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A Biomimetic Model of Chemical Synaptic Transmission Dynamics

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Abstract : *During a synaptic transmission in a mammalian system, biological information gets transferred from one neuron to the next by means of biomolecular signaling. This occurs through the conduction of Calcium ions through nanopore protein channels across the neural cell membrane. This process is vital for all the activities of the living system. The deoxyribonucleic acid (DNA) transcription of specific neural genes in the postsynaptic neuron also plays a major role in the entire process of synaptic transmission dynamics. Several electronic circuits have been proposed for replicating such a neural synaptic communication process. The invention of memristors was a major turning point in the development in this area; it provided for a much more novel, efficient and miniaturized neural circuit emulation and has been substantiated to be the preeminent biomimicry of biochemical mechanism occurring at the synapse. Electronic circuits that imitate biological behavior are called biomimetics. Biomimetics represent the operational characteristics of the biocellular interfaces and communication, biological pathways, or elementary structure and they also assist in the implementation of complex biological phenomena and specialized biomolecular functionality. This paper presents a novel behavioral-level biomimetic circuit model of the synaptic communication process for the biomolecular. This circuit model is proficient for generating excitatory currents, potentials, and summed excitatory potentials, which is transmitted from one neuron to the next.*

Keywords - *Biomimetic, DNA , synaptic transmission*

I. INTRODUCTION

Control and coordination of various functions in living organisms are facilitated through actions of well-organized information transmission systems [6]. In the mammalian system, this is enabled through the presence of an elaborate and complex neuronal network that helps transmit quick information in a cascading process between the interconnected processing elements called neurons. The presence of specialized structures called "synapses" in the neurons help in neuronal signaling process. The synaptic signaling is accomplished in two distinct ways: electrically and chemically, but most mammalian synapses are chemical in nature. It is observed that the synapses are either simple excitatory or inhibitory interconnects between neurons in the network. These interconnects have been adopted for tracing the transmission process thus overcoming the difficulties that would arise from the complex nature and diversity of neuronal network. Electronic modeling of biological system based on these biochemical operations provides biomimetic devices that are more robust with many parallel and efficient processing prospects.

Biomimetic modeling incorporates the operational characteristics of biocellular interfaces in elementary structures and transmission pathways of living systems that assist in complex biological phenomena and specialized biomolecular functions [3]. Transmission dynamics at the neural synaptic junction on a biomolecular level controls all life activities in mammals. Analogies between biological parameters and electronic circuit entities have led to schematic biomimetic models. Movement of ions and molecules through channels present across neuron membrane that strictly maintains concentration gradients across them result in flow of current. The chemical concentration is analogous to a voltage at a circuit node and corresponds to signals in electronic devices that convey information.

Transmission or neuronal signaling is a cascading process whereby information is transferred through biochemical molecules from one neuron to another. Synapse, the point of contact between any two neurons, is the site of transfer and is described best as a space or "synaptic cleft" between the tail end or axon of one neuron (presynaptic neuron) and the dendrites of the adjacent neuron (postsynaptic neuron). As the action potential reaches the end of the axon, the biochemical called the „neurotransmitter" is released into this space and travels across the synaptic cleft to reach the next neuron to alter its electric potential. The initiation and propagation of the inter-neuronal communication process is intricate and specialized, involving excitation and generation of an action potential. The presence of ion transporters and ion channels, the integral membrane proteins of the

neurons, that open or close in response to a membrane potential form the basis of action potential; the former generates transmembrane concentration gradients and the ion channels are channels in the neuronal membrane to allow ions to pass through selectively from one side of the neuronal membrane to the other. The ion gradients set up by the ion transporters is exploited by the ion channels and thus together providing a comprehensive mechanism behind the neuronal ability to generate voltage-sensitive electrical signals [6]. Signal transmission at chemical synapse involves a sequence of events. It is initiated when the action potential arrives at the terminal of the presynaptic neuron. When an action potential arrives at the terminal of the presynaptic neuron there will be opening of voltage-gated calcium channels in the presynaptic membrane allowing an influx of Ca^{2+}; this triggers the synaptic vesicles, special organelles filled with neurotransmitters such as acetylcholine ACh and glutamate, to fuse to the plasma membrane of the presynaptic neuron and then release their contents into the synaptic cleft. The neurotransmitter binds to receptors in the postsynaptic membrane causing a change in its ability to permit ion flow into the postsynaptic cell thus altering the membrane conductance creating an end plate potential sufficient to produce a postsynaptic action potential, thus completing the transfer of signal from one neuron to another. The degradation of neurotransmitters at the synapse results in termination of postsynaptic effects of neurotransmitters [6].

This paper presents a novel behavioral-level biomimetic circuit model of the chemical synaptic communication process for the biomolecular pathways. This model is proficient for generating excitatory currents, potentials, and summed excitatory potentials, which is transmitted from one neuron to the next.

The paper has been organized into five chapters in the following manner. Section II elaborates on the literature survey. It describes in detail the concept of chemical synaptic transmission process and the postsynaptic transmission dynamics. Section III illustrates the proposed behavioral-level model discussed in the paper. Section IV describes the result and analysis. Section V investigates about the relevance of the topic and its importance in the present scenario. It also mentions the possible future scope in this area of study.

II. LITERATURE SURVEY

Neural circuits are the primary components of neural systems that process specific types of information. Neural systems comprise neuron and circuits in a number of discrete anatomical locations in the brain. The cells of the neuron system can be divided into two broad categories. They are nerve cells or neurons and supporting cells called neuroglia or glia. The nerve cells are specialized for electrical signalling over long distances. Neuron and glia share the complement of organelles found in all cells such as [6]: endoplasmic reticulum, golgi apparatus, mitochondria and a variety of other vesicular structures. The most obvious sign of neuronal specialization for communication via electrical signalling is the extensive branching of neurons. The most prominent aspect of this branching for typical nerve cells is the elaborate arborisation of dendrites that arise from the neuronal cell body. They are also referred to as dendritic branches or dendritic processes [11], [6].

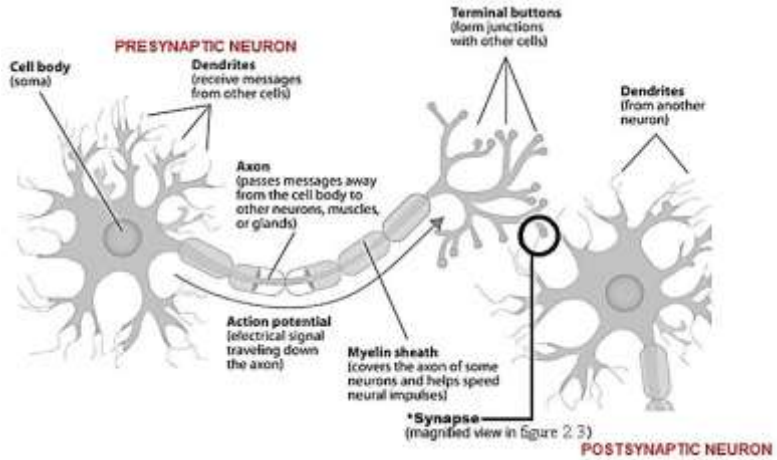

Fig. 1: Neuron and the neuronal synapse [6]

In the neuronal network, a presynaptic terminal is found just adjacent to a postsynaptic cellular specialization that is the target cell. Most synapses have no physical continuity between these pre- and postsynaptic element but instead, these pre- and postsynaptic components signal each other by secretion of

molecules from presynaptic terminal that bind to receptors in the postsynaptic specialization. These neurotransmitter molecules have to traverse an interval of extracellular space between pre- and postsynaptic elements called synaptic cleft. It is the site where extracellular proteins exert their influence on the diffusion, binding and degradation of molecules secreted by the presynaptic terminal. The information conveyed by synapses on neuronal dendrites is then interpreted and read out at the origin of the axon (the portion of nerve cell specialized for signal conduction) to the next site of synaptic interaction.

1. Action potential

Before the arrival of any impulse or when a neuron is not yet stimulated, its membrane is said to be polarized. Under this condition, the electrical charge on the outside of the membrane is positive while the electrical charge on the inside of the membrane is negative. This is so because the ratio of sodium ions (Na^+) on the outside of the neuron to the potassium ions (K^+) on the inside is in the ratio of 3:2. So there are excess sodium ions on the outside of the cell and hence the inside is negative as when compared to the outside. The membrane potential when the neuron is in the polarized or idle state is referred to as the resting potential. It is usually in the range of -40mV to -90mV. It remains at this potential until a stimulus arrives. The Na^+ and K^+ can move to and fro across the neural membrane. This is advocated with the help of Na^+/K^+ pumps that exist on the membrane that allow Na^+ to move inside the neuron and K^+ outside the neuron [6].

When electrical signal is produced by neurons in response to stimulus, it changes the resting membrane potential of the neuron by opening up of "gated-ion channels" on the resting neural membrane instantaneously, allowing Na^+ outside the membrane to flow into the cell. As a result the inside becomes more positive and when the stimulus goes above a particular threshold (each neuron has a particular threshold) the neuron changes from a polarized state to a depolarized state. Action potential is an active response that is generated by a neuron; it is a brief change from a negative to a positive in the transmembrane potential. The amplitude of the action potential is independent of the magnitude of the current used to evoke it. Hence it is called as an "all-or-none" mechanism.

However, if the duration of stimulus is long enough, then multiple action potentials will result. When a signals travels down myelinated axon, the impulse must move at intervals between the non-insulated gaps called nodes of Ranvier that exist between each Schwann cell.

The electrical events that carry signals over distances in the axon are called the action potential. This is a self-generating wave that propagates from the point of initiation in the cell body (referred to as the "axon hillock") to the terminals of the axon, where synaptic contacts made. The axon hillock is the last site in the cell body where membrane potentials propagated from synaptic inputs are summated before being transmitted along the axon. So it is the axon hillock which is the site of action potential initiation [6].

2. Synaptic transmission

The chemical and electrical processes by which information encoded by action potentials is passed on at the synaptic contacts to the next cell in the pathway is called synaptic transmission. The synapses are the functional contacts between the neurons that aid transfer of stimulus and information throughout the nervous system. On the basis of the mechanism involved in transmission, there are two types of synapses [6], [8]: electrical synapse and chemical synapse.

2.1 Electrical synaptic transmission

The gap junctions contain precisely aligned, paired channels in the membranes of the pre- and the postsynaptic neurons, such that each channel pair forms a pore. A variety of substances can simply diffuse through the gap junction pores, passively. The transmission can be bidirectional [6].

2.2 Chemical Synaptic Transmission

Presynaptic terminals (synaptic endings or axon terminals or terminal buttons) and their postsynaptic specializations typically make a chemical synapse that is the most abundant synapse in the nervous system. (The electrical synapse is far rarer.) The secretory organelles in the presynaptic terminals at the chemical synapse are the synaptic vesicles, which are generally spherical structures filled with neurotransmitter molecules. The positioning of synaptic vesicles at the presynaptic membrane and their fusion to initiate neurotransmitter release is regulated by a number of proteins either within or associated with the vesicles. The neurotransmitters released

from the synaptic vesicles modify the electrical properties of the target cell by binding to the neurotransmitter receptors located primarily at the postsynaptic specializations [6], [8].

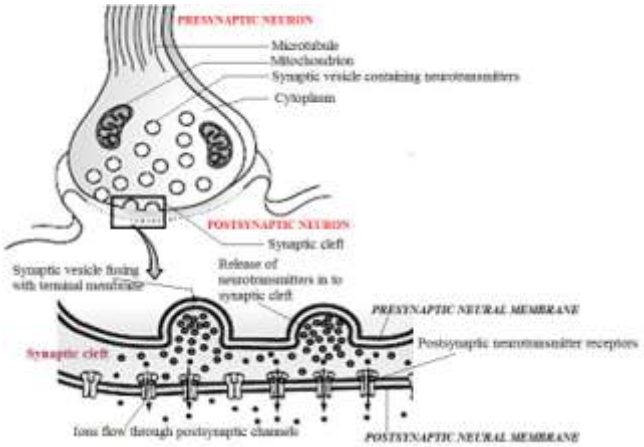

Fig. 2: Chemical synaptic transmission process [6]

2.2.1 How ionic movement produces electrical signal

Electrical potentials are generated across the membranes of neurons. This can be attributed to two reasons:

1. there are differences in the concentrations of specific ions across nerve cell membranes
2. the membranes are selectively permeable to some of these specific ions

These attributes can be explained based on two different kinds of proteins in the cell membrane. They are namely: active transporters & ion channels. Active transporters are proteins that move ions into or out of cells, against their concentration gradients. So, in essence, transporters create ion concentration differences by actively transporting ions against their chemical gradients. Ion channels are transmembrane proteins that contain specialized structures called pores. These pores permit only specific ions to cross the neuronal membrane, or in other words they are selectively permeable to certain ions. Some channels can also sense electrical potential across the membrane. Such "voltage-gated" ion channels open or close in response to the magnitude of membrane potential, allowing membrane permeability to be regulated by this potential. Different channels types are used to discriminate between sodium ions and potassium ions. Conductance is voltage dependent and therefore the channels can sense the voltage drop across the membrane. So they can open only when the voltage reaches appropriate levels. Voltage-sensitive sodium and potassium channels are responsible for macroscopic conductance and currents that underlie the action potential. There are two types of ion channels: selectively permeable to sodium ions and selectively permeable to potassium ions. Both channel types are voltage-gated, meaning they open based on the membrane potential. For each channel, depolarization increases the probability of channel opening; more specifically, it inactivates the Na^+ channels but not the K^+ channels. Hyperpolarization, on the other hand, closes the channel.

2.2.2 Sodium-Potassium pump

The sodium ion (Na^+) efflux is directly associated with simultaneous ATP-dependent influx of K^+. These opposing fluxes of Na^+ and K^+ are operationally inseparable – removal of external K^+ greatly reduces Na^+ efflux and vice versa. These energy-dependent movements of Na^+ and K^+ implicated an ATP hydrolyzing Na^+/K^+ pump in the generation of the transmembrane gradients of both Na^+ and K^+. The pump alternately shuttles these ions across the membranes in a cycle fueled by the transfer of a phosphate group from ATP to the pump protein. The movements of Na^+ and K^+ indicate that the two species of ions are not pumped at identical rates – the K^+ influx is only about two-thirds the Na^+ efflux. Thus, the pump apparently transports two K^+ into the cell for every three Na^+ that are removed. This process is depicted in the Fig. 3. This stoichiometry causes a net loss of one positively charged ion from inside of the cell during each round of pumping, meaning that the

pump generates an electrical current that can hyperpolarize the membrane potential. For this reason, the Na^+/K^+ pump is said to be electrogenic. Since the pumps act much more slowly than ion channels, the current produced by the Na^+/K^+ pump is quite small. Although the electrical current generated by the activity of the Na^+/K^+ pump is small, under special circumstances the pump can significantly influence the membrane potential.

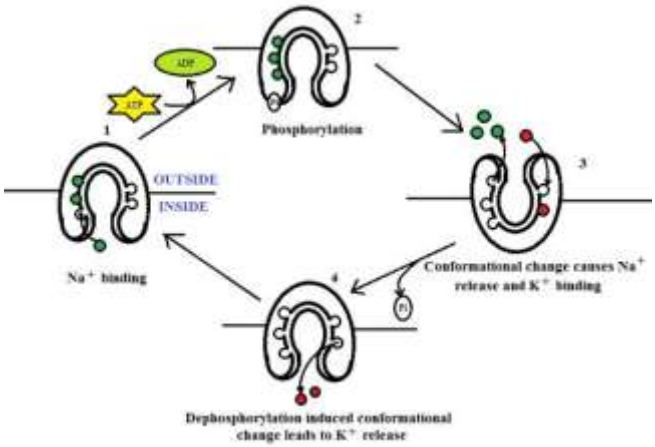

Fig. 3: Ionic movements due to Na^+/K^+ pump

2.2.3 Transmitter secretion and role of calcium ions

The concentration of Ca^{2+} is related to the number of vesicles that fuse with the plasma membrane of the terminal because the presynaptic terminals have Ca^{2+} channels in their plasma membranes that are voltage-sensitive; this regulates the fusion of synaptic vesicles. The study in the area was conducted by Katz and Ricardo Miledi. The amount of neurotransmitter released was found to be sensitive to the exact amount of Ca^{2+} entering the neuron. So Ca^{2+} channels are directly involved in neurotransmission. Thus, presynaptic action potentials open voltage-gated Ca^{2+} channels, with a resulting influx of Ca^{2+}. The Ca^{2+} ions enter the presynaptic terminals and thus causing a rise in the concentration of Ca^{2+} within the terminal; as a result of this it produces effects in the following two ways: firstly, this inflow of Ca^{2+} into presynaptic terminals triggers transmitter release in the absence of presynaptic action potentials and secondly, the presynaptic inflow of calcium chelators (chemicals that bind Ca^{2+} and keep its concentration buffered at low levels) prevents presynaptic action potentials from causing transmitter secretion. These results prove beyond any doubt that a rise in the presynaptic Ca^{2+} concentration is both necessary and sufficient for neurotransmitter release. So, Ca^{2+} serves as a second messenger during transmitter release.

2.2.4 Neurotransmitters receptors

The binding of neurotransmitter receptors either directly or indirectly causes the ion channels in the postsynaptic membrane to open or close. The macroscopic current resulting from the summed opening of many ion channels is called the end plate current (EPC). The EPC is normally inward and it causes the postsynaptic membrane potential to depolarize. This depolarizing change in potential is the end plate potential (EPP). EPP triggers a postsynaptic action potential by opening the voltage-gated Na^+ and K^+ channels.

III. PROPOSED WORK

There are a number of neurotransmitter receptors on the postsynaptic neuron such as NMDA and AMPA [9]. They react differently to the neurotransmitters. AMPA receptors respond immediately to glutamate. They open Na^+ and K^+ ion channels in the postsynaptic neuron. When Na^+ enters the postsynaptic terminal, it depolarizes the postsynaptic membrane. NMDA receptors are slower to respond. They respond after the membrane has depolarized. When glutamate binds to the NMDA receptor, the NMDA receptor changes its shape. The change of shape forces a Magnesium ion out of the channel, effectively unblocking the channel. Ca^{2+} ions normally found outside the cell, race into the inside of the postsynaptic terminal. Ca^{2+} binds to a protein called calmodulin. In turn, calmodulin activates other proteins such as CaMKIV or CaMKII. These kinase molecules are enzymes that perform some very important functions in the cell. It adds a phosphate group

onto other proteins. When a kinase becomes activated, it adds a phosphate to other proteins, called protein substrates. As a result of adding the phosphate groups, these „other proteins" now get altered. CaMKII and CaMKIV activate a number of proteins. Many of these proteins activate other proteins. At the synapses, these protein-to-protein interactions can be noticed. A Ca^{2+} influx causes a series of reactions that result in the activation of cAMP protein kinase. The activated cAMP protein kinase moves to the nucleus of the postsynaptic cell, where it binds to another protein called CREB. CREB controls DNA transcription. When activated, CREB transcribes DNA in the cell nucleus to produce RNA. RNA travels back to the synapse, where it synthesizes new proteins to change the structure of the synapse [4], [2].

1. Basic Working Concept of Postsynaptic Transmission

Process is initiated when an action potential invades the terminal of the presynaptic neuron. The action potential causes a sudden shift in the electrical potential across the membrane. A number of different electrically charged ions rush across the membrane – among these are Ca^{2+} ions which activate vesicles in the presynaptic terminal. These vesicles contain the neurotransmitters such as acetyl choline (ACh) and glutamate. The change in membrane potential caused by the arrival of the action potential leads to the opening of voltage gated Ca-channels in the presynaptic membrane. Because of the steep concentration gradient of the Ca^{2+} across the presynaptic membrane the opening of these channels causes a rapid influx of Ca^{2+} into the presynaptic terminal with the result that the Ca^{2+} of the cytoplasm in the terminal transiently rise to a much higher value. Elevation of the presynaptic Ca^{2+} allows synaptic vesicles to fuse with the plasma membrane of presynaptic neuron. The Ca^{2+}-dependent fusion of synaptic vesicles with the terminal membrane causes their content (neurotransmitters) to be released into the synaptic cleft. Following exocytosis, transmitters diffuse across the synaptic cleft and bind to specific receptors on the membrane of the postsynaptic neuron. The binding of neurotransmitter to the receptors causes channels in the postsynaptic membrane to open (or sometimes to close) thus changing the ability of ions to flow into (or out of) postsynaptic cells. Resulting neurotransmitter-induced current flow alters the conductance and the membrane potential of the postsynaptic neuron, increasing or decreasing the probability that the neuron will fire an action potential. Fig. 4 depicts a macroscopic view of the postsynaptic transmission with detailed description of each stage that occurs in its course.

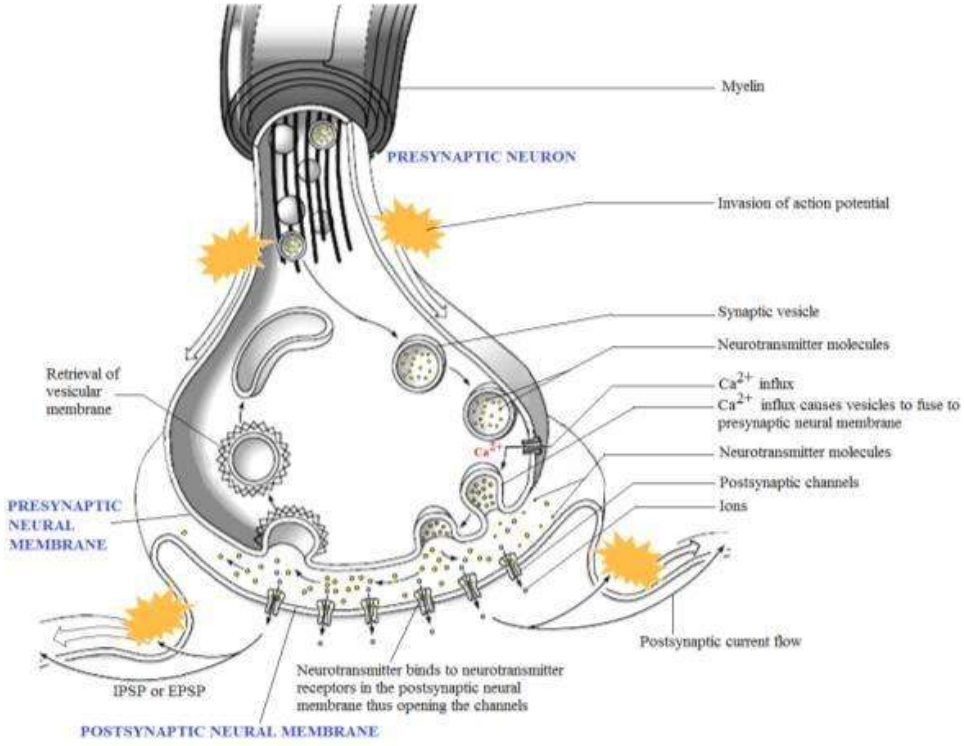

Fig. 4: Macroscopic view of postsynaptic transmission process [6]

2. Block Diagram Description

The block diagram shown in Fig. 5 is the basis on which the simulation for the paper has been carried out. It follows the same steps as already described in section 3.1. However the DNA transcription and RNA translation have not been modeled.

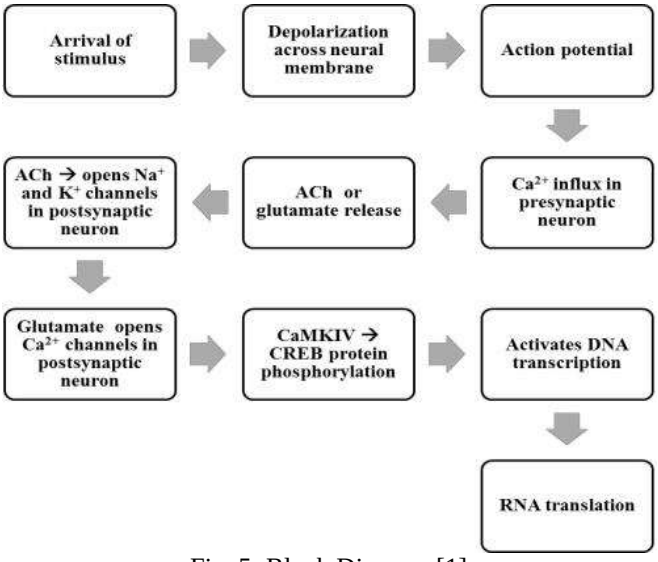

Fig. 5: Block Diagram [1]

IV. RESULT & ANALYSIS

Fig. 6 shows the overview of the various major modules and the basic concept involved in the simulation of the project. It also summarizes the basic functionality of the each module.

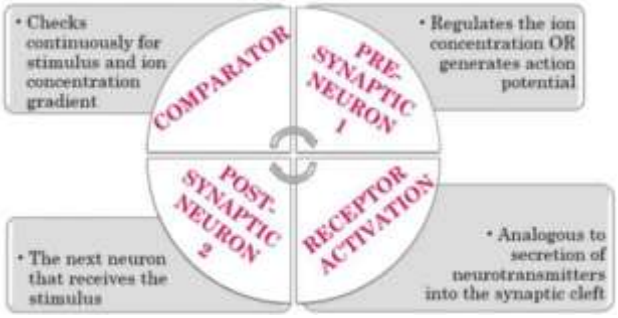

Fig. 6: Overview of simulation modules

The simulation has been carried out separately to depict the postsynaptic neural transmission as well as the transmission along the axon of the nerve cell. The postsynaptic neural transmission involves the transmission of the impulse from one neuron to the next. The first neuron, which is the source of the impulse or stimulus, is called as the presynaptic neuron. The second neuron which receives the signal from the presynaptic neuron is called as the postsynaptic neuron. The synaptic transmission module models the transmission from the presynaptic to the postsynaptic neuron. The synaptic transmission involves a chemical synapse and therefore involves the release of neurotransmitters into the synaptic cleft, under the presence of specific ions and concentration levels. The transmission along the axon involves a series of depolarization and polarization steps along the nerve cell through ion channels, to propagate the action potential along the neuron. This has been depicted in the second module. The modules involved and their functionality have been described in the following sections. The simulation results of the postsynaptic transmission module and the axon transmission module are provided. The simulation has been carried out in Xilinx ISE Design Suite (Version 14.2) platform, programmed in Verilog Hardware Development Language (HDL).

1. Postsynaptic Transmission Module Architecture

The postsynaptic transmission refers to the transmission of the impulse or stimulus or electrical signal from one neuron to the next. The presynaptic neuron transmits the impulse to the postsynaptic neuron by releasing the neurotransmitters into the synaptic cleft between the presynaptic neuron and the postsynaptic neuron. This chemical synaptic transmission is portrayed.

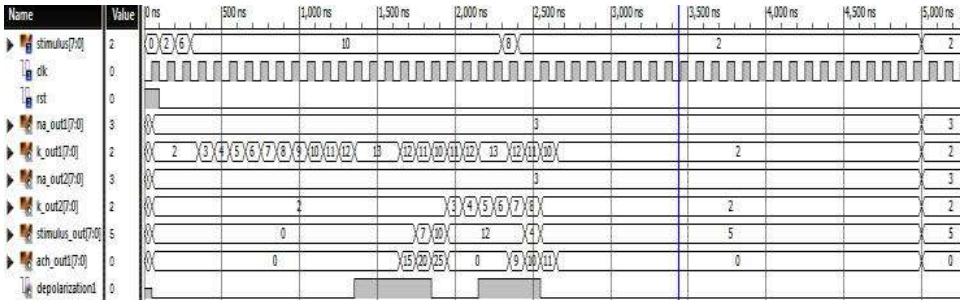

Fig. 7: Waveform for postsynaptic transmission process

2. *Axon Transmission Architecture*

When an impulse travels down a myelinated axon, the impulse must move between the uninsulated gaps between the Schwann cells, the nodes of Ranvier. The processes of depolarization and repolarization occur in these uninsulated nodes of Ranvier by way of which action potentials are generated and the impulse is transmitted along the axon. When a stimulus reaches an idle neuron, the gated ion channels of the polarized neuronal membrane open rapidly allowing the Na^+ ions that were outside the membrane to rush into the neuron. As a result of this, the neuron deviates from a polarized idle state to being depolarized. Polarized state refers to a condition wherein the outside of the membrane is more positive with respect to the inside of the membrane; the inside of the neuron has a net negative potential. On arrival of the stimulus, more positive ions from outside the membrane rush inside the neuron, hence setting up a net positive membrane potential within the neuron. Subsequently, polarization is removed and the threshold is reached. The ion threshold is set to a value of 10. A complete depolarization of the neuron results in the initiation of action potential and the stimulus will be transmitted to the next node of Ranvier along the axon. This process continues along the entire length of the axon before reaching the synaptic terminal of the neuron, after which the postsynaptic transmission process governs the propagation of the impulse to the next neuron.

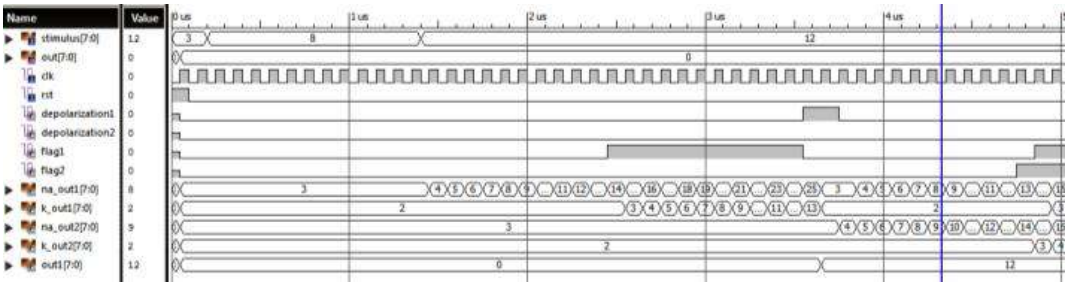

Fig. 8: Waveform obtained for axon transmission process

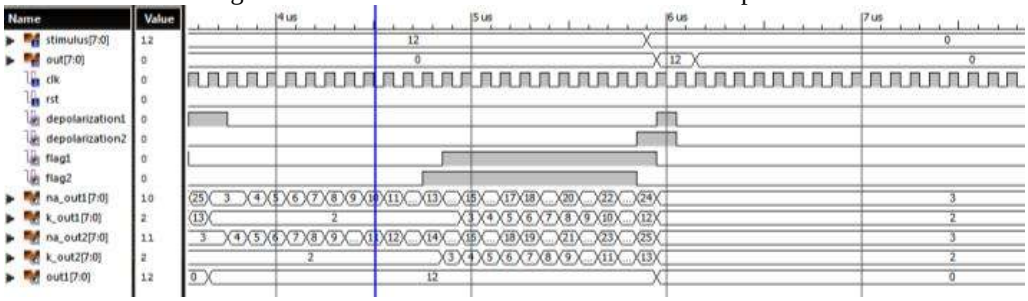

Fig. 9: Waveform obtained for axon transmission process (continued)

V. CONCLUSION & FUTURE SCOPE

This paper has discussed an effective biomimetic scheme for the postsynaptic neural transmission as well as the transmission along the axon, modelled at the behavioral-level. The chemical synaptic transmission process is found to be linked to the formation of proteins. The entire process of protein synthesis initiated by external stimulus has been mimicked.

Biomimetics is the simulation of systems found in living creatures used to solve complex problems in human beings at either micro or macro levels [5]. This can be applied to a multitude of engineering problems such as biomedical, environmental issues to nonconventional energy sources such as solar energy, wind energy, etc. Artificial neural networks (ANNs) have been inspired by the biological neural networks. Novel therapies for neurological disorders involving Epilepsy, Alzheimer's disease, memory, micturition are being sought for, through computational neurosciences using biomimetic modeling. Artificial intelligence (AI) aids in the appreciation of human cognition, requirements of intelligence in general and in the development of artifacts such as intelligent devices and systems that collaborate with humans to augment their capabilities.

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