A computational approach to analysis and control of the mammalian circadian oscillator

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A brief acknowledgement…

Outline

1. An introduction to circadian rhythms
2. Dissertation outline
3. Exploring neurotransmission in the suprachiasmatic nucleus
4. Controlling circadian rhythms

An introduction to circadian rhythms

What are circadian rhythms?

Cassia corymbosa, sketch by Darwin

- Endogenous, entrainable, near-24h oscillations in gene expression, metabolism, or behavior

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Circadian rhythms are ubiquitous

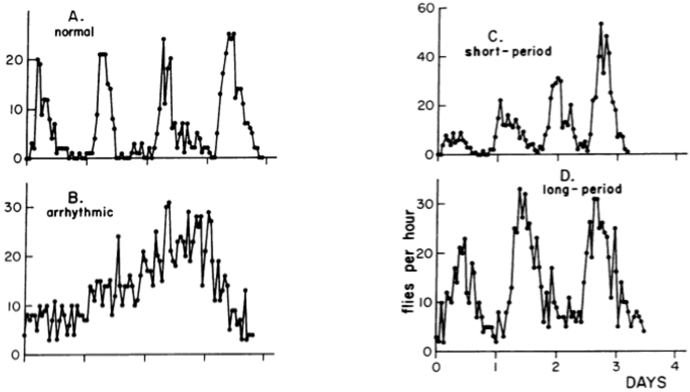

FIG. 1. Eclosion rhythms, in constant darkness, for populations of rhythmically normal and mutant flies, previously exposed to LD 12:12. T = 20°C.

Konopka and Benzer PNAS 1972

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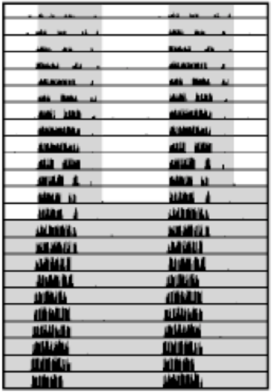

Wild type
$\tau = 23.77 \pm 0.07$ h

(L) van der Horst *at al.* Nature 1999, (R) Takahashi Nat Rev Genet 2017

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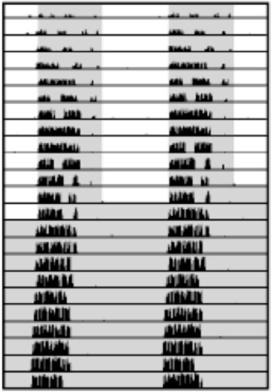

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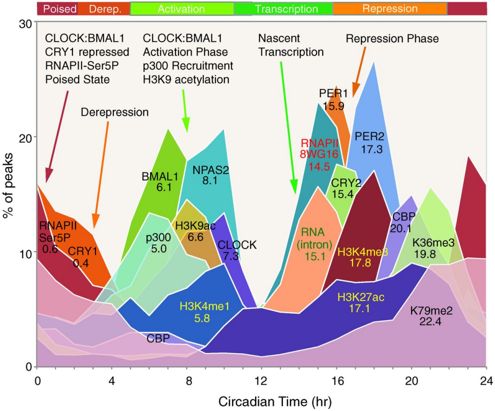

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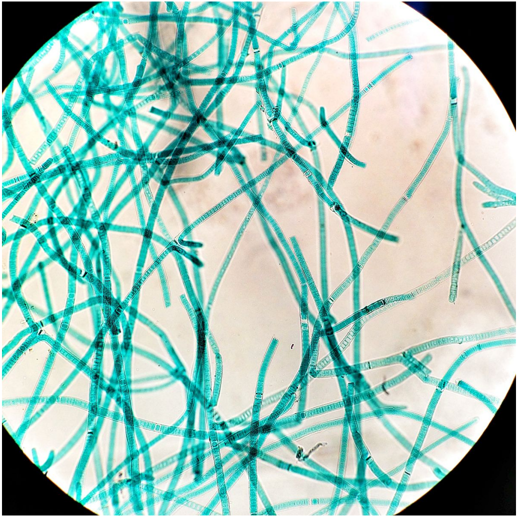

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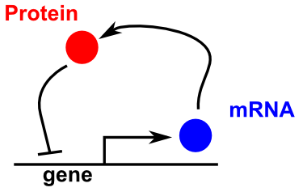
Biological feedback loops drive oscillation



Example: a highly simplified genetic feedback loop.

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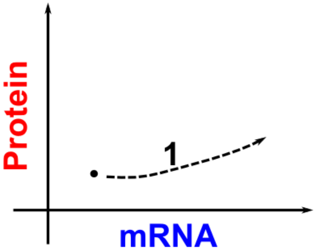

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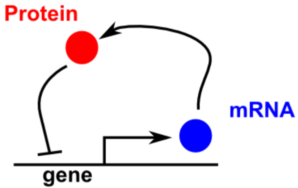

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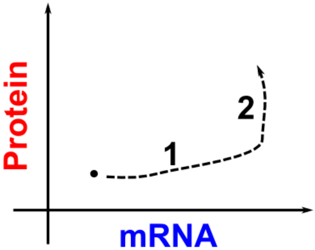

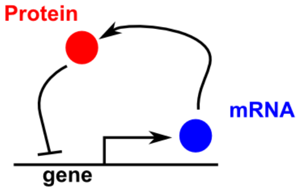

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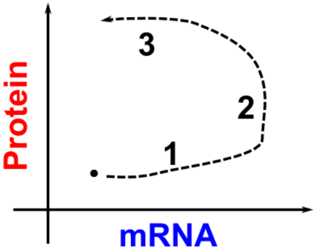

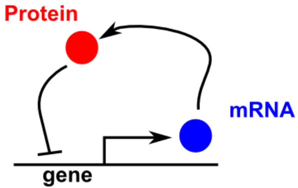

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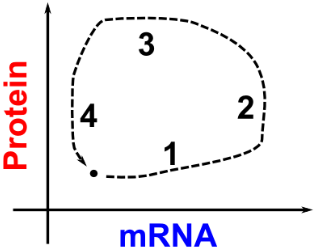

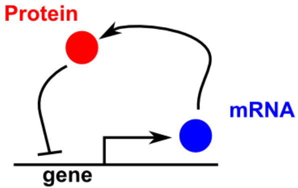

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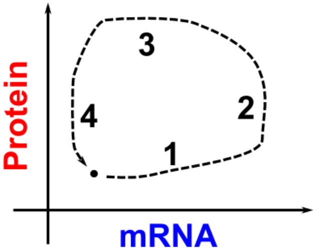
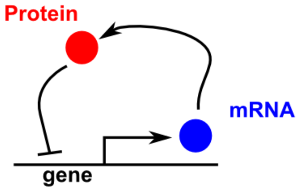
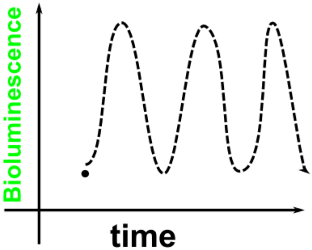


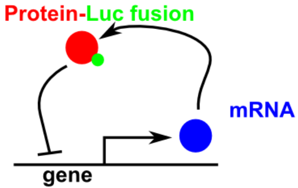


1. mRNA is transcribed.
2. Protein is translated.
3. mRNA is degraded, expression is repressed.
4. Protein is degraded, no mRNA to translate.
5. Repeat.

Example: a highly simplified genetic feedback loop.

Recording from biological feedback loops





Recording from individual circadian oscillators.

Example: a highly simplified genetic feedback loop.

Feedback loops must meet necessary criteria for oscillation

1. Negative feedback

Novak and Tyson, Nat Rev Mol Cell Biol, 2008.

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2. Time delays (intermediates or hysteresis)

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Feedback loops must meet necessary criteria for oscillation

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2. Time delays (intermediates or hysteresis)
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If these criteria are met, molecular concentrations follow a closed, stable, attractive trajectory called the *limit cycle*.

Novak and Tyson, Nat Rev Mol Cell Biol, 2008.

Mathematical structure of a circadian oscillator

Biochemical states $x(t)$ are governed by dynamics:

$$\frac{dx}{dt} = f(x, p, u).$$

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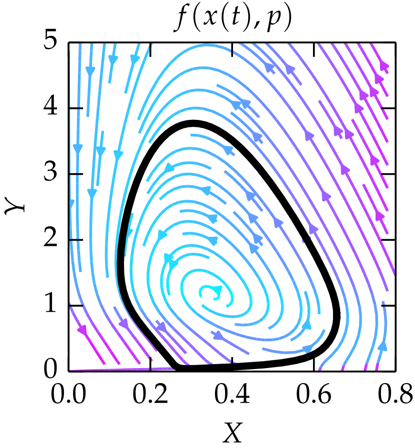
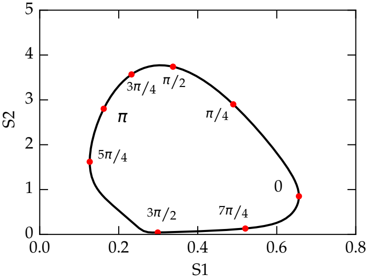


Fig: PC St. John

Defining the phase map

Each point x_0 on the limit cycle can be mapped to a unique phase $\phi \in [0, 2\pi)$ via the mapping Φ.



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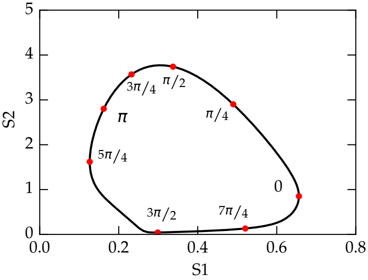
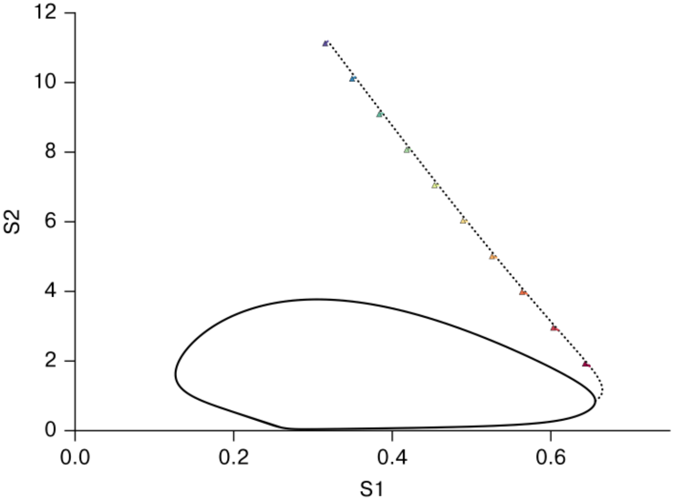


A point not on the limit cycle may be assigned the phase it converges to.

fig: PC St. John

Expansion of phase into state space



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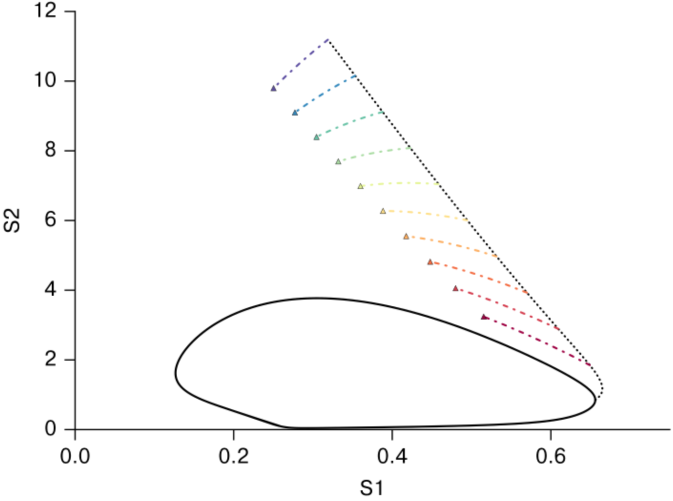

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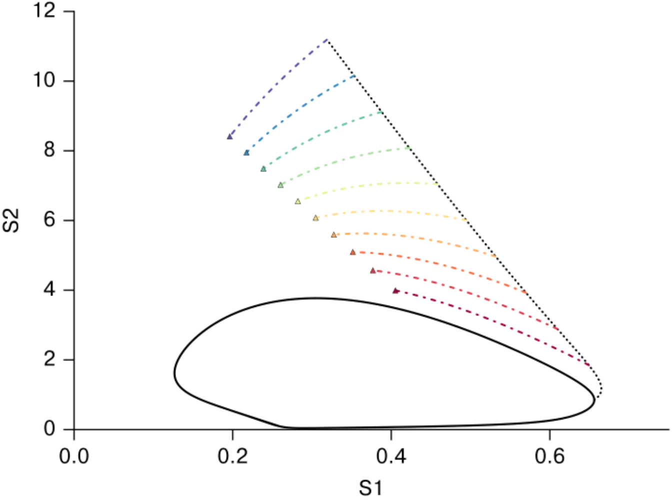

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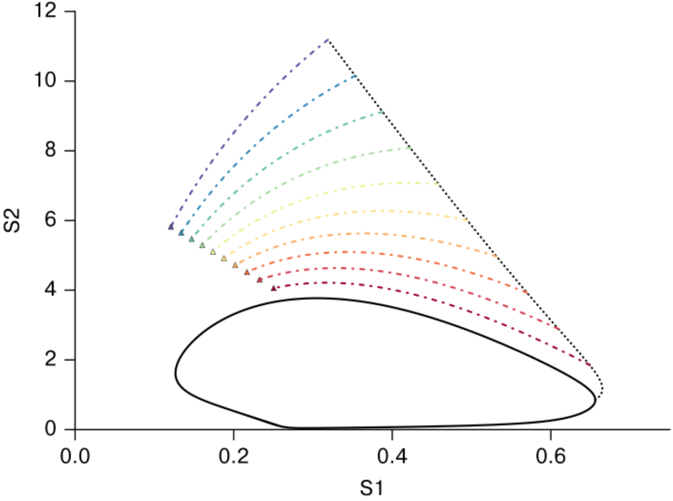

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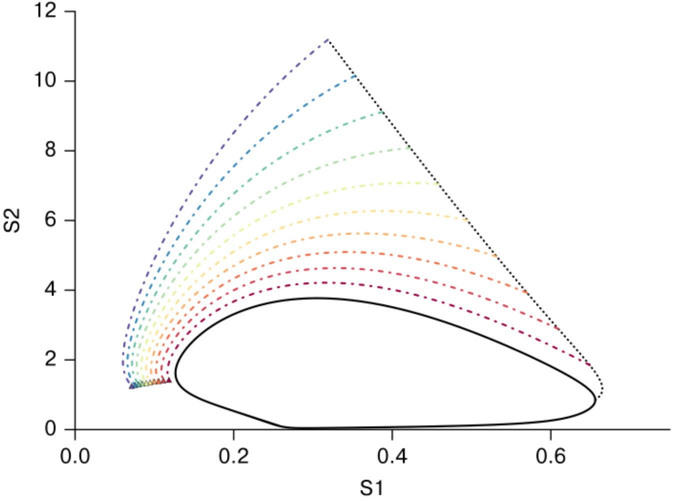

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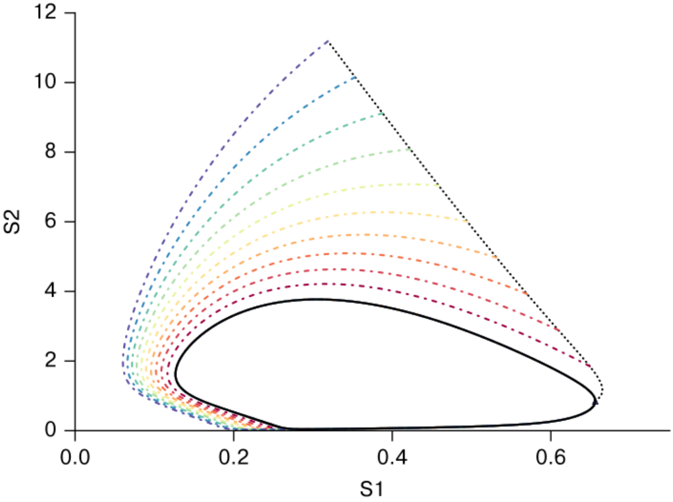
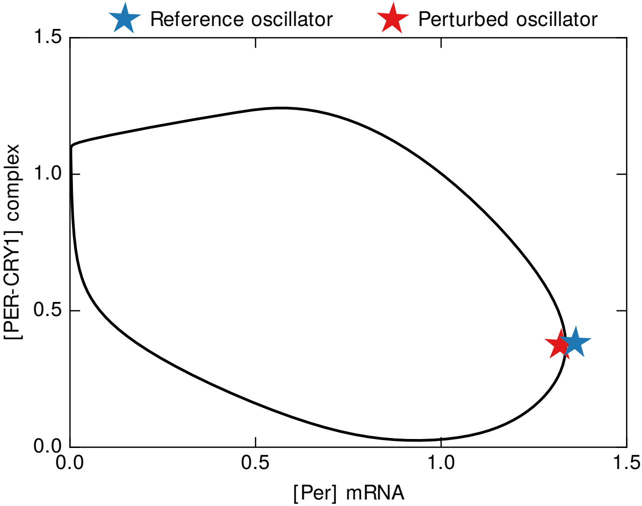


Limit cycle phase responses

A perturbation shifts the oscillator away from the limit cycle.



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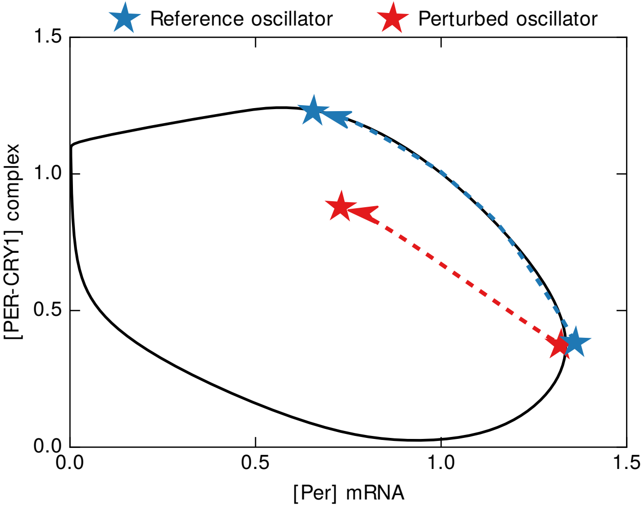
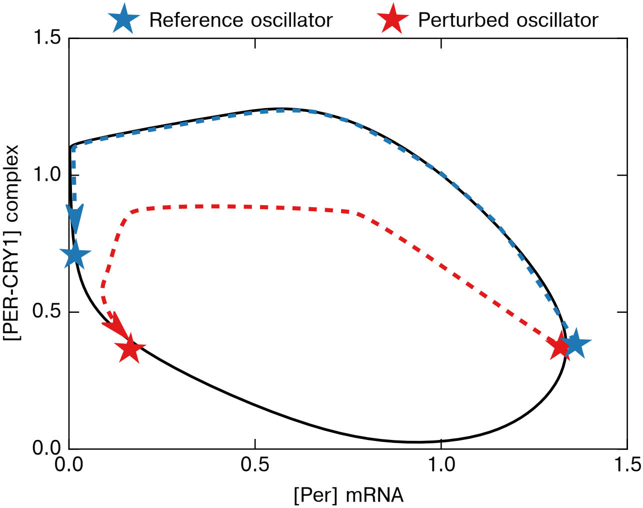


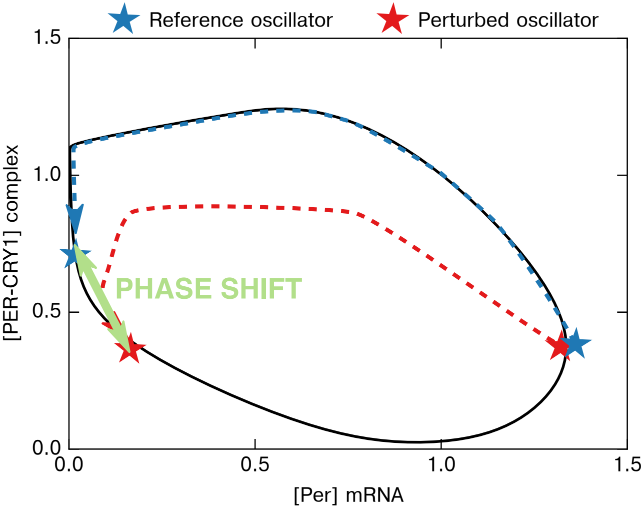
Limit cycle phase responses

System dynamics govern its eventual return.



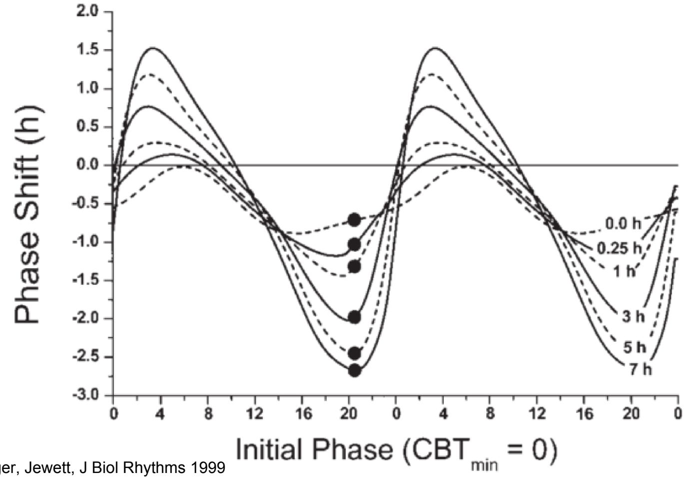
Limit cycle phase responses

The oscillator returns to the cycle with a new phase (advance).



Phase response curves (PRCs)

Describes how the system responds to a perturbation of a certain strength and duration applied at each phase.



Kronauer, Forger, Jewett, J Biol Rhythms 1999

Evidence for a physical limit cycle underlying circadian oscillation

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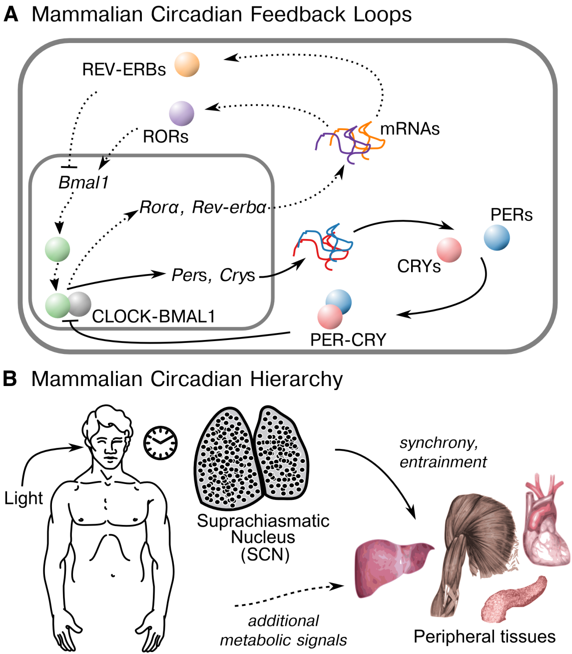
4. Gene networks mimic mathematical structure

The mammalian genetic oscillator and physiological hierarchy

Takahashi Annu Rev Genet 2017
fig: Abel and Doyle, Chem Eng Res Des 2016

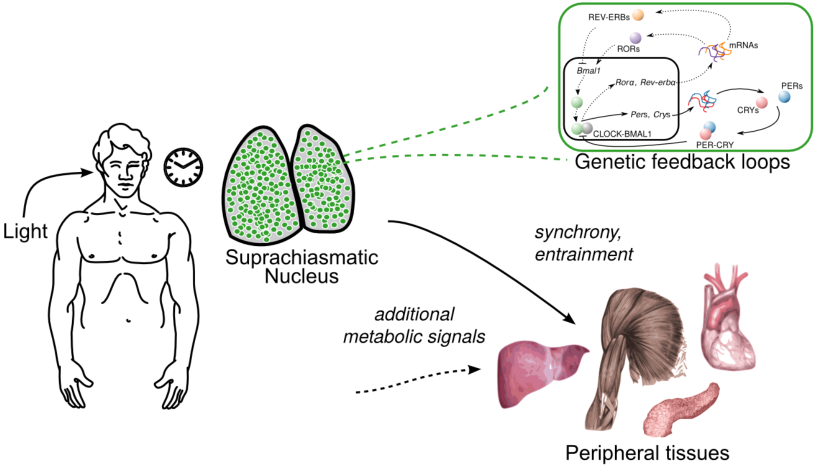


Dissertation outline

Central aims

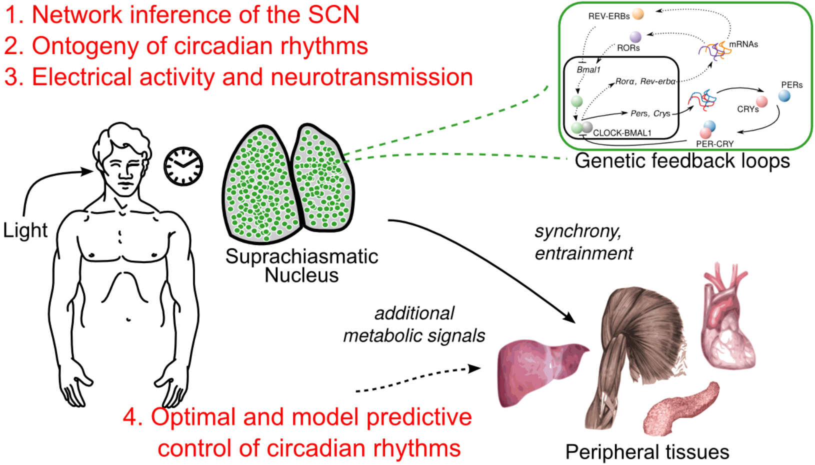
- Understand how communication within the SCN results in synchrony and observed phenomena
- Develop mathematical approaches for controlling circadian rhythms

My dissertation research



My dissertation research

1. Network inference of the SCN
2. Ontogeny of circadian rhythms
3. Electrical activity and neurotransmission



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5. Control of oscillator populations

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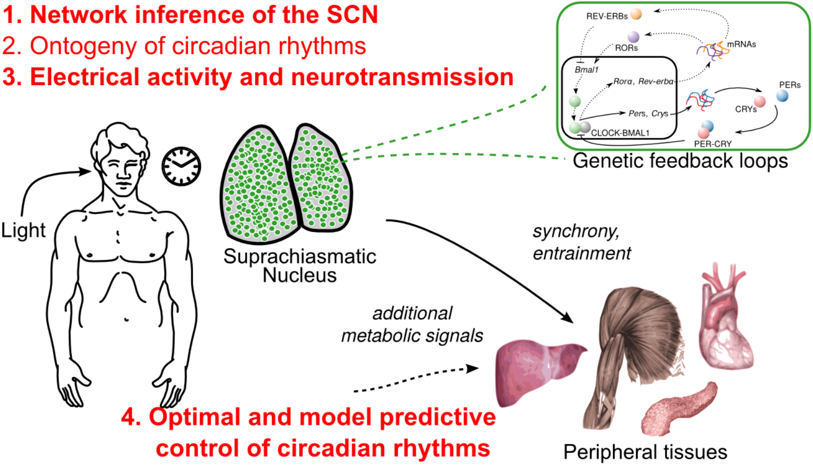

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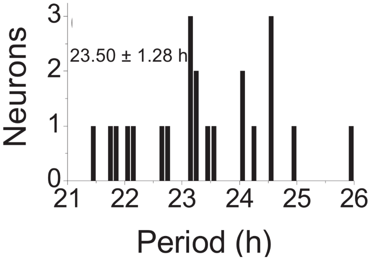
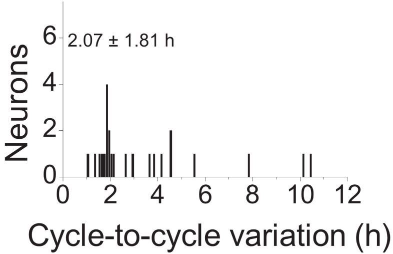
Exploring neurotransmission in the suprachiasmatic nucleus

Neural oscillators must communicate to be effective





Herzog *et al.* J Biol Rhythms 2004

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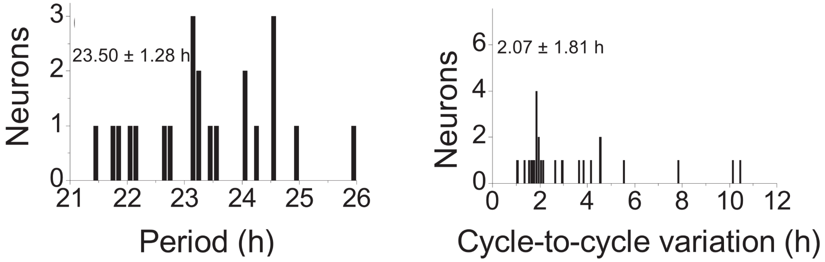

If intercellular communication is interrupted, oscillators lose synchrony and amplitude.

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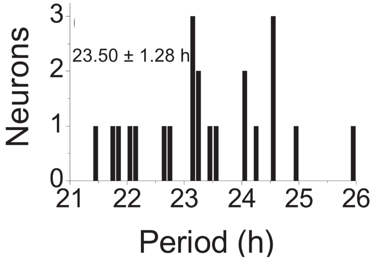

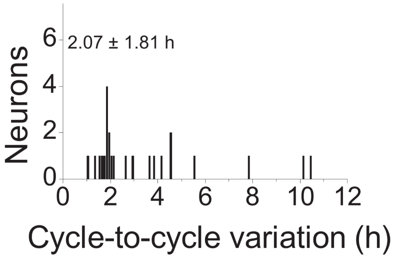

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Challenge: better understand the roles of communication pathways and networks in the context of circadian rhythms.

Herzog *et al.* J Biol Rhythms 2004

Basics of neurotransmission

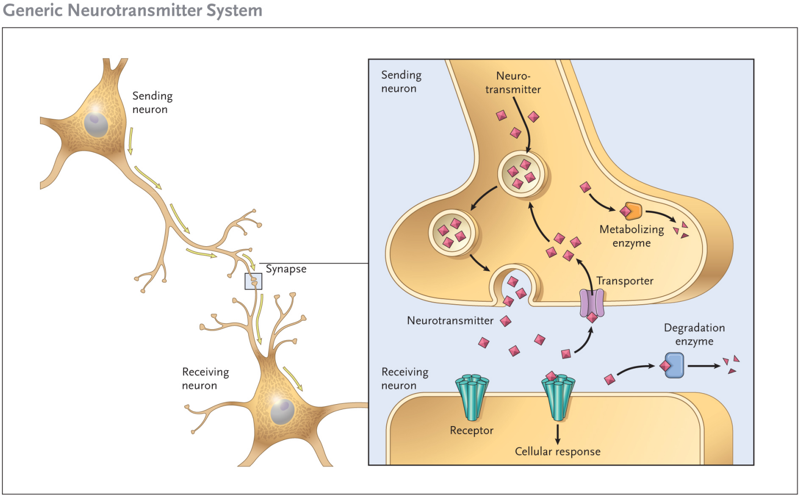
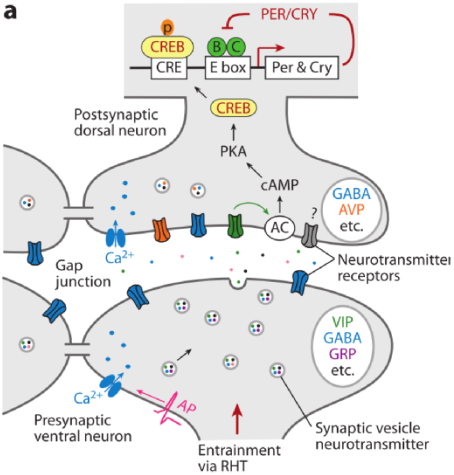


Fig: NIH

Pathways of neurotransmission in the SCN



- Firing drives release of metabotropic neurotransmitters
- Neurotransmitters modulate circadian transcription via CREB

Welsh, Takahashi, Kay Annu Rev Physiol 2010

Question: which neurons are implicated in synchrony?

Experiment: block electrical firing, wait for desynchrony, allow to resynchronize. Infer connectivity with mutual information.

Abel *et al.* PNAS 2016

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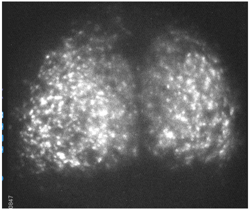

PER2::LUC SCN
collaborator: Daniel Granados-Fuentes, Herzog lab

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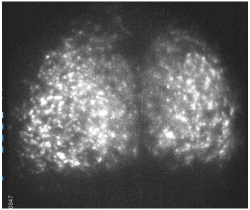

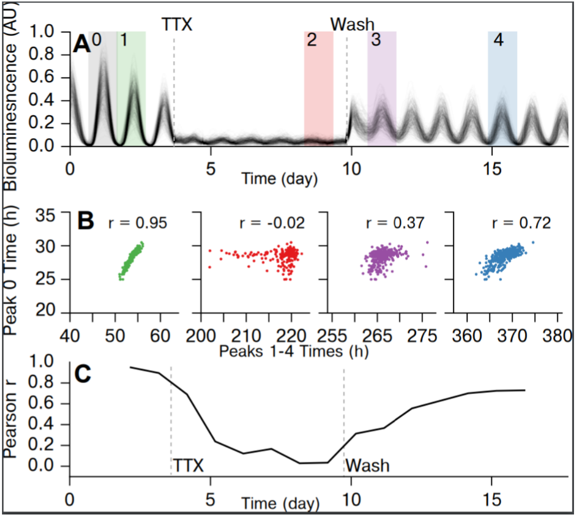

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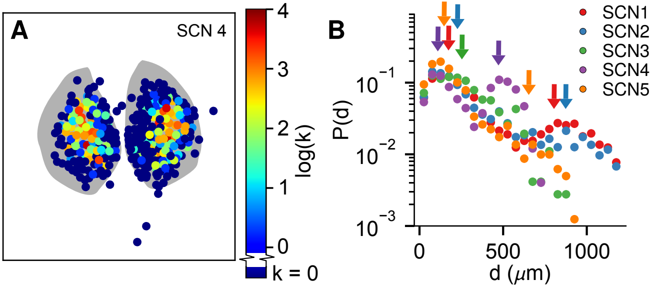
Structure of the SCN network



Small-world, bilateral symmetric, with hubs located in SCN central regions.

Abel *et al.* PNAS 2016

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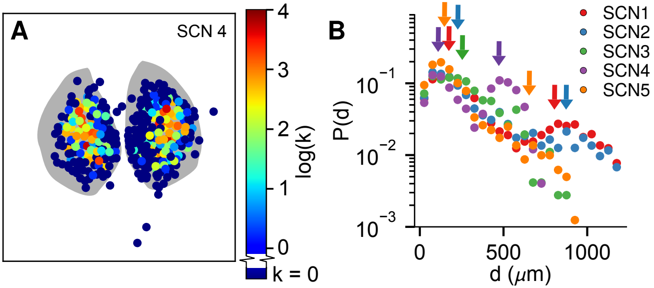

Small-world, bilateral symmetric, with hubs located in SCN central regions.

This does not perfectly correlate to a single known distribution of neurotransmitter expression. Which are involved?

Abel *et al.* PNAS 2016

The role of VIP neurons in synchrony and entrainment

One pathway likely driving this synchrony is VIP.

Aton *et al*. Nat Neurosci 2005

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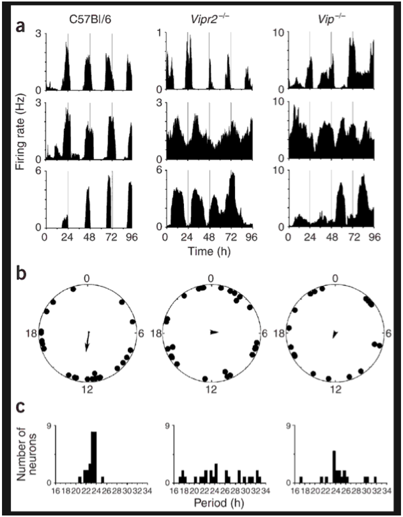

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Study design: investigating role of VIP, electrical neurotransmission, and synchrony

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Mazuski, Abel, Chen, Hermanstyne, Doyle, and Herzog, in revision

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2. Apply those patterns to VIP neurons via optogenetic stimulation.

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2. Apply those patterns to VIP neurons via optogenetic stimulation.
3. Characterize VIP release and circadian response.

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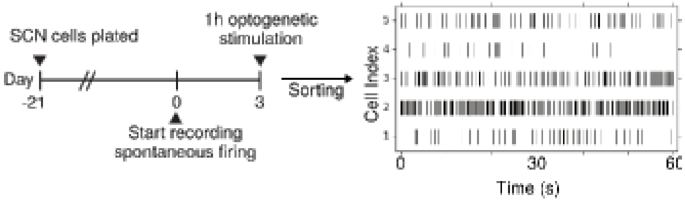
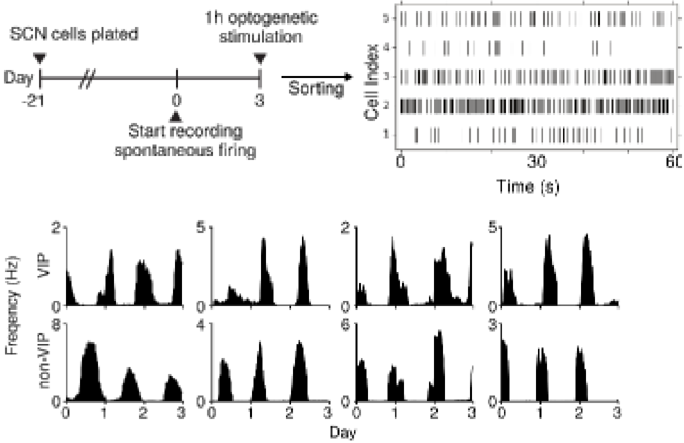
Recording from VIP and non-VIP SCN neurons

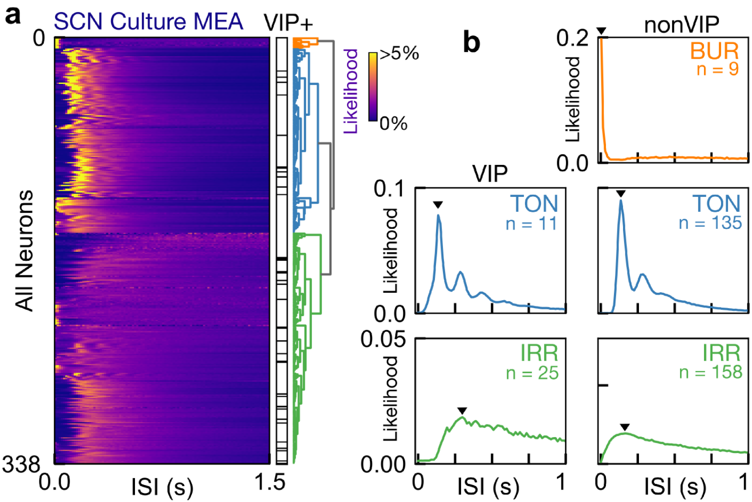


Recording from VIP and non-VIP SCN neurons



Mazuski, Abel, Chen, Hermanstyne, Doyle, and Herzog, in revision

Identifying firing patterns in the SCN



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Optogenetic stimulation triggers VIP release in a frequency-dependent fashion

Apply optogenetic stimulation with constant rate at variable instantaneous frequency.

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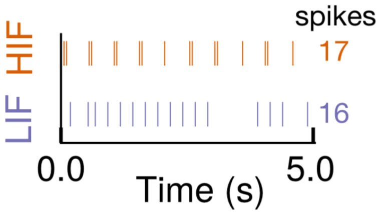

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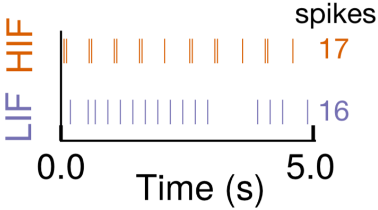
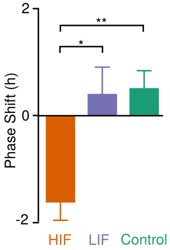
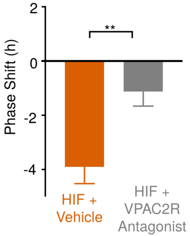
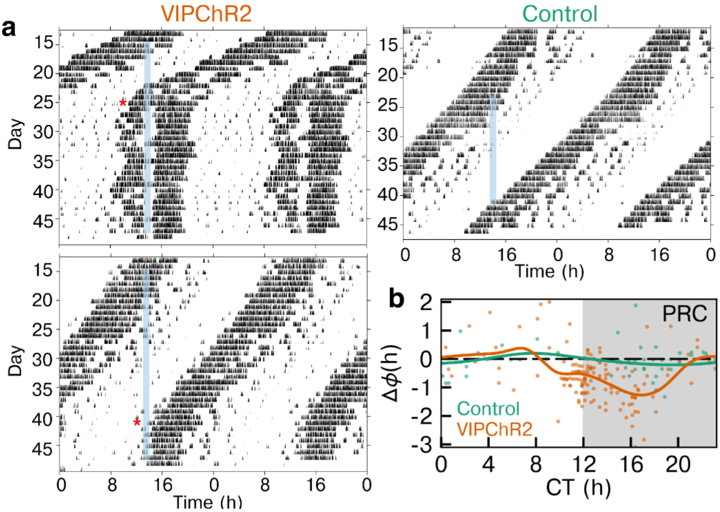


VIP antagonist eliminates phase shift.





Optogenetic stimulation of VIP neurons entrains circadian behavior in vivo via phase delays



Mazuski, Abel, Chen, Hermanstyne, Doyle, and Herzog, in revision

Conclusions: neurotransmission in the SCN

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2. Electrical activity: a fundamental component of the oscillator?

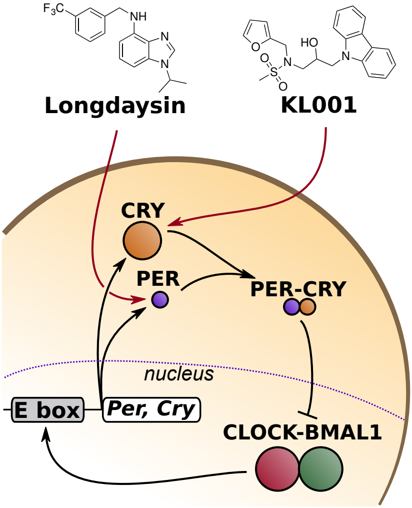
How does this relate to control? Control is the inverse problem.

Controlling circadian rhythms

The search for circadian pharmaceuticals

Potential uses:

- resetting the clock
- "strengthening" oscillation
  - Robustness
  - Amplitude



Hirota *et al.* Science 2012; St. John *et al.* PNAS 2014

The necessity of dynamic pharmaceutical dosing

Traditional pharmaceuticals: phase-agnostic, long half-life

- does not elicit a dynamic response (cannot reset the clock)
- drugs with transient effect discarded

St. John and Doyle PLoS Comp Bio 2015; Abel and Doyle Chem Eng Res Des 2016

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Challenge: drug application timing may result in drastically different responses.

St. John and Doyle PLoS Comp Bio 2015; Abel and Doyle Chem Eng Res Des 2016

Revisiting the mathematical formulation

Consider the smooth dynamical system:

$$\frac{dx}{dt} = f(x, p, u)$$

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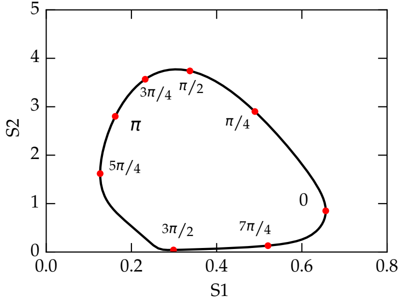
period: T

frequency: $\omega = \frac{2\pi}{T}$

Development of the phase-reduced model



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Abel, Chakrabarty, and Doyle, in revision.

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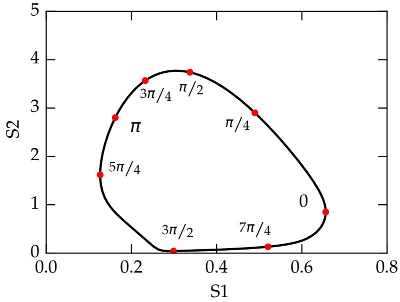

Perform a first-order expansion of $\hat{\Phi}[\theta(t, x_a, u)]$ in u:

$$\begin{aligned}\varphi(t,u) &= \hat{\Phi}[\theta(t,x_a,u)] \\ \frac{d\varphi}{dt} &= \frac{d}{dt}\hat{\Phi}[\theta(t,x_a,u)] \\ &= \omega + \underbrace{\frac{\partial}{\partial t}\frac{\partial \hat{\Phi}[\gamma(t,x_0)]}{\partial u}u(t)}_{\text{linear approx. in } u}\end{aligned}$$

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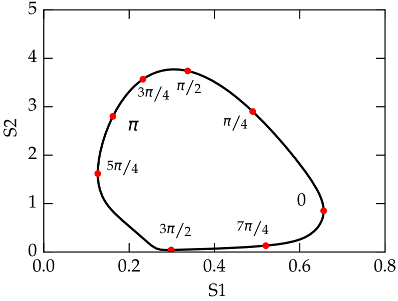

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\end{aligned}$$

Infinitesimal in both time and perturbation magnitude.

Abel, Chakrabarty, and Doyle, in revision.

Development of the phase-reduced model

We incorporate $u(t)$ into the ODE model as a time-dependent modification of parameters p:

$$p(t) = p_0 + u(t)$$

so that $dp = du$.

Taylor *et al.* IEEE Trans Autom Control 2008; see Abel and Doyle, Chem Eng Res Des 2016 for calculation of ipPRC.

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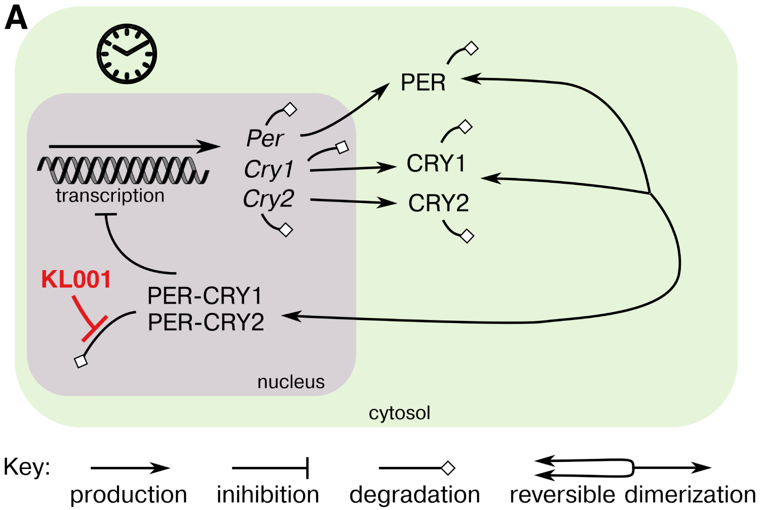
Thus:

$$\boxed{\frac{d\varphi}{dt} = \omega + \frac{\partial}{\partial t}\frac{\partial\hat{\Phi}[\gamma(t, x_0)]}{\partial p}u(t),}$$

where $\frac{\partial}{\partial t}\frac{\partial\hat{\Phi}[\gamma]}{\partial p} = B(t)$ is the infinitesimal parametric phase response curve (ipPRC) for the oscillator on the limit cycle.

Taylor *et al.* IEEE Trans Autom Control 2008; see Abel and Doyle, Chem Eng Res Des 2016 for calculation of ipPRC.

Example: KL001 action



Mechanism: St. John *et al.* PNAS 2014. Fig: Abel, Chakrabarty, and Doyle, in revision

Example: model reduction for phase control

Full limit cycle model

8 material balances (ODEs), 21 kinetic parameters

$$\frac{d\mathbf{p}}{dt} = \frac{v_{txn,\mathbf{p}}}{k_{txn,\mathbf{p}} + (\mathbf{C1N} + \mathbf{C2N})^3} - \frac{v_{deg,\mathbf{p}}\ \mathbf{p}}{k_{deg,\mathbf{p}} + \mathbf{p}} \quad (1)$$

$$\frac{d\mathbf{c1}}{dt} = \frac{v_{txn,\mathbf{c1}}}{k_{txn,\mathbf{c}} + (\mathbf{C1N} + \mathbf{C2N})^3} - \frac{v_{deg,\mathbf{c1}}\ \mathbf{c1}}{k_{deg,\mathbf{c}} + \mathbf{c1}} \quad (2)$$

$$\frac{d\mathbf{c2}}{dt} = \frac{v_{txn,\mathbf{c2}}}{k_{txn,\mathbf{c}} + (\mathbf{C1N} + \mathbf{C2N})^3} - \frac{v_{deg,\mathbf{c2}}\ \mathbf{c2}}{k_{deg,\mathbf{c}} + \mathbf{c2}} \quad (3)$$

$$\frac{d\mathbf{P}}{dt} = k_{tln,\mathbf{p}}\ \mathbf{p} - \frac{v_{deg,\mathbf{P}}\ \mathbf{P}}{k_{deg,\mathbf{P}} + \mathbf{P}} - v_{a,\mathbf{CP}}\ \mathbf{P}\ \mathbf{C1} + v_{d,\mathbf{CP}}\ \mathbf{C1N} - v_{a,\mathbf{CP}}\ \mathbf{P}\ \mathbf{C2} + v_{d,\mathbf{CP}}\ \mathbf{C2N} \quad (4)$$

$$\frac{d\mathbf{C1}}{dt} = \mathbf{c1} - \frac{v_{deg,\mathbf{C1}}\ \mathbf{C1}}{k_{deg,\mathbf{C}} + \mathbf{C1}} - v_{a,\mathbf{CP}}\ \mathbf{P}\ \mathbf{C1} + v_{d,\mathbf{CP}}\ \mathbf{C1N} \quad (5)$$

$$\frac{d\mathbf{C2}}{dt} = \mathbf{c2} - \frac{v_{deg,\mathbf{C2}}\ \mathbf{C2}}{k_{deg,\mathbf{C}} + \mathbf{C2}} - v_{a,\mathbf{CP}}\ \mathbf{P}\ \mathbf{C2} + v_{d,\mathbf{CP}}\ \mathbf{C2N} \quad (6)$$

$$\frac{d\mathbf{C1N}}{dt} = v_{a,\mathbf{CP}}\ \mathbf{P}\ \mathbf{C1} - v_{d,\mathbf{CP}}\ \mathbf{C1N} - \frac{(vdCn - u(t))\ \mathbf{C1N}}{k_{deg,\mathbf{Cn}} + \mathbf{C1N} + \mathbf{C2N}} \quad (7)$$

$$\frac{d\mathbf{C2N}}{dt} = v_{a,\mathbf{CP}}\ \mathbf{P}\ \mathbf{C2} - v_{d,\mathbf{CP}}\ \mathbf{C2N} - \frac{((vdCn - u(t))\ m_{\mathbf{C2N}})\ \mathbf{C2N}}{k_{deg,\mathbf{Cn}} + \mathbf{C2N} + \mathbf{C1N}} \quad (8)$$

Abel, Chakrabarty, and Doyle, in revision.

Example: model reduction for phase control

Effect of control input

Decrease in degradation rates for nuclear dimers.

$$\frac{d\mathrm{C1P}}{dt} = v_{\mathrm{a,CP}}\mathrm{P}\cdot\mathrm{C1} - v_{\mathrm{d,CP}}\mathrm{C1P} - \frac{(vdCn - u(t))\mathrm{C1P}}{k_{\mathrm{deg,Cn}} + \mathrm{C1P} + \mathrm{C2P}},$$

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Abel and Doyle, Chem Eng Res Des 2016

Example: model reduction for phase control

Effect of control input

Calculate the phase sensitivity to yield the phase only formulation:

$$\frac{d\varphi}{dt} = \omega + B(\varphi) \cdot u(t)$$

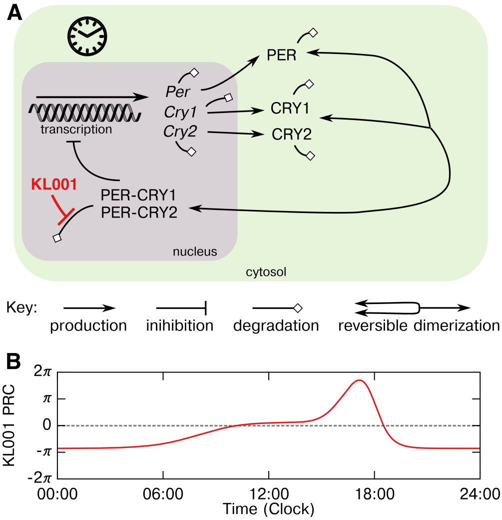
and

$$B(\varphi) = -\frac{\partial}{\partial t} \frac{\partial \hat{\Phi}[\gamma(t, x_0)]}{d(vdCn)}$$

where $B(\varphi)$ is the KL001 ipPRC.

Abel, Chakrabarty, and Doyle, in revision.

ipPRC calculation



Abel, Chakrabarty, and Doyle, Proc. 20th IFAC World Congress 2017.

The phase resetting problem

Oscillator:

$$\frac{d\varphi}{dt} = \omega + B(\varphi) \cdot u(t), \quad \varphi(0) = \phi_0$$

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Environment:

$$\frac{d\varphi_r}{dt} = \omega_r + \Delta\phi_f \delta(t_{shift}) \quad \varphi_r(0) = \phi_0$$

Abel, Chakrabarty, and Doyle, in revision.

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Phase error:

$$\chi(t) = \varphi(t) - \varphi_r(t) \mod 2\pi$$

The terminal condition is $\chi(t_f) = 0$. We want to reach this in minimum time.

Abel, Chakrabarty, and Doyle, in revision.

Optimal phase shifting: fixed endpoint, free time

State dynamics:

$$\dot{\varphi} = \omega + B(\varphi) \cdot u(t) \qquad \text{(ODE)}$$

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Hamiltonian:

$$H(\varphi, \lambda, u) = (\omega + B(\varphi) \cdot u) \cdot \lambda - 1 \qquad \text{(H)}$$

Pontryagin's maximum principle

Maximization condition:

$$H(\varphi, \lambda, u) = \max_{u_{\min} \leq u \leq u_{\max}} \{(\omega + B(\varphi) \cdot u) \cdot \lambda - 1\} \qquad \text{(M)}$$
$$= \omega \cdot \lambda - 1 + \max_{u_{\min} \leq u \leq u_{\max}} \{B(\varphi) \cdot u \cdot \lambda\}$$

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$$u^\star(t) = \begin{cases} u_{\max} & \text{if } B(\varphi) \cdot \lambda > 0 \\ u_{\min} & \text{if } B(\varphi) \cdot \lambda \leq 0 \end{cases}$$

which is **bang-bang control**.

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The terminal condition $\lambda(t_f) = 0$, so costate λ will ever only be either positive or negative. Thus **control input for a specific case depends only on** $\operatorname{sgn}(B(\varphi))$.

Similar result shown for limit cycle model: Zhang, Qiao, Julius Automatica 2016

Optimal control inputs

For an oscillator with desired phase shift $\Delta\varphi_f$, starting at phase $\varphi(0) = \phi_0$, the optimal control input is that for achieving either the positive phase shift:

$$u^+(t) = \begin{cases} u_{\max} & \text{if } B(\varphi) > 0 \\ u_{\min} & \text{if } B(\varphi) \le 0 \end{cases}$$

or the negative phase shift:

$$u^-(t) = \begin{cases} u_{\max} & \text{if } B(\varphi) < 0 \\ u_{\min} & \text{if } B(\varphi) \ge 0 \end{cases}.$$

Abel, Chakrabarty, and Doyle, in revision.

Example: optimal phase shifting

Either **delay** or advance, *not both*

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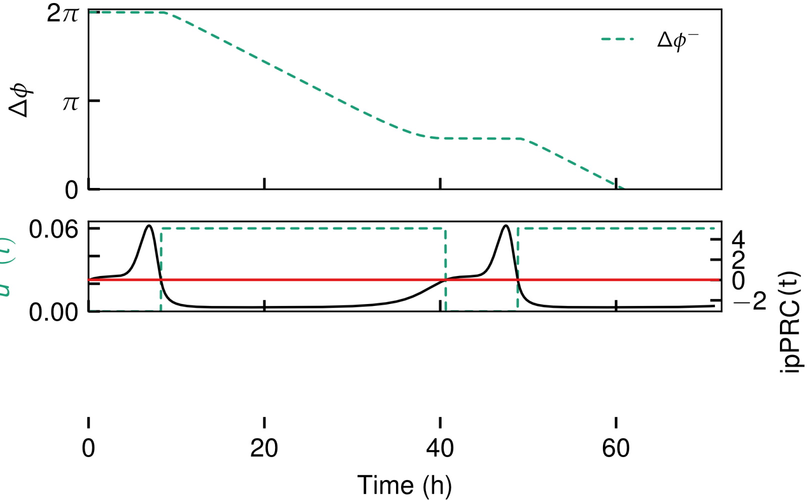

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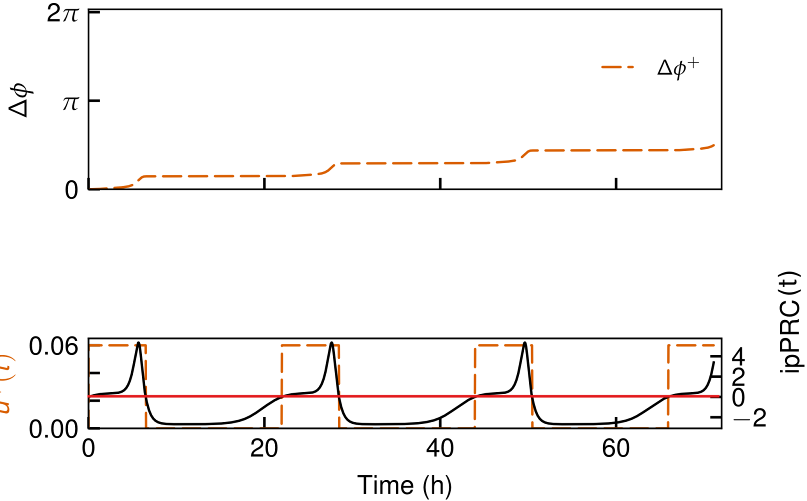
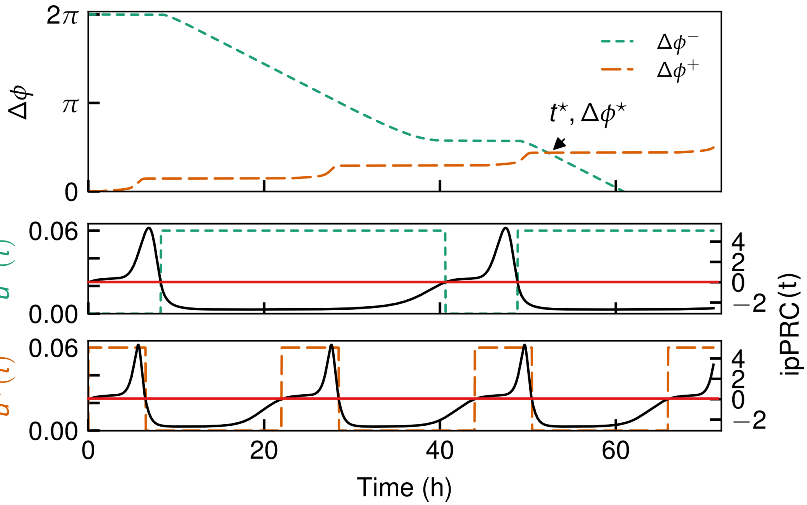
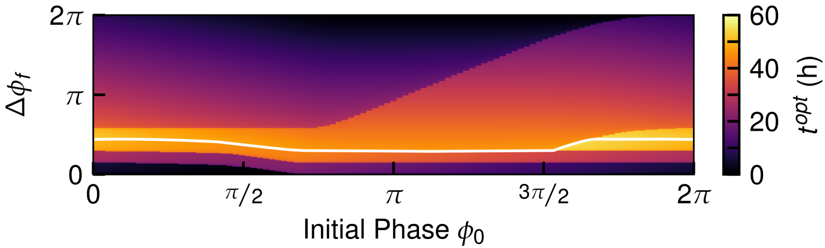


A bound on the time to reset phase

Where these shifts meet is the most "distant" phase.



Optimal control law for any shift



Also allows identification of optimal direction of phase shifting.

Application for model predictive control

MPC is a form of feedback control where control is changed at discrete steps based on an optimization of predicted trajectory.

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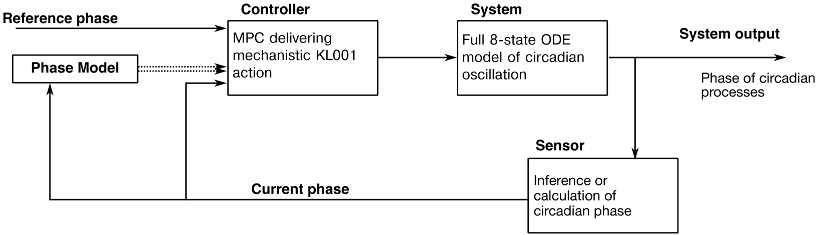

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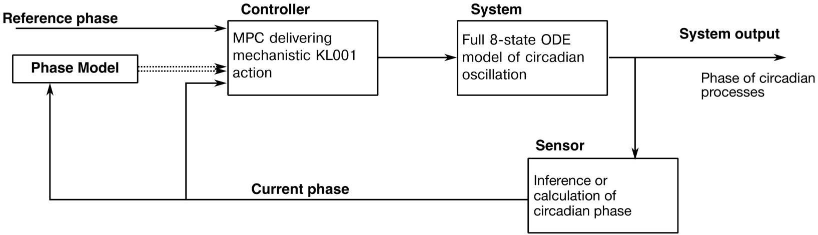
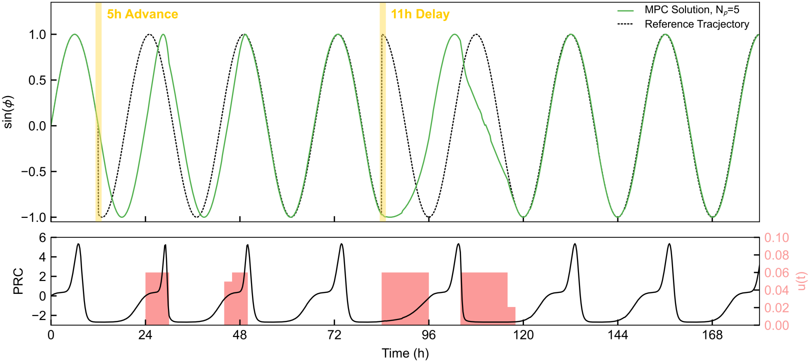


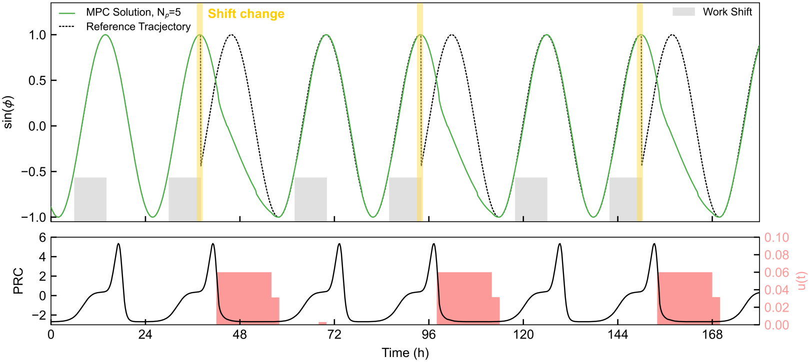
Not shown: bounding error between optimal and model predictive control (Abel, Chakrabarty, and Doyle, in revision).

MPC applied in silico for jet lag



Abel, Chakrabarty, and Doyle, in revision.

MPC applied in silico for rotating shift work



Schedule from Vetter *et al.*, Curr Biol 2015.

Abel, Chakrabarty, and Doyle, in revision.

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    - Upper bounds on error from MPC implementation.

Future study: control of circadian rhythms

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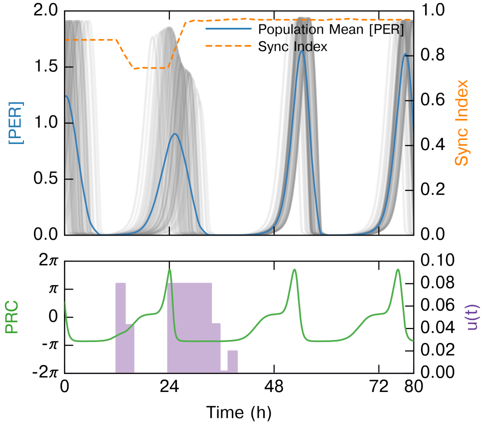

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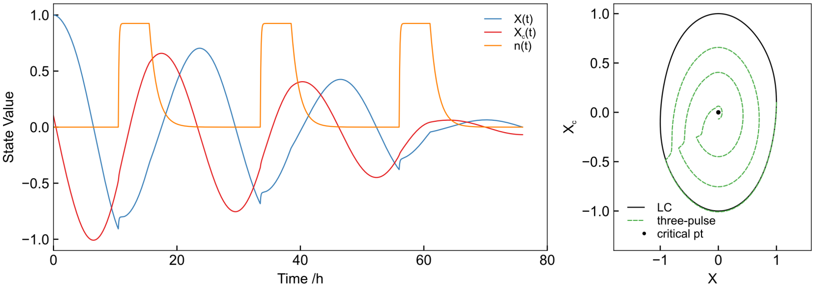

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Collaborator + Committee Member

Prof. Erik Herzog (WUSTL)

DAC & Committee

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Prof. Galit Lahav

Prof. John Higgins

Prof. Charles Czeisler

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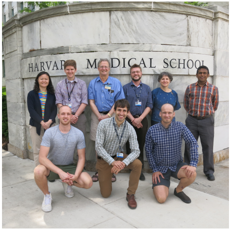
Prof. Elizabeth Klerman (HMS/BWH)

Doyle lab, Harvard University

AMU, Brigham and Women's Hospital



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Dr. Cristina Mazuski
Petzold lab
Dr. Brian Drawert
Klerman lab/BWH
Dr. Amene Asgari
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Dr. Sukwon Jung

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Open questions?