BRIEF REPORT

An equation for the biological transmembrane potential from basic biophysical principles [version 1; peer review: 2 not approved]

Marco Arieli Herrera-Valdez

Laboratorio de Fisiología de Sistemas, Departamento de Matemáticas, Facultad de Ciencias, Universidad Nacional Autónoma de México, Mexico City, CDMX, 04510, Mexico

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Abstract

Biological membranes mediate different physiological processes necessary for life, many of which depend on ion movement. In turn, the difference between the electrical potentials around a biological membrane, called transmembrane potential, or membrane potential for short, is one of the key biophysical variables affecting ion movement. Most of the existing equations that describe the change in membrane potential are based on analogies with resistive-capacitive electrical circuits. These equivalent circuit models assume resistance and capacitance as measures of the permeable and the impermeable properties of the membrane, respectively. These models have increased our understanding of bioelectricity, and were particularly useful at times when the basic structure, biochemistry, and biophysics of biological membrane systems were not well known. However, the parts in the ohmic circuits from which equations are derived, are not quite like the biological elements present in the spaces around and within biological membranes. Using current, basic knowledge about the structure, biophysics, and biochemical properties of biological membrane systems, it is shown here that it is possible to derive a simple equation for the transmembrane potential. Of note, the resulting equation is not based on electrical circuit analogies. Nevertheless, the classical model for the membrane potential based on an equivalent RC-circuit is recovered as a particular case, thus providing a mathematical justification for the classical models. Examples are presented showing the effects of the voltage dependence of charge aggregation around the membrane, on the timing and shape of neuronal action potentials.

Keywords

Transmembrane potential, membrane biophysics, membrane physiology, excitable membrane, computational neuroscience, computational physiology.

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1. **James Weifu Lee** , Old Dominion University, Norfolk, USA

2. **Christian Brosseau**, Université de Bretagne Occidentale, Avenue Le Gorgeu, France

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Corresponding author: Marco Arieli Herrera-Valdez (marcoh@ciencias.unam.mx)

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Introduction

Biological membranes mediate communication between cellular compartments and their surrounding environments (Blaustein *et al.*, 2004; Boron & Boulpaep, 2016; Helman & Thompson, 1982; Sten-Knudsen, 2002). One of the most important biophysical variables affecting, and affected by such communication, is the difference between the electrical potentials inside and outside the cellular membrane, called transmembrane potential, or membrane potential, for short (Johnston *et al.*, 1995; Sperelakis, 2012; Weiss, 1996). Paraphrasing Cole (Cole, 1933), the existence of the membrane potential is, by itself, an indication of the fact that a cell is alive. The ongoing changes in the membrane potential are physiological correlates of cellular activity in different levels of organization, within the cell itself and its surroundings. Therefore, it is important to have a basic understanding of the biophysical principles underlying its behaviour.

The transmembrane potential is generated by the presence of ions of different species on both sides of the membrane (Briggs, 1930; Brooks, 1929) and differences in their passive transmembrane permeabilities (Cole, 1940; Fricke, 1925; Höber, 1936). The membrane potential is also dynamically affected by passive and active transport processes (Blaustein *et al.*, 2004; Boron & Boulpaep, 2016) that underlie electrical signaling and other physiological functions (Eisenberg, 1990; Eisenberg, 1998; Hille, 1992; Höber *et al.*, 1939; Hodgkin & Katz, 1949a; Hodgkin & Katz, 1949b). Conversely, ion transport is itself dependent on changes in the transmembrane potential.

Modeling approaches have been useful to describe electrical and biochemical interactions involving ions, and how they affect the membrane potential (Fricke, 1925; Osterhout, 1933; Teorell, 1935). Many models of biological membranes are based on constructing equivalent electrical circuits (Hermann, 1899; Hermann, 1905) using conservative paradigms like Kirchoff's law of electrical current for RC-circuits (Cole, 1933; Fricke, 1931; Hermann, 1872; Johnson *et al.*, 1989). Of seminal importance, the Hodgkin & Huxley (1952) model describes the changes in membrane potential with a system of differential equations derived from an RC-circuit. The equations in the model are derived by considering an electrical circuit with resistors, a capacitor, and a battery arranged in parallel, respectively representing what is known today as membrane channels, the neighborhood around the membrane, and the membrane potential. The total current in the model is the sum of a "capacitive" current representing flow of electrical charge around the membrane, and different resistive currents representing different transmembrane ion fluxes, now known to be mediated by channels selective to ions of specific types (Hodgkin *et al.*, 1952). Ionic transmembrane currents are, however, not resistive, as ions cross the membrane either by diffusion (Eisenberg, 1998; Neher & Sakmann, 1976), or via mechanical translocation by protein pumps (Gadsby, 2009). However, ions moving across a membrane are not like electrons through a wire and the lipid bilayer of the membrane is not quite like the air-filled space between the plates in a capacitor.

In partial agreement with the basic postulates of models based on equivalent circuits, present knowledge about the molecular structure and biochemistry of biological membranes supports the idea that charged molecules accumulate next to the hydrophilic heads of the lipid bilayer that forms the outer portion of the membrane, and that the density of charge around the membrane is increasing as a function of the membrane potential (Everitt & Haydon, 1968; Wobischall, 1972). One important assumption for the equivalent circuit, is that the charge aggregation around the membrane is proportional to voltage, which implies that the time-dependent rate of change of such a flow is assumed to be constant. Several studies report that the specific membrane capacitance for membranes of multiple cell types is approximately $1 \mu\text{F}/\text{cm}^2$ (Cole & Curtis, 1938a; Cole & Curtis, 1938b; Cole & Hodgkin, 1939; Galligan *et al.*, 2000; Gentet *et al.*, 2000). The charge density around the membrane is, however, not necessarily proportional to the membrane potential (Kilic & Lindau, 2001; Weinberg, 2015). One reason for the potential divergence is that there are multiple problems associated to measuring the membrane capacitance experimentally (Golowasch *et al.*, 2009; Weinberg, 2015). Perhaps the most important issue in this regard is the non-isopotentiality of the electric fields around membranes.

Shown herein, it is possible to derive a simple differential equation that describes the change in the transmembrane potential in a small patch of membrane from basic biophysical considerations, without using electrical circuit analogies. Importantly, a particular case of this generalised formulation explains the phenomenological formulation based on an equivalent circuit originally proposed by Hermann, Hodgkin and Huxley, and others (Hille, 1992). The generalisation and the possibility of explaining an already existing model are in line with the thinking behind the thermodynamic model for transmembrane transport (Herrera-Valdez, 2018), which proposes a general formulation for the molecular fluxes mediated by different physiological transmembrane transport mechanisms, both passive and active, and explains conductance based models as linear approximations around the reversal potential in the case of electrogenic transport.

Once the derivation is explained, it is illustrated with two simple examples of membrane excitability.

Biophysical derivation to describe the transmembrane potential

Consider a small volume Ω containing a small portion of a cellular membrane, together with the extracellular and intracellular compartments in the immediate neighborhood around the membrane. Assume, each of these compartments is filled with physiological solution containing ions of different species, and assume also that the number of ions for each of the different ion species is constant. Let Q_a represent the density of charge around the membrane (Coulombs/ μm^2). Assume also that each of the ion types has some permeability across the membrane, and let Q_m represent the charge density in the space within the lipid bilayer of the membrane (Coulombs/ μm^2). By extension, the

total number of ions in the system and the total charge density $Q_a + Q_m$ (in Coulombs) are constant with respect to time.

Let $U_e(t)$ and $U_i(t)$ (in Volts) represent the electrical potential in the extra- and intracellular compartments, respectively. The difference $v(t) = U_i(t) - U_e(t)$ is the transmembrane potential, or by simplicity, membrane potential. For conceptual simplification, if the extracellular potential is equal to zero, then the transmembrane potential could be thought of as the intracellular potential. Since ions tend to accumulate around the membrane as v increases in size, whether positive or negative, the net charge density (Coulombs/ μm^2) around the membrane can be assumed to be some smooth, monotonic, increasing function $Q_a(v)$, equal to zero for $v = 0$ (Figure 1A).

It follows from the assumption of constant total charge that the time-dependent change in the total charge density is zero. That is,

$$0 = \partial_t Q_a(v(t)) + \partial_t Q_m(t). \quad (1)$$

Here ∂_t represents the instantaneous rate of change with respect to time. Therefore, the term $\partial_t Q_m(t)$ represents the current density (Amperes/ μm^2) carried by different ions across the membrane and $\partial_t Q_a(v(t))$ represents the current density around the membrane.

Equation (1) yields a differential equation for v in terms of the ionic flux across the membrane, normalized by rate of change

Figure 1. (A) Three profiles for $Q_a(v)$, the voltage-dependence of the charge density around the membrane. The three functions can be regarded as similar around $v = 0$ and (B) Rate of change for the three Q_a profiles as a function of voltage.

in charge density around the membrane with respect to v . To see this, note first that applying the chain rule to the term representing the charge density around the membrane yields

$$\partial_t Q_a(v(t)) = \partial_v Q_a \cdot \partial_t v, \quad (2)$$

with $\partial_t v$ in V/s and $\partial_v Q_a$ in Coulombs/ μm^2 per Volt. Also, the current density across the membrane can be thought of as proportional to the total transmembrane flux of charge. Substitution of Equation (2) into Equation (1), and rewriting after solving for $\partial_t v$ yields

$$\partial_t v = \frac{1}{\partial_v Q_a} \partial_t Q_m, \quad (3)$$

where $\partial_t Q_m(t)$ represents the total transmembrane current density carried by the different ion types around the membrane (Amperes/ μm^2). To build specific models, the transmembrane flux $\partial_t Q_m$ can be substituted by a sum of different transmembrane ionic fluxes associated to different physiological transport mechanisms (Herrera-Valdez, 2018).

The multiplicative inverse of $\partial_v Q_a$ can be thought of as a scaling factor for the change in the membrane potential. Note Q_a is cannot be a constant. If Q_a is a linear function of v , then the scaling is a constant. If Q_a is nonlinear as a function of v , then the scaling changes dynamically with v , possibly amplifying or dampening, depending on the way v changes in time. These possibilities are explored by analysing the effects of the profile of charge accumulation around the membrane on the generation of neuronal action potentials.

An important particular case that gives theoretical justification to the equivalent circuit analogy for membranes as a linear approximation is analysed in the following section. Having done that, the behaviour of the dynamics for v are explored using two nonlinear profiles for Q_a (Figure 1A) that behave similarly to the linear case near $v = 0$, but differ in that one saturates, and the other grows exponentially, as the membrane is polarised.

The membrane capacitance from equivalent circuit models

Assume that charge aggregation around the membrane is linear as a function of voltage. That is,

$$Q_a(v) = C_m v,$$

(in Coulombs per μm^2), where C_m is a constant that describes the voltage-dependent rate of charge density around the membrane (Figure 1A, black line). In this case, $\partial_v Q_a = C_m$ (Figure 1B, black line), which means that Equation (3) becomes

$$C_m \partial_t v = -\partial_t Q_m(t, v), \quad (4)$$

as proposed by Hodgkin & Huxley (1952), and others.

The change in the density of charge around the membrane, $\partial_v Q_a$, is in Coulombs per volt per μm^2 , which is equivalent to

farads/ μm^2 , the units used for electrical capacitance. The plates of a capacitor in an electrical circuit are made of conducting media (e.g. metal), and separated by air, or other insulating material. Therefore, this particular case supports the idea that the intra and extracellular media can be thought of as similar to the metal plates in the capacitor, and the membrane can be regarded as analogue to the insulating air layer between the plates.

Two nonlinear voltage dependent profiles for the density of charge around the membrane Q_a with saturation as a function of v

It is arguable that there is a voltage-dependent upper bound for the accumulation of charges around the membrane (Figure 1A, blue curve). That is, if the membrane is polarised to very large voltages (either negative or positive) the charge density around the membrane could be assumed to reach a limit. One possible description for the voltage-dependence of Q_a could be

$$Q_a(v) = 2v_T C_m \cdot \tanh\left(\frac{v}{v_T}\right), \quad (5)$$

where $v_T = k_B T / q_e$ in mV is a thermal potential, with k_B , T , and q_e are Boltzmann's constant, the absolute temperature, and the elementary charge, respectively. The rate of change of Q_a with respect to v is then,

$$\partial_v Q_a(v) = C_m \left[1 - \tanh^2\left(\frac{v}{v_T}\right) \right], \quad (6)$$

(Figure 1B, blue curve). $Q_a(v)$ in this case an odd and increasing function, bounded by the asymptotic values of $\pm 2v_T C_m$, respectively (Figure 1A, blue curve). The graph of $\partial_v Q_a$ in Equation (6) has a symmetrical shape around a local maximum at $v = 0$, always taking positive values (Figure 1B, blue curve). This means that the density of charge around the membrane tends to change less as the membrane is polarised. The amplification factor $1/\partial_v Q_a$ for the rate of change in v increases, and its maximum change occurs when the membrane is not polarised. As a consequence, $1/\partial_v Q_a$ exerts an amplification effect on $\partial_t v$ that is larger for polarised membranes, and has a minimum at $v = 0$.

Exponentially increasing charge density around the membrane

Another possibility similar to the current densities from the thermodynamic model (Herrera-Valdez, 2018), is that $Q_a(v)$ is a hyperbolic sine. In this case

$$Q_a(v) = v_T C_m \sinh\left(\frac{v}{v_T}\right), \quad (7)$$

and

$$\partial_v Q_a(v) = \frac{C_m}{2} \cosh\left(\frac{v}{v_T}\right). \quad (8)$$

The graph of $Q_a(v)$ is odd and increasing with exponential growth in both directions of the v axis (Figure 1A, orange curve), qualitatively opposite to that described earlier for the saturating Q_a with hyperbolic tangent shape. In this case $\partial_v Q_a$ has a "U"

shape with a local minimum value of C_m at $v = 0$, which means that $\partial_v Q_a$ exerts an attenuation effect on $\partial_t v$ that increases as v is further from 0 (Figure 1B, orange curve).

Note the three profiles for the charge density around the membrane presented above can be thought of as approximations of one another around $v = 0$.

Neuronal dynamics assuming voltage dependent density of charge around the membrane

How does the voltage-dependence in the charge-density around the membrane influence the changes in the transmembrane potential? Specifically, what are the effects of the nonlinearities in the voltage-dependence of $\partial_v Q_a$ on the dynamics of the transmembrane potential? To compare the effects caused by the three profiles (tanh, linear, and sinh) for Q_a , the dynamics for the transmembrane potential in a neuron were modelled (Figure 2, blue, black, and orange lines, respectively).

Consider a neuronal membrane and assume that it has three transmembrane transport mechanisms, say, voltage-dependent K^+ and Na^+ channels, and a Na^+-K^+ ATPase. If w represents the proportion of open K^+ channels and the proportion of inactivated Na^+ channels, then the dynamics of the membrane potential can then be written as

$$\partial_t v = -\frac{1}{\partial_v Q_a} [I_{NaK}(v) + I_K(v, w) + I_{Na}(v, w)], \quad (9)$$

$$\partial_t w = R_w(v) [F_w(v) - w], \quad (10)$$

with $\partial_v Q_a$ as in equations Equation (4), Equation (6), and Equation (8). The transmembrane current densities (pA) given by

$$I_{NaK}(v) = a_{NaK} \phi_{NaK}(v), \quad (11)$$

$$I_K(v, w) = a_K w \phi_K(v), \quad (12)$$

$$I_{Na}(v, w) = a_{Na} (1 - w) F_m(v) \phi_{Na}(v), \quad (13)$$

and auxiliary functions for the transmembrane fluxes, the activation rates and the steady state activation of the K^+ channels given by

$$\phi_l(v) = a_l \left[\exp\left(b_l \frac{v - v_l}{v_T}\right) - \exp\left((b_l - 1) \frac{v - v_l}{v_T}\right) \right], \quad (14)$$

Figure 2. Effects of voltage-dependent scaling on the dynamics of a neuronal action potential. The panels on the left column (A,C,E) show time series for v , Q_a , and $1/\partial_v Q_a$, respectively. The blue, black and orange lines correspond to the saturating, linear, and exponential profiles for Q_a , respectively. The panels on the right columns (B,D,F) show the corresponding trajectories of the same variables as a function of $\partial_t v$, the instantaneous change in v with respect to time.

for $l \in \{\text{NaK}, \text{K}, \text{Na}\}$, and

$$R_w(v) = r_w \left[\exp \left(b_w g_w \frac{v - v_w}{v_T} \right) + \exp \left((b_w - 1) g_l \frac{v - v_w}{v_T} \right) \right], \quad (15)$$

$$F_l(v) = \frac{\exp \left(g_l \frac{v - v_l}{v_T} \right)}{1 + \exp \left(g_l \frac{v - v_l}{v_T} \right)}, \quad l \in \{m, w\}. \quad (16)$$

A description of all the parameters and their values can be found in [Table 1](#).

Note that the ranges for the three different profiles for $\partial_v Q_a$ ([Figure 1B](#)) can be ordered by magnitude. The hyperbolic profile

for Q_a yields the lowest values for $\partial_v Q_a$, in comparison to the constant $\partial_v Q_a = C_m$, and the hyperbolic sine profile, which yields the largest values for $\partial_v Q_a$. Therefore, the scaling effects of $1/\partial_v Q_a$ on the change in transmembrane potential can be thought of in the opposite order, with larger effects caused by saturating Q_a , a smaller scaling for the linear profile, and the smallest scaling effect caused by the exponential profile. It is possible to appreciate this by comparing the trajectories of three neuronal action potentials from the same initial conditions ($v_0 = -48$ mV and $w_0 = 0.001$), obtained from the model in equations [Equation \(9\)](#)–[Equation \(16\)](#) using the same parameters ([Herrera-Valdez et al., 2013](#)), and the same initial conditions, except for their Q_a profile ([Figure 2](#)).

As anticipated, the smallest scaling effect on the change in v occurs for the hyperbolic sine profile ([Figure 2](#), orange curves, spike time at 6.62 milliseconds approx), as shown by the longer delay in the action potential in comparison with the linear and saturating profiles ([Figure 2A–B](#), black and blue curves, with spike times at 13.63 and 20.82 milliseconds, respectively). The delays to the action potential can be increased if the initial

Table 1. Parameters for the neuronal dynamics model. The reversal potential for the Na⁺-K⁺ATPase is given by $v_{\text{NaK}} = v_{\text{ATP}} + 3v_{\text{Na}} - 2v_{\text{K}}$. Initial conditions at $v_0 = -48$ mV and $w_0 = 0.001$. Note $1 \mu\text{F}/\text{cm}^2 = 10^{-2}$ pF/ μm^2 .

Parameter	Value	Units	Description
v_T	26.73	mV	Thermal potential
v_{ATP}	-420	mV	Potential associated to the hydrolysis of ATP
v_{Na}	60	mV	Nernst potential for Na ⁺
v_{K}	-90	mV	Nernst potential for K ⁺
v_m	-25	mV	Half-activation potential for the Na ⁺ channels
v_w	0	mV	Half-activation potential for K ⁺
a_{NaKa}	0.04	pA/ μm^2	Current density for the voltage-dependent Na ⁺ -K ⁺ ATPase
a_{K}	16	pA/ μm^2	Current density for the voltage-dependent K ⁺ -channels
a_{Na}	8	pA/ μm^2	Current density for the voltage-dependent Na-channels
g_m	5	-	Activation gain for the Na ⁺ channels
g_w	3	-	Activation gain for K ⁺ channels
r_w	1	ms ⁻¹	Activation rate for K ⁺ channels
s_w	0.4	-	Activation bias gain for the K ⁺ channels
s_{Na}	1/2	-	Rectification bias for the Na ⁺ channels
s_{K}	1/2	-	Rectification bias gain for the K ⁺ channels
s_{NaK}	1/2	-	Rectification bias for the Na ⁺ -K ⁺ ATPase
C_m	0.01	pF/ μm^2	Amplitude for $\partial_v Q_a$, the change in current density around the membrane with respect to voltage.

condition is lower, or decreased if higher, without altering the hierarchy in the scaling effect.

The scaling effects on $\partial_t v$ caused by the three Q_a profiles can also be appreciated in the trajectories of the $(\partial_t v, v)$ -plane, which shows a smaller area contained by the curve for the exponential-profile, in comparison to the areas bounded by trajectories produced by the linear and saturating profiles for Q_a , respectively.

The dynamical ranges for Q_a for the different profiles show smaller departures from 0 in the saturating profile with respect to the other two profiles (Figure 2C–D). This suggests that that measuring charge aggregation around the membrane during action potentials would not necessarily show large differences indicative of the Q_a profile, at least with the assumptions made here.

In contrast, the scaling induced by the inverse of $\partial_v Q_a$ is notorious in both its time-dependence of the scaling factor, and also in its trajectory as a function of $\partial_t v$ (Figure 2E–F). The larger scaling effect of the saturating profile on $\partial_t v$ can be clearly appreciated in Figure 2F, which shows the values of the scaling factors of the saturating profile during the action potential above any of the values from the linear or exponential profiles.

One indirect way of measuring the effects of the scaling factor $1/\partial_v Q_a$ on the change in membrane potential, $\partial_t v$, is to calculate the efficiency of the Na⁺current during the upstroke of the action potential (Carter & Bean, 2009). This is done by calculating the total Na⁺charge during the upstroke, and dividing it by the total charge during the same time interval. Explicitly, if starting from an initial condition $v = v_0$, the time interval between the start of the trajectory and the peak time of an action potential is $[0, T]$

$$E_{\text{Na}} = \frac{\int_{[0,T]} I_{\text{Na}}(v(t)) dt}{\int_{[0,T]} I_{\text{Tot}}(v(t)) dt}. \quad (17)$$

Scaling factors with more dampening effects would cause the Na⁺current to be less efficient.

To further illustrate the scaling effects of the Q_a profiles on $\partial_t v$, the maximum upstroke velocities, the time delays to produce action potentials, and the efficiency of the Na⁺current during the upstroke were calculated from sample trajectories obtained by increasing the values of the initial condition for v (Table (2)). In agreement with the observations made above, the decreasing amplification caused by the saturating and linear profiles (in that order) with respect to the exponential profile were negatively correlated with the efficiency, and the delay to spiking. Nevertheless, it is worth noticing that the differences decrease for larger values of v_0 .

Discussion

A simple equation describing the time evolution of the transmembrane potential has been derived from basic biophysical principles (Equation (3)). The new equation is in line with the derivation of the thermodynamic model (Herrera-Valdez, 2018), in that it only considers basic biophysical principles to describe the elements in a system that include a membrane, and ions in solution. Importantly, the derivation is *not* based on an equivalent circuit analogy, but it is general enough to allow the possibility of obtaining the traditional equation for the equivalent RC-circuit. The derivation draws from basic, current knowledge about the membrane and its surroundings and separately taking into account its ion-impermeable and ion-permeable properties, as referred by early works by Cole and Curtis and other authors. As it is desirable in any generalization, it explains a classical model proposed in seminal work previously done. Explicitly, the expression for the change in voltage-dependent in the charge density around the membrane can be simplified to obtain the so-called “membrane capacitance” in classical models. This is done by assuming that the charge density around the membrane is linearly related to the membrane potential. Interestingly, the term emerges from applying the chain-rule to calculate the time-dependent change in the total charge density around the membrane, which depends on voltage (Coombs *et al.*, 1959; Everitt & Haydon, 1968; Lu *et al.*, 1995).

From a physical perspective, changes in the sign and magnitude of the transmembrane potential should cause the charges around the membrane to redistribute (Huang, 1981; Santos-Sacchi & Navarrete, 2002). Such changes occur within very short times relative to the usual time scales taken into account for studies of membrane excitability, or electrical signalling in general.

Table 2. Maximum rate of change for v with respect to time and efficiency of the Na⁺ current during the upstroke of the action potential for the different Q_a profiles, taking into account different starting values for v .

Q_a profile	tanh	linear	sinh	tanh	linear	sinh
	max $\partial_t v$ (V/s)			Na-efficiency		
$v_0 = -46$ mV	105.951	104.341	103.227	1.07043	1.10979	1.14603
$v_0 = -47$ mV	105.829	103.954	102.423	1.08322	1.13617	1.2005
$v_0 = -48$ mV	105.704	103.442	101.25	1.09777	1.18076	1.29603

One important result from the derivation is that the change in the charge density around the membrane is not necessarily a constant, as evidenced by different reports (Amzica & Neckelmann, 1999; Neher & Marty, 1982; Proks & Ashcroft, 1995; Smith *et al.*, 1997).

For historical interest, prior to 1938 approximately, the hypothesis the membrane would disintegrate at the pass of the excitation wave during an action potential was a source of debate and reason for experimentation (Cole & Curtis, 1938a). The model presented here provides a theoretical argument that explains how changes in $\partial_v Q_a$ can take place without membrane disintegration, and enables the possibility of studying membrane systems without assuming that the amount of charge aggregation around the membrane is proportional to voltage (Everitt & Haydon, 1968; Kilic & Lindau, 2001). Cole and Curtis dismissed that hypothesis on the basis of finding very small changes in the membrane capacitance using a Wheatstone bridge to record currents from squid axons and other preparations. Of note, the change in accumulation of charge around the membrane, commonly called “membrane capacitance” is typically regarded as a constant since around the time of the seminal work of Cole in the decade of 1930’s (Cole & Curtis, 1938b; Cole & Curtis, 1939), and others (Everitt & Haydon, 1968). Further, more recent studies have also found non significant changes in membrane capacitance (Gentet *et al.*, 2000). One problem is that such measurements have been made for membrane potentials around rest. From a theoretical perspective, one reason that experimental measures of membrane capacity have proved to be difficult, is the assumption of isopotentiality, which does not hold almost surely (Chen & Gillis, 2000; Golowasch *et al.*, 2009). Nevertheless, from a physical perspective, the change in the charge density with respect to voltage, $\partial_v Q_a$, can be a non-constant function (Santos-Sacchi & Navarrete, 2002). Indeed, it has been shown

in experimental work involving exo and endocytosis (Neher & Marty, 1982; Proks & Ashcroft, 1995; Smith *et al.*, 1997), and in relation to voltage-gated currents (Kilic & Lindau, 2001). The profiles for saturation and exponential aggregation of charge around the membrane defined above suggest that experimental measures of the impermeable aspect of the membrane as originally called by Cole and Curtis and others, may be even more difficult than previously thought (but see (Kilic & Lindau, 2001)).

Of note, the runs with the saturating Q_a profile suggest a reasonable explanation for the rapid changes during the initiation of an action potential (Naundorf *et al.*, 2006), as they suggest a way to accelerate the initial depolarisation during the action potential upstroke that cannot be obtained from the Hodgkin and Huxley model.

One issue of possible importance is the timing of action potentials in a network context, which, on top of being influenced by local field potential oscillations (time-dependent forcing on Equation (3), could be subject of non-negligible rescaling effects due to voltage-dependent changes in $\partial_v Q_a$ (Amzica & Neckelmann, 1999). Future experimental measurements may shed light on this issue, as it could have large repercussions in our interpretations of network dynamics.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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Christian Brosseau

Université de Bretagne Occidentale, Avenue Le Gorgeu, Brest Cedex, France

I do not recommend the indexing of this manuscript as is because it does not add any substantial physical content to the existing literature. That is not applied physics at the level we expect. This manuscript appears to contain a presentation of data without the in-depth analysis expected. Hence, it is not sufficient to report the outcomes of experiments without drawing out new physics in the interpretation of the results. In this manuscript, there are descriptions of the Figures, but there is little said about their physical significance and what new understanding can be gained from them.

In addition to not satisfying this primary requirement, there are a number of other problems with the manuscript which together make it unsuitable for further review. For example, the English language is not of the standard required for indexing.

The title is misleading: "biological transmembrane potential" should be changed to "cell transmembrane potential".

Several important references dealing with the subject at hand are missing and are eventually not discussed, e.g. "Resistor-capacitor modelling of the cell membrane: a multiphysics analysis", *J. Appl. Phys.*, 129, 011101 (2021).¹

The author should precise the exogeneous voltage excitation and how the temporal variation of the potential can impact the membrane (and cell) parameters which eventually regulate the overall electromechanical behavior of the cell.

Several equations are not based on first principles of physics or result from an educated guess which are not fully substantiated, e.g. Eq. (7); what are the assumptions and limitations associated with this equation? Unclear.

Several statements are also unclearly discussed, e.g. "Consider a neuronal membrane and assume that it has three transmembrane transport mechanisms, say, voltage-dependent K⁺ and Na⁺

channels, and a Na⁺-K⁺ ATPase." How are the ionic channels are considered here?

Since the author does not explain what is the physics associated with the data, how all of this can be actually measured and checked, Fig. 2 is completely not understandable.

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1. Brosseau C, Sabri E: Resistor-capacitor modeling of the cell membrane: A multiphysics analysis. *Journal of Applied Physics*. 2021; **129** (1). [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

No

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 26 November 2020

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James Weifu Lee

Department of Chemistry & Biochemistry, Old Dominion University, Norfolk, VA, USA

Review Comments

This is a quite interesting manuscript, in which, the author tries "to derive a simple equation for

the transmembrane potential". As Dr. Herrera-Valdez indicated, the biophysical origin of membrane potential was indeed not entirely clear in the past 50 years until very recently. Discussions and research efforts on bioenergetics including membrane potential should be encouraged. This reviewer likes Dr. Herrera-Valdez's sprits of out-of-box thinking. However, some of the assumptions in this manuscript seem quite questionable. There are spots that need major improvements before this manuscript could be considered for indexing.

First, Dr. Herrera-Valdez seems not aware of the latest development in the field of protonic bioenergetics and membrane potential. Actually, there is already an unified framework of protonic bioenergetics with a newly formulated membrane potential equation in resolving the issues of the Mitchellian chemiosmosis: a new transmembrane electrostatic proton localization theory that has recently resulted in a new protonic action potential equation (2020 Journal of Neurophysiology, 124 (4): 1029–1044; 2020 Scientific Reports, 10:10304; 2020 ACS journal Omega 5 (28): 17385–17395; Heliyon 4 (2019) e01961; 2015 Bioenergetics 4: 121. doi:10.4172/2167-7662.1000121¹).

This reviewer encourages the author to consider the latest development including the latest membrane potential equation from the transmembrane electrostatic proton localization theory and build a better case for the science of membrane potential.

The manuscript says "let Q_m represent the charge density in the space within the lipid bilayer of the membrane (Coulombs/ μm^2)". This assumption seems quite questionable or problematic. Is there any scientific evidence for the existence of charge density Q_m "in the space within the lipid bilayer of the membrane"? Is the Q_m referring to the charges of membrane phospholipid head groups or something else since the "space within the lipid bilayer of the membrane" is hydrophobic (essentially zero charges)?

The statements "Here ∂_t represents the instantaneous rate of change with respect to time. Therefore, the term $\partial_t Q_m(t)$ represents the current density (Amperes/ μm^2) carried by different ions across the membrane and $\partial_t Q_a(v(t))$ represents the current density around the membrane" need to better be explained and justified. For example, does the $\partial_t Q_a(v(t))$ represents the current density in the bulk liquid phase around the membrane or not?

Author's Eq. 3 seems missing a negative sign.

The manuscript says: "if the membrane is polarised to very large voltages (either negative or positive) the charge density around the membrane could be assumed to reach a limit". Is there any evidence for such a case? In reality, there is no evidence for such a case in any biological systems. But, the author seems arbitrarily use a hyperbolic tangent "tanh" function to describe the voltage-dependence of Q_a (Eq. 5) without justification.

The manuscript also says: "Another possibility similar to the current densities from the thermodynamic model (Herrera-Valdez, 2018), is that $Q_a(v)$ is a hyperbolic sine". Is there any experimental evidence or justification for this case?

So, the manuscript leaves with three cases: linear, hyperbolic tangent "tanh", and hyperbolic sine "sinh"; Which one you want people to believe?

It is questionable whether a paper like that would cause confusion in the field.

Therefore, if the author could objectively address these important issues, this reviewer would consider support the indexing of his revised manuscript.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Protonic bioenergetics and membrane potentials

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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