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PARAMETER STUDIES FOR AN ANALOG MODEL OF BURSTING ELECTRICAL ACTIVITY

Dedicated to the memory of Stavros Busenberg.

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ABSTRACT

In this paper, we briefly summarize some recent progress on the perturbation and computational analysis of models of bursting electrical activity. In particular, we describe a simple polynomial analog model. Results for fast and asymptotic parameter studies of the model are discussed.

1. Introduction

Many excitable cells, such as pancreatic β-cells, exhibit bursting electrical activity (BEA) during which the membrane potential undergoes a succession of alternating silent and active phases. Pancreatic β-cells are responsible for the secretion of insulin, a hormone which is essential in the regulation of blood glucose level. Over the past 12 years, a plethora of mathematical models has been proposed to describe the dynamics of the membrane potential of these cells.

Biophysical models of BEA in these cells (see de Vries et al. [3] for references) typically consist of 3–5 first-order ordinary differential equations and are based on the classical Hodgkin-Huxley description [5] of the membrane potential. These equations consist of a current balance equation for the membrane potential, one or more relaxation equations for ionic channel kinetics, and a concentration balance equation for a chemical which is essential to produce the BEA, e.g., intracellular calcium. At least one of the equations has slow dynamics.

Here, we restrict our discussion to the β-cell models consisting of three coupled first-order ordinary differential equations which can be written in the general form

$$\ddot{u} + F(u, \dot{u}, c) + G(u, c) = \varepsilon H(u, c), \quad (1)$$

$$\dot{c} = \varepsilon \left[\beta h(u, c) - c\right], \quad (2)$$

where u is the dimensionless, nonlinearly transformed membrane potential, c is the slowly varying calcium concentration, and two first-order equations have been combined into a single second-order equation [3,6,7,8]. In general, the functions $F(u, \dot{u}, c)$, $G(u, c)$, $H(u, c)$, and $h(u, c)$ are highly nonlinear and $0 < \varepsilon << 1$.

The dynamics underlying Eqs. (1)-(2) are conveniently described in terms of fast and slow subsystems [3,9] and depend greatly on the values of the model parameters. Parameter categories are:

1. slow parameters - occur only in the slow subsystem,
2. fast parameters - occur only in the fast subsystem,
3. asymptotic parameters - for example, ε in Eqs. (1)-(2),
4. global parameters - occur in both the slow and fast subsystems.

Slow parameter analyses of BEA models are either numerical, asymptotic, or qualitative in nature. In numerical studies of β-cell models [4,8,10], bifurcations in the solution behavior are examined as a function of the glucose-dependent parameter, β. These studies have shown that as β is decreased the behavior of $u(t)$ changes from steady state to periodic bursting, to chaotic bursting, to chaotic spiking, and finally to periodic spiking. Terman [10,11] has proven both the existence of periodic bursting solutions and chaotic continual spiking for restricted ranges of β. Asymptotic analyses [3,6,7,8] have predicted estimates for such ranges as well as explicit expressions for both the silent and active phase durations of periodic bursting solutions. Our focus in these previous studies was the determination of the dependence of the plateau fraction (the ratio of the active phase duration to the period of the BEA) on the glucose parameter, β. The leading-order dependence was found using a combination of singular perturbation methods including multiple scales averaging and Melnikov's method.

In this paper, we study BEA in terms of the fast and asymptotic parameters. To avoid the nonlinear details in the biophysical models, we concentrate on a simplified (analog) model exhibiting the bursting phenomenon. The model is introduced in Section 2 and we briefly describe the fast and slow subsystem analysis. The fast parameter analysis is described in Section 3 and we discuss the dependence on asymptotic parameters in Section 4.

2. The Polynomial Analog Model and Phase-Plane Analysis.

We study a polynomial analog model [6] defined by Eqs. (1)-(2) where

$$F(u, \dot{u}, c) = a\left[(u-\hat{u})^2 - \eta^2\right]\dot{u}, \tag{3}$$
$$G(u, c) = c + u^3 - 3(u+1), \tag{4}$$
$$H(u, c) = \beta h(u, c) - c, \tag{5}$$
$$h(u, c) = u - u_\beta. \tag{6}$$

Note that F and h do not depend on c in this particular model. Figure 1a shows a specific numerical solution of Eqs. (1)-(6) which exhibits the solution behavior typical for β-cell models. The variables u and c are analogous to the membrane potential and the calcium concentration, respectively.

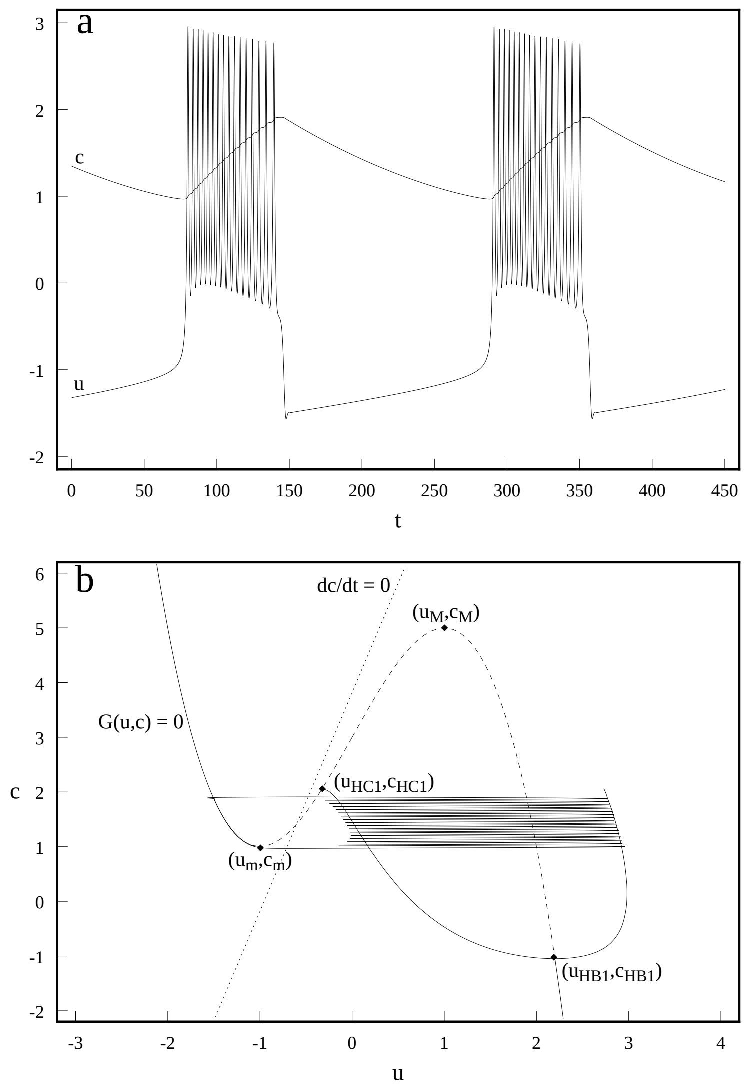

Figure 1: *a*: Solution of Eqs. (1)-(6) for the polynomial β-cell model, with $a = 0.25$, $\hat{u} = 1.5$, $\eta = 0.7$, $\varepsilon = 0.0025$, $\beta = 4.0$, and $u_\beta = -0.954$. *b*: Projection of the solution onto the (u, c)-plane with the global bifurcation diagram of FS and the $\dot{c}$-nullcline. The solid and dashed portions of the $G = 0$ curve indicate stability and instability, respectively.

In the silent phase, both u and c evolve on a slow time scale $\tilde{t} = \varepsilon t$. The leading-order equations for this time scale define the slow subsystem (SS)

$$G(u,c) = 0, \tag{7}$$

$$\frac{dc}{d\tilde{t}} = \beta h(u,c) - c. \tag{8}$$

Conversely, in the active phase, u varies on the fast time scale, t. The corresponding leading-order equations for this fast time scale define the fast subsystem (FS)

$$\ddot{u} + F(u,\dot{u},c) + G(u,c) = 0, \tag{9}$$

$$\frac{dc}{dt} = 0, \tag{10}$$

hence c is treated as a parameter.

Figure 1b shows the solution of Eqs. (1)-(6) projected onto the (u,c)-plane, superimposed onto the global bifurcation diagram for FS. The critical points on the left and middle branches of the cubic nullcline are typically stable fixed points and saddles, respectively. Right branch critical points are spirals whose stability changes from stable to unstable at a Hopf bifurcation at $c = c_{HB1}$. The limit cycles emerging from the Hopf point are stable and terminate at a homoclinic bifurcation at $c = c_{HC1}$. In general, $c_{HB1} < c_m < c_{HC1} < c_M$. Thus, FS is bistable for $c_m < c < c_{HC1}$.

Bursting solutions are possible due to this bistability and the location of the intersection of the $\dot{c}$-nullcline on the middle branch of the cubic (see Figure 1b). The system is governed by SS to the left of this nullcline and by FS to the right of this nullcline. Also, to the left of the $\dot{c}$-nullcline, $\dot{c}$ is negative. Thus, in the silent phase, c slowly decreases while u slowly increases. When $c < c_m$, the solution trajectory is attracted to the stable limit cycle around the right branch of the cubic. Here, $\dot{c}$ is positive, and hence c increases while u oscillates, staying close to the envelope of stable limit cycles. The active phase terminates at the homoclinic connection and the solution trajectory returns to the silent phase along the left branch of the cubic.

Above curve	Bounded by curves	Property
A^+		2 Hopf points on $G = 0 : c_{HB1}, c_{HB2}$
	A^+, A^-	1 Hopf point on $G = 0$: c_{HB1}
B		limit cycles are stable
C		$c_{HB1} < c_m$
	A^{++}, A^+, D	2 homoclinic bifurcations: c_{HC1}, c_{HC2}
	A^+, A^-, D	1 homoclinic bifurcation: c_{HC1}
A^{++}		no homoclinic bifurcations

Table 1: Explanation of curves in Figure 2. For fast parameter pairs $(\eta, \hat{u})$ in the described regions, the fast subsystem possesses the noted property.

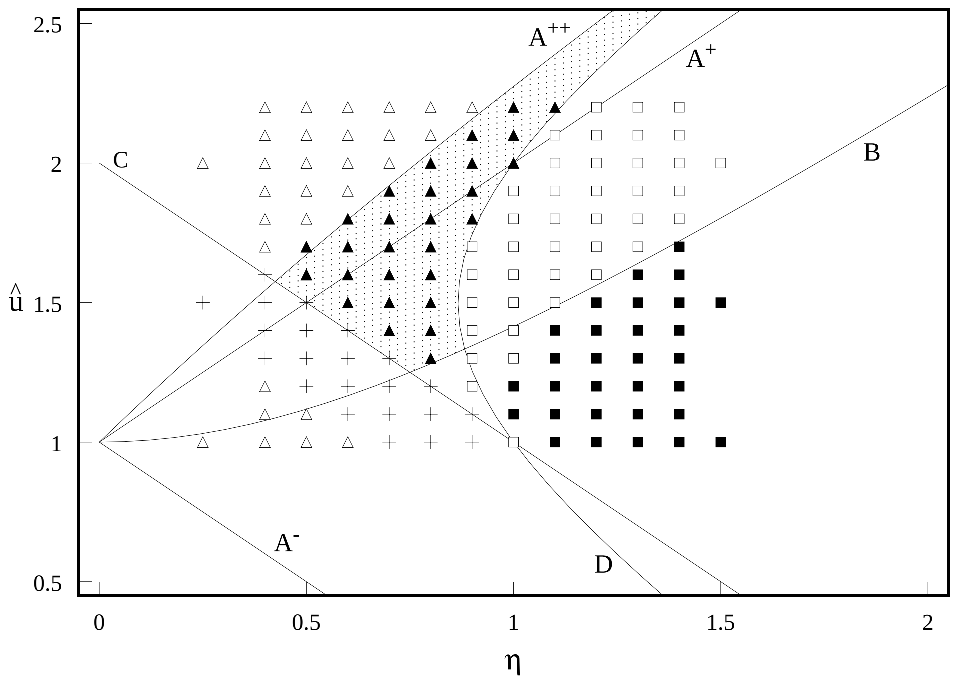

Figure 2: Fast parameter bifurcations. For parameter values inside the shaded region, the model exhibits square-wave bursting.

3. Fast Parameter Analysis

As shown by Pernarowski [6], the fast parameters $\hat{u}$ and η induce a wide variety of different oscillatory behaviors for the model defined by Eqs. (1)-(6). These include (but are not limited to) tapered bursting, beating, nearly parabolic bursting, and square-wave bursting (cf. Figure 2, open triangles, open squares, solid squares, and solid triangles, respectively). Square-wave bursting, the type of bursting discussed in the previous section, is analogous to the BEA in β-cells.

Square-wave bursting can occur only if certain restrictions are placed on FS. For instance, the limit cycles emerging from the Hopf point must be stable and terminate at $c > c_m$. Using a standard Hopf analysis to locate the Hopf points and determine their stability, and Melnikov theory to locate homoclinic bifurcations, each FS restriction corresponds to a curve in the $(\eta, \hat{u})$-plane [6]. These curves are shown in Figure 2 and their properties are summarized in Table 1. Using these results, dynamic bifurcations of the model's behavior are easily deduced. Consider, for example, fixing $\eta = 0.7$ and increasing $\hat{u}$ from 1.5. When $\hat{u}$ lies between curves A^- and A^+, FS has a single Hopf point at $c = c_{HB1}$ on the right branch of the cubic and a corresponding single homoclinic bifurcation at $c = c_{HC1}$. A second Hopf point and homoclinic bifurcation emerge at $c = c_{HB2}$ and $c = c_{HC2}$, respectively, when $\hat{u}$ lies between A^+ and A^{++}. The two homoclinic bifurcations finally coalesce and disappear when $\hat{u}$ lies above A^{++}. Similar bifurcations also have been discussed by Bertram et al. [1].

4. Dependence on Asymptotic Parameters

The asymptotic parameter in Eqs. (1)-(6) is ε, $0 < \varepsilon << 1$, which governs the rate at which the variable c changes and, consequently, the temporal behavior of the bursting solution. Less evident is the subtle effect ε can have on the type of bursting exhibited by Eqs. (1)-(6). Numerical studies [2] have shown that square-wave bursting can persist outside the shaded region shown in Figure 2.

In the region directly above the A^{++} boundary curve and adjacent to the shaded region, there are two Hopf points on the right branch of the cubic but no homoclinic bifurcations. The global bifurcation diagrams of FS in this region are those of tapered bursters. Consistent with this is the tapered bursting solution of Eqs. (1)-(6), with $\varepsilon = 0.001$, shown in Figure 3a. However, when ε is increased to 0.0025, the solution exhibits square-wave bursting instead, shown in Figure 3b. Note that for smaller ε, the dynamics of c are sufficiently slow that trajectories remain close to the envelope of limit cycles and, thus, c can increase to the second Hopf point.

The global bifurcation diagram is a leading-order qualitative picture of the solution structure, i.e., for $\varepsilon = 0$. Thus, the global bifurcation diagrams of FS do change as predicted by the various curves in Figure 2; however, the transitions between the various types of bursting are ε-dependent.

5. Discussion

Parameter studies of models of bursting electrical activity in excitable cells elucidate the wide variety of behaviors attainable from these models. Here, we have summarized both fast and asymptotic parameter studies of a simple polynomial model for BEA. The advantage of the polynomial model is that boundaries between qualitatively distinct global bifurcation behaviors in the fast parameter plane can be obtained analytically. In particular, the region of square-wave bursting, as observed experimentally in β-cells, can be determined explicitly.

We have shown that the size of the asymptotic parameter ε can alter the solution behavior in a given region of the fast parameter plane. Specifically, we have shown that a tapered burster just outside the square-wave burster region can be converted into a square-wave burster by increasing ε sufficiently. This nongeneric behavior is typical near transition boundaries.

The transition boundary we have examined occurs in the fast-asymptotic parameter subspace $(\eta, \hat{u}, a, \varepsilon)$ and bounds a region where the fast-slow subsystem explanation of square-wave bursting remains valid. Such regions should be contrasted to the "tongue-like" regions discussed by Terman [11] in the study of transitions from bursting to continual spiking. In that study, the regions occur in a slow-asymptotic parameter subspace $(\beta, u_\beta, \varepsilon)$.

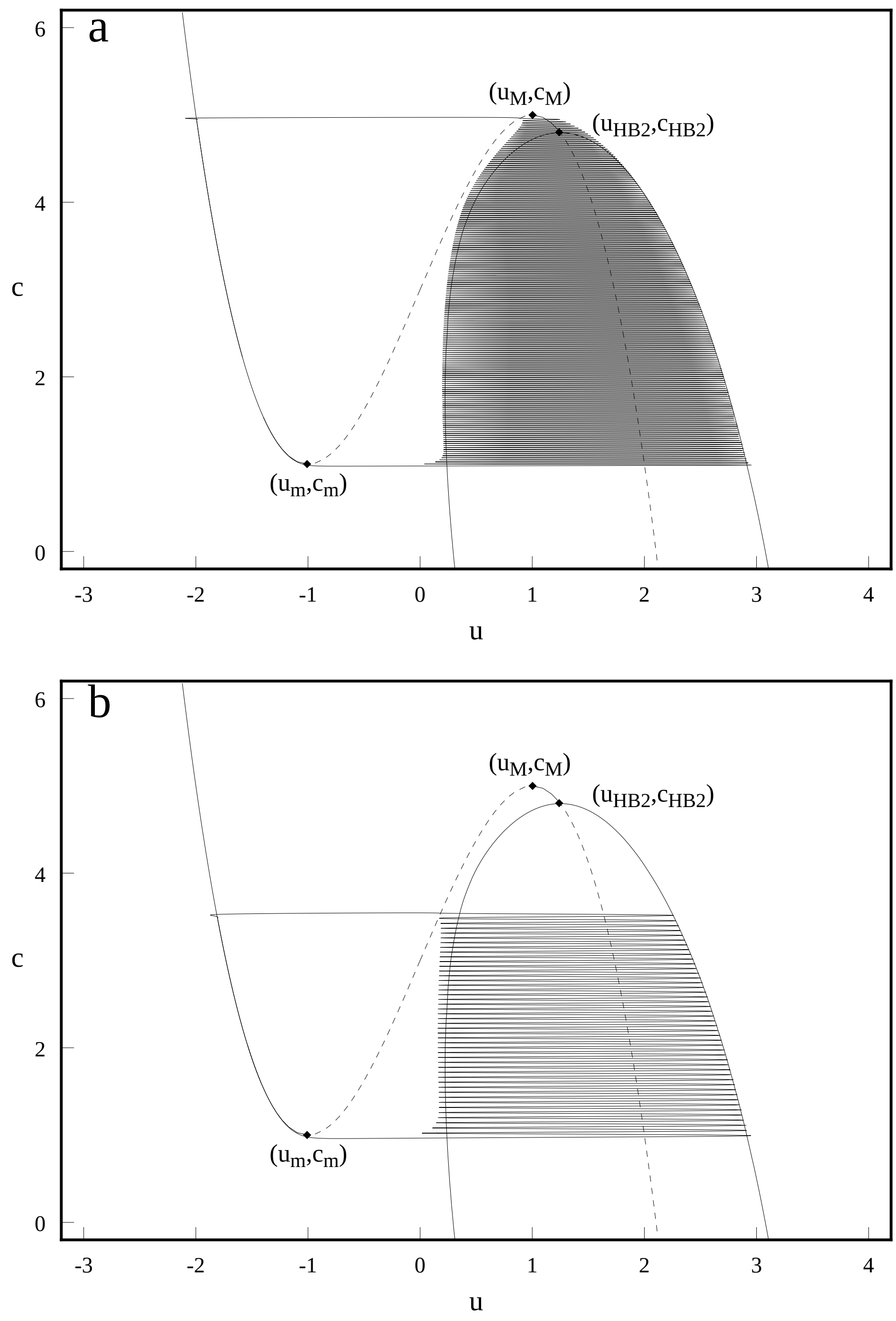

Figure 3: Solution of Eqs. (1)-(6) and global bifurcation diagram of FS, with $\hat{u} = 1.95$. a: Solution with $\varepsilon = 0.001$. b: Solution with $\varepsilon = 0.0025$. Other parameter values are as for Figure 1.

Acknowledgements

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