CHAPTER 20

Time window control: a model for cerebellar function based on synchronization, reverberation, and time slicing

Werner M. Kistler*,1, J. Leo van Hemmen2, and Chris I. De Zeeuw3

*Corresponding author. Tel.: +41(21) 693 3907; Fax: +41(21) 693 5263; e-mail: Werner.Kistler@epfl.ch

1 Center for Neuromimetic Systems, Swiss Federal Institute of Technology, 1015 Lausanne EPFL, Switzerland
2 Department of Physics, Technical University of Munich, 85747 Garching Munich, Germany
3 Department of Anatomy, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands

Introduction

Almost 100 years after the internal structure of the cerebellar cortex (CBCX) has been elucidated by Ramón y Cajal (Ramón y Cajal, 1911) the function of the cerebellum is still a matter of fervent debate. Inspired by the beauty and simplicity of its neuronal wiring, several attempts have been made to explain cerebellar function by means of reductionist models at the level of individual neurons (Braitenberg, 1967; Marr, 1969; Albus, 1971; Ito, 1984). Here we propose a hypothesis of cerebellar function that relies on the new concept of time window control in conjunction with reverberating loops connecting the output of the cerebellum with its major inputs, viz., the mossy fiber and climbing fiber pathway. Periodic inhibitory input to a neuron results in a restriction of firing to those intervals of time where inhibition is weakest, and hence, to well-defined time windows. Here we pose, and answer, the question of whether the notion of time window can be relevant to the cerebellar system and present a model that comprises, apart from the cerebellar cortex, both deep cerebellar nuclei (DCN) and precerebellar brain stem nuclei. It is consistently based on a time coding paradigm that entrusts the control of granule cell firing to cerebellar inhibitory interneurons.

There are three key ideas to the present model, the morphological substrates of which are depicted in Fig. 1. First, we show by means of a detailed single-neuron model that the granule cell/Golgi cell system can operate as a potent gating device admitting only those spikes to the parallel fibers that arrive within short and well-defined time windows. This mechanism can be exploited so as to organize neuronal activity in discrete ‘time slices’ and to discern meaningful information from background noise. Second, we argue that neurons from the DCN are involved in a delayed-reverberating loop that relays cerebellar output-activity via precerebellar nuclei back to the mossy fibers. We show by means of a detailed neuron model that post-inhibitory rebound firing in DCN neurons can function as a robust timing mechanism that reliably produces delays of about 100 ms. The third key element of the model is provided by the dynamics of the network made up of inferior olive (IO), deep cerebellar nuclei, and mesodiencephalic junction (MDJ). We propose that intrinsic oscillatory properties of IO neurons in conjunction with delayed-reverberating loops (see Fig. 1) result in long transients of neuronal activity that are triggered by external input to the IO. This transient activity comes in the form of a sequence of spike
patterns that may act as a ‘neuronal clock’ (Llinás, 1991; Welsh et al., 1995).

A synthesis of the cerebellar time windows and the delayed reverberations in both the mossy fiber and the climbing fiber system result in rich oscillatory dynamics. For instance, synchronous Purkinje cell activity in one cycle is reverberated to the mossy fibers during the next cycle 100 ms later. Provided that the reverberated activity arrives with the correct timing relative to the opening of the granule cell time window, parallel fiber activity in one cycle is, at least partially, determined by the Purkinje cell activity during the previous cycle. Plasticity in the parallel fiber-Purkinje cell system allows the system to learn to react to a certain instance of these activity patterns; that is, to react with a certain temporal relation to external events. This provides a novel explanation of how the cerebellum solves timing tasks on a time scale of several hundreds of milliseconds, which is much longer than the natural millisecond-time scale of ordinary neuronal dynamics.

**Granule cell time windows**

Cerebellar granule cells receive excitatory input from about four mossy fibers and a similar number of inhibitory projections from adjacent Golgi cells (Palay and Chan-Palay, 1974) (Fig. 1). These excitatory and inhibitory synapses meet in a structure called mossy fiber glomerulus so that the mossy fiber synapses can hardly evoke their excitatory effects without the inhibitory control of an accompanying Golgi cell synapse. Golgi cells have recently been shown to fire synchronously, and, less consistently, periodically (Vos et al., 1999; Vos, personal communication). The granule cell may thus receive a periodically modulated inhibition, and may be able to fire an action potential only in a small time interval shortly before the next set of Golgi cell spikes arrive, i.e. when inhibition is weakest. If the Golgi cells are firing asynchronously, inhibitory postsynaptic potentials (IPSPs) overlap partially and the granule cell is probably subject to a more or less constant level of inhibition and therefore unable to fire whenever the mossy fiber spikes arrive. A similar time window mechanism is probably also present in the basket-stellate cell/Purkinje cell system, because excitatory parallel-fiber input to the Purkinje cells is immediately followed by strong basket-cell inhibition delivered through sophisticated synapses that allow Purkinje cells to fire only during a short interval of time (Korn and Axelrad, 1980; Axelrad and Korn, 1982).

We have investigated the excitability of granule cells for various timings of excitatory and inhibitory input activities using a modified version of a detailed multi-compartment model developed for turtle granule cells (Gabbiani et al., 1994). We have extended the original model so as to include GABA_A-ergic synapses with a maximum conductance of 1.5 pS per synapse, a reversal potential of $-75 \text{ mV}$, and a bi-exponential decay with time.
constants of 5 ms (peak amplitude $g_{\text{fast}} = 1.0 \text{ pS}$) and 50 ms (peak amplitude $g_{\text{slow}} = 0.5 \text{ pS}$) as reported for rat granule cells (Tia et al., 1996). Full details are given in Appendix (A).

The simulations shown in Fig. 2 confirm the predicted time window behavior. The granule cell receives inhibition from four Golgi cells firing at 10 Hz each and a volley of four synchronous mossy fiber spikes. If the Golgi cells are firing synchronously, then there is a short time window in which the mossy fiber volley can trigger an action potential (Fig. 2A). If the volley arrives too early, inhibition is still too strong and the firing threshold cannot be reached (Fig. 2B). On the other hand, if the volley arrives too late, then there is not enough time to reach the threshold and the action potential is clipped by the next set of Golgi cell spikes (Fig. 2C). If the Golgi cells are firing asynchronously, then no action potential can be triggered whenever the mossy fiber spikes arrive (Fig. 2D).

In addition to the time window for triggering spikes in granule cells we observe a second effect related to the timing of the resulting granule cell spike. As can be seen in Fig. 3, the granule cell spikes are ‘focused’ to a very narrow interval shortly before the arrival of the Golgi cell spikes. The timing of the granule cell spikes is thus relatively independent of the arrival time of the mossy fibers within the granule cell time window. That is to say, the timing of granule cell spikes can be more precise than the arrival time of mossy fiber spikes.

Figure 3 also demonstrates the dependence of the granule cell time window upon synaptic properties, in particular, on the relative amplitudes of the slow and the fast component of the inhibitory postsynaptic current (IPSC). The slow component in the IPSC is the result of the $\alpha 6$ subunit of the GABA$_A$ receptor, which is a peculiarity of the cerebellar cortex (Farrant and Cull-Candy 1993). It has been shown that the concentration of the $\alpha 6$ subunit and thereby the time course of the IPSC is subject to a systematic modification during development (Tia et al., 1996). Since the expression of the $\alpha 6$ subunit is regulated by the activation of the GABA receptor itself (Ueno et al., 1996; Carlson et al., 1997) we propose that these observations are related to a self-organized process which controls

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**Fig. 2. Granule-cell time window.** A, B, C, membrane potential (mV) as a function of time (ms) in a simulation of a realistic model of turtle granule cells. The vertical arrows indicate the arrival time of four synchronous Golgi cell spikes at $t = 0$ ms and $t = 100$ ms, and four mossy fiber spikes at $t = 70$ ms (A), $t = 60$ ms (B), and $t = 83$ ms (C). The horizontal bar marks the interval during which mossy fiber spikes can trigger an action potential. D, if the same number of Golgi cell spikes arrives asynchronously, here one spike every 25 ms, then mossy fiber spikes are unable to trigger an action potential, whatever their arrival time.
Fig. 3. Focusing of granule cell spikes. As in Figs 2A-C, the granule cell receives four synchronous Golgi cell spikes every 100 ms. The graphs give the firing time of the granule cell $t_{\text{post}}$ as a function of the arrival time $t_{\text{pre}}$ of mossy fiber spikes. Insets show the time course of the conductivity ($\mu$S) of the GABAergic synapse as a function of time (ms); slow and fast component are indicated by dashed lines. A, postsynaptic firing time induced by three synchronous mossy fiber spikes; $g_{\text{slow}} = 0.15 \mu$S, $g_{\text{fast}} = 1 \mu$S. B, postsynaptic firing time induced by four synchronous mossy fiber spikes; $g_{\text{slow}} = 0.5 \mu$S and $g_{\text{fast}} = 1 \mu$S.

the parameters that are critical to the time-window mechanism.

**Delayed reverberation**

Both the excitatory and inhibitory neurons in the DCN receive inhibitory input from Purkinje cells (Fig. 4) (De Zeeuw and Berrebi, 1995; Teune et al., 1998) and presumably both exhibit a strong post-inhibitory rebound firing (Jahnsen, 1986a; Llinàs and Mühlethaler, 1988a; Tempia/Ruigrok personal communication). While the inhibitory DCN neurons project exclusively to the inferior olive (De Zeeuw et al., 1989), the excitatory DCN neurons project to various brain stem nuclei, such as the nucleus reticularis tegmenti pontis in the pons, which is a major source of cerebellar mossy fibers (Murakami et al., 1981; Tsukahara et al., 1983; Verveer et al., 1997).

In order to study the rebound firing mechanism in detail we have devised a single-compartment active-membrane model for DCN neurons; see Appendix (B). Thalamic relay neurons have electrophysiological properties similar to those of DCN neurons (Llinàs, 1988). We have modified an existing model for thalamic relay neurons (McCormick and Huguenard, 1992) so as to reproduce in vitro measurements of current-step responses and gain function of DCN neurons (Llinàs and Mühlethaler, 1988a). Furthermore, the model exhibits low-threshold $Ca^{2+}$ spikes and non-inactivating $Na^{+}$ plateaus, which are characteristic features of DCN neurons (Jahnsen, 1986b; Llinàs and Mühlethaler, 1988b).

We have investigated the timing of rebound spikes as a function of the level and the temporal structure of the preceeding inhibition. Figure 5 shows that once there is a rebound spike, it occurs 100 ms after the onset of inhibition, irrespectively of the number of involved IPSPs and their degree of synchrony. The rebound spike can be even more precisely timed than an individual Purkinje cell spike, because several Purkinje cell spikes are required to trigger a rebound spike. Noise is efficiently reduced because the timing of a rebound spike depends predominantly on the average of the arrival times of the Purkinje cell spikes at a DCN neuron. We thus observe an effect similar to the focusing of granule cell spikes, namely that the precision of a postsynaptic neuron's firing time can be higher than the presynaptic spike arrival times.

**Plasticity at parallel fiber/Purkinje cell synapses**

Combination of time windows and delayed reverberation yields interesting dynamics, if we allow the reverberated activity to return at the CBCX within the granule cell time window. This way the CBCX can lock in on its own output and learn, store, and recall spatiotemporal patterns of neuronal spike activity by adjusting the weights of parallel fiber/Purkinje cell synapses.

Activities of different climbing fibers can arrive synchronously in sagittal zones of the CBCX (Sugihara et al., 1993). The climbing fibers elicit so-called all-or-none complex spikes in the Pur-
kinje cells (Eccles et al., 1966), and in addition they might affect the activity of Golgi cells via climbing fiber collaterals (Palay and Chan-Palay, 1974; see the question mark in Fig. 1). Recurrent axon

Fig. 4. Characteristic synaptology in deep cerebellar nuclei (DCN). A, a double L7-GABA-labeled Purkinje cell terminal contacts both a GABAergic (inhibitory) and a non-GABAergic (excitatory) dendrite in a cerebellar nucleus. The GABA-labeling is visualized by means of 15 nm gold particles (black dots), while the Purkinje cell specific L7-protein is visualized with the use of dark diamino benzidine reaction products (L7-GABA; for details, see De Zeeuw and Berrebi, 1995). B and C, a biotinylated dextran amine labeled Purkinje cell terminal contacts both a dendrite retrogradely labeled with WGA-HRP (thick arrow in B) from the mesodiencephalic junction and a cellbody retrogradely labeled with gold-lectin (arrowheads) from the inferior olive (for details, see Teune et al., 1998). Open arrows in A and C indicate symmetric synapses; closed arrow in A indicates asymmetric synapse.
Fig. 5. Post-inhibitory rebound in DCN neurons. A and B, membrane potential of a model for DCN neurons in response to two (A) and three (B) inhibitory Purkinje cell spikes (arrows). The resulting rebound spike occurs after a delay of approximately 100 ms, irrespectively of the number of Purkinje cell spikes. C, delay $\Delta t$ of the rebound spike after a volley of Purkinje cell spikes as a function of the total synaptic conductivity, i.e. the conductivity per synapse times the number of activated synapses. D, delay of the rebound spike after a volley of three Purkinje cell spikes versus the degree of their synchronicity $\delta t$ (width of the interval containing all three spikes) measured from the center of the Purkinje cell spike volley. Note the plateaus in C and D.

collaterals of the Purkinje cells in turn will inhibit the Golgi cells and thereby allow the granule cells to recover from inhibition (Schulman and Bloom, 1981). Hence the granule cell window will be open after a delay of several tens of milliseconds. In the mean time, those DCN neurons that were inhibited by Purkinje cells fire their rebound spikes, which reverberate to the CBCX via brainstem nuclei and the mossy fiber system. We assume that the delayed opening of the granule cell time window corresponds to the delay imposed by the rebound firing and the reverberating loop. That is to say, the rebound activity caused by the complex spikes returns to the CBCX just in time so as to pass the granule cell/Golgi cell system after the inhibition of granule cells has decayed. The rebound activity is thus relayed to the parallel fibers and can in turn trigger certain subsets of Purkinje cells and Golgi cells. The Golgi cell spikes inhibit the granule cells and close the granule cell time window again. Each pattern of Purkinje cell activity may trigger a new set of Purkinje cells in the next cycle depending on the wiring of the reverberating loop and on the weight matrix of the parallel fiber/Purkinje cell synapses. Thus, the oscillation can continue until external events alter the firing pattern of the inhibitory interneurons.

We show by means of large-network simulations that the biologically plausible mechanisms of plasticity at the parallel fiber/Purkinje cell synapses, i.e. long term potentiation (LTP) and long term depression (LTD), allows the system to learn arbitrary sequences of spike patterns. The network is made up of spike response neurons – a kind of a generalized integrate-and-fire neuron (Gerstner and van Hemmen, 1992, 1994; Kistler et al., 1997). This set-up allows for a qualitative description of different types of neuronal behavior such as adaptation and post-inhibitory rebound. The connectivity is within morphological constraints random so that each pair of neurons in a simulation is assigned an arborization function that gives the probability of their being ‘connected’ as a function of their distance; see Appendix (C).

The nature of the plasticity at the parallel fiber/Purkinje cell synapses may depend on the relative timing of the activities in the climbing fibers and parallel fibers. Recent experimental evidence (Sakurai, 1987; Hirano, 1990; Schreurs et al., 1996; Lev-Ram et al., 1997; see however, Bell et al., 1997) suggests that these synapses are potentiated, if a complex spike occurs within about 10 ms after the corresponding ‘parallel fiber spike’, and that they are depressed if a complex spike arrives within
about 100 ms before a ‘parallel fiber spike’. In this way only those synapses are potentiated that have contributed to the simple-spike firing of the Purkinje cell shortly before or after the arrival of a climbing fiber spike. Other synapses that would make the Purkinje cell fire at an other moment of time are depressed (cf. Hebb’s rule; Hebb, 1949)

In the present model climbing fiber spikes are attributed a two-fold function. First, climbing fiber activities are interpreted as ‘teacher signals’ that indirectly tell Purkinje cells when precisely they have to fire simple spikes. This notion, which is consistent with their immediate triggering of complex spikes, is different from that of climbing fiber spikes serving as error signals (Albus, 1971). Second, climbing fiber spikes might have a synchronizing effect on cerebellar interneurons and initialize the granule cell time window, as we have seen above.

Figure 6A shows the spike trains of neurons involved in a network simulation. We start with an uncorrelated rest activity in the mossy fibers. The pattern the Purkinje cells are about to learn is presented to them by climbing fiber spikes. In the example shown in Fig. 6, climbing fibers have been divided in four groups that subsequently deliver synchronous action potentials every 120 ms. Experimental evidence has been provided by Welsh et al. (1995) who showed that spatio-temporal patterns of climbing fiber activity can be phase-locked to ongoing movements.

As shown in Fig. 6A, the first set of climbing fiber spikes arriving at \( t = 400 \) ms forces the corresponding Purkinje cells to fire complex spikes that inhibit DCN neurons and cause a rebound volley in the mossy fiber pathway at \( t = 518 \) ms. This rebound volley is paired with the second set of climbing fiber spikes that arrive at \( t = 520 \) and again will trigger complex spikes at certain Purkinje cells; and so on. After a few repetitions parallel fiber-Purkinje cell synapses are modified in such a way that a characteristic activity pattern of parallel fibers suffices to trigger the corresponding Purkinje cell, even without a climbing fiber activation. The teacher signal is no longer needed.

Figure 6B shows that after 10 repetitions the pattern has been learned successfully and can be recalled by the first climbing fiber event. We note

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**Figure 6. Cerebellum learning spatiotemporal patterns.** The diagrams show the spike trains of 200 deep cerebellar nuclei neurons (DCN), 1000 granule cells (GrC), 80 Golgi cells (GoC), 200 Purkinje cells (PC), 400 basket or stellate cells (BaC), and the spike trains delivered by 200 mossy fibers (mf) and 200 climbing fibers (cf) as a raster diagram over time. Each short vertical line corresponds to an action potential, but because of limited printing resolution, synchronous spikes of neighboring neurons may merge into one line. A. The climbing fibers have been divided into four groups that subsequently deliver synchronous action potentials every 120 ms (uppermost panel). The following climbing fiber spikes are paired with mossy fiber events that are produced by a rebound mechanism depending on Purkinje cell activity in the previous cycle (see text). The role of the granule cell/Golgi cell system is clearly visible. After synchronization of the Golgi cells at \( t = 400 \) ms, mossy fiber activity is admitted to the parallel fibers (GrC-panel) only during narrow time windows shortly before the Golgi cells fire their action potentials. This results in a concentration of the activity of the various types of neurons in discrete ‘time slices’ centered around the climbing fiber volleys. B. Similar diagram as in A but after the pattern has been learned successfully. A single climbing fiber volley at \( t = 400 \) ms suffices to recall the learned pattern without any further climbing fiber spikes being involved. Note that the complex spike synchrony levels presented in A and B are at the highest end of those that can occur in vivo (for details see De Zeeuw et al., 1996). In addition it should be noted that the average firing frequency of the simple spike activity presented in this diagram is relatively low due to the high level of inhibition. The BaC and DCN cells are not shown in B for clarity of presentation.
that the recall process is stable despite the high level of background noise in the mossy fiber input and the presence of inherent noise due to the stochastic spike triggering process. The present network model also illustrates the importance of climbing fiber synchrony, as has been found experimentally (Bell and Kawasaki, 1972; Llinás et al., 1974; Llinás and Sasaki, 1989; De Zeeuw et al., 1996). Figure 7 shows that if the climbing fiber spikes arrive asynchronously in the cerebellar cortex with a jitter of only 5 ms, then the pattern fails to be recalled. Thus, synchrony of the climbing fiber activity is essential to the recall function.

Self-organization of climbing fiber activity

In the previous section we have seen that the cerebellar network can learn spatiotemporal patterns of spike activity. This set-up required climbing fibers to deliver a teacher signal every 100 ms. The signal is generated by an until now unspecified external mechanism. In this section we will show that electrophysiological properties of inferior olivary (IO) neurons in conjunction with topographic projections between IO, DCN, and mesodiencephalic junction (MDJ) can produce precisely timed sequences of climbing fiber spike patterns. These sequences are hard-wired in the olivo-cerebellar system and may serve as a ‘neuronal clock’ that basically extends the system’s short-term memory beyond several hundreds of milliseconds (see also Ruigrok and Voogd, 1995).

Inferior olivary neurons have oscillatory properties with an intrinsic frequency of about 10 Hz (Llinás and Yarom, 1986; Llinás 1991). The electrophysiological correlates of this behavior are a calcium-dependent potassium current and two different voltage-dependent calcium currents. One of them, the low-threshold somatic calcium current, is also responsible for rebound activation similar to that seen in DCN neurons (Llinás and Yarom, 1981a; Llinás and Yarom, 1981b). Presumably, the subthreshold oscillations and the strong coupling of neighboring neurons via gap junctions (Fig. 8) can result in synchronous climbing fiber activity (Llinás et al., 1974; De Zeeuw et al., 1989) and in a precise timing of the complex spikes (Lampl and Yarom, 1993).

Albeit oscillatory properties exist, there is no sustained super-threshold oscillatory activity in the IO, at least in the absence of pharmacological stimulation (Llinás and Yarom, 1986). Thus, any activity in the IO triggered by some external events finally will die out. We hypothesize that the decay of IO activity is a relatively slow process comprising several periods of 100 ms each (Ruigrok and Voogd, 1995). The sequence of spike patterns that is generated in the wake of this decay can serve as a neuronal clock or as a counter of the periods that have elapsed since the oscillation has been started by some external event.

Delayed reverberating loops between the IO and the DCN also contribute to the slowly decaying oscillations (Fig. 9). In fact, they determine the sequence of firing patterns. One of the loops includes IO neurons that send excitatory collaterals to the inhibitory neurons in the DCN, which in turn project back to the IO (De Zeeuw et al., 1997). Inhibition of IO neurons that is produced by small neurons in the complex of cerebellar and vestibular nuclei (see also Fig. 8), may result in post-inhibitory rebound with a proper delay of about 100 ms (Llinás, 1991). Another reverberating loop comprises the inhibitory input of the Purkinje cells to the DCN neurons, which in turn produce rebound spikes with a certain delay after the complex spike activity of the Purkinje cells. The rebound activity of many of the excitatory neurons in the DCN is relayed through a disynaptic excitatory pathway via the MDJ back to the IO (Figs. 1 and 10). Both loops are topographic in that particular subsets of neurons are directly or indi-
rectly, reciprocally connected to one another (De Zeeuw et al., 1998b). The result is that both pathways form positive feedback loops that deliver excitation with a delay of about 100 ms to the neurons that have been active in the previous cycle. However, in both loops the inputs to the IO, i.e. the inhibitory input from the DCN and the excitatory input from the MDJ, directly synapse onto the olivary dendrites that are electrotonically coupled to each other (Fig. 8), and presumably both inputs can dynamically regulate the domains of the coupled olivary neurons (Llinás and Sasaki, 1989; De Zeeuw et al., 1998b). Thus depending on the precise wiring scheme and status of coupling in the inferior olive a pattern of spike activity in one cycle may induce a new pattern of spike activity in the next cycle 100 ms later; and so forth.

Theoretical considerations (Kistler, 1999) show that a slowly decaying oscillatory activity requires a tuning of the firing threshold of the neurons involved and of the amount of convergence and divergence present in the reverberating loop. Simulations indicate that this tuning can be achieved by means of a self-organized process called anti-Hebbian elimination. In short, initially there are more synaptic connections than required for a slowly decaying activity. During a training phase oscillations are triggered by external inputs to IO neurons and those synapses that are contributing repetitively to the firing of their postsynaptic targets are gradually eliminated with a certain (small) probability (Fig. 9). The elimination process stops when a critical connectivity is left so that oscillations are no longer self-sustained but decay (slowly).

The sequence of spike patterns produced by the resulting connectivity can be used to solve timing tasks as shown in Fig. 11. An external event

Fig. 8. Characteristic synaptology in inferior olive (IO). The electron micrograph shows a small olivary glomerulus containing a core of two dendritic spines (asterisks) coupled by a gap junction (small arrows). The spines are innervated by a double WGA–HRP/GABA labeled terminal derived from the complex of cerebellar and vestibular nuclei in the hindbrain following a combination of anterograde tracing of WGA–HRP and postembedding immunocytochemistry (for details see De Zeeuw et al., 1989). Open arrows and arrow head indicate symmetric and asymmetric synapses, respectively. Closed thick arrow indicates WGA–HRP reaction product. Small black dots are 15 nm gold particles linked to a GABA-antibody.
Fig. 9. Transient activity in reverberating loops connecting DCN, MDJ, and IO. Two external events trigger IO neurons at \( t = 400 \) and \( t = 560 \), respectively. The connectivity between the involved nuclei is the result of anti-Hebbian elimination (see text) and is responsible for the slow decay of activity in the climbing fiber system (upper panel) and DCN neurons (lower panel) shown here in a simulation similar to Fig. 6.

triggers a subpopulation of IO neurons that gives rise to a climbing fiber event at time \( t = 400 \) ms. The subsequent series of mossy fiber-spike patterns that is produced by the ongoing activity in the reverberating loop of DCN, MDJ, and IO is paired with a second climbing fiber event at time \( t = 760 \) ms (Fig. 11A). Purkinje cells thus learn to respond to the first event with a proper delay of 360 ms, even if the second climbing fiber event is omitted (Fig. 11B). Such mechanisms might for example play a role in particular timing sensitive tasks during classical conditioning (for details see Yeo and Hesslow, 1998).

DISCUSSION

We have presented a functional model of the cerebellar network comprising CBCX, DCN, precerebellar nuclei, and IO. The distinguishing feature of the present model is that cerebellar interneurons can be attributed a function that goes beyond a mere regulation of the mean firing rate of the principal neurons (Marr, 1969; Albus, 1971) in that they generate narrow and well-defined time windows for triggering spikes. We have shown that the granule cell/Golgi cell system can discern incoming mossy fiber spikes by their arrival times. This has several interesting consequences. First, time windows allow for an intricate parallel processing, if information for different tasks is organized in different time slices. Second, the overall signal-to-noise ratio is significantly improved if, on the one hand, meaningful spike activity is concentrated in a certain time slice, and background noise, on the other hand, is spread evenly in time.

The second key ingredient of the present model is a delayed reverberating loop that conveys post-inhibitory rebound activity of DCN neurons via precerebellar nuclei back to the mossy fiber system. We have shown by means of a detailed model for DCN cells that post-inhibitory rebound is a robust mechanism to produce precisely timed delays of about 100 ms. The aforementioned granule cell time window thus allows the cerebellar network to lock in on its own output provided that the rebound delay matches the delayed opening of the granule cell time window.

Combination of time windows and delayed reverberation results in a closed system that, in conjunction with long-term plasticity at the parallel fiber/Purkinje cell synapses, is able to learn, store, and recall spatiotemporal patterns of spike activity. Large network simulations (Kistler, 1999; Kistler and van Hemmen, 1999) reflecting the morphological structure of the CBCX predict that the LTD and LTP mechanisms underlying long-term plasticity attribute to climbing fibers the function of a ‘teacher signal’ that tells Purkinje cells when to fire and evoke rebound spikes in the DCN.

Whether plasticity at the parallel fiber/Purkinje cell synapses depends on the timing of climbing fiber and parallel fiber activities is still a controversial issue (see for example Llinás et al., 1997; Bell et al., 1997; Lev-Ram et al., 1997). In the present model a synapse is depressed, if a parallel fiber potential arrives a few tens of milliseconds after a climbing fiber spike. If the timing is the other way around, i.e. if a parallel fiber action potential arrives a few milliseconds before the climbing fiber activity, then the corresponding synapse is potentiated. The present version of plasticity is a generalization of Hebb’s learning rule (Hebb, 1949), because synapses are strengthened only if they are contributing to the firing of the postsynaptic neuron (Gerstner et al., 1996; Markram et al., 1997; Kistler and van Hemmen, 2000).

Apart from learning spatiotemporal patterns the network can solve timing tasks, i.e. the network can learn to respond to an external stimulus with a
variable delay of up to several hundreds of milliseconds. The underlying idea is that reverberating loops comprising DCN, MDJ, and IO can produce long sequences of varying spike patterns that are hard-wired in the reverberating circuit. Synaptic plasticity in the reverberating loop made up of Purkinje cells, DCN, pons, and mossy fiber system allows Purkinje cells to learn when to fire in response to an external event that has started the sequence. This provides – to our knowledge – a novel explanation of how the cerebellum solves timing tasks on a time scale of hundreds of milliseconds (McCormick et al., 1982; Perret et al., 1993; Welsh et al., 1995; Yeo and Hesslow, 1998, De Zeeuw et al., 1998a).

Relation to other models

Every system that deals with temporal patterns inevitably requires a kind of internal clock or

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Fig. 10. Characteristic synaptology in the mesodiencephalic junction (MDJ). The electron micrographs show two examples of terminals in the MDJ anterogradely labeled with WGA–HRP (arrowheads) from the cerebellar nuclei. One terminal (A) contacts a proximal dendrite with gold particles (5–10 nm in diameter; indicated by circles) that are transported retrogradely from the inferior olive, while the other terminal (B) contacts a peripheral dendrite (asterisk) of a non-GABAergic cell that is also contacted by a GABAergic terminal from another source. Closed and open triangles indicate asymmetric and symmetric synapses, respectively.
timing device. Previous models of cerebellar function that explicitly include time – the classical models of Marr (Marr, 1969) and Albus (Albus, 1971) are static – can be classified according to their specific timing mechanisms. An early theory of cerebellar function is that of Braitenberg (1967). Here parallel fibers are used as delay lines and different spatial distances are employed to compensate for different arrival times of mossy fiber spikes so as to discern spatiotemporal spike patterns in the mossy fiber system (Braitenberg, 1993; Braitenberg et al., 1997). A similar idea underlies the work of Meek (1992), who exploits differences in the propagation time of parallel fiber spikes to translate short time differences into a spatial map. To overcome the limited range of attainable delays of only a few tens of milliseconds, different timing mechanisms have been proposed. Moore et al. (1989) postulate the existence of external delay lines in the brain stem and Fiala et al. (1996) employ slow metabotropic glutamate receptors in order to arrive at delays long enough to explain the role of the cerebellum in solving timing tasks. All these models have in common that they require an array of different delays that cover the whole range of delays that are to be learned. Different in this respect is a model of Buonomano (1994) that relies on the granule cell population vector, which is subject to a temporal evolution even for a stationary mossy fiber input.

One of the major delay-generating mechanisms in the present model is post-inhibitory rebound in DCN neurons. Rebound firing seems to be a concept that is ubiquitously used in various parts of the nervous system in order to reliably produce well-defined delays of several tens of milliseconds. Prominent examples are the auditory system of bats (Olsen and Suga, 1991, Carr, 1993) and the visual system of vertebrates, where delays of such a long duration are required for the processing of moving stimuli (Mastronarde, 1987).

In a similar way to Buonomano (1994), the present model does not require an array of different delays but uses the time-dependent granule cell activity as a ‘neuronal clock’. The vital difference between the two models is the manner in which the temporal evolution is imposed upon the granule cell population. Buonomano (1994) assumes a random connectivity between mossy fibers, granule cells, and Golgi cells and relies on the resulting dynamics that is generated by the inner-cortical connections and the mossy fiber input. Severe problems arise, however, from the lacking stability of the dynamics with respect to noise (Buonomano, 1994). We believe that the chaotic nature of the granule cell-Golgi cell dynamics disqualifies it for the proposed task. The present model, in contrast, is based on stable oscillations of neuronal activity between the CBCX, DCN, and pre-cerebellar nuclei.

**Stability properties**

The stability of the present model to noise has been demonstrated by simulations that include both internal (stochastic spike triggering) and external
(noisy, mossy fiber input) noise. Insensitivity to external noise is due to the restriction of firing times to narrow time windows. External noise is effectively blocked by the system’s admitting only those mossy fiber spikes that arrive with the correct timing and rejecting all spikes that arrive outside the granule cell time window. The proviso is that there is a fixed temporal relation between the input signal and the internal state of the cerebellum. At least for the reverberated signals this condition can be fulfilled by tuning the delay after which Purkinje cell spikes reappear in the cerebellar cortex.

The robustness with respect to intrinsic noise results from the quasi-digital mode of information processing and the auto-associative way in which spatiotemporal patterns are stored. Time is divided into well-separated discrete ‘slices’ defined by the time windows during which granule cells and Purkinje cells can fire. Purkinje cells have learned to recognize certain parallel fiber events in an associative and error-tolerant manner. Since the Purkinje cell activity in one cycle is reverberated to the parallel fibers in the next cycle, the whole succession of spike patterns is stable (Gerstner et al., 1993).

Two effects that have been revealed by our simulations of detailed neuron models of granule cells and of DCN neurons further enhance the overall stability to noise. In the time-window mode of operation of granule cells, the firing time of granule cells is insensitive to the arrival time of the mossy fiber volley provided the latter arrives within the time window. Granule cell spikes are thus ‘focused’ into an interval that is even shorter than the granule cell time window. As presented above, a similar effect has been found in the model of DCN neurons that fire a rebound spike in response to a couple of inhibitory Purkinje cell spikes. The rebound spike occurs with a fixed delay of about 100 ms after the Purkinje cell spike volley and is irrespective of the number of spikes in the volley. The timing of a rebound spike is even independent of the temporal spreading of the volley and thus determined by an average over all spikes of the volley. This effectively reduces noise in the rebound firing time. Both effects are crucial to a safe operation of the present model (and of the cerebellum). Otherwise small deviations in spike timing would grow until synchronization is so poor that all neuronal activity in a reverberating loop would cease to exist.

Summary

We present a new hypothesis of cerebellar function that is based on synchronization, delayed reverberation, and time windows for triggering spikes. Our model suggests that granule cells admit mossy fiber activity to the parallel fibers only if the Golgi cells are firing synchronously and if the mossy-fiber spikes arrive within short and well-defined time windows. The concept of time window control organizes neuronal activity in discrete ‘time slices’ that can be used to discern meaningful information from background noise. In particular, Purkinje cell activity can trigger rebound spikes in deep cerebellar nuclei cells, which project via brain stem nuclei and mossy fibers back to the cerebellar cortex. Using a detailed model of deep cerebellar nuclei cells, we demonstrate that the delayed firing of rebound spikes is a robust mechanism so as to ensure that the reverberated activity re-arrives in the mossy fibers just during the granule-cell time window. Large network simulations reveal that synaptic plasticity (LTD and LTP) at the parallel fiber/Purkinje cell synapses that relies on the timing of the parallel fiber and climbing fiber activities allows the system to learn, store, and recall spatiotemporal patterns of spike activity. Climbing fiber spikes function both as teacher and as synchronization signals. The temporal characteristics of the climbing fiber activity are due to intrinsic oscillatory properties of inferior olivary neurons and to reverberating projections between deep cerebellar nuclei, the mesodiencephalic junction, and the inferior olive. Thus, the reverberating loops of the mossy fiber system and climbing fiber system may interact directly with the time windows provided by the circuitry of the cerebellar cortex so as to generate the appropriate spatio-temporal firing patterns in the deep cerebellar nuclei neurons that control premotor systems. In future studies the model will be extended in that high frequency simple spike activities will be included and that their relevance for motor control will be addressed.
Acknowledgements

It is a great pleasure to the authors to thank Herbert Axelrad and Rodolfo Llinás for stimulating discussions and helpful advice, and Fabrizio Gabbiani and Ulrich Hillenbrand for help with the detailed neuron models. W.M.K. gratefully acknowledges financial support from the Boehringer Ingelheim Fonds. C.I.D.Z. gratefully acknowledges support from the HFSP, the Life Sciences Foundation (SLW; no. 805-33.310-p; C.I.D.Z.), which is subsidized by the Netherlands Organization for Scientific Research (NWO), and the support by a NWO project grant (no. 903-68-361). Furthermore, C.I.D.Z. thanks the Graduiertenkolleg 'Multisensorische Interaktion' for a pleasant and fruitful stay in Munich, where this manuscript was finished.

References


**APPENDIX**

(A) Granule cells

We have used a realistic model of cerebellar granule cells that consists of several passive dendritic compartments and one active somatic compartment and contains various Na<sup>+</sup>, K<sup>+</sup>, and Ca<sup>2+</sup> currents. Our granule cell model is identical to that of Gabbiani et al. (1994) except that (a) we have simplified the Ca<sup>2+</sup> dynamics as proposed by Traub et al. (1991) – see below – and (b) we have included GABA<sub>A</sub>-controlled ion channels with a maximum conductance of 1.5 pS per synapse, a reversal potential of −75 mV, and a bi-exponential decay with time constants 5 ms (peak amplitude $g_{fast} = 1.0$ pS) and 50 ms (peak amplitude $g_{slow} = 0.5$ pS), as reported for rat granule cells (Tia et al., 1996). Excitatory synaptic currents are made up of a combination of NMDA and AMPA components as described by Gabbiani et al. (1994).

The innercellular Ca<sup>2+</sup> concentration $[Ca^{2+}]_i$ is given by an ordinary differential equation,

$$\frac{d}{dt} [Ca^{2+}]_i = \phi_i_{Ca} - [Ca^{2+}]_i/\tau_{Ca},$$  \hspace{1cm} (1)

with $i_{Ca}$ being the Ca<sup>2+</sup> influx as described in (Gabbiani et al. 1994) and $\phi = 16 \, mM \, A^{-1} \, ms^{-1}$, a constant that scales the amplitude of Ca<sup>2+</sup> transients produced by an action potential to about 800 nM. The time constant $\tau_{Ca} = 130$ ms describes the decay of a Ca<sup>2+</sup> transient as it is caused by diffusion.

For the sake of completeness and because of a couple of typos in the original work we have summarized the parameters for the activation and inactivation functions for the various types of ion currents in Table 1.

(B) Deep cerebellar nuclei neurons

Deep cerebellar nuclei neurons are described by a single compartment model that is actually a modification of a model developed for thalamic relay neurons (McCormick and Huguenard 1992). The membrane potential $v$ is given by

$$C \frac{d}{dt} v(t) = I_{syn}(t) + \sum I_x(t),$$  \hspace{1cm} (2)

with $C = 0.15$ nF being the membrane capacity, $I_{syn}$ and $I_x$ being the synaptic current and the current through channel $x$, respectively.

Sodium and potassium currents are described by Ohmic equations (Hodgkin and Huxley 1952) of the form

$$I_s = g_s m^3 h (v - E_s),$$  \hspace{1cm} (3)

or

$$I_x = g_x m^p (v - E_x)$$  \hspace{1cm} (4)

in the case of a non-inactivating ion current. The calcium currents $I_c$ and $I_f$ (Huguenard and McCormick 1992) are given by

$$I_c = g_c \frac{[Ca^{2+}]_i e^{-vt_{133}} - [Ca^{2+}]_i}{1 - e^{-vt_{133}}} m^f h v$$  \hspace{1cm} (5)

Activation and inactivation variables $m$ and $h$ evolve according to the usual relaxation equations.
## Table 1

Parameters of a detailed model for turtle granule cells (Gabbiani et al. 1994) as used in this paper. In case of the currents $I_{Na}$ and $I_{KAI}$, the time constants $\tau_i(v) = 1/(\alpha_i(v) + \beta_i(v))$ are subject to a lower bound as it is given in the last column of the table.

<table>
<thead>
<tr>
<th>state</th>
<th>Channel, variable</th>
<th>$\bar{g}_i$ [mS]</th>
<th>$E_i$ [mV]</th>
<th>$p$</th>
<th>$\alpha_i$ [ms$^{-1}$]</th>
<th>$\beta_i$ [ms$^{-1}$]</th>
<th>$\tau_i$ [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$</td>
<td>$m$</td>
<td>70</td>
<td>55</td>
<td>3</td>
<td>$1.5e^{(0.810v+39)}$</td>
<td>$1.5e^{(-0.060v+39)}$</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>$h$</td>
<td>1</td>
<td></td>
<td></td>
<td>$0.12e^{-0.009v+50}$</td>
<td></td>
<td>0.225</td>
</tr>
<tr>
<td>$I_{KDR}$</td>
<td>$m$</td>
<td>19</td>
<td>-90</td>
<td>4</td>
<td>$0.17e^{(0.070v+30)}$</td>
<td></td>
<td>0.17e$^{(0.070v+30)}$</td>
</tr>
<tr>
<td></td>
<td>$h$</td>
<td>1</td>
<td></td>
<td></td>
<td>$[70+6.5e^{-0.06max(0,v+40)}] \cdot 10^{-5}$</td>
<td></td>
<td>1.1$\cdot 10^{-3}[1+e^{(0.090v+44)}]$</td>
</tr>
<tr>
<td>$I_{KAI}$</td>
<td>$m$</td>
<td>3.67</td>
<td>-90</td>
<td>3</td>
<td>$0.35e^{(0.099v+70)}$</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>$h$</td>
<td>1</td>
<td></td>
<td></td>
<td>$0.175e^{-0.003v+80}$</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>$I_{Ca^{2+}}$</td>
<td>$m$</td>
<td>2.91</td>
<td>80</td>
<td>2</td>
<td>$1.6[1+e^{-0.072v-5}]$</td>
<td></td>
<td>0.02(v+8.9)[1-e^{0.3(v+4.9)}]</td>
</tr>
<tr>
<td></td>
<td>$h$</td>
<td>1</td>
<td></td>
<td></td>
<td>$0.005e^{-0.05max(0,v+60)}$</td>
<td></td>
<td>0.005[1-e^{-0.05max(0,v+60)}]</td>
</tr>
<tr>
<td>$I_{KCa}$</td>
<td>$m$</td>
<td>80</td>
<td>-90</td>
<td>1</td>
<td>$2.5/[1+1.5e^{-0.08v}/[Ca^{2+}]]$</td>
<td></td>
<td>1.5/[1+[Ca$^{2+}$]/(0.15e$^{-0.07v}$)]</td>
</tr>
<tr>
<td>$I_h$</td>
<td>$m$</td>
<td>0.09</td>
<td>-42</td>
<td>1</td>
<td>$0.0008e^{-0.0099v+75}$</td>
<td></td>
<td>0.0008 e$^{(0.099v+75)}$</td>
</tr>
<tr>
<td>state</td>
<td>Channel, variable</td>
<td>$g_r$ [µS]</td>
<td>$E$ [mV]</td>
<td>$p$</td>
<td>$m^r_\alpha$, ($h^r_\alpha$)</td>
<td>(\tau^r_\alpha) (ms)</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>-----------</td>
<td>---------</td>
<td>-----</td>
<td>--------------------------</td>
<td>-----------------</td>
<td></td>
</tr>
</tbody>
</table>
| $I_{Na}$ | $m$ | 6.25 | 41 | 3 | \[1 + e^{-0.2(v+40)}\]^{-1} | \[
\frac{0.379(v+38)}{1 - e^{-0.2(v+40)}} \quad \frac{0.258(v+38)}{1 - e^{-0.2(v+40)}} \]
| $h$ | | | | | \[1 + \frac{129.4e^{(v+35)/15}}{1 + e^{17 - v/21}}\]^{-1} | \[
\frac{0.0667e^{-0.5(v+15)}}{1 + e^{13 - v/21}} + \frac{8.62}{1 + e^{13 - v/21}} \]
| $I_{NaP}$ | $m$ | $3.64 \times 10^{-3}$ | 41 | 1 | \[1 + e^{-0.2(v+40)}\]^{-1} | \[
\frac{0.379(v+38)}{1 - e^{-0.2(v+40)}} \quad \frac{0.258(v+38)}{1 - e^{-0.2(v+40)}} \]
| $I_{K1}$ | $m$ | 0.314 | -85 | 4 | \[1 + e^{-0.5(v+60)/3.5}\]^{-1} | \[
0.0888 + \frac{0.240}{e^{-0.5(v+60)/3.5}} + e^{0.5(v+60)/3.5} \]
| $h$ | | | | | \[1 + e^{0.8(v+60)/3.5}\]^{-1} | \[
\frac{0.240}{e^{0.8(v+60)/3.5}} + e^{-0.8(v+60)/3.5} \quad v < -63 \quad v > -63
\]
| $I_{K2}$ | $m$ | 0.210 | -85 | 4 | \[1 + e^{-0.3(v+20)/3.5}\]^{-1} | \[
0.0888 + \frac{0.240}{e^{-0.3(v+20)/3.5}} + e^{0.3(v+20)/3.5} \]
| $h$ | | | | | \[1 + e^{0.8(v+20)/3.5}\]^{-1} | \[
\frac{0.240}{e^{0.8(v+20)/3.5}} + e^{-0.8(v+20)/3.5} \quad v < -73 \quad v > -73
\]
| $I_{K3}$ | $m$ | 0.314 | -85 | 4 | \[1 + e^{-0.5(v+43)/17}\]^{-1} | \[
2.38 + \frac{0.240}{e^{0.5(v+43)/17}} + e^{-0.5(v+43)/17} \]
| $h$ | | | | | \[1 + e^{0.8(v+50)/10.5}\]^{-1} | \[
28.8 + \frac{0.240}{e^{0.8(v+50)/10.5}} + e^{-0.8(v+50)/10.5} \]
| $I_{K4}$ | $m$ | 0.210 | -85 | 4 | \[1 + e^{-0.3(v+43)/17}\]^{-1} | \[
2.38 + \frac{0.240}{e^{-0.3(v+43)/17}} + e^{0.3(v+43)/17} \]
| $h$ | | | | | \[1 + e^{0.8(v+50)/10.5}\]^{-1} | \[
28.8 + \frac{0.240}{e^{0.8(v+50)/10.5}} + e^{-0.8(v+50)/10.5} \quad v < -70 \quad v > -70
\]
TABLE 3
Detailed model of DCN neurons, part 2. The table gives maximum conductivity $g$, reversal potential $E$, equilibrium values ($m$, $h$), and time constants $\tau_m$, $\tau_h$ for activation ($m$) and inactivation variables ($h$). The parameters are compensated for 36.5 centigrade. The capacity of the neuron is $C = 150$ pF.

<table>
<thead>
<tr>
<th>state</th>
<th>Channel variable</th>
<th>$g_\alpha$ [\mu S]</th>
<th>$E_\alpha$ [mV]</th>
<th>$p$</th>
<th>$m_\alpha$, $(h_\alpha)$</th>
<th>$\tau_m$, $(\tau_h)$ [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{K,Ca}$</td>
<td>$m$</td>
<td>0.520</td>
<td>-85</td>
<td>1</td>
<td>$\left[1 + \frac{e^{-v/12}}{2.5\cdot10^7[Ca^{2+}]_l}\right]^{-1}$</td>
<td>$\frac{e^{-v/24} + 2.5\cdot10^7[Ca^{2+}]_l e^{v/24}}{e^{-v/24} + 2.5\cdot10^7[Ca^{2+}]_l e^{v/24}}$</td>
</tr>
<tr>
<td>$I_h$</td>
<td>$m$</td>
<td>0.010</td>
<td>-43</td>
<td>1</td>
<td>$\left[1 + e^{-(v/10)}\right]^{-1}$</td>
<td>$\frac{0.0833 (v - 131)}{\frac{6.67}{1 + e^{-0.072(v - 5)}} + \frac{0.0833 (v - 131)}{e^{-0.13(v - 5)} - 1}}$</td>
</tr>
<tr>
<td>$I_C$</td>
<td>$m$</td>
<td>0.645 $\mu$S/mM</td>
<td>2</td>
<td>2</td>
<td>$\left[1 + e^{-(v - 100/10)}\right]^{-1}$</td>
<td>$\frac{0.193}{e^{-(v - 125/10)} + e^{0.15(v - 125/10)}}$</td>
</tr>
<tr>
<td>$I_{K}$</td>
<td>$m$</td>
<td>0.181 $\mu$S/mM</td>
<td>2</td>
<td>2</td>
<td>$\left[1 + e^{-(v - 49/10)}\right]^{-1}$</td>
<td>$\frac{0.263}{e^{0.062(v - 95/10)} + 0.263 [28 + e^{0.17(v - 95/10)}]}$</td>
</tr>
<tr>
<td>$I_{Na,leak}$</td>
<td></td>
<td>0.0012</td>
<td>41</td>
<td>1</td>
<td>$\left[1 + e^{0.78/10}\right]^{-1}$</td>
<td>$\left{\begin{array}{ll} 0.263 e^{0.062(v - 95/10)} &amp; v &lt; -75 \ 0.263 [28 + e^{0.17(v - 95/10)}] &amp; v &gt; -75 \end{array}\right.$</td>
</tr>
<tr>
<td>$I_{K,leak}$</td>
<td></td>
<td>0.0034</td>
<td>-85</td>
<td>1</td>
<td>[ \]</td>
<td>[ \]</td>
</tr>
</tbody>
</table>
with voltage-dependent equilibrium values and
time constants (Hodgkin and Huxley 1952, Traub et
al. 1991) which are summarized in Tables 2 and 3.
The calcium dynamics is identical to that of
McCormick and Huguenard.

(C) Network model

In the present network simulations we have used a
neuron model – the spike response model – that is
in many aspect similar to but on the other hand
much more general than the standard integrate-and-
fire model (Gerstner and van Hemmen 1992,
potential is given by a combination of pre- and
postsynaptic contributions described by a response
kernel $e$ that gives the form of an elementary
postsynaptic potential and a kernel $\eta$ that accounts
for refractoriness and has the function of an
afterpotential, so that

$$h_i(t) = \sum_{j} J_{ij} \epsilon_j(t - t'_j - \Delta_{ij}) - \sum_j \eta_i(t - t'_j).$$

Here, $h_i$ is the membrane potential of neuron $i$, $J_{ij}$ is
the strength of the synapse connecting neuron $j$ to
neuron $i$, $\Delta_{ij}$ is the corresponding axonal delay from
j to i, and $\{t'_j, f=1, 2, \ldots \}$ are the firing times of
neuron $j$. Causality is respected, if both $\epsilon(s)$ and
$\eta(s)$ vanish identically for $s < 0$. Depending on the
choice for $\epsilon$ and $\eta$, the spike response model can
either reproduce the standard integrate-and-fire
model or even mimic complex Hodgkin-Huxley
type neuron models (Kistler et al., 1997). A typical
choice for $\epsilon_j$ is

$$\epsilon_j(t) = \epsilon(t, \tau_1, \tau_2) \equiv \frac{1}{c} (e^{-\tau_2 t} - e^{-\tau_1 t}) \Theta(t),$$

and

$$c = \left( \frac{\tau_1}{\tau_2} \right)^{\frac{\tau_2 - \tau_1}{\tau_2 - \tau_1}} - \left( \frac{\tau_1}{\tau_2} \right)^{\frac{\tau_2 - \tau_1}{\tau_2 - \tau_1}}$$

where $\tau_{1,2}$ are time constants for the rising
and decaying phase of the postsynaptic potential (cf.
Table 4) and $\Theta$ is the Heaviside step function with
$\Theta(t) = 1$ for $t > 0$ and $\Theta(t) = 0$ elsewhere. Post-
inhibitory rebound in DCN and IO neurons is
described by using an IPSP that includes a
depolarizing component (low-threshold Ca$^{2+}$
spike),

$$-\epsilon_{\text{PR}}(t) = -\epsilon(t, \tau_1, \tau_2) + \kappa \epsilon(t - \Delta_{\text{PR}}, \tau_3, \tau_4).$$

The function $\epsilon$ has been defined in the previous
equation; $\Delta_{\text{PR}}$ is the delay after which the low-
threshold Ca$^{2+}$ spike occurs ($\Delta_{\text{PR}} = 105$ ms and
$\Delta_{\text{PR}} = 112$ ms for DCN and IO neurons, respec-
tively), and $\kappa$ is its amplitude ($\kappa = 0.2$ and $\kappa = 0.22$
for DCN and IO neurons, respectively). The time
constants $\tau_3 = 2$ and $\tau_4 = 5$ give the shape of the Ca$^{2+}$
spike. The fact that the reversal potential of
chloride ions may be close to the resting potential is
taken care of by assuming that IPSPs do not
superpose additively. Instead, only the IPSP pro-
duced by the very last inhibitory action potential is
included; cf. Table 4.

As for the refractory function $\eta$, a simple
exponential decay can be used,

$$\eta_i(t) = \begin{cases} 0 & t < 0 \\ -\infty & 0 < t < t_0 \\ -\eta_0 e^{-\eta_0 t} & t > t_0 \end{cases}$$

Here, $t_0$ determines the duration of the absolute
refractory period where no further spikes can be
triggered at all, and $\eta_0$ and $\tau$ describe the form of
the afterpotential; cf. Table 4.

Firing times are generated by means of a
stochastic process with the probability density
of having a spike at time $t$ being a nonlinear function
of the membrane potential $h(t)$,

$$\operatorname{Prob} \{ \text{spike in } [t, t+dt] \} = \tau_0^{-1} \exp[\beta(h - \theta)] \ dt,$$

with $\tau_0 = 2.5$ ms, noise parameter $\beta^{-1} = 0.01$, and
firing threshold $\theta$. This particular ansatz reflects the
fact that firing an action potential is more or less a
threshold process. Noise, however, can trigger an
action potential even before the threshold is
actually reached.

The firing threshold of the various types of
neuron is also given in Table 4. Instead of including
<table>
<thead>
<tr>
<th></th>
<th>pons</th>
<th>DCN</th>
<th>GrC</th>
<th>GoC</th>
<th>PC</th>
<th>BaC</th>
<th>IO</th>
</tr>
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<tbody>
<tr>
<td>Threshold:</td>
<td>$i_0$</td>
<td>0.03*</td>
<td>1</td>
<td>1.5</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>EPSP:</td>
<td>$\tau_i$/ms</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>$\tau_e$/ms</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>IPSP:</td>
<td>$\tau_i$/ms</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>$\tau_e$/ms</td>
<td>50*</td>
<td>40</td>
<td>20</td>
<td>15</td>
<td>20</td>
<td>50*</td>
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<tr>
<td>IPSPs additive</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>AHP:</td>
<td>$\tau$/ms</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>$i_0$/ms</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>$\tau_0$</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>20</td>
<td>100</td>
</tr>
</tbody>
</table>
external excitatory input to neurons of the pons, a high mossy fiber background activity is obtained by a low firing threshold ($\theta = 0.03$). Subthreshold oscillations in IO neurons are mimicked by periodically reducing the firing threshold of IO neurons to $\theta = 1.5$ every 120 ms.

The connectivity of the network is defined by means of arborization functions that give the probability of two neurons being 'connected' as a function of the type of the neurons and of their distance. Before a simulation is started a particular connectivity is generated according to these arborization functions (cf. Table 5). The synaptic strength $J_{ij}$ and the axonal and synaptic delay $\Delta_{ij}$ that are assigned to these connections are summarized in Table 6.

Plasticity at the parallel fiber/Purkinje cell synapses is described by a differential equation of the form

$$\frac{dJ}{dt} = \left[1 - J(t)\right]S_{cf}(t) \int dt' \ k_{LTD}(t')S_{pf}(t - t').$$

$$- J(t)S_{pf}(t) \int dt' \ k_{LTD}(t')S_{cf}(t - t'). \quad (12)$$

Here, the kernel $k_{LTD}(t')$ describes the amount of weight change that is induced by a climbing fiber spike that arrives $t'$ ms after a parallel fiber spike (Kistler and van Hemmen 1999). As for $k_{LTP}(t')$ the situation is similar except that the role of climbing fiber and parallel fiber spikes are exchanged. We use exponentially decaying kernels,

$$k_{LTP}(t) = c_{LTP} \exp(-t/\tau_{LTP}) \Theta(t), \quad (13)$$

with time constants $\tau_{LTD} = 200$ ms and $\tau_{LTP} = 20$ ms, and amplitude $c_{LTP} = 0.2$. With this ansatz a parallel fiber/Purkinje cell synapse is potentiated if

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**TABLE 5**

Arborization functions used to generate the connectivity that is used in the network simulations. The probability of two neurons $i$ and $j$ being connected depends on the type of the neurons and their distance $r_{ij}$. The probability is given by $\text{Prob} \{J_{ij} \neq 0\} = p[1 + e^{-r_{ij}/\delta}]^{-1}$, where $p$, $q$ and $\delta$ describe the overall probability, the range and the shape of the arborization, respectively.

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the parallel fiber spike arrives within about 20 ms milliseconds before the climbing fiber spike and the synapse is depressed, if the timing is the other way round. If the parallel fiber spike arrives long before the climbing fiber spike, the synapse is not modified.

In the simulation shown in Fig. 11 equation (12) is supplemented by a third term, $-J(t)S_c(t) \int dt' \tilde{\kappa}_{\text{LTD}}(t')S_{\text{pf}}(t-t')$, with $\tilde{\kappa}_{\text{LTP}}(t) = 0.2 \exp(-t/200 \text{ ms}) \Theta(t)$, and $\kappa_{\text{LTP}}(t)$ replaced by $\kappa_{\text{LTP}}(t) = 0.35 \exp(-t/20 \text{ ms}) \Theta(t)$. In this case, a parallel fiber/Purkinje cell synapse is potentiated only if the parallel fiber spike arrives within a few milliseconds before the climbing fiber spike. Otherwise, i.e. if the parallel fiber spike arrives after, or long before the climbing fiber spike, the synapse is depressed.

**Appendix references**


