A Mathematical Study of Electrical Bursting in Pituitary Cells

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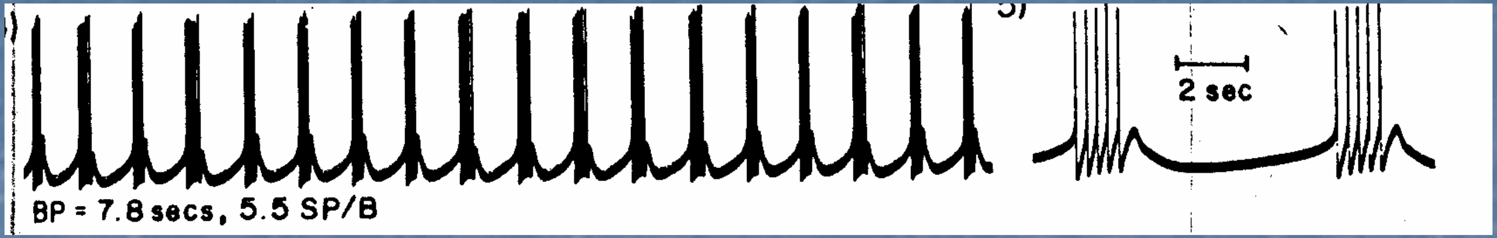
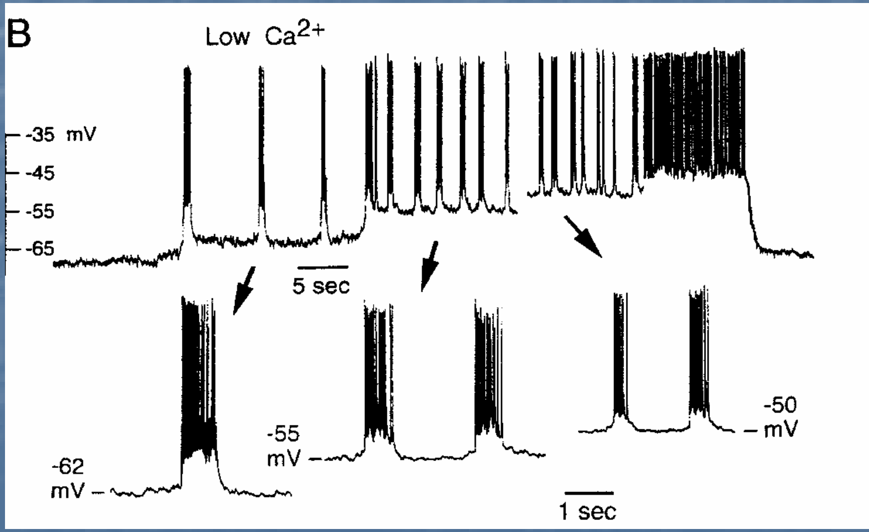
Grant support: National Institutes of Health (DA-19356)
National Science Foundation (DMS-0917664)

Nerve Cells Often Burst



Neuron L3 of the Aplysia abdominal ganglion (Pinsker, J. Neurosci., 40:527, 1977)



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

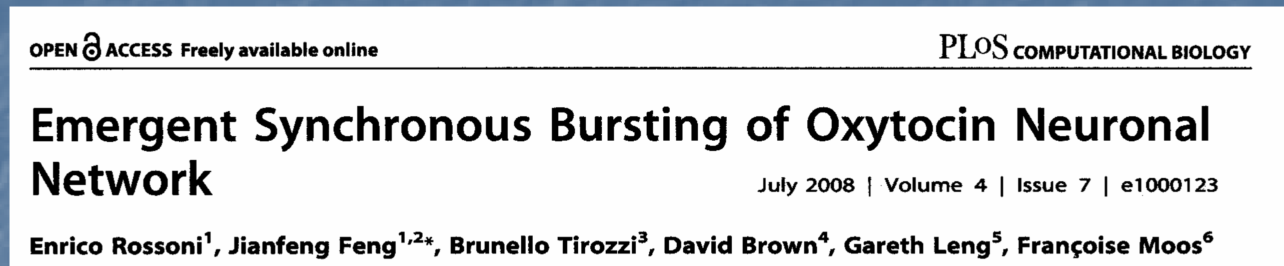
John Rinzel and Young Seek Lee   J. Math. Biol. (1987) 25: 653–675

1990s…

Models of Respiratory Rhythm Generation in the Pre-Bötzinger Complex. I. Bursting Pacemaker Neurons

ROBERT J. BUTERA, JR.,[1,2] JOHN RINZEL,[1–3] AND JEFFREY C. SMITH[1]

New millenium …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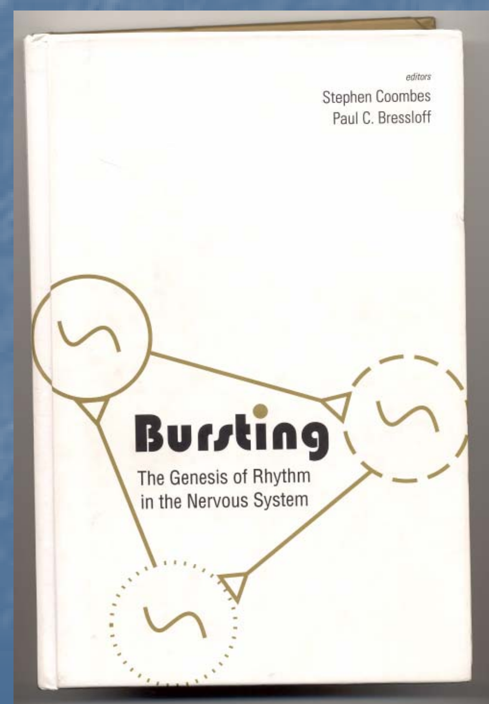
PLoS COMPUTATIONAL BIOLOGY

Emergent Synchronous Bursting of Oxytocin Neuronal Network

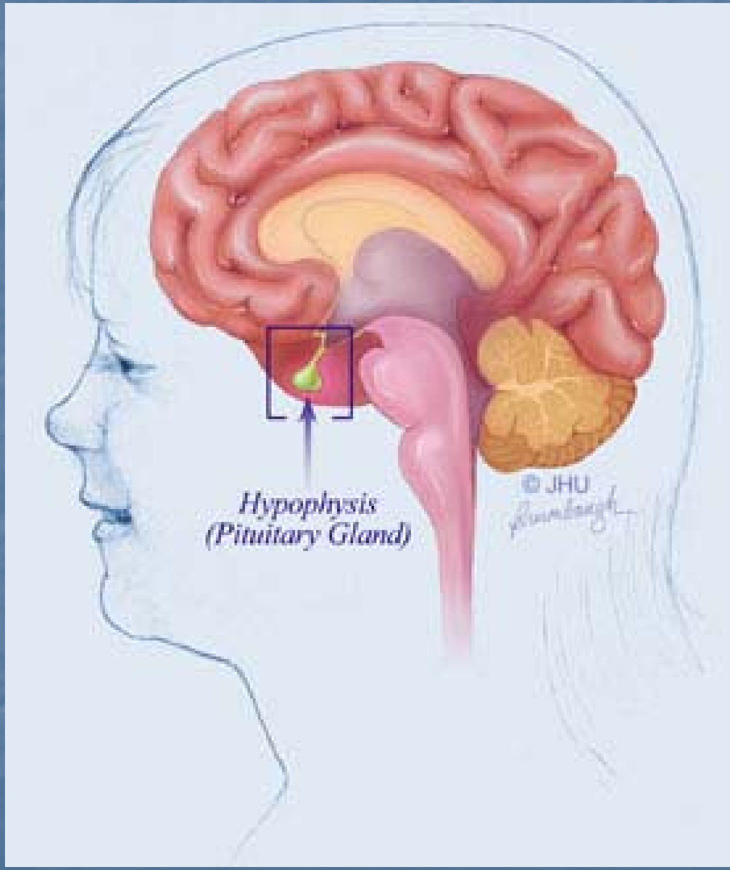
July 2008 | Volume 4 | Issue 7 | e1000123

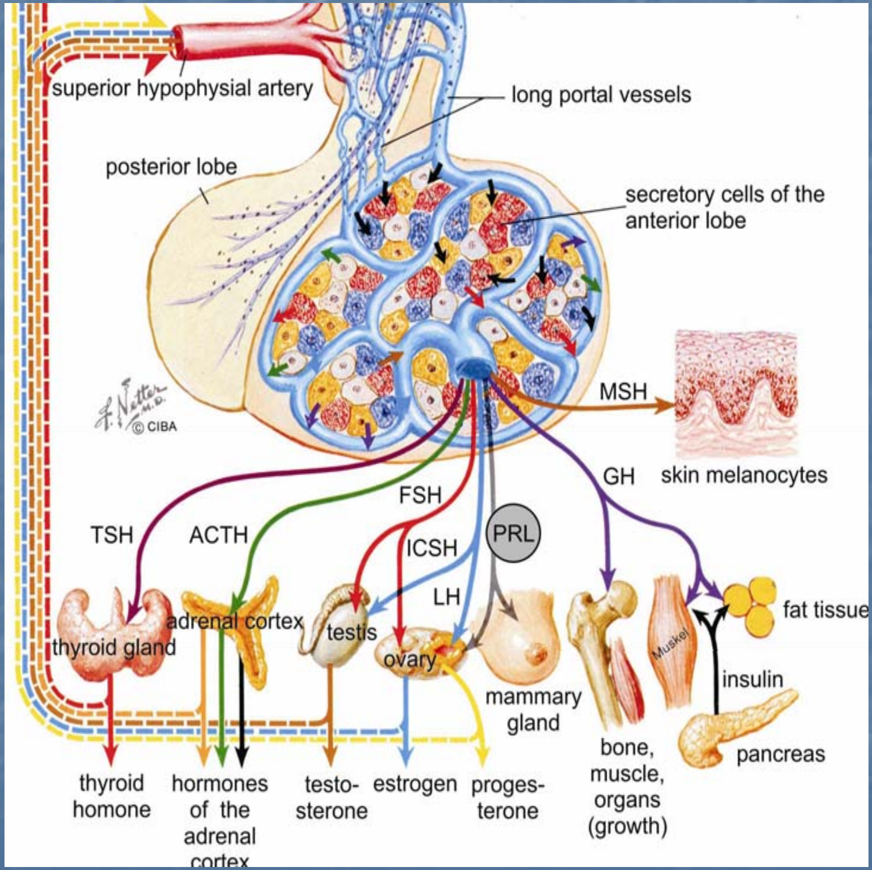
Enrico Rossoni[1], Jianfeng Feng[1,2]*, Brunello Tirozzi[3], David Brown[4], Gareth Leng[5], Françoise Moos[6]

Even a book…

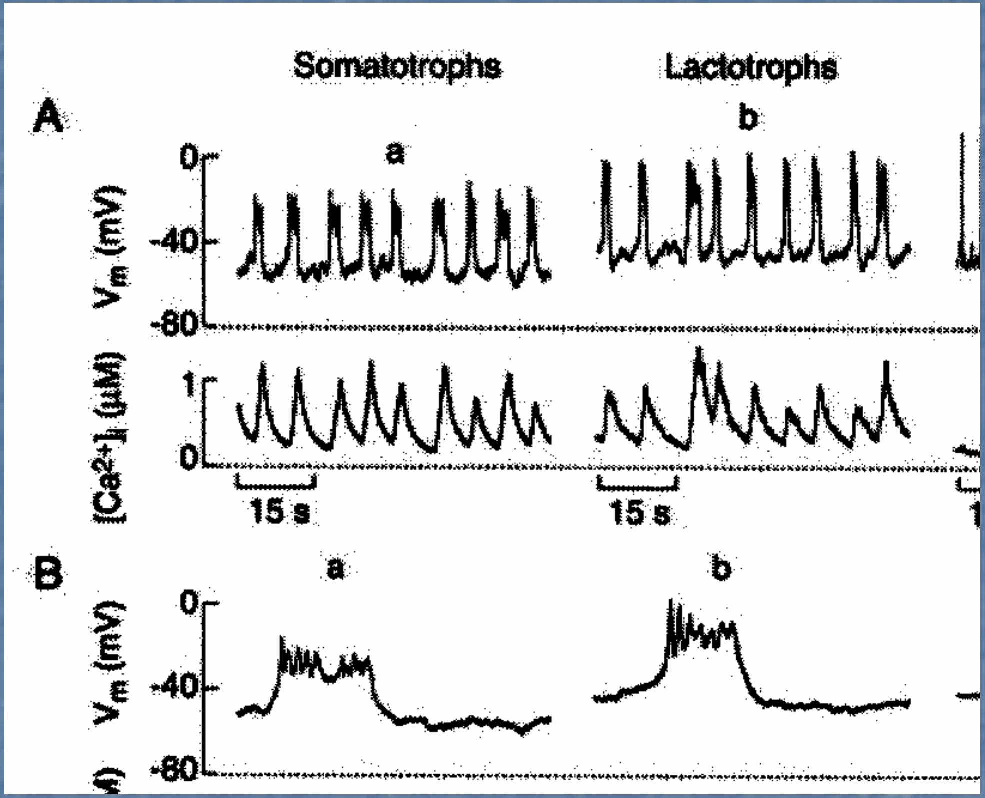


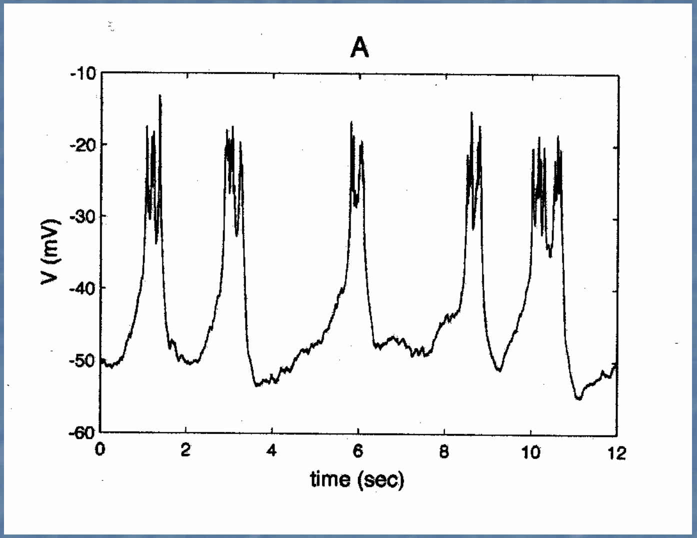
Many pituitary cells are also electrically excitable





Pituitary cells often burst

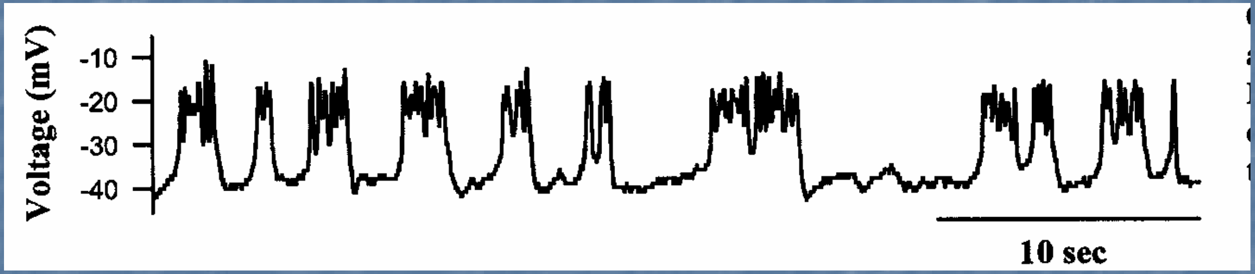




Lactotroph cell line (GH4), courtesy Joel Tabak

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 Ca^{2+} Entry in Anterior Pituitary Cells

The Journal of Neuroscience, August 15, 2001, *21*(16):5902–5915

Fredrick Van Goor,[1] Yue-Xian Li,[2] and Stanko S. Stojilkovic[1]

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

J Neurophysiol 98: 131–144, 2007.
, 2007; doi:10.1152/jn.00872.2006.

Krasimira Tsaneva-Atanasova,[1] Arthur Sherman,[1] Frederick van Goor,[2] and Stanko S. Stojilkovic[2]

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

Joël Tabak · Natalia Toporikova · Marc E. Freeman · Richard Bertram

J Comput Neurosci (2007) 22:211–222
DOI 10.1007/s10827-006-0008-4

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.

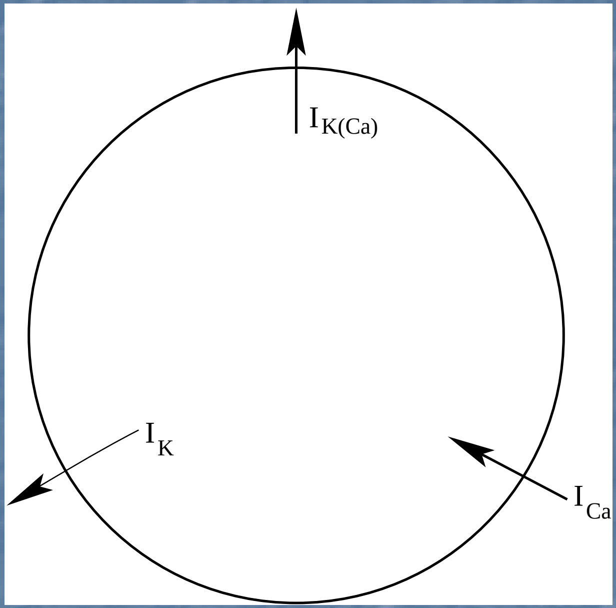
If yes, then the two very different burst patterns are just quantitative variations of one another, and conversion could potentially be seen in the lab (or *in vivo*).

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.

T. R. Chay and J. Keizer, Biophys. J., 42:181, 1983

Electrical activity equations using conservation of charge



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

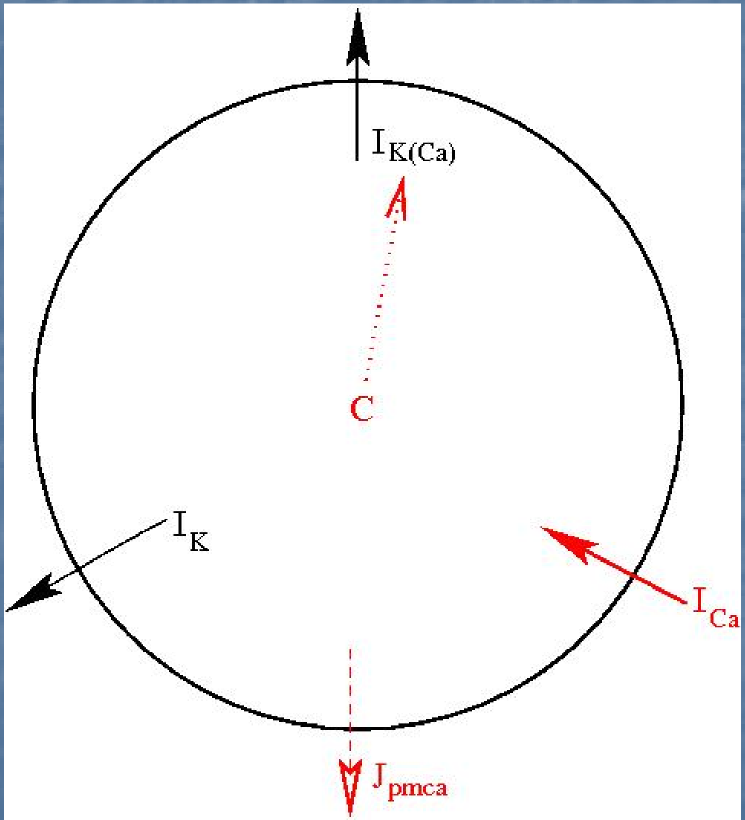
$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n}$$

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

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

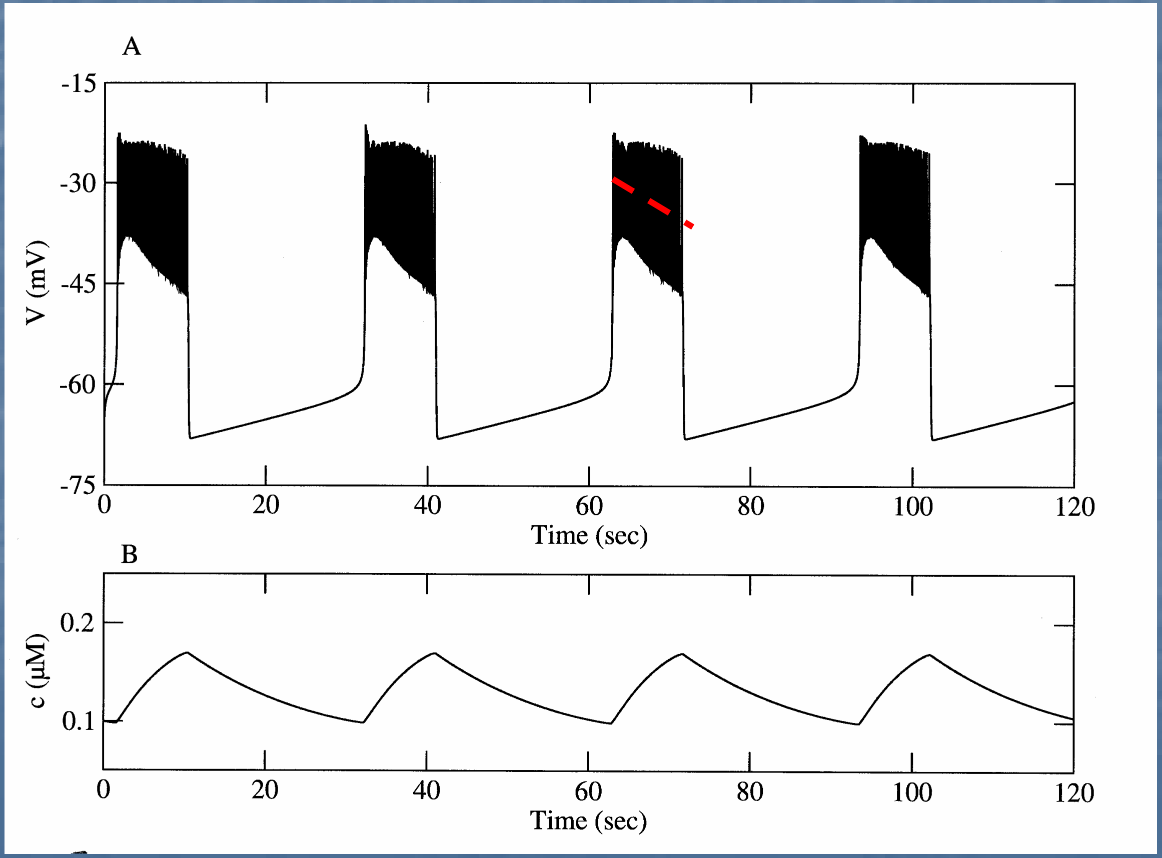
C activates the K(Ca) current

$$g_{K(Ca)} = \bar{g}_{K(Ca)}\left(\frac{c^3}{c^3 + k_d^3}\right)$$

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

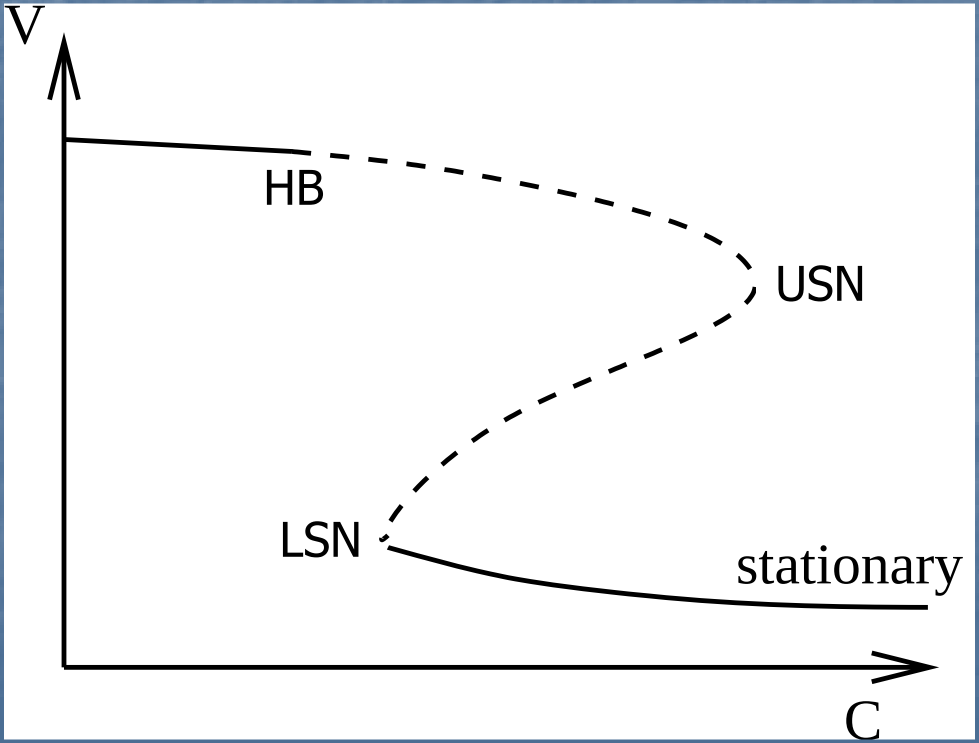


Fast/Slow Analysis

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

Fast/Slow analysis of bursting

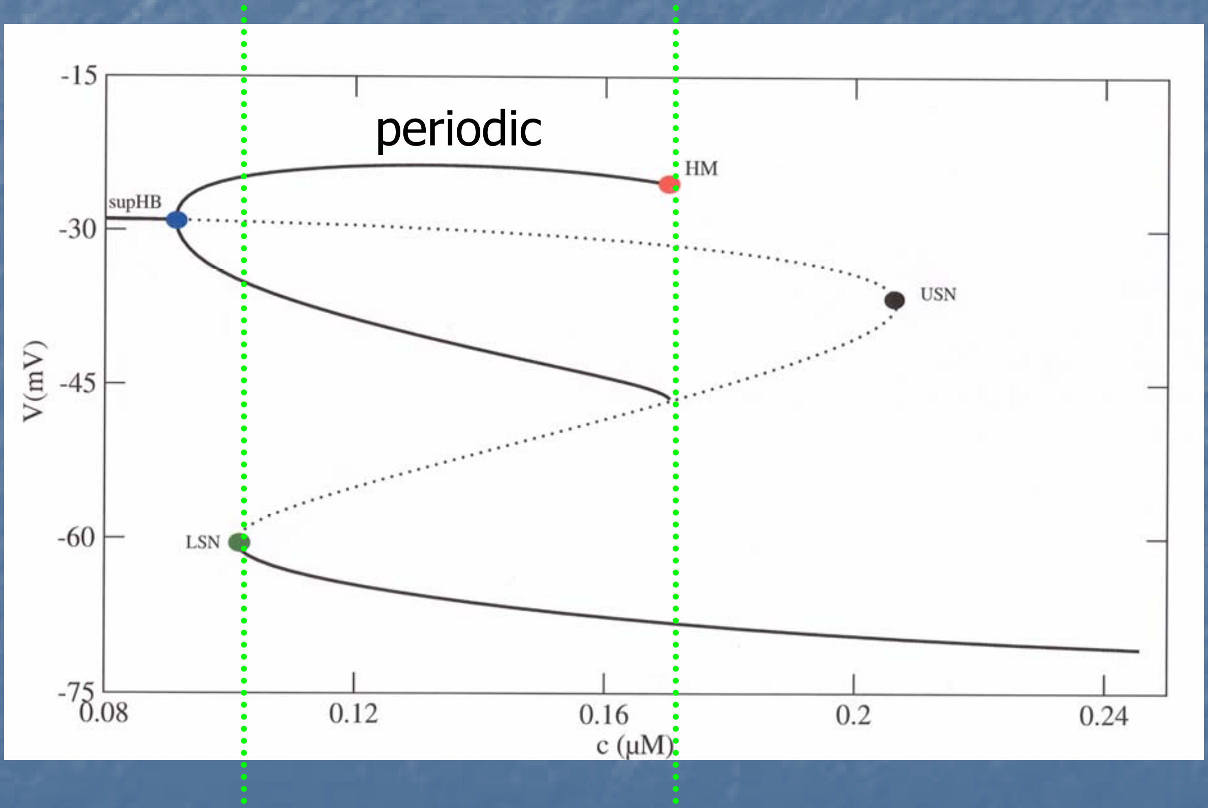
Variables can be separated into those that change rapidly and those that change slowly. In this case, there is only one slow variable (calcium, C). The slow variable is then treated as a bifurcation parameter for the fast subsystem (V and n).



Solid = stable SS
Dashed = unstable SS
HB = Hopf bifurcation
SN = saddle node bifurcation

Spiking Solutions

Next, the branch of periodic spiking solutions is added.



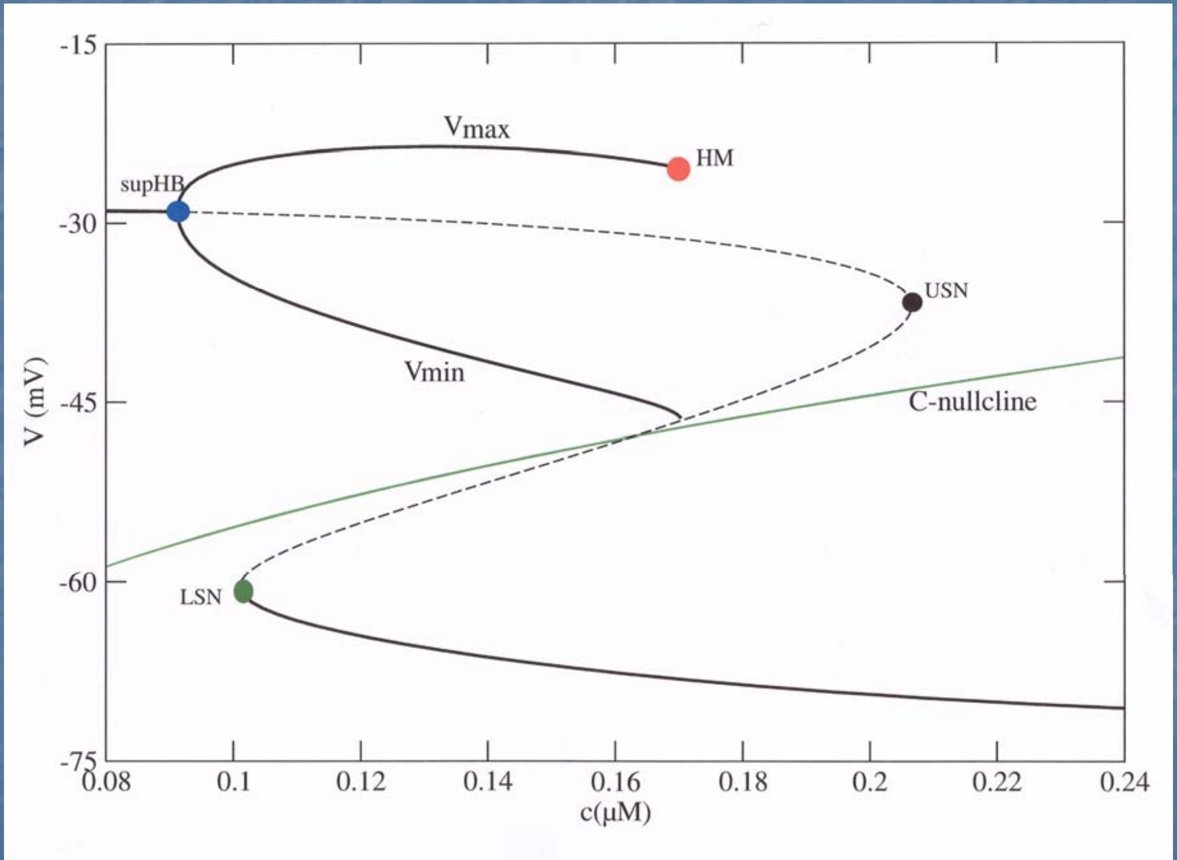
HM=homoclinic bifurcation

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

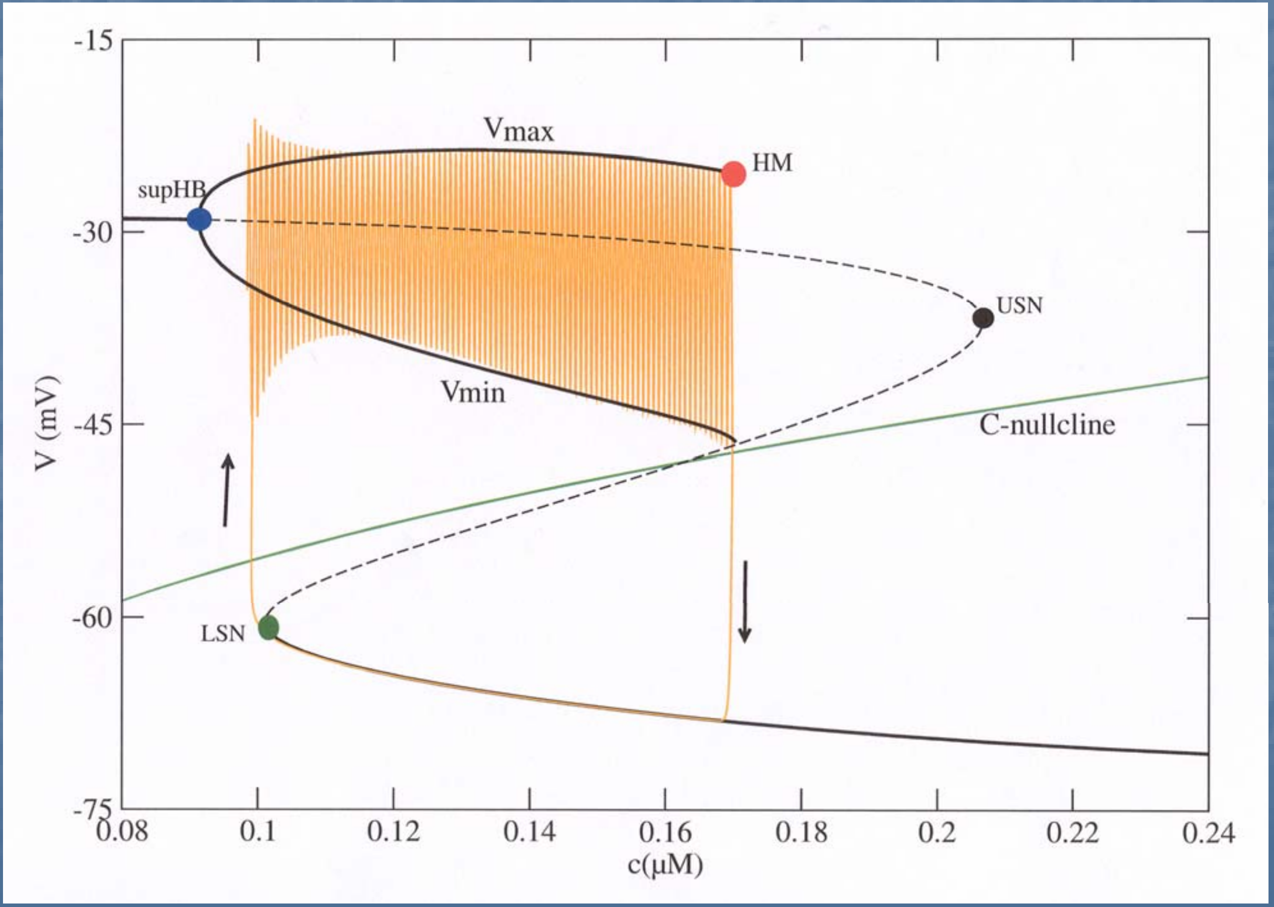
$$\frac{dC}{dt} = 0$$

Below the nullcline

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

Superimpose trajectory

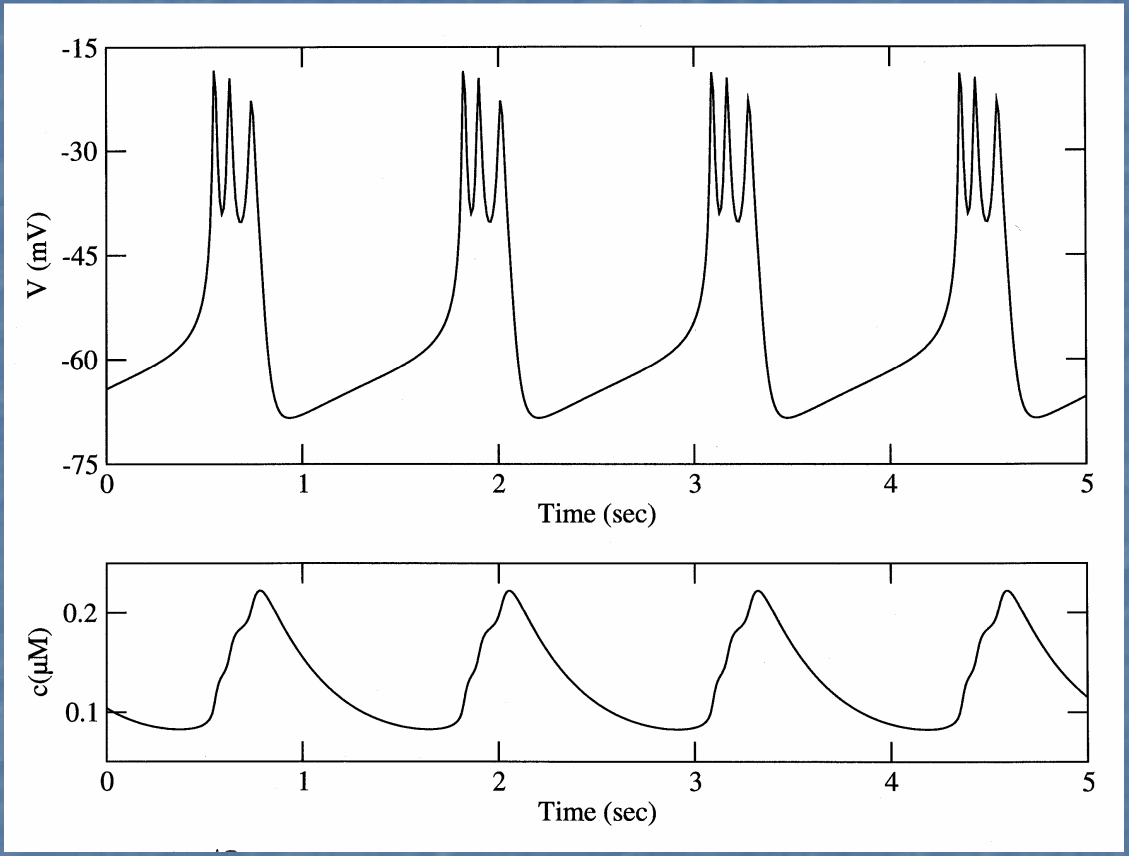
Finally, we superimpose the burst trajectory.



What this tells us

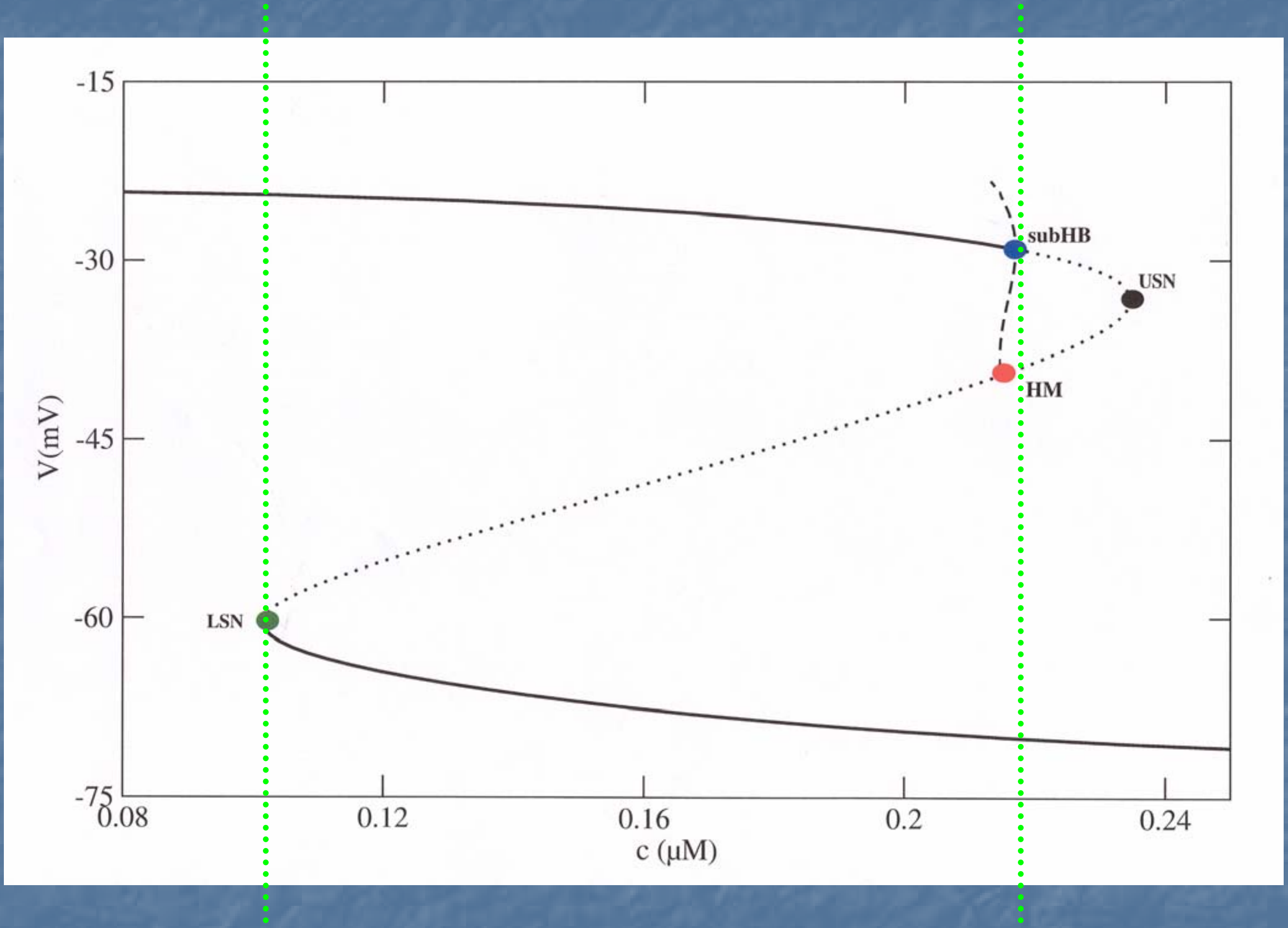
- The spiking should slow down near the end of a burst.
- A short current perturbation should be able to reset the system from silent to active phase (and vice versa).

Bursting with a pituitary model



Shorter duration -- Fewer spikes -- Small spikes

Fast subsystem bifurcation diagram

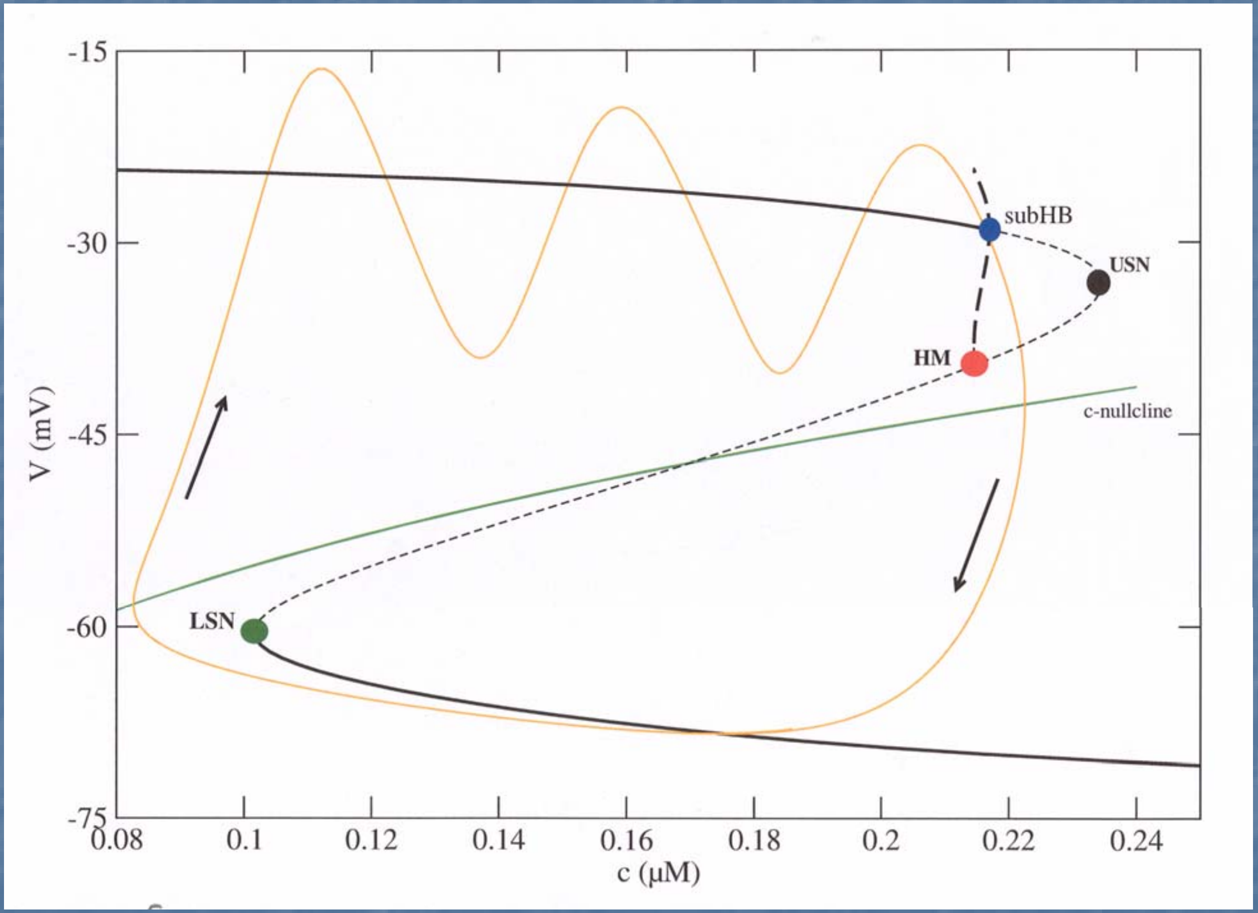


No stable periodic spiking branch!

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

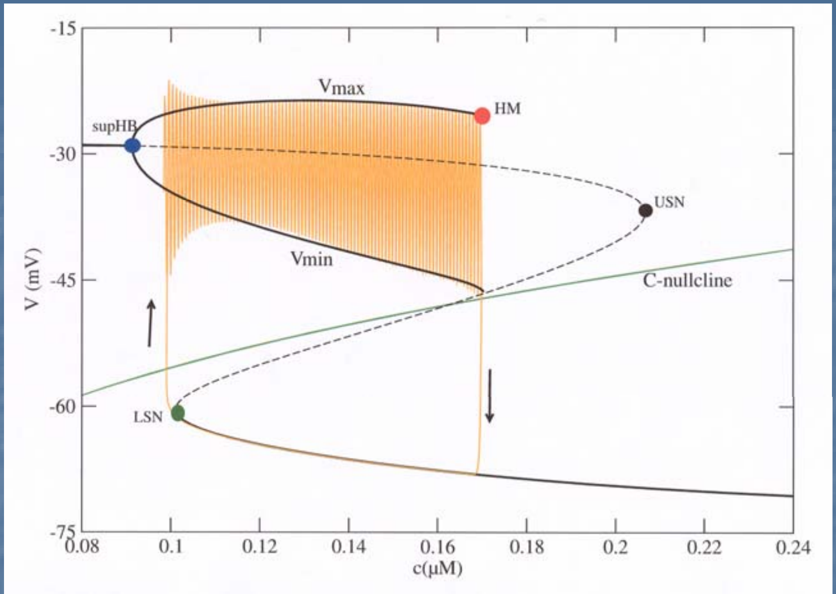
What does this tell us?

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

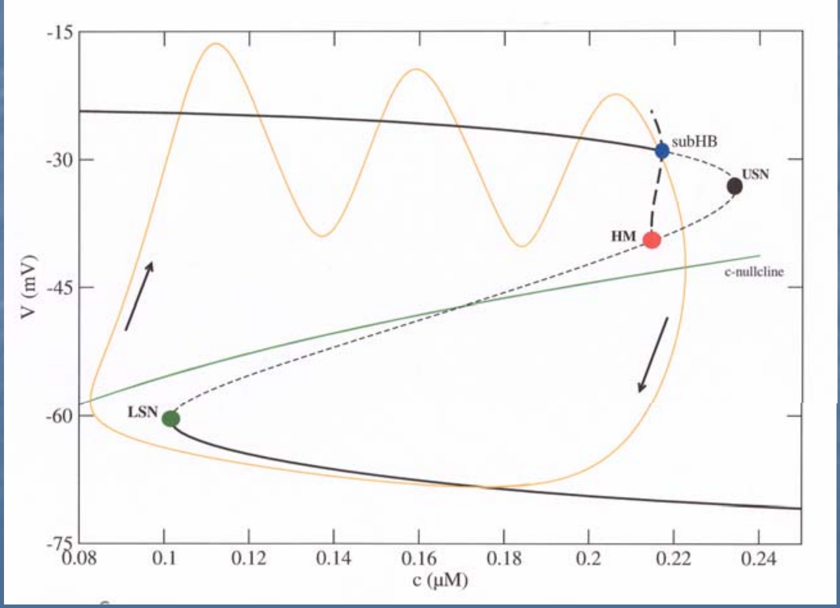
- Spikes will usually get smaller at later stages of the active phase.

- 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



???

Strategy

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.

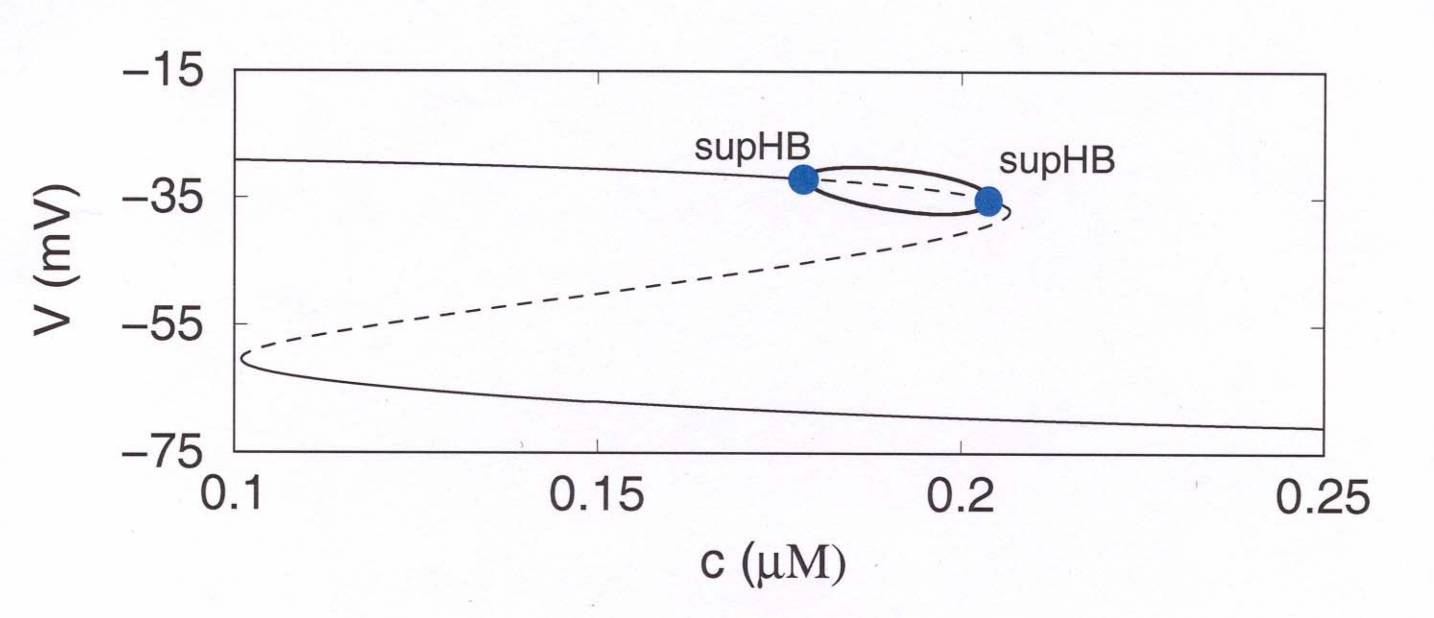
Idea: Speed up the delayed rectifier dynamics

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.

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

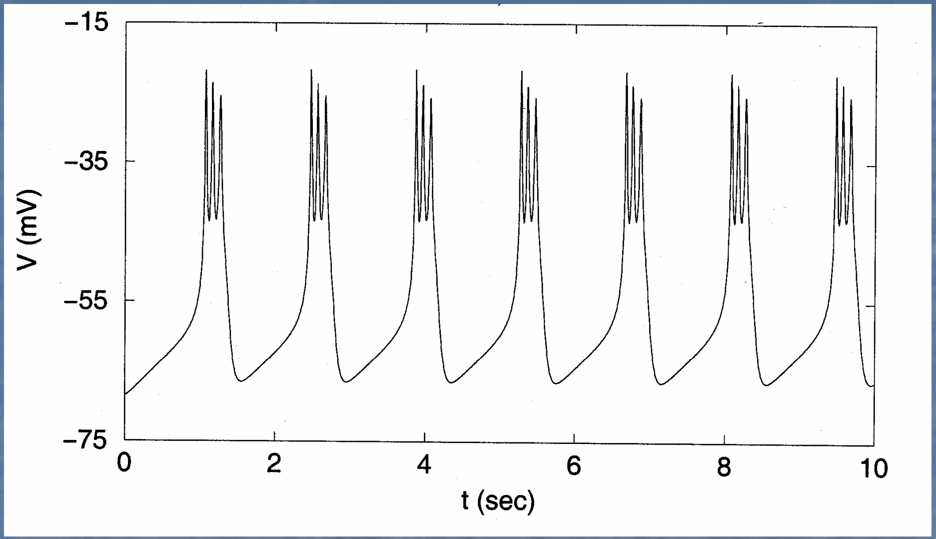
Decrease the time constant τ_n

Idea: Speed up the delayed rectifier dynamics



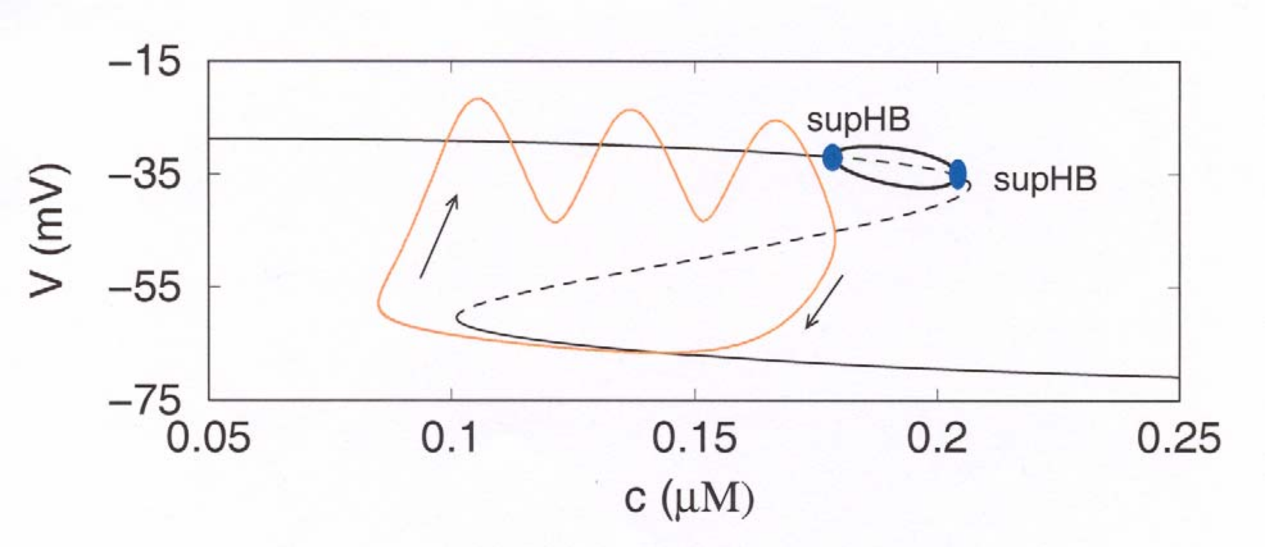
Most of the top branch has stabilized, but the Hopf bifurcations are supercritical, not subcritical as in the pituitary model.

Does this work?



Looks like pseudo-plateau bursting

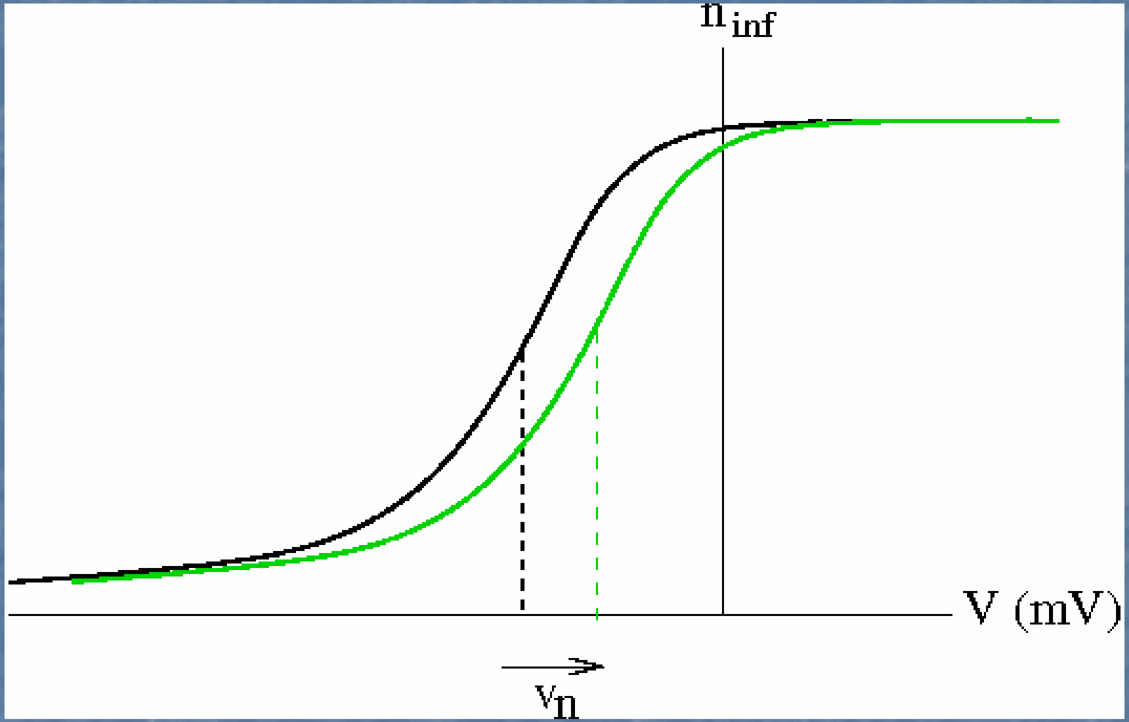
Motion along the z-curve is what we expect for PP bursting



How else can we do this?

Can we get the subcritical Hopf bifurcation as in the pituitary models?

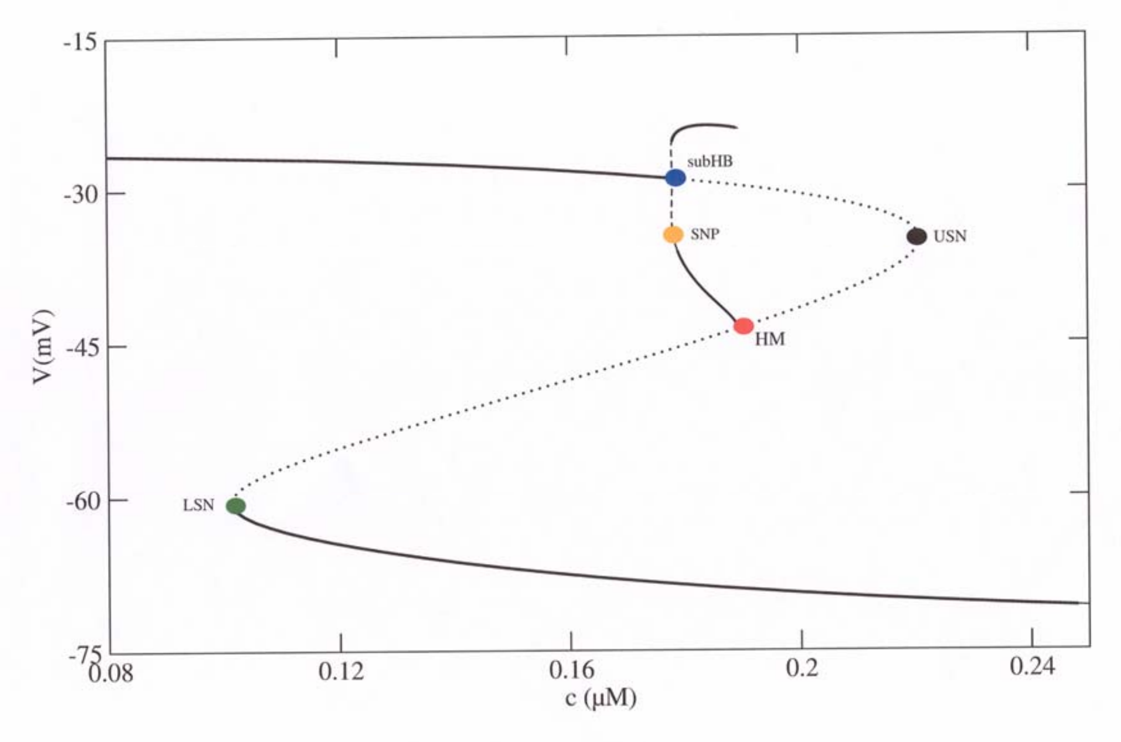
Idea: Make the delayed rectifier activate at a higher voltage



black = old
green = new

This will potentially result in depolarization block, a well-known phenomenon in which a spiking neuron hangs up in a depolarized state.

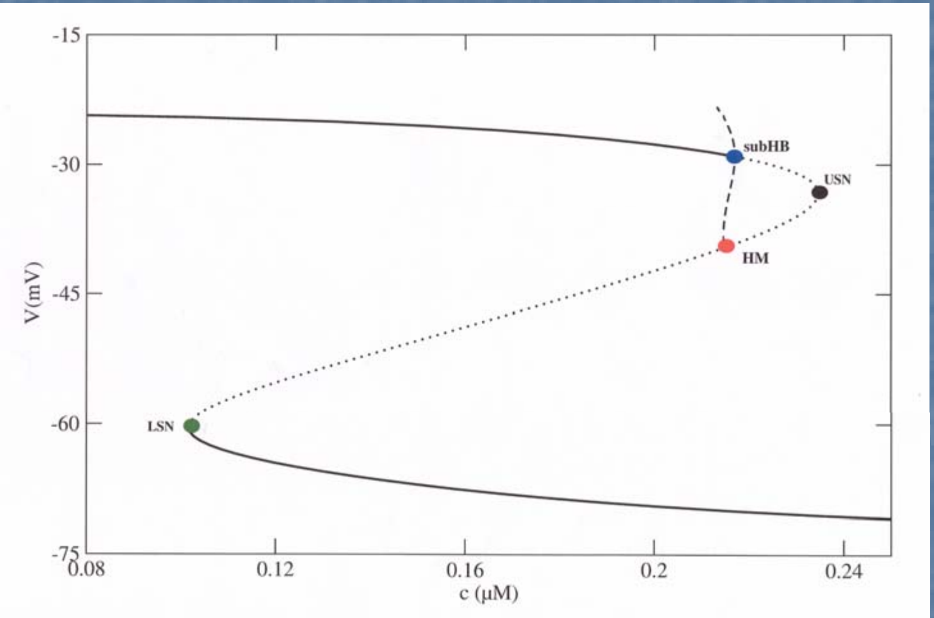
Idea: Make the delayed rectifier activate at a higher voltage



Shifting n_∞ by increasing v_n stabilizes the top branch, as hoped

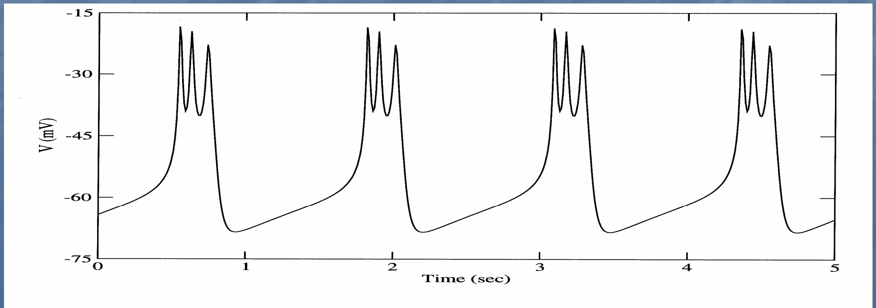
We call bursting with this bifurcation structure transition bursting

Idea: Make the delayed rectifier activate at a higher voltage



Shifting n_∞ even more gives the desired pituitary-like diagram

Pseudo-plateau bursting is produced



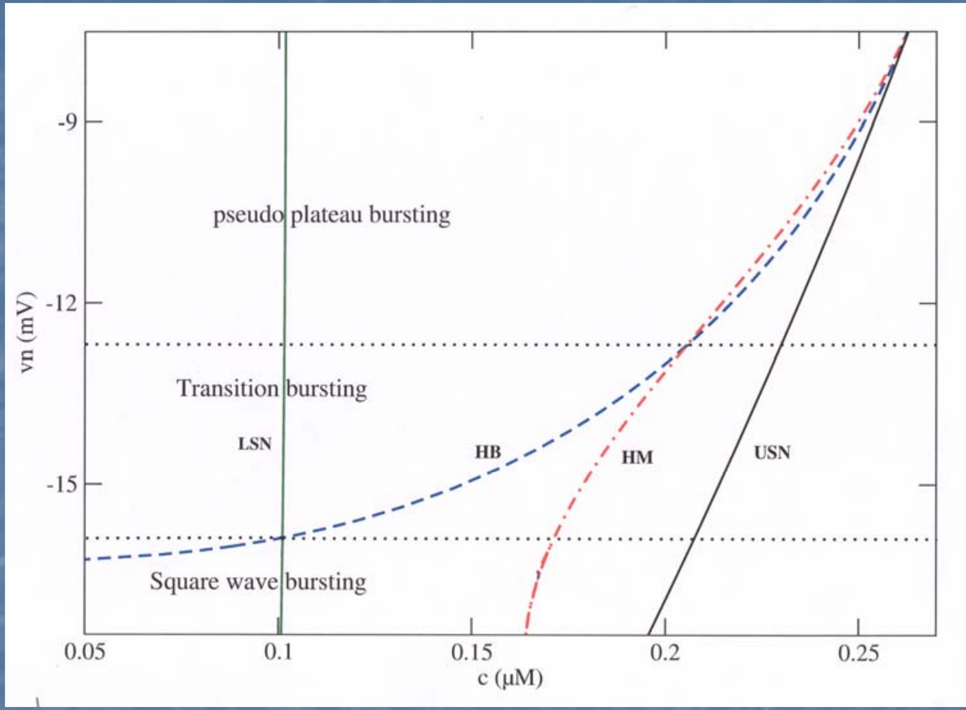
Two-dimensional bifurcation diagrams

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.

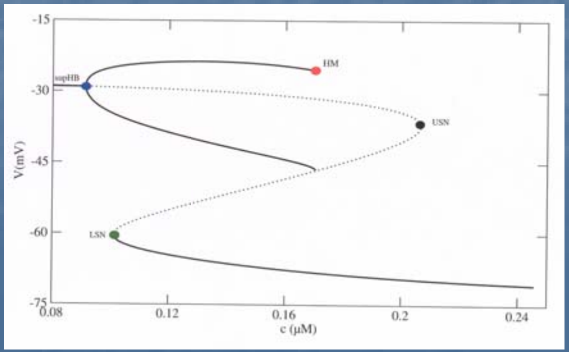
Pseudo-plateau bursting is produced when the Hopf bifurcation is subcritical, and is to the right of the LSN. In this case, LSN < HM < HB.

How these key bifurcation points change with changes in the v_n parameter is summarized in a 2-parameter bifurcation diagram.

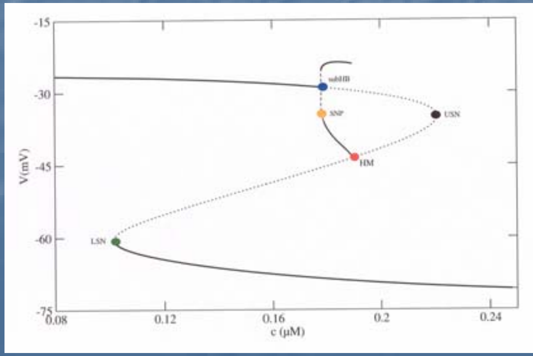
Two-parameter diagram: v_n vs. c



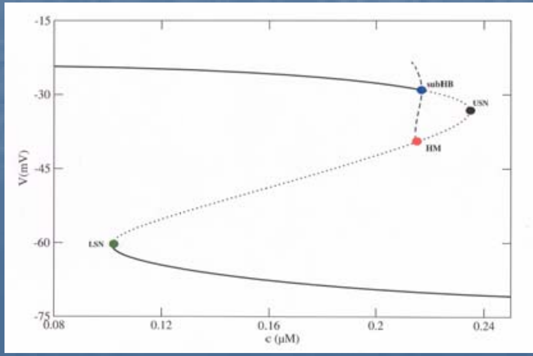
SW



Transition

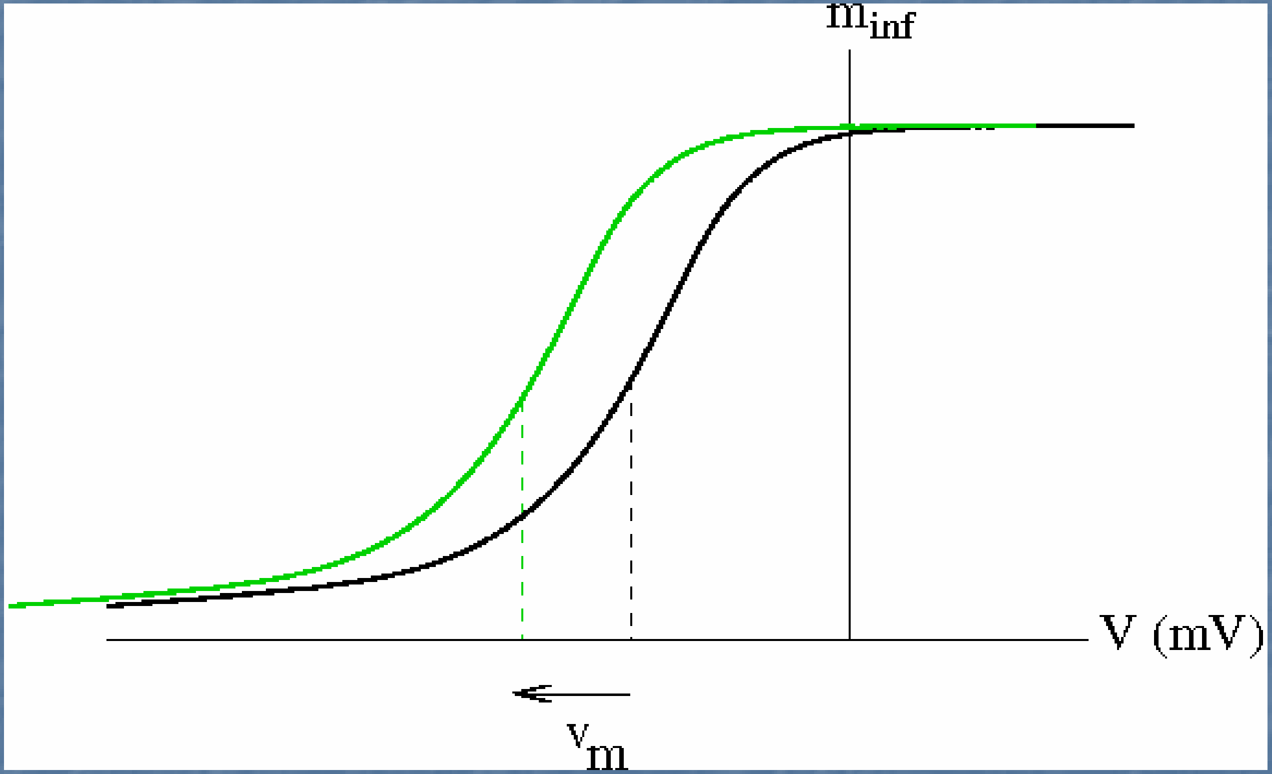


PP



Can we get transitions between SW and PP bursting by changing other parameters?

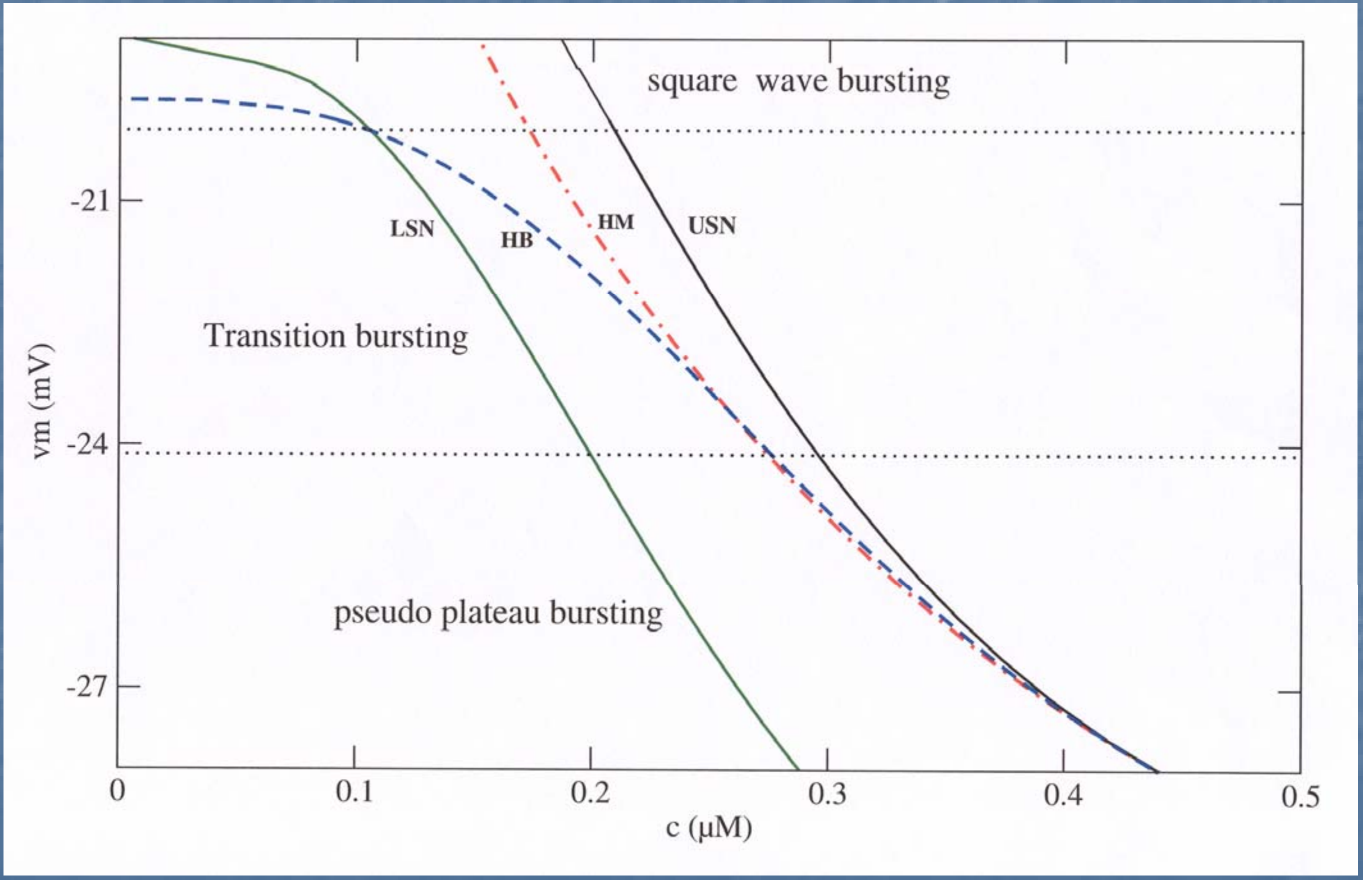
Idea: Make the Ca^{2+} channels activate at lower voltages



black = old
green = new

Reducing v_m translates the activation function leftward

Idea: Make the Ca^{2+} channels activate at lower voltages



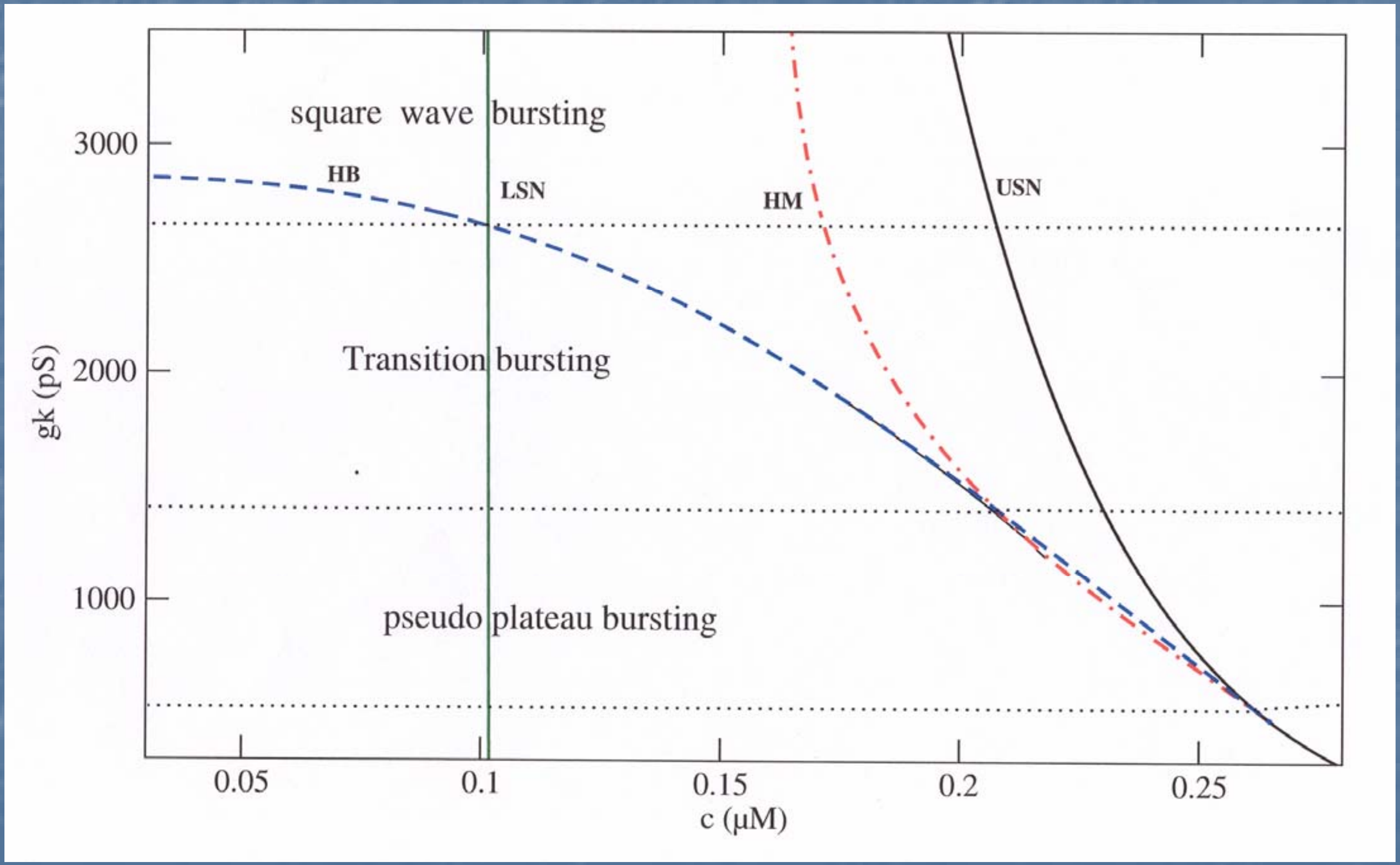
This works

Can a transition be made by changing a channel conductance?

Idea: Decrease the delayed rectifier conductance

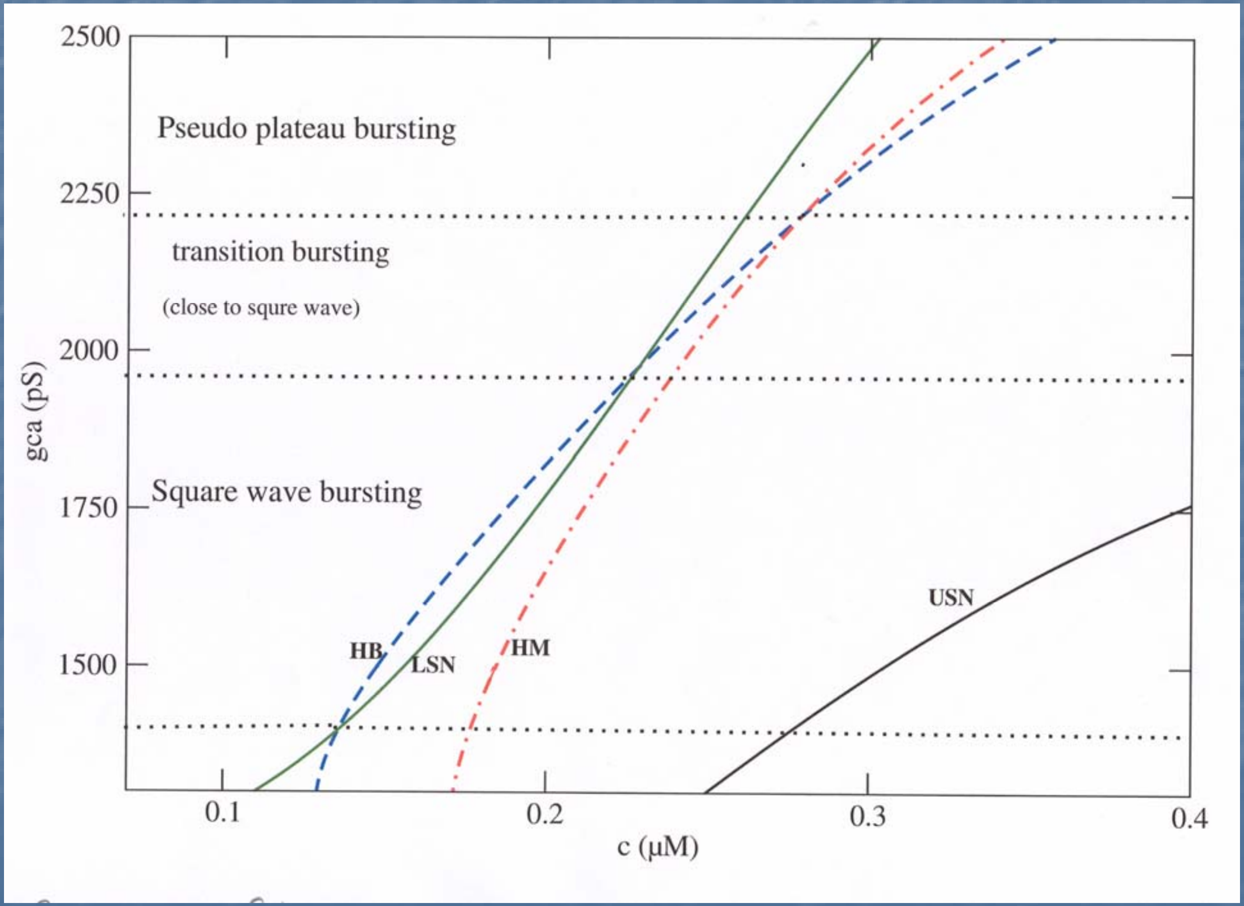
This would have a depolarizing effect on the cell, and could stabilize the top branch of stationary solutions in the z-curve.

Idea: Decrease the Delayed Rectifier conductance



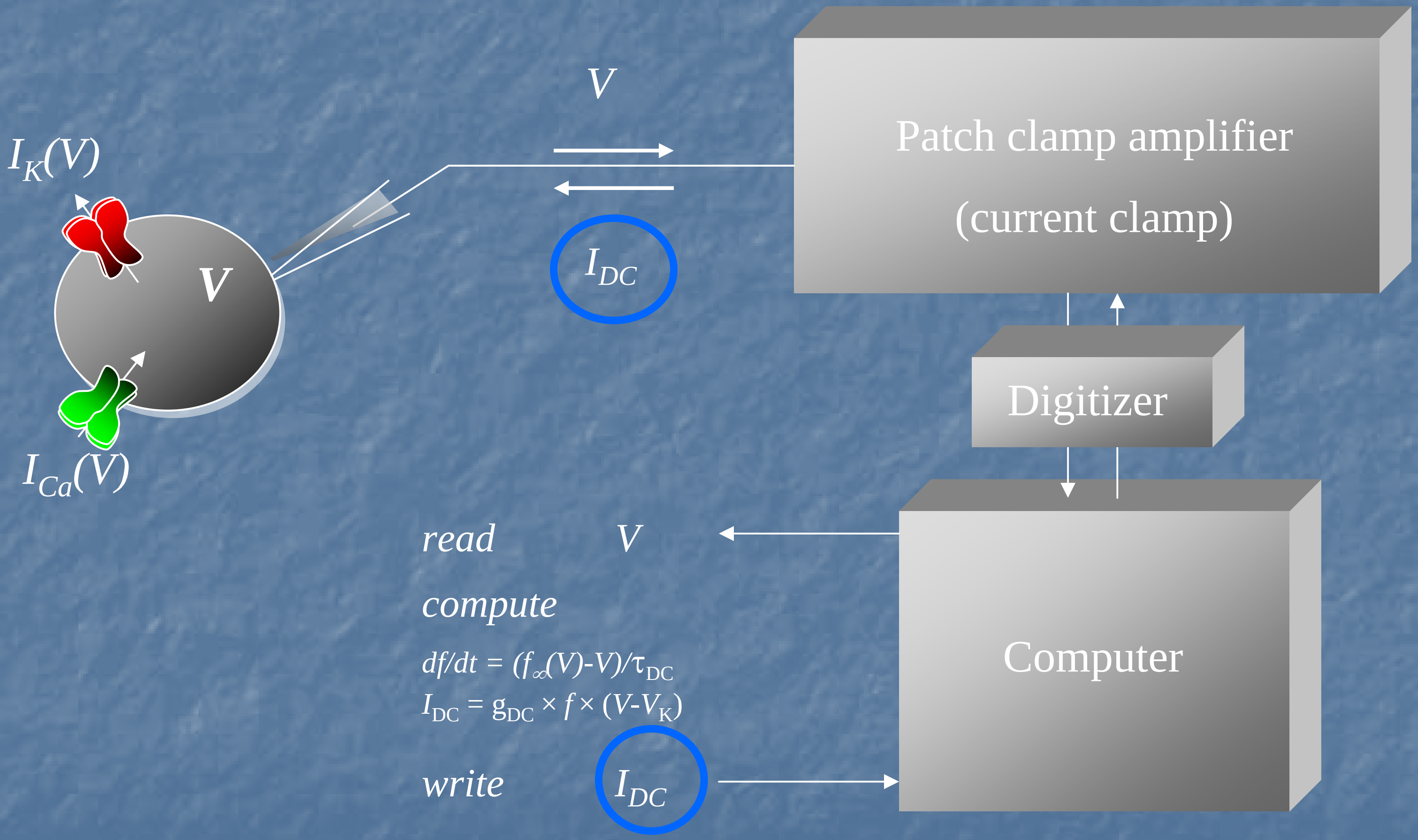
This also works

Idea: Increase the depolarizing Ca^{2+} channel conductance

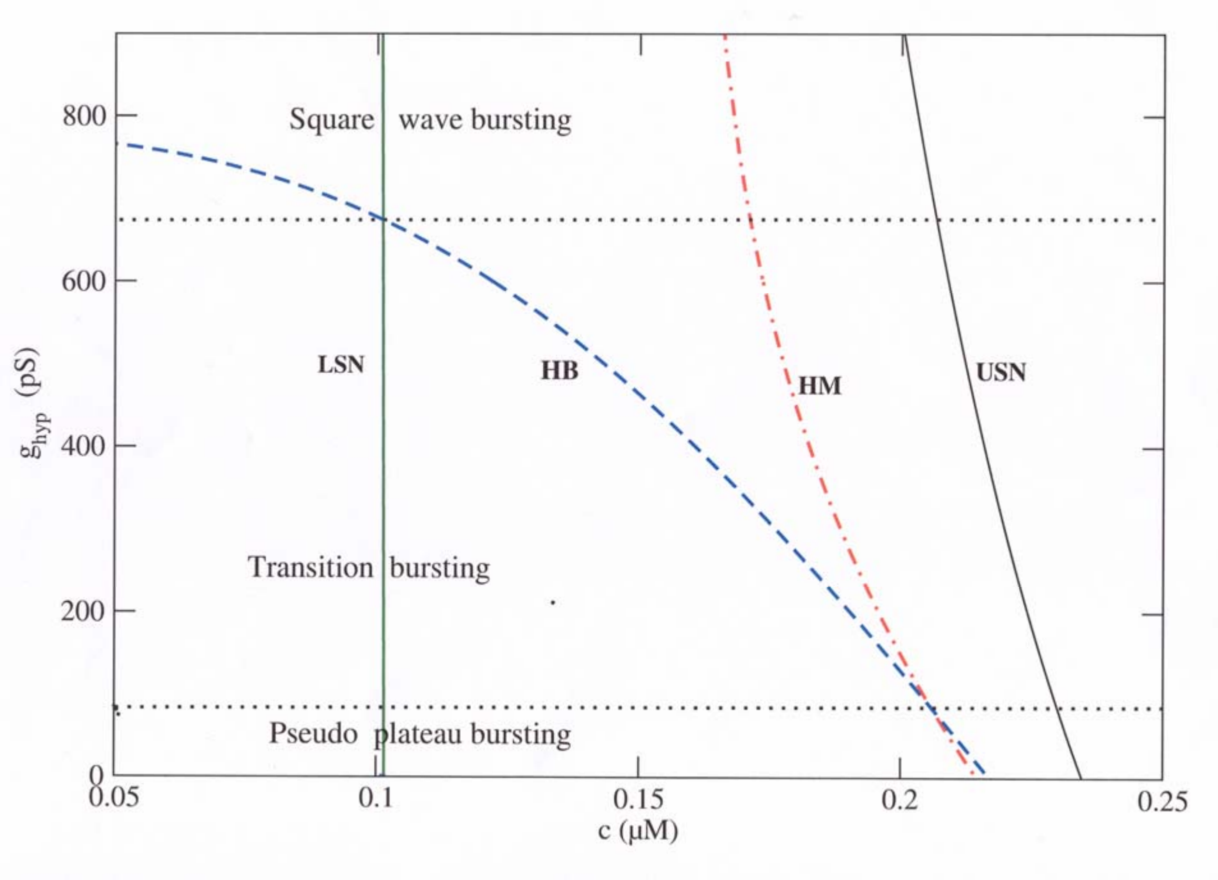


This also works

We can test this in the lab with the Dynamic Clamp



Prediction: Adding a delayed rectifier-like current should convert a pituitary burster to a square wave burster



Does this work?

Stay Tuned…

The End