The Sherman-Rinzel-Keizer Model for Bursting Electrical Activity in the Pancreatic $\beta$-Cell

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Abstract

Pancreatic $\beta$-cells exhibit periodic bursting electrical activity (BEA) consisting of active and silent phases. The Sherman-Rinzel-Keizer (SRK) model of this phenomenon consists of three coupled first-order nonlinear differential equations which describe the dynamics of the membrane potential, the activation parameter for the voltage-gated potassium channel, and the intracellular calcium concentration. These equations are nondimensionalized and transformed into a Liénard differential equation coupled to a single first-order differential equation for the slowly changing nondimensional calcium concentration. Leading-order perturbation problems are derived for the silent and active phases of the BEA on slow and fast time scales. Numerical solutions of these leading-order problems are compared with those for the exact equation in their respective regions. The leading-order solution in the active phase has a limit cycle behavior with a slowly varying frequency. It is observed that the "damping term" in the Liénard equation is small numerically.

Keywords: Bursting electrical activity — Nonlinear oscillators — Limit cycles — Perturbation problems — $\beta$-cells — Sherman-Rinzel-Keizer model

1 Introduction

Bursting electrical activity in excitable cells is a dynamical phenomenon in which the membrane potential undergoes a succession of alternating active and silent phases. The active phase is characterized by a sequence of rapid oscillations and the silent phase is characterized by a slowly changing membrane potential. The overall phenomenon consisting of active and silent phases appears periodic and, in the case of the $\beta$-cell, is associated with a putative slowly oscillating intracellular calcium concentration.

As a biological phenomenon, bursting in the $\beta$-cell is important because it is related to insulin release. In particular, the ratio of the duration of the active phase to the overall period, i.e., the plateau fraction, is proportional to
the rate at which the β-cell releases insulin in response to given glucose concentrations (Ozawa and Sand 1986, Henquin and Meissner 1984, Meissner and Schmelz 1974). These β-cells are located within the pancreas and occur in clusters called the Islets of Langerhans. Early electrophysiological experiments (Dean and Matthews 1970) were performed in vitro on cells within the islets of the mouse. In these experiments, bursting electrical activity (BEA) was observed when isolated mouse islets were bathed in a D-glucose solution. Higher concentrations of glucose result in longer active phases, and for sufficiently high concentrations, only the active phase is present, i.e., there is a complete absence of the silent phase.

Through the use of ionic channel blocking agents and externally applied currents, a variety of ionic channels in the membrane have been identified (Dean and Matthews 1970a,b, Meissner and Schmelz 1974, Atwater et al. 1978a,b,c, Meissner and Preissler 1980). Based on an accumulation of such data, Atwater et al. (1980) devised a biophysical model of BEA in β-cells which led Chay and Keizer (1983) to develop a “minimal” mathematical model. Their model is “minimal” in the sense that it includes the fewest number of ionic transport mechanisms necessary to explain the phenomenon. Since voltage clamp data for β-cells were not available at that time, the channel activation functions in the Chay-Keizer (CK) model were specified by modifying those in the Hodgkin-Huxley (1952) model for electrical activity in the squid giant axon. Other models for BEA in β-cells have been proposed (cf. Keizer, 1988).

Rorsman and Trube (1986) performed voltage clamp experiments on β-cells and curve fitted these channel activation functions to the data. Sherman et al. (1988) obtained an improved fit to Rorsman and Trube’s experimental I-V curve and have incorporated this into their “minimal” model. Although the maximal channel conductances in the Sherman-Rinzel-Keizer (SRK) model differ substantially from those in the earlier CK model, the membrane potentials in both models exhibit the same qualitative behaviors. This apparent contradiction will be resolved in this paper.

As a mathematical phenomenon, BEA depends on fast and slow processes with distinctly different time scales. Comparison of the short time scale of one oscillation in the active phase to the long time scale of the overall active-silent phase period leads naturally to the use of perturbation methods. The “small” parameter on which to base a perturbation analysis is the fraction of free to bound calcium ions, f. However, the main difficulty in performing such an analysis on the CK and SRK models is that they contain nonlinearities which make analytical work difficult and numerical calculations necessary.

From this mathematical point of view, the SRK model is more suitable for analytical treatment since it is linear in the potassium channel activation variable, n. The 20 parameters (10 parameters define the channel activation functions and 10 biological parameters describe the cell membrane electrical properties) contained in the SRK model make numerical computations essential. However, extensive numerical parametric studies are limited by this large number of parameters. Two purposes of applying perturbation techniques to the SRK model are to identify the important parameters in each phase and to determine their
effects on the bursting phenomenon.

In this paper, the SRK equations are nondimensionalized, yielding 15 dimensionless parameters, which is still a large number of parameters. The potassium activation variable, $n$, is scaled so that its values in the active phase are near unity. Also, a dimensionless small parameter, $\varepsilon$, is defined. Then the resulting system of three first-order nonlinear ordinary differential equations is transformed into a system containing a second-order differential equation and a first-order equation. The second-order equation is linear in its derivatives and in the active phase is weakly coupled to the first-order equation.

From these equations, the leading-order problems for the active and silent phases are obtained in separate perturbation analyses involving "fast" and "slow" times. For the active phase, the "fast" time problem has a leading-order solution which is a limit cycle. The period of this limit cycle slowly increases as the calcium concentration increases. A multiple scales procedure applied to the calcium equation yields this slow evolution. As the calcium concentration approaches its maximum value, the rapidly oscillating active phase trajectory passes through a separatrix and the local instability of the solution near the system's leading-order nullcline causes a transition back to the silent phase. The leading-order equation in the active phase can be put in Lienard form with a "damping" term which is $O(1)$ in $\varepsilon$ so the multiple scales procedures of Kuzmak (1959) and Luke (1966) for "strongly nonlinear" oscillators are not strictly applicable. However, it is found that the damping term is numerically small and this leads to the possibility of treating it formally as $o(1)$ in $\varepsilon$.

In Sect. 2, the SRK model is introduced and assumptions leading to the equations are described. Nondimensionalization of the SRK model and scaling considerations are discussed in Sect. 3. Here, the small parameter, $\varepsilon$, is defined. The transformation of the system of three first-order ordinary differential equations to a second-order equation coupled to a first-order equation is given in Sect. 4. Detailed numerical studies of the phenomenon have been carried out and some of the results are presented in Sect. 5. These computations are used to motivate the derivations of the perturbation problems for the active and silent phases presented in Sect. 6. For the leading-order problems, the solution in the active phase is compared to a numerical solution of the exact problem and the trajectory in the silent phase is shown to lie on a leading-order nullcline.

2 The SRK model

The cellular membrane is a phospholipid bilayer and ions can flow between intracellular and extracellular regions through macromolecular pores (channels) imbedded in this bilayer. Generally, intracellular and extracellular concentrations of a given ion are very different and the resulting net charge differences across the membrane produce a potential difference, $V$, normally negative inside relative to the outside. The channels in the bilayer facilitate or impede ionic transport depending on various influences, e.g., the membrane potential. Unlike classical diffusion processes, the rate of ionic transport through the membrane
Sherman-Rinzel-Keizer Model

is not proportional to the difference of intracellular and extracellular concentrations.

The SRK model of β-cell electrical activity (Sherman et al. 1988) is a set of ionic current and concentration balance equations where the $Ca^{2+}$ and $K^+$ ionic transport rates through the membrane are modelled using voltage-, time-, and concentration-dependent channel conductances. The intracellular calcium concentration is small and for the range of $V$ observed during the BEA, calcium ions flow from the extracellular space into the intracellular compartment. Simultaneously the large intracellular potassium concentration drives $K^+$ ions up the electrical potential gradient into the extracellular space through their respective channels.

Spatial effects are neglected by assuming the membrane is an homogenous medium with uniformly distributed channels. Cell parameters such as cell radius, cellular volume, and total membrane capacitance, $C_m$, are each assumed constant. Membrane ionic currents increase intracellular $Ca^{2+}$ concentrations, and uptake of $Ca^{2+}$ (e.g., by the endoplasmic reticulum, mitochondria, or membrane pumps) tends to decrease the intracellular calcium concentration, $Ca_1$, at a rate proportional to $Ca_1$. Only the calcium and potassium ionic currents are assumed essential for BEA in β-cells. The channel conductances associated with these currents were curve fitted by Sherman et al. (1988) to the experimental results on β-cells obtained by Rorsman and Trube (1986). Thus the SRK model consists of the following set of equations:

$$C_m \frac{dV}{dt} = \bar{g}_{Ca} m_{\infty}(V) \bar{h}(V)(V_{Ca} - V) - \bar{g}_n n(V - V_K) - g_{K-Ca}(Ca_1)(V - V_K), \quad (2.1)$$

$$\frac{dn}{dt} = \frac{n_{\infty}(V) - n}{\tau_n(V)}, \quad (2.2)$$

$$\frac{dCa_1}{dt} = f[\alpha \bar{g}_{Ca} m_{\infty}(V) \bar{h}(V)(V_{Ca} - V) - k_{Ca} Ca_1], \quad (2.3)$$

where

$$\alpha = \frac{1}{2V_{cell} F}, \quad F = 96485 \text{ coul/mole is Faraday's constant}, \quad (2.4)$$

and,

$$g_{K-Ca}(Ca_1) = \bar{g}_{K-Ca} \frac{Ca_1}{K_d + Ca_1}, \quad (2.5)$$

$$m_{\infty}(V) = \frac{1}{1 + \exp[(V_m - V)/S_m]}, \quad (2.6)$$

$$\bar{h}(V) = \frac{1}{1 + \exp[(V - V_h)/S_h]}, \quad (2.7)$$

$$n_{\infty} = \frac{1}{1 + \exp[(V_n - V)/S_n]}, \quad (2.8)$$

$$\tau_n(V) = \frac{\bar{\tau}_n}{\exp[(V - V_K)/S_a] + \exp[-(V - V_K)/S_b]}, \quad (2.9)$$
The equation for the membrane potential (2.1) is a current balance equation. The term on the left side represents the membrane capacitive current with capacitance, \( C_m \), while the terms on the right side represent the ionic currents through the membrane due to voltage-gated calcium channels, voltage-gated potassium channels, and calcium-activated potassium channels, respectively. The activation variable, \( n \), associated with the voltage-gated potassium channel is assumed to obey the relaxation equation (2.2) with channel activation function, \( n_{\infty}(V) \), and relaxation time, \( \tau_n(V) \), given by (2.8) and (2.9), respectively. (Equations (2.2) and (2.9) differ from those in the SRK model in that the SRK parameter \( \lambda \) has been absorbed into \( \tau_n \).) Since the relaxation time for the calcium channel's activation variable, \( m \), is much shorter than \( \tau_n(V) \), this variable is replaced by its respective channel activation function, \( m_{\infty}(V) \), given by (2.6).

Table 1. Left table shows comparison of parameter values in SRK and CK models with CK values taken from Chay and Keizer (1985). Right table gives parameter values used to define \( h(V) \), \( m_{\infty}(V) \), \( n_{\infty}(V) \), and \( \tau_n(V) \) in the SRK model.

<table>
<thead>
<tr>
<th>Parameter ( V ) (mV)</th>
<th>SRK</th>
<th>CK</th>
<th>Parameter ( V ) (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_C )</td>
<td>110</td>
<td>100</td>
<td>( V_b )</td>
</tr>
<tr>
<td>( V_K )</td>
<td>-75</td>
<td>-75</td>
<td>( V_h )</td>
</tr>
<tr>
<td>( \bar{g}_C ) (pS)</td>
<td>1400</td>
<td>8000</td>
<td>( V_m )</td>
</tr>
<tr>
<td>( \bar{g}_K ) (pS)</td>
<td>2500</td>
<td>7500</td>
<td>( V_n )</td>
</tr>
<tr>
<td>( \bar{g}_{K-Ca} ) (pS)</td>
<td>30000</td>
<td>50</td>
<td>( S_a )</td>
</tr>
<tr>
<td>( V_{Calc} ) (mV)</td>
<td>1150</td>
<td>905</td>
<td>( S_b )</td>
</tr>
<tr>
<td>( C_m ) (fF)</td>
<td>5310</td>
<td>4524</td>
<td>( S_h )</td>
</tr>
<tr>
<td>( K_d ) (\mu M)</td>
<td>100</td>
<td>1</td>
<td>( S_m )</td>
</tr>
<tr>
<td>( k_{Ca} ) (ms(^{-1}))</td>
<td>.03</td>
<td>.02</td>
<td>( S_n )</td>
</tr>
<tr>
<td>( \kappa_d ) (\mu M)</td>
<td>.472</td>
<td>2.591</td>
<td>( \tau_n )</td>
</tr>
</tbody>
</table>

Equation (2.3) represents a balance equation for the intracellular calcium concentration where \( f \) is the ratio of free to bound calcium ions, assumed to be constant. The first term on the right side of (2.3) represents a calcium concentration increase due to an influx of \( Ca^{2+} \) through the voltage-gated calcium channels where \( \alpha \) is a geometrical factor which accounts for cell shape and volume. The second term represents a decrease in the cytoplasmic \( Ca^{2+} \) concentration due to intracellular buffering. Although many mechanisms for calcium buffering have been observed, the decrease caused by mitochondria, via a glucose-dependent process stimulated by oxidative phosphorylation, is thought to be the most prominent (Chay and Keizer, 1983). With this interpretation of calcium buffering, the rate constant, \( k_{Ca} \), increases with glucose concentration.

A summary of values for the maximal channel conductances, \( \bar{g}_C, \bar{g}_K, \) and \( \bar{g}_{K-Ca} \), the Nernst potentials for calcium and potassium, \( V_C \) and \( V_K \), and the remaining parameters defining the channel activation functions and relaxation time can be found in Table 1.
3 Nondimensionalization and scaling

In order to carry out a systematic perturbation analysis, it is essential to first nondimensionalize and scale the variables. As the choices of dimensionless variables are not unique, the dimensional equations were integrated numerically to help provide some insight into making such choices. Details and some results of the numerical computations are given in Sect. 5.

The membrane potential exhibits BEA and the corresponding calcium concentration has a characteristic "sawtooth" shape (cf. Fig. 1). The approximate ranges of each dimensional dependent variable in the BEA are: 1) membrane potential (mV): \(-66.8 < V < -23.1\); 2) activation variable: \(0.00011 < n < 0.107\); and 3) calcium concentration (\(\mu\)M): \(0.532 < Ca_i < 0.611\).

The activation variable, \(n\), is replaced by a scaled variable, \(\omega\), with numerical values near one in the active phase. Time is nondimensionalized so that the maximum relaxation time associated with the \(K^+\)-channel is approximately equal to one. To nondimensionalize \(Ca_i\), a scaled dissociation constant, \(\kappa_d\) with units of \(\mu\)M, was used. The choices of nondimensionalized (and scaled) membrane potential, activation variable, calcium concentration, and time are:

\[
v \equiv -V/V_K , \tag{3.1}
\]

\[
w \equiv \gamma_K n , \quad \gamma_K \equiv \frac{\bar{g}_K \tau_n}{C_m} , \tag{3.2}
\]

\[
c \equiv Ca_i/\kappa_d , \quad \kappa_d \equiv \frac{C_m K_d}{\bar{g}_K - Ca \tau_n} , \tag{3.3}
\]

\[
t \equiv \tau/\tau_n . \tag{3.4}
\]

Note that \(v\) has been chosen to take on negative values although this is not the natural mathematical choice. However, this choice maintains the physiological intuition associated with \(V\). Denoting differentiations with respect to \(t\) by \(\dot{}\), the corresponding nondimensional ordinary differential equations are:

\[
\dot{v} = i_{Ca}(v) - w(v + 1) - g(c)(v + 1) , \tag{3.5}
\]

\[
\dot{w} = \frac{w_\infty(v) - w}{\tau_w(v)} , \tag{3.6}
\]

\[
\dot{c} = \epsilon[\beta i_{Ca}(v) - c] , \tag{3.7}
\]

where

\[
i_{Ca}(v) = \frac{\gamma_K Ca(v Ca - v)}{(1 + \exp[(v_m - v)/s_m])(1 + \exp[(v - v_h)/s_h])} , \tag{3.8}
\]

\[
g(c) = \frac{\gamma_K}{1 + c/\gamma_K - Ca} , \tag{3.9}
\]

\[
w_\infty(v) = \frac{\gamma_K}{1 + \exp[(v_n - v)/s_n]} , \tag{3.10}
\]

\[
\tau_w(v) = \frac{1}{\exp[(v - v_b)/s_b] + \exp[-(v - v_b)/s_b]} , \tag{3.11}
\]

\]
Fig. 1. One cycle of BEA in transformed variables. a shows the transformed membrane potential $u$. The active phase spikes are numbered from 0 to 21 for comparison purposes in later figures. The insert details the slow frequency decrease of these oscillations. b shows the dimensionless calcium concentration $c$. 
are the dimensionless calcium current, calcium-activated potassium conductance, activation function, and the relaxation time, respectively. The notational changes made in the dimensionless SRK equations permit the 15 dimensionless parameters to be written in the compact form:

\[ v_i = -V_i / \nu_K \quad \text{where} \quad i = \text{Ca}, b, h, m, n, \]  
\[ s_i = -S_i / \nu_K \quad \text{where} \quad i = \text{a}, b, h, m, n, \]  
\[ \gamma_i = \frac{\bar{g}_i \tau_n}{\nu_m} \quad \text{where} \quad i = \text{Ca}, K, K-Ca, \]  
\[ \epsilon = f \tau_n k_Ca, \]  
\[ \beta = \frac{-\alpha V_K \bar{g}_K - C_a}{k_Ca K_d}. \]  

The values of these parameters are summarized in Table 2. Since \( \epsilon / f = 1.125 \), it is evident that the smallness of \( \epsilon \) is a consequence of the small ratio, \( f \), of free to bound intracellular calcium ions.

**Table 2. Dimensionless parameter values for SRK model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SRK</th>
<th>Parameter</th>
<th>SRK</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f )</td>
<td>0.001</td>
<td>( \nu_h )</td>
<td>-0.133</td>
</tr>
<tr>
<td>( \epsilon )</td>
<td>0.001125</td>
<td>( \nu_m )</td>
<td>0.0533</td>
</tr>
<tr>
<td>( \beta )</td>
<td>3.380</td>
<td>( \nu_n )</td>
<td>-0.200</td>
</tr>
<tr>
<td>( \gamma_K )</td>
<td>17.655</td>
<td>( \kappa_a )</td>
<td>0.866</td>
</tr>
<tr>
<td>( \gamma_Ca )</td>
<td>9.887</td>
<td>( \kappa_b )</td>
<td>0.266</td>
</tr>
<tr>
<td>( \gamma_{K-Ca} )</td>
<td>211.864</td>
<td>( \kappa_h )</td>
<td>0.133</td>
</tr>
<tr>
<td>( \nu_Ca )</td>
<td>1.467</td>
<td>( \kappa_m )</td>
<td>0.186</td>
</tr>
<tr>
<td>( \nu_b )</td>
<td>-1.000</td>
<td>( \kappa_n )</td>
<td>0.0746</td>
</tr>
</tbody>
</table>

The approximate ranges of each dimensionless dependent variable in the BEA are: 1) membrane potential: \(-0.878 < \nu < -0.308\); 2) activation variable: \(0.00202 < \nu < 1.88\); and 3) calcium concentration: \(1.13 < c < 1.30\).

Both \( i_{Ca}(\nu) \) and \( u_{Ca}(\nu) \) are positive and monotonically increasing functions of \( \nu \) during the BEA. Their values range from 0.1 to about 1.7 and from near 0.0 to about 3.5, respectively. The relaxation time, \( \tau_n(\nu) \), is concave down and its values range from about 0.44 to 0.58. Also, since \( \gamma_{K-Ca} \gg 1, g(c) \approx c \). Spike periods in the active phase, measured from peak to peak, range from about 3.8 to about 8.9, and are considerably less than the overall active-silent phase period, \( T \approx 380 \).
4 Transformation to a perturbed Liénard form

The nondimensional equation (3.5) can be simplified by introducing the change of variable

\[ u = \ell n(v + 1) \]  \hspace{1cm} (4.1)

which is defined for \( v > -1 \) and whose inverse is given by \( v = e^u - 1 \). Then (3.5) becomes

\[ \dot{u} = e^{-u} i_G(v(u)) - w - g(c), \]  \hspace{1cm} (4.2)

where each term on the right side corresponds to a dimensionless conductance. In particular, the variable \( w \) should be re-interpreted as the dimensionless conductance associated with the voltage-gated potassium channel.

By eliminating \( w \), the two first-order differential equations (3.6) and (4.2) can be combined into a single second-order differential equation which is in a perturbed Liénard form (Minorsky, 1962). This is accomplished by differentiating (4.2) with respect to \( t \) and using equations (3.6), (3.7), and (4.2). The resulting system of differential equations for \( u \) and \( c \) is:

\[ \ddot{u} + F(u)\dot{u} + G(u, c) = \varepsilon H(u, c), \]  \hspace{1cm} (4.3)

\[ \dot{c} = \varepsilon[\beta h(u) - c], \]  \hspace{1cm} (4.4)

where by defining

\[ \Gamma(u) \equiv e^{-u} i_G(v(u)), \quad T_n(u) \equiv \tau_w(v(u)), \quad N(u) \equiv w_{\infty}(v(u)), \] \hspace{1cm} (4.5)

the functions \( F, G, H, \) and \( h \) are given by:

\[ F(u) = \frac{1}{T_n(u)} \frac{d\Gamma(u)}{du}, \] \hspace{1cm} (4.6)

\[ G(u, c) = \frac{N(u) + g(c) - \Gamma(u)}{T_n(u)}, \] \hspace{1cm} (4.7)

\[ H(u, c) = \frac{dg}{dc}(c)[c - \beta h(u)], \] \hspace{1cm} (4.8)

\[ h(u) = i_G(v(u)). \] \hspace{1cm} (4.9)

On the \( t \) time scale, the coupling between (4.3) and (4.4) is weak since \( \dot{c} = O(c) \) with \( \varepsilon \ll 1 \). More specifically, when \( \varepsilon \) is set equal to zero in the system (4.3)-(4.4), \( c \) acts as a parameter in (4.3) which then is in the form of a Liénard differential equation.

Throughout most of the BEA, \( \Gamma(u) \) is concave up and \( h(u) \) is a monotonically increasing function of \( u \). The functions \( \Gamma(u), T_n(u), N(u), \) and \( h(u) \) are each positive, and \( F(u), G(u, c), \) and \( H(u, c) \) have signs which depend on the values of \( u \) and \( c \). In particular, the sign of \( F(u) \) during the active phase is important since it determines whether the damping in (4.3) is positive or negative.

Two advantages in studying the system (4.3)-(4.4) instead of the system (3.5)-(3.7) are: 1) the transformation (4.1) makes (4.3) quasi-linear, i.e., the resulting second-order equation for \( v \) would have been quadratic in \( \dot{v} \) and 2) perturbed second-order differential equations for oscillatory systems are commonly treated in the literature on perturbation theory (Bender and Orszag 1978, Kevorkian and Cole 1981).
5 Numerical results

Computations on the SRK model were carried out on a VAX 3500 using the CMLIB ordinary differential equation solving routine DDRIV3. The routine was set for a Gear integrator and all computations were carried out using double precision. The relative error for most runs was fixed at $10^{-7}$ and the time step was chosen to be sufficiently small so that the details of individual spikes could be resolved graphically.

The solutions $u(t)$ and $c(t)$ were obtained by numerical integration of (4.3)-(4.4) and are represented in Fig. 1. The calcium cycle shown in Figure 1b has values of $c$ which increase during the active phase and decrease during the silent phase. The oscillations of $u(t)$ in the active phase approximately begin and end at those times where $\dot{c} = 0$. The weak coupling between $u$ and $c$ during the active phase is manifest by noting the small amplitude of the oscillations in $c$.

Two-dimensional projections of the 3-dimensional BEA cycle in $(u, \dot{u}, c)$-space are shown in Fig. 2. Figure 2a is the projection onto the $(u, c)$-plane and Fig. 2b is the projection onto the $(\dot{u}, c)$-plane. During the silent phase, the solution lies close to the $\dot{u} = 0$ plane and values of $c$ decrease. When $c$ becomes small a transition to the active phase occurs. During the active phase the solution slowly spirals upwards as $c$ increases. When values of $c$ become large, the oscillation in the active phase terminates, a transition back to the silent phase occurs, and the entire cycle then repeats itself.

For numerical experiments with durations much longer than those shown in Fig. 1, there is a persistence of the bursting and sawtooth patterns exhibited by $u$ and $c$, respectively. Although the accuracy of such experiments may be questioned, it is believed that the phenomenon is periodic. Numerical experiments, where a variety of different initial conditions were used, support the conjecture that the repetitive BEA represents an attractive 3-dimensional limit cycle in $(u, \dot{u}, c)$-space. If an initial condition is chosen which has a value of $c(0)$ larger than the minimum value of $c(t)$ in Fig. 1b, the resulting trajectory approaches the numerical solution in Fig. 1 within one BEA cycle. If $c(0)$ is chosen smaller than the minimum $c(t)$ in Fig. 1b, the initial part of the first active phase can contain extra spikes. Subsequent active phases, however, all contain the same number of spikes.

The existence of two separate time scales is very evident in Fig. 1a. During the silent phase $\dot{u}$ nearly equals zero for a time span of $\Delta t \approx 250$. In contrast, each oscillation of $u(t)$ in the active phase has an amplitude of $O(1)$ and occurs in a time span $\Delta t \approx 5$. Furthermore, there is a slow increase in the frequency of these oscillations which is reminiscent of frequency changes found in other nonlinear oscillators. Also, it is worth noting that the oscillations in the active phase are approximately symmetric about the $\dot{u} = 0$ plane (see Fig. 2a).

The solution crosses the $\dot{c} = 0$ nullsurface (i.e., the surface in the $(u, \dot{u}, c)$-space defined by the right-hand-side of (4.4) equal to zero) in the transition regions connecting the active and silent phases. The position of the middle portion of this nullsurface is between the active and silent phases and explains the increasing/decreasing behavior of $c$ with the active/silent phases of $u$. 
Fig. 2. Projections of one complete BEA cycle onto a the $(u, \dot{u})$-plane and b the $(u, c)$-plane. Dashed curve corresponds to nullcline for Liénard equation.
6 Leading-order perturbation problems

The silent-active phase cycle governed by (4.3)-(4.4) consists of a silent phase, a transition to the active phase, an active phase, and a transition back to the silent phase. A complete perturbation analysis of the BEA cycle requires separate treatments of each part of this cycle coupled with a set of matching conditions. In this section, the leading-order perturbation problems for the active and silent phases are determined systematically from (4.3)-(4.4) for \( \varepsilon \to 0 \). Then the closeness of the solutions of these approximate problems to the exact solution will be shown by comparing the corresponding numerical solutions.

The silent phase is characterized by slow changes of both \( u \) and \( c \) on the \( t \) scale. More specifically, \( du/dc \) is \( O(1) \) in the silent phase (see Fig. 2b) and since \( \dot{c} \) is \( O(\varepsilon) \), then \( u \) must be \( O(\varepsilon) \). A slow time, \( \tilde{t} \), and new dependent variables are defined by

\[
\tilde{t} \equiv \varepsilon t, \quad U(\tilde{t}; \varepsilon) \equiv u(\varepsilon^{-1}\tilde{t}; \varepsilon), \quad C(\tilde{t}; \varepsilon) \equiv c(\varepsilon^{-1}\tilde{t}; \varepsilon).
\]

(6.1)

Both \( U \) and \( C \) undergo \( O(1) \) changes on \( \tilde{t} \) time intervals of \( O(1) \). If \( (') \) denotes differentiation with respect to \( \tilde{t} \), (4.3)-(4.4) become:

\[
\varepsilon^2 U'' + \varepsilon F(U)U' + G(U, C) = \varepsilon H(U, C),
\]

(6.2)

\[
C' = \beta h(U) - C.
\]

(6.3)

Formally, the leading-order silent phase problem is determined by substituting

\[
U(\tilde{t}; \varepsilon) \sim U_0(\tilde{t}) + \varepsilon U_1(\tilde{t}) + \cdots,
\]

(6.4)

\[
C(\tilde{t}; \varepsilon) \sim C_0(\tilde{t}) + \varepsilon C_1(\tilde{t}) + \cdots,
\]

(6.5)

into (6.2)-(6.3), expanding the functions \( F, G, \) and \( H \) in Taylor series, and then setting \( \varepsilon \) equal to zero in the resulting equations. The solution for \( (U_0, C_0) \) is subsequently determined from the algebraic equation

\[
G(U_0, C_0) = 0,
\]

(6.6)

and the first-order differential equation

\[
C'_0 + C_0 = \beta h(U_0).
\]

(6.7)

The algebraic equation (6.6) can be solved explicitly for \( C_0 \) obtaining

\[
C_0 = \gamma_0(U_0) \equiv \frac{\Gamma(U_0) - N(U_0)}{1 + \gamma_{K-C}^{-1}\gamma_0[N(U_0) - \Gamma(U_0)]}.
\]

(6.8)

A confirmation of (6.6) as part of the correct leading-order problem for the silent phase is shown in Fig. 2b \(^3\) where the curve defined by (6.8) has been superimposed onto the numerical solution of (4.3)-(4.4). From (6.2) the

\(^3\) Since this paper does not treat the SRK model as a bifurcation problem, it is more suitable to re-orient the usual "Z" curve (see Fig. 3, Rinzel and Lee 1986) to a backwards "N" curve in the \((u, c)\)-plane.
$G(u, c) = 0$ surface, $S$, is seen to be the leading-order $U'$ nullsurface i.e., with $\varepsilon \to 0$. The surface $S$ divides the $(u, \dot{u}, c)$-space into two regions with $G > 0$ above $S$ and $G < 0$ below $S$. The left branch of $S$ is defined as the points $(u, \dot{u}, c)$ which have values of $u$ less than that at the local minimum of $\gamma_0(u)$ (see Fig. 2b). The middle branch of $S$ has values of $u$ between those at the local minimum and maximum of $\gamma_0(u)$. Finally, the right branch of $S$ has values of $u$ greater than that at the local maximum of $\gamma_0(u)$.

Figure 2b clearly demonstrates that the relationship between $u$ and $c$ defined by the exact equations (4.3)-(4.4) is closely approximated by (6.8) throughout the silent phase. Although this confirms the leading-order trajectory in $(u, \dot{u}, c)$-space, a confirmation of the leading-order dynamics requires a comparison of the dynamics for the approximate and exact solutions. Eliminating $C_0$ in (6.7) using (6.8), the dynamics of the leading-order problem are determined by

$$U'_0 = Z(U_0) \equiv \frac{\gamma_0(U_0) - \beta h(U_0)}{[N'(U_0) - F'(U_0)][1 + \gamma^{-1}_{K-Ca} \gamma_0(U_0)]^2} .$$

(6.9)

The numerical solutions of (6.9) and (6.2)-(6.3) are compared in Fig. 3. The closeness of $U_0(\tilde{t})$ to $U(\tilde{t})$ confirms that the dynamics of the leading-order silent phase solution approximate the dynamics of the exact solution. Also, the leading-order approximation $U_0(\tilde{t})$ breaks down as it approaches the local minimum of $\gamma_0(U_0)$ where $Z(U_0)$ becomes undefined.

Since $C > \beta h(U)$ along the left branch (cf. Fig. 2b), $C' < 0$ from (6.3) and $C$ must decrease as the solution moves along $G = 0$ towards the local minimum of $\gamma_0(U)$. The solution cannot move up the lower part of the middle branch since $C' < 0$, hence it moves away from $S$ into a transition region separating the silent and active phases. As the solution moves through this region, the value of $G$ decreases until the leading-order result (6.6) is no longer valid. The assumption that $du/dt$ is $O(1)$ breaks down and the slow time $\tilde{t}$ in (6.1) is no longer an appropriate variable for a perturbation analysis. From Fig. 2b, the value of $u$ is observed to increase rapidly and a transition to the active phase occurs.

Once the solution enters the active phase, the appropriately scaled equations are (4.3)-(4.4). However, it is clear from Fig. 2b that whereas the rapid oscillations occur on the fast time scale $t$, the slow evolution of $c$ occurs on the slower time scale, $\tilde{t} = ct$. Applying the method of multiple scales, let

$$u(t; \varepsilon) = U(\tilde{t}, \tilde{\varepsilon}; \varepsilon) \sim u_0(\tilde{t}, \tilde{\varepsilon}) + \varepsilon u_1(\tilde{t}, \tilde{\varepsilon}) + \cdots ,$$

(6.10)

$$c(t; \varepsilon) = C(\tilde{t}, \tilde{\varepsilon}; \varepsilon) \sim c_0(\tilde{t}, \tilde{\varepsilon}) + \varepsilon c_1(\tilde{t}, \tilde{\varepsilon}) + \cdots ,$$

(6.11)

where $\tilde{t}$ defined by $d\tilde{t}/dt = \omega(\tilde{t}; \varepsilon)$ is a strained fast time and the $u_i(\tilde{t}, \tilde{\varepsilon})$ and $c_i(\tilde{t}, \tilde{\varepsilon})$, $i = 0, 1, 2, \ldots$, are assumed to be strictly periodic in $\tilde{t}$ with fixed period, $T_p$. Thus (4.3)-(4.4) yield the following leading-order problem for the active phase:

$$\omega^2 \frac{\partial^2 u_0}{\partial \tilde{t}^2} + \omega F(u_0) \frac{\partial u_0}{\partial \tilde{t}} + G(u_0, c_0) = 0 ,$$

(6.12)

$$\frac{\partial c_0}{\partial \tilde{t}} = 0 .$$

(6.13)
Fig. 3. Comparison of exact and leading-order solutions in the silent phase.

For a fixed value of $c_0$ in the range observed during the active phase, (6.12) has a limit cycle solution (see Fig. 4). Therefore, equations (6.12)-(6.13) imply that for time intervals in $\tilde{t}$ of $O(1)$, each cycle in the active phase can be approximated by the single periodic solution, $u_0 = \Omega(\tilde{t} - \phi; c_0)$, of the strictly nonlinear Lienard equation (6.12) in which $c_0$ is a parameter and $\phi$ is the phase. A standard linear stability analysis of (6.12) yields critical points located on the $G = 0$ surface, with the critical points on the middle branch classified as saddle points and on the right branch as unstable spirals.

Equation (6.13) implies that $c_0$ is a function of $\tilde{t}$ only. The evolution of $c_0(\tilde{t})$ is obtained by averaging the equation for $c_1$ in $\tilde{t}$ over the period $T_p$ of the periodic solution of (6.12). Thus the evolution of $c_0$ is determined by

$$\frac{dc_0}{d\tilde{t}} + c_0 = \beta \tilde{h}(c_0) \equiv \frac{\beta}{T_p} \int_0^{T_p} h(\Omega(\tilde{t}; c_0)) d\tilde{t}, \quad (6.14)$$

where $\phi$ has been omitted because $\Omega$ is periodic in $\tilde{t}$. Since the solution $\Omega(\tilde{t}; c_0)$ is not analytically available in general, the function $\tilde{h}(c)$ was computed numerically and is plotted in Fig. 5a. In Fig. 5b the numerical solution of the leading-order active phase problem (6.12)-(6.14) is compared to the numerical solution of the exact equations (4.3)-(4.4). Note that this solution of the leading-order active...
phase problem closely tracks the exact solution, however, the two solutions become phase shifted because the slow time dependence of $\phi$ has not been taken into account.

For "strongly nonlinear" oscillators, Kuzmak (1959) and Luke (1966) have developed a multiple scales perturbation procedure for determining solutions which are valid for times of $O(1/\epsilon)$. Unfortunately, the Kuzmak-Luke multiple scales procedures are not directly applicable to (4.3)-(4.4) since they do not take into account the cumulative effect of the $O(1)$ damping term. This damping term, $F(u)\dot{u}$, and its changes in sign during the active phase are necessary for a limit cycle solution of (6.12) to exist. However, numerical computations reveal that the damping term is numerically small relative to $\ddot{u}$ and $G(u,c)$ in the leading-order active phase equation. In Fig. 6 is plotted $\int^t G(u,c)\,dt$ versus $\dot{u}$ and it is noted that the curve deviates little from the straight line with slope -1. Thus the cumulative effect of $F(u)\dot{u}$ is small and makes the Liénard equation a strongly nonlinear oscillator for which the Kuzmak-Luke method and the near-identity averaging method (Kevorkian 1987) are formally applicable. This approach to the leading-order perturbation problem in the active phase will be explored in a subsequent paper.

Since $0 < \dot{c} = O(\epsilon)$ in the active phase, the exact solution of (4.3)-(4.4)
Fig. 5. Numerically computed $\tilde{h}(c)$, shown in a, is used to compute $u_0(t, \bar{t})$ (i.e. with $\omega=1$ and $\phi$ constant). Comparison of exact and leading-order solutions for $u$ in the active phase are shown in b.
Fig. 6. Comparison of $\int G(u, c)dt$ versus $\dot{u}$ over several cycles in the active phase. Note that the relationship is almost linear with slope equal to -1.

slowly spirals upward in $(u, \dot{u}, c)$-space near the (cylindrically shaped) surface formed by the union of all limit cycle solutions of (6.12). As $c$ increases, the active phase oscillations pass closer and closer to the middle branch of $G = 0$. When the oscillations are sufficiently close, $G$ fails to be $O(1)$, (6.12) no longer admits a limit cycle solution, and (6.12)-(6.14) no longer describe the leading-order behavior of the exact solution. The exact solution can be shown to pass through a narrow “window” near the saddle point of the leading-order active phase problem. This so-called “passage through a separatrix” also occurs in sustained resonance problems (Kevorkian 1987) and requires special consideration (Bourland and Haberman 1989).

Once outside the separatrix, the exact solution makes a transition back to the silent phase (cf. Fig. 2b). As it does, it crosses the $c$ nullcline and the values of $c$ begin to decrease slowly. When the solution nears the left branch of $G = 0$, the leading-order behavior of the exact solution is governed again by (6.6)-(6.7). The silent-active phase cycle then repeats itself creating the bursting phenomenon.
7 Discussion

The goal of the analysis presented in this paper has been to develop a simplified framework for the mathematical analysis of the SRK equations. It has not been the authors' aim to speculate on the validity of the assumptions leading to these equations. The three new results in this paper are nondimensionalization of the SRK equations, transformation of the dimensionless model equations into an equation in perturbed Liénard form which is weakly coupled to a first-order equation, and formulation of the leading-order problems (in $\epsilon$) in the silent and active phases of the BEA.

Parameter studies made without the use of analytical techniques are impractical since the total number of parameters defining the SRK system is large (10 biological parameters and 10 artificial parameters to define the functions $n_{\infty}(V), h(V), m_{\infty}(V)$, and $\tau_{m}(V)$). The nondimensionalized equations contain 15 parameters which, although still large, is a significant improvement.

The nondimensionalization also explains (more precisely) how different biological parameters affect the BEA. (The CK equations can be nondimensionalized in a completely analogous way to the nondimensionalization presented in Sect. 3.) In both the CK and SRK models, the intracellular calcium concentration, $Ca_i$, is nondimensionalized by a scaled dissociation constant which is inversely proportional to the ratio $\tilde{g}_{K-Ca}/K_d$. The values of this ratio (50 and 300 for the CK and SRK models, respectively) differ less than the values of $\tilde{g}_{K-Ca}$ (50 and 30000 for the CK and SRK models, respectively). Consequently, the values of the scaled dissociation constants, $\kappa_d = 0.472$ for the SRK model and $\kappa_d^{(CK)} = 2.591$ for the CK model, are not that different. Therefore, it is evident that the ratio $\tilde{g}_{K-Ca}/K_d$ is more important than the parameter values $\tilde{g}_{K-Ca}$ and $K_d$ for maintaining the BEA. The primary effect of this ratio is to change the range of the intracellular calcium concentration, $Ca_i$.

The transformation (4.1) provides a simpler formulation of (2.1)-(2.3) from which to derive the active and silent phase leading-order perturbation problems of Sect. 6. The leading-order silent phase equations (6.6)-(6.7) are mathematically equivalent to the dimensional silent phase equations presented by Rinzel (1987) but were derived here using a perturbation analysis which involves an explicitly defined slow time $\tilde{t}$. Furthermore, the silent phase analysis presented in Sect. 6 differs from Rinzel's treatment since $c$ is eliminated in (6.9).

As a result of the transformation (4.1), the limit cycle structure of the leading-order active phase problem is expressed explicitly in a single Liénard differential equation. The observation that the damping term is numerically small during each oscillation is important because the Liénard equation then describes a strongly nonlinear oscillator.

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