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ELECTROPHYSIOLOGY OF MEMBRANE POTENTIALS: MATHEMATICAL PHYSIOLOGY AND MATHEMATICAL MEDICINE*

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ABSTRACT

The concepts of mathematical physiology are highly important to understand the foundation of physiology and medicine. The basic and important concepts related to membrane potentials are explained in the present article for unravelling the mathematical physiology approaches and their applications in medicine. Generation and maintenance of resting membrane potentials, equilibrium potentials, action potential, Nernst equation, Fick's laws, Ohm's law, voltage gated channels, 'Goldman – Hodgkin – Katz' (GHK) equation, membrane time constant, Hodgkin–Huxley model (HHM), equivalent circuit model, cable equation etc. and their applications in physiology/ medicine have been discussed. Excitability-that governs the trans-membrane voltage-is considered as a fundamental important physiological property that regulates the functions of muscles, endocrine glands, heart, and nervous system tissues. Unique physiology of all cells represents channels, receptors and transporters that indicates that all cells comprise membrane potential governed by Ohm's law for the relationship among current (I), conductance (C) and membrane potential (V or voltage) i.e. I=CV. The electrically excitable cells (neurons, myocytes etc.) represent much larger resting membrane potential. Furthermore, excitability is determined by the ability of a cell to keep its resting membrane potential when outside forces tend to deviate it. Hence, action potential in highly excitable neurons is generated quite quickly as they can deviate easily from resting membrane potential. The Hodgkin-Huxley model was indeed a fascinating approach for biological systems, but it is quite applied for parametric protein density/kinetic changes than the actual physiological systems. However, further insights provide more interesting facets wherein dynamic-clamp & voltage gated K^+ channels were expressed then in the *Xenopus* oocyte cells, and the phenomenon was found in two-dimensions while combining the parameters of Hodgkin - Huxley model (HHM) with the demonstration of activity-dependence and hysteric-dynamics compared to phase-diagram in view of complexity of the kinetics of slow-inactivating condition. Membrane GHK theory is indeed impressive and has been considered the best and most successful theory. However, it seems incomplete and does provide some aspects clearly violating the basic physicochemical laws. Hence, there is a need of further work to establish an exemplary model verifying well and quantitative potential behaviour with newer interpretations based on adsorption theory and other emerging ideas.

Keywords: Membrane potentials, electrophysiology, membrane theories, mathematical physiology, mathematical medicine, Goldman–Hodgkin–Katz (GHK) theory

INTRODUCTION

The concepts of mathematical physiology are highly important to understand the foundation of physiological science and medicine. The basic physiological mechanisms of excitation and inhibition are the key rules for understanding the functions of excitable cells/ tissues and their diseases. For example, the neurons responding transiently to external forces are less excitable. In other words, changing intracellular or extracellular K^+ concentration has drastic effect on resting membrane potential (RMP), and nerve and muscle cell to reach threshold potential.

Understanding the permeability, equilibrium potentials and pumps is essential for having clear idea of how RMP is generated with negative value (Wright, 2004). Nernst equation(Em = RT/zF * log([ion outside cell]/[ion inside cell]) is used to calculate the equilibrium potential (Veech *et al.,* 1995; Wright, 2004) where Em represents equilibrium potential of the membrane, R is for gas constant(8.314472 J·K-1), T is for temperature Kelvin, F is for Faraday constant (9.65 x 104 C mol-1), Z is one for monovalent ion, 2 for divalent and etc., and RT/F in simple form is 61.5 at normal body temperature (Chrysafides *et al.,* 2021).

Most of the molecules move randomly. If there are a large number of molecules, their motion can be explained using the Fick's law as: $J=-D\ \partial C/\partial x$ (J: molecular flux, D: diffusion coefficient, $\partial C/\partial x$: represents the concentration gradient, whereas Nernst-Planck equation shows: $J=-D\ (\nabla C + Fz\ RT\ \nabla\varphi)$. Here, conservation $\partial C/\partial t + \partial J/\partial x=0$, leads to diffusion equation determination: ($\partial C/\partial t = \partial/\partial x\ (D.\partial C/\partial x)$. The cell membrane is a selective filter and hence uncharged substances move freely across membrane whereas charged substances use multiple types of

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selective ion-channel pores (Hille, 2001) since due to internal hydrophobic membrane structure, they cannot easily perform transmembrane diffusion.

Concentration gradient, electrical gradient and active transport are the factors involved in causing ionic movements via ion-channels. The potential difference of ions creates membrane potential (Vm) or we may say: $V_m = V_i - V_o$ (Where Vi and Vo respectively represent inside and outside potential values). Electrochemical potentials can be expressed as:$\mu=\mu i + ziF\Phi$, where μ is electrochemical potential, μi is chemical potential, z is valency, F is Faraday constant, and Φ is local electrostatic potential.

Ion channel proteins in the membrane are conductor molecules, and Gauss's law explains that conductor in equilibrium position with the current applied (E: electric field) has entirety of the surface charge (Ɛ: permittivity of free space) expressed by: $\Sigma=E\varepsilon_0$. 'Surface charge density' can be the electric charge amount-q in an area-A as: $\sigma = q / A$. The equation: $C(x,t)=f(x2/Dt)$ represents diffusion in a tube by reservoir. However, the other consequences occur by Ohm's law that are described below.

Electrical phenomenon related to membrane potentials specifically the too weak stimuli causing sub-threshold responses collectively explain the physiological basis of excitability. e.g., electrodiffusion Nernst Planck equation, resting membrane potentials, equilibrium potentials, leaky potentials and cable equation.

A force F produced by an electric potential gradient ϕ while effecting the ion with the charge of zq_e (it is the valence x unitary proton charge), tends the respective ion to be velocity related drifting $v_D = \mu F$ (mobility μ relates to diffusion coefficient D). Ionic flux becomes proportional to available ions c(x), and drift speed $J(x) = c(x) v_D$. Experimental studies of ion channels and cortical networks provide newer information in synaptic transmission (Sakmann, 2017).

The present review has been specified to provide some of the basic information of the concepts related to mathematical physiology and mathematical medicine of membrane potentials. The models explaining the maintenance and generation of resting membrane potential, and action potential will be described. The Nernst equation, equilibrium potential, Fick's laws, voltage gated channels GHK equation, membrane time constant, Hodgkin–Huxley model (HHM), equivalent circuit model, cable equation etc. and their applications in physiology/medicine will be discussed.

RESTING MEMBRANE POTENTIAL: MATHEMATICAL PHYSIOLOGY

It is highly important for excitable cells to generate and then maintain RMP. Equilibrium (or reversal) potential (E_{rev}) for each ion is the membrane potential (i.e., where its net flow is zero via any open channels) pertains balanced chemical and electrical forces. Hence, E_{rev} can be calculated by Nernst equation (is ~+60 mV for Na+ and ~-88 mV for K+). Rate of ion exit by concentration gradient is equal to the ionic entrance by electrochemical gradient to establish the equilibrium potential. Hence, the resting membrane potential (RMP) for an ion will be equal to equilibrium membrane potential (EMP) (calculated by Nernst equation) where only that ion can cross the membrane:

$V_m = 61/z \text{ X } \log_{10} [C]_O /[C]_I$

Where V_m is the EMP of an ion, z is the valency of that ion, and $[C]_O$ and $[C]_I$ respectively represent inside and outside concentration of that ion. Both forces (electrical and chemical) are found equal but opposite at the condition of equilibrium, and for potassium ions it is called reversal potential, EK or potassium Nernst potential or $-RT/ zF \ln [K^+]_{in}/ [K^+]_{out}$, (R: gas constant; T:absolute kelvin temperature, z:K^+ valence; and F:Faraday constant.

The Donnan equilibrium explains the presence of high concentration of potassium in and chloride out of the cell, but not explaining the sodium in cell. This is the reason that resting membrane potential in several excitable cells is though around -70 mV near to 'Nernst potentials' for potassium and chloride but varies much from Nernst potential relating to Na+ ion concentration ratio. Pathophysiological, pharmacological, and developmental studies in cellular excitability related to ion channel follow these potential variations (Spinelli *et al.,* 2018). Plasticity of the intrinsic neural excitability has uncovered interesting facets (Debanne *et al.,* 2019).

Despite the best applicability of Nernst equation, RMP is more complex since other factors besides ions are also involved in RMP. The RMP involves cumulative effect of ions where the direction of the flow of sodium and chloride ions is towards intracellular fluid while the former makes the RMP more positive with more impact, and later makes more negative with little impact. The direction of the flow of potassium ion is towards extracellular fluid, and its movement makes the RMP more negative. The organic anions cannot cross the membrane but makes the RMP more negative with little impact. However, the greatest impact concerns to sodium and potassium ions as membrane is most permeable to these ions.

Neuronal cell membranes are more permeable to potassium ions. Sodium ions play role in making a little less negative, the potassium ions bring the RMP near to EMP. Membrane potential is changed leading to action potential occurrence/generation, if permeability of membrane changes via opening or closing of ion channels. Most gated ion-

channels remain in closed state at resting phase. Because of this, the non-gated channels control primarily so that the RMP gets established. Mathematical descriptions for membrane potentials and excitability depend upon electro-diffusion equations though ion channels were not discovered while these concepts were developed.

Reversal potential or Nernst potential occurs at equilibrium as VN=Vi−Ve=RT/zF ln [C]e/[C]i. For understanding the Nernst equation, it is needed to derive Nernst–Planck equation for how the chemical and electrical forces generated by ions balance each other and help understanding the GHK-equation. Assumption in Nernst potential is zero flux (occurrence of electrodiffusive equilibrium condition), with the single-ion consideration e.g., the solution of electrodiffusion-equation of K^+, at zero flux describes Nernst potential V_K. Fick's law of diffusion can be described as: Jdiff=−D $\frac{\partial}{\partial x}$ (D: diffusion-constant). Fick's first law for diffusion concerns to diffusive flux-J for ideal mixtures (Φ) to the concentration gradient: J= -D$\frac{d\Phi}{Dx}$. Transportation of various drugs via e.g. skin can be elaborated by the concept of memory formalism considering the Fick's law involving diffusion coefficient D that does not change with time and position, which explains a better comparison with experimental studies and is alternative to integer-order derivative method (Caputo and Cametti, 2021). Fick's 2nd law describes: $\frac{\partial \varphi}{\partial t} = D\frac{\partial^2 \varphi}{\partial x^2}$, whereas diffusion across the membrane is represented by: J= AD/L (C1 − C2), where change in C1, C2 and L occurs leading to flux changes governed by the Ohm's law. On the other, the carrier mediated diffusion by a saturating Fick's law is governed by: J = Jmax Se – Si / (Se + Ke)(Si + Ki).

Ohm's law (I=$\frac{V}{R}$) can be stated as electric drift in the microscopic version as:Jdrift=−μz $\frac{\partial V}{\partial x}$ where z is valence of ion, μ is the mobility in square centimeter (cm) /volt second, and E≡−∂V/∂x the electric field as gradient potential-V(volts). Higher concentration will mean higher drift that has same dimensions as diffusion flux. Flux (j) is generally described as I/A(I for area, q for quantity), or dq/dt (t for time). Total flux is: Jtotal=−D $\frac{\partial}{\partial x}$−μz$\frac{\partial V}{\partial x}$. Three-dimensional electrostatic interaction in place of previously employed equivalent circuit cable theory models (that dealt closed electric circuits inside and outside the axoplasm on the basis of 'Kirchhoff's law' & 'Ohm's law' has been postulated concerning nerve conduction in unmyelinated and myelinated nerve cells, since various conductive patterns occurring in myelinated and unmyelinated nerves cannot be fully explained following Ohm's law and Kirchhoff's law (Akaishi, 2018). More general form for Einstein relation (kinetic theory) is:D = $\mu k_B T$. The diffusion coefficient and mobility are connected by Einstein's relation (kinetic theory) as: D= $\frac{kT}{q}$ μ (Boltzmann's constant-k; charge q (coulombs); absolute temperature-T)

Diffusion criteria have been postulated since the hydrodynamic argument for weak mass dependence and predicting a stronger mass dependence (Stokes-Einstein relation or hydrodynamic approach instead of kinetic theory approach) pertain less validity, neither explains weak power-law mass dependence (Bhattacharyya and Bagchi, 2000). The total flux (Jtotal) can be written as: Jtotal=−$\frac{\mu kT}{q}\frac{\partial}{\partial x}$−μz$\frac{\partial V}{\partial x}$. Ion transportation via perforated graphine of single layer of atoms revealed similar membrane potential explained by Teorell, Meyer, and Sievers theory depending on Nernst-Planck equation and membrane electroneutrality though certain nonidealities and surface charge control manifest overprediction of theoretical Donnan potential (Ghosh *et al.,* 2018).

Electrostatic forces have been applied in Nernst–Planck equation (Kirby, 2010). Flux per mole and hence current flux can be converted into Nernst–Planck equation (in amperes per square centimeter) as:I=−(uz RT$\frac{\partial}{\partial x}$+uz^{2}F$\frac{\partial V}{\partial x}$). To understand the asymmetric potential energy, lipid interactions were studied (Su *et al.,* 2017). Balance at the equilibrium condition occurs for electric effects and diffusion while considering current as zero as:I=−(uzRT$\frac{\partial}{\partial x}$+uz^{2}F $\frac{\partial V}{\partial x}$)=0. Hence, the equilibrium (or Nernst) potential (Veq) can be written as: Veq ≡ Vin−Vout=− $\frac{RT}{zF}$ln $\frac{in}{out}$.

The 'Fick's first law' or 'Nernst-Planck-equation' explain the linear elevation of water flux with the concentration of salt (Su *et al.,* 2017). Chord Conductance Equation or Millman equation explains the conductance of ions rather than permeability as: Em= $\frac{gK+ E eq,K+ + gNa+ Eeq,Na+ + gCl-Eeq,Cl-}{gK+ +gNa+ + gCl-}$ and osmotic water permeation through a membrane vesicle provides entirely new insights (Su *et al.,* 2017).

MEMBRANE POTENTIALS: MATHEMATICAL PERSPECTIVES

Osmotic pressure with negative charge and flux are represented as:rQ=P1−P2−π1+π2 , and πi = kTCi. Charge balance (z_x) and osmotic balance (same osmolyte each side) are respectively considered as:qw (N_i + K_i− C_i)+z_xq X=qw(N_e + K_e − C_e)=0 and N_i + K_I + C_i + X/w=N_e + K_e + C_e. Highly impressive investigations relate to Hodgkin-Huxley model. There is a key role and high impact of ion channels in regulating almost every cellular

process/function, as invented in the classic theory presented by Hodgkin-Huxley-in 1952 for 'action potential generation (Dixon *et al.,* 2021) with the role of sodium and potassium voltage-dependent ion-channels and a leak/or leaky current ($I_L=I_{cap} + I_{ion}$).

The importance and application of cooperative gating of the ion channels involves the regulation of cardiac functions and activity for tone of the vasculature, regulation of impulse and n velocity of impulse conduction in neuronal/ cardiac muscle cells, fine excitation-contraction coupling occurring in muscle cells, and controlling the pace-making activity in the heart (Dixon *et al.,* 2021). Ionic currents in Ohmic form are as: $c_{M.} \frac{\partial VM}{\partial t} = \frac{a}{2rL} X \frac{\partial 2.VM}{\partial x\, 2} - g_{K.}(V_M - E_K) - g_{Na.}(V_M - E_{Na}) - g_{L.}(V_M - E_L)$.

The leaky conductance g_L is determined by voltage clamp, and leak current is measured as: $I_{Mc} \approx g_L(V_C - E_L)$. The recent advancement in model construction providing mathematical foundations of excitability and properties of involved voltage gated channels (Ori et al., 2020) further explains the concepts of Hodgkin and Huxley theory. Hodgkin & Huxley isolated K^+ current by a special method It was noted that if we know IL and IK, then 'Ohm's law'can be applied as: $g_{Kx}(t) = \frac{IKx(t)}{(VM-EK)}$ and $gx_{Nax}(t) = \frac{IxNa(t)}{(VM-ENa)}$. Incorporating new techniques/ models, emphasis has been given to the issue of high channel measurement with lower dimensionality for attaining physiological functions (Ori *et al.,* 2020).

By employing voltage clamp (Hodgkin and Huxley, 1952), Hodgkin and Huxley expressed potassium conductance as:$g_K = \bar{g}_K n^4$ and sodium conductance as:$g_{Na} = \bar{g}_{Na} m^3 h$.($n^4$ represents that potassium channel is open; maximum conductance as:$\bar{g}_K$ and as:$\bar{g}_{Na}$; gating variables as:n, m, & h for 0-1 values; sodium activation gate open probability serves as m^3; potassium channel all 4 components as identical, and open probability is represented sodium inactivation gate as: h. Electrodiffusion model explains Poisson equations as:$d2\varphi/dx2 = -\lambda^2(c1 - c2)$, and Nernst Planck equation as:$J1 = -D1(dc1/dx + F/RT\ c1\ d\varphi/dx)$ & $J2 = -D2(dc2/dx - F/RT\ c2\ d\varphi/dx)$. In case the channel is short, $L \approx 0 \Rightarrow \lambda \approx 0$, the field will be constant as: $d\varphi/dx = v \Rightarrow dc1/dx - vc1 = -J1$ leading to $J1 = v\ ci - c_e e^{-v}/1 - e^{-v}$, and then to Goldman-Hodgkin-Katz equation as: Iion=P F2/RT V x([C]i− [C]e exp (−zV /RT/1−exp(−zVF/RT). However, if channel is long, $L \approx 0 \Rightarrow 1\lambda \approx 0$, c1=c2 will be $J1 = ce - ci/v1\ (v - v1)$ that is current-voltage expressing as linear curve incorporated by Hodgkin and Huxley (Hodgkin and Huxley, 1952).

Opening rate constant of a voltage-dependent ion channel is influenced by the effect of electrical polarization (Ramírez-SanJuan et al., 2013). This can be written as voltage-dependent rate constants α and β; and at steady-state condition, m ∞(V) and τ(V) time-constant as:$\alpha(V) = A_\alpha \exp(-B_\alpha V)$ and $\beta(V) = A_\beta \exp(-B_\beta V)$. The 'Kramers diffusion theory' explains the open to close state and vice versa, and transition rates as exponential (Ramírez-SanJuan *et al.,* 2013). It depends on thermodynamics with the opening and closing probability rely exponentially on potential-Vs & Vh that are constants represented as:

$$m\infty(V) = \frac{1}{1+\exp.(-(V-Vxh)/Vxs)}$$

Optimizing the leak conductance was done in Squid giant axon (Seely and Crotty, 2010). The voltage-dependent channels open and close and hence, generate the impulse/ action potential to travel along axon, for membrane potentials as:

$CM\frac{dV}{dt} = = -gxNa\,(V - E_{Na}) - gx_K(V - E_K) - gx_L(V - E_L)$, where $I_L \equiv g_L(V - E_L)$ is the leak current, that was elaborated later (Seely and Crotty, 2010).

One effective porous substrate electroporation (PSEP) method was employed wherein impedance measurements are used (Brooks *et al.,* 2022). It is important to know the way ionic movements generate electrical signals via conductors/ insulators, ionic gradient batteries, and membrane capacitor since the GHK equation cannot lead us to understand how the transmembrane ionic gradients generate impulses. Association between potential-V_m and stored charge-q involving proportionality constant C (membrane capacitance that depend on total area of dielectric; and c_M-the specific membrane capacitance-is the capacitance/square centimeter(cm), as:$q \equiv C_M V_M$. Hence i_{cap}-(specific capacitance-current) is equal to $C_M \frac{dxVxM}{dt}$. Brownian dynamics studies were applied to study permeation for ions via K^+ channels deduced from crystallography, and it was found that current-voltage relation is linear in symmetrical-solutions with less than 100 mv applied potential. However, it does not follow 'Ohm law' at higher values of potential. Whereas the reversal-potentials in asymmetrical-solutions agree with Nernst equation (Chung *et al.,* 1999). Hence, ionic current through e.g. potassium channel employing Ohm's law appears as:$I_K = g_K(V_M - E_K)$.

Potassium current per unit area can be determined as:$I_K = g_K(V_M - E_K) = \frac{VM-EK}{rK}$. Various conductive patterns cannot be fully explained following Kirchhoff or Ohm laws, and hence, three-dimensional electrostatic interaction served the best for membrane conductance (Akaishi, 2018). According to Kirchhoff law, current in the cell that is zero ($i_{cap}+I_K$), and have equivalent circuit shows the membrane potential as:$C_M \frac{dVxM}{dt} + \frac{VM-EK}{rK}$ Or $-gx_K(V_M - E_K) =$

- $\frac{VM-EK}{rK}=C_M\frac{dVM}{dt}$. Human body impedance has been analysed by new methods of impedance employing armpit electrode and new equivalent circuit model for the cell (consisting of resistance R and capacitance (C) (Chinen *et al.,* 2015). We may consider I(t)-current source and three parallel-conductances in an equivalent circuit, that can be written as: $i_{ion=} - gx_{Cl}(V_M - E_{Cl}) - gx_K(V_M - E_K) - gx_{Na}(V_M - E_{Na})$. If we divide I(t)-current source with total neuronal area, it becomes: $C_M\frac{dVM}{dt} = -gx_{Cl}(V_M - E_{Cl}) - gx_K(V_M - E_K) - gx_{Na}(V_M - E_{Na}) + I(t)/A$.

The model of equivalent circuit manifests the major components of the PSEP system components (Brooks *et al*., 2022). Or the resting potential $E_R = (g_{Cl}E_{Cl}+g_KE_K+gNaE_{Na})r_M$, and specific membrane resistance r_M is $\frac{1}{gCl+gK+gNa}$,that can be presented as: $C_M\frac{dVM}{dt}=-\frac{VM-ER}{rM}+I(t)/A$. impedance been applied considering R as the electrical resistance of fluid inside and outside the cell, and whereas the C for high frequency conductance of cell membrane (Chinen *et al.,* 2015). However, V_M reaches steady state for passive membrane where conductance and current are constant.

Theoretical explanation is not yet presented for the excitability and threshold mechanism (Ma *et al.,* 2021). Cable theory or cable equation is essentially required as a conventional method for simulating neural recording extracellularly by initially computing the transmembrane currents employing cable equation (Buccino *et al.,* 2019). Geometry of the neuron affects the flow of neuronal information considering approximating by cylinders or cable (with large cross-sectional area) with radius a, and x the distance along the cable showing isopotential compared to spheres for isopotential conditions.

Mechanistic modelling of neurons indeed is an important part of computational neuroscience or neurocomputation that gives opportunity to researchers for simulating and exploring the neuronal activity (Buccino *et al.,* 2019). Classical cable theoretical model describes a partial differential equation for the $V_M(x, t)$-membrane potential with the current, assuming that $R_e=0$, and hence extracellular space is isopotential. The neural localization and parameterization of neural models from extracellular recordings is highly important and cannot be ignored since presence of probe improves the interpretation of extracellular recording (Buccino *et al.,* 2019). The cable will have the total resistance RL (r_L being proportionality constant, for length Δx as: $r_L\Delta x/(\pi a^2)$

Various conductives cannot be fully explained following Kirchhoff/or Ohm law (Akaishi, 2018). However, there are certain merits of Ohm's law and Kirchhoff's law. Variation in intracellular axial current and the transmembrane current are equal, and hence, according to Kirchhoff's law, though there are limitations in it, is applicable (Akaishi, 2018). Assumption of resting potential for zero is for a passive cable. It has been emphasized that quasi-active cable approximation has significant contributions manifested recently (Ceballos *et al.,* 2017). The length constant, or lambda (λ) shows how far a stationary current may affect the voltage along the cable. The larger the value of (λ), the farther the charge will be (Here we require boundary conditions): $V_{ss}(x)=\frac{\lambda rL}{\pi a2}\ I_0e^{-x/\lambda}$. Membrane time constant provides the facility to determine the synaptic excitation and inhibition, and this method works also in voltage clamp mode with some minor changes (Berg and Ditlevsen, 2013). Membrane time constant relates to the way isopotential passive cell gives response to stimulation by current. The signalling does not affect the membrane electrical changes, and written as: $I_M(t)$ $I_M(t)=\frac{I(t)}{4\pi\rho 2}=\begin{cases}\frac{I0}{4\pi\rho 2}\ if\ 0<t<T\\ 0\quad Otherwise\end{cases}$

Membrane time constant τ_M is generally calculated as $\tau = \tau_m C_m$ and it predicts how much fast is the membrane potential Vm in response to injected current (C_m is the capacitance). The membrane time constant τ is for potential V fluctuations for current clamp data (Berg and Ditlevsen, 2013). An ordinary differential equation can be used as in following for measuring the change in membrane potential from rest (V_M) considering C_M as specific membrane capacitance, E_R as cell's resting potential and r_M as specific membrane resistance:

$c_M\frac{dVM}{dt}=-\frac{VM}{rM}+I_M(t)$.

Suggestions for improving the quantitative techniques for steady-state membrane potential modelling have been presented (Fraser and Huang, 2007). In case cell starts at rest condition, then considering it will be: $V_M(t) =\frac{rMI0}{4\pi\rho 2}(1-e^{-t\tau M})$ for $0<t<T$. The membrane time constant is $\tau_M \equiv C_M r_M$, and hence: $V_M(t) = V_M(T)e^{-t\tau M}$ for $t>T$. There are a variety of classical techniques from classical approaches including Gibbs-Donnan-equilibrium, GHK etc and present techniques for cardiac myocyte e.g., current-summing-models of DiFrancesco & Noble, and others or charge-difference-model for skeletal muscle (Fraser and Huang, 2007). Steady-state membrane potential (R_{-INP}-input resistance with input current change ΔI) satisfies and steady-state-membrane-potential-SSMD as $R_{-INP}\Delta I$) and can be written as: $I_0\frac{rM}{4\pi\rho 2}\equiv I_0R_{INP}$

The classical and recent techniques explain interrelationships existing between membrane potential, cell volume and concentration of intracellular ions (Fraser and Huang, 2007). The larger the membrane resistance (r_m) hard it is

for a current to bring a change in membrane potential. The V_M jumps to the steady-state potential, I_0R_{INP} and V_M is:$V_M(t)=r_MI_M(t)$ without membrane capacitance. Classical and recent techniques are useful for experimentation and understanding/ interpreting the integrated concepts in myocyte and skeletal muscle cell (Fraser and Huang, 2007).

There are various models to explain membrane potentials where all ions are permeable, mainly, constant field model or GHK model by Goldman and Nobel laureates-Hodgkin & Katz. GHK model assumes: Iion=P F2/RT where linear model depicts as: Iion=g(V−VN). This model is described relating to constant field equation since it was assumed that the ions move independently, transmembrane electric field is constant and Nernst–Planck equation applies within the membrane (Reuss *et al.,* 2008; Bhadra and Kilogore, 2015).

Chloride conductance in the taste receptor cells in oral cavity (with the possibility of recording in other taste cells from taste buds in the foliate and vallate papillae, nasopharynx, soft palate, and epiglottis) is activated by hypoosmotic stimuli, and the reversal potentials matched closely as described by GHK for chloride conductance (Gilbertson, 2002). Nernst–Planck equation in specific conditions of transmembrane current is as (considering changing transmembrane mobility compared to that in aqueous solution):$I=-u^*z^2F\beta\frac{VM}{l}-u^*zRT\beta\frac{d}{dx}$, $0< x< l$.

To have further insight for the effect of hypoosmotic stimuli on peripheral taste system, it was investigated by using whole-cell patch clamp electrophysiological recording (Gilbertson, 2002). This first-order linear ordinary differential equation having two boundaries generally cannot be solved. But the current I is not known that helps solving both boundary conditions in the form: $I=u^*z^2FVM\beta l\ \frac{u*z2FVM\beta}{l}\ (\frac{oute-\xi-in}{e-\xi-1})$, where $\xi = \frac{zVMF}{RT}$. Membrane asymmetry and transmembrane potential (V_m) have been evaluated MD (molecular dynamic) for all-atoms for membranes with different composition (Lin and Gorfe, 2020). It can be represented in the form of permeability ($P\equiv\frac{\beta u*RT}{lF}$) for single ion as: $I=PzF\xi\ (\frac{oute-\xi-in}{e-\xi-1})$.

The effect of membrane asymmetry on transmembrane potential (V_m) in physiologically important model membranes using Nernst or Goldman-Hodgkin-Katz equations does not provide atomic descriptions for its role on the dynamics of lipid and protein (Lin and Gorfe, 2020). Hence, newer techniques were found more applicable. For multiple number of ions, the GHK is: $VM=\frac{RT}{F}In\frac{P.K[K+]out+P.Na[Na+]out+P.Cl[Cl-]in}{P.K[K+]in+P.Na[Na+]in+P.Cl[Cl-]out}$

It was further noted that synaptic alterations regulate the spontaneous transitions shown in another model (Zhou *et al.,* 2021). Biological neuron models, or spiking neuron models explain the neural function relate to the generation of action potentials or spikes for about one millisecond in duration. The bursting neuronal activities relate to sleep-wakefulness cycle, slow-wave activity during sleep that occurs between tonic and bursting neuronal activities (Zhou *et al.,* 2021).

MATHEMATICAL MEDICINE

Binding caused by diffusion with a binding site that is quite buried can be expressed as: $dxB(t)/dt=-k(t)cxB(t)$ (Berezhkovskii *et al.,* 2011), (k(t): rate coefficient depending on time, and g(r,t):calculation of ligand-site-pair-distribution). Lidocaine binding with sodium channels and influence of anticonvulsant and antiarrhythmic drugs provides binding interaction dynamics (Hussain and Backx, 1997). Antibiotic binding with a certain ligand inside the cell can be obtained to understand the influence caused by changing antibiotic levels in bacteria as well (Abel Zur Wiesch *et al.,* 2017).

$$\frac{dAU}{dt} = ku, fAiB - Ku, rAU$$

Where K is maximum reproductive capacity, Ai is number of antibiotics, AU is unspecifically bound antibiotic, and unspecific binding rate and dissociation rate are represented by $k_{,uf,}$ and $k_{,ur}$.(Abel Zur Wiesch et al., 2017).

It is possible that same channels show various excitability levels, and hence, for improving conductance requires the involvement of the formulation of drift diffusion-procedure (Herrera-Valdez, 2012) represented as:

$$v(t) \approx vL + (v_\circ - vL)\exp(\frac{gL}{C}t)$$

Where gL controls time constants, v to vL

Pathological aspects of microdomain formation during neuronal excitation is highly important. Kindling model of epilepsy shows selective level of excitability for the threshold potential for after-discharges (Ads) and seizures (Hussain et al., 1997).

$$IKNeu= -gKNeun4\ (VNeu - EKNeu)\ SASyn$$

where (KNeu) are neuron potassium channel, E with the KNeu indicates K^+channel reversal-potential, gKNeu as maximum K+ channel conductance, V with Neu is voltage for neuronal membrane & S with Asyn indicates surface-wise synaptic area (Breslin *et al.,* 2018).

The transient receptor potential (TRP) cation M channel (TRPM) or melastatin-member 8-TRPM8, or CMR1-cold & menthol receptor-1 have receptor for testosterone (Hussain *et al.,* 2017; Demirkhanyan *et al.,* 2018; Mohandass *et al.,* 2020). Role of steroid hormones (Qureshi *et al.,* 1988) and a later work (Hussain, 2010) were inter-related to the mentioned reports. Another interesting study suggested that calcineurin inhibits ANP-induced testosterone production (Henesy *et al.,* 2012) represented as:

$$\frac{\text{dfstim}}{\text{dt}} = \text{k3f}\cdot\text{unstim} - \text{k4}\cdot\text{fstim}$$

Where fractions of phosphorylated and dephosphorylated receptors, funstim and fstim are the fractions of unstimulated activities.

Interatomic interactions in hydrogen bonding have been revealed in self-assembly studies (Ahmadi *et al.,* 2016). Similar other interatomic interaction studies (atoms α in AAu and atoms β in AAv) in other quantum mechanical aspects have been used to study spike protein of SARS-CoV-2 virus (Ching *et al.,* 2021) represented as:

AABP(u,v)= ΣαЄuΣβЄvPαi, βj

Planar lipid bilayer studies (Wu et al., 2006; Li et al., 2007; Radhakrishna *et al*., 2022) are quite applied in understanding the process of chanellogenesis. It was revealed that:

$S_{CD} = -1/2 \text{ X } 3\cos^2\theta - 1$. Where order parameters (SCD) were calculated and θ was revealed as instantaneous angle present between the bilayer & C–H bond (Radhakrishna *et al.,* 2022).

CONCLUSION

There are a variety of applications of mathematical physiology concepts in mathematical medicine. For example, hyperkalemia is caused due to elevated plasma levels of K^+ caused by increased intake, reduced renal elimination, increased release from intracellular stores because of tissue damage etc., leading to inactivation of sodium channels, and increase in refractory period, causing major arrhythmias (Simons *et al.,* 2021). Cardiac arrest or arrhythmia may occur owing to myocytes depolarization as most life- threatening consequence of hyperkalemia (Brown and O'Rourke, 2010). On the other hand, hypokalemia causes K+flux to outside cells resulting to hyperpolarization state and difficulty producing impulse causing negative cardiac potential, delayed ventricular repolarization, and re-entrant arrhythmias (Castro and Sharma 2021).

Excitability relates to transmembrane potential changes regulating the functions of neuronal tissues, heart, muscles and endocrine glands (Ori *et al.,* 2020). The unique physiology of all cells represents channels, receptors and transporters that indicates that all cells comprise membrane potential governed by Ohm's law for the relationship among current (I), conductance (C) and membrane potential (V or voltage) i.e. I= CV. The electrically excitable cells (neurons, myocytes etc.) represent much larger resting membrane potential since large number of K^+ channels open in rest. The RMP of cells is mainly due to flow of ions through leak or leaky channels that remain open in resting state (Grider *et al.,* 2021). Furthermore, excitability is determined by the ability of a cell to keep its resting membrane potential when outside forces tend to deviate it. Hence, action potential in highly excitable neurons is generated quite quickly as they can deviate easily from resting membrane potential (Grider *et al.,* 2021).

The Hodgkin-Huxley model (Hodgkin and Huxley, 1952) was indeed a fascinating approach for biological systems but not precisely applied to biological/physiological system. It seems rather implementing to density and kinetics of proteins with respect to parametric changes. However, further insights provide more interesting facets where Xenopus oocytes was expressed for voltage dependent K^+ channels. It was fascinating to predict that in view of the complexity of the kinetics of slow inactivation, the excitability phenomenon was found to be related in combination of HHM theory parameters and activity-depending and hysteric-dynamic process over phase-diagram (Ori *et al.,* 2020).

Membrane GHK theory is indeed impressive and has been considered the best and most successful theory. However, it seems incomplete and does provide some aspects clearly violating the basic physicochemical laws. Hence, there is a need of further work to establish an exemplary model verifying well and quantitative potential behaviour with newer interpretations based on adsorption theory and other emerging ideas.

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