

A Limit Cycle Model about the Entrainment of Circadian Rhythm

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일주기 리듬 편승과 관련된 한계주기궤도

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ABSTRACT : All the organisms on the earth are affected by the repeating signals from the ambient environment caused by the movements of the sun and the earth. Their physiological and behavioral activities such as reproduction, functional pathway of various molecules, and developmental stage, are reflected by the cyclicity whether it is daily(circadian) or annual rhythms. An essential function of circadian rhythms is to provide an internal estimate of the external local time, thereby allowing the organism to program its activities so that they occur at an appropriate time in the daily environment. Of many rhythmic patterns, the circadian rhythms are considered in this review, focusing on the limit cycle, which is a model to investigate the entrainment.

Key words : Cyclicity, Entrainment, Circadian rhythm, Limit cycle, Free running activity, Phase response curve.

요 약 : 현존하는 생물들은 주변 환경에서 오는 반복되는 신호의 영향을 받고 있다. 그 신호는 태양 및 지구의 운동 관계에서 되풀이되어 일어나는 주기적인 변화이다. 생식 및 번식, 세포 내 각종 분자들의 작용, 발생 단계에 일어나는 다양한 변화 등등의 생리학적/행동학적 활동들은 모두 일주기든 연주기든 주기성을 띠고 있다. 일주기 리듬을 통하여 생물들은 근본적으로 주변의 외부 시간에 그 생물 자체가 적응하게 하여, 일상적으로 반복되는 환경에서 적절한 시기에 활동하도록 하는 것이다. 각종 리드미컬한 패턴 중에 편승 변환을 고찰하기 위해 제시된 한계주기궤도에 초점을 맞추어 고찰하고자 한다.

INTRODUCTION

The animals of temperature zone exhibit remarkable seasonal rhythms in physiological and behavioral activities. Of all the respects, reproductive functions demand the greatest energy for the survival of both parents and offsprings. Young are typically born in the favorable seasons such as spring and summer, and fertile matings are scheduled accordingly. In the light of environmental fluctuations that require a heavy load on individuals who time

their effort unsuitably, this is not unexpected. Matching of the timing of reproductive activity to the annual phase of maximal availability and minimal expenditure of energy (the abundance of food and warmer temperatures) is thus of great selective advantage. Although fluctuations in temperature and rainfall can acutely influence the reproductive activity, daylength provides a stable and reliable predictor of future energetic demands that enables animals to initiate long-term acclimation(Gaston & Menaker, 1967; Elliott, 1976; Stetson & Watson-Whitmyre, 1984; Choi, 1996). Therefore, it is believable why photoperiod acts as a proximate regulator of neuroendocrine function in seasonal species. Mammals with short gestation periods, such as rodents, are typically stimulated to reproduce by long days.

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Short days regresses the gonadal activity in both sexes.

The annual cycle of reproduction is mainly affected by the environment which is determined by the sun. The earth revolves the sun on a basis of about one year and the earth itself rotates in a cycle of about 24 hours. The former generates annual rhythm and the latter daily rhythm. The former results in seasonal changes and the latter circadian rhythm, such as sleep-wake cycle. The reproductive activity has a range from the comparative dormancy in the winter to the vivid activity of summer (Gaston & Menaker, 1967; Elliott, 1976; Stetson & Watson-Whitmyre, 1984; Binkley, 1990; Choi, 1996). There are clear differences in the ambient temperature and amount of daylight between the seasons, accompanied by such as the migrations of birds, the opening of blossom and leaves, the mating seasons, and the waking up from hibernation. It is likely to be clear that such changes have long been recognized.

In addition to these annual changes, there are daily rhythms caused by mainly the rotation of the earth. Living things have evolved through the reflection of the daily changes and the responses. The distinction between day and night is one of the most pervasive rhythms being experienced. The time taken for the earth to complete one revolution is about 24 hours. Many aspects of our environment show a daily rhythm with a period of 24 hours as a result of this solar day (Pierpaoli et al., 1996; Waterhouse et al., 2002; Dunlap et al., 2004).

Human beings are mostly diurnal, waking up in the morning and sleeping at night. They have a cyclicity consisting of active and rest times, which is repeated at about 24 hours. When a man was restricted in a cave with everything needed where the environmental cues were completely absent, remarkable results were observed (Pierpaoli et al., 1996; Palmer, 2002; Waterhouse et al., 2002). His biological clock seemed to overcome his mental chaos and guided his body functions in a fairly orderly manner, measuring off days that averaged 24.5 hours in length. It means that the biological clock, when no longer forced into synchrony with the day/night cycle, may run slightly

slower. His rhythm, which is longer than the natural day length, remained out of synchrony with the day/night cycle at the cave entrance for the whole stay underground. Consequent data with more subjects showed circadian sleep/wakefulness rhythms that averaged 24 hours and 40 minutes in length.

Therefore, the circadian rhythms are obviously witnessed and provides some clues in analyzing the interpretation of body for the naturally occurring rhythmical phenomena (Guo et al., 2006). An overriding function of circadian rhythms is to adjust the organism to the external local time, which allows to program its activities to occur at an appropriate phase relationship (phase angle) to the daily environmental cycle. Another important function is to accurately measure the ongoing lapse of time throughout the daily cycle, which is particularly relevant in the case of clock involvement within the compass of sun orientation. The third function of circadian rhythm clock is to provide a measuring stick to estimate the day- and/or night-length so that seasonal phenomena that depend upon estimating the time of year can be regulated appropriately.

This article is to introduce a model of limit cycle to help understand some of the aspects of circadian rhythms.

FREE RUNNING ACTIVITY

The small mammals in temperate zone are almost nocturnal, and they are active at night in looking for the food and escaping from the predator. When the animals' locomotor activity was measured in an alternating 24 hour cycles lighting on and off, they start to move as soon as the light is off, persist the activity during the whole dark period, and stop at the exposure to the light.

Golden hamsters are one of the mammals who show clear wheel running activities mainly at night (Stetson & Watson-Whitmyre, 1976; Wollnik, 1989; Best et al., 1999; Bittman et al., 2007). When the animals were put in normal light/dark cycle mimicking natural cycle in animal room, they run the wheel for the full length of darkness.

Even though they were put in constant darkness, the pattern of their wheel-running activities still continues along with the cycle, called free running activity, as if they were put in the light/dark cycle. Then the rhythms are modified gradually to adjust to the intrinsic biological clock. The phenomenon was interpreted as an imprinted rhythm both inherited from the consequence of evolution and learned from the beginning of life.

The light/dark cycles govern the locomotor activity. The circadian activity is continued in the absence of lighting, but the outcome rhythms become a little longer or shorter than the cycle of 24 hour(Fig. 1). Thus under the constant darkness the inherent period of a circadian rhythm, or oscillator, is expressed in overt output rhythms. These rhythms are generally fairly precise, and the period is called the free-running period(FRP). The period is dependent on a variety of factors such as species specificity, illumination, ambient temperature, developmental factors, and prior history.

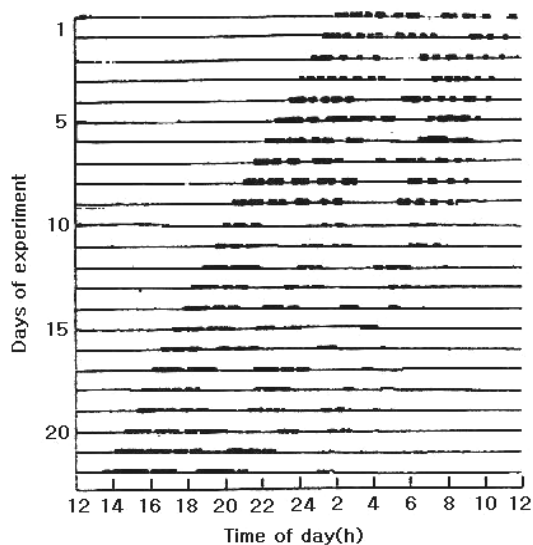


Fig. 1. Free running locomotor activity(wheel-running) of a mouse in constant darkness. A full day is indicated on abscissa, starting with a noon and ending with a noon on the following day. The 23 horizontal lines mean 23 days. The lower lines are the next day of above lines. Note that the onset of the wheel-running activity begins a little earlier than the previous day, displaying less than 24 hours in the period.

Almost all the individuals show FRP nearly 24 hour. In the actogram shown in Fig. 1, the free-running rhythm can be visualized by the actual slope of a line that passes through the activity onset points for each day in constant darkness. The persistence of rhythmic behavior in constant darkness over days or even years leads to the conclusion that daily biological rhythms are based on a self-sustaining oscillator in reality. The physiological time of day actually experienced by an organism directly reflects its internal clock but only indirectly reflects the immediate external conditions of light and dark. This is supported by the observations that the exposure of animals maintained in constant darkness to light modified the onset of the activity. The adjustment of the activity to the abrupt stimuli of light is called entrainment(Best et al., 1999; Gomas et al., 2006). The consequence of entrainment is that the period of the biological rhythm becomes equal on average to that of the entraining stimuli, with a stable phase relationship or phase angle between the entraining and entrained oscillations. An environmental stimuli that can synchronize circadian clocks is referred to as zeitgeber, meaning time giver.

There are a few criteria in establishing that a time cue has truly entrained a free-running rhythm. The period of the overt rhythm must equal to the period of the entraining cycle with a stable phase angle. And after return of the organism to constant conditions(darkness) the free-running rhythm must continue with a phase determined by the entraining cycle.

In nature a variety of environmental factors oscillate over the daily cycle. Some variables include light, temperature, humidity, food availability, and even social cues in a few species(Evered & Clark, 1985). Only a few factors can function as entraining cues in most species. The most important cue is generally the 24 hour solar cycle of light and darkness. Almost all circadian rhythms can be entrained to light-dark cycles. Again, entrainment to a time such as light-dark cycle means that the period of the biological rhythm becomes equal to that of the light-dark

cycle, and the phase relationship between the light-dark cycle and the biological rhythm is stable.

PHASE RESPONSE CURVE

The phase response curve (PRC) is a response of organisms to the constant environmental conditions (Binkley, 1990). For photic entrainment to occur, the circadian oscillator must respond differently to light at different phases of the cycle. The object of entrainment is for the time cue to modify the phase of the internal clock until the internal subjective day corresponds to the external day phase.

The PRC is determined by measuring the onset of wheel running activity as a locomotor activity, by giving a short time (i.e. 1 hour) of light to the animals in the absence of environmental stimulus (light in this case of mice). By the exposure of animals to light the degree of changes of the onset of wheel running activity is measured by the time period in terms of advance or delay (Fig. 2).

The subjective day and night are referred to as the imaginary day and night time that are followed by the

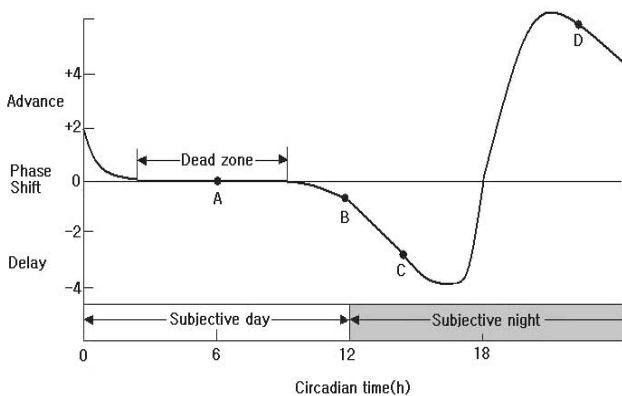


Fig. 2. A typical profile of phase response curve. The animals were kept in constant darkness and light were exposed for 1 hour at different times of a day. The changes of the onset of the wheel running activity was put on Y-axis by hours and exposure time on X-axis (time). Positive numbers show phase advance and negatives phase delay. See the text for the details.

previous light/dark cycle, because there is no light at all. A complete cycle of active and rest period of wheel-running activity, which is in reality not 24 hour, is assumed to be a day of literally 24 hour. The phase of time in a day is called as circadian time (CT), and the time of the onset of running activity is regarded as 12 o'clock (the beginning of subjective night). The first half is called subjective day and the rest subjective night.

Several inferences can be drawn from the PRC regardless of whether the animals are diurnal or nocturnal. The light delayed the running activity up to 1 hour (Fig. 2, B) at the time of the beginning of subjective night to about 3 hours (Fig. 2, C) after the subjective night. But the light advanced the running activity up to 6 hours during from near 8 hours after the subjective night to the beginning of the subjective day. In summary, light exposed to late evening and early night lengthens the cyclicity but light during from middle to late night shortens it (Fig. 2, D and E). There is no effects (Fig. 2, A) of light during the subjective day, which is called as a dead zone (Fig. 2). The phenomenon is likely to happen to human beings. The PRC to light enables the body clock to be adjusted to run in synchrony with our light/dark schedule.

A PRC is a graph of phase shifts on the ordinate plotted against the original circadian phase at which a phase resetting stimulus is administered on the abscissa (Fig. 3). The same data, however, can be plotted as a phase transition curve (PTC). In this alternate format, new circadian phase to which pacemaker is reset is plotted on the ordinate, while the initial circadian phase at which the stimulus was given is plotted on the abscissa.

In Fig. 3, a light pulse given at an initial circadian phase of CT 6 results in no phase shift (Fig. 3, upper left). In the corresponding PTC (Fig. 3, lower left) the new circadian phase is identical to the initial circadian phase for stimuli presented at CT 6. However, a light pulse given at CT 12 invokes a phase delay of approximately 1 hour and resets the pacemaker to a new circadian phase of CT 11 because $12 - 1 = 11$. Thus, at the initial circadian phase of CT 12

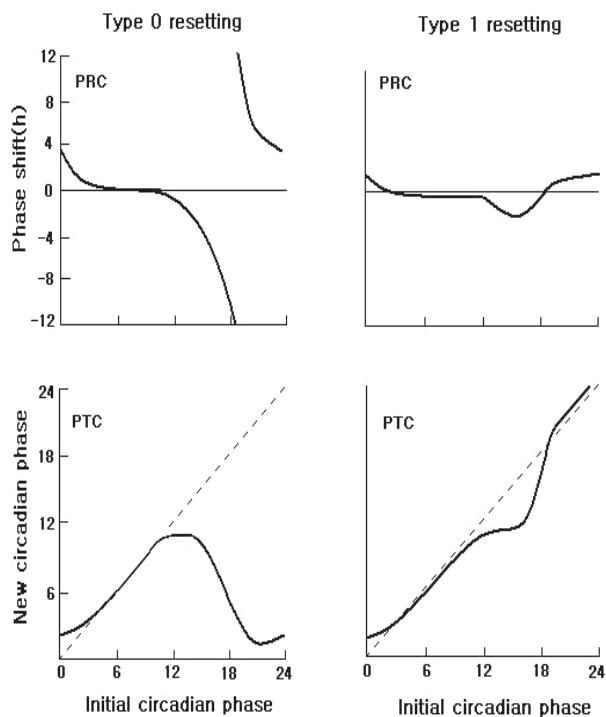


Fig. 3. Types of phase response curves. Left, Type 0 phase response curve and its associated phase transition curve. Right, Type 1 phase response curve and its associated phase transition curve. Phase transition curve is a plot of circadian time of stimulus(initial phase) on the abscissa versus new phase (the phase of the clock after the phase shift) on the ordinate. See the text for the details.

(abscissa) the new circadian phase is plotted as 11 corresponding to the ordinate.

In this type of plotting, a stimulus causing no phase shifts would produce a diagonal line with a slope of 1. This kind of PTC is elicited by weak stimuli(Fig. 3, lower right) and is called by Type 1 PRC. A very strong stimulus that drives the clock to the same phase would yield a PTC with a horizontal line having a slope of 0. That kind of PTC is called Type 0 PRC(Fig. 3, lower left).

Type 1 resetting curve display relatively small responses amounting usually to phase shifts of less than 6 hour, and they display a continuous transition between delays and advances(Fig. 3, upper and lower right). Type 0 PRC plotted as advances and delays show a discontinuous or break point at the transition between delay and advance

phase shifts(Fig. 3, upper left). The break point discontinuity of PRC is merely a plotting convention of arbitrarily assigning phase shifts in one half-cycle of 12 hour as delays and the other half-cycle as advances. it is important to note that the precise waveform of PRC can vary greatly depending on the strength of the zeitgeber stimulus (intensity and/or duration), the amount of time housed in constant conditions(darkness), and previous photoperiodic history.

In many multicellular organisms, there is transient behavior in the initial few cycles after a perturbation by a light stimulus(Binkley, 1990; Best et al., 1999). These transient cycles are thought to reflect the altered phase angle between the overt rhythm and the pacemaker in response to a phase shift because the pacemaker appears to reset rapidly after the perturbations. The phase shifts used in constructing a steady-state PRC should be calculated after the transients have waned and a stable FRP is established.

A LIMIT CYCLE MODEL

In natural condition, predator and prey populations tend to oscillate in time. For example, consider a simple case of mice and cats growing on an island where the mice eat all kinds of crops like grains of rice and cats capture and eat the mice. In a constant environment that has no other predator and prey species, the populations of the mice and cats will oscillate with rhythms that are out of phase with each other(Fig. 4, upper graph). At initial condition, the numbers of mice and cats are both low. Mice are renowned for their fecundity, however, so their numbers begin to increase. As the mouse population increases, more food becomes available for the cats and they reproduce. As the cat population proliferate rapidly, the mice are eaten and their population crashes. Not enough food, henceforth, is available to support the cat population and their numbers are curtailed gradually. When the number of cats is low, the predation pressure on the mice is soothed, and the mouse population grows again.

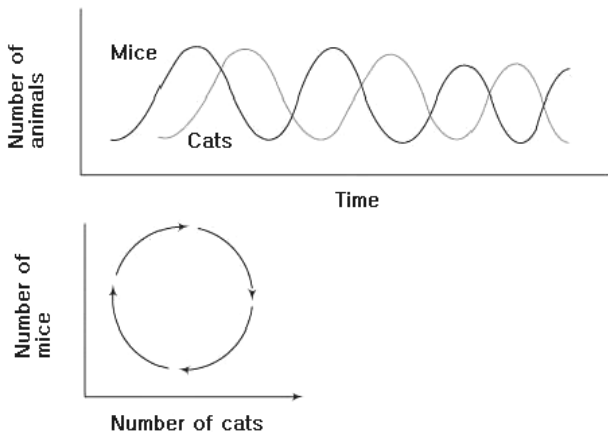


Fig. 4. A simplified limit cycle oscillator derived from animal population dynamics on an isolated island. Upper, population size of predators(cats) and prey(mice) show oppositely phased rhythms. Lower, A limit cycle displays the population oscillations of cats and mice in steady state.

Such a population system can oscillate indefinitely as long as there is a wealthy of crops for the mice. The insight is that both dependent variables, the numbers of each animal, are changing as a function of the same independent variable, time.

Time can be eliminated and the two dependent variables plotted with respect to each other. In this case the dynamics of these population changes can be visualized differently, where the number of cats is plotted against the number of mice. The Fig. 4(lower graph) indicates the population oscillations in steady state. The dimension of the circle will be dependent on the size of the island, the fecundity of the mice and cats, and several other factors, but the cycle will be remained. This type of depiction is called a limit cycle.

Suppose that a hunter visits the island briefly to capture a few cats. The acute effect will be a reduction in cat numbers. Because a lower cat population results in lower predation, the short term effect will be to allow the numbers of mouse to increase for a little longer period. However, the cat population will ultimately resume to grow, and the two interdependent population cycles will return to the original circuit. The only difference is that the phase

will be temporarily altered compared to previous circular trajectory before the hunter visited. Obviously, if the hunter removes all the cats, the limit cycle will cease. A similar change in the phase of the rhythm might follow a drought that lasted long enough that the reduced amount of crops confined mouse growth. A limit cycle that can be perturbed within limits but that later returns by itself to a stable oscillation is referred to as a stable limit cycle.

As mentioned above, stable limit cycle oscillators are characterized by a standard waveform and amplitude to which they return after fairly small perturbation. Limit-cycle models help explain reactions of circadian pacemaker to stimuli such as zeitgeber.

The fundamental modeling concept is that components underlying rhythm generation change rhythmically in time. Consequently, the rhythmic process can be described by a system of differential equations in which these oscillating components are called state variables. State variables define the state of the oscillation. In a constant environment, the parameters can be constant, but the levels of the state variables must, by definition, oscillate periodically.

External stimuli such as zeitgeber may reset a limit cycle oscillator in several ways. one way is by changing the amount of state variables, as the hunter traps cats. Another way is to reset a limit cycle by altering the parameter, as could it be imagined in drought case. Rhythms can also be reset through more complicated means. It is convenient to graphically portray the changes of the state variables in phase space with a simple oscillator consisting of only two state variables, such as numbers of mice and cats.

As applied to circadian oscillators, the limit cycle is the trajectory in phase space around which the values of the state variables change. Each phase of the pacemaker is defined by a particular point on the limit cycle in phase space. If the oscillator is perturbed such that the state variables are pushed off the limit cycle, they will return to the limit cycle. Various different disturbances can move the state variables from the limit cycle. The perturbations can occur at different times corresponding to different points

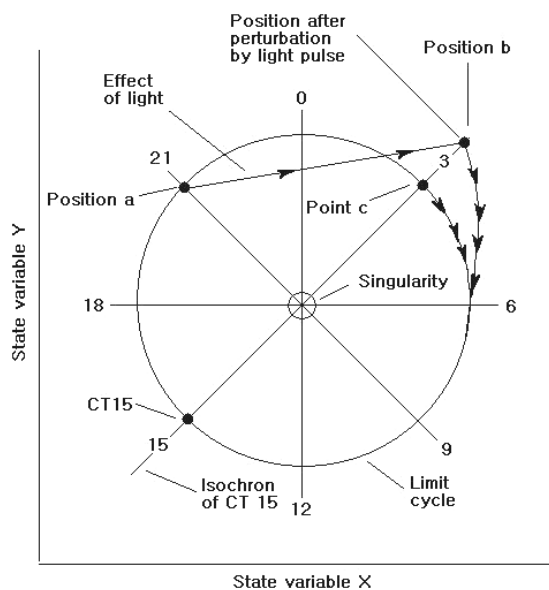


Fig. 5. An illustration of limit cycle showing phase resetting. A stimulus causes movement of state variables from one position to another in phase space. The circadian pacemaker proceeds clockwise around the round limit cycle. The isochrones are shown as straight lines that intersect at the singular point (singularity) in a center within the limit cycle. A light pulse administered to the oscillator when it is at CT 21 (position a) pushed the system to the state indicated by position b on the isochron, corresponding to CT 3. As time proceeds after the exposure to the light stimulus, the perturbed oscillator moves toward the limit cycle so that it becomes indistinguishable from a rhythm initiating at point c on the limit cycle, at CT 3. Because CT 3 may also be regarded as CT 27, the light pulse has advanced the phase of the perturbed oscillator by $27 - 21 = 6$ hours. See the text for the details.

around the cycle, but if it is a stable limit cycle, the values of the state variables will eventually return to the cycle. However, depending on the sizes of the perturbations and the when in the cycle they occur, the variables can return to the limit cycle at different points. The set points in phase space that specify values for the state variables are called isochrones. In Fig. 5, an oscillator at CT 21 (position a) is moved to the isochrone of CT 3 in the state variables. This means that the state variables of the oscillator will return to the limit cycle in phase with another oscillator

that started at CT 3 (position b).

The interpretation of phase resetting from the standpoint of limit cycle is based on the assumption that zeitgeber changes the values of one or more state variables. As a result, the oscillator is perturbed from the limit cycle to another position in phase space.

In Fig. 5, light is proposed to greatly increase the value of variable X while variable Y increases only slightly, so a light pulse given at CT 21 moves the state variables to a position on the isochrone of CT 3. After the light pulse, the state variables return to the limit cycle along the trajectory shown by the arrowed line. When the oscillator reaches the limit cycle, it will be in phase with another oscillator that had started (point c) from CT 3, not from the original CT 21. The oscillator in this case has been phase-advanced by 6 hour.

Isochrones radiate from a point somewhere inside the limit cycle (Gunawan et al., 2007). This center is called as the singularity and is an essentially phaseless point because isochrones of all phases converge there. The singular point could be a relatively stable place such that the state variables could be trapped there infinitely in a non-oscillating state. Or the singularity could be unstable such that state variables entering the singular region would spout back out to the limit cycle. Because isochrones of all phases branch from the singularity, an oscillator whose state variables have been reset to this region could return to the limit cycle along any of the isochrones. In the singular region, tiny differences in the values of the state variables translate into large differences in phase. Therefore, it would be impossible to predict the final phase of an oscillator whose state variables return to the limit cycle after having been in the singular region. An oscillator moved to the singularity could result in arrhythmia if the state variables became stagnant in the singularity.

When the type of perturbation is employed to many phases around the limit cycle, a resetting profile can be derived, which shows the positions to which the state variables are moved immediately after identical resetting

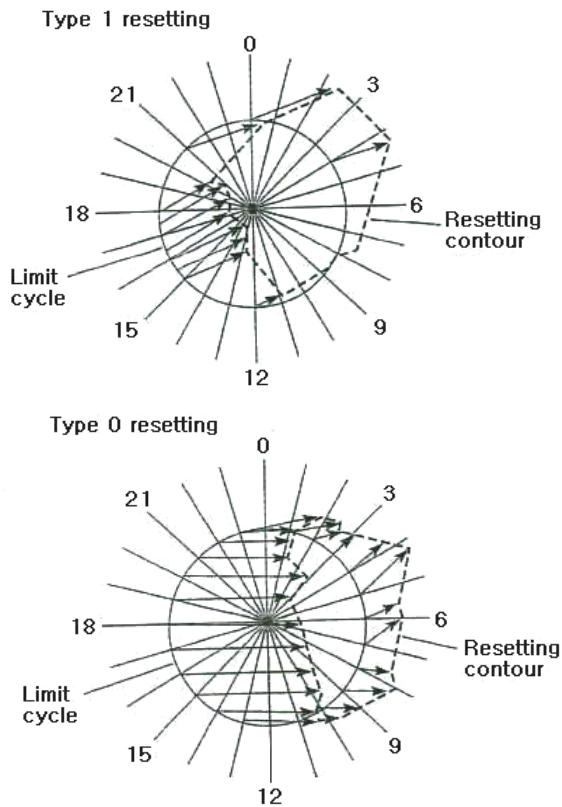


Fig. 6. Limit cycle diagrams for Type 1 versus Type 0 resetting.

Upper, Type 1 resetting in response to light pulses. Lower, Type 0 resetting in response to light pulses. Limit cycles are the circles with isochrons radiating from the central singular points. The bold dashed lines are the resetting contours, the points on the phase space to which the state variables are changed by the resetting stimuli. Resetting of the state variables is illustrated by the arrows from points on the limit cycles to points on the resetting contours. Note that Type 1 limit cycle contains the singularity point in the resetting contour, but Type 0 limit cycle does not.

stimuli are applied at different phases in the oscillation (Fig. 6). The Fig. 6 shows a limit cycle on a basis of the PRC as displayed by Fig. 2.

It might be assumed that stimuli presented at phases in the dead zone would not modify the state variables because no phase shift results from stimuli exposed in the dead zone. Although this could be true for some specific models, it is not a necessity of a limit cycle model. An

alternative analysis is that stimuli administered in the dead zone do result in changes of the state variables, but these altered values move the variables approximately along the same and original isochrone. An case is shown by the perturbations delivered between CT 3 and CT 8 in Fig. 6. All of these perturbations change the values of the state variables, but all the values return to the limit cycle in phase with an oscillation that had never been reset. Therefore, no steady state phase shift results. Consequently, state variables of the oscillator are not necessarily insensitive to the stimulus during the dead zone. In fact the stimulus could induce large changes of the state variables, but these changes do not move the oscillator to a different isochrone. This insight collected from limit-cycle modeling has important implication for identifying the molecular correlates of state variables that is beyond the scope of this review (Klerman, 2005; Hummer et al., 2007; Levi et al., 2007)

As illustrated in Fig. 3 there are two types of PRCs - Type 1 and Type 0. Type 1 PRCs display a relatively low amplitude of phase shifts and a continuous transition between phase delays and advances; Type 0 PRCs show large phase shifts and a discontinuous transition with a break point between two phase shifts.

The switch between these PRC types appears to depend on the strength of the stimuli applied (Gunawan & Doyle, 2007; Rougemont & Naef, 2007). The strength of the stimulus can be modulated by changes in light intensity or duration, drug dosage, or other such factors. As the stimulus strength is gradually increased, the amplitude of the Type 1 PRC increases until there is an abrupt switch to Type 0. There are other factors causing the conversion of Type 1 to Type 0 as well as the varying stimulus strength. These include genetic mutation, background light quality and/or intensity, and developmental stage.

Type 1 resetting is seen if the resetting profile is not moved beyond the singularity (Fig. 6, upper graph). In this case the resetting contour encloses the singularity. But Type 0 resetting is seen if the stimulus strength is strong

enough to move the variables beyond the singular region (Fig. 6, lower graph). In this case the resetting contour does not enclose the singularity.

An important thing at this point is that levels of state variables presumably correspond to real and potentially measuring things. A state variable could be the amount of a clock protein, for instance, and the limit cycle could describe the daily change in the number of protein molecules in the nucleus of a rhythmical cell. A resetting stimulus could be a signal that causes rapid synthesis or destruction of the protein, neurotransmitters, and hormones etc. (Klerman, 2005; Li et al., 2006; Bittman et al., 2007; Levi & Schibler, 2007; Rougemont & Naef, 2007).

Limit cycle concepts establish criteria for deciding whether a candidate molecule is a state variable or not. In the context of entrainment, the limit cycle model makes the strong prediction that the level of at least one state variable should be induced or repressed by light. Limit cycle models of circadian clocks have already made significant contributions.

CONCLUSION

An essential function of circadian rhythms is to provide an internal estimate of the external local time, thereby allowing the organism to program its activities so that they occur at an appropriate time in the daily environment. Various rhythmic environmental stimuli are known to entrain circadian clock. Light-dark cycles are usually thought to be the most important environmental zeitgeber because they are the most consistent from day to day. PRCs are maps of the phase-dependent responses of circadian clocks to zeitgeber.

Limit cycle models have organized data, have established criteria for better understanding, and have made accurate predictions for future investigations. The value of these modeling attempts is likely to increase as the complexity of circadian phenomena is progressively disclosed.

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