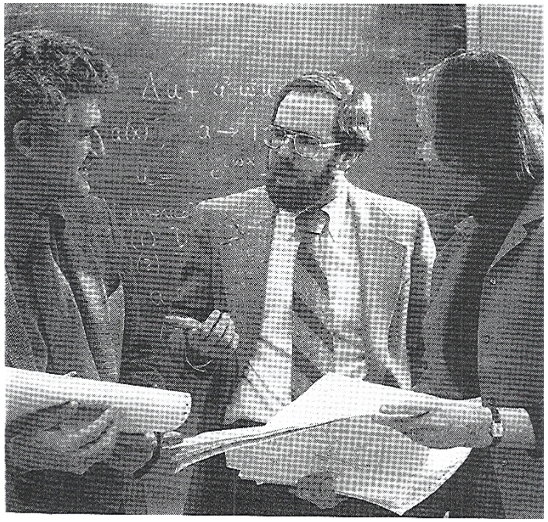
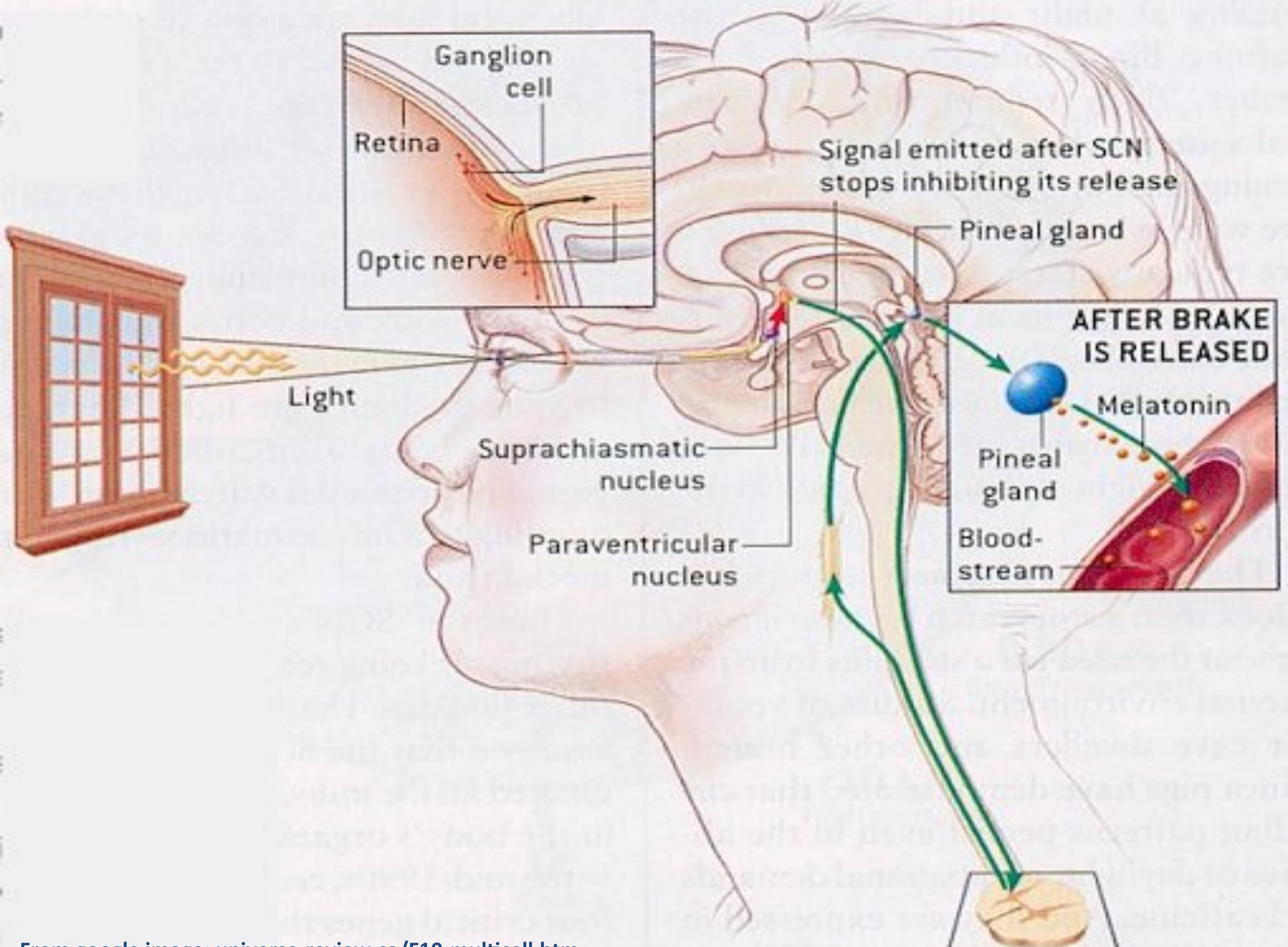
From a network of ~~10,000~~ 20,000 neurons to a smartphone app with ~~125,000~~ 160,000 users linking scales in biological rhythms

Daniel Forger

University of Michigan, Ann Arbor

Many thanks to Charles Peskin





From google image: universe-review.ca/F10-multicell.htm

New tools from modeling

Electrophysiology

\+

Molecular Biology

Multiscale Model

Human Behavior

Many scale of circadian research

Human Behavior

Entrain app

Society

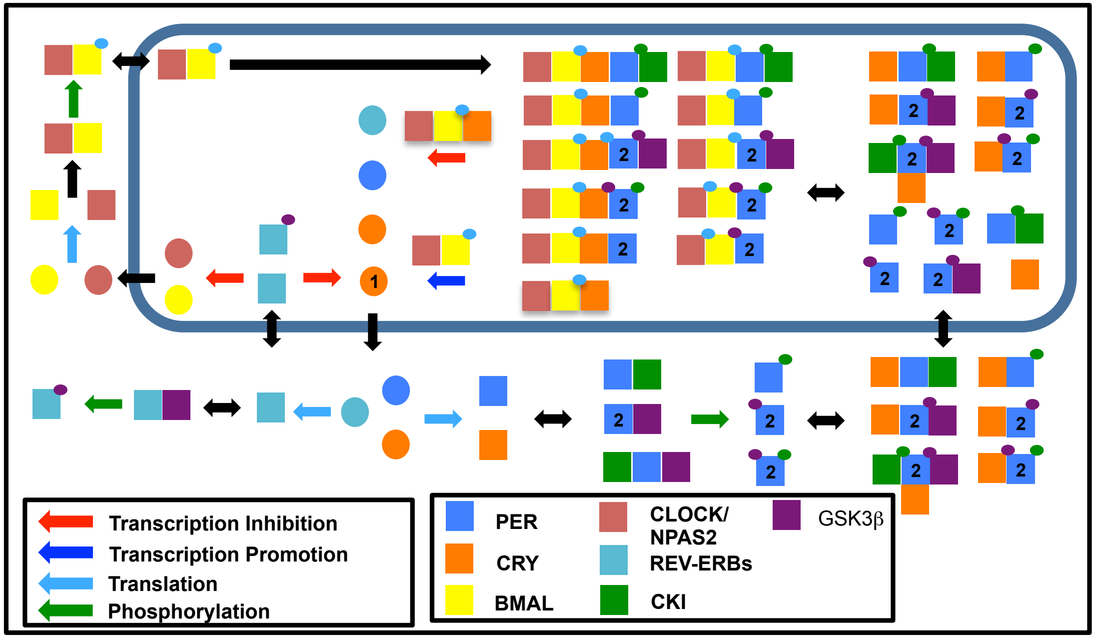
Build a detailed computational model of circadian timekeeping

- Biochemical model (~1000 chemical reactions)
  - Kim and Forger Molecular Systems Biology 2012
  - Min et al. Molecular Cell 2015
- Electrophysiological model (H-H type)
  - Belle et al. Science 2009
  - Diekman et al. PLoS Comp Bio 2013
- 1024 (or more) connected neurons
  - VIP (easy) GABA (hard)
- mSec timescale to weeks

(Billions of electrical signals)

DeWoskin et al. PNAS 2015

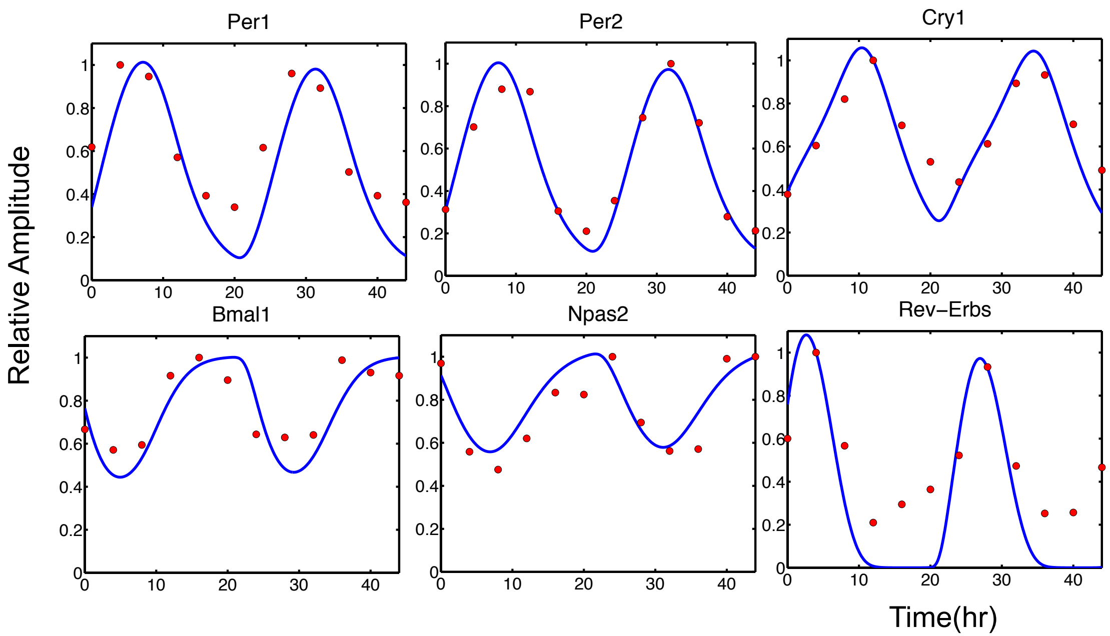
Myung et al. PNAS 2015



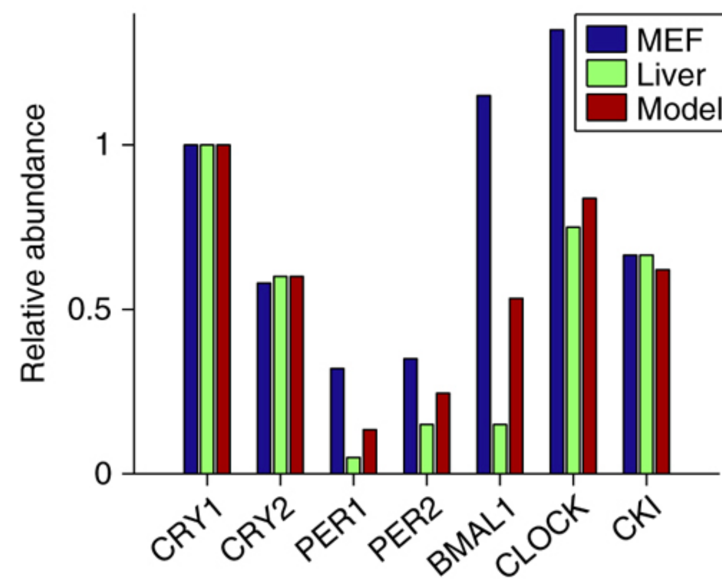
Variables	181
Kinetics	Mass-action
Measured Parameters	15
Estimated Parameters	60
Estimation	SSA
Computing	150 × 8Ghz

Forger & Peskin PNAS (2003)
Kim & Forger, Mol Syst Biol (2012)
Zhou et al. Molecular Cell (2015)

mRNA and Protein Timecourses



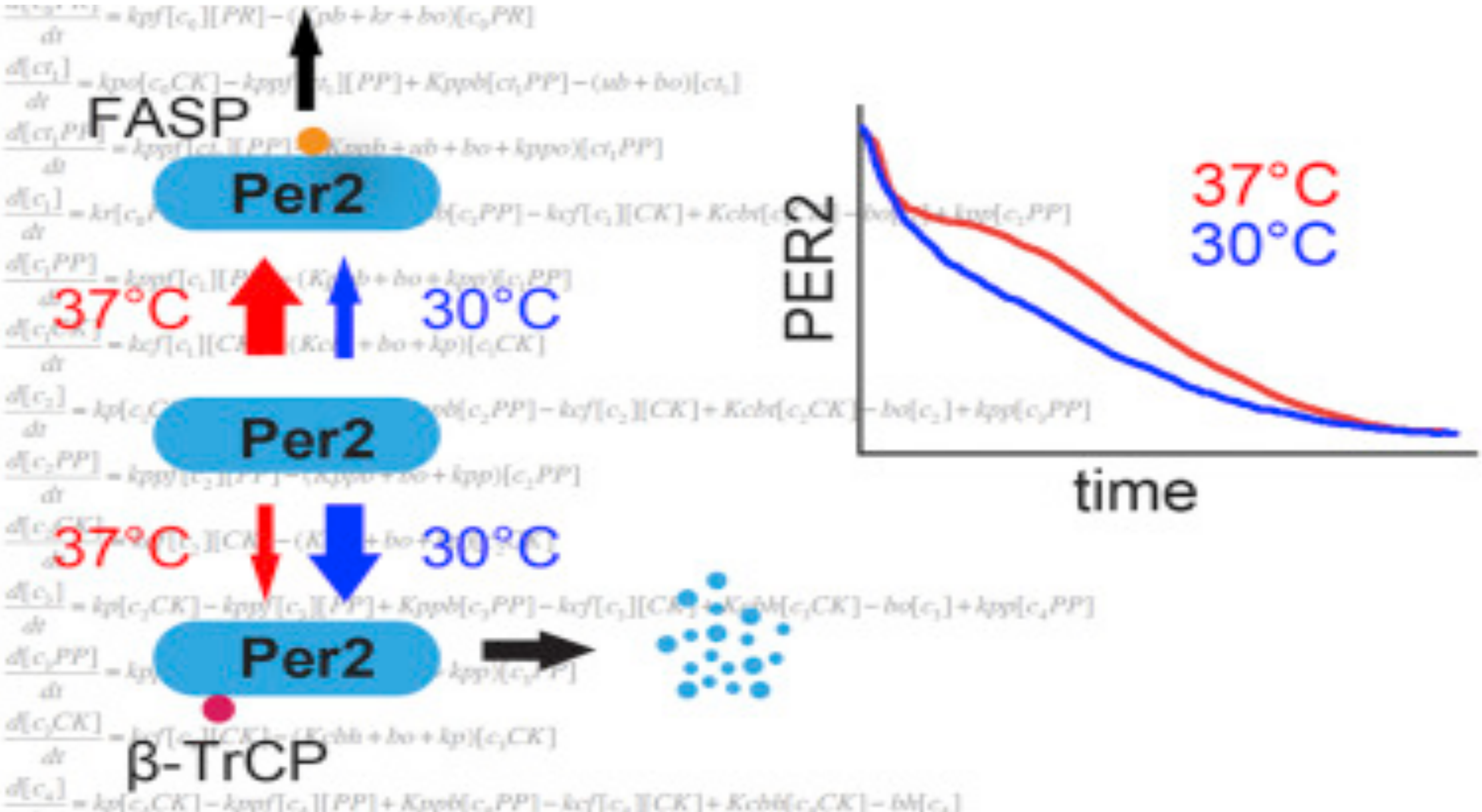
Abundance of Proteins



Phosphoswitch

With Jae Kim and Virshup lab

Zhou et al. Molecular Cell 2015

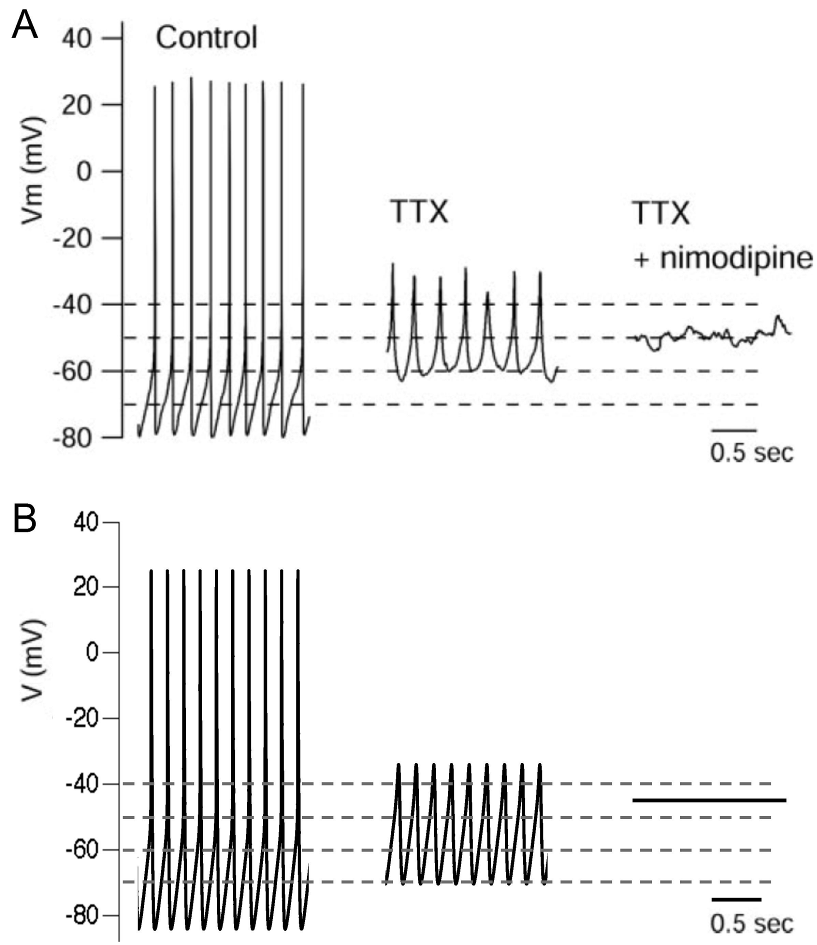


Key new challenges

- How to integrate data from protein structure in biochemical models?
- How to rapidly simulate large numbers of biochemical oscillators?

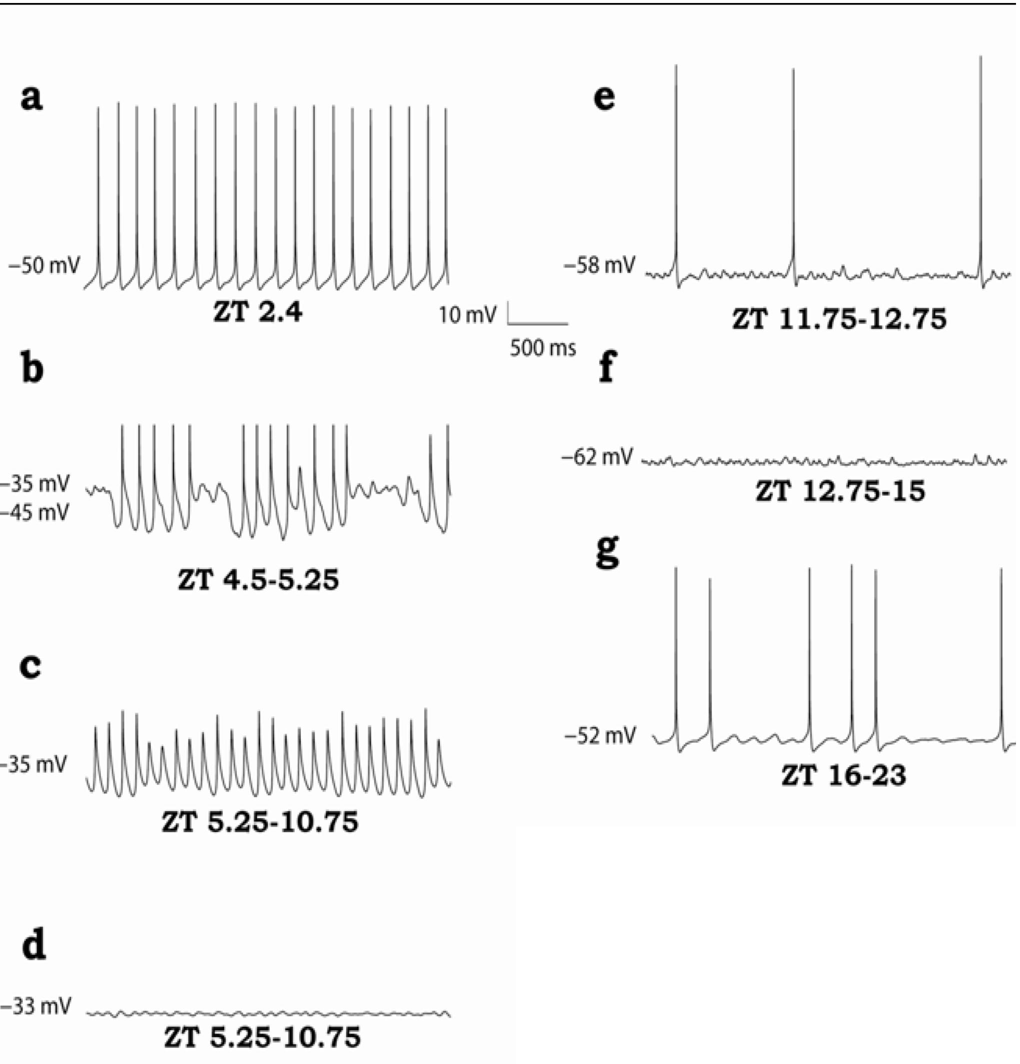
Two modes of activity of SCN neurons

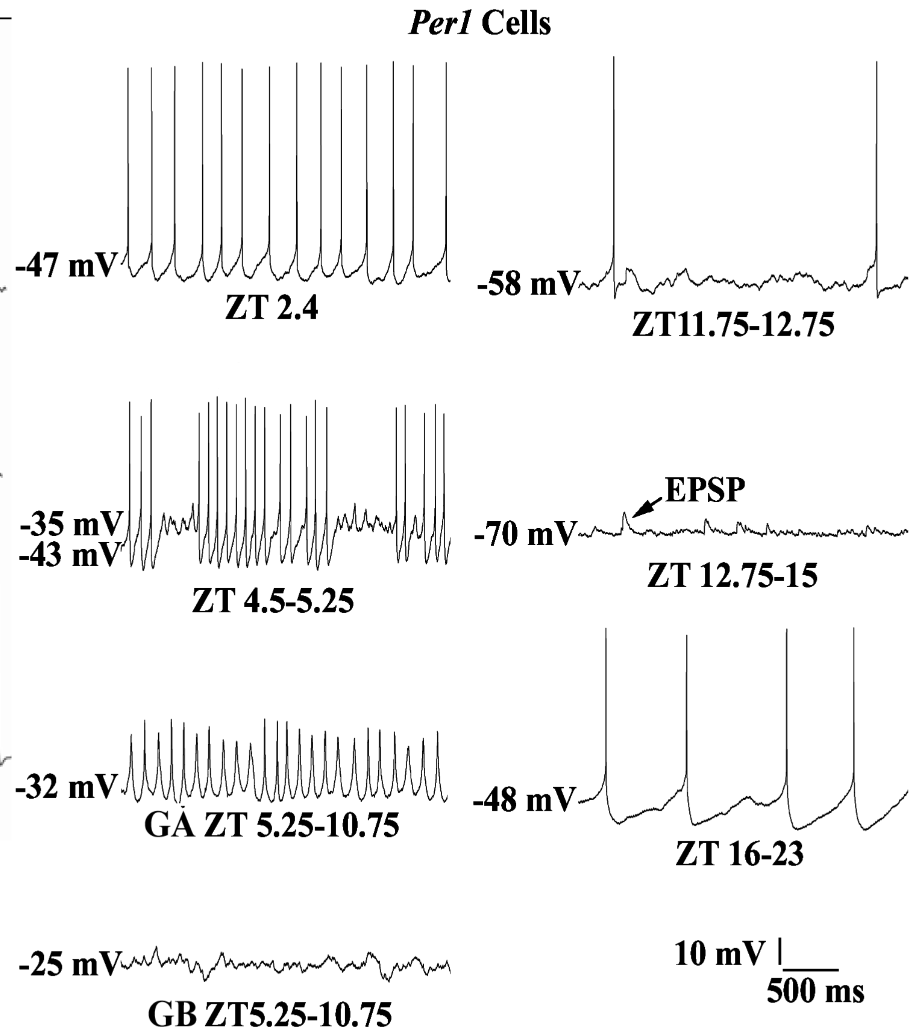
Diekman et al. PLoS Comp. Biology 2013



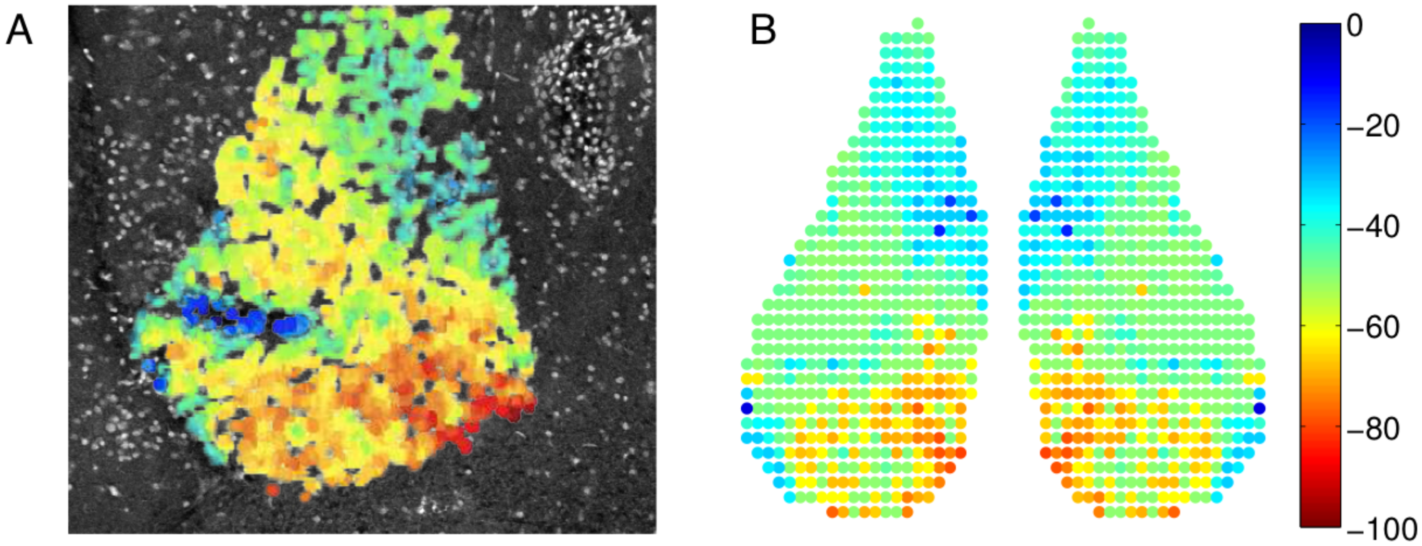
Mino Belle

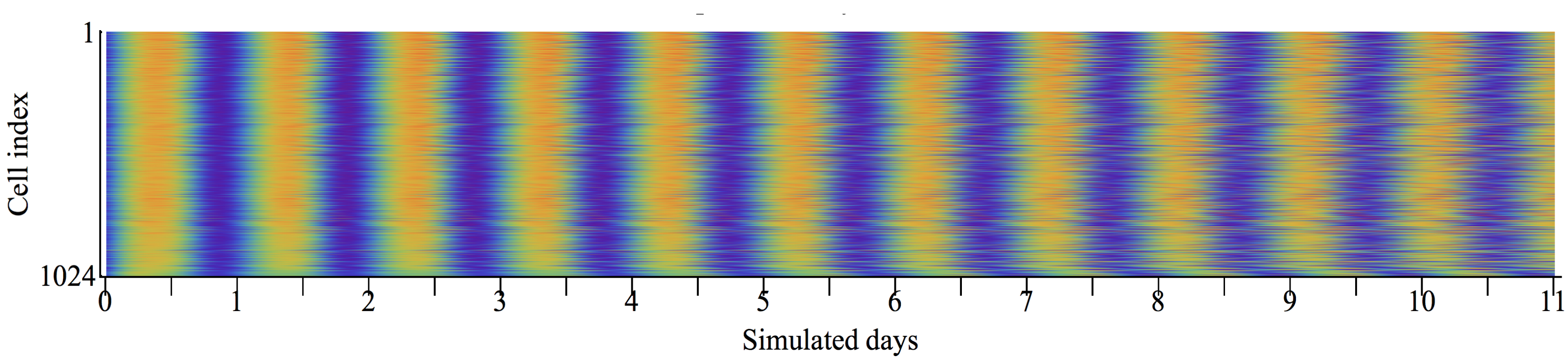
Belle, Diekman, Forger, Piggins, Science, 2009





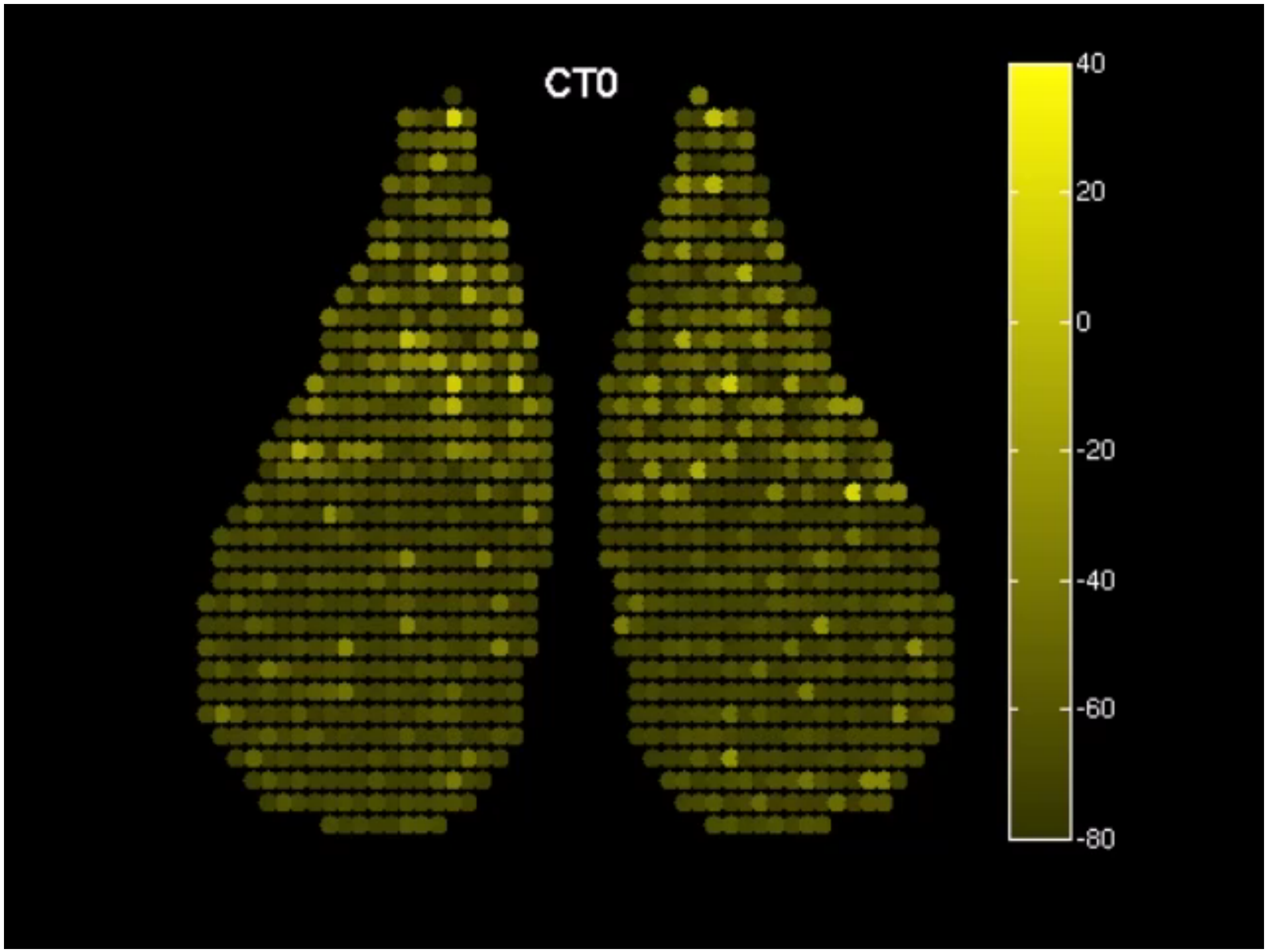
Fit data collected about GABA



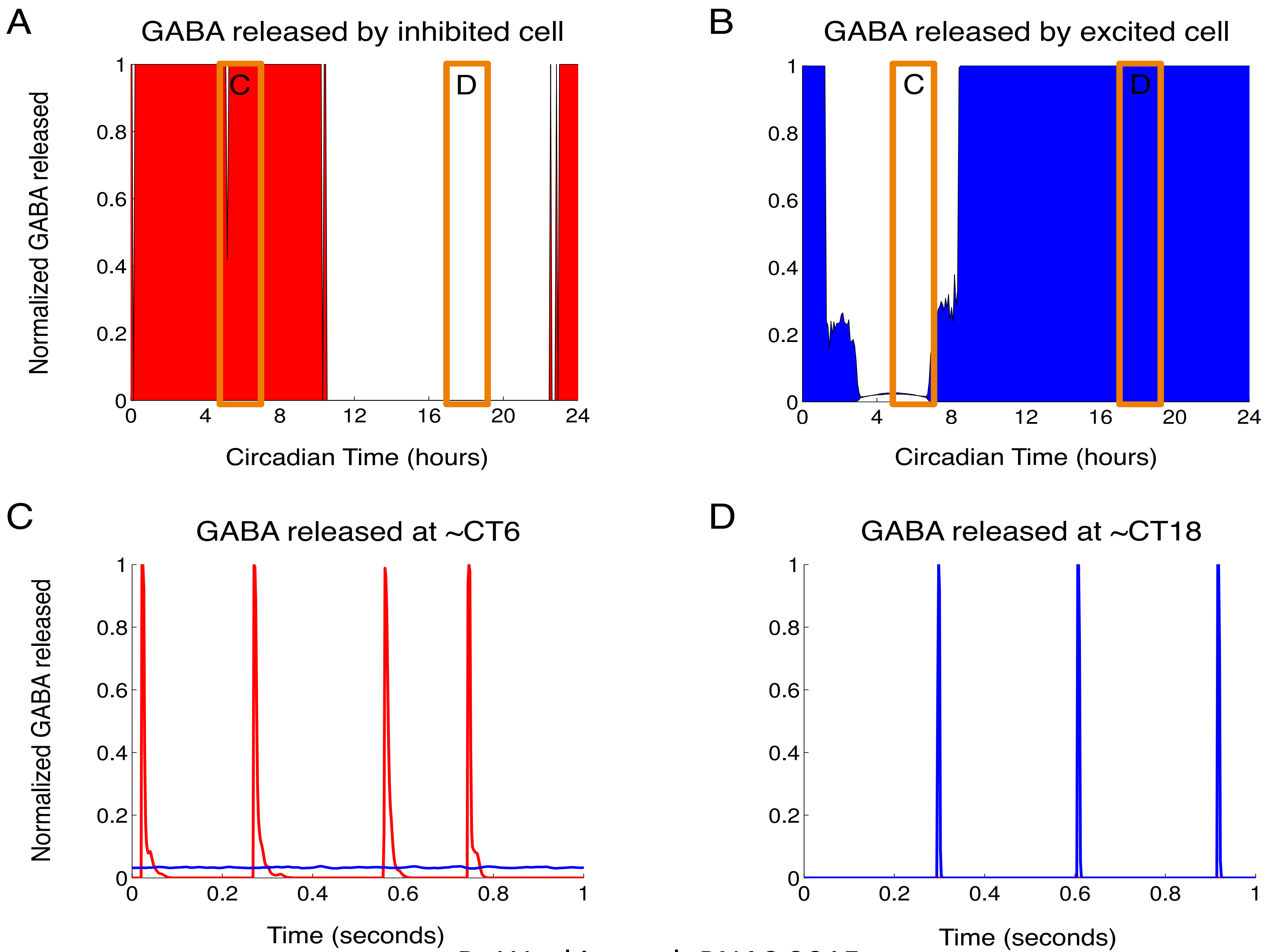


DeWoskin et al. PNAS 2015

Electrophysiology

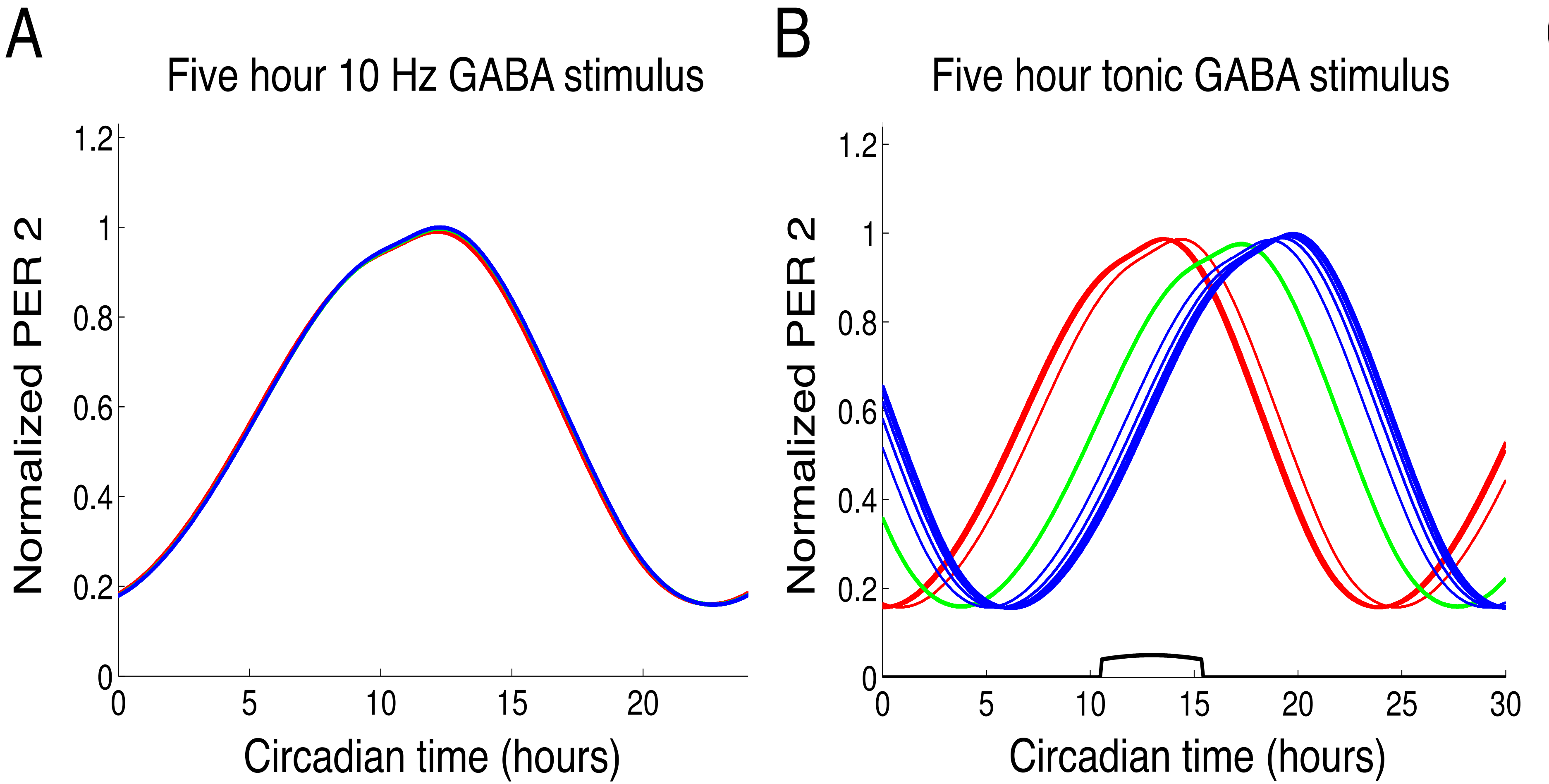


Two GABA signals



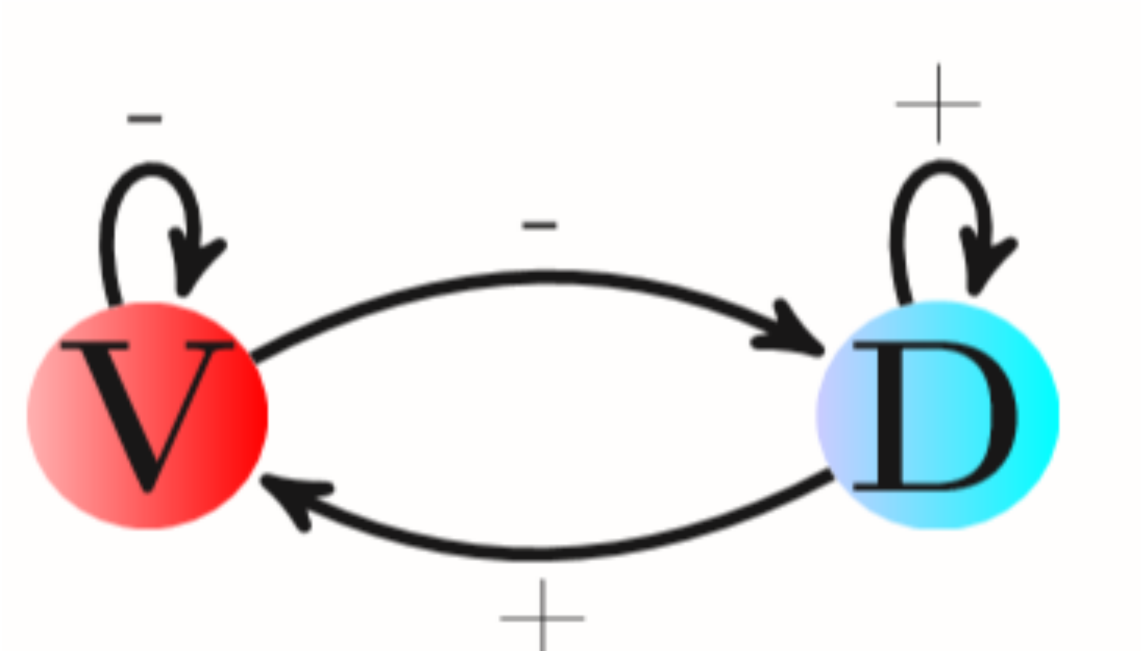
DeWoskin et al. PNAS 2015

Tonic GABA controls phase distribution



DeWoskin et al. PNAS 2015

Tonic GABA coupling in the SCN

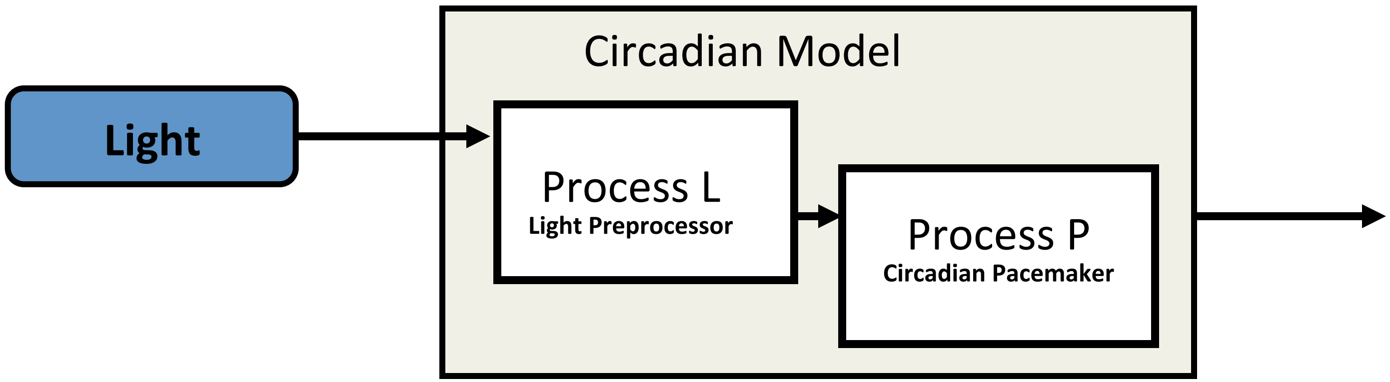


- See Myung et al. PNAS 2015 for large scale simulations and analysis of bioluminescent data
- Explained by SCN aftereffects and Ott-Antonsen theory

Key challenges

- What are all the action potentials doing?
  - Subconscious vision (Stinchcombe and collaborators)
- How can we quickly simulate this system?
  - GPU computing
  - Library method developed by Cai and colleagues
  - Exponential Integrators
  - Population density methods solved by particle methods

Human Circadian System
(Forger, Klerman, Kronauer, Jewett ...)



$$\alpha(I) = 0.05\frac{I^{0.6}}{9500^{0.6}}$$

$$\frac{dn}{dt} = \alpha(I)(1-n) - 0.013n$$

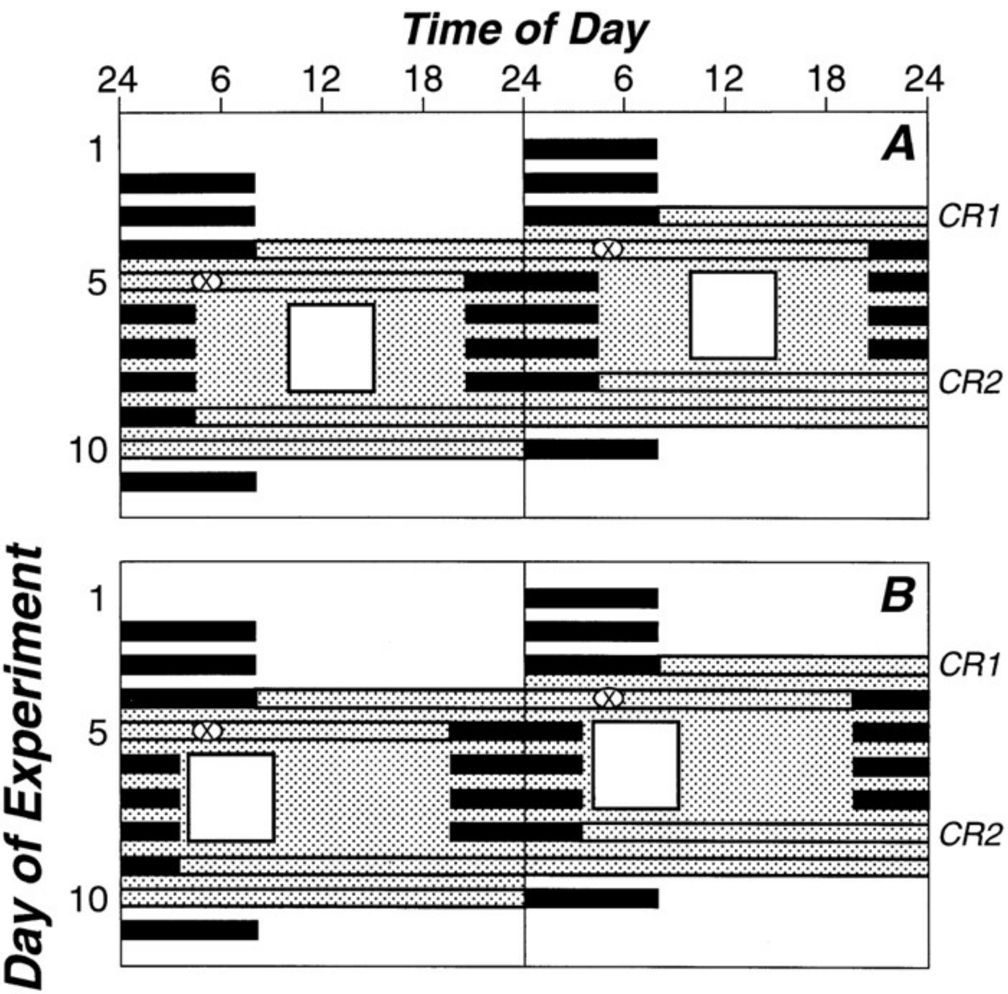
$$B(n,x,x_c) = 19.875(1-0.4x)(1-0.4x_c)\alpha(I)(1-n)$$

$$\frac{dx}{dt} = \frac{12}{\pi}\left(x_c + B(n,x,x_c)\right)$$

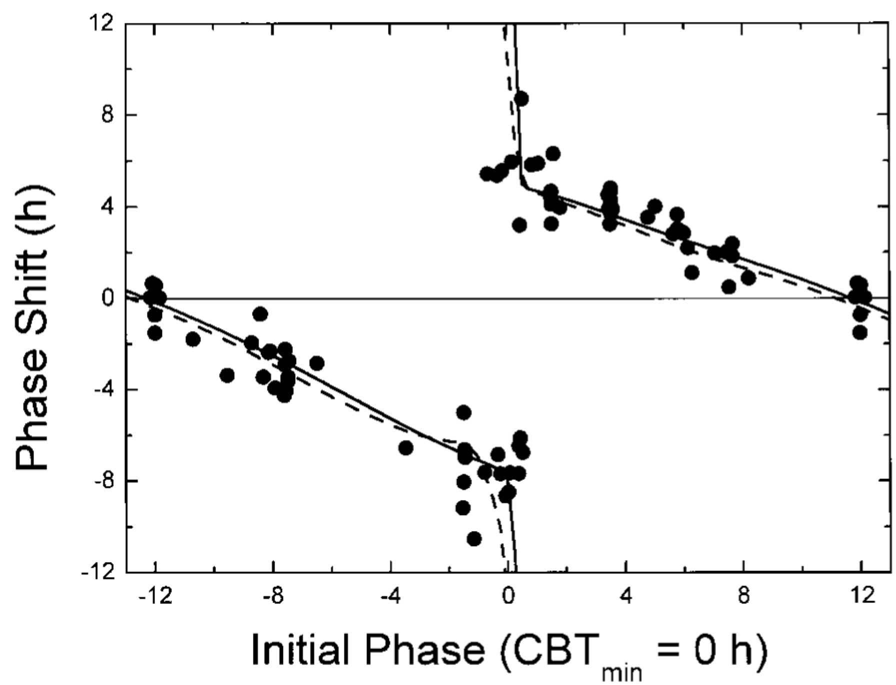
$$\frac{dx_c}{dt} = \frac{12}{\pi}\left(-x\left(0.9901 + 0.55B(n,x,x_c)\right) + 0.23\left(x_c - \frac{4}{3}x_c^3\right)\right)$$

Human Phase Shifting to Light

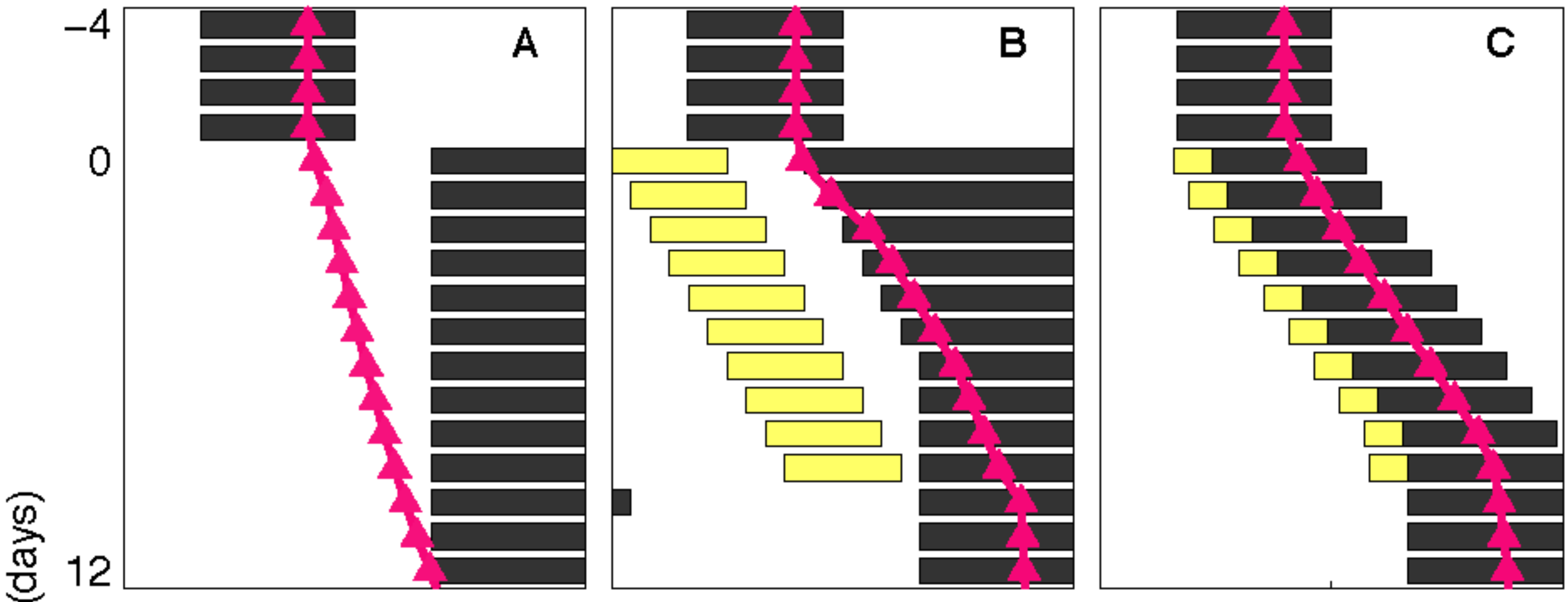
- Jewett et al. AJP 1997



Forger et al. JBR 1999



Evaluation of Schedules

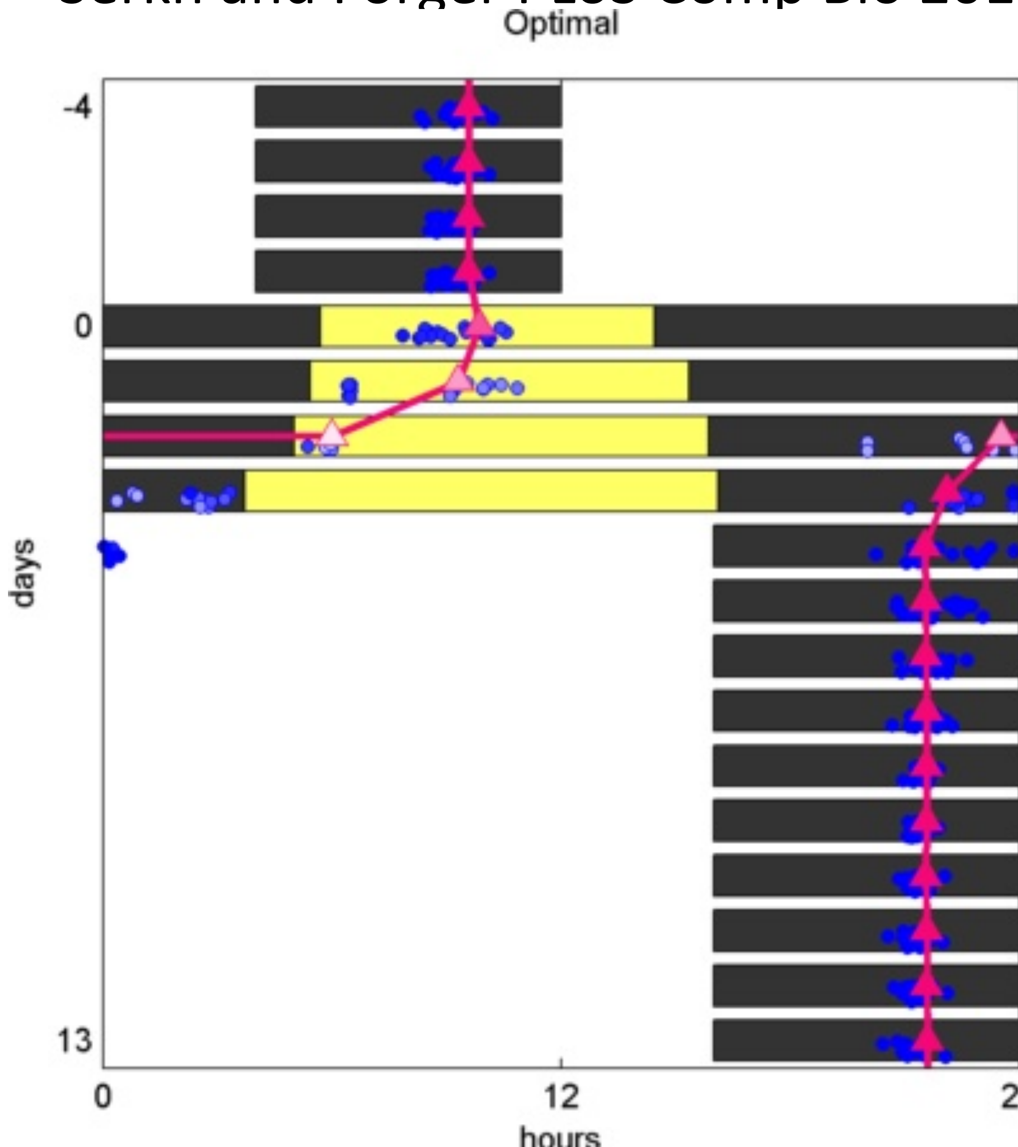


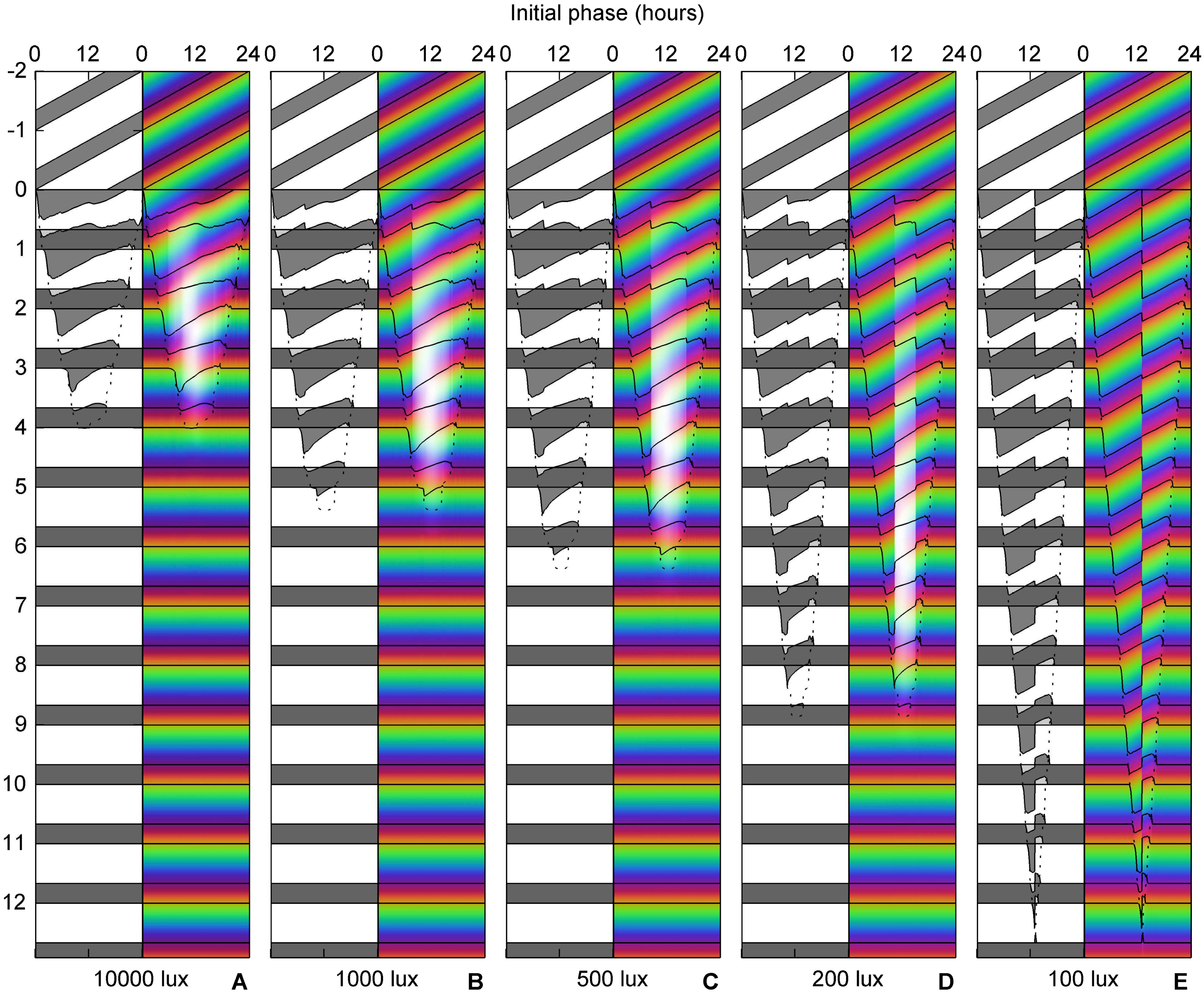
Formulating the problem in terms of optimal control

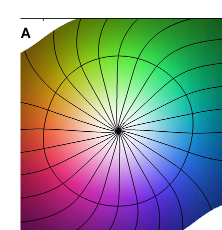
- Starting at a specified state $X(0) = a$, and dynamical system $dX/dt = f(X, u)$ choose a control, $u(t)$, such that for minimum t_f $X(t_f) = X_e(t_f)$
- Too difficult and not applicable
- Instead have a constraint that we are on the correct isochron $\psi(X(t_f), t_f) = 0$ (i.e. have correct phase)
- Have a cost function $\phi = t_f + b|A(X(t_f)) - A(X_e(t_f)|$

Optimal Schedules (with much mathematics)

Serkh and Forger PLoS Comp Bio 2014




Initial phase (hours)
0 12 0 12 24
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
10000 lux
A
1000 lux
B
500 lux
C
200 lux
D
100 lux
E


A

How to test this? Travelers…

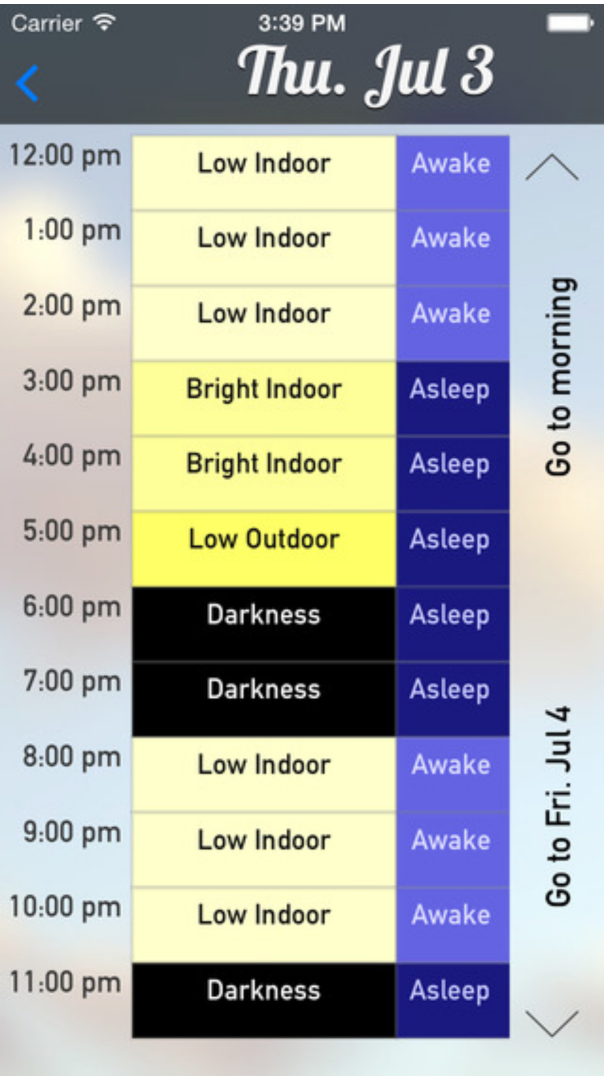
- We provide an app for free which simulates the latest mathematical models on the iPhone and gives you our best guess at an optimal schedule.

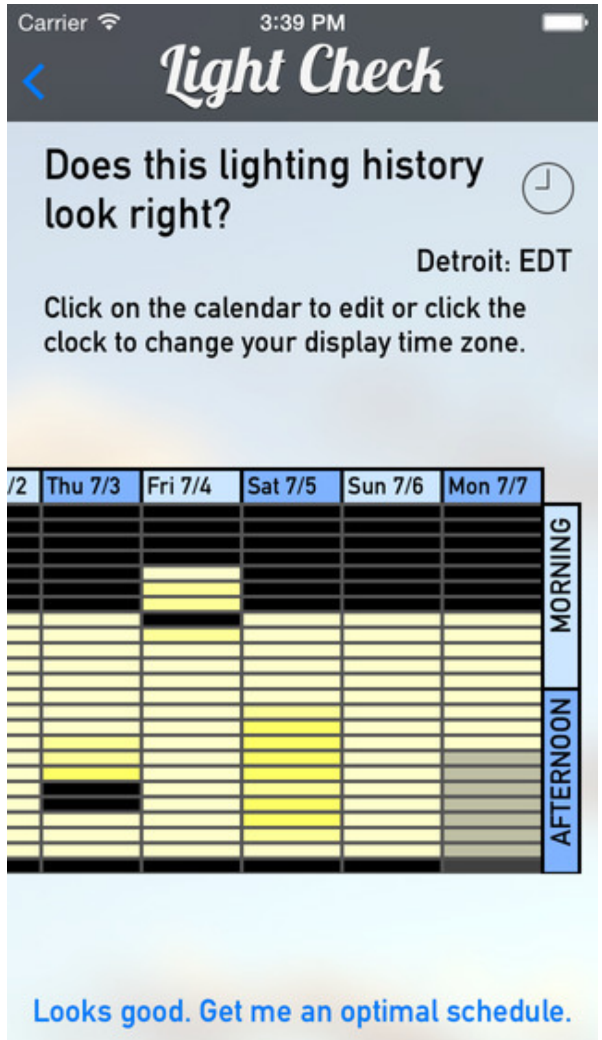
  This is only available in very specialized applications

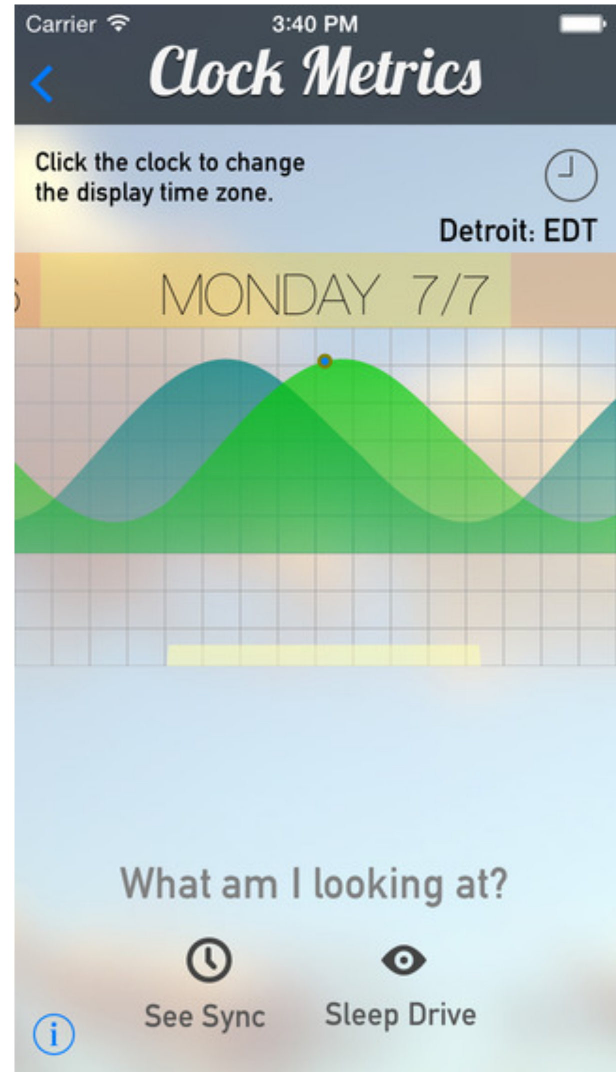
- You provide data on your lighting history, sleep-wake pattern and rate symptoms of jetlag, and demographics

  This could give us the real-world data we need

ENTRAIN
(Olivia Walch and Amy Cochran)







Top 300 Free iPhone Apps for Travel

Filters: » iPhone | » Travel | » Free | » Rank

Rank	Change	App	Price	
#1	↔	*Uber* *Developer:* Uber Technologies, Inc. *Released:* May 20, 2010 in Travel	Free DOWNLOAD	18
#2	↔	*Expedia Hotels & Flights* *Developer:* Expedia, Inc. *Released:* Apr 7, 2011 in Travel	Free DOWNLOAD	10.9
#3	↔	*Google Earth* *Developer:* Google, Inc. *Released:* Oct 27, 2008 in Travel	Free DOWNLOAD	390
#4	↔	*Hotels.com – Hotel Booking and last...* *Developer:* Hotels.com *Released:* Jul 11, 2008 in Travel	Free DOWNLOAD	10.9
#5	↔	*Yelp* *Developer:* Yelp *Released:* Jul 11, 2008 in Travel	Free DOWNLOAD	4.92
#6	↔	*Entrain* *Developer:* The University of Michigan *Released:* Apr 9, 2014 in Travel	Free DOWNLOAD	<0
#7	↑2	*My Disney Experience – Walt Disney...* *Developer:* Disney *Released:* Aug 2, 2012 in Travel	Free DOWNLOAD	150

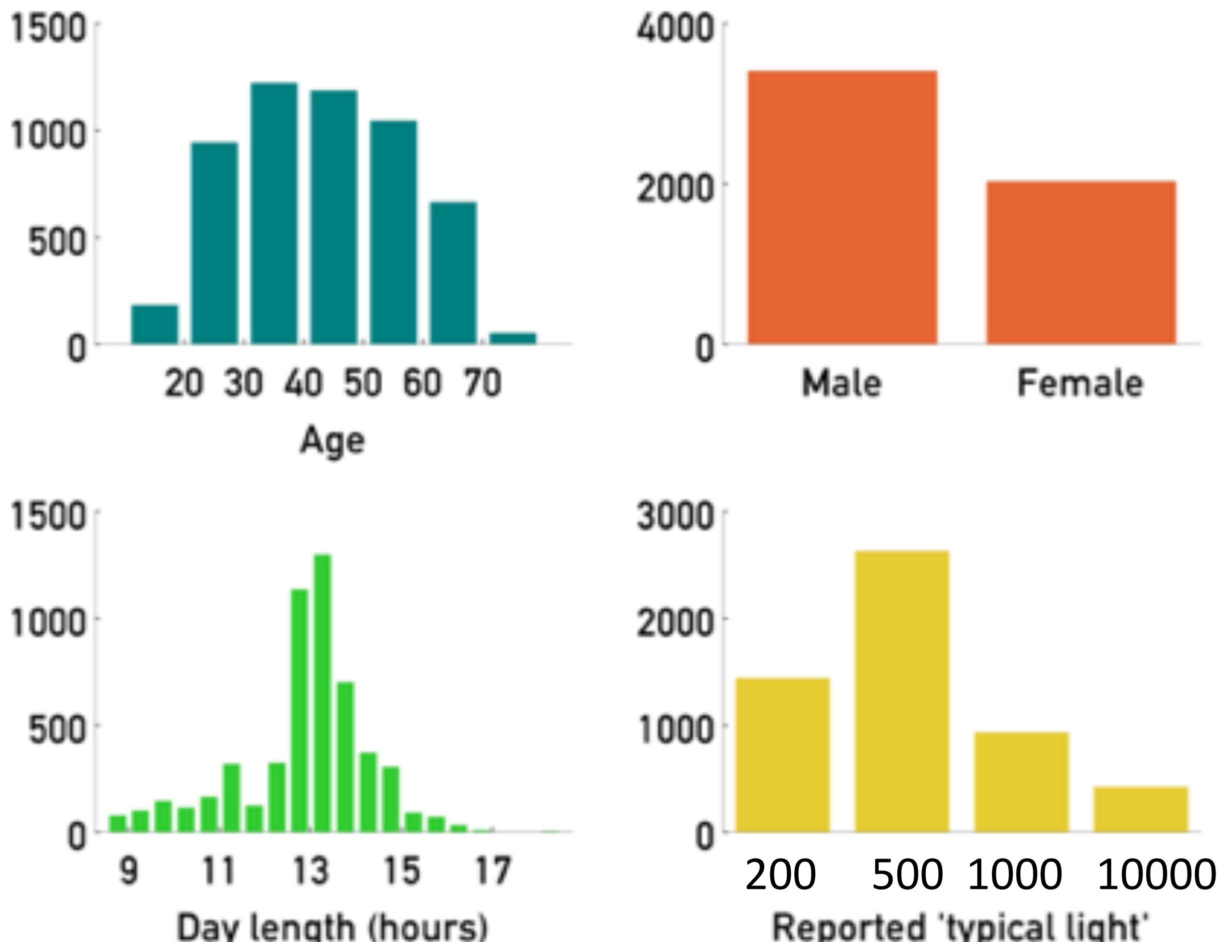
Global Assessment of Sleep

- Walch et al. Science Advances 2016
- Much media attention
- "Oh, Good Morning, Sleep Science, Welcome to the 21st Century." Wired

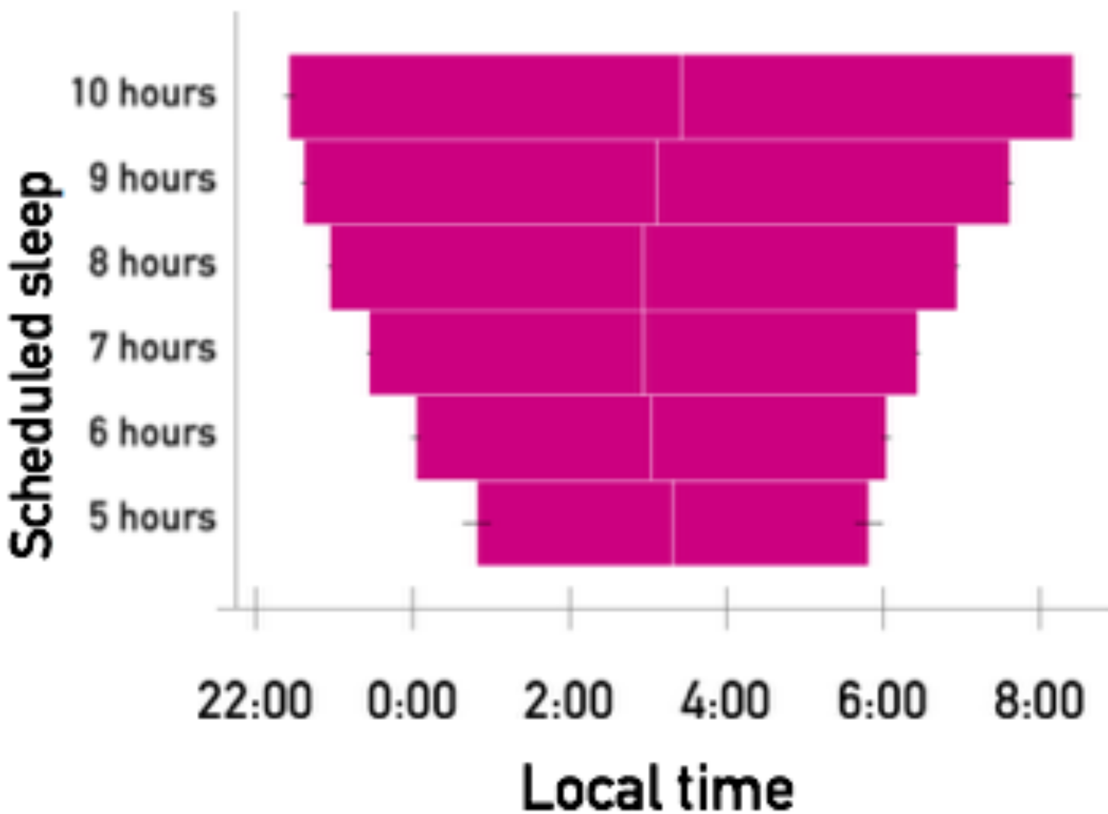
Basic Demographics

- Top three countries contributing data: the United States (45%), Australia (9%), and Canada (5%).
- Top six European countries (UK, France, Spain, Netherlands, Denmark, and Germany) contribute 15%
- Everyone else 25% (no individual country more than 2%)

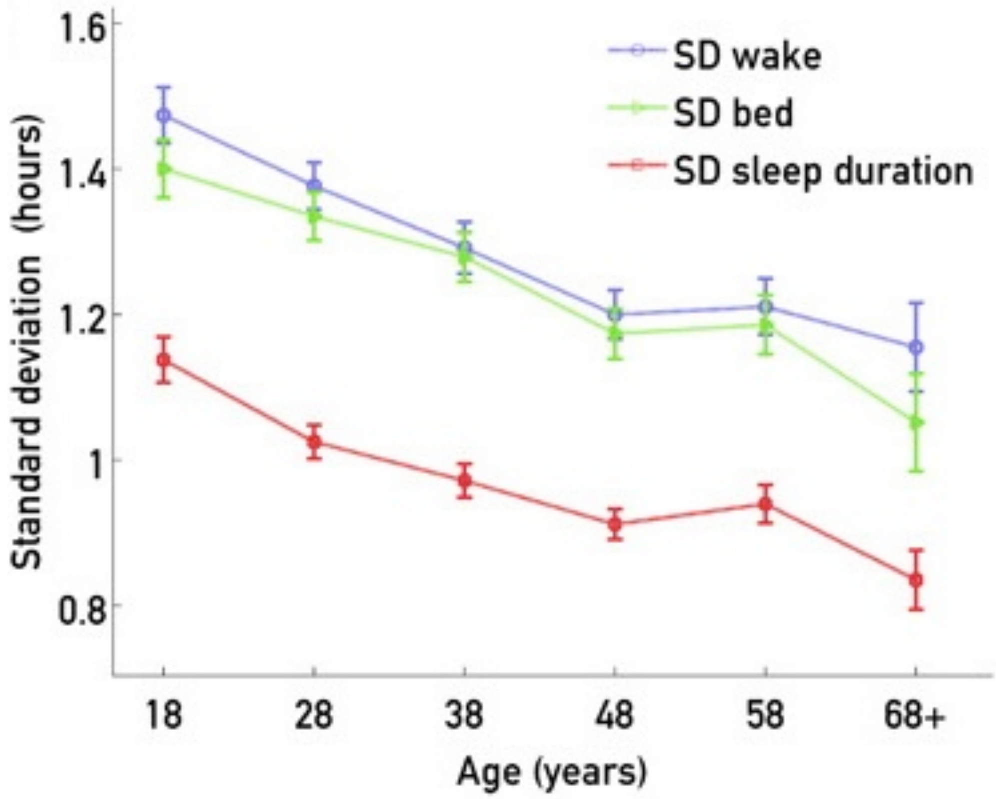
Basic Demographics



Basic Demographics

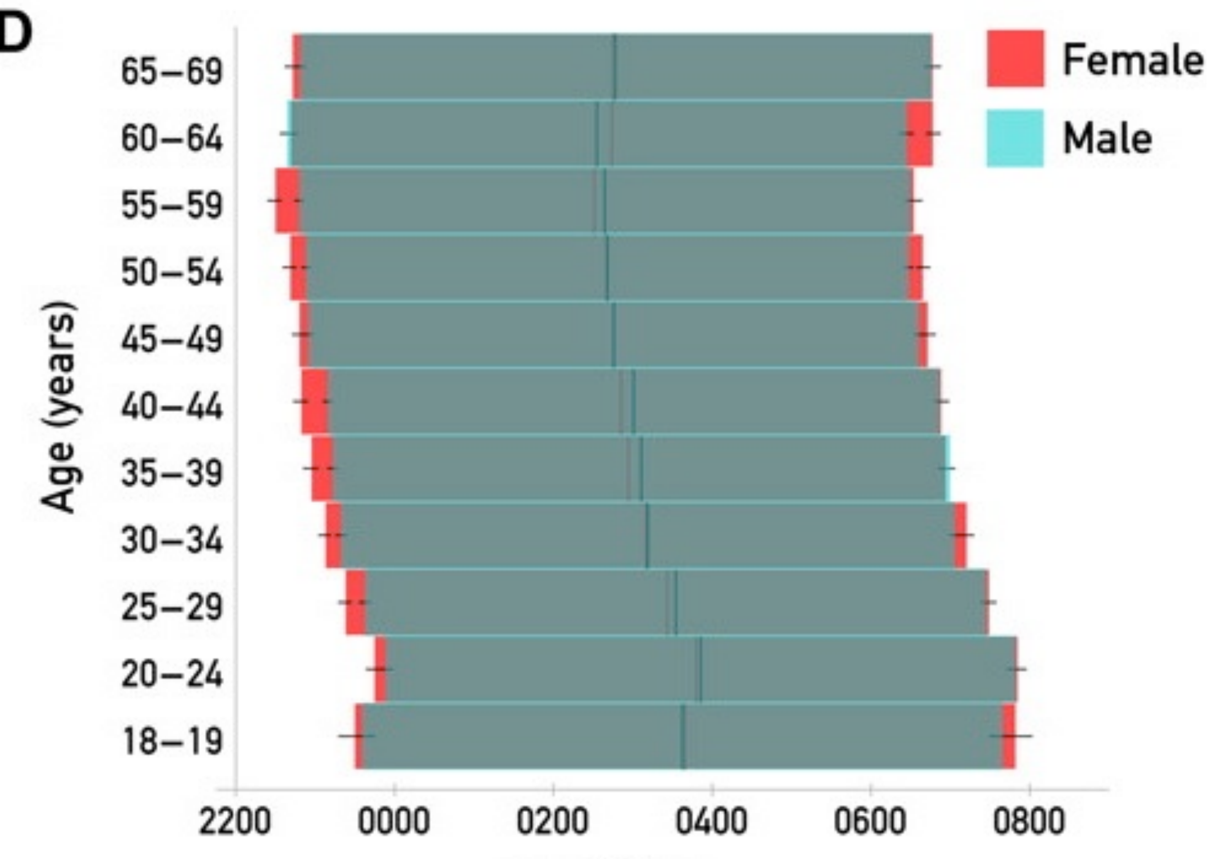


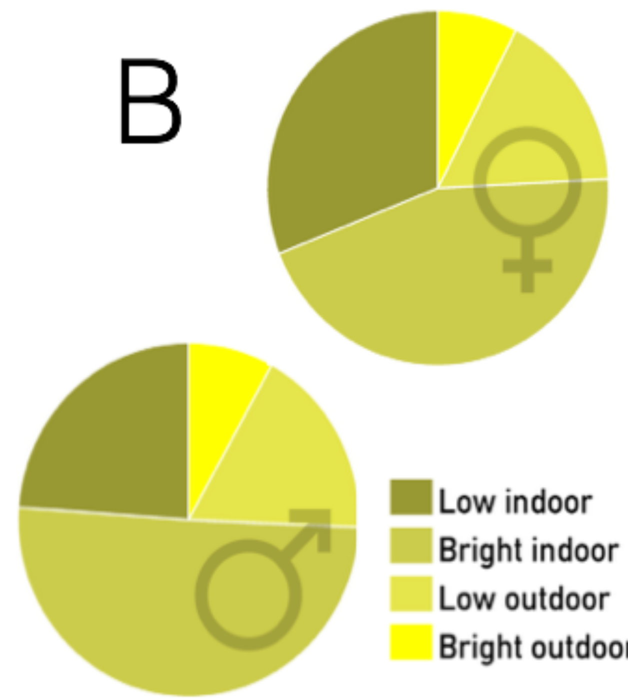
Age and Sleep:
(Also works for coefficient of variation)



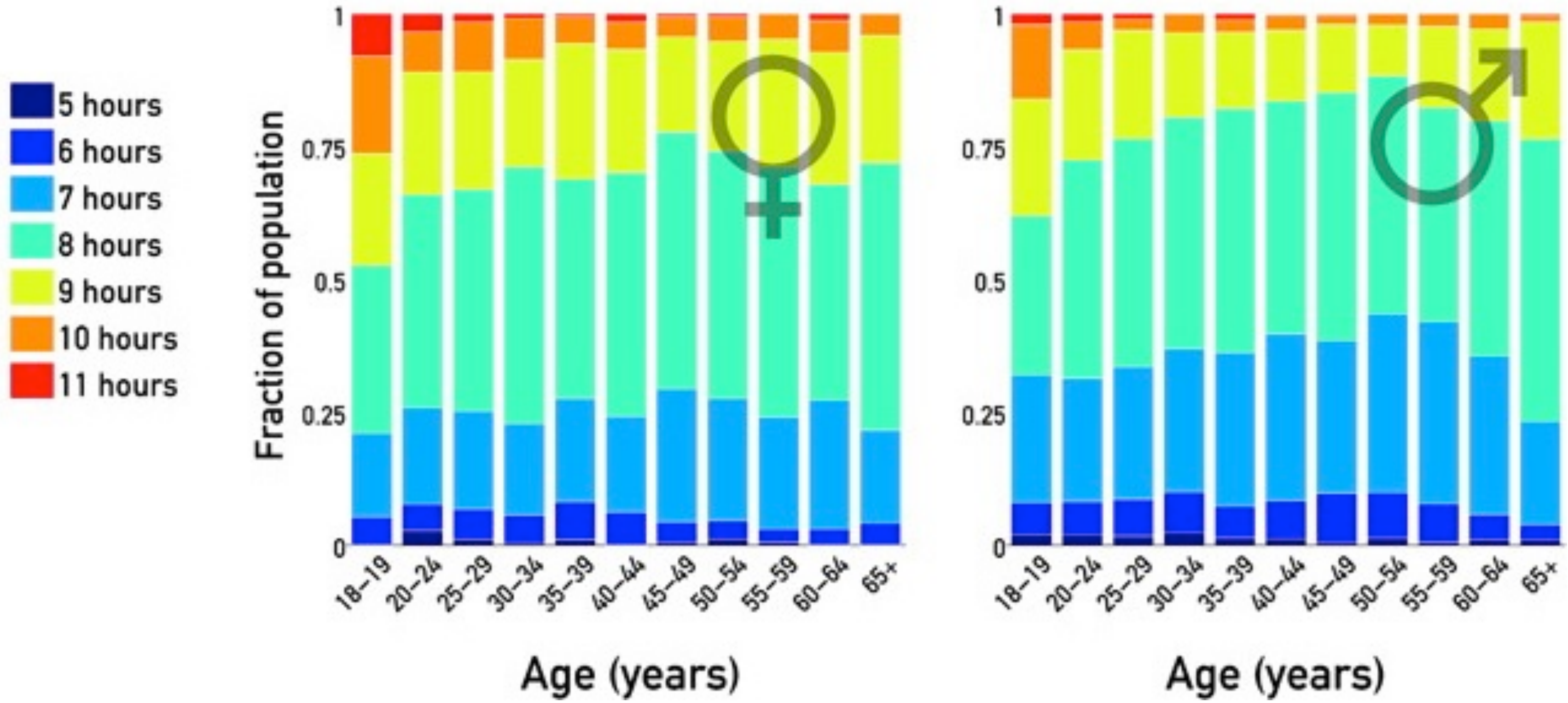
Less variability for outdoor population

Age Sleep and Gender





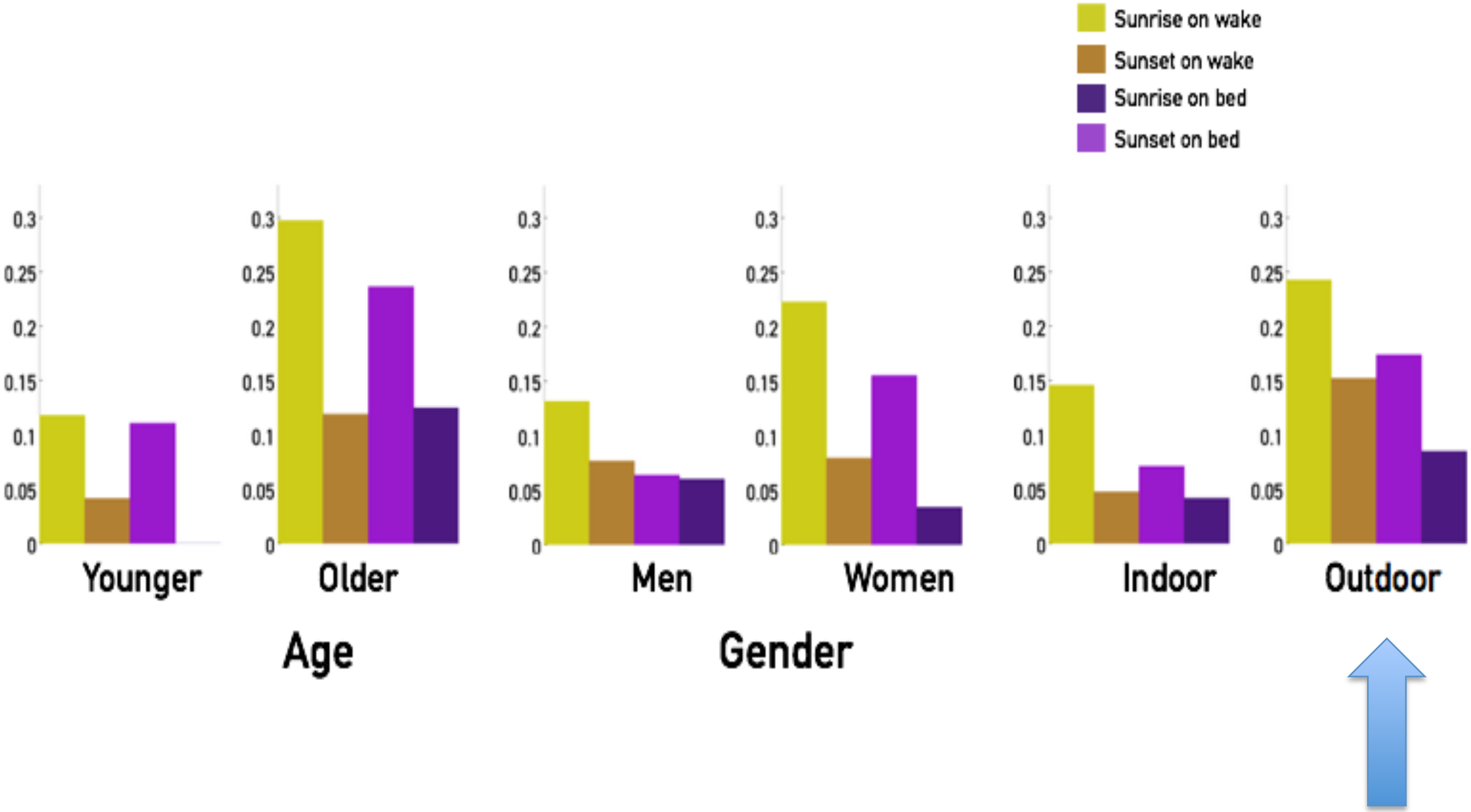
Age and Sleep



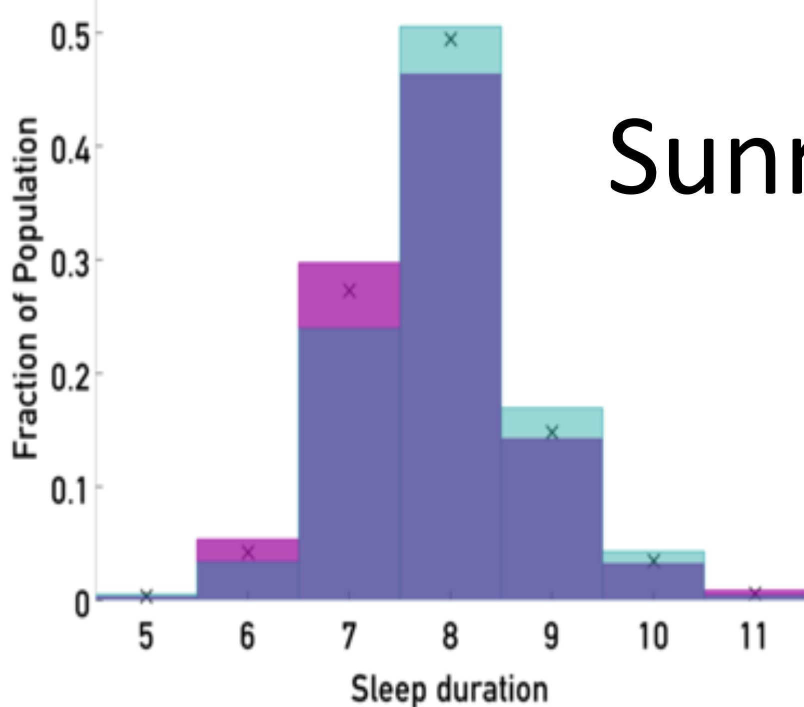
Notes from Statistical Analysis

- Age is most dominant influence on sleep timing
- Gender has the strongest influence on sleep duration.
- The shorter sleep durations during middle age can be attributed primarily to **men** and the group of population reporting **indoor light**.

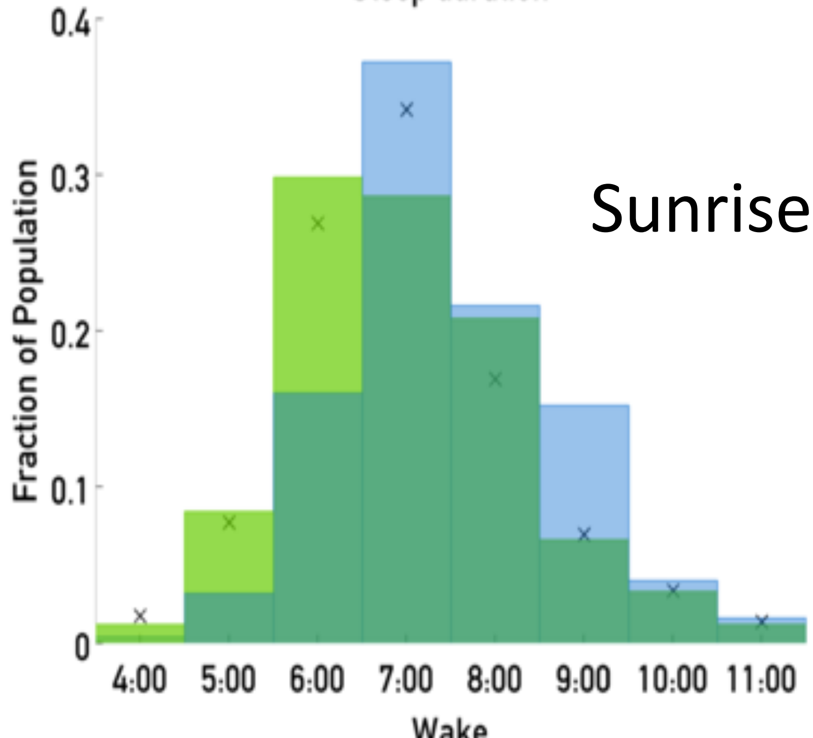
Sunrise, Sunset and Sleep



Sunrise, Sunset and Sleep



Sunrise before 5:30 or after 7:30

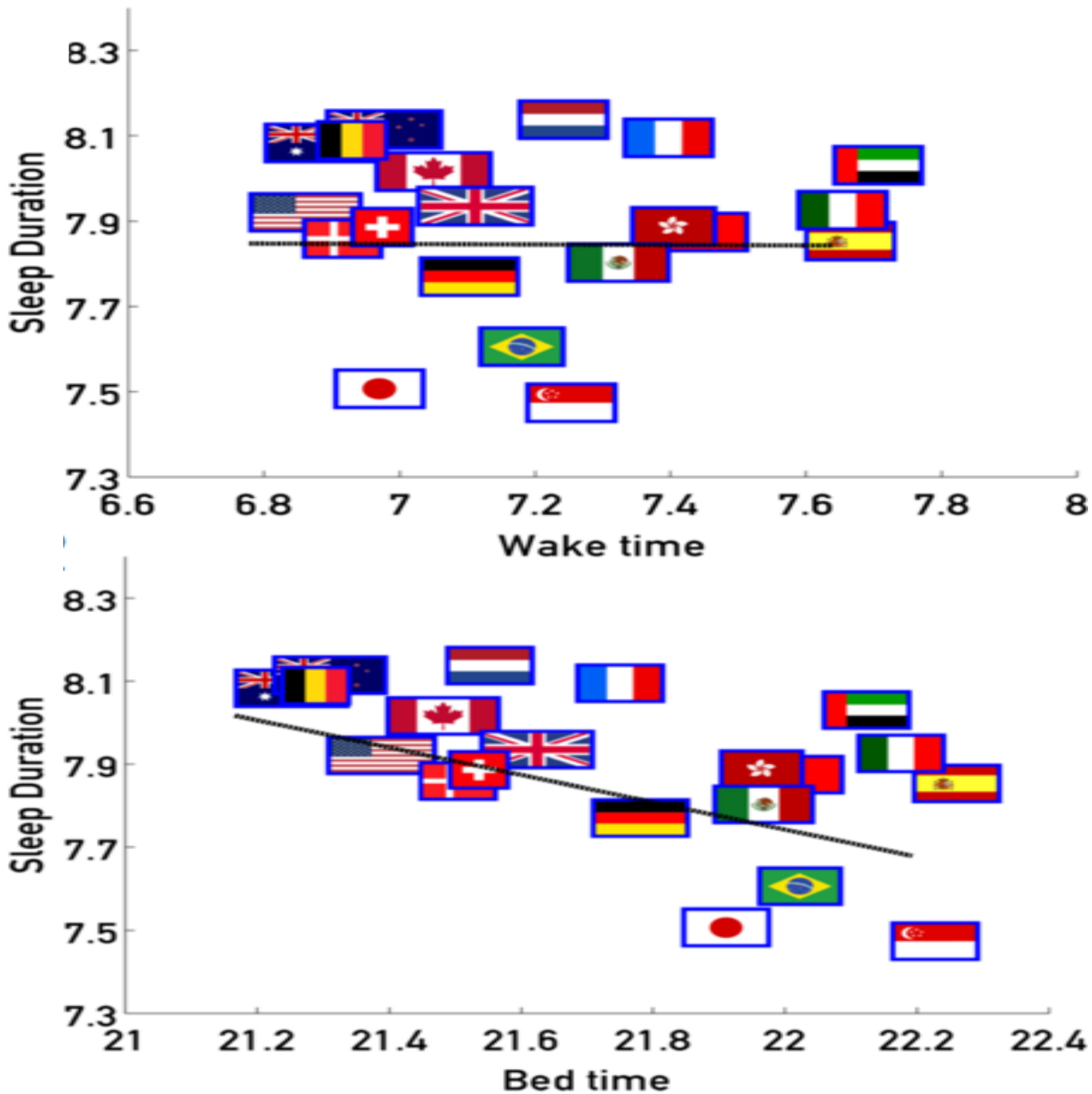


Notes from statistical analysis

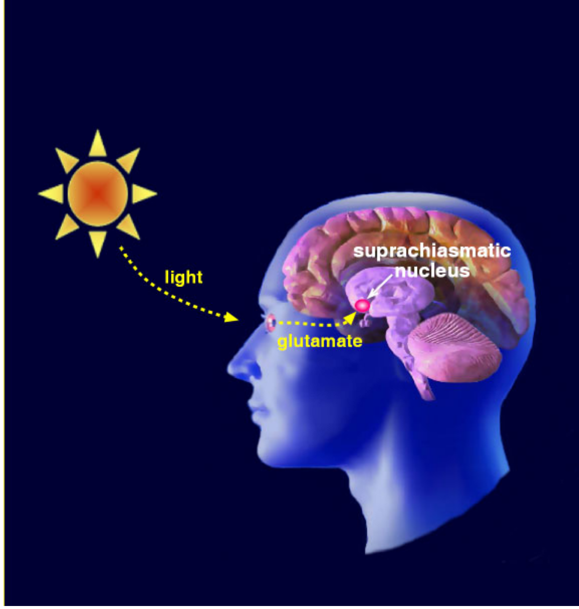
- Later sunsets are correlated with more sleep, mainly through wake
  - More Sleep in summer

- Women, older, and outdoor individuals are more sensitive to changes in sunrise and sunset than men, as indicated by higher regression coefficients.
- Sunset affects wake more than bed
  - Supported by additional simulations

Societal Effects Through Bedtime



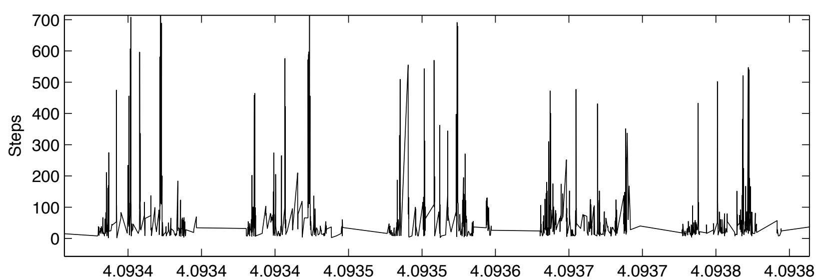
Conclusion

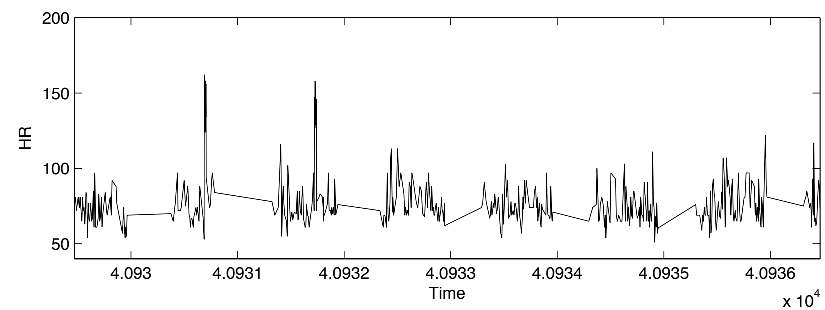


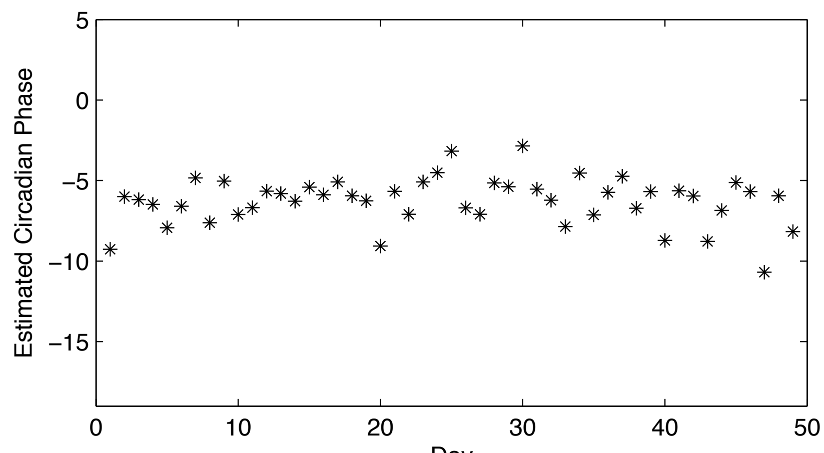
Sleep

Key challenges

- How to incorporate self reported data in models?
- How to include societal effects?
- How to analyze data from smartphones?







Thanks

- Biomathematics program at Army
- Human Frontier Science Program
- AFOSR