Reconstructing extracellular local field potential in cerebellar granular layer networks

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Abstract— **Local field potentials (LFPs) arise from complex interactions of spatial distribution of current sources, time dynamics, spatial distribution of dipoles apart underlying conductive properties of the extracellular medium. We reconstruct LFP in order to test and parameterize the molecular mechanisms of cellular function with network properties. The sensitivity of LFP to local excitatory and inhibitory connections was tested using two novel approaches. In the first, we used a single granule neuron as a model kernel for reconstructing population activity. The second approach consisted using a detailed network model. LTP and LTD could regulate the spatiotemporal pattern of granular layer responses to mossy fiber inputs. The effect of changes in synaptic release probability and modulation in intrinsic excitability of granule cell on LFP was studied. The study revealed cellular function was represented in LFP wave revealing the activity of underlying neurons. Changes to cell during LTP and LTD were reflected by LFP wave as an indicator of the function of granule neurons as spatial pattern generators. Both modeling approaches generated LFP *in vitro* [16] and *in vivo* [17] waveforms as reported in experiments.**

Keywords- Computational Neuroscience, local field potential, modeling, granular layer.

I. INTRODUCTION

The activity in neuronal networks originates from the contribution of multiple interconnected neurons. Local field potentials (LFP) are often recorded by electrophysiologists as a measurement of extracellular activity and in cerebellar granular layer as a population activity. Eccles [1] proposed that LFP and EEG activities are generated by summated postsynaptic potentials arising from the synchronized excitation of neurons. For the cerebellar granular layer, the current view is that EEG and LFPs are generated by synchronized synaptic currents, possibly through the formation of dipoles [2]. The local field potential (LFP) is composed of low-frequency extracellular voltage fluctuations that are thought to reflect synaptic potentials [3] and other slow electrical signals such as spike after-potentials and voltage-dependent membrane oscillations.

Neurophysiologists have used the LFP with increasing frequency in recent years to link neural activity to perception and cognition, including sensory stimuli coding, perceptual binding, attention, and working memory. The local field potential is believed to represent the synchronized input into the observed area, as opposed to the spike data, which represents the output from the area. In the LFP, quick fluctuations in the potential difference are filtered out, leaving only the slower fluctuations. The quick fluctuations are caused by the short inward and outward currents of the action potential. The LFP is thus composed of the well sustained currents in the tissue, typical of the somato-dendritic components.

We have used a detailed network model to reconstruct the ensemble activity of the granular layer network. The main problems lay in reconnecting the subcellular and cellular properties of emerging collective responses *in vivo* onto the combinatorial nature of inputs, the presence of noise and the geometrical nature of the underlying circuitry. The validity of this approach was demonstrated in seminal works on LFP generation in the olfactory bulb [4], [5], [6] and [7]. More recently, computation techniques were applied to the hippocampus in the attempt at deciphering spike generation recorded in certain behavioural conditions [8], [9], [10] and [11].

In this article, two main approaches to reconstruct LFP were undertaken. One was to study whether we could use a single granule neuron as a model kernel for reconstructing population activity. Eccles [2] proposed granule cells as source-sink dipoles during action potential generation due to flow of currents. In our first approach, therefore, the predominant nature of granule cells as dipoles was used to generate various extracellular currents and combining them, a population extracellular LFP was reconstructed. In the second approach, a model of granular layer network was used to extract local field potential from a single point close to the region of interest.

The main focus was to reconstruct granular layer post-synaptic LFP waveform while studying the molecular mechanisms and their impact on the LFP traces. The models could easily regenerate both *in vitro* and *in vivo* traces and the effects of inhibition on the network. The goal was to transfer the knowledge on mechanisms in single cell and understand its impact on the network response.

II. METHODS

A detailed multi-compartmental granule cell model [12] was used to generate extracellular currents, which were then used to generate the local field potential (LFP). NEURON [13] simulation tool was used to obtain single cell extracellular plot values for different synaptic activation patterns of Granule cell. Population model based on the multiple granule cells was analyzed further using MATLAB (Mathworks, USA).

A. Granule cell model

The multi-compartmental granule cell model, which consisted of 52 active compartments including the soma

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with four dendrites and an axon [12], was used to generate all possible combinations of response patterns caused by synaptic activation through mossy fibers and Golgi cells. The currents generated by each compartment were then used to reconstruct the local field potential through the extracellular mechanism implemented in NEURON [13]. This adds two additional electrical resistance-capacitance (RC) layers to the cable model to measure the current that flows out of the cell.

In vitro like behaviors were studied by giving single spike as input via mossy fiber terminals. *In vivo* like behavior was characterized by burst. Short burst means 5 spikes per burst and long burst means 9 spikes per burst. First spike latency was measured from the time of stimulus to peak of the spike. In all models, the stimulus was applied at t=20ms.

B. Simulating LTP/LTD

To study effects of plasticity on the underlying population, we simulated plasticity in the granule cells. Granule cell plasticity could be obtained by modifying intrinsic excitability and release probability [14]. In our models, 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 [15] for higher and lower intrinsic excitability.

C. LFP generation using one granule cell

The neural activity associated with the granule cell population inside the cerebellum have been investigated by recording action potentials of single and multiple units of the granule neuron model [12]. Signal obtained was similar to the recorded potentials using a low impedance tungsten microelectrode *in vitro* [16].

The model approach allows the activity of a number of neurons to contribute to the signal. The unfiltered signal reflects the sum of action potentials from cells in the recording region of interest (ROI). The low-pass filtering removed the excessive noise components from the signal. The model simulations were performed using NEURON [13] while LFP reconstruction was performed using Matlab (Mathworks, USA).

D. LFP generation using granule cell population

Large scale *in vitro* network of granular layer in our model consisted of 700 detailed multi compartmental granule cells [12]. Extracellular mechanism in NEURON [13] was inserted in all compartments to measure extracellular potentials. The sink-source effect [2] hypothesized that the population of granule cells would generate typical field potential components based on action potential activity through the cell. Based on the activity (unpublished data), we categorized the cells to four main types of excitatory patterns (See Table 1).

A smaller subset of the granular layer consisting of 220 cells [12] was used in the *in vivo* model of the network for LFP reconstruction. This estimate for cells was based on the glass electrode recordings of [17].

TABLE I. TYPES OF SYNAPTIC COMBINATION OF CELLS IN THE NETWORK MODEL.

Percentage of cells in the network	Number of excitatory synapse	Number of inhibitory synapse
15	4	1
35	3	2
35	2	3
15	1	4

a. Note most cells have 2 or 3 active excitatory synapses. 4 predominant combinations were used.

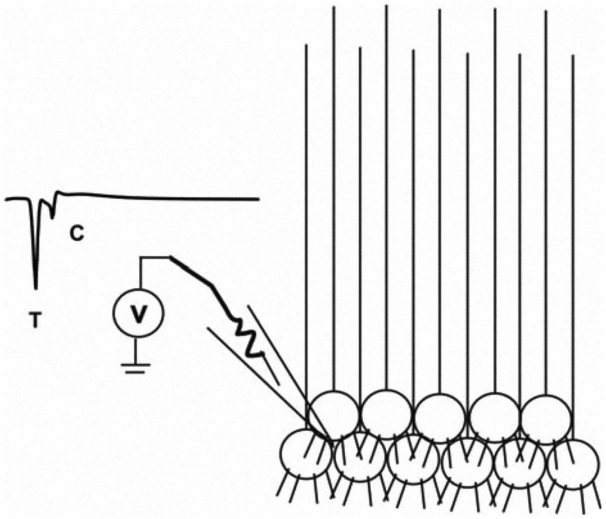

Figure 1. LFP generation in granule cells. The measuring electrode close to the soma collects the somato-dendritic potentials of many cells [17].

Cells were grouped based on excitation and the synaptic connectivity was retained similar as *in vitro* condition (see Table 1).

A single cell recording in the model corresponded to the extracellular field potential of all somato-dendritic compartments. This was later summed with the total number of cells in the network and the summed response was called the local field potential of the network.

All simulations directly yielded the LFP waveform and simulations were performed on NEURON [13].

The LFP extracted from the model had a sampling rate of 40 kHz and was then filtered using butterworth filter (Matlab, Mathworks, USA) with normalized cut-off frequency set at 1 kHz for *in vitro* LFP and 1.1 kHz for *in vivo*. As post-processing, signal smoothing was performed using a Hilbert transform on Matlab (Mathworks, USA) software.

III. LOCAL FIELD POTENTIAL RECONSTRUCTION

The central goal of this study was to assess the utility of the LFP signal reconstruction for evaluating the granular layer processing of neural information. In a real recording (see [16] and [17]) the signal received from each granule cell by the tungsten electrode depends on the distance of the cell from the electrode. We used two main algorithms as indicated in methods to reconstruct LFP. Since the nature of reconstruction of the LFP was

determined by the characteristic nature of underlying cells, the algorithm itself helped decode the activity of the granular layer network. In both algorithms (see III A and B), the number of cells that contributed to the LFP was estimated from previous works as 700 (*in vitro*, see [16]) and 220 (*in vivo*, see [17]) respectively.

A. Algorithm for single neuron based approach

In this approach, the electrotonic compactness of the granule cell (see [18], [19], [20]) and the close packing of granular layer [21] was used to simplify the synchronous activity of the network. The activity of the granular layer network is the sum of activities of individual neurons since granule cells are almost identical and mossy fibre inputs activate the granular layer network synchronously [22]. A single neuron model was used to simulate various synaptic patterns and resulting output corresponded to a general LFP postsynaptic wave as seen in granular layer. The outputs corresponding to various synaptic activation patterns were summed linearly with a noise term corresponding to the distance of the electrode from any particular cell. Some cells closer to the electrode were given no or less noise while cells further had lesser signal-to-noise ratio. The noise in the algorithm was implemented by padding zeros corresponding to time delay encoded by various errors.

Algorithm:

Step 1: Set-up a single granule neuron with a particular synaptic combination and run the model.
Step 2: Extract the extracellular potentials from somato-dendritic compartments as one possible combination.
Step 3: Generate the extracellular response of a single cell for all possible synaptic combinations.
Step 4: for total number of cells, compute
- i) Use random distance as error noise
- ii) Pad zeros before signal of that cell
- iii) Sum all extracellular signals linearly with the padded noise.

Step 5: Total signal obtained is the desired LFP.

The amount of noise (see Fig. 2) was based on post-synaptic latency measurements [23] with a maximum of 3ms delay. The electrode could measure cells that generated extracellular currents with a delay of 0-3ms. In the algorithm, 1ms was equated by padding 40 zeros ahead of the signal. For simplicity sake, delays were assumed to be either 0, 1, 2 or 3 ms.

B. Algorithm for population based approach

A number of granule neurons activated by particular synaptic patterns generated an extracellular potential corresponding to that synaptic input. The neurons were placed randomly and the measuring electrode was supposed to be the center. Any cell that was at a distance further away was assumed to contribute lesser to the generated LFP. Cells closer to the electrode had no or less noise and cells further had more noise or lesser signal-to-noise ratio. The noise in the algorithm was implemented by padding zeros corresponding to various errors.

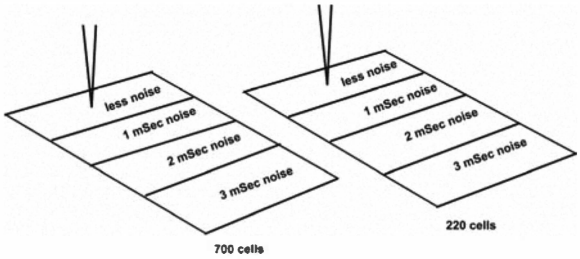

Figure 2. LFP reconstruction based on distance. (Left) LFP measuring electrode *in vitro*. Here 700 cells contributed to the LFP waveform. (Right) *In vivo* LFP wave measurement with 220 cells contributing to the population signal.

Algorithm:

Step 1: Set-up granular network with appropriate number of neurons.
Step 2: Assign synaptic activation pattern to each cell corresponding to adequate percentage (see Table 1).
Step 3: Randomly align the cells so measurement is a combination of all patterns.
Step 4: Extract the extracellular potentials from somato-dendritic compartments as contribution of one cell.
Step 5: for each cell, compute
- i) Random noise correlating to the distance from an electrode/measuring point of interest.
- ii) Pad zeros before signal of that cell

.

Step 6: Sum all extracellular signals for all cells linearly with padded noise. Total signal obtained is the desired LFP.

As in previous single-cell based approach, delays were assumed to be 0, 1, 2 or 3 ms for simplicity sake. Similarly the amount of noise (see Fig. 2) was based on post-synaptic latency measurements [23] with a maximum of 3ms delay. The electrode could measure cells that generated extracellular currents that came with a delay of 0-3ms. In the algorithm, 1ms was equated by padding 40 zeros ahead of the signal.

IV. RESULTS

Both algorithms could reconstruct granular layer *in vitro* LFP waveform indicated as N_{2a} and N_{2b} [16] and *in vivo* waveform with T and C waves [17].

A. In vitro LFP reconstruction

Both algorithms generated the field waveforms *in vitro* and *in vivo,* given their respective inputs. The *in vitro* components contained sharper information all of which the algorithms did not reproduce distinctly.

In the model, the *in vitro* pattern was generated due to the spike based input via the mossy fiber (MF) synapses. At time=20ms, the MF synapses of the cells generate 1 spike to which the cell generates a post-synaptic response.

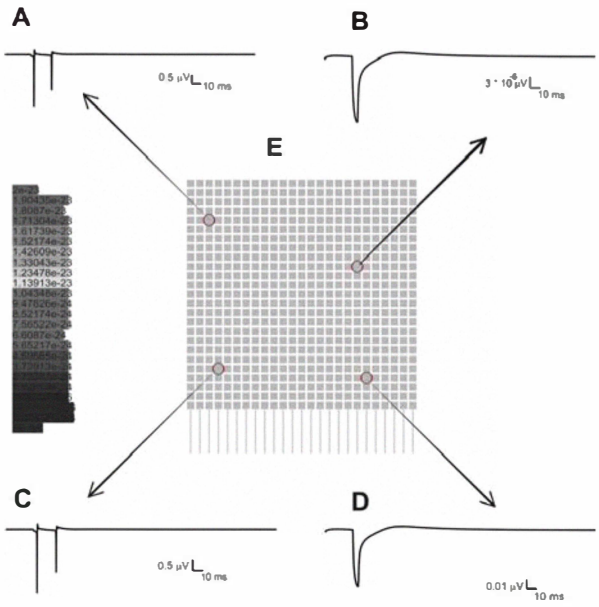

Figure 3. Network contribution to the *in vitro* LFP wave. A, B, C, D are LFP generated from single cells in the network (see III B). E is the full network of 700 cells. Colormap is the activity representation and expresses the amount of excitation in individual neurons in the network. A, C can be seen with both N_{2a} and N_{2b} waves while B, D shows N_{2a} alone. In some cases, such as in the presence of inhibition N_{2b} wave is suppressed.

The post-synaptic response was varied as per input pattern and for a combination of 3MF and 4MF synaptic activation, spikes were generated. With 4MF synapses active, a doublet was seen [12]. Correspondingly the responses generated N_{2a} wave and the doublet caused the N_{2b} wave. With inhibition at time=24ms via GABAergic synapses caused the suppression of the doublet and thereby suppresses the N_{2b} wave. [16]

In the *in vitro* input scenario, with inhibition reduced, the peaks became more pronounced (see gray trace in Fig. 4). *In vitro* LFP in the granular layer could not be produced clearly using single cell approach. The filtering was poor and lesser filtering produced a second wave (unlike the absence of N_{2b} with inhibition). The network approach clearly reproduced the *in vitro* wave and the different combination with inhibition was seen (see Fig. 3).

B. *In vivo LFP reconstruction*

The *in vivo* LFP response was reconstructed to produce the granular layer LFP generated by tactile stimulation [17]. The *in vivo* LFP signal consisted of two waves T, C produced by two bursts along the mossy fibers, one coming from the trigeminal pathway and other from the cortical pathway. T-wave in our models was generated by a short burst along the mossy fibers and C-wave by a longer burst. In our models, T-wave was generated by 5 spikes at 500 Hz along the MF synapses and C-wave by the 9 spikes at 500Hz via the MF synapses.

Both methods (see III A and B) reconstructed the *in vivo* LFP waveform (see Fig. 5).

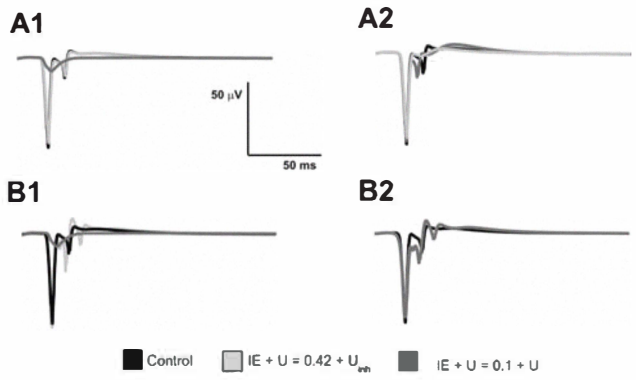

Figure 4. *In vitro* LFP waveform. Each trace is with different plasticity conditions.

C. *Plasticity in LFP waveforms*

Plasticity in granular layer is bidirectional [24]. Given that release probability combined with low or high intrinsic excitability induces plasticity [25], [26], changing the intrinsic excitability in this simulation was equivalent to exploring the consequences of LTD or LTP.

With increased number of excitatory connections and higher intrinsic excitability, there was increased spike amplitude (as seen in LTP) and with low release probability and low intrinsic excitability (as in LTD), decreased spike amplitude was seen although the number of spikes is same (data not shown). Since LFP comprised of spike information, the size and characteristics of LFP was also changed.

Both algorithms showed the LFP changes *in vivo* although the single neuron approach (see Fig. 5) distinctly showed the T/C components generated by the two independent bursts suggesting that they could be from independent granule neuron populations.

D. *Impact of inhibition on LTP/LTD*

The increase in inhibitory connections to granule cells in the underlying network model decreased number of spikes, spike amplitude (especially during bursts when spike arises after the feedback inhibition from Golgi cell) and decreased spike latency. Variations in GABAergic release probability (U_{inh}) such as decrease in U_{inh} from control value (0.34) resulted is increase in number of spikes. Increase in the value of U_{inh} contributed to a reduction of the doublet to a single spike as seen *in vitro*.

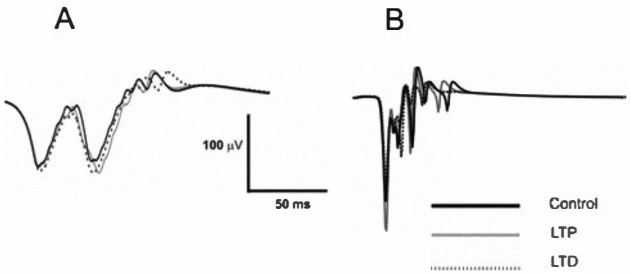

Figure 5. LTP-LTD *in vivo*. A shows the effects of LTP *in vivo* generated using single neuron approach. B. shows LFP *in vivo* generated using network approach. Both methods are compared with LTP and LTD induction through changes in intrinsic excitability and release probability [14].

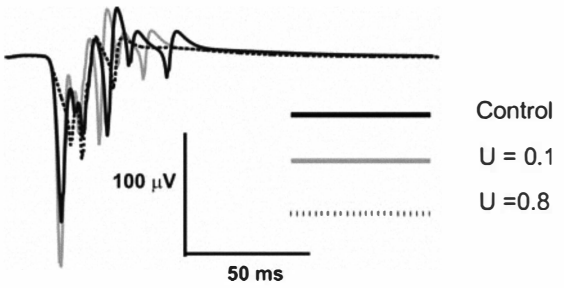

Figure 6. Effects of inhibition on LFP waveform. Control condition is shown as a black trace. Maintaining all other parameters unchanged, release probability of inhibitory synapses were decreased to 0.1 (grey trace) from control value (U_{inh}=0.34) and in another condition, release probability of inhibitory synapses were increased to 0.8 (dotted black trace) from control value (U_{inh}=0.34). Note increased amplitude of grey trace.

The LFP *in vivo* wave reflected this change (see Fig. 6). With low inhibition (gray trace in Fig. 6), as predicted, the amplitude of T-wave increased and C-wave became more prominent. With increased inhibition (dotted black trace in Fig. 6), the *in vivo* LFP wave became noisy and less defined.

Gold [9] studied the effects of constraining *in vivo* models with extracellular potentials. The granule cell model [12] could be used directly without any extra constraints for extracellular LFP reconstruction. Yet soma is main source of currents [18 and 20] so a comparison was made for LFP reconstruction using single compartment models [20] in granular networks.

E. Unreliability of non-detailed models for LFP reconstruction

The results (see Fig. 7) indicated single compartmental models show inaccurate field potentials both in shape and amplitude. The *in vitro* case showed a single impulse instead of the N_{2a} which indicated that timing information alone may be retrieved from single-compartmental models, if used for LFP reconstruction.

V. DISCUSSION

Extracellular field potentials of the cerebellum granular layer have been effectively reconstructed two different approaches to the extracellular currents generated by a detailed multi-compartmental model of the granule cell [12].

The main errors of single compartmental models in LFP generation were related to the size of extracellular action potential, capacitive components and rapid changes in spiking. Signal degradation was seen while filtering LFP traces generated using single-compartment models where relevant signal components were under-sampled thereby making the approach unreliable.

Separate clusters of granule cells could independently generate *in vivo* waves and this was noted to reflect in both approaches. The amount of noise was high in the network-based approach and there were shortcomings in filtering. We feel that the filtering defects were due to absence of non-integer noise values in assigning distances in cells. Overall bad smoothing/loss of signal features were seen *in vitro* and *in vivo*.

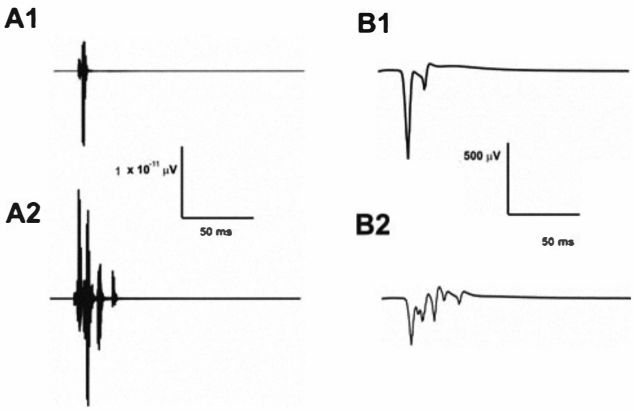

Figure 7. Comparison of single-compartmental and detailed model for LFP reconstruction**.** A1 (*in vitro*) and A2 (*in vivo*) are single-compartment granule neuron model [14] generated traces using network approach. B1 (*in vitro*) and B2 (*in vivo*) are multi-compartment neuron model [12] generated traces using network approach. A1 and A2 are unfiltered traces. Filtering removes most details. B1 and B2 were filtered at 1 kHz.

We assumed extracellular space to be isopotential. The simulations closely followed experimental results suggesting that there was not much non-linearity in the granular layer extracellular space. The variations in the nature of spike with number of spiking cells could suggest that sparse coding could be preserved as suggested by Marr [26] and Albus [27].

The basic rules of granule cell plasticity [14] were the changes of intrinsic excitability and release probability of synapses whose intracellular impacts were previously recorded. Plasticity in LFP waves was nicely reproduced by using the same mechanisms that were studied using intracellular techniques. LFP observed after induction of LTP shows bigger amplitude and wider wave width while LTD shows the depression of width and lesser amplitude in the T/C components of the *in vivo* waveform. This suggests that LFP reflects the overall properties and mechanisms of spiking/non-spiking in single and in neuronal populations.

Single compartments models do not yield sufficient data for extracellular currents due to limited biophysical conditions. The main errors were related to the size of extracellular action potential, capacitive components and rapid changes in spiking. Single compartment based models may however record timing information in case of extracellular action potentials. Electrotonic compactness [20], [12] was not sufficient to reproduce granular layer LFP.

The main predictions are that molecular mechanisms predict how LFP may be generated revealing a key connecting single neuron and population responses.

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