the 200 or so cells of the column (sections 7, 8). The recruitment hypothesis captures some of the attributes of the more exotic "pattern separation" theories proposed by others for the granular layer, but remains within

the realm of physiological folklore and experimental testability (section 9.5).

Some time ago, Szentágothai[89] stated that mossy fibers from different pre-cerebellar sources could terminate at different depths within the granular layer. Arshavskii, et al.,[19] claimed to have shown that slow mossy fibers (from the lateral reticular nucleus) excited only deep granule cells whose parallel fibers had little influence upon Purkinje cells (instead, only Golgi interneurons were affected). On the other hand, Sasaki and Strata[233] and Azzena and Ohno[24] could find no evidence of deep vs. shallow mossy fiber terminations electrophysiologically; nor could Künzle[151] demonstrate them anatomically. No attempt was made, therefore, to account for deep or shallow terminations here.

Figure 3 illustrates the relationship between a reticulocerebellar loop (figure 2), giving rise to slow mossy fibers, and the anterior lobe cerebellar cortex on one side of the midline (no attempt is made to depict crossed projections). Note the introduction of the cortically based sagittal and mediolateral coordinates (section 2.1). The juxtaposed fastigial and interpositus nuclei are seen to receive excitatory collaterals (open circles) of slow mossy fibers as the latter pass upward to the cortex. For the sake of clarity, the cortical granular layer and its hypothetical columns, cortical interneurons and Purkinje cells, and the sagittal branchings of mossy fibers (at the cortical level) are not shown.

2.4.3 Organization of Climbing Fiber Projection

Recent studies in cat have left little doubt not only of the

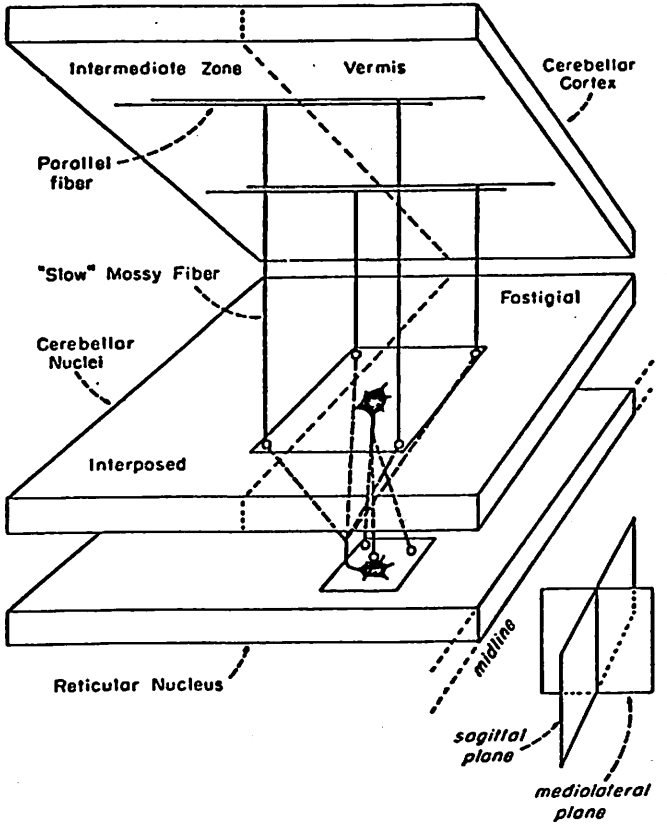

FIGURE 3

Template diagram of a reticulocerebellar loop relationship with the anterior lobe cerebellar cortex. Certain cortical elements are not shown, nor is sagittal mossy fiber branching (see text).

predominantly sagittal distribution of the climbing fiber branches to the cerebellar cortex, but also of the grouping of fiber branches into compact sagittal strips which are the terminal zones of specific ascending spino-olivocerebellar tracts. The topography of the climbing fiber projection has been extensively reviewed[9,29,206,207]. To summarize briefly, climbing fiber branching of some sort was originally predicted when cell counts revealed many fewer olivary cells than Purkinje cells[105,132,234,255]. Extra-olivary sources of climbing fibers[25] could explain this result if such sources could be found. The branching of climbing fibers, however, has been clearly established within single folia[110] and between folia or lobules[12,13,14,15,16,27,106].

The gathering of the climbing fiber projection into sagittal strips in the cerebellar cortex has been demonstrated by Oscarsson in many publications. On the anterior lobe surface these Oscarsson strips are distributed as shown in figure 4 (adapted from Oscarsson[206]): The figure represents a view from above the cortex on one side of the midline (which, of course, lies in the sagittal plane). The vermal and intermediate zone subdivisions of the cortex, and their approximate widths (in mm), are as indicated. Each strip is designated alphabetically; the numerals indicate the widths of each strip. The association of particular strips with different ascending spino-olivocerebellar tracts is taken up elsewhere[36] (see also refs. 29, 183, 206, 207).

It is likely that each Oscarsson strip in figure 4 consists of a still narrower set of sagittal "microstrips," as indicated by unitary recordings of Purkinje climbing fiber responses following either electrical or natural stimulation[104,183,226]. Armstrong[16] has commented

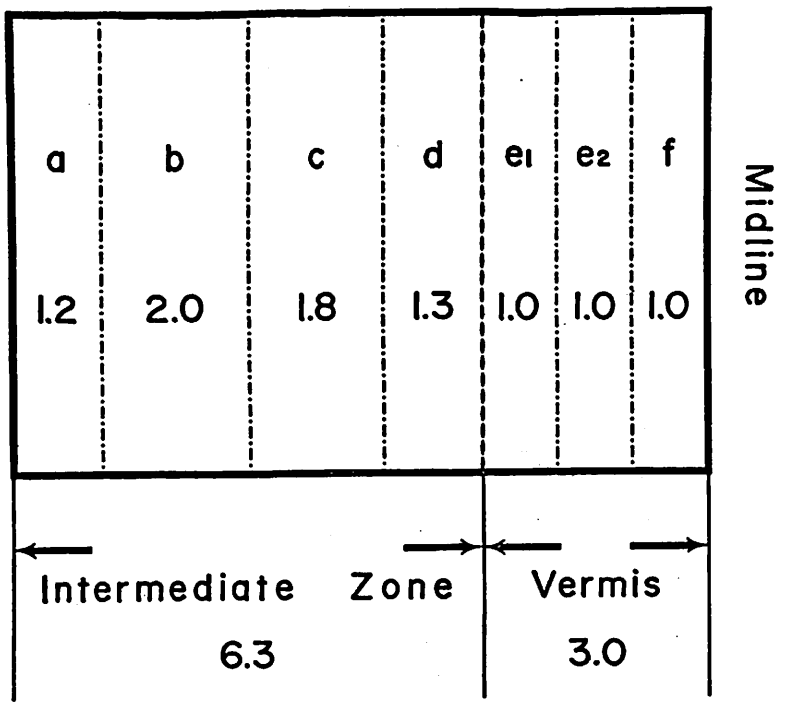

FIGURE 4

Schematic top view of anterior lobe cortex, showing sagittal Oscarsson climbing fiber strips. Widths (mm) as indicated. Adapted from Oscarsson[206].

on the severe ("planar") mediolateral restriction of climbing fiber branches seen through the axon reflex technique. Behavior of the cerebellar module was tested on the computer through simulated microstrip activations, under the assumption that these represented the most basic currency of spino-olivocerebellar information transfer (see section 3.4 for further justification of this assumption). However, simulation behavior and subsequent mathematical analysis (sections 9.3.1, 9.4) indicated that all microstrips comprising an Oscarsson strip must become active within a certain time interval in order that significant alteration of cerebellar spatial activity be accomplished. Implications of that finding are discussed later in this report, and in another[36].

2.4.4 Organization of the Corticonuclear Projection in the Anterior Lobe

Controversy continues in the literature over the exact geometry of the projection of Purkinje axons from the anterior lobe cortex upon the fastigial, interpositus, and Deiters nuclei. For once, the present investigation has adopted the traditional view--that each region of these nuclei receives Purkinje inhibition primarily from a unique, sagittally oriented strip of cortex. Korneliussen[149,150] and Jansen[142] have held that the entire cerebellar cortex (including the hemispheres) can be subdivided into a crosshatch pattern of mediolateral segments and sagittal zones, each "square" having a characteristic relationship to the cerebellar nuclei. The anterior lobe comprises one such square. Within it, Voogt and students[262,263,264] have identified sagittal cortical compartments appearing to project upon different

nuclear zones (in cats, ferrets, and rabbits). Older anatomical investigations[143,266] also support the idea of sagittal corticonuclear organization, although without claiming the sort of precision in it advocated by Voogt. The classical lesion and stimulation experiments of Chambers and Sprague[56,57] (see also refs. 36, 273) also may be interpreted within the sagittal scheme.

Several authors' anatomical and physiological observations[79,83,107,116] admittedly question the above ideas. Some of these objections may be traced to distinctions between the destinations of individual Purkinje cell axons and the nuclear region influenced by groups of such cells. Golgi studies in both the anterior lobe[182] and the cerebellar hemisphere[60] indicate that Purkinje axons tend each to branch in a restricted, conical region of a cerebellar nucleus (see also ref. 266). Thus, individual cells can hardly be expected to exert a widespread nuclear influence. Yet Ito[141] was able to demonstrate that monosynaptic inhibition upon Deiters nucleus cells could be got from an extensive sagittal zone (coinciding well with Voogt's Deiters "strip"[264]) of the anterior lobe. It would seem, then, that each small region of cerebellar nucleus is influenced from the entirety of a sagittal strip. Indeed, Chan-Palay observed that neighboring arborization cones of Purkinje axons (in dentate nucleus) did not necessarily stem from neighboring Purkinje cells in the overlying cortex[59]. Conversely, small cortical lesions involving a group of Purkinje cells might be expected to produce axonal degeneration over an extensive nuclear region, the region corresponding to the cortical strip in which the lesion was made. Eager[81] found that small anterior lobe lesions did lead to degeneration over much of the rostrocaudal

extent of the target cerebellar nucleus. Similar reasoning may account in part for the more recent findings of Brodal and Courville[46,72] in the cerebellar hemispheres and paramedian lobule. Using electrical and natural peripheral stimuli, Eccles and coworkers[96,101] have been unable to find evidence for sagittal inhibitory distributions in either the fastigial or interpositus nuclei (in the former, they do remark that inhibition is more restricted than excitation[96]). However, Ekerot and Larson have recently shown that just the fast mossy inputs excited by the sorts of stimuli used by Eccles (not to mention the inputs arriving on other channels) distribute to several sagittal zones of the anterior lobe cortex[104]. In this light Eccles' findings are not surprising.

Based upon the discussion above, the corticonuclear template of figure 5 was constructed to allow computer simulation: A single Purkinje cell is shown having an inhibitory field extending over a rostrocaudal strip of cerebellar nucleus. In reality, of course (see above), this "single" cell must represent a compact group. The nuclear region inhibited need not be strip-like, although the cortical area influencing it is (see section 2.5). Figure 5 also illustrates, as a reminder, some representative projections of the cerebellar nuclei upon brainstem output nuclei through which the anterior lobe injects its muscular modulation. Once again, crossed projections are not indicated (e.g., between the interpositus and red nuclei); and of course, the red and Deiters nuclei (the latter also receiving a direct cortical projection) are not physically adjacent.

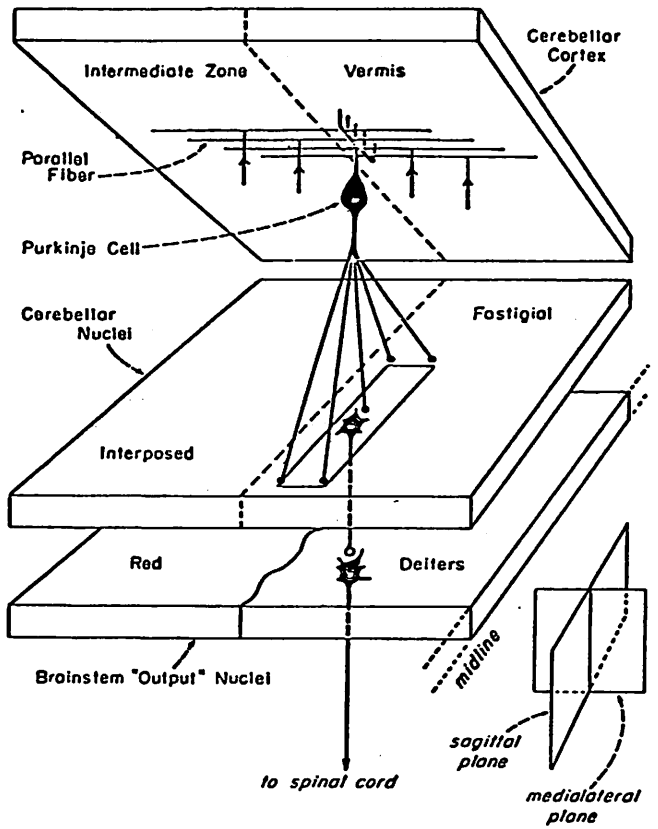

FIGURE 5

Template diagram of anterior lobe corticonuclear projection, showing sagittal zone of influence of small cortical region (see text).

2.4.5 Distribution of Mossy and Climbing Fiber Collaterals to Cerebellar Nuclei

Both slow mossy fibers and climbing fibers are taken to give collateral excitation to the cerebellar nuclei. No explicit "fan-out" is represented for mossy collaterals; mossy fibers are assumed to excite only small neighborhoods about the nuclear regions through which they pass in traveling to the cortex (figure 3). Although this is likely false[58,59,60,182], the already-diffuse branching of the fibers prior to reaching the nuclei (figure 2) would seem to make extensive collateral treatment immaterial. As for climbing fiber collaterals, intra- and extracellular records from cerebellar and Deiters nuclear neurons frequently show an initial EPSP-IPSP (burst-silence extracellularly) sequence resulting from olivary or peripheral stimulation of climbing fibers[92,97,138,250,251]. This sequence likely underlies the periodic burst responses of these cells following harmaline administration[77,152,165]. Presumably the excitatory phase owes itself to climbing fiber collaterals, which must therefore lie in the nuclear region receiving consequent inhibition. It follows from the geometry of the corticonuclear and climbing fiber projections (sections 2.4.3, 2.4.4) that activation of a climbing fiber strip will result in nuclear inhibition in an equivalent "sagittal" area[27,251]. Thus, for simulation it is assumed that climbing fiber collateral excitation is confined to that nuclear region, although explicit experiments on strip effects in the nuclei are lacking (see also ref. 180). The occasional observations of an isolated nuclear EPSP without a following IPSP, triggered by a climbing fiber input[5], show that this is an approximation

(for an anatomical discussion of the problem, see ref. 60).

2.5 Orchestration of Neuronal Activity Among Descending Spinal Pathways by the Anterior Lobe. A Summary of Anterior Lobe Architecture and an Anticipation of Its Function

As described in section 2.4.4, the cortex of the cerebellar anterior lobe can be partitioned into a series of sagittal zones, each with an inhibitory influence confined primarily to a unique cerebellar or vestibular (Deiters) nuclear region. Since each of these nuclear areas seems to excite either a unique descending spinal tract, or a unique combination thereof, it follows that sagittal cortical zones must each govern a unique descending influence upon the musculature. More precisely, since the various descending pathways are functionally (flexor/extensor) specific, then so must be the sagittal zones of the anterior lobe.

Section 2.4.3 described the sagittal strip organization of the climbing fiber projection to the anterior lobe. The question consequently arises, to what degree does an Oscarsson climbing fiber strip correspond to a sagittal cortical zone having influence upon a specific functional group of muscles? While this problem has yet to be examined directly in an experiment, the correspondence must be quite close and is illustrated in figure 6: The figure is an attempt to indicate the functional groups of muscles affected by each sagittal zone of the anterior lobe, the anatomical route by which the effects are conducted, and the climbing fiber strips which may correspond to those zones. The experimental findings leading to the construction of the figure have been examined in detail elsewhere[36], and only a summary will be

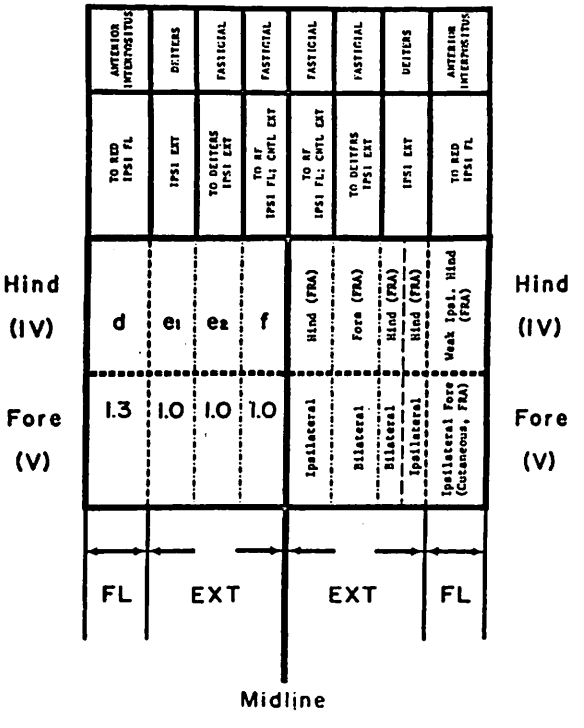

FIGURE 6

Vermal and paravermal, "locomotor" portion of anterior lobe cortex, indicating muscular influences and Oscarsson climbing fiber strip associated with each sagittal zone. Central portion of figure is top view of lobules IV and V of anterior lobe. Oscarsson strips and widths indicated on left (cf. fig. 4); somatotopy and modality of strip inputs given at right. Lower portion of figure gives gross muscular influence of vermal and paravermal zones (FL = flexion; EXT = extension). Upper portion gives immediate cerebellar or vestibular nuclear target of each sagittal cortical zone. Immediately beneath, the brainstem output nucleus (if any) and functional muscular group affected are both indicated. Figure compiled from data presented in ref. 36. See text for details.

given here. As in figure 4, a top view of the anterior lobe is presented in the lower portion of the figure, save that areas on each side of the midline are indicated. Letter designations of climbing fiber strips and their dimensions, given within the strips on the left, are identical to those of figure 4. Representation of the anterior lobe is not continued mediolaterally beyond strip d since more lateral regions seem not to be involved with locomotor modulation[36]. On the sides of the figure anterior lobe rostrocaudal lobules IV and V are indicated, along with the hindlimb-forelimb somatotopy of their influences of the vermal (extensor) and paravermal (flexor) gross sagittal cortical areas. The more detailed muscle specificities of the sagittal corticonuclear projection zones, and the cerebellar (or vestibular) and brainstem output nuclei affected by each zone, are indicated across the top of figure 6. Within the strips on the right of the figure the gross somatotopy and modality specificity of each climbing fiber strip is indicated (these data are of less concern here).

As figure 6 suggests, then, the triggering of a given Oscarsson climbing fiber strip should eventually lead to a change in cerebellar modulation of a particular functional group of muscles. Depending upon the descending pathway mediating the modulation, that influence may also be somatotopic. In any event, discussion might end here if it were not for the presence of fiber connections between the sagittal zones of the anterior lobe: The communication between zones mediated by cortical parallel fibers is obvious. Less so is the activity spillover within both cortex and nuclei made possible by reticulocerebellar recurrent excitation. Owing to the diffuse nature of reticulocerebellar

loops (figure 2), it might seem that the creation of localized activity in one cerebellar sagittal zone would rapidly be diffused into neighboring zones. On the contrary, it will be shown via computer simulations of the cerebellar module (sections 6, 8) that this diffuse recurrent excitation is fundamental to the formation, following climbing fiber strip inputs, of spatially differentiated patterns of neuronal activity within the cerebellar and output nuclei. Activation of a strip will be shown to result in the temporary release of the strip's nuclear target from inhibition. The resulting rebound of the released area is transmitted to a pre-cerebellar reticular nucleus, to be returned to both the cerebellar nuclei and cortex on slow mossy fibers. This diffuse returning excitation is distributed even further mediolaterally by the parallel fibers, resulting in an increase of Purkinje inhibition in the sagittal corticonuclear "compartments" on either side of the originally activated climbing fiber strip. The result, a product of simple lateral recurrent inhibition, is a pattern of excited and inhibited cerebellar nuclear regions--or in other words, a redistribution of activity in descending spinal pathways. Tying the various types of redistribution possible to the various types of locomotor gait is in part the task addressed in another report[36].

3. Physiological Assumptions Employed in the Anterior Lobe Simulation

3.1 Cellular Properties

The cells of the cerebellar module to be explicitly modeled are Purkinje, cerebellar nuclear, and pre-cerebellar reticular nuclear

neurons--or more precisely, aggregates of them (thanks to the spatial scale at which the simulation is run; section 4.3). The literature seems to indicate that each of these cell types exhibits, in the temporal steady-state, spatial and temporal summation of inputs (excitatory or inhibitory), within obvious limits, when those inputs and outputs are specified by firing frequency; an exception occurs, of course, in the Purkinje climbing fiber response (cfr) to be dealt with separately. In the absence of any input the membrane potential of each cell type--Purkinje[89,161], reticular[259,260], and nuclear (Deiters EPSP[89,249]; Deiters or dentate IPSP[89,137,138,250,251])--also appears to decay to resting level with approximately an exponential time course. Consequently, each neuron's membrane potential, m(t), normalized to a resting level of 0 mv, is governed in the simulation by a basic first-order differential equation of the form

$$\tau\dot{m}(t) = -m(t) + 0(I(t)) \qquad (1)$$

where τ is the membrane time constant (in msec), I(t) represents the aggregate of cell input firing frequencies (usually a synaptically-weighted summation), $\dot{m}(t)$ is the time derivative of m(t), and 0 is a "compression function" defined below. The output firing frequency (hz) is obtained by passing the membrane potential through a simple threshold function, $[\ \ ]^+$, defined by

$$[m(t)]^+ = m(t),\ m(t) \geq 0 \qquad (2)$$
$$= 0,\ m(t) < 0$$

Cellular modeling of this sort has been applied by Mortimer to the cerebellar cortex with reliable replication of many of its physiological

phenomena[187]

To account for the absolute refractory period which sets the maximum firing frequency of a neuron, inputs to cells were passed through a compression function of the form

$$0(I(t)) = \Theta(1 - e^{-I(t)/\alpha}) \qquad (3)$$

where Θ establishes the maximum frequency and the ratio Θ/α governs the rapidity of approach to this asymptote. For all cells, here, Θ equalled 1000 hz and Θ/α was unity. Since the firing frequencies of the cells rarely exceeded 300 hz (the Purkinje cfr being the exception)

$$0(I(t)) \approx I(t) \qquad (4)$$

The refractory periods of cells were thus irrelevant to the behavior of the model.

Cerebellar nuclear neurons, since they receive both excitatory and inhibitory inputs (while the others experience only excitation), were each simulated with two differential equations ("EPSP" and "IPSP") to reflect the time course of each process. The requirement arises because, according to the theory of Rall[224], at the nuclear cell axon hillock Purkinje inhibition, thought to arrive largely axosomatically[138,182], will follow a more rapid time course than axodendritic afferent collateral excitation. The net membrane potential of a nuclear cell was obtained by taking the algebraic difference of the "EPSP" and "IPSP" processes. Weisstein[268] justifies this practice, which is also employed by Mortimer[187]

As described earlier, the model's cortical granular layer introduces a granular columnar transfer function and Golgi cell effects;

these will be explained in special sections below.

3.2 One-Dimensional Approximation

To conserve limited computer space and facilitate computation speed, while retaining spatial resolution, only a cross-section of the two-dimensional tissue sheets of figures 3 and 5 was actually simulated. The section was taken along the mediolateral plane, thereby reducing the module to a set of 3 mediolaterally distributed rows of cells.

Mathematically, this is justifiable only if the cellular behavior in the unrepresented sagittal direction is identical with that seen in the cross-section. But the overwhelming sagittal distribution of cortical afferents and efferents, coupled with the substantial "radial" diffuseness of the reticulocerebellar reverberatory loops, would seem essentially to satisfy this requirement--at least within a goodly distance sagittally. Conversely, obtaining solutions for behavior in the cross-section allows one to complete the picture sagittally, as in fact will be done.

3.3 Basic Governing Equations

The cerebellar module resulting from the one-dimensional approximation is schematically illustrated in figure 7, where the variables D, E, F, and G are fan-out (space) constants related to the magnitudes of the (mediolateral) projections between the various layers as indicated; Z, X, Y, and R are generic labels for the membrane potentials of cells in the layers. Table I defines these and other variables seen in the equations below.

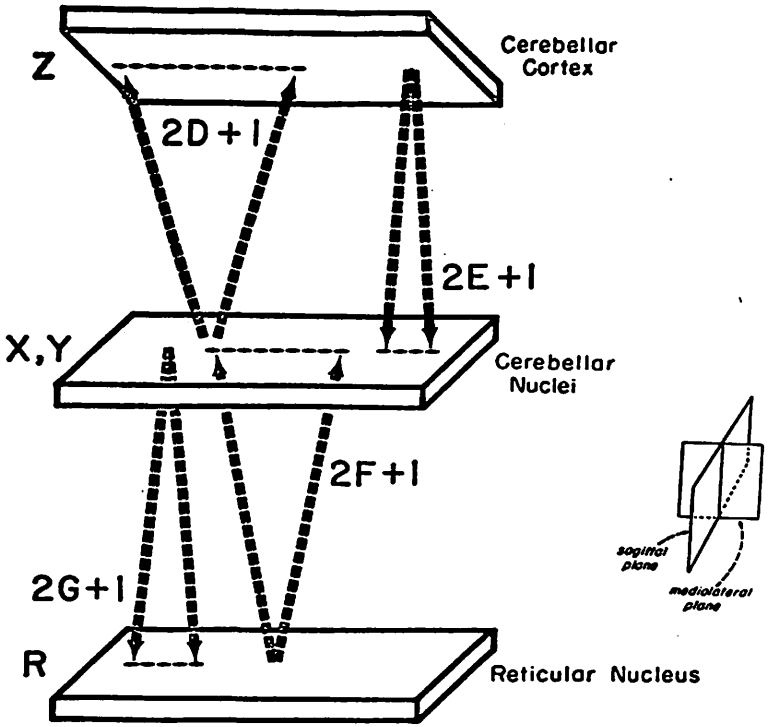

FIGURE 7

Interconnections between elements of the cerebellar module in the one-dimensional approximation. Text explains variables shown.

From figure 7 and the example of equation (1), basic equations governing the behavior of each cell in the cerebellar module, at mediolateral coordinate i and time t, can be written down directly (see Table I).

$$\tau_x \dot{X}(i,t) = -X(i,t) + 0\left(\sum_{j=-F}^{F} w[R(i+j,t)]^+ + \sum_{j=-E}^{E} pC(i+j,t)\right) \quad (5a)$$

$$\tau_y \dot{Y}(i,t) = -Y(i,t) + 0\left(\sum_{j=-E}^{E} p[Z(i+j,t)]^+\right) \quad (5b)$$

$$\tau_r \dot{R}(i,t) = -R(i,t) + 0\left(\sum_{j=-G}^{G} w[X(i+j,t) - Y(i+j,t)]^+ + B\right) \quad (5c)$$

$$\tau_z \dot{Z}(i,t) = -Z(i,t) + 0\left(\sum_{j=-D}^{D} qG([M(i+j,t)]^+)\right) \quad (5d)$$

Notable features of the governing equations are the following: Equation (5a) (defining the cerebellar nuclear cell EPSP) contains a climbing fiber collateral term defined so as to affect that nuclear region to which a climbing fiber strip of the cortex will project (see section 2.4.5). Arbitrarily, the effect of the collateral was given the same weighting (p) as that of the Purkinje cell axon synapse. Equation (5b) (defining the cerebellar nuclear cell IPSP) shows the straightforward effect of the Purkinje corticonuclear projection.

Equation (5c) (defining the behavior of a pre-cerebellar reticular cell) contains an exogenous excitatory term, B, representing a constant level of "background" excitation to these neurons. It is used in simulation to help bring the resting discharges of all simulated neurons throughout the module into their normal physiological ranges.

TABLE I

VARIABLES OF BASIC GOVERNING EQUATIONS

Variable	Units	Description
R(i,t)	mv	Normalized membrane potential of ith reticular neuron as a function of time
Z(i,t)	mv	Normalized membrane potential of ith Purkinje neuron as a function of time
X(i,t)	mv	Depolarizing component of normalized membrane potential of ith nuclear neuron as a function of time
Y(i,t)	mv	Hyperpolarizing component of normalized membrane potential of ith nuclear neuron as a function of time
τ_r	msec	Membrane time constant of reticular neuron
τ_z	msec	Membrane time constant of Purkinje neuron
τ_x	msec	Time constant of membrane depolarization of nuclear neuron
τ_y	msec	Time constant of membrane hyperpolarization of nuclear neuron
2D+1	mm equivalents	Granule cell column-to-Purkinje cell fan-out (length of parallel fiber), D integer ≥ 0
2E+1	mm equivalents	Purkinje-to-nuclear cell fan-out, E integer ≥ 0
2F+1	mm equivalents	Reticular-to-nuclear cell fan-out, F integer ≥ 0
2G+1	mm equivalents	Nuclear-to-reticular cell fan-out, G integer ≥ 0
w	mv/hz	Multiplicative synaptic efficacy of connection from nuclear cell to reticular cell or vice-versa, non-negative
p	mv/hz	Multiplicative synaptic efficacy of connection from Purkinje cell to nuclear cell, or from climbing fiber collateral to nuclear cell, non-negative

TABLE I (cont'd)

Variable	Units	Description
q	mv/hz	Multiplicative synaptic efficacy of parallel fiber-Purkinje cell contact, non-negative
M(i,t)	hz (summed)	Aggregate granule columnar mossy fiber input activity at spatial locus i as a function of time
G	---	Granular columnar transfer function
C(i,t)	hz	Nuclear collateral activity of ith climbing fiber
B	hz	Constant "background" activity of reticular nuclear afferents and cells not attributable to reticulocerebellar recurrent excitation (see text)

Although cerebellar cortical neurons (and perhaps others of this module) do display spontaneous activity in the absence of afference[22,89], background cortical excitation is also suspected to depend upon the activity in cerebellar reticular nuclei--particularly the lateral reticular nucleus[30]. Reticulocerebellar loops have also been suggested as contributing to this activity[138,258,261]. B represents the combination of exogenous afferent and spontaneous activity not attributable to recurrent excitation through such loops. Strength of the latter, of course, is a function of the coupling ("loop gain") between the reticular and cerebellar nuclei. Many combinations of B and recurrent excitation lead to the same background excitation in the module. It will be shown, however, that these combinations are not equivalent in terms of its spatiotemporal response to climbing fiber inputs (sections 4.5, 4.6).

Lastly, equation (5d) (defining the response of the Purkinje neuron) is noteworthy for two reasons. The first is the introduction of functions describing the processing within granule cell columns; these functions will be defined in subsequent sections of their own (3.5, 7.1). The second is the absence of a term defining the action of the climbing fiber upon the Purkinje cell. This complex effect is also treated separately (section 3.4).

Note that no attempt has been made to make the various synaptic weightings functions of the fan-out constants. All spatial weighting functions are "rectangular." This is probably truly appropriate only for the parallel fiber influence; however, without quantitative information on the densities of the other projections, one

may as well make do with rectangles since they lead to simpler stimulation routines.

The time and space (fan-out) constants of the governing equations are quantified in section 4. There also the synaptic efficacies and other parameters are derived.

3.4 Climbing Fiber Effects and Physiology of Strip Inputs

Computer simulation of climbing fiber inputs to the cerebellar module requires specification of the action of individual climbing fibers and of the collective behavior of fibers within cortical Oscarsson strips. Turning first to the former, only the documented physiological consequences of climbing fiber activity on individual Purkinje and nuclear cells were incorporated into computer simulations. That is, no further theoretical propositions on the behavioral import of this activity were entertained prior to examining simulation results (for review of others' ideas on climbing fiber function, see ref. 158). A single activation of a climbing fiber was thus defined by a chain of three events in the cerebellar module:

a. The climbing fiber response (cfr), consisting of a momentary collateral excitation of nuclear cells followed immediately by a burst discharge of a target Purkinje cell inhibiting those nuclear units.

b. The silent period, a shutdown of the Purkinje cell discharge following the cfr.

c. The recovery period, resumption of Purkinje discharge.

Each event will now be discussed separately, beginning with the cfr.

When activated by various of their afferents, olivary cells in cats give rise to a single large action potential followed by a

varying number of smaller, secondary spikes at high frequency[74,75]; this entire complex appears to be transmitted to the cerebellum[75]. There, as reviewed earlier (section 2.4.5), cerebellar nuclear cells are momentarily invaded by climbing fiber collateral excitation prior to being strongly inhibited by the Purkinje cfr. The cfr in cats consists of a burst discharge at a frequency of several hundred herz and lasting 5-8 msec[9,89,192]. Most of this burst seems conducted to the nucleus [140]. The Purkinje cfr in frog is likewise a barrage of, perhaps, slightly lower frequency and longer duration[160] than in cats.

The silent period following the cfr is the latter portion of the Purkinje "inactivation response" of Granit and Phillips[121]. This silencing is observable under a variety of experimental conditions in cats, its duration varying with those conditions. Thus, under anesthetics or decerebration, pauses are regularly seen after the cfr [26,33,53,156,191,192,229], sometimes reported as lasting hundreds of milliseconds[191]. A silent period is also seen in the sleeping cat[174]. Under all these conditions silencing may well be phylogenetically invariant, since it appears present in the frog[195] and alligator (unpublished observation).

The existence of the silent period in awake, intact animals (or in the mesencephalic locomoting cat) is equivocal. Frequent short pauses following the Purkinje cfr are described for awake, moving monkeys[252] and occasionally are noted in lightly anesthetized guinea pigs[27]. Following presumptive cfr's in the mesencephalic cat silencing seems present (ref. 201, fig. 1C). However, Murphy and colleagues see no cfr-related pauses in awake, paralyzed cats[193], nor does Mortimer

find them in awake monkeys following cfr's elicited by startling the animal[188]. It appears that the safest course to steer between these contrasting findings is to assume that when pauses are present in awake animals, they are much shorter than when observed under anesthesia or following decerebration (see below).

Recovery of the Purkinje cell from the silent period is largely determined only by silence-producing mechanisms. That is, cfr-evoked EPSP is largely decayed after 20 msec in both cat and frog[89,160] and hence will have little effect on subsequent discharge if inactivation persists for approximately this period. Bloedel and Roberts[33] (see also refs. 177, 178) suggest that inactivation of the Purkinje spike generating mechanism could silence the cell for at least this interval. In advanced cortices climbing fiber collateral activation of cortical interneurons may result in more prolonged Purkinje shutdown by either direct inhibition (stellate and basket cells) or inhibitory curtailment of Purkinje input (Golgi cells)[26,33,53,156,191,192,229]. These interneuronal effects are not stressed in the present work. The silent period instead will be assumed due only to inactivation of Purkinje spike generation, with a cell's membrane potential continuing to respond normally to inputs. The cfr EPSP will not be carried owing to its substantial decay during silencing (see above). Drawing from this discussion, Table II describes the sequence of events used in simulating climbing fiber (and nuclear collateral) effects.

Certain authors, notably Granit[120] and Bloedel and Roberts[33], have suggested that Purkinje inactivation may be the most significant physiological contribution of climbing fiber input. The theory holds

that, while various cortical mechanisms block Purkinje output after the cfr, collateral activation assists the resulting release of target nuclear cells from inhibition (see also ref. 272). The present simulation results will be seen to support such a view, with some extensions. Lest, however, the simulations be prebiased to this outcome, the Purkinje cfr discharge has deliberately been defined to be of slightly longer duration than usually occurs, while the inactivation period is kept rather short (cf. Table II and the above discussion).

TABLE II

CLIMBING FIBER RESPONSE PARAMETERS

Time (msec)	Purkinje Output (hz)	C(i,t) (hz)	Description
$t < 1$	Z(i,t)	0	---
$1 \leq t \quad 2$	Z(i,t)	200	Nuclear collateral burst
$2 \leq t \quad 10$	500	0	Purkinje cfr
$10 \leq t \quad 26$	0	0	Silent period
$26 \leq t$	Z(i,t)	0	Recovery period

Section 2.4.3 described the entry of climbing fibers into the cerebellar cortex in a series of broad, sagittally-oriented Oscarsson strips, each in turn probably resolvable into smaller microstrips. Evidence exists that fibers to a given Oscarsson strip arise in one (sometimes several) compact regions of the inferior olive[9,17,206].

There is also strong anatomical[145,244] and physiological[166] evidence that neighboring cells of the olive are electronically coupled. In other words, olivary regions giving rise to climbing fibers of Oscarsson strips (or at least the microstrips thereof) may behave somewhat as a syncytium. Synchronization of the cfr's within a climbing fiber strip may be the result[166]. There is some experimental evidence for a tendency to such synchrony[27,226] (Roberts, personal communication). Therefore, strip inputs presented to the cerebellar module in simulations consisted of synchronous climbing fiber volleys throughout the strip. The results, however, indicated that synchrony was a convenience, but not a necessity, for the production of spatially distinct patterns of neural activity within the module (section 9.4). It is the author's opinion that the properties of olivary electronic coupling be investigated mathematically to discover whether "synchrony" is its only outcome. Depending upon the temporal filtering properties of the gap junctions mediating the coupling, either the fast depolarizing, or slow hyperpolarizing, potentials of olivary neurons[74] could selectively be coupled between neighbors. The first type of coupling would probably lead to synchrony; however, the second type would in essence effect lateral inhibition between olivary neurons and could partition the olive into "domains" of active and inhibited populations (each such population projecting into a strip of cerebellar cortex, of course).

3.5 Granular Layer. Aggregate Mossy Fiber Input and Columnar Transfer Function

As was described qualitatively in section 2.4.2, the granular layer of the cerebellar cortex is taken to be divided into hypothetical

columns, each serving to process an aggregate, slow mossy input at specified locations in the granular layer. The aggregate mossy input to the column at mediolateral location j, M(j) (dropping t; see Table I), is defined as the sum of firing frequencies on mossy fibers entering the column. Examining figure 7, and recalling that slow mossy fibers (from the pre-cerebellar reticular nuclei) were considered to undergo no further mediolateral branching between the cerebellar nuclei and cortex (section 2.4.2), it is evident that M(j) is given by

$$M(j) = \sum_{k=-F}^{F} [R(j+k)]^{+} \qquad (6)$$

Section 2.4.2 also mentioned that the processing of M(j) by its granule column into a parallel fiber output was governed by a granular columnar transfer function, here called G (Table I and equation (5d)). In the initial simulations of the cerebellar module, whose results are given in section 6, G was simply an identity transformation:

$$G(M(j)) = M(j) \qquad (7)$$

That is, mossy fiber input was taken to be relayed intact to parallel fibers by the granular layer. In later, revised versions of the simulations (sections 7, 8), G was altered to reflect the possibility of recruitment among granule cells in a column. The rationale for this, and derivation of the recruitment G, are given when the simulation results are presented.

4. Quantifying the Simulation Model

4.1 "Average" Cerebellar Module

Three basic classes of undetermined coefficients are evident from the governing equations (5) of the cerebellar module; namely, membrane time constants, spatial fan-out constants, and synaptic efficacies. The first two of these can be grossly delimited from the literature; a neighborhood for the third is then determinable from certain criteria given in sections 4.5 and 4.6. Experiment has only provided broad bounds for many of these paramters; wide scatter prevails. To combat this uncertainty an "average" paramterization for the module ("average" cerebellar module) was first extracted from existing data and was then subjected to crude performance optimization by parameter variation (section 4.6). In the tables of parameters to follow, values used for the average module are indicated with superscripted bars, while values employed in the actual optimized simulation are denoted by asterisks (*).

4.2 Membrane Time Constants

Time constants were estimated by examining published records of decaying PSP's in each cell type. More rigorous determinations of time constants by means of unitary PSP or current injection techniques are generally unavailable. There results a considerable variance in each parameter deduced by this method, but which was reduced by parameter optimization. Table III contains the various time constants and their sources.

TABLE III

MEMBRANE TIME CONSTANTS

Time Constant	Value (ms)	Reference	Figure(s)	Comment
τ_x	3	137	2,3	Deiters nucleus
	5	89	137	Deiters nucleus
	$\overline{15}$*-20	249	3	Deiters nucleus
τ_y	4	89	130	Deiters nucleus
	5	137	7	Deiters nucleus
	6*	--	--	---
	$\overline{10}$	89	132	Dentate nucleus
	$\overline{10}$	138	139	Dentate nucleus
	30	251	1	Deiters nucleus
	30-50	250	8	Deiters nucleus
τ_r	3	147	2	Lateral reticular nucleus
	3-4	260	1	NRTP
	3-4	259	1	NRTP
	$\overline{5}$*	--	--	---
τ_z	8*	161	2	Frog Purkinje cell
	$\overline{15}$	89	84	Cat Purkinje cell

$\overline{(\ )}$ = Average Parameterization

( )* = Actual Parameterization

4.3 Spatial Fan-Out Constants

Use of the sagittal-mediolateral coordinate system to unify the spatial metric of the cerebellar module (described in an earlier section) is of singular importance in specifying the extent of projections between the cells. Since there are an integral number of cells, governing equations (5) were constructed with integer fan-out constants. Each unit increment of a constant thus represents a fixed number of "millimeter equivalents" of fan-out, calculated as follows:

Recall that the coordinate system is referenced to the cerebellar cortex--that all other components of the module, regardless of their true dimensions, are taken conformally equivalent to it. The spatial scale of the simulation is therefore set by the actual mediolateral dimension of the "locomotor" anterior lobe. Figure 6 (section 2.5), by summation of strip widths, shows this to be approximately 8.6 mm. Now each cell layer of the cerebellar module (i.e., cortical, cerebellar nuclear, and reticular nuclear) was simulated with 100 active cells (section 5). This implies a simulated cell density of

$$\frac{100 \text{ simulated cells}}{8.6 \text{ mm}} = 11.6 \text{ simulated cells/mm} \qquad (8)$$

Thus a single simulated cell represents a cortical region of approximately 0.09 mm (the reciprocal of (8)) and becomes the number of millimeter equivalents represented by a unit change in any fan-out parameter. Relation (8) is used to convert actual fan-out extents (in millimeters) into integral fan-out constants after rounding (see example below).

One may regard the behavior of each model cell as representing the average activity in a group of actual cerebellar cells at some location. The size of this group (in the mediolateral plane), which indicates something of the spatial "grain" of the simulations, is calculable for cat cerebellar cortex using the recent measurements of Palkovits, et al.[212]. They find that approximately 225 Purkinje cells lie along a 2 mm parallel fiber. The 8.6 mm anterior lobe measures 4.3 such lengths, implying that about 968 Purkinje cells span it. Hence, the simulation represents a cortical group size of perhaps 9.7 real cells/simulated cell (mediolaterally). Unfortunately, no estimates can yet be made of the group sizes represented in the remainder of the module.

One may now proceed directly to the calculation of fan-out constants. The results, with references (where available), are given in Table IV. Comments on each calculation follow:

a. 2D+1, granule cell column-to-Purkinje cell fan-out (length of parallel fiber). The length of the parallel fiber in cats has been estimated differently by various authors, as Table IV indicates. An example of fan-out parameter calculation, to illustrate points above, is given for a length of 3 mm (length in the "average" module): Using the reciprocal of (8)

$$2D+1 \text{ (mm equivalents)} = \frac{1}{0.09 \text{ mm}} \text{ (mm equivalent)} \cdot 3 \text{ mm}$$

$$= 33.3 \text{ (mm equivalents)}$$

Thus D = 16 after rounding.

b. 2F+1, reticular-to-nuclear cell fan-out. This parameter, and the two remaining, are difficult to assess. For most of the pre-cerebellar reticular nuclei no quantitative projection information seems to exist. Since different broad divisions of the lateral reticular nucleus have been said to favor entire vermal or hemispherical cortical regions (although with considerable overlap[42,48]), the fan-out from each reticular neuron was varied about an extent approximating hemi-vermal width (3 mm, figure 6).

c. 2E+1, Purkinje-to-nuclear cell fan-out. This is equivalent to the (mediolateral) extent of cerebellar cortex projecting to a given nuclear neuron. Voogt has shown that (in ferret) neither the vermis nor the intermediate zone projects entirely to the same subcerebellar nucleus[264]. Consequently, 2E+1 is probably less than the widths of either of these cortical subdivisions. For the "average" module the width was posited to be about that of a typical Oscarsson climbing fiber strip--1 mm (figure 6, section 2.5). Other values were examined, as shown in Table IV.

d. 2G+1, nuclear-to-reticular cell fan-out. Almost no details of this projection exist, save that it is probably less diffuse than the reticular-to-nuclear return (2F+1; see figure 2 and section 2.3). It was treated as having properties similar to the Purkinje-to-nuclear projection.

4.4 Width of Climbing Fiber Strips

Oscarsson strips within the "locomotor" anterior lobe are

TABLE IV

SPATIAL FAN-OUT CONSTANTS

Constant	Extent (mm)	Value (mm equivalents)	References
D	2.0*	10*	212, 242
	$\overline{3.0}$	$\overline{16}$	89, 246
	5.0	26	111
F	1.8*	9*	---
	2.0	10	---
	$\overline{3.0}$	$\overline{16}$	42, 48
	4.0	20	---
E	0.2	0-1	---
	0.6*	3*	---
	$\overline{1.0}$	$\overline{5}$	---
	2.0	10	---
G	0.4*	2*	---
	$\overline{1.0}$	$\overline{5}$	---
	2.0	10	---

$\overline{(\ )}$ = Average Parameterization

( )* = Actual Parameterization

approximately 1 mm wide (figure 6). However, these strips may resolve into narrower microstrips (sections 2.4.3, 3.4) activated by particular types of peripheral input. Simulated climbing fiber inputs were thus given in strips 0.6 mm wide, in fair agreement with the width of a paravermal microstrip (0.7 mm) found to respond to footpad inputs in cat[226] (Roberts, personal communication).

4.5 Synaptic Efficacies

While the experimental determination of synaptic efficacies in cerebellar systems awaits undiscovered techniques, it is possible to avoid purely trial-and-error methods in specifying them for simulation. To do so one may hypothesize the existence of a unique spatiotemporal steady-state in the cerebellar module, in which neurons of a given type are firing at nearly identical frequencies, unchanging with time. Such a state may correspond to cerebellar activity in the alert, quiet, intact cat (or other animal). In the mesencephalic, treadmill cat the condition may exist during brainstem locomotor center stimulation, but without treadmill activation (and resulting movement); such stimulation appears to produce a generalized elevation of reticular, cerebellar nuclear, and cortical activity[199,201,202,203,204] (for details, see ref. 36). The spatiotemporal steady-state is derived from governing equations (5): a) by setting all derivatives to zero; b) by replacing compression function O with an identity function (equation (4), section 3.1), assuming all neurons to be operating in their linear range; and c) by equating the activities of all neuron types in a layer to a single non-zero value (thereby eliminating spatial

indices). These manipulations (dropping the climbing fiber collateral term), and use of equations (6) and (7) (section 3.5) result in:

$$X = (2F+1)wR \tag{9a}$$

$$Y = (2E+1)pZ \tag{9b}$$

$$R = (2G+1)w(X-Y) + B \tag{9c}$$

$$Z = (2D+1)q(2F+1)R \tag{9d}$$

Defining $\hat{F} = 2F+1$, etc., normalizing by B by defining $X^* = X/B$, etc., and defining $S = X - Y$ (i.e., net nuclear activity, with $S^* = X^* - Y^*$), it is possible to use equations (9) to solve for synaptic efficacies w and q as functions of p as follows:

Following normalization and substitutions

$$X^* = \hat{F}wR^* \tag{10a}$$

$$Y^* = \hat{E}pZ^* \tag{10b}$$

$$R^* = \hat{G}wS^* + 1 \tag{10c}$$

$$Z^* = \hat{D}\hat{F}qR^* \tag{10d}$$

Substracting (10a) from (10b), and substituting (10c) into both that result and into (10d)

$$S^* = \hat{F}w(\hat{G}wS^* + 1) - \hat{E}pZ^* \tag{11a}$$

$$Z^* = \hat{D}\hat{F}q(\hat{G}wS^* + 1) \tag{11b}$$

Collecting terms in w within (11a)

$$\hat{\hat{F}}\hat{\hat{G}}S^*w^2 + \hat{F}w - \hat{E}pZ^* - S^* = 0 \qquad (12)$$

or

$$w^2 + \frac{1}{\hat{\hat{G}}S^*}\, w - \left(\frac{\hat{E}Z^*p + S^*}{\hat{\hat{F}}GS^*}\right) = 0 \qquad (13)$$

or, solving the quadratic in w

$$w(p) = \frac{\frac{-1}{\hat{\hat{G}}S^*} + \sqrt{\frac{1}{(\hat{\hat{G}}S^*)^2} + 4\left(\frac{\hat{E}Z^*p + S^*}{\hat{\hat{F}}GS^*}\right)}}{2} \qquad (14)$$

where the negative root was found to yield a negative w. Returning to equation (11b), solving for q:

$$q(w(p)) = \frac{Z^*}{\hat{\hat{F}}\hat{\hat{D}}(GS^*w(p) + 1)} \qquad (15)$$

Thus, specification of normalized Purkinje (Z*) and nuclear (S*) activity (see below) defines a <u>family</u> of synaptic efficacies by (14) and (15) which will produce this activity. When stability and other considerations are added during parameter optimization (section 4.6), such a family can be further narrowed.

In all simulations, average steady-state values for nuclear and Purkinje cell firing frequencies were taken to be those found by Thach for the alert, quiet monkey--S = 37 hz for nuclear cells and Z = 70 hz for Purkinje[252,254]. Similar activity levels are seen in

cats under various conditions[91,97,138,173,174,201,257] (during mesencephalic locomotion average nuclear frequencies may be somewhat higher [202] and Purkinje frequencies slightly lower[201]). For use in equations (14) and (15) these values must be normalized by B, the magnitude of "background" reticular activity (cells and afferents) not attributed to reticulocerebellar recurrent excitation (see section 3.3). No ready experimental means can dissect out this value from simple observations of R, the reticular steady-state activity. For fixed S and Z, however, increasingly smaller values of B imply increasing recurrent excitation. Table V documents various values of B for S = 37 and Z = 70 according to the amount of reverberation. Parameter optimization (section 4.6) was used to determine its final simulation value.

TABLE V

"BACKGROUND EXCITATION

B (hz)	S* (dimensionless)	Z* (dimensionless)	Comment
37	1.0	1.891	Lowest degree of recurrent excitation
24.667*	1.5*	2.838*	
18.5	2.0	3.784	
$\overline{7.4}$	$\overline{5.0}$	$\overline{9.46}$	
3.7	10.0	18.91	
1.0	37.0	70.0	Highest degree of recurrent excitation

$\overline{(\ )}$ = Average Parameterization

( )* = Actual Parameterization

4.6 Parameter Optimization

Beyond invoking a spatiotemporal steady-state to narrow the choice of synaptic efficacies that remain consistent with other module parameters, an attempt at parameter optimization through variation of "average" parameters was attempted to promote further precision. Parameter variations were done in partial derivative fashion (i.e., by varying but one parameter at a time a small amount) about the "average" values and the effects were evaluated in light of the following two constraints:

1. The spatiotemporal steady-state must be temporally, asymptotically stable, with no class of neurons either firing maximally or inhibitorally silenced.

2. Spatially differentiated activity patterns in the cerebellar nuclei must result from cerebellar afferent activity.

The first constraint reasonably assumes that the resting state is not balanced delicately between "unstable" alternative conditions involving inhibitory or excitatory saturation. The second is merely a restatement of working hypotheses of the Introduction. Methods of rapidly assessing behavior in terms of the contraints (for the purpose of variational analysis) are derived below:

Constraint 1. Steady-state temporal stability of governing equations (5) can be approximately assessed through the eigenvalues of the linearized equations (9) with derivatives resotred; namely:

$$\tau_x \dot{X} = -X + \hat{F}wR \qquad (16a)$$

$$\tau_y \dot{Y} = -Y + \hat{E}pZ \qquad (16b)$$

$$\tau_r \dot{R} = -R + \hat{G}wS + B \qquad (16c)$$

$$\tau_z \dot{Z} = -Z + \hat{D}q\hat{F}R \qquad (16d)$$

In employing equations (14) and (15) to calculate families of synaptic efficacies, the resulting eigenvalues of (16) were simultaneously computed and used to identify stable and unstable choices in the manner illustrated by figure 8: Ignoring the "UD" and "US" lines momentarily, the two graphs show the requisite constraints between the synaptic efficacies which will produce the identical spatiotemporal steady-state for the "average" parameterization of the cerebellar module (Tables III-V). Thus for increasing Purkinje effects on nuclear neurons (increasing p), reticulocerebellar connections must be strengthened (increasing w) and parallel fiber synapses weakened (decreasing q) to maintain the resting condition. The qualitative relations shown were found to be characteristic of all other realistic parameterizations of the module.

The two superimposed lines on figure 8 relate to eigenvalue behavior. Beyond line "US," with increasing p, the eigenvalues have non-negative real parts, indicating a temporally unstable steady-state. The proper choice of synaptic efficacies must therefore lie to the left of this line. Between the "UD" and "US" lines is a region of complex conjugate (stable) eigenvalues characteristic of an underdamped system. Operation of the module here results in somewhat oscillatory temporal phenomena (Note: This region can be absent in other

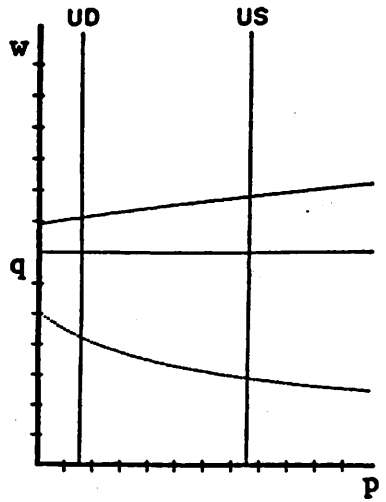

FIGURE 8

Functional relationships between synaptic efficacies got by solving equations (14) and (15). UD and US lines indicate resulting behavior of eigenvalues of equations (16). See text for explanation.

parameterizations). With further decreases in p to the left of the "UD" line the eigenvalues are real and stable--the system is overdamped. Here one expects rather sluggish, non-oscillatory behavior. Parameter optimization under constraint 1 thus involved examination of the "UD" and "US" regions (particularly the latter) with changes in the "average" parameterization. It was required that the stable zone be increased, if possible. This makes temporal phenomena in the module less critically dependent upon the exact parameter choices.

Constraint 2. Prediction of meaningful spatial differentiation in nuclear activity patterns is difficult short of actual simulation trials. Governing equations (5) do not admit of ready, and informative, analytical solutions. With a linearized version of the equations, one could search for spatial "resonances" with Fourier transform techniques, as did Calvert and Meno in modeling the cerebellar cortex[54]. This in fact has been done in section 9.3.1 in an effort to understand the observed behavior of the simulation. The analysis there, however, depends upon knowledge of the temporal behavior of the module got through simulation: It was found where on the temporal frequency spectrum the spatial response curves should be constructed. But before this knowledge existed, simulations were run on a trial basis using various parameterizations (which were already constrained by considerations of stability and steady-state activity) to determine additional empirical correlates of figure 8 attaching to greater nuclear spatial differentiation pursuant to climbing fiber activity. These correlates proved to be:

a. An increased overall magnitude of q.

b. An increased initial (negative) slope of q(w(p)).

Under constraint 2, then, variational analysis sought the goals of (a) and (b).

Table VI records all results of parameter variation analysis in terms of the optimality criteria surrounding constraints 1 and 2. Additionally, the impact on the overdamped zone of figure 8 is noted. Certain time constants were varied only in one direction, since to go the other seemed unrealistic. In Table VII the unequivocally "useful" variations of Table VI are isolated by applying the criteria developed above and were used in setting the final "optimal" simulation parameters; the latter have already been recorded in Tables III-V, save for the final synaptic efficacies used in all simulations, which were:

$w = 0.21$ mv/hz

$p = 0.45$ mv/hz

$q = 0.003$ mv/hz

Employing the appropriate parameters in equation (9c), the reticular nuclear steady-state activity for the simulation model is found to be approximately 64 hz. Such a high degree of reticular excitation (which can be seen experimentally in the lateral reticular nucleus[228]) is essential for the module behaviors to be described below. It should be a matter of some concern in evaluating experimental tests utilizing procedures that may depress reticular centers[30,32] (see section 9.5).

A number of the "useful" variations in Table VII bear on current controversies in the literature: That D be decreased argues for "shorter" parallel fibers, relative to the extent of other projections, to improve spatial effects (Table VI). Similarly, decreasing G suggests evolving a more punctate cerebelloreticular projection. Decreases in time constants τ_y and τ_z both result in more rapid impressment of Purkinje inhibition in the nuclei with changes in parallel fiber activity. The import of these variations is considered in detail in the Discussion (section 9). Adjustments in E, F, or B are each seen to have offsetting effects relative to the constraints (Table VI). Nonetheless, an overall improvement in performance was effected by decreasing F to enhance spatial patterning while increasing B and decreasing E to compensate for the resulting instability.

5. Simulation Methods

Response of the cerebellar module to climbing fiber inputs was identified by solving governing equations (5) on a PDP-15 minicomputer having graphical facilities. Use of fully interactive programming written in FORTRAN and assembly language permitted the conduct of experiments mimicking standard physiological practice, with the advantage of simultaneous monitoring of all cells. Despite the nonlinearities and small time constants of equations (5), it was found that simple Euler integration with 1 msec time increment was adequate to express their behavior. Tests with trapezoidal quadrature (i.e., by appending the next term in a Taylor's series expansion of the

TABLE VI

IMPACT OF PARAMETER VARIATIONS

(+) = Increase in property

(-) = Decrease in property

(0) = No change

( ) = Not applicable

Parameter	Variation	Stability	q	q Slope	Overdamped Zone
τ_x	-	-			-
τ_y	-	+			+
τ_y	+	-			-
τ_r	+	+			-
τ_z	-	+			+
D	+	0	-	-	0
D	-	0	+	0	0
E	+	-	0	+	+
E	-	+	0	-	+
F	+	+	-	0	-
F	-	-	+	+	+
G	+	-	-	0	+
G	-	+	+	0	-
B	+	+	-	-	-
B	-	-	+	+	+

TABLE VII

"USEFUL" PARAMETER VARIATIONS

Parameter	Useful Variation	Overdamped Zone
τ_y	-	+
τ_r	+	-
τ_z	-	+
D	-	0
G	-	-

derivatives of (5) added nothing qualitatively to the results, but did, of course, increase computation time and storage demands of the computer.

It was required that cells on the two boundaries of the simulated module be held at "background" levels--that so-called "edge effects" be suppressed. This two-point boundary condition can be satisfied by solution of equations (5) in a spatial Fourier series of period equal to the width of the module[61]. Such a periodic solution was approximated by attaching to each side of the module's layers 50 additional "ghost" cells whose behavior began the periodic replication of cellular activity inside the layer. To complete this technique the outputs of the ghost cells were used as fan-in inputs to the module, according to the geometrical parameters described above.

Two types of display of simulation activity were provided: The first yielded traditional plots of firing frequency as a function of time for any two cells of the module. The second--of by far the greater interest--depicted the firing frequencies of all cells in any two layers as a function of their mediolateral spatial locus at any given moment. The time sequence of development of this spatial activity was analyzed cinematographically.

6. Simulation Results

6.1 Achievement of Spatiotemporal Steady-State

Application of background excitation B (Table V) to governing equations (5) animates the simulated cerebellar module, causing all cells eventually to assume their resting discharges. The temporal approach of typical cerebellar nuclear and Purkinje cells to this condition is shown in figure 9 (N. Nuclear cell; P. Purkinje cell; both at the same mediolateral coordinate): B initially causes excitation of reticular cells which in turn excite both nuclear and Purkinje cells via "slow" mossy fibers. Almost immediately, however, nuclear activity begins to experience Purkinje inhibition as shown. As nuclear firing wanes, excitation of reticular cells through the cerebelloreticular projection also declines, causing a drop in mossy excitation; the latter further depresses cerebellar nuclear cells and, eventually, Purkinje cells. But with the decline in Purkinje activity, nuclear cells begin to recover from inhibition, the reticulocerebellar loop excitation contributing materially. Beyond this point both Purkinje

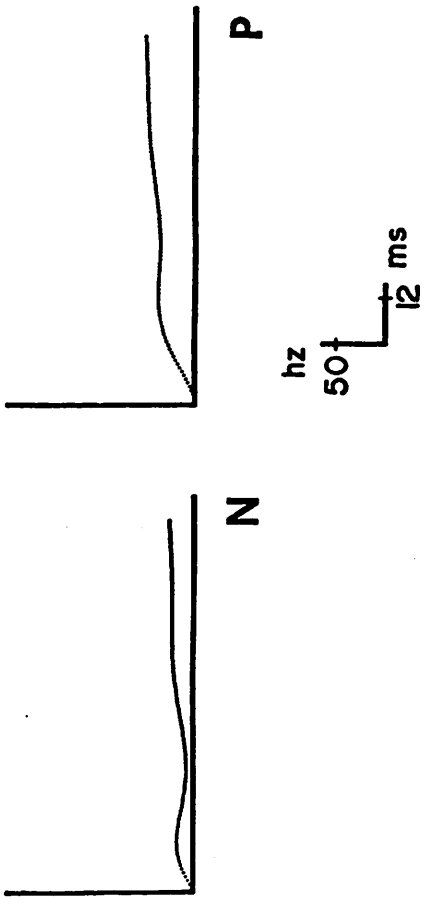

FIGURE 9

Behavior of simulated cerebellar nuclear (N) and Purkinje (P) neurons at same mediolateral spatial coordinate following application of uniform background excitation B to pre-cerebellar reticular nuclei. Firing frequency on vertical axis; time on horizontal.

and nuclear cells slowly increase their activity, levelling off at their spatiotemporal steady-state firing frequencies of 70 hz and 37 hz, respectively.

6.2 Comparison of Simulated and Experimentally-Obtained Single Unit Response

Before the simulated cerebellar module is used to predict novel responses of the cerebellar module to climbing fiber inputs, it is first necessary to check its accuracy in replicating known experimental data. Most such data has already been used to define the performance of various elements of the module. However, it is possible to examine two experimental phenomena which are at least one step removed from the behavioral quirks of individual cell species:

The first test has to do with the operation of the reticulocerebellar loops. Within the simulation, although reticulocerebellar recurrent excitation accounts for only a modest amount of activity, (Table V), it can still be shown to be a potent force by removing the cerebellar cortical inhibition that normally holds it in check. Figure 10 depicts the result of applying B to the module (as in figure 9) with corticonuclear synapses nullified. Unrestrained reticulocerebellar recurrent excitation drives the nuclear cell firing frequency upward approximately exponentially (the eventual saturation of the discharge is not shown). Now Tsukahara[259,261] has conducted an analogous experimental test on the interpositus nucleus (cat). Cerebellar cortical inhibition was removed using picrotoxin i.v., which antagonizes the inhibitory transmitter (GABA). A pulse

was injected antidromically into the loop between the interpositus and NRTP nuclei and the results monitored by intracellular recording in the red nucleus (to which the interpositus projects). Figure 11 A (extracted from Tsukahara[259], fig. 2) shows the response of a red nuclear neuron. As is obvious, following the stimulus (arrow) loop excitation builds and the firing frequency of the cell increases in the qualitative manner of figure 10. That this response is truly due to recurrent excitation in the reticulocerebellar loop was carefully checked by Tsukahara. On this test, then, the simulation appears to agree with experiment. It might be mentioned that Rosén and Scheid[227] cooled the cerebellar cortex in an attempt to eliminate cortical inhibition and then recorded from interpositus neurons following peripheral nerve stimulation. They did not find the explosive buildup of excitation seen by Tsukahara, but did observe greatly enhanced excitatory responses in the nucleus.

A second test involves the responses of cerebellar nuclear neurons to climbing fiber inputs. Recall that the simulated Purkinje cfr and subsequent events (silent period, etc.) were carefully defined, but that nuclear responses were not (save for the influence of climbing fiber collaterals). Seen experimentally, such responses are typified by figures 11 B (from Eccles, et al.[92]; fig. 10) and 11 C (Eccles, et al.[97]; fig. 5). These were obtained in decerebrate cats following brief stimulation of the inferior olive. Figure 11 B shows a series of poststimulus-time histograms of spike probability in a fastigial nucleus neuron following the olivary stimulus (black bar on left); stimulus current was graded from lowest (uppermost histogram)

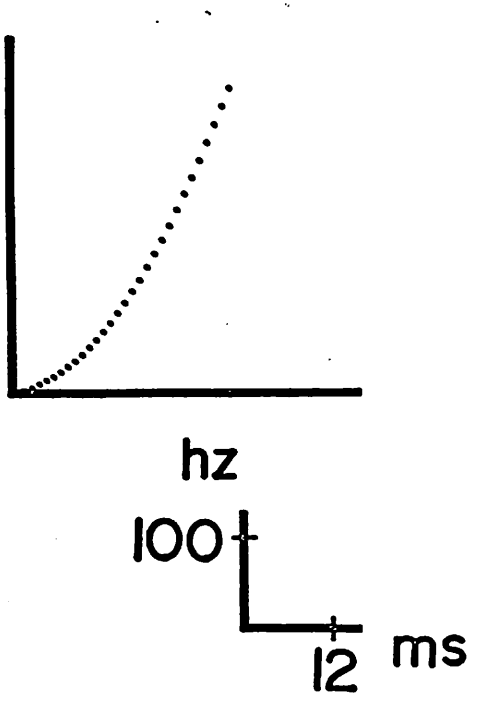

FIGURE 10

Response of cerebellar nuclear cell to application of background B when cerebellar corticonuclear inhibition is nullified. Recurrent excitation drives firing rate explosively upward (discharge saturation not shown). Compare with Figure 11 A.

to highest (lowermost). There appear to be three reliable response phases; an initial sharp excitation, followed by a silencing, and then by a somewhat broader "rebound" excitation. Both excitations and silencing become more pronounced at higher current levels (see below). The two excitatory periods separated by silence are also seen in responses of interpositus neurons to olivary stimuli, shown in figure 11 C. The lower trace is the poststimulus-time histogram, while the upper is the actual extracellular record of the response. Durations of the excitatory and inhibitory periods can be seen to be comparable to those in the fastigial nucleus (figure 11 B).

As "olivary stimulus" can also be given to the simulated cerebellar module by activating a climbing fiber microstrip (which, presumably, is what an actual weak olivary stimulus does). Figure 12 records the module response to a single volley (defined in sections 3.4, 4.4) from one microstrip as seen in a nuclear (N) and a Purkinje (P) cell lying at the same mediolateral coordinate within the region directly affected by the microstrip. The stimulus is presented at the origin of coordinates (the conduction latency from the inferior olive is not represented). It is seen that the nuclear cell is briefly activated by climbing fiber collaterals before being completely suppressed by inhibition from the Purkinje cfr (symbolized by the heavy black bar; the cfr firing frequency (500 hz; Table II) is too high to be shown). Following the cfr the Purkinje cell enters its silent period, releasing the nuclear cell from inhibition. The latter rebounds, assisted by reticulocerebellar recurrent excitation. The

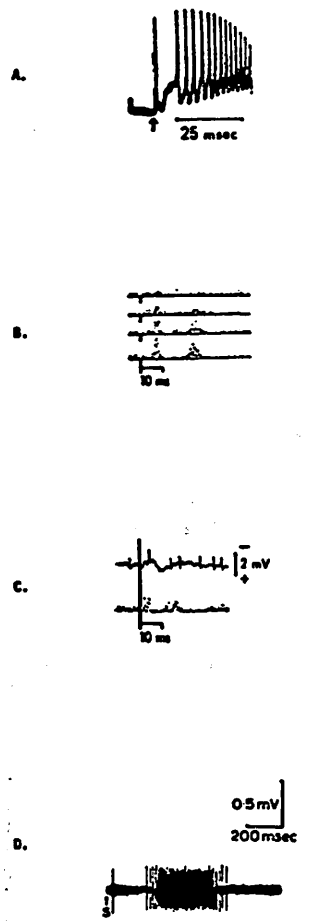

FIGURE 11

Experimental observations corroborating behavior of the simulations. (A; from Tsukahara[259]). Response of red nucleus neuron excited by unchecked reticulocerebellar recurrent excitation; compare with figure 10. (B; from Eccles, et al.[92], C; from Eccles, et al.[97], D; from Armstrong, et al.[10]). Responses of cerebellar nuclear cells to shocks of inferior olive or peripheral nerves, evoking climbing fiber volleys. Compare with figure 12. See text for details.

Purkinje cell then resumes its discharge, re-inhibiting the nuclear cell and causing its return to the "background" firing rate. The slight rebound of the Purkinje neuron following the silent period is caused by increased slow mossy fiber excitation reaching the cortex from the momentarily increased reticulocerebellar recurrent excitation.

Comparison of the simulated nuclear neuron response of figure 12 with those of figures 11 B and C demonstrates their qualitative, if not quantitative, similarity. While poststimulus-time histograms cannot be directly translated into frequency-time plots without additional information, it is clear that the durations of the response epochs (excitations and silencing) and their latencies relative to each other are equivalent in the histograms and in the simulation results.

The investigators who produced the data given in figures 11 B and C gave no detailed explanation of the source of the second, rebound excitatory period in nuclear cells[92,97]. The simulations indicate that the silencing of Purkinje cells following microstrip cfr's could account for it well. The augmenting of both nuclear excitatory phases (and of the silent phase) with increasing olivary stimulus current (figure 11 B) can easily be attributed to the recruitment of more climbing fibers within the strip zone, i.e., a simultaneous increase in collateral excitation, Purkinje inhibition, and subsequent nullification of that inhibition.

Using peripheral nerve and "natural" stimulation, thereby activating both spino-olivocerebellar pathways and other ascending

(mossy fiber) tracts, other authors have observed excitation-silencing-rebound sequences in the cerebellar and Deiters nuclei[10,11,179,248,251,252]. One of the more spectacular examples of such a sequence is the interpositus unit response (to stimulation of a hindlimb nerve in a chloralose cat) shown in figure 11 D (from Armstrong, et al.[10]; figure 1). After the stimulus the cell fires a single spike, is then silent for about 200 msec, and finally rebounds with a flourish. The half-second duration of this rebound is remarkable and does not reflect the simulation results of figure 12. It has been claimed by some that such long-duration responses are produced through the climbing fiber system in the same way described above; olivary stimulation reportedly can provoke the reaction[10]. Mortimer, however, while seeing similar nuclear responses following startle-stimuli given awake monkeys, was unable to correlate them with cfr-related Purkinje cell behavior in the overlying cortex[188]. It will be presumed here, therefore, that the simulation does indeed provide a qualitatively accurate model of cerebellar reactions to climbing fiber inputs at the single unit level. The responses take place in the time frame of figure 12. What that figure cannot show (and what has yet to be studied experimentally) are the effects microstrip activity has upon the spatial distribution of neuronal activity. When this is examined in the next section, then another type of long time-course phenomenon will be seen to emerge.

6.3 Spatial Response Patterns to Single Climbing Fiber Microstrip Inputs

All climbing fiber inputs were presented to a single, centrally located "strip" of the cerebellar module. Dimensions of the strip

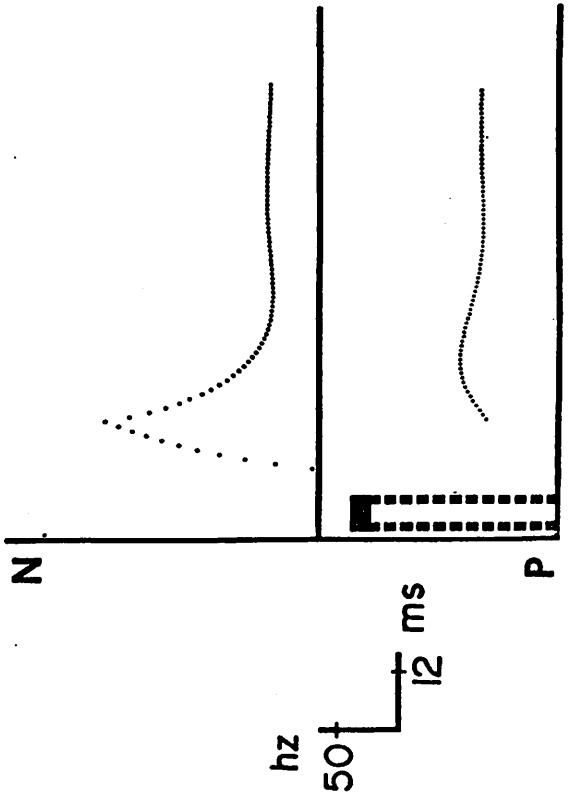

FIGURE 12

Simulated cerebellar nuclear (N) and Purkinje (P) single-unit responses (at same mediolateral coordinate) to a climbing fiber microstrip volley at their location. Black bar is Purkinje cfr. Compare nuclear response with figure 11 (B, C, D).

(0.6 mm) and simulated physiological effects of the cfr have been described earlier (sections 3.4, 4.4). Figures 13-16 portray the spatial distributions of activity in nuclear (N) and Purkinje (P) neurons as they evolve over time before, during, and following a single strip cfr. Each figure is concerned with one of the 3 successive epochs of this activity as follows:

a. Purkinje cfr (figure 13). Prior to presenting the stimulus, the module is placed in the spatiotemporal steady-state (0 msec). Stimulus presentation begins in the first millisecond with a momentary burst of nuclear excitation within the microstrip zone; this reflects the action of climbing fiber collaterals. Immediately thereafter, Purkinje cells of the strip begin their cfr burst at 500 hz (arrows) which will continue for 8 msec. The resultant tremendous buildup of Purkinje inhibition rapidly extinguishes the nuclear burst. Neighboring nuclear cells undergo a small excitation (as do Purkinje cells) owing to increased reticular nuclear (thus, slow mossy fiber) activity brought about by the initial cerebellar nuclear burst.

b. Purkinje silent period (figure 14). Commencement of Purkinje silencing in the 10th millisecond also finds nuclear cells silenced in the cfr strip zone, with the discharges of their neighbors collapsing because of the consequent loss of reticular drive; Purkinje cells bordering the strip likewise show a gradual decline in activity for the same reason (but distributed over a wider area, thanks to the parallel fibers). Inactivation, however, removes Purkinje inhibition from the original nuclear targets of the cfr. They recover rapidly and

a spectacular "rebound" excitation ensues, bolstered by reticulocerebellar recurrent-excitation reminiscent of figure 10. Neighboring cells are also eventually carried upward on this tide. Purkinje neurons begin to feel the same excitation as the inactivation period closes.

c. Recovery period (figures 15, 16). Resumption of Purkinje activity in the strip region immediately begins to quench the nuclear rebound until the affected cells are returned nearly to their original resting discharge rate (see figure 12 and figure 19 below). Even as this quenching proceeds, though, Purkinje discharges are slowly elevated over a broad area because of excitation spreading on the parallel fibers)--an effect due once more to augmented reticulocerebellar interactions transmitted on slow mossy fibers. The ensuing mediolateral spread of inhibition in the nuclear region results in the depression of cells bordering the original excited strip. 50 msec following cfr initiation, then, a hill-and-valley spatial differentiation of nuclear activity has been created along the mediolateral axis. The "hill" coincides with the original climbing fiber strip; the inhibited valleys lie to each side. This, of course, can now be seen as merely a manifestation of classic lateral inhibition made recurrent via reticulocerebellar interchange. However, the pattern--characteristic of simulations reported herein--has the further property of persistence; it survives well beyond the climbing fiber input which initiated it, as is well illustrated in figure 16. Even after 150 msec has elapsed following the original strip input, some vestige of its

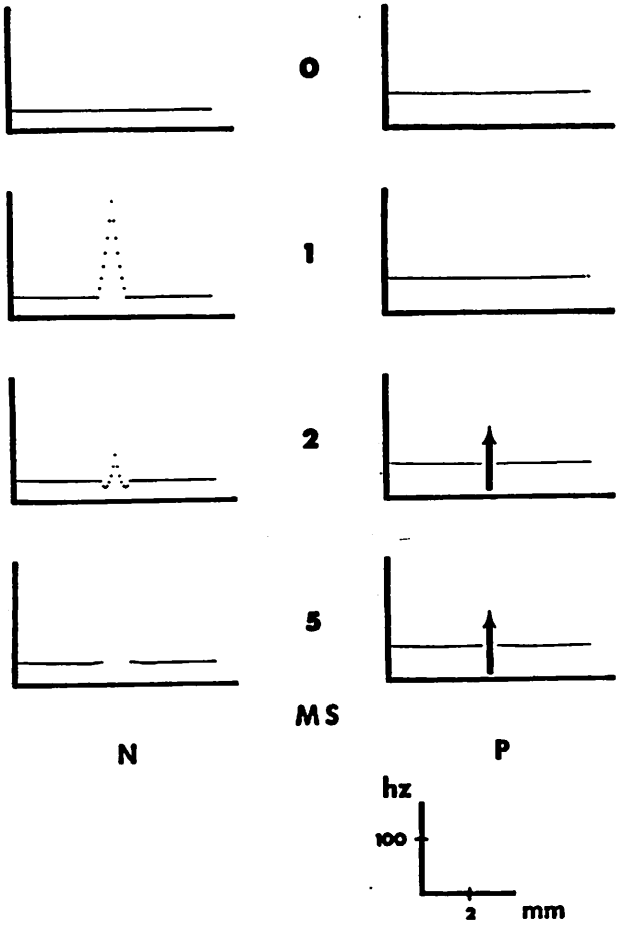

FIGURE 13

Evolution in time of mediolateral spatial activity distribution in cerebellar nuclear (N) and Purkinje (P) cells following isolated microstrip cfr. Firing frequencies on vertical axis; mediolateral location (mm) on horizontal. Time of activity snapshots (msec) shown at center. Black arrows indicate Purkinje microstrip cfr's. Figure shows events only through the time of the cfr.

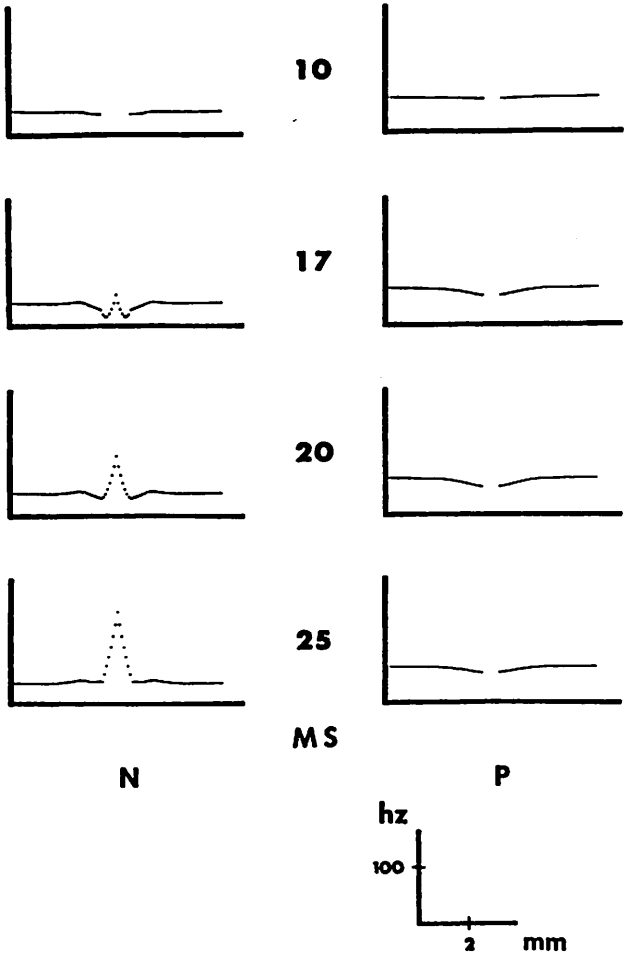

FIGURE 14

Continuation of figure 13 showing evolution of spatial phenomena connected with the period of Purkinje silencing. Note nuclear rebound.

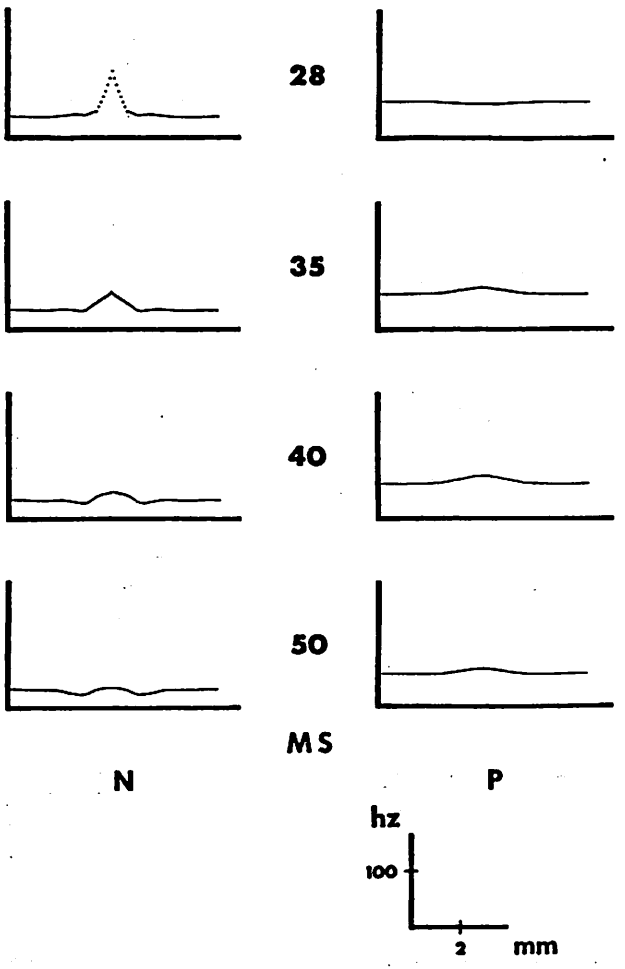

FIGURE 15

Continuation of figure 14 into the Purkinje recovery period. Augmented Purkinje inhibition develops in nuclear areas mediolateral to the original microstrip zone thanks to spread of reticulocerebellar recurrent excitation on parallel fibers.

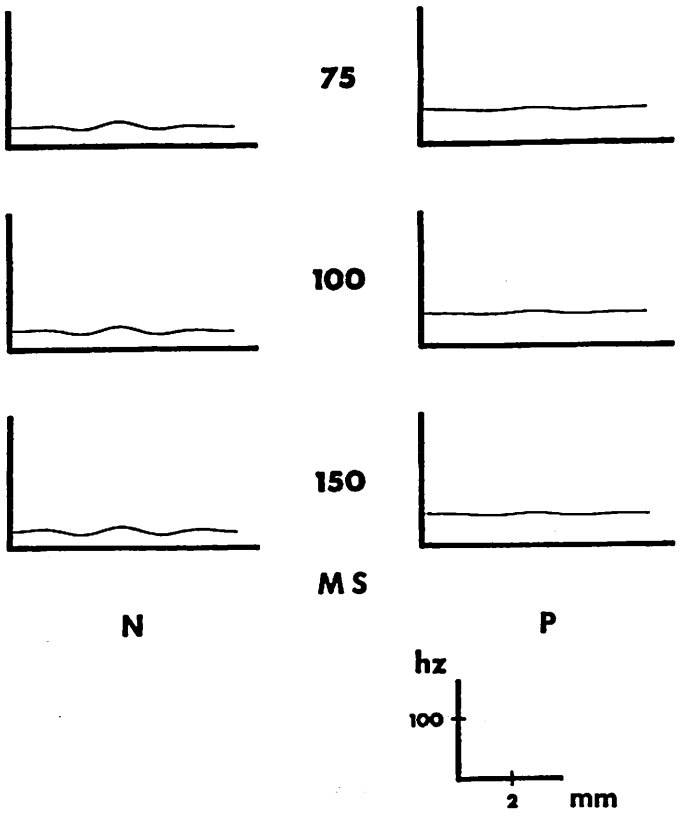

FIGURE 16

Continuation of figure 15 demonstrating the remarkable persistence in the cerebellar nucleus of the hill-and-valley spatial activation pattern left by the single microstrip climbing fiber volley.

spatial effect remains. Such persistence allows the pattern to be potentiated by repeated climbing fiber barrages (examined in the next section). It also has far-flung functional implications addressed both later in this report and elsewhere[36,37].

Tradition holds that the Purkinje cfr and its resulting nuclear inhibition are the critical physiological phenomena the climbing fibers contribute to cerebellar processing. Instead, however, the simulations demonstrate that the Purkinje silent period following the cfr, despite its brevity, is the critical factor with respect to establishing a spatial pattern of neural activity within the cerebellar nucleus. Cfr inhibition should still not be thought superfluous: Examination of figure 14 shows that the production of laterally inhibited nuclear side lobes is begun by cfr inhibition, to be finished during the recovery period (figure 15).

6.4 Potentiation of Spatial Activity Patterns with Repeated Microstrip Inputs

In general, repeated activation of the same climbing fiber strip enhances the vividness of the related nuclear hill-and-valley activation pattern, provided the repetition interval is "short" relative to the pattern's decay. As an example, when the strip of figures 13-16 is activated three successive times at 50 msec intervals, beginning from the steady-state, the potentiation proceeds as in figure 17 (N. Nuclear region. P. Purkinje region). The figure displays snapshots of activity taken 50 msec following each cfr and clearly demonstrates increasing spatial differentiation.

It may reasonably be argued that the 20 hz (50 msec period) cfr repetition rate used in the demonstrations above is "non-physiological" since maximum cfr (or olivary cell burst) frequencies rarely exceed 10 hz under various laboratory conditions[27,152,164,165,251] (but see ref. 75; and reports on awake, especially "behaving," animals support even lower frequencies[193,252,253,254]. However, these lower cfr rates should in no way influence the qualitative results of figure 17. The reason, of course, lies in the long persistence of the patterns. As shown in figure 16, the time constance of persistence is at least 150 msec, allowing pattern potentiation by climbing fiber volleys occurring at 6 hz or less. As will be explored in the next section, that time constant may also be adjustable by alterations of reticulocerebellar recurrent excitation. Thus, only the acquisition rapidity and eventual degree of potentiation can safely be said to be governed by the repetition frequency of strip volleys. In fact, the notion of "repetition" could itself probably be replaced by a more statistical measure of the density of cfr's in a strip.

6.5 Persistence of Spatial Activity Patterns

All spatial patterns of activity created by climbing fiber inputs in the simulations persist for some period of time after those inputs have ceased. The persistence period is significantly longer than the membrane time constants of the cells involved. For example, if the activity pattern created by the 3 successive cfr's of figure 17 is allowed to continue in time with no further inputs, the behavior of figure 18 results (N. Nuclear region. P. Purkinje region): Time 0

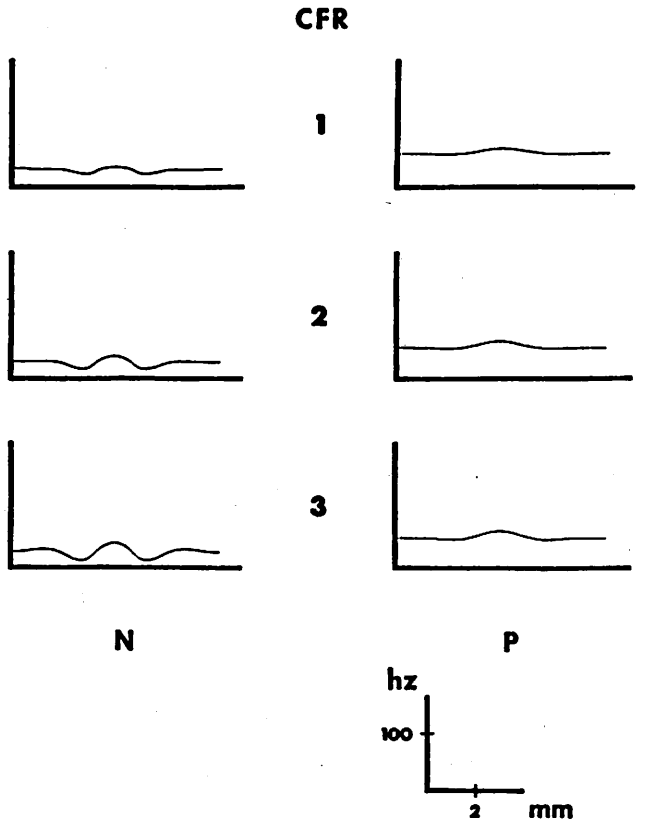

FIGURE 17

Potentiation of spatial activity patterns in cerebellar nuclear (N) and Purkinje (P) regions following each of 3 successive microstrip cfr's at 50 msec intervals. Each snapshot is taken 50 msec following the previous cfr, immediately prior to the next volley. Increasing vividness of the hill-and-valley pattern is obvious following successive volleys.

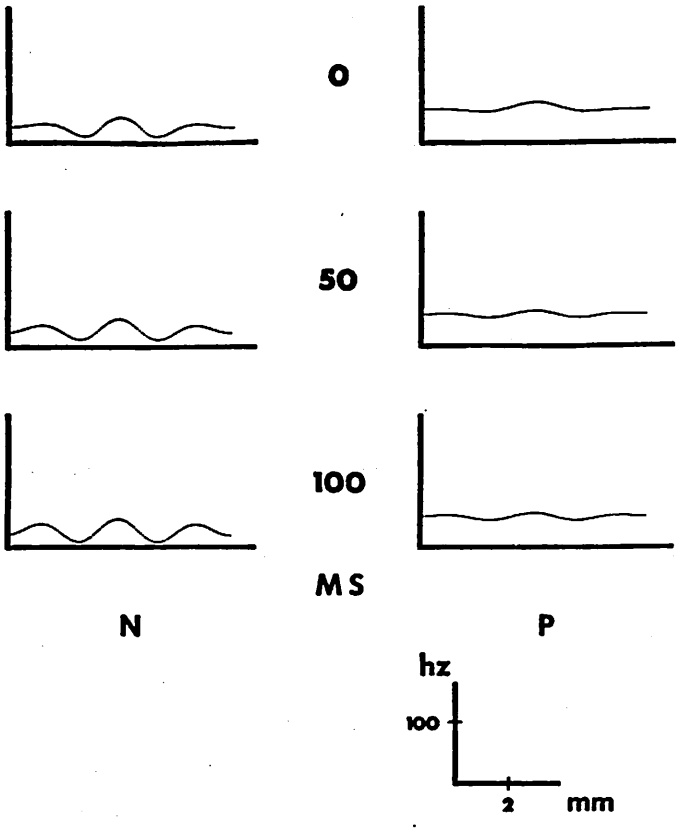

FIGURE 18

Persistence of the potentiated spatial activity pattern following the third cfr of figure 17. An inhibition-disinhibition process is evident, resulting in spatial instability (see text).

corresponds to the state following the third cfr of figure 17. It is clear that both nuclear and Purkinje regions retain their basic activity patterns even after an additional 100 msec have elapsed (cf. figure 16 also). As noted, such persistence is what allows potentiation of the pattern despite long and possibly irregular intervals between climbing fiber activations.

The persistence stems from two processes. The first, and most obvious, is the recurrent excitation supplied by reticulocerebellar loops. It slows the decay of patterns. The time constant of persistence is thus largely adjustable through the gain of those loops.

The second persistence process is the classic inhibition-disinhibition spatial sequence found in most lateral recurrent inhibition systems--a disguised recurrent excitation effect, of sorts. As seen in the later snapshots of figure 18, climbing fiber input has triggered development of a quasi-sinusoidal standing wave of inhibition-disinhibition. The spatial period of the pattern is about 2.4-2.6 mm/c. Note that this spatial "resonance" would make the module especially receptive to simultaneously active Oscarsson climbing fiber strips spaced in a lattice at intervals of about 1.2 mm which perhaps is a significant clue to anterior lobe function (see section 9.3).

The inhibition-disinhibition standing wave will eventually partition the entire module into excited and inhibited regions. Hence, the simulation may be said to suffer from covert "spatial instability" in the sense that inputs restricted in space do not produce similarly restricted outputs. In section 8 below, it will be shown that this problem may disappear when the effects of granule cell recruitment

and Golgi inhibition are accounted for. The present simulations of the unadorned cerebellar module have nonetheless shown that the spino-olivocerebellar system can produce significant alterations in the spatial distribution of anterior lobe neural activity, at least in theory. An unexpected finding was that, once created, these alterations tend to persist in short-term memory fashion for significant lengths of time (say, seconds, with sufficient reticulocerebellar feedback). The persistence leads to the ability to potentiate patterns using climbing fiber inputs that can be well spaced out in time. No appeals to neuronal plasticity were made to achieve these results; the seeming "memory" function is entirely a dynamic process.

6.6 Comparison of Simulated Spatial Activity With Experimental Results

If the behaviors of figures 13-18 are actually characteristic of climbing fiber induced activity in the cat anterior lobe, one must ask if they have been spotted electrophysiologically. Strictly speaking, they have not been--but then neither has the spatial distribution of responses in the anterior lobe been explored beyond the delimiting of strips of cfr's in Purkinje cells. Still, one might at least expect the potentiation effects seen in the simulations to have been noted in individual cerebellar units. Indeed, Gresty and Paul[123] have recently reported that repeated stimulation of one caudate nucleus in cats progressively enhanced the "late facilitation" following each stimulus in the contralateral fastigial nucleus, while in the ipsilateral nucleus an identical response became progressively weaker. This experiment scarcely proves that climbing fibers were responsible

for the potentiation effects (even though it is tempting to equate "late facilitation" with reticulocerebellar rebound excitation); but it does demonstrate that some sort of repeated input leads to an alteration of the spatial distribution of neural activity in the cerebellum.

The Gresty and Paul experiment aside, the weight of evidence would seem to indicate that no potentiation effects occur in cerebellar neurons after repeated climbing fiber activations. The most extreme test of this to date is probably that reported by Eccles[88], who attempted to test Marr's[35,176] and Albus'[1,2] hypothesis that the conjunction of climbing and parallel fiber activity has some sort of plastic effect upon parallel fiber-Purkinje cell synapses. Repeated climbing fiber volleys were given and Purkinje responses carefully monitored; no evidence of any change in any cell's response was noted (i.e., including changes associated with the type of potentiation seen here). Are the simulations therefore incorrect?

To answer that question, "single-unit recordings" were simultaneously made of simulated nuclear and Purkinje cells which responded immediately and predictably to climbing fiber microstrip inputs; this would appear to replicate the bias present in similar physiological experiments. Figure 19 illustrates the results taken from a nuclear (N) and a Purkinje (P) cell (at the same mediolateral coordinates) located centrally within the domain of the active microstrip (see figure 12 for further account of response features). When the simulation is started in the spatiotemporal steady-state, the response of the cells

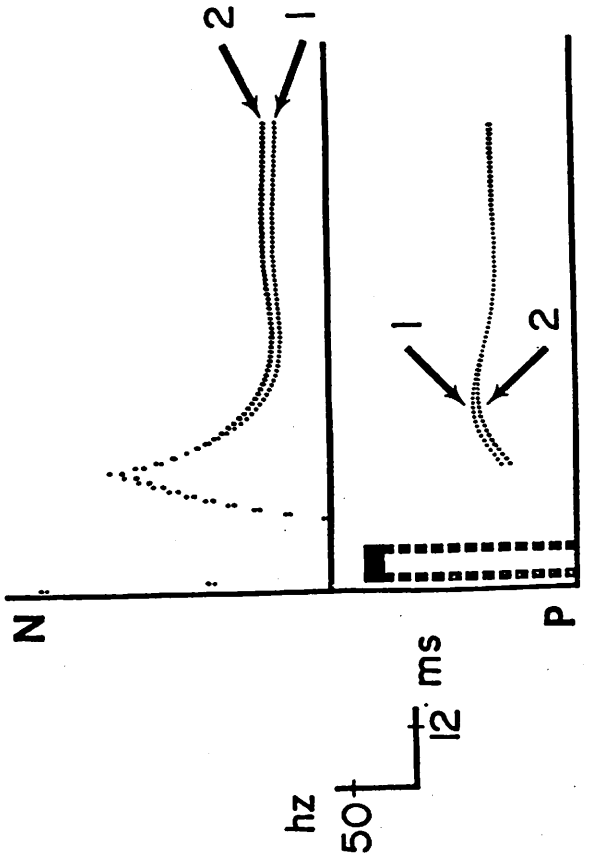

FIGURE 19

Lack of significant changes in the temporal response of single Purkinje (P) and cerebellar nuclear (N) cells following the repeated microstrip volleys which produce potentiation of the spatial activity patterns of many such cells. Nomenclature and curve 1 of each graph are identical to that of figure 12. Curve 2 indicates temporal responses following the third of 3 successive cfr's at 50 msec intervals. The near-equivalence of the two sets of curves suggests the difficulty of assessing changes in cerebellar spatial activity patterns with single-unit technique (see text).

to a climbing fiber input is given by curve 1 (light dots) in both graphs (identical with figure 12). If, however, a hill-and-valley spatial activity pattern has already been created by prior activation of the strip (two volleys at 50 msec intervals; see figure 17), then an additional strip volley produces the cellular responses given by curve 2 (heavy dots). It is obvious that despite the pronounced spatial patterning present in the cerebellar nuclei following this third climbing fiber input (figure 17), the discharge patterns of the two cells are virtually identical with those following the first cfr. This accords with the experimental findings showing no significant changes in discharge properties following repeated cfr's. Therefore, no real conflict appears to exist between the simulations and physiological data (as far as the latter go).

How is it, then, that on a single-unit basis no prolonged effect of the climbing fiber input can be demonstrated, while such an effect is so obvious over space? The answer is equally obvious from figures 17 and 18: Spatial patterning and its potentiation are largely seen in the actions of cells located mediolaterally to the active microstrip--that is, in cells which show neither classic climbing fiber responses, nor particularly rapid activity alterations following such inputs. It is doubtful that such units would be seriously studied physiologically owing to their "unresponsiveness." Such changes as do occur in these units would likely appear to be more fluctuations in "background" (a daily finding in the laboratory) than anything to be paid attention to. And, of course, the time averaging techniques

currently in vogue would likely wash out fortuitous observations of activity alterations.

It may be possible to overcome some of the problems stated above and set up experimental conditions wherein the proposed activity changes following climbing fiber strip activation can be directly demonstrated. For example, it is evident from figures 17 and 18 that patterning is much more evident in the cerebellar nuclei than in the cortex; the nuclei thus become a more attractive target for investigation. This, and other experimental methods, will be taken up in section 9.5.

7. First Revision of the Simulation Model. Granule Cell Recruitment Hypothesis

7.1 Derivation of Recruitment Columnar Transfer Function

Other cerebellar theories have attributed much more sophisticated processing capability to the granular layer of the cerebellar cortex than that of simply summing and relaying mossy fiber excitation to Purkinje cells, even though the simulation results given above (section 6) show that the cerebellar module is capable of non-trivial behavior under a "relay" hypothesis. The minuteness and extreme density of granule cells is somewhat puzzling if mere relaying is all that takes place[88].

In reality, it has been clear for some time that the granular layer is not simply a relay. Several physiological investigations[3,4,117] have demonstrated that the temporal convergence of two mossy fiber inputs of fixed strength will be transmitted very effectively

through the granular layer, while either input presented in isolation may actually be blocked. This suggests that the granular layer may at least function as a summer with a significant threshold.

In the course of studying simulation behavior to exogenous mossy inputs (Boylls, in preparation), it was found that "slow" inputs of a given strength (firing frequency) applied through a punctate locus of pre-cerebellar reticular nucleus (e.g., the lateral reticular nucleus) had an overwhelmingly more potent effect on a given Purkinje cell than an equally strong and punctate "fast" mossy input delivered directly to that cell (say, via the DSCT). This of course owes itself to the fanning out of the reticular input to the cortex and its subsequent reconvergence (via the parallel fibers) on the Purkinje cell. Thus, if the well-known punctateness of fast mossy inputs is to be reflected at all in Purkinje outputs, it follows that one or more of the following propositions should likely hold:

1. The average "fast" input is either much more spatially dense, or is much stronger, than the average "slow" input.

2. Synapses involving fast inputs are much more efficacious than are slow synapses.

3. A mechanism for boosting the strength of punctate inputs must exist in the cortex.

Owing to lack of evidence, it is doubtful whether much can be said one way or the other about propositions (1) and (2). However, a fairly suggestive case, though indirect, can be made regarding (3)--that there may well exist a cortical "boosting" mechanism and that its substrate is recruitment of granule cells by mossy inputs

(recruitment, incidentally, also fits with the threshold behavior to mossy inputs mentioned above):

Consider granule cells to share the common morphology of having roughly spherical somata with radiating dendrites. Each dendrite participates in a mossy fiber glomerulus, but each cell receives no more than one input from a given fiber[213]. Suppose further that the efficacy of a mossy fiber synapse, measured by the amount of current injected into a granule cell per mossy action potential, is similar for all mossy synapses and that the membrane voltage thresholds (measured at the axon hillock) of granule cells are similar as well. Now although granule cells may display from 2 to 7 dendrites, those having 4 or 5 account for over 80% of the total in cat[213]. Thus the number of synapses on each cell of a granular "column" (section 2.4.2) at i receiving aggregate mossy input M(i) (section 3.5) is roughly constant. Assuming that M(i) is distributed uniformly over the column (section 2.4.2), it follows that M(i) injects approximately the same current into all cells of the column. Zucker[274] has shown that the input resistance--and thus the depolarization, V--of a cell under these conditions is proportional to r^{-1}, where r is the cell radius. Consequently, the depolarization sensitivity to any fluctuations in r is

$$\left| \frac{\frac{dV(r)}{dr}}{r} \right| \propto \frac{\frac{1}{r^2}}{r} = \frac{1}{r^3} \qquad (17)$$

The smaller r becomes, then, the more dramatic the fluctuations in M(i)-induced membrane potentials throughout the column with any slight

developmental variations in r. Thus, if the actual voltage thresholds of the cells are similar (as postulated), the column will exhibit an apparent dispersion of firing thresholds as a function of M(i). For the same degree of variance in r, that threshold dispersion will grow more pronounced as the average value of r decreases. Therefore, cells of the column will be systematically recruited with increasing M(i) for r sufficiently small.

Several structural features of the cerebellar cortex could well be viewed as corollaries of possible granule recruitment. The small size of the cells has already been cited as a ploy for producing a wide range of operational thresholds. The high density of cells in each column (at least 225, as calculated in section 2.4.2) allows a continuous recruitment spectrum within the column and promotes uniformity of the recruitment function over columns. Smolyaninov[242] has found that the radii of granule cells are somewhat larger, and the density of cells somewhat lower, in the frog cerebellar cortex than in the cat. Perhaps one could thus conclude that recruitment (or a decided tendency toward it) conveys a selective advantage over phylogeny. Lastly, note that out of the size and density of granule cells required for recruitment necessarily emerges a correspondingly high density of small-diameter, slowly conducting parallel fibers. Other authors have been inspired to assign "reliability"[88,231], "pattern recognition"[2,115,176], and "delay-line"[39,40,41,112,114] functions to these attributes of parallel fibers and their many synapses with Purkinje cells. On the other hand, it is also possible that parallel fiber

properties emerge as epiphenomena of the design of the granular layer.

A test of the effect of granular recruitment upon the simulated anterior lobe cerebellar module requires the derivation of a columnar transfer function, G (Table I; sections 3.3, 3.5). In this derivation it will be assumed that all cells within a column, having a threshold Θ expressed in terms of the aggregate mossy input to the column, will fire at a frequency $\alpha(M(i) - \Theta)$, α a proportionality constant, whenever Θ is exceeded. That is, the cells are assumed to be linear above threshold with exceedingly short membrane time constants (see section 8 as well). These assumptions are more for the sake of simplicity than anything else. Unfortunately, actual recordings of granule cells (which are exceedingly difficult to make) shed little light on the validity of the assumptions[19,94,193,194]. To proceed, let $p(\Theta)$ be a unimodal probability density function indicating the number of granule cells in a column likely to have thresholds around Θ (a multimodal distribution would not materially affect the results). Let M^* be the mean of $p(\Theta)$. Then the number of granule cells recruited at a frequency Θ is $\beta p(\Theta)d\Theta$, where β is the total number of cells in a column. The output of the column, to the parallel fibers, at input frequency $M(i) \geq \Theta$ for cell recruited at Θ is thus

$$\alpha(M(i) - \Theta) \cdot \beta\, p(\Theta)d\Theta = g(M(i) - \Theta)p(\Theta)d\Theta, \qquad (18)$$

where $g = \alpha \cdot \beta$ = a "firing-density" factor.

The total output of the column--the aggregate parallel fiber output--is merely the sum of all outputs of cells recruited for all

$\Theta \leq M(i)$. That summation is presumed to take place within the (linear) Purkinje cells. Thus, the granular columnar transfer function G is defined by

$$G(M(i)) = \int_0^{M(i)} g(M(i) - \Theta)p(\Theta)d\Theta \tag{19}$$

Defining P(Mi)), the cumulative granular columnar threshold distribution as,

$$P(M(i)) = \int_0^{M(i)} p(\Theta)d\Theta \tag{20}$$

equation (19) may be integrated by parts.

$$\begin{aligned} G(M(i)) &= g[M(i)P(M(i)) - \int_0^{M(i)} \Theta p(\Theta)d\Theta \,] \\ &= g[M(i)P(M(i)) - (\Theta P(\Theta)\Big|_0^{M(i)} - \int_0^{M(i)} P(\Theta)d\Theta)] \\ &= g[M(i)P(M(i)) - M(i)P(M(i)) + \int_0^{M(i)} P(\Theta)d\Theta] \\ &= g \int_0^{M(i)} P(\Theta)d\Theta \end{aligned} \tag{21}$$

As a unimodal cumulative distribution function, P(M(i)) will be some type of sigmoid curve. For simulation, this sigmoid was in turn modelled with a parameterized logistic curve of the form (dropping the spatial index, i)

$$P(M) = \frac{1}{1 + e^{-a(M-M^*)}} \tag{22}$$

where $a \geq 0$ is proportional to the maximum slope of the curve (i.e., inversely proportional to the variance about mean M*). With this form for P(M), G(M) becomes

$$G(M) = g[M + \frac{\log(1 + e^{-a(M-M^*)}) - \log(1 + e^{aM^*})}{a} \,] \tag{23}$$

Figure 20 illustrates 3 instances of G(M) and associated P(M). In both (a) and (b), M* = 1000 and g = 1, while a = 0.006 in (a) and a = 0.1 in (b). Note that for M>>M*

$$G(M) = M - M^* \tag{24}$$

In this case the granule cells of the column would be fully recruited and the columnar output reduces conceptually almost to an "identity" G(M) (section 3.5). The slope parameter, a, obviously controls the abruptness of recruiting. Figure 20 C illustrates the case for M* = 606, g = 2, and a = 0.006, which was actually used in simulation. Recruitment now begins at lower levels of mossy intensity, while the full-recruitment output rises twice as fast as the identity case. The method of calculating M* is given below. The choice of a and g was made heuristically merely to produce a clear alternative to an identity transformation.

To test the effects of granule recruitment on the cerebellar module, the spatiotemporal steady-state was chosen equivalent to that of earlier simulations (section 4.5), thereby allowing the same set of synaptic efficacies, etc., to apply to all simulations. This was achieved by choosing the mean, M*, of the granular columnar recruitment

threshold distribution such that (from equations (5d) and (9d))

$$Z^* = (2D + 1)qG((2F + 1)R^*) = \hat{D}q\hat{F}R^* \quad (25)$$

implying, from equation (23), that

$$G(\hat{F}R^*) = g\left[\hat{F}R^* + \frac{\log(1 + e^{-a(\hat{F}R^* - M^*)}) - \log(1 + e^{aM^*})}{a}\right] = \hat{F}R^* \quad (26)$$

Defining $V = e^{a\hat{F}R^*(1-g)/g}$, it can be shown that

$$M^* = \frac{1}{a}\log\left[\frac{V - 1}{e^{-a\hat{F}R^*} - V}\right] \quad (27)$$

where, from (25)

$$R^* = \frac{Z^*}{\hat{D}\hat{F}q} \quad (28)$$

The parameters g and a were stipulated in the above section; (27) was used to evaluate M*.

7.2 Simulation Effects of Granule Cell Recruitment

The spatial effects of granule recruitment upon cerebellar module responses to single climbing fiber microstrip volleys was examined according to the regimen of section 6.3. The recruitment results, illustrated in figures 21 and 22 (N. Nuclear region; P. Purkinje region), will be compared below with the non-recruitment case presented in figures 13-16.

As usual, the module was started in the spatiotemporal steady-state. The immediate reaction to the cfr in both nuclear and Purkinje

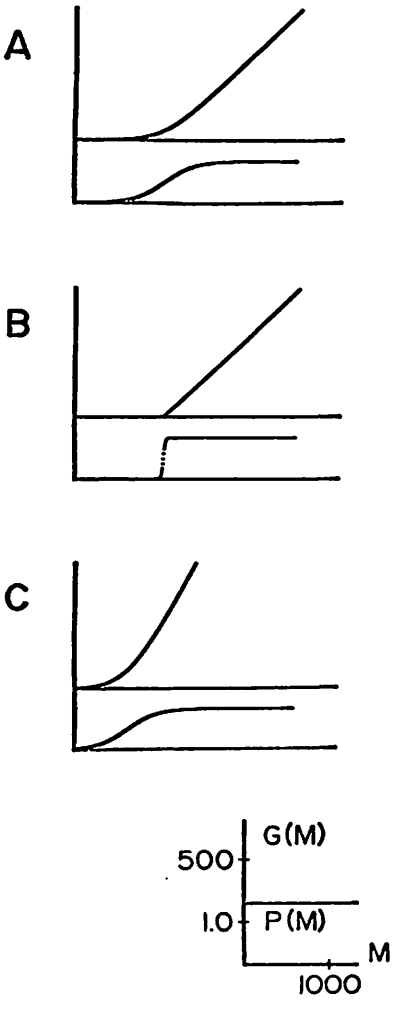

FIGURE 20

Granular columnar transfer function, G, as a function of aggregate columnar mossy fiber input, M, for three forms (A, B, and C) of granular columnar threshold distribution, P. Text describes the three different parameterizations. C is the form used in simulations of granule recruitment effects on the cerebellar module.

cells (i.e., to 9 msec) was virtually identical to that without recruitment and is only sketchily illustrated in figure 21. During the Purkinje silent period, however, significant differences between the recruitment and non-recruitment cases become apparent. At 17 msec the depression of Purkinje cells neighboring the climbing fiber strip is decidedly greater with recruitment than without. This arises out of "de-recruitment" in the granular layer, causing parallel fiber drive to decrease faster than proportionate mossy excitation decreases. With time the rebounding nuclear cells beneath silenced Purkinje units become surrounded by a plateau of mildly excited nuclear cells mirroring these depressed Purkinje neighbors (25 msec).

Recruitment effects are most manifest during the recovery period. At 40 msec, Purkinje activity is driven to a high peak (cf. figure 15 at 40 msec) as strong "slow" mossy firing recruits much of a local granule population (demonstrating, incidentally, the amplification of spatially restricted mossy inputs for which recruitment was postulated; see section 7.1). Nuclear cells are virtually extinguished by the ensuing inhibition, reducing reticular mossy drive and causing a precipitous collapse of Purkinje activity ("de-recruitment" again) by 50 msec. At 60 msec, the nuclear cells have responded to the inhibitory loss by rebounding a second time. Activity out to 100 msec essentially amounts to such continued, but slowly decaying, nuclear and Purkinje oscillations nearly 180^{0} out of phase with each other. Note also that no spatial pattern is formed. Indeed, activity gradually spreads throughout the module in quasi-epileptiform fashion, driving

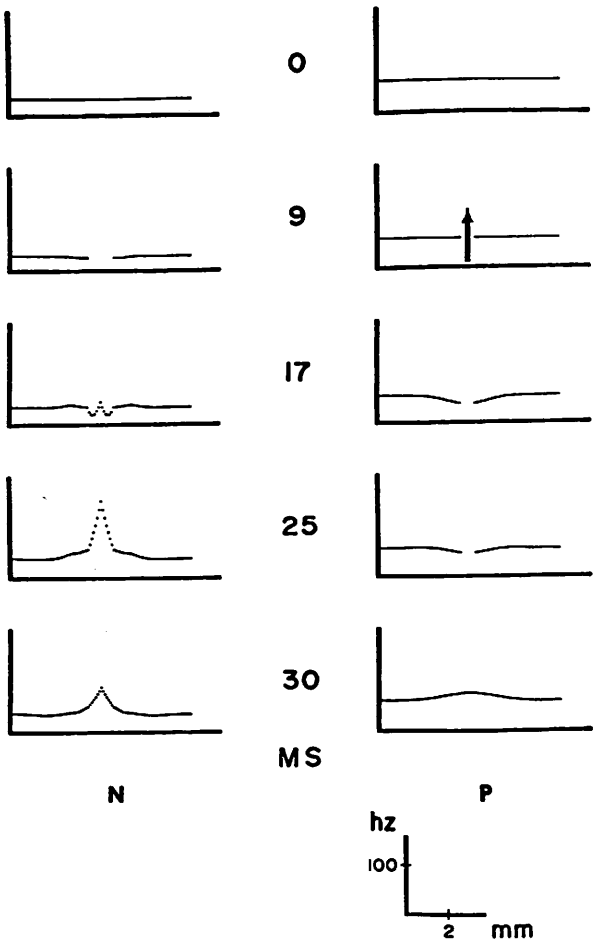

FIGURE 21

Time evolution of spatial distributions of activity in cerebellar nuclear (N) and Purkinje (P) regions following single microstrip cfr volley when granule recruitment is present in the cerebellar module. Format is identical with that of figures 13-16. Present figure shows events through the early recovery period of Purkinje cells.

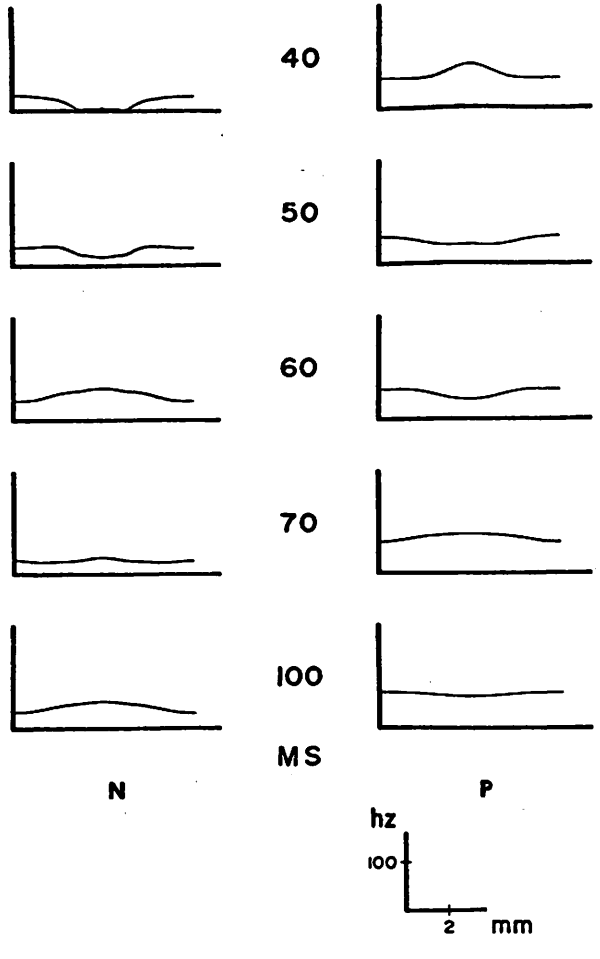

FIGURE 22

Continuation of figure 21 illustrating "seizure" behavior of cerebellar module stemming from granule recruitment (see text).

into synchrony cells within the various layers. The oscillation period, roughly 40 msec (25 hz) is much faster than in typical "seizure" activity, of course.

The rather catastrophic behavior of the cerebellar module with recruitment stems from granule recruitment acting essentially as a time-delay element in the Purkinje negative feedback system that stabilizes the module. Without recruitment, Purkinje silencing after a cfr allows nuclear excitation to lead inhibition momentarily; however, by 40 msec at least, inhibition is sufficiently in phase with excitation (figure 15) to check the latter effectively. This occurs despite the reticular delay interposed between nuclear and Purkinje responses. On the other hand, granule recruitment (figures 21-22) reduces Purkinje inhibition excessively after nuclear excitation has been low (17 msec, 60 msec, 100 msec) and likewise produces excessive inhibition after nuclear activity peaks (40 msec, 70 msec). As a result, inhibition forever chases excitation unstably through the module--thus the comparison of granule recruitment to a time-delay process.

The inexorable spread of synchronous activity over the spatial extent of the module may also be laid to the recruitment-delay of appropriate inhibition. A potential for spatial excitation propagation obviously exists in the diffuse reticulocerebellar nuclear connections. Normally, however, Purkinje inhibition outflanks any such spreading tendency--in the mediolateral plane--mostly because of the extent of the parallel fibers (the mediolateral magnitude of the corticonuclear

projection, is also a factor). This in fact accounts for inhibited side-lobe production in the cerebellar nucleus (figures 15-16). But such outflanking can only occur if inhibition is sufficiently in phase with, or leads, reticulocerebellar recurrent excitation. Inhibition instead lags in the presence of granule recruitment, and figures 21 and 22 show that from 25 msec onward, the spatial extent of nuclear activity always exceeds Purkinje, hence the spreading involvement of the entire module. When one considers the control of excitation spread in the sagittal plane, i.e., where parallel fibers play no role, some intriguing hypotheses arise that are topics for the Discussion (section 9.3.2).

Presuming that recruitment remains an attractive hypothesis for granular layer operation, some method of ridding the cerebellar module of the resulting phase lag in Purkinje inhibition must exist. The most obvious way to compensate for the lag would be to introduce phase lead into the inhibitory pathway, i.e., at essentially any point in the conversion of mossy excitation into Purkinje inhibition. The next section (section 8) considers how the action of Golgi inhibition in the cortex may act to produce this phase lead and what the resulting effects on the cerebellar module might be.

8. Second Revision of the Simulation Model. Introduction of Inhibitory Phase Lead by Golgi Interneurons

8.1 Derivation of the Golgi Influence

Murphy and colleagues[193] have suggested, on the basis of studies in unanesthetized cats, that cortical interneurons are

responsible for the transformation of somewhat "tonic" cortical inputs (produced by muscle stretch) into "phasic" Purkinje outputs; that is, the interneurons introduce phase lead. In response to vestibular inputs in frogs, Llinás and coworkers[168] observed a spectrum of Purkinje reactions, from "tonic" to "phasic," which they attributed to ideosyncrasies of the cells themselves. This interpretation apparently grew from anatomical[133] and physiological[31,161] observations showing a seeming paucity of cortical interneurons and their inhibitory effects. Other findings[230,243], however, indicate a significant presence of inhibitory interneurons in frog cortex. Thus, Murphy's thesis will be accepted here. This section treats the Golgi influence; another (section 9.2.2) considers the role of molecular layer interneurons (basket and stellate neurons).

The cat Golgi neuron is well known[89] to display two dendritic arborizations, one sampling mossy fiber input in the granular layer, the other the parallel fibers. The arborizations are both confined to the radially-symmetric cortical "compartment" in which Golgi inhibition of granule cells is expressed. Whether the compartments of neighboring cells do[111,187,189], or do not[89,211] overlap is not of great concern here. Phylogenetically, it appears that mossy fibers supply the initial inputs to Golgi cells[158]. Neither selachians[93] nor alligators[162] display significant parallel fiber contacts on Golgi dendrites; in frog the molecular layer arborization is only modest[243]. Golgi cells apparently begin their evolutionary careers, in other words, as purely local inhibitory controllers. This local control is amenable to simple analysis:

Figure 23 is a caricature of a cluster of granule cells, X, inhibited by a Golgi cell, Y. X, in turn, may excite Y (i.e., via the parallel fibers). M, a mossy input, excites both X and Y. Synaptic strengths are represented by a and b, with b subject to further special treatment (see below). Then, assuming X and Y are sufficiently depolarized to be firing, a system of differential equations defines their behavior:

$$\tau_1 \dot{X} = -X - aY + M \qquad (29a)$$

$$\tau_2 \dot{Y} = -Y + bX + M \qquad (29b)$$

where $a, b \geq 0$ and $\tau_1, \tau_2 \geq 0$ are the respective membrane time constants.

By differentiating (29a) once again and solving for Y and $\dot{Y}$ in terms of X and its derivatives, a simple equation for X results:

$$\tau_1 \ddot{X} + (1 + \frac{\tau_1}{\tau_2}) \dot{X} + (\frac{1 + ab}{\tau_2}) X = (\frac{1 - a}{\tau_2}) M + \dot{M} \qquad (30)$$

This is in the form of a driven damped harmonic oscillator with terms identified as:

τ_1	"mass"
$\frac{1 + \tau_1}{\tau_2}$	"viscous damping"
$\frac{1 + ab}{\tau_2}$	"spring constant"

$(\frac{1 - a}{\tau_2}) M + \dot{M}$	"forcing function"

If the granule membrane time constant, τ_1, is very small (as is also required for the recruitment analysis in section 7.1), then (30) is approximated by

$$\dot{X} + (\frac{1 + ab}{\tau_2}) X = (\frac{1 - a}{\tau_2}) M + \dot{M} \qquad (31)$$

$$\text{or} \quad (\frac{\tau_2}{1 + ab}) \dot{X} = -X + (\frac{1 - a}{1 + ab}) M + (\frac{\tau_2}{1 + ab}) \dot{M} \qquad (32)$$

This implies, of course, that granule cells will <u>behave</u> as though they have a membrane time constant of $\tau_2/(1+ab)$ and are driven by a linear combination of M and $\dot{M}$; the latter term represents phase lead introduced into the Purkinje input, thereby increasing lead in the cortical output. Judging from the steady-state condition ($\dot{X} = \dot{M} = 0$), it must be that $a \leq 1$, lest the granule output be negative. As a approached 1, the system becomes increasingly "phasic," responding only to changes in mossy input. Note that in the "early phylogenetic" case, in which no parallel fiber Golgi input is present, $b = 0$ and (32) becomes

$$\tau_2 \dot{X} = -X + (1 - a)M + \tau_2 \dot{M} \qquad (33)$$

That is, derivative sensitivity to mossy inputs can still be present; however, the effect of b is to reduce the time constant of the system, thereby speeding up the response to M. This partly could account for the evolution of the Golgi upper dendritic tree (see below). One

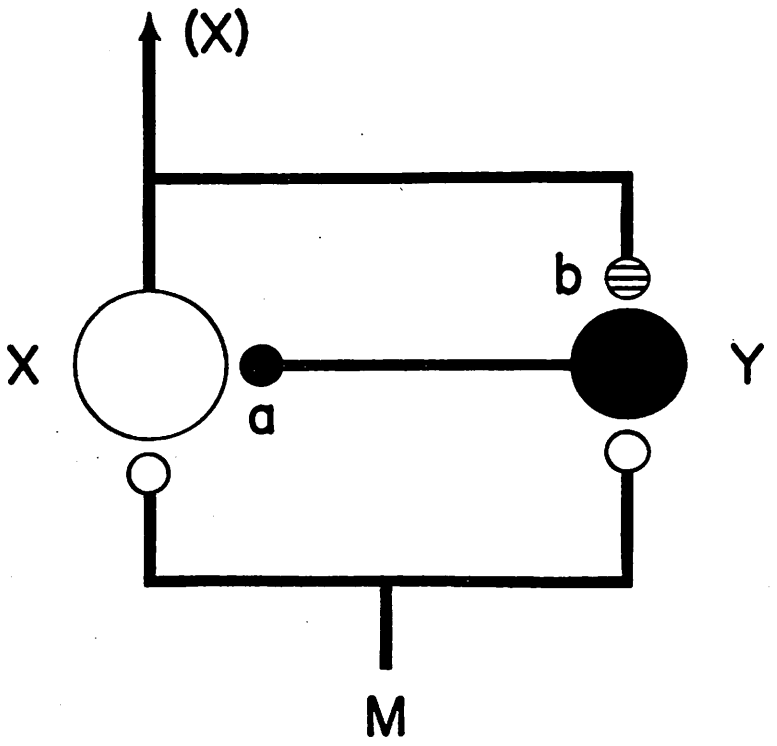

FIGURE 23

Lumped-system circuit diagram of Golgi-granule interaction under the influence of mossy inputs; or the Purkinje cell interaction with molecular layer interneurons (section 9.2.2) under parallel fiber inputs. Text describes significance of the indicated variables.

further point about the general system (30): It is stable for all finite parameter values within the constraints stated, as is evident from the identifications made with the damped harmonic oscillator.

Could molecular layer interneurons also provide phase lead in the Purkinje output? Interactions akin to figure 23 may be envisioned between these interneurons and Purkinje cells, but the effects are not equivalent to the Golgi-granule case, and simple derivative sensitivity may not be their outcome. The Discussion gives details (section 9.2.2).

Beside improving the transient sensititivy of the Golgi-granule system, extension of Golgi dendritic trees into the parallel fibers may also introduce spatial focussing of mossy inputs[89] by recurrent lateral inhibition; such focussing would only appear in the mediolateral plane (for implications, see section 9). So-called "pattern sensitive gating" of mossy signals by Golgi inhibition has been described by Precht and Llinás[223] and supported theoretically by Pellionisz[216] and Mortimer[187]. Recently, Pellionisz has withdrawn his focussing suggestions, claiming instead that the Golgi-granule system may smooth the spatial contour of mossy fiber inputs[217]. No attempt was made to resolve the issue here (in fact, it is easy to show by spatial frequency analysis that either high- or low-pass filtering could obtain depending upon the synaptic efficacies of the Golgi-granule interaction). Instead, to reflect the Golgi influence a transient term was added to the argument of the granular recruitment transfer function, G (section 7.1) as follows

$$G(M(i)) \rightarrow G(M(i) + \dot{R}(i)) \qquad (34)$$

That is, the system was assumed to have a weak ability to "focus" diffuse reticulocerebellar mossy inputs before attending to their rate-of-change. Certain technical limitations vis à vis computer capacity also constrained the form of (34).

8.2 Simulation Effects of Recruitment With Added Golgi Phase Lead in Purkinje Nuclear Inhibition

8.2.1 Spatial Response Patterns to Single Climbing Fiber Microstrip Inputs

The spatial response of the cerebellar module with granule recruitment and Golgi interneuron effects was tested with the microstrip input used in previous sections (6.3, 7.2). The results are presented in figures 24 and 25 (N. Nuclear region; P. Purkinje region) and will be compared with the recruitment-only (figures 21, 22) and non-recruitment (figures 13-16) cases:

Once again, significant differences between this and the earlier simulations are not apparent until the Purkinje silent period (12-25 msec; figure 24). The earlier stages of the silent period are qualitatively similar in both the recruitment-only (figure 21) and Golgi cases, demonstrating "de-recruitment" depression of Purkinje cells neighboring the stimulated strip zone and consequent development of a disinhibited excitation plateau in the cerebellar nucleus surrounding the rebound area. At 17 msec, even greater depression

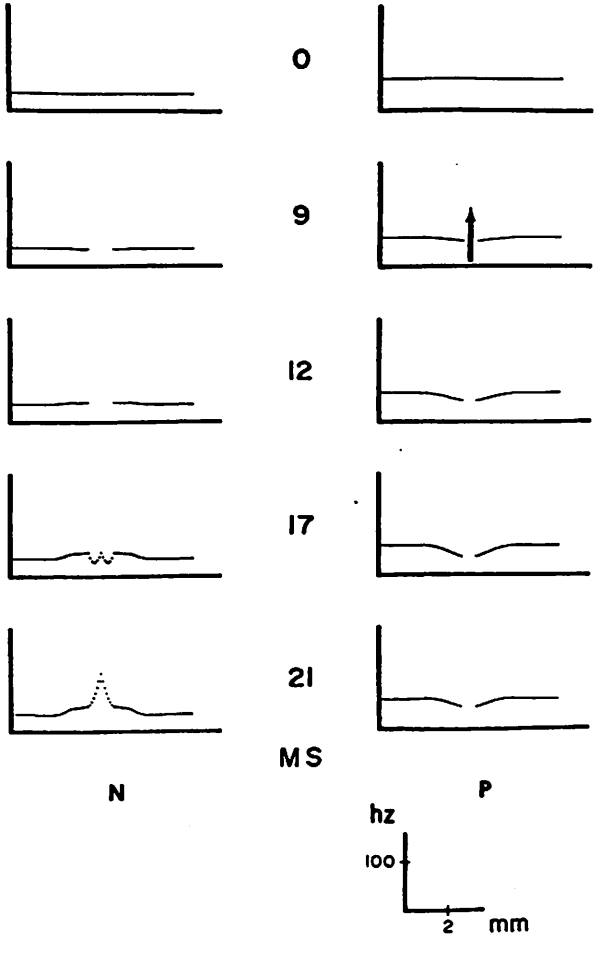

FIGURE 24

Time evolution of spatial activity distributions in cerebellar nuclear (N) and Purkinje (P) regions following a microstrip cfr when both granule recruitment and Golgi inhibition are present. Format is similar to previous figures (13-16 and 21-22).

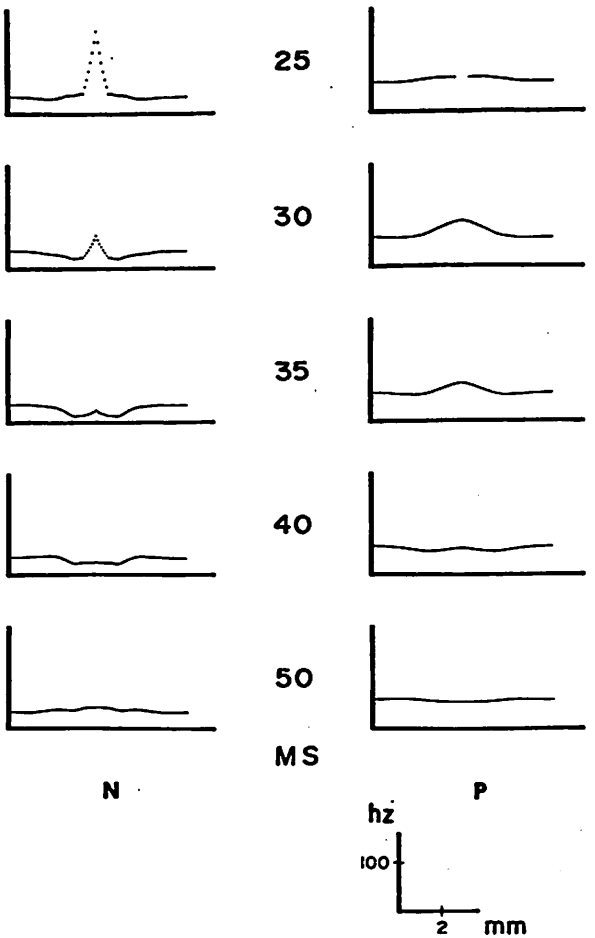

FIGURE 25

Continuation of figure 24, demonstrating how Golgi inhibition stabilizes the time-delay effects of granule recruitment, while retaining the hill-and-valley nuclear patterning characteristic of earlier simulations (figures 13-16).

of Purkinje cells occurs in figure 24 than in figure 21 owing to the added, Golgi-mediated sensitivity of the granular layer to the negative rate-of-change of mossy firing (recall that reticular nuclear activity--hence mossy firing--declines at this time following cfr inhibition of cerebellar nuclear cells). At 25 msec that same transient sensitivity, this time detecting a positive rate-of-change of mossy activity from the rebounding reticulocerebellar loop, has propelled Purkinje inhibition upward, overcoming the usual delay introduced by recruitment (cf. the recruitment-only situation, figure 21, at 25 msec--Purkinje cells are still depressed). The Purkinje activity peaks at 30 msec during recovery (as against 40 msec in figure 22) and the overall response thereafter is highly damped; inhibition now lags excitation by a tolerable amount.

50 msec following the cfr (figure 25) a hill-and-valley spatial pattern of nuclear activity has been created, reminiscent of that left in the non-recruitment simulation at the same moment, under the same conditions (figure 15). In the present instance, however, the pattern is greatly muted for reasons outlined in the following section. The spreading excitation of the recruitment-only simulation does not develop. It will be shown that non-recruitment spatial instability (figure 18) has also been eliminated. Even so, the wave-like flavor of lateral recurrent inhibition still underlies the spatial response of this model, and the module will retain particular sensitivity to strip inputs spaced periodically at the appropriate period mediolaterally (see sections 6.5, 9.3).

8.2.2 Potentiation and Persistence of Activity Patterns Following Repeated Strip Inputs

As in the non-recruitment simulations, three cfr strip activations at 50 msec intervals were given the Golgi simulation to examine potentiation. The resultant pattern was then allowed to develop independently. Figure 26 conveys the outcome of these maneuvers (N. Nuclear region. P. Purkinje region): 0 msec denotes a time 50 msec following the third cfr. Only a very slight potentiation of the nuclear pattern has taken place. The reason for so minute an effect is obvious from the snapshot 50 msec later--the pattern has almost completely decayed. Persistence is short (although again "long" relative to cell membrane time constants), allowing but little potentiation. Note, however, that the system "erases" itself, that spatial instability does not arise.

The weakness of nuclear patterns and their lack of persistence in this case can be traced to the very mossy transient sensitivity (via Golgi inhibition) that, paradoxically, was invoked to stabilize the cerebellar module in the presence of granule recruitment (and which it does do). It is evident that nuclear patterning in the Golgi simulation attempts to follow the basic configuration found in the initial non-recruitment case; that is, an excited nuclear region develops beneath the cortical climbing fiber strip, to be flanked by inhibited "valleys." But owing to transient sensitivity, Purkinje inhibition develops too quickly over the excited nuclear zone; it quashes much of the rebound effect (figure 25, 30-40 msec) which otherwise

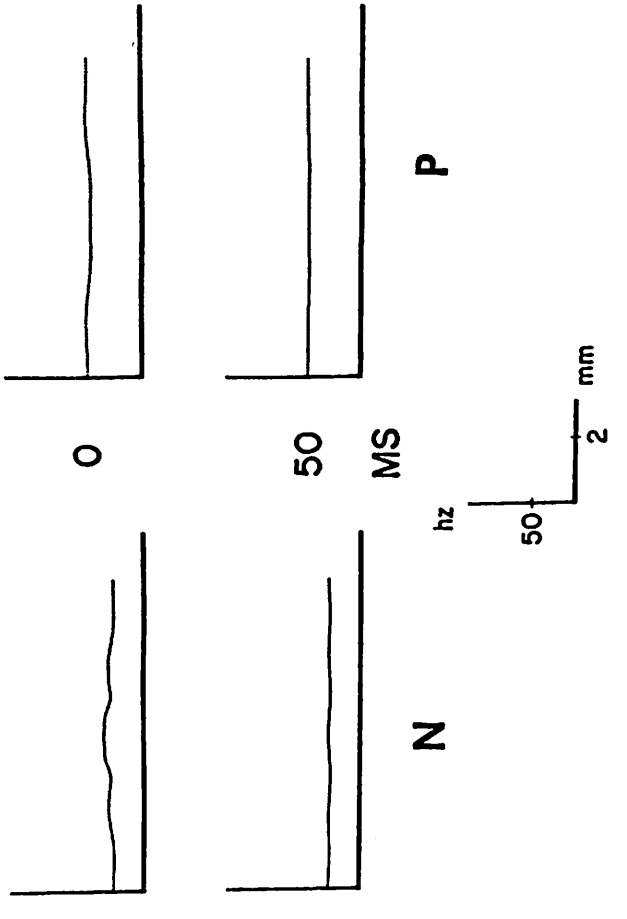

FIGURE 26

Decay of spatially-differentiated nuclear (N) and Purkinje (P) activity patterns created by 3 successive microstrip cfr's at 50 msec when granule recruitment and Golgi inhibition are present. The figure is the counterpart of figure 18. Spatial instability is absent, but both potentiation and persistence are greatly reduced (see text for explanation).

would produce not only the excited "hill," but also (via parallel fibers) the "valleys," according to the earlier findings (figure 15, 35-50 msec).

Computer limitations unfortunately prevented the ready adjustment of the amount of simulated mossy input transient sensitivity mediated by Golgi interneurons (the form of equation (34), which is not entirely satisfactory, was also computer limited). Even so, it seems that the introduction of Golgi effects leads in the right direction so far as correcting recruitment-induced instability is concerned. Had the capacity for titrating transient sensitivity been present in the simulations, it is quite likely that an optimal setting of it could have been achieved which would have left intact the persistence properties of the non-recruitment case while eliminating its spatial instability. It is also quite possible that the sagittally-directed effects of Purkinje axon collaterals and of molecular layer interneurons may also collaborate in adjusting transient sensitivity in Purkinje inhibition so as to promote the persistence of spatial patterning (see section 9.2.2 below). Therefore, it will be assumed in the discussion to follow that the behavior of the initial simulations (section 6) correctly reflects the qualitative behavior of the cerebellar anterior lobe to climbing fiber microstrip inputs even when granular and interneuronal influences are appended.

9. Discussion

9.1 Summary of Results

The commission received in the Introduction (section 1) was

to determine whether or not the spino-olivocerebellar climbing fiber system could play any part in spatially restructuring neuronal activity within the cerebellar anterior lobe, such as almost surely must occur when different locomotor gaits are adopted by cats. The results indicate that this indeed is possible, at least in theory. Those cerebellar nuclear areas affected by an isolated microstrip volley were found to be left in an excited state, while areas receiving from cortical zones mediolaterally adjacent to an active microstrip became depressed. The process creating that type of hill-and-valley spatial pattern was as anticipated in section 2.5: The brief silencing of Purkinje cells following a microstrip cfr momentarily releases the nuclear targets of the microstrip from inhibition. The disinhibited nuclear cells quickly rebound, assisted by recurrent excitation mediated through loops between the cerebellum and the pre-cerebellar reticular nuclei. This rebound excitation is also returned to the cerebellar cortex via slow mossy fibers where, after passing through the granular layer, it is spread mediolaterally away from the active microstrip on the parallel fibers. Consequently, Purkinje inhibition comes to outflank reticulocerebellar excitation (in the mediolateral plane), leading to the formation of laterally-disposed "valley" areas flanking the nuclear region initially disinhibited by the microstrip cfr.

The cerebellar cortex has been described as having a "dead-beat" character[88,89], in that all activity set up within it by some momentary input will decay within, at most, 100 msec (there being no recurrent excitation in the cortex to perpetuate activity). The dead-beat notion has been extrapolated to cerebellar operation as a whole.

The organ is thought to be some sort of on-line computer for the rapid correction of "erroneous movements," necessitating that it clears itself quickly of the residue to previous computations[84,85 88,100]. However, one somewhat unexpected result of the present work is that neuronal activity patterns created in the cerebellum by climbing fiber action do not decay rapidly by any means, which also allows the potentiation of activity patterns by repeated climbing fiber inputs. Reticulocerebellar interactions are responsible for the persistence of cerebellar activity, of course; but, this source of recurrent excitation, lying just outside the cerebellar cortex, is overlooked in the dead-beat hypothesis. If the simulation results are correct and the cerebellum does indeed have a dynamic, short-term memory capacity, can that be reconciled with the idea of the cerebellum as a high-speed, on-line controller of movement? An answer to this question begins to take form in sections 9.2, 9.3, and 9.4 below and is carried much further when the present findings are applied in detail to locomotion[36].

The recruitment of granule cells, introduced as an hypothesis to explain their enormous numbers, small size, high density, fixed number of synapses, etc., was found in itself to have disastrous consequences for the operation of the cerebellar module: Climbing fiber microstrip inputs produced seizure-like spatial propagation of synchronous, oscillatory activity away from the site of the input until the entire module was involved. This reaction proved to be caused by the recruitment-delay of change in Purkinje inhibition relative to like change in nuclear excitation. However, the introduction of Golgi

interneuron influence, which was shown to introduce phase lead (transient sensitivity) into the mossy-Purkinje pathway, readily abolished seizure behavior, restored the spatial patterning set up by climbing fiber volleys, and corrected the earlier spatial instability of the cerebellar module. The qualitative response of the cerebellar module to microstrip inputs, however, appeared to be little affected by the presence or absence of recruitment plus Golgi influences.

Detailed discussion of the simulation results will be divided below into the temporal, and then the spatial, properties of possible climbing fiber effects upon the cerebellar anterior lobe. This will be followed by deductions on the nature of information transmitted through spino-olivocerebellar pathways, and lastly, proposals for experimental tests.

9.2 Temporal Phenomena Attending Activation of Anterior Lobe Climbing Fibers

Mutually offsetting excitatory and inhibitory forces underlie the behavior of the cerebellar module to climbing fiber stimuli. In the quiescent state the recurrent excitation of reticulocerebellar loops is led via the slow mossy fibers to Purkinje cells which then check, by inhibition, this excitation. A climbing fiber strip input in substance acts to arrest for a short time that inhibitory feedback within the strip region by means of Purkinje silencing. The resulting rebound of the recurrent excitation system is then directly responsible both for the "hill" of nuclear activity that develops beneath the strip and (through the lateral inhibition of the parallel fiber-Purkinje cell network) for the abutting mediolateral "valleys" (figures 15, 25).

Three topics related to temporal aspects of this behavior deserve further treatment:

9.2.1 Properties stemming From Reticulocerebellar Recurrent Excitation

a. Stability considerations. In isolation, reticulocerebellar recurrent excitation may be inherently unstable, as in these simulations (figure 10) and actual experiment[259,261] (figure 11 A). Under Purkinje inhibitory control, however, the cerebellar module as a whole can be rendered stable over a goodly range of synaptic efficacies for reasonable choices of cellular membrane time constants (figure 8)--if the effects of granule recruitment are ignored. But in the presence of recruitment, which introduces a destabilizing phase lag in Purkinje inhibition (figures 21, 22) other mechanisms must emerge to secure sufficient coincidence of excitation and stabilizing inhibition in the cerebellar nuclei (e.g., the Golgi inhibition of figures 24, 25). Despite their derivation in the recruitment-free case, the "useful variations" in certain membrane time constants (section 4.6; Tables VI, VII) are now seen simply to reflect this coincidence demand. Increases in τ_r and the already-large magnitude of τ_x (section 4.2; Table III) stall the development of excitation as decreases in τ_y and τ_z speed the impressment of inhibition. Various anatomical features of the cerebellar module may have evolved in accord with these variations. For example, the excitatory recurrent axon collaterals of cerebellar nuclear cells[58,60,138,181] and the axodendritic connections of mossy fiber collaterals[60,138] may both be mechanisms serving

to increase τ_x; an equivalent reticular system (recurrent collaterals[73] and axodendritic synapses[48,185]) could boost τ_r. The reason recurrent collaterals promote time constant increases is the following: Let the membrane time constant of either cell type be τ, membrane potential be m, input firing frequency be I, and aggregate strength of recurrent collateral connections (excitatory) be b (≥ 0). Then the behavior of each such cell is governed by (cf. equation (1), section 3.1).

$$\tau \dot{m} = -m + bm + I \tag{35}$$

Rewritten this is

$$\frac{\tau}{1-b}\dot{m} = -m + \frac{I}{1-b} \tag{36}$$

implying that the cell now responds with an effective time constant of $\tau/1-b$. If $b<1$, the cell remains "stable," but with an increased effective time constant. A further consequence of such recurrent collaterals, however, is that the input synaptic efficacy is also increased by $1/1-b$ (equation (36)). Within the reticulocerebellar loops, that would amount to an increase in w (section 3.3; Table I). Hence, as recurrent collaterals proliferate, the constraints between module synaptic efficacies (figure 8) dictate that parallel fiber-Purkinje synapses (q) must be weakened and Purkinje inhibition (p) strengthened to compensate for the increased w. Very surprisingly, those demands appear also to have been evolutionally met in tandem with anatomically

implementing the remaining "useful" time constant variations as follows:

The axosomatic and proximal dendritic synapses of Purkinje axons upon nuclear cells[59,60,138] should reduce τ_y (a "useful variation"); simultaneously, a desired increase in p is obtained (relative to an axodendritic location for these synapses). Along with w, p is also multiplied by nuclear cell axon collaterals since it governs a cellular input (see above). Such mechanisms as Golgi inhibition (enhancing the dynamic sensitivity of granule cells to mossy inputs) and possible Purkinje dendritic spikes[59,158,167] act to diminish τ_z (useful variation). Additionally, so will any Purkinje-Purkinje mutual interactions via their axon collateral plexuses[89,154,189,209]. The last assertion again follows from equations (34, 35) if such interacting Purkinje cells are treated as a single "average" cell with an inhibitory axon collateral (i.e., $b<0$). It is seen that the effective time constant is now reduced to $\tau/1+|b|$; moreover, the aggregate Purkinje input (parallel fibers) is also scaled by $1/1+|b|$, i.e., there is an effective weakening of q (as desired--see above).

The original proposition that stability requires timing constraints on Purkinje inhibition relative to reticulocerebellar excitation in the cerebellar nuclei superficially resembles comments of Eccles[87,88,90,92] regarding the excitatory-inhibitory clash triggered by exogenous mossy fiber inputs, with the rationale for such timing left to the "computer-like" operation of the cerebellar complex. The present account has gone further, albeit with very crude approximations

meriting verification by simulation, to demonstrate how the timing phenomenon--or precisely, the entire substance of module stability--may emerge from structures and processes seeming isolated, yet actually inextricably intertwined, often mutually dependent, and, perhaps, necessarily co-evolved.

b. Long time-course phenomena. As mentioned in section 9.1, neural activity restricted to the cerebellar cortex may well be rapidly extinguished thanks to the absence of an recurrent excitation[89], yet reticulocerebellar positive feedback greatly extends the global response of the cerebellar module to climbing fiber inputs. The longest membrane time constant employed in the simulations is 15 msec; however, even the highly damped response present with Golgi inhibition persists, very conservatively, for 50 msec (figure 26) following a microstrip input.

Persistence duration is set essentially by the gain of reticulocerebellar feedback (especially when the regeneration attaching to lateral recurrent inhibition is eliminated, as in the presence of Golgi inhibition). The relatively low gain used in these simulations (section 4.5; Table V) produced persistence on the order of hundreds of milliseconds (see figures 16, 18); however, somewhat higher gains could probably extend this to seconds or longer. Recent anatomical studies have also demonstrated the existence of direct connections of the cerebellar nuclei with the inferior olive[80]. Such pathways, along with cerebello-olivary projections via the brainstem output nuclei (e.g., the parvocellular red nucleus[265]), could represent

additional routes allowing recurrent excitation to maintain existing cerebellar activation patterns.

The association of the cerebellum with long time-course events (not involving plasticity) has some experimental support. Clark [62] observed protracted after-effects (a succession of peculiar postures lasting several minutes) following cerebellar cortical surface stimulation in intact cats. In a later repetition of the work, he precociously associated the prolonged phenomena with hypothetical "reverberatory loops," wondering whether the effects were not in fact part of the "normal cerebellar control of muscle synergy[63]." Cerebellar lesions abolished the after-effects. Passouant, et al.[214] have more recently made similar findings, adding the incidental observation that prior olivary stimulation lowers the threshold for producing after-effects following a cortical shock. Nashner (in preparation) found that human subjects with cerebellar disease were unable to maintain the habituation of a long-latency, "functional stretch reflex" in the gastrocnemius, while normal subjects retain the habituation for many seconds. Although hardly conclusive, these observations do appear to implicate the cerebellum in long time-course processes of some sort. Moreover, the simulation studies indicate that an existing correlation between climbing fiber activity and such phenomena may be difficult to observe at the single cell level (section 6.6; figure 19) unless one is more experimentally circumspect (see section 9.5 below).

An appreciation of the advantages of recurrent excitation in neural systems has been slowly evolving from classic theories of

short-term memory (briefly reviewed in ref. 55) to recent studies of motor cortical[23] and spinal[136] reflex mechanisms. Lundberg's hypothesis that positive feedback in spinal FRA pathways may reinforce and prolong central activation effects[171] is cousin to the present conclusions: Reticulocerebellar feedback reinforces and prolongs the consequences of climbing fiber activity. In another report (Boylls, in preparation) such feedback is also implicated in the time integration of certain types of exogenous mossy input.

9.2.2 Temporal Effects of Granule Recruitment and Their Compensation

Several recent theories of neural population dynamics[7,269,270] have exploited the threshold recruitment of large neuron groups in fashioning nonlinear transfer functions. The granule population is implicated in the present work in nonlinearly amplifying punctate mossy fiber inputs, amplification that is elsewhere shown necessary (Boylls, in preparation). Reliable recruitment nonlinearities ensue from exceedingly weak prerequisites--the existence of thresholds and a stationary distribution thereof, a means of summing outputs of recruited cells, and a large number of cells, all of which seem eminently available in the cerebellar cortex and, for that matter, in many other nervous system locales (cf. ref. 270). Recruitment, because it embraces the "unreliability" of granule cells (in threshold) to synthesize interesting functions, is somewhat the antithesis of theories stressing the need to overcome such neural noise[88,231]. To some extent the recruitment hypothesis grows from work of Marr[176], Albus[1,2],

and Pellionisz[217] who have dealt with populations of variable threshold granule cells having outputs summed by Purkinje dendritic trees. Commonality ends beyond this point, however.

Granule recruitment, uncompensated, delays Purkinje inhibition, resulting in "epileptic" module responses to climbing fiber strip inputs; that is, the responses involve spreading, synchronous activity of neuron populations (section 7; figure 21, 22). Added Golgi inhibition alleviates the delays, returning the response to the recruitment-free template (section 6), but with the spatial instability of the latter (figure 18) eliminated. Unfortunately, however, patterning and persistence are attenuated since Golgi-mediated Purkinje sensitivity to mossy fiber transients causes inhibition to develop too quickly in rebounding nuclear regions following Purkinje silencing. The technical limits imposed upon the simulation (section 8.2.2) no doubt played some role in producing this result. However, it is also possible that nuclear spatial patterning and persistence both could be restored if there were a way to remove mossy transient sensitivity, and to reduce the magnitude of recruitment-amplified Purkinje activity, only in an excited strip region. Specifically, the rebound "hill" of nuclear excitation that powers all other spatial activity effects would then develop as in figures 13-15. The inhibited valleys to either side of the hill would form, but would be located in the Golgi-influenced region outside the strip. Consequently, spatial stability would be ensured. And by virtue of the hill's demonstrated persistence in the non-Golgi situation, so might the entire pattern retain both the

persistence and potentiation features of earlier simulations (section 6).

Certain "natural" cortical mechanisms may be evolved, in part, precisely to achieve such strip-limited reduction of transient sensitivity. Those mechanisms are as follows:

a. Purkinje infraganglionic plexus and Golgi cells. The infraganglionic plexus of Purkinje cell collaterals appears to be sagittally oriented in mammals[89,209]; collaterals arising at a given cortical location may course sagittally over several folia[89]. The plexus is positioned to contact the ascending dendrites of Golgi cells (among other elements), and collateral-Golgi synapses at that site[189,209], and closer to the cell body[111,209] are common. Thus, sagittal groups of covarying Purkinje cells, typified by the "hills" and "valleys" created by strip activity, should exert potent inhibitory control over Golgi cells beneath them by means of the infraganglionic plexus. In particular, Golgi inhibition--and consequently, mossy transient sensitivity--will be reduced within the hill region that coincides with an active strip, relative to the surrounding valleys (which will have augmented inhibition and sensitivity). This seems precisely the strip-localized modification demanded above, although simulation tests are required. Also, one wonders about the role of the mysterious Lugaro cells[111] which receive heavy Purkinje axon collateral contacts[209].

b. Purkinje supraganglionic plexus and molecular layer interneurons. Basket and stellate inhibition of Purkinje neurons obeys a well-known sagittal restriction[89,212]. The supraganglionic Purkinje

axon collateral plexus, synapsing on these interneurons[153,154,155,189,209], is often said to have a mediolateral course[89,111,154]; recent work suggests that the plexus may instead distribute sagittally[209] (confusion with myelinated parallel fibers might have occurred in the past[189]). Long-distance excursions of the collaterals (sagittally) have been noted[82,89]. Therefore, the Purkinje-interneuron interaction apparently represents another process distributed along the climbing fiber dimension. By its diffuseness, the reticular, slow mossy input to the cortex should vary quite slowly as a function of the sagittal coordinate along a strip (a condition of the one-dimensional approximation used in simulation); more punctate, "fast" mossy inputs will be ignored. The parallel fiber inflow to a strip-distributed system of Purkinje cells and interneurons may thus be approximated as independent of location, in which case the system reduces to the lumped system of section 8.1, figure 23, and equation (30), with these identifications

X	Purkinje membrane potential
Y	Interneuron membrane potential
M	Aggregate parallel fiber input
τ_1	(Effective) Purkinje membrane time constant
τ_2	Interneuron time constant
a, b	Synaptic efficacies (figure 23; b inhibitory)

The effective Purkinje time constant may be taken as small (thanks to

dendritic spikes, Purkinje-Purkinje interactions, etc.; see section 9.2.1), allowing the approximation that led to equation (32). Rewriting this for b ≥0 (but inhibitory)

$$\left(\frac{\tau_2}{1 - ab}\right) \dot{X} = -X + \left(\frac{1 - a}{1 - ab}\right) M + \left(\frac{\tau_2}{1 - ab}\right) \dot{M} \qquad (37)$$

When the supraganglionic plexus is sparse (as in mice[154,209] and rabbits[154]), b approaches 0 and (37) reduces to the form of equation (33). In other words, the Purkinje-molecular layer interneuron system becomes merely an elaboration of the Golgi-granule interaction. Infraganglionic plexus inhibition of Golgi cells thus is the sole means of achieving strip-reduction of mossy transient sensitivity. But note that when b becomes a factor, as in cats (where Purkinje collateral inhibition of basket cells can be demonstrated[33,163]), the Purkinje cell behaves as though it possessed a time constant of $\tau_2/1-ab$; the response to parallel fiber inputs becomes increasingly sluggish as the product ab increases. This, then, also has the effect of canceling Golgi transient sensitivity. The question is, how is such cancellation to be restricted to active climbing fiber strip regions? One possible answer follows:

Bloedel and Roberts[32] discovered that Purkinje neurons, presumably via their axon collaterals, "dominated" molecular layer interneurons in unanesthetized (decerebrate) cats, but that nembutal overturned the hierarchy (i.e., interneuron inhibition became prominent); this is supported in monkeys[34]. The nembutal effect is partly attributable to either a blocking of conduction, or threshold elevation,

in granule cells[117,118]. Such findings indicate that "dominance switching" is a function of the strength of parallel fiber input. If so, then Purkinje activity must be relatively more dominant over interneuron effects in the "hills" created in active climbing fiber strips than in the "valleys." But this implies an effective increase in b (Purkinje cell collateral impact) in hills, i.e., cancellation of Golgi-mediated mossy transient sensitivity therein, as is desired. Meanwhile, molecular layer interneurons dominance in the valleys augments transient sensitivity. The etiology of such dominance switching as it is known to exist is uncertain; however, bistability follows from equation (37) when $ab \geq 1$: The resultant instability will force one or the other neuron population into dominance.

Cortical interneurons, at least of the molecular layer, are thought to arise phylogenetically in concert with Purkinje axon collaterals[162,163]. The above piecemeal arguments speak more precisely for the co-evolution of granule recruitment, Golgi inhibition, and the infraganglionic collateral plexus. The molecular layer interneurons and supraganglionic plexus seem not so closely tied to these other elements, though their influences can be complementary. It is likely the molecular layer system will be better understood with respect to the modulation of climbing fiber patterns by focussed, "fast" mossy inputs along the strips[67,103] (Boylls, in preparation).

In summary, the cerebellar complex may have a short-term memory capacity, in that spatial activity patterns created by climbing fiber strip volleys persist for significant lengths of time. Some

experimental evidence exists for this. The memory process is dynamic, stemming from reticulocerebellar recurrent excitation and, possibly, from cerebello-olivary connections. However, a potential for instability arises from recurrent excitation and also from recruitment of granule cells. Among the anatomical features of the cerebellar complex which may have evolved to combat such instability are the following:

1. Recurrent axon collaterals in the cerebellar, and precerebellar reticular nuclei.
2. Axodendritic excitatory synapses in these nuclei; axosomatic Purkinje inhibitory synapses in the cerebellar nuclei.
3. Purkinje-Purkinje mutual interactions (inhibition).
4. Golgi interneurons.
5. Purkinje dendritic spikes.
6. Inhibition of Golgi interneurons by the infraganglionic plexus of Purkinje axon collaterals.
7. Molecular layer neurons, insofar as they interact with the Purkinje supraganglionic collateral plexus.

9.3 Spatial Phenomena Attending Activation of Anterior Lobe Climbing Fibers

In the mediolateral plane the cerebellar module reduces to a classical lateral recurrent inhibition network, albeit elaborate. Recent theoretical work on lateral inhibition systems having significant recurrent excitation[186,270] already has shown that the wavelike, persisting activation patterns seen here are one possible trait of

such configurations. Hence, the present results hold no abstract novelty, but nonetheless may be significant in understanding "real" cerebellar operation.

Along the sagittal dimension, cerebellar architecture may also support a less obvious lateral recurrent inhibition scheme with its attendant behaviors. Processing in each of the two planes is considered separately below.

9.3.1 Lateral Recurrent Inhibition in the Mediolateral Plane

Activity patterns deposited in the cerebellar nuclei by climbing fiber strip activation qualitatively resemble the "spatially inhomogeneous steady states" discovered by Wilson and Cowan[270] (see also ref. 186) in their analysis of cerebral cortical and thalamic tissue. The patterns partition nuclear space into regions of differing activity which, following their creation, change but slowly with time--they are in temporal equilibrium, to first approximation. Thus, a spatial Fourier analysis of linearized, recruitment-free governing equations (5) (section 3.3) at temporal equilibrium may serve to connect spatial patterning succinctly with anatomical features giving rise to it. Calvert and Meno[54], in investigating only the cerebellar cortex, also employed Fourier analysis (see, too, the more general work of Marko[175]), but worked without prior knowledge of any de facto time-independent state that might have allowed the direct utilization of the spatial frequency response as a predictor of activity patterns. Use of a Fourier description also led Calvert and Meno to think of the cerebellum as an elaborate filter of its inputs (for the similar

ideas of physiologists, see refs. 113, 190). Yet, with reference to climbing fiber contributions, this metaphor may be highly misleading. The cerebellar complex does not, according to the present findings, "shape" or "modify" climbing fiber signals in the traditional filtering sense for subsequent retransmission. Instead, climbing fiber inputs jar the organ into generating particular activity states that represent de novo information not extractable from the original messages. It would appear, therefore, that the proper application of Fourier analysis to the cerebellar module lies in obtaining its spatial "impulse response" spectrum; the spectrum will reveal the existence of any normal modes of spatial "oscillation" within which the system equilibrates following climbing fiber perturbations.

To begin this analysis, equations (5) are rewritten in continuous, linearized, recruitment-free form at temporal equilibrium (deleting the climbing fiber collateral term):

$$X(k) = \int_{-F}^{F} wR(k + Y)dY \tag{38a}$$

$$Y(k) = \int_{-E}^{E} pZ(k + Y)dY \tag{38b}$$

$$R(k) = \int_{-G}^{G} w(X(k + Y) - Y(k + Y))dY + B \tag{38c}$$

$$Z(k) = \int_{-D}^{D} q \int_{-F}^{F} R(k + \beta + Y)d\beta dY \tag{38d}$$

In the spatial frequency domain, these equations become:

$$X(j\omega) = -2wR(j\omega)\frac{\sin\omega F}{\omega} \tag{39a}$$

$$Y(j\omega) = -2pZ(j\omega)\frac{\sin\omega E}{\omega} \tag{39b}$$

$$R(j\omega) = -2w(X(j\omega) - Y(j\omega))\frac{\sin\omega G}{\omega} + B\,\delta(j\omega) \tag{39c}$$

$$Z(j\omega) = 4qR(j\omega)\frac{\sin\omega F \sin\omega D}{\omega^2} \tag{39d}$$

Defining $S(j\omega) = X(j\omega) - Y(j\omega)$ to be the output of the cerebellar module, equations (39) may be made to yield the spatial impulse response:

$$\frac{S(j\omega)}{\delta(j\omega)} = \frac{2B}{\dfrac{1}{\dfrac{\sin\omega F}{\omega}\left[\dfrac{\sin\omega D \sin\omega E}{\omega^2} - \dfrac{w}{4pq}\right]} + 4w\dfrac{\sin\omega G}{\omega}} \tag{40}$$

For use in (40) synaptic efficacies p, q, w and fan-out constants D, E, F, and G were rescaled in terms of millimeters (rather than millimeter equivalents) according to the values used in the simulations (section 4.3; Table IV). $\mathrm{Log}_e|S(j\omega)/\delta(j\omega)|$ as a function of spatial frequency (c/mm) is plotted in figure 27.

The figure demonstrates that the module impulse response has two prominent resonance points, one at .125 c/mm (8 mm/c period) and a stronger at .445 c/mm (2.25 mm/c period). Though not shown here, the response beyond 0.5 c/mm is greatly attenuated. Now from the behavior of the non-recruitment simulations in section 6 (figures 16 and 18), it appears that the simulated module "rings" quasi-periodically at a spatial period of 2.4-2.6 mm/c (.385-.417 c/mm frequency)

to a climbing fiber microstrip input. Comparison with figure 27 strongly suggests, then, that strip inputs excite the module at its higher frequency (.445 c/mm) resonant mode. Indeed, when equation (40) was re-evaluated using the "millimeter equivalent" parameters of the discrete simulations (which, of course, only approximate the continuity underlying (40)), the behavior of figure 27 was replicated, but with the higher resonance shifted to .41 c/mm (2.44 mm/c period), in good accord with the simulations.

The lower frequency resonance (.125 c/-m) was never observed during simulations, likely because inputs of breadth comparable to its period (8 mm/c) were never applied. Because this resonance involves activation patterns of "locomotor" anterior lobe extent (section 2.5; figure 6), it is tempting to speculate that it may relate to the totality of excitation in this cerebellar subdivision.

In view of the controversy over certain cerebellar anatomical features (e.g., extent of the parallel fiber and of the corticonuclear projection), the impact of these parameters upon nuclear activation patterns, as governed by equation (40), is worth ascertaining. Several approximations, based upon features of the parameterizations used in this work, simplify the task.

1. The spatial extent of the reticulocerebellar projection approximates the length of a parallel fiber. Thus D = F.

2. The corticonuclear and cerebelloreticular projections are sufficiently restricted so that the terms ωE and ωG are small over the interval in ω of interest.

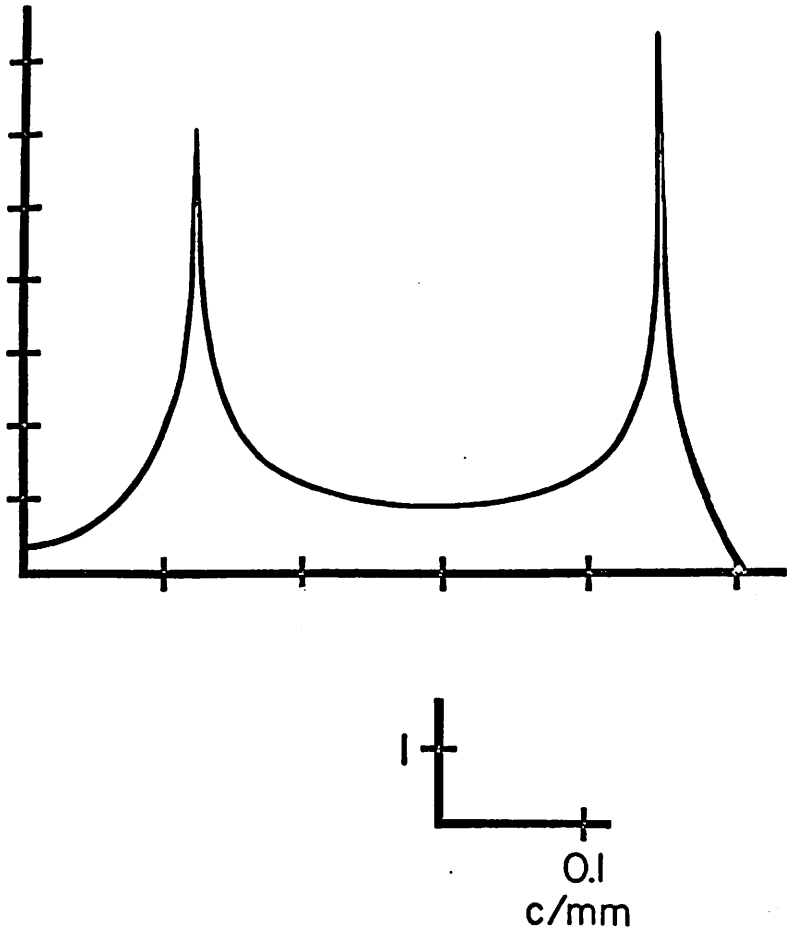

FIGURE 27

Logarithm of equation (40) as a function of spatial frequency (c/mm), illustrating resonance at .445 c/mm, near the frequency of nuclear hill-and-valley patterns triggered by climbing fiber microstrip inputs.

With these approximations, equation (40) becomes

$$\frac{S(j\omega)}{\delta(j\omega)} \approx \frac{2B}{\frac{1}{4pqE\left(\frac{\sin\omega D}{\omega}\right)^2 - w\frac{\sin\omega D}{\omega}} + 4wG} \tag{41}$$

Spatial resonances of (41) will occur at $\hat{\omega}$ whenever

$$4pqE\left(\frac{\sin\hat{\omega}D}{\hat{\omega}}\right)^2 - w\frac{\sin\hat{\omega}D}{\hat{\omega}} = -\frac{1}{4wG} \tag{42}$$

implying a resonance condition

$$\frac{\sin\hat{\omega}D}{\hat{\omega}} = \frac{w}{8pqE} \pm \frac{1}{2}\sqrt{\frac{w}{4pqE}\left(\frac{w}{4pqE} - \frac{1}{w^2\,G}\right)} \tag{43}$$

In gross approximation (w G "large"), this is written

$$\frac{\sin\hat{\omega}D}{\hat{\omega}D} \approx 0^+,\ \frac{w}{4pqDE}\ ;\ \frac{w}{4pqDE} \leq 1\ . \tag{44}$$

Thus, discounting their higher-frequency harmonics, two fundamental resonance points exist, as illustrated in figure 27. One occurs at spatial frequency $f_1 = 1/2D$; since D = 1 mm for a 2 mm parallel fiber length, f_1 = 0.5 c/mm. Another resonance at a lower frequency, f_2, is a function of the value of w/4pqDE, with f_2 varying directly as p,q,D, and E, and inversely as w. From the calculated value of f_1 and the relation $f_2 \leq f_1$, it is evident that f_1 represents the higher-frequency resonance of figure 27, and f_2 the lower. f_1, therefore, presumably rules climbing fiber-induced patterns. Since f_1 is primarily an inverse function of D alone (keeping in mind the strictures

on other parameters which led to this point), it follows that patterning seems to be determined essentially by the inverse of parallel fiber length. Consequently, to sharpen patterning of nuclear activation--that is, to elevate f_1--parallel fiber length should be reduced. Also, the mediolateral extent of the reticulocerebellar projection (F) would require diminution to accord with earlier constraints. The reduction of parallel fiber length was also a recommendation of the earlier parameter optimization (section 4.6; Tables VI, VII) for pattern enhancement. It must be emphasized that "reduction" refers to a small change; too much reduction, aside from violating the premises used in the approximations above, would also result in a breakdown of recurrent inhibition (and thus spatial patterning) in the cerebellar module. Pellionisz, et al.[219], have reported that immobilizing the legs of kittens from birth eventually results in the development of "short" parallel fibers and concomitant cerebellar ataxia. Perhaps the proposed breakdown of recurrent inhibition is responsible for that ataxia.

Is there in fact "shortening" of parallel fibers over phylogeny, possibly indicating an evolutional selection for finer nuclear activation patterns? There may well be, provided that "shortening," along with alterations in any other geometric parameters, is interpreted within the spatial scale upon which a given cerebellum is constructed. Thus, in frog some parallel fibers reportedly traverse the entire cortical extent[167], while in mammals this is not found--implying that, to cortical scale, mammalian fibers truly are "shorter" than frog's (regardless of the absolute length of either). Within

mammals, although there may be a continuous reduction in absolute parallel fiber length from man down through macaque, cat, rat, and mouse[242], a progressive reduction in cerebellar size also obtains through this series; perhaps then, the mouse parallel fiber actually is "longer" than the human relative to cerebellar dimensions.

Conceivably, f_2 above may be adjusted by changes in p, q, w, d, and E so as to coincide with f_1, thereby achieving heightened module response to climbing fiber inputs. The implied alterations would involve:

i. Increasing the mediolateral extent of the cerebellar corticonuclear projection (E).

ii. Lengthening the parallel fiber.

iii. Increasing the strength of parallel fiber synapses (q) and/or Purkinje inhibition.

iv. Weakening existing reverberatory effects (w) (or increasing B, by implication).

The effects of these maneuvers were not tested in simulations. However, invoking (i) would have deleterious influences on temporal stability of the module (section 4.2; Table VI), (ii) would reduce f_1 (the prime patterning determinant), and (iv) dampens pattern persistence. Only (iii) seems constant with earlier derived constraints, provided the demanded change was confined to the Purkinje-nuclear connection (increases of the parallel-Purkinje synaptic strength are to be avoided--see section 9.2.1).

Because the anterior lobe cerebellar module resonates at a spatial period of 2.2-2.6 mm/c to simulated climbing fiber microstrips only 0.6 mm wide (section 4.4), it follows that such stimuli are not the most effective in evoking spatial patterning. Instead, a climbing fiber strip should be on the order of 1.1-1.3 mm wide so as to fit better the "hill" portions of spatial activity patterns having the above period. Curiously enough, the broader Oscarsson climbing fiber strips of the locomotor anterior lobe have approximately this width (section 2.5; figure 6). That correlation, and the fact that Oscarsson strips probably consist of microstrips, may be of exceeding importance in understanding anterior lobe climbing fiber function; much of the entire section below will discuss this (section 9.4). First, however, goings-on in the sagittal plane will be briefly examined.

9.3.2 Sagittal Plane Behavior

The use of a mediolateral, one-dimensional approximation in simulating the cerebellar module requires an assumption of parametric and input homogeneity in the sagittal plane, the evidence for which was discussed in section 3.2. Existence of such homogeneity implies that sagittal module activity patterns emerge simply by replicating the mediolateral results at each sagittal coordinate. When this is done for the pattern arising from activating a single climbing fiber strip (microstrip or Oscarsson strip), figure 28 results. Here the activity levels of cerebellar nuclear cells at various locations in the two dimensions are plotted as proportional

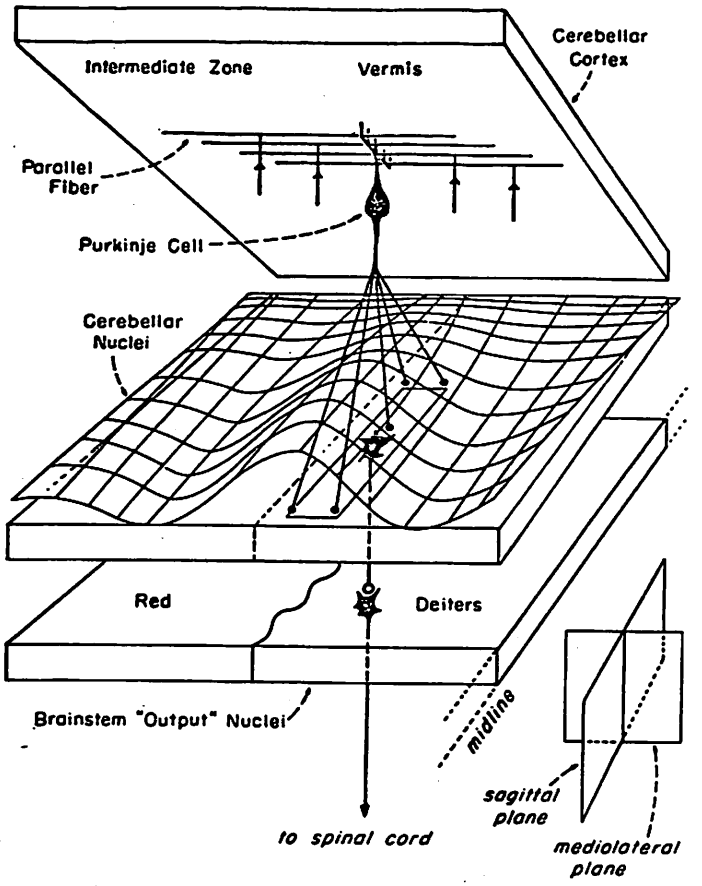

FIGURE 28

Schematic conception (cf. figure 5) of cerebellar nuclear spatial activity patterning following activity of a sagittal Oscarsson climbing fiber strip. Height of the surface indicates relative degree of nuclear excitation. A ridge of activity is left in the nuclear region corresponding to the active Oscarsson strip, while inhibited valleys develop in regions receiving from cortical areas mediolateral to the strip.

to the height of an undulating surface over the cerebellar nuclei; caricatures of the cortex and brainstem "output" nuclei are appended for perspective (cf. section 2.4.4, figure 5). What in mediolateral cross-section was a hill of climbing fiber-induced excitation is now seen to be a sagittally-directed "ridge" flanked by the usual inhibited valleys likewise elongated. The pattern is shown as having a substantial, but limited, sagittal extent; however, this is but a conjecture growing from the following considerations:

a. Facilitation of sagittal excitation spread by reticular feedback. In describing the cerebellar architecture which underlies the cerebellar module, it was briefly noted that reticular mossy fibers distribute indiscriminately in both the sagittal and mediolateral planes (but see ref. 151). The reticulocerebellar system appears designed to flood the module with excitation, as other authors have commented[52,241], and which the simulation results of section 7 affirm: In the absence of appropriately timed lateral inhibition from the cerebellar cortex, wildfire excitation will spread mediolaterally over a cerebellar nucleus following a climbing fiber strip stimulus. The parallel fiber-Purkinje cell network may normally create lateral inhibition which confines reticulocerebellar excitation mediolaterally--but is there an equivalent of that circuitry sagittally? If not, then it would appear that an entire climbing fiber strip region in the cerebellar nuclei would eventually become fused together by the sagittal spread of reticulocerebellar excitation, as is depicted in figure 28. The sagittal branchings of

individual climbing fibers within a strip do fit easily into such a scheme, in that they would simultaneously ignite excitation at numerous points along the strip and thereby speed the fusing process. It is also conceivable, however, that some degree of tempering, sagittal lateral inhibition is mediated by the mechanism next considered:

b. Lateral inhibition effects of the corticonuclear projection. The sagittally-oriented cerebellar corticonuclear projection diagrammed in figure 5 (whose rationale was developed in section 2.4.4) forms an implicit lateral inhibition system upon the cerebellar nuclei. Presumably it would be capable of outflanking spreading reticulocerebellar excitation in a way analogous to the mediolateral operation of the Purkinje-parallel fiber network. Thus, while uniform climbing fiber strip activation would serve to create excitation in a homologous nuclear region, in areas sagittally adjacent to the latter there would be inhibition. For this reason nuclear "ridge" excitation is shown diminishing sagittally in figure 28.

The presence of sagittal lateral inhibition also suggests concomitant sagittal disinhibition beyond inhibited regions at the ends of an excited strip segment. In the nuclei this would take the form of secondary, excited ridges arising in the plane of the original ridge, but separated from it by inhibited gaps. A close-packed system of isolated ridges and inhibited valleys could consequently arise through the activation of multiple strips in the following manner: In the mediolateral plane the spatial frequency selectivity of the

anterior lobe (section 9.3.1) will permit the activation of parallel sagittal strips spaced at the resonant period of 2.2-2.6 mm/c. "Locomotor" anterior lobe Oscarsson strips are approximately 1 mm wide (section 2.5; figure 6). Thus, lattices of alternating active and inactive Oscarsson strips fit directly within the "passband" of the anterior lobe (the behavioral import of such lattices is considered in section 9.4). The impact on the anterior lobe of activating a lattice is schematically illustrated in figure 29. This shows a top view of a nondescript sector of anterior lobe dominated by three sagittal Oscarsson strips (bottom of figure). Portions of two of the strips (vertical hatchings) are taken to be active as a lattice in the middle of the figure. In the mediolateral plane at that site, two "hills" (+) corresponding to the lattice will arise in the underlying cerebellar nuclei, while between the hills will be an inhibited valley (-). However, in the sagittal plane the corticonuclear lateral inhibition described above will inhibit the regions immediately rostral and caudal to the active lattice strip segments. Still further sagittally, disinhibition will produce secondary hills lying in the active strip regions, and between them will be inhibited valleys mediolaterally, just as at the original lattice location. Among the hills and valleys are left the "neutral zones" (NZ) indicated, which processes just described. However, since these zones are disinhibited by the surrounding inhibited valleys in both planes, they will become excited hills, as shown in figure 30. In this way a dense packing of excited and inhibited zones could come about in the cerebellar cortex.

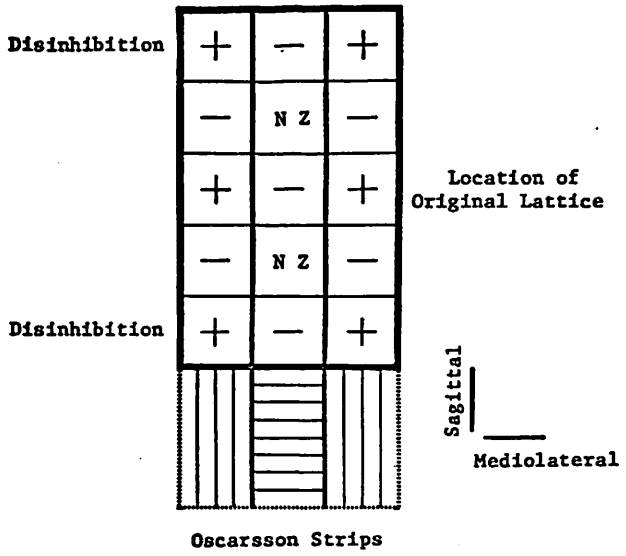

FIGURE 29

Top view of anterior lobe cortical region receiving input from a lattice of two active Oscarsson strip segments (active strips vertically hatched; inactive strip horizontally hatched). Segments are centrally located as shown. Areas of nuclear excitation of resulting are indicated by (+), inhibited areas by (-). Disinhibition takes place at sagittal ends of active strip segments. Neutral zones (NZ) are regions unaffected by immediate inhibition or disinhibition processes (see text).

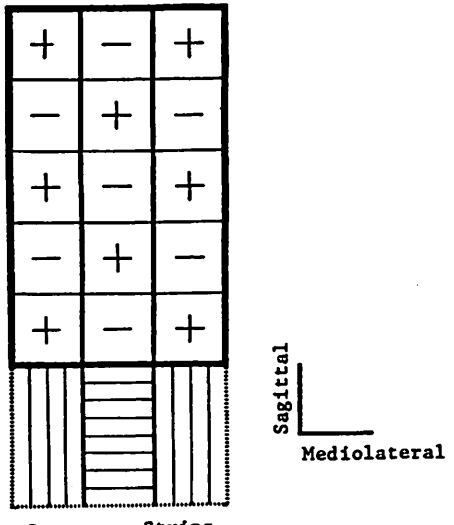

FIGURE 30

Evolution of neutral zones of figure 29 into excited "hill" regions (+). The figure indicates the possibility for dense packing of excitation and inhibition in the cerebellar nuclei if recurrent inhibition is characteristic of processes in the sagittal plane, as well as in the mediolateral.

The discussion above must be treated as sheer speculation until the simulations can be performed which would test it. Nonetheless, ways in which such an organization could bear upon the interaction of the anterior with other cerebellar lobes are explored in a different report[36].

c. Sagittal effects of cortical interneurons and Purkinje axon collaterals. Whatever spatial "focussing" in the mossy-granule transformation Golgi interneurons might produce (earlier section) is likely to act only mediolaterally because of the orientation of parallel fibers implementing Golgi-granule lateral inhibition. Thus, these cells may facilitate emergence of sagittally elongated ridges and valleys of nuclear activation (since no focussing occurs in this plane). In an earlier section it was also argued that Golgi cells should be suppressed within active strip regions and released elsewhere, and that this action will be performed by the infraganglionic plexus of Purkinje axon collaterals. The sagittal orientation of this plexus can now be seen as a means of restricting the inhibition to lie along ridges and valleys as desired. Moreover, in shutting down Golgi inhibition and releasing Purkinje activity at the ends of a strip segment, the plexus intensifies corticonuclear lateral inhibition.

One of the more obvious functions of the sagittally-oriented axon processes of molecular layer interneurons (basket and stellate cells) may be the creation of somewhat uniform silencing of all Purkinje cells between the branches of climbing fibers in an active strip (the interneurons are contacted by climbing fiber collaterals).

"Lateral inhibition" of Purkinje cells at the ends of Oscarsson strips has been described during strip cfr's; climbing fiber collaterals and interneurons are probably involved[229]. Other than at moments of strip activation, however, Purkinje excitation in ridges is expected to dominate molecular interneuron inhibition, while the reverse obtains in "valley" regions (described earlier). Llinás[163] has commented that the sagittal lateral inhibition of Purkinje cells, mediated by stellate and basket units, amounts to lateral facilitation in the cerebellar nuclei. Presumably this would be most apparent in nuclear valleys, perhaps assisting their rapid conversion to ridges when climbing fiber activity patterns change. But it is doubtful that any appreciation for the true richness of this system can be got by such piecemeal speculation without further simulation studies.

To summarize, the process of lateral recurrent inhibition may be fundamental to the creation, through climbing fiber activity, of different cerebellar spatial excitation patterns appropriate to different locomotor gaits. In the mediolateral plane the "locomotor" anterior lobe complex seems to be sharply spatially tuned to the widths of individual Oscarsson climbing fiber strips. Microstrip inputs "ring" the anterior lobe at the Oscarsson spatial frequency. Within certain limits this frequency is most critically dependent upon parallel fiber length and the diffuseness of the slow mossy fiber projection from the pre-cerebellar reticular nuclei.

In the sagittal plane lateral recurrent inhibition may come about through the corticonuclear projection (and reticulocerebellar

loop connections). Lattices of alternating active and inactive Oscarsson strips could give rise to a close-packed array of sagittal excitation ridges and valleys in the cerebellar nuclei. It is also possible that some features of the molecular layer interneuron and Purkinje collateral system are explained by such behavior, but this is a matter for further research.

9.4 The Nature of Spino-Olivocerebellar Messages and Their Encoding

The spino-olivocerebellar system seems clearly, according to the results here, to have the capacity for altering the spatial distribution of neuronal activity within the anterior lobe complex. That system is thus capable of redistributing activity among descending spinal pathways which receive from the cerebellum and in turn influence specific functional groups of muscles. According to the working hypotheses of the Introduction, the purpose of such activity redistribution would be to bring cerebellar locomotor modulation into agreement with muscle usage in the different spinally-selected gaits. If so, then it is information about the current gait which must be transmitted to the cerebellum via spino-olivocerebellar tracts. But in what form is this information?

It was pointed out at the end of section 9.3.1 that climbing fiber microstrips, although observable experimentally (sections 2.4.3, 3.4), do not fit so well into the spatial bandpass of the locomotor anterior lobe as do the broader Oscarsson strips which represent the termination zones of entire spino-olivocerebellar tracts. Moreover,

as was covered in section 2.5, the coincidence of Oscarsson strips with the sagittal compartmentalization of the anterior lobe cortico-nuclear projection implies that each Oscarsson strip relates to a particular functional grouping of muscles (i.e., different uses of flexors and extensors). The simulations demonstrate that activation of a microstrip, and therefore of an Oscarsson strip, will lead to the retention of excitation in the nuclear region corresponding to that strip, and the suppression of regions receiving from adjacent cortical areas. Thus, putting all these facts together:

> When a particular locomotor gait is selected at spinal levels, those spino-olivocerebellar tracts must become active which project into Oscarsson strips corresponding to anterior lobe zones governing the functional groups of muscles utilized in that gait.

The role microstrip activation may play in the awakening of an Oscarsson strip will be considered shortly.

The previous section (9.3.1) introduced the idea of <u>lattices</u> of simultaneously active Oscarsson strips, which is the form of multiple strip activation most naturally suited to the spatial frequency response of the locomotor anterior lobe. The lattices spoken about consisted of groups of alternating active and inactive Oscarsson strips distributed at the resonant spatial period of 2.2-2.6 c/mm. Sparser lattices at subharmonics of this period would also be admissable. No case has yet been made for why any sort of

multiple strip activity should be expected during locomotion, although it is evident that if activation of a single strip relates to the usage of either the flexors or extensors in a particular gait, then at least two strips (on each side of the midline) are required to cover all muscles of the step cycle. A subsequent report[36] details the requirements for multiple strip activity and demonstrates that certain close-packed lattices cover very nicely the flexor and extensor zones of the anterior lobe, enabling predictions of where strip activity should be found during different gaits. Such predictions could be tested in the mesencephalic cat.

Certain authors, notably Eccles[86,95] and more recently, Bloedel[29], have objected to the entire idea of considering either Oscarsson strips or microstrips thereof to be of importance in understanding cerebellar function. Eccles has generally described Purkinje cells responding with cfr's to weak mechanical peripheral stimulation to lie within numerous small colonies, each having a very refined receptive field (especially on the footpads)[98,99]. One cannot help wondering whether these colonies do not in fact represent Oscarsson strips at high resolution, that the weak stimuli used activate but few climbing fibers and their sagittal branches. There can be no question but that both microstrips and Oscarsson strips exist, especially in the light of the purely anatomical demonstrations of Armstrong and Voogt described in earlier sections (2.4.3, 3.4). Armstrong's group has even provided evidence of at least one coinnervated strip lattice of the type described above[14,16] (i.e., two

strips innervated by branches of the same climbing fibers, but separated from each other by a strip-like gap of cortex). Bloedel[29], while accepting the existence of Oscarsson strips, argues that their "stripness" will be hopelessly blurred during actual motor performances owing to the frequent similarities of receptive fields of adjacent strips. In making the statement, Bloedel ignores the different sensory modality specificities known to be present among the strips, which is likely to thin out any "blurring" to some extent. But that aside, Bloedel's hypothesis is directly refuted by the findings of Roberts and Rushmer[226] (Roberts, personal communication) who have recently demonstrated that footpad stimuli akin to those encountered in locomotion produce cfr's in a distinct strip of anterior lobe cortex and not a diffuse arousal of climbing fiber activity. These results and others related to them are explored further elsewhere[36].

The "activity" in an Oscarsson strip, or lattice of strips, by which the anterior lobe is to be informed of spinal gait choices, has to be translated into the separate activities of microstrips, and perhaps even activity within a microstrip. Now the simulations have demonstrated that Purkinje silencing is the primary means whereby climbing fibers initiate the development of spatial activity patterns within the cerebellar complex; this agrees with the conjectures of other authors[9,29,33,120]. Computer work also indicates that such patterns are retained in the cerebellum for significant lengths of time. From these two observations follow a number of ways in which

spinal gait information could be encoded into microstrip activity within an Oscarsson strip:

To consider Purkinje silencing first, the patterning efficacy of an isolated microstrip volley could be measured in terms of the degree of Purkinje silencing it produces. Likewise, the "imperativeness" of the spinal message triggering that microstrip could be similarly graded. One ready method for regulating Purkinje silencing is via the spatial summation of climbing fiber (Scheibel) collateral inputs upon cortical interneurons (for refs., see section 3.4)--that is, through the amount of synchrony of cfr's within a microstrip. The principle is noted, and demonstrated in chloralose cats, by Armstrong[9] and agrees with the observations and speculations of others[27,33]. Electrotonic coupling between cells in a small region of the olive projecting into a microstrip may promote cfr synchrony, as was described in section 3.4. If, as has been suggested[166,244], olivary inputs can regulate the amount of coupling between olivary cells, then coupling adjustment becomes a means for encoding spinal gait messages along a continuum of "importance." The thought should therefore be entertained that microstrip volleys, although appearing to be all-or-nothing events transmitting little information[75], may actually be transmitting a great deal of information in an analog fashion. Indeed, changes in Purkinje silent period duration following successive cfr's are frequently noted[26, 191,192]. What an "important," coupling-producing input "is" behaviorally requires considerable added information about locomotion

itself. This is given in another report[36].

A second method of regulating Purkinje silencing takes advantage of temporal summation onto cortical interneurons that would occur during high-frequency repetition of cfr's, again shown possible by Armstrong[9] with shocks at 500 hz. However, any behavioral occurrences of such bombardments seem not to be systematically documented, although they might possibly be present in cat following "natural" footpad stimulation (Rushmer and Roberts, unpublished). It has also been shown that the inactivation of the Purkinje spike generating mechanism caused by the cfr does not last as long as the cell becomes hyperpolarized[178]; that works against the prolongation of silencing by the temporal summation of inhibition.

The discussion above pertains to individual microstrips, although the regulation of synchrony (and of high-frequency volleys, if they exist) among the microstrips of an Oscarsson strip could as easily be a mechanism for encoding gait information into the latter--that is, for defining what is an "active" strip as distinct from an "inactive." However, to such single-shot encoding schemes must be added some which depend upon the persistence of excitation patterns created by climbing fibers:

In the case of the isolated microstrip, the simulations have demonstrated that repetition of synchronous microstrip volleys, within the persistence time of spatial activity patterns set up in the cerebellar module, will potentiate such patterns. In guinea pig, Bell and Kawasaki[27] have presented evidence of a rough periodicity

in the occurrences of cfr's in sagittally distributed pairs of Purkinje cells. The period was 130 msec--well within the persistence time demonstrated in the simulations (sections 6.3, figure 16; 6.5, figure 18). Bell and Kawasaki did not describe synchronous microstrip cfr's spaced at 130 msec intervals, but only the tendency of one climbing fiber within a microstrip population to fire 130 msec after another, not unlike a statistical renewal process. No peripheral stimuli were given to elicit this phenomenon; it is part of the "background" behavior of the inferior olive. Its causes are essentially unknown. Since climbing fibers all over the anterior lobe no doubt have similar periodicities, it is doubtful any spatial patterning in the cerebellar nuclei arises from it.

It was pointed out above that the regulation of electrotonic coupling in the inferior olive could be used to encode spinal gait messages within microstrips (or even entire Oscarsson strips). Strong coupling, causing cfr synchrony, would help establish nuclear patterning quickly. But then, strong coupling would probably also help produce synchronous strip volleys repeated at 130 msec (or thereabouts); and that, too, by the pattern potentiation process, will also lead quickly to alterations in the spatial distribution of excitation in the cerebellar complex. Therefore, the amounts of microstrip cfr synchrony and periodicity should stand in direct proportion to each other (the best example thus far being the extraordinary synchrony and periodicity of cfr volleys occurring spontaneously following administration of harmaline[77,152,165]). And

the adjustment of olivary electrotonic coupling may thus be a key spino-olivocerebellar encoding mechanism for two different reasons, instead of just one.

It is quite possible once again to extend everything which has been said about microstrip periodicity, synchrony, olivary electrotonic coupling, and so forth, to the Oscarsson strips governing functional muscle groups in different gaits. However, the very subdivision of Oscarsson strips into microstrips suggests that not all possible coding schemes in the spino-olivocerebellar system have been described as yet. While the spatial frequency selectivity of the locomotor anterior lobe requires that an entire Oscarsson strip be "active" to be effective--that most or all of the microstrips therein be generating synchronous (and possibly periodic) cfr's--it is <u>not</u> required that the microstrips be synchronous <u>with respect to each other</u>: The long persistence of effects from each microstrip activation allows the spatial summation of the results of different microstrip activations whether or not they are all synchronous. Thus, microstrips may themselves "stand for something," even though their volleys must be gathered into an Oscarsson strip in order to effect changes in cerebellar spatial activity patterns. Rushmer and Roberts (Roberts, personal communication) have made a very tentative observation showing that the location of a microstrip activated by forelimb cutaneous inputs migrates with respect to the location of those inputs, although always seeming to remain within a well-known "forelimb-cutaneous" Oscarsson strip in the cat anterior lobe. Therefore, one might expect that as the cat locomotes (in the gait appropriate

to that Oscarsson strip), these microstrips are probably all triggered, but at a variety of times--perhaps in a seemingly "random" fashion. Yet the nuclear patterning so elicited will be independent of that timing.

The import of the above paragraph cannot be fully examined here. It touches upon just what is meant by "gait information." Still, one might consider this: If the patterning wrought by climbing fiber activity is designed to remain for a "substantial" time within cerebellar circuitry, stored temporarily by reticulocerebellar recurrent excitation, then what kind of spinal information is appropriate for such storage? Is it the type required for the quick correction of a transient anomaly in one step cycle (e.g., the information supposedly utilized in "load compensation")? Or is it a type appropriate to many step cycles, to the holistic performance of the locomotor act under only slowly changing environmental constraints? If the latter, then again, what is such information? These topics are considered in another report[36].

In summary, the mechanisms encoding information in the spino-olivocerebellar tracts are, in theory:

1. The <u>location</u> of active Oscarsson strips and strip lattices. Location governs which combination of descending spinal pathways will be potentiated and, consequently, which functional groups of muscles (collections of flexors and extensors) will be influenced by cerebellar modulation. Location is thus the primary means by which spinal locomotor circuits inform the cerebellum of the current gait.

2. The degree of electrotonic coupling in the inferior olive. As coupling waxes strong, both synchrony and periodicity of cfr's within individual microstrips (and possibly within entire Oscarsson strips) become more pronounced. Synchrony increases the silent periods of Purkinje cells, so increasing the pattern-creating capacity of each microstrip volley. Periodicity augments spatial activity patterns through potentiation. It is presumed, then, that spino-olivary inputs act somehow to control olivary electrotonic coupling.

A third encoding mechanism--the triggering of individual microstrips by specific types of spinal events--must await full discussion in another paper[36].

9.5 Methods for Experimental Test

Experimental evidence bearing upon the validity of the simulations has been given in sections 6.2 and 6.6, as well as in scattered references in the remainder of the report. The purpose of this section is but to give guidelines for further experimental exploration of the work. Only acute experiments on non-locomoting cats will be considered. Locomotor tests are described in a subsequent paper[36], although some overlap with its material is unavoidable here.

Since the simulations were constructed with the aim of understanding anterior lobe physiology in the locomotor state, it is appropriate that experiments be performed on the anterior lobe complex in an acute preparation capable of locomotion (but not

locomoting). Thus, the preparation of choice is the precollicular decerebrate cat preferably receiving locomotor region (cuneiform nucleus) stimulation during tests. It is possible that a precollicular cat receiving DOPA or chlonidine i.v. might also be acceptable (although no experiments on such a cat have been reported). In any event, it is imperative that all pre-cerebellar reticular nuclei be fully excitable, which absolutely rules out the use of barbiturate anesthetics[30,32,91].

Probably the most important aspect of this work which requires experimental examination is the creation of distinct spatial distributions of cerebellar activity following activation of an Oscarsson strip. As was pointed out in section 6.6, essentially no information on this subject can be got from recordings in the cerebellar cortex. According to the simulations, patterning is more pronounced in the cerebellar nuclei. But then, since each sagittal corticonuclear zone is associated with an entire brainstem output nucleus (sometimes more than one; figure 6, section 2.5), patterning might become most evident through simultaneous recording from two or more of these nuclei. Thus, with recording electrodes in, say, the red and Deiters nuclei, one would weakly stimulate various regions in the medial accessory olive projecting into different Oscarsson strips. The immediate, transient effects of the stimuli would be of no interest. Instead, one would expect to see gradual changes in the "background" activity of red and Deiters neurons relative to one another as the olivary stimuli were repeated. These

changes would differ as a function of olivary locus stimulated (and could be predicted from figure 6 if the activated Oscarsson strip were known). This experiment would also demonstrate the extent of persistence and potentiation of the resulting cerebellar activity patterns, of course. To see these effects, however, the usual time averaging of successive responses in the brainstem nuclei would have to be avoided. Instead, the vagaries of individual cell discharges could be eliminated through spatial averaging--averaging the responses of different cells in the nuclei during equivalent moments in time (i.e., at equivalent times in the history of the repeated olivary stimulus). There may be other ways to at least demonstrate (without a direct association with climbing fiber activity) a short-term dynamic memory capacity in the cerebellum, but these involve the use of spinal reflexes and are covered elsewhere[36].

The importance of Purkinje silencing to the creation of cerebellar activity patterns would likely fall out as an immediate consequence of the above experiment if the Oscarsson strips activated were kept track of. However, the author has already advanced deductions from others' data on the vestibulo-ocular reflex suggesting that certain phenomena of the reflex can only be most easily explained if climbing fibers have a silencing effect on Purkinje cells (ref. 247 and subsequent report[37]).

Demonstration of granule cell recruitment would be quite difficult in a direct manner. An indirect demonstration, and one which would also say something about the role of cortical interneurons

(notably, Golgi cells) in compensating for the side effects of recruitment, would be to eliminate intracortical inhibition through the application of various drugs[28,76,271]. Activation of a climbing fiber strip should then lead to the "cerebellar seizure" shown in section 7.2, which is the result of uncompensated granular recruitment.

The sample of experiments given above is primarily designed to show that most of the major conclusions of this report can indeed be attacked experimentally without a great deal of retooling. Sensational demonstrations, such as a proof that the cerebellum "learns," are not required. There do exist some fairly new, and very powerful, biochemical techniques which could be applied to some of the problems above. However, the elaboration of those techniques will be done elsewhere[36].

10. Conclusion

A new view of cerebellar climbing fiber function has been introduced in this report, and with it a new view of cerebellar operations in general--at least with regard to the anterior lobe role in locomotion. It has been held that anterior lobe outflow must be restructured to mesh with the muscular deployments characteristic of different locomotor gaits. Computer simulations and mathematical analysis have demonstrated that climbing fibers, activated as Oscarsson strip populations, could accomplish such restructuring. In a very restricted sense, then, the cerebellum may be "programmable" through the agency of the spino-olivocerebellar system. The "programs"

are differing distributions of excitation among descending spinal pathways under cerebellar control--or homologously, unique spatial activity patterns within the cerebellar nuclei and cortex set up by microstrip volleys within Oscarsson strips.

The notion of programming carries with it the implication of program storage; and indeed, it has been demonstrated here that the cerebellar complex may have a short-term memory capacity that allows the temporary storage of climbing fiber-induced activity patterns. Crucial to the storage function is reticulocerebellar recurrent excitation, which also makes possible the lateral recurrent inhibition underlying the spatial behavior of cerebellar activity. Thus, climbing fiber volleys in Oscarsson strips effect an extended bias upon the musculature, a bias appropriately thought of more in terms of holistic motor acts rather than the moment-to-moment contractions of individual groups of muscles.

Superimposed upon the slowly changing distributions of cerebellar excitation from the various spinocerebellar and spino-reticulocerebellar mossy fiber pathways. So far as is known, these tracts do convey information about the immediacies of movement. A subsequent report (Boylls, in preparation) demonstrates that pre-existing cerebellar spatial excitation patterns created by climbing fiber activity may channel incoming mossy information into specific cerebellar sagittal zones--in other words, into specific descending pathways and muscle groups. As a result, during locomotion in a specific gait, mossy fiber inputs (regardless of their source) are

inevitably channeled into the muscle groups and linkages thereof which carry out the locomotion. A great deal of mossy information is therefore multipurpose, subject to differing cerebellar interpretations according to the contexts furnished by the spino-olivo-cerebellar system and, ultimately, spinal locomotor circuits.

As this report has attempted to show, at least one role of the climbing fiber in anterior lobe physiology may be quite understandable in terms of available knowledge; no added functional postulates (e.g., plasticity) are required. This is not to say that climbing fibers have no other function than that presented here. Like other fiber systems, they likely guide the ontogenesis of various neural elements in the cerebellar cortex, they may exert "trophic" influences through axoplasmic flow, and so forth. Perhaps they do mediate plastic change. But to place the last alternative ahead of all others, as has been done in many quarters, may well be to expend one's energy studying a third- or fourth-order consequence of climbing fiber activity, rather than its primary effect.

What has been said above about the remote functional possibilities for climbing fibers applies equally to other components of the cerebellar cortex and of the entire cerebellar system. In this report, propositions have been advanced on functions of the granular layer (recruitment for the amplification of certain types of mossy input) and certain cortical interneurons (stabilization of recruitment and recurrent excitation byproducts). The proposals are familiar in terms of functions computed elsewhere in the nervous

system; they are testable with existing physiological techniques. Their impact, according to the simulations, is merely one of refinement of cerebellar calculations--but then, nothing more was expected. On the other hand, granule cells and cortical interneurons might well be part of a pattern recognition scheme, learning device, a clock, or a half-dozen other engineering achievements conveniently replicated within the brain.

Motor control functions are hierarchically arranged. In understanding the cerebellar station within the hierarchy, one should consider that there exist circuits external to the cerebellum which decide if movement is appropriate, and subsequently, what the movement should be and which muscles to employ in it. Only after these executive decisions are specified does cerebellar outflow take on significance. Therefore, despite its anatomical position, the cerebellum is probably quite close to the bottom of the control hierarchy. Climbing fibers might thus be thought the terminals of a "descending" pathway delivering executive information to the cerebellum, while mossy fibers "ascend" to the cerebellum with reports on the performance of lower systems the cerebellum can influence. This scheme, and its more general relevance to the Bernstein paradigm for motor control, will be examined in later reports[36,37].

REFERENCES

1. Albus, J.S., "A theory of cerebellar function," Math. Biosciences 10, 25-61 (1971).
2. Albus, J.S., "The cerebellum: A substrate for list-processing in the brain," in Robinson, H.S., Knight, D.E. (eds.), Cybernetics, Artificial Intelligence, and Ecology, Spartan (New York, 1972).
3. Allen, G.I., Azzena, G.B., Ohno, T., "Role of cerebro-ponto-cerebellar and cerebro-reticulo-cerebellar pathways in the early mossy fiber response," Abstract, Society for Neuroscience 2nd Annual Meeting, Houston, October (1972).
4. Allen, G.I., Azzena, G.B., Ohno, T., "Somatotopically organized inputs from fore- and hindlimb areas of sensorimotor cortex to cerebellar Purkyně cells," Exp. Brain Res. 20, 255-272 (1974).
5. Allen, G.I., Sabah, N.H., Toyama, K., "Effect of fore- and hindlimb nerve stimulation on Deiters' neurones," Brain Res. 25, 645-650 (1971).
6. Allen, G.I., Tsukahara, N., "Cerebrocerebellar communication systems," Physiol. Rev. 54, 957-1006 (1974).
7. Amari, S., "Characteristics of random nets of analog, neuron-like elements," IEEE Trans. SMC 2, 643-657 (1972).
8. Arbib, M.A., Boylls, C.C., Dev,P., "Neural models of spatial perception and the control of movement," in Keidel, W.D., et al. (eds.), Kybernetic und Bionik/Cybernetics and Bionics, R. Oldenbourg (Munich, 1974), pp. 216-231.

9. Armstrong, D.M., "Functional significance of connections of the inferior olive," Physiol. Rev. 54, 358-417 (1974).

10. Armstrong, D.M., Cogdell, B., Harvey, R.J., "Responses of interpositus neurones to nerve stimulation in chloralose anaesthetized cats," Brain Res. 55, 461-466 (1973).

11. Armstrong, D.M., Cogdell, B., Harvey, R.J., "Responses of interpostitus neurones to stimulation of forelimb cutaneous afferents in chloralose-anaesthetized cats," J. Physiol. 245, 28-29P (1975).

12. Armstrong, D.M., Harvey, R.J., Schild, R.F., "Branching of individual olivo-cerebellar axons to terminate in more than one subdivision of the feline cerebellar cortex," J. Physiol. 202, 106-108P (1969).

13. Armstrong, D.M., Harvey, R.J., Schild, R.F., "Climbing fiber pathways from the forelimbs to the paramedian lobule of the cerebellum," Brain Res. 25, 199-202 (1971).

14. Armstrong, D.M., Harvey, R.J., Schild, R.F., "Distribution in the anterior lobe of the cerebellum of branches from climbing fibers to the paramedian lobule," Brain Res. 25, 203-206 (1971).

15. Armstrong, D.M., Harvey, R.J., Schild, R.F., "Cerebello-cerebellar response mediated via climbing fibres," Exp. Brain Res. 18, 19-39 (1973).

16. Armstrong, D.M., Harvey, R.J., Schild, R.F., "The spatial organisation of climbing fibre branching in the cat cerebellum," Exp. Brain Res. 18, 40-58 (1973).

17. Armstrong, D.M., Harvey, R.J., Schild, R.F., "Topographical localization in the olivo-cerebellar projection: An electrophysiological study in the cat," J. Comp. Neurol. 154, 287-302 (1974).

18. Arshavskii, Yu.I., Berkinblit, M.B., Fukson, O.I., Gel'fand, I.M., Orlovskii, G.N., "Origin of modulation in neurones of the ventral spinocerebellar tract during locomotion," Brain Res. 43, 276-279 (1972).

19. Arshavskii, Yu.I., Berkinblit, M.B.,Gel'fand, I.M., Fukson, O.I., Jackobson, V.S., "Functional role of the reticular afferent system of the cerebellum," Moscow (1971).

20. Arshavskii, Yu.I., Berkinblit, M.B., Gel'fand, I.M., Orlovskii, G.N., Fukson, O.I., "Activity of the neurones of the ventral spinocerebellar tract during locomotion," Biophysics 17, 926-935 (1972).

21. Arshavskii, Yu.I., Berkinblit, M.B., Gel'fand, I.M., Orlovskii, G.N., Fukson, O.I., "Activity of the neurones of the ventral spinocerebellar tract during locomotion of cats with deafferentated hindlimbs," Biophysics 17, 1169-1176 (1972).

22. Arshavskii, Yu.I., Berkinblit, M.B., Gel'fand, I.M., Keder-Stepanova, I.A., Smelyanskaya, E.M., Yakobson, V.S., "Background activity of Purkinje cells in the intact and deafferented anterior lobe of the cerebellar cortex of the cat," Biophysics 16, 709-717 (1971).

23. Asanuma, H., "Cerebral cortical control of movement," Physiologist 16, 153-166 (1973).

24. Azzena, G.B., Ohno, T., "Influence of spino-reticulo-cerebellar pathway on Purkyně cells of paramedian lobule," Exp. Brain Res. 17, 63-74 (1973).

25. Batini, C., Pumain, R., "Activation of Purkinje neurons through climbing fibers after chronic lesions of the olivo-cerebellar pathway," Experientia 24, 914-916 (1968).

26. Bell, C.C., Grimm, R.J., "Discharge properties of Purkinje cells recorded on single and double microelectrodes," J. Neurophysiol. 32, 1044-1055 (1969).

27. Bell, C.C., Kawasaki, T., "Relations among climbing fiber responses of nearby Purkinje cells," J. Neurophysiol. 35, 155-169 (1972).

28. Bisti, S., Iosif, G., Strata, P., "Suppression of inhibition in the cerebellar cortex by picrotoxin and bicuculline," Brain Res. 28, 591-593 (1971).

29. Bloedel, J.R., "Cerebellar afferent systems: A review," Progr. Neurobiol. 2, 1-68 (1973).

30. Bloedel, J.R., Burton, J.E., "Electrophysiological evidence for a mossy fiber input to the cerebellar cortex activated indirectly by collaterals of spinocerebellar pathways," J. Neurophysiol. 33, 308-320 (1970).

31. Bloedel, J.R., Llinás, R., "Neuronal interactions in frog cerebellum," J. Neurophysiol. 32, 871-880 (1969).

32. Bloedel, J.R., Roberts, W.J., "Functional relationship among neurons of the cerebellar cortex in the absence of anesthesia," J. Neurophysiol. 32, 75-84 (1969).

33. Bloedel, J.R., Roberts, W.J., "Action of climbing fibers in cerebellar cortex in the cat," J. Neurophysiol. 34, 17-31 (1971).

34. Bloedel, J.R., Gregory, R.S., Martin, S.H., "Action of interneurons and axon collaterals in cerebellar cortex of a primate," J. Neurophysiol. 35, 847-863 (1972).

35. Blomfield, S., Marr, D., "How the cerebellum may be used," Nature 227, 1224-1228 (1970).

36. Boylls, C.C., "A theory of cerebellar function with applications to locomotion. II. The relation of anterior lobe climbing fiber function to locomotor behavior in the cat," Technical Report, Dept. of Computer and Information Science, University of Massachusetts at Amherst (1975).

37. Boylls, C.C., "A theory of cerebellar function with applications to locomotion. III. The control of voluntary movement, the acquisition of skill, and the motor control paradigm of Bernstein,: Some speculations," Technical Report, Dept. of Computer and Information Science, University of Massachusetts at Amherst (1975).

38. Bradley, D.J., Fox, M., Williams, T.D., "A comparison of the effects of stimulation of the red nucleus on the monosynaptic reflex in the forelimb and hindlimb of the cat," Brain Res. 29, 151-154 (1971).

39. Braitenberg, V., "Functional interpretation of cerebellar histology," Nature 190, 539-540 (1961).

40. Braitenberg, V., "Is the cerebellar cortex a biological clock in the millisecond range?" in Fox, C.A., Snider, R.S. (eds.), Progress in Brain Research 25, 334-346 (1967).

41. Braitenberg, V., Atwood, R.P., "Morphological observations on the cerebellar cortex," J. Comp. Neurol. 109, 1-34 (1958).

42. Brodal, A., "The cerebellar connections of the nucleus reticularis lateralis (nucleus funiculi lateralis) in rabbit and cat. Experimental investigations," Acta Psychiat. Neurol. 18, 171-233 (1943).

43. Brodal, A., The Reticular Formation of the Brain Stem; Anatomical Aspects and Functional Correlations, Oliver & Boyd (Edinburgh, 1957).

44. Brodal, A., "Anatomical observations on the vestibular nuclei with special reference to their relations to the spinal cord and the cerebellum," Acta Oto-laryng. Suppl. 192, 24-51 (1964).

45. Brodal, A., Brodal, P., "The organization of the nucleus reticularis tegmenti pontis in the cat in the light of experimental anatomical studies of its cerebral cortical afferents," Exp. Brain Res. 13, 90-110 (1971).

46. Brodal, A., Courville, J., "Cerebellar corticonuclear projection in the cat. Crus II. An experimental study with silver methods," Brain Res. 50, 1-23 (1973).

47. Brodal, A., Szikla, G., "The termination of the brachium conjunctivum descendens in the nucleus reticularis tegmenti pontis. An experimental anatomical study in the cat," Brain Res. 39, 337-351 (1972).

48. Brodal, P., Maršala, J., Brodal, A., "The cerebral cortical projection to the lateral reticular nucleus in the cat, with special reference to the sensorimotor cortical areas," Brain Res. 6, 252-274 (1967).

49. Brodal, A., Pompeiano, O., Walberg, F., The Vestibular Nuclei and Their Connections. Anatomy and Functional Correlations, Oliver and Boyd (Edinburgh, 1962).

50. Brodal, A., Destombes, J., Lacerda, A.M., Angaut, P., "A cerebellar projection onto the pontine nuclei. An experimental anatomical study in the cat," Exp. Brain Res. 16, 115-139 (1972).

51. Brodal, A., Lacerda, A.M., Destombes, J., Angaut, P., "The pattern in the projection of the intracerebellar nuclei onto the nucleus reticularis tegmenti pontis in the cat. An experimental anatomical study," Exp. Brain Res. 16, 140-160 (1972).

52. Bruckmoser, P., Hepp-Reymond, M., Wiesendanger, M., "Cortical influence on single neurons of the lateral reticular nucleus of the cat," Exp. Neurol. 26, 239-252 (1970).

53. Burg, D., Rubia, F.J., "Inhibition of cerebellar Purkinje cells by climbing fiber input," Pflügers Arch. 337, 367-372 (1972).

54. Calvert, T.W., Meno, F., "Neural systems modeling applied to the cerebellum," IEEE Trans. SMC 2, 363-374 (1972).

55. Chamberlain, T.J., Halick, P., Gerard, R.W., "Fixation of experience in the rat spinal cord," J. Neurophysiol. 26, 662-673 (1963).

56. Chambers, W.W., Sprague, J.M., "Functional localization in the cerebellum. 1. Organization in longitudinal cortico-nuclear zones and their contribution to the control of posture, both extrapyramidal and pyramidal," J. Comp. Neurol. 103, 105-129 (1955).

57. Chambers, W.W., Sprague, J.M., "Functional localization in the cerebellum. 2. Somatotopic organization in cortex and nuclei," Arch. Neurol. Psychiat. 74, 653-680 (1955).

58. Chan-Palay, V., "A light microscope study of the cytology and organization of neurons in the simple mammalian nucleus lateralis: Columns and swirls," Z. Anat. Entwickl.-Gesch. 141, 125-150 (1973).

59. Chan-Palay, V., "Afferent axons and their relations with neurons in the nucleus lateralis of the cerebellum: A light microscope study," Z. Anat. Entwickl.-Gesch. 142, 1-21 (1973).

60. Chan-Palay, V., "Neuronal circuitry in the nucleus lateralis of the cerebellum," Z. Anat. Entwickl.-Gesch. 142, 259-265 (1973).

61. Churhill, R.V., Fourier Series and Boundary Value Problems. McGraw-Hill (New York, 1963).

62. Clark, S.L., "Responses following electrical stimulation of the cerebellar cortex in the normal cat," J. Neurophysiol. 2, 19-35 (1939).

63. Clark, S.L., Ward, J.W., "Observations on the mechanism of experimental cerebellar seizures," J. Neurophysiol. 15, 221-234 (1952).

64. Clendenin, M., Ekerot, C.-F., Oscarsson, O., "The lateral reticular nucleus in the cat. III. Organization of component activated from ipsilateral forelimb tract," Exp. Brain Res. 21, 501-513 (1974).

65. Clendenin, M., Ekerot, C.-F., Oscarsson, O., Rosén, I., "The lateral reticular nucleus in the cat. I. Mossy fibre distribution in cerebellar cortex," Exp. Brain Res. 21, 473-486 (1974).

66. Clendenin, M., Ekerot, C.-F., Oscarsson, O., Rosén, I., "The lateral reticular nucleus in the cat. II. Organization of component activated from bilateral ventral flexor reflex tract (bVFRT)," Exp. Brain Res. 21, 487-500 (1974).

67. Cooke, J.D., Larson, B., Oscarsson, O., Sjölund, B., "Origin and termination of cuneocerebellar tract," Exp. Brain Res. 13, 339-358 (1971).

68. Courville, J., "Rubrobulbar fibres to the facial nucleus and the lateral reticular nucleus (nucleus of the lateral funiculus). An experimental study in the cat with silver impregnation methods," Brain Res. 1, 317-337 (1966).

69. Courville, J., "Somatotopical organization of the projection from the nucleus interpositus anterior of the cerebellum to the red nucleus. An experimental study in the cat with silver impregnation methods," Exp. Brain Res. 2, 91-215 (1966).

70. Courville, J., "Connections of the red nucleus with the cerebellum and certain caudal brain stem structures. A review with functional considerations," Rev. Can. Biol. 27, 127-144 (1968).

71. Courville, J., Brodal, A., "Rubrocerebellar connections in the cat. An experimental study with silver impregnation methods," J. Comp. Neurol. 126, 471-486 (1966).

72. Courville, J., Diakiw, N., Brodal, A., "Cerebellar cortico-nuclear projection in the cat. The Paramedian lobule. An experimental study with silver methods," Brain Res. 50, 25-45 (1973).

73. Crichlow, E.C., "Cerebellar excitation of lateral reticular nucleus cells," Brain Res. 25, 195-198 (1971).

74. Crill, W.E., "The neurophysiology of the olivocerebellar system," Int. J. Neurol. 7, 294-301 (1970).

75. Crill, W.E., "Unitary multiple-spiked responses in cat inferior olive nucleus," J. Neurophysiol. 33, 199-209 (1970).

76. Curtis, D.R., Felix, D., "The effect of bicuculline upon synaptic inhibition in the cerebral and cerebellar cortices of the cat," Brain Res. 34, 301-321 (1971).

77. de Montigny, C., Lamarre, Y., "Rhythmic activity induced by harmaline in the olivo-cerebello-bulbar system of the cat," Brain Res. 53, 81-95 (1973).

78. Deura, S., "Patterns of commissural responses in the cerebellar nuclei," Exp. Neurol. 15, 387-400 (1966).

79. Deura, S., "Interaction of corticonuclear and commissural response in the cerebellar nuclei," Brain Res. 12, 344-362 (1969).

80. Dom, R., King, J.S., Martin, G.F., "Evidence for two direct cerebello-olivary connections," Brain Res. 57, 498-501 (1973).

81. Eager, R.P., "Efferent cortico-nuclear pathways in the cerebellum of the cat," J. Comp. Neurol. 120, 81-103 (1963).

82. Eager, R.P., "The mode of termination and temporal course of degeneration of cortical association pathways in the cerebellum of the cat," J. Comp. Neurol. 124, 243-258 (1965).

83. Eager, R.P., "Patterns and mode of termination of cerebellar cortico-nuclear pathways in the monkey," J. Comp. Neurol. 126, 551-566 (1966).

84. Eccles, J.C., "Circuits in the cerebellar control of movement," Proc. Natl. Acad. Sci. 58, 336-343 (1967).

85. Eccles, J.C., "The dynamic loop hypothesis of movement control," in Leibovic, K.N. (ed.), Information Processing in the Nervous System, Springer-Verlag (New York, 1969).

86. Eccles, J.C., "The topography of the mossy and climbing fiber inputs to the anterior lobe of the cerebellum," in Fields, W.S., Willis, W.D. (eds.), The Cerebellum in Health and Disease, W. H. Green (St. Louis, 1970), pp. 231-262.

87. Eccles, J.C., The Understanding of the Brain, McGraw-Hill (New York, 1973).

88. Eccles, J.C., "The cerebellum as a computer: Patterns in space and time," J. Physiol. 229, 1-32 (1973).

89. Eccles, J.C., Ito, M., Szentágothai, J., The Cerebellum as a Neuronal Machine, Springer-Verlag (New York, 1967).

90. Eccles, J.C., Sabah, N.H., Táborříková, H., "Responses evoked in neurones of the fastigial nucleus by cutaneous mechanoreceptors," Brain Res. 35, 523-527 (1971).

91. Eccles, J.C., Sabah, N.H., Táborříková, H., "Excitatory and inhibitory responses of neurones of the cerebellar fastigial nucleus," Exp. Brain Res. 19, 61-77 (1974).

92. Eccles, J.C., Sabah, N.H., Táborříková, H., "The pathways responsible for excitation and inhibition of fastigial neurones," Exp. Brain Res. 19, 78-99 (1974).

93. Eccles, J.C., Táborříková, H., Tsukahara, N., "Responses of the Purkinje cells of a Selachian cerebellum (Mustelus canis)," Brain Res. 17, 57-86 (1970).

94. Eccles, J.C., Táborříková, H., Tsukahara, N., "Responses of the granule cells of the Selachian cerebellum (Mustelus canis),"

95. Eccles, J.C., Provini, L., Strata, P., Táborříková, H., "Topographical investigations on the climbing fiber inputs from forelimb and hindlimb afferents to the cerebellar anterior lobe," Exp. Brain Res. 6, 195-215 (1968).

96. Eccles, J.C., Rantucci, T., Sabah, N.H., Táborříková, H., "Somatotopic studies on cerebellar fastigial cells," Exp. Brain Res. 19, 100-118 (1974).

97. Eccles, J.C., Rosén, I., Scheid, P., Táborříková, H., "Temporal patterns of responses of interpositus neurons to peripheral afferent stimulation," J. Neurophysiol. 37, 1424-1437 (1974).

98. Eccles, J.C., Sabah, N.H., Schmidt, R.F., Táborříková, H., "Cutaneous mechanoreceptors influencing impulse discharges in cerebellar cortex. III. In Purkyně cells by climbing fiber input," Exp. Brain Res. 15, 484-497 (1972).

99. Eccles, J.C., Sabah, N.H., Schmidt, R.F., Táborříková, H., "Integration by Purkyně cells of mossy and climbing fiber inputs from cutaneous mechanoreceptors," Exp. Brain Res. 15, 498-520 (1972).

100. Eccles, J.C., Sabah, N.H., Schmidt, R.F., Táborříková, H., "Mode of operation of the cerebellum in the dynamic loop control of movement," Brain Res. 40, 73-80 (1972).

101. Eccles, J.C., Rantucci, T., Rosén, I., Scheid, P., Táborříková, H., "Somatotopic studies on cerebellar interpositus neurons," J. Neurophysiol. 37, 1449-1459 (1974).

102. Edwards, S.B., "Autoradiographic studies of the projections of the midbrain reticular formation: Descending projections of nucleus cuneiformis," J. Comp. Neurol. 161, 341-358 (1975).

103. Ekerot, C.-F., Larson, B., "Differential termination of the exteroreceptive and proprioceptive components of the cuneocerebellar tract," Brain Res. 36, 420-424 (1972).

104. Ekerot, C.-F., Larson, B., "Correlation between sagittal projection zones of climbing and mossy fibre paths in cat cerebellar anterior lobe," Brain Res. 64, 446-450 (1973).

105. Escobar, A., Sampedro, E.D., Dow, R.S., "Quantitative data on the inferior olivary nucleus in man, cat, and vampire bat," J. Comp. Neurol. 132, 397-403 (1968).

106. Faber, D.S., Murphy, J.T., "Axonal branching in the climbing fiber pathway to the cerebellum," Brain Res. 15, 262-267 (1969).

107. Fanardzhyan, V.V., Oganesyan, E.A., Melik-Mus'yan, A.B.," Morphological and functional organization of cortico-nuclear cerebellar projections," Sechenov, J. Physiol. 58, 1059-1069 (1972).

108. Flumerfelt, B.A., Otabe, S., Courville, J., "Distinct projections to the red nucleus from the dentate and interposed nuclei in the monkey," Brain Res. 50, 408-414 (1973).

109. Forssberg, H., Grillner, S., "The locomotion of the acute spinal cat injected with chlonidine i.v.," Brain Res. 50, 184-186, (1973).

110. Fox, C.A., Andrade, A., Schwyn, R.C., "Climbing fiber branching in the granular layer," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969) pp. 603-611.

111. Fox, C.A., Hillman, D.E., Siegesmund, K.A., Dutta, C.R., "The primate cerebellar cortex. A Golgi and electron microscopic study," in Fox, C.A., Snider, R.S. (eds.), Progress in Brain Res. 25, 174-225 (1967).

112. Freeman, J.A., "The cerebellum as a timing device. An experimental study on the frog," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc., (Chicago, 1969) pp. 397-420.

113. Freeman, J.A., "Responses of cat cerebellar Purkinje cells to convergent inputs from cerebral cortex and peripheral sensory systems," J. Neurophysiol. 33, 697-712 (1970).

114. Freeman, J.A., Nicholson, C.N., "Space-time transformation in the frog cerebellum through an intrinsic tapped delay-line," Nature 226, 640-642 (1970).

115. Gilbert, P.F.C., "A theory of memory that explains the function and structure of the cerebellum," Brain Res. 69, 1-20 (1974).

116. Goodman, D.G., Hallett, R.E., Welch, R.B., "Patterns of localization in the cerebellar cortico-nuclear projections in the albino rat," J. Comp. Neurol. 121, 51-63 (1963).

117. Gordon, M., Rubia, F.J., Strata, P., "The effect of barbiturate anaesthesia on the transmission to the cerebellar cortex," Brain Res. 43, 677-680 (1972).

118. Gordon, M., Rubia, F.J., Strata, P., "The effect of pentothal on the activity evoked in the cerebellar cortex," Exp. Brain Res. 17, 50-62 (1973).

119. Goslow, G.E., Reinking, R.M., Stuart, D.G., "The cat step cycle: Hind limb joint angles and muscle lengths during unrestrained locomotion," J. Morph. 141, 1-42 (1974).

120. Granit, R., The Basis of Motor Control, Academic Press (New York, 1970).

121. Granit, R., Phillips, C.G., "Excitatory and inhibitory processes acting upon individual Purkinje cells of the cerebellum in cats," J. Physiol. 133, 520-547 (1956).

122. Gray, J., Animal Locomotion, W. W. Norton (New York, 1968).

123. Gresty, M.A., Paul, D.H., "Responses of fastigial nucleus neurones to stimulation of the caudate nucleus in the cat," J. Physiol. 245, 655-665 (1975).

124. Grillner, S., "Locomotion in the spinal cat," in Stein, R.B. et al. (eds.), Control of Posture and Locomotion, Plenum (New York, 1973) pp. 515-535.

125. Grillner, S., "Locomotion in the spinal dogfish," Acta. Physiol. Scand. 87, 31-32A (1973).

126. Grillner, S., "On the generation of locomotion in the spinal dogfish," Exp. Brain Res. 20, 459-470 (1974).

127. Grillner, S., "Locomotion in vertebrates: Central mechanisms and reflex interaction," Physiol. Rev. 55, 247-304 (1975).

128. Grillner, S., Shik, M.L., "On the descending control of the lumbosacral spinal cord from the 'mesencephalic locomotor region'", Acta Physiol. Scand. 87, 320-333 (1973).

129. Grillner, S., Zangger, P., "How detailed is the central pattern generation for locomotion?" Brain Res. 88, 367-371 (1975).

130. Hazlett, J.C., Martin, G.F., Dom, R., "Spino-cerebellar fibers of the opossum didelphis marsupialis virginiana," Brain Res. 33, 257-271 (1971).

131. Heglund, N.C., Taylor, C.R., McMahon, T.A., "Scaling stride frequency and gait to animal size: Mice to horses," Science 186, 1112-1113 (1974).

132. Heidary, H., Tomasch, J., "Neuron numbers and perikaryon areas in the human cerebellar nuclei," Acta Anat. 74, 290-296 (1969).

133. Hillman, D.E., "Morphological organization of frog cerebellar cortex. A light and electron microsceopic study," J. Neurophysiol. 32, 818-846 (1969).

134. Hongo, T., Jankowska, E., Lumdberg, A., "The rubrospinal tract. I. Effects on alpha-motoneurones innervating hindlimb muscles in cats," Exp. Brain Res. 7, 344-364 (1969).

135. Hongo, T., Kudo, N., Tanaka, R., "Effects from the vestibulo-spinal tract on the contralateral hindlimb motoneurones in the cat," Brain Res. 31, 220-223 (1971).

136. Houk, J.C., "The phylogeny of muscular control configurations," III. Symposium of Biocybernetics (Leipzig, 1972).

137. Ito, M., "The cerebello-vestibular interaction in cat's vestibular nuclei neurones," Manuscript (1968).

138. Ito, M., "Neurons of cerebellar nuclei," in Brazier, M.A.B. (ed.), The Interneuron, U. California (Los Angeles, 1969) pp. 309-327.

139. Ito, M., "Neurophysiological aspects of the cerebellar motor control system," Int. J. Neurol. 7, 162-176 (1970).

140. Ito, M., Simpson, J.I., "Discharges in Purkinje cell axons during climbing fiber activation," Brain Res. 31, 215-219 (1971).

141. Ito, M., Kawai, N., Udo, M., "The origin of cerebellar-induced inhibition of Deiters neurons. III. Localization of the inhibitory zone," Exp. Brain Res. 4, 310-320 (1968).

142. Jansen, J., "Features of cerebellar morphology and organization," Acta Neurol. Scand, (Suppl.) 51, 197-217 (1972).

143. Jansen, J., Brodal, A., "Experimental studies on the intrinsic fibers of the cerebellum. II. The corticonuclear projection," J. Comp. Neurol. 73, 267-321 (1940).

144. Kashin, S.M., Fel'dman, A.G., Orlovskii, G.N., "Locomotion of fish evoked by electrical stimulation of the brain," Brain Res. 82, 41-47 (1974).

145. King, J.S., Martin, G.F., Bowman, M.H., "The direct spinal area of the inferior olivary nucleus: An electron microscopic study," Exp. Brain Res. 22, 13-24 (1975).

146. Kitai, S.T., Casey, W., Hatada, K., "Intracellular analysis of the lateral reticular nucleus," Fed. Proc. 31, A377 (1972).

147. Kitai, S.T., Hatada, K., Casey, W., "Intracellular analysis of antidromically and synaptically activated lateral reticular neurons," Brain Res. 43, 629-634 (1972).

148. Kling, U., Székely, G., "simulation of rhythmic nervous activities. I. Function of networks with cyclic inhibitions," Kybernetik 5, 89-103 (1968).

149. Korneliussen, H.K., "Cerebellar organization in the light of cerebellar nuclear morphology and cerebellar corticogenesis," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 515-523.

150. Korneliussen, H.K., "Histogenesis of the cerebellar cortex and cortical zones," in Larsell, O., Jansen, J. (eds.), Comparative Anatomy and Histology of the Cerebellum: The Human Cerebellum, Cerebellar Connections, and Cerebellar Cortex, University of Minnesota Press (Minneapolis, 1972), pp. 164-197.

151. Künzle, H., "Autoradiographic tracing of the cerebellar projections from the lateral reticular nucleus in the cat," Exp. Brain Res. 22, 255-266 (1975).

152. Lamarre, Y., de Montigny, C., "Rhythmic activation of the cerebellar climbing fiber input by harmaline," Abstract, Society for Neuroscience 2nd Annual Meeting, Houston, October (1972).

153. Larramendi, L.M.H., "Electron microscopic studies of cerebellar interneurons," in Brazier, M.A.B. (ed.), The Interneuron, U. California (Los Angeles, 1969), pp. 289-307.

154. Larramendi, L.M.H., "Morphological characteristics of extrinsic and intrinsic nerve terminals and their synapses in the cerebellar cortex of the mouse," in Fields, W.S., Willis, W.D. (eds.), The Cerebellum in Health and Disease, W. H. Green (St. Louis, 1970), pp. 63-110.

155. Larramendi, L.M.H., Lemkey-Johnson, N., "The distribution of recurrent Purkinje collateral synapses in the mouse cerebellar cortex. An electron microscope study," J. Comp. Neurol. 138, 451-482 (1970).

156. Latham, A., Paul, D.H., "Spontaneous activity of cerebellar Purkinje cells and their responses to impulses in climbing fibres," J. Physiol. 213, 135-156 (1971).

157. Llinás, R., "Functional aspects of interneuronal evolution in the cerebellar cortex," in Brazier, M.A.B. (ed.), The Interneuron, U. California (Los Angeles, 1969), pp. 329-348.

158. Llinás, R., "Neuronal operations in cerebellar transactions," in Schmitt, F.O. (ed.), The Neurosciences: Second Study Program, Rockefeller U. (New York, 1970), pp. 409-426.

159. Llinás, R., "Frog cerebellum. Biological basis for a computer model," Math. Biosciences 11, 137-151 (1971).

160. Llinás, R., Bloedel, J.R., "Climbing fibre activation of Purkinje cells in the frog cerebellum," Brain Res. 3, 299-302 (1967).

161. Llinás, R., Bloedel, J.R., "Frog cerebellum. Absence of long-term inhibition upon Purkinje cells," Science 115, 601-603 (1967).

162. Llinás, R., Hillman, D.E., "Physiological and morphological organization of the cerebellar circuits in various vertebrates," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc., (Chicago, 1969), pp. 43-73.

163. Llinás, R., Precht, W., "Recurrent facilitation by disinhibition in Purkinje cells of the cat cerebellum," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc., (Chicago, 1969), pp. 619-627.

164. Llinás, R., Volkind, R.A., "Repetitive climbing fiber activation of Purkinje cells in the cat cerebellum following administration of harmaline," Fed. Proc. 31, A377 (1972).

165. Llinás, R., Volkind, R.A., "The olivo-cerebellar system: Functional properties as revealed by harmaline-induced tremor," Exp. Brain Res. 18, 69-87 (1973).

166. Llinás, R., Baker, R., Sotelo, C., "Electrotonic coupling between neurons in cat inferior olive," J. Neurophysiol. 37, 560-571 (1974).

167. Llinás, R., Hillman, D.E., Precht, W., "Functional aspects of cerebellar evolution," in Fields, W.S., Willis, W.D. (eds.), The Cerebellum in Health and Disease, W. H. Green (St. Louis, 1970), pp. 269-291.

168. Llinás, R., Precht, W., Clarke, M., "Cerebellar Purkinje cell responses to physiological stimulation of the vestibular system in the frog," Exp. Brain Res. 13, 408-431 (1971).

169. Løken, A.C., Brodal, A., "A somatotopical pattern in the human lateral vestibular nucleus," Arch. Neurol. 23, 350-357 (1970).

170. Lund, S., Pompeiano, O., "Descending pathways with monosynaptic action on motoneurones," Experientia 21, 602-605 (1965).

171. Lundberg, A., "The significance of segmental spinal mechanisms in motor control," 4th International Biophysics Congress (Moscow, 1972).

172. Mano, N.I., "Simple and complex spike activities of the cerebellar Purkinje cell in relation to selective alternate movement in intact monkey," Brain Res. 70, 381-393 (1974).

173. Marchesi, G.F., Strata, P., "Climbing fibers of cat cerebellum. Modulation of activity during sleep," Brain Res. 170, 145-148 (1970).

174. Marchesi, G.F., Strata, P., "Mossy and climbing fiber activity during phasic and tonic phenomena of sleep," Pflügers Arch. 323, 219-240 (1971).

175. Marko, H., "Die Systemtheorie der homogenen Schichten. I. Mathematische Grundlagen," Kybernetik 5, 221-240 (1969).

176. Marr, D., "A theory of cerebellar cortex," J. Physiol. 202, 437-470 (1969).

177. Martinez, F.E., Crill, W.E., Kennedy, T.T., "Dendritic origin of climbing fiber responses in cat cerebellar Purkinje cells," Fed. Proc. 29, 324 (1970).

178. Martinez, F.E., Crill, W.E., Kennedy, T.T., "Electrogenesis of cerebellar Purkinje cell responses in cats," J. Neurophysiol. 34, 348-356 (1971).

179. Massion, J., Albe-Fessard, D., "Dualité des voies sensorielles afférents contrôlant l'activité du noyau rouge," Electroenceph. Clin. Neurophysiol. 15, 435-454 (1963).

180. Matsushita, M., Ikeda, M., "Olivary projections to the cerebellar nuclei in the cat," Exp. Brain Res. 10, 488-500 (1970).

181. Matsushita, M., Iwahori, N., "Structural organization of the fastigial nucleus. I. Dendrites and axonal pathways," Brain Res. 25, 597-610 (1971).

182. Matsushita, M., Iwahori, N., "Structural organization of the fastigial nucleus. II. Afferent fiber systems," Brain Res. 25, 611-624 (1971).

183. Miller, S., Oscarsson, O., "Termination and functional organization of spino-olivocerebellar paths," in Fields, W.S., Willis, W.D. (eds.), The Cerebellum in Health and Disease, W. H. Green (St. Louis, 1970), pp. 172-200.

184. Mittenthal, J.E., "Reliability of pattern separation by the cerebellar mossy fiber-granule cell system," Kybernetik 16, 93-101 (1974).

185. Mizuno, N., Nakamura, Y., "An electron microscope study of spinal afferents to the lateral reticular nucleus of the medulla oblongata in the cat," Brain Res. 53, 187-191 (1973).

186. Morishita, I., Yajima, A., "Analysis and simulation of networks of mutually inhibiting neurons," Kybernetik 11, 154-165 (1972).

187. Mortimer, J.A., "A cellular model for mammalian cerebellar cortex," Ph.D. Dissertation, U. Michigan (1970).

188. Mortimer, J.A., "Cerebellar responses to teleceptive stimuli in alert monkeys," Brain Res. 83, 369-390 (1975).

189. Mugnaini, E., "The histology and cytology of the cerebellar cortex," in Larsell, O., Jansen, J. (eds.), Comparative Anatomy and Histology of the Cerebellum: The Human Cerebellum, Cerebellar Connections, and Cerebellar Cortex, University of Minnesota Press (Minneapolis, 1972), pp. 201-265.

190. Murphy, J.T., Kwan, H., "Synaptic currents produced in cerebellar cortex by proprioceptive inputs," Abstract, Society for Neuroscience 2nd Annual Meeting, Houston, October (1972).

191. Murphy, J.T., Sabah, N.H., "The inhibitory effect of climbing fiber activation on cerebellar Purkinje cells," Brain Res. 19, 486-490 (1970).

192. Murphy, J.T., Sabah, N.H., "Cerebellar Purkinje cell responses to afferent inputs. I. Climbing fiber activation," Brain Res. 25, 449-467 (1971).

193. Murphy, J.T., MacKay, W.A., Johnson, F., "Responses of cerebellar cortical neurons to dynamic proprioceptive inputs from forelimb muscles," J. Neurophysiol. 36, 711-723 (1973).

194. Murphy, J.T., MacKay, W.A., Johnson, F., "Differences between cerebellar mossy and climbing fibre responses to natural stimulation of forelimb muscle proprioceptors," Brain Res. 55, 263-289 (1973).

195. Nacimiento, A.C., "Spontaneous and evoked discharges of cerebellar Purkinje cells in the frog," in Llinás, R., Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 373-395.

196. Nyberg-Hansen, R., "Functional organization of descending supraspinal fibre systems to the spinal cord. Anatomical observations and physiological correlations," Reviews of Anatomy, Embryology and Cell Biology, Band 39, Heft 2, Springer-Verlag (New York, 1966).

197. O'Leary, J.L., Petty, J., Smith, J.M., O'Leary, M., Inukai, J., "Cerebellar cortex of rat and other animals. A structural and ultrastructural study," J. Comp. Neurol. 134, 401-432 (1968).

198. Orlovskii, G.N., "Spontaneous and induced locomotion of the thalamic cat," Biophysics 14, 1154-1162 (1969).

199. Orlovskii, G.N., "Work of the reticulo-spinal neurones during locomotion," Biophysics 15, 761-771 (1970).

200. Orlovskii, G.N., "Influences of the cerebellum on the reticulospinal neurones during locomotion," Biophysics 15, 928-936 (1970).

201. Orlovskii, G.N., "Work of the Purkinje cells during locomotion," Biophysics 17, 935-941 (1972).

202. Orlovskii, G.N., "Work of the neurones of the cerebellar nuclei during locomotion," Biophysics 17, 1177-1185 (1972).

203. Orlovskii, G.N., "Activity of vestibulospinal neurons during locomotion," Brain Res. 46, 85-98 (1972).

204. Orlovskii, G.N., "Activity of rubrospinal neurons during locomotion," Brain Res. 46, 99-112 (1972).

205. Orlovskii, G.N., Pavlova, G.A., "Response of Deiters' neurons to tilt during locomotion," Brain Res. 42, 212-214 (1972).

206. Oscarsson, O., "The sagittal organization of the cerebellar anterior lobe as revealed by the projection patterns of the climbing fiber system," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 525-537.

207. Oscarsson, O., "Functional organization of spinocerebellar paths," in Iggo, A. (ed.), Handbook of Sensory Physiology, Springer-Verlag (New York, 1973), V. 2, pp. 339-380.

208. Oscarsson, O., Sjölund, B., "Identification of 5 spino-olivocerebellar paths ascending through the ventral funiculus of the cord," Brain Res. 69, 331-335 (1974).

209. Palay, S.L., Chan-Paly, V., Cerebellar Cortex: Cytology and Organization, Springer-Verlag (New York, 1974).

210. Palkovits, M., Magyar, P., Szentágothai, J., "Quantitative histological analysis of the cerebellar cortex in the cat. I. Number and arrangement in space of the Purkinje cells," Brain Res. 32, 1-13 (1971).

211. Palkovits, M., Magyar, P., Szentágothai, J., "Quantitative histological analysis of the cerebellar cortex in the cat. II. Cell numbers and densities in the granular layer," Brain Res. 32, 15-30 (1971).

212. Palkovits, M., Magyar, P., Szentágothai, J., "Quantitative histological analysis of the cerebellar cortex in the cat. III. Structural organization of the molecular layer," Brain Res. 34, 1-18 (1971).

213. Palkovitz, M., Magyar, P., Szentágothai, J., "Quantitative histological analysis of the cerebellar cortex in the cat. IV. Mossy fiber-Purkinje cell numerical transfer," Brain Res. 45, 15-29 (1972).

214. Passouant, P., Cadilhac, J., Baldy-Mouliner, M., "Cerebellar protracted post-effects," Int. J. Neurol. 7, 152-161 (1970).

215. Pellionisz, A., "Computer simulation of the pattern transfer of large cerebellar neuronal fields," Acta Biochim. et Biophys. Acad. Sci. Hung. 5, 71-79 (1970).

216. Pellionisz, A., "Computer simulation of the information preprocessing in the input of the cerebellar cortex," Acta Cybernetica 1, 157-169 (1972).

217. Pellionisz, A., Szentágothai, J., "Dynamic single unit simulation of a realistic cerebellar network model," Brain Res. 49, 83-99 (1973).

218. Pellionisz, A., Szentágothai, J., "Dynamic single unit simulation of a realistic cerebellar network model. II. Purkinje cell activity within the basic circuit and modified by inhibitory systems," Brain Res. 68, 19-40 (1974).

219. Pellionisz, A., Palkovits, M., Hámori, J., Pintér, E., Szentágothai, J., "Quantitative comparison of the cerebellar synaptic organization of immobilized and normal kittens," Proc. IV Internat. Biophys. Congress (Moscow, 1972).

220. Pompeiano, O., "Functional organization of the cerebellar projections to the spinal cord," in Fox, C.A., Snider, R.S. (eds.), Progress in Brain Research 25, 282-321 (1967).

221. Pompeiano, O., Brodal, A., "The origin of vestibulospinal fibers in the cat. An experimental-anatomical study, with comments on the descending medial longitudinal fasciculus," Arch. Ital. Biol. 95, 166-195 (1957).

222. Pompeiano, O., Brodal, A., "Experimental demonstration of a somatotopical origin of rubrospinal fibers in the cat," J. Comp. Neurol. 108, 225-252 (1957).

223. Precht, W., Llinás, R., "Functional organization of the vestibular afferents to the cerebellar cortex of frog and cat," Exp. Brain Res. 9, 30-52 (1969).

224. Rall, W., "Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input," J. Neurophysiol. 30, 1138-1168 (1967).

225. Rinvik, E., Brodal, A., "Experimental studies on the red nucleus and its connections in the cat," Acta Neurol. Scand. 41, 448-449 (1965).

226. Roberts, W.J., Rushmer, D.S., "Activity in cat cerebellar Purkinje cells evoked by passive forepaw movements," Abstract, Society for Neuroscience 4th Annual Meeting, St. Louis, October (1974).

227. Rosén, I., Scheid, P., "Cerebellar surface cooling influencing evoked activity in cortex and in interpositus nucleus," Brain Res. 45, 580-584 (1972).

228. Rosén, I., Scheid, P., "Responses in the spino-reticulo-cerebellar pathway to stimulation of cutaneous mechanoreceptors," Exp. Brain Res. 18, 268-278 (1973).

229. Rubia, F.J., Höppener, U., Langhof, H., "Lateral inhibition of Purkinje cells through climbing fiber afferents?" Brain Res. 70, 153-156 (1974).

230. Rushmer, D.S., Woodward, D.J., "Inhibition of Purkinje cells in the frog cerebellum. I. Evidence for a stellate cell inhibitory pathway," Brain Res. 33, 83-90 (1971).

231. Sabah, N.H., "Reliability of computation in the cerebellum," Biophys. J. 11, 429-445 (1971).

232. Sasaki, K., "Interfolial mossy fiber branching in the cat cerebellum," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 613-617.

233. Sasaki, K., Strata, P., "Responses evoked in the cerebellar cortex by stimulating mossy fibre pathways to the cerebellum," Exp. Brain Res. 3, 95-110 (1967).

234. Schild, R.F., "On the inferior olive of the albino rat," J. Comp. Neurol. 140, 255-259 (1970).

235. Shapovalov, A.I., "Extrapyramidal monosynaptic and disynaptic control of mammalian alpha-motoneurones," Brain Res. 40, 105-115 (1972).

236. Shapovalov, A.I., Shapovalova, K.B., "Activity of α-motor neurons in response to rhythmic stimulation of the red nucleus and influence of strychnine on the rubro-spinal effects," Dokl. Akadem. Nauk SSSR 168, 443-446 (1966).

237. Shapovalov, A.I., Karamjan, O.A., Kurchavyi, G.G., Repina, Z.A., "Synaptic actions evoked from the red nucleus on the spinal alpha-motoneurons in the rhesus monkey," Brain Res. 32, 325-348 (1971).

238. Shapovalov, A.I., Karamjan, O.A., Tamarova, Z.A., Kurchavyi, G.G., "Cerebello-rubrospinal effects on hindlimb motoneurons in the monkey," Brain Res. 47, 49-59 (1972).

239. Shik, M.L., Orlovskii, G.N., Severin, F.V., "Organization of locomotor synergism," Biophysics 11, 1011-1019 (1966).

240. Shik, M.L., Severin, F.V., Orlovskii, G.N., "Control of walking and running by means of electrical stimulation of the midbrain," Biophysics 11, 756-765 (1966).

241. Shofer, R.J., Sax, D.S., Strom, M.G., "Analysis of auditory and cerebrocortically evoked activity in the immature and adult cat cerebellum," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 703-717 and discussion, pp. 717-721.

242. Smolyaninov, V.V., "Some special features of organization of the cerebellar cortex," in Gel'fand, I.M., et al. (eds.), Models of the Structural-Functional Organization of Certain Biological Systems, MIT (Cambridge, Mass., 1969), pp. 251-325.

243. Sotelo, C., "Ultrastructural aspects of the cerebellar cortex of the frog," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc., (Chicago, 1969), pp. 327-367.

244. Sotelo, C., Llinás, R., Baker, R., "Structural study of inferior olivary nucleus of the cat: Morphological correlates of electrotonic coupling," J. Neurophysiol. 37, 541-559 (1974).

245. Székely, G., "Development of limb movements. Embryological physiological and model studies," in Wolstenholme, G.E.W., O'Conner, M. (eds.), Ciba Foundation Symposium: Growth of the Nervous System, J. & A. Churchill (London, 1968), pp. 77-95.

246. Szentágothai, J., "Structuro-functional considerations of the cerebellar neuron network," Proc. IEEE 56, 960-968 (1968).

247. Szentágothai, J., Arbib, M.A., Conceptual Models of Neural Organization, NRP Bull., V. 12, No. 3 (1974).

248. ten Bruggencate, G., Teichmann, R., Weller, E., "Neuronal activity in the lateral vestibular nucleus of the cat. I. Patterns of postsynaptic potentials and discharges in Deiters neurones evoked by stimulation of the spinal cord," Pflügers Arch. 337, 119-134 (1972).

249. ten Bruggencate, G., Teichmann, R., Weller, E., "Neuronal activity in the lateral vestibular nucleus of the cat. II. EPSPs in Deiters neurons mediated by fast conducting fibres of the spinal cord," Pflügers Arch. 337, 135-146 (1972).

250. ten Bruggencate, G., Teichmann, R., Weller, E., "Neuronal activity in the lateral vestibular nucleus of the cat. III. Inhibitory actions of cerebellar Purkinje cells evoked via mossy and climbing fibre afferents," Pflügers Arch. 337, 147-162 (1972).

251. ten Bruggencate, G., Sonnhof, U., Teichmann, R., Weller, E., "A study of the synaptic input to Deiters neurones evoked by stimulation of peripheral nerves and spinal cord," Brain Res. 25, 207-211 (1971).

252. Thach, W.T., "Discharge of Purkinje and cerebellar nuclear neurons during rapidly alternating arm movements in the monkey," J. Neurophysiol. 31, 785-797 (1968).

253. Thach, W.T., "Discharge of cerebellar neurons related to two maintained postures and two prompt movements. II. Purkinje cell input and output," J. Neurophysiol. 33, 537-547 (1970).

254. Thach, W.T., "Cerebellar output: Properties, synthesis, and uses," Brain Res. 40, 89-97 (1972).

255. Tomasch, J., "Numerical capacities of cerebellar cell and fiber systems," Experientia 25, 377-378 (1969).

256. Torvik, A., Brodal, A., "The origin of reticulospinal fibers in the cat. An experimental study," Anat. Rec. 128, 113-137 (1957).

257. Toyama, K., Tsukahara, N., Udo, M., "Nature of the cerebellar influences upon the red nucleus neurons," Exp. Brain Res. 4, 292-309 (1968).

258. Tsukahara, N., "Electrophysiological study of cerebellar nucleus neurones in the dogfish Mustelus Canis," in Llinás, R. (eds.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 251-256.

259. Tsukahara, N., "The properties of the cerebello-pontine reverberating circuit," Brain Res. 40, 67-71 (1972).

260. Tsukahara, N., Bando, T., "Red nuclear and interposate nuclear excitation of pontine nuclear cells," Brain Res. 19, 295-298 (1970).

261. Tsukahara, N., Bando, T., Kitai, S.T., Kiyohara, T., "Cerebello-pontine reverberating circuit," Brain Res. 33, 233-237 (1971).

262. Voogd, J., The Cerebellum of the Cat. Structure and Fibre Connexions, Van Gorcum (Assen, 1964).

263. Voogt, J., "Comparative aspects of the structure and fibre connexions of the mammalian cerebellum," in Fox, C.A., Snider, R.S. (eds.), Progress in Brain Research 25, 94-134 (1967).

264. Voogt, J., "The importance of fiber connections in the comparative anatomy of the mammalian cerebellum," in Llinás, R. (ed.), Neurobiology of Cerebellar Evolution and Development, Am. Med. Assoc. (Chicago, 1969), pp. 493-514.

265. Walberg, F., "Descending connections to the inferior olive. An experimental study in the cat," J. Comp. Neurol. 104, 77-174 (1956).

266. Walberg, F., Jansen, J., "Cerebellar corticonuclear projection studied experimentally with silver impregnation method," J. Hirnforsch. 6, 338-354 (1964).

267. Walberg, F., Pompeiano, O., Brodal, A., Jansen, J., "The fastigio-vestibular projection in the cat. An experimental study with silver impregnation methods," J. Comp. Neurol. 118, 49-76 (1962).

268. Weisstein, N., "A Rashevsky-Landahl neural net simulation of metacontrast," Psych. Rev. 75, 494-521 (1968).

269. Wilson, H.R., Cowan, J.D., "Excitatory and inhibitory interactions in localized populations of model neurons," Biophysical J. 12, 1-24 (1972).

270. Wilson, H.R., Cowan, J.D., "A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue," Kybernetik 13, 55-80 (1973).

271. Woodward, D.J., Hoffer, B.J., Siggins, G.R., Oliver, A.P., "Inhibition of Purkinje cells in the frog cerebellum. II. Evidence for GABA as the inhibitory transmitter," Brain Res. 33, 91-100 (1971).

272. Wylie, R.M., Felpel, L.P., "The influence of the cerebellum and peripheral somatic nerves on the activity of Deiters' cells in the cat," Exp. Brain Res. 12, 528-546 (1971).

273. Yu, J., Tarnecki, R., Chambers, W.W., Liu, C.N., Konorski, J., "Mechanisms mediating ipsilateral limb hyperflexion after cerebellar paravermal cortical ablation or cooling," Exp. Neurol. 38, 144-156 (1973).

274. Zucker, R.S., "Theoretical implications of the size principle of motoneurone recruitment," J. Theor. Biol. 38, 587-596 (1973).