An Interactive Demo Simulation of a single Hodgkin-Huxley-like Model Neuron

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Abstract

An interactive MATLAB-based demo simulation of the electrophysiological behavior of a biological neuron is presented and documented. The differential equations which describe the temporal evolution of the membrane voltage in a biophysical model neuron, are introduced and briefly discussed, together with the default numerical parameters employed in the demo. Several references and fundamental pointers to the literature are provided, with the aim of pointing interested users to further readings. This project was developed for a *multi-media* presentation given for an invited talk, and in the present public release it is intended as a tool for educational purposes. Since the relevant source codes are included and fully commented, this software might also be conveniently employed as a development example for exploring the many advantages of MATLAB data visualization, graphical user interfaces (GUI) and MEX interfaces.

1 Introduction

The present software consists in a MATLAB-based GUI, displaying in *quasi real-time* the temporal evolution of the membrane voltage, characterizing the electrophysiology of a single-compartment biophysical model neuron, upon deterministic/stochastic intracellular current stimulation. It is possible to examine the immediate impact of intracellularly applied currents, emulating a constant amplitude DC stimulus injected under *current-clamp* by an experimenter (e.g. in a *whole-cell patch-clamp* experiment), or the effect of

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an intense synaptic bombardment from a large presynaptic neuronal population, firing asynchronously and making the postsynaptic spike-emission process irregular.

This work was originally developed for a *multi-media* presentation, given for an invited talk, and it is now released under the GNU General Public License, hoping someone else might find it useful. The main purpose of that presentation was to focus the audience interest to a specific (stochastic) electrophysiological regime characterizing the electrical behavior of *in vivo* biological neurons, embedded in a large background population, thus receiving a large amount of excitatory/inhibitory postsynaptic currents in the time unit. Actually, such an approach is starting to be explored experimentally, by computer synthesizing *noisy*-current to be intracellularly injected in *in vitro* experiments (see Chance and Abbott, 2002; Paniski et al., 2002, Rauch et al., 2002; Silberberg et al., 2002; see also Treves, 1993; Amit and Brunel, 1997) [1]. In the present document, technical details and theoretical grounds underlying similar approaches will not be discussed and the interested reader is invited to refer to the literature (see the References).

2 The Matlab-based Linux Release

Thanks to the possibilities offered by `MATLAB` for data visualization and for the easy development of C/C++ software interfaces (i.e. the `MEX` files), it is relatively effortless to provide an educational tool to gain some confidence with the excitable properties of a simulated neuron. The software of the present project, comes as a *.tgz* archive, including the following 8 files:

HH.m	the main MATLAB script, invoked to start the GUI.
HH.fig	the figure file, containing the GUI structure.
hh_step.m	the MEX subroutine, for simulation of the biophysical neuron.
hh_step.mexglx	mex needed by *hh_step.m*.
hh_step.c	source code to compile *hh_step.mexglx*.
rando.c	include file needed to compile *hh_step.mexglx*.
hh.pdf	the present documentation as a *PDF* file.
gpl.txt	The GNU Public License, version 2, as a *txt* file.

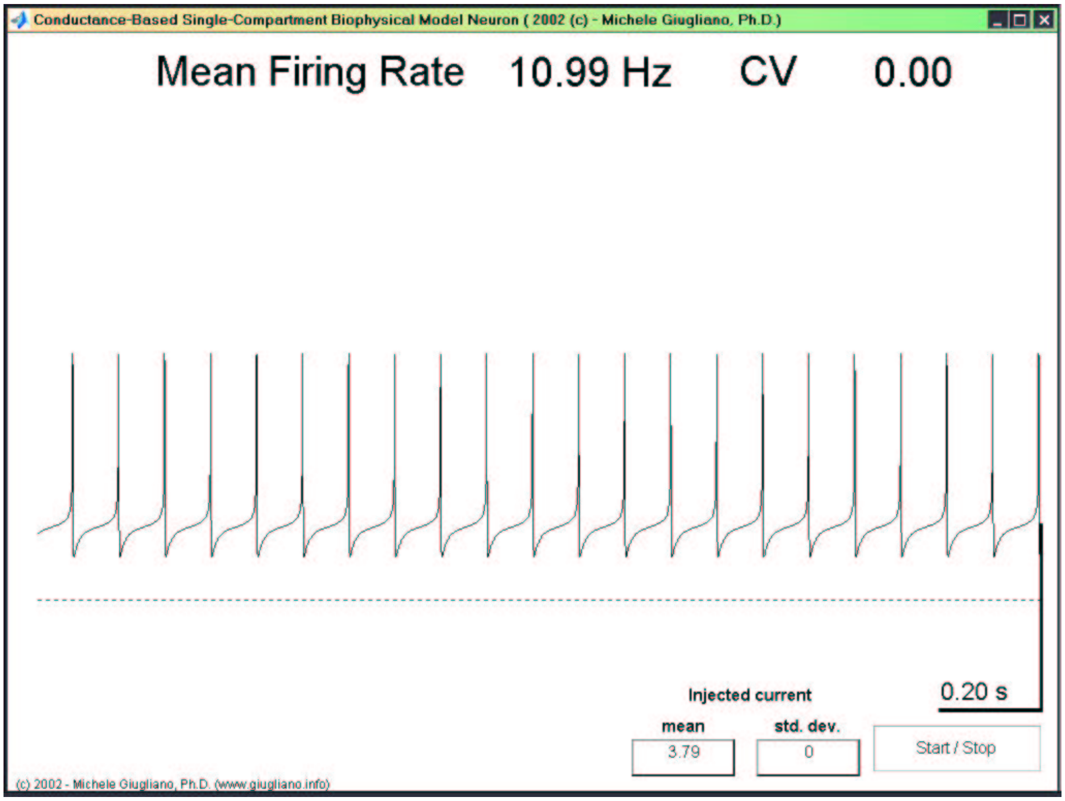
[1] Note: the author developed a data-acquisition package, the *MeeDuck Project*, as an advanced electrophysiological software suite, especially conceived for the exploration of non-conventional and stochastic experimental (multi-channel) protocols. Refer to the *MeeDuck Project* documentation for further details.

3 The Graphical User Interface

The original goal to be achieved was the (*quick-and-dirty*) computer simulation of the electrical behavior of a conductance-based model neuron, while having on a plot window the *quasi real-time* temporal evolution of its membrane voltage, similarly to the screen of an oscilloscope in a real electrophysiological experiment. Although the computational power of the nowadays desktop and laptop PC is increasing, computer performances would not fully be exploited by having `MATLAB` integrating the equations of a model. Actually, this can be performed much more efficiently by writing a C/C++ *ad-hoc* software, implementing and optimizing the best numerical integration methods and numerical strategies. Such a claim should be even stressed more in the context of the simulation (and presentation by a GUI) of a large network of interacting model neuron, where the need of an efficient *low-level* simulation is crucial [2]. It is then apparent that by writing and compiling an ad-hoc routine, all the graphical visualization steps must be then created from scratch. However, `MATLAB` provides an excellent choice for such a need, by exploiting the interface routines to link an external *dll* library (i.e. under Windows) or `MEX` files to a `MATLAB` script.

After launching the GUI (i.e. by typing `HH` at the `MATLAB` prompt) available to the user for interacting with the simulation, a standard window opens and resizes itself according to the current screen resolution. Such an interface is composed by a main plot window, in which the simulated membrane voltage is plotted as a function of time (i.e. thick-line) and compared to the resting-voltage (i.e. dotted-line). A big button labelled `Start/Stop` is placed at the bottom-right corner of the window and it toggles the current state of the simulation (i.e. and visualization), between `on` and `"paused".`At the top of the window, estimates of the simulated mean *action-potentials (APs) emission rate* and of the *coefficient of variation (CV)* of the *inter-spike-interval distribution* (see Koch and Segev, 1998; Dayan and Abbott, 2001), are updated during the simulation, provided that enough AP are emitted by the model neuron. Finally, two edit fields are available near the `Start/Stop` button, for choosing the (statistical) properties of the injected current, indicated by the text labels `mean` and `std.dev.` (i.e. standard deviation). By preliminary setting the `std. dev.` edit field to zero (i.e. accomplished by clicking inside the edit field and inserting the desired numerical value, when the simulation is paused), it is possible to play with the excitable responses of the model neuron to the injection of constant current stimuli, by increasing

[2] Note: the author developed another educational software, similar to the present one and simulating a network of synaptically interacting neurons. Refer to that software package for further details (e.g. www.giugliano.info)



Conductance-Based Single-Compartment Biophysical Model Neuron (2002 (c) - Michele Giugliano, Ph.D.)
0.20 s
Injected current
Start / Stop
(c) 2002 - Michele Giugliano, Ph.D. (www.giugliano.info)

Mean Firing Rate 10.99 Hz CV 0.00

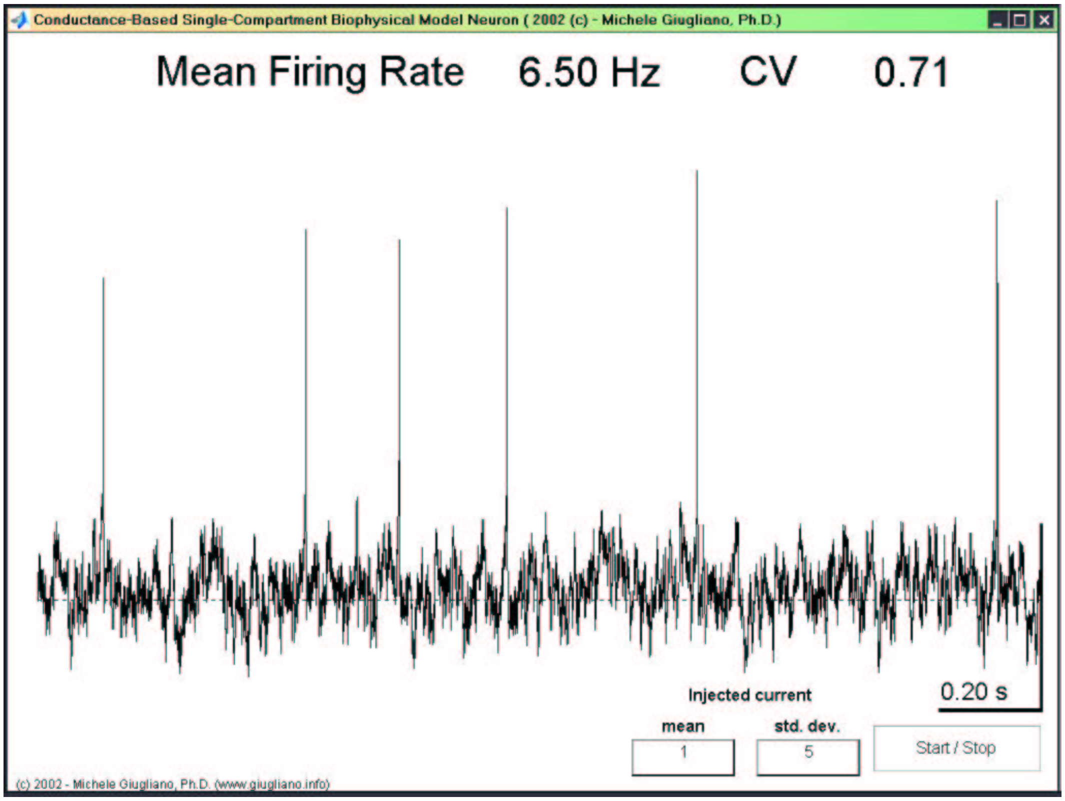
mean 3.79

std. dev. 0

Figure 1: By setting the *std. dev.* edit field to zero and increasing the value indicated by the *mean* edit field, a train of APs is evoked in the simulated neuron.

the value indicated by the `mean` edit field (i.e. specified in $\mu A/cm^2$ - in the range $[-50; 50]\mu A/cm^2$). For negative values of such a current amplitude, the membrane voltage will decrease (i.e. hyperpolarize) similarly to a passive dissipative first-order physical system (e.g. a *RC-circuit*). Conversely, by positive values of the amplitude, the voltage will increase (i.e. depolarize) until it reaches a critical value for excitability, emitting a transient and very fast response (i.e. an AP). Such a phenomenon, well-studied and referred to as *membrane excitability*, occurs when the stimulus current is large enough (see Fig. 1). This corresponds to an *in vitro* injection of a constant amplitude current, and the resulting periodic oscillations characterize, on a first approximation, the response of a biological neuron.

Conversely, by acting on the value set by the *std. dev.* edit field as weel (i.e. specifying the magnitude of the current random fluctuations around the mean value), the time-course of the membrane voltage resembles a *random-*



Conductance-Based Single-Compartment Biophysical Model Neuron (2002 (c) - Michele Giugliano, Ph.D.)

Mean Firing Rate 6.50 Hz CV 0.71

Injected current

mean: 1

std. dev.: 5

Figure 2: By increasing the amplitude of random fluctuations, acting on the value specified by the *std. dev.* edit field, the membrane voltage performs a *random-walk* and the emission of the APs increases its variability.

walk and the emission of the APs increases its variability (see Fig. 2).

The interested reader should note that the values set by the GUI constitute the so-called infinitesimal moments (see Cox and Miller, 1965) of the delta-correlated gauss-distributed stochastic process, whose temporal realizations will be injected into the membrane of the model neuron (Press et al., 1986). As a consequence, it is not entirely correct to address them in terms of a current, as delta-correlated processes do not exist in nature.

4 Model Neuron Definition

In the present section, the definition of the biophysical conductance-based model neuron is introduced and briefly discussed. An updated list of references is reported at the end of this document and interested readers are invited to look at them as sources for the (self)study of the electrophysiological properties of the nervous system (see e.g. Koch and Segev, 1998; Dayan and Abbott, 2001).

The transmembrane neuronal voltage V, computer simulated by the present software and plotted on the GUI window (see Figs. 1 - 2), is assumed to be the same over the entire cell membrane (i.e. by definition of *space-clamp* hypothesis), and to evolve according to the following differential equation.

$$C_m \frac{dV(t)}{dt} = I_{leak} + I_{Na} + I_K + I_{stim} \tag{1}$$

C_m represents the specific membrane capacitance (i.e. the capacitance of a membrane patch of unitary area), while individual membrane current densities included the voltage-dependent *fast-inactivating* sodium I_{Na}, a *delayed-rectifier* potassium current I_K, a leakage current I_{leak} and a synaptic current I_{stim}. Eq. 1 follows immediately from considerations about the conservation of the charge, and relates any change in V to the (non-linear) transmembrane current densities. These currents are approximately proportional to the voltage V, according to a *ohmic*-relation as reported below.

$$\begin{aligned} I_{leak} &= \bar{g}_{leak} \cdot (E_{leak} - V) \\ I_{Na} &= \bar{g}_{Na} \cdot m^3 \cdot h \cdot (E_{Na} - V) \qquad (2) \\ I_K &= \bar{g}_K \cdot n^4 \cdot (E_K - V) \end{aligned}$$

In the previous definitions, E_{leak}, E_{Na} and E_K represent the reversal potentials associated to each membrane current and related to the ionic distributions inside and outside the neuronal membrane. $\bar{g}_{leak}$, $\bar{g}_{Na}$ and $\bar{g}_K$ are the maximal conductances, which in the case of the active sodium and potassium currents, are modulated by activation (i.e. m and n) and inactivation (i.e. h) state variables. Following a classic formalism, originally introduced by Hodgkin and Huxley (1952), such state-variables are associated to non-linear voltage-gated first-order kinetics equations (eqs. 3, 4, 5).

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \tag{3}$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \tag{4}$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \tag{5}$$

Following some considerations about the large heterogeneity of the time-scales characterizing these state-variables, one may speed up the simulation of the model by substituting eq. 3 with eq. 6, consisting in instantaneously setting the sodium activation variable m to its asymptotic value m_∞ (for a in depth discussion see Kepler et al., 1992):

$$m = m_\infty(V). \tag{6}$$

The reduced model is therefore composed by three differential equations (eqs. 1, 4, 5), equivalent to the full model definition (eqs. 1, 3, 4, 5). By defining for the sake of clarity the sigmoidal function $f(x, \theta, \sigma)$, often employed by many authors to fit single-channel experimental recordings,

$$f(x, \theta, \sigma) = \frac{1}{1 + e^{-(x-\theta)/\sigma}} \tag{7}$$

the voltage-dependent asymptotic values and time constants for m, h and n can be expressed in a compact form, and all the numerical parameters are reported in the Appendix.

$$\begin{aligned}
m_\infty(V) &= f(V, \theta_m, \sigma_m) \\
h_\infty(V) &= f(V, \theta_h, \sigma_h) \\
n_\infty(V) &= f(V, \theta_n, \sigma_n) \\
\tau_h(V) &= 0.37ms + 2.78ms \cdot f(V, \theta_{\tau_h}, \sigma_{\tau_h}) \\
\tau_n(V) &= 0.37ms + 1.85ms \cdot f(V, \theta_{\tau_n}, \sigma_{\tau_n})
\end{aligned} \tag{8}$$

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Appendix

In the present section, the numerical parameters employed in the numerical simulation of the conductance-based biophysical model neuron described in the previous sections, are reported.

$V(t_0)$	$0mV$
$h(t_0)$	0
$n(t_0)$	0
C_m	$1\mu F/cm^2$
$\bar{g}_{Na}$	$24mS/cm^2$
$\bar{g}_K$	$3mS/cm^2$
$\bar{g}_{leak}$	$0.25mS/cm^2$
E_{Na}	$55mV$
E_K	$-90mV$
E_{leak}	$-70mV$
θ_h	$-53mV$
σ_h	$-7mV$
θ_{τ_h}	$-40.5mV$
σ_{τ_h}	$-6mV$
θ_m	$-30mV$
σ_m	$9.5mV$
θ_n	$-30mV$
σ_n	$10mV$
θ_{τ_n}	$-27mV$
σ_{τ_n}	$-15mV$