

Parametric analysis of cerebellar LTD in eyelid conditioning

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Available online 9 February 2006

Abstract

The goal of this study is to use a detailed computer simulation of the cerebellum to intercandidate for the eligibility delay and the duration of LTD at the granule to Purkinje synapses. Experimental studies suggest that these synapses are responsible for learning and timing of the conditioned response in eyelid conditioning. The results indicate that there is an abrupt change in conditioning for eligibility delays varying between 100 and 200 ms. Moreover, the results predict that an eligibility delay of 125 ms and a LTD duration of 100 ms show no conditioning for a 50 ms interstimulus interval. Although the existence of the eligibility delay has not been shown experimentally, this prediction is in agreement with suggestions provided by studies related to adaptation in the vestibular-ocular reflex. © 2006 Elsevier B.V. All rights reserved.

Keywords: Cerebellum; Timing; LTD; Computer simulations

1. Introduction

Experimental data regarding eyelid conditioning converge on the important role played by the cerebellum in processing the conditioned and unconditioned stimuli (CS, US) and in sending the motor command for producing the conditioned response (CR). The temporal properties of eyelid conditioning can offer insight about the temporal dynamics of the plasticity induced at the granule to Purkinje synapses during learning. Experimental data [2,5,11] suggest that the induction of LTD at these synapses requires two conditions: (a) an elevated level of Ca^{2+} in Purkinje cell dendrites generated by the firing of a climbing fiber and (b) the binding of glutamate to mGluR when an action potential arrives from a granule cell. Experimental data, however, do not agree on the relative timing of these two processes needed for the induction of LTD. In this study we assume that once a granule cell fires there is a delay, called *eligibility delay*, until the synapse becomes ready for synaptic change. The length of time in which the synapse is eligible for change is called LTD duration (see Fig. 1B). We use a detailed computer simulation of the cerebellum to intercandidate for the eligibility delay and duration of LTD at the granule to Purkinje synapses,

assumed to be involved in learning and timing of the conditioned response.

Many computational models that capture the main results of classical conditioning have been proposed [1,6–8,18,19,21]. Some of them have architectures based on simplified versions of the cerebellum and some use different architectures altogether. Both approaches make speculative statements about the correspondence between the model and the functioning of the cerebellum. As far as cerebellar research is concerned, given the big difference between the implementation of the models and the real cerebellum, their success is premature. They might be considered, however, as departure points for more realistic models of the cerebellum.

2. Key tenets of the model

Mauk and Donegan [13] have proposed a computational model based on a detailed description of the cerebellum [4,9]. As shown in Fig. 1A, the model represents six cerebellar cell types, whose connectivity ratios between layers are based on cerebellum. All the details implemented in the model have an empirical basis. While CS is delivered by the activation of the mossy fibers, the US reaches the cerebellum through the climbing fibers. The command for generating the motor action is provided by the output of the deep nucleus.

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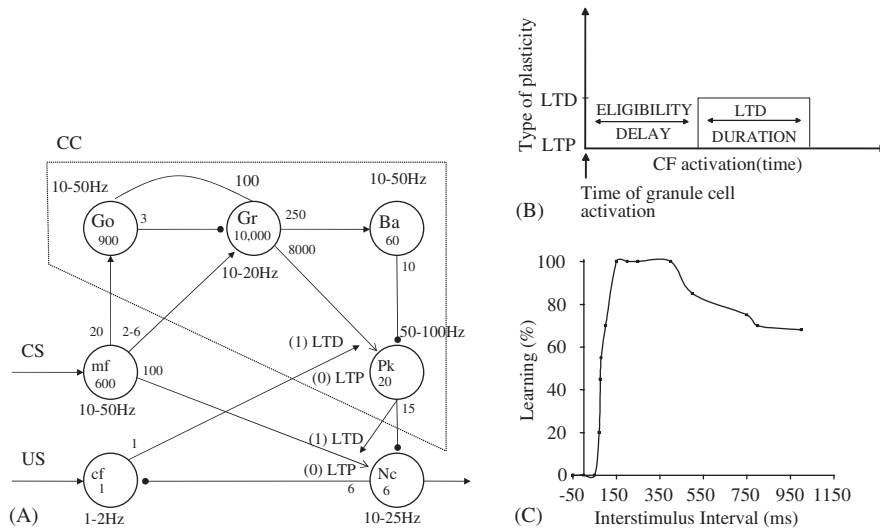


Fig. 1. (A) The architecture of the cerebellum model. Circles represent cell type. cf: climbing fibers, mf, mossy fibers, Go, golgi cells, Gr, granule cells, Ba, basket cells, Pk, Purkinje cells, Nc, nucleus cells, CC, cerebellar cortex. Numbers inside circles represent the number of cells implemented in the simulation. Numbers on edges represent the number of connections implemented between layers of cells. Filled arrows represent nonmodifiable connections whereas open arrows represent sites of plasticity, (B) type of plasticity at the granule to Purkinje synapses as a function of eligibility delay, LTD duration and climbing fiber activation; (C) peak conditioned response as a function of inter-stimulus interval ISI (after [16]).

The model contains two sites of heterosynaptic plasticity, both implicated by experimental data [2,5,10,11,12,22,23]. It is assumed that the synapses at the granule to Purkinje cells undergo plasticity whenever they are activated by the presynaptic granule cell. Moreover, it is assumed that the activity-dependent eligibility for plasticity happens with a certain delay (eligibility delay). If the activation from the climbing fiber occurs within a certain time window (LTD duration) starting from the activation induced by a granule cell, then the synapse undergoes LTD, otherwise it undergoes LTP. As shown in Fig. 1B, the activation of LTD is implemented using a variable that takes only two values, LTD ON and LTD OFF, and does not include details about the underlying molecular mechanisms involved in the induction of plasticity at the granule to Purkinje synapses.

In a similar fashion, with one exception presented below, the model assumes that the synapses at the mossy fibers to nucleus cells undergo plasticity whenever they are activated by the presynaptic cell. The model assumes no eligibility delay at these synapses. Similar to the effect of climbing fibers on granule to Purkinje synapses, the Purkinje cells determine the change in plasticity at the mossy fiber to nucleus synapses. However, there are some important differences. If the Purkinje cells fire above the mean of the LTD and LTP thresholds then they are hyperpolarized. If the Purkinje cells fire above the LTD threshold then the corresponding synapses undergo LTD as long as they have been activated by mossy fibers. In contrast, LTP occurs only when the Purkinje cells change from a hyperpolarized state to a firing rate below the LTP threshold. If the Purkinje cells fire in between the LTP and LTD thresholds then no plasticity occurs even if the synapse is activated by mossy fiber input.

3. How the model learns

When trained using inputs that mimic delay conditioning the model is able to show acquisition, extinction and savings [15,17]. During acquisition, each time the CS is on, more or less the same groups of granule cells become sequentially active. This process starts at the onset of the CS and the further away in time we are from the CS onset the more different are the groups of granule cells that fire each trial. As it will become clear below, this particular behavior of the granule cells allows the model to produce timed conditioned responses.

After the CS onset, there is a delay until the US is delivered. During this time the granule cells that are active stimulate the synapses that are going to be important for the learning of the conditioned response. Since, so far, there is no US, these synapses undergo equal amounts of LTP and LTD which make the Purkinje cells fire and thus still inhibit the nucleus cells. At the time the US is delivered, because the climbing fiber is active, this group of granule synapses undergoes net LTD, which in the long run make the Purkinje cells reduce their firing at this particular moment within the trial. The reduction in Purkinje cell firing disinhibits the nucleus cells which produce a response.

In order for the nucleus cells to produce a response it is not only necessary to reduce the inhibition from the Purkinje cells but also to increase the input from the mossy fibers. This increase is determined by the mossy fibers to nucleus synapses. As mentioned above, these synapses undergo LTP only when the Purkinje cells change from a hyperpolarized state to a firing rate below the LTP threshold. For this reason, the number of trials needed for CR expression is in the range of several hundred,

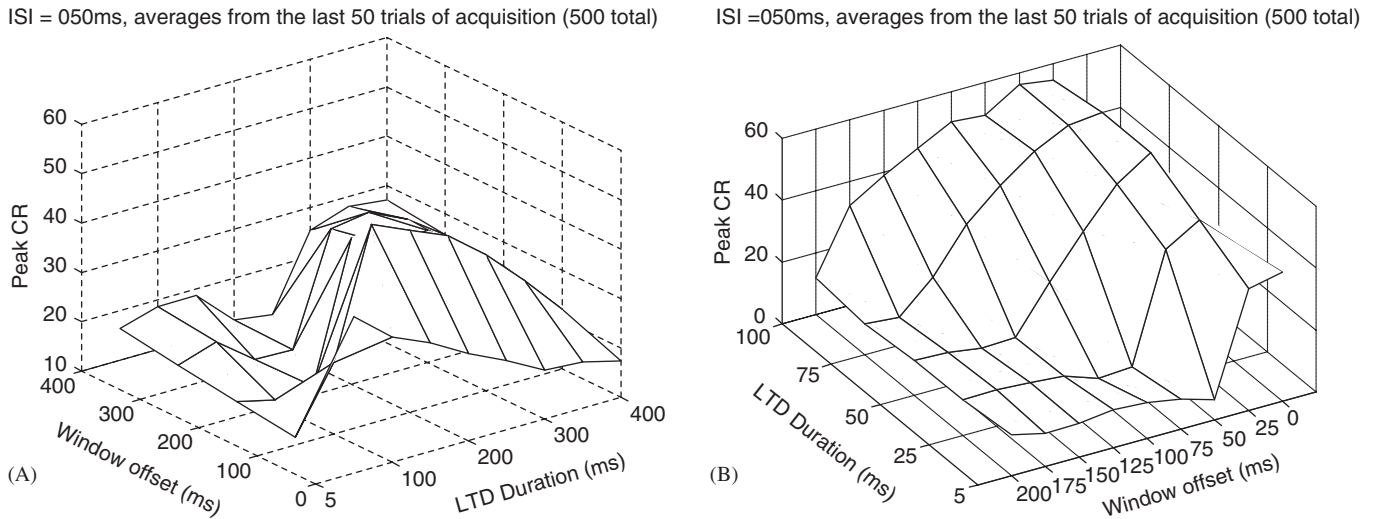


Fig. 2. Peak CR as a function of eligibility delay and LTD duration for a 50 ms ISI. (A) Low resolution and (B) high resolution.

despite the need for fewer trials to induce the change in granule to Purkinje synapses necessary for well timed CRs.

During extinction, the absence of US produces more LTP than LTD at the granule-Purkinje synapses. This process undoes the LTD that occurred during acquisition but only at some of the synapses [14]. This is due to the fuzziness of granule cell groups that become sequentially active starting at the CS onset. Synapses that underwent LTP during acquisition can get even more LTP during extinction and thus help in making the Purkinje cells fire more and thus inhibit the nucleus cells.

4. Computer simulations

The interstimulus interval (ISI) which is the time between the CS onset and US onset, has an effect on the amount of learning showed by the animal. For example, as shown in Fig. 1C, in the case of delay conditioning of the eyelid response, short ISIs up to 80 ms produce no learning. The acquisition of the conditioned response peaks between 200 and 500 ms and then it decays slowly up to a couple of seconds.

The animal not only produces a CR as a consequence of pairing CS and US many times but also it times the CR so that the impact of the oncoming US is reduced. As mentioned before, the ability of the model to show timed responses relies on the sequential activation of different groups of granule cells. This timing mechanism can generate ISI curves similar to the ones obtained experimentally. The only significant difference between the simulated and experimental ISI functions is related to short ISIs. While the model shows conditioning for ISIs smaller than 50 ms, no experimental study so far has obtained conditioning below 50 ms (see Fig. 1C). This discrepancy between the model and the experimental data might be due to the lack of an eligibility delay between the activation of the granule-Purkinje synapse and the

induction of LTD at that synapse. One way to obtain a prediction of the model about the value for the eligibility delay is to conduct a parametric study and find which values produce the ISI function that fits best the experimental data.

In order to obtain this prediction we simulated the model by varying the eligibility delay and LTD duration between 0 and 400 ms with a step of 100 ms. At the same time we varied the ISI by using the following values: 50, 100, 200, 500, 800, and 2000 ms. As expected, the simulated data obtained for ISIs longer than 50 ms were in agreement with experimental data, whereas the shortest simulated ISI (50 ms) showed conditioning for small values of the eligibility delay. The results shown in Fig. 2A indicate that there is an abrupt change in conditioning for eligibility delays varying between 100 and 200 ms. In order to make a better prediction about the possible values for the eligibility delay and the LTD duration we ran the simulated acquisition for the 50 ms ISI by using a finer resolution. We varied the eligibility delay and LTD duration between 0 and 200 ms with a step of 25 ms. The results shown in Fig. 2B predict that an eligibility delay of 125 ms and a LTD duration of 100 ms show no conditioning for a 50 ms ISI.

Although the existence of the eligibility delay has not been shown experimentally, this prediction is in agreement with suggestions provided by studies related to calcium threshold dynamics [3] and adaptation in the vestibular-ocular reflex VOR [20]. Raymond and Lisberger suggested that induction of LTD at the granule to Purkinje synapses has an eligibility delay of 100 ms with a coefficient of variability of 25 ms.

Acknowledgments

This work was supported by the NIMH grants MH 46904 and MH57051.

References

- [1] D. Bullock, J. Fiala, S. Grossberg, A neural model of timed response learning in the cerebellum, *Neural Networks* 7 (1994) 1101–1114.
- [2] C. Chen, R.F. Thompson, Temporal specificity of long-term depression in parallel fiber-Purkinje synapses in rat cerebellar slice, *Learn. Mem.* 2 (1995) 185–198.
- [3] T. Doi, S. Kuroda, T. Michikawa, M. Kawato, Inositol 1,4,5-trisphosphate-dependent Ca^{2+} threshold dynamics detect spike timing in cerebellar Purkinje cells, *J. Neurosci.* 25 (4) (2005) 950–961.
- [4] J.C. Eccles, M. Ito, J. Szentagothai, *The Cerebellum as a Neuronal Machine*, Springer, Berlin, NY, 1967.
- [5] C.F. Ekerot, M. Kano, Long-term depression of parallel fibre synapses following stimulation of climbing fibres, *Brain Res.* 342 (1985) 357–360.
- [6] M.A. Gluck, E.S. Reifsnider, R.F. Thompson, Adaptive signal processing and the cerebellum: models of classical conditioning and VOR adaptation, in: M.A. Gluck, D.E. Rumelhart (Eds.), *Neuroscience and Connectionist Theory*, Lawrence Erlbaum Associates, Hillsdale, NJ, 1990, pp. 131–186.
- [7] S. Grossberg, N.A. Schmajuk, Neural dynamics of adaptive timing and temporal discrimination during associative learning, *Neural Networks* 2 (1989) 79–102.
- [8] C. Hofstotter, M. Mintz, P.F. Verschure, The cerebellum in action: a simulation and robotics study, *Eur. J. Neurosci.* 16 (2002) 1361–1376.
- [9] M. Ito, *The Cerebellum and Neural Control*, Raven Press, New York, 1984.
- [10] M. Ito, Long-term depression, *Ann. Rev. Neurosci.* 12 (1989) 85–102.
- [11] M. Ito, M. Sakurai, P. Tongroach, Climbing fibre induced depression of both mossy fibre responsiveness and glutamate sensitivity of cerebellar Purkinje cells, *J. Physiol.* 324 (1982) 113–134.
- [12] D.J. Linden, J.A. Connor, Cellular mechanisms of long-term depression in the cerebellum, *Curr. Opin. Neurobiol.* 3 (1993) 401–406.
- [13] M.D. Mauk, N.H. Donegan, A model of Pavlovian eyelid conditioning based on the synaptic organization of the cerebellum, *Learn. Mem.* 3 (1997) 130–158.
- [14] M. Mauk, T. Ohyama, Extinction as new learning versus unlearning: considerations from a computer simulation of the cerebellum. *Learn. Mem.* 11 (5) (2004) 566–571.
- [15] J.F. Medina, M.D. Mauk, Simulations of cerebellar motor learning: computational analysis of plasticity at the mossy fiber to deep nucleus synapse, *J. Neurosci.* 19 (1999) 7140–7151.
- [16] J.E. Medina, M.D. Mauk, Computer simulation of cerebellar information processing, *Nat. Neurosci.* 3 (2000) 1205–1211.
- [17] J.F. Medina, K.S. Garcia, W.L. Nores, N.M. Taylor, M.D. Mauk, Timing mechanisms in the cerebellum: testing predictions of a large-scale computer simulation, *J. Neurosci.* 20 (2000) 5516–5525.
- [18] J.W. Moore, J.E. Desmond, N.E. Berthier, Adaptively timed conditioned responses and the cerebellum: a neural network approach, *Biol. Cybern.* 62 (1989) 17–28.
- [19] J.E.W. Moore, L.E. Desmond, N.E. Berthier, D.E.J. Bluis, R.S. Sutton, A.G. Barto, Simulation of the classically conditioned nictitating membrane response by a neuron-like adaptive element: response topography, neuronal firing, and interstimulus intervals, *Behav. Brain Res.* 21 (1986) 143–154.
- [20] J.L. Raymond, S.G. Lisberger, Neural learning rules for the vestibulo-ocular reflex, *J. Neurosci.* 18 (21) (1998) 9112–9129.
- [21] N.A. Schmajuk, J.W. Moore, Effects of hippocampal manipulations on the classically conditioned nictitating membrane response: simulations by an attentional-associative model, *Behav. Brain Res.* 32 (1989) 173–189.
- [22] B.G. Schreurs, D.L. Alkon, Rabbit cerebellar slice analysis of long-term depression and its role in classical conditioning, *Brain Res.* 631 (1993) 235–240.
- [23] E. Schutter, A new functional role for cerebellar long term depression, *Prog. Brain Res.* 114 (1997) 529–542.



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