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Bursting electrical activity is ubiquitous in excitable cells such as neurons and many endocrine cells. The technique of fast/slow analysis, which takes advantage of time scale differences, is typically used to analyze the dynamics of bursting in mathematical models. Two classes of bursting oscillations that have been identified with this technique, plateau and pseudo-plateau bursting, are often observed in neurons and endocrine cells, respectively. These two types of bursting have very different properties and likely serve different functions. This latter point is supported by the divergent expression of the bursting patterns into different cell types, and raises the question of whether it is even possible for a model for one type of cell to produce bursting of the type seen in the other type without large changes to the model. Using fast/slow analysis, we show here that this is possible, and we provide a procedure for achieving this transition. This suggests that the design principles for bursting in endocrine cells are just quantitative variations of those for bursting in neurons.
From Plateau to Pseudo-Plateau Bursting: Making the Transition

Wondimu Teka · Krasimira Tsaneva-Atanasova · Richard Bertram · Joël Tabak

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Abstract Bursting electrical activity is ubiquitous in excitable cells such as neurons and many endocrine cells. The technique of fast/slow analysis, which takes advantage of time scale differences, is typically used to analyze the dynamics of bursting in mathematical models. Two classes of bursting oscillations that have been identified with this technique, plateau and pseudo-plateau bursting, are often observed in neurons and endocrine cells, respectively. These two types of bursting have very different properties and likely serve different functions. This latter point is supported by the divergent expression of the bursting patterns into different cell types, and raises the question of whether it is even possible for a model for one type of cell to produce bursting of the type seen in the other type without large changes to the model. Using fast/slow analysis, we show here that this is possible, and we provide a procedure for achieving this transition. This suggests that the design principles for bursting in endocrine cells are just quantitative variations of those for bursting in neurons.

Keywords Bursting · Pituitary cells · Islets · Calcium · Mathematical model

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1 Introduction

Neurons and endocrine cells display various patterns of electrical activity, spontaneously or in response to stimulation. One of these patterns, periodic bursting, is characterized by periods of fast spiking activity separated by periods of rest. The alternation between these two phases of activity is often controlled by the slow variation of the intracellular calcium concentration. Bursts may allow more efficient neurotransmitter or hormone release than single spikes, without causing as much fatigue or desensitization as continuous spiking. In endocrine cells, the characteristics of the bursting pattern, such as the burst duration or the burst frequency, determine how much Ca\(^{2+}\) enters the cell and in turn determines the level of hormone secretion (Van Goor et al. 2001b).

The spontaneous electrical activity of several anterior pituitary cell types (somatotrophs, lactotrophs, corticotrophs) and pancreatic \(\beta\)-cells isolated from islets have been shown to consist of bursts produced by the opening of voltage-dependent Ca\(^{2+}\) channels (Van Goor et al. 2001b; Stojilkovic et al. 2005; Zhang et al. 2003). Unlike bursts in neurons and \(\beta\)-cells within intact pancreatic islets of Langerhans, the active phase of the bursts exhibits small oscillations around a depolarized voltage, not full blown spikes. Recent models have explained this characteristic feature mathematically: the fast-subsystem bifurcation structure has a bistable region which has, in addition to the standard hyperpolarized stable steady state, a depolarized stable steady state (LeBeau et al. 1998; Tabak et al. 2007; Tsaneva-Atanasova et al. 2007). This is in contrast to models of conventional or plateau bursting, which have a stable oscillatory solution or limit cycle in place of the depolarized steady state (Rinzel 1987). For this reason, these bursts are called *pseudo-plateau bursts*.

The properties of pseudo-plateau bursting are quite different from those of plateau bursting, likely leading to differences in function. For example, the large amplitude, short duration spikes characteristic of plateau bursting would be effective at evoking neurotransmitter release, since low affinity release sites are clustered near Ca\(^{2+}\) channels in synapses and the large depolarization opens the channels. The resulting high-concentration Ca\(^{2+}\) nanodomain then evokes the transmitter release. In contrast, there is no such colocalization of release sites and Ca\(^{2+}\) channels in endocrine cells, and release is evoked by a more spatially averaged Ca\(^{2+}\) signal. Pseudo-plateau bursting is more effective at producing an elevated average Ca\(^{2+}\) concentration than is continuous spiking (Tabak et al. 2007; Van Goor et al. 2001a); the large spikes of plateau bursts are not required.

Given the different characteristics of the two types of bursting, and their divergent distribution into two cell types, it seems likely that the dynamic mechanism for one type of bursting is insufficiently plastic to produce the other type of bursting. Mathematical models of the two bursting types are an ideal platform to investigate the validity of this assertion. Our goal is to determine whether a model for one type of bursting can produce the other type without major structural changes, and if so, to determine the key elements of such a transition. Izhikevich (2000) showed that the same model can produce both types of bursting, but the changes required to make such a transition were not discussed and, importantly, the key elements for the production of one type of bursting versus the other were not investigated.
To understand the conditions that create pseudo-plateau bursting, we start with a well-known model of bursting in pancreatic islets, the Chay–Keizer model (Chay and Keizer 1983), which produces plateau bursting. We show that by changing the values of an appropriate time constant or the half-activation point of the fast, voltage-dependent K$^+$ or Ca$^{2+}$ channels a transition can be made between a plateau and a pseudo-plateau bifurcation structure. We observe similar transitions by varying the maximum conductances of these currents, which is important since conductance variation is more likely to occur from one cell to another or one cell type to another. We demonstrate that the effects of these parameter changes are additive, so there are many pathways through parameter space between plateau and pseudo-plateau bursting. These results suggest that the relationship between the fast K$^+$ and Ca$^{2+}$ currents determines the burst type. More generally, the analysis suggests that the design principles for bursting are similar between neurons and endocrine cells.

2 The Chay–Keizer Model

The Chay–Keizer model (Chay and Keizer 1983) is the first model developed for pancreatic islet electrical activity and has similar structure to most subsequent models. The numerical simulation of this model produces a plateau bursting pattern. Here, we use a modification of the Chay–Keizer model that has fewer variables (Bertram and Sherman 2004, 2005). There are differential equations for three variables: $V$ (membrane potential), $n$ (fraction of activated delayed rectifier K$^+$ channels), and $c$ (cytosolic free Ca$^{2+}$ concentration). The equations are:

$$C_m \frac{dV}{dt} = -(I_{Ca} + I_K + I_{K(Ca)} + I_{K(ATP)})$$  

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

$$\frac{dc}{dt} = -f(\alpha I_{Ca} + k_{PMCA} c)$$

where $C_m$ is the membrane capacitance of the cell, $I_{Ca}$ is an inward Ca$^{2+}$ current, $I_K$ is an outward delayed rectifying K$^+$ current, $I_{K(Ca)}$ is a Ca$^{2+}$-activated K$^+$ current, $I_{K(ATP)}$ is an ATP-sensitive K$^+$ current, $\tau_n$ is the activation time constant for the delayed rectifier K$^+$ channel, $f$ is the fraction of cytosolic Ca$^{2+}$ that is not bound to buffers (ratio of free to total Ca$^{2+}$ in the cell), $\alpha$ converts current into concentration flux and involves the ratio of the cell’s surface area to volume of the cytosol, and $k_{PMCA}$ is the rate of Ca$^{2+}$ extrusion from the cell (the pump rate). The currents in the equations above are:

$$I_K = g_K n(V - V_K)$$  

$$I_{K(ATP)} = g_{K(ATP)} (V - V_K)$$  

$$I_{Ca} = g_{Ca} m_\infty(V)(V - V_{Ca})$$  

$$I_{K(Ca)} = g_{K(Ca)} s_\infty(c)(V - V_K).$$
The steady state activation functions are given by

\[
m_{\infty}(V) = \left(1 + \exp\left(\frac{v_m - V}{s_m}\right)\right)^{-1} \tag{8}
\]

\[
n_{\infty}(V) = \left(1 + \exp\left(\frac{v_n - V}{s_n}\right)\right)^{-1} \tag{9}
\]

\[
s_{\infty}(c) = \frac{c^3}{c^3 + K_d^3} \tag{10}
\]

where \(m_{\infty}\) is the steady state activation function for \(I_{Ca}\), \(n_{\infty}\) is the steady state activation function for \(n\), and \(s_{\infty}\) is the fraction of K(Ca) channels activated by cytosolic \(Ca^{2+}\). These range from 0 to 1. The parameters \(g_K\), \(g_{K(\text{ATP})}\), \(g_{Ca}\), and \(g_{K(Ca)}\) are maximum conductance for the different channel types. Parameters \(V_K\) and \(V_{Ca}\) are Nernst potentials for \(K^+\) and \(Ca^{2+}\), respectively. Parameters \(v_m\) and \(v_n\) are the voltage values where \(m_{\infty}\) and \(n_{\infty}\) are at their half-maximum values. Parameters \(s_m\) and \(s_n\) set the slopes of the sigmoidal \(m_{\infty}\) and \(n_{\infty}\) curves, respectively. Finally, \(K_d\) is the dissociation constant for \(Ca^{2+}\) binding to the K(Ca) channel. Default parameter values are given in Table 1.

The variables \(V\) and \(n\) change much more rapidly than the \(c\) variable. The \(V\) time scale is given by \(\tau_V = C_m/g_{\text{Total}}\), where \(g_{\text{Total}} = g_K n + g_{K(\text{ATP})} + g_{Ca} m_{\infty}(V) + g_{K(Ca)} s_{\infty}(c)\). During a plateau bursting oscillation, the minimum of \(g_{\text{Total}}\) is 217 pS and the maximum is 900 pS. Thus, \(6 \text{ ms} \leq \tau_V \leq 24 \text{ ms}\). The time constant for \(n\) is \(\tau_n = 20 \text{ ms}\). For the slow variable \(c\), the time constant is \(\tau_c = \frac{1}{f_{\text{PMCA}}} = (0.00025)(0.5) = 0.000125 \text{ ms} = 8000 \text{ ms}\). For \(f = 0.01\) (we will use this value of \(f\) later), \(\tau_c = (0.01)(0.5) = 0.005 \text{ ms} = 200 \text{ ms}\), and \(c\) is still slower than \(V\) and \(n\). Thus, the \(V\) and \(n\) variables make up the fast subsystem and the \(c\) variable forms the slow subsystem. In the analysis that follows, we make use of this separation of time scales to analyze the plateau bursting and pseudo-plateau bursting oscillations. This geometric singular perturbation, or fast/slow, analysis was developed by Rinzel (1987) and is typically used to analyze bursting oscillations (Bertram and Sherman 2005; Izhikevich 2000).

**Table 1** Parameter values for the Chay–Keizer model

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<th>Value</th>
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<tr>
<td>(g_{Ca})</td>
<td>1000 pS</td>
<td>(g_K)</td>
<td>2700 pS</td>
</tr>
<tr>
<td>(g_{K(Ca)})</td>
<td>400 pS</td>
<td>(g_{K(\text{ATP})})</td>
<td>180 pS</td>
</tr>
<tr>
<td>(V_{Ca})</td>
<td>25 mV</td>
<td>(V_K)</td>
<td>−75 mV</td>
</tr>
<tr>
<td>(C_m)</td>
<td>5300 fF</td>
<td>(\alpha)</td>
<td>(4.5 \times 10^{-6} \text{ fA}^{-1} \mu M \text{ ms}^{-1})</td>
</tr>
<tr>
<td>(\tau_n)</td>
<td>18.7 ms</td>
<td>(f)</td>
<td>0.00025</td>
</tr>
<tr>
<td>(k_{\text{PMCA}})</td>
<td>0.5 m s(^{-1})</td>
<td>(K_d)</td>
<td>0.3 \mu M</td>
</tr>
<tr>
<td>(v_n)</td>
<td>−16 mV</td>
<td>(s_n)</td>
<td>5 mV</td>
</tr>
<tr>
<td>(v_m)</td>
<td>−20 mV</td>
<td>(s_m)</td>
<td>12 mV</td>
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All simulations and bifurcation diagrams are constructed using the XPPAUT software package (Ermentrout 2002) and computer codes can be downloaded from the following website: http://www.math.fsu.edu/bertram/software/islet. Both one- and two-parameter bifurcation diagrams were constructed using the parameter continuation tool AUTO in XPPAUT.

3 Results

3.1 Transition from Plateau to Pseudo-Plateau Bursting with a Plateau Bursting Model

3.1.1 Fast/Slow Analysis

With the default parameter values, Table 1, the Chay–Keizer model produces a plateau bursting pattern (Fig. 1A). This periodic pattern has two phases: an active...
phase and a silent phase. During the active phase, action potentials or spikes emerge from a depolarized voltage plateau. During the silent phase, the model cell is at a low voltage or hyperpolarized state. During the active phase, Ca\textsuperscript{2+} channels open and \(c\) increases (Fig. 1B). The elevated \(c\) activates the Ca\textsuperscript{2+}-dependent K\textsuperscript{+} channels (K(Ca) channels), which terminate the spiking and hyperpolarize the cell. During the silent phase, the Ca\textsuperscript{2+} channels close and \(c\) declines (Fig. 1B). This deactivates the K(Ca) channels and allows the cell to reach the spike threshold, initiating a new active phase. The fast subsystem is bistable over a range of \(c\) values, where for the same value of \(c\) the model cell could be either spiking or silent.

A model for pituitary lactotrophs (Tabak et al. 2007) produces pseudo-plateau bursting (see Sect. 3.3.1). In this model, bursting is generated due to a fast-activating BK-type (large conductance) K\textsuperscript{+} current. Pseudo-plateau bursting (Fig. 1D) typically has a shorter period than plateau bursting and fewer spikes during the active phase. These spikes may be considerably smaller than in plateau bursting, although this is not required. The Ca\textsuperscript{2+} concentration profiles (Fig. 1E), with \(c\) increasing during the active phase and decreasing during the silent phase, are similar in the two types of bursting.

From the point of view of the underlying dynamics, there are two main differences between the bursting types. One is that the slow variable, \(c\) in our example, is considerably faster in pseudo-plateau than in plateau bursting. In the cells, this difference could reflect differences in cell volumes, buffering capacity of the cell, Ca\textsuperscript{2+} current conductance, or Ca\textsuperscript{2+} pump rate. The simplest way to vary the speed of \(c\) is through the parameter \(f\), the fraction of Ca\textsuperscript{2+} that is unbound by buffers. A larger \(f\) value yields faster variation in \(c\). The second main difference is in the bifurcation structure of the fast subsystem.

As stated earlier, \(c\) varies more slowly than \(V\) and \(n\). In the fast/slow analysis, \(c\) is treated as a parameter of the fast subsystem ((1)–(2)). A bifurcation diagram is then constructed for the fast subsystem dynamics using \(c\) as the bifurcation parameter (Rinzel 1987). Figure 1C illustrates the bifurcation structure for plateau bursting. In the figure, the \(z\)-shaped curve (“\(z\)-curve”) represents the steady states of the fast subsystem. The lower branch of the \(z\)-curve consists of stable nodes corresponding to the hyperpolarized (low-voltage) steady states. The middle branch consists of (unstable) saddle points. The upper branch corresponds to the depolarized (high-voltage) steady states, and has unstable and stable portions. The turning points connecting the three stationary branches are a saddle-node bifurcation (LSN) and an upper saddle-node bifurcation (USN). The upper branch changes from stable to unstable at a supercritical Hopf bifurcation (supHB), which occurs to the left of the LSN. Thus, for a range of \(c\) values there are three steady states of the fast subsystem, but only one is stable.

A branch of stable periodic solutions emerges from supHB and terminates at a homoclinic bifurcation (HM). At HM, there is an infinite-period homoclinic orbit where the periodic solution connects with a saddle point. For a range of \(c\) values, between LSN and HM, the system is bistable between a low-voltage stable steady state and a stable limit cycle (Fig. 1C). This bistability is crucial for the production of bursting with a single slow variable (Bertram and Sherman 2005). On the limit cycle, \(V_{\text{max}}\) and \(V_{\text{min}}\) represent the maximum and minimum voltage of the periodic solution, respectively.
From Plateau to Pseudo-Plateau Bursting: Making the Transition

We now treat the $c-V$ plane (Fig. 1C) as a phase plane with the $z$-curve as a generalized $V$-nullcline projected into the $V-c$ plane. We also project the $c$-nullcline where $dc/dt = 0$. Below the $c$-nullcline $dc/dt < 0$, so the flow is to the left. A phase point starting on the lower branch of the $z$-curve moves leftward toward the LSN. Once the LSN is reached, the phase point moves to the only remaining stable structure, the branch of periodic (spiking) solutions. At this time, the phase point is above the $c$-nullcline and the flow is to the right since $dc/dt > 0$. The phase point oscillates as it travels rightward toward the HM, and once the HM is reached the phase point returns to the lower stationary branch of the $z$-curve. This sequence of events describes one period of the bursting oscillation. In Fig. 1C, the superimposed burst trajectory shows this one cycle of bursting.

The fast subsystem bifurcation structure for pseudo-plateau bursting is shown in Fig. 1E. The primary difference between this diagram and that for plateau bursting is that the stable periodic branch is gone, due to stabilization of the upper branch of the $z$-curve. The stabilized stationary branch ultimately loses stability at a subcritical Hopf bifurcation (subHB), but over a wide range of $c$ values the system is bistable between two steady states. The only branch of periodic solutions is unstable, emerging from the subHB and terminating at a HM.

Now using the $c-V$ plane as a phase plane, we add the $c$-nullcline and the burst trajectory. Since the $c$ dynamics are only marginally slow, the phase point only loosely follows the lower branch of the $z$-curve, and it overshoots the LSN. Once it passes the LSN, the phase point is attracted to the upper branch of the $z$-curve, but the attraction is weak. This results in transient oscillations around the upper branch of the $z$-curve. Once the phase point moves past the subHB, it returns to the lower branch of the $z$-curve. Thus, as with plateau bursting, the silent phase is characterized by flow along the bottom branch of the $z$-curve. However, unlike plateau bursting, the active phase is a weakly damped oscillation around a depolarized steady state (Fig. 1F).

3.1.2 Plateau to Pseudo-Plateau Conversion by Actions on the Delayed Rectifier $K^+$ Current

Can the plateau bursting of Fig. 1A produced by the Chay–Keizer model be converted to pseudo-plateau bursting? If so, what parameter can convert the fast-subsystem bifurcation structure for plateau bursting (Fig. 1C) to that for pseudo-plateau bursting (Fig. 1F)? One potential approach is to decrease the time constant for the $K^+$ channel activation variable $n$ ($\tau_n$ in (2)). In so doing, this negative feedback is accelerated, which eliminates spiking and stabilizes the top branch of the $z$-curve (Bertram et al. 1995). This modification to the Chay–Keizer model leads to the desired pseudo-plateau bursting pattern (Fig. 2A).

While decreasing $\tau_n$ successfully produced pseudo-plateau bursting, the bifurcation structure of the fast subsystem (Fig. 2B) is somewhat different from that of Fig. 1F. In particular, there are a pair of supercritical Hopf bifurcations, rather than a single subcritical Hopf bifurcation on the top branch. While this difference has little, if any, effect on the burst trajectory, it suggests that a different approach to pseudo-plateau bursting would be more appropriate.

How else might pseudo-plateau bursting be achieved? One potential mechanism is to shift the activation curve for $n$, so that the delayed rectifier current activates at...
Fig. 2  Pseudo-plateau bursting generated with the Chay–Keizer model by increasing the speed of K\(^+\) current activation. (A) When \(\tau_n\) is decreased to 17.1 ms and \(f\) is increased to 0.01, pseudo-plateau bursting is produced. (B) The fast-subsystem bifurcation structure, in which the upper branch is stabilized. There are two supercritical Hopf bifurcations connected by a branch of stable periodic solutions, which differs from Fig. 1F.

higher voltages. This is done by increasing the parameter \(v_n\) (voltage value at the midpoint of \(n_\infty\)), which shifts the \(n_\infty(V)\) curve (Fig. 3, the blue solid curve) rightward. When \(v_n\) is increased from \(-16\) mV to \(-14\) mV there is a stabilization of the upper branch of the \(z\)-curve (Fig. 4B). The supercritical Hopf bifurcation characteristic of plateau bursting (Fig. 4A) has moved to the right of the LSN and has become subcritical (Fig. 4B). The unstable periodic branch that emerges gains stability at a saddle-node of periodic (SNP) bifurcation, and the stabilized periodic branch terminates at a HM bifurcation.

The bifurcation structure in Fig. 4B is transitional between that of plateau bursting (Fig. 4A) and that of pseudo-plateau bursting (Fig. 4C) which is achieved by shifting \(n_\infty(V)\) further to the right (Fig. 3, blue dotted curve) by increasing \(v_n\) to \(-12\) mV (point c in Fig. 3). This produces a fast subsystem bifurcation diagram that is identical to that of pseudo-plateau bursting from the lactotroph model (Tabak et al. 2007).

Increasing \(v_n\) converts the bifurcation structure for plateau bursting to that for pseudo-plateau bursting. In addition to the change in the fast-subsystem bifurcation structures brought about through \(v_n\), modification of the speed of the slow variable is required. Using the default value \(f = 0.00025\), plateau bursting (Fig. 5A) is converted to a relaxation-oscillation (Fig. 5B) when \(v_n\) is increased from \(-16\) mV to \(-12\) mV. If this oscillation (Fig. 5B) is superimposed on the fast-subsystem bifurcation...
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**Fig. 3** Steady state functions for the K$^+$ current activation variable $n$ (the $n_\infty(V)$ curve, blue) and the Ca$^{2+}$ current activation variable $m$ (the $m_\infty$ curve, red). When $v_n$ is increased from $-16$ mV (point a) to $-14.5$ mV (point b) or $-12$ mV (point c), the $n_\infty$ curve shifts to the right. This makes the delayed rectifier channels activate at higher voltages. When $v_m$ is decreased from $-20$ mV (point d) to $-22.5$ mV (point e) or $-26$ mV (point f), the $m_\infty$ curve shifts to the left. This makes the Ca$^{2+}$ channels activate at lower voltages. When the $m_\infty$ and $n_\infty$ curves are sufficiently far apart, pseudo-plateau bursting is produced.

Another way to modify the fast subsystem bifurcation structure for conversion from plateau to pseudo-plateau bursting is to decrease the maximum conductance of the delayed rectifier K$^+$ current $g_K$. This is probably the most biophysically plausible approach, since the conductance $g_K$ is determined partly by the number of K$^+$ channels present in the plasma membrane. It is likely that this number varies from cell to cell. As $g_K$ is decreased, the Hopf bifurcation and periodic branch move rightward on the $z$-curve, reflecting the stabilization of the upper stationary branch. When...
Fig. 4 Effects of shifting the $n_\infty(V)$ curve rightward. (A) The bifurcation structure for plateau bursting using default values (Table 1). (B) A transitional bifurcation structure obtained by increasing $v_n$ to $-14$ mV. (C) The bifurcation structure for pseudo-plateau bursting obtained with $v_n = -12$ mV.

$g_k = 1800$ pS, the Hopf bifurcation and periodic branch lie to the right of the LSN, the Hopf bifurcation is subcritical, and there are stable and unstable periodic branches (as in Fig. 4B). When $g_k$ is decreased further to 1000 pS, the subHB and periodic branch move further to the right (very close to the USN), and the stable periodic branch disappears, producing the bifurcation structure for pseudo-plateau bursting (as in Fig. 4C). To produce the pseudo-plateau bursting time course, $f$ is set to 0.01 (as in Fig. 5F).

3.1.3 Plateau to Pseudo-Plateau Conversion by Actions on the Ca$^{2+}$ Current

Other methods for converting plateau to pseudo-plateau bursting are variation of the parameters $v_m$ and $g_{Ca}$, which have significant effects on the depolarizing Ca$^{2+}$ current. When $v_m$ (voltage value at the midpoint of $m_\infty$) is decreased, the $m_\infty(V)$ curve (Fig. 3, red solid curve) shifts leftward. This causes the Ca$^{2+}$ channels to activate at lower voltages. Decreasing $v_m$ has the same effect as increasing $v_n$ on the bifurcation structures. The Hopf bifurcation and periodic branch move to the right, and the top branch of the $z$-curve is stabilized. A transitional bifurcation structure is produced when $v_m$ is decreased to $-23$ mV (as in Fig. 4B). A pseudo-plateau bifurcation struc-
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Fig. 5 Bursting oscillations generated with the Chay–Keizer model and different values of \( f \) and \( v_n \). For the left panels \( v_n = -16 \) mV, and for the right panels \( v_n = -12 \) mV. (A), (B) \( f = 0.00025 \). (C), (D) \( f = 0.005 \). (E), (F) \( f = 0.01 \).

structure is produced when \( v_m = -26 \) mV (as in Fig. 4C). As before, \( f \) must be increased to achieve pseudo-plateau bursting.

A transition from plateau to pseudo-plateau bursting was also achieved by increasing the maximum conductance of the \( \text{Ca}^{2+} \) current \( g_{\text{Ca}} \). However, this also required changing two additional parameters: \( g_K \) was decreased from 2700 pS to 1500 pS and \( v_m \) was increased from -20 mV to -17 mV. Then with \( g_{\text{Ca}} = 2100 \) pS a transitional bifurcation structure was obtained, and with \( g_{\text{Ca}} = 3000 \) pS a pseudo-plateau structure was produced.

3.1.4 Two-Parameter Bifurcation Analysis

The series of one-parameter bifurcation diagrams shown earlier can be summarized using two-parameter bifurcation diagrams, where one of the parameters is the slow variable \( c \) and the other is one of the transition parameters \( v_n, v_m, g_K \) or \( g_{\text{Ca}} \) (Fig. 6).

The curves represent the bifurcation points shown in the previous bifurcation diagrams (Figs. 4A–4C). The curves LSN (green), HB (blue), HM (red), and USN (black) correspond to lower saddle-node, Hopf, homoclinic, and upper saddle-node bifurcation points, respectively. For example the HB curve in Fig. 6A gives the \( c \) value of the Hopf bifurcation of the fast subsystem (Fig. 4) over a range of values of the parameter \( v_n \).
Fig. 6 Two-parameter bifurcation diagrams illustrating regions of plateau and pseudo-plateau bursting. The green (LSN), blue (HB), red (HM), and black (USN) curves represent the lower saddle node, Hopf, homoclinic, and upper saddle node bifurcation points, respectively. (A), (C) The midpoints of activation curves are varied. (B), (D) Current conductances are varied. In panel D, the region below the bottom dotted curve is neither plateau nor pseudo-plateau bursting since the order is $c_{LSN} < c_{HB} < c_{HM} < c_{USN}$.

Most of the curves in Fig. 6 have small positive or small negative slope, so that varying one of the transition parameters greatly affects the locations of these HB, HM, and USN bifurcations. The top two panels show that the LSN curve is almost vertical, so the LSN bifurcation is relatively insensitive to $\nu_n$ and $g_k$.

Important qualitative differences occur in the fast subsystem structure when bifurcation curves in Fig. 6 cross. For example, in Fig. 6A near the bottom the HB bifurcation is to the left of the LSN, which is to the left of the HM, which is to the left of the USN. Thus, the order is $c_{HB} < c_{LSN} < c_{HM} < c_{USN}$, where $c_{HB}, c_{LSN}, c_{HM}$, and $c_{USN}$ are the $c$ values at HB, LSN, HM, and USN, respectively. This is the order of bifurcation values in Fig. 4A, for the case of plateau bursting.

At the lower dotted line in Fig. 6A the HB and LSN curves cross, so that above that line $c_{LSN} < c_{HB}$. In terms of the one-parameter bifurcation structure, this means that the HB is to the right of the lower knee, and that there is an interval of bistability of the upper and lower steady states. This is a transitional form between that of plateau and that of pseudo-plateau bursting. The latter occurs when the HB curve crosses the HM curve (upper dotted curve) so that now $c_{LSN} < c_{HM} < c_{HB} < c_{USN}$. This is the order of bifurcations for pseudo-plateau bursting (Fig. 4C). Thus, the region below...
the bottom dotted curve in Fig. 6A is characterized by plateau bursting, while the region above the top dotted curve is characterized by pseudo-plateau bursting. The middle region is transitional between the two.

In the bifurcation structures in Fig. 4, the top branch of the $z$-curve has stabilized when the negative feedback $K^+$ current is decreased or the positive feedback $Ca^{2+}$ current is increased. The negative feedback is decreased by increasing $v_n$ or decreasing $g_K$. The positive feedback is increased by increasing $g_{Ca}$ or decreasing $v_m$. Increasing $v_n$ or $g_{Ca}$ shifts the bifurcations to the right. As a result, the HB, HM, and USN curves in Figs. 6A and 6D have positive slopes. In both panels (Figs. 6A and 6D), the bottom and top regions are characterized by plateau and pseudo-plateau bursting, respectively. Decreasing (rather than increasing) $g_K$ or $v_m$ shifts the bifurcations rightward, so the HB, HM, and USN curves have negative slopes (Figs. 6B and 6C). The top regions are now characterized by plateau bursting and the bottom regions are characterized by pseudo-plateau bursting.

3.2 Cumulative Properties of Parameter Variations

We have seen that a transition between plateau and pseudo-plateau bursts can be made by changing just one of the parameters $v_n$, $v_m$, $g_K$, or $g_{Ca}$. If more than one parameter is varied, can the transition be achieved by smaller changes in each parameter? Figure 7 illustrates the effects of varying two parameters. Using the default values $v_n = -16$ mV and $v_m = -20$ mV (Fig. 7A (a,d)), plateau bursting is produced. To convert to pseudo-plateau bursting, one could increase $v_n$ to $-12$ mV (point (c,d)), or decrease $v_m$ to $-26$ mV (point (a,f)). Both changes increase the separation between $n_\infty(V)$ and $m_\infty(V)$ (Fig. 3), which is critical for making the conversion to pseudo-plateau bursting. This can also be achieved by varying both $v_n$ and $v_m$ so as to bring about a similar separation in the $n_\infty(V)$ and $m_\infty(V)$ curves. As a result, a transition
from plateau to pseudo-plateau bursting can be made with smaller changes to each parameter. The filled circles on the curve in Fig. 7A display values of $v_n$ and $v_m$ at which pseudo-plateau bursting is produced. Points just above the curve are in the transitional region. Most points on the curve correspond to shifts in both $n_\infty(V)$ and $m_\infty(V)$. For example, at point $(b, e)$, $v_n = -14.5$ mV and $v_m = -22.5$ mV. Increasing $v_n$ to $-14.5$ mV shifts the $n_\infty(V)$ curve rightward (blue dashed curve in Fig. 3) and decreasing $v_m$ to $-22.5$ mV shifts the $m_\infty(V)$ curve leftward (red dashed curve in Fig. 3) so that the two curves are sufficiently far apart to produce pseudo-plateau bursting. In this case, the mid points of the two curves are 8 mV apart, and indeed for all points on the curve $v_n - v_m \approx 8$ mV.

Similarly, Fig. 7B shows the cumulative properties of $v_n$ and $g_k$ parameter variations. The square denotes the initial parameter set for plateau bursting and the points on the curve correspond to pseudo-plateau bursting. As in Fig. 7A, a transition to pseudo-plateau bursting can be achieved with changes in two parameters that are smaller than the change required in either parameter alone. Indeed, even smaller changes are required when three parameters $v_m$, $v_n$, and $g_k$ are varied (not shown).

3.3 Transition from Pseudo-Plateau to Plateau Bursting with a Pseudo-Plateau Bursting Model

3.3.1 Pseudo-Plateau to Plateau Conversion by Actions on the $K^+$ or $Ca_{\text{2+}}^+$ Current

We now use a pseudo-plateau bursting model, for pituitary lactotrophs (Appendix), to show a transition to plateau bursting. Thus, the transition between bursting types is not limited to the Chay–Keizer model but is a more general phenomenon. Figure 1D shows pseudo-plateau bursting with the lactotroph model. The fast subsystem bifurcation structure is shown in Fig. 1F.

We have seen that in the Chay–Keizer model plateau bursting is converted to pseudo-plateau bursting by increasing $v_n$ or $g_{Ca}$, or by decreasing $v_m$ or $g_K$. One potential approach for converting pseudo-plateau to plateau bursting is to work the other way around. This is demonstrated in Fig. 8. With $v_n = -9.5$ mV (panel A) pseudo-plateau bursting is produced. When $v_n$ is decreased to $-15$ mV (and $f$ changed from 0.01 to 0.00025) plateau bursting is produced (panel B). Similarly, increasing $g_K$ from 4 nS to 9 nS converts the pseudo-plateau bursting to plateau bursting (not shown).

Figure 9 shows the transition with two-parameter bifurcation diagrams, which are qualitatively similar to those produced with the Chay–Keizer model (Fig. 6). In some cases, it was not possible to make a transition using the default parameter values (Table 2). Therefore, the values of other parameters were modified before changes to the control parameter ($v_n$, $v_m$, $g_K$ or $g_{Ca}$) were made, as listed in the figure caption. The figure illustrates that, as with the Chay–Keizer model, there are several ways to convert between plateau and pseudo-plateau bursting with the lactotroph model.

4 Discussion

We have shown that a transition can be made between plateau and pseudo-plateau bursting by modifying the fast $K^+$ and $Ca_{\text{2+}}^+$ currents. Using the Chay–Keizer model,
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**Fig. 8** Bursting oscillations using the lactotroph model with parameter values in Table 2. (A) Pseudo-plateau bursting with $v_n = -9.5$ mV. (B) Plateau bursting with $v_n = -15$ mV and $f = 0.00025$

Plateau bursting is converted to pseudo-plateau bursting, and using the lactotroph model, pseudo-plateau bursting is converted to plateau bursting. This illustrates that the plateau bursting exhibited by many neurons and by pancreatic islets are reconcilable with the pseudo-plateau bursting exhibited by many pituitary cells and single beta-cells. Pseudo-plateau bursting is produced from plateau bursting by increasing the separation between the activation functions of the fast depolarizing and hyperpolarizing currents. Alternatively, the conductance of the depolarizing current can be increased or that of the hyperpolarizing current can be decreased. Another change that must be made is the speed of the slow variable, the Ca$^{2+}$ concentration. This was accomplished here by varying $f$, the fraction of Ca$^{2+}$ not bound by buffer. A typical value of $f$ is measured to be 0.01 (Berlin et al. 1994), but there can be as much as an order of magnitude variation of $f$ among cells of the same type (Al-Baldawi and Abercrombie 1995). It has been demonstrated that variation in a cell’s buffering capacity can have a large impact in its electrical behavior, such as conversion from spiking to bursting (Roussel et al. 2006).

The plateau bursting that is common in neurons is characterized by large amplitude spikes, unlike pseudo-plateau bursting which has small amplitude spikes. This could be important for various neuronal functions such as conduction through the axon or neurotransmitter release and can help synchronize activity of several neurons. In contrast, pituitary cells are small and spherical; no axonal conduction is required and global hormone release does not require synchronization among cells. In the neuronal synapse, transmitter-filled vesicles and Ca$^{2+}$ channels are molecularly linked, assuring their close proximity (Sheng et al. 1996). As a result, exocytosis is effectively triggered by action potentials (Mennerick and Matthews 1996). In contrast, short impulse-like depolarizations are ineffective at evoking hormone release from melan-
otrophs (Mansvelder and Kits 1998) and gonadotrophs (Tse et al. 1997), two types of pituitary cells. This suggests that longer depolarization, such as a pseudo-plateau burst, is needed. Indeed, basal secretion does not occur in pituitary gonadotrophs, which spike under basal conditions, but does occur in pituitary somatotrophs and lactotrophs, which often exhibit pseudo-plateau bursting under basal conditions (Van Goor et al. 2001b; Stojilkovic et al. 2005). Finally, spike timing is often important in neurons, but not so in pituitary cells. This is facilitated by the large, well-defined (sharp) spikes produced during plateau, but not pseudo-plateau bursting.

The resetting properties of the two types of bursting are also quite different. As described in Stern et al. (2008), pseudo-plateau bursts are harder to reset between silent and active phases. In addition, while the resetting properties of plateau bursts are fairly obvious (a reset out of the silent phase results in a short next active phase and vice versa), the resetting properties of pseudo-plateau bursts are more complex and in some ways counter-intuitive (see Stern et al. 2008 for details). The different resetting properties of the two types of bursting mean that the two will respond differently to noise in the system, which is common in excitable cells. Despite this and

\begin{table}
\centering
\caption{Parameter values for the lactotroph model}
\begin{tabular}{lll}
\hline
Parameter & Value & Description \\
\hline
$C_m$ & 10 pF & Membrane capacitance of the cell \\
$g_{Ca}$ & 2 nS & Maximum conductance of Ca$^{2+}$ channels \\
$V_{Ca}$ & 50 mV & Reversal potential for Ca$^{2+}$ \\
$v_m$ & $-20$ mV & Voltage value at midpoint of $m_{\infty}$ \\
$s_m$ & 12 mV & Slope parameter of $m_{\infty}$ \\
$g_K$ & 4 nS & Maximum conductance of K$^+$ channels \\
$V_K$ & $-75$ mV & Reversal potential for K$^+$ \\
$v_n$ & $-5$ mV & Voltage value at midpoint of $n_{\infty}$ \\
$s_n$ & 10 mV & Slope parameter of $n_{\infty}$ \\
$\tau_n$ & 30 ms & Time constant of $n$ \\
$\lambda$ & 1.9 & Parameter used to control spiking pattern \\
$g_{K(Ca)}$ & 1.7 nS & Maximum conductance of K(Ca) channels \\
$K_d$ & 0.5 $\mu$M & $c$ at midpoint of $s_{\infty}$ \\
$g_{BK}$ & 0.43 nS & Maximum conductance of BK-type K$^+$ channels \\
$v_f$ & $-20$ mV & Voltage value at midpoint of $f_{\infty}$ \\
$s_f$ & 5.6 mV & Slope parameter of $f_{\infty}$ \\
$g_A$ & 18 nS & Maximum conductance of A-type K$^+$ channels \\
$v_a$ & $-20$ mV & Voltage value at midpoint of $a_{\infty}$ \\
$s_a$ & 10 mV & Slope parameter of $a_{\infty}$ \\
$v_h$ & $-60$ mV & Voltage value at midpoint of $h_{\infty}$ \\
$s_h$ & 5 mV & Slope parameter of $h_{\infty}$ \\
$\tau_h$ & 5 ms & Time constant of $h$ \\
$f$ & 0.01 & Fracation of free Ca$^{2+}$ ions in cytoplasm \\
$\alpha$ & 0.0015 $\mu$F C$^{-1}$ & Conversion from charge to concentration \\
$k_c$ & 0.06 ms$^{-1}$ & Rate of Ca$^{2+}$ extrusion \\
\hline
\end{tabular}
\end{table}
other functional differences, we have shown here that models for the different classes of bursting contain the necessary elements to produce bursting of either class.

This work suggests that differences in the dynamical equilibrium between the fast inward and outward currents underly the differences between the two types of bursting. These differences can be accomplished by changing a single parameter of the inward or outward currents. Such changes in single parameter values could be done experimentally using the dynamic clamp technique (Sharp et al. 1993; Prinz et al. 2004). For example, $I_K$ (K+ current) could be blocked pharmacologically, then reintroduced with the dynamic clamp but with a different $v_n$. This would alter the bifurcation structure underlying bursting. In addition, to switch from one type of burst to the other, we would have to change $f$, the fraction of unbound calcium (Roussel et al. 2006). Thus, it will be possible, in principle, to verify our assertion that changes in two parameters can switch the bursting pattern between plateau and pseudo plateau.

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Appendix A: The Lactotroph Model

The lactotroph model (Tabak et al. 2007) includes differential equations for the variables $V$ (membrane potential), $n$ (fraction of activated delayed rectifier $K^+$ channels), $h$ (fraction of A-type $K^+$ channels that are not inactivated), and $c$ (cytosolic free $Ca^{2+}$ concentration). The equations are:

$$C_m \frac{dV}{dt} = -(I_{Ca} + I_K + I_{K(Ca)} + I_{BK} + I_A) \quad (A.1)$$

$$\frac{dn}{dt} = \frac{\lambda(n_{\infty}(V) - n)}{\tau_n} \quad (A.2)$$

$$\frac{dh}{dt} = \frac{(h_{\infty}(V) - h)}{\tau_h} \quad (A.3)$$

$$\frac{dc}{dt} = -f(\alpha I_{Ca} + k_c c) \quad (A.4)$$

where $I_{Ca}$ is an inward $Ca^{2+}$ current, $I_K$ is an outward delayed rectifying $K^+$ current, $I_{K(Ca)}$ is an SK-type $Ca^{2+}$-activated $K^+$ current, $I_{BK}$ is a fast-activating BK-type $K^+$ current, and $I_A$ is an A-type $K^+$ current. The currents in the equations above are:

$$I_{Ca} = g_{Ca}m_{\infty}(V)(V - V_{Ca}) \quad (A.5)$$

$$I_K = g_Kn(V - V_K) \quad (A.6)$$

$$I_{K(Ca)} = g_{K(Ca)}s_{\infty}(c)(V - V_K) \quad (A.7)$$

$$I_{BK} = g_{BK}f_{\infty}(V)(V - V_K) \quad (A.8)$$

$$I_A = g_Aa_{\infty}(V)h(V - V_K). \quad (A.9)$$

The steady state activation and inactivation functions are given by

$$m_{\infty}(V) = \left(1 + \exp\left(\frac{v_m - V}{s_m}\right)\right)^{-1} \quad (A.10)$$

$$n_{\infty}(V) = \left(1 + \exp\left(\frac{v_n - V}{s_n}\right)\right)^{-1} \quad (A.11)$$

$$s_{\infty}(c) = \frac{c^2}{c^2 + K_d^2} \quad (A.12)$$

$$f_{\infty}(V) = \left(1 + \exp\left(\frac{v_f - V}{s_f}\right)\right)^{-1} \quad (A.13)$$

$$a_{\infty}(V) = \left(1 + \exp\left(\frac{v_a - V}{s_a}\right)\right)^{-1} \quad (A.14)$$

$$h_{\infty}(V) = \left(1 + \exp\left(\frac{V - v_h}{s_h}\right)\right)^{-1} \quad (A.15)$$
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where $m_\infty$ is the steady state activation function for $I_{Ca}$, $n_\infty$ is the steady state activation function for $I_K$, $s_\infty$ is the fraction of K(Ca) channels activated by cytosolic Ca$^{2+}$, $h_\infty$ is the steady state inactivation function for $I_A$, $d_\infty$ is the steady state activation function for $I_{BK}$. These range from 0 to 1.

References


