

Oscillations in the cerebellar cortex: a prediction of their frequency bands

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Abstract: Local recurrent connections endow the cerebellar cortex with an intrinsic dynamics. We performed computer simulations to predict the frequency bands of the oscillations that will most likely emerge. Feedback inhibition from the Golgi to the granule cells induced 10–50 Hz oscillations, the period at resonance being approximately equal to four times the maximum conduction delay generated along the parallel-fiber connections from granule to Golgi cells. In the molecular layer, the interneurons tended to induce fast oscillations (100–250 Hz), having a period equal to about four times the delay over their reciprocal synaptic connections. Finally, although the presence of lateral inhibition among the Purkinje cells has not been firmly established, reciprocal Purkinje-cell synapses are predicted to transform the cerebellar cortex into a potential temporal integrator.

Introduction

Because of its fast responsiveness and the temporal precision with which it operates, the cerebellar cortex is often described as a pure feed forward circuit conveying the mossy-fiber input over granule cells and along parallel fibers to Purkinje cells, which send their axons to the deep cerebellar (or vestibular) nuclei. Plasticity of the synapses connecting the consecutive stages, guided by supervised and unsupervised learning rules, continually adapts the circuit (for reviews see Hansel et al., 2001; Ito, 2001; Barlow, 2002). Inhibitory interneurons likewise sharpen the input–output relationship and control its gain.

Nevertheless, all inhibitory neurons within the cerebellar cortex also make recurrent connections (Palay and Chan-Palay, 1974). Whatever their

function, the resulting feedback endows the circuit with intrinsic dynamics, the simplest manifestation of which would be the emergence of oscillatory activity. Although one of the functions of the cerebellum is likely to dampen mechanical oscillations (Thach et al., 1992), over the years oscillations in a variety of frequency bands have been observed in different experimental settings, suggesting that the cerebellum is also a rhythm generator (Pellerin and Lamarre, 1997; Baçar, 1998; Hartmann and Bower, 1998; Tesche and Karhu, 2000; Courtemanche et al., 2002; Isope et al., 2002).

We recently reported that inhibitory circuits have a resonance frequency which is determined by the average delay time required for one inhibitory neuron to inhibit a nearby inhibitory neuron (Maex and De Schutter, 2003). More particularly, in purely inhibitory networks, the oscillation period at resonance is equal to about four times the average latency to the onset of the evoked inhibitory postsynaptic currents

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(IPSCs). We use this rule in combination with computer simulations to predict the frequency bands of the oscillations likely to arise in the granular layer (through recurrent inhibition from Golgi to granule cells), in the molecular layer (through reciprocal inhibition among the interneurons), and in the Purkinje cell layer (through Purkinje axon collaterals). We do not consider oscillations resulting from reverberation in compound circuits comprising the inferior olive, cerebellar nuclei, thalamus, or neocortex (see Kistler et al., 2000).

Recurrent inhibition from Golgi to granule cells

The dynamics of the Golgi-granule cell feedback loop determines the temporal pattern of parallel-fiber input that Purkinje cells receive from granule cells. In principle, the granule cells could produce synchronous oscillations, fire completely asynchronously, or burst. For each state, we discuss which parameters are critical for its generation, its possible functional significance, and supporting experimental data. Thereafter we examine in which frequency band oscillations presumably emerge.

The asynchronous state

In the asynchronous state, the population of Golgi cells fires incoherently, as do the granule cells. For this state to arise in the granular layer, pairs of Golgi cells along the folial axis must be prevented from firing synchronously to the common excitatory input they receive from parallel fibers (Vos et al., 1999). In models, such a desynchronization could be most readily achieved by increasing the strength of the monosynaptic excitation that Golgi cells receive from mossy fibers (Maex and De Schutter, 1998a). Indeed, mossy fibers diverge over shorter distances within a folium, presumably make fewer but stronger synapses, and fire less coherently than do parallel fibers (Dieudonné, 1998b). Excitation through stronger synapses also deteriorated the spike rhythmicity of single model Golgi cells (Maex and De Schutter, 1998b). In addition, pairs of granule cells lying within the same Golgi axonal arbor must be prevented from synchronizing their spike emission by randomization of the strength and time-course of

the synapses they receive from the common Golgi afferent.

The functional advantage of the asynchronous state is a maximization of the information content of granule cell spikes (Buonomano and Mauk, 1994). If each granule cell would fire at a unique interval after or during the course of stimulation, stimulus time would be mapped on the granule cell population. Long-term depression of the synapses originating from the granule cells selectively active during a particular stimulus phase would then endow the Purkinje cells with the capacity of recognizing temporal stimulus patterns (Steuber and De Schutter, 2002). The usefulness of this temporal coding was demonstrated in semi-realistic simulations of a conditioned response (Buonomano and Mauk, 1994) and a motor coordination task (Schweighofer et al., 1998).

The bursting state

In an alternative state, the granular layer is mostly silent except for bursts of granule-cell spikes evoked, for instance, by sensory stimulation. In models, this behavior could be reproduced by locally applying a bursting mossy-fiber input (Franck et al., 2001). The resulting bursts of the model granule cells were not aborted by inhibition from parallel-fiber activated Golgi cells provided that the patch of active granule cells was small and mossy-fiber activation of Golgi cells weak (Finch and Augustine, 1998; De Schutter and Bjaalie, 2001). Bursts evoked by peripheral stimuli were recently recorded in granule cells in anesthetized rats (Chadderton et al., 2003), and extracellularly from presumed granule cells in anesthetized or decerebrated cats (Eccles et al., 1971). Intrinsic membrane currents through non-inactivating Na^+ and K^+ channels contribute to the bursting behavior of granule cells in vitro (D'Angelo et al., 2001). Bursting of granule cells can enhance the reliability and plasticity of transmission at the parallel-fiber synapses (Casado et al., 2002).

The synchronous state

From theoretical considerations, the delayed feedback from Golgi to granule cells was predicted to induce synchronous oscillations (Maex and De Schutter,

1998a) or traveling waves (Roberts, 1997). As far as we know, most if not all network models of the granular layer exhibited (wanted or unwanted) oscillations at one or another stage of their development. In the next section, we predict that the granular layer has a characteristic frequency restricted to the 10–50 Hz frequency band, the exact value depending on the conduction speed of parallel fibers.

Independently, experimentalists observed that Golgi and granule cells are, more than the average neuron is, intrinsic oscillators. Potent I_{h_i} channels, which rapidly activate during hyperpolarization, induce rebound spikes in rat Golgi cells (Dieudonné, 1998a; Forti et al., 2003). The optimal frequency of alternating hyper- and depolarization is not known, but the firing pattern of a simplified model Golgi cell was most regular at about 11 Hz during parallel-fiber stimulation (Maex et al., 2000). The firing rate of rat granule cells, on the other hand, is maximal at a burst frequency of 3–12 Hz (D'Angelo et al., 2001). This resonance frequency is expected to increase by a factor of two after correction for the 30°C recording temperature.

It is unclear until now how the cerebellum could benefit from synchrony in its granular layer. Not only would synchronous oscillations send regular volleys of parallel-fiber spikes to the Purkinje cells, they would also determine which patterns of mossy-fiber input most easily pass (Kistler et al., 2000). Another conspicuous difference between the synchronous and asynchronous states concerns their effect on gain control. The firing rate of a granule cell depends on the degree of synchrony in the activation of the ten inhibitory synapses it receives on average (Jakab and Hátori, 1988). If the synapses originate from different Golgi afferents, then the summed inhibitory postsynaptic potentials (IPSPs) readily saturate in the synchronous state, because the reversal potential for the $GABA_A$ receptor current is close to the resting membrane potential. In contrast, asynchronously induced IPSPs do not saturate and hold the granule cell in a state of sustained suppression. Figure 1 demonstrates how increasing the number of Golgi afferents hardly affected the firing rate of granule cells in a synchronous network, whereas the increased convergence of Golgi to granule cells suppressed the granule cells in an asynchronous network (Maex and De Schutter, 1998a).

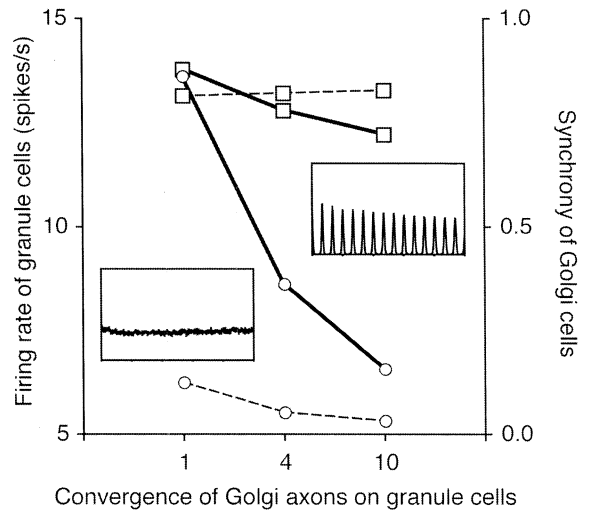


Fig. 1. The firing rate of granule cells is lower in an asynchronous network than in a synchronous network. We varied the degree of convergence from Golgi to granule cells in a synchronous (rectangles) and an asynchronous (circles) model of the granular layer. More particularly, each of the 5355 granule cells received inhibition from either only the closest of the 30 Golgi cells, or from the most nearby 4 or 10 Golgi cells, as indicated on the horizontal axis. The latter two connection schemes implement the innervation of each of the four granule dendrites, versus each of the ten inhibitory synapses, by a different Golgi cell. Individual synaptic strengths were normalized over the synaptic number, so that the mean synaptic current into each granule cell remained approximately constant. The two networks differed only in the number of monosynaptic connections from the mossy fibers to the Golgi cells. In the asynchronous network, each Golgi cell received synapses from a separate, contiguous set of 18 out of the 540 mossy fibers. Increasing the arborization of mossy fibers such that each Golgi cell received 108 (proportionally weaker) synapses sufficed to synchronize the network. The peak conductance of the mossy-fiber activated AMPA channel of Golgi cells was set to 60% of the conductance of the parallel-fiber activated AMPA channel. Solid lines: average firing rate of granule cells. Dashed lines: synchronization index of Golgi cell population. Insets: one-sided autocorrelation histograms of the Golgi cell population (range 0–500 ms) in the asynchronous (left) and synchronous (right) network.

Oscillations in, or close to, the expected 10–50 Hz band were recorded in the granular layer of unres-trained, alert rats (Hartmann and Bower, 1998) and monkeys (Pellerin and Lamarre, 1997; Courtemanche et al., 2002) and, locked to sensory stimulation, over the cerebellar surface of humans (Teschke and Karhu, 2000).

The characteristic frequency

Assuming that synchronous oscillations are able to arise in the granular layer as a resonance phenomenon of the delayed feedback from Golgi to granule cells, we assessed their optimum frequency in a detailed computer model (Maex and De Schutter, 1998a).

The critical parameters, determining the speed of feedback, were updated as follows. The excitatory postsynaptic currents which granule cells evoke in Golgi cells had a minimum latency of 0.5 ms, in addition to a delay proportional to distance due to spike propagation along the parallel fibers (length: 2.5 mm in either direction; conduction speed: 0.1, 0.3, or 0.5 m/s). The IPSCs evoked by Golgi cells in granule cells had a default latency of 0.5 ms. These IPSCs rose with a time-constant of 0.29 ms, and decayed following the sum of a fast and slow exponential with time constants of 4.1 and 22.5 ms, and relative strengths of 40% and 60%, respectively (reversal potential -75 mV; values as reported in Mitchell and Silver, 2003). Their peak conductance was set to 3.1 nS (Mitchell and Silver, 2003) in pure feedback models lacking monosynaptic mossy-fiber excitation of the Golgi cells, and to 1.55 nS in versions of the model in which the Golgi cells also mediated feed forward inhibition from the mossy fibers to the granule cells. A 300 pS membrane conductance was added to simulate tonic inhibition in the granule cells (Hamann et al., 2002).

After randomization of all neurons and synapses, the model granular layer was excited uniformly and continually to a level determined by the average mossy-fiber firing rate. At each excitation level, the degree of synchronous oscillatory activity in the granular layer was quantified from the spike time histograms of the entire Golgi and granule cell populations, using a synchrony index (Maex and De Schutter, 1998a; this index is equivalent to peak power divided by the power at zero frequency).

Figure 2 illustrates that, both in networks with and without feed forward inhibition, power was maximal at a particular level of excitation. This excitation level, and the corresponding oscillation frequency, increased with the value of the parallel-fiber conduction speed. We predicted the optimum frequency from the average delay time d it would take

for one Golgi cell to inhibit or completely disfacilitate another Golgi cell. (Golgi cells are not monosynaptically connected but can be considered to inhibit each other disynaptically over granule cells.) This delay time d comprises the delay time required for a Golgi spike to inhibit a granule cell (the default 0.5 ms synaptic latency) plus the interval between inhibition of the granule cell and disfacilitation of all its efferent Golgi cells, the latter being equal to the sum of the maximal propagation delay generated along parallel fibers and the 0.5 ms synaptic latency (see above). The vertical lines in Fig. 2 are drawn at frequencies equal to $1/(4d)$, and give an approximation of the preferred network frequency for each parallel-fiber conduction speed. It must be noted that to each delay time d , there corresponds an optimal decay time-constant for the IPSC (Maex and De Schutter, 2003). The use of the same IPSC kinetics across the different values of the parallel-fiber conduction speed can therefore explain deviations from the predicted resonance frequencies.

In conclusion, the frequency of the oscillations in a slice preparation will critically depend on the average length of the preserved parallel fibers, and hence on the orientation of their plane of section (see also Maex and De Schutter, 1999, for the effect of varying the parallel-fiber length). Likewise, the oscillation frequency will increase with the parallel-fiber conduction speed, and hence with the recording temperature. The reported speeds vary from less than 0.2 m/s to 0.7 m/s, but we note that the present network model was able to reproduce the *in vivo* responses of rat Golgi cells to peripheral cutaneous stimuli when a 0.3 m/s conduction speed was used (Volny-Luraghi et al., 2002, and discussion therein).

Reciprocal inhibition between the interneurons of the molecular layer

The inhibitory interneurons of the molecular layer (stellate and basket cells) are connected through chemical and electrical synapses, probably forming local networks of synchronized activity (Palay and Chan-Palay, 1974; Kondo and Marty, 1998; Mann-Metzer and Yarom, 1999, 2000).

In a computational study, purely inhibitory networks were found to have a resonance frequency

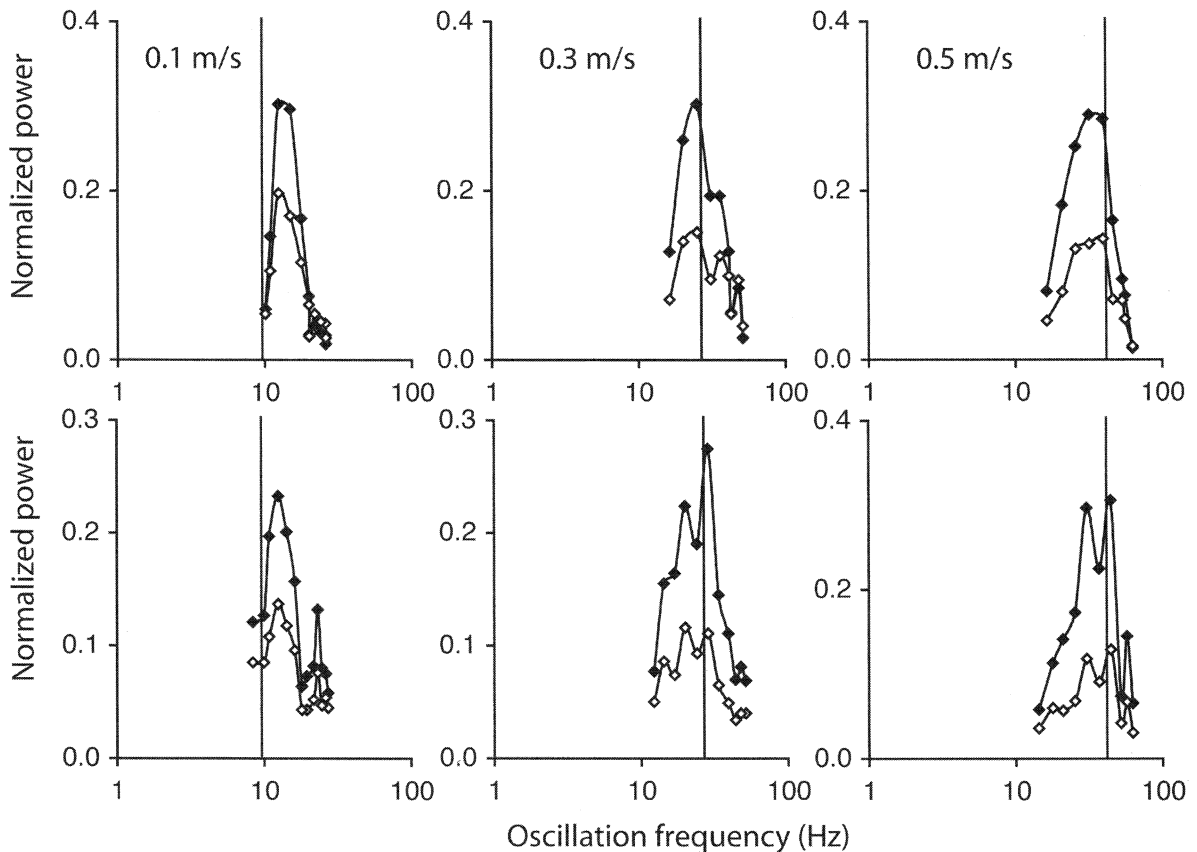


Fig. 2. The granular layer has a characteristic frequency determined by the parallel-fiber conduction speed. The panels show tuning curves obtained from simulations of networks with (upper panels) and without (lower panels) monosynaptic mossy-fiber excitation of Golgi cells, using a conduction speed for parallel fibers of 0.1 m/s (left), 0.3 m/s (middle) or 0.5 m/s (right). Each data point plots the oscillation frequency (horizontal axis) and the corresponding power (vertical axis), obtained at a particular level of excitation, in the population of Golgi cells (closed symbols) and granule cells (open symbols). The tuning curves were constructed by varying the average firing rate of mossy fibers by a factor of 1.41 between simulations. The vertical lines indicate frequencies of 9.6 Hz (speed 0.1 m/s), 26.8 Hz (0.3 m/s) and 41.7 Hz (0.5 m/s).

close to $1/(4d)$, with d the average delay time or latency of the evoked IPSCs (Maex and De Schutter, 2003). Electrotonic coupling through gap junctions improved network synchrony but did not affect the resonance frequency.

The confinement of the interneuron axons within the molecular layer, where they spread less than 300 μm (Sultan and Bower, 1998), the short latency of the IPSCs evoked in paired recordings (mean 1.7 ms at 20–22°C in Kondo and Marty, 1998), and the absence of excitatory neurons capable of polysynaptically interconnecting the interneurons, all suggest

that the average connection delay within the interneuron network is small. Average delay times of 2.5 and 1 ms are predicted to induce resonance at 100 and 250 Hz, respectively. The fast time-course of the IPSCs (3.2 ms half-decay time at 34–35°C in Carter and Regehr, 2002) is near optimal to sustain oscillations in this frequency band.

Local field potential oscillations at 160 Hz, recorded in the cerebellar cortex of alert transgenic mice deficient for the Ca^{2+} -binding proteins calbindin and/or calretinin, were attributed to the interneuron network (Cheron et al., 2004). Older

studies, discussed in Baçar (1998) and Isope et al. (2002), also reported cerebellar oscillations at frequencies of 180 Hz and beyond.

Recurrent Purkinje axon collaterals

A conspicuous finding of the study of Cheron et al. (2004) was that individual Purkinje cells, recorded from during the oscillations, produced regular trains of simple spikes with a rate close to the oscillation frequency (120–160 Hz). This contrasts with the high-frequency oscillations observed in hippocampus and neocortex, which during their occurrence typically suppressed the firing of simultaneously recorded pyramidal neurons (see Whittington and Traub, 2003).

Although an inhibitory network can generate a population rhythm of a frequency an order of magnitude greater than the mean firing rate of its component neurons (Brunel and Wang, 2003), the high discharge rate of the Purkinje cells in conjunction with the depth profile of field potentials reaching their peak amplitude close to the Purkinje cell bodies (Cheron et al., 2004) suggest that the inhibitory Purkinje cells might play an active role in rhythm generation, rather than being the passive recorders of synchronous IPSCs through the interneurons' synapses.

Recurrent axon collaterals make synapses on neighboring Purkinje cells (Palay and Chan-Palay, 1974) and were proposed to synchronize stripes of Purkinje cells (Hawkes and Leclerc, 1989). The recurrent axon is myelinated, has varicosities confined within 300 μm of the parent cell (O'Donoghue and Bishop, 1990) and forms synapses on somata or proximal dendrites, providing in this way a substrate for fast mutual inhibition. In support of a high resonance frequency for the Purkinje cell network is the observation that spontaneous IPSCs in Purkinje cells (although putatively induced by interneurons) are fast decaying as opposed to the typically slow time-course of the Golgi–granule cell IPSC (Puia et al., 1994). However, quantitative predictions require a physiological characterization of the Purkinje–Purkinje cell synapse, and a measurement of the latency and decay time of the IPSCs evoked in paired recordings. As Purkinje collaterals were demonstrated to inhibit also basket cells

(O'Donoghue et al., 1989), it cannot be excluded that fast rhythms are generated by mixed networks containing several types of inhibitory neurons.

Finally, it is worth mentioning that the mere presence of mutual inhibition between the Purkinje cells would have a profound effect on the overall dynamics of the cerebellar cortex. In conjunction with the high spontaneous firing rate of the Purkinje cells and the off-beam inhibition which they receive from stellate cells, the cortex would resemble a circuit for temporal integration designed by Robinson and collaborators (Cannon et al., 1983; Robinson, 1989). Trying to explain temporal integration in the oculomotor system, these authors demonstrated that mutual inhibition increases the effective time-constant of a couple of neurons that receive complementary (push–pull) inputs, enabling them to almost mathematically integrate their inputs over time. Hence Purkinje–Purkinje cell synapses, if present, would extend the time-scale on which the cerebellar cortex is able to operate.

Conclusion

Recurrent inhibition from Golgi to granule cells induces 10–50 Hz oscillations in models of the granular layer, the resonance frequency being determined primarily by the length and conduction speed of the parallel fibers. In the molecular layer, reciprocal synapses between the interneurons are predicted to induce oscillations with a period length about four times the mean synaptic latency (100–250 Hz). Depending also on the strength and time-course of the poorly characterized synapses between Purkinje cells, similar frequencies can be generated in the Purkinje cell layer. Several rhythms observed in the cerebellum *in vivo* fall within these frequency bands. Although all rhythms generated in the cerebellar cortex, due to the nature of its neurons, probably depend on inhibitory synaptic interactions, a definitive elucidation of their mechanisms requires controlled *in vitro* experiments. Such experiments are also needed to resolve the discordance with the hippocampus and neocortex, where interneuron networks produce gamma-frequency oscillations (40 Hz) and where ripples (200 Hz) are accounted for on the basis of axoaxonal

gap junctions between the pyramidal neurons (Whittington and Traub, 2003).

Abbreviations

IPSC inhibitory postsynaptic current
IPSP inhibitory postsynaptic potential

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