

PH 567: Nonlinear Dynamics Project

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

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Abstract

Out of the many biological systems which have been studied from the perspective of nonlinear dynamics, the circadian rhythm has received considerable attention. The circadian rhythm is a natural, internal process that regulates the sleep-wake cycle and repeats on each rotation of the Earth roughly every 24 hours. It is regulated by certain clock cells in the brain. Jet-lag arises from the temporal mismatch between the external stimuli such as daylight and the internal circadian clock. It has been postulated from several studies that jet lag is due to the desynchronization of the clock cells within the brain, followed by resynchronization. Following the analysis of *Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag* by Lu, Z. et al. (2016)[2], we model the cells regulating the circadian rhythm as forced coupled oscillators using the Kuramoto model and reduce the dimensionality of the system using the Ott-Antonsen ansatz to analyse their phase space behaviour in order to explain the asymmetry in the severity of jet-lag often experienced between eastward and westward travel. We also analyse the stability diagram of the forced Kuramoto model and follow the analysis of *Stability diagram for the forced Kuramoto model* by Childs, L. M., & Strogatz, S. H. (2008) [1] to derive the reduced dimensional equation for the model. We also try and generalize the model considering the case when the instantaneous travel approximation breaks down.

The link to our github repository with simulation code reproducing the figures in the paper, as well as extending it can be found [here](#).

1 Introduction and Motivation

All the complex phenomena we take for granted in the world around us can, in principle, be studied using the laws of Physics. However, the systems are often far too complicated for a detailed theoretical or mathematical analysis. A natural setting to study nonlinear dynamics is in biological systems - which are still, to a large extent, not very well understood. There are many factors which play a role in bringing about the dynamics of a biological system, and finding a model which describes the important aspects of the system and fits experiments and gives us a richer understanding of the system is an interesting problem to study.

The mammalian circadian rhythm is regulated by certain Suprachiasmatic Nucleus (SCN) cells in the brain. Jet-lag arises due to the mismatch between external stimuli like daylight and the the internal circadian clock. We model the SCN cells using the forced Kuramoto model, and examine the dynamics of this model when one travels across time-zones. The parameters of the model are estimated from previous biological experiments. The most interesting aspect of the paper under study was that it explains the asymmetry between east-west jet lag. In other words, a journey from point A to point B can induce more jet lag than the corresponding return journey from B to A.

2 The Model under Study

Experimentally, it has been shown that the SCN, which regulates the circadian rhythm comprises 10^4 pacemaker neuronal cells which act like oscillators and synchronize to give healthy circadian rhythms. We model these coupled phase oscillators using the periodically forced Kuramoto model. This describes an infinite number of phase oscillators (in our case $N=10^4 \gg 1$) with random intrinsic frequencies and global sinusoidal coupling and external sinusoidal forcing. The forced Kuramoto model is often used to describe phenomena in which coupled oscillators try to synchronize with each other while also trying to lock onto an external forcing drive. The governing equation for this system of coupled phase oscillators is:

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

- $\theta_i (i = 1, 2, \dots, N)$. are the individual phase angles
- We assume uniform coupling strength (K) for all the oscillators.
- The external forcing sinusoidal term F models the 24-hour period external light signal accounting for stimuli like daylight, which means that $\sigma = \frac{2\pi}{24} h^{-1}$
- ω_i are the natural frequencies of the oscillators. The average time period is experimentally found to be greater than 24 hours. We assume that their distribution is a Lorentzian of the form $g(\omega) = \frac{\Delta}{\pi[(\omega - \omega_0)^2 + \Delta^2]}$ where Δ is the spread of the Lorentzian and ω_0 is the centre.
- The phase quantity $p(t)$ depends on the current time-zone and $\in [-\pi, \pi]$. If time t is defined as the local time of a place, then $p > 0$ (< 0) in all places to the east (west) of this place. This term is important when we shall discuss the dynamics of jet-lag after crossing time-zones.
- We assume that travel is very fast (instantaneous) and therefore if the travel happens at time τ we model p as a step function which changes discontinuously from p_1 to p_2 at $t = \tau$ where p_1 is the phase in the initial time-zone and p_2 is the phase in the destination time-zone.

This microscopic model is more accurate than previously studied macroscopic models. However, the size of the system is far too large to gain insights into the dynamical behaviour of the system. A clever way to reduce the dimensionality of the system is to consider a complex order parameter in a rotating frame with frequency σ defined as $z = \frac{1}{N} \sum_{j=1}^N e^{i[\theta_j(t) - \sigma t - p_2]}$ which is governed by the following dynamical equation

$$\dot{z} = \frac{1}{2} [(Kz + F) - z^2(Kz + F)^*] - (\Delta + i\Omega)z \text{ where } \Omega = \sigma - \omega_0 \quad (2)$$

If an individual is in a steady entrained state before travel (circadian rhythm synchronized with the local time), then after travelling, the order parameter is $z_{st} e^{i(p_1 - p_2)}$, where z_{st} the stable fixed point of the dynamical equation of z with $p = p_2$ if it exists. Because the traveller's biological clock is not aligned with the local time at the destination, the recovery takes place in the next few days while the order parameter evolves to a stable fixed point. We model the recovery from jetlag using \dot{z} for $t \geq \tau$ with the initial condition $z(\tau) = z_{st} e^{i\Delta p}$, $\Delta p = p_1 - p_2$. We measure the level of the deviation from full recovery by the distance between the order parameter and the stable fixed point, $|z(t) - z_{st}|$.

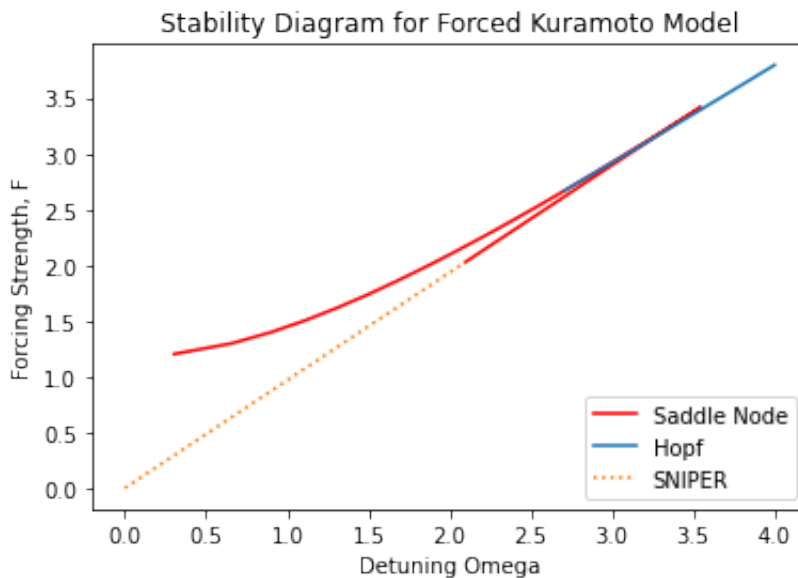
The model is powerful due to the dramatic reduction in dimensionality in spite of considering the individual phase oscillators, but it has a few limitations as it neglects spatially structured coupling within the SCN, both attractive and repulsive interactions of SCN pacemaker cells, and potential influence on diurnal timing from other organs of the body.

Dynamics and Recovery from Jet Lag

We study the attractors of the equation (2). Based on different values of the parameters K, F, Δ and Ω , the nature of the phase portrait changes as several bifurcations occur. Based on the analysis in [1] we plot the stability diagram for the forced Kuramoto model in Figure 1.

- We label three types of dynamics - A with a stable fixed point, B with a repelling fixed point and stable limit cycle and C with a stable fixed point, an unstable fixed point and a saddle point.
- The stable fixed points all have a negative imaginary part because Ω has been taken positive, as the time period of the circadian oscillators is greater than the 24-hour periodic forcing function.
- Unlike in type A and C, in type B, the attractor is a limit cycle, and not a fixed point. This means that even once the initial trajectory settles down in the attractor, the person does not have a well-defined sleep cycle, but rather daily variations of their sleep-wake time.
- Intuitively we expect the phase of the circadian oscillators to adjust by advancing or delaying depending on which is closer to the target phase - for a journey less than 12 hours, we expect the compensation to take place by advancing the phase while travelling east, and by delaying when travelling westward.
- This is not always the case. In the illustration of type C dynamics (Figure 2b), we can see the dynamics corresponding to 2 journeys to the same destination - one by travelling 8.5 hours eastward and the other by travelling 9.5 hours eastward. The initial positions for these two journeys lie on different sides of the stable manifold of the saddle point. Therefore, one of them goes clockwise to the stable point, implying the mechanism of phase delaying, whereas the other trajectory moves towards the fixed point in an anticlockwise manner, by phase advancing.
- While type A dynamics (Figure 2a) lacks the saddle point, the trajectories look similar to those discussed above for type C dynamics because the parameters for A are near the saddle node bifurcation point and retain their local character (the ghost of the saddle node bifurcation).

Figure 1: Bifurcation curves are shown with respect to the strength F and detuning of the external forcing, which have been nondimensionalized by the width of the distribution of the oscillators' natural frequencies.



Reference parameter set

We now estimate a reasonable set of the parameters (K, F, Ω , and Δ) corresponding to a typical healthy person. The severity of jet-lag varies from one individual to another and so once we have set our “typical” parameter set as a reference point, we will then study the effect of parameter deviations. Our choice of a typical parameter set is based on the following:

1. Larger $|z|$ corresponds to greater synchrony, and pacemaker cells in the SCN should be in a fairly synchronized state, so the stable fixed point of the order parameter should have a large amplitude.

2. An individual confined to a dark enclosure may have substantial regularity in his sleep cycle so the system can synchronize when $F = 0$.
3. Here, we will take 24.5 h as the average period of circadian rhythms, as estimated by a recent study.
4. The east-west asymmetry is because on average, 1 h per day is needed for retraining one's phase after an eastward travel while for westward it is 1.5 h. Also, since 9-h eastward travel corresponds to the border between jet-lag recovery by phase advancing or delaying, it is considered most disruptive.

Based on the above, we choose

$$\Delta = 3.8 \times 10^{-3} (\text{rad} \cdot \text{h}^{-1}), \quad \Omega = 1.4\Delta = 2\pi/24 - 2\pi/24.5, \quad K = 4.5\Delta, \quad F = 3.5\Delta$$

as our reference parameter set. (For this set type A dynamics applies.)

Fig. 3 shows recovery curves corresponding to several eastward and westward travels, where $|z(t) - z_{st}|$ is plotted versus time. We take recovery from jet-lag to have occurred when $|z(t) - z_{st}|$ drops below 0.2.

Parameter dependence

- While studying parameter dependence, we keep Δ constant at our reference value as it only corresponds to change in the time scale of the dynamics.
- The parameter K , which represents the oscillator coupling strength, controls the degree of synchronization for fixing values of the external drive, F . In Fig. 4(a), the recovery time is plotted in a range of K for several cross-time-zone journeys with the other two parameters at their reference values. For K/Δ between 2.0 and 8.0 we have type A dynamics, whereas when K/Δ exceeds 8.0, we have type C dynamics. Hence, the large recovery time for eastward 9-h travel is due to the newly born saddle point that is very close to its initial point.
- The parameter F controls the magnitude of the external drive which includes factors such as sunlight, cloudiness, geographical latitude and seasonality. Our intuitive notion that recovery time should decrease with increasing F since recovery from jet-lag is facilitated by being out in bright sunlight (effectively increasing F), is consistent with what is observed in Fig. 4(b) on plotting recovery time in a range of F for several journeys with the other two parameters fixed at reference level (plot A dynamics).
- The parameter $\Omega = \sigma - \omega_0$ is the difference between the external drive frequency σ (corresponding to a 24 h day) and the average of the pacemaker cells' natural frequencies ω_0 . In Fig. 4(c), recovery time is plotted in a range of Ω from -3.7 to 3.7 for several journeys with the other two parameters fixed, where we observe that the eastward and the westward recovery time curves are reflections of each other about the $\Omega/\Delta = 0$ axis.

3 Summary of results

The following are the plots reproduced to understand how the cells regulating the circadian rhythm work.

Figure 2: Trajectories of order parameters corresponding to different time-zone travels for types C & A dynamics.

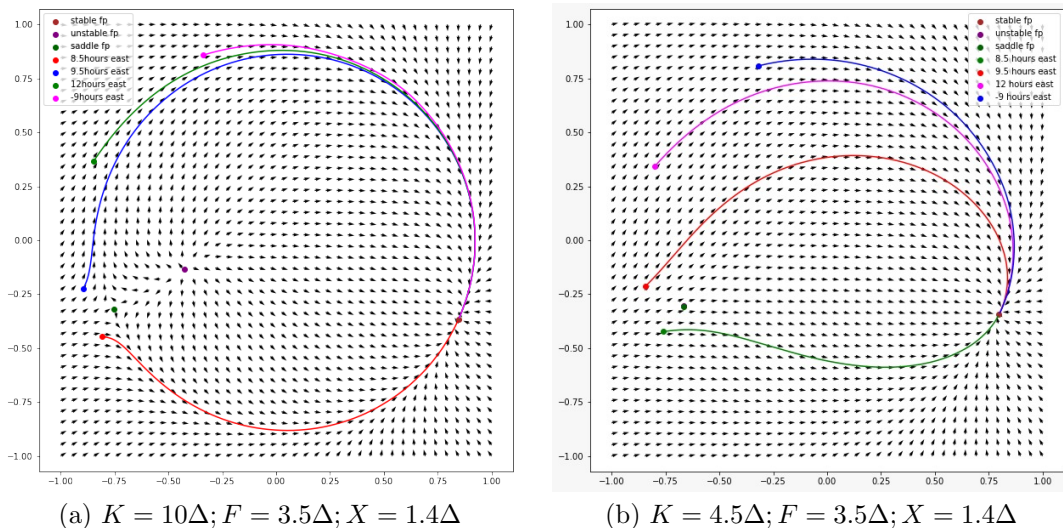


Figure 3: Recovery curve from several eastward & westward travels with different numbers of time-zones crossed

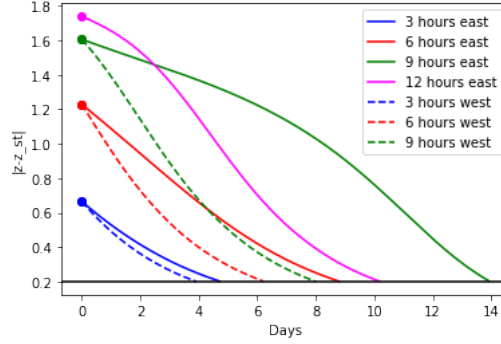
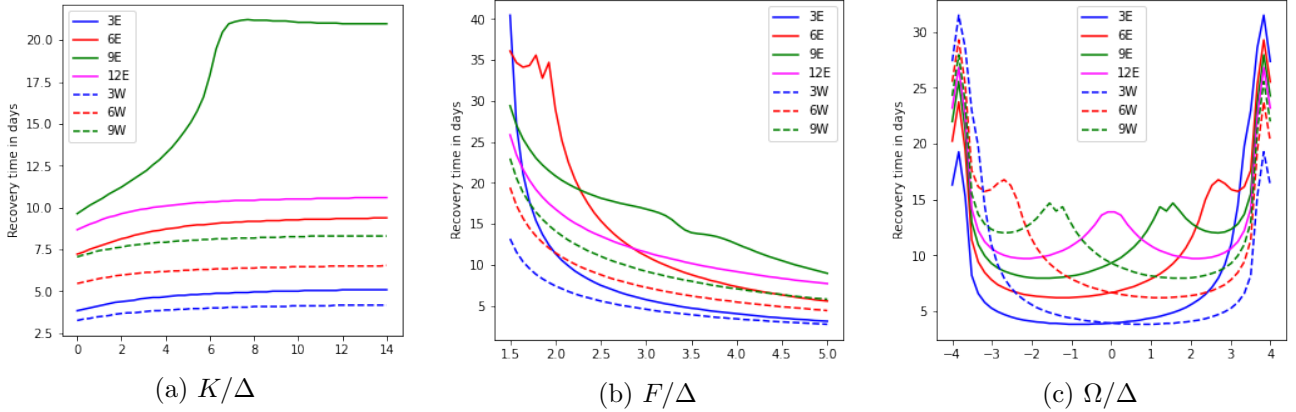


Figure 4: Recovery time dependence on K (a), F (b), and X (c) with the non-varying parameters kept at the reference values in equations. In each case, x-axis represents the corresponding parameter value.



4 Conclusion

In this project, we used a simplified phase oscillator model of the individual SCN cells, which despite not reflecting the complex mechanisms governing the circadian rhythm, has the great advantage of allowing an exact reduction of the high dimensional microscopic dynamics to that of a relatively simple low dimensional system for the evolution of the macroscopic system state. Then we model the dynamics of resynchronization of the SCN following rapid cross-time-zone travel, i.e., jet-lag. We saw how this approach enabled us to understand very well the east/west jet-lag asymmetry and also analyse the responses of different individuals to cross-timezone travel simply by studying the parameter dependence.

5 Open questions

5.1 Relaxation of the Rapid Travel Approximation

Realistically, the travel time for a 12 hour time zone change (say India to USA) will be of the order of half a day, making it not completely negligible as compared to travel times. Here we try to investigate the dynamics of such a continuous phase change. Analogous to original model, we introduce $w = \frac{1}{N} \sum_{i=1}^N e^{(\theta_i - \sigma t - p(t))}$. Comparing to our

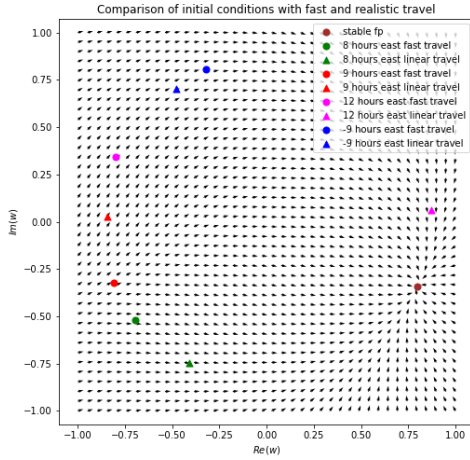
original $z = \frac{1}{N} \sum_{i=1}^N e^{(\theta_i - \sigma t - p_2)}$, we can write $w(t) = z(t) \cdot e^{-i(p(t) - p_2)}$. So, with product rule of derivative, we can expand $\dot{w}(t) = \dot{z}(t) \cdot e^{-i(p(t) - p_2)} - i \frac{dp}{dt} w$ where \dot{z} is as described previously. Here, we will always start our model with $w(0)$ being the stable node of the earlier model (assuming well tuned circadian rhythm before travel). Our model will thus be described by a smooth function which we can write as

$$p(t) = \begin{cases} p_1 & t \leq 0 \\ p(t) & 0 \leq t \leq \tau \\ p_2 & t \geq \tau \end{cases}$$

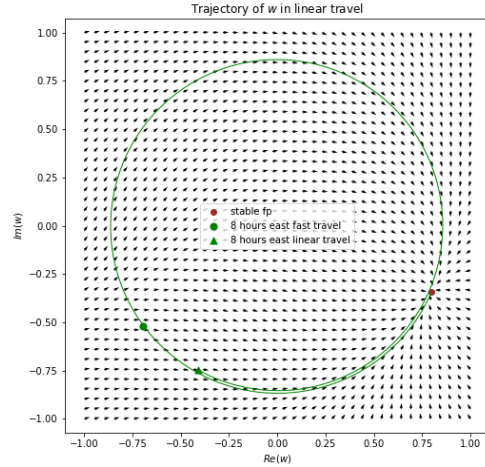
where τ is the travel time. With this model we can see that, as $\tau \rightarrow 0$, we can see $\dot{w} \approx -i \frac{dp}{dt} w$ for $t \leq \tau$ and so we can integrate this directly, to get $w(\tau) = w(0) e^{-i(p_2 - p_1)\tau}$ which matches well with our initial conditions of fast travel

assumption. We can integrate the general model with appropriate model of $p(t)$ in general, numerically to get the ‘correct’ starting point of recovery.

Below, we have tried to integrate this model numerically with an assumption that p is linear between 0 to τ and the results are presented below. The travel time τ is assumed to be equal to the lag in phase. We suspect that the plots generated have some mistakes, since the code produces wrong result in $\tau \rightarrow 0$ limit (τ independent from lag in this limit.)



(a) Difference between initial conditions of linear vs fast travel



(b) Trajectory for linear travel

5.2 Changing the forcing function

We have assumed that the forcing function is a sinusoidal function with a frequency of 24 hours. A more physical model may be a periodic function which is clamped at the zero because during the day the intensity of light varies, peaking around noon, but at night, the intensity of ambient light is negligible. When we generalise the forcing function, it is difficult to employ the Ott-Antonsen ansatz for dimensionality reduction as the differential equation is non-linear and has implicit functions of the phase, so we cannot treat it by taking a Fourier decomposition of the forcing function of choice. We would possibly have to numerically integrate for a very large number of oscillators to study the system.

Apart from these, since many features concerning the coupling of SCN pacemaker cells are unknown, we did not consider the possible heterogeneous connectivity patterns which may play an important role in the resynchronization of circadian oscillators. The basic uncoupled phase oscillator ($d\theta_j/dt = \omega_j$) could also be replaced by other phase oscillator descriptions while still allowing reduction of dimensions. Hence these are the points which can be further studied, whilst making the significant changes to this model, in order to understand jet-lag better, while increasing the precision of our study.

Appendix

We analyse the forced Kuramoto model in the the continuum limit $N \rightarrow \infty$. The state of the system is described by a density function $f(\theta, \omega, t)$. f is defined such that at time t , the fraction of oscillators with phases between θ and $\theta + d\theta$ and natural frequencies between ω and $\omega + d\omega$ is given by $f(\theta, \omega, t)d\theta d\omega$. Therefore by definition

$$\int_{-\infty}^{\infty} \int_0^{2\pi} f(\theta, \omega, t) d\theta d\omega = 1 \text{ and } g(\omega) = \int_0^{2\pi} f(\omega, \theta, t) d\theta$$

The evolution of f is given by the continuity equation $\frac{\partial f}{\partial t} + \frac{\partial}{\partial \theta}(fv) = 0$ where $v(\theta, \omega, t)$ is the velocity field on the circle corresponding to the forced Kuramoto model as $N \rightarrow \infty$,

$$v(\theta, \omega, t) = (\omega - \sigma) + K \int_{-\infty}^{\infty} \int_0^{2\pi} \sin(\theta' - \theta) f(\theta', \omega', t) \times d\theta' d\omega' - F \sin \theta$$

We write this succinctly using the order parameter $z(t)$ (in the continuum limit) and note that the double integral in the expression for the velocity can be written as $Im(Kze^{-i\theta})$, so the continuity equation is now:

$$\frac{\partial f}{\partial t} + \frac{\partial}{\partial \theta} \left(f \left\{ (\omega - \sigma) + \frac{1}{2i} [(Kz + F)e^{-i\theta} - (Kz + F)^* e^{i\theta}] \right\} \right) = 0$$

Solving and analysing the system in this form is also difficult. Ott and Antonsen considered only the family of densities f which satisfied $f_n(\omega, t) = [\alpha(\omega, t)]^n$ for all $n \geq 1$. If α evolves as $\frac{d\alpha}{dt} = \frac{1}{2}(Kz + F)^* - i(\omega - \sigma)\alpha - \frac{1}{2}(Kz + F)\alpha^2$ and z satisfies $z(t) = \int_{-\infty}^{\infty} \alpha^*(\omega, t)g(\omega)d\omega$ then this ansatz satisfies the amplitude equations for all n . For a Lorentzian $g(\omega)$ and if $\alpha(\omega, t)$ can be analytically continued from the real ω -axis into the lower half of the complex ω -plane for all $t \geq 0$; that $|\alpha(\omega, t)| \rightarrow 0$ as $Im(\omega) \rightarrow -\infty$; and that $|\alpha(\omega, 0)| \leq 1$ for real ω in the complex ω -plane, one can evaluate the above expression using contour integration. This gives us the evolution equation for the order parameter z to be $\frac{dz}{dt} = \frac{1}{2} [(Kz + F) - (Kz + F)^* z^2] - [\Delta + i(\sigma - \omega_0)] z$

Link to Code Repository

<https://github.com/mahadevans2432/NLD-Project#nld-project>

References

- [1] Lauren M Childs and Steven H Strogatz. “Stability diagram for the forced Kuramoto model”. In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 18.4 (2008), p. 043128.
- [2] Zhixin Lu et al. “Resynchronization of circadian oscillators and the east-west asymmetry of jet-lag”. In: *Chaos: An Interdisciplinary Journal of Nonlinear Science* 26.9 (2016), p. 094811.