Synchronization of Purkinje Cell Pairs along the Parallel Fiber Axis: A Modeling Study

Sergio Solinas, Reinoud Maex and Erik De Schutter
Laboratory for Theoretical Neurobiology
Born-Bunge Foundation
University of Antwerp-UIA
2610 Wilrijk, Belgium
sergio, reinoud, erik@bbf.uia.ac.be

Abstract

Spontaneous synchronization of Purkinje cell pairs in the cerebellar cortex is implicitly predicted by many theories of cerebellar function (e.g.the beam theory of Eccles [19]). We show that monosynaptic parallel fiber excitation is not able to synchronize model Purkinje cell pairs, unless unrealistically high percentages of input are shared (80%). On the other hand, synchrony is already significant when only a realistic amount, 10%, of the inhibitory input is shared. Thus, inhibitory interneurons could synchronize Purkinje cell pairs through a monosynaptic pathway. Still, parallel fibers could synchronize Purkinje cell pairs through a disynaptic pathway over inhibitory inter-neurons.

Introduction

Morphological studies show that neurons with a large dendritic arborization in the molecular layer of the cerebellar cortex, Purkinje (PC) and Golgi cells (Goc), share a large part of their excitatory input. Nearby PCs can share up to 50% of their parallel fibers (PF) afferents[6]. Synchrony of Goc pairs along the PF axis was predicted[17] and subsequently observed[16], while PC pairs did not show synchronous firing[20]. Why do PC pairs not synchronize? Here, we predict the minimal distance between PC pairs needed to achieve synchronous firing based on morphological data and computer simulations.

Methods

The Model Purkinje Cell

Our simulations are based on the high detailed PC model with 4550 compartments described previously by De Schutter and Bower[2, 3]. PF contacts are modeled by AMPA receptor channels and contacts from molecular layer interneurons by $GABA_A$ channels. The experimentally measured peak currents are on average 7 pA[1] and 20 pA[13], respectively. The synaptic peak conductances needed to generate these somatic currents were calculated in the model PC during simulated voltage clamp of the soma (holding potential -60 mV[13] and -70 mV[1] respectively), in order to compensate them for an incomplete space clamping of the dendritic tree and for the low input resistance of the model PC[3]. Without modifications, the average peak IPSC was reasonably close to the observed[13], but the peak conductance of the AMPA channels had to be multiplied by 5.

The synaptic time course was modeled with a dual exponential function.

In vitro, AMPA channels have an opening time constant of 2.1 ms, and a closing time constant of 5.8 ms at 23°C [1]. The $GABA_A$ channel rise and decay time constants are 1.65 ms and 9.3 ms at 23°C [13], respectively. Given that the temperature dependency of PF to PC transmission is described by a Q_{10} factor of 1.4[14], the AMPA and $GABA_A$ time constants had to be divided by 1.6 for conversion to a model temperature of 37°C [2]. We additionally multiplied the maximum conductances by the same factor[8]. Finally, the parameters of simulated synapses are: peak somatic EPSC 11.2 pA, AMPA channel peak conductance 1.4 nS and kinetics $\tau_{\text{on}} = 1.3$ms and $\tau_{\text{off}} = 3.6$ms; peak somatic IPSC 32 pA, $GABA_A$ channel peak conductance 3.5 nS and kinetics $\tau_{\text{on}} = 1$ms and $\tau_{\text{off}} = 5.8$ms. Synaptic plasticity was not modeled.

The Model Molecular Layer Interneuron

The molecular layer interneuron (MLI: stellate or basket cell) is modeled as a single compartment with active membrane[17]. We tuned the model MLI by manipulating the reversal potential of the leak current to achieve a spontaneous firing rate of 12 spikes/s[4]. Excitatory and inhibitory synapses are modeled by AMPA and $GABA_A$ receptor channels. In vitro the peak IPSC measures 60 pA at 21°C[10] and the $GABA_A$ channel opening and closing time constants are 0.33 ms and 10.5 ms[10], respectively. The peak EPSC is a free parameter of our model (range 50-2200 pA). The EPSC time course can be fit with good approximation by an alpha function with a time constant of 1.5 ms at 23°C[12]. Assuming a Q_{10} factor of 1.4[14], we divide the AMPA channel time constant by 1.6 and those for the $GABA_A$ channel by 1.7, and multiply the maximum conductances by the same factors[8]. Finally, the

parameters of simulated synapses are: peak somatic IPSC 100 pA, $GABA_A$ channel peak conductance 1.9 nS kinetics τ_{on}0.17ms and τ_{off}5.53ms; AMPA channel peak conductance 0.5-59.4 nS kinetics τ0.9ms.

The model MLIs surround the model PC and are randomly positioned in the molecular layer with a density of 40,000 cells per mm^3[6, 11]. The number of presynaptic MLIs is fixed to 170 for each PC[18, 11]. Out of these, 50 MLIs from the inner third of the molecular layer were connected like basket cells to a single $GABA_A$ synapse on the PC main dendrite or soma[5]. The other 120 presynaptic stellate cells make multiple synaptic contacts on the PC dendritic tree (mean 9[18] with a coefficient of variation of 0.5). We normalize the synaptic strength by the average number of contacts. MLIs are interconnected with each other through an average of 4 afferent inhibitory synapses[10] (connection probability 0.054).

The Parallel Fiber Afferents

In the present stage of implementation excitatory input to the PCs and MLIs is provided by random spike train generators. They represent the PF afferents to the cerebellar cortex. Random spike elements are placed at the PF bifurcation points and connect only to AMPA channels within 2.5 mm along the PF axis and 20 μm in the other two directions[15](connection probability 0.003). The PF conduction speed is set to 0.5 m/sec. For practical reasons, only 1% of the real population of granule cells (grcs) is simulated. The grc population is the largest of the CNS. We assume only a fraction to be active at rest following recent in vivo recordings where most of grcs were silent.

Results

Firing Properties of Isolated Purkinje Cells

A synaptically driven isolated model PC is very sensitive to the balance between its excitatory and inhibitory conductances. More particularly, for a given rate of excitatory synaptic activation, realistic in vivo firing patterns could only be reproduced within a narrow range of inhibitory input rates. Fig.1 shows this effect for two different synaptic models tested, one without (upper panels) and one with activation of basket cell terminals (lower panels). Different combinations of inhibitory and excitatory inputs lead to different firing rates (left panels) and coefficients of variation (right panels) for the model PC spike trains. In all reported simulations the model PC did not fire dendritic Ca^{2+} spikes.

Nevertheless, our results indicate that MLIs driven by PFs in the feed-forward network are able to deliver the appropriate amount of inhibitory input to their postsynaptic PCs and this way dynamically balance the excitatory input. Indeed, if the firing rate of MLIs to different levels of PF input follow the solid line in the upper left panel of Fig.1, then the model PC will keep firing realistically over wide ranges of grc firing rates.

When basket cells are included (lower panels) the strong PF to MLI synapses and the large IPSCs elicited by basket cells enhance the variability of model PC spike train.

Synchronization of Purkinje Cell Pairs

Next, we examine the degree of synchronous firing between pairs of model PCs, for varying combinations of the percentage of shared excitatory and

inhibitory input. In this part of the research synaptic kinetics for AMPA receptors have a opening time constant of 0.5 ms, and a closing time constant of 1.2 ms[7]. Here we simulate realistically only the model PC (in pairs) while all its afferents are random spike generators out of which a percentage, varying from simulation to simulation, is shared among the two model PCs.

Pairs of model PC sharing only excitatory input in different percentages did not show clear peaks (Z-score > 3) in their cross-correlogram unless the amount of common input was $> 80\%$, and inhibitory inputs were independent. On the other hand, shared inhibition could cause correlation in pairs of model PC when no more than 10% of them was shared and excitatory inputs were independent. From morphological studies[6, 15] we know that each PF makes, on average, from 135 to 172 synapses on PCs per mm and will cross 250 PC dendritic trees. Thus the probability of connection ranges from 0.540 to 0.688. We calculate the probability for a PF crossing two PC dendritic trees to connect both of them as the conditional probability of making a synapse with the second one once it has already contacted the first one. Since the connection probability is the same for the two connections, and they are independent events, the conditional probability is equal to the probability of making only one synapse. Two neighboring PCs should share from 50 to 70% of their excitatory input. Thus, even PCs with adjacent soma's cannot be synchronized by a common excitatory input.

Alternatively, synchrony could be achieved by common inhibition through the monosynaptic pathway. Assuming the PC dendritic tree to be a square 250μm large and 300μm high[5] and based on the extension of the MLI axonal process (285μm sagittal axis, 80μm PF axis, 100μm [18]), we can calculate the dimensions of a single PC inhibitory basin (520μm sagittal axis, 160μm

PF axis, 300μm radial axis). That corresponds to 1000 MLIs, out of which only 17% contacts the PC. The probability that one MLI, located in the afferent basin of two nearby PCs would contact both of them is the product of the single contact probability, 3%, since they are independent events. The number of MLIs that could contact two PCs located on the PF axis decreases with a rate of 6.25 MLIs per mm and is 0 for PC separated by more than 160μm. Thus, a PC pair separated by 90μm would share 10% of its inhibitory input and should synchronize.

Conclusions

We conclude that the common PF input to pairs of PC cannot be strong enough to induce significant synchronous firing through a monosynaptic pathway. On the other hand, the common inhibitory input to PCs located in the same PF beam and separated by at most 90μm should induce synchronous firing. This result does not exclude synchronization of PC pairs separated by longer distance along the PF axis. Recent experimental results suggest that a single PF spike can elicit a post synaptic potential in the molecular layer inhibitory inter-neurons, and that inhibitory input induces long inter spike intervals in PC firing[9]. Thus PF input would be able to synchronize PC pairs through a disynaptic pathway. We are currently investigating this possibility.

References

[1] B Barbour. Synaptic currents evoked in purkinje cells by stimulating individual granule cells. *Neuron*, 11:759-69, 1993.

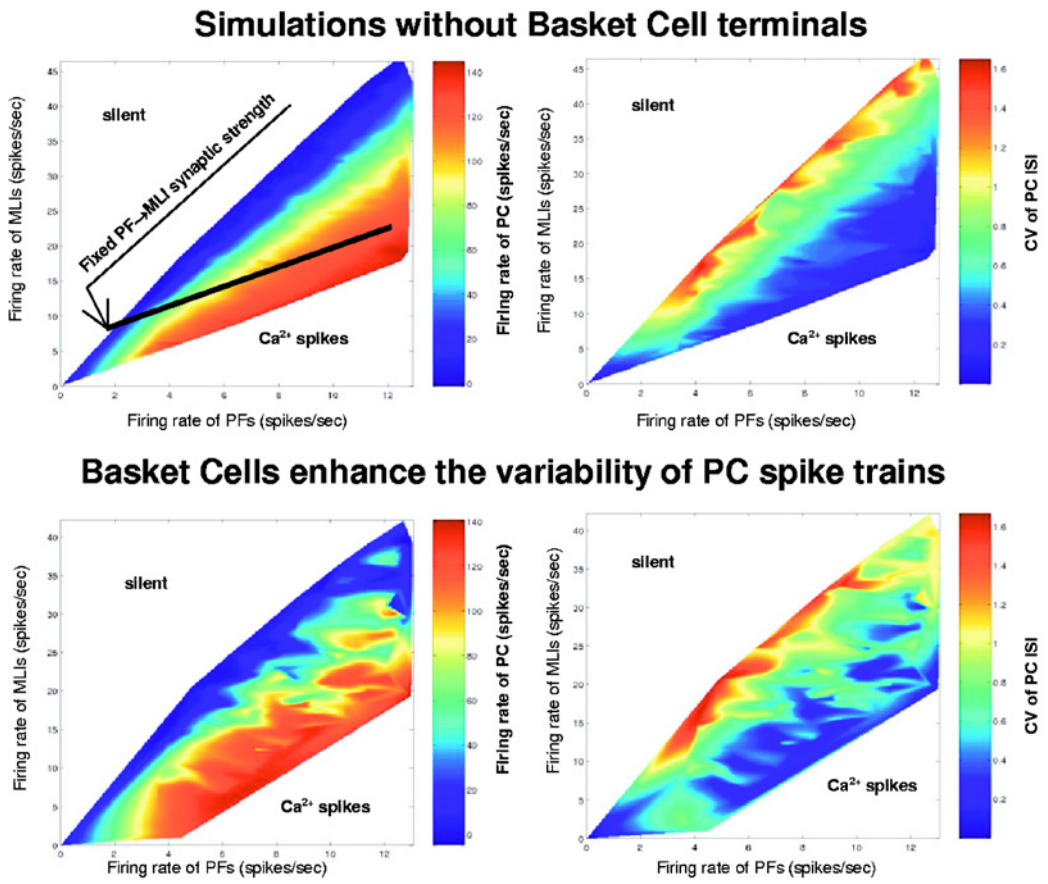

Figure 1: The synaptically-driven model Purkinje cell fires realistic simple-spike trains for broad ranges of PF and MLI firing rates. Left panels report the model PC average firing rate, right panels its coefficient of variation. Each data point used for interpolation is the average over 5 seconds simulation, 600 simulations in total. For a given strength of PF to MLI synapses the black line would provide the average MLIs firing rate and the firing characteristics of the model PC. Any line parallel to the border between two colors would correspond to a feed-forward network providing a total input to the model PC independent on the PF firing rate. In this condition the model PC does not change its firing pattern depending on PFs firing rate.

[2] E. De Schutter JM. Bower. An active membrane model of the cerebellar purkinje cell. I. simulation of current clamps in slice. *J. Neurophysiol.*, 71:375-400, 1994.

[3] E. De Schutter JM. Bower. An active membrane model of the cerebellar purkinje cell. II. simulation of synaptic responses. *J. Neurophysiol.*, 71:401-419, 1994.

[4] M. Häusser B.A. Clark. Tonic synaptic inhibition modulates neuronal output pattern and spatiotemporal synaptic integration. *Neuron*, 19:665-78, 1997.

[5] J.C. Eccles. The cerebellum as a computer: patterns in space and time. *J Physiol*, 229:1-32, 1973.

[6] R. J. Harvey and R. M. Napper. Quantitative studies on the mammalian cerebellum. *Prog Neurobiol*, 36:437-63, 1991.

[7] A. Roth M. Häusser. Compartmental models of rat cerebellar purkinje cells based on simultaneous somatic and dendritic patch-clamp recordings. *J Physiol*, 535:455-72, 2001.

[8] B. Hille. *Ionic Channels of Excitable Membranes*. Sinauer, 1991.

[9] D. Jaeger and J. M. Bower. Synaptic control of spiking in cerebellar purkinje cells: dynamic current clamp based on model conductances. *J Neurosci*, 19(14):6090-101, 1999.

[10] S. Kondo and A. Marty. Synaptic currents at individual connections among stellate cells in rat cerebellar slices. *J Physiol*, 509:221-32, 1998.

[11] L. Korbo B. Bo Andersen O. Ladefoged and A. Møller. Total numbers of cell types in rat cerebellar cortex estimated using an unbiased stereological method. *Brain Research*, 609(1-2):262-8, 1993.

[12] B. Barbour BU Keller I. Llano A. Marty. Prolonged presence of glutamate during excitatory synaptic transmission to cerebellar purkinje cells. *Neuron*, 12:1331-43, 1994.

[13] C. Pouzat and S. Hestrin. Developmental regulation of basket/stellate cell→purkinje cell synapses in the cerebellum. *J Neurosci*, 17(23):9104-12, 1997.

[14] WG. Regehr PP. Atluri. Determinants of the time course of facilitation at the granule cell to purkinje cell synapse. *J Neurosci.*, 16(18):5661-71, 1996.

[15] C. Pichitpornchai J. A. Rawson and S. Rees. Morphology of parallel fibres in the cerebellar cortex of the rat: an experimental light and electron microscopic study with biocytin. *J Comp Neurol*, 342:206-20, 1994.

[16] BP Vos R Maex A Volny-Luraghi E De Schutter. Parallel fibers synchronize spontaneous activity in cerebellar golgi cells. *J Neurosci.*, 19(11):RC6, 1999.

[17] R. Maex E.De Schutter. Synchronization of golgi and granule cell firing in a detailed network model of the cerebellar granule cell layer. *J Neurophysiol.*, 80:2521-37, 1998.

[18] F. Sultan and J. M. Bower. Quantitative golgi study of the rat cerebellar molecular layer interneurones using principal component analysis. *The Journal of Comparative Neurology*, 393:353-73, 1998.

[19] J.C. Eccles M. Ito J. Szentágothai. *The Cerebellum as a Neuronal Machine*. Springer-Verlag, 1967.

[20] JR. Bloedel TJ Ebner. Correlation between activity of purkinje cells and its modification by natural peripheral stimul. *J Neurophysiol.*, 45:948-61, 1981.