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Biologically inspired circuit model for simulation of glutamate gated ion channels of the postsynaptic membrane at synaptic cleft

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ABSTRACT

Background: Enzyme modified field effect transistor (ENFET) may be used to represent the variable conductance of transmitter-gated ion channels in the postsynaptic region of the neuron. **Purpose:** The objective of this work is to develop a simple analog circuit model that can simulate the function of neurotransmitter glutamate gated ion channels of postsynaptic membrane at the synaptic cleft. **Method:** In this paper, Glutamate sensitive ENFET is incorporated into the Hodgkin-Huxley (H-H) circuit model of the postsynaptic membrane at the synaptic cleft. **Result:** Simulation of the circuit model yields an output representing the membrane potential of the synaptic region. Simulation is performed in MATLAB environment for excitatory action of synapses. **Conclusion:** This model can be used in neuro-bioengineering programs for simulation of binding activity and electrical activity of the postsynaptic region.

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Introduction

Electrical engineers and neuroscientists have traditionally utilized the Hodgkin-Huxley model as a circuit analog of the axonal membrane. The postsynaptic region functions as the input or "front-end" of the neuron. The electrical behavior of the membrane may be represented by the network (Figure 1). Current can be carried through the membrane either by charging the membrane capacity or by movement of ions through the resistances in parallel with the capacitance. 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 of a conductance. Thus the sodium current (I_{Na}) is equal to the sodium conductance (g_{Na}) multiplied by the difference between the membranes potential (E) 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.[1]

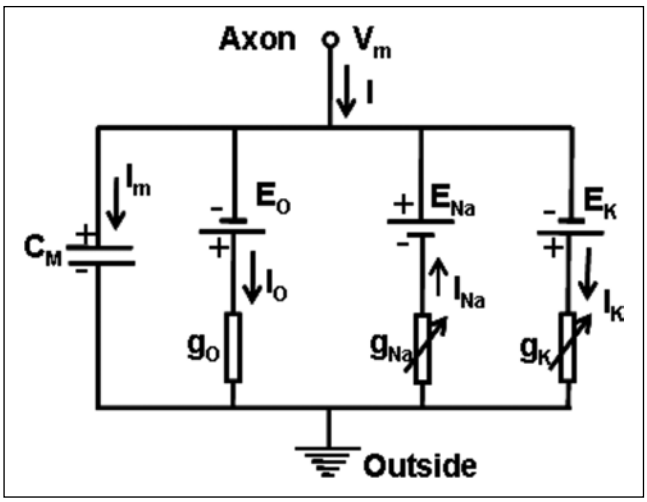


Fig. 1: H-H model.

The influence of membrane potential on permeability can be summarized by stating: first, that depolarization causes a transient increase in sodium conductance and a slower but maintained increase in potassium conductance; secondly, that these changes are graded and that they can be reversed by repolarizing the membrane. In order to decide whether these effects are sufficient to account for complicated phenomena such as the action potential and refractory period, it is necessary to obtain expressions relating the sodium and potassium conductance's to time and membrane potential.[2–4]

The total membrane current is divided into two components: a capacitive current and an ionic current. Thus total membrane current:

$$I = I_C + I_{ion}$$

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

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

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.

Glutamate as neurotransmitter

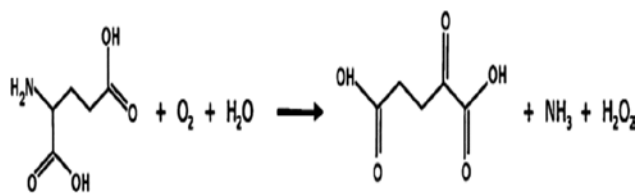
Glutamate is a non essential amino acid. It is the primary excitatory neurotransmitter in the human central nervous system. Changes in synaptic efficacy, including long-term potentiation and long-term depression of excitatory synaptic transmission, are considered to be the neuronal bases for learning and memory and are regulated by glutamate, amongst other neurotransmitters.[5] In presynaptic terminals, glutamate is stored

in vesicles in the axon, and it is released by an increased concentration of intracellular Ca^{2+} due to the activation of voltage gated channels for calcium. The glutamate released in the synaptic cleft binds to its receptor on the postsynaptic terminals, and it produces an excitatory postsynaptic potential (EPSP).[6] Glutamate can also induce neurotoxicity, and it has therefore been implicated as a potential contributor to the pathogenesis of several central nervous system neurodegenerative disorders, for example Alzheimer's disease, Parkinson's disease.[7]

Glutamate sensitive ENFET: In simplest case, the binding reaction may be represented as:

$$\text{Glutamate} + \text{Receptor (closed)} \underset{k_2}{\overset{k_1}{\leftrightarrow}} \text{Glutamate} - \text{Receptor (open)} \qquad \text{equation (1)}$$

where k_1 and k_2 are the forward and backward rate constants respectively.[8] 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.[5] 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:



L-glutamate 2-oxoglutarate

The enzymatic reactions on the modified electrode surface involved in the detection of glutamate are as follows:[9]

$$\text{L-Glutamate} + O_2 \rightarrow \text{2-Oxoglutarate} + H_2O_2 \qquad \text{reaction (1)}$$

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e^- \qquad \text{reaction (2)}$$

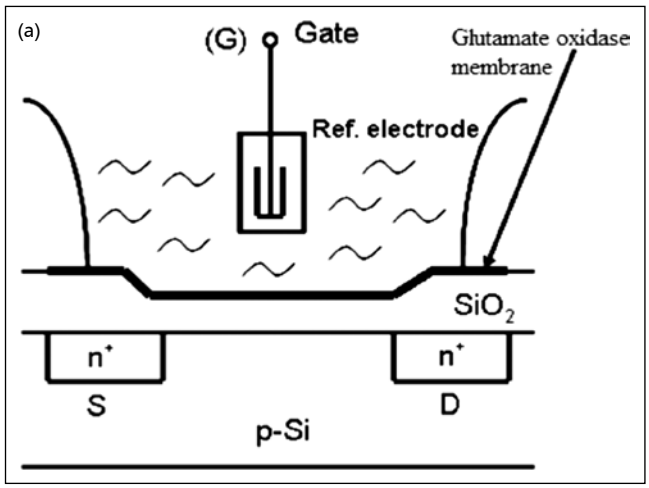
The reaction (1), glutamate is oxidized via the enzyme GlOx (Glutamate oxidase) to 2-Oxoglutarate and H_2O_2 then reaction (2) is dissociated via the oxidation reaction giving one mole of O_2, two electrons and two moles of H^+.

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, $V_{TH}(IS)$, 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:

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

β is the geometric sensitivity parameter given by

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



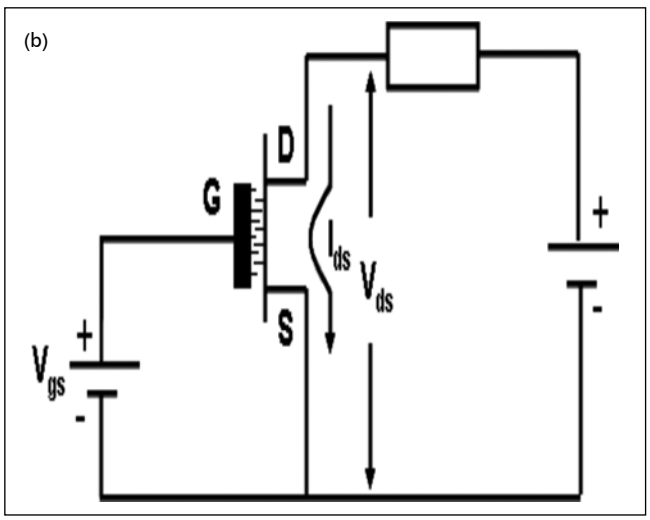


Fig. 2: Glutamate ENFET (a) Schematic diagram (b) Electronic diagram.

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_{TH} (IS) is the threshold voltage of the ENFET. In ENFET, β and V_{gs} are constants and $V_{TH}(IS)$ is the only input variable. Thus G_{ds} is dependent on the threshold voltage, $V_{TH}(IS)$, analogous to the conductance of ion channels of postsynaptic membrane dependent on the binding activity. The neurotransmitter gated ion channels can therefore be represented by glutamate sensitive ENFET due to its variable nature of conductance with respect to voltage. Glutamate-receptor binding activity is a time dependent phenomenon and therefore number of opening of transmitter gated ion channels will be varying with respect to time. $V_{TH}(IS)$ in equation (2) can, therefore, be modeled as:[10,11]

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

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.

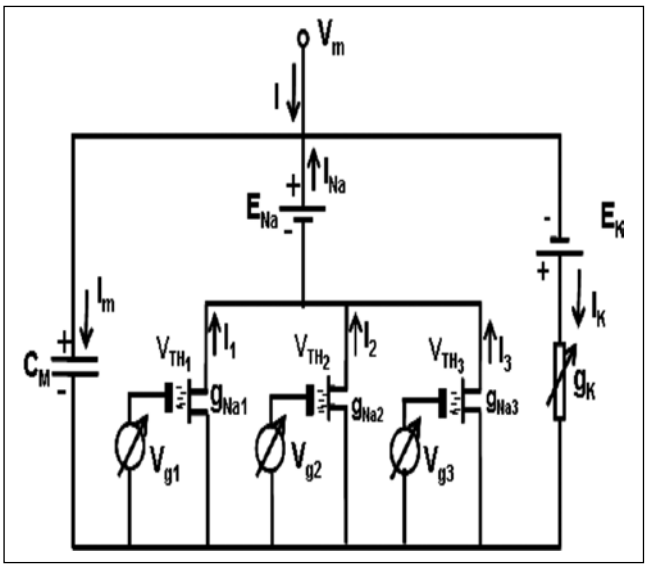


Fig. 3: Circuit model for Postsynaptic membrane.

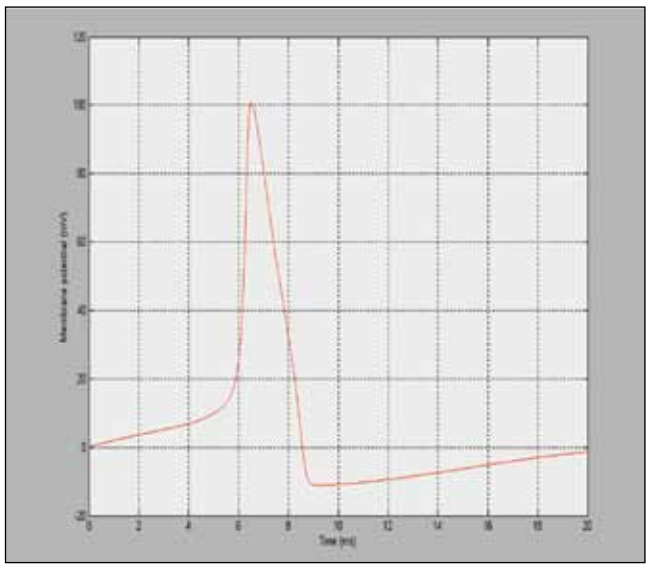


Fig. 4: Simulated result of postsynaptic membrane potential.

Modeling neuron for excitatory synapse

The modeling for excitatory synapse is shown below (Figure 3). 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. Vg_1, Vg_2 and Vg_3 are the voltages applied to the reference electrodes of the ENFETs. The 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[11]: $C_m = 1\ \mu F$ per cm^2, $g_K = 36$ mS per cm^2, $E_{Na} = 115$mV and $E_K = -12$mV and $I = 0$. The specifications for three n-channel ENFETs are $L = 15\ \mu m$, $W = 2\ \mu m$, $t_{ox} = 100$ nm, $\mu = 600\ cm^2/V\text{-sec}$. The parameters for exponential function in equation (3), applied to each ENFET inputs are: $V_{THO} = -10$ mV, $t_m = 600\ \mu sec$, $k_1 = k_2 = 5$ msec. The three gates to source voltage of three ENFETS i.e Vg_1, Vg_2 and Vg_3 are kept constants at 1Volt 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.

Results

The MATLAB simulation outputs are shown below (Figure 4). The waveform represents the normal postsynaptic membrane potential with respect to time. V_m is established by spatial summation and temporal integration of the glutamate-gated sodium current. When V_m exceeds the threshold in the range of 20 mV to 90 mV, the voltage gated sodium channels open causing initiation of an action potential.

Discussion

Similar studies can be carried out using wider sample size, involving different parameters required for initiating different pathways for disease occurrence in patient. Simulation of biological model in this study shows it as an supplementary step to presently existing biological studies involving *in vivo* and *in vitro* models for various degenerative diseases such as AD, AMD, stroke.[12–19] Approaches used to create these *in vitro in vivo* models provides an idea as to how these conditions could be utilised in simulating the models based on sensor and emitter technology. Recently, the advances in information technology has led to systems approach by intimating two different sciences in order to enhance our understanding, without compromising the dynamics of living entity.

Conclusions

We show that glutamate-sensitive ENFET can be used as circuit analog to simulate the excitatory postsynaptic potential. This biologically motivated model may become a useful research and teaching unit both in neurology and bioelectronics area. The basic idea of the model can be used for other types of neurotransmitter-gated channels and can reproduce a wide variety of electrical responses.

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