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A detailed three-dimensional model of the cerebellar granular layer

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Abstract

We constructed a detailed three-dimensional model of the cerebellar granular layer. Explicit implementation of glomeruli allows modelling of glomerulus-specific phenomena as neurotransmitter spillover and modulation of the tonic inhibition of granule cells. Scaling the network size affects the pattern separation capabilities.

Keywords: Cerebellum; Granule cell; Glomerulus; Golgi cell; Pattern separation

1. Introduction

The granular layer receives input primarily from mossy fibres, which synapse on the excitatory granule cells and to a lesser extent on the inhibitory Golgi cells. The axons of the granule cells, the parallel fibres, form the main output of the granular layer. Apart from making excitatory synapses on the Purkinje cell dendritic trees, they also make connections with Golgi cells. These Golgi cells in turn make inhibitory connections to granule cells.

The fact that the number of parallel fibres is much larger (ratio >100) than the number of mossy fibres has inspired many cerebellar theories. According to these theories the granular layer might have a role as a pattern separator [10], which in turn would facilitate learning at the parallel fibre–Purkinje cell synapse. The recoding is especially dependent upon the exact connectivity between mossy fibres and granule cells.

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Most models of the granular layer to date are one-dimensional model, representing one 'beam' [9,10]. The 3D model presented here is able to represent more realistically the connectivity between the different types of cells and other elements as the mossy fibres.

Furthermore, the 3D layout of the model allows the exploration of interactions between different 'beams' and it facilitates the integration of the other cerebellar cortex layers, the Purkinje cell layer and the molecular layer [15], into the model.

2. The granular layer model

2.1. Components of the granular layer model

The main components of the granular layer model are:

1. the granule cells (GrCs),
2. the Golgi cells (GoCs),
3. the glomeruli (Glmi),
4. the mossy fibres (MFs).

Densities of the various cell types and fibres differ somewhat per species [6]. We therefore used experimental data as much as possible from a single species, the rat. The density of granule cells is very high: $4 \times 10^6/\text{mm}^3$ [8]. The ratio of granule cells versus GoCs is about 400 [8], while the ratio of GrCs versus glomeruli has been estimated to be 28 (data from cat [6]). Within one folium a mossy fibre gives rise to an average of 16 glomeruli. Unipolar brush cells and Lugaro cells were not included in the present model.

2.2. Granule cells

The granule cell model (based upon [9]) has one compartment of 10 μm diameter and a specific membrane capacitance of 1 $\mu F/cm^2$. The fact that GrCs contain extrasynaptic $GABA_A$ receptors of which the effective conductance can be modulated, i.e. increased by several hundreds of picosiemens (by an acetylcholine-dependent process [14]), has been incorporated into the model.

The model contains 6 types of active membrane channels: a fast Na^+ channel, a delayed rectifier K^+ channel, an A-type K^+ channel, a high-voltage activated Ca^{2+} channel, a Ca^{2+} activated K^+ channel and an anomalous inward rectifier Na^+/K^+ channel.

The MF to GrC synapse contains AMPA and NMDA receptors with the following characteristics. The peak conductance of the AMPA receptor is (732 pS), the rise time constant is 0.13 ms, and there are three decay time constants—0.42, 2.71 and 15.5 ms—respectively, contributing 60%, 29% and 11% to the peak conductance [11]. The NMDA receptor is modelled with a peak conductance of 647 pS and a rise and decay time constant of respectively, 1 and 13.3 ms [9]. The strengths of these synapses

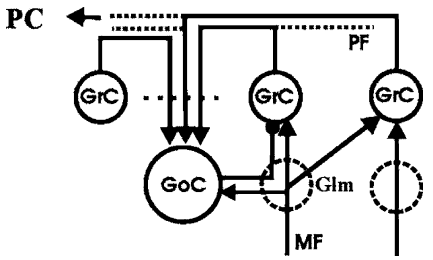

Fig. 1. The connectivity within the granular layer.

were tuned to reproduce the experimental finding that at least two MF spikes within a short temporal interval are required to excite a GrC [3].

The GoC to GrC synapse contains a $GABA_A$ synapse with a peak conductance of 600 pS [2] and rise and decay time constants of 0.3 and 9.0 ms, respectively.

2.3. Golgi cells

Golgi cells are represented by a one-compartmental model [9]. Because of the lack of detailed data regarding the type of channels present in the Golgi cell, similar channels as in the GrC case were chosen and the firing behaviour was tuned to experimental data [5]. Both the excitatory synapses from mossy fibres as well as parallel fibres contain AMPA receptors.

2.4. Mossy fibres and glomeruli

The glomerulus is an anatomical structure around a mossy fibre terminal, where a high number of synapses (like MF to GrC and GoC to GrC synapses) are concentrated together in a small area, which is enwrapped by a glial sheath. Due to the combination of the glial sheat (preventing diffusion of neurotransmitters) and the high density of synapses, spillover phenomena are likely to occur (see e.g. [4]).

The modulation of the tonic inhibition of GrCs (by regulation of its effective membrane conductance) is another example of a process that takes place at the level of the glomerulus and is implemented in this model.

3. Connectivity

3.1. MF to GrC connections

On average there are 4.17 [6] GrC dendrites. They are assumed to receive input from 4 different MFs (at the sites of 4 different Glmi). The maximum dendrite length determines at which Glmi it can connect to MFs (Fig. 1). Most dendrites are shorter than 30 μm (13.59 μm average) [6].

This connectivity was modelled by making connections at 4 randomly chosen Glmi within a range the range of the maximum dendrite length (set to 30 μm).

3.2. MF to GoC connections

The number and strength of MF connections to GoCs is less well known although it has been estimated that four MF spikes within a short temporal window can excite a GoC [5]. The connection range of MFs to GoCs is assumed to be similar as in the MF to GrC case.

3.3. GrC to GoC connections

The mean length of PFs (L_{PF}) is 2.2 mm in each direction [13]. The intervaricosity interval (IVI) decreases with distance along the parallel fibre (average IVI: 5.2 μm, 3.7 μm proximally and 7.4 μm distally). The strength of a synaptic connection also decreases with the distance along the PF. Eighty percent of these varicosities represent contacts with Purkinje cells. A minority of 11% makes contact with either GoCs, stellate cells or basket cells. Based on these data the average number of PF to GoC synapses per GoC can be calculated. Assuming that 5% of the PF varicosities represent synapses with GoCs, this number is 16000.

3.4. GoC to GrC connections

Each GrC dendrite has 3–5 digits. Since on average 60% of the digits are contacted by GoC axons [7], there are on average 10 GoC to GrC synapses. It is unknown to which degree these synapses represent different GoC axons, but it suggests that the connections are confined to a small neighbourhood or are very sparse. The model allows to explore the different possibilities.

3.5. The mossy fibre trajectory within the granular layer

The MF trajectories through the granular layer and the distribution of MF rosettes along them determine the distribution in space of the input signals. It has been estimated that a MF gives rise to an average of 16–17 rosettes (MF terminals) along its way through one folium [6], with an average interglomerular distance of 70 μm [12]. Within a folium a MF tends to be parallel with the dendritic organization of Purkinje cells. But because the exact distribution of MF rosettes is unknown, it is possible to specify different distributions in the model.

4. Implementation

4.1. Parameters and boundaries

The model has been implemented in Genesis [1] in a way that the parameters controlling the dimensions of the system and connectivity distributions can be easily adapted. Especially in cases where the connectivity distribution of a certain type of connection is poorly known this can be helpful.

In the model the GrCs, GoCs and Glmi are regularly (or stochastically with a uniform distribution) distributed on a lattice, representing the modelled part of the granular layer. To reduce the influence of boundary effects on the GrCs, the GrCs were distributed over a slightly smaller area than the Glmi and GoCs.

4.2. Scaling

Modelling even a small part of the granular layer using realistic densities for the various types of cells is computationally too intensive. A MF patch, which spans in transverse direction a considerable fraction of the PF length and in sagittal direction several times the width of a Purkinje cell dendritic tree, contains already more than a million GrCs.

The simulation of this amount of conductance-based cells is one or two orders more than computationally acceptable, especially when the model is extended to include the other cerebellar cortex layers.

Reduction of the network size can be achieved by changing the number of GrCs and MFs (and the number of Glmi accordingly). Synaptic strengths like that of the GrC to GoC synapse are scaled up to compensate for the reduced number of inputs they receive. Other parameters like the connectivity ranges are left unchanged.

However many important characteristics of the MF input—PF output transformation, e.g. the mutual information and the amount of pattern separation, are expected to depend in a sensitive and nontrivial way upon parameters as the number of GrCs and MFs. To perform scaling properly, the input–output transformation and the scaling thereof are currently under investigation.

5. For further reading

The following references may also be of interest to the reader: [12,13].

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