# Mixed Mode Oscillations Underlie Bursting in Pituitary Cells

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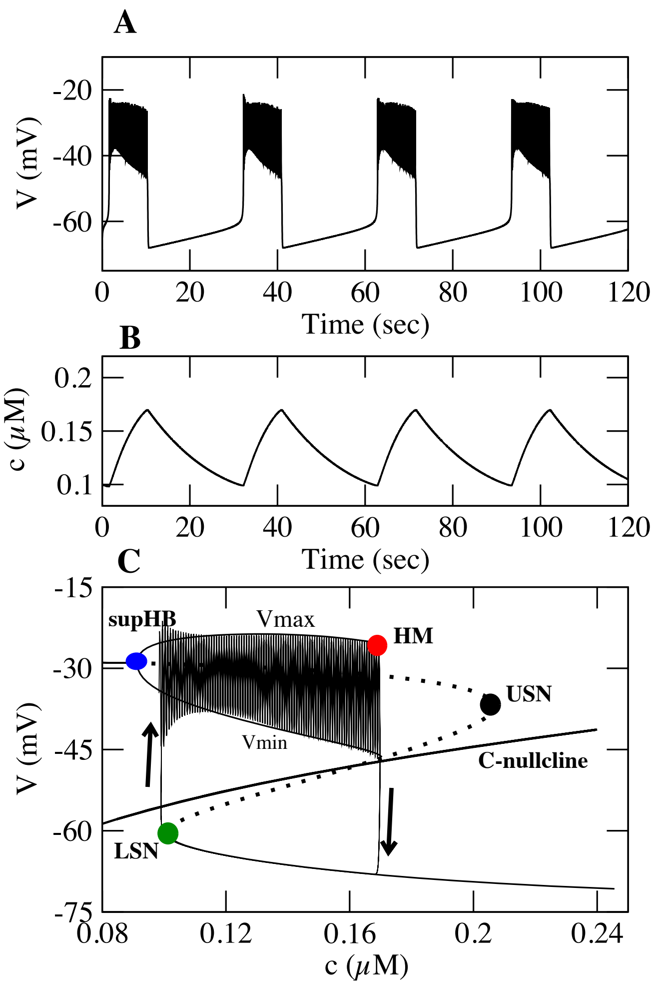
# Fast-Slow Analysis: a Powerful Tool for Understanding Plateau Bursting




$$\dot{V} = f(V, n, c)$$

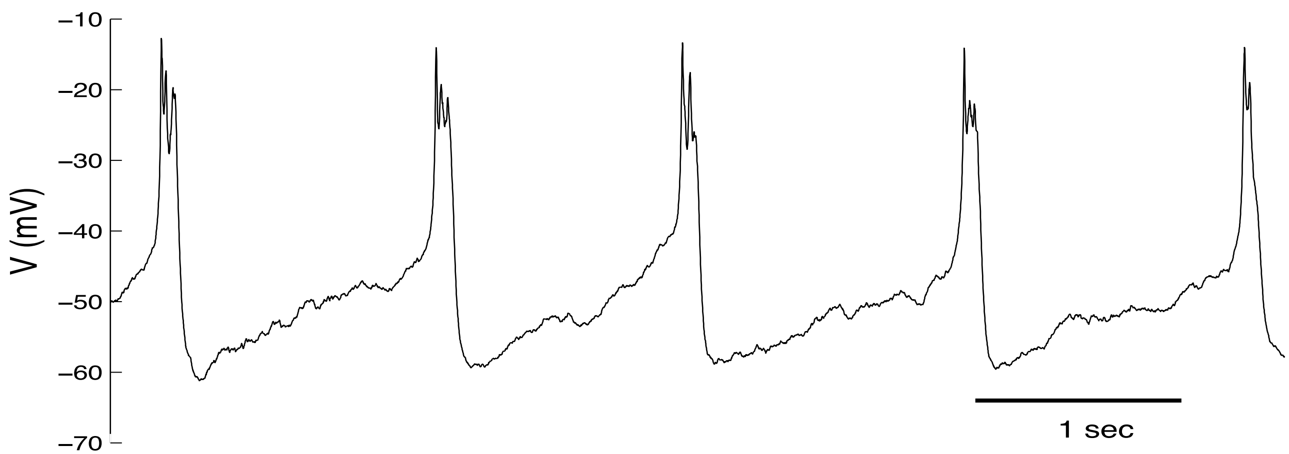
$$\dot{n} = g(V, n)$$

$$\dot{c} = \varepsilon h(V, c)$$

Analysis in the limit

$$\varepsilon \rightarrow 0$$

# Pseudo-Plateau Bursting Occurs in Some Pituitary Cells

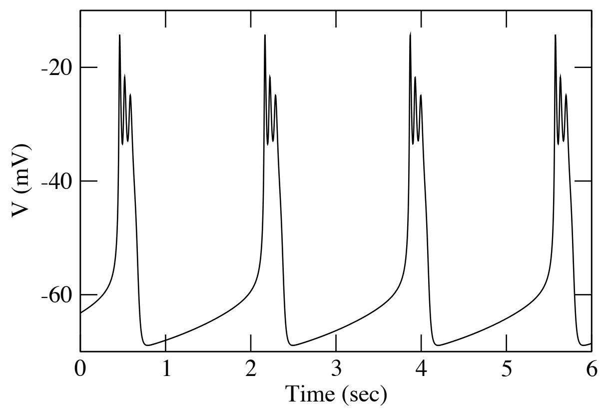


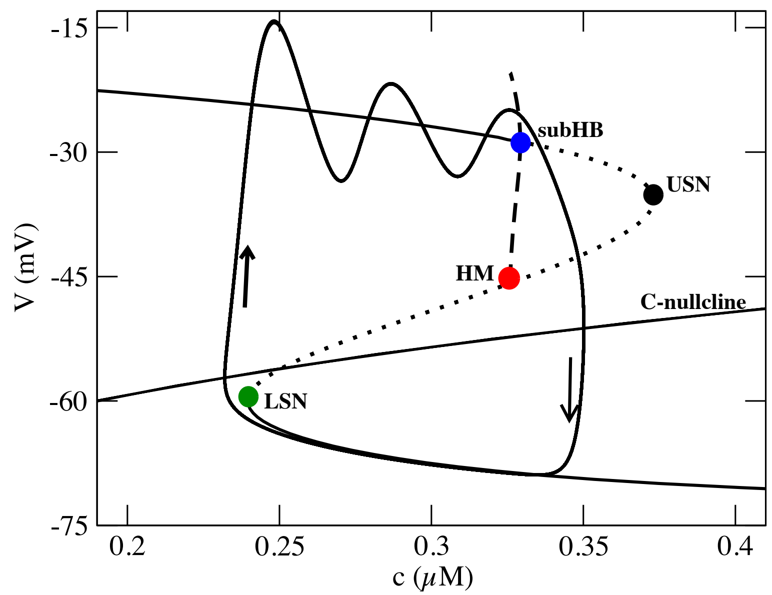

Electrical recording from a GH4 pituitary cell line

Bursts are short and the spikes have very small amplitude.

Characteristic of bursting in pituitary lactotrophs and somatotrophs

# Pseudo-Plateau Bursting Presents New Challenges




Trajectory does not follow the z-curve, and
there is no periodic spiking branch!

# An Alternate Approach

$$\varepsilon \dot{V} = f(V, n, c)$$

$$\dot{n} = g(V, n)$$

$$\dot{c} = h(V, c)$$

Analyze the reduced system obtained in the limit $\varepsilon \to 0$

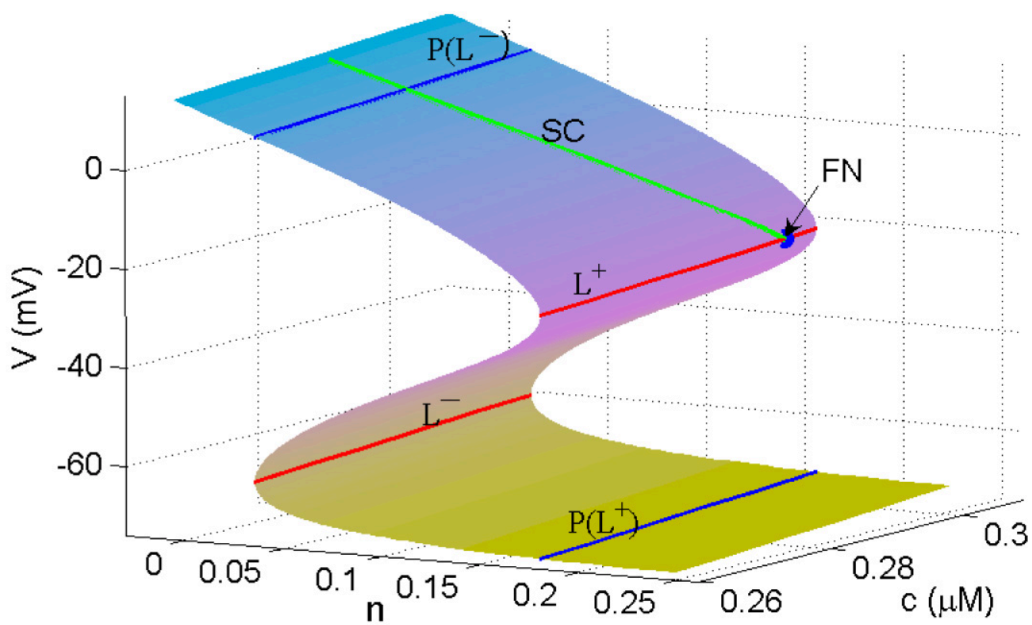
Voltage V is in a state of quasi-equilibrium with *n* and *c*

# The Critical Manifold

Surface in 3-space where V is at quasi-equilibrium

RHS of V-ODE: $f(V,n,c) \equiv -(I_{Ca} + I_K + I_{SK} + I_{BK})$

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



# The Reduced and Desingularized Systems

RHS of V-ODE: $$f(V,n,c) \equiv -(I_{Ca} + I_K + I_{SK} + I_{BK})$$

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

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

$\frac{dn}{dt}$ $\frac{dc}{dt}$

Reduced system: $$-\frac{\partial f}{\partial V}\frac{dV}{dt} = g(V,n)\frac{\partial f}{\partial n} + h(V,c)\frac{\partial f}{\partial c}$$

$$\frac{dc}{dt} = h(V,c)$$

=0 on folds

With *n* satisfying

$$f(V,n,c) = 0$$

Desingularized system: $$\frac{dV}{d\tau} = g(V,n)\frac{\partial f}{\partial n} + h(V,c)\frac{\partial f}{\partial c} \equiv F(V,n,c)$$

$$\frac{dc}{d\tau} = -h(V,c)\frac{\partial f}{\partial V}$$

with $\tau \equiv -\left(\frac{\partial f}{\partial V}\right)^{-1} t$

# Equilibria of the Desingularized System

Equilibrium Conditions

$$\frac{dV}{d\tau} = F(V,n,c) = 0 \qquad \frac{dc}{d\tau} = -h(V,c)\frac{\partial f}{\partial V} = 0$$

Regular Singularity

$$g(V,n) = 0$$
$$h(V,c) = 0$$

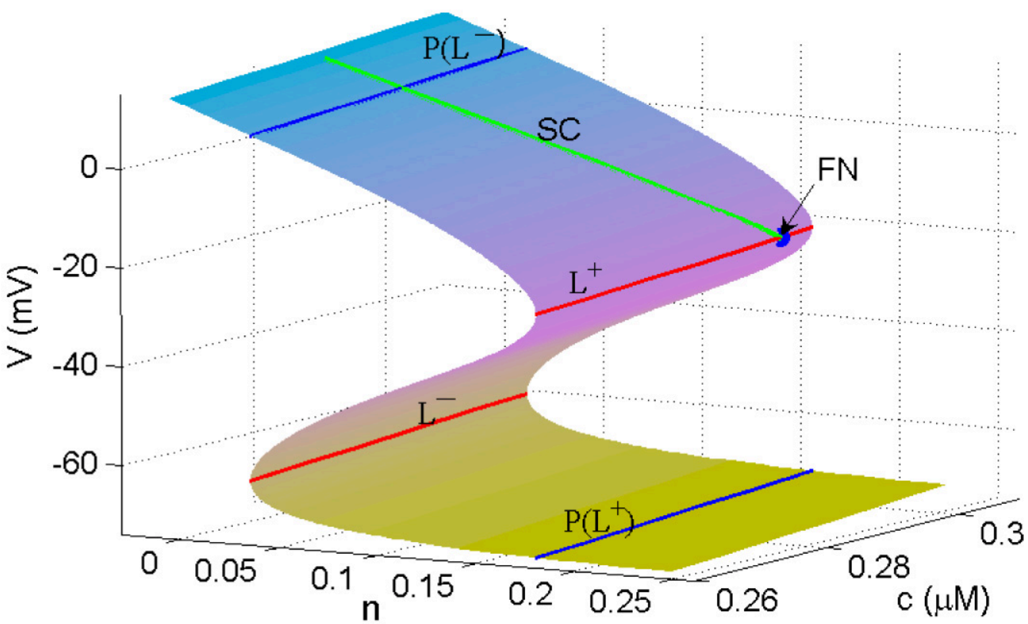
Folded Singularity

$$\frac{\partial f}{\partial V} = 0$$

(On a fold curve of S)

Folded Node: A folded singularity with two real eigenvalues

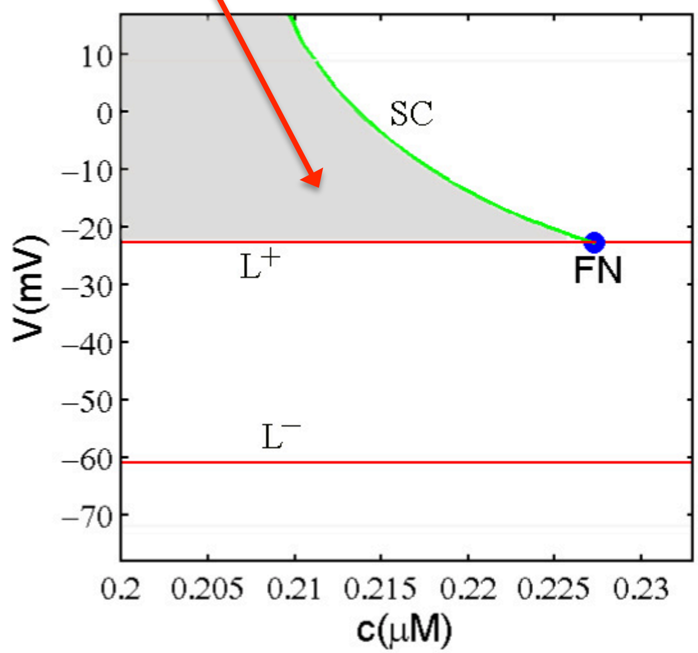
# There is a Folded Node on the Top Fold Curve



# Singular Canards

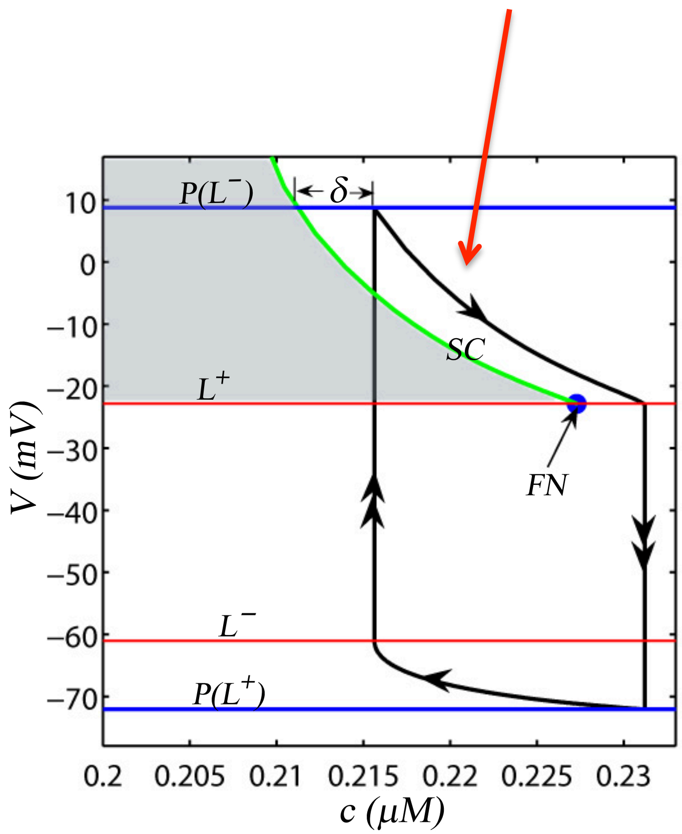
An entire sector of singular canards enter the folded node (FN) from the top (attracting) sheet and travel for some distance along middle (repelling) sheet.

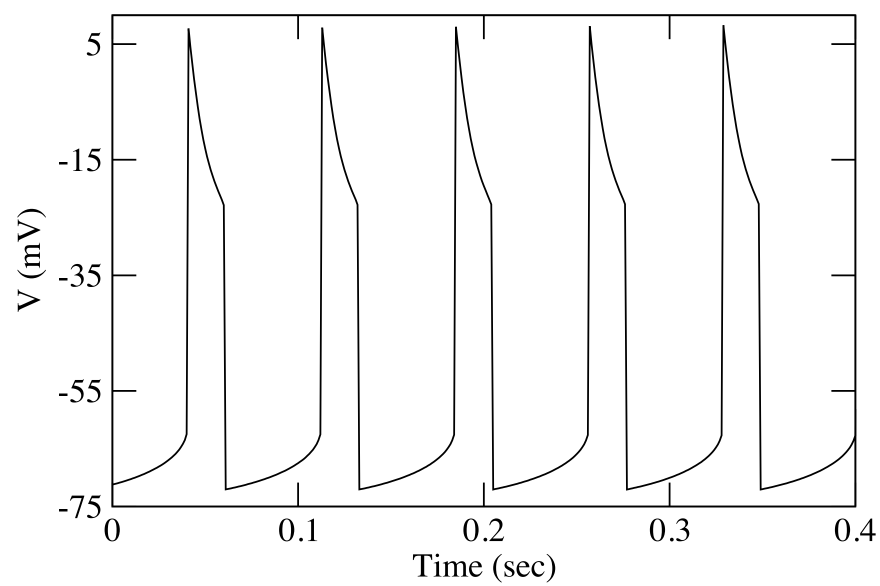
This sector is the Singular Funnel, delimited by the fold curve $L^+$ and the Strong Canard (SC).



# Relaxation Oscillations

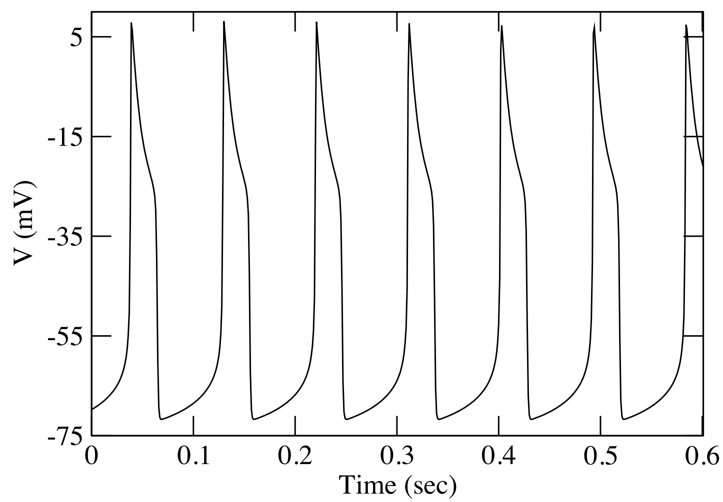
These are periodic solutions that do not enter the singular funnel.



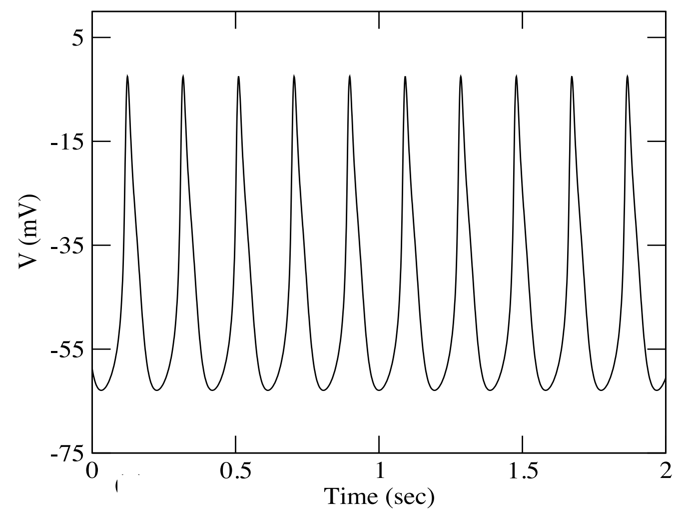



# Continuous Spiking

For ε away from 0, the relaxation oscillations transform into a continuous train of impulses.




$C_m$=0.5 pF

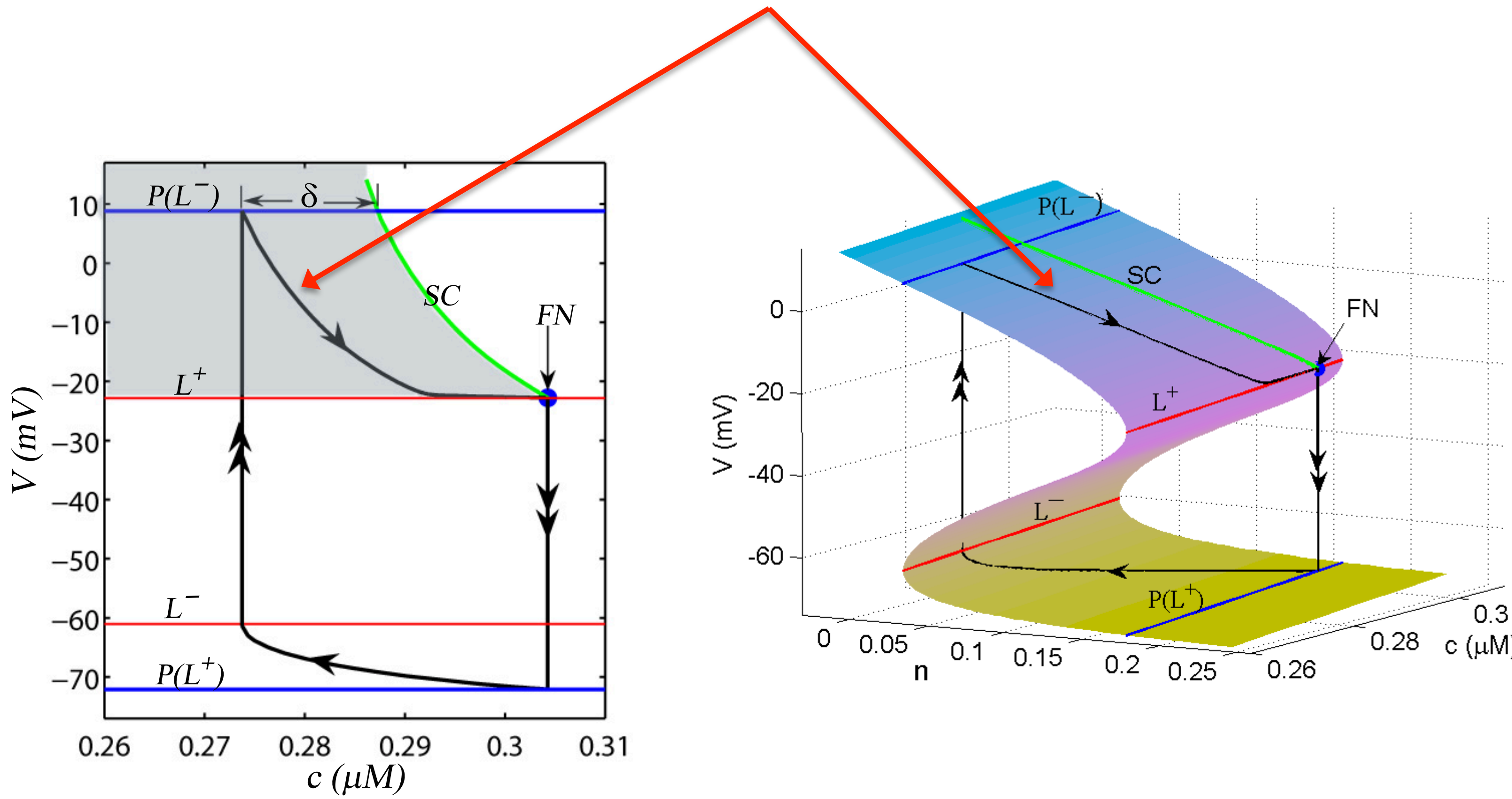



$C_m$=10 pF

$C_m \approx 5$ pF in lactotrophs/somatotrophs

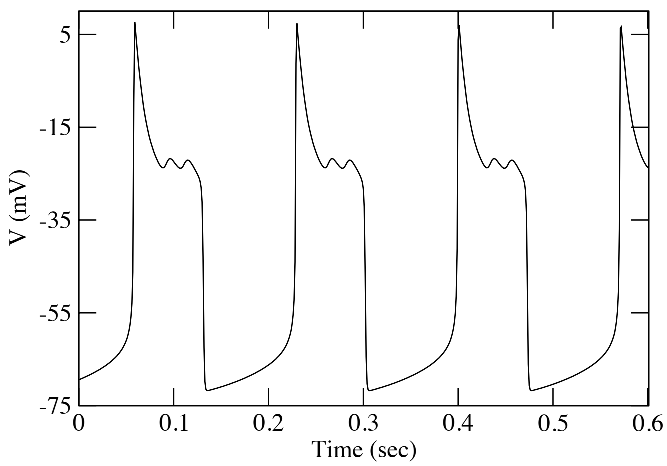
# Mixed Mode Oscillations

These are formed from periodic orbits that enter the singular funnel.

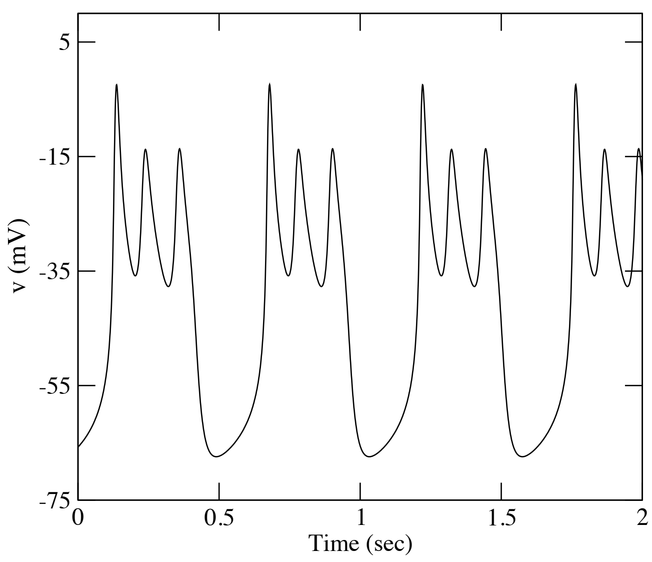


# Pseudo-Plateau Bursting

For ε away from 0, small oscillations emerge in the vicinity of the folded node. These, combined with the large jumps, form mixed mode oscillations, which in this context, are called pseudo-plateau bursting.




$C_m$=0.5 pF

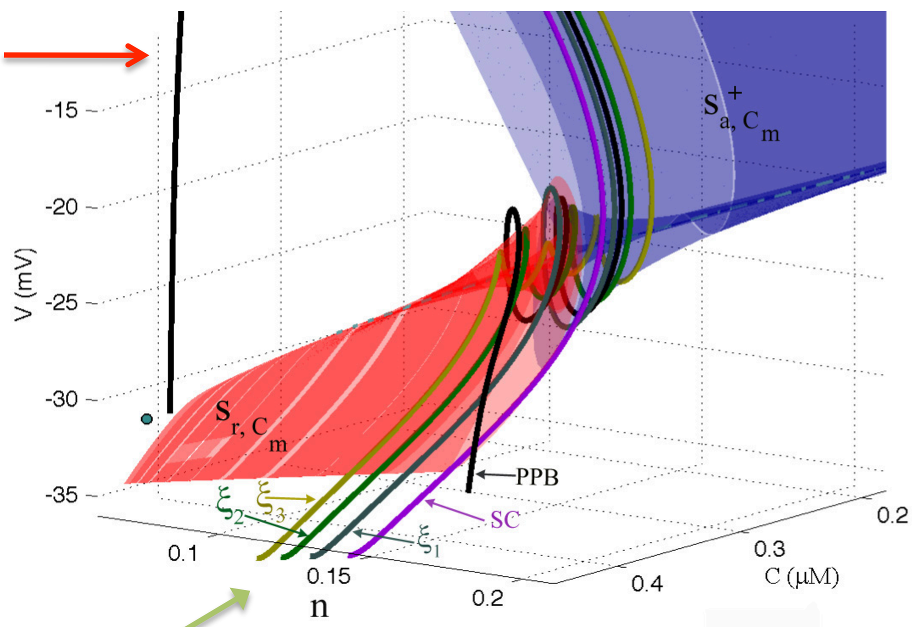



$C_m$=10 pF

# Oscillations Emerge Due to a Twisted Slow Manifold

The sheets of the critical manifold perturb smoothly to form the slow manifold for ε>0 (Fenichel theory). This is not true in the neighborhood of the folded node, where the perturbed sheets become twisted to preserve uniqueness of solutions.

Bursting orbit

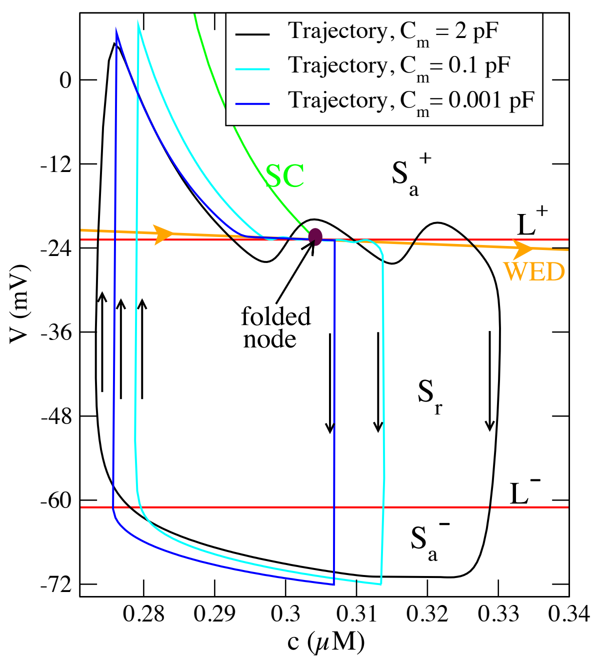



Secondary canards

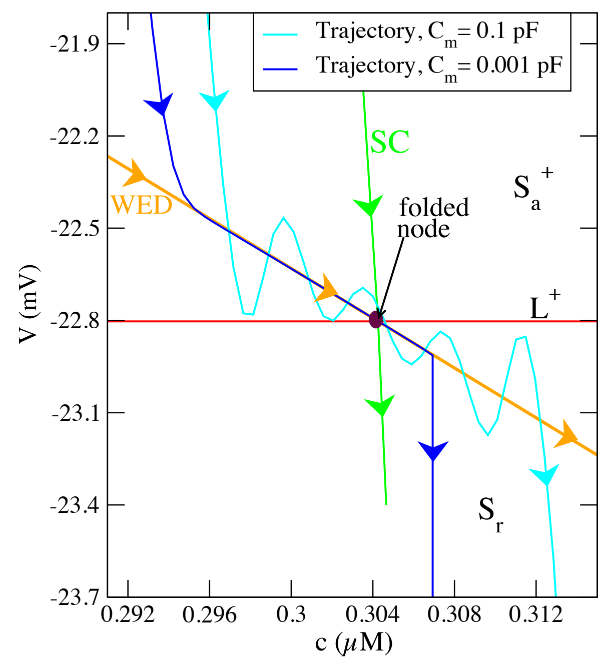
See Desroches et al., Chaos, 18:015107, 2008

# From Singular Orbit to Bursting

Transformation of the periodic orbit as ε (or the membrane capacitance $C_m$) is increased.




magnified view



# Conclusion

The pseudo-plateau bursting oscillations produced by at least some models of pituitary cells are canard-induced mixed mode oscillations

This work is soon to be submitted as "What is Pseudo-Plateau Bursting?", Teka, Tabak, Vo, Wechselberger, Bertram

Go to Wondimu Teka's talk in Mathematical Neuroendocrinology II (Tuesday at 8:55 AM) to hear more about pseudo-plateau bursting