

The Critical Synaptic Number for Rhythmogenesis and Synchronization in a Network Model of the Cerebellar Granular Layer

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Abstract

In the granular layer of the cerebellum, the population of excitatory neurons (granule cells) is reciprocally connected to the population of inhibitory neurons (Golgi cells), but there are no synapses between the neurons within either population. In a realistic network model, both Golgi and granule cells start firing synchronously and at very regular time intervals upon stimulation of granule cells with random mossy fiber input ([3]). Because the granule cell population is disproportionately large, we wondered whether the massive convergence from granule to Golgi cells were essential to obtain this regular firing pattern. Here, we demonstrate that only a small, critical number of synapses from granule to Golgi cells is required. The critical number of synapses is largely independent of the size of the granule cell population, but depends on the number of input channels to the network (the number of mossy fibers), on the strength of the input applied (the mossy fiber firing rate), and on its spatial homogeneity.

The Granular Layer Model

Model Circuitry

The model granular layer is a Wilson-Cowan-like circuit ([5]) with inhibitory neurons (Golgi cell, Gocs), excitatory neurons (granule cells, grcs) and mossy fiber afferents (MFs), all aligned along an array representing the parallel-fiber axis of the cerebellum. The MFs provide excitation to grcs, each grc having a unique set of four MF afferents (A in Fig. 1). The grc axons split in two branches, which run as parallel fibers (PFs) in opposite directions over a distance of 2.5 mm and provide wide-range excitation to Gocs. The number of grc afferents to Gocs, and hence the number of parallel-fiber (PF) synapses per Goc (B in Fig. 1), is varied in the model by altering either the number of grcs or the grc \Rightarrow Goc connection probability P . Finally, the sparse Gocs, regularly spaced at 0.3 mm intervals, exert local inhibition upon grcs, each grc receiving inhibition from only its closest Goc (C in Fig. 1). The effect of the number of PF-synapses on the dynamics of the network is the

subject of this study.

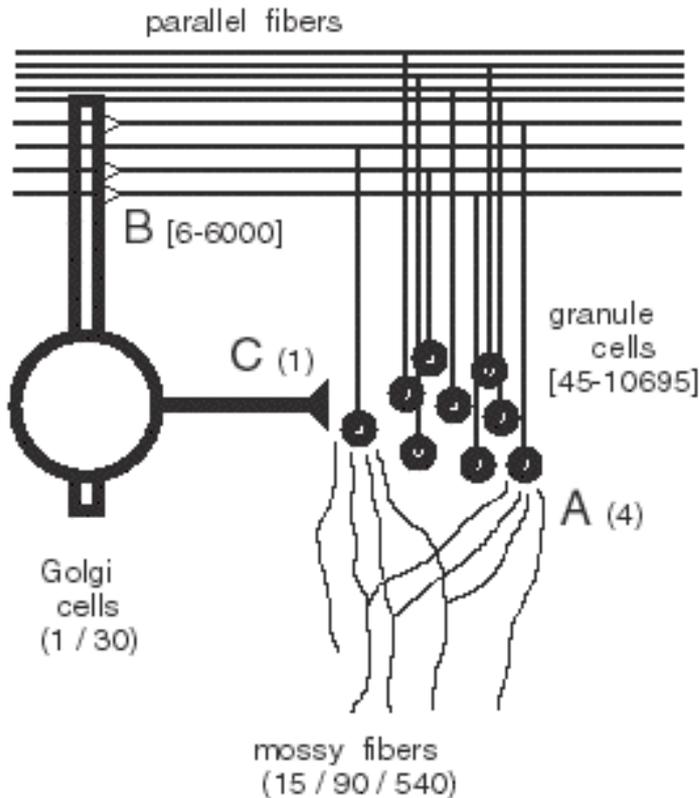


Figure 1

The synaptic relation between mossy fibers (MFs), granule cells (grcs) and Golgi cells (Gocs) in the model. There were 15, 90 or 540 MFs, 1 or 30 Gocs, and from 45 to 10695 grcs. A, B, and C indicate the synapses from MFs to grcs (excitatory, from grcs to Gocs (the PF-synapses, excitatory) and from Gocs to grcs (inhibitory). The associated numbers indicate the degree of convergence from the presynaptic to the postsynaptic population: each grc has 4 MF afferents; each Goc presynaptic to the postsynaptic population: each grc has 4 MF afferents, each Goc has on average between 6 and 6000 grc afferents (and hence PF-synapses) and each grc receives inhibition from a single Goc. There are no Goc-Goc or grc-grc synapses.

Model Golgi Cells, Granule Cells and Mossy Fibers

Golgi and granule cells are spiking, isopotential compartments with six voltage-gated channels obeying Hodgkin-Huxley dynamics. The Gocs are active spontaneously (average rate 8 spikes/s). The grcs have a high firing threshold and need at least two of their four MF afferents fire together to become activated. MFs are modeled as independent spike trains with interspike intervals having a Poisson interval distribution (except for a 5 ms refractory period). Unless otherwise stated, all MFs fire at the same average rate of 40 spikes/sec.

Model Synapses

MFs depolarize their efferent grcs through fast (AMPA-activated, peak < 2 ms) and slow synaptic channels (NMDA-activated, peak 13 ms). The PF-excitation of Gocs is always fast, but the slowly conducting PFs generate considerable delays (0-5 ms) between the initiation of a spike in a source grc and its arrival at a PF synapse. Finally, the inhibitory postsynaptic potentials

in grcs, caused by Goc spikes, peak after 8 ms.

Normalization of Synaptic Strength

Because strong PF excitation of Gocs supports synchronization and rhythmogenesis ([3]), the effect of varying the number of PF synapses on Gocs was studied using a clamped global synaptic strength, i.e. the weight of an individual PF synapse was always divided by the number of PF synapses on the efferent Goc.

Randomization

Finally, the resting potentials of Golgi and granule cells and the weights of all synapses have been randomized in order to simulate more biological conditions and to prevent the network from becoming locked in a non-stable steady-state (see ([3]) for more details).

The Synchronization Index

The membrane potential responses of the model Gocs and grcs were numerically computed with a Crank-Nicholson method (20 micro s integration step) using an extended version of GENESIS ([2]). During 10 seconds network time, all spikes from a (grc or Goc) population were counted in 1 ms bins. At the end, the 10 s population spike time histogram was autocorrelated in 1 ms steps over a 1 s offset range. A synchronization index (SI) expresses both the sharpness and the periodicity of the peaks of the autocorrelogram (AC). To this end, a cosine's period T was optimized to yield a maximal internal product with the AC. After normalization, $0 \leq SI \leq 1$

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

Note that the SI is a combined metric of rhythmogenesis and synchronization.

Simulation Results

Networks were simulated with 30 Gocs and varying numbers of grcs and MFs. Each curve in Fig. 2 plots the SI of the Goc population from a set of networks with a fixed number of MFs and grcs (see legend) but with varying connection probabilities P from grcs to Gocs, and hence with varying average numbers of PF synapses per Goc. It appears that all SI curves steeply rise with the number of PF synapses per Goc, until a saturation level is reached. More importantly, it is the absolute number of PF synapses which matters, and not their relative number or the connection probability P . In networks with low numbers of MFs (see the 15 MFs curves), the SI also depends on the number of grcs, but in a sense opposite to what would be expected if the connection probability P were important : the more sparsely connected networks perform best (large numbers of grcs, hence low connection probabilities to achieve a given number of PF synapses)!

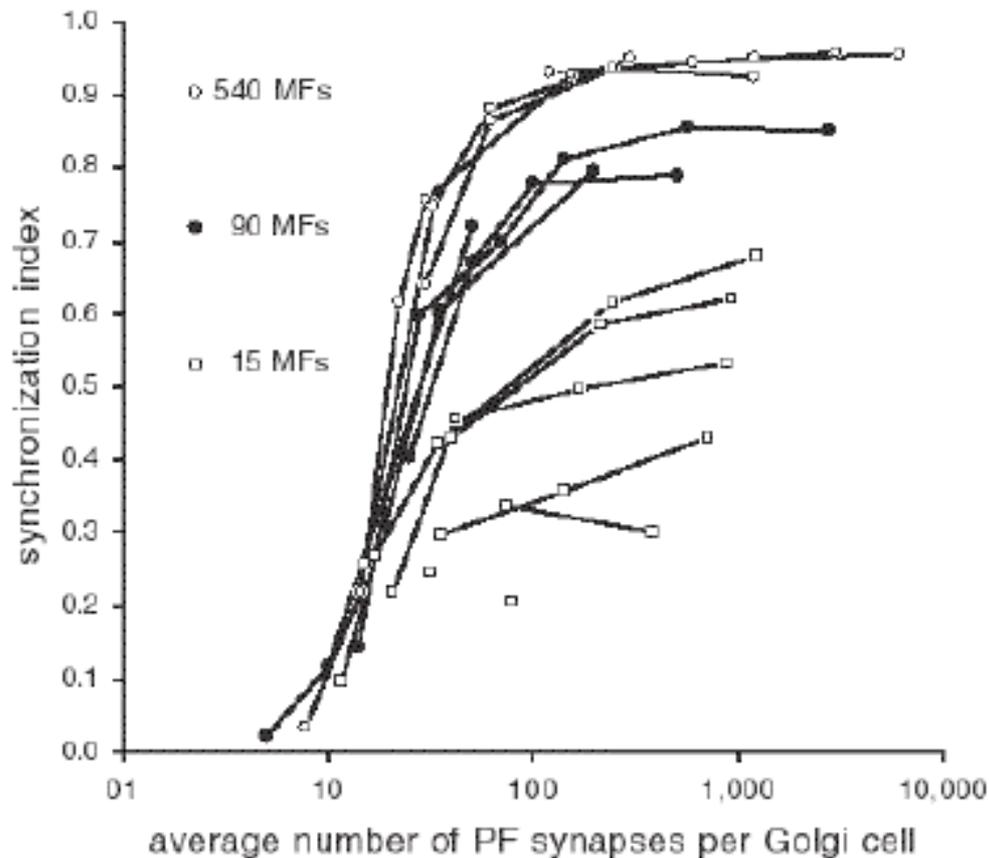


Figure 2

The effect of the average number of parallel fiber synapses per Golgi cell on the synchronization index of the Golgi cell population. The parameters varied were the number of MFs, the number of grcs and the connection probability P from grcs to Gocs. Each curve connects SIs obtained from networks with 45, 105, 462, 810, 990, 1155 or 1365 grcs and 15 MFs, networks with 87, 345, 855, 4662 grcs and 90 MFs, and networks with 537, 2145, 5355 or 10695 grcs and 540 MFs. The rightmost point of each curve is from the maximally connected network ($P=1$). Because the number of PF synapses in a maximally connected network scale with the number of grcs, these points can be used to rank the curves by increasing number of grcs ([3]).

In order to find out why the Goc SI decreased at low numbers of PF synapses, we simulated networks containing only a single Goc, this way ruling out incoherent firing between different Gocs as a possible cause. As can be seen in Fig. 3A, the single-Goc networks (thick curves) yielded SIs similar to those from the corresponding standard (30 Goc) networks (thin curves), but also declined at low numbers of PF synapses.

We next tried to *increase* incoherent firing between Gocs by randomizing the firing rate of the afferent grcs. To this end, the average firing rates of the individual MFs were uniformly distributed between 5 and 75 Hz, with the population mean unchanged at 40 Hz. As a consequence, the average firing rates of the 5355 (or 1365) grcs formed a wide distribution with a coefficient of variation (CV) >0.5 . It is to be expected that when the number of PF synapses decreases in these networks, the variation between Gocs in the average rate of activation of their PF synapses will increase. As a

consequence, the SIs were lower than in the standard model, where the CV of the grc firing rate measured only about 0.2 (compare thick and thin curves in Fig. 3B).

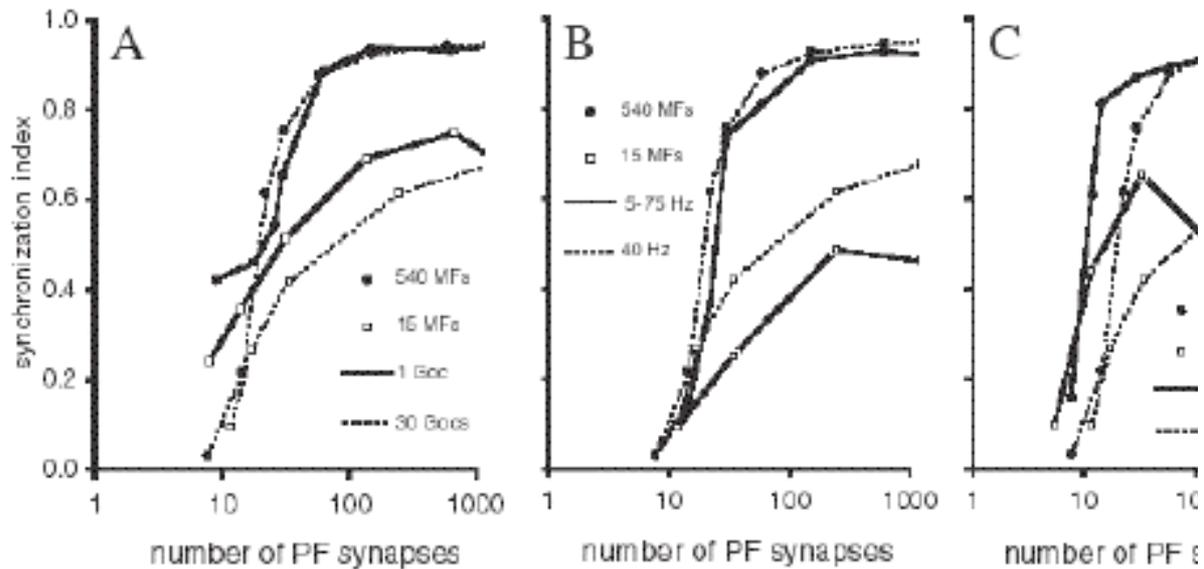


Figure 3

The Golgi cell synchronization index versus the average number of parallel fiber synapses on Golgi cells for three network manipulations. The networks contained 540 MFs and 5355 grcs or 15 MFs and 1365 grcs

A. The 30 Gocs were replacded by a single Goc.

B. The variance in firing rate between grcs was increased by assingning each MF afferent a separate firing rate taken from a uniform distribution between 5 and 75 spikes/s (population mean unchanged at 40 spikes/s).

C. All MFs have average firing rates of 100 instead of 40 spikes/s. The thin curves in each panel are from the corresponding standard models and have been copied from Figure 2.

Finally, the rate of activation of all PF synapses was increased by raising the average firing rates of all MFs from 40 to 100 Hz. This led to a leftward shift of the SI-curves, and to a marked decrease in the number of PF synapses critical to synchronize the network (Fig. 3C).

Discussion

Accurate timing of spikes within a rhythm requires in the first instance a sufficient number of afferents ready to excite the neuron when the instant to fire arrives (the end of the oscillation cycle), and second the absence of strong and brisk inputs which could activate the neuron too early. Both prerequisites are fulfilled when there is some steady level of input with a low variance, as when a constant depolarizing current is injected into the soma. This reasoning applies well to the model grcs for which it has been shown ([3]) that their slow NMDA channels (see 1.3) stabilized the rhythm, despite their completely random activation by MFs. Note however that in grcs, suppression before the end of a cycle is provided by feedback inhibition from Golgi cells, while in a current-injection experiment it is due only to the spike afterhyperpolarization.

We try to apply the same reasoning to explain how varying the numbers of

MFs, grcs and PF synapses affected synchronization and rhythmogenesis in our model Gocs (Fig. 2). Gocs receive excitation through PF synapses from a large population of grcs and with variable delays (see 1.3). A lower variance of synaptic activation across time can first be realized in Gocs by increasing their numbers of PF synapses, by which a single synapse, due to the normalization procedure, generates a smaller postsynaptic effect. There is however a limit on the gain from increasing the number of PF synapses, because many synapses will be systematically co-activated. In other words, the pool of uncorrelated PF synapses is limited. This coactivation of synapses can explain the decrease in SI produced by decreasing the numbers of MFs and grcs. Indeed, the following combinatorial analysis of the numbers of MFs, grcs and PF-synapses demonstrates that the fraction of co-activated synapses decreases with the numbers of MFs and grcs in the network.

Each model grc has a unique set of four MF afferents, the only requirement being that two afferent MFs in a set lie not further apart than a spatial range S along the array of MFs (expressed in units of the fixed inter-mossy-fiber distance). In the network, a grc was created for every such legitimate combination of MFs. It can be shown then ([3]) that the number of grcs in the network (or the density of grcs and hence the number of PF synapses on Gocs) approximates $\#MF(S-1)(S-2)(S-3)/6$, where $\#MF$ is the number of MFs (or their density). If it is further assumed that two MF afferents should fire together to ignite a grc (see 1.2), then the number of grcs activated by an effective pair of MFs will on average be $(S-2)(S-3)$. Hence, the fraction of PF synapses activated by the simultaneous firing of two MFs will be proportional to $1/\#MF(S-1)$, or inversely proportional to the number (density) of MFs and decreasing with the number (density) of grcs. Hence the more MFs (grcs) in the network, the less PF synapses are systematically co-activated or, for a given number of PF synapses, the larger the number of independently activated PF synapses. This could explain the rise in SI with the number of MFs, and, at least for the 15 MF networks (Fig. 2), the rise in SI with the number of grcs.

Another way to look at the effect of the number of grcs on the SI is to consider the population of grcs as a combinatorial expander of the MF input space ([1], [4]). Indeed, in a network with only 15 MFs, a Goc can receive (disynaptic) excitation from at most 15 single MFs, but on the other hand from 105 duplets, 455 triplets and 1365 quadruplets of MFs. When the number of MFs is high however, this expansion effect is expected to become less important. In fact, a Goc in a network with 540 MFs and 5355 grcs can easily have, through a set of only 10 PF synapses, a "receptive field" comprising 40 single MF afferents (assuming that the ten afferent grcs have nonoverlapping sets of four MF afferents).

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