Realistic modeling of large-scale networks: spatio-temporal dynamics and long-term synaptic plasticity in the cerebellum

Egidio D'Angelo[1,2] and Sergio Solinas[2,3]

[1]Department of Physiology, University of Pavia, Via Forlanini 6, I-27100, Pavia, Italy.
[2]Brain Connectivity Center, Istituto Neurologico IRCCS Fondazione C. Mondino, Via Mondino 2, I-27100 Pavia, Italy
[3]Consorzio Interuniversitario per le Scienze Fisiche della Materia (CNISM), Via Bassi 6, I-27100 Pavia, Italy

{dangelo,solinas}@unipv.it

Abstract. A large-scale computational model of the cerebellum granular layer has been adapted to generate long-term synaptic plasticity in response to afferent mossy fiber bursts. A simple learning rule was elaborated in order to link the average granule cell depolarization to LTP and LTD. Briefly, LTP was generated for membrane potentials >-40 mV and LTD for membrane potentials <-40 mV. The result was to generate LTP and stronger excitation in the core of active clusters, which were surrounded by LTD. These changes were accompanied by a faster and stronger spike generation compared to the surround. These results reproduce the experimental observations and provide a valuable and efficient tool for implementing autonomous learning algorithms in the cerebellar neuronal network.

Keywords: NEURON, cerebellum, LTP, LTD, granule cells, modeling.

1 Introduction

Realistic large-scale representations of central neuronal networks can be obtained using the NEURON simulator[1]. These networks implement a bottom-up approach, which can provide important validations and predictions about network activity. Realistic models are tightly bound to experiments, with which usually co-evolve. We present here the case of the granular layer of the cerebellum (Fig. 1), a basic version of which has recently been published[2].

The cerebellar network is composed of a little number of neuronal types connected through a well defined architecture[3,4,5]. This has simplified the development of network models, which have been elaborated in several steps. Initially, realistic detailed representations of single granule cells and Golgi cells have been generated revealing that the whole set of complex properties of intrinsic excitability and synaptic transmission can be reproduced by appropriate mechanisms derived from experimental observations. Then, the single cell models have been used to generate the network model, which proved able to reproducing all known granular layer spatio-temporal dynamics [2] and reconnecting molecular and cellular properties of the granule cell to global network computations[6,7,8,9,10].

The granule cells conductance-based models have been based on a large amount of experimental information (e.g. see [11,12,13,14,15,16,17,18,19]. These models allowed explaining properties like resonance [20,21] and synaptic plasticity[21], Na channel localization and spike generation [22], stochastic release and mutual information (MI) transfer [23].

The Golgi cell conductance-based models have also been based on a experimental information[24,25] although more limited than for the granule cells. These models allowed explaining pace-making and resonance, adaptation, phase-reset and rebound excitation[26,27,28,29]. Synaptic transmission has also been reproduced (Cesana, Dieudonne, D'Angelo and Forti, in preparation).

The current version of the large-scale model contains as many as 105 granule cells and several tens of Golgi cells with all the synapses in between. This model is currently under extension with an algorithm capable of generating long-term synaptic plasticity and reconfiguring network activity.

1.1 LTP and LTD rules

Long-term synaptic plasticity at the mossy fiber – granule cell synapse is induced by NMDA receptor activation and by the consequent calcium influx in a voltage-dependent manner[19,30,31,32]. It has been shown that Golgi cell inhibition, by preventing granule cell depolarization, can effectively regulate the balance between LTP and LTD in response to high-frequency mossy fiber trains[33]. A robust NMDA receptor-dependent calcium influx occurs above -40 mV and can drive LTP. Between -40 mV and -50 mV, the contribution of the NMDA channels is modest. Moreover, mGlu receptors can generate a voltage-independent calcium influx, probably though release from intracellular stores enhancing LTP and inducing LTD (this latter mechanism occurred at low frequency but may also be extended for high-frequencies at low voltages) [30,31,34]. Therefore we have used the following simple plasticity rule for LTP and LTD generated by a short high-frequency train:

LTP for average Vm > -40 mV
LTD for average Vm < -40 mV

Experimentally, LTP and LTD have been reported to reflect changes in release probability [19,31]. This parameter in our models is reported explicitly [2,21] and can therefore be modified by activity.

2 Methods

The large scale model used for these simulations is the same as that published previously[2], except for the fact that the number of synapses between mossy fibers and Golgi cell has been increased from 50 to 150. This allowed accelerating the rate of Golgi cell synaptic depolarization, improving control over the timing of inhibition. With a bundle 23 active mossy fibers, the granule cell cluster included 625 granule

cells and inhibition in granule cells peaked in about 4.3±0.9 ms. Therefore, this cluster reproduces properties compatible with those observed experimentally [7,29,33,35,36]. In these simulations, all the mossy fiber granule cell synapses were initially set at the release probability, p=0.42. Then, the mossy fibers bundle was stimulated with a 3-spikes at 300 Hz train. The average membrane depolarization of the activated granule cells was then computed and used to modify p according to the plasticity rule illustrated above. After p modification, the net was stimulated again and the results compared.

3 Results

The response of the granular layer was organized in center - surround according to previous reports [33,35,36] (Fig. 2A). This occurred because the core provides both the strongest excitation of granule cells and the strongest lateral inhibition through Golgi cells. While the percentage of active granule cells was 11% in control (p=0.42), the percentage decreased with LTD (p=0.2) and increased with LTP (p=0.8). Interestingly, the number of discharging granule cells decreased from center (where it was as high as 50%) to periphery of the active area, in agreement with the "center-surround" mechanism [13]. The increase in p was accompanied by an anticipation of the first spike and by an increase in the number of spikes per cell (Fig. 2B), in agreement with the "time-window" mechanism [7].

The voltage-dependent plasticity rule reported above influenced the center-surround, in that the center became broader with a sharp transition between discharging and non discharging granule cells. The overall percentage of discharging cells increased to 21%. This result was compared to the case of a uniform change in release probability over the whole cluster. In this case, the size of the discharging core changed remarkably, with a contraction at p=0.2 (5% discharging cells) and an expansion at p=0.8 (22% discharging cells). The profile of the discharging area obtained at p=0.8 was very similar to that observed applying the voltage-dependent plasticity rule (Fig. 2C).

4 Discussion

This work reports a simple and efficient plasticity rule for implementing use-dependent synaptic changes in response to incoming input trains. The rule is based on the well-known voltage dependence of NMDA channel opening, which brings about a proportional regulation of intracellular calcium concentration [31,32]. It remains to be demonstrated whether a fine representation of internal calcium dynamics, which are influenced by mGlu receptors as well as by voltage-dependent calcium channels and calcium release from intracellular stores, could modify the results. The fact that the changes in cluster organization caused by the voltage-dependent plasticity rule and by a homogeneous change in release probability were similar, indicates that granule cell discharge is strongly influenced by synaptic inhibition. This latter prevented granule

cell firing outside the core independent from release probability. However, clearly, non discharging granule cells with low release probability would be even more disadvantaged while responding to incoming inputs, generating a sharp edge between core and periphery.

The changes in network response obtained in these simulations strongly resemble those observed experimentally. Indeed, multi-electrode array recordings and voltage-sensitive dye imaging have shown that, following induction of long-term synaptic plasticity, LTP is condensed in the center and LTD in the surround [33,35,36]. This result directly addresses the mechanism through which the cerebellar granular layer is supposed to operate. Incoming inputs need to be separated and selectively amplified and filtered [37,38]. Since LTP and LTD regulate the transmission properties in terms of spike delay and frequency, the generation of sharp center-surround structures would eventually generate effective reconfigurable spatio-temporal filters [39,40].

The present method remapping plasticity over average depolarization could be automated, causing release probability to change in accordance to specific granule cell response patterns. This could allow generating autonomous machine learning exploiting the computational and plastic properties of cerebellar neuron and synapses.

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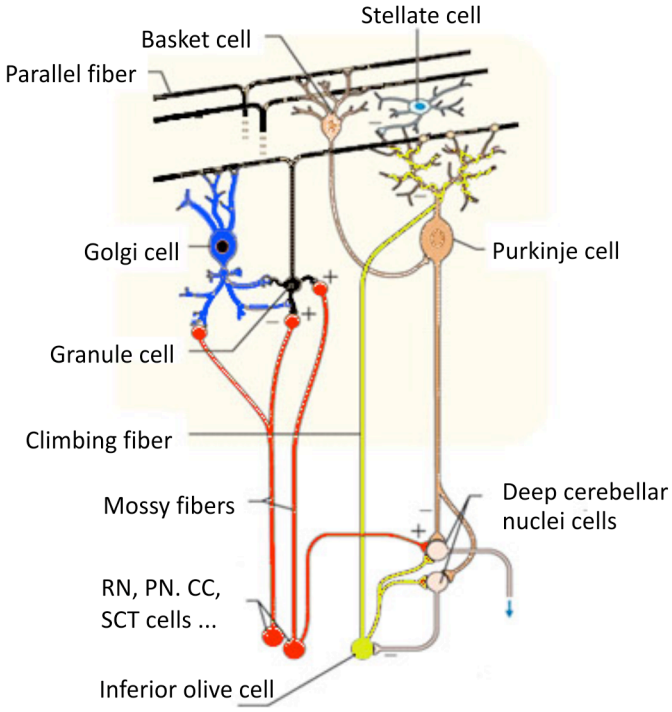

Fig. 1. Schematic representation of the cerebellar circuit. The granule cell represents the gate to the cerebellar cortex. It receives excitatory connection from mossy fibers and sends its axon to the molecular layer forming the parallel fibers, which activate the Golgi cells, the Purkinje cells and the molecular layer inhibitory interneurons (stellate and basket cells). Note the double feed-back and feed-forward inhibitory loop formed by the Golgi cells. Other elements of the cerebellar cortex are also indicated.

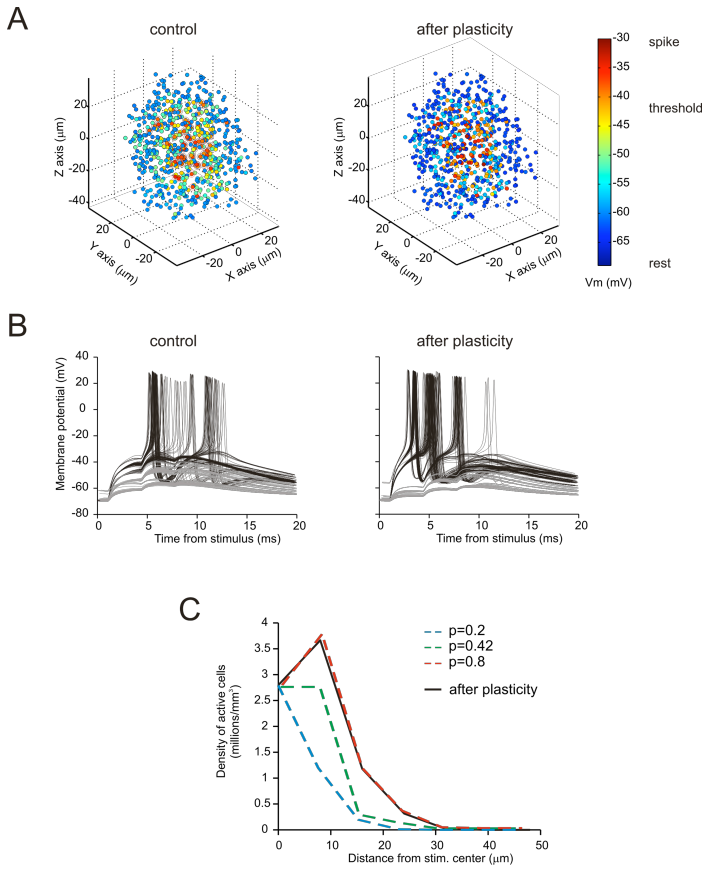

Fig. 2. Network response modifications induced by LTP and LTD. (A) Granule cells are represented by dots with a color corresponding to their membrane potential. Note that a few discharging cells (red) are addensed in the core. After induction, an area of LTP is manifest in the core and an area of LTF in the surround.(B) Granule cell making spikes become more numerous after LTP. Moreover, spikes occur earlier. (C) The density of active granule cells (i.e. those making spikes) is distributed from center to periphery of the cluster. The density changes remarkably with a uniform change in release probability. The change caused by the voltage-dependent learning rule is almost indistinguishable from that caused by p=0.8.

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