A simple description of biological transmembrane potential from simple biophysical considerations and without equivalent circuits

Marco Arieli Herrera-Valdez[1,✉]
[1] Systems Physiology Laboratory, Department of Mathematics,
Facultad de Ciencias, Universidad Nacional Autónoma de México, CDMX, México.
✉ marcoh@ciencias.unam.mx

Abstract

Biological membranes mediate different physiological processes necessary for life, including but not limited to electrical signalling, volume regulation, and other different forms of communication within and between cells. Ion movement is one of the physical processes underlying many of such processes. 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 equations available to describe the change in membrane potential are based on analogies with resistive-capacitative electrical circuits. These equivalent circuit models were originally proposed in seminal studies dating back to 1872, and possibly earlier, and assume resistance and capacitance as measures of the permeable and the impermeable properties of the membrane, respectively. These models have been successful in shedding light on our understanding of electrical activity in cells, especially 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 possible to derive a simple, equation describing local changes in the transmembrane potential that is not based on electrical circuit analogies. The classical model for the membrane potential based on an equivalent RC-circuit is recovered as a particular case from the general derivation presented here, and concepts like the membrane capacitance can be explained as particular cases of the new equation. Modelling examples are presented to illustrate the use of the derivation, and the effects of changes in the voltage dependence of charge aggregation around the membrane on the timing and shape of neuronal action potentials.

1 Introduction

Biological membranes mediate communication between cellular compartments and their surrounding environments (Blaustein et al., 2004; Boron and Boulpaep, 2016; Helman and 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 membrane, called transmembrane potential, or membrane potential for short (Johnston et al., 1995; Sperelakis, 2012; Weiss, 1996). Paraphrasing Cole (1933), the existence of the membrane potential is, by itself, an indication of the fact that a cell is alive, and changes in the membrane potential are physiological correlates of cellular activity, which has effects on its micro environment, and possibly on other neighbouring cells. By extension, the membrane potential is a key determinant of electrical

and biochemical signalling in different levels of biological organisation, so basic understanding the biophysical principles underlying its behaviour is important.

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 and Boulpaep, 2016) that underlie electrical signaling and other physiological functions (Eisenberg, 1998, 1990; Hille, 1992; Höber et al., 1939; Hodgkin and Katz, 1949a,b). On the converse, 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, 1905, 1899) using conservative paradigms like Kirchoff's law (Cole, 1933; Fricke, 1931; Hermann, 1872; Johnson et al., 1989). Of seminal importance, the Hodgkin and Huxley (1952) model describes the changes in membrane potential with a system of differential equations derived from an RC-circuit with resistors, a capacitor, and a battery arranged in parallel, respectively representing what is known today as membrane channels, its surrounding compartments, and the membrane potential. The total current in the model is the sum of a "capacitative" current representing electrical flow 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 and Sakmann, 1976) or via mechanical translocation by protein pumps (Gadsby, 2009) 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 agreement with the basic postulates of models based on equivalent circuits, current knowledge of 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 and Haydon, 1968; Wobschall, 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 constant. Several studies report that the specific membrane capacitance for membranes of multiple cell types is approximately 1 μF/cm^2 (Cole and Curtis, 1938a,b; Cole and Hodgkin, 1939; Galligan et al., 2000; Gentet et al., 2000). However, the charge density around the membrane is, however, not necessarily proportional to the membrane potential (Kilic and Lindau, 2001; Weinberg, 2015); in potential contradiction to the idea of a constant membrane capacitance as a function of voltage. 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.

It is possible to derive a simple differential equation that describes the change in the transmembrane potential in a small patch of membrane by taking into account the charge densities of ions in

and around the membrane, 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. Briefly, a general expression for the voltage-dependent change in the charge around the membrane can be simplified to obtain the so-called "membrane capacitance" 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 and Haydon, 1968; Lu et al., 1995). The generalisation and the possibility of explaining an already existing model are in line with the thinking behind the thermodynamic model for transmembrane transport by Herrera-Valdez (2018), a general formulation for physiological transmembrane transport mechanisms, both passive and active, which explains conductance based models as linear approximations.

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

2 Biophysical derivation to describe the transmembrane potential

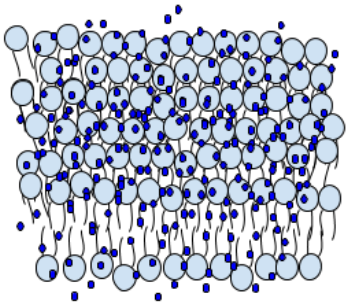
Consider a small volume Ω containing a small portion of a cellular membrane, together with the extracellular and intracellular compartments in the immediate neighborhood around the membrane (Fig. 1). Assume, each of these compartments is filled with physiological solution containing ions of different species, and assume also that the number of ions for the different ion species is constant. By extension, the total number of ions in the system and the total charge (in Coulombs) are constant in time too. Assume also that each of the ion types has some permeability across the membrane and as a consequence, there is a time-dependent charge density $Q_m(t)$ in the space within the lipid bilayer of the membrane.

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 can be thought of as the intracellular potential. Since ions tend to accumulate around the membrane as v increases, 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 $v = 0$ (Fig. 1).

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

$$0 = \partial_t Q_a(v(t)) + \partial_t Q_m(t). \tag{1}$$

Here ∂_t represents the instantaneous rate of change with respect to time. Therefore, 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.



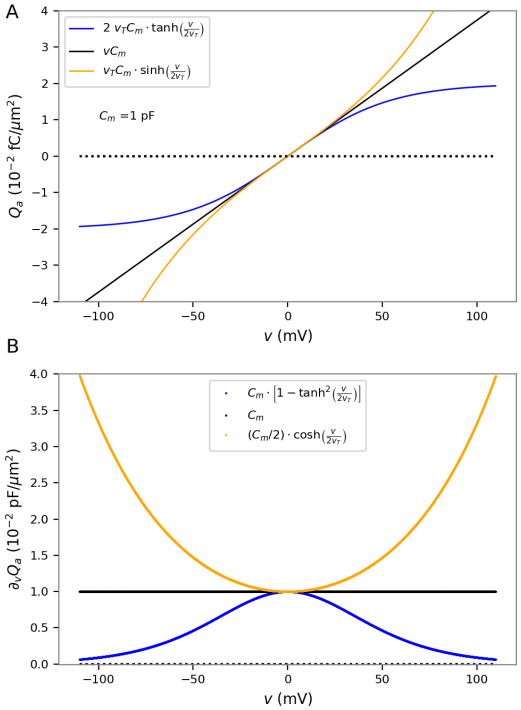


Figure 1: (Above) Schematic showing a plasma membrane with ions around and within the space in the lipid bilayer. (A) Three profiles for $Q_a(v)$, the voltage-dependence of the charge density around the membrane. The three functions can be regarded as similar around $v = 0$ and (B) Rate of change for the three Q_a profiles as a function of voltage changes as a function of voltage (bottom)

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

$$\partial_t Q_a(v(t)) = \partial_v Q_a \cdot \partial_t v, \tag{2}$$

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

$$\partial_t v = -\frac{1}{\partial_v Q_a}\ \partial_t Q_m. \tag{3}$$

where $\partial_t Q_m(t)$ represents the total transmembrane current density carried by the different ion types around the membrane (Amperes/μm^2).

The multiplicative inverse of $\partial_v Q_a$ can be thought of as a scaling factor for the change in the membrane potential. If the profile for $Q_a(v)$ is nonlinear, then the scaling varies dynamically, possibly amplifying or dampening the way that v changes in time. One way to explore this possibility is to examine how the profile of charge accumulation around the membrane affects the dynamics of a neuronal action potential.

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).

An important particular case that gives theoretical validation to the equivalent circuit analogy for membranes is quickly analysed by defining Q_a explicitly in the following section. Having done that, the behaviour of the dynamics for v are explored using two more profiles for Q_a (Fig. 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.

2.1 Linear accumulation of charge around the membrane and the membrane capacitance from the 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 (Fig. 1A, black line). In this case, $\partial_v Q_a = C_m$, which means that equation (3) is then

$$C_m \, \partial_t v = -\partial_t Q_m(t, v), \tag{4}$$

as proposed by Hodgkin and Huxley (1952), among others (Fig. 1B, black line).

The change in charge density around the membrane, $\partial_v Q_a$, is in coulombs per volt per μm^2, which is equivalent to farads/μm^2, the same units 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, and the membrane can be regarded as analogue to the insulating air layer between the plates.

2.2 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 an upper bound for the accumulation of charges around the membrane (Fig. 1A, blue curve) as a function of voltage. That is, if the membrane is polarized to very large voltages (either negative or positive) the charge density around the membrane could be assumed to reach a limit. If this is the case, then the dependence of Q_a on voltage would be given by

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

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. The rate of change of Q_a with respect to v is then,

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

The graph of $Q_a(v)$ is odd and increasing, bounded by the asymptotic values of $\pm 2C_m$, respectively (Fig. 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 (Fig. 1B, blue curve). This means that the charge density around the membrane does not change much when 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 (minimal amplification). 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,

$$Q_a(v) = v_T C_m \sinh\left(\frac{v}{2v_T}\right), \tag{7}$$

and

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

The graph of $Q_a(v)$ is odd and increasing with exponential growth in both directions of the v axis (Fig. 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 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 (Fig. 1B, orange curve).

The nonlinear dependence of $\partial_v Q_a$ from equations (6) and (8) could produce very different effects on the dynamics of the transmembrane potential.

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

2.3 Neuronal dynamics assuming voltage dependent density of charge around the membrane

The dynamics for the transmembrane potential in a neuron were modelled for to compare the effects caused by the three profiles ($\tanh$, linear, and $\sinh$) for the density of charge around the membrane Q_a (Fig. 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

$$\partial_t v = -\frac{1}{\partial_v Q_a}\left[I_{\mathrm{NaK}}(v) + I_{\mathrm{K}}(v,w) + I_{\mathrm{Na}}(v,w)\right] \tag{9}$$

$$\partial_t w = R_w(v)\left[F_w(v) - w\right] \tag{10}$$

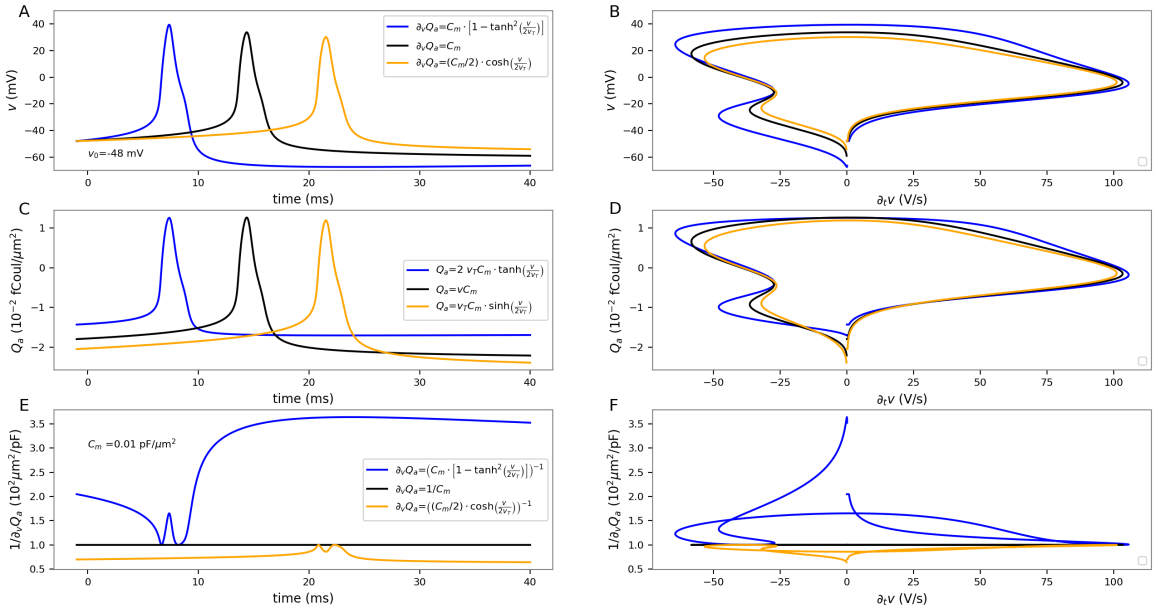


Figure 2: Effects of voltage-dependent scaling by the change in charge density around the membrane, on the dynamics of a neuronal action potential. The panels on the left column (A,C,E) show time series for v, Q_a, and $1/\partial_v Q_a$, respectively. The blue, black and orange lines correspond to the 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.

with transmembrane currents (pA) given by

$$I_{\rm NaK}(v) = a_{\rm NaK}\phi_{\rm NaK}(v) \tag{11}$$
$$I_{\rm K}(v,w) = a_{\rm K} w \phi_{\rm K}(v) \tag{12}$$
$$I_{\rm Na}(v,w) = a_{\rm Na}(1-w)F_m(v)\phi_{\rm Na}(v) \tag{13}$$

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

$$\phi_\iota(v) = a_\iota \left[\exp\left(b_\iota \frac{v-v_\iota}{v_T}\right) - \exp\left((b_\iota - 1)\frac{v-v_\iota}{v_T}\right)\right], \quad \iota \in \{\rm NaK, K, Na\} \tag{14}$$
$$R_w(v) = r_w \left[\exp\left(b_w g_w \frac{v-v_w}{v_T}\right) + \exp\left((b_w - 1) g_\iota \frac{v-v_w}{v_T}\right)\right], \tag{15}$$
$$F_\iota(v) = \frac{\exp\left(g_\iota \frac{v-v_\iota}{v_T}\right)}{1+\exp\left(g_\iota \frac{v-v_\iota}{v_T}\right)}, \quad \iota \in \{m, w\} \tag{16}$$

A description of all the parameters and their values can be found in Table 1.

Table 1: Parameters for the neuronal dynamics model. The reversal potential for the Na^+-K^+ATPase is given by $v_{\mathrm{NaK}} = v_{\mathrm{ATP}} + 3v_{\mathrm{Na}} - 2v_{\mathrm{K}}$. Initial conditions at $v_0 = -48$ mV and w_0=0.001. Note 1 μF/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	1	pF	Amplitude for Q_a, the current density around the membrane

Note that the ranges for the three different profiles for $\partial_v Q_a$ (Fig. 1) can be ordered by magnitude. The hyperbolic profile for Q_a yields the lowest values for $\partial_v Q_a$, followed by the constant $\partial_v Q_a = C_m$, surpassed by the hyperbolic sine profile that yields the largest values for $\partial_v Q_a$. Therefore, the scaling effects of $1/\partial_t Q_a$ on the change in transmembrane potential can be thought of in the opposite order, with larger effects caused by Q_a with the saturating profile, a smaller scaling for the linear profile, and the smallest scaling effect for 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 Eqs. (9)-(16) using the same parameters (Herrera-Valdez et al., 2013), except for their Q_a profile (Fig. 2).

As anticipated, the smallest scaling effect on the change in v occurs for the hyperbolic sine profile (Fig. 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 (Fig. 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 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 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 (Fig. 2C-D). This means that measuring charge aggregation around the membrane during action potentials would not necessarily show large differences indicative of the Q_a profile. However, 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 $\partial_t v$ (Fig. 2E-F). The larger scaling effect of the saturating profile on the time-dependent change in v can be clearly appreciated in Fig. 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 $1/\partial_t Q_a$ on the change in membrane potential, is to calculate the efficiency of the Na^+current during the upstroke of the action potential. In brief, this is done by calculating the total Na^+charge during the upstroke, and dividing it by the total charge during the same time interval. To further illustrate the scaling effects of the Q_a profiles on $\partial_t v$, a small sample was obtained increasing the values of the initial condition for v, and the maximum upstroke velocities, spike times, and efficiency of the Na^+current during the upstroke were calculated in each case (Table (2)). In agreement with the observations made above, the larger amplification effect of the saturating and linear profiles (in that order) with respect to the exponential profile was well correlated with the efficiency and delay to spiking for each comparison of Q_a profiles. Nevertheless, it is worth noticing that the differences are less noticeable for larger values of v_0.

For the simulations shown above, the efficiencies increased for the saturating, linear, and exponential Q_a profiles, respectively, reflecting the decreased effect of the scaling factor $1/\partial_v Q_a$ on $\partial_t v$, upon depolarization (Table 2).

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 profiles taking into account different starting voltages.

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

3 Discussion

A simple equation describing the time evolution of the transmembrane potential has been derived from basic principles (equation (3)). 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 and explain the so-called "membrane capacitance" as a particular case; a desirable property of any generalisation. The derivation draws from current knowledge about the structure of the membrane and its transmembrane proteins, and stems from a separating the ion-impermeable and ion-permeable aspects of the membrane, as referred by Cole and Curtis and other authors. The new equation is

in line with the derivation of the 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.

From a physical perspective, changes in the sign and magnitude of the transmembrane potential should cause changes in the density of charges around the membrane (Huang, 1981; Santos-Sacchi and Navarrete, 2002). Nevertheless, The membrane capacitance is typically regarded as a constant measure (Cole and Curtis, 1939). One important result from the derivation is that the change in the charge density around the membrane is not necessarily a constant, as initially found in early works experiments works (Cole and Curtis, 1938b; Everitt and Haydon, 1968), and evidenced in different reports (Amzica and Neckelmann, 1999; Neher and Marty, 1982; Proks and Ashcroft, 1995; Smith et al., 1997). Interestingly, prior to 1938 approximately, the hypothesis the membrane would disintegrate at the pass of the excitation wave in an action potential was a source of debate and reason for experimentation (Cole and Curtis, 1938a). Later on, Cole and Curtis dismissed that hypothesis on the basis of finding very small changes in the membrane capacitance using experiments a Wheatstone bridge. However, the change in the charge density with respect to voltage, $\partial_v Q_a$, can be a non-constant function, as it has been shown in experimental work involving exo and endocytosis (Neher and Marty, 1982; Proks and Ashcroft, 1995; Smith et al., 1997), and in relation to voltage-gated currents (Kilic and Lindau, 2001). The model presented here also provides a theoretical argument that indirectly dismisses the idea that a change in $\partial_v Q_a$ is indicative of membrane disintegration, enables the possibility of studying membrane systems without assuming that the amount of charge aggregation around the membrane is proportional to voltage (Everitt and Haydon, 1968; Kilic and Lindau, 2001), and suggest that new experimental protocols should be designed to measure the membrane capacitance, at different voltages instead of near the resting potential (already polarized membrane).

From a theoretical perspective, one reason that experimental measures of membrane capacity have proved difficult, is the assumption of isopotentiality, which does not happen almost surely (Chen and Gillis, 2000; Gentet et al., 2000; Golowasch et al., 2009). 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 called by Cole and Curtis, may be even more difficult than previously thought (but see Kilic and 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

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 and Neckelmann, 1999). Future experimental measurements may shed light on this issue, as it could have large repercussions in our interpretations of network dynamics.

Funding. PAPIIT-UNAM (IA208618,IN228820), and PAPIME-UNAM (PE114919)

References

Florin Amzica and DAG Neckelmann. Membrane capacitance of cortical neurons and glia during sleep oscillations and spike-wave seizures. *Journal of neurophysiology*, 82(5):2731–2746, 1999.

M.P. Blaustein, J.P.Y. Kao, and D.R. Matteson. *Cellular physiology*. Elsevier/Mosby, 2004. ISBN 0323013414.

Walter F Boron and Emile L Boulpaep. *Medical Physiology E-Book*. Elsevier Health Sciences, 2016.

George Edward Briggs. The accumulation of electrolytes in plant cells—a suggested mechanism. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character*, 107(750):248–269, 1930.

SC Brooks. The accumulation of ions in living cells-a non-equilibrium condition. *Protoplasma*, 8(1): 389–412, 1929.

Peng Chen and Kevin D Gillis. The noise of membrane capacitance measurements in the whole-cell recording configuration. *Biophysical Journal*, 79(4):2162–2170, 2000.

Kenneth S Cole. Electric conductance of biological systems. In *Cold Spring Harbor symposia on quantitative biology*, volume 1, pages 107–116. Cold Spring Harbor Laboratory Press, 1933.

Kenneth S Cole. Permeability and impermeability of cell membranes for ions. In *Cold Spring Harbor Symposia on Quantitative Biology*, volume 8, pages 110–122. Cold Spring Harbor Laboratory Press, 1940.

Kenneth S Cole and Howard J Curtis. Electric impedance of nitella during activity. *The Journal of general physiology*, 22(1):37–64, 1938a.

Kenneth S Cole and Howard J Curtis. Electrical impedance of nerve during activity. *Nature*, 142 (3587):209–210, 1938b.

Kenneth S Cole and Howard J Curtis. Electric impedance of the squid giant axon during activity. *The Journal of general physiology*, 22(5):649–670, 1939.

Kenneth S Cole and Alan L Hodgkin. Membrane and protoplasm resistance in the squid giant axon. *The Journal of general physiology*, 22(5):671–687, 1939.

JS Coombs, DR Curtis, and J Co Eccles. The electrical constants of the motoneurone membrane. *The Journal of physiology*, 145(3):505–528, 1959.

B. Eisenberg. Ionic channels in biological membranes: natural nanotubes. *Accounts of chemical research*, 31(3):117–123, 1998.

R. S. Eisenberg. Channels as enzymes. *Journal of Membrane Biology*, 115(1):1–12, 1990.

CT Everitt and DA Haydon. Electrical capacitance of a lipid membrane separating two aqueous phases. *Journal of theoretical biology*, 18(3):371–379, 1968.

Hugo Fricke. The electric capacity of suspensions with special reference to blood. *The Journal of general physiology*, 9(2):137–152, 1925.

Hugo Fricke. The electric conductivity and capacity of disperse systems. *Physics*, 1(2):106–115, 1931.

D.C. Gadsby. Ion channels versus ion pumps: the principal difference, in principle. *Nature Reviews Molecular Cell Biology*, 10(5):344–352, 2009.

J. J. Galligan, K. J. LePard, D. A. Schneider, and X. Zhou. Multiple mechanisms of fast excitatory synaptic transmission in the enteric nervous system. *Journal of the autonomic nervous system*, 81 (1-3):97–103, 2000.

Luc J Gentet, Greg J Stuart, and John D Clements. Direct measurement of specific membrane capacitance in neurons. *Biophysical journal*, 79(1):314–320, 2000.

Jorge Golowasch, Gladis Thomas, Adam L Taylor, Arif Patel, Arlene Pineda, Christopher Khalil, and Farzan Nadim. Membrane capacitance measurements revisited: dependence of capacitance value on measurement method in nonisopotential neurons. *Journal of Neurophysiology*, 102(4): 2161–2175, 2009.

SI Helman and SM Thompson. Interpretation and use of electrical equivalent circuits in studies of epithelial tissues. *American Journal of Physiology-Renal Physiology*, 243(6):F519–F531, 1982.

L Hermann. Ueber eine wirkung galvanischer ströme auf muskeln und nerven. *Archiv für die gesamte Physiologie des Menschen und der Tiere*, 5(1):223–275, 1872.

L Hermann. Beiträge zur physiologie und physik des nerven. *Archiv für die Gesamte Physiologie des Menschen und der Tiere*, 109(3-4):95–144, 1905.

Ludimar Hermann. Zur theorie der erregungsleitung und der elektrischen erregung. *Archiv für die gesamte Physiologie des Menschen und der Tiere*, 75(11-12):574–590, 1899.

Marco Arieli Herrera-Valdez. A thermodynamic description for physiological transmembrane transport [version 2; referees: 2 approved]. *F1000Research*, 7(1468), 2018. doi: https://doi.org/10.12688/f1000research.16169.2.

Marco Arieli Herrera-Valdez, Erin Christy McKiernan, Sandra Daniela Berger, Stephanie Ryglewski, Carsten Duch, and Sharon Crook. Relating ion channel expression, bifurcation structure, and diverse firing patterns in a model of an identified motor neuron. *Journal of Computational Neuroscience*, pages 1–19, 2013.

B Hille. *Ionic Channels of Excitable Membranes*. Sinauer Associates, Sinauer Associates, Inc. Sunderland, Mass. 01375, 1992.

Rudolf Höber. Membrane permeability to solutes in its relations to cellular physiology. *Physiological Reviews*, 16(1):52–102, 1936.

Rudolf Höber, Marie Andersh, Josephine Höber, and Bernard Nebel. The influence of organic electrolytes and non-electrolytes upon the membrane potentials of muscle and nerve. *Journal of Cellular and Comparative Physiology*, 13(2):195–218, 1939.

A. L. Hodgkin and A. F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *Journal of Physiology*, 117:500–544, 1952.

AL Hodgkin and B Katz. The effect of calcium on the axoplasm of giant nerve fibres. *Journal of Experimental Biology*, 26(3):292–294, 1949a.

Alan L Hodgkin and Bernard Katz. The effect of sodium ions on the electrical activity of the giant axon of the squid. *The Journal of physiology*, 108(1):37–77, 1949b.

Alan L Hodgkin, Andrew F Huxley, and Bernard Katz. Measurement of current-voltage relations in the membrane of the giant axon of loligo. *The Journal of physiology*, 116(4):424–448, 1952.

CL Huang. Membrane capacitance in hyperpolarized muscle fibres. *The Journal of physiology*, 313 (1):207–222, 1981.

David E Johnson, Johnny Ray Johnson, John L Hilburn, and Peter D Scott. *Electric circuit analysis*, volume 3. Prentice Hall Englewood Cliffs, NJ, 1989.

D. Johnston, S. M. S. Wu, and R. Gray. *Foundations of cellular neurophysiology*. MIT press Cambridge, MA, 1995. ISBN 0262100533.

Gordan Kilic and Manfred Lindau. Voltage-dependent membrane capacitance in rat pituitary nerve terminals due to gating currents. *Biophysical journal*, 80(3):1220–1229, 2001.

Chin-Chin Lu, Anatolii Kabakov, Vladislav S Markin, Sela Mager, Gary A Frazier, and Donald W Hilgemann. Membrane transport mechanisms probed by capacitance measurements with megahertz voltage clamp. *Proceedings of the National Academy of Sciences*, 92(24):11220–11224, 1995.

Björn Naundorf, Fred Wolf, and Maxim Volgushev. Unique features of action potential initiation in cortical neurons. *Nature*, 440(7087):1060, 2006.

Erwin Neher and A Marty. Discrete changes of cell membrane capacitance observed under conditions of enhanced secretion in bovine adrenal chromaffin cells. *Proceedings of the National Academy of Sciences*, 79(21):6712–6716, 1982.

Erwin Neher and Bert Sakmann. Single-channel currents recorded from membrane of denervated frog muscle fibres. *Nature*, 260(5554):799–802, 1976.

Winthrop John Vanleuven Osterhout. Permeability in large plant cells and in models. *Ergebnisse der Physiologie und experimentellen Pharmakologie*, 35(1):967–1021, 1933.

Peter Proks and Frances M Ashcroft. Effects of divalent cations on exocytosis and endocytosis from single mouse pancreatic beta-cells. *The Journal of physiology*, 487(2):465–477, 1995.

Joseph Santos-Sacchi and Enrique Navarrete. Voltage-dependent changes in specific membrane capacitance caused by prestin, the outer hair cell lateral membrane motor. *Pflügers Archiv*, 444 (1-2):99–106, 2002.

Paul A Smith, Hiroshi Sakura, Barbara Coles, Nigel Gummerson, Peter Proks, and FM Ashcroft. Electrogenic arginine transport mediates stimulus-secretion coupling in mouse pancreatic beta-cells. *The Journal of physiology*, 499(3):625–635, 1997.

Nicholas Sperelakis. *Cell physiology source book: essentials of membrane biophysics*. Elsevier, 2012.

Ove Sten-Knudsen. *Biological Membranes: Theory of transport, potentials and electric impulses*. Cambridge University Press, 2002.

Torsten Teorell. An attempt to formulate a quantitative theory of membrane permeability. *Proceedings of the Society for Experimental Biology and Medicine*, 33(2):282–285, 1935.

Seth H Weinberg. Membrane capacitive memory alters spiking in neurons described by the fractional-order hodgkin-huxley model. *PloS one*, 10(5), 2015.

T. F. Weiss. *Cellular biophysics, volume 2: electrical properties*. MIT Press, 1996.

Darold Wobschall. Voltage dependence of bilayer membrane capacitance. *Journal of Colloid and Interface Science*, 40(3):417–423, 1972.