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Par : BENSANIA Abderraouf
BEN DIB Abdelhak

Thème

Biological Neuron Modelling

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Devant le jury :

SADOUNI Radhwan	Grade : MCB	Université : Ghardaia	**Président**
LADJAL Boumediene	Grade : MAA	Université : Ghardaia	**Examinateur**
KIFOUCHE Abdessalam	Grade : MAA	Université : Ghardaia	**Encadreur**

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INTRODUCTION

Neuroscience is one of the main research topics of this century; it is a highly interdisciplinary science encompassing the biological, psychological, and mathematical dimensions involved in the study of the central nervous system. It is a field that has many contributions from other specialties such as; chemistry, physics, biology, biophysics and mathematics. And for that matter, students and researchers from the different disciplines must be able to communicate with one another and to understand at some basic level what colleagues from other disciplines do and what their findings imply globally for neuroscience. this latter implies the use of the techniques from those other disciplines (fields) to help find explanations to how the neural structures work and more importantly, to analyze the physiology of the nervous system and serve the results on the hands of humanity to use.

The nervous system is a highly complex network of nerves and cells that carry signals to and from the brain and spinal cord to various parts of the body. The nervous system includes both the Central nervous system and Peripheral nervous system. The Central nervous system is made up of the brain and spinal cord and The Peripheral nervous system is made up of the Somatic and the Autonomic nervous systems. in our project we shed the light on the central nervous system (often abbreviated as CNS), where we go through its components and organisms.

The brain and the spinal cord are the parts of the centrals nervous that control the whole human body and each of the two is composed of other parts and has its own unique structure, we try to be a little bit specific about the parts we mention and not to go so deep trying not to steer away from the subject.

The neuron is the fundamental unit of the nervous system; it is basically a cell responsible for receiving sensory input from all parts of the body and the external world, for sending motor commands to our muscles, and for transforming and relaying the electrical signals at every step in between. There are three main kinds of neurons; sensory neurons, motor neurons and interneurons. Through the neuron passes an electrical message called the **action potential**, this latter is caused by a stimulus from other neurons and the ionic mechanism of the plasma

membrane. Scientists have been proposing models of the neuron throughout the last century, and these models are getting simpler by the time. Models in neuroscience can play a critical role by providing a framework for integration of necessarily incomplete datasets, thereby providing insight into the mechanisms of neural function.

Fundamental and famous model in neuroscience was described by Hodgkin and Huxley in 1952. They generated a formalism for the dynamics of the membrane potential of the giant squid axon, describing measurements of sodium, potassium, and leakage currents. Their model can be represented by an equivalent electronic circuit of the axon's membrane in which a capacitor models the membrane's capacity and several voltage-dependent resistors represent its ion channel. Another model is widely used nowadays is the Integrate and –Fire model, the RC-based integrate-and-fire model (often called the Leaky IF model) was introduced long before the H&H formalism in 1907 by Lapicque. Later on, The IF model had many variants some of them being Quadratic IF and the Exponential IF. [1][2]

In the last chapter we zoom in a little bit on the two models (HH and IF), where we take a look at the analysis of the models and how the equation were served to us to use , and we use the widely famous and the most used application in academic researches MATLAB, and get to know how it uses its tools and built-in function to solve those models.

Chapter 01

Biology of the Nervous Systems

Chapter 01: Biology of the Nervous Systems

1.1 Introduction:

The human nervous system is highly complex and very difficult to evaluate, it selects, sorts the huge amount of information received from our bodies and surroundings essentially, its main task is to ensure that the organism adapts to the environment. The nervous system can be divided into peripheral nervous system and the central nervous system which we are going to discuss in this chapter.

1.2 The Central Nervous System (CNS):

The central nervous system is the organism responsible of the control over behavior, in other words it integrates the received information sent by receptors to the central nervous system to be interpreted and acted upon it also coordinates and influences the activity of all parts of the body including consciousness, movement feelings, ideas speech and memory. The basic unit of the CNS is neuron, billions of existing neurons allow different parts of the body to communicate with each other through the brain and from the spinal cord [3].

1.3 Anatomy of the Central Nervous System:

The CNS consists of two parts: the brain and spinal cord. The brain is protected by the cranium. The spinal cord is continuous with the brain and lies caudally to the brain, protected by the vertebrae. The spinal cord reaches from the base of the skull, continues through or starting below the foramen magnum, and terminates roughly level with the first or second lumbar vertebra, occupying the upper sections of the vertebral canal.

1.3.1 Brain:

The brain is a mass of nerve tissue in the anterior end of an organism. Works as an organizer and distributor of information in higher vertebrates, it is also the center of learning. The human brain weighs approximately 1.4 kg (3 pounds) and is made up of billions of cells called neurons. There are two types of matter in the brain. Grey matter and White matter; Grey matter named for its pink-ish grey color, this tissue is abundant in all the parts of the brain (cerebrum,

cerebellum and brainstem), it contains most of the brain's neural cell bodies. Structure within the grey matter serves to process and store information received from sensory organs and other organs of the grey matter. White matter, on the other hand, works as the carrier of impulses to and from the grey matter, it is mainly composed of myelinated nerve fibers and a small amount of neural cell bodies, myelin (a substance made of protein and fats) creates an insulating layer around the nerves therefore it gets the name white matter [3].

The brain is composed of four main parts: cerebrum, diencephalon, cerebellum and brainstem figure 1.1.

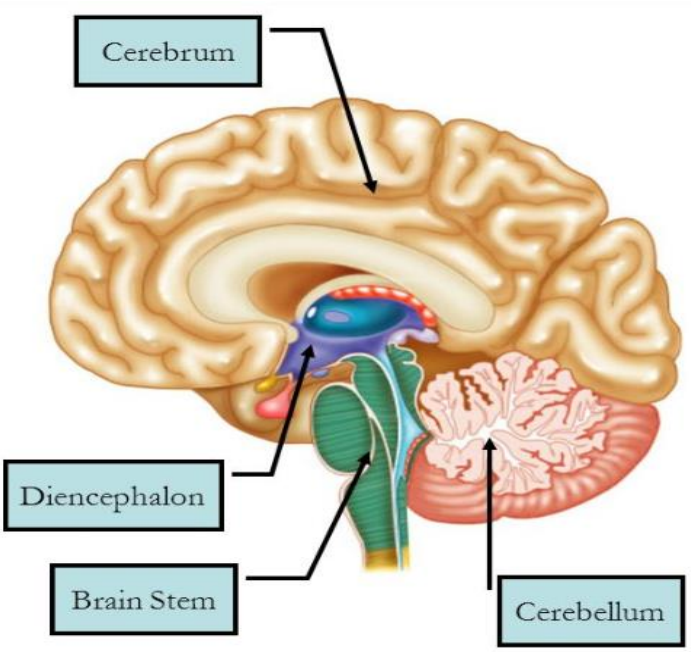

Figure 1. 1:the major parts of the brain [4].

1.3.1.1 Cerebrum:

The cerebrum is the largest part of the human brain is almost completely divided in two by a vertical slit, these two parts are called cerebral hemispheres, the surface of the hemispheres is covered by 3 to 5 mm thick layer of grey matter, and this layer is called cerebral cortex. The cerebral cortex is generally classified into four lobes: **Parietal lobe, Occipital lobe, Frontal lobe and the Temporal lobes** (as shown in figure 1.2)**,** these lobes are classified based on their overlying neurocranial bones each of the lobes contains cortical **association areas.** The frontal lobe is involved in voluntary motor functions, personality, social behavior and

language. The parietal lobe is situated between the occipital and frontal lobes, it is responsible for the perception of various sensations such as: pain, touch and pressure for example: the recognition of size and shapes of objects. The temporal lobes are responsible for processing sensory inputs for the retention of visual memory, language comprehension and emotion association. And it also where the **primary auditory cortex** sits.

The occipital lobe is the most posterior part of the cerebrum, and it's where the primary visual cortex is located hence its cortical association area is responsible for vision [5].

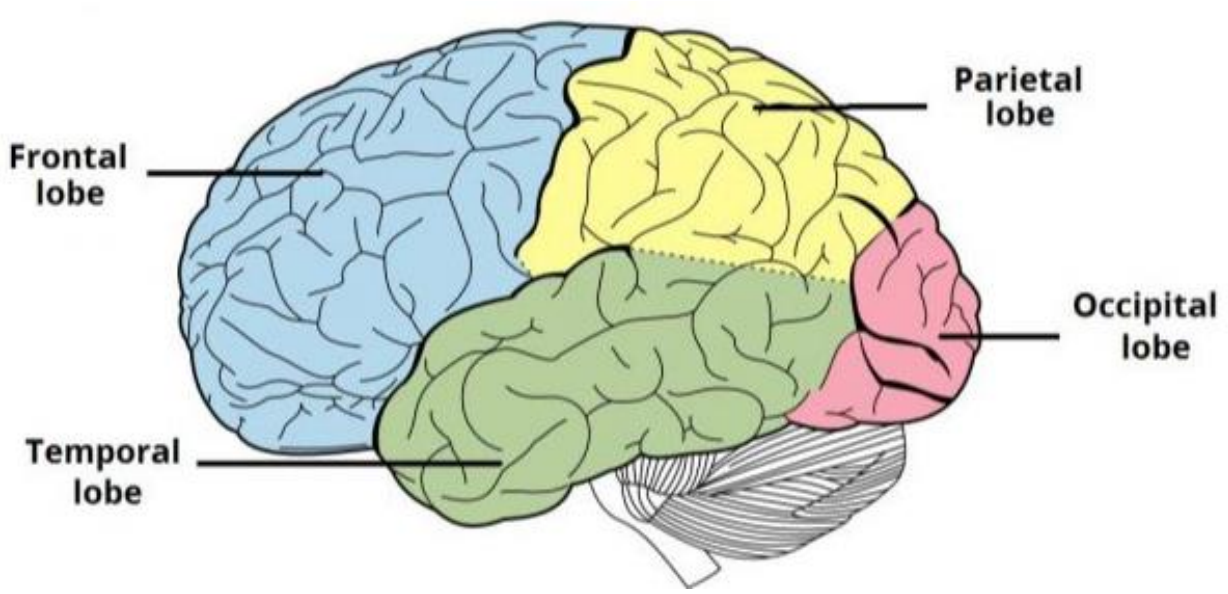

Figure 1. 2: The lobes of the cerebral cortex [6].

I.3.1.2 Diencephalon:

The diencephalon occupies the central part of the brain, and is situated between the telencephalon and the midbrain [7], it is also considered as an extension of the brainstem. It consists of distinct structures that are on either side of the third ventricle (one of four connected fluid-filled cavities comprising the ventricular system within the mammalian brain), including the thalamus, the hypothalamus (including the posterior pituitary), the epithalamus and the sub-thalamus. Despite being a relatively small part of the central nervous system in terms of mass, the diencephalon plays a number of critical roles in healthy brain and bodily function, from regulating wakefulness to controlling the autonomic nervous system.

- **Thalamus:**

The thalamus makes up most of the mass of the diencephalon. The thalamus is described as a relay because almost all sensory information that proceeds to the cortex first stops in the thalamus before being sent on to its destination. The structure is subdivided into a number of nuclei that possess functional specializations for dealing with particular types of information. Sensory information thus travels to the thalamus and is routed to a nucleus tailored to dealing with that type of sensory data. Then, the information is sent from that nucleus to the appropriate area in the cortex where it is further processed.

The thalamus doesn't deal just with sensory information, however. It also receives a huge amount of information from the cerebral cortex, and it is involved with processing that information and sending it back to other areas of the brain. Due to its involvement in these complex networks, the thalamus plays a role in a number of important functions ranging from sleep to consciousness [8].

- **Hypothalamus:**

The hypothalamus is a small part of the diencephalon. This portion of the brain has several functions. It monitors the chemical composition of blood. The hypothalamus acts as a relay station between the cerebrum and the lower autonomic centers. It controls hormone secretion by the pituitary gland and also controls the appetite. The other structures (the epithalamus and the subthalamus) are just as important as their previous but we are not going to mention in them due to the fact that they are poorly understood or have a function that doesn't serve our interest in this project [8].

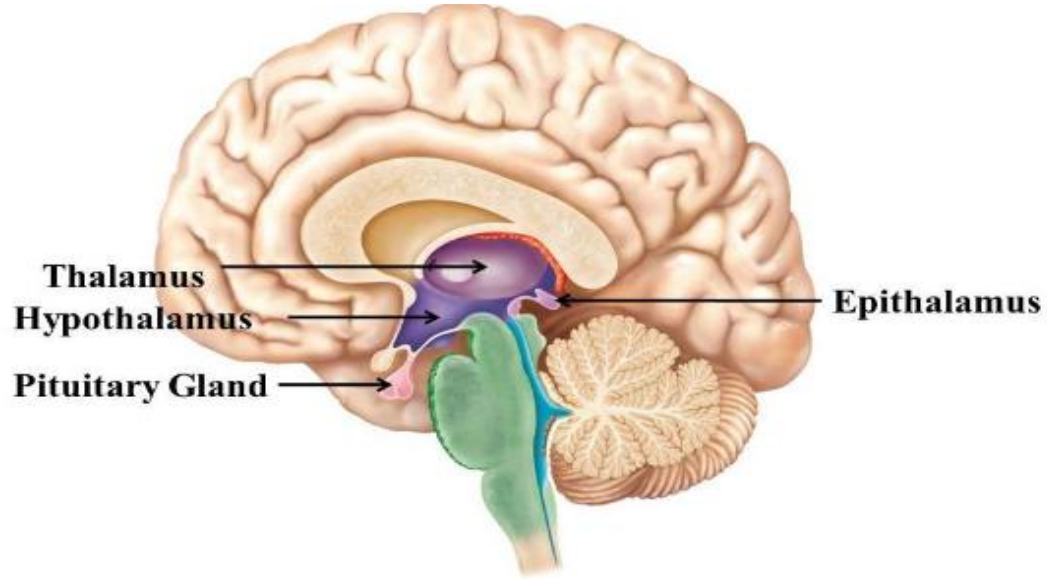

Figure 1. 3: The different structures of the diencephalon [8].

1.3.1.3 Cerebellum:

The cerebellum is located below the brain, behind the brainstem and above the spinal cord, and is made of gray and white matter at the back of the skull. It contributes to coordination, accuracy, and timeliness of movement, receives input from the sensory systems of the spinal cord and other parts of the brain, and integrates these inputs to control motor activity. Congenital anomalies and genetic diseases can affect the cerebellar function, which leads to neuromuscular disorders and loss of integrated muscle control may make standing difficult due to cerebellar damage, leading to movement disorders.

There are three ways in which the cerebellum can be divided into parts - anatomical lobes, Zones, and Functional divisions [9].

- **Anatomical Lobes**:

The cerebellum is characterized by three anatomical lobes: the anterior lobe, the posterior lobe and the flocculonodular lobe. These lobes are evolutionarily among the oldest parts of the brain, and they play a major role in balance and spatial orientation [10].

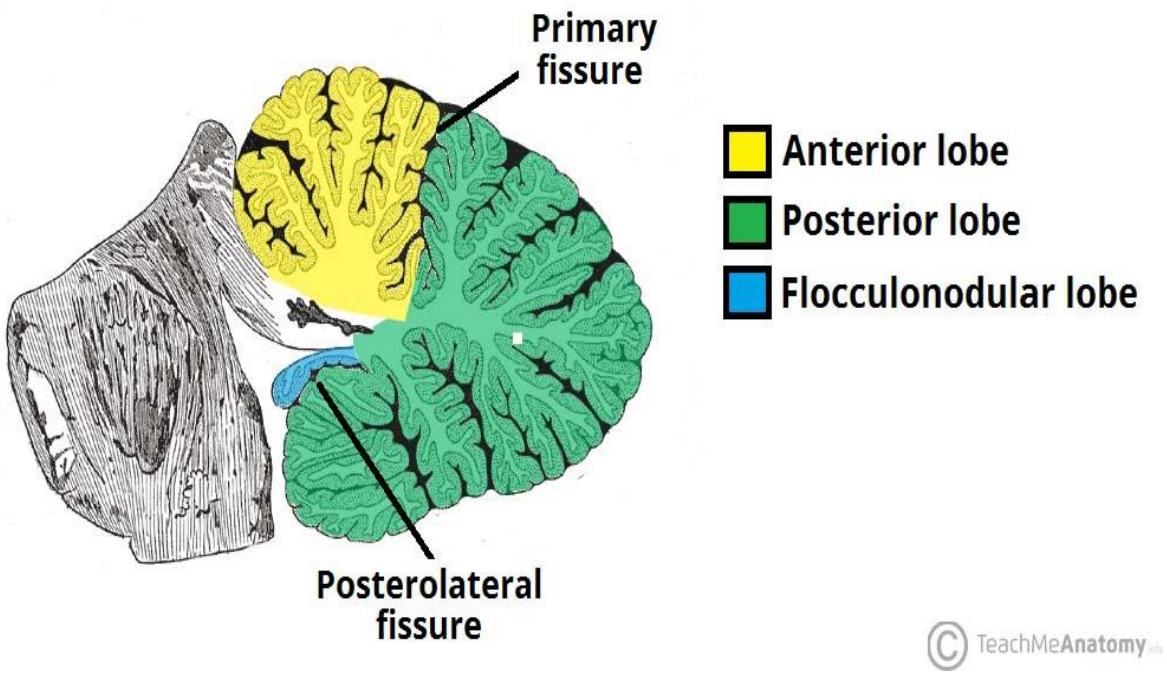

Figure 1. 4: Anatomical lobes of the cerebellum [10].

Regions:

There are the vermis in the midline of the cerebellum. Both lateral lobes of the vermis are the intermediate zone. Lateral to the intermediate zone are the lateral hemispheres. There is no difference in gross structure between the lateral hemispheres and intermediate zones [10].

- **Functional Divisions:**

The cerebellum is divided according to the function it performs. There are three functional areas of the cerebellum – the cerebro-cerebellum, the spino-cerebellum and the vestibule-cerebellum [10].

- **Cerebro-cerebellum**:

The largest division, formed by the lateral hemispheres. It is involved in planning movements and motor learning. It receives inputs from the cerebral cortex and pontine nuclei, and sends outputs to the thalamus and red nucleus. This area also regulates coordination of muscle activation and is important in visually guided movements [10].

- **Spino-cerebellum**: It is a medial region of the cerebellum. The spinal cerebellum receives somatosensory input from the spinal cord, and the spinal cerebellum integrates these physical inputs to modulate descending motor commands to facilitate movement, maintain balance, control posture, muscle tone, and stereotypical movements; like walking; constipation, jumping, etc..

- **Vestibulo-cerebellum:** The cerebellum region is involved in balance, vestibular reflexes, and eye movements and is located in the flocculonodular lobe that receives vestibular and visual information [10].

1.3.1.4 Brainstem:

The **brainstem** is the distal part of the brain it represents the upward continuation of the spinal cord that is made up of the midbrain, pons and medulla oblongata. The brainstem has integrative functions being involved in cardiovascular system control, respiratory control, pain sensitivity control, alertness, awareness, and consciousness. All of these brainstem functions are enabled because of its unique anatomy, since it houses cranial nerve nuclei and is a passageway for many important neural pathways, therefore brainstem damage is a very serious and often life-threatening problem [11].

- **Midbrain:**

The midbrain also known as **mesencephalon,** located between the pons and the diencephalon, it is home to many reflex centers such as righting, postural, and audiovisual reflexes. The midbrain is subdivided into three parts: tenctum, tegmentum, and the ventral tegmental area.

- **Pons:**

the pons is located between the midbrain and the medulla and anterior and slightly superior to the cerebellum, it connects the medulla to the higher brain centers .The pons contains nuclei that deal primarily with sleep, swallowing, bladder control, hearing, equilibrium, taste, eye

movement, facial expressions, facial sensation, and posture ,and it houses the pneumotaxic center which is responsible for generating and maintaining the rhythm of respiration [12].

- **Medulla oblongata:**

The medulla oblongata or medulla is the most caudal part of the brainstem continuous with the spinal cord, it contains the cardiac, dorsal and ventral respiratory groups, and vasomotor centers, which are the most vital centers in the brain because they deal with heart rate, breathing regulation, and blood pressure. It is also known that one side of the brain controls the opposite side of the body due to the existence of some nerves that cross over the medulla [12].

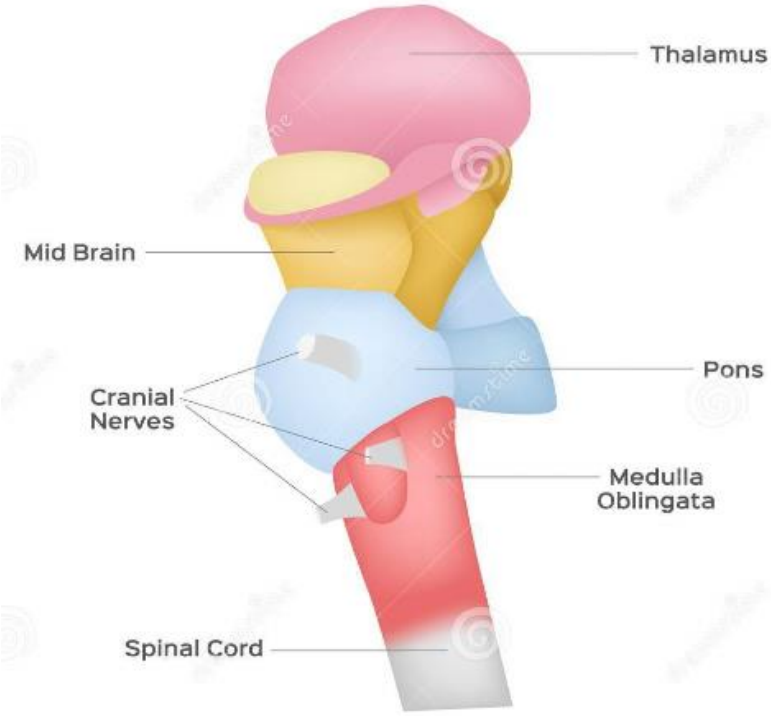

Figure 1. 5 : an illustration of the brainstem [13].

1.3.2 Spinal cord:

The **spinal cord** is a long, thin, fragile, tubular structure made up of nervous tissue; it is 40 to 45 cm-long and has the thickness of a little finger; it is the downward continuation of the medulla down the vertebral canal. It extends from the upper border of the atlas to end in a

tapering extremity, the conus medullaris, opposite the lower border of the first lumbar vertebra, or at the level of the intervertebral disk between the upper two lumbar vertebrae [12].

The spine (**vertebral column**) is made up of a column of bones called vertebrae (plural of vertebra) which encloses a central canal (the **vertebral canal**) that protects the spinal cord, between the vertebrae are disks of cartilage that protects the spine and gives it flexibility.

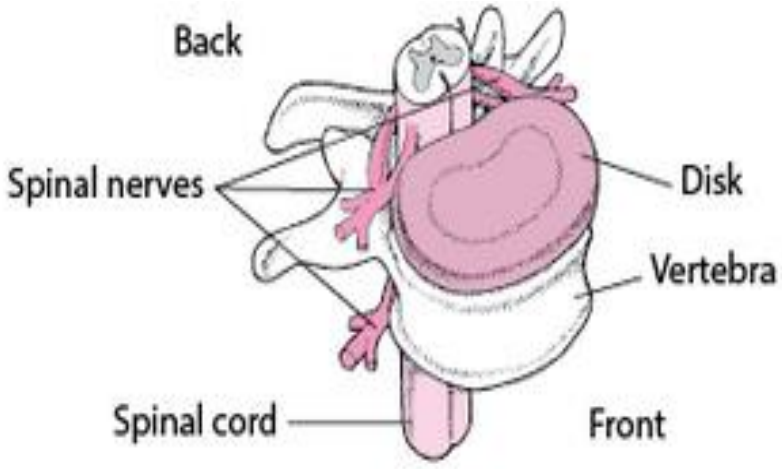

Figure 1. 6: an illustration of a thoracic vertebra [14].

1.3.2.1 Meninges:

Meninges, plural of meninx, which is the Greek term for membrane and it refers to the tissue covering the CNS (brain and spinal cord) providing a supportive framework for the cerebral and cranial vasculature, (figure I.6).Dura mater, arachnoid mater, and the Pia mater are the layers of these meninges, in between the Pia and the arachnoid mater there is a space called subarachnoid space, this later contains CSF (cerebrospinal fluid) that serves as a cushion between the delicate CNS and the skull or the spine.

The meninges have a protective and supportive function as well other various specializations, such as the production, circulation and absorption of the CSF [15].

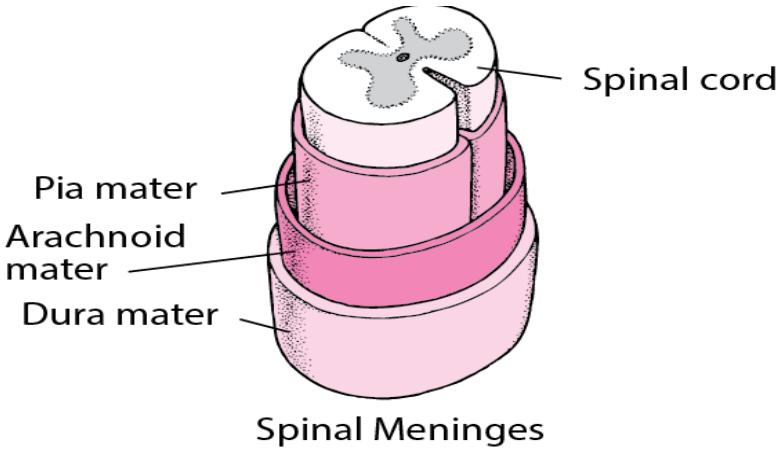

Figure 1. 7: the spinal meninges [14].

1.3.2.1.a Dura mater:

The dura mater, also called pachymeninx, forms a continuous collagenic sheet surrounding intracranial and spinal nervous structures. The dura is the outermost layer of all three membranes; it is thick, tough fibro-elastic layer of cells.

In the spinal cord the dura mater forms a tubular sac that is attached to the bones only at the region of the foramen magnum, this sac end at the level of the second sacral vertebra. [16].

1.3.2.1.b Arachnoid mater:

The arachnoid is a thin fibrous meninx that forms a cover to all the CNS, the arachnoid and pia layer are often considered as one due to the spider-web like vascular connective tissue between them, from which the arachnoid gets its name and the space between the last two is called subarachnoid space [17]. The CSF circulates within the subarachnoid space (which is continuous with the CSF of the brain) providing more physical protection by cushioning impacts.

1.3.2.1.c Pia mater:

The pia mater is the innermost layer, it is a thin, delicate, translucent membrane, this membrane adheres tightly to the surface of the spinal cord following all of its curves. The pia is pierced by blood vessels that nourish the spinal cord [18].

1.3.2.2 Spinal nerves:

The spinal nerves are mixed nerves, which means; they transmit sensory information from the organs to the CNS and convey motor signals to the muscles and organs from the CNS. In the human body there 31 pairs of spinal nerves, these lasts emerge from the vertebral column through the intervertebral foramina between the adjacent vertebrae, and they are grouped as follows: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1coccygeal. In the clinical studies, the abbreviations C, T, L, S and Co followed by the appropriate numerals are used to indicate each single spinal nerve respectively. Each spinal nerve is attached to the spinal cord by a ventral (anterior) and a dorsal (posterior) root, and each root is formed by six to eight rootlets that extend throughout the whole length spinal cord segments. The ventral rootlets are made up of axons of motor neurons and dorsal rootlets are made up of axons of sensory neurons (figure I.7).

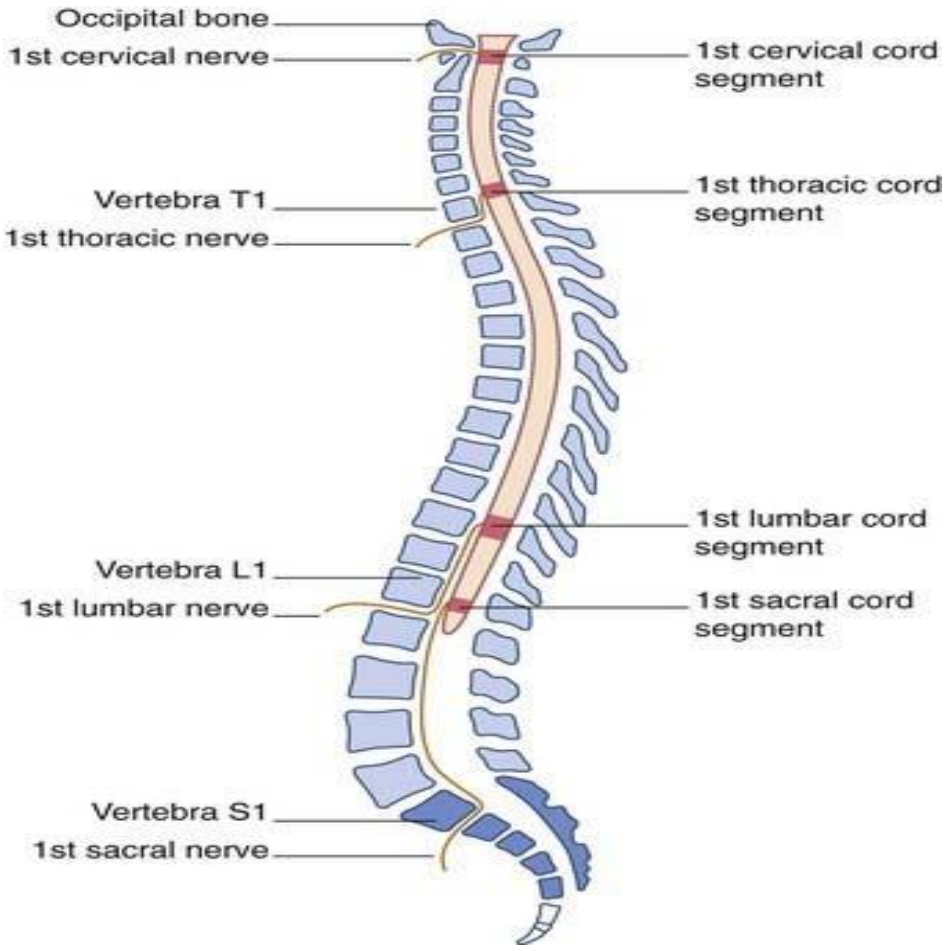

Figure 1. 8: an illustration of the spinal nerves' segments [19].

1.4 Conclusion:

The human body is amazingly complicated and vast, especially the CNS. In this chapter we went through the biology of the CNS, its major divisions and sub-divisions in order to provide a clearer picture of how it's made and slightly more, how it works. However, we couldn't mention all the sub-divisions due to their complication and limitations of the resources about them.

Chapter 02
Biological neuron model

Chapter 02: Biological neuron model

2.1 Introduction:

Neuroscience is one of the most important major research topics of this century. the origin of neural networks comes from the mathematical modelling of the human brain is the most complex system and understanding how it works is difficult but computational neuroscience has the potential to generate theories of function performed by the brain From what we have to be able to exploit the resources and technical conceptual of computational research and to find explanations for how the neural structures achieve their effects and functions are executed by neural structures this led neuroscientists to share biological measurements with computational neuroscientists to convert them to an emulator growth. Many neuron models have been proposed.

2.2 Historical:

The origin of the inspiration for artificial neural networks dates back to 1890 when W. James, a famous American psychologist, introduced the concept of associative memory [20], In 1949, the psychologist Hebb, wrote The Organization of Behavior [21], a work which pointed out the fact that neural pathways are strengthened each time they are used, a concept fundamentally essential to the way humans learn. In 1958, the psychologist F. Rosenblatt, conducted a work on perceptron. In 1969 Minsky and Papert wrote a book in which demonstrated the limits of the perceptron proposed by Rosenblatt. In particular, its inability lies in solving nonlinear problems. The revival of this discipline resumed in 1982 thanks Hopfield ended up demonstrating the value of fully connected networks. Hopfield describe the recurrent artificial neural network serving as content-addressable memory system [20].

The field of neural networks has witnessed significant progress, enough to attract a great deal of attention and fund further research. Today, neural networks discussions are occurring everywhere. Advancement beyond the current commercial applications appears to be possible, and research is advancing the field on many fronts. Chips based on the neural theory are emerging and applications to complex problems developing. Clearly, today is a period of transition for neural network technology.

2.3 The biological neuron:

2.3.1 Definition:

From the Merriam Webster dictionary; a neuron is a grayish or reddish granular cell that is the fundamental functional unit of nervous tissue transmitting and receiving nerve impulses and having cytoplasmic processes which are highly differentiated frequently as multiple dendrites or usually as solitary axons.

In other words, a neuron is a cell in the nervous system capable of communicating and processing information. All the common types of neurons that we find are made up of dendrite, axon, synapses and cell body.

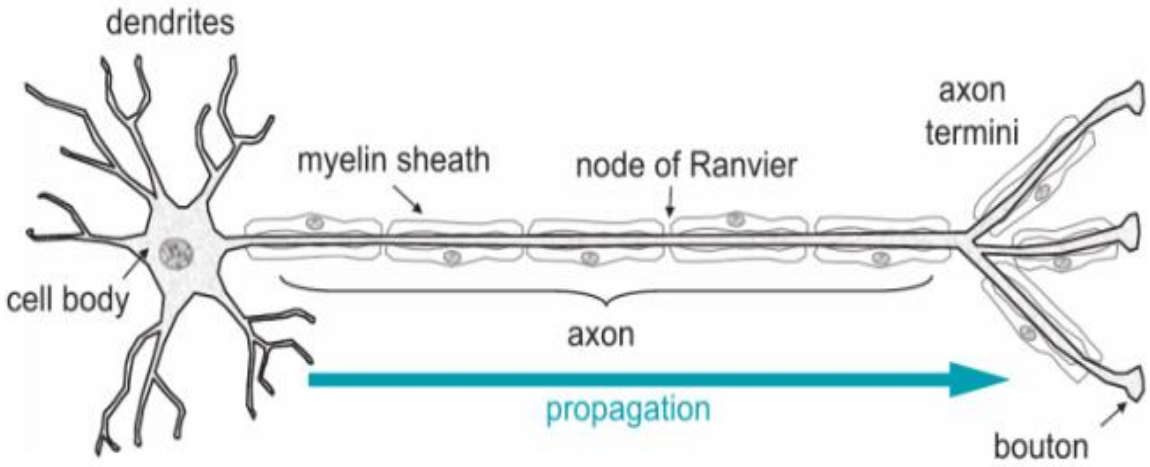

Figure 2. 1: The biological neuron [22].

- **Dendrite:**

Dendrites are branches that come from the cell body and allow synaptic connections to the neuron; they ensure the continuity of the propagation of information between the different neurons that make up the information path. The dendrites are differentiated from the axon by irregular contours and by a diameter which decreases as we move away from the soma. Dendrites are the main surface for receiving information [23].

- **Axon:**

The axon is cylindrical in shape and its diameter is less than that of a dendrite and, in humans, its length can be 1 meter long, transmits signals emitted by the cell body to other neurons, the axon is surrounded by a myelin sheath which speeds up the signal propagation

except at nodes of Ranvier. A Ranvier node is a periodic gap in the insulating sheath (myelin) in which the electrical signal is replenished, it serves to facilitate the rapid conduction of nerve impulses [23].

- **Synapses:**

The role of synapses is fundamental in allowing nerve cells to communicate with each other, There are two types of synapses: chemical synapses in which nerve impulses chemically pass through neurotransmitters It's considered as an intermediary of conveying information, and electrical synapses in which the signal is transmitted directly to the postsynaptic neuron without transmission delay [23].

- **The soma:**

The shape of the cell body varies according to the type of neuron; in most cases, it can be pyramidal, ovoid or spherical, its size in the human body is about 20 microns, and its membrane thickness is about 5 nm. The cell body carries genetic information, maintains the neuron's structure, and provides energy to drive activities [23].

2.3.2 Plasma membrane:

The plasma membrane defines the neural border of the neuron and acts to control the movement of substances into and out of the cell, and it is composed of a lipid bi-layer crossed by several types of proteins, ion channels (K^+, Na^+ and Cl^-) and the Na^+ / K^+ pump. Both sides of the membrane have the same ionic species (K^+, Na^+ and Cl^-); the intracellular liquid have a higher amount of K^+ than the other side, while extracellular medium have higher amounts of Na^+ and Cl^-. There are other types of ions, including calcium Ca^{2+} and other anions A^- which are basically proteins and amino acids [23].

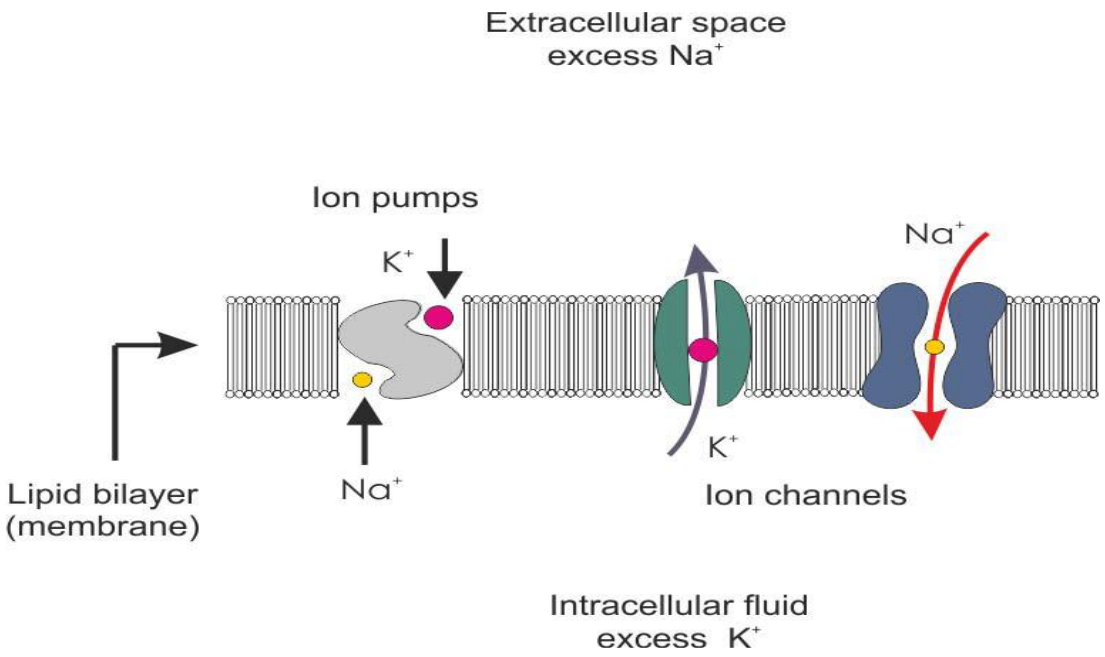

Figure 2. 2: an illustration of the plasma membrane showing the ionic channels and pumps [24].

2.3.3 Classification of neurons:

We can classify neurons according to several criteria some of them being:

2.3.3.A Structural classification:

Polarity: Unipolar neuron have only one process that includes both the axon and the dendrites, though, unipolar neurons can only be found in invertebrate animals, their unipolar neurons don't have dendrites, so the unipolar neuron in humans is actually called "pseudo-unipolar" neuron, not to mention that unipolar neurons are exclusively sensory neurons. Bipolar neurons have two processes that extend from each side of the cell body one is the axon and the other is the dendrite. Lastly, the multi-polar neuron; which are every other neuron that is neither unipolar nor bipolar, they have one axon and two dendrites or more [25] [26].

There are other types of neurons that can be classified according to their location or shape, we mention a few:

- Basket cell; interneurons that form a dense plexus (network of nerves) of terminals around the soma of a target neuron found in the cortex and cerebellum.
- Purkinje cell; which is a huge neuron in the cerebellum.
- Pyramidal cells; which basically neurons with triangular soma.

- Betz cell; large motor neuron.

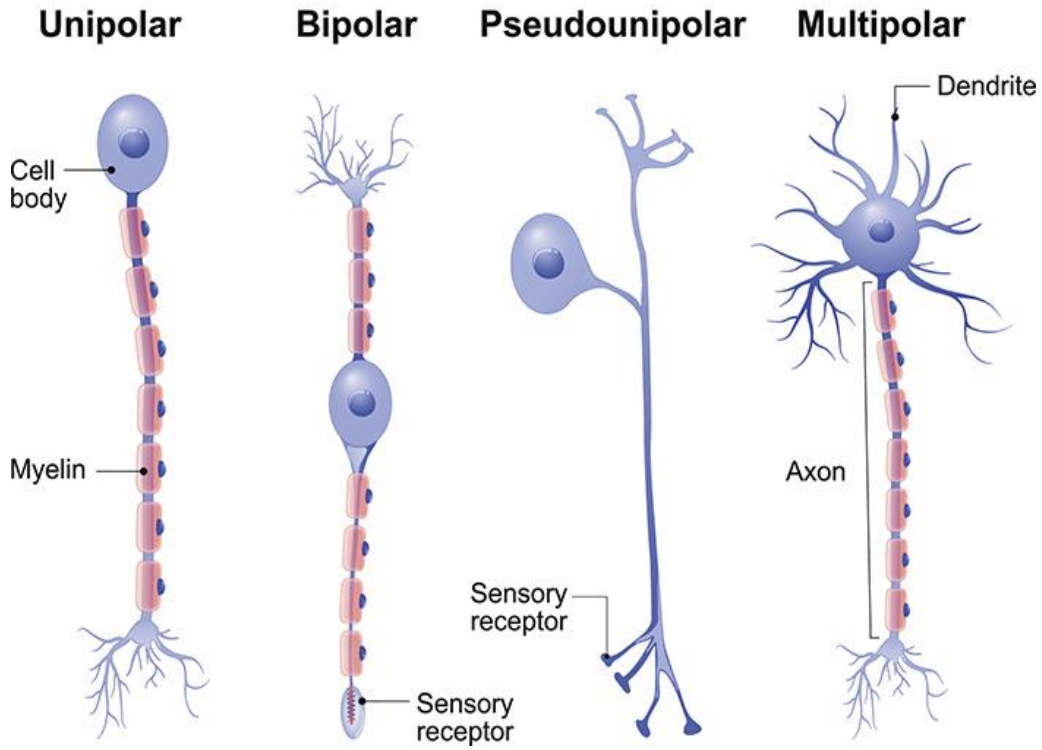

Figure 2. 3: classification of neurons by polarity (from university of Queensland website) [27].

2.3.3.B Functional classification:

Takes into account the direction of the propagation of the nerve pulse according to the CNS; we distinguish:

Sensory neurons which are usually called afferent neurons, these are the neurons that transmit information from the sensory organs to the brain, the information here is said to be ascending. Motor neurons also called efferent: their task is to transmit information that comes from the brain to the muscle, the information here is said to be top-down Interneurons: serve as a junction between sensory neurons and motor neurons.

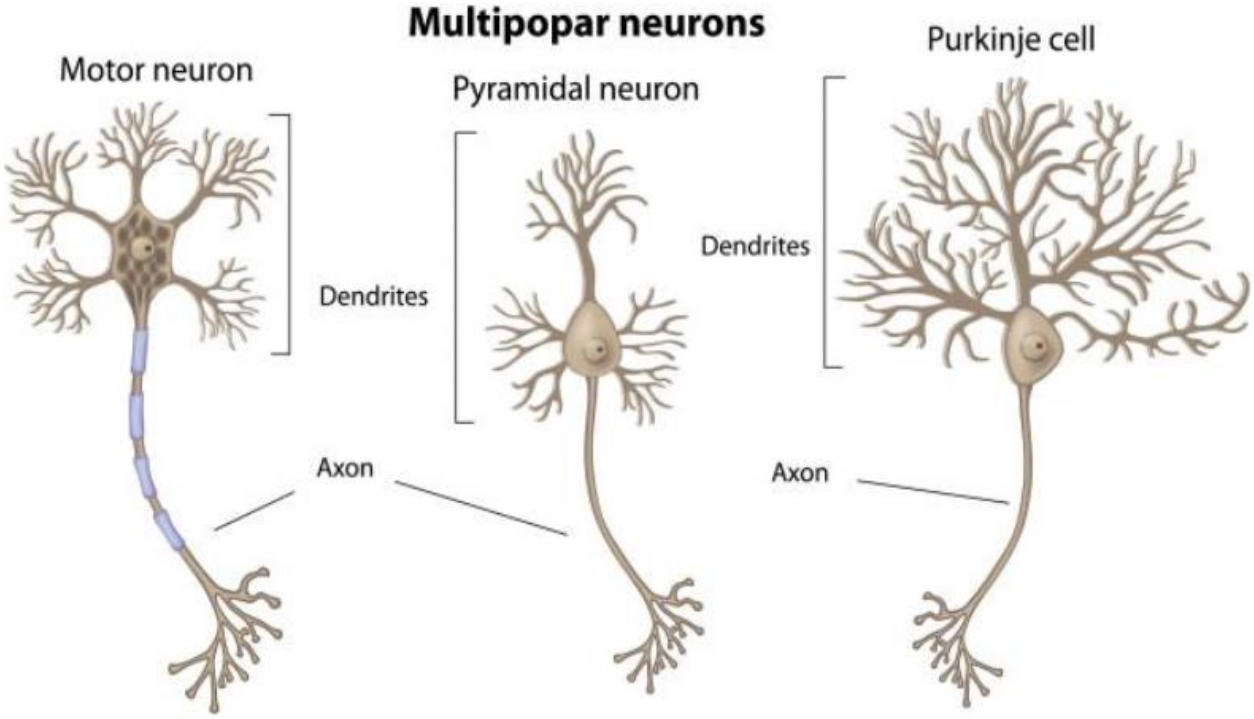

Figure 2. 4:other types of neurons [28].

2.4 The physiology of neurons:

The imbalance in the types of ions found inside and outside of the neuron means that this latter is at rest, this imbalance exists due to the fact that ion channels only allow small ions such as K^+ to pass through but not the same for Na^+. The imbalance of ions causes an imbalance in electrical which is crucial for the neuron's ability to send signals.

At system equilibrium and on the assumption of total impermeability of the membrane to different ionic species, their concentrations on either side of this barrier are subject to two constraints:

- Electroneutrality: in both media the positive and negative charges are equal.
- Osmotic equilibrium: total intra and extracellular particle concentrations are identical. Under these conditions and despite the difference in ionic concentrations maintained constant by active transport, the transmembrane voltage (the difference between the intra and extracellular potentials) is zero.

Now suppose that the membrane is permeable to only one type of ion. This time, the balance between diffusion and electrostatic transport results in a non-zero transmembrane potential, the value of which is given by the Nernst-Planck law:

$$E_{ions} = \frac{RT}{ZF} \ln\left(\frac{[ion]_e}{[ion]_i}\right) \quad (2.1)$$

Where:

- R: perfect gas constant.
- T: absolute temperature.
- Z: valence of the ion.
- F: Faraday constant.
- $[ion]_e$ and $[ion]_i$ internal and external ion concentrations.

2.4.1 The resting potential:

The charges in the inside of the neuron differ from the outside, thus, the cell (neuron) is said to be polarized. At this point the intracellular medium is more electronegative compared to the extracellular medium as a result of the abundance of Na^+ on the outside and the negative anions on the inside, this polarization causes a difference in potential at rest called the resting potential. In mammals, this latter can be in the range of -65 mV or so, this value might seem to be very low but it is very important for the neuron to function [29].

2.4.2 The action potential:

A neuron can be charged either positively or negatively when it is stimulated by an input from another neuron, if the incoming signal renders the inside of this latter more positive, it becomes positive enough to reach a certain threshold that can reach the range of 58 mV in mammals, this threshold is called the threshold of excitation. The ion channels open along the axon (due to condition mentioned before) allowing high amounts of Na^+ ions to move into the intracellular medium, this flood of ions Na^+ makes the inside highly positively charged causing the neuron to fire (send a signal), and as origin of the word fire, an action potential is just like a gun, you either shoot or you don't. Once the neuron reaches the threshold the shot is fired, and that the reason action potential is said to function in an **All-Or-None** mode [29].

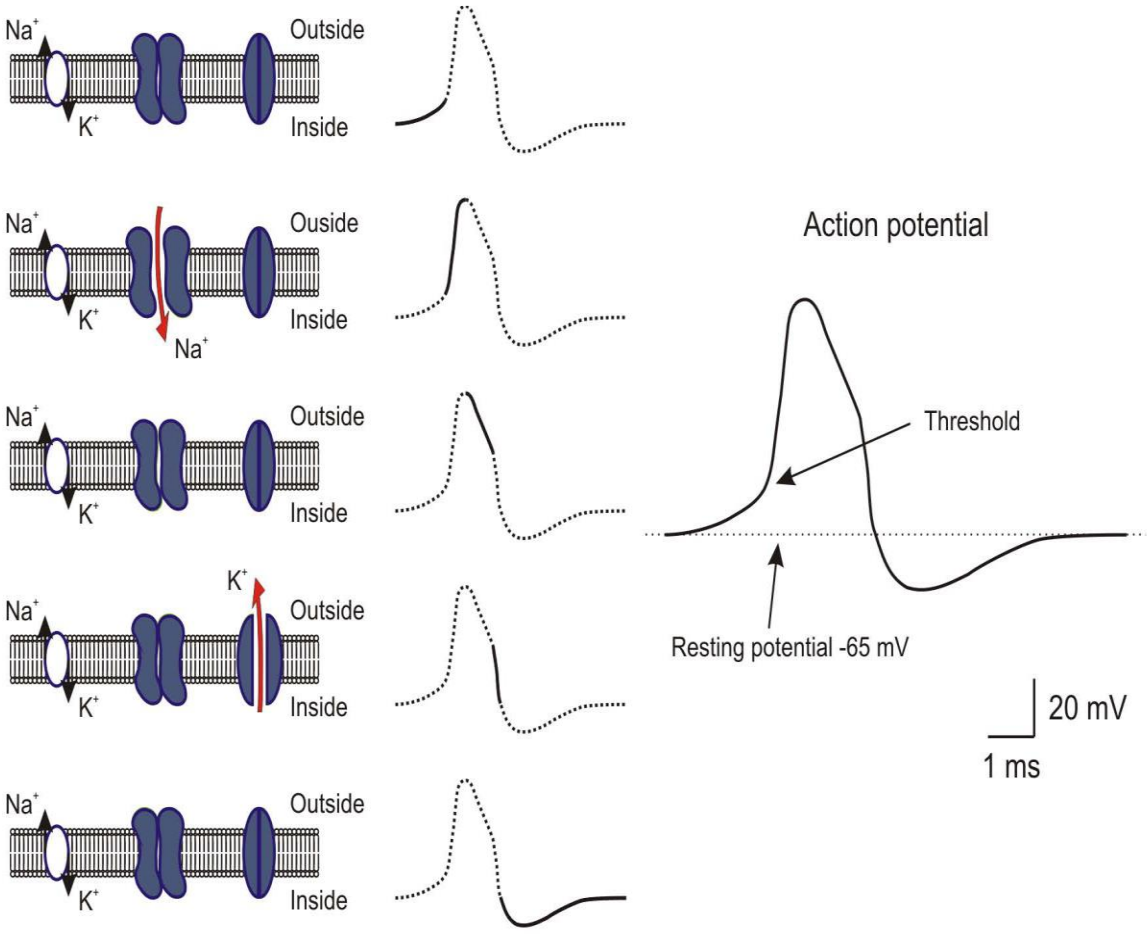

Figure 2. 5: Ionic mechanisms of action potentials [24].

2.5 Biological neuron models:

Before we talk about neuron models, we need to ask these questions first; why modelling? why not just stick to experiments? The first reason we need modelling is that many properties and variables are not experimentally accessible or manipulatable and models allow complete control over those parameters individually or jointly, also neurons and networks are nonlinear complex systems. Modelling also does not necessitate animal sacrifices and more importantly it takes less time than experiments.

After we clarified the reason behind modelling, we need to know what a neuron model is. A neuron model is a mathematical description of the properties of a neuron, mostly using differential equations as a basis of this description. Basically, a neuron model is aims to explain the mechanism behind the operations of the plasma membrane and the changes of potentials in it and the ion channels within it [21].

As it is the way in every other science, different theories come to life whether sharing or opposing the points of view, Neuroscience is no different, there has been various neuron models developed throughout the years, in this chapter we are going to list some of the popular models.

2.5.1 Hodgkin-Huxley model:

In 1952, Alan Hodgkin and Andrew Huxley proposed the first biologically relevant mathematical model, which was a result to their experiments on the giant squid axon; later in 1963 they were awarded a Nobel Prize in physiology and medicine for their ground-breaking researches.

The two scientists demonstrated how the membrane potential is responsible for the membrane's ionic permeability. And during the experiments on the giant squid, Hodgkin and Huxley found three types of currents; sodium, potassium and leaky currents. All these properties were characterized to provide a mathematical model to prove they are sufficiently taken into account for generating action potential [30].

The basic hypothesis of the HH model (shorts for Hodgkin-Huxley model) is to consider the neuron as an electrical circuit; the membrane is represented by a capacitor while the sodium and potassium flows are modeled as variable electrical conductances. [24], the model is often represented as shown in figure (2.6):

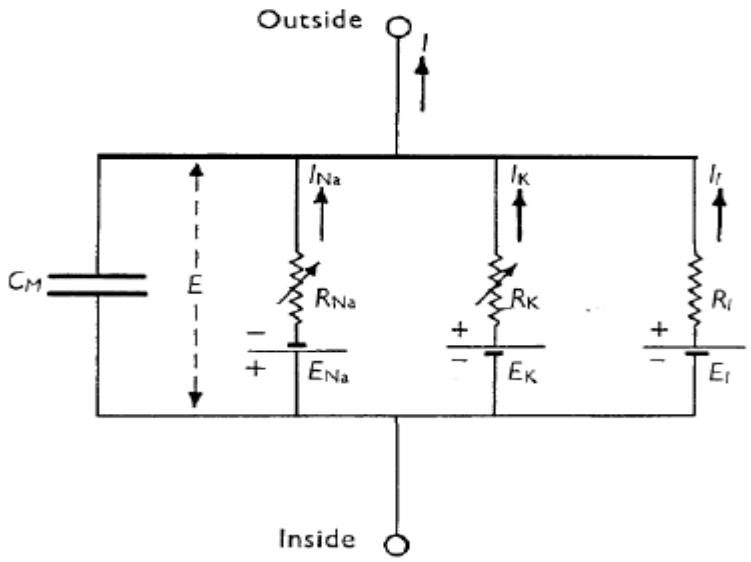

Figure 2. 6: Equivalent electrical circuit for a membrane [30].

In which:

I: Represents the total membrane current (positive inward current)

Ii: Represents current density carried by ions (inward current positive)

V: Represents the membrane potential

C_M: Represents the membrane capacitance (assumed constant)

The HH model is described by the following equations:

$$-CM\ \frac{dV}{dt} = n\,4\,\bar{g}_k\,(V - E_k) + m3h\bar{g}_{Na}\,(V - E_{Na}) + \bar{g}_L(V - E_l) - I \tag{2.2}$$

$$\frac{dn}{dt} = \frac{\alpha n - n}{\tau n} \tag{2.3}$$

$$\frac{dm}{dt} = \frac{\alpha m - m}{\tau m} \tag{2.4}$$

$$\frac{dh}{dt} = \frac{\alpha h - h}{\tau h} \tag{2.5}$$

For the Hodgkin and Huxley model, non-linearity and complexity (4 Differential equations, for V, n, m and h) make its analytical resolution and visualization of dynamics in phase space difficult. This is why two-dimensional scale models are used much more, in order to reconstruct the essential characteristics of the complete model without affecting its behavior too

much. Although the Hodgkin-Huxley model is more biologically realistic (because it takes into account many characteristics of the phenomenon), it remains very little used because of its high complexity.

The simpler two-dimensional models (sometimes called abstract models), on the other hand, provide a view of complete solutions through numerical analysis in the phase plane. This provides a geometric explanation of the important phenomena linked to the excitability of the system and to the mechanisms that lead to the generation of action potentials. From the model of Hodgkin and Huxley, we will qualitatively justify the ideas at the base of the reduction of its system to two dimensions.

2.5.2 FtizHugh-Nagumo model:

In 1961, Fitzhugh suggested a simplified model that he called in his paper the Bonhoeffer-van der Pol model [21], which he derived in 1960 as a simplification of the HH equations, and the reason behind this naming is that the Fitzhugh model had a nonlinear oscillator (Van der pol's relaxation oscillator) that was used as relaxation oscillator by Van der Pol. A year later, the equivalent electronic circuit to this system was created by J.Nagumo, Arimoto and Yoshizawa.

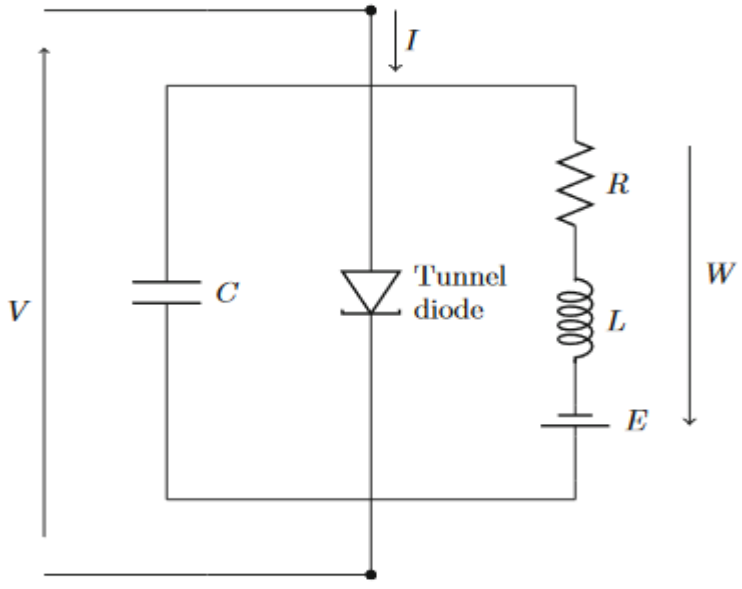

Figure 2. 7: Nagumo's equivalent circuit (from Nagumo et al 1962)[31].

In its basic form, the model consists of two coupled, nonlinear ordinary differential equations, one of which describes the fast evolution of the neuronal membrane voltage, the other representing the slower "recovery" action of sodium channel inactivation and potassium channel activation. Phase plane analysis of the FN model provides qualitative explanations of several aspects of the excitability exhibited by the HH model, including all-or-none spiking, excitation block, and the apparent absence of a firing threshold

$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I \tag{2.6}$$

$$\frac{dw}{dt} = \varphi(v + a - bw) \tag{2.7}$$

In the HH system the variables V and m (sodium activation) have similar time courses and the variables n (potassium activation) and h (sodium inactivation) also have similar time courses. However, in the FN system, v and m are regarded as mimicked by a single variable v (t), and n and h are mimicked by a single variable w which is called as the recovery variable.

2.5.3 The integrate-and-fire neuron model

Integration and fire neurons are a model that is described by the dynamics of neuron membrane potentials, v(t), proposed by Louis Lapicque in (1907), is a very simple model of the neuronal voltage, and is divided into two parts: firstly below the threshold in the absence of an injection of current, and secondly when the voltage reaches the threshold of the action potential, by the movement of the injected currents that charge The membrane, In its simplest form, the membrane potential is assumed to literally integrate the input current:

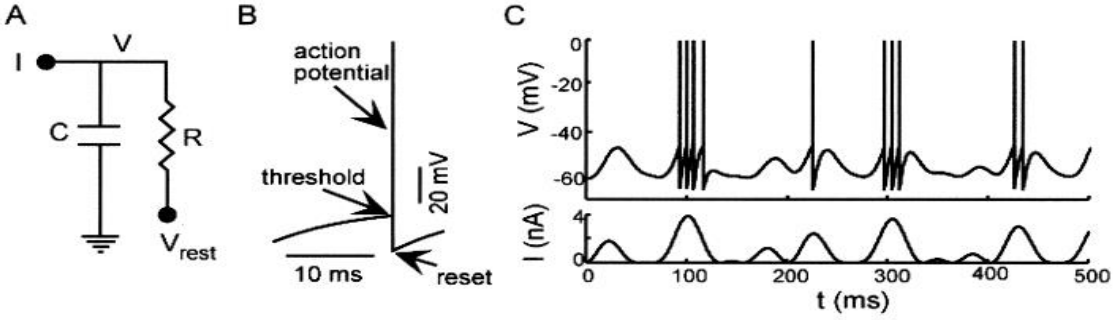

Figure 2. 8: The integrate-and-fire model of Lapicque [32].

A: The equivalent circuit with membrane capacitance **C** and membrane resistance **R**. **V** is the membrane potential, V_{rest} is the resting membrane potential, and I is an injected current.

B: is the voltage trajectory of the model. When **V** reaches a threshold value, an action potential is generated and V is reset to a subthreshold value.

C : An integrate-and-fire model neuron driven by a time varying current. The upper trace is the membrane potential and the bottom trace is the input current [33][34][32].

the integrate-and-fire neuron:

$$r_{theory} = \frac{1}{t_{isi}} = \begin{cases} \tau_m \ln\left[\frac{R_m + I_0 + E_L - V_{reset}}{R_m I_0 + E_L - V_{th}}\right]^{-1} & \text{, if } I_0 > I_{threshold} = \frac{V_{th} - E_L}{R_m} \quad (2.8) \\ 0 & \text{, if } I_0 \leq I_{threshold} \ \frac{V_{th} - E_L}{R_m} \quad (2.9) \end{cases}$$

Neuron receiving constant current input $I_e=I_0$=constant and $I_{threshold}$ is the minimum level of current injection needed to make the neuron fire

2.5.4 The Morris-Lecar model:

The Morris-Lecar model (Catherine Morris and Harold Lecar (1981)), It is a biological neuron model tasked with producing a variety of oscillatory behavior regarding Ca^+ and K^+ conduction in giant barnacle muscle fibers. This model is a reduction version of the four-dimensional Hodgkin-Huxley model. When a depolarizing current is applied to the barnacle muscle fibers it produces a wide range of electrical activity, experimental work by a group of researchers indicates that giant barnacle muscle fibers contain potential K^+ and Ca^+ currents along with a K^+ current that is activated by intracellular Ca. Their model involves only a fast activating Ca current, a delayed rectifier K current, and a passive leak. And this is what their simulations illustrate in a good explanation of their experimental measurements [35].

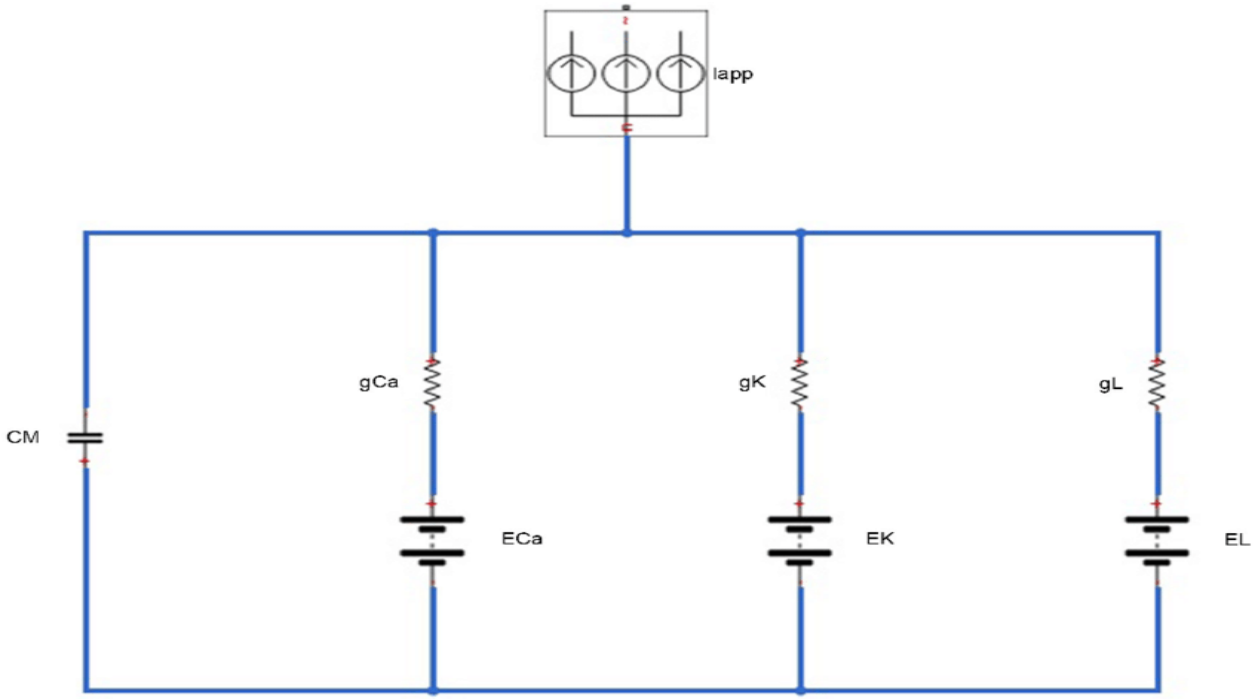

Figure 2. 9: Equivalent Circuit for model[35].

the model is given by two differential equations:

$$\begin{cases} C_M \frac{dy}{dx} = I_{app} - g_L(V - E_L) - g_k n\,(V - E_K) - \mathrm{g_{ca}} m_{\infty}(V)(V - E_{ca}) \\ \qquad = I_{app} - I_{ion}(V, n) \end{cases} \tag{2.10}$$

$$\frac{\mathrm{dn}}{\mathrm{dt}} = \frac{\varphi(n_{\infty}(V) - n)}{\tau_n(V)} \tag{2.11}$$

With the auxiliary functions given by

$$m_{\infty}(\mathrm{V}) = \frac{1}{2}[1 + \tan h\,((V - V_1)/V_2)] \tag{2.12}$$

$$\tau_n(V) = 1/\cosh(\frac{V - V_3}{2V_4}) \tag{2.13}$$

$$n_{\infty}(V) = \frac{1}{2}[1 + tanh(\frac{V - V_3}{V_4})] \tag{2.14}$$

And

$$\mathrm{Iion\,(V, n)} = \mathrm{g_L\ (V - EL)} + \mathrm{g_k\,n\,(V - Ek)} + \mathrm{g_{ca}}\, m_{\infty}(\mathrm{V})(\mathrm{V - Eca}) \tag{2.15}$$

Where **V** demonstrates membrane potential, and **n** the activation variable of the persistent $\mathbf{K}^{+}$ current, so it is a two-dimensional vector (V, n) . $\mathbf{E_K}$, $\mathbf{E_{Ca}}$, and $\mathbf{E_L}$ denote the Nernst equilibrium potentials. $\mathbf{I_{app}}$ demonstrates the injected current and $\mathbf{I_{ion}}$ the ionic current. Parameter **φ** is a temperature factor. $\mathbf{L_g}$ is leak membrane conductance; $\mathbf{g_k}$ is potassium membrane conductance and $\mathbf{g_{ca}}$ is calcium membrane conductance. Moreover, $\mathbf{C_M}$ is the total membrane capacitance. Also, the voltage-sensitive steady-state activation function $\boldsymbol{m}_{\infty}\mathbf{(V)}$ and $n_{\infty}\mathbf{(V)}$, and the time constant $\boldsymbol{\tau_n(V)}$ can be measured experimentally [35].

2.5.5 Hindmarsh-Rose model:

Hindmarsh-Rose model was first implemented in 1970s by Connor et al, which was similar to the 4-dimension HH model. In 1982 Rose and Hindmarsh simplified the six-dimension Connor-Stevens model to a two dimension model (eq2dHR) by transformation of variables, and later in 1989 their model was extended to a three-dimension model by adding a slow variable to describe the sub-threshold of the inward and outward currents.

As for the HH model simulating the giant squid axon and the Morris-Lecar model simulating the barnacle axon (specifically, the *Balanus Nubilus*), HR simulated the pond snail Lymnea.

The HR model is modification of the FN model, which is a simpler polynomial model that mimics the HH model. The original model was written as:

$$\dot{x} = \emptyset(x) + I \tag{2.16}$$

$$\dot{y} = \varphi(x) - y \tag{2.17}$$

Where:

$$\emptyset(x) = -ax^3 + bx^2 \tag{2.18}$$

$$\varphi(x) = -dx^2 c \tag{2.19}$$

In which two variables x and y are the membrane potential and recovery variable (also called spiking variable), respectively, and a term I is the externally applied current. The parameters a, b, c, and d are four positive constants, which are often assumed as a = 1, b = 3, c = 1, and d = 5, respectively. [36].and after adding the third equation that allows the analysis of numerous behaviors the model became like follows:

$$\dot{x} = -ax^3 + bx^2 + I \tag{2.20}$$

$$\dot{y} = -dx^2 - y + c \tag{2.21}$$

$$\dot{z} = r\,(s\,(x - x_1) - z) \tag{2.22}$$

The variable z is the bursting variable and the constant x_1 is the resting potential of the model. The newly added parameters r and s are two positive constants but r is very small. Thus, a new variable z, a slowly evolving current, is coupled into the first equation of the two-dimensional model (1) to tune the externally applied current I. The parameters are usually assumed $x_1 = \frac{8}{5}$; r = 4 and r which governs the time scale of the neural adaptation and is something of the order of 10^{-3} [37].

2.6 Conclusion:

The aim of this chapter was to introduce several elementary notions of neuroscience. In particular,

We have seen how "real" neurons are extremely complex biophysical and biochemical entities. As we went through the classification of neurons mentioning the most general types, and the parts of a neuron. The Understanding the physiology of the neuron makes a stepping stone towards creating neuron models or making hardwares according to those models. The 1907 Integrate-and-Fire model was one of the first to describe how action potentials in neurons are the result of electrical activity. Since then, many improvements have been made. In 1952, Hodgkin and Huxley further improved this by adding in terms for active Na+ and K+ ion channels and modelling the opening and closing of these. Today, their model is the most widely accepted in neuroscience, although many models have appeared to simplify its predecessor by allowing many modifications to allow for simpler computational operations. The FN model was the first to follow on the steps of the HH model and then the Hindmarsh-Rose model which was more like a combination of the two.

Chapter 03

Simulation and Analysis

Chapter 03: Simulation and analysis

3.1 Introduction:

In the previous chapter we introduced neural modelling, and the basic of the physiology of the neuron and we mentioned some popular models. In this chapter we will try to delve deeper into the analysis of two of the most famous models, the Hodgkin-Huxley and the Integrate-and-Fire models, which are two of the first models ever used in computational and biophysical neuroscience. We will also try to simulate these two models using the most famous academic programming language MATLAB, but first, what is MATLAB? .

3.2 MATLAB:

MATLAB (MATrix LABoratory) is a fourth-generation high-level programming language and interactive environment for numerical computation, visualization and programming.

MATLAB is specialized in the field of digital matrix computing. All objects defined in MATLAB are therefore by means of vectors and matrixes / tables of numbers. An important set of operators and basic MATLAB functions facilitate their manipulation and operations such as for example the product and the matrix inversion (inv), the transposition (') or the calculation of the eigenvalues (eig) are part from the standard library. Many other functions used for the creation and manipulation of matrices and arrays (diag, fliplr, flipud, rot90, rand, ones, zeros, linspace, logspace) are also available in number [38].

MATLAB is in the form of a Workspace, where a command interpreter performs MATLAB operations and functions. The sources of these are available, written in MATLAB "language", even in C or FORTRAN. The user can modify them as they wish, but being inspired by them, they can above all create and add their own functions [39].

3.2.1 MATLAB's Power of Computational Mathematics:

MATLAB is used in every facet of computational mathematics. Following are some commonly used mathematical calculations where it is used most commonly:

- Dealing with Matrices and Arrays
- 2-D and 3-D Plotting and graphics

- Linear Algebra
- Algebraic Equations
- Non-linear Functions
- Statistics
- Data Analysis
- Calculus and Differential Equations
- Numerical Calculations
- Integration
- Transforms
- Curve Fitting
- Various other special functions

3.2.2 Features of MATLAB:

Following are the basic features of MATLAB:

- It is a high-level language for numerical computation, visualization and application development.
- It also provides an interactive environment for iterative exploration, design and problem solving.
- It provides vast library of mathematical functions for linear algebra, statistics, Fourier analysis, filtering, optimization, numerical integration and solving ordinary differential equations.
- It provides built-in graphics for visualizing data and tools for creating custom plots.
- MATLAB's programming interface gives development tools for improving code quality, maintainability, and maximizing performance.
- It provides tools for building applications with custom graphical interfaces.
- It provides functions for integrating MATLAB based algorithms with external applications and languages such as C, Java, .NET and Microsoft Excel.

MATLAB also offers several functions intended for the (numerical) resolution of linear or non-linear differential equations by the method of Runge-Kutta (ode23 and ode45), numerical integration (trapz, quadetquad8) , the search for solutions of algebraic (roots) or transcendent (fzero) equations, the creation and manipulation of polynomials (poly, polyder, polyval, conv, deconv), the fast Fourier transform (fft, fft2 , ifft). Functions specific to the processing of data (experimental, such as those obtained in the laboratory), comme min, max, mean, cumsum, sort, std, diff, as well as those relating to interpolation (polyfit, interp1) are all very practical tools for the engineer analyzing a practical or theoretical problem [38].

In addition to the basic software, depending on the chosen configuration, MATLAB also offers a series of toolboxes dedicated to specific technical fields [39], for example:

- signal processing and Communications
- image and video Processing
- control systems
- test and measurement
- computational finance
- computational biology

The MATLAB graphical interface is undoubtedly one of the strong points of the software and facilitates the plotting of curves and obtaining high quality 2D or 3D graphics (plot, stairs, stem, hist, mesh, surf, plot3). The Handle Gra-phics module offers the possibility of fully controlling this interface, thus allowing the user to format all the elements of a graphic, to create his own menus (uimenu) as well as graphic objects such as sliders (elevators), buttons, pop-up menus (uicontrol) with surprising ease.

Simulink is nothing more than another MATLAB toolbox allowing, using an advanced graphical interface, the fast and easy construction as well as the simulation of complex functional diagrams, containing linear, non-linear or even non-stationary systems, including logical operators, mathematical analysis tools [38].

3.3 Hodgkin-Huxley model:

Hodgkin and Huxley's goal from these experiments was to determine the laws that control how ions move in and out of a neuron during an action electrical activity. While experimenting, Hodgkin and Huxley knew that the action potential is associated with a flow of sodium and potassium ions. They also knew that the rate and amplitude of the action potential are determined by concentrations of sodium on the outside of the neuron. Their main assumption for their experiments was that the membrane current can be divided into a capacitance as well as an ionic current which depends on the movement of sodium and potassium through the membrane.

3.3.1 Hodgkin-Huxley model analysis:

The first step of this analysis was to divide the total membrane current into a capacity current and an ionic current:

$$I = C_M \frac{dV}{dt} + I_i \tag{3.1}$$

They chose to model the capacity current and ionic current in parallel because they found that the ionic current when the derivative was set to zero and the capacity current when the ionic current is set to zero were similar.

$$I_i = I_{Na} + I_K + I_L \tag{3.2}$$

Where I_{Na} is the sodium current, I_K is the potassium current and I_L is the leakage current.

With:

$$I_{Na} = g_{Na}(V - V_{Na}) \tag{3.3}$$

$$I_K = g_K(V - V_K) \tag{3.4}$$

$$I_L = g_L(V - V_L) \tag{3.5}$$

g_K and g_{Na} are the potassium and sodium conductances per unit area, respectively, V_K and V_{Na} are the potassium and sodium reversal potentials, respectively, and g_l and V_l are the leak conductance per unit area and leak reversal potential, respectively.

Originally, the voltage in those equations was written with E symbol but it was changed for practical purposes [25], with:

$$V_{Na} = E_{Na} - E_r \tag{3.6}$$

$$V_K = E_K - E_r \tag{3.7}$$

$$V_L = E_L - E_r \tag{3.8}$$

Where, E_{Na} and E_K are the equilibrium potentials for the sodium and potassium ions. E_L is the potential at which the 'leakage current' due to chloride and other ions is zero; E_r is the absolute value of the resting potential. V, V_{Na}, V_k and V_L can then be measured directly as displacements from the resting potential.

Hodgkin and Huxley considered that each of the channels should be made up of four independent components, each of which can be open or closed. In the case of potassium channels, these four components would be identical with a probability of n being in the open position (potassium activation), and it was similar for the other gates with; m for sodium gating and h for sodium channel inactivation.[30]

For the potassium conductance:

$$I_k = n^4 \bar{g}_K (V - E_k) \tag{3.9}$$

With:
$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \tag{3.10}$$

Where $\bar{g}_K$ is a constant with the dimensions of conductance/cm^2 which represents the maximal conductance of potassium, α_n and β_n are rate constants which vary with voltage but not with time and have dimensions of [time]$^{-1}$, they represent the rate of opening and closing of the potassium activation channels, with α_n being the opening state.[30]

In addition, α_n and β_n are now written:

$$\alpha_n = \frac{n_\infty}{\tau_n} \tag{3.11}$$

$$\beta_n = \frac{1 - n_\infty}{\tau_n} \tag{3.12}$$

Where:

$$n_{\infty} = \frac{\alpha_n}{\alpha_n + \beta_n} \tag{3.13}$$

$$\tau = \frac{1}{\alpha_n + \beta_n} \tag{3.14}$$

The two physiologists found for a final relation for the gating control rates the following equations:

$$\alpha_n = 0.01(V + 10) / \left[\exp\frac{V+10}{10} - 1\right] \tag{3.15}$$

$$\beta_n = 0.125 \exp(V/80) \tag{3.16}$$

The sodium conductance is described by the equation:

$$I_{Na} = m^3 h \bar{g}_{Na}(V - E_{Na}) \tag{3.17}$$

With;

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \tag{3.18}$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \tag{3.19}$$

$\bar{g}_{Na}$ is the maximal conductance for the sodium, α_m is the rate at which the sodium activation rates are open and β_n is the rate of gate closing. And for the inactivation gates α_h and β_h being the closing and opening rate respectively.

The leaky current was described by the following equation:

$$I_L = \bar{g}_L(V - E_L) \tag{3.20}$$

The deduction of α's and β's expressions follows from the same reasoning used for the potassium rate constants, with the only difference that now there are two first order differential equations rather than only one. and the results were[30]:

$$\alpha_m = 0.1(V + 25) / \left[\exp\frac{V+25}{10} - 1\right] \tag{3.21}$$

$$\beta_m = 4 \exp(V/18) \tag{3.22}$$

$$\alpha_h = 0.07 \exp(V/20) \tag{3.23}$$

$$\beta_h = 1/\left[\exp\frac{V+30}{10} + 1\right] \tag{3.24}$$

Now we summarize the equations that makes the HH model :

$$I = CM\ \frac{dV}{dt} + n\ 4\ \bar{g}_k\ (V\ - E_k\ )\ +\ m3h\bar{g}_{Na}\ \ (V\ - E_{Na})\ +\ \bar{g}_L(V\ - E_l) \tag{2.2}$$

$$\frac{dn}{dt} =\ \alpha_n\ (1 - n)\ - \beta_n\ n \tag{3.10}$$

$$\frac{dm}{dt} =\ \alpha_m\ (1 - m)\ - \beta_m\ m \tag{3.18}$$

$$\frac{dh}{dt} =\ \alpha_h\ (1 - h)\ - \beta_h\ h \tag{3.19}$$

$$\alpha_n = 0.01(V + 10)/\left[\exp\frac{V+10}{10} - 1\right] \tag{3.15}$$

$$\beta_n = 0.125 \exp(V/80) \tag{3.16}$$

$$\alpha_m = 0.1(V + 25)/\left[\exp\frac{V+25}{10} - 1\right] \tag{3.21}$$

$$\beta_m = 4 \exp(V/18) \tag{3.22}$$

$$\alpha_h = 0.07 \exp(V/20) \tag{3.23}$$

$$\beta_h = 1/\left[\exp\frac{V+30}{10} + 1\right] \tag{3.24}$$

In this section we breakout the matlab code used for the simulation. Where we implement the forward EULER method

Forward EULER's method:

The forward Euler method is a method for solving ordinary differential equations using the formula $y_{n+1} = y_n + hf(x_n, y_n)$

which advances a solution from x_n to x_{n+1} . this method increments a solution through an interval using a step h while using derivative information.

3.3.2 The action potential simulation:

The action potential along with the corresponding plots for the time course of the gating parameters have been presented in this section. These plots were obtained from computer simulations, with differential equations handled using the forward Euler approximation method.

The action potential of the HH model shown in (figure 3.1)below depicts the rapid upstroke (depolarization) resulting from increased sodium conductance, which eventually inactivates at ~40mV, followed by repolarization as result of increased potassium currents which proceeds to sub- resting membrane potential – hyper polarization, and an eventual return and beyond the V_{rest} = -65mV.

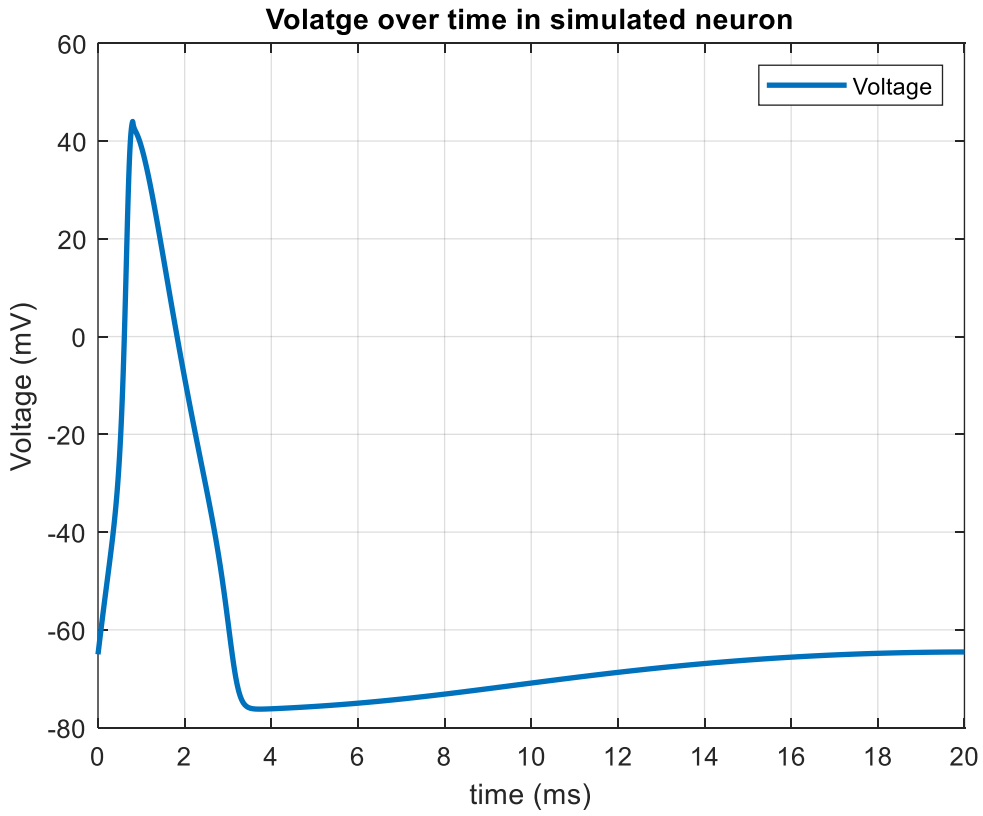

Figure 3. 1: The action potential for the HH model.

The ascending phase of the curve is caused by the activation of the voltage-dependent sodium channels, due to depolarization, which allows a very large number of Na + ions to enter the cell. The potential therefore grows, initially becoming less and less negative and subsequently positive, tending, without reaching it, to the value of the Nernst potential for Na +. Meanwhile, before the peak, the potassium channels open, which have a slower kinetics than those of sodium. This causes a leakage of K + ions from the membrane and the curve, after reaching the maximum value, takes on gradually smaller voltage values since the membrane is repolarizing to return to the equilibrium value. The repolarization phase, which allows the potential to return to the resting value E_m (resting potential), includes a transient hyper polarization phase during which the membrane potential assumes more negative values than E_m all these are further explained in the next figure.

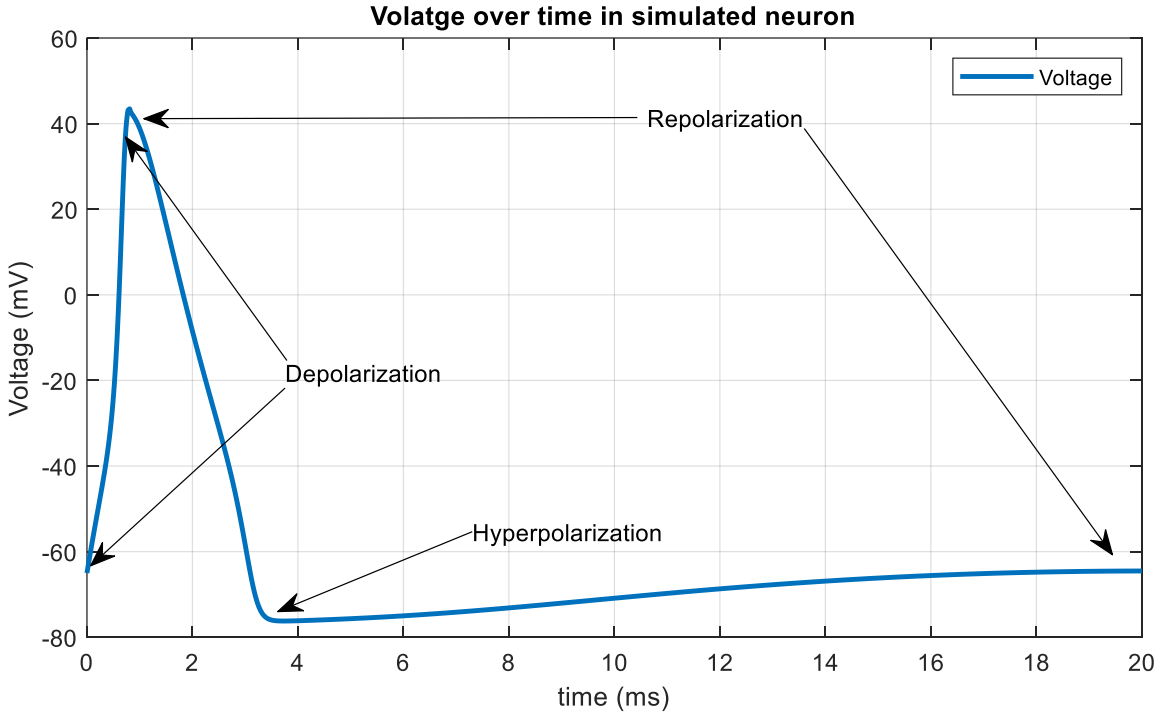

Figure 3. 2: the stages of the membrane potential.

The parameters used in the simulation of the model were extracted from the original paper of Hodgkin and Huxley as shown in the table:

constant	Chosen value
$C_{M\ (}\mu F/cm^2)$	1
$V_{Na\ (}mV)$	-115
$V_K\ (mV)$	12
$V_L\ (mV)$	-10.12
$\bar{g}_{Na\ (}m.mho/cm^2)$	120
$\bar{g}_k\ (m.mho/cm^2)$	36
$\bar{g}_L\ (m.mho/cm^2)$	0.3

Table : the original parameters used in the HH model [30].

The conductance of the membrane, for the sodium and potassium channels, do not remain constant over the time in which the action potential develops but vary both as a function of time and as a function of voltage. As we have seen previously, these conductance are proportional to the maximum value reachable by the conductance itself (g_{Na} and g_K) and by variables that are solutions of first-order differential equations: m, h, n. The variables m, h, n are dimensionless and assume values included in the interval [0,1].this process is explained more in the figures .

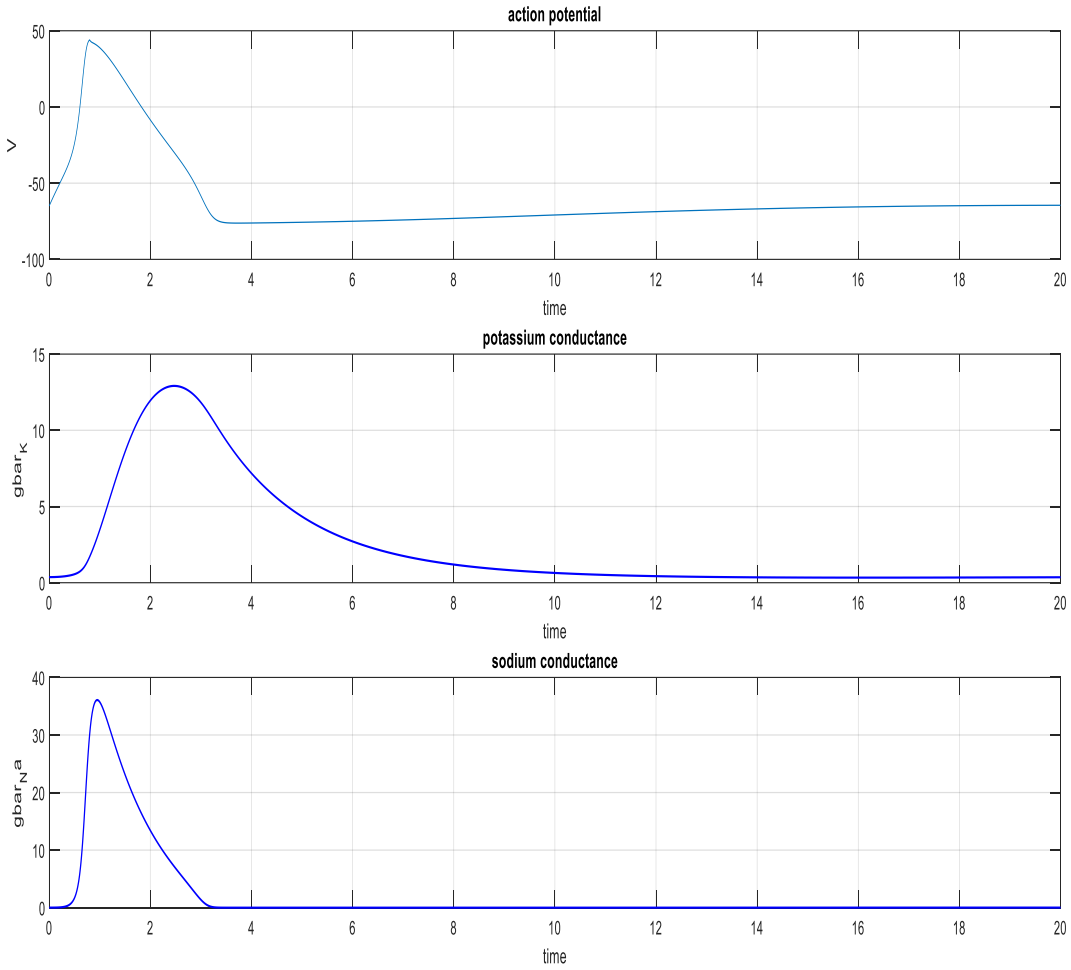

Figure 3. 3: Conductances for Potassium and Sodium in Stimulated Neuron.

The curves for m, h and n are placed in relation to the evolution of the action potential, in such a way as to easily view the various phases that crosses the neuronal membrane after receiving an external stimulus. For sodium, in correspondence with the action potential spike, we will have a probability tending to 1 of activated channels: in fact the entry of Na + ions during depolarization results in the further opening of channels for this ion, from when the voltage-dependent channels are activated. In the repolarization phase this probability decreases as the mechanism self-regulates causing potassium channels (the curve for the fraction n of activated potassium channels in fact grows with a certain delay compared to that for m) and therefore the output of the K + ions, in correspondence with this we will have a progressive inactivation of the

voltage-dependent sodium channels in order to bring the membrane potential back to the initial polarization. The curve for h shows a specular evolution with respect to this reason: during the repolarization phase, the fraction of inactivated channels grows from a value close to zero and settles at approximately 0.5, indicating that each channel of the previously activated sodium has a 50% chance of being inactivated during this phase . The evolution of n is similar to m only with some differences; one of these differences is that the potassium activation occurs later with respect to the voltage spike, the second reason is that the K^{+}channels maintain a non-zero probability of being active even after the end of the repolarization phase.

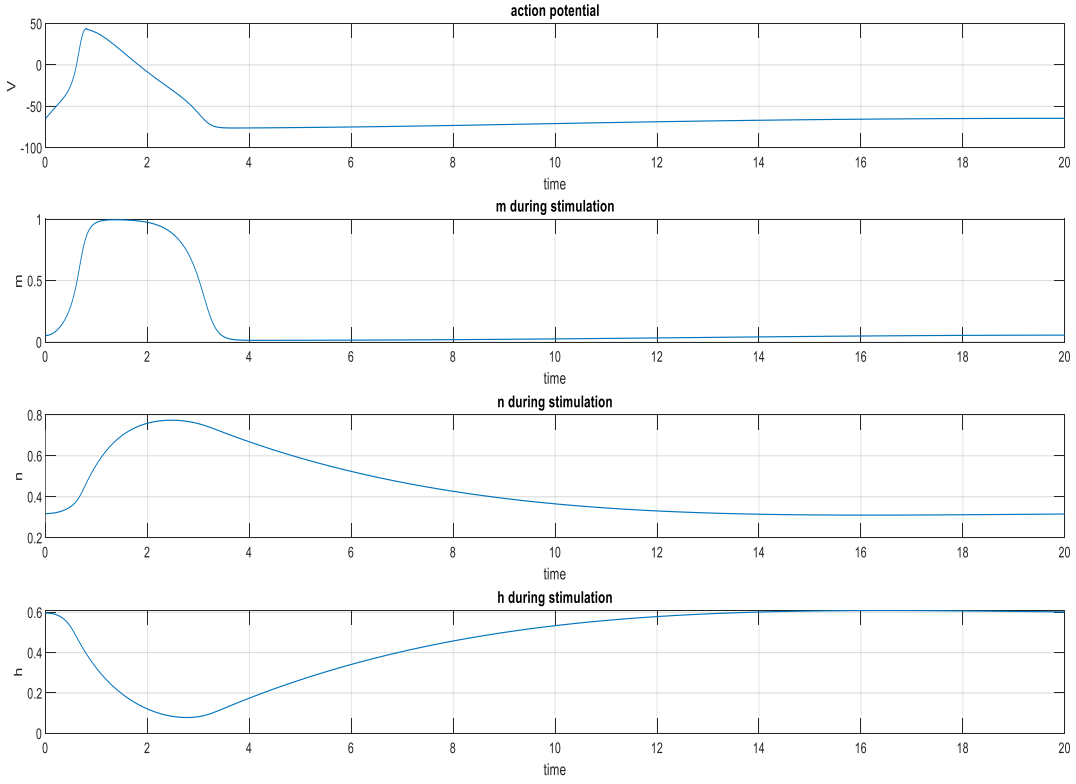

Figure 3. 4: evolution of the m, n and h the gating probabilities in comparison to action potential.

HH model is mainly a nonlinear complex model, due to the fact that it contains 4 differential equations implementing the ionic channels currents (and the variables related m, n and h) , which makes it harder to solve , but after using the different numerical methods it shows

how simple and realistic it was , in order to create the curve above the numerical method used was the Euler method.

3.4 Integrate-and-Fire model:

3.4.1 Mathematics of the integrate-and-fire neuron:

The neuron in this model can be simulated with a leaky behaves like an electric circuit consisting of a resistor and a parallel capacitor, the time constant, and resting potential E_m . In the simplest transformation of these models, all active membrane vectors, including the synaptic input and the entire membrane conductance is modeled as a single passive leakage term, this version is called the passive or leaky integrate-and-fire model, and the membrane potential is determined by equation:

$$c_m \frac{\mathrm{dV}}{\mathrm{dt}} = -\mathrm{i}_m + I_e A \tag{3.25}$$

$$c_m \frac{\mathrm{dV}}{\mathrm{dt}} = -\bar{g}_L (V - E_L) + I_e A \tag{3.26}$$

It is convenient to multiply equation (3.26) by the specific membrane resistance, which in this case is given by $r_m=1/\bar{g}_L$. This cancels the factor of g_L on the right side of the equation and leaves a factor $c_m r_m= \tau_m$ The electrode current ends up being multiplied by r_m/A, which is the total membrane resistance R_m. Thus, the basic equation of the passive integrate-and-fire models is:

$$\tau_m \frac{\mathrm{dV}}{\mathrm{dt}} = E_L - V + R_m I_e \tag{3.27}$$

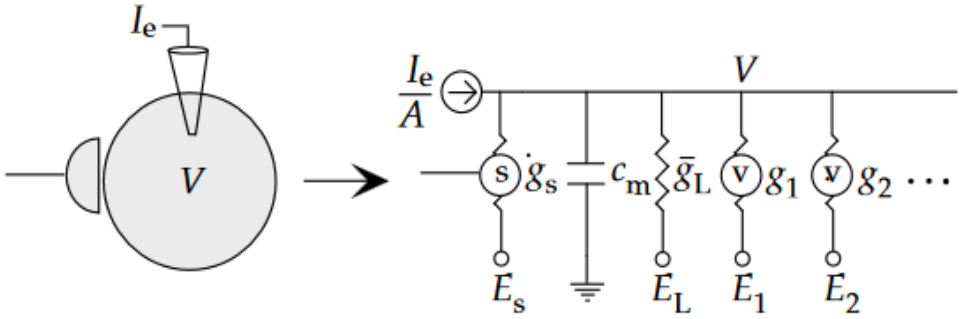

Figure 3. 5: The equivalent circuit for a one compartment neuron model [34].

In case we want to generate action potentials in the model, equation (3.27) is augmented by the rule that whenever V reaches the threshold value V_{th}, an action potential is fired and the potential is reset to V_{reset}. Equation (3.27) indicates that when $I_e=0$, when it receives no current injection the membrane potential relaxes exponentially with time constant τ_m to $V=E_L$. Thus, E_L is the resting potential of the model cell, the sub threshold potential V(t) can easily be computed by solving the equation (3.27) for the voltage of this cell when it receives current injection I_e :

$$V(t) = E_L + R_m I_e + (V(0) - E_L - R_m I_e)\exp(-t/\tau_m) \tag{3.28}$$

Where $V(0)$ is the value of V at time t = 0. This solution can be checked by substituting it into equation (3.27).It is valid for the integrate-and-fire model only as long as V stays below the V threshold, Suppose that at t=0, the neuron has just fired an action potential and is thus at the reset potential, so that $V(0)=V_{reset}$. The next action potential will occur when the membrane potential reaches the threshold, that is, at a time t= tisi when:

$$V(t_{isi}) = V_{th} + E_L + R_m I_e + (V_{reset} - E_L - R_m I_e)\exp(-t_{isi}/\tau_m) \tag{3.29}$$

By solving for t_{isi}, we can determine the interspike interval for constant I_e, where t_{isi} is the interspike interval for an integrate-and-fire neuron receiving constant current input $I_e=I_0=$ constant and $I_{threshold}$ is the minimum level of current injection needed to make the neuron fire. injected current relationship for the integrate-and-fire model neuron [34]:

$$r_{theory} = \frac{1}{t_{isi}} = \begin{cases} \tau_m \ln\left[\frac{R_m+I_0+E_L-V_{reset}}{R_m I_0+E_L-V_{th}}\right]^{-1} & \text{, if } I_0 > I_{threshold} = \frac{V_{th}-E_L}{R_m} \\ 0 & \text{, if } I_0 \le I_{threshold} \ \frac{V_{th}-E_L}{R_m} \end{cases} \tag{3.30}$$

3.4.2 Modelling the subthreshold voltage dynamics:

As a first step, we will model the subthreshold dynamics of the model governed by equation (3.27), we can determine the parameters in the model ,Define the vectors that will hold our final results such as the time and voltage, and current and assign their initial values corresponding to t=0. Integrate the equation of the model to obtain the values . Make pretty plots of our results.

we set the voltage to start at rest and didn't inject any current so the voltage stayed constant -70 mv.

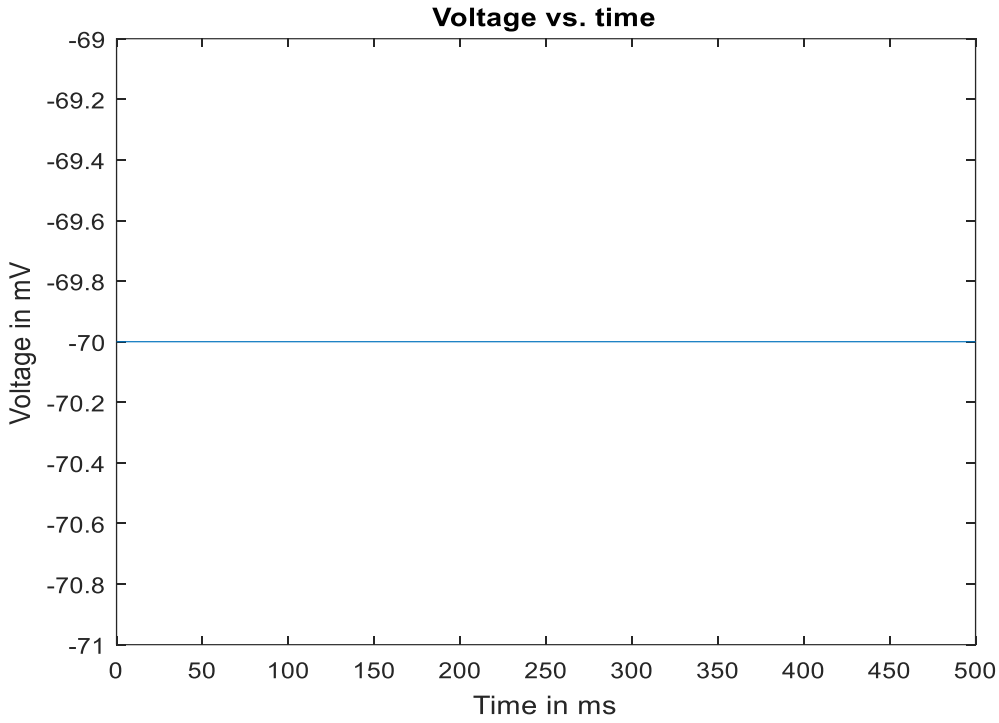

Figure 3. 6: Curve showing rest latency before injection.

When increasing injecting 1nA magnitude of pulse of current we observe:

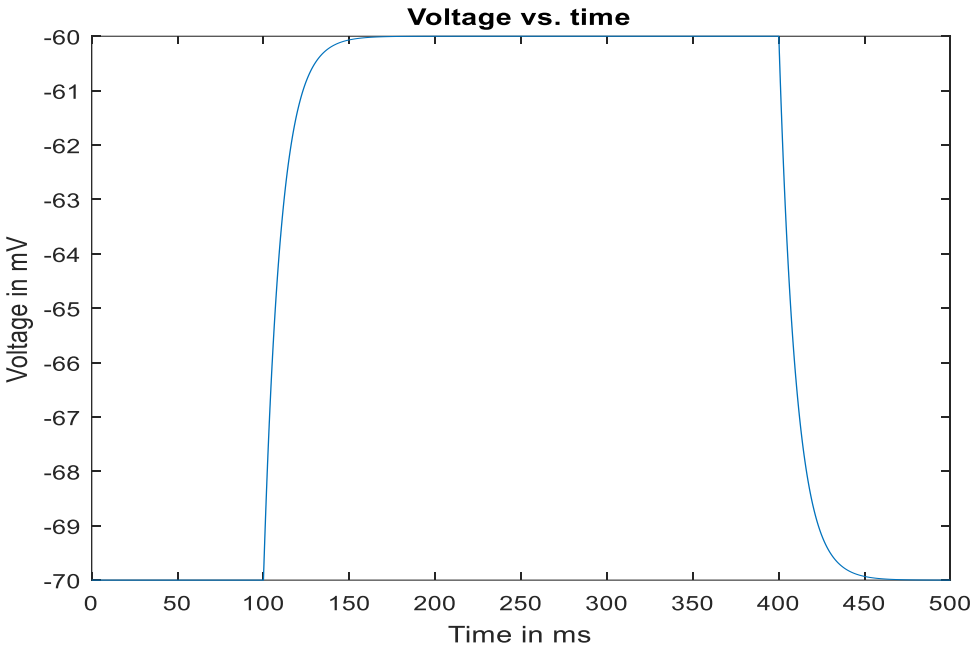

Figure 3. 7: Curve showing magnitude of pulse of injected current.

The curve shows the significant change in voltage that the value of the pulse of the injected current gets so that it rises exponentially to about -60 millivolts starting at t = 100, then regresses exponentially at t = 400 (both rise and decay with time constants τ = 10 ms) As shown In the figure(3.7).

We notice that the neurons have not reached the threshold V_{th}, so we will make some adjustments until it reaches the threshold V_{th}, by resetting the voltage back to V_{rest}, using the rules MATLAB:

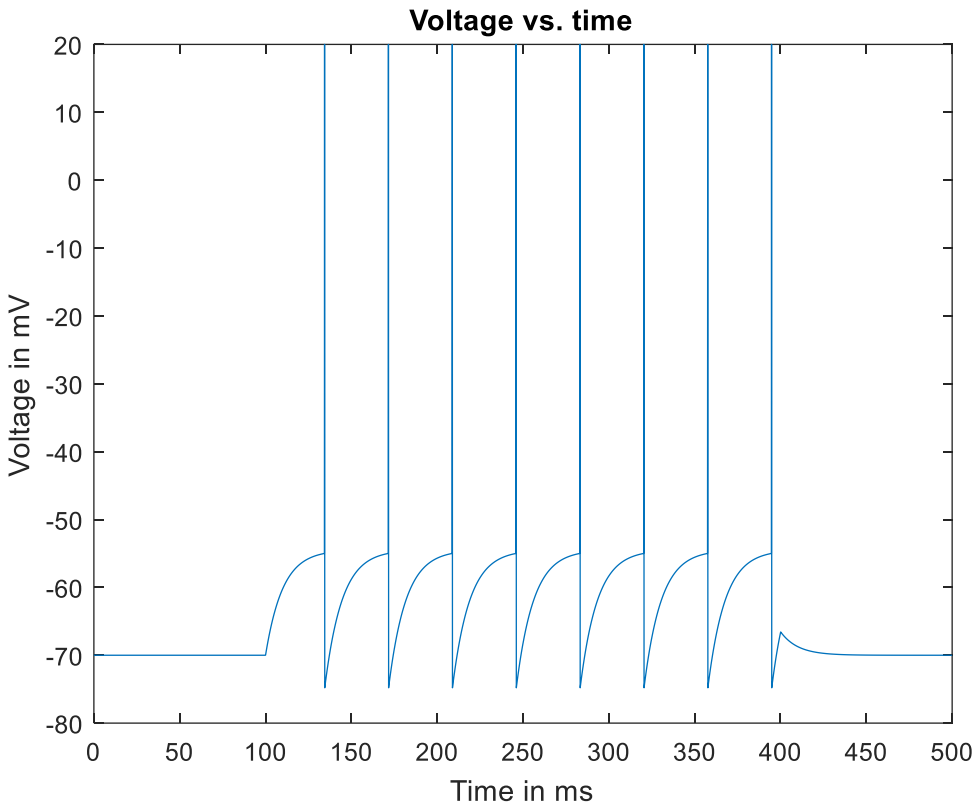

Figure 3. 8: Membrane voltage trajectory and spikes foran integrate-and-fire model with an added current

We see that the neuron readjusts its voltage every time it reaches V_th = -55 mV, and the real neuron displays an adaptation to the rate of rise,before settling to a steadystate value. Finally, we would like to compute the average firing rate of the cell during the time of stimulation. A cell's average firing rate R_{ave} over a specified period of time is the number of spikes produced over the specified time period, when we choose the period of time to be from immediately after one spike's occurrence to immediately after the next spike's occurrence. This time period between spikes is known as the interspike interval and is denoted by t_{isi}. The corresponding firing rate is $r_{isi} = 1/t_{isi}$,

we will more simply calculate R_{ave} by counting the number of spikes that occurred during the stimulation period and then dividing by this time period. , we compare this value to the value of risi . To count the number of spikes, we add a new variable to our code called Numnumber that we set initially to zero (since no spikes have occurred at the beginning of the simulation) and that we increase in value by 1 every time a spike occurs. Next we'd like to compare the theoretical

value for the firing rate of the integrate-and-fire neuron $r_{isi}=1/t_{isi}$ (equation (6)) to the value of Rave we calculated . We'll do this for several values of I_Stim (magnitude of pulse of injected current [nA]). Now we're also going to want to make separate plots for each run so Will define a variable PlotNum corresponding to the number of plots. Then we Initialize PlotNum to zero above the for loop , and it increase by 1 every time we step through the for loop. After running the code. This should produce the following panels, the first and the second with no spikes and the latter ones with increasing numbers of spikes as shown:

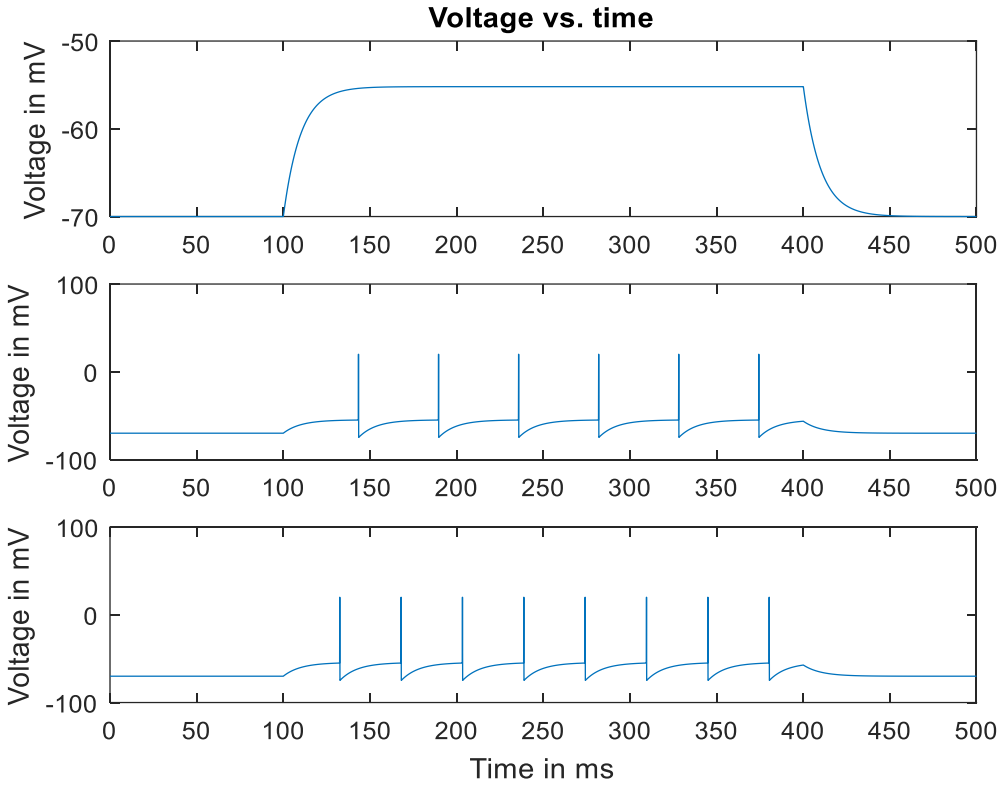

Figure 3. 9: A curve showing the increase in the current injected into the nerve cell and the increase in its firing rate.

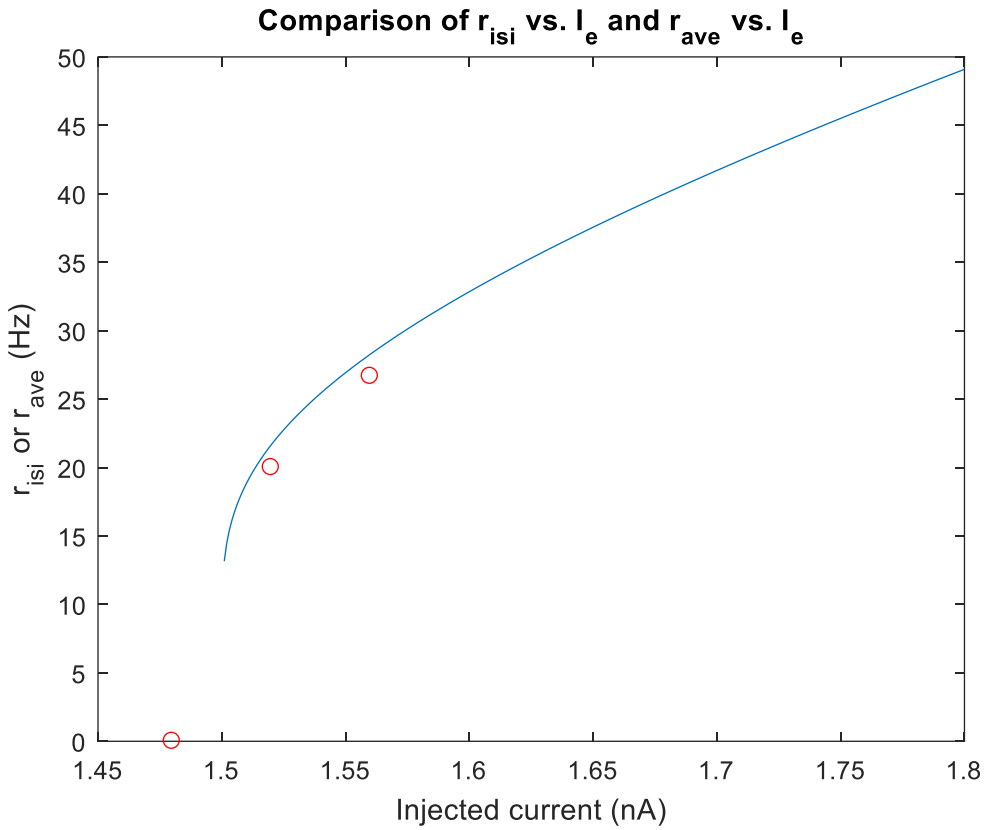

Figure 3. 10: Comparison of r_{isi} vs I_e and r_{ave} vs I_e

The values used in the program:

dt = 0.1	time step [ms]
t_end = 500	total time of run [ms]
t_StimStart = 100	time to start injecting current [ms]
t_StimEnd = 400	time to end injecting current [ms]
E_L = -70	resting membrane potential [mV]
V_th = -55	spike threshold [mV]
V_reset = -75	value to reset voltage to after a spike [mV]
V_spike = 20	value to draw a spike to, when cell spikes [mV]
R_m = 10	membrane resistance [MOhm]
tau = 10	membrane time constant [ms]
I_Stim	magnitude of pulse of injected current [nA]
Numnumber	holds number of spikes that have occurred

3.5 Differences between the HH model and IF model:

Firstly, the HH model Good at capturing quantitatively diversity of dynamical features of real neurons, for example the ionic exchanges and concentrations of each ion (potassium and sodium), but its downside is that it is Highly non-linear, and contains large number of variables therefore it is hard to analyze mathematically, also the Simulations of networks of HH neuron are computationally expensive.

Secondly, the IF model; it is too simple to reproduce diversity of dynamical features of real neurons, Can be analyzed mathematically (at both neuron and network levels), Possible to simulate very large networks of such neurons

General Conclusion:

In this work we try to provide a clear picture about neural modelling and some aspects of neuroscience, where we use medical, physiological and mathematical concepts to clarify the problematic posed while modelling a neuron.

We started this work by providing an introduction of the Central nervous system, where we talk about its anatomy; where we define the brain and its lobes and divisions from the cerebrum and cerebellum to the diencephalon and brainstem; we also mention the subdivisions of each of the previous parts. One of these parts is the diencephalon which is the center of the whole brain and the responsible for the distribution of signals all around neural structures around it, we talk a little bit about the spinal cord and its construction and how the nerve are organized and symbolized by the scientists in the field.

In the second chapter, we delve deeper inside the structure mentioned before, where we talk about the major unit of the nervous system (CNS and PNS); that is the neuron, we give a brief definition to its components and the types of neuron existing according to those components or functions. After that we explain thoroughly the physiology of the neuron and introduce the term action potential to the scene where it was the main character of the play, by understanding the physiology we lay a platform for modelling and the reasons behind it and then we mention some of the famous and widely used neuron models.

In this project we focused on the two of the widely used models; Hodgkin and Huxley model and Integrate-and-Fire model, we use the Matlab programming language to provide a code for simulating the mentioned models. For the HH model code we use the original parameters from the experiments on the giant squid axon and we use the Euler method to calculate the derivation for the gating probability variables at each time step to use it plotting the evolution of the action potential and the conductances of the ionic gates.

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Abstract

Neuroscience has been the interest of the world since the beginning of the XX th century, that led to the birth of many theories and researches about neural structures. Neuron models made it easier for scientists from all related fields to understand how these structures work.

In this dissertation we define the anatomy of the central nervous system, and we delve deeper by studying neurons, its biology and physiology, as well as the models created to represent that physiology. Two of the models being the Integrate-and-Fire and the Hodgking&Huxley models, we simulate these models using the Matlab language and the built-in functions and tools that comes with it.

Keywords: neuron, model, Hodgking&Huxley, IF, MATLAB, physiology.

Résumé

Les neurosciences ont été l'intérêt du monde depuis le début du XXe siècle, qui a conduit à la naissance de nombreuses théories et les recherches sur les structures neuronales. Les modèles de neurones ont permis aux scientifiques de tous les domaines connexes de comprendre plus facilement le fonctionnement de ces structures. Dans cette mémoire, nous définissons l'anatomie du système nerveux central, et nous approfondissons en étudiant les neurones, sa biologie et sa physiologie, ainsi que les modèles créés pour représenter cette physiologie. Deux des modèles étant les modèles Intègre-et-Tire et Hodgking&Huxley, nous simulons ces modèles en utilisant le langage Matlab et les fonctions et outils intégrés qui l'accompagnent.

Mots clés : neurone, modèle, Hodgking&Huxley, Intègre-et-Tire, MATLAB.

ملخص

كان علم الأعصاب محط اهتمام العالم منذ بداية القرن العشرين ، مما أدى إلى ظهور العديد من النظريات والابحاث على الهياكل العصبية. سهلت نماذج الخلايا العصبية (العصبون) على العلماء في جميع المجالات ذات صلة لفهم كيفية عمل هذه الهياكل. في هذه المذكرة، نذكر تشريح الجهاز العصبي المركزي، ونتعمق من خلال دراسة الخلايا العصبية وبيولوجياتها وفيزيائياتها، وكذلك النماذج التي تم إنشاؤها لتمثيل هذا الفيزيائيات . اثنان من هذه النماذج هما نموذجي Integrate-and-Fire وHodgking&Huxley , حيث نقوم بمحاكاة هذه النماذج باستخدام لغة Matlab والوظائف والأدوات المدمجة مع البرنامج.

كلمات مفتاحية : عصبون, نموذج, ماتلاب,خلايا عصبية,Hodgking&Huxley .