Harnessing Mathematical Models to Decode Sleep and Circadian Health

Ruby Kim
Postdoctoral Assistant Professor
Department of Mathematics
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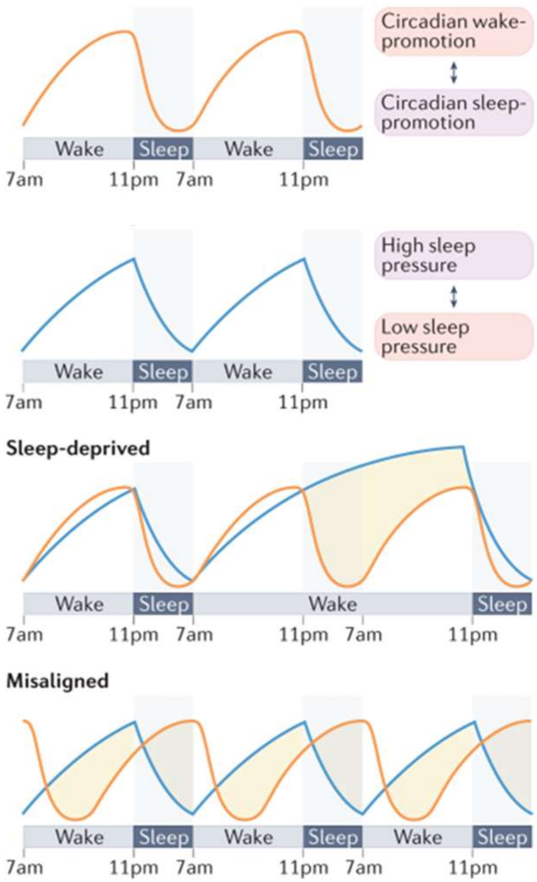
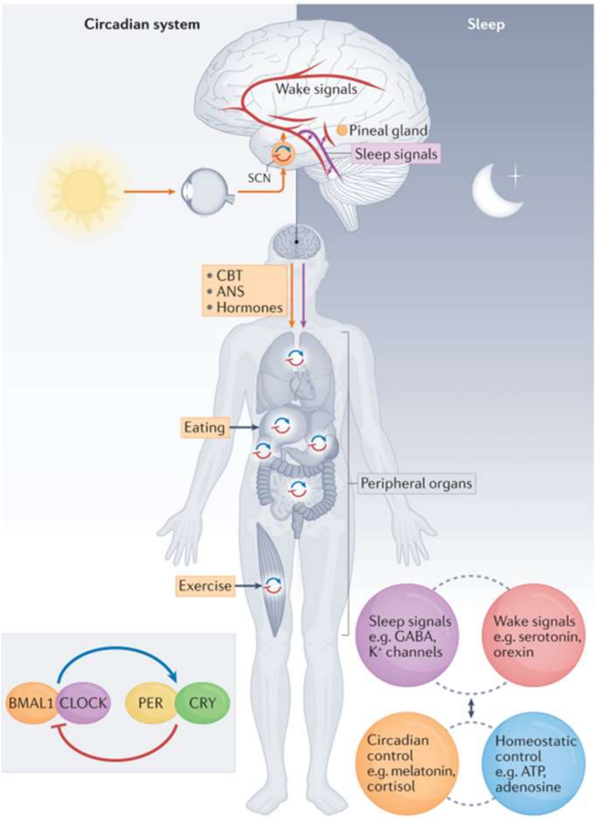
Mammoth Cave Study: Self-Sustained, Internal Rhythms

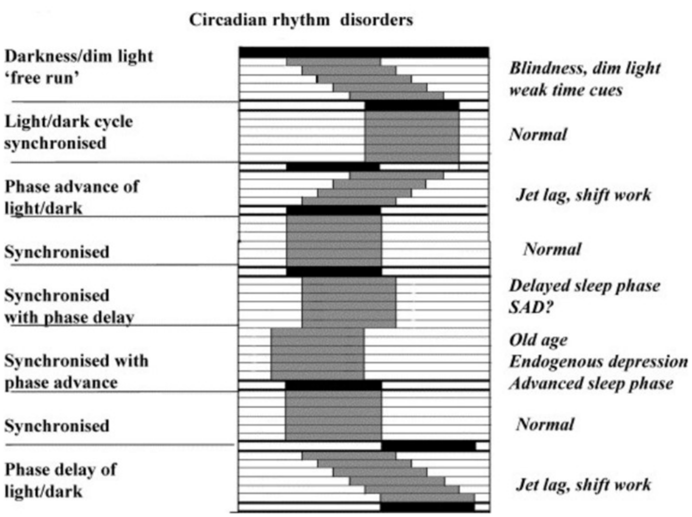
Kleitman and Richardson, 1938
32 days in Mammoth Cave, Kentucky
University of Chicago Library

Circadian Rhythms and Two-Process Model





Lane et al., Nat Rev Genet (2023)

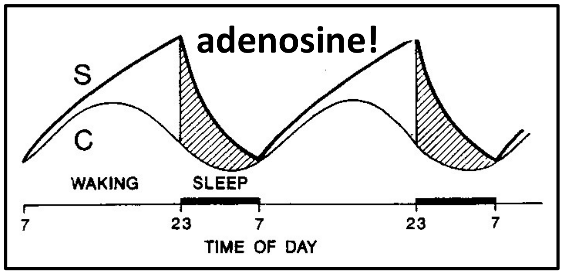


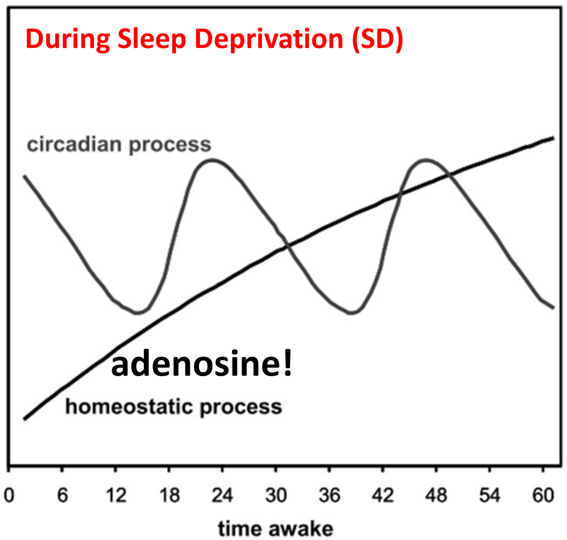
Arendt et al. (2005)

Two-Process Model of Fatigue

Sleep (S) Drive

Circadian (C) Drive



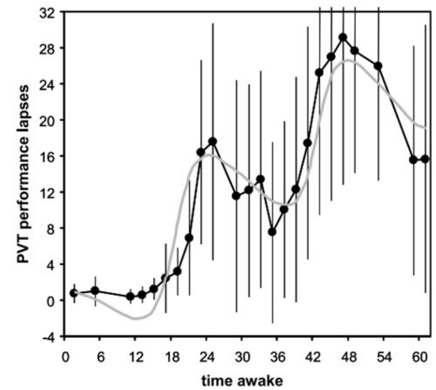


Psychomotor Vigilance Test

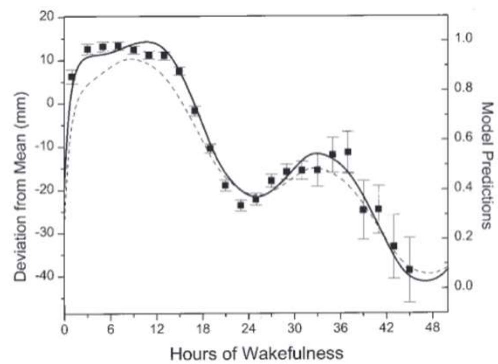
Test for reaction time

Visual Analog Scale

Self-reported alertness

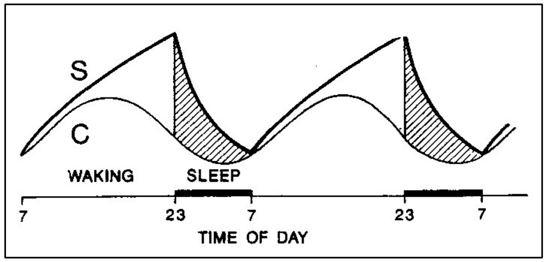


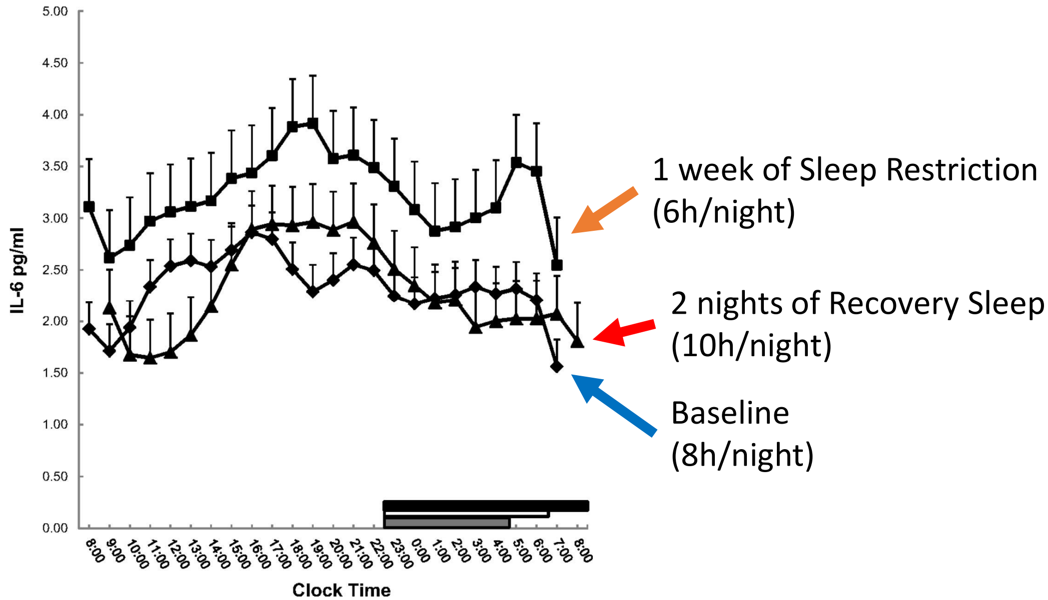
Van Dongen et al., Industrial Health (2009)



Jewett et al., JBR (1999)

Evidence of Two-Process Dynamics





Pejovic et al. (2013)

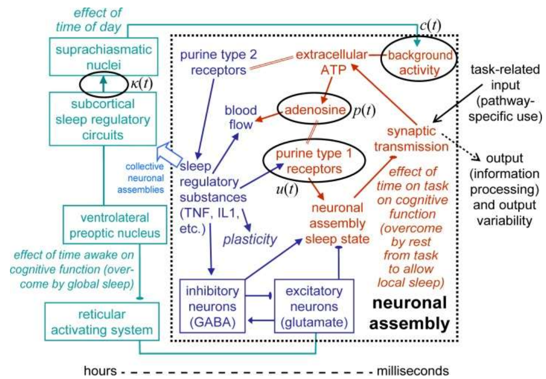
- Interleukin-6 (IL-6) is a protein associated with fatigue
- We can build mathematical models of
  1. sleep drive,
  2. circadian drive, and
  3. a physiological output

Sleep Drive (Adenosine)
McCauley et al. (2013)

1. **sleep drive**
2. circadian drive
3. physiological output

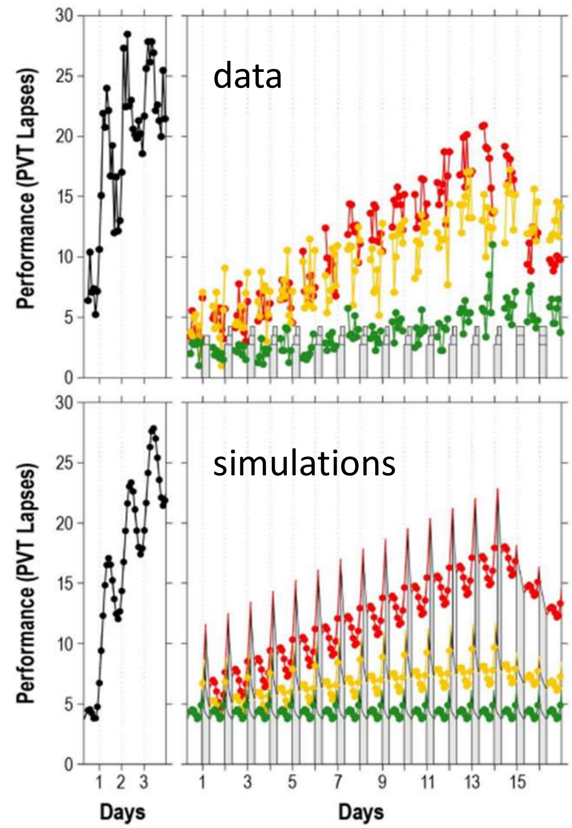
State variables ***p(t)*** and ***u(t)***
- ***p***: extracellular adenosine
- ***u***: adenosine receptor density

Time-dependent processes
- Circadian clock and sleep/wake



$$\begin{bmatrix} \frac{dp}{dt} \\ \frac{du}{dt} \end{bmatrix} = \begin{bmatrix} \alpha_w & \alpha_w \beta_w \\ 0 & \eta_w \end{bmatrix} \begin{bmatrix} p \\ u \end{bmatrix} + \begin{bmatrix} g_w(t) \\ 0 \end{bmatrix}$$ during wake

$$\begin{bmatrix} \frac{dp}{dt} \\ \frac{du}{dt} \end{bmatrix} = \begin{bmatrix} \alpha_s & \alpha_s \beta_s \\ 0 & \eta_s \end{bmatrix} \begin{bmatrix} p \\ u \end{bmatrix} + \begin{bmatrix} g_s(t) \\ 1 \end{bmatrix}$$ during sleep



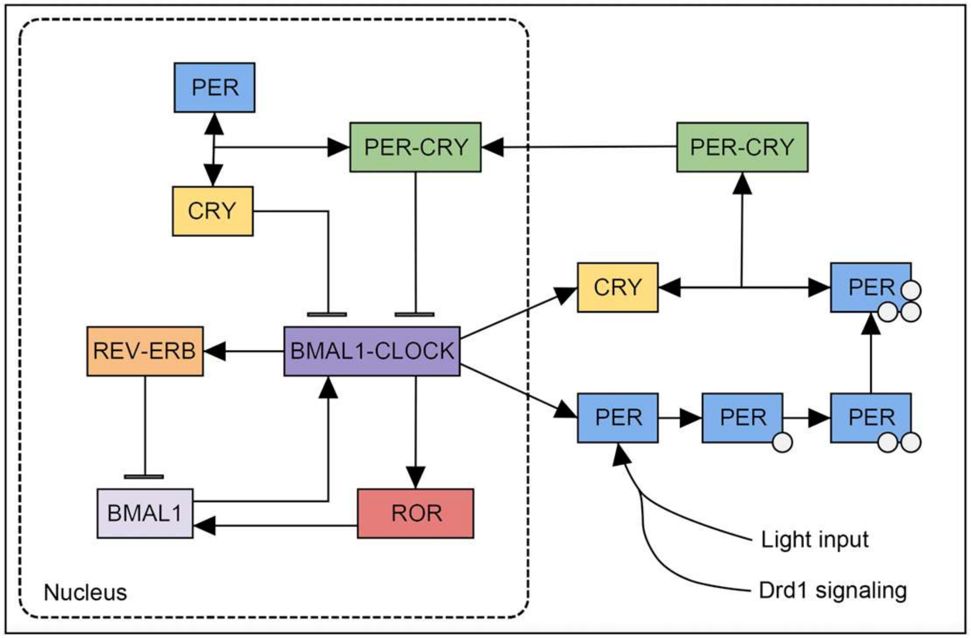
4h/night

6h/night

8h/night

Mechanisms of Circadian Rhythms

Kim & Reed (2021)



$$\frac{dP_1}{dt} = r_1\, L(t)\, f(BC, P_4, K_d) - r_2 P_1,$$

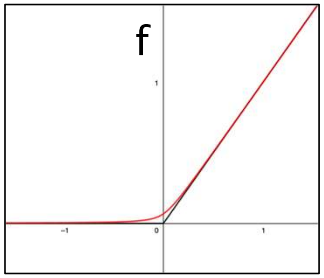
Protein sequestration	$BC + P_4 \rightleftharpoons BC\ P_4$

Concentration of free BMAL1-CLOCK (*BC*):

$$f(BC, P_4, K_d) = \frac{BC - P_4 - K_d + \sqrt{(BC - P_4 - K_d)^2 + 4K_d BC}}{2}$$

Taking $K_d \to 0$ gives

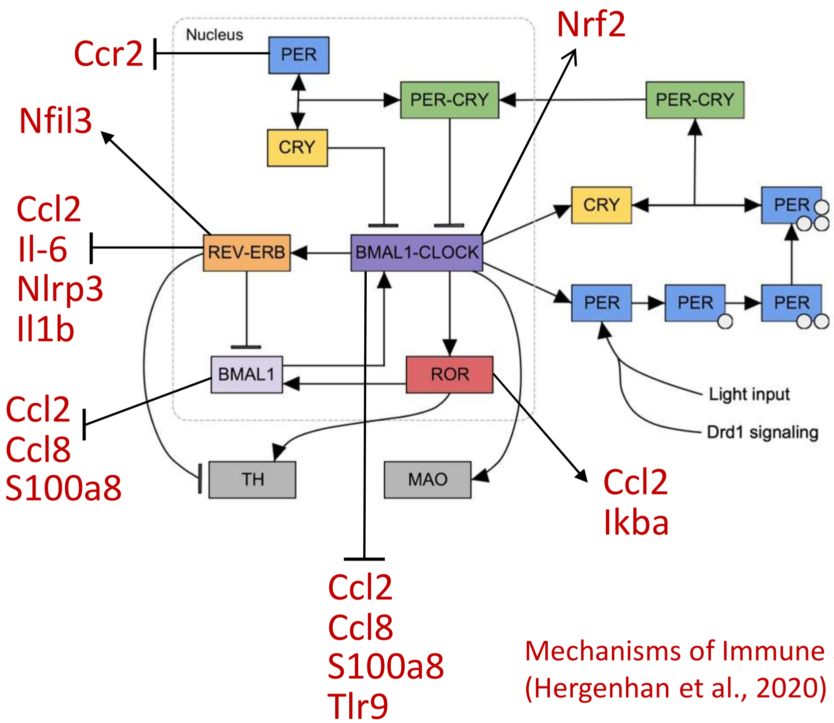
$$f_0(BC, P_4) = \frac{BC - P_4 + |BC - P_4|}{2} = \begin{cases} BC - P_4, & BC > P_4 \\ 0, & BC \le P_4. \end{cases}$$

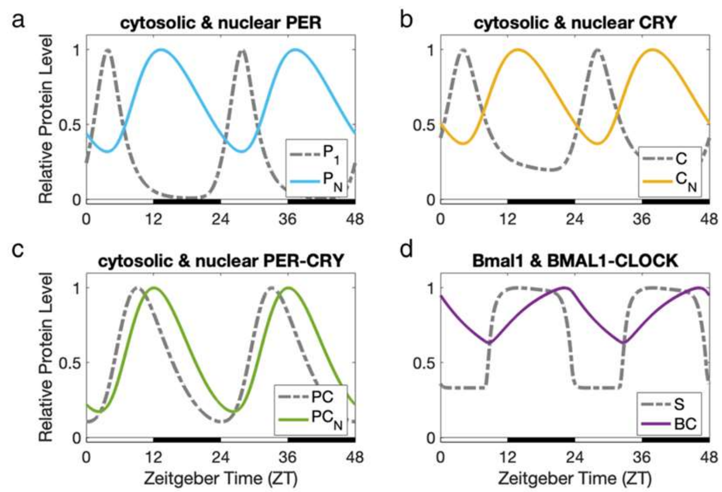


Circadian Drive

Circadian control of the Immune System

ODE Model of Molecular Clock (Kim and Reed, 2021)

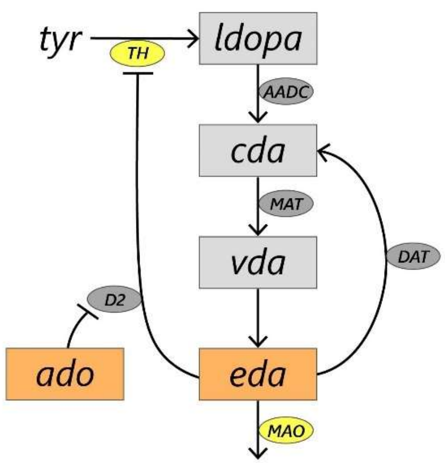




Mechanisms of Immune System Modulation
(Hergenhan et al., 2020)

Physiological Output (Dopamine)

- Dopamine is an important neurotransmitter involved in alertness

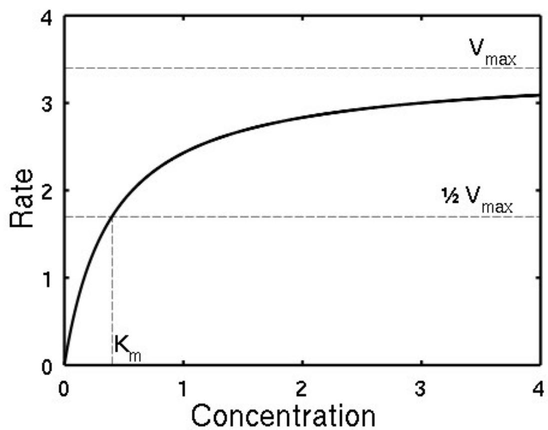


- *ado*: adenosine
- *eda*: extracellular dopamine

$$ldopa' = C_{TH}(t)V_{TH}(cda, eda, ado) - V_{AADC}(ldopa)$$
$$cda' = V_{AADC}(ldopa) - V_{MAT}(cda, vda) + V_{DAT}(eda) - k_{cda}cda$$
$$vda' = V_{MAT}(cda, vda) - fire(t)vda$$
$$eda' = fire(t)vda - V_{DAT}(eda) - C_{MAO}(t)V_{CATAB}(eda) - k_{eda}eda$$

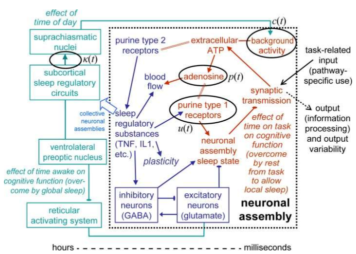
Michaelis-Menten Kinetics:

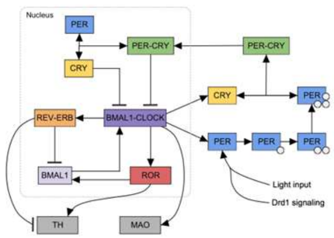
$$V_{AADC}(ldopa) = \frac{V_{max}}{K_m + ldopa}$$

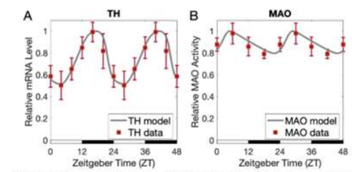


Two-process Model Reimagined

1. sleep drive
2. circadian drive
3. physiological output





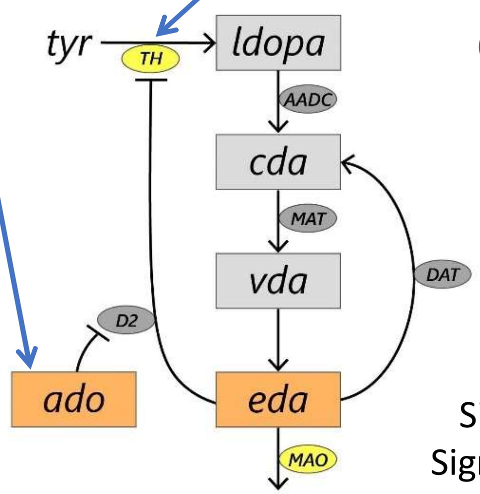


Model predictions against rat midbrain data from Chung et al. (2014) and Hampp et al. (2008).

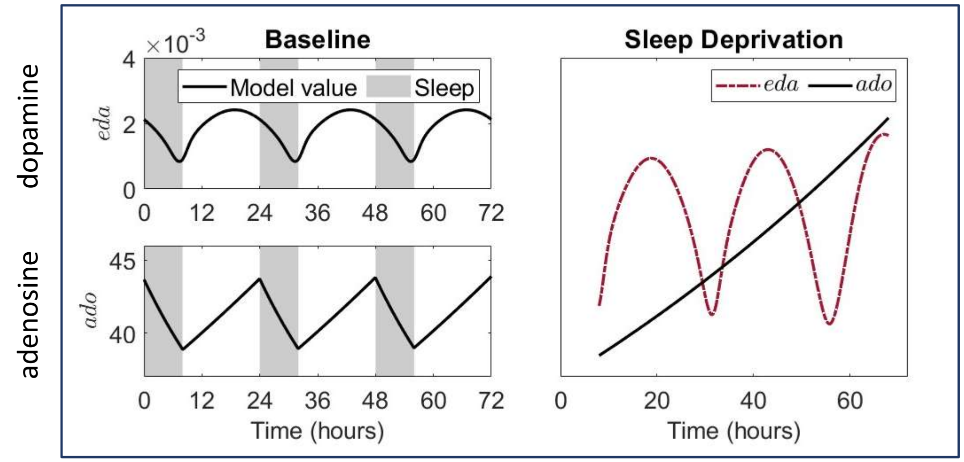
1. Sleep Drive

2. Circadian Drive

3. Dopamine System

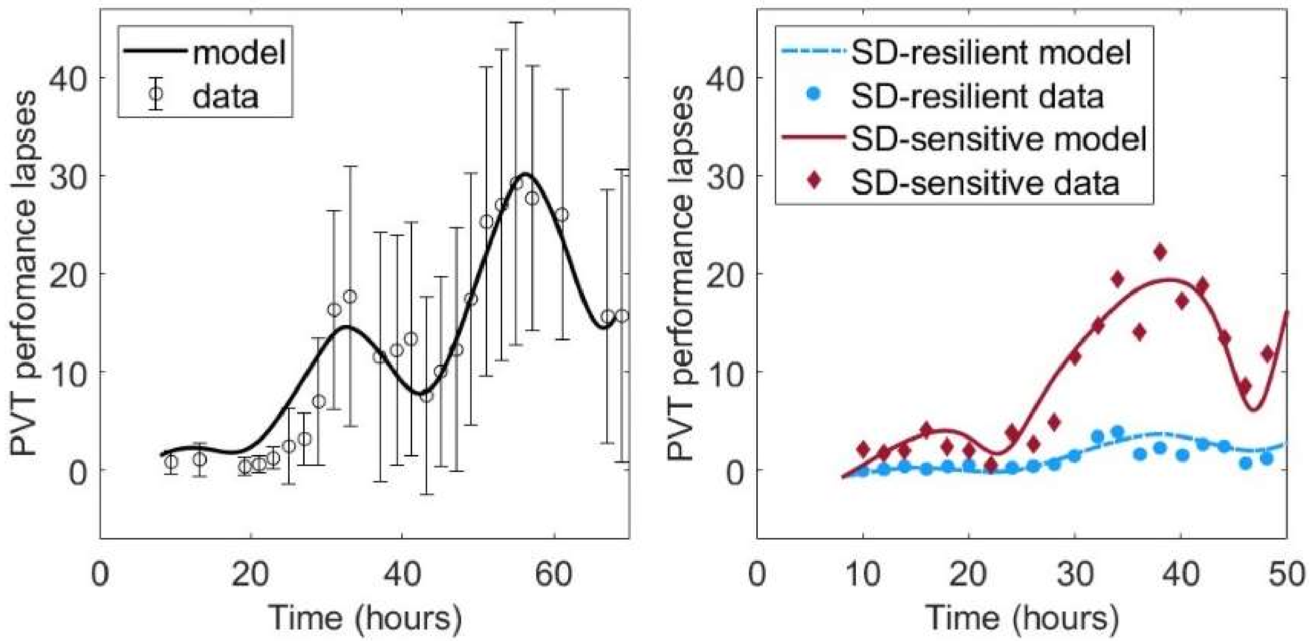


ODE model fit to data (Kim and Reed, 2021)



Signal for **Sleep Drive**: Adenosine (ado)
Signal for **Circadian Drive**: Dopamine (eda)

Predicting Fatigue



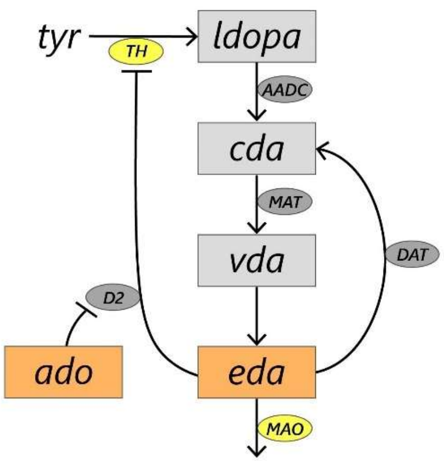
Psychomotor Vigilance Test

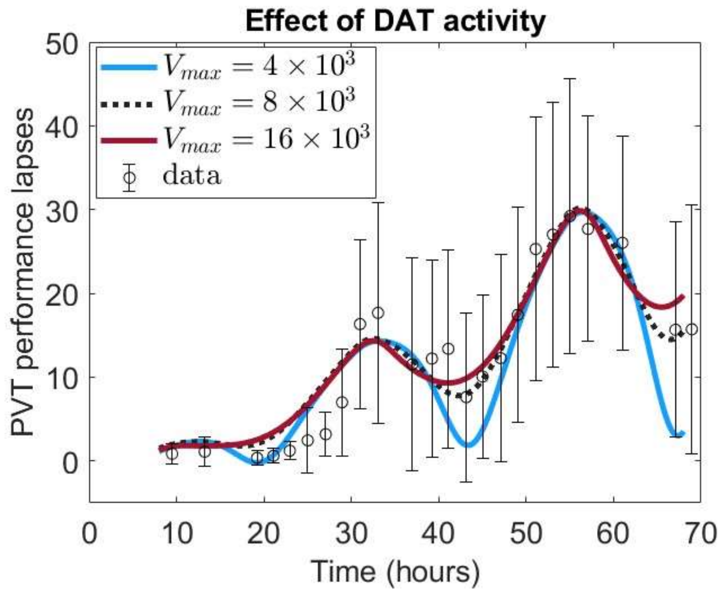
$$G(ado) = m_{ado} ado - b_{ado}$$

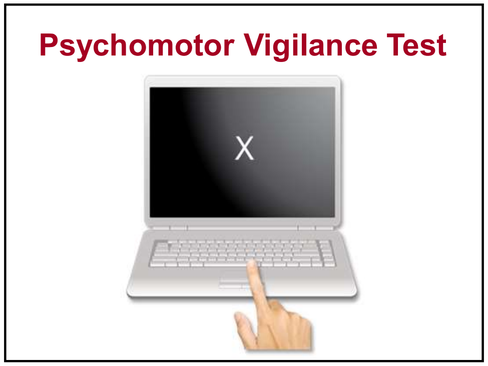
$$H(eda) = -m_{eda} eda - b_{eda}$$

$$pvt = G(ado)\frac{H(eda)}{K_{eda} + H(eda)} - b_{pvt}$$

Predicting Fatigue



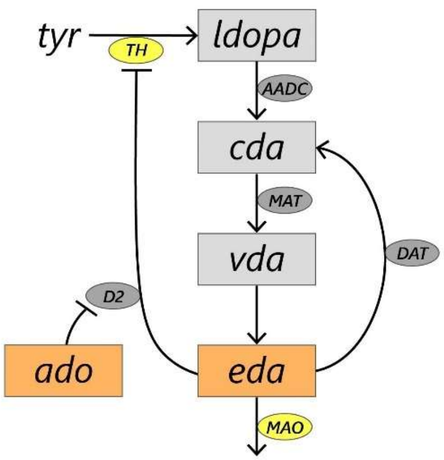


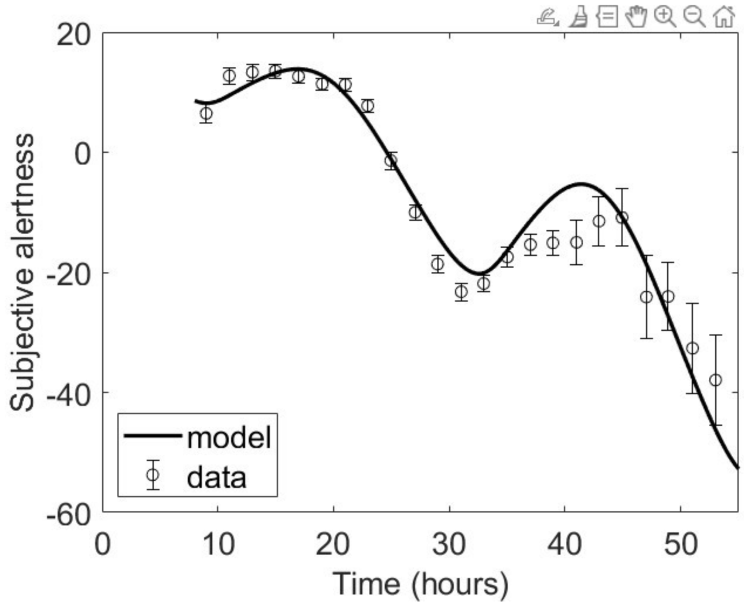


- Dopamine transporter (DAT) activity varies from individual to individual
- DAT is a target for cocaine, amphetamine, and methamphetamine, and for some drugs prescribed for attention deficit hyperactivity disorder (ADHD)

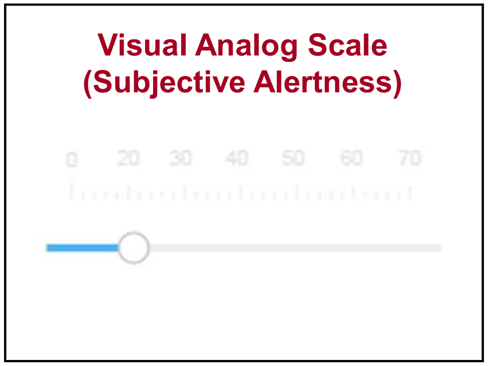
Predicting Fatigue

- Output of model can be chosen to study data of interest, as some function of adenosine and dopamine



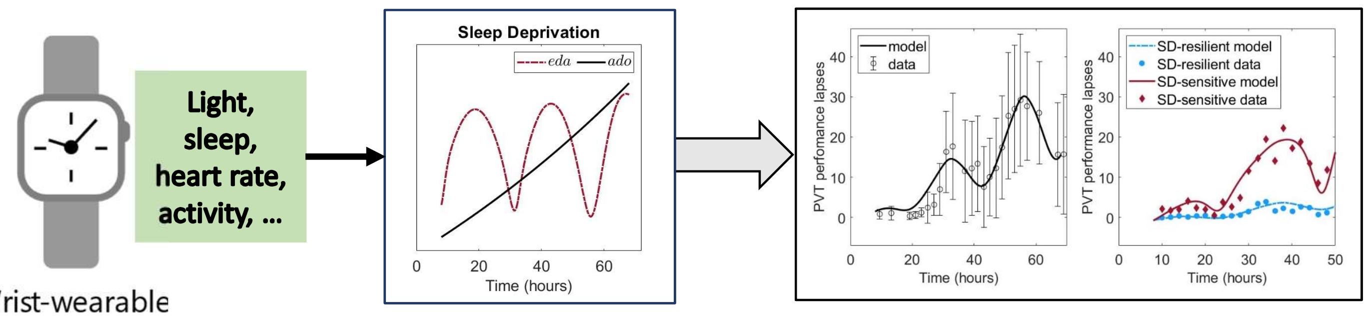


$$alertness = -G(ado)\frac{H(eda)}{K_{eda} + H(eda)} - b_{alertness}$$



Model Calibrated to Data from Wrist-Wearable Devices

Intern Health Study
Michigan Medicine



Wrist-wearable device

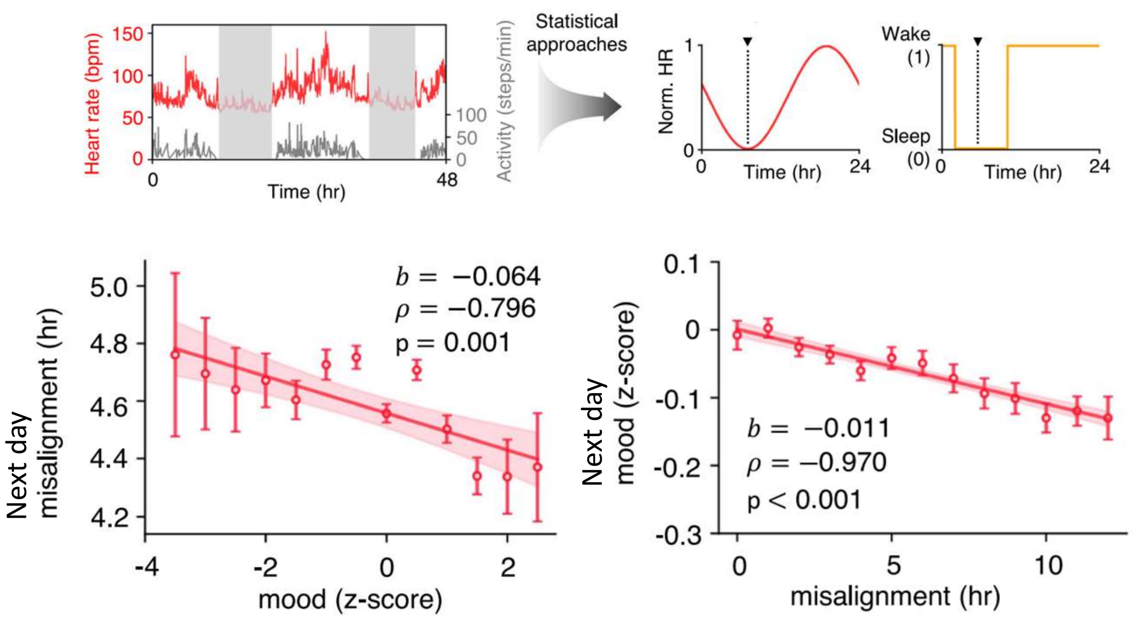
Mechanistic Models

Predictions

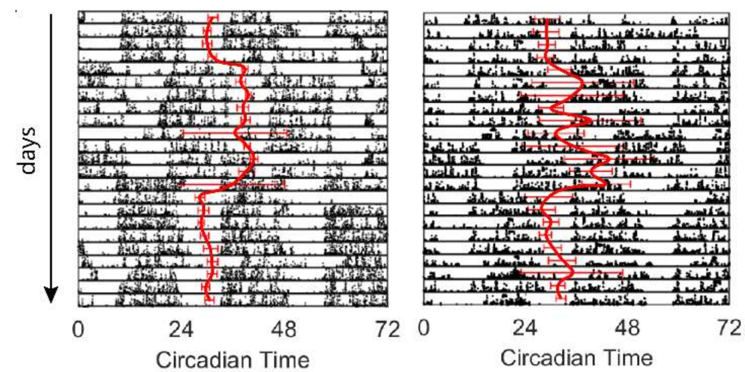
- Mechanistic models taking inputs from real-time physiological data
- Models can be individualized and updated dynamically

Circadian Misalignment Detected in Data

Lee, M., et al. (Accepted at npj Digital Medicine)



- Mathematical models are used to estimate phase of heart rate (HR) circadian rhythms and sleep midpoint
- HR rhythms and sleep can be misaligned
- Circadian misalignment is associated with health issues (e.g. low mood scores)



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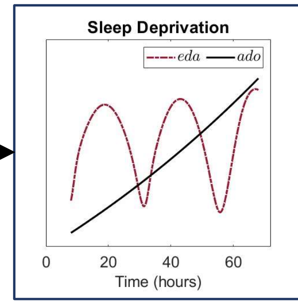
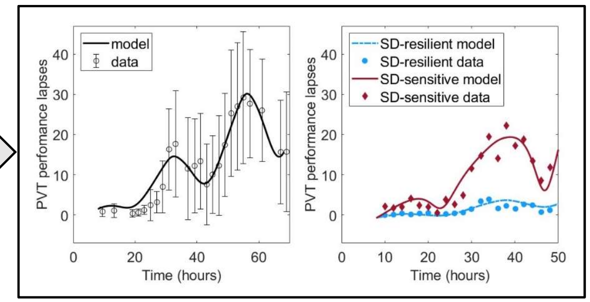
Integrating Models with Real-World Data

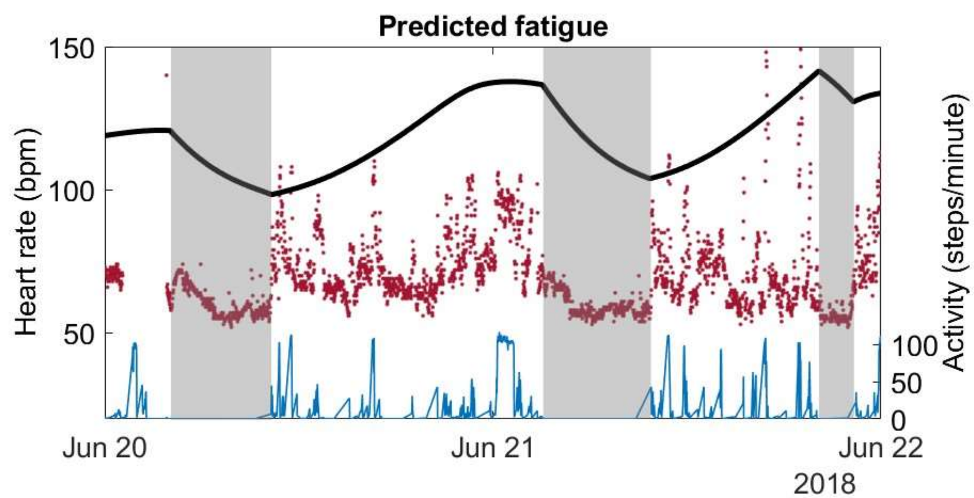
Intern Health Study
Michigan Medicine

Light, sleep, heart rate, activity, …

Wrist-wearable device

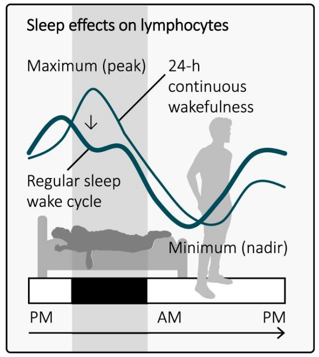


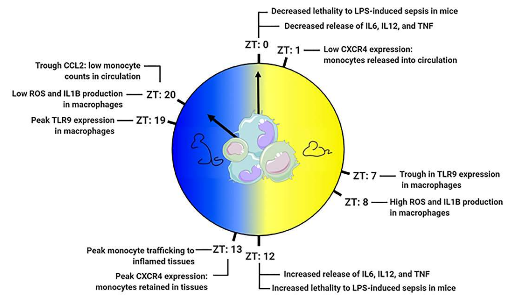


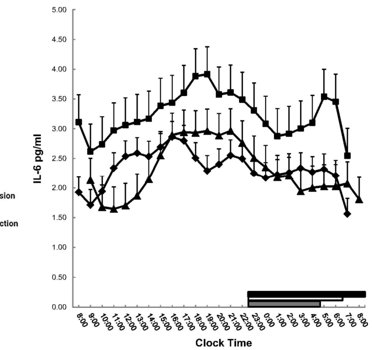


Future Work

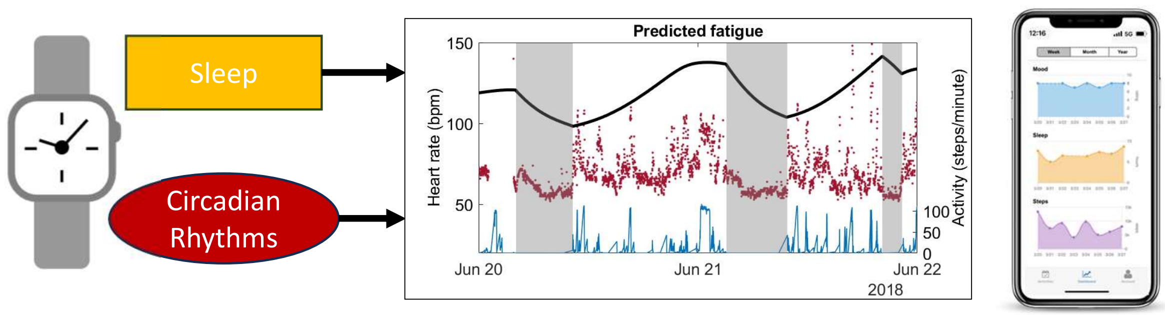
Investigate Mechanisms
Of Two-Process Dynamics





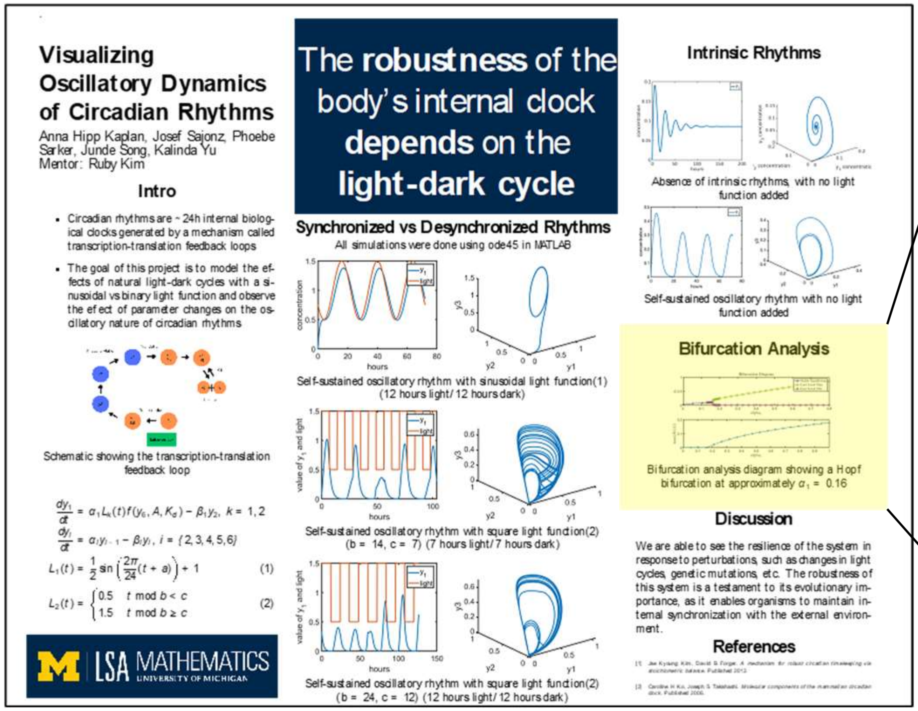


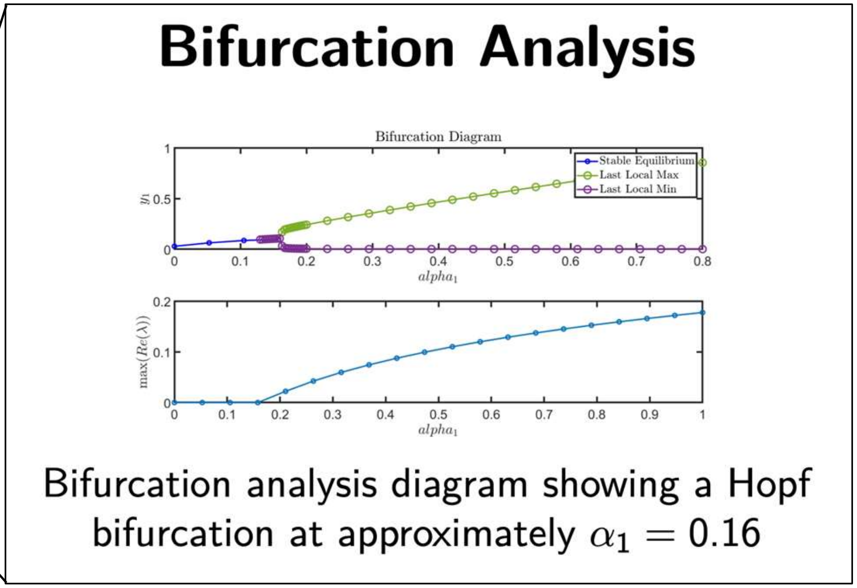
Integrate Models
with Wearable Devices



Dynamics of Mechanistic Models

- Mechanistic Models are a great tool for learning about Dynamical Systems concepts!





Dynamics of Mechanistic Models

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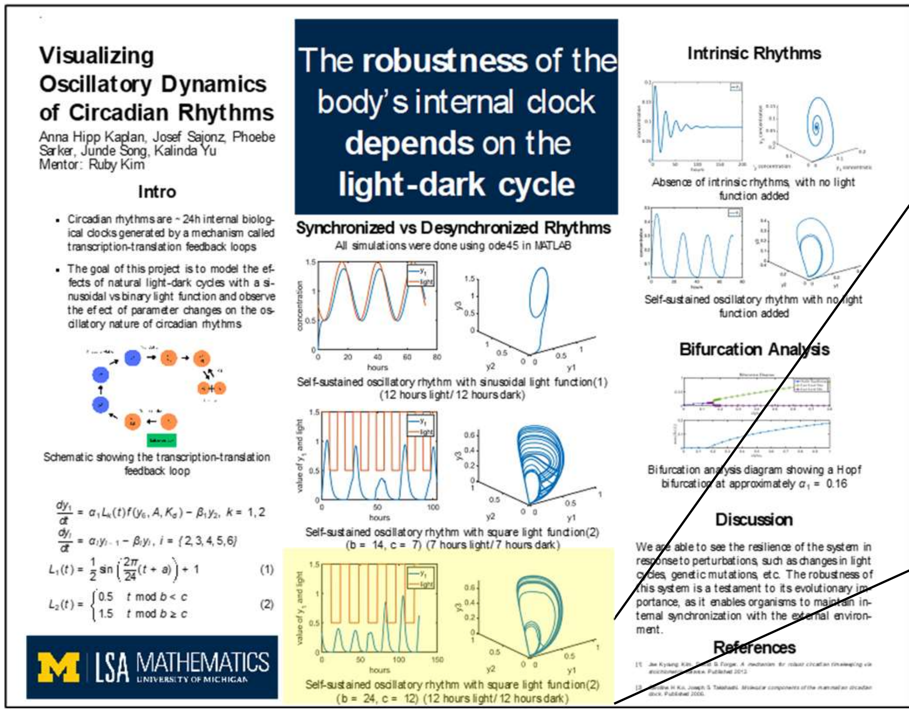

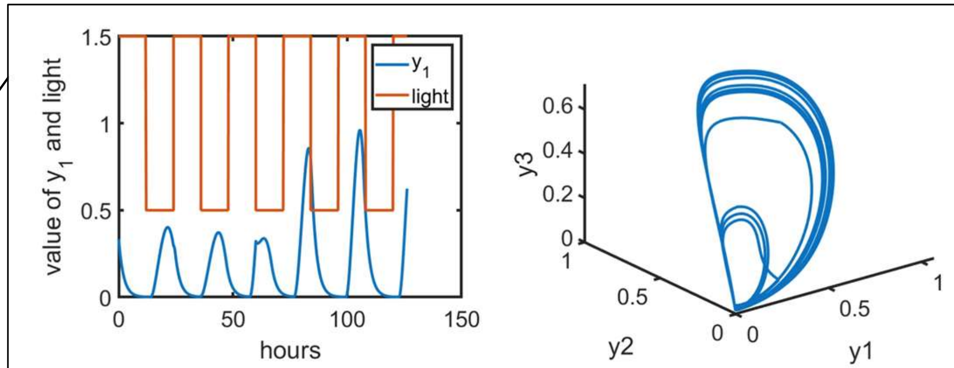

Self-sustained oscillatory rhythm with square light function(2)
(b = 24, c = 12) (12 hours light/12 hours dark)

Acknowledgments

Collaborations

Single-Cell Model
Michael Reed
H. Frederik Nijhout
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Intercellular Signaling
Daniel Forger
Guanhua Sun
James Hazelden

Intern Health Study
Yu Fang
Srijan Sen

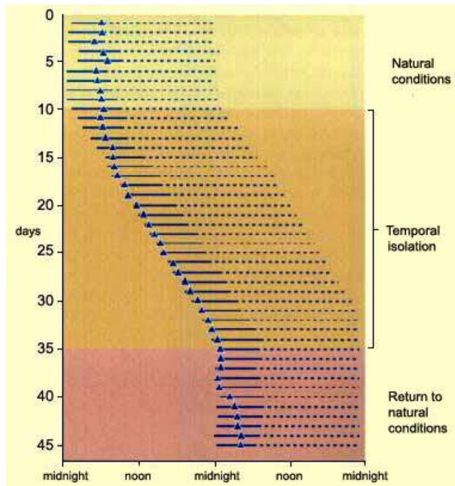
Undergraduate Project
Anna Kaplan
Josef Sajonz
Phoebe Sarker
Junde Song
Kalinda Yu

Thank you for listening!

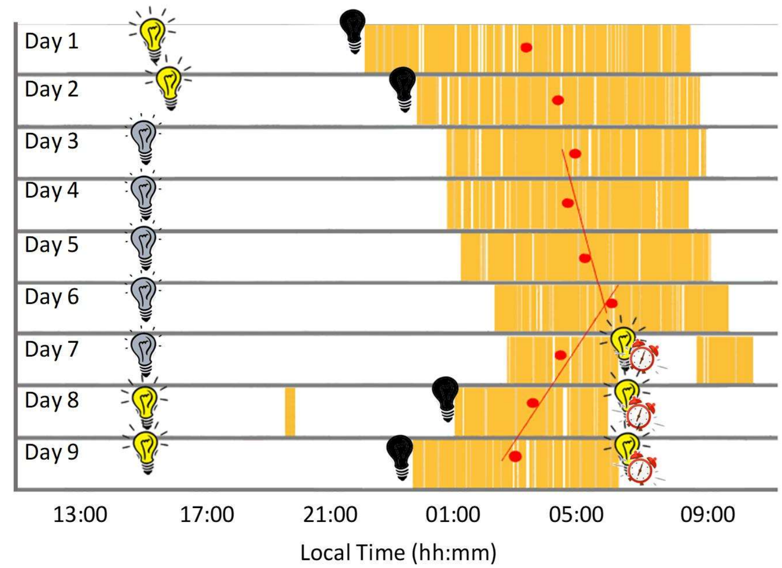
Reach me by email:
rshkim@umich.edu

Circadian Rhythms: Temporal Isolation Experiments

Kleitman and Richardson, 1938
32 days in Mammoth Cave, Kentucky
University of Chicago Library



thebrain.mcgill.ca
Adapted from Dement, 1976



Bonmati-Carrion et al., Frontiers in Physiology, 2020