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MATHEMATICAL MODELLING OF ACTION POTENTIAL IN NEUROBIOLOGY

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Abstract*: Signal processing in living organisms is a challenging interdisciplinary scientific area that roots through physiology and brings together efforts of biologists, chemists, physicists, mathematicians, engineers and computer scientists. Successful treatment of mental disorders and artificial intelligence are amongst the broad range of possible applications.*

In this article, different mathematical models for nerve signal propagation are reviewed including the famous electrical model of Hodgkin and Huxley, and the more recent thermodynamic model of Heimburg and Jackson.

Keywords: *neuron membrane, ion channel, action potential, Hodgkin–Huxley model, lipids, melting transition, thermodynamics.*

INTRODUCTION

Neurons are electrically excitable cells that maintain voltage gradients across their membranes due to the concentration differences of ions such as sodium (Na^+), potassium (K^+), chloride (Cl^-) and calcium (Ca^{2+}) between the inside (intracellular) and outside (extracellular) region. The value of the potential difference in the absence of activity at the neuron's dendrites and axon, known as the *resting potential* of the cell is typically about –65 mV referenced to the fluid surrounding the neuron. Most neurons can be stimulated by their inputs into producing a large change in the membrane potential (up to about +20 mV) for a brief period of time (about 1 ms). The electrochemical pulse called the *action potential* travels rapidly along the cell's axon, and activates synaptic connections with other neurons. The membrane at rest is *polarized* since the resting potential is negative with respect to the outer tissue fluid of the extracellular region. Raising the membrane potential toward zero volts is called *depolarization*.

The molecular structure and organization of the neuronal membrane play a significant role in understanding biological signal processing. Most of the membrane is composed of the phospholipid bilayer which is assumed impermeable to water and to the major ions Na^+, K^+, Ca^{2+}, and Cl^-. Thus, it acts as an electrical insulator to current flow by these ions. The membrane also contains numerous proteins that span the membrane wall from cytoplasm (interior of the neuron) to the extracellular region, and form pores or *channels* that allow or block current flow of particular types of ions. In the open state they are permeable to the passage of their specific ions, while in the closed state they are impermeable to the same ions. For some of these proteins the open or closed state of the channel is determined by the electric potential difference (voltage) across the cell membrane and they are called *voltage-gated channels.* For other proteins, the so-called ligand-gated channels, the open or closed state depends on the binding of a neurotransmitter molecule at a receptor site on the extracellular side of the membrane.

The model by Hodgkin and Huxley [HH] from 1952 on the physiology of the squid giant axon is the currently accepted model for the nerve pulses. It gives an electrical description of the action potential based on conductors (ion channels) and on a capacitor (the lipid membrane). However, during the pulse propagation other phenomena have been observed such as physical expansion of nerves and exertion by a force normal to the membrane surface, reversible heat production and the absence of net heat release, changes in anisotropy and fluorescence of the lipid membrane probes, etc. [HJ1, HJ2, AJH, VLHGJH]. All of these features that accompany an action potential could not be

explained by the ionic currents. In the recent works of Heimburg and Jackson [HJ1, HJ2, AJH, VLHGJH] a revised view of the action potential is proposed based on the laws of thermodynamics and the assumption that membrane lipids play a fundamental role in the propagation of nerve pulses. The authors describe how pulses propagating in nerve membranes resemble propagating sound waves and give a thermodynamic explanation of the effect of anesthetics and the induction of action potentials by local nerve cooling, as well as a broad range of phenomena associated with a propagating nerve pulse.

The relevance of the extended Fisher—Kolmogorov equation to nerve signaling has been discussed in the last section of this paper, however further study is necessary to elucidate this possibility.

THE HODGKIN-HUXLEY MODEL

Following the book of R. Wells [W], let $[X]_i$ and $[X]_o$ denote the concentration (in moles per liter) inside the cell and in the extracellular region of the ion X, respectively. Then the voltage V_X representing the potential difference in concentrations $[X]_i$ and $[X]_o$ is given by the *Nernst potential*

$$V_X = \frac{kT}{ze}\ln\left(\frac{[X]_o}{[X]_i}\right).$$

Here k = 1.38066·10^{-23} joules/kelvin is the Boltzmann constant, T is the absolute temperature in kelvin, z in the valence, and e, the elementary charge, is the charge carried by a single proton (e = 1.60219·10^{-19} coulombs). In the model by Hodgkin and Huxley [HH], the *membrane potential*, V_m, is determined by contributions from all the Nernst potentials and is dependent on the permeability of the membrane (the electric conductance) for each different type of ion. Thus, Hodgkin and Huxley find V_m using an electric circuit model.

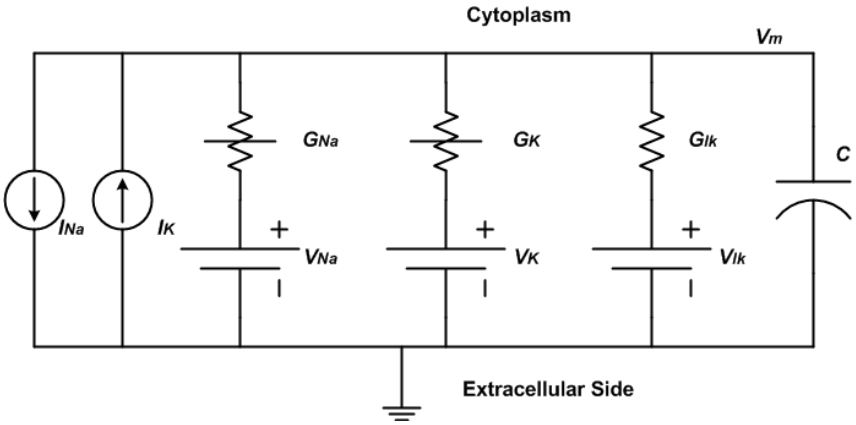

Fig.1 The Hodgkin & Huxley electric circuit model, [HH]

By common convention, the electric potential in the extracellular region is taken as the reference ground potential and the cytoplasmic electric potential is measured relative to this ground. Hence, the membrane potential V_m represents the total electric potential difference across the wall of the membrane. The storage of free ions within the cytoplasm is represented by a circuit element called a capacitor. The capacitance C relates the total charge Q (in coulombs) of the stored ions to the membrane voltage according to

$$Q = CV_m.$$

The value of C depends only on the thickness of the membrane, its surface area, and its composition of phospholipids and proteins. A typical capacitance value per unit area of cell surface is about 1 μF/cm^2 HH].

The batteries in the figure represent the electrochemical Nernst potentials for each type of ion. Battery V_{lk} , the so-called 'leakage potential' is used to model unidentified ionic constituents of the system. Although frequently associated with chloride ions, in fact V_{lk} and its associated conductance G_{lk} are used to account for unknowns encountered in physiological studies.

The effect of non-zero permeability on the flow of ion currents is represented through the various conductors depicted in the figure. By Ohm's law, ion current flow through a conductor is proportional to the voltage difference across the conductor, namely

$$I_X = G_X (V_X - V_m).$$

Here G_X represents the conductance of ion X. The horizontal lines added to the conductor symbols in Figure 1 denote that their conductance values are voltage-dependent. This is because G_{Na} and G_K in this figure represent voltage-gated sodium and potassium ion channels. The leakage conductance is generally not membrane-voltage-dependent, thus the lack of a horizontal line in the lk conductor symbol. Current sources I_{Na} and I_K represent the action of the molecular pumps that maintain the resting cell in its electrochemical equilibrium.

The basic law governing the relationship between V_m and the Nernst potentials is Kirchhoff's current law: The sum of the currents leaving any node in a circuit equals zero. In the case of Figure 1, Kirchhoff's law elucidates how charge accumulates on the capacitor. For the membrane capacitor,

$$Q = CV_m \quad \Rightarrow \quad \frac{dQ}{dt} = I_C = C\frac{dV_m}{dt}.$$

Using this capacitor law and applying Kirchhoff's law gives us

$$C\frac{dV_m}{dt} + G_{Na}(V_m - V_{Na}) + I_{Na} + G_K(V_m - V_K) - I_K + G_{lk}(V_m - V_{lk}) = 0.$$

Further, since the sodium and potassium terms in the above equation are time functions, the ion concentrations can be expressed by the steady-state concentrations and the time variation in concentrations due to current supplied by the pumps. For the sodium potential, this expression can be written

$$V_{Na} = \frac{kT}{e}\ln\left(\frac{[Na^+]_o + [\Delta Na^+]}{[Na^+]_i - [\Delta Na^+]}\right) = \frac{kT}{e}\ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right) + \frac{kT}{e}\ln\left(\frac{1 + [\Delta Na^+]/[Na^+]_o}{1 - [\Delta Na^+]/[Na^+]_i}\right),$$

where $[\Delta Na^+] > 0$ is the change in Na^+ concentrations as a function of time due to current flow from the sodium pump. The first term in the sum on the right-hand side is the equilibrium potential of the battery, denoted as E_{Na}. The second term represents the change in battery voltage, ΔV_{Na}, that would take place from charge pumping. Because the pump current I_{Na} replenishes the battery, in steady-state equilibrium $G_{Na}\,\Delta V_{Na} - I_{Na} = 0$. A similar result is obtained for the potassium pump. Using E_K to represent the equilibrium potential for potassium given by the Nernst equation, the differential equation is rewritten as

$$C\frac{dV_m}{dt} = -G_{Na}(V_m - E_{Na}) - G_K(V_m - E_K) - G_{lk}(V_m - V_{lk}). \qquad (1)$$

Hodgkin and Huxley [HH] had discovered the existence of two distinct types of voltage-gated ion channels whose conductance was a function of V_m. Today they are known as transient channels (Na^+) and persistent channels (K^+). A transient channel has two ion gates, the activation gate on the outer side of the membrane, and the inactivation gate on the inner side. Accordingly, this channel has three states: (1) deactivated (activation gate closed, inactivation gate open); (2) activated (both gates open); and (3) inactivated (inactivation gate closed). A persistent channel has only two states, activated and deactivated, because it has only one gate.

The Hodgkin and Huxley statistical model of channel conductance holds that individual channel gates open or close independently of one another (but as a function of membrane voltage) in a probabilistic fashion. Let π_o and π_c denote the probability a gate is open or closed, respectively. By the convention $\pi_o + \pi_c = 1$, or $\pi_c = 1 - \pi_o$. The rate at which closed gates transition to an open state is governed by a rate constant, α, which has units of 1/time and is a function of membrane voltage but not of time. The rate at which open gates transition to the closed state is governed by another rate constant, β. The probability of a gate being in the open state is then governed by the first-order rate equation

$$\frac{d\pi_o}{dt} = \alpha(1-\pi_o) - \beta\pi_c .$$

Let n denote the open probability of the potassium channel, and the constant g_K denote the maximum potassium channel conductance. By empirical experiments, Hodgkin and Huxley found they could express the K^+ channel conductance as

$$G_K = g_K.n^4 .$$

Furthermore, let the open probability for the activation gate of the sodium channel be denoted by the symbol m, and the open probability for the inactivation gate be denoted by the symbol h. The sodium channel conductance is a function of both m and h. Letting g_{Na} denote the maximum sodium channel conductivity, Hodgkin and Huxley found the empirical expression for the sodium channel conductance to be

$$G_{Na} = g_{Na}.m^3h .$$

The complete Hodgkin-Huxley model [HH] consists of the differential equation (1) for the circuit of Figure 1 and the three differential equations describing the rate processes. Summarizing the four model equations, we get

$$\begin{aligned} C\frac{dV_m}{dt} &= -G_{Na}(V_m - E_{Na}) - G_K(V_m - E_K) - G_{lk}(V_m - V_{lk}) \\ \frac{dn}{dt} &= -(\alpha_n + \beta_n)n + \alpha_n \\ \frac{dm}{dt} &= -(\alpha_m + \beta_m)n + \alpha_m \\ \frac{dh}{dt} &= -(\alpha_h + \beta_h)n + \alpha_h . \end{aligned} \qquad (2)$$

Equations (2) are coupled through the dependence of the rate "constants" $\alpha_n, \beta_n, \alpha_m, \beta_m, \alpha_h, \beta_h$ on V_m and the dependence of the conductances G_X on the

probabilities *n*, *m*, and *h*. Thus the system represented by equations (2) is equivalent to a representation in terms of a fourth-order nonlinear ordinary differential equation.

Nowadays, after the pioneering work of Nobel laureates Hodgkin and Huxley [HH], many more different ion channels, pumps and exchangers are known, as well as their applications to cardiac cells and the roles of ionic currents in arrhythmia mechanisms, [NR, SWPWB, HVVR, PG].

THE THERMODYNAMIC MODEL BY HEIMBURG AND JACKSON

As various authors have noted, action potentials are accompanied by reversible mechanical dislocations, changes in volume and temperature, and changes in fluorescence, turbidity, and birefringence. In particular, data indicate that heat release is exactly in phase with the action potential, and that there is no net heat release after completion of the action potential, (cf. [HJ1, HJ2, AJH, VLHGJH] and references therein). As pointed out in [HJ1], the isentropic behavior of the nerve pulse is considered in Hodgkin's book [H], where it is noted that the heat release and absorption response during the action potential are important but not understood.

In a series of papers from 2005 to 2011 T. Heimburg and A. Jackson have proposed a new thermodynamic approach towards deeper understanding of the nerve pulse propagation. Their electromechanical description based on thermodynamics allows for correct predictions of many of the observed properties of nerve signal propagation such as the change in

membrane potential, the reversible heat, the induction of axon potentials through local nerve cooling, the physical expansion of nerves during the action potential, and the action of anesthetics.

Careful studies on the structure of lipid biomembranes show that such lipids display melting transitions at a specific temperature where both the lateral and chain order of the lipid molecules are lost. The low and high temperature phases are called solid-ordered and liquid-disordered, respectively, indicating the simultaneous change in lateral crystalline arrangement and chain order. They are also known as gel and fluid phase, respectively. In the order–disorder transitions membranes absorb heat while the transition from lipid fluid to gel state is associated with the release of heat. Body temperature (for bacteria: the growth temperature) is slightly above that of the lipid melting transition.

When the nerve membrane is subjected to a propagating action potential, a region of the membrane is compressed locally and forced through the transition from fluid to gel state. This increases the local density of the medium and creates a wave. As the membrane can be considered a long and narrow cylinder, lipid membranes thus have the properties required for the generation and propagation of solitons. A soliton is a self-reinforcing solitary wave that maintains its shape while it travels at a constant speed along the membrane. Solitons can propagate over extended distances without loss of energy. The soliton model for nerve pulse propagation proposed by Heimburg and Jackson [HJ1] suggests that action potentials cause a transient transition of the membrane from fluid to gel state with the associated production of latent heat and the reabsorption of an identical quantity of heat as the system returns to the fluid state. Heimburg and Jackson [HJ1] also suggest that the action potentials consist of propagating density pulses and show that stable propagating density pulses in cylindrical lipid membranes can be obtained provided that the membrane exists in a physical state slightly above the melting transition.

Following [HJ1], let us denote by $H_0(T)$, $V_0(T)$ and $A_0(T)$ the temperature-dependent enthalpy, specific volume and specific area of the gel phase respectively, and let $\Delta H(T)$, $\Delta V(T)$ and $\Delta A(T)$ be the excess of these parameters associated with the melting transition. It has been found experimentally that the volume and area changes in the chain melting transition are proportional to the changes in enthalpy

$$\Delta V(T) = \gamma_V \, \Delta H(T)$$
$$\Delta A(T) = \gamma_A \, \Delta H(T)$$

with constants of proportionality γ_V, γ_A approximately the same for various artificial lipids and for biological membranes, [EGH]. Since the heat capacity (c_P), the isothermal volume compressibility (κ_T^V) and the lateral compressibility (κ_T^A) are related to fluctuations in enthalpy, volume, and area, using the fluctuation dissipation theorem Heimburg and Jackson have obtained the elastic constants as functions of the heat capacity

$$\kappa_T^V = \kappa_{T,0}^V + \frac{\gamma_V^2 T}{V} \Delta c_P$$
$$\kappa_T^A = \kappa_{T,0}^A + \frac{\gamma_A^2 T}{A} \Delta c_P$$

Here $\kappa_{T,0}^V$ and $\kappa_{T,0}^A$ are the compressibility constants outside of the transition range.

The adiabatic compressibilities relevant for sound propagation can be determined from the isothermal compressibilities. Using Maxwell's relations one can show that

$$\kappa_S^V = \kappa_T^V - \frac{T}{V \, c_P} \left(\frac{dV}{dT} \right)_P^2$$
$$\kappa_S^A = \kappa_T^A - \frac{T}{A \, c_P} \left(\frac{dA}{dT} \right)_P^2 .$$

It has been found experimentally and theoretically that the adiabatic compressibility is in general frequency dependent [HJ1]. Since the sound propagation velocity in elastic media is expressed as function of the adiabatic compressibility by

$$c = \frac{1}{\sqrt{\rho^A \kappa_S^A}}$$

where ρ^A is the lateral area density, the sound velocity is frequency dependent and hence dispersion occur in the lipid melting transition.

On the other hand, close to the melting transition Heimburg and Jackson [HJ1] have shown that κ_S^A depends sensitively on temperature and therefore also on density. Both the liquid and gel phases are relatively incompressible. Heimburg and Jackson have shown that at densities near the phase transition where the two phases co-exist, a small increase in pressure can cause a significant increase in density by converting liquid to gel. Near this phase transition, the compression modulus (the reciprocal of κ_S^A) is dramatically smaller. Thus the sound velocity, *c*, can be approximated as

$$c^2 = \frac{1}{\rho^A \kappa_S^A} = c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2$$

with $p < 0, q > 0$ and $c_0 = 1/\sqrt{\rho_0^A \kappa_S^A}$ is the velocity of small amplitude sound.

As the lipid membrane can be interpreted as long and narrow cylinder, the sound propagation along the membrane is considered only in one dimension, *x*. The

hydrodynamic equation for the propagation of such a density pulse in the presence of dispersion is given by

$$\frac{\partial^2}{\partial t^2}\Delta\rho^A = \frac{\partial}{\partial x}\left[c^2\frac{\partial}{\partial x}\Delta\rho^A\right] - h\frac{\partial^4}{\partial x^4}\Delta\rho^A$$

or

$$\frac{\partial^2}{\partial t^2}\Delta\rho^A = \frac{\partial}{\partial x}\left[\left(c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2\right)\frac{\partial}{\partial x}\Delta\rho^A\right] - h\frac{\partial^4}{\partial x^4}\Delta\rho^A$$

describing the changes of the lateral membrane density $\Delta\rho^A = \rho^A - \rho_0^A$ (ρ_0^A is the lateral area density in the fluid phase of the membrane) as a function of time and space. Here the dispersive effects discussed above are introduced by a dispersive term, $-h\frac{\partial^4}{\partial x^4}\Delta\rho^A$ with $h > 0$. The propagating solitons are examined of the form $\Delta\rho^A(z)$ with $z = x - \nu t$ and are solutions of the fourth-order ODE

$$\nu^2\frac{\partial^2}{\partial z^2}\Delta\rho^A = \frac{\partial}{\partial z}\left[\left(c_0^2 + p\Delta\rho^A + q(\Delta\rho^A)^2\right)\frac{\partial}{\partial z}\Delta\rho^A\right] - h\frac{\partial^4}{\partial z^4}\Delta\rho^A$$

satisfying $\Delta\rho^A \to 0$ as $|z| \to \infty$.

THE EXTENDED FISHER—KOLMOGOROV EQUATION

Many biological structures exhibit *liquid-crystal* behavior. In particular, biological membranes and cell membranes are a form of liquid crystal [CXZ]. These liquid crystal membrane phases can also host important proteins such as receptors freely “floating” inside, or partly outside, the membrane.

The anisotropy of liquid crystals causes them to exhibit *birefringence*. That is, light that enters the crystal is broken up into two oppositely-polarized rays that travel at different velocities. Observation of a birefringent material between crossed polarizing filters reveals striking *patterns* and color effects.

The liquid crystals in a *nematic* phase are composed of rod-like molecules with the long axes of neighboring molecules aligned approximately to one another. The description of this anisotropic structure involves an analysis of order. An *order parameter* is used to describe the orientational order of a nematic liquid crystal and the distinction between phases in equilibrium in thermodynamic processes [U].

Kolmogorov, Petrovskii and Piskunov [KPP] in 1937 proposed a nonlinear second-order diffusion equation as a model for the spread of a successful gene within a natural biological population. In the field of spatial pattern formation this equation, later known as Fisher—Kolmogorov equation (FK), is the prototype equation for the study of front propagation in bistable systems. The FK equation represents a bistable system with two spatially homogeneous stable states at ± 1 and an unstable state at 0. In the extended Fisher—Kolmogorov equation (EFK)

$$\frac{\partial\phi}{\partial t} = \frac{\partial^2\phi}{\partial x^2} - \gamma\frac{\partial^4\phi}{\partial x^4} + \phi - \phi^3, \quad \gamma > 0,$$

originating from the studies of phase transitions near critical points, the bistabe dynamics remain. EFK has been proposed by Dee and Van Saarloos [DS] who have showed that fronts propagating into an unstable state can dynamically create a periodic array of kinks. These kinks separate large regions in which the system is essentially in one of the two

stable states. The pattern behind the front is rather different from those found in instabilities.

As discussed in [DS], examples of such behavior occur in the dynamics of fronts near the Fréedericksz transition in liquid crystals. This is the effect of deformation in liquid crystals due to the application of an electric field. Let us consider the case where liquid crystal molecules are aligned parallel to the cell surface and an electric field is applied perpendicular to the cell. At first, as the electric field increases in magnitude, no change in alignment occurs. However at a threshold magnitude of electric field, deformation occurs where the molecules change its orientation from one molecule to the next. The occurrence of such a change from an aligned to a deformed state is called a Fréedericksz transition.

The author suggests that the processes discussed in the last section are relevant to the nerve signal processing but at this stage further study is necessary.

ACKNOWLEDGEMENTS

This paper is supported by University of Ruse under Project 2017-FPNO-03. The author is grateful to Dr. P. Gurkovski for numerous discussions on the subject and encouragement in writing the manuscript.

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МАТЕМАТИЧЕСКО МОДЕЛИРАНЕ НА ПОТЕНЦИАЛА НА ДЕЙСТВИЕТО В НЕВРОБИОЛОГИЯТА

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Резюме: *Обработката на сигнали при живите организми е предизвикателна интердисциплинарна област с корени във физиологията и свързва усилията на биолози, химици, физици, математици, инженери и компютърни специалисти. Успешното лечение на ментални увреждания и изкуствения интелект са в големия диапазон на възможните приложения.*

В тази статия се представят различни математически модели при разпространението на нервни импулси като известния електричен модел на Ходжкин-Хаксли, както и съвременния термодинамичен модел на Хеймбург и Джаксън.

Ключови думи: *невронна мембрана, йонен канал, потенциал на действието, модел на Ходжкин-Хаксли, липиди, преход при топене, термодинамика.*

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ISSN 1314-3077