A map-based approach to understanding circadian modulation of sleep

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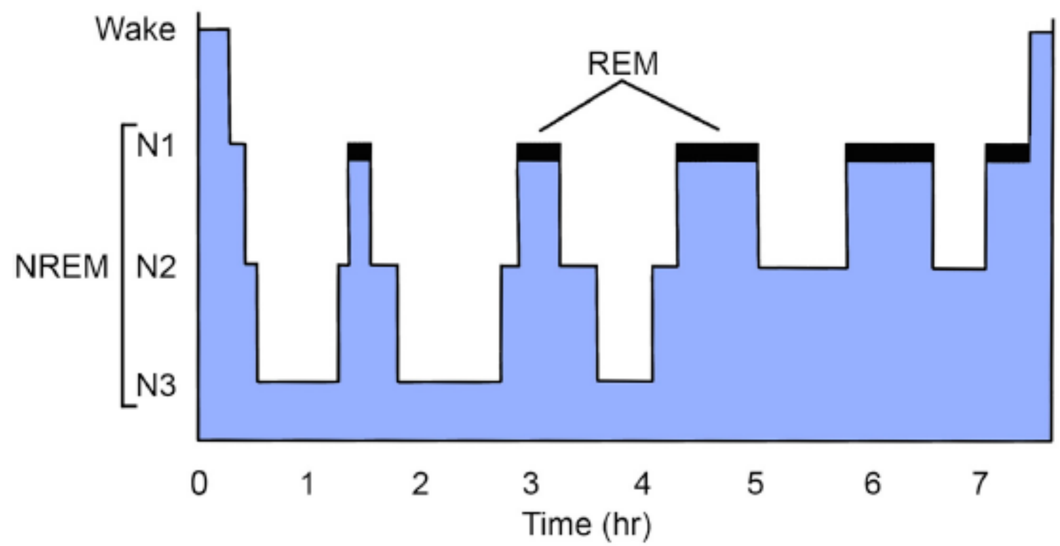
Overview

- Motivation
- Sleep/wake network model
- 1-D map
  - Algorithm for map
  - Map for different REM behavior patterns
  - Bifurcations in map as homeostatic parameter varies
- Conclusions and future directions

Human sleep/wake behavior

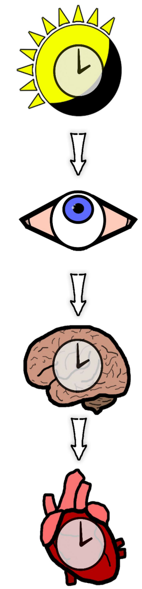
- Normal adult human sleep occurs in a consolidated nighttime period
- Sleep includes both rapid-eye movement (REM) sleep and non-REM (NREM) sleep
- Over the course of the night, people cycle between NREM and REM sleep approximately every 90 minutes

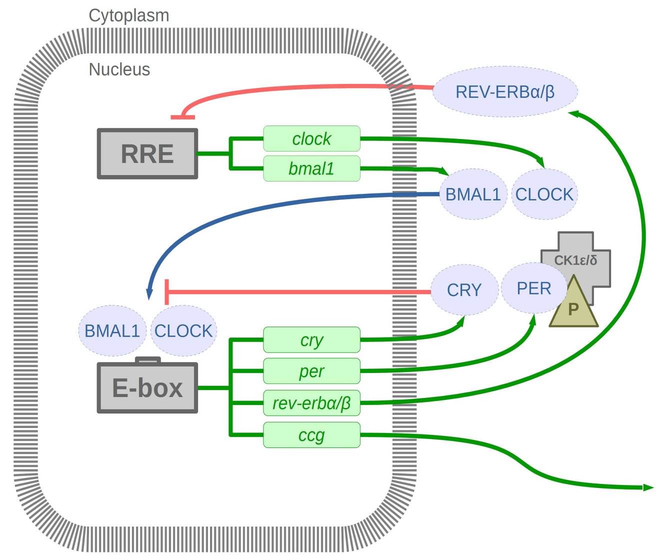


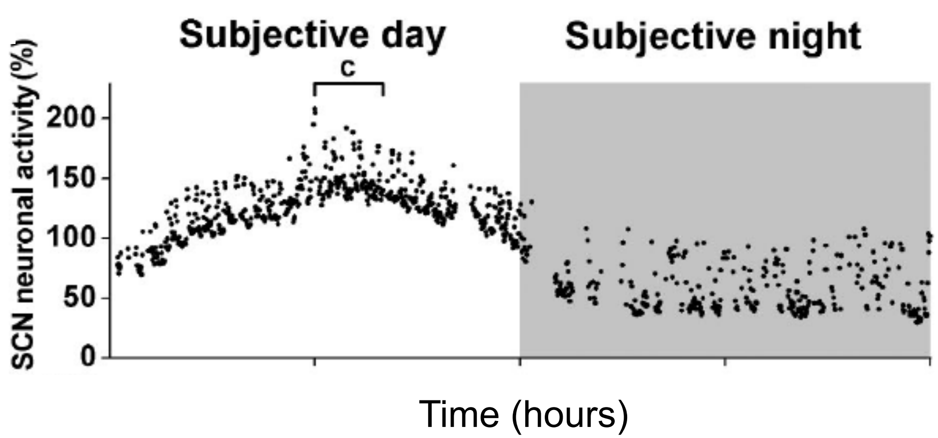
Scammell et al., Neuron, 2017

Circadian rhythms

- *Circa dia*: "about a day;" approximately 24 hours
- Biological rhythm observed in nearly all species
- Generated by molecular clock in neurons within the suprachiasmatic nucleus of the hypothalamus (SCN)
- Clock modulates firing of SCN neurons







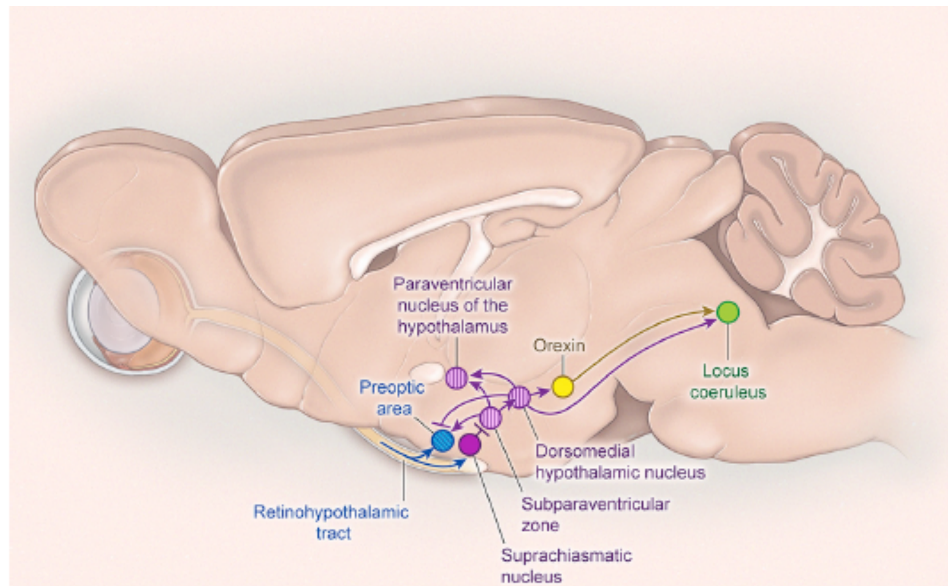
Tsimakouridze, Fronters in Pharma, 2015

Deboer et al., Nature Neurosci, 2003

SCN modulates timing of sleep/wake behavior

- SCN entrains to the environmental light/dark cycle
- SCN acts as master pacemaker and determines timing of sleep/wake behavior
- Perturbations to entrained system result in misalignment of behavior and circadian phase

Neural pathways that regulate circadian modulation of sleep

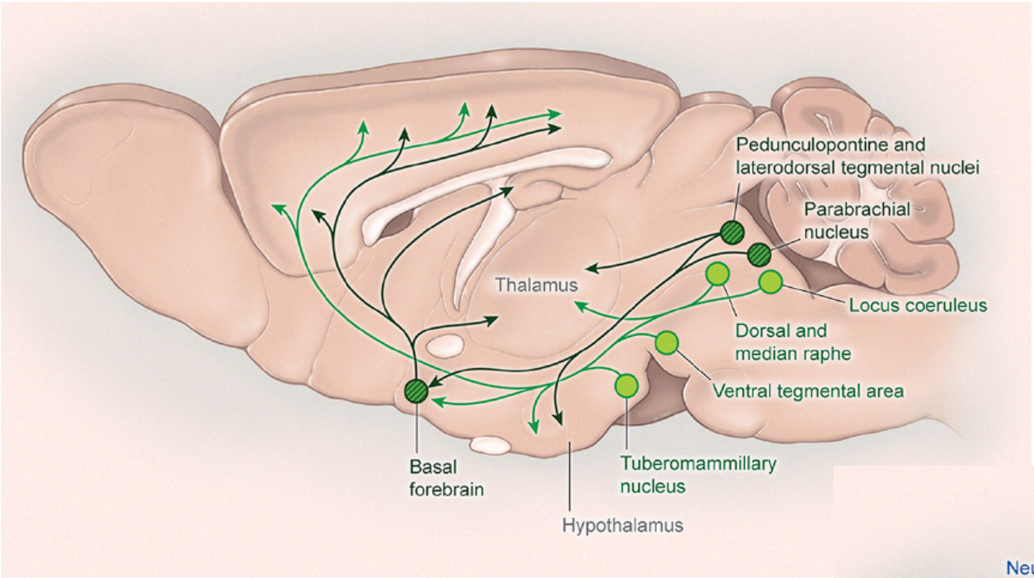


Scammell et al., Neuron, 2017

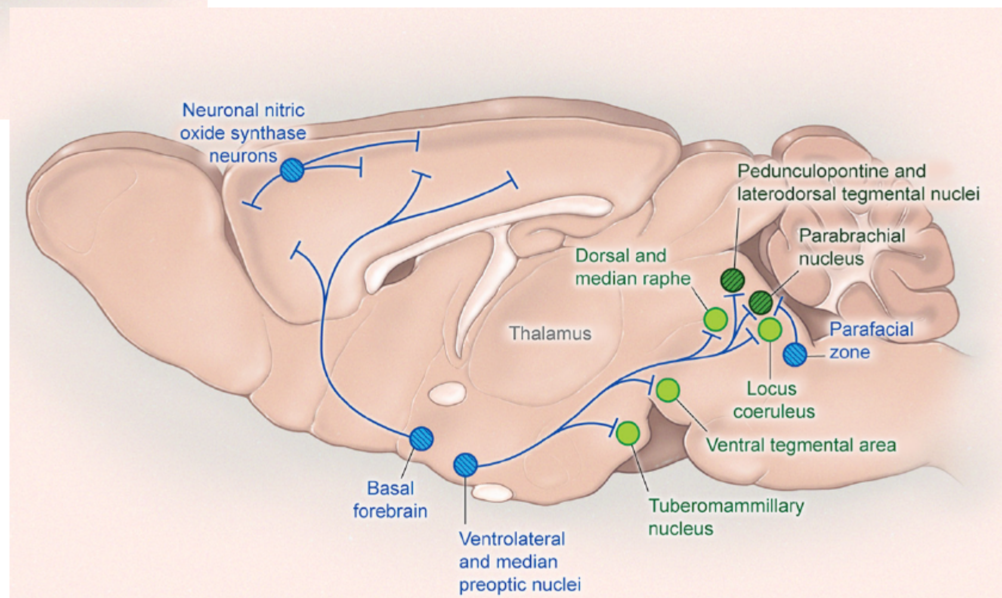
Goal

Use mathematical modeling and analysis to investigate circadian modulation of sleep/wake behavior and the dynamics of re-entrainment.

Physiology of sleep/wake regulation



Wake-promoting pathways

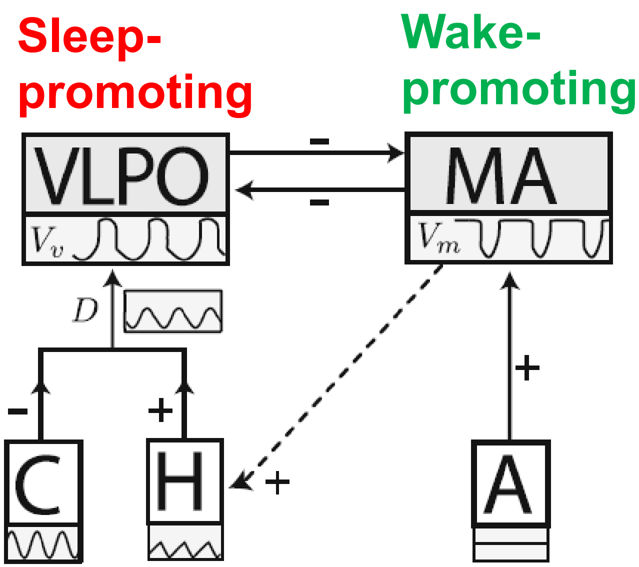


NREM-promoting pathways

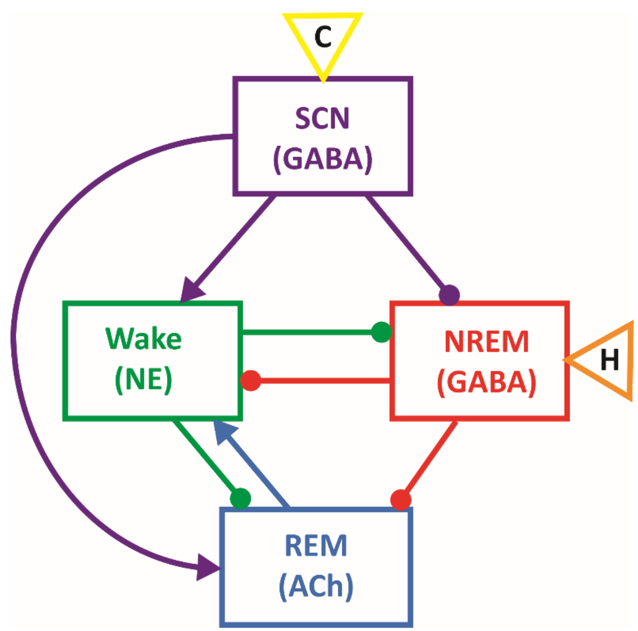
Scammell et al., Neuron, 2017

Models of the sleep/wake regulatory network

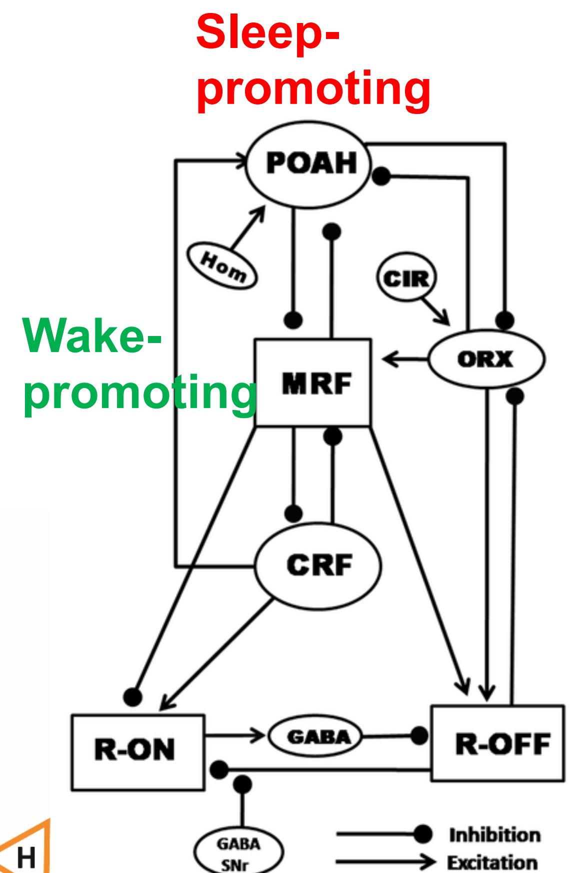
- Competing hypotheses for the structure of the network have led to multiple mathematical models



Phillips and Robinson, 2007, 2008



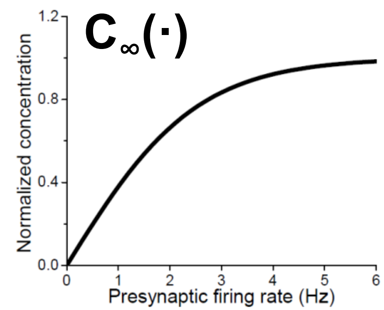
Diniz Behn and Booth, 2010, 2011, 2013

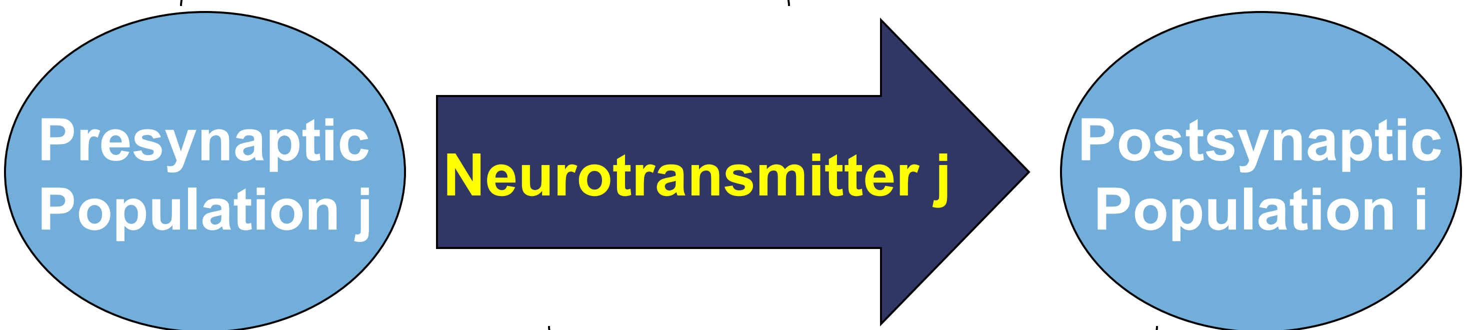


Kumar et al., 2012

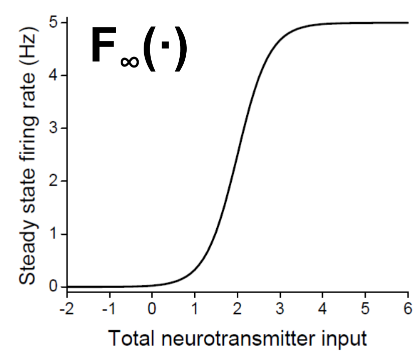
Reduced population firing rate model formalism

$$C_{X\infty}(F_X) = \tanh(F_X / \gamma_X)$$





$$\frac{df_i}{dt} = \frac{F_\infty(\sum g_j c_j) - f_i}{\tau_f}$$



Diniz Behn and Booth, J Neurophysiol, 2010

Reduced sleep/wake regulatory network model

Wake: $$F_W' = \frac{F_{W\infty}[g_{N,W} C_{N\infty}(F_N) + g_{R,W} C_{R\infty}(F_R) + g_{W,W} C_{W\infty}(F_W)] - F_W}{\tau_W}$$

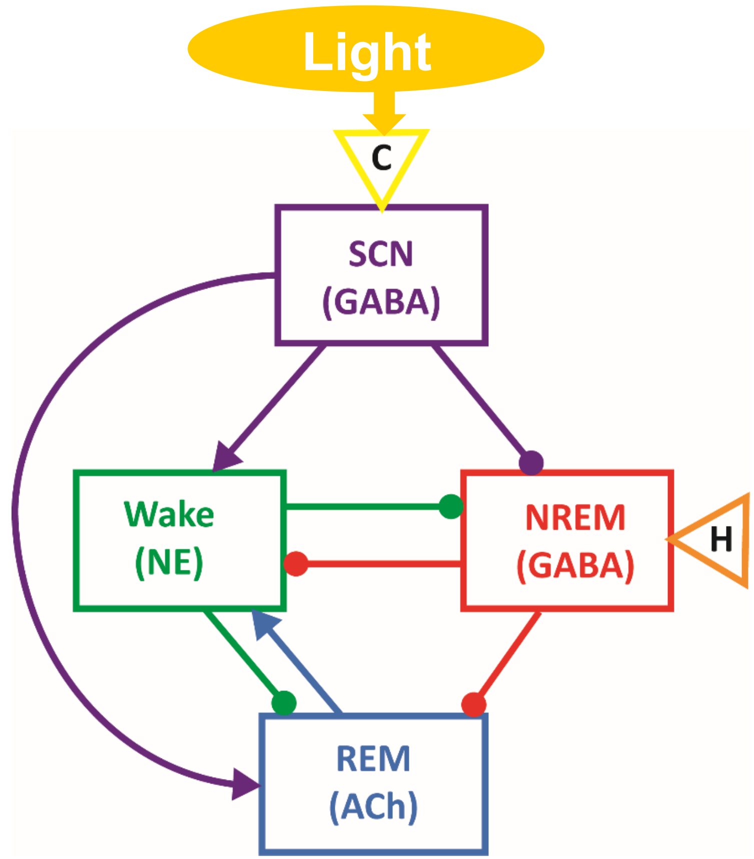
NREM: $$F_N' = \frac{F_{N\infty(h)}[g_{W,N} C_{W\infty}(F_W) + g_{N,N} C_{N\infty}(F_N)] - F_N}{\tau_N}$$

REM: $$F_R' = \frac{F_{R\infty}[g_{W,R} C_{W\infty}(F_W) + g_{N,R} C_{N\infty}(F_N) + g_{R,R} C_{R\infty}(F_R)] - F_R}{\tau_R}$$

$$F_{X\infty}(c) = \frac{X_{\max}}{2}(1 + \tanh((c - \beta_X)/\alpha_X)); \quad C_{X\infty}(F_X) = \tanh(F_X/\gamma_X)$$

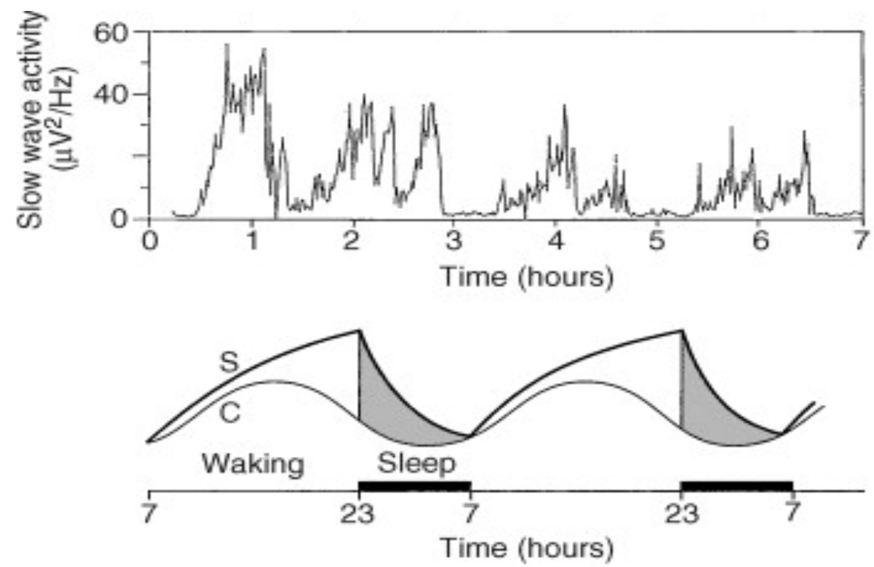
Homeostatic and circadian drives

- Interactions in the sleep/ wake regulatory network are modulated by homeostatic and circadian drives
- Homeostatic drive represents sleep need that increases with time awake
- Circadian drive represents sleep need that varies with time of day



Homeostatic sleep drive

- Denoted by H
- Fit to time course of slow wave activity
- Mimics effect of adenosine
- Promotes activity of NREM-promoting population



$$H' = \begin{cases} (h_{\max} - H) / \tau_{hw} & \textbf{during wake} \\ -(H - h_{\min}) / \tau_{hs} & \textbf{during sleep states} \end{cases}$$

Kilduff et al., Cell, 2011

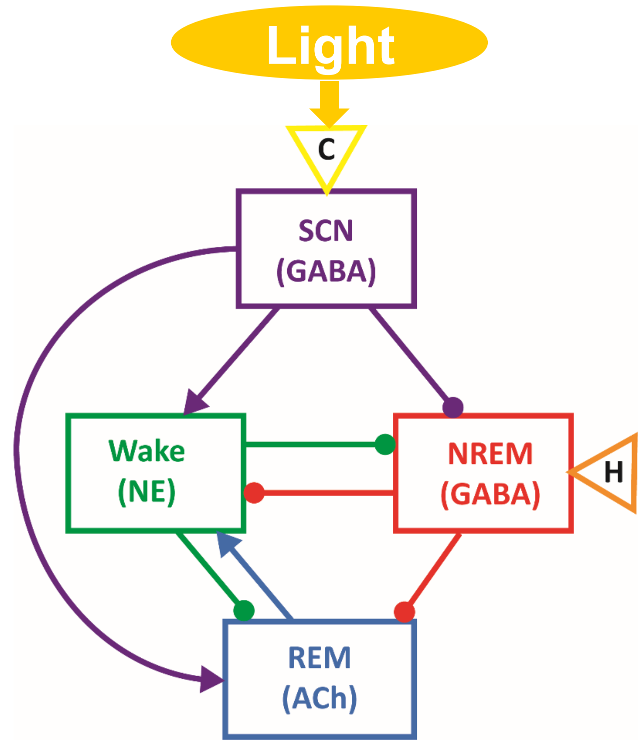
Circadian drive

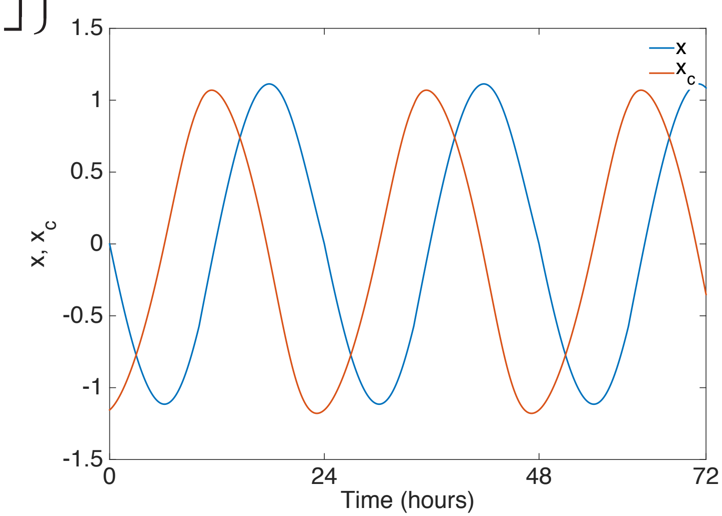
- Human circadian pacemaker represented as modified van der Pol oscillator (Forger et al., 1999):

$$\frac{dx}{dt} = \frac{\pi}{12}(x_c + B)$$

$$\frac{dx_c}{dt} = \frac{\pi}{12}\left\{\mu\left(x_c - \frac{4x_c^3}{3}\right) - x\left[\left(\frac{24}{0.99669\tau_x}\right)^2 + kB\right]\right\}.$$

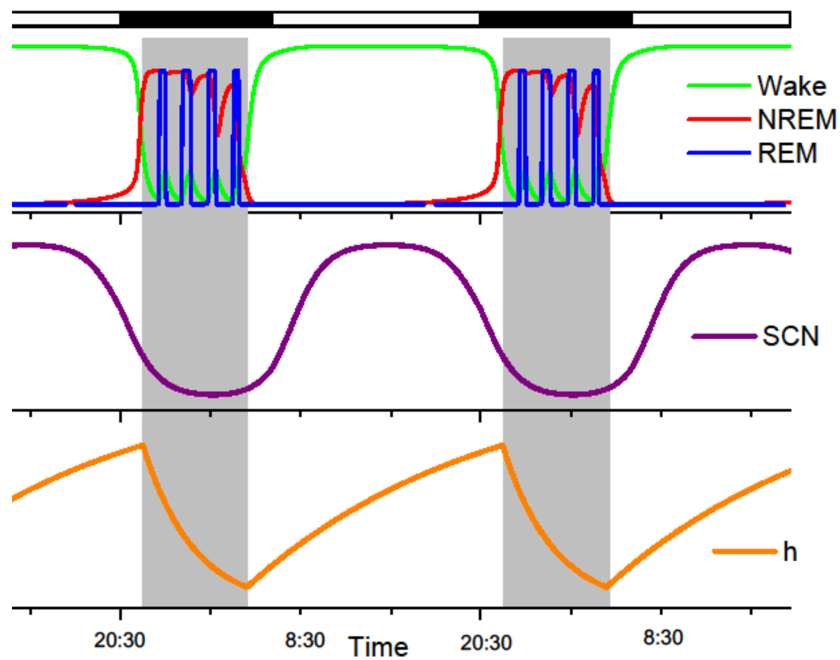
- Can be entrained to external light schedule with light input mediated through B





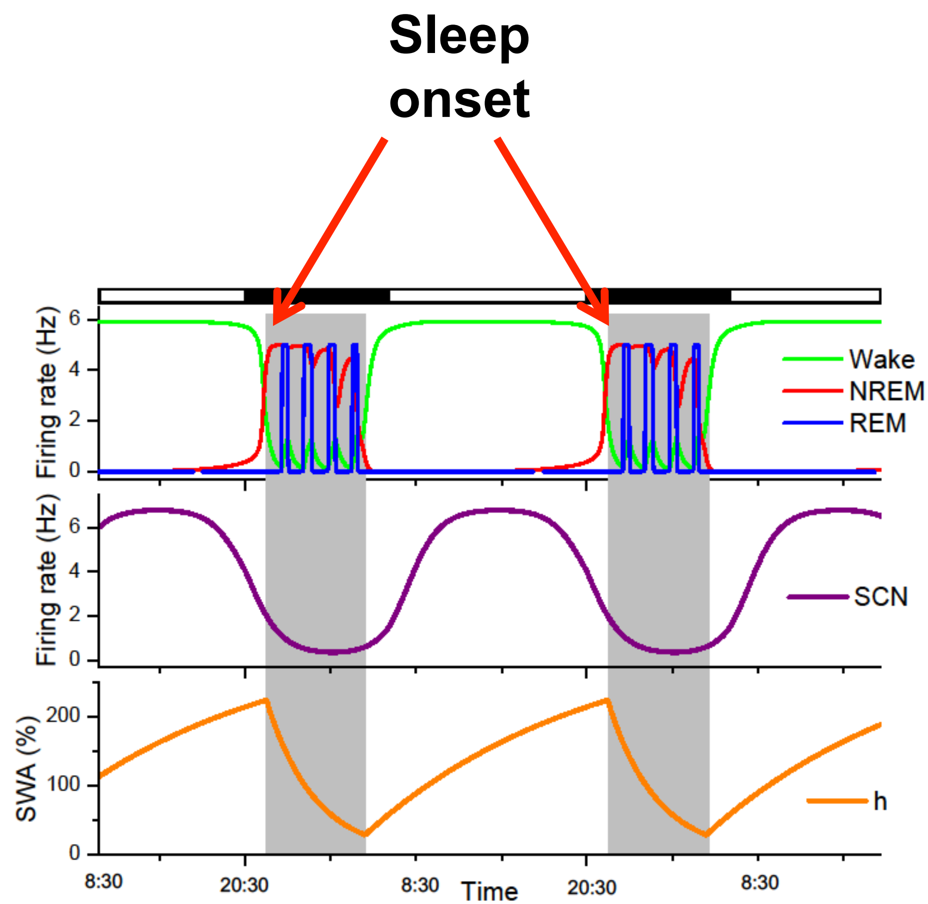
Simulated stereotypical human sleep

- Behavioral state determined by activity of neuronal populations
- Under normal conditions, sleep cycle and circadian rhythm are synchronized
- More interesting dynamics occur in de-synchronizing situations:
  - All-nighters
  - Sleep deprivation & recovery
  - Shift work



Map construction

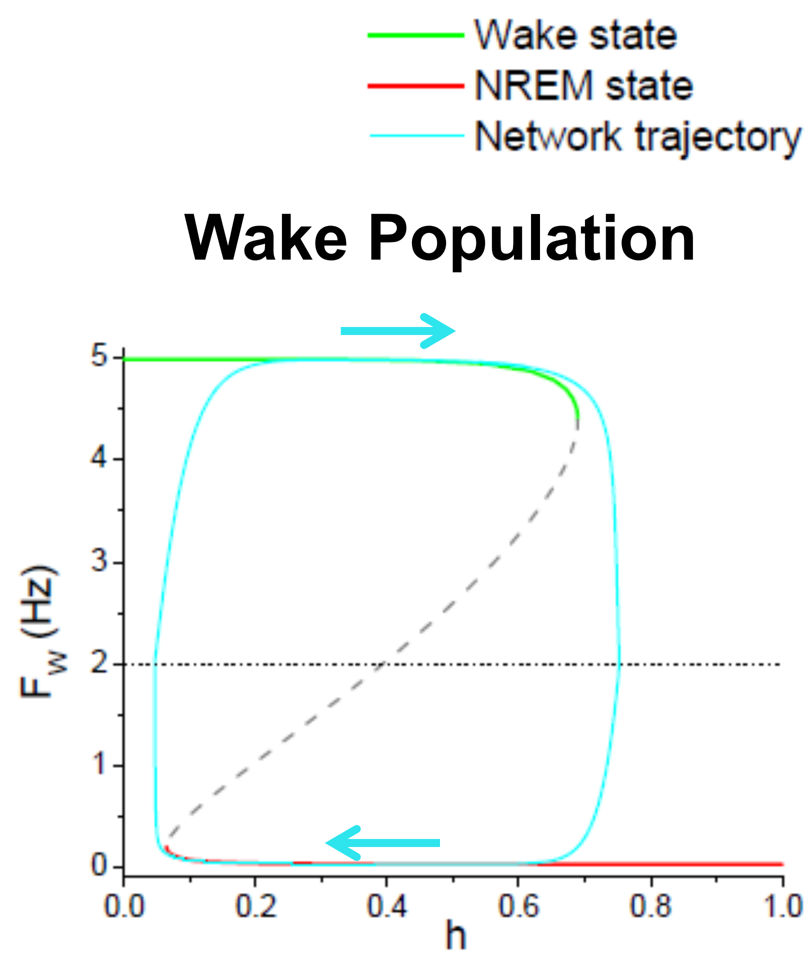
- Numerically constructed a 1-D map to describe dependence of sleep on circadian phase in full model
- Simulated the model from initial conditions corresponding to sleep onset occurring at different circadian phases
  - Algorithm to define sleep onset in high dimensional model



Booth, Xique, & Diniz Behn, SIAM J Appl Dyn Sys, to appear

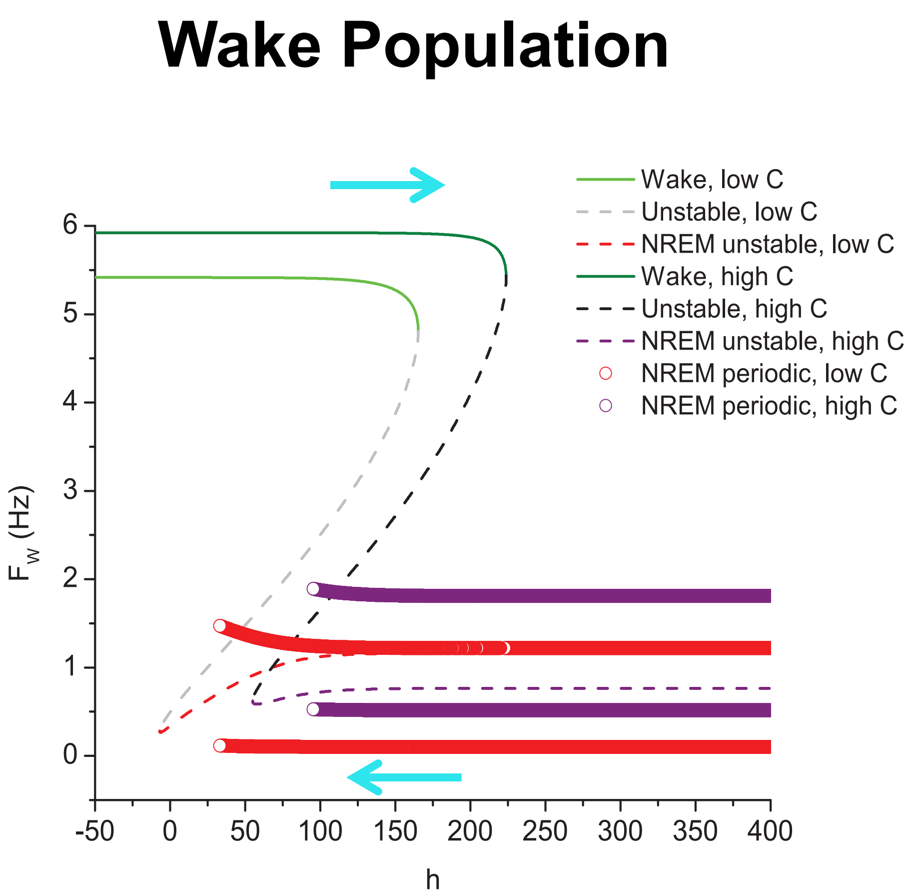
Transitions between sleep and wake correspond to movement around hysteresis loop

- Fast-slow decomposition with slow parameter h
- Stable wake and NREM states form Z-shaped steady state curve
- Sleep onset corresponds to upper knee of Z



Diniz Behn & Booth, SIAM J Appl Dyn Sys, 2012

Circadian modulation introduces another slow variable



- 3 time scales in system
  - Neuronal dynamics are fast
  - Homeostatic drive and circadian modulation are slow
- Circadian modulation slowly varies Z
- Sleep onset tracks position of knee in full high-dimensional space

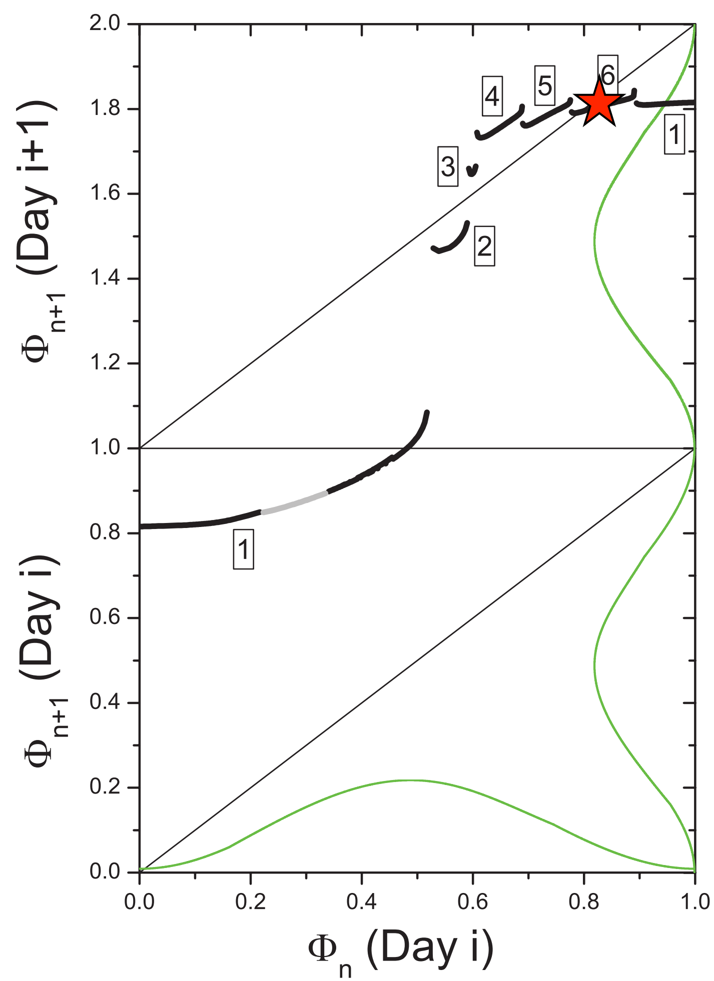
Booth, Xique,& Diniz Behn, SIAM J Appl Dyn Sys, to appear

Numerical algorithm for computing a 1D map for this model

- Compute **appropriate** initial conditions for sleep onset for each circadian phase
  - Sleep onset occurs at upper saddle-node point so this specifies network variables
  - Use two-parameter numerical continuation to determine the values of the remaining circadian variables
- For each set of ICs, simulate full model and track circadian phase of subsequent sleep onsets

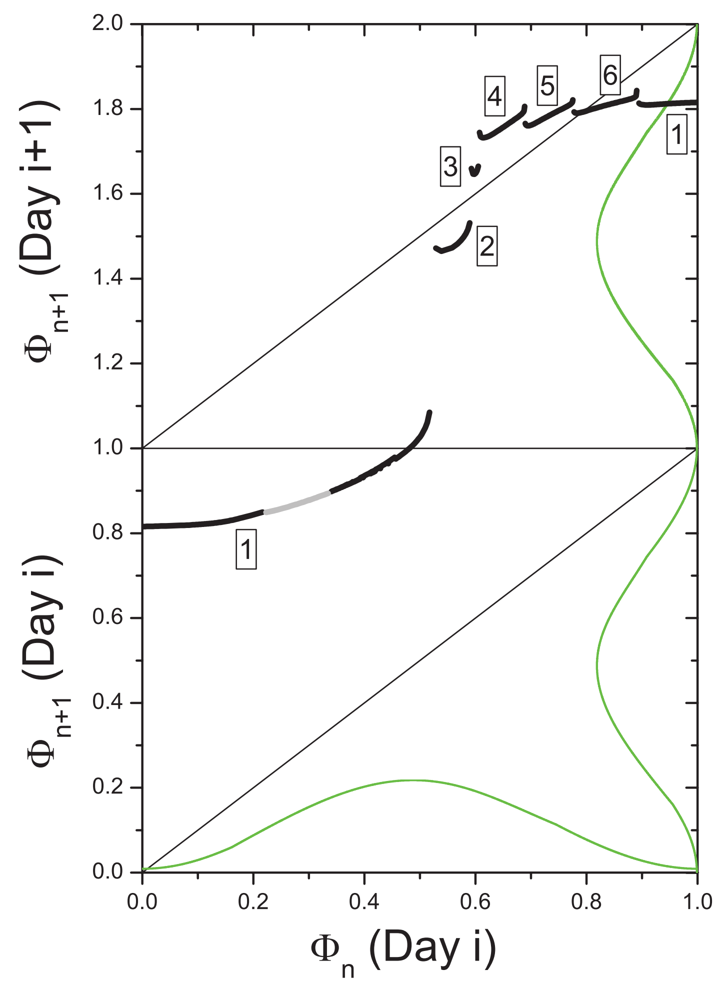
1D map for full model

- Computed map of Φ_{n+1} as a function of Φ_n
- Vertical discontinuities between different branches of map
- Fixed point of map (★) at Φ=0.793 corresponds to entrained case
- Slope < 1 (~0.35) at fixed point indicates stability



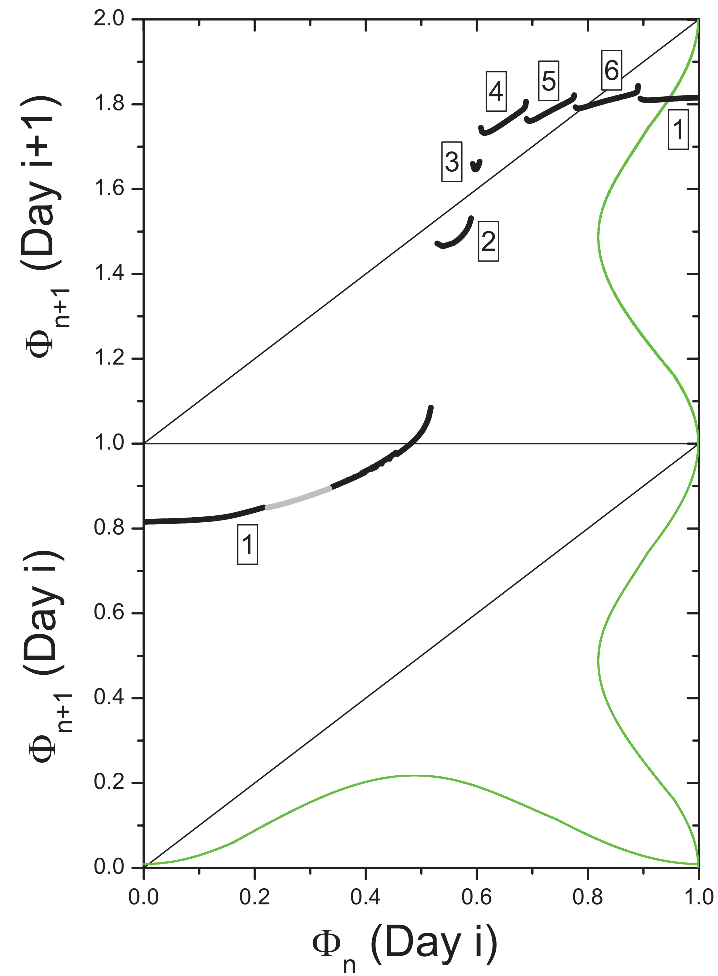
Wake-promoting zone in 1D map

- In grey region, sleep onset did not immediately occur from the given ICs
  - Initially, F_W decreased and F_N increased
  - Then variables reversed directions
- Related to system time scales
- To force transition, used ICs on unstable manifold of saddle associated with upper saddle-node point
- Refer to this region as “wake-promoting zone”



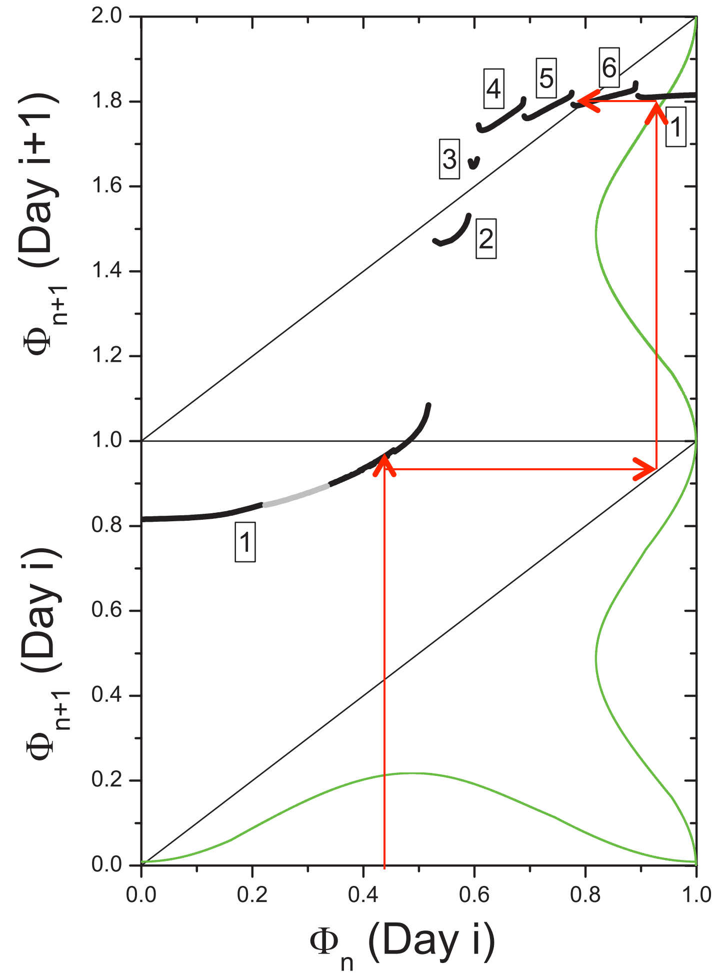
Different branches of map associated with different numbers of REM bouts

- Sleep cycle associated with fixed point has 4 REM bouts
- Branches 2 & 6 also have 4 REM bouts
- Branches 3, 4, & 5 have more REM bouts
- Branch 1 has only 3 REM bouts

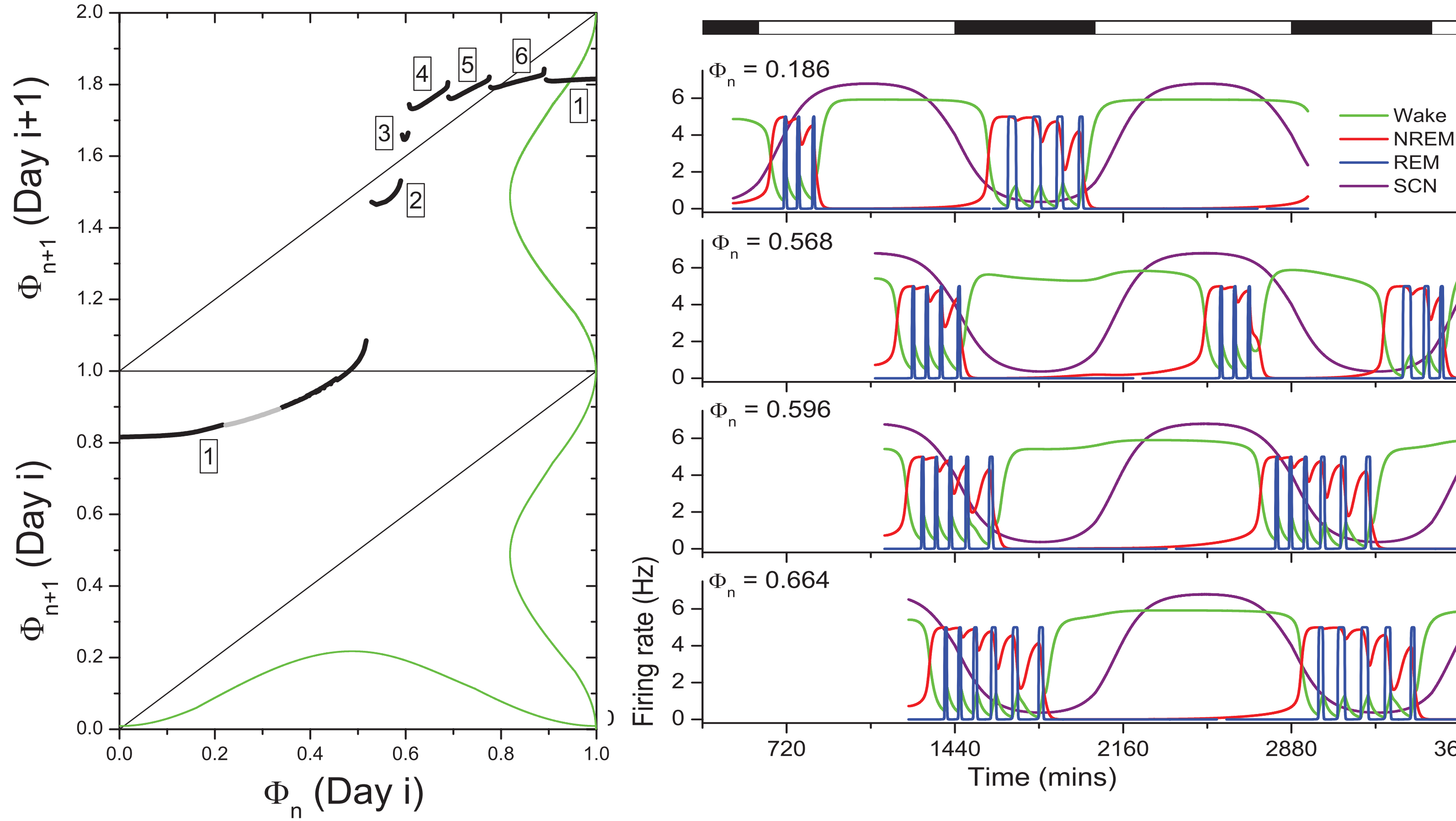


Tracking re-entrainment using 1D map

- Cobwebbing on this map shows re-entrainment dynamics
- Iterates converge to stable fixed point
- Re-entrainment typically occurs after 2-4 days



Trajectories corresponding to different initial phases



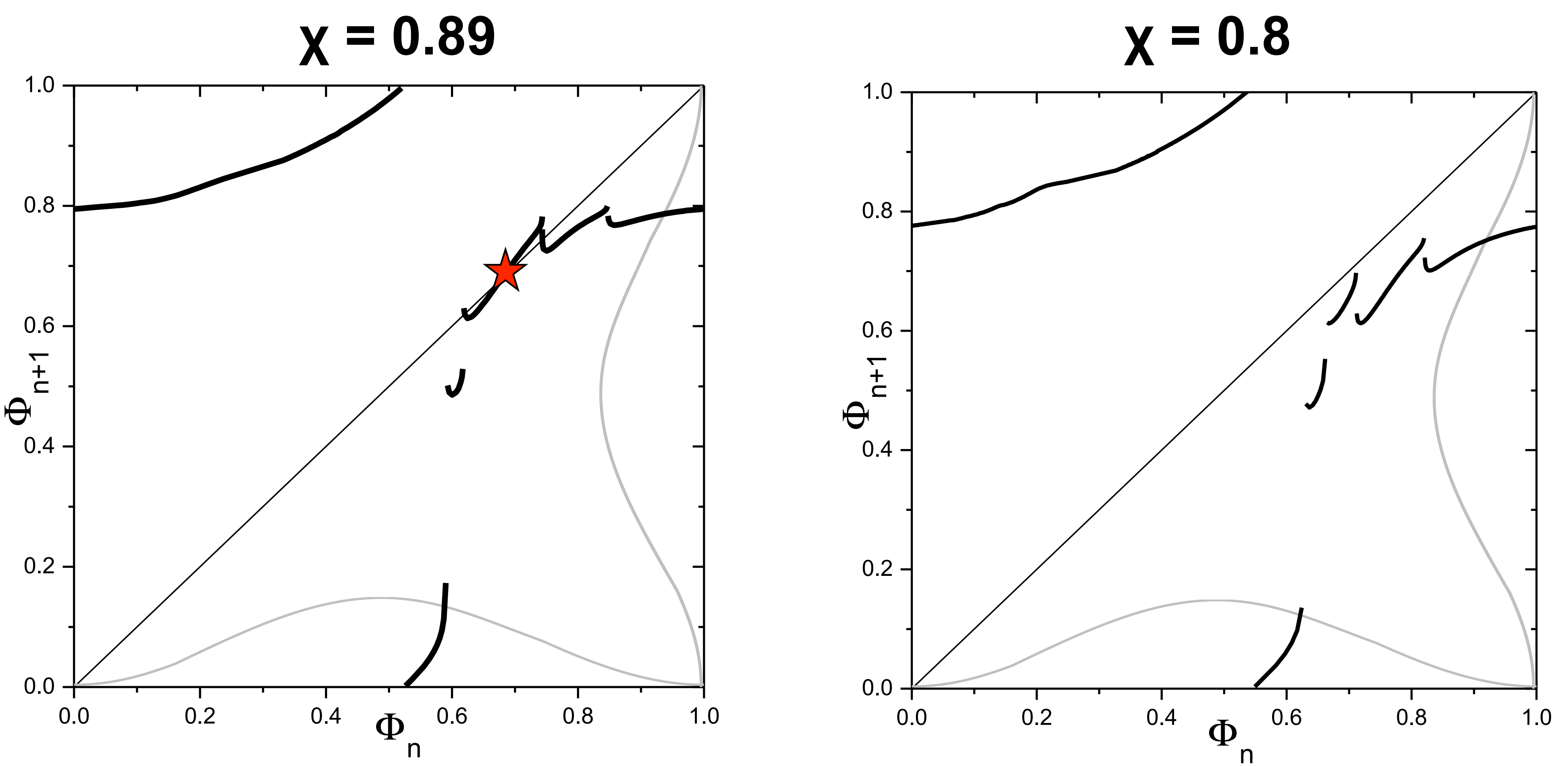
Time scale of homeostatic sleep drive

- Time course of slow wave activity changes in early childhood
- May play a role in transitions from napping to non-napping behavior in early childhood
- Introduced scaling parameter χ to investigate bifurcations in sleep patterns as h time scale varies

$$h' = \frac{(H_{max} - h)}{\chi\ \tau_{hw}} H[F_W - \theta_W] - \frac{h}{\chi\ \tau_{hs}} H[\theta_W - F_W]$$

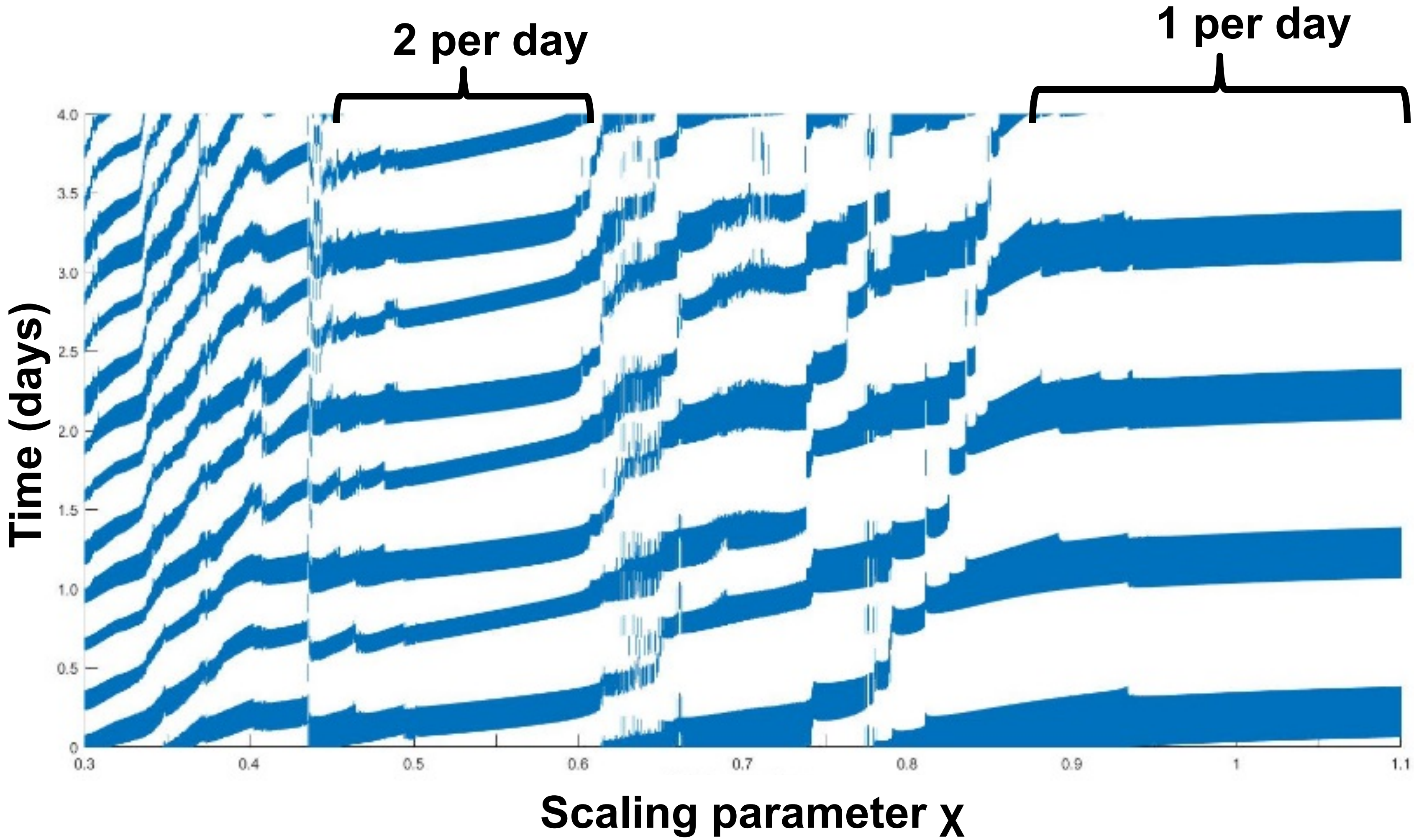
Maps as χ decreases

- Fixed point for synchronized solution loses stability
- Fixed point loses existence due to discontinuity

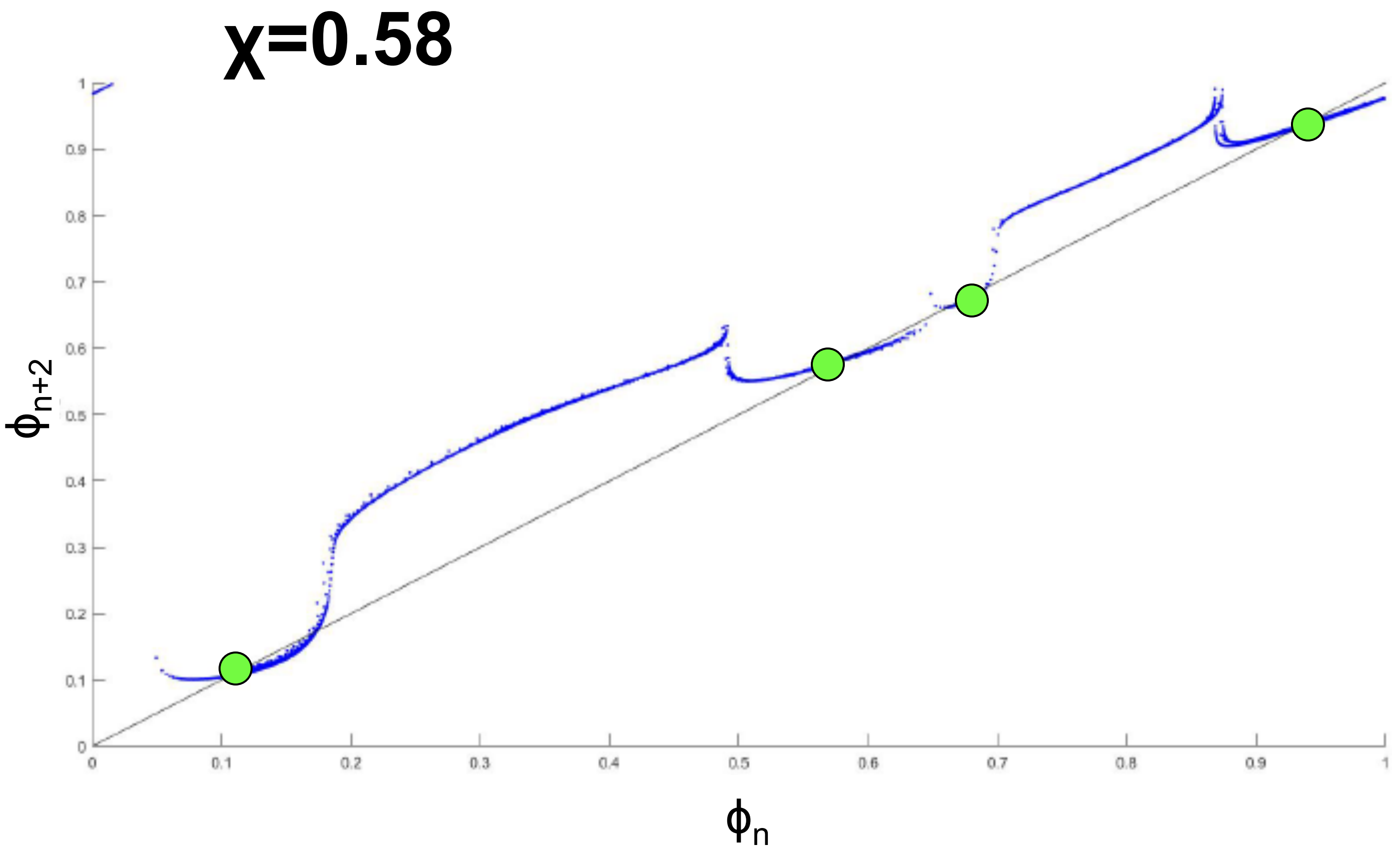


Bifurcations in number of daily sleep episodes

- As χ decreases more sleep episodes occur per day

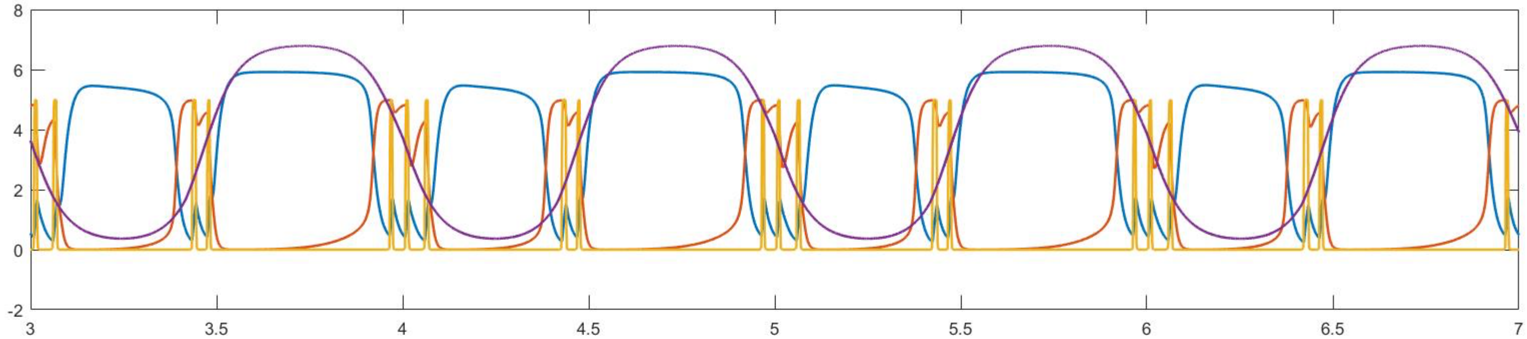


2^{nd} iterate map to examine region with 2 sleep cycles per day

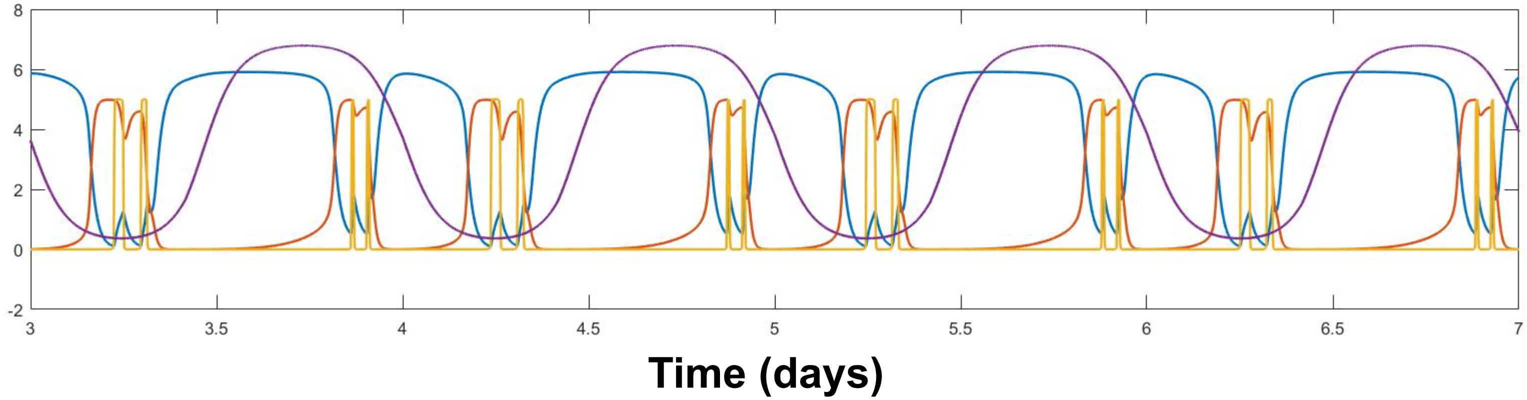


For χ=0.58, two stable two cycles

Early & Late Nighttime Sleep



Nap/ Nighttime Sleep



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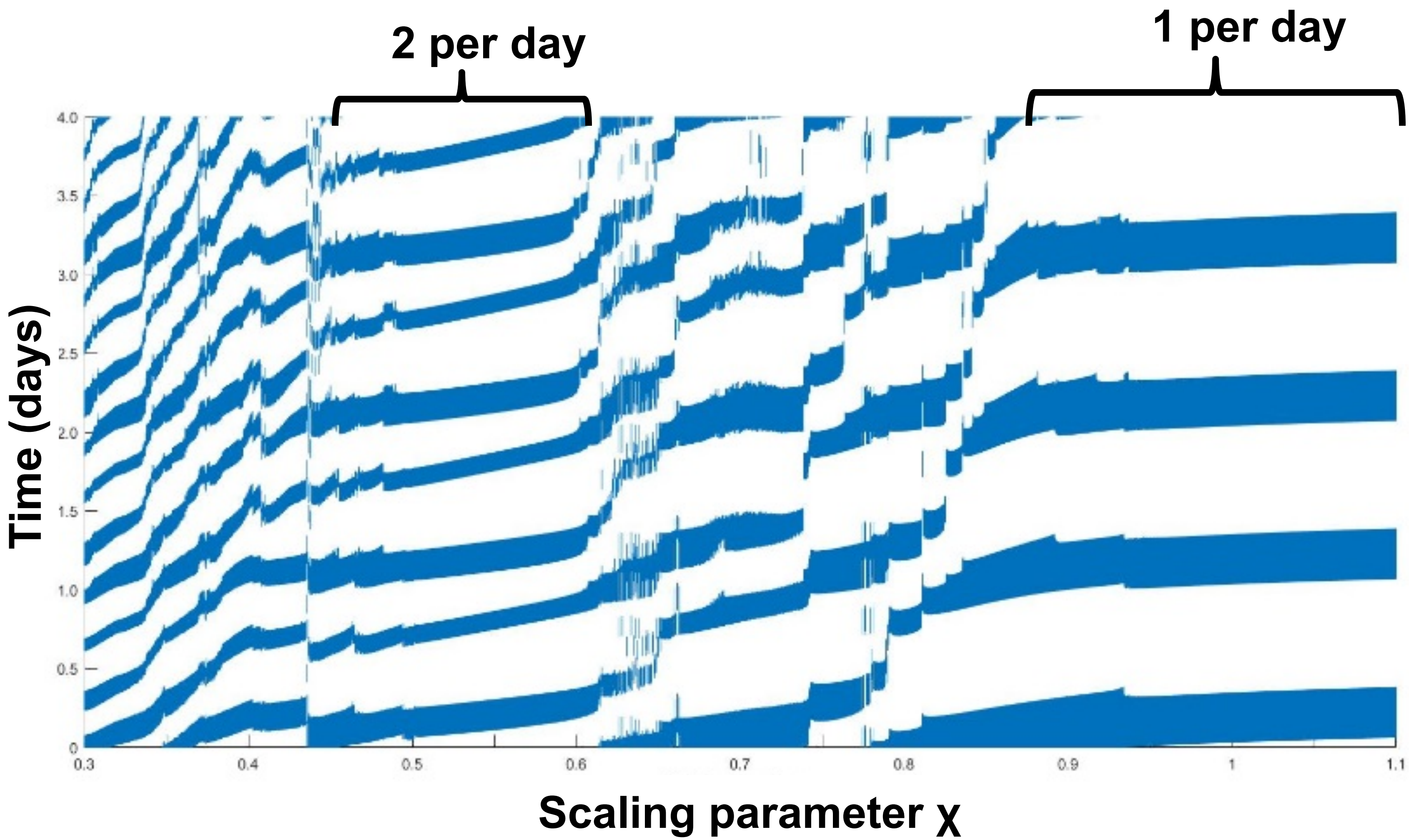
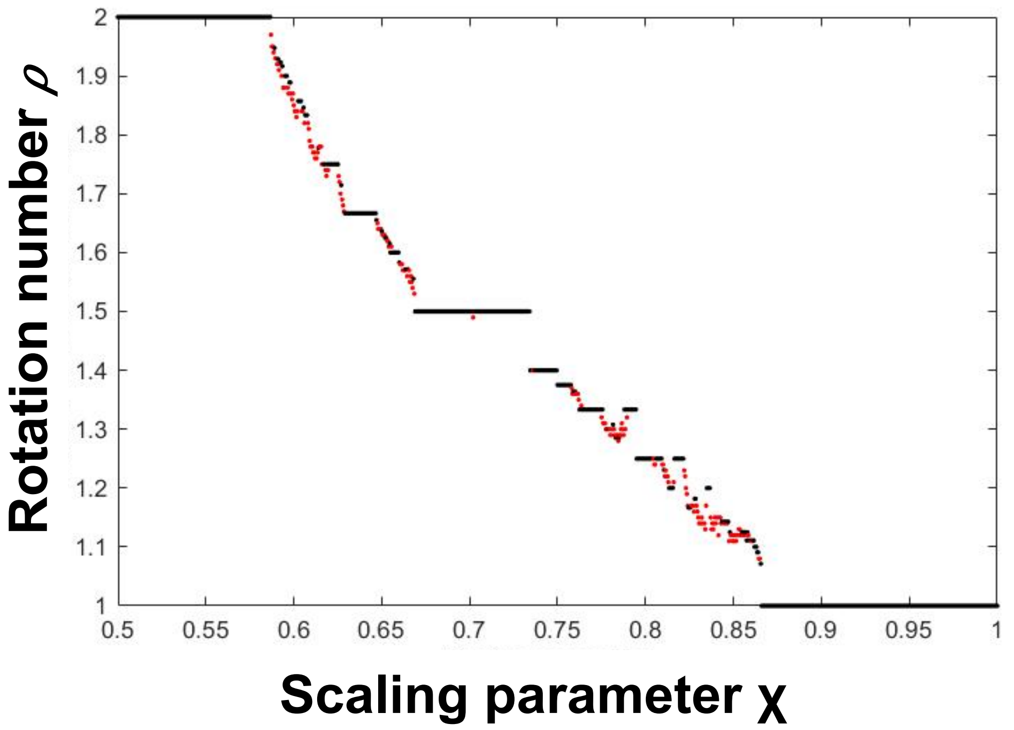


Devil's staircase structure in number of daily sleep episodes

- M = number of sleep episodes and N = number of days in periodic solution
- Define rotation number

$$\rho = M / N$$

- Examine how ρ changes as a function of χ
- Consistent with a ***border collision*** bifurcation

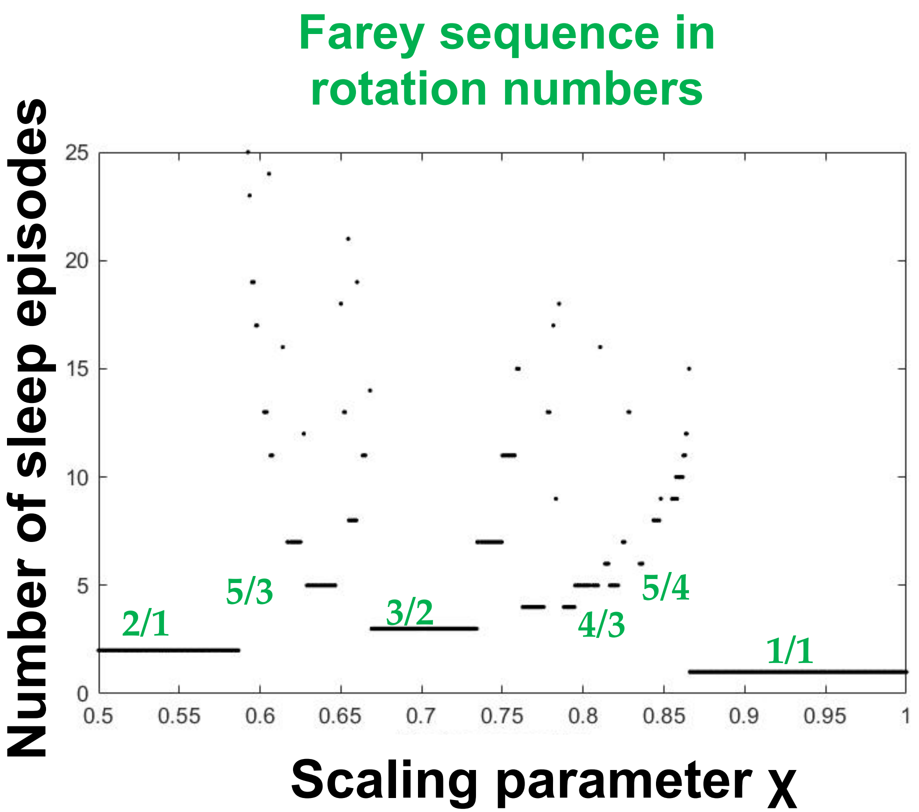


Red points = no stable periodic solution found

Period-adding behavior in number of daily sleep episodes

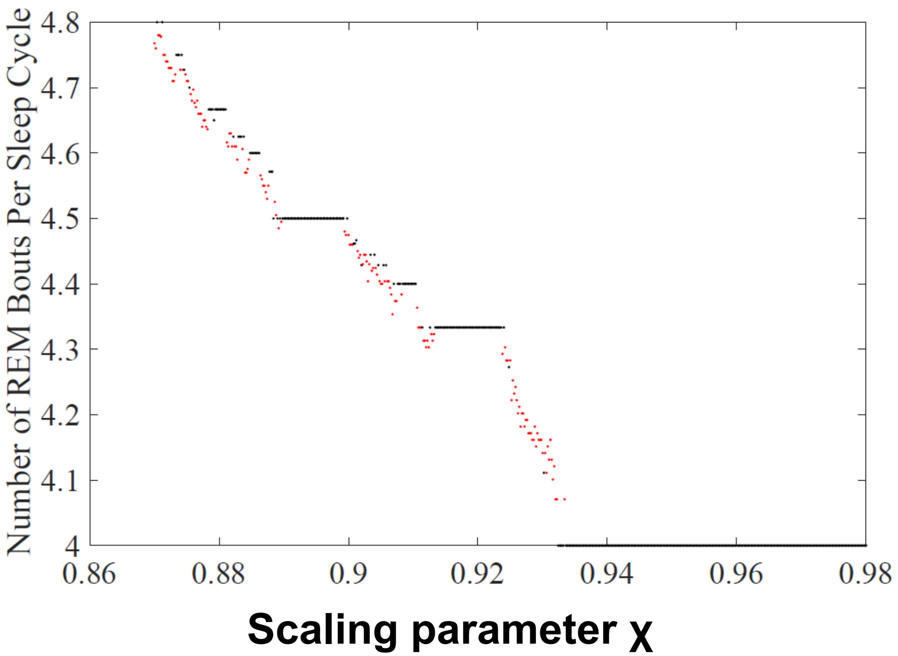
- Rotation numbers follow a Farey sequence
- If the rotation numbers a/b and c/d of two disjoint intervals are Farey neighbors (|ad-bc|=1), then between them, there is a cycle with a rotation number = their Farey sum:

$$\frac{a}{b} \oplus \frac{c}{d} = \frac{a+c}{b+d}$$



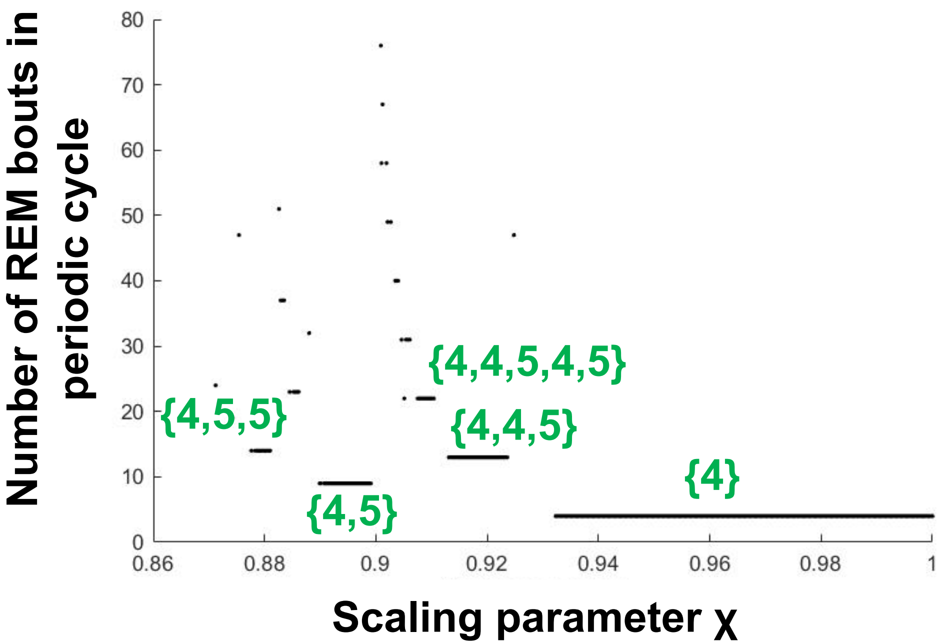
Period-adding bifurcation in number of REM episodes

- When fixed point loses stability, the number of REM bouts per night alternates between 4 and 5



Red points = no stable periodic solution found

Patterns of REM bouts "add"



Conclusions & future work

- 1D maps for sleep-wake network
  - Provide insight into circadian modulation of sleep
  - Can be used to predict re-entrainment after desynchronization of sleep and circadian rhythms
  - Establish a framework for understanding bifurcations of sleep-wake patterns as model parameters vary
  - Implications for developmentally-mediated changes
- Current work includes
  - Analysis of interactions of multiple slow time scales in the system
  - Using maps to understand recovery from sleep deprivation

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