The Function of Cerebellar Golgi Cells Revisited

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Abstract
The inhibitory interneurons of the cerebellar cortex have received very little attention compared to the granule and Purkinje cells, and Golgi cells are no exception. Theoretical considerations of the function of Golgi cell functions have evolved little since from the late sixties and experimental studies were sparse until the last few years. Recent modeling and *in vivo* experimental studies by our group, combined with *in vitro* experimental studies by others, have provided new insights into the properties of these cells which necessitate a revisiting of their function.

The connectivity of the Golgi cell
The anatomical facts are rather simple. The numerically most important input to the cerebellum is the mossy fiber system (Murphy and Sabah, 1971; Brodal and Bjaalie, 1997). If we limit ourselves to this input, the anatomy of cerebellar cortex can be described as a two-layered network. The input layer, corresponding to the granular layer, processes the incoming mossy fiber signals and transmits them by the parallel fiber system to the output layer, consisting mainly of the Purkinje cells. In both layers activity is controlled by inhibitory neurons, the Golgi cells in the input layers, and the basket and stellate cells in the output layer.
Mossy fibers activate both the excitatory granule cells and the inhibitory Golgi cells (Fig. 1A). The granule cell axon forms the parallel fibers, which not only transmit information to the output layer, but also provide additional excitatory input to Golgi cells. Each Golgi cell in turns inhibits the many granule cells present within the range of its axonal arbor (Eccles *et al*., 1966) with probably some overlap between adjacent Golgi cells. The combination of the parallel fiber excitation of Golgi cells with their inhibition of granule cells constitutes a feedback inhibition circuit (Fig. 1C). The direct excitation of Golgi cells by mossy fibers (Fig. 1B) provides a feed-forward connection. It should be noted, however, that the existence of mossy fiber contacts onto Golgi cells couldwere not be confirmed found in electron microscopal reconstructions of cerebellar glomeruli (Jakab and Hámori, 1988).

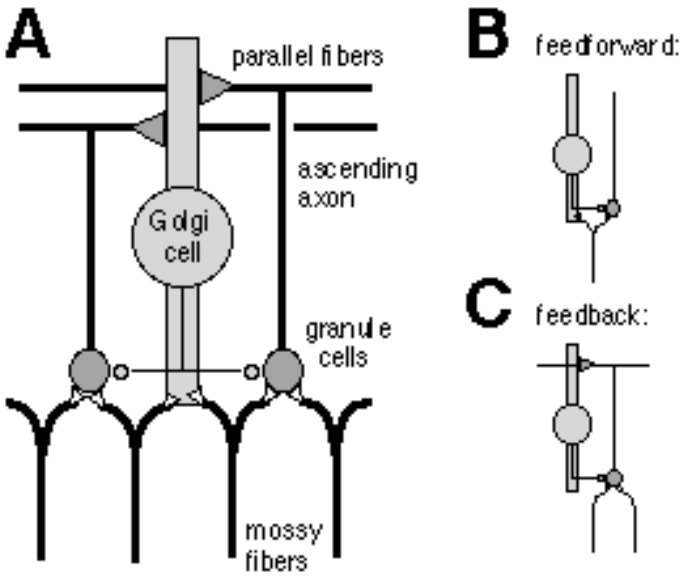

Figure 1

Schematic representation of the connectivity of the granular layer.

A. Mossy fibers form excitatory synapses with Golgi cells and granule cells (triangles), which in turn excite Golgi cells by the parallel fibers. Golgi cells make inhibitory contacts onto granule cells (circles).

B. Representation of the components forming a feedforward inhibition loop.

C. Representation of the components forming a feedback inhibition loop.

The classic view: feedback performs gain control

An early proposal on the function of Golgi cell inhibition was formulated by Eccles *et al*. (1967). They suggested that "this Golgi cell inhibition would suppress the discharges from all weakly excited granule cells, and thus would serve to focus the response to those granule cells strongly excited by the mf input".

Marr (1969), and most theoreticians since, formulated the function of Golgi cells differently. He saw them subserving the need of keeping "the numbers of active parallel fibres ... reasonably small over quite large variation in the number of active mossy fibres" and therefore introduced the concept of Golgi cells setting "the threshold of granule cells". In Marr's model Golgi cells regulate the codon size wich is the number of mossy fiber inputs onto a granule cell that need to be co-activated to make it cross reach threshold. In this theory it is important that "the codon size set for a particular mossy fibre input must depend only on that input; so that the same input is always translated into the same parallel fibres". Albus (1971), having an engineering background, used the word "automatic gain control" to describe the feedback inhibition by Golgi cells. In both these theories gain control is assumed to keep the total output of the granular layer, i.e. the number of active parallel fibers, relatively constant over time. Marr suggests a ranges of 500-9,000 active granule cells contacting a single Purkinje cell, while Albus proposes a temporally and spatially constant activity level of about 1% of

the parallel fibers of about 1%.
Marr was the first to distinguish between the role of the "descending" (or basal) dendrites of the Golgi cell which probably receive the mossy fiber contacts and its "ascending" (or apical) dendrites on which parallel fiber synapses are located. He provided the first with a local and fast sampling role and the latter with a more delayed and global sampling function. "One cannot say that the local or global sample will always give the best solution." He proposed that the Golgi cell would perform an exclusive-OR function: only the strongest activated dendrite should determine Golgi cell output. This means that the mossy fiber and parallel fiber excitatory inputs are not allowed to summate. Though Marr did not specify his reasons in detail it is likely that synaptic summation would make the Golgi cell response too non-linear, leading to an unpredictable codon size. He notes that "refutation of this would be awkward but not fatal". Modern insights into the passive properties of dendrites and into the synaptic control over spike initiation make this part of his proposal unlikely, unless it is implemented by a very specific form of inhibition (Koch, 1998). Moreover, intracellular recordings from Golgi cells in rat cerebellar slice show that mossy fiber synapse responses are stronger than parallel fiber ones (Dieudonné, 1998a), suggesting that the first input would dominate if an exclusive-OR arrangement was implemented.
Later modeling studies by Pellionisz and Szentagothai (1973) demonstrated that a simple network model implementing either a pure mossy fiber activation of Golgi cells or a binary OR function between mossy and parallel fiber excitation performed good gain control over the parallel fiber activation during steady mossy fiber input, which largely confirmed Marr's view. In contrast, a network model with pure parallel fiber activation of Golgi cells caused a focusing effect similar to that proposed by Eccles *et al*. (1967). But while these modeling results were innovative at the time they were produced (Pellionisz and Szentagothai, 1973), they are not up to modern standards as no parameter space evaluation was performed to evaluate their robustness. Nevertheless, the latter results contradict Albus' intuition. He considered the difference in time delays between the mossy fiber feed-forward and parallel fiber feedback paths more important. For him the gain control function of the feedback pathway dominated and "the mossy fiber inputs to Golgi cells probably serve to stabilize parallel fiber rates under transient conditions". Keeler (1990) returned to the distinction between the effect of local compared to long-range sampling on threshold setting and suggested that the Golgi cell would operate as an "arbitrator in a bidding scheme".

Important features of a gain control circuit

At this point it is useful to consider the properties of a gain control function in more detail. First, in later parts of this review paper we will criticize the proposed gain control function of Golgi cells. Let us already point out, however, that because of the presence of the feedback inhibitory loop, it is

inevitable that Golgi cells provide to some degree of a gain control over granule cell output. As has been pointed out by many authors before, such gain control could be quite useful in cerebellar cortex. Indeed, because of the massive excitatory projection to Purkinje cells, receiving more than 150,000 parallel inputs in the rat (Harvey and Napper, 1991), it may indeed be important to prevent granule cells from collectively firing at very high rates in response to strong mossy fiber input. If not in the context of a coding scheme as proposed by Marr (1969), Albus (1971) and (Ito, 1984), then maybe just to prevent excessive excitation of Purkinje cells up to possible neurotoxic levels (Brorson *et al*., 1995; Strahlendorf *et al*., 1998). But, considering the strong stimulus-evoked modulations in Purkinje cell firing rate that can often be observed (Simpson *et al*., 1989; Fu *et al*., 1997), it seems rather unlikely that the total parallel fiber activity is kept relatively constant like Albus proposed, considering the strong stimulus-evoked modulations in Purkinje cell firing rate that can often be observed (e.g. Fu et *al*., 1997; Simpson *et al*., 1989). A more realistic statement may be that a perfect gain controller should constrain the total parallel fiber activity impinging onto a Purkinje cell to a physiological range.
An important consideration in this context is the time frame over which the Golgi cell is presumed to exert its gain control function. In essence all the above theories by Marr and Albus are based on a rate-coding assumption (Rieke *et al*., 1997). The cerebellum is assumed to code information by the average firing rate of units, e.g. Marr (1969) formulates it as "a signal in a mossy fibre is represented by a burst of impulses lasting many tens of milliseconds; and that a signal from a Purkinje cell is represented by a prolonged increase in its firing rate". In later paragraphs we will argue that typical Golgi cell responses to punctate stimuli are so accurately timed and short that a rate coding scheme is unlikely. While not everybody may agree to such a statement, most would concur that changes in spike frequencies over time windows of only a few tens of msecs are relevant to cerebellar function in sensorimotor coordination and in timing in general (Welsh *et al*., 1995; Raymond *et al*., 1996; Ivry, 1997; Thach, 1998). In other words, a perfect gain controller will have to operate on this tens of msecs time scale to be useful for cerebellar processing. If the gain controller is only concerned with preventing neurotoxicity it might still be effective if it operates over much longer time scales.
Before considering the possible gain control function of Golgi cells in more detail, recent modeling and experimental results from our laboratory will be reviewed. More information about these results can be found at http://www.cerebellum.org.

A network model predicts synchronous dynamics

Previous modeling studies of cerebellar cortex have always been based on the mean firing rates of cerebellar neurons (e.g. by using logical units (Moore *et al*., 1989) or rate coding units (Chauvet and Chauvet, 1995; Schweighofer

et al., 1998)). Two previous modeling studies have considered to some degree the temporal dynamics specific to spiking neurons Fujita (1982) predicted that Golgi cells would cause phase differences between co-activated granule cells. But this model made a large number of simplifying assumptions (e.g. Golgi cells behave as non-leaky integrator units which is not what is observed in the slice preparation (Dieudonné, 1998b)) and did not actually simulate the spiking dynamics. The model by Pellionisz and Szentagothai (1973) computed spike times of logical units. While the authors did not recognize the importance of this observation, their model produced oscillatory patterns of parallel fiber activity when parallel fiber input to Golgi cells dominated (their Fig. 8).

Such oscillatory dynamics are a consequence of well-known, but unique, property of the granule cell - Golgi cell circuit. In fact, the feedback inhibition loop is absolutely completely pure as no synaptic connections exist between granule cells or between Golgi cells (Ito, 1984; Voogd and Glickstein, 1998), which is in contrast to circuits in cerebral cortex. Based on theoretical considerations Freeman (1972) already recognized that such a pure feedback circuit would be driven to oscillatory dynamics, but he did not realize that it exists in the cerebellar cortex.

Therefore, retrospectively, it should have come as no surprise that we found our spiking neuron network model of the cerebellar granular layer to be highly prone to synchronous oscillations (Maex and De Schutter, 1998b). A typical example of such a simulation is shown in the raster plots of Fig. 2A. Initially no input is provided (the mossy fibers are silent). Granule cells do not fire spontaneously (D'Angelo *et al*., 1995), but Golgi cells do (Dieudonné, 1998b) and in the network this results in a desynchronized firing (Fig. 2A left). Immediately upon activation of the mossy fibers, however, Golgi cells synchronize and start firing rhythmically. The granule cells are entrained in this synchronous oscillation, but they fire a bit less precisely (as evidenced by the broader peaks in their autocorrelogram in Fig. 2C) and often skip cycles (Fig. 2A bottom).

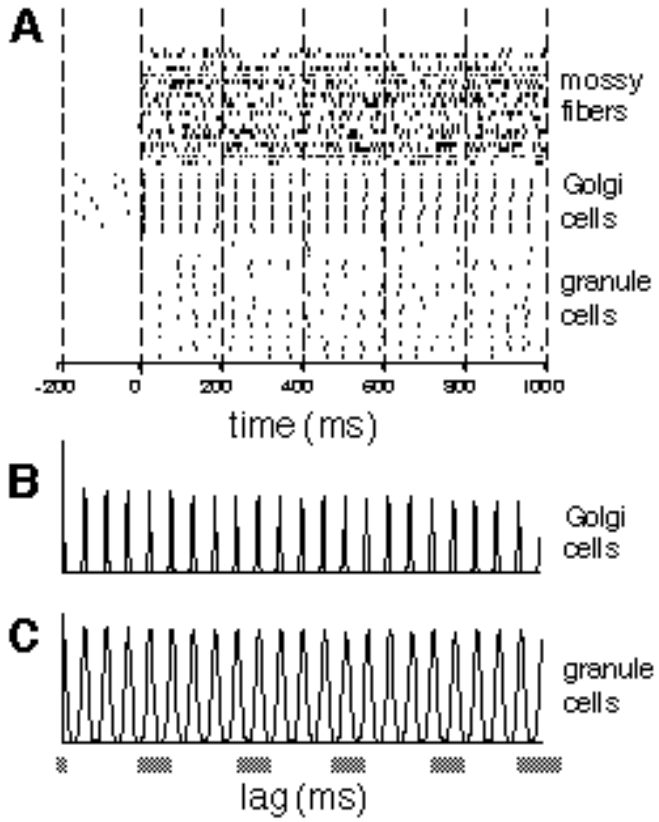

Figure 2

Simulation of network dynamics in the granular layer.

A. Raster plots of activity in a subset of mossy fibers, Golgi cells and granule cells.

B. Autocorrelogram of the Golgi cell population.

C. Autocorrelogram of the granule cell population. The mossy fiber input is initially silent, after 200 msec mossy fibers start firing randomly with average firing rates of 5 to 75 Hz. Total network size was 30 Golgi cells, 5355 granule cells and 540 mossy fibers, with an average 602 parallel fiber synapses on each Golgi cell. Golgi and granule neurons were modeled as single compartments containing several voltage and calcium-gated channels. See Maex and De Schutter (1998b) for more details.

The generation of these synchronous oscillations is easily explained by the intrinsic dynamics of the feedback inhibition circuit. Lets first consider a single Golgi cell and its population of postsynaptic granule cells. Inhibitory neurons can exert a strong influence on the exact timing of action potentials in their target neurons (Lytton and Sejnowski, 1991; Cobb *et al*., 1995). The simulated granule cells tend to fire when inhibition is at its lowest, which is just before the next Golgi cell spike. Because a single Golgi cell inhibits many granule cells (Palkovits *et al*., 1971), this means that a large population of granule cells shall fire at about the same time. The loosely synchronous granule cell activity excites the Golgi cell and causes it to fire immediately, leading to the establishment of a synchronized oscillation within this small circuit (comparable to "the comparator circuit" of Kammen *et al*., (1989)). The unique structure of the cerebellar cortex couples many of these oscillatory circuits together through the common parallel fiber input to the Golgi cells.

Consequently the long parallel fibers (Pichitpornchai *et al*., 1994) cause Golgi cells and granule cells located along the same transverse axis to fire synchronously.
It is important to realize that this is a *dynamic* property of the circuitry: once the granular layer is activated beyond a minimum level the most stable form of spiking is a synchronous oscillation (Maex and De Schutter, 1998b). This has several consequences. First, the synchronization is immediate upon activation (Fig. 2), there is no delay due to the slow parallel fiber conduction velocity (Maex and De Schutter, 1999). Second, the accuracy of synchronization will increase with increased network activity, which corresponds to an increased Golgi cell firing rate (Maex and De Schutter, 1998b). This leads to a fire-rate dependency of the synchronization (Maex *et al*., 1998). Third, the synchronization requires a minimal number of weak parallel fiber synapses onto each Golgi cell (Maex and De Schutter, 1998a). The strength of parallel fiber synapses onto Golgi cells is indeed rather small (Dieudonné, 1998b). Fourth, synchronization occurs despite the slow conduction velocities of the parallel fibers (Vranesic *et al*., 1994) and entrains Golgi cells over the complete extent of the transverse axis where mossy fibers are activated, even if this is much longer than the mean parallel fiber length.
These observations emphasize the importance of the parallel fiber excitation of Golgi cells. Direct mossy fiber input to Golgi cells can desynchronize the network as it may cause Golgi cell spikes which are not coupled to the oscillatory pattern. In simulations we found that this depended on the relative strength of mossy fiber compared to parallel fiber synapses. As long as the total synaptic conductance of all mossy fiber inputs onto a Golgi cell did not exceed that of all parallel fiber inputs, which are individually weaker (Dieudonné, 1998a,b) but probably much more numerous (e.g. Pellionisz and Szentagothai, 1973), the network dynamics were unaffected (Maex and De Schutter, 1998b).

Parallel fibers synchronize Golgi cells

The network model predicted that Golgi cells receiving common parallel fiber input should synchronize. As the dynamics described in the previous paragraph depend on common parallel fiber excitation one expects that Golgi cells which are separated along the parasagittal axis will not fire synchronously, unless they are so close to each other that their dendritic trees may overlap (Dieudonné, 1998b).
These predictions were confirmed using multi single unit recordings of spontaneous Golgi cell activity in the cerebellar hemisphere of the anesthetized rat (Vos *et al*., 1999a). Two or three electrodes were placed in one of two orientations: transverse or sagittal. Golgi cells were identified based on their characteristic spiking patterns (Edgley and Lidierth, 1987; Van Kan *et al*., 1993; Atkins *et al*., 1997) and their positions in the granular layer were confirmed histologically. The results were independent of the kind

of anesthesia used.
A total of 42 Golgi cell pairs in 38 ketamine-xylazine anesthetized rats were recorded. Of these 26 pairs were positioned along the transverse axis, with the other pairs along the sagittal axis. Synchronization was measured as the height of the central peak in the normalized cross-correlogram. All transverse pairs except one showed a highly significant coherence. An example of a pair of Golgi cells along the tranverse axis is shown in Fig. 3. The synchrony between these cells was highly significant. The central peak had a z-score of 6.4 (range for all: 3.0-9.3), but was rather wide (half-width of 21 ms, range: 11.5-39.5 ms). Conversely, in 12 out of 16 sagittal pairs no synchrony could be found. The remaining 4 sagittal pairs showed low levels of coherence (z-score < 4), but in each of these 4 pairs the Golgi cells were located within 200 micro m from each other.

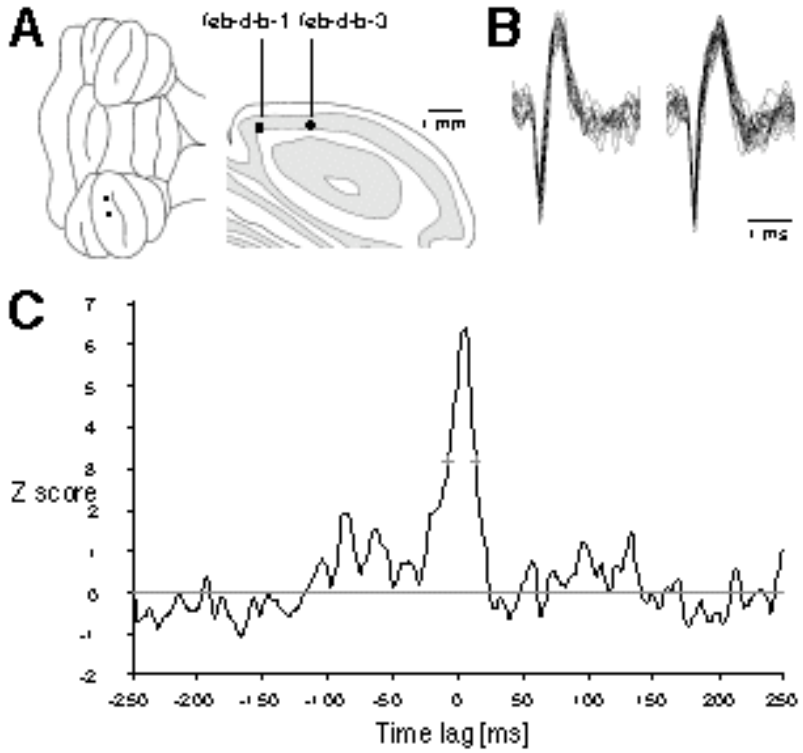

Figure 3
Synchronous activity of two Golgi cells simultaneously recorded in anesthetized rat.
A. Location of recording sites in crus II.
B. Examples of extracellular waveforms of each cell.
C. Normalized cross-correlogram. See Vos *et al*. (1999a) for more detail on experimental methods.

These findings confirm the first prediction generated by our network simulations. Additionally, as also predicted by the model, the accuracy of synchronization, evidenced by increasing z-scores and decreasing widths, increased with Golgi cell firing rate (Fig. 1 of Vos *et al*., 1999a). This has the important implication that synchronization may be much more accurate in awake animals, compared to the loose synchrony observed in the

anesthetized rat. The only data available from awake animals to date are field potential recordings (Pellerin and Lamarre, 1997; Hartmann and Bower, 1998), which are more suitable for measuring oscillatory activity than our single unit recordings. The studies in awake animals have indeed demonstrated the presence of oscillations in the granular layer that may correspond to those predicted by the model.

Stimulus-evoked responses of Golgi cells

We will summarize the results described in the companion paper (Vos *et al*., 1999c) and elsewhere (Vos *et al*., 1999b) because they are relevant to the discussion presented next. Golgi cell receptive fields for punctate tactile stimuli are very large and often bilateral which is in contrast to the fractured somatotopy observed in field potential recordings (presumably mostly reflecting activation of mossy fiber synapses; e.g. Shambes *et al*., 1978; Bower *et al*., 1981; Bower and Kassel, 1990). Within these receptive fields one can distinguish different response patterns which consist usually of two components, an early one reflecting trigeminal inputs and a later one reflecting corticopontine activation, as was also found in granular layer field potential recordings (Bower *et al*., 1981; Morissette and Bower, 1996). Especially the early component of the response is highly accurate in timing and a subclass of responses with two or more sharp peaks in this component can be distinguished. This subclass can be evoked from only a restricted area of the face and has a very short latency. It probably reflects direct mossy fiber activation of the Golgi cell. Because of their large receptive fields the other response types are presumably caused by parallel fiber activation. Finally, most of the Golgi cell responses are distinguished by a long silent period following the excitatory response.

Is gain control the main function of Golgi cells?

Because of the feedback connectivity it is inevitable that Golgi cells perform some level of gain control over the output of granule cells. This does not imply, however, that gain control is their only, or even main, function. In this section we will argue, based on the response characteristics described earlier, that Golgi cells are bad gain controllers. To put these arguments in perspective it is useful to repeat our definition of an ideal gain control circuit first. It should keep parallel fiber input to a Purkinje cell within a range which is much smaller than the range of possible mossy fiber input activities (Marr, 1969), and it should operate on the order of tens of msec.
A first question to consider is whether the large receptive fields observed in Golgi cell responses are compatible with a gain control function. In view of the large receptive fields a tactile stimulus on a small part of the face will lead to inhibition of most of the granule cells in crus I/II, even though many of them actually receive mossy fiber input from other parts of the face. The usefulness of such a diffuse inhibition for a gain control circuit will depend

on how Purkinje cells are excited by granule cell activity. If one believes that Purkinje cells are activated by parallel fiber beams (Eccles *et al*., 1967), without distinction of the origin of the parallel fiber signal, then the observed arrangement would seem best. The large receptive fields of Golgi cells are probably due to parallel fiber activation (Vos *et al*., 1999b,c), which would ensure a good global sampling of parallel fiber activity for the gain controller. But if Purkinje cells are mainly activated by underlying granule cell activity, as demonstrated in electrophysiological recordings (Bower and Woolston, 1983) and in recent optical imaging (Cohen and Yarom, 1998, 1999), then local sampling is needed. Indeed, it is presumed that the restricted Purkinje cell responses are due to activation by synapses from the ascending granule cell axon (Gundappa-Sulur *et al*., 1999) while parallel fiber synapses seem much less effective in exciting the cell (Cohen and Yarom, 1998). This means that the large receptive fields of Golgi cells would be rather unsuitable for controlling the gain of Purkinje cell excitation.

The large receptive fields fit better with the "arbitrator in a bidding scheme" function suggested by Keeler (1990). A more intuitive way of describing this effect is that the granular layer circuitry performs lateral inhibition along the parallel fiber axis. Note that while the effects are similar to those of classic lateral inhibition, with a potential for implementation of a "first area activated wins all" scheme, the mechanisms are not. The parallel fibers provide lateral *excitation* to the *inhibitory* Golgi cells so that a highly activated patch of granule cells can lead to inhibition of nearby patches. More recent recordings suggest that the size of the stimulus may be an important parameter in this lateral inhibition (Volny-Luraghi *et al*., 1999).

While the importance of the large receptive fields will depend on how Purkinje cells are excited *in vivo*, the fine and accurate timing of Golgi cell responses is difficult to reconcile with fast gain control. These responses do not fit well with a rate coding scheme as the average firing rate is a poor measure of the true Golgi cell response, consisting of a few accurately timed spikes within 30 msec followed by a silent period of 100 msec or more (e.g. Fig. 5). In fact, the average firing rate of Golgi cells changes only very little when their responses to tactile input are averaged over 300 ms (Fig. 8 of Vos *et al*., 1999b). As a consequence, it is unlikely that Golgi cells can provide smooth inhibiton of granule cells. While it is not possible to isolate granule cells responses *in vivo*, one can estimate their firing rates to some degree from the simple spike patterns in Purkinje cells. Fig. 4 shows an example of a cross-correlogram between a Golgi cell and a nearby Purkinje cell during spontaneous activity. A pronounced dip is observed which peaks just past the zero time point. This indicates that on average a single Golgi cell spike is sufficient to diminish granule cell activity so much that the Purkinje cell is less likely to spike for more than 100 msec. In other words, Golgi cell inhibition does not maintain a steady parallel fiber activation of Purkinje cells during the tens of msec following each Golgi cell spike.

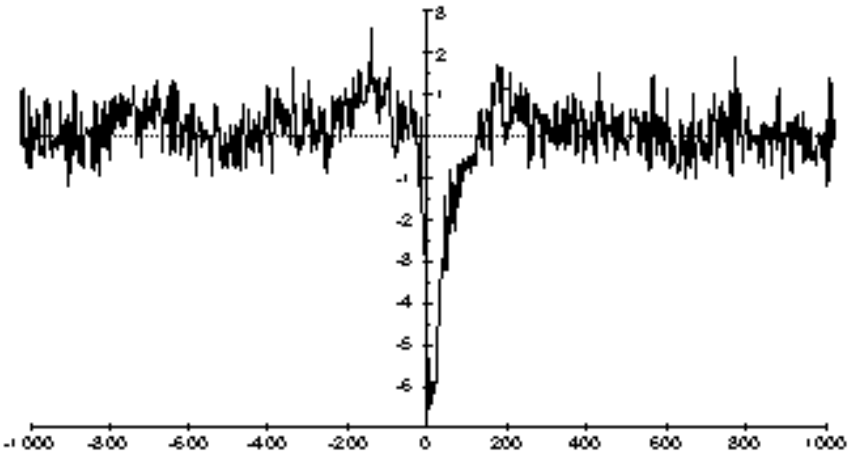

Figure 4

Cross-correlogram between spontaneous activity of a Golgi cell and of a Purkinje cell recorded in crus IIA of the anesthetized rat. Notice the large dip in Purkinje cell activity starting at the time of the Golgi cell spike (zero time point) and during more than 100 msec.

This clearly violates our definition of an ideal gain controller. In fact, it can be interpreted as an overcompensation of the signal by the gain controller as Golgi cell spiking seems to lead to below average activity of granule cells. Notice also that it would have been perfectly possible to design the circuitry so that this problem does not arise. If Golgi cells were much faster firing neurons and if they didn't show silent periods their rate could vary much more smoothly, which would allow for a continuously varying inhibition of granule cells as opposed to the discrete inhibition observed in Figs 4-5. The fact that this is not the case for Golgi cells implies that they have not been optimized by evolution to perform an ideal gain control function.
The significance of the long silent period that follows the initial Golgi cell response evoked by tactile stimulation (Fig. 5) is even more difficult to explain in the context of a gain control function. Silent periods are also present in other parts of the somatosensory system (Mountcastle *et al*., 1957; Mihailoff *et al*., 1992; Nicolelis and Chapin, 1994), where they are assumed to be the consequence of local feedforward inhibition loops (Dykes *et al.*, 1984). Note, however, that in somatosensory cortex these silent periods are observed in excitatory neurons while inhibitory neurons remain active (Brumberg *et al*., 1996). This is clearly not the case in the granular layer where a silent period is observed in the inhibitory neuron.

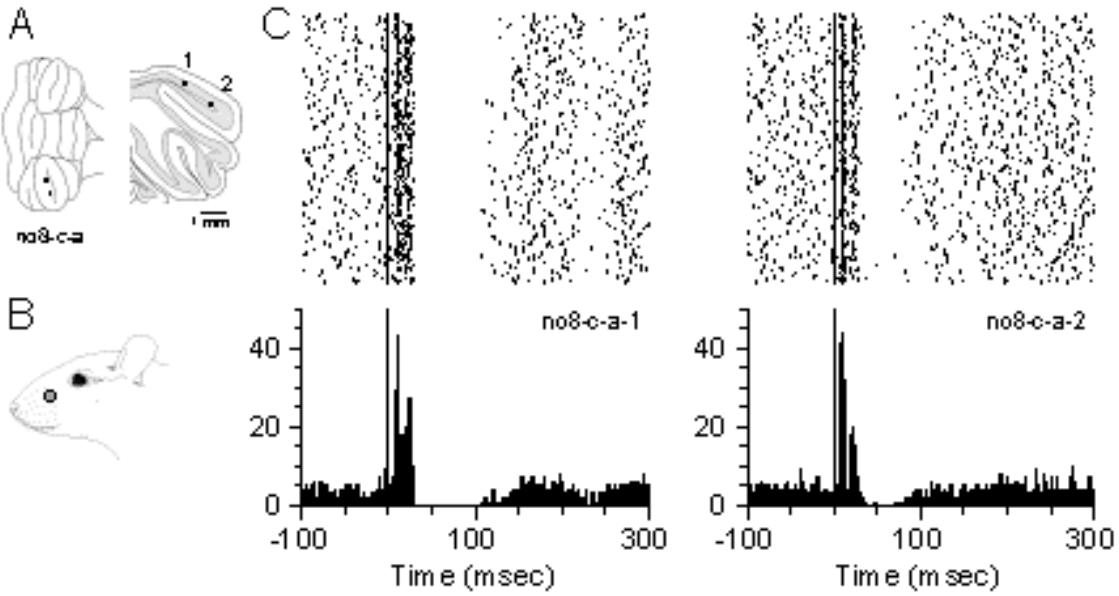

Figure 5

Responses to tactile stimulation around the A1 vibrissa of two Golgi cells simultaneously recorded in crus IIA of the anesthetized rat. Notice large difference in duration of the silent period after the excitatory response. See Vos *et al*. (1999b) for more detail on experimental methods.

It is not known what the excitatory granule cells do during this silent period. Theoretical analysis shows that this depends on what causes the silent periods observed in Golgi cell responses. Four potential sources can be distinguished which may very well operate together. First, it is likely that the diminished mossy fiber input due to the silent periods observed elsewhere in the somatosensory system plays a role. But this cannot be the only explanation as simultaneously recorded Golgi cells can show different duration silent periods in response to the same stimulus (Fig 5), indicating that factors intrinsic to Golgi cells (Dieudonné, 1998b) or local circuit effects contribute. One such local circuit effect may be the strong tonic component of granule cell inhibition which has recently been described in cerebellar slice preparations (Brickley *et al*., 1996; Wall and Usowicz, 1997). This tonic inhibition is probably caused by Golgi cell activity resulting in a spillover of GABA within the glomerulus (Rossi and Hamann, 1998), which then activates high affinity receptors on granule cells (Nusser *et al*., 1998). It is therefore expected to correlate with the amplitude of Golgi cell responses, similar to the correlation between the duration of the silent period and the excitatory response amplitude (Fig. 8 of Vos *et al*., 1999b). The tonic inhibition of granule cells will cause an interruption of parallel fiber excitation to the Golgi cell, enhancing the effect of diminished mossy fiber input during the silent period. Another local circuit effects could be inhibition of the Golgi cell by molecular layer interneurons (Dieudonné, 1995). Compared to tonic inhibition, which may cause a complete silencing of local granular layer activity, molecular layer inhibition of Golgi cells and/or an afterhyperpolarisation intrinsic to Golgi cells (Dieudonné, 1998b) will cause a

disinhibition of local granule cells. While these effects are opposite, both seem unsuitable for a gain control circuit. As both effects may have important implications for how the cerebellum operates it will be important to elucidate the cause of the silent periods.

A beam of activated Golgi cells

In the previous section we raised serious doubts about the role of Golgi cells as gain controllers. In this and the following section we will speculate on alternative functions of Golgi neurons.
An overall conclusion of the results reviewed here is that the parallel fiber input to Golgi cells does not only provide for a feedback inhibition of granule cells but also conveys a spatial organization onto Golgi cells. Indeed, while both old (Bower and Woolston, 1983) and new (Cohen and Yarom, 1998, 1999) experimental data demonstrate the absence of parallel fiber beams at the level of Purkinje cell activity as proposed by Eccles and colleagues in the sixties, our multi-unit recordings indicate that Golgi cells are organized into such beams (Vos *et al*., 1999a). Moreover, the stimulus-evoked responses can be explained only by assuming an important contribution of the parallel fibers which transfer signals from distant mossy fiber receptive fields (Vos *et al*., 1999b,c).
The functional importance of this particular spatial organization may be twofold. First, as already mentioned above, due to their large receptive fields Golgi cells can provide a form of lateral inhibition along the parallel fiber axis. Second, by synchronizing the firing of granule cell spikes (e.g. Fig. 2), they may organize granule cells into functional assemblies (König and Schillen, 1991; Nicolelis *et al*., 1997) along the parallel fiber axis.

The control of timing of granule cell spiking

A consistent finding in our modeling and experimental work is that Golgi cells exert a strong control over the timing of granule cell spikes. The network model predicts that granule cells will preferentially spike just before their afferent Golgi cell (Fig. 2) and the example in Fig. 4 suggests indeed a strong effect of Golgi cell activation on the timing of granule cell spikes. This control over timing of granule spikes could have could have functional consequences at many levels.
At the cellular level Golgi cells entrain granule cells into an oscillatory rhythm which may make the latter more prone to burst (i.e. fire a few spikes at high frequency). Such behavior can be observed in the network model for certain ranges of parameter values (unpublished observations) and burst firing has been observed in granule cells in slice (D'Angelo *et al*., 1998). Similar to what has been described in many invertebrate systems (Calabrese and De Schutter, 1992; Marder and Calabrese, 1996), an oscillatory pattern of inhibition may thus turn regular spiking granule cells into bursting neurons. This would have important functional consequences as the parallel fiber

synapse onto Purkinje cells is quite sensitive to high frequency activation, which preferentially activates the metabotropic glutamate receptor (Batchelor and Garthwaite, 1997; Tempia *et al*., 1998) leading to calcium release from intracellular stores (Finch and Augustine, 1998).

At the network level Golgi cells impose a loose synchronization onto granule cells lying along the same parallel fiber axis (Figs. 2 and 3). Such synchronization may contribute to the transformation of spatial patterns present in the mossy fiber input into temporal patterns which are transmitted along the parallel fiber system. Hopfield (1995) hypothesized that the nervous system might use the relative phase lags between spikes to encode information. In the context of pattern recognition such a temporal code has the advantage of being much less sensitive to stimulus amplitude than standard rate codes. Because the mossy fiber input to the cerebellar cortex has a patchy, fractured somatotopy (Shambes *et al*., 1978; Bower *et al*., 1981; Bower and Kassel, 1990) tactile stimuli are expected to co-activate several patches in the granular layer (see also Peeters *et al*., 1999). In other words, mossy fiber inputs caused by different stimuli may be distinguished, at least partially, by the complex spatial pattern of activation of patches. But how can such a pattern be recognized by Purkinje cells, especially if one assumes a population coding of the signal? Because of the extended length of the parallel fibers (Mugnaini, 1983; Pichitpornchai *et al*., 1994) signals originating from granule cells in multiple patches will become mixed together, making their origin and their relation to each other obscure unless one can rely on the relative timing of the spikes. By synchronizing granule cell spiking along the parallel fiber axis it becomes possible to convert the spatial code implicit in the patchy pattern of mossy fiber activity into a reliable temporal code of phase differences between parallel fiber spikes originating in distinct patches. Even though the variable conduction velocities of parallel fibers (Bernard and Axelrad, 1991; Vranesic *et al*., 1994) will cause small phase differences between spikes from identical patches, each temporal pattern of phase differences recorded at a particular location along the transverse axis of the folium will correspond to a unique spatial pattern of mossy fiber activation. In support of this hypothesis we have found that the only stimulus aspect that determines the fine temporal shape of Golgi cell responses is the receptive field being activated (which determines the spatial pattern of input), while stimulus amplitude or frequency have little or no effect (Vos *et al*., 1999b,c).

But many questions remain to be answered before the temporal code hypothesis can be taken for granted. First, in anesthetized rats the synchronization of Golgi cells is rather loose, but it is predicted to be much more accurate in awake animals (Maex *et al*., 1998; Vos *et al*., 1999a). Nevertheless it remains to be proven that sufficiently precise synchronization can be achieved to support temporal coding. Next, it remains unclear if Purkinje cells can decode this temporal information. Our Purkinje cell model (De Schutter and Bower, 1994a,b) is a very poor coincidence detector (De Schutter, 1998; Santamaria *et al*., 2000). This is not surprising as the active dendrite of Purkinje cells does not contain fast

sodium channels (Stuart and Häusser, 1994), but, instead, much slower activating calcium channels (Regan, 1991; Usowicz *et al*., 1992) which will determine its window of temporal integration. So while Braitenberg et al. (1997) and Meek (1992) have proposed that Purkinje cells would act as coincidence detectors of externally generated temporal patterns (they do not assume any processing by the granular layer), we have suggested instead that these temporal patterns specifically change the Purkinje cell responsiveness to activation of its ascending granule cell axon synapses, with an effect similar to a complex filtering function (De Schutter, 1995, 1998). An alternative hypothesis is that Purkinje cells may learn to recognize particular temporal patterns (Steuber and Willshaw, 1999).

Conclusions

We have presented experimental evidence that Golgi cells perform poorly as gain controllers at the time scales of interest for cerebellar motor control. While their true function in cerebellar cortex remains to be proven, our modeling and experimental data suggest the presence of beams of Golgi cells being synchronized by common parallel fiber input. This may result in lateral inhibition by Golgi cells, but also in a tight control over the timing of granule spikes which could implement a temporal code. Additional modeling and experimental work is needed to clarify these issues.

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