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A NEURAL MODEL OF TIMED RESPONSE LEARNING IN THE CEREBELLUM

Running Title: Model of Cerebellar Timing

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ABSTRACT

A spectral timing model is developed to explain how the cerebellum learns adaptively timed responses during the rabbit’s conditioned nictitating membrane response (NMR). The model posits two learning sites that respectively enable conditioned excitation and timed disinhibition of the response. Long-term potentiation of mossy fiber pathways projecting to interpositus nucleus cells allows conditioned excitation of the response’s adaptive gain. Long-term depression of parallel fiber-Purkinje cell synapses in the cerebellar cortex allows learning of an adaptively timed reduction in Purkinje cell inhibition of the same nuclear cells. A spectrum of partially timed responses summate to generate an accurately timed population response. In agreement with physiological data, the model Purkinje cell activity decreases in the interval following the onset of the conditioned stimulus, and nuclear cell responses match conditioned response (CR) topography. The model reproduces key behavioral features of the NMR, including the properties that CR peak amplitude occurs at the unconditioned stimulus (US) onset, a discrete CR peak shift occurs with a change in interstimulus interval (ISI) between conditioned stimulus (CS) and US, mixed training at two different ISIs produces a double-peaked CR, CR acquisition and rate of responding depend unimodally on the ISI, CR onset latency decreases during training, and maladaptively-timed, small-amplitude CRs result from ablation of cerebellar cortex.

Keywords—Adaptive Timing, Cerebellum, Conditioning, Hippocampus, Interpositus Nucleus, Learning, Long-Term Depression, Long-Term Potentiation, Neural Networks, Nictitating Membrane Response
1. Introduction

The cerebellum has been considered a possible locus of motor learning for many years (Albus, 1971; Brindley, 1964; Ito, 1970; Grossberg, 1969; Marr, 1969). Evidence has accumulated during the last three decades in support of this idea. Studies have shown that the cerebellum is essential for the repair of dysmetric saccadic eye movements (Optican & Robinson, 1980), adaptation of the vestibulo-ocular reflex (VOR) (Ito, 1984; Lisberger, 1988), and the acquisition and expression of conditioned eyelid responses (Thompson, 1990; Daum et al., 1993), as well as other motor learning tasks.

More recently, the cerebellum has been implicated in the timing of behavioral responses. In a study by Keele and Ivry (1990), cerebellar patients demonstrated increased variability in a timed finger-tapping task, in judging the duration of an interval between two tones, and in the perception of the relative velocities of visual stimuli. Perrett et al. (1993) reported that the cerebellar cortex adaptively delays the conditioned nictitating membrane response (NMR) of the rabbit, such that the response occurs at the expected time of an aversive stimulus. This suggests that cerebellar context-dependent motor learning may be augmented by an additional ability to delay responses to contextual events until a behaviorally relevant time.

Since the hippocampus has also been implicated in timing behavioral responses (Solomon, 1980), the cerebellum and hippocampus may share this function. Neural mechanisms underlying the hippocampal adaptive timing function were proposed by Grossberg, Merrill, and Schmajuk (Grossberg & Merrill, 1992; Grossberg & Schmajuk, 1989), among others. It is now important to consider the possibility that similar neural mechanisms may be the basis of the timing function in the cerebellum. The model presented in this paper shows how a basic computational competence may be achieved by distinct brain regions which have different functional roles in the control of behavior. In particular, a spectral timing mechanism analogous to the proposed hippocampal mechanism is presented for cerebellar cortex. First, behavioral, anatomical, and physiological data implicating cerebellar involvement in the rabbit NMR are reviewed to motivate the model and results.

2. NMR Behavioral Data

The rabbit NMR may be conditioned to an initially neutral tone or light stimulus by repeated pairings of this conditioned stimulus (CS) with a corneal air-puff or periorbital shock unconditioned stimulus (US). After repeated pairings in the normal rabbit, a conditioned response (CR) anticipates the expected arrival of the US and initiates eyelid closure prior to the onset of the US. If the CS is repeatedly and
consistently presented without the US, the CR gradually disappears. In the a common experimental paradigm, delay conditioning, the CS remains on at least until the onset of the US and in many cases coterminates with the US. In trace conditioning there is a temporal separation between the offset of the CS and onset of the US. The duration between the onset of the CS and the onset of the US is referred to as the interstimulus interval (ISI), in either case.

Gluck, Reifsnider and Thompson (1990) have summarized the five key features of the conditioned NMR topography as follows. First, CR peak amplitude occurs at US onset. Second, a discrete CR peak shift occurs with a change in ISI. Third, mixed training at two different ISIs produces a double-peaked CR, as shown for example in Figure 1. Fourth, CR acquisition and rate of responding depend on ISI. The ISI-dependency is unimodal with a peak at the optimal ISI of about 400ms. Lastly, CR onset latency decreases during training. The model we propose for adaptive timing and motor learning in the cerebellum captures all of these key features.

3. Cerebellar Involvement in the NMR

The basic cerebellar and epi-cerebellar circuitry and nomenclature are depicted in Figure 2. Cerebellar cortical cell types are shown above the dashed line; cerebel-
Figure 2. Basic neuronal circuitry and neurotransmitters in the cerebellum and epi-cerebellar nuclei. Cell types above the dashed line are cerebellar cortical neurons. Inhibitory neurons, black; Excitatory neurons, white. PC, Purkinje cell; GO, Golgi cell; BA, basket cell; ST, stellate cell; GR, granule cell; PF, parallel fiber; MF, mossy fiber; CF, climbing fiber; N, cerebellar nuclear cell; LN, local-circuit inhibitory neuron in cerebellar nucleus; PN, precerebellar neuron that issues mossy fibers; IO, inferior olive; GL, glutamate. (Sources: Ito 1984, Fig. 3; Chan-Palay 1977, Figs. 11-9, 11-18, 14-11)

lar nuclear cell types and important epi-cerebellar structures appear below the dashed line. The existence of the inhibitory nuclear cell circuit involving cell type LN in the figure has been described for the cerebellar dentate nucleus (Chan-Palay, 1977), and is likely to be found in the interpositus as well, since the nuclei are similar in their fine structure and synaptic organization (Angaut & Sotelo, 1973).

Thompson (1990) has described the circuitry involved in NMR conditioning (Figure 3). This model is supported by extensive anatomical and physiological data (Gluck, Reifsnider & Thompson, 1990; Thompson, 1990; Thompson et al., 1987). The US input enters via the trigeminal nerve to the principle sensory trigeminal nucleus (V). There is a direct pathway for the eye-blink reflex to the abducens (VI) and accessory abducens nuclei, the site of motor neurons effecting the NMR. The tone CS excites cells that project from the ventral cochlear nucleus to the pons. There are subsequently two pathways through the cerebellar interpositus nucleus, a direct pathway and a pathway through the cerebellar cortex which modulates the
Figure 3. Neural circuitry involved in classical conditioning of the NMR. Inhibitory synapses, ⊥, others excitatory. PC, Purkinje cell; MF, mossy fiber; CF, climbing fiber; IP, cerebellar interpositus nucleus; RN, red nucleus; PN, pontine nucleus; DAO, dorsal accessory olive; VCN, ventral cochlear nucleus; V, fifth cranial nucleus; VI, sixth cranial nucleus; VII, seventh cranial nucleus; CS, conditioned stimulus; US, unconditioned stimulus; NMR, nictitating membrane response. (Adapted from Thompson, 1990)

The output of the interpositus is to the red nucleus, which projects to the motor nuclei. Inhibitory paths from interpositus to the inferior olive and trigeminal nucleus, shown as dashed lines in the figure, exist as well.

Theoreticians have long hypothesized that the signal which induces learning in the cerebellum is the climbing fiber input (Albus, 1971; Grossberg, 1969; Ito, 1984; Marr, 1969). In the NMR conditioning paradigm, US delivery, or direct stimulation of US-activated pathways, is a necessary condition for learning. Lesions of the inferior olive, the source of climbing fibers, prevent learning and cause extinction of previously learned CRs (McCormick et al., 1985). Direct stimulation of the spinal trigeminal nucleus (Schreurs, 1988) or the dorsal accessory olive (Thompson, 1990) can serve as a US for conditioning the NMR. Thus, the climbing fiber signal does appear to act as a teaching signal in the NMR preparation.

As depicted in Figure 2, the climbing fiber signal is delivered to both the Purkinje cell dendritic tree and the nuclear cell. This anatomy is consistent with a hypothesis that learning can occur at both locations. However, the specific site of
learning in the cerebellum has been debated (Ito, 1989; Lisberger, 1988). Early theories of cerebellar function (Albus, 1971; Grossberg, 1969; Marr, 1969) proposed that the cerebellar cortex was the principal locus of memory. Conjunctive activation of parallel fibers and climbing fibers was postulated to modify the efficacy of parallel fiber-Purkinje cell synapses. Experimental evidence has been found for this modification (Hirano, 1990; Ito, 1989). Others have suggested that the site of learning is in subcortical nuclei that receive Purkinje axons. We are unaware of direct evidence for particular learning mechanisms at the cerebellar nuclear cell. Still, several studies have shown that some cerebellar-mediated learning is retained following cerebellar cortical lesions (Lavond et al., 1987; Lisberger, 1988; Woodruff-Pak et al., 1993; Yang et al., 1991).

Three key features of cerebellar physiology in the conditioned NMR paradigm are summarized here. First, the topography of cerebellar interpositus nuclear cell activation matches the topography of the CR (McCormick & Thompson, 1984; Thompson et al., 1987). Second, Purkinje cells projecting to these nuclear cells show a decrease in simple spike firing frequency occurring after the CS and throughout the US period (Berthier & Moore, 1986; Thompson, 1990). Third, Purkinje cells display complex spikes (due to climbing fiber bursts) coinciding with the onset of the US during learning (Berthier & Moore, 1986). Our model of adaptive timing in the cerebellum also accounts for these three aspects of cerebellar physiology.

4. The Hippocampus and Spectral Timing

The rabbit NMR can be conditioned in the absence of the hippocampus (Orr & Berger, 1985). However, neurons in hippocampus display activation profiles that match the topography of the CR in the NMR conditioning task (Berger et al., 1976; Berger & Thompson, 1978; Clark et al., 1984; Solomon et al., 1986). In addition, hippocampal lesions can sometimes disrupt timing of the CR in trace conditioning (Port et al., 1986a; Solomon et al., 1986) and more complicated paradigms (Orr & Berger, 1985; Port et al., 1986b). This experimental data has implicated the hippocampus in the timing of the NMR.

To explain how the hippocampal neural network can adaptively time the CR, Grossberg and Schmajuk (1989) proposed the spectral timing model. The spectral timing mechanism has four conceptual operations that enable evolution of correct response firing by a process of variation and selection. First, a spectrum of independent, localized activities is generated from a singular stimulus event. The variable rates of increase that distinguish elements of the spectrum distribute the times at which these activities reach their maximum values throughout a succeeding interval. Second, a process acting on the localized activities limits the interval during
which an activity will be near maximal. In the Grossberg-Schmajuk simulations, a chemical transmitter habituates in an activity-dependent fashion and modulates, or gates, the activity in its pathway. These gated activities all begin to grow at the onset of a CS, but reach their peak values at a range of distinct times, after which they decay. Third, these gated activities trigger learning by adaptive weights, or long term memory (LTM) traces, in their respective pathways. Some gated activities are large at the particular ISI when the US becomes large; others are small. The temporally well-correlated LTM traces grow large; the others do not. Each LTM trace multiplies its gated signal, thereby amplifying the signals in those pathways that, at least partially, correlate with the US. Fourth, all the LTM-gated signals from the entire population add up to form the total output. Although no individual signal is well-timed, the population response peaks at the ISI and exhibits all of the five key properties summarized by Gluck, Reifsnider, and Thompson (1990).

The spectral timing model of hippocampus was further developed and integrated into a more general theory of the neural bases of reinforcement learning and recognition learning (Grossberg & Merrill, 1992). This theory suggests how the timed hippocampal trace that is observed during NMR conditioning in the dentate-CA3 hippocampal circuit may be used to adaptively time several important functions, such as reinforcement learning, attention to motivationally relevant cues, and inhibition of orienting responses. However, as discussed above, the NMR can also be conditioned in the absence of the hippocampus. The fact that in many cases this response will be appropriately timed indicates that other neural pathways may be capable of independently timing responses. From the perspective of the Grossberg-Merrill model, the hippocampal timing circuit prepares the motivational and attentional preconditions for the response, but does not compute the parameters of the response itself.

5. Cerebellar Involvement in NMR Timing

As already discussed, cerebellar cortical lesions may disrupt the conditioned NMR, but only rarely is it completely abolished and learning prevented. The extent of behavioral incapacitation appears to correlate with the rostro-caudal extent of the lesion (Thompson, 1990; Perrett et al., 1993). This section reviews data indicating that some cerebellar cortical lesions can produce deficits in response timing.

In a delay conditioning paradigm, McCormick and Thompson (1984) found that lesions of the ansiform lobule of the cortex produce maladaptively-timed CRs which occur too soon after the CS. Some studies have not found deficits in CR timing following cerebellar cortical lesions (Woodruff-Pak et al., 1985; Woodruff-Pak et al., 1993). However, these lesions apparently did not encompass all of the
parasagittal zone which projects to dorsolateral anterior interpositus nucleus. Lesions including anterior, ansiform, paramedian lobes, and lateral vermis, flocculus, and paraflocculus, are reported to affect the timing of the CR (Logan et al. submitted).

Recently, Perrett et al. (1993) studied the effect of cerebellar cortical lesions on delay conditioned NMRs. They used two tones, CS1 and CS2, as conditioned stimuli for two different ISIs. Only rapid, small-amplitude CRs could be conditioned after the most extensive lesions of cerebellar cortex including anterior lobe. These rapid, or un-timed, CRs are plotted on the same time scale as normal CRs (pre-lesion) in Figure 4. The authors suggest that learning of a CR at the interpositus nucleus may be modulated by cerebellar cortical learning that adaptively times the response.

Figure 4. Cerebellar cortical lesion effects on NMR topography. CS1 trained to ISI of 150ms; CS2 trained to ISI of 750ms. A, anterior lobe; S, ansiform lobe; P, paramedian lobe. (Reprinted with permission from Perrett, Ruiz, and Mauk, 1993.)
Studies have shown that CRs can be adaptively timed even when the CS in a delay conditioning task consisted of direct activation of the mossy fibers by electrical stimulation (Steinmetz, 1990). This suggests that the cerebellum may be able to time the response to the US. Since mossy fibers are stimulated directly in this experiment, the data (McCormick & Thompson, 1984; Berthier & Moore, 1986) imply that either the ISI is bridged entirely by a cerebellar cortical process, or by a process involving both cerebellar cortex and cortical targets that project back to cerebellar cortex. Regarding the latter, it has been hypothesized, for example, that the cerebellum receives recurrent feedback via the hippocampus (Berger at al., 1986; Schmajuk & DiCarlo, 1991). However, hippocampal ablation does not eliminate timing in all cases. We infer that the cerebellar cortex contributes to adaptive timing of the response.

As described in Section 3, interpositus nuclear cell response correlates with the behavioral response. Since mossy fibers project directly to interpositus (Steinmetz & Sengelaub, 1992), nuclear cell response must be properly timed by some associated circuit. Perrett et al. (1993) suggest that mossy fiber activation of cerebellar nuclear cells leads to expression of the CR in the absence of cortical inhibition via Purkinje cells. Therefore, we propose that classical conditioning of a CS-CR association occurs in parallel via a fast pathway through the cerebellar nuclei and via an adaptively timed pathway through Purkinje cells in cerebellar cortex. Normally, Purkinje cells inhibit the nuclear cells and thereby block the expression of the CR. Cortical conditioning produces an appropriately timed reduction in Purkinje cell activity, thereby opening a gate that allows expression of the CR. Prior to conditioning, CR expression could be prevented before the mossy fiber activity has had time to traverse the cortical circuit, if the Purkinje cells are spontaneously active, producing tonic inhibition of the nuclear cells in the absence of the CS. Purkinje cells have been found to exhibit a spontaneous, steady-state discharge of up to 70 impulses/s (Thach, 1972).

6. Spectral Timing in the Cerebellum

In this section, we describe a spectral timing model for the cerebellar cortex. In this model, the numerous cerebellar granule cells are assumed to respond at different rates to the mossy fiber input. The granule cell axons bifurcate in the molecular layer into parallel fibers. The spectrum of integration rates for these cells produces activations on parallel fibers with different rise times. Parallel fibers excite both Purkinje cells and Golgi cells (Eccles et al., 1967). The Golgi cells provide inhibitory feedback to the granule cells. This inhibitory feedback pathway attenuates each granule cell activation in time, leaving a spectrum of timed activation peaks which can be the basis of learning an adaptively timed response. There are many more
Figure 5. Intrinsic granule cell response spectrum and Golgi feedback circuit. A: Cerebellar circuit components. B: Golgi cell activations. C: Parallel fiber spectrum. Parameters: $\alpha_s=0.2, \beta_s=10,$ $CS=1, \alpha_G=0.1, \beta_G=5, \gamma_G=0.02, a=12, b=4, \mu_f=0.5, \beta_x=4, \delta=0.1, \alpha_j=24/(1+j), j=0,\ldots,17, \text{CS onset at } t=0.$

Granule cells than any other cell type in the brain and each mossy fiber may contact as many as 600 granule cells (Ito, 1984), so it is plausible that parallel fibers emerging from these granule cells can carry a full spectrum of rise times. The basic components of this hypothesis are depicted in Figure 5. The principles involved are made explicit by a detailed mathematical representation.

Let the CS activate a mossy fiber input, $s$, of the cerebellum. This input is retained in short-term memory by the following differential equation in time $t$.

$$\frac{ds}{dt} = -\alpha_s s + \beta_s (1-s) \left( CS + s \right)$$

(1)

Variable $s$ obeys a membrane equation (1) in which $s$ has a maximal activation level, nominally chosen to be 1. The CS is stored in the short term memory variable, $s$, by this mechanism (Grossberg & Merrill, 1992). The mossy fibers distribute the signal to granule cells dispersed throughout a large region of the cerebellar cortex (Snider & Stowell, 1944).

The mossy fiber signal energizes a spectrum of granule cell activations $x_j$ by

$$\frac{dx_j}{dt} = \alpha_j \left[ (1-x_j) s - \beta_x (x_j + \delta) G_j \right]$$

(2)

These signals $x_j, j=0,\ldots,N$, are zero prior to the onset of $s$. When $s$ is on, these sig-
nals grow toward 1 at variable rates determined by the $\alpha_j$. The $\alpha_j$ define a spectrum of rates from fast to slow (Figure 5B). When the mossy fiber signal $s$ exceeds the Golgi cell signal $G_j$ in (2), the granule cell is depolarized (or activated), but when the Golgi cell activity nears that of the mossy fiber input the granule cell is actively inhibited and inactivated. The $x_j$ granule cell activities give rise to thresholded, sigmoidal signals

$$f(x_j) = \frac{a (x_j - \mu_f)^+}{1 + b (x_j - \mu_f)^+}^2, \quad (3)$$

where notation $[x]^+$ means $\max(x,0)$. These signals propagate along the parallel fiber axons, whereby they activate both Golgi and Purkinje cells (Figure 5A).

The activity of the Golgi cells is modeled by the equations

$$\frac{dG_j}{dt} = -\alpha_G G_j + \beta G_j (1-G_j) (\gamma G^s + f(x_j)). \quad (4)$$

As shown in Figure 5C, the granule cell-Golgi cell feedback circuit produces a spectrum of activity peaks distributed throughout the CS-US interval (and beyond) in response to the onset of the CS. These spectral signals are delivered to the parallel fiber-Purkinje cell synapses where they can be used to learn and read-out an adaptively timed response, by using the adaptive weights to select those activity peaks that are correlated in time with the US. This parallel fiber-Purkinje cell synaptic efficacy, $z_j$, is the substrate of learning in the cerebellar cortex (Grossberg, 1969; Marr, 1969). These LTM traces gate the $f(x_j)$ signals to produce a net adaptively timed signal $f(x_j)z_j$ from each spectral pathway.

It has been experimentally established that conjunctive activation of parallel fibers and climbing fibers produces long term depression (LTD) of the synaptic efficacy between the active parallel fibers and the Purkinje cell (Hirano, 1990; Ito, 1989). When only the parallel fibers are stimulated, long term potentiation (LTP) of synaptic efficacy results (Hirano, 1990; Sakurai, 1988). These synaptic modification processes appear consistent with general synaptic modifications observed in many brain regions, up to a sign change. Many central synapses undergo LTP at high depolarization levels and LTD at lower depolarization levels (Artola & Singer, 1993). At the parallel fiber-Purkinje cell synapse the situation appears to be reversed. At high depolarizations, produced by the strong climbing fiber input, LTD is produced, while at lower depolarizations, produced by parallel fibers acting alone, LTP is produced. Thus it appears that the climbing fiber pathway, which
delivers a signal dependent on the US via the inferior olive, acts as a teaching signal, and learning is mediated by LTD at the synapses. This is balanced by LTP processes acting at the synapses in the presence of a CS but the absence of the US.

As discussed above, a Purkinje cell must be inactivated from its spontaneous firing level to release the nuclear cell and allow the CR to be expressed. But how can LTD at the parallel fiber-Purkinje cell synapse lead to inhibition of the Purkinje cell below the spontaneous activity level? An answer is suggested by the fact that parallel fibers also strongly activate stellate and basket cells which inhibit Purkinje cells. Ito (1989, p. 87) notes that one reason for early failures to detect LTD using mass field potentials is that parallel fiber stimulation produces strong stellate and basket cell activity, and this activity does not undergo LTD. In other words, parallel fibers stimulate the inhibitory interneurons as well as the Purkinje cells. These interneurons produce a graded inhibitory postsynaptic potential in Purkinje cells (Midtgaard, 1992). While the synaptic weight between parallel fibers and Purkinje cells is modifiable, the efficacy of the parallel fiber to basket and stellate cells is not modified by climbing fiber input (Ito, 1984, p. 129). Nor are basket or stellate cell synapses on Purkinje cells modifiable. If the inhibitory and excitatory influences on Purkinje cell activity are initially in balance, then LTD at parallel fiber-Purkinje cell excitatory synapses, which correlates in time with the US onset, can lead to an increased net inhibition of Purkinje cell activity. This adaptively-timed attenuation of Purkinje cell spontaneous activity can be used to open the nuclear gate through which the conditioned response may be expressed.

These excitatory and inhibitory influences on the Purkinje cell interact in a complex manner. The total excitatory postsynaptic potentials are approximated by

\[ J^+ = \sum_{j=1}^{N} f(x_j) z_j \]  \hspace{1cm} (5)

The inhibitory postsynaptic potentials satisfy

\[ J^- = \sum_{j=1}^{N} f(x_j) k_j \]  \hspace{1cm} (6)

Here, the inhibitory interneurons receive the same spectrum of activities from the parallel fibers as does the Purkinje cell. In the case of the interneurons, however, these signals are gated by fixed, unmodifiable coefficients \( k_j \), which represent the transmission efficacies through the interneurons and their synapses.
These activities could represent activity in a single Purkinje cell or alternatively in a population of Purkinje cells taken from a region of cerebellar cortex. Although the later is more likely, it is often easier to describe and simulate the model using a lumped approximation. Therefore, the net activity over the population of Purkinje cells carrying the spectral signals is approximated by

\[ p = 1 + f_p (J^+ - J^-) \]  

Here, the baseline level of spontaneous activity at the cell body or axon hillock is set to a nominal level of 1. We do not model the excitation of the Purkinje cell by climbing fiber activity. The function

\[ f_p(x) = \frac{\gamma_p \text{sgn}(x)x^2}{1 + x^2} \]  

is a signed, compressive function of the total inhibitory and excitatory activity in the dendrites, which sets limits on the maximum and minimum effects on spontaneous firing.

From equation (7) it can be seen that the Purkinje cell inhibits a nuclear-mediated CR when the inhibitory \( J^- \) and excitatory \( J^+ \) influences are in balance. This occurs, for example, when \( z_j = k_j \) for all \( j \). Since all \( z_j \) and \( k_j \) cannot be assumed to be initially balanced, there must be some process that acts to balance the excitatory and inhibitory activities. We hypothesize that this process involves the projection from the cerebellar nucleus to the inferior olive and the spontaneous activity of inferior olivary cells which project to the cerebellum as climbing fibers. Measurements of Purkinje cell activity in vivo reveal that spontaneous climbing fiber signals occur at a rate of 1.5/s (Ito, 1984, p. 101), or 2-4/s (Thompson, 1990). This rate increases during learning and decreases once a behavior is well-learned (Thach et al., 1982; Thompson, 1990). In addition, if the inferior olive is cooled or lesioned, Purkinje cell responses rapidly increase (Benedetti et al., 1985; Savio & Tempia, 1985). Thus, the spontaneous activity of the inferior olive appears to maintain the \( z_j \) at a lower level than would otherwise be obtained. The inhibitory projection from interpositus to inferior olive reduces climbing fiber activity when the cerebellar nucleus is active. When the \( k_j \)'s are smaller than the \( z_j \)'s, the responses from the cerebellar nucleus would be eliminated and inferior olivary activity would increase. When the \( k_j \)'s are larger than the \( z_j \)'s, responses from the cerebellar nucleus would be increased and inferior olivary responses decreased, such that the \( z_j \)'s would tend to increase. If no US is present to maintain the \( z_j \)'s less than \( k_j \)'s, the \( z_j \)'s will tend to increase such that a natural balance is achieved between the inhibitory and excita-
Rather than model the inferior olivary cells' discrete responses, we lump this balancing process with the LTM equation for the parallel fiber-Purkinje cell synaptic efficacy. The LTM equation is

$$\frac{dz_j}{dt} = \beta_z f(x_j) \left[ k_j - z_j - \alpha_z Cz_j \right] \tag{9}$$

Each LTM trace, $z_j$, responds to the timed spectral component $f(x_j)$ and a US-activated climbing fiber signal $C$. In equation (9) learning in $z_j$ is enabled by the gating signal $f(x_j)$. Once enabled, learning causes LTD of the synaptic weight via term $(-\alpha_z Cz_j)$. If $C = 0$, then $z_j$ spontaneously recovers via term $(k_j - z_j)$. This allows the initially arbitrary weights $k_j$ and $z_j$ to balance such that $k_j$ equals $z_j$ in the absence of the US. The same US teaching signal $C$ is distributed to all Purkinje cell dendrites that carry the $x_j$ spectrum.

The Purkinje cell population activity, $p$, projects to a population of nuclear cells. This projection is inhibitory as determined experimentally (Ito, 1984). Within the interpositus nucleus there are two types of neurons receiving the cortical projection, large projection neurons that carry the CR, and small neurons that form local inhibitory circuits within the interpositus. These components of the model are shown in Figure 6. The nuclear cells also receive a direct excitatory input from the

Figure 6. Basic components and variables of cerebellar adaptive timing model. Inhibitory neurons, black; Excitatory neurons, white. PN, pontine nucleus; IO, inferior olive. Explanations of variables in text.
mossy fibers carrying the CS representation, s (Steinmetz & Sengelaub, 1992). This connection is made through an adaptive weight w. The large projection nuclear neuron activity is governed by

\[
\frac{dq}{dt} = \gamma_q (-q + sw - p - f_r(r)) \tag{10}
\]

with

\[
f_r(r) = \frac{([r - \mu_r]^+)^2}{\sigma_r^2 + ([r - \mu_r]^+)^2} \tag{11}
\]

being the signalling function of the local circuit inhibitory nuclear neuron. The local circuit neuron activity is governed by

\[
\frac{dr}{dt} = -\alpha_r r - \gamma_r p + \beta_r (1 - r) (s + q) \tag{12}
\]

We assume that this local circuit neuron, due to its small size, is strongly influenced by Purkinje cell inhibition such that it remains inactive for most normal operation. This interneuron serves to transform all tonic mossy fiber inputs into the cerebellar nuclear cell into phasic outputs whenever Purkinje cell activity is so low that it is disinhibited. As shown below, it enables us to simulate the short duration response observed by Perrett et al. (1993) following cortical ablation.

Since the climbing fiber that the large nuclear cell receives is the teaching signal, this allows the US to affect a weight adjustment at the mossy fiber-nuclear cell synapse. This weight adjustment is modeled by

\[
\frac{dw}{dt} = s \left( -\alpha_w w + \beta_w (1 - w) C \right) \tag{13}
\]

In this case, initially \( w=0 \) and LTP is produced by conjunctive s and C activity. LTD is produced at lower depolarizations by activation of s alone.

7. Simulations of the Model for Adaptive Timing in the Cerebellum

To demonstrate the effectiveness of the model given in equations (1)-(13), the results of simulations of these equations are presented in this section. A single set of parameters was used for all the simulation results presented below.
The \( x_i \)'s spectrum of integration rates, the \( \alpha_i \)'s, are randomly-selected values from the interval \([1.35,12]\). This interval of rates is chosen to generate a spectrum spanning at least 1s and to prevent learning of CRs at very short ISIs. The number \( N \) of spectral components is chosen to be 100. The inhibitory interneuron weights \( k_i \) are also chosen randomly from the interval \([0.25,1.25]\). Figure 7 depicts the inhibitory spectral components \( f(x_i)k_i \) for the simulations. The adaptive weights \( z_j \) are initialized nominally to 1. Prior to paired training, an initial phase of the simulation balances the initial random differences between the excitatory and inhibitory pathways by equation (9).

To simplify the computation each signal \( x_j, G_j, \) and \( z_j \), given by equations (2), (4), and (9), was integrated independently using a fourth order Runge-Kutta algorithm. The remaining differential equations were also integrated independently using the Runge-Kutta fourth order method. A fixed time step of 0.01 was used for all simulations. Other parameters used in the simulations are \( \alpha_s=0.2, \beta_s=10, \alpha_G=0.1, \beta_G=5, \gamma_G=0.02, \alpha_r=12, \beta_r=4, \delta=0.1, \gamma_p=0.9, \alpha_p=10, \beta_p=1, \gamma_d=100, \alpha_c=0.05, \mu_c=0.2, \alpha_t=5, \beta_t=30, \gamma_t=200, \alpha_w=0.001, \) and \( \beta_w=10 \). To simulate the delay conditioning paradigm, CS input was set to 1 for \( t>0 \), and the US signal \( C \) is set to 1 for a single time step at the designated ISI. The duration of each simulated trial was 1s. That is, a trial lasted from the onset of the CS at \( t=0 \), through the US period, to \( t=1s \). These 1s trials were repeated to produce conditioning. Figure 8 shows the progress of the Purkinje cell activity \( p \) during learning over 100 CS-US pairings with an ISI of 0.5s. This conditioning followed 100 trials without a US to allow the balancing of the \( k_i \)'s and \( z_i \)'s. Figure 9 shows the progress of the nuclear cell output \( q \) for this same simulation. The reason for the difference in the \( q \) traces from those of \( p \) is that \( q \) is also influenced by learning at the nuclear cell level. Note that a nuclear cell response has been sculpted out of the random initial spectrum as shown in Figure 7. This nuclear cell response has a peak near the expected time of the US and the topography of the nuclear cell response models the behavioral topography of the CR. In addition, as learning progresses the onset latency of the response gradually shifts in time toward the CS onset time.

A dual-ISI paradigm was also simulated for this model. CS-US pairings were made with alternating 0.25s and 0.7s ISIs. Figure 10 shows the nuclear cell response \( q \) on the first 20 extinction trials after 100 such pairings. The model clearly demonstrates the double-peaked response observed in the rabbit NMR experiments (Figure 1). Assuming that the strength of the CR activity profile corresponds to a behavioral rate of responding, Figure 10 also demonstrates that the rate of responding is dependent on ISI. Figure 11 shows this dependency in more detail.

For Figure 11, paired conditioning was first performed at an ISI of 0.65s until the CR reached asymptotic levels. Conditioning at this ISI was then terminated and
**Figure 7.** The random spectrum $f(x_j)k_p$, $j=1,\ldots,100$, for the cerebellar adaptive timing model. Parameters given in text.

**Figure 8.** Progressive reduction of Purkinje cell output $p$ over 100 CS-US pairings with an ISI of 0.5s. Each line is the trace of the signal over 1 second of simulation. Parameters given in text.

**Figure 9.** Increase of nuclear cell output $q$ over 100 CS-US pairings with an ISI of 0.5s. Each line is the trace of the signal over 1 second of simulation. Parameters given in text.
Figure 10. Doubled-peaked nuclear cell output $q$ on the first 20 extinction trials after 100 CS-US pairings with alternating ISIs of 0.25s and 0.7s. Parameters in text.

Figure 11. Progress of nuclear cell response $q$ during conditioning first at an ISI of 0.65s, followed by conditioning at an ISI of 0.35s, and finally at an ISI of 0.15s. Every third trial is shown. Parameters in text.

Figure 12. Nuclear cell response $q$ after conditioning and cortical ablation. Following the conditioning experiment of Figure 9, $p$ is set to zero. Parameters given in text.
conditioning at an ISI of 0.35s begun. As shown in the Figure a discrete peak shift occurred to the new ISI. That is, a CR with a peak at 0.35s began to develop while the peak at 0.65s decayed. When the CR at 0.35s reached asymptotic levels of responding, the ISI was again changed, this time to 0.15s. A second discrete peak shift occurred. Figure 11 clearly shows that the dependency of the CR on ISI is an invert-U shaped function with a maximum near 0.4s.

Ablation of the cerebellar cortex in this model, obtained by setting \( p=0 \) in equations (10) and (12), yields the nuclear cell response topography observed by Perrett et al. (1993) in the NMR (Figure 12). Once \( w \) has become potentiated through conditioning, removal of Purkinje cell input allows a large amplitude response to s. In the absence of Purkinje cell inhibition, this response is quickly shut off by the inhibitory local circuit neuron, resulting in a small, phasic response similar to that observed by Perrett et al (1993). This is shown in Figure 12 when the simulation of Figure 9 was followed by cortical ablation.

8. Discussion

The spectral timing model proposed for the cerebellum in this paper is analogous to the hippocampal spectral timing model. As in the hippocampal model, timed responses are assumed to be generated at many different local sites, the outputs of these sites are adaptively filtered and pooled to derive an accurately timed response, and the timed response acts to gate the outputs of a fast pathway in the network. The spectral timing model for the cerebellum reproduces the key features of the behavioral and physiological data outlined in Sections 2 and 3. In particular, CR peak amplitude occurs at US onset (Figure 9); CR onset latency decreases during training (Figure 9); a discrete CR peak shift occurs with a change in ISI (Figure 11); mixed training at two different ISIs produces a double-peaked CR (Figure 10); CR acquisition and rate of responding is an inverted-U function of ISI with a maximum at about 400ms (Figure 11); the interpositus nuclear cell response matches CR topography (Figure 9); Purkinje cell activity decreases during the CS-US interval (Figure 8); and finally, following cortical ablation, a maladaptively-timed, small-amplitude CR is generated (Figure 12).

The mechanism described in Section 6 for spectrum generation utilizes the Golgi feedback circuit to produce phasic responses from a tonic input. It has previously been recognized, based on the cerebellar anatomy, that Golgi cell inhibition should quench tonic parallel fiber activity allowing only a phasic response (Llinás & Walton, 1990). Spectrum production also depends on the distribution of values of \( \alpha_i \), which appear as rate variables in the granule cell activations. This suggests an interpretation in terms of membrane time constants. However, when equation (2) is reexpressed as
it becomes clear that $\alpha_j$ can also be thought of as a connection strength variable that applies to both Golgi and mossy fiber inputs to granule cells. This suggests an interpretation in which spatial gradients are used to create the temporal spectrum. A similar mechanism was used in the adaptive filter model of the cerebellum proposed by Fujita (1982a). This mechanism relies on variation in the transmission efficacy from mossy fibers to granule cells, as in (14), for the generation of a spectrum of phase shifts to a sinusoidal input. Due to its linear formulation, Fujita’s model only works for periodic inputs of sufficient frequency. The spectral timing model on the other hand is designed to handle the discrete events characteristic of classical conditioning paradigms. This requires that a temporal response which lasts far into the future be generated from a singular event.

In support of Fujita’s model, Ito (1984) cited experimental evidence for a distribution of phase shifts in the simple spike response of floccular Purkinje cells with vestibular stimulation. In the NMR preparation, long-duration Purkinje cell activity following CS onset is supported by Purkinje cell recordings (Berthier & Moore, 1986; Thompson, 1990). However, we are not aware of direct evidence for long-duration activities in granule cells or parallel fibers. Therefore, it is possible that the long-duration activity observed in Purkinje cells may be due to other mechanisms.

Our research has considered several different mechanisms for timing in the cerebellum, although only one is presented above. One alternative is to shift the site of signal attenuation to the parallel fiber-Purkinje cell synapses, such that transmission at the synapse is gradually inactivated during the response. This formulation retains the computational form of the original Grossberg-Schmajuk proposal, and posits slow rise times for the responses from the Golgi-granule cell system. To completely avoid long-duration responses on parallel fibers, a model must rely on the intrinsic dynamics of Purkinje cells. Purkinje cells are known to exhibit complex \( Ca^{++} \) dynamics in the dendrites which can \textit{interalia} lead to long-duration plateau potentials \textit{in vitro} (Llinás & Sugimori, 1980, 1992). We have developed models of Purkinje cell \( Ca^{++} \) dynamics which demonstrate the feasibility of this approach for timing responses. The degree to which such mechanisms act \textit{in vivo} needs further experimental study.

Other researchers have proposed cerebellar models which perform a timing function in the NMR preparation (Bartha, Thompson & Gluck, 1991; Braitenberg, 1961; Moore, Desmond & Berthier, 1989). The Bartha et al. model utilizes sinusoidal inputs of different frequencies to the cerebellar cortex. The cortex performs a

\[
\frac{dx_j}{dt} = (1 - x_j) \alpha_j s - (x_j + \delta) \beta x \alpha_j G_j
\]
Fujita-like adaptive filtering operation on these signals to extract a behaviorally relevant timing signal (Gluck, Reifsnider & Thompson, 1990). A limitation with this model is that the signals are not generated within the cerebellar circuitry. This makes it difficult to explain the Steinmetz (1990) data where non-sinusoidal, direct mossy fiber stimulation is used as a CS. This functionality may be able to be recovered by the use of recurrent pathways within the cerebellum to set up oscillations of different frequencies.

Delay lines are used to obtain the long-duration responses in the Braitenberg and Moore et al. models. Brainstem delay line mechanisms are known, as in sound localization circuitry (Carr & Konishi, 1988), but these appear to provide delays of no more than a few milliseconds. Similarly, the signal propagation delay that could be produced along a parallel fiber appears to be limited to about 25ms, given that parallel fibers are not more than 5mm long and conduct at about 0.2m/s (Freeman, 1969). To get behaviorally significant delays with this approach, it appears that signals would have to be recurrent to the cerebellar cortex. In fact, recurrent pathways do exist from Purkinje cell targets to parallel fibers (Chan-Palay, 1977), but their functional role has yet to be determined. The modeling and functional importance of these and other recurrent pathways both within the cerebellum and between epi-cerebellar structures remains to be addressed.

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