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TOPICAL REVIEW — Soft matter and biological physics

Dominant phase-advanced driving analysis of self-sustained oscillations in biological networks*

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Oscillatory behaviors can be ubiquitously observed in various systems. Biological rhythms are significant in governing living activities of all units. The emergence of biological rhythms is the consequence of large numbers of units. In this paper we discuss several important examples of sustained oscillations in biological media, where the unit composed in the system does not possess the oscillation behavior. The dominant phase-advanced driving method is applied to study the skeletons and oscillatory organizing motifs in excitable networks and gene regulatory networks.

Keywords: self-sustained oscillation, complex networks, gene networks, dominant phase-advanced driving approach

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1. Introduction

Oscillatory behavior is an indication of temporally periodic dynamics of a system, and it can be ubiquitously observed in various systems, ranging from physics and chemistry to biology.[1,2] The behaviors are mathematically described by the existence of a typical time scale that repeatedly emerges in the evolution. Physically the emergence of the rhythmic feature of a system may originate from numerous different scenarios. Self-sustained oscillation, also called the limit cycle, which is defined as a typical nonlinear dynamical behavior, has received a great deal of attention throughout the last century.[3]

The emergence of sustained oscillations is an interesting topic in studies of nonlinear systems. The essential mechanism of sustained oscillation is the existence of feedback, but the source of feedback depends strongly on different situations. In mechanical systems, for example, the conventional Van der Pol oscillator, the adjustable damping provides the key mechanism for the energy compensation to sustain a stable limit cycle. The damping becomes positive to dissipate energy when the amplitude is large and becomes negative to compensate energy when the amplitude is small. This provides a feedback mechanism to maintain the stable oscillation. Stability analysis can well present the dynamical mechanism of the limit-cycle motion. There are a lot of historic examples and models in describing this typical oscillatory dynamics, regular or chaotic, and these studies have also been well applied in many different systems.

Self-sustained oscillations in complex systems consisting of a large number of units with no oscillatory dynamics have become of great interest in recent years.[4–8] Because each unit in the system does not exhibit an oscillatory behavior, the feedback mechanism of sustained oscillations should be due to the collaborative feedback of units. It is thus very interesting and important to explore the mechanism of oscillatory dynamics when these units interact with each other, and to study how a number of non-oscillatory nodes organize themselves to present a collective oscillatory phenomenon.[9] Recent studies of the so-called complex networks stimulated by milestone works on small-world[10] and scale-free networks[11] provide a powerful platform in revealing self-organizations in complex networks.[12–16]

The topic of self-sustained oscillations in complex systems was largely motivated by an extensive study and a strong background of systems biology. Non-oscillatory systems exist ubiquitously in biological systems, e.g., the gene segments and neurons. People have extensively studied such common behaviors in nature, such as oscillations in genetic regulatory networks,[4,17–25] neural networks, and brains.[5–8,26–33]

The exploration of the key determinants of collective oscillations is a great challenge. Recent progresses indicate that, although the collective self-sustained oscillation emerges from the organization of units in the system, only a small number or some of key units play the dominant role in giving rise to the collective dynamics. We may call them the self-

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organization core or the oscillation source. Theoretically, diverse self-sustained oscillatory activities and related determining mechanisms have been reported in different kinds of excitable complex networks. For example, we discovered that one-dimensional Winfree loops may support self-sustained target group patterns in excitable small-world networks.[34,35] We have also revealed the center nodes and small skeletons to sustain target-wave-like patterns in excitable homogeneous random networks.[36–41] The mechanism of long-period rhythmic synchronous firings in excitable scale-free networks has been explored to explain the temporal information processing in neural systems.[42] On the other hand, node dynamics in biological networks depends crucially on different systems. For example, the gene dynamics is totally different from the excitable dynamics, and the network structures are also different. We have revealed the fundamental building blocks of sustained oscillations in gene regulatory networks and studied the interesting chaotic dynamics and its mechanism.[43–45]

The present paper gives a brief review of our recent studies on self-sustained oscillations of interacting non-oscillatory units. We demonstrate our results by studying excitable networks and gene regulatory networks. The dominant phase-advanced driving (DPAD) method is an effective approach in revealing the fundamental organization of collective oscillations.

2. The dominant phase-advanced driving method

An important subject in revealing the coordination of units is to explore the core structure and dynamics in the organization process of a large number of non-oscillatory units. DPAD is a dynamical method that can find the strongest cross driving of the target node when a system is in an oscillatory state. Here, we briefly recall the dynamical DPAD structure.[36–41]

Given a network consisting of N nodes with nonoscillatory local dynamics described by well-defined coupled ordinary differential equations, there are M ($M > N$) links among these different nodes. We are interested in the situation when the system displays a global self-sustained oscillation and all nodes that are individually non-oscillatory become oscillatory. It is our motivation to find the mechanism supporting the oscillation in terms of the network topology and oscillation time series of each node.

Let us first clarify the significance of nodes in a network with sustained oscillations by comparing their phase dynamics. Obviously the oscillatory behavior of an individually nonoscillatory node is driven by signals from one or more interactions with advanced phases, if such a phase variable can be properly defined. We call such a signal the phase-advanced driving (PAD). Among all phase-advanced interactions the interaction giving the most significant contribution to the given node can be defined as the dominant phase-advanced driving (DPAD). Based on this idea, the corresponding DPAD for each node can be identified. By applying this network reduction approach the original oscillatory high-dimensional complex network of N nodes with M vertices/interactions can be reduced to a one-dimensional unidirectional network of size N with M' unidirectional dominant phase-advanced interactions.

An example of clarifying the DPAD is shown in Fig. 1(a). The black curve denotes the given node as the reference node. Many nodes linking directly to this reference can be checked when a given network is proposed. Suppose there are three nodes whose dynamical time series are labeled by green, blue, and red curves, respectively. The green curve exhibits a lagged oscillation to the reference curve, therefore one calls it the phase-lagged oscillation. The blue and red curves provide the drivings for exciting the reference node, so these curves are identified as PAD. The blue one presents the earliest oscillation and makes the most significant contribution thus it is the DPAD.

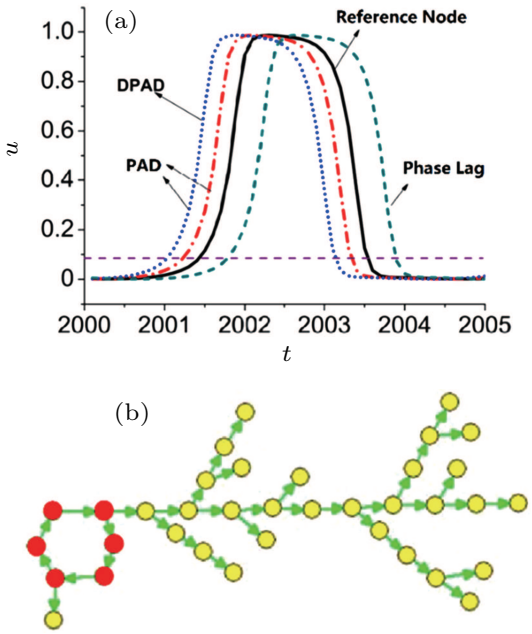


Fig. 1. (color online) (a) A schematic plot of the DPAD. As comparisons, the reference oscillatory time series, a usual PAD and a phase-lagged node dynamics are also presented, respectively. (b) An example of a simplified (unidirectional) network in terms of the DPAD scheme. (Adapted from Ref. [38]).

Figure 1(b) gives an illustration of a DPAD structure consisting of one loop and the nodes outside the loop radiated from the loop. For excitable node dynamics, as shown below, the red nodes form a unidirectional loop that acts as the oscillatory source, and the yellow nodes beyond the loop form paths for the propagation of oscillations.

The DPAD structure reveals the dynamical relationship between different nodes. Based on this functional structure,

we can identify the loops as the oscillation source, and illustrate the wave propagation along various branches. All the above ideas are generally applicable to diverse fields for self-sustained oscillations of complex networks consisting of individual non-oscillatory nodes. In the following sections we focus on self-sustained oscillations in excitable networks and regulatory gene networks. One can find that both types of system possess a common feature, that is, only a small number of units participate in the global oscillation, and some fundamental structures play dominant roles in giving rise to oscillatory behaviors in the system, although the organizing cores differ for these two types of networks.

3. Oscillation sources and wave propagations on excitable networks

We first take the representative excitable dynamics as a prototype example to reveal the mechanism of global oscillations. Cooperation among units in the system leads to an ordered dynamical topology to maintain the oscillatory process. In regular media, the oscillation core of a spiral wave is a self-organized topological defect. People have also found that the loop topology is significant in maintaining the self-sustained oscillation. For example, as early as in 1914, Mines suggested the importance of the loop structure in oscillations of cardia media.[46] Jahnke and Winfree proposed the dispersion relation in the Oregonator model.[47] Courtemanche *et al.* studied the stability of the pulse propagation in one-dimensional (1D) chains.[46] If a loop composed of excitable nodes can produce self-sustained oscillations, one may call it the Winfree loop.

It is not difficult to understand the loop topology as a basic structural basis of collective oscillation for a network of non-oscillatory units. An excitable node in a sustained oscillatory state must be driven by other nodes. To maintain such drivings, a simple choice is the existence of a looped linking among interacting nodes. A local excitation leads to a pulse and is propagated along the loop to drive other nodes in order, which forms a feedback mechanism of repeated driving. Furthermore, the oscillation along the loop can be propagated by nodes outside the loop and spread throughout the system. The propagation of oscillation in the media gives rise to the wave patterns.

The loop structure is ubiquitous in real networks and plays an important role in network dynamics. Recurrent excitation has been proposed to be the reason supporting self-sustained oscillations in neural networks. The DPAD method can reveal the underlying dynamic structure of self-sustained waves in networks of excitable nodes and the oscillation source. In complex networks, numerous local regular connections coexist with some long-range links. The former plays an important role in target wave propagation and the latter is crucial for maintaining the self-sustained oscillations.

We use the Bär–Eiswirth model to describe the excitable dynamics and consider an Erdos–Renyi (ER) random network. The network dynamics is described by

$$\dot{u}_i = -\frac{1}{\varepsilon}u_i(u_i-1)\left(u_i-\frac{v_i+b}{a}\right) + D\sum_{j=1}^{N}A_{i,j}(u_j-u_i), \tag{1a}$$

$$\dot{v}_i = f(u_i)-v_i. \tag{1b}$$

Variables $u_i(t)$ and $v_i(t)$ describe the activator and the inhibitor dynamics of the i-th node, respectively. The function $f(u)$ takes the following piecewise form:

$$f(u)=\begin{cases}0, & \text{if } u<1/3,\\ 1-6.75u(u-1)^2, & \text{if } 1/3\le u<1,\\ 1, & \text{if } u>1.\end{cases} \tag{2}$$

The relaxation parameter $\varepsilon \ll 1$ represents the time ratio between the activator u and the inhibitor v. The dimensionless parameters a and b denote the activator kinetics of the local dynamics and the ratio $u_{\mathrm{T}}=b/a$ can effectively control the excitation threshold. D is the coupling strength between linking nodes. $\boldsymbol{A}=\{A_{i,j}\}$ is the adjacency matrix. For a symmetric and bidirectional network, the matrix is defined as $A_{i,j}=A_{j,i}=1$ if there is a connection linking nodes i and j, and $A_{i,j}=A_{j,i}=0$ otherwise. The impact of the network structure on global dynamics has been extensively studied in the last two decades.[12–16]

We study the random network in Fig. 2(a) as a typical example. Without couplings among nodes, each excitable node is non-oscillatory, i.e., they evolve asymptotically to the rest state $u=v=0$ and will stay there perpetually unless some external force drives them away from this state. When a node is kicked from its rest state by a stimulus large enough, the unit can be excited by its own internal excitable dynamics.

With the given network structure and parameters, one studies the dynamics of the system by starting from different sets of random initial conditions. The system evolves asymptotically to the homogeneous rest state in many cases. However, one still finds a small portion of tests which eventually exhibit global self-sustained oscillations. The spatiotemporal patterns given in Figs. 2(b) and 2(c) are two different examples of these oscillatory (both periodic and self-sustained) states.

One can unveil the mechanism supporting the oscillations and the excitation propagation paths by using the DPAD approach. In Figs. 2(d) and 2(e), the reduced directed networks corresponding to the oscillatory dynamics by using the DPAD method are plotted. For the case with dynamics shown in Fig. 2(b), the single dynamical loop plays the role of the oscillation source, with cells in the loop exciting sequentially to maintain the selfsustained oscillation, as shown in Fig. 2(d). We can observe waves propagating downstream along several tree branches rooted at various cells in the loop. If we

plot the spatiotemporal dynamics along these various paths by re-arranging the node indices according to the sequence in the loop, we can find regular and perfect wave propagation patterns. This indicates that the DPAD structure well illustrates the wave propagation paths. For the case with dynamics shown in Fig. 2(c), the corresponding DPAD structure given in Fig. 2(e) is a superposition of two sub-DPAD paths, i.e., there are two organization loop centers, where two sustained oscillations are produced in two loops and propagate along the trees.

The DPAD structures in Figs. 2(d) and 2(e) clearly show the distinctive significance of some units in the oscillation which cannot be observed in Figs. 2(b) and 2(c) where units evolve in the homogeneous and randomly coupled network, and no unit takes any priority over others in topology. Because the unidirectional loop works as the oscillation source, the units in the loop should be more important to the oscillation.

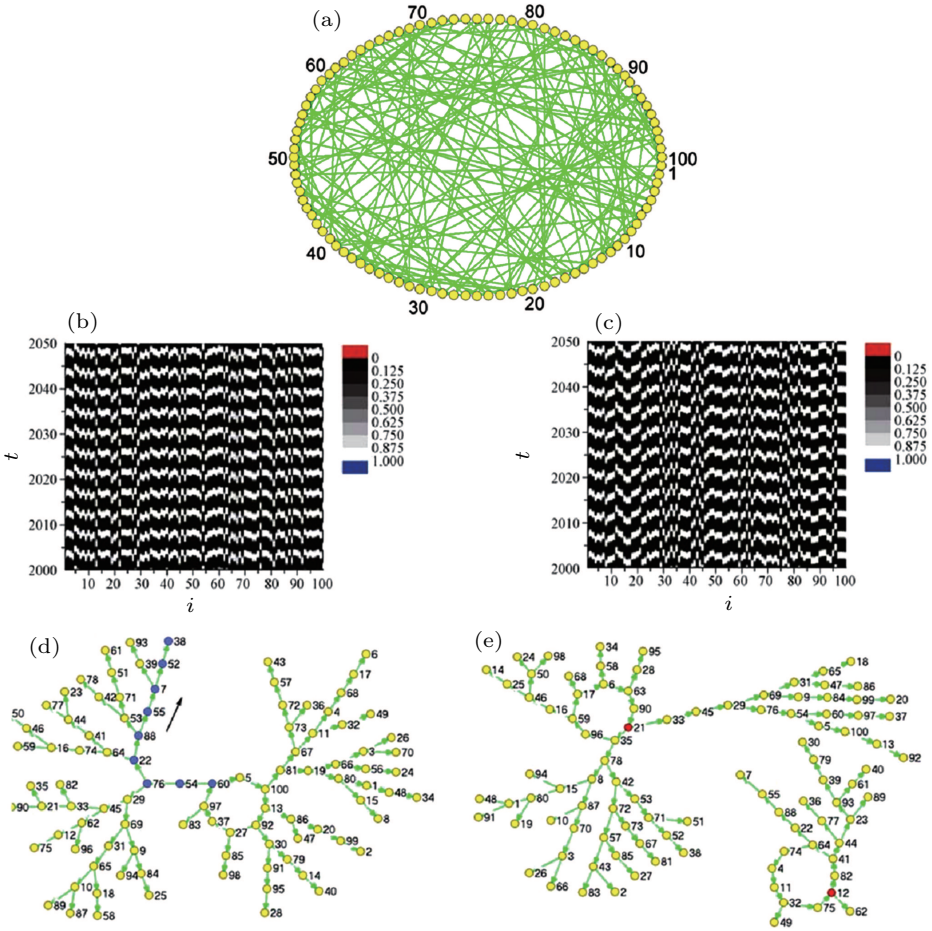


Fig. 2. (color online) (a) An example of a random network with $N = 100$ nodes, and each node connects to other nodes with the same degree $k = 3$. (b), (c) The spatiotemporal evolution patterns of two different oscillatory states in the same network shown in panel (a) by starting from different initial conditions. Both patterns display the evolution of local variable u. The nodes are spatially arranged according to their indices i. (d) The DPAD structure corresponding to the oscillation state in panel (b), where a loop and multiple chains are identified; (e) the DPAD structure corresponding to the oscillation state in panel (c), where two independent subgraphs are found with each subgraph containing a loop and numerous chains. (Adapted from Ref. [38]).

4. Minimum Winfree loop and self-sustained oscillations on excitable networks

Studies on the emergence of self-sustained oscillations in excitable networks indicate that regular self-sustained oscillations can emerge. However, whether there is an intrinsic mechanism in determining the oscillations in networks is still unclear. For example, for Erdos–Renyi networks, whether the connection probability is related to sustained oscillations is an open topic.

In this section we study the occurrence of sustained oscillation depending on the linking probability on excitable ER random networks, and find that the minimum Winfree loop (MWL) is the intrinsic mechanism in determining the emergence of collective oscillations. Furthermore, the emergence of sustained oscillation is optimized at an optimal connection probability (OCP), and the OCP is found to form a one-to-one relationship with the MWL length. This relation is well understood that the connection probability interval and the OCP for supporting the oscillations in random networks are exposed to be determined by the MWL. These three important quantities can be approximately predicted by the network structure anal-

ysis, and have been verified in numerical simulations.[48]

One adopts the Bär–Eiswirth model (1) on ER networks with N nodes. Each pair of nodes are connected with a given probability P, and the total number of connections is $PN(N-1)/2$. By manipulating P, one can produce a number of random networks with different detailed topologies for a given P.

We introduce the oscillation proportion

$$P_{\rm OS} = N_{\rm OS}/N_{\rm ALL} \tag{3}$$

as the order parameter to quantitatively investigate the influence of the system parameters on self-sustained oscillations in random networks, where $N_{\rm ALL}$ is the total number of tests starting from random initial conditions for each set of parameters, and $N_{\rm OS}$ is the number of self-sustained oscillations counted in $N_{\rm ALL}$ dynamical processes.

In Figs. 3(a)–3(d) the dependence of the oscillation proportion $P_{\rm OS}$ on the connection probability P for different parameters a, b, ε, and D on ER random networks with $N = 100$ nodes is presented. It is shown from all these curves that the system can exhibit self-sustained oscillation in a certain regime of the connection probability and no oscillations are presented at very small or very large P. Moreover, an OCP $P = P_{\rm OCP}$ for supporting self-sustained oscillations can be expected on ER random networks. The number of self-sustained oscillations increases as the parameter a is increased (Fig. 3(a)), while $P_{\rm OS}$ decreases as b is increased (Fig. 3(b)). Moreover, the OCP for supporting self-sustained oscillations is independent of the parameters a and b. Figure 3(c) reveals the dependence of $P_{\rm OS}$ on the relaxation parameter ε. It is shown in Fig. 3(c) that as ε is increased, $P_{\rm OS}$ decreases remarkably. Increasing the coupling strength D is shown to enhance the sustained oscillation (Fig. 3(d)).

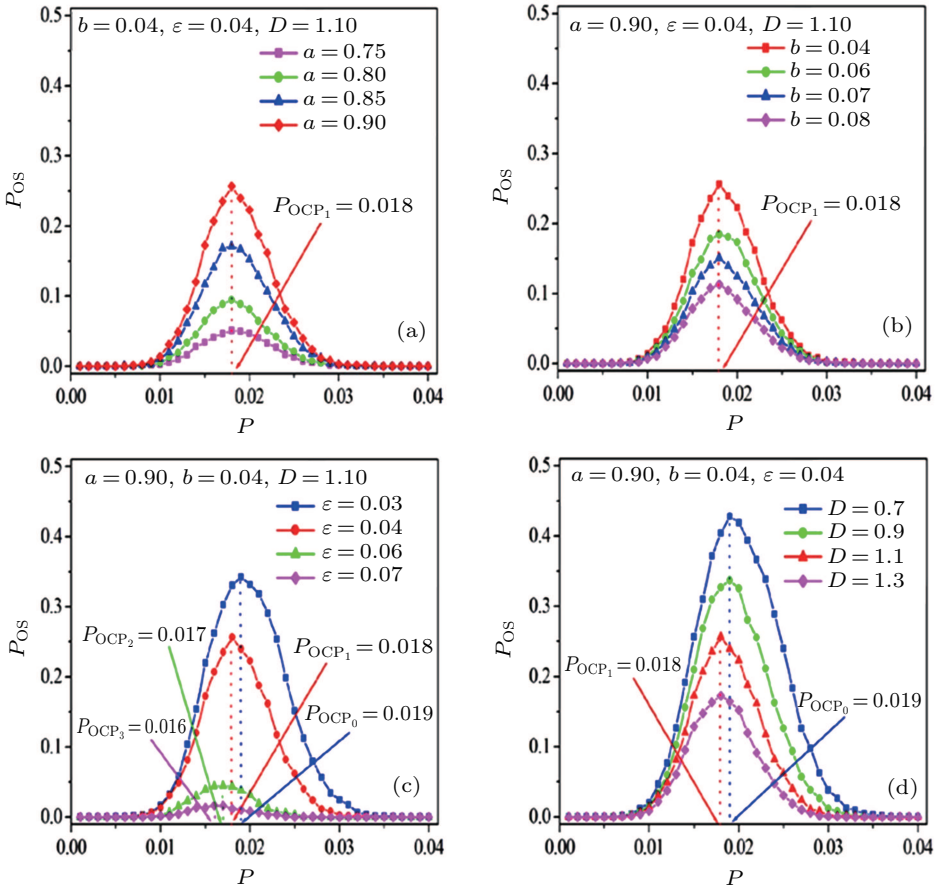


Fig. 3. (color online) The dependence of the oscillation proportion $P_{\rm OS}$ on the connection probability P at different system parameters on excitable ER random networks. The OCPs $P_{\rm OCP}$ for supporting self-sustained oscillations on ER networks at different parameters are indicated. (Adapted from Ref. [48]).

The emergence of collective self-sustained oscillations has also been observed in Section 3, and the non-trivial dependences of the collective oscillations on the parameters especially the connection probability P are very interesting. As discussed above, the excitable wave propagating along an excitable loop can form a 1D Winfree loop which serves as the oscillation source and maintains the self-sustained oscillation in excitable complex networks. Figure 4(a) presents the dependence of the sustained-oscillation period T of the 1D Winfree loop on the loop length, where a shorter/longer period is

expected for a shorter/longer loop length. However, due to the existence of the refractory period of excitable dynamics, a too short 1D Winfree loop cannot support sustained oscillations, implying a minimum Winfree loop length $L_{\min}$ for a given set of parameters. Moreover, the sustained oscillation ceases for the shortest loop length, corresponding to the MWL.

In Fig. 4(b), $P_{\rm OCP}$ is found to build a one-to-one correspondence to $L_{\min}$ indicating that the emergence of collective oscillations is essentially determined by the MWL. This correspondence can be understood by analyzing the following two tendencies. First, as discussed above, a network must contain a topological loop with a length that is not shorter than the MWL, i.e.,

$$L \geq L_{\min}. \tag{4}$$

Second, the average path length (APL) of a given network should be large enough so that

$$d_{\rm APL} \geq L_{\min} - 1. \tag{5}$$

These two tendencies propose the necessary conditions for the formation of a 1D Winfree loop supporting self-sustained oscillations. Moreover, the first condition leads to the lower critical connection probability, which by violating the network cannot support sustained oscillations. The second condition gives rise to the upper critical connection probability when the APL is so short that the loops are too small to support oscillations. In Fig. 4(c), the probability of the loop length being larger than the MWL length is computed against the connection probability P of an ER network. An increasing dependence can be clearly seen, and a lower threshold exists. As shown in Fig. 4(d), the probability of an ER network with the APL satisfying $d_{\rm APL} \geq L_{\min} - 1$ is plotted against P. A decreasing relation and an upper threshold can be found. The necessary condition for sustained oscillation should be a joint probability satisfying both $L > L_{\min}$ and $d_{\rm APL} \geq L_{\min} - 1$. The dependence of this joint probability on the connection probability P is the product of the curves in Figs. 4(c) and 4(d), which naturally leads to a humped tendency, shown in Fig. 4(e), where an OCP is expected for the largest joint probability. This gives a perfect correspondence to the results proposed in Fig. 3.

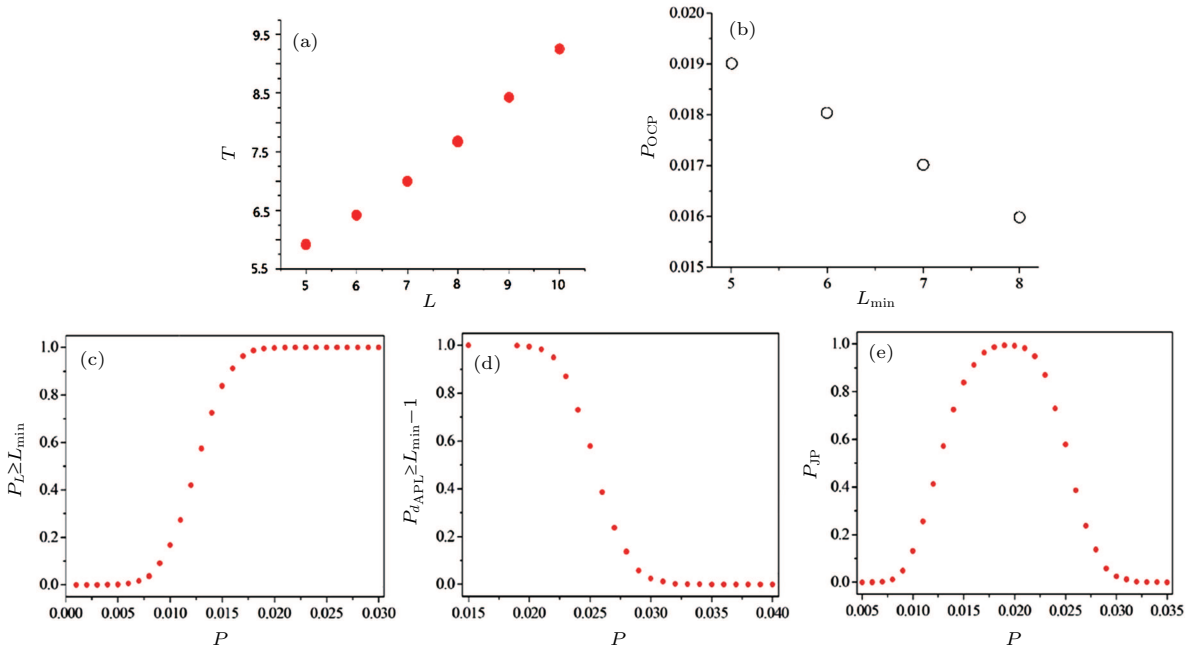


Fig. 4. (color online) (a) The dependence of the oscillation period of a Winfree loop on the loop length. Below the MWL length $L_{\min}$ the oscillation ceases. (b) The dependence of the OCP on the MWL $L_{\min}$. (c) The dependence of the proportion of network structures satisfying $L \geq L_{\min}$ on the connection probability P. (d) The dependence of the proportion of network structures with an APL satisfying $d_{\rm APL} \geq L_{\min} - 1$ on P. (e) The dependence of the joint probability (JP) on P. The MWL with the length $L_{\min} = 6$ is used as the example. (Adapted from Ref. [48]).

Self-sustained oscillation on networks is important for various activities in biological activities. The mechanism of self-sustained oscillation lies on the loop topology embedded in networks. The dependence of self-sustained oscillations on the system parameters reveals that these phenomena are related to the loop topology and dynamics, and are essentially determined by the MWL. The one-to-one correspondence between the optimal connection probability and the MWL length is revealed. The MWL is the key factor in determining the collective oscillations on ER networks.[49,50]

5. Chaotic oscillations in gene regulatory networks

Gene regulatory networks (GRNs), as a kind of biochemical regulatory networks in system biology, can be well de-

scribed by coupled differential equations (ODEs) and have been extensively explored in recent years. The ODEs describing biochemical regulation processes are strongly nonlinear and often have many degrees of freedom. We are concerned with the common features and network structures of GRNs.

Different from the excitable networks above, positive feedback loops (PFLs) and negative feedback loops (NFLs) have been identified in various biochemical regulatory networks and found to be important control modes in GRNs.[20–24] Self-sustained oscillation, birhythmicity, bursting oscillation and even chaotic oscillations are expected for these objects. Specifically chaos may occur in GRNs with a small number of units, which have seldom been reported before. The study of oscillations and chaos in small GRNs is of great importance in understanding the mechanism of gene regulation processes in very large-scale GRNs. Network motifs as subgraphs can appear in some biological networks and they are suggested to be elementary building blocks that carry out some key functions in the network.

Various types of motifs producing some simple functions have been explored and studied, such as sign-sensitive accelerators or delays of feed-forward loop, tunable biological oscillations of coupled NFL and PFL, and so on. In this section, we apply the concept of motifs to investigate the oscillatory and even chaotic dynamics in GRNs. We define a chaotic motif as the minimal structure with the simplest interactions that can generate chaos. It is our motivation to unveil the relation between network structures and the existence of oscillatory and chaotic behaviors in GRNs. We mainly concentrate on chaotic behaviors of autonomous GRNs and answer some very fundamental questions, for example, the mechanism of the rareness of chaos in GRNs basic building blocks/motifs for chaotic motions in complex GRNs, and so on.

We consider the following GRN model:

$$\frac{\mathrm{d}p_i}{\mathrm{d}t} = f_i(\boldsymbol{p}) - p_i, \tag{6}$$

where $(\boldsymbol{p}) = (p_1, p_2, \ldots, p_N)$ and the function $f_i(\boldsymbol{p})$ satisfies the following form:

$$f_i(\boldsymbol{p}) = \begin{cases} A_i(\boldsymbol{p}), & \text{for activive regulation only,} \\ R_i(\boldsymbol{p}), & \text{for repressive regulation only,} \\ A_i(\boldsymbol{p})R_i(\boldsymbol{p}), & \text{for joint regulation.} \end{cases} \tag{7}$$

The active regulation function is

$$A_i(\boldsymbol{p}) = act_i^h/(act_i^h + K^h), \tag{8}$$

and the repressive regulation function is written as

$$R_i(\boldsymbol{p}) = K^h/(rep_i^h + K^h), \tag{9}$$

where

$$act_i = \sum_{j=1}^{N} \alpha_{ij} p_j, \tag{10}$$

$$rep_i = \sum_{j=1}^{N} \beta_{ij} p_j, \tag{11}$$

$i, j = 1, 2, \ldots, N$ and p_i is the expression level of gene i, $0 < p_i < 1$. The adjacency matrices $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ determine the network structure of the system, which are defined in such a way that $\alpha_{ij} = 1$ if gene j activates gene i, $\beta_{ij} = 1$ if gene j inhibits gene i, and $\alpha_{ij} \cdot \beta_{ij} = 0$ for no dual-regulation of gene i by gene j. $act_i(rep_i)$ represents the sum of active (repressive) transcriptional factors to node i. The regulated expression of genes is represented by Hill functions with cooperative exponent h and activation coefficient K, characteristic for many real genetic systems.

One may search for chaotic motions extensively in low-dimensional GRNs described by ODEs by using M samples from random network structures, parameter distributions and initial variable conditions. The asymptotic states are finally recorded and classified into three different types: steady states, periodic oscillation states, and chaotic states. The observation reveals that while most of the tests evolve to steady states, indeed some tests (still many) tend to periodic oscillations. The asymptotic chaotic states are extremely rare.

Although the above experiments indicate a rare presentation of chaotic motion, we can adopt an alternative strategy to exhibit more proportions of chaos. One can aim at some period-m (mp) states and study various bifurcation sequences to chaos by continually varying parameters. Therefore, all the previously mp states can be classified to chaotic solutions. In this way we again search for chaos by randomly choosing parameters and initial conditions but within the classes of periodic networks. One can find considerably richer chaotic behaviors than the previous attempt, and all these samples can be used for studying the mechanism of chaos in GRNs. It can be inferred that oscillations in coupled GRNs are rather robust against parameter sets.

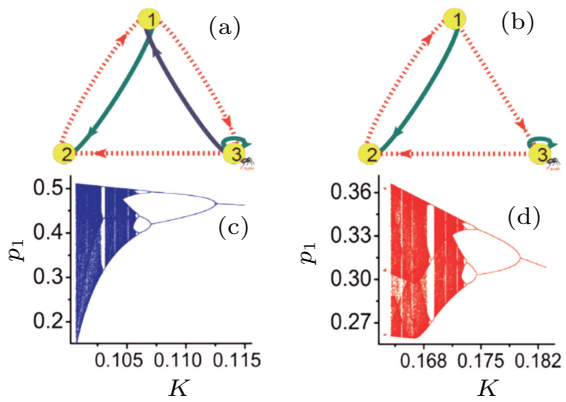


Fig. 5. (color online) A 3-node chaotic motif. (a), (b) Two 3-node chaotic GRNs, where solid/dashed lines denote active/repressive regulations. (c), (d) Bifurcation diagrams of (a) and (b), respectively by plotting peak values of p_1 as a function of K with $h = 3.00$. (Adapted from Ref. [43]).

One may analyze the chaotic behaviors of some chaotic samples to study the mechanism of chaos. A 3-node GRN is plotted in Fig. 5(a), which exhibits chaos by varying the parameters shown in Fig. 5(c). We are concerned with the minimal structure to produce chaos. In order to do this, different links/interactions are deleted in different tests and the structure of Fig. 5(b) is eventually found by deleting a single interaction $3 \to 1$ (solid arrow) from Fig. 5(a), in which chaos can still be maintained. Further deleting any cross coupling interaction between different nodes from Fig. 5(b) can definitely suppress chaos no matter how the system parameters, initial conditions, and self-regulations are varied. It is interesting that GRNs in Figs. 5(a) and 5(b) show similar types of bifurcation sequences to chaos as shown in Figs. 5(c) and 5(d). Therefore, the deleted interaction is not essential for chaotic behaviors, while the remaining cross interactions and the two feedback loops in Fig. 5(b) are all crucial for the chaotic motion. The topology presented in Fig. 5(b) can be considered as the 3-node chaotic motif of GRNs with a minimal structure persisting chaotic gene regulation.

A similar concept of chaotic motif can be defined for 4-node GRNs. In Fig. 6 we do exactly the same as Fig. 5 for three 4-node GRNs. From Fig. 6(a) we delete two interactions $1 \to 2$, $3 \to 2$ to get Fig. 6(b) and further delete $1 \to 3$ to get Fig. 6(c). It can be found from similar bifurcation sequences to chaos presented in Figs. 6(d)–6(f) that those deleted interactions are unessential for chaos. Further removal of any of the cross interactions left can entirely suppress chaos. Then the topology in Fig. 6(c) is a minimal 4-node reduced network as a 4-node chaotic motif.

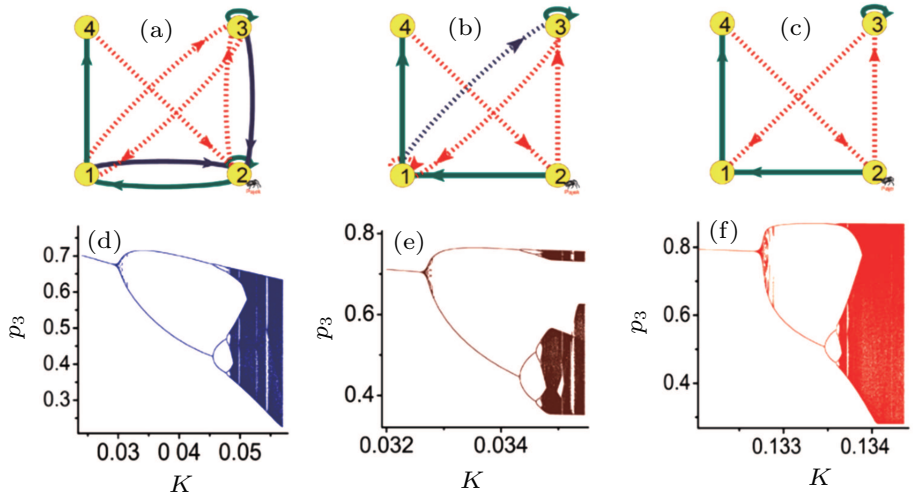


Fig. 6. (color online) A 4-node chaotic motif. The same as Fig. 5 with three 4-node GRNs considered. (a)–(c) Three 4-node chaotic GRNs, where solid/dashed lines denote active/repressive regulations. (d)–(f) Bifurcation diagrams of (a)–(c), respectively by plotting peak values of p_3 as a function of K with (d) $h = 2.00$, (e) $h = 2.35$, and (f) $h = 2.50$. (Adapted from Ref. [43]).

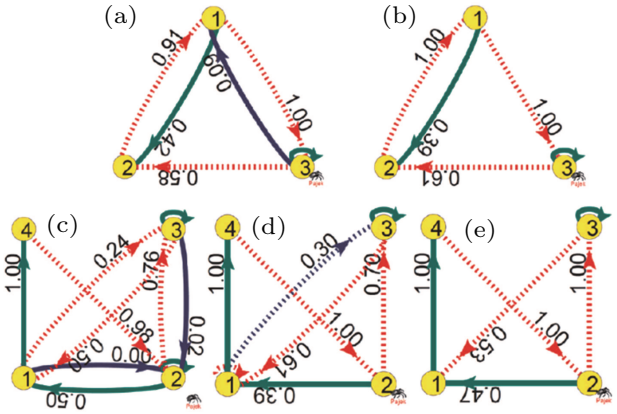


Fig. 7. (color online) Chaotic GRNs of Figs. 5 and 6 described by DTF distributions with the DTF associated to all cross interactions. It is shown that most of the interactions reducible for chaos have almost zero DTFs, which are in good accordance with the previous numerical results. (Adapted from Ref. [43]).

The above studies extensively explored chaotic motifs. Chaos is due to the complicated competitions among various oscillatory modes and the intricate drivings among different nodes, so it is crucial to explore the driving relationships in GRNs quantitatively. One may apply the concept of DPAD and the extended DPAD time fraction (DTF) analysis. DPAD is a dynamical method that can find the strongest cross driving of the target node at any time instant when a system is in an oscillatory state, and DTF ρ describes the driving contributions of all cross interactions to the target node during some given long period. $\rho \in [0, 1]$, i.e., when $\rho = 1$, there is only one cross interaction to the target node, while when $\rho \approx 0$ the driving effect of the given interaction to the target node is so weak that one can delete this link.

It is remarkable that all the above chaotic motifs discussed can be well explained by the DPAD relationships and the DTF analysis. In Figs. 7(a) and 7(b), one calculates the DTFs for all cross interactions which are depicted. It is interesting to see that the DTF of the interaction $3 \to 1$ in Fig. 7(a) has $\rho_{3\to1} \approx 0$ while the other cross interactions are nearly 1.0 or comparable

to each other. The comparable DTFs of the interactions $1 \to 2$ and $3 \to 2$ in Fig. 7(b) imply the competition between the two NFLs of $2 \to 1 \to 3 \to 2$ and $2 \to 1 \to 2$ in the chaotic motif, which is responsible for the chaos generation. This DTF analysis quantitatively explains why the interaction $3 \to 1$ is not crucial and why all the chaotic motif of Fig. 7(b) is irreducible.

In Fig. 7(c), the 4-node motif is presented with the DTF contributions computed and labeled. It can be found that $\rho_{1\to2} \approx 0$ and $\rho_{3\to2} \approx 0$, which contribute little to chaotic motion. The graph can be reduced to Fig. 7(d). The chaotic motif of Fig. 7(e) is obtained by further removing $1 \to 3$, which has a much smaller DTF than the other links.

6. Conclusion and perspectives

To summarize, in this paper we have extensively studied the sustained oscillations ubiquitously existing in biological systems, where the self-organization among units plays an important role. We are particularly interested in the case when each unit in the complex system does not exhibit oscillatory behavior. The emergence of sustained oscillations is first revealed by proposing the DPAD approach, through which the self-organization source of oscillations is found. The DPAD method is useful in understanding the driving relation among units. On the basis of the DPAD structures we can easily identify the oscillation sources and wave propagation paths in oscillatory complex networks. As two examples, the excitable networks and the gene regulatory networks are adopted as two practical applications.

By studying the sustained oscillations of excitable networks, one may find that sustained oscillation is initiated by the existence of Winfree loops. The oscillatory motion is produced in a loop and propagated along different paths, and this gives rise to the wave propagation patterns in a network. It is hard to clearly observe the propagating route, while one may vividly find it in terms of the DPAD method. Moreover, we also find that the minimum Winfree loop is the intrinsic mechanism in determining the emergence of collective oscillations on excitable ER random networks. Furthermore, the emergence of sustained oscillation is optimized at an optimal connection probability, and the OCP is found to form a one-to-one relationship with the MWL length.

For collective oscillations on gene regulatory networks, we focus on the basic core (motif) for exhibiting oscillatory dynamics. Different from the relative simple loop structure as basic source emerging sustained oscillations, we find more complicated behaviors. Furthermore, we extensively search for chaos in low-dimensional GRNs. We find various chaotic motifs as the minimal building blocks for chaotic motions. The mechanism of chaos originates from the competitions between different oscillatory modes, and the DPAD method and DPAD time fraction analysis can give a quantitative explanation of these competitions on chaotic GRNs.

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References

[1] Glass L and Mackey M C 1988 *From Clocks to Chaos: The Rhythms of Life* (Princeton: Princeton University Press)
[2] Goldbeter A 1996 *Biochemical Oscillations and Cellular Rhythms* (Cambridge: Cambridge University Press)
[3] Ott E 2002 *Chaos in Dynamical Systems* (Cambridge: Cambridge University Press)
[4] Glass L 2001 *Nature* **410** 277
[5] Elowitz M B and Leibler S 2000 *Nature* **403** 335
[6] Selverston A I and Moulins M 1985 *Ann. Rev. Physiol.* **47** 29
[7] Buzsaki G and Draguhn A 2004 *Nature* **304** 1926
[8] Vogels T P, Rajan K and Abbott L F 2005 *Ann. Rev. Neurosci.* **28** 357
[9] Zheng Z G 2004 *Collective Behaviors and Spatiotemporal Dynamics in Coupled Nonlinear Systems* (Beijing: Higher Education Press) (in Chinese)
[10] Watts D J and Strogatz S H 1998 *Nature* **393** 440
[11] Barabási A L and Albert R 1999 *Science* **286** 509
[12] Albert R and Barabási 2002 *Rev. Mod. Phys.* **74** 47
[13] Fang J Q, Wang X F, Zheng Z G, Li X, Di Z R and Bi Q 2007 *Prog. Phys.* **27** 361 (in Chinese)
[14] Boccaletti S, Latora V, Moreno Y, Chavez M and Hwang D U 2006 *Phys. Rep.* **424** 175
[15] Arenas A, Díaz-Guilera A, Kurths J, Moreno Y and Zhou C S 2008 *Phys. Rep.* **469** 93
[16] Newman M 2010 *Networks: An Introduction* (London: Oxford University Press)
[17] Hasty J, McMillen D, Isaacs F and Collins J J 2001 *Nat. Rev. Genet.* **2** 268
[18] Novak B and Tyson J J 2008 *Nat. Rev. Mol. Cell Biol.* **9** 981
[19] Goldbeter A 2002 *Nature* **420** 238
[20] Elowitz M B and Leibler S 2000 *Nature* **403** 335
[21] Ferrell Jr J E, Tsai T Y C and Yang Q 2011 *Cell* **144** 874
[22] Gardner T S, Cantor C R and Collins J J 2000 *Nature* **403** 339
[23] Ozbudak E M, Thattai M, Lim H N, Shraiman B I and van Oudenaarden A 2004 *Nature* **427** 737
[24] Tsai T Y C, Choi Y S, Ma W, Pomerening J R, Tang C and Ferrell J E 2008 *Science* **321** 126
[25] Decroly O and Goldbeter A 1982 *Proc. Natl. Acad. Sci. USA* **79** 6917
[26] Huang X H, Zheng Z G, Hu G, Wu S and Rasch M J 2015 *New J. Phys.* **17** 035006
[27] Zhang F F and Zheng Z G 2012 *J. Univ. Shanghai Sci. & Tech.* **34** 138 (in Chinese)
[28] Chen L and Aihara K 1995 *Neur. Net.* **8** 915
[29] Hutcheon B and Yarom Y 2000 *Trend. Neur.* **23** 216
[30] Herz A V M, Gollisch T, Machens C K and Jaeger D 2006 *Science* **314** 80
[31] Mandelblat-Cerf Y, Novick I and Vaadia E 2011 *PloS ONE* **6** e21626
[32] Li N, Daie K, Svoboda K and Druckmann S 2016 *Nature* **532** 459
[33] Burke J F, Zaghloul K A, Jacobs J, *et al.* 2013 *J. Neuro.* **33** 292
[34] Qian Y, Huang X D, Hu G and Liao X H 2010 *Phys. Rev. E* **81** 036101
[35] Qian Y, Liao X H, Huang X D, Mi Y Y, Zhang L S and Hu G 2010 *Phys. Rev. E* **82** 026107
[36] Liao X H, Xia Q Z, Qian Y, Zhang L S, Hu G and Mi Y Y 2011 *Phys. Rev. E* **83** 056204
[37] Qian Y 2014 *Phys. Rev. E* **90** 032807

[38] Liao X H, Qian Y, Mi Y Y, Xia Q Z, Huang X Q and Hu G 2011 *Front. Phys.* **6** 124
[39] Ye W M, Zhang Z Y, Lv B B, Di Z R and Hu G 2012 *Chin. Phys. B* **21** 060203
[40] Liao X H 2011 *Self-sustained Oscillations in Excitable Complex Networks* (Ph. D. Dissertation) (Beijing: Beijing Normal University) (in Chinese)
[41] Mi Y Y, Zhang L S, Huang X D, Qian Y, Hu G and Liao X H 2011 *Europhys. Lett.* **95** 58001
[42] Mi Y Y, Liao X H, Huang X H, Zhang L S, Gu W F, Hu G and Wu S 2013 *Proc. Natl. Acad. Sci. USA* **110** E4931
[43] Zhang Z Y, Ye W M, Qian Y, Zheng Z G, Huang X H and Hu G 2012 *PLoS ONE* **7** e39355
[44] Zhang Z Y, Li Z Y, Hu G and Zheng Z G 2014 *Europhys. Lett.* **105** 18003
[45] Zhang Z Y, Huang X H, Zheng Z G and Hu G 2014 *Sci. Sin.* **44** 1319 (in Chinese)
[46] Courtemanche M, Glass L and Keener J P 1993 *Phys. Rev. Lett.* **70** 2182
[47] Jahnke W and Winfree A T 1991 *Int. J. Bif. Chaos* **1** 445
[48] Qian Y, Cui X H and Zheng Z G 2017 *Sci. Rep.* **7** 5746
[49] Zhang L S, Gu W F, Hu G and Mi Y Y 2014 *Chin. Phys. B* **23** 108902
[50] Zhang L S, Liao X H, Mi Y Y, Qian Y and Hu G 2014 *Chin. Phys. B* **23** 78906