MATHEMATICAL PHYSICS
Submitted: October 2020

ACTION POTENTIAL

PROJECT REPORT

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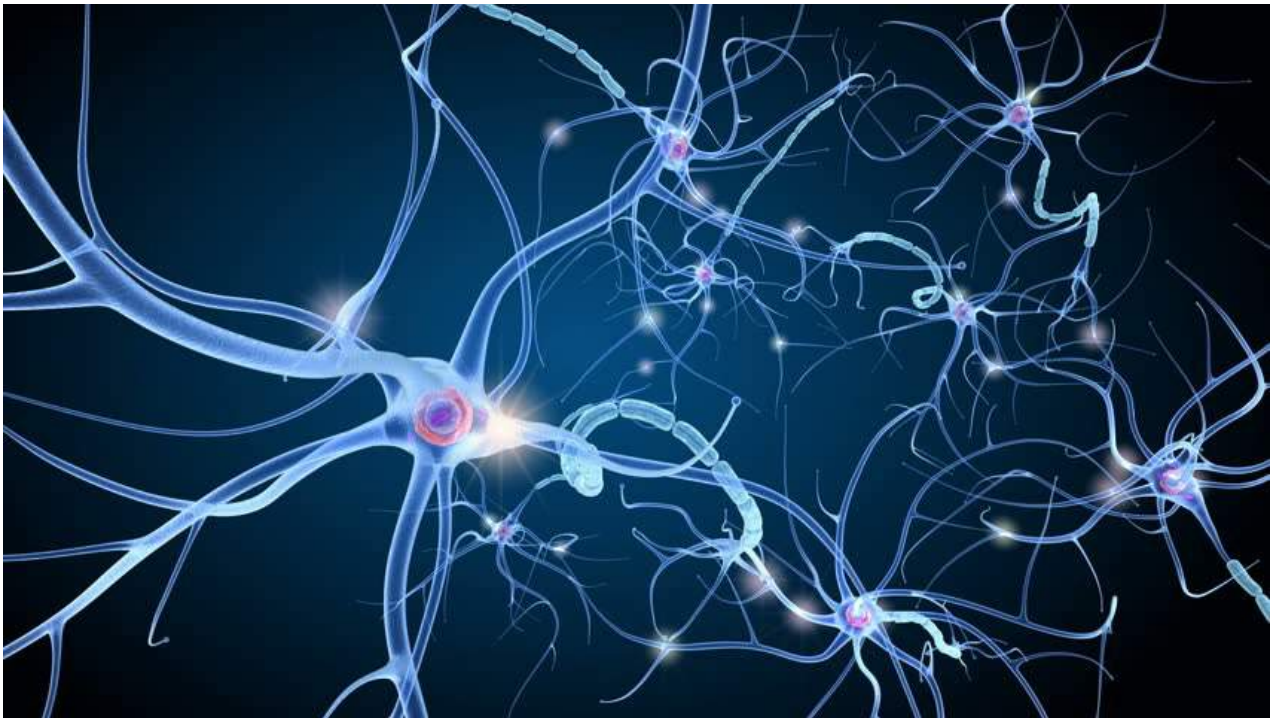

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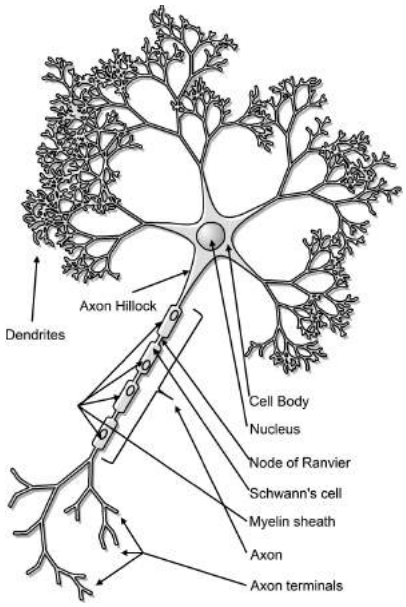
ABSTRACT—This Document presents an overview of Mathematical Models described for the Stimuli and Propagation of Action Potential in Cortical Nervous Tissues using Fundamental Laws of Physics. The agenda of fabricating this project is to illuminate a concept that inculcates the complete Sciences i.e.- Physics, Mathematics, Chemistry and Biology while majorly highlighting the Operations of Mathematical Modeling i.e. the Art of translating problems from an Application area into tractable Mathematical Formulations whose Theoretical and Numerical Analysis provides an insight, answers and guidance useful for the originating Application. Since, we present Mathematical Modeling , the topics that incurred in our Application were Partial Differential Equations, Numerical Analysis, Vector Calculus and Bifurcation Theory of Non-Dynamical Systems. Therefore a brief overview of all the mentioned topics can be found in the document.

EXCITABILITY— To understand electrical signaling in cells, it is helpful (and not too inaccurate) to divide all cells into two groups: excitable cells and non-excitable cells. Many cells maintain a stable equilibrium potential. For some, if currents are applied to the cell for a short period of time, the potential returns directly to its equilibrium value after the applied current is removed, known as Non-Excitable Cells.However, there are cells for which, if the applied current is sufficiently strong, the membrane potential goes through a large excursion, called an action potential, before eventually returning to rest. Such cells are called excitable.The most obvious advantage of excitability is that an excitable cell either responds in full to a stimulus or not at all, and thus a stimulus of sufficient amplitude may be reliably distinguished from background noise. In this way, noise is filtered out, and a signal is reliably transmitted.

THE NEURON— Neurons are the primary components of the Nervous System, which is further classified as Peripheral and Central Nervous Systems which can further be subdivided and studied.Neurons are the very cells in our body that are responsible for the propagation of Electrical Impulses which practically implies every move we make and every thought that incurs into our mind. There exist approximately 86 Billion neurons in the human brain.

The adjoining figure illustrates the structure of a neuron in detail , a major consideration is The Dendrite, The Cell Body ,The Axon, Nodes of Ranvier and The Myelin Sheath..



The Dendrites are projections of a neuron that propagate the Electrochemical Stimulation received from other neuronal cells to the Cell Body.

The Cell Body contains the Nucleus and is the site of synthesis of virtually all neurons proteins and membranes.

The Axon, known as the Nerve Fibre, is the portion of the nerve cell that carries nerve impulses away from the Cell Body towards its terminals.

The Myelin Sheath is an insulating Layer that forms around nerves and allows electrical impulses to transmit quickly and efficiently along the nerve cells.

The Nodes of Ranvier are gaps in the myelin coverage along Axons and consists of Voltage gated K^+ and Na^+ channels.

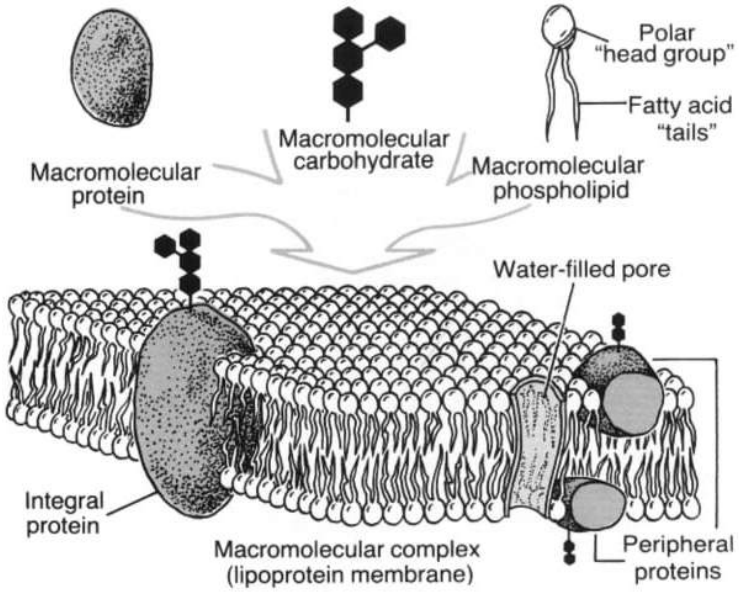
THE ACTION POTENTIAL— The relatively Static Membrane Potential of quiescent cells is known as the **Resting Potential**, it exists due to the differences in membrane permeabilities for Potassium, Sodium, Calcium and Chloride ions.Whereas, **Action Potential** is defined as a fast , transistors and propagating change of the Resting Membrane Potential ,it is essentially an explosion of electrical activity that is created by depolarizing current.

THE INITIATION— In the nervous system , a synapse is a structure that permits a neuron to pass an electrical or chemical signal to another neuron or to the target effector cell**.**While Neurotransmitters are chemical messengers released from synaptic vesicles into the synaptic cleft where they are received by neurotransmitter receptors on the target cell.

Now, when these neurotransmitters are detected by the receptors, there occurs a change in the potential of the extracellular fluid due to the chemical changes incorporated by the neurotransmitters.This lens to a change in the Resting Potential and hence may arise a possibility for the generation of the Action Potential.

ION CHANNELS AND MEMBRANES—The cell membrane provides a boundary separating the internal workings of the cell from its external environment. More importantly, it is selectively permeable, permitting the free passage of some materials and restricting the passage of others, thus regulating the passage of materials into and out of the cell. It consists of a double layer (a bilayer) of phospholipid molecules about 7.5 nm (75 angstroms) thick . The membrane also contains water-filled pores with diameters of about 0.8 nm, as well as protein-lined pores, called **Membrane Channels**, channels allow passage of specific molecules. Both the intracellular and extracellular environments consist of, among many other things, a dilute aqueous solution of dissolved salts, primarily NaCl and KCl, which dissociate into Na^+, K^+, and Cl^- ions. The cell membrane acts as a barrier to the free flow of these ions and maintains concentration differences of these ions.

Ionic transport is important for many cell processes, but is essential for neural phenomena. Ions and molecules can be moved by both active and passive processes. Water crosses the membrane passively through osmosis, which is controlled via ion concentrations, allowing the cell to regulate its volume. Ions



also cross the membrane passively via diffusion through pores. Differences in ion concentration drive water osmotically, and create an electrical potential across the membrane, known as the **membrane potential**. Active processes include pumps that exchange sodium in the cell for potassium and pumps that remove calcium from the cell. The pump works against concentration gradients, and so requires energy (in the form of ATP) to operate.

II ION MOVEMENT IN EXCITABLE CELLS

☐ *Mathematical Background Theory:*

Vector Calculus—

Line Integral—In mathematics, a line integral is an integral where the function to be integrated is evaluated along a curve. The terms path integral, curve integral, and curvilinear integral are also used; contour integral is used as well, although that is typically reserved for line integrals in the complex plane.

The function to be integrated may be a scalar field or a vector field. The value of the line integral is the sum of values of the field at all points on the curve, weighted by some scalar function on the curve (commonly arc length or, for a vector field, the scalar product of the vector field with a differential vector in the curve).This weighting distinguishes the line integral from simpler integrals defined on intervals.

In qualitative terms, a line integral in vector calculus can be thought of as a measure of the total effect of a given tensor field along a given curve. For example, the line integral over a scalar field (rank 0 tensor) can be interpreted as the area under the field carved out by a particular curve. This can be visualized as the surface created by z = f(x,y) and a curve C in the xy plane. The line integral of f would be the area of the "curtain" created—when the points of the surface that are directly over C are carved out.

For a vector field $F : U \subseteq R^n \to R^n$, the line integral along a piecewise smooth curve $C \subset U$, in the direction of r, is defined as

$$\int_C \mathbf{F}(\mathbf{r}) \cdot d\mathbf{r} = \int_a^b \mathbf{F}(\mathbf{r}(t)) \cdot \mathbf{r}'(t)\, dt.$$

where · is the dot product, and r: [a, b] → C is a bijective parametrization of the curve C such that r(a) and r(b) give the endpoints of C.

A line integral of a scalar field is thus a line integral of a vector field, where the vectors are always tangential to the line.

Line integrals of vector fields are independent of the parametrization r in absolute value, but they do depend on its orientation. Specifically, a reversal in the orientation of the parametrization changes the sign of the line integral.

Fundamental Theorem of Line Integrals— One way to write the Fundamental Theorem of Calculus is:

$$\int_a^b f'(x)\,dx = f(b) - f(a).$$

That is, to compute the integral of a derivative f′ we need only compute the values of f at the endpoints. Something similar is true for line integrals of a certain form.

The Fundamental Theorem of Line Integrals states that suppose a curve C is given by the vector function r(t), with a=r(a) and b=r(b). Then,

$$\int_C \nabla f \cdot d\mathbf{r} = f(\mathbf{b}) - f(\mathbf{a}),$$

Proof.

We write $\mathbf{r} = \langle x(t), y(t), z(t)\rangle$, so that $\mathbf{r}' = \langle x'(t), y'(t), z'(t)\rangle$. Also, we know that $\nabla f = \langle f_x, f_y, f_z\rangle$. Then

$$\int_C \nabla f \cdot d\mathbf{r} = \int_a^b \langle f_x, f_y, f_z\rangle \cdot \langle x'(t), y'(t), z'(t)\rangle\,dt = \int_a^b f_x x' + f_y y' + f_z z'\,dt.$$

By the chain rule, $f_x x' + f_y y' + f_z z' = df/dt$,

where f in the context means f(x(t), y(t), z(t)), a function of t. In other words all we have is,

$$\int_a^b f'(t)\,dt = f(b) - f(a).$$

In this context, $f(a) = f(x(a), y(a), z(a))$. Since $\mathbf{a} = \mathbf{r}(a) = \langle x(a), y(a), z(a)\rangle$, we can write $f(a) = f(\mathbf{a})$—this is a bit of a cheat, since we are simultaneously using f to mean $f(t)$ and $f(x, y, z)$, and since $f(x(a), y(a), z(a))$ is not technically the same as $f(\langle x(a), y(a), z(a)\rangle)$, but the concepts are clear and the different uses are compatible. Doing the same for b, we get

$$\int_C \nabla f \cdot d\mathbf{r} = \int_a^b f'(t)\,dt = f(b) - f(a) = f(\mathbf{b}) - f(\mathbf{a}).$$

This theorem, like the Fundamental Theorem of Calculus, says roughly that if we integrate a "derivative-like function" (f′ or ∇f) the result depends only on the values of the original function (f) at the endpoints.
If a vector field F is the gradient of a function,F=∇f , we say that F is a conservative vector field. If F is a conservative force field, then the integral for work,∫ c F·dr , is in the form required by the Fundamental Theorem of Line Integrals. This means that in a conservative force field, the amount of work required to move an object from point a to point b depends only on those points, not on the path taken between them.

Divergence and Curl— are two measurements of vector fields that are very useful in a variety of applications.divergence measures the tendency of the fluid to collect or disperse at a point, and curl measures the tendency of the fluid to swirl around the point. Divergence is a scalar, that is, a single number, while curl is itself a vector. The magnitude of the curl measures how much the fluid is swirling, the direction indicates the axis around which it tends to swirl.
The gradient of f is defined as:

$$\nabla f = \left\langle \frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z} \right\rangle.$$

A useful mnemonic for this (and for the divergence and curl, as it turns out) is to let

$$\nabla = \left\langle \frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right\rangle,$$

that is, we pretend that ∇ is a vector with rather odd looking entries. Recalling that $\langle u, v, w\rangle a = \langle ua, va, wa\rangle$, we can then think of the gradient as

$$\nabla f = \left\langle \frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right\rangle f = \left\langle \frac{\partial f}{\partial x}, \frac{\partial f}{\partial y}, \frac{\partial f}{\partial z} \right\rangle,$$

that is, we simply multiply the f into the vector.

The divergence and curl can now be defined in terms of this same odd vector ∇ by using the cross product and dot product. The divergence of a vector field $\mathbf{F} = \langle f, g, h\rangle$ is

$$\nabla \cdot \mathbf{F} = \left\langle \frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z} \right\rangle \cdot \langle f, g, h\rangle = \frac{\partial f}{\partial x} + \frac{\partial g}{\partial y} + \frac{\partial h}{\partial z}.$$

The curl of $\mathbf{F}$ is

$$\nabla \times \mathbf{F} = \begin{vmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial z} \\ f & g & h \end{vmatrix} = \left\langle \frac{\partial h}{\partial y} - \frac{\partial g}{\partial z}, \frac{\partial f}{\partial z} - \frac{\partial h}{\partial x}, \frac{\partial g}{\partial x} - \frac{\partial f}{\partial y} \right\rangle.$$

DIVERGENCE THEOREM—
Suppose V is a subset of Rn (in the case of n = 3, V represents a volume in three-dimensional space) which is compact and has a piecewise smooth boundary S (also indicated with ∂V = S). If F is a continuously differentiable vector field defined on a neighborhood of V, then

$$\iiint_V (\nabla \cdot \mathbf{F})\, dV = \oiint_S (\mathbf{F} \cdot \mathbf{n})\, dS.$$

The left side is a volume integral over the volume V, the right side is the surface integral over the boundary of the volume V. The closed manifold ∂V is oriented by outward-pointing normals, and n is the outward pointing unit normal at each point on the boundary ∂V. (dS may be used as a shorthand for ndS.) In terms of the intuitive description above, the left-hand side of the equation represents the total of the sources in the volume V, and the right-hand side represents the total flow across the boundary S.

☐ *Physical Laws That Dictate Ion Movement:*

▶ FICK's Law of Diffusion—

"

Diffusion takes place *down* the concentration gradient and is *everywhere* directly proportional to the magnitude of that gradient, with proportionality constant *D*.

"

$$J_{\text{diff}} = -D\frac{\partial[\text{C}]}{\partial x},$$

where *J* is diffusion flux (molecules/sec-cm^2); *D* is the diffusion coefficient (cm^2/sec); and [C] is the concentration of ion (molecules/cm3). The negative sign indicates that J flows from high to low concentration. Concentrations are used for dilute solutions; otherwise the activity of solutes should be used.

▶ OHM's Law for Drift—

Charged particles (e.g., ions) in a system will experience an additional force, resulting from the interaction of their electric charges and the electric field in the biological environment. The flow of charged particles in an electric field can be described by

$$\begin{aligned} J_{\text{drift}} &= \partial_{el} E \\ &= -\mu z[\text{C}]\frac{\partial V}{\partial x}, \end{aligned}$$

where /drift is the drift flux (molecules/sec-cm2), del is electrical conductivity (molecules/V-sec-cm), E is electric field (V/cm) = -dV/dt, V is electric potential (V), ц is mobility (cm2/V-sec), z is the valence of the ion (dimensionless), and [C] is the concentration.

The equation states drift of positively charged particles takes place down the electric potential gradient and is everywhere directly proportional to the magnitude of that gradient, with the proportionality constant equal to цz[C].

The Einstein Relation Between Diffusion and Mobility—

Einstein in 1905 described diffusion as a random walk process. He demonstrated that the frictional resistance exerted by the fluid medium is the same for drift as it is for diffusion at thermal equilibrium, and diffusion coefficient and mobility can be related by,

$$D = \frac{kT}{q}\mu,$$

where κ is Boltzmann's constant (1.38 x 10^{23} joule/ °K), T is absolute temperature (°K), and q is the charge of the molecule (C).

This relationship formally states that diffusion and drift processes in the same medium are additive, because the resistances presented by the medium to the two processes are the same. This relationship greatly simplifies the quantitative descriptions of ion movement in biological systems, since ions in living cells usually are influenced by both concentration and electric potential gradients.

Space-Charge Neutrality—

In a given volume, the total charges of cations is *approximately* equal to the total charge of anions, i.e.,

$$\sum_i z_i^C e[C_i] = \sum_j z_j^A e[C_j],$$

where z_i^c is the valence of cation species *i,* z^A_j is the valence of anion species *j, e* is the charge of a monovalent ion; and [Q] and [C*j]* are concentrations of ion species.

Space-charge neutrality holds for most parts of living bodies. The only exception is within the cell membrane due to separation of charges. The amount of uncompensated ions needed to charge the electric field across the membrane is very small. Even for the smallest cells, more than 99.9% of all ions are compensated by ions of the opposite

$$\int_\Omega \frac{\partial c}{\partial t}\, dV = \int_\Omega (q - \nabla \cdot \mathbf{J})\, dV.$$

charge. The principle of space-charge neutrality therefore holds in any volume in the biological system except within the plasma membrane.

☐ *The Nernst Equation—*

Under physiological conditions, ion movement across the membrane is influenced by both electrical field and concentration gradients. This is because ion concentrations inside and outside the cell are different, and electric field is nonzero within the plasma membrane due to separation of charges across the membrane.

Separation of ions across a cell membrane is caused by selective permeability, usually to K^+ , of the cell membrane. This allows K+ ions to diffuse out of the cell, down their concentration gradient ($[K^+]m > [K^+]out$)» resulting in net negative charges inside the cell and positive charges outside the cell. Such charge separation results in the electric field across the membrane pointing inward while the membrane is at rest.

Since diffusion plays such an important role in determining intracellular ionic concentrations, we briefly examine a mathematical model of it. This discussion will also introduce another kind of mathematical model: a partial differential equation (PDE). Given a region of space Ω, we denote by c = c(x, t) the concentration of the ion of interest as a function of space and time over Ω. Letting q be the production of c per unit volume defined over Ω and J the vector flux of c defined along the boundary of Ω, with n the unit normal to the boundary, we obtain the following conservation law:

$$\frac{\partial}{\partial t}\int_\Omega c\, dV = \int_\Omega q\, dV - \int_{\partial\Omega} \mathbf{J}\cdot\mathbf{n}\, dA.$$

The Equation essentially states that : the rate of change of c in Ω = production − loss through boundary: this is an example of a conservation law.)
By the divergence theorem,,as referred above, we have

$$\int_{\partial\Omega} \mathbf{J}\cdot\mathbf{n}\, dA = \int_\Omega \nabla\cdot\mathbf{J}\, dV,$$

so that for a fixed region Ω becomes

$$\frac{\partial c}{\partial t} = q - \nabla\cdot\mathbf{J}.$$

This integral conservation law holds for any fixed region Ω, and since the region is arbitrary, the integrand must be identically zero. We therefore obtain a partial differential equation (PDE) describing the rate of change of c:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + q.$$

To close this equation, we need an expression for the ion flux J, in terms of c. Fick's law, as referenced above, matches our intuitive understanding that ions tend to flow from regions of high concentration to those of low concentration. Substituting Fick's law with diffusion coefficient D into, we obtain

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D \frac{\partial c}{\partial x}\right) + q,$$

and if D is constant, the right hand side may be written D $\partial^2 c/\partial x^2$: the classical "heat equation" first proposed by Fourier to describe heat conduction. In steady state, with no local production (eg: release of bound ions such as Ca^{2+} from the endoplasmic reticulum), the concentration profile is linear. This is easily checked.

The ion flux under the influence of both concentration gradient and electric field can be written by combining the diffusion and drift flux, i.e.,

$$\begin{aligned} J &= J_{\text{drift}} + J_{\text{diff}} \\ &= -\mu z[\mathrm{C}]\frac{\partial V}{\partial x} - D\frac{\partial[\mathrm{C}]}{\partial x}. \end{aligned}$$

By using Einstein's relation, we can express the diffusion coefficient in terms of mobility, and thus simplify the flux equation.

$$J = -\left(\mu z[\mathrm{C}]\frac{\partial V}{\partial x} + \frac{\mu k T}{q}\frac{\partial[\mathrm{C}]}{\partial x}\right).$$

The above Equation is the Nernst-Planck equation (NPE) of the ion flux form (J is in molecules/ sec-cm^2). If one divides J by Avogadro's number, one can obtain the NPE of the molar form. NPE in molar form:

$$\begin{aligned} \mathbf{J} &= J/N_A = \frac{-\mu z[\mathrm{C}]}{N_A}\frac{\partial V}{\partial x} - \frac{\mu k T}{N_A q}\frac{\partial[\mathrm{C}]}{\partial x} \\ &= -\left(u z[\mathrm{C}]\frac{\partial V}{\partial x} + u\frac{RT}{\mathrm{F}}\frac{\partial[\mathrm{C}]}{\partial x}\right). \end{aligned}$$

Since current is the product of ion flux and the charge it carries, the NPE of the current density form can be obtained by multiplying the molar flux by the total molar charge, zF. NPE in current density form:

$$I = \mathbf{J} \cdot zF = -\left(uz^2F[\mathrm{C}]\frac{\partial V}{\partial x} + uzRT\frac{\partial[\mathrm{C}]}{\partial x}\right)$$

where J is expressed in mol/sec-cm2; NA is Avogadro's number (6.02 x 1023/mol); R is the gas constant (1.98 cal/°K-mol); F is Faraday's constant (96,480 C/mol); и is ц/NA : molar mobility (cm2/V-sec-mol); and I 2 is A/cm .

The Nernst-Planck equation describes the ionic current flow driven by electrochemical potentials (concentration gradient and electric field). The negative sign indicates that I flows in the opposite direction as f^ and in the opposite (same) direction as if z is positive (negative). This equation describes the passive behavior of ions in biological systems. Ions flow down their concentration gradients and the electric fields. It is the equation that is most widely used for ion flux in neurophysiology. In later sections and chapters, we will apply this equation to many physiological conditions. Several fundamental equations describing electric current flow across the membrane will be derived from this equation.

The NPE gives the explicit expression of ionic current in terms of concentration and electric potential gradients. If one examines the electric current across the cell membrane, it is very important to determine under what condition the net cross-membrane current is zero, i.e., the membrane is at rest. This condition can easily be derived from the NPE by setting the total cross-membrane current to zero, i.e.,

$$I = -\left(uz^2F[\mathrm{C}]\frac{\partial V}{\partial x} + uzRT\frac{\partial[\mathrm{C}]}{\partial x}\right) = 0.$$

$$\frac{\partial V}{\partial x} = \frac{-RT}{zF}\frac{1}{[\mathrm{C}]}\frac{\partial[\mathrm{C}]}{\partial x} \rightarrow \int_{x_1}^{x_2}\frac{dV}{dx}dx = -\frac{RT}{zF}\int_{x_1}^{x_2}\frac{d[\mathrm{C}]}{[\mathrm{C}]dx}dx.$$

Change variables:

$$\int_{V_1}^{V_2} dV = -\frac{RT}{zF}\int_{[\mathrm{C}]_1}^{[\mathrm{C}]_2}\frac{d[\mathrm{C}]}{[\mathrm{C}]}.$$

Therefore,

$$V_2 - V_1 = -\frac{RT}{zF}ln\frac{[\mathrm{C}]_2}{[\mathrm{C}]_1}.$$

The membrane potential of a cell is defined

$$V_m \stackrel{\text{def}}{=} V_{\text{in}} - V_{\text{out}}.$$

The equilibrium potential of ion i, defined as the cross-membrane potential at which membrane current carried by ion i equals zero, is therefore

$$E_i = V_m(I_i = 0) \stackrel{\text{def}}{=} V_{\text{in}} - V_{\text{out}} = \frac{RT}{zF} \ln \frac{[\text{C}]_{\text{out}}}{[\text{C}]_{\text{in}}}$$

☐ *Transport of Ions—*

There are proteins in the plasma membrane of most animal cells that are capable of pumping ions from one side of the membrane to the other, often against their concentration gradients. The actions of such proteins often consume energy, which in some cases comes from the chemical potential of other ions.

Ions whose concentration gradients are maintained through their Plasma Membranes are said to be ***actively distributed.***

Ion Distribution that does not require any energy as stated above in the care of Active Distribution, is called ***Passive Distribution****.*

If a cell membrane is permeable to several ion species, and if no active transport is present for these ions, the ions are said to be *passively distributed* and the membrane potential of this cell should be equal to the equilibrium potential (determined by Nernst equation) of each of these ions, i.e.,

$$V_m = \frac{RT}{zF} \ln \frac{[\text{C}]_{\text{out}}}{[\text{C}]_{\text{in}}}$$

for all permeable ions,

Let C^{+m} = cation of valence m ; A^{-n} = anion of valence n. Then

$$\left[\frac{C_{\text{out}}^{+m}}{C_{\text{in}}^{+m}}\right]^{\frac{1}{m}} = \left[\frac{A_{\text{in}}^{-n}}{A_{\text{out}}^{-n}}\right]^{\frac{1}{n}}.$$

This is the Donnan rule of equilibrium,

Taking the example of the frog muscle, where K^+ and Cl^- are the two permeable ions at rest, then at Donnan equilibrium,

$$\frac{[\text{K}^+]_{\text{out}}}{[\text{K}^+]_{\text{in}}} = \frac{[\text{Cl}^-]_{\text{in}}}{[\text{Cl}^-]_{\text{out}}}.$$

In most cells, there are a sizable number of negatively charged molecules (A^-, proteins, etc.) in the cytoplasm that are not permeant to the membrane, and because of space-charge neutrality,

$$[K^+]_{in} = [Cl^-]_{in} + [A^-]_{in} \text{ and } [K^+]_{out} = [Cl^-]_{out}.$$

These relations plus the Donnan rule for K^+ and Cl^- yield

$$[K^+]_{in}^2 = [K^+]_{out}^2 + [A^-]_{in}[K^+]_{in}.$$

Therefore,

$$[K^+]_{in} > [K^+]_{out} \text{ and } [Cl^-]_{out} > [Cl^-]_{in}.$$

These results indicate that even without active transporters, the concentration of K^+ inside is higher than that outside of the cell, and the opposite is true for Cl^- .

The origin of these ion distribution differences is the existence of intracellular impermeable anions. These anions attract more K+ into the cell and expel more CI- out of the cell, in accordance with the principles of space-charge neutrality.

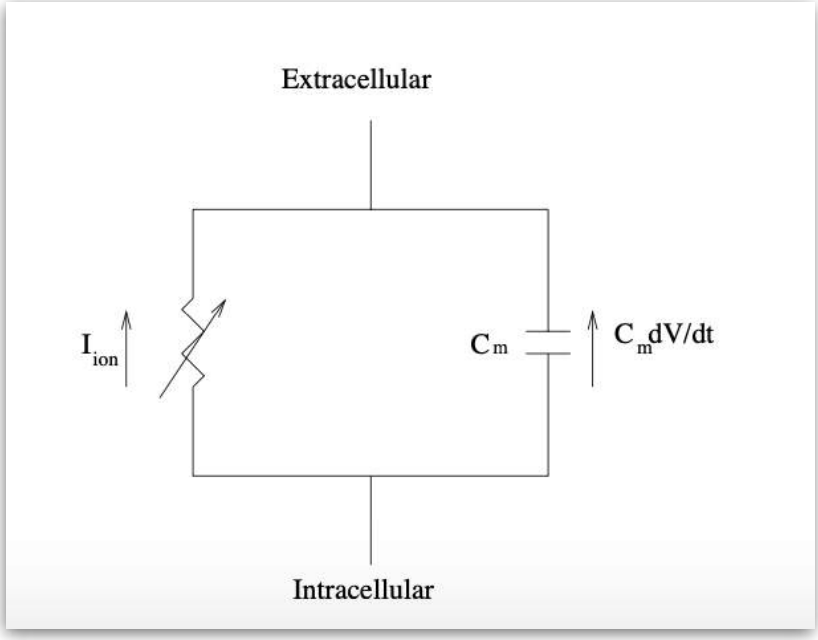
In conclusion, the concentration gradients across the membrane of animal cells are maintained by two processes. In some cells, active trans- porters are abundant and thus ions are mainly distributed actively across the membrane. In other cells, where fewer transporters exist, passive distribution may take a substantial role in maintaining concentration gradients across the cell membrane.

☐ *Relation Between Membrane Current and Potential—*

Assuming that the membrane has constant capacitance per unit area, the cross-membrane ion current is proportional to the rate of change of membrane potential, with the capacitance the constant of proportionality. There is also a negative sign, since a positive current (outward), results in reduced potential inside the cell:

$$C_m \frac{dV}{dt} = -I_{ion}. \tag{A.}$$

The above Equation can be understood from Kirchhoff's loop law applied to the circuit of Fig. below. The ionic current depends on the membrane conductance for that ion, as well as the Nernst and membrane potentials. Each ion has its own Nernst potential, and since different channels are permeable to specific ions, each ion has a different membrane conductance, which usually depends on the membrane potential. Various conductance forms are used in the H-H model.


Extracellular
I_{ion}
C_m
$C_m dV/dt$
Intracellular

III HODGKIN - HUXELY MODEL

The last equation defined, essentially described how the cell membrane can be modeled as a capacitor in parallel with an ionic current, resulting in the equation

$$C_m \frac{dV}{dt} = -I_{ion}.$$

where V, generally, denotes the internal minus the external potential ($V = V_i - V_e$). In the squid giant axon, as in many neural cells, the principal ionic currents are the Na^+ current and the K^+ current. Although there are other ionic currents, primarily the Cl^- current, in the Hodgkin–Huxley theory they are small and lumped together into one current called the *leakage current*. Since the instantaneous *I–V* curves of open Na^+ and K^+ channels in the squid giant axon are approximately linear, the above equation becomes

$$C_m \frac{dv}{dt} = -\bar{g}_K n^4 (v - v_K) - \bar{g}_{Na} m^3 h (v - v_{Na}) - \bar{g}_L (v - v_L) + I_{app}$$

where I_{app} is the applied current.

The above equation is a first-order ordinary differential equation and can be written in the form :

$$C_m \frac{dV}{dt} = -g_{eff}(V - V_{eq}) + I_{app}$$

where $g_{eff} = g_{Na} + g_K + g_L$ and $V_{eq} = (g_{Na}V_{Na} + g_K V_K + g_L V_L)/g_{eff}$.

V_{eq} – the membrane resting potential and is a balance between the reversal potentials for the three ionic currents.

In fact, at rest, the Na^+ and leakage conductances are small compared to the K^+ conductance, so that the resting potential is close to the K^+ equilibrium potential. The quantity $R_m = 1/g_{eff}$, the passive membrane resistance, is on the order of 1000 Ω ^{2} cm . The time constant for this equation is

$$\tau_m = C_m R_m$$

in regards of 1 msec. It follows that, with a steady applied current, the membrane potential should equilibrate quickly to

$$V = V_{\text{eq}} + R_m I_{\text{app}}.$$

For sufficiently small applied currents this is indeed what happens. However, for larger applied currents the response is quite different, the only possible explanation for these differences is that the conductances are not constant but depend in some way on the voltage.

Voltage and Time Dependency on Conductances—

- The key step to sorting out the dynamics of the conductances came from the development of the voltage clamp. A voltage clamp fixes the membrane potential, usually by a rapid step from one voltage to another, and then measures the current that must be supplied in order to hold the voltage constant.
- Since the supplied current must equal the transmembrane current, the voltage clamp provides a way to measure the transient transmembrane current that results.
- The crucial point is that the voltage can be stepped from one constant level to another, and so the ionic currents can be measured at a constant, known, voltage. Thus, even when the conductances are functions of the voltage (as is actually the case), a voltage clamp eliminates any voltage changes and permits measurement of the conductances as functions of time only.
- Hodgkin and Huxley found that when the voltage was stepped up and held fixed, at a higher level, the total ionic current was initially inward, but at later times an outward current developed.
- They argued that the initial inward current is carried almost entirely by Na^+, while the outward current that develops later is carried largely by K^+
- Hodgkin and Huxley were able to use a clever trick to separate the total ionic current into its constituent ionic parts. They replaced 90% of the extracellular Na+ in the normal seawater bath with choline (a viscous liquid vitamin B complex found in many animal and vegetable tissues), which rendered the axon non-excitable but changed the resting potential only slightly. Since it is assumed that immediately after the voltage has been stepped up, the ionic current is all carried by Na^+, it is possible to measure
- The initial Na^+ currents in response to a voltage step. Note that although the Na^+ currents can be measured directly immediately after the voltage step, they cannot be measured directly over a longer time period, as the total ionic current begins to include a contribution from the K^+ current.

- If we denote the Na^+ currents for the two cases of normal extracellular$Na^+$and zero extracellular Na^+ by $I_N{}^1{}_a$ an $I_N{}^2{}_a$ respectively ,then the ratio of the two currents,

$$I^1_{\mathrm{Na}}/I^2_{\mathrm{Na}} = K$$

- Next, Hodgkin and Huxley made two further assumptions. First, they assumed that the Na+ current ratio K is independent of time and is thus constant over the course of each voltage clamp experiment. In other words, the amplitude and direction of the Na+ current may be affected by the low extracellular Na+ solution, but its time course is not. Second, they assumed that the K+ channels are unaffected by the change in extracellular Na+ concentration. There is considerable evidence that the Na+ and K+ channels are independent. To complete the argument, since $I_{\mathrm{ion}} = I_{\mathrm{Na}} + I_{\mathrm{K}}$, and $I^1 = I^2$, it follows that $I^1 - I^1 = I^2 - I^2$, and K K ion Na ion Na

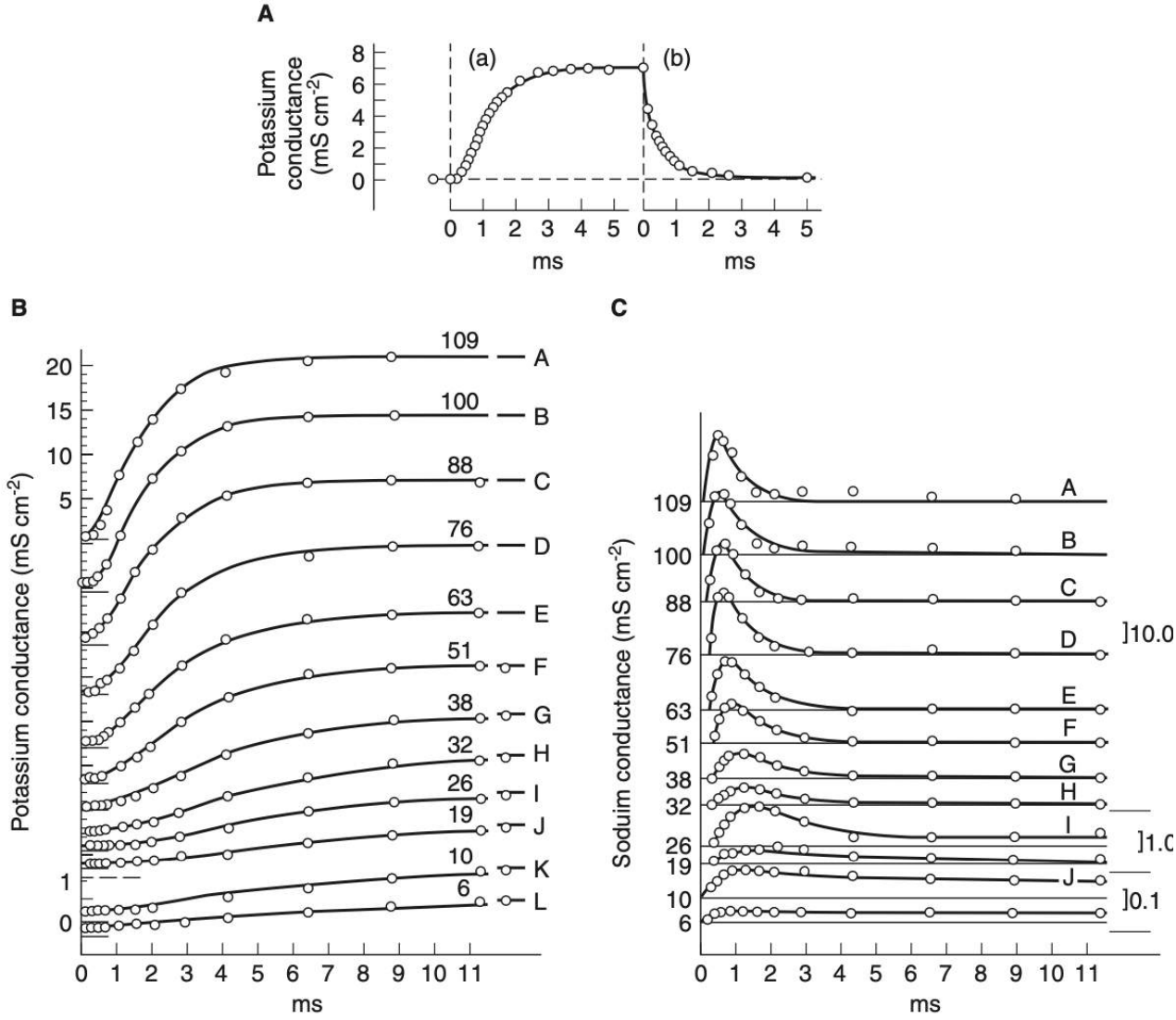
$$I^1_{\mathrm{Na}} = \frac{K}{K-1}(I^1_{\mathrm{ion}} - I^2_{\mathrm{ion}}),$$
$$I_{\mathrm{K}} = \frac{I^1_{\mathrm{ion}} - KI^2_{\mathrm{ion}}}{1-K}.$$

- Hence, given measurements of the total ionic currents in the two cases, and given the ratio K of the Na^+ currents, it is possible to determine the complete time courses of both the Na^+ and K^+ currents. Finally, from knowledge of the individual currents, one obtains the conductances as

$$g_{\mathrm{Na}} = \frac{I_{\mathrm{Na}}}{V - V_{\mathrm{Na}}}, \qquad g_{\mathrm{K}} = \frac{I_{\mathrm{K}}}{V - V_{\mathrm{K}}}.$$

- Samples of Hodgkin and Huxley's data are shown in Fig. The plots show ionic conductances as functions of time following a step increase or decrease in the membrane potential.

- The important observation is that with voltages fixed, the conductances are time-dependent. For example, when V is stepped up and held fixed at a higher level, g_{K} does not increase instantaneously, but instead increases over time to a final steady level.Both the time constant of the increase and the final value of g_{K} are dependent on the value to which the voltage is stepped. Further, g_{K} increases in a sigmoidal fashion, with



a slope that first increases and then decreases. Following a step decrease in the voltage, g_K falls in a simple exponential fashion .

☐ This particular feature of g_K—a sigmoidal increase coupled with an exponential decrease—is important in what follows when we model g_K. The behavior of g_{Na} is more complex. Following a step increase in voltage, g_{Na} first increases, but then decreases again, *all at the same fixed voltage*. Hence, the time dependence of g_{Na} requires a more complex model than for that of g_K.

The Potassium Conductance—

From the experimental data , it is reasonable to expect that g_K obeys some differential equation,

$$\frac{dg_K}{dt} = f(v,t)$$

say, where $v = V - V_{eq}$; i.e., v is the difference between the membrane potential and the resting potential.

Hodgkin and Huxley realized that it would be easier to write g_K as some power of a different variable, n say, where n satisfies a first-order differential equation. Thus, they wrote

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

for some constant g^- . The fourth power was chosen not for physical reasons, K but because it was the smallest exponent that gave acceptable agreement with the experimental data. The secondary variable n obeys the differential equation

$$\tau_n(v)\frac{dn}{dt} = n_\infty(v) - n, \tag{A.}$$

for some functions $\tau_n(v)$ and $n_\infty(v)$ that must be determined from the experimental data in a manner that is described below. Equation (A.) is often written in the form

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

$$\begin{aligned} n_\infty(v) &= \frac{\alpha_n(v)}{\alpha_n(v)+\beta_n(v)}, \\ \tau_n(v) &= \frac{1}{\alpha_n(v)+\beta_n(v)}. \end{aligned} \tag{B.}$$

At elevated potentials $n(t)$ increases monotonically and exponentially toward its resting value, thereby turning on, or *activating*, the K^+ current. Since the Nernst potential is

below the resting potential, the K^+ current is an outward current at potentials greater than rest. The function $n(t)$ is called the K^+ *activation*.

It is instructive to consider in detail how such a formulation for g_K results in the required sigmoidal increase and exponential decrease. Suppose that at time $t = 0$, v is increased from 0 to v_0 and then held constant, and suppose further that n is at steady state when $t = 0$, i.e., $n(0) = n_\infty(0)$. For simplicity, we assume that $n_\infty(0) = 0$, although this assumption is not necessary for the argument. Solving (B.) then gives

$$n(t) = n_\infty(v_0)\left[1 - \exp\left(\frac{-t}{\tau_n(v_0)}\right)\right]$$

which is an increasing curve (with monotonically decreasing slope) that approaches its maximum at $n_\infty(v_0)$. Raising n to the fourth power gives a sigmoidally increasing curve as required. Higher powers of n result in curves with a greater maximum slope at the point of inflection. However, in response to a step decrease in v, from v_0 to 0 say, the solution for n is

$$n(t) = n_\infty(v_0)\exp\left(\frac{-t}{\tau_n(0)}\right)$$

in which case n^4 is exponentially decreasing, with no inflection point.

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

The Sodium Conductance—

The time dependence for the Na^+ conductance is more difficult to unravel. From the experimental data it is suggested that there are two processes at work, one that turns on the Na^+ current and one that turns it off. Hodgkin and Huxley proposed that the Na^+ conductance is of the form

$$g_{Na}(v) = \bar{g}_{Na} m^3 h,$$

and they fitted the time-dependent behavior of m and h to exponentials with dynamic

$$\frac{dw}{dt} = \alpha_w(1 - w) - \beta_w w,$$

where w = m or h. Because m is small at rest and first increases, it is called the sodium activation variable, and because h shuts down, or inactivates, the Na+ current, it is called the sodium inactivation variable. When h = 0, the Na+ current is completely inactivated.

The Hodgkin Huxley Equations—

The Hodgkin–Huxley equations for the space-clamped axon are—

$$C_m \frac{dv}{dt} = -\bar{g}_{\mathrm{K}} n^4 (v - v_{\mathrm{K}}) - \bar{g}_{\mathrm{Na}} m^3 h (v - v_{\mathrm{Na}}) - \bar{g}_{\mathrm{L}} (v - v_{\mathrm{L}}) + I_{\mathrm{app}}$$

$$\begin{aligned}
\frac{dm}{dt} &= \alpha_m (1 - m) - \beta_m m, \\
\frac{dn}{dt} &= \alpha_n (1 - n) - \beta_n n, \\
\frac{dh}{dt} &= \alpha_h (1 - h) - \beta_h h.
\end{aligned}$$

The specific functions α and β proposed by Hodgkin and Huxley are, in units of $(\mathrm{ms})^{-1}$

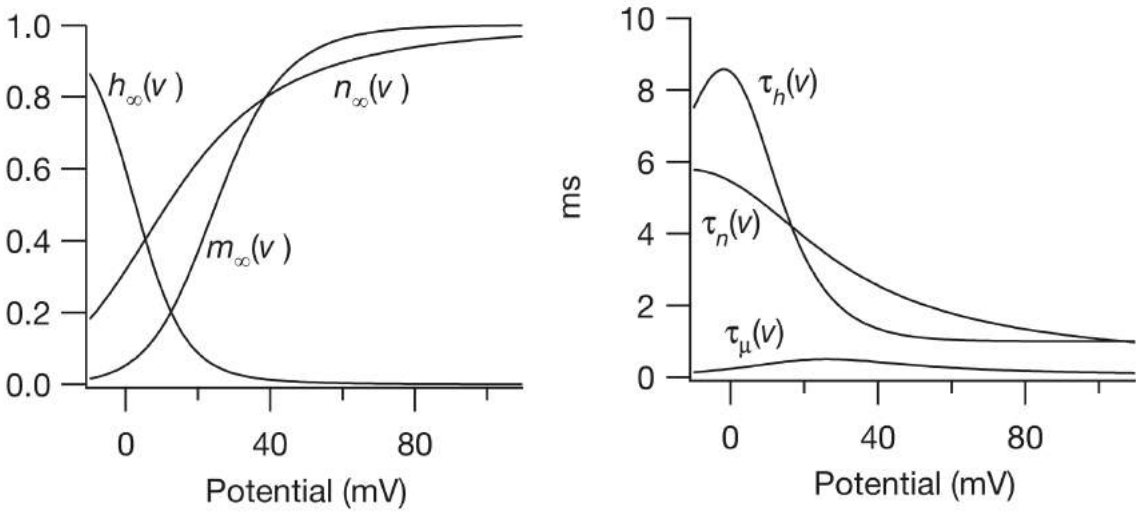
$$\begin{aligned}
\alpha_m &= 0.1 \frac{25 - v}{\exp\left(\frac{25 - v}{10}\right) - 1}, \\
\beta_m &= 4 \exp\left(\frac{-v}{18}\right), \\
\alpha_h &= 0.07 \exp\left(\frac{-v}{20}\right), \\
\beta_h &= \frac{1}{\exp\left(\frac{30 - v}{10}\right) + 1}, \\
\alpha_n &= 0.01 \frac{10 - v}{\exp\left(\frac{10 - v}{10}\right) - 1}, \\
\beta_n &= 0.125 \exp\left(\frac{-v}{80}\right).
\end{aligned}$$

For these expressions, the potential v is the deviation from rest ($v = V - V_{eq}$), measured in units of mV, current density is in units of μA/cm^2, conductances are in units of mS/cm^2, and capacitance is in units of μF/cm . The remaining parameters are:

$$\bar{g}_{Na} = 120, \qquad \bar{g}_K = 36, \qquad \bar{g}_L = 0.3, \qquad C_m = 1,$$

with (shifted) equilibrium potentials $v_{Na} = 115$, $v_K = -12$, and $v_L = 10.6$.

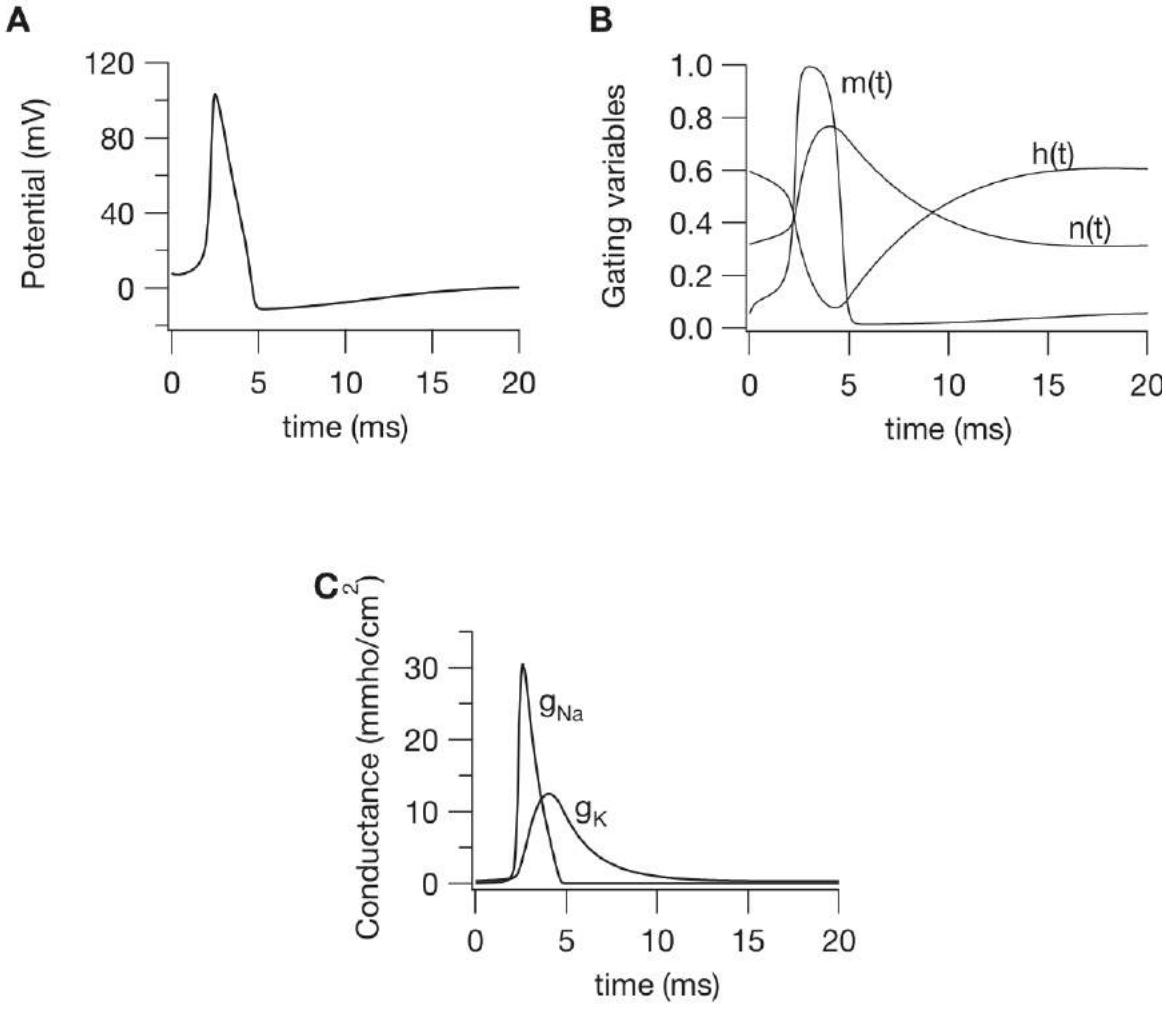
For example, the Hodgkin–Huxley Na+ gating equations can be derived from the assumption that the Na^+ channel consists of three "m" gates and one "h" gate, each of which can be either closed or open. If the gates operate independently, then the fraction of open Na+ channels is m^3h, where m and h obey the equation of the two-state channel model. Similarly, if there are four "n" gates per K^+ channel, all of which must be open for K^+ to flow, then the fraction of open K+ channels is n^4.



The Actual Process—

- If g_{Na} and g_K were constant, that would be the end of the story. The equilibrium at $v = 0$ would be a stable equilibrium, and, following any stimulus, the potential would return exponentially to rest.
- But since g_{Na} and g_K can change, the different currents can exert their respective influences. The actual sequence of events is determined by the dynamics of m, n, and h.
- The most important observation for the moment is that $\tau_m(v)$ is much smaller than either $\tau_n(v)$ or $\tau_h(v)$, so that $m(t)$ responds much more quickly to changes in v than either n or h.

- We can now understand why the Hodgkin–Huxley system is an excitable system. As noted above, if the potential v is raised slightly by a small stimulating current, the system returns to its stable equilibrium.
- However, during the period of time that the potential v is elevated, the Na+ activation m tracks m∞(v). If the stimulating current is large enough to raise the potential and therefore m∞(v) to a high enough level (above its threshold), then before the system can return to rest, m will increase sufficiently to change the sign of the net current, resulting in an autocatalytic inward Na+ current. Now, as the potential rises, m continues to rise, and the inward Na+ current is increased, further adding to the rise of the potential.
- If nothing further were to happen, the potential would be driven to a new equilibrium at v_{Na}. However, here is where the difference in time constants plays an important role.
- When the potential is at rest, the Na+ inactivation variable, h, is positive, about 0.6. As the potential increases, h∞ decreases toward zero, and as h approaches zero, the Na+ current is inactivated because gNa approaches zero. However, because the time constant τh(v) is much larger than τm(v), there is a considerable delay between turning on the Na+ current (as m increases) and turning off the Na+ current (as h decreases).
- The net effect of the two different time scales of m and h is that the Na^{+} current is at first turned on and later turned off, and this is seen as an initial increase of the potential, followed by a decrease toward rest.
- At about the same time that the Na+ current is inactivated, the outward K+ current is activated. This is because of the similarity of the time constants τn(v) and τh(v). Activation of the K+ current drives the potential below rest toward vK. When v is negative, n declines, and the potential eventually returns to rest, and the whole process can start again.
- There are four recognizable phases of an action potential: the upstroke, excited, refractory, and recovery phases. The refractory period is the period following the excited phase when additional stimuli evoke no substantial response, even though the potential is below or close to its resting value. There can be no response, since the Na+ channels are inactivated because h is small. As h gradually returns to its resting value, further responses once again become possible.



Solutions to the HH Equations—

Euler's Method

To find the shape of a curve that has a given starting point and satisfies a certain differential equation, the Euler method will calculate the slope of a given point once that point has been calculated. If the actual curve starts at the initial point, a0, that is given, the slope can be calculated at that point. Assuming that the next point, a1, is extremely close to a0 it can be found on the tangential line. From a1 a new slope and tangential line can be calculated leading to the arrival of the next point along the second tangential line called a2. This iteration is completed over time to form a curve that will closely model the actual curve.

Let's start with a general first order IVP

$$\frac{dy}{dt} = f(t, y) \qquad y(t_0) = y_0$$

where f(t,y) is a known function and the values in the initial condition are also known numbers. Function is continuous and differentiable at each points in domain. So, let's assume that everything is nice and continuous so that we know that a solution will in fact exist.

We want to approximate the solution to near t= t0. We'll start with the two pieces of information that we do know about the solution. First, we know the value of the solution at t=t0 from the initial condition. Second, we also know the value of the derivative at t=t0. We can get this by plugging the initial condition into f(t,y) into the differential equation itself. So, the derivative at this point is.

$$\left.\frac{dy}{dt}\right|_{t=t_0} = f(t_0, y_0)$$

Now, we may recall that these two pieces of information are enough for us to write down the equation of the tangent line to the solution at t=t0. The tangent line

$$y = y_0 + f(t_0, y_0)(t - t_0)$$

If t1 is close enough to t0 then the point y1 on the tangent line should be fairly close to the actual value of the solution at t1, or y(t1). Finding y1y1 is easy enough. All we need to do is plug t1 in the equation for the tangent line.

Now, we would like to proceed in a similar manner, but we don't have the value of the solution at t1 and so we won't know the slope of the tangent line to the solution at this point. This is a problem. We can partially solve it however, by recalling that y1 is an approximation to the solution at t1. If y1 is a very good approximation to the actual value of the solution then we can use that to estimate the slope of the tangent line at t1.
So, let's hope that y1 is a good approximation to the solution and construct a line through the point (t1,y1) that has slope f(t1,y1). This gives

$$y = y_1 + f(t_1, y_1)(t - t_1)$$

Now, to get an approximation to the solution at t=t2we will hope that this new line will be fairly close to the actual solution at t2 and use the value of the line at t2 as an approximation to the actual solution,

$$y_2 = y_1 + f(t_1, y_1)(t_2 - t_1)$$

We can continue in this fashion. Use the previously computed approximation to get the next approximation. So,

$$y_3 = y_2 + f(t_2, y_2)(t_3 - t_2)$$
$$y_4 = y_3 + f(t_3, y_3)(t_4 - t_3)$$
$$etc.$$

In general, if we have tn and the approximation to the solution at this point, yn, and we want to find the approximation at tn+1 all we need to do is use the following and we can simplify the formula.

$$y_{n+1} = y_n + f(t_n, y_n) \cdot (t_{n+1} - t_n)$$

Runge Kutta method

In the forward Euler method, we used the information on the slope or the derivative of *y* at the given time step to extrapolate the solution to the next time-step. Runge-Kutta methods are a class of methods which judiciously uses the information on the 'slope' at more than one point to extrapolate the solution to the future time step. The most commonly used Runge-Kutta method is the fourth-order Runge-Kutta method or simply “RK4”.

Given a differential equation with the initial condition:

$$\frac{dy}{dt} = f(t, y) \qquad y(t_0) = y_0$$

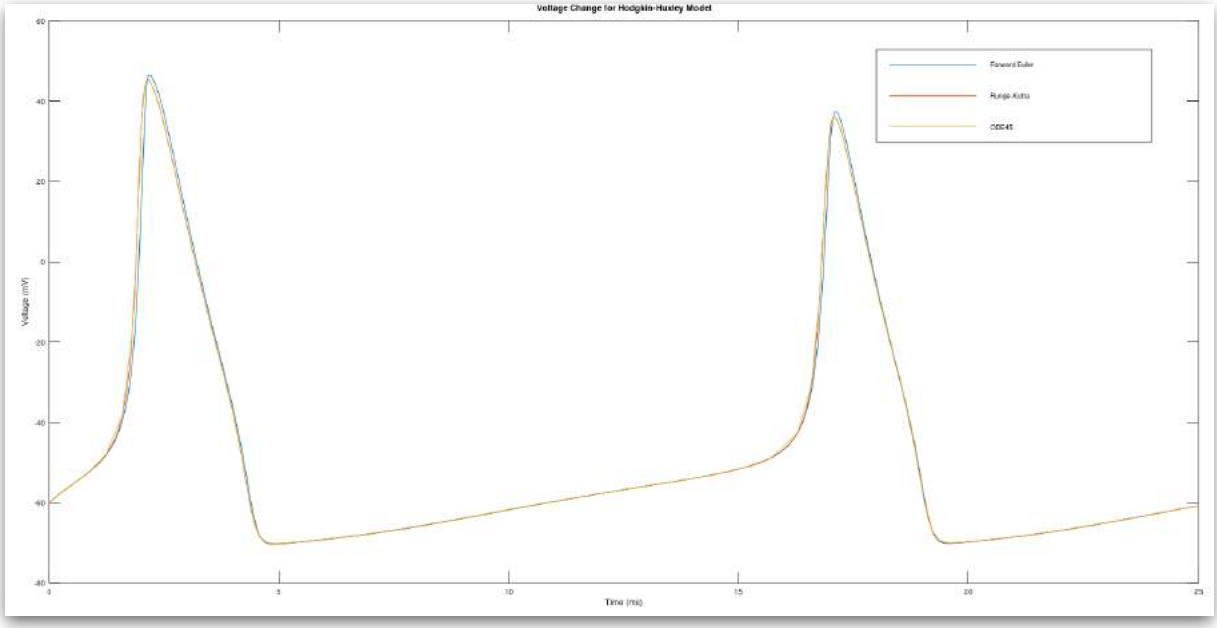
the RK4 method yields

$$y_{n+1} = y_n + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$

$$k_1 = h \cdot f(t_n, y_n), k_2 = h \cdot f\left(t_n + \tfrac{1}{2}h, y_n + \tfrac{1}{2}k_1\right), k_3 = h \cdot f\left(t_n + \tfrac{1}{2}h, y_n + \tfrac{1}{2}k_2\right), k_4 = h \cdot f(t_n + h, y_n + k_3)$$

The next point on the curve is determined by the previous point in addition to the weighted averages of four different increments. The first increment, k1, is the Euler increment seen above. It takes into consideration the slope of the tangent of the previous point with the step size. The second increment is based on the slope of the tangent at the center of the step. The third increment is the slope in the middle, with respect to the second increment. Finally, the fourth increment is the slope at the end of the step.

Using above numerical methods HH equation was analyzed and plotted using GNU-OCTAVE. Solving the Hodgkin-Huxley model with numerical methods provided a solution familiar to the action potentials discussed. All parts of the action potential are present including the rapid uprise, downfall and unexcitable phase. Each different numerical method provides extremely similar action potentials.


Voltage Change for Hodgkin-Huxley Model
Forward Euler
Runge-Kutta
ODE45
Voltage (mV)
Time (ms)

IV WAVE PROPAGATION

Background Theory

In Mathematics and Sciences, a non-linear system is a system in which the change of the output is not proportional to the change of the input. In the specific case of *Non-Linear Dynamical System*, changes in variables over time exist and are chaotic, unpredictable or counterintuitive, contrasting with much simpler linear systems.

As a solution to the above problem, ***Bifurcation Theory*** is used, it is the mathematical study of variations in the qualitative or topological structure and solutions of a family of differential equations

Bifurcation can be classified as—

Local Bifurcations:

A local bifurcation occurs when a parameter change causes the stability of an equilibrium (or fixed point) to change. In continuous systems, this corresponds to the real part of an eigenvalue of an equilibrium passing through zero.
The topological changes in the phase portrait of the system can be confined to arbitrarily small neighborhoods of the bifurcating fixed points by moving the bifurcation parameter close to the bifurcation point.

Local Bifurcation can further be classified as—

Saddle Node Bifurcation

The following example illustrates the saddle-node bifurcation:

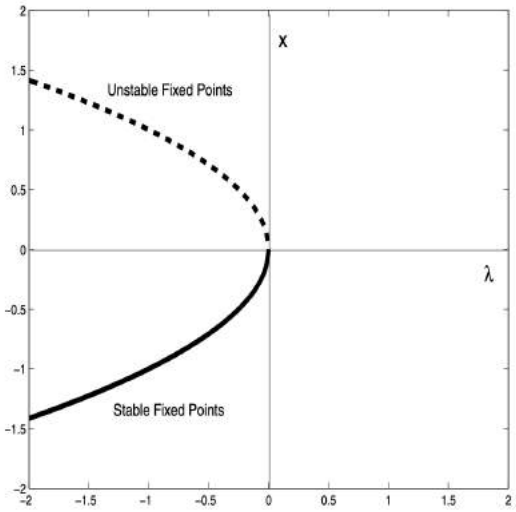
$$x=\lambda+x. \qquad (2)$$

Here, λ is a fixed (bifurcation) parameter and may be any real number. We wish to solve this equation for a given value of λ and to understand how qualitative features of solutions change as the bifurcation parameter is varied.

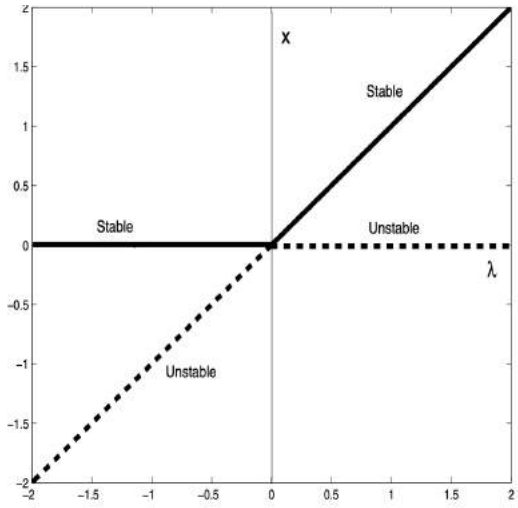
Consider, for example, the fixed points of (2) for different values of the bifurcation parameter. We may recall that fixed points are those values of x where the right hand side of (2) is zero. If $\lambda < 0$ then (2) has two fixed points; these are at $x=\pm \sqrt{-\lambda}$.If $\lambda=0$ then there is only one fixed point ,at x=0 ,and if $\lambda > 0$ then there are no fixed points of (2). To determine the stability of the fixed points, we let $f_\lambda(x) \equiv \lambda + x^2$ denote the right hand side of (2). A fixed point x_0 is stable if $f_\lambda'(x_0) < 0$. Here, differentiation is with respect to x. Since $f'(x) = 2x$, it follows that the $-\sqrt{-\lambda}$ fixed point at is stable and the fixed point at $+\sqrt{-\lambda}$ is

unstable.A very useful way to visualize the bifurcation is shown in Fig 2 (left). This is an example of a bifurcation diagram. We plot the fixed points $x = \pm \sqrt{-\lambda}$ as functions of the bifurcation parameter. The upper half of the fixed point curve is drawn with a dashed line since these points correspond to unstable fixed points, and the lower half is drawn with a solid line since these points correspond to stable fixed points. The point $(\lambda,x) = (0,0)$ is said to be a bifurcation point. At a bifurcation point there is a qualitative change in the nature of the fixed point set as the bifurcation parameter varies.

A basic feature of the saddle-node bifurcation is that as the bifurcation parameter changes, two fixed points, one stable and the other unstable, come together and annihilate each other. A closely related example is $x' = -\lambda + 2x$. There are no fixed points for $\lambda<0$ and two for $\lambda>0$. Hence ,two fixed points are created as λ increases through the bifurcation point at $\lambda = 0$. This is also referred to as a saddle-node bifurcation



Saddle Node Bifurcation



Transcritical Bifurcation

Transcritical Bifurcations—

Considering the equation

$$x' = \lambda x - x2 \qquad (3)$$

We may note that $x = 0$ is a fixed point for all values of λ; moreover, there is a second fixed point at $x = \lambda$.

To determine the stability of the fixed points, we let $f_\lambda(x) \equiv \lambda x - x^2$ denote the right hand side of (3). Since $f_\lambda'(x) = \lambda - 2x$, it follows that the fixed point at $x = 0$ is stable if $\lambda < 0$ and is unstable if $\lambda > 0$. The fixed point at $x = \lambda$ is stable if $\lambda > 0$ and is unstable if $\lambda < 0$.

The bifurcation diagram corresponding to this equation is shown in Fig.above (right). We may plot values of the fixed points versus the bifurcation parameter λ. Solid curves represent stable fixed points, while dashed curves represent unstable fixed points. We may note that there is an exchange of stability at the bifurcation point $(\lambda, x) = (0, 0)$ where the two curves cross.

Pitchfork Bifurcation—

Considering the equation

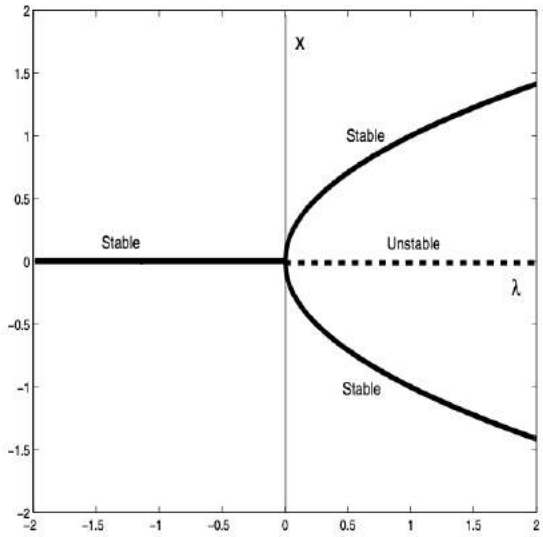
$$x' = \lambda x - x^3 \qquad (4)$$

If $\lambda \leq 0$, then there is one fixed point at $x = 0$. If $\lambda > 0$, then there are three fixed points. One is at $x = 0$ and the other two satisfy $x^2 = \lambda$. In order to determine the stability of the fixed points, we let $f_\lambda(x) \equiv \lambda x - x^3$. Note that $f'(x) = \lambda - 3x^2$. It follows that $x = 0$ is stable for $\lambda < 0$ and unstable for $\lambda > 0$. Moreover ,if $\lambda > 0$ then both fixed points $x = \pm \sqrt{\lambda}$ are stable.
The bifurcation diagram corresponding to (4) is illustrated in Fig below (left). There are actually two types of pitchfork bifurcations; (4) is an example of the supercritical case. An example of a subcritical pitchfork bifurcation is

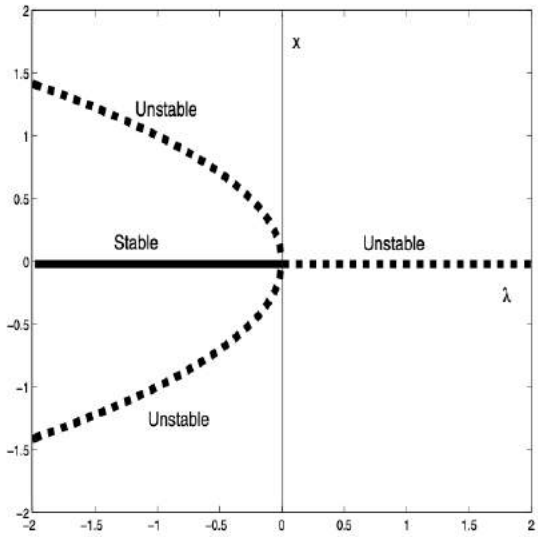
$$x' = \lambda x + x^3 \qquad (5)$$

The bifurcation diagram for this equation is shown in Fig 3 (right). Here, $x_0 = 0$ is a fixed point for all λ. It is stable for $\lambda < 0$ and unstable for $\lambda > 0$.

If $\lambda < 0$, then there are two other fixed points; these are at $x_0 = \pm \sqrt{\lambda}$.Therefore, both these fixed points are unstable.



Supercritical Pitchfork



Subcritical Pitchfork

Bistability and Hystresis—

Considering example of a scalar ordinary differential equation is:

$$x' = \lambda + 3x - x^3 \qquad (6)$$

The bifurcation diagram corresponding to (6) is shown in Fig. below. The fixed points lie along the cubic $x^3 - 3x - \lambda = 0$. There are three fixed points for $|\lambda| < 2$ and one fixed point for $|\lambda| > 2$. We note that the upper and lower branches of the cubic correspond to stable fixed points, while the middle branch corresponds to unstable fixed points. Hence, if $|\lambda| < 2$ then there are two stable fixed points and (6) is said to be bistable.

There are two bifurcation points. These are at $(\lambda, x) = (-2, 1)$ and $(\lambda, x) = (2, -1)$ and both correspond to saddle-node bifurcations. Suppose we slowly change the parameter λ, with initially $\lambda = 0$ and x at the stable fixed point $-\sqrt{3}$. As λ increases, (λ,x) remains close to the lower branch of stable fixed points. This continues until $\lambda = 2$ when (λ, x) crosses the saddle-node bifurcation point at $(\lambda, x) = (2, -1)$. The solution then approaches the stable fixed point along the upper branch. We now decrease λ to its initial value $\lambda = 0$. The solution remains on the upper branch. In particular, $x = \sqrt{3}$ when $\lambda = 0$. Note that while λ has returned to its initial value, the state variable x has not. This is an example of what is often called a hysteresis phenomenon.

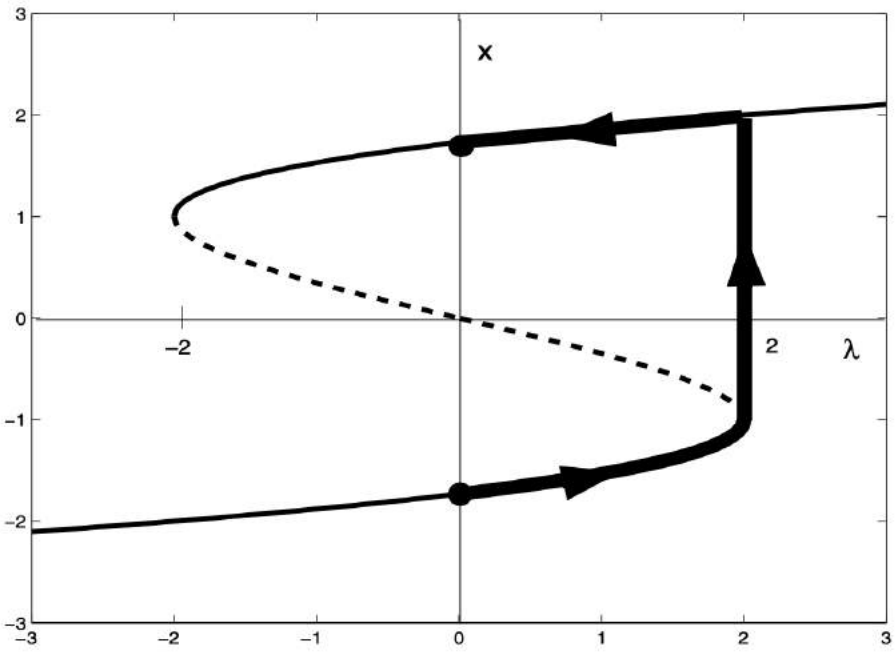


Fig. 4. Example of hysteresis.

Hoph Bifurcation—

We consider systems of the form

$$x' = f(x,y,\lambda)$$

$$y' = g(x,y,\lambda) \qquad (10)$$

It will be convenient to write this system using vector notation. Let

$$u = (x, y)^T \text{ and } F(u,\lambda) = (f(x, y, \lambda), g(x, y, \lambda))^T .$$

Then (10) becomes

$$u' = F(u,\lambda).$$

We note that nothing described here depends on (10) being a two dimensional system. The following characterization of a local bifurcation point holds in arbitrary dimensions.

We suppose that u0 is a fixed point of (10) for some value, say $\lambda 0$, of the bifurcation parameter. This simply means that $F(u0,\lambda 0) = 0$. We will need to consider the Jacobian matrix J of F at u0. We say that u0 is a hyperbolic fixed point if J does not have any eigenvalues on the imaginary axis. An important result is that if u0 is hyperbolic, then $(u0,\lambda 0)$ cannot be a bifurcation point. That is, a necessary condition for $(u0,\lambda 0)$ to be a bifurcation point is that the Jacobian matrix has purely imaginary eigenvalues. Of course, the converse statement may not be true.

Global Bifurcations—

Global bifurcations occur when 'larger' invariant sets, such as periodic orbits, collide with equilibria. This causes changes in the topology of the trajectories in the phase space which cannot be confined to a small neighborhood, as is the case with local bifurcations.

Global Bifurcations can further be classified as:

- **Homoclinic Bifurcation—** when limit cycle collides with Saddle Point**.**
- **Heteroclinic bifurcation—** in which a limit cycle collides with two or more saddle points.

  Heteroclinic bifurcations are of two types: resonance bifurcations and transverse bifurcations. Both types of bifurcation will result in the change of stability of the heteroclinic cycle. At a resonance bifurcation, the stability of the cycle changes when an algebraic condition on the eigenvalues of the equilibria in the cycle is satisfied.

  A transverse bifurcation of a heteroclinic cycle is caused when the real part of a transverse eigenvalue of one of the equilibria in the cycle passes through zero. This will also cause a change in stability of the heteroclinic cycle.

TRAVELING WAVE SOLUTIONS—

One of the most important features of neurons is the propagating nerve impulse and this clearly requires consideration of spatial dynamics. The nerve impulse corresponds to a traveling wave solution and there has been extensive research on the mathematical mechanisms responsible for both the existence and stability of these types of solutions.

Traveling Wave solutions for the FitzHugh-Nagumo Equations which are essentially a reduced model of the HH Equations.

The FitzHugh - Nagumo equations can be written as:

$$\begin{aligned} v_t &= v_{xx} + f(v) - w \\ w_t &= \epsilon(v - \gamma w). \end{aligned} \tag{7}$$

Here, (v ,w) are functions of (x ,t), $x \in R$ and $t \geq 0$. Moreover, $f(v) = v(1 - v)(v - a)$,

$0 < a < 1/2$, ε is a small singular perturbation parameter, and γ is a positive constant chosen so that the curves $w = f(v)$ and $v = \gamma w$ intersect only at the origin.

A traveling wave solution of (7) is a solution of the form (v(x, t), w(x, t)) = (V (z), W (z)), z = x + ct; that is, a traveling wave solution corresponds to a solution that propagates with constant shape and velocity. The velocity is c as in not known a priori. We also assume that the traveling wave solution satisfies the boundary conditions $\lim_{Z\to\pm\infty}$(V (z), W (z)) = (0, 0).

We may note that a traveling wave solution corresponds to a solution of the first order system of ordinary differential equations

$$\begin{aligned} V' &= Y \\ Y' &= cY - f(V) + W \\ W' &= \frac{\epsilon}{c}(V - \gamma W) \end{aligned} \tag{8}$$

together with the boundary conditions

$$\lim_{z\to\pm\infty}(V(z), Y(z), W(z)) = (0, 0, 0) \tag{9}$$

Hence, a traveling wave solution corresponds to a homoclinic orbit of a first order system. This homoclinic orbit will exist only for special values of the velocity parameter c.

One can use geometric singular perturbation methods, to construct a singular homoclinic orbit in which ε is formally set equal to zero. One needs to then rigorously prove that this singular solution perturbs to an actual homoclinic orbit that lies near the singular orbit for ε sufficiently small.

The singular orbit is constructed as follows. As before, the singular orbit consists of four pieces, as shown in Fig. below. Two of these pieces correspond to the silent and active phases and the other two pieces correspond to the jump-up and jump-down between these phases. As before, we consider both fast and slow time scales.

The jump-up and jump-down pieces correspond to solutions of the fast equations. These are obtained by simply setting ε = 0 in (8). The resulting equations are:

$$\begin{aligned} V' &= Y \\ Y' &= cY - f(V) + W \\ W' &= 0 \end{aligned} \tag{10}$$

We may note that W must be constant along this solution. For the jump-up (or front), we set W ≡ 0 and look for a solution of the first two equations of (8) that satisfy

$$\lim_{z\to-\infty}(V, Y) = (0, 0) \quad \text{and} \quad \lim_{z\to+\infty}(V, Y) = (1, 0)$$

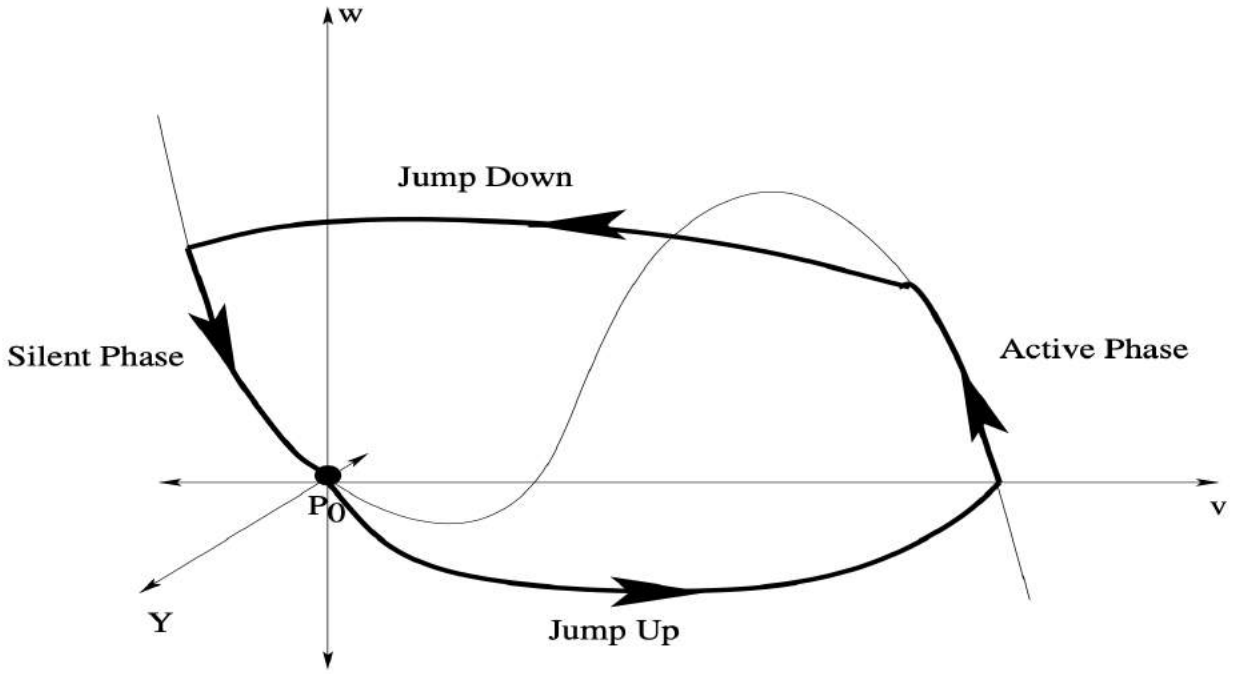
It is well known that there exists a unique solution for a unique value of the parameter c. We denote this parameter as c_0. This is the velocity of the wave in the limit $\varepsilon \to 0$.

For the jump-down (or back) we set $W \equiv W_0$, where W_0 is chosen so that if $c = c_0$ then there exists a solution of the first two equations in (10) such that $\lim_{z\to-\infty}(V,Y,W_0)$ lies along the right branch of the cubic $W = f(V)$ and $\lim_{z\to+\infty}(V,Y,W_0)$ lies along the left branch of this cubic. This is shown in Fig. below. We note that W_0 is indeed uniquely determined.

We now consider the pieces of the singular traveling wave solution corresponding to the silent and active phases. We introduce the slow time scale $\eta = \varepsilon z$ and then set $\varepsilon = 0$ to obtain the slow equations

$$Y = 0$$
$$W = f(V)$$
$$\dot{W} = \frac{1}{c_0}(V - \gamma W)$$

Here W corresponds to differentiation with respect to η. These equations demonstrate that during the silent and active phases, the singular solution lies along the cubic curve defined by W = f (V), Y = 0. The complete singular homoclinic orbit is shown in Fig. below.



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