Journal of Computational Neuroscience 5, 17–33 (1998)

A Mathematical Model of the Cerebellar-Olivary System I: Self-Regulating Equilibrium of Climbing Fiber Activity

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Received March 5, 1997; Revised March 5, 1997; Accepted May 16, 1997

Action Editor: Eve Marder

Abstract. We use a mathematical model to investigate how climbing fiber-dependent plasticity at granule cell to Purkinje cell (gr→Pkj) synapses in the cerebellar cortex is influenced by the synaptic organization of the cerebellar-olivary system. Based on empirical studies, gr→Pkj synapses are assumed to decrease in strength when active during a climbing fiber input (LTD) and increase in strength when active without a climbing fiber input (LTP). Results suggest that the inhibition of climbing fibers by cerebellar output combines with LTD/P to self-regulate spontaneous climbing fiber activity to an equilibrium level at which LTP and LTD balance and the expected net change in gr→Pkj synaptic weights is zero. The synaptic weight vector is asymptotically confined to an equilibrium hyperplane defining the set of all possible combinations of synaptic weights consistent with climbing fiber equilibrium. Results also suggest restrictions on LTP/D at gr→Pkj synapses required to produce synaptic weights that do not drift spontaneously.

Keywords: long-term depression, long-term potentiation, parallel fiber, Purkinje cell

The comprehensive characterization of cerebellar anatomy and synaptic physiology provided in large part by Eccles et al. (1967), and by many others, has permitted subsequent research to address the functions and information processing of the cerebellum at a relatively specific and detailed level of analysis. For example, much of the work investigating the cerebellum's possible role in motor learning was anticipated by Marr's (1969) explicitly stated theory suggesting how climbing fiber-dependent plasticity at synapses in the cerebellar cortex could mediate motor learning. Although considerable evidence indicates that the cerebellum mediates several well-characterized forms of motor learning, many quite disparate ideas regarding the function of the cerebellum remain the subject of spirited debates. We believe, as Marr apparently did, that resolution of these issues will arise in large part from an understanding of the information processing task that is accomplished by the synaptic organization of the cerebellum. This goal seems relatively tractable since the same simple synaptic organization is repeated throughout the extent of the cerebellum. This uniformity suggests that the cerebellum performs a single computation that is applied to all functions it performs, whether they are motor, sensory, or cognitive. This may provide the opportunity to apply information derived from relatively tractable forms of motor learning to a better understanding of the potential cerebellar contribution to nonmotor and perhaps even cognitive tasks such as timing (Keele and Ivry, 1990; Ivry, 1993), shifting attention (Akshoomoff and Courchense, 1992), language (Leiner et al., 1993), and sensory acquisition (Gao et al., 1996).

One of the many advantages provided by the extent to which the synaptic organization of the cerebellum has been characterized is the ability to augment empirical

studies with biologically constrained computer simulations, mathematical models, and explicitly stated, neuron-based theories. Indeed, numerous models of cerebellar function have been proposed (Braitenberg, 1967; De Schutter, 1995; Eccles, 1973; Llinas and Walton, 1979; Pellionisz and Llinas, 1979, 1980), many attempting to relate synaptic changes to motor learning (Albus, 1971; Bullock et al., 1994; Fujita, 1982; Gilbert, 1974; Marr, 1969; Mauk, 1997; Mauk and Donegan, 1997; Raymond et al., 1996; Thach, 1980; Thach et al., 1992).

Here we employ a mathematical model of the cerebellar-olivary system (the cerebellum and its climbing fiber input from the inferior olive) to address the specific information processing that is accomplished by the cerebellum. In particular, we address the functional consequences of the low frequency (1 to 4 Hz) and fairly regular spontaneous activity of climbing fiber inputs to the cerebellum. As noted by Gilbert (1975), this activity poses difficult problems for motor learning theories of cerebellum, which generally suppose that (1) climbing fibers are activated by movement errors or commands, (2) these inputs induce plasticity (LTD) at coactive gr→Pkj synapses, and (3) this plasticity improves subsequent execution of the same movement. This raises the question as to what prevents spontaneous activity of climbing fibers from saturating LTD at all gr→Pkj synapses, which would preclude the possibility that those synapses could store memories of previous motor adaptation.

To address this issue we constructed a mathematical representation of the cerebellar-olivary system that incorporates an explicit rule for bidirectional plasticity at gr→Pkj synapses (that is, both LTD and LTP) that is based on previous empirical findings (Ito, 1989; Sakurai, 1989). In short, gr→Pkj synapses are assumed to decrease in strength when active in the presence of a climbing fiber input (LTD) and increase when active in the absence of a climbing fiber input (LTP).[1] Since this rule implies that gr→Pkj synapses are modified each time they are active, the spontaneous activity of climbing fibers would make the strength of gr→Pkj synapses sensitive to the proportion of times that synapse activity results in LTD relative to LTP. The main result of our analysis is that spontaneous climbing fiber activity may be self-regulated by the connectivity of the cerebellar-olivary system to an equilibrium level at which the effects of LTD and LTP balance and the expected net change in gr→Pkj synaptic weights would be zero. In contrast, our results suggest that alternative rules for the induction of LTP that do not require gr→Pkj synaptic activity would promote runaway changes in synaptic weights or would require the absence of spontaneous climbing fiber activity. These results imply that the spontaneous activity of climbing fibers, when regulated by cerebellar output, may help maintain gr→Pkj synaptic weights constant unless systematically perturbed—as may occur when movements require adaptation.

Methods

Core Assumptions of the Model

The basic approach we employ is to construct a series of mathematical relations that capture the basic features of the synaptic organization of the cerebellum, of LTD and LTP at gr→Pkj synapses, and that represent the activity of each cell in terms of its synaptic inputs. These equations can then be used to analyze the qualitative relationships between activity, plasticity, and the circuitry of the cerebellum. Mathematical feasibility of this analysis requires the model to be linear. Specifically, this means that the activity of each cell is determined by the linear sum of its active excitatory inputs minus the sum of its active inhibitory inputs. This linear assumption is clearly not biologically accurate, but it provides an approximation of the overall tendency of neurons to be more active as their excitatory inputs increase and less active with increasing inhibitory input. This approximation may be especially reasonable for the cerebellum since the spontaneous activity of Purkinje cells, nucleus cells, and climbing fibers suggests that each excitatory and inhibitory input has the opportunity to increase or decrease postsynaptic activity. The other linear limitation is that synaptic weights must be unbounded (that is, there is no maximum or minimum limit). Our results suggest that biologically relevant nonlinearities can be added without qualitatively changing the conclusions of the present model, and results from computer simulations in which bounded synaptic weights and nonlinear input/output functions have been incorporated support this expectation (Medina and Mauk, 1995).

Cerebellar-Olivary Synaptic Organization

The synaptic organization of the cerebellar-olivary system relevant to the present model is shown

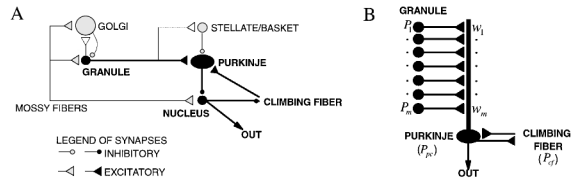

Figure 1. A schematic representation of the synaptic organization of the cerebellum. A. The components of the cerebellum addressed in the present model are depicted with solid lines and symbols. Purkinje cells receive excitatory synaptic inputs from a large number of granule cells and from a single climbing fiber. Cells in the cerebellar nuclei, which provide the output of the cerebellum, are inhibited by Purkinje cells and inhibit climbing fibers. These projections are topographically organized such that a Purkinje cell appears to contribute to the modulation of its own climbing fiber. B. A schematic representation of the model. Each granule cell is assumed to have a background level of activity P_i, and the excitatory synapse onto the Purkinje cell has a strength or weight w_i. Purkinje activity P_{pc} is determined by the linear sum of the m synaptic currents $\{P_i w_i\}$. The pathway from Purkinje cells through nucleus cells to climbing fibers contains two inhibitory synapses and is, for simplicity, modeled as a direct excitatory connection.

schematically in Fig. 1A. Each Purkinje cell receives excitatory synaptic inputs from a large number of granule cells (80,000 to 200,000) and from a single climbing fiber (Ito, 1984). Purkinje cells inhibit neurons in the cerebellar nuclei that, in turn, inhibit climbing fibers both directly (Anderson et al., 1988; Angaut and Sotelo, 1989; de Zeeuw et al., 1989) and possibly via the red nucleus (Weiss et al., 1990). Since anatomical and electrophysiological evidence suggests that these projections are topographically organized (Armstrong et al., 1974; Groenewegen and Voogd, 1977; Groenewegen et al., 1979; Houk and Gibson, 1986; Oscarsson, 1980; Ruigrok and Voogd, 1990; Yu et al., 1985), we assume that Purkinje activity influences its own climbing fiber input. Since the pathway from the cerebellar cortex to the inferior olive contains two inhibitory synapses in series, we employ the simplification shown schematically in Fig. 1B in which the pathway from the cerebellar cortex to the inferior olive is treated as a direct excitatory connection.

Although many Purkinje cells, nucleus cells, and climbing fibers are undoubtedly involved in the production of a particular movement, the regular synaptic organization of the cerebellar cortex suggests that the activity of the cells shown in Fig. 1B may be taken as representative of their respective populations. We therefore consider only a single Purkinje cell and its associated climbing fiber.

Generalized LTD/P

Based on empirical observations (Ito, 1989; Ito and Kano, 1982), we assume in the present model that LTD is induced by pairing gr→Pkj synaptic activity with climbing fiber input. The implementation of generalized LTD then requires an additional rule for LTP, specifying the circumstances in which gr→Pkj synapses increase in strength. Based on empirical data and supported by theoretical results described below, we incorporate the rule that gr→Pkj synapses increase in strength when active in the absence of a climbing fiber input. Since both LTD and LTP require the synapse to be active, we refer to this rule as gr→Pkj driven, generalized LTD (LTD/P).

To formalize this LTD/P rule we use discrete time steps of duration Δt, chosen to approximate the period of influence over which a single climbing fiber input promotes LTD in coactive gr→Pkj synapses. Studies suggests that Δt is likely to be in a range from tens to hundreds of ms (Ekerot and Oscarsson, 1981; Tank et al., 1988), although the precise value is not critical to the arguments that follow. Next we make the simplifying assumption that during any given time step both climbing fiber and granule inputs can be modeled as stochastic processes such that P_{cf} is the probability of a climbing fiber spike and P_i is the probability of a spike (or burst of spikes, depending on which is required for the induction of plasticity) in the ith gr→Pkj synapse[2]. Let w_i denote the current weight of the ith gr→Pkj synapse, and let δ^- denote the decrement in synaptic weight produced by a single LTD event. On any given time step the change in w_i due to LTD, denoted by Δw_i^{LTD}, can then be approximated by the expression

$$\Delta w_i^{\text{LTD}} = -\delta^- P_i P_{\text{cf}} \tag{1}$$

showing that on average the ith gr→Pkj synaptic weight undergoes a decrement in magnitude of size δ^- proportional to the joint probability that the synapse is active and a climbing fiber input is present. Similarly, letting δ^+ denote the increment in synaptic weight produced by a single LTP event, the change in w_i due to LTP (Δw_i^{LTP}) can be approximated by the expression

$$\Delta w_i^{\text{LTP}} = \delta^+ P_i (1 - P_{\text{cf}}). \tag{2}$$

These two expressions may then be combined into a single equation for the expected change in synaptic

weight, $\Delta w_i = \Delta w_i^{\mathrm{LTD}} + \Delta w_i^{\mathrm{LTP}}$, on any given time step,

$$\Delta w_i = P_i[\delta^+(1 - P_{\mathrm{cf}}) - \delta^- P_{\mathrm{cf}}]. \tag{3}$$

Linear Input/Output Relations

As noted above, mathematical feasibility requires the assumption that the input-output properties of both Purkinje cells and climbing fibers can be reasonably approximated by linear functions. Thus, a measure of the expected value of the Purkinje cell membrane current arising from a single gr→Pkj synapse is given by the synaptic weight w_i multiplied by the probability that the synapse is active, P_i. The total current I_{pc} is then given by the sum of such terms over all gr→Pkj synapses,

$$I_{\mathrm{pc}} = \sum_{i=1}^{m} w_i P_i = \vec{w} \cdot \vec{P}, \tag{4}$$

where m is the number of gr→Pkj synapses and the second equality introduces a convenient vector notation that we will employ extensively.

The average number of Purkinje cell simple spikes per time step, P_{pc}, is then taken to be a linear function of the synaptic current generated by granule cell input,

$$P_{\mathrm{pc}} = I_{\mathrm{pc}}, \tag{5}$$

where the weights are scaled such that $0 \leq P_{\mathrm{pc}} \leq 1$. The actual Purkinje cell activity is then given by $P_{\mathrm{pc}} \cdot P^{\max}$, where $P^{\max}$ is the maximum number of spikes possible in a time step.

To obtain an expression for the probability of a climbing fiber spike, P_{cf}, we again assume a linear dependence on the effective excitatory influence from Purkinje cells,

$$P_{\mathrm{cf}} = P_{\mathrm{pc}}. \tag{6}$$

Results

Spontaneous Climbing Fiber Activity is Regulated to an Equilibrium Level

Setting the right side of Eq. (3) to zero yields an expression for the level of spontaneous climbing fiber activity at which the effects of LTD and LTP balance and the expected net change in gr→Pkj synaptic weights is zero,

$$P_{\mathrm{cf}}^{(\infty)} = \delta^+/(\delta^+ + \delta^-), \tag{7}$$

where we use the term $P_{\mathrm{cf}}^{(\infty)}$ to represent the equilibrium climbing fiber firing probability. We call this the equilibrium level of spontaneous climbing fiber activity because at this level gr→Pkj synaptic weights, Purkinje activity, and climbing fiber activity remain constant. By substituting this definition of $P_{\mathrm{cf}}^{(\infty)}$, Eq. (3) may be rewritten in the more intuitive form

$$\Delta w_i = P_i(\delta^+ + \delta^-)\big[P_{\mathrm{cf}}^{(\infty)} - P_{\mathrm{cf}}\big], \tag{8}$$

showing that for LTD/P, synaptic weights decrease when climbing fiber activity is greater than the equilibrium value ($P_{\mathrm{cf}} > P_{\mathrm{cf}}^{(\infty)}$), increase when the climbing fiber activity is less than the equilibrium value ($P_{\mathrm{cf}} < P_{\mathrm{cf}}^{(\infty)}$), and show no net change when climbing fiber activity is in equilibrium ($P_{\mathrm{cf}} = P_{\mathrm{cf}}^{(\infty)}$).

We now show that LTD/P combines with the synaptic organization of the cerebellar-olivary system to produce a self-regulating equilibrium in which P_{cf} is driven to the equilibrium value $P_{\mathrm{cf}}^{(\infty)}$ from any initial point. This behavior can be illustrated by a simple example. When climbing fiber activity is above equilibrium, LTD events would be favored over LTP events (relative to their equilibrium ratio), and gr→Pkj synaptic weights would drift downward. This would decrease both Purkinje cell and climbing fiber activity until climbing fiber equilibrium is reached. An inverse series of events would restore equilibrium when climbing fiber activity is below equilibrium.

This self-regulating equilibrium can be demonstrated explicitly by combining Eq. (8) for the change in synaptic weights with Eq. (6) for the coupling between Purkinje cells and climbing fibers. This yields an expression for the change in climbing fiber activity in terms of the current value of P_{cf},

$$\Delta P_{\mathrm{cf}} = -\frac{1}{N}\big[P_{\mathrm{cf}} - P_{\mathrm{cf}}^{(\infty)}\big], \tag{9}$$

where the number of time steps to relax to equilibrium is represented by the parameter N, given by

$$N = \frac{1}{\vec{P}^2(\delta^+ + \delta^-)}. \tag{10}$$

(The actual time required for climbing fiber activity

to relax back to the equilibrium level is then given by $\tau = N\Delta t$.)

Equation (9) shows that the change in climbing fiber activity is proportional to the difference between the current and equilibrium levels of climbing fiber activity. Since the proportionality constant is negative, the level of climbing fiber activity will decay to the equilibrium value from any initial point.

This self-regulating property of the cerebellar-olivary system is illustrated in Fig. 2. The influence of LTD alone is shown in Fig. 2A, where the expected change in synaptic weights (Δw_i) is shown as a function of climbing fiber activity (upper panel).

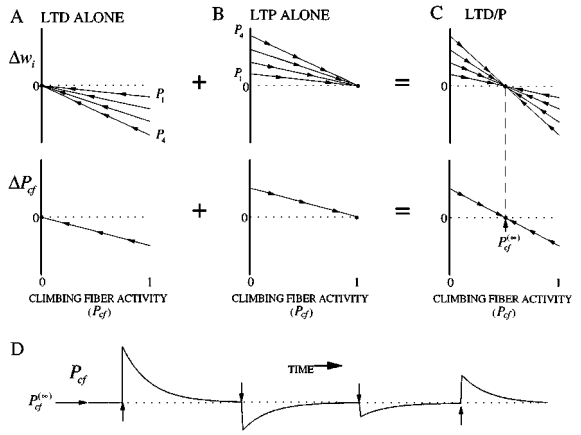

Figure 2. In combination with the synaptic organization of the cerebellum, LTD/P leads to a stable equilibrium at which the expected net change in climbing fiber activity and the expected net change in gr→Pkj synaptic weights are zero. A. The action of LTD alone on the expected change in synaptic weights (top panel) and the expected change in climbing fiber activity (bottom panel) as a function of the current climbing fiber activity. Unopposed by LTP, gr→Pkj synaptic weights would decrease in proportion both to the level of climbing fiber activity and to the activity of the synapse. The behavior for four arbitrary levels of background activity is shown, where P_1 through P_4 represent increasing levels of activity. Decreases in synaptic weights would lead to decreases in climbing fiber activity (shown by flow arrows) until both climbing fiber activity and the expected change in gr→Pkj synaptic weights are zero. B. The same analysis applied to the action of LTP alone. Synaptic weights would increase in proportion to the activity of the synapse with a magnitude that decreases in proportion to climbing fiber activity. Synaptic weights and climbing fiber activity would increase until climbing fibers are always active and no further LTP is possible. C. Combining LTD and LTP produces a stable equilibrium. Climbing fiber activity is driven to an equilibrium value $P_{\mathrm{cf}}^{(\infty)}$, at which the expected change in climbing fiber activity is zero (bottom panel) and the expected net change in all gr→Pkj synaptic weights is also zero, independent of their activities (top panel). D. Solutions to Eq. (9) show the return of climbing fiber activity to the equilibrium value following positive or negative perturbations (arrows). The number of time steps to approach equilibrium is given by Eq. (10).

According to Eq. (1), Δw_i decreases linearly with P_{cf} with a slope that is proportional to background activity of the synapse (P_i) such that the expected change in synaptic weights is zero when climbing fiber activity is zero. The figure shows this relationship for four levels of background activity (P_1 through P_4 arranged smallest to largest). As shown in the lower panel, Eq. (9) predicts that under the action of only LTD (when $\delta^+ = 0$ and thus $P_{\mathrm{cf}}^{(\infty)} = 0$), ΔP_{cf} also decreases linearly with P_{cf} with an intercept at $P_{\mathrm{cf}} = 0$. Thus, in the absence of LTP, synaptic weights would decrease at a rate proportional to their background activity while simultaneously driving climbing fiber activity to zero, as illustrated by the direction of the arrows in Fig. 2A.

Similarly, the influence of LTP alone is shown in Fig. 2B. According to Eq. (2), the expected change in synaptic weights decreases linearly with P_{cf} with a slope that again is proportional to background activity, P_i, but where the family of curves now intercepts the abscissa at $P_{\mathrm{cf}} = 1$. Likewise, it follows from Eq. (9) that under the action of LTP alone (when $\delta^- = 0$ and thus $P_{\mathrm{cf}}^{(\infty)} = 1$), ΔP_{cf} will decrease linearly as P_{cf} increases such that $\Delta P_{\mathrm{cf}} = 0$ at $P_{\mathrm{cf}} = 1$. As indicated by the arrows, synaptic weights increase under the influence of LTP alone until climbing fiber activity reaches $P_{\mathrm{cf}} = 1$.

When these LTD and LTP rules are combined to form a single LTD/P rule, the relationships depicted in Fig. 2C are obtained. There is now a common intercept for the family of curves at a value of P_{cf} between zero and one. This means that all gr→Pkj synaptic weights are stable (that is, do not drift) at the equilibrium level of climbing fiber activity regardless of their background level of activity. This is the key factor that provides for the stability of synaptic weights. As shown explicitly by Eq. (9) and indicated by the arrows depicting the direction of flow, the level of climbing fiber activity is always driven toward the common equilibrium point at which ΔP_{cf} and each Δw_i are zero. Solutions to Eq. (9) are plotted in Fig. 2D, which shows P_{cf} as a function of time. Following any perturbation away from equilibrium, the level of climbing fiber activity returns exponentially to the equilibrium value, $P_{\mathrm{cf}}^{(\infty)}$, where the number of time steps to return to equilibrium is given by Eq. (10).

Not All Combinations of gr→Pkj Synaptic Weights are Possible

The results presented above suggest that LTD/P combines with the synaptic organization of the cerebellar-

olivary system to produce a self-regulating equilibrium level of climbing fiber activity at which the expected net change in all gr→Pkj synaptic weights is zero. These results imply that not all combinations of gr→Pkj synaptic weights are possible. Given the set of background activities for all gr→Pkj synapses, $\{P_i\}$, only those synaptic weight vectors that produce an equilibrium level of Purkinje cell activity are stable. For example, two cases in which all gr→Pkj synaptic weights are either very large or very small could not both sustain an equilibrium level of climbing fiber activity. If the system were at equilibrium when all the weights were at one extreme, shifting the weights to the other extreme would result in activity that was either above or below equilibrium.

One technique for visualizing this limited set of stable weight vectors is to use a graphical representation of a synaptic weight vector space as shown for two dimensions (two synapses) in Fig. 3A. Each axis represents the weight of a single gr→Pkj synapse, and each combination of weights for the two synapses is represented by a unique point in this two-dimensional space. The length of each axis corresponds to the physiological range over which the synaptic weight can vary. For this two-dimensional example the synaptic weight combinations that accomplish climbing fiber equilibrium fall along a line, as shown in Fig. 3B. This can be demonstrated by noting that equilibrium requires that $\sum w_i P_i = P_{\text{pc}}^{(\infty)}$, which for two synapses takes the form of the equation for a line ($w_2 = \frac{-P_1}{P_2} w_1 + \frac{P_{\text{pc}}^{(\infty)}}{P_2}$). Since the slope term is $-P_1/P_2$, the orientation of this equilibrium line is determined by the set of background activity values $\{P_i\}$. This can be illustrated graphically by ploting the background activity vector ($\vec{P}$) in a two-dimensional space as shown in Fig. 3C (note that for clarity the axes have been inverted to avoid overlap with the $\vec{w}$-vector space). Since the slope of the activity vector is P_2/P_1, the equilibrium line (with slope $-P_1/P_2$) is perpendicular to $\vec{P}$. In this two-dimensional example, P_1 is larger than P_2, which reduces the potential set of circumstances in which w_1 can be large relative to w_2. Thus, the likelihood that a synaptic weight can be strong decreases as its background activity increases.

This graphical representation is useful for illustrating three points. First, the equilibrium line describes the set of synaptic weight combinations that produce an equilibrium level of climbing fiber activity. Second, if the synaptic weight vector does not lie on the equilibrium line, then climbing fiber activity will be different from the equilibrium value, and this will lead to synaptic changes that return the weight vector to the equilibrium line. Third, since Eq. (8) shows that

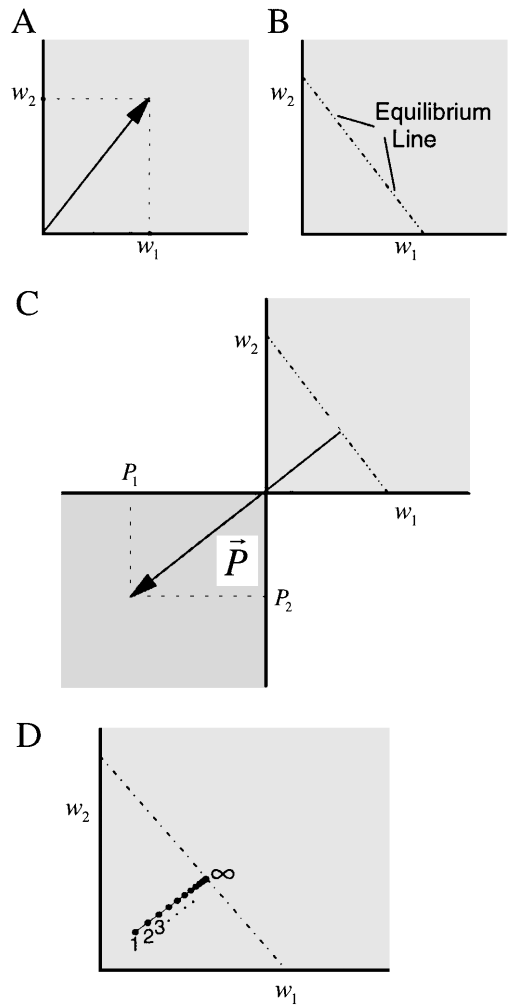

Figure 3. A geometric interpretation of the constraints imposed on the synaptic weight vector by climbing fiber equilibrium. A. All combinations of synaptic weights (all synaptic weight vectors) can be represented in a hypothetical space in which each dimension represents the weight of an individual synapse. A two-dimensional space for two synapses is shown. Each point in this space (shaded region) corresponds to a unique combination of synaptic weights where the magnitude of each weight is given by the projection onto the associated axis. B. To satisfy the equilibrium condition $\vec{w} \cdot \vec{P} = P_{\text{pc}}^{(\infty)}$, stable synaptic weight vectors are restricted to a surface that has one dimension less than the weight vector space—an equilibrium hyperplane for a large number of synapses—but in this two-synapse example it is an equilibrium line. The equilibrium hyperplane/line represents the space of all possible weight vectors consistent with equilibrium levels of Purkinje cell and climbing fiber activity. C. The orientation of the equilibrium hyperplane is determined by the background activity of the gr→Pkj synapses, $\vec{P}$. This is illustrated by plotting the background activity vector $\vec{P}$ in a two-dimensional space (darker shading) with the axes inverted with respect to the synaptic weight vector space (lighter shading). An arbitrarily selected granule cell activity vector is shown. The equilibrium line is perpendicular to $\vec{P}$. D. Following a fixed perturbation, the weight vector would return exponentially along a perpendicular to the equilibrium hyperplane, depicted here as a sequence of steps (1, 2, 3, . . . , ∞).

changes in the weight vector are proportional to $\vec{P}$, the weight vector will return to the equilibrium line via the shortest path, along the axis of $\vec{P}$ and perpendicular to the equilibrium line, as shown in Fig. 3D.

LTP Must be gr→Pkj Driven

Although there is a growing appreciation that synaptic plasticity must be bidirectional or generalized (Artola et al., 1990; Dudek and Bear, 1993; Mulkey and Malenka, 1992), the originally studied forms of plasticity, such as hippocampal long-term potentiation (LTP) and cerebellar LTD, are far better characterized than their counterparts—hippocampal LTD and cerebellar LTP. With this in mind, we have used the present mathematical model to investigate the behavior expected when LTD is generalized by other forms of LTP. From this analysis, we identify properties required of LTP rules to achieve stability of synaptic weights within the cerebellar-olivary system—properties displayed by the form of LTP that has been observed empirically.

We begin by considering the appearance of gr→Pkj synapse and climbing fiber stability when Δw_i and ΔP_{cf} are plotted as functions of P_{cf}. First, Fig. 2C (lower panel) shows that when climbing fiber activity is stable, ΔP_{cf} plotted as a function of P_{cf} has a negative slope and crosses zero at a value of P_{cf} between zero and one. Second, when gr→Pkj synapses are stable, each line describing Δw_i as a function of P_{cf} crosses zero at the same value of P_{cf} where ΔP_{cf} is also zero (Fig. 2C, upper panel). In contrast, Fig. 4 provides a graphical illustration of unstable synaptic weights. Although climbing fiber activity is depicted as stable in this example, the lines describing Δw_i as a function of P_{cf} cross zero at different values of P_{cf}. Thus, at the level to which P_{cf} is asymptotically driven, many of the synaptic weights are either increasing or decreasing. It is clear that in this case there exists no single value of climbing fiber activity at which all synaptic weights could be stable.

Comparison of Figs. 2C and 4 illustrates that stability requires that the entire family of curves giving Δw_i and ΔP_{cf} as functions of P_{cf} share a common intercept. This requirement imposes an important restriction on the form of LTP used to generalize LTD. Since LTD scales each graph along the right ordinate proportional to P_i (Fig. 2A), for every curve to cross zero at the same value of P_{cf} requires that LTP also scales each curve along the left ordinate by an amount proportional to P_i. Thus, LTP and LTD must be equally sensitive to

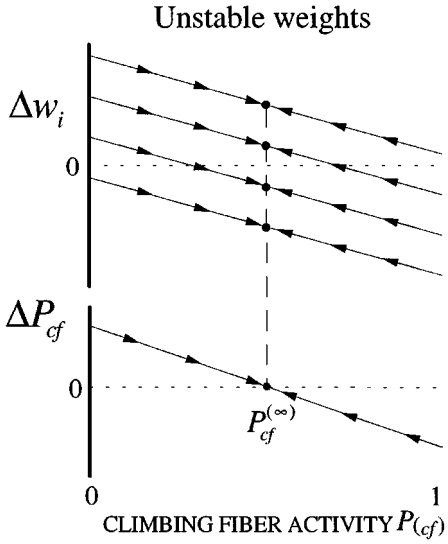

Figure 4. An example of instability at gr→Pkj synapses. For an LTP rule in which climbing fiber activity is stable and does not drift but that produces unstable gr→Pkj synaptic weights (that is, those that drift spontaneously), the resulting LTD/P exhibits the graphical features shown: (1) ΔP_{cf} plotted as a function of P_{cf} has a negative slope and crosses zero at a finite value (lower panel), and (2) Δw_i plotted as a function of P_{cf} (upper panel) does not cross zero *for all synapses* at the same value of P_{cf} where ΔP_{cf} is also zero (dotted vertical line). In this example, gr→Pkj synaptic weights are not stable since there is no common value of climbing fiber activity at which $\Delta w_i = 0$ for all synapses (dotted line to upper panel).

the activity of the synapse, P_i. We can formalize this result as follows. Given the assumed form of LTD, then the change in the weight of the ith synapse due to generalized-LTD is given by the expression

$$\Delta w_i = f(P_i, P_{\text{cf}}) - \delta^- P_i P_{\text{cf}}, \tag{11}$$

where $f(P_i, P_{\text{cf}})$ expresses LTP as a general function of the inputs to the synapse during the time step under consideration. Factoring out P_i, Eq. (11) can be rewritten as

$$\Delta w_i = P_i \left[\frac{f(P_i, P_{\text{cf}})}{P_i} - \delta^- P_{\text{cf}} \right]. \tag{12}$$

From the requirement that $\Delta w_i = 0$ at equilibrium for all values of P_i, it follows that the quantity $f(P_i, P_{\text{cf}})/P_i$ must be independent of P_i, so that $f(P_i, P_{\text{cf}})$ must itself be proportional to P_i. Thus, the simultaneous stability of all synaptic weights implies that LTP must be gr→Pkj driven. The change in the synaptic weight due to LTP can therefore be written

most generally as

$$f(P_i, P_{cf}) = P_i h(P_{cf}), \tag{13}$$

where the function $h(P_{cf})$ represents the dependence on P_{cf}. In the above analysis we assumed that LTP is induced whenever a gr→Pkj synapses is active in the absence of a climbing fiber input. This corresponds to the assignment $h(P_{cf}) = \delta^+(1-P_{cf})$ in Eq. (13). However, stability is achieved whenever, relative to LTD, the dependence of LTP on climbing fiber activity (that is, $h(P_{cf}) - \delta^- P_{cf}$) is a monotonically decreasing function of P_{cf}.

Non-gr→Pkj Driven LTP Rules Produce Unstable Synaptic Weights

The above results demonstrate that only gr→Pkj-driven LTP rules are stable when used to generalize LTD. However, it is instructive to examine in further detail how non-gr→Pkj-driven LTP rules lead to instabilities. Here we consider three forms of LTP: (1) climbing fiber driven, in which synaptic weights increase when not active in the presence of a climbing fiber input, (2) inactivity driven, in which inactive synapses increase in strength when the climbing fiber is also inactive, and (3) activity independent, or drift, in which synapses increase in strength by a fixed amount each time step.

Compared to gr→Pkj-driven LTP, the roles of gr→Pkj input and climbing fiber input are reversed in climbing fiber-driven LTP. Therefore, the direction of synaptic weight changes is controlled by background activity (P_i), and the frequency of LTD and LTP events is controlled by climbing fiber activity. The predicted properties of climbing fiber-driven LTP can be illustrated by employing an analysis similar to that used with Fig. 2. Since the direction of change is determined by P_i, the synaptic weights will not be stable; the weights of synapses whose background activity is less than a critical value (that is, $P_i < P^0$ where $P^0 = \delta^+/(\delta^+ + \delta^-)$; see Appendix A) are expected to increase for all values of P_{cf} greater than zero. Similarly, synapses where $P_i > P^0$ are expected to decrease in strength for all values of P_{cf} greater than zero. Thus, whenever $P_{cf} \neq 0$, the synaptic weights tend to a bimodal distribution with the more active synapses moving toward minimum values and the less active synapses toward maximum values. This leads to two distinct parameter regimes depending on the total background synaptic activity. When overall background synaptic activity is relatively low such that the quantity $P^* = \sum P_i^2 / \sum P_i$ is less than P^0 (Appendix A), the slope of the ΔP_{cf} versus P_{cf} curve is positive and climbing fiber activity increases at an accelerating rate as shown in Fig. 5A by the arrows flowing away from zero. Since this regime is clearly unstable, we restrict our attention to the case where $P^* > P^0$ for which the slope of the ΔP_{cf} versus P_{cf} curve is negative and climbing fiber activity flows toward the minimum physiological value of P_{cf}, which in the present model is taken to be zero. Although climbing fiber activity tends to a stable equilibrium when $P^* > P^0$, this form of plasticity is not truly stable since the only conditions under which gr→Pkj synaptic weights would remain constant are when $P_{cf} = 0$, which is inconsistent with observations that climbing fibers are active both spontaneously (Armstrong and Rawson, 1979; Keating and Thach, 1995) and in response to movement errors (Gellman et al., 1985; Sears and Steinmetz, 1991; Watanabe, 1984).

The last two alternative forms of non-gr→Pkj-driven plasticity, corresponding to either inactivity-driven or activity-independent LTP, exhibit the same qualitative behavior, and we therefore restrict our analysis to the latter. Plots of ΔP_{cf} versus P_{cf}, shown in Fig. 5B, indicate that climbing fiber activity is driven toward a stable equilibrium point (for activity independent LTP, the condition $\delta^- \gg \delta^+$ must also be satisfied for climbing fiber stability). However, the changes in the synaptic weight vector do not go to zero when climbing fiber activity is at equilibrium. Rather, gr→Pkj synaptic weights are driven toward a bimodal distribution (Appendix B); synapses whose activity exceeds P^* continuously decrease, whereas synapses whose activity is less that P^* continuously increase. Thus, LTD/P rules of this type may lead to stable levels of climbing fiber activity but are intrinsically unstable with respect to gr→Pkj synaptic weights.

The Ratio δ^+: δ^- Must be the Same for All gr→Pkj Synapses

We demonstrated above that the stability of gr→Pkj synapses requires that the induction of both LTD and LTP must be equally dependent on the activation of the synapse. Equation (7) also shows that climbing fiber equilibrium requires that the ratio $\delta^+ : \delta^-$ is the same for all gr→Pkj synapses. Otherwise, synapses for which the ratio is large will continually increase in strength,

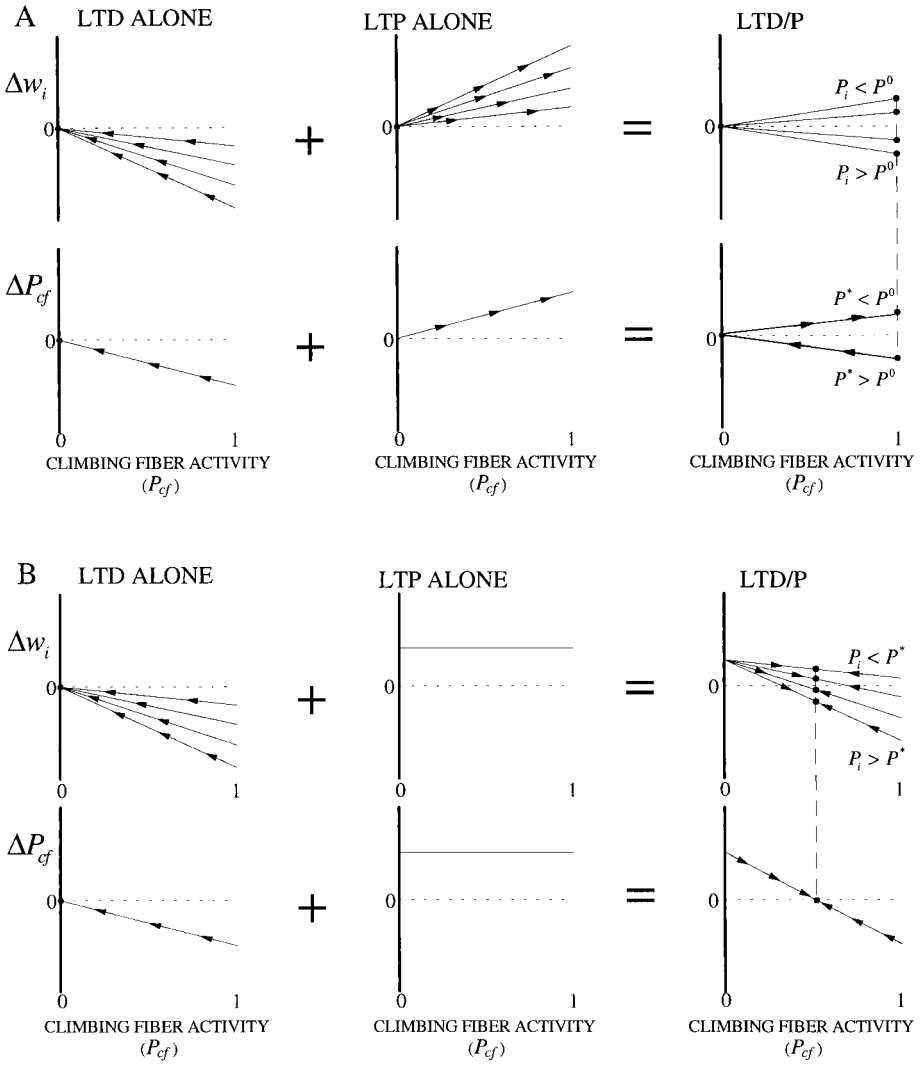

Figure 5. Graphical analysis of unstable LTP rules. A. Analysis of climbing fiber driven LTP, in which synaptic weights increase if not active during a climbing fiber input. When combined with LTD, this rule exhibits two qualitatively different dynamical regimes. When $P^* < P^0$, where $P^* = \sum P_i^2 / \sum P_i$ and $P^0 = \delta^+/\delta^+ + \delta^-$, climbing fiber activity increases without bound in the linear model, or more realistically is driven to its maximum physiological value. In contrast, when $P^* > P^0$, climbing fiber activity is driven to zero. Since climbing fibers are known to be spontaneously active *in vivo*, climbing fiber driven LTP will produce a bimodal distribution in which the weights of less active synapses ($P_i < P^0$) saturate at their maximum values and the weights of more active synapses ($P_i > P^0$) saturate at their minimum values. B. Analysis of activity independent LTP, in which synaptic weights increase by a fixed amount each time step independent of granule and climbing fiber input. When combined with LTD, climbing fiber activity is driven to a stable intermediate value, but synaptic weights will be distributed bimodally; synapses active above a threshold level of activity ($P_i > P^*$) will be driven to their minimum physiological values, whereas synapses active below this level ($P_i < P^*$) are driven to their maximum physiological values.

and synapses for which the ratio is small will continually decrease.

This requirement places constraints on rules intended to limit synaptic weights between minimum and maximum boundaries. For example, our results predict that unstable synaptic weights would be produced by a commonly applied rule (for example, Bullock et al., 1994), where changes in synaptic weights become smaller as the weight approaches a chosen maximum or minimum value (for example, δ^+ and δ^- become functions of the synaptic weights such that $\delta^+ \propto [w^{\max} - w_i]$ and $\delta^- \propto [w_i - w^{\min}]$). As shown

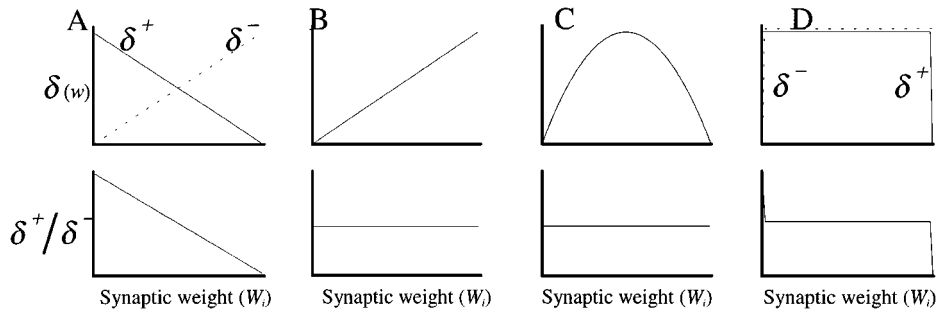

Figure 6. A graphical representation of rules designed to restrict synaptic weights within a finite range. A. A commonly used rule in which increments and decrements in strength (δ^+ and δ^-) decrease as the weight approaches the upper or lower boundary, respectively (upper panel). As shown in the lower panel, this rule makes the ratio $\delta^+ : \delta^-$ vary as a function of the synaptic weight, in which case synaptic weights drift to a single stable value. B. A single lower bound can be implemented by making both δ^+ and δ^- equally sensitive to the current synaptic weight. As shown in the lower panel, this makes the ratio $\delta^+ : \delta^-$ constant for all synaptic weights. C. Implementing both upper and lower bounds requires that δ^+ and δ^- both decrease as a boundary is approached. D. Implementing hard boundaries in which synaptic weights are simply prevented from leaving the allowed range can be achieved by a rule similar in form to the soft rule shown in C. This rule makes synaptic weights stable except very near the boundary (within the distance δ^+ or δ^- from the boundary).

in Fig. 6A, this rule makes the ratio $\delta^+ : \delta^-$ depend on the synaptic weight, and as such, the ratio could be different for every synapse. Synapses at which this ratio is high would increase in strength and synapses where the ratio is low would drift down.

It is possible however to limit synaptic changes so that weights remain within a finite range. For instance, a minimum synaptic weight of zero can be imposed without disrupting stability by making the amplitudes of both LTD and LTP events dependent on the current synaptic weight—for example, $\delta^- \rightarrow w_i\delta^-$, $\delta^+ \rightarrow w_i\delta^+$. This prevents negative synaptic weights by decreasing the size of each change as the weight approaches zero. Since the ratio $\delta^+ : \delta^-$ is unaffected by such a rule (Fig. 6B), our results suggest that synaptic weight stability would not be disrupted, although this rule might produce asymmetric rates of learning and unlearning. Hypothetically, limits on both maximum and minimum synaptic weights could be imposed if both δ^+ and δ^- are proportional to the term $(w^{\max} - w_i)(w_i - w^{\min})$. The ratio $\delta^+ : \delta^-$ would not depend on the synaptic weight w_i (Fig. 6C), and the synaptic weights would be limited because the amplitudes of both LTD and LTP events decrease as the weight approaches either the upper or lower boundary.

An alternative method for imposing limits on synaptic weights can be accomplished by preventing further changes in the same direction when the synaptic weights reach a boundary. As shown in Fig. 6D, this "hard" boundary condition is similar in form to the soft boundary condition shown in Fig. 6C. Thus, a step nonlinearity of this type should only the affect stability of the synaptic weights that are within a single step from the boundary.

Discussion

We have used a formal mathematical model to analyze plasticity at gr→Pkj synapses within the larger context of the synaptic organization of the cerebellar-olivary system. This approach was motivated in part by apparent shortcomings of cerebellar theories based on climbing fiber-induced plasticity at these synapses (Albus, 1971; Marr, 1969). In particular, we have addressed the need for changes at gr→Pkj synapses to be bidirectional and have addressed the spontaneous activity displayed by climbing fibers. To represent this spontaneous activity in the model it was useful to employ a stochastic formalism in which neural activity is represented by the probability of firing an action potential during discrete time steps chosen to reflect the duration of action of a single climbing fiber input. The main results of this analysis are (1) when LTD is complemented with one form of LTP (gr→Pkj driven), the resulting bidirectional LTD/P appears to combine with the synaptic organization of the cerebellar-olivary system to produce a self-regulating equilibrium of climbing fiber activity: (2) at this equilibrium, LTD and LTP events would balance such that the expected net change in the strength of gr→Pkj synapses is zero; and (3) other forms of LTP would either lead to runaway increases or decreases in the weights of gr→Pkj synapses or are incompatible with spontaneous climbing fiber activity.

Linear Models

A number of arguments suggest that the self-regulating equilibrium predicted by our results is not peculiar to the linear mathematical idealizations we have employed. First, our results do not require a particular set of parameters. The present model contains only three free parameters—the amplitudes of LTD and LTP events and the duration of the discrete time steps. Although the real values of these parameters are not known, any biologically plausible value is consistent with our results (an example of a non-biologically plausible value would be if the discrete time step or the size of LTD or LTP events were zero). In addition, the linear input and output properties assumed for Purkinje cells and climbing fibers are simply a mathematical convenience and are not an essential feature underlying our results. For example, both Purkinje cells and climbing fibers could be more accurately represented by sigmoidal functions with finite onset thresholds and maximum rates of activity. Although such nonlinearities would prevent an analytical solution, the general behavior of Purkinje cells and climbing fibers predicted by our results would not be affected. Even with sigmoidal input and output functions, increases in Purkinje cell activity would increase climbing fiber activity. Thus, increases in Purkinje activity would still produce more LTD events relative to LTP events, which would drive the activity of Purkinje cells and climbing fibers toward their equilibrium levels. The self-regulating equilibrium of climbing fiber and Purkinje cell activities predicted by our results therefore appears to be a robust feature that arises from the connectivity of the cerebellar-olivary system combined with the properties of LTD and LTP. Finally, our results suggest several ways in which the amplitudes of both LTD and LTP could depend in a biologically realistic, nonlinear fashion on the synaptic weights without altering the equilibrium stability predicted by our results.

Cerebellar-Olivary Equilibrium

The present analysis suggests that LTD/P leads to the stability of both climbing fiber activity and of gr→Pkj synaptic weights. Since LTD/P predicts that synapses are modified each time they are active, the spontaneous activity of climbing fibers implies that changes in gr→Pkj synaptic weights will be stochastically distributed with a frequency related to the activity of each synapse and a net direction determined by the level of climbing fiber activity. This portrays the behavior of gr→Pkj synapses as relatively dynamic. Synaptic weights may change often, fluctuating around a mean value, but net changes occur only when there is an imbalance between LTD and LTP events. We have shown that the synaptic organization of the cerebellar-olivary system may lead to a dynamic modulation of climbing fiber activity such that the net synaptic change under normal circumstances (no error-elicited climbing fiber inputs) is zero. Recently, Keating and Thach (1995) suggested that spontaneous climbing fiber activity prevents the saturation of LTP at gr→Pkj synapses. Our results suggest how climbing fiber activity is regulated to the precise level that could accomplish this task.

The present analysis also suggests that the summed activity of the Purkinje cells projecting to a common nucleus cell likewise tends to an equilibrium. This follows from the regulation of climbing fiber activity by cerebellar output and implies to a first approximation that the total synaptic current to Purkinje cells is regulated to a level that achieves climbing fiber equilibrium. More important, this result indicates that when a set of synapses is altered, others must subsequently change in the opposite direction to maintain equilibrium. This has important implications for the behavior of gr→Pkj synapses within the context of motor adaptation that will be considered in the paper that follows. It also indicates that not all combinations of synaptic weights are possible. Only those that achieve Purkinje cell/climbing fiber equilibrium (given the background activity of the population of granule cells) are stable. Any deviation from this set of valid synaptic weight vectors would produce nonequilibrium levels of climbing fiber activity, which would in turn induce a net change in synaptic weights, according to the background activity of each synapse, unit equilibrium is restored.

Characteristics of Stable and Unstable LTP Rules

Although the emphasis in this analysis has been on gr→Pkj-driven LTP as suggested by empirical data (Hirano, 1990; Sakurai, 1987, 1989; Salin et al., 1996; Schreurs and Alkon, 1993; Shibuki and Okada, 1992), one of our goals was to compare the behavior of the cerebellar-olivary system using different rules for LTP. From this analysis we have identified two properties required of cerebellar LTP to achieve stable synaptic weights in the cerebellar-olivary system: LTP must be

driven by gr→Pkj activity and, relative to LTD, must decrease as a function of climbing fiber activity.

First, our results show that LTP must be driven by gr→Pkj activity—that is, increases in strength are only possible when the synapse is active. We have shown that certain rules for LTP that are not gr→Pkj driven can lead to stable levels of climbing fiber activity, but they prevent the simultaneous stability of all gr→Pkj synapses. Thus, even at a stable level of climbing fiber activity these rules would produce run away increases or decreases in synaptic weights. These results imply that the stability of gr→Pkj synapses requires that the induction of LTD and LTP be equally sensitive to the activity of the synapse. One way to view the mechanisms that are responsible for heterosynaptic forms of synaptic plasticity such as LTD is in terms of the interactions between a cellwide signal (activated by climbing fiber inputs) and a synapse-specific signal. In this context, our analysis predicts that the induction of LTD and LTP must be equally sensitive to the synapse specific signal. This suggests, but does not demand, that the activation of a particular glutamate receptor subtype is permissive for *both* LTD and LTP. For example, activation of the metabotropic glutamate receptor appears to be necessary for LTD induction (Linden et al., 1991). It may be that activation of this receptor subtype in the presence of high calcium leads to LTD and its activation during lower calcium levels leads to LTP (however, see Salin et al., 1996).

Second, our results show that the expected increases in synaptic weights due to LTP must, relative to LTD, be a decreasing function of climbing fiber activity. When this condition is violated, as with climbing fiber-driven LTP, the potential exists that gr→Pkj synapses will not be stable at any finite value of climbing fiber activity. In contrast, a dependence on decreasing climbing fiber activity is built directly into gr→Pkj driven LTP since synapses are assumed to increase only when active in the absence of a climbing fiber input. This phenomenological restriction does not, however, preclude the possibility that activation of the synapse-specific signal always initiates the processes that produce LTP and additionally contributes to the activation of the superimposed or competing processes that induce LTD. As long as the LTD processes are larger or in some way dominate the LTP processes, the net contribution of LTP on synaptic strength would be a decreasing function of climbing fiber activity.

Our analysis also suggests that the relative amplitudes of the synaptic weight changes induced by LTP and LTD events (the ratio $\delta^+ : \delta^-$) must be the same for all gr→Pkj synapses. This requirement is necessary to ensure that the same value of climbing fiber activity achieves a balance between LTP and LTD at all gr→Pkj synapses. There is at present no empirical data indicating whether or not this rather restrictive condition is satisfied. However, if the mechanisms that mediate the expression of plasticity at gr→Pkj synapses involve discrete steps in strength, then the constancy of the ratio $\delta^+ : \delta^-$ would arise naturally. Since it must be the case that LTD and LTP have opposite actions on a common expression mechanism (two independent mechanisms would simply saturate), then δ^+ would either be equal to, or an integer ratio of, δ^-.

Finally, our analysis suggests that the rule for LTD/P could be modified to allow the amplitudes of the changes in the synaptic weight produced by both LTD and LTP events to depend on the current value of the synaptic weight. Such rules are only stable, however, when the functional dependence on the synaptic weight is identical for both LTD and LTP. Otherwise, there is only a single value of the synaptic weight which is stable during normal levels of background activity. Although LTD/P rules that violate this principle have recently been employed in models of cerebellar plasticity associated with eyelid conditioning (Bullock et al., 1994), the present results suggest that in such models all synaptic weights would go to a single value, denying their ability to encode memories for previous motor learning.

Empirically Testable Predictions

Our results predict that LTP at gr→Pkj synapses should be activity dependent and input specific. Although these properties have been demonstrated for LTD at gr→Pkj synapses, to our knowledge similar information is not available for LTP at the same synapses. Another prediction is that LTD and LTP at gr→Pkj synapses are opposing processes in the sense that each must reverse the effects of the other. Although a recent study suggests that cerebellar LTP is expressed presynaptically (Salin et al., 1996), whereas LTD is clearly postsynaptic, the ability of LTP to reverse LTD (or vice versa) has not yet been tested. However, LTD/P at hippocamal CA1 synapses display all of these properties—activity dependence, input specificity, and mutual reversal (Dudek and Bear, 1992)—highlighting the plausibility that gr→Pkj synapses could display the same properties.

A variety of experimental manipulations could be used to test the prediction that climbing fiber activity is self-regulated to an equilibrium level. Inactivation of the climbing fibers, such as with a local anesthetic, should gradually increase simple spike activity in Purkinje cells that receive climbing fiber input from the region affected by the anesthetic. This increase would reflect the occurrence of LTP events unopposed by LTD. On removal of the anesthetic, simple spike activity should return to normal. Two results generally consistent with this prediction have been reported. Inactivation of climbing fibers by cooling of the inferior olive, or by injection of lidocaine, increased Purkinje cell simple spike activity, which reversed when the inactivation was removed (Montarolo et al., 1982; Demer et al., 1985).

The complement result is also predicted by our results. By interrupting the inhibitory input to the climbing fibers from the cerebellum by infusion of an antagonist of the inhibitory transmitter GABA, complex spikes (from climbing fiber inputs) in the corresponding Purkinje cells should increase quickly, whereas simple spike activity should decrease gradually. This prediction follows from the notion that without appropriate regulation, spontaneous climbing fiber activity would be too high, leading to more LTD than LTP. These effects should also reverse as the antagonist is removed.

It should also be possible to increase climbing fiber input artificially by repetitive stimulation of climbing fibers at a frequency higher than their normal equilibrium level. If this stimulation were delivered for a period of time, it should produce more LTD than LTP. At the termination of the stimulation, our results predict that simple spike activity would be decreased from baseline, and complex spike activity would be decreased. These effects should gradually reverse as equilibrium is restored. This experiment could also be used to measure the time course of return to equilibrium since the temporal properties of the stimulation could be controlled precisely.

Implications for Theories Regarding a Cerebellar Role in Motor Learning

Since the seminal theories of Marr and of Albus there has been considerable debate regarding the putative role of the cerebellum and cerebellar synaptic plasticity in motor adaptation (Bloedel et al., 1991; Ito, 1982; Lisberger, 1988; Llinas and Welsh, 1993; Thompson, 1986; Welsh and Harvey, 1992). From this debate a number of objections to cerebellar theories of motor adaptation have emerged, many of which are discussed in the paper that follows. However, with the present analysis we have addressed one such objection—that the spontaneous activity of climbing fibers should saturate gr→Pkj synaptic weights at their minimum values and thus leave them incapable of mediating motor adaptation. Fujita (1982) partially addressed this issue by assuming that gr→Pkj synapses both increase and decrease in strength by an amount proportional to a variable error signal, presumably related to the level of climbing fiber activity. However, this model provides no physiologically based explanation for either the explicit rules governing the induction of plasticity at gr→Pkj synapses or for how climbing fiber activity is regulated to prevent run away changes in synaptic strength. In contrast, Gilbert (1975) assumed that coactivation of gr→Pkj synapses and a climbing fiber input leads to persistent changes only when the climbing fiber input is combined with a noradrenergic input from the locus coeruleus. However, this theory does not involve bidirectional synaptic weight changes, and the ability to induce LTD *in vitro* suggests that the integrity of the locus coeruleus or the action of norepinephrine is not required for cerebellar mediated motor adaptation.

A model that incorporates bidirectional plasticity was also proposed by Sejnowski (1977) in which weight changes are proportional to the covariance between climbing and parallel fiber inputs. Our LTD/P rule and the covariance rule of Sejnowski are formally similar when a granule cell is active. They differ only when a gr→Pkj synapse is silent: in the covariance rule, synapses undergo a constant amount of LTP each time step, whereas in our LTD/P rule synapses are not eligible to change when they are not active. Since the constant amount of LTP in this covariance rule is proportional to the background granule cell activity, this theoretical rule is consistent with the constraints on LTP that our analysis indicates are required to produce stable synaptic weights. The rationale in the present study for excluding changes in synaptic weights when synapses are not active are empirical rather than theoretical. Indeed, our results clearly indicate that incorporating the covariance rule into the cerebellar-olivary system would produce stable synaptic weights, even in the presence of nonzero background activity.

When properly regulated, as our analysis suggests, the spontaneous activity of climbing fibers ensures that gr→Pkj synapses are stable, independent of their

activity. This form of stability may have several advantages over the notion that gr→Pkj synapses are stable because they are not activated or modified between episodes of motor adaptation, as implied by the model proposed by Bullock et al. (1994). In such models, stability is apparently obtained by assuming that activity in each gr→Pkj synapse participates in encoding only one stimulus/context—the presentation of a particular tone in Pavlovian eyelid conditioning for example—and is not active at any other time. Bullock et al. show how the induction of LTD at those synapses activated by a cue stimulus could lead to the acquisition of a conditioned response elicited when the cue is presented. The retention of this response is ensured since the synapses are never active at any other "noncue" time. If they were, then the conditioned responses would exhibit spontaneous extinction away from the training sessions with a rate proportional to the amount of nontone activity displayed by the synapses. However, the need for each stimulus/context to be encoded by the activity of a unique subset of granule cells with no overlap with any other subsets appears to be an unrealistic assumption that would severaly limit the amount of information that could be encoded by the population of granule cells (for example, Marr, 1969). In contrast, with properly regulated spontaneous climbing fiber activity, the weights of gr→Pkj synapses would remain stable even if occasionally active in other contexts. Thus, rather than representing a potential shortfall of theories of LTD-dependent motor adaptation, the present results suggest that the spontaneous activity of climbing fibers serves an important function.

Recently, De Schutter (1995) proposed that LTD can be induced by coactivation of granule cell inputs to a Purkinje cell (that is, without a climbing fiber input) and that this mechanism provides a form of negative feedback that adjusts the overall amount of synaptic input to Purkinje cells. Our results suggest that the self-regulation of climbing fiber activity could accomplish the same feedback regulation. The limitations on the synaptic weight vector suggested by our results would maintain a well-regulated level of average synaptic input to Purkinje cells. But, unlike the De Schutter hypothesis, the regulation of climbing fiber activity would also prevent overall decreases in the synaptic input to Purkinje cells. One seemingly advantageous consequence of such bidirectional regulation is that Purkinje cell activity could be modulated over a wide dynamic range, and would not, for example, be limited to only very high or very low amounts of activity. Although the De Schutter hypothesis is presented as an argument against climbing fiber mediated motor learning as proposed by Marr and by Albus, we see no reason that these mechanisms are mutually exclusive. Certainly, to dismiss cerebellar-mediated motor learning based on climbing fiber-regulated cerebellar plasticity on the basis of De Schutter's hypothesis seems unwarranted.

The ideas in the present article are consistent with the basic tenets of the Marr and Albus theories. Our results imply that motor adaptation could occur when the equilibrium maintained by the cerebellar-olivary system is systematically disturbed—such as when a movement error repeatedly occurs in a particular context. If movement errors increase the probability of climbing fiber activity (and thus the likelihood of LTD relative to LTP events) then the gr→Pkj synapses encoding that context would undergo a net decrease in strength. This would disturb climbing fiber equilibrium which would be restored by a subsequent increase in gr→Pkj synapses according to their background activity. Thus, our results suggest that this motor adaptation involves two phases of plasticity, an LTD dominated phase during the period of increased climbing fiber activity, and a subsequent LTP dominated phase in which equilibrium is restored. These issues are investigated further in the article that follows (Kenyon et al., 1998).

Appendix A: Climbing Fiber-Driven LTP

Climbing fiber-driven LTP, in which synaptic weights decrease when the synapse is not active during a climbing fiber input, can be formalized in the context of the present model by the expression

$$\Delta w_i^{\mathrm{LTP}} = \delta^+ P_{\mathrm{cf}}(1 - P_i). \tag{14}$$

Combining Eq. (14) with the expression for LTD (Eq. (1)) yields

$$\Delta w_i = P_{\mathrm{cf}}(\delta^+ + \delta^-)(P^0 - P_i), \tag{15}$$

where we define the term $P^0 = \delta^+/(\delta^+ + \delta^-)$. Setting Eq. (15) to zero indicates that synaptic weights are stable only under two conditions—when $P_{\mathrm{cf}} = 0$ or when $P_i = P^0$. Synapses with background activity greater than P^0 will decrease in strength and those with background activity less than P^0 will increase in strength. From Eq. (6), we see that multiplying both sides of Eq. (15) by P_i and summing over all synapses yields an expression for the expected change in climbing fiber

activity,

$$\Delta P_{\mathrm{cf}} = P_{\mathrm{cf}}(\delta^+ + \delta^-)\sum P_i(P^0 - P^*), \qquad (16)$$

where we define the term $P^* = \sum P_i^2 / \sum P_i$. Equation (16) indicates that when $P^* > P^0$, climbing fiber activity will be stable since the relationship between ΔP_{cf} and P_{cf} is negative. In contrast, when $P^* < P^0$, climbing fiber activity will continually increase.

Appendix B: Inactivity Driven and Activity-Independent LTP

Inactivity driven LTP, where synaptic weights increase when both the synapse and the climbing fiber inputs are silent, can be formalized with the following:

$$\Delta w_i^{\mathrm{LTP}} = \delta^+(1 - P_{\mathrm{cf}})(1 - P_i), \qquad (17)$$

whereas activity-independent LTP, where synaptic weights increase each time bin independent of activity, can be expressed as

$$\Delta w_i = \delta^+. \qquad (18)$$

Combining Eq. (1) for LTD with Eq. (17) or (18) yields the predicted form of generalized LTD for inactivity-driven and activity independent LTP, respectively:

$$\Delta w_i = \delta^+(1 - P_{\mathrm{cf}})(1 - P_i) - \delta^- P_{\mathrm{cf}} P_i, \qquad (19)$$

$$\Delta w_i = \delta^+ - \delta^- P_i P_{\mathrm{cf}}. \qquad (20)$$

Equation (6) shows that multiplying both sides of Eqs. (19) and (20) by P_i and summing over all synapses yields expressions for the expected change in climbing fiber activity for inactivity-driven and activity-independent forms of LTP, respectively. After a little rearranging, these become

$$\Delta P_{\mathrm{cf}} = -\delta^+\left(\sum P_i\right)\left[(1 - P^*) + \frac{\delta^-}{\delta^+}P^*\right] \times\left(P_{\mathrm{cf}} - P_{\mathrm{cf}}^{\prime(\infty)}\right), \qquad (21)$$

$$\Delta P_{\mathrm{cf}} = -\delta^- \vec{P}^2\left(P_{\mathrm{cf}} - P_{\mathrm{cf}}^{\prime(\infty)}\right), \qquad (22)$$

where the equilibrium levels of climbing fiber activity for inactivity-driven and activity-independent LTP, denoted, respectively, by $P_{\mathrm{cf}}^{\prime(\infty)}$ and $P_{\mathrm{cf}}^{\prime\prime(\infty)}$ are given by

$$P_{\mathrm{cf}}^{\prime(\infty)} = \frac{1}{1 + \frac{\delta^-}{\delta^+}\frac{P^*}{1-P^*}}, \qquad (23)$$

$$P_{\mathrm{cf}}^{\prime\prime(\infty)} = \frac{\delta^+}{\delta^-}\frac{1}{P^*}. \qquad (24)$$

Equations (21) and (22) show that for both inactivity-driven and activity-independent LTP, ΔP_{cf} depends negatively on (that is, is a decreasing function of) P_{cf}. Both forms of LTP therefore lead to climbing fiber stability; however, for activity independent LTP we must further require that $\delta^+ < P^*\delta^-$ so that $P_{\mathrm{cf}}^{\prime\prime(\infty)} < 1$.

Finally, substituting Eqs. (23) and (24) for $P_{\mathrm{cf}}^{\prime(\infty)}$ and $P_{\mathrm{cf}}^{\prime\prime(\infty)}$ into Eqs. (19) and (20) for Δw_i, we find after some rearranging that

$$\Delta w_i = -\left[\delta^+\left(1 - P_{\mathrm{cf}}^{\prime(\infty)}\right) + \delta^-\right](P_i - P^*) \qquad (25)$$

$$\Delta w_i = -\frac{\delta^+}{P^*}(P_i - P^*), \qquad (26)$$

which shows that for both forms of LTP, synaptic weights will be distributed bimodally. The weights of synapses for which $P_i < P^*$ will increase at climbing fiber equilibrium, while the weights of synapses for which $P_i > P^*$ will decrease.

Acknowledgments

The authors gratefully acknowledge J.H. Byrne, K.S. Garcia, B. Mensh, and C. Canavier for their valuable comments in the preparation of this manuscript. Supported in part by MH46904 (MDM) and MH10683 (GTK).

Notes

1. The term *active* may refer to a spike or alternatively a burst of spikes that exceeds a specific threshold. The results apply equally in either case.
2. For simplicity, we assume that the individual granule cells fire independently and correlations between individual synaptic weights and P_{cf} can be ignored.

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