

# **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 that is, in turn, 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 to describe transmembrane transport derived from thermodynamic principles

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## Abstract

Cells communicate with their environments using transmembrane molecular transport that is, in turn, mediated by proteins that facilitate diffusion (channels), or alternatively, translocate ions against the electrochemical gradient (pumps). 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 pumps or open channels is presented here. The functional form of the flux was obtained from thermodynamic first principles. Further, taking a slightly different approach, the *same* generic formulation mentioned above can be obtained from the Nernst-Planck equation for the case of channel-mediated electrodiffusion. The generic formula can be regarded as the product of an amplitude term and a driving force term. 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 neurons 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). Of particular interest, 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 through 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 alike. 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 macroscopically, is the difference in 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 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 channels, and also by pumps.

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

## 2 Methods

### 2.1 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:

$$\vec{J}_M = -\mu_M (kT \nabla C_M + q z_M C_M \nabla U), \quad (1)$$

where  $U$  represents a smoothly varying electric field,  $z_M$ ,  $\mu_M$ , and  $C_M$  are, respectively, the valence, electrical mobility, and concentration of  $i$ . The elementary charge (Coulombs) is  $q$ ,  $k$  is Boltzmann's constant (mJ/K), and  $T$  is the absolute temperature ( $^{\circ}K$ ). Taking a macroscopic perspective, assume that  $C_M$  and  $U$  only change in the transmembrane direction and the membrane delimits two compartments, denoted as 0 and 1 for external and internal, respectively. Note the *transmembrane potential* is then  $v = U_1 - U_0$ . The trajectory traversed by the ion as it crosses the membrane can be parametrized by a real variable  $x$ , taking values  $a$  and  $b$  at the intra- and extracellular edges of the membrane pore. Then it is possible to think of equation (1) as one-dimensional. To simplify notation, let  $v_T = kT/q$  and use  $[M]_k$  with  $k \in \{0, 1\}$  to represent the extra- and intracellular concentrations of  $M$ , respectively. From (1), the transmembrane voltage at which there is no net transmembrane flux of  $M$ , called *Nernst potential* for  $i$ , is given by

$$v_M = \frac{v_T}{z_M} \ln \left( \frac{[M]_0}{[M]_1} \right), \quad (2)$$

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

$$\frac{[M]_0}{[M]_1} = \exp \left( \frac{z_M}{v_T} v_M \right). \quad (3)$$

Now assume that a pore is a revolution volume with cross sectional area  $A(x)$ . Then, the current in cross section is given by

$$I(x) = q z_M A(x) J_M(x), \quad (4)$$

for each  $x \in [a, b]$ . The current from (4) can be assumed to be constant as a function of  $x$  (Endresen et al., 2000; Hille and Schwarz, 1978). Using the integrating factor  $\exp(z_M U/v_T)$  and integrating over  $[a, b]$  gives

$$I = z_M B^{-1} T \left[ C_1 \exp \left( \frac{z_M U_0}{v_T} \right) - C_0 \exp \left( \frac{z_M U_1}{v_T} \right) \right], \quad (5)$$

where  $C_1 = C(a)$ ,  $C_0 = C(b)$ ,  $U_1 = U(a)$ , and  $U_0 = U(b)$ . The term

$$B = \frac{1}{\mu_M q k} \int_a^b \frac{1}{A(x)} \exp \left( \frac{z_M U}{v_T} \right) dx \quad (6)$$

describes the dependence of the current on the shape of the pore, but can be approximated by constant (Eisenberg, 1998, 1999; Hille and Schwarz, 1978). Equation (5) can then be conveniently rewritten as

$$I = z_M B^{-1} T C_1^{1-s} C_0^s \left[ \left( \frac{C_1}{C_0} \right)^s \exp \left( \frac{z_M U_0}{v_T} \right) - \left( \frac{C_1}{C_0} \right)^{s-1} \exp \left( \frac{z_M U_1}{v_T} \right) \right]. \quad (7)$$

## 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



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

$$\frac{\alpha}{\beta} = \exp\left(-\frac{\Delta G}{kT}\right), \quad (9)$$

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

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

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 Energy required to transport one ion across the membrane

The energy required for transmembrane transport of a molecule  $i$  from compartment  $a$  to compartment  $b$  can be expressed as

$$\Delta G_M = qz_M (v_M - v) (a_M - b_M), \quad (11)$$

(see Blaustein et al., 2004, for details). If  $\Delta G_M > 0$ , the transport occurs against the electrochemical gradient for  $i$ , 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. Note that when  $a - b < 0$ , the sign of  $\Delta G_M$  is the opposite of the sign of  $v_M - v$ .

## 3 Results

### 3.1 Electrodiffusive transport

Assume that the total length of the pore is  $l$ . If the pore region is regarded as solid of revolution with constant-valued cross sections with respect to  $U$ , then  $U$  behaves as a 1-dimensional function across the pore. As a consequence, there is an  $s \in [0, 1]$  and a corresponding point  $x_s = a + sl$  along the length of the pore such that  $U_s = U(x_s)$

and

$$U_1 - U_s = sv, \quad U_s - U_0 = (1-s)v, \quad s \in (0, 1) \quad (12)$$

The potential  $U_s$  can then be used to rewrite the current (5) in terms of the transmembrane potential:

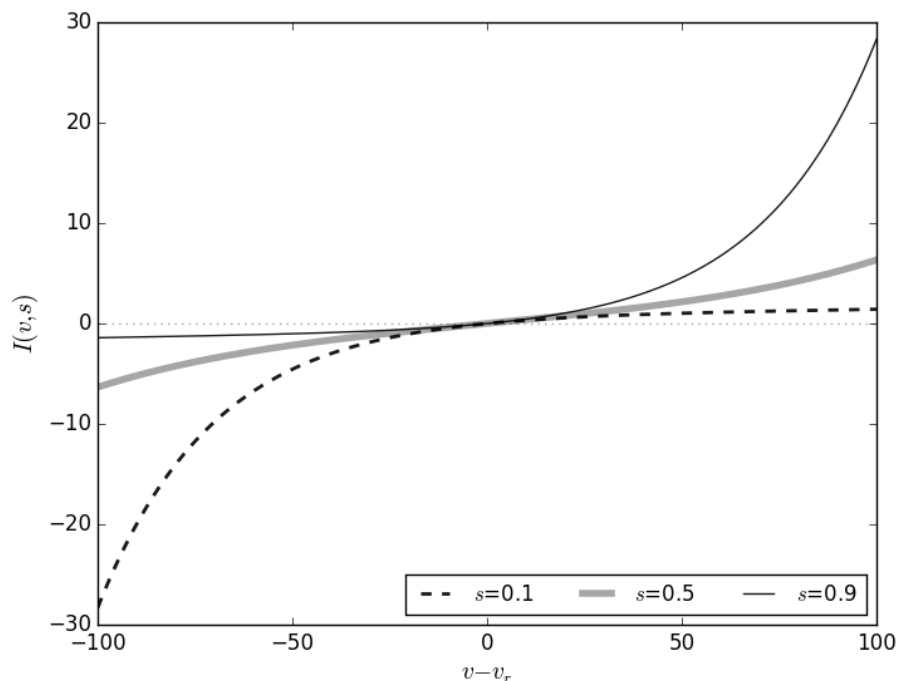
$$I(v; s) = z_M T D \left[ C_1 \exp\left(\frac{z_M s v}{v_T}\right) - C_0 \exp\left(\frac{z_M (s-1) v}{v_T}\right) \right], \quad (13)$$

with  $D = B^{-1} \exp(z_M U_s / v_T)$ . If needed, the dependence of the current on the Nernst potential for the ion  $i$  can then be realized by combining equations (3) and (7) into (13) so that,

$$I(v; s) = z_M T D C_0^s C_1^{1-s} \left[ \exp\left(\frac{z_M s (v - v_M)}{v_T}\right) - \exp\left(\frac{z_M (s-1) (v - v_M)}{v_T}\right) \right]. \quad (14)$$

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

Equations (13) and (14) 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. Whole membrane or whole patch currents can be obtained by adding gating and a factor that accounts for the number of channels to the terms outside the parentheses in (13) or (14).



**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  $s=0.9$ .

### 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. (6),

$$D^{-1} = \frac{v_T}{az_M\mu_M qk} \exp\left(\frac{z_M s v}{v_T}\right) \left[ \exp\left(-\frac{z_M v}{v_T}\right) - 1 \right]. \quad (15)$$

As a consequence,

$$I(v; s) = -a\mu_M q^2 z_M^2 C_0^s C_1^{1-s} \left[ \frac{\exp\left(\frac{z_M s(v-v_M)}{v_T}\right)}{\exp\left(\frac{z_M s v}{v_T}\right)} \right] \left[ \frac{1 - \exp\left(-\frac{z_M(v-v_M)}{v_T}\right)}{1 - \exp\left(-\frac{z_M v}{v_T}\right)} \right]. \quad (16)$$

**Symmetry of the reference point  $x_s$  with respect to inner and outer compartments.** For the symmetric case  $m=1/2$ , equation (14) can be simplified for into

$$I = 2z_M DT \sqrt{C_0 C_1} \sinh \left[ \frac{z_M(v - v_M)}{2v_T} \right]. \quad (17)$$

In addition, if the cross sectional radius of the pore is constant (see Eqn. (16)), then

$$I = -2a\mu_M q^2 z_M^2 \sqrt{C_0 C_1} \left[ \frac{\sinh\left(\frac{z_M}{2v_T}(v - v_M)\right)}{\sinh\left(\frac{z_M}{2v_T}v\right)} \right]. \quad (18)$$

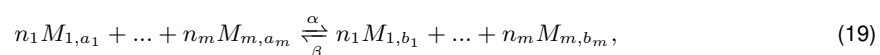
**Constant temperature and concentrations.** If the absolute temperature and the transmembrane concentrations can be assumed to be constant, then  $2a\mu_M q^2 z_M^2 \sqrt{C_0 C_1}$  can be replaced by a constant representing the maximum amplitude of the current through a single open channel (Nonner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

## 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 Possibly simultaneous transmembrane ionic transport

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



where  $a_i, b_i \in \{0, 1\}$ ,  $i \in \{1, \dots, m\}$ , representing the source and target compartments, respectively. The number of ions of each type involved in the transport is represented by  $n_i$ ,  $i \in \{1, \dots, m\}$ . The scheme (19) is generic, so the translocation of the ions could be that mediated by either a pump, or an open channel. The energy  $\Delta G_m$

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):

$$\Delta G_m = \sum_{i=1}^m \Delta G_i = \sum_{i=1}^m n_i z_i (v_i - v)(a_i - b_i), \quad (20)$$

as given by equation (11). Notice that (20) 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

$$\Delta G = \Delta G_m + \Delta G_{ATP}. \quad (21)$$

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

### 3.2.2 Flux due to transport

From (19), 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

$$r = f(T) \prod_{i=1}^m [M_i]_0^{n_i(a_i-b_i)s} [M_i]_1^{n_i(a_i-b_i)(1-s)} \quad (22)$$

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 (20) or (21):

$$\begin{aligned} \phi = r \left\{ \exp \left[ \frac{s}{v_T} \left( -v_{AB} + \sum_{i=1}^m (a_i - b_i) n_i z_i (v - v_i) \right) \right] \right. \\ \left. - \exp \left[ \frac{(s-1)}{v_T} \left( -v_{AB} + \sum_{i=1}^m (a_i - b_i) n_i z_i (v - v_i) \right) \right] \right\} \end{aligned} \quad (23)$$

where  $v_{AB} = v_{ATP}$  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 (2) into (23):

$$\phi = r \exp \left[ \frac{s}{v_T} \left( -v_{AB} + \sum_{i=1}^m (a_i - b_i) n_i z_i v \right) \right] \prod_{i=1}^m \left( \frac{[M_i]_1}{[M_i]_0} \right)^{s n_i (a_i - b_i)} \left\{ 1 - \exp \left[ \frac{1}{v_T} \left( v_{AB} - \sum_{i=1}^m (a_i - b_i) n_i z_i v \right) \right] \prod_{i=1}^m \left( \frac{[M_i]_1}{[M_i]_0} \right)^{-n_i (a_i - b_i)} \right\}. \quad (24)$$

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 pumps 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)	$n_i$	$a_i$	$b_i$	$a_i - b_i$	$\Delta G_i$	$\sigma$	$v_r$
Ca <sup>2+</sup> ATPase	Ca <sup>2+</sup>	1	1	0	1	$\Delta G_{Ca} = 2q_e(v_{Ca} - v)$	1	$2v_{Ca} + v_{ATP}$
Na <sup>+</sup> -K <sup>+</sup> ATPase	Na <sup>+</sup>	3	1	0	1	$\Delta G_{Na} = 3q_e(v_{Na} - v)$	1	$3v_{Na} - 2v_K + v_{ATP}$
	K <sup>+</sup>	2	0	1	-1	$\Delta G_K = -2q_e(v_K - v)$		
Na <sup>+</sup> -Ca <sup>2+</sup> exchanger	Na <sup>+</sup>	3	0	1	-1	$\Delta G_{Na} = -3q_e(v_{Na} - v)$	-1	$-3v_{Na} + 2v_{Ca}$
	Ca <sup>2+</sup>	1	1	0	1	$\Delta G_{Ca} = 2q_e(v_{Ca} - v)$		
Na <sup>+</sup> -K <sup>+</sup> -Cl <sup>-</sup> symporter	Na <sup>+</sup>	1	0	1	-1	$\Delta G_{Na} = -q_e(v_{Na} - v)$	0	-
	K <sup>+</sup>	1	0	1	-1	$\Delta G_K = -q_e(v_K - v)$		
	Cl <sup>-</sup>	2	0	1	-1	$\Delta G_{Cl} = 2q_e(v_{Cl} - v)$		
K <sup>+</sup> -Cl <sup>-</sup> symporter	K <sup>+</sup>	1	1	0	1	$\Delta G_K = q_e(v_K - v)$	0	-
	Cl <sup>-</sup>	1	1	0	1	$\Delta G_{Cl} = -q_e(v_{Cl} - v)$		
Na <sup>+</sup> -H <sup>+</sup> exchanger	Na <sup>+</sup>	1	0	1	-1	$\Delta G_{Na} = -q_e(v_{Na} - v)$	0	-
	H <sup>+</sup>	1	1	0	1	$\Delta G_H = q_e(v_H - v)$		
Na <sup>+</sup> channel	Na <sup>+</sup>	1	0	1	-1	$\Delta G_{Na} = -q_e(v_{Na} - v)$	-1	$v_{Na}$
K <sup>+</sup> channel	K <sup>+</sup>	1	1	0	1	$\Delta G_K = q_e(v_K - v)$	1	$v_K$
Ca <sup>2+</sup> channel	Ca <sup>2+</sup>	1	0	1	-1	$\Delta G_{Ca} = -2q_e(v_{Ca} - v)$	-2	$v_{Ca}$
Cl <sup>-</sup> channel	Cl <sup>-</sup>	1	0	1	-1	$\Delta G_{Cl} = q_e(v_{Cl} - v)$	-1	$v_{Cl}$

### 3.2.3 Electrogenic transport and the generic formulation for current

Recall that the transport (19) is *electrogenic* whenever the sum of the charges that cross in a single event is distinct from zero. In terms of the scheme (19), electrogenic transport satisfies

$$\sigma = \sum_{i=1}^m n_i z_i (a_i - b_i) \neq 0. \quad (25)$$

As a consequence, the rates  $\alpha$  and  $\beta$  from (19) 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

$$v_r = v_{\text{ATP}} + \sum_{i=1}^m n_i z_i v_i (a_i - b_i). \quad (26)$$

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

$$v_r = \sum_{i=1}^m n_i z_i v_i (a_i - b_i). \quad (27)$$

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

$$I = qf(T)\sigma \left\{ \prod_{i=1}^m [M_i]_1^{n_i(a_i-b_i)} \exp \left[ \frac{s}{v_T} \left( -v_{AB} + \sum_{i=1}^m (a_i - b_i) n_i z_i v \right) \right] - \prod_{i=1}^m [M_i]_0^{n_i(a_i-b_i)} \exp \left[ \frac{(s-1)}{v_T} \left( -v_{AB} + \sum_{i=1}^m (a_i - b_i) n_i z_i v \right) \right] \right\}. \quad (28)$$

The generic formulation in (28) reduces to (13) 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 (13), equation (28) can take different functional forms, which can be useful for different purposes (see Tables 2 and 3). Moreover, the generic macroscopic description of current (28) includes the electrodiffusive current in (13) as a particular case (Table 2). As noted before, if  $s = 1/2$ , then equation (28) transforms into

$$I = 2qf(T)\sigma \prod_{i=1}^m ([M_i]_0[M_i]_1)^{n_i(a_i-b_i)/2} \sinh \left( \frac{-v_{AB} + \sum_{i=1}^m n_i z_i (a_i - b_i) (v - v_i)}{2v_T} \right). \quad (29)$$

### 3.3 Whole membrane currents and channel gating

The formulation in Eq. (17) 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:

$$I_M = p_M N_M \tilde{a}_M T M_0^s M_1^{1-s} S \left[ \frac{z_M (v - v_M)}{v_T}, s_i \right]. \quad (30)$$

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  $\bar{a}_i$  representing the maximum current amplitude through the membrane. Furthermore,  $\bar{a}_i$  can be regarded as an indicator of channel expression because it is a multiple of the number of channels in the

**Table 2:** Generic formulations for transmembrane flux mediated by different pumps or channels. For channels, it is assumed that only one ion can cross at any given time. The direction of motion of the transport for each ion is indicated by  $\sigma$  (Eq. (25)). The terms that correspond to the amplitudes are abbreviated in all cases.

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

membrane. The quantity  $N_i p_i$  can be thought of as the average number of open channels permeable (see Aldrich et al. (1983) for an interesting perspective in this regard). The proportion  $p_i$  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  $p_i$  will be discussed in the following paragraphs.

### 3.3.1 Generic formulation for gating

While fitting currents recorded using voltage-clamp mode, Hodgkin and Huxley noted that for some of the voltage commands, especially the lower ones, the time course of the current had a sigmoidal shape, slow-changing at first, then changing almost linearly, and then slowly changing as it converged exponentially toward a steady state. In consideration of the above, Hodgkin and Huxley decided to fit the time course of gating by using powers of linearly changing variables. 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

$$\left\{ \partial_t u = u^k (F_u - u) C_u, \quad k = 0, 1, \dots \right\}, \quad (31)$$

which display sigmoidal behavior. If gating is voltage-dependent, the steady state  $F$  and rate  $C$  can be written explicitly as

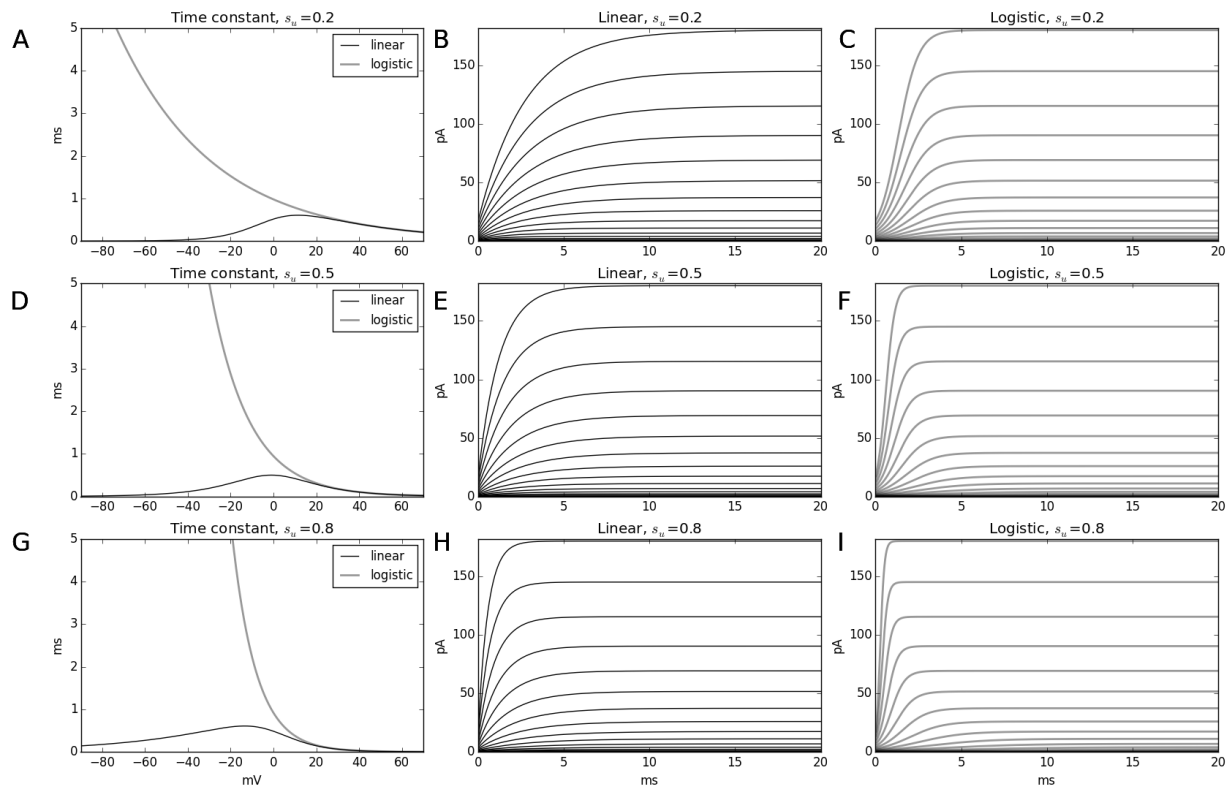
$$F_u(v) = \frac{\exp\left(g_u \frac{v-v_u}{vT}\right)}{1 + \exp\left(g_u \frac{v-v_u}{vT}\right)}, \quad (32)$$

$$C_u(v) = r_u \left[ \exp\left(s_u g_u \frac{v-v_u}{vT}\right) + \exp\left(g_u (s_u - 1) \frac{v-v_u}{vT}\right) \right], \quad (33)$$

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). For fixed  $v$ , the family (31) 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 quadratic 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 (30) in combination with the generic gating formulation from (31)-(33) 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  $K_v 2$  (homologous to Shab in *Drosophila* (Herrera-Valdez et al., 2013; Herrera-Valdez, 2012)). The combination of currents mediated by pumps and channels is used to construct a low-dimensional model of cardiac pacemaking. The generic formulation for current in (28) is used in combination with the gating from (31)-(33). 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 null-clines 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.



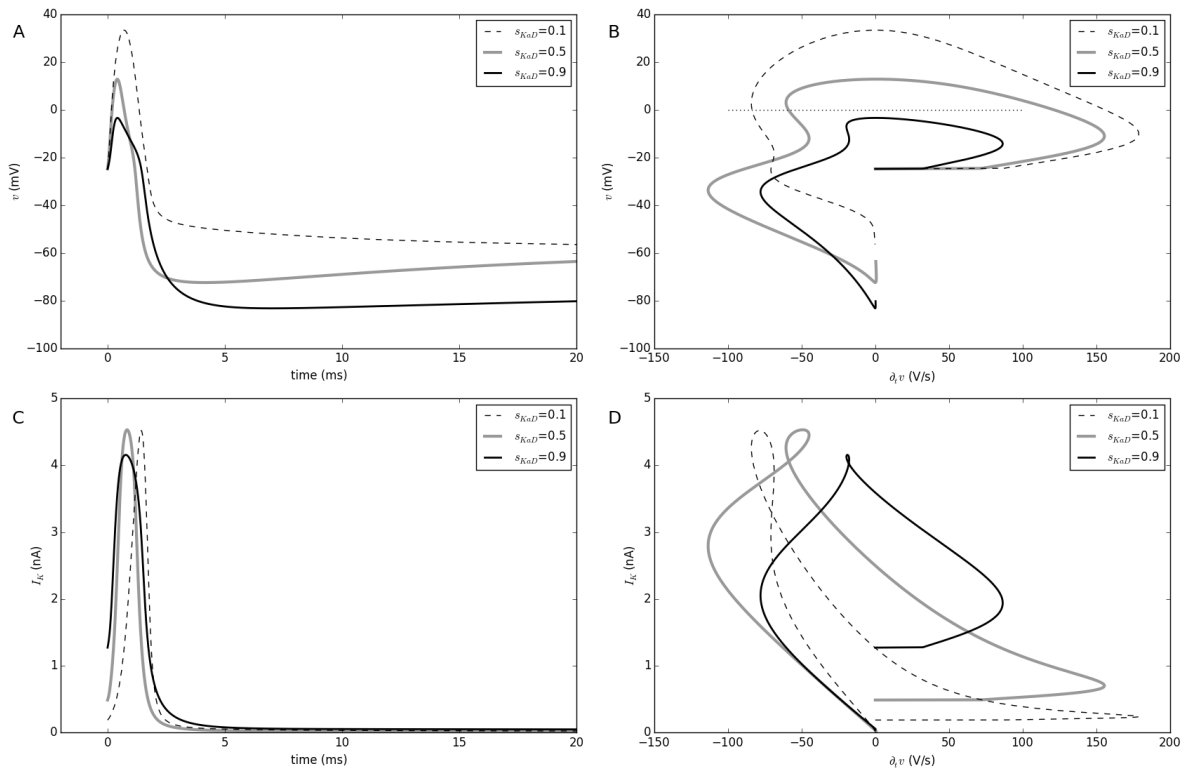
**Figure 2:** Simulation of currents mediated by Shab ( $K_v2$ ) delayed rectifier channels, recorded in voltage clamp experiments. The currents were modelled using the particular case (30) of (28) for different values of the symmetry constant in the driving force and the symmetry constant in the activation 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).

## 4.1 Voltage clamp dynamics

The functions (31)-(33) can be used to fit currents from voltage-clamp recordings, including those of sigmoidal shape (see simulation of  $K_v2$  current in voltage clamp in Fig. 2), without using powers in the gating variables. 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 (31) 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  $k>1$ ).

## 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



**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  $I_K(t)$ . **D.** Contribution of the  $K^+$  current to the change in  $v$ ,  $(\partial_t v, I_K(v))$ .

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

$$C_m \partial_t v = -I_{Na}(v, w) - I_K(v, w) - I_{NaK}(v) - I_S(t), \quad (34)$$

$$\partial_t w = w [F_w(v) - w] C_w(v), \quad (35)$$

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 (28) (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  $s_K = 0.5$  and  $s_K = 0.9$  is similar and occurs earlier dur-

ing the action potential in comparison to the inwardly rectifying case  $s_K = 0.1$  (Fig. 3C). The maximum downstroke speed of the action potential occurs for  $s_K = 0.5$ . Notably, the downstroke speed has similar values for  $s_K = 0.1$  and  $s_K = 0.9$  (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 (28) to model a calcium current mediated by L-type  $\text{Ca}_v1.3$  channels, a delayed-rectifier current, a current mediated by a  $\text{Na}^+-\text{Ca}^{2+}$  exchanger, and a  $\text{Na}^+-\text{K}^+$  ATPase. In addition, the change in the intracellular  $\text{Ca}^{2+}$  concentration can be modeled with a variable  $c$  with linear dynamics attracted toward a steady state value  $c_\infty$ , with increases proportional to the total transport of  $\text{Ca}^{2+}$  ions via L-type channels and the  $\text{Na}^+-\text{Ca}^{2+}$  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

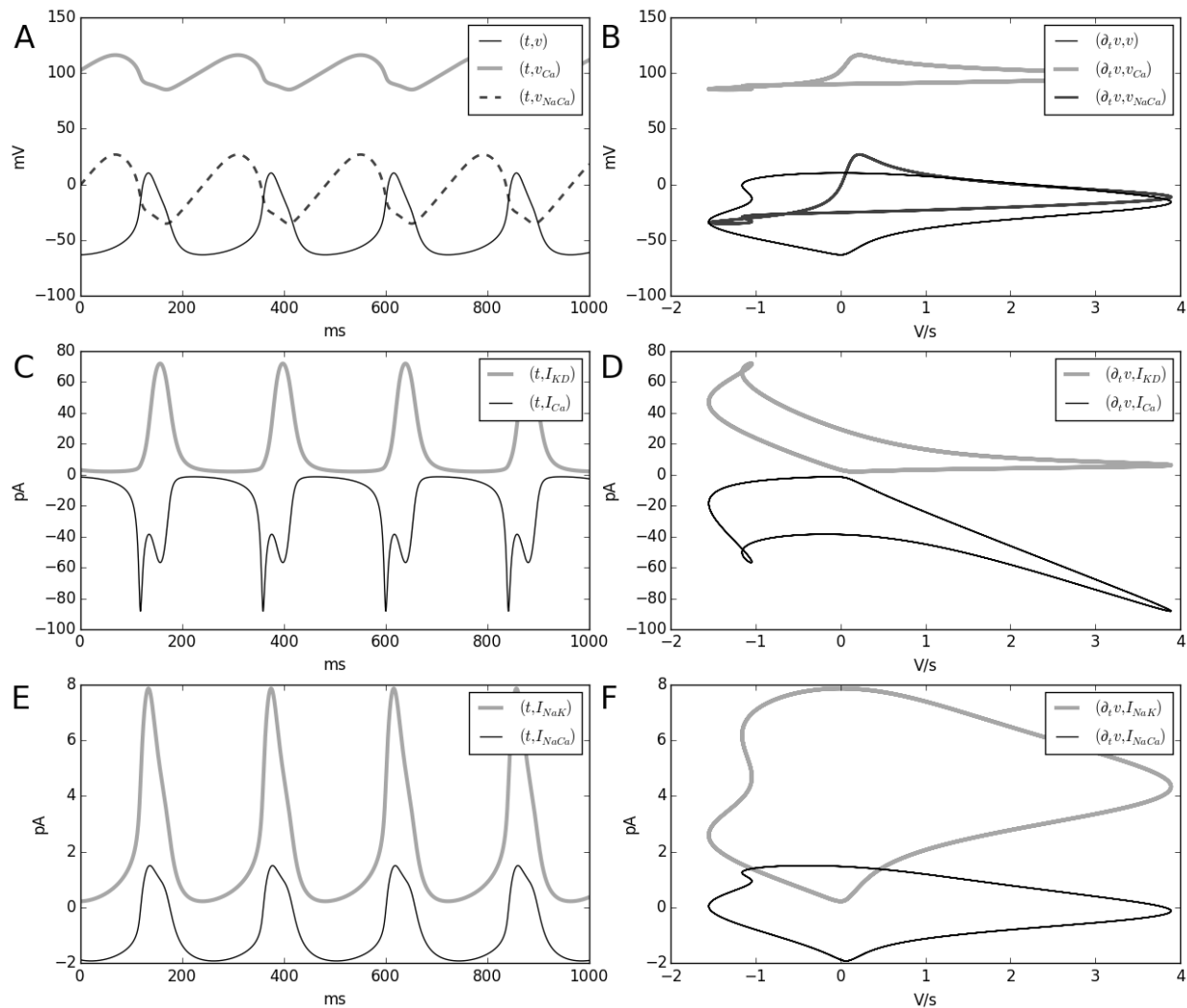
$$C_m \partial_t v = -I_{\text{Ca}}(v, w, c) - I_{\text{K}}(v, w, c) - I_{\text{NaK}}(v) - I_{\text{NaCa}}(v, c), \quad (36)$$

$$\partial_t w = w [F_w(v) - w] C_w(v) \quad (37)$$

$$\partial_t c = r_c (c_\infty - c) - k_c [I_{\text{Ca}}(v, w) - I_{\text{NaCa}}(v, c)] \quad (38)$$

The model (36)-(38) 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 (28) and the inclusion of  $\text{Ca}^{2+}$  dynamics into the system (36)-(38) 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 (36)-(38) include a double activation of the  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{K}^+$  channels, a simplification that does not prevent or affect the double activation of the L-type  $\text{Ca}^{2+}$  channels during the action potential (Herrera-Valdez and Lega, 2011; Mitchell and Schaeffer, 2003). That double fluctuation is reflected in the Nernst potential for  $\text{Ca}^{2+}$ , 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  $\text{Ca}^{2+}$  current. By extension, the reversal potential for the Na-Ca exchanger,  $v_{\text{NaCa}} = 3v_{\text{Na}} - 2v_{\text{Ca}}$  also has two decaying phases that are related to the secondary activation of the  $\text{Ca}^{2+}$  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).



**Figure 4:** Central sinoatrial node dynamics using the system (36)-(38).

## 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 (28) yield a quantitatively accurate and generic macroscopic description of transmembrane currents (Blaustein et al., 2004; Hille, 1992). In particular, the macroscopic description of the electrodiffusive flux across a transmembrane pore can be readily adjusted to currents mediated by channels permeable to  $K^+$ ,  $Na^+$ , and  $Ca^{2+}$ , (Almers and McCleskey, 1984; Hille and Schwarz, 1978) recorded experimentally (see Herrera-Valdez et al., 2013).

It is important to mention that the particular case of the electrodiffusion formulation (30) 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



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

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

**Table 4:** Parameters used in the different simulations.

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

approximation to enrich the dynamics of  $K^+$  currents in [Hodgkin and Huxley](#) models based on data from the squid axon. The formulation presented here was independently obtained by the author, but in a more general setting in a more general setting.

Importantly, Eq. (14) 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 (28). 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 (28) 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 results presented here support the hypotheses advanced by [Gadsby \(2009\)](#) and other researchers, that *channel and pump-mediated transport are macroscopically equivalent*.

A yet a additional improvement over currently available models is that the formulation in (28) enables the calcula-

tion of the null cline associated to the intracellular calcium concentration in models like (36)-(38), by simply solving for  $c$ . Also, the alternative formulation for activation in (31) 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 (31) 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 (28) combined with (31)-(33) 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 (28).

## 5.1 Summary and conclusions

The generic formulation (28) 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.

## Supplementary information

### Logistic equation: solution and time constant for evolution

Consider a logistic equation of the form

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

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

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

$$= \frac{1}{a} \left[ \log \left( \frac{u_0 (u(t) - a)}{u(t) (u_0 - a)} \right) \right] \quad (41)$$

Therefore,

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

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

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