

Review

## Phase resetting and its possible role in biological rhythms

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### 1. Introduction

The living organisms show various rhythms with periods ranging from a micro second to a hundred years. The former is the rhythm of bio-molecules and the latter that of a human life, for instance. The respiration, heart beat, locomotion and alternation of generations are also examples of the biological rhythm. The sleep-wake rhythm of the period of 24 hours is observed and the blood pressure, body temperature, hormone secretion and so forth vary with the same period.

Any biological rhythm can be observed through an event, for instances, the initiation of action potential in the case of pacemaker neuron, waking-up in the sleep-wake rhythm, and the R-wave of the electrocardiogram in the heart beats.

Biological rhythms are influenced by externally applied stimulus. For example, the sleep-wake rhythm is affected by the rotation of the earth. In fact, experiments on the sleep-wake rhythm of a human subject elucidate the period is not 24 hours but about 25 hours if he is kept alone in the environment without a cue on the time. This is called the entrainment of the sleep-wake circadian rhythm to the rotation of the earth.

A possible mechanism of the entrainment is provided using a concept of phase resetting.

If a biological oscillator receives a perturbation, timings of the repetitive events after the perturbation are altered. Change in the timing of the succeeding event from the preceding ones is called the phase-resetting. The amount of phase resetting depends on the magnitude of a perturbation and on the phase in the oscillation when it is applied.

This article is written based on the lecture at the annual meeting of some academic society by the present author and explains briefly the

phase resetting and its possible role in biological rhythms. In Sec. 2, the notion of phase resetting is introduced using a radial isochron clock. In Sec. 3, the response of a limit cycle oscillator to an externally applied perturbation is explained. Phase-locked and chaotic responses and others show up when the oscillator is exposed to a periodic stimulus train. In Sec. 4, a possible role of the phase resetting is shown in the dynamic stability in human locomotion against perturbation. In Sec. 5, symmetry breaking in human locomotion is discussed in connection with bifurcation of the solutions of a non-linear dynamical system describing a coupled oscillator.

### 2. A simple limit cycle oscillator, the RIC

A limit cycle oscillator is often used to model a biological rhythm. One of the main reasons is that the rhythm itself possesses properties which are not explained unless a non-linear dynamical system is assumed. Moreover, the rhythm could be described by a single variable, the phase, although it is essentially an event in the space of two dimensions or more. To understand this more precisely, let us consider a simple limit cycle oscillator called the radial isochron clock (the RIC hereafter) (Winfree, 1975). This clock is described by a dynamical system of two variables in the polar coordinate:

$$\begin{cases} \dot{r} = Kr(1-r), \\ \dot{\theta} = 2\pi, \end{cases} \quad (1)$$

where,  $r \in R^+ = [0, \infty)$ ,  $\theta \in S^1$  (= a unit circle circumference) and  $K \gg 1$  is a positive constant. A trajectory starting from any initial point in the phase plane, except the origin, i. e., the equilibrium point of the clock, winds counter-clockwise around it and approaches eventu-

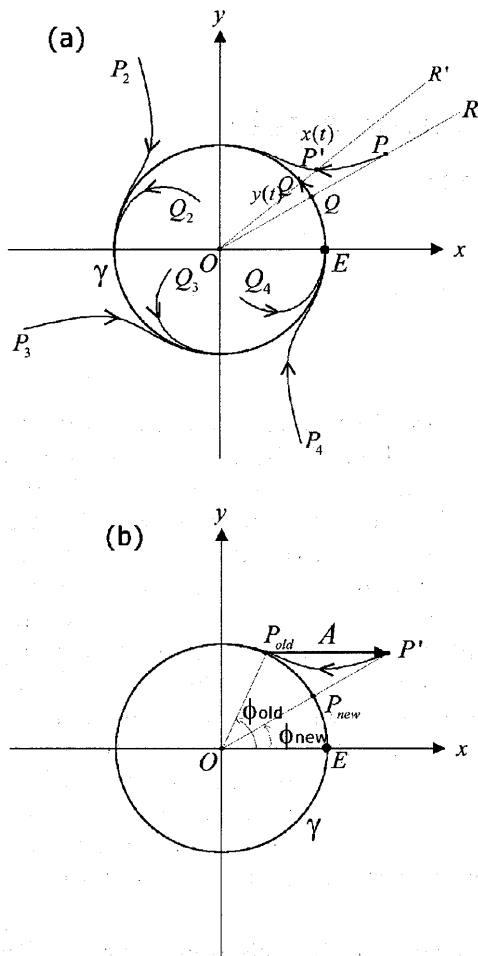


Fig. 1 The radial isochron clock with limit cycle  $\gamma$ . (a) Trajectories starting from various initial points and a schematic explanation of eq (1), (b) Phase shift of a state point on  $\gamma$  due to a brief perturbation  $A$

ally a unit circle ( $\gamma$ ) as the limit cycle. Fig. 1(a) illustrates trajectories starting from  $P_i$  and  $Q_i$  ( $i = 2, 3, 4$ ) in the phase plane. Note that a state point on the unit circle  $\gamma$  runs along it with constant angular velocity  $2\pi$  and hence the lap time is the unity. Take a reference point  $E$  on the limit cycle and call the half line starting from the origin  $O$  and passing the point  $E$  the event line<sup>1)</sup>. Take also the  $xy$  coordinate in such a way that the  $x$ -axis coincides with the half line.

1) When we see a biological rhythm, we find an observable event such as "waking up" in the sleep-wake cycle, "the action potential" in the case of a pacemaker neuron, "the R-wave" in the ECG and so forth. We consider such an event takes place when the state point of the oscillator underlying the rhythm crosses the event line.

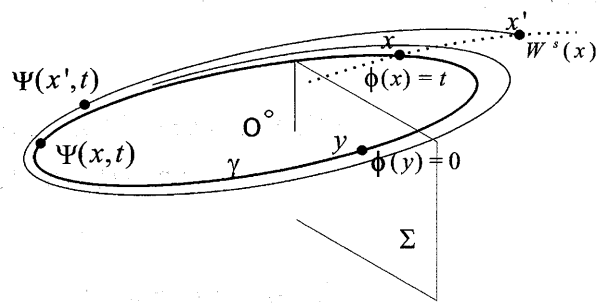


Fig. 2 A limit cycle  $\gamma$  in the three dimensional space. The isochron of a state  $x \in \gamma$ ,  $W^s(x)$ , is depicted by the dotted line. The equilibrium point of the system is represented by a circle dot  $\circ$

### Isochrons and Phases

Let  $x(t)$  and  $y(t)$  be the trajectories starting at a point  $P$  and a limit-cycle point  $Q$  both on the radius  $OR$ , respectively (see Fig. 1(a)). Because the angular and the radial dynamics of a state point are independent with each other in the case of the RIC (see eq(1)), points  $x(t)$  and  $y(t)$  are always on the same radius rotating around the origin  $O$  but the point  $x(t)$  approaches the point  $y(t) \in \gamma$ , the intersection of  $\gamma$  and the radius passing through  $x(t)$ , as the time  $t$  elapses (see the line  $OR'$  in Fig. 1(a)). Hence, the straight line  $OR$  radiating from the origin is called an isochron of the RIC. Any straight line radiating from the origin constitutes an isochron of the RIC. Let us consider a limit cycle oscillator in the three dimensional space: Describe the limit cycle by  $\gamma$ . A state point on  $\gamma$  continues to move along it forever if no perturbation is applied. Let  $T$  be the time for the state point to go around the limit cycle. Take a plane  $\Sigma$  which crosses  $\gamma$  transversally as shown in Fig. 2<sup>2)</sup>.

Let the crossing point of  $\gamma$  with  $\Sigma$  be  $y$ . The time for a state point starting from  $y$  at time 0 and reaching a state  $x \in \gamma$  be  $\tau(x)$ . Then  $0 \leq \tau(x) \leq T$ . Since  $T$  can be equated to 0, we may put  $0 \leq \tau(x) < T$ . Therefore, we consider a one-to-one map  $\tau$  between time  $t$ , ( $0 \leq t < T$ ) and a point  $x$  on  $\gamma$ :  $t = \tau(x)$ . Let us call  $\tau(x)$  the time phase of  $x \in \gamma$ . We then normalize the time-phase  $\tau(x)$  by dividing it by  $T$  and denote the fraction by  $\tau(x)$  newly.

For a point  $x'$  off the limit cycle  $\gamma$ , it is pos-

2) Suppose that every time a state point crosses the plane  $\Sigma$ , the system generates a marker such as an action potential in the case of a pacemaker neuron, for instance. The plane  $\Sigma$  corresponds to the event line in the two dimensional case.

sible to define the time-phase as follows: First we note that the point  $x'$  approaches the limit cycle  $\gamma$  eventually. Denote here the time evolution of a system's state  $x$  by  $\Psi(x, t)$ , i. e., let  $\Psi(x, t)$  express the state point at time  $t$  which has started from a state  $x$  at time 0. Suppose that a state point  $x'$  off  $\gamma$  and a point  $x$  on  $\gamma$  start at the same time  $t=0$ . After time  $t$ ,  $x'$  and  $x$  evolve to  $\Psi(x', t)$  and  $\Psi(x, t)$ , respectively. If  $\Psi(x', t)$  approaches  $\Psi(x, t)$ , i. e., if the distance between  $\Psi(x', t)$  and  $\Psi(x, t)$  tends to zero with  $t$ , we consider that  $x'$  is on the isochron of the state  $x \in \gamma$ . Thus we define the isochron  $W^s(x)$  of a state  $x \in \gamma$  as follows:

$$W^s(x) = \{x' \in M : \lim_{t \rightarrow \infty} \text{dis}(\Psi(x', t), \Psi(x, t)) = 0\}, \quad (2)$$

where  $M$  denotes the region of attraction of the limit cycle.  $W^s(x)$  represents a set of state points  $x'$  that possess the same time-phase as the point  $x \in \gamma$  eventually (Kawato, 1981). In this way, any  $x'$  in the attractive region of  $\gamma$  can be characterized by the isochron.

The response of a nonlinear oscillator with a stable limit cycle to a single brief stimulus (perturbation) can be described by the relation between the phases before and after the stimulus which we call the old and the new phases, respectively (Nomura *et al.* 1993). Let  $x \in \gamma$  be a state point right before a perturbation is applied and  $x' \in \gamma$  the state point right after the perturbation. Namely, the state point  $x$  is moved to the point  $x'$  by the perturbation.

Suppose that  $x' \in W^s(x)$ ,  $y \in \gamma$ , i. e., the point  $x'$  has the same time-phase as the point  $y \in \gamma$ . Let  $\tau(x)$  and  $\tau(x') \equiv \tau(y)$  denote the old and the new phases, respectively. Let us represent the relation between the old and the new phases by a map:  $\Phi: S^1 \rightarrow S^1$ :

$$\tau(y) = \Phi(\tau(x)), \quad \text{or} \quad \tau_{\text{new}} = \Phi(\tau_{\text{old}}). \quad (3)$$

We call the graph of  $\Phi$  a basic phase transition curve (BPTC). If the difference  $\Delta\tau = \tau_{\text{new}} - \tau_{\text{old}}$  is positive, the amount describes the phase advance due to the perturbation. If it is negative, the perturbation causes the phase delay.  $\Delta\tau$  is called the phase reset (see Fig. 1 (b)). The plot of  $\Delta\tau$  against  $\tau_{\text{old}}$  is called the phase response curve (the PRC). This curve shows that the time phase of a limit cycle oscillator can be controlled by an appropriately applied perturbation at a suitable time-phase of the state point.

The position of a state point on the limit cycle  $\gamma$  can also be represented by the geometrical phase: We define the event line as the geometrical phase 0. Then, the geometrical phase  $\theta(x)$  of  $x \in \gamma$  is defined as the angle between the radius connecting the equilibrium point and the point  $x$  and the event line measured counterclockwise and normalized by  $2\pi$ . The geometrical phase may have one-to-one correspondence to the state point  $x \in \gamma$ . But note that it is not always the case. If it is the case, we note also that the geometrical phase  $\theta(x)$  of a state  $x \in \gamma$  are related with the time phase  $\tau(x)$  by a map  $g$ :

$$\theta = g(\tau) \quad (4)$$

and the function  $g$  can be inverted in some way:

$$\tau = g^{-1}(\theta). \quad (5)$$

It is possible to define the old and new geometrical phases and their relationship  $\Phi$ , i. e., the basic PTC (the BPTC), as we did for the time phase. Let us denote the BPTC for the geometrical and the time phases by  $\Phi_\theta$  and  $\Phi_\tau$ , respectively. Provided that eqs (4), (5) hold, one has

$$\tau(x') = g^{-1}(\Phi_\theta(g(\tau(x)))), \quad (6)$$

and hence

$$\Phi_\tau = g^{-1} \circ \Phi_\theta \circ g. \quad (7)$$

Let us return to the RIC (Nomura *et al.* 1994 a). We apply a single pulse stimulus  $A$  to a state point on  $\gamma$  in such a way that it displaces the state instantaneously by an amount  $|A|$  in the positive or negative direction parallel to the  $x$ -axis depending on the sign of  $A$  (see Fig. 1(b)). Since isochrons are straight lines through the origin in the case of the RIC,  $x'$  and  $y$  on the line  $OP'$  share the same isochron, and since both geometrical and time phases coincide with each other, i. e.,  $\theta(x) = g(\tau(x)) = \tau(x)$  for any  $x \in \gamma$ , the phase after the RIC receives a perturbation can be analytically computed. In fact, the following relation holds:

$$\tau_{\text{new}} = \frac{1}{2\pi} \arctan\left(\frac{\sin 2\pi\tau_{\text{old}}}{A + \cos 2\pi\tau_{\text{old}}}\right) \quad (8)$$

Fig. 3 illustrates the phase response curve (the PRC) of the RIC to various sizes of per-

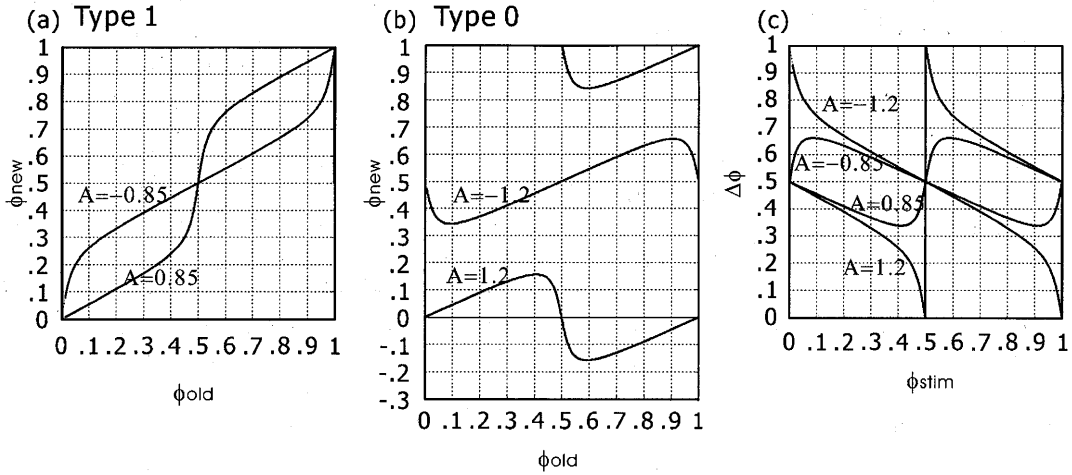


Fig. 3 (a) The basic phase transition curves (BPTCs) for  $A=1.2$  and  $A=-0.85$ . (b) The basic phase transition curves (BPTCs) for  $A=1.2$  and  $A=-1.2$ . (c) The phase response curves (the PRCs) of the RIC for the brief perturbations

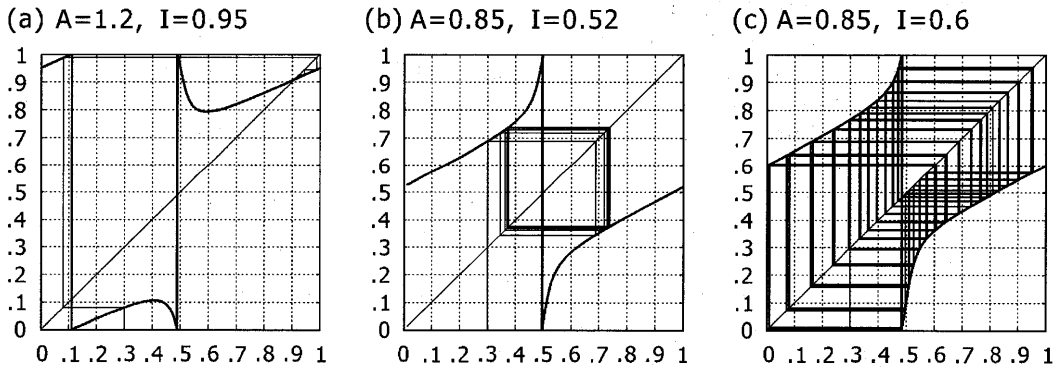


Fig. 4 Three examples of the orbit. (a) the 1:1 phase-locking, (b) the 2:1 phase locking, (c) the quasi-periodic orbit

turbation. Note that the average slope of the BPTC (a) is unity and hence the BPTC is called type 1. In (b), by subtracting one from the right half of the curve for  $A=1.2$  one has a continuous curve as shown in the lower part. The average slope of each curve is 0 and hence the BPTC is called type 0.

### 3. The Phase Transition Curve (the PTC) and Phase Locking

Nomura *et al.* (1994a) described the response of the RIC to a periodic pulse train of period  $I$  measured in the unit of  $T$  (see also references quoted therein). If the period of the stimulus is not too small compared with unity, the state point displaced away from the limit cycle by the  $n$ -th stimulus is practically back on the

limit cycle when the  $n+1$ -th stimulus is applied. Let  $\tau_n$  be the time-phase of  $x_n \in \gamma$  when the  $n$ -th stimulus is applied, and  $\tau_n'$  be that of the perturbed point  $x_n'$ . Then the relation  $\tau_n' = \Phi_\tau(\tau_n)$  holds. The  $n+1$ -th stimulus is applied after time  $I$  and its time phase  $\tau_{n+1}$  is expressed as follows:

$$\tau_{n+1} = \Phi_\tau(\tau_n) + I \pmod{1} \equiv f_I(\tau_n) \quad (9)$$

The map  $f_I: S^1 \rightarrow S^1$  in eq(9) is called the phase transition curve (the PTC) and is obtained by shifting the BPTC upward by  $I$ , provided that it is expressed as the time phase<sup>3)</sup>. The map  $f_I: S^1 \rightarrow S^1$ , eq(9), is sometimes called a

3) This is an advantage of using the time phase to express the PTC.

Poincaré map. Note that for any initial phase  $\tau_0$ , the map  $f_I(\tau)$  leads inductively to define the sequence  $\{\tau_n\}$  as follows:

$$\tau_n = f_I(\tau_{n-1}) = f_I^2(\tau_{n-1}) = \dots = f_I^p(\tau_0) \quad (10)$$

The successive time phases  $\tau_0, \tau_1, \dots$ , separated by the fixed interval  $I$  can be plotted on the PTC (see Fig. 4). We call a locus of the sequence  $\{\tau_n\}$  an orbit. If  $\tau_p = \tau_0$  and  $\tau_n \neq \tau_0$  for  $1 \leq n < p$  with  $n$  and  $p$  being positive integers,  $\{\tau_n\}$  is called a periodic sequence or a periodic orbit of period  $p$ . A periodic orbit of period  $p$  is called to be stable if the following equation holds:

$$\left| \frac{\partial f_I^p}{\partial \tau}(\tau_0) \right| = \prod_{j=0}^{p-1} \left| \frac{\partial f_I}{\partial \tau}(\tau_j) \right| < 1. \quad (11)$$

A periodic orbit with  $|\partial f_I^p(\tau_0)/\partial \tau| = 0$  is called a superstable orbit. A superstable orbit contains one or more external points of the PTC as its periodic point(s).

Thus, the behavior of an oscillator exposed to a periodic pulse train can be described approximately but acceptably by the one dimensional map (PTC), provided that  $I$  is not too small. If the map  $f_I$  has a stable periodic point(s) of period  $P(f_I^p(\tau) = \tau)$ , timings between the input perturbation and the oscillator output (the event) are fixed. In this case, we call the oscillator output is phase locked.

See Fig. 4(a) and (b). Let us consider the periodic points  $\tau_0, \tau_1, \dots, \tau_{p-1}$ . As is already mentioned,  $\tau_i$  is the time-phase of the oscillator right before the  $i$ -th perturbation is applied ( $i=0, 1, \dots, p-1$ ). The phase of the perturbed state right after the perturbation is  $\tau_i' = \Phi_\tau(\tau_i)$ , i. e., the phase of the perturbed state is reset to  $\tau_i' = \Phi_\tau(\tau_i)$ . We called the difference  $\tau_i' - \tau_i$  the amount of the phase reset. Now, the  $(i+1)$ -th perturbation is applied after time  $I$ , i. e., at time  $\tau_i' + I$ . If  $[\tau_i' + I] = n_i$ , where  $[x]$  denotes the integer part of  $x$ , the state point crosses the event line  $n_i$  times and hence the oscillator generates the events  $n_i$  times, before it receives  $(i+1)$ -th perturbation at the phase  $\tau_i' + I - [\tau_i' + I] \equiv \tau_i' + I \pmod{1}$  ( $i=0, 1, \dots, p-1$ ). In this way, the oscillator receives  $p$  perturbations and the time phase of the oscillator right before the  $p$ -th perturbation is  $\tau_0$  again at the steady state and the same situations are repeated. In other words, while the system receives  $p$  periodic perturbations, it generates  $q = n_0 + n_1 + \dots + n_{p-1}$  events and a sequence of these events is repeated. Hence we call this situation as the

$p:q$  phase locking. Fig. 4(a) provides an example of the periodic point of  $p=1$ , where  $\tau_0 = 0.9085\dots, \tau_0' = 0.9585\dots$ . Parameters are set as  $A=1.2$  and  $I=0.95$ . Everytime a perturbation is applied, the phase advances by  $\tau' - \tau = 0.5$  and then the oscillator generates an event before the next perturbation is applied at the phase  $\tau_0 = 0.9085\dots$ . This is an example of the 1:1 phase locking. Fig. 4(b) depicts the case where parameters are set as  $A=0.85$  and  $I=0.52$ . The periodic points are  $\tau_0 = 0.3755\dots$  and  $\tau_1 = 0.7386\dots$ . Since  $\tau_0' = \Phi_\tau(\tau_0) = 0.2186\dots$  and  $\tau_0' + I = \tau_1 = 0.7386\dots < 1$ , hence the oscillator does not cross the event line. While  $\tau_1' = \Phi_\tau(\tau_1) = 0.8555\dots$  and  $\tau_1' + I = 1.3755\dots$ . We note that  $[1.3755\dots] = 1$  and  $1.3755\dots \pmod{1} = 0.3755\dots = \tau_0$ . Thus the phase of the state point takes  $\tau_0$  again. In this case, the oscillator crosses the event line and it generates the event before it receives the third perturbation. This provides the 2:1 phase-locked response. In (c), the time phase shifts bit by bit at every time when a perturbation is applied and the oscillator's outputs are not phase-locked but quasi phase-locked.

Fig. 5 illustrates examples of the responses to periodic stimuli, showing how the the events indicated by the longer arrows entrain the periodic stimuli whose timings are shown by the shorter arrows. In Fig. 5(c) the response

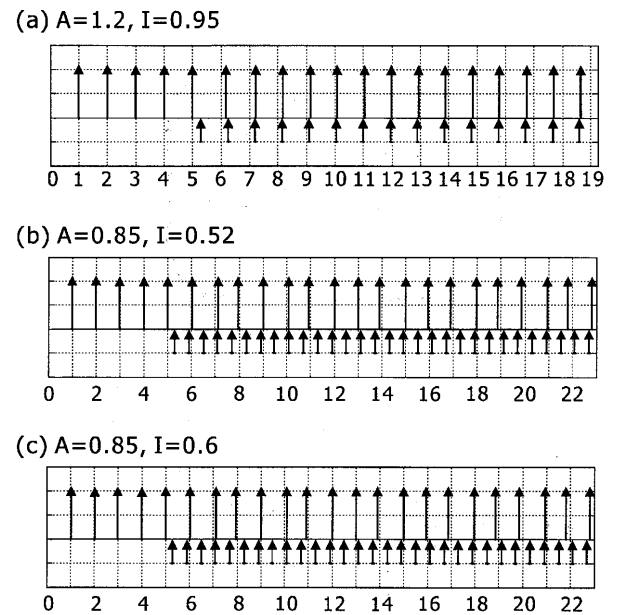


Fig. 5 Responses of the RIC to periodic stimulus trains. (a) 1:1 phase-locked response,  $A=1.2, I=0.95$ , (b) 2:1 phase-locked response,  $A=0.85, I=0.52$ , (c) a quasi-periodic response,  $A=0.85, I=0.6$

is quasi-periodic and no entrainment takes place. There is a case where a chaotic response occurs to a periodic stimulus train. If the period of stimulus is much shorter than the unity, the phase locking disappears sometimes but various features including chaos show up in the sequence  $\{\tau_n\}$ .

The sleep-wave rhythm is a circadian rhythm with period of about 25 hours and is phase-locked to the 24 hours environmental rhythm (the entrainment).

Segundo *et al.* (1991a, b) studied using crayfish on the influence, through an inhibitory synapse, of pacemaker discharges upon the pacemaker neurons in the slowly adapting stretch receptor organ (SAO). These neurons discharge with an almost constant interspike interval  $N$ . Fig. 6(a) illustrates a diagram of the experimental setup. The inhibitory fiber IF transmits a controlled pre-synaptic spike train with constant interval  $I$  and elicits IPSPs in the SAO pacemaker neuron, which modifies the SAO pacemaker discharges. The instants when the SAO fires were observed.

They obtained the series  $\{T_i\}$  and  $\{\phi_i\}$  where  $T_i$  denotes the interval between the  $(i-1)$ -th and the  $i$ -th SAO spikes, and  $\phi_i$ , the phase, the interval between the  $i$ -th SAO spike and the last inhibitory spike preceding it (see Fig. 6 b). The phase thus defined is expressed as a fraction between 0 and 1 after suitable nor-

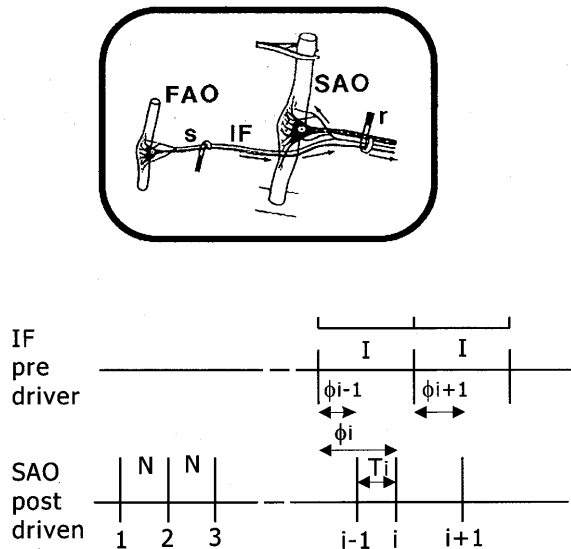


Fig. 6 (a) Diagram of the living preparation (modified from Segundo *et al.*, 1991a), (b) inhibitory periodic input from FAO (the fast adapting stretch receptor organ and the corresponding SAO output

malization by  $I$  (not by  $N$ ). Phases 0 and 1 are equated. These series provide the input and output spike trains and these experimental data were analyzed in the framework of theories of nonlinear dynamics and of stochastic point processes. The basic plots were used to display the interval  $T_i$  or the phase  $\phi_i$  against the index  $i$  of each spike or its occurrence time  $t_i$ . See Fig. 7. Return maps were also used. Responses were categorized into four classes, which were  $p:q$  locking, intermittent, messy erratic and messy stammering responses in terms of pacemaker neuron discharges and their relation with the driver's discharges. The intermittency is discharges practically locked most of the time but were occasionally non-locked for a brief period. Conjecturing as to a hypothetical nonlinear dynamical system underlying neuronal activity, they suggested that locked, intermittent, and messy erratic responses reflected, respectively, limit cycles, quasiperiodicity and strange attractors on or around twodimensional tori. Messy stammering would be due largely to noise when the

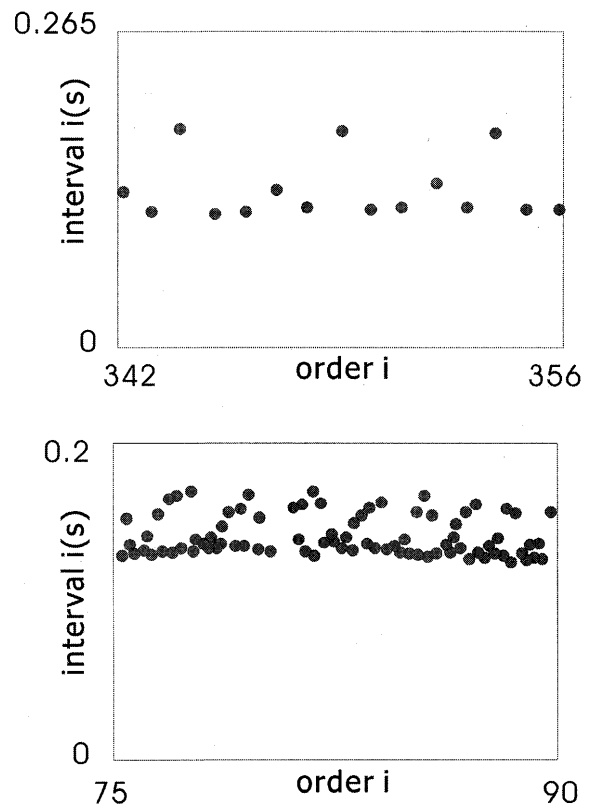


Fig. 7 (a) A locked response of SAO to the inhibitory periodic input, where  $N/I=0.38$ , (b) an intermittent response for  $N/I=0.44$

membrane fluctuates near its firing threshold.

Nomura *et al.* (1994b) discussed the BVP oscillator as a model of the SAO pacemaker neurons, analyzed its responses to periodic stimuli, and considered the joint implications of their model and the physiological experiments by Segundo *et al.* (1991a, b). They also proposed a modified RIC with slow and fast dynamics and used it as a model of the SAO pacemaker neurons.

#### 4. Locomotion and the dynamic stability

Research on the mechanism of human locomotion has over one hundred years history in the brain science and it has been one of the central problems in the field. At the beginning of the last century, Sherrington and Laslett (1903) observed that a central pattern generator in the spinal cord (the spinal CPG hereafter) plays an essential role in the locomotion control of quadrupeds and possibly of a man. Since then, the CPG has been investigated in the framework.

Recently, human bipedal locomotion draws attention among robotics engineers. One of the main features of human locomotion is that even if it is disturbed by an externally applied perturbation, a man hardly falls down, indicating that human locomotion has dynamic stability.

Transient response of the locomotion to a perturbation is called a stumbling reaction. Yamasaki *et al.* (2003) tried to elucidate functional roles of the phase reset possibly used for the neural control of human locomotion including the stumbling reaction. To this end, they proposed a model of the locomotion control system, which consists of five subsystems including the brain, the spinal CPG and the musculo-skeletal system. Each of these subsystems is considered as a dynamical system consisting of appropriate states and capable of exhibiting dynamical stability such as limit cycle oscillation. The musculo-skeletal subsystem was modeled by a double pendulum, which receives both muscle torque and externally applied force perturbation (the ground reaction force was not considered for simplicity, since their interest was to study the stability of motion of a double pendulum to external forces.). Perturbations applied to the musculo-skeletal system during the steady state walking push the state point of the locomotion control system on the limit cycle away from it,

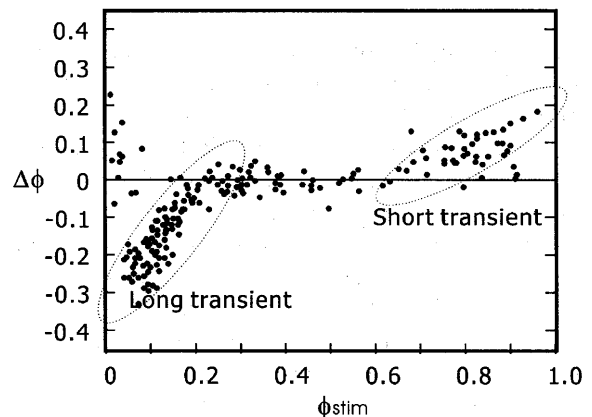


Fig. 8 Plot of the phase responses of human walking on the treadmill (modified from Nomura *et al.*, 1998). The right shank was pulled backward impulsively during steady state walking. The long (several) and short (a few) transient steps of walking were necessary to obtain the plot depending on the perturbation phase  $\phi_{stim}$  as indicated by ellipses

either outside or inside the basin of attraction of the limit cycle. Under these assumptions and others, they studied the locomotion control system. They also provided the phase response curve of the system modeled by a double pendulum, which resembled the PRC obtained during perturbed human walking (Nomura *et al.*, 1998 and see Fig. 8).

They also analyzed the bipedal locomotion using a model with 7 joints based on the locomotion control system. Their mathematical analysis suggested the phase reset of the spinal CPG plays functional roles in locomotion control mainly in two ways: 1) an appropriate amount of the phase reset for a given perturbation can contribute to relocating the system's state point outside the basin of attraction of the limit cycle back inside. 2) it can also be useful in reducing the convergence time or the so-called setting time (the time necessary for the state point to return back the limit cycle). These functions can be rephrased as follows: a given perturbation applied during a normal steady-state walking may induce transient changes in the motion trajectory, such as the stumbling and corrective reaction, or may even result in critical changes such as falling. An appropriate amount of the phase reset of the walking rhythm can help shorten the transient duration needed for reestablishing the original steady-state walking and also prevent the walker from falling.

## 5. Symmetry breaking in human locomotion

According to the study of Sherrington, gait of quadruped locomotion is generated by the spinal CPG. It can be assumed that the CPG generates various types of oscillation pattern responding to the strength of electrical or chemical perturbation. In order to explain the alternative firings of motoneurons for generating the locomotion, Asai *et al.* (2003) proposed a CPG model which consists of a pair of neural nets symmetrically connected with inhibitory connections (each of which is called a half center), although the structure of the spinal CPG neural network is uncovered yet physiologically.

The CPG model is expected to show alternative firings in view of the model structure, but the relation between the model structure and the oscillation patterns is not simple but depends on the dynamics of the half center model. Asai *et al.* described each of half centers by the FitzHugh-Nagumo equation (synonymous with the BVP model) and connected both centers with inhibitory connections. Moreover, they assumed that each half-center is regulated by a signal from the higher motor center and the output from the half center stimulates the motor neuron to the lower leg to generate locomotion. The half centers are equal with each other and there is no master-slave relationship between them, differently from the model of entrainment discussed in the previous sections where a limit cycle oscillator as a slave oscillator was stimulated periodically by a master oscillator. Nevertheless, minute symmetry breaking in the expression of the equations describing the half-center and/or small difference in the strength of signals from the central nervous system to half-centers may cause diversity in the locomotion patterns of the lower legs. They studied bifurcation of the solution of the CPG dynamical system due to the change in the values of parameters such as the coupling coefficients, signal amplitude and so forth, provided that the structure of the CPG model possesses complete symmetry.

By obtaining the normal form of a dynamical system (Golubitsky and Shaeffer, 1985), they also showed that the solution of the CPG model can be classified roughly into two groups: cooperative and dis-cooperative oscillating patterns. The CPG model shows in-phase and out-phase oscillations. They call

these a cooperative oscillating pattern. They also showed that the cooperative pattern breaks down into a dis-cooperative one despite of complete symmetry of the CPG. These are characteristic features of the CPG models. Furthermore, Asai *et al.* (2003) combined cooperativity breaking in the CPG model with disorder in cooperativity between the lower limbs of a patient of Parkinson disease in pedaling special pedals (the left and right pedals can move independently with each other). In the CPG model, cooperativity breaking emerges due to strength difference of the downgoing signal from the higher central nervous system to each of two half-centers. They also showed that non-cooperative and dis-cooperative pedaling patterns shown by clinical patients are well reproduced by the oscillatory patterns of the CPG model and both strengths of the signals from the higher motor center to each of half-centers and their difference played important roles in generation and breaking down of the cooperative oscillation patterns.

Porta *et al.* (1996) showed an interesting experimental result on the circulatory system of a decerebrate cat. In this experiment, they aimed to obtain the influence of respiratory rhythm on the sympathetic nerve activity. They observed the temporal change of the spike frequency of the sympathetic nerve system which controls the heart beat of the anaesthetized animal under various circumstances. The spike frequency varies with respiration rhythms showing 1:1 or 1:2 phase locking. But  $n:m$  phase locking or even quasi-periodic non-periodic (chaotic) phase locking are also observed under the conditions 1) vein block, 2) artery constriction, 3) vagal nerve disconnect, 4) spinal cord disconnect and their combinations.

## 6. Conclusions and discussions

In the present article, we explained the phase resetting using a simple model of a limit cycle oscillator, the RIC, and its possible roles in biological rhythms. Biological rhythms can be modeled using more sophisticated oscillators but the phase resetting can be explained in the same framework as that of the RIC.

We note here that there are two essentially different basic phase transition curves (BPTC), depending on the strength of the perturbation. Effects of perturbing a limit cycle oscillator, the RIC in this case, are schematically depicted



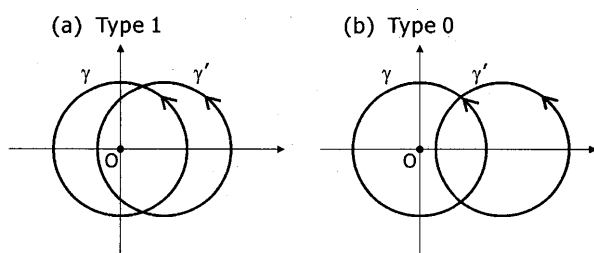


Fig. 9 The circles  $\gamma$  and  $\gamma'$  indicate the limit cycle and the perturbed limit cycle, respectively. (a) Type 1, (b) Type 0

in Fig. 9. Perturbations shift the limit cycle  $\gamma$  and result in the perturbed cycle  $\gamma'$ . If the perturbed cycle encloses the equilibrium point, type 1 phase resetting takes place. If the perturbed cycle does not enclose the equilibrium point, one has type 0 phase resetting. See Fig. 9 and Fig. 3(a, b). For more precise discussion, see Glass and Winfree (1984).

Nomura *et al.* (1994a) discussed the behavior of a pacemaker neuron exposed to a periodic pulse train using a modified RIC. They discussed a coupled system of two equal half-centers as a CPG model and showed emergence of cooperative motion as well as the symmetry breaking in the system's behavior.

Much has been done both experimentally and theoretically on the phase reset in the framework of biological rhythms. However, the present article is not a review paper and hence we did not mention the history and the present circumstance of the studies on the phase resetting.

Finally let us mention the role of noise in the response of the SAO pacemaker as suggested by Segundo *et al.* (1991a, b). Influence of noise cannot be neglected on the dynamics of some phenomenon. In fact, information processing in the microscopic level of biology, for instance, the sensory receptor, makes active use of the environmental noise (Segundo *et al.*, 1994). A simulation study using the van der Pol equation suggests that environmental fluctuation may cause an essential change in the behavior of a dynamical system<sup>4</sup>.

Suppose that nonlinear equations are perturbed by noise. There are two ways that noise

affects the equations. Noise can affect a system in an additive manner and/or in a multiplicative manner. It provides essential changes in a bifurcation structure of the noise-free system due to Stratonovich and in fact this can be confirmed by a simulation experiment. Thus role of noise can not be neglected because it sometimes affects the behavior of a system essentially. Noise is not merely noise. The change in responses due to bifurcation is generally drastic. May the living organism accept such a drastic change provided that it behaves subject to a noise-free dynamical system? In reality, a control system realizes smooth and redundant motion by interfering nonlinearity of the system with environmental noise. Noise can stabilize system's responses and serve to make the system robust. According to our computer simulation, noise may also serve to make the system's input-output relation linear. Noise has been considered as nuisance in the conventional science, but it possibly plays a role in the emergence of biological functions.

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4) The van der Pol equation is described as  $\ddot{x} + \mu(1-x^2)\dot{x} + \omega^2x = 0$ . The equilibrium point  $(x, \dot{x})$  of the equation is  $(0, 0)$  and the point is stable if  $\mu < 0$  and unstable if  $\mu > 0$ . In the latter case, the system shows the limit cycle oscillation. The FHN equations are obtained by the Liénard transformation of the present equation.

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