

An optimal connection radius for long-range synchronization

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Summary

We demonstrate, by means of computer simulations of a realistic cerebellar circuit model, the existence of an optimal axonal length (connection radius) for establishing long-range synchronous oscillations. Beyond the optimal axonal length, conduction delays hamper synchronization. The conduction delays also co-determine the oscillation frequency, making synchrony frequency-dependent. Large conduction delays and also doublet firing may stabilize low-frequency oscillations.

Introduction

The brain operates by allocating various functions to highly dedicated, strictly circumscribed and mostly somatotopically organized areas. At the same time the brain has an integrating function, which it accomplishes through spatial convergence of this distributed activity onto integration areas. Another mechanism for integration has been considered over the last years : temporal convergence on the time axis, i.e. coincidence of distributed spikes on a millisecond scale (von der Malsburg, 1981). In this respect, it has been proposed that long-range synchronous oscillations, which have been recorded experimentally in many systems of different species, couple distributed activity to produce unifying perceptions and motor coordination (see Farmer (1998) for a recent review).

Neurons fire in synchrony when they undergo correlated fluctuations of their membrane potential, which will occur if they receive common synaptic input from shared afferents. Synchronization is stronger the more input is shared (Maex *et al.*, 1999). The finite axonal length and conduction speed, however, put constraints on the amount of input that can be received simultaneously and on the distance over which synchrony can be established by monosynaptic connections.

Modeling studies have demonstrated that lateral coupling of local oscillators in a chain entrains these oscillators in a global synchronous oscillation extending over distances much larger than the (monosynaptic) connection radii (Kammen *et al.*, 1989; König & Schillen, 1991; Lansner & Ekeberg, 1994; Traub *et al.*, 1996; Crook *et al.*, 1997; Maex & De Schutter, 1998b). Such local oscillators usually consist of reciprocally connected populations of excitatory and inhibitory neurons. A subpopulation of neurons in each local oscillator spreads its activity to the neighbouring oscillators in the

chain. Increasing the connection radii of these neurons increases the amount of synaptic input shared between distant oscillators, enhancing their synchrony, but the prolonged propagation of spikes along the axons will disperse in time the activation of their synapses as well. Hence there is a trade-off between the objective of connecting as many neurons as possible, by the usage of long connection radii, and the objective of activating common synapses simultaneously.

A model of the cerebellar granular layer

The cerebellar cortex and particularly its granular layer have a unique architecture (Palay & Chan-Palay, 1974). The excitatory interneurons (granule cells) are so numerous that they constitute the largest neuronal population of the brain. Granule cells receive excitation exclusively from mossy fibres, which are extremely numerous as well, in an unusual fashion : each granule cell has a different set of (on average) four mossy fibre afferents. The axons of granule cells bifurcate and run as parallel fibres (PFs) in two opposite directions, making en passant synapses on Golgi cells. Golgi cells in turn provide feedback inhibition to granule cells. This unidimensional connection pattern from granule to Golgi cells contrasts with the radial, isotropic connection patterns observed in most other brain areas like neocortex. Moreover, PFs are 4.5-5 mm long in rats (Pichitpornchai *et al.*, 1994). This length, together with the consideration that PFs constitute quantitatively the largest axonal pathway in the brain, makes the parallel fibre system particularly suited for the study of long-range synchronization.

We have previously shown, in a granular layer computer model, that random mossy fibre activity very readily entrains Golgi and granule cells along the entire parallel fibre axis in a synchronous rhythmic firing pattern (Maex & De Schutter, 1998a,b). Each Golgi cell behaves as a local oscillator through the interactions with its surrounding granule cells, while PFs couple neighbouring oscillators through the synapses they also make on more distant Golgi cells (Fig. 1).

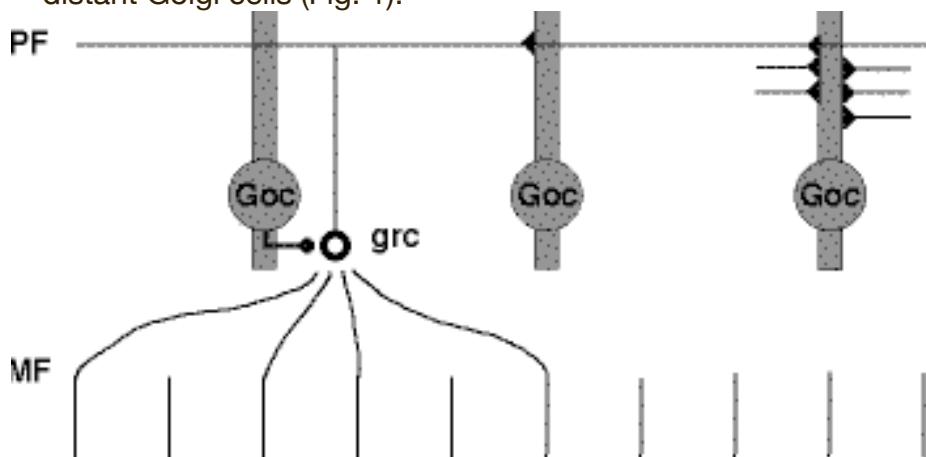


Figure 1

The synaptic relationships between mossy fibres (MF), granule cells (grc), grc axons or parallel fibres (PF) and Golgi cells (Goc).

Here we study the effect of PF length and PF conduction speed on the

synchronization process. It must be noted that these PF parameters do not only have an effect on the coupling between oscillators (Golgi cells) and hence on long-range synchronization, but also on the coupling between Golgi and granule cells and hence on the oscillation frequency.

Modeling methods

We simulated the one-dimensional standard model described in Maex & De Schutter (1998a,b). Its complete implementation in Genesis-scripts can be found at the URL: <http://www.tnb.ua.ac.be/models/network.shtml>. The component granule and Golgi cells are unipotential compartments with voltage-gated channels and they reproduce well the electrical and synaptic excitability of actual neurons in vitro. Mossy fibres are random generators of binary 'spikes', and fire all at the same average rate.

The following parameters were customized for the present study on long-range synchrony : number of Golgi cells : 240; number of granule cells : 7155; number of mossy fibres : 720; average number of PF synapses on each Golgi cell : 100; PF conduction speed : 200 mm/s (Cohen & Yarom, 1998).

Given an inter-Golgi-cell distance of 0.3 mm, the simulated array measured 7.2 cm. It was further assumed that synapses are uniformly distributed along the entire length of the PF axonal radius (which equals half the PF length). Because on average one hundred PFs randomly connected to each Golgi cell, the PF conduction delays to each particular Golgi cell were almost uniformly distributed between zero and the maximum delay, which equals half the PF length divided by the PF conduction speed.

A metric for synchrony and rhythmicity : the synchronization index (SI).

Synchrony and rhythmicity were calculated from the spike trains produced by the central 60 Golgi cells of the one-dimensional array during a 10 s simulation. All spikes were compiled in a common spike time histogram with a 1 ms binwidth. The resulting time series was autocorrelated, and the degree of modulation of the autocorrelogram (AC) expressed as :

$$SI = \frac{\sum_{n=1}^{1000} \cos\left(2\pi \frac{n\Delta t}{T}\right) AC(n\Delta t)}{\sum_{n=1}^{1000} AC(n\Delta t)} \quad \Delta t = 1ms$$

in which T is the period optimized to yield a maximal value of SI (Maex & De Schutter, 1998a,b).

This synchronization index is a value between 0.0 and 1.0 and is a combined metric for rhythmicity and synchrony. It is analogue to the coefficient of the first harmonic cosine in a Fourier series representation of the autocorrelogram.

The effect of parallel fibre length on long-range synchronization and on the oscillation frequency

We first established that the degree of synchrony did not depend on the total number of simulated Golgi cells or on the inter-Golgi cell distance.

Simulations were thereafter run on an array with a fixed number of 240 Golgi cells, and the firing rate, oscillation period T and synchronization index SI were calculated for various lengths of PFs. As mentioned above, SI measures the presence of synchronous oscillations in a population of 60 Golgi cells, spanning a distance of 18 mm, during a 10 s interval. Calculating SI over smaller Golgi cell ranges yielded larger values, but this did not change the shape of the relation between SI and the parameters varied. Note also that the present model has suboptimal numbers of mossy fibres, granule cells and PF synapses on Golgi cells, and that the SI values are therefore lower than those reported in our previous studies.

As explained in the introduction, we expected synchrony to be optimal at a particular PF length. In addition, it must be taken into account that the Golgi-granule cell feedback loop operates as an oscillator with a period which is determined mainly by two factors : an intrinsic delay, which changes in proportion to the PF length and in inverse proportion to the PF conduction speed, and an extrinsic driving force, the mossy fibre input. We therefore expected to find different optimal PF lengths when different conduction speeds or different strengths of mossy fibre input were used. These principles are illustrated below. In Fig. 2, two parameters were varied independently : the PF length (horizontal axis) and the average mossy fibre firing rate (labels, in spikes/s). The PF conduction speed was fixed at 0.2 m/s. With very weak mossy fibre input (10 spikes/s), the network did not synchronize well. With intermediate values, synchrony was tuned about an optimal PF length. This optimal PF length decreased from 10 mm to 5 mm when the mossy fibre firing rate was raised from 15 to 67 spikes/s. With very strong excitation (100 spikes/s mossy fibre firing rate) synchrony was almost lost again.

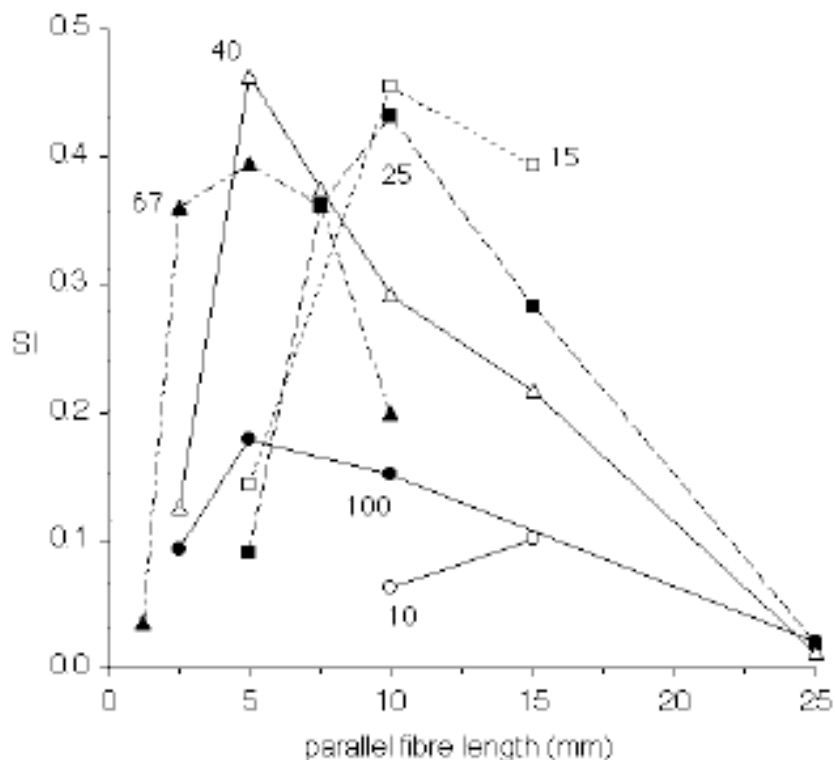


Figure 2

The effect of parallel fibre length on synchronization index (SI) for various mossy fibre firing rates (labels in spikes/s)

To gain more insight in the tuning mechanism, we plotted along the vertical axis of Fig. 3 the oscillation periods T used to calculate the SI values of Fig. 2 (with the formula above). Let us first explain how this figure is composed. Each curve corresponds to an SI curve of Fig. 2, and plots the oscillation period T obtained at various PF lengths using a particular mossy fibre firing rate (labels in spikes/s as in Fig. 2). On each curve, the point at the PF length producing the largest SI value in Fig. 2 is enlarged. As a reference, the straight line through the origin has a slope of $1/(4 * \text{PF conduction speed})$, and indicates how the oscillation period would increase with PF length if its value were just incremented at each PF length with the resulting mean conduction delay. (The factor 4 arises because spikes travel only along one PF branch, i.e. half the PF length, and because we consider the mean PF delay from a uniform distribution, i.e. half the maximum delay.)

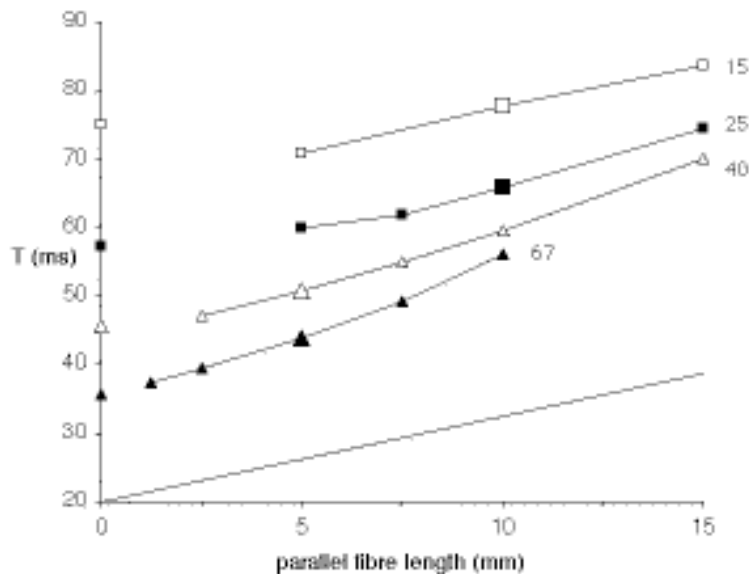


Figure 3

The effect of parallel fibre length on oscillation period T for various mossy fibre firing rates (labels in spikes/s)

The symbols overlying the vertical axis indicate for each mossy fibre firing rate the theoretically optimal oscillation period. This optimal period T_{opt} was calculated as the inverse of the average firing rate of Golgi cells, because rhythmicity is optimal when all interspike intervals are exactly equal to T_{opt} . It could be determined unequivocally for each mossy fibre firing rate because networks with different PF lengths produced similar Golgi cell firing rates. Hence, there exists for each mossy fibre firing rate an oscillation period T_{opt} that predicts the PF length at which rhythmicity should be optimized. However, SI does not only measure rhythmicity but also synchronicity, and this explains why T_{opt} did not always predict the optimal PF lengths found in Fig. 2. Indeed, a comparison between the theoretically optimal oscillation periods T_{opt} (symbols overlying the vertical axis) and the actual periods T

obtained at the optimal PF lengths for synchronization in Fig. 2 (large symbol on each curve in Fig. 3) indicates that several mechanisms were involved in the tuning process.

First, at high mossy fibre firing rates (lower curves in Fig. 3 : 40 and 67 spikes/s), the periods T at the optimal PF lengths for synchronization (enlarged symbols) were larger than T_{opt} (same symbols on vertical axis), and hence the optimal PF lengths were larger than those predicted from T_{opt} .

Probably the advantage of connecting more Golgi cells outweighed a suboptimal oscillation frequency.

Second, these lower curves had larger slopes than would be expected from increased conduction delays alone (compare with line through origin). This excess increase of oscillation period T with PF length was caused by doublet firing. When PFs increased in length, granule cells located at large distances activated PF synapses on a Golgi cell after increasing delays compared to nearby granule cells. The resulting prolonged excitation of Golgi cells through dispersed activation of their PF synapses made them fire twice in a single cycle. The interval between the spikes of a doublet added to the prolonged conduction delay, and raised the slope of the T curve. The presence of doublets in the Golgi cell spike trains lowered the value of S/I at high PF lengths, but only in a gradual way (Fig. 2). Indeed, the doublets had also a stabilizing effect through the enhanced inhibition they provoked in granule cells, whose oscillation periods increased to the same extent.

Third, at low mossy fibre firing rates (upper curve, 15 spikes/s), the oscillation period at the optimal PF length for synchronization (large open square on upper curve) was equal to the theoretical optimum T_{opt} (open square on vertical axis). In this case, the oscillations even became stabilized by large PF conduction delays. Indeed, shortening the delays by increasing the PF speed had an adverse effect on S/I at this mossy fibre firing rate. The favourable effect of conduction delays at low-rate mossy fibre input can be understood as follows. We pointed out previously (Maex & De Schutter, 1998b) that low-rate input generated optimal oscillation periods T_{opt} that were too long to be bridged by the transient inhibitory effect exerted by a single Golgi cell spike on granule cells. By increasing the PF length, however, the 'premature' granule cell spikes are delayed and activate the Golgi cells at the right time, i.e. after completion of the entire oscillation cycle. At this low mossy fibre firing rate, temporal dispersion of PF activation did not cause doublet firing in Golgi cells because only a fraction of the granule cells produced a spike during a single oscillation cycle.

The finding that delays contributed to the stabilization of low-frequency oscillations could be confirmed by varying the PF conduction speed using a fixed PF length of 5 mm. The highest value of S/I was obtained at a 0.5 m/s PF conduction speed when mossy fibres fired at 40 spikes/s, whereas the optimal speed was only 0.1 m/s for a 15 spikes/s mossy fibre firing rate.

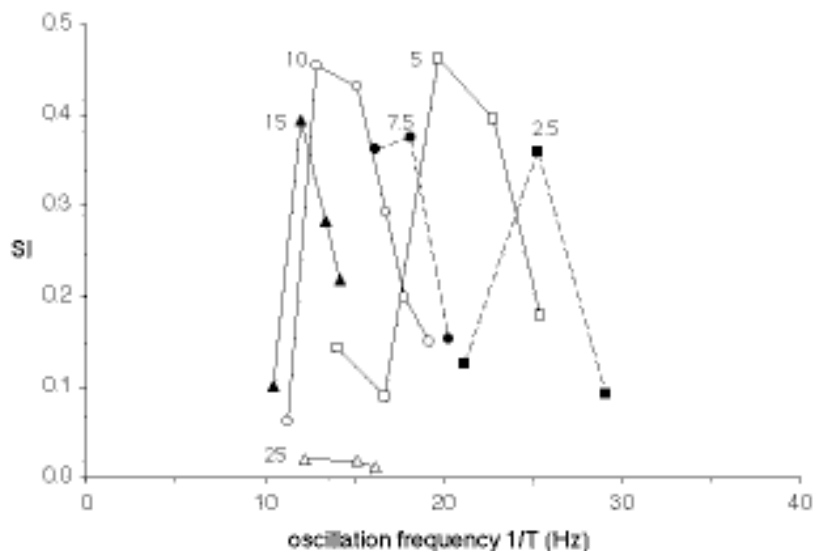


Figure 4

Temporal-frequency selectivity of synchronization index for parallel fibres of various lengths (label in mm).

Finally, we combined the data of Figs. 2 and 3 in Fig. 4 by plotting on the horizontal axis the oscillation periods T obtained at various PF lengths (labels in mm) and mossy fibre firing rates, and on the vertical axis the corresponding values of SI . PFs of a given length produced long-range synchrony within a limited band of frequencies. As expected, short (2.5 mm) and long (10 mm) PFs synchronized preferentially fast and slow oscillations, respectively. We want to note that other parameters besides PF length determined the horizontal position of these tuning curves as well. For example, using a slower time-course for the inhibitory effect of Golgi on granule cells shifts these curves toward lower frequencies, whereas higher PF conduction speeds shift them to higher frequencies.

Discussion

The present simulations were performed as part of an investigation into the computational function of the granule cell layer of the cerebellum. It was recently proposed by us that the granular layer might be designed as a rhythm generator. In a realistic network model, Golgi and granule cells fired rhythmically when random mossy fibre input was applied. This rhythmic activity could be synchronized along the entire length of the parallel fibre axis. Recently it has been confirmed by means of multi-electrode recordings in anesthetized rats that almost all pairs of Golgi cells positioned along the same parallel fibre axis do fire synchronized (Vos *et al.*, 1999).

If temporal patterning of parallel fibre activity were the ultimate goal of the granular layer circuit, its parameters would be expected to have been optimized to that objective during evolution. In a previous communication (Maex & De Schutter, 1998a), we have shown that the rhythm became more accurate when networks with larger numbers of mossy fibres, granule cells and PF synapses on Golgi cells were simulated. Actually, the large numbers of the afferents (mossy fibres) and interneurons (granule cells) are a very characteristic feature of the cerebellum.

We have here demonstrated that parallel fibres not only strengthen synchrony by entraining more Golgi cells, but that the delays resulting from their length and from their finite conduction speed will have an influence on the resonant frequency of the granular layer circuit. To make reliable predictions about the exact contribution of PF length to cerebellar functioning, more quantitative data are needed about granular layer physiology in vivo.

In rats, PFs are 4.5-5 mm long (Pichitpornchai *et al.*, 1994) and propagate spikes at a speed of 0.2-0.3 m/s (Vranesic *et al.*, 1994). Oscillatory granular layer field potentials over a range of frequencies have been observed in behaving rats (at about 8 Hz, both intra- and interhemispheric; Hartmann & Bower, 1998) and monkeys (15 Hz; Pellerin & Lamarre, 1997). Several parameters of the circuit that are needed to draw quantitative conclusions from the present modeling study remain unknown however : the firing rate of granule and Golgi cells, the average mossy fibre firing rate, and the exact time course of Golgi to granule cell inhibition. The latter two parameters determined, together with the PF length and conduction speed, the oscillation frequency in the model.

Nevertheless several hypotheses can be formulated : i) parallel fibres might have a maximal length and conduction speed, these values being finite because of cytoarchitectural constraints; ii) the PF length, and/or the PF conduction speed might be optimized to perform a temporal filtering and to enhance synchrony within a limited band of firing rates; iii) a final hypothesis, that according to Fig. 4 the parallel fibre system might be involved in a form of frequency analysis, deserves less consideration since the observed variations in PF length and PF conduction speed are small.

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