Coupled oscillators and applications to human sleep and circadian rhythms

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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 : Sleep – Circadian – Human – Model – Oscillator

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 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 periodicities 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 h 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 24-25h. 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-h environment.

There is a interplay among jet lag or a rotating shift work schedule and sleep-wake cycle, the circadian cycle. The effects of jet lag, shift work schedules and insomnia affect economically to million of people each year. This phenomenon encourages to research on the human sleep and circadian rhythms.

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 and its equations may be solved analytically. The resulting analytical 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 we briefly discuss, dynamical systems and it's basic concepts. Section 3 reviews the trivial case of uncoupled oscillators. In Section 4, analyze the 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 (1990)'s model " Oscillator death".

2. Dynamical Systems and it's basic concepts [2]

2.1 Introduction

There are two main types of dynamical system: differential equation and iterated maps. Differential equations describe the evolution of systems in continuous time, where as iterated maps arise in problems where time is discrete. The theory of dynamical systems deals with the evolution of systems. It describes processes in motion, tries to predict the future of these systems or processes and understand the limitations of these predictions.

2.2 Asymptotic behavior of dynamical system

Asymptotic behavior refers to the long-term evolution of the solutions of the dynamical system as time goes to infinity. The subset of the phase space on which the trajectories reside at t $\rightarrow +\infty$ are called limit sets. These limit sets organize the vector flow in their 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 fixed point.

2.3 Fixed Points and Stability

Consider any ***one-dimensional system*** $\dot{x} = f(x)$.

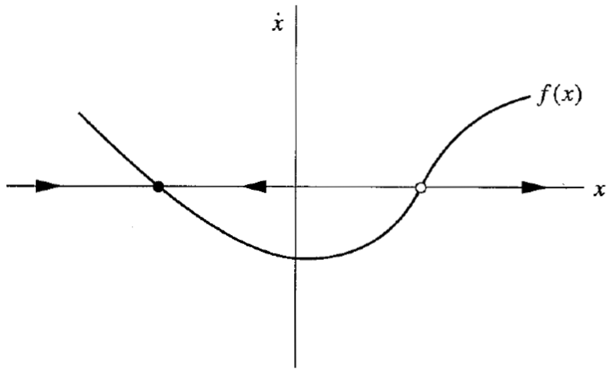


Figure 2.3.1

A picture like Figure 2.3.1, which shows all the qualitatively different trajectories of the system, is called a phase portrait.The appearance of the phase portrait is controlled by the fixed points $x*$, defined by $f(x^*) = 0$; they correspond to stagnation points of the flow.The solid black dot it a stable fixed point, where the local flow is toward it and the open dot is an unstable fixed point, the flow is away from it. The fixed points represent equilibrium solution, which is also called "Steady" in term of the original differential equation. An equilibrium is defined to be stable if all sufficiently small disturbances away from it damp out in time. Further, stable equilibria are represented geometrically by stable fixed points and unstable equilibria, in which disturbances grow in time, are represented by unstable fixed points.

A two- dimensional linear system is as system of the form;

$$\dot{x} = ax + by$$
$$\dot{y} = cx + dy$$

where a, b, c, d are parameters. This system can be written more compactly in matrix form as ;

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

Where

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}$$

and

$$x = \begin{bmatrix} x \\ y \end{bmatrix}$$

Such a system is liner in the sense that if $\mathbf{x}_1$ and $\mathbf{x}_2$ are solution, the so is any liner combination $c_1\mathbf{x_1} + c_2\mathbf{x_2}$. Then $\dot{\mathbf{x}} = 0$ when $\mathbf{x} = 0$, so $\mathbf{x}^* = 0$ is always a fixed point for any choice of A.

Classification of Fixed Point

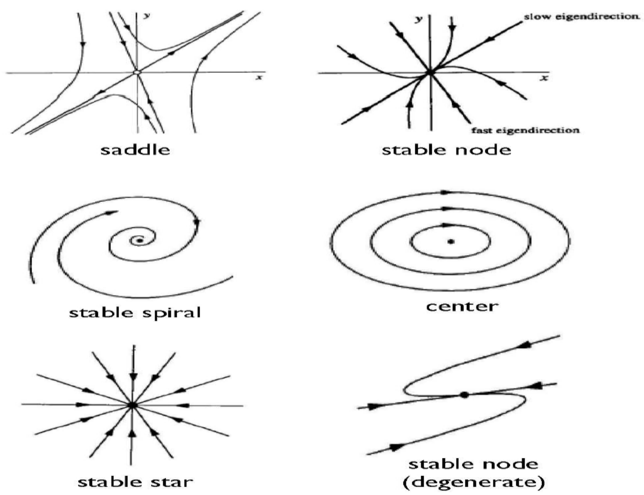


Figure 2.3.2: Fixed point -Two-dimensional systems. Not shown: unstable versions of node, spiral, and star (reverse direction of arrows to turn stable into unstable).

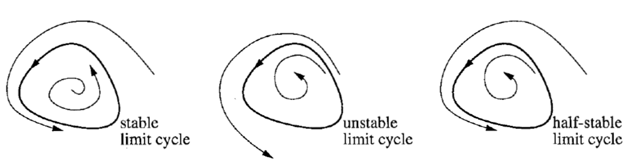
Figure 2.3.2 summarized the major type of fixed points. For two-dimensional system, there are five generic types of fixed points. They are classified according to the eigenvalues of the linearized dynamics at the fixed point. For a real $2x2$ matrix, the eigenvalues must be real or else must be a complex conjugate pair. The five types of fixed points are then

$\lambda_1 > 0, \lambda_2 > 0$: (1) unstable node
$\lambda_1 > 0, \lambda_2 < 0$: (2) saddle point
$\lambda_1 < 0, \lambda_2 < 0$: (3) stable node
$Re(\lambda_1) > 0, \lambda_2 = \lambda_1^*$: (4) unstable spiral
$Re(\lambda_1) < 0, \lambda_2 = \lambda_1^*$: (5) stable spiral

Where λ s are eigenvalues.

2.4 Limit cycles

A Limit cycle is an isolated closed trajectory. This mean that neighboring trajectories are not closed ; they spiral either towards or away from the limit cycle.



If all neighboring trajectories approach the limit cycle, we say the limit cycle is stable or attracting. Otherwise the limit cycle is unstable or in exceptional cases, half-stable.

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.

Saddle-Node Bifurcation

The saddle-node bifurcation is the basic mechanism by which fixed points are 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.

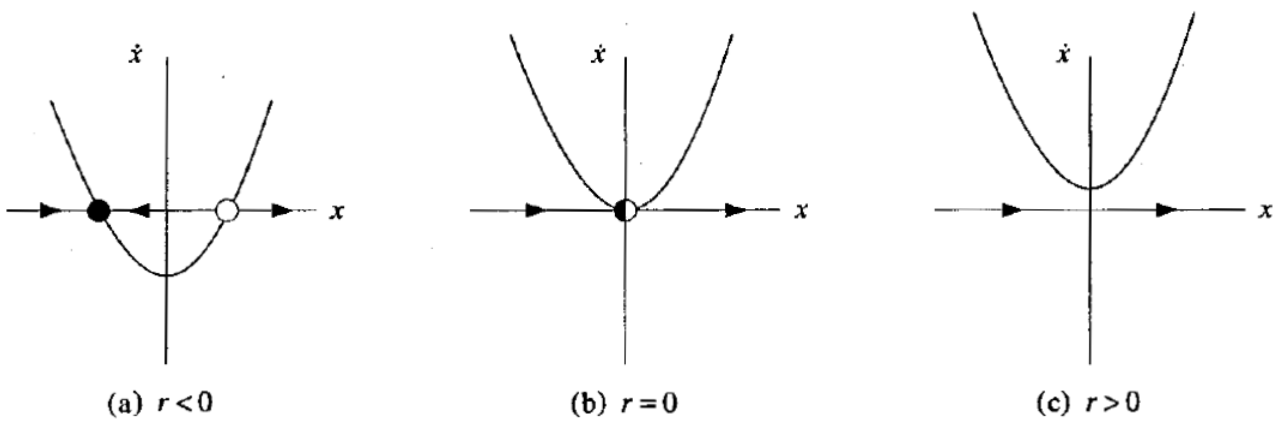


Figure 2.5.1

$r < 0$, there are two fixed, one stable and one unstable. When $r = 0$, the fixed points coalesce into a half-stable fixed point at $x^* = 0$. For $r > 0$ no fixed point present in the system. In this example, a bifurcation occurred at $r = 0$, since the vector field for $r < 0$ and $r > 0$ are qualitatively different.

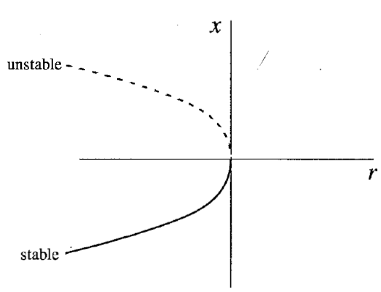


Figure 2.5.2

Figure 2.5.2 is bifurcation diagram for the saddle-node bifurcation.

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

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

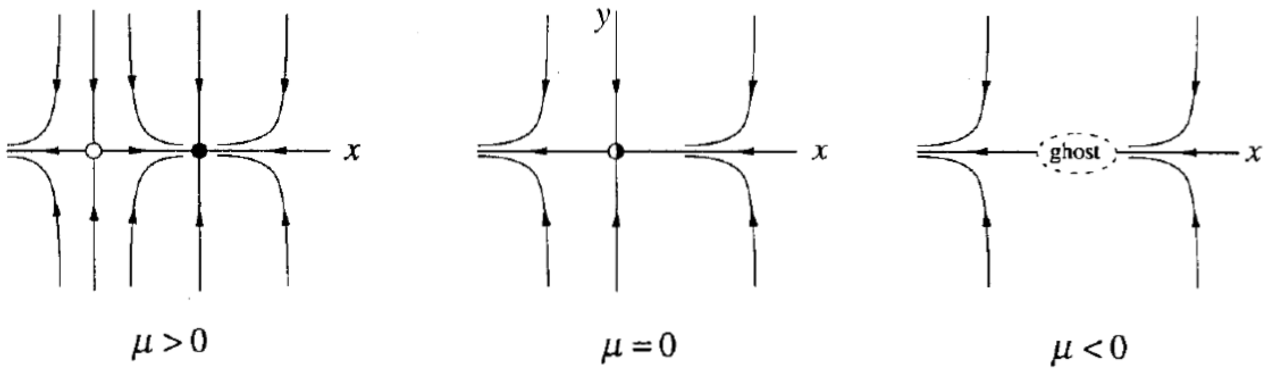


Figure 5.2.3

For $\mu > 0$, there are two fixed points, as stable at $(x^*, y^*) = (\sqrt{\mu}, 0)$ and a saddle at $(-\sqrt{\mu}, 0)$. As μ decrease, the saddle and node approach each other, then collide when $\mu = 0$ and finally disappear when $\mu < 0$.

Hopf Bifurcation

bifurcation involving the change in the number or stability of a periodic solution, or limit cycle, is a periodic bifurcation. A Hopf bifurcation is a periodic bifurcation in which a new limit cycle is born from a stationary solution.
Suppose a two -dimensional system has a stable fixed point. There are two ways to for stable fixed point to lose stability. If the fixed point is stable, the eigenvalues λ_1, λ_2 must both lies in the left half-plane Re $\lambda, 0$.

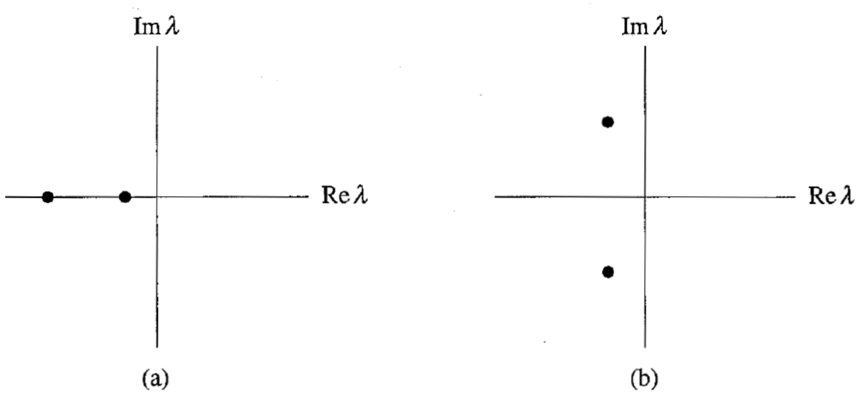


Figure 5.2.4
Then there are two possible pictures; either eigenvalues are both real and negative (Figure 5.2.4 a) or they are complex conjugates (Figure 5.2.4 b). To destabilize the fixed point, we nee one or both of the eigenvalues to cross into the right half-plain as μ varies. :

* 1 real eigenvalue passes through $\lambda = 0$ (zero-eigenvalue bifurcations), This is the saddle-node which we discussed above.
* 2 complex conjugate eigenvalues cross into right half plane; Hopf Bifurcation

Supercritical Hopf Bifurcation occurs if exponentially damped oscillation changes to growth at μ_c, and becomes small limit cycle oscillation about formerly steady state. In terms of the flow in phase space, a Supercritical Hopf bifurcation occurs when stable spiral changes into unstable spiral surrounded by small limit cycle.

Consider the following simple example;

$\dot{r} = \mu r - r^3$
$\dot{\theta} = \omega + br^2$

where μ controls stability at origin,ω gives frequency of infinitismal oscillations, b determines dependence of frequency on larger amplitude.

Eigenvalues $\lambda = \mu \pm \omega$ cross imaginary axis from left to right.

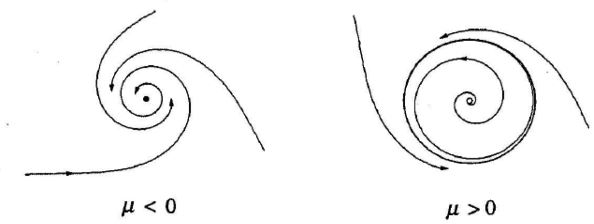


Figure 2.5.5

Rules of Thumb for Supercritical Hopf Bifurcations;

* Size of limit cycle grows continuously from zero, and increases proportionally to $\sqrt{\mu - \mu_C}$ close to μ_c.
* Frequency of limit cycle $\approx$ Im $\lambda + O(\mu - \mu_c)$ near μ_c
* Limit cycle is elliptical. Its shape becomes distorted as μ moves away from μ_c.
* Eigenvalues follow curvy path (see figure).

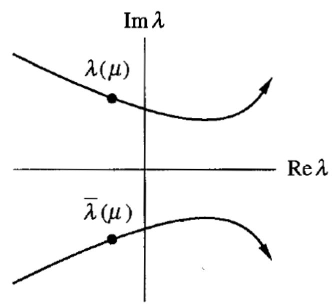


Figure 2.5.6

3. Uncoupled System [2]

3.1 *Introduction*

One of the important two-dimensional phase space is the torus and has the natural phase space for system of the form

$$\dot{\theta}_1 = f_1(\theta_1, \theta_2)$$

$$\dot{\theta}_2 = f_2(\theta_1, \theta_2)$$

where f_1 and f_2 are periodic in both arguments. For instance, simple model of ***coupled oscillators*** is given by

$$\dot{\theta}_1 = \omega_1 - C_1 \cos 2\pi(\theta_2 - \theta_1)$$

$$\dot{\theta}_2 = \omega_2 + C_2 \cos 2\pi(\theta_1 - \theta_2) \quad (1)$$

where θ_1, θ_2 are the *phases* of the oscillators, $\omega_1, \omega_2 > 0$ are their natural frequencies and $C_1, C_2 \geqslant 0$ are *coupling constants.*

The trivial case of ***uncoupled oscillators,*** where $C_1, C_2 = 0$ gives some interesting phenomenon. Then equations (1) reduces to

$$\dot{\theta}_1 = \omega_1$$

$$\dot{\theta}_2 = \omega_2$$

Then the corresponding trajectories are straight lines with constant slope $d\theta_2/d\theta_1 = \omega_2/\omega_1$. Depending on whether slop is a rational or an irrational one there are two qualitatively different cases.

Case 1: A rational slope

Then $\omega_1/\omega_2 = p\,/\,q$, where p, q are some integers with no common factors. If we regard θ_1 and θ_2 as points on the circle, θ_1 completes p revolutions in the same time that θ_2 completes q revolution. Therefore, in this case all trajectories are closed orbits on the torus.

For example, if $p = 3$, $q = 2$ Figure 3.1.1 shows the phase portrait.

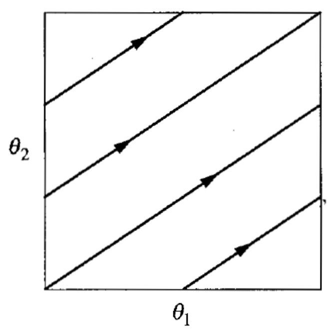


Figure 3.3.1

Case 2: An irrational slope

Then every trajectory winds around endlessly on the tours. They are never intersection itself or never quite closing. This flow is called ***quasiperiodic***.

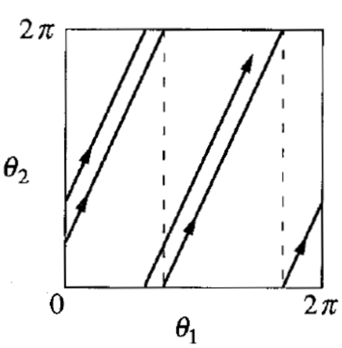


Figure 3.3.2

How can we be sure the trajectories never close? Any closed trajectory necessarily makes an integer number of revolution in both θ_1 and θ_2; hence the slope would have to be rational, contrary to assumption. Further, when the slop is irrational, each trajectory is ***dense*** on the torus, which means each trajectory comes arbitrarily close to any given point on the torus. However the trajectory does not pass through each point; it just comes arbitrarily close. Quasiperiodicity is significant, as it is a new type of long-term behavior, which only occurs on the torus. Strogatz [2]

4. PHASE Model

4.1 *Introduction*

Strogatz discussed main findings of free-run experiments of Circadian rhythm in section 2. Experimental Data [1]. 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.

Further he reviewed many other regularities which were presented throughout the world literature on internally dsynchronized subjects. In this section, we revisit a simple model, Strogatz proposed, which can illuminate this empirical relationships. In particular, the relation between sleep length and circadian phase of sleep onset is discussed in section 4.5.

Strogatz [1] used the equation (1) to model the interaction between human-circadian rhythms and the sleep-wake cycle. 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 *Model structure* [1]

The structure of the PHASE model is summarized in Fig.4.2.1 [1]. θ_1 and θ_2 are the phases of the two oscillators which are real numbers and we considered them as point on the circle of unit circumference. The governing equations are

$$\dot{\theta}_1 = \omega_1 - C_1 \cos 2\pi(\theta_2 - \theta_1) \quad (1a)$$
$$\dot{\theta}_2 = \omega_2 - C_2 \cos 2\pi(\theta_1 - \theta_2) \quad (1b)$$

where ω_1, ω_2 are intrinsic frequencies and C_1, C_2 are coupling strengths.

The overdot signifies time differentiation. 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 speed 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.

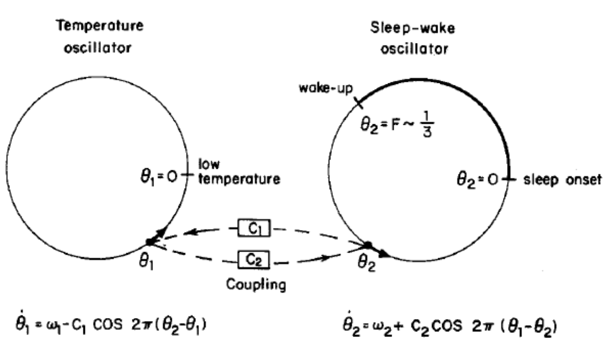


Figure 4.2.1

We adopt the conventions that oscillator #1 drives the circadian temperature rhythm and oscillator #2 drives the sleep-wake cycle. Sleep is defined to occupy some fraction F of theθ_2 circle:

$$\begin{aligned} \theta_2 &= 0 \text{ at sleep onset} \\ \theta_2 &= F \text{ at wake-up} \end{aligned} \quad (2)$$

Here $0 \leqslant F \leqslant$, and typically $F \backsim \frac{1}{3}$, since people sleep 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 *Synchrony* [1]

To study the synchronization and desynchronization of the constituent oscillators, consider the phase difference.

$$\psi = \theta_1 - \theta_2 \tag{3}$$

Subtracting the equation in (1) we see

$$\dot{\psi} = \Omega - C \cos 2\pi\psi \tag{4}$$

where

$$\Omega = \omega_1 - \omega_2 \tag{5}$$

and

$$C = C_1 + C_2 > 0 \tag{6}$$

Here 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, so the $\dot{\psi} = 0$ has a solution. Otherwise the phase-difference ψ continues to grow as one oscillator periodically over takes the other. This desynchronized case will be considered in Sect.4.4. For not consider the synchronized case, i.e., assume

$$K = \left| \frac{C}{\Omega} \right| > 1 \tag{7}$$

Then the internally synchronized phase relation ψ^* is obtained by solving (4) for $\dot{\psi} = 0$;

$$\psi^* = \pm \frac{1}{2\pi} \cos^{-1} \left(\frac{\Omega}{C} \right) \tag{8}$$

These are two solution implicit in (8); the stable one is that for which $d\dot{\psi}/d\psi < 0$.Here the range of $\cos^{-1}$ is taken as $[0, \pi]$, so

$$\psi^* = (-1/2\pi) \cos^{-1} \left(\frac{\Omega}{C} \right) \tag{9}$$

is the stable solution.

Using (8) we can also find the "compromise" frequency ω^* adopted by the synchronized system. During internal synchrony (1) becomes

$$\dot{\theta}_1 = \omega_1 - C_1 \left(\frac{\Omega}{C} \right) \tag{10}$$

$$\dot{\theta}_2 = \omega_2 - C_2 \left(\frac{\Omega}{C} \right) \tag{11}$$

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

$$\omega^* = \frac{C_1 \omega_2 + C_2 \omega_1}{C_1 + C_2} \tag{12}$$

This frequency differs from the intrinsic frequencies ω_1 and ω_2 by amounts $\Delta\omega_1$ and $\Delta\omega_2$:

$$\Delta\omega_1 = \omega^* - \omega_1 = -C_1 \Omega / C \tag{13}$$

and

$$\Delta\omega_2 = \omega^* - \omega_2 = C_2\Omega/C \tag{14}$$

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

$$\left|\frac{\Delta\omega_2}{\Delta\omega_2}\right| = \left|\frac{C_1}{C_2}\right| \tag{15}$$

Estimates of the absolute magnitudes of the parameters C_1, C_2, for human subjects are as follows;

4.3.1 Parameter estimates for human subject

The earlier Eqs.(8- 14) 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. Hence we expect

$$C_1 << C_2 \tag{16}$$

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

$$C_2 \sim \text{frequency difference } \omega \text{ observed at onset of desynchrony} \tag{17}$$

Choosing units where $\omega = 1$, a typical value of ω would be

$$\Omega \sim 1/6 \cong 0.16 \sim 6 \text{ day beat period} \tag{18}$$

Hence

$$C_2 \sim 0.16 \tag{19}$$

From (13), (14), (16), and (18)

$$\Delta\omega_2 \sim 0.16 \tag{20}$$

To obtain C1, we recall Wever's [1] result that after desynchrony, the temperature cycle shortens by ~ 0.7 h. for a synchronized period of 25.5h, this corresponds to

$$\omega^* = 24.8/25.5 \cong 0.97 \tag{21}$$

Since

$$\Delta\omega_1 = \omega^* - \omega_1$$
$$\sim 0.97 - 1.0$$

$$\sim -0.03 \tag{22}$$

We find from (13) and (14) that

$$C_1 = |C_2\Delta\omega_1/\Delta\omega_2| \sim 0.03 \tag{23}$$

$$|C_1/C_2| \sim |0.03/0.16| \sim 1/5 \tag{24}$$

4.4 *Desynchrony*

Equation (4) 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 biologist call ”internal relative coordination” [1]. The oscillators periodically move through a full cycle of mutual phase relations, with a ”beat” frequency β, obtained as follows. From (4) the time required for ψ to change from 0 to 1 is $1/\beta$, given by

$$1/\beta = \int_0^{1/\beta} dt = \int_0^1 \frac{d\psi}{\Omega - C\cos 2\pi} \tag{25}$$

$$= (\Omega^2 - C^2)^{1/2} \tag{26}$$

(For a derivation of the beat frequency, see subsection 4.4.1 Exact solution for $\theta_1 and \theta_2$) Hence the beat frequency β satisfies

$$\beta = (\Omega^2 - C^2)^{1/2} \tag{27}$$

$$= \Omega \left(1 - \frac{C^2}{\Omega^2}\right)^{-1/2} \tag{28}$$

Two special cases:

(i) For C = 0, the beat frequency reduces to $\beta = \Omega = \omega_1 - \omega_2$, the noninterractive beat frequency.
(ii) As $C \to |\Omega|, \beta \to 0$ according to a square root dependence (28). 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 $C_1 = 0$, i.e. there is no feedback onto the circadian pacemaker. As discussed in the subsection 4.3.1 Parameter estimates for human subject, 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 scaling time such that

$$\omega_1 = 1 \tag{29}$$

We obtain

$$\theta_1(t) = t \tag{30}$$

As shown in subsection 4.4.1, Equation (4) may be solved exactly to yield a complicated (but monotonic and hence invertible) function $\psi(t)$. Rather than writing this function explicitly here, it will be referred to simply as $\psi(t)$.
Having solved for $\theta_1(t)$ and $\psi(t)$, we obtain $\theta_2(t)$:

$$\theta_2(t) = \theta_1(t) - \psi(t) \tag{31}$$

$$= t - \psi(t) \tag{32}$$

4.4.1 Exact solution for θ_1 and θ_2

We consider the system

$$\dot{\theta}_1 = 1 \tag{33}$$

$$\dot{\theta}_2 = \omega + C\cos 2\pi(\theta_1 - \theta_2) \tag{34}$$

This system subsumes Eq (1) of Sect. 4.2, for the case $C_1 = 0$. Time is scaled so the $\omega_1 = 1$; then ω_2 becomes ω and C_2 becomes C in this new notation.
Let

$$\psi = \theta_1 - \theta_2 \tag{35}$$

Then

$$\dot{\psi} = 1 - \omega - C\cos 2\pi\psi \tag{36}$$

$$= \Omega - C\cos 2\pi\psi \tag{37}$$

where

$$\Omega = 1 - \omega \tag{38}$$

Rescale time again: Set

$$T = \Omega t \tag{39}$$

and let

$$\psi' = d\psi/dT \tag{40}$$

Then

$$\psi' = 1 - k\cos 2\pi\psi \tag{41}$$

where

$$k = C/\Omega \tag{42}$$

Here k represents a dimensionless constant; desynchrony occurs when

$$K < 1 \tag{43}$$

Equation (41) can be solved by separation of variables, followed by integration. Using the substitution we obtain

$$T + \text{constant} = \int \frac{d\psi}{1 - k\cos 2\pi\psi} \tag{44}$$

$$= \left(\frac{1}{\pi(1+k)b}\right)\tan^{-1}(x/b) \tag{45}$$

where

$$b^2 = (1-k)/(1+k) \tag{46}$$

Equation (45) may be solved for x and then for ψ to yield

$$\psi(t) = (1/\pi)\tan^{-1} u(t) \tag{47}$$

where

$$u(t) = b\tan(\pi\beta t + C_0) \tag{48}$$

$$\beta = \Omega(1-k^2)^{1/2} \text{ is the beat frequency} \tag{49}$$

$$C_0 = \tan^{-1}((1/b)\tan\pi\psi_0) \tag{50}$$

$$\psi_0 = \psi(t=0) \text{ is the initial condition} \tag{51}$$

$$b^2 = (1-k)/(1+k) \tag{52}$$

$$k = C/(1-\omega)\text{is the dimensionless coupling} \tag{53}$$

The Eqs. (47) - (53) solve the equation given by (35) for the desynchronized case assumed in (43). Then θ_1 and θ_2 are easily solved for, as shown in Eqs.(30),(32) of Sect.4.4

Monotonicity of $\theta_2(t)$

Around the discussion of Fig.4.5, it was stated that $\theta_2(t)$ is monotonic function of t, for certain reasonable choices of parameters. All that is required in fact is $C < |\Omega|$ (the condition characterizing desynchrony) and $\omega_2 > 1/2$ (activity rhythm period is less than $\sim 50h$). The monotonicity of θ_2 is established as follows:
$\omega_2 > 1/2 \Rightarrow \omega_2 > 1-\omega_2$

$\Rightarrow \omega_2 > \Omega$ (from (30) and (5))
$\Rightarrow \omega_2 + \Omega\cos 2\pi\psi > 0$ for all ψ
$\Rightarrow \omega_2 + C_2\cos 2\pi\psi > 0$, Since $C_2 \leqslant C \leqslant |\Omega|$
$\Rightarrow \dot{\theta}_2 > 0$ (from (1))
$\Rightarrow \theta_2(t)$ is monotone in t, as required.

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 ρ of the sleep episode on the phase ϕ_s of the circadian temperature cycle at sleep on set. The experimental findings [1] shows that sleep episodes beginning near the temperature trough tend to be short ($\sim 7h$), while those beginning near the temperature maximum are long ($\sim 15h$). The robustness of the $\phi_s : \rho$ relationship came as a surprise, and has been discussed extensively in the literature [1]. Many theoretician have used it as a benchmark to test their models [1]. Hence it is of interest to derive the form of the $\phi_s ; \rho$ relationship predicted by the PHASE model.

According to the convention established in (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 calculate the $\phi_s : \rho$ relationship it is most convenient to choose a new origin of time, with t = 0 at sleep onset, i.e.

$$\theta_2(0) = 0 \tag{54}$$

$$\theta_1(0) = \phi_s \tag{55}$$

$$\psi(0) = \theta_1(0) - \theta_2(0) = \phi_s \tag{56}$$

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

$$\theta_2(\rho) = F \tag{57}$$

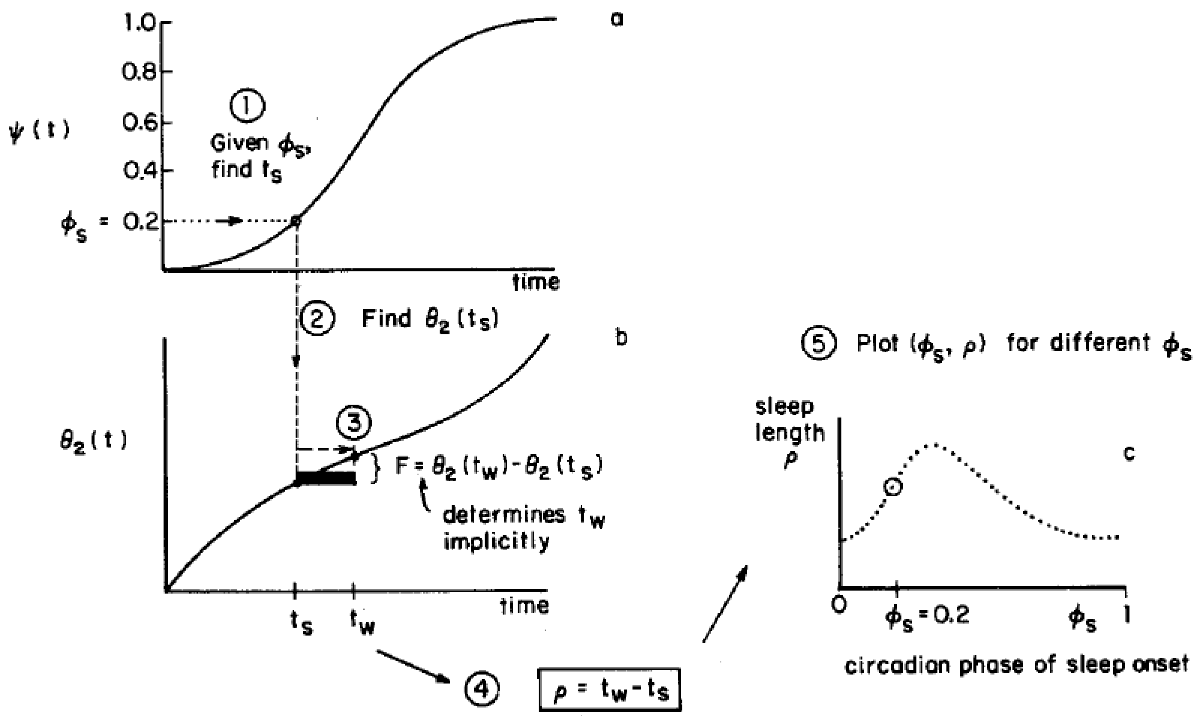


Figure 4.5

$$\theta_1(\rho) = \phi_s + \rho \tag{58}$$

$$\psi(\rho) = \phi_s + \rho - F \tag{59}$$

Together (56) and (59) constitute an implicit set of equations for ρ, as a function of ϕ_s and F. Because of the trigonometric form of ψ (see Eqs.(47), (48) of section 4.4.1), the solution for ρ requires graphical or numerical techniques.

One such graphical method is indicated in Fig. AS shown in Sect. 4.4 and yield the curves $\theta_2(t)$ and $\psi(t)$. Initial condition 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 $\theta_2 = 0$. To find $\rho(\phi_s)$, we follow a multi-step procedure (Fig):

(i) Choose ϕ_s, the phase of sleep onset.
(ii) Find t_s such that $\psi(t_s) = \phi_s$. This is always possible since ψ is invertible.
(iii) Reading t_s as the time of sleep onset, find (the first) t_s such that $\theta_2(t_w) = \theta_2(t_s) + F$.
(iv) Thus t_w represents the time of wake-up and so $\rho = t_w - t_s$. As Fig. 5b reveals, long sleeps arise 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 (Fig. 5C), as observed in real data []. Figure 5 c also mimics the sheared sinusoidal shape of the observed $\phi_s : \rho$ relation [(Fig.3a)].

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

$$g = \psi^{-1} \text{ and } h = \theta_2^{-1} \tag{60}$$

From step (ii) above,

$$g(\phi_s) = t_s \tag{61}$$

Thus

$$\rho(\phi_s) = h(\theta_2(g(\phi_s)) + F) - g(\phi_s) \tag{62}$$

Equation (62) is the first instance of an exact expression for the $\phi_s : \rho$ relation derived from a mathematical model of the sleep-wake cycle.

5. Oscillator Death and bifurcation on a torus [3]

Since about 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:

$\dot{\theta}_1 = \omega_1 + \sin\theta_1 \cos\theta_2,$
$\dot{\theta}_2 = \omega_2 + \sin\theta_2 \cos\theta_1$

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 [4].

Consider the equations;

$$\dot{\theta}_1 = \omega_1 + \sin\theta_1 \cos\theta_2 \tag{63}$$

$$\dot{\theta}_2 = \omega_2 + \sin\theta_2 \cos\theta_1 \tag{64}$$

Where $\omega_1, \omega_2 \geq 0$

Let $\phi = \theta_1 + \theta_2$ and $\psi = \theta_1 - \theta_2$ Then using standard trigonometric formulas we can show that the system has following equivalent forms;

$$\dot{\phi} = \omega_1 + \omega_2 + \sin\phi \text{ and } \dot{\psi} = \omega_1 - \omega_2 + \sin\psi \tag{65}$$

Hence the system is **uncoupled** in these variables. It follows that

1. Case $\omega_1 > \omega_2 + 1$ Oscillators ”independent”, The solution are quasi-periodic, with two periods.
Since $\omega_1 + \omega_2 > \omega_1 - \omega_2 > 1$, from 5.1 Notes

$$\phi = \mu_1 t + \Phi \text{ and } \phi = \mu_2 t + \psi \text{ where } \mu_1 > \mu > 0 \tag{66}$$

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

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

$$\theta_1 = \frac{\mu_1 + \mu_2}{2} t + \frac{1}{2}(\Phi + \Psi) \text{ and } \theta_2 = \frac{\mu_1 - \mu_2}{2} t = \frac{1}{2}(\Phi - \Psi) \tag{67}$$

instead of the uncoupled phases $\theta_j = \omega_j(t - t_{0j})$. The frequencies are not constant either, that is:

$$\dot{\theta}_1 = \frac{\mu_1 + \mu_2}{2} + \frac{1}{2}(\dot{\Phi} + \dot{\Psi}) \text{ and } \dot{\theta}_2 = \frac{\mu_1 - \mu_2}{2} + \frac{1}{2} + (\dot{\Phi} - \dot{\Psi}) \tag{68}$$

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

2. Case $\omega_1 = \omega_2 + 1$. **Bifurcation into (out of) phase locking.** Φ has the same form as in (63), but the equation for Ψ in (65) has a semi-stable critical point $\Psi = \pi/2 + 2n\pi$. 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 situation in item 1 as $\omega_1 - \omega 2$ decrease to 1. Then μ_2 decrease to 0 and T_2 increase to ∞. Hence ψ becomes very slowly varying - a constant for "short enough" time periods, and the oscillator's behavior approximates that of a phase locked one, with a common frequency.

Consider the situation in item 3 as $\omega_1 - \omega_2$ increase to 1. Then ψ_u and ψ_s coalesce into $\psi_u = \psi_s = \pi/2$ and the behavior limits to the one here.

3. Case $|\omega_2 + 1| < \omega_1 < \omega_2 + 1$. **Phase lock is a global attractor**. Since $|\omega_1 - \omega_2| < 1$, the equation for ψ in (65) has two critical points, one unstable (call it ψ_u) and another a stable global attractor (call it ψ_s). Thus a constant phase difference $\psi = \psi_s$ is a global attractor. On the other hand $\omega_1 + \omega_2 > 1$ and "5.1 Notes" yields

$$\phi = \mu_1 t + \Phi \text{ where } \mu_1 > 0 \text{ and } \Phi \text{ is periodic of period } T_1 = \frac{2\pi}{\mu_1} \tag{69}$$

$$\text{Thus, the attracting solution is } \theta_j = \frac{1}{2}\mu_1 t + \frac{1}{2}(\Phi - (-1)^j \psi_s) \tag{70}$$

So that the tow oscillators run with a common (variable) frequency $\omega = \frac{1}{2}\mu_1 + \frac{1}{2}\dot{\Phi}$. This solution is limit cycle, with period $T - 1$.

4. Case $\omega_1 + \omega_2 = 1$. **Bifurcation from/to oscillator death to /from phase locking**. The equation for ψ in (65) has "the same" two critical points, ψ_u and ψ_s in item 3, while the equation for ϕ has a single, semi-stable, critical points $\pi/2 + 2n\pi$. The system then approaches, as t $\to \infty$, the critical point $\phi = \pi/2 + 2n\pi$ and $\psi = \psi_s$. But this point is semi-stable, so a small perturbation can take ϕ out of equilibrium. Then ϕ increases by 2π, till it reaches the critical point again $(n \to n+1)$.

The case in item 5 approaches the behavior hear as $\omega_1 + \omega_2$ decrease to 0 and T_1 increases to ∞. Hence ϕ becomes very slowly varying - a constant for "short enough" time periods. The case in item 5 approaches the behavior here as $\omega_1 + \omega_2$ increase to 1, because then ϕ_u and ϕ_s coalesce into $\pi/2 + 2n\pi$.

5. Case $\omega_1 + \omega_2 < 1$. **Oscillator death**. Since the ω_j are positive, $|\omega_1 - \omega_2| < 1$. Thus both equation in (65) have critical points, one unstable in each (ϕ_u and ψ_u), and another a stable global attractor in each (ϕ_s and ψ_s). Thus the system in (63) and (64) has global attractor (a stable node), given by

$$(\theta_1, \theta_2) = \frac{1}{2}(\phi_s + \psi_s, \phi_s - \psi_s) \tag{71}$$

Note that $\frac{1}{2}(\phi_s + \psi_u, \phi_s - \psi_u)$ 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. Case $\omega_2 = \omega_1 + 1$. **Bifurcation into (out of) phase locking**. This case it the same as the one in item 2, via the system symmetry $\theta_1 \leftrightarrow \theta_2$.

7. Case $\omega_2 > \omega_1 + 1$. **Oscillators "independent", The solutions are quasi-periodic, with two periods.** This is the same as the one in item2, via the system symmetery $\theta_1 \leftrightarrow \theta_2$.

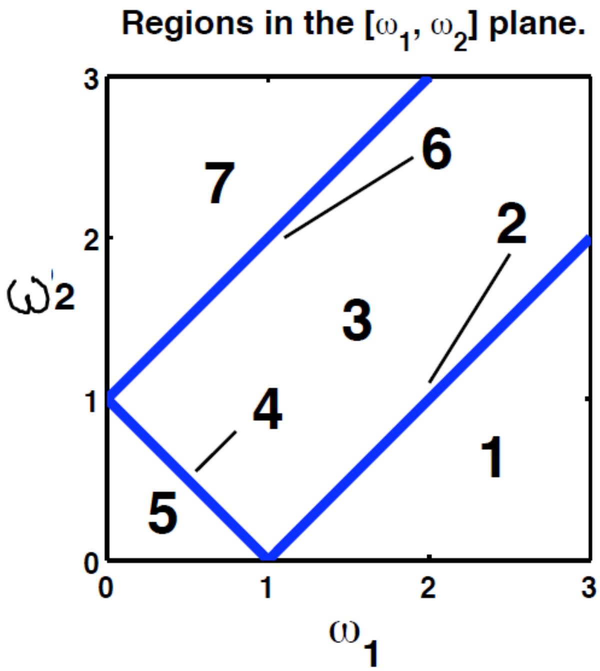


Figure 5.1: Oscillator death and bifurcation in the plane. Regions in the positive quadrant of the [ω_1, ω_2] - plane corresponding to different behaviors (63) and (64) can have. The boundaries between the regions correspond to bifurcations. These are;

2, where $\omega_1 - \omega_2 = 1$

4, where $\omega_1 + \omega_2 = 1$; and

6, where $\omega 2 - \omega_1 = 1$

5.1 Notes for Section 5

Consider the equation

$$\dot{\phi} = 1 - K\sin\phi, \text{ where } 0 < K < 1 \text{ and}$$

$$\phi(t_0) = 0$$

$$\frac{d\phi}{1 - K\sin\phi} = \int_{t_0}^{t} dt$$

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

Let $F(x) = f(x) + ax$

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

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

$f(2\pi) = f(0) = 0$, thus f is 2π periodic,

F is invertible and

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

Where Φ is 2π periodic , since

$$F(2\pi) = f(2\pi) + 2\pi a = 2\pi a$$

Therefore,

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

$$\phi(2\pi) = F^{-1}(2\pi a) - 2\pi = 0$$

Thus,

$$\phi(t) = \mu(t - t_0) + \Phi(\mu(t - t_0))$$

$$\boxed{\phi(t) = \mu t + \phi(\mu t)}$$

Note that $\sin(\phi_*(t))$ is periodic in t, of period $T = \frac{2\pi}{\mu}$
$M = average(\sin\phi)$

$$M = \frac{1}{T}\int_0^T \sin(\phi_*(t))dt = \frac{1}{T}\int_0^{2\pi} \frac{\sin\phi}{1 - K\sin\phi} d\phi$$

$$= \frac{\mu}{2\pi}\left[\frac{1}{k}\int_0^{2\pi} \frac{K\sin\phi - 1}{1 - K\sin\phi} + \frac{1}{K}\int_0^{2\pi} \frac{1}{1 - K\sin\phi}\right]$$

$$= \frac{\mu}{2\pi}\left[-\frac{2\pi}{K} + \frac{2\pi a}{K}\right]$$

$$= \frac{\mu}{K}\left(\frac{1}{\mu} - 1\right) = \frac{1 - \mu}{K}$$

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

$$= \int_0^t \sin(\phi_*(s))ds - Mt \Big| \text{ substitution } \phi = \phi_*(s)$$

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

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

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

$$= -\frac{1}{K}\Big[\mu t + \phi(\mu t)\Big] = \frac{1}{K}t - \frac{1}{K}t + \frac{\mu}{K}t$$

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

Thus,

$$\phi_*(t) = \mu t - K\Phi(\mu t)$$

Thus,

$$\Phi(\mu t) = \int_0^t \Big(\sin(\mu s - K\Phi(\mu s)) - M\Big) ds \Big| \frac{d}{dt}$$

$\mu\Phi'(\mu t) = \sin(\mu t - K\Phi(\mu t)) - M$

$\mu\Phi' = \sin(\mu t)\cos(K\Phi) - cos(\mu t)sin(K\Phi) - M$

Note that $a = 1 + \frac{K^2}{2} + O(K^4)$,

$\mu = \frac{1}{a} = 1 - \frac{k^2}{2} + O(K^4)$

Thus,

$$\left(1 - \frac{k^2}{2} + O(K^4)\right)\Phi' = \sin(\mu t)\left(1 + O(K^2)\right) - \cos(\mu t)\big(K + O(K^3)\big) - \frac{1}{2}K + O(K^3)$$

$\Phi' = \sin(\mu t) + O(K)$

Therefore,

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

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

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