Mathematical Analysis of Bursting Electrical Activity in Nerve and Endocrine Cells

Richard Bertram
Department of Mathematics and Programs in Neuroscience and Molecular Biophysics
Florida State University

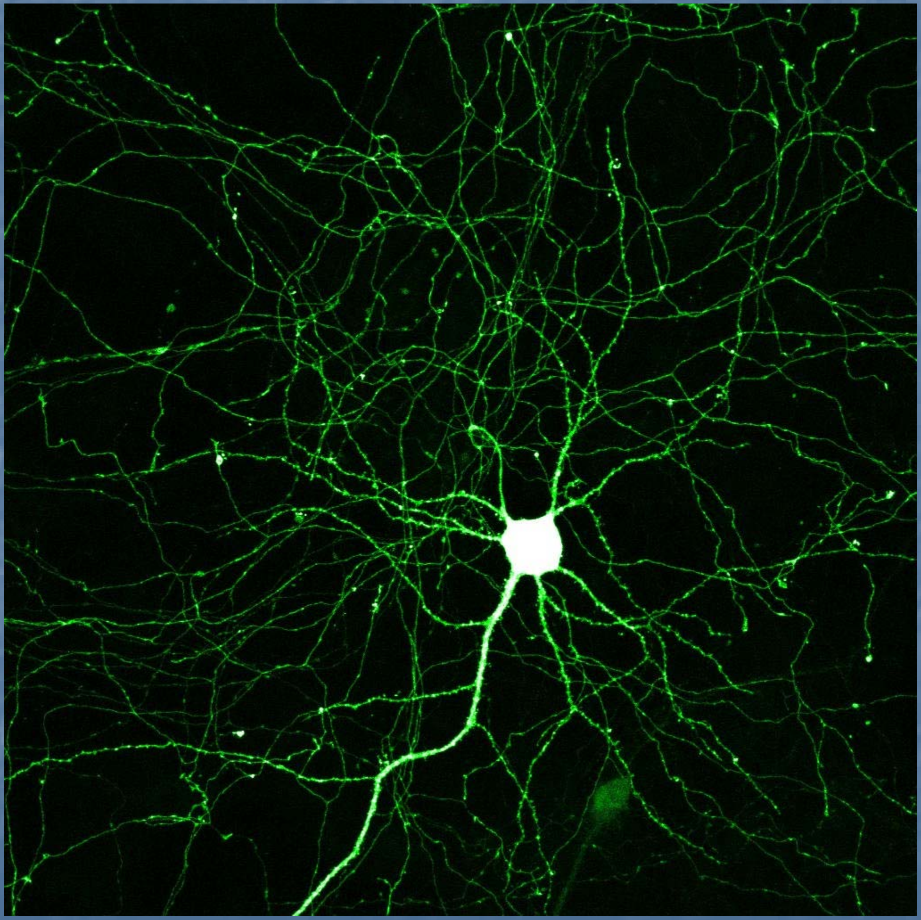
Collaborators on This Project

Florida State University

Dr. Joel Tabak
Dr. Maurizio Tomaiuolo

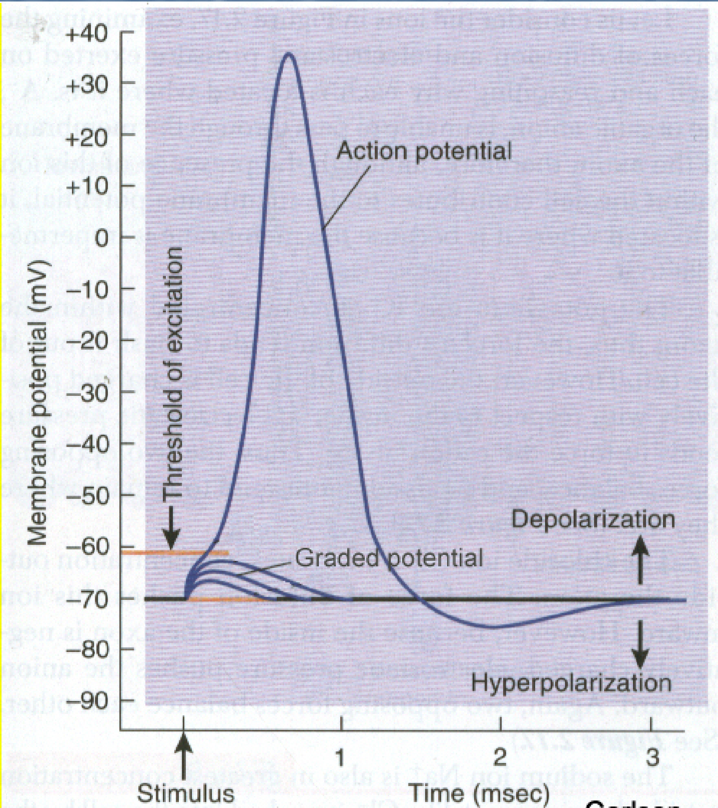
Grant support: National Institutes of Health (NIH-DA19356)

Image of a Neuron



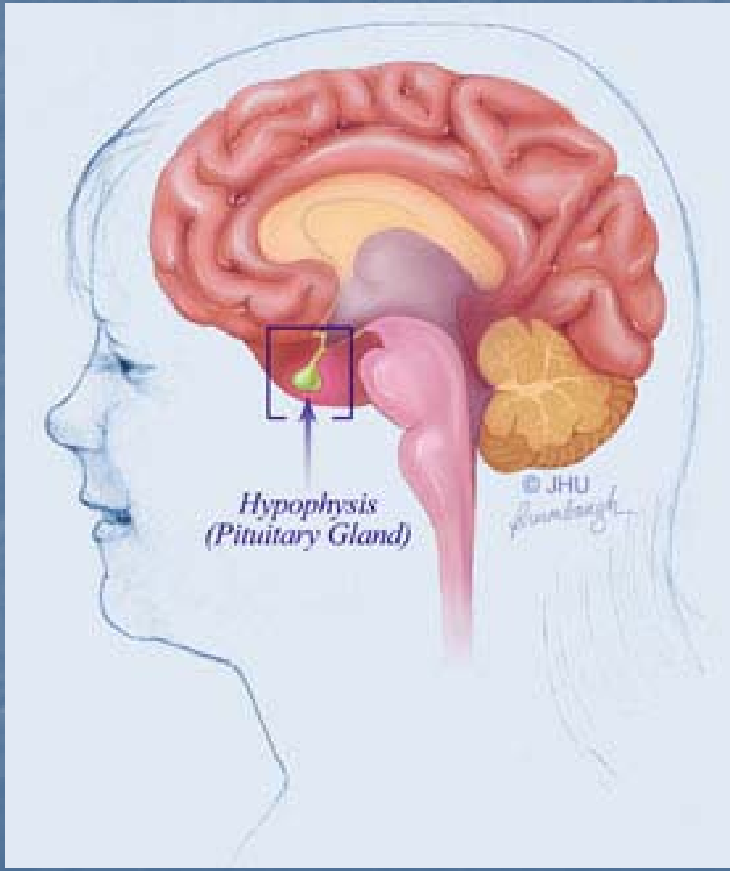
Neurons are Electrically Excitable

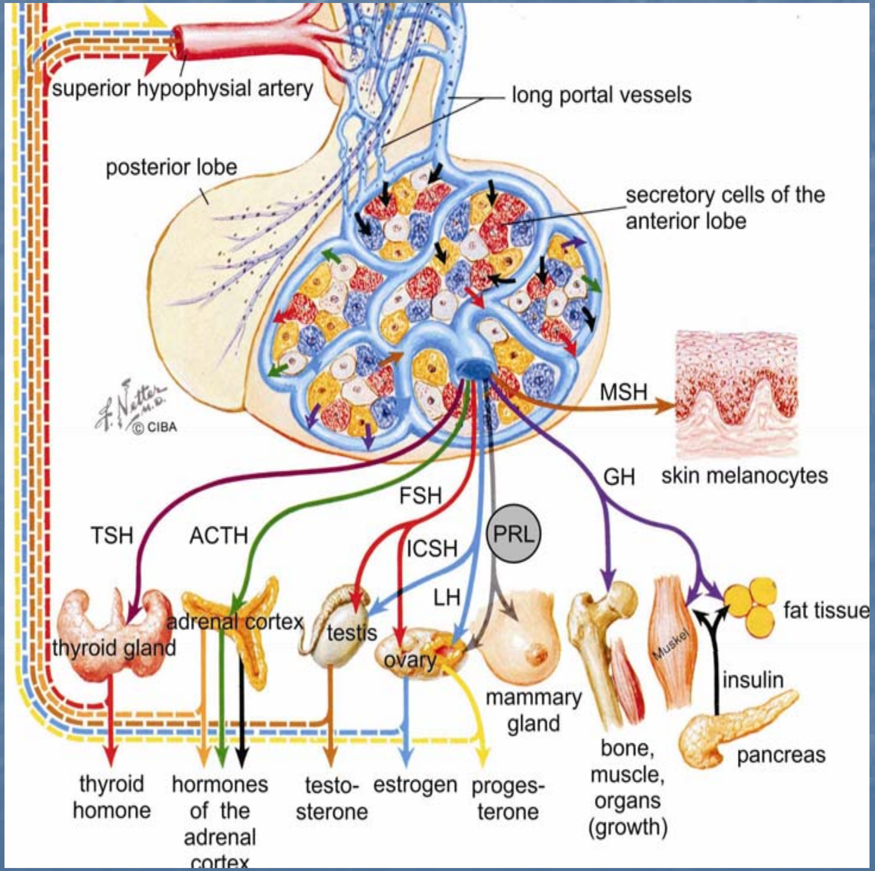
Information is transmitted through electrical impulses.



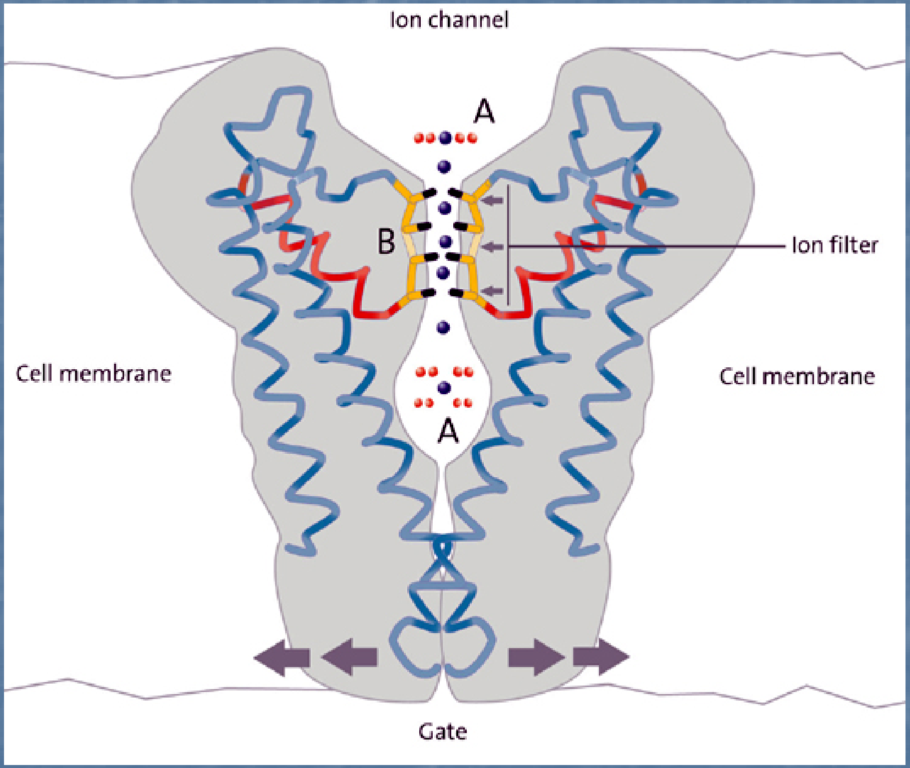
Carlson Figure 2.17

Many Endocrine Cells are Also Electrically Excitable



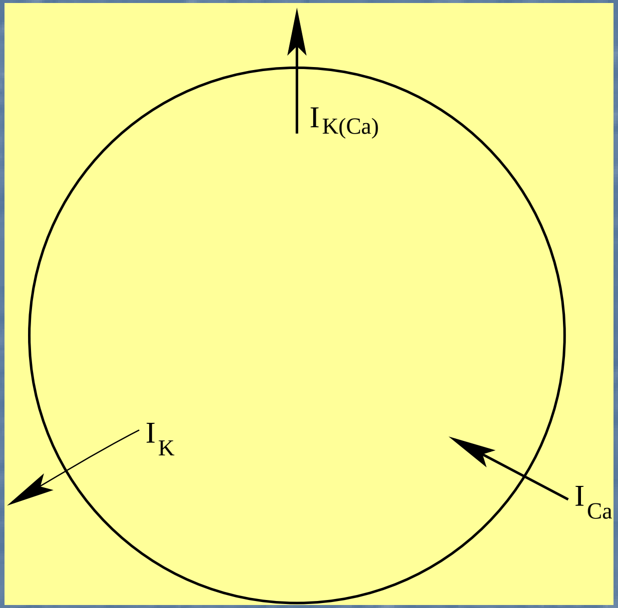


Electrical Activity is Due to Ion Channels



These are proteins in the plasma membrane that open and close depending on the voltage drop across the membrane.

Electrical Activity Equations Using Conservation of Charge

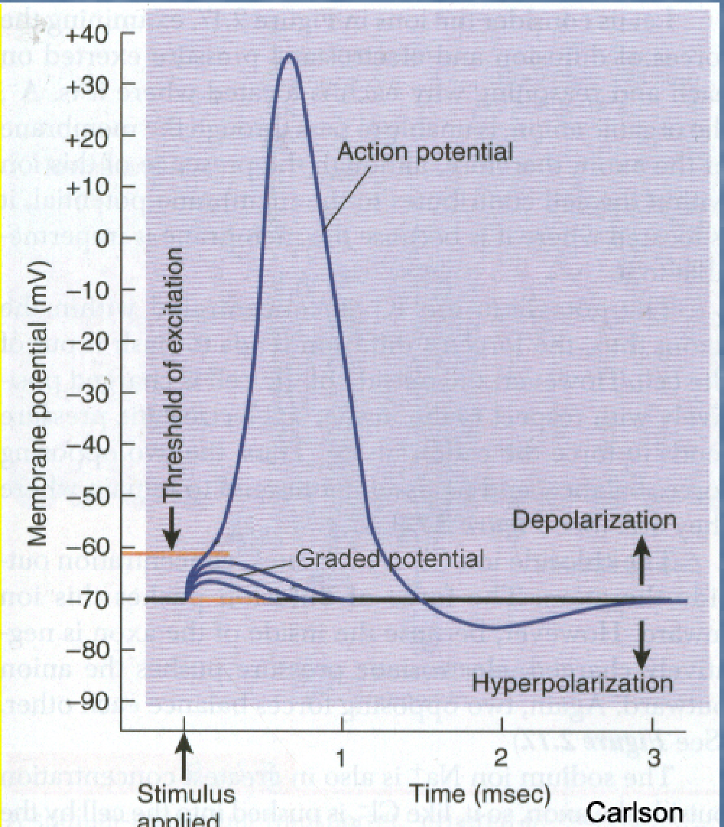


$$\frac{dV}{dt} = -(I_{Ca} + I_K + I_{K(Ca)})/C_m$$

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

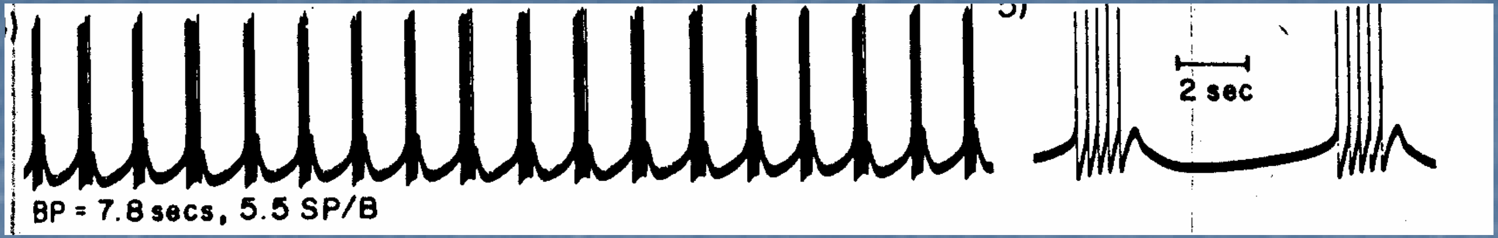
V = voltage (mV)
t = time (msec)
n = fraction of open K^+ channels

Sufficient for Spiking

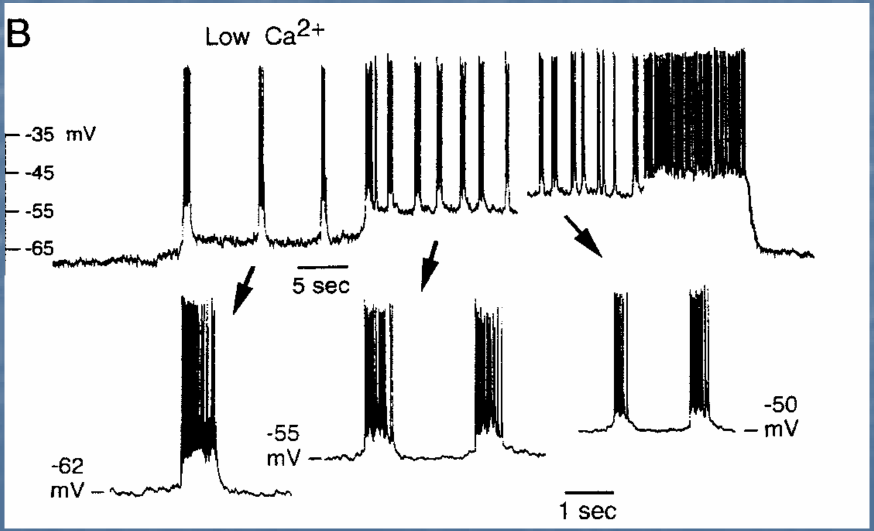


Carlson
Figure 2.17

Nerve Cells Often Burst

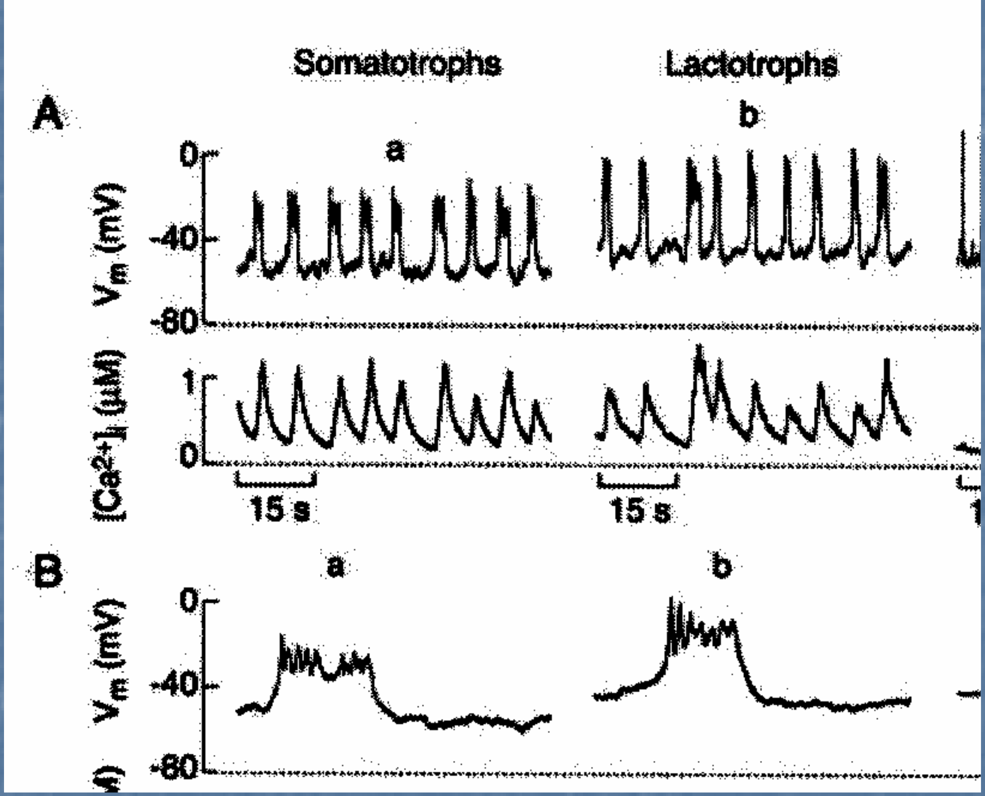


Neuron L3 of the Aplysia abdominal ganglion (Pinsker, J. Neurosci., 40:527, 1977)



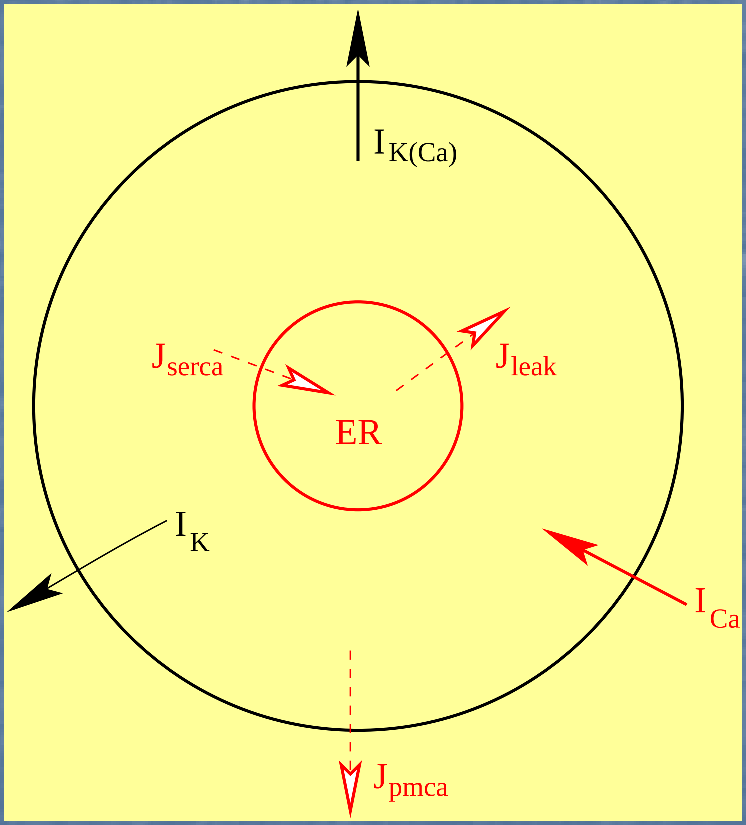
Neuron from the pre-Botzinger complex (Butera et al, J. Neurophysiol, 81:382, 1999)

Pituitary Cells Also Burst



Bursting in isolated cells (Van Goor et al, J. Biol. Chem., 276:33840, 2001)

What Clusters Spikes into Bursts?



$$\dot{c} = f\,(J_{leak} - J_{serca} - \alpha I_{Ca} - k_c c)$$
$$\dot{c}_{ER} = f_{ER}\left(V_{cyt}/V_{ER}\right)(J_{serca} - J_{leak})$$

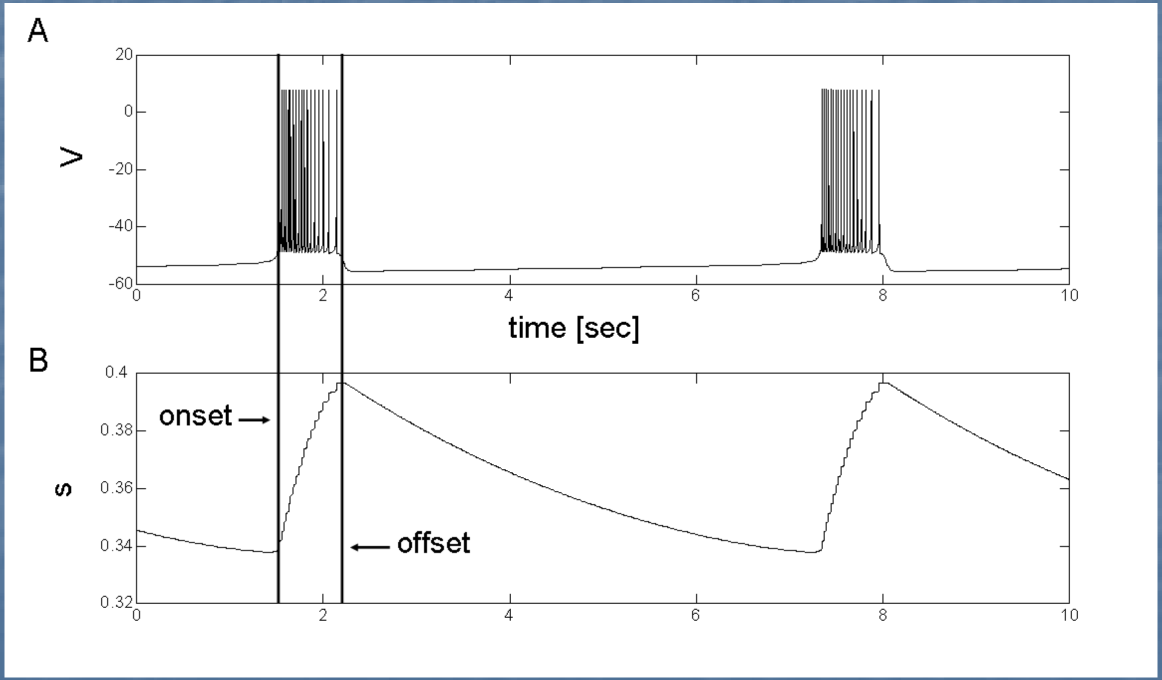
C = free calcium concentration in the cytosol

C_{ER} = free calcium concentration in the Endoplasmic Reticulum (ER)

Cytosolic calcium feeds back onto the membrane through $I_{K(Ca)}$

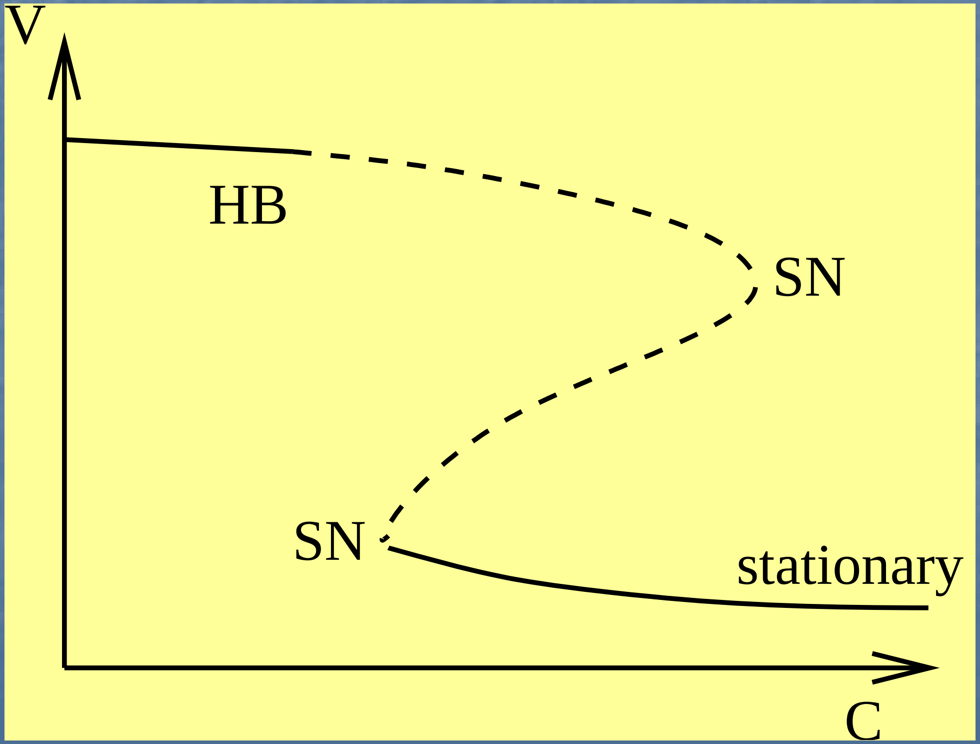
What Clusters Spikes into Bursts?

Calcium (called "s" below) builds up and activates the K(Ca) current, shutting off the spiking. When calcium recovers to a low level spiking restarts.



Fast/Slow Analysis of Bursting

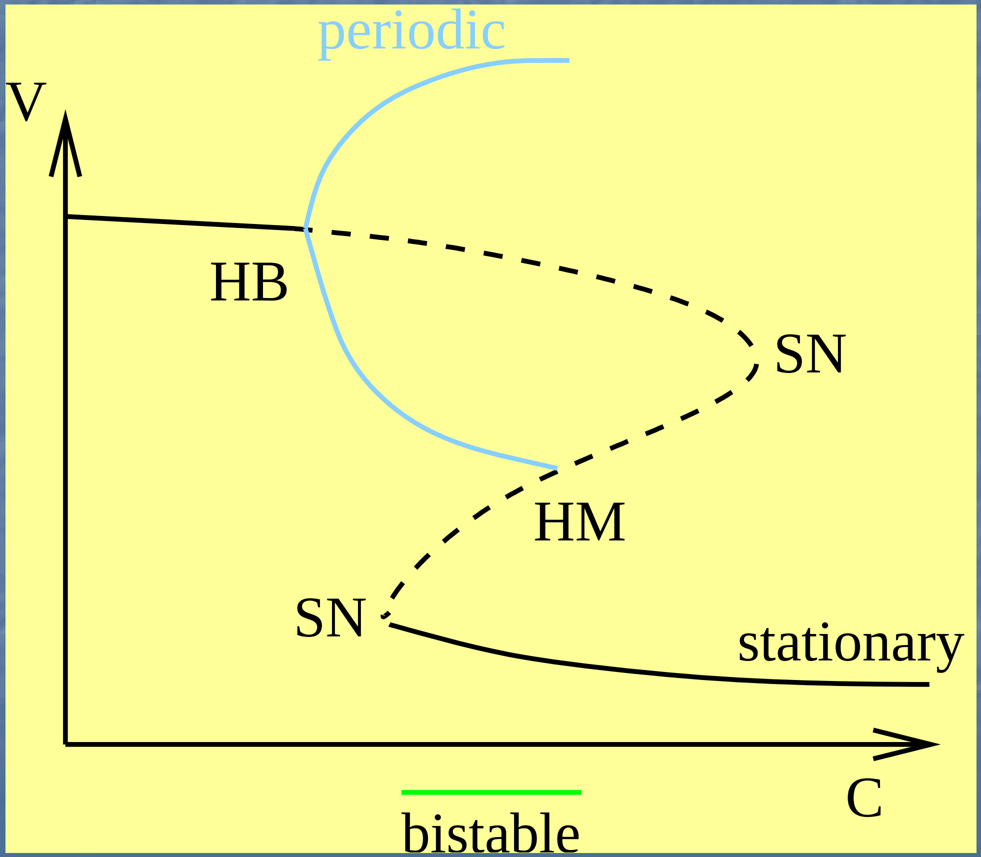
Variables can be separated into those that change rapidly and those that change slowly. In this case, there is only one slow variable (calcium, C). The slow variable is then treated as a bifurcation parameter for the fast subsystem.



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

Spiking Solutions

Next, the branch of periodic spiking solutions is added.

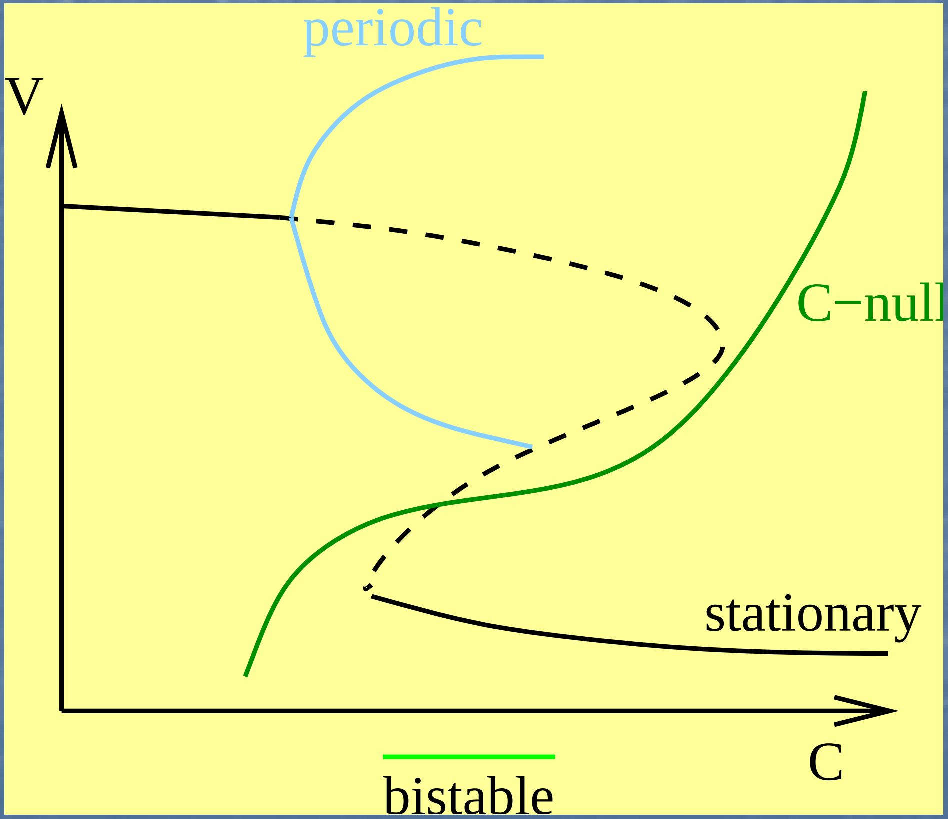


Blue curves = min and max of the periodic spiking solutions

IMPORTANT: The fast subsystem is bistable.

Slow Variable Dynamics

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



The C-nullcline is the curve where

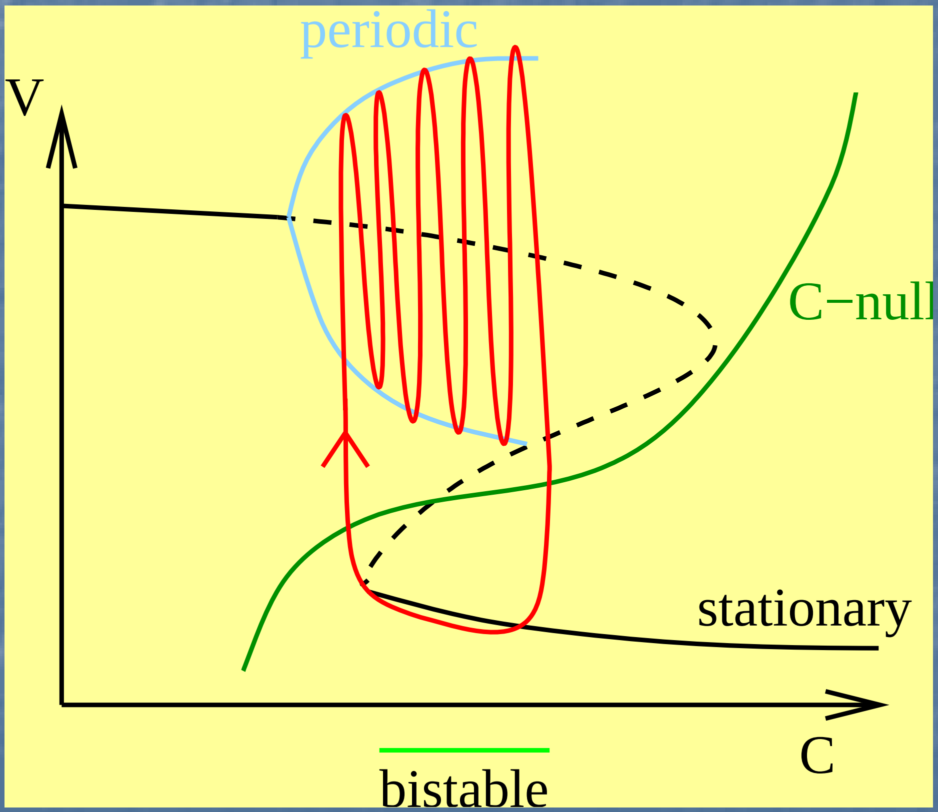
$$\frac{dC}{dt} = 0$$

Below the nullcline

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

Superimpose Trajectory

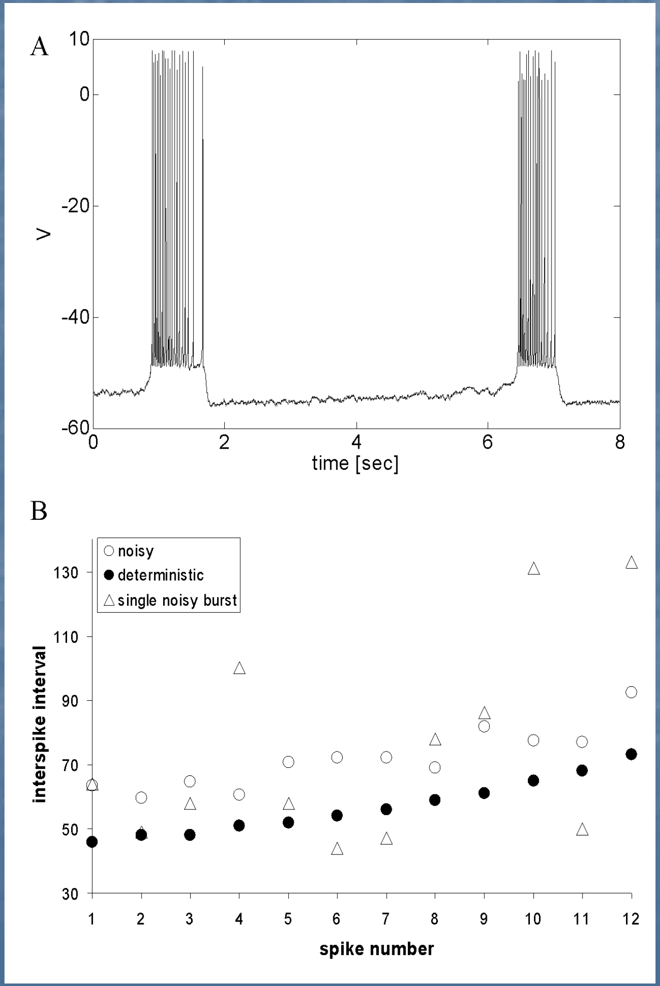
Finally, we superimpose the burst trajectory.



Red curve = trajectory of the bursting oscillation

Interspike Interval Increases for Type 1 Bursting

This bursting is called type 1 or square wave bursting. A feature of this type is that the interspike interval increases during the burst. But this feature is largely lost if the system is noisy.

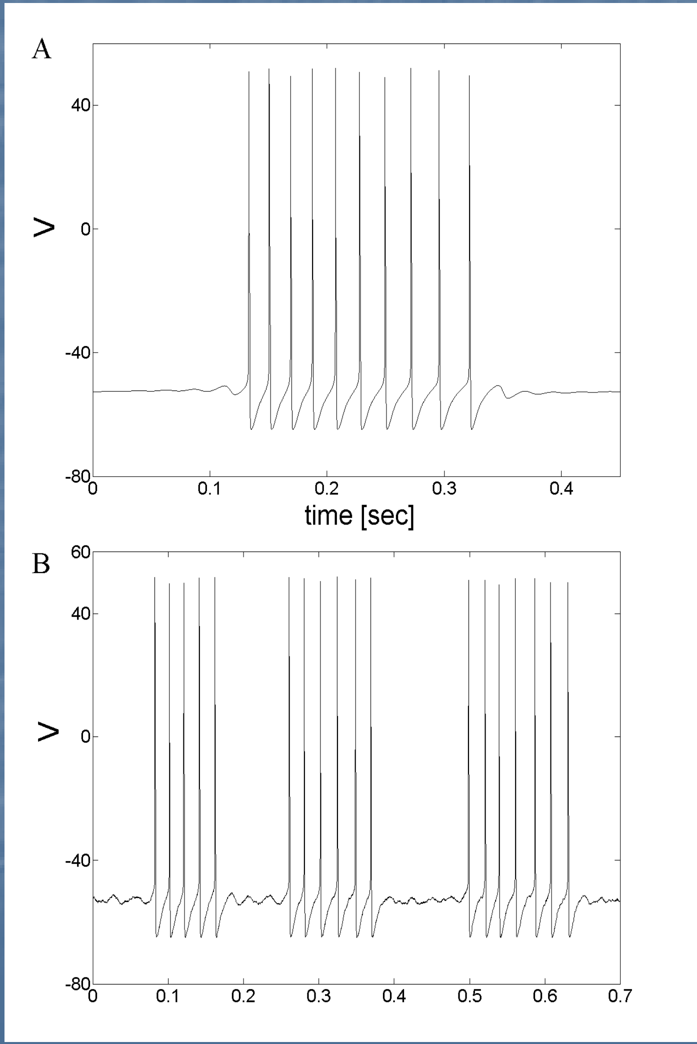


Type 3 Bursting

This type of bursting exhibits subthreshold oscillations immediately before and after each burst. These oscillations are largely obscured by noise.

No Noise

With Noise



Noise is Bad, and Ubiquitous

Noise makes it hard to distinguish between these two types of bursting.

Unfortunately, all neural systems are noisy.

Goal: Use Noise to our Advantage

How?

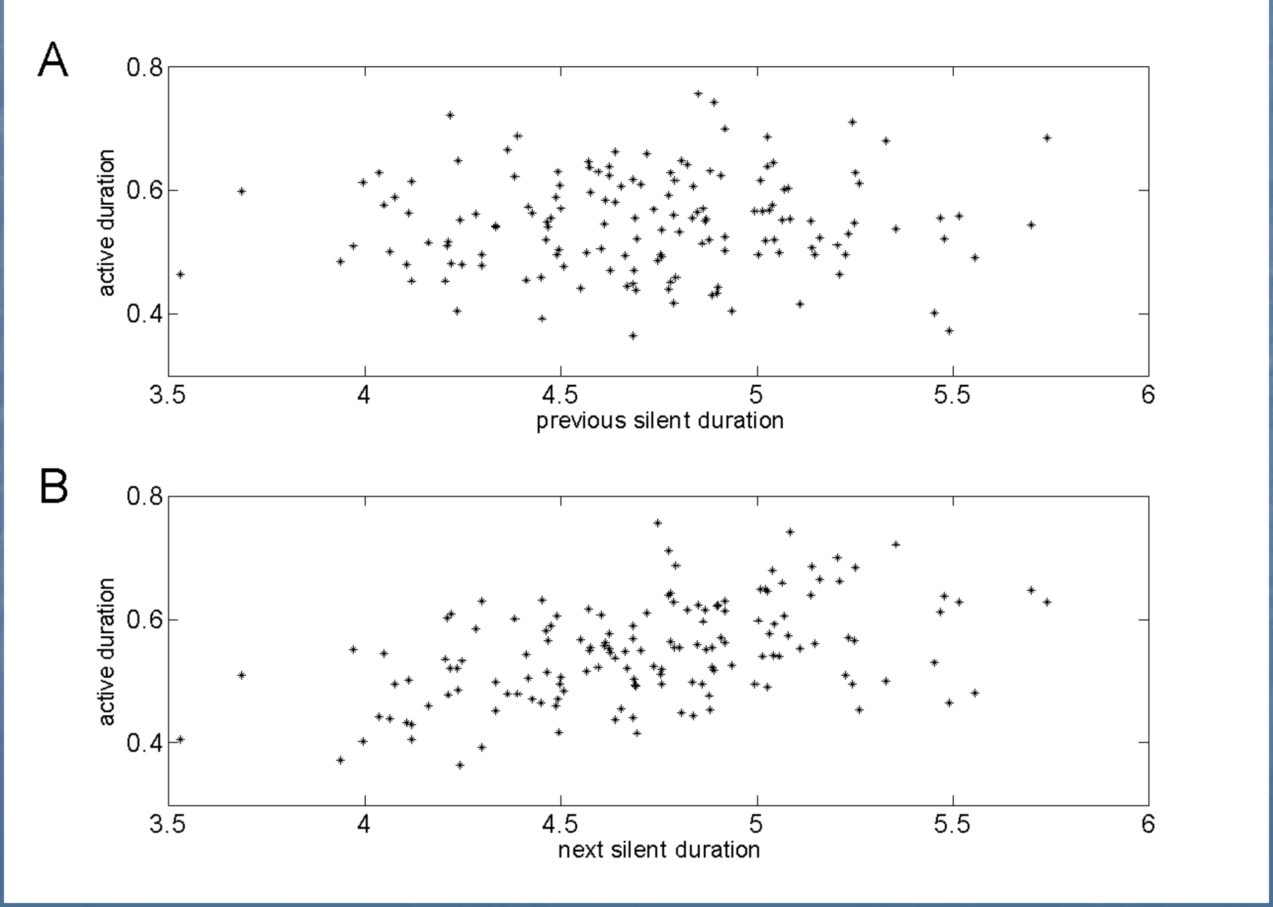
Idea: Maybe noise affects the initiation and the termination of a burst differently.

Active/Silent Phase Scatter Plots

Type 1 Bursting Model

No correlation
r=0.4, p=0.62

Significant correlation
r=0.47, p<0.005

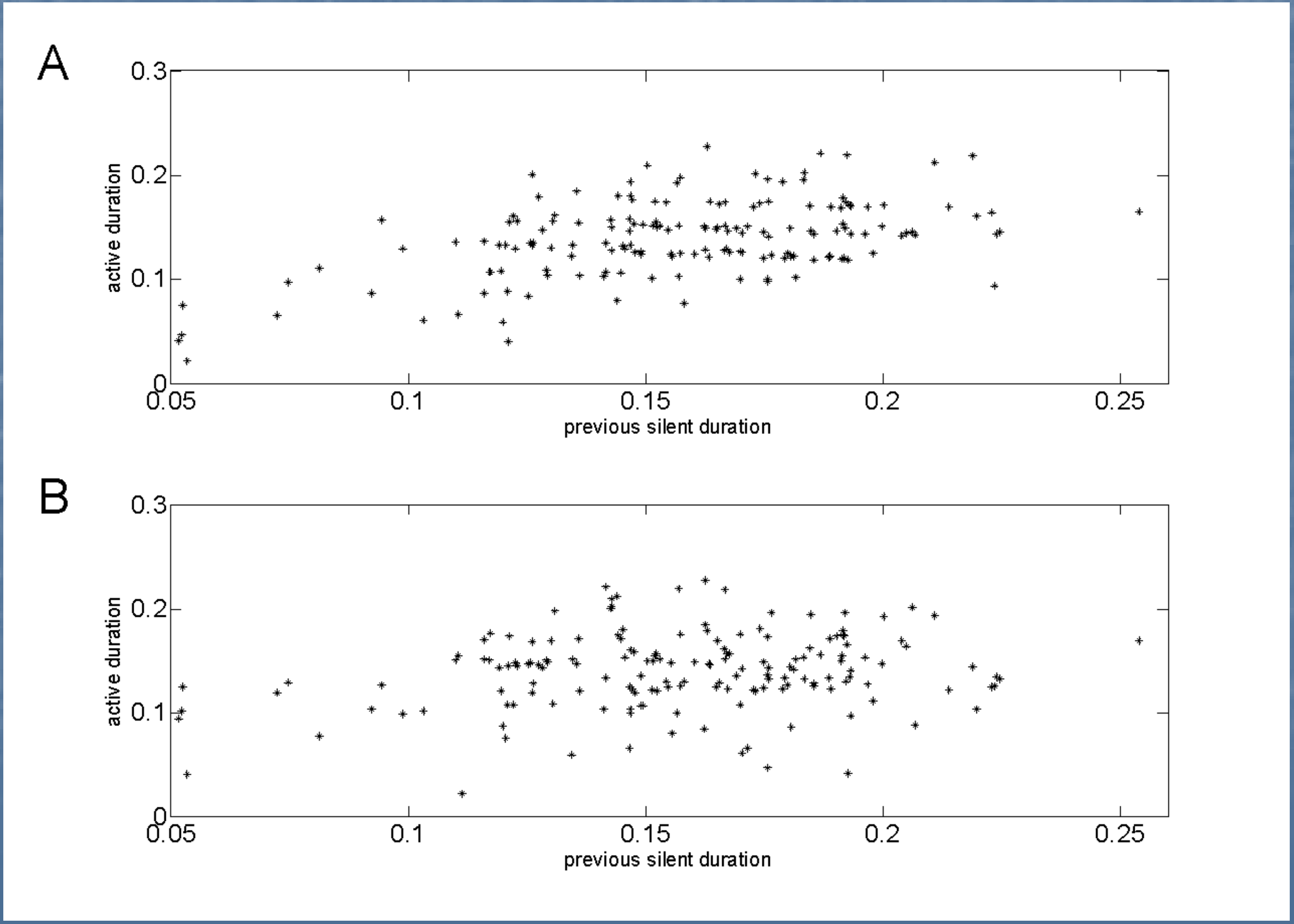


Active/Silent Phase Scatter Plots

Type 3 Bursting Model

Significant correlation
r=0.40, p<0.005

No Correlation
r=0.19, p=0.015



Noise is Good, and Ubiquitous

In the presence of noise, one can use scatter plots of active/silent phase durations to distinguish type 1 from type 3 bursting. This only requires the voltage trace, so is very applicable in an experimental setting.

All neural systems are noisy!

Why the Difference in Correlation Patterns

Type 1 bursting: burst starts at saddle node bifurcation
burst ends at homoclinic bifurcation

Homoclinic bifurcations are more sensitive to noise, so active phase duration is more variable than silent phase duration

Type 3 bursting: burst starts at subcritical Hopf bifurcation
burst ends at saddle node of periodics bifurcation

Subcritical Hopfs are more sensitive to noise, so silent phase duration is more variable than active phase duration

These differences yield the differences in correlation patterns

That’s all folks!