Information Processing Via Post-Synaptic EPSP-Spike Complex and Model-based Predictions of Induced Changes During Plasticity in Cerebellar Granular Neuron

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ABSTRACT

Understanding functional role of spike bursts in the brain circuits is vital in analyzing coding of sensory information. Information coding in neurons or brain cells happen as spikes or action potentials and excitatory post-synaptic potentials (EPSPs). Information transmission at the Mossy fiber- Granule cell synaptic relay is crucial to understand mechanisms of signal coding in the cerebellum. We analyzed spiking in granule cells via a detailed computational model and computed the spiking-potentiation contributing to signal recoding in granular layer. Plasticity is simulated in the granule cell model by changing the intrinsic excitability and release probability of the cells.

Excitatory post synaptic potentials and spikes on varying Golgi cell (GoC) inhibition and Mossy fiber(MF) excitation were analyzed simultaneously with the effect of induced plasticity changes based on the timing and amplitude of the postsynaptic signals. It is found that a set of EPSPs reaching maximum threshold amplitude are converted to less number of high amplitude EPSPs or spikes. Exploring the EPSP-spike complex in granular neurons reveal possible mechanisms and quantification of information encoding in individual neurons of the cerebellar granular layer. Therefore, our study is potentially an important estimation of cerebellar function.

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Categories and Subject Descriptors

I.2.6 [**Connectionism and neural nets**], I.6.4 [**Model Validation and Analysis**], I.6.6 [**Simulation Output Analysis**], J.3 [**Medical information systems**]

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Key words

Computational neuroscience, plasticity, EPSP, action potentials, granule cells, cerebellum.

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1. INTRODUCTION

The cerebellum [11] is divided into different functionally- distinct regions. There is a need for analysis on the functionalities and behavior of the two independent processing regions; Granular layer and Purkinje cell layer [16]. Understanding how the input layer of the cerebellum i.e., Granular layer process incoming information is crucial because its output forms a major part of the output of cerebellar cortex [13]. Specific connection geometry exists between Mossy fibers (MF), Granule Cells (GrC) and Golgi cells (GoC) in the Granular layer [18].

Granular layer is hypothesized to perform sparse recording of the MF into a sparse representation that permits noise reduction by GoC which generate lateral inhibition [15]. Due to the limited set of combinations of MF excitatory and GoC inhibitory inputs, there are a discrete number of synaptic connections for studying the relationship between input and output in the MF-GrC relay. We adopt a stochastic model of the Granule cell [1] [2] [3] where each synapse is constituted by few releasing sites comprising of pre synaptic dynamics and release mechanisms.

Long-term changes in synaptic strength named as synaptic plasticity is one of the important neuro chemical foundations of learning and memory [6] [10]. Introduced by Donald Hebb in 1949, plasticity is supposed to provide the cellular basis for learning and memory and takes the form of either Long Term Potentiation (LTP) or Long Term Depression (LTD). [4] [5].A high frequency signal, HFS (typically 100 Hz) induces a strong glutamate release into the synapse and depolarizes the postsynaptic neuron [14]. The depolarization induced by successive excitatory postsynaptic potentials (EPSPs) overlap and cumulatively produces action potentials or spikes. Amount of neurotransmitters released into the synaptic cleft activates postsynaptic receptors to elicit a postsynaptic response. During MF- GrC LTP, there is an enhancement in neurotransmitter release and intrinsic excitability of GrC [1] [7]. LTD expression was associated with a decrease in release probability of the mossy fibre, showing changes opposite to those characterizing LTP [24]. Therefore induction of plasticity by changing the intrinsic excitability of the GrC and excitatory release probability of MF [7] [4] at MF-GrC synapses changes the spike train /EPSP train response of GrC [16].

This paper reports the impact of release probability and intrinsic excitability changes on mossy-fibre granule cell relay and related post-synaptic granule cell responses in terms of both EPSPs and spikes[8][9]. Most studies consider spikes as the major information carrying component in neurons. Here we explore both spikes and EPSPs and study how EPSP-spike complex are modulated in terms of information encoding in single neurons. We also predict the regulatory effect of Golgi cell inhibition on granule cell firing.

2. METHODS

2.1 Mathematical Biophysics

Detailed multi-compartmental GrC model [3] was used and simulations were performed by varying the excitatory (E) and inhibitory (I) inputs, as indicated in results and in figures. As in [3], GrC has 0-4 excitatory and 0-4 inhibitory connections. All simulations were performed using the NEURON simulator [21]. Effects of blocking inhibition by adding Gabazine was also simulated by setting GABAergic conductance in inhibitory fibers to zero.

2.1 Inducing LTP/LTD

By modifying intrinsic excitability and release probability [7], we simulated plasticity in the GrC. We modified intrinsic excitability by changing ionic current density or gating. We modified the on-off gating characteristics of sodium channel to modify sodium activation and inactivation parameters [3] for higher and lower intrinsic excitability. Three cases were studied where the intrinsic excitability of the GrC is Low (Low Intrinsic Excitability), Normal (Control) and High (High Intrinsic Excitability). The release probability (U) of MFs was varied from 0.1 to 0.4 for cells with low intrinsic excitability and from 0.5 to 0.8 for cells with high intrinsic excitability while the Control value remained as 0.416 in simulations for normal cells. Release probability of Inhibitory synapses (U_{inh}) was kept at the Control value of 0.34 for all the three cases. Input signals of frequency 100 Hz was applied to the MF-GC

relay for a time window of 200ms. The output voltage and timing for the entire simulation was recorded for the entire time window of 200ms with a discretization time step of 0.025ms. The resting potential of the GrC in the model is fixed at -70mV and the EPSP to spike transition voltage was measured at -0.55mV. The EPSPs and spikes generated for the induced LTP and LTD states were then quantified and compared with the Control values measured. This was done for various synaptic activation patterns seen in GrC *in vitro* and *in vivo* in order to find the effects in GrC firing. The MF inputs were varied from 1 to 4 and the GoC inputs were varied from 0 to 5. The post-synaptic response of GrC was then studied by applying input signals of varying frequencies. *In vitro* like behaviors were studied by giving single spike as input via MF terminals. *In vivo* like behaviors were characterized by short bursts (5 spikes per burst).

First spike latency was measured from the time of input stimulus to time of the peak of the output spike. The excitatory stimulus was applied at t = 20ms and inhibitory stimulus at t = 24ms. The EPSP / spike amplitude was measured from the resting voltage of -70mV to the voltage of the peak of the EPSP/spike generated.

3. RESULTS

3.1. Variation in EPSP/spike Ratio During LTP and LTD by Varying Number of Synaptic Inputs.

The EPSPs and spikes generated were found to be very sensitive to the inhibitory- excitatory balance of the MF-GC relay. Increase in MF excitatory inputs tends to reduce the number of EPSPs generated while it increased the number of spikes generated. As GoC inhibition was increased, EPSPs tend to increase but the spiking activity of the GrC decreased. As expected, there was an increase in total number of spikes generated and decrease in total EPSPs generated during LTP induction while there was a decrease in total spikes generated and an increase in total EPSPs generated during LTD. One Mossy fiber combined with zero or more inhibitory connections always produced zero spikes but produced maximum EPSPs. Synchronous activation of two or more mossy fibers was required in the model for spike generation (Figure 1A to E).

3.2. Variation in EPSP/spike Ratio by Varying MF Release Probabilities.

The simulations with varying release probabilities and measuring the EPSP-spike response for the different excitatory- inhibitory input combinations revealed an increase in release probability decreased the number of EPSPs while increase in release probability increased Spiking (Figure 2 A, B). The percentage of EPSPs generated during LTD was 67.5 % while during LTP was 32.5%. The percentage of spikes produced during LTP was 31.4 % while during LTD was 68.6 %. The increase – decrease pattern of EPSP –spike complex is found to follow a symmetric behavior. Release probability change affected GrC firing only if a proper excitatory – inhibitory balance was maintained in the cell (Data not shown).

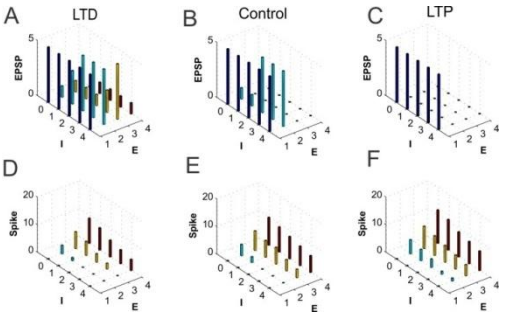

Figure 1: Count of EPSP peaks and spike during LTD, Control and LTP. The number of EPSPs and spikes generated for the In vivo like behavior in the different GoC inhibitory (I) and MF excitatory (E) levels.

3.3. Variation in EPSP/spike Amplitude During LTP and LTD by Varying Number of Synaptic Inputs.

Amplitude of both the EPSP and spike trains was recorded for a fixed time window during LTP

and LTD where MF excitation and GoC inhibition were kept steady. MF-GC LTP was associated with increase in EPSP/spike amplitude. Similarly MF-GC LTD was associated with decrease in EPSP/spike amplitude (Figure 3 A, B).

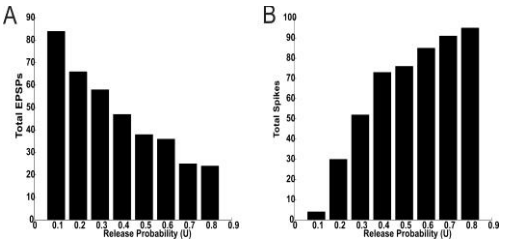

Figure 2: Total EPSPs (A) and spikes (B) generated while varying the MF release probability.

During LTP, reduced EPSP amplitude is observed for successive EPSPs while inducing LTD showed increased EPSP amplitude amongst successive EPSPs. There is a tendency for saturation as simulation time advances. No such adaptation is seen for successive spike amplitude during LTP and LTD.

3.4 Variation in EPSP/spike Amplitudes During LTP and LTD by Varying MF Release Probabilities.

The simulation for varying release probabilities; 0.1 to 0.4 for cells with low intrinsic excitability and 0.5 to 0.8 for cells with high intrinsic excitability were performed. The amplitude of both EPSPs and spikes generated were recorded and it was observed that the increase in U increased the EPSP amplitude. Increased release probability together with proper excitatory-inhibitory balance of the synaptic connections hence increased the probability of an EPSP to be turned into spikes.

The resting state of the cells were fixed at -70 mV and above the threshold of -55mV, the spikes show the same behavior with the increase in U. (Figure 4 A, B).

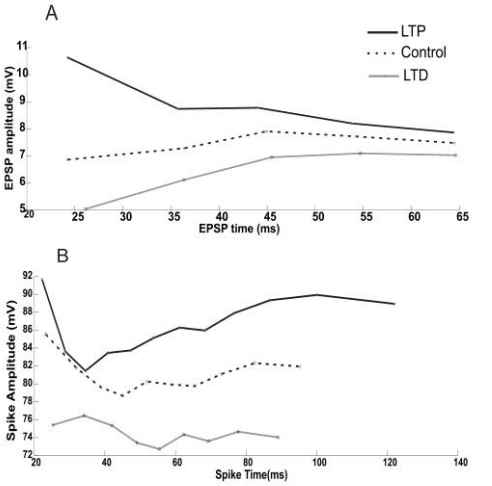

Figure 3: EPSP-spike amplitude during LTP and LTD. Both EPSPs (A) and spikes (B) Show a reduction in amplitude (from the control) during LTD while an increase in amplitude (from the control) during LTP.

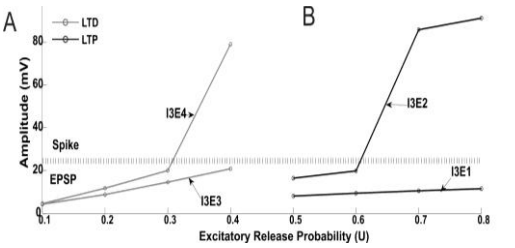

Figure 4: U Vs Amplitude of EPSP/spike. The induced LTD (A) and LTP (B) show the same behavior for EPSPs and spikes. Increase in U increases the amplitude for combinations of (E) Excitatory and (I) Inhibitory inputs.

3.5 Variations in First EPSP/spike Latency During LTP and LTD by Varying Synaptic Inputs.

The first EPSP-spike latency of MF-GrC is studied by varying the MF excitation and GoC inhibition during LTP and LTD.

Table 1: First EPSP latency during LTP and LTD and its dependence on Inhibitory (I) and Excitatory inputs (I).

Time of first EPSP (ms)			
	LTD	**Control**	**LTP**
I0E1	26.5	27.55	29
I0E2	27.15	29.425	0
I0E3	28.125	0	0
I0E4	0	0	0
I2E1	26.1	24.25	24.2
I2E2	24.15	24.15	0
I3E1	25.975	24.2	24.15
I3E2	24.125	24.125	0

First EPSP latency of MF-GrC under LTD and LTP was found to be sensitive to the GoC cell inhibition. In the absence of Go inhibition, the first EPSP latency was decreased during LTD from the control while it was increased during LTP. In the presence of GoC inhibition, the first EPSP latency was increased during LTD and decreased during LTP irrespective of MF excitation (see Table 1).

MF-GC LTD was associated with an increase in first spike latency with respect to the Control while LTP was associated with decrease in first spike latency irrespective of inhibition or excitation (see Table 2).

Sensitivity of initial EPSP-spike latency to MF inputs alone and GoC inhibition alone were then analyzed, varying one parameter while the other parameter was kept constant, for fixed release probability. On increasing GoC inhibition, initial EPSP latency is found to decrease during LTD, Control and LTP (Figure 5A). With the increase in GoC inhibition, initial spike latency is considerably increased during LTD, preserved during LTP and Control. (Figure 5B). Increase in MF excitation does not guaranty the reduction in initial EPSP timing during LTD. (Figure 5C). Increase in MF inputs alone tends to decrease the initial spike timing in LTD, Control and LTP. (Figure 5D).

The behavior of initial EPSP timing in the presence and absence of GoC inhibition, while varying MF inputs during LTD was found to be different.

Table 2: First spike latency during LTP and LTD. MF-GC LTD was associated with an increase in first spike latency from the Control while LTP is associated with decrease in first spike latency irrespective of inhibition (I) or excitation (E).

Time of first spike (ms)			
	LTD	**Control**	**LTP**
I0E1	0	0	0
I0E2	43.075	33.325	24.4
I0E3	33.475	24.625	22.875
I0E4	25.275	23.225	22.2
I2E3	43.7	24.65	22.875
I2E4	36.075	23.225	22.2
I4E3	0	24.675	22.875
I4E4	43.55	23.225	22.2

In the absence of GoC inhibition, the increase in MF inputs produced late EPSPs while in the presence of GoC inhibition, increase in MF inputs produced early EPSPs. But four MF inputs produced late EPSPs than the 3 MF inputs (Figure 6).

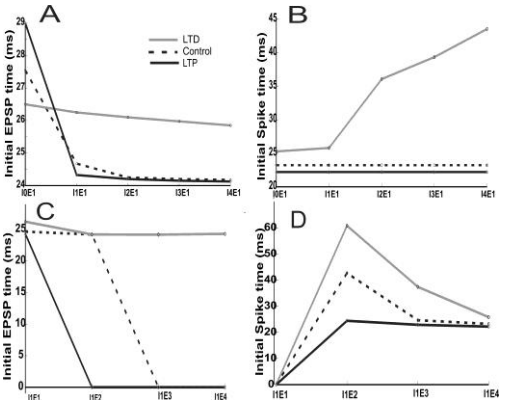

Figure 5: Initial EPSP-spike latency Vs MF inputs and Go Inhibition during LTD, Control and LTP. A: Variation of initial EPSP latency with change in Go inhibition. B: Variation of initial spike latency with

change in Go inhibition. C: Variation of initial EPSP latency with change in MF inputs. D: Variation of initial spike latency with change in MF inputs.

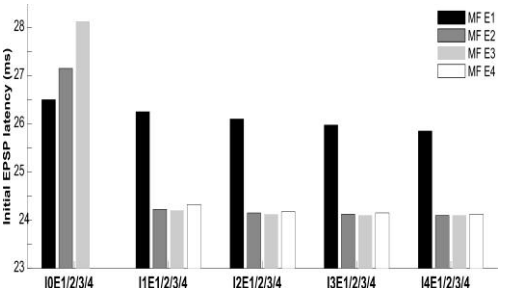

Figure 6: Initial EPSP latency in the presence and absence of GoC inhibition in LTD condition.

3.6 Variation in First EPSP/spike Latency During LTP and LTD by Varying MF Release Probabilities.

The simulation for varying release probabilities; 0.1 to 0.4 for cells with low intrinsic excitability and 0.5 to 0.8 for cells with high intrinsic excitability were performed. Presence of Inhibitory input reduced the EPSP latency while absence of inhibitory inputs increased the EPSP latency (Figure 7).

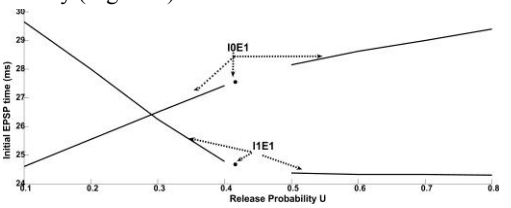

Figure 7: Change in EPSP latency with the increase in release probability (with and without inhibition). The points at release probability 0.416 represents the amplitude value measured at Control.

Increase in release probability decreased the initial spike latency during LTD irrespective of inhibition or excitation. But the initial spike latency is preserved during LTP (Figure 8).

3.7 Temporal Summation of EPSP Amplitude on Increasing the Input Frequency.

Increasing and decreasing NMDA current enhances time-window for temporal summation [25].

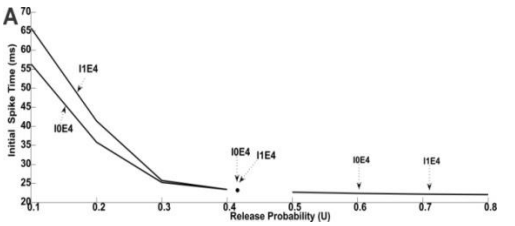

Figure 8: Change in spike latency with the increase in release probability (with and without inhibition). The point at release probability 0.416 represents the amplitude value measured at Control

However to study the effect of frequency of the input signal on the output component is analyzed during LTD, Control and LTP conditions for different MF excitation and GoC inhibition levels. In all the cases, increase in frequency of the input signal (decrease in delay between the input pulses) increased the amplitude of the output. It was found that a high frequency signal changes a set of EPSP's into a spike for the different GoC inhibitory and MF excitatory combinations [20]. As the frequency is increased from 100 Hz to 1000 Hz, there was a small increase in amplitude of each of the EPSPs and when it reached some threshold amplitude, the EPSPs were converted into lesser number of higher amplitude EPSPs (Figure 9A). When the intrinsic excitability of the cell and release probability of MF input was high enough, these EPSPs were found to be converted into spikes (Figure 9B).

4. DISCUSSION

In this paper, we extensively analysed strong and weak postsynaptic responses of granule cell neurons in terms of the total number, amplitude and latency of EPSP-spike complexes. These parameters analyzed eventually help us to quantify the effects of LTP and LTD in the output firing response of GrC [17][19]. LTP or LTD can alter

several functional aspects of GrC firing. In this attempt we showed that specific temporal dynamics and geometry of connections eventually determine the circuit output [12]. We propose that the topology of connections play a critical role in the expressions of long-term plasticity in the granule cells.

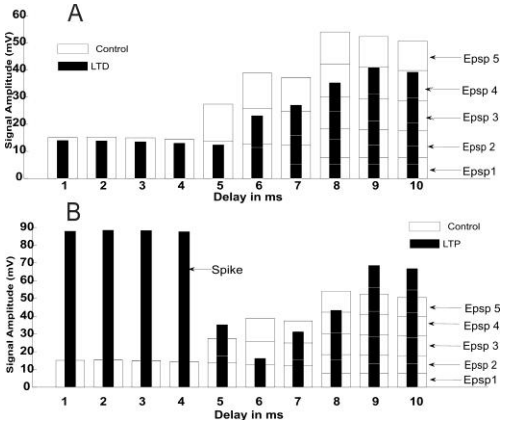

Figure 9: Additive effect of EPSPs to form spikes with the increase in frequency of the input signal. The Additive effect is preserved during LTD, Control and LTP.

The simulations indicate that the first spike latency is modulated with the change in intrinsic excitability and release probability. Mossy fibers were stimulated with a 100-Hz, 200-ms train determining excitatory EPSP temporal summation and spike activation in the granule cell. This work supports the hypothesis [25] that EPSP temporal summation is critical for reaching spike threshold but, once firing begins, it is efficiently regulated by postsynaptic ionic conductance.

The main results in this paper are increase in number and earlier activation of high amplitude spike bursts during LTP and the exactly reverse results during LTD. Another main result is the depression seen for the EPSPs in terms of total number, and amplitude during LTP while enhancement of the above properties of EPSPs during LTD. The sensitivity of initial EPSP timing towards GoC inhibition is well established during LTD. The simulations study the effects due to presence and absence of GABAergic inputs and the decrease and increase respectively for the initial EPSP time is suggested as potential modulatory mechanism induced by inhibition in granule cells.

By increasing MF release probability, four main predictions are quantified. Increase in release probability increases the number of spikes while it decreases the number of EPSPs. The percentage increase/decrease during LTP and LTD for the EPSP-spike complex is found to be matching so that the total burst activity remained steady. Also, increase in release probability increased the amplitude of EPSPs and spikes. This leads to temporal summation of EPSPs turning to spikes. This behavior persisted during LTP and LTD. The sensitivity of initial EPSP time to GoC inhibition explained above persisted even with the increase in release probability during LTD. Increase in release probability produced early spikes during LTD. spikes in LTP preserved their initial timing irrespective of release probability change [23].

The study estimates the contributions of EPSP-spike complexes during information coding. By favoring selected combinations of mossy fiber inputs, MF-GrC LTP would then improve pattern recognition, the primary function attributed to the cerebellar Mf-GrC relay. The present study has its due importance as it explores how cerebellar granule neurons store and process information in terms of EPSP-spike combinations [22] and plasticity studies indicate its huge potential for cerebellar memory since there are 1011 granule cells and four times as many MF-GrC synapses. Such a study is potentially an important estimation of cerebellar function.

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