



Event-driven simulation of cerebellar granule cells

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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., Nieuws, 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.

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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; Nieuws 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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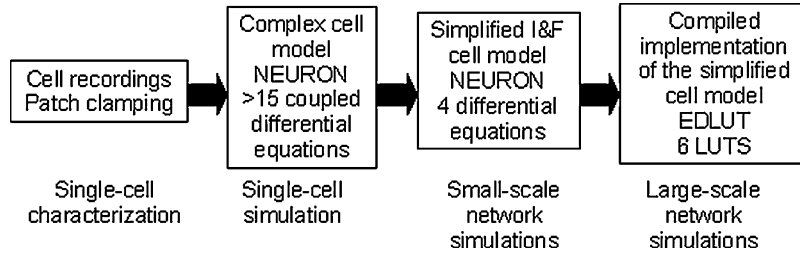


Fig. 1. Simplified-model obtaining process.

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:

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

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

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

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

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

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}).

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

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

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 conductances (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:

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

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

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).

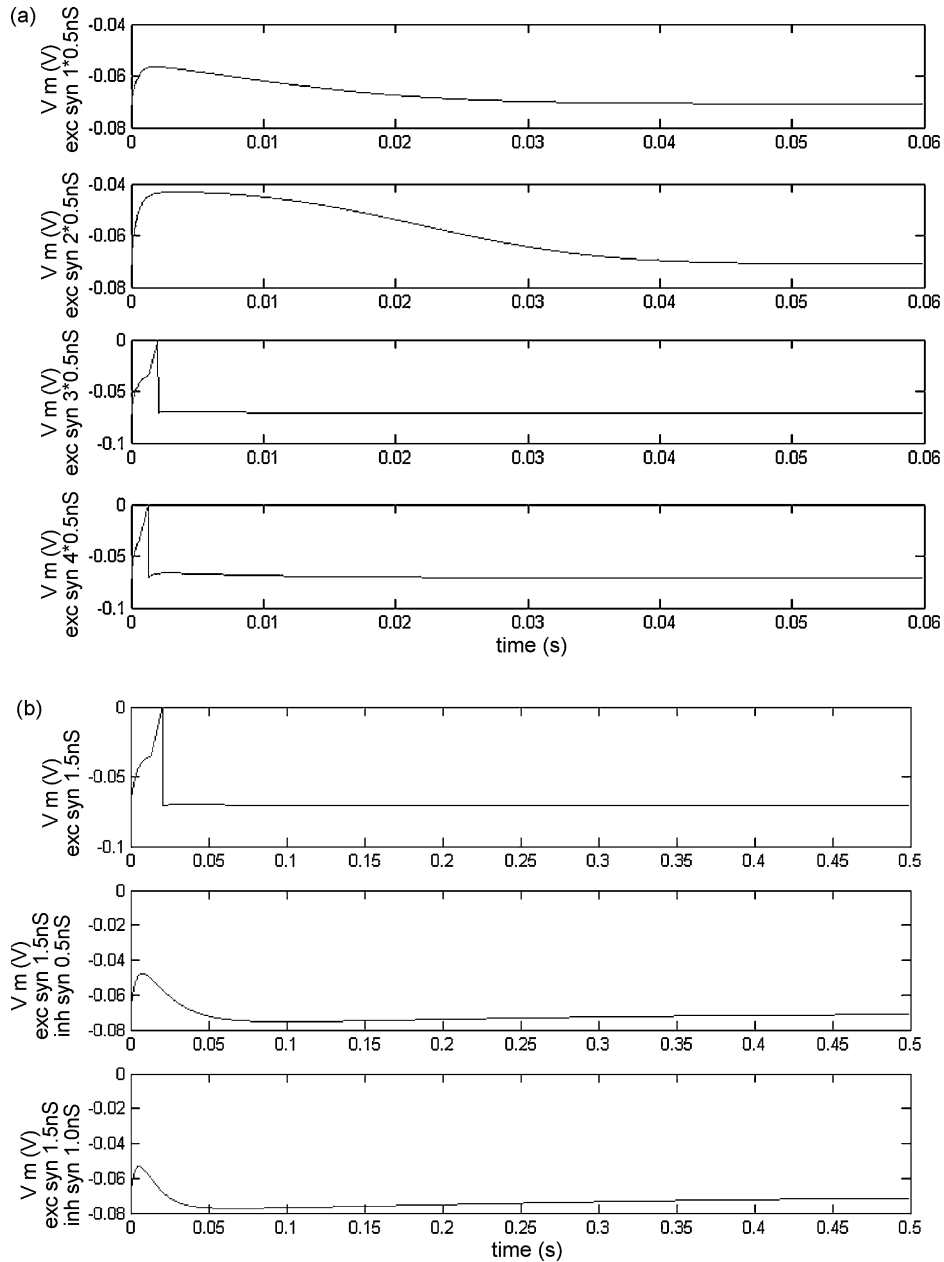


Fig. 2. Synaptic activation of a granule cell. (a) Membrane potential evolution when receiving a spike through 1, 2, 3 or 4 excitatory synapses (conductance of each synapse 0.5 nS). (b) Membrane potential evolution when receiving a spike through an excitatory synapse or through an excitatory synapse and an inhibitory synapse (conductance of the excitatory synapse 1.5 nS , conductance of inhibitory synapse 0.5 and 1.0 nS).

If we focus on evaluating the dynamics of the cell model, we must consider: oscillatory, resonance and bursting behaviours.

All the simulation results generated with EDLUT require updating the neuron state variables (retrieving their values from the LUTs) only in certain simulation instants, these instants are marked with “X” on the plots. The simulation on EDLUT can efficiently jump in time from one instant to the next one driven by input and output neural events.

4.1. Subthreshold rhythmic oscillations

The membrane potential evolution in the absence of high input activity from other cells shows a rhythmic oscillatory behaviour (Fig. 3). This oscillatory state makes the neuron more sensitive to input activity depending on the phase of this activity with

regard to the phase of the oscillation. Moreover, the coupling of those oscillations with the spiking mechanisms constitutes the base of the resonance behaviour. As shown in Fig. 3 this feature has been captured into the characterizing tables in which EDLUT simulator is based and therefore both implementations (on NEURON and on EDLUT) produce equivalent subthreshold oscillatory behaviours.

Fig. 4 (a) shows how this subthreshold rhythmic oscillation can also take place when the neuron receives spike trains through excitatory synapses. In Fig. 4(b) it is shown how with specific synaptic weights only excitatory spikes received in certain periods produce output spikes. This depends on the exact timing of these spikes with respect to the subthreshold oscillations of the membrane potential (therefore stimuli are selected depending on their phase).

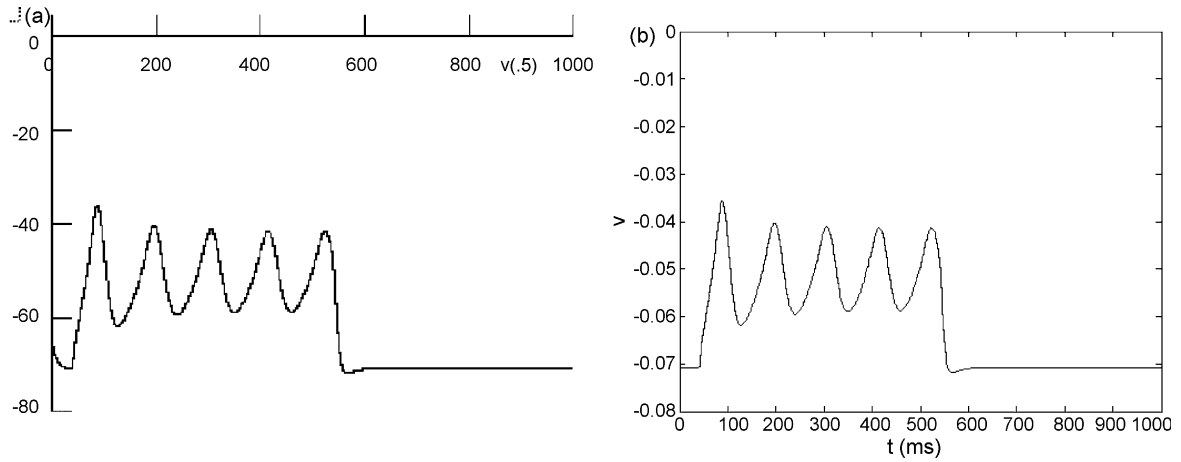


Fig. 3. Subthreshold oscillations of the membrane potential produced by a 4 pA current during 500 ms. (a) Simulation with the NEURON of the simplified model (Bezzi et al., 2004). (b) Equivalent behavioural lookup tables of EDLUT.

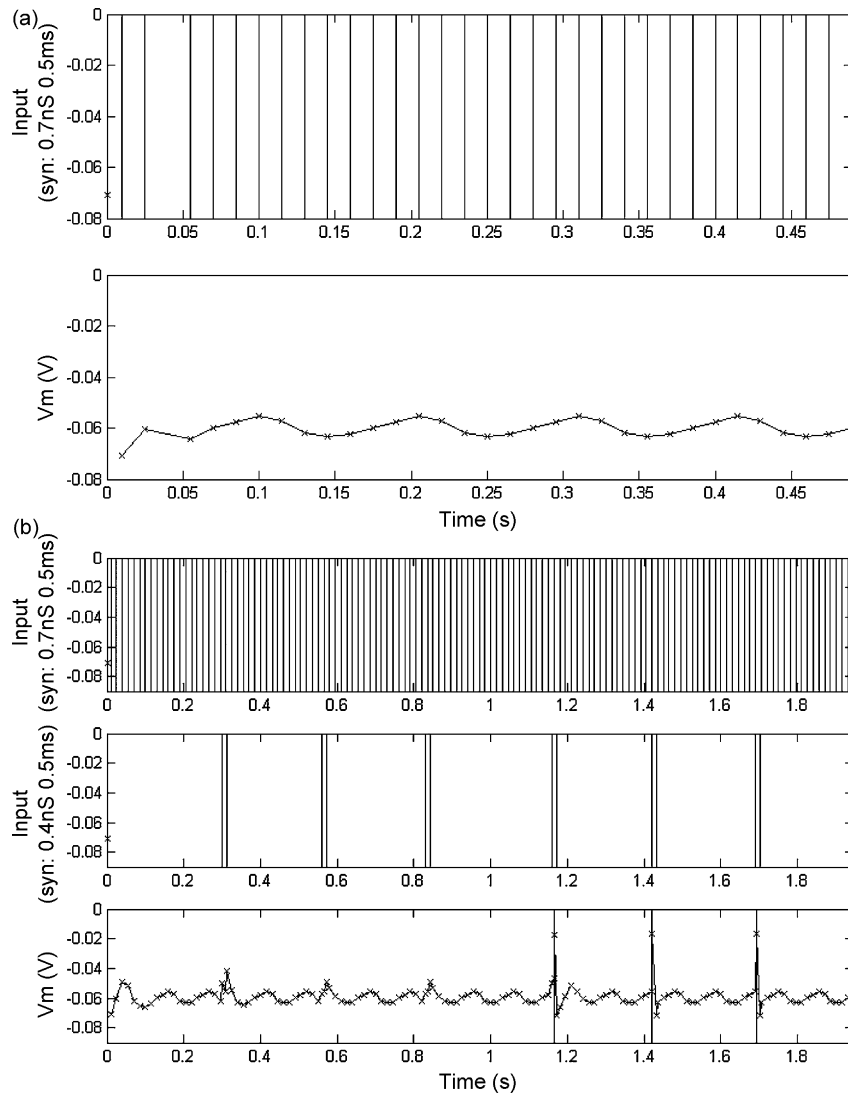


Fig. 4. Simulation with EDLUT of subthreshold oscillations in response to input spike trains (neuron state variables are updated only at times marked with a cross). (a) Subthreshold oscillations of the membrane potential produced by input spike trains. (b) Selection depending on the stimulus phase: The first three doublets are received in the same phase of the membrane-potential oscillation (when the neuron is more resistant to fire), the last three doublets are received in a phase in which the neuron is more susceptible to fire.

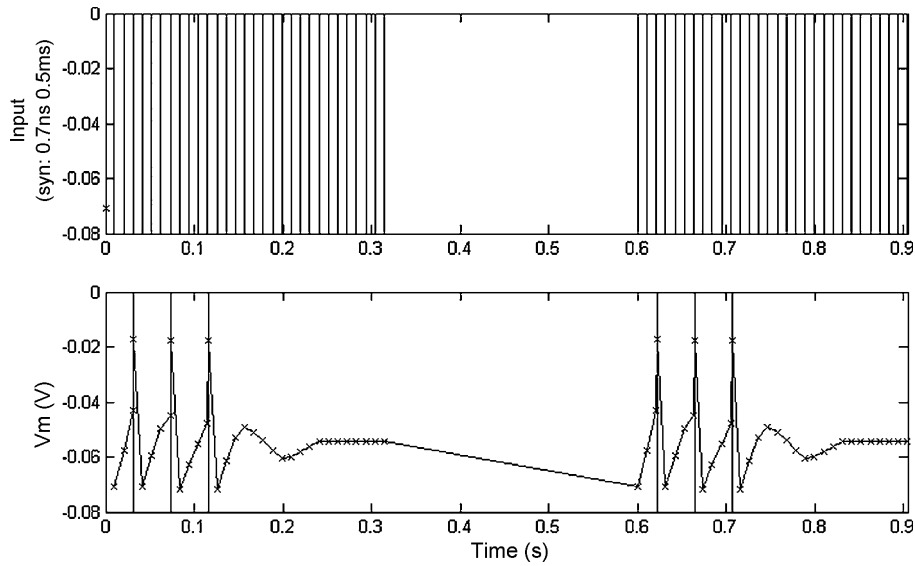


Fig. 5. Simulation with EDLUT of bursting behaviour. Triplets in response to input spike trains of 95 Hz.

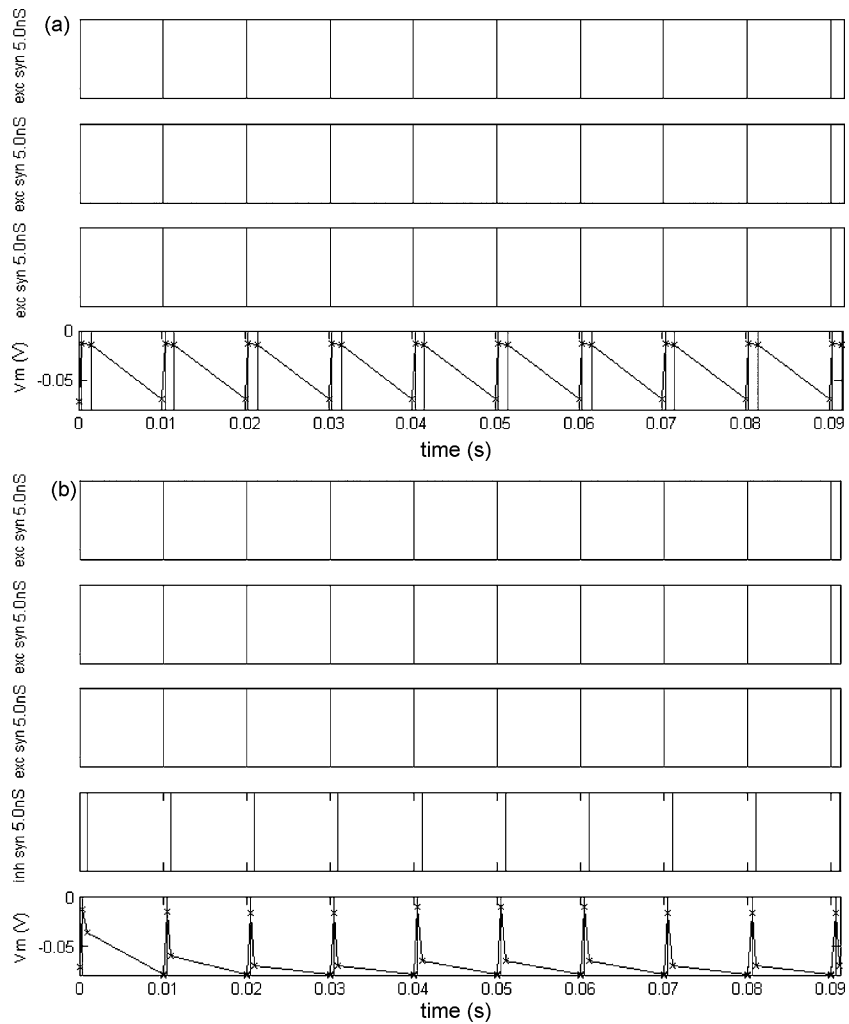


Fig. 6. Spike suppression. (a) Simulation with EDLUT of doublets in response to 100 Hz spike trains through 3 excitatory synapses of 0.5 nS. (b) The second spike of each output doublet is suppressed due to the activation of the inhibitory synapse (conductance 5.0 nS) with a spike train of 100 Hz delayed 1 ms.

4.2. Bursting behaviour

The bursting behaviour of the granule cells seems to play an important role in reliably transmitting significant stimuli. The effect of short spike bursts (two or three spikes) into the target Purkinje cells is significantly higher than single spikes (Coenen et al., 2007). In Fig. 5 it is shown how the cell model is able to produce short bursts in response to intense input activity. If a delay is introduced between excitation and inhibition spike trains, the second spike in the output doublets is specifically prevented (Fig. 6).

4.3. Resonance behaviour

In Fig. 7 (a) it is shown how injecting oscillatory currents ($4-6\cos(\omega)\text{pA}$) that match the resonance cell frequency (10 Hz) produces output spikes while injecting oscillatory input currents at other frequency (1 Hz) does not produce any output spike. Fig. 7(b) shows the maximum membrane-potential (vm) depolarization when injecting the same oscillatory currents as before. Fig. 7(c) shows the output-spike bursting frequency (fspk) in response to the same input current. In Fig. 7(d) it is shown that this effect can be

also observed when input spike trains with a certain spacing produce significantly higher responses (resonance). Therefore when the input spike train tunes the inherent temporal dynamics of the cell it generates more active responses.

5. Accuracy validation

In this section we evaluate the accuracy of the model captured on lookup tables that are used in the EDLUT approach. For this purpose we run some reference simulations using intensive numerical calculation (Euler method with a very short integration time constant ($0.5\mu\text{s}$)) with the original differential equations of the simplified model Bezzi et al. (2004). After this, we perform the same simulations in EDLUT. Finally we compare the output spike trains obtained by the two approaches calculating the van Rossum distance (van Rossum, 2001) normalized by the number of spikes (a measure of the distance between two spike trains). In this way we measure the difference between the EDLUT output spike train and the one obtained with the original model using intensive calculation method.

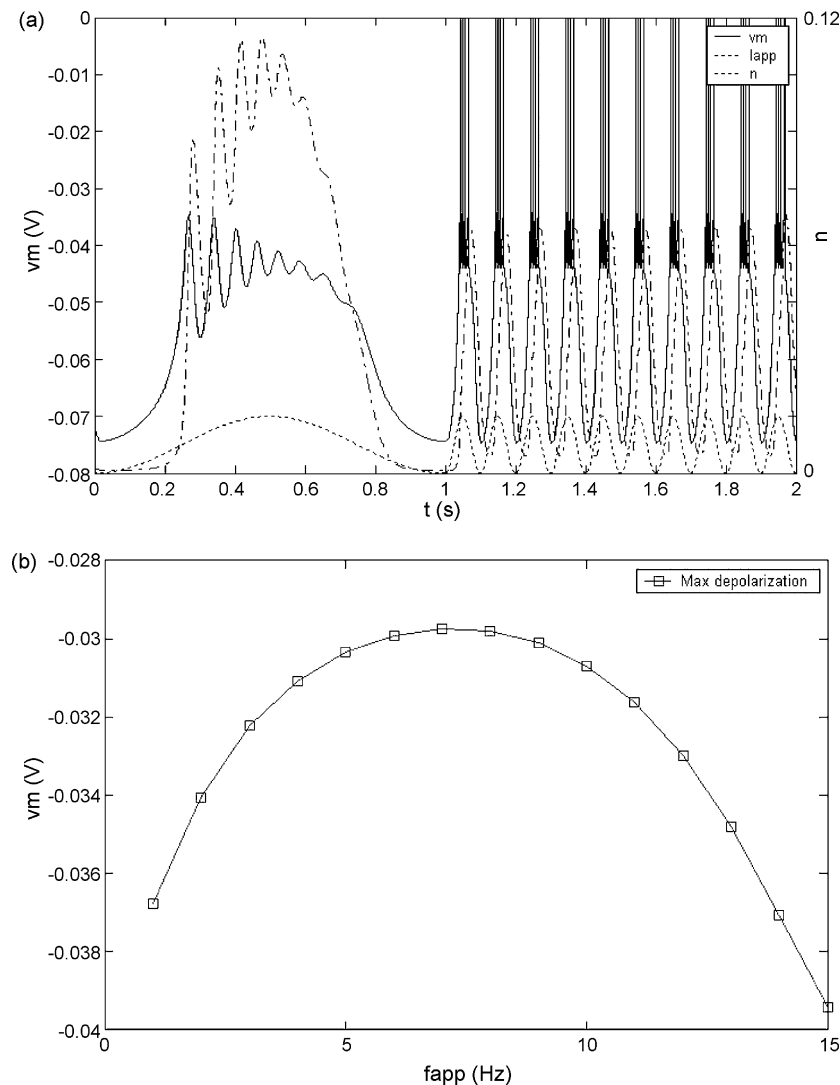


Fig. 7. Resonance behaviour. (a) Time-driven simulation of non-resonant frequency filtering. (b) Time-driven simulation showing the maximum depolarization of the membrane potential depending on the input-current frequency (action-potential generation mechanism disabled). (c) Time-driven simulation showing the output bursting frequency depending on the input-current frequency. (d) Simulation with EDLUT of input-burst selectivity depending on quiescent period.

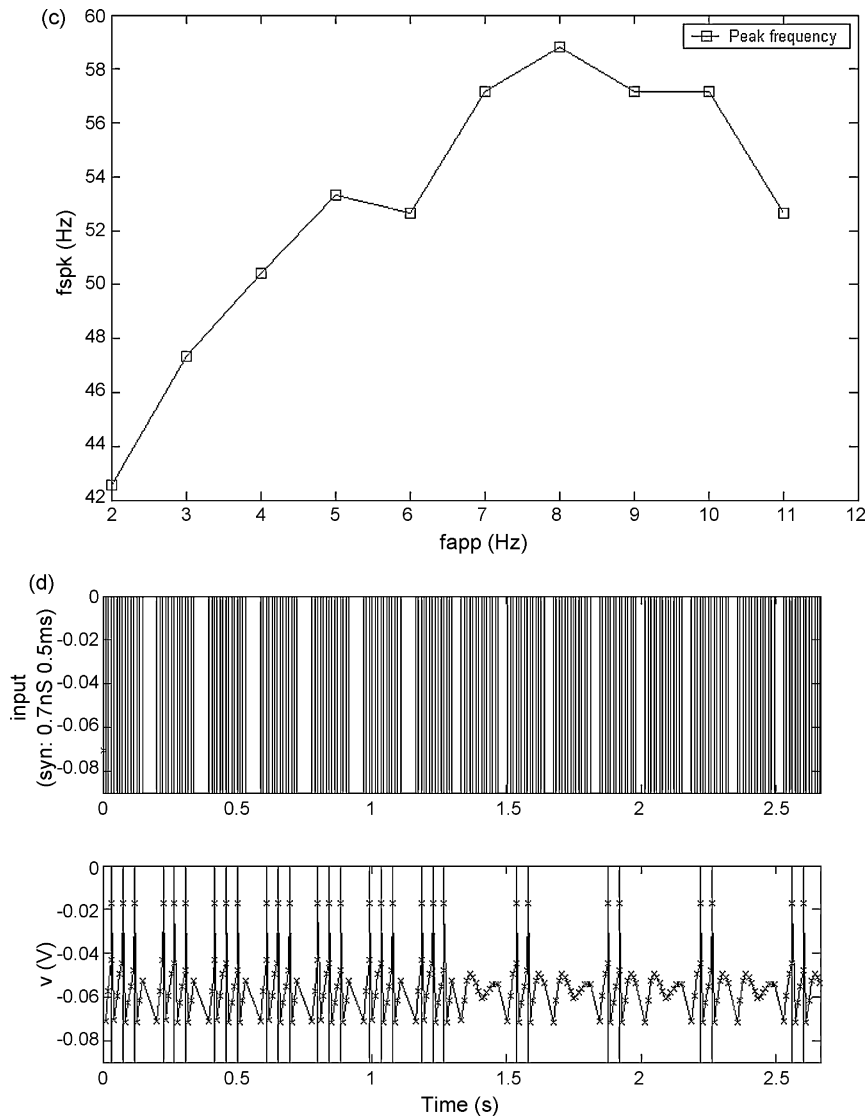


Fig. 7. (Continued).

To make the accuracy evaluation more informative we use three 100 Hz input spike trains (Poisson distribution with 0.8 standard deviation). The results are shown in Fig. 8. The curve shown in Fig. 8(a) represents the van Rossum distance (with a time constant of 10 ms) (van Rossum, 2001), between the reference output spike trains obtained using Euler integration method with a very short time step ($0.5 \mu\text{s}$) and other spike trains generated by simulations done with longer time steps. EDLUT simulator using the tables described in Section 3, produces spike trains with 0.184 of normalized van Rossum distance. Fig. 8(b) illustrates how the output spike train calculated with Euler integration method highly depends on the time step. EDLUT tables emulate the cell behaviour obtained with the Euler calculation with a short time constant ($0.5 \mu\text{s}$).

6. Computation requirements and performance

EDLUT simulator allows efficient simulation of large-scale spiking neural networks, since its performance (computation speed) does not depend on the network size but on the network activity. This simulator is especially suitable for neural structures with

sparse coding. This is the case of the granular layer (Smith et al., 2000). We have simulated a medium-scale granular layer with 2000 granule cells (and 4 Golgi cells) which produces sparse coding in the parallel fibers (i.e. at the granule cell outputs). The network receives and generates around 800 external spikes per second and produces an internal activity of around 1 million of spikes per second (encoded sparsely throughout the granular layer). Under these conditions, we are able to compute around 1.8 Millions of spikes per second (on an Intel Xeon CPU at 2.8 GHz), which reveals to be better than real time. The granule-cell characterizing table consumes 4MB and the network topology consumes 2.5MB of RAM. The cell characterization tables take 5 s to be calculated (using the Runge–Kutta method) and this needs to be done only once before the network simulations. This outstanding computing performance can be exploited to address massive studies about how different input patterns or connecting weights affect the network behaviour. For instance to study different levels of inhibition provided by the Golgi cells (Forti et al., 2006; Philipona and Coenen, 2004) or which input codes (through the mossy fibers) optimize the information transmission in this layer (D'Angelo et al., 2005; Coenen et al., 2007; Bezzi et al., 2006, 2004).

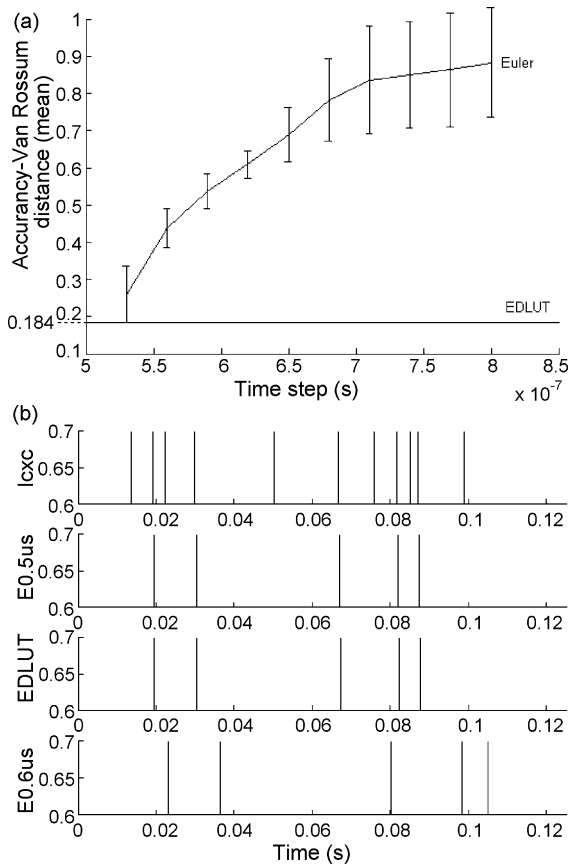


Fig. 8. Accuracy comparison. (a) Normalized van Rossum distance for the EDLUT output train and a simulation using Euler integration with different time steps. (b) Output trains produced by EDLUT and Euler simulations of 0.5 and 0.6 μ s.

7. Discussion

We have implemented using an event-driven lookup-table simulator, an integrate-and-fire neuron model with extended dynamical properties to allow oscillatory, bursting and resonance behaviours. This allows the use of efficient event-driven simulation engines such as EDLUT (Ros et al., 2006) to address large-scale network simulations. We have validated the model reproducing oscillatory, bursting and resonance behaviours easily in different experiments. This validates the model and illustrates how cell models can be compiled into tables to allow simulations with event-driven schemes based on behavioural lookup tables. We have measured the accuracy of the implemented model with several simulations comparing the results obtained through direct numerical calculation with the ones obtained with the LUT-based event-driven scheme (EDLUT simulator). Finally we have evaluated how this simulation engine achieves outstanding performance when simulating large-scale networks in which the activity is sparse (as happens in the granular layer). Future work will address specific network simulations to evaluate the impact of the cell temporal dynamics in the network behaviour. Cell dynamics are usually neglected in large-scale simulations. However we believe that these biological properties represent also a computational key factor to take into account. At the input stage of the cerebellum these properties could be involved in learning as well as in network oscillations at theta frequency. The event-driven scheme, implemented in EDLUT simulator, represents a step toward real-

time network simulations with a high degree of detailed biological characteristics.

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References

- Albus, J.S., 1971. A theory of cerebellar function. *Math. Biosci.* 10, 25–61.
- Armano, S., Rossi, P., Taglietti, V., D'Angelo, E., 2000. Long-term potentiation of intrinsic excitability at the mossy fiber - granule cell synapse of rat cerebellum. *J. Neurosci.* 15, 5208–5216.
- Bezzi, M., Nieuws, T., Arleo, A., D'Angelo, E., Coenen, O.J.-M.D., 2004. Information transfer at the mossy fiber - granule cell synapse of the cerebellum. In: 34th Annual Meeting, Society for Neuroscience, San Diego, CA, USA.
- Bezzi, M., Nieuws, T., Arleo, A., D'Errico, A., D'Angelo, E., Coenen, O.J.-M.D., 2006. Quantitative characterization of information transmission in a single neuron. In: The EPFL-Latsis Symposium—Dynamical Principles for Neuroscience and Intelligent Biomimetic Devices, Lausanne.
- Bezzi, M., Nieuws, T., Coenen, O.J.-M., D'Angelo, E., 2004. An integrate-and-fire model of a cerebellar granule cell. *Neurocomputing* 58–60, 593–598.
- Bower, J.M., Beeman, B., 1998. *The Book of GENESIS*. Springer-Verlag, New York.
- Cartwright, J.H.E., Piro, O., 1992. The dynamics of Runge-Kutta methods. *Int. J. Bifurcation Chaos* 2, 427–449.
- Coenen, O.J.-M.D., Arnold, M.P., Sejnowski, T.J., Jabri, M.A., 2001. Parallel fiber coding in the cerebellum for life-long learning. *Autonomous Robots* 11 (3), 291–297.
- Coenen, O., Bezzi, M., Arleo, A., Nieuws, T., D'Errico, A., D'Angelo, E., 2007. Information theoretic quantification of neural transmission following changes in release probability. *Computational and Systems Neuroscience (COSYNE 07)*, Salk Lake City, UTAH.
- D'Angelo, E., Nieuws, T., Bezzi, M., Arleo, A., Coenen, O.J.-M.D., 2005. Modeling Synaptic Transmission and Quantifying Information Transfer in the Granular Layer of the Cerebellum. *Lecture Notes Comput. Sci.* 3512, 107–114.
- D'Angelo, E., Nieuws, T., Maffei, A., Armano, S., Rossi, P., Taglietti, V., Fontana, A., Naldi, G., 2001. Theta-frequency bursting and resonance in cerebellar granule cells: experimental evidence and modeling of a slow K⁺-dependent mechanism. *J. Neurosci.* 21 (3), 759–770.
- Forsythe, G.E., Malcolm, M.A., Moler, C.B., 1977. *Computer Methods for Mathematical Computations*. Prentice-Hall, Englewood Cliffs, NJ.
- Forti, L., Cesana, E., Mapelli, J., D'Angelo, E., 2006. Ionic mechanisms of autorhythmic firing in rat cerebellar Golgi cells. *J. Physiol.* 574 (3), 711–729.
- Hines, M.L., Carnevale, N.T., 1997. The NEURON simulation environment. *Neural Comput.* 9, 1179–1209.
- Hodgkin, A.L., Huxley, A.F., 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* 117, 500–544.
- Izhikevich, E.M., 2001. Resonance-and-fire neurons. *Neural Netw.* 14, 883–894.
- Kandel, E.R., Schwartz, J.H., Jessell, T.M., 2000. *Principles of Neural Science*. McGraw-Hill Professional Publishing, New York.
- Magistretti, J., Castellini, L., D'Angelo, E., 2006. Kinetic and functional analysis of transient, persistent, and resurgent sodium currents in rat cerebellar granule cells in situ. *J. Physiol.* 573, 83–106.
- Mapelli, J., D'Angelo, E., 2007. Synaptic inhibition determines the spatial organization of long-term synaptic plasticity at the input stage of the cerebellum. *J. Neurosci.* 27 (6), 1285–1296.
- Marr, D., 1969. A theory of the cerebellar cortex. *J. Physiol.* 202, 437–470.
- Nieuws, T., Sola, E., Mapelli, J., Saftencu, E., Rossi, P., D'Angelo, E., 2006. Regulation of repetitive neurotransmission and firing by release probability at the input stage of cerebellum: experimental observations and theoretical predictions on the role of LTP. *J. Neurophysiol.* 95, 686–699.
- Philipona, D., Coenen, O.J.-M.D., 2004. Model of granular layer encoding of the cerebellum. *Neurocomputing* 58–60, 575–580.
- Richardson, M., Brunel, N., Hakim, V., 2003. From sub-threshold to ring-rate resonance. *J. Neurophysiol.* 89, pp. 2538–2554.
- 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 Comput.* 18 (12), 2959–2993.
- Rossi, P., Mapelli, L., Roggeri, L., Gall, D., Kerchov d'Exaerde, A., Schiffmann, S.N., Taglietti, V., D'Angelo, E., 2006. Long-lasting inhibition of constitutive inward rectifier currents in cerebellar granule cells by synaptic activation of GABAB receptors. *Eur. J. Neurosci.* 24 (2), 419–432.
- Smith, G.D., Cox, C.L., Sherman, S.M., Rinzal, J., 2000. Fourier analysis of sinusoidally-driven thalamocortical relay neurons and a minimal integrate-and-fire-or-burst model. *J. Neurophysiol.* 83 (1), 588–610.
- van Rossum, M.C.W., 2001. A novel spike distance. *NeuralComputation* 13, 751–763.