

# Bursting and Bursting Analysis

**Richard Bertram**

Department of Mathematics and  
Programs in Neuroscience and Molecular  
Biophysics

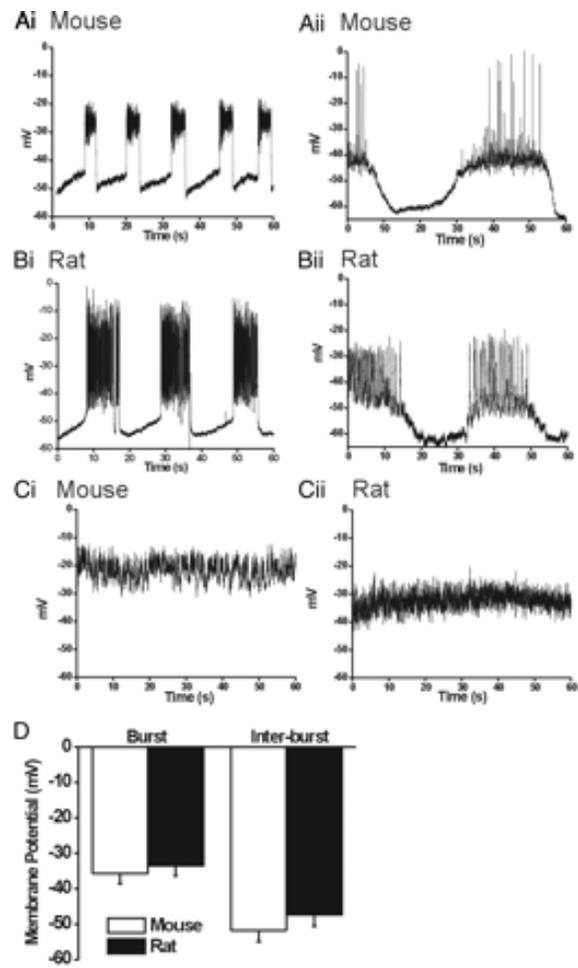
Florida State University  
Tallahassee, Florida 32306

**Bursting** consists of periodic clustering of electrical impulses. It occurs in many nerve and endocrine cells. These include:

- thalamic neurons
- hypothalamic neurons
- cortical neurons
- spinal cord
- neurons of the pre-Bötzinger complex in brain stem
- pituitary cells
- pancreatic  $\beta$ -cells

The burst period ranges from tens of milliseconds (many neurons), to a few seconds (pituitary cells), to several minutes ( $\beta$ -cells). The example below shows

bursting in a pancreatic islet, composed of a cluster of insulin-secreting  $\beta$ -cells.



## Why bursting?

There are several possible physiological roles of bursting. These include:

- Bursting avoids desensitization of receptors
- Bursting can amplify neurotransmitter secretion
- Bursting can relieve presynaptic inhibition
- Bursting encodes two time scales, while periodic spiking encodes only one
- Bursting is more robust than a single spike; better for use in central pattern generators

Other roles are likely to be revealed over time.

Today, we will look at several mathematical models that produce bursting oscillations, and see how

the oscillation can be analyzed using a [geometric singular perturbation analysis](#).

Modified Morris-Lecar Model

We modify the Morris-Lecar model by adding a current that responds to the **calcium** concentration in the cell. This current is **Ca<sup>2+</sup>-activated K<sup>+</sup> current**,  $I_{K(Ca)}$ . There are several possible formulations, but we use:

$$I_{K(Ca)} = \bar{g}_{K(Ca)} \left( \frac{Ca_c^3}{Ca_c^3 + K_D^3} \right) (V - V_K) \quad (1)$$

where a Hill function with exponent 3 is used to describe the Ca<sup>2+</sup> activation.

With this current, the Morris-Lecar model becomes:

$$\frac{dV}{dt} = -[I_{Ca} + I_K + I_L + I_{K(Ca)}]/C \quad (2)$$

$$\frac{dw}{dt} = \lambda [w_\infty(V) - w] / \tau(V) \quad (3)$$

For now we will treat Ca<sup>2+</sup> as a constant parameter.

The parameter  $\lambda$  is introduced so that we can eas-

ily change the speed of the recovery variable  $w$ . By making  $\lambda$  small we make  $w$  slow compared to  $V$ . Set  $\lambda = 0.01$ , then:

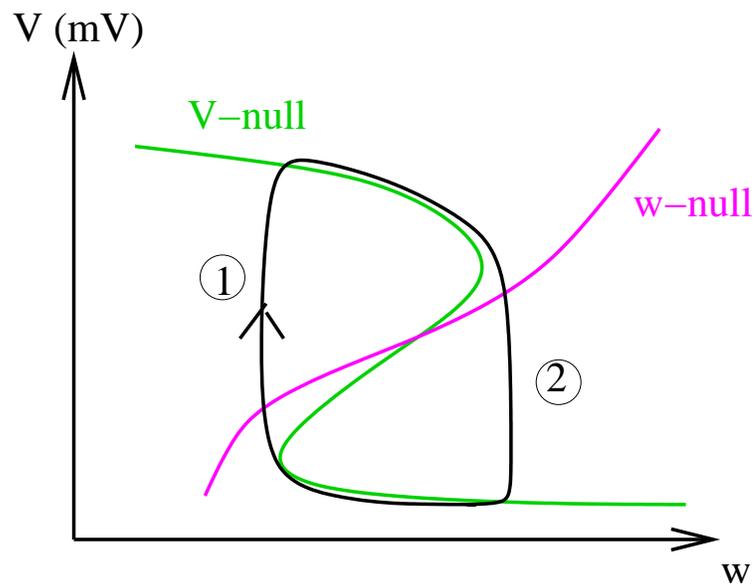


Figure 1: Phase portrait of relaxation oscillation,  $\lambda = 0.01$

This is called a **relaxation oscillation**. With such an oscillation the phase point travels along the nullcline of the fast variable except for jumps at the knees. The variable time courses look like:

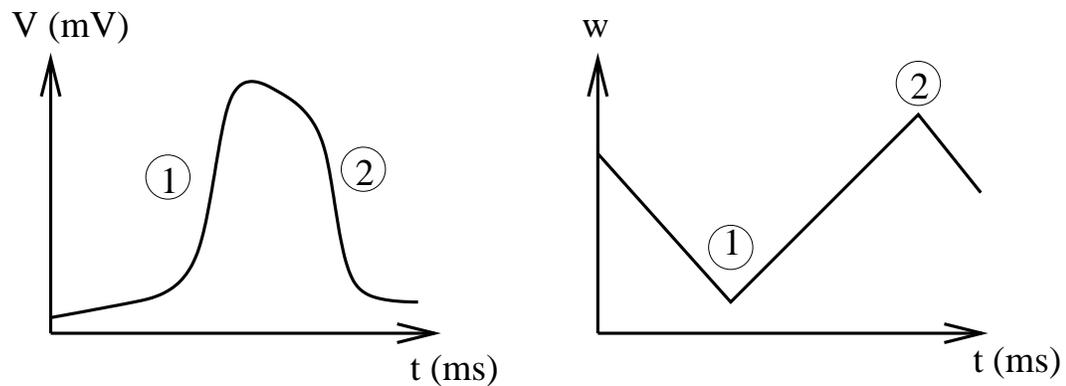


Figure 2: Relaxation oscillation time courses,  $\lambda = 0.01$

These time courses look quite different from those of a sinusoidal oscillation. We return later to relaxation oscillations, but now increase  $\lambda$  100-fold to  $\lambda = 1$ . Now both variables change at comparable speeds. Phase portraits at three values of calcium concentration  $Ca_c$  are shown below. Increasing  $Ca_c$  translates the  $V$ -nullcline leftward.

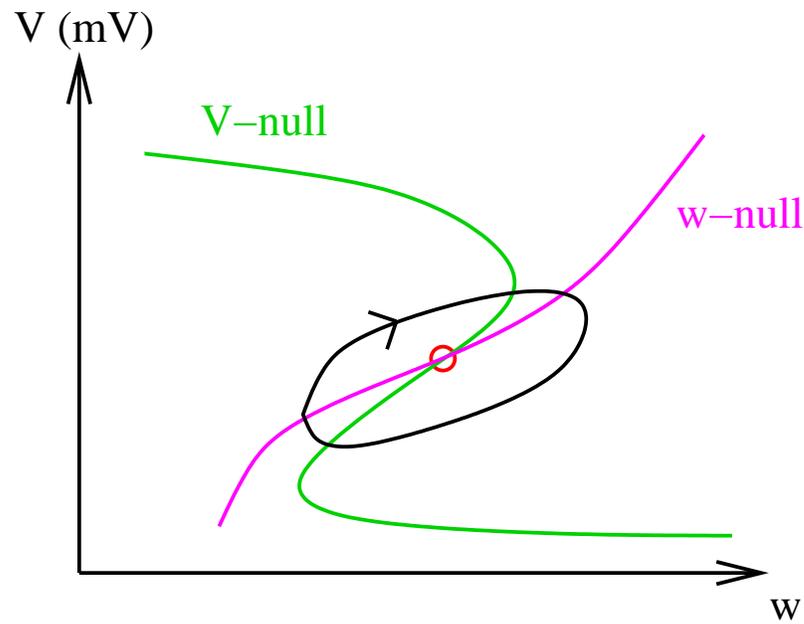


Figure 3: Oscillation with  $\lambda = 1$  and  $Ca_c = 0.1 \mu\text{M}$ .

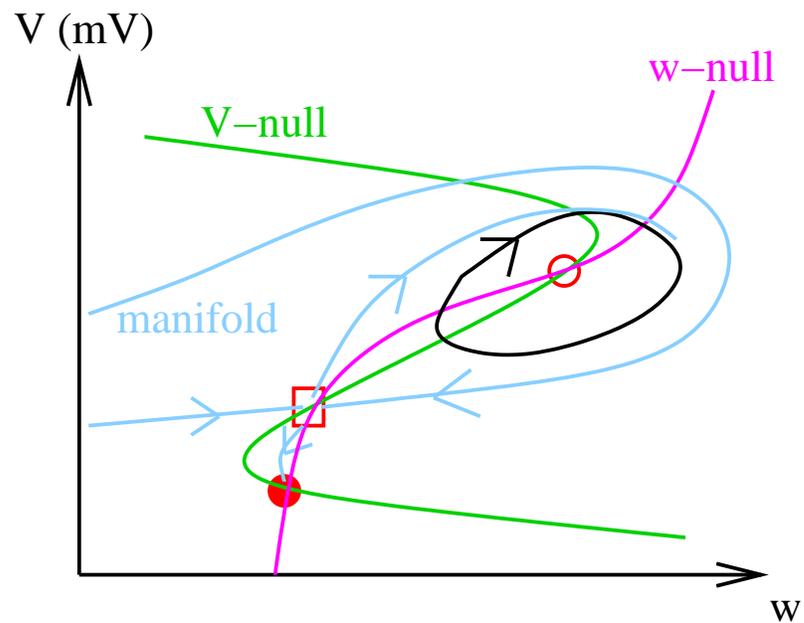


Figure 4: The system is bistable when  $Ca_c = 0.15 \mu\text{M}$ . Basins of attraction are separated by the two branches of the stable manifold.

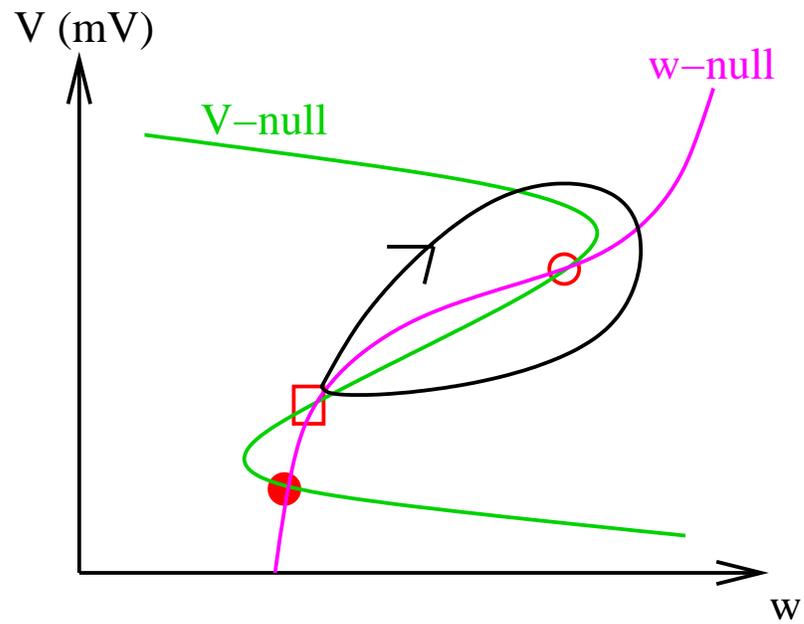


Figure 5: At about  $Ca_c = 0.165 \mu\text{M}$  one branch of the stable manifold connects with a branch of the unstable manifold, creating a **homoclinic orbit**.

This can all be summarized with a **bifurcation diagram** of the  $V$ - $w$  system:

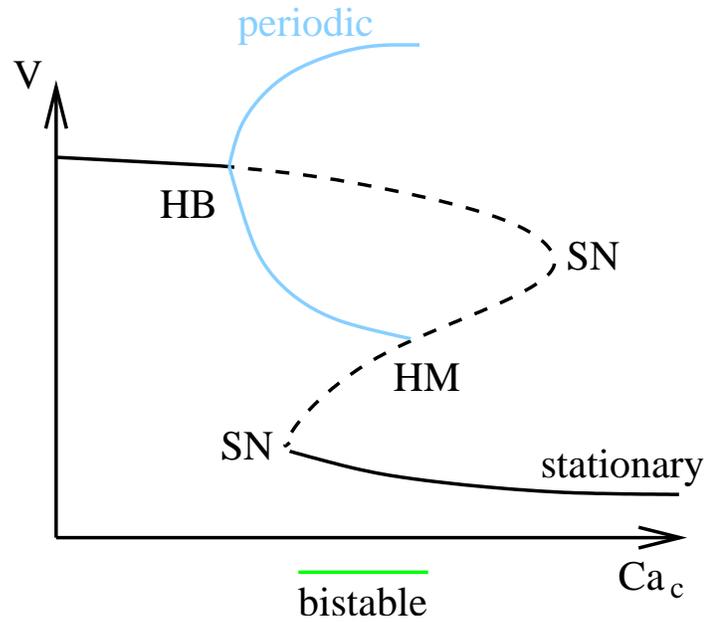


Figure 6: Bifurcation diagram with bifurcation parameter  $Ca_c$ . SN=saddle-node, HB=Hopf, HM=homoclinic.

### Calcium Dynamics

We now bring in the  $Ca_c$  dynamics. During an impulse,  $Ca^{2+}$  enters the cells through the  $Ca^{2+}$  channels. It is also pumped out of the cell by  $Ca^{2+}$  pumps.

$$J_{in} = -\alpha I_{Ca} \quad (4)$$

$$J_{out} = k_{pmca} Ca_c \quad (5)$$

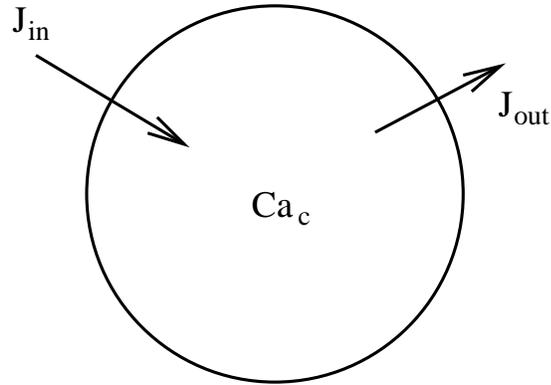


Figure 7:  $\text{Ca}^{2+}$  fluxes in a typical cell.

Then,

$$\frac{dCa_c}{dt} = f_c(J_{in} - J_{out}) \quad (6)$$

$$= -f_c(\alpha I_{Ca} + k_{pmca} Ca_c) \quad (7)$$

where  $f_c$  is the fraction of  $\text{Ca}^{2+}$  that is free (i.e., not bound by  $\text{Ca}^{2+}$  buffers in the cytosol).

spiking  $\Rightarrow |I_{Ca}|$  large  $\Rightarrow Ca_c$  increases

silent  $\Rightarrow |I_{Ca}|$  small  $\Rightarrow Ca_c$  decreases

We now look at the trajectory of the full 3-dimensional system in the  $V-Ca_c$  plane. This is superimposed on the bifurcation diagram of the  $V-w$  [fast subsystem](#),

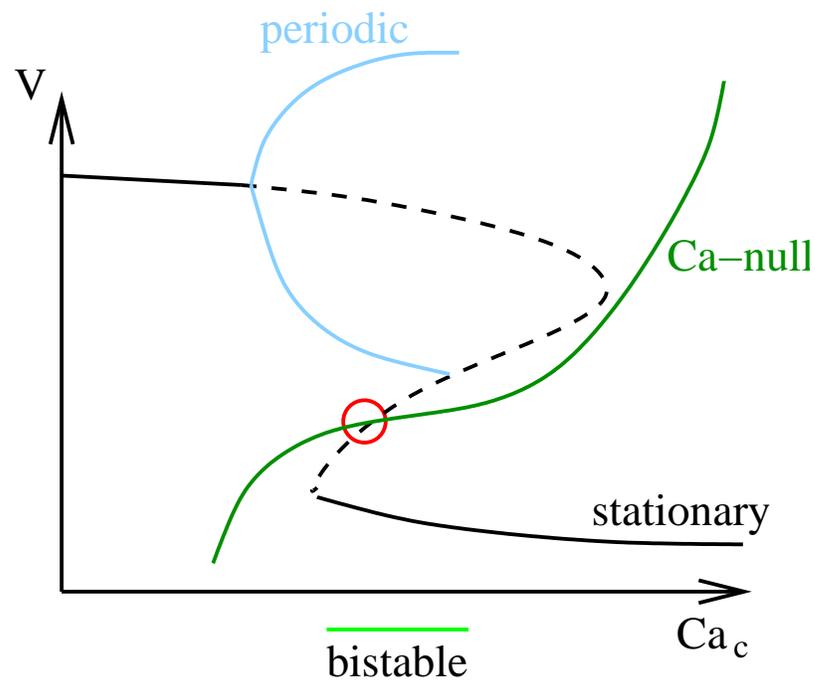


Figure 8: Slow manifold (z-curve) superimposed with the  $Ca_c$ -nullcline.

which is called the **slow manifold** or **z-curve**.

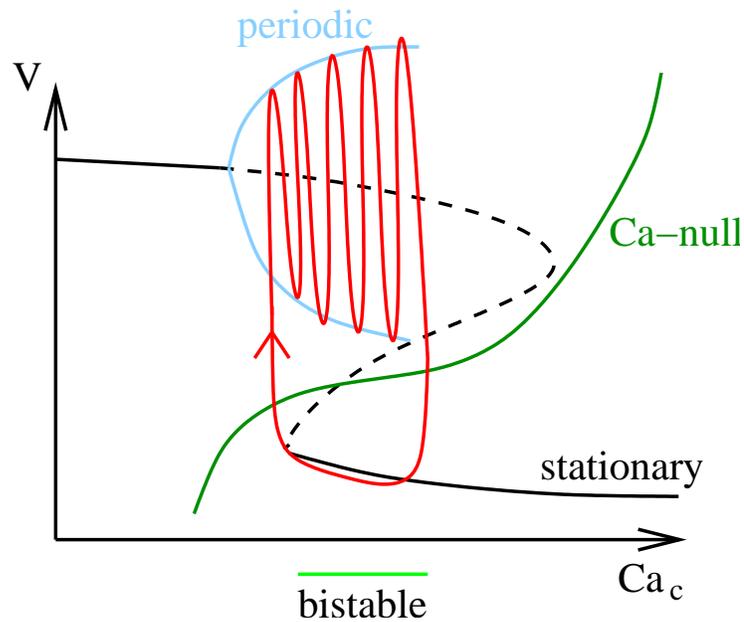
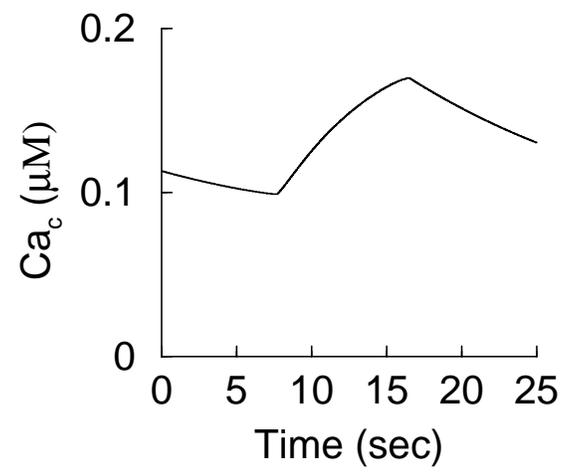
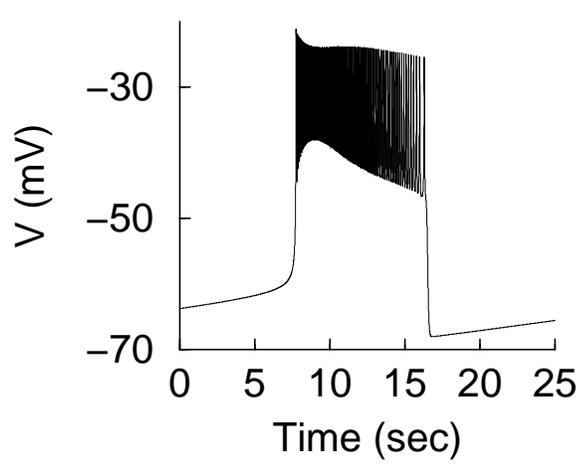


Figure 9: Slow manifold (z-curve) superimposed with the  $Ca_c$ -nullcline and the bursting trajectory of the full system.

This geometric analysis where we treat one variable as a slowly-changing parameter of the fast subsystem is called **fast/slow analysis** or **geometric singular perturbation analysis**.



## How are bursting oscillations and relaxation oscillations related?

For each value of  $Ca_c$  where a periodic (spiking) solution exists calculate the average  $V$  over one period of the oscillation. Plot this **average voltage curve**, which begins at the Hopf bifurcation and ends at the homoclinic bifurcation.

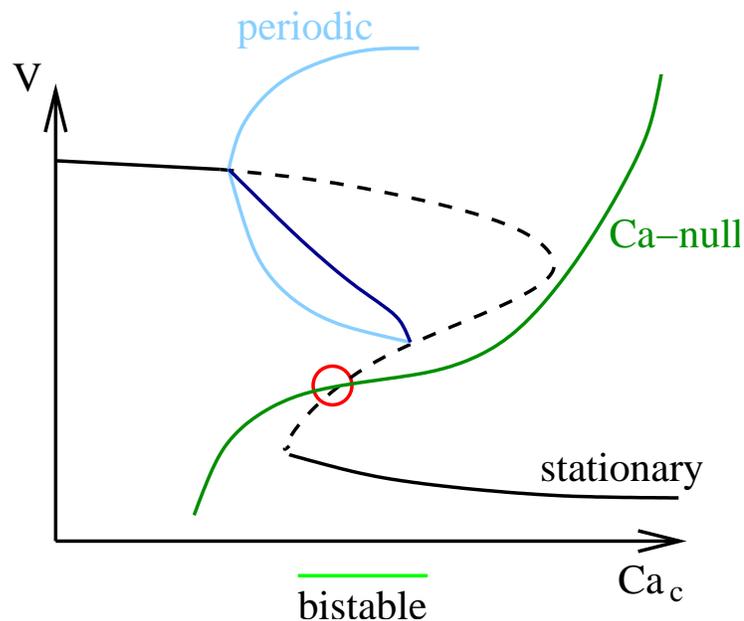


Figure 11: Z-curve and  $Ca_c$ -nullcline along with the average voltage curve (dark blue).

Now superimpose the burst trajectory, but using a moving average with  $V$  averaged over a period of a single spike. Then we have a **relaxation oscillation**!

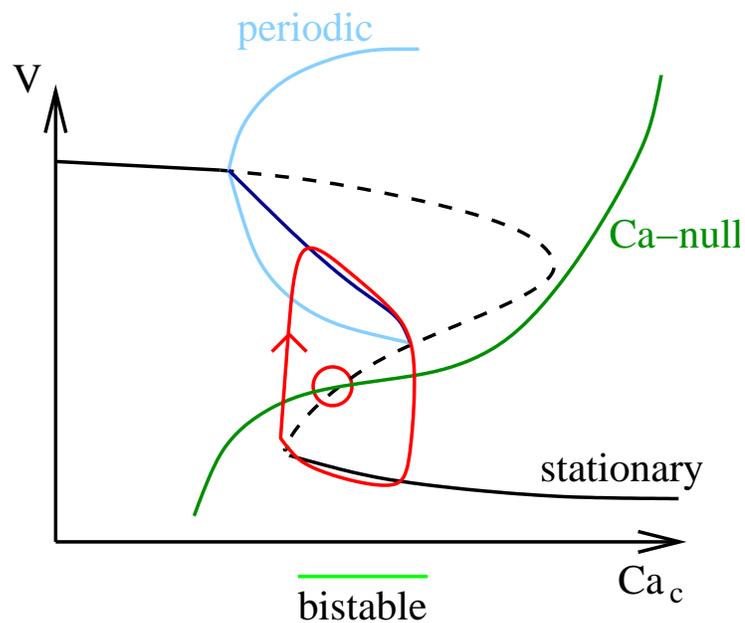


Figure 12: Z-curve and  $Ca_c$ -nullcline along with the average voltage curve (dark blue) and the moving average of the burst trajectory (red).

What happens if the  $\text{Ca}^{2+}$  nullcline is translated downward so that it intersects the bottom branch of the z-curve?

What happens if it intersects the average  $V$  curve?

These are extreme cases that limit the range of bursting. Intermediate cases, where the intersection is on the middle branch between the lower knee and the homoclinic, give variation in the burst period and **plateau fraction**.

$$\text{plateau fraction} = \frac{\text{active duration}}{\text{burst period}}$$

cell silent  $\Rightarrow$  plateau fraction = 0

cell continuously spiking  $\Rightarrow$  plateau fraction = 1

How does plateau fraction vary as the intersection on the middle branch is changed from near the knee to near the homoclinic?

## Calcium Handling in the Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** is an organelle that processes proteins that are bound for the plasma membrane. It is also a storehouse for  $\text{Ca}^{2+}$ . The illustration below shows some important  $\text{Ca}^{2+}$  fluxes between compartments.

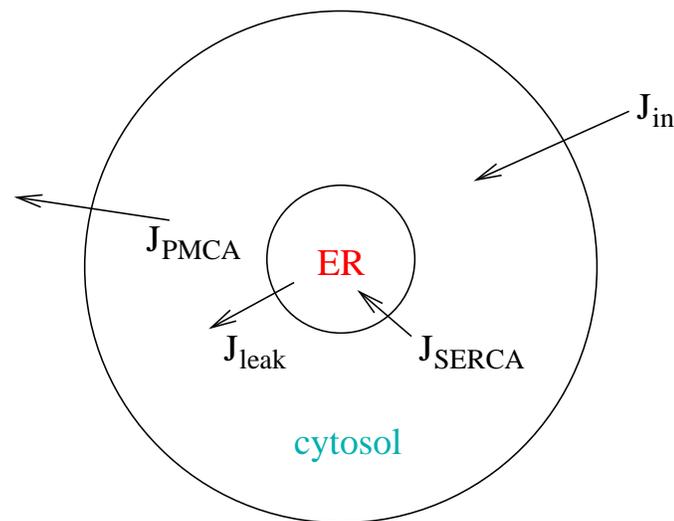


Figure 13:  $\text{Ca}^{2+}$  fluxes into and out of cytosol and ER.

With this new ER compartment the cytosolic  $\text{Ca}^{2+}$  equations must be modified, and a new ODE intro-

duced.

$$\frac{dCa_c}{dt} = f_c(J_{in} - J_{PMCA} - J_{SERCA} + J_{leak}) \quad (8)$$

$$\frac{dCa_{ER}}{dt} = f_{ER}\mu(J_{SERCA} - J_{leak}) \quad (9)$$

where  $\mu = V_c/V_{ER}$  is the **volume fraction**.

The **Ca<sup>2+</sup> leak** out of the ER is proportional to the concentration gradient:

$$J_{leak} = k_{leak}(Ca_{ER} - Ca_c)$$

and a reasonable model for flux through **SERCA pumps** (SERCA=Sarco-Endoplasmic Reticulum ATPase) is

$$J_{SERCA} = k_{SERCA}Ca_c .$$

Because of the size differences in the flux terms there are typically big differences in the  $Ca_c$  and  $Ca_{ER}$  dynamics:

- $Ca_c$  is small and changes relatively rapidly

- $Ca_{ER}$  is large and changes slowly

Changes in  $Ca_{ER}$  typically have no direct influence on the cell's membrane potential. However, they do affect the  $Ca_c$  nullcline:

$$Ca_c = \frac{-\alpha I_{Ca} + k_{leak} Ca_{ER}}{k_{PMCA} + k_{SERCA} + k_{leak}} \quad (10)$$

The nullcline is now more vertical and it moves when  $Ca_{ER}$  changes.

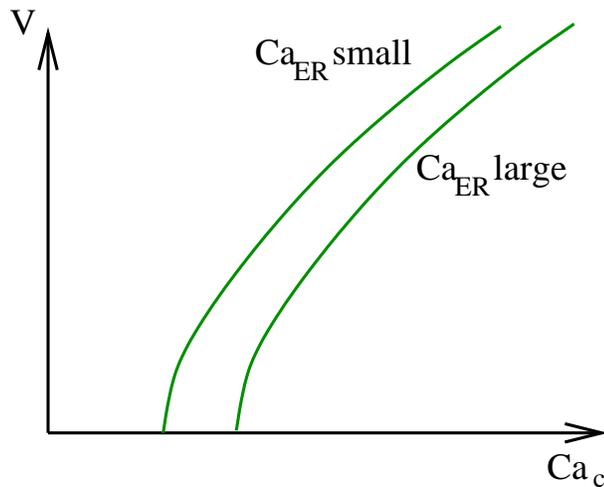


Figure 14: The  $Ca_c$  nullcline changes with  $Ca_{ER}$ .

Because the  $Ca_c$ -nullcline is now more vertical, it intersects the periodic and stable stationary branches of the z-curve, so that bursting does not occur if  $Ca_{ER}$  is held constant.

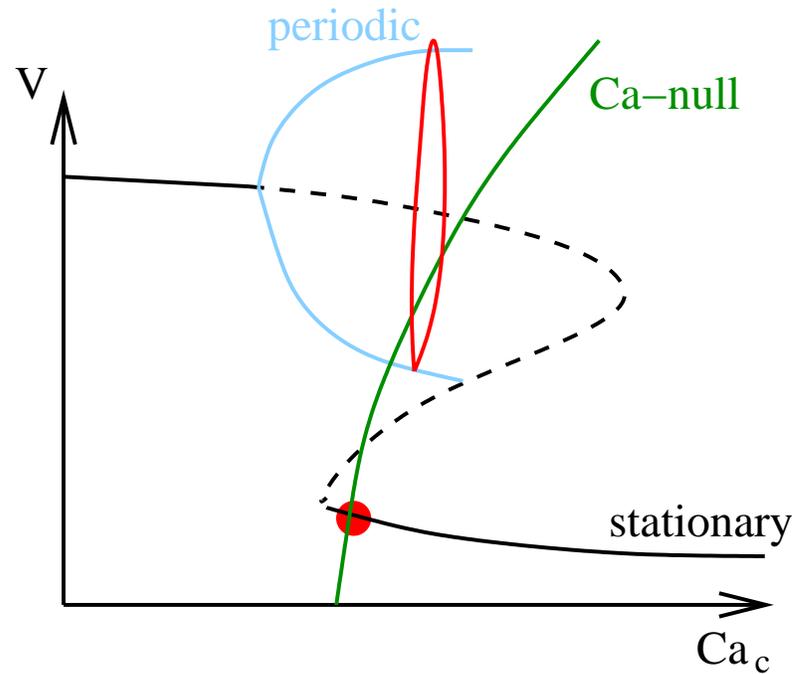


Figure 15: With  $Ca_{ER}$  frozen bursting cannot occur.

Suppose that the system starts out spiking (**A**).

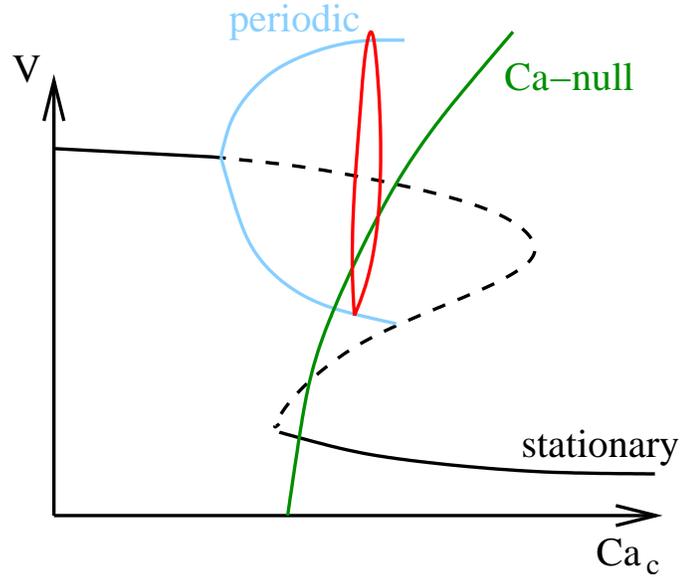


Figure 16: (**A**) The system is assumed to start out spiking.

This brings  $Ca^{2+}$  into the cell through  $Ca^{2+}$  channels, and some of the  $Ca^{2+}$  is pumped from the cytosol to the ER, causing  $Ca_{ER}$  to slowly increase. This translates the  $Ca_c$  nullcline rightward, eventually moving it past the homoclinic bifurcation, so that spiking is terminated and the silent phase begun (**B**).

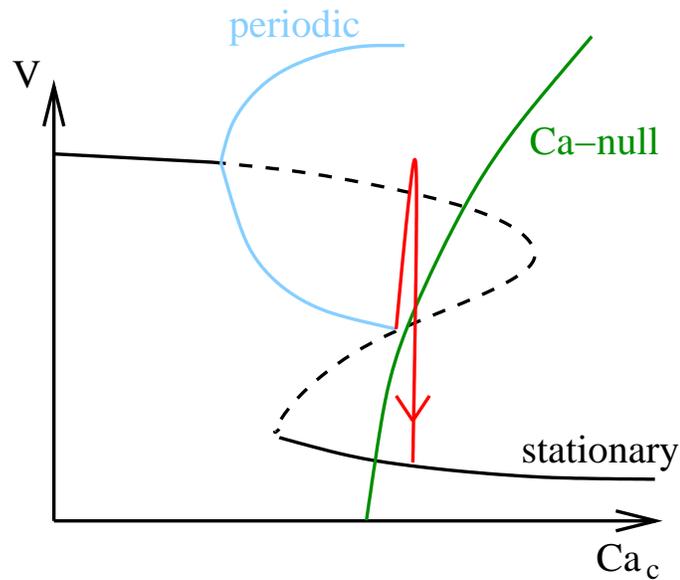


Figure 17: **(B)** As  $Ca_{ER}$  increases during the active phase the  $Ca_c$  nullcline moves rightward, eventually terminating the active phase.

The phase point now moves along the bottom branch of the z-curve toward the stable steady state. At the same time, but more slowly,  $Ca_{ER}$  declines and shifts the nullcline (and steady state) leftward **(C)**.

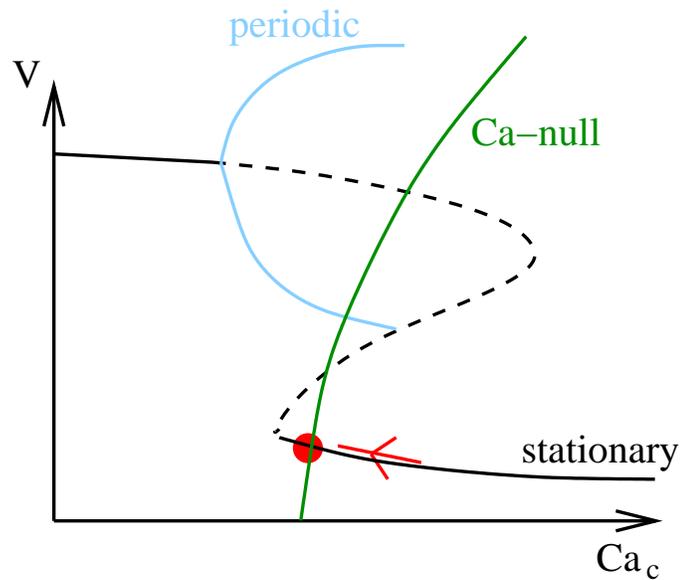


Figure 18: **(C)** As  $Ca_{ER}$  decreases during the silent phase the  $Ca_c$  nullcline moves leftward, dragging the phase point with it.

Eventually the nullcline moves past the lower knee, terminating the silent phase and restarting the active phase **(D)**.

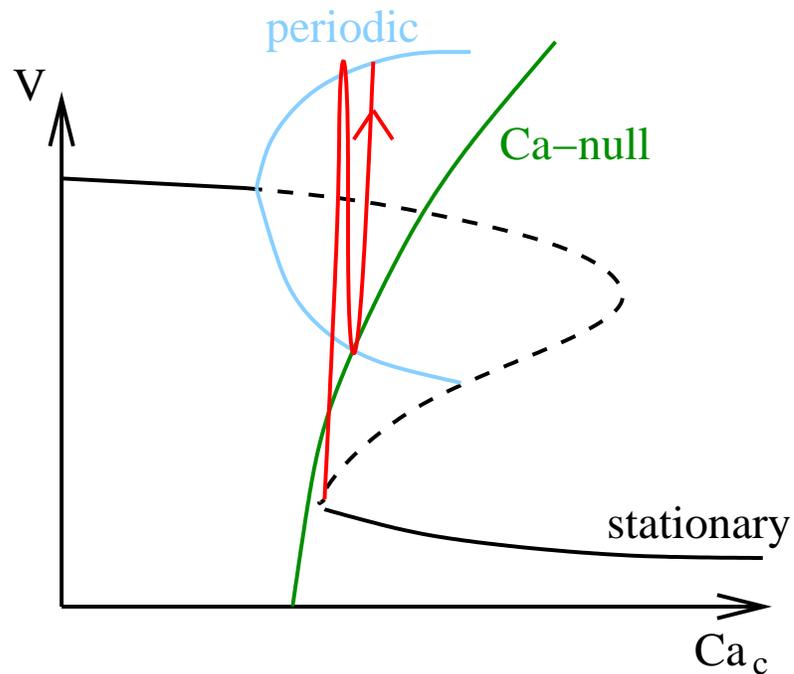


Figure 19: (D) Eventually the  $Ca_c$  nullcline moves past the lower knee, ending the silent phase.

The end result is bursting which is driven by both cytosolic  $Ca^{2+}$  and the ER  $Ca^{2+}$  dynamics. When the nullcline does not intersect deep into the periodic and stationary branches the cytosolic and ER components contribute about equally, producing **medium bursting**. Note the different shapes of the  $Ca_c$  and  $Ca_{ER}$  time courses.

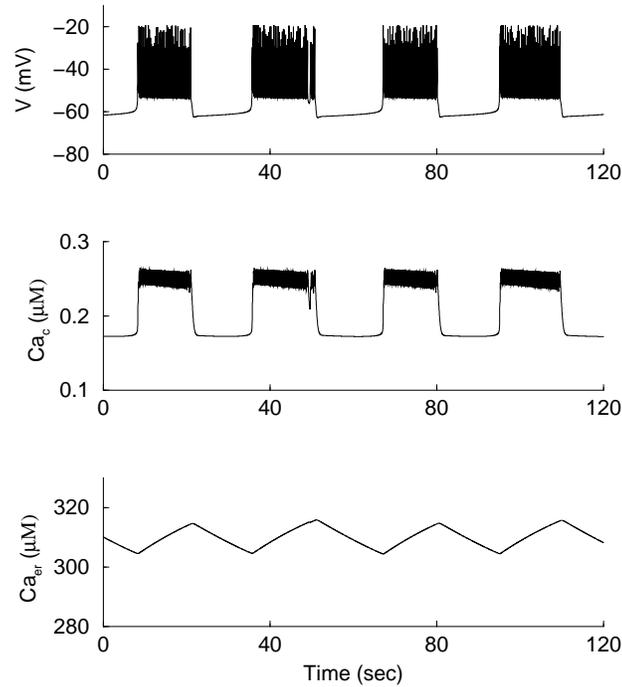


Figure 20: When  $Ca_c$  and  $Ca_{ER}$  dynamics contribute about equally medium bursting is produced.

When the  $Ca_c$  nullcline intersects deep in the periodic and stationary branches the ER  $Ca^{2+}$  concentration must change a great deal to pull the system from one phase to the other. Since  $Ca_{ER}$  changes slowly, this results in **slow bursting**.

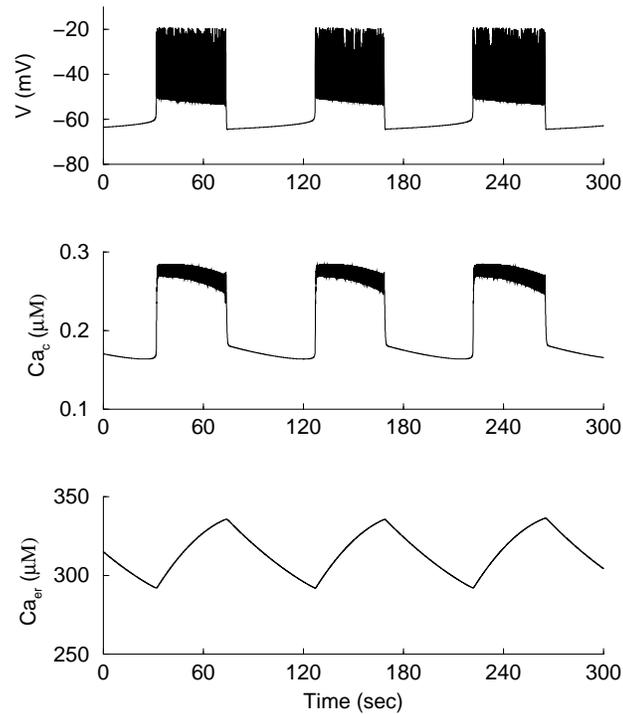


Figure 21: When the nullcline intersects deep into the periodic and stationary branches slow bursting results.

**Bottom line:** The addition of the ER  $\text{Ca}^{2+}$  store/sink greatly increases the range of burst periods that can be produced.

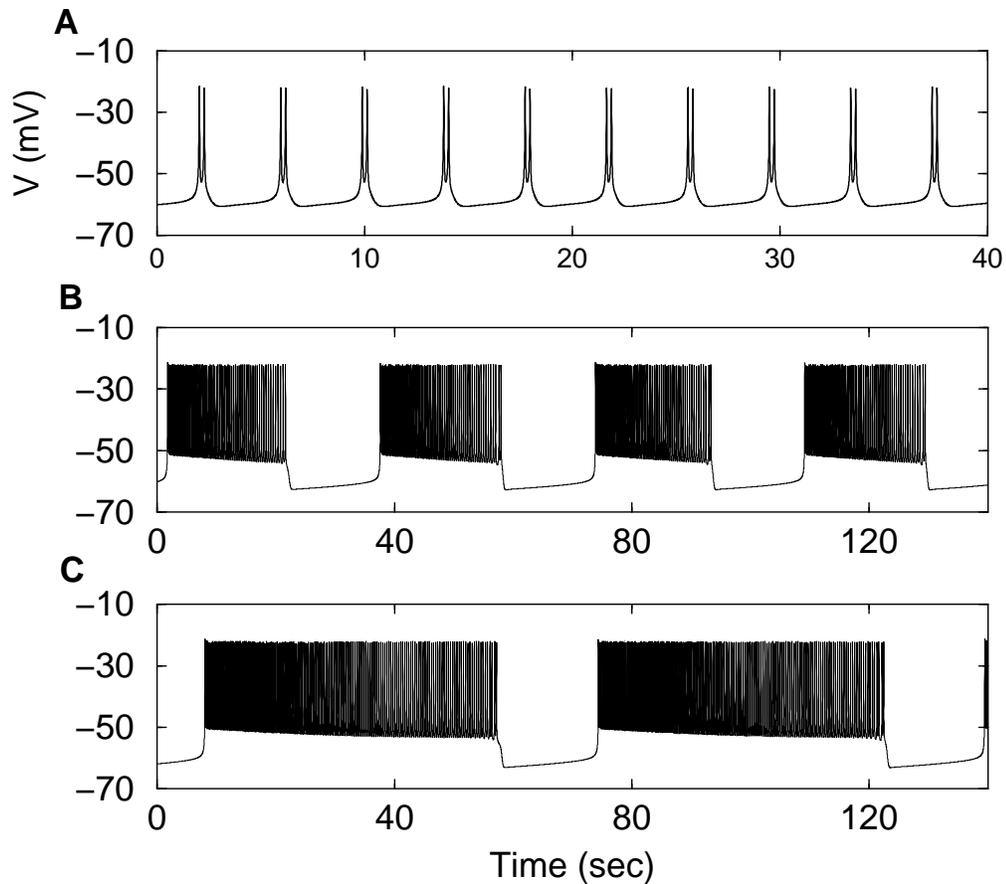
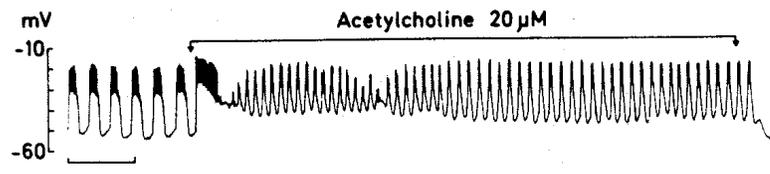


Figure 22: Bursting goes from fast to slow as the  $K(Ca)$  current conductance is decreased from 1000 pS (top) to 500 pS (middle) to 370 pS (bottom).

There is evidence for this effect of  $Ca_{ER}$  on the burst period in pancreatic islets. When the rate of release from the ER is increased by activating  $IP_3$  receptors with the neurotransmitter Acetylcholine (ACh), bursting gets much faster (Henquin *et al.*,

Endocrinology, 122:2134, 1988).



## References

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2. J. Rinzel, G.B. Ermentrout, *Analysis of neural excitability and oscillations*, in “Methods in Neuronal Modeling: From Synapses to Networks”, C. Koch and I. Segev (ed.), MIT Press, 1998.