Mixed Mode Oscillations as a Mechanism for Pseudo-Plateau Bursting

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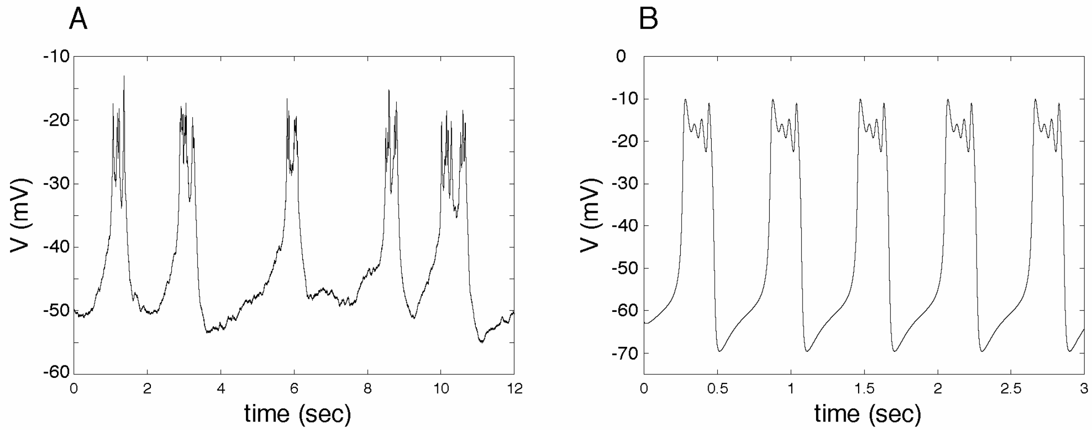
Central Aim

Understand the dynamics of a novel form of bursting in a model for excitable endocrine cells

Pseudo-Plateau Bursting Often Occurs in Endocrine Cells

Perforated patch recording
from a GH4 pituitary cell line



Simulation from a mathematical
model (Toporikova et al., 2008)

There are Several Models That Produce Pseudo-Plateau Bursting

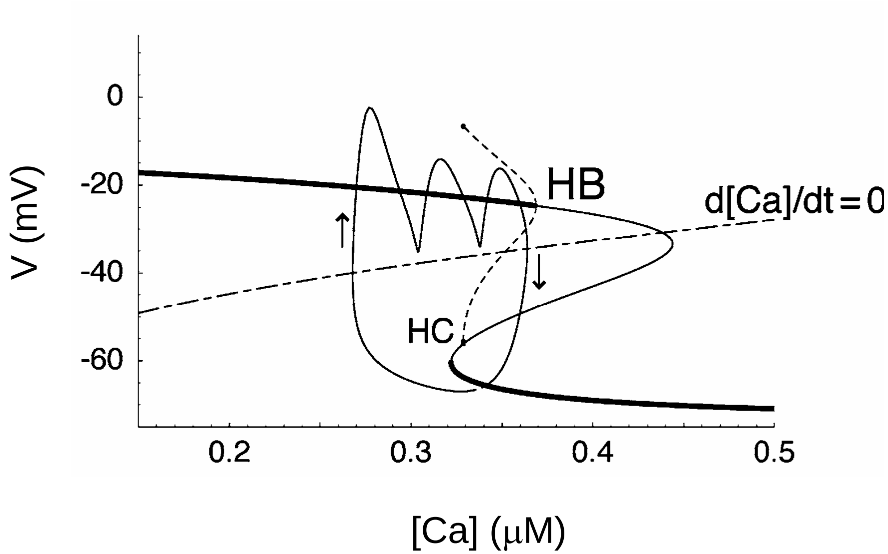
Lactotrophs: Tabak et al., J. Comput. Neurosci., 2007
Toporikova et al., Neural Computation, 2008

Somatotrophs: Tsaneva-Atanasova et al., J. Neurophysiol., 2007

Corticotrophs: LeBeau et al., J. Theoretical Biology, 1998
Shorten et al., J. Theoretical Biology, 2000

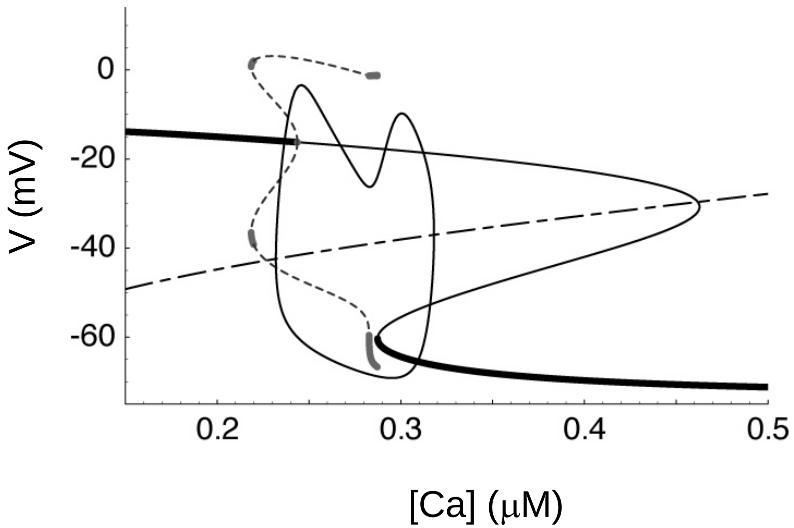
Single β-Cells: Zhang et al., Biophysical J., 2003

Typical Pseudo-Plateau Fast-Subsystem Bifurcation Structure



Unlike square-wave bursting (plateau bursting), the top branch of the z-curve is stabilized; there is no stable spiking branch.

One Form of Pseudo-Plateau Bursting has a Different Structure



What is the mechanism of this bursting oscillation?

The Mathematical Model

Calcium concentration has been removed; not necessary for the bursting.

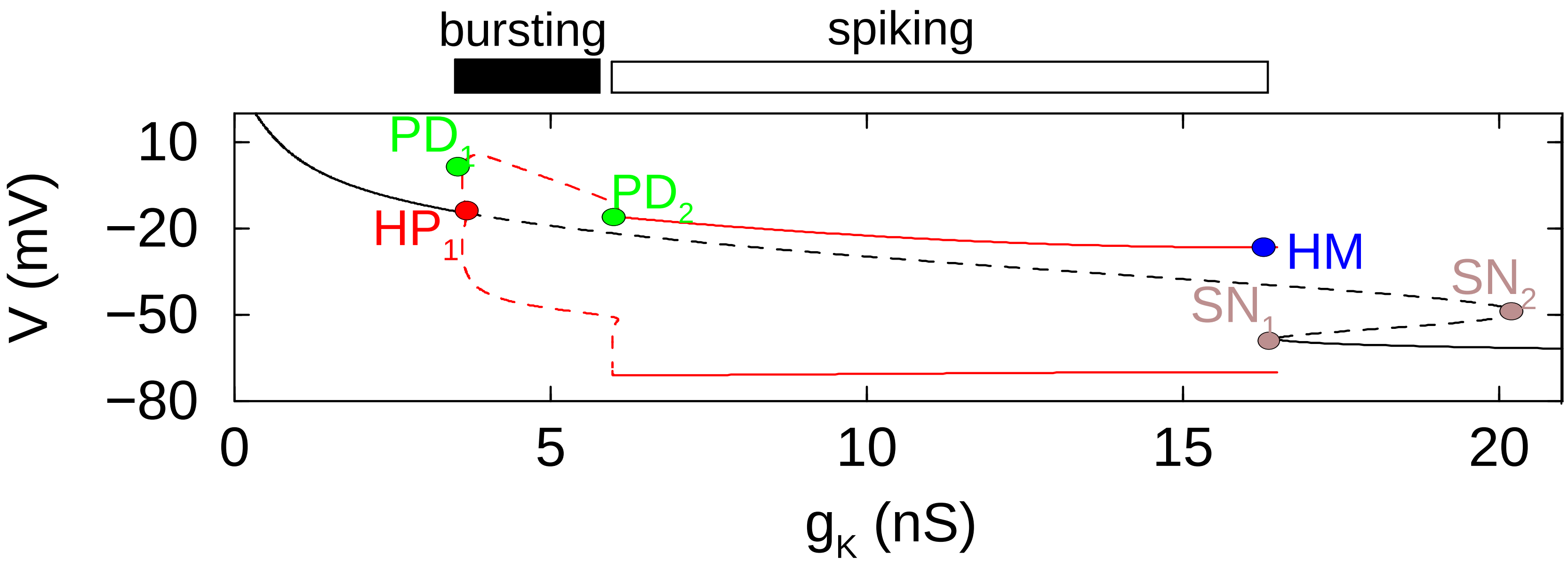
$$C\frac{dV}{dt} = g_{Ca}m_{\infty}(V)(V_{Ca} - V) + g_K n(V_K - V) + g_A a_{\infty}(V)e(V_K - V) + g_L(V_K - V)$$

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

$$\tau_e \frac{de}{dt} = e_{\infty}(V) - e$$

The *n* and *e* variables change on a slower time scale than *V*. There are 2 slow variables and 1 fast variable.

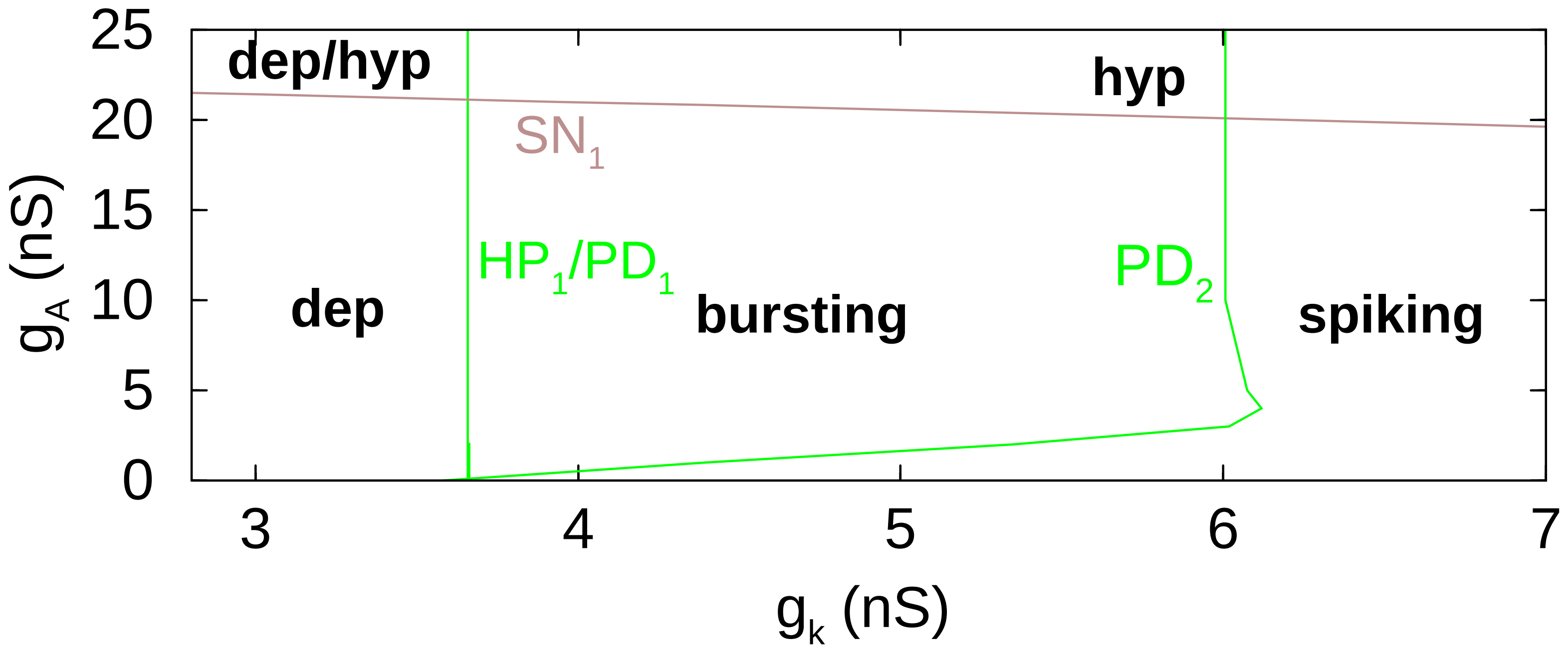
Bursting Occurs Over a Range of g_K Values



Black = stationary

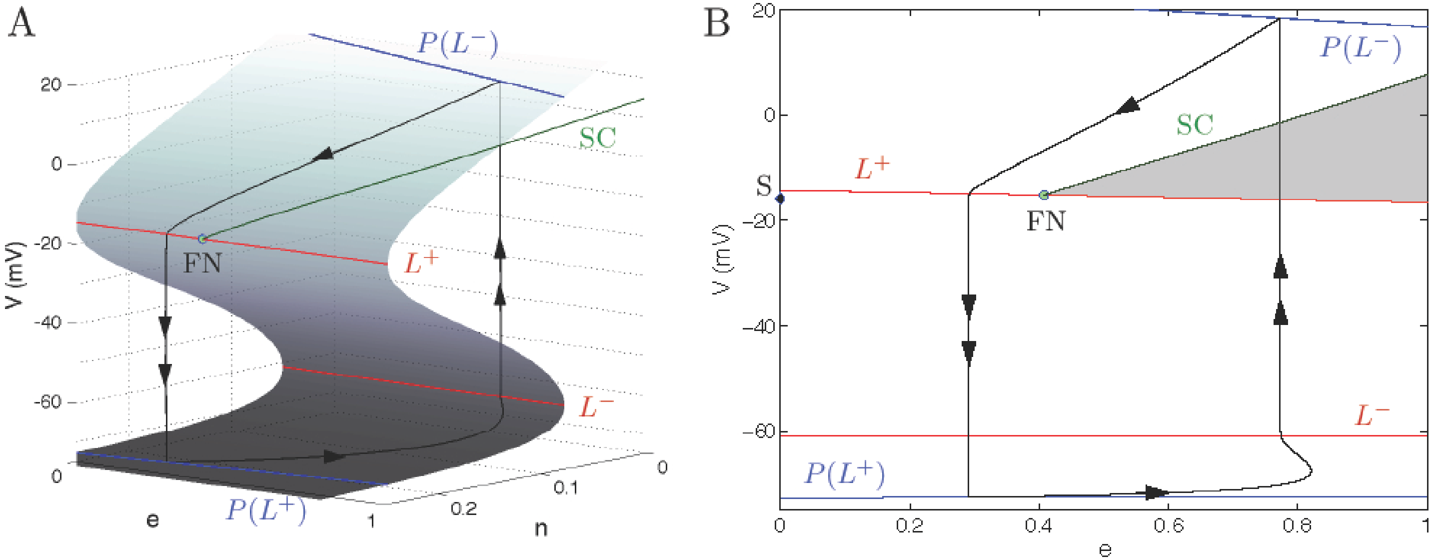
Red = periodic (spiking)

Bursting Occurs in a Region of the g_K-g_A Parameter Space



Parameters are the maximum conductances corresponding to the two slow variables.

Mechanism of Bursting: Go to the Singular Limit ($C \rightarrow 0$)



Parameters set to produce **spiking**.

The spiking solution becomes a relaxation oscillation on the critical manifold; this is the quasi-equilibrium surface for the V variable.

The Reduced and Desingularized Systems

Goal: Derive equations for the flow on the critical manifold.

RHS of V-ODE: $$f(V,e,n) \equiv -(I_{Ca} + I_K + I_A + I_L)$$

Critical manifold: $$S \equiv \{(V,e,n) \in \Re^3 : f(V,e,n) = 0\}$$

Dynamics on S: $$\frac{d}{dt} f(V,e,n) = \frac{d}{dt} 0$$

Reduced system: $$-\frac{\partial f}{\partial V}\frac{dV}{dt} = \left(\frac{e_\infty - e}{\tau_e}\right)\frac{\partial f}{\partial e} + \left(\frac{n_\infty - n}{\tau_n}\right)\frac{\partial f}{\partial n}$$ with $n = n(e,V)$

=0 on folds

$$\frac{de}{dt} = \left(\frac{e_\infty(V) - e}{\tau_e}\right)$$

Desingularized system: $$\frac{dV}{d\tau} = \left(\frac{e_\infty - e}{\tau_e}\right)\frac{\partial f}{\partial e} + \left(\frac{n_\infty - n}{\tau_n}\right)\frac{\partial f}{\partial n} \equiv F(V,e,n)$$ with $\tau \equiv -\left(\frac{\partial f}{\partial V}\right)^{-1} t$

$$\frac{de}{d\tau} = -\left(\frac{e_\infty - e}{\tau_e}\right)\frac{\partial f}{\partial V}$$

Folded Singularity

A **folded singularity** of the reduced system is an equilibrium of the desingularized system that occurs on a fold curve, and satisfies

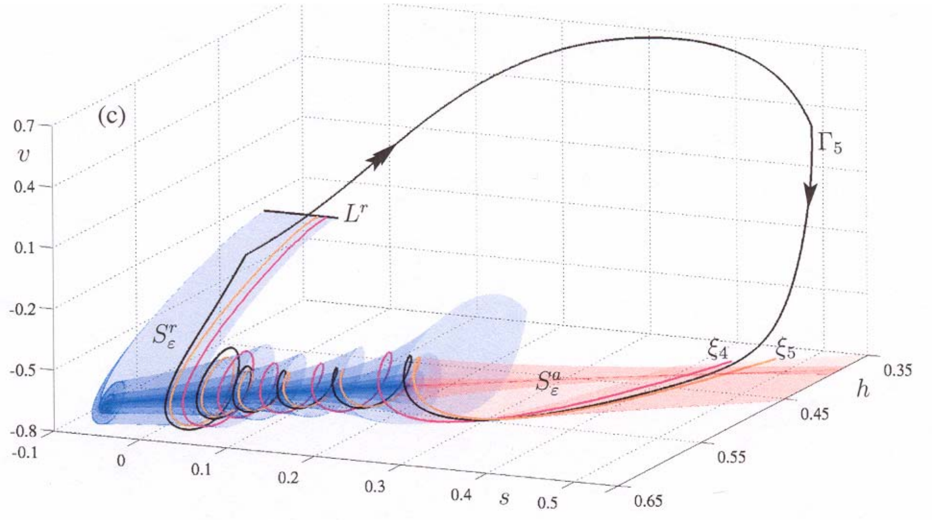
$$f(V,e,n)=0$$ on the critical manifold

$$F(V,e,n)=0$$ *V* time derivative is 0 in desingularized system

$$\frac{\partial f}{\partial V}=0$$ on a fold curve of *S*

Folded Node Singularity

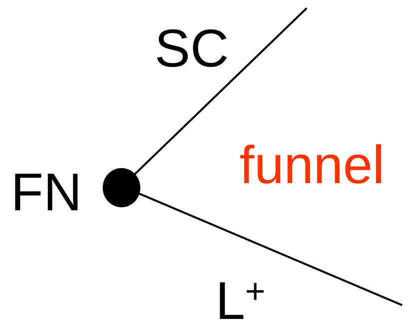
A **folded node singularity (FN)** is a folded singularity with negative real eigenvalues. For small values of *C* (large, but not infinite, time scale separation) the slow manifold is twisted in the neighborhood of the FN.



From Desroches et al., Chaos, v. 18, 2008

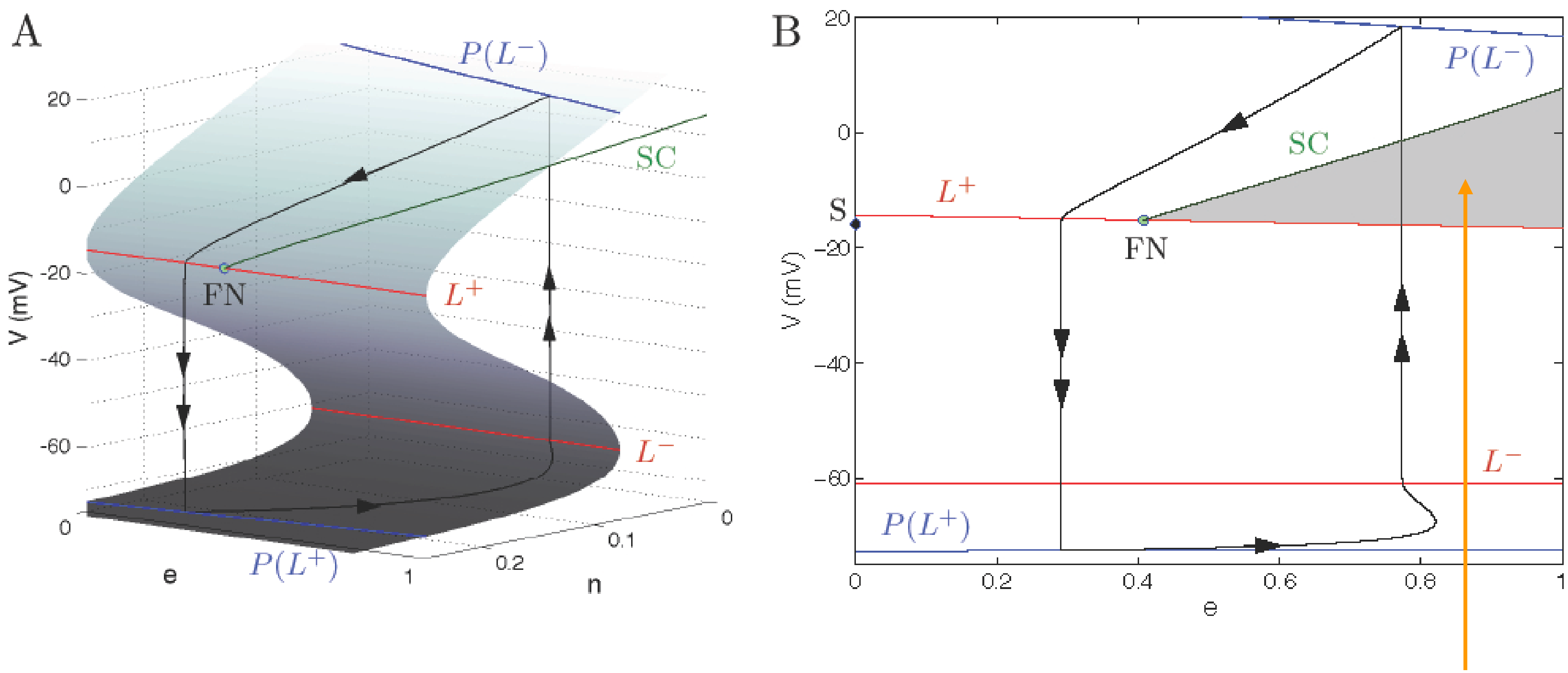
The Singular Funnel

The **singular funnel** of a folded node is delimited by the fold curve (*L^+*) and the strong singular canard (SC). This is the trajectory that is tangent to the eigendirection of the strong eigenvalue of the FN.



In the singular limit, trajectories entering the funnel move through the FN in finite time and follow the middle sheet of *S* for some time. For small, but non-zero *C*, corresponding trajectories exhibit small oscillations due to the twisted slow manifold.

Relaxation Oscillations (Spiking) do not Enter the Singular Funnel

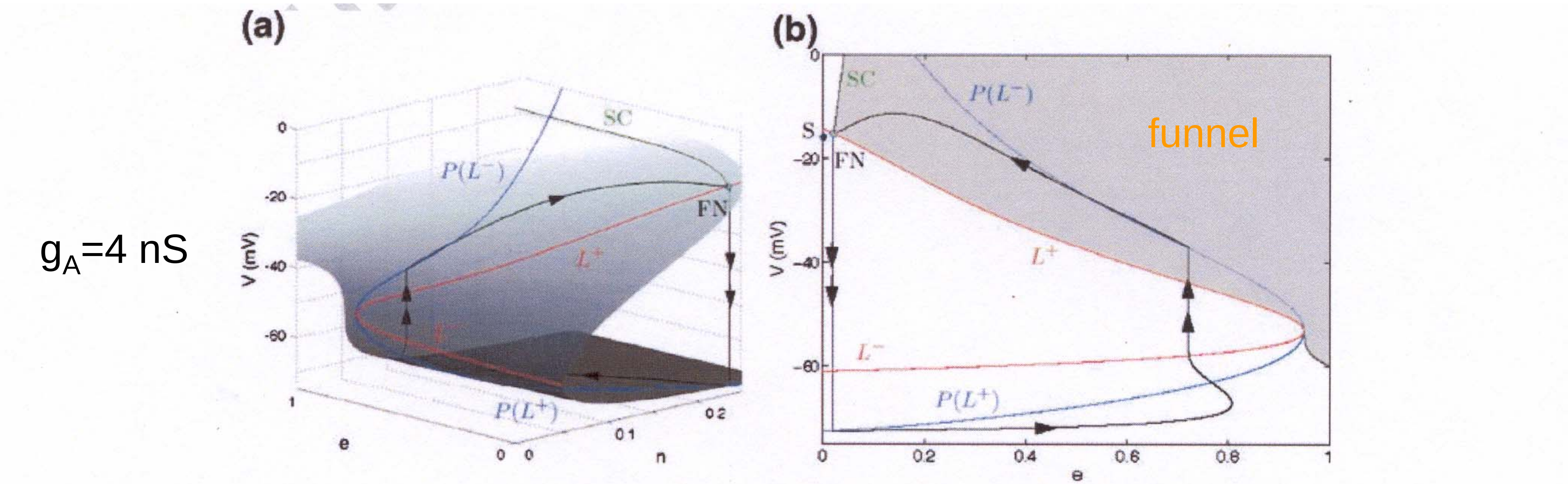


g_A=0.2 nS

funnel

Mixed-Mode Oscillations (Bursting) Enter the Singular Funnel

g_A=4 nS



For small *C*, the trajectory oscillates once it jumps up. The small oscillations in combination with the large jumps is a mixed-mode oscillation. The small oscillations are the "spikes" of the pseudo-plateau burst.

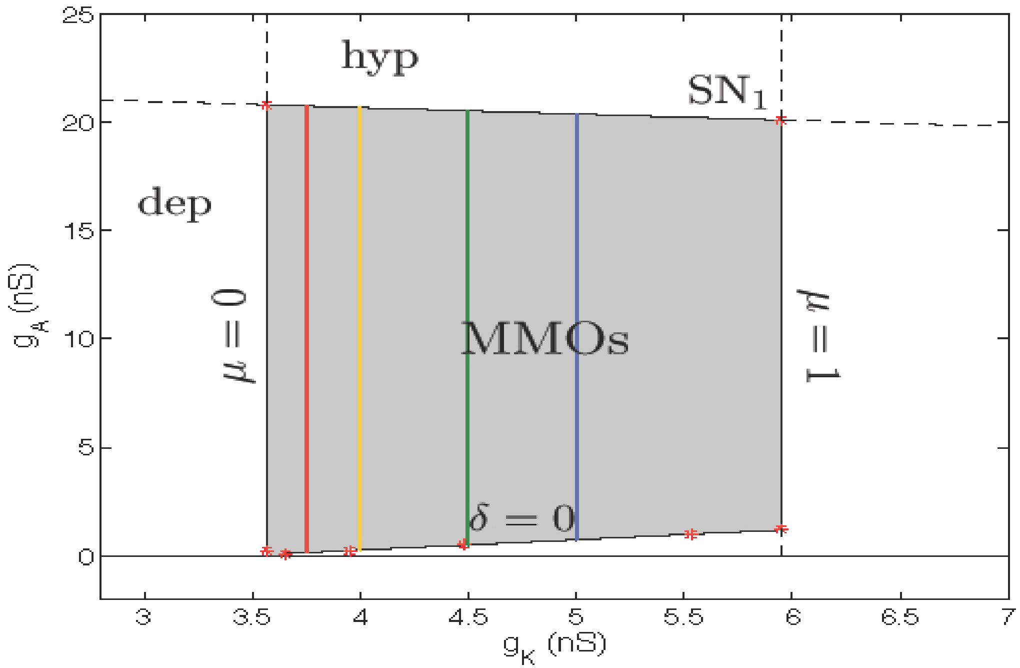
Canard Theory Provides the Bursting Borders

μ is eigenvalue ratio $\mu = \frac{\lambda_1}{\lambda_2} \in (0,1)$

$\mu = 0$

FN becomes a folded saddle, only one canard

For *C>0* this is a Hopf bifurcation



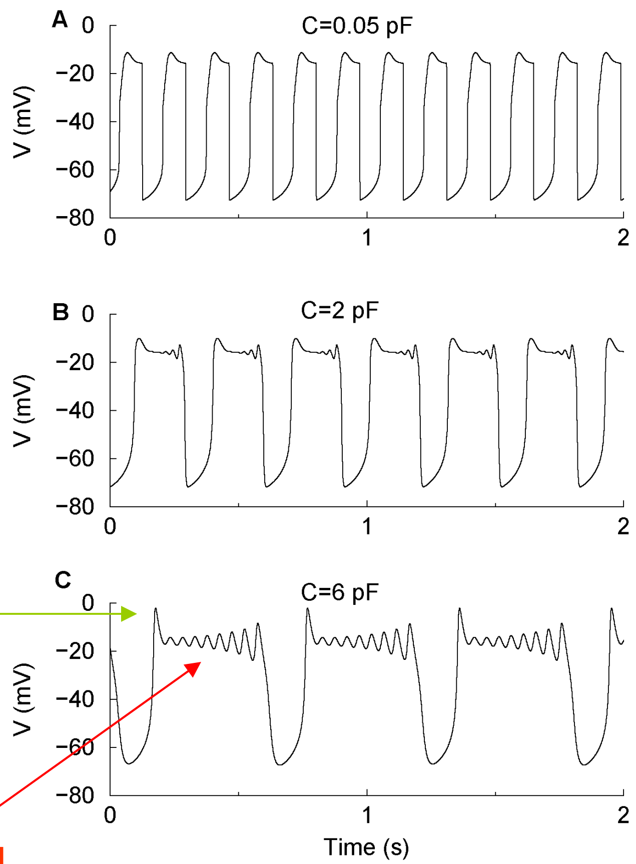
$\mu = 1$

Degenerate FN. To the right it becomes a folded focus, with no canards.

δ is the distance of the singular orbit from the SC, within the singular funnel. δ>0 in the MMO region.

Spikes Emerge as C is Increased

Due to jump up



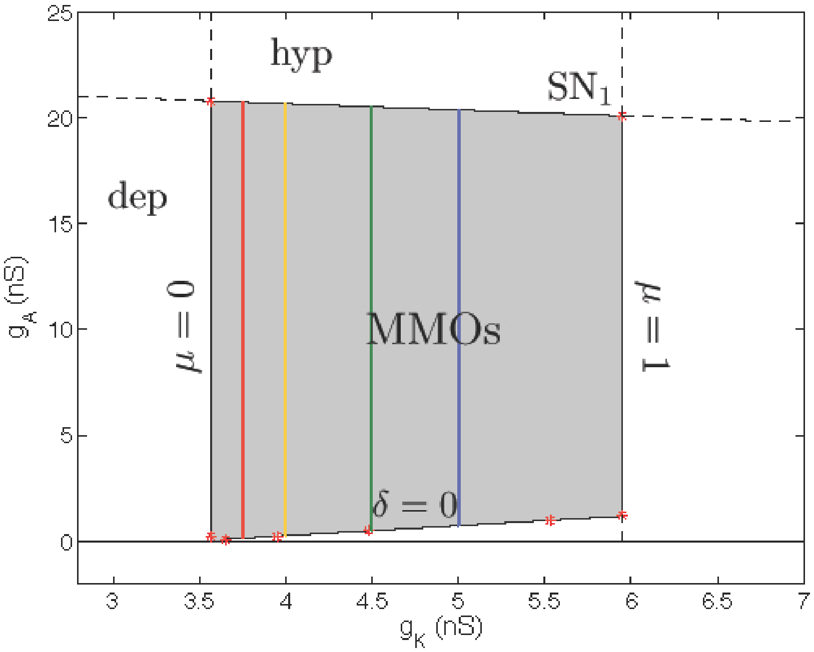
Due to the FN

Maximum Number of Small Oscillations is Given by a Formula

For *C* sufficiently small, $$s_{\max} = \left[\frac{\mu + 1}{2\mu} \right]$$

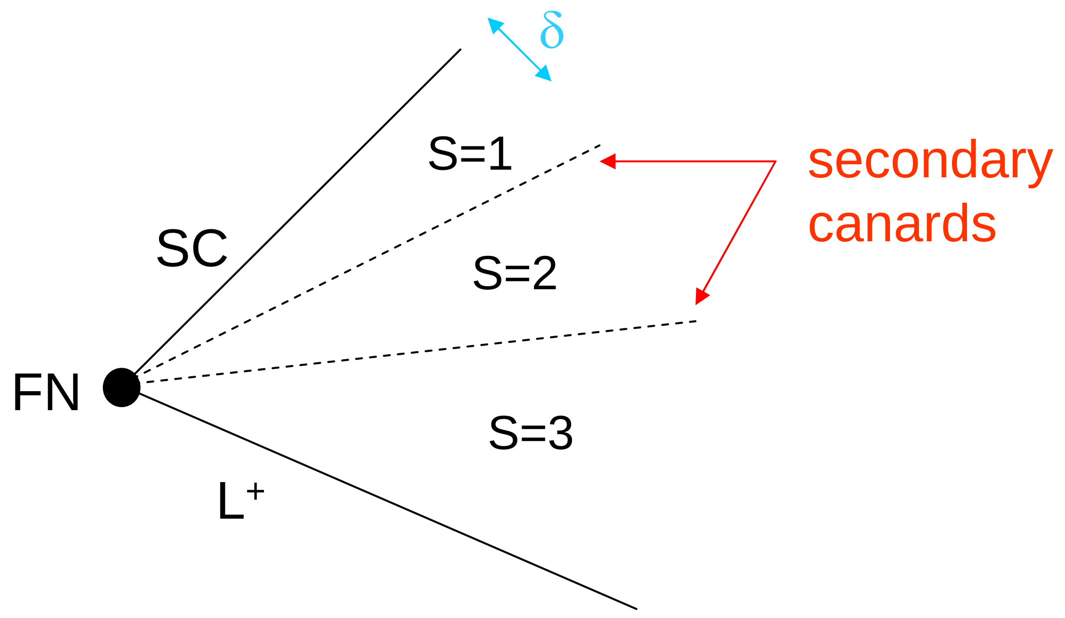
where [ ] is the greatest integer function. For derivation see Wechselberger, SIAM J. Dyn. Syst., 2005. This is insensitive to changes in g_A.

Blue: s_{max}=1
Green: s_{max}=2
Yellow: s_{max}=5
Red: s_{max}=12



Actual Number of Small Oscillations Determined by Where the Singular Trajectory Enters the Funnel

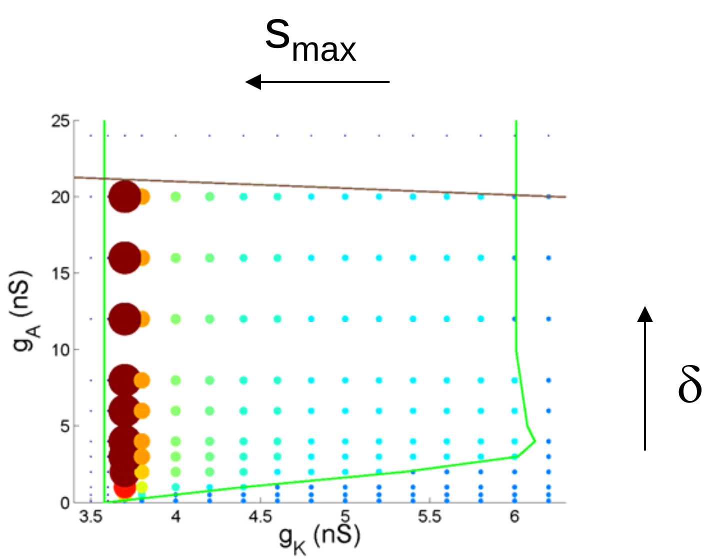
For *C* small and S_{max}=3:



Number of small oscillations increases with δ, the distance from the SC.

Numerical Simulation Agrees with the Canard Theory

Number of spikes per burst, with *C*=2 pF.



Small, dark blue = spiking
Small, light blue = burst with 2 spikes
Large, red = burst with 53 spikes

Thank You!

(Postdoc position available)