Coupled Oscillators and Applications to Human Sleep and Circadian Rhythms

Keven Calderon

Department of Mathematics
College of Staten Island, City University of New York
Thesis Adviser: Jesenko Vukadinovic, PhD

Contents

Abstract

A simple model for human circadian system is studied. The behavior of humans and other animals is differentiated by precise 24-hour cycles of rest and activity, sleep and restlessness. These cycles termed circadian rhythms and represent a fundamental adaptation of organisms to a pervasive environmental stimulus; the solar cycle of light and dark. A fundamental property of circadian rhythm is that it is free-running, and continues with a period close to 24 hours in the absence of light cycles or other external cues. The sleep-wake and body temperature rhythms are assumed to be determined by a pair of coupled nonlinear oscillators described only by phase variables. This article presents principles of mathematical modeling on human circadian system and how other important two-dimensional phase space systems work.

Key words: Circadian—Oscillator—Model—Sleep—Human

1 Introduction

The circadian cycle has been studied mathematically using oscillators and other non-linear dynamical models to describe features of sleep-wake rhythms. A review of early mathematical models of sleep-wake cycle is given by Professor Steven H. Strogatz [1]. The free run studies of human subjects which lived alone clock-less environment, absence of external light-dark cycle and other 24 hour periodicity of the outside word had been analyzed by Czeisler and Wever. Their experimental data discovered some surprising regularities in timing of the subjects' spontaneous sleep episodes. In many mathematical model, postulated at least a pair of oscillators to describe occurrence of "Spontaneous internal desychronization" between the sleep-wake cycle and various autonomic circadian rhythms. Strogatz emphasized that a free-running subject unknowingly lives on a "day" which is longer than 24 hours during internal desynchronization. More precisely, a free-running subject lives 30-50 hr long day and during this period their body temperature and neuroendocrine variables controlled by the circadian pacemaker continue to oscillate with a stable period of 24-25 hr. This phenomenon does not occur in real life. In ordinary life, on regular schedule, the circadian and sleep-wake rhythms are typically phase-locked to one another and to the 24-hr environment.

The purpose of this article is to revisit the simple model of the human sleep-wake cycle proposed by Steven H. Strogatz [1]. This model based on two-dimensional phase space on tours, which the equations may be solved analytically, as well as numerically. The resulting analytically transparency allows us to sort out which of the observed phenomena follow from simple mathematical consideration alone, as distinct from those which require some additional biological explanation.

The remainder of this paper is organized as follows: Circadian models incorporating light responses have been seen, for some parameter ranges, to exhibit multiple dynamic behaviors, including coexistence of a steady state and an oscillating solution or coexistence of two oscillating solutions. Therefore, in Section 2 a discussion on dynamical systems and its basic concepts including: asymptotic behavior, stability of fixed points for one and two dimensional systems and their classifications, bifurcation theory, as well as dynamical system on a circle. Section 3 reviews the general case of uncoupled oscillators. In Section 4, an analysis is done on Strogatz's simple model of the human sleep-wake cycle, and finally in Section 5 indicates how Oscillators death and bifurcations on a torus works using the Ermentrout and Kopell's (1990) model "Oscillator death".

2 Dynamical Systems [1]

2.1 Introduction

Vaguely speaking, a dynamical system is in which a function describes the time dependence of a point in a geometrical space.They're two main types of dynamical system: differential equation and iterated maps. The differential equations part involves the evolution of systems in continuous time, while the iterated maps, often times called a difference equation, contain problems where time is discrete. Examples of modeling continuous-time dynamical system are: swinging clock pendulum, the flow of water in a pipe and population dynamics. An example of a model in difference equations is the logistic map.

2.2 Asymptotic Behavior

An asymptotic behavior of a dynamical system refers to the long-term evolution of the solutions of the system as time goes to infinity. The subset of the phase space on which the trajectories reside at $t \to \infty$ is known as a limit set. These limit sets consider the dynamical system:

$$\begin{cases} \dot{x_1} = f_1(x_1, \ldots, x_n) \\ \vdots \\ \dot{x_n} = f_n(x_1, \ldots, x_n) \end{cases}$$

(where $\dot{x}$ is known as time derivative) as a vector field, where the limit sets organizes their flow in their own vicinity. A limit set is called an *attractor* if all trajectories in the neighborhood moved towards this limit set and a *repellor* if the vector flow is directed away from the limit set. The simplest kind of limit set is an equilibrium point or a fixed point.

2.3 Fixed Points and Their Stability

In a simple case where $n = 1$ in the system above, we have a one-dimensional system: $\dot{x} = f(x)$, where the fixed point of $\dot{x}$ is obtained by setting the equation $\dot{x} = f(x) = 0$, where a fixed point would be denoted as x^*. However, obtaining any fixed point for a n-dimensional system follows as:

$$\begin{cases} \dot{x_1} = f(x_1, \ldots, x_n) = 0 \\ \vdots \\ \dot{x_n} = f(x_1, \ldots, x_n) = 0 \end{cases}$$

Consider a *one-dimensional* dynamical system $\dot{x} = f(x)$ on the real line $\mathbb{R}^2$.

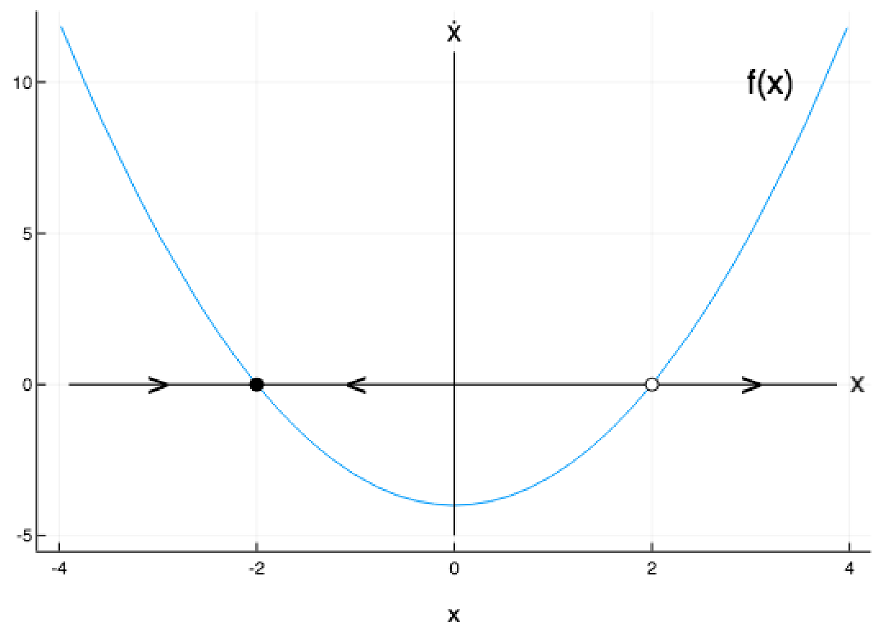

Figure 1: A plot of $\dot{x} = f(x)$ with two fixed points.

The figure above shows that $f(x)$ has two solutions. These solutions, or fixed points, are determine their stability by the signs from the left and right of the fixed point. The first fixed point on the far left shows that it is stable since $f(x) < 0$ to the right and $f(x) > 0$ is positive to the left, therefore the flow will go towards the fixed point, making it stable, denoted as a closed circle. The other fixed point to the right is unstable due to the fact that $f(x) < 0$ to the left of the fixed point and $f(x) > 0$ to the right of the fixed point, thus making it unstable, denoted as an opened circle.

A *two-dimensional* dynamical system is in the form:

$$\begin{cases} \dot{x_1} = ax_1 + bx_2 \\ \dot{x_2} = cx_1 + dx_2 \end{cases}$$

where a,b,c, and d are parameters.
This system can be modified in the form of a matrix system:

$$\dot{\mathbf{x}} = A\mathbf{x}$$

where A is a 2×2 matrix and $\dot{\mathbf{x}}$ and $\mathbf{x}$ are 2×1 vectors, in which this equation can be viewed as:

$$\begin{bmatrix} \dot{x_1} \\ \dot{x_2} \end{bmatrix} = \begin{bmatrix} a & b \\ c & d \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

Generally, this system is linear in the sense that if $\mathbf{x}_1$ and $\mathbf{x}_2$ are solutions to $\dot{\mathbf{x}}$, thus so is any linear combination $c_1\mathbf{x}_1 + c_2\mathbf{x}_2$. Note that when $\dot{\mathbf{x}} = 0$ then $\mathbf{x} = 0$, if $\det(A) \neq 0$; however, for any $A, \mathbf{x}^* = 0$ will always be a fixed point for any A.

Unlike a one-dimensional dynamical system where a fixed point is simply stable or unstable (or semi-stable in some cases), a two-dimensional systems have more in depth classifications of a fixed point.

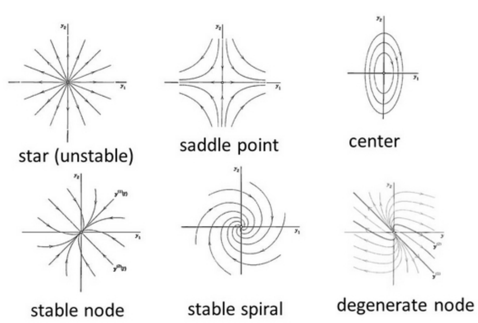

Figure 2: Few of the Types of Fixed points

Figure 2 above summarizes general types of fixed points in a two-dimensional system. Typically, they are five different types of fixed points: nodes, saddle, stars, spirals and centers. They are classified according to the the matrix's A eigenvalues of the linearized dynamics at the fixed point. For a real 2×2 matrix, the eigenvalues must be real or else must be a complex conjugate pair. The five fixed points are then classified by their eigenvalues (denoted as λ) such that:

1. $\lambda_1 > 0, \lambda_2 > 0$ implies that the fixed point, $\mathbf{x}^*$, is an unstable node.
2. $\lambda_1 > 0, \lambda_2 < 0$ denotes that $\mathbf{x}^*$ is a saddle point.
3. $\lambda_1 < 0, \lambda_2 < 0$ denotes that $\mathbf{x}^*$ is a stable node.
4. $Re(\lambda_1) > 0, \lambda_1 = \lambda_2$ denotes that $\mathbf{x}^*$ is an unstable spiral.
5. $Re(\lambda_1) < 0, \lambda_1 = \lambda_2$ denotes that $\mathbf{x}^*$ is a stable spiral.

Although one can use the eigenvalues to determine the classification of a fixed point, one can also use a geometric interpretation of the classification of any fixed point.

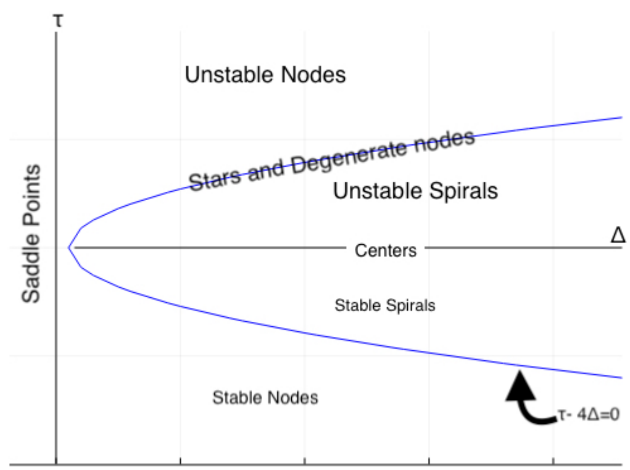

Figure 3: A diagram of the classifications of a fixed point in a two-dimensional system, where $\Delta = \lambda_1 \lambda_2$ and $\tau = \lambda_1 + \lambda_2$

2.4 Flows on the Circle

For the most part, one can focus a one-dimensional system $\dot{x} = f(x)$, which can be visualized as a vector field on the line; however, one can also consider a new type of differential equation and its corresponding phase space:

$$\dot{\theta} = f(\theta)$$

The equation above corresponds to a vector field on the circle, where θ is a point on the circle and $\dot{\theta}$ is the velocity vector at that point. Similar to the line, the circle is one-dimensional, but it has a unique property: flows in one direction, i.e. a particle can eventually return to its starting place as shown in the figure below:

Figure 4: A vector field on the circle with a positive angular velocity.

Generally speaking, with this scenario, vector fields on the circle can provide the most basic model of systems that can oscillate.

2.4.1 Uniform Oscillator

A point on a circle is often called an angle or *phase*. A simple case of an oscillator is when the phase θ changes uniformly:

$$\dot{\theta} = \omega$$

where ω is a constant, thus the solution to this equation is

$$\theta(t) = \omega t + \theta_0,$$

which corresponds to uniform motion around the circle at an angular frequency ω. This solution, $\theta(t)$, is considered to be periodic because $\theta(t)$ changes by 2π, and therefore returns to the same point on the circle after time $T = \frac{2\pi}{\omega}$, where T is the *period* of the oscillation.

2.4.2 Nonuniform Oscillator

The equation

$$\dot{\theta} = \omega - a\sin(\theta)$$

arises in many different applications in science and engineering, more specifically with biology on oscillating neurons, firefly flashing rhythms, and the human sleep-wake cycle.

To analyze the equation above, assume that $\omega > 0$ and $a \geq 0$ for convenience. The result for a negative ω and a are similar. A typical graph of $f(\theta) = \omega - a\sin(\theta)$ is shown below in figure 5:

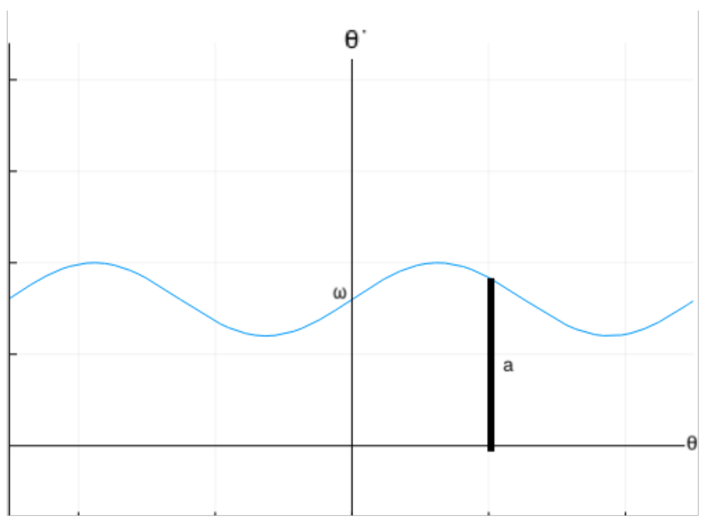

Figure 5: a typical graph of a nonuniform oscillator where ω is the mean and a is the amplitude.

The parameter a introduces a *non-uniformity* in the flow around the circle: the flow is at is fastest at $\theta = -\frac{\pi}{2}$ and at its slowest at $\theta = \frac{\pi}{2}$. When a is slightly less than ω, the oscillation is very spasmodic. When $a = \omega$, the system stops oscillating altogether: a semi-stable fixed point has been created at $\theta = \frac{\pi}{2}$. Last, when $a > \omega$, the semi-stable fixed point is split into two fixed points: one stable and one unstable.

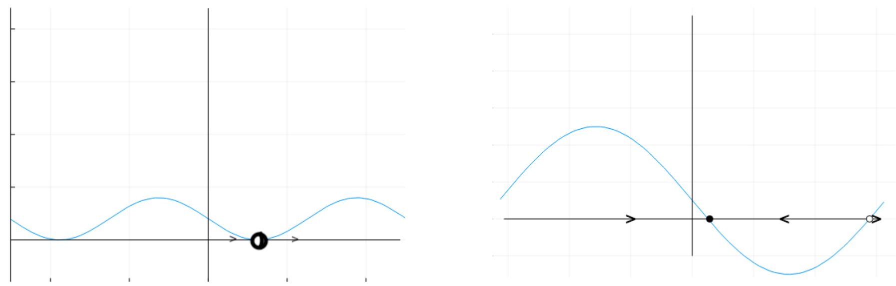

Figure 6: On the left is when $a = \omega$ with a semi-stable fixed point and the other on the right $a > \omega$ with two fixed points.

The same information can be shown by plotting the vector fields on the circle below:

Figure 7: Far left vector field shows a semi-stable fixed point when $a = \omega$ and the right shows a vector field with two fixed points when $a > \omega$

2.5 Bifurcations

A qualitative change in the behavior of a system upon a parameter variation is called bifurcation. Examples include changes in the number or stability of fixed points, closed orbits, or saddle connection as a parameter is varied.

The *saddle-node* bifurcation is the basic mechanism in which fixed points are either created and destroyed. As a parameter is varied, two fixed points move toward each other, collide, and mutually annihilate. The prototype example of a saddle-node bifurcation is given by the first order system:

$$\dot{x} = r + x^2$$

where r is a parameter, and $x^* = \pm\sqrt{-r}$. Thus, if $r < 0$ then there exist two fixed points that are stable and unstable. If $r = 0$ then there will be a semi-stable fixed point. If $r > 0$ then there will be no fixed point in the system since x^* will produce a complex solution. With all of the information above, one can used this to produce a graph that is called a *bifurcation diagram*. With this graph, one can view for what values of r will produce a system that will contain fixed points or not.

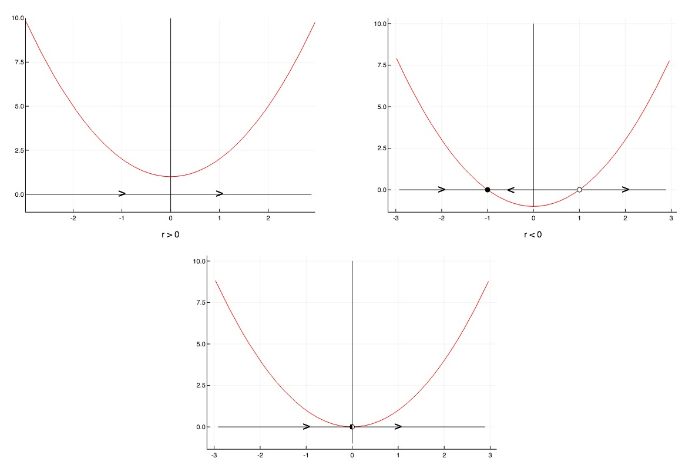

Figure 8: The three graphs shows the typical graph for $\dot{x} = r + x^2$ as the signs for r varies.

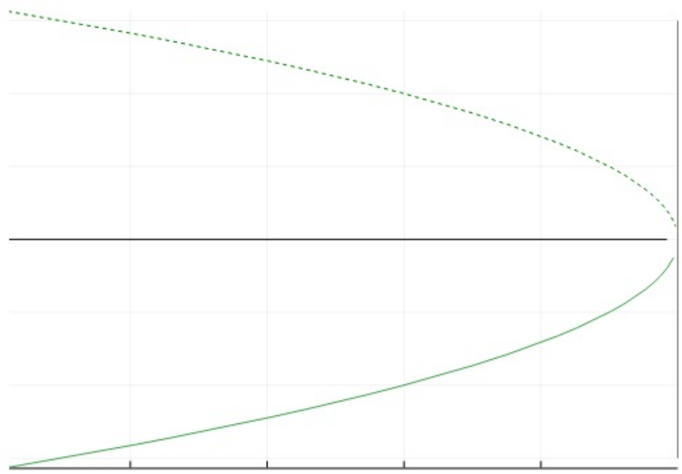

Figure 9: This is a graph of the bifurcation diagram with the independent variable begin r and the dependent variable being x^*. The dotted curve shows when the system, $\dot{x}$, is unstable for the parameter r.

For two-dimensional system, consider the following prototypical example:

$$\begin{cases} \dot{x} = \mu - x^2 \\ \dot{y} = -y \end{cases}$$

In the x-direction,the bifurcation behavior is similar as discussed previously with a one-dimensional; however,the y-direction's motion is exponentially damped since the solution to $\dot{y}$ is negative.

As before, the fixed points of this system occurs when $\dot{x} = 0$ and $\dot{y} = 0$. So the two fixed points of this system occurs at $(x^*, y^*) = (\sqrt{\mu}, 0)$ and $(-\sqrt{\mu}, 0)$. As the values of μ decreases, the saddle and node approach each other, while at $\mu = 0$ is where they will collide and the fixed points dissipate when $\mu < 0$, in which it becomes a "ghost" since no fixed points occur.

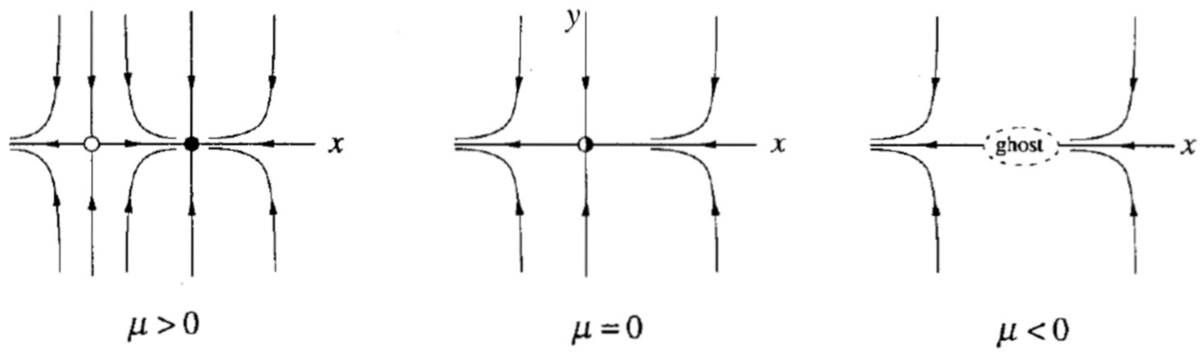

Figure 10: The figure shows how for a varying parameter μ, creates fixed points and how it destroys them. For $\mu > 0$ the two fixed points are $(\mu, 0)$ and $(-\mu, 0)$ in which they are stable and unstable respectively.

3 Coupled and Uncoupled Oscillators

3.1 Introduction

Like a dynamical system in rectangular coordinates, a dynamical system on the circle can be viewed in two-dimensions. Its phase space is the *torus* and it's the natural phase space for the system of the form:

$$\begin{cases} \dot{\theta}_1 = f_1(\theta_1, \theta_2) \\ \dot{\theta}_2 = f_2(\theta_1, \theta_2) \end{cases}$$

where f_1 and f_2 are periodic in both arguments.

A simple model of *coupled oscillators* is given by

$$\begin{cases} \dot{\theta}_1 = \omega_1 + K_1 \sin(\theta_2 - \theta_1) \\ \dot{\theta}_2 = \omega_2 + K_2 \sin(\theta_1 - \theta_2) \end{cases}$$

where θ_1, θ_2 are the *phases* of the oscillators, $\omega_1, \omega_2 > 0$ are their *natural frequencies*, and $K_1, K_2 \geq 0$ are known as the *coupling constants*.

In order to illustrate some of the general features of the flow on the tours, imagine two points going around in a circle at instantaneous rate of change

$\dot{\theta}_1, \dot{\theta}_2$. Another way of looking at it is to consider coordinates θ_1, θ_2, in which they are analogous to latitude and longitude.

Figure 11: A generalization on how a single point traces a trajectory.

However, this makes it very difficult to draw phase portraits, thus we view it in a square with periodic boundary conditions. But if a trajectory runs of an edge, it reappears on the opposite edge.

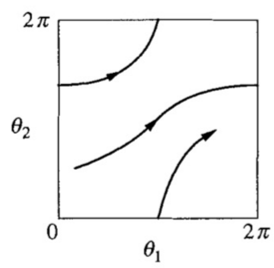

Figure 12: Phase portraits of the tours on a square with periodic boundary conditions.

3.2 Uncoupled Oscillators

The trivial case of uncoupled oscillators, where $K_1, K_2 = 0$ contains some interesting results. With the coupling constants being 0, this reduce the equation into $\dot{\theta}_1 = \omega_1, \dot{\theta}_2 = \omega_2$. The corresponding trajectories on the square will produce straight lines with constant slopes $\dfrac{d\theta_2}{d\theta_1} = \dfrac{\omega_2}{\omega_1}$. However, there will be two cases depending on whether the slope is rational or irrational.

For the case of being *rational*, in which $\dfrac{\omega_2}{\omega_1} = \dfrac{p}{q}$, where p, q are some integers with no common factors. In this scenario, all trajectories are closed orbits on the tours, because θ_1 completes p revolution in the same time that θ_2 completes q revolution.

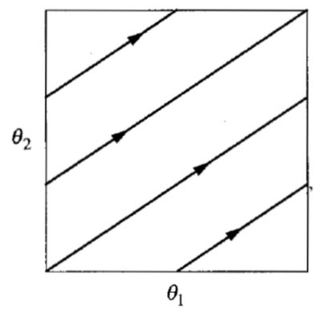

Figure 13: A trajectory with rational slope

If the trajectory was to be plotted on the torus, a *trefoil knot* will be produced.

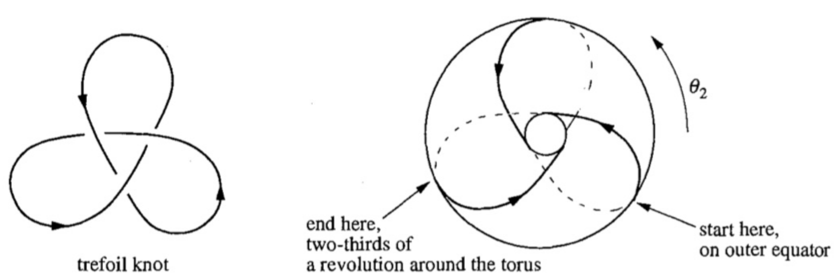

Figure 14: An image of a trefoil knot and the trefoil knot on the tours from a view from the top of the tours.

The second case where the slope is *irrational*, the flow is said to be *quasi-periodic*, meaning that every trajectory goes around endlessly on the torus, never intersecting itself and yet never quite closing.

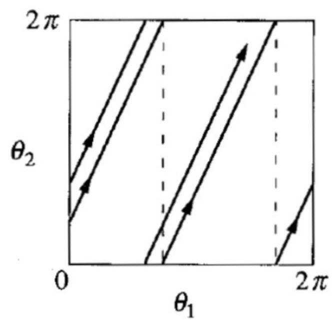

Figure 15: A trajectory that has irrational slope which is known to be quasi-periodic.

Quasi-periodicity is significant, especially in a scenario like this because quasi-periodicity only occurs on the torus and it is a new type of a long-term behavior.

3.3 Coupled Oscillators

The dynamics can be analyzed by viewing the *phase difference* by setting $\phi = \theta_1 - \theta_2$, thus the model can be observed as

$$\begin{aligned}\dot{\phi} &= \dot{\theta}_1 - \dot{\theta}_2 \\ &= \omega_1 - \omega_2 - (K_1 + K_2)\sin(\phi)\end{aligned}$$

in which this is now a nonuniform oscillator as observed in 2.4.2. Two fixed points will emerge if $|\omega_1 - \omega_2| < K_1 + K_2$ and none if $|\omega_1 - \omega_2| > K_1 + K_2$. A saddle-node bifurcation will occur if $|\omega_1 - \omega_2| = K_1 + K_2$.

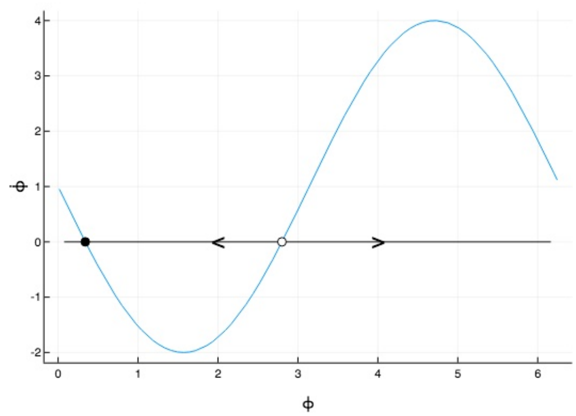

Figure 16: A graph of $\dot{\phi}$. All the trajectories are asymptotically approaching the stable fixed point.

Now suppose there are two fixed points defined as:

$$\sin(\phi^*) = \frac{\omega_1 - \omega_2}{K_1 + K_2}$$

As shown in figure 13, all trajectories of $\dot{\phi}$ are asymptotically approaching the stable fixed point. Thus, on the torus, the trajectories of the system θ_1, θ_2 approach a stable *phase-locked* solution, in which the oscillators are separated by a constant phase difference ϕ^*.

4 PHASE Model [2]

4.1 Introduction

Strogatz discussed main findings of free-run experiments of Circadian rhythm in section 2 of his article "Human sleep and circadian rhythms: a simple model based on two coupled oscillators". He emphasized that there were apparent regularities which were consistent across internally desynchronized subjects:

1. Long sleep episode begin near high temperature and shorter sleep episodes begin near the temperature through.

2. Almost all awakening occur on the rising limb of the temperature cycle and practically none occurs in the quarter-cycle before the temperature minimum.

3. Many sleep episodes begin at one of two peak phases in the circadian cycle-near the temperature maximum.

This model is based on two pacemakers: Circadian rhythm of body temperature and the sleep-wake cycle. These pacemakers are assumed to be coupled. Each accelerates or slows the other depending only on their mutual phase relation and this model ignores such variables as amplitude, where observes only phase. This simple mathematical model uses the assumptions that its component oscillators have circular state spaces and more importantly they only interact through phase differences.

4.2 The Structure of the Model

Strogatz [2] used the equation of a coupled oscillators, as shown in section 3.1, to model the interaction between human-circadian rhythms and the sleep-wake cycle. However in this model he uses a different structure, but it still behaves the same way as shown in section 3.1

$$\begin{cases} \dot{\theta}_1 = \omega_1 - C_1 \cos 2\pi(\theta_2 - \theta_1) \\ \dot{\theta}_2 = \omega_2 + C_2 \cos 2\pi(\theta_1 - \theta_2) \end{cases}$$

where θ_1 and θ_2 are the phases of the two oscillators which are real numbers and we considered them as points on the circle of unit circumference. ω_1, ω_2 are intrinsic frequencies and C_1, C_2 are coupling strengths.

All the parameters are taken to be non-negative. The chosen form of the coupling is such that the first oscillator slows down and the second speeds up when they are in phase. This property is suggested by the observed modulations of sleep-wake cycle lengths as the activity and temperature rhythms cross through each other during internal desynchronization.

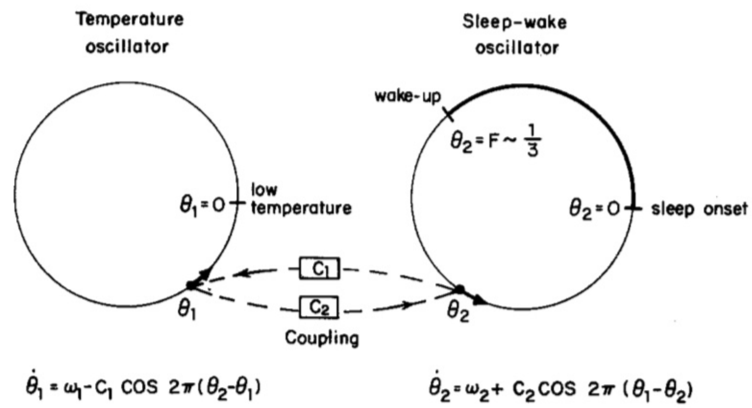

Figure 17: Structure of the PHASE model. Sleep-wake and temperature rhythms are controlled by different "phase-only" oscillators, but these oscillators are coupled.

In this model, low temperature occurs when $\theta_1 = 0$ and sleep occurs when $0 \leq \theta_2 \leq F$, where F is a parameter controlling the sleep fraction. We adopt the conventions that the first oscillator drives the circadian temperature rhythm, while the second oscillator drives the sleep-wake cycle. Sleep is defined to occupy some fraction F of the θ_2 circle:

$$\theta_2 = 0 \qquad \text{at sleep onset}$$
$$\theta_2 = F \qquad \text{at wake-up.}$$

In this situation, $0 \leq F \leq 1$, and usually $F \sim 1/3$, since people about a third of the time. Since sleep onset during internal synchrony occurs near low temperature, we take $\theta_1 = 0$ as circadian phase 0, the minimum of the endogenous temperature cycle.

4.3 Synchronicity

To analyze the synchronization and desynchronization of the constituent oscillators, consider the phase difference:

$$\psi = \theta_1 - \theta_2$$

such that

$$\dot{\psi} = \dot{\theta}_1 - \dot{\theta}_2$$

where we can see that the equation can be viewed as

$$\dot{\psi} = \Omega - C\cos(2\pi\psi)$$

where

$$\Omega = \omega_1 - \omega_2$$

$$C = C_1 + C_2 > 0$$

In this particular case, Ω is the difference of the intrinsic frequencies of the two oscillators and C is the total coupling in the system. Synchrony is enforce when the total coupling C is larger than the magnitude $|\Omega|$ of the frequency difference, thus $\dot{\psi} = 0$ has a solution. If $\dot{\psi}$ did not have a solution otherwise, the phase- difference continues to grow as one oscillator periodically over takes the other. This idea is as one oscillator periodically take over the other known as desynchronicity.

In the case for synchronicity, assume

$$K = |\frac{C}{\Omega}| > 1$$

Then the internally synchronized phase relation $\dot{\psi}$ is obtained by solving the equation above for $\dot{\psi} = 0$.

$$\psi^* = \pm\frac{1}{2\pi}\cos^{-1}(\frac{\Omega}{C})$$

The solutions for ψ^* are implicit. The stable solution is for which $\frac{d\dot{\psi}}{d\psi} < 0$. Recall that the range for $\cos^{-1}(x)$ is $[0, \pi]$, therefore

$$\psi^* = -\frac{1}{2\pi}\cos^{-1}(\frac{\Omega}{C})$$

is the stable solution.

Using the equation for ψ^*, the *compromise frequency* denoted as ω^* which is adapted by the synchronized system. During internal synchrony, the system becomes:

$$\begin{cases} \dot{\theta}_1 = \omega_1 - C_1(\frac{\Omega}{C}) \\ \dot{\theta}_2 = \omega_2 - C_2(\frac{\Omega}{C}) \end{cases}$$

Since $\dot{\theta}_1 = \dot{\theta}_2 = \omega^*$ during synchrony, either the two equations simplifies to

$$\omega^* = \frac{C_1\omega_2 + C_2\omega_1}{C_1 + C_2}$$

This frequency differs from the intrinsic frequencies ω_1 and ω_2 by amounts of $\Delta\omega_1$ and $\Delta\omega_2$, where $\Delta\omega_1$ and $\Delta\omega_2$ are

$$\Delta\omega_1 = \omega^* - \omega_1 = -C_1\frac{\Omega}{C}$$

and

$$\Delta\omega_1 = \omega^* - \omega_2 = C_2\frac{\Omega}{C}$$

Note that during synchrony the oscillators' frequencies are shifted from their intrinsic values in proportion to the coupling strengths:

$$|\frac{\Delta\omega_1}{\Delta\omega_2}| = |\frac{C_1}{C_2}|$$

4.4 Desynchronicity

The phase difference equation $\dot{\psi}$ corresponds to desynchrony when $K < 1$, i.e. when $C < |\Omega|$. The phase difference ψ between the oscillators always increases, sometimes slowly and sometimes rapidly, exhibiting what circadian biologists call "internal relative coordination". The oscillators periodically move through a full cycle of mutual phase relations, with a *beat* frequency β, obtained as follows. From $\dot{\psi}$ the time required for ψ to change from 0 to 1 is $\frac{1}{\beta}$, given by:

$$\frac{1}{\beta} = \int_0^{\frac{1}{\beta}} dt = \int_0^1 \frac{d\psi}{\Omega - C\cos(2\pi\psi)}$$

(Derivation of the beat frequency is in 4.7 Exact solutions)
Thus the beat frequency β satisfies

$$\beta = (\Omega^2 - C^2)^{\frac{1}{2}}$$
$$= \Omega(1 - \frac{C^2}{\Omega^2})^{-\frac{1}{2}}$$

With β, they're will be two special cases:

1. For $C = 0$, the beat frequency reduces to $\beta = \Omega = \omega_1 - \omega_2$,the non-interactive beat frequency.

2. As $C \to |\Omega|$, then $\beta \to 0$ according to a square root dependence for β. Thus the tendency to synchronize grows rapidly as C approaches the critical coupling.

An analytically convenient special case of the model is that in which $C_1 = 0$, in other terms, there is no feedback onto the circadian pacemaker. As discussed in the parameters estimates for human subjects section, this is a reasonable first approximation, and it will be assumed in what follows.

Let the arbitrary zero of time be chosen such that $\theta_1(0) = 0$. Then the scaling time

$$\omega_1 = 1$$

we obtain

$$\theta_1(t) = t$$

.

As shown in the exact solutions sections, $\dot{\psi}$ may be solved exactly to produce a sophisticated (yet monotonic and importantly, an invertible) function $\psi(t)$.

Having solved for $\theta_1(t)$ and $\psi(t)$, we obtain θ_2:

$$\theta_2(t) = \theta_1(t) - \psi(t)$$

$$= t - \psi(t)$$

.

4.5 Model Prediction of an Empirical Relationship

The model's prediction of various empirical relations give only implicit solution. For example, consider the model's prediction of the dependence of the duration (denoted as ρ) of the sleep episode on the phase ϕ_s of the circadian temperature cycle at sleep on set. The experimental findings [2] shows that sleep episodes beginning near the temperature trough tend to be short (~ 7 hr), while those beginning near the temperature maximum are long (~ 15 hr). The condition of ϕ_s: ρ relationship came as a surprise, and has been discussed extensively in the literature and many theoretician have used it as a benchmark to test their models [2]. Hence it is of interest to derive the form of the ϕ_s: ρ relationship predicted by the PHASE model.

According to the protocol of θ_2 in 4.2, sleep duration ρ is given by the time required for θ_2 to move from 0 to F. The circadian phase ϕ_s of sleep onset is given by θ_1 when $\theta_2 = 0$. To compute the ϕ_s: ρ relationship, it is most convenient to choose a new origin of time, with $t = 0$ at sleep onset, meaning:

$$\theta_2(0) = 0$$

$$\theta_1(0) = \phi_s$$

$$\psi(0) = \theta_1(0) - \theta_2(0) = \phi_s$$

.

Now to find the time at which wake-up occurs, we seek ρ such that:

$$\theta_2(\rho) = F$$

$$\theta_1(\rho) = \phi_s + \rho$$

$$\psi(\rho) = \phi_s + \rho - F$$

Together, $\psi(0)$ and $\psi(\rho)$ form an implicit set of equations for ρ, as a function of ϕ_s and F. Due to the trigonometric form of ψ, the solution for ρ requires graphical or numerical techniques.

One such graphical method is indicated in figure 18 below.

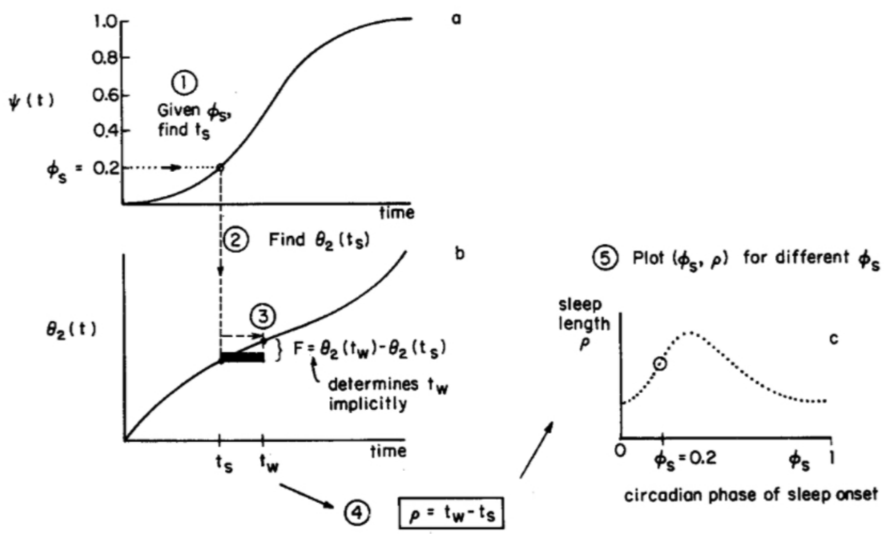

Figure 18: Graphical construction of ϕ_s: ρ relationship in the PHASE model.

As shown in section 4.4 and the exact solutions section, the governing equations, with $C_1 = 0$ may be integrated exactly to yield the curves $\theta_2(t)$ and $\psi(t)$. Initial conditions were $\theta_1(0) = \theta_2(0) = 0$, and the integration continued until all mutual phase relations ψ between 0 and 1 had been attained. Thus, all possible circadian phases of sleep onset are attained, since $\phi_s = \psi$ when $\theta_2 = 0$. In order to find $\rho(\phi_s)$, a multi-step procedure is to be followed by using figure 18.

i. Choose ϕ_s, the phase of sleep onset.

ii. Find t_s, such that $\psi(t_s) = \phi_s$. This is doable since ψ is an invertible function.

iii. Regarding t_s as the time of sleep onset, find (the first) t_w such that $\theta_2(t_w) = \theta_2(t_s) + F$.

iv. Therefore t_w represents the time of wake-up and so $\rho = t_w - t_s$. As figure 18 graph b shows that long sleep arises when the phase of mid-sleep falls near the inflection point of $\theta_2(t)$. Thus the longest sleeps are predicted to begin in the first half of the circadian cycle.

The steps of the graphical construction can be summarized in term of ψ^{-1} and θ_2^{-1}, the inverse functions to $\psi(t)$ and $\theta_2(t)$, respectively.

For notational simplicity, let

$$g = \psi^{-1}$$

and

$$h = \theta_2^{-1}$$

From step (ii),

$$g(\phi_s) = t_s$$

From step (iii),

$$t_w = h(\theta_2(t_s) + F) = h(\theta_2(g(\phi_s)) + F)$$

.

Therefore,

$$\rho(\phi_s) = h(\theta_2(g(\phi_s)) + F) - g(\phi_s)$$

.

The equation above is the first instance of an exact expression for the ϕ_s: ρ relation derived from a mathematical model of the sleep- wake cycle.

4.6 Parameter Estimates for Human Subjects

The equations shown in section 4.3, specifically from ψ^* onward, those equations may be used to estimate the coupling strengths C_1, C_2 for typical human subjects. When internal synchrony is lost, the period of the sleep-wake cycle lengthens by much more than that of the temperature cycle shortens.

Here we expect:

$$C_1 << C_2$$

Since $\Omega = C$ at the onset of desynchorony, and $C = C_1 + C_2 \sim C_2$, the frequency difference Ω provides an estimate of C_2:

$$C_2 \sim \text{frequency difference } \Omega \text{ observed at onset of desynchrony}$$

Choosing units where $\omega_1 = 1$, a typical value of Ω would be

$$\Omega \sim \frac{1}{6} \cong 0.16(\sim 6 \text{ day beat period})$$

Hence,

$$C_2 \sim 0.16$$

From $\Delta\omega_1$ and $\Delta\omega_2$ and the information above,

$$\Delta\omega_2 \sim 0.16$$

To obtain C_1, we use Wever's result that after desynchrony, the temperature cycle shortens by ~ 0.7 hr. For a synchronized period of 25.5 hr, this corresponds to

$$\omega^* = \frac{24.8}{25.5} \cong 0.97$$

.

Since

$$\Delta_1 = \omega^* - \omega_1$$

$$\sim 0.97 - 1.0$$

$$-0.03$$

we find from Δ_1, and Δ_2 that

$$C_1 = |\frac{C_2 \Delta_1}{\Delta_2}|$$

$$\sim 0.03$$

$$|\frac{C_1}{C_2}| \sim |\frac{0.03}{0.16}| \sim \frac{1}{5}$$

4.7 Exact Solution for θ_1 and θ_2

We consider the system

$$\begin{cases} \dot{\theta}_1 = 1 \\ \dot{\theta}_2 = \omega + C\cos(2\pi(\theta_1 - \theta_2)) \end{cases}$$

This system is similar to the PHASE model in section 4.2, but for this case $C_1 = 0$. Time is scaled so that $\omega_1 = 1$; then ω_2 become ω and C_2 becomes C in this new notation.

Let

$$\psi = \theta_1 - \theta_2$$

.

Then

$$\dot{\psi} = 1 - \omega - C\cos(2\pi\psi)$$

$$= \Omega - C\cos(2\pi\psi)$$

where

$$\Omega = 1 - \omega$$

.

Rescale time again: set

$$T = \Omega t$$

and let

$$\psi' = \frac{d\psi}{dT}$$

Then

$$\psi' = 1 - k\cos(2\pi\psi)$$

where

$$k = \frac{C}{\Omega}$$

Here k represents a dimensionless coupling constant; desynchrony occurs when

$$k < 1$$

The equation $\psi^{'}$ can be solved by separation of variables, followed by integration but using the substitution

$$x = \tan(\pi\psi)$$

we obtain the following

$$T + constant = \int \frac{d\psi}{1 - k\cos(2\pi\psi)}$$

$$= (\frac{1}{\pi(1+k)b}) \arctan(x/b)$$

where

$$b^2 = (1-k)/(1+k)$$

The equation that solved $\psi^{'}$ may be solved for x and then for ψ to produce

$$\psi(t) = (1/\pi)\arctan(u(t))$$

where

$$\begin{aligned} u(t) &= b\tan(\pi\beta t + C_0) \\ \beta = \Omega(1-k^2)^{1/2} &\text{is the beat frequency} \\ C_0 &= \arctan((1/b)\tan(\pi\psi_0)) \\ \psi_0 = \psi(t=0) &\text{is the intial condition} \\ b^2 &= (1-k)/(1+k) \\ k = C/(1-\omega) &\text{is the dimensionless coupling.} \end{aligned}$$

These equations above solve the equation by $\dot{\psi}$ for the desynchronized case assumed by $k < 1$. Then θ_1 and θ_2 are easily solved for.

Monotonicity of $\theta_2(t)$

Around the discussion of figure 18, it was mentioned that $\theta_2(t)$ is a monotonic function of t, for certain reasonable choice of parameters. All that is needed is $C < |\Omega|$ and $\omega > 1/2$ (activity rhythm period is less than ~ 50 hr). The monotonicity of θ_2 is derived as follows:

$$\begin{aligned}\omega_2 > 1/2 &\implies \omega_2 > 1 - \omega_2 \\ &\implies \omega > \Omega \text{by } \omega_1 = 1 \text{ and } \Omega = \omega_1 - \omega_2 \\ &\implies \omega_2 + \Omega\cos(2\pi\psi) > 0, \forall\psi \\ &\implies \omega_2 + C_2\cos(2\pi\psi) > 0, \text{since} C_2 \leq C \leq |\Omega| \\ &\implies \dot{\theta}_2 > 0, \text{from the model} \\ &\implies \theta_2(t), \text{is monotone in } t, \text{ as required.}\end{aligned}$$

5 Bifurcation on the Tours and Oscillator Death[3]

Since about the 1960 mathematical biologists have been studying simplified model of coupled oscillators. Oscillator Death in System of coupled Neural Oscillators by Ermentrout and Kopel is one of the interesting models. In a paper on system of neural oscillators, Eremntrout and kople illustrated the notion of "Oscillator death" with the following model:

$$\begin{cases}\dot{\theta}_1 = \omega_1 + \sin(\theta_1)\cos(\theta_2) \\ \dot{\theta}_2 = \omega_2 + \sin(\theta_2)\cos(\theta_1)\end{cases}$$

Where $\omega_1, \omega_2 \geq 0$

In this section we classify all the different behavior that the solution to the above equation have as the parameters vary in the positive quadrant of $[\omega_1, \omega_2]$ - plane and describe each bifurcation.

Using the equations above, let $\phi = \theta_1 + \theta_2$ and $\psi = \theta_1 - \theta_2$. Then by trigonometric formulas, we can show that the system has the following equivalent forms:

$\dot{\phi} = \omega_1 + \omega_2 + \sin(\phi)$ and $\dot{\psi} = \omega_1 - \omega_2 + \sin(\psi)$

Thus, the system is *uncoupled* in these variables. With this information, it follows that:

1. **If $\omega_1 > \omega_2 + 1$ then Oscillators are *independent*, the solutions are quasi-periodic, with two periods**

   Since $\omega_1 + \omega_2 > \omega_1 - \omega_2 > 1$ from the information from 5.1,

   $\phi = \mu_1 t + \Phi$ and $\phi = \mu_2 t + \Psi$ where $\mu_1 > \mu > 0$

   Φ is periodic of period $T_1 = \dfrac{2\pi}{\mu_1}$ and Ψ is periodic of period $T_2 = \dfrac{2\pi}{\mu_2}$

   There is neither phase locking, nor oscillator death. Each oscillator oscillates independently, although with greatly modified phases:

   $\theta_1 = \dfrac{\mu_1 + \mu_2}{2} t + \dfrac{1}{2}(\Phi + \Psi)$ and $\theta_2 = \dfrac{\mu_1 - \mu_2}{2} t = \dfrac{1}{2}(\Phi - \Psi)$

   instead of the uncoupled phases $\theta_j = \omega_j(t - t_j)$. The Frequencies are not constant either that is:

   $\dot{\theta}_1 = \dfrac{\mu_1 + \mu_2}{2} + \dfrac{1}{2}(\dot{\Phi} + \dot{\Psi})$ and $\dot{\theta}_2 = \dfrac{\mu_1 - \mu_2}{2} = \dfrac{1}{2} + (\dot{\Phi} - \dot{\Psi})$

   Finally, not that the solution are quasi-periodic, with period T_1 and T_2. When checking for periodicity or quasi-periodicity, it is vital to keep in mind the θ_1 and θ_2 are angles, so that behavior of the form $\theta_j = \mu t$ corresponds to a period $T = \dfrac{2\pi}{\mu}$.

2. **If $\omega_1 = \omega_2 + 1$, then bifurcation into phase locking**. Φ has the same form as $\dot{\theta}_1$; however, the equation for Ψ in $\dot{\psi}$ has a semi-stable critical point $\Psi = \pi/2 + 2n\pi$,for some integer n. Phase locking is semi-stable: small perturbation can take the system out of phase lock. Then the phase Ψ difference increases by 2π, and phase locking occurs again.

   Consider the scenario in case 1, as $\omega_1 - \omega_2$ decreases to 1. Then μ_2 decreases to 0 and T_2 blows up to inf. Therefore, ψ becomes very slow varying- a constant for "short enough" time periods, and the oscillator's behavior approximates that of a phase locked one, with a common frequency.

3. **If $|\omega_2 + 1| < \omega_1 < \omega_2 + 1$, then the phase lock is a global attractor**. Since $|\omega_1 - \omega_2| < 1$, the equation for ψ has two fixed points, a stable one (denoted as ψ_s) and an unstable one (denoted as ψ_u). Thus a constant phase difference $\psi = \psi_s$ is a global attractor. Another thing is that $\omega_1 + \omega_2 > 1$ and 5.1 produces

$\phi = \mu t + \Phi$ where $\mu_1 > 0$ and Φ is periodic of period $T_1 = \dfrac{2\pi}{\mu_1}$

Therefore the attracting solution is $\theta_j = \frac{1}{2}\mu_1 t + \frac{1}{2}\dot{\Phi}$. This solution is known as a limit cycle, with a period $T - 1$.

4. **If $\omega_1 + \omega_2 = 1$, then bifurcation to oscillator death to phase locking**. The equation for ψ has the same critical points ψ_u and ψ_s as in the third scenario, while the equation for ϕ has a single, semi-stable fixed points $\pi/2 + 2n\pi$. The system then approaches, as $t \to \inf$, to the fixed point $\phi = \pi/2 + 2n\pi$ and $\phi = \phi_s$. However, this point is semi-stable, so a small disturbance can take ϕ out of equilibrium. Then ϕ increases by 2π, til it reaches the critical point again.

5. **If $\omega_1 + \omega_2 < 1$, then oscillator death**. Since the ω_j are positive, $|\omega_1 - \omega_2| < 1$. Thus both equations $\dot{phi}$ and $\dot{psi}$ have fixed points, one unstable for each (ϕ_u and ψ_u), and another which is a stable global attractor (ϕ_s and ψ_s). Therefore the system has a global attractor, given by
$$(\theta_1, \theta_2) = \frac{1}{2}(\phi_s + \psi_s, \phi_s - \psi_s)$$
Remark: $\frac{1}{2}(\phi_s + \psi_u, \phi_s - \psi_u)$ and $\frac{1}{2}(\phi_u + \psi_s, \phi_u - \psi_s)$ are saddles, while $\frac{1}{2}(\phi_u + \psi_u, \phi_u - \psi_u)$ is an unstable node.

6. **If $\omega_2 = \omega_1 + 1$, then a bifurcation into (out of) phase locking**. This is the same as case 2, by the system's symmetry.

7. **If $\omega_2 > \omega_1 + 1$, then oscillators "independent", the solutions are quasi-periodic, with two periods**. This is the same thing as case 1 by the systems symmetry.

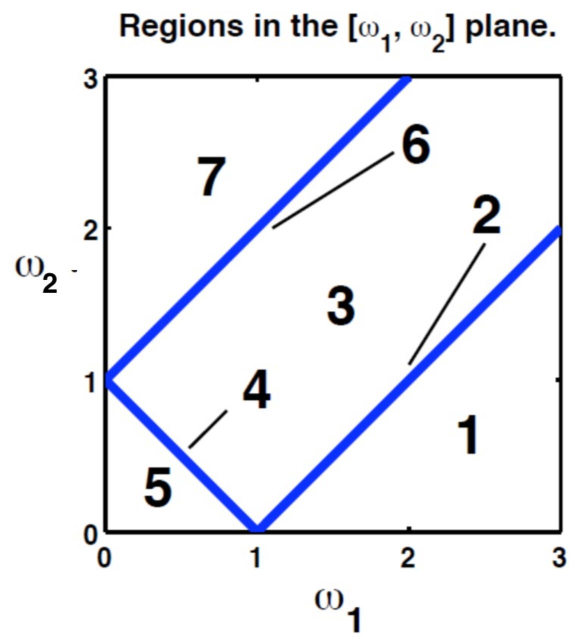

Figure 19: Oscillator death and bifurcation in the plane. Regions in the positive quadrant of the $[\omega_1, \omega_2]$-plane corresponding to different behaviors $\dot{\theta}_1, \dot{\theta}_2$ have. These are: 2: where $\omega_1 - \omega_2 = 1$, 4: $\omega_1 + \omega_2 = 1$ and 6: where $\omega_2 - \omega_1 = 1$

5.1 Analysis on Section 5

Consider

$$\begin{cases} \dot{\phi} = 1 - K\sin(\phi); 0 < K < 1 \\ \phi(t_0) = 0 \end{cases}$$

Let $a = \frac{1}{2\pi}\int_0^{2\pi} \frac{d\phi}{1 - K\sin(\phi)}$; let $\mu = \frac{1}{a}$

By separation of variables:

$\int_0^{\phi(t)} \frac{d\phi}{1 - K\sin(\phi)} = t - t_0$

Let $F(x) = \int_0^x \frac{d\phi}{1 - K\sin(\phi)} = \int_0^x (\frac{1}{1 - K\sin(\phi)} - a)d\phi + ax$

where $f(x) = \int_0^x (\frac{1}{1 - K\sin(\phi)} - a)d\phi$
So $f(0) = f(2\pi) = 0$, so f is periodic with a period of 2π.
Thus

$$F' > 0 \implies \exists F^{-1}$$

.

Now let

$$\Phi(\frac{1}{a}y) = F^{-1}(y) - \frac{y}{a}$$

$$\Phi(2\pi) = F^{-1}(2a\pi) - 2\pi$$

Note: $F(2\pi) = \int_0^{2\pi} \frac{d\phi}{1 - K\sin(\phi)} = 2\pi a \implies F^{-1}(2\pi a) = 2\pi$
So $\Phi(2\pi) = 0$.
Therefore,

$$F^{-1}(y) = \Phi(\frac{y}{a}) + \frac{y}{a}$$

where Φ is 2π- periodic.
So

$$F(\phi(t)) = t - t_0 \implies \phi(t) = F^{-1}(t - t_0) = \mu(t - t_0) + \Phi(\mu(t - t_0))$$

Let $\phi_*(t) = \mu t + \Phi(\mu t)$
Note that $\sin(\phi_*)$ is $\frac{2\pi}{\mu} = T$ periodic.
Let $M = \frac{1}{T}\int_0^T \sin(\phi_*(t))dt$
By change of variables

$$\frac{1}{T}\int_0^{2\pi} \frac{\sin(\phi)}{1 - K\sin(\phi)}d\phi = \frac{1-\mu}{K}$$

Let

$$\theta(\mu t) = \int_0^t (\sin(\phi_*(s)) - M)ds$$

$$= \int_0^{\phi_*(t)} \frac{\sin(\phi)}{1 - K\sin(\phi)}d\phi - \frac{1-\mu}{K}t$$

$$= -\frac{1}{K}\Phi(\mu t)$$

Thus, $\phi_*(t) = \mu t - K\theta(\mu t)$
Now let

$$\Theta(\mu t) = \int_0^t [\sin(\mu t - K\theta(\mu t)) - M] ds$$

Take a derivative with respect to t

$$\mu\Theta^{'}(\mu t) = \sin(\mu t - K\theta(\mu t)) - M$$

$$\implies \mu\Theta^{'}(\mu t) = \sin(\mu t)\cos(K\theta(\mu t)) - \cos(\mu t)\sin(K\theta(\mu t)) - M$$

Recall that $a = 1 + \frac{K^2}{2} + O(K^4)$
$\mu = \frac{1}{a} = 1 - \frac{K^2}{2} + O(K^4)$
Thus,

$$(1 - \frac{K^2}{2} + O(K^4))\Theta^{'} = \sin(\mu t)(1 + O(K^2) - \cos(\mu t)(K + O(K^3)) - \frac{1}{2}K + O(K^3)$$

$$\Theta^{'} = \sin(\mu t) + O(K)$$

Therefore,

$$\Theta = 1 - \cos(\mu t) + O(K)$$

and

$$\phi_* = \mu t - K\cos(\mu t) + O(K^2)$$

6 Discussions

We have shown that a simple model of the human sleep-wake cycle can account for a variety of phenomena observed in temporal isolation experiments. The model proposed -here is the first analytically tractable model of the human circadian system, yet its performance is comparable to that of more elaborate models proposed by others. However there are a number of limitations in the present study. First, we have concentrated on the autonomous sleep-wake dynamics revealed in free-run experiments. While this is a necessary first step, one would ultimately like to address the entrainment of the human circadian system by external synchronizers, and its disruption during jet lag or rotating shift work schedules.A second limitation of our approach is its phenomenological character. The model parameters do not correspond in any obvious way to anatomical, neural, or pharmacological entities. It is also unclear how to relate the human circadian system to that of other organisms including mammals.Finally, the model proposed here treats sleep as a homogeneous state. It ignores the fascinating questions surrounding the various stages of sleep: rapid eye-movement (REM) sleep, in which dreams occur; slow-wave sleep, the deepest stage which in pathological cases is associated with bedwetting, sleepwalking, and night terrors; and the lighter stages of non-REM sleep, which mediate the transitions between dreaming, deep sleep, and wakefulness. These sleep stages oscillate in a 90-min cycle, and the interaction of this REM/non-REM cycle with the circadian cycle represents one of the most exciting open problems of theoretical sleep research.

References

1. Strogatz, S.H (1994), Nonlinear Dynamics and Chaos, with applications to Physics, Biology, Chemistry, and Engineering : Westview press 1994

2. Strogatz, S.H. (1987), Human sleep and circadian rhythms: a simple model based on two coupled oscillators. J.math. Biol.25: 327-347

3. Erementrout, G.B., and Kopell, N.(1990) Oscillator death in systems of coupled neural oscillators SIAM J. Appl.Math. 50, 125.

4. Rodolfo R. Rosales (2014), Answers to P-set 9, Dept Math, MIT, Web 11 Nov, 2014