PHYSICAL REVIEW E **67**, 056215 (2003)

Receptors as a master key for synchronization of rhythms

Seido Nagano*
Fundamental Research Labs, NEC Corporation, 34 Miyukigaoka, Tsukuba, Ibaraki 305-8501, Japan

(Received 5 July 2002; published 23 May 2003)

A simple, but general, scheme to achieve synchronization of rhythms is proposed. It can handle both external synchronization and self-synchronization within a single mathematical framework. In this scheme, external linear stimulations can be converted into internal nonlinear stimulations by the mathematical model receptor without breaking the regular motions of limit cycle oscillators. Thus, even a small external periodic stimulation can work very efficiently for achieving synchronization. Stimulation via model receptors is much more effective for synchronization than mechanically forced stimulations, and the phenomenon called *N:M* phase locking $(N\neq 1, M\neq 1)$ can be suppressed in the weak coupling domain, too.

DOI: 10.1103/PhysRevE.67.056215 PACS number(s): 05.45.Xt, 87.19.−j

Synchronization of rhythms plays a central role in system control both in science and in technology. There are two kinds of synchronizations: one is external synchronization, the other is self-synchronization. External synchronization and self-synchronization are also called frequency entrainment and mutual synchronization, respectively. For external synchronization, external periodic stimulation is needed, but it is not necessary for self-synchronization. An example of external synchronization is a circadian rhythm [1]. Synchronous swinging of pendulums of clocks on a wall [2], flashing of fireflies [3], and the intracellular cyclic adenosine $3',5'$-monophosphate production cycles between the cellular slime mold amoebae [4,5], when they are starved, are examples of the self-synchronization. Because of the importance of synchronization of rhythms, its study started in the 17th century and there is a large body of literature now [6]. However, in many cases, proposed theories so far are rather complex or too simple and their applications have been limited to their small related areas. This is reflecting the complexity of real individual synchronization phenomena. For example, even in the case of circadian rhythm, a complex mechanism is involved both in genetics and in biochemistry. No single theory can explain every detail of all synchronization phenomena in nature. However, synchronization of rhythms itself is obviously a very simple phenomenon. Thus, if we have a general mathematical scheme for studying synchronization beforehand, it is surely helpful for finding the underlying mechanism of synchronization. This paper intends to propose such a scheme.

In biological systems, mutually coupled oscillators, which interact with the external environment, and receptors are ubiquitous. Thus, a previously developed receptor scheme [7–9] is generalized and mathematically simplified very much in order to handle both external synchronization and self-synchronization within the same scheme. It is also to be shown that synchronization, in general, is achieved as a result of the competition between two kinds of nonlinearities: one is nonlinearity within individual oscillators, the other is the nonlinearity to couple between oscillators via model receptors. In the current scheme, external small stimulations from other oscillators can be converted into internal nonlinear stimulations by the model receptor without breaking the regular motions of limit cycle oscillators. Thus, even a small external periodic stimulation can work very effectively for achieving synchronization.

The proposed generalized receptor scheme for synchronization is as follows (Fig. 1). Let oscillators be described by

$$dx_j/dt = X_j(x_j, y_j),$$
$$dy_j/dt = Y_j(x_j, y_j), \tag{1}$$

and they have a limit cycle, where $X_j(x_j,y_j)$ and $Y_j(x_j,y_j)$ are functions of x_j and y_j. We regard one of two variables x_j and y_j as the density of a virtual diffusible chemical (virtual ligand), which is produced individually, and the other as the activity of a sensor (virtual receptor) to detect it (see Ref. [8] for the detail). Thus, when the same type of virtual chemical is provided externally, Eq. (1) should be modified as

$$dx_j/dt = X_j(x_j, y_j),$$
$$dy_j/dt = Y_j(x_j + \gamma_j x_j^{out}, y_j), \tag{2}$$

or

$$dx_j/dt = X_j(x_j, y_j + \gamma_j y_j^{out}),$$
$$dy_j/dt = Y_j(x_j, y_j), \tag{3}$$

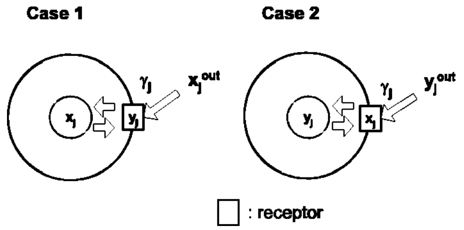

FIG. 1. Schematic view of a receptor-ligand coupling scheme for synchronization. Case 1: y_j is regarded as the activity of the receptor; x_j and x_j^{out} are the internal and the external stimuli, respectively, both of them are regarded as ligands; and γ_j is the sensitivity of the receptor. Case 2: x_j is the activity of the receptor; y_j and y_j^{out} are the internal and the external stimuli, respectively; both of them are also regarded as ligands. In both cases, it is assumed that two variables x_j and y_j constitute a limit cycle oscillator.

---

[*] Present address: Department of Applied Chemistry, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga 525-8577, Japan.

1063-651X/2003/67(5)/056215(4)/$20.00

©2003 The American Physical Society

depending on whether we regard x_j, y_j as ligandlike density and receptorlike activity, respectively [we call Eq. (2) case 1] or vice versa [we call Eq. (3) case 2]. Where we regard x_j^{out} and y_j^{out} as extraoscillatory ligandlike densities, γ_j is the sensitivity of the receptor of the jth oscillator. In the case of self-synchronization [8], we set $x_j^{out} \equiv \Sigma_i x_i$ and $y_j^{out} \equiv \Sigma_i y_i$. Depending on the problem to be handled, summation Σ_i covers every oscillator or self-term and just neighbor oscillators. On the other hand, we substitute x_j^{out} or y_j^{out} with external periodic stimulation for handling the external synchronization. The above procedure can work as a synchronization scheme in general.

Let us consider why such simple procedures given by Eqs. (2) or (3) can work as a general synchronization scheme. As we know, a limit cycle oscillator has a tendency to return to regular periodic oscillation. Therefore, when x_j and x_j^{out} or every oscillator are not synchronized, irregular oscillations are always produced, for example, in Eq. (2). But individual limit cycle oscillators have a tendency to return to regular periodic oscillation forever; namely, an effort to eliminate irregular oscillations can continue forever within every oscillator until synchronization is achieved. But it is only if individual oscillatory motion itself is not destroyed. This is true in Eq. (3), too. Oscillators cannot be synchronized within the current scheme if they are not limit cycle oscillators. Besides, every amplitude of x_j can be different in the synchronized state and only synchronization of rhythms can be expected.

Since the current biological receptor scheme has been developed inductively from a modeling study of cellular slime mold, the validity of the scheme must be tested numerically on a case-to-case basis. Although the current scheme may look very simple, it should be noticed that the coupling between oscillators in Eqs. (2) and (3) is also of nonlinear type. The effect of coupling via model receptors is, thus, tremendous as explained later.

To check the validity of the current scheme, we use the following two well-known nonlinear equations with a limit cycle. One is the van der Pol equation [10],

$$\frac{d^2x}{dt^2} + \epsilon(x^2-1)\frac{dx}{dt} + \omega_0^2 x = 0, \tag{4}$$

or

$$\frac{dx}{dt} = y \equiv X(x,y),$$

$$\frac{dy}{dt} = -\epsilon(x^2-1)y - \omega_0^2 x \equiv Y(x,y), \tag{5}$$

where ω_0 is the intrinsic frequency and ϵ is the positive constant to represent the strength of nonlinearity. The other is the Brusselator model equation [11] given by

$$\frac{dx}{dt} = a-(b+1)x + x^2 y \equiv X(x,y),$$

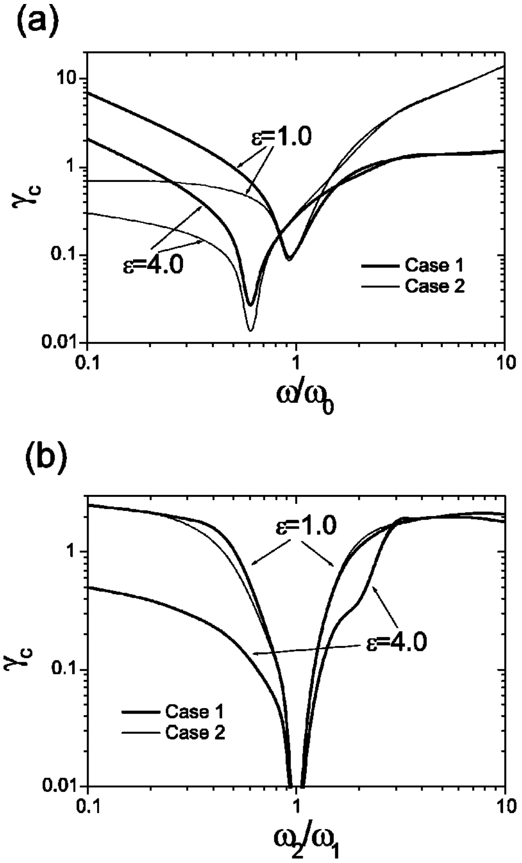

FIG. 2. (a) External synchronization area of the van der Pol oscillator, where the sinusoidal stimulation is applied. Synchronization is achieved when $\gamma \geqslant \gamma_c$, where the value of γ is the sensitivity of the receptor and that of ϵ stands for the strength of nonlinearity of the van der Pol oscillator. The frequency of sinusoidal stimulation is ω, and the intrinsic frequency of the van der Pol oscillator is $\omega_0 = 1$. (b) Self-synchronization area of two van der Pol oscillators. Synchronization is achieved when $\gamma \geqslant \gamma_c$. Intrinsic frequencies are $\omega_1 = 1.0$ and ω_2. In both (a) and (b), cases 1 and 2 used Eqs. (2) and (3), respectively. Note that, compared with the external synchronization, mutual synchronization of oscillators of the same type can be easily achieved. See also Fig. 6.

$$\frac{dy}{dt} = bx - x^2 y \equiv Y(x,y), \tag{6}$$

where we use $a = 1.0$ and $b = 2.1$ so that Eq. (6) has a limit cycle.

In our first test case, we apply the current scheme to external synchronization. Since the equation

$$\frac{d^2x}{dt^2} + \epsilon(x^2-1)\frac{dx}{dt} + \omega_0^2 x = \gamma \cos \omega t, \tag{7}$$

has been extensively investigated [12–14], we adopt it as a first test case, where $\gamma \cos \omega t$ is the external periodic stimulation [we call Eq. (7) case 3]. As Fig. 2(a) shows, synchronization was achieved when $\gamma \geqslant \gamma_c$ in the domain of $0.1 \leqslant \omega/\omega_0 \leqslant 10.0$, where $\omega_0 = 1.0$. Here, $x^{out} = \cos \omega t$ in Eq. (2) (case 1) and $y^{out} = \cos \omega t$ in Eq. (3) (case 2). Two examples

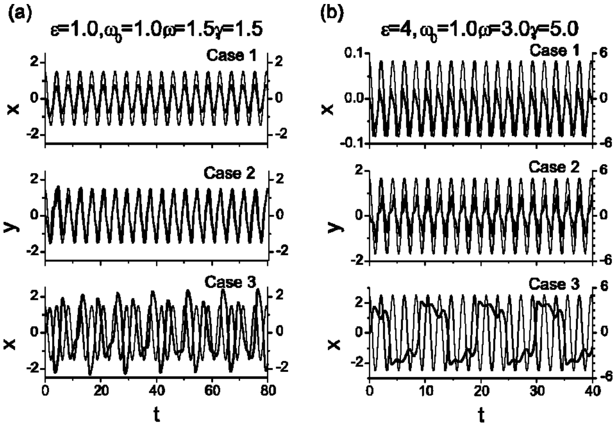

FIG. 3. (a),(b) External synchronization between the van der Pol oscillator of intrinsic frequency $\omega_0 = 1$ (thick line, its scale is on the left axis) and the external periodic stimulus of the frequency ω (thin line, its scale is on the right axis). The parameter ϵ stands for the strength of nonlinearity of the van der Pol oscillator. The parameter γ is the sensitivity of the receptor, where $x^{out} = \cos \omega t$ and Eq. (2) were used in case 1, $y^{out} = \cos \omega t$ and Eq. (3) were used in case 2, and Eq. (7) was used in case 3. In case 3 of (b), 5:1 phase locking is clearly observed.

are shown in Fig. 3. In the case of Brusselator model, $x^{out} = \cos(\omega t + \pi) + 1$ in Eq. (2) (case 1) and $y^{out} = \cos(\omega t + \pi) + 1$ in Eq. (3) (case 2) so that both x^{out} and y^{out} are nonnegative [see Fig. 4(a)].

In the case of Eq. (7), synchronization between external periodic stimulation and van der Pol oscillator is expected when stimulation frequency ω and the intrinsic frequency of the van der Pol oscillator (ω_0) are not so different. On the other hand, the phenomenon N:M phase locking [12,13] ($N \neq 1, M \neq 1$) [see, for example, case 3 in Fig. 3(b)] is expected to occur when the two frequencies are very different from each other, and there are M cycles of spontaneous rhythms at fixed phase for each N cycles of external stimulus. It is also known that two rhythms are completely independent when the ratio between the two frequencies is not rational. However, as shown in Fig. 3(b), 1:1 synchronization was achieved in this scheme even where the N:M ($N \neq 1, M \neq 1$) phase locking phenomenon was observed in case 3 (for more detail, see Fig. 12.12 in Ref. [12] or Fig. 7.3 in Ref. [13]). Not only the suppression of N:M ($N \neq 1, M \neq 1$) phase locking, but also the quality of synchronization has been significantly improved in general [see, e.g., Fig. 3(a)]. To see more details of the above-described situation, we use Taylor's expansion $Y(x + \gamma x^{out}, y) \sim Y(x,y) + \partial Y(x,y)/\partial x \gamma x^{out}$ when γ is small, then from Eq. (2) we can derive

$$\frac{d^2x}{dt^2} + \epsilon(x^2 - 1)\frac{dx}{dt} + \omega_0^2 x = -\left(\omega_0^2 + 2\epsilon x \frac{dx}{dt}\right)\gamma \cos \omega t, \tag{8}$$

where $x dx/dt$ is not a large term because x is an oscillatory variable and x and dx/dt are close to out of phase. When ω_0 is large or ϵ is small, namely, when nonlinearity is small, Eq. (8) becomes an example of case 3 (e.g., Fig. 5). This means that recovering force to return to the limit cycle is weaker in case 3 compared to case 1 so N:M phase locking can not be suppressed. It is because the effective coupling constant ($\omega_0^2 \gamma$) is larger than γ. This comparison is made only for understanding better the current scheme. More rigorous analytical comparison between the two schemes is difficult due to nonlinearities included in the current scheme.

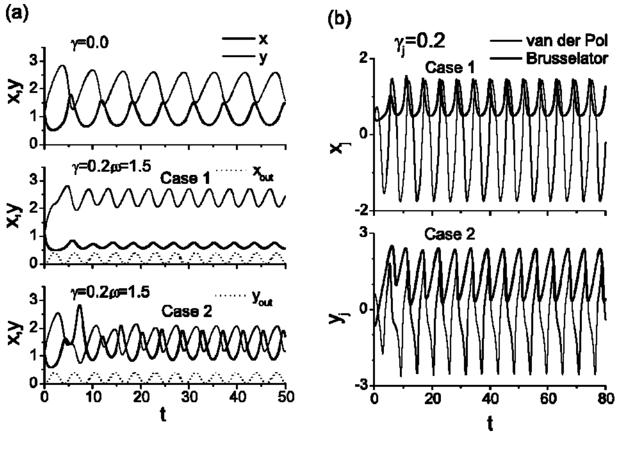

FIG. 4. (a) External synchronization of the Brusselator when the sinusoidal stimulation is applied. Here, $x^{out} = \cos(\omega t + \pi) + 1$ was used in case 1, and $y^{out} = \cos(\omega t + \pi) + 1$ was used in case 2. (b) Self-synchronization between the Brusselator and the van der Pol oscillator.

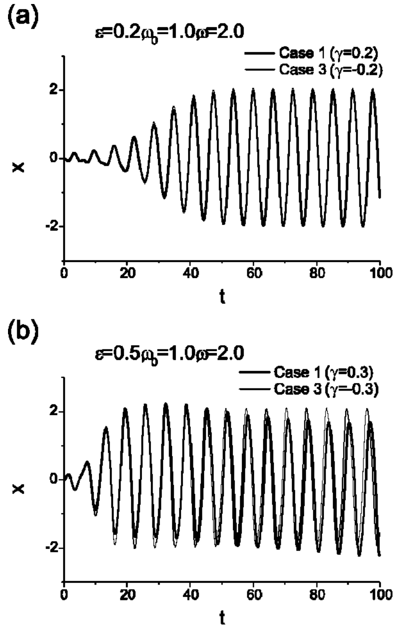

FIG. 5. Case 3 is an approximation of case 1. When γ is small and nonlinearity of van der Pol oscillator is weak, these cases become identical.

Next, we apply the current scheme to self-synchronization. Figure 6(a) shows the synchronization of two van der Pol oscillators. As shown in Fig. 2(b), synchronization was achieved when $\gamma \geqslant \gamma_c$ in the domain of $0.1 \leqslant \omega_2/\omega_1 \leqslant 10.0$, where $\omega_1 = 1.0$. Figure 2 shows that higher

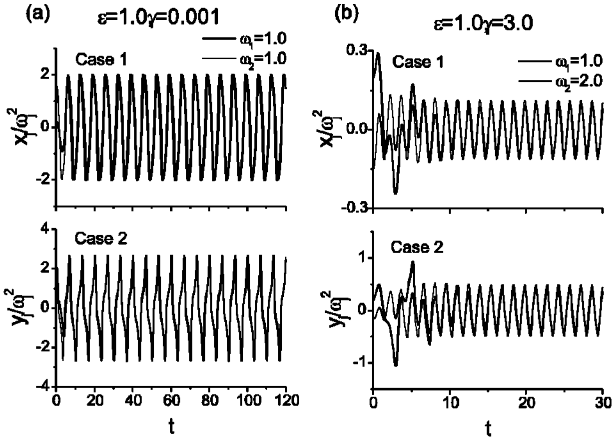

FIG. 6. Examples of the self-synchronization of two van der Pol oscillators: cases 1 and 2 for Eqs. (2) and (3), respectively. Here, $x_1^{out}=x_2^{out}=x_1+x_2$ was used in Eq. (2), and $y_1^{out}=y_2^{out}=y_1+y_2$ was used in Eq. (3). Even very weak sensitivity of the receptor is sufficient for achieving self-synchronization when the intrinsic frequencies of the two oscillators are the same.

sensitivity of receptors is necessary for the external synchronization than self-synchronization. Another example is the synchronization between the van der Pol oscillator and the Brusselator [Fig. 6(b)]. This type of self-synchronization has not been reported yet, but it is not so surprising because the current scheme does not require that every oscillator should be of the same type. In Eq. (1), every (X_j, Y_j) can be a different type.

Since Hayashi reported the $N{:}M$ phase locking [12,13] $(N\neq 1, M\neq 1)$ of the van der Pol oscillator in the presence of external sinusoidal stimulation in 1964, it has been generally taken as an avoidable phenomenon; namely, in the conventional scheme of case 3 [Eq. (7)], a cascade of phase locking events with different winding ratios occur as we gradually change the ratio of frequencies. However, the current work has proved that there is a scheme to overcome the $N{:}M$ phase locking $(N\neq 1, M\neq 1)$ even in the weak coupling domain, and 1:1 phase locking has been always achieved in any frequency ratio as shown in Fig. 2. Due to the nonlinearity of coupling between oscillators, the common frequency in the synchronized state can be different from the original frequencies of individual oscillators. Namely, every oscillator has a tendency to look for a common frequency for the coupled oscillator system depending on the coupling strength.

For achieving self-synchronization, a term of diffusive type, $k(x_2-x_1)$, is often added to Eq. (1) expecting that $x_2-x_1\rightarrow 0$ $(t\rightarrow\infty)$ in the synchronized state. However, Figs. 3 and 4 show that $x_2-x_1\rightarrow 0$ $(t\rightarrow\infty)$ cannot be achieved in the synchronized state unless all oscillators are of the same type. When oscillators are of different types, only rhythm synchronization is achieved and amplitudes of individual oscillators are generally different in the synchronized state.

To the author's knowledge, no other scheme has ever succeeded in handling external synchronization and the self-synchronization within the same mathematical framework. The derived scheme may look very simple mathematically, but it is a very powerful scheme as numerically demonstrated in this paper. It was clarified that biological receptors work as apparatuses that can convert external stimulus to the form of nonlinear interaction within individual oscillators. Thus, synchronization is achieved as a result of competition between two kinds of nonlinearities: one is nonlinearity within individual oscillators, the other is the nonlinearity to couple between oscillators via receptors. The current biological receptor scheme has been inductively generalized from the modeling study of cellular slime mold, it is not a rigorous mathematical proof. Thus, it does not exclude any possibility of another type of synchronization scheme. Nonetheless, the biological receptor scheme should significantly help in understanding the synchronization phenomena in biology since groups of limit cycle oscillators and receptors are ubiquitous in biological systems.

---

[1] J.S. Takahashi, Annu. Rev. Neurosci. **18**, 531 (1995).
[2] C. Huygens, *Hologium Oscillatorium* (Muguet, Paris, 1673), p. 117.
[3] J. Buck and E. Buck, Nature (London) **211**, 562 (1966).
[4] S. Nagano, Phys. Rev. Lett. **80**, 4826 (1998).
[5] S. Nagano, Dev., Growth Differ. **42**, 541 (2000).
[6] A.S. Pikovsky, M.G. Rosenblum, and J. Kurths, *Synchronization: A Universal Concepts in Nonlinear Sciences* (Cambridge University Press, Cambridge, 2001).
[7] S. Nagano, Prog. Theor. Phys. **103**, 229 (2000).
[8] S. Nagano, Prog. Theor. Phys. **107**, 861 (2002).
[9] S. Nagano, in *Microbial Development under Environmental Stress*, edited by J.C. Gutierrez (Research Signpost, Trivandrum, India, 2002), pp. 1–16.
[10] B. van der Pol, Philos. Mag. **2**, 978 (1926).
[11] G. Nicolis and I. Prigogine, *Self-Organization in Non-Equilibrium Systems. From Dissipative Structures to Order Through Fluctuation* (Wiley, New York, 1977).
[12] C. Hayashi, *Nonlinear Oscillations in Physical Systems* (McGraw-Hill, New York, 1964).
[13] L. Glass and M.C. Mackey, *From Clocks to Chaos* (Princeton University Press, Princeton, 1988).
[14] J.M.T. Thompson and H.B. Stewart, *Nonlinear Dynamics and Chaos*, 2nd ed. (Wiley, New York, 2002).