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An integrate-and-fire model of a cerebellar granule cell

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Abstract

We present a simple spiking model that extends the classical integrate-and-fire neuron to reproduce the different dynamical behaviors observed in cerebellar granule cells. The model is two dimensional: in addition to the membrane potential V, we consider a gating variable that models a slow K^+ current. This current plays a major role in generating the rhythmic behavior and resonance in the model. Despite its simplicity this model is able to reproduce most of the properties observed in granule cell recordings and in numerical simulations with high-dimensional Hodgkin–Huxley models.

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Keywords: Cerebellum; Integrate-and-fire neuron; Resonance

1. Introduction

The cerebellum is involved in many aspects of motor control and sensorimotor coordination. The architecture of the cerebellar cortex is well defined and is composed of three layers: the granular, molecular and Purkinje cells layer. The major afferents to the cerebellum are the mossy fibers that carry sensory and neocortical informations and that make synapses onto the granule cells in the input layer, the granular layer, of the cerebellum. The cerebellar granular layer contains a large number of granule

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cells (on the order of 10^{12} in humans, i.e., more than the overall number of neurons in the cerebral cortex) and there are $\approx 10^3$ as many granule cells as mossy fibers. The granule cells have been suggested to be involved in expansion recoding [8] that would be used to decorrelate and build a sparse representation of mossy fibers inputs for further processing in the molecular and Purkinje layers [1,8,10].

A granule cell represents the basic computational unit of the granular layer since they receive the external inputs and transmit their output to the Purkinje cells. A clear understanding of single-cell properties, as well as a biophysically reasonable model, yet computationally simple, are needed before studying the behavior of the granular layer network as a whole. A granule cell shows interesting responses even in rather simple experimental conditions. Resonance and bursting behaviors have been observed in rat cerebellar granule cells in patch-clamp recordings [4]. Oscillations and resonance are suggested to arise from the interplay between a slow repolarizing potassium current $I_{\text{K-SLOW}}$ and fast persistent depolarizing sodium current $I_{\text{Na-P}}$. These conclusions are supported by experimental studies as well as by a detailed Hodgkin–Huxley model of a granule cell written in the NEURON simulation software [4]. This single-compartment model is a set of 15 coupled differential equations that mimics the evolution of 10 different ionic currents, plus additional equations for intracellular calcium concentration and for membrane potential. The model reproduces the time course of measured ionic currents under different conditions, as well as oscillatory, resonance and bursting behaviors of granule cells. Even though these Hodgkin–Huxley-type models are biophysically precise and can reproduce in great detail the dynamics of neurons, they are computationally inefficient for simulating large networks due to the large numbers of coupled differential equations involved. In addition, they are often difficult to understand and analyze due the presence of several coupled equations and parameters, and relatively simple phenomena can be obscured by the complexity of the model. A possible strategy is to use simpler models such as integrate-and-fire model [7]. An integrate-and-fire neuron, in its simplest form, is a simple linear integrator with a threshold mechanism for spike generation: When the membrane potential crosses a certain threshold, the neuron spikes, and the potential is reset. Despite its simplicity it can generate very realistic-looking spike trains. This basic integrate-and-fire neuron has been extend in to model many interesting non-linear phenomena observed in neurons, such as oscillations [9], resonance [5] and bursting [11].

We propose here a two-dimensional integrate-and-fire model for studying the behavior a single granule cell. Our simplified model can be directly related to the multidimensional model presented in [4] and mentioned above. Basically, the simplified model is obtained by removing all the currents involved in spike generation, and considering the fast currents as instantaneous ones. This mapping helps the calibration of the parameters that can be easily derived from the more detailed model, which in turn is finely tuned to match the biophysical data. In our model we have considered the following active currents: a fast sodium current $I_{\text{Na-p}}$, a fast inward rectifier current $I_{\text{K-ir}}$ and a slow potassium current $I_{\text{K-slow}}$. In addition, we have a passive leakage current I_{Leak} and an external applied current I_{App}. The fast currents $I_{\text{Na-p}}$ and $I_{\text{K-ir}}$ have relaxation times of the order of a few milliseconds. Therefore, compared to $\simeq 60$ ms for $I_{\text{K-slow}}$, these fast currents can be considered instantaneous and we can replace the

kinetics of their gating functions with the corresponding steady state values ($a_\infty(V)$ and $m_\infty(V)$, respectively). In addition, all the currents needed for spike generation are not explicitly considered, since we model it with a simple threshold process. The simplified neuron can be described by the two equations

$$C\frac{dV}{dt} = g_{\text{K-slow}}\ (V - V_K)n(V,t) + I_{\text{Active}} + I_{\text{Leak}} - I_{\text{App}},$$

$$\frac{dn}{dt} = \frac{n - n_\infty}{\tau_n},$$

where V is the potential across the membrane with a capacitance C, and

$$I_{\text{Active}} = g_{\text{K-ir}}(V - V_K)m_\infty(V) + g_{\text{Na-p}}(V - V_{\text{Na}})\ a_\infty(V),$$

$$I_{\text{Leak}} = g_{\text{LeakA}}(V - V_{\text{LeakA}}) + g_{\text{GABA-A}}(V - V_{\text{GABA-A}}).$$

I_{Active} is the sum of active currents (for sake of clarity we have separated the contribution of $I_{\text{K-slow}} = g_{\text{K-slow}}\ (V - V_K)\ n(V,t)$ from this expression) and I_{Leak} is the contribution of the two leakage currents: non-specific and *GABA-A*. Finally, $n(V,t)$ is the time-dependent gating variable that regulates $I_{\text{K-slow}}$ dynamics. This model still presents a large numbers of parameters (see Table 1); their number can be further reduced by introducing dimensionless parameters, such as measuring the conductance in C/τ unit, or by merging together the currents with no explicit dependence on time (i.e., I_{Active}) and, of course, replacing the two passive leakage resistors with the corresponding equivalent circuit. However, in order to keep clear the biological meaning of each parameter, in this paper we will keep all the equations in their original form. In Table 1, we show the parameter values used in all simulations, following Ref. [4], whose choices are based on experimental data. We tested our model with a variety of external inputs; following the experiments in [4], we will focus here on two different inputs: a current step and an sinusoidal current. In Fig. 1 we show the repetitive firing of the simplified model. We injected a strong depolarizing current step, 10 and 20 pA in Fig. 1A and B respectively, the neuron starts firing regularly with a slight adaptation. The input–output relationship for the neuron is shown in Fig. 2A. The frequency increases linearly with the input current in a range of 8–32 pA. Below 8 pA, our neuron with the current set of parameters does not reach the spiking threshold, in agreement with experimental [1,2] and previous modeling (see Fig. 8A in Ref. [4]) results. Decreasing the input current the neuron shows persistent sub-threshold oscillations. Phase plane analysis, varying $g_{\text{K-slow}}$, shows that the mechanism for the onset of oscillations is an Hopf bifurcation (i.e., frequency at onset has a non-zero minimum), and in the oscillatory state, the corresponding period does not vary greatly with $g_{\text{K-slow}}$. Sub-threshold oscillatory phenomena can strongly affect the temporal coding capability of the neuron (e.g., see [5,9] making it sensitive to the timing of the stimulus: a stimulus can evoke a spike or not depending on how its arrival time is related to the phase of oscillation.

Injecting sinusoidal currents of different frequency we observe a resonant response, see Fig 2B. In this simulation, we have added a sinusoidal current of frequency f to

Table 1
This table reports the values of parameters used in the model

Parameters of the model				
Current type	g_{max}, (μS/cm^2)	V_{rev} (mV)	Gating function parameters	
Ionic currents				
$I_{\text{K-ir}}$	900	-84.69		$A_m = 1.28$
			$m_\infty = \frac{1}{1 + A_m \exp(-\frac{v - v_{m0}}{k_m})}$	$v_{m0} = -83.94$ mV
				$k_m = 14.49$ mV
$I_{\text{Na-p}}$	20	-87.39		$v_{a0} = -42$ mV
			$a_\infty = \frac{1}{1 + \exp(-\frac{v - v_{a0}}{k_a})}$	$k_a = 5$ mV
$I_{\text{K-slow}}$	180	-84.69		$v_{n0} = -30$ mV
			$n_\infty = \frac{1}{1 + \exp(-\frac{v - v_{n0}}{k_n})}$	$k_n = 6$ mV
				$A_{\alpha n} = 3.3\ \text{s}^{-1}$
			$\tau_n = \frac{1}{\alpha_n + \beta_n}$	$A_{\beta n} = 3.3\ \text{s}^{-1}$
				$v_{\alpha n0} = -30$ mV
			$\alpha_n = A_{\alpha n} \exp((v - v_{\alpha n0})/k_{\alpha n0})$	$k_{\alpha n0} = 40$ mV
				$v_{\beta n0} = -30$ mV
			$\beta_n = A_{\beta n} \exp((v - v_{\beta n0})/k_{\beta n0})$	$k_{\beta n0} = -20$ mV
I_{LeakA}	56.8	-58		
$I_{\text{GABA-A}}$	21.7	-65		
Others parameters: $C = 1\ \mu\text{F/cm}^2$, $V_{th} = -25$ mV				

g_{max} is the maximum conductance value used for each current, V_{rev} is the ionic reversal potential and V_{th} is the spiking threshold. The values of parameters are derived from Ref. [5].

a weak depolarizing step

$$I_{\text{App}} = I_0 + I_1 \sin(2\pi f t),$$

with $I_0 = 2$ pA and $I_1 = 4$ pA in the case shown in Fig 2B., spike bursts are generated in correspondence with the positive phase of the oscillatory current. We measured the spike frequency within the burst as the average interspike intervals between following spikes. The resonance frequency is in the range of 6–10 Hz and in good agreement with experimental observations [4]. Resonant neurons can play an important role in temporal coding; e.g., one can activate selectively a certain neuron sending a burst at its resonant frequency [5].

In conclusion, we have proposed a two-dimensional model of a neuron that is able to capture the main features of a cerebellar granule cell behavior, such as oscillations and resonance. This simplified model can be derived from a multi-dimensional Hodgkin–Huxley neuron introduced in [4]. The use of a low-dimensional model has the advantage of a greater computational efficacy, that allows to implement large scale networks and

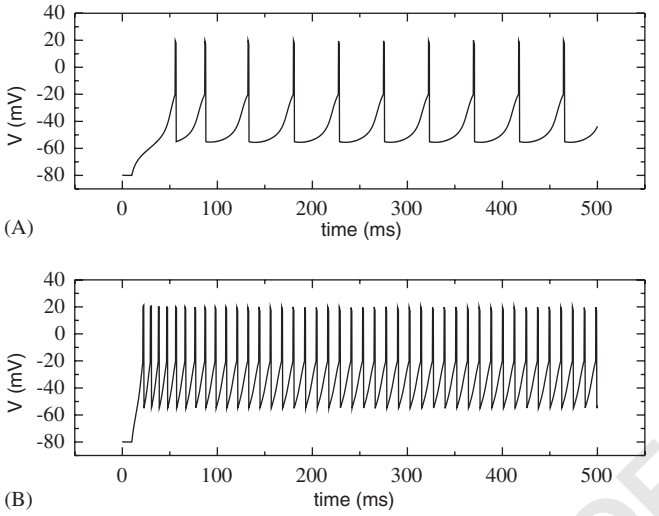

Fig. 1. Current clamp simulations: Two traces are shown: (A) 10 pA, (B) 20 pA.

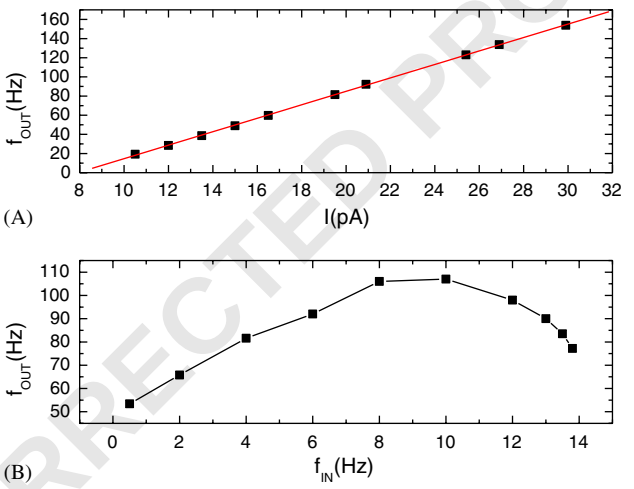

Fig. 2. Excitability properties. (A) The f–I curve show a linear relationship with 7.0 Hz/pA. (B) Resonance is reproduced by a step of 2 pA plus a sinusoidal wave of 4 pA amplitude with variable frequency.

of an easier identification of critical elements, sometimes obscured from the many details present in multidimensional models.

2. Uncited references

[3,6]

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