From Plateau to Pseudo-Plateau Bursting: Making the Transition

Wondimu Teka

Department of Mathematics
Florida State University
Tallahassee, FL
Collaborators and support

J. Tabak  Department of Biological Science,  Florida State University
R. Bertram  Department of Mathematics,  Florida State University
K. Tsaneva-Atanasova  Department of Engineering Mathematics,  Bristol University

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Bursting oscillations

- An excitable cell can produce a group of spikes.
- Bursting is the alternation between a group of spikes and resting state.
Bursting in neurons

Properties: long burst duration, and large amplitude and high frequency of spikes. These may be important for fast transmission of information.


Anterior pituitary cells

Pituitary gland:
- It controls the functions of the other endocrine glands.
- It produces growth hormone, prolactin and others.

Anterior pituitary cells: somatotrophs, lactotrophs, corticotrophs, gonadotrophs and thyrotrophs.
Bursting in anterior pituitary cells

Properties: short burst duration, and small amplitude and small frequency of spikes. These may be important for slow, coordinated hormone release.

Bursting oscillations in a GH4 pituitary cell.

Neurons and pituitary cells have different structures and functions, and produce different bursting patterns.

Question

How can a neuronal burster be converted to a pituitary burster (or vice versa)?
The model

We use a modification of the Chay-Keizer model for bursting in our analysis. This is a well-studied and well-known model that produces neuron-like bursts.

The Chay-Keizer model

\[
\frac{dV}{dt} = -\left( I_{Ca} + I_K + I_{K(Ca)} + I_{K(ATP)} \right)/C_m
\]

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

- \( V \)= voltage (mV)
- \( t \)= time (msec)
- \( n \)= fraction of open delayed rectifying \( K^+ \) channels

\( I_{Ca} = \) \( Ca^{2+} \) current

\( I_K = \) delayed rectifying \( K^+ \) current

\( I_{K(Ca)} = \) \( Ca^{2+} \)-activated \( K^+ \) current

\( I_{K(ATP)} = \) ATP-sensitive \( K^+ \) current
The Chay-Keizer model: $\text{Ca}^{2+}$ dynamics

\[
\frac{dc}{dt} = -f_{\text{cyt}}(\alpha I_{\text{Ca}} + J_{\text{PMCA}})
\]

\[J_{\text{PMCA}} = k_{\text{PMCA}} \cdot c\]

c activates the $K(\text{Ca})$ channels;

\[
g_{K}^{\text{(Ca)}} = \overline{g}_{K}^{\text{(Ca)}} \frac{c^3}{c^3 + k_d^3}
\]
Bursting oscillations using Chay-Keizer model

Most neuronal models produce **plateau (square wave) bursting**: long burst duration, high frequency and large amplitude of spikes.
Bursting oscillations using a pituitary model

Pituitary models produce bursting which has underdamped oscillations. This bursting type is pseudo plateau bursting: Short burst duration, small spikes, fewer spikes.
Fast-slow analysis of bursting in neurons

The fast subsystem is bistable between the stable periodic solution and stable lower steady state.

z-curve = stationary solution
solid = stable
dot = unstable

Bifurcations:
HB = Hopf
HM = homoclinic
USN = upper saddle-node
LSN = lower saddle-node
Superimpose the burst trajectory

\[ \frac{dc}{dt} > 0 \]

\[ \frac{dc}{dt} < 0 \]
Fast-slow analysis of pituitary bursting

No stable spiking branch; the fast subsystem is bistable, consisting of stable upper and lower stationary branches; subcritical Hopf bifurcation.
Fast-slow analysis of pituitary bursting

The burst trajectory of the full system is superimposed.
Question

How can we make a transition from one bursting pattern to the other?
Steps: from plateau to pseudo-plateau

1. Make the slow variable, $c$, much faster. This results in short burst duration and the burst trajectory moves rapidly along the fast subsystem bifurcation structure. To get this, just increase $f_{cyt}$.

\[
\frac{dc}{dt} = -f_{cyt}(\alpha I_{Ca} + J_{PMCA})
\]

2. Modify parameter values that can cause significant changes to the upper part of the fast subsystem bifurcation structure. In this step, there are 4 approaches.
1. Make the delayed rectifier activate at a higher voltage

This is done by Increasing $v_n$. This shifts the $n_\infty$ curve to the right.

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

Red = old curve
Blue = new curve
Increasing $v_n$ stabilized the top branch.

Bursting with this bifurcation structure called **transition bursting**.

$$v_n = -14 \text{ mV}$$

$$f_{cyt} = 0.01$$
Effects of increasing $v_n$ further

When $v_n$ is increased further, the limit cycle and HB move further to the right, and the upper branch becomes stable. This results in the bifurcation structure for pseudo-plateau bursting.
$f_{cyt}$ is increased and burst trajectory is superimposed.
Two-parameter bifurcation structure

c-values at the bifurcation points:

- plateau bursting:
  \[ \text{supHB} < \text{LSN} < \text{HM} < \text{USN} \]

- Transition bursting:
  \[ \text{LSN} < \text{subHB} < \text{HM} < \text{USN} \]

- Pseudo-plateau bursting:
  \[ \text{LSN} < \text{HM} < \text{subHB} < \text{USN} \]

By using a two-parameter bifurcation diagram, we can determine the regions for these bursting patterns.
Two-parameter bifurcation structure: $v_n$ vs. $c$
Two-parameter bifurcation structure: $v_n$ vs. $c$
Two-parameter bifurcation structure: $v_n$ vs. $c$
2. Make the Ca\textsuperscript{2+} channels activate at a lower voltage

Decrease $v_m$ shifts the $m_\infty$ curve to the left and stabilize the top branch of the z-curve. This results in pseudo-plateau bursting.

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

![Graph showing plateau bursting, transition bursting, and pseudo-plateau bursting with equations and variables marked on the axes.](image-url)
More biophysically plausible approaches

3. Decreasing the delayed rectifier channel conductance

4. Increasing Ca\(^{2+}\) channel conductance

In all four approaches, making the cell more excitable converts the plateau bursting to pseudo-plateau bursting.
Conclusions

1. A transition from plateau to pseudo-plateau bursting is made by making
   a. the cell more excitable and
   b. the slow variable faster

2. Using opposite changes, a transition is made from pseudo-plateau to plateau bursters.

3. The results suggest that the mechanisms for bursting in endocrine cells are just quantitative variations of those for bursting in neurons.
THANK YOU!

QUESTIONS