BioSystems 94 (2008) 10–17

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

Event-driven simulation of cerebellar granule cells

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ARTICLE INFO

Article history:
Received 31 May 2007
Received in revised form 31 October 2007
Accepted 23 May 2008

Keywords:
Spiking neurons
Cerebellum
Granule cell
Event-driven simulation
Lookup table
Bursting
Subthreshold oscillations
Resonance

ABSTRACT

Around half of the neurons of a human brain are granule cells (approximately 10^{11} granule neurons) [Kandel, E.R., Schwartz, J.H., Jessell, T.M., 2000. Principles of Neural Science. McGraw-Hill Professional Publishing, New York]. In order to study in detail the functional role of the intrinsic features of this cell we have developed a pre-compiled behavioural model based on the simplified granule-cell model of Bezzi et al. [Bezzi, M., Nieus, T., Arleo, A., D'Angelo, E., Coenen, O.J.-M.D., 2004. Information transfer at the mossy fiber—granule cell synapse of the cerebellum. 34th Annual Meeting. Society for Neuroscience, San Diego, CA, USA]. We can use an efficient event-driven simulation scheme based on lookup tables (EDLUT) [Ros, E., Carrillo, R.R., Ortigosa, E.M., Barbour, B., Ags, R., 2006. Event-driven simulation scheme for spiking neural networks using lookup tables to characterize neuronal dynamics. Neural Computation 18 (12), 2959–2993]. For this purpose it is necessary to compile into tables the data obtained through a massive numerical calculation of the simplified cell model. This allows network simulations requiring minimal numerical calculation. There are three major features that are considered functionally relevant in the simplified granule cell model: bursting, subthreshold oscillations and resonance. In this work we describe how the cell model is compiled into tables keeping these key properties of the neuron model.

1. Introduction

The cerebellum is a well structured neural system conformed by three layers: granular, molecular and Purkinje layer. The granular layer contains approximately 10^{11} granule cells that represent in number of neurons half of the cells of the whole human brain (Kandel et al., 2000). The granule cells receive their inputs through the mossy fibers. The axons of the granule cells are called parallel fibers that connect with different Purkinje cells. The granular layer represents a highly divergent structure (there are approximately 10^3 granule cells per mossy fiber). Therefore they seem to be responsible for building a sparse representation of the mossy fibers inputs (Marr, 1969; Albus, 1971; Coenen et al., 2001; D'Angelo et al., 2005). But the dynamical properties of the cell are still under study (Magistretti et al., 2006; Armano et al., 2000; D'Angelo et al., 2005; Nieus et al., 2006; Mapelli and D'Angelo, 2007; Rossi et al., 2006) and detailed cell models are being built to evaluate the functional role (D'Angelo et al., 2001) of these dynamics. The neuron models can be simulated with different simulators (NEURON (Hines and Carnevale, 1997), Genesis (Bower and Beeman, 1998), EDLUT (Ros et al., 2006)) at different levels of detail. Recently an efficient event-driven lookup-table-based simulator (EDLUT) (Ros et al., 2006) has been developed to allow large-scale network simulations based on pre-compiled models and therefore avoiding intense numerical calculation during the neural-network simulation. Using EDLUT requires compiling previously the single cell behaviour into tables. This is done by means of massive calculation to characterize how the cell state changes in response to an input spike (depending on its initial status). For this purpose, lookup tables (LUTs) are built compiling the characteristic cell status traces in response to input spikes. Once these tables are built we can run event-driven large-scale network simulations without redoing any numerical calculation. The neuron state can be retrieved from these cell-characterizing LUTs at any instant in response to any input spike.

After building up cell models based on characterizing LUTs we need to validate the model in two ways:

1. *Accuracy validation*. The number of samples in each dimension of the table can be critical to the accuracy of the table-based cell approach. Therefore we simulate the cell model with a classical numerical calculation method (for instance, Euler method with a very short time step) and we compare the output spike train obtained in response to different input spike trains with the

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doi:10.1016/j.biosystems.2008.05.007

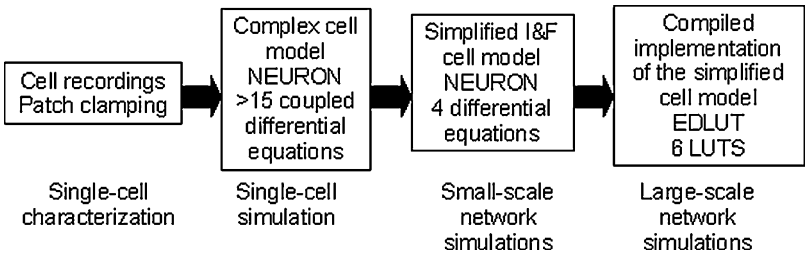

Fig. 1. Simplified-model obtaining process.

results obtained using EDLUT simulator. The comparison of the output spike trains obtained by the two methods is done using the van Rossum distance (van Rossum, 2001).

2. *Functional validation*. Key cell features must be kept. If we want to abstract a cell model that includes certain cell features that are considered relevant we also need to validate that the table-based model is able to reproduce the cell features under study.

2. Integrate-and-fire cerebellar granule-cell model

A detailed Hodgkin–Huxley model (Hodgkin and Huxley, 1952), of a granule cell defined in NEURON (with more than 15 differential equations describing its dynamics) was built to reproduce in detail the cell dynamics and evaluate the significant variables of the model (D'Angelo et al., 2001). Based on that model, Bezzi et al. (2004) presented a simplified integrated-and-fire cell model with threshold mechanism which kept important dynamical properties of the granule cell, such as subthreshold oscillations (Richardson et al., 2003), resonance (Izhikevich, 2001) and bursting (Smith et al., 2000). The model is based on two main variables: the membrane potential (V_x) and a gating variable that models a slow K^+current. Fig. 1 illustrates the process from cell behaviour characterization based on neurophysiologic cell recordings to network simulations based on simplified compiled models.

The simplified model described in Bezzi et al. (2004) is defined with the following equations:

$$C\frac{dV}{dt} = g_{k-\text{slow}}(V - V_k)n(V,t) + I_{\text{Active}} + I_{\text{Leak}} - I_{\text{Syn}} \quad (1)$$

$$\frac{dn}{dt} = \frac{n - n_\infty}{\tau_n} \quad (2)$$

where V and C are the neuron membrane potential and capacitance respectively while I_{Active} and I_{Leak} are dynamic currents of the model defined by the following expressions

$$I_{\text{Active}} = g_{k-\text{ir}}(V - V_k)m_\infty(V) + g_{\text{Na}-p}(V - V_{\text{Na}})a_\infty(V) \quad (3)$$

$$I_{\text{Leak}} = g_{\text{LeakA}}(V - V_{\text{LeakA}}) + g_{\text{GABA-A}}(V - V_{\text{GABA}-A}) \quad (4)$$

Finally we have complemented the model to include the cell synapses as input-driven conductances. I_{Syn} represents the synaptic-mediated current through the excitatory and inhibitory input-driven conductances (g_{exc} and g_{inh}).

$$I_{\text{Syn}} = (V - V_{\text{exc}})g_{\text{exc}}(t) + (V - V_{\text{inh}})g_{\text{inh}}(t) \quad (5)$$

$$\frac{dg_{\text{exc}}}{dt} = -\frac{g_{\text{exc}}}{\tau_{\text{exc}}}; \frac{dg_{\text{inh}}}{dt} = -\frac{g_{\text{inh}}}{\tau_{\text{inh}}} \quad (6)$$

Excitatory and inhibitory conductances (g_{exc} and g_{inh}) depend on the value of the conductances when they were updated the last time and the time passed since then. Each time a new input spike is received the conductaces (G_{inh} or G_{exc}) are set to a specific value that depends on the synaptic weight. Synaptic-conductance dynamics are modelled as exponential functions:

$$g_{\text{exc}}(t) = \begin{cases} 0, & t < t_0 \\ G_{\text{exc}}e^{-(t-t_0)/\tau_{\text{exc}}}, & t \geq t_0 \end{cases} \quad (7)$$

where t_0 is the input-spike arrival time and τ_{exc} and τ_{inh} are the temporal constants of the synaptic conductances.

3. Table-based approach

The neuron behaviour has been compiled into six tables. In order to use the event-driven simulator (EDLUT) the neuron state (membrane potential, synaptic conductances and other variables such as the gating variable n) need to be defined as functions of the neuron state at the instant in which it was updated the last time. Since it is an event-driven scheme the neuron state is updated each time that an event is produced (output spikes) or an input event is received (input spikes).

The model has been compiled into the following tables:

- One table of five dimensions for the **membrane potential**, $V_m = f(\Delta_t, g_{\text{exc0}}, g_{\text{inh0}}, n_0, V_0)$.
- One table of five dimensions for the **gating variable**, $n = f(\Delta_t, g_{\text{exc0}}, g_{\text{inh0}}, n_0, V_0)$.
- Two tables of two dimensions for the **conductances**, $g_{\text{exc}} = f(\Delta_t, g_{\text{exc0}})$, $g_{\text{inh}} = f(\Delta_t, g_{\text{inh0}})$.
- Two tables of 4 dimensions for the **firing prediction**, $t_f = f(g_{\text{exc}}, g_{\text{inh}}, n_0, V_0)$ and t_f end $= f(g_{\text{exc}}, g_{\text{inh}}, n0, V_0)$.

For each dimension we used a different number of samples (indicated into parentheses): $\Delta_t(44)$, g_{exc0} (10), g_{inh0} (10), n_0 (18) and V_0 (30). Therefore the larger tables require 2.37×10^6 samples (approximately 9.04 MB). The whole cell model requires 4.87×10^6 samples (19.04 MB). Once the characterizing tables are compiled using Runge–Kutta method (Forsythe et al., 1977; Cartwright and Piro, 1992), numerical calculation is almost not required during network simulations. Then we evaluate the accuracy of the model and also validate its key features (bursting, rhythmic subthreshold oscillations and resonance).

4. Experimental results

Here we show some illustrative simulations in which the behaviour of the cell model described in NEURON is compared with the behaviour of the model compiled into tables and simulated with EDLUT (Ros et al., 2006). The presented model can reproduce synaptic activation of a granule cell. Activation of 1 and 2 synapses makes subthreshold EPSPs which, in the immediately subthreshold region, become slower due to activation of persistent Na current. Activation of 3 synapses elicits a spike, which occurs with shorter delay by activating 4 synapses (Fig. 2 (a)). Inhibitory synapses can reduce the EPSP and prevent firing (Fig. 2(b)). All these properties are typical of granule cells (e.g. D'Angelo et al., 2005).