Resynchronization of Circadian Oscillators and the East-West Asymmetry of Jet-Lag

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Collaborators:

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- Tom Antonsen
- Ed Ott

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TREND
Training and Research Experiences in Nonlinear Dynamics

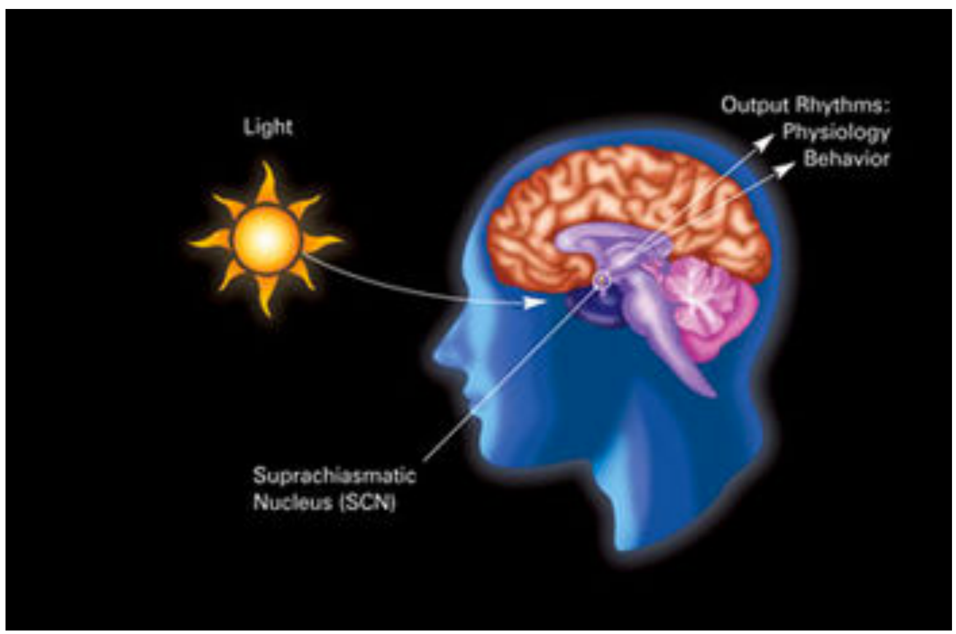
Overview

- **Goal:** Gain insights into the how circadian rhythms respond to long distance travel
- **Approach:** Model synchronization of circadian oscillators using the forced Kuramoto model; apply dimension reduction techniques for tractability
- **Applications and extensions:** Devise better strategies for combating jet-lag; guide the formulation of more accurate models.

Lu, Klein-Cardeña, Lee, Antonsen, Girvan, and Ott. "Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag." *Chaos* (2016).

Background: Suprachiasmatic Nucleus

- Region of hypothalamus know to regulate circadian rhythms
- Consists of ~10^4 neuronal pacemaker cells
- Synchronization of these cells is important for maintenance of healthy circadian rhythms

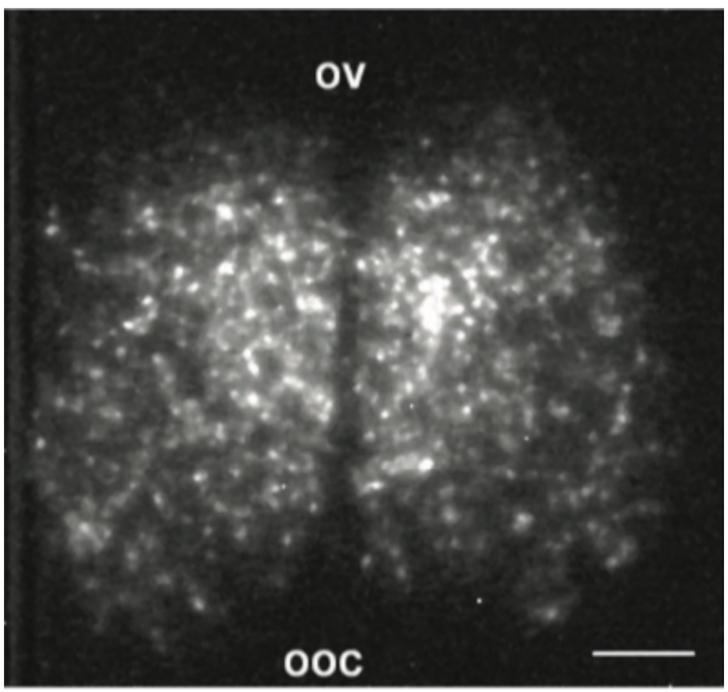


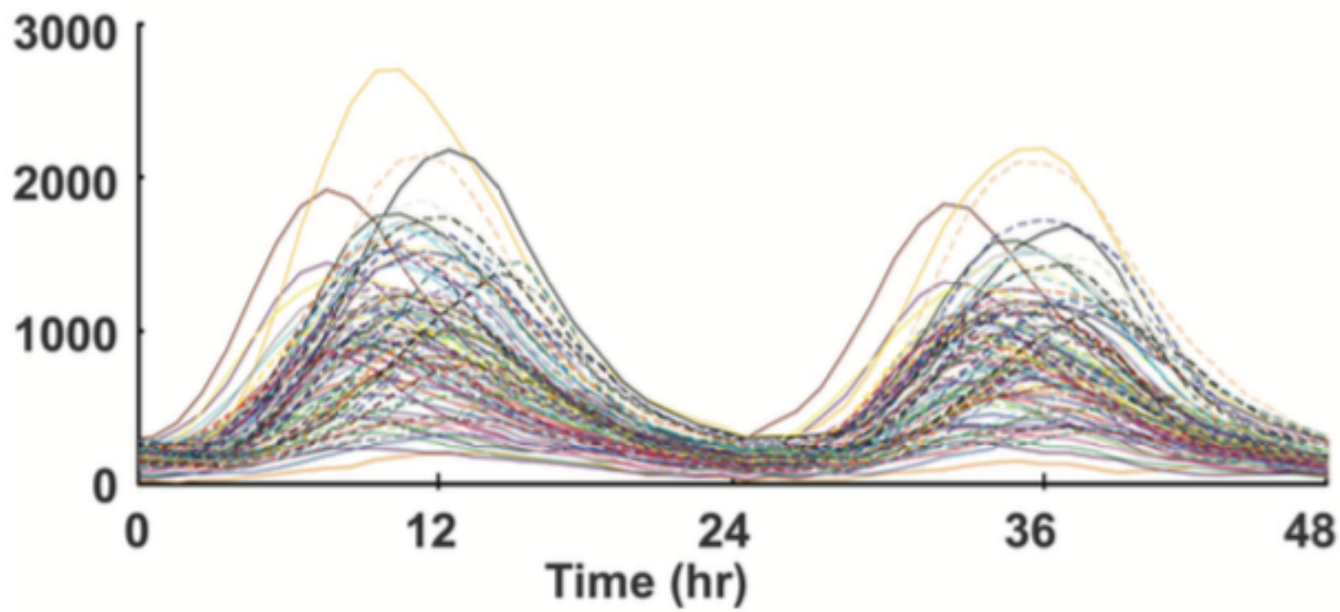
from Wikipedia

Synchronization with no external drive

- Each of ~10^4 neurons oscillates in a synchronized way with period ~24 hours.
- Oscillations reflect changes in expression levels of mPre1 protein or firing rate
- Synchronization happens even *without* external drive.

SCN of Mice





Yamaguchi, et al. *Science* 2003

Kuramoto model for SCN with no drive

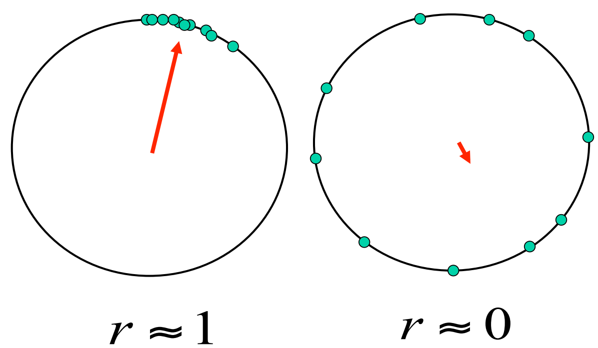
The classic Kuramoto model with all-to-all coupling:

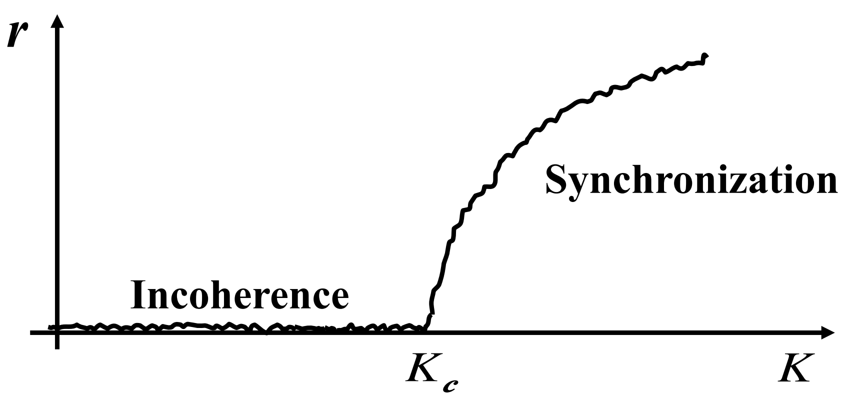
$$\dot{\theta}_i = \omega_i + \frac{K}{N}\sum_{j=1}^{N}\sin\left(\theta_j - \theta_i\right)$$

Here ϑ_i is the phase of oscillator i and ω_i is its frequency, which is distributed according to some pdf.

Complex order parameter:

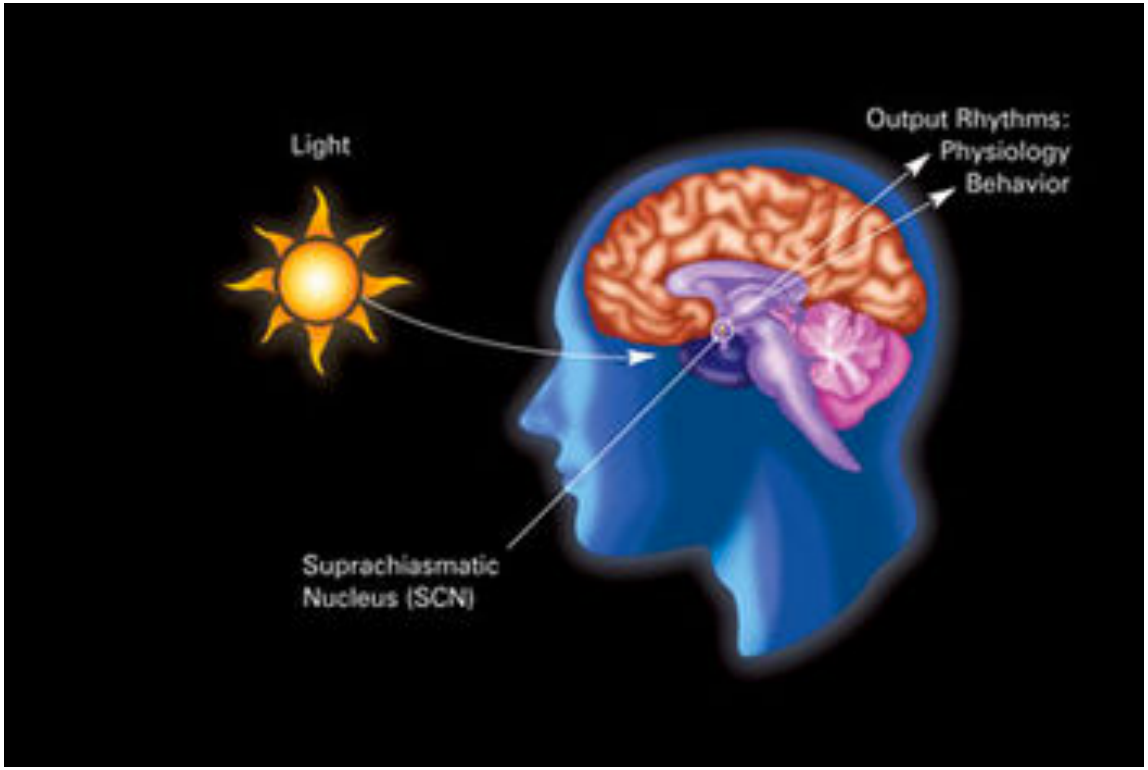
$$re^{i\psi} = \frac{1}{N}\sum_{j=1}^{N} e^{i\theta_j}$$





- If the frequency spread is too large compared to coupling strength K → incoherence
- Onset of synchronization takes at critical value of K, which depends on the distribution of frequencies

Synchronized *and* Entrained



- Neurons in SCN are not only synchronized but also entrained to the 24 hr/day external day-night cycle
- We need a model with external driving force (e.g., light, meals, your alarm clock, etc.)

Modeling recovery from jet-lag

- Jet-lag, also called desynchronosis, results from disruption of the body's circadian rhythms due to rapid long-distance travel
- People report more severe jet-lag after traveling eastward than westward.
- We use the Kuramoto model with external drive to study recovery from jet-lag

Forced Kuramoto Model

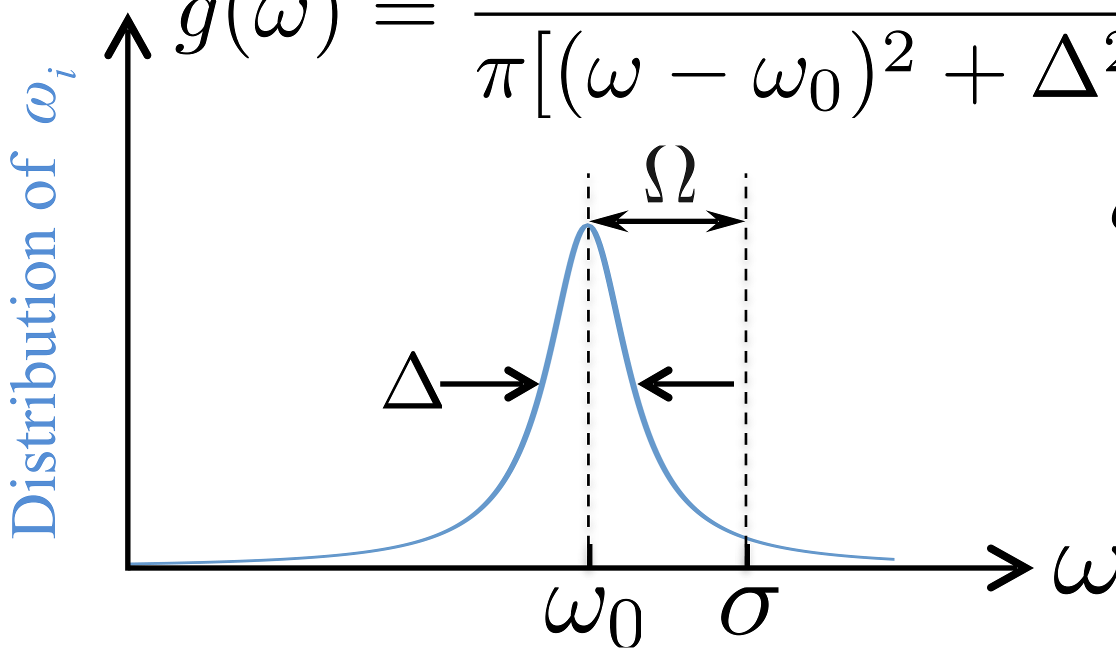
$$\frac{d\theta_i}{dt} = \omega_i + \frac{K}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i) + F\sin(\sigma t - \theta_i + \phi)$$

natural frequency

coupling from other neurons

24hr periodic external driving with phase shift ϕ

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



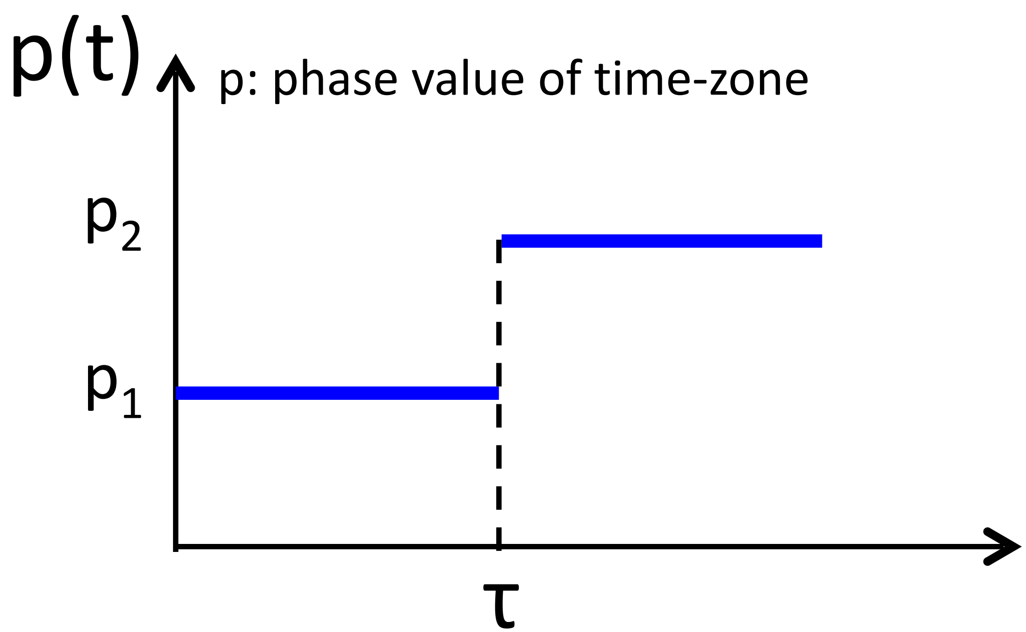
$$\sigma = \frac{2\pi}{24}(\mathrm{hr})^{-1}$$

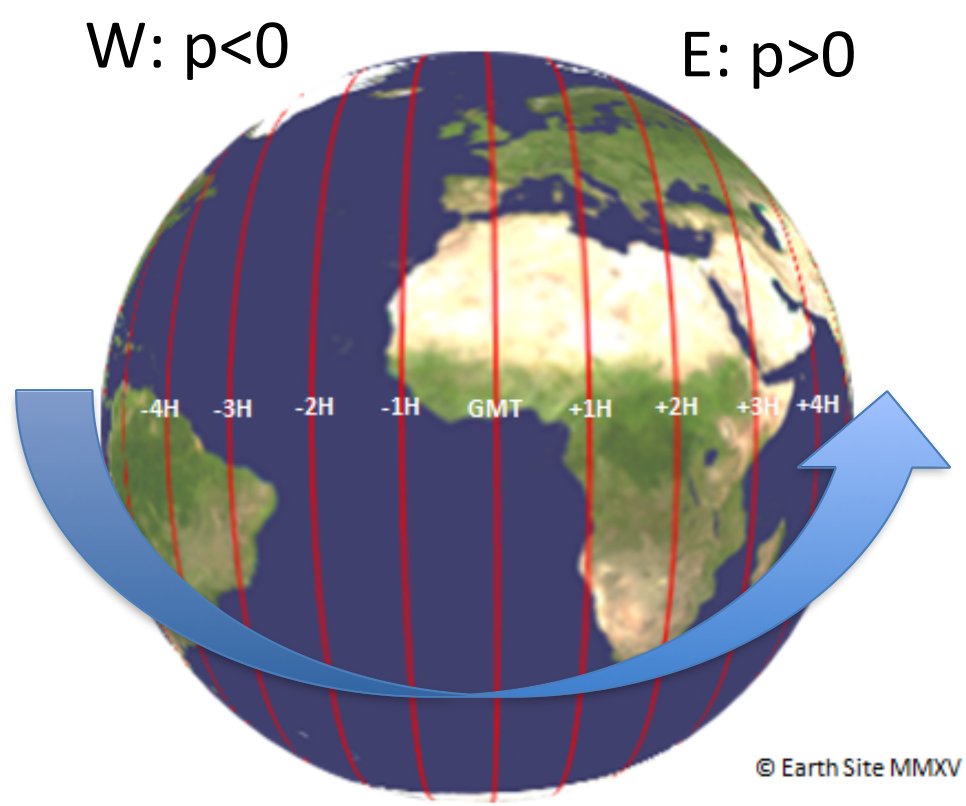
Antonsen, Faghih, Girvan, Ott, and Platig, *Chaos* (2008)
Childs and Strogatz, *Chaos* (2008)

Studying Jet-lag with the Forced Kuramoto Model

$$\frac{d\theta_i}{dt} = \underbrace{\omega_i}_{\text{natural frequency}} + \underbrace{\frac{K}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i)}_{\text{coupling from other neurons}} + \underbrace{F\sin(\sigma t - \theta_i + p(t))}_{\text{24hr periodic external driving @ time-zone } p}$$

Approximation for high-speed travel:



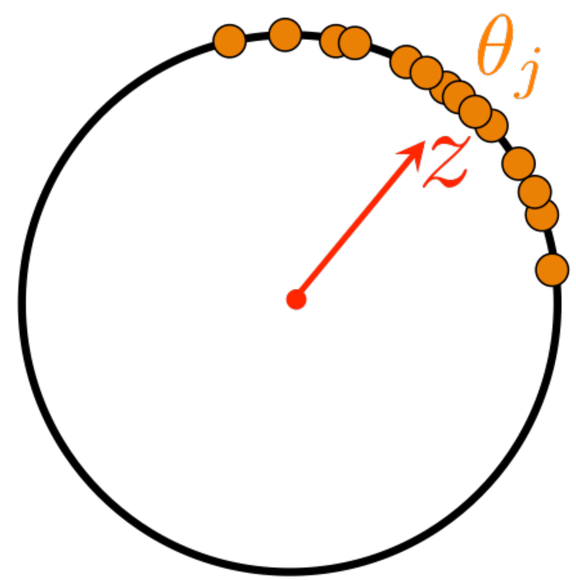


Modeling Jet-lag

$$\frac{d\theta_i}{dt} = \underbrace{\omega_i}_{\text{natural frequency}} + \underbrace{\frac{K}{N}\sum_{j=1}^{N}\sin(\theta_j - \theta_i)}_{\text{coupling from other neurons}} + \underbrace{F\sin(\sigma t - \theta_i + p(t))}_{\text{24hr periodic external driving @ time-zone } p}$$

Order parameter z:

$$z = \frac{1}{N}\sum_{j=1}^{N} e^{i[\theta_j(t) \underline{-\sigma t - p(t)}]}$$



$$z(t) \to z^* \text{ : entrained state}$$

Discontinuous change of order parameter due to fast travel:

$$z(\tau^+) = z(\tau^-)e^{-i(p_2 - p_1)}$$

Dimension Reduction Technique:
Ott-Antonsen Ansatz

- Take the continuum limit, N ➞ ∞
- System described by time-dependent distribution of oscillator phases and frequencies, $f(\theta,\omega,t)$
- Ott-Antonson ansatz postulates a particular form of $f(\theta,\omega,t)$ which allows us to write down a differential equation for the order parameter:

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

K : coupling strength
F : driving strength
Δ : frequency distribution spread
Ω : frequency difference

$$\frac{2\pi}{24} - \omega_0 = \Omega$$

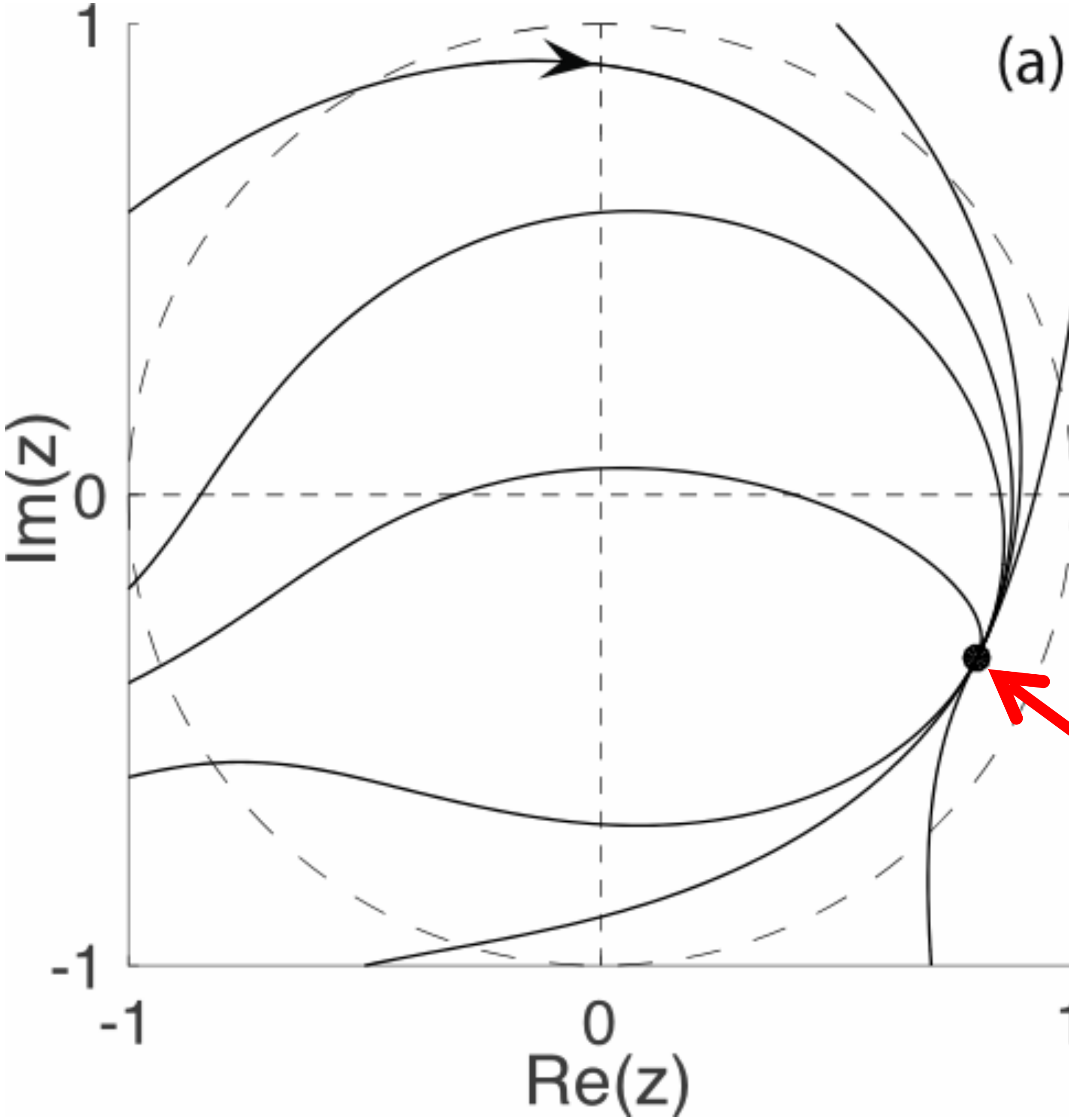
Three Types of Re-entrainment Diagrams

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

- **Type A:** Only one fixed point (stable)
- **Type B:** An attracting limit cycle
- **Type C:** Three fixed points (one stable, one unstable, and one saddle)

By dividing the whole equation by Δ, only three parameters: K/Δ, F/Δ, and Ω/Δ, affect the phase diagram.

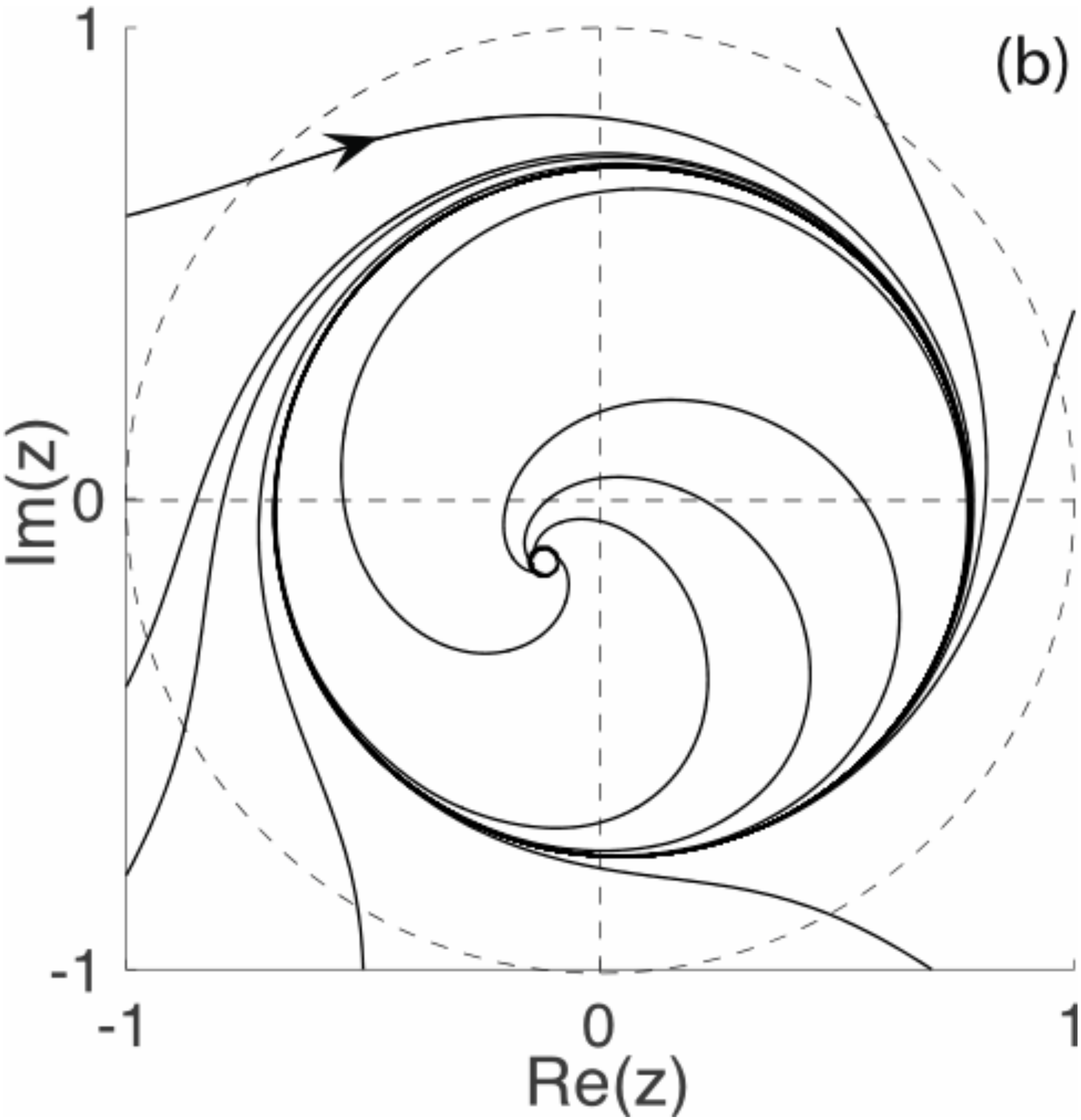
Type A Dynamics



$$K = 4.5\Delta,$$
$$F = 3.5\Delta,$$
$$\Omega = 1.4\Delta.$$

Entrained state z*

Type B Dynamics

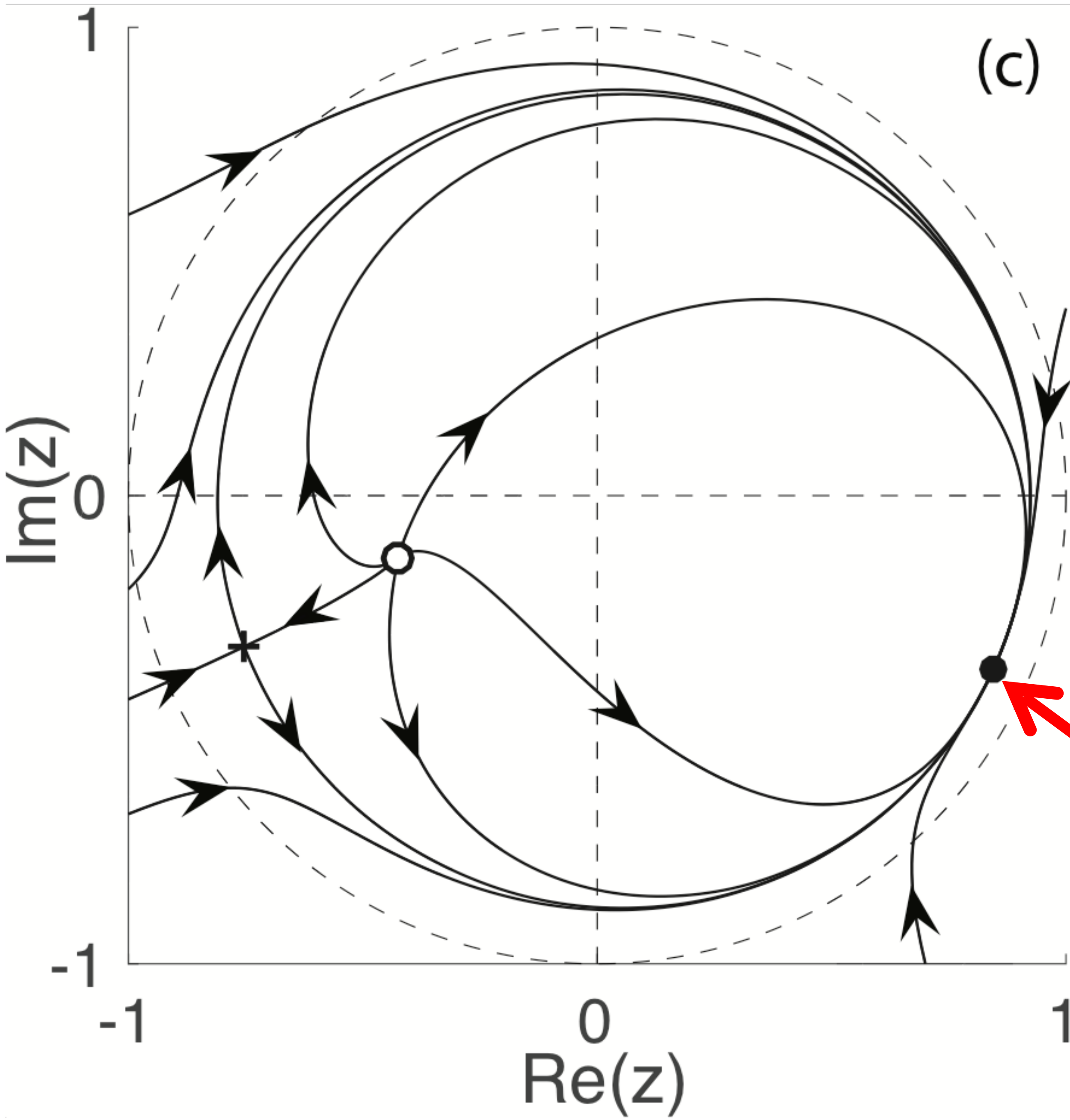


$$K = 4.5\Delta,$$
$$F = 0.65\Delta,$$
$$\Omega = 1.4\Delta.$$

A->B Hopf bifurcation

No entrained state

Type C Dynamics

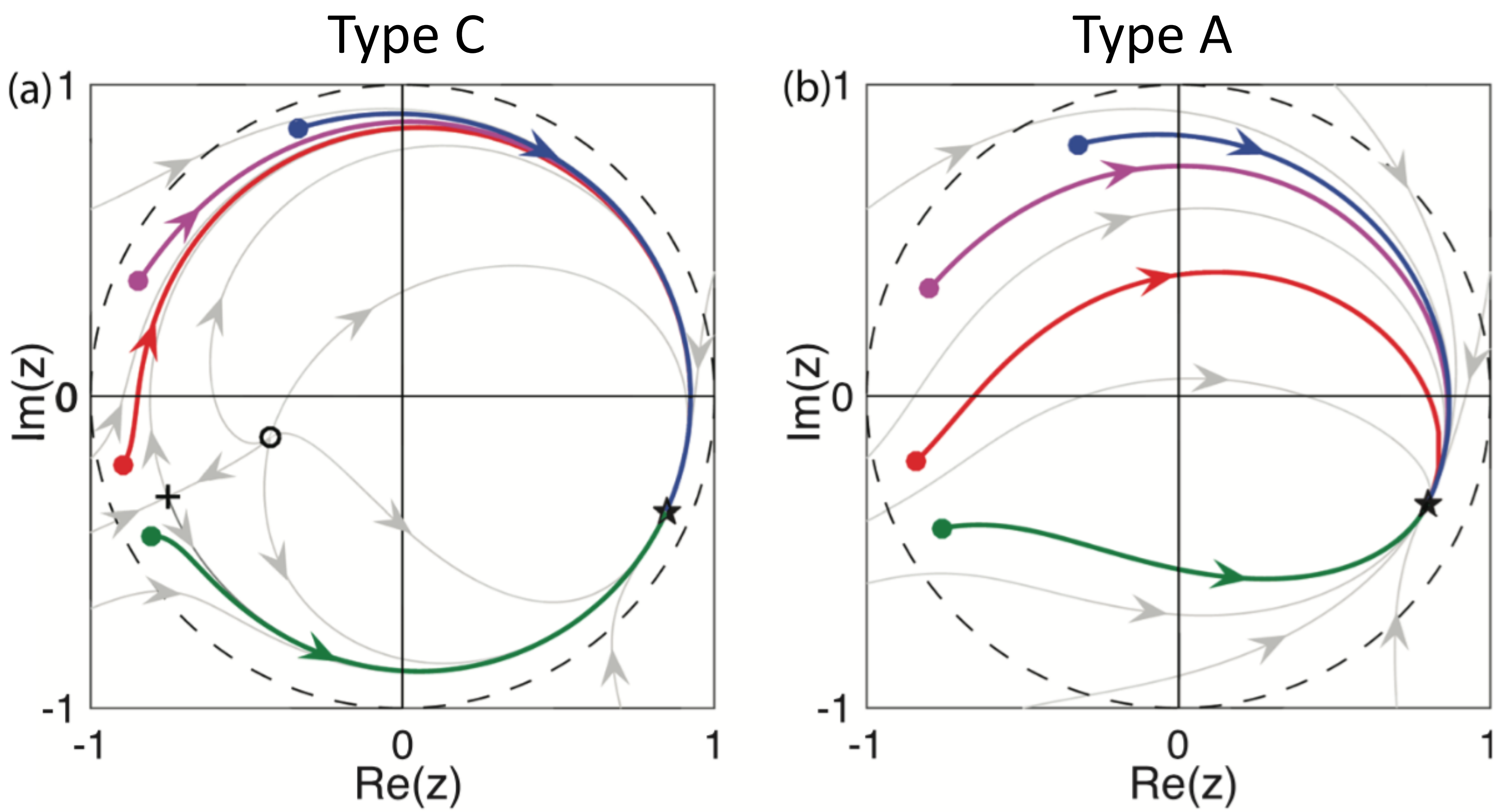


$$K = 10\Delta,$$
$$F = 3.5\Delta,$$
$$\Omega = 1.4\Delta.$$

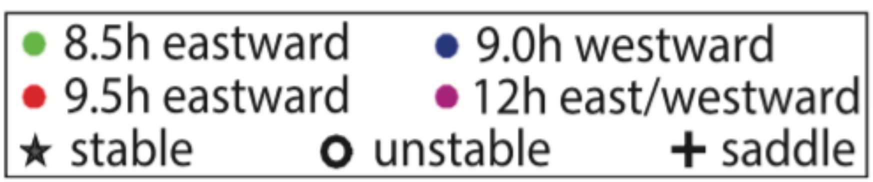
Entrained state z*

East-West Asymmetry of Jet-lag

Visualizing relaxation to the fixed point for slightly different parameter sets



Start at fixed point for pre-travel time-zone; end at new time-zone fixed point



Eastward travel over 9 time-zones corresponds to the border of the phase advancing/delaying recoveries.

Estimating model parameters

- Oscillators should be able to synchronize even when F=0 (based on experimental studies of individuals without external drive)
- Experiments suggest that the period of individual circadian oscillators is slightly longer than 24 hours (around 24.5 hours)
- Studies suggest that phase readjustments are about 1 hour/day for eastward travel and 1.5 hours/day for westward travel

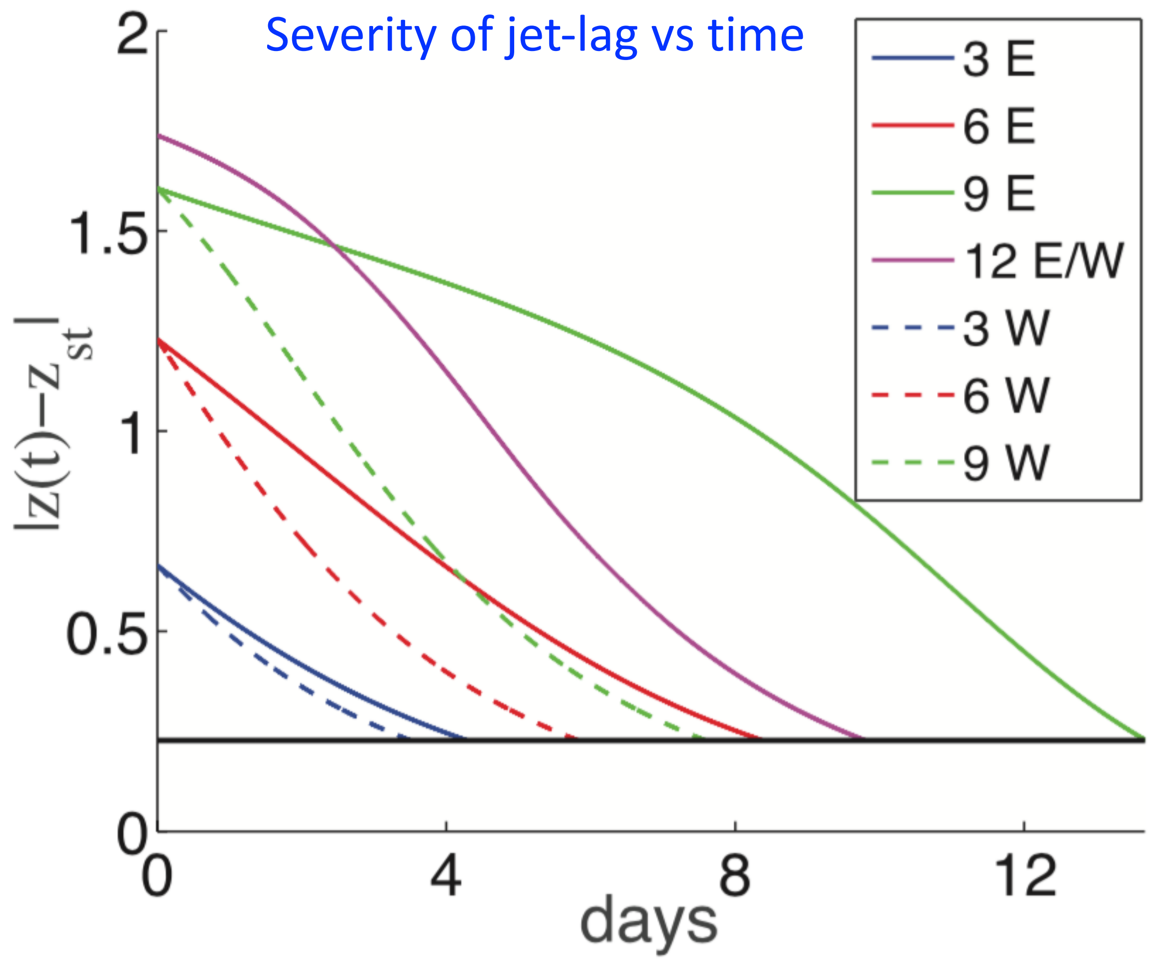
Recovery Curves for Typical Individual

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

$$\Omega = 1.4\Delta = 2\pi/24 - 2\pi/24.5,$$

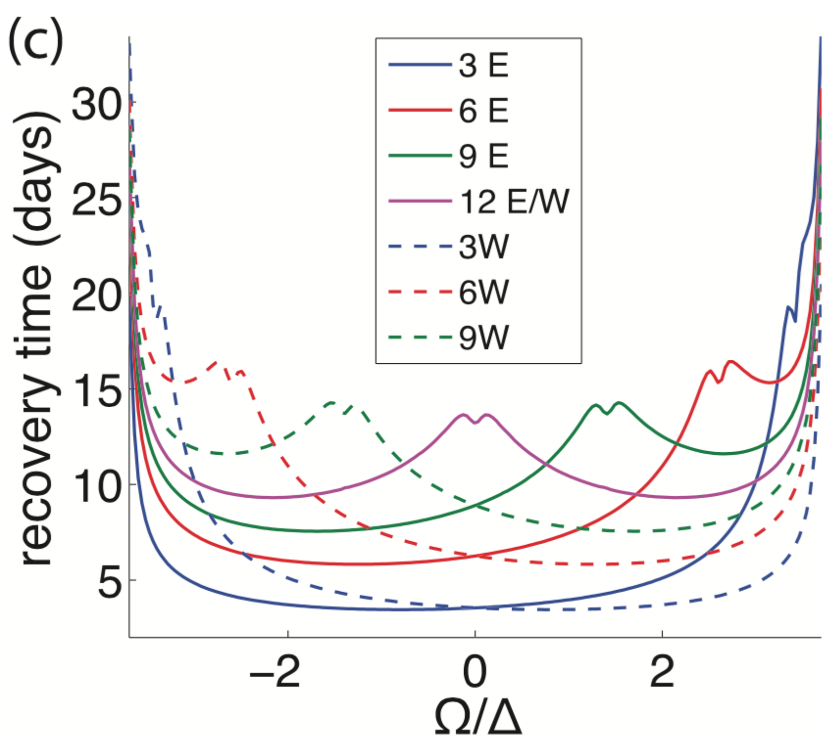
$$K = 4.5\Delta,$$

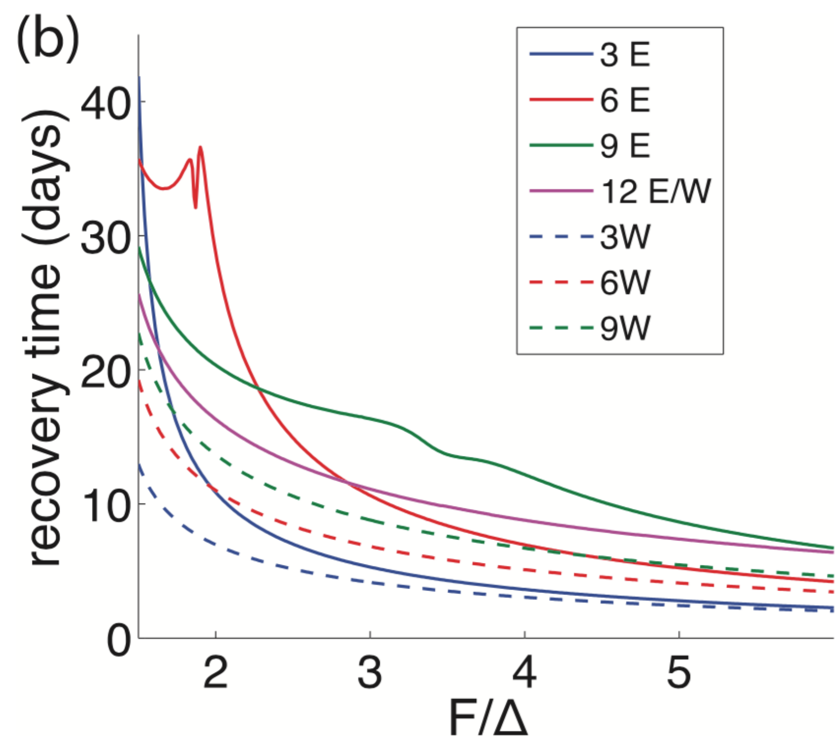
$$F = 3.5\Delta,$$



Slightly longer than 24 hour natural period leads to large asymmetries in recovery times for eastward vs. westward travel. Model helps explain the dynamics of this effect.

Parameter Dependence





Eastward worse than westward because natural period is slight longer than 24 hours (Ω>0).

Advice: Try to increase F (e.g, get sunshine, limit artificial light at night, use alarm clocks thoughtfully)

Closing Thoughts

- **Summary:** Analyzing the forced Kuramoto model gives us insights into nonlinear dynamics of jet-lag recovery. Natural period *slightly* > 24 hours → *Large* East-West asymmetry of jet-lag
- **Advantages of our approach:**
  - Captures the microscopic dynamics of interacting pacemaker cells
  - Reducible to a low-dimensional macroscopic description
  - Provides a dynamical understanding of the East-West asymmetry of jet-lag
- **Future directions:**
  - More realistic phase oscillator descriptions
  - Incorporating heterogeneous connectivity patterns
  - Better estimates of model parameters

Lu, Klein-Cardeña, Lee, Antonsen, Girvan, and Ott. "Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag." *Chaos* (2016).

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J. J. Potterat et al, Sexually Transmitted Infections, 78 (2002). Pp. i159-i163