RESEARCH ARTICLE

REVISED A thermodynamic description for physiological transmembrane transport [version 3; peer review: 2 approved]

Marco Arieli Herrera-Valdez

Department of Mathematics, Facultad de Ciencias, Universidad Nacional Autonoma de Mexico, CDMX, 04510, Mexico

v3 **First published:** 14 Sep 2018, **7**:1468
https://doi.org/10.12688/f1000research.16169.1
Second version: 21 Nov 2018, **7**:1468
https://doi.org/10.12688/f1000research.16169.2
Latest published: 19 May 2021, **7**:1468
https://doi.org/10.12688/f1000research.16169.3

Abstract

A general formulation for both passive and active transmembrane transport is derived from basic thermodynamical principles. The derivation takes into account the energy required for the motion of molecules across membranes and includes the possibility of modeling asymmetric flow. Transmembrane currents can then be described by the general model in the case of electrogenic flow. As it is desirable in new models, it is possible to derive other well-known expressions for transmembrane currents as particular cases of the general formulation. For instance, the conductance-based formulation for current turns out to be a linear approximation of the general formula for current. Also, under suitable assumptions, other formulas for current based on electrodiffusion, like the constant field approximation by Goldman, can be recovered from the general formulation. The applicability of the general formulations is illustrated first with fits to existing data, and after, with models of transmembrane potential dynamics for pacemaking cardiocytes and neurons. The general formulations presented here provide a common ground for the biophysical study of physiological phenomena that depend on transmembrane transport.

Keywords

Transmembrane transport, ion channels, passive transport, active transport, rectification, bidirectional assymetric flow, AMPA-Kainate receptor, excitable cell

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 3 (revision) 19 May 2021		
version 2 (revision) 21 Nov 2018	✓ report	
version 1 14 Sep 2018	? report	✓ report

1. **Kyle C.A. Wedgwood**, University of Exeter, Exeter, UK

2. **Moisés Santillán**, Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV), Monterrey, Mexico

Any reports and responses or comments on the article can be found at the end of the article.

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

Author roles: Herrera-Valdez MA: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by UNAM-PAPIIT IA208618.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Herrera-Valdez MA. **A thermodynamic description for physiological transmembrane transport [version 3; peer review: 2 approved]** F1000Research 2021, **7**:1468 https://doi.org/10.12688/f1000research.16169.3

First published: 14 Sep 2018, **7**:1468 https://doi.org/10.12688/f1000research.16169.1

REVISED **Amendments from Version 2**

The manuscript has been edited to correct minor typos and rephrase sentences for clarity throughout the document and also, to include data and two sections that were previously in supplementary files. In more detail, formulas were corrected in one header and in the last column of Table 1; corrections have also been made in other sections where the reversal potential for the Na-Ca transport is mentioned. Also, amplitude descriptions in the third column of Table 3 and Table 4 were shortened, and some parameter values were adjusted in Table 3. The data in Figure 3 is now included in Table 2. The two sections added to the manuscript contain the derivation of the Goldman constant field approximation from the general formula derived in the article, and a model of neuronal membrane potential dynamics that uses the general formulation for transport.

Any further responses from the reviewers can be found at the end of the article

Introduction

One of the most important physiological mechanisms underlying communication within and between cells is the transport of molecules across membranes. Molecules can cross membranes either passively (Stein & Litman, 2014), or via active transport (Bennett, 1956). Molecules are passively transported across a membrane when they move along their (electro)chemical gradient. In contrast, active transport involves transmembrane motion of molecules against their electrochemical gradients. One important functional distinction between channels and pumps is that the rate of transport for channels is generally several orders of magnitude faster than the rate for pump-mediated transport (Gadsby, 2009; Ussing, 1949a). Such differences are reflected in the sizes of different transmembrane fluxes typically observed in excitable cells (Herrera-Valdez & Lega, 2011).

Passive transport may occur through transmembrane proteins (Hille, 1992; Stein & Litman, 2014) that may be selective for molecules of specific types (Almers & McCleskey, 1984; Doyle *et al.*, 1998; Favre *et al.*, 1996), typically mediating (electro)diffusion through them. Sometimes these proteins are also gated by conformational changes triggered by different signlling mechanisms. Passive transport has also been observed in pores spontaneously formed within synthetic lipid bilayers (Blicher & Heimburg, 2013), which could also occur in natural conditions (Gurtovenko & Anwar, 2007). One example of importance in the context of energy homeostasis is the transport of monosaccharides and other similar molecules through GLUT transporters. GLUT transporters first bind to their substrates, triggering a conformational change that allows the substrate to cross in the direction of its chemical gradient (e.g. GLUT5 is highly specific to fructose, Mueckler & Thorens (2013)). Channels are another important class of transmembrane proteins that typically mediate fast passive transport, often displaying selectivity for specific ion types, gated by changes in the membrane potential (Covarrubias *et al.*, 1991; Peng & Wu, 2007) or the binding of a ligand molecule (e.g. AMPA-Kainate synaptic receptors, Bowie (2002)).

Active transport is mediated by transmembrane proteins commonly called pumps, or carriers, that mechanically translocate the molecules they transport (Bennett, 1956; Ussing, 1949b; Ussing, 1949c). The energy for primary active transport is usually obtained from biochemical reactions (e.g. ATPases, light-driven pumps). For instance, the energy to transport molecules against their (electro)chemical gradient via ATPases is obtained from hydrolysis of ATP (Chapman, 1973). In secondary and tertiary active transport, the electrochemical gradient of at least one the ion types provides the energy to transport other molecules against their (electro)chemical gradient (Skou, 1965). Two large classes of non-primary active transport pumps are the symporters and counterporters, carrying at least two types of molecules in the same, or in opposite directions, respectively, with at least one type against its electrochemical gradient. For instance Na-H exchangers carry Na^+ and H^+ in opposite directions, typically using the driving force from Na^+. In contrast, K-Cl symporters carry K^+ and Cl^- in the same direction, which means that one of the two ion types is carried against its concentration gradient. This is because the K^+ and Cl^- concentration gradients are typically oriented in opposite directions. As a consequence, the movement of one of the two ions releases energy from its electrochemical gradient, enabling the transport of the other ion against its gradient.

Theoretical models of transmembrane transport play a critical role in developing our understanding of the function and mechanisms underlying electrical signalling and cellular excitability (Barr, 1965; Cole, 1965; DiFrancesco & Noble, 1985; Endresen *et al.*, 2000; Gadsby, 2009; Goldman, 1943; Kell, 1979; Kimizuka & Koketsu, 1964; Läuger, 1973; Stevens & Tsien, 1979; Wiggins, 1985a; Wiggins, 1985b; Wiggins, 1985c), and some of its associated pathologies (Ashcroft, 2005; Marbán, 2002). The best known transmembrane transport models include the widely used conductance-based formulation from the seminal work of Hodgkin & Huxley (1952), the Goldman-Hodgkin-Katz equation (Goldman, 1943; Hodgkin & Katz, 1949; Pickard, 1976), and several other expressions for carrier and channel mediated transport with many different functional forms (DiFrancesco & Noble, 1985; Rasmusson *et al.*, 1990a; Rasmusson *et al.*, 1990b; Rosenberg & Wilbrandt, 1955). Other formulations for *ionic* transport across membranes derived from biophysical principles available in the literature include those in the work by Jacquez & Schultz (1974); Kimizuka & Koketsu (1964); Pickard (1969); Pickard (1976). See also Jacquez (1981) and similar work by Endresen *et al.* (2000), and those in the excellent book by Johnston *et al.* (1995). Such formulations describe the relationship between the activity and permeability of ions across membranes, and the transmembrane potential. However general models that describe physiological transport including passive and active transport of charged or non-charged molecules, with bidirectional but possibly asymmetric flows, are still missing. The work presented here builds upon the results previously mentioned by describing transport macroscopically in terms of the energy required to move molecules across a membrane. The result is a general formulation with a common functional form for both passive and

active transport (Herrera-Valdez, 2014) that also includes a term that regulates the asymmetry in the flow (rectification). The details of the derivation and examples of fits to experimental data and features like asymmetric bidirectional flow can be found in the next section. An application of the general formulation is illustrated with models for the transmembrane potential dynamics in cardiac pacemaker cells and striatal fast spiking interneurons. A derivation and connection of the general formula with existing formulations like the Goldman expression for current can be in the paragraphs below.

General formulation for transmembrane flux and current

Work required for transmembrane molecular fluxes

Consider a system consisting of a biological membrane surrounded by two aqueous compartments (e.g. extracellular and intracellular). Assume, to start with, that the compartments contain molecules of a single type s (*e.g.* Na^+, K^+, glucose), possibly in different concentrations. Let ΔG_s be the energy required for the transport of the molecules across the membrane in a specific direction (e.g. inside to outside). To write an expression for ΔG_s it is necessary to take the direction of motion of the s-molecules into account. To do so, label the extracellular and intracellular compartments as 0 and 1, respectively, and let c_s and $d_s \in \{0, 1\}$ represent the source and the destination compartments for the transport of the s-molecules. The pair $(c_s, d_s)=(0,1)$ represents inward transport and the pair $(c_s, d_s)=(1,0)$ represents outward transport. The work required to transport n_s molecules of type s from compartment c_s to compartment d_s can then be written as

$$\Delta G_s = n_s(c_s - d_s)\left[\mathrm{kT}\ln\left(\frac{[s]_0}{[s]_1}\right) - \mathrm{q}z_s v\right], \tag{1}$$

(Aidley, 1998; Blaustein *et al.*, 2004; De Weer *et al.*, 1988) where T, k, q, z_s, $[s]_0$, and $[s]_1$ represent the absolute temperature (°K), Boltzmann's constant (1.381 $\times 10^{-23}$ Joules/°Kelvin), the elementary charge (1.60217733 $\times 10^{-19}$ Coulombs/molecule), the valence, the extracellular, and the intracellular concentrations for the molecules of type s, respectively. The variable v represents the transmembrane potential. Two particular cases are worth noticing. First, if s is an ion, then $z_s \neq 0$ and Equation (1) becomes

$$\Delta G_s = \mathrm{q}z_s n_s (c_s - d_s)(v_s - v), \tag{2}$$

where v_s is the Nernst potential for the s-molecules[1] (Nernst, 1888). Second, if the s-molecules are not charged, then $z_s = 0$ and the work required to move the s-type molecules from c_s to d_s simplifies to

$$\Delta G_s = n_s(c_s - d_s)\mathrm{kT}\ln\left(\frac{[s]_0}{[s]_1}\right). \tag{3}$$

If $\Delta G_s < 0$, then the molecules can be transported passively (*e.g.* electrodiffusion), decreasing the electrochemical gradient for s across the membrane. In contrast, if $\Delta G_s > 0$, the transmembrane transport of s from c_s to d_s is not thermodynamically favourable, which means the transport from c_s to d_s requires energy that is not available in the electrochemical gradient for s (active transport). As a consequence, active transport of s would increase the driving force for the motion of s across the membrane.

Joint transmembrane transport of different types of molecules

To find an expression that describes a more general transport mechanism, assume that transport takes place as single events in which molecules of m different types move in parallel, or possibly sequentially (e.g. first Na^+, then K^+), across the membrane. Let S be a set that represents the types of molecules that are jointly transported in a single event. For instance, for Na^+-H^+ exchangers, $S = \{Na^+, H^+\}$, with $m = 2$. The energy required to transport these molecules is the sum of the energies required to transport each type of molecule in S. In other words,

$$\Delta G_S = \sum_{s \in S} \Delta G_s. \tag{4}$$

As before, transport is thermodynamically favourable when $\Delta G_S \leq 0$. If not, extra energy is required. To distinguish between these two cases, define the total energy ΔG of the transport mechanism, possibly including an extra source of energy, as

$$\Delta G = \delta_{\mathrm{Ext}} \Delta G_{\mathrm{Ext}} + \Delta G_S, \tag{5}$$

where $\delta_{\mathrm{Ext}} = 1$ if $\Delta G_S > 0$, and 0 otherwise. If $\Delta G_S > 0$, then the energy from ATP hydrolysis or any other sources represented by $\delta_{\mathrm{Ext}}\Delta G_{\mathrm{Ext}}$ should be negative and larger in size in comparison to ΔG_S, so that $\Delta G \leq 0$, making the transport thermodynamically possible. In particular, for ATP-driven transport, the extra energy supplied by hydrolysis of ATP (Tanford, 1981; De Weer *et al.*, 1988) is

$$\Delta G_{\mathrm{ATP}} = \Delta G^0_{\mathrm{ATP}} + \mathrm{kT}\ln\left(\frac{[\mathrm{ADP}]_1[\mathrm{P}_i]_1}{[\mathrm{ATP}]_1}\right) = \mathrm{q}v_{\mathrm{ATP}}, \tag{6}$$

with $[\mathrm{ATP}]_1$, $[\mathrm{ADP}]_1$, and $[\mathrm{P}_i]_1$ representing, respectively, the intracellular concentrations of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and inorganic phosphate (P_i) (De Weer *et al.*, 1988). The potential $v_{\mathrm{ATP}} \approx -450$ mV (Endresen *et al.*, 2000), but could vary depending on the intracellular amounts of ATP, ADP, and P_i (De Weer *et al.*, 1988). The first term in Equation (6) represents the "standard" change in Gibbs free energy for the hydrolysis of ATP[2]. Similar expressions

[1] The transmembrane potential for which there is a zero net flux of s-ions across the membrane, as given by the Nernst-Planck equation, is

$$v_s = \frac{\mathrm{kT}}{z_s \mathrm{q}}\ln\left(\frac{[s]_0}{[s]_1}\right).$$

[2] The change in Gibbs free energy in "standard" conditions of ATP, ADP and P_i at concentrations of 1M and a water concentration of approximately 55M, yields $\Delta G^0_{\mathrm{ATP}}$ between -28 and -34 kJ/mol, (Bergman *et al.*, 2010)). The second term in Equation (6) depends on a reaction quotient [ADP] [P_i] /[ATP], which explains deviations of ΔG from the standard change.

could be derived for active transport driven by light, or other sources of energy. The concentrations of ATP, ADP, and P_i are assumed to be constant in most models presented here, but it should be noted that such concentrations are not necessarily constant, and in fact, may vary a lot in some cases, as it is the case for skeletal muscle (Wackerhage *et al.*, 1998).

Flux due to transmembrane transport

The formulation in Equation (5) can be combined with Equation (1) to derive a generalised expression for flux and model different known mechanisms of physiological transmembrane transport, possibly combining the transport of different molecules simultaneously (e.g. Na-H exchange). In this case, the forward direction of the transport would be described by the combined forward transport of each of the different molecules under consideration. For instance, the source and target compartments for Na^+ and Ca^{2+} are different in Na-Ca exchangers. The stoichiometry for the transport mediated by Na-Ca exchangers in the forward direction involves three Na^+ molecules moving inward (along their electrochemical gradient) in exchange for one Ca^{2+} molecule moving outward (against their electrochemical gradient) (Mullins, 1979; Venetucci *et al.*, 2007).

Let α and β be the flux rates in the forward and backward directions, in units of molecules per ms per μm^{-2}. These rates depend, *a priori*, on the energy required for the transport of the molecules in S. The net *flux* rate associated to the net transmembrane transport, can then be written as

$$\Phi(\Delta G) = \alpha(\Delta G) - \beta(\Delta G). \tag{7}$$

How do α and β depend on ΔG? The steady state relationship between the energy ΔG and the the forward and backward flow rates, hereby represented by α and β, can be expressed by means of a Boltzmann distribution (Boltzmann, 1868) as

$$\frac{\alpha}{\beta}(\Delta G) = \exp\left(-\frac{\Delta G}{\mathrm{kT}}\right). \tag{8}$$

Assuming that α and β are continuous functions, the rates α and β can be rewritten as

$$\alpha = r\exp\left(-b\frac{\Delta G}{\mathrm{kT}}\right), \qquad \beta = r\exp\left((1-b)\frac{\Delta G}{\mathrm{kT}}\right), \tag{9}$$

where r and b represent the rate at which the transport takes place (molecules per ms per μm^{-2}) and the bias of the transport in one of the two directions (b = 1/2 means the transport is symmetrical relative to the point at which ΔG=0). Note that the functional form of the α and β in Equations (9) are similar to those by Butler (1924); Erdey-Grúz & Volmer (1930). Also, notice that the steady state relationship between α and β in Equation (8) can be obtained from Equations (9), for any r and any b. However, it should be the case that r and b vary in specific ranges depending on the physicochemical characteristics of the pore through which molecules cross the membrane, and in general, on the transport mechanism. As already mentioned, the rate r should be larger for electrodiffusive transport mediated by ion channels, in comparison to the slower transport rates for facilitated diffusion and active transport meditated by carrier proteins and pumps. The rate r may depend on temperature (Sen & Widdas, 1962), the transmembrane potential (Starace *et al.*, 1997), the concentrations inside and outside of the membrane (Yue *et al.*, 1990), and other factors (Novák & Tyson, 2008). If the parameter $b \in [0, 1]$, then $b\Delta G$ and $(b-1)\Delta G$ have opposite signs and can be thought of as the energies required to the transport of the molecules in S in the forward and backward directions, respectively, with b biasing the transport in the forward direction when close to 1, and in the backward direction when close to 0 (Figure 1).

The flux can then be written explicitly combining Equation (7) and Equation (9) to obtain,

$$\Phi(\Delta G) = r\left[\exp\left(-b\frac{\Delta G}{\mathrm{kT}}\right) - \exp\left((1-b)\frac{\Delta G}{\mathrm{kT}}\right)\right]. \tag{10}$$

Taking the above observations into account, it is possible to combine Equation (4) and Equation (5), to write an expression similar to Equation (8) for the steady state balance between the forward and backward transport of all the molecules in S (see Table 1 for examples of different transport mechanisms with their energies and total charge movements).

Flux and current

After substitution of the formulas for ΔG from Equation (4) and Equation (5) into Equation (10), the flux rate resulting from simultaneously transporting molecules in S across the membrane can be written explicitly as

$$\Phi = r\left[\prod_{s\in S}\left(\frac{[s]_0}{[s]_1}\right)^{bn_s(d_s-c_s)}\exp\left(b\frac{\eta v-\delta_{\mathrm{Ext}}v_{\mathrm{Ext}}}{v_{\mathrm{T}}}\right) - \prod_{s\in S}\left(\frac{[s]_0}{[s]_1}\right)^{(b-1)n_s(d_s-c_s)}\exp\left((b-1)\frac{\eta v-\delta_{\mathrm{Ext}}v_{\mathrm{Ext}}}{v_{\mathrm{T}}}\right)\right], \tag{11}$$

where $v_{\mathrm{T}} = \mathrm{kT/q}$ and

$$\eta = \sum_{s\in S} n_s(c_s - d_s)z_s, \tag{12}$$

represents the net number of charges moved across the membrane. Note that v_{Ext} should be v_{ATP} for ATPases. The first, more complex, form of the flux in Equation (11) could be useful when working with models for which changes in the concentrations of different molecules are relevant.

If the transport is electrogenic, then the product $q\eta$ (in Coulombs) represents the net charge moved across the membrane, relative to the extracellular compartment. Non electrogenic transport yields $\eta = 0$, which means the flow does not depend on the transmembrane potential, and

$$\Phi = r\left[\prod_{s\in S}\left(\frac{[s]_0}{[s]_1}\right)^{bn_s(d_s-c_s)}\exp\left(-b\frac{\delta_{\mathrm{Ext}}v_{\mathrm{Ext}}}{v_{\mathrm{T}}}\right) - \prod_{s\in S}\left(\frac{[s]_0}{[s]_1}\right)^{(b-1)n_s(d_s-c_s)}\exp\left((1-b)\frac{\delta_{\mathrm{Ext}}v_{\mathrm{Ext}}}{v_{\mathrm{T}}}\right)\right]. \tag{13}$$

If only ions are involved in the transport, the flux simplifies to

$$\Phi = r\left\{\exp\left[b\left(\frac{\eta v - v_o}{v_{\mathrm{T}}}\right)\right] - \exp\left[(b-1)\left(\frac{\eta v - v_o}{v_{\mathrm{T}}}\right)\right]\right\}, \tag{14}$$

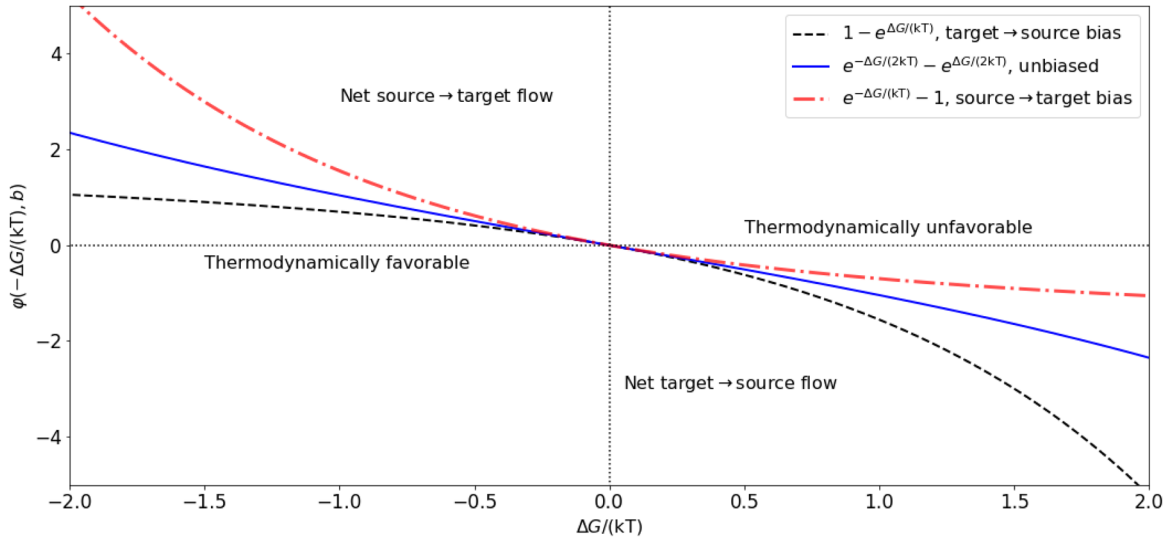

Figure 1. Fluxes biased in the target→source (backward, *b*=0.1, black dashed line), source→target (forward, *b*=0.9, red dash-dot line), or showing no rectification (*b*=0.5, blue solid line). The energy ΔG_S necessary can be found on the right axis if the transport is primary active, and on the left axis when transport is secondary active or passive. Extra energy from ATP hydrolysis or other sources added to ΔG_S shift the total energy to the left axis and make the transport thermodynamically possible. See Table 1 for examples.

where

$$v_o = \delta_{\text{Ext}} v_{\text{Ext}} + \sum_{s \in S} n_s z_s (c_s - d_s) v_s. \tag{15}$$

The quantity v_o/η can be thought of as a reversal potential. If $\eta < 0$, then positive charge is transported inward, or negative charge is transported outward. In contrast, $\eta > 0$ means that positive charge is transported outward or negative charge transported inward. For instance, inward electrodiffusion of single Na^+ ions gives $\eta = -1$, which can be thought of as loosing one positive charge from the extracellular compartment in each transport event.

Transmembrane current. A flux that results in electrogenic transport (Equation (11) and Equation (14)) can be converted to current density after multiplication by $q\eta$. In short form,

$$i = q\eta\Phi \tag{16}$$

with qr in Amperes/m^2 or equivalent units.

Substitution of Equation (11) or Equation (14) into Equation (16) yields a general formula for the current generated by transmembrane ionic flux (Figure 2), that uses the same functional form for channels (protein or lipid) and pumps. Recall that Equation (16) can also be written explicitly in terms of the transmembrane concentrations of one or more of the ions involved using Equation (11). It is possible to derive expressions for r that take into account biophysical variables like temperature and the shape and length of the pore through which the molecules cross (Endresen *et al.*, 2000; Pickard, 1969).

Special cases and examples

A number of nontrivial and important properties of transmembrane ionic currents, including rectification, are also described by Equation (16). Also, different models for current already in the literature can be obtained by making approximations or setting particular cases from Equation (16). Examples include electrodiffusive currents that result from integration of the Nernst-Planck equation along the length of membrane pore (Jacquez & Schultz, 1974; Johnston *et al.*, 1995; Pickard, 1969). Of particular interest, conductance-based currents are linear approximations of the formulation (16), around the reversal potential for the current.

Lower order approximations to the general formulation and conductance based models. The general current from Equation (16) can be rewritten as a series around the reversal potential v_o to obtain useful approximations with possible computational or analytical advantages. To do so, rewrite equation Equation (16) using Taylor's theorem (Courant & John, 2012; Spivak, 2018) to obtain

$$i = q\eta r\left[\left(\frac{\eta v - v_o}{v_T}\right) + \left(b - \frac{1}{2}\right)\left(\frac{\eta v - v_o}{v_T}\right)^2 + \left(\frac{3b^2 - 3b + 1}{3!}\right)\left(\frac{\eta v - v_o}{v_T}\right)^3 + \ldots\right]. \tag{17}$$

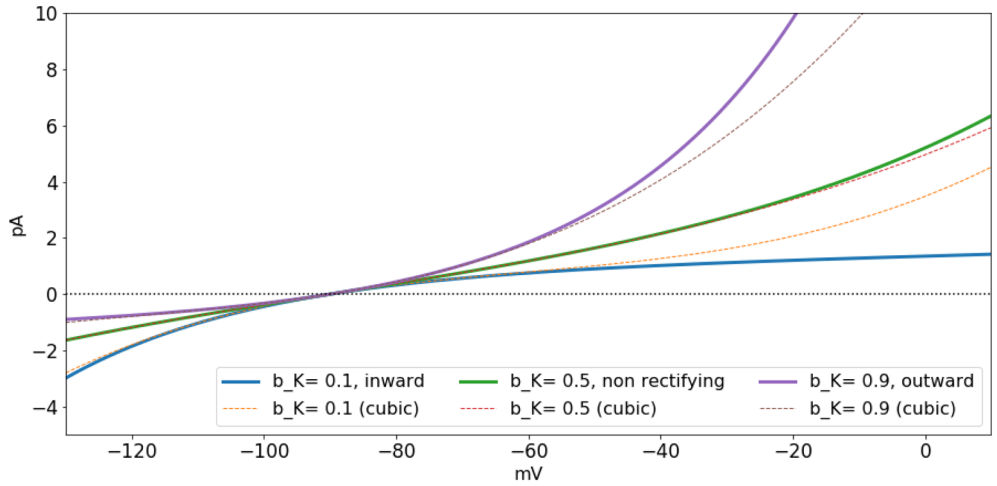

Figure 2. Currents mediated by K-electrodiffusion for $b_K \in \{0.1, 0.5, 0.9\}$ using the general formulation (solid lines) and its cubic approximation (dashed lines). Inward rectification occurs for $b_K < 1/2$ and outward rectification for $b_K > 1/2$ and $qr_KN_K = 1$.

Conductance-based currents (Hodgkin & Huxley, 1952) can then be obtained as linear approximations of the general current around v_o,

$$i \approx g\left(v - \frac{v_o}{\eta}\right), \tag{18}$$

where $g = \eta^2 qr/v_T$ is in units of nS/μm^2. For instance, the linear approximation for the current through open sodium channels around v_{Na} in Equation (18) gives $g_{Na} = qr_{Na}/v_T$, and $v_o/\eta_{Na} = v_{Na}$, with $\eta_{Na} = -1$, so that $i_{Na} \approx g_{Na}(v - v_{Na})$.

Note that if the truncation order is larger than 1, then approximations from Equation (17) include the rectification parameter b. One already known consequence is that conductance-based currents do not capture rectification.

The Goldman constant field approximation is a particular case of the general formulation. The Goldman-Hodgkin-Katz equation describing the transmembrane current carried by ions of type x is given by

$$I_x = g_x v\left[\frac{x_0 - x_1 \exp\left(z_x \frac{v}{v_T}\right)}{1 - \exp\left(z_x \frac{v}{v_T}\right)}\right], \tag{19}$$

where x_j, $j \in \{0, 1\}$, represent the extra and intracellular concentrations of an ion of type x.

Multiplying the numerator and denominator of Equation (19) by $x_1^{b-1}x_0^b \exp[(b-1)z_x v/v_T]$, and algebraically rearranging terms yields,

$$I_x = A_x\left[\exp\left(bz_x \frac{v - v_x}{v_T}\right) - \exp\left((b-1)z_x \frac{v - v_x}{v_T}\right)\right], \tag{20}$$

where

$$A_x = \frac{g\, v\, x_1^{1-b} x_0^b}{\exp\left(bz_x \frac{v}{v_T}\right) - \exp\left((b-1)z_x \frac{v}{v_T}\right)}, \tag{21}$$

is an amplitude term that can be approximated by a constant (Endresen *et al.*, 2000; Herrera-Valdez & Lega, 2011; Nonner & Eisenberg, 1998; Nonner *et al.*, 1998, Equation 25 and Equation 26).

Asymmetric bidirectional flow causes rectification. If the flux of molecules across a membrane is mediated by proteins, it can be biased in either the outward or the inward direction (Hollmann *et al.*, 1991; Riedelsberger *et al.*, 2015). This was first called "anomalous rectification" by Katz (1949), who noticed that K^+ flows through muscle membranes more easily in the inward, than in the outward direction (Adrian, 1969; Armstrong & Binstock, 1965). It was later found that some K^+ channels display the bias in the opposite direction (Woodbury, 1971). The former type of K^+ current rectification is called inward, and the latter outward (Figure 2).

Rectification is thus a bias in one of the two directions of transport. The type of rectification (inward or outward) depends on the molecules being transported and on the structure of the proteins mediating the transport. Flux rectification is not only displayed by ions, as shown by molecules like glucose, which may cross membranes via GLUT transporters bidirectionally and asymmetrically, even if the glucose concentration is balanced across the membrane (Lowe & Walmsley, 1986).

Rectification can be described by setting b in Equation (11) to values different from 1/2 and it becomes more pronounced as b is closer to 0 or 1. These values represent biases in the transport

toward the source, or the target compartment, respectively. As a consequence, rectification yields an asymmetry in the graph of $\alpha - \beta$ as a function of ΔG (Figure 1). For electrogenic transport, rectification can be thought of as an asymmetric relationship between current flow and voltage, with respect to the reversal potential v_o. The particular case $b = 1/2$ (non rectifying) yields a functional form for current similar to that proposed by Pickard (1969), and later reproduced by (Endresen *et al.*, 2000), namely

$$i = 2q\eta r \sinh\left(\frac{\eta v - v_o}{2v_T}\right). \quad (22)$$

From here on, subscripts will be used to represent different transport mechanisms. For instance, the current for a Na-Ca pump will be written as i_{NaCa}.

Electrodiffusion of K^+ through channels ($\eta = 1$ and $v_o = v_K$), is outward for $v > v_K$, and inward for $v < v_K$. The K^+ current through the open pore is therefore

$$i_K = qr_K\left\{\exp\left[b_K\left(\frac{v - v_K}{v_T}\right)\right] - \exp\left[(b_K - 1)\left(\frac{v - v_K}{v_T}\right)\right]\right\}. \quad (23)$$

Current flow through inward rectifier K-channels (Riedelsberger *et al.*, 2015) can be fit to values of $b_K < 1/2$. For instance,

$$i_{Kin} = qr_K\left[1 - \exp\left(\frac{v_K - v}{v_T}\right)\right], \quad (b_K = 0), \quad (24)$$

describes a current generated by a K^+ flow that is limited in the outward direction, similar to the currents described originally by Katz (1949). Analogously, $b_K > 1/2$ limits the inward flow. For example, the current

$$i_{Kout} = qr_K\left[\exp\left(\frac{v - v_K}{v_T}\right) - 1\right], \quad (b_K = 1), \quad (25)$$

describes outward rectification (Riedelsberger *et al.*, 2015).

Based on the work of Riedelsberger *et al.* (2015) on K^+ channels, inward (outward) rectification arises when the S4 segment in K^+ channels is located in the inner (outer) portion of the membrane. These two general configurations can be thought of in terms of ranges for the parameter b_K, namely, $b_K < 1/2$ for inward, and $b_K > 1/2$ for outward rectification (Figure 2).

In general, ion channels are typically formed by different subunits, that combined produce structural changes that may result in rectified flows. For instance, non-NMDA glutamatergic receptors that can be activated by kainic acid and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), display different permeabilities to Na^+, K^+, and Ca^{2+} depending on the subunits that form the receptor (Hollmann *et al.*, 1991). In particular, the Ca^{2+} currents recorded in oocytes injected with combinations of GluR1 and GluR3 cRNA have different steady state amplitudes and show different levels of rectification (Figure 3).

Primary active transport. The **Na-K ATPase** is a primary active transporter that uses the energy from the hydrolysis of one molecule of ATP for the uphill transport of 3 Na^+ ions outward

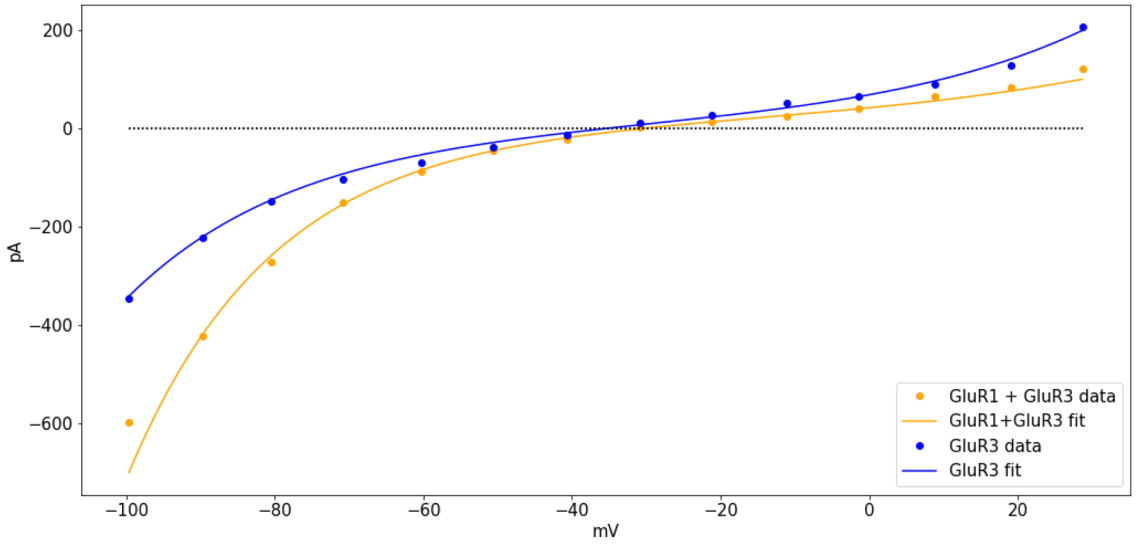

Figure 3. Currents mediated by AMPA-Kainate receptors with different ionic permeabilities (different reversal potentials) and different degrees of rectification caused by differences in the sub-unit composition of the receptors. Currents were recorded from oocytes injected with GluR3 cRNA (blue), or a combination of GluR1 and GluR3 cRNA (orange), in Ca^{2+} ringer solution after activation by AMPA. The curves were fit with(v_o, b, rq) = (–30, 0.45, 21), for GluR3 and (v_o, b, rq) = (–35, 0.35, 20), for GluR1+GluR3. Data was digitised from Figure 3B in the article by Hollmann *et al.* (1991) (Table 2).

and 2 K^+ ions inward in each cycle ($\eta_{NaK} = 1$), respectively (De Weer *et al.*, 1988). The reversal potential $v_{NaK} = v_{ATP} + 3v_{Na} - 2v_K$ (Table 1), in a single transport event (Chapman, 1973; Gadsby *et al.*, 1985; Garrahan & Glynn, 1967; Post & Jolly, 1957). As a consequence, the transport kinetics of the Na-K ATPase reverse for potentials smaller than v_{NaK} (De Weer *et al.*, 1988).

The current-voltage relationships recorded from Na-K ATPases in guinea pig ventricular cells are shaped as hyperbolic sines (Gadsby *et al.*, 1985). Those currents would be fit with $b_{NaK} \approx 1/2$, yielding

$$i_{NaK}(v) = 2qr_{NaK}\sinh\left(\frac{v - v_{NaK}}{2v_T}\right). \quad (26)$$

In response to steroids like strophandin, the voltage-dependence of the Na-K ATPase current has been reported to show a plateau as v increases past the reversal potential for the current (Nakao & Gadsby, 1989). In such cases, the Na-K

Table 1. Energy required for transmembrane transport mediated by different passive and active mechanisms.

Pump or channel	Molecule (s)	n_s	c_s	d_s	$c_s - d_s$	$\Delta G_s = qz_s n_s (c_s - d_s)(v_s - v)$	η	v_o	$\alpha/\beta = \exp\left(-\frac{\Delta G}{kT}\right)$
Cl^- channel	Cl^-	1	0	1	-1	$\Delta G_{Cl} = q(v_{Cl} - v)$	1	v_{Cl}	$\left(\frac{[Cl]_0}{[Cl]_1}\right)\exp\left(\frac{v}{v_T}\right)$
K^+ channel	K^+	1	1	0	1	$\Delta G_K = q(v_K - v)$	1	v_K	$\left(\frac{[K]_1}{[K]_0}\right)\exp\left(\frac{v}{v_T}\right)$
Na^+ channel	Na^+	1	0	1	-1	$\Delta G_{Na} = -q(v_{Na} - v)$	-1	$-v_{Na}$	$\left(\frac{[Na]_0}{[Na]_1}\right)\exp\left(-\frac{v}{v_T}\right)$
Ca^{2+} channel	Ca^{2+}	1	0	1	-1	$\Delta G_{Ca} = -2q(v_{Ca} - v)$	-2	$-2v_{Ca}$	$\left(\frac{[Ca]_0}{[Ca]_1}\right)\exp\left(-2\frac{v}{v_T}\right)$
Na^+-K^+ ATPase	Na^+ K^+	3 2	1 0	0 1	1 -1	$\Delta G_{Na} = 3q(v_{Na} - v)$ $\Delta G_K = -2q(v_K - v)$	1	$v_{ATP} + 3v_{Na} - 2v_K$	$\left(\frac{[Na]_1}{[Na]_0}\right)^3\left(\frac{[K]_0}{[K]_1}\right)^2\exp\left(\frac{v - v_{ATP}}{v_T}\right)$
Ca^{2+} ATPase	Ca^{2+}	1	1	0	1	$\Delta G_{Ca} = 2q(v_{Ca} - v)$	2	$v_{ATP} + 2v_{Ca}$	$\left(\frac{[Ca]_1}{[Ca]_0}\right)\exp\left(\frac{2v - v_{ATP}}{v_T}\right)$
H^+ ATPase	H^+	1	1	0	1	$\Delta G_H = q(v_H - v)$	1	$v_{ATP} + v_H$	$\left(\frac{[H]_1}{[H]_0}\right)\exp\left(\frac{v - v_{ATP}}{v_T}\right)$
Na^+-Ca^{2+} exchanger	Na^+ Ca^{2+}	3 1	0 1	1 0	-1 1	$\Delta G_{Na} = -3q(v_{Na} - v)$ $\Delta G_{Ca} = 2q(v_{Ca} - v)$	-1	$2v_{Ca} - 3v_{Na}$	$\left(\frac{[Na]_0}{[Na]_1}\right)^3\left(\frac{[Ca]_1}{[Ca]_0}\right)\exp\left(-\frac{v}{v_T}\right)$
Na^+-I^- symporter	Na^+ I^{-1}	2 1	0 0	1 1	-1 -1	$\Delta G_{Na} = -2q(v_{Na} - v)$ $\Delta G_1 = -q(v_1 - v)$	-1	$-v_1 - 2v_{Na}$	$\left(\frac{[Na]_0}{[Na]_1}\right)^2\left(\frac{[I]_0}{[I]_1}\right)\exp\left(-\frac{v}{v_T}\right)$
Na^+-H^+ exchanger	Na^+ H^+	1 1	0 1	1 0	-1 1	$\Delta G_{Na} = -q(v_{Na} - v)$ $\Delta G_H = q(v_H - v)$	0	$v_H - v_{Na}$	$\left(\frac{[H]_1}{[H]_0}\right)\left(\frac{[Na]_0}{[Na]_1}\right)$
K^+-Cl^- symporter	K^+ Cl^-	1 1	1 1	0 0	1 1	$\Delta G_K = q(v_K - v)$ $\Delta G_{Cl} = -q(v_{Cl} - v)$	0	$v_K - v_{Cl}$	$\left(\frac{[K]_1}{[K]_0}\right)\left(\frac{[Cl]_1}{[Cl]_0}\right)$
Na^+-K^+-Cl^- symporter	Na^+ K^+ Cl^-	1 1 2	0 0 0	1 1 1	-1 -1 -1	$\Delta G_{Na} = -q(v_{Na} - v)$ $\Delta G_K = -q(v_K - v)$ $\Delta G_{Cl} = 2q(v_{Cl} - v)$	0	$2v_{Cl} - v_{Na} - v_K$	$\left(\frac{[Na]_0}{[Na]_1}\right)\left(\frac{[K]_0}{[K]_1}\right)\left(\frac{[Cl]_0}{[Cl]_1}\right)^2$

ATPase current can be assumed to be inwardly rectifying and fit with values of $b_{\mathrm{NaK}} \approx 0$, so that,

$$i_{\mathrm{NaK}}(v) = \mathrm{q} r_{\mathrm{NaK}} \left[1 - \exp\left(\frac{v_{\mathrm{ATP}} + 3v_{\mathrm{Na}} - 2v_{\mathrm{K}} - v}{v_{\mathrm{T}}} \right) \right], \tag{27}$$

or alternatively,

$$i_{\mathrm{NaK}}(v) = \mathrm{q} r_{\mathrm{NaK}} \left[1 - \left(\frac{[\mathrm{Na}]_0}{[\mathrm{Na}]_1} \right)^3 \left(\frac{[\mathrm{K}]_1}{[\mathrm{K}]_0} \right)^2 \exp\left(\frac{v_{\mathrm{ATP}} - v}{v_{\mathrm{T}}} \right) \right]. \tag{28}$$

The rectification for the Na-K pump ATPase has also been reported to occur in small neurons of the dorsal root ganglion in rats (Hamada *et al.*, 2003). The alternative expression (28) also explains qualitatively different behaviors of the Na-K current as a function of the transmembrane concentrations of Na^+ and K^+. For instance, if either $[\mathrm{Na}]_1$ or $[\mathrm{K}]_0$ increase and $v > v_{\mathrm{NaK}}$, then the amplitude of i_{NaK} would increase at a smaller rate of change in comparison to when $v < v_{\mathrm{NaK}}$, which grows exponentially in size. This is also in line with reports of non significant changes in the transport by Na-K ATPases in response to elevated intracellular Na^+ during heart failure (Despa *et al.*, 2002), in which the transmembrane potential is likely to be depolarised.

Secondary active transport. An example of a pump that mediates secondary active transport is the *Na-Ca exchanger*, which takes 3 Na^+ ions from the extracellular compartment in exchange for one intracellular Ca^{2+} ion in forward mode (Pitts, 1979; Reeves & Hale, 1984). The reversal potential for the current is $v_{\mathrm{NaCa}} = 2v_{\mathrm{Ca}} - 3v_{\mathrm{Na}}$, with $\eta_{\mathrm{NaCa}} = -1$. Assuming $b_{\mathrm{NaCa}} = 1/2$, the Na-Ca current can be rewritten as

$$i_{\mathrm{NaCa}}(v) = 2\mathrm{q} r_{\mathrm{NaCa}} \sinh\left(\frac{v - v_{\mathrm{NaCa}}}{2v_T} \right). \tag{29}$$

The driving force $v - v_{\mathrm{NaCa}}$ could reverse in sign with large enough increases in the intracellular concentration of Ca^{2+}, or in the membrane potential. As a result, the current could have a dual contribution to the change in transmembrane potential, as predicted by some theoretical models of cardiac pacemaker activity (Rasmusson *et al.*, 1990a; Rasmusson *et al.*, 1990b).

Electrodiffusive transport. Consider transmembrane electrodiffusive transport of a single ionic type x, with z_x and v_x representing the valence and the Nernst potential for ions of type x, respectively. In this case, the reversal potential satisfies

$$v_o = n_x (c_x - d_x) z_x v_x = \eta_x v_x,$$

which means that η_x can be factorised in the argument for the exponential functions and the general expression (16) can be rewritten as

$$i_x(v) = \mathrm{q}\eta_x r_x \left\{ \exp\left[\eta_x b_x \left(\frac{v - v_x}{v_T} \right) \right] - \exp\left[\eta_x (b_x - 1) \left(\frac{v - v_x}{v_T} \right) \right] \right\}. \tag{30}$$

In the absence of rectification ($b_x = 0.5$) the formula simplifies to

$$i_x(v) = 2\mathrm{q} r_x \sinh\left(\frac{v - v_x}{2v_T} \right). \tag{31}$$

since hyperbolic sines change signs if their arguments do. For calcium channels,

$$i_{\mathrm{Ca}}(v) = 4\mathrm{q} r_{\mathrm{Ca}} \sinh\left(\frac{v - v_{\mathrm{Ca}}}{v_T} \right). \tag{32}$$

See Jacquez & Schultz (1974); Pickard (1969) Table 1 for other examples.

The applicability of the general formulations described above is illustrated next with models of cardiac and neuronal membrane potential.

Transmembrane potential dynamics

To illustrate applications for the formulations discussed earlier, let us build a general model of transmembrane potential dynamics. For simplification purposes, consider only one such mechanism, labelled as $l \in \{1, ..., M\}$, with $p_l N_l$ active sites (e.g. channels), where N_l is the number of membrane sites where the proteins mediating the lth transport mechanism are found, and p_l is the proportion of active sites (activation might depend on voltage or a ligand). Let η_l, and r_l respectively represent the net number of charges moved in each transport event, and the rate of molecular transport per unit area (molecs $\mathrm{ms}^{-1} \cdot \mu\mathrm{m}^{-2}$) of a single protein mediating the lth current, $l \in \{1, ..., M\}$. Then the product $\eta_l r_l \mathrm{q}$ represents the current density of a single protein of type l (Coulombs/sec $\mu\mathrm{m}^2$), and the total current mediated by the lth mechanism in a patch of membrane can be written as $\bar{a}_l p_l \varphi_l(v)$ with $\bar{a}_l = \eta_l N_l r_l \mathrm{q}$ (in $\mathrm{pA}/\mu\mathrm{m}^2$), and

$$\varphi_l(v) = \exp\left[b_l \left(\frac{\eta_l v - v_l}{v_T} \right) \right] - \exp\left[(b_l - 1) \left(\frac{\eta_l v - v_l}{v_T} \right) \right], \tag{33}$$

where v_l/η_l represents the reversal potential for the lth current, $l \in \{1, ..., M\}$. There is experimental evidence for some ion channels that supports the replacement of $\eta_l r_l \mathrm{q}$ for a constant (Nonner & Eisenberg, 1998). For instance, it is reasonable to assume that the single channel current for many types of Na^+channels is 1 pA (Aldrich *et al.* (1983)). Assuming that the change in charge density with respect to voltage (typically referred to as membrane capacitance in conductance-based models) is a constant C_m ($\mathrm{pF}/\mu\mathrm{m}^2$, Herrera-Valdez (2020)), the time-dependent change in transmembrane potential can then be written as

$$\partial_t v = -\sum_{l=1}^{M} a_l p_l \varphi_l(v), \tag{34}$$

with v in mV and $a_l = \bar{a}_l / C_M$ in mV/mS (pA/pF) represents the normalized current amplitude for the lth transport

mechanism, $l \in (1, ..., N)$. Note that only electrogenic transport mechanisms are included.

Cardiac pacemaking in the sinoatrial node

The pacemaking dynamics of cells in the rabbit sinoatrial node (Figure 4) can be modelled as low dimensional dynamical systems based on the assumption that v changes as a function of a combination of channel-mediated electrodiffusion and pumping mechanisms involving Ca^{2+}, K^+, and Na^+ (Herrera-Valdez & Lega, 2011; Herrera-Valdez, 2014). Explicitly, assume that Ca^{2+} transport is mediated by L-type Ca^{2+} channels (Mangoni *et al.*, 2003) and Na^+-Ca^{2+} exchangers (Sanders *et al.*, 2006). K^+ transport is mediated by delayed-rectifier voltage-activated channels (Shibasaki, 1987), and Na^+-K^+ ATPases (Herrera-Valdez & Lega, 2011; Herrera-Valdez, 2014).

The temporal evolution for v can then be described by

$$\partial_t v = -J_{\mathrm{NaK}}(v) - J_{\mathrm{NaCa}}(v,c) - J_{\mathrm{CaL}}(v,w,c) - J_{\mathrm{KD}}(v,w), \tag{35}$$

where w represents the proportion of activated K^+ channels (and also, the proportion of inactivated Ca^{2+} channels) (Av-Ron *et al.*, 1991; Herrera-Valdez & Lega, 2011). The variable c represents the intracellular Ca^{2+} concentration. The transmembrane currents (normalised by the membrane capacitance), are given by

$$J_{\mathrm{NaK}}(v) = a_{\mathrm{NaK}}\,\varphi_{\mathrm{NaK}}(v), \tag{36}$$

$$J_{\mathrm{NaCa}}(v,c) = a_{\mathrm{NaCa}}\,\varphi_{\mathrm{NaCa}}(v,c), \tag{37}$$

$$J_{\mathrm{KD}}(v,w) = a_{\mathrm{KD}}\,w\,\varphi_{\mathrm{KD}}(v), \tag{38}$$

$$J_{\mathrm{CaL}}(v,w,c) = a_{\mathrm{Ca}}(1-w)F_m(v)\,\varphi_{\mathrm{Ca}}(v,c), \tag{39}$$

where φ_x is a difference of exponential functions as defined in Equation (16), with $x \in \{\mathrm{NaK}, \mathrm{NaCa}, \mathrm{KD}, \mathrm{CaL}\}$.

The steady state for the activation of voltage-dependent channels in the model is described by a generic function of the form

$$F_u(v) = \frac{exp\left(g_u \dfrac{v - v_u}{v_T}\right)}{1 + exp\left(g_u \dfrac{v - v_u}{v_T}\right)}, \quad u \in \{m, w\} \tag{40}$$

with labels m and w used for L-type Ca^{2+} and delayed rectifier K^+ channels, respectively. F_u is increasing as a function of

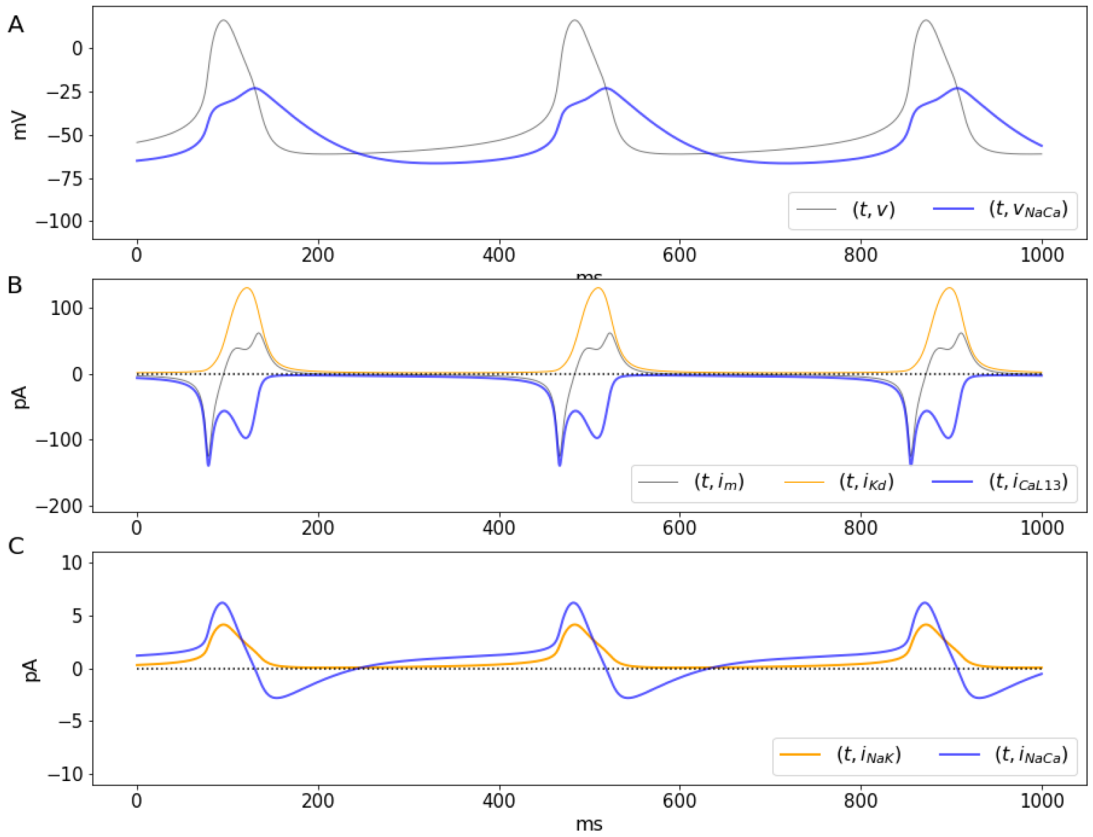

Figure 4. Central sinoatrial node pacemaking dynamics using the system (35)–(42). A. Transmembrane potential (gray) and the reversal potential v_{NaCa} (blue) as a function of time. **B**. Dynamics of large calcium (blue) and potassium (orange) currents in pA. The total current shown by a gray line labelled as i_m. **C**. Currents mediated by NaK ATPases (orange) and Na-Ca exchangers (blue), respectively. Notice the carrier mediated currents (**C**) are about one order of magnitude smaller than those mediated by channels shown (**B**).

v, with a graph of sigmoidal shape (Herrera-Valdez & Lega, 2011). The parameters g_u and v_u represent the steepness and the half-activation potential, respectively. The voltage-dependent activation for the L-type Ca^{2+} channels (Equation (39)) is assumed to be fast (quasi-steady state), so it is described by the function $F_m(v)$ (Av-Ron *et al.*, 1991; Herrera-Valdez & Lega, 2011; Rinzel & Ermentrout, 1989).

The activation of K^+ currents recorded in voltage-clamp experiments often displays sigmoidal time courses that resemble logistic population dynamics (Covarrubias *et al.*, 1991; Hodgkin & Huxley, 1952; Tsunoda & Salkoff, 1995). The dynamics of the proportion of activated K^+ channels, w, evolve according to

$$\partial_t w = w^{k_w}[F_w(v) - w]R_w(v), \tag{41}$$

where F_w and R_w respectively representing the voltage-dependent steady state and rate (1/ms) for the opening of K_d channels (Willms *et al.*, 1999).

The rate of activation for K^+ channels is a voltage-dependent function of the form

$$R_w(v) = r_w\left[exp\left(b_w g_w \frac{v - v_w}{v_T}\right) + exp\left((b_w - 1)g_w \frac{v - v_w}{v_T}\right)\right], \tag{42}$$

where b_w represents a bias in the conformational change underlying channel activation. The function R_w has the shape of a hyperbolic cosine when b_w is 1/2.

During pacemaking oscillations, the intracellular Ca^{2+} concentration may change 10-fold or more (Rasmusson *et al.*, 1990a; Rasmusson *et al.*, 1990b). Therefore, the system includes an equation for the dynamics for c, assuming linear convergence to a steady state c_∞ in the absence of Ca^{2+} fluxes, and an increase proportional to the total transport of Ca^{2+} ions through L-type channels and Na^+-Ca^{2+} exchangers (Figure 4). Explicitly,

$$\partial_t c = r_c(c_\infty - c) - k_c[J_{CaL}(v,w,c) - J_{NaCa}(v,c)], \tag{43}$$

where k_c (μM/mV) represents the impact of the transmembrane Ca^{2+} fluxes on the intracellular Ca^{2+} concentration. The term $-r_c\, c$ can be thought of as a generic form of buffering and other transport mechanisms contributing to decrease the intracellular Ca^{2+} concentration. The minus sign in front of k_c accounts for the fact that the sign of the J_{CaL} is negative. The sign in front of J_{NaCa} is because the forward flux of Ca^{2+} mediated by the Na-Ca exchanger is opposite to that of electrodiffusive Ca^{2+}. The transmembrane concentrations of Na^+ and K^+ across the membrane are assumed to change negligibly (Herrera-Valdez & Lega, 2011; Rasmusson *et al.*, 1990a; Rasmusson *et al.*, 1990b).

The solutions of Equations (35)–(43) with parameters as in Table 3 reproduce important features of the membrane dynamics observed in the rabbit's central sinoatrial node, including the period (*ca.* 400 ms), amplitude (*ca.* 70 mV), and the maximum $\partial_t v$ (<10 V/s) of the action potentials (Zhang *et al.*, 2000).

A number of interesting features of ionic fluxes can be observed from closer examination of the solutions of Equation (35)–Equation (43). First, the Na-Ca current reverses during pacemaking, as $v = v_{NaCa}$ (Figure 4A, blue line). Between the initial depolarisation and until the maximum downstroke rate, approximately, $v_{NaCa} < v$, which means that $J_{NaCa} > 0$. Then, Ca^{2+} extrusion by the Na-Ca exchanger occurs only for a brief period of time during the downstroke and also after each action potential (Figure 4C, blue line). Second, as previously reported in different studies involving spiking dynamics, the time course of the Ca^{2+} current shows a partial inactivation with a double peak (Figure 4B, blue line) around a local minimum (Carter & Bean, 2009; Rasmusson *et al.*, 1990a; Rasmusson *et al.*, 1990b), and in agreement with data from voltage-clamp experiments (Mangoni *et al.*, 2006). A number of models have been constructed in attempts to reproduce the double activation by making extra assumptions about gating (Rasmusson *et al.*, 1990a; Rasmusson *et al.*, 1990b). For instance, some models include a second activation variable, or multiple terms in the steady state gating, or in the time constant for activation or inactivation. However, the explanation for the

Table 2. Current-voltage relationships for AMPA-Kainate receptors composed of different subunits. The data was digitized from Figure 3B in the article by Hollmann *et al.* (1991), using the *ginput* function from the python module matplotlib (Hunter, 2007).

v-command (mV)	GluR1+GluR3	GluR3
mV	pA	pA
-99.6354	-597.802	-347.253
-89.7348	-423.077	-223.077
-80.453	-272.527	-148.352
-70.8619	-151.648	-104.396
-60.3425	-87.9121	-69.2308
-50.5967	-45.0549	-38.4615
-40.6961	-21.978	-14.2857
-30.7956	2.1978	9.89011
-21.2044	12.0879	27.4725
-11.1492	25.2747	50.5495
-1.40331	39.5604	64.8352
8.80663	63.7363	89.011
19.0166	83.5165	128.571
28.7624	119.78	205.495

Table 3. Parameters for the cardiac SAN pacemaker model. The amplitudes a_l can be thought of as $\bar{a}_l/C_M$ where C_M is a constant that represents the rate of change in charge around the membrane as a function of v, and $l \in \{CaL, K, NaK, NaCa\}$.

Parameter	Value	Units	Description
C_M	30	pF	Membrane capacitance
$\bar{a}_{Ca}$	1	pA	Amplitude for the L-type Ca^{2+} current
$\bar{a}_K$	100	pA	Amplitude for the K^+ current
$\bar{a}_{NaK}$	1	pA	Amplitude for the Na^+-K^+ current
$\bar{a}_{NaCa}$	3	pA	Amplitude for the Na^+-Ca^{2+} current
$a_{Ca} = \bar{a}_{Ca}/C_M$	0.0333	pA/pF	Amplitude for the normalized L-type Ca^{2+} current
$a_K = \bar{a}_K/C_M$	3.3333	pA/pF	Amplitude for the normalized K^+ current
$a_{NaK} = \bar{a}_{NaK}/C_M$	0.03333	pA/pF	Amplitude for the normalized Na^+-K^+ current
$a_{NaCa} = \bar{a}_{NaCa}/C_M$	0.1	pA/pF	Amplitude for the normalized Na^+-Ca^{2+} current
v_{ATP}	-420	mV	Potential ATP hydrolysis
v_{Na}	60	mV	Nernst potential for Na^+
v_K	-89	mV	Nernst potential for K^+
$v_{NaK} = 3v_{Na} - 2v_K + v_{ATP}$	-62	mV	Reversal potential for the for Na^+-K^+ ATPase current
$v_{NaCa} = 2v_{Ca} - 3v_{Na}$	–	mV	Reversal potential for the for Na^+-Ca^{2+} current ($\boldsymbol{v}_{Ca}$ depends continuously on $[Ca]_i$)
v_{m13}	-25	mV	Half-activation potential for Ca_{v13} L-type Ca^{2+}-current (Mangoni *et al.*, 2003)
v_w	-25	mV	Half-activation potential for the transient K^+-current (Shibasaki, 1987)
g_{m13}	5	–	Activation slope factor for the Ca_{v13} L-type Ca^{2+}-current
g_w	3.6	–	Activation slope factor for the K^+-current (Shibasaki, 1987)
r_w	0.005	s^{-1}	Activation rate for the cardiocyte K^+-current
k_w	0.3	–	Exponent for the K^+ -activation variable
b_w	0.35	–	Activation slope factor for the K^+-current
b_{NaK}	0.35	–	Non-rectification bias for the Na^+-K^+-current
b_K	0.1	–	Rectification for the transient K^+-current (Shibasaki, 1987)
b_{Na}	0.5	–	Non-rectification bias for the transient Na^+-current
b_{Ca}	0.5	–	Non-rectification bias for the Ca_{v13} L-type Ca^{2+}-current
c_∞	0.1	μM	Minimal (resting) intracellular Ca^{2+}-concentration
r_c	0.02	ms^{-1}	Ca^{2+} removal rate
k_c	0.00554	–	Conversion factor between Ca^{2+} current and intracellular Ca^{2+} concentration

double peak can be much simpler. The calcium current J_{CaL} is a negative-valued, non monotonic function for $v < v_{Ca}$, which can be thought of as a product of a amplitude term that includes gating and the function φ_{CaL}. The normalised current J_{CaL} has a local minimum (maximum current amplitude) around -10 mV (Figure 4B, blue line and Figure 5A, blue line), after which the current decreases, reaching a local maximum as the total current passes through zero, at the peak of the action potential around 10 mV (Figure 4B, where $\partial_t v = 0$). The first peak for the Ca^{2+} current occurs when v reaches the maximum depolarisation rate (Figure 5B). As v increases (e.g. upstroke of the action potential). The second peak for the current occurs as the membrane potential decreases, and passes again through the region where the maximal current occurs (local minimum for J_{Ca}). The two local minima for J_{CaL} occur at different amplitudes because of the difference in the evolution of v during the upstroke and the downstroke of the action potential (Figure 5A, blue line, and Figure 5B, where $\partial_t v = 0$). It is important to remark that the dual role played by w is not the cause of the double activation. This is illustrated by analysing the behaviour of a non-inactivating J_{CaL} without the inactivation component (Figure 5A, gray line). The double activation can also be observed in models in which the activation of K^+ channels and the inactivation of Ca^{2+} or Na^+ channels are represented by different variables (Rasmusson *et al.*, 1990a) and in dynamic voltage clamp experiments on neurons in which there are transient and persistent sodium channels (Carter & Bean, 2009).

The double peak in the Ca^{2+} current reflects on the intracellular Ca^{2+} concentration (Figure 6, gray line), and by extension, on the Nernst potential for Ca^{2+} (Figure 6, blue line), which display two increasing phases and two decreasing phases, respectively. The first and faster phase in both cases occur during the initial activation of the L-type channels. The second phase occurs during the downstroke, as second peak of the Ca^{2+} current occurs. As a consequence, the reversal potential for the Na-Ca exchanger, $v_{NaCa} = 2v_{Ca} - 3v_{Na}$ (Figure 6, orange line) also has two phases, this time increasing. Increasing the intracellular Ca^{2+} (Figure 6, gray line) concentration decreases the Nernst potential for Ca^{2+}, and vice versa. By extension, v_{NaCa}, becomes larger when c increases. Ca^{2+} enters the cell in exchange for Na^+ that moves out when $v > v_{NaCa}$, during most of the increasing phase and the initial depolarisation phase of the action potential (blue lines in Figure 4A and C, and Figure 6).

Fast spiking interneuron dynamics

To construct of a simple model for the dynamics of a fast spiking (FS) striatal interneuron, assume the transmembrane potential depends on three currents respectively mediated by Na-K pumps, non-inactivating K^+ channels, and Na^+ channels with transient dynamics, with voltage-dependent gating in both channels. It is also assumed that the proportion of activated K^+ is represented by a variable $w \in [0, 1]$, which also represents the proportion of inactivated Na^+ channels (Av-Ron *et al.*, 1991; Rinzel, 1985). That is, $1 - w$ represents the proportion of non-inactivated Na^+ channels. Since w models the activation of a *population* of channels, it makes sense assume that its dynamics follow a logistic scheme, without adding extra powers to w. This also follows the experimentally observed dynamics which have been reported repeatedly, including those of delayed-rectifier K^+ currents recorded in voltage clamp (see for instance Figure 3 in Hodgkin & Huxley, 1952).

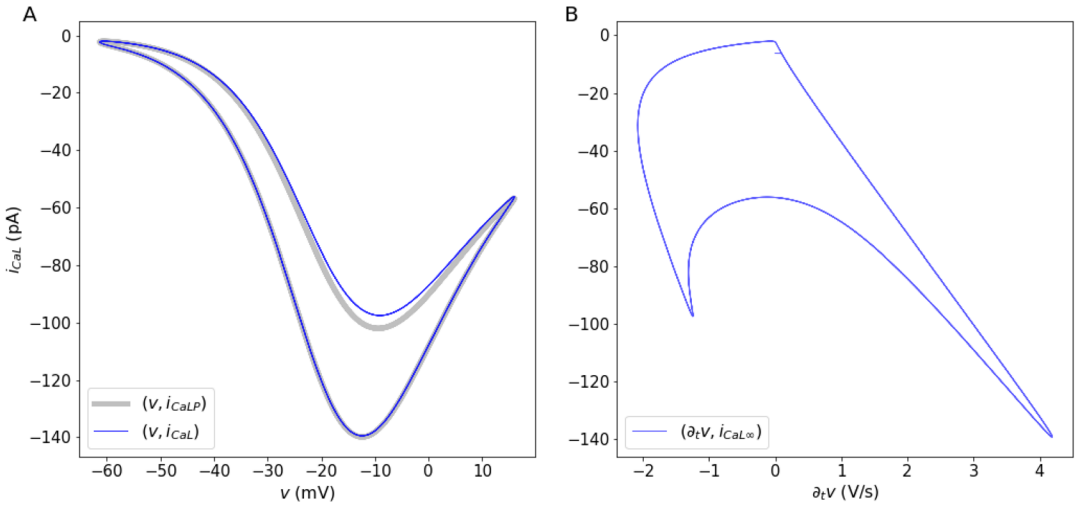

Figure 5. Dynamics of the calcium current and double activation during pacemaking oscillations. A. Behaviour of the inactivating L-type Ca^{2+} current with respect to the transmembrane potential (blue line) and a non-inactivating current (gray line). Notice that two points with locally maximum current amplitude occur during the action potential. The local minimum with larger current values occurs during the upstroke of the action potential. The local minimum with smaller current values occurs during the downstroke of the action potentials. (**B**) Calcium current as a function of the time-dependent change in v. The maximum rate of change for v occurs when the calcium current reaches its maximum amplitude.

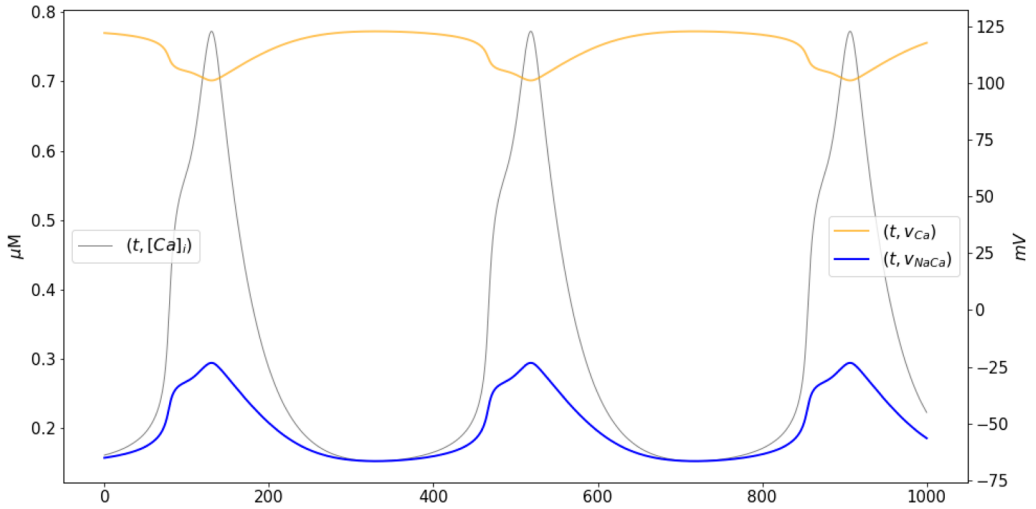

Figure 6. Calcium dynamics during pacemaking. Time courses of the intracellular calcium concentration (gray, left axis), the Nernst potential for Ca^{2+} (orange, right axis), and the reversal potential for the Na-Ca exchanger (blue, right axis). Notice the two phases of calcium increase that occur in agreement with the double peak observed in the calcium current (see Figure 4B, blue trace).

Explicitly, the dynamics for the FS-interneuron membrane can be described by a system with two coupled differential equations of the form

$$\partial_t v = -(1-w)F_m(v)a_{NaT}\psi_{NaT}(v) - wa_{KaD}\psi_{KaD}(v) - a_{NaK}\psi_{NaK}(v), \quad (44)$$

$$\partial_t w = w^{k_w}[F_w(v) - w]R_w(v), \quad (45)$$

The activation rate for K^+ channels depends is a voltage-dependent functions R_w and F_w as defined for the cardiac pacemaking model. It is also assumed that the activation of sodium channels is at a quasi steady state as a function of v.

Striatal FS interneurons display maximum $\partial_t v$ between 100 and 200 V/s. In current clamp mode, most neurons are silent, and show transitions between rest and repetitive spiking at a rheobase current of approximately 90 pA, with initial firing rates between 50 and 60 Hz and a delay to first spike in the transition that decreases as the stimulus amplitude increases (Figure 7, parameters in Table 4).

To include these properties into the model, the membrane capacitance was specified first, then the maximum $\partial_t v$ was adjusted by fitting the parameter a_{NaT}, and then the contributions for the K^+ channels and the Na-K ATPase are set to obtain spiking and fit the rheobase. The model in Equations (44)–(45) reproduces dynamics observable in fast spiking neurons in CA1 (Erisir *et al.*, 1999) or in the striatum (Orduz *et al.*, 2013; Tepper *et al.*, 2010).

Even though FS-interneuron spiking is conditional to the reception of input, the dynamics of the system can be thought of as qualitatively similar to those observe in the SAN. Within the time of a single spike, and by extension during the repetitive spiking regime, if v increases, w also increases, but at a slower rate in comparison to v. This is because the activation w is always moving toward its steady state value, which increases as v increases. Once w increases, the Na^+ current tends to decrease and the K^+ current tends to increase, thereby causing a decrease in v. The slower dynamics in w relative to those in v capture the delay between the amplification caused by the Na^+ current and the recovery caused by the negative feedback of the K^+ current. The current mediated by Na/K-ATPase acts as an extra attracting force toward v_{NaK} that increases nonlinearly as the distance between v and v_{NaK} increases.

Discussion

A general, macroscopic model for transmembrane fluxes has been derived by directly calculating the work required to transport molecules across the membrane. The derivation is based on a general thermodynamic scheme that takes into account the rate, stoichiometry, and the direction in which the molecules are transported across the membrane. These biophysical parameters are then combined to write expressions for directional fluxes based on van't Hoff (1884) and Arrhenius (1889) formulations, weighted as in the Butler/Erdey-Gruz/Volmer equation (Butler, 1924; Erdey-Grúz & Volmer, 1930). The result is a general description of the transmembrane molecular flux as a difference of exponential functions (Equation (16)) that describes the transport dynamics of molecules in the "forward" and "backward" directions, relative to a source compartment. This general description describes transport due to electrodiffusion mediated by channels, and also translocation mediated by pumps (Table 1). The two exponential functions depend on a common expression involving the

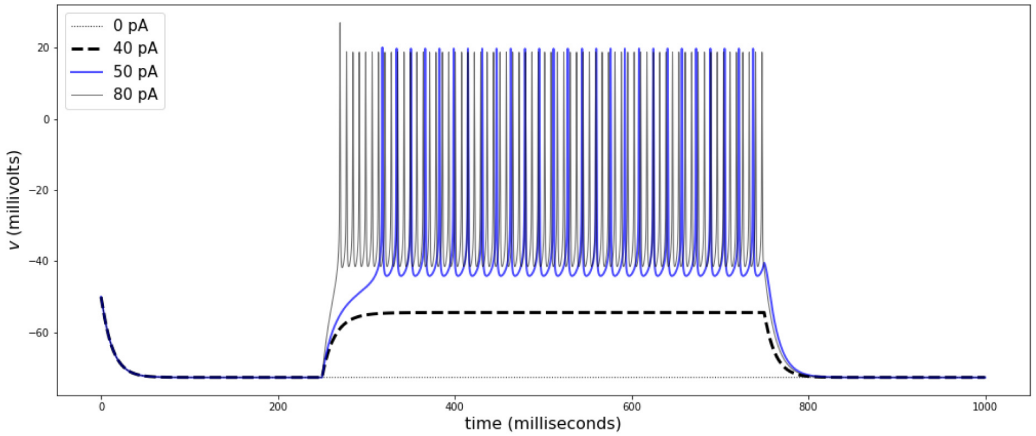

Figure 7. Rest to spiking transitions of FS interneuron under current clamp. The traces show responses to current-clamp stimulation of different amplitudes. The transition between rest and spiking with a rheobase occurs between 40 and 50 pA, as shown for some FS neurons in the mouse striatum (Orduz *et al.*, 2013). The traces correspond to stimulation amplitudes of 0 (gray dots), 40 (black dashed line), 50 (blue), and 80 pA (gray). Parameters can be found in Table 4.

Table 4. Parameters for the fast spiking interneuron model.

Parameter	Value	Units	Description
Current amplitudes and capacitance for the neuronal membrane model			
C_m	30	pF	Membrane capacitance
$\bar{a}_{NaK}$	67	pA	Amplitude for the Na^+-K^+ ATPase current
$\bar{a}_K$	4400	pA	Amplitude for the delayed-rectifier K^+ current
$\bar{a}_{Na}$	1400	pA	Amplitude for the transient Na^+ current
v_{ATP}	-430	mV	Potential ATP hydrolysis
$v_{NaK} = 3v_{Na} - 2v_K + v_{ATP}$	-72	mV	Reversal potential for the for Na^+-K^+ ATPase current
v_K	-89	mV	Nernst potential for K^+
v_{Na}	60	mV	Nernst potential for Na^+
v_{mT}	-17	mV	Half-activation potential for the transient Na^+-current
v_w	-5	mV	Half-activation potential for the transient K^+-current
g_{mT}	5	–	Activation slope factor for the transient Na^+-current
g_w	4	–	Activation slope factor for the K^+-current
r_w	2	s^{-1}	Activation rate for the neuronal K^+-current
k_w	1	–	Activation exponent for the K^+-current
b_w	0.3	–	Activation slope factor for the K^+-current
b_{NaK}	0.5	–	Non-rectification for the Na^+-K^+-current
b_K	0.5	–	Non-rectification for the transient K^+-current
b_{Na}	0.5	–	Non-rectification for the transient Na^+-current

transmembrane concentrations of the molecules being transported, and possibly the transmembrane potential when transport is electrogenic.

Rectification, an asymmetry in the flow during transport, is typically modelled modifying the dynamics of the gating variables for the current. The general formulas for transmembrane transport include a bias term b that controls the relative contribution of inward and outward fluxes the transport. Hence, different types of rectification can be described by favouring one of the directions for transport, conceptually in line with the "anomalous rectification" originally reported by Katz (1949) for K^+ in muscle cells. The bias term is *not* part of any gating mechanism. Instead, it represents the asymmetry in bidirectional flux. For instance, in K^+ channels, the inward (outward, respectively) rectification occurs when the fourth transmembrane segment of the channel (S4) is located closer to the intracellular (extracellular) portion of the membrane in its open configuration (Riedelsberger *et al.*, 2015). There are other reports that show that asymmetries in bidirectional transport occur as a consequence of changes in the three dimensional structure of the protein mediating the transport (Halliday & Resnick, 1981; Quistgaard *et al.*, 2013). Therefore, the rectification term can be thought of as representing a structural component of the transmembrane protein through which molecules move (Figure (3)). Outward rectification in K^+ channels can be explained, for instance, by biasing the flux of K^+ the forward (outward) direction ($b_K > 1/2$). Instead, inward rectification can be obtained by biasing the transport in the backward (inward) direction ($b_K < 1/2$). It is important to remark that non-rectifying currents with $b = 1/2$ are nonlinear functions of ΔG, which shows that the nonlinearity of the current-voltage relationships is not the defining characteristic of rectification; as argued in some textbooks (see Kew & Davies, 2010).

The formulation for transmembrane flux may be rewritten in different alternative forms that can be found throughout the literature (see Equation (11) and Equation (14), Goldman, 1943; Johnston *et al.*, 1995). Of particular interest, the widely used conductance-based models for current from the seminal work of Hodgkin & Huxley (1952) turn out to be linear approximations of the general current described here (Herrera-Valdez, 2012; Herrera-Valdez, 2014). This explains why the Hodgkin & Huxley (1952) model captures many of the defining features of action potential generation, in spite of modelling ionic currents as if they were resistive. Another interesting case is that electrodiffusive transmembrane currents derived from the Nernst-Planck equation (Nernst, 1888; Planck, 1890), turn out particular cases of the general formulation presented here (see also Herrera-Valdez, 2014, for details). Examples include the constant field approximation (Clay *et al.*, 2008; Hille, 1992; Johnston *et al.*, 1995), the non-rectifying currents proposed by Endresen *et al.* (2000), and more general electrodiffusive currents that includes a bias term accounting for rectification (Herrera-Valdez, 2014; Johnston *et al.*, 1995).

Possibly of interest to mathematicians working on bifurcation theory, a third order approximation (Equation (17)), can be used to construct models resembling the Fitz-Hugh system (FitzHugh, 1955; FitzHugh, 1961; Fitz-Hugh, 1966), which yield very close approximations to the full model, while keeping biophysical characteristics of real systems like rectification and specific ionic permeabilities, and the multiplicative interaction between the slow variable w and the fast variable v; properties that the Fitz-Hugh polynomials do not have. Third order approximations also open the possibility of expanding on the analysis of dynamical systems based on these general formulas to study normal forms and bifurcations. Depending on the ions involved in each transmembrane transport mechanism, the third order approximations for current can be shown to be very close to the full function in Equation (16) (Figure 2). Another possible use of the third order approximations could be to construct network models that take into account nonlinearities included in the general formulation, but at a reduced computational cost in comparison to the full model. This possibility is currently being tested and will be reported in the near future. A similar comparison has been made between the full model and the conductance-based approximation taking a dynamical systems perspective and also by means of computational simulations in Herrera-Valdez (2012).

One question of interest because of its possible impact on the interpretation of results from existing modelling studies is how do the excitability and the resulting dynamics in a model of membrane dynamics change when using the thermodynamic transmembrane currents or their approximations? The question has been addressed in a study in which two simple neuronal models with currents mediated by Na^+ and K^+, each equipped with the same biophysical gating properties and the same relative contributions for the currents, but one with currents as in Equation (22), the other with conductance-based currents. The two models display a number of qualitative and quantitative differences worth considering while making the choice of a model in theoretical studies (Herrera-Valdez, 2012). For a start, the two models are not topologically equivalent across many ratios of the relative contributions of K^+ and Na^+ channels (Herrera-Valdez, 2012); as would be expected by the fact that conductance-based formulations are only linear approximations of the general currents, around the reversal potential for each current. One of the most notable differences between the general formulation and the conductance-based formula is the contribution of the nonlinear, high order terms from Equation (16), which results in more realistic upstrokes for action potentials and an overall increased excitability; in this case characterised in terms of the minimum sustained current necessary to produce at least one action potential (Herrera-Valdez, 2012). The increased excitability of the membrane with the general formulation is due, in part, to the large, exponential contribution of the open Na^+ and Ca^{2+} channels, but not the K^+ channels, to the change in the transmembrane potential near rest. The time course of the Na^+ current during the beginning of the action potential

with the general model is much sharper than that of the conductance-based formulation, resulting in a faster upstroke of the action potential; and in better agreement with observations in cortex and other tissues (Naundorf *et al.*, 2006). It is important to remark that the sharper increase in the change of the membrane potential shown using the general formulation is a consequence of the nonlinear driving force terms of the current in the general model (the flux term in the general formulation), and not in the activation dynamics for the transient Na^+ current. The nonlinearities unravelled by the general formulation could thus be part of the explanation for the observed sharpness at the beginning of the action potential upstroke observed in different experiments. However, such nonlinearities do not rule out other contributions, such as cooperation between Na channels, or the effects of spatial differences in Na-channel densities, as pointed out by Brette (2013) for the case of action potentials in cortical pyramidal cells. In the models presented here, the sharpness in the upstrokes of neuronal action potentials combine nonlinear factors including the flux given by the general formulation, channel densities, and gating that does not follow linear, but logistic-like dynamics.

The general formulation for both passive and active transmembrane transport can be thought of as a tool that facilitates the construction and analysis of models of membrane potential dynamics. The generality and versatility of the thermodynamic transmembrane transport formulations is illustrated with models of cardiac pacemaking interneuron fast spiking. The ion fluxes in the model are assumed to be mediated by two different types of voltage-gated channels and two different types of pumps, all represented with the *same* functional form (see DiFrancesco & Noble (1985); Herrera-Valdez & Lega (2011); Rasmusson *et al.* (1990b) for examples in which that is not the case).

One important advantage of the general formulation is that it includes the possibility of explicitly estimating the number of channels or pumps mediating each of the transport mechanisms of interest. This has proven to be useful to study the relative contributions of different currents to the excitability of neurons (see Herrera-Valdez *et al.*, 2013) and cardiocytes (Herrera-Valdez, 2014).

Another extension of possible interest is that of modelling the transmembrane transport between organelles and the cytosolic compartment, which can be done by directly replacing the difference $c_s - d_s$ with -1 or 1, in Equation (1), accounting for the direction of transmembrane motion of molecules relative to the outer compartment. This and other generalisations enable the possibility of studying the interdependence between electrical excitability across tissues and animal species (Herrera-Valdez *et al.*, 2013), and its cross-interactions with metabolism and other processes of physiological importance, all from a general theoretical framework with common formulations.

Implications for experimentalists. One of the main advantages of the general expressions is that fits to ionic currents can be made straight from the voltage-clamp data without much effort, and without having to calculate conductances, which amounts to imposing the assumption that the current-voltage relationship is linear. Fits to experimental currents can then be directly put into equations describing the change in the membrane potential, and model membrane dynamics of interest without having to make many extra adjustments, as it is the case for most conductance-based models restricted to data.

The model for current in Equation (22) has been used to construct simplified models for the membrane dynamics of different cell types using experimental data. Examples include fast spiking interneurons in the mice striatum (Figure 7), motor neurons in *Drosophila melanogaster* (Herrera-Valdez *et al.*, 2013), pyramidal cells in the young and ageing hippocampus of rats (McKiernan *et al.*, 2015), medium spiny neurons in the mouse striatum (Suárez *et al.*, 2015), rabbit sinoatrial node cells (Herrera-Valdez, 2014), and other types of excitable cells (McKiernan & Herrera-Valdez, 2012).

Conclusions

A general model that describes physiological transmembrane transport of molecules has been derived by considering basic thermodynamical principles. The model unifies descriptions of transport mediated by channels and pumps, it can model biases in either one of the directions of flow, and it can be easily converted into a model for current in the case of electrogenic transport. As it is desirable in all models, the general expressions can be thought of as extensions of some previous models. In particular, it is shown that the conductance-based model for current turns out to be a first order approximation of the general formulation.

The general formulation presented here can be used to build general models of phenomena involving transmembrane transport using a unified framework (Shou *et al.*, 2015).

Data availability

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

Acknowledgements

The author wishes to thank Joceline Lega, Timothy Secomb, and Raphael Gruener at the University of Arizona; Jose Bargas-Diaz and Antonio Laville from the Cellular Physiology Institute at UNAM; and Erin C. McKiernan from the Physics Department at UNAM for all the time spent in discussions that helped to solidify and deepen the ideas presented in this paper.

References

Adrian RH: **Rectification in muscle membrane.** *Prog Biophys Mol Biol.* 1969; **19**(2): 339–369.
PubMed Abstract | Publisher Full Text

Aidley DJ: **The Physiology of Excitable Cells**. Cambridge University Press, 4 edition, 1998; ISBN 0521574153,9780521574150.
Reference Source

Aldrich RW, Corey DP, Stevens CF: **A reinterpretation of mammalian sodium channel gating based on single channel recording.** *Nature.* 1983; **306**(5942): 436–441.
PubMed Abstract | Publisher Full Text

Almers W, McCleskey EW: **Non-selective conductance in calcium channels of frog muscle: calcium selectivity in a single-file pore.** *J Physiol.* 1984; **353**(1): 585–608.
PubMed Abstract | Publisher Full Text | Free Full Text

Armstrong CM, Binstock L: **Anomalous rectification in the squid giant axon injected with tetraethylammonium chloride.** *J Gen Physiol.* 1965; **48**(5): 859–872.
PubMed Abstract | Publisher Full Text | Free Full Text

Arrhenius S: **Über die reaktionsgeschwindigkeit bei der inversion von rohrzucker durch säuren.** *Zeitschrift für physikalische Chemie.* 1889; **4U**(1): 226–248.
Publisher Full Text

Ashcroft FM: **ATP-sensitive potassium channelopathies: focus on insulin secretion.** *J Clin Invest.* 2005; **115**(8): 2047–2058.
PubMed Abstract | Publisher Full Text | Free Full Text

Av-Ron E, Parnas H, Segel LA: **A minimal biophysical model for an excitable and oscillatory neuron.** *Biol Cybern.* 1991; **65**(6): 487–500.
PubMed Abstract | Publisher Full Text

Barr L: **Membrane potential profiles and the Goldman equation.** *J Theor Biol.* 1965; **9**(3): 351–356.
PubMed Abstract | Publisher Full Text

Bennett HS: **The concepts of membrane flow and membrane vesiculation as mechanisms for active transport and ion pumping.** *J Biophys Biochem Cytol.* 1956; **2**(4 Suppl): 99–103.
PubMed Abstract | Publisher Full Text | Free Full Text

Bergman C, Kashiwaya Y, Veech RL: **The effect of pH and free Mg^{2+} on ATP linked enzymes and the calculation of Gibbs free energy of ATP hydrolysis.** *J Phys Chem B.* 2010; **114**(49): 16137–16146.
PubMed Abstract | Publisher Full Text

Blaustein MP, Kao JPY, Matteson DR: **Cellular physiology**. Elsevier/Mosby, 2004; ISBN 0323013414.
Reference Source

Blicher A, Heimburg T: **Voltage-Gated Lipid Ion Channels.** *PLoS One.* 2013; **8**(6): e65707.
PubMed Abstract | Publisher Full Text | Free Full Text

Boltzmann L: **Studien über das Gleichgewicht der lebendigen Kraft zwischen bewegten materiellen Punkten**. kk Hof-und Staatsdruckerei. 1868.

Bowie D: **External anions and cations distinguish between AMPA and kainate receptor gating mechanisms.** *J Physiol.* 2002; **539**(Pt 3): 725–733.
PubMed Abstract | Publisher Full Text | Free Full Text

Brette R: **Sharpness of spike initiation in neurons explained by compartmentalization.** *PLoS Comput Biol.* 2013; **9**(12): e1003338.
PubMed Abstract | Publisher Full Text | Free Full Text

Butler JAV: **Studies in heterogeneous equilibria. Part II.—the kinetic interpretation of the nernst theory of electromotive force.** *Trans Faraday Soc.* 1924; **19**: 729–733.
Publisher Full Text

Carter BC, Bean BP: **Sodium entry during action potentials of mammalian neurons: incomplete inactivation and reduced metabolic efficiency in fast-spiking neurons.** *Neuron.* 2009; **64**(6): 898–909.
PubMed Abstract | Publisher Full Text | Free Full Text

Chapman JB: **Letter: On the reversibility of the sodium pump in dialyzed squid axons. A method for determining the free energy of ATP breakdown?** *J Gen Physiol.* 1973; **62**(5): 643–6.
PubMed Abstract | Publisher Full Text | Free Full Text

Clay JR, Paydarfar D, Forger DB: **A simple modification of the Hodgkin and Huxley equations explains type 3 excitability in squid giant axons.** *J R Soc Interface.* 2008; **5**(29): 1421–1428.
PubMed Abstract | Publisher Full Text | Free Full Text

Cole KS: **Electrodiffusion models for the membrane of squid giant axon.** *Physiol Rev.* 1965; **45**(2): 340–79, ISSN 0031-9333.
PubMed Abstract | Publisher Full Text

Courant R, John F: **Introduction to calculus and analysis I**. Springer Science & Business Media, 2012.

Covarrubias M, Wei AA, Salkoff L: **Shaker, Shal, Shab, and Shaw express independent K^+ current systems.** *Neuron.* 1991; **7**(5): 763–773.
PubMed Abstract | Publisher Full Text

Despa S, Islam MA, Weber CR, *et al.*: **Intracellular Na^+ concentration is elevated in heart failure but Na/K pump function is unchanged.** *Circulation.* 2002; **105**(21): 2543–2548.
PubMed Abstract | Publisher Full Text

De Weer P, Gadsby DC, Rakowski RF: **Voltage dependence of the Na-K pump.** *Annu Rev Physiol.* 1988; **50**(1): 225–241.
PubMed Abstract | Publisher Full Text

DiFrancesco D, Noble D: **A model of cardiac electrical activity incorporating ionic pumps and concentration changes.** *Philos Trans R Soc Lond B Biol Sci.* 1985; **307**(1133): 353–398.
PubMed Abstract | Publisher Full Text

Doyle DA, Morais Cabral J, Pfuetzner RA, *et al.*: **The structure of the potassium channel: molecular basis of K^+ conduction and selectivity.** *Science.* 1998; **280**(5360): 69–77.
PubMed Abstract | Publisher Full Text

Endresen LP, Hall K, Høye JS, *et al.*: **A theory for the membrane potential of living cells.** *Eur Biophys J.* 2000; **29**(2): 90–103.
PubMed Abstract | Publisher Full Text

Erdey-Grúz T, Volmer M: **Zur theorie der wasserstoff überspannung.** *Zeitschrift für Physikalische Chemie.* 1930; **150A**(1): 203–213.
Publisher Full Text

Erisir A, Lau D, Rudy B, *et al.*: **Function of specific k+channels in sustained high-frequency firing of fast-spiking neocortical interneurons.** *J Neurophysiol.* 1999; **82**(5): 2476–2489.
PubMed Abstract | Publisher Full Text

Favre I, Moczydlowski E, Schild L: **On the structural basis for ionic selectivity among Na^+, K^+, and Ca^{2+} in the voltage-gated sodium channel.** *Biophys J.* 1996; **71**(6): 3110–3125.
PubMed Abstract | Publisher Full Text | Free Full Text

FitzHugh R: **Mathematical models of threshold phenomena in the nerve membrane.** *Bull Math Biol.* 1955; **17**(4): 257–278.
Publisher Full Text

FitzHugh R: **Impulses and Physiological States in Theoretical Models of Nerve Membrane.** *Biophys J.* 1961; **1**(6): 445–466.
PubMed Abstract | Publisher Full Text | Free Full Text

Fitz-Hugh R: **Mathematical models of excitation and propagation in nerve.** Publisher Unknown, 1966.
Reference Source

Gadsby DC: **Ion channels versus ion pumps: the principal difference, in principle.** *Nat Rev Mol Cell Biol.* 2009; **10**(5): 344–352.
PubMed Abstract | Publisher Full Text | Free Full Text

Gadsby DC, Kimura J, Noma A: **Voltage dependence of Na/K pump current in isolated heart cells.** *Nature.* 1985; **315**(6014): 63–65.
PubMed Abstract | Publisher Full Text

Garrahan PJ, Glynn IM: **The behaviour of the sodium pump in red cells in the absence of external potassium.** *J Physiol.* 1967; **192**(1): 159–174.
PubMed Abstract | Publisher Full Text | Free Full Text

Goldman DE: **Potential, Impedance, and Rectification in Membranes.** *J Gen Physiol.* 1943; **27**(1): 37–60.
PubMed Abstract | Publisher Full Text | Free Full Text

Gurtovenko AA, Anwar J: **Ion transport through chemically induced pores in protein-free phospholipid membranes.** *J Phys Chem B.* 2007; **111**(47): 13379–13382.
PubMed Abstract | Publisher Full Text

Halliday D, Resnick R: **Fundamentals of physics**. John Wiley & Sons, 1981.
Reference Source

Hamada K, Matsuura H, Sanada M, *et al.*: **Properties of the Na^+/K^+ pump current in small neurons from adult rat dorsal root ganglia.** *Br J Pharmacol.* 2003; **138**(8): 1517–1527.
PubMed Abstract | Publisher Full Text | Free Full Text

Herrera-Valdez MA: **An equation for the biological transmembrane potential from basic biophysical principles [version 1; peer review: 1 not approved].** *F1000Res.* 2020; **9**(676): 676.
Publisher Full Text

Herrera-Valdez MA: **Membranes with the same ion channel populations but different excitabilities.** *PLoS One.* 2012; **7**(4): e34636.
PubMed Abstract | Publisher Full Text | Free Full Text

Herrera-Valdez MA, Lega J: **Reduced models for the pacemaker dynamics of cardiac cells.** *J Theor Biol.* 2011; **270**(1): 164–176.
PubMed Abstract | Publisher Full Text

Herrera-Valdez MA: **Geometry and nonlinear dynamics underlying electrophysiological phenotypes in biophysical models of membrane potential.** *Dissertation.* Ph.D. in Mathematics. University of Arizona. 2014.

Herrera-Valdez MA, McKiernan EC, Berger SD, *et al.*: **Relating ion channel expression, bifurcation structure, and diverse firing patterns in a model of an identified motor neuron.** *J Comput Neurosci.* 2013; **34**(2): 211–29.
PubMed Abstract | Publisher Full Text

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

Hodgkin AL, Huxley AF: **A quantitative description of membrane current and its application to conduction and excitation in nerve.** *J Physiol.* 1952; **117**(4): 500–544.
PubMed Abstract | Publisher Full Text | Free Full Text

Hodgkin AL, Katz B: **The effect of sodium ions on the electrical activity of giant axon of the squid.** *J Physiol.* 1949; **108**(1): 37–77.
PubMed Abstract | Publisher Full Text | Free Full Text

Hollmann M, Hartley M, Heinemann S: **Ca2+ permeability of KA-AMPA--gated glutamate receptor channels depends on subunit composition.** *Science.* 1991; **252**(5007): 851–853.
PubMed Abstract | Publisher Full Text

Hunter JD: **Matplotlib: A 2d graphics environment.** *Computing in Science & Engineering.* 2007; **9**(3): 90–95.
Publisher Full Text

Jacquez JA, Schultz SG: **A general relation between membrane potential, ion activities, and pump fluxes for symmetric cells in a steady state.** *Mathematical Biosci.* 1974; **20**(1–2): 19–25.
Publisher Full Text

Jacquez JA: **A general relation between membrane potential, ion activities, and pump fluxes for nonsymmetric cells in a steady state.** *Mathematical Biosciences.* 1981; **53**(1–2): 53–57.
Publisher Full Text

Johnston D, Wu SMS, Gray R: **Foundations of cellular neurophysiology**. MIT press Cambridge, MA, 1995; ISBN 0262100533.
Reference Source

Katz B: **Les constantes electriques de la membrane du muscle.** *Arch Sci Physiol.* 1949; **3**: 285–299.
Reference Source

Kell DB: **On the functional proton current pathway of electron transport phosphorylation. An electrodic view.** *Biochim Biophys Acta.* 1979; **549**(1): 55–99.
PubMed Abstract | Publisher Full Text

Kew JNC, Davies CH: **Ion channels: from structure to function**. Oxford University Press, USA, 2010.
Publisher Full Text

Kimizuka H, Koketsu K: **Ion transport through cell membrane.** *J Theor Biol.* 1964; **6**(2): 290–305.
PubMed Abstract | Publisher Full Text

Läuger P: **Ion transport through pores: a rate-theory analysis.** *Biochim Biophys Acta.* 1973; **311**(3): 423–441.
PubMed Abstract | Publisher Full Text

Lowe AG, Walmsley AR: **The kinetics of glucose transport in human red blood cells.** *Biochim Biophys Acta.* 1986; **857**(2): 146–154.
PubMed Abstract | Publisher Full Text

Mangoni ME, Couette B, Marger L, *et al.*: **Voltage-dependent calcium channels and cardiac pacemaker activity: from ionic currents to genes.** *Prog Biophys Mol Biol.* 2006; **90**(1–3): 38–63.
PubMed Abstract | Publisher Full Text

Marbán E: **Cardiac channelopathies.** *Nature.* 2002; **415**(6868): 213–8.
PubMed Abstract | Publisher Full Text

Mangoni ME, Couette B, Bourinet E, *et al.*: **Functional role of L-type $Ca_v1.3$ Ca^{2+} channels in cardiac pacemaker activity.** *Proc Natl Acad Sci U S A.* 2003; **100**(9): 5543–5548.
PubMed Abstract | Publisher Full Text | Free Full Text

Mueckler M, Thorens B: **The SLC2 (GLUT) family of membrane transporters.** *Mol Aspects Med.* 2013; **34**(2–3): 121–138.
PubMed Abstract | Publisher Full Text | Free Full Text

Mullins LJ: **The generation of electric currents in cardiac fibers by Na/Ca exchange.** *Am J Physiol.* 1979; **236**(3): C103–C110.
PubMed Abstract | Publisher Full Text

McKiernan EC, Herrera-Valdez MA, Marrone DF: **A biophysical, minimal model to explore age-related changes in ion channel gene expression and excitability in ca1 pyramidal cells.** *Society for Neurosciences Annual Meeting.* Session 628: Learning and Memory: Aging III, Poster 628.10/AA45., 2015.
Reference Source

McKiernan EC, Herrera-Valdez MA: **From spinal cord to hippocampus: links between bifurcation structure, ion channel expression, and firing patterns in a variety of neuron types.** *BMC Neurosci.* 2012; **13**(Suppl 1): P121.
Publisher Full Text | Free Full Text

Nakao M, Gadsby DC: **[Na] and [K] dependence of the Na/K pump current-voltage relationship in guinea pig ventricular myocytes.** *J Gen Physiol.* 1989; **94**(3): 539–565.
PubMed Abstract | Publisher Full Text | Free Full Text

Naundorf B, Wolf F, Volgushev M: **Unique features of action potential initiation in cortical neurons.** *Nature.* 2006; **440**(7087): 1060–3.
PubMed Abstract | Publisher Full Text

Nernst W: **Zur kinetik der in lösung befindlichen körper.** *Zeitschrift für physikalische Chemie.* 1888; **2**(1): 613–637.
Publisher Full Text

Nonner W, Chen DP, Eisenberg B: **Anomalous mole fraction effect, electrostatics, and binding in ionic channels.** *Biophys J.* 1998; **74**(5): 2327–2334.
PubMed Abstract | Publisher Full Text | Free Full Text

Nonner W, Eisenberg R: **Ion permeation and glutamate residues linked by Poisson-Nernst-Planck theory in L-type calcium channels.** *Biophys J.* 1998; **75**(3): 1287–1305.
PubMed Abstract | Publisher Full Text | Free Full Text

Novák B, Tyson JJ: **Design principles of biochemical oscillators.** *Nat Rev Mol Cell Biol.* 2008; **9**(12): 981–91.
PubMed Abstract | Publisher Full Text | Free Full Text

Orduz D, Bischop DP, Schwaller B, *et al.*: **Parvalbumin tunes spike-timing and efferent short-term plasticity in striatal fast spiking interneurons.** *J Physiol.* 2013; **591**(13): 3215–3232.
PubMed Abstract | Publisher Full Text | Free Full Text

Peng IF, Wu CF: **Differential contributions of Shaker and Shab K^+ currents to neuronal firing patterns in *Drosophila*.** *J Neurophysiol.* 2007; **97**(1): 780–94.
PubMed Abstract | Publisher Full Text

Pickard WF: **Generalizations of the goldman-hodgkin-katz equation.** *Math Biosci.* 1976; **30**(1–2): 99–111.
Publisher Full Text

Pickard WF: **A postulational approach to the problem of ion flux through membranes.** *Math Biosci.* 1969; **4**(1–2): 7–21.
Publisher Full Text

Pitts PJ: **Stoichiometry of sodium-calcium exchange in cardiac sarcolemmal vesicles. Coupling to the sodium pump.** *J Biol Chem.* 1979; **254**(14): 6232–6235.
PubMed Abstract

Planck M: **Ueber die Potentialdifferenz zwischen zwei verdünnten Lösungen binärer Electrolyte.** *Annalen der Physik.* 1890; **276**(8): 561–576.
Publisher Full Text

Post RL, Jolly PC: **The linkage of sodium, potassium, and ammonium active transport across the human erythrocyte membrane.** *Biochim Biophys Acta.* 1957; **25**(1): 118–128.
PubMed Abstract | Publisher Full Text

Quistgaard EM, Löw C, Moberg P, *et al.*: **Structural basis for substrate transport in the GLUT-homology family of monosaccharide transporters.** *Nat Struct Mol Biol.* 2013; **20**(6): 766–8.
PubMed Abstract | Publisher Full Text

Rasmusson RL, Clark JW, Giles WR, *et al.*: **A mathematical model of electrophysiological activity in a bullfrog atrial cell.** *Am J Physiol.* 1990a; **259**(2 Pt 2): H370–H389.
PubMed Abstract | Publisher Full Text

Rasmusson RL, Clark JW, Giles WR, *et al.*: **A mathematical model of a bullfrog cardiac pacemaker cell.** *Am J Physiol.* 1990b; **259**(2 Pt 2): H352–H369.
PubMed Abstract | Publisher Full Text

Reeves JP, Hale CC: **The stoichiometry of the cardiac sodium-calcium exchange system.** *J Biol Chem.* 1984; **259**(12): 7733–7739.
PubMed Abstract

Riedelsberger J, Dreyer I, Gonzalez W: **Outward Rectification of Voltage-Gated K^+ Channels Evolved at Least Twice in Life History.** *PLoS One.* 2015; **10**(9): e0137600.
PubMed Abstract | Publisher Full Text | Free Full Text

Rinzel J, Ermentrout GB: **Analysis of neural excitability and oscillations**, Methods in neuronal modeling: From synapses to networks, 1989; 135–169.
Publisher Full Text

Rinzel J: **Excitation dynamics: insights from simplified membrane models.** *Fed proc.* 1985; **44**(15): 2944–2946.
PubMed Abstract

Rosenberg T, Wilbrandt W: **The kinetics of membrane transports involving chemical reactions.** *Exp Cell Res.* 1955; **9**(1): 49–67.
PubMed Abstract | Publisher Full Text

Sanders L, Rakovic S, Lowe M, *et al.*: **Fundamental importance of Na^+-$Ca2^+$ exchange for the pacemaking mechanism in guinea-pig sino-atrial node.** *J Physiol.* 2006; **571**(Pt 3): 639–49.
PubMed Abstract | Publisher Full Text | Free Full Text

Sen AK, Widdas WF: **Determination of the temperature and pH dependence of glucose transfer across the human erythrocyte membrane measured by glucose exit.** *J Physiol.* 1962; **160**(3): 392–403.
PubMed Abstract | Publisher Full Text | Free Full Text

Shibasaki T: **Conductance and kinetics of delayed rectifier potassium channels in nodal cells of the rabbit heart.** *J Physiol.* 1987; **387**(1): 227–50.
PubMed Abstract | Publisher Full Text | Free Full Text

Shou W, Bergstrom CT, Chakraborty AK, *et al.*: **Theory, models and biology.** *eLife.* 2015; **4**: e07158.
PubMed Abstract | Publisher Full Text | Free Full Text

Skou JC: **Enzymatic basis for active transport of Na^+ and K^+ across cell membrane.** *Physiol Rev.* 1965; **45**(3): 596–618.
PubMed Abstract | Publisher Full Text

Spivak M: **Calculus on manifolds: a modern approach to classical theorems of advanced calculus**. CRC Press, 2018.
Reference Source

Starace DM, Stefani E, Bezanilla F: **Voltage-dependent proton transport by the voltage sensor of the *Shaker* K^+ channel.** *Neuron.* 1997; **19**(6): 1319–1327.
PubMed Abstract | Publisher Full Text

Stein WD, Litman T: **Channels, carriers, and pumps: an introduction to membrane transport**. Elsevier, 2014.
Publisher Full Text

Stevens CF, Tsien RW: **Ion permeation through membrane channels**. Raven Press, 1979; **3**.

Suárez P, Herrera-Valdez MA, Bargas J, *et al.*: **Un modelo biofísico de neuronas estriatales de proyección que toma en cuenta la contribución de canales de calcio cav3.** *Escuela de Otoño de Biomatemáticas, Jalapa, Veracruz, México.* 2015.
Reference Source

Tanford C: **Equilibrium state of ATP-driven ion pumps in relation to physiological ion concentration gradients.** *J Gen Physiol.* 1981; **77**(2): 223–229.
PubMed Abstract | Publisher Full Text | Free Full Text

Tepper JM, Tecuapetla F, Koós T, *et al.*: **Heterogeneity and diversity of striatal gabaergic interneurons.** *Front Neuroanat.* 2010; **4**: 150.
PubMed Abstract | Publisher Full Text | Free Full Text

Tsunoda S, Salkoff L: **The major delayed rectifier in both Drosophila neurons and muscle is encoded by Shab.** *J Neurosci.* 1995; **15**(7 Pt 2): 5209–5221.
PubMed Abstract | Publisher Full Text

Ussing HH: **The distinction by means of tracers between active transport and diffusion.** *Acta Physiol Scand.* 1949a; **19**(1): 43–56.
Publisher Full Text

Ussing HH: **The active ion transport through the isolated frog skin in the light of tracer studies.** *Acta Physiol Scand.* 1949b; **17**(1): 1–37.
PubMed Abstract | Publisher Full Text

Ussing HH: **Transport of ions across cellular membranes.** *Physiol Rev.* 1949c; **29**(2): 127–155.
PubMed Abstract | Publisher Full Text

van't Hoff JH: **Etudes de dynamique chimique**. Muller, 1884; **1**.
Reference Source

Venetucci LA, Trafford AW, O'Neill SC, *et al.*: **Na/Ca exchange: regulator of intracellular calcium and source of arrhythmias in the heart.** *Ann N Y Acad Sci.* 2007; **1099**(1): 315–325.
PubMed Abstract | Publisher Full Text

Wackerhage H, Hoffmann U, Essfeld D, *et al.*: **Recovery of free ADP, P_i, and free energy of ATP hydrolysis in human skeletal muscle.** *J Appl Physiol (1985).* 1998; **85**(6): 2140–2145.
PubMed Abstract | Publisher Full Text

Wiggins PM: **The relationship between pump and leak: Part 1. application of the butler-volmer equation.** *Bioelectrochem Bioenerg.* 1985a; **14**(4–6): 313–326.
Publisher Full Text

Wiggins PM: **Relationship between pump and leak: Part 2. a model of the Na, K-atpase functioning both as pump and leak.** *Bioelectrochem Bioenerg.* 1985b; **14**(4–6): 327–337.
Publisher Full Text

Wiggins PM: **Relationship between pump and leak: Part 3. electrical coupling of Na^+-solute uptake to the Na, K-atpase.** *Bioelectrochem Bioenerg.* 1985c; **14**(4–6): 339–345.
Publisher Full Text

Willms AR, Baro DJ, Harris-Warrick RM, *et al.*: **An improved parameter estimation method for Hodgkin-Huxley models.** *J Comput Neurosci.* 1999; **6**(2): 145–168.
PubMed Abstract | Publisher Full Text

Woodbury JW: **Eyring rate theory model of the current-voltage relationships of ion channels in excitable membranes.** *Advances in Chemical Physics: Chemical Dynamics: Papers in Honor of Henry Eyring*. 1971; **21**: 601–617.
Publisher Full Text

Yue DT, Backx PH, Imredy JP: **Calcium-sensitive inactivation in the gating of single calcium channels.** *Science.* 1990; **250**(4988): 1735–1738.
PubMed Abstract | Publisher Full Text

Zhang H, Holden AV, Kodama I, *et al.*: **Mathematical models of action potentials in the periphery and center of the rabbit sinoatrial node.** *Am J Physiol Heart Circ Physiol.* 2000; **279**(1): H397–H421.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 22 November 2018

https://doi.org/10.5256/f1000research.18524.r40941

✔ **Kyle C.A. Wedgwood**
Living Systems Institute, College of Engineering, Maths and Physical Sciences, Centre for Biomedical Modelling and Analysis, University of Exeter, Exeter, UK

I am pleased to report that the author has done a great job in addressing all of my (and reviewer 2's) comments.

I therefore now recommend this article for indexing without further modification.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 30 October 2018

https://doi.org/10.5256/f1000research.17657.r38997

✔ **Moisés Santillán**
Moisés Santillán's Quantitative Biology & Complex Systems Lab, Center for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV), Monterrey, Nuevo León, Mexico

I found this paper quite interesting. It introduces a mathematical formulation for ion transport across cell membranes, based in thermodynamic principles. The author further shows that other, more common formulations, are special cases of the more general one introduced here. Finally, the author employs the introduced formulation to study the dynamics of SA pacemaker cells, and is able to explain the experimentally-observed double activation of calcium channels.

Overall, I have a good opinion of this paper and recommend its indexing. There are only a few minor points that should be addressed:

1. Page 3, first column, beginning of last paragraph: Eq. (10) is referred to before being introduced.

2. In my opinion, Eq. (8) is not self-evident, and its origin should be explained.

3. Same thing for Eq. (33).

4. The procedure to estimate the parameter values in Table 2 must be explained. Moreover, a parameter sensitivity analysis should be performed to assess the robustness of the obtained results.

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

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

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

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 03 Nov 2018

Marco Arieli Herrera-Valdez, Universidad Nacional Autonoma de Mexico, CDMX, Mexico

The answers to comments made by reviewers are written in italics after each comment.

Answers to comments from reviewer 2

Overall, I have a good opinion of this paper and recommend its indexing. There are only a few minor points that should be addressed:

1. Page 3, first column, beginning of last paragraph: Eq. (10) is referred to before being introduced.

Corrected the error in the cross reference.

2. In my opinion, Eq. (8) is not self-evident, and its origin should be explained.

Added a reference pointing to a Boltzmann distribution.

3. Same thing for Eq. (33).

Added a reference for the work of Willms et al., 1999.

4. The procedure to estimate the parameter values in Table 2 must be explained. Moreover, a parameter sensitivity analysis should be performed to assess the robustness of the obtained results.

The reviewer points to a very important issue. There are different publications and books addressing the robustness of conductance-based models (which are similar to the current one), from a dynamical systems perspective, using bifurcation theory. That being said, I agree that the parameter sensitivity analysis should be done for completeness, as this is a different model, but that analysis is beyond the scope of this paper. Nevertheless, parameter sensitivity analysis is addressed in a publication currently in preparation. In that publication, I address a few issues, including whether the gating formulas yield correct predictions in consideration of the work of Hodgkin and Huxley and the powers used for the fits on voltage clamps, and whether the relationships between parameters are correct, as a consequence of the modeling using those powers. It is worth mentioning that the parameters are in line with the experimentally measured magnitudes for cardiocytes and neurons, as those being modeled.

Competing Interests: No competing interests to declare.

Reviewer Report 01 October 2018

https://doi.org/10.5256/f1000research.17657.r38363

Kyle C.A. Wedgwood
Living Systems Institute, College of Engineering, Maths and Physical Sciences, Centre for Biomedical Modelling and Analysis, University of Exeter, Exeter, UK

Thank you for inviting me to review the article entitled "A thermodynamic description for physiological transmembrane transport". This article presents a unifying mathematical formulation for passive and active transport across plasma membranes. This is achieved by considering the energy required to achieve transport of the molecules. For active transport, in which molecules are transported against their concentration gradient, the required energy is positive. In contrast, passive movement down a concentration gradient does not require energy transfer. In previous modelling frameworks, active and passive transport have been described via distinct models for pumps and channels respectively. The major contribution of this paper is to combine these models into one formulation.

After presenting the initial mathematical formulation, the article proceeds to make comparisons with existing literature and demonstrates that earlier mathematical models of channels are special cases of the more general framework. The article ends with an example in which the full model can explain a double activation event of Ca^{2+} channels, which cannot be done so satisfactorily by existing models.

In general, the article is well-written, with arguments made concisely and coherently. Aside from a few points which require further clarification, I believe that this article is sufficiently rigorous and of interest to the community to warrant publication. In particular, channel and pump models have long been used in the mathematical study of excitability in cell membranes. These models have been used to support and guide experimental studies as well as advancing the applied mathematics field in its own right. As such, improvements to these models should be welcomed by the field.

I will now address specific issues with the article:

1. In general, I believe that the figure captions could do with expanding to guide the reader's eyes to the features of the plot that they should be focusing on.

2. p2, first paragraph: At present, the discussion of passive and active transport in the Introduction is a little confusing. In particular, there are transmembrane proteins that undergo conformational changes to transport molecules down their concentration gradient and channels that achieve this by effectively forming pores through the membrane (so that further conformational change is not needed to effect transport). Furthermore, the reference Blicher & Heimberg, 2013 reports on spontaneous (protein-free) formation of channels in synthetic membranes. Whilst this is an interesting topic, it should be made clearer how this relates to physiological membranes. Finally, it might also be useful to the reader to give an example of how some of the different pump configurations work (e.g. uniporter, symporter) to facilitate understanding of where energy transfer is required.

3. p2, 3rd paragraph: "Examples of fits to..." This is not a sentence. Please revise.

4. p2, 3rd paragraph: The author should highlight what "noncentral issues" they are referring to.

5. p2, 5th paragraph, minor: It would be useful to highlight that c_s, d_s \in {0,1}.

6. p2, Eq. (1): v is not defined.

7. p2, footnote, minor: Change "log" to "ln" here for consistency with Eq. (1) and (3).

8. p3, 2nd paragraph: It would be good to clarify in this first sentence the distinction between \Delta G and \Delta G_s (or avoid using the former entirely).

9. p3, 2nd paragraph: S = {Na,H} typo here.

10. p3, Eq. (5): Similarly to point (7), it is not clear what \Delta G represents here.

11. p3, Eq. (6): Terms in this equation need defining properly in several regards. Firstly, \Delta G_{ATP}^0 should be defined. Secondly, it should be made clear that concentrations are intracellular (as opposed to in Eq. (1) (3), which correspond to both extra- and intracellular compartments). This is particularly confusing for P_i in which the subscript could easily be misread as being an intracellular label. Finally, it is not clear how the equality \Delta GA_{TP} = qv_{ATP} holds. Perhaps, as in footnote (1), it could be made clear that this relies on the definition of the reversal potential for ATP.

12. p3, Eq. (6): I would also here like to take the opportunity to raise a point about the general framework. The models here account for the energy required to move molecules with and against their concentration gradients. In cases of active transport, as indicated by Eq. (10), ATP is then hydrolysed to meet the energy deficit required to power the pump. This then means that the concentration of ATP, relative to ADP is then changing. Indeed, at maximal rates of exercise, the ATP concentration in skeletal muscle can fall by up to 20% of its initial value. Moreover, in certain cell types, local ratios between ATP and ADP affect the opening and closing of ion channels (e.g. K_{ATP}). Eq. (10) implies that ATP and ADP in the cell are constant, in spite of the necessity that it must change. One must, therefore, conclude that an assumption is being made that ATP changes are small relative to the total amount of ATP. This assumption should be stated, or a discussion around how changes to ATP concentrations effect Eq. (10) should be made.

13. p3, final paragraph of first column: Wrong equation being referred to.

14. p3, Eq. (9): A physical interpretation for parameters r and b should be given. Additionally, and referring back to my previous comment (1), the text here discusses the relative magnitudes of r for electrodiffusive and active transport. Thus, this point should make clear that ion channels should be faster than both facilitated diffusion through carrier proteins and active transport via pumps.

15. p4, Eq. (11): For consistency with Eq. (5), 'Extra' in the subscripts should read 'Ext'. Also, it should be noted that v_{Extra} should be the v_{ATP} from Eq. (6).

16. p4, "In particular, for electrodiffusive (passive) transport of ions of type l": It is not clear what the author is referring to here (or how it is different from what is written in Eq. (15)).

17. p4, "The first, more complex form...": Does the author mean to reference Eq. (11) here?

18. p4, After Eq. (16), minor: "Ampere" needs capitalising.

19. p5, Table 1: Is v_0 here the same as in Eq. (15)? If so, the dependency on v_{Ext} seems to have disappeared.

20. p6, Fig. 2: What is plotted on the ordinate axis in this graph? It appears to have units of pA, but the text says that this is a plot of alpha/beta, which should be dimensionless.

21. p8, "Electrodiffusive transport": I'm not really sure what the point of this section is since the results presented here have mostly been mentioned previously in this manuscript.

22. p8, after Eq. (31): Is the N written here supposed to be N_l? Also, there is a typo after Eq. (31) (with -> where).

23. p9, Eq. (33): m is not defined.

24. p9, Eq. (35-39): Change symbol for current to i_x for consistency with previous equations.

25. p9, after Eq. (39): Presumably, the author here means that the intracellular Ca2+ concentration changes (rather than the extracellular). This should be clarified. Also, the text below Eq. (40) appears to imply a distinction between free and bound Ca^{2+}, but there is no buffering process described in the model, which may cause confusion.

26. p9, Fig. 2: Please state what i_m and i_{CaL13} are in these plots.

27. p10, Table 2: The units of \bar{a} are inconsistent with the main text.

28. p12, "Another possible use of the third order approximations is in the construction of network models.": Please could the author state what they mean here?

29. p13, discussion on action potential shape: I was wondering if the author could here compare their argument surrounding the shape of the action potential near initiation with those put forward here (Brette, 2013[1]), which puts forward a case for multi-compartment models to describe the sharpness of the spike.

30. SI1, after (A3): There appears to be a reference missing here.

31. SI2: Headers are required in these data files so that the values herein can be related to the physical quantities they represent.

32. It would be useful for the author to upload any code used to generate the plots in the article.

References

1. Brette R: Sharpness of spike initiation in neurons explained by compartmentalization.*PLoS*

Comput Biol. 2013; **9** (12): e1003338 PubMed Abstract | Publisher Full Text

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

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

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

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

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

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Nov 2018

Marco Arieli Herrera-Valdez, Universidad Nacional Autonoma de Mexico, CDMX, Mexico

The answers to comments made by reviewers are written in italics after each comment.

Answers to comments from Reviewer 1

Thank you for inviting me to review the article entitled "A thermodynamic description for physiological transmembrane transport". This article presents a unifying mathematical formulation for passive and active transport across plasma membranes. This is achieved by considering the energy required to achieve transport of the molecules. For active transport, in which molecules are transported against their concentration gradient, the required energy is positive. In contrast, passive movement down a concentration gradient does not require energy transfer. In previous modelling frameworks, active and passive transport have been described via distinct models for pumps and channels respectively. The major contribution of this paper is to combine these models into one formulation.
After presenting the initial mathematical formulation, the article proceeds to make comparisons with existing literature and demonstrates that earlier mathematical models of channels are special cases of the more general framework. The article ends with an example in which the full model can explain a double activation event of Ca2+ channels,

which cannot be done so satisfactorily by existing models.
In general, the article is well-written, with arguments made concisely and coherently. Aside from a few points which require further clarification, I believe that this article is sufficiently rigorous and of interest to the community to warrant publication. In particular, channel and pump models have long been used in the mathematical study of excitability in cell membranes. These models have been used to support and guide experimental studies as well as advancing the applied mathematics field in its own right. As such, improvements to these models should be welcomed by the field.
Thank you for your comments. They make the article clearer and better.. Please find answers to each of them below.

I will now address specific issues with the article:

1. In general, I believe that the figure captions could do with expanding to guide the reader's eyes to the features of the plot that they should be focusing on.

I have added phrases pointing to specific parts of the graphs or mentioning specific things to notice in each of the figures.

2. p2, first paragraph: At present, the discussion of passive and active transport in the Introduction is a little confusing. In particular, there are transmembrane proteins that undergo conformational changes to transport molecules down their concentration gradient and channels that achieve this by effectively forming pores through the membrane (so that further conformational change is not needed to effect transport). Furthermore, the reference Blicher & Heimberg, 2013 reports on spontaneous (protein-free) formation of channels in synthetic membranes. Whilst this is an interesting topic, it should be made clearer how this relates to physiological membranes. Finally, it might also be useful to the reader to give an example of how some of the different pump configurations work (e.g. uniporter, symporter) to facilitate understanding of where energy transfer is required.

The first paragraph in p2 has been rewritten taking into account the above observations.

3. p2, 3rd paragraph: "Examples of fits to..." This is not a sentence. Please revise.

Thank you, corrected.

4. p2, 3rd paragraph: The author should highlight what "noncentral issues" they are referring to.

Rewrote the paragraph for clarity and punctuality.

5. p2, 5th paragraph, minor: It would be useful to highlight that cs, ds \in {0,1}.

Highlighted

6. p2, Eq. (1): v is not defined.

Added definition

7. p2, footnote, minor: Change "log" to "ln" here for consistency with Eq. (1) and (3).

Changed log to ln

8. p3, 2nd paragraph: It would be good to clarify in this first sentence the distinction between \Delta G and \Delta G_s (or avoid using the former entirely).

Corrected.

9. p3, 2nd paragraph: S = {Na,H} typo here.

Corrected.

10. p3, Eq. (5): Similarly to point (7), it is not clear what \Delta G represents here.

Added a phrase to explain it.

11. p3, Eq. (6): Terms in this equation need defining properly in several regards. Firstly, \Delta GATP0 should be defined. Secondly, it should be made clear that concentrations are intracellular (as opposed to in Eq. (1) (3), which correspond to both extra- and intracellular compartments). This is particularly confusing for Pi in which the subscript could easily be misread as being an intracellular label. Finally, it is not clear how the equality \Delta GATP= qvATP holds. Perhaps, as in footnote (1), it could be made clear that this relies on the definition of the reversal potential for ATP.

Added square brackets and subindices to indicate that the intracellular concentrations of ADP, ATP, and Pi are intracellular. Also corrected a typo, there was an extra q in the term for ΔG_0

12. p3, Eq. (6): I would also here like to take the opportunity to raise a point about the general framework. The models here account for the energy required to move molecules with and against their concentration gradients. In cases of active transport, as indicated by Eq. (10), ATP is then hydrolysed to meet the energy deficit required to power the pump. This then means that the concentration of ATP, relative to ADP is then changing. Indeed, at maximal rates of exercise, the ATP concentration in skeletal muscle can fall by up to 20% of its initial value. Moreover, in certain cell types, local ratios between ATP and ADP affect the opening and closing of ion channels (e.g. KATP). Eq. (10) implies that ATP and ADP in the cell are constant, in spite of the necessity that it must change. One must, therefore, conclude that an assumption is being made that ATP changes are small relative to the total amount of ATP. This assumption should be stated, or a discussion around how changes to ATP concentrations effect Eq. (10) should be made.

Added a comment about the assumptions and a comment about the possibility of changes in concentration for ATP, ADP, and Pi

13. p3, final paragraph of first column: Wrong equation being referred to.

Corrected cross reference

14. p3, Eq. (9): A physical interpretation for parameters r and b should be given. Additionally, and referring back to my previous comment (1), the text here discusses the relative magnitudes of r for electrodiffusive and active transport. Thus, this point should make clear that ion channels should be faster than both facilitated diffusion through carrier proteins and active transport via pumps.

Added clarification and phrases providing interpretation for the two parameters.

15. p4, Eq. (11): For consistency with Eq. (5), 'Extra' in the subscripts should read 'Ext'. Also, it should be noted that vExtra should be the vATP from Eq. (6).

Added clarification and deleted the "ra" in the extra suffix.

16. p4, "In particular, for electrodiffusive (passive) transport of ions of type l": It is not clear what the author is referring to here (or how it is different from what is written in Eq. (15)).

Rephrased the sentence for correction.

17. p4, "The first, more complex form...": Does the author mean to reference Eq. (11) here?

Moved the sentence up to the paragraph with Eq. (11) and added the cross reference

18. p4, After Eq. (16), minor: "Ampere" needs capitalising.

Corrected

19. p5, Table 1: Is v0 here the same as in Eq. (15)? If so, the dependency on vExt seems to have disappeared.

vExt is not written in those cases where it is zero.

20. p6, Fig. 2: What is plotted on the ordinate axis in this graph? It appears to have units of pA, but the text says that this is a plot of alpha/beta, which should be dimensionless.

Corrected text.

21. p8, "Electrodiffusive transport": I'm not really sure what the point of this section is since the results presented here have mostly been mentioned previously in this manuscript.

Added sentences making the point more explicit and took away the sentence in previous paragraphs where the single ion energy was discussed to avoid repetition.

22. p8, after Eq. (31): Is the N written here supposed to be N_l? Also, there is a typo after Eq.

(31) (with -> where).

Changed N for M to avoid confusion.

23. p9, Eq. (33): m is not defined.

Changed the order in which equations are presented and rephrased so that variables and parameters are better explained

24. p9, Eq. (35-39): Change symbol for current to ix for consistency with previous equations.

The currents in equations 35-39 are normalized by the membrane capacitance. Therefore, to avoid abuse of notation, added a note remarking the change in the letter for the functions, explaining it is due to normalization.

25. p9, after Eq. (39): Presumably, the author here means that the intracellular Ca2+ concentration changes (rather than the extracellular). This should be clarified. Also, the text below Eq. (40) appears to imply a distinction between free and bound Ca2+, but there is no buffering process described in the model, which may cause confusion.

Added sentences to clarify these points.

26. p9, Fig. 2: Please state what im and iCaL13 are in these plots.im represents the total current.

Added a sentence to the figure caption.

27. p10, Table 2: The units of \bar{a} are inconsistent with the main text.

Corrected by deleting the bars in the table for normalized amplitude entries. \bar{a} is in pA, a = \bar{a}/Cm in pA/pF

28. p12, "Another possible use of the third order approximations is in the construction of network models.": Please could the author state what they mean here?

Expanded the sentence to clarify the point. The idea is to use cubic approximations to build network models taking advantage of the possible reduction in computational cost. However, as is explained in the paragraph, cubic approximations need to be tested first to address possible issues that may arise from using approximations.

29. p13, discussion on action potential shape: I was wondering if the author could here compare their argument surrounding the shape of the action potential near initiation with those put forward here (Brette, 20131), which puts forward a case for multi-compartment models to describe the sharpness of the spike.Added a comment about the results in the paper by Brette, 2013.

Thank you for pointing it out. Added a reference to his work too.

30. SI1, after (A3): There appears to be a reference missing here.

Edited the reference, it is for Equation 31.

31. SI2: Headers are required in these data files so that the values herein can be related to the physical quantities they represent.

Edited data files to include headers.

32. It would be useful for the author to upload any code used to generate the plots in the article.

Uploaded the code in an jupyter notebook.

Competing Interests: The author declares no competing interests.