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Interacting networks of sleep and wake-promoting neurons and their role in triggering arousals from sleep

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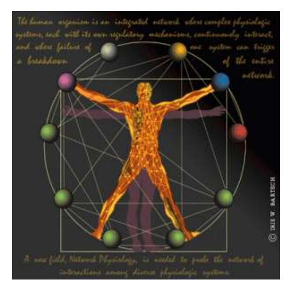
Tradition of Excellence
Bar-Ilan University
אוניברסיטת בר-אילן



Acknowledgements

Collaborators:

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Lior Appelbaum *– Faculty of Life Sciences, Bar-Ilan Univ.*

Plamen Ch. Ivanov *– Keck Laboratory for Network Physiology, Boston University*

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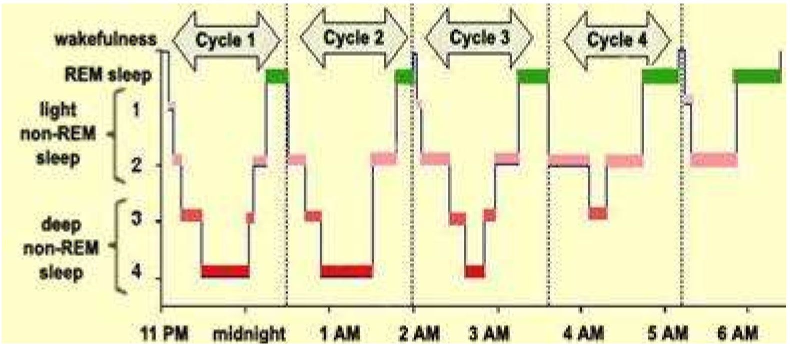
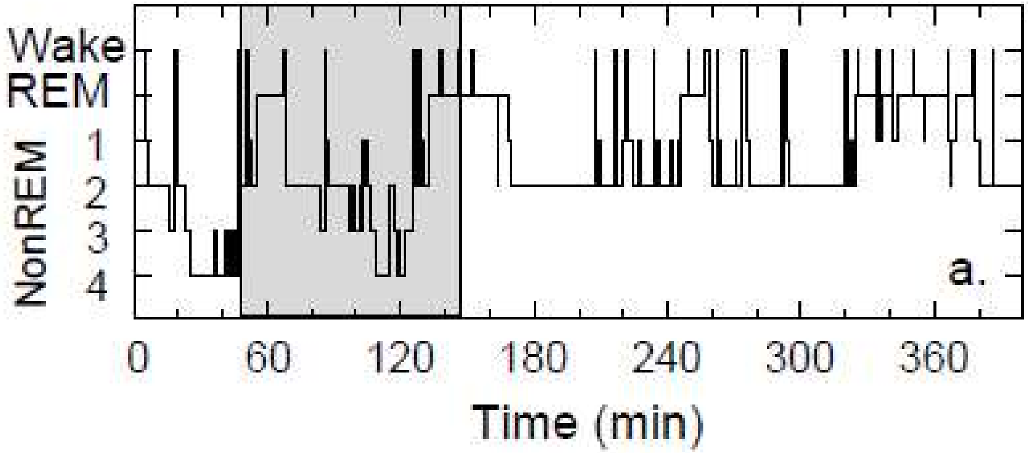
Sleep dynamics – Conventional view and Observations

Sleep dynamics exhibit ultradian rhythms with ~ 90 min period comprised of light sleep, deep sleep and REM sleep → "Sleep Cycle"

Textbook:



Reality:

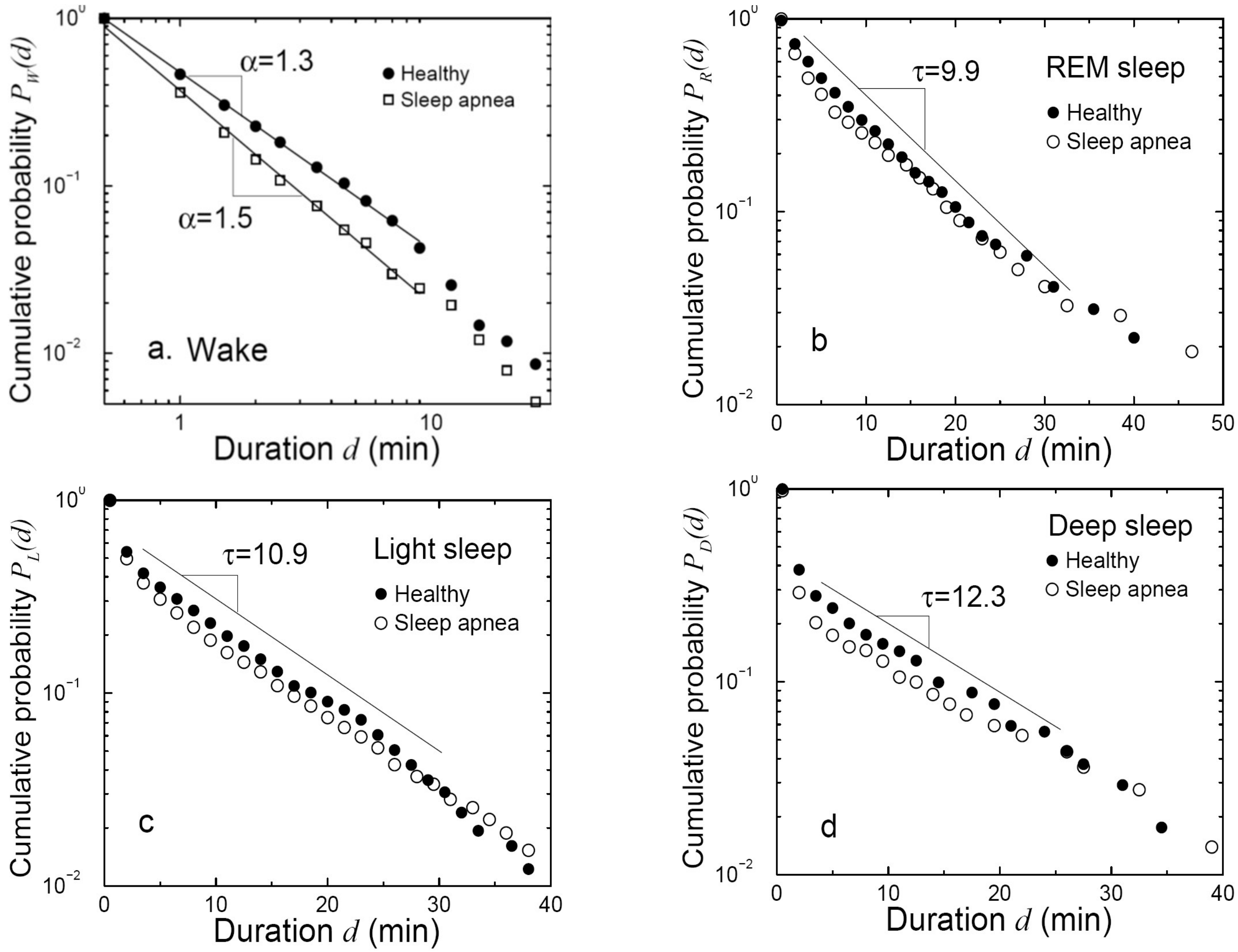


• Brief awakenings from sleep (arousals) on scales of sec to min <u>appear random</u> in time and occur throughout the sleep period

Probability distributions of arousal and sleep-stage durations

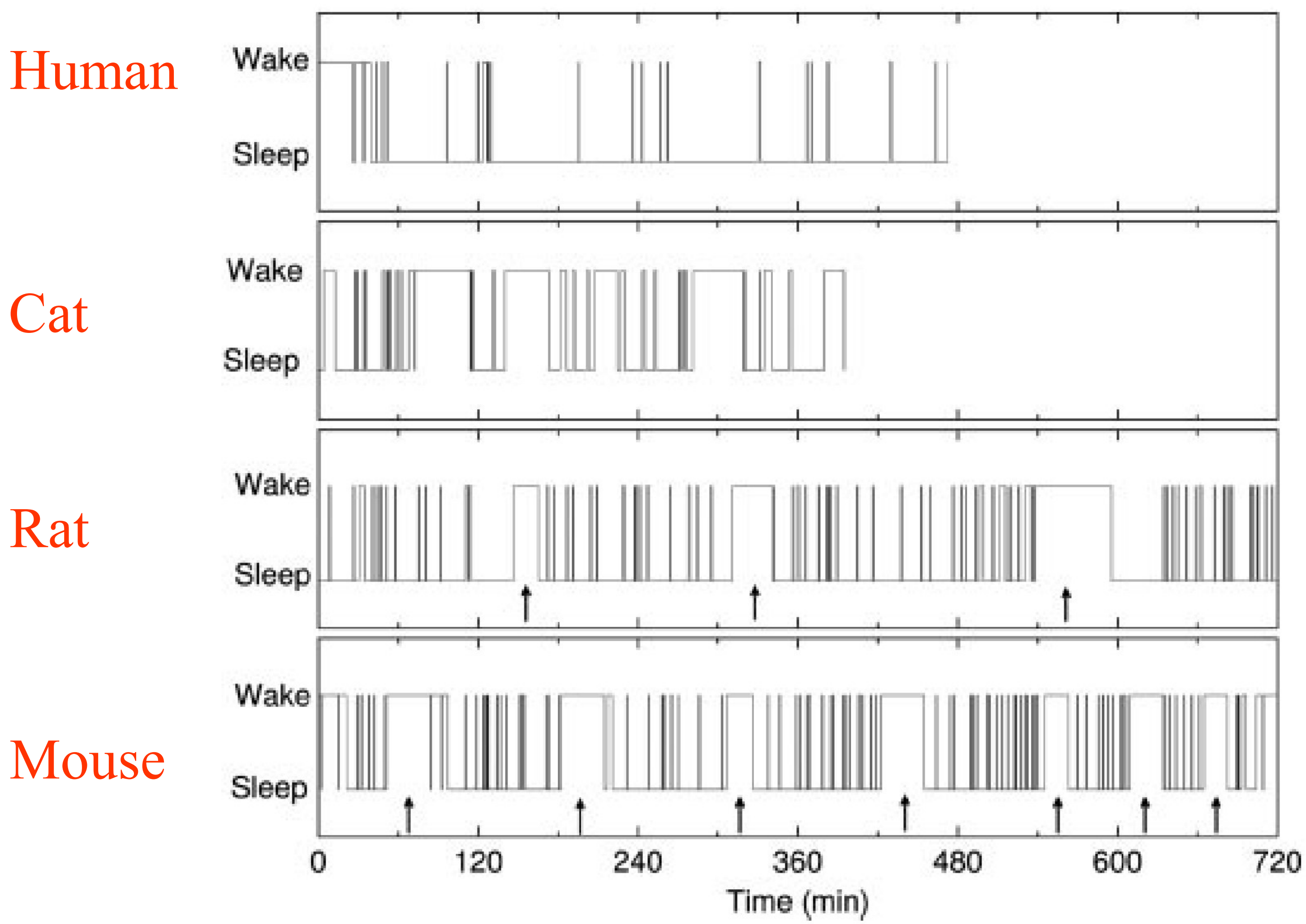
$P_k(d) \equiv \int_d^\infty p_k(r)\, dr$ … cumulative probability distribution

$p_k(d)$ … probability density function to find sleep stage k with duration d



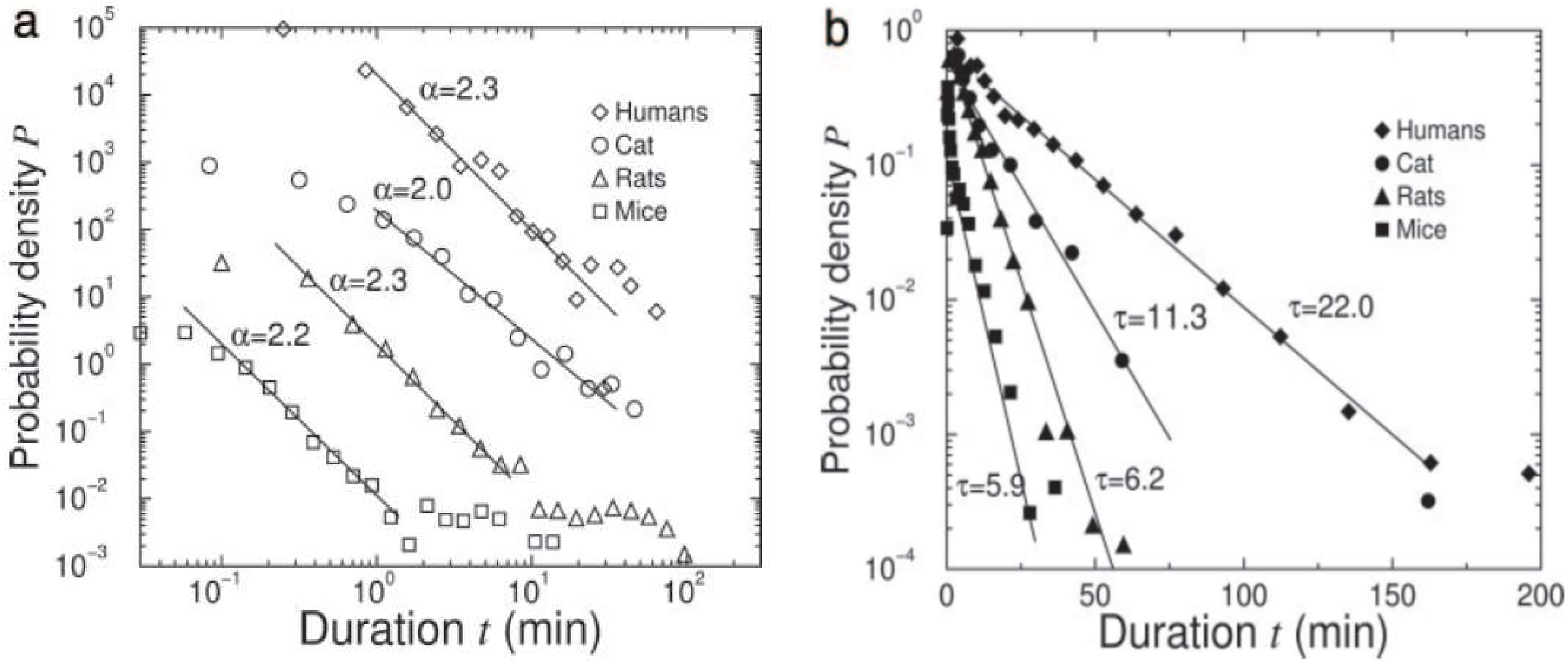
Lo, Bartsch, Ivanov, EPL 102, 10008 (2013)

Probability distributions of arousal/sleep durations across species



Lo, Ivanov et al., PNAS 101, 17545 (2004)

Probability distributions of arousal/sleep durations across species



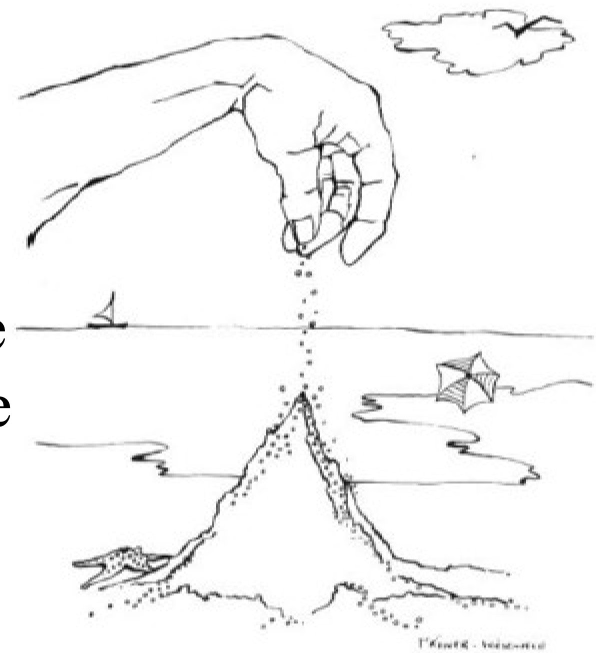
→ **Co-existence of both scale-invariant (power-law) and exponential (with a characteristic time scale) processes as an output of a single sleep regulatory mechanism across various mammalian species**

→ **Has not been observed in other integrated physiological systems under neural regulation**

Lo, Ivanov et al., PNAS 101, 17545 (2004)

Relation to self-organized criticality (SOC)

Sandpile Metaphor



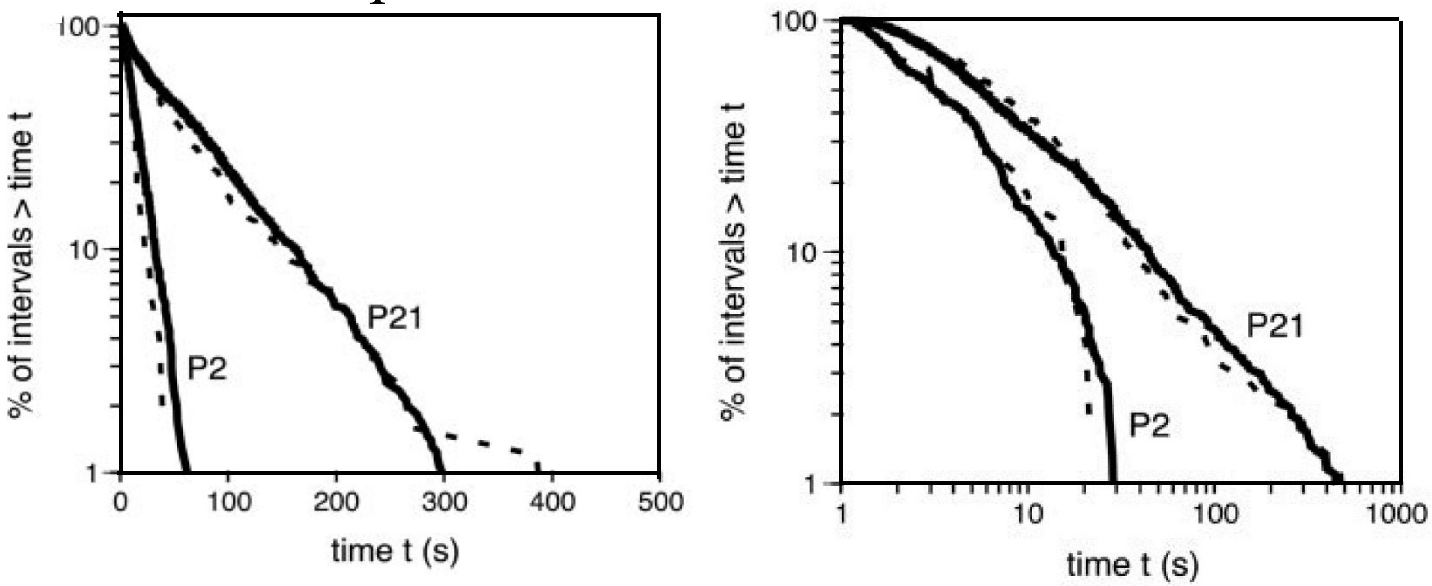
- Bak-Tang-Wiesenfeld model
- slowly driven
- non-equilibrium steady state
- avalanche of any size
- power law statistics of avalanche size
- waiting times between avalanches are exponentially distributed
- Bak: “self-organized criticality”

Jens Feder et. al (1995): SOC found in rice piles

Basmati Rice!

Dynamic characteristics of sleep/wake transitions – Scaling changes with maturation in rats

Sleep Wake



Power-law during wake gradually emerges with maturation.

M.S. Blumberg, A.M.H. Seelke, S.B. Lowen, K.A.E. Karlsson, “Dynamics of sleep-wake cyclicity in developing rats”, *PNAS* **102**: 14860 (2005).

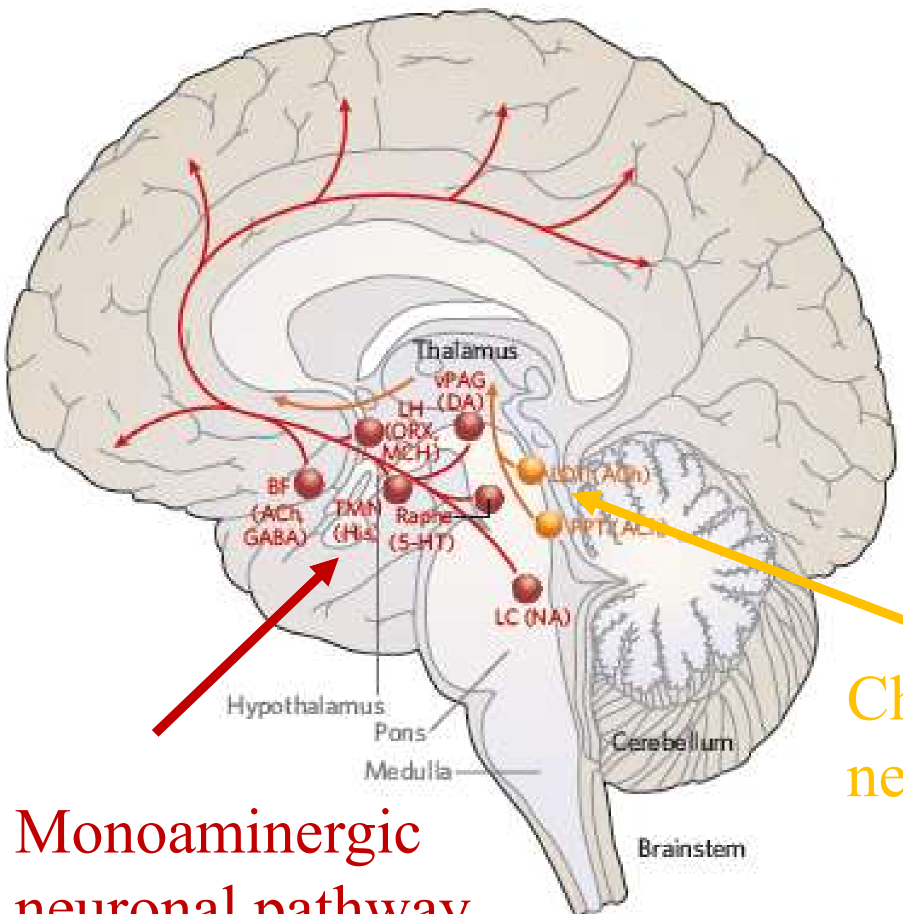
Modeling arousal dynamics

Question: Can we come up with a simple model including a network of sleep- and wake-promoting neurons to reproduce the observed arousal/sleep dynamics?

Previous work by Lo, Ivanov et al., EPL 57, 625 (2002):
biased diffusion model

Neuronal groups and pathways involved in sleep/wake generation

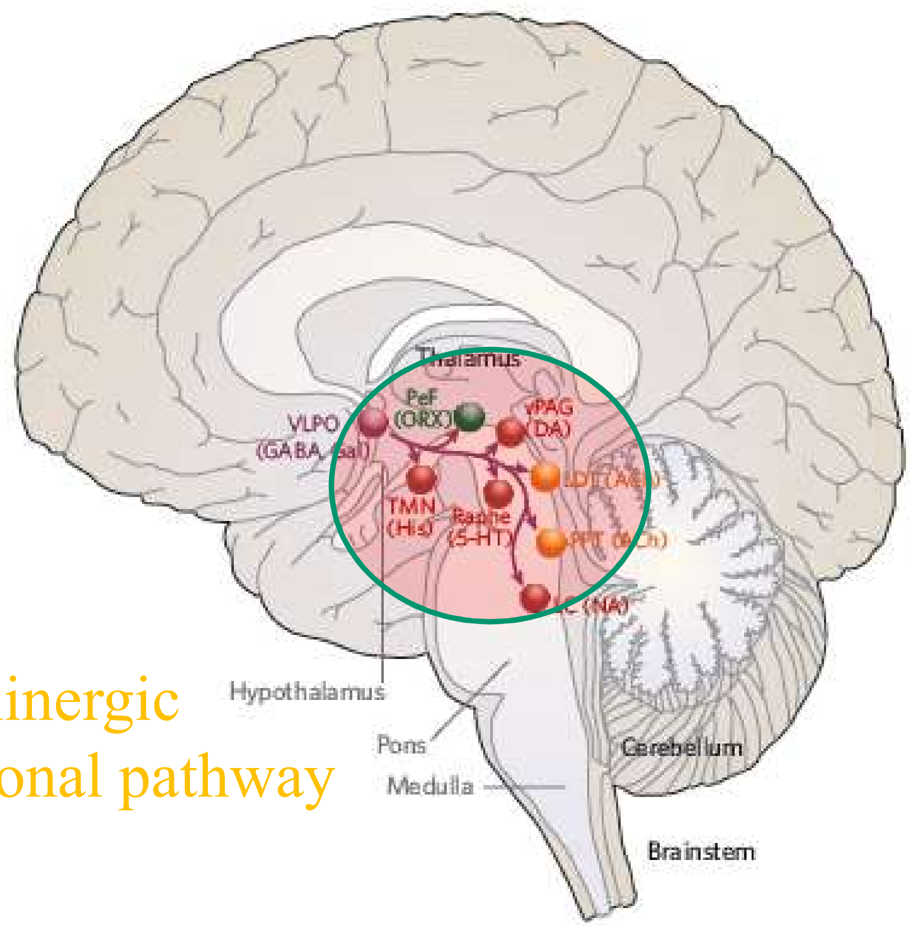
Wake promoting



Monoaminergic neuronal pathway

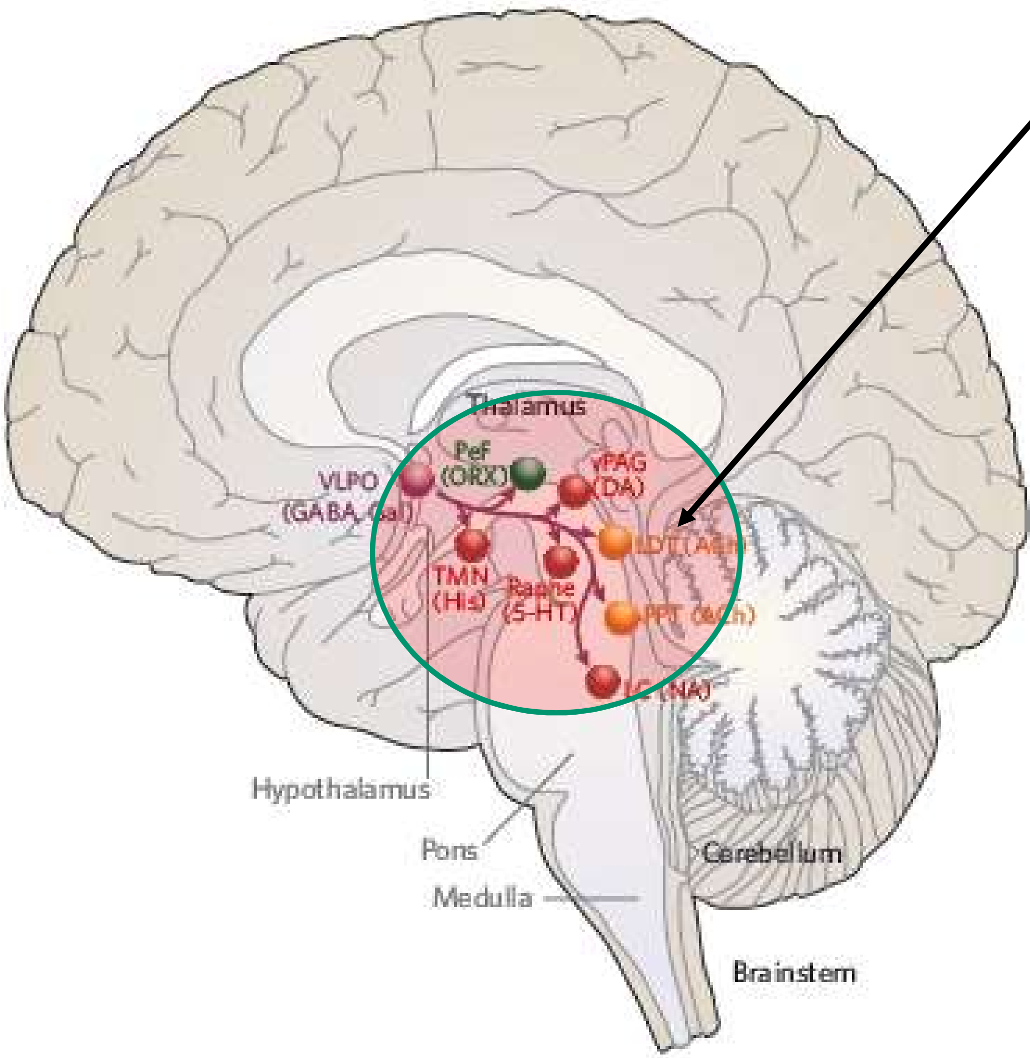
Cholinergic neuronal pathway

Sleep promoting



Neuronal groups and pathways involved in sleep/wake generation

During Sleep



Wake promoting neurons are suppressed by VLPO but still have intrinsic noise "neuronal noise"

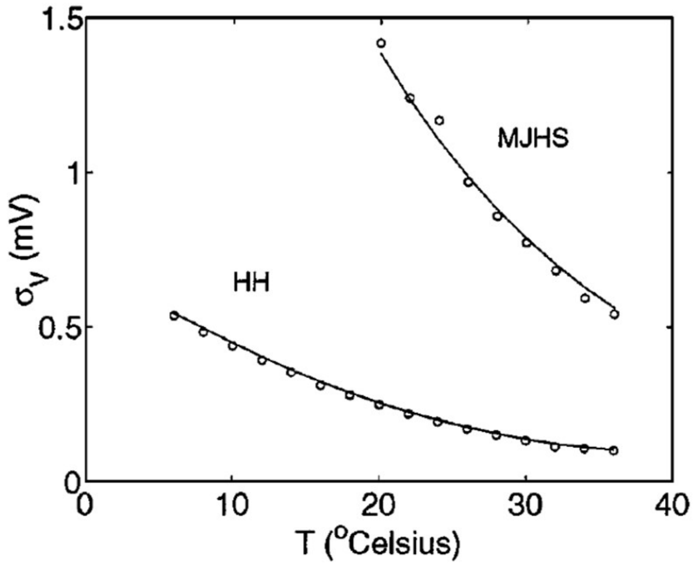
Neuronal noise – origin and characteristics

"neuronal noise" = subthreshold voltage fluctuations

Two main sources (Manwani and Koch, Neural Comput. 11, 1831 (1999)):

1) stochastic openings and closings of voltage gated membrane channels

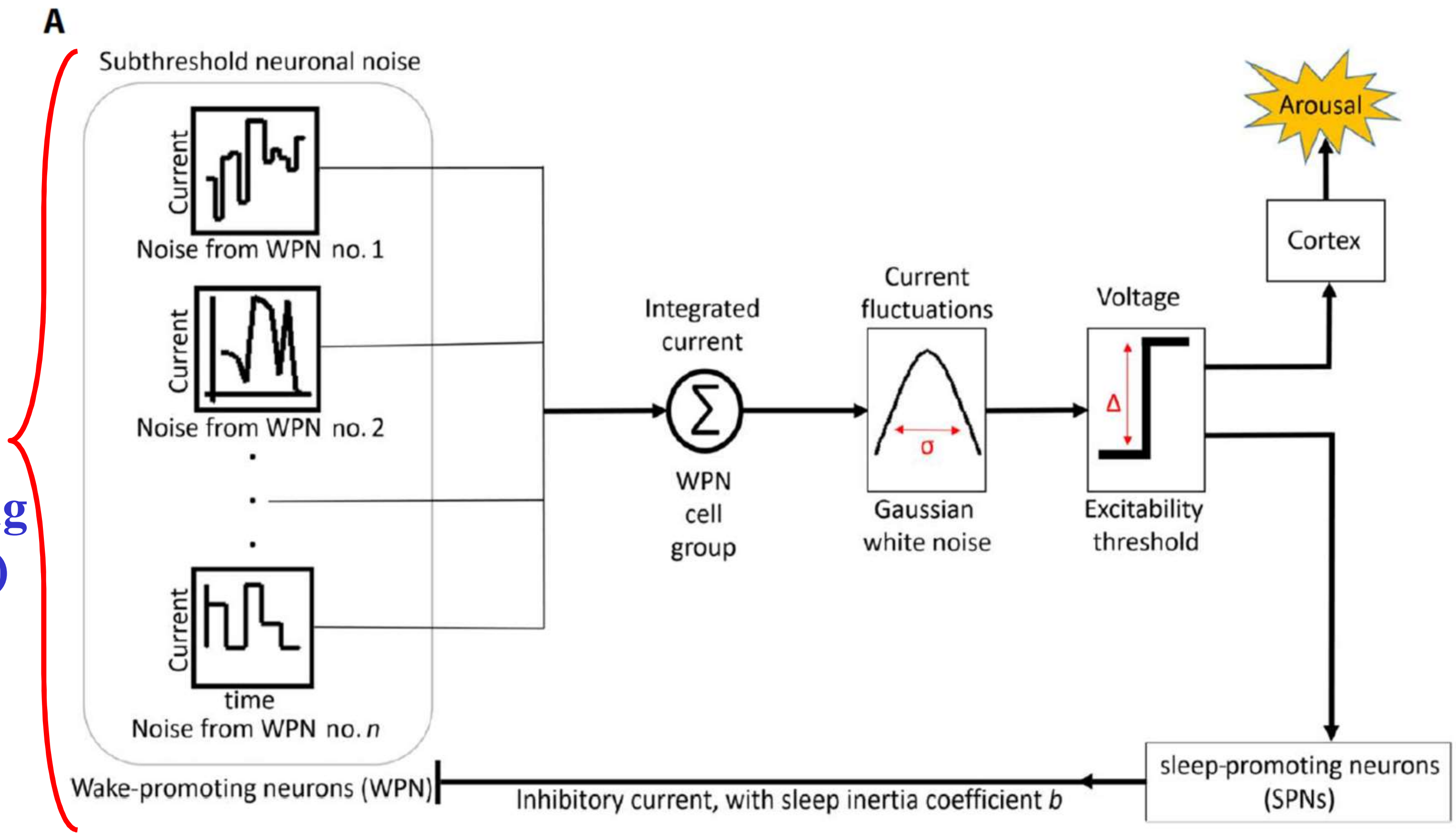
2) random background synaptic activity



subthreshold voltage fluctuations are temperature dependent and decrease with increasing temperature (Steinmetz et al., J. Comput. Neurosci. 9, 133 (2000))

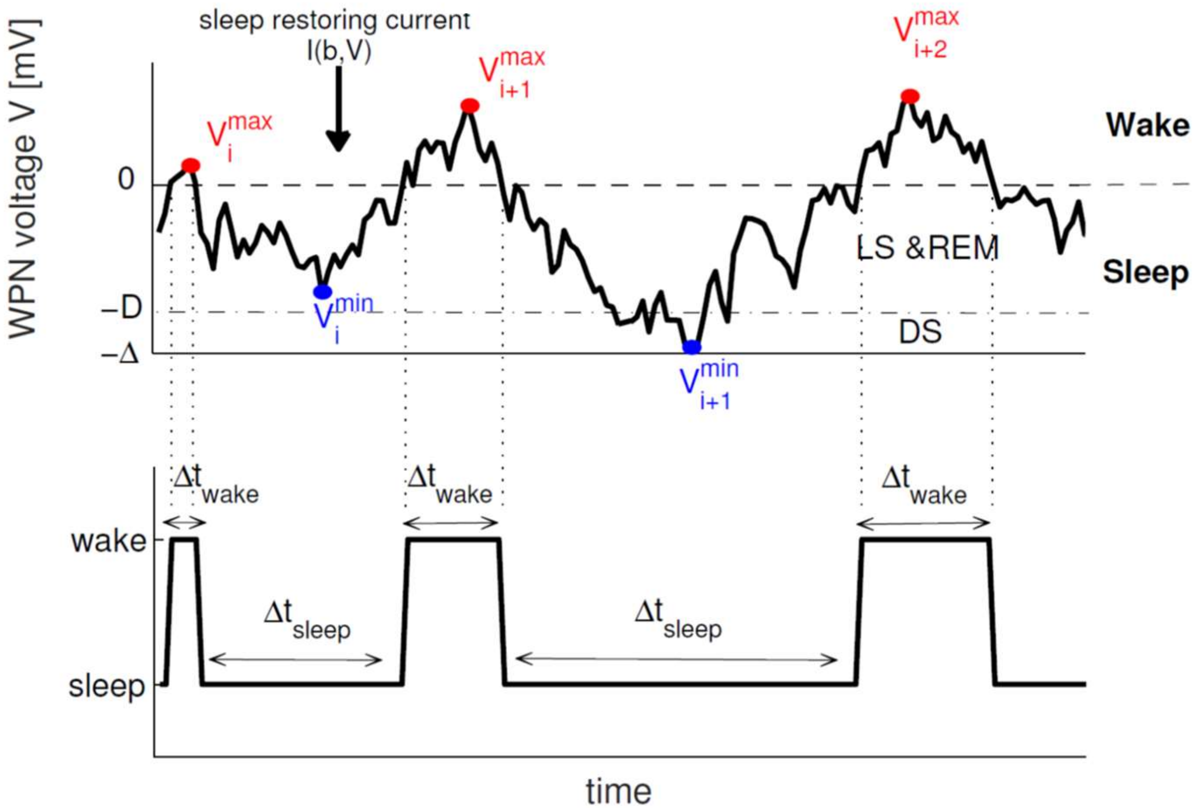
Modeling arousal dynamics: integrated neuronal noise of WPN can trigger arousal

Network of wake-promoting neurons (WPN)



Dvir et al., Science Advances 4, eaar6277 (2018)

Modeling arousal dynamics: integrated neuronal noise of WPN can trigger arousal



during sleep

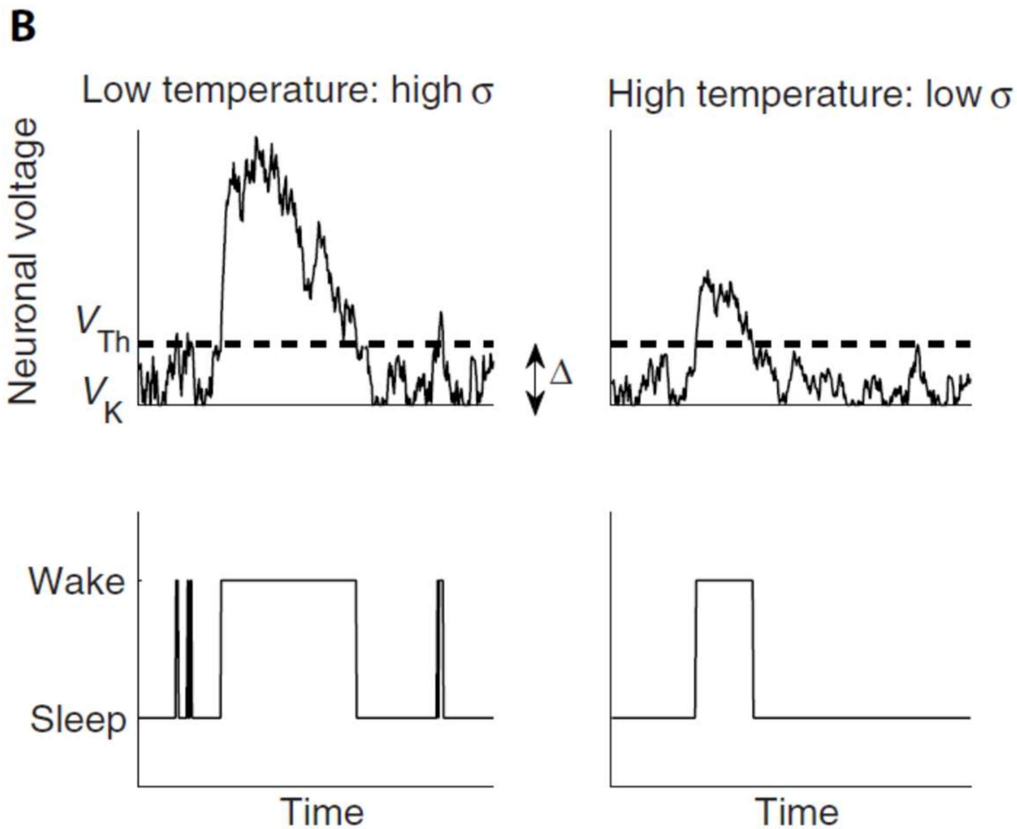
$$dV = \sigma \cdot dw \quad \text{for } -\Delta \le V < 0$$
$$V = -\Delta \quad \text{for } V < -\Delta$$

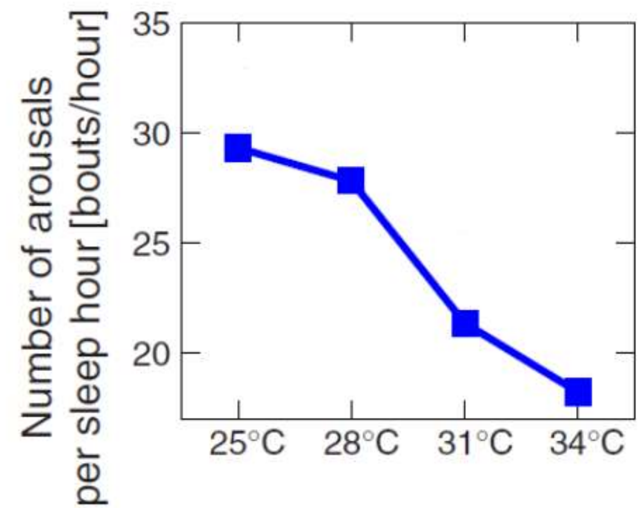
during arousal

$$dV = -\frac{b}{V+1} \cdot dt + \sigma \cdot dw, \ \text{for} V \ge 0$$

$I = -b \cdot C/(V+1)$ Sleep restoring current

Modeling arousal dynamics: lower temperature yields more arousals?





during sleep

$$dV = \sigma \cdot dw \quad \text{for } -\Delta \le V < 0$$
$$V = -\Delta \qquad \text{for } V < -\Delta$$

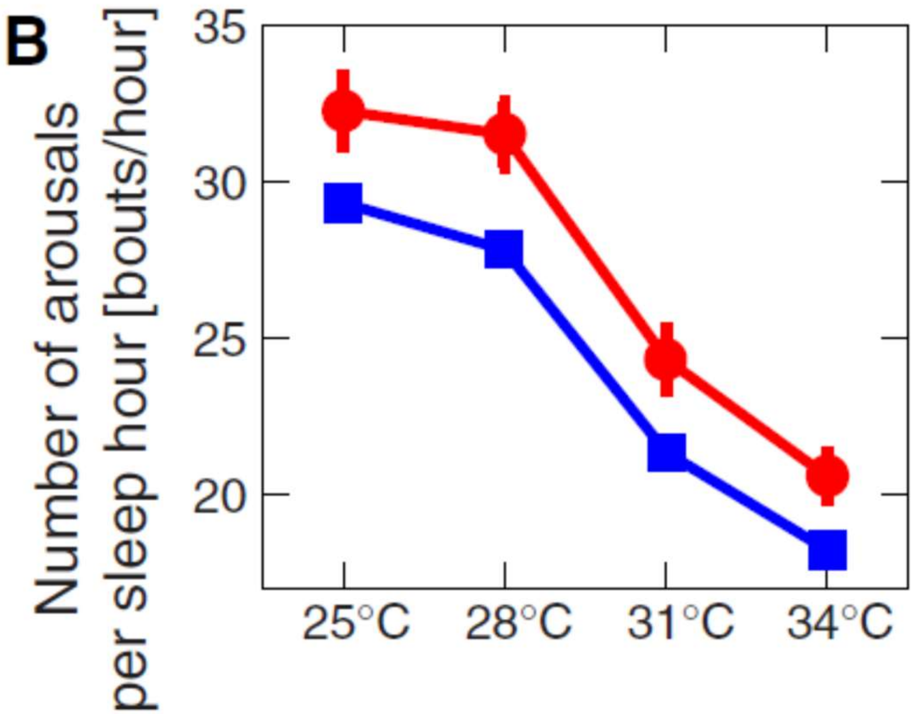
during arousal

$$dV = -\frac{b}{V+1} \cdot dt + \sigma \cdot dw, \ \text{for} V \geq 0$$

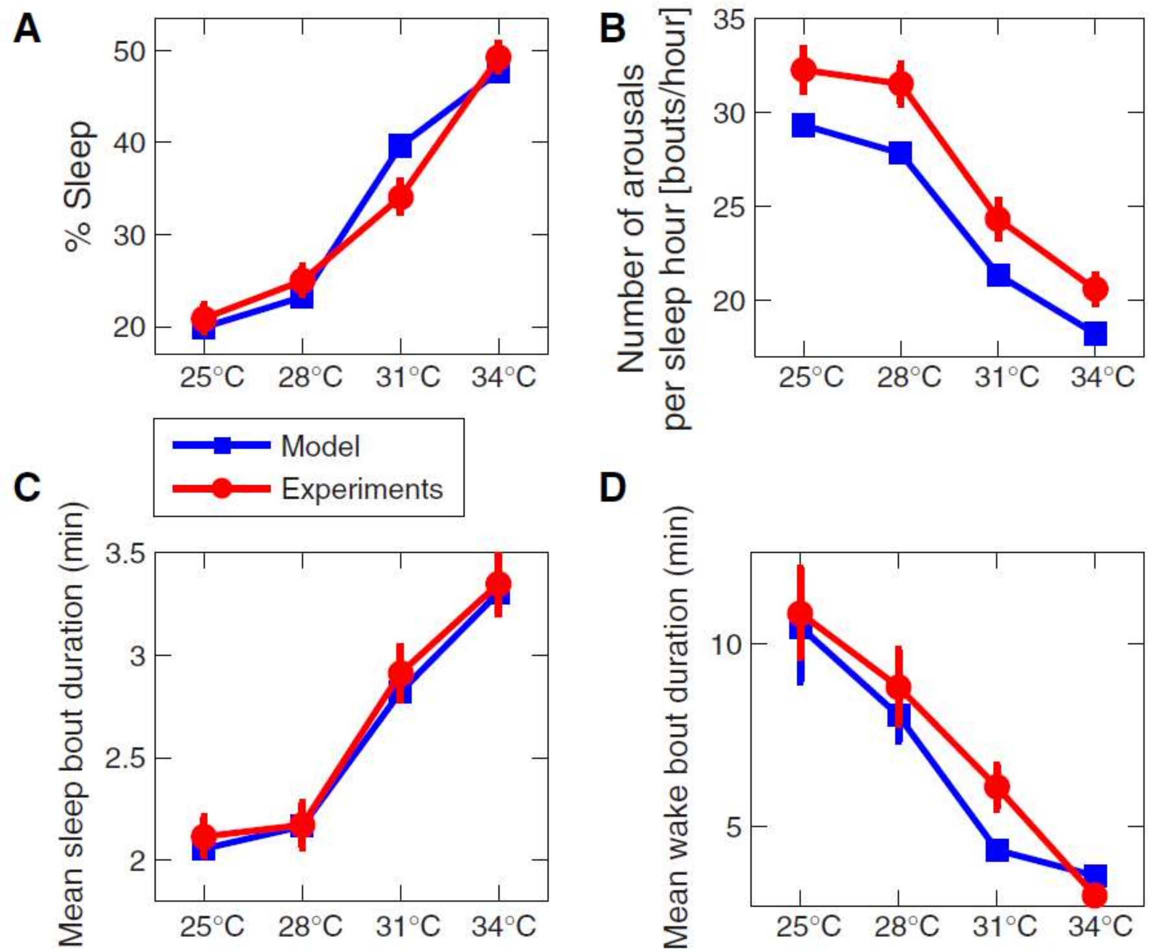
$I = -b \cdot C/(V+1)$ Sleep restoring current

How to test model prediction experimentally?

Experiment on fish!



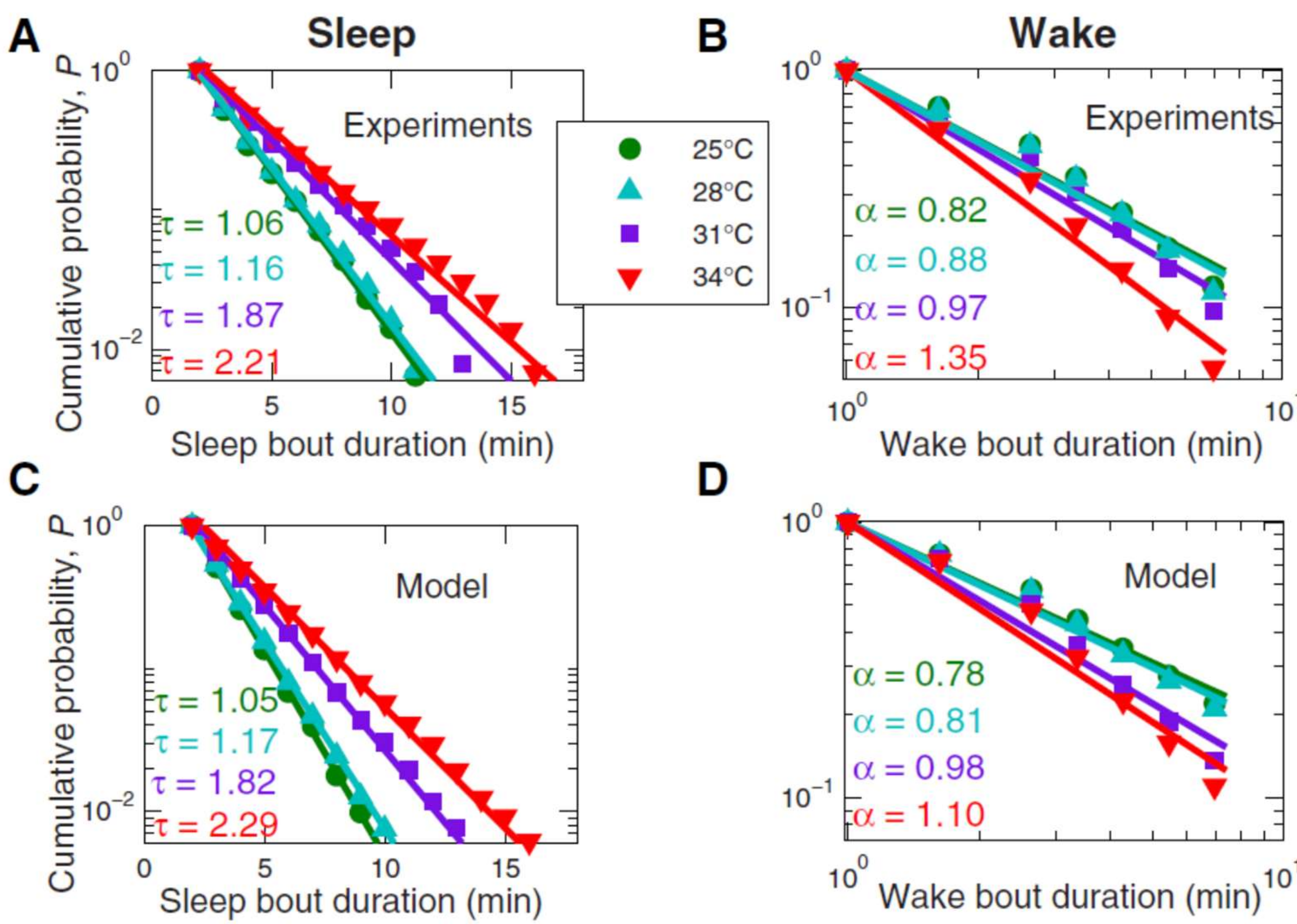
Modeling dynamics of sleep/wake transitions



• ***Model agrees with data for both wake and sleep intervals***

Dvir et al., Science Advances 4, eaar6277 (2018)

Modeling arousal dynamics: distribution of wake and sleep bout durations



τ (characteristic time of sleep bout duration) increases with Temp

α (power law exponent for wake bout durations) increases with Temp

Summary

• brief arousals are an integral part of healthy sleep regulation, and are found in mammalian and non-mammalian species

• arousal durations show power-law distribution (scale-invariant), sleep stage durations show exponential distribution (scale-specific)

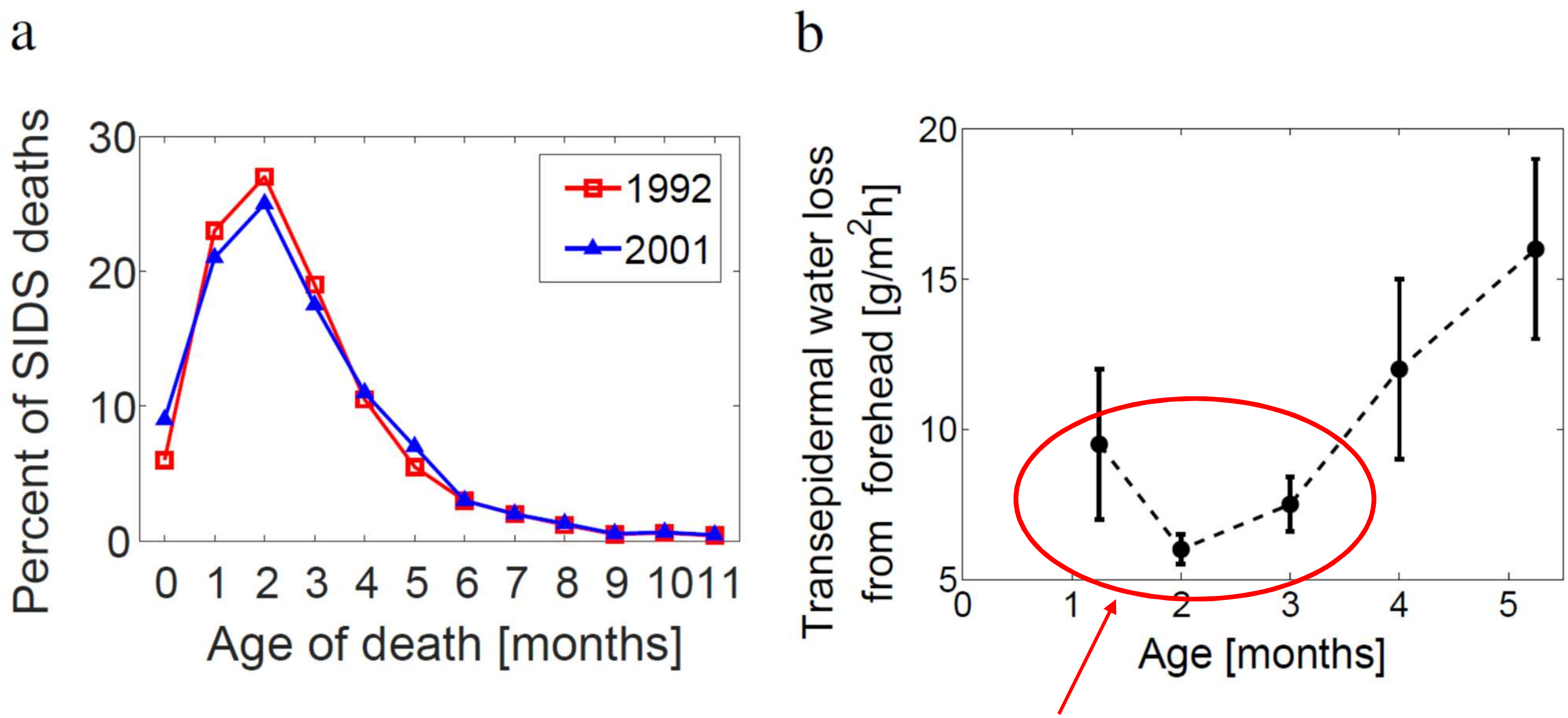
• accumulated neuronal subthreshold voltage fluctuations in wake-promoting neurons can possibly be an origin of spontaneous brief arousals during sleep

• arousal statistics changes with temperature (more arousals at lower temp) at least for ectothermic animals

Why do we care?

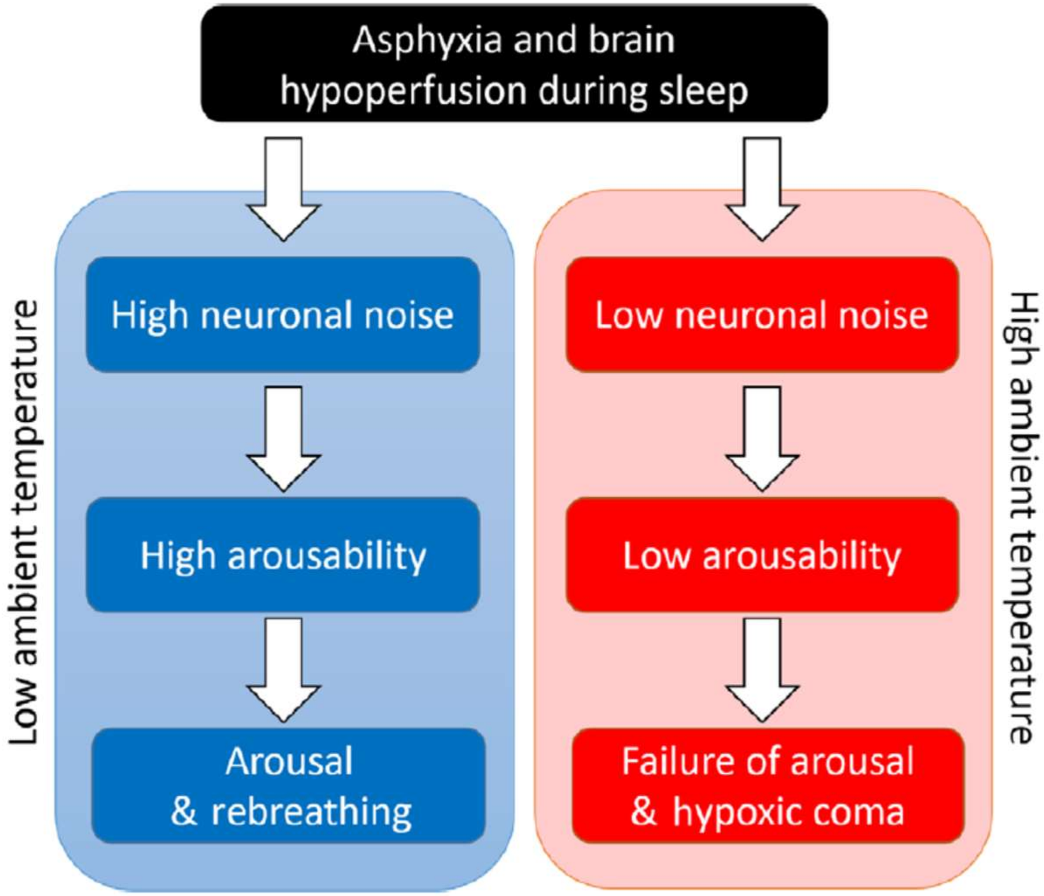
Significance

Sudden Infant Death Syndrome (SIDS)



Thermoregulation in very young infants not fully developed (show ectothermic traits similar to fish); more susceptible to higher ambient temperature and in higher risk for SIDS

Sudden Infant Death Syndrome (SIDS)



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