Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag

Lu et al, 2016

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Biological Motivation

What are circadian rhythms?

The Circadian Clock

Circadian rhythms are 24-hour cycles determining periodicity in various physiological processes, including nervous system activity and hormone production, which influences sleeping and feeding patterns. These rhythms are regulated by endogenous networks of gene activity and can be modulated by changes in the environment, such as sunlight and temperature.

Source: *www.kevincredible.com*

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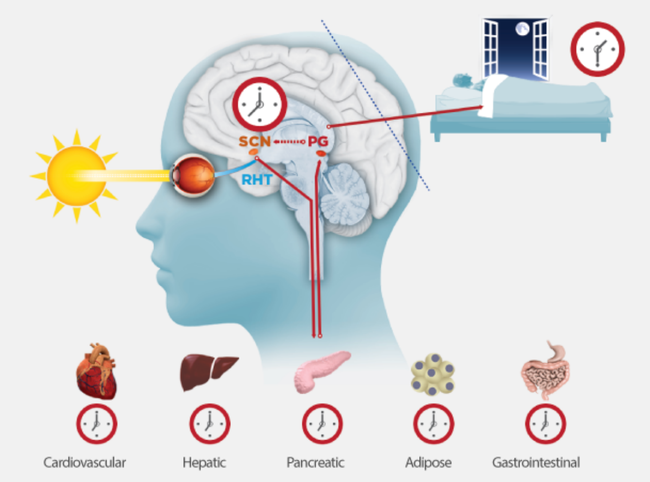
Where is the pacekeeper



[1]

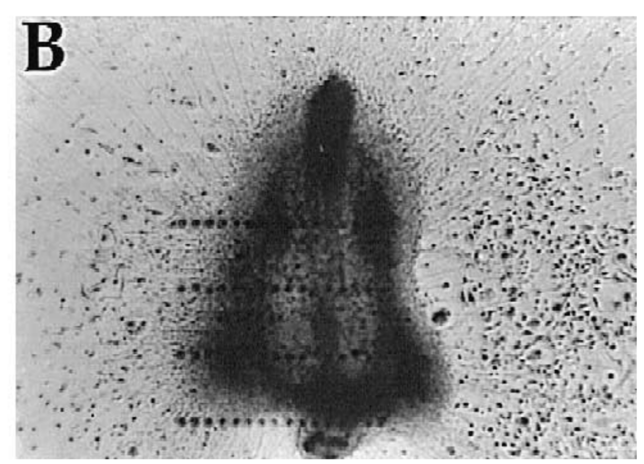
[1] https://www.non-24pro.com/physiology-of-non-24.php

Perspective: A tale of 2 clocks

Some observations of the endogenous circadian regulator

- "... a molecular model has emerged to explain the behavioral phenotype found in Clock mutants, but the physiological link between genes and behavior is lacking." *Herzog et al, 1998*
- " Classic work ... has shown that the SCN are both necessary and sufficient for the generation of circadian activity rhythms in rodents" *Mohawk et al, 2012*
- "However, when the SCN population is coupled, the effects of these mutations are non-cell autonomous. This occurs as a consequence of the intercellular coupling in the SCN network, which is capable of rescuing a cell autonomous defect in the individual cell" *Mohawk et al, 2012*

Measuring the SCN



Herzog et al, 1997

Measuring the SCN

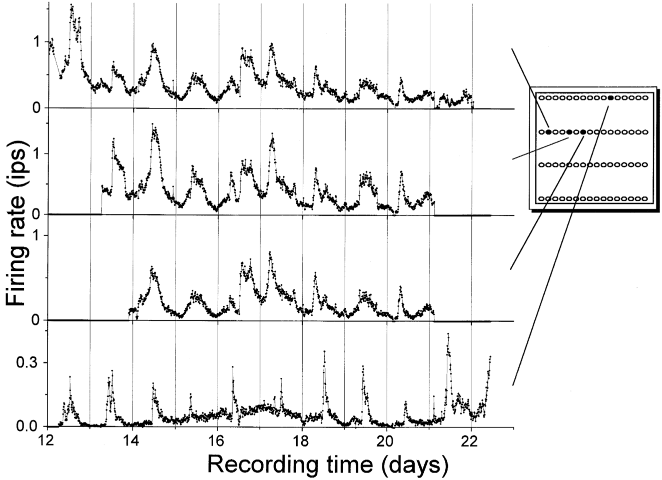


Fig. 4. Four SCN cells in the same explant recorded on 4 electrodes exhibit circadian rhythms in firing rate that are in phase with each other. The schematic shows the location of the 4 recording electrodes within the 0.6 mm × 0.6 mm array. Cross-correlations between each of these rhythms peaked close to 0 h indicating that these cells were synchronized. Recording began after 16 days in vitro and data from recording days 12–23 were used in the cross-correlation analysis.

Dynamical Modeling

What is a dynamical model?

- Given knowledge of a system (biological, physical, chemical, engineered), *can we predict the state of the system in the future if we have information about its current state?*

The Initial Value Problem

Given:

$$\dot{x}(t, a) = f(t, x, a)$$
$$x(t_0) = x_0$$

Compute:

$$x(t, a)|_{x(t_0)=x_0}$$

Population Models

Exponential growth:

$$\frac{dN}{dt} = rN$$
$$N(t_0) = N_0$$
$$\implies N(t) = N_0 e^{rt}$$

Population Models

The Logistic Growth Model

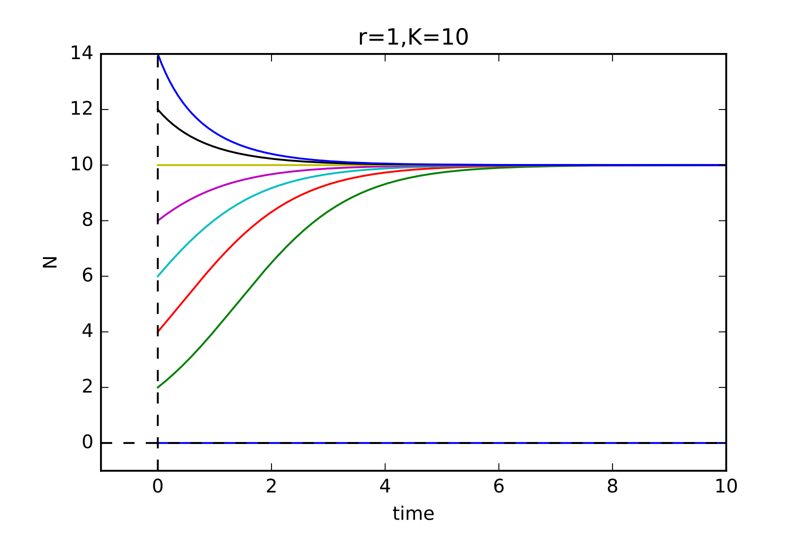
$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$

Population Models

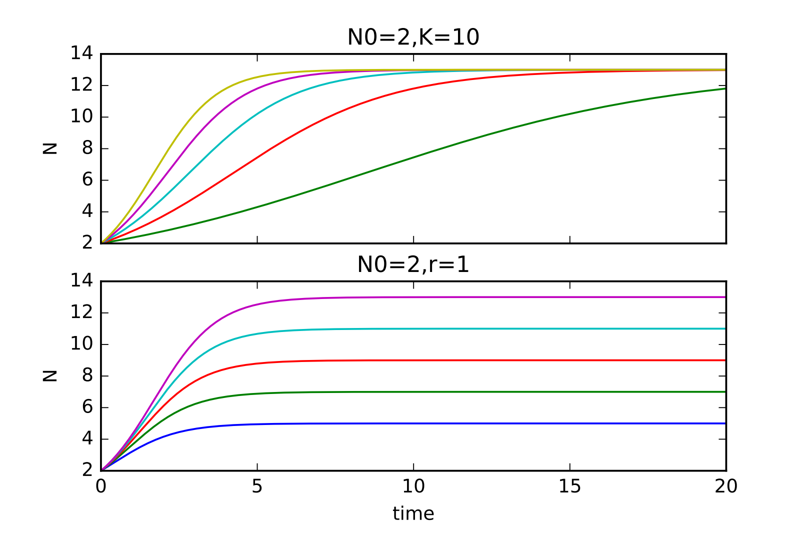
The Logistic Growth Model

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$
$$\implies N(t) = \frac{KN_0}{N_0 + (K - N_0)e^{-rt}}$$

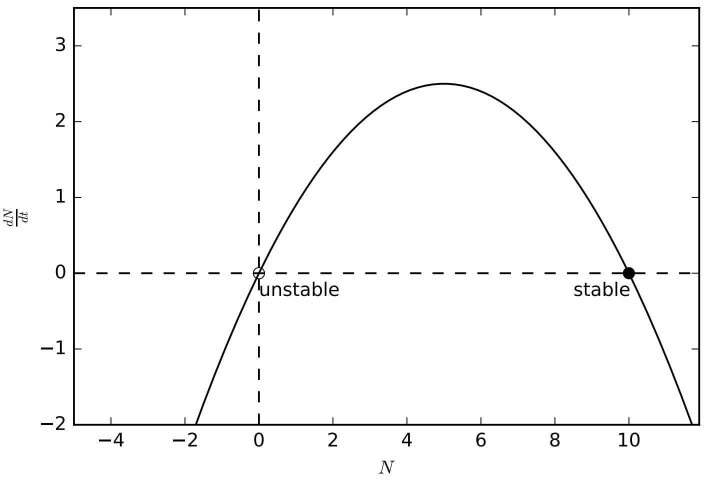
Population Dynamics



Dependence on parameters



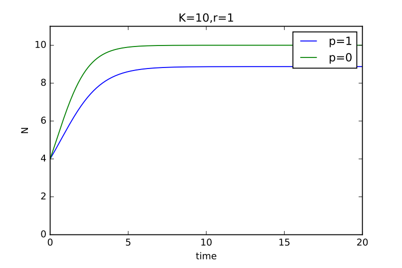
Qualitative behavior



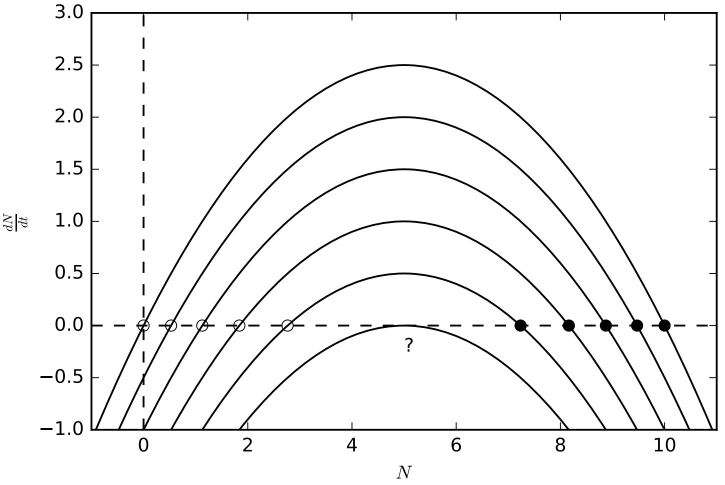
Adding complexity: Harvesting

Consider a population size-independent ‘harvest’:

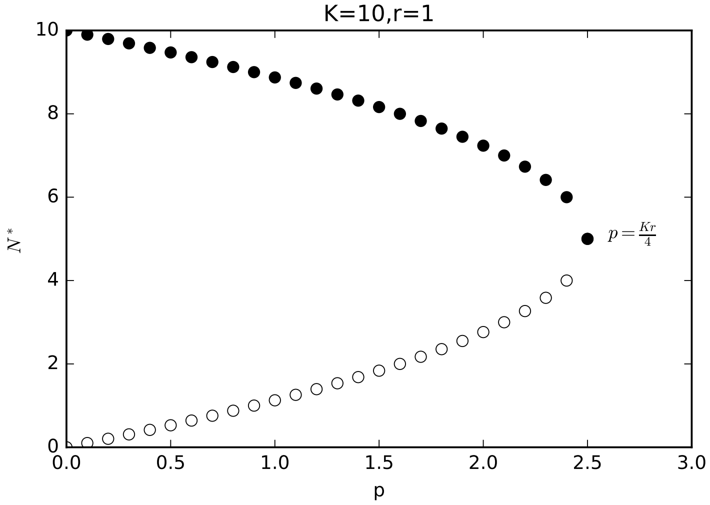
$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right) - p$$



Qualitative Behaviour



Qualitative Behaviour



Mathematical Formulation

Modeling neurons

We model synchronization of SCN cells using the forced Kuramoto model, which consists of a large population of coupled phase ocillators (modeling individual SCN cells) with heterogenous intrinsic frequencies and external periodic forcing.

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Evolution of the Kuramoto Model

$$\frac{d\theta}{dt} = \omega$$

Evolution of the Kuramoto Model

$$\frac{d\theta_i}{dt} = \omega_i$$

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$$\frac{d\theta_i}{dt} = \omega_i + \sum_{j=1}^{N} K_{ij} \sin(\theta_j - \theta_i)$$

Evolution of the Kuramoto Model

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

The Order Parameter

$$\frac{1}{N}\sum_{j=1}^{N}\sin(\theta_{\mathrm{j}}-\theta_{\mathrm{i}})=\frac{1}{N}\sum_{j=1}^{N}\mathrm{Im}(e^{i(\theta_{\mathrm{j}}-\theta_{\mathrm{i}})})$$

$$\frac{1}{N}\sum_{j=1}^{N}\mathrm{Im}(e^{i(\theta_{\mathrm{j}}-\theta_{\mathrm{i}})})=\mathrm{Im}(re^{i\psi})$$

$$z=re^{i\psi}$$

The Jet Lag Model

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

What is the range of values chosen for ω_i?

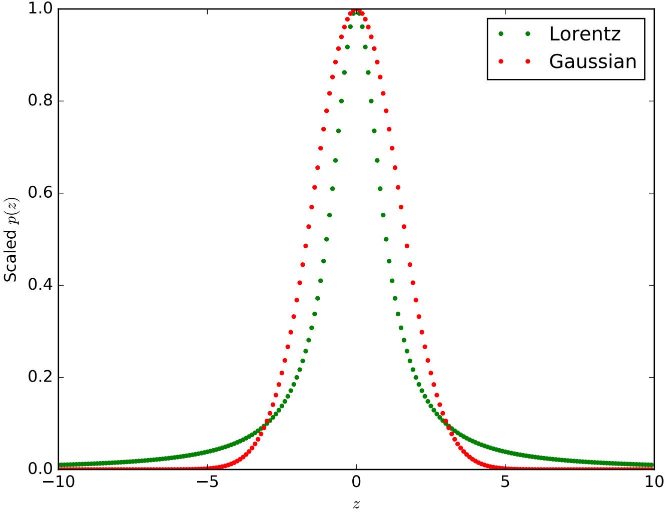
The Jet Lag Model

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

What is the range of values chosen for ω_i?

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

The Jet Lag Model



The Jet Lag Model

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

What is N biologically?

What is N in this analysis?

What is the interpretation of this K?

The Jet Lag Model

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

$$p(t) = \begin{cases} p_1, & t \leq \tau \\ p_2, & t > \tau \end{cases}$$

Complex order formulation

$$\frac{d\theta_i}{dt} = \omega_i + \frac{K}{N}\sum_{i=1}^{N}\sin(\theta_j - \theta_i) + F\sin(\sigma t - \theta_i + p_2)$$

$$\theta_i \to \sigma t + p_2$$

$$z = \frac{1}{N}\sum_{j=1}^{N} e^{i(\theta_\mathrm{j} - \sigma t - p_2)}$$

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

Kuramoto Oscillator

The Jet Lag Model

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

$$z(\tau) = z_{st} e^{i\Delta p} \quad \Delta p = p_1 - p_2$$

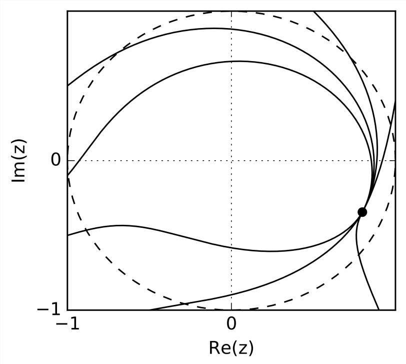
- **Target Variable:** The level of deviation from recovery is expressed as $|z(t) - z_{st}|$.

Parameters

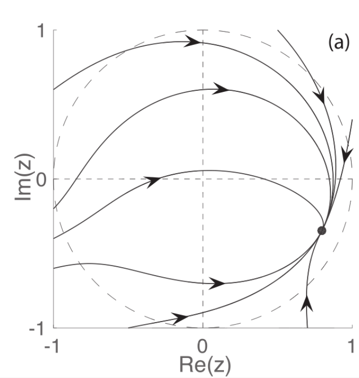
- F is the amplitude of each oscillator represents forcing factor
- K represents the coupling factor
- $\Omega = \sigma - \omega_0$ is the difference between external force and natural frequency
- $|z(t) - z_{st}|$ is the level of deviation from environment
- Δ is the spread of the natural frequency distribution

Results

Dynamics: Type A



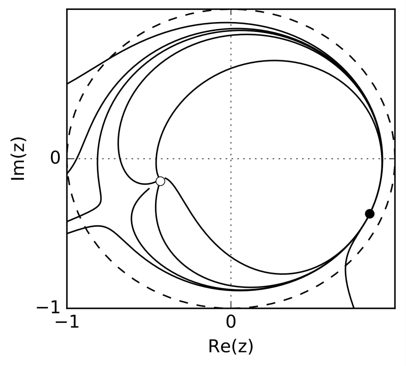
(a) Generated Plot



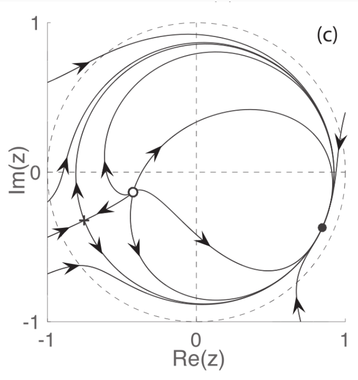
(b) From Paper

Figure 1: $K = 4.5\Delta \quad F = 3.5\Delta \quad \Omega = 1.4\Delta$

Dynamics: Type C



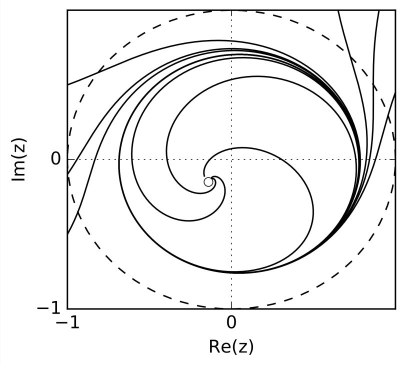
(a) Generated Plot



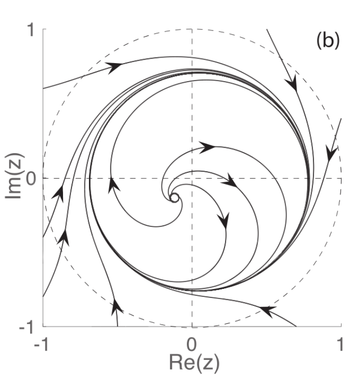
(b) From Paper

Figure 2: $K = 10.0\Delta \quad F = 3.5\Delta \quad \Omega = 1.4\Delta$

Dynamics: Type B



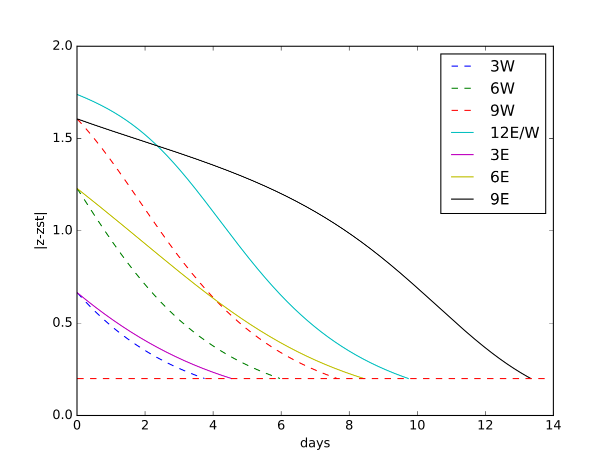
(a) Generated Plot



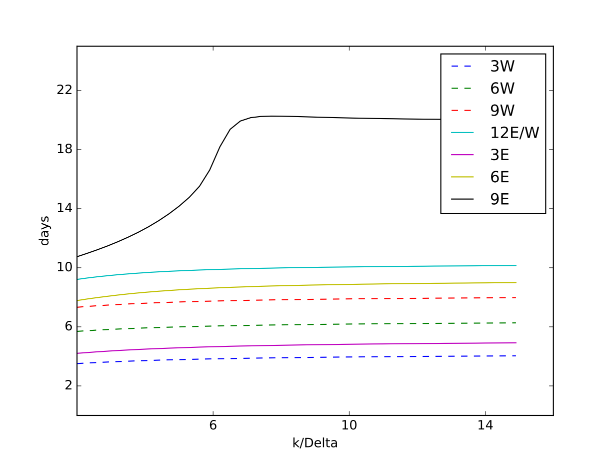
(b) From Paper

Figure 3: $K = 4.5\Delta \quad F = 0.65\Delta \quad \Omega = 1.4\Delta$

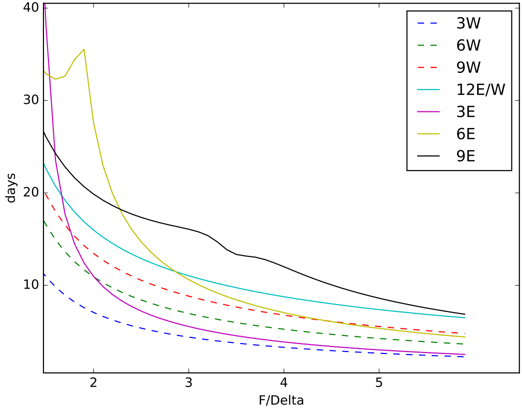
Recovery Time



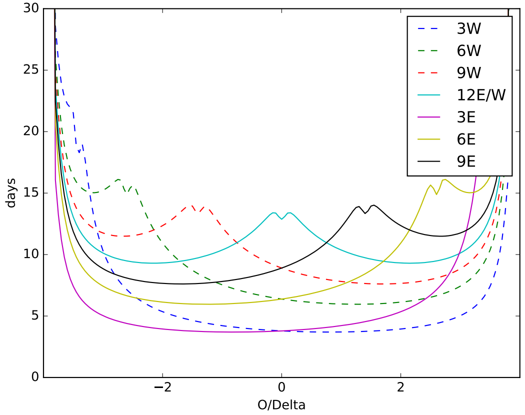
Recovery Time(K)



Recovery Time(F)



Recovery Time(Ω)



Criticism and Discussion

Criticism

- Biological relevance of parameters
- Including zeitgebers
- Other models of coupling oscillators
- Time scale problems
- Interpretation of fixed points

https://github.com/amoghpj/Scripts-for-Lu-et-al-2016

Questions?