Abstract

This thesis aims at contributing towards development of electronic circuit analog of post synaptic membrane of neuron and relevant biologically motivated models for its simulation to predict the behavior of post synaptic membrane dependent on neurotransmitter-receptor binding activity.

Modeling of neuron has played important roles in the field of network to describe the dynamics of both single neurons and neuronal networks as well as in neuroscience for simulation of receptor function and electrical activity of the postsynaptic neuron. Based on applications, two main classes of models of neurons have been implemented in silicon, namely Integrate-and-Fire (I-F) model and Conductance based model.

The concept of Integrate-and-Fire (I-F) model was first given by Lapicque, in the year 1907. Lapicque modeled the neuron using an electric circuit consisting of a parallel capacitor and resistor to represent the capacitance and leakage resistance of the cell membrane. This remarkable achievement stresses that, in neural modeling, studies of function do not necessarily require an understanding of mechanism. Significant progress is possible if a phenomenon is adequately described, even if its biophysical basis cannot be modeled. Ever since its inception, its variants have been successfully used in describing the dynamics of both single neurons and neuronal networks. These models have been found to be suitable for many theoretical and computational studies over decades. But one of the main drawback of these type of models that they cannot correctly reproduce the neuronal dynamics close to the firing threshold. What is essential for a neuron to correctly reproduce the neural dynamics that it has to spend a significant amount of time far away from firing threshold.
In 1952, Hodgkin and Huxley published a paper on membrane current and its applications to conduction and excitation in nerves that is cited by many authors in the context of conductance based neuron models. They have conducted a series of experiments to study in great detail the properties of postsynaptic membrane. On the basis of these experiments, they have given a quantitative description of membrane current and its application to conduction and excitation in nerve. From these experimental results, they have proposed an equivalent circuit to account for the resistive and capacitive properties of a patch of membrane. This circuit is known as Hodgkin and Huxley (H-H) model. Since 1952, led by Hodgkin and Huxley, many electronic circuits have been developed to reproduce the behavior of nerve axons. Due to the inclusion of many biological phenomena of postsynaptic membrane through conductances, this model can reproduce electrophysiological measurements to a high degree of accuracy. H-H model is, therefore, considered as one of the most basic models in neuroscience and still widely used today. But these models have not explained the function of synapses on which the variable permeability of postsynaptic membrane arises.

In this research work attempts have been made in a very modest way to contribute the following:-

(1) Analog integrated circuit models of neuron are developed to emulate the behavior of real neuron and simulated in ORCAD. Simple neuron models have been developed and simulated by considering each dendrite as one spiking source. The model has been developed by considering (i) Dendrite is supposed to be consisting of three regions; each receives three inputs from three nearby neurons. Each input to a specific dendritic region is connected with the synaptic weight values to
represent the synaptic action. Effect of all these three inputs is then spatially integrated and brought to a single point value. It is assumed that this integration process takes place separately inside the soma. Each integrated output generates an action potential if it is crosses a threshold value, which is required for impulse to be transmitted through the axon to the postsynaptic neuron via synapse, and (ii) the three outputs through the axon are again connected with the synaptic weight values before reaching postsynaptic neuron. This is done to emulate the synaptic mechanism of real biological neuron. A comparator integrates these outputs and generates a voltage i.e. membrane voltage. Action potential is triggered when the membrane voltages reaches a specific threshold value.

(2) Simple integrate-and-fire based model both for excitatory and inhibitory synapses has been developed by considering a synapse to be made of presynaptic terminals, cleft and postsynaptic membrane. The overall effect of all presynaptic terminals is integrated and then reduced to a single point. The single point value is compared with threshold to produce an output. Simulation of the model yields an output representing the overall membrane potential of the postsynaptic region. Simulation is performed in ORCAD both for normal (excitatory) and unhealthy (inhibitory) states and results are compared with the previously obtained data and a good agreement is obtained.

(3) 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 metal-oxide semiconductor field effect transistor
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. 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. Simulation is performed in MATLAB environment both for excitatory and inhibitory actions of synapses and the results are presented. These results are analyzed and compared with the previously obtained data and a good agreement is obtained.

(4) ISFET based electrical models both for excitatory and inhibitory actions of neurons have been developed. Similarity between MOSFET and ISFET indicates that like MOSFET, ISFET can also function as a voltage controlled conductance. But since ISFET can 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 ISFET based analog is incorporated into the Hodgkin-Huxley (H-H) model of neuron to substitute the variable Na⁺ and Cl⁺ conductances. 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 applied to ISFET. The 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. Simulation results are presented and compared with the results obtained by previous researchers.

(5) 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 acetylcholine 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.

The results obtained from simulation leads to the conclusion that ISFET based model is more advantageous because it can be modified into specific neurotransmitter sensitive ENFET leading to the simultaneous measurement of neurotransmitter that binds with the receptor sites of the postsynaptic membrane. Measurement of neurotransmitter plays an important role in the field of neurology. ISFET based approach may also make the research area more wide in near future.