MATHEMATICAL MODELS OF EXCITATION AND PROPAGATION IN NERVES

A DISSERTATION
submitted in partial fulfilment of the
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of
MASTER OF ENGINEERING
in
ELECTRICAL ENGINEERING

By

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C_E_R_T_I_F_I_C_A_T_E

Certified that the dissertation entitled, 'MATHEMATICAL MODELSOF EXCITATION ANDPROPAGATION IN NERVES', which is being submitted by Jagdish Prasad in partial fulfilment for the award of the degree of Master of Engineering in Electrical Engineering (Measurement and Instrumentation) of the University of Roorkee, Roorkee, is a record of bonafide work carried out by him under my supervision and guidance. The matter embodied in this dissertation has not been submitted for the award of any other degree or diploma.

This is further certified that he has worked for the period about 8 months from Feb., 1980 to October, 1980 for preparing this dissertation at this University.

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Dated: Nov. 29, 1980

A C K N O W L E D G E M E N T S

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CHAPTER - 1

INTRODUCTION

Interest in the clinical application of electrical stimulation of nerves, both peripherally and centrally is growing rapidly. Thousands of patients are now being treated for chronic pain using both superficial and implanted electrodes. Glenn have developed an electrophrenic respirator which has been implanted in nearly 100 patients with inadequate or no respiratory function. Waters have reported on a series of stroke victims in which paralyzed muscles of the leg are activated electrically during ambulation to improve walking. Experimental work is under way to develop neuroelectric prostheses for the deaf and blind. As these clinical efforts multiply, it becomes imperative that a model of nerve stimulation be available to provide an analytical foundation for the study of signal propogation and nerve excitation.

Over the course of the last two centruies many physical systems have been linked to nerves and many mathematical models proposed as representing nerve characteristics.

In almost all the papers only steady state conditions were considered; i.e. threshold is determined only for a pulse of infinite duration. Threshold for finite duration pulses must then be obtained by reference to an experimentally determined strength duration curve. Two excellent papers were presented by Hallgren and Donard to analyse a model for the electrical properties of a myelinated nerve fiber that allows the computation of strength duration curves for arbitrary electrode

configurations. In addition, the time varying transverse membrane current and membrane potential at each of the nodes of Ranvier are determinable from the model for sub threshold stimuli and for supra threshold stimuli upto the time of initiation of the action potential. In these paper he assumed a constant membrane conductance for sub threshold stimuli.

But in the present work as mathematical model is presented for the study of membrane potential at different node of Ranvier under sub threshold stimuli by considering a monopolar electrode placed directly over and 1 mm away from one of the nodes. Here it will be considered that membrane conductance is a complex function of voltage and time under subthreshold stimulus condition. Rest assumptions are the same as described in the above two recent papers.

The dissertation is consisting of five chapters. First chapter lays stress on the development and application of the field of neural modeling in neurology and also gives the organisation of the present dissertation. Structural aspects of the neuron are discussed in second chapter. Third chapter presents review of neural modeling considering research work in this field upto 1979. General theory and results including the electrical model and mathematical model theory and a light on the solution of differential equation appears in forth chapter and fifth chapter gives conclusion and discussion.

CHAPTER - 2

GENERAL ANATOMY AND PHYSIOLOGY OF NEURONS [4, 13, 15]

2.1 Structural Consideration

The nervous systems of multicellular organism are typically composed of ensembles of neurons or nerve cells. It is an elementary unit that transmit the information in an electrical form from nervous system to other part of the body and vice versa. These may be arranged in a simple net or in complex arrays. There are some 10^{10} neurons in the human central nervous system consisting of the brain and spinalcord. The anatomical counter part of the idealised neuron is illustrated in Fig. (2.1). Classical studies with the light microscope suggest that the neuron is divisible into a small process dendrite, the cell body or some, a long process axon and the terminal region.

Thousands of fibers are typically grouped together to form nerves. A bundle of nerves is called a trunk. The same trunk carries afferent (toward the brain) fibers from sensory recipters and efferent (away from the brain fibers to muscles). The neuron, in common with other cells is surrounded by a complex plasma membrane whose thickness is estimated to be between 50 and 150A^{o}. Neurons excite in an all or non fashion, the axon may be represented by an Insulator as in Fig. (2.2). The inner and outer faces are changed the hollow shall is filled with one conducting medium (cytoplasm) and immersed in another (inter cellular fluid). When the axon in stimulated the surface potential changes (action on spikepot). Inputs to the

neuron may occur at many points on its surface. The majority of the inputs however enter through the dendrites which consist of single to many branched structures extending from the cell body. At their terminal ends the twings of dendritic trees interface with extensions from other neurons or sensory cells. The specialised structures called synapses, seen at the junction between neurons, are of prime importance for they contain the mechanism for information flow from one cell to another. The integrative process takes place either in the dendrite structure or in the soma. If the algebraic sum of input excitations exceeds a threshold level, the cell fibres generating a signal which is actively transmitted down the length of the axon to the terminal regions.

As noted there is a considerable variation in the size of nerve cells. It is difficult to estimate the length of dendrites however they probably reach a maximum of 2 mm in the outer layer of the cerebral cortex Axon length varies from a minimum in the order of 50 microns to a maximum of several meters in large mammals. In vertebrates large sensory and motor fibers may have diameters of 20 to 25 micron. Axons with diameter less than 0.5 micron are found in sensory ganglia. In the squid there are about 20 giant nerve fibers with diameters ranging upto 1 mm. The largest two of these fibers are more than 20 cm long.

Various types ofneuron are depicted in Fig. (2.3).

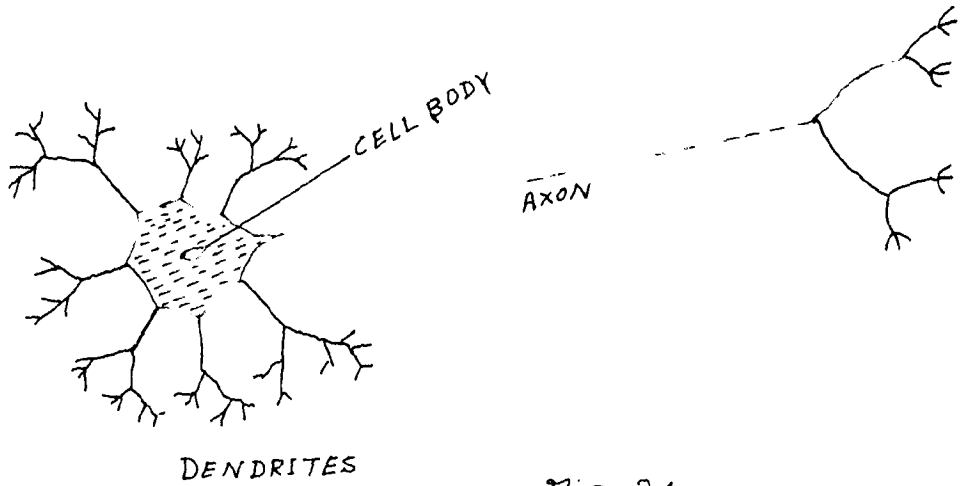


FIG-2.1

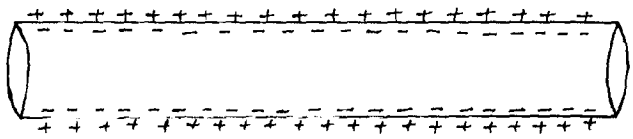


FIG-2.2

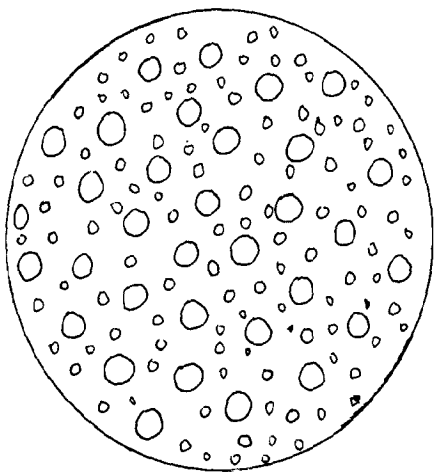


FIG-2.4

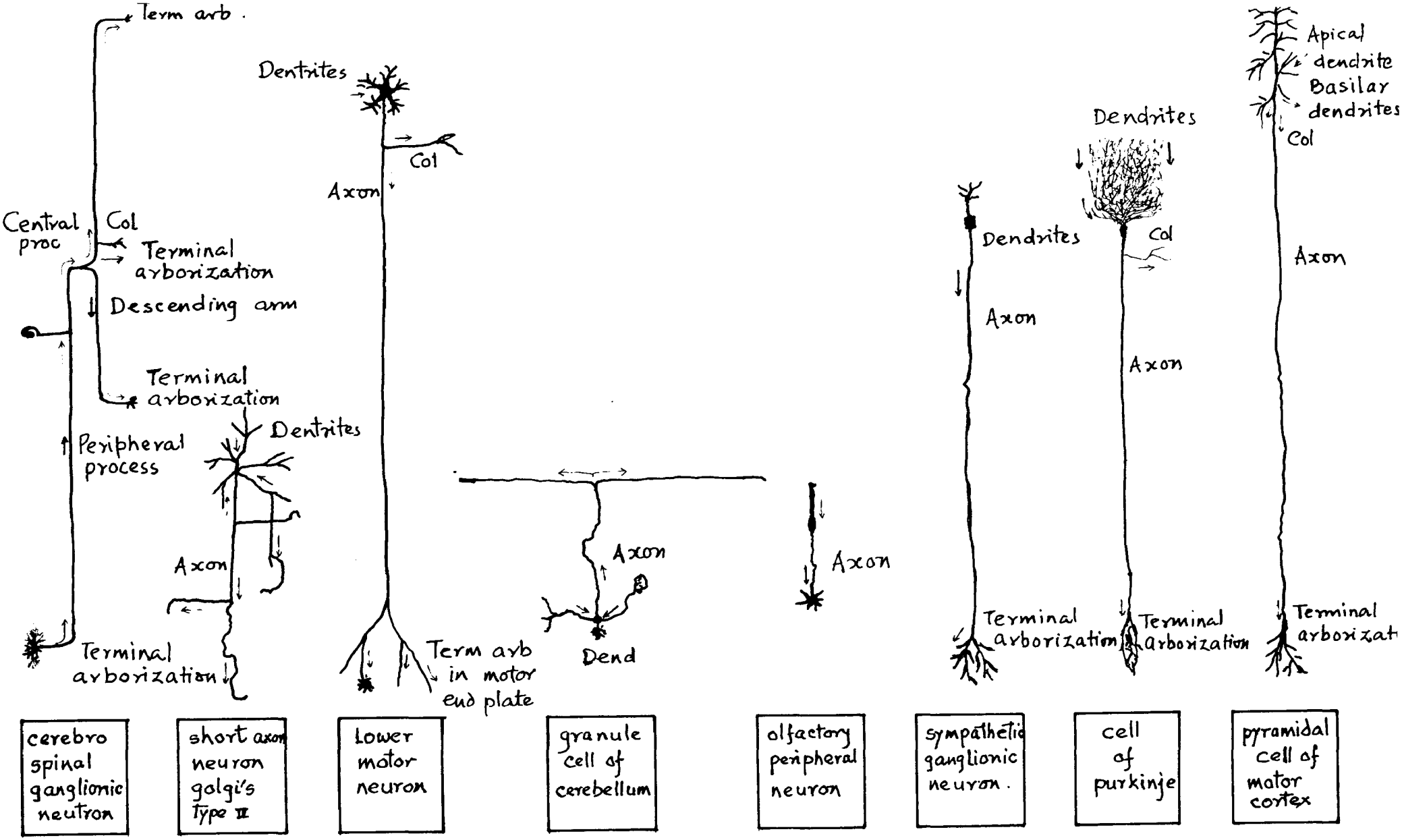

Term arb.
Central proc
Col
Terminal arborization
Descending arm
Terminal arborization
Peripheral process
Dentrites
Axon
Terminal arborization
Dentrites
Col
Axon
Term arb in motor end plate
Axon
Dend
Axon
Dendrites
Axon
Terminal arborization
Dendrites
Col
Axon
Terminal arborization
Apical dendrite
Basilar dendrites
Col
Axon
Terminal arborizat
cerebro spinal ganglionic neutron
short axon neuron golgi's Type II
lower motor neuron
granule cell of cerebellum
olfactory peripheral neuron
sympathetic ganglionic neuron.
cell of purkinje
pyramidal cell of motor cortex

FIG. 2.3

As the cross section of Fig. (2.4) shows a typical nerve trunk includes a wide range of axon sizes. The largest fibers are mylinated that is, there insulation is a relatively thick layer of a fatty substance myelin. The walls of unmyelinated fibers also consist of fatty molicule but these are not visible in figure because they are only 100A° thick.

The nerve axon has frequently been said to be analogous to a leaky sub marine cable or core conductor where the external medium resistance per unit length is low, and the internal resistance per unit length is moderate and near the same order of magnitude as the resting membrane resistance of a unit length of axon. propagation of an impulse along the length of an axon appears to be described rather well by the differential equation relating longitudinal and transverse current. The speed of impulse propagation should increase with increasing axonal diameter because the internal longitudinal resistance is inversely properlional to the square of the diameter while the membrane resistance is inversely propertional to the diameter. This is observed experimentally.

There are two large classes ofnerve fibers:

2.1.1 Unmyelinated fibers:

It resembles a tube that is filled with a weak solution mostly of potassium ions (K^+) and relatively large organic negative ions. The fiber is surrounded by the interstitial

fluid of the body essentially a $Na^{+}cl^{-}$ solution. Total internal and external concentration are about the same.. The diameter of the fibers ranges between 0.3 and 1.3μ. The conduction speed for typical fibers is 1.73×10^{6} diameters per second indicating speeds between 0.5 and 2.3 m/sec.

Because of random thermal movements and differences between internal and external concentrations that are maintained by metabolic activity. The inside of the fiber at rest displays a potential of v = -70 mv with respect to the outside. This corresponds to an electric field within the membrane of 70 mv/100A° = 70000 volt/cm. By way of comparision the dielectric strength of insulating oil is about 100000 volt/cm. It turn out that the fiber signal is a spike that is accompanied by breakdown of the membrane this breakdown in fact regenerates the signal. The fiber operates with a threshold of about -60 mv. when the inside at any point become more positive than this value the breakdown is triggered. The membrane becomes permeable to sodium ions for some 2 m sec: as the ions enter the fiber, the voltage increases to approximately +30 mv. After the 2 m sec interval there is an additional 2 m sec refractory interval during which the membrane becomes a relatively good insulator again. Because the disturbance is 4 m sec wide. The maximum possible frequency is 250 Hz. The excess sodium ions that leaked in are slowly and more or less continuously pumped out with energy supplied by the

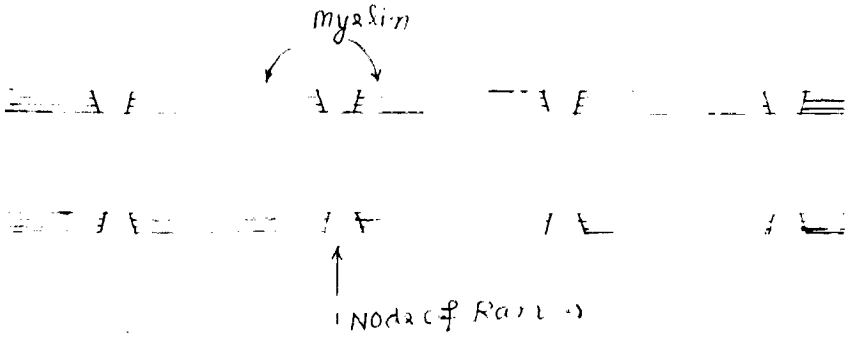
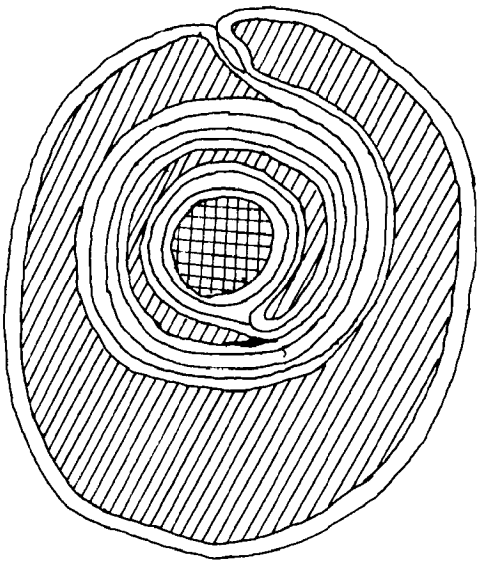


FIG - 2.5



FIG(2.6)

metabolic activity. The -70 mv resting voltage may be regarded as a d.c. component that is superimposed on the 100 mv peak spike known as an action potential that actually constitutes the axon signal.

2.1.2 Myelinated fibers:

Its conduction speed upto 120 m/sec is considerably greater than that of the unmyelinated axon. On the other hand, the relatively thick layer of myelin presents a space problem only one third of the fibers in mammalian nerve trunk those involved with rapid muscular response. The myelin sheath is periodically interrupted by the nodes of Ranvier (Fig.2.5), in which the cross section is substantially that of an unmyelinated fiber. It is at the nodes that the action potential is regenerated in the usual way by an inward diffusion of sodium ions between one node and the next the fiber behaves like a passive RC cable, that is if a 100 mv spike originate at a particular node it will appear at the next node with increased width and reduced height. The height is normally sufficient to overcome easily the minimum threshold requirement of 20 mv peak so that regeneration takes place. Fiber external diameter (de) range between 1 and 22μ . In contrast to the unmyelinated structure in which the membrane thickness remains constant at 100A° the myelin thickness is approximately proportional to fiber diameter.

Large nerve fibers are characterized by the fact that they are surrounded by a myelin sheath of mainly lipoid material

as shown in Fig. (2.6). The myelin sheath in turn is surrounded by a specialized type of cell called the Schwann cell. According to present concepts, the myelin sheath actually consists of many layers of Schwann cell membrane which were left behind as the cell body rotated around the axon during growth. The nodal region is characterized by its low electrical resistance. This geometry imparts certain constraints on conduction in myelinated axons.

The plasma membrane surrounding a neuron can be investigated by using electron micros copy and X-ray diffraction method Additional information on the properties of the membrane has been deduced from permeability, electrical conductivity, and surface tension measurements.

The presence of the myelin sheath around large axons tends to alter the mode of propagation in this type of fiber. The sheath which may be composed of a considerable number of tight turns of 120A° thick lamina, has low electrical conductivity and functions much as insulating material on a metallic wire. The node of Ranvier is covered only by Schwann cell cytoplasm and form a functional point of view, the axon plasma membrane is bare at the node. Activation in myelinated axons, therefore occurs at a nodal region and produces a local circuit current which completes the closed loop via adjacent nodes. As current flow is constrained primarily to nodal areas, current density is relatively high at these circumscribed sites. For

this reason activation jumps from node to node, and this phenomenon is called saltatory conduction.

Aconnective - tissue system binds individual peripheral nerve fibers into a nerve trunk. Individual axons are covered by a connective tissue tube called the endoneurium. Bundle of nerve fibers are bound together by a laminated capsule, the perineurium, which has alternating layers of connective tissue and endothetial cell in mammals. The entire nerve trunk is enveloped by a system of loose connective tissue, the epineurium. The sheaths appear to act as a diffusion barrier between the fibers within the nerve trunk and the extra cellular fluid space.

The individual axons which make up the nerve trunk may vary in terms of diameter, myelin sheath thickness and other electrical properties. There are four separable classes of axon types known as A, B, sc, and drc. Type A fibers are myelinated and have thelargest diameter. Type B fibers are some what narrower and are more thinly myelinated. The c fibers are small and not myelinated. Since the nerve trunk consists of a collection of axons differing in both size and type and therefore with different conduction velocities, propagation proceeds dispersively. As a result, the shape of an action potential initiated at one end varies as a function of axial distance.

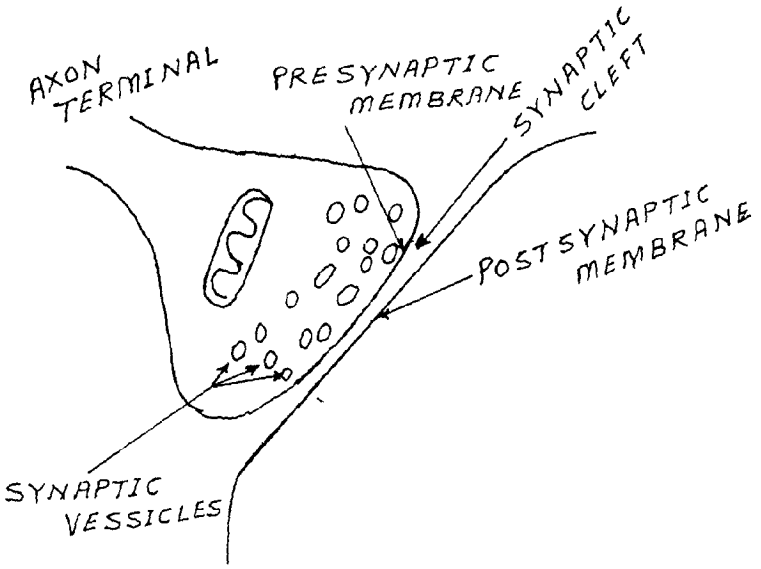

AXON TERMINAL
PRESYNAPTIC MEMBRANE
SYNAPTIC CLEFT
POST SYNAPTIC MEMBRANE
SYNAPTIC VESSICLES

Fig-2.7

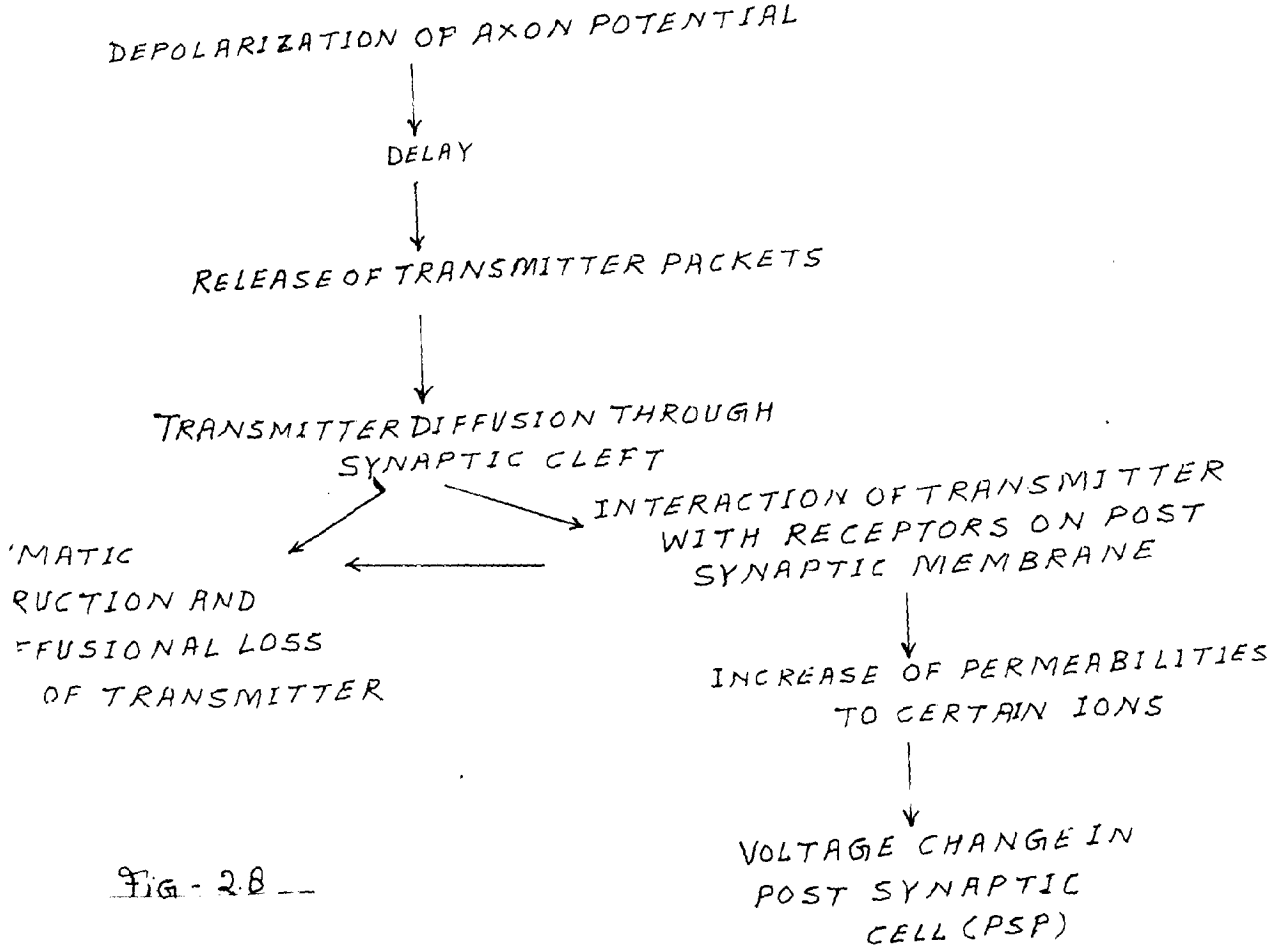

DEPOLARIZATION OF AXON POTENTIAL
DELAY
RELEASE OF TRANSMITTER PACKETS
TRANSMITTER DIFFUSION THROUGH SYNAPTIC CLEFT
INTERACTION OF TRANSMITTER WITH RECEPTORS ON POST SYNAPTIC MEMBRANE
'MATIC
RUCTION AND
FFUSIONAL LOSS
OF TRANSMITTER
INCREASE OF PERMEABILITIES TO CERTAIN IONS
VOLTAGE CHANGE IN POST SYNAPTIC CELL (PSP)

Fig-2.8

2.2 Synaptic Junction

Synapses are the sites of information transfer from one neuron to another, the mechanism of synaptic action have long been one of neuro physiology's central concerns. With modern techniques our knowledge about synaptic function has increased rapidly. The synapse may be defined as a constellation of structures including an axon terminal and its contents, the immediately adjacent dendritic (or muscle) membrane and the narrow space separating axon terminal from dendrites, the synaptic cleft. The axon terminal membrane adjacent to the synaptic cleft is called the presynaptic membrane and its dendritic counterpart is known as the post synaptic membrane. In electron micrographs a synapse is characterized by certain membrane specializations and especially by numerous circular or ellipsoidal profiles in the axon terminal adjacent to the presynaptic membrane, the synaptic vesicles. The features of synaptic structure are illustrated in Fig. (2.7).

When a nerve impulse arrives at an axon terminal, it sets into motion a sequence of events that eventually leads to a characteristic voltage fluctuation in the post synaptic cell. After a delay terminal depolarization produces the release of a special chemical (termed transmitter substance, or simply transmitter) from the axon terminal membrane adjacent to the synaptic cleft. The transmitter diffuses rapidly across the narrow 200 to 500 A° gap and interacts with the post synaptic

membrane. This interaction results in a change in permeability of the post synaptic membrane to certain ions and the movement of these ions under their concentration and voltage gradients produces the fluctuation in the post synaptic cell voltage termed the post synaptic potential (PSP). Transmitter is simultaneously destroyed rapidly or slowly depending upon the synapse under consideration, so that its duration of action is relatively brief from less than a millisecond to perhaps several hundred milliseconds. This sequence of event is illustrated in Fig. (2.8).

2.3 Electrical Properties

The gradients between the axoplasm and external medium are the energy sources for instantaneous dissipative processes occuring during the action potential. During a nerve impulse, sodium ions flow into the axoplasm and potassium ions flow out. Both of these processes tend to discharge or reduce the potential of the respective batteries by reducing the sodium and potassium ion gradients across the membrane. Such losses along with non-specific leakage are restored by utilizing energy from metabolism to transport or pump sodium ions out of the axoplasm and push potassium ions from the sea water back into the axoplasm. The amount of energy lost per action potential is very low because only a few picomoles of sodium and potassium ions move across the membrane with each impulse. It is a common misconception that this transport system pump or recharging process is identical to or related to the Excitation. Hodgkin and Keynes showed that although they were able

to stop the pump by means of metabolic poison, electrical activity persisted and tens thousands of action potentials could be generated for hours with only a small diminution in height.

The membrane capacitance of the squid axon has been measured frequently and found to be in the order of 1 mF/cm^2 of membrane area. This remarkably high value appears to arise from the extreme thinness (75A°) of the membrane and from the reasonably large dielectric constant of the phospholipid material of which the membrane is composed. Artificial membrane made from animal lipid material usually exhibit capacitances of the same order of magnitude per unit area. With a steady potential of -70 mv across the membrane, a voltage gradient in the order of 100 kilovolts per cm exist. Experimentally it has been found that this potential can be increased by atleast 50 percent before an apparent breakdown take place. It is also interesting to note that the membrane may recover completely after incipient breakdown lasting only a few milliseconds. Furthermore it has been found that the capacitance is constant to within a few percent whether the nerve is inactive expassing strong currents under various voltage conditions. It has the important properties of regulating the rate of rise and fall of an action potential in a nerve axon and of averaging a number of input signals in synaptic (junctional) and soma (cell body) regions.

The membrane conductances which are the main keys to the understanding of the cycle of excitation and recovery. Without outside disturbances, the membrane potential will reside between the leakage and potassium equilibrium potentials and remain quiescient there because the resting value of the potassium and leakage conductances for this potential are considerably higher than the sodium conductance. However when the potential is moved to the neighbourhood of -40 to -50 millivolts on the inside, the sodium conductance undergoes an explosive increase so that the potential across the membrane is dominated by the sodium equilibrium potential and battery and the membrane interior very rapidly approaches a positive potential of some 50 mv. The high conductance of the sodium pathway is not maintained and promptly reverts to its original level. At the same time the potassium conductances goes through a delayed increase. The net effect of these two changes is to bring the membrane potential back to near the potassium equilibrium value within about 3 ms (for a temperature 6.3°C). Then as the potassium conductance gradually decreases. The membrane potential settles back down to the original unperturbed value within another 5 to 10 ms.

By making the K^+ and Na^+ conductances as a continuous functions of time and membrane voltage, Hodgkin and Huxley were able to describe with good accuracy the axonal current voltage relationship while Hodgkin and Huxley specifically state that their equations were only intended to be an emperical description of the ionic currents. The sodium conductance will

be described with the standard Hodgkin - Huxley formalism.

$g_{Na} = \bar{g}_{Na} m^3 h$. $\bar{g}_{Na}$ is a normalisation factor, m and h are functions of membrane voltage and of time which vary between 0 and 1. Similarly potassium conductance will be described as

$$g_K = \bar{g}_K n^4$$

$\bar{g}_K$ is a normalisation factor, n is a function of membrane voltage and of time. While leakage conductance is independent of membrane voltage and time it depend only the temperature variation. Temperature has a large effect on the rate of rise of sodium conductance but a relatively small effect on its maximum value.

CHAPTER - 3

MATHEMATICAL MODELS OF NEURON [7,8,10]

A model is something simple made by a scientist to help him understand something complicated. A model can consist of mathematical equation an imaginary molecular structure obeying the laws of physics or a machine which is physically different from the original phenomenon but which simulates its behaviour. All three types of models are of use in neurophysiology.

Most models that have appeared during the last half century or so have taken the form of chemical systems, electronic circuits, mathematical for-mulation or computer simulations.

Considerable advantages and serious short comings are found in each although for a given modeling problem there is generally little difficulty in selecting the most appropriate technique. Since mathematical, electronic and computer simulation models comprise the majority of contemporary analogs.

Mathematical models have great utility in limited domains. They are invaluable in cases where the number of variables is reasonably limited and nonlinearities do not present severe analytical difficulties. An outstanding application is found in the analyses of membrane biophysics. In certain special cases, however, mathematical models of network behavior are extremely well qualified. This is particularly true for statistical treatment of large ensembles and for the analysis

of large scale electrical activity such as wave formation and propagation. Electronic models can simulate continuous variable nonlinear operations accurately and economically. Providing real time signals that may be observed while experimental conditions are manipulated, they permit a rapid and effective kind of observer model interaction not easily achieved by other techniques. There is considerable advantage to direct observation of wave-forms, phase relationship, modulations and time dependent interaction while stimuli and model parameters are changed. Such advantage is most effective for the modeling of one or a few inter connected units. For large networks however, both observation and manipulation of parameter and connections become very difficult.

Analog computer have advantages similar to those of electronic models, but tend to be slow and cumbersome. Both have the advantage over mathematical models that they do not tend to compel over simplification. The growing speed and storage capabilities of digital computers carry great promise for flexible, realistic modeling. The special problems that arise with large network simulation are more readily handled by digital computation than by other techniques. It seems likely that high speed digital computers will ultimately provide one of the most satisfactory means for modeling complex neural systems.

An additional powerful advantage of computer simulation is that the models can be made to work faster than their prototypes and many more experiments can be run. Finally, an

important asset of digital simulation is that the use of discrete symbols permits complete control and observation of assigned variables.

The representation of the neural pathways of a neuro-muscular system in a digital simulation necessitates a simple mathematical description of neural function which can be implemented economically in terms of computer time and storage requirement. Fig. (3.1) shows a monosynaptic pathways through a single neuron which is regarded as a processor of electrical signals: It represent the path of incoming signals from an axon which has only one synapse with the neuron represented and it assumes no other active synapses. The usual chemical transmission phenomenon found in synapses permits their representation as rectifying blocks.

The earliest models of nervous systems arose from considerations of neuro muscular action. The fact that nerves activate muscles was known as long ago as the Ptolemaic period, but only in the past hundred years has man begun to resolve two mysteries inherent in this knowledge: how does nerve conduct, and how does muscle contract? For many centuries these two question were dealt with as one, so that an early nerve model was usually one half of a nerve-muscle model.

At least from the time of the pregalenic physician, Erasistratus, until well after the time of Glisson in the seventeenth century, the contraction of muscle was thought to be a result of swelling or increase in muscle volume. The

commonly viewed picture was that of a long, inflatable tube whose ends came closer together as the tube was pumped up. The postulated role of nerve was to induce this swelling. The theory of nervous conduction, therefore held that a liquid or gas flowed through pipelike nerves to inflate the muscles, a concept that probably culminated with Descartes's theories in the seventeenth century.

Descartes compared the nerves of animals with the water pipes in the hydraulic machines and automata of his time. This comparison was not simply metaphorical: Descartes considered these machines to be good models of conduction in nerve. In fact he used these machines to demonstrate the plausibility of his theories of nervous conduction and muscular contraction. Among these theories, by the way, are some of the earliest discussions of involuntary reflexes and reciprocal innervation of muscle. According to Descartes that the spirits passed from the human brain through the hollow nerves to the muscles causing contraction or relaxation depending on their quantity. The flow of animal spirits in a nerve was controlled by valves located at each junction. The valves were either under the direct control of the pineagland or indirectly controlled by it through flow and pressure differences in different nerves, when the muscles were filled with animal spirits they swelled in the middle and the ends contracted; when emptied they relaxed.

The mechanistic views of Descartes influenced many seventeenth century scientist. Among these was Borelli, who proposed a number of mechanical models of muscle, most of which were based on the rhombohedron. If the edges of a rhombohedron are fixed in length the distance between opposite vertices will decrease over a considerable range of increasing volume. He used this analogy to show the consistency between swelling and contraction and to calculate the forces necessary for muscle contraction under load.

In the last half of the seventeeth century at least three physiologists, Grisson, Lower and Swammerdam independeltly demonstrated that muscle volume did not increase during contraction inspite of these results the so called "Baloon theory" persisted into the eighteenth century. Haller in the eighteenth century proposed that muscle was no longer considered simply a passive device waiting to be inflated or swollen by some action of nervous fluid: It was now thought to contain all the components necessary for contraction, needing only a stimulus to set it off. Haller himself proposed several interesting possibilities about stimulus transmission through a nerve. One of these was in the form of an analogy one might call it the croquet model of nerve. Suppose nerve were constructed of a long row of spheres - each in contact with both of its neighbours. If one were to rap the first sphere sharply, the last one would fly off almost instantaneously and would stimulate the muscle including contraction.

Newton postulated that nerves were solid but transparent and that excitation was propagated as optical vibrations through them, exactly as he supposed light was propagated in the ether. In this as in most matters, Newton's influence was very strong and these postulates dominated early eighteenth century concepts of nervous transmission. Cavendish built an electric model of the ray and with that model he was able to convience a previously skeptical scientific community that the shock of the ray could indeed caused by electricity.

Between 1840 and 1850, du Bois Reymond constructed a pair of very sensitive galvanometers with them he was able to measure electric currents associated with both nerve and muscle activity. Heperformed experiments not only with living nerve and muscle but also with electro chemical analogs of both.

In 1883 Hermann worked with a core model 2 m long, stimulated at one end with repetitive current pulses. He found electrotonic currents that sometimes attained their maximum value only after the polarizing current was off. As in nerve there were two successive, unequal phases of current, the first being in the same direction as the polarising current, the second opposite. He attributed the second phase to recovery from polarisation. In addition to matteucci, Hermann and Bernstein, a number of physiologists were employing core models to aid in their understanding of the properties of nerve. Some of the simplest of these models were devised by Hering. He

simply filled hollow grass stems or the exoskeletons of crayfish antennae with salinesolution. These models exhibited electronic spread even without the central metallic conductor and its progressive polarization.

Between 1900 and 1910, however, the membrane theory began to command the attenuation of physiologists and the popularity of core conductor began to wane Kernleiter models were applicable to electronic spread, but the newly postulated mechanisms of action potential propagation were much more exciting. One of the explanation was Bernstein's ionic hypothesis. Along with it came a new electro-chemical model, the iron wire model.

Lillie's first mention of the analogy between neural propagation and the spread of excitation over passivated (oxidized) iron appeared in 1916. If an iron wire is immersed in concentrated nitric acid, its surface is oxidized and becomes insensitive to further attack when the wire is transferred to dilute nitric acid. If part of the wire is artificially activated the activation spreads. Lillie showed that in these and many other ways the iron wire behaves like the nerve fiber.

Bishop and Bonhoeffer and his colleagues were responsible for many new experiments and analyses; frank modelled saltatory conduction; Yamagiwa attempting to model synaptic

activity, examined interactions among contiguous iron wire models. Further diversity is found in the voltage-clamp clamp experiments of Tasaki and Bak and in the relaxation oscillation studies of carricaburu. Other electro-chemical systems have provided analogs similar to the iron nitric acid one: the mercury hydrogen proxide model and the cobalt chromic acid model are representive. Electro-chemical models represent only one of many classes of neural models to appear since the time of de Bois Reymond. Hill and Frank used complicated hydraulic model to illustrate their ideas about excitation. Other authors such as Rushton, Katz, Hodgkin and Huxley and Grundfest used electrical circuit analogs for this purpose.

Other models were used for exploring or predicting consequences of specific theories of excitation or conduction. Sutherland for example, proposed a gyroscopic model to test his theory that nervous conduction was due to torsional vibrations travelling along a fiber. Fabre and Schmitt constructed electronic models in the late 1930's to explore theories of excitation. These neuron models probably were the first to be made with electronic circuits and they demonstrated a new kind of flexibility and simplicity in model making.

During the 1930's another type of neural model appeared, the mathematical model. The earliest of these proposed by Rashevsky was based on the proposition that processes of excitation in nerve could be described completely by two time factors. The

two time factors are time constant in two ordinary, first-order, linear differential equations. The dependent variables of the equations either are membrane potential and threshold potential or excitation and inhibition. The time factor for each variable relate its rate of change to its displacement from equilibrium. The two time factor models were all similar.

In addition to mathematical models of excitation there appeared several mathematical models of conduction. In this case they were based on linear differential equations Rashevsky and Rushton both proposed such models.

1943 McCulloch and Pitts published a revolutionary concept in mathematical neural modeling viewing the all or non behavior of neurons as a first order importance, they proposed to treat neural systems with discrete rather than continuous mathematics. McCulloch and Pitts applied Boolian algebras and set theory rather than differential equations. They were able to prove that the behavior of all networks of nerve like threshold elements can be treated by the propositional calculus, and that given any logical expression a net of such elements having corresponding function can be found.

Modeling studies with the formal neuron expanded in several directions. Minsky used the McCulloch - Pitts model to examine learning; whereas McCulloch - Pitts had been interested in deterministically connected nets, Minsky examined the properties of random nets.

A new kind of mathematical model appeared in 1952 providing analysis rather than mere description of excitation in nerve. Hodgkin and Huxley having inserted small silver electrodes inside the giant axon of squid, made detailed measurements of voltage and time dependencies of currents across the axon membrane. They consolidated and formalised these data into a set of four simultaneous differential equations describing the hypothetical time course of events during spike generation and propagation. The system proposed by Hodgkin and Hyxley is basically one of dynamic opposition of ionic fluxes across the axon membrane. The membrane itself forms the boundary between two liquid phases the intracellular fluid and the extra-cellular fluid as shown in Fig. (3.2). The intra cellular fluid is rich in potassium ions and immobile organic anions while the extra cellular fluid contains an abundance of sodium ions and chloride ions. Under equilibrium conditions the inside approximately 70 mv negative with respect to the outside.

Atleast, the membrane is slightly permeable to the potassium, sodium and chloride ions so these ions tend to diffuse across the membrane. Under these conditions the membrane is much more permeable to chloride and potassium than it is to sodium. Sodium ions are actively transported from the inside of the membrane to the outside at a rate just sufficient to balance the inward leakage. The relative sodium

ion concentrations on both sides of the membrane are thus fixed by the active transport rate and the net sodium flux across the membrane is effectively zero. The potassium ion, on the other hand tend to move out of the cell while chloride ions tend to move into it. The inside of the cell thus becomes negative with respect to the outside, when the resulting potential becomes sufficient to balance the inward diffusion of potassium with an inward drift equilibrium is established.

Most of the Hodgkin - Huxley data is based on measurements of the trans membrane current in response to an imposed stepwise reduction of membrane potential. By varying the external ionic concentrations Hodgkin and Huxley were able to resolve the trans membrane current into the active components the potassium ion current and the sodium ion current. They found that while the membrane permeabilities to chloride and most other inorganic ions were relatively constant, the permeabilities to both potassium and sodium were strongly dependent on membrane potential. In response to a suddenly applied depolarization, the sodium permeability rises rapidly to a peak and then declines exponentially to a steady value. The potassium permeability, on the other hand rises with considerable delay to a value which is maintained as long as the membrane remains depolarized.

The magnitudes of both the potassium and the sodium permeabilities increase monotonically with increasing depolarization. A small imposed depolarization will result in an

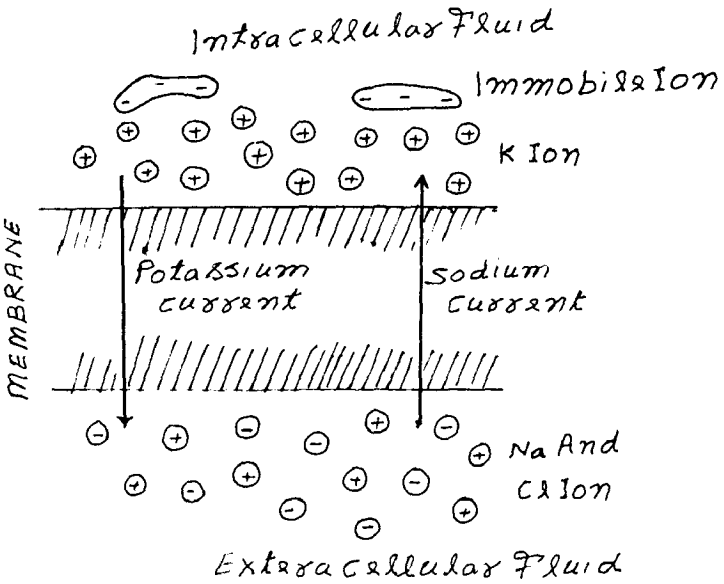


Fig-3.2

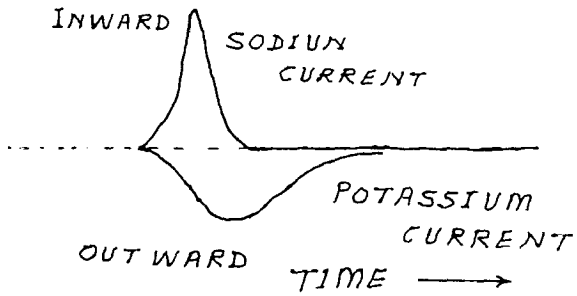


Fig-3.3

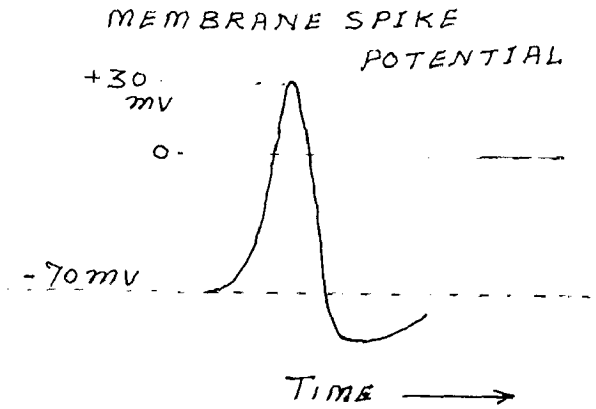


Fig-3.4

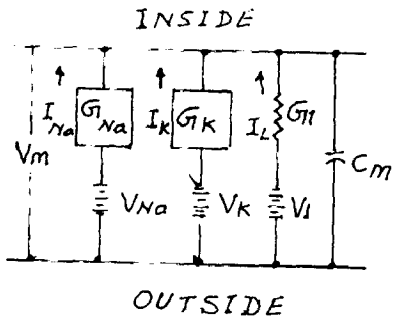


Fig-3.5

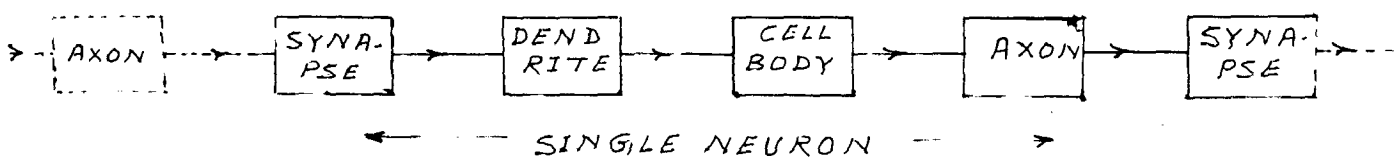


Fig-3.1

immediately increased sodium permeability. The consequent increased influx of sodium ions produces further depolarization and the process becomes regenerative, producing the all or none spike potential. At the peak of this spike, the sodium conductance begins to decline while the delayed potassium conductance increases. Recovery is brought about by an efflux of potassium ions and both ionic permeabilities fall rapidly as the membrane is repolarized. The permeability to potassium however falls less rapidly than that to sodium. These actions are schematized in Fig. (3.3) and (3.4) which show the potassium ionic currents and the measured spike potential.

By defining the net driving force, on any given ion species as the difference between the membrane potential and the equilibrium potential. For that ion, and by describing permeability change in terms of equivalent electrical conductance changes, Hodgkin and Huxley reduced the ionic model to the equivalent circuit of Fig. (3.5).

The basic equation for this circuit relates the rate of change of the voltage, V_m across the membrane capacitance C_m to the sum of the currents in the three shunt pathways.

$$\frac{dV_m}{dt} = \frac{1}{C_m} (I_L + I_K + I_{Na})$$

The three currents are given by the following identities:

$$I_L = G_L (V_L - V_m)$$

$$I_K = G_K (V_K - V_m)$$

$$I_{Na} = G_{Na}(V_{Na} - V_m)$$

where I_L is the leakage current due to all ions other than potassium and sodium, G_L is the equivalent conductance of the membrane to those other ions, I_K and I_{Na} are the potassium and sodium ion currents, respectively and G_K and G_{Na} are the equivalent transmembrane conductance to those ions.

Cole and Moore observed longer membrane conductance than Hodgkin and Huxley but agreed that the slow onset of the potassium conductance was best matched by a first order equation taken to the 4th power. However it was also found that for strong hyperpolarization preceding the experimental test pulse the first order equation needed to be raised to the 25th power in order to match the data.

Several other alternative formulations have been proposed for the slow turning on of the potassium current. Next let the potassium conductance be a function of n_K which in turn was given by

$$n_K = n_{K\infty} (1 - e^{-a_K t})$$

where both n_K and a_K are voltage dependent. From statistical considerations Fitzhugh developed the following expression for G_K.

$\sigma_i = \bar{\sigma}\, o^{-u}$ where u is given by

$$u = u_\infty + (u_0 - u_\infty)o^{-t/\tau}$$

Gillo has proposed an alternative equation in which he set $\sigma_i = \beta_i n$. The variable n is derived from kinetic considerations and is described by

$$\frac{dn}{dt} = \alpha(V)(1-n)n\,(1-6n+n^2 - n^3) - \beta(V)n^2(1-6n+6n^2-n^3)$$

Although these formulations do match the experimental data (given by Hodgkin and Huxley) better than the original formulation, they do not make an appreciable difference in the shape of the action potential.

Electric diffusion model has been suggested by a number of workers over a period of many years. Finkelstein and Mauro have given a comprehensive treatment of equivalent circuit model and Nernst Planck equations. Cohn and Cooley have run extensive computer calculations with similar formulation and note that the calculated 10 to 20 nano second time constants of ~~the~~ ion redistribution do not match the 1 millisecond constant of the squid membrane.

In addition to his significant contribution to the ion diffusion membrane model Goldman has recently proposed a structural model in which an interaction between Ca^{++} ions and membrane surface constituents is used to account for the membrane conductance changes seen in the voltage clamp. Goldman

has developed the equations and shown a similarity of form between his calculations for sodium and potassium conductance and those observed experimentally. Mullins (1959) has proposed a model in which electrostatic pressure alters the size of pores in the membrane so as to alter the ionic selectivity ratio of sodium to potassium to change. His model matches several of the main characteristics observed in voltage clamp experiments. Cole[illegible] and Mullins are to be applauded for this difficult but important attempt to start with a molecular model and work with physical chemistry method toward a match of the voltage clamp data. It seems that this type of approach will be the most useful and powerful in leading us to an understanding of excitation in the nerve membrane.

The advent of digital and analog computer concepts and technology well established by the mid 1950's added new dimensions to the foundations on which neurophysiological research is based. A particular modelling procedure is going to be used a digital computer for simulating human neuromuscular activity. The digital computer has several disadvantages as a brain for modelling particularly its lack of speed and capacity when the simulation of the response of dynamic system is required. It does however possess many overriding attractive features. So, models of many kinds began to come of age.

'Hall' proposed a contemporary neural model and concluded that the contributions of the dendrites to the electrical

properties of whole neurons has been greatly underestimated. In defending this work he used two mathematical models of dendritic trees. The first an equivalent cylinder model was used in cases where excitation was assumed to arise in one end spread into symmetrical dendritic trees. Rall also applied his dendritic model to the problem of estimating membrane time constants. For symmetrical trees or for a symmetric distribution of conductance in dendritic trees. Rall used a second, more general model known as compartmental model. This can be used to handle any specified dendritic structure. Rall used the compartmental model to study spatial and temporal summation of synaptic potential generated in various parts of dendritic trees.

Rall developed an electronic analog that simulated the ionic current of squid giant axon. The model was designed to reproduce the physiological data of Hodgkin and Huxley with emphasis on the sub threshold data. The model consist of seven parallel electronic circuits. Four of them are designed to match the squid axon data of Hodgkin and Huxley. The other three circuit represent synaptic current pathways. Rall showed mathematically how the oscillations can result from the Hodgkin - Huxley model. problems of electrical excitability were also explored with this model. The spontaneous spike tend to occur on the depolarization phase of these oscillations.

Analysis techniques analogous to those used in non-linear mechanics were successfully applied by Rinzel in

cator to elucidate some of the consequences of the Hodgkin-Huxley equations in addition he extracted from these equations a minimum parameter model that he calls the Reinhoffer vector Pol model. This model was not intended to be a quantitatively accurate model of squid axon membrane but rather to represent in the simplest mathematical form these interactions responsible for basic neural properties.

Perkel studied the pulse processing in single neurons by means of a digital computer. It is interesting to note that Perkel's model had an advantage not present in many other digital computer simulation of neural element in this model, time was not quantized but was treated as a continuous variable. Perkel's model was a fairly simple minimum parameter model. Rupfmuller and Jenik developed electronic neuron models specifically designed to be analogs of mammalian motoneurons. These models were intended primarily for studies of pulse processing in single cells and small nerve nets. Report has also demonstrated addition and multiplication of energy frequencies for two pulse train inputs to a single mathematical neuron model.

Herman used a minimum parameter electronic model to examine the theoretical input out put properties of a single neuron. This model provides spatial and temporal summation time variable threshold, all or none pulse output, absolute and relative refractoriness and graded inhibition. By appropriately simple passive elements (diodes, resistors, capacitors), a variety of synaptic properties, accomodation, subpeak firing after effects can be obtained.

Coleman (1964, 1965) has proposed a molecular reaction sequence to account for both sodium conductance transients. Kinetic cycle to accomodate both conductances. Armstrong (1969) has described a kinetic reaction sequence equivalent to the Hodgkin and Huxley (52) formulation of the potassium conductance in squid axon. Hoyt (1968) has proposed another reaction sequence for the sodium conductance in the squid axon while moore and Jacobson (1971) have developed a kinetic reaction possibilities for the sodium conductance in frog nodes. Hoyt and Adelman (1972). It has been suggested that actual nerve membrane may deviate from the Hodgkin - Huxley model in by the existence of a pronounced inactivation shift. Wherein the apparent steady state sodium inactivation measured by double pulse experiments is a function of the size of the test pulse. Hoyt has reported an abstract model for the fast transient system physical representations of the Hoyt model can involve the existence of a rate constant dependent on dv/dt rather than V (Jakobsson 1973). In 1975 Jakobsson again reported a transient gated state model for sodium permeability in excitable membranes. J.W. Moore (1976) proposed a kinetic model for the sodium conductance system in squid axon. Coleman (1975) proposed a three state kinetic model of sodium conductance changes in myelein giant axon in terms of a generalized second order variable. Recently in 1977, Connor and Walter has proposed a modified four branch model and a five branch model for crustacean axons.

In 1970 a model has been proposed by Colin Boyd and Hermanes for the generation of single motor unit potential routinely observed in the clinical E.M.G. examination of the normal Macaca brachii muscle he represent the single fiber activity by a dipole.

In 1979 an electronic model representing a small patch of neural membranes described by Brodwick. The patch circuit is incorporated into a discrete element ladder network: axon model.

CHAPTER - 4

ANALYSIS OF EXISTING MATHEMATICAL MODEL OF FIBER

4.1 General Theory

A myelinated nerve fiber can be approximated by the equivalent electrical network shown in Fig. (4.1). Symbols for variables and constants and the values of constants used are given in Table I. The assumption generally follow those of Rushton except that it is assumed here that the second term in ionic current is neglected under sub threshold condition. The validity and effect of these assumption is considered in succeeding section. Following Fitzhugh it is assumed that the fiber is infinitely long with nodes that are regularly spaced. Both inter nodal distance and axon diameter are assumed to be proportional to fiber diameter. The nodal gap width is considered to be a constant for all fiber diameters which implies that the nodal membrane area is also proportional to fiber diameter.

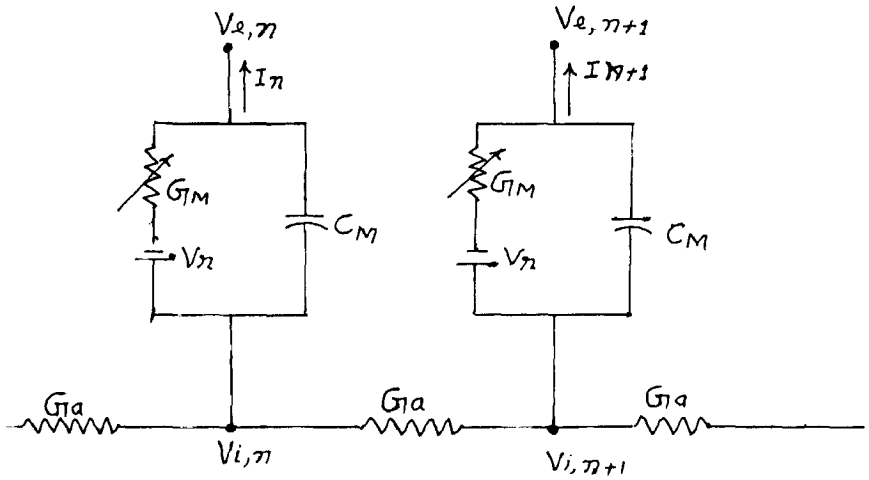
The inter nodal conductance G_a can be calculated from:

$$G_a = \pi d^2 / 4 \rho_i L$$

The membrane impedance is represented by a capacitor C_m and conductance G_m in parallel which are given by

$$C_m = c_m \pi d l$$

and $$G_m = g_m \pi d l$$



ELECTRICAL EQUIVALENT NETWORK

Fig-4.1

Note that all three of these components are proportional to fiber diameter ($G_0 \propto d$ since $L \propto d$). For a given diameter G_0 and G_1 are constant but G_2 is in general a complex function of the membrane potential.

This model assumes that the electrical potential outside the fiber is determined only by the external current. Since outside the nerve fiber and the electrode geometry, undisturbed by the presence of the fiber. This is reasonable since the dimensions of a single nerve fiber are small and because our interest is limited to the period of time prior to excitation (before internally generated current becomes significant). The small dimensions of the fiber also allow the simplification that the external surface of the membrane at any one node is at an equipotential. This implies that variations in the membrane current density over the nodal surface can be neglected. Here it will be assumed that the medium external to the nerve fiber is infinite and isotropic. This assumption is not vital to the model, and both anisotropic and finite external mediums can be considered. Calculation of the potential throughout the medium, of course, becomes more complex as more realistic models for the external environment are formulated.

APPENDIX A

Variables and Constants

Variables

t	time (microseconds)
V_n	membrane potential at node n minus the resting potential (mv)
I_n	membrane current at node n
$V_{e_o n}$	external potential at node n
$V_{i_o n}$	internal potential at node n
G_a	axial internodal conductance
G_m	nodal membrane conductance
C_m	nodal capacitance
D	fiber diameter (external myelin diameter)
d	axon diameter (internal myelin diameter)
L	inter node length
G_{Na}	sodium conductance
G_K	potassium conductance
G_l	leak conductance
I	stimulus current

Constants

ρ_i	110 Ω-cm cytoplasm resistivity
ρ_o	300 Ω-cm resistivity of external medium

Contd...

C_m	$2\mu F/cm^2$ membrane capacitance/unit area
g_m	30.0 mho/cm^2 membrane conductance/unit area
ℓ	2.5μm nodal gap width
L/D	100 ratio of inter nodal space to fiber diameter
d/D	0.7 ratio of axon and fiber diameters
$\bar{g}_L$	30.3 mho/cm^2 leak conductance
$\bar{g}_{Na}$	120 mho/cm^2 sodium maximum conductance
$\bar{g}_K$	36 mho/cm^2 potassium maximum conductance
V_r	-70 mv resting potential

The membrane current at node n is equal to the sum of the incoming axial currents and to the sum of the capacitive and ionic current through the membrane.

$$C_m \frac{dV_n}{dt} + I_{i,n} = G_a (V_{i,n-1} - 2V_{i,n} + V_{i,n+1})$$

The ionic current at node n is then given by $G_n V_n$. Substituting this into above equation, it can be shown that the myelinated fiber is described by the following infinite set of linear, first order differential equations.

$$\frac{dV_n}{dt} = \frac{\lambda}{C_m}\left[\left\{V_{n-1} + V_{e,n-1} + V_r - 2\,(V_n + V_{e,n} + V_r)\right.\right.$$

$$\left.\left. + V_{e,n+1} + V_{n+1} + V_r\right\} - G_n V_n\right]$$

$$\frac{dV_n}{dt} = \frac{1}{C_n}\left[G_0(V_{n-1} - 2V_n + V_{n+1} + V_{e,n-1} - 2V_{e,n} + V_{e,n+1}) - G_n V_n\right]$$

where V_n is given by $V_{1,n} = V_{e,n} = V_n$. The initial conditions are simply $V_n(0)$ = 0 for all n because of the capacitance ($n = \ldots -2, -1, 0, 1, 2, \ldots$) C_n shunting each node.

An approximate solution can be obtained by selecting a finite set of differential equations that enclose the node of interest and then integrating the finite set to obtain the membrane potentials. If the set of differential equations is large enough it can safely be assumed that the membrane potential at the boundary nodes exist all nodes outside the selected set is zero. Here we have consider only eleven node including the node below the electrode and five adjacent node on each side, therefore V_6, V_7, V_8 ... equal to zero. A more general solution of the above differential equation can be found out as,

$$\frac{dV_n}{dt} = -\left(\frac{G_n + 2G_0}{C_n}\right)V_n + \frac{G_0}{C_n}(V_{e,n-1} - 2V_{e,n} + V_{e,n+1} + V_{n-1} + V_{n+1})$$

$$\frac{dV_n}{dt} + \left(\frac{G_n + 2G_0}{C_n}\right)V_n = \frac{G_0}{C_n}(V_{e,n-1} - 2V_{e,n} + V_{e,n+1} + V_{n-1} + V_{n+1})$$

this differential equation of the form

$$\frac{dy}{dx} + Py = Q$$

where P and Q are the function of time or constant.

To solve such an equation,

$$I.F = e^{\int P\,dx}$$

multiply both sides by integrating factor.

$$e^{\int \left(\frac{C_n + 2G_n}{C_n}\right) dt} \times \left[\frac{dV_n}{dt} + \left(\frac{C_n + 2G_n}{C_n}\right) V_n\right] =$$

$$e^{\int \left(\frac{C_n + 2G_n}{C_n}\right) dt} \cdot \frac{G_n}{C_n} (V_{n-1} + V_{n+1} + V_{e,n-1} - 2V_{e,n} + V_{e,n+1})$$

Integrating we have

$$V_n e^{\left(\frac{C_n + 2G_n}{C_n}\right) t} = \frac{C_n}{(C_n + 2G_n)} e^{\left(\frac{C_n + 2G_n}{C_n}\right) t} \cdot \frac{G_n}{C_n} (V_{n-1} + V_{n+1}$$

$$+ V_{e,n-1} - 2V_{e,n} + V_{e,n+1}) + K$$

$V_n(0) = 0$ for all n.

$$K = -\frac{G_n}{C_n} (V_{e,n-1} - 2V_{e,n} + V_{e,n+1}) \frac{C_n}{(G_n + 2G_n)}$$

$$V_n e^{\left(\frac{C_n + 2G_n}{C_n}\right) t} = \frac{C_n}{(G_n + 2G_n)} e^{\left(\frac{C_n + 2G_n}{C_n}\right) t} \cdot \frac{G_n}{C_n} (V_{n-1} + V_{n+1}$$

$$+ V_{e,n-1} - 2V_{e,n} + V_{e,n+1}) - \frac{C_n}{C_n} (V_{e,n-1} - 2V_{e,n}$$

$$+ V_{e,n+1})$$

$$V_{n+e^{-\left(\frac{G_n + 2G_o}{C_n}\right)t}} = \left(\frac{G_o}{G_n + 2G_o}\right)\left[e^{-\left(\frac{G_n + 2G_o}{C_n}\right)t}(V_{n-1}+V_{n+1}) + (V_{e,n-1}-2V_{e,n}+V_{e,n+1})\left(e^{-\left(\frac{G_n+2G_o}{C_n}\right)t}-1\right)\right]$$

$$V_n = \left(\frac{G_o}{(G_n + 2G_o)}\right)\left[(V_{n-1}+V_{n+1}) + (V_{e,n-1}-2V_{e,n}+V_{e,n+1})\left(1 - e^{-\left(\frac{G_n + 2G_o}{C_n}\right)t}\right)\right]$$

Calculation of the external potential at each node is easy for the case considered here for a monopolar spherical electrode in an isotropic medium, the electrical potential at a distance r from the electrode is simply

$$V_e = \frac{\rho_e I}{4\pi r}$$

Current flowing toward the electrode is considered to be positive. Once the location of the electrode with respect to the nerve has been established. It is straight forward to calculate the potential at each node using the above equation. Note that the external potential is time invariant when the stimulus current is constant as in this example. This is a convenient, but not necessary simplification to this model. Because of the assumed symmetry of the electrode geometry the external potential at nodes n and -n is equal for all $n \neq 0$ which implies that the membrane poten. and current at node n and -n will be identical.

The rate at which excitation will initially occur can be predicted from the sub threshold response. Excitation will occur at the rate at which the membrane potential is a maximum during the time of stimulus application. This rate will be referred as excitation rate. As the stimulus is increased to threshold or supra threshold value the membrane conductance of the excitation rate changes during the stimulus as the membrane become more permeable to sodium ions. But in the present work it is considered that the membrane conductance is a complex function of membrane potential and time under sub threshold condition also. The change in membrane conductance is observable by using the Hodgkin and Huxley empirical formulation. Total membrane conductance is constituted mainly by three components those are sodium conductance, potassium conductance and leakage conductance. Out of those three component first two are the function of voltage and time.

Sodium conductance can be defined by empirical relationship such as,

$$g_{Na} = \bar{g}_{Na} \; m^3 h$$

where $\bar{g}_{Na}$ is the maximum sodium conductance

and m and h are defined as

$$\frac{dm}{dt} = \alpha_m \, (1 - m) - \beta_m . m$$

$$\frac{dh}{dt} = \alpha_h \, (1 - h) - \beta_h . h$$

where α's and β's are function of V but not of t. These equations may be given a physical basis if sodium conductance is assumed to be proportional to the number of sites on the inside of the membrane which are occupied simultaneously by three activating molecules but are not blocked by an inactivating molecule m then represents the proportion of activating molecules on the inside and h is the proportion of inactivating molecules on the outside. α_m or β_h and β_m or α_h represent the transferate constant in two directions. The solution of the above equations which satisfy the boundary conditions $m = m_0$ and $h = h_0$ at $t = 0$ are

$$m = m_\infty - (m_\infty - m_0) \exp(-t/\tau_m)$$

$$h = h_\infty - (h_\infty - h_0) \exp(-t/\tau_h)$$

where,

$$m_\infty = \alpha_m/(\alpha_m+\beta_m) \quad \text{and} \quad \tau_m = 1/(\alpha_m + \beta_m)$$

$$h_\infty = \alpha_h/(\alpha_h+\beta_h) \quad \text{and} \quad \tau_h = 1/(\alpha_h + \beta_h)$$

Similarly the potassium con-ductance is

$$g_K = \bar{g}_K n^4$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n . n$$

where $\bar{g}_K$ is a maximum potassium conductance. α_n and β_n are rate constants which vary with voltage but not with time and have dimension of $(m.sec)^{-1}$. n represents the proportion of the particles in a certain position.

The solution of the equations which satisfy the boundary condition that $n = n_o$ when $t = 0$ is

$$n = n_\infty - (n_\infty - n_o) \exp(-t/\tau_n)$$

where $n_\infty = \alpha_n/(\alpha_n + \beta_n)$

and $\tau_n = 1/(\alpha_n + \beta_n)$

The value of these rate constants at absolute temperature (295.16 K) for different value of polarisation is given by the following equations :

$$\alpha_n = 0.36\ (V-22)\left[1 - \exp\left(\frac{22-V}{3}\right)\right]^{-1}$$

$$\beta_n = 0.4\ ((13-V)\left[1 - \exp\left(\frac{V-13}{20}\right)\right]^{-1}$$

$$\alpha_h = 0.1\ (-10-V)\left[1 - \exp\left(\frac{V+10}{6}\right)\right]^{-1}$$

$$\beta_h = 4.5\left[1 + \exp\left(\frac{45-V}{10}\right)\right]^{-1}$$

$$\alpha_n = 0.02\ (V-35)\left[1 - \exp\left(\frac{35-V}{10}\right)\right]^{-1}$$

$$\beta_n = 0.03\ (10-V)\left[1 - \exp\left(\frac{V-10}{10}\right)\right]^{-1}$$

Initial conditions.

$n(o) = 0.0005$

$h(o) = 0.0249$

$n(o) = 0.0268$

Membrane conductance can be calculated for different value of depolarization and time and resubstited in the original differential equation which can be solved for a better value of membrane potential, as described previously.

4.2 Results

The sub threshold response of a 20 μm diameter fiber to a 0.1 m.A A pulse of infinite duration is shown in Fig. (5.1). Figure shows the change in membrane potential at the node below the electrode and at the five adjacent nodes. Membrane potential with respect to time is shown by smooth curve when we consider membrane conductance is a constant quantity and dotted line correspond to membrane potential while G_m is a complex, function of voltage and time. Upto 2nd node this change in membrane potential can be observed from the Table 4 very accurately.

The values of different constant is calculated as:

Inter nodal conductance,

$$G_a = \frac{\pi d^2}{4 \rho_i L} = \frac{3.14 \times (14 \times 10^{-4})^2}{4 \times 110 \times 0.2}$$

$$G_a = 0.06997183 \ \mu \text{ mho.}$$

membrane conductance,

$$G_m = g_m \pi d l$$

$$G_m = 30.4 \times 10^{-3} \times \quad \times 14 \times 10^{-4} \times 2.5 \times 10^{-4}$$

$$G_m = 0.033426546 \times 10^{-6} \text{ mho.}$$

and mutual capacitance

$$C_{12} = C_{11} \pi a^2$$

$$= 2 \times 10^{-3} \times \times 16 \times 10^{-3} \times 2.5 \times 10^{-3}$$

$$= 2.2992249 \text{ pF}$$

The value of external potential at the node below the electrode and adjacent nodes is given in the Table 2.

TABLE - 2

Sl. No.	Node	External potential (V_e) mv
1	0	23.079261
2	1	10.670699
3	2	5.7091116
4	3	3.9267307
5	4	2.9611112
6	5	2.3754702
7	6	1.9925047
8	7	1.700009

A better results can be evaluated by changing the original differential equation in the matrix form and then apply some numerical methods. I have tried the solution by applying Runge-Kutta method and used the computer to solve

DATA - 3

Membrane Potential (mV)	t = 10 μs	20 μs	40 μs	60 μs	80 μs	100 μs
V_5	0.0335702	0.038256	0.1064041	0.110263	0.1110319	0.1112080
V_4	0.2594069	0.3715701	0.4083552	0.404223	0.4075021	0.4081707
V_3	0.7704105	1.132207	1.3662505	1.4104037	1.4205050	1.4206000
V_2	2.1050366	3.1492663	3.5030635	3.5365523	3.552304	3.5530370
V_1	6.2330031	9.0373030	10.901164	11.320304	11.400402	11.420050
V_0	17.812759	25.910235	31.260595	32.371004	32.599737	32.64000

TABLE - 4

Membrane Potential	t = 10 μs	20 μs	40 μs	60 μs	80 μs	100 μs
V_5	0.0606489	0.088233	0.1064846	0.1102601	0.1110411	0.1112026
V_4	0.2552452	0.3713347	0.4481479	0.4640375	0.4673243	0.4680041
V_3	0.7774493	1.1309775	1.3650101	1.4134081	1.4234192	1.4254902
V_2	2.1614507	3.1443437	3.7947768	3.9295316	3.9573651	3.963123
V_1	6.2215884	9.0509144	10.923169	11.31089	11.39101	11.407583
V_o	17.774836	25.859167	31.235265	32.414319	32.736196	32.887488

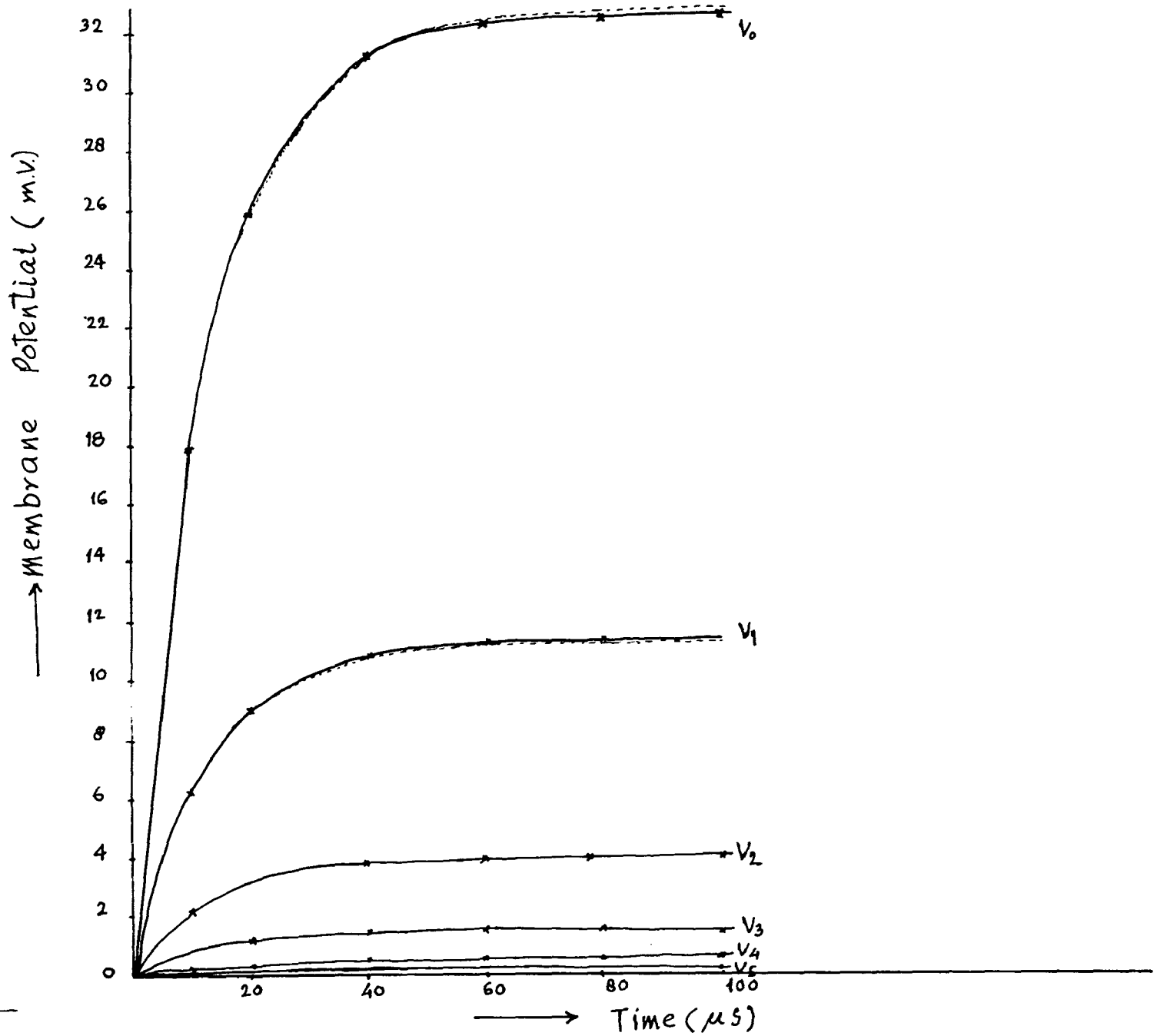

Membrane Potential (m.v.)
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
20
40
60
80
100
Time (μs)
V0
V1
V2
V3
V4
V5

Fig 5.1

such differential equation but I have not succeded to match the exact results, but I am sure that results come out by this procedure will be more accurate in comparision to the results tabluted in the present discussion. The procedure adopted to solve the differential equation is given as follows:

The original differential equation can be written as:

$$\frac{dV_n}{dt} = \frac{G_n}{C_m} V_{n-1} - \left(\frac{G_n + 2G_n}{C_m}\right) V_n + \frac{G_n}{C_m} V_{n+1} + \frac{G_n}{C_m} \cdot (V_{e,n-1} - 2V_{e,n} + V_{e,n+1})$$

Then differential equation of the form

$$\frac{dy}{dt} = A \times y + C$$

where A is a (n x n) tri-diagonal matrix

C is a known (n x 1) column vector

For the node below the electrode and four adjacent node above equation in the matrix form can be written as:

$$\begin{bmatrix} \dot{V}_0 \\ \dot{V}_1 \\ \dot{V}_2 \\ \dot{V}_3 \\ \dot{V}_4 \end{bmatrix} = \begin{bmatrix} -\left(\frac{G_n+2G_n}{C_m}\right) & \frac{2G_n}{C_m} & 0 & 0 & 0 \\ \frac{G_n}{C_m} & -\left(\frac{G_n+2G_n}{C_m}\right) & \frac{G_n}{C_m} & 0 & 0 \\ 0 & \frac{G_n}{C_m} & -\left(\frac{G_n+2G_n}{C_m}\right) & \frac{G_n}{C_m} & 0 \\ 0 & 0 & \frac{G_n}{C_m} & -\left(\frac{G_n+2G_n}{C_m}\right) & \frac{G_n}{C_m} \\ 0 & 0 & 0 & \frac{G_n}{C_m} & -\left(\frac{G_n+2G_n}{C_m}\right) \end{bmatrix} \begin{bmatrix} V_0 \\ V_1 \\ V_2 \\ V_3 \\ V_4 \end{bmatrix}$$

$\dot{y}$ A y

$$+ \begin{bmatrix} 2V_{e_1} - 2V_{e_0} \\ V_{e_0} - 2V_{e_1} + V_{e_2} \\ V_{e_1} - 2V_{e_2} + V_{e_3} \\ V_{e_2} - 2V_{e_3} + V_{e_4} \\ V_{e_3} - 2V_{e_4} + V_{e_5} \end{bmatrix}$$

C

$$\frac{dy}{dt} = f(y,t) = A \times y + C$$

Assume $\Delta t = 2$

given $y(o) = 0$

Now apply Runge Kutta method to get the solution,

$$K_1 = f(t_o, y_o) + C$$

$$K_2 = A \times (y_o + \frac{K_1}{2}) + C$$

$$K_3 = A \times (y_o + \frac{K_2}{2}) + C$$

$$K_4 = A \times (y_o + K_3) + C$$

$$y_1' = y_o + \frac{\Delta t}{6} (K_1 + 2K_2 + 2K_3 + K_4)$$

To get the membrane potential at different values of time it will be better to make a computer programme of the above procedure.

4.3 Assumptions

In this analysis it is assumed that the surface of each node is at an equipotential equal to $V_{e,n}$ which is defined to be the external potential at the point occupied by node n, but calculated by assuming the fiber is not present. There will be of course be some variation in potential over the nodal surface due to the finite size of the fiber. This variation is not easily calculated because of the distortion of the external field in the neighbourhood of the fiber: however, the variation in external potential over the nodal surface will not differ significantly from $V_{e,n}$ at least in comparision with the difference in potential between node n and its adjacent nodes. By a similar argument the potential on the inner surface of node n will vary, but the variation will be small in comparision with the difference in internal potential adjacent nodes. Therefore, the axial current flowing into node n and the total membrane current at node n will be approximately equal to $G_a (V_{i,n-1} - 2V_{i,n} + V_{i,n+1}$ This current will flow from node n with an approximately. Uniform distribution as previously assumed. There will be some distortion of this flow because of the external gradient due to the applied stimulus, but this will be a small effect.

A second component of current exists which has been neglected in this analysis. This is due to the current flowing in the external medium when the stimulus is applied.

the current density at a distance of 1 mm from the monopolar electrode is 0.0 mV/cm^2 for a stimulus current of 0.1 mA. With the fiber present some of this current will flow through node 0 entering on the far side and exiting on the near side. An exact calculation of this component would require a complex three dimensional analysis.

The most serious error in the model is introduced by the assumption that the myelin sheath is a perfect insulator which it is not. Tasaki found the resistance and capacitance of the myelin sheath to be 200 m.m and 1.6 μF/cm respectively. The effect of current leaking through the myelin sheath is difficult to assess without resorting to a much more complex simulation which would include sets of partial differential equations to describe the change in potential along the inter nodal regions as well as the nodes. Due to the complexity of this simulation, this has not been done.

In the original differential equation $C_n V_n$ represent the ionic current when it is assumed that G_m is a function of membrane potential and also then this term can be expressed as $G_{Na}\ (V - V_{Na}) + G_K (V - V_K) + \bar{G}_\ell\ (V - V_\ell\ )$ or $G_n V_n = V_n (G_{Na} + G_K + \bar{G}_\ell\ ) - (G_{Na} V_{Na} + G_K V_K + \bar{G}_\ell\ V_\ell\ )$.

Under sub threshold conditions it is assumed that second term is negligible in comparison to first one.

Because V_{Na} is a negative quantity which will substract from other two term inside the bracket. Therefore the overall value of second term will be negligible. Due to this assumption some error will be introduced in the calculation of membrane potential which will comes out, some what higher in comparision to exact value. The shape of the curves will remain same only there will be slight change in membrane potential.

CHAPTER - 5

CONCLUSION

Although, H.H. model, has been accepted upto now, as the fundamental model and only slight changes or modifications have been introduced by researcher later on taking into account sub threshold, threshold or supra threshold conditions of the nerve fiber with modifying assumption regarding dielectric constant of the sheath, conductance of membrane for sodium and potassium or potential at different points of the fiber etc. The author has considered the change in membrane conductance as a function of voltage and time in sub threshold region while in previous papers it had been assumed constant. The other constant have been referred to the Donald R. McNeal's paper. The potential at the boundary node and outside the selected set of nodes is assumed zero, although itisnot a very accurate assumption. The result considering membrane conductance constant and taking its variation into account have been plotted. It is obvious that as we consider the membrane conductance a variable parameter, a function of voltage and time the potential at different points or nodes of the neuron rises. The plots obtained match in a certain manner with R. Hallgren paper.

By using numerical methods for the solution of differential equation on computer we can get more accurate result, as the author has also tried but the incompletion is regretted and left for future. By computer we can calculate the potentials at different nodes with very small time interval which

will produce better and accurate results. An important point for future work is thought to defy the assumption regarding the potential outside the selected set of nodes and considering their effect also will be more near to physiological facts.

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