Optimal Timing Control of Biological Oscillators

using Augmented Phase Reduction
(based on Isochrons and Isostables)

Bharat Monga   Jeff Moehlis

Department of Mechanical Engineering
University of California, Santa Barbara
Santa Barbara, CA 93106-5070

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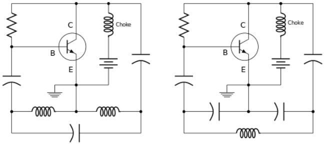
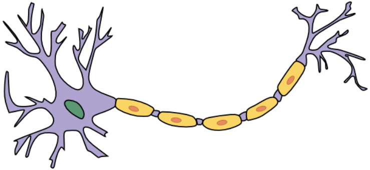
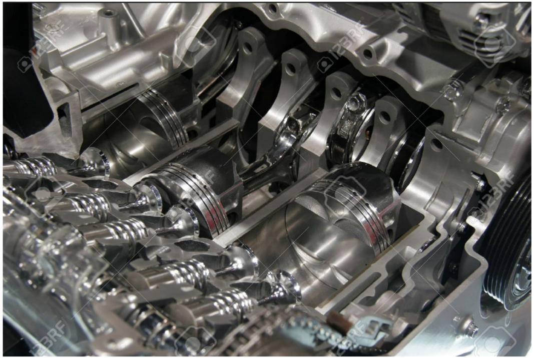
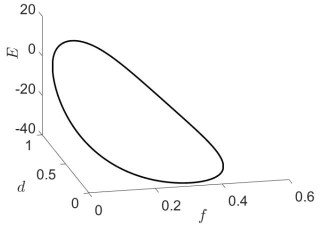
Periodic orbits are ubiquitous in dynamical systems theory







YNI model of SA Node cells in rabbit heart



$$C_m \cdot dE/dt = i_m - (i_s + i_{Na} + i_K + i_h + i_l)$$

$$dy/dt = \alpha_y(1-y) - \beta_y \cdot y$$

$$i_s = (0.95d + 0.05)\cdot(0.95f + 0.05)\cdot \bar{i}_s$$

$$\alpha_d = \frac{1.045\times10^{-2}(E+35)}{1-\exp(-(E+35)/2.5)} + \frac{3.125\times10^{-2}E}{1-\exp(-E/4.8)}$$

$$\beta_d = \frac{4.21\times10^{-3}(E-5)}{\exp((E-5)/2.5)-1}$$

$$\alpha_f = \frac{3.55\times10^{-4}(E+20)}{\exp((E+20)/5.633)-1}$$

$$\beta_f = \frac{9.44\times10^{-4}|E+60|}{1+\exp(-(E+29.5)/4.16)}$$

$$\bar{i}_s = 12.5(\exp((E-30)/15)-1)$$

$$i_{Na} = m^3 \cdot h \cdot \bar{i}_{Na}$$

$$\alpha_m = \frac{E+37}{1-\exp(-(E+37)/10)}$$

$$\beta_m = 40\exp(-5.6\times10^{-2}(E+62))$$

$$\alpha_h = 1.209\times10^{-3}\exp(-(E+20)/6.534)$$

$$\beta_h = \frac{1}{\exp(-(E+30)/10)+1}$$

$$\bar{i}_{Na} = 0.5(E-30)$$

$$i_h = q\cdot\bar{i}_h$$

$$\alpha_q = \frac{3.4\times10^{-4}(E+100)}{\exp((E+100)/4.4)-1} + 4.95\times10^{-5}$$

$$\beta_q = \frac{5\times10^{-4}(E+40)}{1-\exp(-(E+40)/6)} + 8.45\times10^{-5}$$

$$\bar{i}_h = 0.4(E+25)$$

$$i_K = p\cdot\bar{i}_K$$

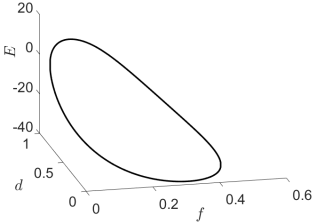
$$\alpha_p = \frac{9\times10^{-3}}{1+\exp(-(E+3.8)/9.71)} + 6\times10^{-4}$$

$$\beta_p = \frac{2.25\times10^{-4}(E+40)}{\exp((E+40)/13.3)-1}$$

$$\bar{i}_K = \frac{0.7(\exp(0.0277(E+90))-1)}{\exp(0.0277(E+40))}$$

$$i_l = 0.8(1-\exp(-(E+60)/20))$$

YNI model of SA Node cells in rabbit heart



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Standard phase reduction

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Definition

An Isochron is a set of initial conditions that asymptotically converge to a periodic orbit together at the same phase.

$$
\begin{aligned}
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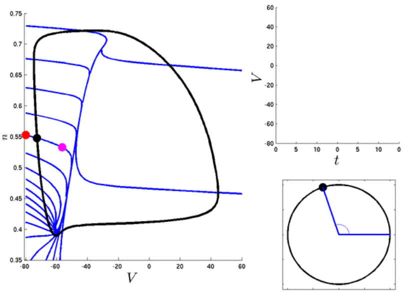
$$



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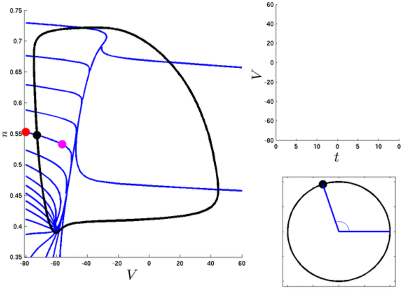

Definition

An Isochron is a set of initial conditions that asymptotically converge to a periodic orbit together at the same phase.

Standard phase reduction

$$\dot{x} = F(x) + U(t)$$

$$\frac{d\theta}{dt} = \omega + \underbrace{\left.\frac{\partial\theta}{\partial x}\right|_{\gamma(t)}}_{\mathcal{Z}(\theta)} U(t)$$

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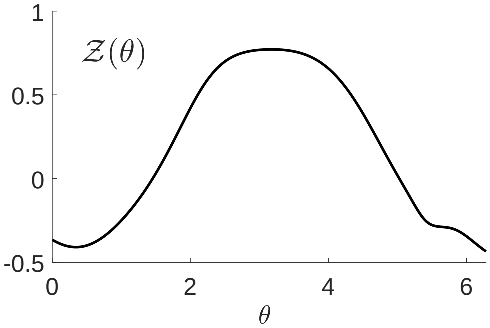
Standard Phase Reduction

$$\dot{\theta} = \omega + \mathcal{Z}(\theta)U(t)$$



First component of PRC for YNI model

Standard phase reduction

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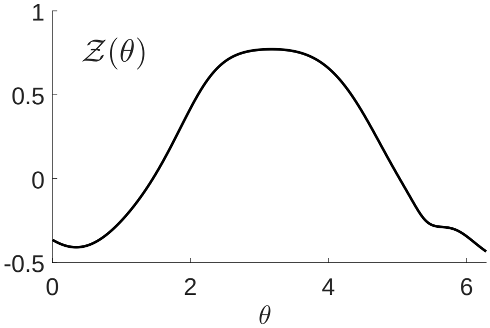

First component of PRC for YNI model

- Experimentally feasible
- No information about transversal dynamics

Isostables

Stable fixed point

For a system with a stable fixed point, an *Isostable* is a set of points in phase space that approach the fixed point together.

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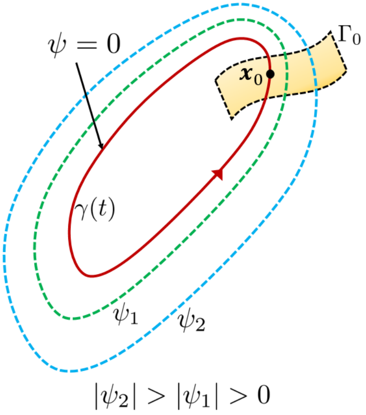
Stable fixed point

For a system with a stable fixed point, an *Isostable* is a set of points in phase space that approach the fixed point together.

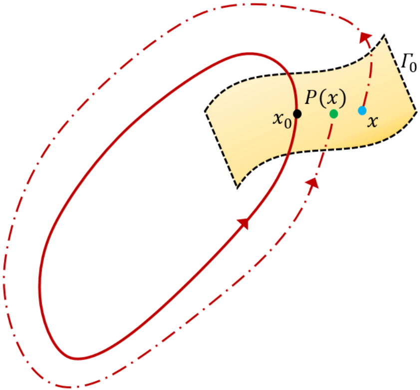
Stable periodic orbit

For a system with a stable periodic orbit, an *Isostable* is a set of points in phase space that converge to the periodic orbit together but at different phases.



Augmented phase reduction

$$P : \Gamma_0 \to \Gamma_0; \qquad x \to P(x)$$



Augmented phase reduction

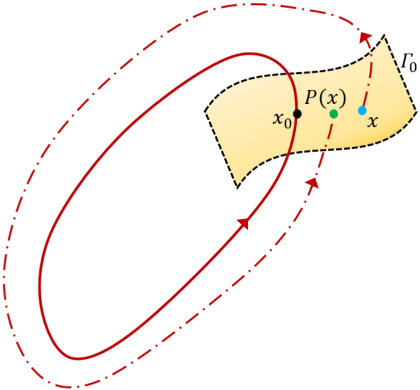
$$P : \Gamma_0 \to \Gamma_0; \qquad x \to P(x)$$

$$\lambda_i, \; v_i$$

$$k_i = \frac{\log \lambda_i}{T}$$

$$\dot{\psi}_i = k_i \psi_i$$

$$k_i < 0 \;\Rightarrow\; \psi_i \to 0$$



Augmented phase reduction

$$\dot{x} = F(x) + U(t)$$

$$\frac{d\psi_i}{dt} = k_i\psi_i + \underbrace{\frac{\partial\psi_i}{\partial x}\bigg|_{\gamma(t)}}_{\mathcal{I}_i(\theta)} U(t)$$

Augmented phase reduction

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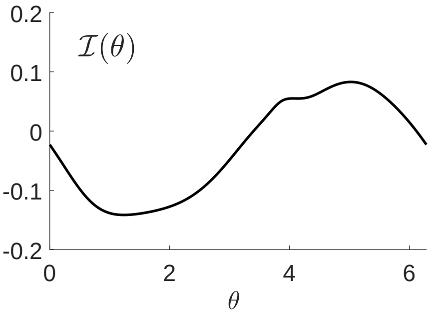
$$\frac{d\psi_i}{dt} = k_i\psi_i + \underbrace{\left.\frac{\partial \psi_i}{\partial x}\right|_{\gamma(t)}}_{\mathcal{I}_i(\theta)} U(t)$$

Augmented Phase Reduction[1]

$$\dot{\theta} = \omega + \mathcal{Z}(\theta)U(t)$$
$$\dot{\psi}_i = k_i\psi_i + \mathcal{I}_i(\theta)U(t)$$



First component of IRC for YNI model

[1] D. Wilson, J. Moehlis, Physical Review E 94, (5) (2016)

Optimal timing control

$$\dot{x} = F(x) + U(t)$$

Control objective

Change the period of an oscillator using minimum energy input while minimizing the oscillator's transversal distance to the uncontrolled periodic trajectory.

Optimal timing control

$$\dot{x} = F(x) + U(t)$$

Control objective

Change the period of an oscillator using minimum energy input while minimizing the oscillator's transversal distance to the uncontrolled periodic trajectory.

Assumption 1: Only one of $k_i \approx 0$.
Assumption 2: Only one degree of actuation: $U(t) = [u(t),\ 0, \ldots, 0]^T$.
Augmented phase reduction becomes

$$\dot{\theta} = \omega + \mathcal{Z}(\theta) u$$
$$\dot{\psi} = k\psi + \mathcal{I}(\theta) u$$

Optimal timing control

With augmented phase reduction

Cost function

$$\int_0^{T_1} \left[\alpha u^2 + \beta \psi^2 + \lambda_1 \left(\dot{\theta} - \omega - \mathcal{Z}(\theta) u \right) + \lambda_2 \left(\dot{\psi} - k\psi - \mathcal{I}(\theta) u \right) \right] dt$$

Optimal timing control

With augmented phase reduction

Cost function

$$\int_0^{T_1} \left[\alpha u^2 + \beta\psi^2 + \lambda_1\left(\dot{\theta} - \omega - \mathcal{Z}(\theta)u\right) + \lambda_2\left(\dot{\psi} - k\psi - \mathcal{I}(\theta)u\right)\right] dt$$

Euler-Lagrange equations

$$\dot{\theta} = \omega + \mathcal{Z}(\theta)u$$
$$\dot{\psi} = k_1\psi + \mathcal{I}(\theta)u$$
$$\dot{\lambda}_1 = -\left(\lambda_1\mathcal{Z}'(\theta) + \lambda_2\mathcal{I}'(\theta)\right) u$$
$$\dot{\lambda}_2 = 2\beta\psi - k\lambda_2$$
$$u = \frac{\lambda_1\mathcal{Z}(\theta) + \lambda_2\mathcal{I}(\theta)}{2\alpha}$$

Boundary conditions

$$\theta(0) = 0 \qquad \theta(T_1) = 2\pi$$
$$\psi(0) = 0 \qquad \psi(T_1) = 0$$

Solve the 2 point BVP using Newton iteration

Optimal timing control

Algorithm A (based on augmented phase reduction)

$$\int_0^{T_1} \text{Euler-Lagrange equations}$$

↓

$$U(t) = \begin{cases} \left[\frac{\lambda_1(t)\mathcal{Z}(\theta(t))+\lambda_2(t)\mathcal{I}(\theta(t))}{2\alpha},\ 0,\dots,0\right]^T & 0 \le t \le T_1 \\ [0,\ 0,\dots,0]^T & t > T_1 \end{cases}$$

↓

$$x(t) = \int_0^t [F(x) + U(t)]\, dt$$

Optimal timing control

With standard phase reduction[2]

Cost function

$$\int_0^{T_1} \left[\alpha u^2 + \lambda_1 \left(\dot{\theta} - \omega - \mathcal{Z}(\theta) u\right)\right] dt$$

Euler-Lagrange equations

$$\dot{\theta} = \omega + \mathcal{Z}(\theta) u$$

$$\dot{\lambda}_1 = -\lambda_1 \mathcal{Z}'(\theta) u$$

$$u = \frac{\lambda_1 \mathcal{Z}(\theta)}{2\alpha}$$

Boundary conditions

$$\theta(0) = 0 \qquad \theta(T_1) = 2\pi$$

Solve the 2 point BVP using Newton iteration

[2] J. Moehlis, E. Shea-Brown, H. Rabitz, JCND, 1 (4) 395 (2006) 358367

Optimal timing control

Algorithm S (based on standard phase reduction)

$$\int_0^{T_1} \text{Euler-Lagrange equations}$$

↓

$$U(t) = \begin{cases} \left[\frac{\lambda_1(t)\mathcal{Z}(\theta(t))}{2\alpha},\ 0, \ldots, 0\right]^T & 0 \le t \le T_1 \\ [0,\ 0, \ldots, 0]^T & t > T_1 \end{cases}$$

↓

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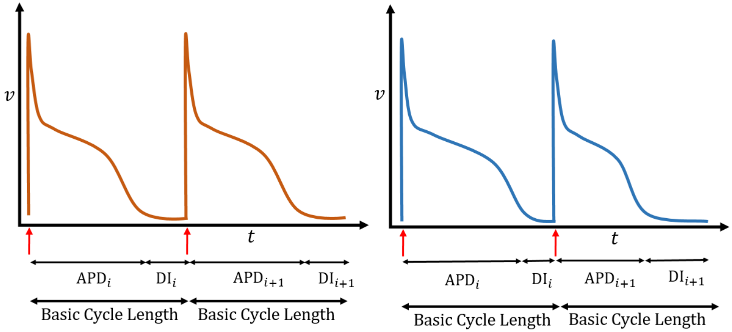
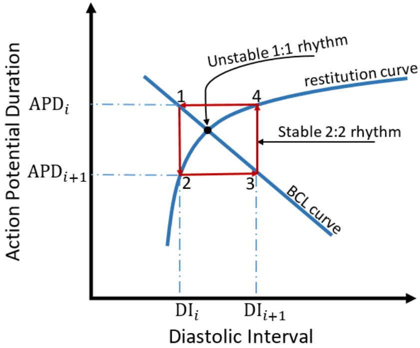
Controlling cardiac pacemaker cells



- Action Potential Duration (APD)
- Diastolic Interval (DI)
- Basic Cycle Length (BCL)
- Period doubling bifurcation: 1:1 rhythm $\longrightarrow$ 2:2 rhythm (Alternans)

In the simplest model:

- *restitution curve:* $\mathrm{APD}_{i+1} = f(\mathrm{DI}_i)$
- *BCL curve:* $\mathrm{APD}_i + \mathrm{DI}_i = \mathrm{BCL}$



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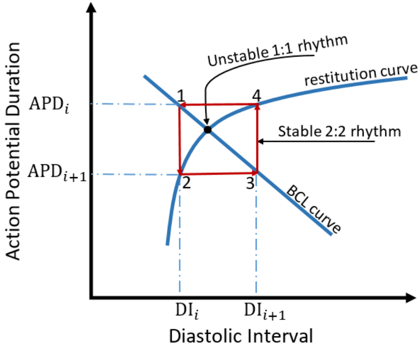
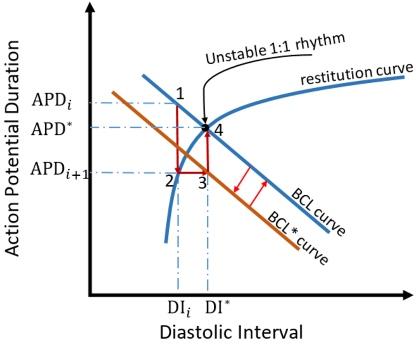




Control objective: Stabilize the unstable 1:1 rhythm by changing the BCL for 1 period

YNI model of SA node cells in rabbit heart

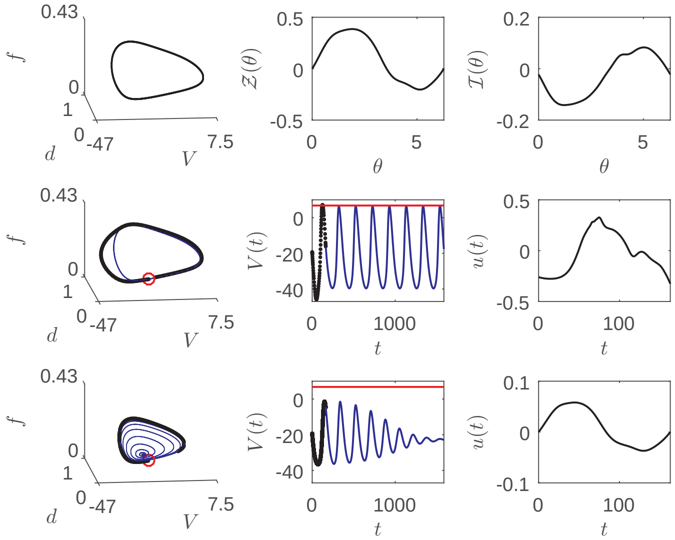
7 Dimensional
Pacemaker Cell Model

$$\dot{V} = \frac{\sum I_l}{C} + u(t),$$

$$\dot{y} = \alpha_y(1 - y) - \beta_y y.$$

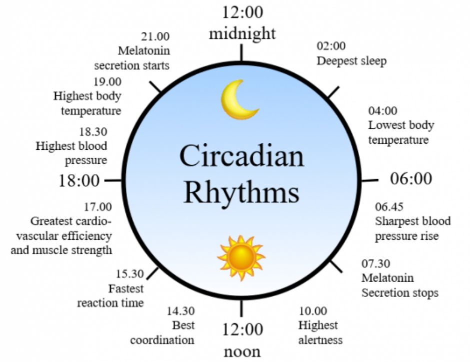
$$T_1 = 0.8\,T$$

$$k = -0.00135$$



Controlling circadian oscillators

- Suprachiasmatic nucleus (SCN) maintains circadian rhythm
- Asynchrony with the external day and night cycle can lead to several physiological disorders
- how do we remove this asynchrony?
  - Using drugs (e.g. Melantonin)
  - exposure to a timed light stimulus



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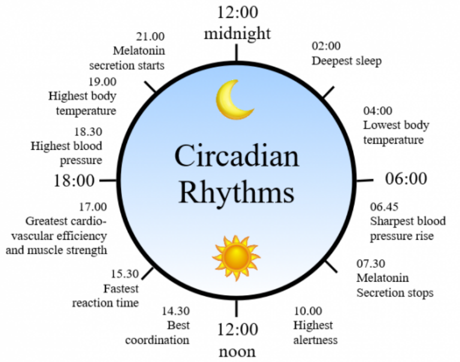


- Imagine someone going on a vacation from New York city to London
- The new day and night cycle would be 5 hours behind his circadian rhythm
- Reduce circadian rhythm period by 20%($\approx$ 5 hrs)!

Controlling circadian oscillators

3 Dimensional
Gene Regulation Model

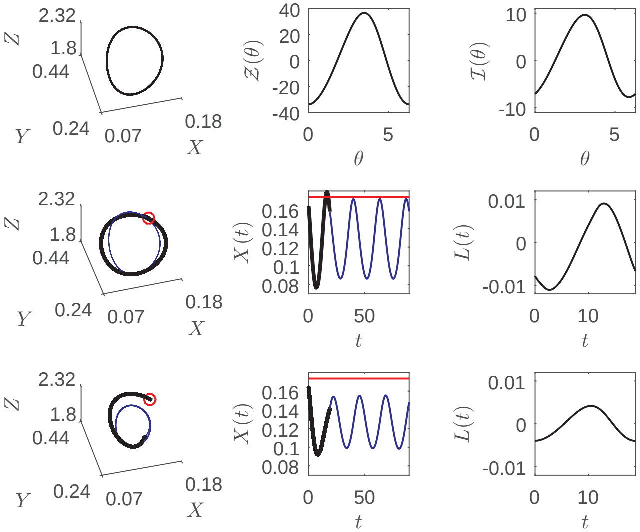
$$\dot{X} = v_1 \frac{K_1^4}{K_1^4 + Z^4} - v_2 \frac{X}{K_2 + X} + L(t),$$

$$\dot{Y} = k_3 X - v_4 \frac{Y}{K_4 + Y},$$

$$\dot{Z} = k_5 Y - v_6 \frac{Z}{K_6 + Z}.$$

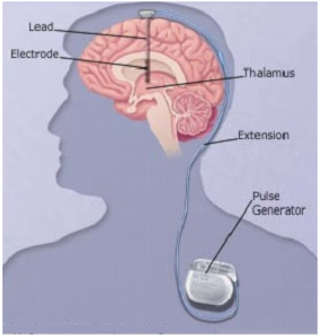
$$T_1 = 0.8T$$

$$k = -0.0021$$



Controlling neurons

- Essential and parkinsonian tremor affect millions of people worldwide
- Pathological neural synchronization in the thalamus and STN brain region
- Deep brain stimulation: high frequency high energy pulsatile waveform
- Stimulation hypothesized to desynchronize the neurons
- Can we do this in a more optimal way?



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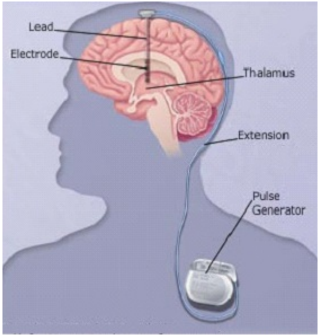
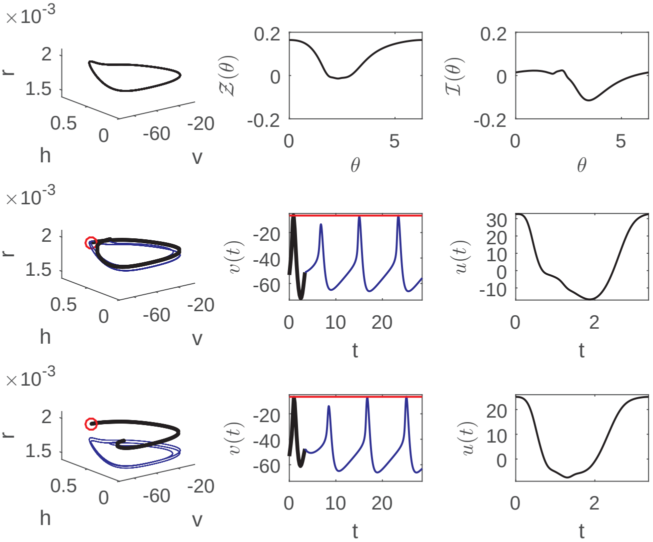
  - Start at a single neuron level
  - **Goal**: Change the period for one oscillation



3 Dimensional
Thalamic Neuron Model

$$\dot{v} = \frac{\left(\sum -I_l + I_b\right)}{C_m} + u(t),$$
$$\dot{y} = \left(y_{\inf} - y\right)/\tau_y.$$

$T_1 = 0.4T$
$k = -0.0226$



Controlling Hopf normal form

$$\dot{x} = ax - by + (x^2 + y^2)(cx - dy) + u(t),$$
$$\dot{y} = bx + ay + (x^2 + y^2)(dx + cy).$$

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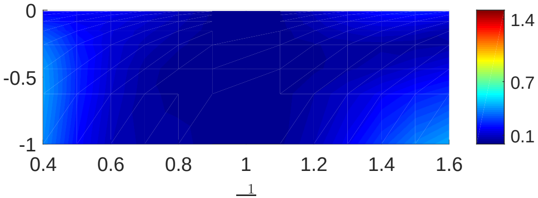
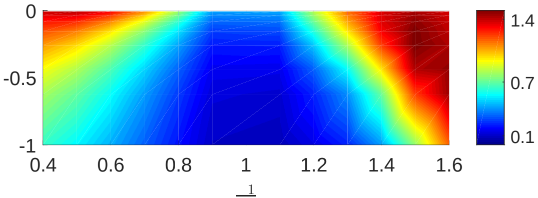
Alg. A



Alg. S



Conclusion

Standard phase reduction (Algorithm S) $\longleftrightarrow$ Augmented phase reduction (Algorithm A)

- Optimal timing control algorithm has potential to
  - eliminate cardiac alternans
  - aid in treating jet lag
  - help with motor symptoms of essential and parkinsonian tremor