Chapter 1
Introduction

Neuro-Engineering is one of the emerging areas of Biomedical Engineering. Modeling the electrical activity of the brain is essential for design and development of biomedical instruments for clinical applications such as diagnosis and cure of various brain disorders. It also plays an important role in understanding the normal functioning of the brain. This as multidisciplinary field wherein medical science information is attended by engineering techniques.

In this chapter the concept of neuron cell action potential generation is explained and the waveform of the action potential is described. Then the phenomenon of EEG genesis in the macro column due to synchronous activity in cortex is considered .To understand the functional organization of the brain, a model for communication between different regions of the brain is developed using electronics and computer analogue. For this model various circuit analogues are used to describe the functions of brain regions. Literature survey, in the field of brain modeling and data for our work are presented in this chapter.

1.1 Introduction

Neural processes, such as perception, coordination, cognition, etc are carried out via the propagation of electrical impulses through the brain. These impulses give rise to electromagnetic fields that can be measured extracranially by sensitive recording devices. The measurement of electric potentials over time on the scalp is referred to as electroencephalography (EEG). The brain electrical activities are reflected in the EEG signals observed on the scalp surface.

Electroencephalography (EEG) was first introduced in 1924 by the German physician Hans Berger. The basic principle remained unchanged, although today's electronics and software greatly facilitate EEG analysis.

Electroencephalography (EEG) localizes neural electrical activity using noninvasive measurement of electrical signals. Among the available imaging techniques EEG has better temporal resolution. This temporal resolution allows us to explore the timing of basic neural processes at the level of cell assemblies. EEG source localization draws on a wide range of signal processing techniques like digital filtering, three-dimensional image analysis, array signal processing, image modeling and reconstruction.

Brain imaging is a relatively new and multidisciplinary research field that encompasses techniques devoted to a better understanding of the human brain through noninvasive imaging of the electrophysiological, homodynamic, metabolic processes that underlie normal and pathological brain functions. These imaging techniques are powerful tools for studying neural processes of brain. Clinical applications include improved understanding and treatment of serious neurological and neuropsychological disorders such as intractable epilepsy, schizophrenia, depression, and Parkinson and Alzheimer's diseases [34].

Other imaging methods are (functional magnetic resonance imaging, fMRI; positron emission tomography, (PET); single photon emission computed tomography, (SPECT). EEG is one of the non-invasive observations methods of the underlying electrophysiological processes. The sources of EEG are directly related to the neuroelectrophysiology of brain cells. Modeling the production of electric potentials on the scalp necessitates taking the complex geometry and the conductivity properties of the head tissues into account. The estimation of the generators of the EEG is a problem with

no unique solution, and physiologically based models and algorithms are required to produce plausible estimation of these sources.

Although fMRI demonstrates high spatial resolution (~1mm), its effective temporal resolution (~1-2sec) is limited by relatively slow blood hemodynamics. In contrast EEG can measures the brain activity in millisecond, but its spatial resolution is in cm due to the lack of realistic head models and robust inverse procedures. Recent studies in finite element (FE) head modeling and inverse localization promise a better spatial resolution for realistic head modeling based on MR images. Therefore combining fMRI and EEG using finite element method (FEM) premises high spatio temporal resolution for brain imaging. In addition, they provide complementary insight into the mechanism of brain activity: blood oxygenation level dependant (BOLD) contrast in fMRI and electrical activity in EEG.

1.2 Thesis Organization:

The objective is to study the important aspects of the electric source of the brain such as generation, distribution transmission, loading and observations with both qualitatively and quantitatively. For spatial and temporal aspect of EEG study, source localization and signal analysis are two major aspects in this thesis.

With understanding of central nervous system anatomy and EEG genesis, the electric field distribution in different layers such as brain, skull, scalp, is studied along with electrical properties of various tissues. This information is used to develop the electrical network model which can be an alternative tool for understanding the electrical activity of the CNS and EEG changes under different situations. Clinical EEG data is used for analysis using signal processing tools. From the signal analysis each frequency component with its source amplitudes are mapped at each observation point of the EEG electrodes. Latter, these frequency sources are used for the network model development.

While studying the generation, distribution, and signal analysis as engineering approach, we have correlated the medical science information for this interdisciplinary approach is essential for design and development of biomedical instruments for diagnosis and cure of brain disorders.

Also space and time study of EEG is essential for functional brain mapping. For this the head geometry is borrowed from imaging techniques such as MRI and the

temporal information is added from EEG. Signal. Source localization study with signal analysis is the appropriate approach for modeling the electrical activity of the brain.

1.3 Various Modeling Techniques of Nervous System

There are different approaches for modeling the brain and central nervous system (CNS) [7]. The head is considered as a spherical volume conductor for source location and called as forward problem with electrical and magnetic consideration [11]. Behavioral modeling for psychological studies, mechanical modeling of brain structures. Microscopic level modeling of the basic unit such as neuron for the development of artificial neural network, modeling of signal propagation through the nerve considered as a cylindrical core conductor etc.

However in most of the efforts are to locate the source in the brain, which helps to study the brain disorders and understanding the functions of the brain.

Modeling technique of biological system such as temperature regulation, blood pressure regulations are some of the approaches [76].

1.4 Basic Neurophysiology

An imbalance of charge across a membrane is called a membrane potential. The major contribution to membrane potential in animal cells comes from imbalances in small ions (e.g., Na, K). The maintenance of this imbalance is an active process carried out by ion pumps.

The cytoplasm of most cells (including neurons) has an excess of negative ions over positive ions (due to active pumping of sodium ions out of the cell). By convention this is referred to as a negative membrane potential. Typical resting potential is -70 mV. Ion pumps require energy to carry ions across a membrane up a concentration gradient (they *generate* a potential). Ion channels allow ions to flow across a membrane down a concentration gradient (they *dissipate* a potential).

A cell is said to be electrically polarized when it has a non-zero membrane potential. A dissipation (partial or total) of the membrane potential is referred to as a depolarization, while restoration of the resting potential is termed repolarization. Ion channels can switch between 'open' and 'closed' states. If an ion channel can switch its state due to changes in membrane potential, it is said to be voltage-sensitive. A membrane

containing voltage-sensitive ion channels and/or ion pumps is said to be an excitable membrane.

An idealized neuron consists of soma or cell body, which contains nucleus and performs metabolic functions. Dendrites: receive signals from other neurons through synapses. Axon: propagates signal away from soma. Terminal branches: form synapses with other neurons.

The junction between the soma and the axon is called the axon hillock. The soma sums (integrate) currents input from the dendrites. When the received currents result in a sufficient change in the membrane potential, a rapid depolarization is initiated in the axon hillock. The depolarization is caused by opening of voltage-sensitive sodium channels that allow sodium ions to flow into the cell. The sodium channels only open in response to a partial depolarization, such that when a threshold voltage is exceeded

As sodium floods in, the membrane potential reverses, the interior potential is now positive relative to the outside. This positive potential causes voltage-sensitive potassium channels to open, allowing K^+ ions to flow out. The potential overshoots (becomes more negative than) the resting potential.

The fall in potential triggers the sodium channels to close, setting the stage for restoration of the resting potential by sodium pumps. This sequential depolarization, polarity reversal, potential overshoot and repolarization is called an action potential. The figures (Fig 1.1 to Fig 1.4) below show the mechanism of action potential. The action potential varies for cells at different locations such as heart, muscles. Here we are interested in the neuron cell action potential in the brain region.

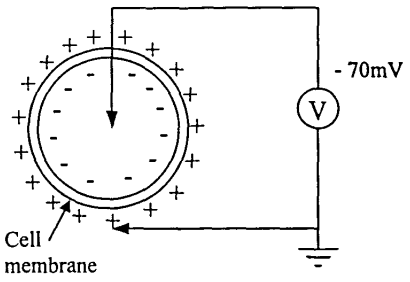


Fig.1.1: Polarized cell with its resting potential

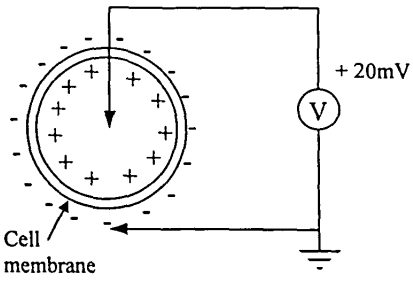


Fig.1.2: Depolarized cell during an action potential

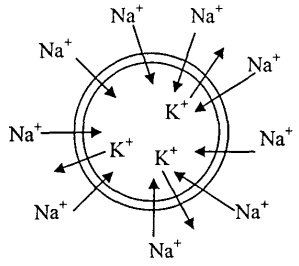


Fig.1.3: Depolarization of a cell. Na^+ ions rush into the cell while K^+ ions attempt to leave.

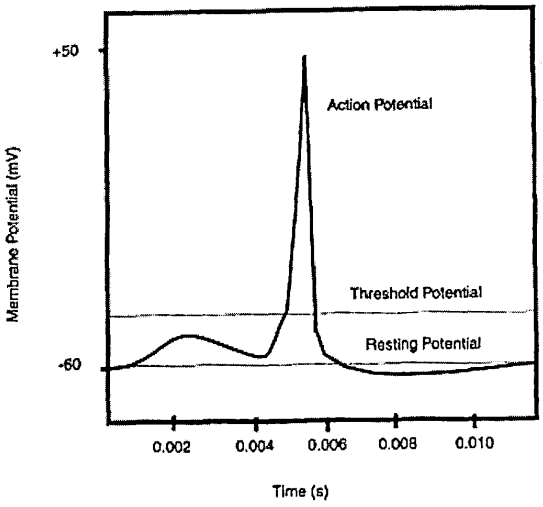


Fig.1.4 Action Potential Waveform

The action potential is not the movement of voltage or ions but the flow along these ion channels opening and closing moving down the axon. This movement of the ion channels explains why the action potential is slow relative to the normal flow of electricity. The normal flow of electricity is the flow of electrons in an electrical field and electricity travels at the speed of light while these ion channel movement are considerably slow. These are mechanical movements and cannot move at the speed of light.

1.5 EEG Genesis: Sources of EEG: Electrophysiological Basis

EEG is the technique that exploits what Galvani, at the end of the 18th century, called "animal electricity." Today it is better known as electro physiology. Despite the apparent simplicity in the structure of the neural cell, the biophysics of neural current flow relies on complex models of ionic current generation and conduction. Roughly, when a neuron is excited by other and possibly remotely located neurons via an afferent volley of action potentials, excitatory postsynaptic potentials (EPSPs) are generated at its apical dendritic tree. The apical dendritic membrane transiently depolarize and consequently extracellularly electronegative with respect to the cell soma and the basal dendrites. This potential difference cause a current to flow through the volume conductor from the non excited membrane of the soma and basal dendrites to the apical dendritic tree sustaining the EPSPs.

Some of the current takes the shortest route between the source and the sink by traveling within the dendritic trunk. Conservation of electric charges imposes that the current loop be closed with extra cellular current flowing even through the most distant part of the volume conductor. Intracellular current are commonly called primary currents, while extra cellular currents are know as secondary, return or volume currents.

Both primary and secondary currents contribute to fields outside the head and to electric scalp potentials, but spatially structured arrangements of cells are of crucial importance to the superposition of neural currents such that they produce measurable fields. Macro columns of tens of thousands of synchronously activated large pyramidal cortical neurons are thus believed to be the main EEG generators because of the coherent distribution of their large dendritic trunks locally oriented in parallel, and pointing perpendicularly to the cortical surface. The current associated with the EPSPs generated among their dendrites are believed to be at the source of most of the signals detected in EEG because they typically last longer than the rapidly firing action potentials traveling along the axons of excited neurons. Indeed calculation suggest each synapse along a dendrite may contribute as little as a 20 fA-m current source, probably too small to measure in EEG. Empirical observations instead suggest we are seeing sources on the order of 10 nA-m, and hence the cumulative summation of millions of synaptic junctions in a relatively small region. Nominal calculations of neuronal density and cortical thickness suggest that the cortex has a macro cellular current density on the order of

100nA/mm^2. If we assume the cortex is about 4 mm thick, then a small patch 5 mm × 5mm would yield a net current of 10 nA-m, consistent with empirical observations and invasive studies.

At a larger scale, distributed networks of collaborating and synchronously activated cortical areas are major contributors to EEG signals. These cortical areas are compatible processes in terms of dynamically interacting cell assemblies. Although cortical macro columns are assumed to be the main contributors to EEG signals, some authors have reported scalp recordings of deeper cortical structures including the hippocampus cerebellum and thalamus.

1.6 The Macrocoloumn in Cerebral Cortex as the Source of EEG:

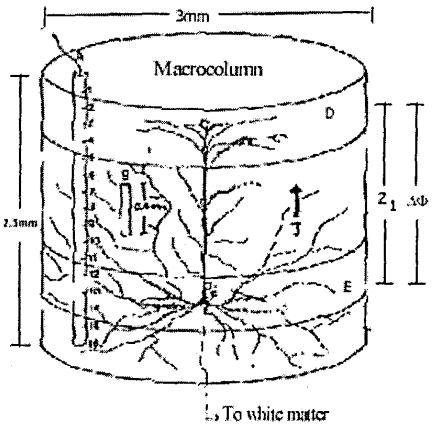


Fig.1.5 a: A Macrocolumn of Neocortex
(Figure added with permission From Prof.P.L.Nunz)

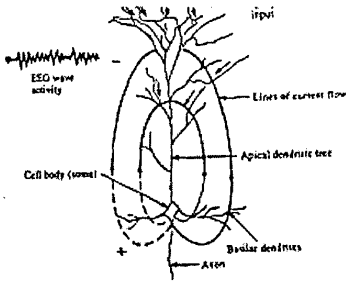


Fig.1.5 b: Electrogenesis of cortical field potentials

The macro column (fig.1.5a) is defined by the spatial extent of axon branches (E) that remains within the cortex [3].The large pyramidal cell (c) here is one of about $10^5$to 10^6 neurons in the macrocolumn. Approximately 80% cortical cells are pyramidal cells, and nearly all pyramidal cells send an axon into the white matter, which re-enters the cortex at some distant location. Each large pyramidal cell has about 10^4 to 10^5 synaptic inputs (F), which cause micro current sources and sinks s(r, t) along membrane surfaces.

sinks over sources in region D cause a net outward macroscopic current density J and macroscopic potential difference $\Delta\Phi$ across the cortex.

Fig.1.5b shows electro genesis of cortical field potentials for a net excitatory input to the apical dendritic tree of a typical pyramidal cell. For the case of a net inhibitory input, polarity is reversed and the apical region becomes a source (+). Current flow to and from active fluctuating synaptic knobs on the dendrites produces wave-like activity [27]. The formation of dipole layer in the cortex is shown in figure 1.6 and 1.7 below.

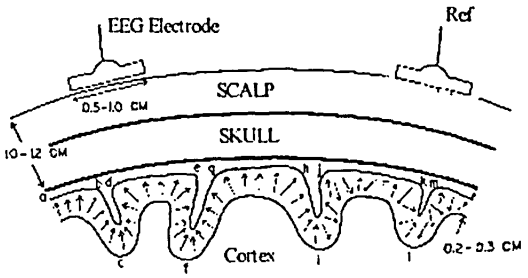


Fig.1.6: Genesis of cortical field potentials due to multiple dipole sources.

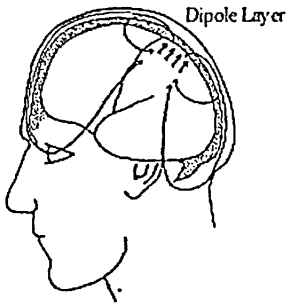
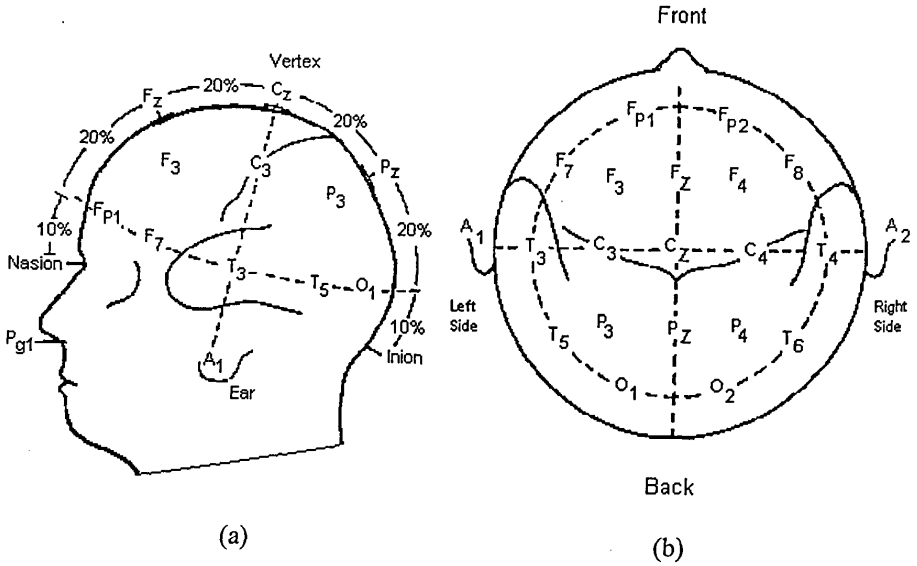


Fig 1.7: Dipole layer in the cortex layer

1.7 Electroencephalography (EEG) Measurement

The 10-20 system (Fig 1.8) is based on the relationship between the location of an electrode and the underlying area of cerebral cortex. Each point on this figure to the left indicates a possible electrode position. Each site has a letter (to identify the lobe) and a number or another letter to identify the hemisphere location. The letters F, T, C, P, and O stand for Frontal, Temporal, Central, Parietal and Occipital. (Note that there is no "central lobe", but this is just used for identification purposes.) Even numbers (2,4,6,8) refer to the right hemisphere and odd numbers (1,3,5,7) refer to the left hemisphere. The z refers to an electrode placed on the midline. Also note that the smaller the number, the closer the position is to the midline.



(a) (b)

Fig.1.8: (a) Side view (b) Top view

Fig. 1.8: The "10" and "20" refer to the 10% or 20% interelectrode distance

1.8 Comparison with Other Techniques such as EMG, MEG, EOG, ECG

Electroencephalography (EEG) localizes neural electrical activity using noninvasive measurements of external electrical magnetic signals. Among the available functional imaging techniques EEG uniquely have temporal resolutions below 100 ms. This temporal precision allows us to explore the timing of basic neural processes at the level of cell assemblies .EEG source localization draws on a wide range of signal processing techniques including digital filtering, three-dimensional image analysis array signal processing image modeling and reconstruction and more recently, blind source separation and phase synchrony estimation. We describe the underlying models currently being used EEG source estimation and describe the signal processing steps required to compute these sources. In particular we describe methods for computing the forwards field for known source distribution.

Brain metabolism and neurochemistry can be studied using radioactively labeled organic molecules Such as glucose metabolism or dopamine synthesis. Images of dynamic changes in the spatial distribution of these probes as they are transported and chemically modified within the brain, can be formed using positron emission tomography (PET). These images have spatial resolutions as high as 2mm; however, temporal resolution is limited by the dynamics of the processes being studied, and by photon counting noise to several minutes. For more direct studies of activity one can investigate local homodynamic changes. As neurons become active, they induce very localized changes in blood flow and oxygenation levels that can be imaged as a correlate of neural activity. Homodynamic changes can be detected using PET, functional magnetic resonance imaging (fMRI) and transcranial optical imaging methods. Of these fMRI is currently the most widely used method and can be readily performed using a standard 1.5t clinical MRI magnet, although an increasing fraction of studies are now performed on higher field (3-45t) machines for improved signal to noise ratio and resolutions. fMRI studies are capable of producing spatial resolutions as high as 1-3mm; however, temporal resolution is limited by the relatively slow homodynamic response, when compared to electrical neural activity. In addition to limited temporal resolution, interpretation of MRI data is complicated by the rather complex relationship between the blood oxygenation level dependent (BOLD) changes that are detected by fMRI and the underlying neural

activity. Regions of Bold changes in fMRI images do not necessarily have one-to-one correspondence with regions of neural activity.

EEG and EMG are two complementary techniques that measure respectively the magnetic induction our-side the head and the scalp electric potentials produced by electrical activity in neural cell assemblies. They directly measure electrical brain activity and offer the potential for superior temporal resolution when compared to PET or fMRI, allowing studies of the dynamics of neural net- works or cell assemblies that occur at typical time scale of the order of tens of milliseconds. Sampling of electromagnetic brain signals at millisecond intervals is readily achieved and is limited only by the multichannel analog to digital conversion rate of the measurements. Unfortunately, the spatial resolving power of EEG does not, in general, match that of PET and fMRI. Resolution is limited in both EEG and EMG by the relatively small number of spatial measurements, a few hundred in EEG versus tens of thousands or more in PET or fMRI and the inherent ambiguity of the underlying static electromagnetic inverse problem. Only by lacing restrictive models on the sources of EEG signals can we achieve resolution similar to those of fMRI and PET.

1.9 Computer Analogue and Information Flow in the Brain.

Functional organization of human brain is modeled with modern electronics and computer circuit analogue.

This section is divided in two parts. The first part is the review of nervous systems and covers microscopic anatomy of the brain with the neuron as a basic building block. The recent development in communication with Nitric Oxide (NO) gas through blood is also considered.

In the second part a new approach is used for modeling the functional organization of the brain. Analogy between the electronics circuit and different parts of the brain is summarized in a tabular form and models are developed for anatomical components of the brain with their interconnections.

The interconnected model development may help in understanding the functional organization and information flow in the brain, which is required for VLSI design for implanting the part of the brain with electronics chips, a step closer to the Bionic Brain [74].

1.10 Part – I:

1.10.1. Anatomy of the Nervous System in Brief

The Nervous System is subdivided in two parts (i) Central Nervous System (CNS) and (ii) Peripheral Nervous system. The CNS consists of Brain, spinal cord and glial cells. Peripheral nervous system consists of sensory nervous and motor nervous system. Peripheral nervous system is divided in to somatic sensory nervous system, which has the control over auditory and visual pathways, while the autonomic nervous system is involved with emotional responses and control of smooth muscles in various parts of the body.

Organization of the Brain

There is a great amount of redundancy and adaptability in the brain. Certain functions are indicated for certain parts of the brain. It must be realized that these parts seem to play a predominant role in those functions and that the other parts of the brain also undoughtly involved. Knowledge of the actual function of various parts of the brain is still unknown.

Two hemispheres of the brain are connected by corpus collosum. Left hemisphere controls the right part of the body and vice versa. Cerebral cortex contains 9 billion neurons and which has many inward folds to provide greater surface area. This can be viewed as a 'multilayer PCB' in electronics technology due to inner folds. Neurons are also interconnected for efficient information processing. Brain controls the muscles in various parts of the body via the spinal cord. Important parts of the brain are such as medulla, pons, cerebellum, thalamus, reticular activation system (RAS), hypothalamus, Basal ganglia, cerebrum, etc.

The functional organization can be studied by considering the CNS as a network of computers with timers, oscillators, data acquisition, and signal processing and communication capabilities. Only complicated responses are controlled by the brain as a large central computer, which is connected to number of small satellite computers in the spinal cord. The control system is functioning with real time dynamic load balancing for computation and decision-making.

Neuron: The Basic Building Block of Nervous System

The basic unit of nervous system is a neuron. Neuron is a single cell with cell body called as soma, one or more input fibers called as dendrites and long transmitting fiber called axon. There are three types of neurons as shown in Fig1.8

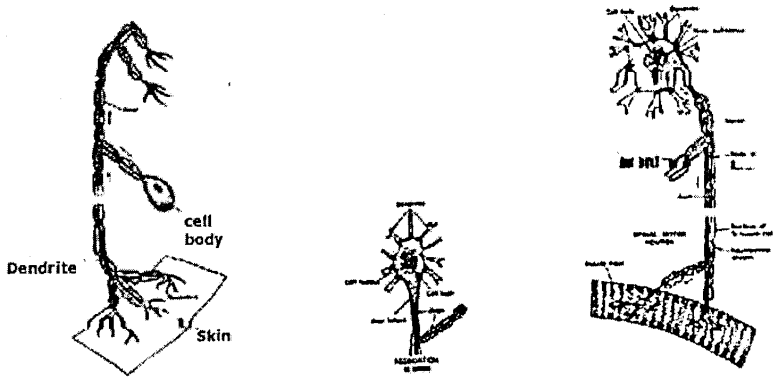


Fig.1.9: (a) Spinal sensory neuron (b) Association neuron (c) Spinal motor neuron.

1. Sensory neuron: which gives input to the brain from sensory parts such as audio, video, touch inputs.
2. Association neuron: which process the sensory information locally and send signals to the higher functional part of the brain. They integrate various inputs to produce the appropriate output response and transmit them to motor neurons for body control.
3. Motor Neuron: It takes input locally or from the brain and transfer to the muscle fiber.

Neuronal Communication

The neuronal communication is in electrical form. The chemical transmission give rise to ionic potential and seasonal current is developed on axon of the neuron. Axon can be considered as a cable conductor. The information is nothing but a spike discharge.

Steps in Neuronal Communication:

1. When neurons are excited they generate action potentials.
2. Information is transmitted in the form of spike discharge pattern.

3.An action potential is initiated in the neuron usually at the cell body or axon hillock. It is propagated down the axon to the axon terminals where it can be transmitted to other neurons.

4. The axon of one neuron excites the dendrites or cell body of another.

Sensing parameters such as intensity, direction is proportional to frequency of spike in the pattern. The neuron can be considered as an oscillator (Fig 1.10) when it generates equidistance spike patterns. Association neuron is functioning as a local decision making block and it modulates the output depending upon the various inputs. It can be considered as an arithmetic unit (Fig 1.11). Synapses can be considered as interconnections of multiple inputs and multiple outputs circuit of AND and NOR gates (Fig.1.12).