A unifying theory for physiological transmembrane transport derived from thermodynamic principles

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Abstract

Cellular homeostasis involves transmembrane molecular transport mediated by membrane-spanning proteins. Such proteins either carry the molecules across the membrane, or facilitate their diffusion. A generic formulation that describes transmembrane fluxes, derived from basic thermodynamic principles, and describing fluxes mediated by carrier proteins or by open channels using the same functional form is presented here. An alternative derivation from the Nernst-Planck equation that yields the same generic formulation can be obtained for the case of channel-mediated electrodiffusion. In general terms, the generic formulation is a product of an amplitude and a driving force. The amplitude models properties of the protein mediating the transport including basal rates of transport. The driving force term that depends non-linearly on the transmembrane concentrations of the molecules being transported, and possibly the transmembrane potential. The model applied for channel mediated currents is capable of displaying rectification. Further, an extension for channel gating derived en passage allows fitting of currents recorded in voltage-clamp without using powers for the gating variables. The generic formulation explicitly shows that the basal rate at which ions cross the membrane is the main macroscopic difference between currents mediated by carrier proteins and channels. Many functional forms that were not always derived from the same assumptions can be found in modelling studies of transmembrane transport, especially those studies focusing on the membrane potential of excitable cells. The derivations presented here unify the theory of biological transmembrane transport. Of particular interest, electrogenic transmembrane fluxes described with the general formulation can be converted to currents for the construction of models of membrane excitability; all based on the same assumptions and having the same functional form. The applicability of the generic derivations presented here is illustrated with models of excitability for neurones and pacemaker cardiocytes.

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 DiFrancesco and Noble, 1985; Rasmusson et al., 1990a,b).

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. If the molecules are ions, the electric field adds to the thermal fluctuations underlying diffusion and may produce electrodiffusive transport. The energy required for TT is directly related to the the (electro)chemical gradient of one or more of the molecules being transported. When molecules are transported along their (electro)chemical gradients across the membrane, energy is released (Hille, 1992). In contrast, cells may obtain the necessary energy for transport against the electrochemical gradient of one or more molecules from biochemical reactions like the breakdown of adenosine triphosphate. TT may be mediated by proteins like channels and uniporters, which move molecules along their (electro)chemical gradient (Eisenberg, 1999; Hille, 1992), or though carriers such as symporters, antiporters (Veenhoff et al., 2002), and ATPases (Stahl and Baskin, 1990), which move at least one family of molecules against their (electro)chemical

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gradient. For the sake of consistency, the name "transporter" will be applied herein to refer to *any* protein mediating transport, as is the case for channels and all carrier proteins mentioned above; antiporters and ATPases will be called pumps.

It is possible to derive expressions to describe the energy required for TT using thermodynamical principles about the energy required for transport. It should then be possible to derive generic, macroscopic formulations for the molecular flux resulting from TT and its associated current if TT is electrogenic. Such expressions could then be used to model transport mediated by both channels and carriers. An alternative derivation that yields the same generic expressions can be obtained for electrodiffusive current through *open* channels, thought of as "holes in the wall" (Eisenberg, 1998; Gadsby, 2009), with fluxes described by the Nernst-Planck equation. The generic expressions accurately describe different properties of the fluxes mediated by carriers and channels, including rectification. As already mentioned, the expressions for such fluxes have the same functional forms, which addresses one especially interesting issue: the macroscopic similarity between channel- and carrier-mediated transport (Gadsby, 2009). In short, the models for TT presented here explain why carrier and channel mediated fluxes are macroscopically similar, except for their rates, typically slower for carrier-mediated transport. An alternative formulation for gating that captures the sigmoidal behaviour observed in some voltage-clamp experiments is also provided, to complete the model of currents mediated by channels. Such a model enables the possibility of not using powers to adjust currents from voltage-clamp. The expressions mentioned above generalize those previously derived by Kimizuka and Koketsu (1964), Butler and Volmer (Bockris and Reddy, 1945), and Endresen et al. (2000). Examples of implementation of the formulations obtained here are discussed in models of membrane potential for neurons and cardiac cells.

2 Methods

2.1 Numerical simulations and graphs

All the simulations and graphics presented here were performed on personal laptop computers with the Linux Kubuntu operating system (ver 10-13) or MacOS version X, 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 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

$$A \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} B. \tag{1}$$

The kinetic scheme (1) 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 conformational changes that occur in channel gating. The steady state balance between the forward and backward reactions is given by

$$\frac{\alpha}{\beta} = \exp\left(-\frac{\Delta G}{\mathrm{k}T}\right), \tag{2}$$

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where ΔG represents the energy required for the reactions steady state. The forward and backward rates in (2) can be expressed as

$$\alpha = r\exp\left(-s\frac{\Delta G}{\mathrm{k}T}\right), \quad \beta = r\exp\left[(1-s)\frac{\Delta G}{\mathrm{k}T}\right], \tag{3}$$

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 (1) over time. In particular, if 1 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.

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),

$$\vec{J} \;=\; -\mu\left(\mathrm{k}T\nabla C + \mathrm{q}zC\nabla U\right), \tag{4}$$

where U represents a smoothly varying electric field, z, μ, and C 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). C and U are assumed to be smooth functions. Equation (4) can be transformed into

$$\vec{J} \;=\; -\mu\mathrm{k}T\exp\left(-\frac{zU}{v_T}\right)\nabla\left[C\exp\left(-\frac{zU}{v_T}\right)\right] \tag{5}$$

The Nernst potential for M. Let C_0 and C_1 respectively represent the concentrations of M in the intra- and extracellular compartments. Let $v_T = \mathrm{k}T/\mathrm{q}$. From (4), the transmembrane voltage at which there is no net transmembrane flux of M ($\vec{J} = 0$), called *Nernst potential* for M, is given by

$$v_M = \frac{v_T}{z}\ln\left(\frac{C_0}{C_1}\right), \tag{6}$$

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

$$\frac{C_0}{C_1} = \exp\left(z\frac{v_M}{v_T}\right). \tag{7}$$

3 Results

3.1 Generic formulations for transmembrane transport

Consider a general case in which m different molecular families are simultaneously transported across the membrane. The flux caused by the simultaneous transport of the m different kinds of molecules depends on the free energy involved in the transport of each kind of ion, and possibly, the energy provided by the hydrolysation of ATP, or some other source.

The TT of the m molecular families mentioned above can be described as follows. Assume that n_i molecules of type i move from compartment a_i to compartment b_i, $i \in \{1,...,m\}$, at a rate α, as described by the scheme

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(1). Use 0 or 1 for each of the compartments a_i and b_i, with $a_i \neq b_i$, $i \in \{1, ..., m\}$ with 0 and 1 representing the extra- and intracellular compartments, respectively (Blaustein et al., 2004; Chapman, 1978) For instance, if $(a_i, b_i) = (0, 1)$, then the ith molecular familiy is transported from outside, to inside the membrane; transport from inside to outside of the membrane would be represented by $(a_i, b_i) = (1, 0)$.

Now assume that the transported molecules are ions. The energy ΔG_m required for the transport of the m ionic families is the sum of the energies that correspond to the transport of each ion under consideration (Blaustein et al., 2004; Chapman, 1978),

$$\Delta G^m = \sum_{i=1}^{m} \Delta G_i = \sum_{i=1}^{m} n_i z_i (v_i - v)(a_i - b_i). \tag{8}$$

A similar formulation can be used for non-ionic families.

Notice that ΔG^m can be calculated for ions or for non-charged molecules, in which case their flux depends on diffusion, but not on electrical drift. If $\Delta Gm \leq 0$, then the transport dissipates enough energy from the electrochemical gradient of at least one of the ions being transported. The total change in energy involved in the transport would be $\Delta G = \Delta G^m$. 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

$$\Delta G = \Delta Gm + \Delta G_{\text{ATP}}. \tag{9}$$

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.

3.1.1 Flux due to transport

The transmembrane flux of the m molecular families mentioned above 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

$$r = f(T) \prod_{i=1}^{m} [M_i]_{a_i}^{n_i(a_i - b_i)(1-s)} [M_i]_{b_i}^{n_i(a_i - b_i)s} \tag{10}$$

for some increasing function of T that captures the temperature dependence of the transport rate (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 $r > 0$. The flux resulting from a single transport event can be obtained by assuming that transport occurs with forward and backward rates α and β, respectively, with a steady state balance (Onsager, 1931) given by equation (2). Combining equation(3) with equation (9) in the case of primary active transport, or with equation (8) for the case in which TT does not require an extra source of energy (*e.g.* secondary active transport, or channel-mediated transport) gives

$$\begin{aligned} \phi \quad = \quad & r \left\{ \exp\left[\frac{s}{v_T} \left(-v_{AB} + \sum_{i=1}^{m} (a_i - b_i)\, n_i z_i (v - v_i) \right) \right] \right. \\ & \left. - \exp\left[\frac{(s-1)}{v_T} \left(-v_{AB} + \sum_{i=1}^{m} (a_i - b_i)\, n_i z_i (v - v_i) \right) \right] \right\} \end{aligned} \tag{11}$$

where $v_{AB} = v_{\text{ATP}}$ 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 by replacing

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the terms from equation (11) that involve Nernst potentials by the transmembrane concentrations (see equation (6)),

$$\begin{aligned}\phi &= r\exp\left[\frac{s}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i v\right)\right]\prod_{i=1}^{m}\left(\frac{[M_i]_{a_i}}{[M_i]_{b_i}}\right)^{sn_i(a_i-b_i)}\\ &\left\{1-\exp\left[\frac{1}{v_T}\left(v_{AB}-\sum_{i=1}^{m}(a_i-b_i)\,n_i z_i v\right)\right]\prod_{i=1}^{m}\left(\frac{[M_i]_{a_i}}{[M_i]_{b_i}}\right)^{-n_i(a_i-b_i)}\right\}.\end{aligned} \tag{12}$$

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

Table 1: Energy required for transmembrane transport mediated by different translocators or channels. 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^+	3	1	0	1	$\Delta G_{\mathrm{Na}}=3q_e(v_{\mathrm{Na}}-v)$	1	$3v_{\mathrm{Na}}-2v_{\mathrm{K}}+v_{\mathrm{ATP}}$
	K^+	2	0	1	-1	$\Delta G_{\mathrm{K}}=-2q_e(v_{\mathrm{K}}-v)$		
Na^+-Ca^{2+} exchanger	Na^+	3	0	1	-1	$\Delta G_{\mathrm{Na}}=-3q_e(v_{\mathrm{Na}}-v)$	-1	$-3v_{\mathrm{Na}}+2v_{\mathrm{Ca}}$
	Ca^{2+}	1	1	0	1	$\Delta G_{\mathrm{Ca}}=2q_e(v_{\mathrm{Ca}}-v)$		
Na^+-K^+-Cl^- symporter	Na^+	1	0	1	-1	$\Delta G_{\mathrm{Na}}=-q_e(v_{\mathrm{Na}}-v)$	0	–
	K^+	1	0	1	-1	$\Delta G_{\mathrm{K}}=-q_e(v_{\mathrm{K}}-v)$		
	Cl^-	2	0	1	-1	$\Delta G_{\mathrm{Cl}}=2q_e(v_{\mathrm{Cl}}-v)$		
K^+-Cl^- symporter	K^+	1	1	0	1	$\Delta G_{\mathrm{K}}=q_e(v_{\mathrm{K}}-v)$	0	–
	Cl^-	1	1	0	1	$\Delta G_{\mathrm{Cl}}=-q_e(v_{\mathrm{Cl}}-v)$		
Na^+-H^+ exchanger	Na^+	1	0	1	-1	$\Delta G_{\mathrm{Na}}=-q_e(v_{\mathrm{Na}}-v)$	0	–
	H^+	1	1	0	1	$\Delta G_{\mathrm{H}}=q_e(v_{\mathrm{H}}-v)$		
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}

3.1.2 Electrogenic transport and the generic formulation for current

The transmembrane flux described in equation (12) is *electrogenic* whenever the sum of the charges that cross the membrane per unit time is nonzero. In other words, electrogenic transport satisfies

$$\sigma=\sum_{i=1}^{m}n_i z_i\,(a_i-b_i)\neq 0. \tag{13}$$

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As a consecuence, the flux depends on v and a reversal potential

$$v_r = v_{AB} + \sum_{i=1}^{m} n_i z_i v_i \left(a_i - b_i\right). \tag{14}$$

where $v_{AB} = v_{\mathrm{ATP}}$ for primary active transport and $v_{AB} = 0$ otherwise. (see table 1). The current resulting from electrogenic transport is then $\mathrm{q}\sigma\phi$. Explicitly,

$$\begin{aligned} I &= \mathrm{q}f(T)\sigma\left\{\prod_{i=1}^{m}[M_i]_{a_i}^{n_i(a_i-b_i)}\exp\left[\frac{s}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}\left(a_i-b_i\right)n_k z_k v\right)\right]\right. \\ &\quad \left.-\prod_{i=1}^{m}[M_i]_{b_i}^{n_i(a_i-b_i)}\exp\left[\frac{(s-1)}{v_T}\left(-v_{AB}+\sum_{i=1}^{m}\left(a_i-b_i\right)n_i z_i v\right)\right]\right\}. \end{aligned} \tag{15}$$

Notice that the generic formulation in (15) describes the case in which one kind of ion crosses the membrane along its electrochemical gradient, as it happens with channels. Equation (15) can take different functional forms, which can be useful for different purposes (see Tables 2 and 3). For instance, if $s = 1/2$, then equation (15) transforms into

$$I = 2\mathrm{q}f(T)\sigma\prod_{i=1}^{m}\left([M_i]_{b_i}[M_i]_{a_i}\right)^{n_i(a_i-b_i)/2}\sinh\left(\frac{-v_{AB}+\sum_{i=1}^{m}n_i z_i\left(a_i-b_i\right)\left(v-v_i\right)}{2v_T}\right). \tag{16}$$

3.2 Electrodiffusive transport

Now consider an open pore, as it would be the case for an ion channel, allowing an ion M to cross the membrane. The trajectory traversed by M across the membrane can be regarded as a curve $\gamma(x)$ parametrized with a one dimensional variable $x \in [0,1]$, where $\gamma_0 = \gamma(0)$ and $\gamma_1 = \gamma(1)$ represent the extra- and intracellular ends of the membrane, respectively. Taking into account the direction of the parametrization for γ, a one dimensional version of the flux from the Nernst-Planck equation (5) can then be rewritten as

$$J(x) = \vec{J}\left(\gamma(x)\right) = -\mu\mathrm{k}T\exp\left(-\frac{zU(\gamma(x))}{v_T}\right)\partial_x\left[C(\gamma(x))\exp\left(\frac{zU(\gamma(x))}{v_T}\right)\right] \tag{17}$$

where ∂_x represents the instantaneous change with respect to x. The terms $C(\gamma(x))$ and $U(\gamma(x))$ represent, respectively, the concentration of M and the electric field along γ. If the ion density in cross section inside the pore is assumed to be constant, then the current in cross section can be written as

$$I = -z\mathrm{q}A(\gamma(x))J(x), \quad x \in [0,1], \tag{18}$$

where $A(x)$ is the cross sectional area of the pore at $\gamma(x)$. Notice the sign of the current reflects the direction of the parametrization γ: inward fluxes of positively charged ions should generate negative currents (similarly for outward fluxes of negatively charged ions) and outward fluxes of negatively charged ions should generate positive currents (similarly for inward fluxes of negatively charged ions). The current across the pore can be obtained after combining equations (5) and (18), rearranging terms, and integrating along a trajectory between the intracellular and the extracellular edges of the membrane (in the positive sense of the current) to obtain

$$I = zTB\left[C_1\exp\left(\frac{zU_1}{v_T}\right) - C_0\exp\left(\frac{zU_0}{v_T}\right)\right], \tag{19}$$

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with $C_x = C(\gamma(x))$, $U_x = U(\gamma(x))$, $x \in \{0,1\}$ represent the concentration and the electric field at the extra- and intracellular edges of the membrane, respectively. The term B is given by

$$B^{-1} = \frac{1}{\mu \mathrm{qk}} \int_0^1 \frac{\exp\left(\frac{zU(-\gamma(x))}{v_T}\right)}{A(x)} dx. \tag{20}$$

which describes the dependence of the current amplitude on the shape of the pore, but in the absence of temperature changes, B can be replaced by a constant (Endresen et al., 2000; Nonner and Eisenberg, 1998).

Recall that the transmembrane potential is $v = U_1 - U_0$. Since the field U varies smoothly across the membrane, there is a point $s \in [0,1]$ with $U_s = U(\gamma(s))$ such that

$$U_1 - U_s = sv, \quad U_s - U_0 = (1-s)v, \tag{21}$$

The potential U_s can then be inserted into (19) to write the current in terms of the transmembrane potential. To do so, combine expressions (19) and (21) to obtain

$$I = zTD\left[C_1 \exp\left(\frac{zsv}{v_T}\right) - C_0 \exp\left(\frac{z\,(s-1)\,v}{v_T}\right)\right], \tag{22}$$

with $D = B\exp\left(zU_s/v_T\right)$. Then, rewrite equation (22) as

$$I = zTDC_1^{1-s}C_0^s\left[\left(\frac{C_1}{C_0}\right)^s \exp\left(\frac{zsv}{v_T}\right) - \left(\frac{C_1}{C_0}\right)^{s-1} \exp\left(\frac{z(s-1)v}{v_T}\right)\right]. \tag{23}$$

The dependence of the current on the Nernst potential for the ion M can then be realised by combining equations (7) and (23) into (22) so that,

$$I = zTDC_1^{1-s}C_0^s\left[\exp\left(zs\frac{v-v_M}{v_T}\right) - \exp\left(z\,(s-1)\,\frac{v-v_M}{v_T}\right)\right]. \tag{24}$$

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

The generic macroscopic formulation for current in equation (15) includes the electrodiffusive current in equation(22) as a particular case (Table 2). Equations (22) and (24), herein referred to as a DD current, are macroscopic descriptions of transmembrane current driven by electric *drift and diffusion* through an open channel. Expressions for voltage-dependent gating that will be presented in later sections will be combined with equations (22) or (24) 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.

3.2.1 Possible simplifications

Pore with constant cross-sectional area. One possible simplification is to assume that $A(x) = a$, a constant. From Eqn. (20),

$$D^{-1} = \frac{v_T}{az\mu \mathrm{qk}} \exp\left(\frac{zsv}{v_T}\right)\left[\exp\left(-\frac{zv}{v_T}\right) - 1\right]. \tag{25}$$

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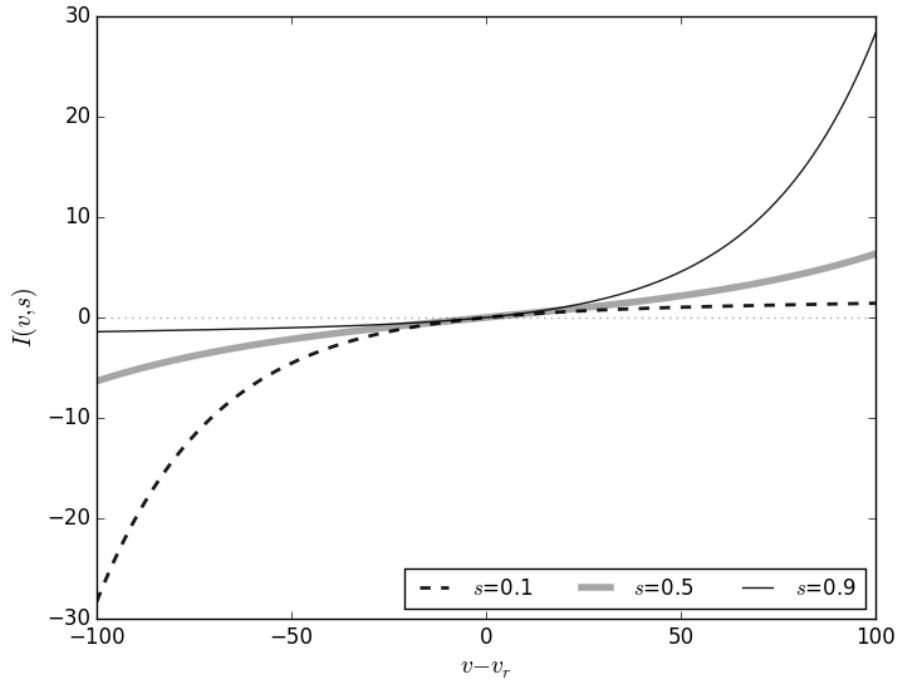

Figure 1: Shape of the curve $I(v;s)$ for different values of s and a reversal potential v_r. Note the inward rectification for s=0.1 and outward rectification for s=0.9.

As a consequence,

$$I = -a\mu \mathrm{q}^2 z^2 C_1^{1-s} C_0^s \left[\frac{\exp\left(\frac{zs(v-v_M)}{v_T}\right)}{\exp\left(\frac{zsv}{v_T}\right)}\right]\left[\frac{1-\exp\left(-z\frac{(v-v_M)}{v_T}\right)}{1-\exp\left(-z\frac{v}{v_T}\right)}\right]. \tag{26}$$

Symmetry of the reference point x_s with respect to inner and outer compartments. For the symmetric case s=1/2, equation (24) can be simplified for into

$$I = 2zDT\sqrt{C_0 C_1}\sinh\left[z\frac{(v-v_M)}{2v_T}\right]. \tag{27}$$

In addition, if the cross sectional radius of the pore is constant (see Eqn. (26)), then

$$I = -2a\mu \mathrm{q}^2 z^2 \sqrt{C_0 C_1}\left[\frac{\sinh\left(z\frac{v-v_M}{2v_T}\right)}{\sinh\left(z\frac{v}{2v_T}\right)}\right]. \tag{28}$$

Constant temperature and concentrations. If the absolute temperature and the transmembrane concentrations can be assumed to be constant, then $2a\mu \mathrm{q}^2 z^2\sqrt{C_0 C_1}$ can also be replaced by a constant that represents the maximum amplitude of the current through a single open channel (Nonner and Eisenberg, 1998).

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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. (27) can be extended for a membrane containing several hundreds or thousands of channels permeable to an ion M. Assume that there are N channels in the membrane and let $p \in [0,1]$ represent the proportion of open channels. The *gated*, whole membrane current through those channels can then be written as:

$$I_M = pN\tilde{a}zTC_0^s C_1^{1-s}\, S\left(z\frac{(v-v_M)}{v_T}, s\right). \tag{29}$$

where $S(y,s) = \exp(sy)\left[1-\exp(-y)\right]$. If the transmembrane concentrations and the absolute temperature are constant, then $N\tilde{a}zTC_0^s C_1^{1-s}$ can be thought of as a constant $\bar{a}$ representing the maximum current amplitude through the membrane. Furthermore, $\bar{a}$ can be regarded as an indicator of channel expression because it is a multiple of the number of channels in the membrane. The quantity pN 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 depends on the gating mechanism of the channel, which, in turn, may depend on voltage, the concentration of a ligand, or both.

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3.3.1 Logistic formulation for gating

As already mentioned, the generic expressions for current derived here apply for transport through open channels. Voltage- or ligand-dependent gating have 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. A widely used deterministic formulation for gating involves variables that represent activation or inactivation, taking values between 0 and 1, as originally proposed by Hodgkin and Huxley (1952). 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 gating variables are then raised to powers typically larger than, or equal to 1, to adjust the dynamics of currents obtained from voltage-clamp experiments. 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 a sigmoidal shape, slowly increasing at first, then increasing almost linearly, and then slowly changing again as they converged exponentially toward a steady state. Hodgkin and Huxley fit the time course of gating in such currents by adjusting powers of linearly changing activation variables m and n of the Na^+ and K^+ currents, thereby obtaining the 3th and 4th powers for m and n .

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

$$\left\{\partial_t u = u^k \left(F_u - u\right) C_u, \quad k = 0, 1, ...\right\}, \tag{30}$$

which display sigmoidal behaviour when k>0, for initial conditions far enough from F_u. 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 (29). 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

$$F_u(v) = \frac{exp\left(g_u \frac{v-v_u}{vT}\right)}{1 + exp\left(g_u \frac{v-v_u}{vT}\right)}, \tag{31}$$

$$C_u(v) = r_u \left[exp\left(s_u g_u \frac{v-v_u}{vT}\right) + exp\left(g_u(s_u - 1)\frac{v-v_u}{vT}\right)\right], \tag{32}$$

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 for ligand- or ligand and voltage-gated currents (Destexhe et al., 1994). For fixed v, the family (30) 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 $1/C_u(v)$. 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

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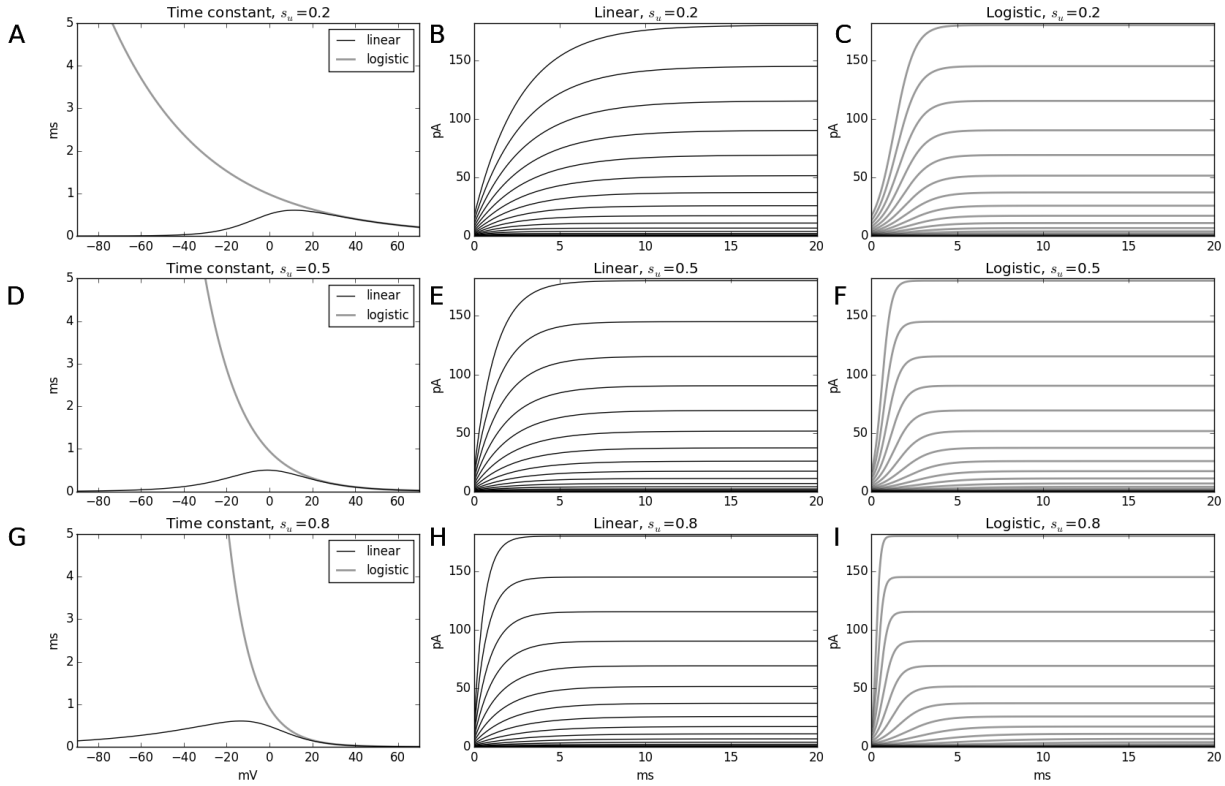

Figure 2: Simulation of currents mediated by Shab (K_v2) delayed rectifier channels, as would be recorded in voltage clamp experiments. The currents were modelled using the particular case (29) of (15) for different values of the symmetry constant in the driving force and the symmetry constant in the 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 convergence toward the attractor point F_u in this case is $(C_u(v)F_u(v))^{-1}$ (see Appendix 5.1). The change $\partial_t u$ as a function of u in 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.

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 (29) in combination with the generic gating formulation from (30)-(32) is used to simulate currents recorded in what would be a voltage-clamp experiment. The effects of K^+ channel rectification on the dynamics of excitability in neurons are explored using the generic DD formulation for currents mediated by K_v2 channels (homologous to Shab in *Drosophila* (Herrera-Valdez et al., 2013; Herrera-Valdez, 2012). Further, a combination of currents mediated by carriers and channels is used to construct a low-dimensional model of cardiac pacemaking. 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. See Tables 3

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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 (30)-(32) for the cases $k = 0$ and $k = 1$. Simulations of the dynamics of current with gating variable u displaying 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 (30) 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. One advantage of not using powers for the gating variables in models of TT is that it enables the possibility of calculating nullclines for the system.

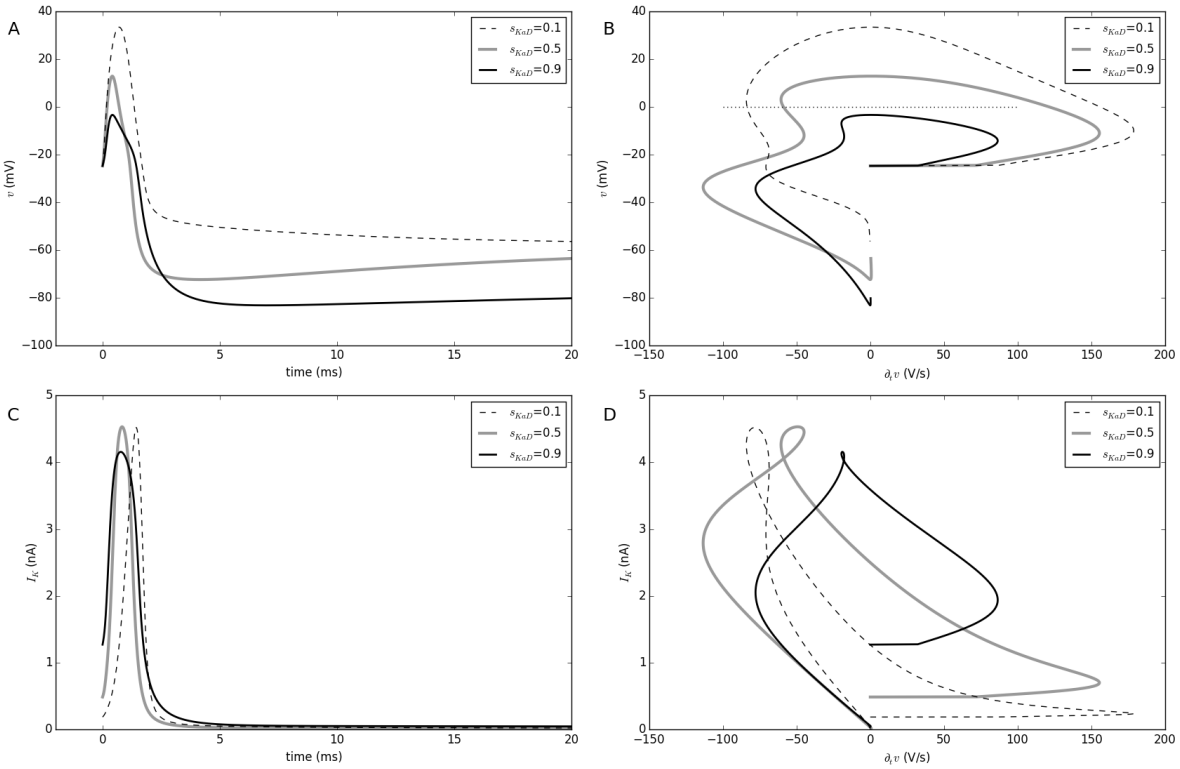

Figure 3: Neuronal dynamics for the rectification parameter $s_K \in \{0.1, 0.5, 0.9\}$. **A.** Action potentials starting from $(v_0, w_0) = (25, 0.01)$. **B.** $(\partial_t v, v)$ curve for the trajectories shown in A. **C.** Dynamics for $I_{\mathrm{K}}(t)$. **D.** Contribution of the K^+ current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

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

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membrane in this case can be modeled with a 2-dimensional system of the form

$$C_m \partial_t v = -I_{\mathrm{Na}}(v,w) - I_{\mathrm{K}}(v,w) - I_{\mathrm{NaK}}(v) - I_S(t), \quad (33)$$

$$\partial_t w = w\,[F_w(v) - w]\,C_w(v), \quad (34)$$

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}, 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 s_{K} for a K^+ current modelled with (15) (see Tables 3 and 4). In general, action potentials become faster and 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 (15) 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 (Herrera-Valdez and Lega, 2011). 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 channels and 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

$$C_m \partial_t v = -I_{\mathrm{Ca}}(v,w,c) - I_{\mathrm{K}}(v,w,c) - I_{\mathrm{NaK}}(v) - I_{\mathrm{NaCa}}(v,c), \quad (35)$$

$$\partial_t w = w\,[F_w(v) - w]\,C_w(v) \quad (36)$$

$$\partial_t c = r_c\,(c_\infty - c) - k_c\,[I_{\mathrm{Ca}}(v,w) - I_{\mathrm{NaCa}}(v,c)] \quad (37)$$

The model (35)-(37) 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 (15) and the inclusion of Ca^{2+} dynamics into the system (35)-(37) allows 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 (35)-(37) include

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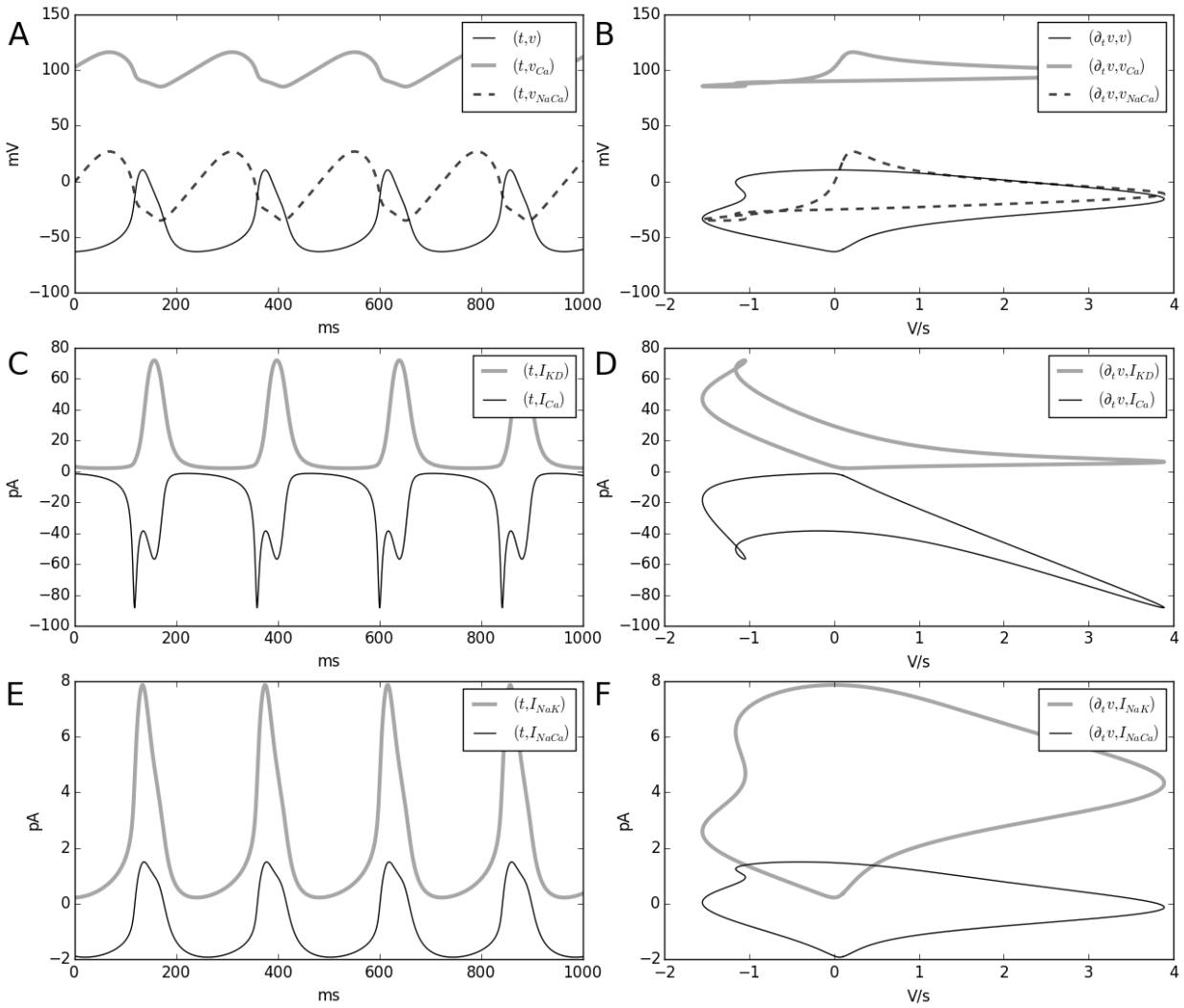

Figure 4: Central sinoatrial node dynamics using the system (35)-(37).

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 po-

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tential, 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

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

5 Discussion

The most important assumption for the TT models presented here is that the electrochemical gradients of the transported 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 (15) 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 (15) yields the conductance based formulation proposed by Hodgkin and Huxley when truncated to a first order approximation around the Nernst potential of the

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ion (Herrera-Valdez, 2012). 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 (15) enables fitting of rectifying 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 (29) 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 (29) 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 (29) is the conductance-based current (Herrera-Valdez, 2012). It is important to mention that the particular case of the electrodiffusion formulation (29) 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. (15) 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 carries (15). 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. jThe particular case where $m = 1$ in (15) tells us that *electrodiffusion through a channel as described by the Nernst-Planck equation is macroscopically can be thought of as if it was ionic "transport" across the membrane by a carrier protein*, one ion at a time. As a consequence, the modelling results 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 (15) enables the calculation of the null cline associated to the intracellular calcium concentration in models like (35)-(37), by simply solving for c. Also, the alternative formulation for activation in (30) 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 (30) 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 the parameters s_u, r_u, and k 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 (15) combined with (30)-(32) opens the possibility of different modeling studies aimed at understanding the role of channel heterogeneity in the excitability of cells. In particular, a systematic modelling study of heterogeneities in populations of channels, possibly including different subtypes or splice variants (see

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for instance Lin et al., 2009; Shipston, 2001) is underway. Another interesting application of the general formulation is the study of short-term plasticity and heterogeneity of channel populations in network models with synaptic currents written with (15).

5.1 Summary and conclusions

The generic formulation (15) was derived from basic macroscopic considerations about the changes in free energy that occur in TT. An alternative derivation for a particular case involving electrodiffusive TT 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). As shown by the application of the models to the simulation of activity of excitable cells of different types, varying the balance between the maximum amplitudes for the currents and the membrane capacitance is enough to obtain membrane dynamics that correspond to the different electrophysiological profiles observed in 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, and 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

Energy required to transport an ion across the membrane

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

$$\Delta G_M = \mathrm{q} z_M \left(v_M - v\right)(a-b), \tag{38}$$

(Blaustein et al., 2004). If $\Delta G_M < 0$, then the transport can take place without an additional source of energy. If $\Delta G_M > 0$, then the energy required for the transport must be provided by an external source that does not involve the electrochemical gradients of the ions being transported.

Logistic equation: solution and time constant for evolution

Consider a logistic equation of the form

$$\partial_t u = u(a-u)r, \quad u(0) = u_0 \tag{39}$$

The analytical solution for (39) can be obtained by separation of variables as follows:

$$\begin{aligned} -rt &= \int_0^t \frac{\partial_s u}{u-a} ds \\ &= \frac{1}{a}\left(\int_{u_0}^{u(t)} \frac{1}{u-a} - \frac{1}{u} du\right) \\ &= \frac{1}{a}\left(\int_{u_0}^{u(t)} \frac{du}{u-a} - \int_{u_0}^{u(t)} \frac{du}{u}\right) \\ &= \frac{1}{a}\left[\log\left(\frac{u(t)-a}{u_0-a}\right) - \log\left(\frac{u(t)}{u_0}\right)\right] \qquad (40) \\ &= \frac{1}{a}\left[\log\left(\frac{u_0\left(u(t)-a\right)}{u(t)\left(u_0-a\right)}\right)\right] \qquad (41) \end{aligned}$$

Therefore,

$$\begin{aligned} u_0\left(u(t)-a\right) &= u(t)\left(u_0-a\right)\exp\left(-art\right) \\ -au_0 &= u(t)\left[\left(u_0-a\right)\exp\left(-art\right) - u_0\right] \\ u(t) &= \frac{au_0}{u_0 - \left(u_0-a\right)\exp\left(-art\right)} \end{aligned} \tag{42}$$

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

Steady state for the intracellular calcium concentration (equation (37))

Then, the steady state for c cequation (37) is given by

$$0 = r_c\left(c_\infty - c\right) - k_c\left(I_{\mathrm{CaL}} - I_{\mathrm{NaCa}}\right) \tag{43}$$

To calculate the solutioin c_*, we will use equation (15) for the two currents I_{NaCa} and I_{CaL}.

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First, notice that the changes in energy required for the activity of the Na^+-Ca^{2+} exchanger are given by equation (15) with $n_{\mathrm{Na}} = 3$, $n_{\mathrm{Ca}} = 2$, and $a_{\mathrm{Na}} = b_{\mathrm{Ca}} = 0$ and $b_{\mathrm{Na}} = a_{\mathrm{Ca}} = 1$. As a result,

$$\Delta G_{\mathrm{Na}} = 3q_e\left(v - v_{\mathrm{Na}}\right) \tag{44}$$

$$\Delta G_{\mathrm{Ca}} = 2q_e\left(v_{\mathrm{Ca}} - v\right) = q_e\left[-2v + v_T \ln\left(\frac{[Ca]_0}{[Ca]_1}\right)\right] \tag{45}$$

The total energy required for transport in this case is thus

$$\begin{aligned}\Delta G_{\mathrm{NaCa}} &= \Delta G_{\mathrm{Na}} + \Delta G_{\mathrm{Ca}} \\ &= q_e\left[v + 3v_{\mathrm{Na}} - v_T \ln\left(\frac{[Ca]_0}{[Ca]_1}\right)\right]\end{aligned} \tag{46}$$

The forward and backward rates for the Na^+-Ca^{2+} exchanger are then

$$\alpha = r_{\mathrm{NaCa}}\left(\frac{[Ca]_1}{[Ca]_0}\right)^s \exp\left(-s\frac{v + 3v_{\mathrm{Na}}}{v_T}\right) \tag{47}$$

$$\beta = r_{\mathrm{NaCa}}\left(\frac{[Ca]_1}{[Ca]_0}\right)^{1-s} \exp\left[(1-s)\frac{v + 3v_{\mathrm{Na}}}{v_T}\right]. \tag{48}$$

From equation (10), let $r_{\mathrm{NaCa}} = a_{\mathrm{NaCa}}[Ca]_0^s[Ca]_1^{1-s}$. The current mediated by the Na^+-Ca^{2+} exchanger can then be written as

$$\begin{aligned}I_{\mathrm{NaCa}} &= -r_{\mathrm{NaCa}}\left[\left(\frac{[Ca]_1}{[Ca]_0}\right)^s \exp\left(-s\frac{v + 3v_{\mathrm{Na}}}{v_T}\right) - \left(\frac{[Ca]_1}{[Ca]_0}\right)^{1-s} \exp\left[(1-s)\frac{v + 3v_{\mathrm{Na}}}{v_T}\right]\right] \\ &= -r_{\mathrm{NaCa}}[Ca]_0^{-s}[Ca]_1^{s-1}\left[[Ca]_1 \exp\left(-s\frac{v + 3v_{\mathrm{Na}}}{v_T}\right) - [Ca]_0 \exp\left[(1-s)\frac{v + 3v_{\mathrm{Na}}}{v_T}\right]\right] \\ &\approx -a_{\mathrm{NaCa}}\left[[Ca]_1 \exp\left(-s\frac{v + 3v_{\mathrm{Na}}}{v_T}\right) - [Ca]_0 \exp\left[(1-s)\frac{v + 3v_{\mathrm{Na}}}{v_T}\right]\right].\end{aligned} \tag{49}$$

Similarly, the L-type Ca^{2+} current is given by

$$I_{\mathrm{CaL}} = a_{\mathrm{CaL}}\left\{[Ca]_1 \exp\left(2s\frac{v}{v_T}\right) - [Ca]_0 \exp\left[2(s-1)\frac{v}{v_T}\right]\right\}. \tag{50}$$

Recall that $c = [Ca]_1$ in the system (35)-(37). Therefore,

$$c_* = \frac{r_c c_\infty + k_c[Ca]_0\left\{a_{\mathrm{CaL}} \exp\left[2(s-1)\frac{v}{v_T}\right] + a_{\mathrm{NaCa}} \exp\left[(1-s)\frac{v+3v_{\mathrm{Na}}}{v_T}\right]\right\}}{r_c + k_c\left\{a_{\mathrm{CaL}} \exp\left(2s\frac{v}{v_T}\right) + a_{\mathrm{NaCa}} \exp\left(-s\frac{v+3v_{\mathrm{Na}}}{v_T}\right)\right\}} \tag{51}$$

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