

Minimal Models of Bursting Neurons: How Multiple Currents, Conductances, and Timescales Affect Bifurcation Diagrams*

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Abstract. After reviewing the Hodgkin–Huxley ionic current formulation, we introduce a three-variable generic model of a single-compartment neuron comprising a two-dimensional fast subsystem and a very slow recovery variable. We study the effects of fast and slow currents on the existence and stability of equilibria and periodic orbits for the fast subsystem, presenting a classification of currents and developing graphical tools that aid in the analysis and construction of models with specified properties. We draw on these to propose a minimal model of a bursting neuron, identifying biophysical parameters that can shape and regulate key characteristics of the membrane voltage pattern: bursting frequency, duty cycle, spike rate, and the number of action potentials per burst. We present additional examples from the literature for comparison and illustration, and in a companion paper [*SIAM J. Appl. Dyn. Syst.*, 3 (2004), pp. 671–700], we construct a model of an insect central pattern generator using these methods.

Key words. bursting neurons, motoneurons, fast-slow systems, bifurcation, stability

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1. Introduction. In this and a companion paper [1] we develop and analyze a generic model of a bursting neuron and assemble a set of such models, suitably adapted to interneurons and motoneurons, to model a central pattern generator (CPG) for insect locomotion. We have two main goals: to integrate and extend a body of work, largely in theoretical and mathematical neuroscience, that enables (semi-) analytical studies of bursting neurons, while maintaining sufficient biophysical detail for comparisons with experimental data; and to use this to derive a model of a CPG that reveals how key locomotive properties may be determined by individual neurons and the network as a whole. In this first paper we show how complex models can be reduced and develop the analytical methods; in [1] we construct the CPG model.

The first dynamical neural model based on biophysical data was due to Hodgkin and Huxley [2], and their description of the action potential (AP) and ionic currents in the giant axon of the squid has been vastly extended and generalized in the half century since. Detailed axonal and dendritic geometry can be included, for example, at the unicellular level. However,

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behaviors even as simple as scratching or breathing require *networks* of neurons, and the resulting firing patterns depend on three levels of activity: intracellular, synaptic, and network. Models ignoring any of these levels risk oversimplification [3], perhaps especially in invertebrates, in which relatively few neurons may be responsible for such diverse behaviors as searching, walking, and running [4, 5]. The wealth of neurophysiological data collected since Hodgkin and Huxley’s paper has led to rather complicated models (e.g., [6, 7, 8]), some multicompartmental and including seven or more ionic currents, that require on the order of ten ODEs and fifty parameters per cell. These models are specific to particular animals and even to in vitro preparations and, not being amenable to analytical comparative studies, do not readily reveal general principles. In this paper and [1] we seek a balance between such complexity and simpler phenomenological models employing phase oscillators [9, 10] or connectionist circuits [11] that have been used to study network connectivity effects.

Bursting oscillations have been widely studied, mostly at the single-cell level, e.g., [12, 13, 14, 15, 16, 17]; general classifications have been proposed [18, 19, 20, 21, 22], and polynomial reductions have been developed and thoroughly analyzed [23, 24, 25]. Some network studies have also recently been done [17, 26]. When limited experimental data is available, as in [17] and the CPG model of [1], generic models and broad parameter variations can still lead to testable hypotheses and provide motivation to verify novel predictions [27]. However, while asymptotic reductions and polynomial approximations aid mathematical analyses, they often obscure biophysical effects that must be retained if one is to understand how internal components and architecture, as well as proprioceptive sensing and commands from higher centers, can influence a network [28].

Single-current effects on individual cells are qualitatively understood, but collective influences have not been fully explored. We therefore devote this first paper to analyzing how multiple (fast and slow) currents conspire to affect the location and stability of equilibria and limit cycles, with a view to determining how biophysical parameters can effect changes in behavioral variables such as spike rate, bursting frequency, duty cycle, and number of APs per burst. Our methods identify currents which are unessential to the bursting mechanism, suggest dimensional reductions, and provide guidelines for “designing” bursters with desired behaviors when intracellular biophysical data is lacking. Thus, while they are used in [1] to model an insect CPG, these methods offer a more general set of tools for studying the neural basis of rhythmogenesis. Indeed, comparisons with several existing models are noted in passing, and a specific example is given in section 4.3. In developing these tools, we have profited from many earlier studies, including those of Rose and Hindmarsh [29, 14, 16] (on $I-v$ steady state curves) and of FitzHugh [30] and Rose and Hindmarsh [14, 31] (on combining gating variables). Here we treat only third order models with one very slow recovery variable; we note that Smolen, Terman, and Rinzel [32] considered two slow variables. Specific references to these and other relevant papers and models will be made in the course of the paper.

This paper is organized as follows. After reviewing basic ideas of single-compartment ion-channel models and noting the role of disparate timescales in section 2, we describe a three-variable generic model of a bursting neuron in section 3. We identify and analyze the effects of individual current and conductance parameters on branches of equilibria and periodic orbits and their bifurcations, and then in section 4 we lay out a “minimal” model for a bursting neuron, of sufficient flexibility to represent both interneurons and motoneurons

in the CPG application of [1]. We identify biophysical parameters that shape the bursting pattern and hence will determine key behavioral characteristics, and we illustrate further by showing how an example (the Sherman–Rinzel–Keizer (SRK) model [13]) can be modified to produce different behaviors. We summarize in section 5.

2. Ion-channel models. Bursting, the clustering of spikes followed by a refractory period of relative quiescence, can vary substantially in form and function [22, 33, 21]. The mechanism can be described qualitatively as the interaction of two subsystems dynamically separated by their intrinsic time scales: a faster one, typically governed by sodium and potassium channels, which can either be at rest or exhibit (periodic) oscillations, and a slow subsystem driving the first through its quiescent and oscillatory states in a quasi-static manner [34, 35]. The slower mechanism can be attributed to the accumulation of intracellular calcium ions (referred to as calcium dynamics [33]) or to other slow voltage-dependent processes (e.g., [17]). In many cases, bursting models can therefore be framed as singularly perturbed systems [36]:

$$(2.1a) \quad \dot{\mathbf{u}} = \mathbf{f}(\mathbf{u}, c),$$

$$(2.1b) \quad \dot{c} = \delta g(\mathbf{u}, c),$$

where the vector $\mathbf{u} = [v, \mathbf{w}] \in \mathbb{R}^{N+1}$, v denotes the cell membrane voltage, $\mathbf{w} = [w_1, \dots, w_N]^T$ represents a collection of N gating variables w_i to be explained below, and $\delta \ll 1$ is a small parameter. The variable c may represent calcium concentration or, more generally, any (very) slowly varying quantity responsible for bursting.

The subset of *fast* equations (2.1a) generally takes the Hodgkin–Huxley (HH) form [2] and can be written as follows [37]:

$$(2.2a) \quad C\dot{v} = -I_{\text{ion}}(v, w_1, \dots, w_n, c) + I_{\text{ext}}(t),$$

$$(2.2b) \quad \dot{w}_i = \epsilon_i \frac{w_{i\infty}(v) - w_i}{\tau_i(v)}, \quad i = 1, \dots, N.$$

The first equation (2.2a) describes the voltage dynamics, with C denoting the cell membrane capacitance, I_{ion} transmembrane ionic currents, and $I_{\text{ext}}(t)$ exogenous input currents, including synaptic and external inputs. Equations (2.2b) describe the first order kinetics of variables w_i that gate the ionic currents (see below), with ϵ_i a positive temperature-like parameter (not necessarily small). At steady state, gating variables approach voltage-dependent limits $w_{i\infty}(v)$, usually described by sigmoidal functions:

$$(2.3) \quad w_{i\infty}(v; k_{i0}, v_{i_{th}}) = \frac{1}{1 + e^{-k_{i0}(v - v_{i_{th}})}},$$

where k_{i0} determines the steepness of the transition occurring at a threshold potential $v_{i_{th}}$. Gating variables can be either *activating* ($k_{i0} > 0$), with $w_{i\infty} \approx 1$ for depolarized voltages $v > v_{i_{th}}$ and $w_{i\infty} \approx 0$ for hyperpolarized levels $v < v_{i_{th}}$, or *inactivating* ($k_{i0} < 0$), with $w_{i\infty} \approx 1$ when hyperpolarized and $w_{i\infty} \approx 0$ when depolarized.¹ The voltage-dependent “time constant” τ_i is generally described by

$$(2.4) \quad \tau_i(v; k_{i0}, v_{i_{th}}) = \text{sech}(k_{i0}(v - v_{i_{th}})),$$

¹It is sometimes useful to retain $k_{i0} > 0$ in (2.3) and express inactivation via $1 - w_i$.

and, as implied in (2.3)–(2.4), the constants k_{i_0}, v_{ith} determining w_{i_∞} and τ_i are often taken to be the same for a given ion channel [38].

The term I_{ion} in (2.2a) is the sum of all ionic currents I_α . Ions move across the membrane via channels which are permeable to specific species (possibly more than one per channel), and they can be thought of as being in either of two states: open or closed. The total conductance associated with a given (sufficiently large) population of channels can be expressed as the (constant) maximal conductance $\bar{g}_\alpha$ for all channels open, multiplied by the fraction of open channels. Thus, each ionic current can generally be described as Ohmic and written in the form

$$(2.5) \quad I_\alpha(v, \mathbf{w}, c) = \bar{g}_\alpha \cdot \gamma_\alpha(v, w_1, \dots, w_N, c) \cdot (v - E_\alpha);$$

more complicated “rectifying” conductances, such as those expressed by the Goldman–Hodgkin–Katz formula [39] can also be represented in this manner. Here E_α is the (Nernstian) reversal potential, α denotes the ion type, typically $\alpha \in \{\text{Na}, \text{K}, \text{Ca}, \text{Cl}, \text{L}\}$, L denoting the leakage current, and $\gamma_\alpha(v, \mathbf{w}, c)$ is a voltage-, gate-, and possibly c -dependent conductance factor for channels selective to ion α . To describe this dependence, Hodgkin and Huxley [2] introduced fictive gating particles and represented γ_α with one or two² activating and inactivating gating variables $w_i, w_j \in [0, 1]$, raised to integral powers a and b :

$$(2.6) \quad \gamma_\alpha(v, \mathbf{w}, c) = \zeta(v) \xi(c) w_i^a w_j^b.$$

The exponents a, b can be thought of as representing the number of subunits within a single channel necessary to open it; see Figure 1b. Probabilistic models based on this approach closely reproduce experimental data for large channel numbers [41].

A first possible simplification is to restrict the exponents a, b in (2.6) to unity. A rigorous approach would require a change of variable $z = w_i^a$, etc., as in [14], but two observations are pertinent. (i) Some models do have currents with exponent 1: e.g., Morris and Lécar [38] and extensions thereof to bursting models [37], I_T in Plant [42], I_K in Sherman, Rinzel, and Keizer [13], I_K in Keizer and Smolen [43], and $I_{K(M)}, I_{K(C)}, I_{K(AHP)}$ in [39, pp. 200–203]. (ii) More importantly, this restriction is not as severe as it may seem; for the steady state expression (2.3) at least, one can show that $w_\infty^a(v; k_0, v_{th})$ can be approximated by another sigmoidal function raised to the power 1 but with different coefficients $\bar{w}_\infty(v; \bar{k}_0, \bar{v}_{th})$. Taylor-expanding w_0^a , we can locally match the two functions to first order via the parameters $\bar{k}_0, \bar{v}_{th}$, and we have checked that for sigmoidal functions the pointwise match is acceptable, with maximum error of around 5% on the whole real line (results not shown).

In spite of the variety of ions and gating mechanisms, conductances come in two forms [44, 3]: persistent and transitory (see Figure 1). The names refer to steady state properties of w_{i_∞} : persistent activating or inactivating conductances being active, respectively, above or below a threshold, and transitory conductances being active only in a “window” of voltages. The former are described by a single gating variable, whereas a combination of activating and inactivating gating variables is used for transitory conductances. We will comment further on the functions $\zeta(v)$ and $\xi(c)$ in (2.6), but we anticipate that they can capture rectifying properties as described by the Goldman–Hodgkin–Katz equation [39], or “mixed” conductances, to be defined subsequently.

²An exception with three gating variables appeared in the model of Beeler and Reuter [40].

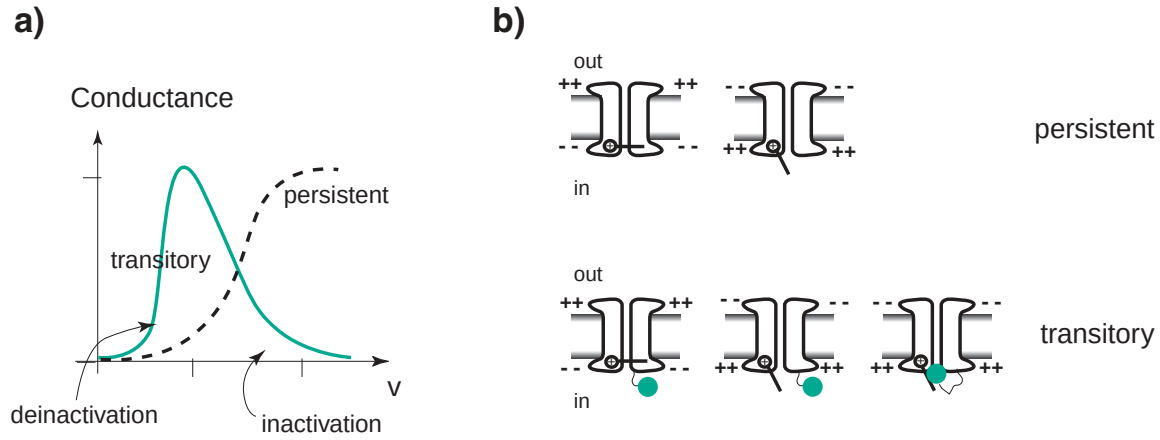


Figure 1. Conductances in the HH formalism. (a) Qualitative dependence of persistent (dashed) and transitory conductances (solid). (b) Caricature of mechanisms underlying the opening and closure of the channels, with voltage increases to the right. Persistent conductances are represented by a voltage-dependent gating variable which continually opens the channel, allowing ionic transport; transitory conductances have an additional secondary mechanism that blocks the channel at voltages above the active range.

We note that the coupling in (2.2) occurs only in the first equation (2.2a); gating variables are not directly coupled. This structure enables simplified analyses, as we now indicate (cf. [16]). A neuron may possess a dozen distinct ion channels [3], but if qualitative or semi-quantitative characteristics are adequate, a reduced model having fewer variables may suffice [30, 37]. If some ionic timescales τ_j in (2.2b) are significantly faster than others, we may (formally) set the corresponding gating variables at their equilibrium values $w_j = w_{j\infty}(v)$. Likewise, functionally related variables with similar timescales may be lumped together (cf. [37]), and this is not atypical; see the comment below on hypothesis H1. Those variables whose channel dynamics have been equilibrated will henceforth be denoted by $n_i(v) = n_{i\infty}(v)$; the (slower) gating variables w_j whose evolution equations are retained will be denoted by m_j . In general several such variables may be retained, but we shall henceforth restrict our attention to the case of a single slow variable, m , noting that in some cases this might represent a combination of two or more gating variables that move in step; see [30, 33] and the Rose–Hindmarsh model [14] in Appendix A.

The above reduction process, which was pioneered in FitzHugh’s polynomial reduction of the HH model [30] (cf. [23, 14, 24]) and may be justified via geometric singular perturbation theory [36], considerably simplifies analyses but at the expense of obscuring some of the biophysics. We will therefore develop a three-dimensional model in this spirit but retaining the link to biophysical parameters. Pernarowski [24] and more recently De Vries [25] have amply demonstrated the richness and relevance of three-dimensional models in describing several distinct bursting behaviors.

3. A third order model. Most neurons have many more membrane conductances than the two measured by Hodgkin and Huxley (e.g., Connor and Stevens [45], Plant [42], Chay and Keizer [12], McCormick and Huguenard [46]); one or two sodium conductances, two or

three different types of calcium conductances, and many different potassium conductances are common [39]. In this section we will develop a framework to analyze the collective contributions of single ionic currents, with the goal of showing how biophysical parameters influence the existence and stability of equilibria and periodic orbits in the fast subsystem (2.2), and hence illuminating the global dynamics of the coupled fast-slow system (2.1).

We consider a class of models characterized by the following hypotheses:

H1. Existence of a single relatively slow (nonequilibrated) variable m in the fast subsystem.

H2. Multiplicative dependence of conductances on gating variables, voltage, and the very slow variable c : $\gamma(v, \mathbf{w}, c) = \zeta(v) \xi(c) \prod_i \sigma_{\alpha_i}(w_i)$.

The first hypothesis could be rephrased as “homogeneous dependence on one slow variable.” In fact m may describe more than one channel, pairs of the form $\bar{g}_{\alpha_1} \sigma_{\alpha_1}(m) \zeta_{\alpha_1}(v)(v - E_{\alpha_1}) + \bar{g}_{\alpha_2} \sigma_{\alpha_2}(m) \zeta_{\alpha_2}(v)(v - E_{\alpha_2})$ being allowed. This is not as atypical as it may seem; see, e.g., the reduced models of Rose and Hindmarsh [14] (Appendix A) and Butera, Rinzel, and Smith [17] (Appendix C). The first hypothesis also implies that reduction to a three-dimensional system is possible (cf. [23, 22, 37, 25, 24] and references therein), and it allows for a wealth of different behaviors [35]. The second hypothesis formalizes a common assumption which holds for all models of which we are aware.

Under these hypotheses, we can formulate a rather general model. We will not commit to a particular choice of ionic currents until later, when we will be able to justify our choices for a “minimal” model. The principle channels allow the passage of four ions: sodium, potassium, chloride (or sometimes generic leakage ions), and calcium [3]. They are often highly selective, each admitting only one ionic specie. Calling the *relatively* slow gating variable m and using the above four ions, we can express the model as

$$(3.1a) \quad C\dot{v} = - \sum_i I_{\alpha_i} + I_{\text{ext}},$$

$$(3.1b) \quad \dot{m} = \frac{\epsilon}{\tau_m(v)} [m_{\infty}(v) - m],$$

$$(3.1c) \quad \dot{c} = \frac{\delta}{\tau_c(v)} [c_{\infty}(v) - c],$$

where $\delta \ll \epsilon \ll 1/C = \mathcal{O}(1)$ and the single currents $I_{\alpha}(v, \mathbf{w}, c)$ are each of the type (2.6) and $\alpha \in \{\text{Na}, \text{K}, \text{Ca}, \text{Cl}, \text{L}, \text{KCa}\}$.³ As noted by Rinzel and Ermentrout [37], there are several mechanisms which could provide the slow negative feedback required for bursting, in which c cycles periodically, causing transitions between fixed points and limit cycles in the fast (v, m) subsystem (see also [43]). For simplicity, we choose a very slow persistent potassium current (essentially the I_{KS} of Butera, Rinzel, and Smith [17]; see Model 2 in Appendix C and cf. [14, 17, 32]), but the results adapt to other mechanisms as shown in the example of section 4.3.

Given that the remaining gating variable m is slow relative to the voltage (spike) timescale, while c evolves yet more slowly, (3.1) has three time scales: the “fast” gating variables implicit in I_{α} , with $w_i = n_i(v)$ where appropriate, evolve on scales of order 1, the slower variable m

³In the following an additional subscript $()_f$ or $()_s$ will be added, e.g., K_f or K_s , to distinguish between fast and slow currents specific to a particular ion (here K).

evolves on a scale of order ϵ , and the very slow c dynamics has order δ . Such singularly perturbed systems have the appeal that the dynamic evolution can be separated according to the disparate time scales [36]. In the present case, currents can be divided into three groups: fast, instantaneously equilibrated currents, dynamic currents that evolve on the time scale of interest, and very slow variables that may be regarded as pseudostationary. The resulting simplification provides insight into the influence of single currents as part of a larger group.

3.1. The fast subsystem. We first analyze the fast subsystem (3.1a)–(3.1b). Since it varies very slowly, c will initially be treated as fixed, its dynamical effects being addressed subsequently. Hypothesis H1 implies that we can group the fast variables in (3.1a), write them as $I_{fv}(v)$, and separate them from the slow current of the form $I_s(v, m) = \sigma_{sm}(m)I_{sv}(v)$ (see, e.g., the Rose–Hindmarsh and Butera–Rinzel–Smith models [14, 17] given in Appendices A and C). This factorization is always possible for a single slow current by hypothesis H2 and extends to two (or more) provided that $\sigma_{\alpha_1}(w) = \sigma_{\alpha_2}(w)$; cf. [14] and Appendix A. Thus we can write (3.1a)–(3.1b) more explicitly as

$$(3.2a) \quad C\dot{v} = -[I_{fv}(v) + \sigma_{sm}(m)I_{sv}(v)] + I_{\text{ext}},$$

$$(3.2b) \quad \dot{m} = \frac{\epsilon}{\tau_m(v)}[m_\infty(v) - m].$$

In (3.2a) the subscripts sm and sv reflect functional dependence on the (slow) gating variable m and voltage v ; note that the former enters only via $\sigma_{sm}(m)$. The voltage-dependent fast and slow currents I_{fv} and I_{sv} are given by

$$(3.3) \quad I_{fv}(v) = \sum_i \bar{g}_{\alpha_i} \sigma_i(n_i(v)) \cdot \zeta_i(v)(v - E_{\alpha_i}),$$

$$(3.4) \quad I_{sv}(v) = \bar{g}_{\alpha_s} \zeta_s(v)(v - E_{\alpha_s}).$$

As argued in section 2, the slow current gating variable enters (3.2a) as

$$(3.5) \quad \sigma_P(m) = m \quad \text{or} \quad \sigma_T(m) = m(1 - m).$$

We will call these cases *dynamically* persistent and *dynamically* transient, respectively, adding the term “dynamically” because persistent and transitory usually refer to steady state properties (cf. Figure 1); we are concerned here with currents whose dynamical dependence on the slow gating variable w makes them *appear* persistent or transitory.

The functions $\zeta_i(v)$ can often be assumed constant, but in some cases this does not suffice. A common counterexample is a transitory conductance with one gating variable significantly faster than the other, e.g., a fast activating and slowly inactivating sodium current $I_{\text{NaP-h}}$ [17] (Model 1 in Appendix C). In this case, setting the fast n_i at steady state, the conductance can be expressed in the form (3.4), with $\zeta(v) = n_{1\infty}(v)$. Such currents should properly be called “mixed,” since they are dynamically persistent, having the form $\sigma_{sm}I_{sv}$ in (3.2a), but appear transitory at steady state, due to the product of two gating variables.

3.1.1. Fixed points: One current. We now analyze the effect of the ionic currents in (3.2) on the location of fixed points of the fast subsystem. We begin with single currents.

We start by noting that separation into fast and slow currents (cf. (3.2)) has no influence on the location and number of fixed points because at such points all gating variables and currents are in equilibrium and can be expressed in terms of the voltage-dependent functions $n_{i\infty}(v)$ and $m_{\infty}(v)$.⁴ The fixed points are therefore completely determined by the zeros of the right-hand side of (3.2a), called the $I_{ss} - v$ curve, sometimes written $I(v)$; this is the function measured in a voltage-clamp experiment. Moreover, we need only consider the case $\zeta(v) = 1$. Indeed, when this does not hold, the results are similar to the transitory current case, because the nonlinearity in $\zeta(v)$ acts as an additional linear or exponential multiplicative term, which does not change the qualitative form of $I(v)$.

Generic currents are described by

$$(3.6) \quad I(v) = \bar{g} \cdot \sigma(v; k_0, v_{th}) \cdot (v - E)$$

and depend upon four parameters: $\bar{g}$, k_0 , v_{th} , and E . Figure 2 shows typical examples of the dependence on these. In [47] we show how all known currents fall into one of the four classes above. Here σ is of either form in (3.5), and the gating variable w is set to equilibrium, i.e., $w = w_{\infty}(v)$ (cf. (2.3)). We note the following.

The *maximal conductance* $\bar{g}$ acts as a scaling factor, affecting the values of critical points and their locations.

The *Nernst potential* E fixes the unique value of voltage $v = E$ for which the current vanishes.

For transitory conductances, the current asymptotically approaches zero as $v \rightarrow \pm\infty$, but only as $v \rightarrow -\infty$ for persistent conductances. E also affects locations and values of the extrema.

The *threshold voltage* v_{th} affects locations and values of extrema. For transitory conductances they approximately coincide with the voltage that globally minimizes (maximizes) the current for $v_{th} < E$ ($v_{th} > E$). When $v_{th} > E$, the current is “essentially” monotonically increasing for physiological values of k_0 . For persistent currents, the relative location of the threshold voltage v_{th} with respect to the reversal potential E can substantially influence the shape of $I(v)$. When $v_{th} < E$ (subreversal threshold), I has a distinct shape with a pronounced minimum (Figure 2a), e.g., I_{Na} in the HH equations [2]. If $v_{th} > E$ (superreversal threshold), the minimum is negligible, e.g., the potassium current I_K in the HH equations [2] (Figures 2c, d).

The *slope* k_0 determines the extent of the transition region from the inactive state $I \approx 0$ to the active state. For very small values of k_0 , the currents tend to be linear over a wide range. In the limit $k_0 \rightarrow \infty$ the currents approach piecewise linear functions, and transitory currents are nonzero over only a very narrow range.

The substantial dips evident in Figures 2a, b are of particular importance in practice, since they imply regions of negative resistance characteristic (NRC) in the steady state $I_{ss} - v$ curves. As recognized experimentally by Wilson and Wachtel [48] in 1974, this is a necessary condition for bursting. We may anticipate that it is also necessary for Hopf (H) bifurcations. It is appreciable only when the threshold voltage is less than the Nernst potential, i.e., $v_{th} < E$. Since persistent currents play an important role, we conclude by noting that in the subreversal case and for slopes higher than a critical value $k_0 > k_{cr} = \frac{2}{E - v_{th}}$ that is usually exceeded in

⁴For clarity, we drop the subscript α but recall that each current comes with its own set of four parameters.

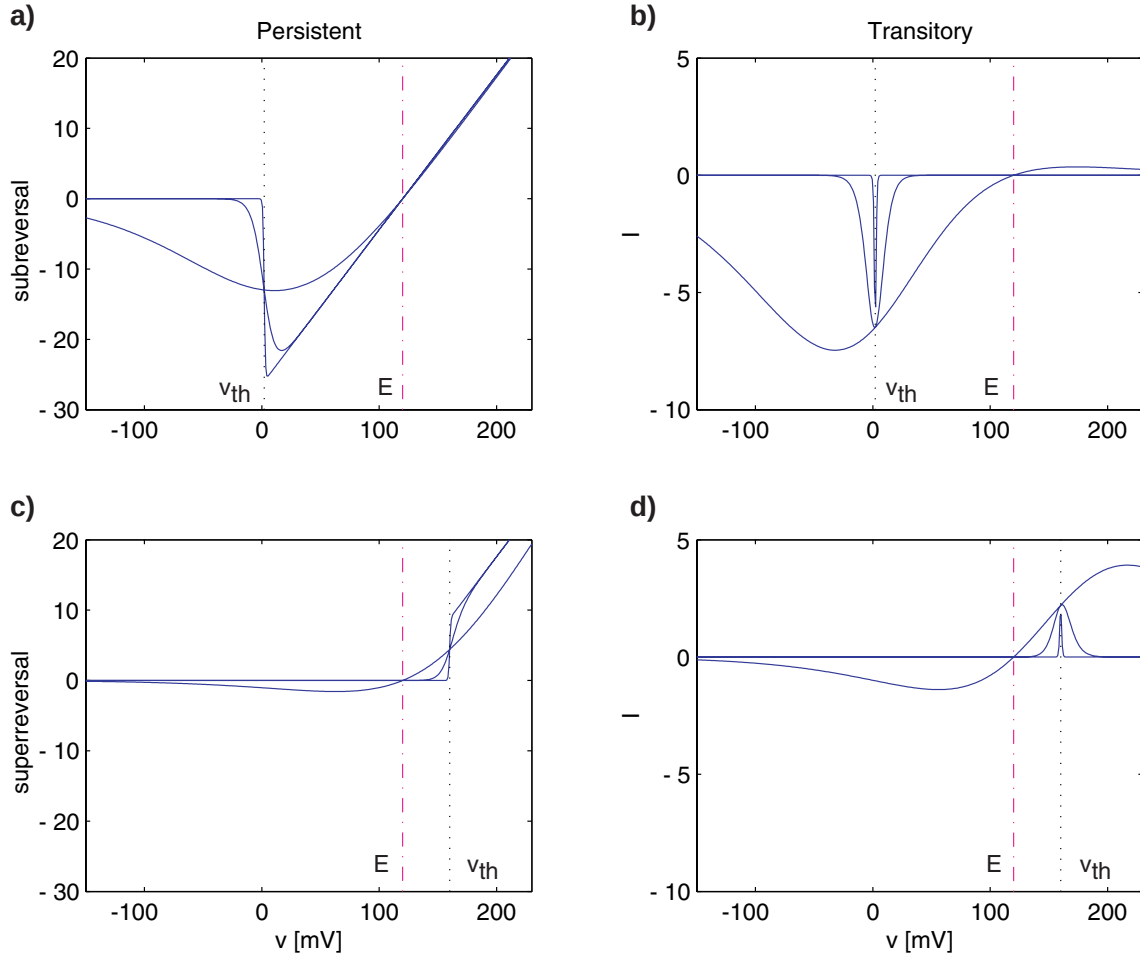


Figure 2. Persistent (left) and transitory (right) ionic currents for different values of the slope parameter $k_0 = 0.02, 0.2$, and 2 (a typical value is 0.1 , e.g., [2, 38]). We illustrate with a calcium current of the form (3.6), with maximal conductance $\bar{g}_{Ca} = 4.4 \text{ mS/cm}^2$ and reversal potential $E_{Ca} = 120 \text{ mV}$ and show the $I_{ss} - v$ curves (3.6) for the two conductance cases of (3.5). Dotted and dash-dotted vertical lines show the threshold voltage v_{th} and reversal potential E . (a) Persistent subreversal $v_{th} = 0 \text{ mV} < E$. (b) Transitory subreversal. (c) Persistent superreversal $v_{th} = 160 \text{ mV} > E$. (d) Transitory superreversal. Note that transitory currents typically exhibit smaller ranges than persistent currents ($\approx 20\%$; note differing scales on ordinate I).

physiological ranges, the minimum is bounded below by $I_{\min} \geq \bar{g} \cdot (v_{th} - E)$. Finally, we note that *passive conductances* or passive currents, like the leakage $I_L = g_L \cdot (v - E_L)$ can be described as a degenerate subclass of persistent currents with zero slope: $k_0 = 0$.

The current I_{ext} enters (3.2a) as a purely additive term, so for any voltage $v = \bar{v}$, one can find a current I such that the fixed point is at $\bar{v}$. Hence only the general shape of the $I_{ss} - v$ curve is relevant in determining the possible number of fixed points. We may therefore conclude that *existence of an NRC “dip” can introduce up to two new fixed points.*

3.1.2. Fixed points: Multiple currents.

Linear or passive currents. In the absence of leakage or other linear currents, the existence of at least one fixed point, typically at low voltage values, is no longer guaranteed. Apart from this, passive currents (with positive conductance) cannot generate, but only destroy, fixed points (see discussion below).

Nonlinear currents. As described above, the most relevant feature is the creation of local minima in the $I_{ss} - v$ curve, but if $v_{th} > E$, the resulting dips are negligibly small (Figures 2c, d). We will therefore consider the subreversal case $v_{th} < E$. For simplicity we discuss only persistent currents, but one can also give bounds for transitory ones. For equilibrated gating variables $w = n_\infty(v)$ of the form (2.3) the persistent currents and their (voltage) derivatives are

$$\begin{aligned} I_P &= \bar{g} \cdot n_\infty \cdot (v - E), \\ I'_P &= \bar{g} \cdot n_\infty \cdot [k_0(1 - n_\infty)(v - E) + 1], \\ I''_P &= \bar{g}k_0 \cdot n_\infty \cdot (1 - n_\infty) [k_0(1 - 2n_\infty)(v - E) + 2]; \end{aligned} \quad (3.7)$$

hence the minimum occurs at

$$I_{P_{\min}} = \bar{g} \left(\bar{v} - E + \frac{1}{k_0} \right), \quad (3.8)$$

where $\bar{v}$ is implicitly defined by $(1 - n_\infty(\bar{v}))(\bar{v} - E) = -\frac{1}{k_0}$. The addition of a current can destroy the local “dip” of a pre-existing current. A sufficient condition for this is that the derivative of the new current be larger in magnitude than the pre-existing one; if the added current always increases more than the other decreases, no local minimum survives. It is therefore useful to estimate the maximum slope of I_P , which is obtained at its inflexion point to the left of E :

$$I'_{P_{\min}} = \frac{\bar{g}}{4} [k_0(\tilde{v} - E) + 2]. \quad (3.9)$$

Here the voltage $\tilde{v}$ is implicitly defined by $(1 - 2n_\infty(\tilde{v}))(\tilde{v} - E) = -\frac{2}{k_0}$. As anticipated, $I_{P_{\min}}$ is bounded below by $\bar{g}(v_{th} - E)$, achieved in the limit $k_0 \rightarrow +\infty$. In the same limit, the minimum derivative is unbounded and tends to $-\infty$. Therefore, any nonlinear current can create up to two new fixed points.

One can show this in general; in particular, consider the limit of high thresholds $k_{0_i} \rightarrow \infty$ for all i , and let the individual voltages be ordered as $v_{th_1} < E_1 < v_{th_2} < E_2 < \dots < v_{th_N} < E_N$. In this limit one can define “influence windows” $U_i = [v_{th_i}, E_i]$ such that $n_j(v) \approx 0$ or 1 for all $j \neq i$; i.e., in the i th window only the current I_{α_i} is “turning on or off”; the others are all inactive or fully active. Suppose further that $I_j = I_{P_j} = \bar{g}_{\alpha_j} n_j(v) (v - E_{\alpha_j})$ is persistent. Then, it follows that the total current and its derivative are

$$I = \sum_{i \neq j} \bar{g}_{\alpha_i} (v - E_{\alpha_i}) + I_{P_j} \quad \text{and} \quad I' = \sum_{i \neq j} \bar{g}_{\alpha_i} + I'_{P_j}. \quad (3.10)$$

(In (3.10) we set $\bar{g}_{\alpha_i} = 0$ for inactive currents.) From (3.9), I'_{P_j} can be arbitrarily large and negative, and analogous arguments hold for transitory currents. We note that, for increasing

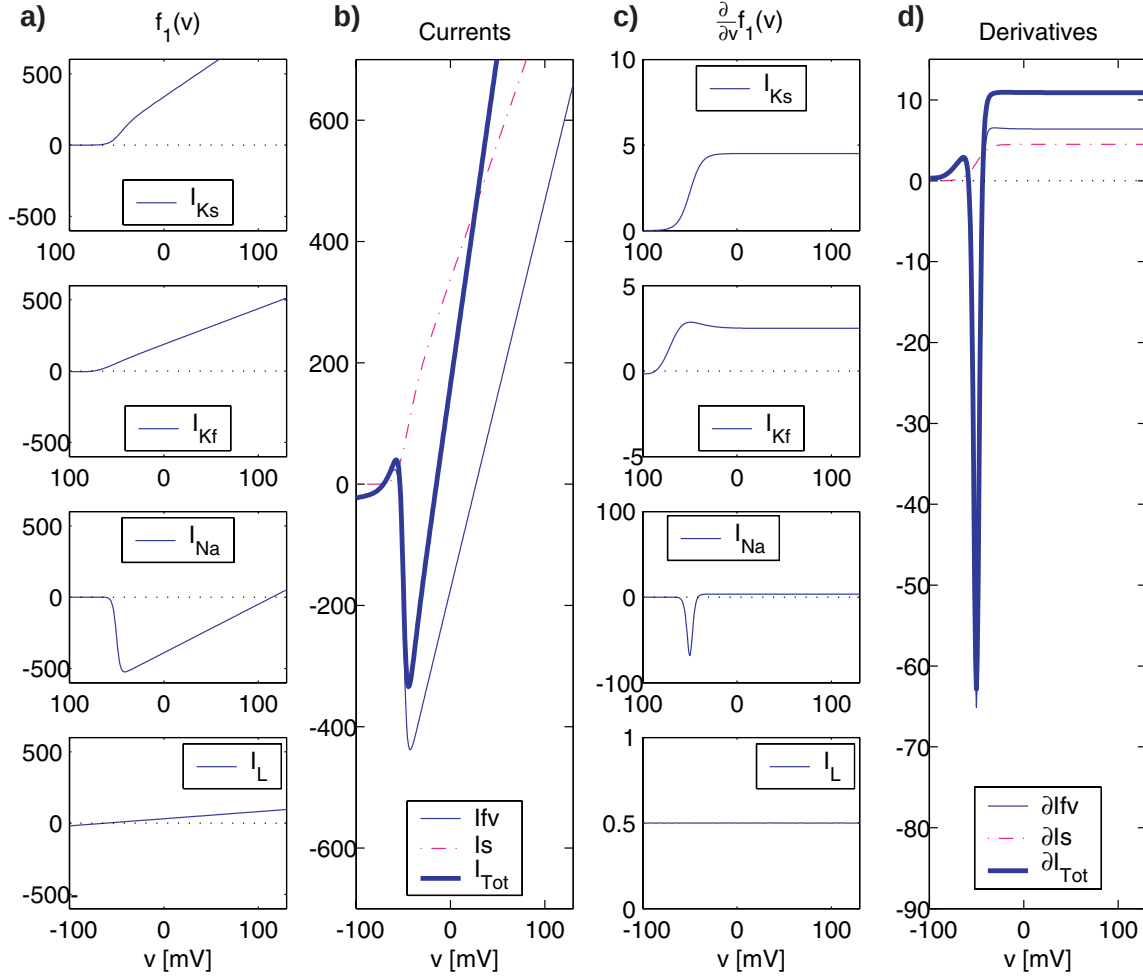


Figure 3. An example of four ionic currents: a slow potassium current I_{Ks} , two fast potassium and sodium currents I_{Kf} and I_{Na} , and a leakage current I_L . Parameters are as follows: $\bar{g}_{Ks} = 4.5$, $E_K = -75$, $v_{th_{Ks}} = -50$, $k_{0_{Ks}} = 0.08$; $\bar{g}_{Kf} = 2.5$, $v_{th_{Kf}} = -70$, $k_{0_{Kf}} = 0.05$; $\bar{g}_{Na} = 3.4$, $E_{Na} = 115$, $v_{th_{Na}} = -50$, $k_{0_{Na}} = 0.25$; $\bar{g}_L = 0.5$, $E_L = -60$, with units as given in section 4. Leftmost panels (a) show the $I_{ss} - v$ curves for the individual ionic currents. (b) The fast currents are collected in I_{fv} and are shown solid, the slow current I_{sv} is shown dash-dotted, and the sum $I_{Tot} = I_{ion}$ is shown bold. In (c) the derivatives of the single ionic currents are shown, and (d) shows the derivative with respect to v of the collected fast currents (dashed), the derivative of the slow current (dash-dotted), and their sum (bold), which gives the coefficient $a = \frac{I_{ion}}{\partial v}$ of section 3.1.3.

numbers of currents N , $\sum_i^N \bar{g}_{\alpha_i}$ tends to increase since constant terms g_{α_i} are added which activate in the sequence $v_{th_1}, \dots, v_{th_N}$. Therefore, the more currents there are, the less likely it is that they produce new fixed points, unless their conductances or slopes are very large.

Figure 3 shows an example with four ionic currents: two fast, I_{Kf} and I_{Na} ; one slow, I_{Ks} ; and a leakage current I_L . The leftmost panels show the steady state $I_{ss} - v$ curves for the individual currents, which are then collected in I_{fv} and I_s and added to give the total current I_{ion} shown in Figure 3b.

Conclusion. From the above analysis, we can summarize the major result as follows. *Each additional nonlinear current can, for suitable $\bar{g}, k_0, v_{th}, E$, create a new local “dip” and hence two additional fixed points may arise; cf. [31]. Leakage currents guarantee one fixed point for any value of the applied current.*

Here we have emphasized the role of the $I_{ss} - v$ curve in determining fixed points, due to its biophysical relevance. Indeed, this is the characteristic measured in voltage-clamp experiments, and can therefore be directly related to data. Alternatively, fixed points may be found at intersections of the v - and m -nullclines of (3.2) (e.g., [49, 22, 37, 33]).

3.1.3. Stability. In this section, we analyze the stability of fixed points. We concentrate on slow dynamically persistent currents, which are more common in reduced models, but we also discuss slow transitory currents. Rewriting (3.2) as

$$(3.11) \quad \begin{aligned} \dot{v} &= -\frac{1}{C}[I_{fv}(v) + \sigma_{sm}(m)I_{sv}(v) + I_{\text{ext}}] \stackrel{\text{def}}{=} f_1(v, m), \\ \dot{m} &= \frac{\epsilon}{\tau_m(v)}[m_\infty(v) - m] \stackrel{\text{def}}{=} \epsilon f_2(v, m) \end{aligned}$$

and linearizing yield a Jacobian of the form

$$(3.12) \quad Df = \begin{bmatrix} -\frac{1}{C} a & -\frac{1}{C} b \\ d\epsilon & -e\epsilon \end{bmatrix}.$$

If we define the total ionic current $I_{\text{ion}} = -(I_{fv} + \sigma_{sm}I_{sv})$, then the coefficients evaluated at a fixed point p are given by

$$(3.13) \quad a = \frac{\partial I_{\text{ion}}}{\partial v} \big|_p, \quad b = \frac{\partial I_{\text{ion}}}{\partial m} \big|_p, \quad d = \frac{m'_\infty}{\tau_m} - \frac{(m_\infty - m)\tau'_m}{\tau_m^2} \big|_p, \quad e = \frac{1}{\tau_m} \big|_p.$$

Here a represents the variation of the ionic current with respect to voltage, sometimes called the instantaneous $I - v$ curve [37] or the *slope conductance curve* [41]. The coefficient b reflects the dependence of the ionic current on the slow variable, and d and e are entirely determined by the gating dynamics. Observing that the sigmoid (2.3) has the property that its derivatives can be expressed in terms of the function itself, e.g., $w'_\infty = k_0 w_\infty(1 - w_\infty)$, we may write

$$(3.14) \quad \begin{aligned} a &= I'_{fv} + \sigma_{sm}I'_{sv}, & b &= \frac{\partial \sigma_{sm}}{\partial m} I_{sv}, \\ d &= k_0 \frac{m_\infty(1 - m_\infty)}{\tau_m}, & e &= \frac{1}{\tau_m}, \end{aligned}$$

where $(\cdot)' = \frac{\partial}{\partial v}(\cdot)$ and the derivatives of the conductance factors σ_{sm} are given by $\frac{\partial \sigma_P}{\partial m} = 1$ and $\frac{\partial \sigma_T}{\partial m} = 1 - 2m$ for dynamically persistent and dynamically transitory conductances, respectively (cf. (3.5)). In computing d we note that the second term in the general expression of (3.13) vanishes at fixed points. Also note that d and e are always positive.

As noted above, the particular structure of (2.2) implies that at the fixed points all gating variables are explicit functions of voltage. In addition, and importantly, as we noted at the end of section 3.1.1, any voltage value $v = \bar{v}$ can be made a fixed point by suitable choice

of external current I_{ext} . Therefore, the Jacobian entries a, b, d, e of (3.13) can all be reduced to explicit functions of voltage at the fixed point $\bar{v}$. This substantially simplifies the stability analysis, reducing it to a characterization in terms of $\bar{v}$ alone.

The eigenvalues of (3.12) are determined by the determinant $\text{Det}Df$ and trace $\text{Tr}Df$ and the necessary conditions for H and saddle-node (SN) bifurcations [50] may be written

$$(3.15a) \quad a_H = -\epsilon e C, \quad ae + bd > 0,$$

$$(3.15b) \quad a_{SN} = -\frac{bd}{e}.$$

Using (3.14), we observe that the ratio $-\frac{d}{e}$ appearing in (3.15b) is given by

$$(3.16) \quad -\frac{d}{e} = -k_0 m_\infty (1 - m_\infty)$$

and depends only on the (slow) gating dynamics; it is affected neither by the addition of fast currents nor by whether the slow current is dynamically persistent or transitory, activating or inactivating. In addition it depends neither on the maximal conductance $\bar{g}_\alpha$ nor on the reversal potential E_α , but only on the slope k_{0_α} and threshold voltage v_{th_α} . It is a negative bell-shaped function tending exponentially to 0^- for $v \rightarrow \pm\infty$; e.g., see Figure 5c. We can therefore focus on the coefficients a and b .

Coefficient a . The slope conductance curve is composed of the terms I'_{fv} and $\sigma_{sm}I'_{sv}$ (cf. (3.14)). It is often stressed [41, 39] that stability cannot be inferred from the slope of the $I_{ss} - v$ curve. Indeed, $I'_{ss} = \frac{\partial I_{\text{ion}}}{\partial v}$ would be equal to a if all currents were fast, but in the presence of slow currents, this is no longer true. Gathering N fast currents, using (3.3), we have

$$(3.17) \quad \frac{\partial I_{\text{ion}}}{\partial v} = I'_{fv} = \sum_{i=1}^N \bar{g}_{\alpha_i} \sigma'_i \zeta_i(v)(v - E_{\alpha_i}) + \bar{g}_{\alpha_i} \sigma_i \zeta'_i(v)(v - E_{\alpha_i}) + \bar{g}_{\alpha_i} \sigma_i \zeta_i(v),$$

where $\sigma'_i = \frac{\partial \sigma(n_i(v))}{\partial v}$. However, if one of the currents is slow, then we have

$$(3.18) \quad \begin{aligned} \frac{\partial I_{\text{ion}}}{\partial v} = & \sum_{i=1}^{N-1} [\bar{g}_{\alpha_i} \sigma'_i \zeta_i(v)(v - E_{\alpha_i}) + \bar{g}_{\alpha_i} \sigma_i \zeta'_i(v)(v - E_{\alpha_i}) + \bar{g}_{\alpha_i} \sigma_i \zeta_i(v)] \\ & + \bar{g}_{\alpha_j} \sigma_j \zeta'_j(v)(v - E_{\alpha_j}) + \bar{g}_{\alpha_j} \sigma_j \zeta_j(v), \end{aligned}$$

and the analogue of the first term $\bar{g}_{\alpha_i} \sigma'_i(v - E_{\alpha_i})$ in the summation does not appear for the slow current j .

Figure 4 shows the case of $\zeta_i(v) = 1$, in which (3.18) simplifies to

$$(3.19) \quad \frac{\partial I_{\text{ion}}}{\partial v} = \sum_{i=1}^{N-1} [\bar{g}_{\alpha_i} \sigma'_i(v - E_{\alpha_i}) + \bar{g}_{\alpha_i} \sigma_i] + \bar{g}_{\alpha_j} \sigma_j.$$

Since $\sigma'_P = k_0 n(1 - n)$ and $\sigma'_T = k_0 n(1 - n)(1 - 2n)$ (from (2.3) and (3.5); cf. (3.7)), the first term in the sum is a hump or a “dipole” for dynamically persistent or transitory currents,

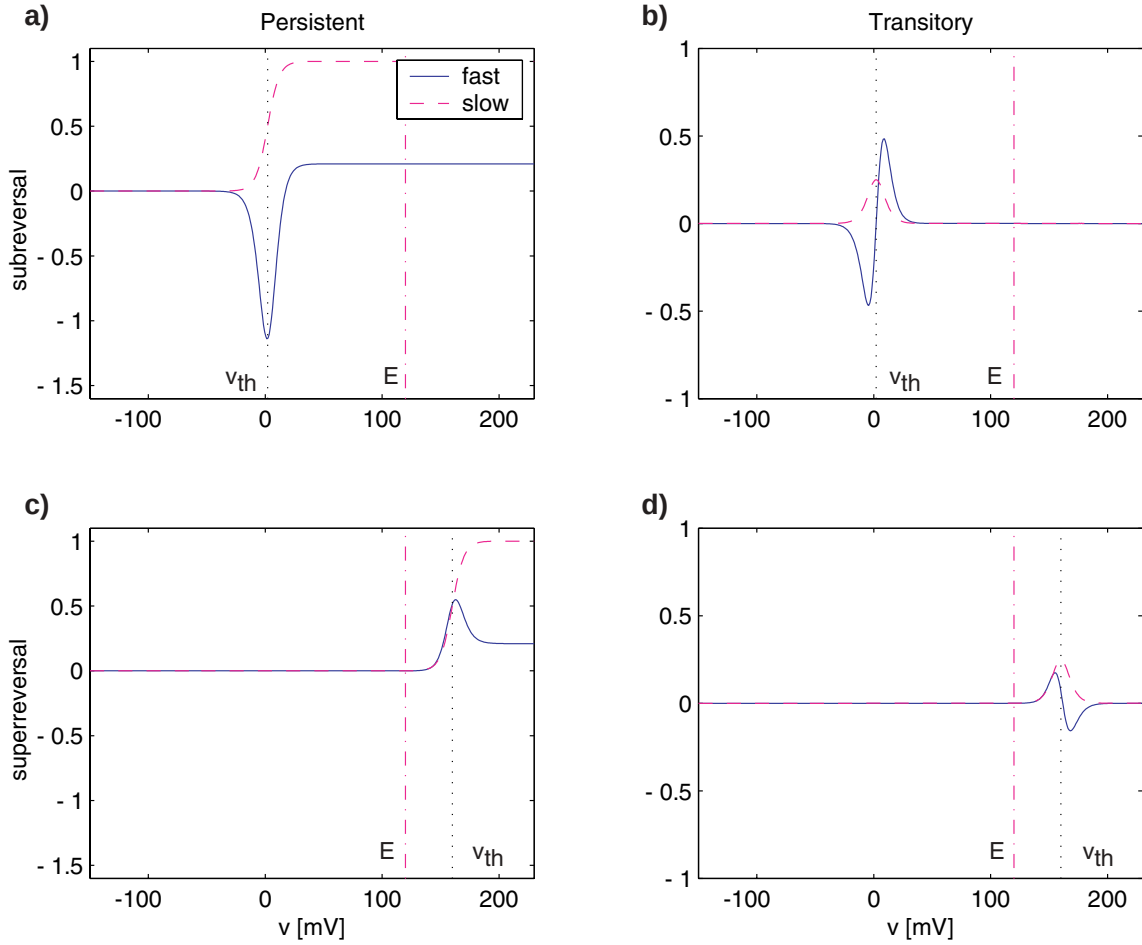


Figure 4. Derivatives of persistent ionic currents (left) and transitory currents (right), showing how they differ for fast (solid) and slow (dashed) currents. See Figure 2 for steady state $I_{ss} - v$ curves. This example shows a calcium current of the form (3.6), with maximal conductance $\bar{g}_{Ca} = 4.4 \text{ mS/cm}^2$, and reversal potential $E_{Ca} = 120 \text{ mV}$, with $k_0 = 0.2$. Dotted vertical line shows the threshold voltage v_{th} ; dash-dotted vertical line shows the reversal potential E . (a) Persistent subreversal $v_{th} < E$, here $v_{th} = 0 \text{ mV}$. (b) Transitory subreversal. (c) Persistent superreversal $v_{th} > E$, here $v_{th} = 160 \text{ mV}$. (d) Transitory superreversal. Observe that slow currents always give positive contributions to the derivative (coefficient a).

respectively. If current j is slow, then the derivative $\frac{\partial I_{\alpha}}{\partial v} > 0$ for both types of currents, but if j is fast, then $\frac{\partial I_{\alpha}}{\partial v}$ can change sign. In the persistent case, this will only happen for subreversal currents (Figures 4a and 4c), whereas it always holds in the transitory case (Figures 4b and 4d).

Reviewing the four-current example of Figure 3, we observe how the individual currents contribute to determine $a = \frac{\partial I_{ion}}{\partial v}$ depicted in Figure 3d. I_{Kf} is a typical example of a persistent superreversal current whose derivative is shown in Figure 3c (second down). I_{Na} exemplifies a fast subreversal persistent current whose derivative is shown in Figure 3c (third down); cf. I_{NaP} in [17], Model 2 of Appendix C. The linear leak I_L gives a constant contribution to a ; see

Figure 3c (bottom). I_{Ks} is a slow (dynamically and statically) persistent current; see Figure 3c (top). Note the difference between the two potassium currents. The slow current I_{Ks} , also present in the HH equations [2], yields a term $a_{Ks} = g_{Ks}m_{\infty Ks}$ (Figure 3c₁), whereas the fast current I_{Kf} yields the term $a_{Kf} = \bar{g}_{Kf}k_{Kf}n_{\infty Kf}(1 - n_{\infty Kf})(v - E_K) + \bar{g}_{Kf}n_{\infty Kf}$ (Figure 3c (second down)). The difference is not very marked here, but, as shown in Figure 4a, it can be more substantial and sufficient to change the stability of a fixed point. The single terms $\frac{\partial I_{\alpha}}{\partial v}$ are constant for $v \rightarrow \pm\infty$.

Coefficient b . This coefficient describes the dependence of the ionic current upon the (relatively) slow gating variable m . For dynamically persistent and transitory currents, one obtains

$$(3.20) \quad b_P = I_{sv} \quad \text{and} \quad b_T = (1 - 2m_{\infty})I_{sv}.$$

For dynamically persistent currents b_P has the same sign as I_{sv} ; hence if, as usually, $I_{sv} = v - E_{\alpha_s}$ is linear, then b_P is strictly positive for all $v > E_{\alpha_s}$.

It is now relatively easy to analyze the behavior of fixed points. One computes the dependence of a on $\bar{v}$ at a fixed point; when a crosses one of the values a_{SN} or a_H defined by (3.15), stability changes and a bifurcation occurs. An example is shown in Figure 5 for a system with the currents of Figure 3. The condition $\text{Tr} = 0$, satisfaction of which with $\text{Det} > 0$ results in an H bifurcation, is depicted in Figure 5a. Note that the term $-\epsilon\epsilon$ is small only in a relatively narrow range of voltages because $e(v) = \frac{1}{\tau_m(v)} \rightarrow +\infty$ for $v \rightarrow \pm\infty$; asymptotic analysis is therefore of little help for global understanding. Figure 5c shows the term $-\frac{d}{e}$, which multiplied by b_P or b_T gives the condition $\text{Det} = 0$. For persistent currents, the SN condition a_{SN} is shown in Figure 5b. Since a_{SN} is always positive for $v < E_{Ks}$, the SN and the H bifurcations can never occur in that range, but only at more depolarized levels than the reversal potential of the slow variable, here E_{Ks} . We note that since ϵ will only change the shape of $\text{Tr} = 0$ (by flattening it), the above observation suggests that there is a lower bound for these bifurcations and, as $\epsilon \rightarrow 0$, the location of these points will not change much. The determinant is positive for $a > -b\frac{d}{e}$, above the bold lines in Figures 5b and 5d for dynamically persistent and transitory conductances, respectively. Finally, Figure 5e shows the two boundaries with a superimposed for the example of Figure 3. This reveals a first crossing of a_H for $\bar{v}_{H_1} \approx -58 \text{ mV}$ giving rise to an H bifurcation, followed by two intersections of a_{SN} at $\bar{v}_{SN_1} \approx -57.8 \text{ mV}$ and $\bar{v}_{SN_2} \approx -44.3 \text{ mV}$ and finally a second H bifurcation at $\bar{v}_{H_2} = -43.8 \text{ mV}$, giving the bifurcation sequence H, SN, SN, H. In the next section we will exploit this approach to explore the effect of parameter variations.

3.2. Bifurcation diagrams for the fast subsystem. The collective effect of parameters describing single currents are best exemplified in bifurcation diagrams. The discussion of section 3.1.3 immediately translates to a bifurcation diagram with external current I_{ext} as the bifurcation parameter. The diagrams given below were computed numerically using a Newton–Raphson algorithm to determine fixed points and a continuation algorithm to follow their branches. However, the “constructive” single current analysis developed above more clearly reveals the causes and parameter sensitivities responsible for changes in the structure and sequence of bifurcations along branches of equilibria, so we also display this information in the form of $I_{ss} - v$ and slope conductance curves. In the following we will assume $\zeta(v) = 1$ for simplicity.

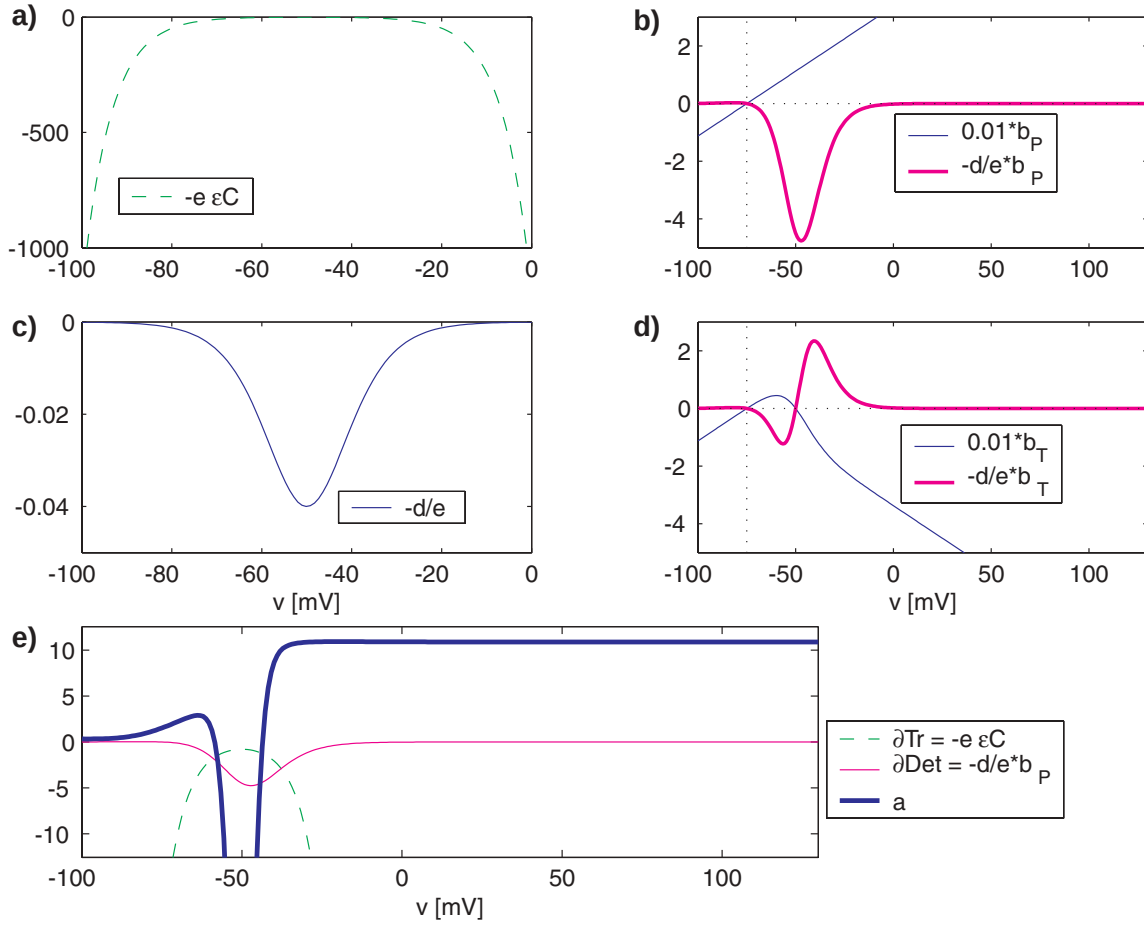


Figure 5. (a) The H bifurcation condition $a_H = -\epsilon\epsilon C$ (3.15a): $\text{Tr}Df < 0$ (> 0) above (below) dashed curve; (b) rescaled b_P (solid) and the SN bifurcation condition $a_{SN} = -b_P d/e$ (3.15b) (bold); (c) the term $-d/e$; (d) rescaled b_T (solid) and the SN bifurcation condition $a_{SN} = -b_T d/e$ (bold). (e) Shows the H condition as in (a) (dashed), the SN condition as in (b) (solid), and the coefficient a (bold) for the system of four currents given in Figure 3. Other parameters are $C = 20$, $\epsilon = 0.04$. Note that voltage (v) scales differ.

3.2.1. Fast currents. We consider a simple case with three ionic currents: a slow persistent potassium current I_{Ks} , a fast persistent calcium current I_{Ca} , and a leakage current I_L , similar to the original work of Hodgkin and Huxley [2].⁵ The term

$$b \frac{d}{e} = k_0 m_\infty (1 - m_\infty) \cdot I_{sv} \cdot \begin{cases} 1, & \text{dynamically persistent,} \\ (1 - 2m_\infty), & \text{dynamically transitory,} \end{cases}$$

which gives the SN condition (3.15b), depends only on the slow gating parameters. The bifurcation sets (3.15) are therefore affected neither by adding fast currents nor by changes

⁵Sodium and calcium currents differ in their reversal potentials $E_{Na} = 50\text{mV}$ and $E_{Ca} = 120\text{mV}$ and in the fact that the sodium current in [2] is transitory, whereas the calcium current considered here is persistent, as in [38].

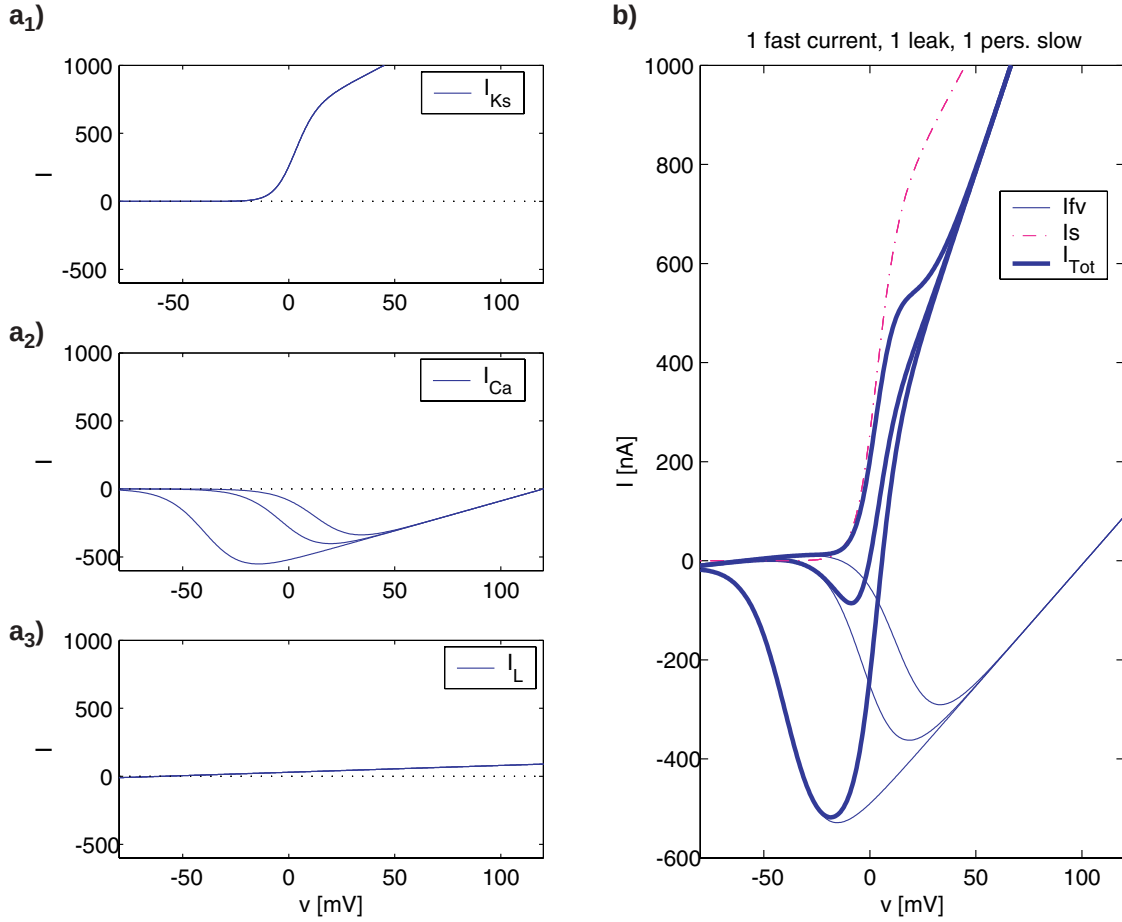


Figure 6. Dependence of the total ionic current on variation of threshold voltage v_{th} of a fast calcium current. Parameters are as follows: $\bar{g}_{Ks} = 8.0$, $E_K = -80$, $v_{th_{Ks}} = 2$, $k_{0_{Ks}} = 0.2$; $\bar{g}_{Ca} = 4.4$, $E_{Ca} = 120$, $v_{th_{Ca}} = -38, -1.2, +15$ from lower to upper curves in (a2) and (b), $k_{0_{Ca}} = 0.11$; $\bar{g}_L = 0.5$, $E_L = -60$. Units are as given in section 4.

in their parameters. For illustrative purposes, we show the effect of two such parameters: the threshold voltage v_{th} of a fast persistent inward current such as I_{Na} or I_{Ca} , and the slope of its fast gating variable k_0 .

Threshold voltage v_{th} . The effect of v_{th} on the $I_{ss} - v$ curve is shown in Figure 6, its effect on the slope conductance curve (coefficient a) in Figure 7, and the resulting bifurcation diagrams in Figure 8. Increasing values of v_{th} shift the minimum of $\frac{\partial I_{Ca}}{\partial v}$ to the right. For low thresholds, the corresponding bifurcation diagram has two SN points (see Figure 8c₁). Increasing v_{th} , an H bifurcation emerges from the higher (more depolarized) SN bifurcation point in a Takens–Bogdanov (TB) bifurcation [50] (see Figure 8c₂). Further increase causes the SN points to coalesce and disappear in a codimension two “cusp” bifurcation [50], leaving two H bifurcations (see Figure 8c₃ (cf. Rinzel and Ermentrout [37] and Koch [41] for discussions of the latter)).

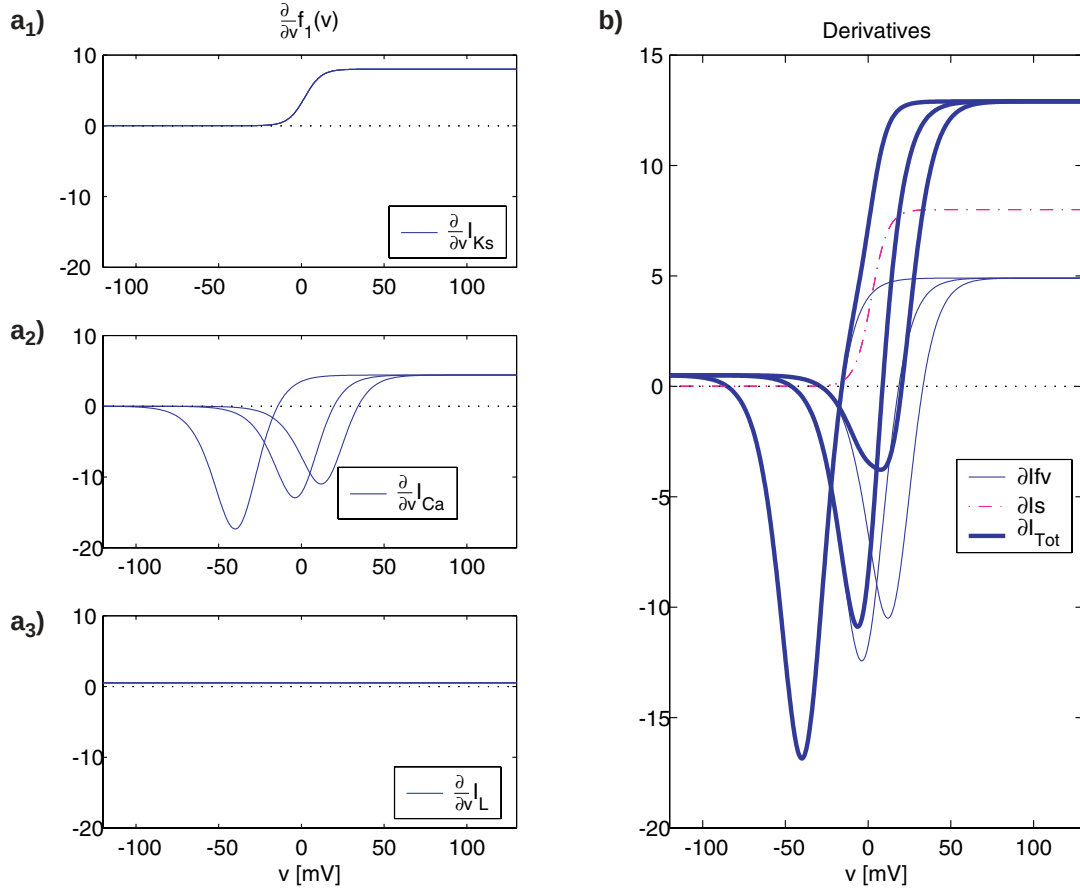


Figure 7. Dependence of the total slope conductance curve a on variation of threshold voltage v_{th} of a fast calcium current. Parameters as in Figure 6.

Also note that the cases of Figures 8a₂–c₂ and a₃–c₃ can explain the smooth transition from Class I to Class II spiking [20] without appealing to an extra current (e.g., an I_A current) as in Connor and Stevens [51], [41, pp. 159, 190]. Rinzel and Ermentrout [20] stated that this was possible with a model similar to the one used here by changing v_{th_K} ; Figure 8 should provide some further insight.

Slope k_0 . Despite the fact that a steeper transition in the sigmoid (2.3) has a negligible effect on the steady state curves (Figures 9a₁–a₂), it can substantially change the bifurcation structure via the increased slope that causes a substantial negative peak in $\frac{\partial I_{Ca}}{\partial v}$ (see Figures 9b₁–b₂). Moreover, due to global bifurcations in which limit cycles disappear (see [50] and below), the topological difference between the two cases involves more than simply removing one (local) H bifurcation point (see Figures 9c₁–c₂).

Maximal conductance of leakage current $\bar{g}_L$. Because of its relevance to the bursting dynamics in the following section, we end by noting that the effect of the (linear) leakage current is simply a vertical shift of a . The resulting bifurcation diagram (not shown) goes from the sequence SN, SN, H to SN, SN as $\bar{g}_L$ increases.

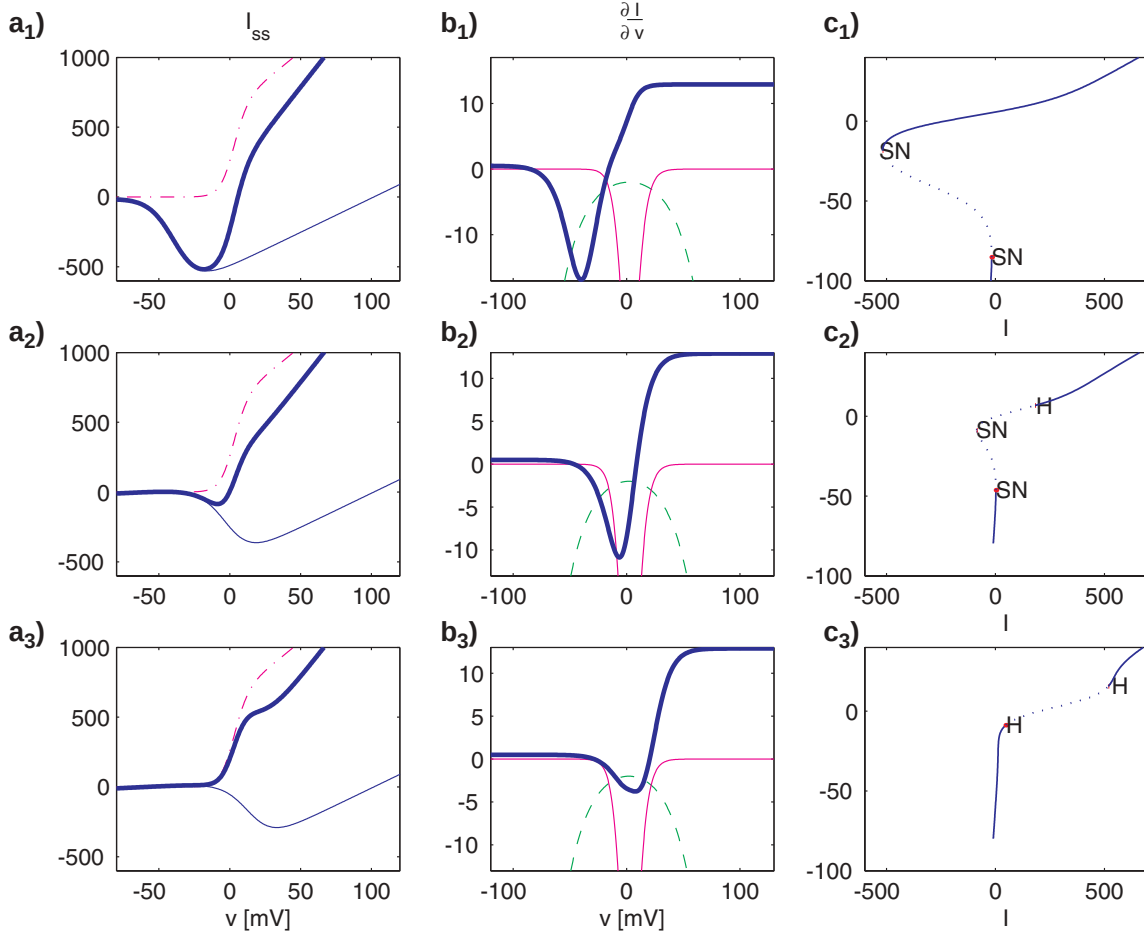


Figure 8. Dependence of a fast calcium current upon variation of the threshold voltage v_{thCa} . Parameters as in Figure 6 with $v_{thCa} = -38, -1.2, +15$ from top row to bottom; in addition $C = 20$, $\epsilon = 0.1$. Left panels show the steady state $I_{ss} - v$ curves from Figure 6: fast current (solid), slow current (dash-dotted), and total current (bold). Middle panels show the relevant terms for stability from Figure 7: $Det = 0 \Leftrightarrow a = -\frac{bd}{e}$ (solid), $Tr = 0 \Leftrightarrow a = -eeC$ (dashed), and $a = \frac{\partial I_{ion}}{\partial v}$ (bold). Right panels show the corresponding bifurcation diagrams.

3.2.2. Slow currents. Slow current parameters also affect the bifurcation sets (3.15). Figure 10 shows the effect of threshold voltage changes on a slow outward current, such as I_K . Bifurcation points are shifted and the coefficient a changes its form via $\sigma_{sm}(m_\infty(v))$, which appears in the second term in $a = I'_{fv} + \sigma_{sm}I'_{sv}$. The resulting bifurcation diagrams show transitions can occur from SN, SN to SN, SN, H and back to SN, SN as v_{th} increases.

Conclusion. The introduction of each current with a nonoverlapping “window of influence” can produce another pair of equilibria. Thus “snaking” branches with multiple SN bifurcations can appear. Up to two H bifurcations can be introduced, associated with at least one SN pair. H bifurcations may also occur in the absence of SN bifurcations when the branch does not double back. Coincident H and SN (TB) bifurcations can be obtained by varying a second parameter in addition to I_{ext} .

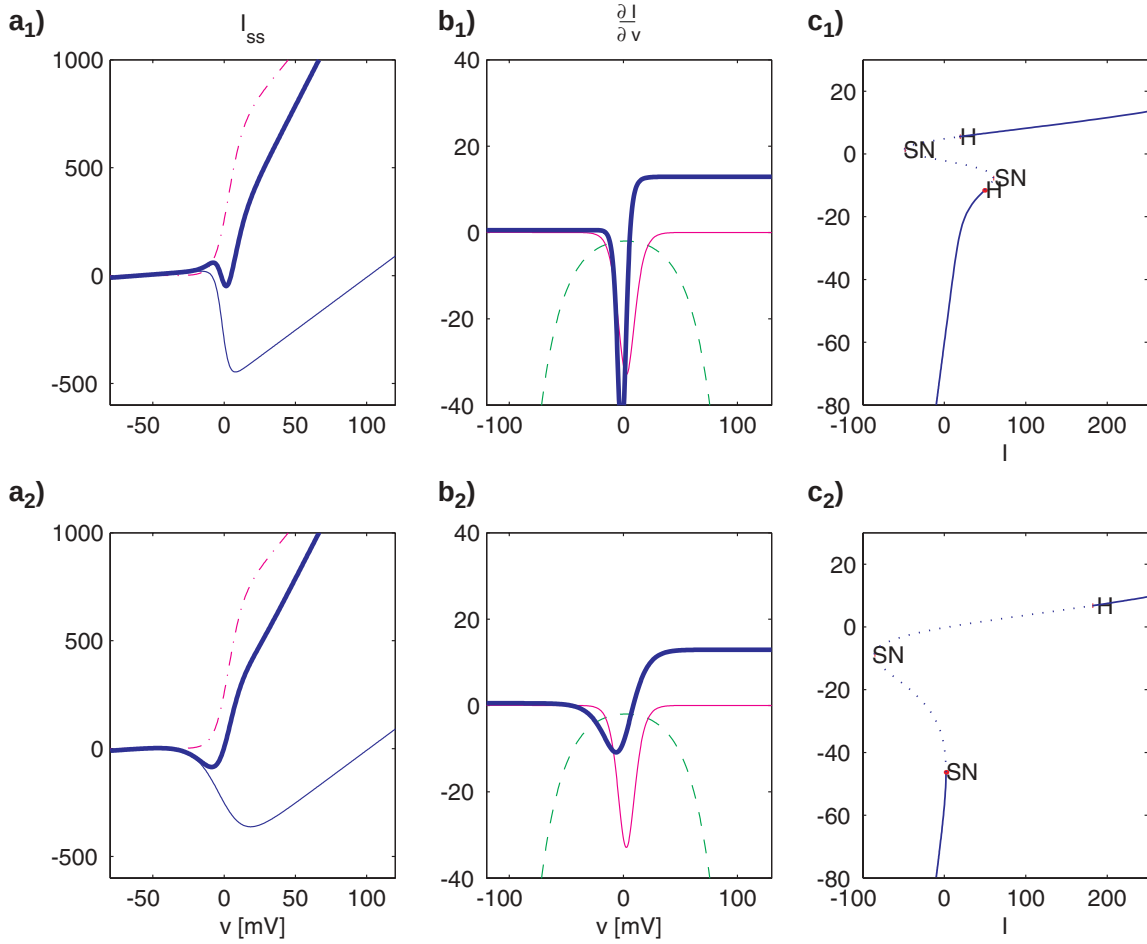


Figure 9. Dependence of a fast calcium current upon variation of slope k_0 . Left panels show the steady state $I_{ss} - v$ curves: fast current (solid), slow current (dash-dotted), and total current (bold). Middle panels show the relevant terms for stability: $\text{Det} = 0 \Leftrightarrow a = -\frac{bd}{e}$ (solid), $\text{Tr} = 0 \Leftrightarrow a = -\epsilon\epsilon C$ (dashed line), and $a = \frac{\partial I_{\text{ion}}}{\partial v}$ (bold). Right panels show the corresponding bifurcation diagrams.

3.2.3. Bifurcations in terms of c . The bifurcation diagrams of Figures 8, 9, and 10 use external current I_{ext} as parameter. In the full system (3.1) the slow variable c drives the fast subsystem from regime to regime; hence, we must recast the above results in terms of c , which enters the fast equation (3.1a) via a current such as $I_{\text{KS}} = \bar{g}_{\text{KS}}c(v - E_{\text{K}})$. To do this we consider a two-parameter bifurcation diagram of the original system (3.1) and then slice it with an appropriate plane. For illustrative purposes, we will treat (3.1) with three internal currents $I_{\text{Ca}}, I_{\text{KS}}, I_{\text{L}}$ and an external current I_{ext} , as in [38].

We compare the membrane voltage equations of (3.1a),

$$(3.21) \quad C\dot{v} = -[\bar{g}_{\text{L}}c_{\text{L}}(v - E_{\text{L}}) + f_1(v, m)] + I_{\text{ext}},$$

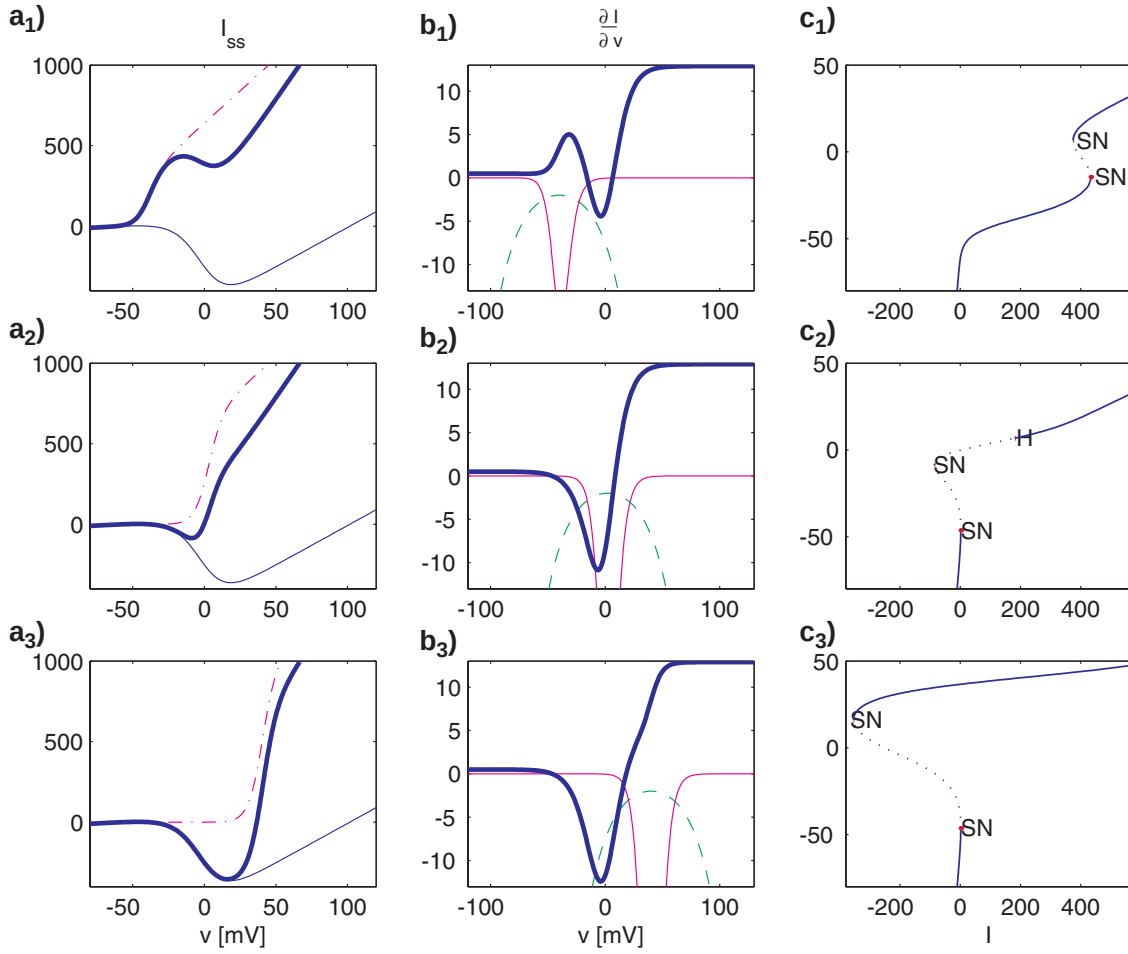


Figure 10. Dependence of a slow current upon variation of the threshold potential v_{th} for a potassium current. Left panels show the steady state $I_{ss} - v$ curves: fast current (solid), slow current (dash-dotted), and total current (bold). Middle panels show the relevant terms for stability: $\text{Det} = 0 \Leftrightarrow a = -\frac{bd}{e}$ (solid), $\text{Tr} = 0 \Leftrightarrow a = -eC$ (dashed), and $a = \frac{\partial I_{ion}}{\partial v}$. Right panels show the corresponding bifurcation diagrams.

with an analogous system with an additional current I_{KS} ,

$$(3.22) \quad C\dot{v} = -[\bar{g}_L(v - E_L) + f_1(v, m) + \bar{g}_{KS}c(v - E_K)];$$

here $f_1(v, m) = \bar{g}_{Ca}n_\infty(v)(v - E_{Ca}) + \bar{g}_K m(v - E_K)$ denotes the unchanged fast currents. Equations (3.21) and (3.22) are equivalent provided that we set the “leakage” factor c_L and the current I_{ext} in (3.21), respectively, equal to

$$(3.23) \quad c_L = 1 + \frac{\bar{g}_{KS}}{\bar{g}_L} c \quad \text{and} \quad I_{ext} = \bar{g}_{KS} c E_K + \bar{g}_L(1 - c_L)E_L.$$

The desired bifurcation diagram of equilibrium voltage as a function of c is therefore a “slice” of the two-parameter $(v, \bar{g}_L c_L)$ bifurcation surface above the line defined by eliminating c

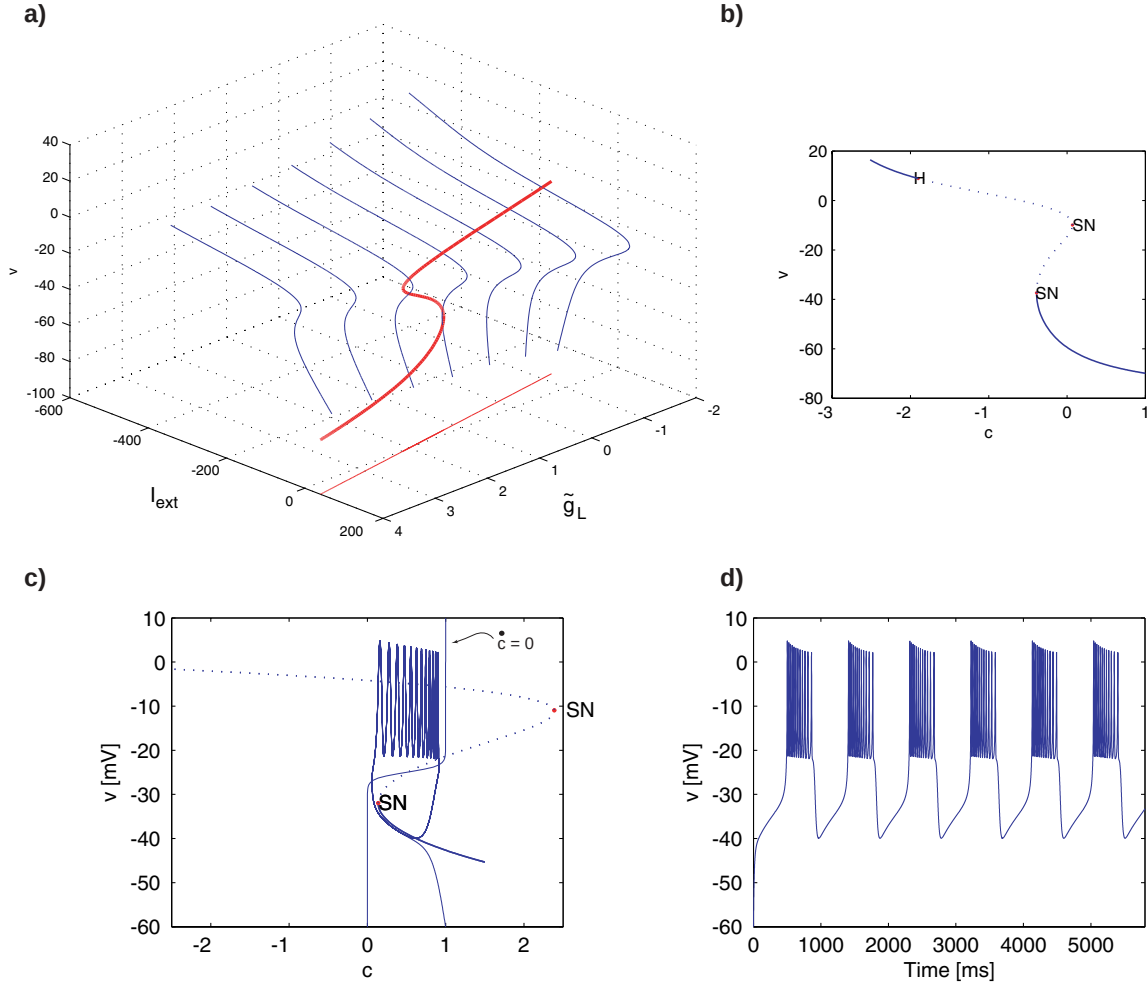


Figure 11. Bifurcations with respect to c . (a) The two-parameter bifurcation surface as a function of I_{ext} and $\bar{g}_L = \bar{g}_L c_L$; also shown is the bifurcation slice (bold) and its projection (3.24) (dashed). (b) The slice as a function of c ; note the two SNs and an H bifurcation. (c) The $\dot{v} = 0$ and $\dot{c} = 0$ nullclines and a typical bursting trajectory projected onto the (c, v) plane. (d) Voltage time history exhibiting bursts.

from (3.23):

$$(3.24) \quad I_{\text{ext}} = \bar{g}_L (E_L - E_K) (1 - c_L).$$

Figure 11 shows an example. Note that the line (3.24) is almost perpendicular to the I_{ext} -axis on Figure 11a; this is due to the fact that the difference between the leakage reversal potential E_L and the potassium reversal potential E_K is very small in this case; also note that the signs of the terms in (3.23)–(3.24) imply that the c -bifurcation diagram is reversed in comparison to the I -diagrams of Figures 8, 9, and 10, having the higher v branch extending to the left (see Figure 11b). Finally, we note that the maximal conductance associated with the very slow variable $\bar{g}_{KS}$ does not influence the slice location (3.24). Rather, changes in $\bar{g}_{KS}$,

which enters the current I_{KS} of (3.22) multiplicatively, horizontally compress or expand the orbit projected on the (c, v) plane (Figure 11), a fact that will be useful in section 4.2.

3.3. The bursting mechanism. As anticipated at the beginning of this section, bursting results from hysteretic transitions between a quasi-static quiescent state and a periodic (spiking) state, driven by the slow variable c . Thus, given the bifurcation diagram in c , the dynamics of the third order model can be elucidated in the limit of small δ . Here we discuss a typical bifurcation diagram, with the sequence SN, SN, H as in Figure 11b (cf. Figure 10c₂ or Figure 8c₂). The vectorfield of (3.1c) indicates that $c \in [0, 1]$ will decrease when $c > c_\infty(v)$ and increase when $c < c_\infty(v)$. As c slowly evolves, the fast subsystem (3.1a)–(3.1b) remains close to its stable fixed point until the left-hand SN bifurcation on the lower branch is reached. When c passes this point, the state quickly jumps to the coexisting stable limit cycle (see Figure 11c). During this spiking oscillation, the average voltage is sufficiently high that c increases, until the cycle is destroyed as the limit cycle collides with the saddle point (the middle branch) in a saddle-loop (SL) or homoclinic bifurcation, or the right-hand SN occurs on the cycle itself (SNLC) [50]. Figure 11c shows the former case. It may also happen that the H bifurcation is subcritical [50] and the relevant stable limit cycle is born in an SN of periodic orbits (SNPO).

4. A minimal bursting model. The bursting mechanism identified above includes a branch of stable equilibria terminating in an SN and a branch of limit cycles terminating in a global homoclinic bifurcation, or possibly destroyed by a second SN of fixed points occurring on the limit cycle. A minimal model therefore requires only the “nose” or NRC on the lower equilibrium branch, and an H bifurcation to create the periodic orbit on the upper branch. This can be captured by a fast persistent (inward) current. In the model discussed in [20], based on the two-variable Morris–Lécar equations [38], it is a calcium current; in Butera, Rinzel, and Smith’s model 2 [17] (cf. Appendix C) it is a persistent sodium current I_{NaP} , with almost the same functional expression, the only difference being the exponent of the gating variable which is 1 in [38] and 3 in [17].

The following results were obtained for a persistent inward current with a reversal potential of $E = 120mV$, consistent with calcium, which we called I_{Ca} . We believe that analogous results could be obtained with a persistent sodium current with reversal potential around $E = 50mV$, but specific biophysical data is unavailable for CPG neurons in the cockroach, so we cannot identify a specific current, responsible for the fast spikes. In addition we have a slow (outward) current I_K and a leakage current I_L . The bursting mechanism will be caused by an additional very slow potassium current I_{KS} (essentially the same as I_{KS} in [17, Model 2]; see also [39]) that plays the same role of the calcium-activated potassium current I_{KCa} in the Sherman–Rinzel–Keizer (SRK) model: it hyperpolarizes (decreases) the membrane voltage when v is highly depolarized (i.e., in the bursting regime). Our main results should carry over when a calcium-dependent potassium current is used for the bursting mechanism as presented in the example below using the SRK model [13]. Therefore, we consider the system

$$(4.1) \quad \begin{aligned} C\dot{v} &= -[I_{Ca} + I_K + I_L + I_{KS}] + I_{ext}, \\ \dot{m} &= \frac{\epsilon}{\tau_m(v)} [m_\infty(v) - m], \end{aligned}$$

$$\dot{c} = \frac{\delta}{\tau_c(v)} [c_\infty(v) - c].$$

The currents in (4.1) are specified by

$$(4.2) \quad \begin{aligned} I_{Ca} &= \bar{g}_{Ca} n_\infty(v)(v - E_{Ca}), & I_K &= \bar{g}_K m \cdot (v - E_K), \\ I_L &= \bar{g}_L (v - E_K), & I_{KS} &= \bar{g}_{KS} c \cdot (v - E_K). \end{aligned}$$

The steady state gating and timescale functions are of the types (2.3)–(2.4); in particular, $m_\infty(v)$ and $c_\infty(v)$ are both sigmoidal functions $(1 + e^{-k_0(v-v_{th})})^{-1}$, where $m_\infty(v)$ is defined by k_{0K}, v_{thK} and $c_\infty(v)$ by k_{0KS}, v_{thKS} . The parameters given in Table 1 were adopted for the work described in this section. The maximal conductances are expressed in mS/cm^2 , the reversal and threshold potentials in mV , the slope coefficients in mV/s , and the capacitance C in $\mu F/cm^2$. All parameters excepting $C, \bar{g}_K, \epsilon, \delta$ are the same as in Morris and Lécar [38, 20], $\bar{g}_K = 9$ being slightly higher than their value $\bar{g}_K = 8$. With the application to follow in [1] in mind, the parameters C, ϵ , and δ , which independently determine the time scales of v, m , and c , are set to match typical cockroach data.

Table 1
Parameter values for the bursting model.

$\bar{g}_{Ca}$	=	4.4	E_{Ca}	=	120	v_{thCa}	=	-1.2	k_{0Ca}	=	0.11
$\bar{g}_K$	=	9.0	E_K	=	-80	v_{thK}	=	2.0	k_{0K}	=	0.2
$\bar{g}_{KS}$	=	0.25				v_{thKS}	=	-27	k_{0KS}	=	0.8
$\bar{g}_L$	=	2.0	E_L	=	-60						
C	=	1.2	ϵ	=	4.9	δ	=	0.052	I_{ext}	=	35.6

4.1. Silence, bursting, and beating. The existence of a resting potential and a limit cycle for the fast subsystem ensures that the cell can exhibit two states: silent or beating (persistent spiking). As we saw in section 3.3, to obtain bursting, these states must coexist over some parameter range. Moderate increases in external current I_{ext} leave the (v, c) -bifurcation diagram almost unchanged in shape but shift it rightward, causing the intersection of the nullclines to move from the lower, to the middle, and finally to the upper branch (Figures 12a₁–a₄). This effects a continuous change from silence to bursting to beating (Figures 12b₁–b₄). Similar results (not shown) can be obtained by changing the threshold voltage in the function $c_\infty(v)$.

The bursting frequency can be changed by over an order of magnitude (0.8–19.6 Hz) via the bias current I_{ext} (Figures 12(a₂, b₂)–(a₃, b₃)). This agrees with Butera, Rinzel, and Smith [17], in which variations from 0.05–1 Hz were found, but it is accompanied by an increase from five to nine APs. Since fast motoneurons encode force in terms of AP numbers, the latter should also be adjustable *without* substantial frequency change. This is possible in regimes with few APs per burst (Figures 12(b₃, b₅)).

4.2. Shaping the bursts. In the following we will concentrate on five parameters and show how they can affect the properties of the bursts. We anticipate that not all will be plausibly adjustable *in vivo*; in particular, we will show how one can fix the parameters C, ϵ , and δ to match timescales and key features in systems of interest, providing a “baseline” model, and how the adjustable parameters (I_{ext}, g_{KS}) affect this model. While I_{ext} cannot be

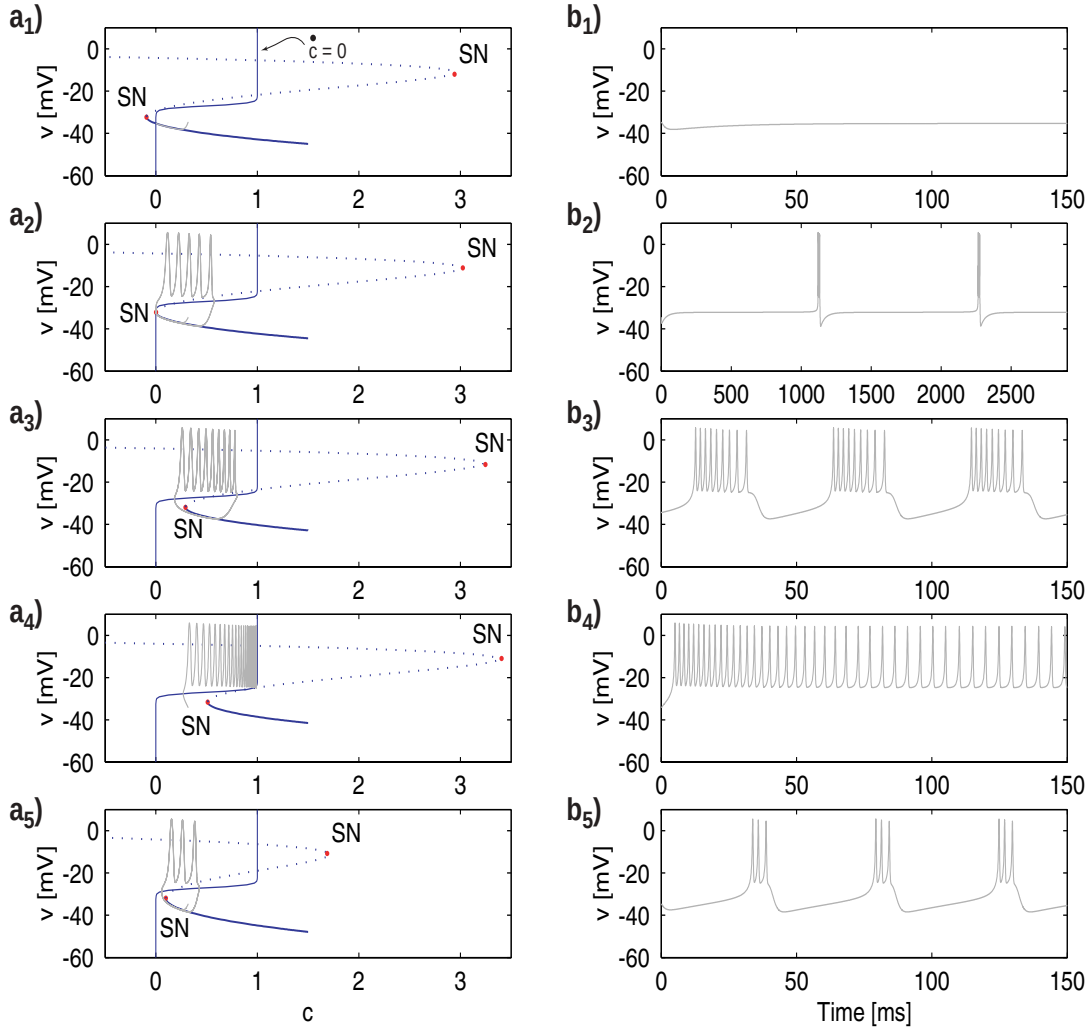


Figure 12. Left panels (a₁)–(a₅) show bifurcation diagrams of the fast subsystem of (4.1) and projections of the bursting trajectory (grey line) onto (c, v) plane. The $\dot{c} = 0$ nullcline (solid) is also shown. Parameters are as in Table 1, unless stated otherwise. Right panels (b₁)–(b₅) show the membrane voltage v versus time. (a₁)–(b₁) Silence: the $\dot{c} = 0$ nullcline intersects the stable branch of the bifurcation diagram and there is one (stable) fixed point for (4.1); $I_{ext} = 34.5$. (a₂)–(b₂) Low frequency bursting: $f = 0.8$ Hz; $I_{ext} = 35.346$. Notice that each burst has five spikes and note extended time scale in (b₂). (a₃)–(b₃) High frequency bursting: $f = 19.6$ Hz; $I_{ext} = 38$. (a₄)–(b₄) Beating: the system has a stable limit cycle with $c \approx \text{const}$; $I_{ext} = 40$. (a₅)–(b₅) Changing $\bar{g}_{KS}$ to 0.35 (in place of $\bar{g}_{KS} = 0.19$ in previous cases) contracts the bifurcation diagram, affecting the duty cycle; $I_{ext} = 37$.

adjusted independently via, e.g., synapses from central nervous system (CNS) neurons, both it and $\bar{g}_{KS}$ can be modulated by synaptic inputs and by neurotransmitters, so both of these control parameters are biophysically plausible in vivo.

- (i) The capacitance C basically sets the frequency of the fast spiking. Here it was set to 1.2 in order to obtain fast spikes on the order of 1ms.

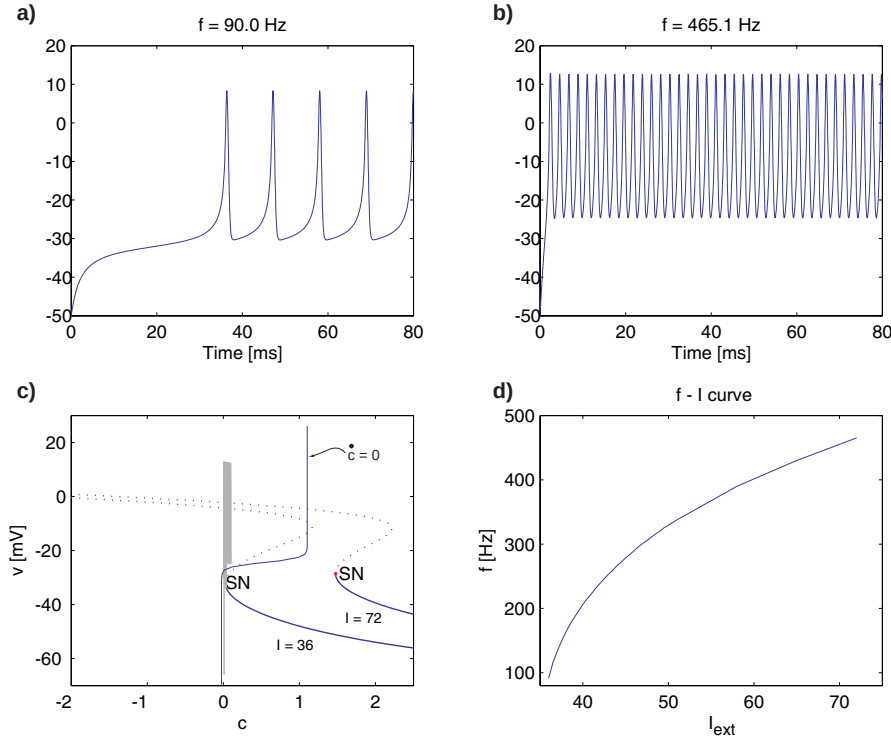


Figure 13. Regulating spiking frequency by changing input current I_{ext} . Varying I_{ext} from 36 (a) to 72 (b) spans the frequency range from 90 to 465 Hz. The $\dot{v} = 0$ nullcline moves rightward as I_{ext} increases (c), taking the limit cycle further from the homoclinic bifurcation. (d) The resulting $f-I$ curve. Parameters as in Table 1, except $\bar{g}_{KS} = 0.5$, $\epsilon = 2.0$, $\delta = 10^{-4}$.

- (ii) The parameter ϵ can play a central role as also suggested in the next illustrative example, at the end of section 4. Recalling Figure 5, we observe that the H condition $a_H = -\epsilon e C$ is the only one depending on the parameter ϵ . A decrease in ϵ therefore makes the curve $a_H = -\epsilon e C$ shallower, shifting the H bifurcation point to more depolarized levels. This, in turn, “drags” the global homoclinic bifurcation to the left. Assuming that the very slow dynamics is unchanged, this suggests that the number of spikes in a burst should decrease, because the homoclinic bifurcation moves closer to the SN bifurcation.
- (iii) The parameter δ is responsible for the recovery variable time scale and therefore determines a “baseline” bursting frequency.
- (iv) The bias current I_{ext} can have several effects. It can influence the bursting frequency, especially when the nullcline $\dot{c} = 0$ of the very slow variable is fairly close to the SN bifurcation (Figure 12(a₂)-(a₃)).

I_{ext} can affect the spiking frequency as shown in Figure 13, for which we set $\delta = 10^{-4}$ and bursting is so slow that behavior resembles a regular spiking neuron. (In the companion paper [1] this will be used to model slow cockroach motoneurons which spike in the range 90–400 Hz [52, 53].) A lower bound for maximum spiking frequency

is given by $\omega_0 = \sqrt{\epsilon(ae + bd)/C}$ at the H bifurcation, and since the cycle is destroyed via a homoclinic bifurcation [50], there is no limit to minimum frequency in principle; however, away from the H bifurcation the $f - I$ curves for these neurons are rather flat (see, e.g., discussion in [41]: 53–138 Hz in the HH model, 19–28 Hz in FitzHugh–Nagumo, and 50–70 Hz in Morris–Lécar [38]). At least in the relaxation oscillator limit, frequency is essentially fixed by the dynamics on the slow manifold, which does not significantly change away from the H bifurcation (Figure 13d was obtained near the homoclinic bifurcation).

I_{ext} can also affect the number of APs per burst, but we note that the (percentage) variation is minimal when the number of APs per burst is large and becomes increasingly more important when there are few APs per burst (~ 4 –5).

- (v) The conductance g_{KS} is central in determining the duty cycle: the fraction of the period occupied by the burst. Recalling that the slice of the bifurcation diagram does not depend on $\bar{g}_{\text{KS}}$ (3.24), and that this maximal conductance enters multiplicatively in I_{KS} (3.22), we see that increases (decreases) in its value respectively expand (contract) the projected orbit in the c -direction, without changing the values of the corresponding $\bar{v}_{\text{SN}}$ and $\bar{v}_H$. The location of the homoclinic bifurcation responsible for disappearance of the cycle shifts in this deformation process. The time spent in each regime varies inversely with distance to the $\dot{c} = 0$ nullcline; thus, in going from $\bar{g}_{\text{KS}} = 0.19$ to 0.35 (Figures 12a₃ to 12a₅), the quiescent fraction of the cycle increases since the lower branch of the $I_{\text{ss}} - v$ curve moves closer to the nullcline. Figures 14(a,b) show how bursting frequency and duty cycle can be independently changed by a suitable combination of the parameters I_{ext} and $\bar{g}_{\text{KS}}$. I_{ext} primarily affects frequency, especially at higher values of $\bar{g}_{\text{KS}}$; $\bar{g}_{\text{KS}}$ affects both frequency and duty cycle.

Summary. *The model parameters C , ϵ , and δ in (4.1) may be chosen to match timescales of fast spikes (C), approximate number of APs per burst (ϵ), and baseline bursting frequency (δ). Depending on the number of APs per burst, two regimes can be identified: high (~ 15 APs) or low (~ 4 APs). In the high regime, bursting frequency is modulated by I_{ext} ; in the low regime, I_{ext} influences both bursting frequency and number of APs per burst. In the high regime g_{KS} primarily affects the duty cycle; in the low regime it affects both duty cycle and number of APs per burst.*

To satisfy changing behavioral demands CPGs must produce wide variations in cycle frequency, relative timing, and activity levels in motoneurons and muscles. One might therefore expect that the four key characteristics—bursting frequency, duty cycle, number of APs per burst, and spiking frequency—should be *independently* adjustable, since they serve different physiological functions (e.g., in locomotion, bursting sets the stepping frequency, and slow motoneuron spike rates and fast motoneuron APs determine muscle force, via calcium release dynamics). Such flexibility may seem impossible with only the two parameters I_{ext} and g_{KS} . Moreover, since conductance changes are slower, adjustments might not be possible on compatible timescales, and as we have noted above, I_{ext} is in any case not directly accessible in vivo.

Here we anticipate a solution that evolution may have achieved via “division of labor”; more details will be given in [1]. Insect CPGs comprise at least six bursting interneurons, each of which drives fast (bursting) motoneurons D_f and slow (spiking) motoneurons D_s . Stepping

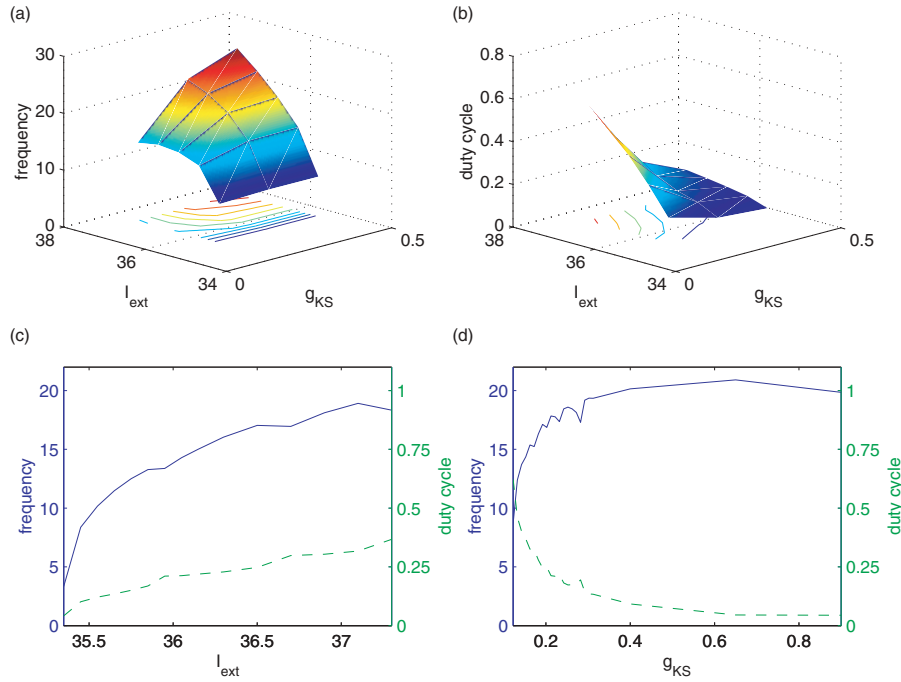


Figure 14. Bursting frequency (a) and duty cycle (b) dependence on I_{ext} and $\bar{g}_{KS}$, showing that I_{ext} primarily affects frequency at higher values of $\bar{g}_{KS}$ (see contour lines), but $\bar{g}_{KS}$ simultaneously affects duty cycle and frequency. (c), (d): Slices for constant $\bar{g}_{KS} = 0.19$ and constant $I_{ext} = 36.5$; frequency shown solid and duty cycle dashed.

frequency and duty cycle can be set at the network level by synaptic currents from CNS and local reflexive feedback circuits, which effectively change CPG input currents I_{ext} and conductances g_{KS} . For reasons to be explained in [1], these two parameters together with external currents to slow motoneurons completely define the operational regime of the latter. Fast motoneurons, which grade force via the number of APs per burst, require more subtle treatment. As noted above, they can be modulated by their input currents and conductances, but these parameters also affect their bursting frequencies. Here network properties come to the rescue: unilaterally connected motoneurons “follow” CPG neurons provided that their bursting frequencies are close enough, in which case they entrain to the CPG bursting frequency over finite current and conductance ranges. This renders the D_f bursting frequency independent of these parameters, which therefore affect only the number of APs per burst. In summary, independent controls can be obtained by synergy of individual and network properties using (i) three different sets of bursters with five biophysical parameters and (ii) a network with appropriate leader-follower connections.

4.3. An illustrative example. We now illustrate how the foregoing analysis can help one to modify existing models to produce desired behaviors, perhaps when precise parameter details, or even current types, are unavailable. Specifically, we show how the SRK model [13], first introduced by Chay and Keizer [12], can be adapted to yield different duty cycles and numbers of APs per burst.

The SRK model may be written

$$\begin{aligned}
 C_m \dot{v} &= -\bar{g}_K n(v - E_K) - I_{Ca}(v) - g_{KCa}(Ca) \cdot (v - E_K), \\
 \dot{n} &= \lambda \frac{n_\infty(v) - n}{\tau_n(v)}, \\
 \dot{Ca} &= f(-\alpha I_{Ca}(v) - k_{Ca} Ca)
 \end{aligned}
 \tag{4.3}$$

(cf. [37] and a slightly modified version in [33, p. 192]). Here,

$$\begin{aligned}
 I_{Ca}(v) &= \bar{g}_{Ca} m_\infty(v) h_\infty(v) (v - E_{Ca}), \\
 g_{KCa}(Ca) &= \bar{g}_{KCa} \frac{Ca}{K_d + Ca},
 \end{aligned}
 \tag{4.4}$$

and $n_\infty, m_\infty, h_\infty$ are standard HH-type equilibrium functions (see Appendix B for functional forms and parameters). The model has a potassium current $I_K = \bar{g}_K n(v - E_K)$, a fast transitory calcium current I_{Ca} , and a very slow calcium-dependent potassium current $I_{KCa} = g_{KCa}(Ca) \cdot (v - E_K)$. Intracellular calcium affecting the conductance via (4.4) has its own dynamics given in the last equation of (4.3).

To compare (4.3) with (4.1) more directly, we first rewrite the system so that the calcium-dependent potassium current $I_{KCa} = g_{KCa}(Ca)(v - E_K)$ is linear in a new very slow variable

$$c = \frac{Ca}{K_d + Ca}.
 \tag{4.5}$$

Differentiating (4.5), we find $\dot{c} = \frac{K_d}{(K_d + Ca)^2} \dot{Ca}$, and inverting (4.5) to obtain $Ca = K_d \frac{c}{1-c}$, we have

$$\begin{aligned}
 C_m \dot{v} &= -\bar{g}_K n(v - E_K) - I_{Ca}(v) - \bar{g}_{KCa} c(v - E_K), \\
 \dot{n} &= \lambda \frac{n_\infty(v) - n}{\tau_n(v)}, \\
 \dot{c} &= f \frac{(1-c)^2}{K_d} \left(-\alpha I_{Ca}(v) - k_{Ca} K_d \frac{c}{1-c} \right),
 \end{aligned}
 \tag{4.6}$$

with I_{Ca} as given above. The nullclines of the $\dot{c}$ equation are now

$$c = 1 \quad \text{and} \quad c = \frac{\alpha \bar{g}_{Ca} m_\infty(v) h_\infty(v) (v - E_K)}{\alpha \bar{g}_{Ca} m_\infty(v) h_\infty(v) (v - E_K) - k_{Ca} K_d}.$$

For the parameters of [13] the nullcline $\dot{c} = 0$ behaves as in our model, in the relevant region of voltages (Figure 15a₄).

The current $\bar{g}_{KCa}$ enters (4.3) as does $\bar{g}_{KS}$ in (4.1)–(4.2); we can therefore expect that changing $\bar{g}_{KCa}$ will primarily affect the duty cycle. Figures 15a₁–b₁ reveal that this is the case, although the bursting frequency also changes. In fact, since $K_d \gg Ca$, the conductance g_{KCa} is essentially proportional to c , (4.5) is in its linear regime, and (4.3)–(4.4) is close to (4.1)–(4.2).

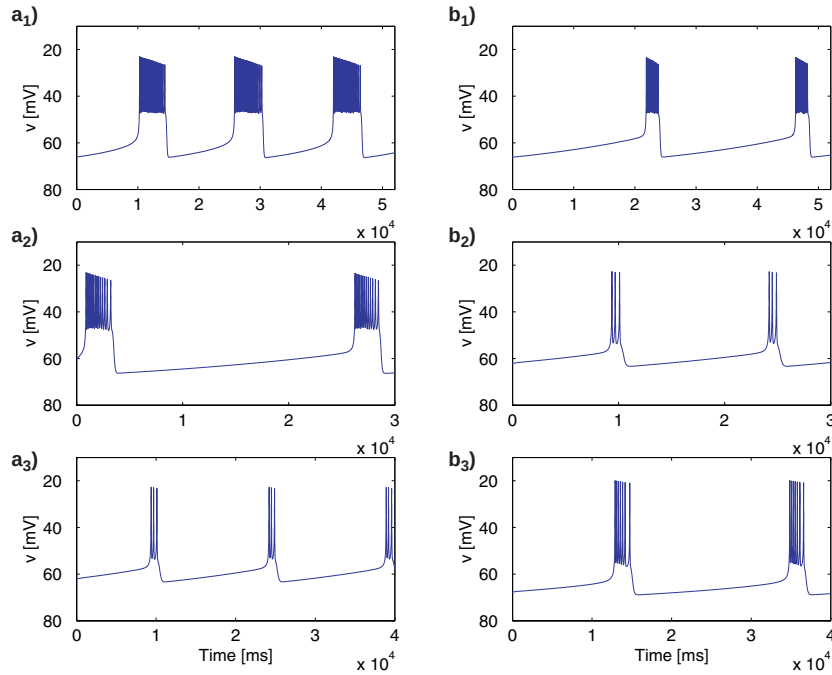


Figure 15. Bursts in the SRK model. Panels (a₁), (b₁) Duty cycle changes due to $\bar{g}_{KCa}$: $\bar{g}_{KCa} = 30000$, left, and 41750, right. (a₂), (b₂) Effect of λ on numbers of APs: $\lambda = 1.7$, left, and 1.55, right. (a₃), (b₃) Effect of added external currents on AP numbers and bursting frequency: $I_{ext} = 0$, left, and -550 , right.

To adjust the number of spikes per burst, we could change membrane capacitance C , but this has very little effect on spike numbers and drastically reduces their magnitudes (results not shown). Adding bias currents also has little effect, since the system is in a high AP number/burst regime. However, decreasing the parameter λ ($\sim \epsilon$ in (4.1)) reduces the number of APs from 22 to 2–3; this is accompanied by a moderate increase in bursting frequency (Figure 15(a₂–b₂)). In this regime, an additional bias current has a much stronger influence, permitting adjustment of AP numbers without drastically changing the bursting frequency (Figure 15(a₃–b₃)).

5. Conclusions. This paper develops a minimal model for a bursting neuron. We retain sufficient biophysical detail to permit appropriate parameter choices and variations to reproduce experimental data, while striving for generality and relative simplicity. Much current research concerns subcellular details of ionic currents, channels, and molecular messengers [43, 54, 17], but despite the ability of such detailed models to reproduce experimental data (e.g., [6, 7, 8]), their complexity and sensitivity to parameter variations render them effectively unanalyzable. We believe that massive simulations or experiments alone do not provide global understanding, which profits more from the identification of a few key mechanisms. We hope to extract these by judicious *selection*, rather than inclusion, of biological data, and in doing so to provide a flexible and tractable mathematical framework within which biological hypotheses can be investigated and novel experiments suggested.

To this end, we review ion channel models of HH type and propose a generic three-dimensional ODE (4.1)–(4.2) that exploits the presence of three disparate timescales and obviates the detailed analysis of multiple currents, although we show how additional currents can be classified and incorporated, and their influences investigated via steady state current-voltage curves and their derivatives. We note that some currents increase complexity without adding new qualitative behaviors, and thus can be neglected, at least in a first approximation. Our procedure yields guidelines for creating models of specific behaviors, and we use it here to select a minimal set of currents necessary to produce bursting, and to understand the role of biophysical parameters such as conductances and bias currents in determining the bursting frequency, duty cycle, spike rates, and numbers of APs per burst. We further illustrate by showing how duty cycles and AP numbers can be adjusted in the SRK model.

Previous work of Bertram et al. [21], Rinzel and Lee [18], Rinzel [19], Izhikevich [35], and others, summarized in [33], develops a topological classification of bursting mechanisms, based on the types of bifurcations that the fast subsystem undergoes as c (or I_{ext}) varies. This illuminates the phase space geometry. The present treatment is more analytical in nature and allows one to determine if specific currents with particular “influence windows” $U_i = [v_{th_i}, E_i]$ can introduce new folds and hence SN bifurcations, or otherwise change stability types of equilibria in the fast subsystem. Although our classification is in terms of steady state properties of ionic currents and does not reveal all details of the periodic orbits, it nonetheless allows one to adjust periodic orbit branches in the fast subsystem, via the reduced $\dot{c} = 0$ nullcline and $\dot{v} = 0$ bifurcation set, and hence to tune burst properties.

In the paper [1] we will show how the bursting model (4.1)–(4.2), along with a single equation describing synaptic dynamics, may be used as the basic subunit in building a model of an insect CPG and motoneurons.

Appendix A. A Rose–Hindmarsh model. Rose and Hindmarsh [14, p. 273] considered the following model for a repetitively firing neuron:

$$(A.1) \quad C\dot{v} = -[\bar{g}_{\text{Na}}m^3h(v - E_{\text{Na}}) + g_{\text{L}}(v - E_{\text{L}}) + g_{\text{K}}n^4(v - E_{\text{K}}) - g_{\text{A}}a^3b(v - E_{\text{K}})] + I,$$

where the five gating variables m, h, n, a, b are described by the usual first order kinetics (2.2b). From this they obtained the third order system

$$(A.2) \quad \begin{aligned} C\dot{v} = & -[-3\bar{g}_{\text{Na}}m_{\infty}^3q(v - E_{\text{Na}}) + 3A\bar{g}_{\text{Na}}b_{\infty}m_{\infty}^3(v - E_{\text{Na}})] \\ & - [0.85\bar{g}_{\text{Na}}m_{\infty}(v - E_{\text{Na}}) + \bar{g}_{\text{L}}(v - E_{\text{L}}) + \bar{g}_{\text{K}}q(v - E_{\text{K}})] \\ & - [\bar{g}_{\text{s}}s_{\infty}(v - E_{\text{s}}) + \bar{g}_{\text{out}}z(v - E_{\text{K}}) - I], \\ \dot{q} = & \frac{q_{\infty}(v) - q}{\tau_q(v)}, \\ \dot{z} = & \frac{z_{\infty}(v) - z}{\tau_z(v)}. \end{aligned}$$

In reducing the six-dimensional model they employed a slow gating variable q that combines both sodium and potassium channels, and, numerically confirming that $\tau_b(v) \approx \tau_n(v)$, they replaced *both* τ_b and τ_n by the average value $\tau_q(v) = \frac{1}{2}(\tau_b(v) + \tau_n(v))$.

Appendix B. The SRK model. The SRK model results of section 4.3 were obtained for (4.3)–(4.4), where n_∞ , m_∞ , and h_∞ are the standard HH equilibrium functions

$$(B.1) \quad n_\infty = \frac{1}{1 + e^{\frac{V_n - v}{S_n}}}, \quad m_\infty = \frac{1}{1 + e^{\frac{V_m - v}{S_m}}}, \quad h_\infty = \frac{1}{1 + e^{\frac{v - V_h}{S_h}}},$$

and

$$(B.2) \quad \tau_n(v) = \frac{\gamma}{e^{\frac{v - \bar{V}}{a}} - e^{-\frac{v - \bar{V}}{b}}}, \quad \alpha = \frac{1}{2V_{\text{Cell}}F}.$$

The parameters used in section 4.3 are given in Table 2.

Table 2

Parameter values for the SRK model for bursting pancreatic β -cells.

$\bar{g}_{\text{Ca}}$	= 1400 pS	E_{Ca}	= 110 mV
$\bar{g}_{\text{K}}$	= 2500 pS	E_{K}	= −75 mV
$\bar{g}_{\text{KCa}}$	= 30000 pS		
C_m	= 5310 fF	V_{Cell}	= 1150 μm^3
F	= 96.487 Coul/mMol	K_d	= 100 μMol
λ	= 1.7	k_{Ca}	= 0.03 m/s
V_n	= −15 mV	S_m	= 5.6 mV
V_m	= 4 mV	S_m	= 14 mV
V_h	= −10 mV	S_h	= 10 mV
a	= 65 mV	b	= 20 mV
γ	= 60 ms	$\bar{V}$	= −75 mV
f	= 0.001		

Appendix C. Bursting pacemaker neurons in the pre-Bötzinger complex. Butera, Rinzel, and Smith [17] considered two possible models for bursting pacemaker neurons in the pre-Bötzinger complex. Model 1 takes the form

$$(C.1) \quad \begin{aligned} C\dot{v} &= -[I_{\text{NaP}} + I_{\text{Na}} + I_{\text{K}} + I_{\text{L}} + I_{\text{tonic-e}}] + I_{\text{app}}, \\ \dot{n} &= \frac{\epsilon}{\tau_n(v)} [n_\infty(v) - n], \\ \dot{h} &= \frac{\delta}{\tau_h(v)} [h_\infty(v) - h], \end{aligned}$$

with $I_{\text{tonic-e}}$ and I_{app} fixed biases and the other currents specified by

$$(C.2) \quad \begin{aligned} I_{\text{Na}} &= \bar{g}_{\text{Na}} m_\infty^3(v) (1 - n) \cdot (v - E_{\text{Na}}), & I_{\text{K}} &= \bar{g}_{\text{K}} n^4 \cdot (v - E_{\text{K}}), \\ I_{\text{L}} &= \bar{g}_{\text{L}} (v - E_{\text{L}}), & I_{\text{NaP}} &= \bar{g}_{\text{NaP}} m_\infty(v) h \cdot (v - E_{\text{Na}}). \end{aligned}$$

The time course of inactivation of the sodium gating channel (h in the original HH equations [2]) as stated in [17] is “assumed to be of similar dynamics as n and is approximated by $h = (1 - n)$ ” [55, 56]. As in Appendix A, this is an instance of a single gating variable (n) associated to two different ionic channels (I_{Na} and I_{K}).

Model 2 takes the form

$$\begin{aligned}
 (C.3) \quad C\dot{v} &= -[I_{\text{NaP}} + I_{\text{KS}} + I_{\text{Na}} + I_{\text{K}} + I_{\text{L}} + I_{\text{tonic-e}}] + I_{\text{app}}, \\
 \dot{n} &= \frac{\epsilon}{\tau_n(v)} [n_{\infty}(v) - n], \\
 \dot{k} &= \frac{\delta}{\tau_k(v)} [k_{\infty}(v) - k].
 \end{aligned}$$

In addition to a leakage current $I_{\text{L}} = \bar{g}_{\text{L}}(v - E_{\text{L}})$, the currents in (C.3) are

$$\begin{aligned}
 (C.4) \quad I_{\text{Na}} &= \bar{g}_{\text{Na}} m_{\infty}^3(v) \cdot (v - E_{\text{Na}}), & I_{\text{K}} &= \bar{g}_{\text{K}} n^4 \cdot (v - E_{\text{K}}), \\
 I_{\text{KS}} &= \bar{g}_{\text{KS}} k(v - E_{\text{K}}), & I_{\text{NaP}} &= \bar{g}_{\text{NaP}} m_{\infty}(v) \cdot (v - E_{\text{Na}}).
 \end{aligned}$$

Note that I_{NaP} does not inactivate as in model 1.

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