

Computationally Efficient Bio-realistic Reconstructions of Cerebellar Neuron Spiking Patterns

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ABSTRACT

Simple spiking models have been known to replicate detailed mathematical models firing properties with reliable accuracy in spike timing. We modified the adaptive exponential integrate and fire mathematical model to reconstruct different cerebellar neuronal firing patterns. We were able to reconstruct the firing dynamics of various types of cerebellar neurons and validated with previously published experimental studies. To model the neurons, we exploited particle swarm optimization to fit the parameters. The study showcases the match of electro-responsiveness of the neuronal models to data from biological neurons. Results suggest that models are close reconstructions of the biological data since frequency and spike-timing closely matched known values and were similar to those in previously published detailed computationally intensive biophysical models. Such spiking models have a number of applications including design of large-scale circuit models in order to understand physiological dysfunction and for various computational advantages.

Categories and Subject Descriptors

I.6 [Simulation and Modeling]: Types of Simulation – *Discrete event*

General Terms

Algorithms, Design, Theory.

Keywords

Computational Neuroscience, Integrate and Fire Model,

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Cerebellum, Neurons.

1. INTRODUCTION

Sensory information in the brain is encoded by neurons as spikes which represents action potential[10]. Mathematical models have been known to be employed in order to understand neural encoding. Modeling large-scale circuits helpful to understand neural function. However large-scale models are computationally expensive and may not be scalable to biological actuality. Simplified spiking models were predominantly used in the construction of large-scale networks of different brain regions. These models were defined to be biologically plausible yet computationally efficient[13]. Several spiking models [13, 24, 28] have been used to reproduce spike dynamics. The aim of this paper was to develop simple spiking models to mimic bio-realistic neuronal firing patterns of rat cerebellum usable for large-scale circuit models. We preferred adaptive exponential integrate and fire mathematical model (AdEx)[24] to reconstruct the firing patterns of cerebellar neurons. This model uses an adaptation variable to modify response with significant accuracy in spike timing [2, 11, 15, 19]. Adapting nine parameters, we show that the model reproduced cerebellar neuronal firing patterns.

Cerebellum granular layer forms largest neuronal population in the mammalian brain receiving excitatory input from mossy fibers and inhibition via synapses from interneurons like Golgi cell [1, 5, 7, 8, 12, 21][22]. It contains primarily 5 neuron types: granule (GrC), Golgi (GoC), Purkinje (PC), deep cerebellar nuclei (DCN) and inferior olive (IO) cells. Stellate and Basket cells function as inhibitory interneurons inhibiting Purkinje cell dendritic tree. Granule and deep cerebellar nuclei neurons are glutamatergic (excitatory) in nature while other neurons are GABAergic (inhibitory) However, in this paper, we have excluded two cell types (stellate and basket) since our focus was mainly on granular layer network circuitry and relay of signals to Purkinje layer.

In this paper, we reproduced neuronal firing patterns using computationally efficient simple spiking models which can mimic

spike timing as well as spiking properties without reproducing ion channel dynamics and spatial geometry. Since detailed models contain many ion channel dynamics, simulating at network level makes them computationally expensive. We have showed the reconstruction of *in vitro* and *in vivo* firing dynamics and electro responsiveness of biophysical models using adaptive integrate-and-fire neuron models.

Parametric values were estimated through an exploratory search using particle swarm optimization technique in the parameter space. With fine-tuned parameters, AdEx integrate and fire model reproduced known cerebellar neuronal firing patterns. In order to validate the biophysical patterns reproduced by AdEx integrate and fire model, we used simulations of standard electrophysiological current clamp protocol to plot frequency-current relationship and validated it to experimental data. Some of the cerebellar interneurons are spontaneously firing in nature [26]. To simulate such neurons, we set the injected current to zero and then adjusted the rest of the parametric values to attain the desired neuronal firing behavior.

2. METHODS

This study aims at reproducing spiking dynamics based on experimental data from p17-23 rat cerebellum [6, 22]. Detailed models such as deep cerebellar nuclei [27], Purkinje cell [17], inferior olivary [20] were used as references for physiological data for matching the firing patterns.

2.1 Simple Neuronal Model

We have used adaptive exponential integrate and fire model (AdEx) [24] as an elegant model to reconstruct firing dynamics of cerebellar neurons. The model involved two equations (Eq. 1 and 2), Eq. 1 regulated the state of the neuron (membrane potential) and Eq. 2 regulated the adaptation constant.

$$C \frac{dV}{dt} = -g_L(V - E_L) + g_L * \Delta T * \exp\left(\frac{V - V_T}{\Delta T}\right) - w + I \quad (1)$$

$$\tau_w \frac{dw}{dt} = a(V - E_L) - w \quad (2)$$

where, C is the membrane capacitance, g_L represents leak conductance, E_L denotes resting potential, ΔT represents slope factor and V_T denotes threshold potential. Variable ‘ w ’ describes the adaptation factor within the membrane potential and ‘ a ’ represents the relevance of sub-threshold adaptation [4]. Here, exponential term resembles similar phenomena to that of early activation of voltage-gated sodium channels. ‘ I ’ refers to injected current applied from external source.

The model upon reaching peak threshold would reset to its resting potential and the hyperpolarization did not need any extra dynamics.

If ($V > 30$ mV) then

$$V = V_r$$

$$w = w + b$$

V_r refers to resting membrane potential and ‘ b ’ refers to spike-triggered adaptation constant. Passive membrane time constant is modeled as (Eq. 3):

$$\tau_m = C_m / g_L \quad (3)$$

Current injection was used to reproduce current clamp protocol and synaptic dynamics (injecting synaptic current, I_{syn}). Here, synaptic properties were reproduced using simple kinetic schemes for α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

(AMPA) receptor, N-methyl-D-aspartate (NMDA) receptor and gamma-Aminobutyric acid (GABA) receptor. AMPA receptor kinetics was adapted from [3] while NMDA receptor kinetics (Eq. 8, 9 & 10) adapted from [23].

$$gnmda = mgblock(vv) * (Ron + Roff) * gmax * nmdafactor \quad (8)$$

$$inmda = gnmda * (vv - 0) \quad (9)$$

$$mgblock = 1 / (1 + \exp(0.062 * -vv * \left(\frac{mg}{3.57}\right))) \quad (10)$$

Where, Ron refers to receptor on state and $Roff$ refers to receptor off state. ‘ $gmax$ ’ refers maximal conductance and ‘ $nmdafactor$ ’ refers to scaling factor. ‘ $mgblock$ ’ refers to magnesium block dynamics which regulates gating of NMDA channels. ‘ vv ’ refers to the AdEx integrate and fire model membrane potential.

For simulating inhibitory dynamics, GABA (Eq. 11, 12, 13 & 14) has been modeled with the following equations which was also adapted from [3].

$$ggaba = B - A \quad (11)$$

$$B = -\frac{B}{\tau_{au2}} \quad (12)$$

$$A = -\frac{A}{\tau_{au1}} \quad (13)$$

$$igaba = ggaba * (vv + 70) \quad (14)$$

Where, τ_{au1} and τ_{au2} are time constants. ‘ A ’ and ‘ B ’ expressions control the GABA dynamics.

2.2 Parametric Values for Cerebellar Neurons

Table 1 shows parametric values for reconstructing firing models of cerebellum. For all simulations, we used variable time step method (dt) in NEURON. We have obtained the parametric values for different neurons through optimization. While fine-tuning the parameters of the mathematical model, we have taken frequency and spike time prediction into consideration for accuracy. Spike timing of these spiking models was approximately ± 2 milliseconds (ms) when compared with detailed biophysical models. Manual choice of parameter variables was avoided since it was time-consuming and was substituted by particle swarm optimization technique.

2.2.1 Parameter fit using PSO

Using Particle Swarm Optimization (PSO) [25], the parameters of AdEx integrate and fire model were estimated to the best fit. In the implementation, a swarm of particles were considered in the assigned parametric space (l_o , u_o) with lower (l_o) and upper (u_o) boundaries. Two equations were mainly used for updating particle velocity (Eq. 4) and particle position (Eq. 6).

$$v = v + c1 * rand(0,1) * [pbest - present] + c2 * rand(0,1) * [gbest - present] \quad (4)$$

Where v refers to particle velocity, $pbest$ refers to particle best initial position and $present$ refers to present position, $gbest$ refers to global best position. ‘ $c1$ ’ and ‘ $c2$ ’ are used as learning factors.

Algorithmic implementation for neuronal parameters using PSO:

1. Solutions are considered as random particles.
2. Fitness value for each particle is calculated.

3. Check if the fitness value is better than the previous best fitness values and then update the particle best with this new best fitness value.
4. Steps 2 and 3 are repeated for all solutions.
5. Particle with the best fitness value is considered as global best.
6. Particle velocity was updated using the below equation
$$v = v + c1 * rand(0,1) * [pbest - present] + c2 * rand(0,1) * [gbest - present] \quad (5)$$
7. Positions are updated based on the velocity. 'x' refers to position
$$x = x + v \quad (6)$$
8. Steps 6 and 7 are repeated for each solution.

Table 1 Parametric values used for different types of neurons

Parameter	Value					Description
	GrC	GoC	PC	IO	DCN	
C	1	511	100	350	200	Membrane Capacitance
gL	10	13.1	10	10	10	Leak Conductance
EI	-70	-58	-65	-65	-70	Reversal Potential
ΔT	2	7	2	2	2	Slope Factor
VT	-50	-60	-50	-50	-50	Threshold Voltage
τ_w	0.71	14.65	1	1	8	Adaptation time constant
I	20	0	0	0	0	Injected Current
A	-10	-20	-13	-13	-20	Subthreshold adaptation
B	265	1033	260	1200	675	Spike-triggered adaptation

2.2.2 Similarity measure

A measure was used for comparing spike trains from experimental data or validated biophysical models with that of the spiking model [14]. Several measures miss the temporal structure in spike trains [14]. Many earlier studies [4, 14–16, 18] reported the usage of coincidence factor Γ which can be computed easily.

So we ran the spiking model and counted the number of spike trains and estimated total number of coincidences between model and data (or trace from previously published detailed models). In one of the earlier studies by [25], it was shown that temporal window size parameter (δ) could be 4 ms [25]. This coincidence factor (Eq. 7) (also called as gamma factor in [25]) is defined by:

$$\Gamma = \left(\frac{2}{1-2\delta r_{exp}} \right) \left(\frac{N_{coin} - 2\delta N_{exp} r_{exp}}{N_{exp} + N_{model}} \right) \quad (7)$$

where, N_{coin} is the number of coincidences, N_{exp} and N_{model} refer to number of spikes in experimental and model spike trains

respectively and r_{exp} refer to average firing rate in experimental train [25]. We, thereby, used coincidence factor as fitness function for particle swarm optimization method in order to generate AdEx integrate and fire model parameter values.

3. RESULTS

3.1 Model Reconstructs Granule Neuron Properties *in vitro* and *in vivo*

We reproduced the *in vitro* and *in vivo* granule neuron firing properties with good spike-time precision. Our reference model was multi-compartmental granule neuron [9], where the input arriving through mossy fibers could be a single spike (*in vitro*) or burst (*in vivo*). Simple spiking models not only reproduces external injected current properties but also synaptic properties.

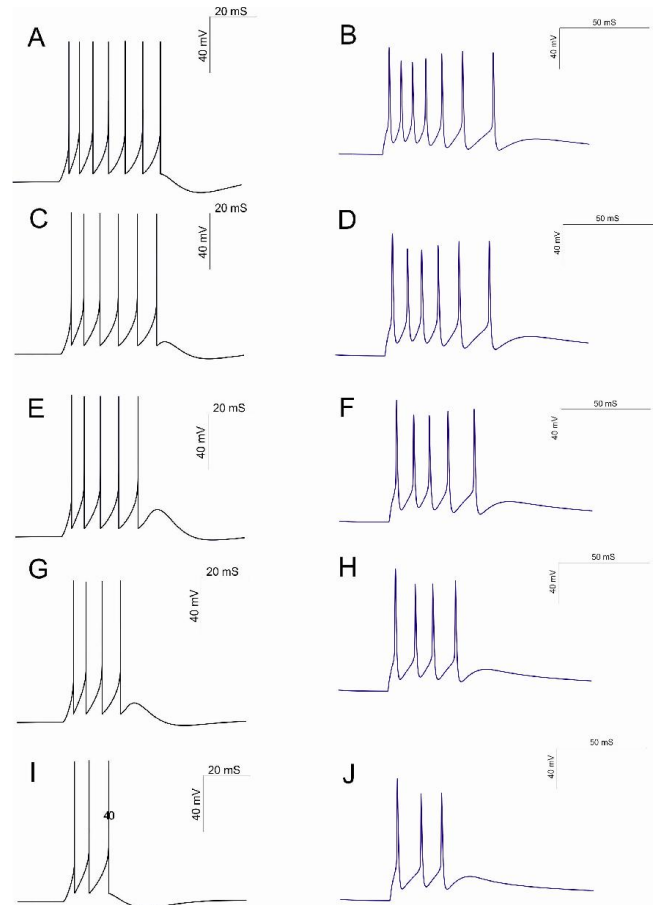


Figure 1. *In vivo* granule neuron firing properties for AdEx integrate and fire model and biophysical model. Left side (A, C, E, G, I) shows firing properties for different combinations of excitatory and inhibitory inputs in AdEx integrate and fire model. Right side (B, D, F, H, J) shows firing properties in biophysical model for different combinations. Fig. 3A and 3B show for 4 excitatory inputs with no inhibitory inputs. Fig. 3C and 3D show for 4 excitatory input with 1 inhibitory input. Fig. 3E and 3F show for 4 excitatory inputs with 2 inhibitory inputs. Figs. 3G and 3H show for 4 excitatory inputs with 3 inhibitory inputs. Figs. 3I and 3J show for 4 excitatory inputs and 4 inhibitory inputs.

Each model neuron (AdEx integrate and fire) received different excitatory and inhibitory connections. Excitatory inputs are given through mossy fibers and inhibitory inputs through Golgi cell. Figure 1 shows firing patterns for *in vivo* like input through mossy fibers mimicking short burst observed in experimental scenario. A single granule cell can receive excitatory input from four different mossy fibers and 4 inhibitory inputs from Golgi cell. Inhibitory input is given to the granule cell with a delay of 4 ms when compared to excitatory input. Figure 1 shows that all different combinations (E4I0, E4I1, E4I2, E4I3, E4I4) were repeated for both simple spiking model as well as biophysical model. The simple spiking model showed frequency match for all the combinations and almost similar spike-timing. Runtime for simulations was 100 ms. Variation of around ± 4 ms was seen when compared which was significant in considering the model as accurate. While detailed mathematical GrC model took 3.85 seconds for 200ms simulation time, simple spiking model took 0.04 seconds for 200 ms simulation time, for *in vivo* like burst-input receiving 4 excitatory inputs and 1 inhibitory input.

3.2 Computational Reconstructions of Spike Dynamics of Cerebellar Neurons

We were able to simulate cerebellar neuronal firing patterns (see Figure 2) with AdEx integrate and fire neuron. All models demonstrated comparable frequency and spike timing to that of detailed mathematical models. We have also used current clamp technique to check the frequency with varying current amplitude. Comparison has been made for different current amplitudes between simple spiking model and detailed model. Since spike-timing is very crucial to simulate large-networks, we aimed at precise spike-timing for these simple spiking neurons. We also tested *in vitro* and *in vivo* firing patterns of multi-compartmental granule cell model [9] and replicated the same with the simple spiking model.

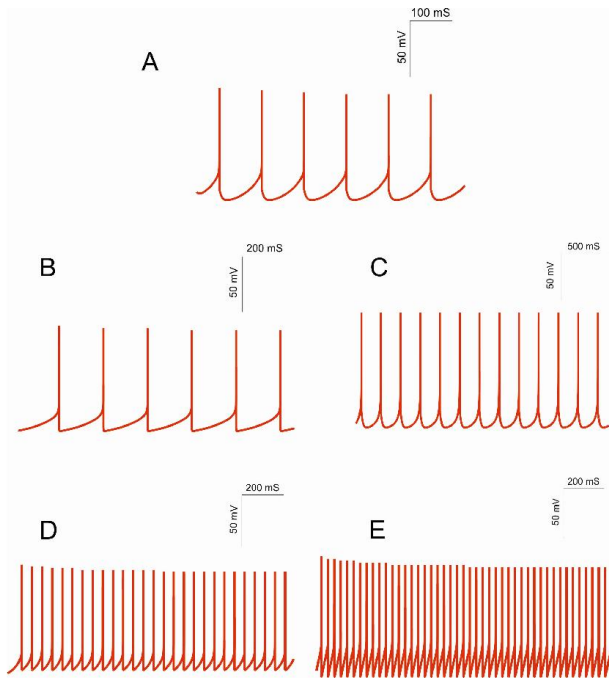


Figure 2. Cerebellar neuronal firing patterns with AdEx integrate and fire model. (A) Firing property for Deep Cerebellar Nuclei (DCN) (B) Firing property for Inferior Olivary Neuron (C) Firing property for Golgi cell (D) Firing

property for Purkinje cell. (E) Firing property for granule neuron.

Except granule cell, all other neurons have spontaneous firing nature. Granule cell adapted from D'Angelo paper[6] was used with 8 pA current injected to get repetitive spiking. AdEx integrate and fire model was used to simulate similar electrophysiological behavior of adapted granule cell model. Golgi cell adapted from [26] was used and its frequency was known to be around 8Hz. Simple spiking model was used to simulate similar electrophysiological behavior.

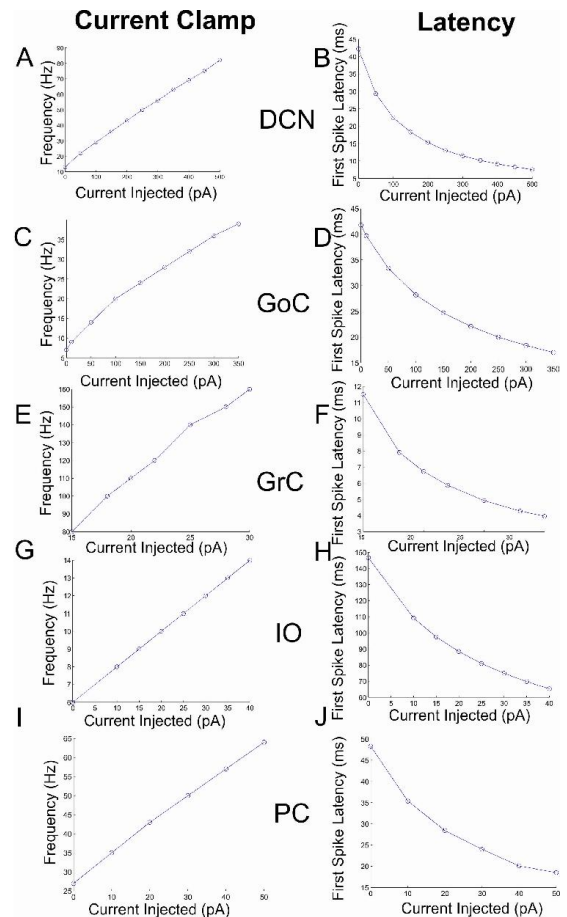


Figure 3. Current clamp and First-spike latency plots. A, C, E, G, I show current clamp graphs for DCN, GoC, GrC, IO and PC. While B, D, F, H, J show latency graphs for the same.

Deep cerebellar nuclei (DCN) behavior was adapted from the physiological data given in [27]. We have used the brain slice recording of spontaneous firing DCN and generated AdEx integrate and fire model firing behavior in similar fashion. Purkinje cell electrophysiological behavior reported in [17] was used to match electro-responsiveness of AdEx integrate and fire model. Llinas [20] reported that inferior olivary neurons fire with 4-8 Hz frequency and AdEx integrate and fire model was tuned to mimic similar frequency in firing. All the models showed closely significant similarity to frequency and spike timing as in experimental data [17,27]. To check the range of robustness, we applied current clamp across various ranges and obtained the respective frequencies for different models. Also, we obtained

first spike-latency for these different models as a measure of validity.

3.3 Neuronal Electroresponsiveness Properties

For different models, we injected current and observed frequency as well as latency. Frequency graphs (see Figure 3) showed gradual increase with injected current and latency graphs showed gradual decrease with increase in current amplitude (pA). For each cell, the injected current range was different. Golgi cell allowed current injections in the range of 10 pA to 350 pA while smaller and electrotonically compact granule cells allowed range between 15 pA to 30 pA. DCN was injected with current range from 50 pA to 500 pA while Purkinje cell was injected with current from 10 pA to 50 pA. Inferior olivary neuron injected current range was from 10 pA to 40 pA. The injected currents were in tune with experimental protocols on brain slices. These results also suggest that the manual tuned simple spiking models replicated recorded neuronal firing patterns with considerable accuracy.

4. DISCUSSION

In this paper, we were able to computationally reconstruct single neuron firing patterns using AdEx integrate and fire model. Both current clamp and latency graphs showed the reproducibility across multiple ranges of injected current. Synaptic dynamics incorporated through the equations showed that both frequency and spike timing could be matched closely to experimental data and comparable with those of detailed mathematical models although a variation of +/- 4ms for long bursts was observed.

These types of models could be used for constructing large-scale networks to simulate tissue function or reconstructing EEG or fMRI-BOLD signals. Although AdEx integrate and fire models could reproduce known firing neuronal patterns, not all characteristics of the active neuronal cable can be reconstructed as seen with detailed models with multi-state ion-channel behaviors. Simulation time was realistic when compared to the unrealistic long computation times with detailed models [9]. Burst-burst transmission modality in granule neuron and high frequency firing critical for the granular layer could be reconstructed [22]. Combining granule neurons and Golgi cell, this study can be extended to build a large-scale network model of the cerebellum input layer that will help to understand coincidence detection properties and spatial pattern separation of sensory and tactile inputs received by the cerebellum. This work is an attempt in modeling spike dynamics of a central neural circuit in order to understand physiological dysfunctions such as ataxia and to reconstruct long sought spatio-temporal filtering predicted by the Motor learning theory [1].

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