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Delayed reverberation through time windows as a key to cerebellar function

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Abstract. We present a functional model of the cerebellum comprising cerebellar cortex, inferior olive, deep cerebellar nuclei, and brain stem nuclei. The discerning feature of the model being time coding, we consistently describe the system in terms of postsynaptic potentials, synchronous action potentials, and propagation delays. We show by means of detailed single-neuron modeling that (i) Golgi cells can fulfill a gating task in that they form short and well-defined time windows within which granule cells can reach firing threshold, thus organizing neuronal activity in discrete 'time slices', and that (ii) rebound firing in cerebellar nuclei cells is a robust mechanism leading to a delayed reverberation of Purkinje cell activity through cerebellar-reticular projections back to the cerebellar cortex. Computer simulations of the whole cerebellar network consisting of several thousand neurons reveal that reverberation in conjunction with long-term plasticity at the parallel fiber-Purkinje cell synapses enables the system to learn, store, and recall spatio-temporal patterns of neuronal activity. Climbing fiber spikes act both as a synchronization and as a teacher signal, not as an error signal. They are due to intrinsic oscillatory properties of inferior olivary neurons and to delayed reverberation within the network. In addition to clear experimental predictions the present theory sheds new light on a number of experimental observation such as the synchronicity of climbing fiber spikes and provides a novel explanation of how the cerebellum solves timing tasks on a time scale of several hundreds of milliseconds.

1 Introduction

Almost all neurons in the cerebellar cortex being inhibitory, it seems obvious that Nature has taken care to *prevent* neurons from firing, or, as we will propose here, to prevent neurons from firing outside short and well-defined time windows. In fact, all excitatory pathways in the cerebellar cortex are paralleled by strong and sophisticated inhibitory projections. The granule cells receive excitatory input from the mossy fibers *and* inhibitory input from the Golgi cells, which in turn are excited directly by the mossy fibers and indirectly by the parallel fibers. Excitatory and inhibitory synapses are closely packed together in mossy fiber glomeruli, which insures that there is no excitatory mossy fiber synapse without a corresponding inhibitory Golgi cell synapse. A similar connectivity is present in the Purkinje/basket cell system. Both Purkinje cells (PCs) and basket cells receive excitatory input from the parallel fibers and the basket cells send inhibitory input to nearby PCs.

In either case there is probably only a short time interval after the arrival of a valley of excitatory mossy fiber or parallel fiber spikes in which the target neuron can reach firing threshold before inhibition becomes effective. Both granule cells and PCs can thus only be fired by a sharp pulse of simultaneously arriving action potentials. This observation has implications for the quest of the neuronal code used by the cerebellum: It is the synchronicity of probably a large number of spikes which carries information that is meaningful to the cerebellar cortex.

In the following we present a model of the cerebellum and its associated nuclei that relies on synchronicity and precise timing of individual action potentials. The main building blocks of our model are synaptic plasticity at the parallel fiber-Purkinje cell (pf-PC) synapses, the granule cell-Golgi cell system performing a gating task, and post-inhibitory rebound in neurons from the deep cerebellar nuclei (DCN) and inferior olive (IO). Post-inhibitory rebound is the central mechanism which on the one hand converts inhibitory input to action potentials and on the other hand provides a robust mechanism to produce delays of about 100 ms which is the natural time scale of our model.

1.1 Time windows for triggering spikes

One of the key elements of our model is the observation that synchronous repetitive firing of the Golgi cells produces narrow time windows within which the granule

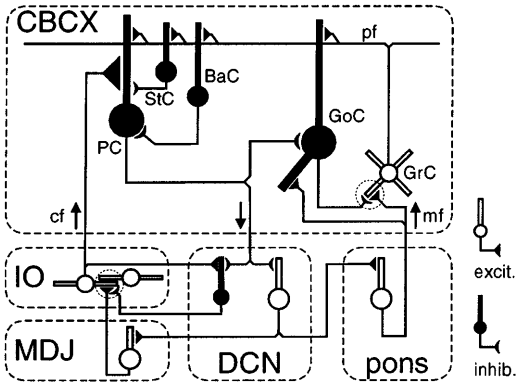

Fig. 1 Cerebellar network. Inhibitory neurons are black, excitatory neurons are open circles. The following abbreviations are used: PC (Purkinje cell), GoC (Golgi cell), GrC (granule cell), BaC (basket cell), StC (stellate cell), pf (parallel fiber), mf (mossy fiber), cf (climbing fiber), CBCX (cerebellar cortex), IO (inferior olive), MDJ (mesodiencephalic junction), DCN (deep cerebellar nuclei)

cells can reach firing threshold. If all Golgi cells with overlapping axonal arborization are firing periodically and synchronously, each granule cell within this region 'sees' a periodically modulated inhibitory potential. The granule cell is thus able to reach firing threshold only during a short time interval before the Golgi cells are firing their next spike, that is, when inhibition is weakest. If the Golgi cells fire asynchronously, the IPSPs from several Golgi cells overlap partially and the granule cells are exposed to a more or less constant level of inhibition which prevents or suppresses firing of the granule cells. Because of the restriction of the granule cell firing events to narrow time windows, parallel fiber spikes reach nearby PCs *coincidently*, which is necessary in order to bring them near firing threshold [1, 2].

The second key element of our model is the observation that the output of the cerebellum is reverberated to the cerebellar cortex via the mossy fibers and with a delay that corresponds to the delayed opening of the granule cell time window. This idea is supported by several experimental observations. First, the neurons in the DCN show pronounced post-inhibitory rebound firing [3, 4]. This rebound firing is probably responsible for long-latency responses in DCN neurons after electrical stimulation of the IO [5, 6] or might be involved indirectly in long-latency responses in IO neurons after stimulation of the mesodiencephalic junction (MDJ) [7]. Second, there are strong excitatory connections between the DCN and the nucleus reticularis tegmenti pontis (NRTP) [8, 9], which belongs to the pons and is a source of cerebellar mossy fibers [10]. This circuitry seems to be well-designed to function as an excitatory reverberating loop [11]. Thus, neurons in the DCN respond to a volley of synchronous PC spikes with rebound spikes that occur reliably and with a constant delay of about 100 ms after the arrival of the PC spikes. Because of the excitatory projections from the DCN to the NRTP, action potentials in the DCN reappear in the mossy fibers after another few milliseconds. If the summed delay of post-inhibitory rebound and synaptic transmission matches the delayed opening of the granule cell window, we obtain a closed loop and the cerebellum can lock in on information that is directly related to preceding output signals.

1.2 Learning spatio-temporal patterns

Although it is now known what the cerebellum is actually doing, there is ample evidence for the involvement of the cerebellum in a broad variety of different tasks such as motor coordination [10, 12–15], timing tasks in classical conditioning experiments [16, 17], or even cognitive tasks [18–20]. With regard to the uniform architecture of the cerebellar cortex it is tempting to speculate that the cerebellum is performing a universal and fundamental task that can be used as a building block for higher functions. A task that matches this criterion is learning spatio-temporal patterns.

We have seen in the previous section that synchronous PC activity can reverberate to the cerebellar cortex within about 100 ms. Given the correct timing of granule cell window and delayed reverberation, the reverberated signal can in turn trigger PCs and thus start a sustained oscillation. The subset of PCs that is triggered in a certain cycle depends on the set of active PCs in the previous cycle and is determined by the wiring of the reverberating loop and by the weight matrix of the pf-PC synapses. Given a means to adjust these synaptic weights, the cerebellar network can store and recall spatio-temporal patterns of spike activity.

There is recent evidence for the dependence of long-lasting changes in the strength of pf-PC synapses upon the precise timing of parallel fiber and climbing fiber spikes. It has been reported [21, 22] but see [23] that long-lasting depression of the synaptic strength (LTD) is observed only if the climbing fiber spike *precedes* the parallel fiber spikes and that in contrast the synapse is strengthened if the timing is the other way round, or if parallel fiber spikes arrive at the PC without a subsequent climbing fiber pulse [24–26]. These findings are incompatible with the interpretation of climbing fiber spikes as an 'error signal' that tells the PC when *not* to fire [27], because an error signal can only be generated after the error has occurred, and the climbing fiber signal cannot depress those synapses that had fired the PC in order to prevent this error the next time. Instead, climbing fiber spikes operate as teaching signals [28] in the sense that they tell PCs when precisely they are to fire an action potential. This is consistent with the very primary effect of a climbing fiber spike, viz., the triggering of a complex spike.

The mechanism of learning a spatio-temporal pattern is as follows. Suppose a mossy fiber event, i.e., a number of coincident mossy fiber spikes, arrives at the cerebellar cortex within the granule cell time window. Suppose further that a set of climbing fiber spikes reaches the cerebellar cortex within a short time interval of about 10 ms after the mossy fiber event. In agreement with experimental findings, we assume that this constellation potentiates those pf-PC synapses that have been activated a short time, say 10 ms, *before* the arrival of the climbing

fiber spikes, i.e., those synapses that have been activated by the mossy fiber event. In addition, there is depression in all synapses that become active during an interval of about 100 ms *after* the occurrence of the climbing fiber spikes. Consequently, the firing of those PCs that have been activated by a climbing fiber signal is bound to the occurrence of the mossy fiber event. After a few repetitions the mossy fiber event *alone* will suffice to trigger the PCs. Because of the reverberating circuit, synchronous firing of a set of PCs produces a new mossy fiber event 100 ms later on. Another volley of climbing fiber spikes can be used to train a second set of PCs to respond to the second mossy fiber event. This can be repeated and long sequences of PC firing patterns can thus be learned and recalled by the very first mossy fiber event.

1.3 Inferior olivary neurons as a neuronal clock

Inferior olivary neurons show intrinsic oscillatory behavior which is due to their electrophysiological properties and to an extensive coupling with gap junctions [29, 30]. In addition, there are two reverberating loops that further support 10-Hz oscillations in the IO; cf. Fig. 1. As for the first loop, IO neurons send collaterals to inhibitory neurons from the DCN which in turn project back to the IO in a topographic fashion [31, 32]. These DCN neurons can fire only a short volley of action potentials because they are inhibited themselves shortly after they have received input from the IO by complex spikes from the PCs triggered by the very same volley of climbing fiber spikes. IO neurons show pronounced post-inhibitory rebound [29] and a volley of inhibitory DCN spikes will thus produce action potentials in their target neurons in the IO with a delay of about 100 ms and, once more, we are left with a *delayed* reverberating loop. The second loop comprises complex spikes in PCs which elicit rebound spikes in excitatory DCN neurons as explained above. Rebound activity in DCN neurons is conveyed to the IO by a di-synaptic pathway via neurons from the MDJ and can trigger action potentials in IO neurons again after an overall delay of 100 ms [7].

We propose that electrophysiological properties of IO neurons and the architecture of the network are particularly well suited to produce sequences of ever-differing patterns of climbing fiber spikes that can be used as a neuronal clock [33] that is probably involved in all kinds of timing-tasks attributed to the cerebellum. An external event, e.g. a conditioned stimulus in a classical conditioning experiment, produces a certain pattern of IO activity, which in turn gives rise to another pattern in the next yele due to delayed reverberation, and so forth. Each pattern of climbing fiber activity is accompanied by a certain parallel fiber pattern as explained in the previous section. Some hundreds of milliseconds later, another external event, e.g., the unconditioned stimulus in the afore mentioned experiment, triggers complex spikes in a different group of PCs. Due to synaptic plasticity, these PCs will learn to recognize the parallel fiber pattern that is the reminiscence of the first event and will fire action potentials with the proper delay measured from the onset of the first event even if the second, viz., the unconditioned stimulus is omitted. The existence of spatial-temporal patterns of climbing fibers, which is predicted by the present model, has been demonstrated in a recent study of a simple motor task in rat [34]. This provides a – to our knowledge – novel explanation of how the cerebellum solves timing tasks on a time scale of hundreds of milliseconds, that is significantly longer than the millisecond time scale usually attributed to neuronal dynamics.

2 Methods

In the following we give a brief overview of the methods that we have applied. Further details can be found in [35].

2.1 Granule cell model

In order to demonstrate that the Golgi cell-granule cell system forms a potent gating device that admits only spikes arriving within narrow time windows, we have investigated the spike triggering mechanism for various timings of mossy fiber and Golgi cell spikes using a realistic multi-compartment model of turtle granule cells [36].

The model consists of several passive dendritic compartments and one active somatic compartment and contains various Na^+, K^+, and Ca^{2+} currents. Our granule cell model is identical to that of Gabbiani et al. [36] except that (i) we have simplified the Ca^{2+} dynamics as proposed by Traub et al. [37] and that (ii) we have included $GABA_A$-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 $\bar{g}_{fast} = 1.0$ pS) and 50 ms (peak amplitude $\bar{g}_{slow} = 0.5$ pS), as reported for rat granule cells [38]. Excitatory synaptic currents are made up of a combination of NMDA and AMPA components as described in [36].

2.2 Deep cerebellar nuclei neurons

To our knowledge there are no detailed voltage-clamp studies of DCN neurons, but DCN neurons do have electro-physiological properties similar to those of thalamic cells [4, 39]. Starting from a model of thalamic relay neurons [40] we have developed a single compartment model of DCN neurons containing various Na^+, K^+, and Ca^{2+} currents. We were able to reproduce plots of the firing frequency versus the injected current as well as the response to small de- and hyper-polarizing current pulses measured in guinea-pig DCN neurons [3]. Furthermore, the model exhibits low-threshold Ca^{2+} spikes and non-inactivating Na^+ plateaus, which are characteristic features of DCN neurons [4, 41].

We arrived at the final parameter setting by scaling the original model [40] by a factor 0.5 in order to account for the small size of DCN neurons [3] and to get the passive membrane response to small current pulses right. We have substituted the correct reversal potential

of K^+ [41] for DCN neurons and adjusted the leak current conductivity so as to get a resting potential of -57 mV. The mixed cation current I_h has been replaced by a modified version of the anomalous rectifying current [42] because this produced a better fit of the 'sag' in the membrane potential during hyper-polarizing pulses. Finally, the activation and inactivation curves of the transient calcium current I_T have been shifted slightly and the inactivation dynamics has been slowed down in order to reproduce the response to hyper-polarizing current pulses [3]. Inhibitory synapses are implemented as CI^- conductances (reversal potential -73.4 mV, max. conductance 50 nS) and an exponential decay (time constant 5 ms) so as to reproduce the time course of spontaneous IPSPs [41].

2.3 Network model

We have performed extensive computer simulations of a model of the cerebellar cortex and the associated nuclei. The neurons are described by the spike response model [43–45] and each neuron is characterized by the shape of its postsynaptic potentials, firing threshold, and after-hyperpolarization. This setup allows for a qualitative description of different types of neuronal behavior such as adaptation and post-inhibitory rebound. The connectivity of the network is, within morphological constraints, taken to be random. That is, neurons are assigned arborization functions that give the probability of two neurons being synaptically connected as a function of their distance. The set of arborization functions is chosen so as to reflect the numbers of converging and diverging projections between cerebellar neurons described in the literature. The neurons included in the simulation are located along a narrow parasagittal strip. Axonal and synaptic delays are explicitely taken into account. Noise is included in the dynamic by adopting a stochastic spike triggering criterion that allows for an action potential even if the membrane potential is roughly 0.5 percent below threshold. The threshold itself corresponds typically to the amplitude of 10 EPSPs. The restriction of firing times to certain phases of the subthreshold oscillations observed in IO neurons [46] has been mimicked by periodically modulating the firing threshold of the simulated IO neurons.

In order to obtain long sequences of spike patterns in the climbing fiber system, a certain (sparse) amount of connectivity between IO, DCN, and MDJ is required. In our simulations this connectivity is the result of anti-Hebbian elimination of synapses, i.e., we start with a connectivity slightly higher than required and eliminate those synapses with a certain small probability that are contributing repetitively to the firing of a postsynaptic neuron.

Plasticity at pf-PC synapses is implemented as explained above, i.e., a synapse is depressed, if a parallel fiber spike arrives within 100 ms after a climbing fiber spike. The synapse is potentiated, if a parallel fiber spike is followed by an climbing fiber spike within 10 ms.

3 Results

3.1 Granule-cell time window

Figure 2 shows the results of a simulation of a realistic multi-compartment model of cerebellar granule cells. The granule cell is fed with input from four Golgi cells and with a volley of four synchronous mossy fiber spikes with a variable timing relative to the Golgi cell spikes. We have investigated the excitability of the granule cell and the timing of the granule cell spike for synchronous and asynchronous Golgi cell activity.

The simulations confirm the postulated time-window behavior. A granule cell that receives inhibitory input from Golgi cells can fire only if (i) the presynaptic Golgi cells fire synchronously and (ii) if the mossy fiber spikes arrive with the correct timing relative to the Golgi cell spikes, i.e., within a narrow and well-defined time window. Though a weak synchronization of Golgi cells has so far been observed only in a transversal direction [47], we would expect that common input to Golgi cells located within a parasagittal micro zone results in synchronous Golgi cell activity as well. In any case, a selective synchronization of Golgi cells which is crucial for the time window mechanism seems to be a natural assumption. Later on it Sect. 3.3 we will see that there is indeed a

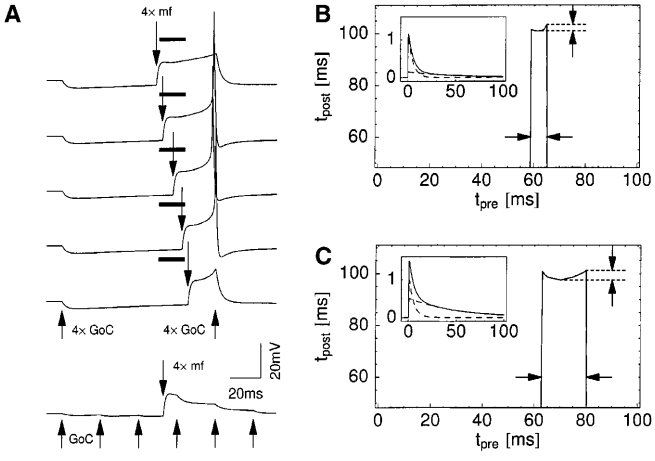

Fig. 2 Granule cell time window. **A**, membrane potential as a function of time in a simulation of a realistic model of turtle granule cells. The vertical arrows in the five uppermost traces indicate the arrival times of volleys of synchronous Golgi cell (GoC; arrows pointing up) and mossy fiber spikes (mf; arrows pointing down) containing 4 spikes each. The fat horizontal bar marks the interval during which mossy fiber spikes can trigger an action potential. If the same number of Golgi cell spikes arrives asynchronously, here one spike every 25 ms (lowest trace), then 4 synchronous mossy fiber spikes are unable to trigger an action potential, whatever their arrival time. The graphs in **B** and **C** give the firing time of the granule cell t_{post} as a function of the arrival time t_{pre} of a volley of n synchronous mossy fiber spikes. **B**, $n = 3$, $\bar{g}_{slow} = 0.5$. In both plots the granule cell receives four synchronous Golgi cell spikes every 100 ms and $\bar{g}_{fast} = 1$ pS. Variability in the timing (arrows) of the postsynaptic spikes is significantly smaller than of the presynaptic spikes ('spike focusing'). The insets show the synaptic conductivity (pS) as a function of time (ms) – slow and fast component are indicated by dashed lines

mode of the underlying network dynamics where Golgi cells are firing periodically *and* synchronously.

Examination of the timing of the granule cell spikes reveals that granule cell spikes occur always within a few milliseconds before the Golgi cell spikes arrive. The timing of the granule cell spike is thus virtually *independent* of the timing of the mossy fiber volley within the time window; cf. 2. This 'focusing' of granule cell spikes is clearly in favor of a mechanistic interpretation of the cerebellum in terms of synchronicity and precise spike timing.

Figure 2 also reveals that the width and the position of the granule cell time window depends on the strength of the inhibitory synapses, in particular, on the peak amplitude of the slow component of the IPSCs. Controlling the time course of the IPSC by regulating the peak amplitude of its slow component is thus a means of tuning the time window's properties. A systematic modification of this parameter has been observed during development in rat [38] and, as a natural explanation, we propose that this is related to the tuning of the time window.

3.2 Post-inhibitory rebound

Any system that is able to handle spatio-temporal patterns inevitably requires timing mechanisms operating on the desired time scale. The present model relies on 10 Hz oscillations in the IO and on post-inhibitory rebound of DCN neurons in order to produce well-defined delays of about 100 ms.

In order to demonstrate that DCN neurons are able to generate delays of the required length in a reliable and robust manner, we have investigated the timing of rebound spikes for different numbers and different timings of the incoming PC spikes using a realistic model of DCN neurons. It has turned out that a certain minimum amount of inhibition is required to trigger a rebound spike. If, however, a rebound spike is triggered, then it occurs with a delay of about 100 ms after the onset of the inhibition, irrespectively of the number of elementary IPSPs involved or of the distribution of their arrival times; cf. Fig. 3. This result seems to be confirmed by recording from rat DCN neurons [48, Fig. 3] where a single IPSP elicits a rebound spike after 130 ms and a burst of ten IPSPs results in a slightly shorter delay of 115 ms (cf. our Fig. 3B). The delay produced by a burst of IPSPs is apparently insensitive to an additional hyper-polarization (125 ms at -70 mV instead of 115 ms at -60 mV).

In a way similar to the focusing effect in granule cells, the postsynaptic rebound spike can be timed more precisely than an individual PC spike, if the rebound is triggered by a couple of IPSPs and the residual noise is thus reduced by an intrinsic averaging of the PC-spike arrival times.

3.3 Network simulations

Simulations of the cerebellar network have revealed the existence of two different firing modes in the PCs;

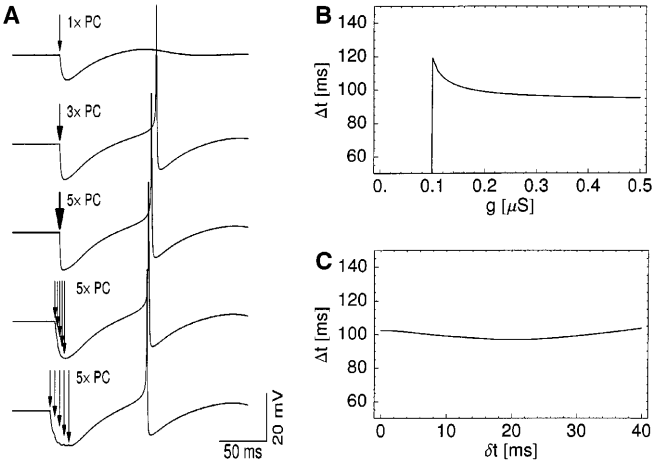

Fig. 3 Post-inhibitory rebound in DCN neurons. **A**, membrane potential of a detailed model for DCN neurons in response to varying amounts of PC inhibition (arrows). The resulting rebound spike occurs after a delay of approximately 100 ms, irrespectively of the number of PC spikes or their degree of synchrony. **B**, delay Δt of the rebound spike after a volley of PC spikes as a function of the total synaptic conductivity, i.e., the conductivity per synapse times the number of activated synapses. **C**, delay of the rebound spike after a volley of three PC spikes versus the degree of their synchrony δt (width of the interval containing all three spikes) measured from the center of the PC spike volley. Note the plateaus in B and C which reflect the robustness of the timing of the rebound spike with respect to its elicitation

cf. Fig. 4. In the first mode, PCs are firing more or less incoherently at a high rate, thus producing high levels of inhibition at Golgi cells and dis-inhibition at granule cells, which results in a high parallel fiber activity that sustains the PC firing rate. A *synchronous* volley of mossy fiber spikes, however, can induce a transition to the second mode that is characterized by PCs firing coherently at about 10 Hz. After Golgi cells have been inhibited through PC collaterals, granule cells recover from inhibition within the next 100 ms. Rebound activity in the DCN produced by the PC spike volley thus arrives within the granule cell time window and the resulting parallel fiber volley triggers both Purkinje and Golgi cells and the oscillation starts over again. The role of the granule cell/Golgi cell system is clearly visible in Fig. 4. 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'. Asynchronous climbing fiber spikes de-synchronize the network and induce a transition back to the first mode.

In the simulation shown in Fig. 4 the weight matrix of pf-PC synapses contained no structure. We now show that a systematic modification of these synapses, as it is a consequence of the described mechanism of synaptic plasticity, allows the cerebellum to store spatio-temporal patterns of PC activity. The pattern the PCs are about to learn is presented to them by climbing fiber spikes. The first set of climbing fiber spikes at $t = 400$ ms in Fig. 5. A forces the corresponding PCs to fire complex spikes

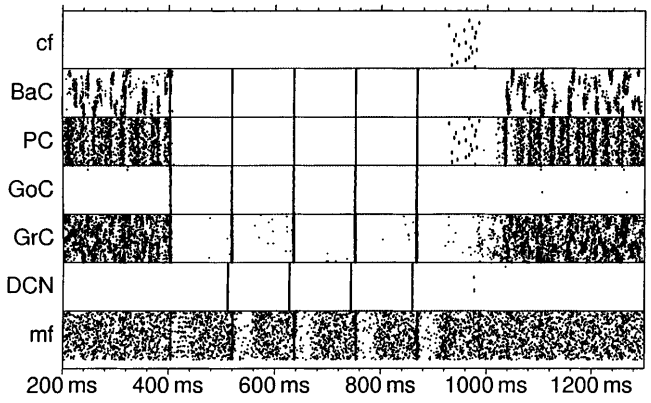

Fig. 4 Two modes of operation in a simulation of the cerebellar network. The diagrams show the spike trains of 200 DCN neurons (DCN), 1000 granule cells (GrC), 80 Golgi cells (GoC), 200 PCs (PC), 400 basket cells (BaC), and the spike trains delivered by 200 mossy fibers (mf) and 200 climbing fibers (cf) as a raster diagram over time. Each short vertical line corresponds to an action potential, but because of limited printing resolution, synchronous spikes of neighbouring neurons may merge into one line. The volley of synchronous mossy fiber spikes at $t = 400$ ms and the climbing fiber spikes around $t \approx 1000$ ms are generated externally

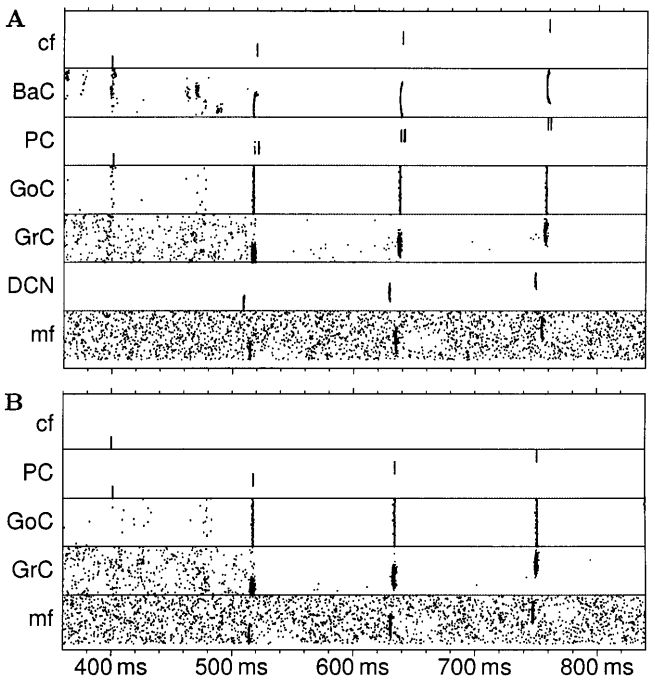

Fig. 5 Cerebellum learning spatio-temporal patterns. **A** The PCs are trained by climbing fiber spikes which are delivered subsequently every 120 ms by four groups of climbing fibers (uppermost panel). **B** Similar diagram as in **A** but after the pattern has been learned successfully. A single climbing fiber volley at $t = 400$ ms suffices to recall the learned pattern

that inhibit DCN neurons and cause a rebound volley to arrive on the mossy fiber system at $t \approx 518$ 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 PCs which in turn produce rebound spikes in DCN neurons–and so on.

After a few repetitions, pf-PC synapses are modified in such a way that a characteristic parallel fiber pattern suffices to trigger the PC, even without a climbing fiber spike. Figure 5B shows that after 10 repetitions the pattern has been learned successfully and can be recalled, for instance, by the first climbing fiber event. We note 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 simulations also demonstrate the importance of climbing fiber synchrony. 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 (data not shown).

Up to now, climbing fiber spikes have been imposed externally on the network. We finally show that sequences of climbing fiber spike patterns as they are generated by intrinsic oscillatory properties of IO neurons and by reverberating loops between IO, DCN, and MDJ can be used as a neuronal clock forming tasks in classical conditioning experiments. In Fig. 6A two external events trigger IO neurons at $t = 400$ and $t = 760$, respectively, and give rise to slowly decaying transients of climbing fiber activity. Each set of climbing fiber spikes produces complex spikes in the corresponding PCs and, thus, produces a certain pattern of parallel fiber activity in the next cycle, as seen before. The pairing of the second event with the parallel fiber pattern at $t \approx 760$ induces a modification of the strength of pf-PC synapses so that PCs will fire action potentials in response to this parallel fiber pattern even if the external event is omitted; cf. Fig. 6B. The network is thus able to learned the time difference between a conditioned stimulus (first event) and an unconditional stimulus (second event) and to respond to the first stimulus with the *correct delay*, which can be as long as several hundreds of milliseconds, even though the second stimulus is omitted.

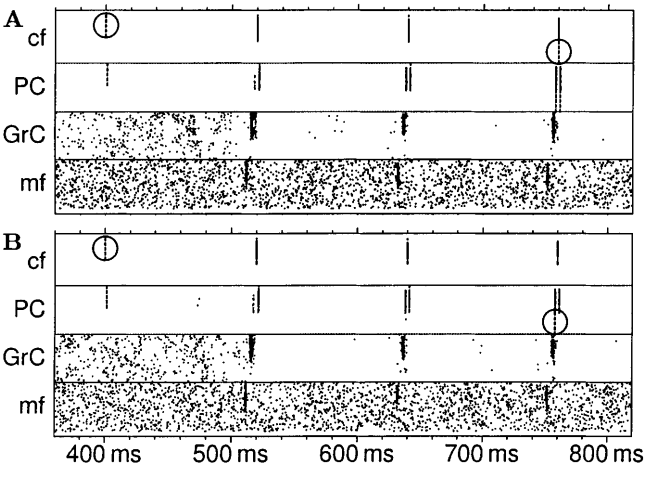

Fig. 6 Cerebellar network performing a timing task. **A** Two external events trigger certain subpopulations of IO neurons giving rise to two climbing fibre events at $t = 400$ and $t = 760$, respectively, (circles) and a transient activity in the aftermath. **B** After a few repetitions of the external stimuli, the first event alone (circle at $t = 400$) suffices to evoke the correctly timed response in the PCs (circle at $t = 760$)

4 Discussion

We have presented a model of the cerebellum that provides a functional description of the cerebellar cortex and the associated nuclei in terms of volleys of synchronous spikes and the precise timing of individual action potentials. Cerebellar interneurons are entrusted with a function that goes beyond a mere regulation of the activity of the principal neurons in that they form short and well-defined *time windows* within which PCs and granule cells can reach firing threshold. Whereas the firing of individual neurons is restricted to short time windows, the synchronization of certain sub-populations of neurons results in a confinement of neuronal activity to discrete time slices. This might be a general and very powerful paradigm for neuronal information processing and similar mechanisms have been found to be involved in intricate coding schemes in the hippocampus [49] and the olfactory system [50].

Almost one hundred years after the internal structure has been elucidated by Ramón y Cajal [51] the function of the cerebellum is still unknown. We have therefore contented ourselves with the demonstration that the present model is able to learn, store, and recall spatio-temporal patterns of neuronal activity or, more precisely, sequences of discrete activity patterns every 100 ms. This ability comprises the generation of specific activity patterns on a behaviorally relevant time scale as they are required for motor control [33, 52]. Extraordinary electrophysiology properties of IO and DCN neurons in conjunction with the topology of the network are thus at the base of how the cerebellum can solve timing tasks on a time scale much longer than the millisecond time scale usually attributed to neuronal dynamics.

4.1 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. 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 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.

The robustness with respect to intrinsic noise results from the quasi-digital mode of information processing and the auto-associative way in which spatio-temporal patterns are stored. PCs have learned to recognize certain parallel fiber events in an associative and error-tolerant manner. Since the PC activity in one cycle is reverberated to the parallel fibers in the next cycle, the whole succession of spike patterns is stable [53].

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. First, the firing time of granule cells is insensitive to the arrival time of a mossy fiber volley provided it arrives within their time window. Granule cell spikes are thus 'focused' into an interval that is even shorter than the granule cell time window. Second, the rebound spikes fired by DCN neurons occur with a fixed delay of about 100 ms after the PC spike volley independent of the number of spikes in the volley and their temporal spreading. Both effects are crucial to a safe operation of the present model. Otherwise small deviations in spike timing would grow until synchronization is so poor that all neuronal activity in the reverberating loop would cease to exist.

4.2 Conclusion

To our understanding, the most appealing aspect of the present model is the fact that it sheds new light on a number of previously unrelated experimental observations. We have shown, for instance, that climbing fiber spikes must arrive coincidently at the cerebellar cortex with millisecond precision in order to properly synchronize cerebellar neurons – a result that is in perfect accord with experimental findings [54–56] and that explains the tuning of propagation velocities in climbing fibers [57] and electrophysiological peculiarities in the IO such as gap junctions and sub-threshold oscillations [29, 30, 33, 46]. Furthermore, we were able to show that experimental results concerning the timing of parallel fiber and climbing fiber spikes required for LTD and LTP are in accord with a supervised learning paradigm which is, however, different from the classical error-signal paradigm [27].

In addition to the explanation of previous observations the model allows for clear experimental predictions, e.g., regarding the firing time of granule cells relative to the Golgi cell firing, namely, the restriction of granule cell spikes to narrow time windows. Other predictions concern correlations between synchronous PC activity and mossy- and climbing- fiber activity 100 ms later on due to delayed reverberating loops, or the existence of patterns in the simple spike activity of a population of PCs on a time scale of several hundreds of milliseconds.

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References

1. Axelrad H, Korn H (1982) Exp Brain Res Suppl 6:412–439
2. Heck D (1993) Neurosci Lett 157:95–98
3. Jahnsen H (1986) J Physiol (Lond) 372:129–147
4. Llinás R, Mühlethaler M (1988) J Physiol (Lond) 404:241–258
5. Armstrong DM, Cogdell B, Harvey RJ (1975) J Physiol (Lond) 248:489–517
6. Ruigrok TJH (1997) in Progress in Brain Research, eds. De Zeeuw CI, Voogd J (Elsevier Science, Amsterdam), pp. 167–192

7. Ruigrok TJH, Voogd J (1995) Eur J Neurosci 7:679–693
8. Murakami F, Ozawa NN, Katsumaru H, Tsukahara H (1981) Neurosci Lett 25:209–213
9. Tsukahara N, Bando T, Murakami F, Oda Y (1983) Brain Res 274:249–259
10. Ito M (1984) The Cerebellum and Neural Control (Raven Press, New York)
11. Verveer C, Hawkins RK, Ruigrok TJH, De Zeeuw CI (1997) Brain Res 766:289–296
12. Lisberger SG (1982) Trends Neurosci 5:437–441
13. Thach WT, Goodkin HP, Keating JG (1992) Annu Rev Neurosci 15:403–442
14. Glickstein M (1993) in Memory Concepts–1993. Basic and clinical aspects, eds. Anderson P, Hvalby , Paulsen O, Hökfelt B (Excerpta Medica, Amsterdam), pp. 127–135
15. Houk JC, Buckingham JT, Barto AG (1996) Behav Brian Sci 19:368–383
16. McCormick DA, Thompson RF (1984) J Neurosci 4:2811–2822
17. Perret SP, Ruiz BP, Mauk MD (1993) J Neurosci 13:1708–1718
18. Ivry RB, Keele SW (1989) J Cogn Neurosci 1:136–152
19. Leiner HC, Leiner AL, Dow RS (1993) Trends Neurosci 16
20. Daum I, Ackermann H (1995) Behav Brain Res 67:201–210
21. Schreurs BG, Oh MM, Alkon DL (1996) J Neurophysiol 75
22. Lev-Ram V, Jiang T, Wood J, Lawrence DS, Tsien RY (1997) Neuron 18:1025–1038
23. Bell CC, Han VZ, Sugawara Y, Grant K (1997) Nature 387:278–281
24. Sakurai M (1987) J Physiol (Lond) 394:463–480
25. Hirano T (1991) J Physiol (Paris) 85:145–153
26. Salin PA, Malenka RC, Nicoll RA (1996) Neuron 16:797–803
27. Albus JS (1971) Math Biosci 10:25–61
28. Marr D (1969) J Physiol (Lond) 202:437–470
29. Llinás R, Yarom Y (1981) J Physiol (Lond) 315:549–567
30. Llinás R, Yarom Y (1986) J Physiol (Lond) 376:163–182
31. De Zeeuw CI, Alphen AM, Hawkins RK, Ruigrok TJH (1997) Neurosci 80:981–986
32. De Zeeuw CI, Simpson JI, Hoogenraad CC, Galijart N, Koekkoek SKE, Ruigrok TJH (1998) Trends Neurosci 21:391–400
33. Llinás R (1991) in Motor Control:Concepts and Issues, eds. Humphrey DR, Freund HJ (Wiley, New York), pp. 223–242
34. Welsh JP, Lang EJ, Sugihara I, Llinás R (1995) Nature 374:453–457
35. Kistler WM, van Hemmen, JL, De Zeeuw CI (2000) in Cerebellar Modules:Molecules, Morphology, and Function, eds. Gerrits NM, Ruigrok TJH, De Zeeuw CI Progress in Brain Research (Elsevier, Amsterdam)
36. Gabbiani F, Midtgaard J, Knoepfl T (1994) J Neurophys 72:999–1009
37. Traub RD, Wong RKS, Miles R, Michelson H (1991) J Neurophysiol 66:635–650
38. Tia S, Wang JF, Kotchabhakdi N, Vicini S (1996) J Neurosci 16:3630–3640
39. Llinás R (1988) Science 242:1654–1664
40. McCormick DA, Huguenard JR (1992) J Neurophysiol 68:1384–1400
41. Jahnsen H (1986) J Physiol (Lond) 372:149–168
42. Spain WJ, Schwindt PC, Crill WE (1987) J Neurophysiol 57:1555–1576
43. Gerstner W, van Hemmen JL (1992) Network 3:139–164
44. Gerstner W, van Hemmen, JL (1994) in Models of Neural Networks II, eds. Domany E, van Hemmen JL, Schulten K (Springer, New York)
45. Kistler WM, Gerstner W, van Hemmen JL (1997) Neural Comput 9:1015–1045
46. Lampl I, Yarom Y (1993) J Neurophysiol 70:2181–2186
47. Vos BP, Maex R, Volny-Luraghi A, De Schutter E (1999) J Neurosci 19:(RC6), 1–5
48. Aizenman CD, Manis PB, Linden DJ (1998) Neuron 21:827–835
49. O'Keefe J (1993) Curr Opin Neurobiol 3:917–924
50. Laurent G (1996) Trends Neurosci 19:489–496
51. Ramón y Cajal S (1911) Histologie du Systéme Nerveux de I'homme et des Vertébrés (Maloine, Paris)
52. Vallbo AB, Wessberg J (1993) J Physiol (Lond) 469:673–691
53. Gerstner W, Ritz R, van Hemmen JL (1993) Biol Cybern 69:503–515
54. Bell CC, Kawasaki T (1972) J Neurophysiol 35:155–169
55. Llinás R, Sasaki K (1989) Eur J Neurosci 1:587—602
56. Lang EJ, Sugihara I, Llinás R (1996) J Neurophysiol 76:255–275
57. Sugihara I, Lang EJ, Llinás R (1993) J Physiol. (Lond.) 470:243–271