A Mathematical Study of Electrical Bursting in Pituitary Cells

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Nerve Cells Often Burst


Neuron from the pre-Botzinger complex (Butera et al, J. Neurophysiol, 82:382, 1999)
What is the Function of Bursting?

- The active phases of spiking enhance the **signal-to-noise ratio** for accurate synaptic transmission.
- The silent phases allow postsynaptic receptors to rest, reducing receptor **desensitization**.
This phenomenon has motivated mathematical studies over the past few decades

1970s...

Mathematical Description of a Bursting Pacemaker Neuron by a Modification of the Hodgkin-Huxley Equations
R. E. Plant and M. Kim
Biophysical Journal Volume 16 1976

1980s...

Dissection of a model for neuronal parabolic bursting
John Rinzel and Young Seek Lee

1990s...

Models of Respiratory Rhythm Generation in the Pre-Bötzingher Complex. I. Bursting Pacemaker Neurons
Robert J. Butera, Jr.,1,2 John Rinzel,1,3 and Jeffrey C. Smith1
New millenium ...

Emergent Synchronous Bursting of Oxytocin Neuronal Network

Enrico Rossoni¹, Jianfeng Feng¹,², Brunello Tirozzi³, David Brown⁴, Gareth Leng⁵, Françoise Moos⁶

Even a book...
Many pituitary cells are also electrically excitable.
Pituitary cells often burst

Van Goor et al, JBC, 276:33840, 2001
As do single insulin-secreting pancreatic β-cells

Zhang et al., Biophys. J., 84:2852, 2003
In pituitary cells, it has been shown that cytosolic calcium levels are much greater in bursting cells than in spiking cells (van Goor et al., J. Neurosci., 21:5902, 2001). Secretion should also be greater.
Modeling studies have recently been performed for pituitary bursting.

Paradoxical Role of Large-Conductance Calcium-Activated K⁺ (BK) Channels in Controlling Action Potential-Driven Ca²⁺ Entry in Anterior Pituitary Cells

Fredrick Van Goor, Yue-Xian Li, and Stanko S. Stojilkovic

Mechanism of Spontaneous and Receptor-Controlled Electrical Activity in Pituitary Somatotrophs: Experiments and Theory

Krasimira Tsaneva-Atanasova, Arthur Sherman, Frederick van Goor, and Stanko S. Stojilkovic

Low dose of dopamine may stimulate prolactin secretion by increasing fast potassium currents

Joël Tabak, Natalia Toporikova, Marc E. Freeman, and Richard Bertram

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Mechanisms for bursting are different in pituitary and neuronal models.
Central Question

Can a model neuronal burster be converted to a pituitary burster (or vice versa) by changing one or more system parameter?

If no, then the ionic mechanisms driving the two burst patterns are fundamentally different, possibly reflecting developmental differences in neurons and pituitary cells.

If yes, then the two very different burst patterns are just quantitative variations of one another, and conversion could potentially be seen in the lab (or \textit{in vivo}).
The Model

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

Electrical activity equations using conservation of charge

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

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

\( V \) = 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

It is assumed that Ca\(^{2+}\) channels activate instantaneously when V is depolarized.
What clusters spikes into bursts?

C = free calcium concentration in the cytosol

\[
\dot{c} = -f(\alpha I_{Ca} + J_{pmca})
\]

C activates the K(Ca) current

\[
g_{K(Ca)} = \bar{g}_{K(Ca)} \left( \frac{c^3}{c^3 + k_d^3} \right)
\]
What clusters spikes into bursts?

Calcium builds up and activates the $K(Ca)$ current, shutting off the spiking. The spiking restarts when $Ca^{2+}$ concentration recovers to a low level.

Square Wave Bursting
Fast/Slow Analysis

We use a geometric analysis technique developed by John Rinzel to better understand the bursting.
Fast/Slow analysis of bursting

Variables can be separated into those that change rapidly and those that change slowly. In this case, there is only one slow variable (calcium, C). The slow variable is then treated as a bifurcation parameter for the fast subsystem (V and n).

Solid = stable SS
Dashed = unstable SS
HB = Hopf bifurcation
SN = saddle node bifurcation
Next, the branch of periodic spiking solutions is added.

IMPORTANT: The fast subsystem is bistable between LSN and HM, with coexisting stable periodic and stationary solutions for the same $c$ values.

This bifurcation diagram is often called a $z$-curve.
Slow variable dynamics

Next we add the dynamics of the slow variable, calcium, back in.

The C-nullcline is the curve where

$$\frac{dC}{dt} = 0$$

Below the nullcline

$$\frac{dC}{dt} < 0$$
Finally, we superimpose the burst trajectory.
What this tells us

- The spiking should slow down near the end of a burst.
- A short current perturbation should be able to reset the system from silent to active phase (and vice versa).
Bursting with a pituitary model

Shorter duration -- Fewer spikes -- Small spikes
Fast subsystem bifurcation diagram

No stable periodic spiking branch!

Bistable between two stationary branches of solutions

subHB = subcritical Hopf bifurcation
Fast/Slow analysis of pituitary bursting

This is called **pseudo-plateau bursting** since there is no stable spiking solution.
What does this tell us?

- Spiking is not following a stable periodic branch, so we can’t say anything about how spike frequency will vary during a burst.

- Spikes will usually get smaller at later stages of the active phase.

- It will be difficult to reset from silent to active phase, since there is no stable spiking limit cycle basin of attraction to perturb into (for full analysis see Stern et al., Bull. Math. Biol., 70:68, 2008).
How can we get from **??** to **???**?
1. **Speed up** the slow variable, so that the trajectory moves more quickly along the fast subsystem bifurcation diagram. Easy to do: increase “f”, the fraction of cytosolic Ca$^{2+}$ that is unbound by buffers.

2. Change the value of a parameter that makes the branch of stable oscillatory solutions go away and **stabilizes the top branch** of stationary solutions.
Idea: Speed up the delayed rectifier dynamics

This $K^+$ current is responsible for voltage repolarization during a spike. It provides delayed negative feedback to the membrane, so speeding it up should eliminate the action potentials, stabilizing the depolarized branch of the z-curve.

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

Decrease the time constant $\tau_n$
Idea: Speed up the delayed rectifier dynamics

Most of the top branch has stabilized, but the Hopf bifurcations are supercritical, not subcritical as in the pituitary model.
Does this work?

Looks like pseudo-plateau bursting

Motion along the z-curve is what we expect for PP bursting.
How else can we do this?

Can we get the subcritical Hopf bifurcation as in the pituitary models?
Idea: Make the delayed rectifier activate at a higher voltage

This will potentially result in depolarization block, a well-known phenomenon in which a spiking neuron hangs up in a depolarized state.
Idea: Make the delayed rectifier activate at a higher voltage

Shifting $n_\infty$ by increasing $v_n$ stabilizes the top branch, as hoped. We call bursting with this bifurcation structure transition bursting.
Idea: Make the delayed rectifier activate at a higher voltage

Shifting $\eta_\infty$ even more gives the desired pituitary-like diagram

Pseudo-plateau bursting is produced
Two-dimensional bifurcation diagrams

A key feature of square wave bursting is that the Hopf bifurcation is supercritical, so that the Hopf (HB) is to the left of the homoclinic (HM) bifurcation in the 1-parameter bifurcation diagrams. Also, the HB is to the left of the lower saddle node bifurcation (LSN). Thus, HB < LSN < HM.

Pseudo-plateau bursting is produced when the Hopf bifurcation is subcritical, and is to the right of the LSN. In this case, LSN < HM < HB.

How these key bifurcation points change with changes in the $v_n$ parameter is summarized in a 2-parameter bifurcation diagram.
Two-parameter diagram: $v_n$ vs. $c$
Can we get transitions between SW and PP bursting by changing other parameters?
Idea: Make the Ca$^{2+}$ channels activate at lower voltages

Reducing $v_m$ translates the activation function leftward

black = old

green = new
Idea: Make the Ca\textsuperscript{2+} channels activate at lower voltages

This works
Can a transition be made by changing a channel conductance?
Idea: Decrease the delayed rectifier conductance

This would have a depolarizing effect on the cell, and could stabilize the top branch of stationary solutions in the z-curve.
Idea: Decrease the Delayed Rectifier conductance

This also works
Idea: Increase the depolarizing \( \text{Ca}^{2+} \) channel conductance

This also works
We can test this in the lab with the Dynamic Clamp

\[ \frac{df}{dt} = \frac{(f_x(V) - V)}{\tau_{DC}} \]

\[ I_{DC} = g_{DC} \times f \times (V - V_K) \]
Prediction: Adding a delayed rectifier-like current should convert a pituitary burster to a square wave burster.
Does this work?

Stay Tuned...
The End