Glutamate gated spiking Neuron Model

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ABSTRACT

Background: Biological neuron models mainly analyze the behavior of neural networks. Neurons are described in terms of firing rates viz an analog signal. **Purpose:** The Izhikevich neuron model is an efficient, powerful model of spiking neuron. This model is a reduction of Hodgkin-Huxley model to a two variable system and is capable of producing rich firing patterns for many biological neurons. **Methods:** In this paper, the Regular Spiking (RS) neuron firing pattern is used to simulate the spiking of Glutamate gated postsynaptic membrane. **Results:** Simulation is done in MATLAB environment for excitatory action of synapses. **Conclusions:** Analogous simulation of spiking of excitatory postsynaptic membrane potential is obtained.

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Introduction

A typical neuron can be divided into three functionally distinct parts: dendrites, soma, and axon. Dendrites play the role of the 'input device' that collects signals from other neurons and transmits them to the soma. The soma is the central processing unit. If the total input exceeds a certain threshold, then an output signal is generated. The junction between two neurons is called a synapse. The neuronal signals consist of short electrical pulses. The pulses, so-called action potentials or spikes, have an amplitude of about 100 mv and typically a duration of 1-2 ms. The form of the pulse does not change as the action potential propagates along the axon. A chain of action potentials emitted by a single neuron is called a spike train - a sequence of stereotyped events which occur at regular or irregular intervals. Since all spikes of a given neuron look alike, the form of the action potential does not carry any information. Rather, it is the number and the timing of spikes which matter. Action potentials in a spike train are usually well separated. Even with very strong input, it is impossible to excite a second spike during or immediately after a first one.¹

One of the most important neuron models in computational neuroscience is the Hodgkin-Huxley model. Based on their 1952 experiments on the giant axon of the squid, Hodgkin and Huxley developed a mathematical model describing neuron membrane potential and the flow of ions through channels in the membrane. In the Hodgkin-Huxley model (Figure 1) the cell membrane is considered as a capacitor. An input current I applied to the membrane may be split into a current which charges the capacitor I_{cap} and a current that passes through the ion channels I_{chan} .²

$$I = I_{cap} + I_{chan}$$

The ionic current is divided into components carried by sodium and potassium ions I_{Na} and I_K respectively, and a small 'leakage current' (I_o) made up by chloride and other ions. Each component of the ionic current is determined by a driving force which may conveniently be measured as an electrical potential difference and a permeability coefficient which has the dimensions

Fig. 1: H-H model.

of a conductance. Thus the sodium current (I_{Na}) is equal to the sodium conductance (g_{Na}) multiplied by the difference between the membrane potential (V_m) and the equilibrium potential for the sodium ion (E_{Na}). The experiments suggest that g_{Na} and g_K are functions of time and membrane potential, but that E_{Na} , E_K , E_o , C_M and g_o may be taken as constant.^{3,4}

$$I = I_m + I_o - I_{Na} + I_K$$

$$= C_M(dV_m/dt) + g_o(V_m - E_o) - g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)$$

where V_m represents the postsynaptic membrane potential established by the ionic and capacitive membrane current, C_M is the capacitance of the lipid bilayer of postsynaptic membrane, t is time. The Hodgkin-Huxley model is biophysically meaningful but very expensive to implement. The motive of this paper is

to develop a simple analog circuit model that can simulate the spiking of glutamate gated postsynaptic membrane.

Glutamate sensitive ENFET

Glutamate is a non essential amino acid. It is the primary excitatory neurotransmitter in the human central nervous system. In simplest case, the binding reaction may be represented as:

where k_1 and k_2 are the forward and backward rate constants respectively.⁵ The field effect transistor (FET) gate surface plays an important role in the sensitivity and stability of the sensor. Each surface layer possesses certain pH sensitivity and can, therefore, detect minute changes in pH close to the electrolyte/insulator interface. Tantalum pentoxide (Ta_2O_5) is a promising gate oxide material for sensoric purposes, as it has a large number of surface sites that leads to a large buffer capacity.⁶ The glutamate sensitive ENFET is prepared by immobilizing glutamate oxidase on the surface of gate oxide (Ta_2O_5) (Figure 2). It is based on the biocatalyzed hydrolysis of L-glutamate in the presence of glutamate oxidase in accordance with the chemical reaction:

The enzymatic reactions on the modified electrode surface involved in the detection of glutamate are as follows:⁷

The proton generated in this reaction changes the pH inside the enzyme which is registered by the underlying ion sensitive FET. The threshold voltage of such device, $V_{\text{TH}}(\text{IS})$, is a function of pH of solution dependent on the concentration of glutamate. For very small value of drain to source voltage of ENFET, V_{ds} , the conductance of such ENFET can be expressed as:

$$G_{\text{ds}} = \beta(V_{\text{gs}} - V_{\text{TH}}(\text{IS})) \quad \text{equation (2)}$$

β is the geometric sensitivity parameter given by

$$\beta = \mu C_{\text{ox}} (W/L)$$

where C_{ox} is the oxide capacity per unit area, W and L are the width and the length of the channel respectively, and μ is the electron mobility in the channel. V_{gs} is the voltage applied to the reference electrode and $V_{\text{TH}}(\text{IS})$ is the threshold voltage of the ENFET. $V_{\text{TH}}(\text{IS})$ in equation (2) can, therefore, be modeled as:^{8,9}

$$V_{\text{TH}}(\text{IS})(t) = V_{\text{THO}}[(1 - \exp(-k_1 t) + \exp(-k_2 t)U(t - t_m))] \quad \text{equation(3)}$$

Fig. 2: Glutamate ENFET (a) Schematic diagram (b) Electronic diagram.

where k_1 and k_2 are time constants analogous to the rate constants of equation (1), $U(t - t_m)$ is the Heaviside function and V_{THO} is the threshold voltage proportional to the maximum attainable conductance, when all the transmitter-gated channels for Na^+ ions are open.

Spiking neuron model

The simplest form of spiking neural model includes time and gives their output in the form of spikes. A spiking model is a mathematical model which describes how input spike trains (sequences of timings) are mapped to an output spike train. Thus the output can be characterized by

$$S = (t_i; i = 1, 2, \dots, n), t_i < t_{i+1}$$

Where t_i is the i^{th} spike train in a train of n spikes.¹⁰

In this paper, a simple spiking model represented by equation (4), (5) is as biologically plausible as the Hodgkin-Huxley model, yet as computationally efficient as the integrate-and-fire model. The model is a reduction of the Hodgkin-Huxley model to a two variable system. Two ordinary differential equations describe the membrane potential v and a recovery variable u by:

$$dv/dt = 0.04v^2 + 5v + 140 - u + I \quad \text{equation (4)}$$

$$du/dt = a(bv - u) \quad \text{equation (5)}$$

with an after-spike reset rule:

$$\text{if } v \geq 30 \text{ then } v \leftarrow c, u \leftarrow u + d \quad \text{equation (6)}$$

Here v and u are dimensionless variables, and a , b , c , and d are dimensionless parameters. The variable v represents the membrane potential of the neuron and u represents a membrane recovery variable, which accounts for the activation of K^+ ionic currents and inactivation of Na^+ ionic currents, and it provides negative feedback to v . After the spike reaches its apex (+30 mV), the membrane voltage and the recovery variable are reset according to the equation (6). Synaptic currents or injected dc-currents are delivered via the variable I .¹¹ The model can exhibit firing patterns of all known types of cortical neurons with the choice of parameters: a , b , c and d . In this paper, regular spiking (RS) neuron is used to generate spike. The Regular spiking (RS) neuron (Figure 3) has four model parameters a , b , c and d . The parameter a describes the time scale of the recovery variable u . Smaller values result in slower recovery. Typical value of a is 0.02. The parameter b describes the sensitivity of

Fig. 3: Showing the firing pattern of a regular spiking neuron.

Fig. 4: Schematic diagram of a single spike together with Afterhyperpolarization (AHP) and afterdepolarization (ADP).

the recovery variable u to the subthreshold fluctuations of the membrane potential v . Its value is 0.2. The parameter c describes the after-spike reset value of the membrane potential v caused by the fast high-threshold K^+ conductances. Its value is $c = -65$ mV. The parameter d describes after-spike reset of the recovery variable u caused by slow high-threshold Na^+ and K^+ conductances. A typical value is $d = 8$.¹²

Methods

RS neurons generate 'regular' action potentials. Their synaptic function is excitatory. The slow potential of the RS neuron begins to rise due to the input from some other neurons. When the potential reaches at the threshold of the RS neuron, the neuron fires. Immediately after the firing, the slow potential U_i is lowered to a reset value U_r which is lower than the rest potential U_o and after passing the period of absolute refractoriness T_{RS} it resumes rising again. This process of lowering and rising of the potential represents afterhyperpolarization (AHP) and afterdepolarization (ADP) observed in the membrane potential of RS neuron (Figure 4).¹³

The strategy that is used to produce spiking in the glutamate gated postsynaptic membrane is governed by a) integrating set of differential equations with incoming spikes inducing discrete changes in the state variables and outgoing spikes are triggered by a threshold condition b) using Euler's forward approximation method. The modeling for excitatory synapse is shown in Figure 5. The leakage current I_o is considered to be small enough to be neglected. Since only sodium channels are responsible for excitatory action, the postsynaptic membrane is divided into three patches to represent spatial summation of the sodium current controlled by

$$I_{Na} = I_1 + I_2 + I_3$$

$$I = I_m + I_o - I_{Na} + I_k$$

$$I = C(dv_m/dt) + g_o(V_m - E_o) - g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)$$

where g_{Na} is the total sodium conductance and g_K is the non-gated potassium conductance. V_{g1} , V_{g2} and V_{g3} are the voltages applied to the reference electrodes of the ENFETs. The

Fig. 5: Circuit model for Postsynaptic membrane.

membrane potential V_m is obtained by spatially and temporally varying g_{Na} of glutamate-gated sodium channels.

Simulation

The component values assigned in the model for MATLAB simulation are taken from reference:¹⁴ $C_m = 1 \mu\text{F}$ per cm^2 , $g_K = 36 \text{ mS}$ per cm^2 , $E_{Na} = 115 \text{ mV}$ and $E_K = -12 \text{ mV}$ and $I = 0$. The specifications for three n-channel ENFETs are $L = 15 \mu\text{m}$, $W = 2 \mu\text{m}$, $t_{ox} = 100 \text{ nm}$, $\mu = 600 \text{ cm}^2/\text{V}\cdot\text{sec}$. The parameters for exponential function in equation (3), applied to each ENFET inputs are: $V_{TH0} = -10 \text{ mV}$, $t_m = 600 \mu\text{sec}$, $k_1 = k_2 = 5 \text{ msec}$. The three gates to source voltage of three ENFETs i.e V_{g1} , V_{g2} and V_{g3} are kept constants at 1 Volt each. The three input parameters of ENFET namely V_{TH1} , V_{TH2} and V_{TH3} dependence on concentration of glutamate are applied in a staggered sequence at 0.01 msec intervals. This is done to simulate the time variation in glutamate transmitter-receptor binding with respect to different patches of postsynaptic membrane. The values assigned for regular spiking neuron model parameters: $a = 0.02$, $b = 0.2$, $c = -65$, $d = 8$.

Results

The MATLAB simulation outputs are shown in figure 6. The waveform represents the normal postsynaptic membrane potential with respect to time. Membrane potential, V_m is established by spatial summation and temporal integration of the glutamate-gated sodium current. In this model, action potential takes the form of spikes and occurs during the time period of the pulse. Here the action potential is exhibited whenever V_m reaches the threshold in the range of -60 mV and after that the action potential is reset when it reaches 40 mV .

Conclusions

The figure above shows an analogous simulation showing the response of the model to a time varying injected current. The

Fig. 6: Simulated result of excitatory postsynaptic membrane potential.

three glutamate gated sodium channels are staggered at 0.01 ms time interval which simulates the time variation in transmitter-receptor binding with respect to different patches of post synaptic membrane. The work shows that glutamate-sensitive ENFET can be used as a circuit analog to simulate the spiking of excitatory postsynaptic membrane potential.

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