Modeling Synaptic Transmission and Quantifying Information Transfer in the Granular Layer of the Cerebellum

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Abstract. Neurons communicate through spikes; their arrangement in different sequences generates the neural code. Spikes are transmitted between neurons via synapses; the mechanism underlying synaptic transmission involves numerous processes including neurotransmitter release and diffusion, postsynaptic receptor activation, and intrinsic electroresponsiveness. Based on available experimental data and theoretical considerations, we have developed a realistic model predicting the dynamics of neurotransmission at the mossy fiber - granule cell synapse of the cerebellum. The model permits systematic investigation of the multiple mechanisms regulating synaptic transmission and provides predictions on the role of the numerous factors driving synaptic plasticity. The model is also employed to quantify information transfer at the mossy fiber - granule cell synaptic relay. This work was funded in part by the EU SpikeForce project (IST-2001-35271 www.spikeforce.org).

1 Introduction

Neurons communicate through sequences of stereotyped pulses, called spikes or action potentials, which are transmitted between them at the synapses (Fig. 1). There, the presynaptic spike train is transformed and converted into a postsynaptic signal. The information content of these spike trains can be assessed by considering either the precise timing of action potentials or their average frequency [1, 2]. The former approach tends to be more efficient from the informative viewpoint because it captures the fine temporal structure of the neural signal (e.g., the interspike interval distribution). In addition, the temporal pattern of the spike train can affect the dynamics of the synaptic contacts, and hence the processing. For instance, short-term memory effects (i.e., short-term facilitation and depression) may regulate postsynaptic temporal summation in a time-dependent manner [3, 4]. Accordingly, to fully understand information

J. Cabestany, A. Prieto, and D.F. Sandoval (Eds.): IWANN 2005, LNCS 3512, pp. 107–114, 2005.

processing in neuronal assemblies it is useful to develop detailed models accounting for the main biological features. We also need theoretical tools that allow us to quantify the ability of the specific model to transmit information at different levels of resolutions, and to asses the robustness of this process. In this regard, information theory [5] has proved to be suitable for studying information processing in different brain areas [1]. Within this framework it is possible to quantify the amount of information that a given set of neural responses provides about a specific set of stimuli or a set of upstream neuron activities. Furthermore, Shannon information and similar quantities can be used to investigate the coding strategies or the contribution of spatial and temporal correlations to the information transmission [6, 7].

The cerebellum is one part of the brain responsible for the learning and the automatic execution of coordinated movements, particularly those too rapid for conscious feedback control. Besides its direct importance in clinical research (motor coordination diseases), there are several other motivations for focusing on this system. First, it permits a detailed experimental characterization at different levels: molecular, single cell, and neural population, both *in vitro* and *in vivo*. Second, it represents an excellent test bed to investigate how microscopic interactions at the single cell level can initiate complex collective behavior (cerebellar functions) at the population level. Third, from an application point of view, implementing biomimetic cerebellar models to control mobile robots or industrial processes may augment their ability to learn and coordinate their actions in complex contexts.

The cerebellar input layer is of particular interest: it is characterized by a huge number (10^{11}) of tiny cells (granule cells) that, according to classical theories of Marr and Albus [8, 9], are able to encode afferent information into a sparse representation that facilitates discrimination of very similar inputs. In this study, we focus on the mossy fiber - granule cell synapse, which is the major site of plasticity in the cerebellum granular layer. The next section presents the main characteristics of this synapse. Section 3 introduces a detailed biophysical model of this system. Section 4 describes an information-theoretic approach for studying information processing at this site quantitatively.

2 Synaptic Transmission at the Cerebellar Granular Layer

Mossy fibers (MFs) are the primary afferents to the cerebellar cortex and convey multimodal sensory inputs to the granule cells (GCs). The MF-GC synaptic transmission constitutes the core of the granular layer computation and has complex temporal dynamics [10, 11] capable of regulating the input-output relationship via synaptic gain modulation [9, 12].

Neurophysiological data suggest that long-term potentiation (LTP) can enhance the probability of release of neurotransmitters at the MF-GC synapse [13], and that GCs tend to discharge in bursts *in vivo* [14]. At a finer scale, several factors can influence the relationship between neurotransmitter release and GC

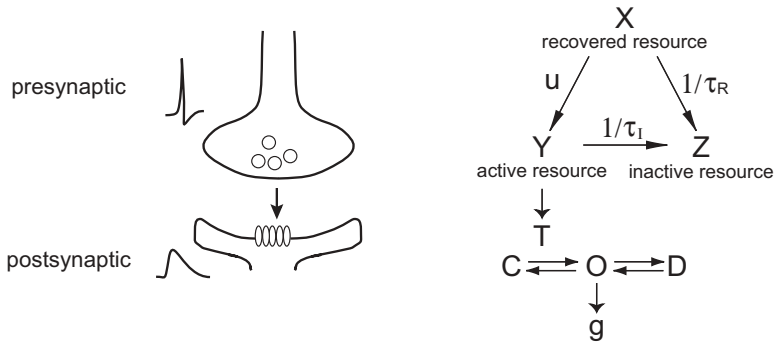

Fig. 1. Synaptic transmission and modeling. (Left) Synaptic processing transforming an incoming spike into a postsynaptic response. (Right) Schematic representation of the processes involved in determining the change of postsynaptic conductance (g) and the generation of excitatory postsynaptic currents (EPSC). X denotes the transmitter resources available for release, Y is the amount of released transmitter, and Z represents the amount of recovered transmitter. The time constants of recovery of releasable transmitter (τ_R), facilitation (τ_F), and inactivation (τ_I), are indicated together with u, the probability of release. T denotes the glutamate concentration, while C, O, and D indicate the postsynaptic receptor state 'closed', 'open', and 'desensitize', respectively

firing. The intense glutamate spillover observed in the cerebellar glomerulus, by protracting AMPA and NMDA receptor activation [15, 16, 17], generates opposing processes like receptor desensitization and temporal summation of excitatory postsynaptic potentials (EPSP) [18]. Moreover, postsynaptic voltage-dependent currents determine complex regulation of spike discharge [19, 20]. Because these factors interact in a complex non-linear manner, no firm statement can be given a priori on burst processing at the MF-GC synapse and its regulation during LTP. Hence, we developed a model of synaptic transmission at the MF-GC relay accounting for the interaction of these multiple effects.

3 A Model of the MF-GC Synaptic Transmission

Our aim was to conjugate fundamental aspects of neurotransmission derived from physiological recordings with a detailed reconstruction of postsynaptic electroresponsiveness. A model of the GC derived from our previous study [20] was updated based on recent experimental data. GCs are electrotonically compact [18, 21, 17], hence there is little need to simulate dendrites and a monocompartmental structure was employed. The GC model includes four identical and independent synapses. The NEURON simulator [22] was employed to implement and validate the model.

The simulation of a single excitatory postsynaptic current (EPSC) involves modeling the neurotransmitter release at the presynaptic site, the diffusion of the neurotransmitter within the synaptic cleft, and the postsynaptic receptor

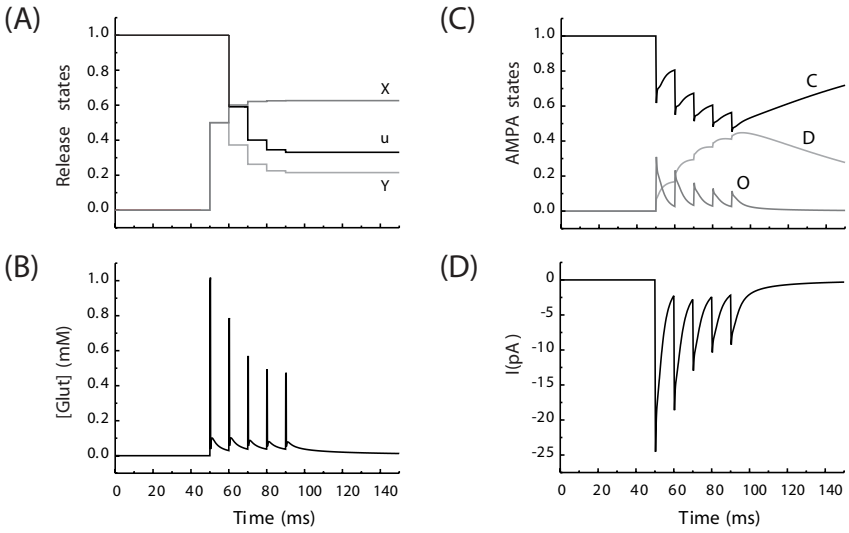

Fig. 2. AMPA current parameters during a voltage-clamp simulation (-70mV). A burst at 100 Hz stimulates the MF. (A) Evolution of the presynaptic variables X, Y, and u. The decrease of u determines synaptic depression. (B) Diffusion protracts the glutamate waveform. (C) Evolution of postsynaptic receptor states. Note the decrease of open states and accumulation of desensitization. (D) Temporal summation of AMPA EPSCs

dynamics [23]. The situation becomes even more complicated when considering a multiple release-site synapse; this is due to the stochastic activation of different receptor clusters and to the diffusion of neurotransmitters between synaptic sites [24]. In the model, the state of the presynaptic terminal is computed according to a three-state scheme adapted from [25]. When a presynaptic spike arrives, a proportion u of the transmitter resource X is transferred into an amount of released transmitter Y (Fig. 1). Depletion of the resource X causes synaptic depression (another component of synaptic depression depends on postsynaptic receptor desensitization, see below). Synaptic facilitation is governed by the activity-dependence of the transmitter release u.

GC postsynaptic responses are generated through both direct release from active zones onto corresponding postsynaptic receptors and spillover of glutamate from neighboring releasing sites [16, 17]. In the model, the glutamate concentration T for AMPA receptors, which are located into the cleft, is obtained by combining a synaptic pulse (T_s) with a diffusion wave (T_d), while NMDA receptors are only activated by the diffusion wave T_d. The released glutamate acting on AMPA receptors is generated with a 1 mM - 0.3 ms squared pulse, which has been shown to approximate transmitter action in the cleft properly [23]. Diffusion is simulated with 2D Crank equation [26, 24, 27]. Glutamate binding to postsynaptic receptors activates kinetic schemes governed by microscopic first-order transitions, leading to the open state $O(T)$. The AMPA postsynaptic current is reproduced with a $D = C = O$ scheme (D and C are the 'desensitize'

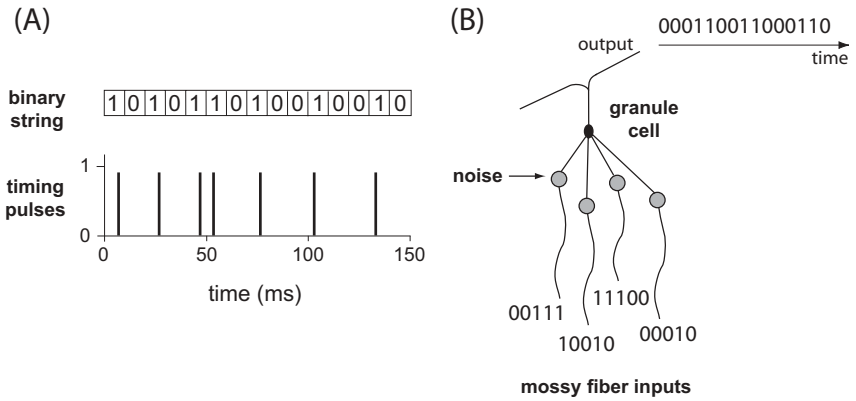

Fig. 3. (A) A spike train can be represented by a binary string of 0 and 1. The string depends on the precision chosen for time discretization. (B) A GC receives four MF inputs and generates an output spike train. The GC response is affected by the multiple voltage- and time-dependent mechanisms of its membrane. Noise is introduced mainly by stochastic vesicular release, which is explicitly modeled. Appropriate construction of the input and output strings permits MI calculation

and 'closed' state, respectively) [27], the NMDA current with a more complex scheme derived from [28]. It follows that we can compute the EPSC composed of AMPA (Fig. 2) and NMDA currents. Once coupled to the excitable mechanisms endowed in our previous GC model [20], the present system reproduces the main aspects of GC synaptic excitation [18].

4 Information Transmission at the MF-GC Synapse

Shannon mutual information (MI) [5] provides a natural mathematical framework to answer the question *how much* information is transmitted by the neural patterns. Our aim was to understand how information is transmitted by the GC through the MF-GC relays, and how it is affected by various factors related to the intrinsic organization of the circuit. The GC constitutes an ideal system for MI calculation since the number of possible inputs is very reduced compared to other brain cells due to the limited number of afferent MFs to each GC (4 on average). To represent the stochasticity of neurotransmission accurately we developed a stochastic version of the model presented above in which the neurotransmitter release was probabilistic (the release at individual sites was an *all-or-none* event determined once a random number between 0 and 1 passed a release probability threshold). This stochastic model was used for the mutual information computation.

In a typical simulation all spike trains were digitalized (Fig. 3A), and a controlled set of stimuli $\mathcal{S}$ (each stimulus being formed by 4 input spike trains, Fig. 3B) was chosen. Then, we recorded the elicited neural responses $r \in \mathcal{R}$ when one stimulus $s \in \mathcal{S}$ was repeatedly presented with a known a priori proba-

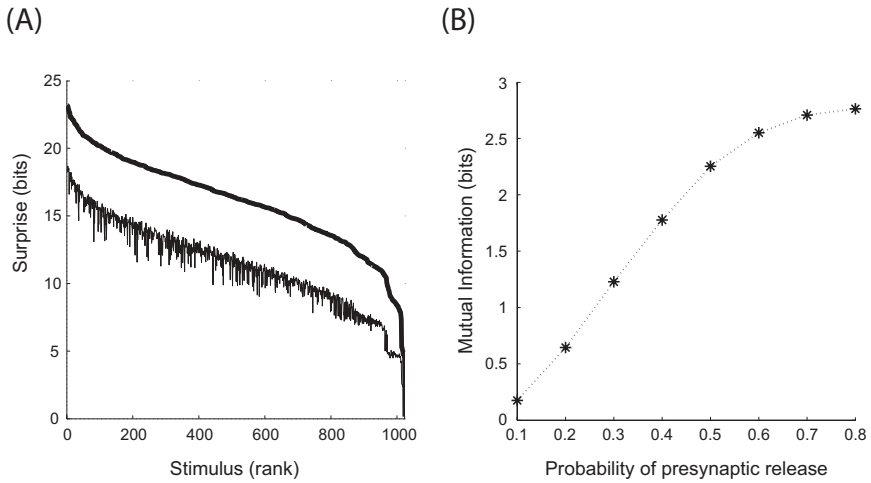

Fig. 4. (A) Information theoretic *surprise* contained in the spike count (thin line) and in the binary string representation (thick line) - see text. Stimuli are ordered by their values of binary string surprise. (B) MI as a function of neurotransmitter probability of release. Simulation parameters: the stimulus set was composed by 1024 spike trains randomly drawn from a Poisson distribution (average firing rate 10 Hz, time bin 5 ms, length of the binary string 10 bins). The same stimulus was presented to the four MFs

bility $p(s)$. Once we collected all the data, we estimated the corresponding joint probabilities, $p(r, s)$, and the probability distribution of responses averaged over the stimuli, $p(r)$. The mutual information was computed using:

$$I(\mathcal{R};\mathcal{S}) = \sum_{s\in\mathcal{S}} \sum_{r\in\mathcal{R}} p(r,s)\ \log_2 \left[\frac{p(r,s)}{p(r)p(s)}\right] \tag{1}$$

Shannon MI provides a quantitative measure of the averaged information transmitted through the synapse by a set of responses given a set of input spike trains (or vice-versa). We were also interested in identifying those stimuli that were best encoded by the GC. Thus, we computed the stimulus specific contribution to the MI (namely, the *surprise* $I(s) = \sum_{r\in\mathcal{R}} p(r|s) \log_2 \frac{p(r|s)}{p(r)}$). This allowed us to find the most informative set of stimuli, and understand in which conditions the cell coding capability was optimized.

Previous results [29] indicated that the temporal structure of the spike train conveyed a large fraction of the total information transmitted. In the simulation of Fig. 4, the MI measured was only 0.44 bits when the neuron response was represented only by its spike count (total number of spikes), whereas it was 0.73 bits when the full binary string representation was used (Fig. 3). In other words, considering the spike train temporal structure resulted in a 75% increase of information transmitted. Fig. 4A shows the value of the *surprise* calculated using spike counts (thin line) and binary strings (thick line). Stimulus surprise analysis determined that the most informative stimuli were usually characterized by high

correlation between the MFs (not shown), suggesting a role for GCs as correlation detectors across their different afferents. In addition, the results suggest that, when LTP occurs at the MF-GC synapse, the overall information transfer is enhanced in the system (Fig 4B), whereas stimulus specific information for the most informative stimuli reaches a maximum at an intermediate value of release probability (not shown).

5 Conclusions

The development of detailed spiking models was another step towards understanding the information transfer and the coding in the cerebellum granular layer [30]. A simplification of the model currently underway will allow us to construct large and realistic networks. Their implementation into hybrid software-FPGA circuits and efficient software [31] will eventually provide the basis for robotic and industrial implementations.

References

1. Rieke, F., Warland, D., Steveninck, R.R., Bialek, W.: Spikes - Exploring the neural code. The MIT Press (1997)
2. Gerstner, W., Kistler, W.M.: Spiking Neuron Models. Cambridge University Press (2002)
3. O'Donovan, M.J., Rinzel, J.: Synaptic depression: a dynamic regulator of synaptic communication with varied functional roles. Trends Neurosci **20(10)** (1997) 431–433
4. Buonomano, D.V.: Decoding temporal information: A model based on short-term synaptic plasticity. J Neurosci **20(23)** (2000) 1129–1141
5. Shannon, C.E.: A mathematical theory of communication. Bell System Technical J **27** (1948) 379–423
6. Panzeri, S., Schultz, S.R., Treves, A., Rolls, E.T.: Correlations and the encoding of information in the nervous system. Proc Royal Soc London B: Biol Sci **266** (1999) 1001–1012
7. Bezzi, M., Diamond, M., Treves, A.: Redundancy and synergy arising from correlations in large ensembles. J Comput Neurosci **12** (2002) 165–174
8. Marr, D.: A theory of cerebellar cortex. J Physiol **202(2)** (1969) 437–470
9. Albus, J.S.: A theory of cerebellar function. Math Biosc **10** (1971) 25–61
10. Braitenberg, V.: Is the cerebellar cortex a biological clock in the millisecond range? Prog Brain Res **25** (1967) 334–346
11. Medina, J.F., Garcia, K.S., Nores, W.L., Taylor, N.M., Mauk, M.D.: Timing mechanisms in the cerebellum: testing predictions of a large-scale computer simulation. J Neurosci **20(14)** (2000) 5516–5525
12. Mitchell, S.J., Silver, R.A.: Shunting inhibition modulates neuronal gain during synaptic excitation. Neuron **38(3)** (2003) 433–445
13. Sola, E., Prestori, F., Rossi, P., Taglietti, V., D'Angelo, E.: Increased neurotransmitter release during long-term potentiation at mossy fibre-granule cell synapses in rat cerebellum. J Physiol **557** (2004) 843–861

14. Chadderton, P., Margrie, T.W., Häusser, M.: Integration of quanta in cerebellar granule cells during sensory processing. Nature **428(6985)** (2004) 856–860
15. Rossi, P., Sola, E., Taglietti, V., Borchardt, T., Steigerwald, F., Utvik, J.K., Ottersen, O.P., Köhr, G., D'Angelo, E.: NMDA receptor 2 (NR2) C-terminal control of NR open probability regulates synaptic transmission and plasticity at a cerebellar synapse. J Neurosci **22(22)** (2002) 9687–9697
16. DiGregorio, D.A., Nusser, Z., Silver, R.A.: Spillover of glutamate onto synaptic AMPA receptors enhances fast transmission at a cerebellar synapse. Neuron **35(3)** (2002) 521–533
17. Cathala, L., Brickley, S., Cull-Candy, S., Farrant, M.: Maturation of EPSCs and intrinsic membrane properties enhances precision at a cerebellar synapse. J Neurosci **23(14)** (2003) 6074–6085
18. D'Angelo, E., De Filippi, G., Rossi, P., Taglietti, V.: Synaptic excitation of individual rat cerebellar granule cells in situ: evidence for the role of NMDA receptors. J Physiol **484** (1995) 397–413
19. D'Angelo, E., Rossi, P., Armano, S., Taglietti, V.: Evidence for NMDA and mGlu receptor-dependent long-term potentiation of mossy fiber-granule cell transmission in rat cerebellum. J Neurophysiol **81(1)** (99) 277–87
20. D'Angelo, E., Nieus, T., Maffei, A., Armano, S., Rossi, P., Taglietti, V., Fontana, A., Naldi, G.: Theta-frequency bursting and resonance in cerebellar granule cells: experimental evidence and modeling of a slow k+-dependent mechanism. J Neurosci **21(3)** (2001) 759–770
21. Silver, R.A., Cull-Candy, S.G., Takahashi, T.: Non-NMDA glutamate receptor occupancy and open probability at a rat cerebellar synapse with single and multiple release sites. J Physiol **494** (1996) 231–250
22. Hines, M.L., Carnevale, N.T.: NEURON: a tool for neuroscientists. Neuroscientist **7(2)** (2001) 123–135
23. Destexhe, A., Mainen, Z.F., Sejnowski, T.J.: Synthesis of models for excitable membranes, synaptic transmission and neuromodulation using a common kinetic formalism. J Comput Neurosci **1(3)** (1994) 195–230
24. Barbour, B.: An evaluation of synapse independence. J Neurosci **21(20)** (2001) 7969–84
25. Tsodyks, M.V., Markram, H.: The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. Proc Nat Acad Sci USA **94(2)** (1997) 719–23
26. Neher, E., Sakaba, T.: Estimating transmitter release rates from postsynaptic current fluctuations. J Neurosci **21(24)** (2001) 9638–54
27. Saftenku, E.: Modeling of slow glutamate diffusion and AMPA receptor activation in the cerebellar glomerulus. J Theor Biol (in press) (2005)
28. Rosenmund, C., Feltz, A., Westbrook, G.L.: Synaptic NMDA receptor channels have a low open probability. J Neurosci **15(4)** (1995) 2788–2795
29. Bezzi, M., Nieus, T., Arleo, A., D'Angelo, E., Coenen, O.J.M.: Information transfer at the mossy fiber-granule cell synapse of the cerebellum. Soc Neurosci Abs **827.5** (2004)
30. Philipona, D., Coenen, O.J.M.: Model of granular layer encoding in the cerebellum. Neurocomputing **58-60** (2003) 575–580
31. Boucheny, C., Carrillo, R.R., Ros, E., Coenen, O.J.M.D.: Real-time spiking neural network: an adaptive cerebellar model. In: Proc 8th Int. Work-Conf Artif Neural Net, Springer-Verlag LNCS (2005)