The Dynamics of Puberty

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What is Puberty?

Puberty is the transient period between childhood and adulthood during which reproductive function is attained.

Why is it an important problem?

- Decline in the average age of puberty: 15 $\downarrow$ 9 years in girls, 17 $\downarrow$12 in boys in the past century.

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- Neurological disorders e.g. epilepsy.

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- Obesity.

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  Early onset of puberty is associated with:

- Reproductive disorders.
- Neurological disorders e.g. epilepsy.
- Obesity.
- Breast cancer.

Neurological control of Puberty

- Network of brain cells: Gonadotropin-Releasing Hormone neurons or GnRH neurons in the Hypothalamus central to pubertal onset.

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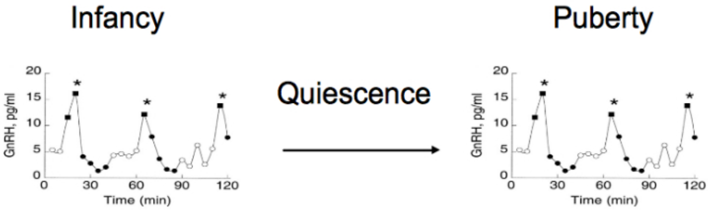

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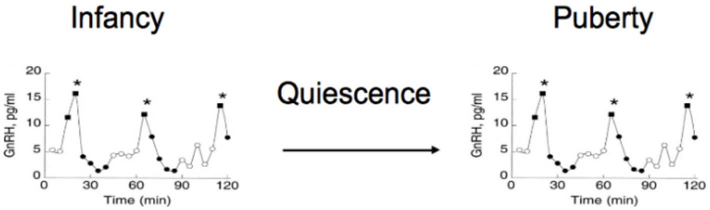
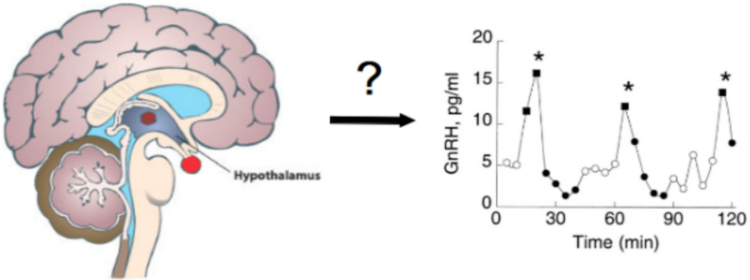
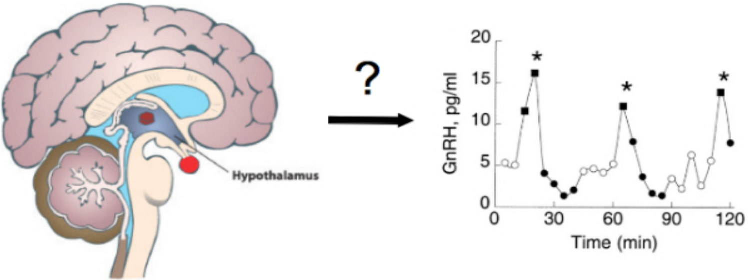


- The onset of puberty is a consequence of increase in secretion of GnRH from GnRH neurons.

Neurological control of Puberty

- 

Neurological control of Puberty

- 

- How does the activity of GnRH neurons change across puberty?

Neuroscience

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- Neuroscience is the study of the nervous system comprising a specialized network of cells called neurons.

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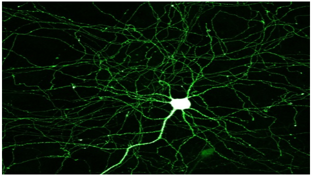
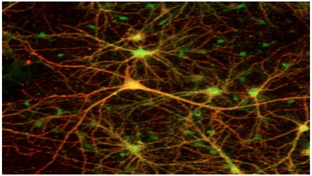
- Stained single neuron



- Stained network of neurons



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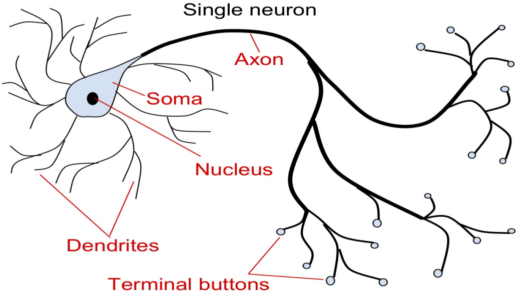
- Schematic diagram of a neuron



Action Potential

- The fundamental unit of information in nerve cells or neurons is the electrical impulse or *action potential*

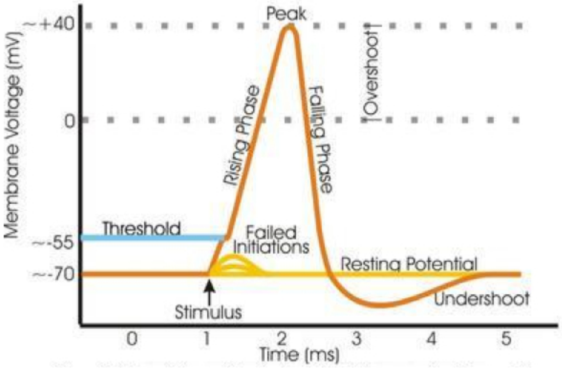


Figure: An Action Potential

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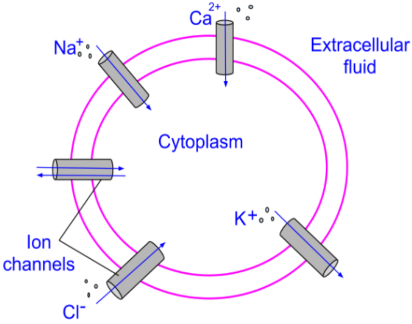
How are electricity and neuron related?

Ion channels: Portals that allow ions of specific types (e.g., potassium ions K^+ to cross the membrane.



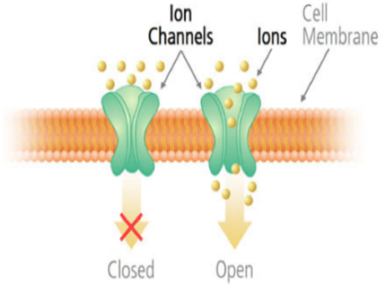
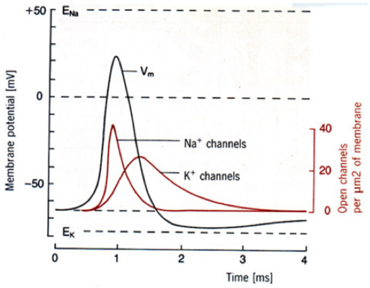


Figure: Schematic diagram of a cell membrane

Modeling ion channels

$$I_K = \underbrace{\color{red}{g_K(V)}}_{\text{Voltage-gated conductance}} (V - \underbrace{E_K}_{\text{Reversal potential}})$$

$$= \underbrace{\underbrace{\color{red}{\overline{g_K}\; n(V)}}_{\text{(Maximum conductance) (Activation function)}}}_{\text{Fraction of open } K^+ \text{ channels}}$$

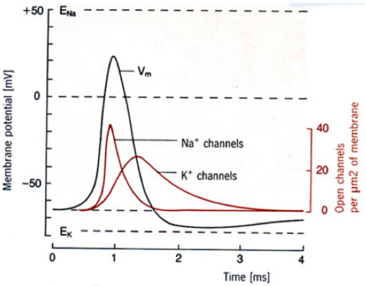


Modeling ion channels

- Hyperpolarizing currents: Falling phase

$$I_K = \overline{g_K}\, n(V)\, (V - E_K)$$

$$I_L = g_L\, (V - E_L)$$



Modeling ion channels

- Hyperpolarizing currents: Falling phase

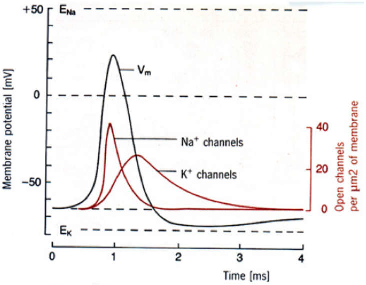
$$I_K = \overline{g_K}\; n(V)\; (V - E_K)$$

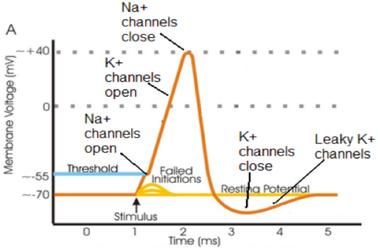
$$I_L = g_L\; (V - E_L)$$

- Depolarizing currents: Rising phase

$$I_{Na} = g_{Na}(V)\; (V - E_{Na})$$

$$= \overline{g_{Na}}\; m(V)\; h(V)\; (V - E_{Na})$$





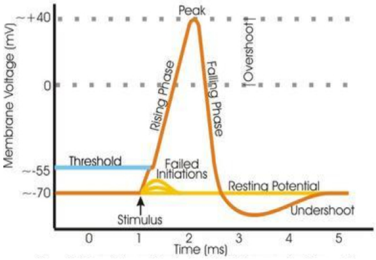
Modeling the neuron

Membrane potential:

$$\frac{dV}{dt} = \frac{1}{C}(I_{\text{app}} - I_{\text{Na}} - I_K - I_L)$$

Activation variables:

$$\frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)}, \qquad x = n, m, h$$



Reducing the dimension of a model

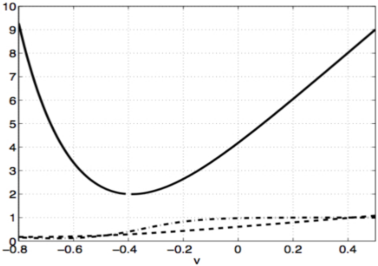


Figure: $\frac{1}{\tau_m(V)}$(solid), $\frac{1}{\tau_h(V)}$(dash-dotted), $\frac{1}{\tau_n(V)}$(dotted)

$m = m_\infty(V) \implies$ Dimension reduced from 4 to 3 !

Example

The Morris-Lecar Model

The Morris-Lecar Model: Equations

Equations:

$$\frac{dV}{dt} = \frac{1}{C}(I_{\text{app}} - I_K - I_{\text{Ca}} - I_L)$$

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)}$$

$$\frac{dw}{dt} = \frac{w_\infty(V) - w}{\tau_n(V)}$$

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$$I_{\text{Ca}} = \overline{g_{\text{Ca}}}\ m(V)\ (V - E_{\text{Ca}})$$

$$I_K = \overline{g_K}\ w(V)\ V - E_K)$$

The Reduced Morris-Lecar Model

$$m = m_\infty(V) \;!$$

Equations:

$$\frac{dV}{dt} = \frac{1}{C}(I_{\text{app}} - I_K - I_{\text{Ca}} - I_L) \tag{1}$$

$$\frac{dw}{dt} = \frac{w_\infty(V) - w}{\tau(V)} \tag{2}$$

The Morris-Lecar Model: $w - V$ phase plane analysis

V - nullcline: Set (2) $= 0$

$$I_{\text{app}} - I_{Ca} - I_K - I_L = 0 \implies w = \frac{I_{\text{app}} - I_{Ca} - I_L}{g_K(V - E_K)}$$

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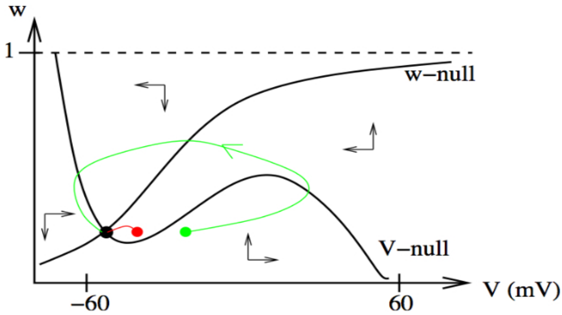

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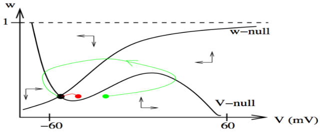

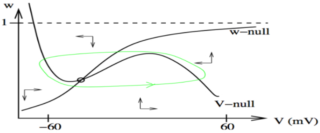

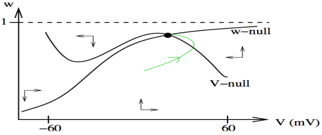

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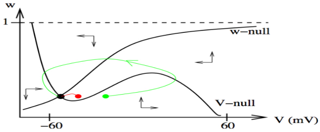

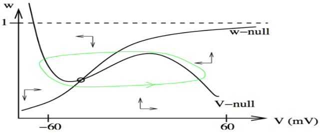

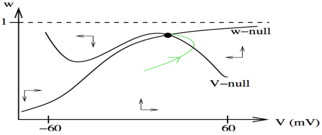

$I_{\text{app}} = 0$ pA, Hyperpolarized resting state.

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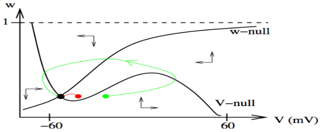

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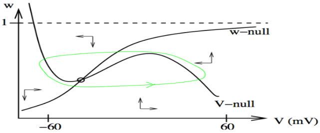


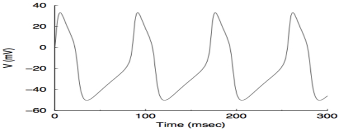
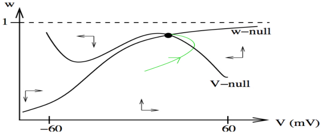
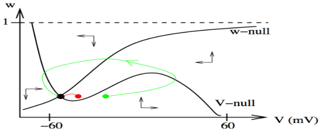


Figure: $I_{\text{app}} = 100$ pA, Oscillations



The Morris-Lecar Model: $w - V$ phase plane analysis



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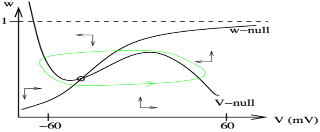


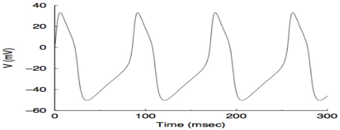
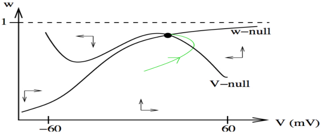
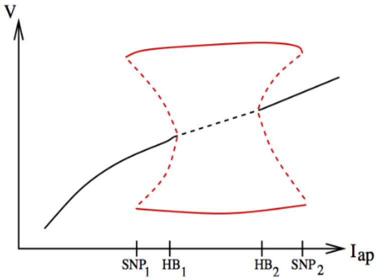


Figure: $I_{\text{app}} = 100$ pA, Oscillations



$I_{\text{app}} = 250$ pA, Depolarized resting state.

The Morris-Lecar Model: Bifurcation analysis



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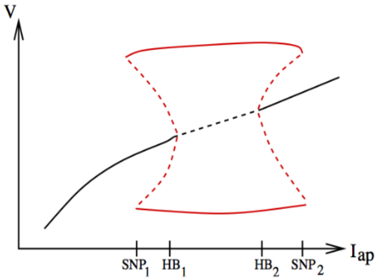


Figure: Bifurcation diagram. Black: fixed points, Red: periodic branch

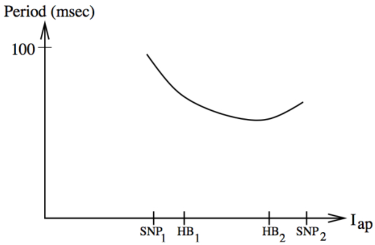
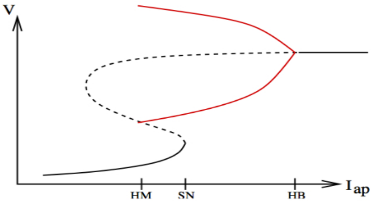
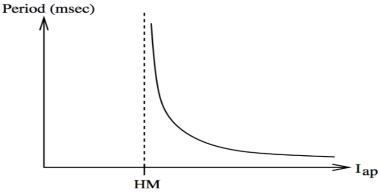


Figure: Period of oscillatory solution

Infinite period or Homoclinic bifurcation





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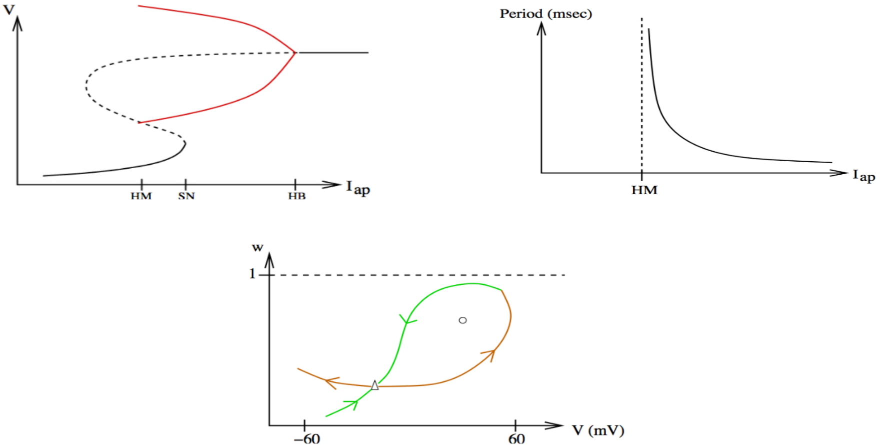


Figure: Homoclinic orbit in phase plane.

Back to more biology

How do neurons communicate?

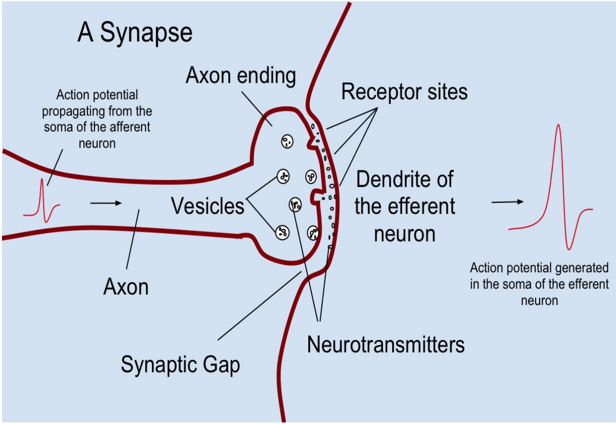
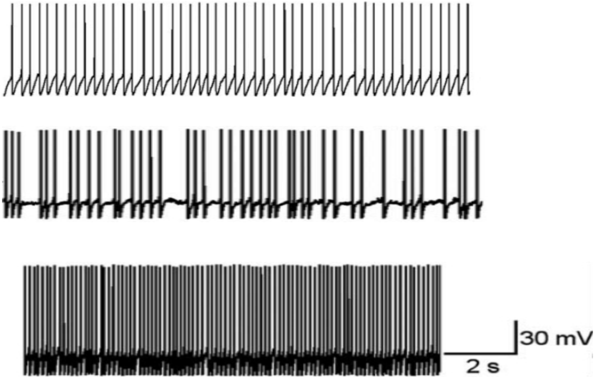


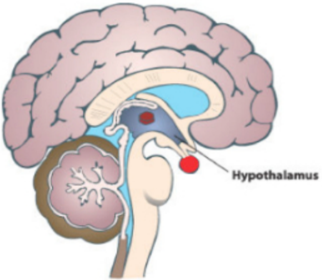
Figure: A synapse

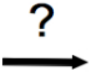
Firing rate

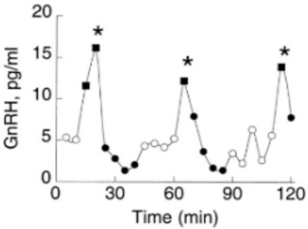
Intensity of the external stimulus or communication among neurons is encoded in the frequency or firing rate of the action potential.



Neuronal activity and hormone release

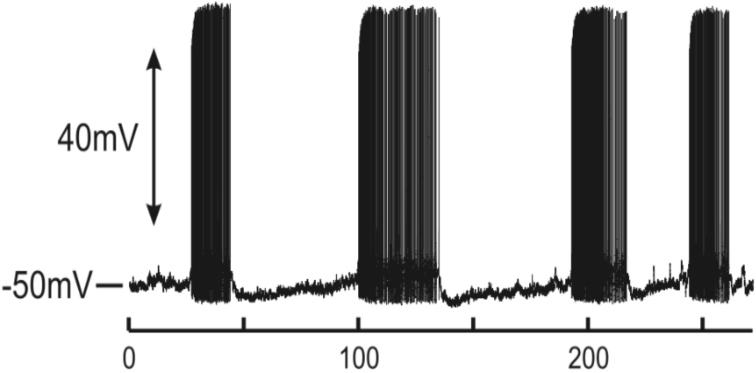






Bursting

Periodic clustering of electrical impulses.



Bursting $\Longrightarrow$ hormone release

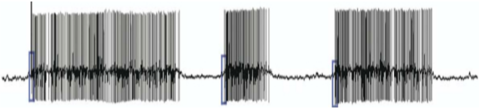
- Neuron 1

- Neuron 2

- Synchronized periods within bursting episodes amplifies hormone release

Bursting $\implies$ hormone release

- Neuron 1



- Neuron 2

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Bursting $\implies$ hormone release

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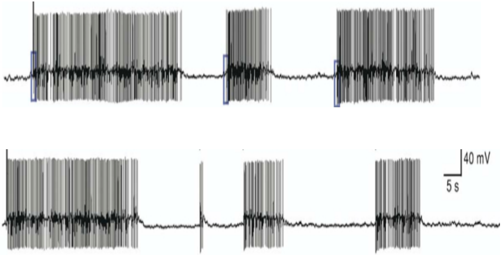

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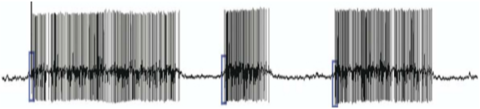
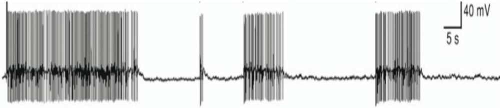


- Neuron 2



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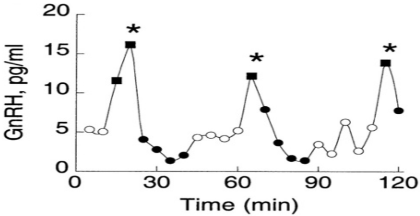


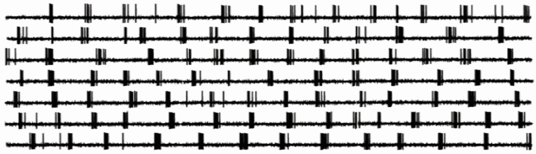
GnRH neuronal activity

Infancy

$\downarrow$

Puberty

GnRH neuronal activity



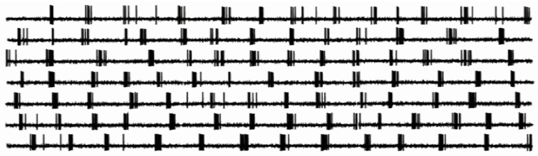
Infancy

↓

Puberty

GnRH neuronal activity

Infancy



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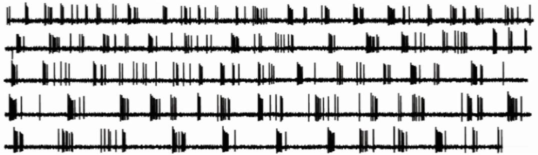
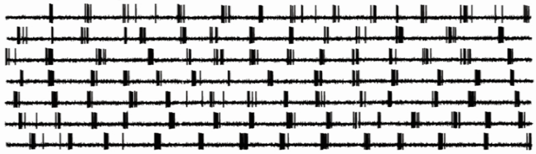


Puberty

GnRH neuronal activity

Infancy



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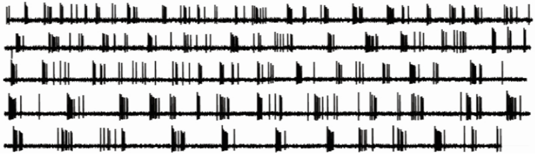
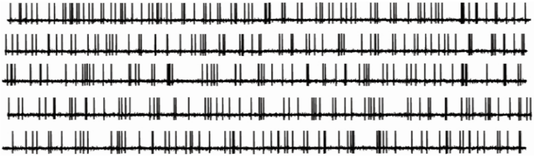


Puberty



GnRH: pubertal transition

- How do changes in currents and neurotransmitters drive the transition in firing activity?

GnRH: pubertal transition

- How do changes in currents and neurotransmitters drive the transition in firing activity?

- How does the transition to irregular firing drive pulsatile GnRH release?

GnRH model

Membrane potential:

$$\frac{dV}{dt} = \frac{1}{C}(I_{app} - I_{Na} - I_{CaL} - I_K - I_{SK} - I_L)$$

Activation variables:

$$\frac{dx(t)}{dt} = \frac{x_\infty(V) - x(t)}{\tau_x}$$

Results

$$\frac{dV}{dt} = \frac{1}{C}(I_{app} - I_{Na} - I_{CaL} - I_K - I_{SK} - I_L)$$

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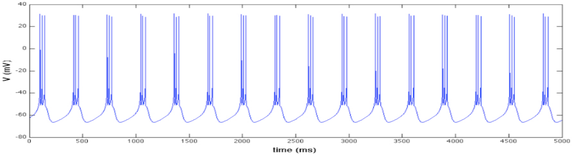
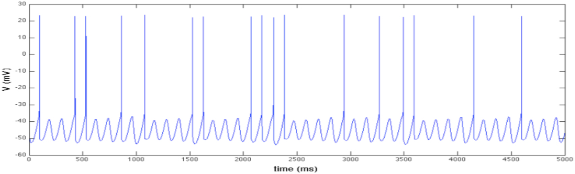
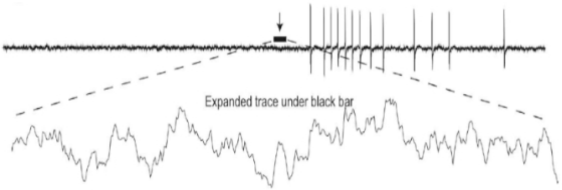
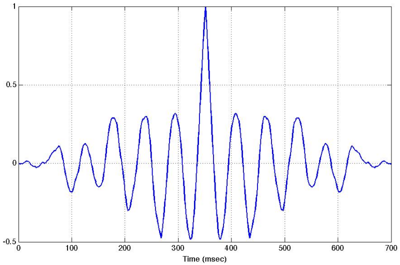




Subthreshold oscillations





Three dimensional reduced GnRH model

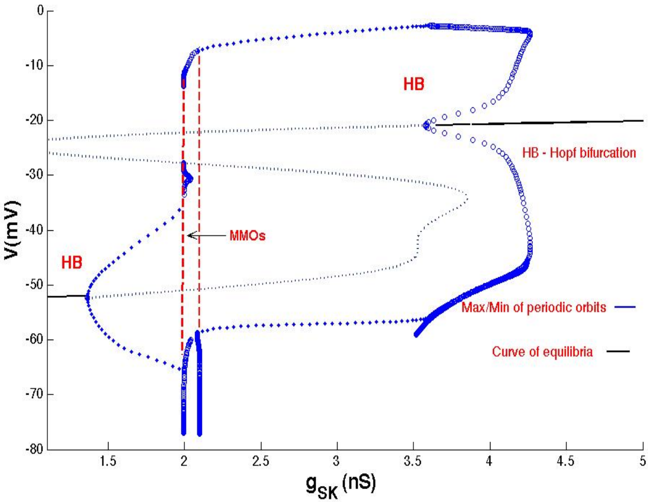
Equations:

$$C_m \frac{dV}{dt} = I_{app} - I_{Na} - I_{CaL} - I_K - I_{SK} - I_L$$

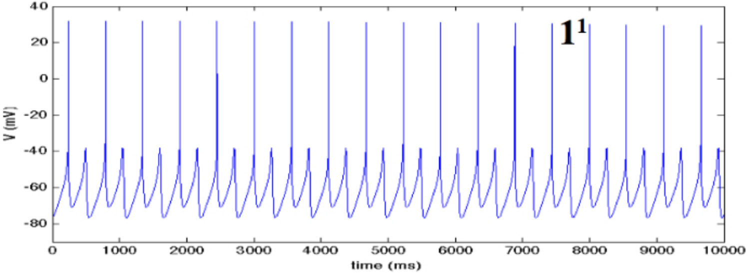
$$\frac{dp(t)}{dt} = \frac{p_\infty(V, Ca_s) - p(t)}{\tau_p}$$

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

Bifurcation analysis



MMOs: Physiological Role ?



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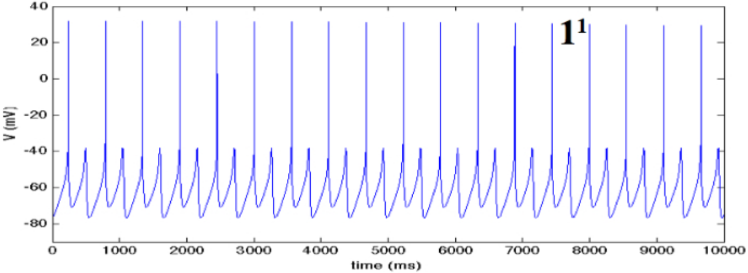

Current Hypothesis (suggested by the mathematical model):

MMOs prepare the cell to fire at a given frequency that can be synchronized with other cells in the network so that the cell can participate in the population rhythm.

Geometric singular perturbation analysis

Fast-Slow systems

Let $x \in \mathbb{R}^n$, $y \in \mathbb{R}^m$, $\epsilon \ll 1$

Fast subsystem:

$$\begin{aligned} \epsilon \frac{dx}{dt} &= f(x, y) \\ \frac{dy}{dt} &= g(x, y) \end{aligned} \tag{3}$$

Let $x \in \mathbb{R}^n$, $y \in \mathbb{R}^m$, $\epsilon \ll 1$

Fast subsystem:

$$\epsilon \frac{dx}{dt} = f(x, y) \qquad (3)$$
$$\frac{dy}{dt} = g(x, y)$$

$$\frac{dx}{dt} = \mathcal{O}(\frac{1}{\epsilon}), \ \frac{dy}{dt} = \mathcal{O}(1) \implies \text{x evolves much faster!}$$

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Slow subsystem: $\tau = \frac{t}{\epsilon}$

$$\frac{dx}{d\tau} = f(x,y) \qquad (4)$$
$$\frac{dy}{d\tau} = \epsilon g(x,y)$$

Fast-Slow systems

Set $\epsilon = 0$ in (3):

$$f(x,y) = 0$$
$$\frac{dy}{dt} = g(x,y)$$

$\mathcal{S} := \{(x,y) : \; f(x,y) = 0\}$ is called the Critical Manifold.

Fast-Slow systems

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$\mathcal{S} := \{(x, y) : \ f(x, y) = 0\}$ is called the Critical Manifold.

Set $\epsilon = 0$ in (4):

$$\frac{dx}{d\tau} = f(x, y)$$
$$\frac{dy}{d\tau} = 0$$

y can be treated as a parameter !

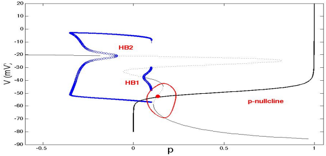
Example: 3d GnRH model

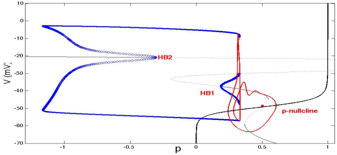
Define: $\tau = \frac{t}{k_t}$, $\epsilon = \frac{C_m}{k_t \; g_{\max}}$. Rewrite equations:

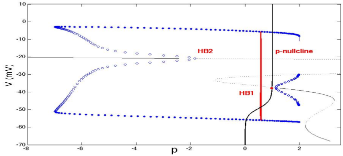
$$
\begin{aligned}
\epsilon \frac{dV}{d\tau} &= \hat{I}_{app} - \hat{I}_{Na} - \hat{I}_{CaL} - \hat{I}_{K} - \hat{I}_{SK} - \hat{I}_{L} \\
\epsilon \frac{dn}{d\tau} &= \frac{n_{\infty}(V) - n}{\hat{\tau}_n(V)} \\
\frac{dp}{d\tau} &= p_{\infty}(V) - p
\end{aligned}
$$

Fast-Slow bifurcation analysis

Fast-Slow bifurcation analysis

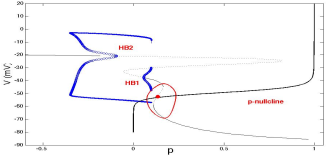


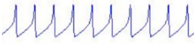


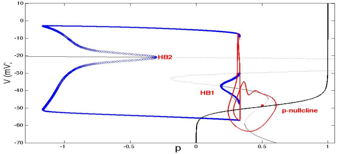


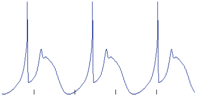
$g_{SK} = 2nS$, 

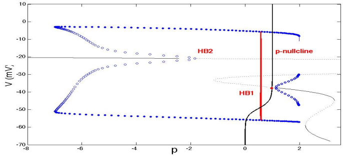
Fast-Slow bifurcation analysis



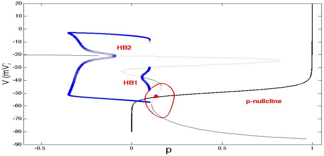
$g_{SK} = 2nS$, 

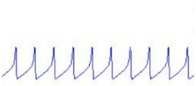


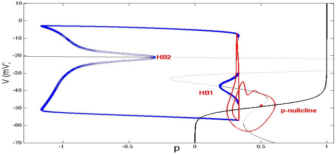
$g_{SK} = 0.7nS$, 

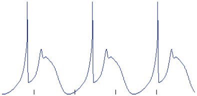


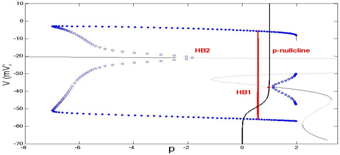
Fast-Slow bifurcation analysis

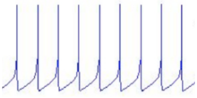


$g_{SK} = 2nS,$ 



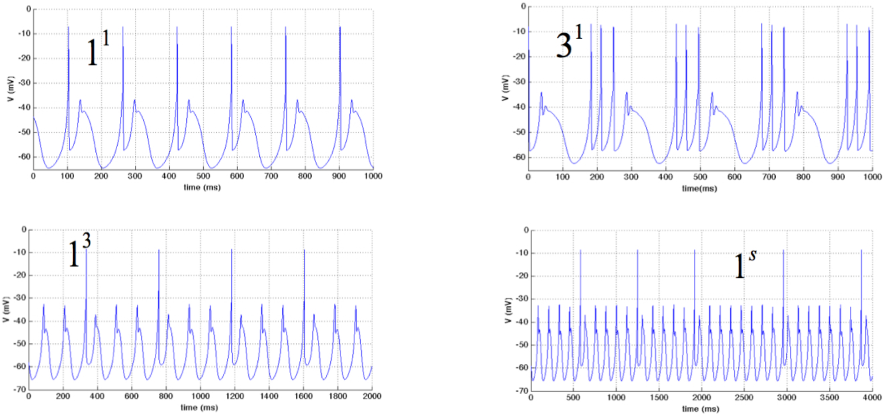
$g_{SK} = 0.7nS,$ 



$g_{SK} = 0.2nS,$ 

Mixed Mode Oscillations (MMOs)

L: Large-amplitude, s: Small-amplitude, MMO patterns: L^s



Poses interesting mathematical questions

Example: Canards

The Van Der Pol Oscillator: $y'' + \beta\left(y^2 - 1\right)y' + y = a$

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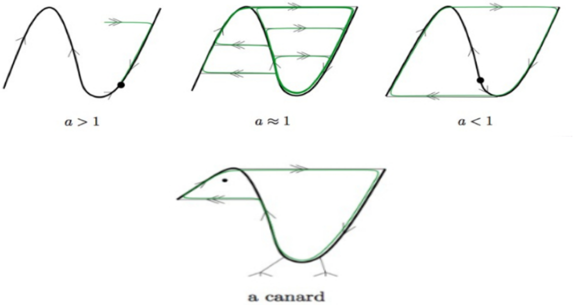
The Van Der Pol Oscillator: $y'' + \beta\,(y^2 - 1)\,y' + y = a$

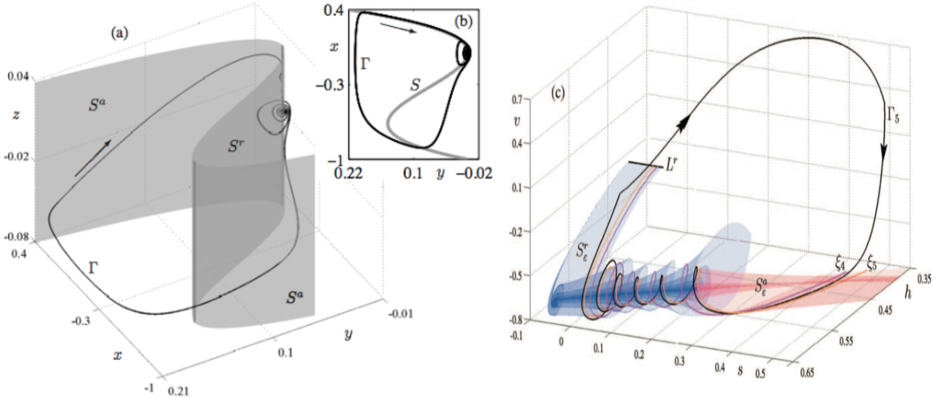
$$\epsilon\,\dot{x} = f(x,y)$$
$$\dot{y} = g(x,y)$$

Critical manifold: $f(x,y) = 0$



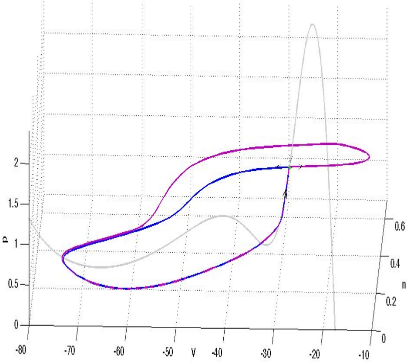
Canards in dimension $\geq$ 3

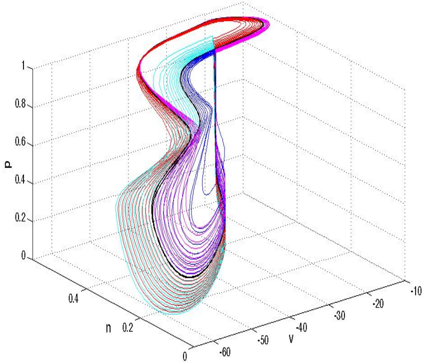
Intersection of stable and unstable invariant manifolds in the vicinity of the fold $\implies$ MMOs



3d GnRH system: MMO mechanism

Small and large - amplitude homoclinic orbits in close vicinity of each other $\implies$ Complex dynamics





Concluding remarks

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- Provide insight into dynamical mechanisms underlying biological phenomena.

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Mathematical models

- Provide insight into dynamical mechanisms underlying biological phenomena.
- Make testable predictions.
- Source of new mathematical questions.

Thank you!

Advisor: Dr. Janet Best, Dept. of Mathematics, OSU

Collaborator: Dr. Kelly Suter, Dept. of Biology, UTSA

Dept. of Mathematics, Trinity College

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