Modeling the temporal architecture of sleep-wake transition dynamics

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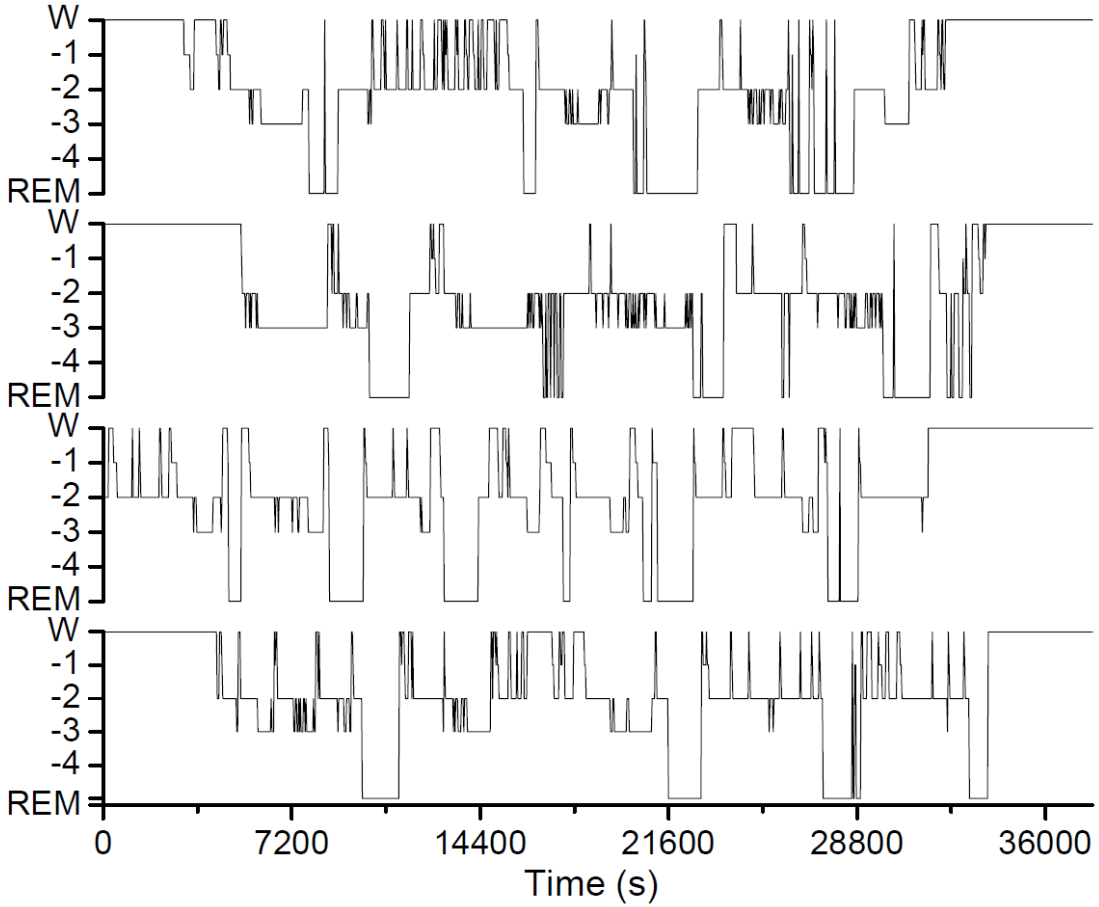
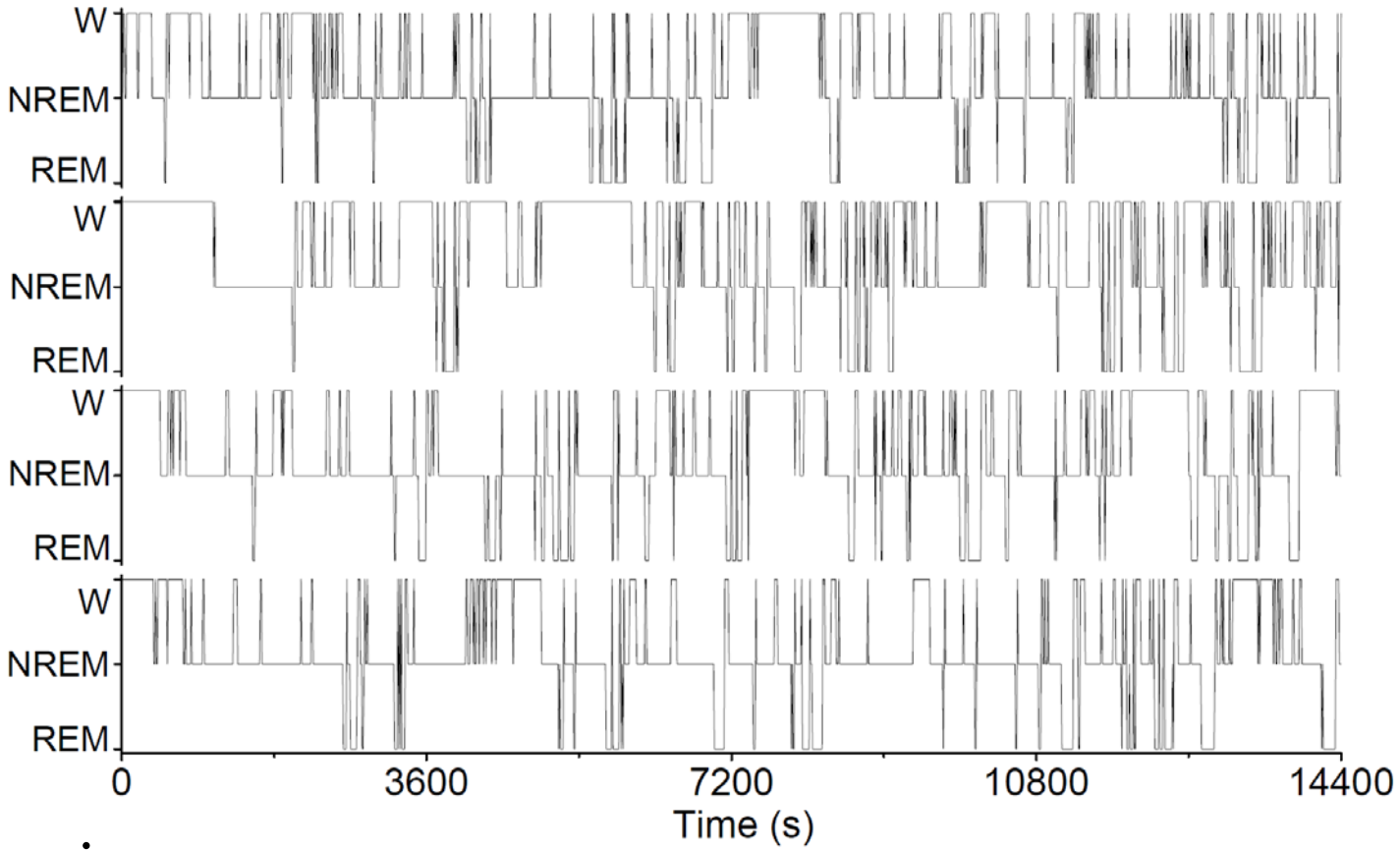
Human sleep temporal architecture



- NREM-REM cycling (~90 min cycle length)
- Healthy sleep is fragmented by brief wake bouts

Human sleep recordings from SHHS (dceweb1.case.edu/serc)

Rat sleep temporal architecture

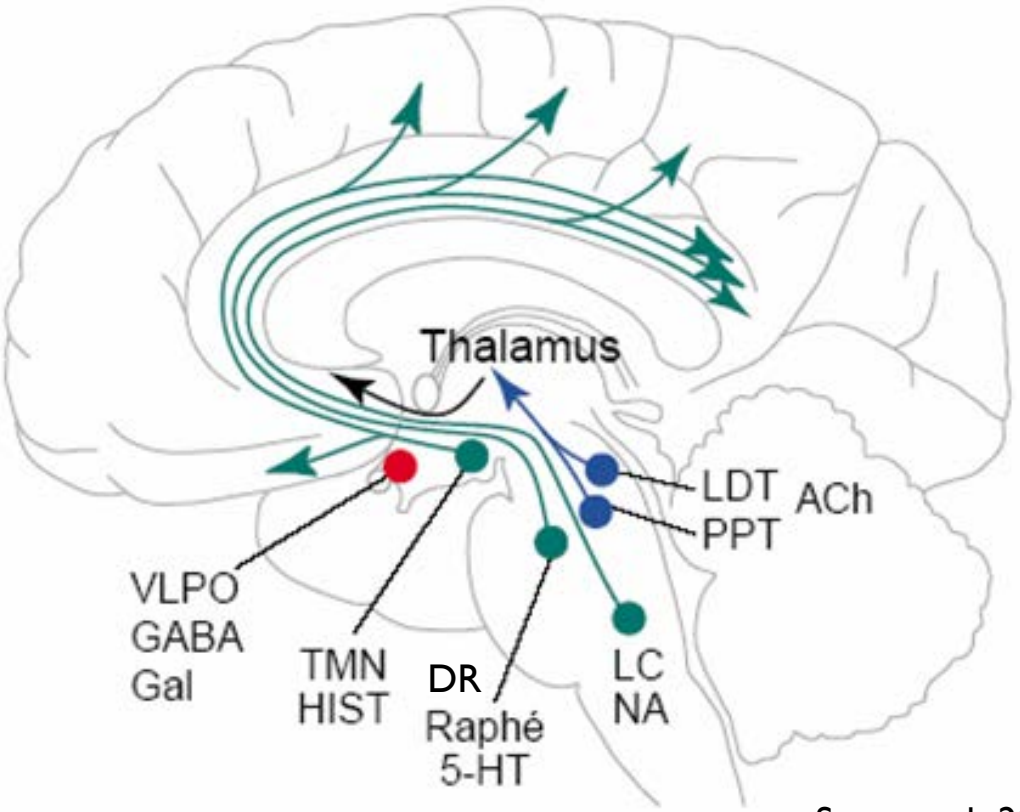


- Polyphasic
- Highly fragmented with variable state dynamics

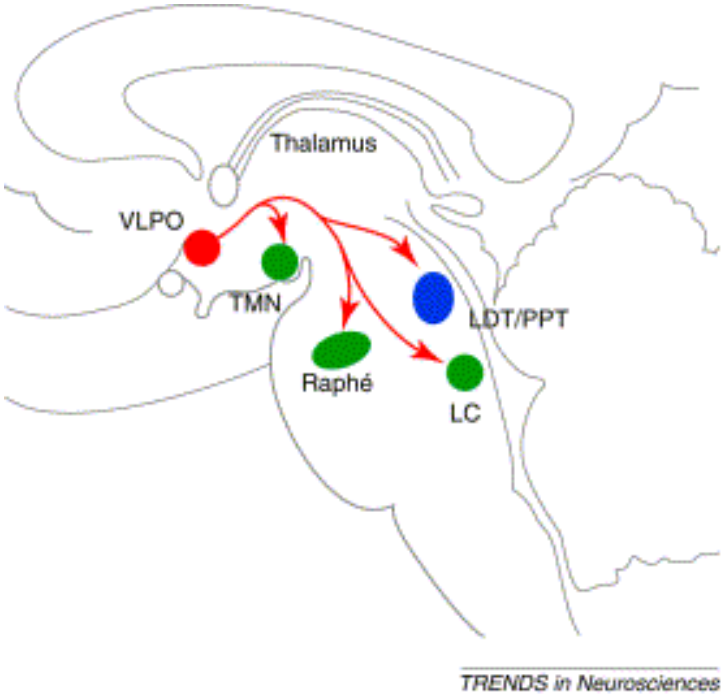
Rat sleep in the light period recordings courtesy of George Mashour (Anesthesiology, U of Michigan)

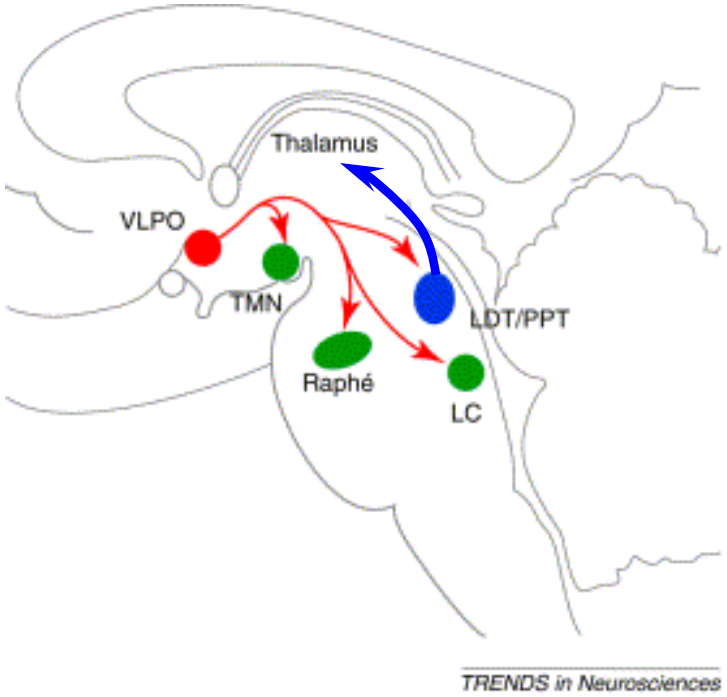
Anatomy and physiology of sleep-wake regulation

- High activity in LC/DR/TMN and LDT/PPT promotes wake
- Wake characterized by high expression of norepinephrine (NE), serotonin (5-HT) and acetylcholine (ACh) to thalamus and cortical regions



Saper et al., 2001





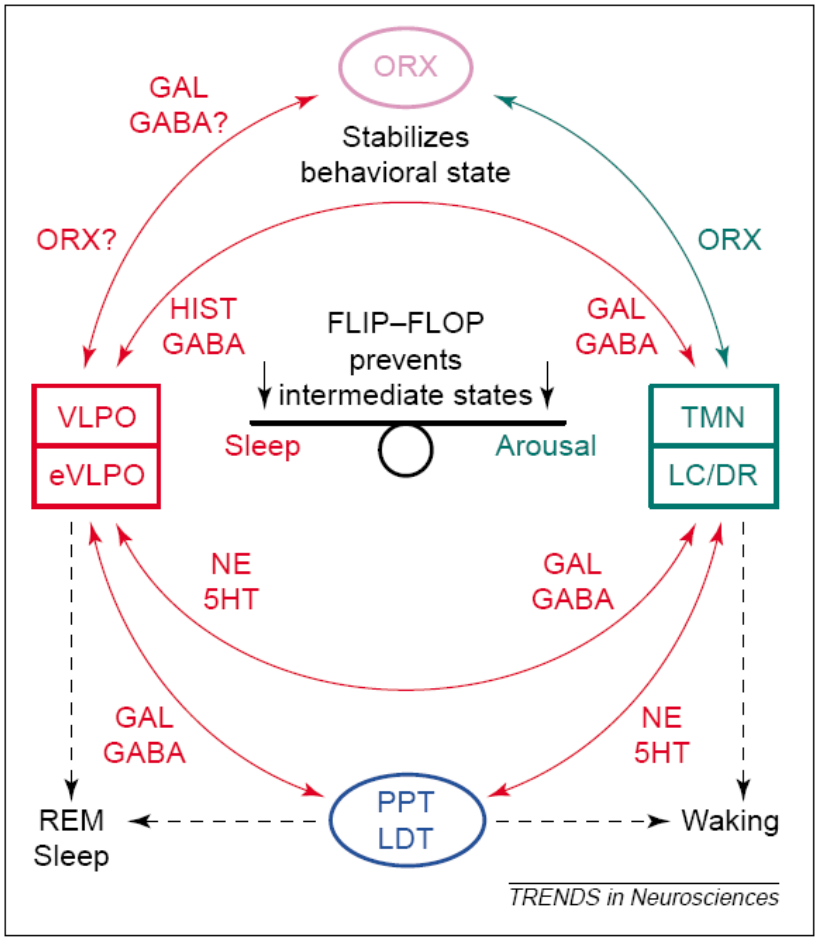
Sleep states characterized by low activity in LC/DR/TMN.

VLPO neurons have high activity during sleep and GABAergic projections to LC/DR/TMN

In REM sleep, cholinergic populations reactivate. ACh in thalamus and brainstem induce REM characteristics.

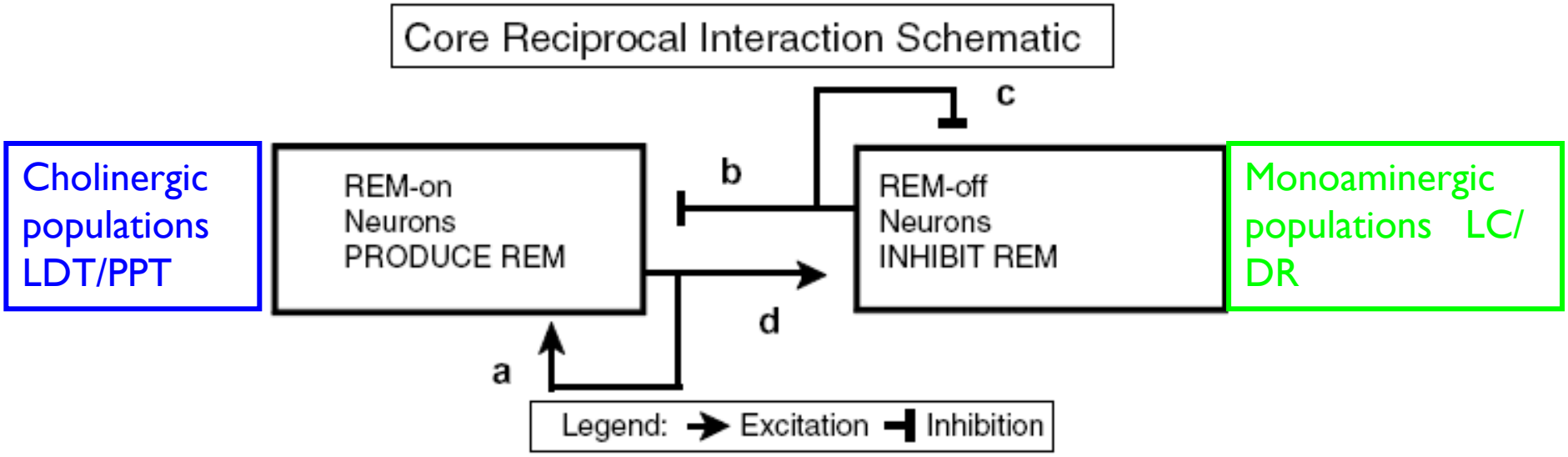
Sleep-wake flip-flop switch

- Mutual inhibitory synaptic projections between wake-active populations and VLPO suggests bistable flip-flop switch
- Dynamics of mutual inhibition could account for:
  - Fast transitions between states
  - Stability of sleep and wake states



Saper CB et al, The sleep switch: hypothalamic control of sleep and wakefulness, *TINS* 2001

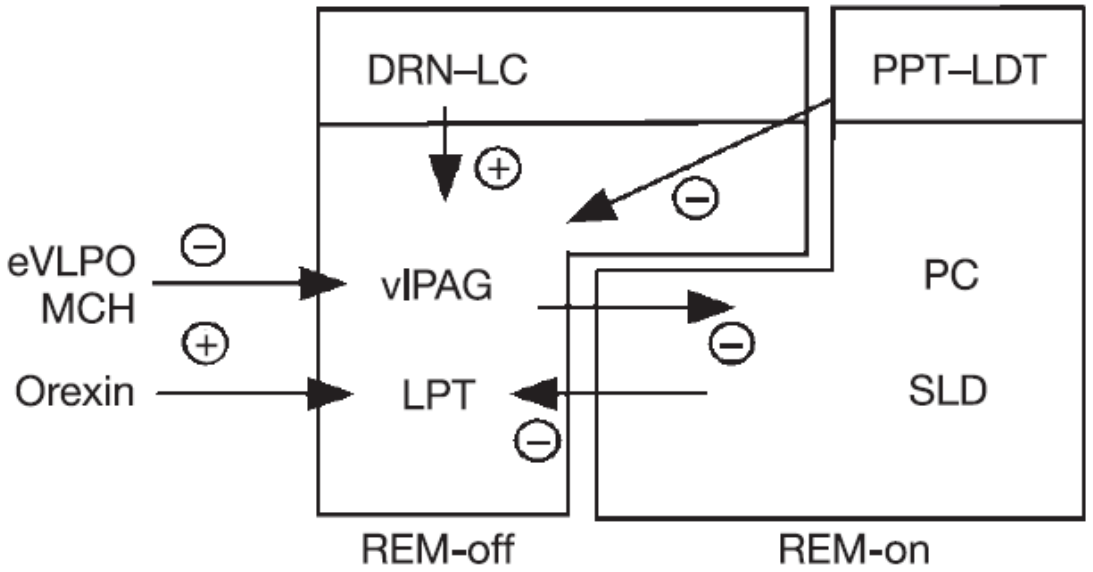
Reciprocal Interaction model for REM sleep cycling



- Monoaminergic inhibition from LC/DR inhibits REM-on subpopulation of LDT/PPT
- Cholinergic excitation from LDT/PPT activates LC/DR to terminate REM-on activity

McCarley RW and Massaquoi SG, A limit cycle model of the REM sleep oscillator, *Am J Physiol* 1986

REM-on/REM-off flip-flop switch

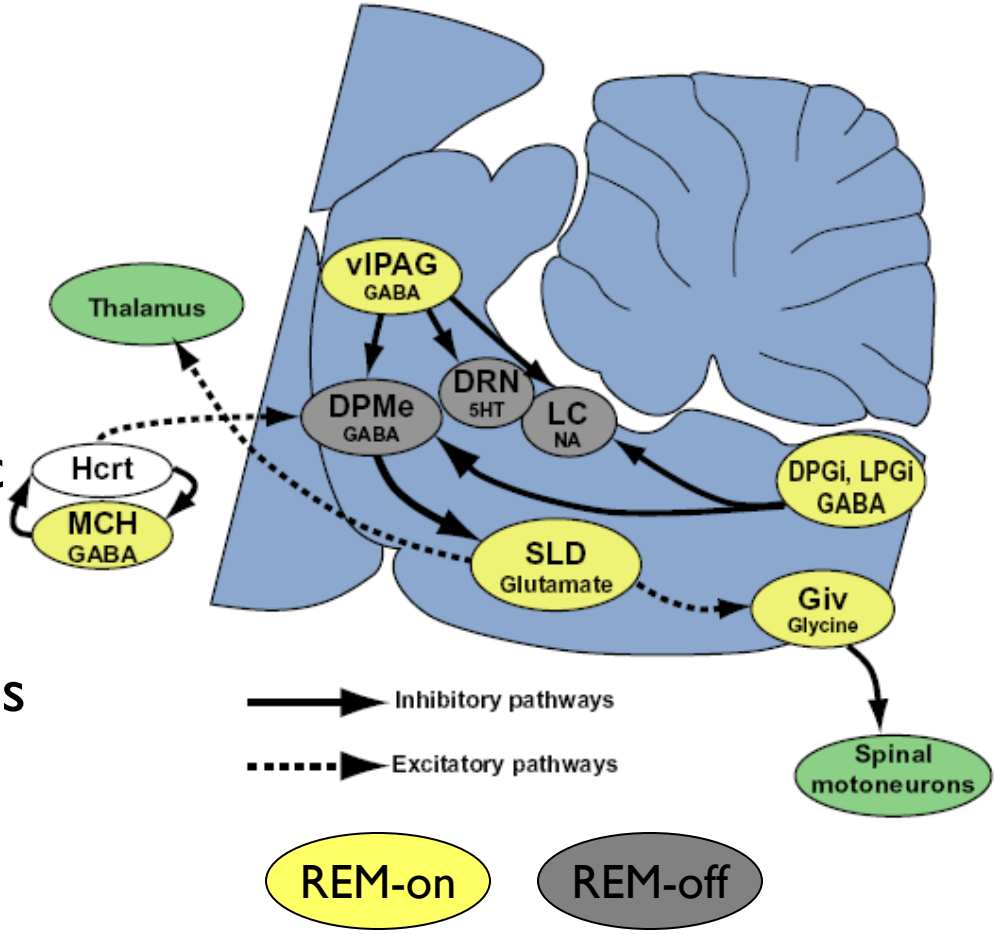


- REM-on: Sublaterodorsal nucleus (SLD), precoeruleus (PC)
- REM-off: Ventrolateral periaqueductal grey matter (vlPAG), lateral pontine tegmentum (LPT)
- Mutual GABAergic projections between REM-on and REM-off populations

- Lu, Sherman, Devor, Saper, A putative flip-flop switch for control of REM sleep, *Nature*, 2006.

GABAergic-glutamatergic hypothesis for REM generation

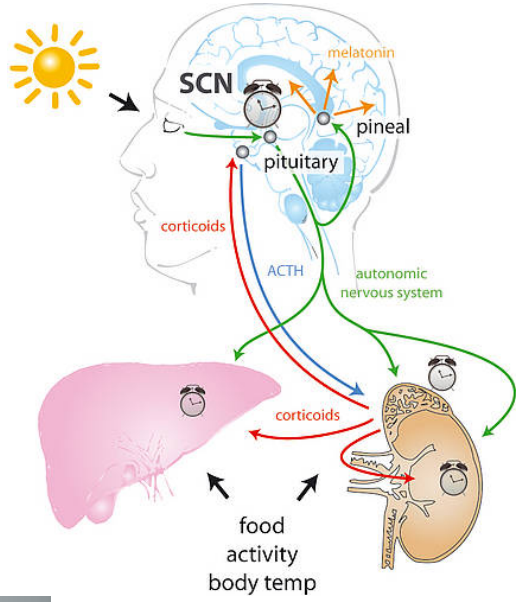
- REM-on: Sublaterodorsal nucleus (SLD), dorsal paragigantocellular reticular nucleus (DPGi), Ventrolateral periaqueductal grey matter (vlPAG)
- REM-off: Deep mesencephalic reticular nucleus (DPMe)
- Inhibitory projections are distributed among populations



- Luppi et al, Paradoxical (REM) sleep genesis: The switch from an aminergic–cholinergic to a GABAergic–glutamatergic hypothesis, *J Phyiol Paris*, 2007.

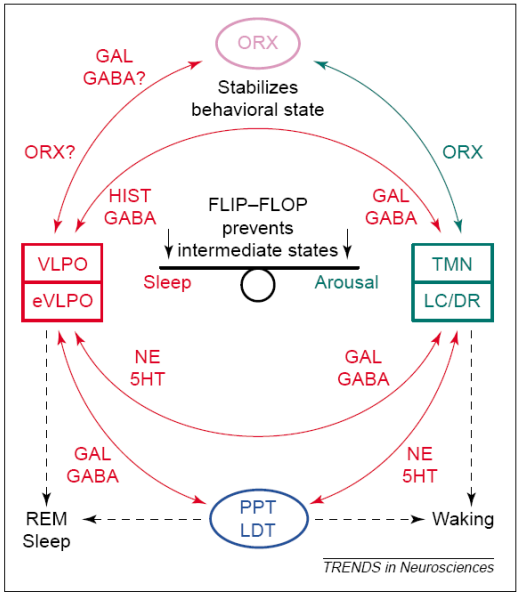
Multiple time scales of sleep-wake dynamics

1. Daily 24 hour rhythm of wake and sleep
   - Mediated by Suprachiasmatic Nucleus (SCN)

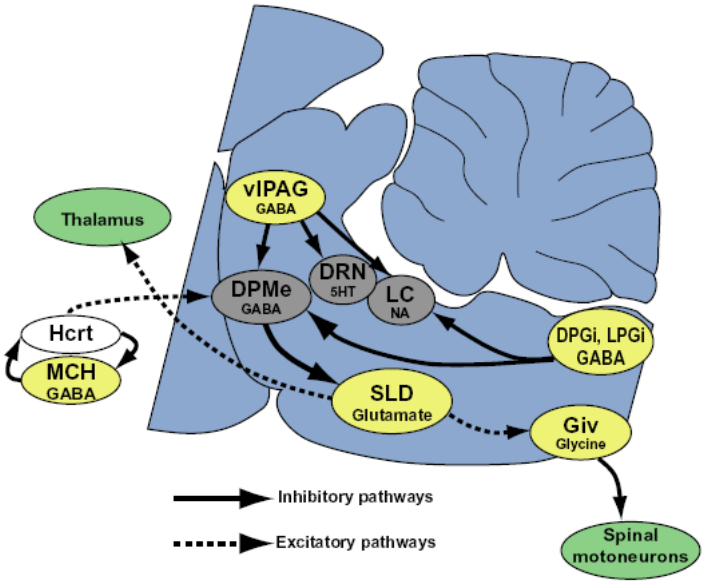


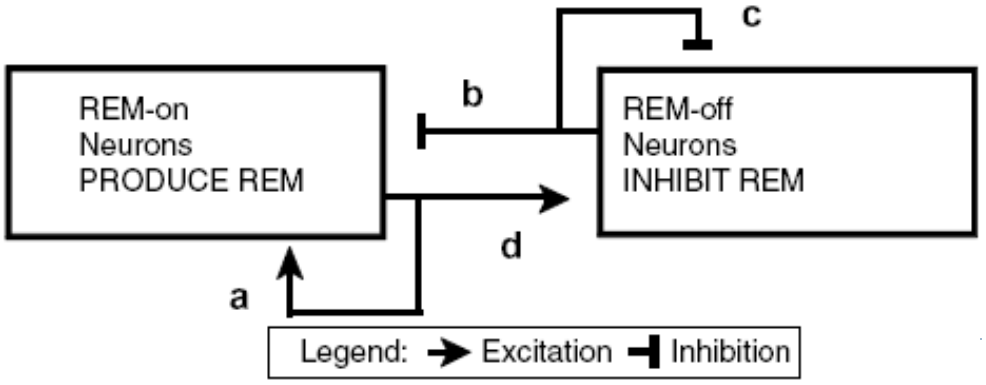
2. Homeostatic sleep drive (< 24h)
   - Mediated by adenosine

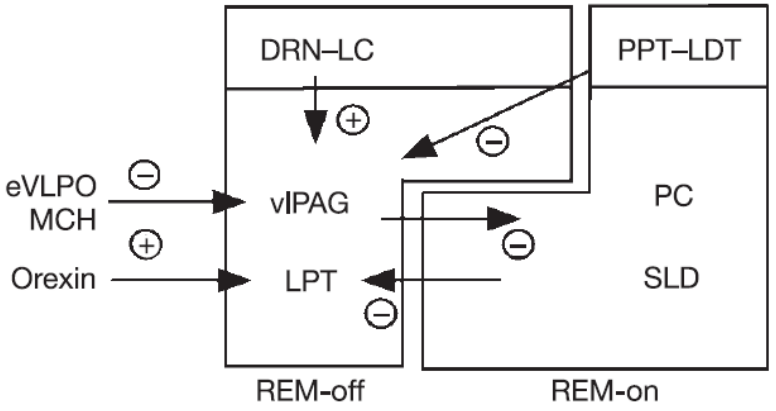
Proposed neuronal sleep-wake regulatory networks



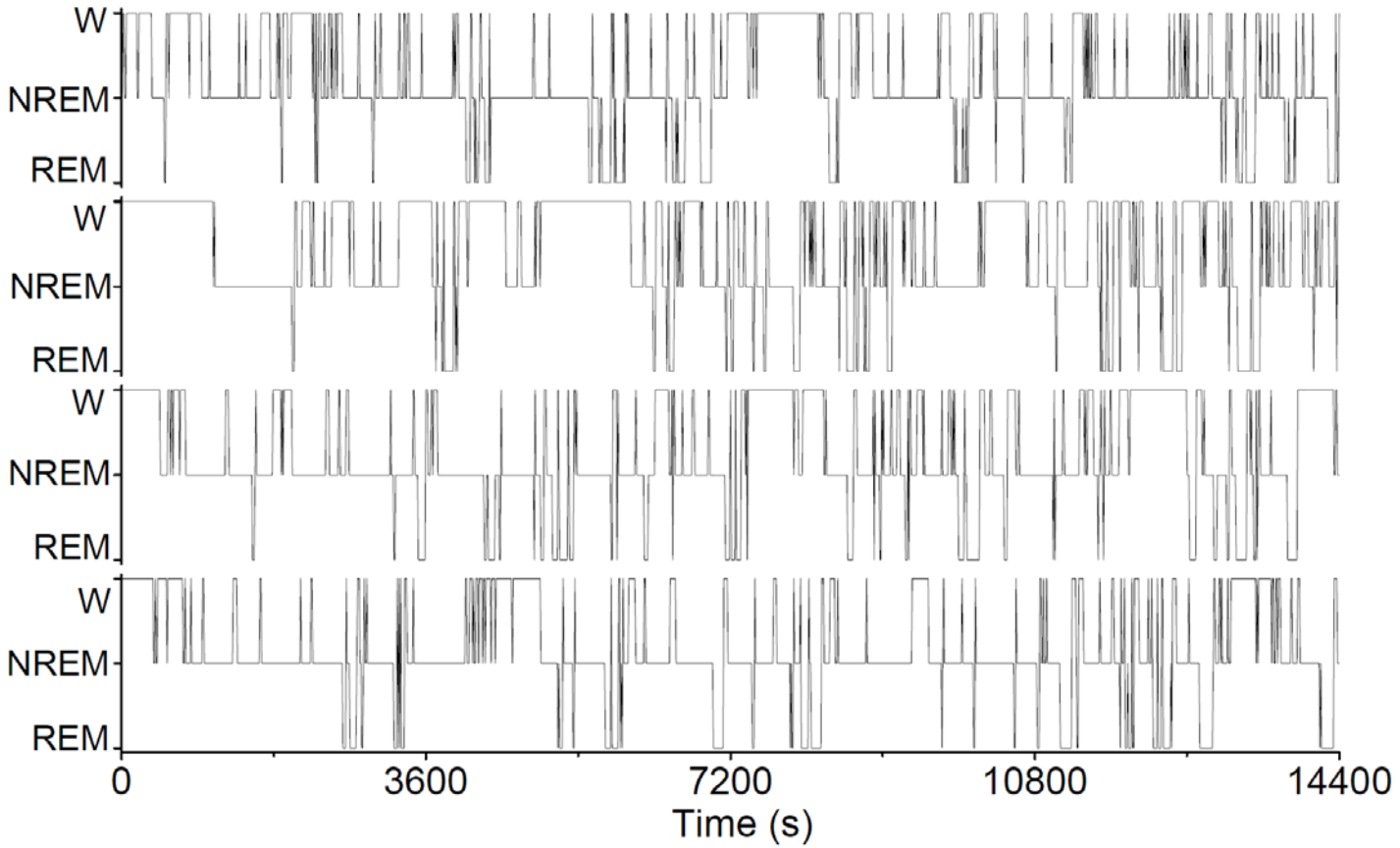
All based on underlying deterministic network







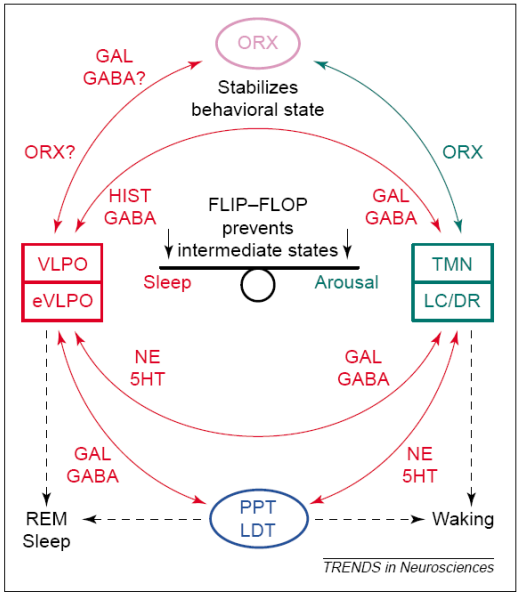
Rat sleep temporal architecture



- Can deterministic network model replicate actual sleep-wake temporal architecture?

Rat sleep in the light period recordings courtesy of George Mashour (Anesthesiology, U of Michigan)

How to model neuronal sleep-wake regulatory networks?



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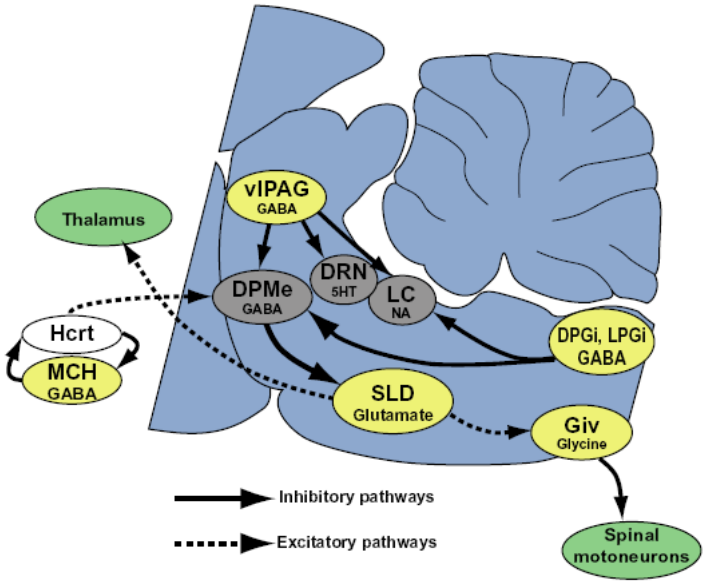
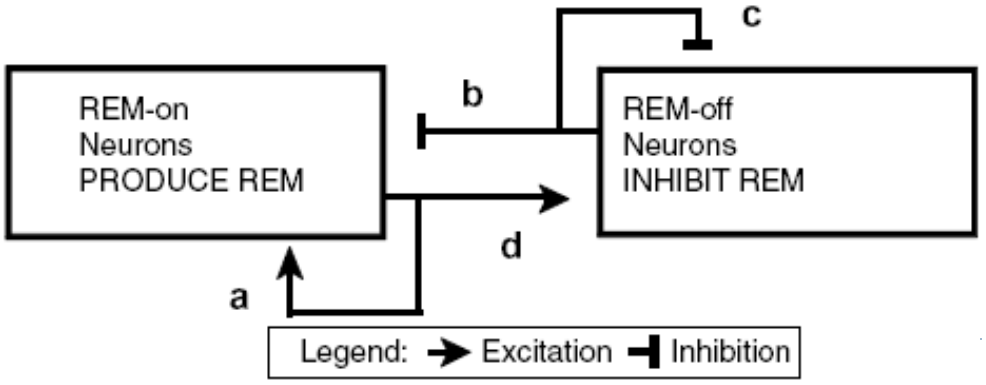
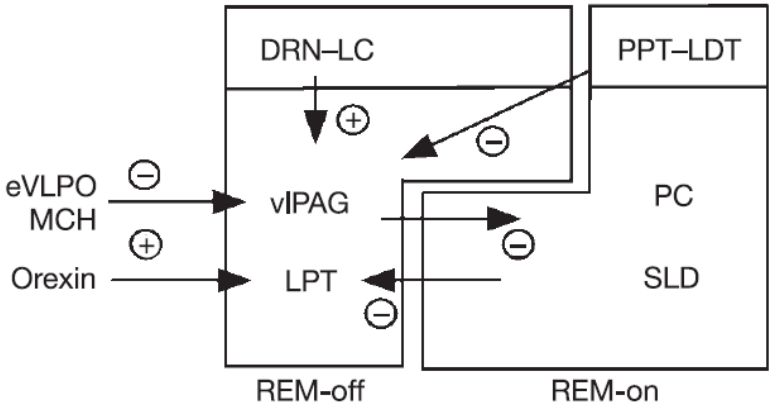






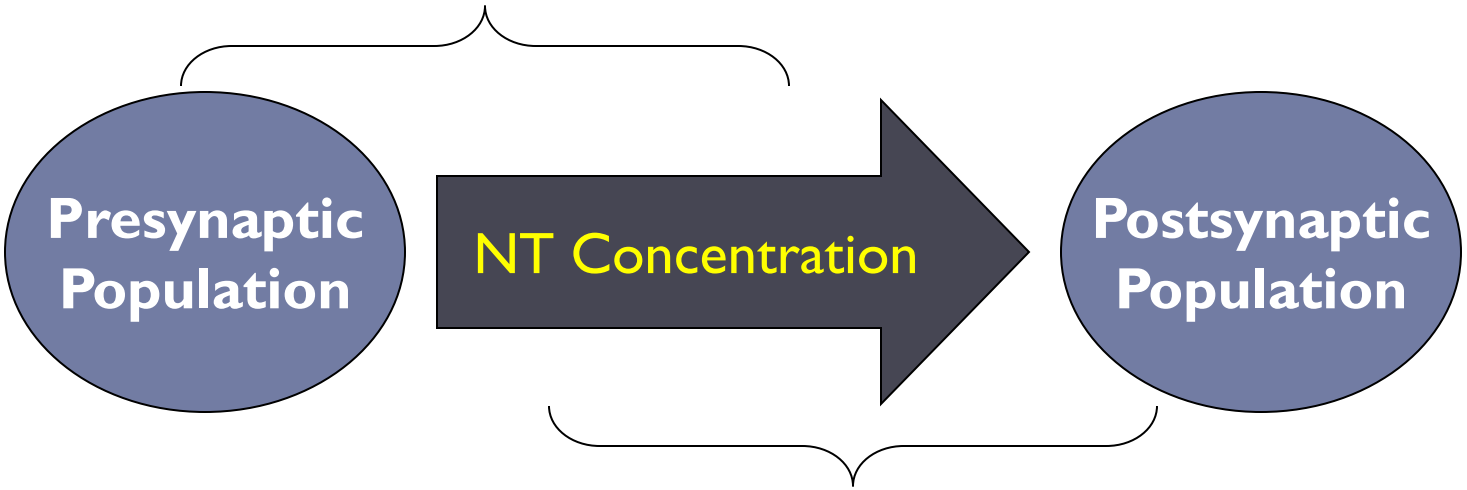
Why a firing rate model?

- Population activity levels determine behavioral state
- Rhythms of firing in these populations appear to be less important than the neuromodulatory environments they create
- Time scale of sleep-wake behavior much longer than ms time scale of individual neuronal activity

- Variable of interest: $F_X(t)$ = average firing rate of neurons in population *X* in Hz

Firing rate model formalism

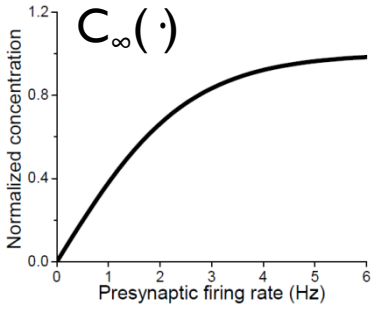
Dependence of total NT release on presynaptic firing rate

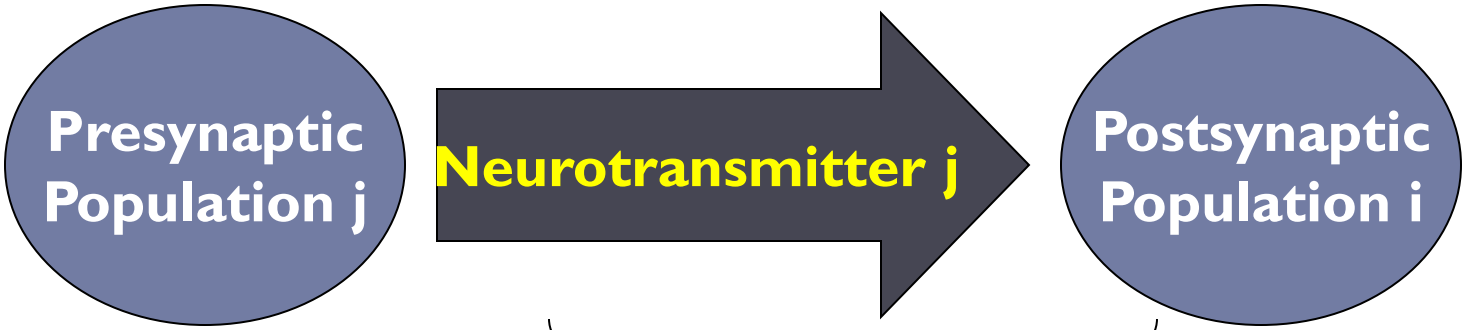


Dependence of postsynaptic firing rate on total NT concentration

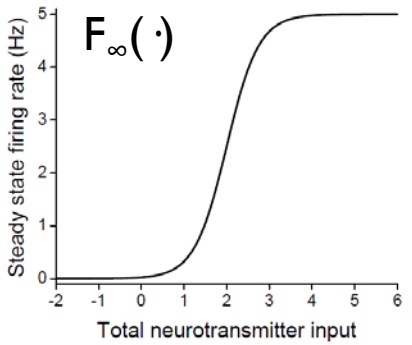
Neurotransmitter/population firing rate model formalism

$$\frac{dc_j}{dt} = \frac{C_\infty(f_j) - c_j}{\tau_j}$$



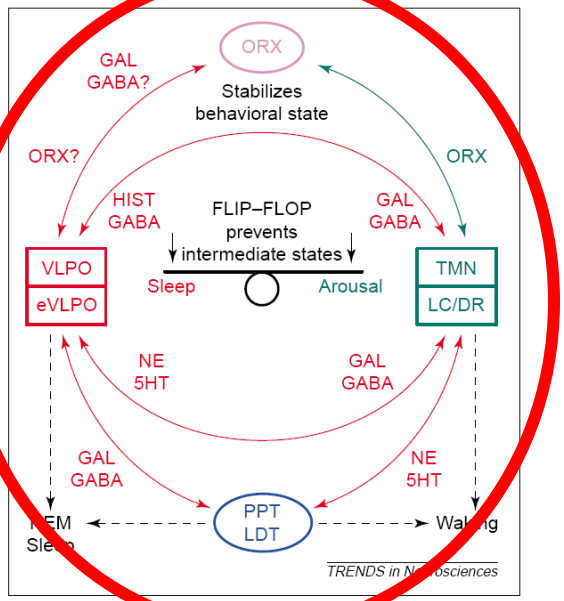


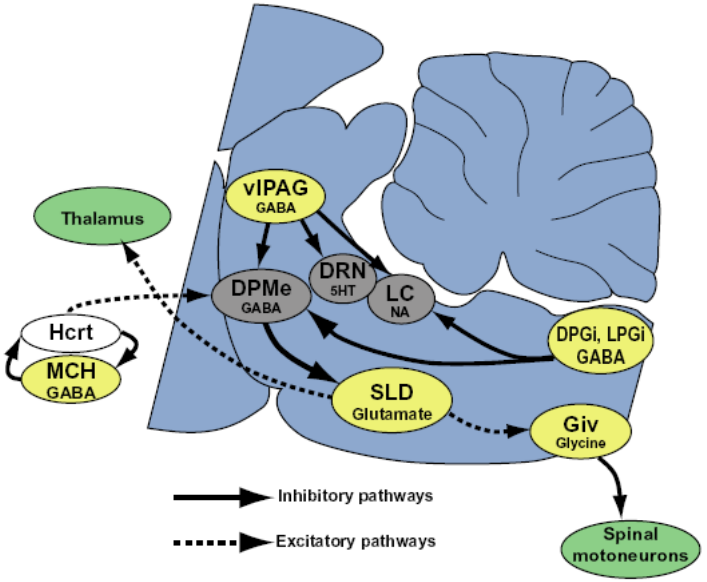
$$\frac{df_i}{dt} = \frac{F_\infty(\sum g_j c_j) - f_i}{\tau_f}$$

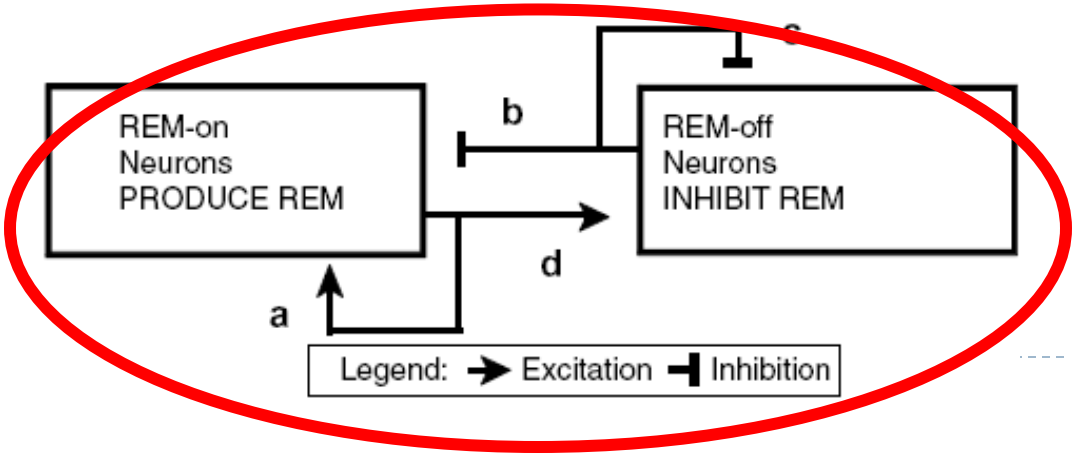


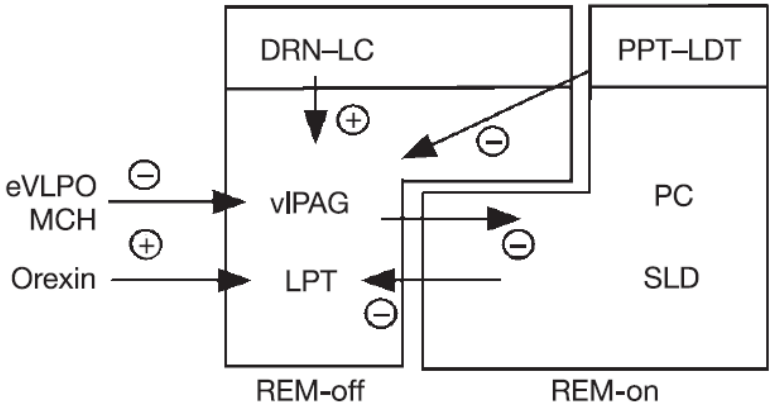
Diniz Behn and Booth, J Neurophysiol, 2010

What sleep-wake regulatory network to model?

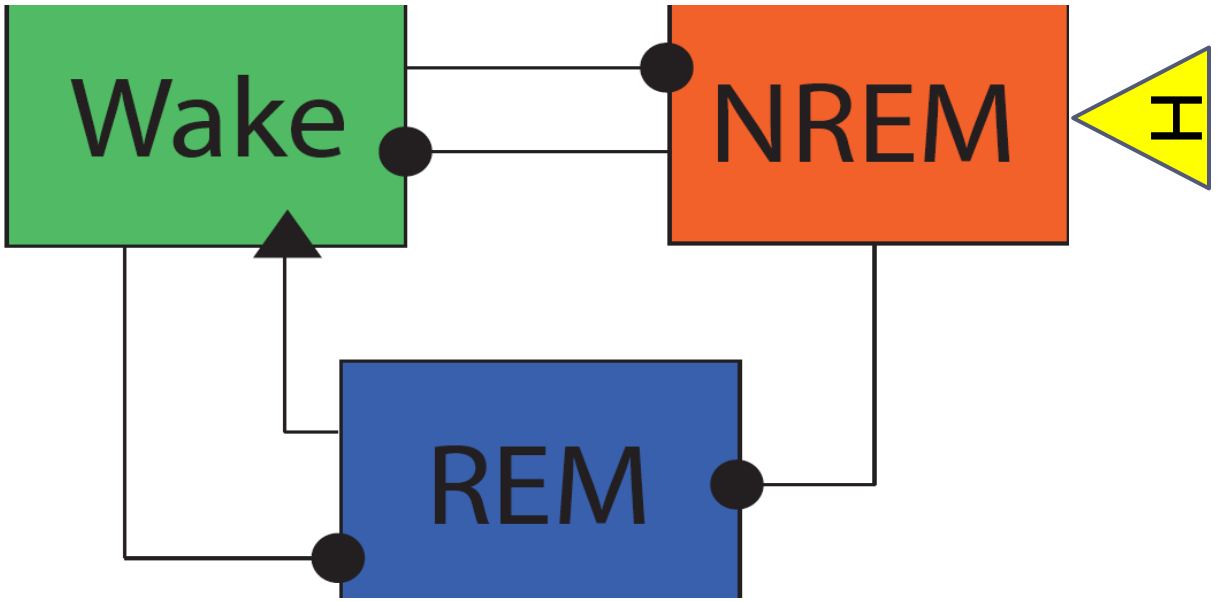








Minimal 3-state sleep-wake regulation network



- Sleep homeostat, H, drives slow transitions between wake and sleep states
- H modulates activation of NREM population mimicking action of adenosine on VLPO

Diniz Behn and Booth, SIAM J Appl Dyn Sys 2011

Reduced sleep-wake regulatory network model

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

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

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

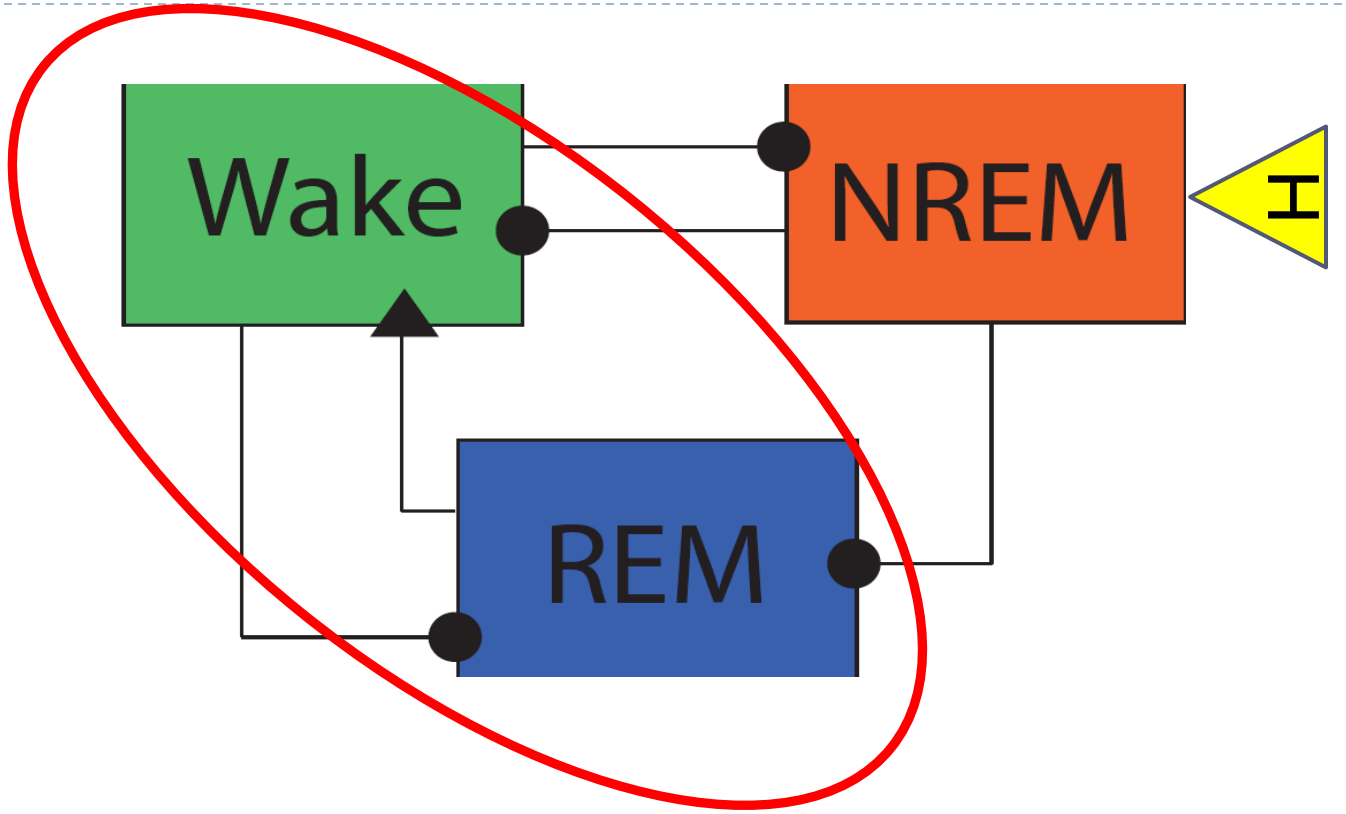
$$h' = \begin{cases} \dfrac{1-h}{\tau_2} & \text{when } F_W \geq \theta_W \\ \dfrac{-h}{\tau_1} & \text{when } F_W < \theta_W \end{cases}$$

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

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

$$X = W, N, R$$

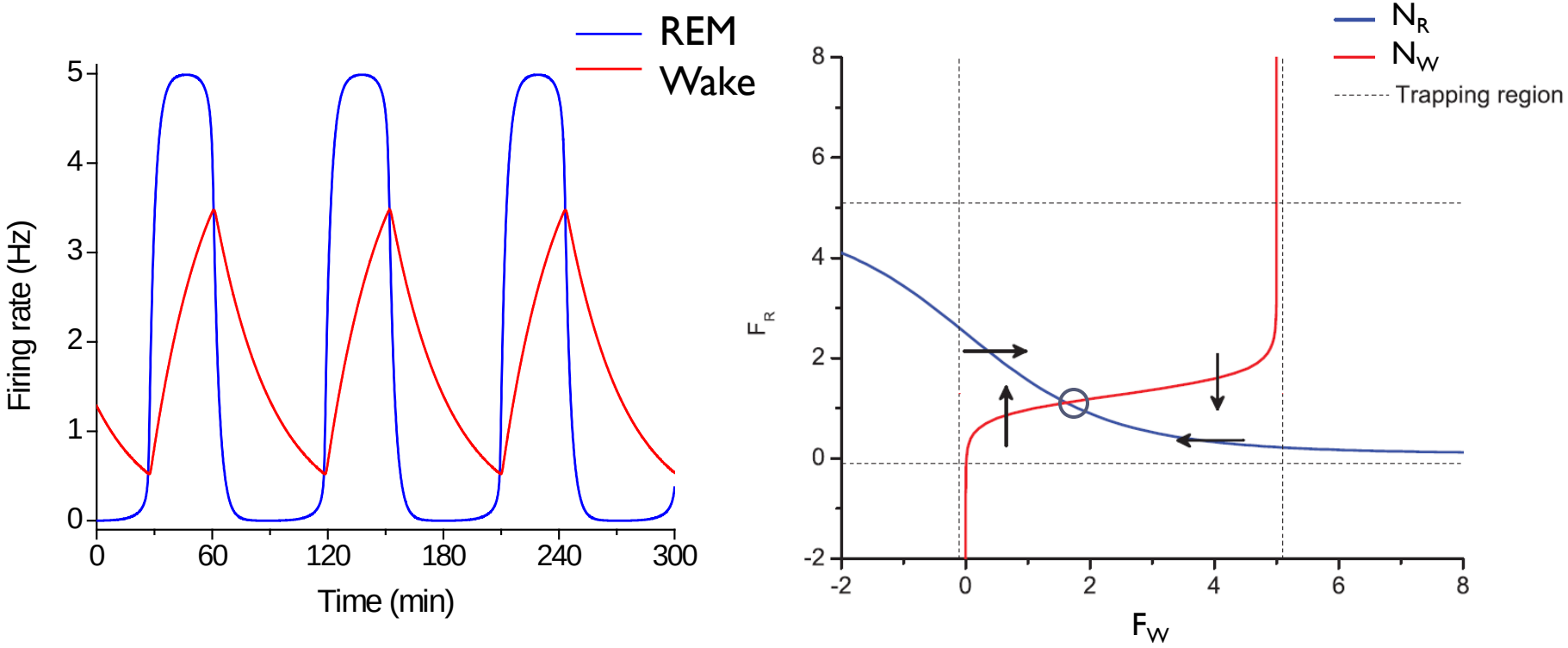
Minimal 3-state sleep-wake regulation network



- Consider dynamics of isolated reciprocal interaction subnetwork

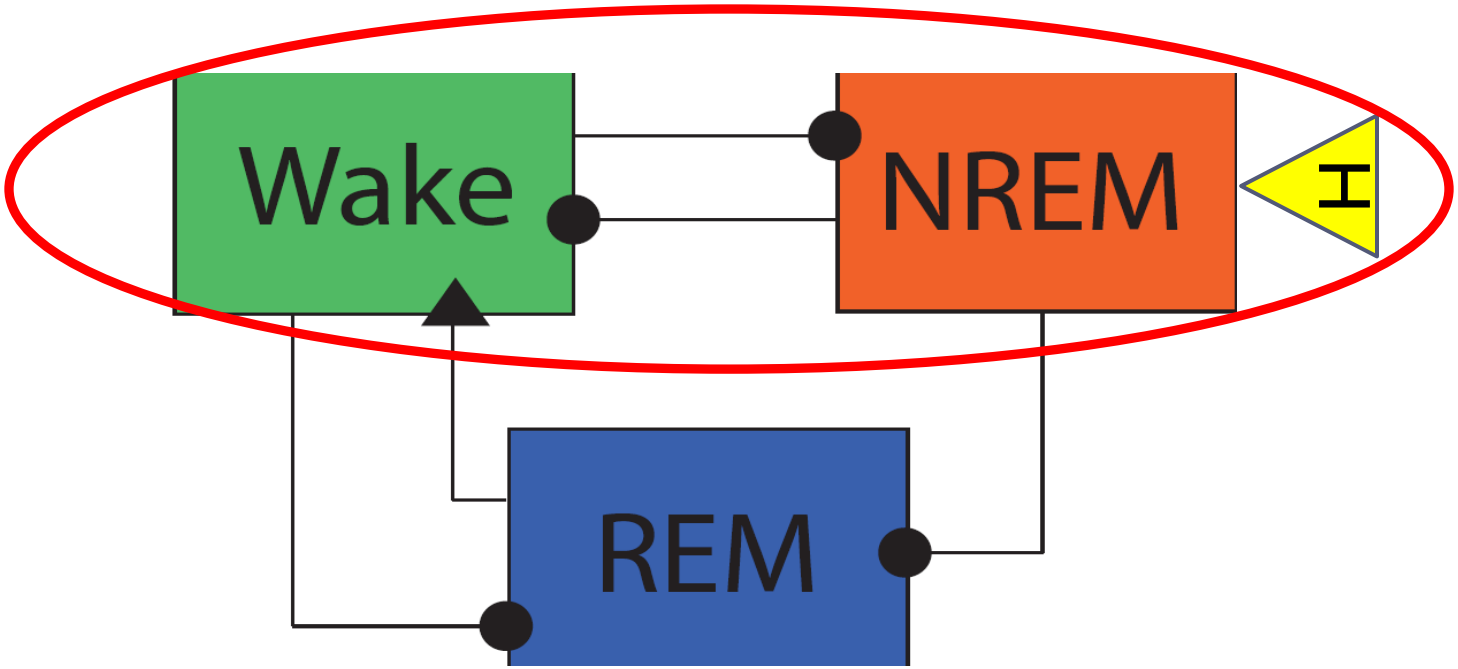
Diniz Behn and Booth, SIAM J Appl Dyn Sys 2011

Reciprocal Interaction network admits stable limit cycle solutions



- By Poincare-Bendixson Theorem, stable cycling exists when all fixed points are unstable

Minimal 3-state sleep-wake regulation network

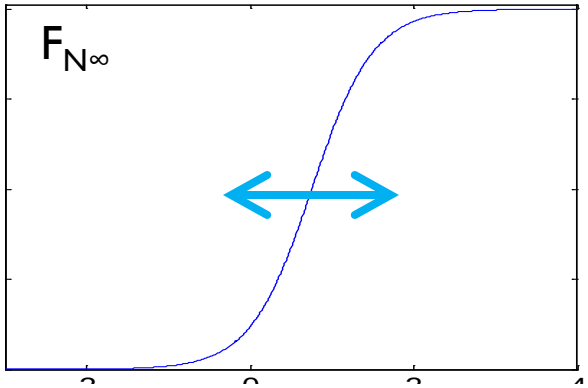


- Consider dynamics of isolated mutual inhibition subnetwork

Action of homeostatic sleep drive

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

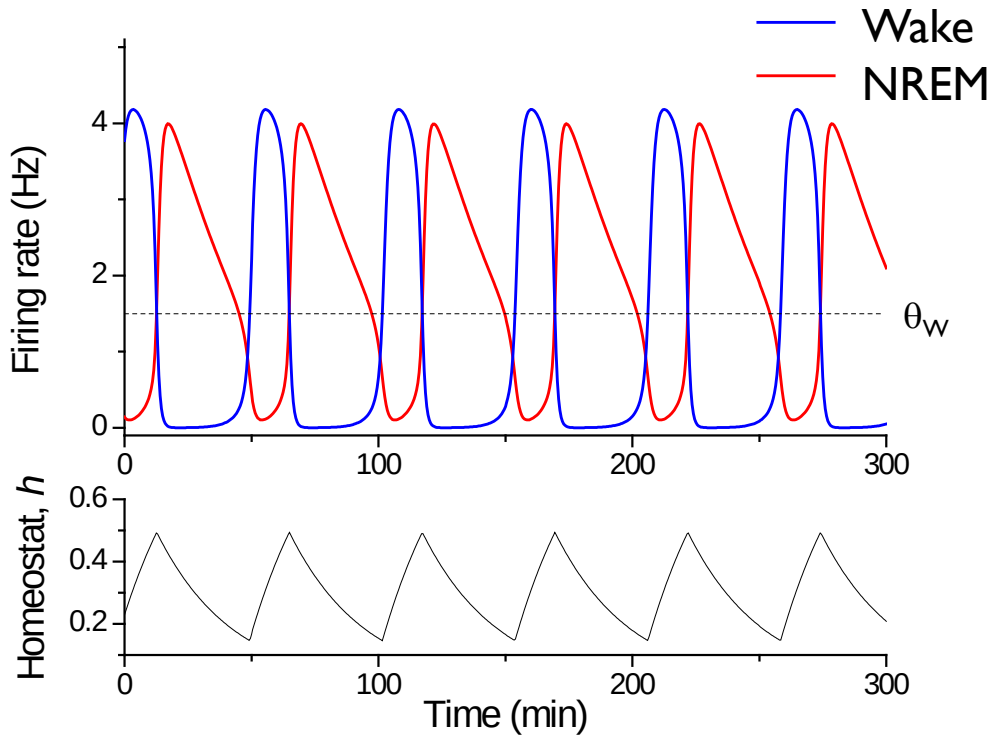
$$h' = \begin{cases} \dfrac{1-h}{\tau_2} & \text{when } F_W \geq \theta_W \\ \dfrac{-h}{\tau_1} & \text{when } F_W < \theta_W \end{cases}$$

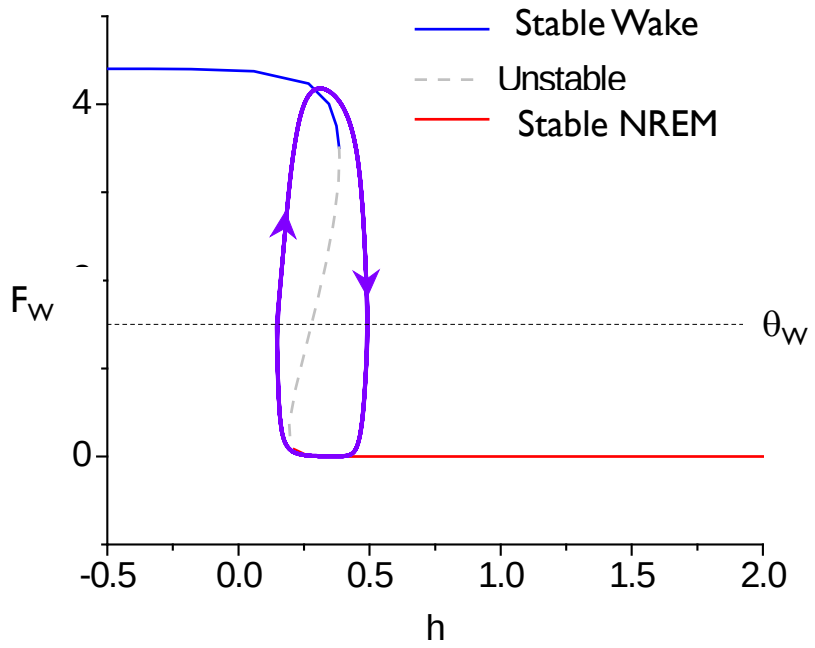


$$F_{N\infty}(c) = \frac{N_{\max}}{2}(1 + \tanh((c - \beta_N(h)) / \alpha_N))$$

Hysteresis loop cycling in mutual inhibition subnetwork

- Exploit slowly varying h(t) for a Fast-Slow Decomposition
  - Let h be a parameter and compute steady state solutions for values of h = [0,1]

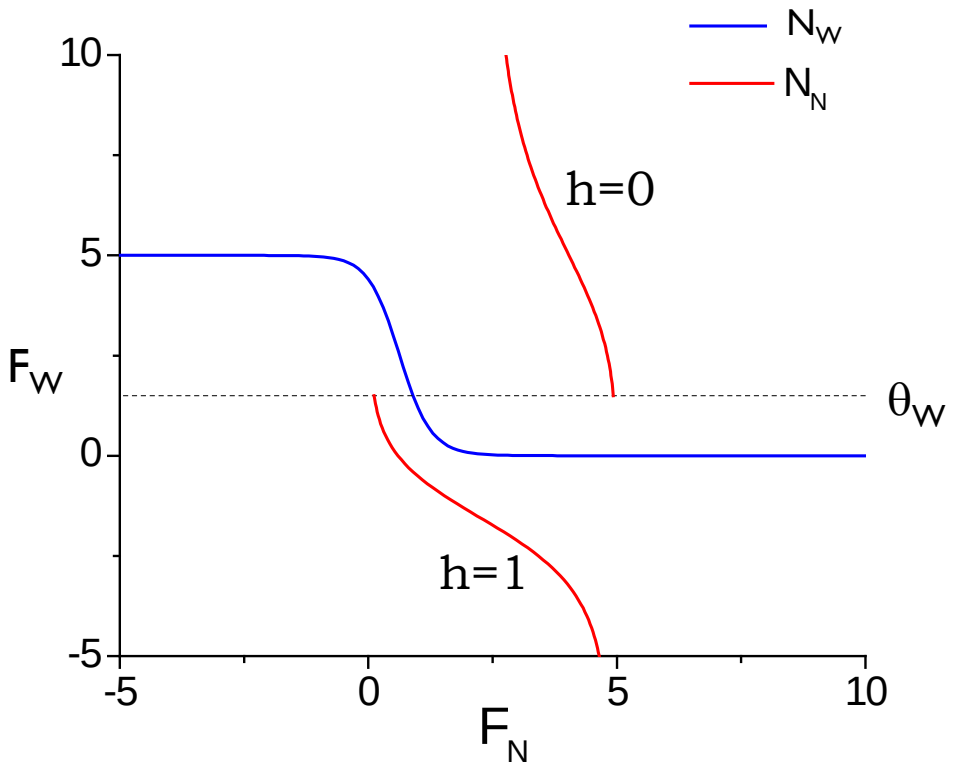




- Sleep homeostat h acts on slower time scale

Condition for existence of hysteresis-loop cycling

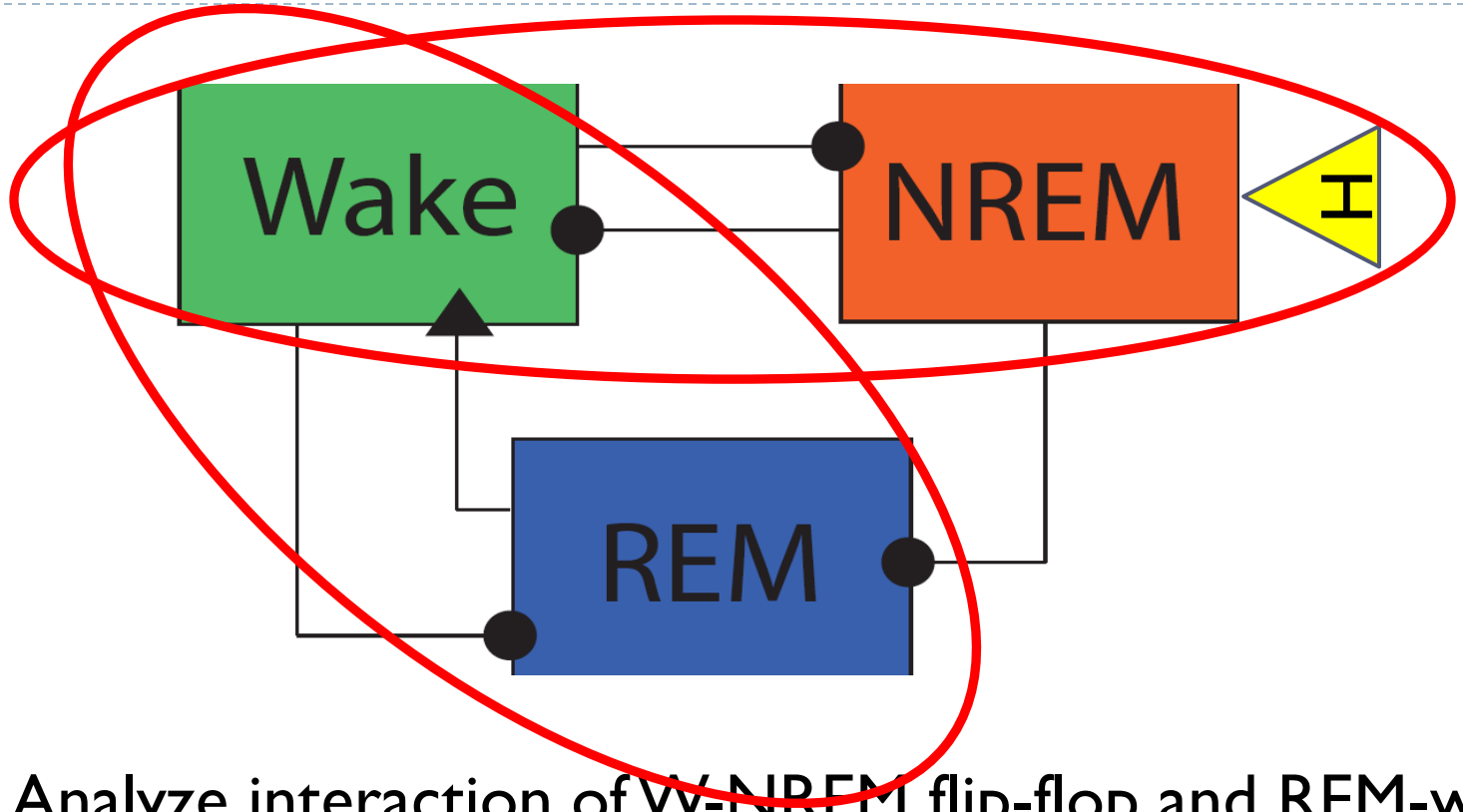
- Discontinuity in h(t) introduces discontinuity in F_N nullcline



Hysteresis-loop cycling possible if no intersection of discontinuous F_N nullcline and F_W nullcline

Diniz Behn, Ananthasubramanian and Booth, submitted

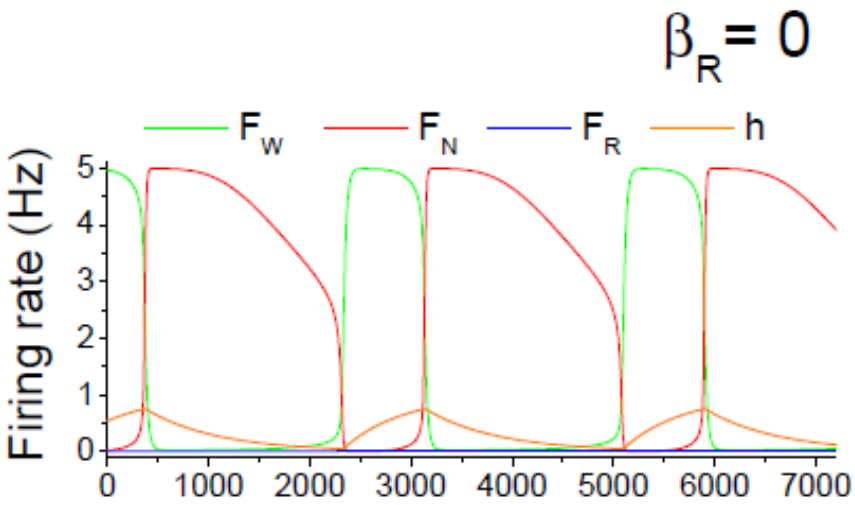
Minimal 3-state sleep-wake regulation network

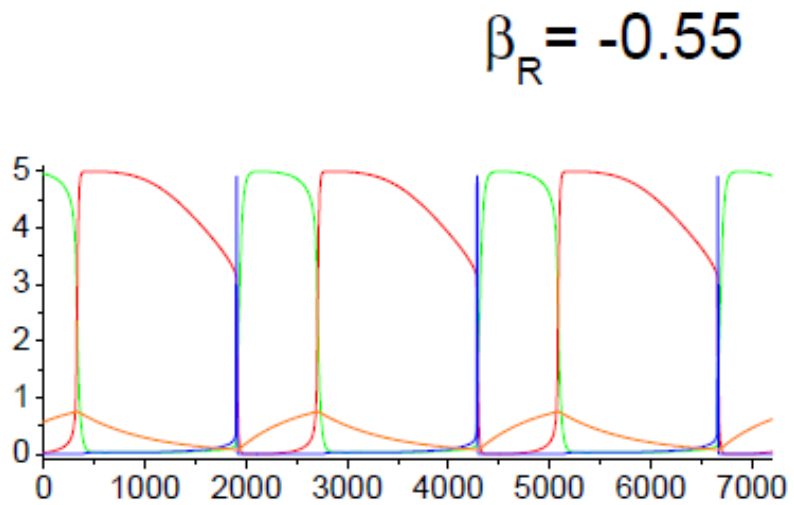


- Analyze interaction of W-NREM flip-flop and REM-wake reciprocal interaction
- Consider dynamics as half-activation threshold for REM population, β_R, is varied

Diniz Behn and Booth, SIAM J Appl Dyn Sys 2011

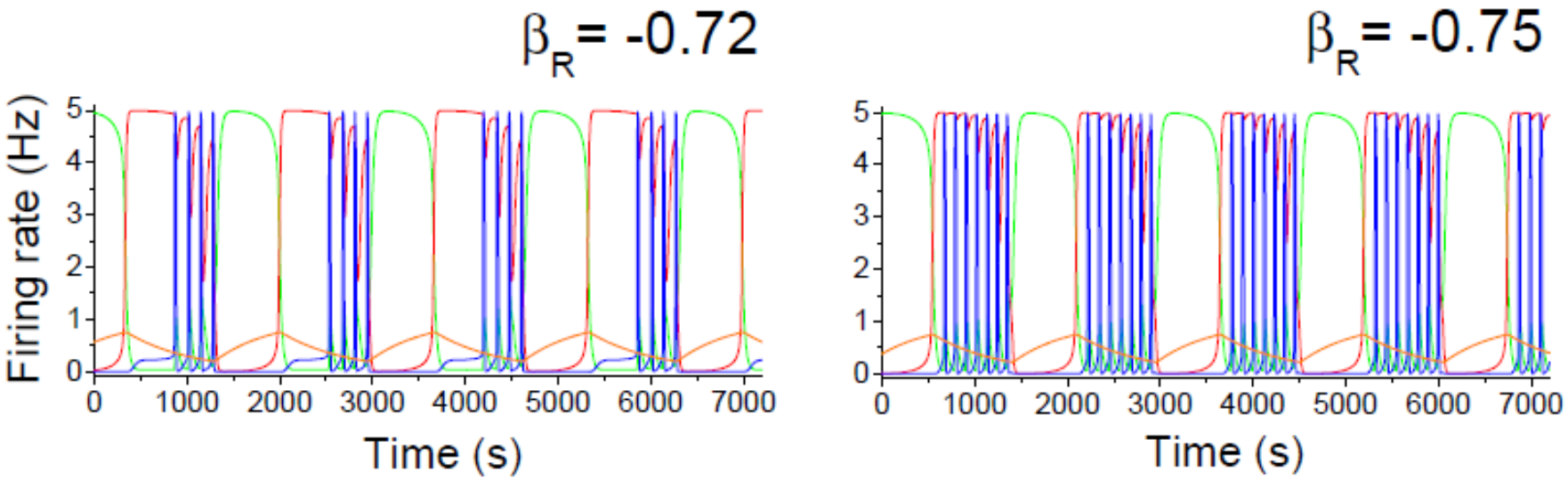
Dynamics as activation threshold of REM population, β_R, is decreased





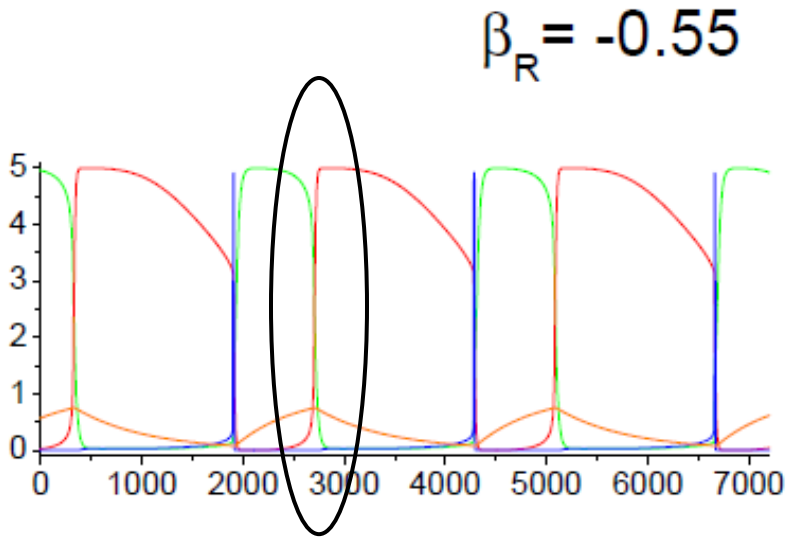
- High β_R: REM population doesn't activate;
- Low β_R : REM population activates transiently at NREM-to-wake transition

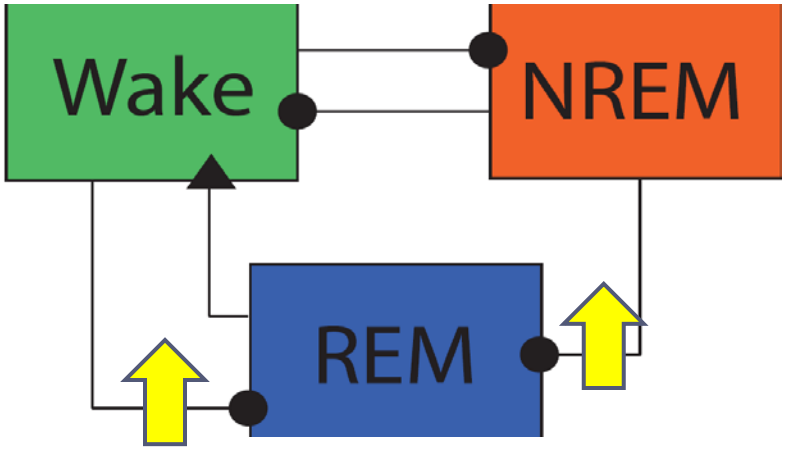
Dynamics as activation threshold of REM population, β_R, is decreased



- Lower β_R : Periodic REM cycling during NREM, with brief post-REM wake activation

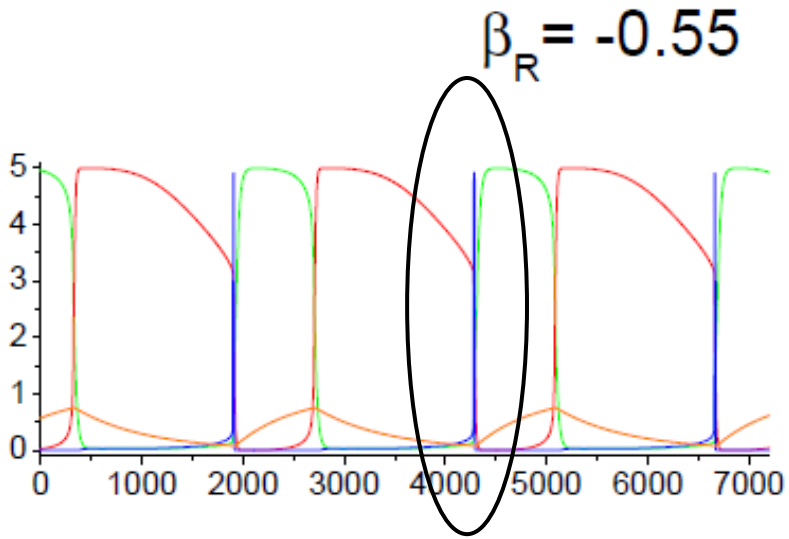
Network structure provides for wake – NREM – REM transition dynamics

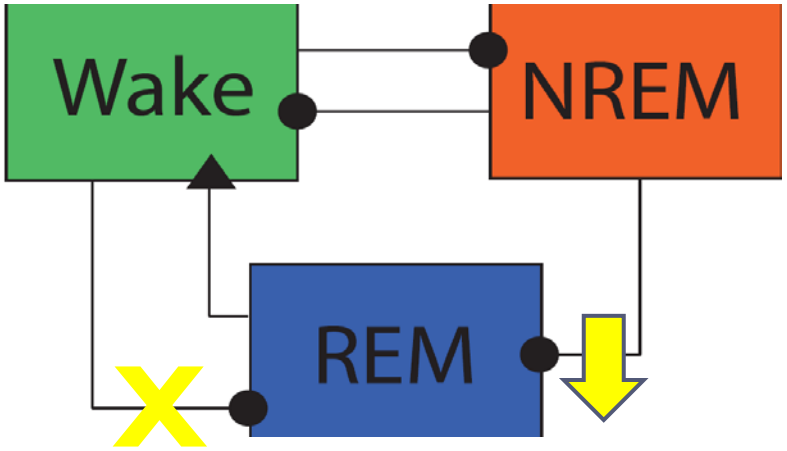




- Wake to NREM transition occurs due to homeostatic activation of NREM population
  - REM population receives inhibition from Wake and increasing inhibition from NREM as it activates
  - NREM is activated when Wake inactivates

Network structure provides for wake – NREM – REM transition dynamics

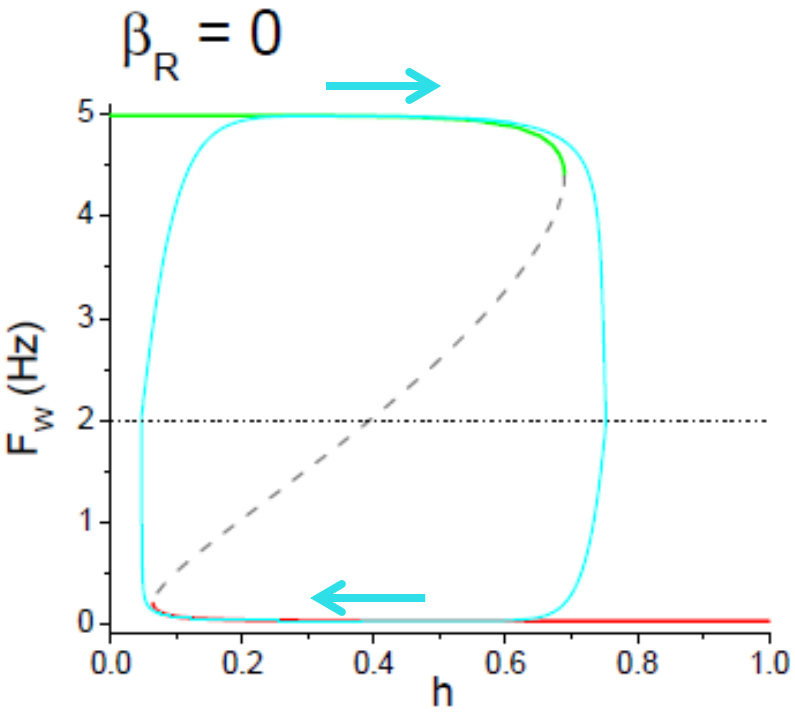




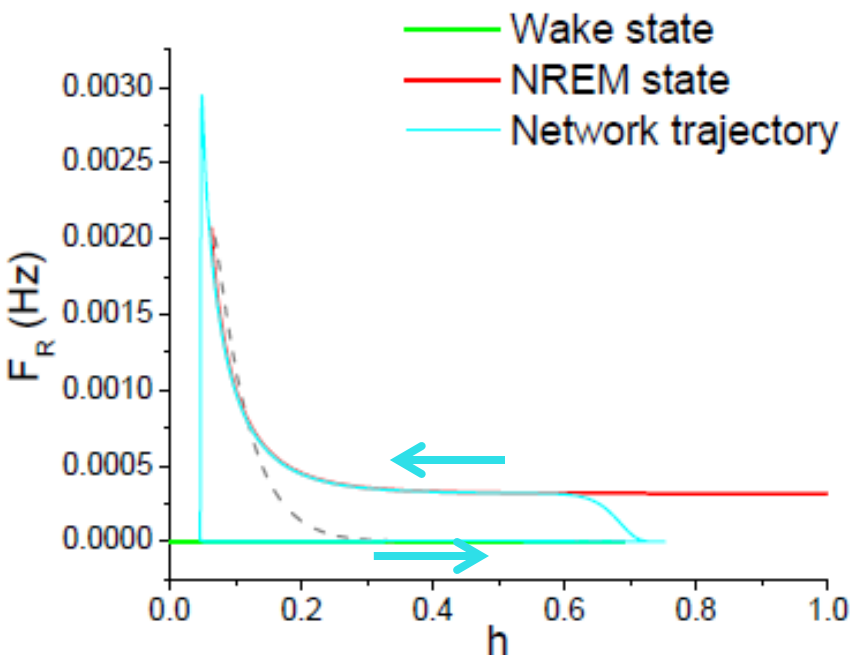
- NREM to wake transition occurs due to homeostatic *inactivation* of NREM population
  - Inhibition to REM population decreases as NREM inactivates
  - Wake inhibition to REM increases as it activates

Fast-Slow Analysis: Bifurcation structure with respect to slow variable h

Wake Population



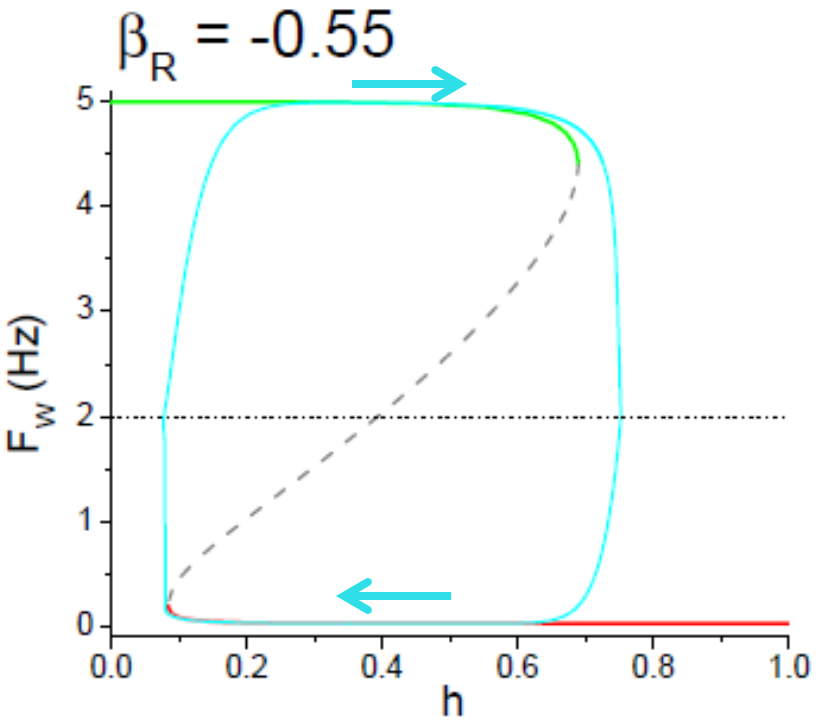
REM Population



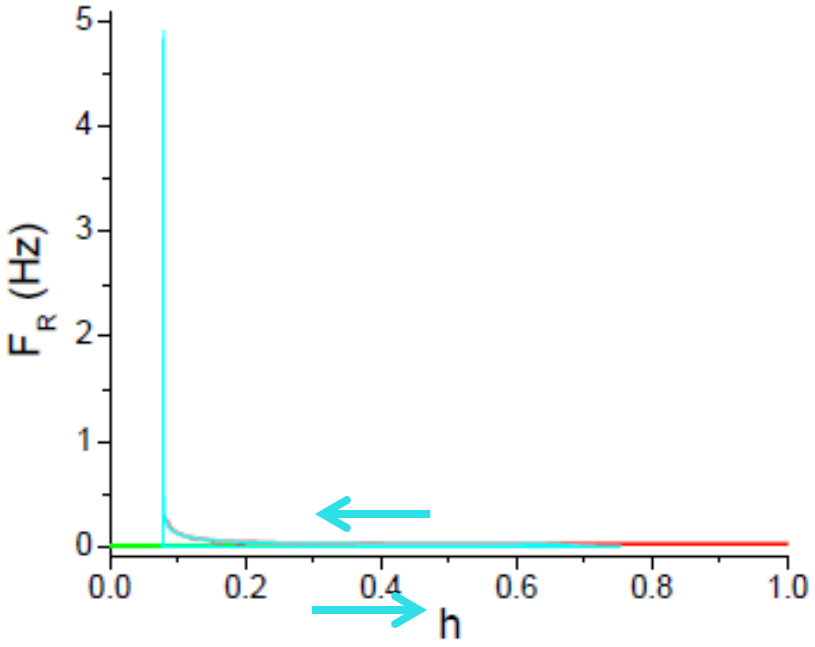
- High β_R: Stable wake and NREM states form Z-shaped steady state curve; trajectory follows hysteresis loop
- Wake: h increases; Sleep: h decreases

Fast-Slow Analysis: Bifurcation structure with respect to slow variable h

Wake Population



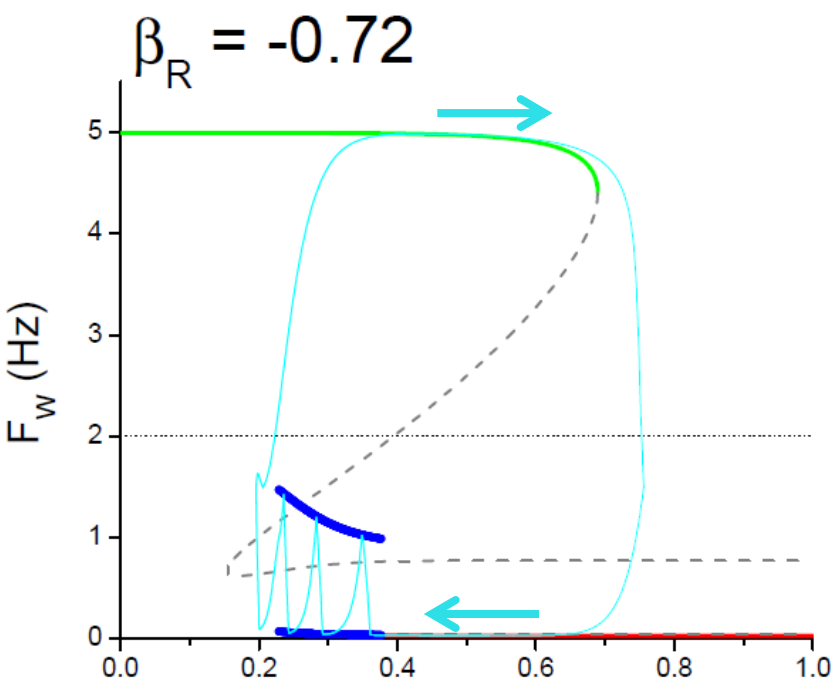
REM Population



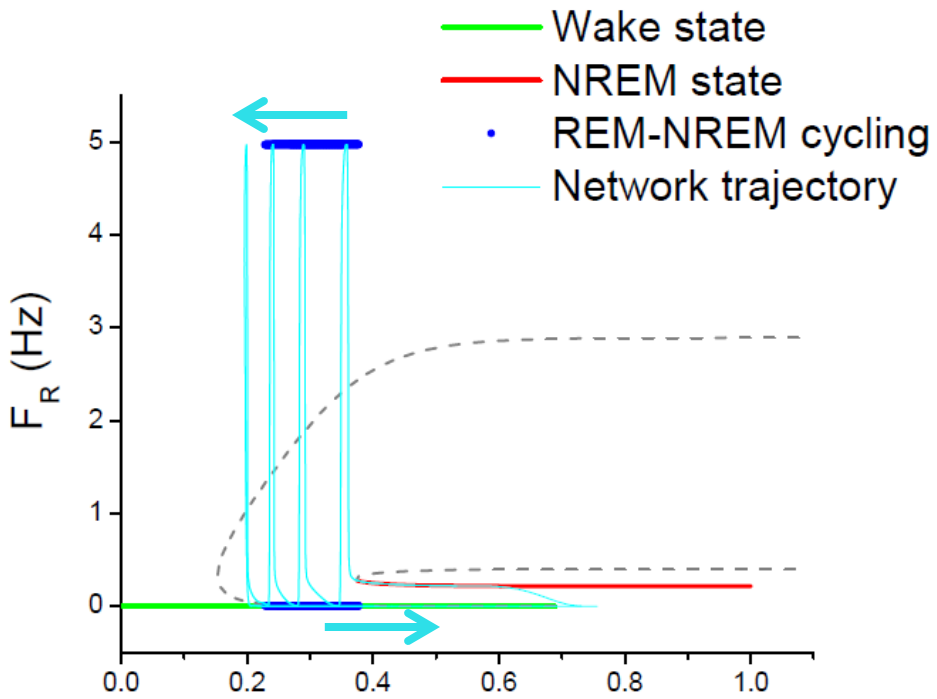
- Low β_R : REM exhibits high-amplitude transient at saddle-node point on NREM stable branch

Fast-Slow Analysis: Bifurcation structure with respect to slow variable h

Wake Population



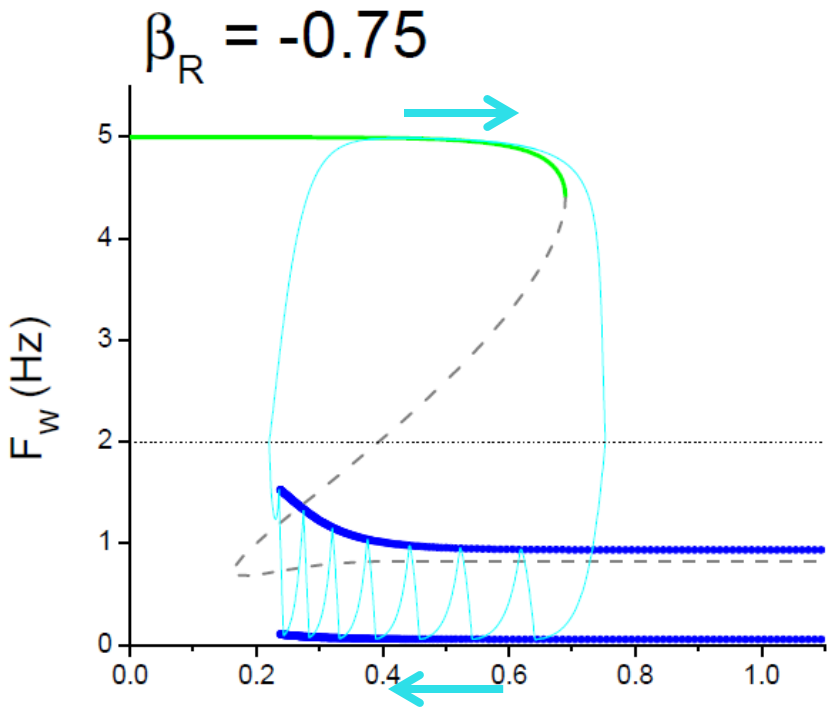
REM Population



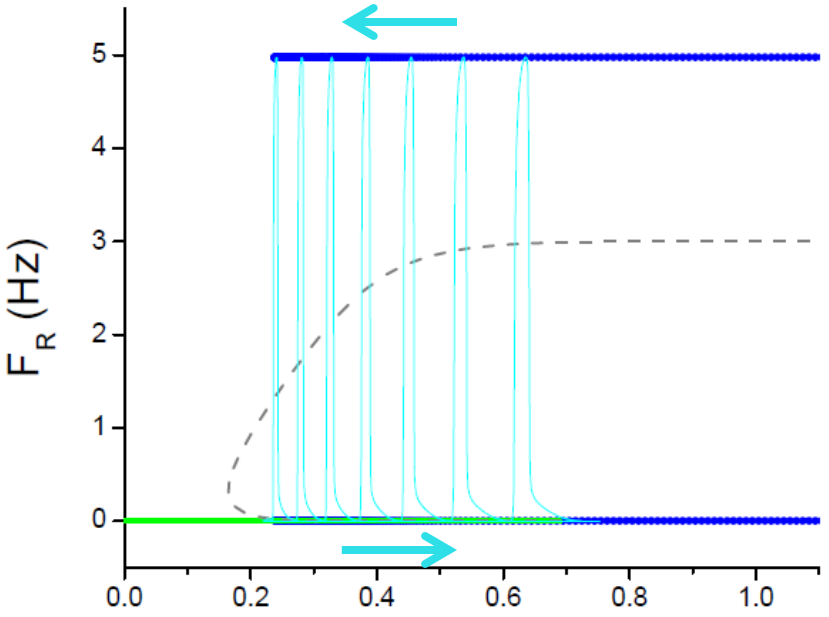
- Lower β_R: Stable branch of periodic high-amplitude REM / low-amplitude wake oscillations appears over small h interval

Fast-Slow Analysis: Bifurcation structure with respect to slow variable h

Wake Population

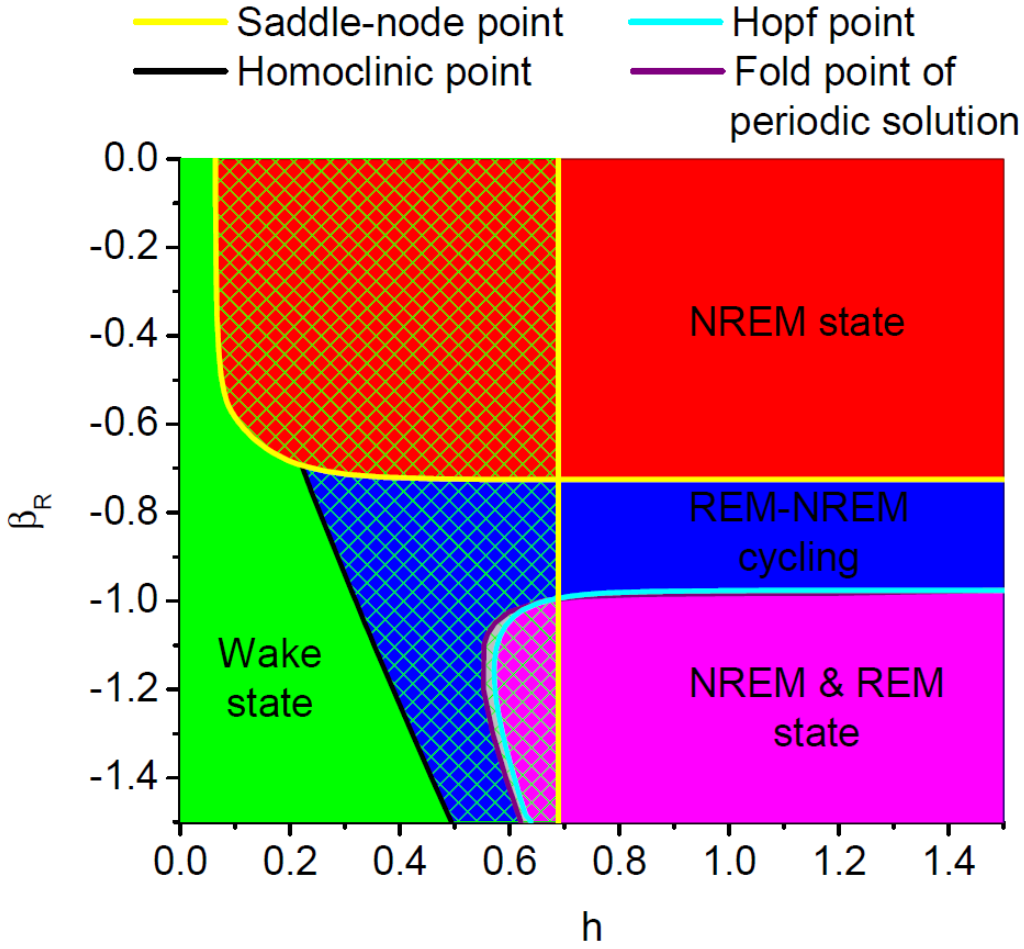


REM Population



- Lower β_R: Periodic branch replaces steady NREM state branch, REM oscillations occur during entire sleep state

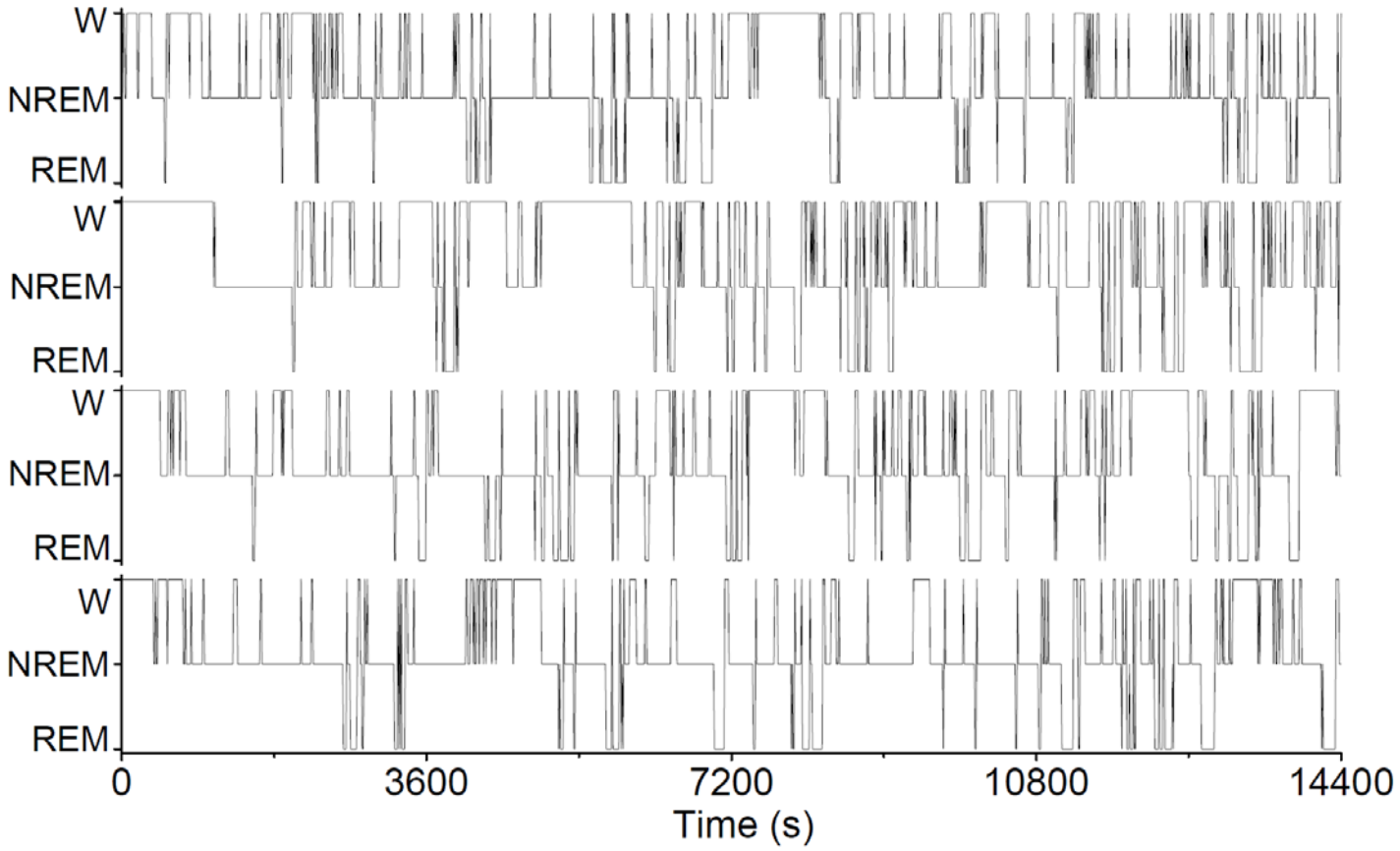
Bifurcation diagram in β_R and h



- Hatching indicates bistability with steady wake state

Diniz Behn and Booth, SIAM J Appl Dyn Sys 2011

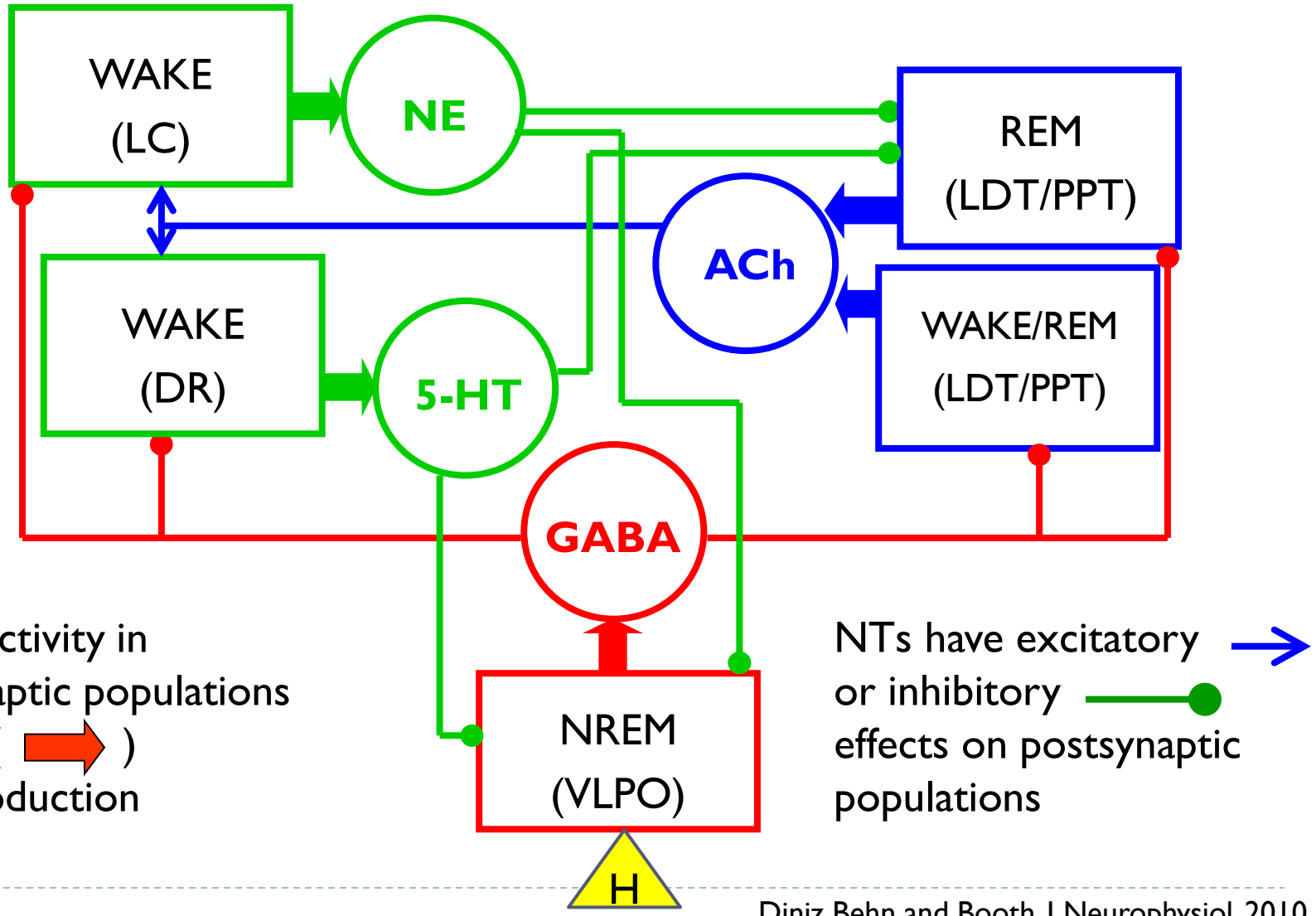
Rat sleep temporal architecture



- Can this network generate actual sleep-wake dynamics?

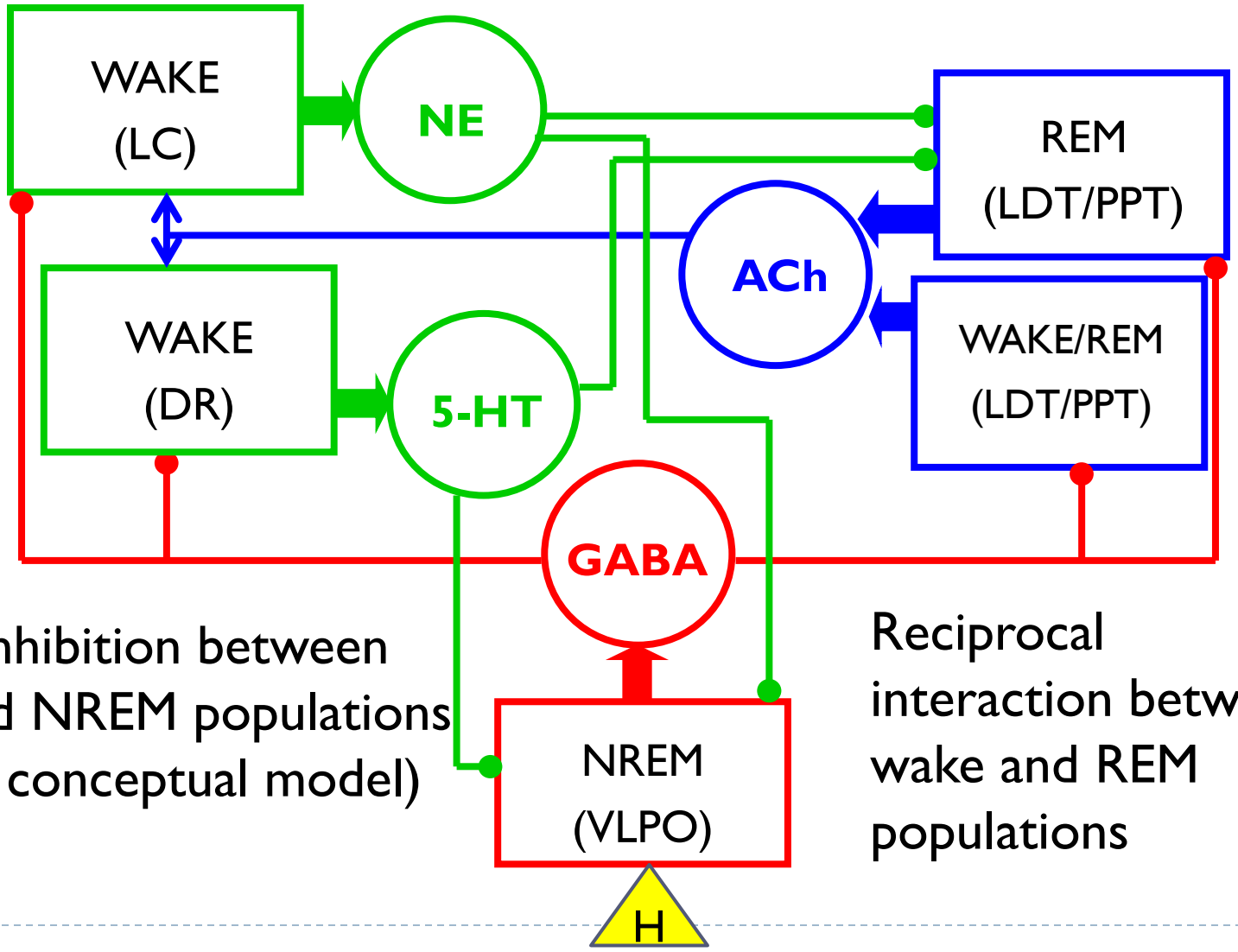
- Rat sleep in the light period recordings courtesy of George Mashour (Anesthesiology, U of Michigan)

Neuronal population and neurotransmitter interaction network for sleep-wake regulation



Diniz Behn and Booth, J Neurophysiol, 2010

Neuronal population and neurotransmitter interaction network for sleep-wake regulation



Mutual inhibition between wake and NREM populations (flip-flop conceptual model)

Reciprocal interaction between wake and REM populations

Sleep-wake regulatory network model

$$f_{LC}' = \frac{f_{LC\infty}(g_{A-LC}\,c_A - g_{N-LC}\,c_N - g_{G-LC}\,c_G + \eta) - f_{LC}}{\tau_{LC}}$$

$$\frac{dc_N}{dt} = \frac{\sigma_N c_{N\infty}(f_{LC}) - c_N}{\tau^N}$$

$$f_{DR}' = \frac{f_{DR\infty}(g_{A-DR}\,c_A - g_{S-DR}\,c_S - g_{G-DR}\,c_G + \eta) - f_{DR}}{\tau_{DR}}$$

$$\frac{dc_S}{dt} = \frac{\sigma_S c_{S\infty}(f_{DR}) - c_S}{\tau^S}$$

$$f_{VLPO}' = \frac{f_{VLPO\infty}(-g_{N-VLPO}\,c_N - g_{S-VLPO}\,c_S - g_{G-VLPO}\,c_G) - f_{VLPO}}{\tau_{VLPO}}$$

$$\frac{dc_G}{dt} = \frac{\sigma_G c_{G\infty}(f_{VLPO}) - c_G}{\tau^G}$$

$$f_R' = \frac{f_{R\infty}(g_{A-R}\,c_A - g_{N-R}\,c_N - g_{S-R}\,c_S - g_{G-R}\,c_G) - f_R}{\tau_R}$$

$$\frac{dc_{AR}}{dt} = \frac{\sigma_{AR} c_{AR\infty}(f_R) - c_{AR}}{\tau^A}$$

$$f_{WR}' = \frac{f_{WR\infty}(g_{A-WR}\,c_A - g_{G-WR}\,c_G) - f_{WR}}{\tau_{WR}}$$

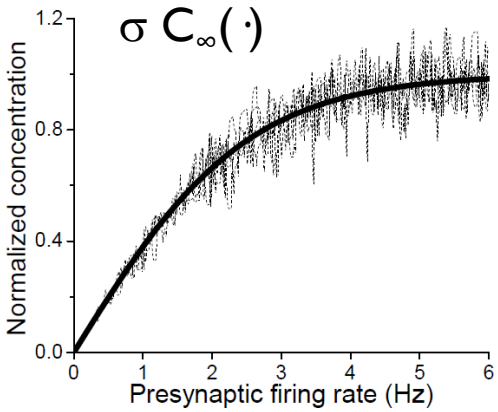
$$\frac{dc_{AWR}}{dt} = \frac{\sigma_{AWR} c_{AWR\infty}(f_{WR}) - c_{AWR}}{\tau^A}$$

Homeostatic sleep drive promotes NREM sleep

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

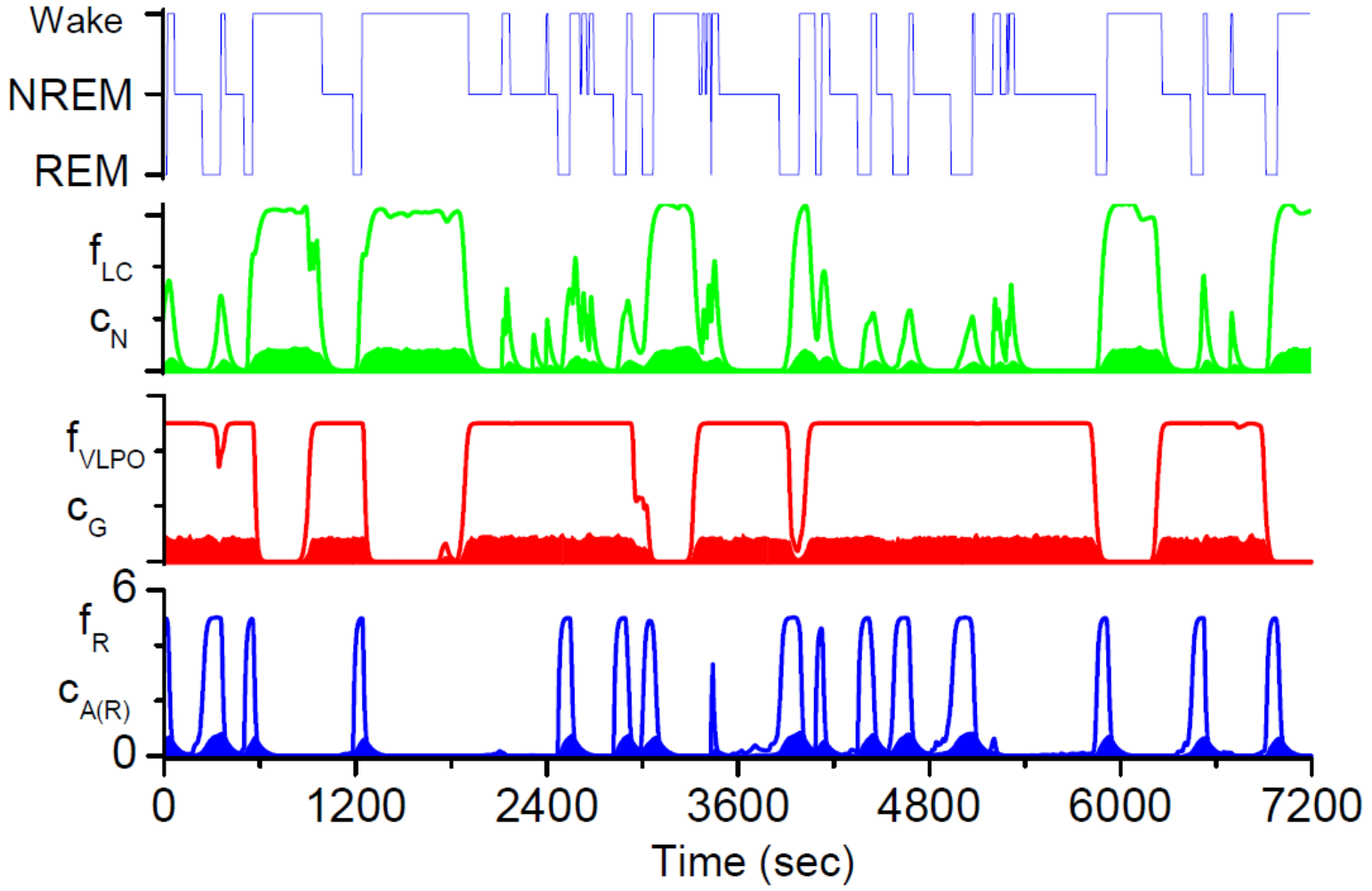
Stochastic elements in model

- Variable neurotransmitter release
  - simulating stochasticity of synaptic transmission

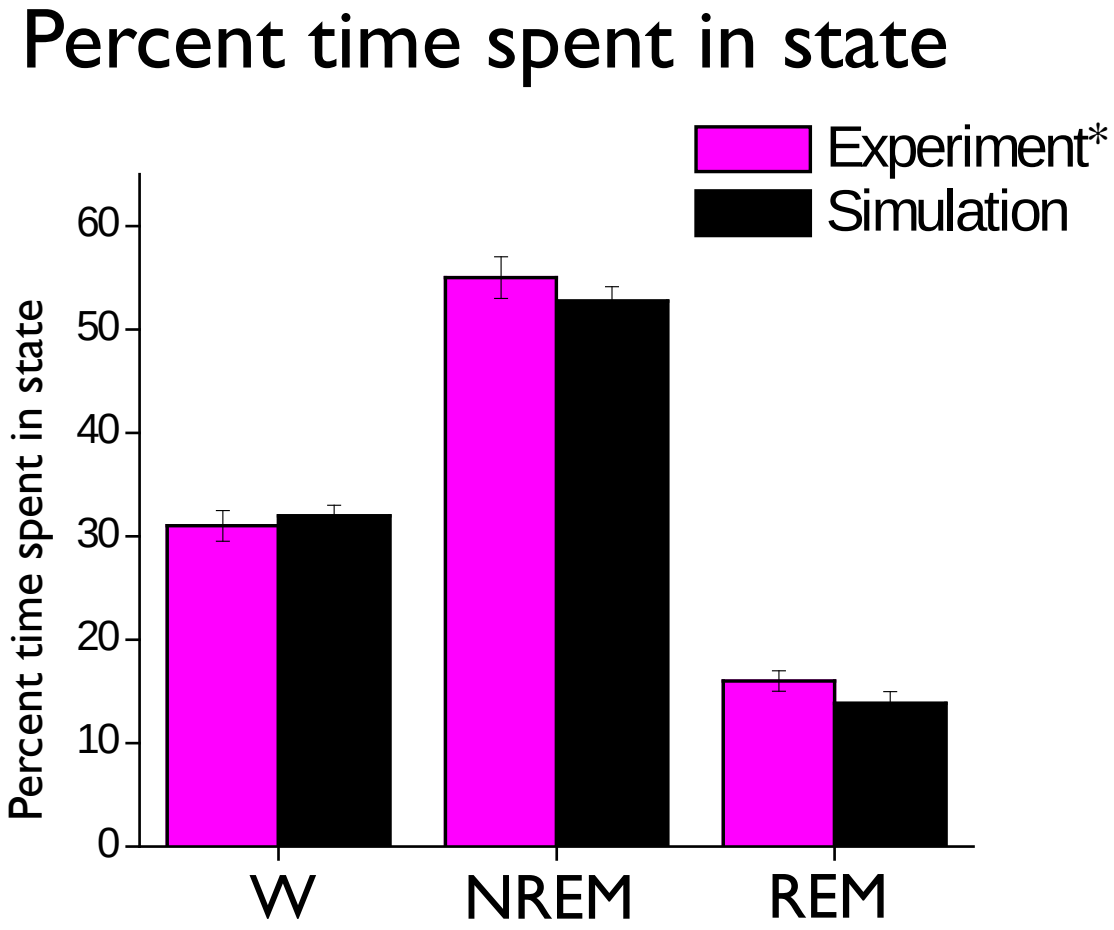


- Variable homeostatic sleep drive
  - simulating stochasticity of adenosine levels & action
- Random excitatory inputs to populations
  - simulating excitatory afferent activity from other brain regions

Simulated rat sleep-wake behavior

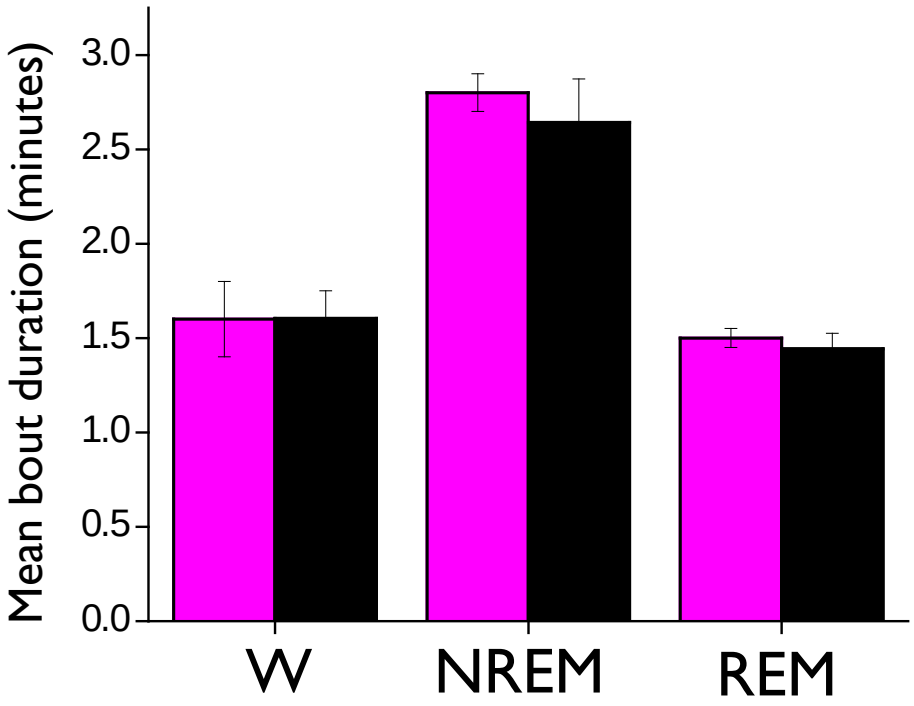


Simulations fit to general characteristics of wake, NREM sleep, and REM sleep

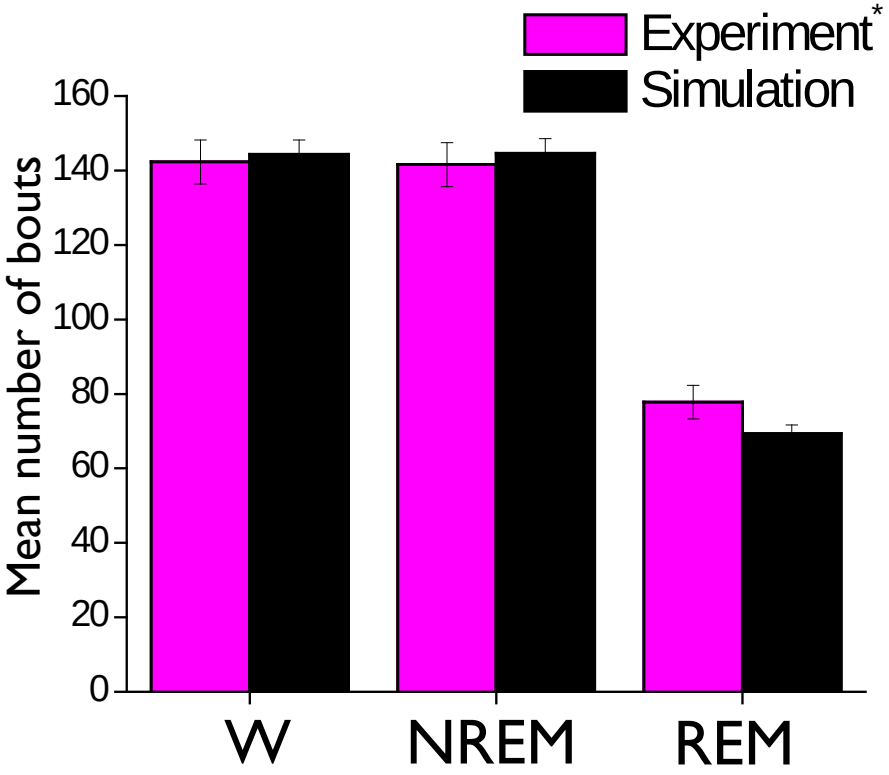


• Experimental data from Blanco-Centurion et al., J. Neurosci., 2007 of 12-hr rat sleep recording during light period

Mean bout duration

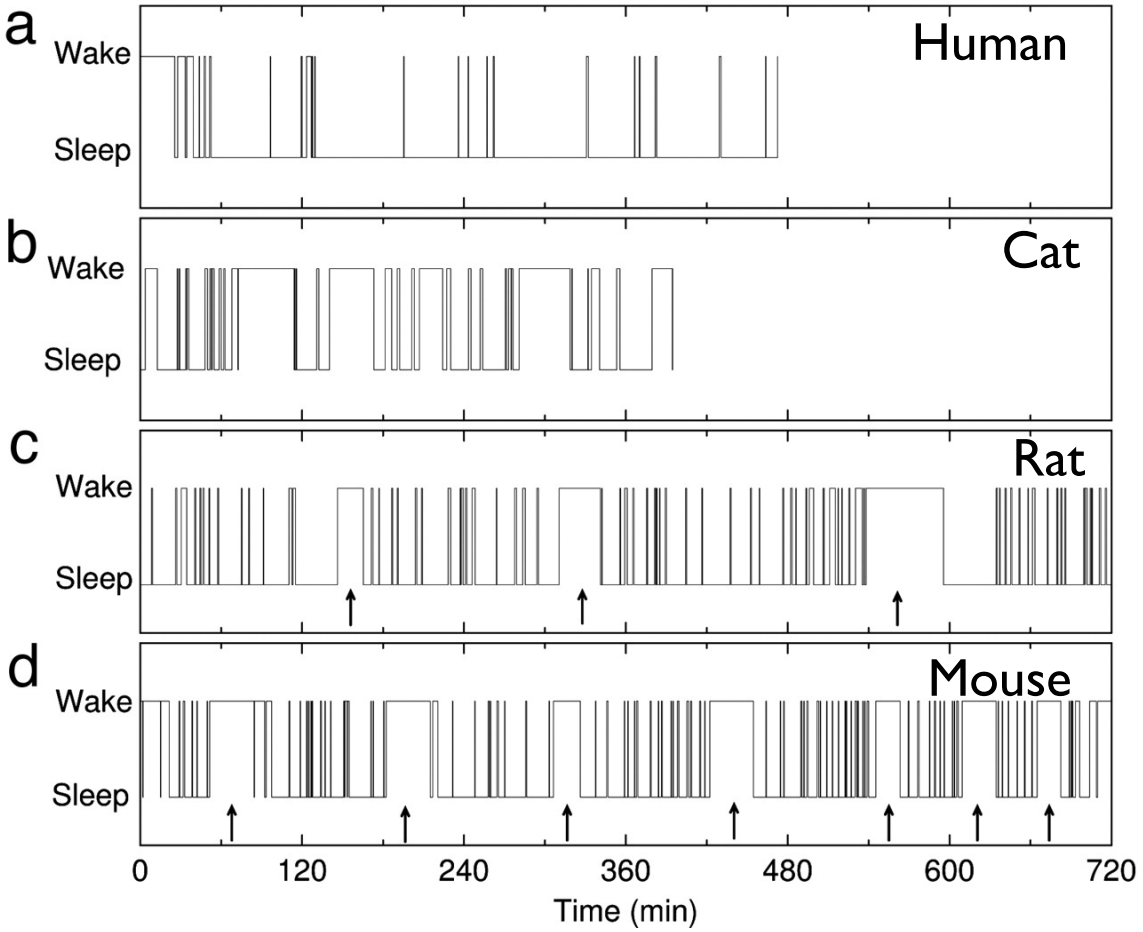


Mean number of bouts



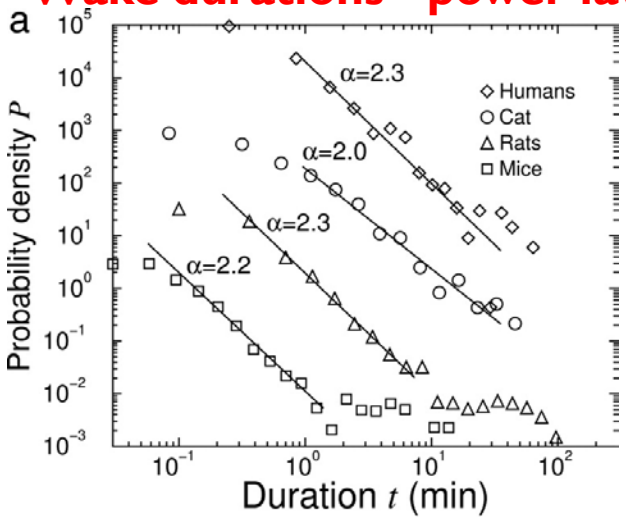
• Experimental data from Blanco-Centurion et al., J. Neurosci., 2007 of 12-hr rat sleep recording during light period

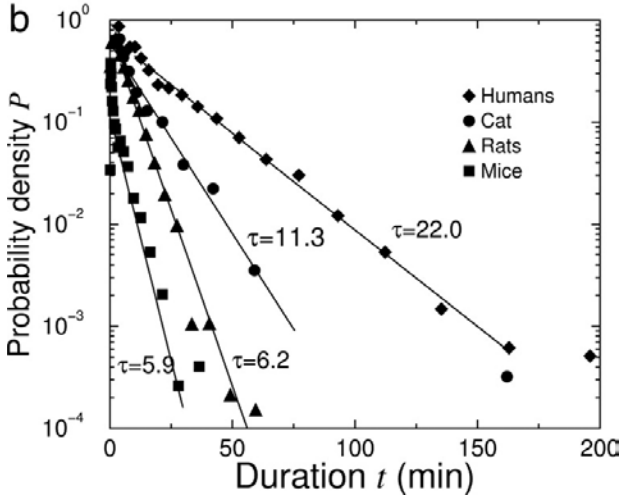
Temporal dynamics of sleep-wake patterning in different species



Lo C et al. PNAS 2004;101:17545-17548

Wake durations - power law

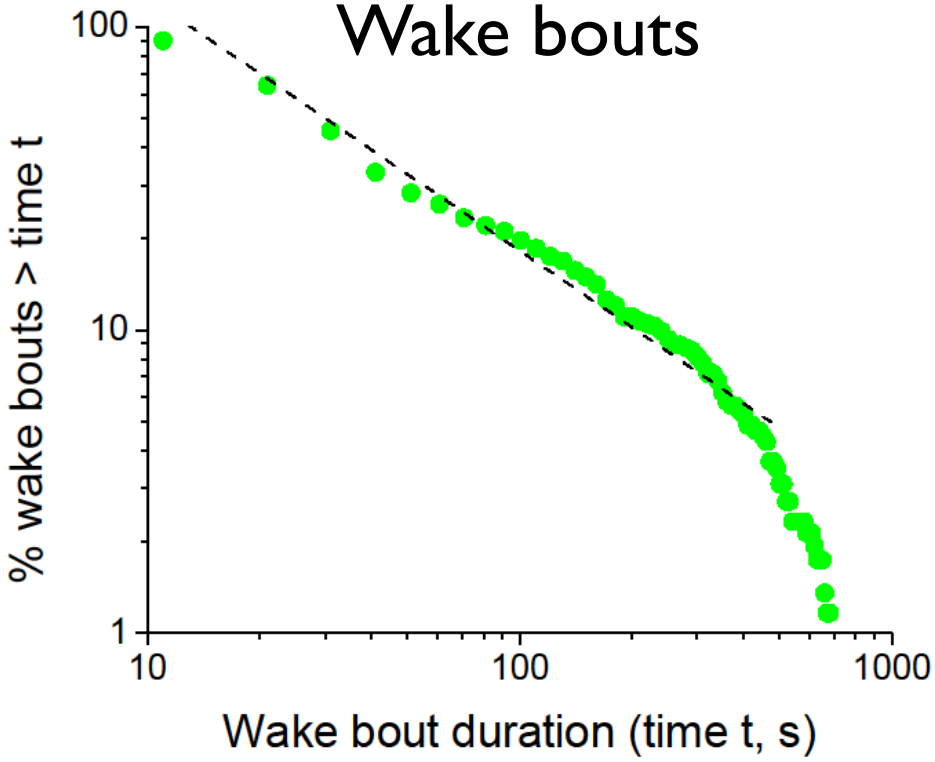




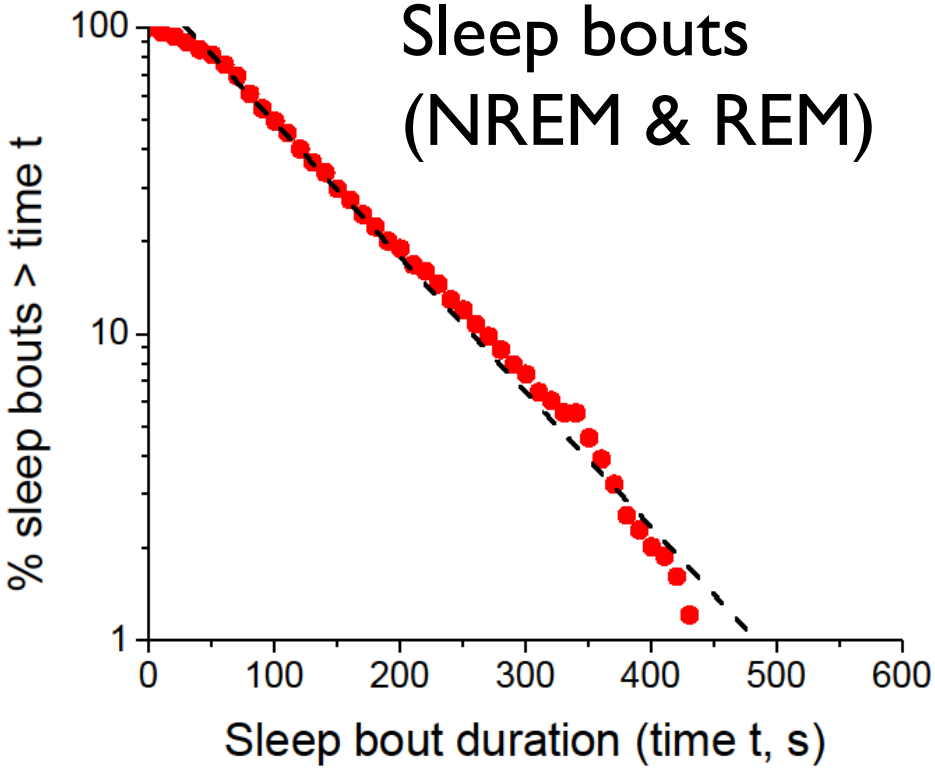
Sleep durations - exponential

PNAS

Full model can generate bout length distributions with appropriate characteristics



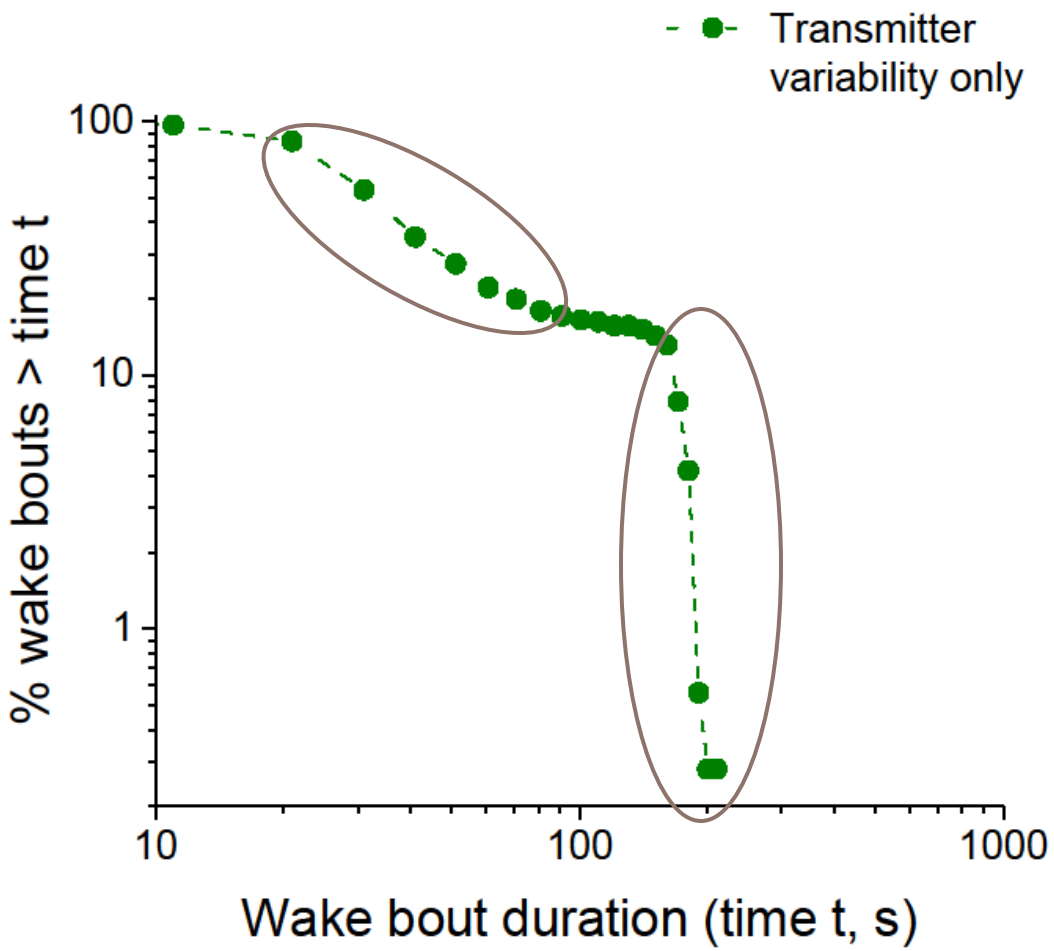
Power law fit: 861 $t^{(-0.837)}$
(r^2=0.9724)



Exponential fit: 135.8 $e^{(-0.01\ t)}$
(r^2=0.9882)

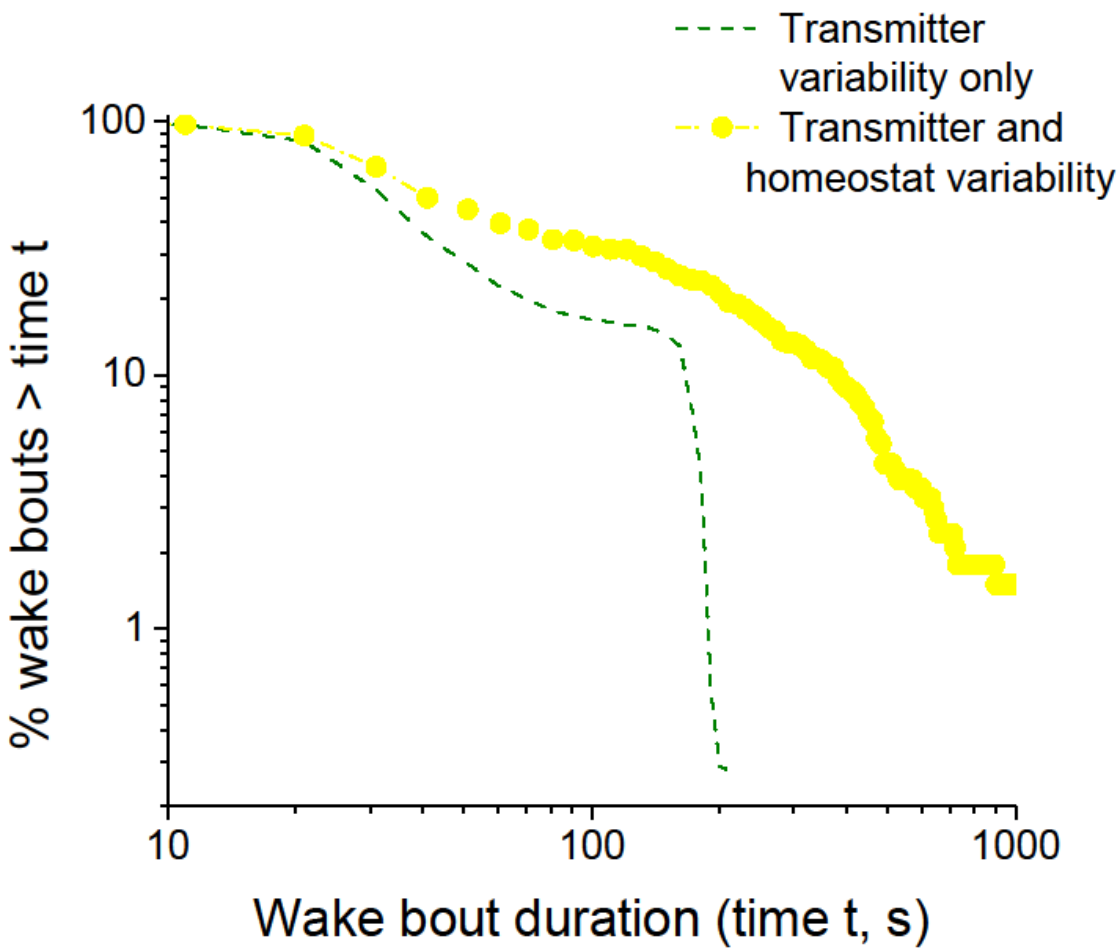
Diniz Behn and Booth, IEEE EMBC, 2011

Power law-like wake bout distribution



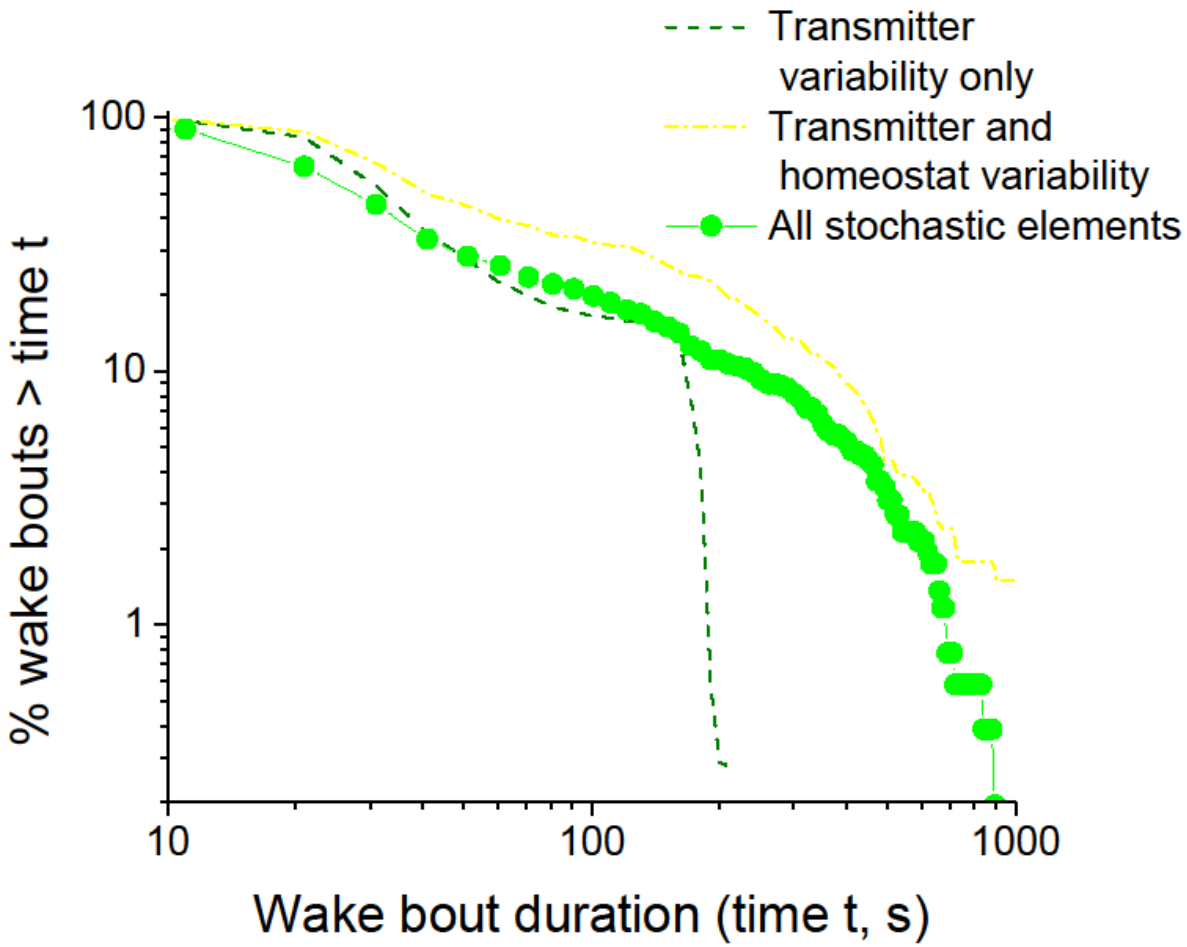
- With only transmitter variability, wake bout distribution is *bimodal*
  - Homeostatically controlled long wake bouts
  - Post-REM short wake bouts

Power law-like wake bout distribution



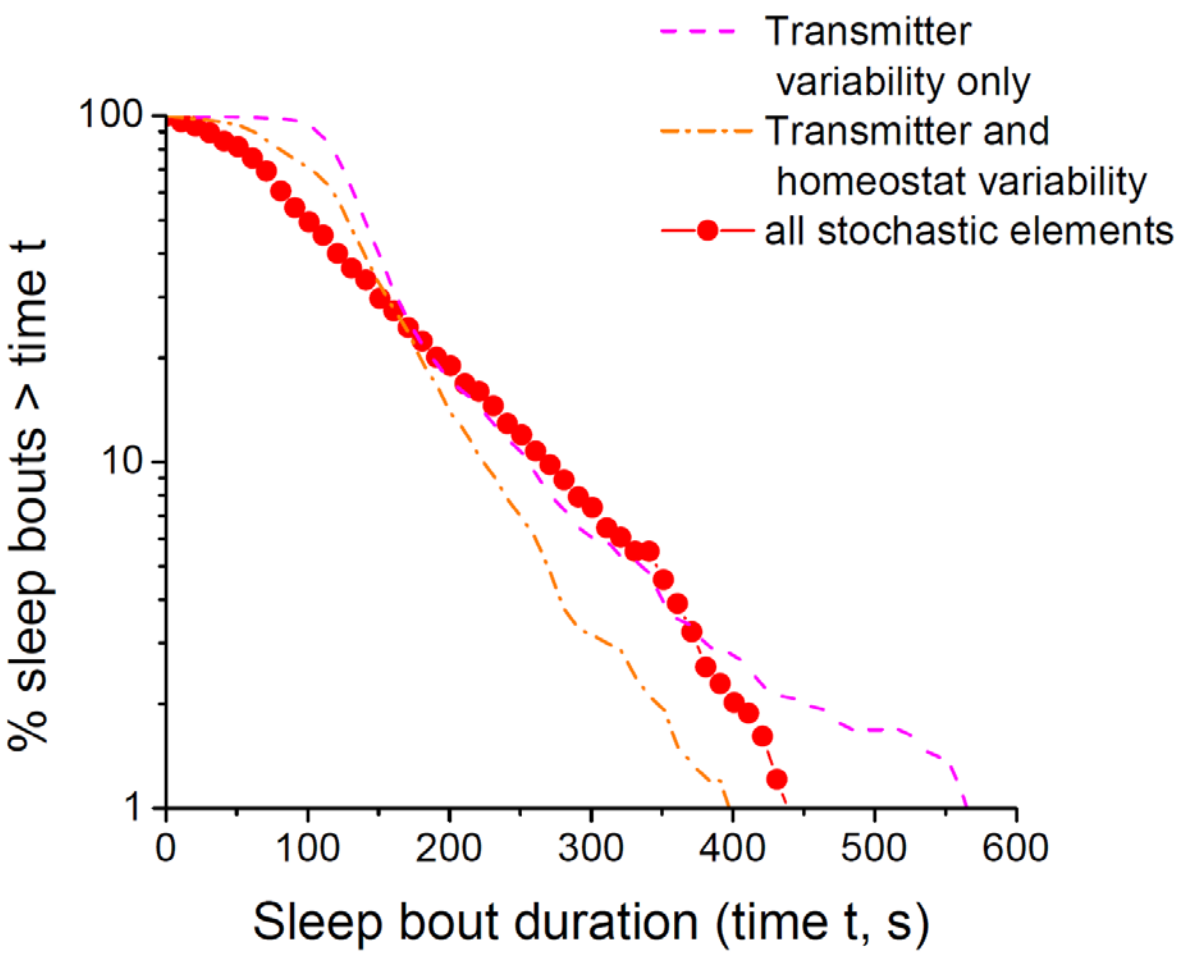
- Variability in homeostat levels introduces more variance in durations of long wake bouts

Power law-like wake bout distribution



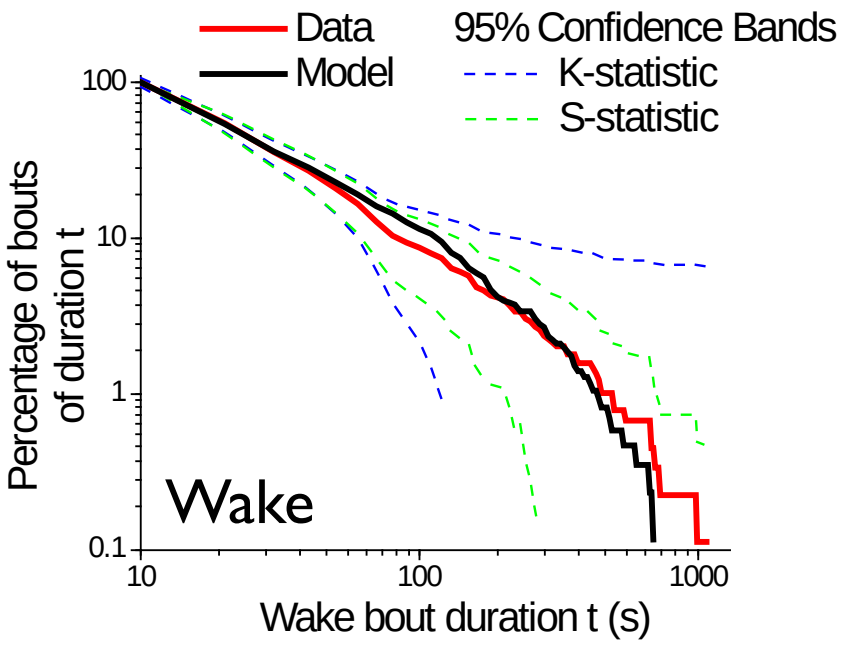
- Random inputs to wake populations generate many brief wake bouts
  - Contribute to initial power-law profile

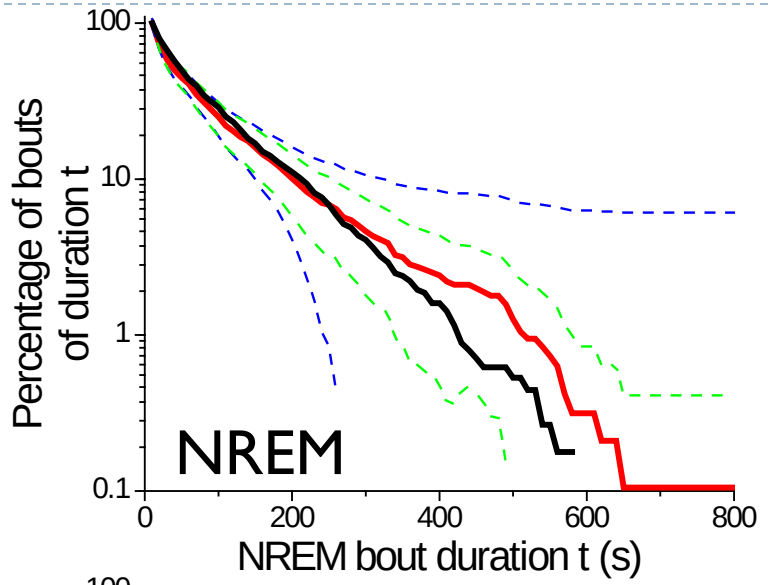
Exponential sleep (NREM & REM) bout distribution

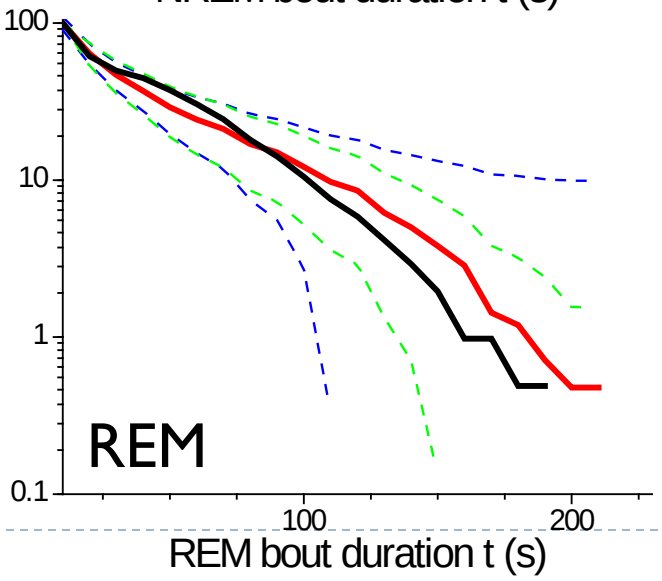


- Longest sleep bout durations show exponential distribution
  - variable termination of sleep states by wake
- Randomly initiated brief wake bouts fragment sleep
  - contribute to initial exponential profile

Current work: Analyzing model fit to bout distributions from experimental data







Investigating diverse sleep properties using the model

- Simulate experiments that manipulate sleep-wake network by microinjection of neurotransmitter agonists/antagonists (Diniz Behn and Booth, J Neurophysiol, 2010)
- Investigate circadian modulation of sleep-wake patterning and bi-directional coupling between sleep-wake network and the SCN (Fleshner et al, Phil Trans Royal Soc A, 2011)
- Comparative analysis of sleep-wake dynamics generated by different network structures, i.e. mutual inhibition network for REM generation (Diniz Behn et al, submitted)

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