Coherent coupling of feedback loops: a design principle of cell signaling networks
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1 INTRODUCTION

Biological networks keep their regulatory functions robust against external and internal perturbations. For instance, the fate decision mechanism of a bacteriophage life cycle is robust against small perturbations at its promoter region (Little et al., 1999). Escherichia coli is capable of chemotaxis over a wide range of chemo-attractant concentrations (Alon et al., 1999; Yi et al., 2000). Drosophila melanogaster establishes segmental polarity against variations in its initial states or molecular interaction strengths (Ingolia, 2004; von Dassow et al., 2000). As such, the robustness of biological networks can be interpreted in various ways according to their cellular contexts and functions. In this article, we consider the robustness of a network defined as the capability of maintaining the equilibrium state against initial state perturbations. The status of a biological regulatory network varies by starting from an initial state and converging to some equilibrium state. In this case, a ‘robust’ network should be able to keep the same stable equilibrium state to a certain extent for a given perturbation to its initial state. In this respect, the robustness can be measured by a probability with which the equilibrium state is maintained against perturbations in the initial state.

Deciphering the design principle about the robustness of biological networks is one of the most challenging issues in systems biology. Some previous studies have proposed a feedback loop, a circular chain of interactions, as an important design principle for realizing the robustness of biological networks (Kitano, 2004a; Kwon and Cho, 2007a, 2008; Kwon et al., 2007). For example, the negative feedback loop between MDM2 and p53 enables to maintain an optimal level of p53 and to create appropriate dynamics of p53 expression level changes for a given DNA damage (Lev Bar-Or et al., 2000). The Xenopus cell cycle is also known to be robustly controlled against a certain level of perturbations with the help of several feedback loops engaged (Morohashi et al., 2002). However, most of the previous studies have usually focused on the role of individual feedback loop. On the other hand, we note here that feedback loops actually exist in the form of multiple coupled feedback loops in many biological systems such as those of budding yeast polarization (Ozbudak et al., 2005), eukaryotic chemotaxis (Weiner et al., 2002) and Ca 2+ spikes (Keizer et al., 1995). For large complex networks containing a number of coupled feedback loops, the role of feedback loops in realizing the robustness is not yet fully understood. Hence, we investigate in this article the dynamical characteristics induced by coupled feedback loops in large-scale cell signaling networks. To this end, we considered two large-scale signaling networks: the hippocampal CA1 neuronal signal transduction network (Ma’ayan et al., 2005) and the canonical cell signaling network composed of 49 canonical pathways obtained from http://stke.sciencemag.org/. We found that most of the feedback loops in these networks are coupled with a large number of other feedback loops. More interestingly, we observed that the coupled feedback loops are formed by coherent coupling in terms of the types (i.e. positive or negative) of feedback loops. To reveal the reason why such coherently coupled feedback loops prevail, we have undertaken extensive computational simulations using Boolean network models. Through the simulation studies, we found that such a topological characteristic contributes to retaining the robustness against initial state perturbations.
2 PRELIMINARIES

2.1 The topological characteristics of a network in terms of coupled feedback loops

Coupled feedback loops are ubiquitously found in various signaling networks and they are related to some distinctive dynamics. So, the coupled feedback loops can be a good topological measure of classifying networks as illustrated in Figure 1. The three networks in Figure 1 have the same numbers of nodes and links (10 nodes and 14 links), but they are completely different from each other if we consider the feedback loops involved. The network in Figure 1a has no feedback loop. On the other hand, the networks in Figure 1b and 1c include many feedback loops. However, these two networks also differ in a way that all the feedback loops in the network of Figure 1b are not interlinked while those in the network of Figure 1c are complicatedly coupled with each other. As illustrated in this example, the coupled feedback loops embedded in a given signaling network can be used as an important measure of topological characteristics.

2.2 Coherent versus incoherent coupling of feedback loops

Each link of a network can be assigned with either a positive sign for activating regulation or a negative sign for inhibitory regulation. Then, the sign (or type) of a feedback loop can easily be determined by the parity of the number of positive links and that of negative links involved. If the parity number is even or zero, the feedback loop is positive; otherwise, it is negative. Based on the sign of a feedback loop, the notion of coherent coupling of feedback loops is defined as follows: when two feedback loops with the same sign are interlinked (i.e. by sharing a common link), it is called a coherent coupling; otherwise, it is called an incoherent coupling. The type of coupling can affect the dynamics of a network as illustrated by an example in Figure 2. In this example, a network with three nodes and four links is considered where two feedback loops are coupled. Positive and negative feedback loops constitute a coherent coupling in Figure 2a and b, respectively. On the other hand, an incoherent coupling is shown in Figure 2c. The second column of each figure shows a state transition diagram based on a Boolean network model with a conjunctive update function. From the state transition diagram, we can measure the robustness of a network. For instance, in Figure 2a, when the initial state is ‘110’ (this represents the initial state values of x, y and z in sequence), the network converges to ‘000’ state. On the other hand, if the initial state ‘110’ changes to ‘111’ by some perturbation at z, the network converges to ‘111’ which is different from the original attractor ‘000’. Each list in the third column shows all pairs of states converging to different attractors by perturbation given at only one of the nodes. The number of pairs of states converging to different attractors in the network with an incoherent coupling (Fig. 2c) is relatively larger than that in the network with a coherent coupling (Fig. 2a and b). As shown in this example, the coherent or incoherent coupling is an important factor for determining the dynamics of a network. In this article, we investigate the effect of coherent couplings on the robustness of large-scale networks.

3 MATERIALS AND METHODS

3.1 Large-scale real cell signaling networks

In this article, we have investigated two large-scale real cell signaling networks. One is the signal transduction network of the hippocampal CA1 neuron of mice composed of 545 proteins and their 1258 interactions with 952 positive and 306 negative signs (Ma’ayan et al., 2005). The other one is the canonical cell signaling network. To construct the network, we first gathered all the 49 canonical pathways (not specific to any organism or cell type) from the database of Science, STKE http://stke.sciencemag.org/. We extracted the information of each node and link from the corresponding pathway data and integrated those into one large-scale network. All the neutral interactions in the database are excluded in constructing this network. This network consists of 735 proteins and 1328 interactions with 933 positive and 395 negative signs.

3.2 Boolean network models

A Boolean network model is composed of a set of Boolean variables and the regulatory relationships between the variables. This model has been widely
We have employed the Boolean network model here and described the attractors. These attractors can describe various behaviors of biological systems such as multi-stability, homeostasis and oscillations. A network is considered robust if all the links in a non-intersection sub-link is independently assigned a value of either 1 (‘on’) or 0 (‘off’). A directed link \((v_i, v_j)\) denotes either a positive (‘activating’) or negative (‘inhibiting’) relationship from \(v_i\) to \(v_j\). The value of each variable \(v_i\) at time \(t+1\) is determined by the values of other \(k_i\) variables \(v_1, v_2, \ldots, v_{k_i}\), having a link to \(v_i\) at time \(t\) according to the Boolean function \(f_i: [0, 1]^k \rightarrow [0, 1]\). Hence, the update rule is represented by \(v_i(t+1) = f_i(v_1(t), v_2(t), \ldots, v_{k_i}(t))\) where either a logical conjunction or a disjunction can be used to integrate the signed relationships in \(f_i\). For instance, if a Boolean variable \(v\) has a positive relationship from \(v_1\) and a negative relationship from \(v_2\), the conjunction and disjunction update rules result in \(v(t+1) = v_1(t) \land \neg v_2(t)\) and \(v(t+1) = v_1(t) \lor v_2(t)\), respectively.

Given a network with \(N\) Boolean variables, a state denotes a vector composed of \(N\) Boolean variables; there are \(2^N\) states in total. Each state can transit to another state according to the Boolean update function. We have constructed a state transition network that describes the transition of all the states. A state trajectory in the state transition network starts from an initial state and converges to either a fixed-point or a limit-cycle attractor. These attractors can describe various behaviors of biological systems such as multi-stability, homeostasis and oscillations. A network is considered robust if the trajectories starting from different initial states converge to a same attractor. More specifically, we define the robustness of a network with respect to initial state mutations as follows: let us consider \(S\), a set of pairs of states \((s, s')\) whose Hamming distance is one (the Hamming distance between two states is defined as the number of Boolean variables of different values). In this case, the Boolean variable having a different value indicates the state whose initial value is mutated. There are \(2^N - 1\) such pairs of states in total. Then, the robustness of a network is defined as the ratio of the number of pairs of states whose trajectories converge to a same attractor to the total number of pairs of states in \(S\). The initial state mutation represents an abnormal (or malfunctioning) status of a protein or gene caused by a mutation.

### 3.3 Definition of coupled feedback loops

Given a network composed of a set of nodes and a set of links between the nodes, a feedback loop means a closed simple cycle where nodes are not revisited except the starting node and the ending node. For instance, \(v_0 \rightarrow v_1 \rightarrow v_2 \rightarrow \cdots \rightarrow v_L\) is a feedback loop of length \(L \geq 1\) if there are links from \(v_{l-1}\) to \(v_l\) \((l = 1, 2, \ldots, L)\) with \(v_0 = v_N\) and \(v_L \neq v_0\) for \(j, k \in \{0, 1, \ldots, L\} - \{i\}\). To define the coupling of feedback loops, let us first define a sub-link of a feedback loop. Given a feedback loop \(P = v_0 \rightarrow v_1 \rightarrow v_2 \rightarrow \cdots \rightarrow v_L\), a sub-link \(v_0 \rightarrow u_0 \rightarrow u_1 \rightarrow \cdots \rightarrow u_M\) is a sequence of links of length \(M\) with respect to \(P\) if there is \(i \in \{0, \ldots, L\}\) such that \(v_{i+j} = u_j\) for \(j = 0, \ldots, M\). Like the sign of a feedback loop, the sign of a sub-link is determined by the parity between the number of positive links and that of negative links involved. If there is a non-empty common sub-link between two feedback loops, we say that there is a coupling between the feedback loops. In addition, we define the intersection length as the number of common links.

### 3.4 Average expectation ratio of coherent couplings

In Figure 3, we have compared the ratio of coherent couplings in real cell signaling networks with the average expectation ratio. The average expectation ratio means the expected ratio of coherent couplings over the random networks that have the same coupled structure with a randomly assigned sign of each link. A detailed computational procedure of the average expectation ratio is as follows: let us assume that a real signaling network \(G = (V, A)\) with \(A_+\) positive and \(A_-\) negative links has \(K\) pairs of coupled feedback loops, \((P_1, Q_1), (P_2, Q_2), \ldots, (P_K, Q_K)\) where \(M_i(N_i)\) denotes the difference of the intersection length from the length of \(P_i\) \((Q_i)\), respectively. Then, if all the links in a non-intersection sub-link is independently assigned with a positive (negative) sign with the probability of \(|V_+|/|V|\) \((|V_-|/|V|)\), respectively, the probability of having a positive sub-link of length \(N\) is

\[
p(N) = \sum_{j=1}^{N/2} \binom{N}{j} (|A_+|/|A|)^j (1-|A_+|/|A|)^{N-j}.
\]

Thus, the probability of coherent coupling is as follows:

\[
C(P_i, Q_i) = p(M_i) \times p(N_i) + (1-p(M_i)) \times (1-p(N_i)).
\]

For an independent random assignment of a sign to each link, the average expectation ratio of the coherent coupling is defined as

\[
\frac{1}{K} \sum_{i=1}^{K} C(P_i, Q_i).
\]
We have examined the distribution of feedback loops in two large-scale signaling networks—the hippocampal CA1 neuronal signal transduction network and the canonical cell signaling network (see Materials and Methods for details). In particular, we have investigated the proportion of couplings among the feedback loops (Table 1). For all the feedback loops of length smaller than 10, we found that there are many coherent feed-forward subnetworks that include the same node. In addition, we have observed that feedback loops are coupled with more than 1,000 other feedback loops. There are very few feedback loops that are not interlinked with other feedback loops. This implies that the coupled feedback loops are ubiquitously present and thereby form important network motifs in cell signaling networks (Kim et al., 2008).

We have further examined the coherent and incoherent couplings of those coupled feedback loops. Figure 3 shows the ratio of the number of coherent couplings over the total number of couplings along with the intersection length which is defined as the number of common links between a pair of coupled feedback loops (see Section 3 for details). To determine whether the ratio is relatively high or not, we have compared it with the average expected ratio of those coupled feedback loops. Figure 4, each node represents a feedback loop of length smaller than 10 and the link connecting two nodes means that there is a coupling between the two corresponding feedback loops. Although there is little difference between the numbers of positive and negative feedback loops, we find that coherent couplings (red triangle points) are more frequently observed than incoherent couplings (blue circle points). In addition, we examined an example sub-network whose feedback loops are most coherently coupled with each other (Fig. 5). In Figure 5, we find that there are many coherent feed-forward subnetworks that actually induce the coherent couplings. For instance, there are four paths from PTPα to PLCγ whose effects are all positive. These substructures induce the coherent couplings among feedback loops.

### 4 RESULTS

#### 4.1 Coupling of feedback loops in large-scale signaling networks

We have examined the distribution of feedback loops in two large-scale signaling networks—the hippocampal CA1 neuronal signal transduction network and the canonical cell signaling network (Kim et al., 2003). For instance, in the regulatory network of inducing the phenotype variations in bacteria, some epigenetic traits are represented by multiple fixed-point attractors (Smits et al., 2006). This multistability is a common feature of adaptive processes in bacteria. In addition, mitogen-activated protein kinase cascades in animal cells (Bhalla et al., 2002; Ferrell and Machleder, 1998; Pomerening et al., 2003). For instance, in the regulatory network of inducing the phenotype variations in bacteria, some epigenetic traits are represented by multiple fixed-point attractors (Smits et al., 2006). This multistability is a common feature of adaptive processes in bacteria.

| The number of couplings | Hippocampal CA1 network | Canonical cell signaling network |
|-------------------------|-------------------------|---------------------------------|
| \( C = 0 \)             | 1                       | 6                               |
| \( 1 \leq C \leq 100 \) | 6                       | 16                              |
| \( 101 \leq C \leq 1000 \) | 23                      | 59                              |
| \( 1001 \leq C \leq 2500 \) | 268                     | 496                             |
| \( 2501 \leq C \leq 5000 \) | 1591                    | 802                             |
| \( 5001 \leq C \leq 10000 \) | 5849                    | 15240                           |
| **Total**               | **7738**                | **16619**                       |

As observed from the real signaling networks, the ratio of coherent couplings is relatively large. So, we were intrigued by the reason behind this feature and investigated the advantages of this particular topological characteristic with respect to network dynamics. Since we learned from previous studies that a simple network motif composed of a single or two coupled feedback loops is related to the robust behavior of biological networks (Kitano, 2004a, b), let us investigate the effect of coherent couplings on such robustness by using a Boolean network model (see Section 3 for details). Here, the robustness of a Boolean network is defined as the probability with which initial state mutations do not cause the network to converge to a new attractor. The ‘attractor’ has an important meaning in biological network dynamics. In a Boolean network model, a state trajectory starts from an initial state and eventually converges to either a fixed-point or a limit-cycle attractor. So, these attractors represent the various dynamical behaviors of biological networks such as multistability, homeostasis and oscillations (Bhalla et al., 2002; Ferrell and Machleder, 1998; Pomerening et al., 2003). For instance, in the regulatory network of inducing the phenotype variations in bacteria, some epigenetic traits are represented by multiple fixed-point attractors (Smits et al., 2006). This multistability is a common feature of adaptive processes in bacteria. In addition, mitogen-activated protein kinase cascades in animal cells (Bhalla et al., 2002; Ferrell and Machleder, 1998; Pomerening et al., 2003). For instance, in the regulatory network of inducing the phenotype variations in bacteria, some epigenetic traits are represented by multiple fixed-point attractors (Smits et al., 2006). This multistability is a common feature of adaptive processes in bacteria.
We note that this result is also consistent with the observation from Machleder, 1998) and the cell-cycle regulatory circuits in Saccharomyces cerevisiae and Xenopus (Pomerening et al., 2003; Sha et al., 2003) are known to possess such multistable attractors. On the other hand, the transcriptional regulatory network of mRNAs for Notch signaling molecules shows an oscillation with a 2-h cycle by Hes1 transcription (Hirata et al., 2002) and this corresponds to a limit-cycle attractor. Such a Hes1 oscillation is found in various cell types. As can be seen from these examples, attractors represent the essential dynamics of biological networks. We can therefore interpret the change of attractors due to some mutations as a loss of robustness. This concept has been widely employed in a number of previous studies (Ciliberti et al., 2007; Huang et al., 2005; Kitano, 2004a; Li et al., 2004).

We have compared the ratio of coherent couplings in random Boolean networks and that in robust Boolean networks (Fig. 6). Since the measure of robustness defined in this article depends on the number of attractors, we have compared those networks having the same number of attractors. In all the cases, it turns out that the ratio of coherent couplings in robust Boolean networks is higher than that in random Boolean networks. Moreover, the same result was obtained irrespective of the network size, the number of feedback loops, and the ratio of positive links (see Fig. S1 of Supplementary Material).

We note that this result is also consistent with the observation from real signaling networks. In summary, these suggest that the relatively high ratio of coherently coupled feedback loops strengthens the robustness of signaling networks against state perturbations. Such a relationship between robustness and coherent couplings can be explained in terms of the basin size of attractors in a state transition space. Given an attractor, its basin size indicates the proportion of initial states which converge to the attractor. So the basin size is related to the robustness. In other words, if a network induces a large basin, it can be more robust than those inducing relatively small basins. In this respect, we have further investigated the robustness of Boolean networks (Table 2). In particular, we compared the maximal basin size of two network groups: one group of networks containing no incoherent coupling and the other group of networks containing at least one incoherent coupling. We found that the networks without having any incoherent coupling induce a larger basin than those containing incoherent couplings. Hence, we can infer that incoherent couplings prevent the occurrence of attractors having a large basin and thereby the networks containing incoherent couplings are likely to be less robust.

### 4.3 The robustness achieved by coherently coupled feedback loops is evolutionarily stable

In the previous sections, we have revealed that the coherently coupled feedback loops are ubiquitously found network motifs in signaling networks and showed through Boolean network modeling and simulations that such topological characteristics endow the signaling networks with robustness. We have further investigated whether the robustness is an evolutionarily stable property or not. There can be some changes in a signaling network such as the loss of an existing interaction link or the addition of a new interaction link. Those topological changes can occur in a relatively short evolutionary time interval, particularly for higher eukaryotes with large regulatory regions (Ciliberti et al., 2007; Stone and Wray, 2001). In this regard, we have considered a ‘neighbor network’ obtained from a given original network by deleting or adding a link, and then investigated the robustness of such neighbor networks (Fig. 7). It turns out that the neighbor networks of robust networks are still relatively robust compared to random networks. This suggests that the robustness is not easily broken by evolutionary changes such as addition or deletion of links. We infer that coherently coupled feedback loops not only induce the robustness but also make such a property be sustained against evolutionary changes.
Table 2. The maximal basin size of Boolean networks depending on the incoherent feedback loops involved

| Network group                                      | Number of attractors | #   | Mean | SD   | P-value          |
|---------------------------------------------------|----------------------|-----|------|------|------------------|
| Networks containing no incoherent coupling         | 3                    | 1000| 0.732| 0.193| < 1.0 × 10^{-15}|
| Networks containing incoherent couplings           | 3                    | 1000| 0.667| 0.164|                  |
| Networks containing no incoherent coupling         | 4                    | 1000| 0.675| 0.225| < 1.0 × 10^{-15}|
| Networks containing incoherent couplings           | 4                    | 1000| 0.561| 0.176|                  |
| Networks containing no incoherent coupling         | 5                    | 1000| 0.615| 0.213| < 1.0 × 10^{-15}|
| Networks containing incoherent couplings           | 5                    | 1000| 0.520| 0.163|                  |

Fig. 6. Comparison of the ratio of coherent couplings between robust and random Boolean networks. (a) Networks having three attractors. (b) Networks having four attractors. (c) Networks having five attractors. For the random networks, 1000 Boolean networks with $|V| = 12$ and $|A| = 17$ are randomly generated. For the robust networks, 1000 Boolean networks with $|V| = 12$ and $|A| = 17$ are generated such that the robustness is kept for the top 5% of the random Boolean networks. The ratio of coherent couplings is plotted against the intersection length.

Fig. 7. Distributions of the average robustness of neighbor networks. The upper graph shows the results of 1000 random Boolean networks with $|V| = 12$ and $|A| = 17$, and the lower graph shows the results of 1000 robust Boolean networks with $|V| = 12$ and $|A| = 17$. For simplicity, networks having only four attractors and seven feedback loops were considered in this case, but the same held for any other cases.

has been known that a feedback loop can realize the robustness in a relatively simple network, there has been little attention to the design principle regarding the robustness of a large-scale signaling network where a number of feedback loops are complicatedly coupled with each other. Through investigations into the large-scale signaling networks, we found that the number of coherent couplings in signaling networks is much larger than that of incoherent couplings. To discover the underlying reason of such topological characteristic, we have carried out extensive computer simulations based on Boolean network models. The simulation results have shown that the networks containing coherently coupled feedback loops are more robust than other networks containing incoherently coupled feedback loops. In addition, we found that coherent couplings make the networks induce a large basin of an attractor. From these results, we infer that the coherent coupling of feedback loops realizes the robustness against state perturbations by inducing a large size basin. Moreover, we found that the robustness obtained by such coherent couplings is not easily broken by deletion or addition of interactions. This implies that the coherent coupling of feedback loops might be an evolutionary design principle of signaling networks devised to achieve the robustness.

5 CONCLUSION

In this article, we have investigated the topological characteristics of signaling networks in terms of coupled feedback loops. Although it has been known that a feedback loop can realize the robustness in a relatively simple network, there has been little attention to the design principle regarding the robustness of a large-scale signaling network where a number of feedback loops are complicatedly coupled with each other. Through investigations into the large-scale signaling networks, we found that the number of coherent couplings in signaling networks is much larger than that of incoherent couplings. To discover the underlying reason of such topological characteristic, we have carried out extensive computer simulations based on Boolean network models. The simulation results have shown that the networks containing coherently coupled feedback loops are more robust than other networks containing incoherently coupled feedback loops. In addition, we found that coherent couplings make the networks induce a large basin of an attractor. From these results, we infer that the coherent coupling of feedback loops realizes the robustness against state perturbations by inducing a large size basin. Moreover, we found that the robustness obtained by such coherent couplings is not easily broken by deletion or addition of interactions. This implies that the coherent coupling of feedback loops might be an evolutionary design principle of signaling networks devised to achieve the robustness.

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