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Time windows and reverberating loops: a reverse-engineering approach to cerebellar function

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We review a reverse-engineering approach to cerebellar function that pays particular attention to temporal aspects of neuronal interactions. This approach offers new vistas on the role of GABAergic synapses and reverberating projections within the olivo-cerebellar system. More specifically, our simulations show that Golgi cells can control the ring time of granule cells rather than their ring rate and that Purkinje cells can trigger precisely timed rebound spikes in neurons of the deep cerebellar nuclei. This rebound activity can reverberate back to the cerebellar cortex giving rise to a complex oscillatory dynamics that may have interesting functional implications for working memory and timed-response tasks.

Keywords:
theoretical model – cerebellum – olivary nucleus – cerebellar nuclei

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Introduction

Traditionally, brain research deals with questions of how certain structures of the brain accomplish their specific task such as how visual information is processed in the striate cortex or how movements are coordinated by the motor system. With the dawn of neuro-informatics and neuro-physics a different approach became available. Instead of asking how a certain function might be implemented in a given network we can first try to understand the intrinsic dynamical properties of the network before we look for functional applications of the found behavior. For the cerebellum, the latter approach seems to be particularly well suited for several reasons. First, the function of the cerebellum is still a matter of fervent debate. The scope of functions attributed to the cerebellum ranges from 'classical' motor coordination[1–3] to processing of sensory data[4–6] and cognitive functions.[7–9] On the other hand, the olivo-cerebellar system is one of the few substructures of the mammalian central nervous system where the intrinsic microcircuitry is known in considerable detail. Not surprisingly though, there have been multiple attempts to explore the function of the cerebellum in a bottom-up fashion; most of them, however, were biased by the 'motor-coordination doctrine'.[3,10–13] Here, we pursue a reverse-engineering approach that tries to elucidate cerebellar function in a bottom-up fashion by incorporating as much of the currently available information on the neuronal circuitry as possible, but without making any assumptions on their purpose. The dynamical behavior that we find is then re-evaluated with respect to its potential functional role.

Following the tradition of Marr[3] and Albus[10] we start out from anatomical and morphological data of the olivo-cerebellar system; cf. Figure 1. However, we go one important step further in that we pay particular attention to temporal aspects of the neuronal dynamics. The present theory is thus based throughout on a time-coding paradigm, i.e., neuronal activity is described in terms of spikes and ring times rather than mean ring rates. This allows us to concentrate on several electrophysiological peculiarities of the involved neurons such as rebound depolarization in neurons of the deep cerebellar nuclei and subthreshold oscillations in olivary neurons.

Granule cell time windows

What is the role of inhibitory synapses? Most people would agree that inhibitory synapses control the ring rate of the postsynaptic neuron. This may be true in pyramidal cells where a large number of excitatory and inhibitory projections converge on the dendritic tree, but in small neurons that are contacted by only a few presynaptic neurons the answer can be more complicated. Granule cells receive inhibitory input from about four Golgi cells that fire rather regularly with low discharge rates and a minimum interspike interval of about 20 ms.[15–17] At any instance of time there are thus at most a few inhibitory postsynaptic currents active—if any—and it clearly makes a difference whether these conductances are activated simultaneously or not. Furthermore, the level of inhibition that the granule cell experiences is highly variable in time and so is the cell's excitability. Hence, the timing of any excitatory input relative to the activation of the inhibitory synapses is of

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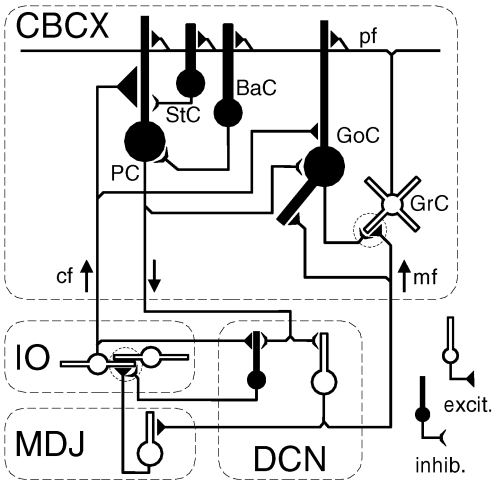

Figure 1
Schematic drawing of the cerebellar network. Excitatory and inhibitory neurons are shown as empty and filled circles, respectively. The following abbreviations are used. CBCX, cerebellar cortex; IO, inferior olive; MDJ, mesodiencephalic junction; DCN, deep cerebellar nuclei; PC, Purkinje cell; StC, stellate cell; BaC basket cell; GoC, Golgi cell; GrC, granule cell; pf, parallel fiber; cf, climbing fiber; mf, mossy fiber (modified from ref. 14).

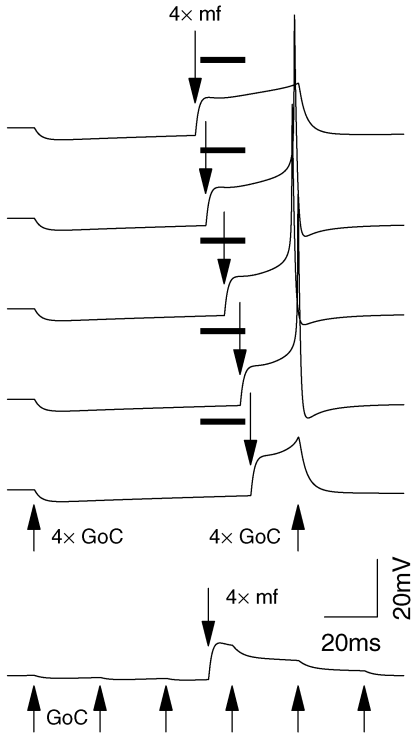

Figure 2
Simulation of a cerebellar granule cell illustrating the time-window mechanism. The granule cell receives input from four Golgi cells and four mossy fibers; the arrows indicate spike arrival times. If the Golgi cells are firing synchronously (upper traces) the granule cell can reach ring threshold only if the mossy fiber spikes arrive within a narrow time window (horizontal bar). If Golgi cells are firing asynchronously, the granule cell cannot fire whenever the mossy fiber spikes arrive (bottom) (from ref. 20).

fundamental importance and can determine whether the granule cell will fire a spike or not. We thus claim that Golgi cells control the ring *time* of granule cells rather than their ring rate.

In order to corroborate this statement we have investigated the excitability of granule cells as a function of the relative timing of excitatory and inhibitory synaptic input by means of a computational model of a turtle granule cell.[14,18,19] The results are summarized in Figure 2. The granule cell receives via its four dendrites input from four Golgi cells and four mossy fibers. We first assumed that the Golgi cells were perfectly synchronized and fire periodically at a rate of 10 Hz. We then activated the mossy fiber input at various timings relative to the Golgi cell spikes. It turned out that mossy fiber spikes can trigger the granule cell but only if the mossy fiber spikes arrive during a narrow and well-defined *time window* shortly before the Golgi cells fire, i.e. when inhibition is weakest. If the mossy fiber spikes arrive too early then the inhibition from the previous volley of Golgi cell spikes is still too strong and the granule cell cannot reach ring threshold. On the other hand, if the spikes arrive too late, then there is not enough time for the spike to build up before the next set of Golgi cell spikes hit the synapses.

In a second set of *in computo* experiments we assumed that the Golgi cells were firing asynchronously. The granule receives the very same amount of inhibitory input spikes as before, viz. four spikes per 100 ms, but evenly distributed over the whole interval. The corresponding IPSPs thus overlap partially and the cell is more or less constantly inhibited. The bottom trace in Figure 2 shows the corresponding simulation. We found that in this case the granule cell cannot reach ring threshold whenever the mossy fiber spikes arrive. This clearly shows that it is not only the amount of inhibitory input but also its temporal structure and timing relative to an excitatory input that determine whether the postsynaptic cell is firing or not.

There are interesting functional implications for this phenomenon. First, the activity of the granule cells and therewith the parallel fiber activity can be controlled by synchronizing or de-synchronizing the Golgi cell population. Second, information reaching the cerebellar cortex via the mossy fiber pathway can be selected by the arrival time of the corresponding action potentials since only those spikes that reach the granule cells during the appropriate time window can actually trigger the cell. This mechanism can improve the signal-to-noise ratio significantly, if meaningful information is concentrated within the time windows while noise is evenly distributed in time.

Post-inhibitory rebound firing in deep cerebellar nuclei neurons

The only output of the cerebellar cortex, the Purkinje cells, are *inhibitory*.[21,22] Traditionally, the Purkinje cells

are therefore thought to merely have a modulatory influence on the deep cerebellar nuclei (DCN), which are driven by climbing fiber and mossy fiber collaterals. This, however, is once more an understatement regarding the functional role of inhibitory synapses.

In DCN neurons release from hyperpolarization triggers a low-threshold calcium current that leads to a depolarization of the membrane and a burst of regular sodium spikes.[23–26] Through this mechanism of post-inhibitory rebound, Purkinje cells can actively drive their postsynaptic target neurons even in the absence of additional input from excitatory synapses.[14,19,25]

Figure 3 shows simulations that illustrate the triggering of action potentials by inhibitory synaptic input. The simulations are based on a recently developed model of a DCN neuron[19] which receives purely inhibitory input through five groups of GABAergic synapses. In Figure 3A each group is independently activated by a random (Poisson) spike train with an average rate of 20 Hz resulting in a somatic membrane potential that is fluctuating around the resting potential. No spikes are triggered. In Figure 3B the neuron receives the same amount of input but now the synapses are activated in a synchronized manner. This triggers several action potentials despite the fact that the model neuron is not spontaneously active.

The reason why the inhibitory input has to be synchronized in order to elicit rebound spikes is readily understood. Post-inhibitory rebound relies on the release from inhibition and, hence, there has to be a pause in the inhibitory spike trains in order to allow the DCN neuron to recover from inhibition and fire its rebound spikes. If the neuron receives spike trains from several independent presynaptic neurons then the probability to have a pause in all presynaptic neurons simultaneously is rather low. However, if the neurons are synchronized then this probability is significantly increased. This interpretation is further corroborated by Figure 3C which shows the correlation of pre- and postsynaptic spikes for a simulation similar to that shown in Figure 3B. The histogram gives the number of presynaptic spikes that precede any postsynaptic rebound spike by a certain amount of time. Negative time intervals indicate that the presynaptic spike occurred before the rebound spike. Note the pause of

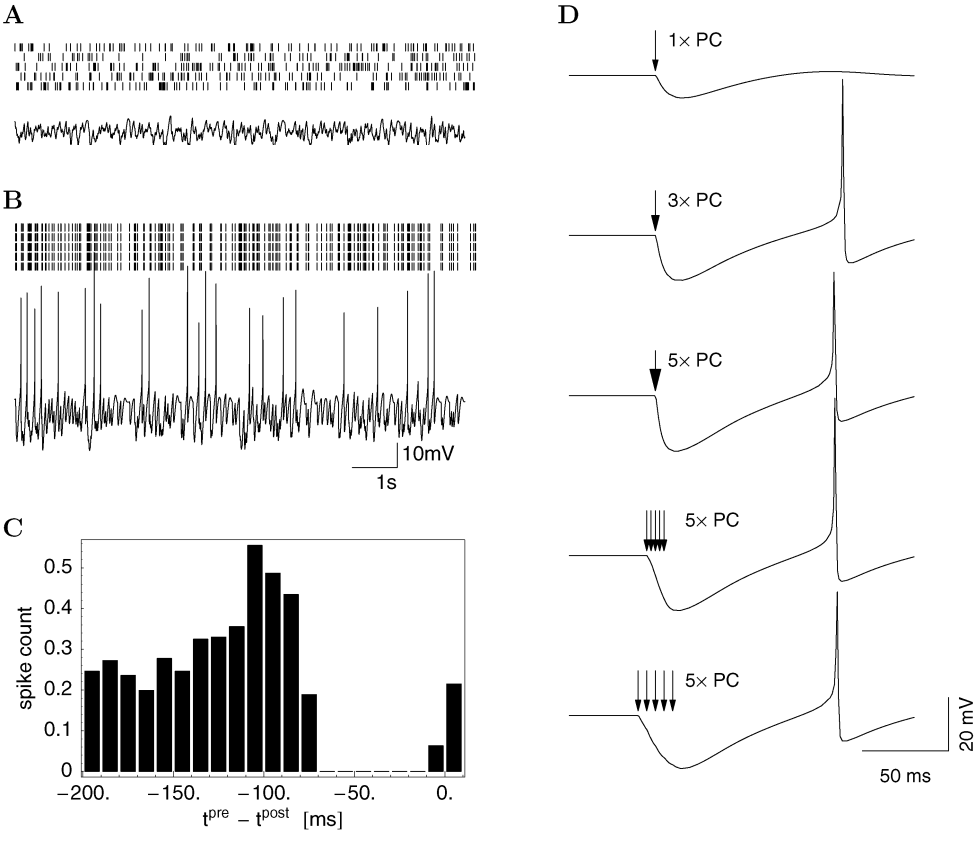

Figure 3

Triggering of rebound spikes in a DCN neuron by activation of inhibitory synapses. (A) Asynchronous activation of inhibitory synapses does not trigger rebound spikes. The graph shows the membrane potential of the model neuron as a function of time. The raster diagram in the upper part of the diagram represents the spike trains that reach the neuron via five independent groups of synapses. (B) Activation of inhibitory synapses in a synchronous manner elicits rebound spikes. (C) Correlation of pre- and postsynaptic action potentials. The histogram gives the (averaged) number of presynaptic spikes that precede any rebound spike by ($t^{pre} - t^{post}$) ms. (D) Simulation of a DCN neuron that receives a volley of Purkinje cell spikes. The arrival time of the spikes is marked by arrows. Simulations are adapted from the model of Kistler et al.[19] to account for a decay time constant of 13.6 ms of the inhibitory postsynaptic currents.[27,28]

about 50 ms that precedes every rebound spike. Furthermore, the number of presynaptic spikes is substantially increased about 100 ms before the rebound spike indicating that the rebound spike is actively triggered by these spikes.

The hump in the correlation diagram of pre- and postsynaptic spikes (Figure 3C) at $t^{pre} - t^{post} = -100$ ms shows that rebound spikes occur with a delay of about 100 ms after the volley of inhibitory spikes. In order to look more closely into the timing of rebound spikes we performed another set of simulations where we delivered a single volley of spikes to the model DCN neuron; cf. Figure 3D. Our findings are twofold. First, triggering of rebound spikes is a threshold process since a certain minimum amount of inhibitory spikes is necessary in order to elicit rebound spikes. Second, the rebound spike occurs with a delay of about 100 ms after the arrival of the inhibitory volley. Moreover, the timing is robust with respect to the size of the volley and its temporal dispersion. This means that even if the number of spikes within the volley is further increased, the rebound spike occurs with a constant delay of 100 ms—and not earlier.

In summary, triggering of action potentials by activation of excitatory and inhibitory synapses are on an equal footing in DCN neurons. Nevertheless, there is a crucial difference with respect to the timing of the action potential because post-inhibitory rebound introduces an additional delay of about 100 ms in the triggering of the spike. This delay can be of great functional importance as we will see below.

Delayed reverberating loops

In many papers inspired by the groundbreaking work of Marr[3] and Albus[10] the cerebellum is conceived as a feed-forward structure with two inputs, viz. mossy and climbing fibers, and one output, the projecting neurons from the deep cerebellar nuclei. According to the classical theory of cerebellar function the cerebellum receives sensory and proprioceptive information via the mossy fiber pathway, performs a certain computation on this data, and delivers the result via its Purkinje cells and the deep cerebellar nuclei. The computation itself is regulated through the climbing fibers that are supposed to provide a kind of error signal.[3,10,29] One of the shortcomings of this view is that in reality the feed-forward structure is not as clear-cut as it might appear. The complications arise from feed-back projections that connect the output of the cerebellum with its input fiber systems. More specifically, there are both inhibitory and excitatory projections from the deep cerebellar nuclei to the inferior olive,[30–32] which is the source of the climbing fibers. In addition there are excitatory projections from the DCN to pontine nuclei that in turn are a source of cerebellar mossy fibers.[33–36] Moreover, there are direct excitatory projections from the DCN to the cerebellar cortex leading to mossy fiber-type terminals in the granule cell layer;[37–40] cf. Figure 1. Most interestingly, all these projections are topographically organized. Due to these feed-back projections the 'input' to the cerebellum is not an independent variable but depends at least partially on the output of the cerebellum itself.

In the light of the previous sections the above mentioned feed-back projections form the basis of an interesting dynamical structure. We have argued that a volley of Purkinje cell spikes followed by a pause in the simple spike activity can trigger rebound spikes in DCN neurons with a delay of about 100 ms. These spikes are relayed to the climbing fiber and mossy fiber system. If we assume that the rebound activity arrives at the cerebellar cortex with an overall delay that matches the delayed opening of the granule cell time window then the rebound spikes can directly participate in the triggering of Purkinje cells. We are thus left with a delayed reverberating loop where volleys of Purkinje cell spikes trigger rebound spikes that in turn (re-)trigger Purkinje cells and so forth. The duration of each cycle is mainly determined by the delay of the rebound ring.

In order to form a delayed reverberating loop, the timing of the rebound firing and the decay of the Golgi cell–granule cell inhibition has to be matched. There is no obvious explanation for how the timing can be tuned during development, but there is evidence that some of the parameters that control the granule cell time windows *are* modified systematically during ontogenesis. $GABA_A$ receptors in granule cells contain both the $\alpha 1$ and the $\alpha 6$ subtype. The latter subtype, which is restricted to cerebellar granule cells,[41] is responsible for the extraordinarily slow time constant of about 50 ms that governs the decay of inhibitory postsynaptic currents in granule cells.[42] Most interestingly, the ratio of $\alpha 1$ and $\alpha 6$ subtypes, and therefore the kinetics of Golgi cell-granule cell inhibition changes systematically during development.[42] Moreover, studies in cell culture have shown that the expression of the $\alpha 6$ subunit is regulated by the activation of $GABA_A$ receptors themselves.[43–45] All the prerequisites for a self-organized tuning of the granule-cell time window thus seem to be present.

Reverse-engineering the cerebellar circuitry

Almost all cerebellar neurons are inhibitory. It thus seems as if nature has taken care to prevent neurons from ring or—as we propose here—to prevent neurons from firing outside narrow time windows. One of the motifs of the cerebellar circuitry is forward inhibition; cf. Figure 4A. All excitatory projections in the cerebellar cortex are paralleled by an inhibitory projection. Granule cells and Golgi cells share the same mossy fiber input but the former are inhibited by the latter. Similarly, Golgi cells and Purkinje cells receive both input from the parallel fibers but Golgi cells are inhibited by Purkinje cell collaterals. Finally, parallel fibers excite both Purkinje

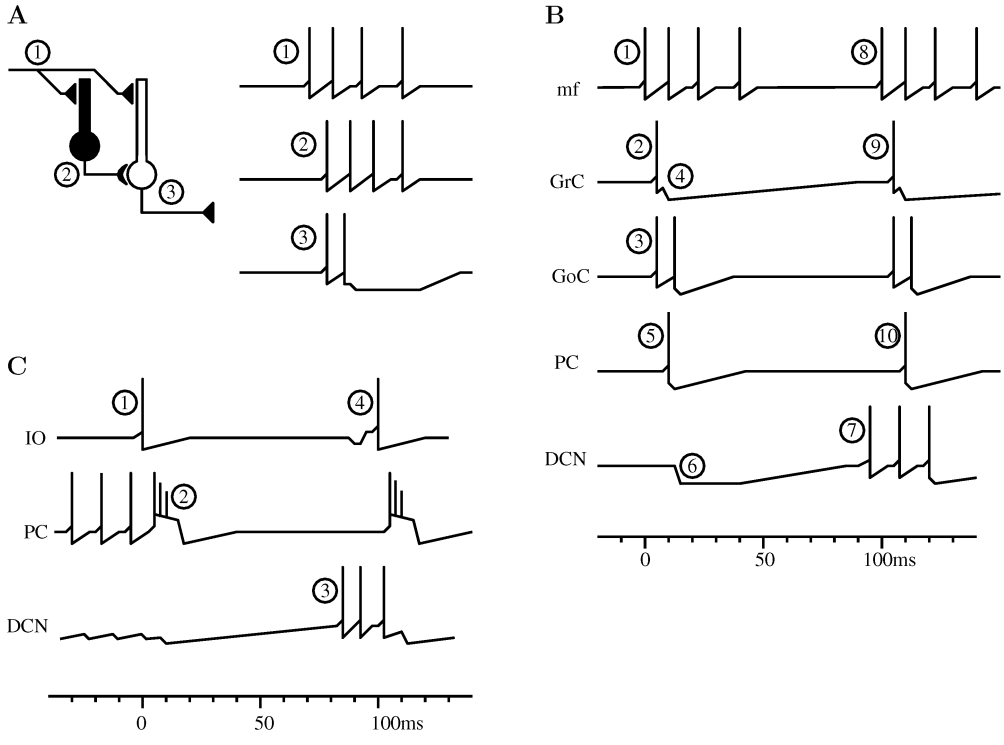

Figure 4
Reverse-engineering the cerebellar cortex. (A) Forward inhibition is a prevalent motif of cerebellar circuitry. An excitatory (open symbol) and an inhibitory neuron (filled symbol) share the same excitatory input. A sudden onset of spike activity in the input fiber (1) activates both neurons (2,3). Due to the forward inhibition there is only a narrow time window for the excitatory neuron to fire (3). (B) Schematics of the neuronal dynamics involved in the reverberating loop connecting cerebellar output with the mossy fiber system (see text). (C) Schematics of the neuronal dynamics involved in the reverberating loop connecting cerebellar output with the climbing fiber system (see text).

cells and their inhibitory counterparts, basket and stellate cells. What is the rational for this motif?

From a rate-coding perspective the circuit of Figure 4A looks as if the inhibitory neuron would control the gain or the threshold of its excitatory companion.[3] The firing threshold of a neuron, however, has to be set before excitatory input reaches the cell. The forward-inhibition network shown in Figure 4A exhibits one additional synaptic transmission step for the inhibitory pathway so that the setting of the threshold is delayed by a few milliseconds with respect to the excitatory signal. Therefore, the gain- or threshold-setting interpretation does only make sense for stationary signals, i.e., for signals that are only slowly varying in time. Since the cerebellum is involved in the control of all kinds of rapid movements with rapidly varying signals it is worth looking more closely at the timing within this network.

Both neurons in Figure 4A receive excitatory input from the same fiber system and can therefore be triggered simultaneously. Inhibition from the inhibitory cell, however, can reach its excitatory companion only with a delay of a few milliseconds due to the additional synaptic transmission step. In case of a sudden onset of spike activity in the excitatory pathway (cf. Figure 4A, (1)) both the excitatory (3) and the inhibitory neuron (2) get activated simultaneously. For the excitatory neuron there is only a narrow time window to fire at most one or two spikes before inhibition becomes effective (3). The circuit of Figure 4A can thus operate as a high-pass filter that transmits only the rising edge of a spike packet.

In the previous section we have discussed the possibility that synchronous Purkinje cell activity triggers rebound spikes in the DCN. The rebound activity is reverberated back to the cerebellar cortex and can participate in the triggering of another subpopulation of Purkinje cells. Figure 4B shows schematically what is going on. Let's start with a sudden onset of mossy fiber activity (denoted by 1 in Figure 4B) that may be due to an external event such as, e.g., tipping the skin of the animal. This event will simultaneously trigger granule cells (2) and Golgi cells (3). Immediately after the granule cell has fired it is inhibited by the previously activated Golgi cell (forward inhibition) or by Golgi cells that are activated by the granule cells via parallel fiber–Golgi cell synapses (4). The induced granule cell activity may be sufficient to trigger Purkinje cells (5) that in turn inhibit DCN neurons (6) and Golgi cells via their axon collaterals. The granule cell activity can also trigger stellate and basket cells that inhibit Purkinje cells. At this point all neurons are inhibited and especially Purkinje cells will pause firing because of the basket/stellate cell inhibition and the cease of granule cell firing. These are the

conditions required for DCN neurons to fire rebound spikes (7) that reverberate to the cerebellar cortex and show up as an increased mossy fiber activity (8). In the mean time, the Golgi cell inhibition in granule cells has decayed and granule cells are ready to fire again (9). The resulting parallel fiber activity can then (re-)trigger Purkinje cells (10).

Note that the population of Purkinje cells that is finally activated by the rebound activity is not necessarily identical to the population of Purkinje cells that triggered the rebound. Depending on the wiring of the reverberating loop any population of Purkinje cells will activate a certain set of parallel fibers in the next cycle that in turn trigger a characteristic set of Purkinje cells depending on the weight distribution of parallel fiber–Purkinje cell synapses. The network is thus able to store long sequences of spike patterns if the weights of parallel fiber–Purkinje cell synapses are adjusted accordingly.[14,19]

The role of the topographic projections from the DCN to the IO can be analyzed in a similar vein; cf. Figure 4C. Climbing fiber spikes (1) trigger complex spikes in the corresponding Purkinje cells that are usually followed by a pause in the simple spike activity (2). During this pause DCN neurons can recover from inhibition and re rebound spikes (3). The rebound activity is reverberated back to the IO directly by inhibitory projections or indirectly by an excitatory pathway via the mesodiencephalic junction (MDJ). Depending on the wiring of this loop another set of IO neurons will be activated with a total delay of about 100 ms (4).

In addition to the oscillatory state sketched in Figure 4B there is also an asynchronous state of the olivocerebellar system where a high Purkinje cell activity inhibits Golgi cells via Purkinje cell axon collaterals so as to dis-inhibit granule cells that in turn sustain the Purkinje cell's high simple spike firing rate. Simulations have shown that the network can exhibit a bistability with respect to the oscillatory and the asynchronous state.[14] Discrete external events that reach the cerebellar cortex either via the mossy fiber or the climbing fiber pathway can induce transitions between these two states; cf. Figure 5.

The inferior olive as a neuronal clock

The delayed triggering of rebound spikes in DCN neurons in conjunction with topographic projections from the DCN to the IO can support a 10 Hz oscillation. Interestingly, the network feedback is in resonance with the intrinsic oscillatory properties of IO neurons. Slice recordings reveal sub-threshold oscillations of the membrane potential at about 10 Hz[46–48] and multi-electrode recordings from the cerebellar cortex show an oscillatory component in the population activity of complex spikes.[49–50] In addition, IO neurons that innervate the same microzone tend to fire synchronously[49–51] (but see ref. 52, an effect that is commonly attributed to the gap junctional coupling of IO neurons.[32,53,54] Individual IO neurons, however, produce irregular spike trains with a mean firing frequency of about 1 Hz.

These observations can collectively be accounted for by the time window model of IO activity.[14,19] In short, the activity of IO neurons that innervate the same microzone is characterized by narrow time windows that encompass their potential firing times. Due to the oscillatory properties of IO neurons, there is a time window every 100 ms during which neurons can fire an action potential. Since the firing frequency of individual IO neurons is only about 1 Hz each neuron fires on average only in 1 out of 10 time windows. Consequently, the population activity shows a 10 Hz oscillation with a high degree of synchrony whereas individual neurons are firing irregularly at a much lower rate.

There is a longstanding discussion about the source of the irregularity observed in neuronal spike trains. It is impossible to decide *a priori* whether the irregularity is just noise or whether it actually contains information that is meaningful to the biological system. In the case of the olivo-cerebellar system, however, a mathematical model demonstrated that the irregularity in the IO activity is not necessarily due to noise but can instead be the result of the connectivity within the reverberating loop.[55]

Figure 6 shows an example of a simulation of a detailed multi-compartment model of 20 electrotonically coupled IO neurons that are embedded in the delayed reverberating loop made up of cerebellar cortex, DCN, and MDJ. At time $t = 0$ a short depolarizing current pulse is delivered to neurons 1–6 in order to trigger an action potential. In the wake of this stimulation each neuron produces an apparently irregular spike train, but the precise pattern of spikes is determined by the wiring scheme of the reverberating loop. If external input to the IO can be neglected during a certain period of time, then the whole sequence of spike patterns depends only on the initial firing pattern. Restoring a certain initial pattern will elicit the same sequence of spike patterns; a different initial pattern, however, will start different spike patterns. Therefore, the network can represent simultaneously 'what' and 'when' information on external events that have triggered IO activity. The 'what' information is stored in the actual sequence of spike patterns because different events trigger different sequences. The 'when' information is contained in the current firing pattern within a given sequence because a certain firing pattern occurs only at a certain time after the sequence has started.

We have argued before that the output of the cerebellar cortex reverberates back to the mossy fiber system and can influence the parallel fiber activity. The clocking signal produced by the olivo-cerebellar loop will thus leave a distinct trace in the parallel fiber activity where it can easily be detected by Purkinje cells. The olivocerebellar loop can hence serve as a combination of a working memory that retains information on external

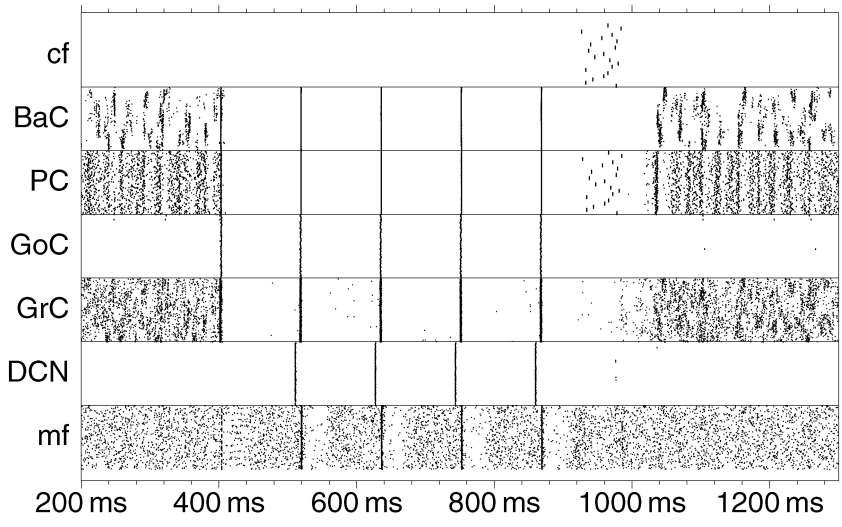

Figure 5
Two modes of operation in a simulation of the cerebellar network. The diagrams show the spike trains of 200 DCN neurons (DCN), 1000 granule cells (GrC), 80 Golgi cells (GoC), 200 PCs (PC), 400 basket cells (BaC), and the spike trains delivered by 200 mossy fibers (mf) and 200 climbing fibers (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 neighboring neurons may merge into one line. Externally generated volleys of synchronous mossy fiber spikes at $t = 400$ ms and the climbing fiber spikes around $t \approx 1000$ ms induce transitions between the asynchronous and the oscillatory state of the olivo-cerebellar system (from ref. 14).

events for a few 100 ms and a neuronal clock that allows the cerebellum to respond with a certain delay to these events.[55]

Spike-timing dependent synaptic plasticity

The working memory property of the IO discussed in the previous section does not rely on any form of synaptic plasticity. Information about external events is stored in the ongoing network activity without any reorganization of the network circuitry. In order to retrieve this information and to react to a particular event within a certain interval of time a tuning of synaptic transmission is necessary. Parallel fiber-Purkinje cell synapses are the natural candidate for the site where this form of learning can take place.

The present theory is based throughout on a time coding paradigm, i.e., we have assumed that the timing of action potentials carries meaningful information. If we want to include learning consistently into the present model we thus need a form of synaptic plasticity that somehow relies on spike timing.[56–59] Noteworthily, there is ample evidence that plasticity of parallel fiber-Purkinje cell synapses is indeed controlled by the relative timing of climbing and parallel fiber spikes.[60–64]

A recent modeling study has shown that spike-timing dependent synaptic plasticity endows the network with the capability to learn to react with a certain delay to an external signal.[19] Figure 7 shows an example of a large network simulation based on simple integrate-and-fire-type neurons.[65–67] An external event at time $t = 400$ ms such as an auditory or visual cue activates a subset of IO neurons (marked 'CS' in Figure 7A). About 350 ms later another stimulus, e.g., an air puff to the eye (US), is delivered that triggers an unconditioned response (UR). The pairing of the US with the ongoing activity in the aftermath of the CS results in a tuning of the parallel fiber Purkinje cell synapses so that after a couple of repetitions the CS alone is sufficient to elicit the conditioned response (CR) with proper timing, even if the US is omitted; cf. Figure 7B.

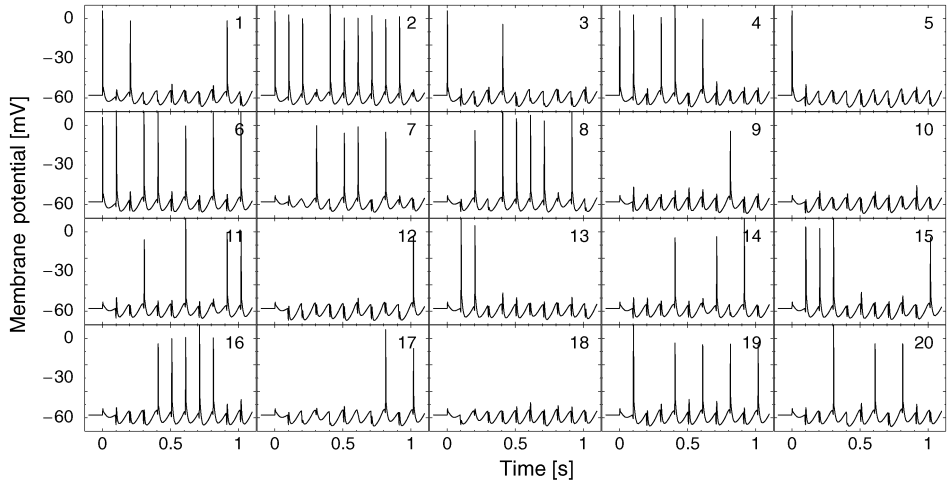

Figure 6
Simulation of a detailed multi-compartment model of 20 IO neurons coupled by gap junctions together with delayed reverberating projections (from ref. 55).

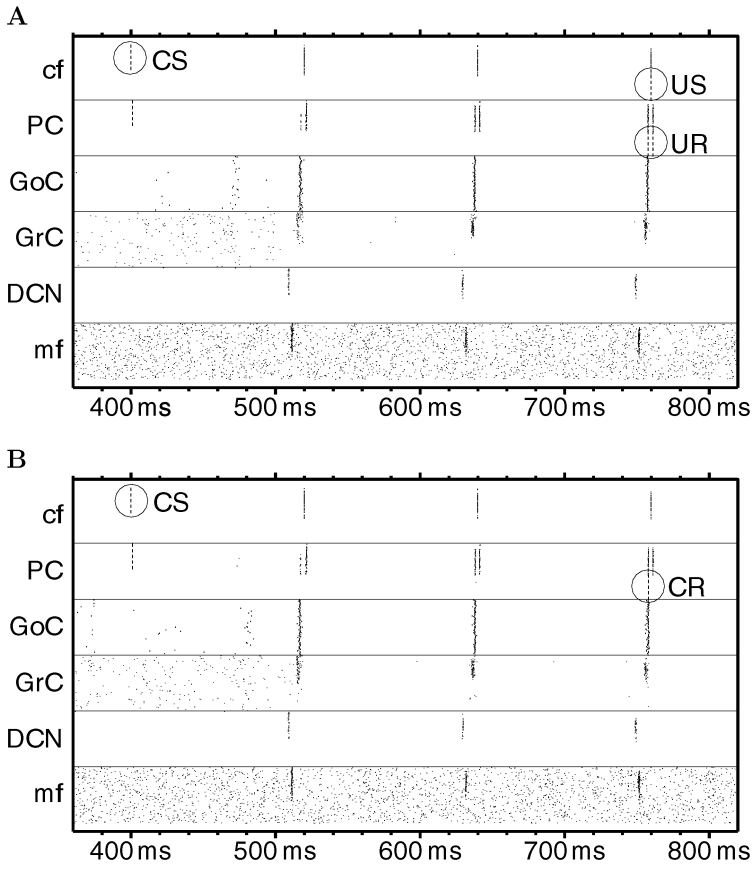

Figure 7
Raster plot of the spike activity in a simulation of the cerebellar network (similar plot as in Figure 5). (A) Classical conditioning experiment. A conditioned (CS) and an unconditioned stimulus (US) are presented repeatedly with a fixed delay. (B) After conditioning the CS suffices to trigger the conditioned response (CR) (from ref. 19). Note that the cf and mf pathways in this simulation are not used in the standard fashion for classicial conditioning (see also ref. 80) in that the climbing fibers are used for both CS and US.

Discussion

We have highlighted two features of the olivo-cerebellar system that we consider to be particularly interesting—the delayed triggering of rebound activity in DCN neurons by volleys of synchronous Purkinje cell spikes and the reverberating projections that connect the output of the cerebellum with its input fiber systems. In a reverse-engineering approach we have investigated the corresponding dynamical and functional properties by a combination of mathematical models, detailed single-neuron models, and large-scale network simulations. Our work is based on a time-coding paradigm that allowed us to study the role of synchronization and timing of action potentials. We found that 'inhibitory' GABAergic synapses can have a function that clearly goes beyond a mere regulation of the postsynaptic firing rate. Our simulations indicate that Golgi cells control the firing time of postsynaptic granule cells rather than their ring rate. Furthermore, neurons can be driven actively by GABAergic input. DCN neurons, for example, respond with rebound bursts to pauses in the simple spike activity of presynaptic Purkinje cells.

The present theory is particularly interesting in the context of certain recent experimental results. Schwarz and Welsh[68] report that a brief electrical stimulation in the motor cortex induces highly structured trains of complex and simple spike activity that outlast the duration of the stimulus by several hundreds of millisecond. This observation together with precisely timed long-latency responses in the complex spike activity reported by several authors[68–71] are among the principle predictions of our theory. In contrast to the tentative explanation given by Schwarz and Welsh[68] we argue that the rebound firing in the DCN together with the reverberating network are responsible for the long-latency response rather than purely intra-olivary effects. Moreover, the network effects that we have described, especially the gating of mossy fiber input by the granule cell time window mechanism, result in a modulation of the simple spike activity that is very much in keeping with the complex spike-related simple spike modulation reported by Schwarz and Welsh.[68]

Another interesting observation has been reported by Yamamoto et al.[72] who found a wave of synchronous complex spikes that is propagating in a medio-lateral direction with a velocity that surprisingly coincides with the conduction velocity of the parallel fibers. The above considerations can provide a natural explanation for this phenomenon. A volley of parallel fiber spikes can trigger Purkinje cells as well as basket or stellate cells. Due to the forward inhibition the Purkinje cells will fire only a short burst of simple spikes followed by a pause that is generated by basket/stellate cell inhibition. This pause allows DCN neurons to recover from inhibition and to fire a burst of rebound spikes. Due to the topographic organization of the reverberating loop the rebound activity will trigger those IO neurons that project to the

same microzone where the initial simple spike burst occurred. The result is a wave of synchronous complex spikes that travels at the parallel fiber conduction velocity in the medio-lateral direction. Whereas Yamamoto et al.[72] propose an explanation in terms of a propagation of sub-threshold signals in the IO, we argue that it is once more the network as a whole that is generating the observed behavior. In addition, our argumentation has the appealing aspect that it accounts automatically for the velocity of the wave. The existence or non-existence of oscillatory activity in the olivo-cerebellar system is still a controversial issue. Field potential oscillations in the granule cell layer at a frequency of 7 to 8 Hz have been reported for awake, behaving rats[73] and with a slightly higher frequency of 13–18 Hz in primates.[74] These oscillations were restricted to periods where the animal was in a state of 'attentive rest' and disappeared as soon as a movement was initiated. Consistently, Keating and Thach[75,76] (but see refs. 77 and 78) have found no indication for rhythmic activity in the climbing fibers nor in the deep cerebellar nuclei of a monkey performing a simple reaching task. In the anesthetized preparation, Golgi cells in rat show a tendency to fire at a frequency of about 10 Hz and are coarsely synchronized along the parallel fiber beam.[16]

We have demonstrated that the olivo-cerebellar network can exhibit a bistability between an asynchronous state with high levels of Purkinje cell and granule cell activity and an oscillatory state that is characterized by network oscillations at about 10 Hz and a high degree of coherence within and between different types of neurons. Transitions between these two modes of operation can be induced by mossy fiber or climbing fiber activation. The oscillatory state is a consequence of the intrinsic connectivity of the olivo-cerebellar system and as such not reliant on external input. In agreement with the experimental findings we thus expect a cessation of the oscillatory activity as soon as the external input dominates over the internally reverberated activity as it might be the case when a movement is started. It has been argued that the field potential oscillations in the granule cell layer reflect the baseline dynamic state of the sensory system.[73] Here, we have shown that actually a lot of information processing can go on during this 'baseline state'. Discrete sensory events can trigger complex sequences of spike patterns that retain information on the type and the timing of the stimulus over several hundreds of milliseconds. This is a novel explanation for how long intervals of time can be handled by fast neurons and may be important in classical conditioning and delayed-response tasks.[79,80] The finding that sensory input is translated into spatio-temporal patterns of spike activity is in favor of the hypothesis that the cerebellum is not only involved in motor control but also in the direct processing of sensory information.[4,6]

Any model is bound to describe reality in a selective and idealized way. In the present case, 'detailed' neuron models have a grossly simplified morphology, do not contain the full set of ion channels, and do not describe their somato-dendritic distribution. The network models contain only a limited number of neurons, are based on a highly schematic integrate-and-fire type of neuron model, and show an idealized degree of synchrony. Some of these 'short-comings' are due to technical constraints, others simply reflect our lack of knowledge. Nevertheless, we believe that these models can provide valuable insight into neuronal dynamics and cerebellar function. The large number of neurons in reality, for example, can compensate for the reduced degree of synchrony. If there is a large number of neurons, then the network can tolerate a higher noise level of individual neurons than some of the simulations. Even though we are still far from understanding cerebellar function we believe that the present approach can inspire future research by offering new vistas on synaptic integration and cerebellar dynamics.

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