The role of network structure in circadian system adaptation

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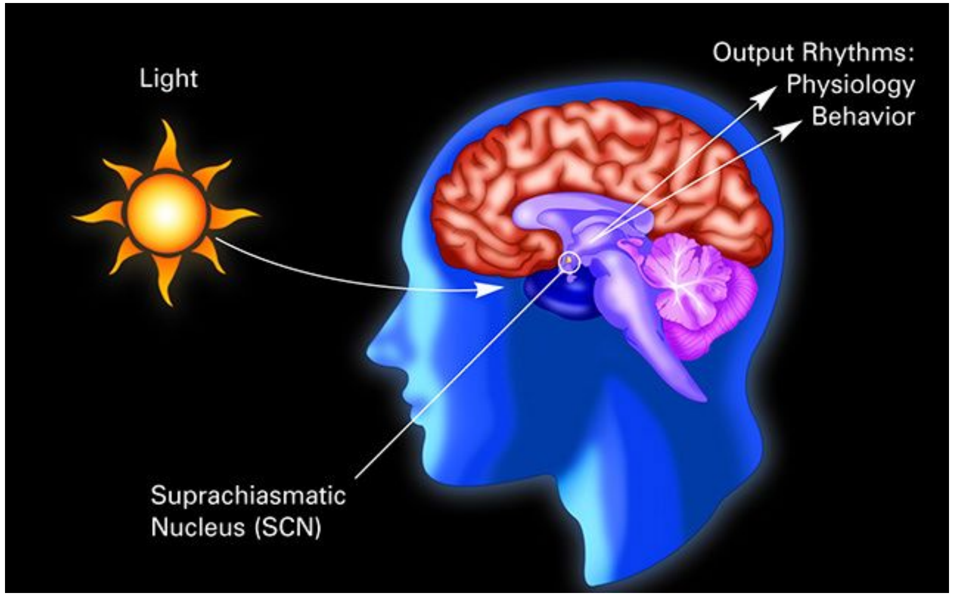
Background: the body keeps time

- Circadian rhythms: biological rhythms with period ~ 24 hours
- Robust: rhythms persist in constant conditions
- Almost every cell has its own molecular clock: feedback loops regulate biological clock proteins
- Adaptation to environment: **strongly influenced by light**



sunlight cues neuronal signals in the suprachiasmatic nucleus, the brain's master clock, which in turn coordinates biological clocks regulating functions throughout the body, and consequential behaviors

Source: NIGMS, National Institute of Health (USA)

Jet lag

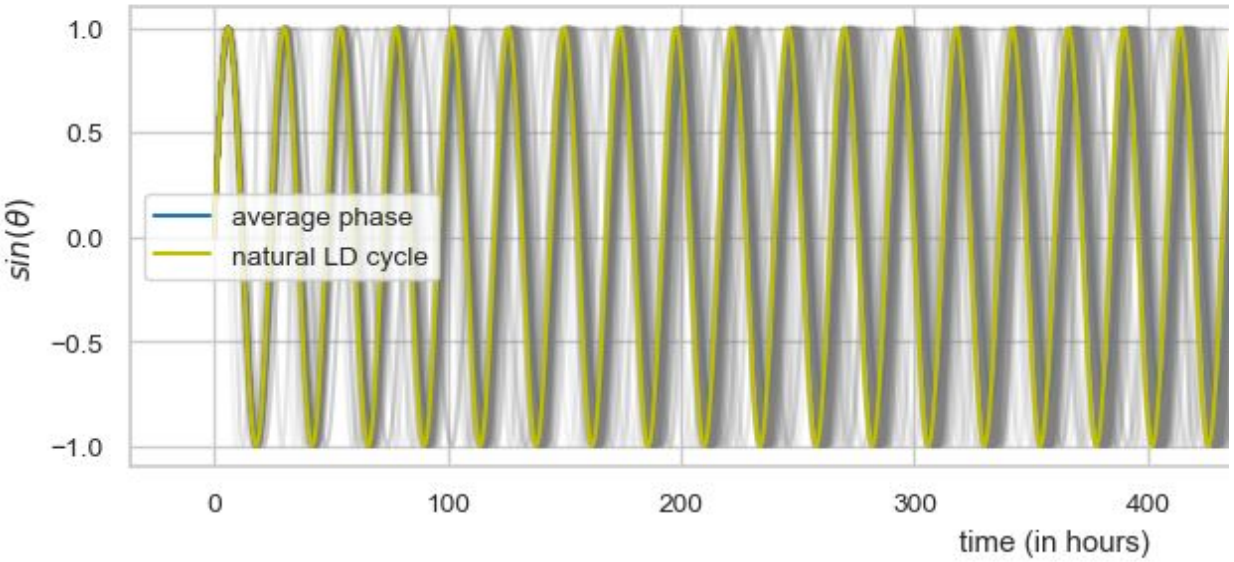
- The body clock adjusts gradually to the new time zone
- Severity increases with the number of time zones crossed
- **Recovery depends on direction: Eastward is more difficult on average**

Waterhouse, Jim, et al. The lancet (2007)

The SCN as a coupled oscillator network

A network of N coupled phase oscillators (forced Kuramoto model)

$$\frac{\mathrm{d}\theta_i(t)}{\mathrm{d}t} = \omega_i + \frac{K}{\sum_j^N A_{ij}} \sum_{j=1}^{N} A_{ij} \sin(\theta_j(t) - \theta_i(t)) + F \sin(\sigma t - \theta_i(t) + \tau \frac{2\pi}{24})$$



Phase of i^{th} oscillator = θ_i
Natural frequency of i^{th} oscillator = ω_i

σ = Frequency of the external drive
τ = time zones traveled
K = coupling strength

The SCN as a coupled oscillator network

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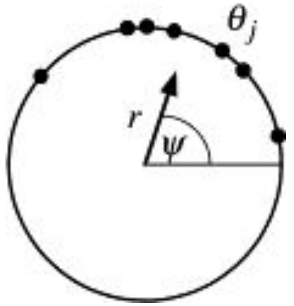
Order parameter are derived
from average vector z.
r = phase coherence,
Ψ = average phase.

$$z(t) = r(t) e^{i\psi(t)} = \sum_{j=1}^{N} e^{i\theta_j(t)}$$



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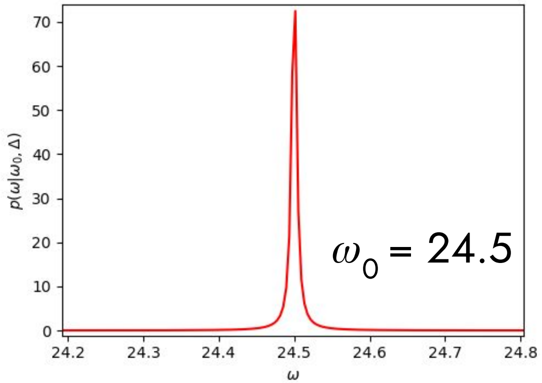
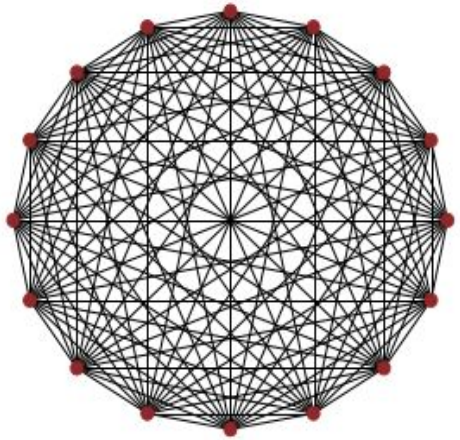


$$\Delta = 3.8 \times 10^{-3}\ (\mathrm{rad} \cdot \mathrm{h}^{-1}),$$

$$K = 4.5\Delta$$

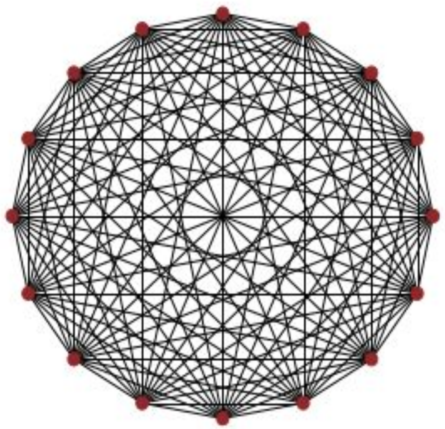
$$F = 3.5\Delta$$



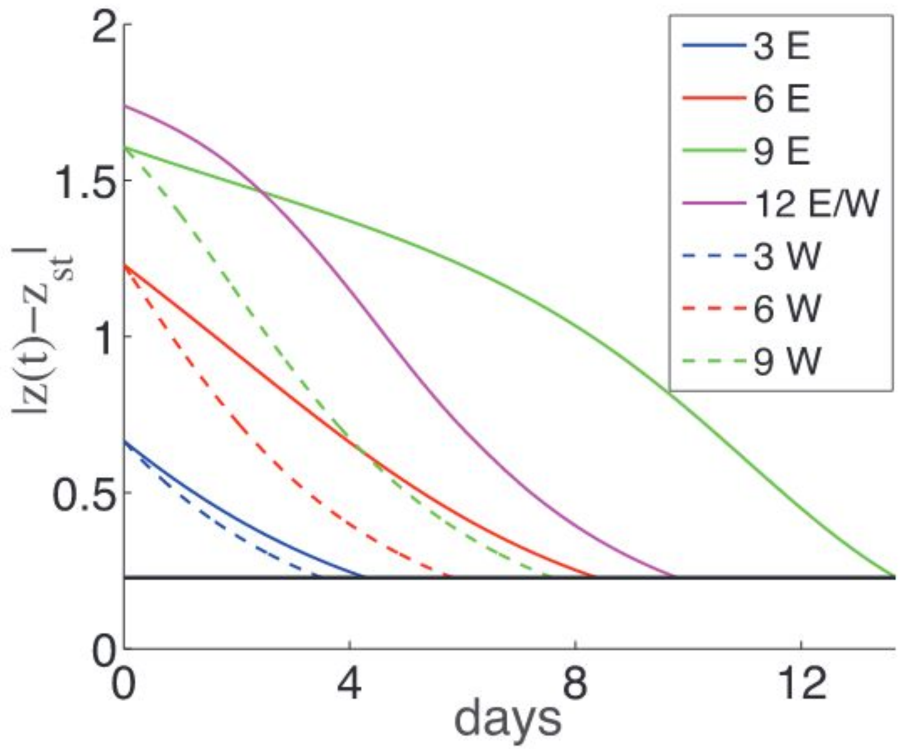
$$g(\omega) = \frac{\Delta}{\pi\left[(\omega - \omega_0)^2 + \Delta^2\right]}$$

Lu, Zhixin, et al. Chaos: An Interdisciplinary Journal of Nonlinear Science (2016)

Jet lag recovery: east-west asymmetry



All-to-all connected network



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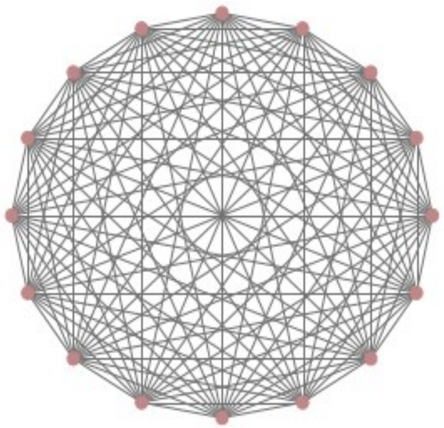
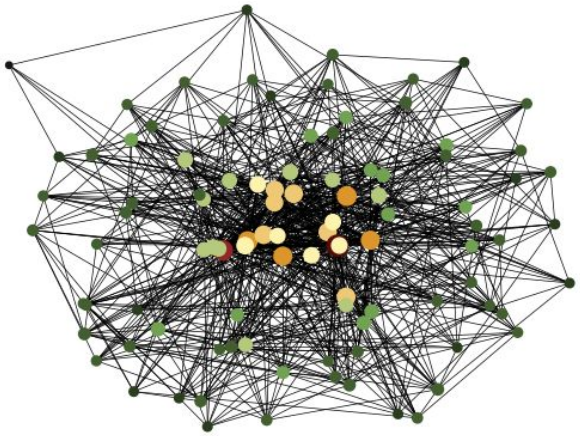
All connected network: realistic?



For circadian network:

- Density (ϱ) < 0.1 (estimate)



Gu, Changgui, et al. Frontiers in Physiology (2021)

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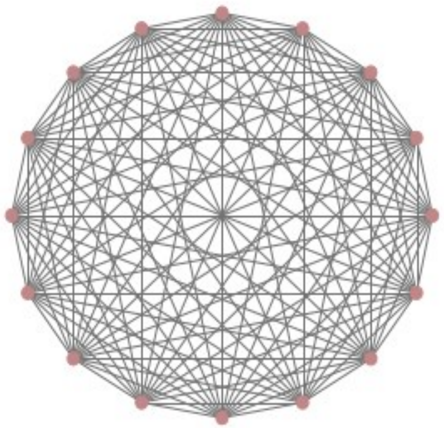

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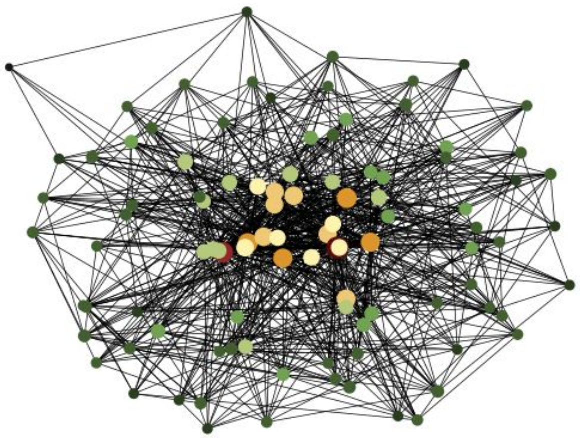
For circadian network:

- Density (ϱ) < 0.1 (estimate)
- Presence of hubs and hierarchical structure



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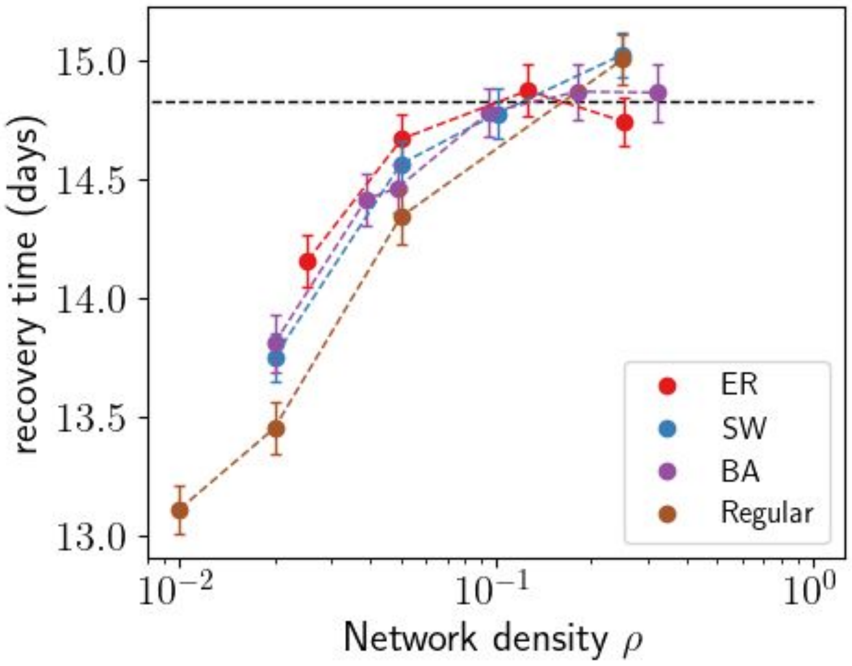
Gu, Changgui, et al. Frontiers in Physiology (2021)

Sparse vs dense: role of density

Sparse networks (ϱ < 0.1) take less time to re-entrain for larger time zone travels

shown on right: recovery times for travel of 10 time zones Eastward

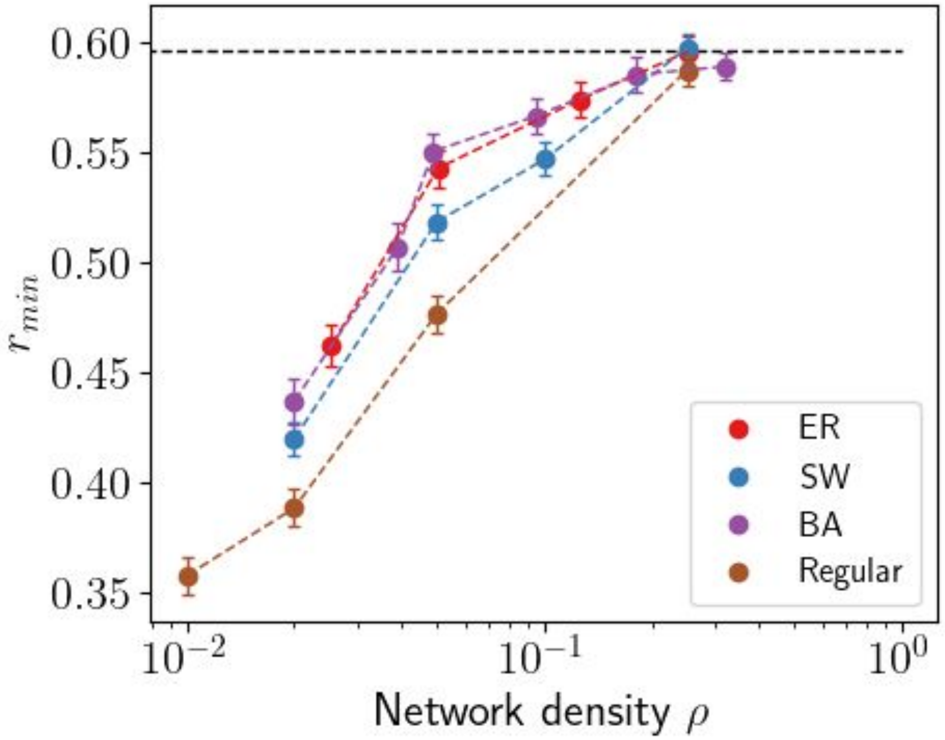


Recovery times for Erdős–Rényi networks (ER) networks, small world (SW) networks, Barabási–Albert networks (BA), and regular ring networks at different densities (ϱ)

Sparse networks: microscale structure

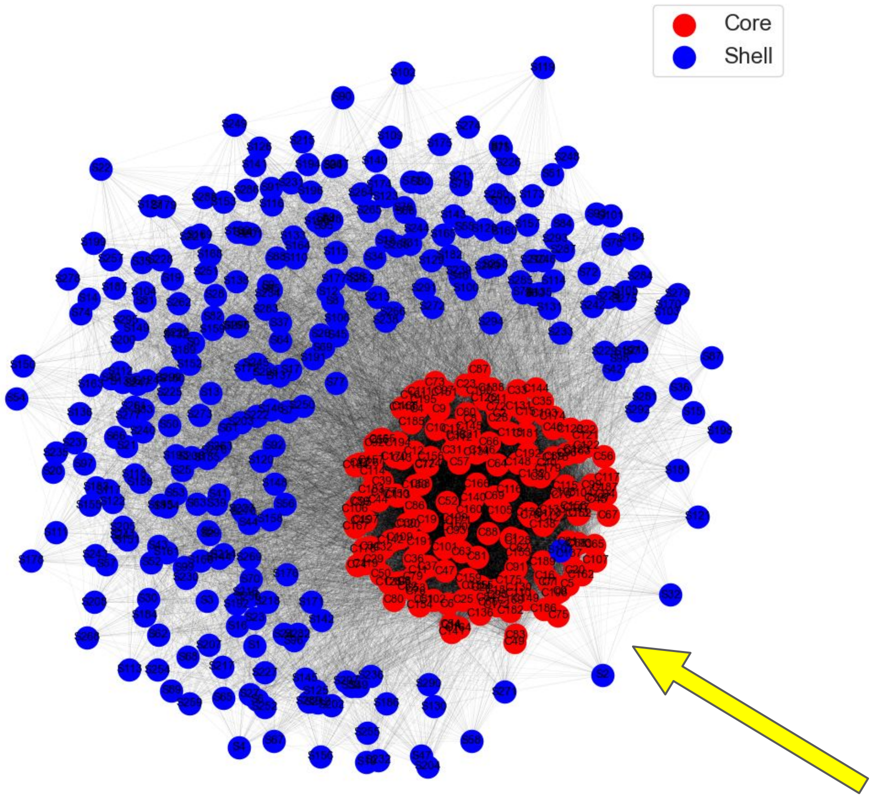
Sparse networks (ϱ < 0.1) show less phase coherence

shown on right: minimum phase coherence (r_{min}) for travel of 10 time zones Eastward



Minimum order parameter (r_{min}) for Erdős–Rényi networks (ER), small world networks (SW), Barabási–Albert networks (BA), and regular ring networks for different network densities

Experimental results: core-shell structure



$\varrho_{core} >> \varrho_{shell}$, $N_{core} < N_{shell}$

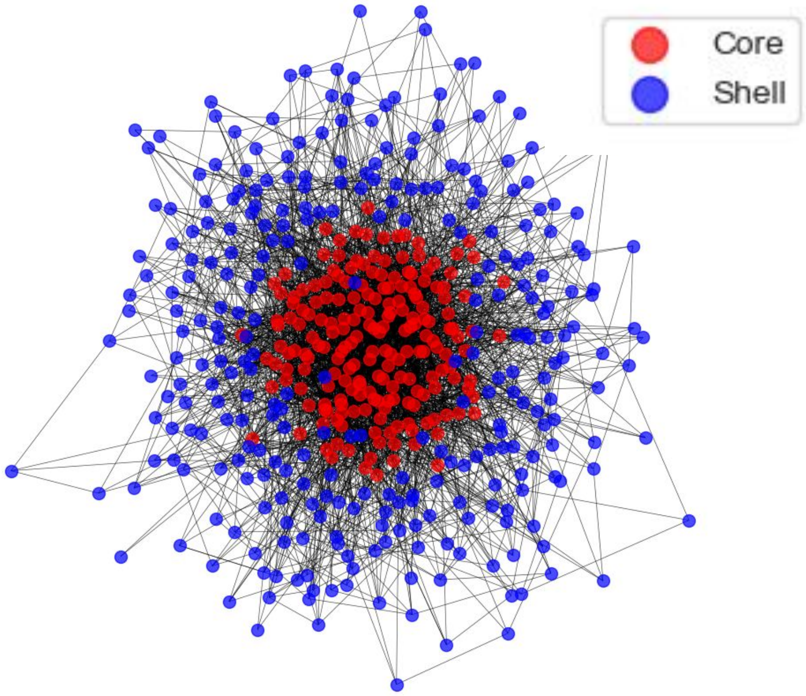
$F_{shell} = 0$

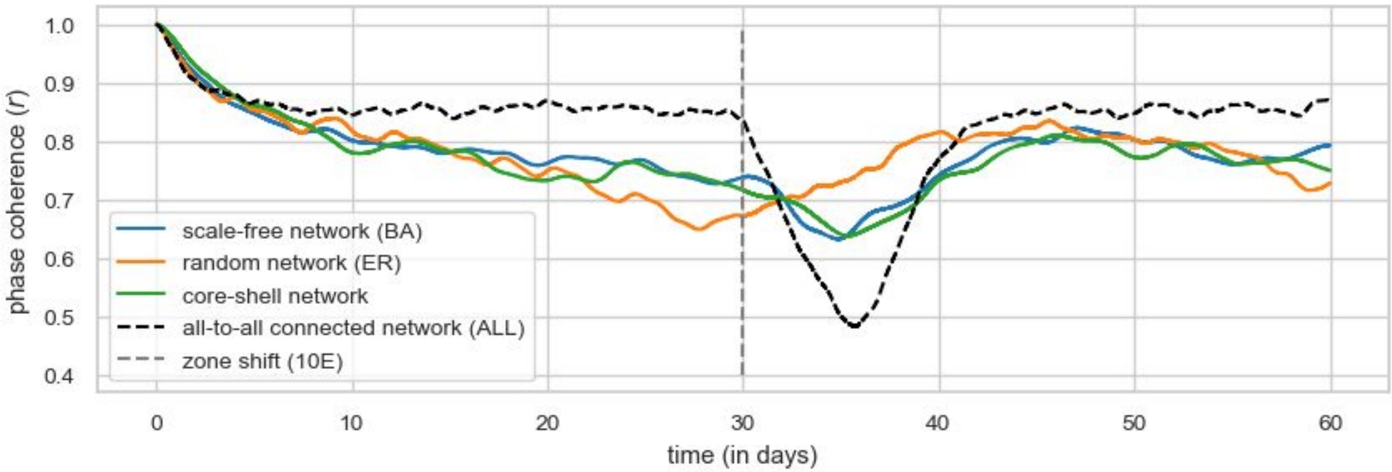
Only the core receives light input

(Based on bioluminescence studies)

Kim, Hyun, et al. *PLoS Computational Biology* 18.6 (2022): e1010213.

Core-shell structure adapts efficiently



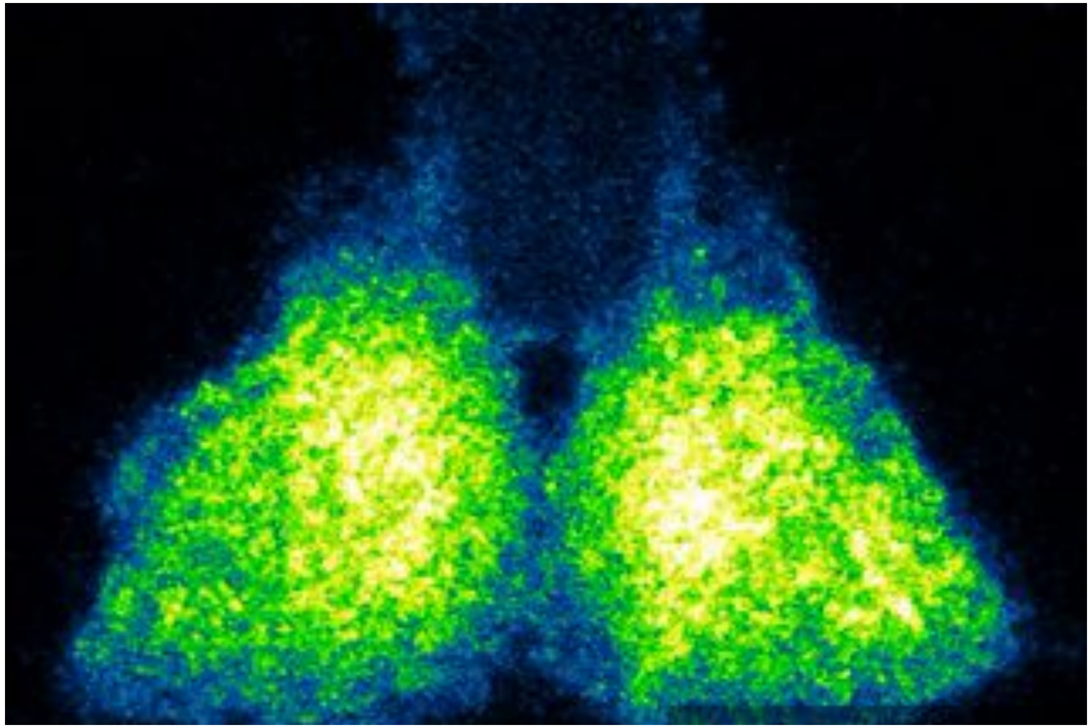


$\varrho_{CS} = 0.05,\ \varrho_{SS} = 0.05,\ \varrho_{CC} = 0.375$

More to be done!

Kim, Hyun, et al. *PLoS Computational Biology* 18.6 (2022): e1010213.

Summary and takeaways



Circadian rhythm of PER2::LUC bioluminescence recorded from cultured mouse SCN neurons over a period of several days. credits: Joseph Takahashi lab at UT Southwestern, Dallas, Texas.

- Realistic models of central circadian network suggest sparse structure
- Sparse networks take slightly less time for recovery on average, BUT have lower phase coherence ($|z| < 0.5$)
- Efficient recovery requires a balance: Core-shell structure
- Next: fine-tuning, dynamical network

Northwestern University

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SIMONS FOUNDATION

NSF

Thank you!

Questions?

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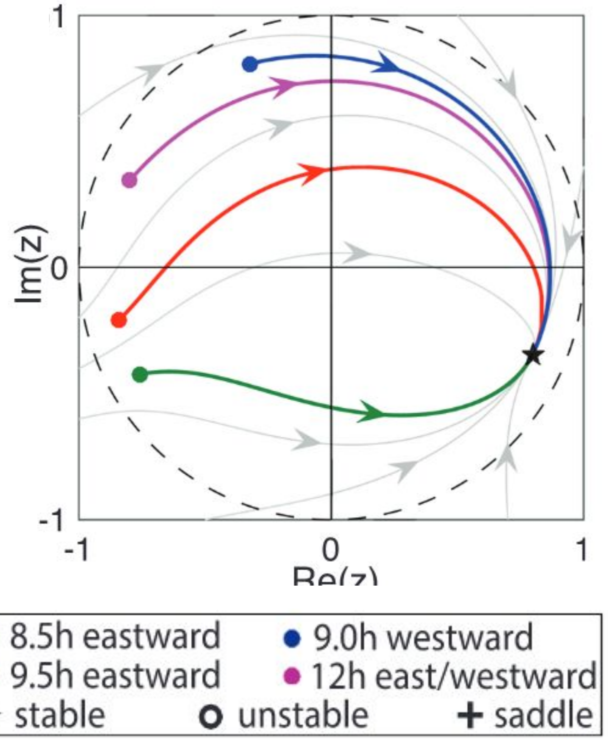
2. Lu, Z., Klein-Cardeña, K., Lee, S., Antonsen, T. M., Girvan, M., & Ott, E. (2016). Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag. Chaos: An Interdisciplinary Journal of Nonlinear Science, 26(9).
3. Gu, Changgui, Jiahui Li, Jian Zhou, Huijie Yang, and Jos Rohling. "Network structure of the master clock is important for its primary function." Frontiers in Physiology 12 (2021): 678391.

Modeling jet lag recovery



$$\dot{z} = \frac{1}{2}\left[(Kz + F) - z^2(Kz + F)^*\right] - (\Delta + i\Omega)z,$$

Deviation from full recovery is given by

$$|z(t) - z_{st}|$$

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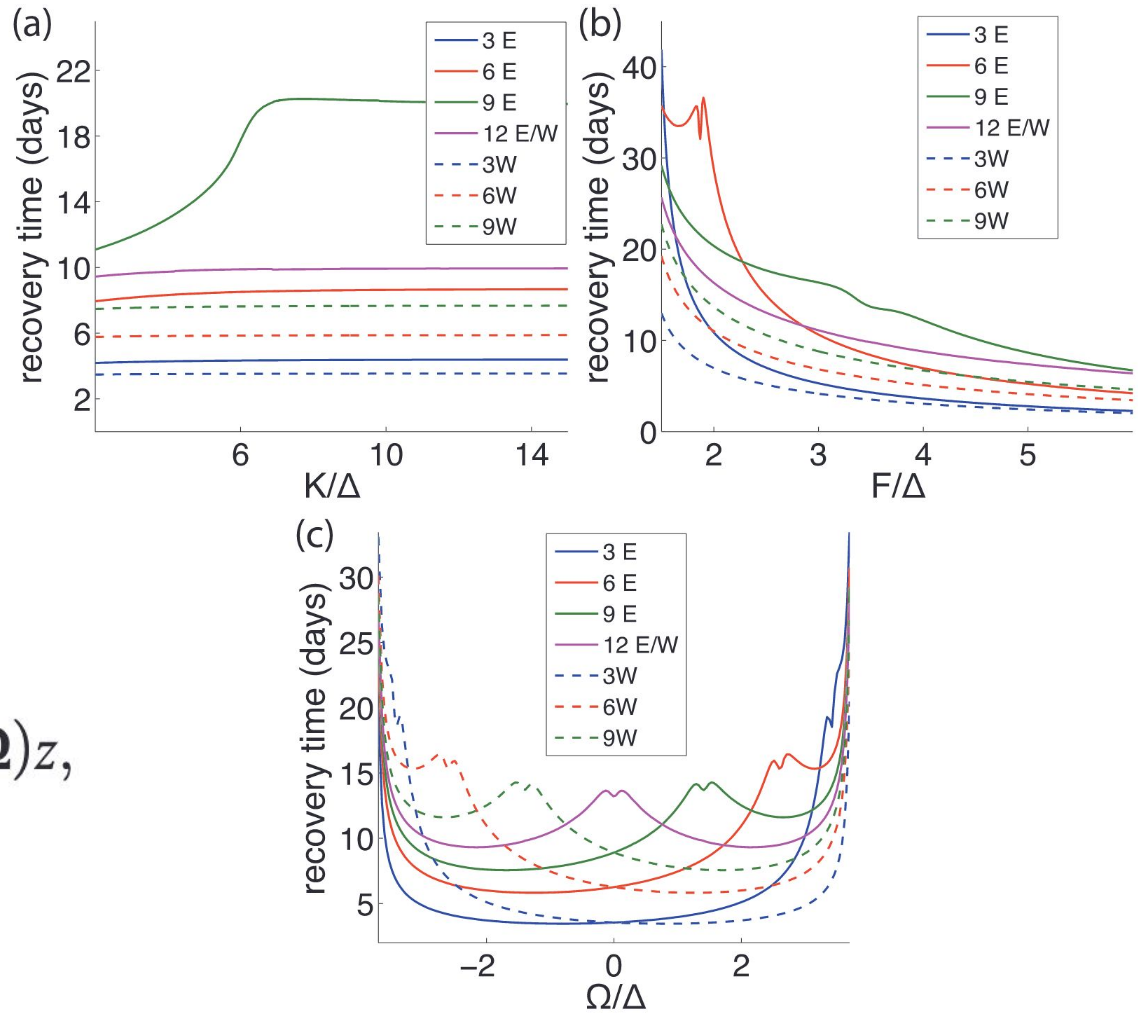

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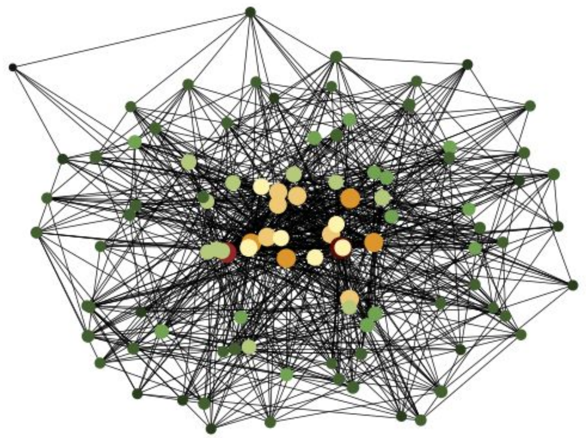
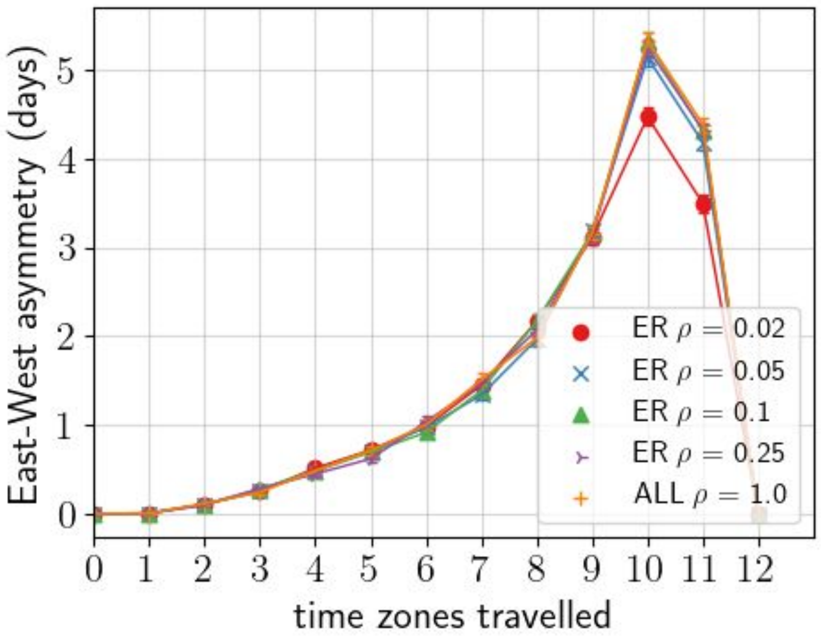


Dense networks (ϱ > 0.1) show similar levels of East-West asymmetry as fully connected network



asymmetry in recovery times in the Erdős–Rényi networks at different ϱ