Chapter 7

Some Aspects of Development of Biologically Motivated Circuit Models of Synapses
Some Aspects of Development of Biologically Motivated Circuit Models of Synapses

In this chapter a study on the development of three biologically motivated/inspired synapse models has been carried out. The modeling theories and description of the models and their simulation results have been presented and compared with the previously obtained results.

7.1 Introduction:

In the first synapse model, the variable conductance of ion channels of post synaptic neuron, dependence on the transmitters diffused through the synaptic cleft and bind with the receptor sites of the post synaptic membrane of neuron, is represented by MOSFET. MOSFET is chosen because it functions as a voltage controlled conductance in the linear region, analogous to the variable conductance of the transmitter gated ion channels of post synaptic region of neuron. This analog is incorporated into the famous Hodgkin-Huxley (H-H) model of neuron at the synaptic cleft. Simulation is performed in MATLAB environment both for excitatory and inhibitory actions of synapses and the results are presented.

In the second synapse model, the variable conductance of postsynaptic membrane of neuron dependence on the neurotransmitter-receptor binding activity is represented by ion-sensitive field effect transistor (ISFET). ISFET functions not only as a voltage controlled conductance but can also be converted into an enzyme modified field effect transistor (ENFET) and therefore can provide a means of measurement of specific neurotransmitters.
that bind with the receptor sites of postsynaptic membrane. This analog is incorporated into the Hodgkin-Huxley (H-H) model of neuron to substitute the variable Na⁺ and Cl⁻ conductances. Simulation is performed in MATLAB environment both for excitatory and inhibitory states and results are presented.

In the third synapse model, the variable conductance of postsynaptic membrane of neuron dependence on the acetylcholine-receptor binding activity is represented by enzyme modified field effect transistor (ENFET) sensitive to acetylcholine. Acetylcholine sensitive ENFET functions not only as a voltage controlled conductance but can also provide a means of measurement of specific neurotransmitters that bind with the receptor sites of postsynaptic membrane. This analog is incorporated into the Hodgkin-Huxley (H-H) model of neuron to substitute the variable Na⁺ conductance. Simulation is performed in MATLAB environment both for normal (excitatory) and pathologic states and results are presented.

7.2 Biologically Motivated Circuit Model of Neuron for Simulation of Excitatory and Inhibitory Actions of Synapses:

The communication between two neurons is one directional communication. The function of postsynaptic neuron may, therefore, be considered to be an input to the next neuron. Modeling of neuron is, therefore, performed for postsynaptic neuron.

The postsynaptic membrane consists of a lipid bilayer and transmembrane protein ion channels. Some ion channels such as sodium, chloride etc. are controlled by the neurotransmitters that bind with the receptor sites, i.e. the amount of ionic current is dependent upon the activity of the transmitter-
receptor binding. In simplest case, the binding reaction may be represented as[1]

\[
\text{Neuro-transmitter} + \text{Receptor(Closed)} \xrightarrow{k_1} \text{Neuro-transmitter - Receptor(Open)} \quad (7.1)
\]

Where \(K_1\) and \(K_2\) are the forward and backward rate constants respectively. The transmitter gated channels, therefore, have variable conductance dependence on the binding activity of transmitters. Transmitter gated ion channels can, therefore, be represented by MOSFET, because as discussed in chapter 4, MOSFET functions as a voltage controlled conductance in its linear region. Rewriting the governing equation from chapter 4 (equation 4.20):

\[
G_{DS} = \beta(V_{GS} - V_t) \quad (7.2)
\]

\(\beta\) is the geometric sensitivity parameter given by

\[
\beta = \mu C_{ox} \frac{W}{L} \quad (7.3)
\]

Where \(C_{ox}\) is the oxide capacity per unit area, \(W\) and \(L\) are the width and the length of the channel respectively, and \(\mu\) is the electron mobility in the channel. \(V_{GS}\) is the gate to source voltage and \(V_t\) is the threshold voltage of the MOSFET. In MOSFET, \(\beta\) and \(V_t\) are constants and \(V_{GS}\) is the only input variable. Thus \(G_{DS}\) is dependent on gate voltage \(V_{GS}\), analogous to the conductance of ion channels of postsynaptic membrane dependent on the binding activity. Thus, considering the transmitter-receptor binding activity, the H-H model for membrane can be modified as shown in Fig. 7.1. Here \(V_{SN}\) and \(V_{SL}\) are gate voltages applied to MOSFETs that control the conductances \(g_{Na}\) and \(g_{Cl}\) respectively.

Gate voltage is a time dependent voltage given by [1].
\[ V_g(t) = V_0 \left[ (1 - \exp(-k_1 t)) + \exp(-k_2 t)U(t - t_m) \right] \]  

(7.4)

Where \( K_1 \) and \( K_2 \) are time constants analogous to the rate constants of equation (7.1), \( U(t-t_m) \) is the Heaviside function and \( V_o \) is a voltage proportional to the maximum attainable conductance, when all the transmitter-gated channels for a specific ion are open.

Fig. 7.1: Biologically motivated model of postsynaptic membrane
7.2.1 Modeling Neuron for Excitatory Synapse:

The circuit model for excitatory synapse is shown in Fig. 7.2. 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 $g_{Na1}$, $g_{Na2}$, and $g_{Na3}$, where

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

So that, $I = I_m - I_{Na} + I_K$

$$= C_m \frac{dV_m}{dt} - g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)$$

(7.6)

Where $g_{Na}$ is the total Sodium conductance and $g_K$ is the total Potassium conductance.

The membrane potential $V_m$ is obtained by spatially and temporally varying $g_{Na}$ of transmitter-gated sodium channels.
The component values assigned in the model for MATLAB simulation are taken from literature [1] and are given in Table 7.1. The specifications for three n-channel MOSFETS, the parameters for exponential function in equation (7.4), applied to each MOSFET inputs are also given in Table 7.1.
TABLE 7.1
DIFFERENT COMPONENTS USED IN THE PROPOSED MODEL OF EXCITATORY SYNAPSE

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameter</th>
<th>Parameter Details</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>$C_M$</td>
<td>Membrane Capacitance</td>
<td>Farad</td>
<td>1 $\mu$F per cm$^2$</td>
</tr>
<tr>
<td>02</td>
<td>$g_K$</td>
<td>Potassium Conductance</td>
<td>Mho</td>
<td>1 mS per cm$^2$</td>
</tr>
<tr>
<td>03</td>
<td>$E_{Na}$</td>
<td>Sodium Potential</td>
<td>Volt</td>
<td>60mV</td>
</tr>
<tr>
<td>04</td>
<td>$E_K$</td>
<td>Potassium Potential</td>
<td>Volt</td>
<td>-90mV</td>
</tr>
<tr>
<td>05</td>
<td>$L$</td>
<td>Channel Length</td>
<td>Meter</td>
<td>15 $\mu$m</td>
</tr>
<tr>
<td>06</td>
<td>$W$</td>
<td>Channel Width</td>
<td>Meter</td>
<td>2 $\mu$m</td>
</tr>
<tr>
<td>07</td>
<td>$t_{ox}$</td>
<td>Oxide Thickness</td>
<td>Meter</td>
<td>100 nm</td>
</tr>
<tr>
<td>08</td>
<td>$\mu$</td>
<td>Electron mobility</td>
<td>cm$^2$/V-sec</td>
<td>600 cm$^2$/V-sec</td>
</tr>
<tr>
<td>09</td>
<td>$V_o$</td>
<td>Voltage proportional to the maximum attainable conductance</td>
<td>Volt</td>
<td>2 Volts</td>
</tr>
<tr>
<td>10</td>
<td>$t_m$</td>
<td>Time</td>
<td>Second</td>
<td>600 $\mu$sec</td>
</tr>
<tr>
<td>11</td>
<td>$k_1 = k_2$</td>
<td>Time Constant</td>
<td>Second</td>
<td>0.8 msec</td>
</tr>
</tbody>
</table>

7.2.2 Modeling Neuron for Inhibitory Synapse:

The modeling for inhibitory synapse is shown in Fig. 7.3. Considering only Cl$^-$ channels to be responsible for inhibitory action, the post synaptic membrane is divided into three patches to represent spatial summation of the Chloride current controlled by $g_{Cl_1}$, $g_{Cl_2}$ and $g_{Cl_3}$, where

$$I_{Cl} = I_1 + I_2 + I_3$$  \hspace*{1cm} (7.7)

So, that, $I = I_m + I_{Cl} + I_K$

$$= C_m \frac{dV_m}{dt} + g_{Cl}(V_m - E_{Cl}) + g_K(V_m - E_K)$$  \hspace*{1cm} (7.8)
Where $g_{Ci}$ is the total Chlorine conductance and $g_K$ is the total Potassium conductance.

The membrane potential $V_m$ is obtained by spatially and temporally varying $g_{Ci}$ of transmitter-gated Chlorine channels.

The component values assigned in the model for MATLAB simulation, the specifications for three p-channel MOSFETS, and the parameters for exponential function in equation (7.4), applied to each MOSFET inputs are given in Table 7.2.
TABLE 7.2
DIFFERENT COMPONENTS USED IN THE PROPOSED MODEL OF INHIBITORY SYNAPSE

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameter</th>
<th>Parameter Details</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>C_M</td>
<td>Membrane capacitance</td>
<td>Farad</td>
<td>1 μF per cm²</td>
</tr>
<tr>
<td>02</td>
<td>g_k</td>
<td>Potassium conductance</td>
<td>Mho</td>
<td>1 mS per cm²</td>
</tr>
<tr>
<td>03</td>
<td>E_Cl</td>
<td>Chloride potential</td>
<td>Volt</td>
<td>-100 mV</td>
</tr>
<tr>
<td>04</td>
<td>E_K</td>
<td>Potassium potential</td>
<td>Volt</td>
<td>-90 mV</td>
</tr>
<tr>
<td>05</td>
<td>L</td>
<td>Channel length</td>
<td>Meter</td>
<td>15 μm</td>
</tr>
<tr>
<td>06</td>
<td>W</td>
<td>Channel width</td>
<td>Meter</td>
<td>2 μm</td>
</tr>
<tr>
<td>07</td>
<td>t_ox</td>
<td>Oxide thickness</td>
<td>Meter</td>
<td>100 nm</td>
</tr>
<tr>
<td>08</td>
<td>u</td>
<td>Electron mobility</td>
<td>cm²/V·sec</td>
<td>600 cm²/V·sec</td>
</tr>
<tr>
<td>09</td>
<td>v_o</td>
<td>Voltage proportional to the maximum attainable conductance</td>
<td>Volt</td>
<td>-5 Volts</td>
</tr>
<tr>
<td>10</td>
<td>t_m</td>
<td>Time</td>
<td>Second</td>
<td>850 μsec</td>
</tr>
<tr>
<td>11</td>
<td>k_1 = k_2</td>
<td>Time constant</td>
<td>Second</td>
<td>0.8 msec</td>
</tr>
</tbody>
</table>

7.2.3 Results:
The MATLAB simulation outputs are shown in Fig. 7.4. The top waveform represents the normal postsynaptic membrane potential. Here V_m is established by spatial summation and temporal integration of the transmitter gated sodium current and non-gated potassium current. Simulation results indicate that when V_m exceeds a threshold in the range of -60 to -40 mV, an action potential initiates which illustrates an EPSP. The bottom waveform represents the inhibitory action. It illustrates an IPSP with sufficient amplitude for triggering an action potential in negative direction.
Fig. 7.4: Simulation results of excitatory and inhibitory actions of postsynaptic membrane. Top waveform represents the EPSP and bottom waveform represents the IPSP.

Here, MOSFET based electrical models both for excitatory and inhibitory actions of neurons have been developed. Postsynaptic membrane is divided into three patches to represent spatial summation of gated currents. Temporal integration of the currents is achieved by modeling exponentially varying time dependent gate voltage applied to MOSFET. This model can be used in neurobioengineering area for simulation of neurotransmitter-receptor binding activity and electrical activity of the postsynaptic neuron.

The results obtained from simulation of proposed circuit models of synapse for excitatory and inhibitory actions using MOSFET are compared with those
of the other proposed models and models reported by previous researchers and are given in Table 7.8.

### 7.3 Modeling Neuron for Simulation of Transmitter Gated Ion Channels of Postsynaptic Membrane at Synaptic Cleft:

In this work, the variable conductance of postsynaptic membrane of neuron dependence on the neurotransmitter-receptor binding activity is represented by Ion Sensitive Field-Effect Transistor (ISFET). This work starts with thorough study on ISFET.

#### 7.3.1 Ion Sensitive Field-Effect Transistor (ISFET):

The exploitation of field effect concept for measurement of ions in aqueous solution has given the birth of a new class of chemical sensors known as Ion Sensitive Field Effect Transistors (ISFET). This device was first reported by Bergveld in 1970, who used it for the measurement of ionic in and effluxes around a nerve [2]. This work was described in detail in 1972 [3] which is now cited by most authors as a pioneering publication in the field of ISFET development. Bergveld demonstrated that if the metal gate of ordinary Metal Oxide Semiconductor Field Effect Transistor (MOSFET) is omitted and the silicon dioxide layer is exposed to an electrolyte, the characteristics of the device are then affected by the ionic activity of the electrolyte and hence this device functions as an ion-sensitive transducer. At the same time Matsuo and Wise developed a similar device using silicon nitride as a sensitive sub gate layer, which greatly improved the sensor performance [4]. These pioneering works prompted further research in the field of ISFETOLOGY resulting into a large number of publications devoted to various aspects of ISFET development [5]. Due to their small dimensions, these devices were initially
meant for biomedical applications and almost all papers at that time, described
ISFETs as future tools for electrophysiological measurements and were
therefore published in biomedical journals [5]. Nevertheless, with the new
possibilities for electrophysiology measurements, research on ISFETs went in
the direction of ion sensing in general, not specifically biomedical. Since
1970, led by Bergveld, more than 600 papers, devoted on ISFETs and another
170 on related biosensors, such as Enzyme FETs (ENFETs) [6]–[11],
ImmunoFETs (IMFETs) [12], DNA biosensor [13] etc. appeared in many
world’s leading journals on biomedical, electron devices, sensors and
actuators, biosensors and bioelectronics, biotechnology advances etc. These
devices exhibit several advantages over conventional ion-selective electrodes.
The advantages of these devices are given below [14]–[15]:

1. The history of silicon usage for developing a wide range of sensors is
   well reviewed by Middelhock [16].

2. ISFETs are very robust and durable. Unlike many conventional
   sensors, ISFET probes withstand cleaning with a toothbrush.

3. The ISFETs are mass-produced by integrated circuit (IC) group
   technology, which make them very small and cost effective.

4. ISFETs can be stored dry and require little routine maintenance.

5. ISFETs can be used over an extremely wide temperature range and are
   sterilizable.

6. ISFETs have potential for on-chip circuit integration leading to the
   development of micrototal analysis system (μ-TAS) [17] or lab-on-
   chip system [18].
7. Both computation and detection can be performed on the same chip with a buffer electronic system of information processing and storage.

8. ISFETs can be made multifunctional by a combination of membranes.

9. The insulating surface of ISFET contains reactive groups, which can be used for covalent attachment of organic molecules and polymers. ISFETs can, therefore, be converted into biosensors and bioelectronic devices [19] which are now regarded as promising tools in medicine, biotechnology, environmental control, agriculture, food industry and defense.

7.3.1.1 Theory of ISFET:

Ion Sensitive Field Effect Transistor (ISFET) is in fact a Metal Oxide Semiconductor Field Effect Transistor (MOSFET) in which metal gate is replaced by a complex structure sensitive to hydrogen ion concentration. The schematic representation of a MOSFET and an ISFET is given in Fig. 7.5, as well as their common electronic diagram.

![Fig. 7.5(a): Structure of MOSFET](image)
Fig. 7.5(b): Schematic of ISFET

Fig. 7.5(c): Electronic Diagram of ISFET
It is obvious that ISFET is obtained by replacing the standard metal gate of a MOSFET with a reference electrode, a chemically sensitive insulator between which presents a measured electrolyte. The gate voltage is applied to the reference electrode and the electrolyte closes the electric Gate-Source circuit. ISFET is therefore fundamentally a MOSFET and hence the theoretical description of MOSFET is essential to describe ISFET's theory. The most important equation of MOSFET is the threshold voltage, \( V_{\text{TH(MOS)}} \), which is defined as the value of gate voltage (\( V_G \)) that is necessary to cause surface inversion and is given by [20]

\[
V_{\text{TH(MOS)}} = \Phi_M - \Phi_{Si} - \frac{Q_{\text{ox}} + Q_{\text{ss}} + Q_B}{C_{\text{ox}}} + 2\Phi_f
\]  

(7.9)

where,

- \( 2\Phi_f \): semiconductor surface inversion potential,
- \( \Phi_f \): Fermi potential of the semiconductor,
- \( Q_B \): semiconductor depletion charge per unit area,
- \( \Phi_M \): work function of the gate metal in volts,
- \( \Phi_{Si} \): work function of bulk semiconductor i.e. extrinsic semiconductor (in volts),
- \( Q_{\text{ss}} \): the fixed surface-state charge per unit area at the insulator-semiconductor interface,
- \( C_{\text{ox}} \): capacitance per unit area of the oxide, and
- \( Q_{\text{ox}} \): accumulated charge in the oxide.
Here all terms are purely physical in nature. In case of the ISFET, the same fabrication process is used, resulting in the same constant physical part of the threshold voltage. But the introduction of electrolyte between the reference electrode and the insulator, produces two more potentials: the constant potential of the reference electrode, $E_{\text{ref}}$ and the interfacial potential $\psi_0 + \chi^{\text{sol}}$ at the solution/oxide interface, where $\psi_0$ is the surface potential, shown to be a function of the solution pH and $\chi^{\text{sol}}$ is the surface dipole potential of the solvent having a constant value. Therefore, the equation for the ISFET threshold voltage is as follows [15]:

$$V_{TH(IS)} = E_{\text{ref}} - \psi_0 + \chi^{\text{sol}} - q_0 - \frac{Q_{\text{ox}} + Q_{\text{sd}} + Q_B}{C_{\text{ox}}} + 2\phi_f$$  \hspace{1cm} (7.10)

The general expressions for the drain current of the MOSFET in the non-saturated and saturated mode are respectively [21]:

$$V_{DS} = \beta \left( V_{GS} - V_{TH(MOS)} \right) V_{DS} - \frac{1}{2} V_{DS}^2$$  \hspace{1cm} (7.11a)

$$I_{DS} = \frac{1}{2} \beta \left( V_{GS} - V_{TH(MOS)} \right)^2$$  \hspace{1cm} (7.11b)

where $\beta = C_{\text{ox}} \mu \frac{w}{l}$  \hspace{1cm} (7.11c)

where

$\mu$ = electron mobility,

$w$ = width of the channel,

$l$ = length of the channel,

$V_{GS}$ = Gate-Source voltage in volts, and
\[ V_{DS} = \text{Drain-Source voltage in volts.} \]

In MOSFET, the parameter \( \beta \) is a design constant and \( V_{DS} \) is kept constant by the applied electronic circuit. Moreover, the fabrication processes for MOSFET devices are so well controlled that \( V_{TH(MOS)} \) is also a constant. Thus, \( V_{GS} \) is the only input parameter. In conventional MOSFET, therefore, \( I_{DS} / V_{DS} \) curves are drawn as a function of \( V_{GS} \) as shown in Fig. 7.6 (a).

If proceeded like MOSFET then the general expressions for the drain current of ISFET in the non-saturated and saturated mode can be directly written respectively as:

\[
I_{DS} = \beta \left[ (V_{GS} - V_{TH(IS)}) V_{DS} - \frac{1}{2} V_{DS}^2 \right] \tag{7.12a}
\]

\[
I_{DS} = \frac{1}{2} \beta \left( V_{GS} - V_{TH(IS)} \right)^2 \tag{7.12b}
\]

where \( \beta = C_{ox} \frac{\mu}{l} \) \tag{7.12c}

Since ISFET is a sensing device i.e., an ion sensor, the input parameter should be \( V_{TH} \). And since \( V_{TH} \) can be chemically modified via the interfacial potential at the electrolyte/oxide interface, \( \Psi_0 \), the \( I_{DS} / V_{DS} \) curves are recorded as a function of pH of the solution as shown in Fig. 7.6(b). This effect is due to the relation \( \Psi_0 = f(\text{pH}) \). This analysis clearly indicates that an ISFET is electronically identical to a MOSFET and can be seen as an electronic device, with one additional feature: its threshold voltage can be chemically modified via the interfacial potential at the electrolyte/oxide interface.

This analysis also gives the answer of debates regarding the need of reference electrode. Since field effect concept is explored in ISFET, to charge the
electrolyte–insulator–semiconductor (EIS) structure, which is analogous to metal–oxide–semiconductor (MOS) structure, with the gate oxide as insulator, needs two connections – one in silicon and the other in the electrolyte. In order that the electrolyte terminal can be connected to one terminal of the voltage source, a reference electrode is required so that the reference electrode and electrolyte together can substitute the metal gate of MOSFET which is connected to one terminal of voltage source, i.e. $V_{GS}$ [21].

![Fig. 7.6(a): Drain current vs. drain to source voltage at various Gate voltage of a MOSFET](image)
7.3.1.2 ISFET Operational Principle:

The mechanism responsible for the change in surface charge can be explained by well known site-binding theory introduced in 1973 by Yates et al. [22] to describe the properties of an oxide aqueous electrolyte interface and was generalized in 1986 by Fung et al [23] to characterize ISFETs with oxide insulators. According to this theory, the insulating surface contains hydroxyl groups (OH) which can be protonated (thus positively charged) or deprotonated (thus negatively charged) depending on the concentration of the hydrogen ions in the electrolyte. The surface hydroxyl groups which can bind hydrogen ions are called binding sites. In case of SiO$_2$ insulator, it is assumed
that it has only one kind of $H^+$-specific binding site represented by $\text{SiOH}$, $\text{SiO}^-$ and $\text{SiOH}^+$. The ionization reactions are:

\[
\text{SiOH} \rightleftharpoons \text{SiO}^- + H^+
\]

\[
\text{SiOH} + H^+ \rightleftharpoons \text{SiOH}_2^+
\]

with $H^+$ representing the protons in the vicinity of the surface. It is thus clear that the originally neutral surface may become a positive site or negative site by accepting or donating protons from or to the electrolyte solution respectively. As a result of these chemical reactions at the interface, the originally neutral oxide surface containing only neutral sites is converted into a charged surface having positive and negative charge sites. The resulting surface charge depends on an excess of one type of charged site over the other and is a function of the solution pH. For this reason $H^+$ and $\text{OH}^-$ are referred to as potential determining ions for this interface. Besides the potential determining ions, electrolyte has other anions and cations called electrolyte ions. These electrolyte ions form ion pairs with oppositely charged surface sites or groups - a process known as surface complexation. The formation of surface complexes also readjusts the acid – base equilibrium and affects the surface charge by partly compensating the charged sites. Of course, the distribution of ions in the electrolyte solution can be well explained by using Gouy – Chapman – Stern theory [24]. According to this theory, two layers are formed in the electrolyte solution. Double layer consists of Stern inner layer and a diffuse layer. Inner layer consists of two planes namely inner Helmholtz plane (IHP) and outer Helmholtz plane (OHP). IHP is the locus of centers of adsorbed ions which form pairs with the charged surface sites as already discussed in surface complexation. The OHP is the locus of the centers of the
hydrated ions with the closest approach to the surface. The diffuse layer extends from the OHP to the bulk of solution and contains the nonspecifically absorbed ions that behave as an ionic cloud and balanced by the uncompensated surface sites. With this model, the electrical double layer behaves as two capacitors $C_H$ and $C_D$ in series where $C_H$ is the Helmholtz capacitance and $C_D$ is the diffused layer capacitance as shown in Fig. 7.7.

![Diagram of electrical double layer](image-url)
Fig. 7.7(b) Charge and potential distribution of an ISFET for pH < pH_{pzc}
7.3.1.3 ISFET Modeling:

Modeling of ISFET provides important tools for prediction of function of the device for different new sensing materials that can be used to make devices with enhanced sensitivity. Since the introduction of site-binding model, many models have been developed—some are physico-chemical and some are based on SPICE (Simulation Program with Integrated Circuit Emphasis). But irrespective of different approaches, basic objective of ISFET modeling is to obtain a relationship of the form $\Psi_0 = f(pH)$ and almost all models have considered the condition of charge neutrality of an electrolyte-insulator-semiconductor (EIS) system in conjunction with the site binding theory and
electrical double layer theory. The aim of this section is to describe some mathematical quantities used for many ISFET models.

Considering site-binding theory, let us denote SiOH$_2^+$, SiOH, SiO$^-$ positive, neutral and negative surface sites of insulating surface. Exchange of the potential determining ions with these sites can be described as follows:

\[
\ce{SiOH_2^+ + H^+ <=> SiOH + HSiOH^2+} \\
\ce{SiOH <=> SiO^- + HSiOH^+}
\]

Under equilibrium conditions, the amphoteric dissociation constants are given by:

\[
K_+ = \frac{[SiOH][H^+]_s}{[SiOH_2^+]} \quad (7.13)
\]

\[
K_- = \frac{[SiO^-][H^+]_s}{[SiOH]} \quad (7.14)
\]

The subscript in $[H^+]$ means that the concentration of protons is near the surface of the insulator, and $[SiOH_2^+]$, $[SiOH]$, and $[SiO^-]$ are the concentration of the proton binding sites present in the oxide surface.

Now according to the Boltzmann distribution, the relation between the concentration of an ion species $X$ at a location $i$ in the electrolyte double layer, $[X]_i$, and the concentration of the same species at the bulk electrolyte, $[X]_b$, is

\[
[X]_i = [X]_b \exp \left( -\frac{q\psi_i}{kT} \right)
\]
Therefore, equations (7.13) and (7.14) may be rewritten respectively as

\[ K_+ = \frac{[\text{SiOH}][\text{H}^+]}{[\text{SiOH}_2^+]} \exp\left(-\frac{q\psi_0}{kT}\right) \]  \hspace{1cm} (7.15)

\[ K_- = \frac{[\text{SiO}^-][\text{H}^+]}{[\text{SiOH}]} \exp\left(-\frac{q\psi_0}{kT}\right) \]  \hspace{1cm} (7.16)

Using this basic site binding model, Bousse et al. [25] develops a simple model and proven to be applicable for an ISFET surface of SiO\(_2\) and Al\(_2\)O\(_3\). According to this model, the resulting equation for the surface potential is

\[ \Psi_0 = 2.3 \frac{kT}{q} \left( pH_{pzc} - pH \right) \frac{\beta}{\beta + 1} \]  \hspace{1cm} (7.17)

Where, \( pH_{pzc} \) is the value of the pH for which the oxide surface is electrically neutral and \( \beta \) determines the final sensitivity.

In 1996, based on the same site binding theory, a new model was developed by R.E.G. Van Hal et al [26]. This model explores the well known equation for capacitance \( Q = CV \), where \( Q \) is the surface charge, \( C \) is the double layer capacitance at the interface and \( V \) is the surface potential denoted by \( \psi_0 \). According to this model, \( \psi_0 \) can be expressed as

\[ \Delta \Psi_0 = -2.3 \frac{kT}{q} \Delta pH_{bulk} \]  \hspace{1cm} (7.18)

With

\[ \alpha = \frac{1}{\left(2.3kTC \frac{\text{diff}}{q^2 \beta}\right) + 1} \]  \hspace{1cm} (7.19)
Where $\beta$ symbolizes the ability of the oxide surface to deliver or take up protons called buffer capacity of the surface and $C_{diff}$ is the differential double layer capacitance, $\alpha$ is a dimension less sensitivity parameter varying between 0 and 1, depending on the intrinsic buffer capacity.

Considering electrolyte ions, the surface complexation due to anions and cations of electrolyte solution can be represented by the following chemical reactions:

$$SiOH^+_2 - A^- \underset{k^-}{\overset{k^+}{\rightleftharpoons}} SiOH^+_2 + A^-$$

$$SiO^- - C^+ \underset{k^-}{\overset{k^+}{\rightleftharpoons}} SiO^- + C^+$$

Here the left hand sides represent the bindings with the surface charge groups. The dissociation constants at equilibrium can again be written as:

$$K_+ = \frac{[SiOH^+_2][A^-]}{[SiOH^+_2 - A^-]} \quad (7.20)$$

$$K_- = \frac{[SiO^-][C^+]}{[SiO^- - C^+]} \quad (7.21)$$

Using Boltzmann distribution, we have

$$[C^+]_b = [C^+]_b \exp\left(-\frac{q\psi \beta}{kT}\right) \quad \text{and} \quad [A^-]_b = [A^-]_b \exp\left(\frac{q\psi \beta}{kT}\right)$$

Therefore, the equations (7.20) and (7.21) may be rewritten as

$$K_+ = \frac{[SiOH^+_2]}{[SiOH^+_2 - A^-]} C^0 \exp\left(\frac{q\psi \beta}{kT}\right) \quad (7.22)$$
where \( C^0 \) is the electrolyte bulk concentration such that \( [C^+] = [A^-] = C^0 \).

On the oxide surface, there is a fixed number of surface sites per unit area, \( N_s \):

\[
N_s = [\text{SiOH}^+] + [\text{SiOH}_2^+] + [\text{SiO}^-] + [\text{SiO}^- - C^+] + [\text{SiOH}_2^+ - A^-]
\]  

(7.24)

Depending on the chemical equilibrium of the surface sites, a surface charge density \( \sigma_0 [C/m^2] \) exists:

\[
\sigma_0 = q \left( [\text{SiOH}_2^+] - [\text{SiO}^-] + [\text{SiOH}_2^+ - A^-] - [\text{SiO}^- - C^+] \right)
\]

(7.25)

The combination of equations (7.13) to (7.16) and (7.21) to (7.22) yields [27]:

\[
\sigma_0 = qN_p \frac{[H^+]_c - K_+ K_-}{(K_+ K_- + K_+ K_-) + [H^+]_c [H^+]_c + K_+ K_- + K_+ K_+ K_- [C^+]_c}
\]

(7.26)

The charge density at IHP, \( \sigma_\beta [C/m^2] \) is:

\[
\sigma_\beta = q \left( [\text{SiOH}_2^+ - A^-] - [\text{SiO}^- - C^+] \right)
\]

(7.27)

The diffuse layer charge density, \( \sigma_d [C/m^2] \) is [20]:

\[
\sigma_d = -\sqrt{8kT \varepsilon_0 \varepsilon_r C^0} \sinh \left( \frac{q \psi d}{2kT} \right)
\]

(7.28)

where \( \varepsilon_r \) is the dielectric constant of the solution, \( \varepsilon_0 \) is the permittivity of the free space and \( C^0 \) is the ion concentration in the bulk electrolyte. \( k \) is the Boltzmann constant and \( T \) is the absolute temperature.

The charge neutrality of the system requires that

\[
\sigma_d + \sigma_\beta + \sigma_0 + \sigma_s = 0
\]

(7.29)
where semiconductor surface charge density $\sigma_s$ is given by [28]:

$$\sigma_s = 2\varepsilon_s e_0 kT \left[ n_0 \left( \exp \left( \frac{-\varphi_{s}}{kT} \right) + 1 \right) - p_0 \left( \exp \left( \frac{-\varphi_{s}}{kT} \right) - 1 \right) \right]$$

(7.30)

where $\varepsilon_s$ is the silicon relative permittivity and $p_0$ and $n_0$ are the equilibrium hole and electron concentration.

The charges and the potentials at the interfaces are related by the following equations:

$$\psi_0 - \psi_B = \frac{\sigma_0 + \sigma_s}{C_1}$$

(7.31a)

$$\psi_B - \psi_d = -\frac{\sigma_d}{C_2}$$

(7.31b)

$$\psi_d - \psi_0 = \frac{\sigma_s}{C_0}$$

(7.31c)

where $C_1$ and $C_2$ are the unit area capacitances of the inner and outer Helmholtz layers respectively and $C_0$ is the unit area capacitance of the insulator film.

The system of equations that can describe an ideal electrolyte-insulator-semiconductor (EIS) structure can now be described as follows: equations (7.13) through (7.16) and (7.20) through (7.28) represent the reaction at the electrolyte-insulator interface and the charge potential relationships in the electrolyte diffused layer and oxide surface. The condition for charge neutrality is given by equation (7.29). The charge potential relationship on the semiconductor surface is given by the equation (7.30). The link between the different regions such as OHP, IHP, oxide surface and semiconductor surface
of the system is contained in equations (7.31). It is obvious from the equations (7.31a) and (7.31c) that the semiconductor surface potential is dependent on the oxide surface potential $\Psi_0$ and hence the measurement of $\sigma_e$ will provide a means of obtaining the surface potential $\Psi_0$ at the electrolyte-oxide interface. The dependence of the oxide surface potential $\Psi_0$ on the pH can be verified by solving the set of equations mentioned above. Some values required for simulation purpose, collected from various papers have been presented in Table 7.3.

### Table 7.3: Some values required for simulation

<table>
<thead>
<tr>
<th>Materials</th>
<th>Values of $\frac{K_+}{K_+}$</th>
<th>Values in $\mu F/\text{cm}^2$</th>
<th>Values of $\frac{K_+}{K_-}$</th>
<th>Number of binding sites</th>
<th>Types of binding sites</th>
<th>pH$_{pzc}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO$_2$</td>
<td>$63.1 \times 10^{-\text{\textsuperscript{3}}}$ $15.8$</td>
<td>120 20</td>
<td>0.317 0.9</td>
<td>-</td>
<td>Nsil</td>
<td>3</td>
</tr>
<tr>
<td>Si$_3$N$_4$</td>
<td>$63.1 \times 10^{-\text{\textsuperscript{3}}}$ $15.8$</td>
<td>120 20</td>
<td>0.317 0.9</td>
<td>$1.0 \times 10^{-10}$</td>
<td>Nsil $&amp;$ Nnit</td>
<td>6.8</td>
</tr>
<tr>
<td>Al$_2$O$_3$</td>
<td>$79.9 \times 10^{-\text{\textsuperscript{10}}}$ $12.6 \times 10^{-\text{\textsuperscript{9}}}$</td>
<td>120 20</td>
<td>0.317 0.9</td>
<td>-</td>
<td>Nsil</td>
<td>8.5</td>
</tr>
</tbody>
</table>

### 7.3.1.4 ISFET Technology:

As mentioned above, ISFETs are fundamentally MOSFETs, therefore, the classic microelectronic technology of integrated circuits (IC) is also the basic technology used in ISFET development. The fabrication step is similar to the process of the p-channel or n-channel metal gate MOSFETs. ISFETs are fabricated with silicon films on sapphire wafers (SOS). The gate SiO$_2$ film is thermally grown on the surface of the substrate at about 1000°C. But unlike the MOSFETs, the selection of gate dielectric coating of ISFETs is important
as protonation/deprotonation of this material is influenced by the pH of the electrolyte. The various methods used for fabrication of these coatings are plasma enhanced chemical vapor deposition (PCVD), plasma anodic oxidation, evaporation by electron beam, sputtering etc. [29]. The pH response of different types of oxide coatings is presented in Table 7.4. As far as physical shape is concerned, most ISFETs have source, drain and gate on the same side of the chip but there are also those in which drain-source and gate are placed on the opposite sides of the substrate [30]. The specifications of various ISFETs fabricated at different institutes, laboratories, groups etc. are given in Table 7.5 [31] – [33]. The review by Sergei V. Dzyadevych et al., describe the development of ISFETs including the technology in details [15]. The latest investigations concern the miniaturization of reference electrodes for field effect sensors compatible with silicon chip technology [34], the integration of biosensors based on ISFETs into a flow-injection analysis system and the development of nanoscale ISFETs.

<table>
<thead>
<tr>
<th>Sensitive layer</th>
<th>pH range</th>
<th>Sensitivity (mV / pH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO₂</td>
<td>2-5</td>
<td>25-48</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>2-12</td>
<td>53-57</td>
</tr>
<tr>
<td>Si₃N₄</td>
<td>2-12</td>
<td>46-56</td>
</tr>
<tr>
<td>Ta₂O₅</td>
<td>2-12</td>
<td>56-57</td>
</tr>
</tbody>
</table>
ISFET are microelectronic/nanoelectronic devices and have been found to be growing interest in the rapidly developing field of bioelectronics encompassing a very wide spectrum of applications. Many ISFET based pH electrodes have been reported in recent years, most of which are in the state of commercialization. A good number of companies, including giants in this field are involved in their manufacturing and marketing. They have even been presenting the advantages of ISFET based pH electrodes via various media to promote the development of ISFET based sensors such as CHEMFET, ENFET, BIOFET, and DNAFET etc. The advantages that they have highlighted are unbreakable, portable, fast response, easy to store and clean for repeated use. They can also be used for direct measurement in complex aqueous and semisolid samples like cheese, meat, etc and have potential for on-chip circuit integration leading to the development of micrototal analysis system and can also be mass-produced by existing integrated circuit(IC) batch production technology. Due to these advantages, extensive research is being carried out in a number of Universities/laboratories across the globe to develop various ISFET based biosensors mainly for biomedical, bio-

<table>
<thead>
<tr>
<th>Institutes/laboratories/groups</th>
<th>Sensitive layer</th>
<th>$I_D / V_D$ ($\mu$A /V)</th>
<th>pH range</th>
<th>Sensitivity (mV/pH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIMD (Ukraine)</td>
<td>$\text{Si}_3\text{N}_4$</td>
<td>200 /1</td>
<td>2-12</td>
<td>30-40</td>
</tr>
<tr>
<td>LASS (France)</td>
<td>$\text{SiO}_2$ / $\text{Si}_3\text{N}_4$</td>
<td>100 / 1</td>
<td>3-9</td>
<td>40-50</td>
</tr>
<tr>
<td>ESIEE (France)</td>
<td>$\text{Si}_3\text{N}_4$</td>
<td>200/1</td>
<td>7-12</td>
<td>15</td>
</tr>
<tr>
<td>ITIMS (Vietnam)</td>
<td>$\text{SiO}_2$</td>
<td>200-500 / 0.2-1</td>
<td>2.5-8</td>
<td>11-13</td>
</tr>
</tbody>
</table>
analytical, food processing, defense applications. Though, a series of reliable and promising results have been obtained, no successful commercial version of ISFET based biosensor is available so far. Keeping these factors in view, it is expected that like the ISFET based pH electrode, attempts to commercialize the biosensors will also be made in near future. In view of the future perspective of nano technology, efforts have also been made by the Bioelectronics Division of Tezpur University with special emphasis on modeling of different geometries of ISFET devices at very small dimensions such as the Cylindrical ISFET, Conical ISFET etc.

7.3.2 ISFET Based Modified H-H Model:

Referring to the equation (7.12a), for very small value of drain to source voltage, \( V_{DS} \), the conductance of ISFET in its linear region can be written as

\[
\frac{I_{DS}}{V_{DS}} = \beta (V_{GS} - V_{TH(IS)})
\]

or,

\[
G_{DS} = \beta (V_{GS} - V_{TH(IS)}) \tag{7.32}
\]

where, \( \beta = \mu C_{ox} \frac{W}{l} \) \tag{7.33}

In equation (7.32), \( \beta \) 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. Thus, considering the transmitter-receptor binding activity, the H-H model for membrane can be modified as shown in Fig. 7.8. Here \( V_{gN} \) and \( V_{gl} \) are fixed gate voltages applied to the reference electrodes of ISFETs.
and $V_{TH1}$ and $V_{TH2}$ are the respective threshold voltages of ISFETs that control the conductances $g_{Na}$ and $g_{Cl}$ respectively.

![Modified H-H model of Postsynaptic membrane](image)

Neurotransmitter-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 (7.32) can, therefore, be modeled as given in equation (7.4):

$$V_{TH(IS)}(t) = V_{TH0}[1 - \exp(-k_1 t) + \exp(-k_2 t)U(t-t_m)]$$  \hspace{1cm} (7.34)

Where $K_1$ and $K_2$ are time constants analogous to the rate constants of equation (7.9), $U(t-t_m)$ is the Heaviside function and $V_{TH0}$ is the threshold voltage proportional to the maximum attainable conductance, when all the transmitter-gated channels for specific ions are open.
7.3.2.1 Modeling Neuron for Excitatory Synapse:

The modeling for excitatory synapse is shown in Fig. 7.9. 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 $g_{Na1}$, $g_{Na2}$, and $g_{Na3}$, where

$$I_{Na} = I_1 + I_2 + I_3$$  \hspace{1cm} (7.35)

So that, $I = I_m - I_{Na} + I_K$

$$= C_m \frac{dV_m}{dt} - g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)$$  \hspace{1cm} (7.36)

Where $g_{Na} = g_{Na1} + g_{Na2} + g_{Na3}$ and $g_K$ is the total Potassium conductance.

The membrane potential $V_m$ is obtained by spatially and temporally varying $g_{Na}$ of transmitter-gated sodium channels.
The component values assigned in the model for MATLAB simulation are taken from reference [35] and are given in Table 7.6. The specifications for three n-channel ISFETs as well as the parameters for exponential function in equation (7.34), applied to each ISFET inputs are also given in Table 7.6. The three gate to source voltages of three ISFETs i.e., $V_{g1}$, $V_{g2}$ and $V_{g3}$ are kept constants at 1 Volt each. The three input parameters of ISFETs namely $V_{TH1}$, $V_{TH2}$ and $V_{TH3}$ are applied in a staggered sequence at 1.5 msec intervals. This is done to simulate the time variation in neurotransmitter–receptor binding with respect to different patches of postsynaptic membrane in accordance with reference [35].
7.3.2.2 Modeling Neuron for Inhibitory Synapse:

The modeling for inhibitory synapse is shown in Fig. 7.10. Considering only Cl⁻ channels to be responsible for inhibitory action, the post synaptic membrane is divided into three patches to represent spatial summation of the Chloride current controlled by $g_{Cl}^1$, $g_{Cl}^2$ and $g_{Cl}^3$, where

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

(7.37)

So, that, $I = I_m + I_{Cl} + I_K$

$$= C_m \frac{dV_m}{dt} + g_{Cl}(V_m - E_{Cl}) + g_K(V_m - E_K)$$

(7.38)
Where $g_{Cl} = g_{Cl1} + g_{Cl2} + g_{Cl3}$ and $g_K$ is the total Potassium conductance.

The membrane potential $V_m$ is obtained by spatially and temporally varying $g_{CI}$ of transmitter-gated Chlorine channels.

![Fig. 7.10: ISFET based Circuit model for inhibitory action of synapse](image)

Table 7.7 summarizes the component values assigned in the model for MATLAB simulation for inhibitory action of synapse. The specifications for three p-channel ISFETs as well as the parameters for exponential function in equation (7.34), applied to each ISFET inputs are also given in Table 7.7. The three gate to source voltages of three ISFETs i.e $V_{g1}$, $V_{g2}$ and $V_{g3}$ are kept
constants at 1 Volt each. The three input parameters of ISFETs namely $V_{TH1}$, $V_{TH2}$ and $V_{TH3}$ are applied in a staggered sequence at 1.5 msec intervals. This is done to simulate the time variation in neurotransmitter-receptor binding with respect to different patches of postsynaptic membrane.

**TABLE 7.7**
**DIFFERENT COMPONENTS USED IN THE PROPOSED MODEL OF INHIBITORY SYNAPSE**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameter</th>
<th>Parameter Details</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>$C_M$</td>
<td>Membrane Capacitance</td>
<td>Farad</td>
<td>1 $\mu$F per cm$^2$</td>
</tr>
<tr>
<td>02</td>
<td>$g_K$</td>
<td>Potassium Conductance</td>
<td>Mho</td>
<td>1 mS per cm$^2$</td>
</tr>
<tr>
<td>03</td>
<td>$E_{CI}$</td>
<td>Chloride Potential</td>
<td>Volt</td>
<td>-100 mV</td>
</tr>
<tr>
<td>04</td>
<td>$E_K$</td>
<td>Potassium Potential</td>
<td>Volt</td>
<td>-90 mV</td>
</tr>
<tr>
<td>05</td>
<td>$I$</td>
<td>Membrane Current</td>
<td>Ampere</td>
<td>0 A</td>
</tr>
<tr>
<td>06</td>
<td>$L$</td>
<td>Channel Length</td>
<td>Meter</td>
<td>15 $\mu$m</td>
</tr>
<tr>
<td>07</td>
<td>$W$</td>
<td>Channel Width</td>
<td>Meter</td>
<td>2 $\mu$m</td>
</tr>
<tr>
<td>08</td>
<td>$t_{OX}$</td>
<td>Oxide Thickness</td>
<td>Meter</td>
<td>100 nm</td>
</tr>
<tr>
<td>09</td>
<td>$\mu$</td>
<td>Electron mobility</td>
<td>cm$^2$/V-sec</td>
<td>600 cm$^2$/V-sec</td>
</tr>
<tr>
<td>10</td>
<td>$V_{THO}$</td>
<td>Threshold Voltage</td>
<td>Volt</td>
<td>5 Volts</td>
</tr>
<tr>
<td>11</td>
<td>$t_m$</td>
<td>Time</td>
<td>Second</td>
<td>850 $\mu$sec</td>
</tr>
</tbody>
</table>

**7.3.2.3 Results:**

The MATLAB simulation outputs are shown in Fig. 7.11. The top waveform represents the normal postsynaptic membrane potential. Here $V_m$ is established by spatial summation and temporal integration of the transmitter gated sodium current and non-gated potassium current. Simulation results indicate that when $V_m$ exceeds a threshold in the range of -60 to -40 mV, an action potential initiates which illustrates an EPSP. The bottom waveform represents the
inhibitory action. It illustrates an IPSP with sufficient amplitude for triggering an action potential in negative direction. The simulated EPSP and IPSP are very similar to the experimentally recorded ones, i.e., with real excitatory and inhibitory actions of postsynaptic membrane.

![Graph showing EPSP and IPSP](image)

**Fig 7.11** Simulation results of excitatory and inhibitory actions of postsynaptic membrane. Top waveform represents the EPSP and bottom waveform represents the IPSP.

ISFET based electrical models both for excitatory and inhibitory actions of neurons have been developed. Postsynaptic membrane is divided into three patches to represent spatial summation of gated currents. Temporal integration of the currents is achieved by modeling exponentially varying time dependent threshold voltage of ISFET. The main aim of this work is to show that ISFET can be used as circuit analog to simulate the excitatory and inhibitory postsynaptic potentials with an additional advantage possibility of measurement of neurotransmitters diffused through the synaptic cleft by...
converting the ISFET into neurotransmitter sensitive ENFET [8]. This biologically motivated model may become a useful research and teaching unit both in neurology and bioelectronics areas.

The results obtained from simulation using ISFET are also compared with those reported by previous researchers and with the other proposed models and are given in Table 7.8.

### Table 7.8
COMPARISON OF SIMULATION RESULTS

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Excitatory</th>
<th>Inhibitory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Threshold limit to initiate action potential</td>
<td>Time to attain peak value</td>
</tr>
<tr>
<td>[1]</td>
<td>-65 mV to -50 mV</td>
<td>1 ms</td>
</tr>
<tr>
<td>[35]</td>
<td>-60 mV to -40 mV</td>
<td>3 ms</td>
</tr>
<tr>
<td>Present Work of 7.2</td>
<td>-60 mV to -40 mV</td>
<td>1 ms</td>
</tr>
<tr>
<td>Present Work of 7.3</td>
<td>-60 mV to -40 mV</td>
<td>1 ms</td>
</tr>
</tbody>
</table>
7.4 Biologically Inspired Circuit Model for Simulation of Acetylcholine Gated Ion Channels of the Postsynaptic Membrane at Synaptic Cleft:

The purpose of this work is to develop a simple analog circuit model that can simulate the function of neurotransmitter acetylcholine gated ion channels of postsynaptic membrane at the synaptic cleft. Simulation is performed in MATLAB environment for excitatory actions of synapses both for normal and pathologic states.

It has been mentioned in the previous section that ISFET can be converted into Enzyme Modified Field Effect Transistor (ENFET) by immobilizing specific enzyme on its gate surface. Acetylcholine sensitive ENFET devices have practical applications, specially in the analysis of phosphorous pesticides or nerve gases. In view of its practical implications a description of such devices are discussed below.

7.4.1 Acetylcholine (ACh):

The acetylcholine (ACh) is a chemical compound which acts as a neurotransmitter in both the peripheral nervous system (PNS) and central nervous system (CNS). ACh is the only neurotransmitter used in the motor division of the somatic nervous system (Sensory neurons use glutamate and various peptides at their synapses). ACh is also the principal neurotransmitter in all autonomic ganglia. ACh basically acts as excitatory neurotransmitter, but can work as inhibitory neurotransmitter. ACh behaves as an excitatory neurotransmitter at neuromuscular junctions. But, it slows down the heart rate
when functioning as an inhibitory neurotransmitter. Acetylcholine is considered to be the first neurotransmitter which was identified.

Acetylcholine functions both in the PNS and in the CNS as a neuromodulator. In the PNS, acetylcholine activates muscles, and is a major neurotransmitter in the autonomic nervous system. In the CNS, acetylcholine and the associated neurons form a neurotransmitter system, the cholinergic system, which tends to cause anti-excitatatory actions.

In the PNS, when acetylcholine binds to acetylcholine receptors on skeletal muscle fibers, it opens ligand-gated sodium channels in the cell membrane. Sodium ions then enter the muscle cell, initiating a sequence of steps that finally produce muscle contraction. Although acetylcholine induces contraction of skeletal muscle, it acts via a different type of receptor (muscarinic) to inhibit contraction of cardiac muscle fibers.

In the CNS, ACh has a variety of effects as a neuromodulator upon plasticity, arousal and reward. ACh has an important role in the enhancement of sensory perceptions when we wake up and in sustaining attention. Damage to the cholinergic (acetylcholine-producing) system in the brain has been shown to be plausibly associated with the memory deficits associated with Alzheimer's disease.

Acetylcholine and the associated neurons form a neurotransmitter system, the cholinergic system from the brainstem and basal forebrain that projects axons to many areas of the brain. In the brainstem it originates from the Pedunculopontine nucleus and dorsolateral tegmental nuclei collectively known as the mesopontine tegmentum area or pontomesencephalotegmental complex. In the basal forebrain, it originates from the basal optic nucleus of
Meynert and medial septal nucleus. In addition, ACh acts as an important internal transmitter in the striatum, which is part of the basal ganglia. It is released by a large set of interneurons with smooth dendrites, known as tonically active neurons or TANS.

Acetylcholine is synthesized in certain neurons by the enzyme choline acetyltransferase from the compounds choline and acetyl-CoA. The enzyme \textit{acetylcholinesterase} converts acetylcholine into the inactive metabolites choline and acetate. This enzyme is abundant in the synaptic cleft, and its role in rapidly clearing free acetylcholine from the synapse is essential for proper muscle function. Certain neurotoxins work by inhibiting acetylcholinesterase, thus leading to excess acetylcholine at the neuromuscular junction, thus causing paralysis of the muscles needed for breathing and stopping the beating of the heart.

There are two main classes of acetylcholine receptor (AChR), nicotinic acetylcholine receptors (nAChR) and muscarinic acetylcholine receptors (mAChR). They are named for the ligands used to activate the receptors.

Nicotinic AChRs are ionotropic receptors permeable to sodium, potassium, and chloride ions. They are stimulated by nicotine and acetylcholine. They are of two main types, muscle type and neuronal type. The former can be selectively blocked by curare and the latter by hexamethonium. The main location of nicotinic AChRs is on muscle end plates, autonomic ganglia (both sympathetic and parasympathetic), and in the CNS. The disease myasthenia gravis, characterized by muscle weakness and fatigue, occurs when the body inappropriately produces antibodies against acetylcholine nicotinic receptors,
and thus inhibits proper acetylcholine signal transmission. Over time, the motor end plate is destroyed.

Muscarinic receptors are metabotropic, and affect neurons over a longer time frame. They are stimulated by muscarine and acetylcholine, and blocked by atropine. Muscarinic receptors are found in both the CNS and the PNS, in heart, lungs, upper GI tract and sweat glands [36].

7.4.2 Acetylcholine-sensitive ENFET:

The application of enzymes as bioactive matrices for tailoring of biosensors and bioelectronic devices is of substantial basic and practical importance. The organization of biosensor and bioelectronic devices requires the integration of the biomaterial, e.g. enzyme, with a transducer to generate an electronically contacted assembly that enables the electronic transduction of biorecognition or biocatalytic events occurring on the transducer.

Electrical contacting of redox-proteins and electrode supports can be accomplished by the application of diffusional electron-transfer mediators, by tethering of redox-relay on the enzyme and by the immobilization of redox biocatalysts in redox-polymer systems.

The assembly of monolayers and multilayers of biomaterials on electronic supports can be used as a general method to organize biosensing systems. The thin sensing interfaces of monolayer/multilayer assemblies provide matrices that lack diffusion barriers for the analyte penetration. Redox-relay-tethered enzyme layers assembled on electrodes, surface-reconstitution of apo-proteins on redox-relay/cofactor composite layers, and crosslinking of complex composite layers consisting of redox-enzyme / cofactor / redox-relay units were reported as electrically contacted enzyme-electrodes for electrochemical
sensing. Similarly, antigen monolayers associated with electrodes or oligonucleotide-functionalized electrodes can be used for the electrochemical detection of antibodies and DNA, respectively.

The application of silicon-based microelectronics, and particularly ion-sensitive field-effect transistors (ISFETs) as transduction elements for biocatalytic transformations and biological recognition events, is a challenging subject in bioelectronics and analytical chemistry. Enzyme-based field-effect transistors, ENFETs, are based on biocatalytic reactions affecting the charge at the gate surface, and producing an electronic signal dependent on the enzyme substrate concentration. The sensing performance of the ENFET is affected by the integration method of the enzymes and the ISFET device. The immobilization of enzymes in thick polymer films (such as polyvinylchloride, polyacrylamide hydrogels or polyurethane) on ISFET devices, or the construction of membrane- (e.g. Nafion or polyvinylpyridine) covered crosslinked enzyme matrices on the ISFET, yield active ENFET sensing devices. These bioelectronic systems, however, suffer from basic limitations associated with diffusion barriers of the substrates through the polymer membranes, leading to slow response times and moderate sensitivities. The organization of monolayer/multilayer enzyme-based ISFET could substantially improve the response-times and analytical performance of the ENFET devices. ENFETs can be fabricated by the nano-engineering of the electronic device with a nanoporous thin film that is functionalized with a biocatalytic enzyme-monolayer. The Acetylcholine-Sensitive ENFET is in fact an ISFET whose gate surface is immobilized with enzyme, acetylcholine-esterase.
Fig. 7.12 outlines the configuration of this ENFET device. Field-effect transistors with an Al₂O₃ gate is used as the transducer of the ENFET. An Ag / AgCl-electrode is used as a reference electrode. The differential output signal between the source of the ENFET device and the reference electrode is recorded with a semiconductor parameter analyzer keeping the drain current ($I_d$) and source-drain voltage ($V_{ds}$) constant. The schematic diagram as well as its electronic diagram is shown in Fig. 7.13. The equation 7.39 summarizes the biocatalytic transformation stimulated by the acetylcholine-esterase enzyme that is used to generate ENFET sensor sensitive to acetylcholine.

![Fig. 7.12: General configuration of ENFET.](image-url)
Fig. 7.13: Acetylcholine ENFET (a) Schematic diagram (b) Electronic diagram
The proton generated in this reaction alters the pH at the gate surface which is registered by the underlying ISFET. These changes in the pH affect the potential of the gate interface and consequently affect the potential difference between the gate and the source electrode \( (V_{GS}) \) when \( I_D \) and \( V_{DS} \) are kept constant.

Since it is essentially an ISFET, the governing equation with reference to the equation (7.32) can therefore be written as-

\[
G_{DS} = \beta \left( V_{GS} - V_{TH(ENFET)} \right)
\]  
\[
(7.40)
\]

Where, as previous \( \beta = \mu C_{OX} \frac{W}{L} \)  
\[
(7.41)
\]

Here \( V_{TH(ENFET)} \) is a function of pH of solution dependent on the concentration of acetylcholine. Response of such a particular device with respect to \( V_{GS} \) is shown in Fig. 7.14 [8].
7.4.3 Circuit Model based on Acetylcholine Sensitive ENFET:

Referring to equation (7.40) i.e.

\[ G_{DS} = \beta(V_{GS} - V_{TH(ENFET)}) \]

In ENFET, \( \beta \) and \( V_{GS} \) are constants and \( V_{TH(ENFET)} \) is the only input variable. Thus \( G_{DS} \) is dependent on the threshold voltage, \( V_{TH(ENFET)} \), analogous to the conductance of ion channels of postsynaptic membrane dependent on the...
binding activity. The acetylcholine gated ion channels can therefore be represented by acetylcholine sensitive ENFET due to its variable nature of conductance with respect to voltage.

In case of excitatory action, acetylcholines (Ach) are released by the presynaptic terminals into the synaptic cleft. Acetylcholines diffuse through the cleft and bind with specific receptor sites of post synaptic membrane. These receptors are called nicotinic acetylcholine receptors (AChR). The acetylcholine – receptor binding activity initiates the opening of sodium channels causing the flow of sodium ions into the cell. If a sufficient number of channels open, then the membrane potential exceeds the threshold for initiating an action potential.

In the case of pathologic state, the number of functional receptor sites in the post synaptic membrane is reduced. This is caused by an autoimmune disease, called myasthenia gravis, where the host manufactures antibodies. These antibodies destroy acetylcholine receptors in the post synaptic membrane at the synaptic cleft causing the reduction of functional receptors and hence the neurotransmitter – receptor binding activity at the postsynaptic membrane. In this condition, sufficient numbers of channels are not open to initiate an action potential and as a result the patient suffers from muscle weakness [35].

In simplest case the acetylcholine – receptor binding activity is governed by the chemical reaction [35]-

\[
2\text{ACh} + \text{AChR (closed)} \xrightleftharpoons{K_1}{K_2} 2\text{Ach} - \text{AChR (open)}
\]  

(7.42)

Where \(K_1\) and \(K_2\) are the forward and backward rate constants respectively.
Acetylcholine-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. $V_{TH(ENFET)}$ in equation (7.40) can, therefore, be modeled as [35]:

$$V_{TH(ENFET)}(t) = V_{THO}\left[1 - \exp(-k_1 t) + \exp(-k_2 t)U(t-t_m)\right]$$

(7.43)

Where $K_1$ and $K_2$ are time constants analogous to the rate constants of equation (7.42), $U(t-t_m)$ 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.

The circuit model for post synaptic membrane is shown in Fig. 7.15. 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 $g_{Na_1}$, $g_{Na_2}$, and $g_{Na_3}$, where

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

(7.44)

So that, $I = I_m - I_{Na} + I_K$

$$= C_m \frac{dV_m}{dt} - g_{Na}(V_m - E_{Na}) + g_K(V_m - E_K)$$

(7.45)

Where $g_{Na}$ is the total sodium conductance and $g_K$ is the non-gated potassium conductance. $V_{g_1}$, $V_{g_2}$ and $V_{g_3}$ 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 acetylcholine-gated sodium channels.
Fig. 7.15: Circuit model for Postsynaptic membrane

The component values assigned in the model for MATLAB simulation are taken from reference [35] and are given in Table 7.9. The specifications for three n-channel ENFETs and the parameters for exponential function in equation (7.21), applied to each ENFET inputs are also given Table 7.9. The three gate 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 acetylcholine are applied in a staggered sequence at 1.5 msec intervals. This is done to simulate the time variation in acetylcholine transmitter–receptor binding with respect to different patches of postsynaptic membrane [35].

In order to reduce the number of functional receptors caused by autoimmune disease, $V_{THO}$ is considered as -1 volt. The time constants $k_1$ and $k_2$ are considered as 1.5msec to prolong the rate of acetylcholine-receptor binding activity.

**TABLE 7.9**
**DIFFERENT COMPONENTS USED IN THE PROPOSED MODEL OF SYNAPSE**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameter</th>
<th>Parameter Details</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>$C_m$</td>
<td>Membrane Capacitance</td>
<td>Farad</td>
<td>1 $\mu$F per cm²</td>
</tr>
<tr>
<td>02</td>
<td>$g_K$</td>
<td>Potassium Conductance</td>
<td>Mho</td>
<td>1 mS per cm²</td>
</tr>
<tr>
<td>03</td>
<td>$E_Na$</td>
<td>Sodium Potential</td>
<td>Volt</td>
<td>60mV</td>
</tr>
<tr>
<td>04</td>
<td>$E_K$</td>
<td>Potassium Potential</td>
<td>Volt</td>
<td>-90mV</td>
</tr>
<tr>
<td>05</td>
<td>$I$</td>
<td>Membrane Current</td>
<td>Ampere</td>
<td>0 A</td>
</tr>
<tr>
<td>06</td>
<td>$L$</td>
<td>Channel Length</td>
<td>Meter</td>
<td>15 µm</td>
</tr>
<tr>
<td>07</td>
<td>$W$</td>
<td>Channel Width</td>
<td>Meter</td>
<td>2 µm</td>
</tr>
<tr>
<td>08</td>
<td>$t_{ox}$</td>
<td>Oxide Thickness</td>
<td>Meter</td>
<td>100 nm</td>
</tr>
<tr>
<td>09</td>
<td>$\mu$</td>
<td>Electron mobility</td>
<td>cm²/V·sec</td>
<td>600 cm²/V·sec</td>
</tr>
<tr>
<td>10</td>
<td>$V_{THO}$</td>
<td>Threshold Voltage</td>
<td>Volt</td>
<td>-2 Volts</td>
</tr>
<tr>
<td>11</td>
<td>$t_m$</td>
<td>Time</td>
<td>Second</td>
<td>600 µsec</td>
</tr>
<tr>
<td></td>
<td>$k_1 = k_2$</td>
<td>Time Constant</td>
<td>Second</td>
<td>0.8 msec</td>
</tr>
</tbody>
</table>
7.4.4 The Result:

The MATLAB simulation outputs are shown in Fig 7.16. The top waveform represents the normal postsynaptic membrane potential and the bottom waveform represents the postsynaptic membrane potential in the case of pathologic state. It is seen that when $V_m$ exceeds the threshold in the range of -60mV to -45mV, more or less all the sodium channels open and initiates an action potential. But during pathologic state, the membrane potential degrades due to reduction of functional receptors and hence no action potential is developed.

![Simulated result of postsynaptic membrane potential](image-url)
The aim of this work is to show that acetylcholine-sensitive ENFET can be used as circuit analog to simulate the excitatory postsynaptic potential with an additional advantage: measurement of concentration of acetylcholine diffused through the synaptic cleft. This biologically motivated model may become a useful research and teaching unit both in neurology and bioelectronics areas. 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.

The results obtained from simulation of the proposed model are compared with those reported by previous researchers and with the other proposed models and are given in Table 7.10.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Threshold limit to initiate action potential</th>
<th>Time to attain peak value</th>
<th>Total duration of EPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>- 65 mV to - 50 mV</td>
<td>1 ms</td>
<td>3.5 ms</td>
</tr>
<tr>
<td>[35]</td>
<td>- 60 mV to - 40 mV</td>
<td>3 ms</td>
<td>6 ms</td>
</tr>
<tr>
<td>Present Work of 7.2</td>
<td>- 60 mV to - 40 mV</td>
<td>1 ms</td>
<td>3.5 ms</td>
</tr>
<tr>
<td>Present Work of 7.3</td>
<td>- 60 mV to - 40 mV</td>
<td>1 ms</td>
<td>3.5 ms</td>
</tr>
<tr>
<td>Present Work of 7.4</td>
<td>- 60 mV to - 45 mV</td>
<td>1 ms</td>
<td>3.5 ms</td>
</tr>
</tbody>
</table>

**7.5 References:**

[1] Levine, M. D. Fare, T. L. Eisenberg, M. F. A Physiologic Based Circuit Model of Excitation & Inhibition in the postsynaptic region, *IEEE*


