Complex Dynamics in the Granual Layer of the cerebellum: Large-Scale Computational Reconstructions

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Abstract

Realistic modeling of the cerebellum granular layer has remained an unresolved issue. Now the availability of detailed single neuron codes and of a wealth of experimental results on single cell and network functions in vitro and in vivo has allowed reconsidering the issue. We have constructed a detailed computational model of the cerebellum granular layer and mapped it against several cellular and network constraints including:

1) center-surround organization
2) time-windowing
3) non-linear filtering
4) theta-frequency oscillations

the model, purely based on microscopic properties (connectivity and single-neuron functions) has been able to reproduce these four higher-level effects. Therefore, the granular layer model is proving a powerful tool for predicting cerebellar computations.

Methods

The principal structural and functional requirements implemented in the network are:

(1) To create appropriate number of cells and synapse while respecting convergence / divergence ratios. In this manner, Golgi cells (GoCs) generate lateral inhibition, for which substantial anatomical (Eccles et al., 1967) and functional evidence (Mapelli and D'Angelo, 2007) has been reported. On the present scale, mossy fibers are unbranched.

(2) To create statistical variability in the number of connections and in their weights (Gaussian distribution with mean = 1 and s.d. = 0.4; e.g. Medina and Mauk, 2000).

(3) To have a background activity in mossy fibers yielding sparse activation of granule cells.

(4) To endow GoCs (Forti et al., 2006) and SC/BCs (Armstrong et al., 1969) with autorhythmic activity.

(5) To endow synapses and neurons with appropriate ionic channels and receptors and intracellular calcium control mechanisms, which have been previously investigated experimentally and translated into single cell and single-synapse models (D'Angelo et al., 2001; Nieus et al., 2006; Solinas et al., 2007a,b; Diwakar et al., 2009).

(6) All models have been adapted from their original temperature T_{orig} to T_{sim}=37 °C according to the equation $Q_{10} = (T_{sim}-T_{orig})/10$ (Gutfreund et al., 1995; see also Traub and Llinas, 1979; Traub et al., 1991; Vanier and Bower, 1999). We have used: Q_{10} = 3 for ionic channel gating, Q_{10} = 2.4 for receptor gating, Q_{10} =1.5 for ionic channel permeation, Q_{10} =1.3 for neurotransmitter diffusion, Q_{10} =3 for Ca^{2+} pumps and buffers, Q_{10} = 1.3 - 1.7 (granule cell – Golgi cell) for intracellular Ca^{2+} diffusion.

Here we show results from simulations of a cubic portion of the granular layer (edge =100 µm). The structure of network connections was generated applying simple rules, most of which can be directly extracted from original works on the cerebellar architecture (e.g. see Eccles et al., 1967):

- The granule cell (GrC) dendrites could not reach glomeruli farther than 40 µm (mean dendritic length 13.6 µm).
- One GrCs was not allowed to project more than one dendrite inside the same glomerulus.
- Only one GoC axon was allowed to enter a single glomerulus inhibiting all the GrC dendrites therein.
- Each GoC was allowed to access at most 40 glomeruli resulting in a maximum 2000 GrCs inhibited by the same GoC.
- GoCs were allowed to receive excitation from 50 glomeruli and 100 GrCs randomly selected within the simulated cube.
- A GoC axon entering into one glomerulus was prevented from accessing the neighboring glomeruli, which shared GrCs with the just accessed glomerulus.

The "mesh" configuration of the network was built after removing the last connectivity rule , so that GoCs were connected to GrC spread all over the network. Each GoC was provided with an inhibitory input from SC/BC comprising two categories. One, equivalent to 6 SC/BC, provided a background rhythmic inhibition at 17 Hz. The other, equivalent to a maximum of 50 SC/BCs, provided dynamic inhibition through GrCs and parallel fibers, implementing a disinhibitory loop.

Conclusions

This work reports the first detailed simulation of the cerebellum granular layer network, in that membrane and synaptic mechanisms are reproduced with high biophysical detail (D'Angelo et al., 2001; Nieus et al., 2006; Solinas et al., 2007a, b; Diwakar et al., 2009 and references therein) and circuit structure is reproduced beyond statistical connectivity.

The model matched the fundamental circuit functional properties of coincidence detection (Jörntell and Ekerot, 2006) and lateral inhibition (Mapelli and D'Angelo, 2007).

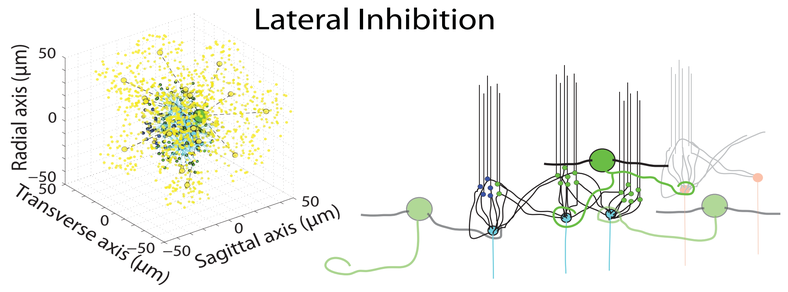
The model accounted for granular layer responses to:

- localized mossy fiber bursting generating center-surround responses and time windowing (D'Angelo and De Zeeuw, 2009)
- frequency modulated bursts revealing a high-pass filter with a rapid growth between 50 and 100 Hz, as observed in VSD recordings (Mapelli et al., 2009)
- diffused random mossy fiber activity generating synchronous oscillations (Courtemanche et al., 2009; Maex and De Schutter, 1999).

The model, further than reproducing the main functional patterns of the granular layer, provides the basis for investigating the contribution of single neurons to networks activity and, viceversa, the network drive on single neurons. Investigating this interaction may provide clues on the intimate mechanisms of network processing (Buzsàki, 2006).

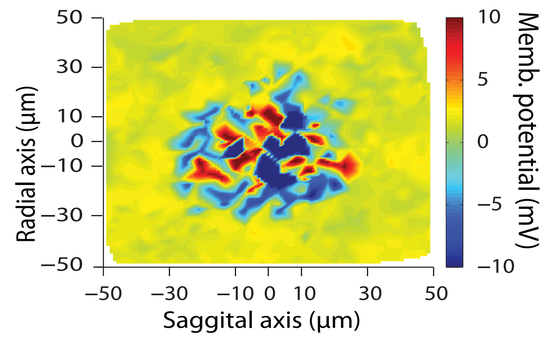
Spatial and Temporal Patterns

Lateral Inhibition

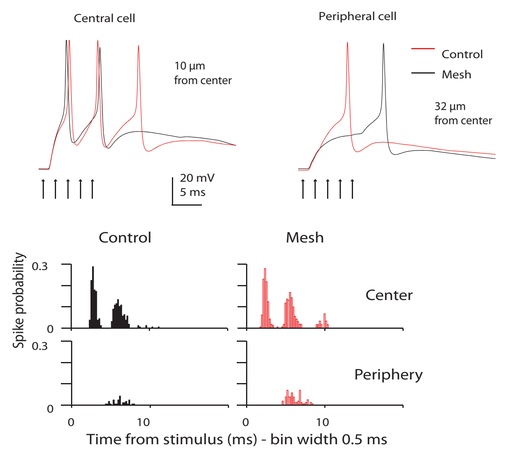


Targets influenced by bursting glomeruli (cyan dots). There are one GoC (green), its target GrCs (yellow and green dots) and the GrCs contacting the bursting glomeruli (blue and green dots). Some GrCs receive only indirect inhibition (yellow transparent dots), some receive both excitation and inhibition (green dots), and others only excitation (blue spheres). All GrCs receive an equal number of excitatory and inhibitory synapses (only the paths activated by the bursts and through a single GoC are shown). Schematics of network connectivity (same color code as in A-B). Golgi cells dendrites and axons are drawn in black and green, respectively

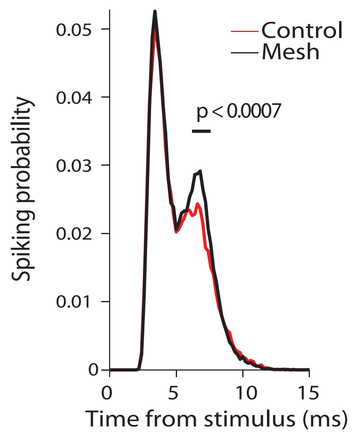
Excitation versus Inhibition



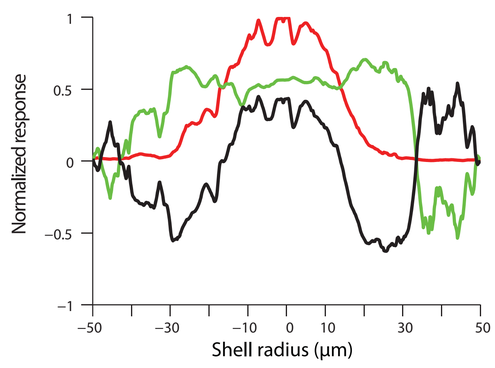
Time Windowing



Responses in the core have shorter latency and higher spike numbers than in the periphery of the activated area.

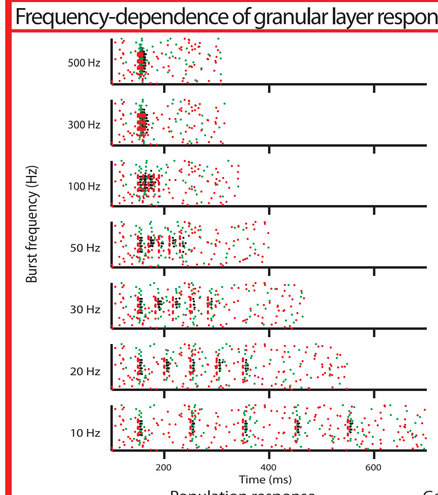


Topology of inhibition

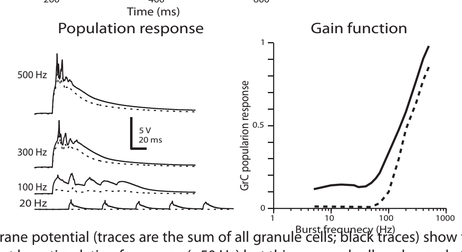


The profile of excitation (red) and inhibition (green) were used to obtain the Mexican-hat profile revealing lateral inhibition (black). Excitation was obtained on the first spike and inhibition on the second spike (red and green rectangles in B, respectively).

Frequency-dependence of granular layer responses

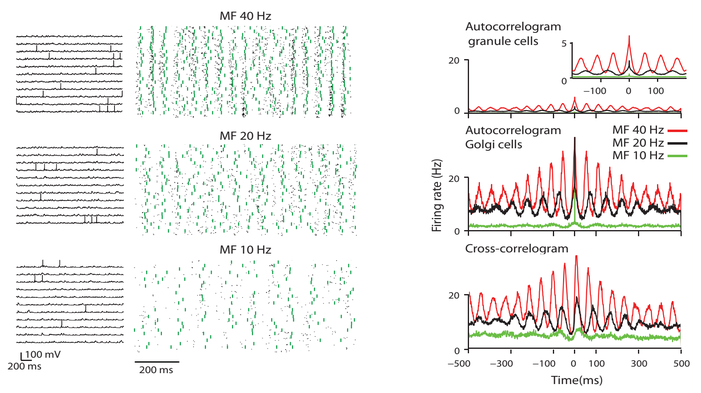


The raster plots show the response of all GrCs (blue dots) and GoCs (green dots) to a mf bursts (5 spikes at 10-500 Hz) delivered to 8 glomeruli (red dots) over a background activity at 1 Hz.

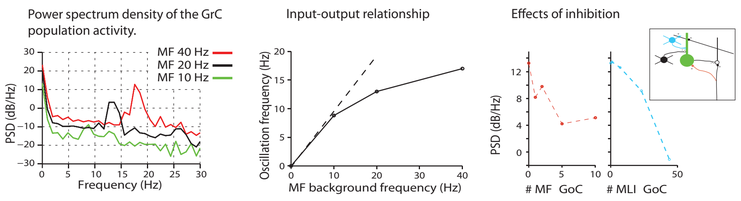


The GrC membrane potential (traces are the sum of all granule cells; black traces) show temporal summation already at low stimulation frequency (<50 Hz) but this was markedly enhanced at high frequencies (>50 Hz). This effect was reduced by switching off NMDA receptors, which sustained temporal summation at low frequency. The gain function (lower panel) showed a steep increase above 50 Hz. Blocking NMDA receptors the responses were markedly depressed with a specific loss of transmission at low frequency (dashed traces).

Background activity and oscillations



The response of granule cells to different frequencies of mf random activity. The coherent activity was not detectable in the activity of individual GrCs (membrane potential traces, left panels). The raster plots (right panels) of GrCs (blue dots) and GoCs (green dots), although also revealing a sparse activity, show that this is organized in repetitive coherent patterns above input frequencies of 20 Hz.



	number	div.	conv.	transmitter	receptors	spillover	previous models
glomeruli	315						
GrC	4096						Nieus et al., 2006
GoC	27						Solinas et al., 2007a, b
SC/BC	270						
Mf→GrC		1:53	4:1	glutamate	AMPA, NMDA	yes	Nieus et al., 2006
mf→GoC		1:3.6	50:1	glutamate	AMPA, NMDA	yes	This paper– Cesana, Forti, Dieudonne, D'Angelo, unpublished
GrC→GoC (pf)		1:100	100:1	glutamate	AMPA, NMDA, kainate	no yes yes	This paper - from literature data
GoC→GrC		1:600	4:1	GABA	GABA-A (a1, a6)	yes	Mapelli et al., 2009 – Nieus, Solinas, Mapelli, D'Angelo unpublished
SC/BC→GoC		6:1	10:1	GABA	α-function	-	This paper

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