Mathematical Aspects of Bursting Oscillations in Nerve and Endocrine Cells

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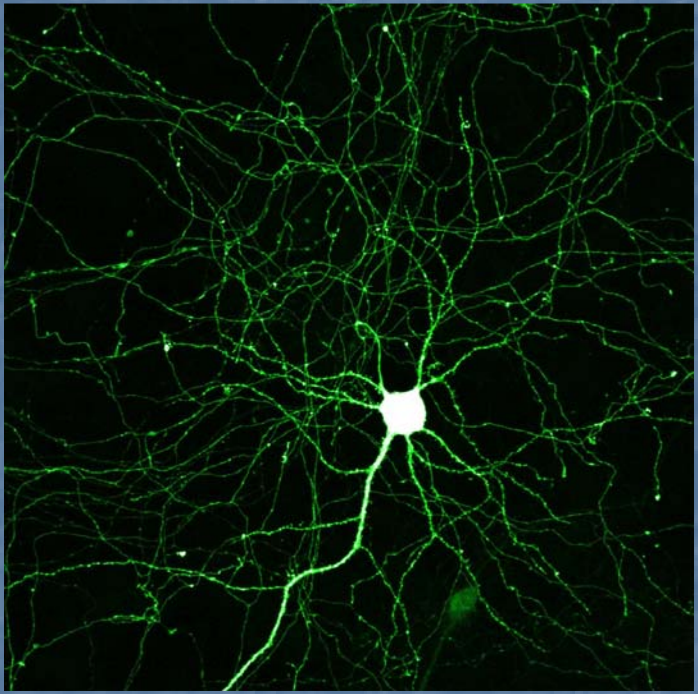
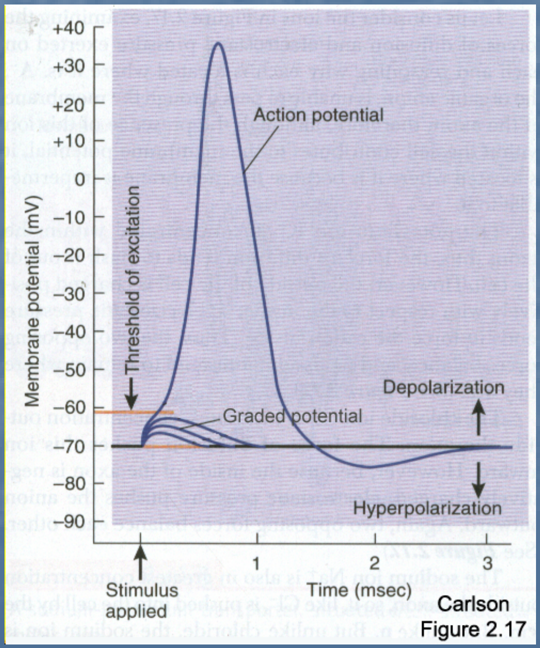
Electrical Impulse is the Basic Unit of Information in Neurons

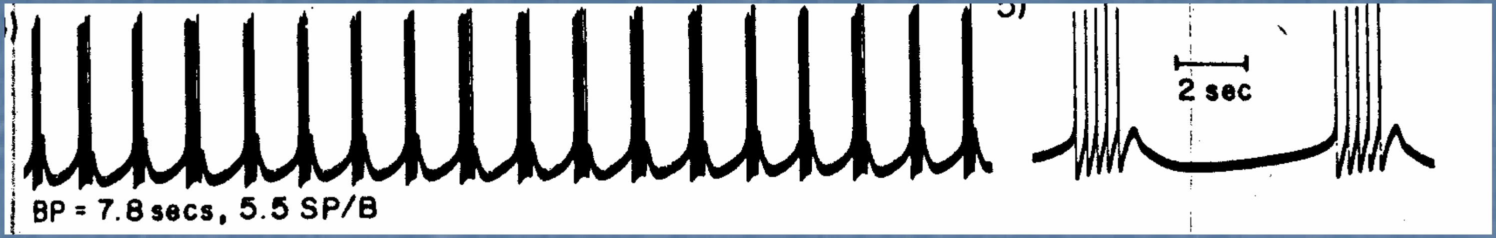


Stained neuron

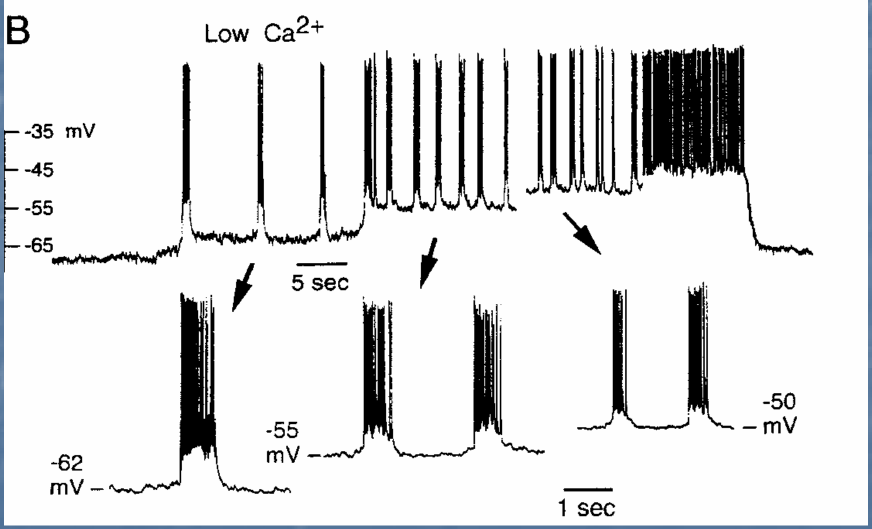


Electrical impulse or action potential

Bursting is Ubiquitous in Nerve Cells



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



Neuron from the pre-Botzinger complex (Butera et al, J. Neurophysiol, 81:382, 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.

Chapter 1: Relaxation Oscillations

The Morris-Lecar Model

Published in 1981 in Biophysical Journal. A simple model for electrical impulses.

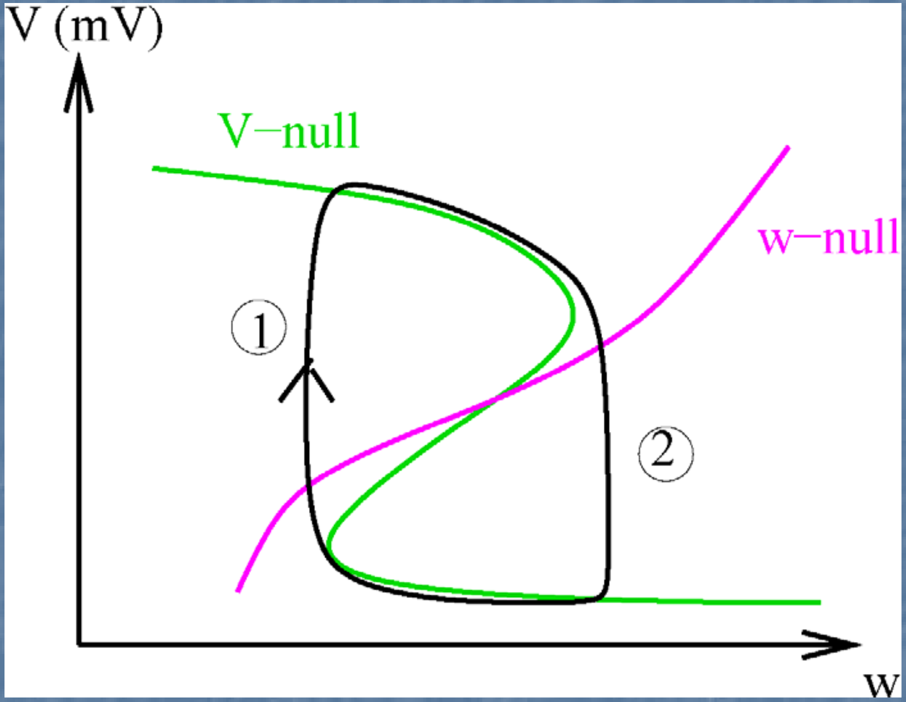
$$\frac{dV}{dt} = -\left[I_{Ca} + I_K(w)\right]/C$$

I_{Ca} provides the impulse upstroke, I_K provides the downstroke.

$$\frac{dw}{dt} = \lambda\left[w_\infty(V) - w\right]/\tau_w$$

w is a recovery variable, whose rate of change is modulated by the parameter λ.

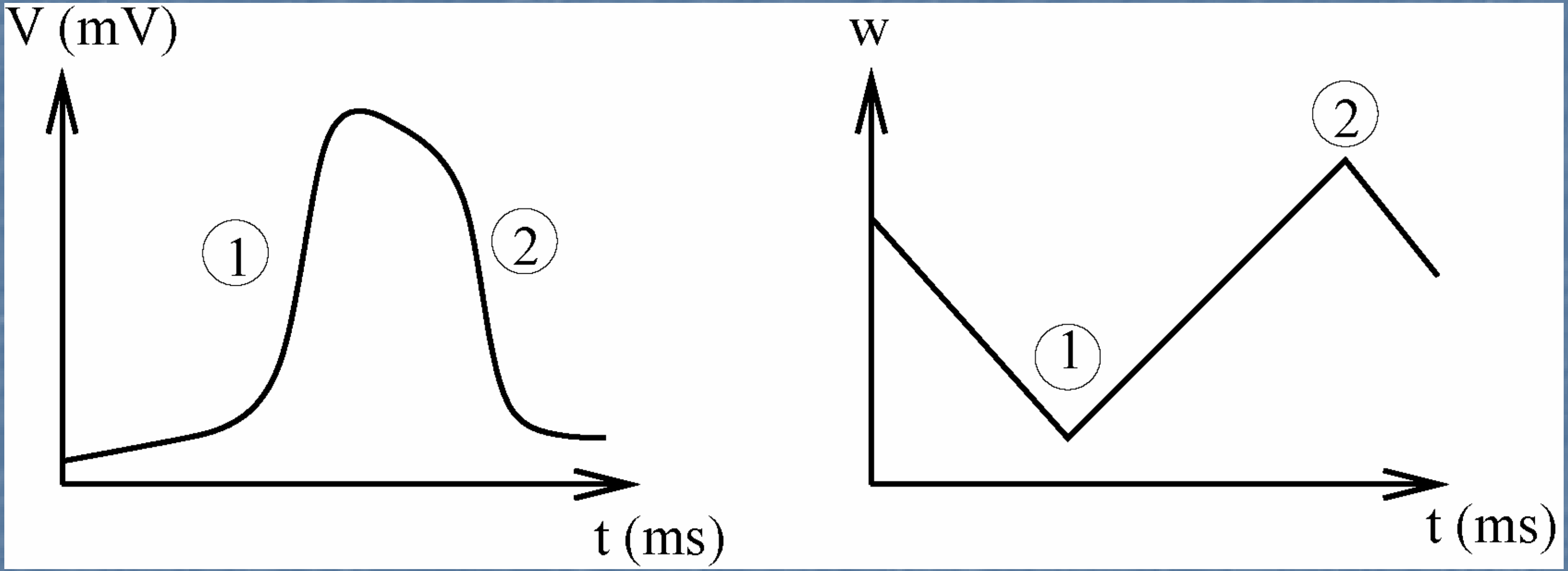
Relaxation Oscillations with λ Small



Nullclines: Set derivatives to 0
Black curve: System trajectory

Relaxation Oscillations with λ Small

$$\lambda = 0.01$$

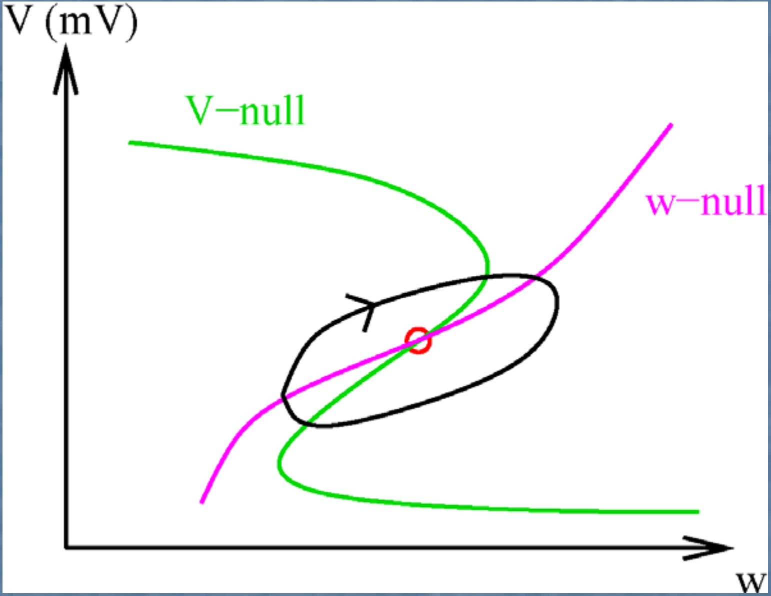


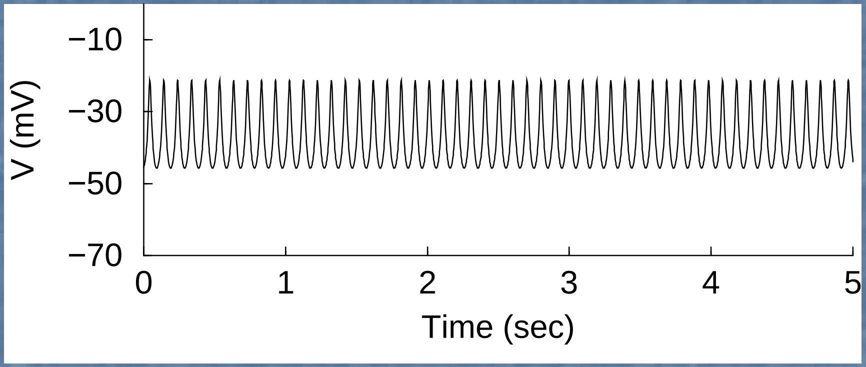
V exhibits plateau behavior

w exhibits sawtooth behavior

Impulse-Like Oscillations when λ Near 1

$$\lambda = 1$$





continuous train of impulses

Chapter 2: Bursting

The Chay-Keizer Model

This was published in 1983 in Biophysical Journal as a description of bursting in pancreatic islets. Here, we use a hybrid of the Morris-Lecar model and the Chay-Keizer model.

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

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

$$\frac{dw}{dt} = \lambda\left[w_\infty(V) - w\right]/\tau_w$$

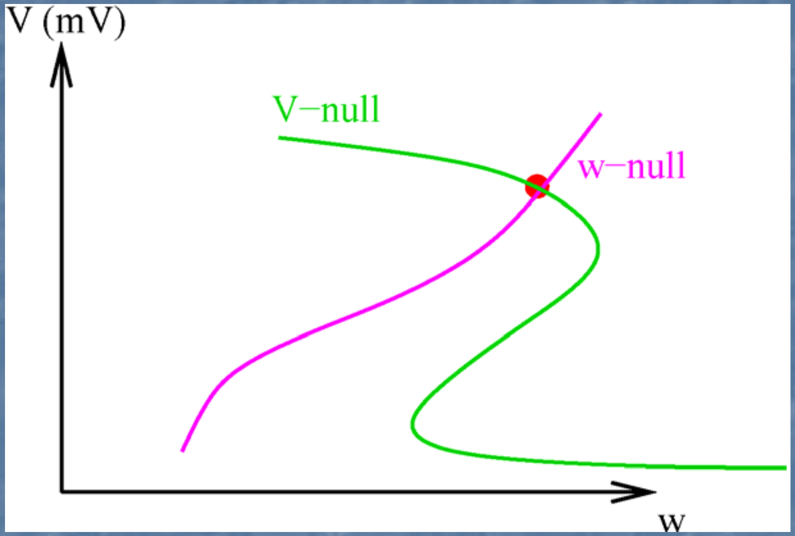
The new current builds up slowly during spiking and acts to inhibit the cell. The accumulation variable is s.

$$\frac{ds}{dt} = \left[s_\infty(V) - s\right]/\tau_s$$

$$\tau_s >> \tau_w / \lambda$$

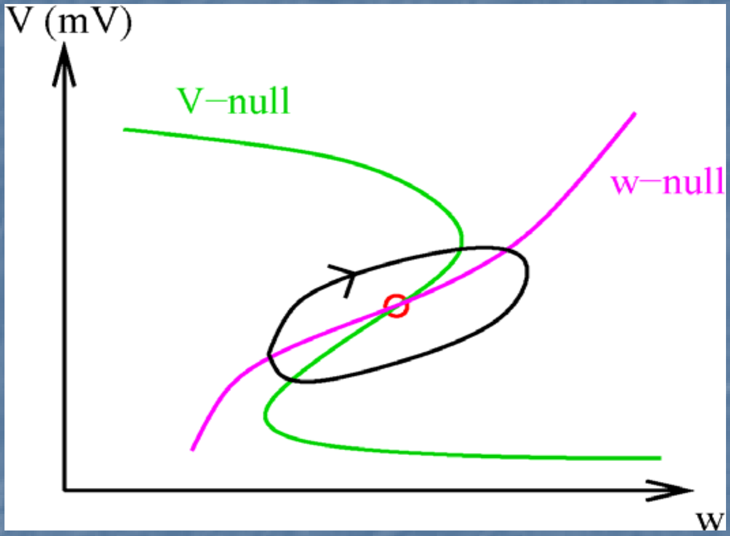
Fast/Slow Analysis

Since s changes much more slowly than V or w, treat it as a parameter of the fast subsystem (V and w variables). This s changes the V-nullcline.



$s = s_1$

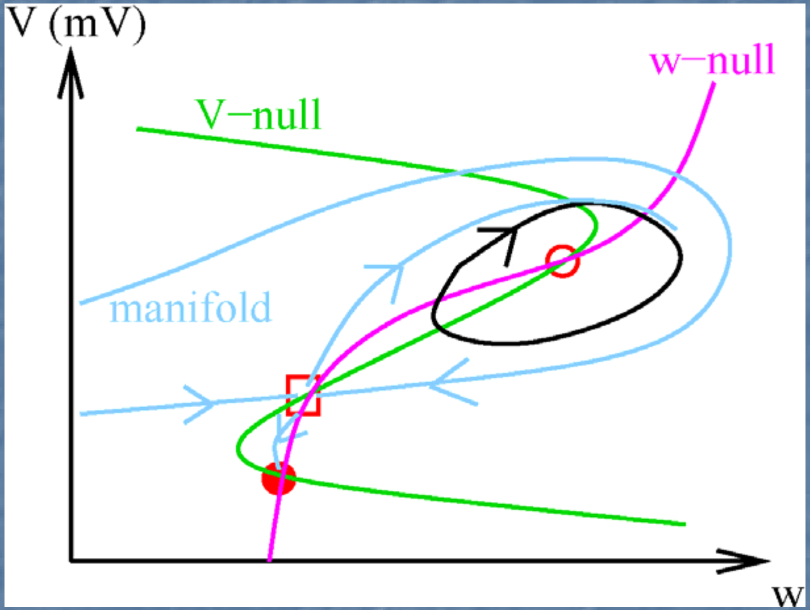
high-voltage steady state



$s = s_2 > s_1$

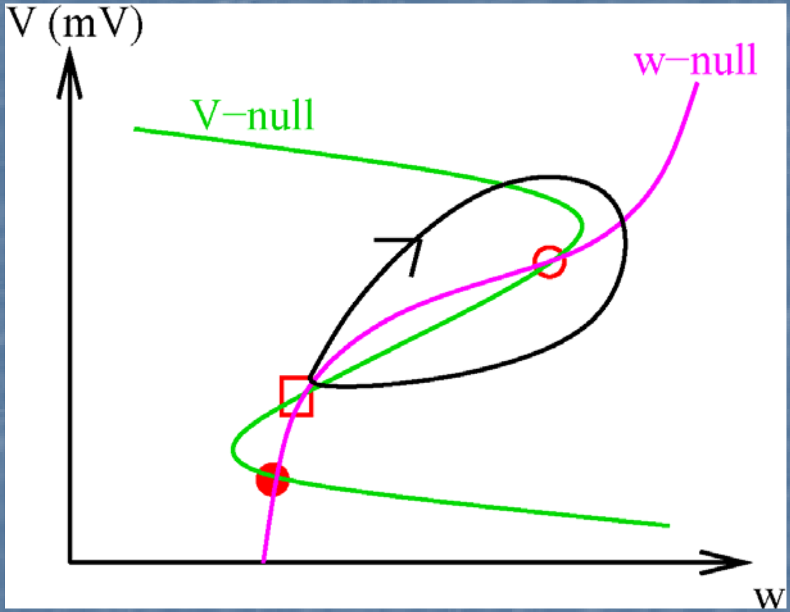
stable limit cycle

Fast/Slow Analysis



$$s = s_3 > s_4$$

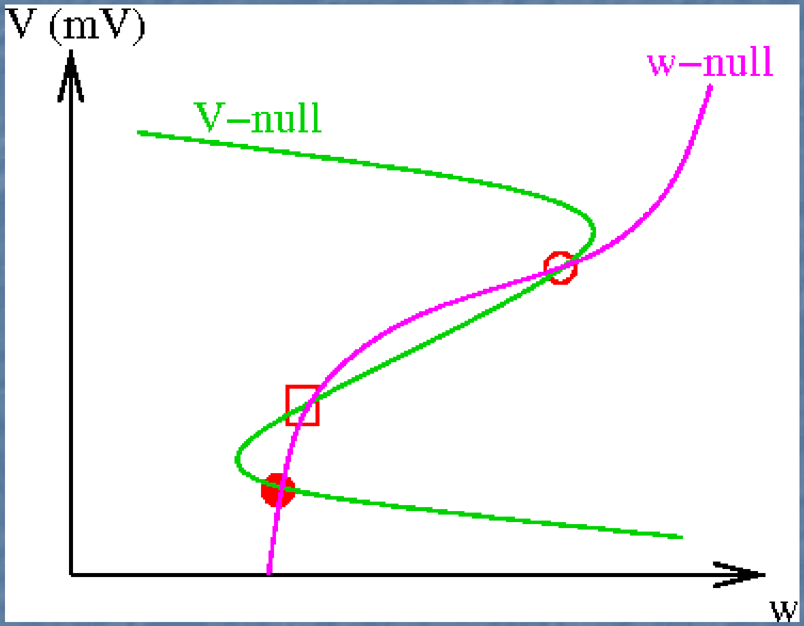
bistable between limit cycle and steady state

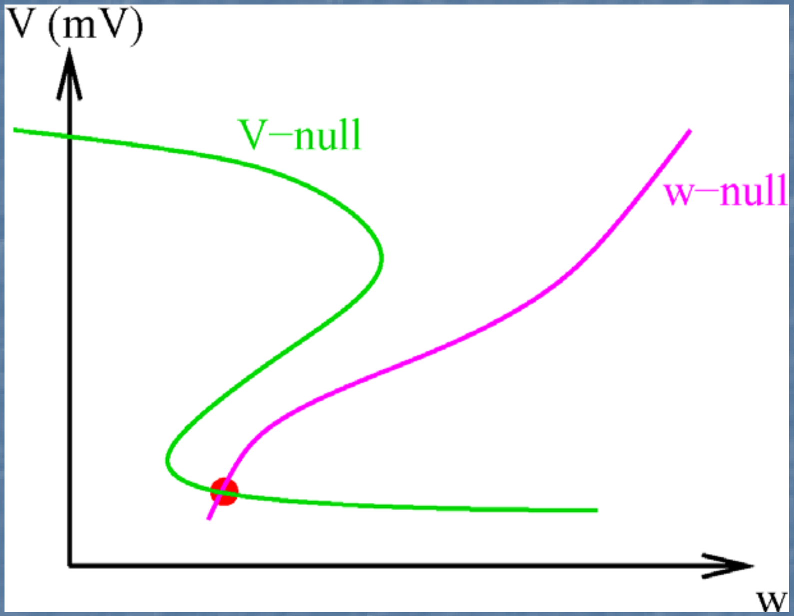


$$s = s_4 > s_5$$

infinite-period homoclinic orbit and stable steady state

Fast/Slow Analysis





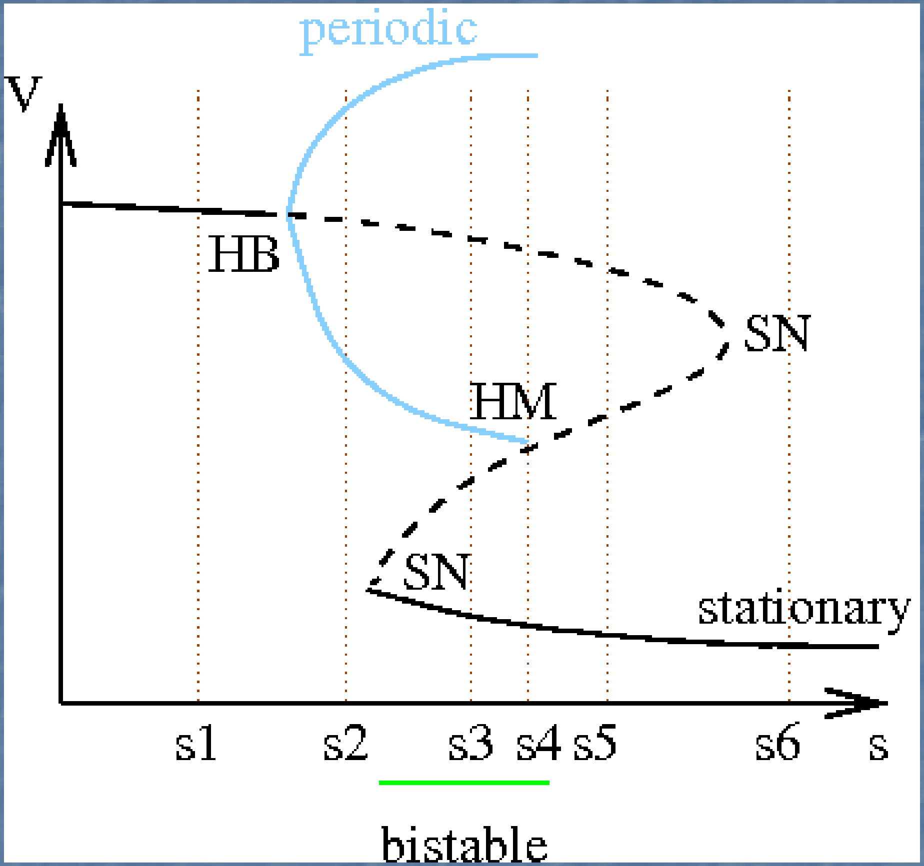
$$s = s_5 > s_4$$

$$s = s_6 > s_5$$

three steady states, one stable

low-voltage stable steady state

Dynamic Behavior Summarized

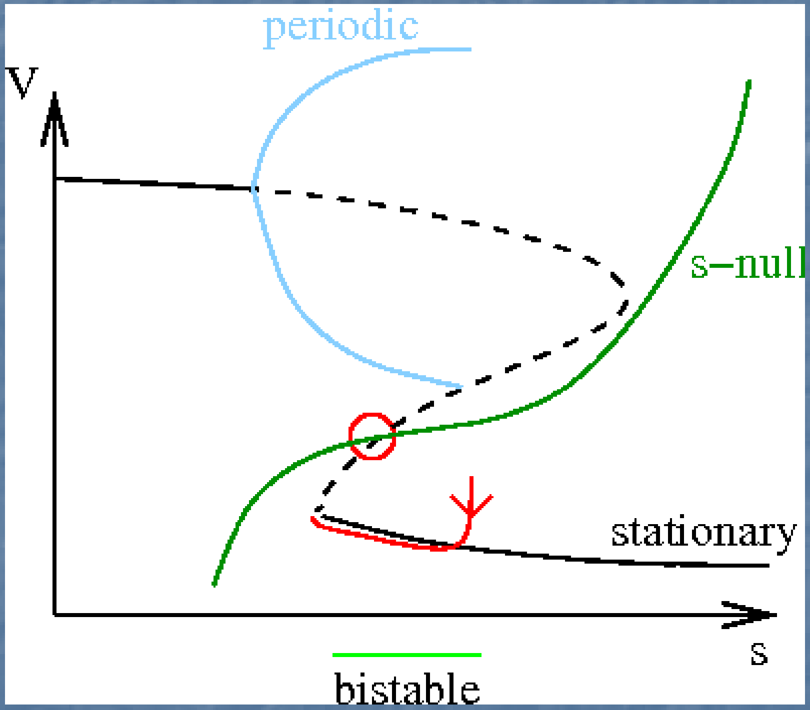


HB=Hopf bifurcation
HM=Homoclinic bifurcation

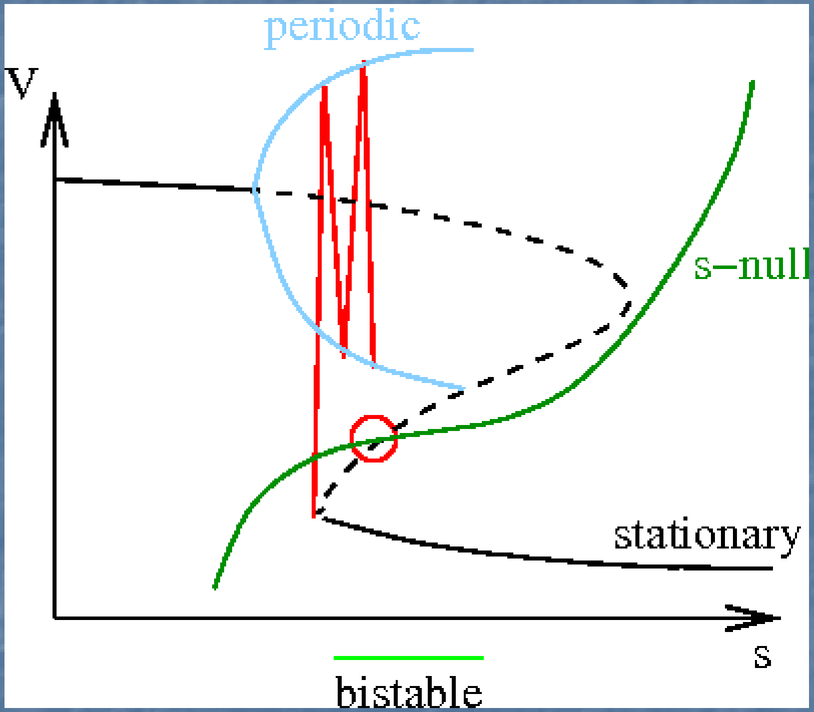
SN=Saddle-Node bifurcation

Dynamics of the Full 3-D System

Silent phase

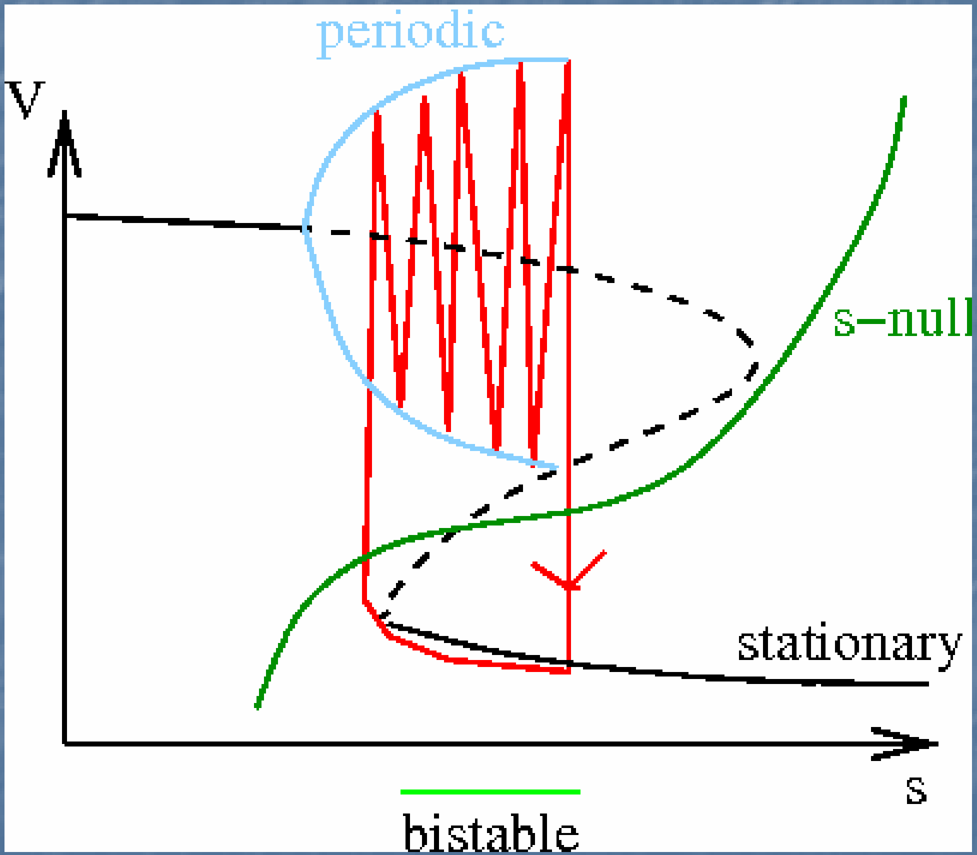


Active phase



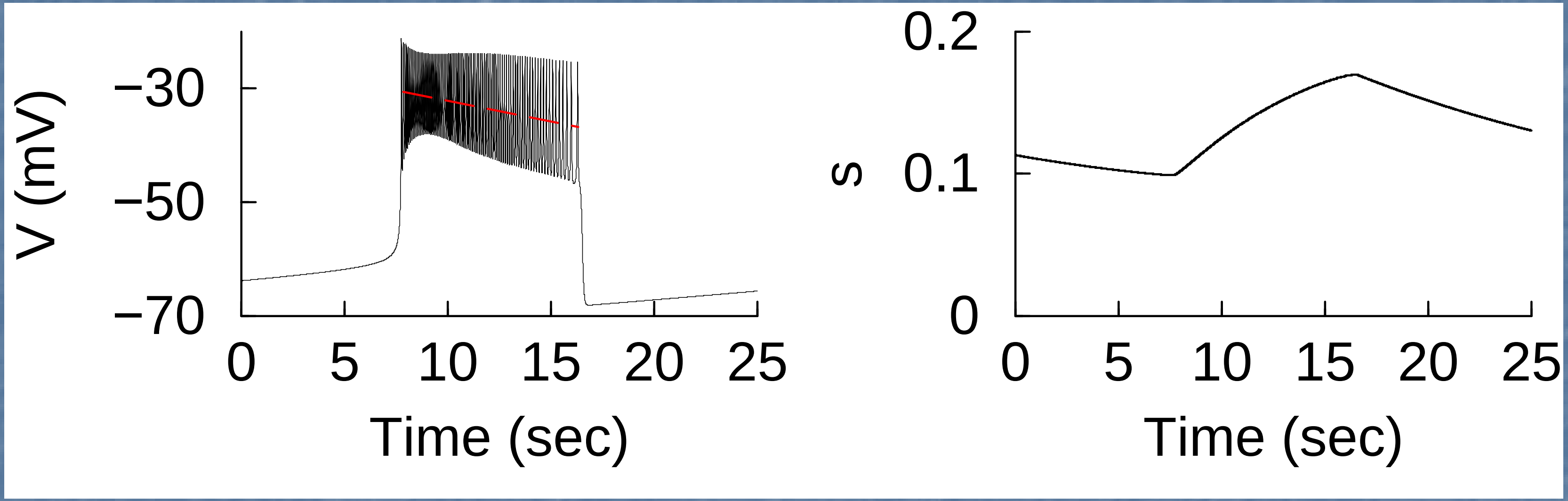
Red circle=unstable steady state of full system

Dynamics of the Full 3-D System



Red=bursting trajectory

Bursting: A Generalized Relaxation Oscillation



Red dashed = average voltage

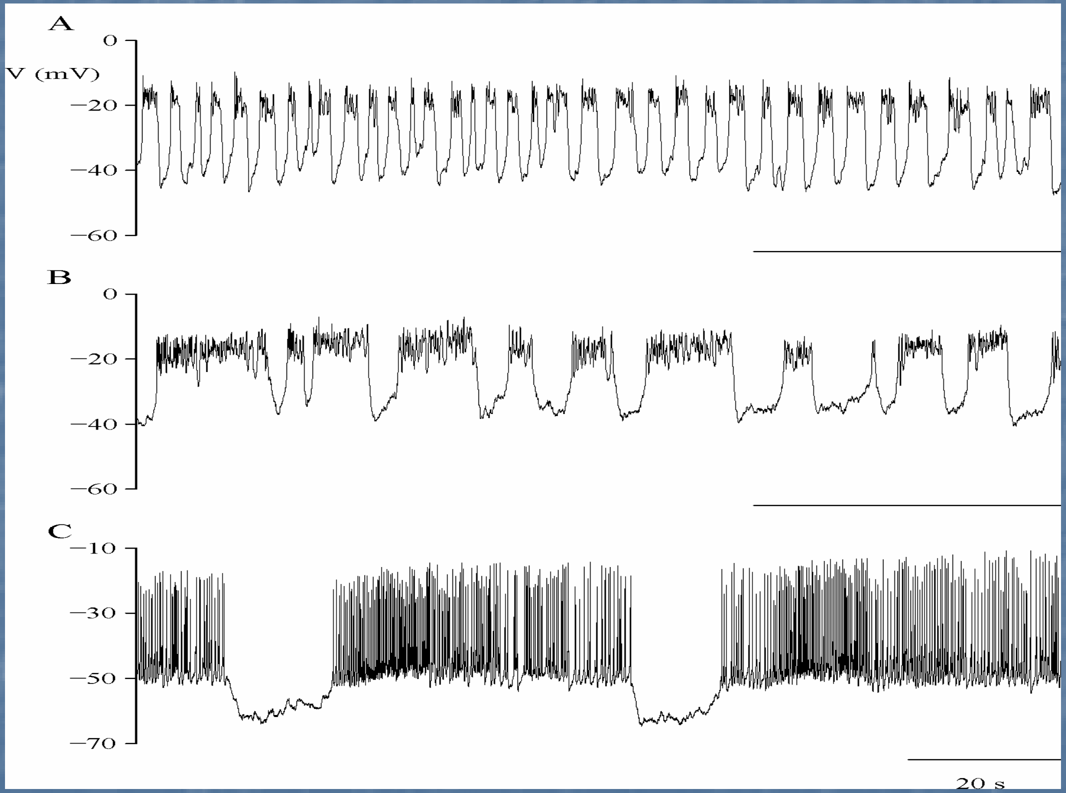
Chapter 3: Phantom Bursting

How Can We Explain the Wide Range of Islet Bursting Periods?

Period~2 sec

Period~5 sec

Period~60 sec



Electrical recordings from single β-cells (A,B) and a β-cell cluster (C).
Thanks to Les Satin and Min Zhang.

Introduce a Second Slow Variable

Replace the slow variable s with s_1, then add a second slow variable s_2.

$$\frac{ds_1}{dt} = \left[s_{1\infty}(V) - s_1\right] / \tau_{s1}$$

$$I_{K1} = g_{K1} s_1 (V - V_K)$$

$$\frac{ds_2}{dt} = \left[s_{2\infty}(V) - s_2\right] / \tau_{s2}$$

$$I_{K2} = g_{K2} s_2 (V - V_K)$$

The second slow variable is much slower than the first.

$$\tau_{s1} = 1\sec$$

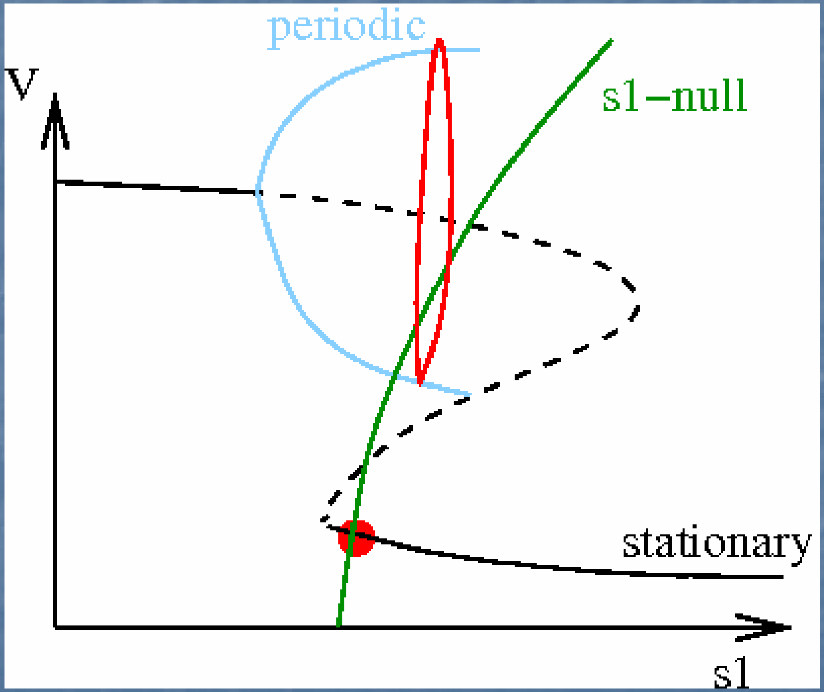
Could be cytosolic Ca^{2+}

$$\tau_{s2} = 2\min$$

Could be ER Ca^{2+}

The Death of Bursting

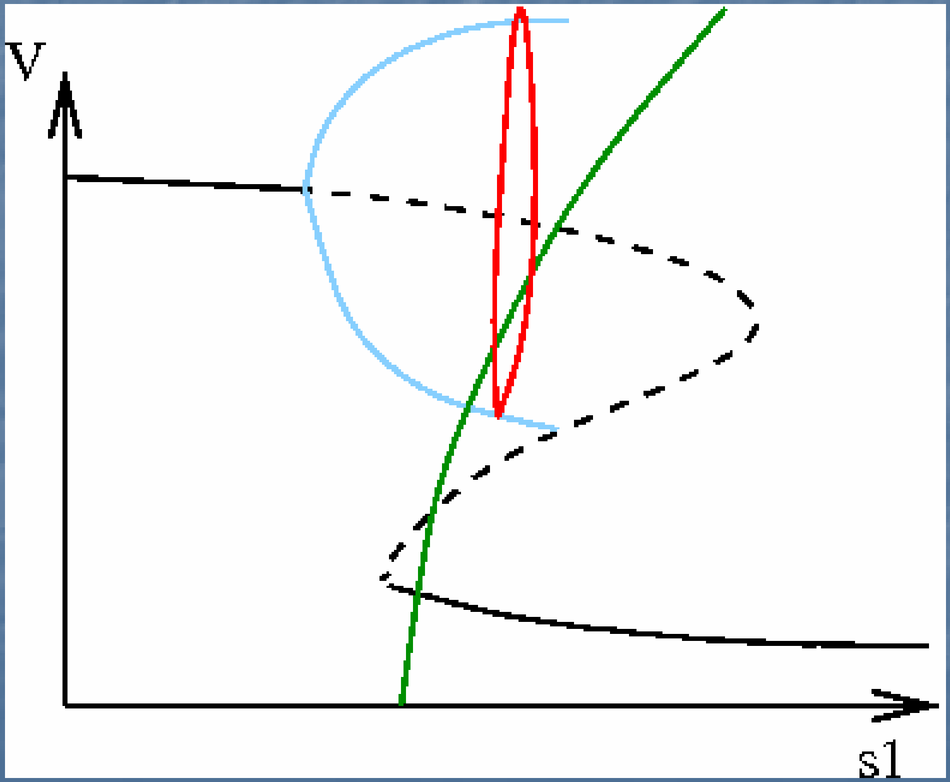
With the right choice of the g_{s1} and g_{s2} parameters the z-curve and the s_1 nullcline intersect in such a way that bursting does not occur when the s_2 variable is clamped.



System is bistable between continuous spiking or rest.

Enter the Phantom

Suppose the system starts out spiking. Unclamp s_s and let it evolve according to its differential equation.

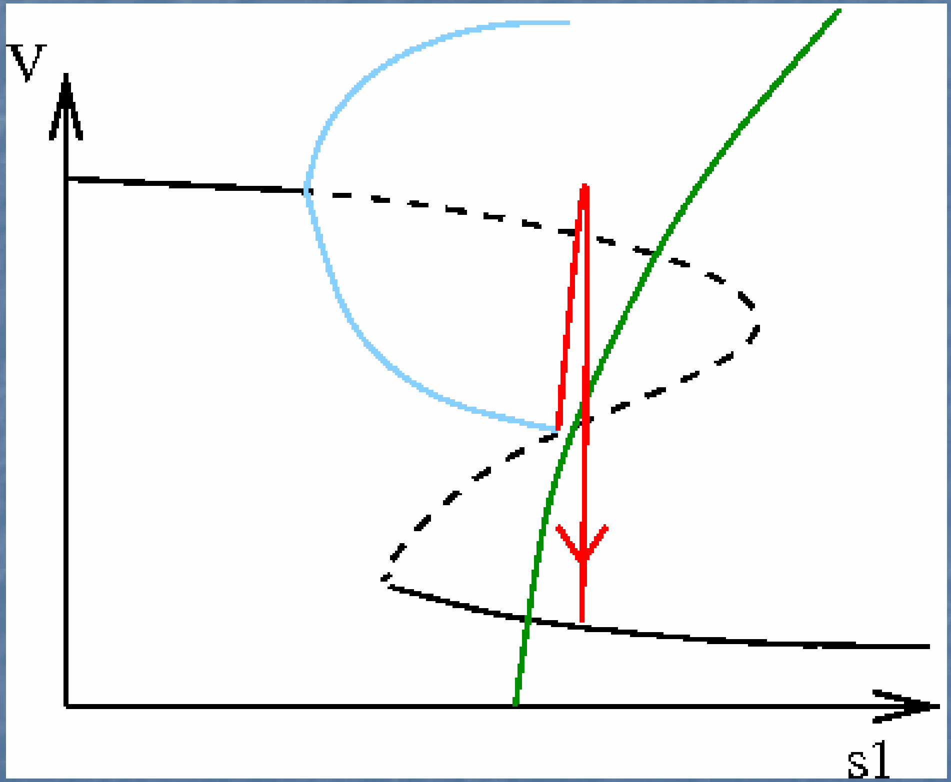


V high $\Rightarrow$ S_2 increases

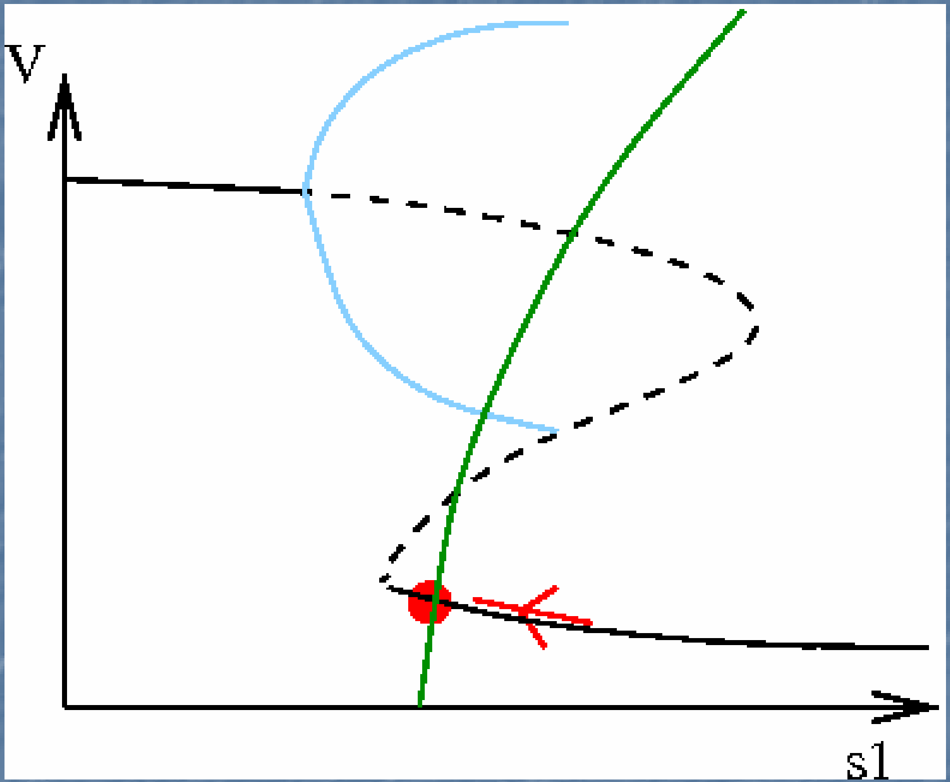
S_2 increases $\Rightarrow$ z-curve shifts leftward

Next Time Point

The z-curve eventually shifts so that the HM bifurcation moves past the nullcline. The trajectory escapes the active phase.

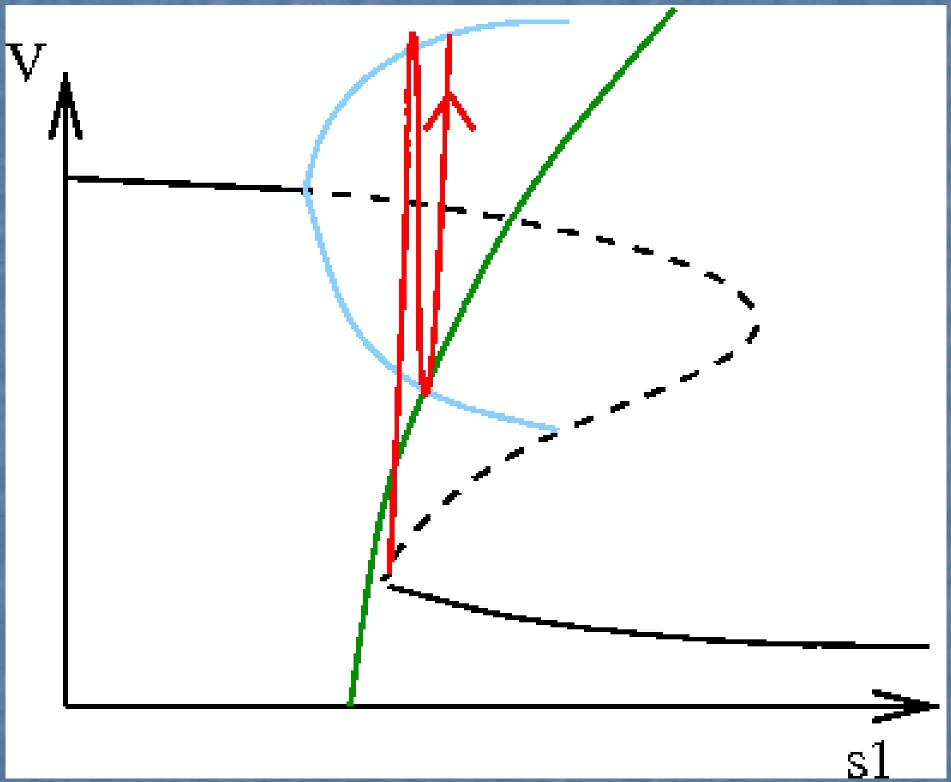


The Next Time Point



The trajectory moves along the bottom branch until it reaches the pseudo-steady state. This slowly drifts leftward as s_2 declines and the z-curve moves rightward.

The Next Time Point



The z-curve moves past the nullcline, allowing the trajectory to escape the bottom branch and re-enter the spiking phase.

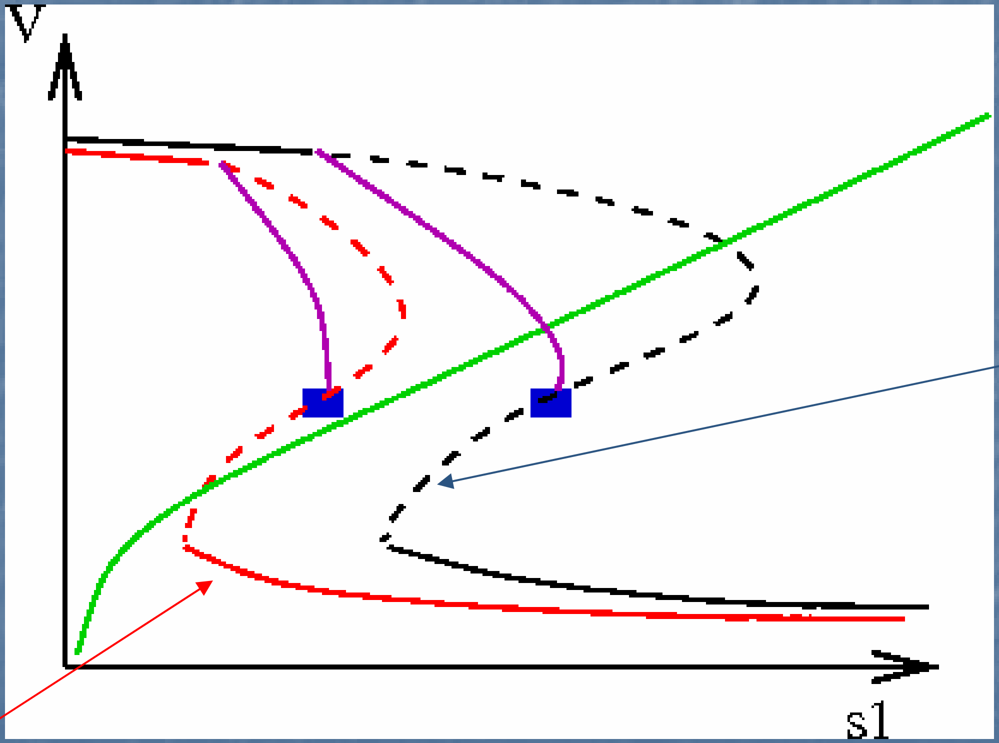
Phantom Bursting

End result: Phantom Bursting, in which the burst period is driven by the actions of more than one slow process.

The role played by the two slow variables depends on how deeply the slow nullcline intersects the periodic and/or stable stationary branch.

Stretching the z-curve

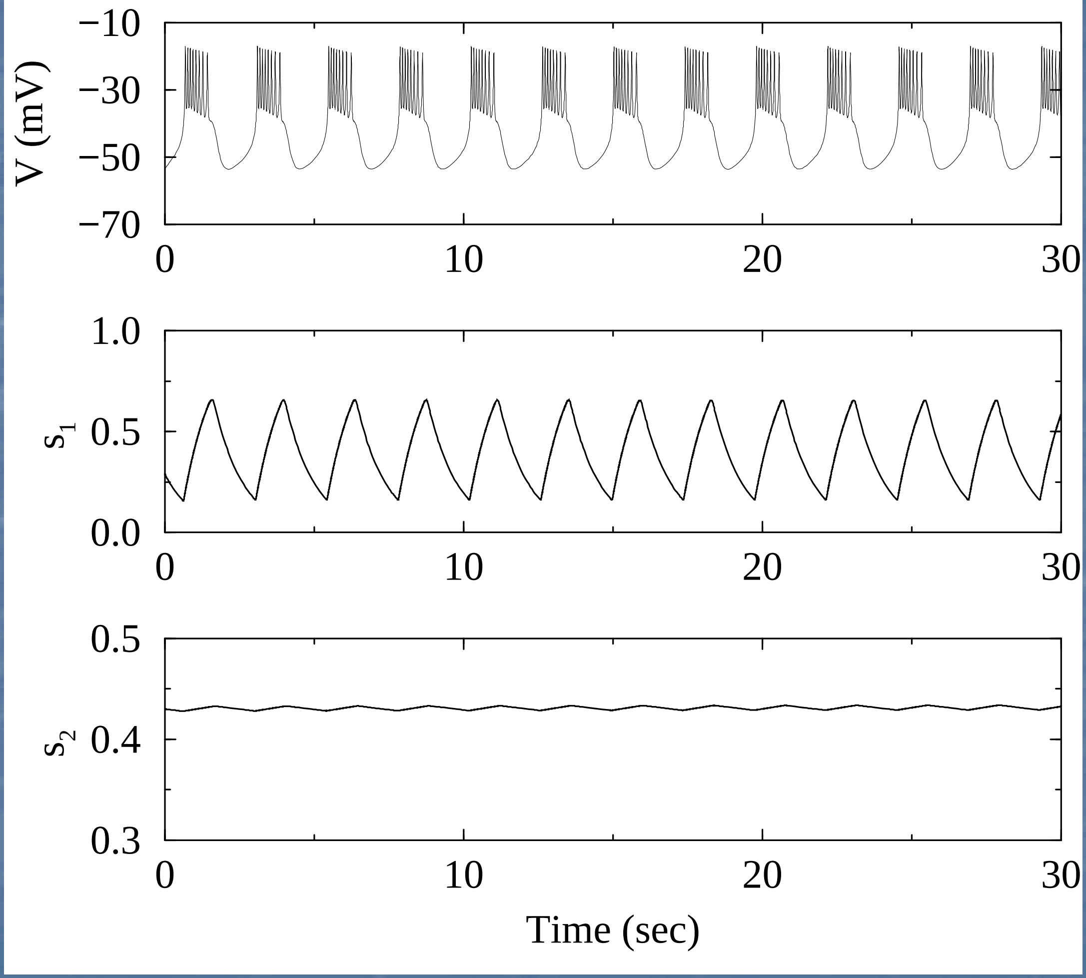
Decreasing the g_{s1} parameter stretches the z-curve and shifts it rightward.



g_{s1} small

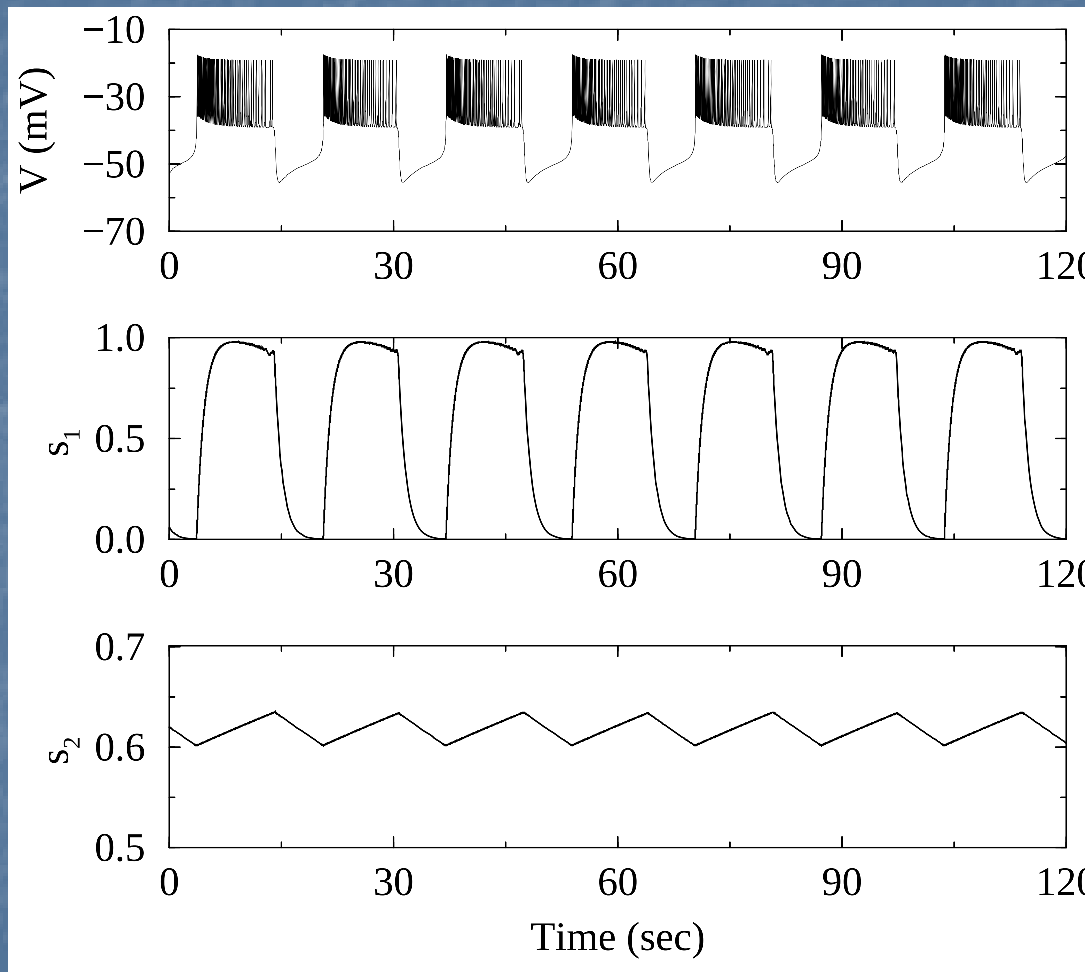
g_{s1} large

Fast Bursting with g_{s1} Large



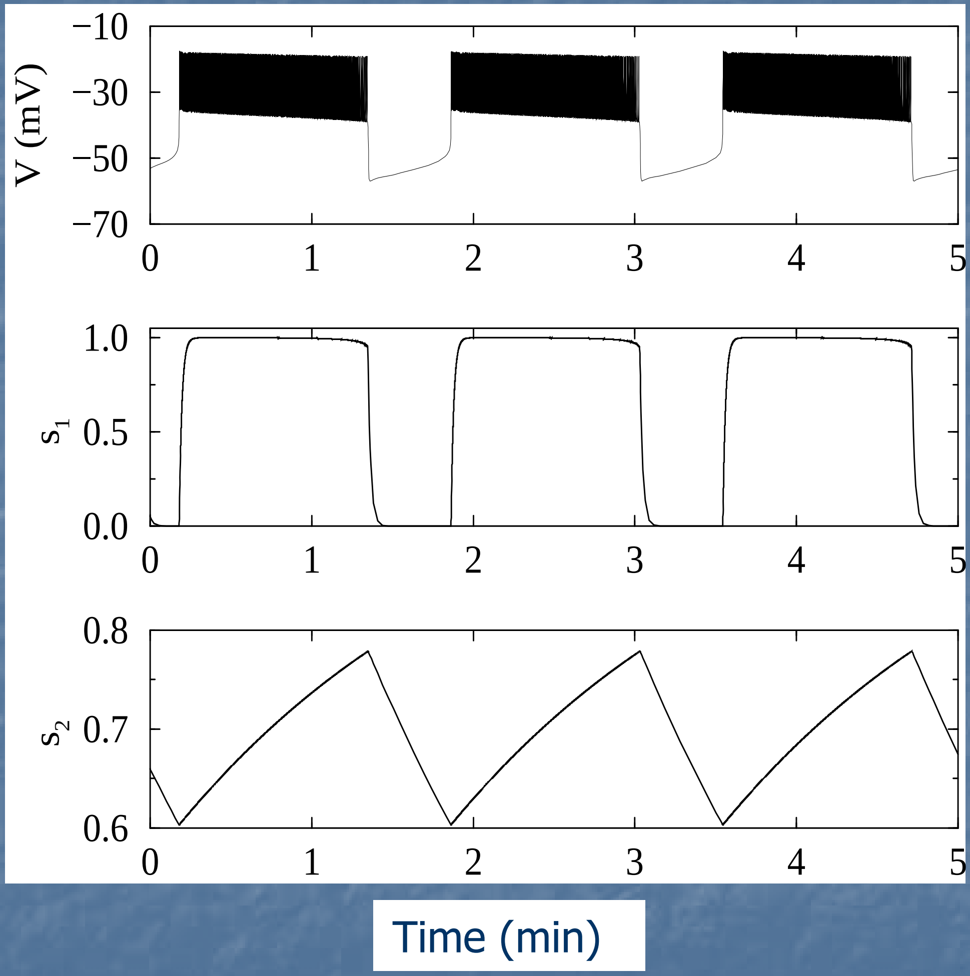
Bursting driven solely by variation in the s_1 variable

Medium Bursting with Smaller g_{s1}



Variation in both slow variables drives the bursting

Slow Bursting with Small g_{s1}

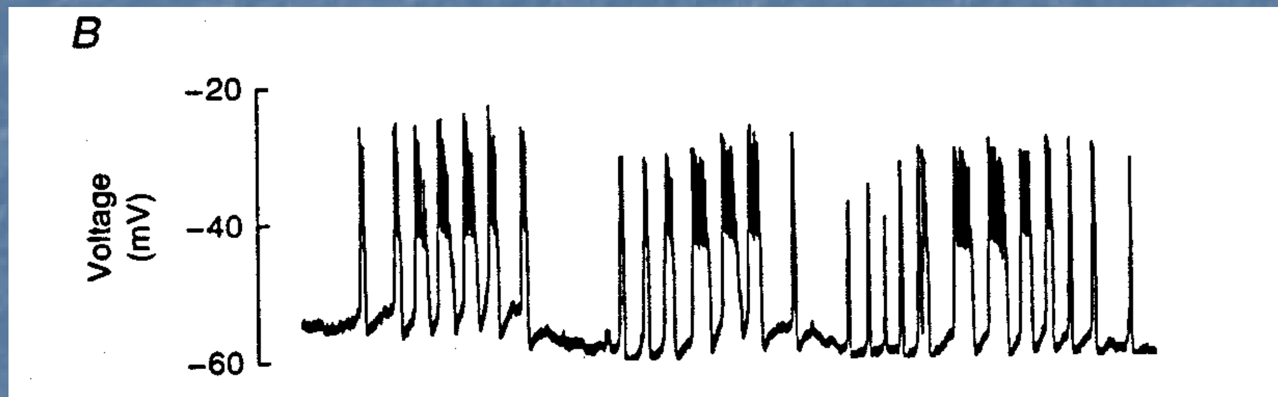


Bursting driven by slow variation in the s_2 variable

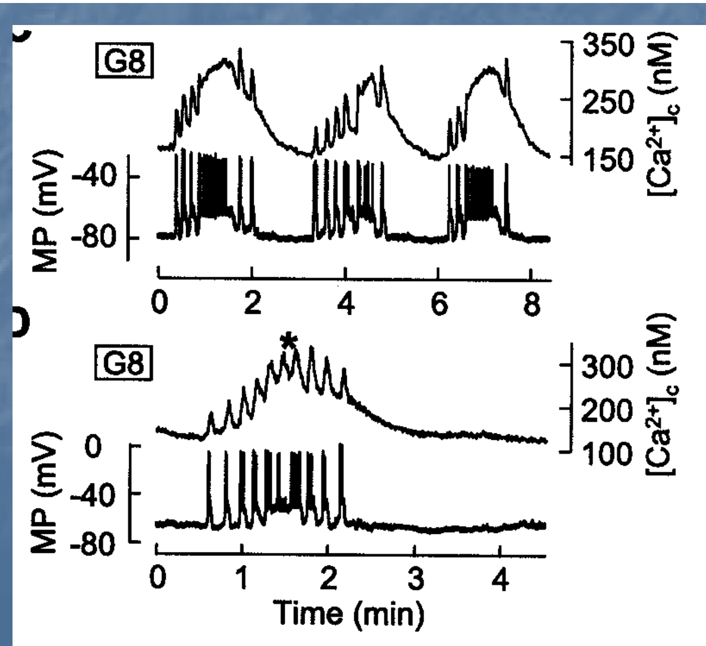
The Last Chapter: Compound Bursting

Compound Bursting Occurs in Pancreatic β-Cells and GNRH Neurons

Barbosa et al. (1998)



Beauvois et al. (2006)



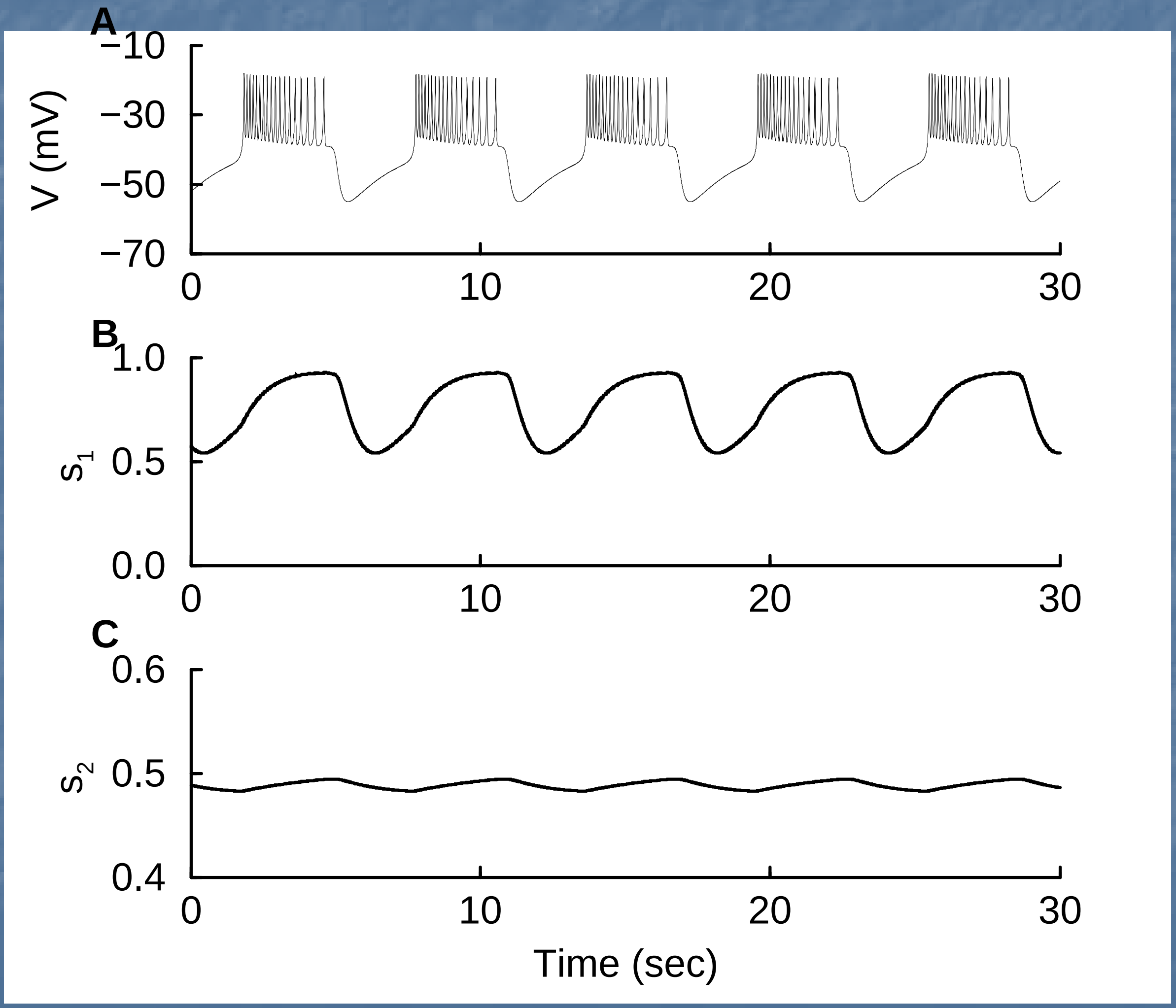
Can the phantom bursting mechanism produce compound bursting?

Hypothesis: Yes, it can, but parameters must be adjusted so that s_2 clusters fast bursts together into episodes instead of making the bursts longer.

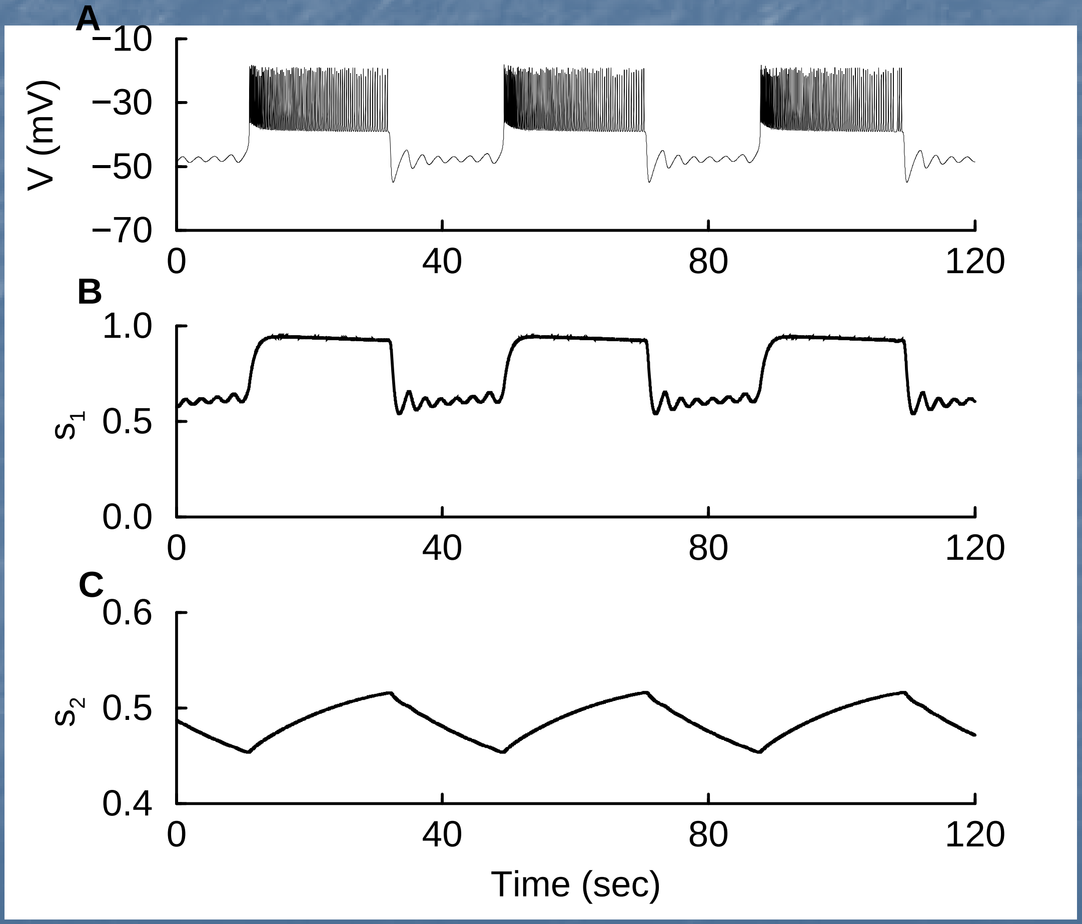
Approach: Get a student to do it!

The student: Wendy Cimbora

Fast Bursting Looks Similar



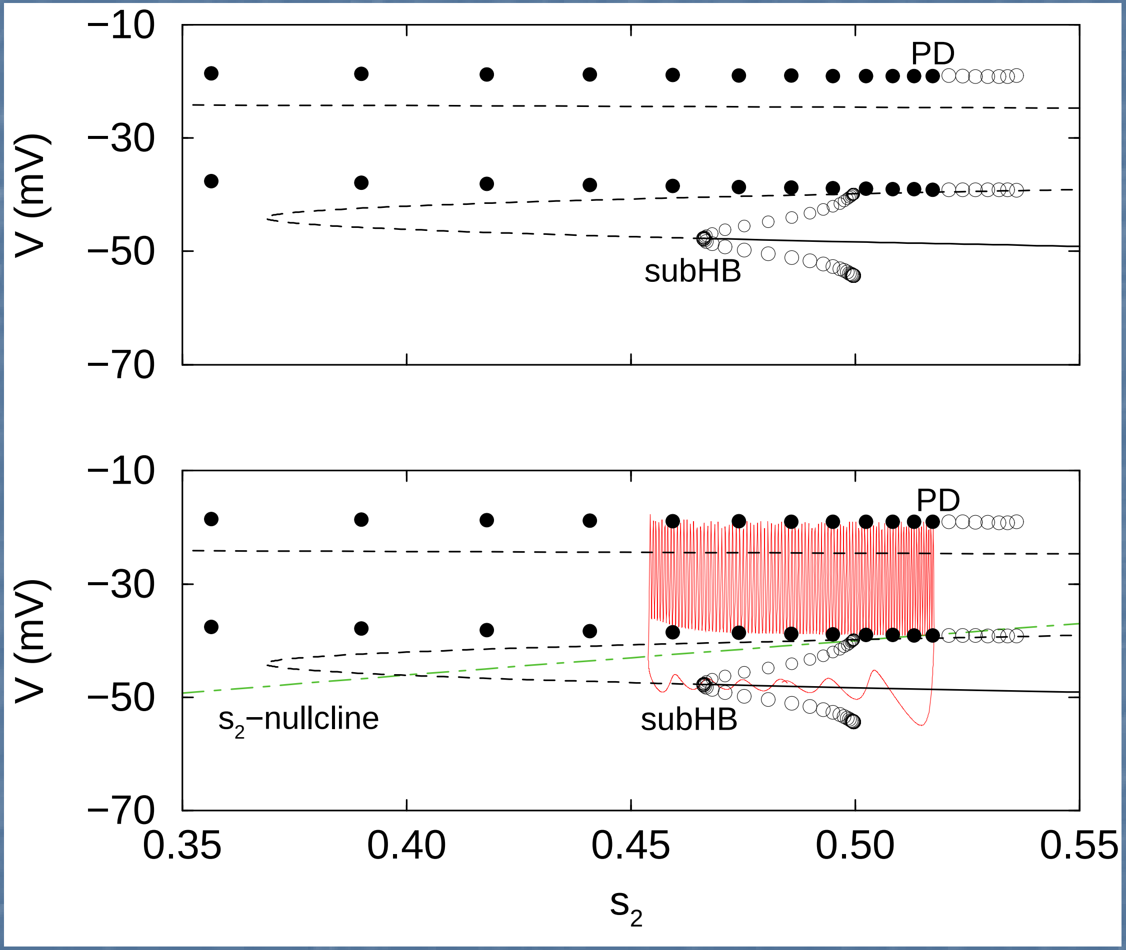
Reduce g_{s1}: Slow Bursting with Subthreshold Oscillations



Why the Subthreshold Oscillations?

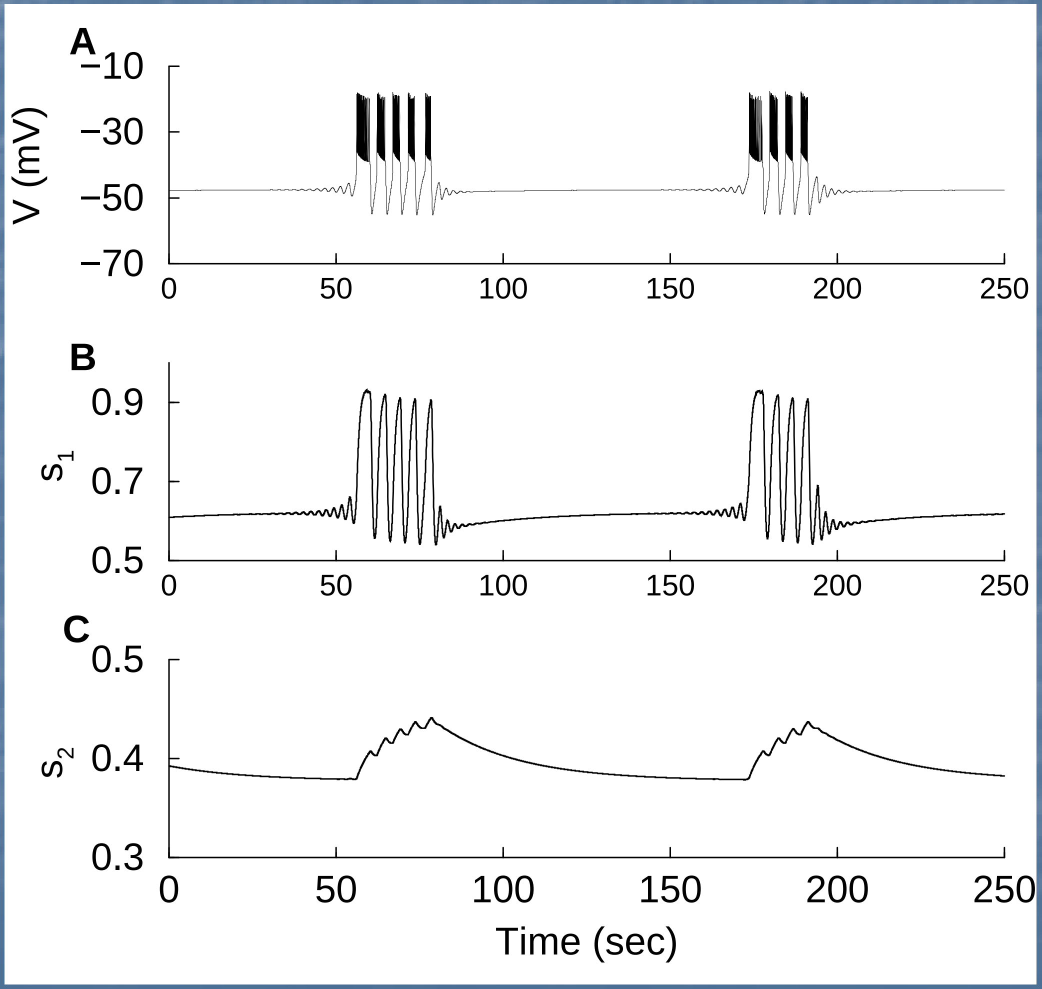
Can't tell using the fast/slow analysis as before. Instead, treat s_2 as the slow parameter for the V-n-s_1 subsystem. That is, treat s_1 as a fast variable.

Why the Subthreshold Oscillations?

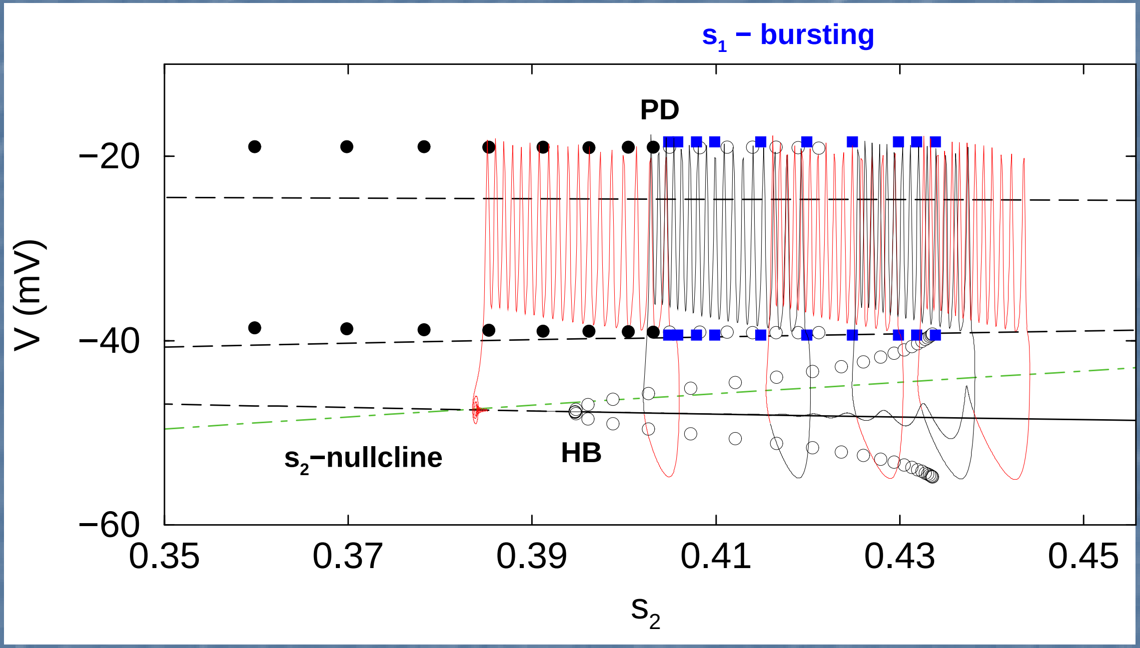


subHB=subcritical Hopf bifurcation PD=period doubling bifurcation

Reduce g_{s1} Further: Compound Bursting



Why it Happens



New branch of stable fast bursting oscillations, where the fast bursting is driven by s_1.

The End

Collaborators on this work

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Wendy Cimbora – Florida State University
Joe Rhoads – Florida State University

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Thank You!