A unifying theory to describe transmembrane transport derived from thermodynamic principles

Herrera-Valdez. A unifying theory of physiological transmembrane transport Cellular homeostasis involves transmembrane molecular transport mediated by proteins that enable molecular transport along, or against the (electro) chemical gradient of the molecules being transported. Transmembrane transport has been modelled in many studies using many functional forms that were not always derived from the same assumptions. A generic formulation that describes transmembrane fluxes regardless of whether they are mediated by carrier proteins or by open channels is presented here. The functional form of the flux was obtained from basic thermodynamic principles. Further, taking a slightly different approach, the same generic formulation mentioned above can also be obtained from the Nernst-Planck equation for the case of channel- mediated electrodiffusion. The generic formulation can be regarded as the product of an amplitude term and a driving force term, both nonlinear functions of the transmembrane concentrations of the molecules and possibly the transmembrane potential. The former captures the characteristics of the membrane-spanning protein mediating the transport and the latter is a non-linear function of the transmembrane concentrations of the ions. The generic formulation explicitly shows that the basal rate at which ions cross the membrane is the main difference between currents mediated by pumps and channels. Electrogenic transmembrane fluxes can be converted to currents to construct models of membrane excitability in which all the transmembrane currents have the same functional form. The applicability of the generic derivations presented here is illustrated with models of excitability for neurones and pacemaker cardiocytes.

A unifying theory of physiological transmembrane transport derived from basic thermodynamic principles

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Abstract

Cellular homeostasis involves transmembrane molecular transport mediated by proteins that enable molecular transport along, or against the (electro) chemical gradient of the molecules being transported. Transmembrane transport has been modelled in many studies using many functional forms that were not always derived from the same assumptions. A generic formulation that describes transmembrane fluxes regardless of whether they are mediated by carrier proteins or by open channels is presented here. The functional form of the flux was obtained from basic thermodynamic principles. Further, taking a slightly different approach, the *same* generic formulation mentioned above can also be obtained from the Nernst-Planck equation for the case of channel-mediated electrodiffusion. The generic formulation can be regarded as the product of an amplitude term and a driving force term, both nonlinear functions of the transmembrane concentrations of the molecules and possibly the transmembrane potential. The former captures the characteristics of the membrane-spanning protein mediating the transport and the latter is a non-linear function of the transmembrane concentrations of the ions. The generic formulation explicitly shows that the basal rate at which ions cross the membrane is the main difference between currents mediated by pumps and channels. Electrogenic transmembrane fluxes can be converted to currents to construct models of membrane excitability in which all the transmembrane currents have the same functional form. The applicability of the generic derivations presented here is illustrated with models of excitability for neurones and pacemaker cardiocytes.

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1 Introduction

The transport of molecules across cellular membranes, hereby referred to as transmembrane transport (TT), is necessary to maintain cellular function and by extension, systemic activity (Blaustein et al., 2004). In particular, electrogenic TT takes place when the net charge transported by ions per unit time is nonzero, creating currents that may, in turn, trigger different electrical or biochemical signalling cascades. Many phenomena involving TT have been modeled mathematically, especially since the seminal work of Goldman (1943) and Hodgkin and Huxley (1952). Nevertheless, the functional forms that have been used to represent fluxes generated by TT are numerous and have not always been derived from the same assumptions (see for instance Rasmusson et al., 1990a,b). The energy required for TT is provided by the (electro)chemical gradient of one or more of the molecules being transported, or liberated by a biochemical reaction like the breakdown of adenosine triphosphate. TT can be thought of as a change in the free energy of a system formed by the membrane, the two compartments around it, the molecules in both sides, and the force fields that affect them. The energy stored in the electrochemical gradients across the membrane is released when molecules are transported along their gradients, and increases when molecules cross in the opposite direction (Hille, 1992). We can write expressions for the energy required to transport molecules across the membranes using thermodynamical principles. It should then be possible to derive generic, macroscopic formulations for the molecular flux resulting from TT.

TT may be mediated by proteins like channels and uniporters, which move molecules along their electrochemical gradient, or though carriers such as symporters, antiporters (Veenhoff et al., 2002), and ATPases (Stahl and Baskin, 1990), which move of at least one family of molecules against its electrochemical gradient. The latter proteins are herein called *translocators* and the name "transporter" will be applied herein to refer to *any* protein mediating transport, as is the case for channels and translocators. One especially interesting issue that we address, is the similarity between channel- and translocator-mediated transport. For consideration, one of the main macroscopic differences between them can be found in the orders of magnitude of their associated fluxes. In brief, we derive generic expressions with the same functional forms that accurately describe different properties of the fluxes mediated by translocators and channels, including rectification. Further, an alternative formulation for channel gating capable of capturing the sigmoidal behaviour observed in some voltage-clamp experiments is also provided.

We start with a derivation of a generic expression for the current resulting from transmembrane ionic transport based on thermodynamic considerations. We then derive expressions for the current through *open* channels thought of as ”holes in the wall” (Eisenberg, 1998; Gadsby, 2009) by considering the Nernst-Planck equation. In other words, we derive a generic formulation for whole-membrane, as well as single-channel currents for any given type of ion channel using two approaches. The resulting expressions are generalizations of those previously derived by Kimizuka and Koketsu (1964), Butler and Volmer (Bockris and Reddy, 1973), and Endresen et al. (2000). The first formulation is obtained by considering the electrodiffusive transmembrane flux of ions across the membrane, as described by the Nernst-Planck equation. The second approach is to consider the energy required to transport ions across the membrane. The second derivation can be used to model transport mediated by both channels and translocators.

Examples of implementation of the formulations obtained here are discussed in models of membrane potential for neurons and cardiac cells.

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2 Methods

2.1 Numerical simulations and graphs

All graphics and simulation presented here were performed on personal laptop computers with Linux Kubuntu operating system (ver 10-13) or MacOSX, using the Python Language, version 2.7, available at http://www.python.org with the modules scipy (Jones et al., 2001–) and matplotlib (Hunter, 2007).

2.2 Electrodiffusion and Nernst potentials

Consider an ionic species M (*e.g.* K^+, Na^+, Ca^{2+}, Cl^-). The flux of M across an open pore in the membrane is the sum of the fluxes caused by diffusion and electrical drift, which can be described combining the Einstein relation (Einstein, 1905) and the Nernst-Planck equation (Weiss, 1996a,b) as:

$$\vec{J}_M = -\mu_M \left(\mathrm{k}T\nabla [M] + \mathrm{q}z_M [M] \nabla U \right), \tag{1}$$

where U represents a smoothly varying electric field, z_M, μ_M, and $[M]$ are, respectively, the valence, electrical mobility, and the concentration of M. The elementary charge (Coulombs) is q, k is Boltzmann's constant (mJ/K), and T is the absolute temperature (^{o}K). Taking a macroscopic perspective, assume that (M) and U only change in the transmembrane direction and the membrane delimits two compartments labeled as a and b. Let $v_T = \mathrm{k}T/\mathrm{q}$.

It is possible to use the one-dimensional version of equation (1) by assuming that the trajectory traversed by an ion M across the membrane can be parametrised by a real variable x, taking values between 0 and the width of the membrane, $W \approx 8 \times 10^{-9}$ m (Keener and Sneyd, 1998). Assume further that the pore through which the ions are crossing is a revolution volume with cross sectional area $A(x)$. Then, the current for each cross section is given by

$$I(x) = \mathrm{q}z_M A(x) J_M(x), \quad x \in [0, W]. \tag{2}$$

The current from (2) can be assumed to be constant as a function of x (Endresen et al., 2000; Hille and Schwarz, 1978). Combining equation (2) and (1) with an integrating factor $\exp\left(z_s U/v_T \right)$ to yield,

$$I = -\mu_M \mathrm{k}\mathrm{q} z_M A(x) T \exp\left(-\frac{z_M U}{v_T}\right) \partial_x \left[[M] \exp\left(\frac{z_M U}{v_T}\right)\right]. \tag{3}$$

It is possible to integrate between 0 and W to obtain the total current across the membrane to obtain

$$I = z_M B^{-1} T \left[[M](0) \exp\left(\frac{z_M U(0)}{v_T}\right) - [M](W) \exp\left(\frac{z_M U(W)}{v_T}\right)\right]. \tag{4}$$

The term

$$B = \frac{1}{\mu_M \mathrm{q}\mathrm{k}} \int_a^b \frac{1}{A(x)} \exp\left(\frac{z_M U}{v_T}\right) dx \tag{5}$$

describes the dependence of the current on the shape of the pore, but can be approximated as a constant (Eisenberg, 1998, 1999; Hille and Schwarz, 1978).

Nernst potential. For simplicity, let $[M]_a = [M](0)$ and $[M]_b = [M](W)$, where a and b denote the intra, and extracellular compartments. From (1), the transmembrane voltage at which there is no net transmembrane flux of M

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($\vec{J}_M = 0$), called *Nernst potential* for M, is given by

$$v_M = \frac{v_T}{z_M} \ln\left(\frac{[M]_b}{[M]_a}\right), \tag{6}$$

which can be rewritten to yield a relationship between the extra- and intracellular concentrations of M as

$$\frac{[M]_b}{[M]_a} = \exp\left(\frac{z_M}{v_T} v_M\right). \tag{7}$$

2.3 Kinetics of reversible processes

Phenomena like molecular transport across the membrane and conformational changes in proteins, such as channel gating, can be thought of as reversible reactions of the form

$$A \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} B. \tag{8}$$

The kinetic scheme (8) may be used as a framework to model different phenomena involved in transmembrane transport. For example, an exchange of molecules across the membrane mediated by a transporter, or the open $\rightarrow$ close conformational change that occurs in channel gating. The steady state balance between the forward and backward reactions is given by

$$\frac{\alpha}{\beta} = \exp\left(-\frac{\Delta G}{\mathrm{k}T}\right), \tag{9}$$

where ΔG represents the energy required for the reactions steady state. The forward and backward rates in (9) can be expressed as

$$\alpha = r \exp\left(-s\frac{\Delta G}{\mathrm{k}T}\right), \quad \beta = r \exp\left[(1-s)\frac{\Delta G}{\mathrm{k}T}\right], \tag{10}$$

where r is a basal rate for the transport event and $s \in [0,1]$ accounts for the possibility asymmetry with respect to the energy required for the forward and backward reactions (Blaustein et al., 2004; Chapman, 1978; Endresen et al., 2000; Willms et al., 1999). The difference $\alpha - \beta$ gives information about the change in A and B from (8) over time. In particular, if 8 represents molecular transport across the membrane, the difference $\alpha - \beta$ can be thought of as a multiple of the total transmembrane flux of the molecules under consideration.

2.3.1 Energy required to transport an ion across the membrane

If M is an ion, the energy required for transporting M from a point a to a point b can be expressed as

$$\Delta G_M = \mathrm{q} z_M (v_M - v) \tag{11}$$

(Blaustein et al., 2004). If $\Delta G_M > 0$, the transport occurs against the electrochemical gradient for M, in which case a source of energy not involving the transported ions is required for the transport. If $\Delta G_M < 0$, the transport can take place without an additional source of energy.

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3 Results

3.1 Electrodiffusive transport

The assumption that the transmembrane region along the pore in which transport occurs is represented by a variable x between 0 and W, allows us to write the transmembrane potential $v = U(0) - U(W)$. Recall that the field U is assumed to vary smoothly across the membrane. Then, there is an $s \in [0, 1]$ and a corresponding point sW along the x-axis that parametrizes the pore such that

$$U(0) - U(sW) = sv, \quad U(sW) - U(W) = (1 - s)v, \tag{12}$$

Recall that

$$I = z_M B^{-1} T \left[[M]_a \exp\left(\frac{z_M U(0)}{v_T}\right) - [M]_b \exp\left(\frac{z_M U(W)}{v_T}\right)\right]. \tag{13}$$

The potential $U(sW)$ can then be inserted into (13) and write the current in terms of the transmembrane potential. Then, combine expressions (13) and (12) to obtain

$$I(v; s) \quad = \quad z_M T D \left[[M]_a \exp\left(\frac{z_M s v}{v_T}\right) - [M]_b \exp\left(\frac{z_M \, (s-1) \, v}{v_T}\right)\right], \tag{14}$$

with $D = B^{-1} \exp\left(z_M U_s / v_T\right)$. Then, rewrite equation (14) as

$$I(v; s) = z_M T D \, [M]_a^{1-s} \, [M]_b^s \left[\left(\frac{[M]_a}{[M]_b}\right)^s \exp\left(\frac{z_M s v}{v_T}\right) - \left(\frac{[M]_a}{[M]_b}\right)^{s-1} \exp\left(\frac{z_M (s-1) v}{v_T}\right)\right], \tag{15}$$

where s is a symmetry parameter between 0 and 1. The dependence of the current on the Nernst potential for the ion i can then be realised by combining equations (7) and (15) into (14) so that,

$$I(v; s) \quad = \quad z_M T D \, [M]_a^{1-s} \, [M]_b^s \left[\exp\left(\frac{z_M s \, (v - v_M)}{v_T}\right) - \exp\left(\frac{z_M \, (s-1) \, (v - v_M)}{v_T}\right)\right]. \tag{16}$$

Note that the valence guarantees that the current has the correct sign in case the ion under consideration has negative valence (Fig. 1).

Equations (14) and (16) are macroscopic descriptions of transmembrane current driven by electric *drift and diffusion* through an open channel that will be herein referred to as a DD current. Expressions for voltage-dependent gating that will be presented in later sections will be combined with equations (14) or (16) to simulate whole membrane or whole patch, voltage-gated currents. Models of transmembrane potential dynamics will be constructed after that to show the applicability of these derivations.

3.1.1 Possible simplifications

Pore with constant cross-sectional area. One possible simplification is to assume that $A(x) = a$, a constant. From Eqn. (5),

$$D^{-1} \quad = \quad \frac{v_T}{a z_M \mu_M \mathrm{qk}} \exp\left(\frac{z_M s v}{v_T}\right) \left[\exp\left(-\frac{z_M v}{v_T}\right) - 1\right]. \tag{17}$$

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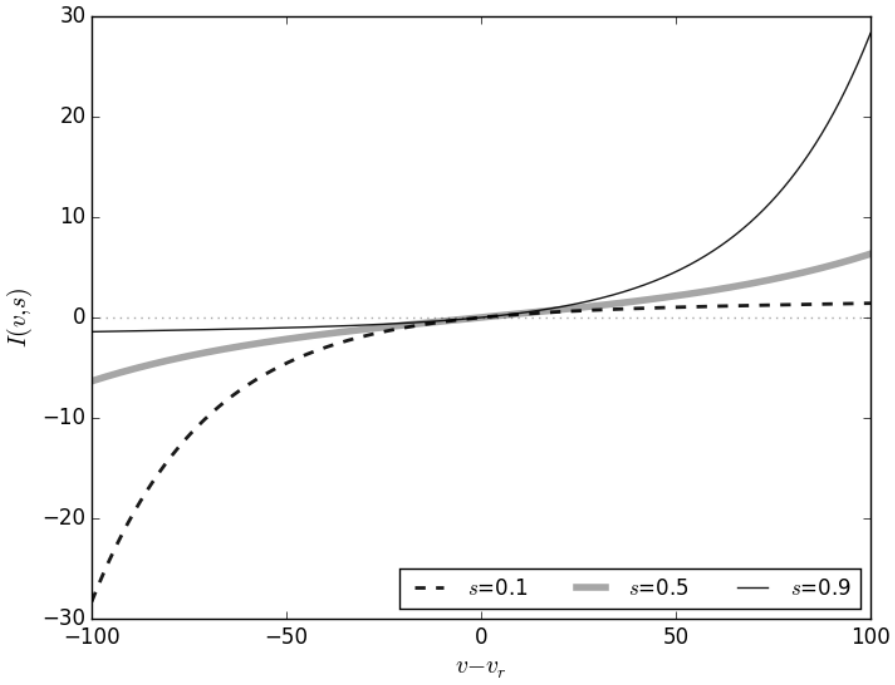

Figure 1: Shape of the curve $I(v;s)$ for different values of s and a reversal potential v_r. Note the rectification for s=0.1 and s=0.9.

As a consequence,

$$I(v;s) = -a\mu_M \mathrm{q}^2 z_M^2 [M]_a^{1-s} [M]_b^s \left[\frac{\exp\left(\frac{z_M s(v-v_M)}{v_T}\right)}{\exp\left(\frac{z_M s v}{v_T}\right)}\right]\left[\frac{1-\exp\left(-\frac{z_M(v-v_M)}{v_T}\right)}{1-\exp\left(\frac{-z_M(v)}{v_T}\right)}\right]. \quad (18)$$

Symmetry of the reference point x_s with respect to inner and outer compartments. For the symmetric case m=1/2, equation (16) can be simplified for into

$$I = 2z_M DT\sqrt{[M]_a [M]_b}\sinh\left[\frac{z_M(v-v_M)}{2v_T}\right]. \quad (19)$$

In addition, if the cross sectional radius of the pore is constant (see Eqn. (18)), then

$$I = -2a\mu_M \mathrm{q}^2 z_M^2\sqrt{[M]_a [M]_b}\left[\frac{\sinh\left(\frac{z_M}{2v_T}(v-v_M)\right)}{\sinh\left(\frac{z_M}{2v_T}v\right)}\right]. \quad (20)$$

Constant temperature and concentrations. If the absolute temperature and the transmembrane concentrations can be assumed to be constant, then $2a\mu_M \mathrm{q}^2 z_M^2\sqrt{[M]_a [M]_b}$ can be replaced by a constant representing the maximum amplitude of the current through a single open channel (Nonner and Eisenberg, 1998).

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3.2 Generic formulations for transmembrane transport

Now consider a more general case in which m different ions are simultaneously transported across the membrane. The flux caused by the simultaneous transport of the m different kinds of ions depends on the free energy involved in the transport of each kind of ion, and possibly, the energy provided by the hydrolyzation of ATP, or some other source.

3.2.1 Simultaneous transmembrane ionic transport

The transmembrane transport of molecules M_1,...,M_m can be macroscopically described by the reversible kinetic scheme (Blaustein et al., 2004; Chapman, 1978)

$$n_1 M_{1,a_1} + ... + n_m M_{m,a_m} \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} n_1 M_{1,b_1} + ... + n_m M_{m,b_m}, \tag{21}$$

where $a_i, b_i \in \{0,1\}$, $i \in \{1,...,m\}$, representing the source and target compartments, respectively. The numbers 0 and 1 represent the extra- and intracellular compartments, respectively. For instance, if $(a_i, b_i) = (0,1)$, then the ith molecule is transported from outside, to inside the membrane; transport from inside to outside of the membrane direction would be represented by $(a_i, b_i) = (1,0)$. The number of ions of each type involved in the transport is represented by n_i, $i \in \{1,...,m\}$. The scheme (21) is generic, so the translocation of the ions could be that mediated by either a translocator or an open channel. The energy ΔG_m required for the transport of the m ions is the sum of the energies that correspond to the transport of each ion under consideration (Blaustein et al., 2004; Chapman, 1978):

$$\Delta G_m = \sum_{i=1}^{m} \Delta G_i = \sum_{i=1}^{m} n_i z_i (v_i - v)(a_i - b_i), \tag{22}$$

as given by equation (11). Notice that (22) can be calculated for ions or for molecules without a charge, in which case the Nernst potential depends on diffusion, but not on electrical drift. If $\Delta G_m \leq 0$, then the transport dissipates energy from the electrochemical gradient of at least one of the ions being transported and that energy is sufficient to complete the movement of the m molecules and $\Delta G = \Delta G_m$. In contrast, if $\Delta G_m > 0$, then transport is primary active and it requires the energy from an additional source, such as the breakdown of ATP into ADP^- and P^+. In that case, the total energy for the transport is

$$\Delta G = \Delta G_m + \Delta G_{\text{ATP}}. \tag{23}$$

Recall that $v_{\text{ATP}} \approx -450$ mV. As a consequence, if one molecule of ATP is hydrolized for the transport, then $\Delta G_{\text{ATP}} = -450\text{q}$. Examples of different energies required for some transporters can be found in table 1.

3.2.2 Flux due to transport

From (21), the transmembrane flux is given by a function of the form $\phi = r(\alpha - \beta)$ where r is a rate that depends on temperature, the concentrations and stoichiometry of the molecules being transported, and possibly other factors. For instance, the basal rate r can be of the form

$$r = f(T) \prod_{i=1}^{m} [M_i]_a^{n_i(a_i - b_i)(1-s)} [M_i]_b^{n_i(a_i - b_i)s} \tag{24}$$

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for some increasing function of T that captures the dependence of transport rate on temperature (Schoolfield et al., 1981; Sizer, 2006; Stearn and Action, 2009).

Taking the extracellular compartment as a reference, inward fluxes occur when $r < 0$ and outward flux occurs when $r > 0$. Explicitly, the flux resulting from a single transport event can be obtained by combining (10) with (22) or (23) :

$$\begin{aligned}\phi &= r\left\{\exp\left[\frac{s}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i(v-v_i)\right)\right]\right.\\ &\left.-\exp\left[\frac{(s-1)}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i(v-v_i)\right)\right]\right\}\end{aligned} \tag{25}$$

where $v_{AB} = v_{\mathrm{ATP}}$ for primary active transport, and 0 for secondary active transport, or transport through open channels. A useful alternative expression in terms of the transmembrane concentrations can be obtained replacing the Nernst potential from (6) into (25):

$$\begin{aligned}\phi &= r\exp\left[\frac{s}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i v\right)\right]\prod_{i=1}^{m}\left(\frac{[M_i]_a}{[M_i]_b}\right)^{sn_i(a_i-b_i)}\\ &\left\{1-\exp\left[\frac{1}{v_T}\left(v_{AB}-\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i v\right)\right]\prod_{i=1}^{m}\left(\frac{[M_i]_a}{[M_i]_b}\right)^{-n_i(a_i-b_i)}\right\}.\end{aligned} \tag{26}$$

As before, the subscripts 0 and 1 indicate external and internal compartments relative to the membrane.

3.2.3 Electrogenic transport and the generic formulation for current

Recall that the transport (21) is *electrogenic* whenever the sum of the charges that cross in a single event is distinct from zero. In terms of the scheme (21), electrogenic transport satisfies

$$\sigma = \sum_{i=1}^{m} n_i z_i\,(a_i - b_i) \neq 0. \tag{27}$$

As a consecuence, the rates α and β from (21) depend on v and a reversal potential that depends on the Nernst potentials for the transported ions (Table 1). If the transport is primary active, then

$$v_r = v_{\mathrm{ATP}} + \sum_{i=1}^{m} n_i z_i v_i\,(a_i - b_i)\,. \tag{28}$$

In contrast, if the transport event does not require an extra source of energy, then

$$v_r = \sum_{i=1}^{m} n_i z_i v_i\,(a_i - b_i)\,. \tag{29}$$

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Table 1: Energy required for transmembrane transport mediated by different translocators or channels. For channels, it is assumed that only one ion can cross at any given time. The source and target compartments for each ion i are represented by a and b respectively. The direction of motion of the transport for each ion is indicated by $a - b$. The reversal potentials are noted in those cases where transport is electrogenic.

Pump or channel	Ion (i)	n_i	a_i	b_i	$a_i - b_i$	ΔG_i	σ	v_r
Ca^{2+} ATPase	Ca^{2+}	1	1	0	1	$\Delta G_{\mathrm{Ca}} = 2q_e(v_{\mathrm{Ca}} - v)$	1	$2v_{\mathrm{Ca}} + v_{\mathrm{ATP}}$
Na^+-K^+ ATPase	Na^+ K^+	3 2	1 0	0 1	1 -1	$\Delta G_{\mathrm{Na}} = 3q_e(v_{\mathrm{Na}} - v)$ $\Delta G_{\mathrm{K}} = -2q_e(v_{\mathrm{K}} - v)$	1	$3v_{\mathrm{Na}} - 2v_{\mathrm{K}} + v_{\mathrm{ATP}}$
Na^+-Ca^{2+} exchanger	Na^+ Ca^{2+}	3 1	0 1	1 0	-1 1	$\Delta G_{\mathrm{Na}} = -3q_e(v_{\mathrm{Na}} - v)$ $\Delta G_{\mathrm{Ca}} = 2q_e(v_{\mathrm{Ca}} - v)$	-1	$-3v_{\mathrm{Na}} + 2v_{\mathrm{Ca}}$
Na^+-K^+-Cl^- symporter	Na^+ K^+ Cl^-	1 1 2	0 0 0	1 1 1	-1 -1 -1	$\Delta G_{\mathrm{Na}} = -q_e(v_{\mathrm{Na}} - v)$ $\Delta G_{\mathrm{K}} = -q_e(v_{\mathrm{K}} - v)$ $\Delta G_{\mathrm{Cl}} = 2q_e(v_{\mathrm{Cl}} - v)$	0	–
K^+-Cl^- symporter	K^+ Cl^-	1 1	1 1	0 0	1 1	$\Delta G_{\mathrm{K}} = q_e(v_{\mathrm{K}} - v)$ $\Delta G_{\mathrm{Cl}} = -q_e(v_{\mathrm{Cl}} - v)$	0	–
Na^+-H^+ exchanger	Na^+ H^+	1 1	0 1	1 0	-1 1	$\Delta G_{\mathrm{Na}} = -q_e(v_{\mathrm{Na}} - v)$ $\Delta G_{\mathrm{H}} = q_e(v_{\mathrm{H}} - v)$	0	–
Na^+ channel	Na^+	1	0	1	-1	$\Delta G_{\mathrm{Na}} = -q_e(v_{\mathrm{Na}} - v)$	-1	v_{Na}
K^+ channel	K^+	1	1	0	1	$\Delta G_{\mathrm{K}} = q_e(v_{\mathrm{K}} - v)$	1	v_{K}
Ca^{2+} channel	Ca^{2+}	1	0	1	-1	$\Delta G_{\mathrm{Ca}} = -2q_e(v_{\mathrm{Ca}} - v)$	-2	v_{Ca}
Cl^- channel	Cl^-	1	0	1	-1	$\Delta G_{\mathrm{Cl}} = q_e(v_{\mathrm{Cl}} - v)$	-1	v_{Cl}

The current resulting from electrogenic transport is then $\mathrm{q}\sigma\phi$. Explicitly,

$$I = \mathrm{q}f(T)\sigma\left\{\prod_{i=1}^{m}[M_i]_a^{n_i(a_i-b_i)}\exp\left[\frac{s}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}(a_i-b_i)\,n_k z_k v\right)\right]\right.$$
$$\left.-\prod_{i=1}^{m}[M_i]_b^{n_i(a_i-b_i)}\exp\left[\frac{(s-1)}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i v\right)\right]\right\}. \quad (30)$$

The generic formulation in (30) reduces to (14) for the case in which one kind of ion crosses the membrane along its electrochemical gradient, as it happens with channels. As shown for equation (14), equation (30) can take different functional forms, which can be useful for different purposes (see Tables 2 and 3). Moreover, the generic macroscopic description of current (30) includes the electrodiffusive current in (14) as a particular case (Table 2). As noted before,

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if $s = 1/2$, then equation (30) transforms into

$$I = 2\mathrm{q}f(T)\sigma \prod_{i=1}^{m} \left([M_i]_b [M_i]_a\right)^{n_i(a_i-b_i)/2} \sinh\left(\frac{-v_{AB} + \sum_{i=1}^{m} n_i z_i \left(a_i - b_i\right)\left(v - v_i\right)}{2v_T}\right). \quad (31)$$

Table 2: Generic formulations for transmembrane flux mediated by different translocators or channels. For channels, it is assumed that only one ion can cross at any given time. The terms that correspond to the amplitudes are abbreviated in all cases.

Pump or channel	$\phi(v, 1/2)$
Ca^{2+} ATPase	$A_{\mathrm{Ca}P} \sinh\left(\frac{2v-2v_{\mathrm{Ca}}-v_{\mathrm{ATP}}}{2v_T}\right)$
Na^{+}-K^{+} ATPase	$A_{\mathrm{NaK}} \sinh\left(\frac{v-3v_{\mathrm{Na}}+2v_{\mathrm{K}}-v_{\mathrm{ATP}}}{2v_T}\right)$
Na^{+}-Ca^{2+} exchanger	$A_{\mathrm{NaCa}} \sinh\left(\frac{v-2v_{\mathrm{Ca}}+3v_{\mathrm{Na}}}{2v_T}\right)$
Na^{+}-K^{+}-Cl^{-} cotransporter	$A_{\mathrm{NaKCl}} \sinh\left(\frac{v_{\mathrm{K}}-2v_{\mathrm{Cl}}+v_{\mathrm{Na}}}{2v_T}\right)$
K^{+}-Cl^{-} cotransporter	$A_{\mathrm{KCl}} \sinh\left(\frac{v_{\mathrm{Cl}}-v_{\mathrm{K}}}{2v_T}\right)$
Na^{+}-H^{+} exchanger	$A_{\mathrm{NaH}} \sinh\left(\frac{v_{\mathrm{H}}-v_{\mathrm{Na}}}{2v_T}\right)$
Na^{+} channel	$A_{\mathrm{Na}} \sinh\left(\frac{v-v_{\mathrm{Na}}}{2v_T}\right)$
K^{+} channel	$A_{\mathrm{K}} \sinh\left(\frac{v-v_{\mathrm{K}}}{2v_T}\right)$
Ca^{2+} channel	$A_{\mathrm{Ca}} \sinh\left(\frac{v-v_{\mathrm{Ca}}}{v_T}\right)$
Cl^{-} channel	$A_{\mathrm{Cl}} \sinh\left(\frac{v-v_{\mathrm{Cl}}}{2v_T}\right)$

3.3 Whole membrane currents and channel gating

The formulation in Eq. (19) can be extended for a membrane containing several hundreds or thousands of channels permeable to an ion M. Assume that there are N_M channels in the membrane and let channel $p_M \in [0, 1]$ be a gating variable. The *gated*, whole membrane current through a channel can then be written as:

$$I_M = p_M N_M \tilde{a}_M T \left[M\right]_a^{1-s} \left[M\right]_b^{s} S\left[\frac{z_M\left(v - v_M\right)}{v_T}, s\right]. \quad (32)$$

If the transmembrane concentrations and the absolute temperature are constant, then $N_i \tilde{a}_i T M_0^s M_1^{1-s}$ can be thought of as a constant $\bar{a}_M$ representing the maximum current amplitude through the membrane. Furthermore,

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$\bar{a}_M$ can be regarded as an indicator of channel expression because it is a multiple of the number of channels in the membrane. The quantity $N_M p_M$ can be thought of as the average number of open channels (see Aldrich et al. (1983) for an interesting perspective in this regard). The proportion p_M depends on the gating mechanism of the channel, which, in turn, may depend on voltage, the concentration of a ligand, or both. Different expressions for p_M will be discussed in the following paragraphs.

3.3.1 Logistic formulation for gating

As already mentioned, the generic expressions for current derived here apply for transport through open channels. Channel gating, which can be voltage- or ligand-dependent, has not been included in the derivation yet. Channel gating has been modelled with different deterministic and stochastic approaches (Bean and Rios, 1989; Hodgkin and Huxley, 1952; Hoshi et al., 1994; Mazzanti and DeFelice, 1990; Vandenberg and Bezanilla, 1991; Willms et al., 1999), all of which involve a probability of opening expressed in terms of variables or states that represent activation and inactivation processes. The typical deterministic formulations for a gating involve variables, representing activation or inactivation, taking values between 0 and 1, as originally proposed by Hodgkin and Huxley. The dynamics of one such variable, say u, are linear, converging toward a steady state u_∞ at a certain rate r_u. In turn, u_∞ and r_u may depend on voltage, the presence of a ligand, or both. The approach described above seems to work quite well to model membrane dynamics involving activation and inactivation in channels. However, some aspects of this approach have been questioned by some authors (for instance, see Aldrich et al., 1983). One key issue is that currents recorded in voltage-clamp mode often display sigmoidal time courses. In fact, Hodgkin and Huxley noted that for some of the voltage commands, especially the ones for lower voltages, the time course of the current had an increasing, sigmoidal shape, slow-changing at first, then increasing almost linearly, and then slowly changing as it converged exponentially toward a steady state. Hodgkin and Huxley fit the time course of gating in such currents by adjusting powers of linearly changing variables like the ones described above. As a result, they obtained the 3th and 4th powers the activation variables for the Na^+ and K^+ currents.

For an alternative approach, the activation and inactivation profiles of currents recorded in voltage-clamp can be described by solutions to equations from the family

$$\left\{\partial_t u = u^k \left(F_u - u\right) C_u, \quad k = 0, 1, ...\right\}, \tag{33}$$

which display sigmoidal behavior when k>0. The whole membrane current mediated by N channels with volgate-gated activation and inactivation processes modeled by variables p and q can then be written as $pqNI$ where I is written as in equation (32). The case $k = 1$ is of particular interest here since many voltage-dependent gating processes display sigmoidal time courses (Hodgkin and Huxley, 1952).

If gating is *voltage-dependent*, the steady state F and rate C can be written explicitly as

$$F_u(v) = \frac{exp\left(g_u \frac{v-v_u}{vT}\right)}{1 + exp\left(g_u \frac{v-v_u}{vT}\right)}, \tag{34}$$

$$C_u(v) = r_u \left[exp\left(s_u g_u \frac{v - v_u}{vT}\right) + exp\left(g_u (s_u - 1)\frac{v - v_u}{vT}\right)\right], \tag{35}$$

which can be derived by considering the energy required for voltage-dependent gating, as previously described (Endresen et al., 2000; Herrera-Valdez et al., 2013; Willms et al., 1999). Similar expressions can be obtained

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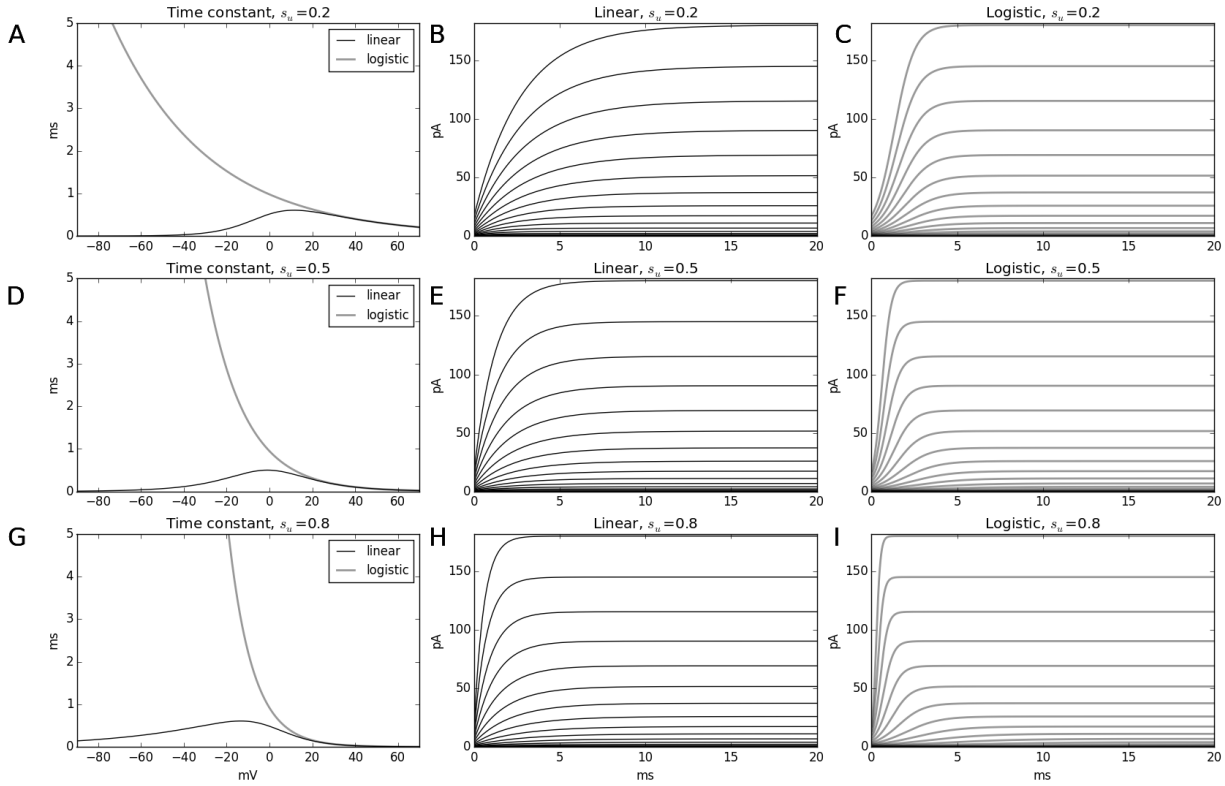

Figure 2: Simulation of currents mediated by Shab (K_v2) delayed rectifier channels, recorded in voltage clamp experiments. The currents were modelled using the particular case (32) of (30) for different values of the symmetry constant in the driving force and the symmetry constant in the activation dynamics. Parameters: v_u=1 mV, g_u =3, $s_u \in \{0.2, 0.5, 0.8\}$, $(r_u, k) \in \{(0.2, 0), (1, 1)\}$, voltage commands starting at -110 mV in steps of 10, , v_K=-89.0, s_K=1/2, maximum current amplitude in the open channel $\bar{a}_K$=10 nA (constant temperature and transmembrane concentrations).

for ligand- or ligand and voltage-gated currents (Destexhe et al., 1994). For fixed v, the family (33) contains the linear equations used by Hodgkin and Huxley (1952) and the logistic equation as particular cases (for details see Feller, 1940; Kaplan and Glass, 2012; Ricklefs, 1967; Strogatz, 1994). For the linear case ($k = 0$), the parameter s_u controls the symmetry of the time constant $1/C_u$ as a function of v. The solutions for the linear case always converge toward $F_u(v)$ at a rate $C_u(v)$. In other words, *i.e.* there is a unique, asymptotically stable (attractor) fixed point (Kaplan and Glass, 2012; Strogatz, 1994) with a time constant given by $1/C_u$. In contrast, the logistic case ($k = 1$) has two fixed points, a repeller at $u_* = 0$ and one attractor at $u_* = F_u(v)$, respectively. The time constant for convergence toward the attractor point F_u in this case is $(C_u(v)F_u(v))^{-1}$ (see Appendix 5.1). The change in u is the logistic case has cuadratic shape, reaching a maximum at $F_u(v)/2$, which explains why the dynamics of any solution starting from an initial condition $u_0 < F_u(v)/2$ have sigmoidal shape.

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4 Applications

The applicability of the results presented earlier is illustrated with simulations of phenomena related to ionic transport. Specifically, the dynamical behaviour of channel-mediated currents modeled with (32) in combination with the generic gating formulation from (33)-(35) is used to simulate currents recorded in what would be a voltage-clamp experiment. Then the dynamics of excitability in neurons are explored using the generic DD formulation as a function of rectification in K^+ currents mediated by K_v2 (homologous to Shab in *Drosophila* (Herrera-Valdez et al., 2013; Herrera-Valdez, 2012). The combination of currents mediated by translocators and channels is used to construct a low-dimensional model of cardiac pacemaking. The generic formulation for current in (30) is used in combination with the gating from (33)-(35). One particularly interesting aspect of the generic gating formulation proposed here is that it allows a formulation of currents without using powers in the gating terms, which permits the calculation of nullclines and enables the possibility of bifurcation analysis based on analytical results. This is illustrated briefly with the simulation of cardiac pacemaking. See Tables 3 and 4 for details about the currents and the parameters used in the simulation.

4.1 Currents recorded in voltage-clamp mode

Consider the system (33)-(35) for the cases $k = 0$ and $k = 1$. Simulations of the dynamics of current with gating variable u having different time courses can be obtained by systematically varing the parameters (v_u, g_u, r_u, s_u). Larger values of s_u shift the peak in the time constant as a function of v (Fig. 2A, D, G), and result in sharper current profiles (Fig. 2B, E, H for k=0, or C, F, I for k>1). The solutions of equation (33) for $k > 0$ and initial conditions far enough from the asymptotic state for u, have an initial period of slow change followed by an asymptotic approach to the steady state (see Fig. 2C, F, and I for the case k>1).

Simulations like those shown in Fig. 2 can be used to find gating parameters from currents recorded in voltage-clamp, including those of sigmoidal shape, but without using powers in the gating variables.

4.2 The effects of rectification on neuronal excitability

A simple 2D model of neuronal dynamics can be constructed assuming that K^+ and Na^+ are the only ions that cross the membrane via Na^+-K^+ ATPases, and voltage-dependent K^+ and Na^+ channels. The dynamics of the membrane in this case can be modeled with a 2-dimensional system of the form

$$C_m \partial_t v = -I_{\mathrm{Na}}(v,w) - I_{\mathrm{K}}(v,w) - I_{\mathrm{NaK}}(v) - I_S(t), \tag{36}$$

$$\partial_t w = w\left[F_w(v) - w\right] C_w(v), \tag{37}$$

where v and w represent the membrane potential and the proportion of activated K^+-channels, respectively. The change in membrane potential depends on transmembrane currents I_{NaK}, I_{K}, and I_{Na}, which are described in Table 3 and Fig. 3. The current $I_S(t)$ represents forcing that could be provided by current injection, or the fluctuations of the local field potential.

The effects of rectification in the potassium current I_{K} can be readily observed by varying the rectification parameter for a K^+ current modelled with (30) (see Tables 3 and 4). In general, action potentials become faster and

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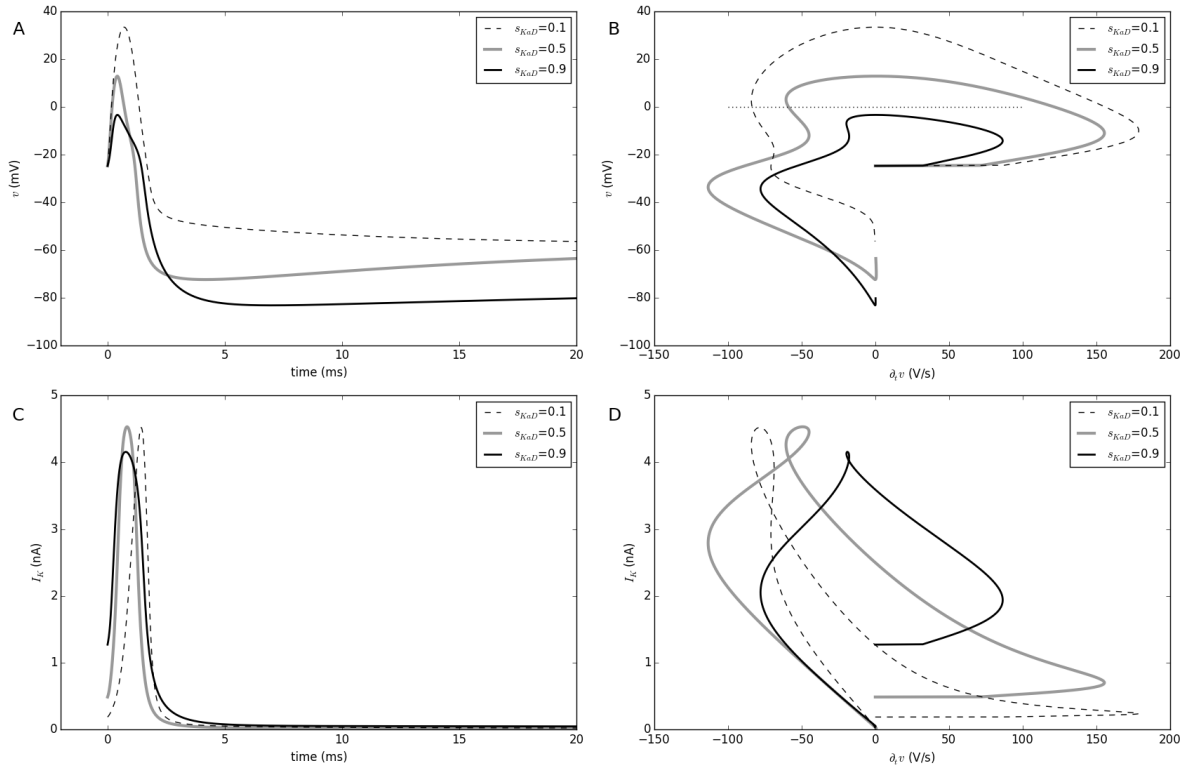

Figure 3: Neuronal dynamics for the rectification parameter $s_K \in \{0.1, 0.5, 0.9\}$. **A.** Action potentials starting from $(v_0, w_0) = (25, 0.01)$. **B.** $(\partial_t v, v)$ curve for the trajectories shown in A. **C.** Dynamics for $I_{\mathrm{K}}(t)$. **D.** Contribution of the K^+ current to the change in v, $(\partial_t v, I_{\mathrm{K}}(v))$.

of larger amplitude for smaller values of s_{K}. Inwardly rectifying currents (s_{K}=0.1, Hibino et al., 2010) increase the excitability of the membrane, whereas outwardly rectifying currents (s_{K}=0.9) have the opposite effect (Fig. 3A). The velocity of the action potential increases for inwardly rectifying channels (Fig. 3B) because inward rectification delays the K-current (compare values of s_{K} 0.1, 0.5, and 0.9 in Fig. 3C). The total amplitude and overall time course of the K-current does not change for s_{K}, but its contribution to the change in membrane potential is delayed for inward rectifiers (Fig. 3C). Also, the activation of the K^+ current for $s_{\mathrm{K}} = 0.5$ and $s_{\mathrm{K}} = 0.9$ is similar and occurs earlier during the action potential in comparison to the inwardly rectifying case $s_{\mathrm{K}} = 0.1$ (Fig. 3C). The maximum downstroke speed of the action potential occurs for $s_{\mathrm{K}} = 0.5$. Notably, the downstroke speed has similar values for $s_{\mathrm{K}} = 0.1$ and $s_{\mathrm{K}} = 0.9$ (Fig. 3B,D). Overall, smaller values of the parameter s_{K} increase the excitability of the membrane.

4.3 Cardiac pacemaking

A low dimensional model of membrane dynamics that describes cardiac pacemaking (Herrera-Valdez and Lega, 2011) can be constructed using the general formulation (30) to model a calcium current mediated by L-type $Ca_v1.3$ channels, a delayed-rectifier current, a current mediated by a Na^+-Ca^{2+} exchanger, and a Na^+-K^+ ATPase. In addition, the change in the intracellular Ca^{2+} concentration can be modeled with a variable c with linear dynamics attracted toward a steady state value c_∞, with increases proportional to the total transport of Ca^{2+} ions via L-type

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channels and the Na^+-Ca^{2+} exchangers (Fig. 4). The explicit form of the currents can be found in table 3 and the parameters for the simulations can be found in table 4. The resulting equations have the form

$$C_m \partial_t v = -I_{\mathrm{Ca}}(v,w,c) - I_{\mathrm{K}}(v,w,c) - I_{\mathrm{NaK}}(v) - I_{\mathrm{NaCa}}(v,c), \quad (38)$$

$$\partial_t w = w\left[F_w(v) - w\right] C_w(v) \quad (39)$$

$$\partial_t c = r_c\left(c_\infty - c\right) - k_c\left[I_{\mathrm{Ca}}(v,w) - I_{\mathrm{NaCa}}(v,c)\right] \quad (40)$$

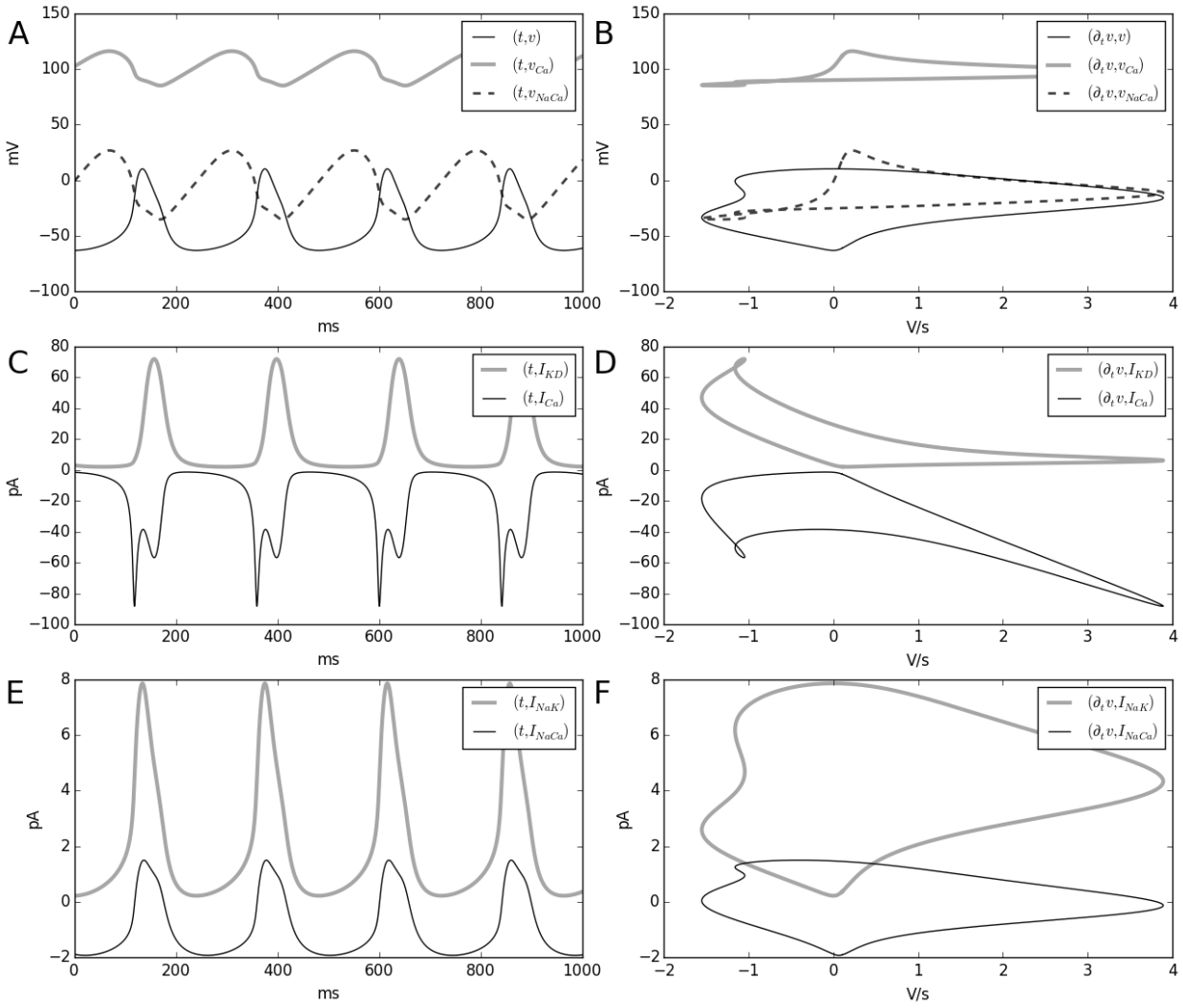

Figure 4: Central sinoatrial node dynamics using the system (38)-(40).

The model (38)-(40) is capable of reproducing important features of the membrane dynamics observed in the rabbit's central sinoatrial node, including the period, amplitude, and maximum speed of the action potentials (Zhang et al., 2000).

The general formulation for current in (30) and the inclusion of Ca^{2+} dynamics into the system (38)-(40) allows

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us to appreciate important details about the different currents that contribute to the change in v, especially the ones mediated by Na-Ca exchangers and L-type Ca-channels. For instance, the dynamics of the system (38)-(40) include a double activation of the Ca^{2+} current, as previously reported in different studies of cardiac dynamics (Fig. 4C,D, Rasmusson et al., 1990a,b). Importantly, the secondary activation occurs for the L-type Ca^{2+} current, which does not have a second activation variable or multiple terms in the steady state for activation (see for instance Rasmusson et al., 1990a,b). The secondary activation is possible because of the slow time constant for inactivation, which allows the Ca^{2+} current to increase as the action potential starts decaying, before inactivation takes place. Notice that in this case inactivation is assumed to be linearly related to the activation of the K^+ channels, a simplification that does not prevent or affect the double activation of the L-type Ca^{2+} channels during the action potential (Herrera-Valdez and Lega, 2011; Mitchell and Schaeffer, 2003). That double fluctuation is reflected in the Nernst potential for Ca^{2+}, which displays two decreasing phases, the first and faster one during the initial activation of the L-type channels, the second during the double peak of the Ca^{2+} current. By extension, the reversal potential for the Na-Ca exchanger, $v_{\mathrm{NaCa}} = 3v_{\mathrm{Na}} - 2v_{\mathrm{Ca}}$ also has two decaying phases that are related to the secondary activation of the Ca^{2+} channels Fig. 4A-D. The reversal potential for the Na-Ca exchanger also fluctuates around the membrane potential, taking values above v during the diastolic depolarization and below v during the peak of the action potentials (Fig. 4A,B). During these short periods of time, the Na-Ca exchanger current reverses and becomes an outward current (Fig. 4E,F).

Table 3: Transmembrane currents used in the models. All defined in terms of the auxiliary functions $S(y,s) = e^{ys}\left(1-e^{-y}\right)$, $C(y,s) = e^{ys}\left(1+e^{-y}\right)$, and $F(y) = \frac{e^y}{1+e^y}$.

Current	Amplitude	Driving force	Description
Channels			
I_{Na}	$(1-w)\bar{a}_{\mathrm{Na}}F\left(g_{mT}\frac{v-v_{mT}}{v_T}\right)$	$S\left(\frac{v-v_{\mathrm{Na}}}{v_T}, s_{\mathrm{Na}}\right)$	Transient Na^+ current
I_{K}	$w\bar{a}_{\mathrm{K}}$	$S\left(\frac{v-v_{\mathrm{K}}}{v_T}, s_{\mathrm{K}}\right)$	Delayed-rectifyier K^+ current
I_{Ca13}	$\tilde{a}_{\mathrm{Ca13}}c^{1-s_{\mathrm{Ca13}}}(1-w)F\left(g_{m13}\frac{v-v_{m13}}{v_T}\right)$	$S\left(2\left(\frac{v-v_{\mathrm{Ca}}}{v_T}\right), s_{\mathrm{Ca}}\right)$	L-type current mediated by Ca_{v13} channels
Pumps			
I_{NaK}	$\bar{a}_{\mathrm{NaK}}$	$S\left(\frac{v-v_{\mathrm{NaK}}}{v_T}, s_{\mathrm{NaK}}\right)$	Na^+-K^+ ATPase current
I_{NaCa}	$\tilde{a}_{\mathrm{NaCa}}c_i^{1-s_{\mathrm{NaCa}}}$	$S\left(\frac{v-v_{\mathrm{NaCa}}}{v_T}, s_{\mathrm{NaCa}}\right)$	Na^+-Ca^{2+} exchanger current

5 Discussion

The most important assumption for the modelling proposed here is that the electrochemical gradients of the molecules are the main determinants for the transmembrane ionic transport. The time courses of the transport events modelled here are fast enough to guarantee that the models and assumptions made to obtain the general formulation (30) yield a quantitatively accurate and generic macroscopic description of transmembrane currents (Blaustein et al., 2004; Hille, 1992). One interesting aspect of the formulation is that, the particular case of symmetric transport of a single ion ($m = 1, s = 1/2$) of the generic formulation (30) yields the conductance based formulation proposed by

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Table 4: Parameters used in the different simulations.

Parameter	Value	Units	Description
C_m	20	pF	Membrane capacitance
Neuronal membrane			
$\bar{a}_{\mathrm{Na}}$	1	nA	Maximum amplitude for the transient Na^+ current
$\bar{a}_{\mathrm{K}}$	16	nA	Maximum amplitude for the delayed-rectifier K^+ current
$\bar{a}_{\mathrm{NaK}}$	0.05	nA	Maximum amplitude for the Na^+-K^+ ATPase current
Central SAN membrane			
$\tilde{a}_{\mathrm{Ca}}$	2	pA/mM	Maximum amplitude for the L-type Ca^{2+} current
$\bar{a}_{\mathrm{K}}$	180	pA	Maximum amplitude for the K^+ current
$\tilde{a}_{\mathrm{NaCa}}$	20	pA/mM	Maximum amplitude for the Na^+-Ca^{2+} current
$\bar{a}_{\mathrm{NaK}}$	2	pA	Maximum amplitude for the Na^+-K^+ current

Hodgkin and Huxley when truncated to a first order approximation around the Nernst potential of the ion. In other words the conductance based formulation for current is a linear approximation of the generic approximation of the generic formulation presented here. The generality of the new formulation (30) enables fitting of currents recorded experimentally (see Herrera-Valdez et al., 2013). Importantly, the fitting includes the nonlinear parts of the currents, which, in turn, are important determinants of the whole-membrane dynamics (Fig. 3).

The generic formulation (32) is a significant improvement over the conductance-based model (Hodgkin and Huxley, 1952) for several reasons. First, currents mediated by channels are electrodiffusive, not resistive, which means that their representation as resistors in the so-called equivalent circuit is not physically correct (McAdams and Jossinet, 1996; Zhang and Wakamatsu, 2002). Second, the nonlinear dependence of the driving force terms in the currents from (32) yields a more accurate representation of experimentally recorded data, including different nonlinearities such as rectification (Hille, 1992). Third, it can be readily shown that the truncation to first order of the Taylor series of the current given by equation (32) is the conductance-based current (Herrera-Valdez, 2012). It is important to mention that the particular case of the electrodiffusion formulation (32) was first published by Kimizuka and Koketsu (1964) and later by Endresen et al. (2000). One particular case, the constant field approximation version, has been used in several modelling studies. For instance, Clay et al. (2008) used the constant-field approximation to enrich the dynamics of K^+ currents in Hodgkin and Huxley-like models based on data from the squid axon. The formulation presented here was independently obtained by the author, but in a more general setting. As a result, the expressions for flux and current are also more general, and include the formulations mentioned above as particular cases.

Importantly, Eq. (16) works for transport mediated by transporters in general. Notably, the current formulation for channel-mediated electrodiffusion is a particular case of the general formulation for translocators (30). The equivalence provides theoretical support to the idea that channel-mediated transport is macroscopically similar to transport mediated by carrier proteins such as uniporters, symporters, antiporters and ATPases. In all cases, transport can be written as a the product of an amplitude term and a driving force term. In other words, the case $m = 1$ of (30) tells us that *electrodiffusion through a channel as described by the Nernst-Planck equation is macroscopically equivalent to ionic "translocation" across the membrane by a carrier protein*, one ion at a time. Therefore, the modelling re-

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sults presented here support the hypotheses advanced by Gadsby (2009) and other researchers, that *channel and pump-mediated transport are macroscopically equivalent*.

Another improvement over currently available models is that the formulation in (30) enables the calculation of the null cline associated to the intracellular calcium concentration in models like (38)-(40), by simply solving for c. Also, the alternative formulation for activation in (33) adds a new steady state at $u = 0$, which could be interpreted as a non-activated state repelling state. If u is a population of channels, this non-activated state would only be possible if all channels are blocked or otherwise unable to activate. In fact, the case where $k = 1$, $u = 0$ in equation (33) yields an unstable fixed point once v and the parameters for F_u and C_u are fixed within a physiologically meaningful range. It is worth remark that the value $u = 0$ is unlikely to occur. However, the formality of multiplying u to the linear term $F_u(v) - u$ adds richness to the dynamics of u and opens the possibility for better fits to experimental records (see Shab current fits in Herrera-Valdez et al., 2013). In sum, adjustment of s_u, r_u, and k in enables the possibility of including sharper changes in the dynamics of u and have sigmoidal temporal dynamics without having to include powers in the gating variables, which sometimes complicates the analysis for the lack of closed-form expressions for the null clines.

The generality of the formulation (30) combined with (33)-(35) opens the possibility of a the systematic modelling study of heterogeneities in populations of channels, possibly including different subtypes or splice variants (see for instance Lin et al., 2009; Shipston, 2001). Another interesting application of the general formulation is that of short-term plasticity in network models with synaptic currents written with (30).

5.1 Summary and conclusions

The generic formulation (30) was derived from basic macroscopic considerations about the changes in free energy that occur in transmembrane transport. An alternative derivation for a particular case involving electrodiffusive transmembrane transport can be made from the Nernst-Planck equation yielding equivalent results. The functional form in both cases can be regarded as the product of an amplitude term and a driving force term, which shows that, macroscopically, carrier and channel-mediated currents are equivalent, as already suggested by Gadsby (2009). Importantly, in the absence of other changes, varying the balance between the maximum amplitudes for the currents and the membrane capacitance is enough to obtain membrane dynamics for different kinds of excitable cells (see table 4). Finally, the simplicity and homogeneity of the generic formulations presented here also enables the possibility of constructing network models with synaptic inputs of different types that are easy to simulate in personal computers. The details of this last application will be discussed at length in a following publication.

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Supplementary information

Logistic equation: solution and time constant for evolution

Consider a logistic equation of the form

$$\partial_t u = u(a-u)r, \quad u(0) = u_0 \tag{41}$$

The analytical solution for (41) can be obtained by separation of variables as follows:

$$\begin{aligned} -rt &= \int_0^t \frac{\partial_s u}{u-a} ds \\ &= \frac{1}{a}\left(\int_{u_0}^{u(t)} \frac{1}{u-a} - \frac{1}{u} du\right) \\ &= \frac{1}{a}\left(\int_{u_0}^{u(t)} \frac{du}{u-a} - \int_{u_0}^{u(t)} \frac{du}{u}\right) \\ &= \frac{1}{a}\left[\log\left(\frac{u(t)-a}{u_0-a}\right) - \log\left(\frac{u(t)}{u_0}\right)\right] \qquad (42) \\ &= \frac{1}{a}\left[\log\left(\frac{u_0\left(u(t)-a\right)}{u(t)\left(u_0-a\right)}\right)\right] \qquad (43) \end{aligned}$$

Therefore,

$$\begin{aligned} u_0\left(u(t)-a\right) &= u(t)\left(u_0-a\right)\exp\left(-art\right) \\ -au_0 &= u(t)\left[\left(u_0-a\right)\exp\left(-art\right) - u_0\right] \\ u(t) &= \frac{au_0}{u_0-\left(u_0-a\right)\exp\left(-art\right)} \end{aligned} \tag{44}$$

Notice then that the time constant for convergence toward steady state is $(ar)^{-1}$.

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