MODELING AN EPILEPTIC BRAIN USING DISCRETE
AND CONTINUOUS NEURAL NETWORK MODELS

by

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The work described in this thesis was carried out by me under the supervision of Dr. R.P.K.C. Malmini Ranasinghe and Prof. Asiri Nanayakkara and a report on this has not been submitted to any University or any other institution for another Degree/Diploma.

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I/We certify that the above statement made by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation.

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ABSTRACT

Various neural network models on epileptic behavior of the human brain were investigated. Several experimental studies have been carried out to simulate behavior of human epileptic brain recently. One of such experiment is the study carried out by Schiff et. al. to study the firing behavior of neural networks in hippocampus slices of rat brain. In that study human epileptic brain activity was introduced using the high potassium concentration ($[K^+]_o$), where slices from the hippocampus of the temporal lobe of rat brain were exposed to artificial cerebrospinal fluid. Before introducing the high potassium concentration, it was observed that signals recorded from brain slices contained no spikes while with the introduction of high potassium concentration, spikes appeared in random intervals as in the case of brain having epilepsy.

The brain-slice experiment mentioned above has been examined using both discrete and continuous neural network models. This discrete model was based on the model developed by Biswal et. al. and Dasgupta et. al (BD model). In this model, the effect of high potassium medium was introduced through a Hebbian learning mechanism which is switched on during the simulation under reduced inhibition. The sub-passes which play a crucial role in reproducing experimental results in BD model are found to be not necessary when random weights at different stages of the simulation are introduced.

A continuous biophysical neural network model was also developed to describe the outcome of the brain-slice experiment mentioned above. In addition, effect of the input
current and the potassium concentration changes on dynamics of a single neuron and population of neurons were investigated.

It was found that the maps of network activities exhibits stable stationary states and bursting states like trajectories similar to those were found in experiments on hippocampus slices. The discrete and continuous neural network models developed in this work were able to successfully reproduced the experimental results.
CHAPTER 1

INTRODUCTION

The brain is a complex system, which evolves parallel to the environment and is very sensitive to time. That is, almost all processes in the brain are dynamic in nature. They are called dynamic because, under the influence of change in the environment, the state of the activities of the brain changes with time from their equilibrium state. To understand and model the brain, we need to know its structure and its functions. Several experimental studies [1-6] have been carried out in the past to understand brain functions such as memory, control of movements and higher mental functions. Several research projects on mathematical and computational neuroscience have been carried out in order to model human brain [7-11]. If there exist a universal (or very general) model for the brain then many functions of the living brain can be explained and predicted with it.

During the last ten years or so, there has been great interest in simulating brain activities using Neural Networks [1, 2]. It is well known today that neural networks can be used as universal approximates for unknown or complicated functions of dynamical systems such as the human brain [7-9]. A neural network consists of several processing units interconnected in a predetermined manner to accomplish a desired task. This processing unit named as artificial neuron is a model, based on biological neuron architecture and its activities. Most of the neural network models and their dynamics,
developed so far, have been based on the results obtained from experimental work. Two of the most popular types of neural network models which mimic the biological phenomena of the central nervous system are the discrete neural network models governed by difference equations and the continuous neural network models governed by differential equations [1, 2, 7, 8].

Parallel to the above mentioned research work on modeling the normal human brain, there has been a growing interest in developing mathematical and computational models associated with brain disorders [2, 7, 8, 10]. Neural modeling research is currently a very active scientific field involving substantial work based on biological phenomena in the central nervous system [9, 11, 12]. Studies carried out on brain disorders include serious diseases such as Alzheimer’s disease, Parkinson’s disease and Epilepsy.

Epilepsy is a chronic medical condition produced by temporary changes in the electrical function of the brain, causing seizures which affect awareness, movement, or sensation. Epilepsy is thought to be a disease of pathological synchrony between the neurons affecting ~1% of the world’s population. Although drug therapy is effective in many patients, 25% are not responsive to anticonvulsant drugs. In addition, up to 50% of those receiving regular medication suffer major side effects. Surgical treatment is another one associated with serious complications. An alternative method to control the disease is electrical stimulation. The key to a better life for hundreds of people with epilepsy depends on this type of research work.
One of the signatures of the human epileptic brain during periods of time in between seizures is the presence of brief burst of focal neuronal activity known as interictal spikes. Often such spikes emanate from the same region of the brain from which the seizures are generated but the relationship between the spike patterns and seizure onset remains unclear [1, 2, 8, 10]. There have been several in vitro and in vivo experimental studies [4-6, 13-19] carried out on healthy animal brain (Rat Brain) to understand epilepsy in the human brain. In order to introduce the epileptic behavior on healthy rats, a method called kindling has been used. Kindling is considered to be a very effective method for studying epilepsy and it is the mechanism used for generating epilepsy in brain tissues taken from laboratory healthy rats either by increasing the outside potassium concentration or by applying electrical stimulations to neurons in their brain tissues. In a high potassium medium, burst are generated, as collection of high amplitude spikes separated by regions with very low activity. In a neural network model, if these bursts occurred in a regular manner then the model represents normal brain behavior. On the other hand, if bursts occurred in an irregular manner, then the model represents epileptic brain activities. Therefore kindling is very important phenomenon when studying epilepsy [2, 4, 21, 22].

Recently, Schiff et al studied the firing behavior of neural networks in hippocampal slices of rat brain [4]. They made hippocampal slices produce interictal like spikes by using the high potassium concentration ([K$^+$]$_o$) (Chemical Kindling), where slices from the hippocampus of the temporal lobe of a rat brain were exposed to high potassium concentration to induce epilepsy. Before introducing the high potassium concentration, it was observed that signals recorded from brain slices contained no spikes or bursts, but
random noise. With the introduction of the high potassium concentration, spikes or bursts appeared at random intervals as in the case of a brain having epilepsy. These spikes were made periodic by applying controlled electric pulses in a predetermined manner [4].

The above mentioned experimental studies led to several investigations through computer simulations using neural network models. These neural network models were based on results obtained from clinical and \textit{in vitro} experimental studies. In the literature, a number of neural network models have been developed to investigate the behavior of a human epileptic brain. Mehta et al [20] have developed and studied a discrete neural network model in which repeated electrical stimuli (Electrical Kindling) produced epileptic behavior. Their results are consistent with the hypothesis that epileptic behavior is due to the formation of a large number of excitatory synapses arising in the context of the operation of Hebb's rule. In recent papers [21, 22], the previously described experiment on rats has been modeled computationally by a discrete neural network model consisting of a local field having time delays and asymmetric properties. In general, few biophysical properties of the central nervous system have been included in discrete neural network models. Therefore it is more realistic to use continuous neural network models for simulating epileptic brain activities.

The most detailed and well known continuous neural network models of epileptic abnormalities have been developed by Traup et al [2, 23-26] over several years. They have investigated the CA3 area of the hippocampus using a complex, multi-compartmental model. The reason for modeling the CA3 area of the hippocampus is, that in the CA3
region, highly synchronized electrical activities, EEG spikes and sharp waves occur with certain types of epileptic activity. Recently it has been shown that a much simplified, two-compartmental model of hippocampus pyramidal neurons is still able to produce many abnormal neural activities [27, 28]. More recently this two-compartmental model was modified by Av-Ron et. al. [29] as a single-compartment model for hippocampus pyramidal neurons. Franaszczuk et al [30] carried out several studies on this single-compartment pyramidal neuron model to understand changes of its dynamics due to environmental changes.

In any dynamical system, complicated and aperiodic motions, which are highly sensitive to initial conditions, are called Chaos. That is, when the system is chaotic, two states starting from very close initial conditions will produce final states, which are far away from each other. Therefore chaotic behavior is random and unpredictable. In certain neural networks, dynamics become chaotic due to the fact that the equations involved are nonlinear and the network architecture is complex [31, 32]. In general one wishes to avoid or otherwise control chaos in a neural network to improve its activity. One can control or convert the chaotic motion to regular motion by minimal changes to its accessible parameters or variables [33, 34]. Similarly, the chaotic nature of the biological system can be controlled by applying external manipulations [35-38].

The main objective of this thesis is to simulate the epileptic brain slice experiment in [4] by using neural network models. In particular, it covers two different types of models in neural networks, namely, models based on discrete neural networks and continuous neural
networks. In both cases we modeled the epileptic brain activity by simulation. We also demonstrated the application of controlling chaos for the discrete neural network model.

This thesis is organized as follows. In chapter 2, basic information and terminology associated with epilepsy and hippocampus are given in detail. The experimental work by Schiff et. al. is also described in chapter 2. Chapter 3 deals with the basic discrete neural network models, which have been used to study the brain functions. These include the necessary modifications and different learning methods, which have been made to obtain desired network activity in simulations.

A detailed description of normal and epileptic brain activities simulated by the discrete neural network model in [21, 22] is presented in chapter 4. Chapter 5 deals with the biophysical neuron models, which are used in the continuous neural network models. Different neuron models and their activities in the simulation are also presented in chapter 5. The detailed application of normal and epileptic brain activities simulated by a single compartmental neuron model is presented in chapter 6. In chapter 7, our studies, modifications made on existing neural network models and the results of the simulation of the rat brain slice experiment are presented. The presented results are based on both discrete and continuous neural network models. The summary and conclusion about the modeling of an epileptic brain using neural networks are presented in chapter 8.
CHAPTER 2

EXPERIMENTAL WORK IN EPILEPSY

2.1 Introduction

Epilepsy afflicts between 1% and 2% of the world’s population. While many anti-epileptic drugs currently exists, at least 20% of all epileptic patients are still not kept seizure-free by pharmacological treatments. For many of these patients, the only remaining option is surgical resection of the seizure focus. Scieff et. al. [4] have demonstrated that it may be possible to apply techniques from non-linear dynamics to manipulate in vitro epileptic form bursting. These bursts are thought to be analogous to interictal spikes, which are seen on EEG between seizure episodes [39-41].

2.2 Epilepsy and Hippocampus

Every cerebral activity detectable by electroencephalography (EEG) is a reflection of synchronous neuronal activity. Epilepsy, by definition, is the propensity to have seizures. The neuronal firing patterns leading to epileptic symptoms are called epileptic form bursting. Epileptic form bursts take the form of large-scale, neurons-synchronized activities. Epileptic seizures, however, are abnormal, temporary manifestations of
dramatically increased neuronal synchrony, either occurring regionally (Partial Seizures) or bilaterally (General Seizures) in the brain. Both clinical and experimental data suggest that alteration of neurotransmission and reorganization of synaptic connection may contribute to the development of epileptic activity [2].

![Diagram of Human Brain](image)

**Figure 2.1:** Hippocampus in the human brain.

One of the signatures of the human epileptic brain during periods of time in between seizures is the presence of brief burst of focal neuronal activity known as interictal spikes. Often such spikes emanate from the same region of the brain from which the seizures are generated but the relationship between the spikes patterns and seizure onset remains unclear. This idea raises, two questions relating to epileptic tissue:

1. What are the functional differences among neurons in neural tissue in epileptic conditions?
(2) How are seizures, the defining event of epilepsy, and interictal bursts, a much shorter event that is a hallmark of epileptic patient, generated and what are their functional differences?

To answer these questions, there are several experimental studies [2, 13-19, 37] carried out on pyramidal neurons in CA1, CA2 and CA3 regions of rat hippocampus under various epileptic conditions. The literature cites both extra-cellular and intra-network casual factors influencing epileptic activity. Head trauma, stroke, cellular mechanisms, and chemical imbalances in the brain are the key factors influencing epilepsy. It is widely accepted that epileptic symptoms in the brain are rooted in increased excitatory neural connections coupled with or in lieu of increased neural network inhibition. Therefore, a detailed study made on the population activity of the hippocampus neurons should reveal more information on epilepsy than a study made on a single neuron in the same region.

The hippocampus as shown in figure 2.1, is one of the most studied areas of the brain. It has attracted interest for its role in neurological disorders, including epilepsy. Hippocampus is an important part of the brain for memory and formation of new memories through learning. It is anatomically the simplest type of cortex, with the principal neurons aligned in a single layer. It has three subdivisions that are denoted as CA1, CA2 and CA3. The major neuron type in the hippocampus is the pyramidal type. The number of pyramidal neurons at CA1 region in the human hippocampus is relatively more than CA2 and CA3. These groups of neurons produce excitation in their postsynaptic neurons. Also there is low
number of inhibitory neurons in these regions with respect to their characteristic locations and axonal distributions. These neurons can mediate either fast or slow types of inhibition.

![Diagram of hippocampus anatomy and composition](image)

**Figure 2.2:** Abstraction of hippocampus anatomy and composition.

### 2.3 Synaptic Organizations and Their Functions

The hippocampus has become the primary region in the mammalian brain for the study of the synaptic basis of memory and learning. It contains one projection neuron type, which is confined to a single layer, and it receives inputs from all sensory systems and
association areas. Figure 2.2 showed that the anatomical structure of pathways (synaptic circuits) in the hippocampus region.

![Diagram of hippocampus neuron connections]

**Figure 2.3:** Schematic synaptic circuit diagram of hippocampus neuron connections at the human brain. The excitatory connections are denoted by continuous line and inhibitory connections are denoted by disjoint line.

The major pathways within the hippocampus neurons are given below:

(i) The *perforant path* (PP), originating in entorhinal cortex (EC).

(ii) The *mossy fibers*, suprapyramidal and infrapyramidal, connecting dentate granule (DG) neurons to CA3 pyramidal neurons and hilar neurons.
(iii) The Schaffer collaterals of CA3 pyramidal axons, making en-passant synapses onto CA1 pyramidal neurons.

(iv) The commissural connections.

(v) The recurrent excitatory connections between CA3 pyramidal neurons and between CA1 pyramidal neurons.

(vi) Inhibitory circuitry, with inhibitory neurons excited either by local pyramidal neuron collaterals or by afferent fibers or both.

In the hippocampus, neurons are interconnected to each other through different types of synaptic connections (Excitatory or Inhibitory) as shown in figure 2.3. Now we describe a schematic description of the hippocampus formation in brain. Information enters the hippocampus through layer 2 entorhinal neuron by the perforant path, which projects into dentate gyrus, CA3 and CA1 areas. In addition to its perforant path inputs, CA3 receives a lesser number of mossy fibre synapses from dentate granule neurons. The axon of the CA3 pyramidal neuron projects commissurally, recurrently within CA3, and also forwarded to area CA1 by the Schaffer collateral pathway. Information leaves the hippocampus via back projection from the entorhinal cortex to CA1 and the subiculum, and also via the fornix to the mammillary bodies and anterior nucleus of the thalamus [2].
2.4 Epileptic Activities in Hippocampus

We concentrate here on area CA3 of hippocampus. Most isolated hippocampus neurons are regular spiking neurons, and remaining are endogenous busters [10]. Spontaneous epileptic form events are much more in hippocampus than the other areas in the brain. Neuronal activity in the hippocampus is highly synchronized during certain behavioral states and during epileptic form activity. Such synchronous activity includes rhythmical EEG waves, sharp waves and other EEG transients (Both Normal and Pathological) and seizure discharges. The variation of number of neurons in CA1 region and the formation of excitatory connection in CA3 region are the important source for epilepsy in hippocampus. Sudden changes in these regions initiate the abnormal behavior in that region and spread to other part of the brain.

Due to high excitation spontaneous bursts of synchronized neuronal activity is originated in a region known as the third part of the CA3. Input signals from the CA3 bursts are propagated through a recurrent collateral fibre tract (the Schaffer Collateral Fibers) to CA1, where electrographic seizure-like symptoms can frequently be observed.
2.5 *In Vitro* Experiment on Rat Hippocampus

Recently, there have been great interests in generating human epileptic brain activities in rat brain. Particularly, several experimental studies have been carried out on hippocampal slices of rat brain. Recently, Schiff et al [4] studied the firing behavior of neural networks in rat brain. They made hippocampal slices to produce epileptic behavior by using the chemical kindling (High Potassium Concentration $[K^+]_0$ Model). In their experiment, transverse slices 400 μm thick were prepared from the hippocampus with a tissue chopper and placed in an interface-type perfusion chamber at 32-35° C. Slices were perfused with artificial cerebrospinal fluid (ACSF) flowing at 2 ml/min and composed of 155 mM $Na$, 136 mM $Cl$, 3.5 mM $K$, 1.2 mM $Ca^{2+}$, 1.2 mM $Mg^{2+}$, 1.25 mM $PO_4^4$, 24 mM $HCO_3$, 1.2 mM $SO_4$ and 10 mM dextrose. Extra-cellular and intra-cellular recordings were made on pyramidal neurons.

Neurons in the pyramidal layer were identified as pyramidal neurons if they respondent with short latency spikes to antidromic stimulation and manifested spike frequency accommodation during sustained depolarization. After 90 min incubation, slices were tested for viability by recording a greater than 2 mV unitary population spike in the stratum pyramidale of CA1, in response to stimulation of Schaffer collateral fibers in the stratum radiatum with 100 μs constant current 50-150 μA square-wave pulses delivered at 0.1 Hz through tungsten microelectrodes. It was observed that signals recorded from hippocampal slices contained no burst, but random noise. With confirmation of viability,
the perfusate was switched to ACSF containing 8.5 mM [K$^+$]\textsubscript{o} and 141 mM [Cl]. After 15-20 minutes of high [K$^+$]\textsubscript{o} perfusion, spontaneous bursting could be recorded from CA3a or CA3b. At times, double pulses consisting of pair of 100 $\mu$s pulses with 150 $\mu$s inter-pulse intervals were used.

In order to introduce the epilepsy, the slices from the hippocampus of the temporal lobe of the rat brain are exposed to artificial cerebrospinal fluid containing 6.5-10 mM [K$^+$]\textsubscript{o}. After exposure to high [K$^+$]\textsubscript{o}, spontaneous burst of synchronized neuronal activity is originated in a region known as the third part of the CA3. Impulses from the CA3 bursts are propagated through a recurrent collateral fibre tract from CA3 to CA1, where electrographic seizure-like symptoms can frequently be observed. With the introduction of high potassium concentration, burst appeared in a random interval as in the case of human brain having epilepsy.

Schiff et. al. [4] made a detail study to answer following questions:

(1) Is there evidence for deterministic chaotic behavior in this preparation?

(2) Could such activity be controlled?
According to their study, the answer they found for both questions is yes. In order to control this chaotic behavior, Periodic Pacing (PP), Demand Pacing (DP) and Anti-Control (AC) methods were used by them in the experiment.

In our research work we carried out detail theoretical and computational studies to simulate behavior of human epileptic brain by neural networks. Our objective is to simulate the epileptic brain behavior in this experiment by using discrete and continuous neural network models.
CHAPTER 3

DISCRETE MODELS IN NEURAL NETWORK

3.1 Introduction

There are two types of neural network models used in simulation of Brain Functions; discrete models and continuous models. In this chapter, we concentrate on discrete neural network models where as continuous models are addressed in the Chapter 5. In discrete neural network models, input, output and state variables vary in discrete manner with time. Each processing unit in the neural network receives several inputs and produces a single output after analyzing inputs using predetermined rules. Figure 3.1 shows a schematic structure of an artificial neuron.

![Diagram of an artificial neuron]

**Figure 3.1**: Mathematical Model of an Artificial Neuron.

When processing inputs, all the inputs are not treated equally and weights ($W$) may be used to introduce discrimination on inputs. Generally, if input, output and state variables are known (at $t = t_n$) then input, output and state variables for the next time
step \( t = t_{n+1} \) are determined by solving a set of difference equations in discrete neural network models.

Rest of this chapter is devoted for describing three well-known discrete neural network models in detail. The following sections outline the key developments in discrete neural network models in the literature.

### 3.2 McCulloch-Pitts (MCP) Neuron Model

In 1943, Warren McCulloch and Walter Pitts [7] established a model to represent a neuron in discrete form based on biological neuron. The influence of the other neurons in the population on this model was introduced as input signals. Then these input signals were used to form a weighted sum to produce the output signal by determining its activation. If this sum exceeds some threshold value then the neuron will fire, otherwise it will be at rest. This neuron has two distinct output states in the process, such that it is equal to one or zero depending on whether it is firing or quotient respectively. Combinations of these neurons (Computing Elements) can be used to realize several logic functions (conjunction, disjunction and negation) in computations. Equations (3.1) and (3.2) describe the detail neuron model in the input output form.

The governing equation of the neuron dynamics can be described in an explicit form. In MCP neuron model, the activation value \( (x) \) is given by a weighted sum of its \( m \) input values \( (a_i) \) and a bias term \( (b) \). The output signal \( (s) \) is a non-linear function \( f(x) \) of the activation value \( x \). The governing equation of this model is given by:
Activation Value: $x = \sum_{i=1}^{m} w_i a_i - b$ (3.1)

where $w_i, i = 1, 2, \ldots, m$ are weights for the input.

Output signal: $s = f(x)$ (3.2)

We determine the output signal of the neuron by the binary output function with the following logic:

$$f(x) = \begin{cases} 1 & \text{if } x > 0 \\ 0 & \text{if } x \leq 0 \end{cases}$$ (3.3)

![Diagram of McCulloch-Pitts Model of a Neuron](image)

**Figure 3.2:** McCulloch-Pitts Model of a Neuron

In MCP neuron model, all data flows in one direction and no feedback mechanism has been introduced. Figure 3.2 shows a schematic structure of a MCP model of a
neuron. In any model based on MCP neurons, weights are fixed [1]. Therefore this
model does not have the capacity to learn from the environment. However, we can
perform several logic functions with MCP based neural network models.

On the other hand a new model can be constructed consisting of MCP neurons with
feedback mechanism. Let us called such model as MCPWF (Meaning MCP with
Feedback). Each neuron in this model receives a single input in addition to a weighted
feedback from its output. Using a proper threshold value and these two inputs, a new
output is produced, a unit time later. MCPWF neurons can be used to build sequential
digital circuits by introducing unit time delay property. Since they have the feedback
property, MCPWF neurons can be used as memory neurons.

In 1954, Donald Hebb [1] proposed a learning scheme, which changes the
connection weights until it produces the improved output compared to the desired result
[42]. His law became a fundamental learning rule in the neural network literature. Next
section we will discuss the Hopfield model and the implementation of Donald Hebb
learning rule in detail.

3.3 Hopfield Neural Network Model

Johan Hopfield has made important contributions to both theory and application of
feedback neural network models [43, 44]. Hopfield model consists of MCPWF, where
the output of each neuron is feedback with weights $w_{ij}$ to all the other neurons. That is,
this model is fully connected feedback network with symmetric weights. The output
function of the neuron is taken as bipolar (±1) rather than 0 and 1 as in the MCP neuron.

The governing equations of this model is given by:

\[ S_i = f(x_i) = \text{sgn}(x_i) = \begin{cases} +1 & \text{if } x_i \geq 0 \\ -1 & \text{if } x_i < 0 \end{cases} \]  

(3.4)

and \( x_i = \sum_{j=1}^{N} w_{ij} S_j - \theta_i \)

(3.5)

where \( \theta_i \) is the threshold for the neuron \( i = 1, 2, \ldots, N \)

**Figure 3.3:** Hopfield Neural Network Model. Each neuron in the population receives input from all the other neurons and sends its output to all the other neurons. All the connections are weighted. The output of the whole network is determined by combining the outputs of all the neurons in the population according to predetermined aggregation rule.
Figure 3.3 shows a schematic of the structure of a Hopfield neural network model, which consists of a set of $N$ interconnected neurons, which update their activation values asynchronously and independent of other neurons. The activation values are binary. Originally, Hopfield chose activation values as 1 or 0, but using values $+1$ or $-1$ gives some advantages in mathematical analysis.

### 3.3.1 Hopfield Net Algorithm for Storing and Recalling a Set of Bipolar Patterns

A major application of the Hopfield network is to construct associative memory. In this case, the weights of the connections between the neurons are calculated according to patterns which are to be stored in the network. If one of the stored patterns is input to the network then the output of the network converges to the same pattern. If the network input with noise or incomplete test pattern then it will iterate to a stable state, which is in some sense "near" to one of the stored pattern in the memory. The Hebb rule can be used to store such patterns.

Now we describe the algorithm for storing and recalling set of patterns in Hopfield neural networks in detail [42]. Suppose the network consists of $N$ fully connected neurons with each neuron having hard-limiting bipolar threshold output function. Let $\mathbf{z}_k$, $k = 1, 2, \ldots, q$ be the vectors to be stored. The vectors $\{\mathbf{z}_k\}_{k=1}^q$ are assumed to have bipolar components, i.e., $\xi_{ki} = \pm 1$, $i = 1, 2, \ldots, N$. 

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Step 1: Assign the connection weights

\[
\begin{align*}
   w_{ij} = \begin{cases} 
   \frac{1}{N} \sum_{k=1}^{q} \xi_{ki} \xi_{kj}, & \text{for } i \neq j \\
   0, & \text{for } i = j 
   \end{cases}
\end{align*}
\]  

(3.6)

where \(1 \leq i, j \leq N\)

Step 2: Initialize the network output with given unknown input pattern \(\xi_0\)

\[
S_i(0) = \xi_0i \quad \text{for } i = 1, 2, \ldots, N
\]  

(3.7)

where \(S_i(0)\) is the output of the neuron \(i\) at time \(t = 0\)

Step 3: Iterate until convergence

\[
S_i(t+1) = \text{sgn} \left[ \sum_{j=1}^{N} w_{ij} S_j(t) \right], \quad \text{for } i = 1, 2, \ldots, N
\]  

(3.8)

The process is repeated until the outputs remain unchanged with further iteration. The steady outputs of the neurons represent the stored pattern that best matches the given input.
In the Hopfield model weights are updated by the following rule. If two neurons have synapses of same type (Excitatory or Inhibitory) and they fire simultaneously, then the strength (Efficiency) of the synapse is increased otherwise there is no change in the weight value.

Let \( w_{ij}(t) \) is the weight of the connection in between \( i^{th} \) and \( j^{th} \) neurons at time \( t \) and the weight changes are proportional to the correlation between the \( i^{th} \) and \( j^{th} \) neurons at time \( t \). We can describe this by the following differential equation.

\[
\frac{d w_{ij}(t)}{dt} = -w_{ij}(t) + S_i(t)S_j(t) \tag{3.9}
\]

where \( S_i(t)S_j(t) \) is the product of the post-synaptic and pre-synaptic neuron variables for the \( i^{th} \) and \( j^{th} \) neuron at time \( t \).

An energy function for the Hopfield network is defined by the following equation

\[
E = -\frac{1}{2} \sum_{ij} w_{ij}S_i S_j \tag{3.10}
\]
where the connection between pairs of neurons are described by synaptic weight values such that $w_{ii} = 0$ and $w_{ij} = w_{ji}$, $i \neq j$ for $i, j = 1, 2, \ldots, N$.

The energy function with symmetric connection always decreases when neurons are updated asynchronously. In asynchronous update, a neuron is selected at random and then its new state is computed.

When the new input vector is applied, this network moves from state to state until it stabilizes. The stable state is determined by the network weights, the current inputs, and the threshold value. Even if the input vector is partially incorrect or incomplete, the network stabilizes to the state closest to the one desired. This neural network model is very useful in the field of memory based models implementations. This model is used by researchers to make detail study on the hippocampus in the human brain, which will be discussed later.

### 3.4 Spin Glass Neural Network Model

Spin-glass models, which exhibit features of learning, memory and pattern recognition, have become the focus of exciting numerical and analytical studies [45, 46]. Analogy with spin glass models in condensed matter Physics, neurons are assigned states, which correspond to spin states in a solid. Each spin is affected by the spins of the other spins, thermal noise, and can flip between two possible states ($+1$ and $-1$). That is, in this model, each neuron is viewed as an Ising Spin with two possible states: an ‘up’ position or a ‘down’ position depending on whether the neuron has, or has not,
fired an electrochemical signal. This is a neural network model that can be seen as an extension to Hopfield networks to include hidden neurons, with a stochastic update instead of deterministic update rule. The weights are still symmetric. This model may be useful in understanding the generation of rhythmic patterns in biological systems.

Now we represent the neuron as a spin and explain the dynamics of the Ising Spin system interacting with a heat bath at temperature $T$. This stochastic process provides the link between the dynamics of neural networks and the thermo dynamical treatment. The operation of the network based on the physical principle of annealing. Annealing is a process whereby a material is heated and then cooled very, very slowly to a freezing point. As a result, the crystal lattice, which is formed in the process, is highly ordered, without any impurities, such that system is in a state of very low energy. A stochastic update, in which a neuron becomes active with a probabilistic rule, is used. The energy minimizations rule is given in the next sections.

In the update process, neuron state changes randomly between $-1$ and $+1$. The probability function $P$ is defined in terms of a parameter called temperature $T$. A neuron $i$ is selected at random for updating. The output is updated according to the probabilistic update rule, specified by the probability that the output $S_i = -1$ or $+1$ with respect to the local field $h_i$.

$$ S_i = \begin{cases} -1 & \text{with probability } P(h_i) \\ 1 & \text{with probability } 1 - P(h_i) \end{cases} \quad (3.11) $$
\[ P(h_i) = \frac{1}{1 + \exp(-2h_i/T)} \] (3.12)

where \( h_i \) is the "Local Field" \( \sum_j w_{ij}S_j \)

For \( T = 0 \) we get the original deterministic Hopfield rule. For \( T \to \infty \) the neuron states flip completely randomly. In between zero and infinity, \( P(h_i) \) is assigned to be sigmoid function.

In the energy minimization process, at each step, select a neuron and calculate the energy difference \( \Delta E \) between its current state and its flipped state.

If \( \Delta E \leq 0 \) then flip the neuron

If \( \Delta E > 0 \) flip the neuron with the probability \( \exp\left(-\frac{\Delta E}{T}\right) \)

After around \( N \) such steps, this temperature is lowered further and the cycle is repeated.

If the temperature in cycle \( k \) satisfies \( T_k \geq \frac{T_0}{\log(1+k)} \) for every \( k \) and \( T_0 \) is large enough, then the system will converge to the minimum energy configuration with unit probability.
At low temperatures there is a strong basis in favour of states with low energy, but the time required to reach equilibrium may be long. At higher temperatures the bias is not so favorable but equilibrium is reached faster. A good way to beat this trade-off is to start at high temperature and gradually reduce it. At high temperatures, the network will ignore small energy differences and will rapidly approach equilibrium. In doing so, it will perform a search of the coarse overall structure of the space of global states, and will find a good minimum at that coarse level. Using this method minimum can be reached however the convergence will be very slow. This type of model is used by researchers to make detail study on the structure and functions of the memory in the human brain.

In this chapter we have reviewed the properties of the discrete neural network models and discussed some basic learning rules based on them. While developing discrete neural networks for specific applications, the weights are adjusted in a systematic manner using learning rules. In particular, we made our study on the associative memory concepts and its related learning features. These concepts are very useful to make study on human brain functions and their related applications.
CHAPTER 4

APPLICATION OF DISCRETE NEURAL NETWORK MODELS IN EPILEPSY

4.1 Introduction

Recently there have been great interests in simulating brain activities using discrete neural networks [1, 7, 8]. Particularly, several experimental and computational studies have been carried out to simulate behavior of human epileptic brain [1, 7, 8, 10, 16-19]. In this chapter, we will discuss a study based on the discrete neural network models in epilepsy. Recently, Schiff et al [4] studied the firing behavior of neural networks in hippocampal slices of rat brain. One of the distinctive features of the human epileptic brain during periods of time in between seizures is the presence of brief bursts of focal neuronal activity known as interictal spikes. In their study, this feature was introduced by using the high potassium concentration ([K⁺]₀) model, where slices from the hippocampus of the temporal lobe of the rat brain were exposed to artificial cerebrospinal fluid. Before introducing the high potassium concentration, it was observed that signals recorded from brain slices contained no spikes, but random noise. With the introduction of “chemical kindling” or high potassium concentration, spikes appeared in random intervals as in the case of brain having epilepsy.
In the literature, this experiment has been modeled computationally by a discrete neural network with a local field having time delays and anti-symmetric properties [21, 22]. Time delays and anti-symmetric properties were introduced to represent biological structures, which do not have symmetric synaptic connections. In reference [21, 22], Hebbian learning mechanism was introduced under reduced inhibition to simulate the effects of high potassium concentration. This way they were able to create spikes with random inter-spike intervals as in the case of the experiment. We chose the discreet neural network model proposed by Biswal et. al. and Dasgupta et. al. (BD model) in [21, 22] for our preliminary study.

4.2 The Neural Network Model and Its Dynamics

In this section, first we describe the neural network model used in [21, 22] for the slice experiment simulation. Then we describe the sub-passes update (SPU) method and the network bursting dynamics with respect to kindling. Their network model is fully (All to All) connected network with symmetric and anti-symmetric weights. Each neuron in this model receives a single input as a weighted feedback from other neurons output. The output function of the neuron is taken as binary 1 or 0 with respect to the sign of its local field.

Here we describe BD model, which consists of \( N \) neurons having states \( \{S_i\}, i = 1, \ldots, N \), each of which is excitatory \( (S_i = 1) \) or inhibitory \( (S_i = 0) \) representing firing or quiescent states. The state of the neuron is given by the binary output function with the following logic:
\[ S_i(t+1) = \begin{cases} 1 & \text{if} & h_i(t) \geq 0 \\ 0 & \text{if} & h_i(t) < 0 \end{cases} \] (4.1)

where “time” \( t \) is discrete and termed as “passes” and \( h_i(t) \) is the “local field” of the \( i^{th} \) neuron at time \( t \) and it is given by.

\[ h_i(t) = \sum_{j=1}^{N} \left[ \left( w_{1ij} - b \right) S_j(t) + \lambda \left( w_{2ij} - b \right) S_j(t - \tau) \right] \] (4.2)

where both \( w1 \) and \( w2 \) are the synaptic weights, \( b \) is the relative strength of inhibition, \( \lambda \) is the relative strength of delayed signal, and \( \tau \) is the time delay associated with the delayed signal.

BD model consists of some important physical properties to represent biological structures. They are asymmetric synaptic connections, time delay factor, excitation and inhibition. In general, the network dynamics depends on the state of the neuron \( S_i \) and the strength of synaptic connections \( w1 \) and \( w2 \). These are the key factors influence the network dynamics in the simulation. First we initialize the synaptic strength by random weights to store some low-active patterns (LAP) in the network model. The LAP represents the particular state of network in the time evolution, which consists of very small number of excitatory neurons and the rest of the neurons are inhibitory at that time. If \( p \) is the number of excitatory neurons in the pattern with \( p \ll N \) then the pattern
is called as low-active patterns (LAP). Now we will explain the method to store LAP in the network through synaptic weights.

A fixed number (say \(q\)) of LAP ("memories") \(\left\{ \xi_{i}^{\mu} \right\}, \ i = 1, \ldots, N; \ \mu = 1, \ldots, q\)

are stored in the synaptic connections as:

\[
wl_{ij} = \Theta \left( \sum_{\mu=1}^{q} \xi_{i}^{\mu} \xi_{j}^{\mu} \right), \quad w_{ii} = 0
\]  

(4.3)

and

\[
w_{2ij} = \Theta \left( \sum_{\mu=1}^{q} \xi_{i}^{\mu+1} \xi_{j}^{\mu} \right), \quad w_{2ii} = 0, \text{ with } \xi_{i}^{q+1} = \xi_{i}^{1}
\]

(4.4)

where \(\Theta(m) = \begin{cases} 1 & \text{if } m > 0 \\ 0 & \text{if } m \leq 0 \end{cases}\)

(4.5)

In the simulation, the network state at time \(t = 1\) is initialized by the first pattern stored in the memory and update \(N\) neurons through SPU method mentioned above. The SPU method will be discussed later. At each time step, a number of excitatory neurons in the population is used to determine the net activity of the network.
The net activity of the network is given by the equation:

\[ S_{up}(t) = \sum_{i=1}^{N} S_i(t) \]  \hspace{1cm} (4.6)

To simulate low-amplitude oscillations of the net activity of the network in the absence of any external stimulus, the net activity of each memory \( \sum_{\mu=1}^{N} \xi_{i\mu} \) is set at a value \( p \), which is much less than the number of neurons (i.e. \( p \ll N \)). The \( p \) excitatory (or "active") neurons are chosen randomly. With appropriate choice of values of the parameters \( \lambda \) and \( b \) (for \( \lambda > 1 \) and \( b < 1 \)), the network exhibits low-amplitude oscillations. The values of the parameters used in the simulations are \( N = 200 \), \( q = 20 \), \( p = 10 \), \( b = 0.6 \), \( \lambda = 2 \), \( \tau = 2 \). Note that, if the BD model has been properly constructed with synaptic matrices and with a proper time delay term then the network evolves from one pattern to the next pattern in the memory. In BD model, time delay \( \tau \) is introduced in the last term of the equation (4.2). For updating the \( i^{th} \) neuron state at time \( t \), we need the information of the \( i^{th} \) neuron at time \( (t-2) \). For this purpose we need to store the state information of all the neurons during the previous two time steps in the evolution.

4.3 Stochasticity of the Network Dynamics

Generally, the network dynamics is strongly depending on the update rule in the time evolution of the energy minimization. In BD model, the update process is as follows. First, one of the neuron is selected at random for updating. Then its local-field
is calculated, and its state variable $S_i$ is set to 0 or 1 depending on the sign of the local-field $h_i(t)$. This process is repeated $N$ number of times ($N$ may be the number of neurons in the network) before the next time step begins. However, it is important to note that some neurons may be updated more than once in a given time step and some neurons never get updated in that time step.

In this study, three updating methods have been tested. The first method is the fixed sequential updating (FSU). In this method, a specific random sequence for updating the $N$ neurons is chosen in the first time step and uses the same sequence, to update the neurons in subsequent time steps. When using FSU, for most update sequences, the network remains in low-amplitude oscillation mode and for certain update sequences, the network seems to have high-amplitude oscillations. In the second method, parallel updating (PU), method, all the neurons are updated simultaneously at every time step. However, in order to introduce irregularly bursting dynamics in the network, the third method called “sub-pass update (SPU) method” has to be introduced.

4.4 Implementation of Sub-Passes Update Method

In the simulation, at each time step, neurons in the network are updated $N$ times serially. During the update, neurons are chosen at random one by one and updated using the update rules given in equations (4.1) and (4.2). In the updating process, previously updated neuronal information is used for subsequent updates of neurons in the same time step. Since the time delay information is needed for the update ($\tau$ in equation (4.2)), history of state of the neurons has to be kept in the memory. According to the
equation (4.2), we need only the information of neurons from \( \tau \) number of past time steps. Therefore keeping total history of neurons in all past time steps is unnecessary. In order to keep only the necessary information in the memory, “sub-passes” are introduced. That is, one pass consists of several “sub-passes”. During each sub-pass we update chosen neurons using equations (4.7) and (4.8). At the end of final sub-pass in a given pass, the net activity is calculated by the equation (4.6). In a single sub-pass, small numbers of neurons are updated according to the following equations. Please note that equations given below are same as (4.1) and (4.2) but have additional sub-pass index \( sp \) in the place of the variable \( t \).

\[
T[i][sp] = \begin{cases} 
1 & \text{if } h[i][sp] \geq 0 \\
0 & \text{if } h[i][sp] < 0 
\end{cases} \tag{4.7}
\]

\[
h[i][sp] = \sum_{j=1}^{N} \left\{ \left( w1[i][j] - b \right) T[i][sp] + \lambda \left( w2[i][j] - b \right) T[i][sp - \tau] \right\} \tag{4.8}
\]

Now we describe the detail algorithm for the storing and recalling set of patterns in BD model with SPU method. If we assume that \( m \) number of neurons are updated in each sub-pass then we have \( nsp (=N/m) \) number of sub-pass in one pass. Also assume that time delay \( \tau \) is \( (2^nsp) \).
Step 1: Construct $q$ number of low active random patterns ("memories")

\[ \xi[i][\mu] \text{ for } i = 1, 2, \ldots, N \text{ and } \mu = 1, 2, \ldots, q \text{ such that each pattern satisfies } \sum_{i=1}^{N} \xi[i][\mu] = p << N. \]

Step 2: Construct the synaptic matrices $w1[i][j]$ and $w2[i][j]$ for $i, j = 1, 2, \ldots, N$ such that they satisfy equations (4.3), (4.4) and (4.5).

Step 3: At $t = 1$, set $sp = 2^{*nsp} + 1$, $\tau = (2^{*nsp})$. Construct matrices $S[i]$, $T[i][sp]$, for $i = 1, 2, \ldots, N$ and $sp = 1, 2, \ldots, (2^{*m}+1)$. Initialize the matrix $T$ such that $T[i][sp] = \xi[i][1]$ for $i = 1, 2, \ldots, N$ and $T[i][j] = 0$ for $i = 1, 2, \ldots, N$ and $j = 1, 2, \ldots, 2^{*nsp}, 2^{*nsp} + 2, \ldots, (2^{*m} + 1)$.

Step 4: Choose a neuron at random (say $r$) and update its state according to the sign of the local field (4.8). To calculate local field, $T[j][sp]$ and $T[j][sp - \tau]$ for $j = 1, 2, \ldots, N$ are needed in (4.8). The new state of the $r^{th}$ neuron at $sp^{th}$ sub-pass $T[r][sp]$ is given by the equation (4.7). Repeat this updating process until $m$ number of neurons are updated, i.e. sub-pass is completed. Then go to step 5.

Step 5: If (one pass completed, i.e. $sp = 2^{*m}$) then $S[i] = T[i][2^{*m}+1]$ for $i = 1, 2, \ldots, N$ and go to step 7 else $T[i][sp - \tau] = T[i][sp]$ and $T[i][sp+1] = T[i][sp]$ for $i = 1, 2, \ldots, N$, set $sp = sp + 1$, and go to step 4.
Step 7: The net activity of the network at time $t$ is given by $S_{up}(t) = \sum_{i=1}^{N} S[i]$. 

Set $t = t + 1$, $sp = (2^{*}nsp + 1)$. If ($t <$ intended total time of the simulation) then go to step 4. Otherwise print results and exit.

Reference to the above algorithm, the network evolves from one pattern to the next pattern in the memory and effectively produces the low-amplitude mode oscillation. When the neurons are updated by SPU method, we observed the low-amplitude oscillation of the net activity $S_{up}(t)$ around an average value $p = 10$ as shown in figure 4.1.

![Image of network dynamics](image)

**Figure 4.1:** Network dynamics of low-amplitude mode oscillation by SPU.

4.5 Spontaneously Bursting Dynamics

As mentioned earlier, kindling is a phenomenon in which a part of the brain is externally stimulated, either through electric pulses or through chemicals. Kindling is considered to be a very good model for studying epilepsy. In order to chemically
simulate the excess excitability (or epileptic behavior) in brain slices experiments, brain slices were bathed in a high-potassium medium. This process is called chemical kindling and induces spontaneous bursting in hippocampal slices. We have described more information about experimental simulations of epileptic activity through high potassium concentration model in the chapter 2. In the BD model, the chemicals kindling effect is simulated through a Hebbian learning mechanism described in the following way.

During first 50 initial passes under reduce inhibition (i.e., $b$ in (4.2) is reduced from 0.6 to 0.24 during this period), it is checked whether the conditions $S_i = 1$ and $S_j = 1$ for more than $t_2$ times, during $t_1$ consecutive passes are satisfied for $i, j = 1, 2, \ldots, N$ with $i \neq j$. If these conditions are satisfied by specific $i$ and $j$, then the synaptic strength $w_{1,ij}$ is set to 1. In BD model $t_1 = 10$ and $t_2 = 6$ [21, 22].

![Graph](image.png)

**Figure 4.2:** Network dynamics with burst by sub-passes update method
Figure 4.3: Inter-spike intervals in irregular order in smoothened dynamics

In the process, Hebbian mechanism generates many excitatory synaptic connections and increase connectivity between different memories, in turn, leads to the formation of a new bursting activity (Epileptic Behavior) in the dynamics corresponding to excess correlated firing of the neurons. The dynamics of the kindled network with SPU method showed spontaneous bursting at irregular time intervals as shown in figure 4.2. The observed result is similar to the spontaneous population bursting observed in the brain-slice experiment.

As mentioned earlier, in order to simulate “burst”, the network was kindled with SPU method by changing $w_{1,y}$ to 1, for first fifty passes under reduced inhibition. In order to calculate the inter-spike interval accurately, the net activity is smoothened by a “low-pass filtered” through the following equation.
\[ S_{sm}(t) = \frac{1}{t_{sm}} \sum_{t'=t-t_{sm}+1}^{t} S_{up}(t') \], where \( t_{sm} = 40 \) (4.9)

The smoothened network activity with spikes at irregular time intervals is shown in figure 4.3. Note that bursts in the network without smoothening, now appear as “spike” in the smoothened network. By applying the SPU method alone with smoothening, the high random variability of the inter-spike intervals are observed in the simulation. Therefore the underlying stochasticity in the updating scheme is an essential requirement for the network to exhibit spontaneous bursting similar to that was observed in brain slices experiments. In simulated results, irregularity of the inter-spikes intervals shows the chaotic behavior of the BD model.

These inter-spikes intervals were made periodic by applying external electric pulses with constant amplitude and period. We will describe detail study of the BD model and application of chaos control method in the chapter 7.

In this chapter, we have reviewed one of the discrete neural network models proposed in the literature for simulating the brain slice experiment described in chapter 2. We have studied the BD model in detail by implementing their model and testing various scenarios with it. The details of BD model (SPU methods) were obtained through the private communication with Biswal et al. In particular, we made detail studies on normal and epileptic brain activities and sensitivity of the results to various parameters in the model. This study enhanced the knowledge and understanding of our knowledge on the Epileptic Brain Functions.
CHAPTER 5

CONTINUOUS MODELS IN NEURAL NETWORKS

5.1 Introduction

Several types of continuous neural network models have been used in simulation of brain functions. In this chapter, we concentrate on continuous neural network models with biophysical properties. In continuous neural network models, input, output and state variables vary in continuous manner with time. Usually these networks consist of processing units, which have biophysical properties of the real neurons in the central nervous system. The basic governing equations of the neuron dynamics are in the form of differential equations between the variables and the parameters.

5.2 General form of Neuron Model and Population Model

Here we describe a general neuron model consisting of two coupled differential equations; one for the membrane potential and the other one for the so-called relaxation variable.

\[
\frac{dX}{dt} = F(X, W, t)
\] (5.1)
\[
\frac{dW}{dt} = G(X, W, t)
\]  \hspace{1cm} (5.2)

where \(X\) denotes output variable (Voltage or Current) of the neuron, \(W\) is the relaxation variable, which describes the dynamics of the neuron with respect to its output \(X\) at time \(t\). A continuous neural network model for finite number of neurons is constructed by interconnecting all the neurons in the population [47]. Neurons in this network are interconnected and intercommunicated by means of different type of synapses. The values of the strength of synapses are optimized to satisfy the input-output relationship or desired output. The input-output characteristics of a neuron are described by the activation function \(f\). The argument of \(f\) is usually constructed with the synaptic and other inputs received by the neuron. These inputs depend on the activities of the other neurons (Membrane Potential, Firing Rate, etc.) in the network. The activities of the \(n\) neurons in the network are represented by the dynamical variables \(x_i\), where the index \(i\) runs from 1 to \(n\). Therefore the rate of change of activity of neurons is defined by \(n\) differential equations of the form:

\[
\tau \frac{dx_i}{dt} = -x_i - f(h_i) \text{ for } i = 1, \ldots, n \hspace{1cm} (5.3)
\]

where \(h_i = b_i + \sum_{j=1}^{n} w_{ij} x_j\) \hspace{1cm} (5.4)

where \(x_i\)'s denote output variables (voltage or current) of the neuron, \(w_{ij}\)'s are the synaptic weights which quantify the strength of the synapses between the neurons \(i\) and
The bias term $b_i$ represents input from sources outside the network. The time constant $\tau$ describes how rapidly the variable $x_i$ responds to changes in input. In the rest of this chapter we will discuss about the neuron models that produce single action potential, limit cycles and bursting behavior for the input current as the external excitation [48].

![Diagram of ions surrounding the membrane of the neuron.](image)

**Figure 5.1:** Schematic diagram for the ions surrounding the membrane of the neuron. Neuron membrane separates the inside of the neuron from outside and acts as a capacitor. Ions can move across the membrane in both directions through the very small gates in the neuron membrane.

### 5.3 Biophysical Properties of the Neuron

A great deal is known about the biophysical mechanisms, which are responsible for generating neuronal activities. This knowledge provides a basis for constructing neuron models. The neuron membrane is a lipid bilayer 3 to 4 nm thick and it is essentially impermeable to most charged molecules.
This insulating feature causes the neuron membrane to act as a capacitor by separating the charges lying along its interior and exterior surfaces as shown in figure 5.1. By convention, the potential of the extra-cellular fluid outside neurons is defined to be zero mV. Under normal conditions, neuronal membrane potentials ($V$) vary over a range from about $-90$ mV to $+50$ mV.

The difference in ion concentration generates an electrical potential, which plays an important role in neuron dynamics. The potential difference across the neuron membrane biases the flow of ions in or out of a neuron. This biasing effect of the electrical potential can be overcome by an opposing concentration gradient. Ions can move across the membrane and leave the interior of the neuron only if they have sufficient thermal energy to overcome the energy barrier produced by the membrane potential. Therefore the flow of ions out of the cell is proportional to the ion concentration times the Boltzmann factor. The rate at which ions flow into the cell is proportional to the outside ion concentration. Let the concentration of ions inside and outside of the neuron are denoted by $[\text{ion}]_i$ and $[\text{ion}]_o$. The net flow of ions will be zero when the inward and outward flows are equal. The particular potential that satisfies this balancing condition is denoted by $E_{\text{ion}}$.

$$
[\text{ion}]_o = [\text{ion}]_i \exp \left( \frac{zE_{\text{ion}}}{V_T} \right)
$$

where $V_T$ is the potential difference at the temperature $T$, and $z$ is the valence of ion.
Hence the relationship between the equilibrium potential $E_{ion}$ and the ion concentration become:

$$E_{ion} = \frac{V_T}{z} \ln \left( \frac{[ion]_o}{[ion]_i} \right)$$ (5.6)

where $E_{ion}$ is the reversal potential of the ion that satisfies the balancing equation and $z$ is the valence of ion.

Equation (5.6) is the well-known Nernst equation and from this equation we can calculate the reversal potentials for $Na^+$, $K^+$ and $Ca^{2+}$ ions with respect to the inside and outside concentrations. Table 5.1 illustrates the concentration and reversal potential for major ions.

<table>
<thead>
<tr>
<th>$ion$</th>
<th>$ion = Na^+$</th>
<th>$ion = K^+$</th>
<th>$ion = Ca^{2+}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[ion]_i$</td>
<td>50 mM</td>
<td>400 mM</td>
<td>0.4 mM</td>
</tr>
<tr>
<td>$[ion]_o$</td>
<td>440 mM</td>
<td>20 mM</td>
<td>10 mM</td>
</tr>
<tr>
<td>$E_{ion}$</td>
<td>+55 mV</td>
<td>-75 mV</td>
<td>+145 mV</td>
</tr>
</tbody>
</table>

**5.3.1 Membrane Current**

Electric forces and diffusion are responsible for driving ions through channel pores. Voltage difference between the exterior and interior of the neuron produces force on ions. The concentration of $Na^+$ and $Ca^{2+}$ are higher outside the neuron than the
inside while $K^+$ is more concentrated inside of the neuron than the outside. The equilibrium potential level ($E_j$) is defined as the membrane potential at which the current flow due to electric forces, cancels the diffusive flow. The current flowing across the membrane through all of its ion channels is called the membrane current ($I_j$) of the neuron and is defined as product of driving force ($V - E_j$) and conductance function $g_j(V, t)$. The total membrane current ($i_m$) is given as a sum of membrane currents due to each ion.

$$i_m = \sum_j I_j = \sum_j g_j(V, t) (V - E_j)$$

(5.7)

where symbol $j$ represents the corresponding ions.

By the conservation of electric charge the applied current $I_{ext}$ should be equal to the sum of capacitive current $I_C(t)$ which changes the membrane capacitance $C_m$ and the membrane current $i_m$ that passes through the ion channels. Thus

$$I_{ext} = I_C(t) + i_m$$

(5.8)

If $V$ is the voltage across the capacitor (Membrane) then the charging current is given by the following equation:

$$I_C(t) = C_m \frac{dV}{dt}$$

(5.9)
From equations (5.8) and (5.9), we obtain the nonlinear differential equation for the neuron dynamics as:

\[ C_m \frac{dV}{dt} = -i_m + I_{ext} \]  \hspace{1cm} (5.10)

where \(i_m\) is the sum of the ionic currents, which pass through the neuron membrane.

5.4 Hodgkin-Huxley (HH) Neuron Model for Action Potentials

The HH equations are the starting point for detailed neuron models, which account for numerous ion channel currents and different types of synaptic currents. From series of experiments on the giant axon of squid, Hodgkin-Huxley succeeded in measuring ion currents and modeling neuron dynamics in terms of differential equations. This model is important reference model for the derivation of other improved neuron models that have spiking and bursting activities.

The HH model [9] for the generation of the action potentials, in its single-compartment form, is constructed by introducing the membrane current in equation (5.10) as the sum of a transient \(I_{Na}\) current, a delayed-rectified \(I_K\) current and a leakage \(I_L\) current. The leakage current takes care of other channel types, which are not included explicitly. The membrane current is the product of driving force and conductance, which depend on the voltage and time. The total membrane current is written as
\[ i_m = g_{Na}(V, t)(V - E_{Na}) + g_{K}(V, t)(V - E_{K}) + g_L(V - E_L) \]  \hspace{1cm} (5.11)

where \( g_j(V, t) \)'s are the conductance functions and \( E_j \)'s are the resting potentials of the sodium, potassium and leakage currents. More detail about the model is given bellow:

**Figure 5.2:** Schematic Circuit diagram for the HH neuron model. This consists of three important membrane ion currents. At the equilibrium, the difference in ion concentration produces a reversal potential that can be represented by a battery to produce respective ion current in the circuit diagram.
The membrane potential \( V \) of the HH neuron is given by the differential equation

\[
C_m \frac{dV}{dt} = I_{\text{ext}} - I_{Na} - I_K - I_L \tag{5.12}
\]

where \( C_m \) is the membrane capacitance and it is chosen to be 1.0 \( \mu F/cm^2 \). The membrane ionic current equations are given by

\[
I_{Na} = g_{Na} m^3 h (V - E_{Na}) \tag{5.13}
\]

\[
I_K = g_K n^4 (V - E_K) \tag{5.14}
\]

\[
I_L = g_L (V - E_L) \tag{5.15}
\]

where \( m, n \) and \( h \) are the gating variables. Activation and inactivation variables are defined by the differential equation:

\[
\frac{dW}{dt} = \alpha_W (V) (1 - W) - \beta_W (V) W \quad \text{for} \quad W \in \{m, n, h\} \tag{5.16}
\]

Table 5.2 illustrates the rate functions used for the gating variables \( m, n \) and \( h \) of the HH neuron model.
Table 5.2: Rate functions of the gating variables of the HH neuron

<table>
<thead>
<tr>
<th></th>
<th>$W = m$</th>
<th>$W = n$</th>
<th>$W = h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_m (V)$</td>
<td>$\frac{0.1(V + 40)}{1 - \exp(-0.1(V + 40))}$</td>
<td>$\frac{0.01(V + 55)}{1 - \exp(-0.1(V + 55))}$</td>
<td>$0.07 \exp(-0.05(V + 65))$</td>
</tr>
<tr>
<td>$\beta_m (V)$</td>
<td>$4 \exp(-0.0556(V + 65))$</td>
<td>$0.125 \exp(-0.0125(V + 65))$</td>
<td>$\frac{1.0}{(1 + \exp(-0.1(V + 35)))}$</td>
</tr>
</tbody>
</table>

Table 5.3: Ion maximal conductance and reversal potentials

<table>
<thead>
<tr>
<th>Variable, $j$</th>
<th>$j = Na^+$</th>
<th>$j = K^+$</th>
<th>$j = L$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductance, $g_j$ (mS/cm$^2$)</td>
<td>120.0</td>
<td>36.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Reversal Potential $E_j$ (mV)</td>
<td>50.0</td>
<td>-77.0</td>
<td>-54.387</td>
</tr>
</tbody>
</table>

Table 5.3 illustrates conductance’s and the respective reversal potentials of the ions. Hodgkin-Huxley calculated resting potentials and conductance functions from their experimental results. If there is no external current to a neuron then the neuron stays at its resting state and the membrane potential is equal to $-65.0$ mV. If there is an external input current injected into the neuron then it produces electric pulse as an action potential or a spike. In the simulation, action potentials are generated by neurons. Figure 5.3(a) shows an action potentials generated by single neuron where as figure 5.3(b) shows how the input current varies with time; (in this case it is a step function).
Figure 5.3: (a) Output membrane potential $V(t)$, (b) input current in the Hodgkin-Huxley model during the firing of an action potential as single spike.

Figure 5.3 shows that, small amount of input current excites the neuron from its resting state (near below - 60.0 mV) to a firing or an active state (about 40.0 mV), making the action potential to vary around 100.0 mV in durations of 1 or 2 ms. After firing is taken place, the membrane potential of the neuron goes back to its resting state after 10 ms as shown in figure 5.3(a).

Next section we will discuss about a neuron model, which produces chain or continuous action potentials as limit cycles or continuously spiking references to an
external input current. This neuron, modeled by the Connor and Steven, is an extension of HH neuron model.

5.5 Connor-Steven (CS) Neuron Model for Chain of Action Potentials

In the previous section, we discussed the generation of single action potentials by HH neuron model. When a small amount of constant input current is applied, Hodgkin-Huxley neuron produces a single action potential and returns to its resting level. On the other hand, the Connor-Steven neuron produces chain of action potentials or it fires continuously. This model also has a potassium current, a leakage current, a fast sodium current as in the HH neuron model and an additional current called “A-type potassium current”. The role of the A-type potassium current is to increase the time between the action potentials by deactivating the membrane potential of the neuron.

The membrane potential \( V \) of the CS neuron is given by the differential equation (5.12) of HH neuron, with additional \( A \)-current. The \( A \)-current equation is given by

\[
I_A = -g_A a^3 b (V - E_A)
\]  

(5.17)

where \( a \) and \( b \) are gating variables for \( A \)-current, \( g_A \) is the conductance function and \( E_A \) is the resting potential of the \( A \)-current.
Table 5.4 illustrates the rate functions used in equations (5.13), (5.14) for the gating variables $m$, $n$ and $h$, of the CS neuron model.

**Table 5.4: Rate functions of the gating variables of the CS neuron**

<table>
<thead>
<tr>
<th></th>
<th>$W = m$</th>
<th>$W = n$</th>
<th>$W = h$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_w(V)$</td>
<td>$\frac{0.38(V + 29.7)}{1 - \exp(-0.1(V + 29.7))}$</td>
<td>$\frac{0.02(V + 45.7)}{1 - \exp(-0.1(V + 45.7))}$</td>
<td>$0.266\exp(-0.05(V + 48))$</td>
</tr>
<tr>
<td>$\beta_w(V)$</td>
<td>$15.2\exp(-0.0556(V + 54.7))$</td>
<td>$0.25\exp(-0.0125(V + 55.7))$</td>
<td>$\frac{3.8}{1 + \exp(-0.1(V + 18))}$</td>
</tr>
</tbody>
</table>

The activation and inactivation variables of the $A$-current dynamics is defined by the following differential equation:

$$
\tau_W(V) \frac{dW}{dt} = W_\infty(V) - W \text{ for } W \in \{a, b\}
$$

(5.18)

The $A$-current is described directly in terms of gating variables of the form

$$
\tau_a(V) = 0.3632 + \frac{1.158}{1 + \exp(0.0497(V + 55.96))}
$$

(5.19)

$$
a_\infty(V) = \left( \frac{0.0761\exp(0.0314(V + 94.22))}{1 + \exp(0.0346(V + 1.17))} \right)^3
$$

(5.20)
\[
\tau_b(V) = 1.24 + \frac{2.678}{(1 + \exp(0.0624(V + 50)))}
\]  
(5.21)

\[
b_\infty(V) = \left( \frac{1}{1 + \exp(0.0688(V + 53.3))} \right)^4
\]  
(5.22)

Table 5.5 illustrates the respective channel maximum conductance and reversal potential of the ion, leakage current and applied A-current are given below.

**Table 5.5:** Ion, leakage current and applied A-current maximal conductance and reversal potentials.

<table>
<thead>
<tr>
<th>Variable, j</th>
<th>( j = Na^+ )</th>
<th>( j = K^+ )</th>
<th>( j = L )</th>
<th>( j = A )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductance, ( g_j ) (mS/mm²)</td>
<td>1.2</td>
<td>0.2</td>
<td>0.003</td>
<td>0.477</td>
</tr>
<tr>
<td>Reversal Potential ( E_j ) (mV)</td>
<td>55.0</td>
<td>-72.0</td>
<td>-17.0</td>
<td>-75.0</td>
</tr>
</tbody>
</table>

**Figure 5.4:** Train of action potentials of the CS neuron for the constant input current in the absence of A-type potassium current.
In the absence of the external input current, the membrane potential remains constant at a resting value around \(-68\) mV. In the simulation, the dynamics of CS neuron changes with various combinations of currents. The fast sodium and delayed-rectifier potassium currents produce different dynamics in CS neuron and the resulting action potentials are repeating continuously as shown in figure 5.4. In the absence of \(A\)-type potassium currents, CS neuron model is equivalent to HH neuron model. However unlike HH neuron model, CS neuron model produces very fast action potentials for the constant input current.

![Figure 5.5: Train of action potentials of the CS neuron for the constant input current in the presence of \(A\)-type potassium current.](image)

Figure 5.5 shows generation of an action potential for particular value of input current with additional \(A\)-type potassium current. The main role of the \(A\)-type potassium current is to increase the time between the action potentials by deactivating the membrane potential of the neuron. It is evident from figures 5.4 and 5.5 that the time
difference between the action potentials becomes large when A-type potassium is introduced.

![Membrane Potential Graph]

**Figure 5.6:** Membrane potential of the neuron for the negative and positive external input current from zero to 50 ms and from 50 ms to 200 ms

In the CS Neuron Model the action potential for the negative input current $I_{ext} (= -0.1 \text{ nA/cm}^2)$ is delayed from zero to 50 ms. Then the neuron membrane potential slowly increases and produces train of action potentials as shown in figure 5.6, when the input current $I_{ext}$ become positive (e.g. $I_{ext} = +0.1 \text{ nA/cm}^2$).

### 5.6 Huguenard-McCormick (HM) Neuron Model for Bursting

In this section we discuss a bursting neuron model, which is entirely different from previous two spiking models. This bursting neuron model is extended version of the CS neuron model by adding calcium current based on the data obtained from
thalamic relay neurons in thalamus. HM neuron model is proposed for bursting neuron by Huguenard-McCormick [9].

The membrane potential \( V \) of the HM neuron is given by the CS neuron differential equation (5.12) with (5.17) and additional calcium current. The equation for this calcium current is given by

\[
I_{Ca} = g_{Ca} M^2 H(V - E_{Ca})
\]  
(5.23)

where \( g_{Ca} = 0.013 \) mS/mm², \( E_{ca} = 120 \) mV with \( M \) and \( H \) satisfy the differential equation of the form (5.18) with the following gating functions:

\[
\tau_M(V) = 0.612 + (\exp(-(V + 132)/16.7) + \exp((V + 16.8)/18.2))^{-1}
\]  
(5.24)

\[
M_\infty(V) = \frac{1}{1 + \exp(-(V + 57)/6.2)}
\]  
(5.25)

\[
\tau_H(V) = \begin{cases} 
\exp((V + 467)/66.6) & \text{if } V < -80 \text{ mV} \\
28 + \exp(-(V + 22)/10.5) & \text{if } V \geq -80 \text{ mV}
\end{cases}
\]  
(5.26)

\[
H_\infty(V) = \frac{1}{1 + \exp((V + 81)/4)}
\]  
(5.27)
In a simulation, this type of neuron produces single burst with the duration around 50 ms. In the bursting period, calcium ion concentration inside the neuron slowly increases and terminates the bursting activity in the process.

![Graph](image)

**Figure 5.7:** The additional $Ca^{2+}$ current causes a burst of action potentials in the HM model.

A transient $Ca^{2+}$ conductance acts, in many ways, like a slower version of the transient $Na^+$ conductance that generates action potentials. Instead of producing an action potential, a transient $Ca^{2+}$ conductance generates a slower transient depolarization sometimes called a $Ca^{2+}$ spike. This transient depolarization causes the neuron to fire a burst of action potentials, which are $Na^+$ spikes riding on the slower $Ca^{2+}$ spike.

Figure 5.7 shows that the neuron hyperpolarizes for the period from zero to 50 ms due to the negative current. In the absence of the external current, a burst of $Na^+$
spikes was generated due to an underlying $Ca^{2+}$ spike. In this model also the additional $A$-type potassium current creates delay in the firing.

5.7 Calcium Activated Potassium Channels

The calcium ions are particularly important as they contribute to the ionic current across the membrane and control some potassium channels. The respective control is mediated by the inside calcium concentration ($[Ca^{2+}]_i$) of the neuron. These calcium dependent potassium channels are responsible for important electrophysiological properties of the neurons in different areas of the brain. To insert this behavior into the neuron model, the conductivity of calcium dependent potassium current is evaluated from the internal calcium concentration of the neuron. The calcium dependent potassium current is modeled by equation

$$I_K(Ca) = g_K(Ca) \left( \left[ Ca^{2+} \right]_i \right)^4 (V - E_K)$$  \hspace{1cm} (5.28)

where $g_{K(Ca)} = 0.035 \text{ mS/mm}^2$ and $E_K = -72.0 \text{ mV}$

The inside calcium concentration of the neuron is described by a linear differential equation:

$$\tau_Ca \frac{d}{dt} \left[ Ca^{2+} \right]_i = \left[ Ca^{2+} \right]_i + A_Ca \cdot I_Ca$$  \hspace{1cm} (5.29)
where $I_{Ca}$ in (5.23) is the calcium current across the membrane, $\tau_{Ca} = 200$ ms is the time constant that governs the decay of the calcium transient and $A_{Ca}$ is a constant that scales the amplitude of the calcium transient as it is produced during an action potential.

We note earlier that HH neuron single spike dynamics changes to chain of spikes by CS neuron model. Similarly CS neuron spiking dynamics changes to single bursting dynamics by an additional invert calcium current. Further, the CS neuron model with invert calcium currents and calcium dependent potassium currents introduce the periodic bursting dynamic as observed in the central nerves system.

The calcium current during these bursts causes a considerable increase in inside calcium concentration. This activates the calcium dependent potassium currents, along with the inactivation of the calcium currents, terminate the burst.

Table 5.6: Membrane currents of the three different neuron models.

<table>
<thead>
<tr>
<th>Hodgkin-Huxley</th>
<th>Connor-Steven</th>
<th>Huguenard-McCormick</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na} = g_{Na}m^3h(V - E_{Na})$</td>
<td>$I_{Na} = g_{Na}m^3h(V - E_{Na})$</td>
<td>$I_{Na} = g_{Na}m^3h(V - E_{Na})$</td>
</tr>
<tr>
<td>$I_{K} = g_{K}n^4(V - E_{K})$</td>
<td>$I_{K} = g_{K}n^4(V - E_{K})$</td>
<td>$I_{K} = g_{K}n^4(V - E_{K})$</td>
</tr>
<tr>
<td>$I_{L} = g_{L}(V - E_{L})$</td>
<td>$I_{L} = g_{L}(V - E_{L})$</td>
<td>$I_{L} = g_{L}(V - E_{L})$</td>
</tr>
<tr>
<td>$I_{A} = g_{A}a^3b(V - E_{A})$</td>
<td>$I_{A} = g_{A}a^3b(V - E_{A})$</td>
<td>$I_{A} = g_{A}a^3b(V - E_{A})$</td>
</tr>
<tr>
<td>$I_{Ca} = g_{Ca}M^3H(V - E_{Ca})$</td>
<td>$I_{K(Ca)} = g_{K(Ca)}[Ca^{2+}]^n(V - E_{K})$</td>
<td></td>
</tr>
</tbody>
</table>
One of the factors which affects the inter-burst interval is the time it takes for the inside calcium concentration to return to its low equilibrium level. This low level deactivates the calcium dependent on potassium current, allowing another burst to be generated. Therefore by adding all ion currents to the neuron model, neuron can fire action potentials as spikes at a steady rate or as periodic bursting, which are common feature of the neuron in the central nerves system. Table 5.6 illustrates the membrane current equations of the above models.

5.8 Synaptic Functions and their Interaction Current

In the neural population, neurons are interconnected and they intercommunicate with each other through synapses. Synapse is the gap junction between neurons. There are two different types; electrical synapse and chemical synapse. In general, synaptic current is evaluated from the dynamical activities between the neurons in the population. For an electrical synapse, the synaptic current of the post-synaptic neuron is directly calculated by

\[ I_{syn} = g_{syn} (V_{post} - V_{pre}) \]  

(5.30)

where the coefficient \( g_{syn} \) takes different values for two different directions of the synaptic current. \( V_{post} \) and \( V_{pre} \) are the membrane potential of the post-synaptic neuron and pre-synaptic neuron.
At a chemical synapse, firing of pre-synaptic neuron results in release of neurotransmitter, which induces changes in the membrane conductance of the post-synaptic neuron at the site of the synapse. Instead of developing a mathematical model for this chemical process in the synapse junction, we describe it as an explicitly time-dependent conductance function $g_{syn}(t)$ that produces the effective changes whenever a pre-synaptic spike arrives at the synapse. The current passes through the synapse depends, as usually, on the difference of its reversal potential $E_{syn}$ and the actual value of the membrane potential,

$$I_{syn}(t) = g_{syn}(V_{pre}, t)(V_{post} - E_{syn})$$  \hspace{1cm} (5.31)

where the parameter $E_{syn}$ and the function $g_{syn}(V_{pre}, t)$ can be used to characterize different types of synapses.

In general, a superposition of exponentials is used for conduction functions. For an inhibitory synapse, $E_{syn}$ equals the reversal potential of potassium ions (about $-75.0$ mV), whereas for excitatory synapses $E_{syn} \approx 0.0$ mV.

### 5.8.1 Stimulation by Synaptic Current

We have considered an isolated neuron that is activated by external input current $I_{ext}$. In a more realistic situation, single neuron is a part of a larger population and the input current $I_{in}(t)$ is generated by the activity of the other pre-synaptic neurons. That is,
each pre-synaptic spike generates post-synaptic current pulse. The total input current received by the post-synaptic neuron $i$, is the sum over all current pulses,

$$I_i(t) = \sum_j w_{ij} \sum_k g\left(t - t^{k}_{j}\right)[V_i(t) - E_{syn}]$$  \hspace{1cm} (5.32)

where the factor $w_{ij}$ is a measure of the efficacy of the synapse from pre-synaptic neuron to post-synaptic neuron $i$, the function $g\left(t - t^{k}_{j}\right)$ is the post-synaptic neuron conductance generated by a $k^{th}$ spike of the $j^{th}$ pre-synaptic neuron and the parameter $E_{syn}$ is the reversal potential of the synapse. In the literature, a function of the form $x \exp(-x)$ is generally used for the conduction function $g$ to introduce the synaptic current in the neural population [9, 12].
CHAPTER 6

APPLICATION OF CONTINUOUS NEURAL NETWORK MODELS IN EPILEPSY

6.1 Introduction

In this chapter we will discuss the application of continuous neural network models in epilepsy. Recently, there have been great interests in simulating human epileptic brain activities by using continuous neural networks, which incorporated the biophysical properties of the central nervous system [2, 9, 11, 12]. Epilepsy is a neurological disorder characterized by the occurrence of seizures (i.e., Ictal Activity). During an epileptic seizure, certain part of the brain generates oscillations that spread throughout the brain and affect its normal functioning. A method called kindling is considered to be a very good model for studying epilepsy. The mechanism of generating epilepsy in a laboratory brain tissue either by increasing high potassium concentration in extracellular medium or applying electrical stimulation to the brain is called kindling. If the weight of the excitation is sufficiently large, bursts are generated. Bursts are the collection of high amplitude spikes separated by regions with very low activity.

Our aim of this chapter is to present results of our study on effects of external input currents on neuron dynamics. The external input currents and the synaptic weights
(Strength) of the population neurons are the two most important factors for generating epileptic behavior in neural population.

6.2 Single-Compartment Model

Now, we describe the continuous neural network model used in our detail study. Neuron models that describe the membrane potential by a single variable \( V \) are called single-compartment models [29, 30]. The rate of change of the membrane potential is proportional to the rate at which charge builds up inside the neuron. The rate of charge buildup is, in turn, equal to the total amount of current entering the neuron. The relevant currents are those arising from all membrane ion currents and input external current \( I_{ext} \) (Stimuli) injected into the neuron through electrodes in experimental settings. Therefore the basic governing equation for single-compartment model is given by

\[
C_m \frac{dV}{dt} = -(I_{Na} + I_K + I_L + I_A + I_{Ca} + I_{K(Ca)}) + I_{ext} \tag{6.1}
\]

where \( C_m = 1.0 \ \mu F/cm^2 \) is the membrane capacitance and \( I_A \) and \( I_L \) are the transient current and the leakage current respectively. Other currents are the ionic currents, which are labeled according to the ionic symbol.

Equations for membrane ionic currents, transient currents and other currents such as leakage current are given by
\[ I_{Na} = g_{Na} m_{\infty}^3 (V) (1 - W) (V - E_{Na}) \]  \hspace{1cm} (6.2)

\[ I_K = g_K W^4 (V - E_K) \]  \hspace{1cm} (6.3)

\[ I_L = g_L (V - E_L) \]  \hspace{1cm} (6.4)

\[ I_A = g_A A_{\infty} (V) B (V - E_K) \]  \hspace{1cm} (6.5)

\[ I_{Ca} = g_{Ca} X^2 \frac{K_C}{K_C + C} (V - E_{Ca}) \]  \hspace{1cm} (6.6)

\[ I_K(Ca) = g_K(Ca) \frac{C}{K_d + C} (V - E_K) \]  \hspace{1cm} (6.7)

where \( W \) is the recovery variable, \( X \), and \( B \) are respectively the calcium channel activation variable and the transient potassium channel inactivation variable. \( C \) is the intercellular calcium concentration. \( K_C (= 2.0) \) and \( K_d (= 0.5) \) are the constants of calcium concentration function.

The dynamics of the variable \( W \), \( X \) and \( B \) are governed by the following differential equations
\[ \tau_W(V) \frac{dW}{dt} = W_\infty(V) - W \]  \hspace{1cm} (6.8)

\[ \tau_W(V) = \frac{1}{\lambda} \left( \exp \left[ a^W (V - V_W) \right] + \exp \left[ -a^W (V - V_W) \right] \right)^{-1} \]  \hspace{1cm} (6.9)

\[ \tau_B \frac{dB}{dt} = B_\infty(V) - B \]  \hspace{1cm} (6.10)

\[ \tau_X \frac{dX}{dt} = X_\infty(V) - X \]  \hspace{1cm} (6.11)

\[ \frac{dC}{dt} = K_p \left( -g_{Ca} X^2 + \frac{K_C}{K_C + C} (V - E_{Ca}) \right) - RC \]  \hspace{1cm} (6.12)

where \( \lambda (= 0.08) \) is a temperature-related parameter, \( \tau_B (= 10.0 \text{ ms}) \) is the relaxation time of \( B \), \( \tau_X (= 25.0 \text{ ms}) \) is the relaxation time constant of \( X \), \( K_p (= 0.0002) \) is the conversion factor from calcium current to concentration and \( R (= 0.006) \) is the removal rate constant of the intracellular calcium concentration.
Table 6.1: The maximum voltage for gating variable $p$ (denoted by $V_p$) and the maximum slope for gating variable $p$ (denoted by $a^p$) are given below, here for $P \in \{m, W, A, B, X\}$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$p = m$</th>
<th>$p = W$</th>
<th>$p = A$</th>
<th>$p = B$</th>
<th>$p = X$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a^p$</td>
<td>0.065</td>
<td>0.055</td>
<td>0.02</td>
<td>-0.095</td>
<td>2.0</td>
</tr>
<tr>
<td>$V_p$ mV</td>
<td>-31.0</td>
<td>-35.0</td>
<td>-20.0</td>
<td>-70.0</td>
<td>-45.0</td>
</tr>
</tbody>
</table>

The limiting values $m_\infty(V)$, $A_\infty(V)$, $W_\infty(V)$, $B_\infty(V)$ and $X_\infty(V)$ in (6.2), (6.8), (6.9), (6.10) and (6.11) are given by

$$P_\infty(V) = \left[1 + \exp\left(-2a^P (V - V_P)\right)\right]^{-1} \text{ for } P \in \{m, A, W, B, X\} \quad (6.13)$$

Table 6.2: The conductance of and reversal potential of the ion channels.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$q = Na$</th>
<th>$q = K$</th>
<th>$q = L$</th>
<th>$q = A$</th>
<th>$q = Ca$</th>
<th>$q = K(Ca)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_q$ (mS/cm$^2$)</td>
<td>120.0</td>
<td>15.0</td>
<td>0.3</td>
<td>12.5</td>
<td>1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>$E_q$ (mV)</td>
<td>55.0</td>
<td>-72.0</td>
<td>-50.0</td>
<td>-72.0</td>
<td>124.0</td>
<td>-72.0</td>
</tr>
</tbody>
</table>

In the rest of the section, we describe the implementation of the model. Differential equations in (6.1), (6.8), (6.10), (6.11) and (6.12) were solved numerically using the forward Euler method with the time step of 0.01 ms. Choosing a small time step gives additional benefit of decreasing the error associated with determining the time of occurrence of action potentials. The small amount of input current excites the neuron
from its resting state (-65.0 mV) to firing state (about 45.0 mV) making the action potential to be about 100.0 mV. After firing, neuron membrane potential reaches to its resting state as shown in figure 6.1.

![Graphs showing current and membrane potential over time](image)

**Figure 6.1:** (a) The input current $I_{ext}(t)$ and (b) Membrane potential $V(t)$ in the model during the firing of an action potential.

### 6.3 Application of the Model

Our objective here is to find the effect of the external input current on the neuron dynamics. These studies will help us to understand the neuron population dynamics and develop a better model to simulate the slice experiment by continuous neural network
models. In the rest of this chapter, we present results from our study on activity of single neurons and population of neurons, due to changes in input currents.

We solved the differential and other related equations from (1) to (6) of the single neuron dynamics for a given external input current $I_{ext}$. If there is no external current (i.e. $I_{ext}(t) = 0$ for all $t$) then no action potential was observed and the membrane potential converges to its resting value $V_{rest} = -65.0$ mV. However for a small change in input current to the neuron produces an action potential.

Figure 6.2: Limit cycle behavior of the action potential of a single neuron for constant input current. (a) Duration is 1000 ms. (b) Same as (a) but plotted between intervals from 400 ms to 600 ms.
If the input current changes with respect to time, then the response of the neuron membrane potential also changes according to nature of the input. That is, if the external input current as in pulse forms then the membrane potential is sensitive to the amplitude (Pulse Height), length of the application time (Width) and absence of input current application (Inter Pulse Interval). Single neuron responses to different input currents are shown in figures 6.2, 6.3 and 6.4. We observed that the action potential shows regular behavior (or Limit Cycles) for constant input currents $I_{ext} = 2.0 \ \mu A/cm^2$. This type of activity represents the normal brain dynamics (Regular Behavior). In this case, we observed constant inter-spike intervals as shown in figure 6.2.

![Figure 6.3: Spiking dynamics of the neuron for random input current as pulse](image)

On the other hand we can simulate epileptic brain signals (Irregular Behavior) by a single neuron if we apply input current at random time intervals. In this case we observed that the spikes were occurred in an irregular manner as shown in figure 6.3.

We observed the regular bursting behavior, as shown in figure 6.4(a) for constant periodic input current $I_{ext} (= 10.0 \ \mu A/cm^2)$ injected at regular interval. The irregular
bursting, as shown in figure 6.4(b) occurred when the neuron received constant input current $I_{\text{ext}} = 10.0 \, \mu\text{A/cm}^2$ as a random pulse.

![Graph showing membrane potential over time](image)

**Figure 6.4:** Single neuron behavior with respect to the external input current. (a) Periodic bursting behavior for periodic external pulse input current. (b) Irregular bursting behavior for irregular external pulse input current.

### 6.4 Neuron Population Dynamics

In general, neurons receive input signals through dendrites from other neurons in the population. In the neuronal population, neurons are interconnected to each other in
complex manner by synaptic connections. In our network, neuronal population consists of finite number of identical neurons, which are grouped into two, according to their synaptic connections. These two groups are named as excitatory and inhibitory populations as in the case of real brain tissue. In this section we will investigate the effect of the external input current and the potassium concentration on neuronal population dynamics. We simulate the interaction of neurons in the population by introducing synaptic current in the differential equation (6.1).

6.4.1 Synaptic Current

The interaction term between the neurons is defined as synaptic current in between the pre-synaptic and post-synaptic neurons in the population. This current is calculated from the dynamic activity of the neurons in the population. The synaptic current from pre-synaptic neurons to the post-synaptic neuron is defined by:

\[
I_{syn}(t) = A \sum_{j=1}^{N_{syn}} w_j g_j(t - \tau_j)(V - E_{syn})
\]

(6.14)

\[
g_j(t) = g_{syn} \sum_{i=1}^{N(t)} \left( \exp\left(\frac{(t_i - t)}{\tau_d}\right) - \exp\left(\frac{(t_i - t)}{\tau_0}\right) \right)
\]

(6.15)

where \(g_j(t)\) is the conductance function, \(t_i\) denotes time of the occurrence of \(i^{th}\) action potential in pre-synaptic neurons. \(\tau_j\) is the synaptic delay, \(\tau_d (= 3.0 \text{ ms})\) and \(\tau_0 (= 0.5 \text{ ms})\)
represent, respectively, decay time and onset time constants of a post-synaptic potentials (PSP). \( g_{syn} \) (= 0.0066 mS/cm\(^2\)) is the synaptic conductance constant, \( w_j \) is synaptic weight (modeled as an integer in the range 0 – 120). \( E_{syn} \) is the synaptic reversal potential (equal to \(-10.0 \text{ mV} \) and \(-72.0 \text{ mV} \), respectively for excitatory and inhibitory synapses). \( A \) is the post-synaptic amplitude parameters are equal to 0.0112 mS/cm\(^2\) and 0.0224 mS/cm\(^2\) respectively for excitatory and inhibitory neurons, \( N(t) \) is the number of past action potentials from \( t = 0 \), and \( N_{syn} \) is the number of synaptic inputs.

### 6.4.2 Neural Population Model

In the simulation we used a network of 81 excitatory and 9 inhibitory neurons to simulate a small region of the brain tissue. Each neuron receives two excitatory and three inhibitory inputs from pre-synaptic neurons, which were randomly selected at each time. This network model is activated by randomly selected four neurons from the excitatory population. These four neurons receive input currents from an external source and produce output, representing the background activity of the neural network. In the population, neuronal bursting dynamics is affected by the changes in the excitation synaptic weight. We investigated the population behavior of all neurons in the model for different excitation synaptic weights while fixing inhibition synaptic weights. If the synaptic weight is very or if the synaptic connection is absent then all the neurons are at the resting state. We observed some neurons become active when the synaptic weight value slowly increasing. That is, the background activities spared to the other neurons in the population through the synapse and activate them to active mode (Spiking or Bursting). For some low value range of synaptic weights we observed the
asynchronized spiking behavior in the population as shown in figure 6.5(a) and it
changed to synchronized bursting behavior as shown in figure 6.5(b) for high excitation
synaptic weights.

![Figure 6.5](image1.png)

**Figure 6.5:** Dynamics of the neuronal population. (a) The asynchronized spiking
behavior observed for low excitation synaptic weights. (b) Same as (a) but for
high excitation synaptic weights and it shows synchronized bursting dynamics.

In summary, in this chapter we investigated the dynamics of a single neuron due to
different input currents and population of neurons dynamics due to changes in the
excitation synaptic weights. We observed that the single neuron behavior depends on
the nature of the input current.
In the population, neuron dynamics strongly depends on the synaptic weights and whether the synaptic weights type is excitatory or inhibitory. As a result, we were able to simulate the normal brain (Regular Behavior) and epileptic brain (Irregular Behavior) signals by changing the environment of the neural system.
CHAPTER 7

SLICE EXPERIMENT BY SIMULATION

7.1 Introduction

As mentioned in the introduction, our objective here is to simulate the epileptic brain behavior (Chaotic) occurred in the brain slice experiment, which is described in chapter 2, by using neural network models. To achieve this objective, we made several studies on theoretical and computational aspects of neural networks models, which are based on central nerves system. We have studied and tested these models in detail. The results of this study were presented in previous chapters 3, 4, 5 and 6. We have developed two simulation models, one is based on discrete models and the other one is based on continuous models, to simulate epileptic brain slice experiment. In this chapter, we present results of our simulation models.

7.2 Simulation of Epileptic Brain by Discrete Neural Network Model

To simulate the epileptic brain activity, one of the models we chose is the discrete neural network model as described in the chapter 4. The described BD model is a modified and extended version of the Hopfield and Spin Glass neural networks models. First we
describe the model, parameters and update methods used in our simulation. Our neural network model consists of $N$ McCulloch-Pitts (Binary) neurons, each of which can take the values 0 or 1 according to the sign of the local field. Initially a fixed number of low-active patterns are stored in the memory by the same method described in the BD model. Note that the net activity of each memory is set at value $p << N$. That is, in each pattern, the numbers of active neurons are very small.

Table 7.1: Network State and Memory Patterns Observed in the Simulation.

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The values of the parameters used in our simulation are taken as same as in the BD model. The network consists of $N (= 200)$ number of neurons, $q (= 20)$ is the number of patterns stored in the memory, $p (= 10)$ is the number of active neurons in the each pattern, $b (= 0.6)$ is the relative strength of inhibition, $\lambda (= 2)$ is the relative strength of the delayed signal, $\tau (= 2$ passes) is the time delay associated with the delayed signal. In order to check the network activity in the simulation, we initialized the network state (i.e., $\{S_i\}_{i=1}^N$) at time $t = 1$, by the first pattern (i.e., $\mu = 1$) in the memory (i.e., $\{e^{\mu}\}_{\mu=1}^N$) and updated the neurons $N$ times in distinct random order at each time step. In the time evolution, the similarity in between the network state $\{S_i(t)\}_{i=1}^N$ at the time step $t$ and the memory pattern $\{e^{\mu}\}_{\mu=1}^N$ is calculated by the overlap function, $m^\mu$:

$$m^\mu(t) = \sum_{i=1}^{N} e^{\mu}_i S_i(t), \quad \mu = 1, 2, \ldots, q$$ (7.1)

The network evolution is found to follow the each pattern in the memory in a sequential order. That is, if the network state is coincided with the one of the stored patterns in the memory then $m^\mu(t)$ is 10 otherwise its value is less than ten. The results are shown in table 7.1. Further we checked the network dynamics for different update methods in the simulations.
In general, the order of updates of weights and activation functions affect the neural network dynamics and hence change the state of the network [7, 10]. In a neural network model, the change of synaptic weights with respect to time is called synaptic plasticity or activity-dependent learning [42-44]. In our model, the governing equation of synaptic plasticity is similar to the explicit-learning equation (4.3) described in chapter 3 (i.e., \( \Delta w_{ij}(t) = \xi_i^{m} \xi_j^{m} \)). The governing equation for the synaptic plasticity is given by

\[
 w_{ij}(t+1) = w_{ij}(t) + S_i(t)S_j(t) \quad \text{for } i, j = 1, 2, \ldots, N 
\]  

(7.2)

where \( S_i(t) \) and \( S_j(t) \) are the states of the neurons at time \( t \).

To update the network state, we introduced another important property in the central nervous system. In the central nervous system, the numbers of active neurons are much less than that of inactive ones [1, 7, 9]. Initially this property is introduced to the network model by storing low-active patterns in the memory. In a similar way, a small numbers of neurons are updated at each time step in order to establish low active property in the simulation. At each time step, in between 20% to 30% of the neurons in the network are randomly selected and their states are updated according to their local fields. During this process, synaptic weights \( w_1 \) and \( w_2 \) are updated for a small time period (\( t = 50 \) passes) corresponds to the total time (\( t = 4000 \) passes) as follows.

\[
 w_{1rj}(t+1) = w_{1rj}(t) + S_r(t)S_j(t) 
\]  

(7.3)

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\[ w_{2rj}(t+1) = w_{2rj}(t) + S_r(t)S_j(t), \]  

(7.4)

where \( j = 1, \ldots, N \) and \( r \) which is chosen at random, is the index of the neuron to be updated in the network at \( t^{th} \) time step.

We call this approach as random update with synaptic plasticity (RUWSP). In the RUWSP method, synaptic weights are either get strengthened or remain the same (i.e., \( w_{1r}(t+1) \geq w_{1r}(t) \) and \( w_{2r}(t+1) \geq w_{2r}(t) \)). We update the weight states for a short time allowing the network to learn the environment changes. That is, our neural network model with RUWSP method enables us to study the scope of the generic dynamics in the simulations.

![Figure 7.1: Network dynamics of low-amplitude oscillation mode.](image)

Now describe our results obtained by applying RUWSP method in the simulation. When a small number of neurons are updated at a random sequence (Not Necessarily
Distinct) with synaptic plasticity method, we observed noisy low-amplitude oscillations of
the net activity $S_{up}$ around an average value $p = 10$ as shown in figure 7.1.

![Graph showing network bursting dynamics by kindling](image)

**Figure 7.2:** Network bursting dynamics by kindling

![Graph showing inter-spike intervals in irregular order](image)

**Figure 7.3:** Inter-spike intervals in irregular order

In order to introduce the bursting activity, the chemical kindling was implemented by
changing the symmetric weights in random order with respect to the active neurons in the
population. For the first fifty seconds under reduced inhibition (i.e., the relative strength of
inhibition b is reduced from 0.6 to 0.24 during this period), the network was kindled with 
RUWSP method by changing $w_{1,\ell}$ to 1 as compared to the same condition described in the 
chapter 4. The kindled network activity with bursts is shown in figure 7.2. To introduce 
spikes in the process, the net activity is smoothened by a “low-pass filter” (equation (4.9)) 
described in chapter 4. The smoothened network activity with spikes is shown in figure 7.3. 
It was found that maps of inter-spike intervals exhibit recurrent unstable-periodic-orbit 
(UPOs) like trajectories similar to those found in experiments on hippocampal slices.

However, in order to control the chaotic or random nature of the ISIs in the slice 
experiment, Periodic Pacing (PP), Demand Pacing and Anti-Control (AC) methods were 
used by Schiff et al [7].

![Figure 7.4: Poincare plot of the inter-spike interval of the kindled neural network.](image)

The inter-spike intervals are collected from the duration of 50,000 ms simulation. 
In a chaotic system the points intersect with a line of identity $I_{n+1} = I_n$ are known 
as unstable fixed points.
In our simulation, neural network model with RUWSP method is very sensitive to the variation in parameters and initial conditions. (e.g., the network size, synaptic weights, updates rule and input variables). Generally, the chaotic behavior observed in simulations can be control by introducing minimal changes to its accessible parameters or variables in the model [18]. We apply periodic pacing chaos control methods to control the randomness in inter-spike intervals (ISI's) observed in our simulation.

As mention in the introduction, in chaotic systems, the long-term behavior is very sensitive to initial conditions. A key feature of such systems is that they contain an infinite number of unstable periodic fixed points. In our simulated results, the obtained spikes are in irregular form and inter-spike intervals are irregular as shown in figure 7.3. The Poincare section is $(I_n, I_{n+1})$ in figure 7.4 shows the chaotic nature of the network activity.

In general, chaos in a dynamical system (Exponential Sensitivity to Initial Conditions), can be controlled by changing parameters in the system [34]. That is, for certain values of parameters, systems behave regular manner while for other values they behave chaotically. Carefully chosen small perturbations of an accessible parameter or variable can stabilize one of many unstable periodic orbits (UPOs) embedded in the phase space flow.

Here we apply the PP method for controlling chaos in the network model, which was discussed in [4]. If a chaotic system admits no accessible system parameter, it may be
possible to control the system by altering system variables. Suppose we move the variables along a specific direction $\mathbf{u}$. If the Poincare section $(I_n, I_{n+1})$ is given by:

$$ I_{n+1} = f(I_n) $$  \hspace{1cm} (7.5)

and we define a new form by

$$ I_{n+1} = f'(I_n, p) = f(I_n + pu). $$  \hspace{1cm} (7.6)

Then we proceed with the method known as OGY proposed in [33, 34]. Here we need to identify the location of the unstable fixed point $\mathcal{I}$ (i.e., Time Interval), to implement the periodic pacing control method. In our simulation, the unstable fixed-point $\mathcal{I}$ is found to be 215. This value was calculated from the data $(I_n, I_{n+1})$ by using the method described in [21, 22]. The periodic pacing control method is very simple to implement in the process.

![Graph of $S_{\text{sm}}$ vs Time](image).

**Figure 7.5:** Controlled (- -) and non-controlled (-) dynamics of the network.

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In order to control the randomness, the network was stimulated (reduce the inhibition strength from 0.6 to 0.24 for five passes) at fixed intervals having length $I^*$, irrespective of the occurrence of natural spikes. As a result, we observed that the naturally occurring ISIs larger than $I^*$ disappeared. The controlled dynamics is shown in figure 7.5 (chaotic dynamic by - line, and control dynamic by -- line).

In summary, we simulated the slice experimental results using discrete neural network by introducing random weights at different stages of the simulation. The network behavior was found to be very sensitive to its parameters, initial state and the update rule with respect to time. Note that we obtained our results in this chapter without using sub-passes update method, which were referred in chapter 3. In the rest of this chapter, we describe the epileptic brain activity by continuous neural networks models.

### 7.3 Simulation of Epileptic Brain by Continuous Neural Network Model

We believe that, lack of biophysical properties of the individual neurons, makes the above described discrete neural network model inappropriate for studying the collective dynamical behavior of the biological neural structure. Therefore we made further study on other neural network models, which have possible biophysical properties of the biological neurons in the central nerves system. In chapter 5, we described the important biophysical properties of neuron models and modification ideas to improve various activities such as spiking or bursting.
For the purpose of simulating brain-slice experiment, we decided to have our simulation model based on the model proposed by Av-Ron et.-al. [29]. Before developing our model for neural population, we investigated a single compartment model (SCNM), which was described in chapter 6. Then we construct our population model extending the SCNM. Purpose of studying SCNM is to find out the sensitivity of neuron output to changes in outside potassium concentration and changes in external input current. Governing equations and parameter values were chosen from the neuron model, described in chapter 6. The governing equations are (6.1) to (6.15). First we fixed potassium concentration at higher value than the value used by Av-Ron et. al. [29].

We ran the simulation for 1000 ms. During this time the input current was kept at a fixed value. We repeated the simulation for 31 values of input current. These 31 values are chosen between 0 $\mu$A/cm$^2$ to 15.0 $\mu$A/cm$^2$ with the step size of 0.5 $\mu$A/cm$^2$. Panel (a) of the figure 7.6 shows the membrane potential of the neuron for the fixed input current 2.0 $\mu$A/cm$^2$. It is evidence from the figure 7.6(a) that the number of spikes are higher compare to the number of spikes observed when the potassium concentration is lower. When the input current was increased to 15.0 $\mu$A/cm$^2$ the spiking became bursting as shown in panel (b) of the figure 7.6. If there is no external input current injected into the neuron then the neuron stays at its resting state and the value of the membrane potential of the neuron is around $- 61.0$ mV.
Figure 7.6: Resting (dark line), spiking and bursting mode of the neuron model for the different external input currents.

The second group of tests made on SCNM was to change the outside potassium concentration of the neuron while keeping the external input current at a fixed value of 0.0 $\mu$A/cm$^2$. Please note that instead of changing outside potassium concentration directly we use the relationship between potassium concentration $[K^+]_o$ and the reversal potential $E_K$ given by
\[ E_K = \frac{V_T}{z} \ln \left( \frac{[K^+]_o}{[K^+]_i} \right) \] (7.7)

(where \( V_T \) is the potential difference at the temperature \( T \) and \( z \) is the valance of potassium ion). In this case the simulation was run for 50 ms. The reason for reducing the simulation time to 50 ms from 1000 ms is that the aim of this test is to find out when the first spike occurs for higher values of potassium concentration. The outcome of this test is shown in figure 7.7. It is evident from the figure 7.7 that when \( E_K \) is equal to \(-72.0 \text{ mV}\), the neuron is at its resting potential throughout the 50 ms period.

**Figure 7.7:** In the absence of external input current, panel shows the response of the neuron for three different \( E_K \) s. This Neuron is at its resting potential (i.e., below \(-60 \text{ mV}\)) when \( E_K = -72 \text{ mV} \). Note the change in the time of occurrence of the action potential due to changes in \( E_K \).
During the simulation, it was observed that when $E_K$ was higher than $-67.0$ mV, only one spike occurred during the duration of 50 ms. However, when $E_K$ was increased to $-65.0$ mV three spikes occurred during the same period. Then we extend the time of the simulation to 1000 ms. Outcome of this simulation is shown in figure 7.8. During this simulation input current was kept at $10.0 \ \mu$A/cm$^2$. Figure 7.8 clearly shows that by increasing $E_K$, action of the neuron can be increased.

**Figure 7.8:** Activity of the neuron for the outside potassium concentration changes. Neuron activities are: input resistance (●), number of spikes (*), inter-spike interval (+) and excitability (——). The input current $I_{ext} = 10.0 \ \mu$A/cm$^2$. 


Figure 7.9: Neuron-bursting dynamics at high potassium concentration (a) for constant input current (b) for random input current.

As the last test on the SCNM, we increased and kept the reversal potential at a fixed value of $-72.0$ mV. Then we ran the simulation for the constant input current $10.0 \, \mu A/cm^2$ and random input currents. In the random input current, both the period and the amplitude were chosen randomly. Again we ran the simulation for 1000 ms. Figure 7.9 shows the outcome of this experiment. Panel (a), which is drawn for the constant input current, shows the periodic bursting of the membrane potential. Please note that interval between first two bursts is different from the rest and it occurred during transient period and should be
ignored. The panel (b), which corresponds to random input current, shows bursting with random inter-burst intervals, which have been seen in brain-slice experiments.

The conclusions we made from above tests were as follows:

(i) When the potassium concentration is low, the number of spikes increases with the increase of the concentration. When the potassium concentration is high than a critical value then the neuron starts bursting.

(ii) By increasing potassium concentration, the activity of the neuron can be increased.

(iii) When potassium concentration is high (above the critical value), constant input current produces periodic bursting where as random input current produces non-periodic bursting or random bursting.

Having studied the SCNM, we developed our neuron model for the brain-slice experiment described in chapter 2, by using above mention observations (i), (ii) and (iii). Our model consists of $N$ neurons, which are connected to each other by synaptic connections. Neurons in this model receive input signals from the all other neurons and send output signals to every neuron in the population. All the neurons in this model (as shown in figure 7.10) are identical and they are grouped into two according to their
synaptic connections. These two groups are named as excitatory (ex) and inhibitory (in) populations as in the case of the real brain tissue.

**Figure 7.10:** Schematic diagram of randomly connected neural network of 90 neurons for the brain tissue model. The network consists of 81 excitatory neurons (open circles) and 9 inhibitory neurons (filled circles). Each neuron has connections to two excitatory neurons and three inhibitory neurons. These connections are chosen randomly for each neuron in the population. Additionally, four selected excitatory neurons (marked by arrows from left) are continuously activated by excitatory input pulses at random interval.

The equation (6.1) governing SCNM was modified for the population model by introducing an additional current, which provides the influence of the other neurons on a
given neuron. In order to introduce effects of the excitatory and inhibitory neurons properly, we use separate differential equations:

\[
C_m \frac{dV_{i}^{ex}}{dt} = -F(V_{i}^{ex}) - I_{syn}^{ex}(V_{i}^{ex}) + I_{ext} \tag{7.8}
\]

\[
C_m \frac{dV_{j}^{in}}{dt} = -F(V_{j}^{in}) - I_{syn}^{in}(V_{j}^{in}) \tag{7.9}
\]

where \( C_m \) is the membrane capacitance, \( V_{i}^{ex} \) and \( V_{j}^{in} \) are the membrane potential of the excitatory and inhibitory neurons in the population respectively. The variable \( i \) goes up to number of excitatory neurons \( (m) \). Similarly the variable \( j \) goes up to number of inhibitory neurons \( (n) \). All the membrane ion currents are represented by a nonlinear function \( F \). \( I_{syn}^{ex}(V_{i}^{ex}) \) and \( I_{syn}^{in}(V_{j}^{in}) \) are the synaptic current functions of excitatory and inhibitory neurons in the population respectively and \( I_{ext} \) is the external input current.

The non-linear function \( F(V) \) is given by

\[
F(V) = I_{Na}(V) + I_{K}(V) + I_{L}(V) + I_{A}(V) + I_{Ca}(V) + I_{K(Ca)}(V) \tag{7.10}
\]

where \( I_{Na}(V) \), \( I_{K}(V) \), \( I_{L}(V) \), \( I_{A}(V) \), \( I_{Ca}(V) \) and \( I_{K(Ca)}(V) \) are given by equations (6.2), (6.3), (6.4), (6.5), (6.6) and (6.7).
The interaction term $I_{syn}$ is calculated from the dynamic activity of the neurons in the population. The synaptic current function for the $i^{th}$ excitatory and $j^{th}$ inhibitory neurons are respectively, given by:

\[
I_{syn}^{ex}(v_i^{ex}) = -\sum_k w_{ex,ex} G(v_k^{ex})(v_i^{ex} - E_{syn}^{ex}) - \sum_l w_{ex,in} G(v_l^{in})(v_i^{ex} - E_{syn}^{in})
\]

(7.11)

\[
I_{syn}^{in}(v_j^{in}) = -\sum_k w_{in,ex} G(v_k^{ex})(v_j^{in} - E_{syn}^{ex}) - \sum_l w_{in,in} G(v_l^{in})(v_j^{in} - E_{syn}^{in})
\]

(7.12)

where $G$ is the conductance function given in the equation (6.15), $E_{syn}^{ex}$ and $E_{syn}^{in}$ are the synaptic reversal potentials of the excitatory and inhibitory connection types respectively, $w_{ex,ex}$, $w_{ex,in}$, $w_{in,ex}$ and $w_{in,in}$ are the synaptic weights respectively for excitatory-to-excitatory (excitation), inhibitory-to-excitatory (inhibition), excitatory-to-inhibitory (excitation) and inhibitory-to-inhibitory (inhibition).

The external input current $I_{ext}$ is injected to $r$ number of neurons in the excitatory population. These $r$ neurons are chosen at random in the beginning of the simulation and we continuously injected the $I_{ext}$ to these neurons in the total duration of the simulation.
Figure 7.11: Membrane potential of the six neurons from population of ninety neurons, which were randomly selected in the simulation. The partially synchronized bursting occurs as shown in the upper panel (a) for low potassium concentration and increased abnormal bursting occurs as shown in the lower panel (b) for high potassium concentration.

We simulate this model with following parameter values. $N = 90$, $m = 81$, $n = 9$, $C_m = 1.0$, $E_{syn}^{ex} = -10$, $E_{syn}^{in} = -72$, $w_{ex,ex} = 60$, $w_{ex,in} = -120$, $w_{in,ex} = 120$, $w_{in,in} = -120$, $r = 4$, $I_{ext} \leq 10.0 \mu A/cm^2$ and the other parameters of the conductance function are that same
as in the equation (6.15). In the simulation, each neuron receives synaptic currents from two excitatory and three inhibitory neurons, which were randomly selected at each time (i.e., in equation (7.11) and (7.12), $k$ goes up to 2 and $l$ goes up to 3).

Please note that in order to introduce kindling, we used high potassium concentration as in the case of the real brain-slice experiment. Also to simulate epilepsy, a random current is used as $I_{\text{ext}}$. Figure 7.11 shows the outcome of the simulation, which ran for 5000 ms for low and high potassium concentrations. The upper panel of the figure 7.11, which is drawn for low potassium concentration, shows periodic bursting representing a normal brain. On the other hand lower panel shows the membrane potentials for high potassium concentration. Since the inter-burst intervals in this case are random, we conclude that it represent the epileptic brain.

In the real brain-slice experiment, which was conducted for 100 s period produced approximately 10 burst with random inter-burst intervals. In order to simulate our model to produce few bursts with random inter-burst intervals, we searched the parameters, which influence the time between bursts. The control of number of bursts for a given time period is necessary since our previous simulation, which ran for 5000 ms produced too many bursts. We found that among all the parameters in the model, only one parameter, $I_{\text{ext}}$ influences the time between bursts.
Figure 7.12: Epileptic brain signals by continuous neural network model. The simulation was run for 100 s. The x-axis represents the time and y-axis represents the number of neurons firing at that time.

Figure 7.12 shows 100 s of the recorded time for four trials of the simulation at high potassium concentration. The four traces show the randomness in the time between peaks of number of neurons firing. During the time between the peaks only one or two neurons fired. We found that it takes very long time to run our simulation to 100 s due to the limitations of the computer speed. In order to run this simulation 100 s, it taking one week real time.
CHAPTER 8

SUMMARY AND CONCLUSIONS

The main objective of this project is to simulate epileptic brain behavior occurred in the brain-slice experiment described in chapter 2. To simulate this experiment we used both discrete and continuous neural networks models. Our discrete neural network model is based on the model developed by Biswal and Dasgupta (BD) [21, 22]. Their model employs fixed weights, which are predetermined and kept fixed throughout the simulation. Therefore, BD model imposes unnecessary restriction on the network in the simulation. We overcame this restriction by using random weights and producing the outcome of the experiment described in chapter 2. Further in the BD model sub-passes, which were described in chapter 4 have been used. These sub-passes were found to be arbitrary and therefore that make their model less appealing. On the other hand the introduction of random weights at different stages (initial stage, update rule and kindling method which induce epilepsy) of the simulation enable us to simulate the experiment without sub-passes. Our discrete neural network behavior is found to be very sensitive to the network parameters, initial state and update rule and hence choice of parameter values for simulating the model is very narrow.

After testing several continuous neural network models, which have been used in the past for the simulation of various brain functions, we decided to base our continuous neural
network model on the model developed by Av-Ron et. al. [25]. We started our investigation on single compartment neuron model and studied effects of high potassium concentration and variability of constant input currents on the network dynamics. We found that when the potassium concentration is low, the number of spikes increases with the increase of the concentration. However when the concentration is higher than a critical value, neuron bursts without spiking. Therefore by increasing potassium concentration the activity of the neuron can be increased. When potassium concentration is high (above the critical value) constant input current produces periodic bursting while random input current produces non-periodic bursting or random bursting.

Having studied single compartmental neuron model in detail we developed the population model, which simulates the brain tissue of the experiment described in chapter 2. Again we investigated network dynamics of this model for different synaptic weights of excitatory neurons, changes in external input current and when the outside potassium concentration of the neuron is high. For some low values of synaptic weights of excitatory neurons, we observed the asynchronized spiking behavior and it changed to synchronized bursting behavior for higher values.

By choosing appropriate values for the outside potassium concentration of the neuron (i.e., $E_K$ changed from - 80.0 mV to – 72.0 mV) and choosing random input currents, we were able to simulate brain-slice experiment, which was described in chapter 2 successfully. These spikes were made periodic by applying controlled electric pulses in a predetermine manner like discrete neural network model.
However when the external input current is a constant, the bursting were periodic and representing the normal brain. Because of the lack of biophysical properties of the individual neurons in discrete models, we believe that continuous neural network models are more suitable for simulating brain functions in general and epileptic brain in particular.

More research work on epilepsy and new types of neural network models are needed to fully understand and construct a robust model, which describes all aspects of this chronic disease epilepsy.
REFERENCES


APPENDIX

LIST OF PUBLICATIONS


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