Entangled gene regulatory networks with cooperative expression endow robust adaptive responses to unforeseen environmental changes

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Living organisms must respond to environmental changes. Generally, accurate and rapid responses are provided by simple, unidirectional networks that connect inputs with outputs. Besides accuracy and speed, however, biological responses should also be robust to environmental or intracellular noise and mutations. Furthermore, cells must also respond to unforeseen environmental changes that have not previously been experienced, to avoid extinction prior to the evolutionary rewiring of their networks, which takes numerous generations. To address the question how cells can make robust adaptation even to unforeseen challenges, we have investigated gene regulatory networks that mutually activate or inhibit, and have demonstrated that complex entangled networks can make appropriate input-output relationships that satisfy such adaptive responses. Such entangled networks function when the expression of each gene shows sloppy and unreliable responses with low Hill coefficient reactions. To compensate for such sloppiness, several detours in the regulatory network exist. By taking advantage of the averaging over such detours, the network shows a higher robustness to environmental and intracellular noise as well as to mutations in the network, when compared to simple unidirectional circuits. Furthermore, it is demonstrated that the appropriate response to unforeseen environmental changes, allowing for functional outputs, is achieved as many genes exhibit similar dynamic expression responses, irrespective of inputs including unforeseen inputs. The similarity of the responses is statistically confirmed by applying dynamic time warping and dynamic mode decomposition methods. As complex entangled networks are commonly observed in the data in gene regulatory networks whereas global gene expression responses are measured in transcriptome analysis in microbial experiments, the present results give an answer how cells make adaptive responses and also provide a novel design principle for cellular networks.

Author summary

Recent experimental advances have demonstrated that cells often have appropriate, robust responses to environmental changes, including those that have not previously been experienced. It is known that accurate and rapid responses can be achieved by simple unidirectional networks that connect straightforwardly input and outputs. However, such responses were not robust to perturbations. Here we have made numerical evolution of gene regulatory networks with mutual activation and inhibitions, and uncovered that complex entangled networks including many feedforward and feedback paths can make robust input-output responses, when each gene expression is not accurate. Remarkably, they make appropriate responses even to unforeseen environmental changes, as are supported by global, correlated responses across genes that are similar for all input signals. The results explain why cells adopt complex gene regulatory networks and exhibit global expression changes, even though they may not be advantageous in terms of their energy cost or response speed. The present results are consistent with the recent experiments on microbial gene expression changes and network analyses. This investigation provides insights into how cells survive fluctuating and unforeseen unpredictable environmental changes, and gives a universal conceptual framework to go beyond the standard picture based on a combination of network motifs.

Introduction

Living organisms, generally respond appropriately to environmental changes by adapting their internal states to the new conditions. In cells, chemical compositions, in particular gene expression levels, are adjusted to adapt to novel environments. Information on the environmental change is transmitted via a signal transduction network to regulate gene expression patterns.

For a cell to make an appropriate response rapidly and accurately, it will be relevant to transfer the input signal to the output expression pattern unidirectionally through a sequence of chemical responses. Indeed, such unidirectional circuits are ubiquitously observed as direct connections or feed-forward networks from the input in the signal transduction networks. How these unidirectional networks achieve appropriate input-output relationships has previously been extensively investigated [1–3].

Real cellular networks, however, are often much more complex. They include many components and are entangled. Sometimes such unidirectional circuits may be extracted as a part of the complex network, but it is not clear whether they have the same function as has been determined in isolation [4, 5]. They generally do not function independently, as the networks are entangled. Why cells have adopted such complex networks, however, is not completely understood.

There are further requirements for cellular responses beyond being quick and accurate. For instance, they

should be robust to perturbations [6–10], as the environmental conditions surrounding living organisms normally fluctuate [11–13]. Moreover, each process controlling the cellular concentrations of chemicals is generally stochastic, as the number of molecules involved is sometimes not very large [14–16]. In addition to the robustness to fluctuations and noise, there is another postulate, an ‘adaptive response to an unforeseen challenge (AUC)’, as put forward by Braun [17]: Cells must manage to respond to and survive under unforeseen environmental changes that are not expected by the prescribed input-output responses. In particular, even when cells experience a novel environment for which appropriate output responses are not yet prepared, they have to survive to some degree to avoid extinction, as it takes many generations for the appropriate evolutionary changes to occur. Responses to unforeseen challenges are thus required without rewiring the gene regulatory network (GRN) via genetic evolution [18–20].

Direct unidirectional networks optimized for given input-output relationships are not expected to be robust. Further, it will be difficult to achieve AUCs with them. If this is the case, and if a complex network can have advantages over unidirectional networks, with regard to robustness and AUCs, this may explain why biological networks are so complex and entangled. However, it is not yet evident if a complex network with many degrees of freedom acquires such robustness and AUCs, as they do not always have functional robustness. It is thus necessary to understand which types of complex networks can have a higher capacity for robustness and AUCs than simple unidirectional networks and to uncover design principles for such networks.

Previously we have evolved GRNs to achieve appropriate input-output relationships. In addition to simple direct or feed-forward networks, we have uncovered another type of entangled network consisting of many components, that can generate an appropriate input-output relationship as a cooperative response of many genes [21]. In particular, this cooperative response emerges when each gene expression is sloppy, that is, with a low Hill coefficient as observed in a real GRN [22–25]. Here, we explore whether this class of networks achieves higher capacity in noise robustness and AUCs than traditional direct or feed-forward networks.

Results

We adopted a simplified GRN model [8, 21, 26–30] and investigated the networks evolved so that, for each given input, one prescribed output gene (target) is expressed, by defining the fitness of the expression patterns of the given output genes (Eq (2)). Each input stimulated one of the input genes and was transmitted to the output genes through the middle-layer genes (ML-genes). As described in [21], three types of networks evolved depending on the sensitivity (corresponding to the Hill coefficient)

of the gene expression dynamics: direct connections (Direct type) and feed-forward networks having side paths (FF-network type) that showed rapid and accurate responses evolved when each gene’s response was sensitive (large β), whereas complex entangled networks with cooperative responses of many genes (Cooperative type) evolved when each response was sloppy (small β). The three types showed different characteristics in their network structures, and these were most discernible when their core structures were compared. The core structure was obtained by removing paths successively, one-by-one, as long as the corresponding output genes response for each input was preserved (e.g., maintaining fitness > 0.8) (Fig 1). The Direct and FF-network types adopted unidirectional circuits from the input to the output genes. The Cooperative network type, however, involved many genes and its network was entangled. In this case, with the input, a few genes were locally excited, whereas global inhibition by many other genes followed. The characteristic structure of local excitation and global inhibition (LEGI [31]) was common in this Cooperative type. Here, it is of note that the evolutionary simulations were carried out to preserve the total path number of the networks, and the redundant paths out of the core structure remained for all types.

FIG. 1: Typical examples of the three types of core network structures. The core structures were obtained by removing the dispensable paths from the evolved fittest structure for each type. Gray and black circles show the input and output genes, respectively, and the numbers indicate their correspondences. Red bold arrows represent excitatory regulations, and blue dotted arrows denote inhibitory regulations. (a) Direct type with $y_T = 0.5$ and $\beta = 10^{1.75}$, (b) FF-network type with $y_T = 1.0$ and $\beta = 10^{1.5}$, and (c) Cooperative type with $y_T = 0.5$, and $\beta = \sqrt{10}$.

Noise robustness

Robustness to noise was investigated first. A white Gaussian noise term with amplitude ξ was added to the time evolution of each expression level (Eq (1)) for the ML-genes (Fig 2 (a)) or stimulated input genes (Fig 2 (b)), and the corresponding Langevin equations were

FIG. 2: **Noise robustness.** (a, b) Dependence of fitness (ordinate) on noise strength ξ (abscissa). The average fitness values for each noise level are plotted using 5 different networks that evolved without noise for each parameter set. Noise was added to all ML-genes (a) or to an input gene stimulated by an external input (b). (c) Dependence of the fitness (ordinate) on mutation, i.e., the expected number of removed paths from the core structures (abscissa). Results of the Direct type (D: purple + and x), the FF-network type (F: green x and $\square$), and the Cooperative type (C: blue * and o) are shown.

simulated. When the noise term was added to the ML-genes, the Direct type was the most fragile and the fitness was drastically reduced by the noise (Fig 2 (a)). The FF-network and the Cooperative types showed noise robustness, as their signal transduction routes were multitracked and noise could be canceled out along the pathways. Furthermore, the Cooperative type was more robust to smaller amounts of noise, with $\xi < 0.1$. This was because the entangled network enabled the averaging out of noise, not only on each gene at the endpoint of multitrack paths but also on every gene in the network. It is of note that the noise canceling effect was independent of how many genes affected each output gene. An output gene had interaction paths with 6.1 genes in the Direct type, 13.0 genes in the FF-network type, and 11.0 genes in the Cooperative type, on average. In addition, the total number of paths in a network was set to be the same for all types. Hence, there was no correlation between the number of paths of interacting genes and noise robustness.

We also studied robustness against noise to an input gene (Fig 2 (b)). Again, the Direct type was largely influenced by the input noise as the noise effect was transmitted directly via the straight paths. The FF-network type was less robust than the Direct type. This is because its feed-forward network amplifies the input noise as well as the external signal. The Cooperative type had higher robustness to the input noise. Again, the noise could be reduced via the detour paths in the pathways.

Here, the path distance between input and output genes (i.e., the number of intermediate ML-genes between them) was irrelevant to the noise robustness. The shortest distance was similar for the three types, and the input and corresponding output genes were connected by one or two ML-genes. The noise was reduced not through a long-connected pathway but through multitrack, parallel paths.

Mutational robustness

Robustness against the mutational changes in the GRN were then considered. Here, some paths, especially those that constituted a core structure, were inevitable for responses, but some other paths were not necessary to achieve high levels of fitness. The robustness against the removal of the latter was trivial. Thus, mutational robustness should be defined as a fitness change when indispensable paths were removed. Consequently, we studied mutational robustness against the number of removed paths that constituted a core structure (Fig 2 (c)).

The Direct type had no mutational robustness, as the response was destroyed when any path that constituted a core structure was removed. The other two network types were more robust against mutational changes as their core structures contained detour paths. Even when a route connecting an input-output pair was disconnected, the external signal could still be transmitted by way of the detour paths. However, the FF-network and the Cooperative types were different in that the core structure of the former was separated according to each input-output pair, but not in the latter. Hence, their mechanisms of mutational robustness differed. In the FF-network type, when a path forming a core structure was removed, the response of a corresponding output gene dropped off, but the responses of the other output genes were hardly influenced. In contrast, in the Cooperative type with the LEGI structure, the responses of all output genes were weakened when any path in a core structure were removed. However, the decline was smaller as the Cooperative type included a larger number of alternative detour paths.

In the evolutionary process so far, we have fixed each parameter (response sensitivity corresponding to the Hill coefficient β and a constant threshold for expression y_T) of each gene to a common value and optimized the network structure for the given parameter values. We also studied the robustness to the changes in these parameter values (Fig 3). The Direct and FF-network types maintained a response only within a parameter range for each

FIG. 3: **Mutational robustness.** (a) Phase diagram of the three types with regard to the β (abscissa) and y_T (ordinate) as estimated from the numerical simulations (the phase boundaries were obtained analytically [21]); Direct type (D: area with horizontal lines), FF-network type (F: area with vertical lines), and Cooperative type (C: blank area). (b–d) Changes in the fitness values against the shift in parameters. By using the network evolved from the parameters pointed by $\times$, fitness was computed for the parameter values (β, y_T) in the figure. (b) Direct type with $y_T = 0.5$ and $\beta = 10^{1.75}$, (c) FF-network type with $y_T = 1.0$ and $\beta = 10^{1.5}$, (d) Cooperative type with $y_T = 0.5$, and $\beta = \sqrt{10}$. The white curves indicate the phase boundaries.

type, and the response often disappeared outside of their parameter range. On the other hand, the Cooperative type could maintain the response beyond the parameter range corresponding to its phase. This is because the LEGI structure includes the core structures for both the Direct and FF-network types within.

Tolerance to erroneous input

Thus far, the external input S_{ext} was maintained at a steady value for $t \geq 0$ in our model. Responses to a pulse input signal that was applied only for a brief time ($0 \leq t \leq \tau$) were then investigated. These signals represent an erroneous input due to environmental fluctuations. It is of note that the time scale for the response dynamics of each gene were set to be scaled to 1.

The FF-network type was more tolerant than the Direct type with simpler motifs. Indeed, the feed-forward motif has been reported to be tolerant to pulse-type inputs [2]. Interestingly, the Cooperative type was more tolerant to the pulse input than the FF-network type. In the Cooperative type, many ML-genes needed to change their expression levels in a sequential order before an output gene responded. An input gene stopped responding after a pulse interval, and the following ML-genes stopped responding before they stimulated the output gene. Thus, output genes avoided erroneous responses against a pulse input.

FIG. 4: **Incidence of erroneous responses to a pulse input.** The occurrence frequency of a response larger than 0.9 upon a pulse input by a corresponding target gene (ordinate) is plotted against the pulse duration time τ (abscissa). Results of the Direct type (purple + and $\times$), the FF-network type (green $\times$ and $\square$), and the Cooperative type (blue * and $\circ$), are shown using the same networks as in Fig 2.

Adaptive responses to unforeseen challenges

All living organisms must survive unforeseen environmental changes to avoid extinction. However, evolution is not an easy solution for survival, as it requires the expense of time. If there are no individuals adapted to a new environment prior to beneficial evolutionary changes, they will go extinct. It is essential for cells

FIG. 5: **Responses to an unforeseen input.** The response to an unforeseen input was calculated using the fittest networks evolved under each β (abscissa) and y_T (ordinate) values. The probability that the maximum response was larger than 0.01 (left) and the normalized probability compared with a case of random networks with each parameter value (right) are shown. The white curves show phase boundaries between the three types: Direct type (D), FF-network type (F), and Cooperative type (C).

to respond to a new environment to some degree without evolutions rewiring of the GRN, and this is referred to as an ‘adaptive response to an unforeseen challenge (AUC)’ [17].

We studied the possibility of the AUCs using the following procedure: we prepared a GRN model by doubling the number of input and output genes but maintained the number of ML-genes. Using only half of the input-output pairs, networks were evolved to optimize their fitness, that is, to give postulated output responses to the inputs. Here, half of the input and output genes were not used for the fitness, and hence they were not related to the original evolution. After the original evolution, we studied the responses of unused output genes when one of the unused input genes was activated. The response for this non-evolutionary input without further changes in the GRN is shown in Fig 5. Large responses to unforeseen inputs were observed in the Cooperative type networks, whereas there were almost no responses with the FF-network type. The Direct type had modest responses; however, this was because its core structure was so simple that even the addition of a random network could generate a response. In addition, such responses were rarer with larger network sizes. Hence, almost no response was expected in a network with many genes. The time course in the re-evolutionary process is shown in S1 Fig.

Resemblance of response dynamics between evolutionary and unforeseen inputs

One reason why networks of the Cooperative type realize the AUC is that many ML-genes exhibit similar dynamics in response to the activation of any input gene. They also behave in a similar manner even when an unforeseen input gene that is not used for original evolution is activated. Here, we quantitatively studied the resemblance of the response dynamics of ML-genes with different input signals using dynamic time warping (DTW), as shown in Fig 6 [32–34]. DTW analyzes the similarity

between the data of the two time-series taking into account their elongation and parallel shifts in the time axis direction.

For the Cooperative type, the ML-gene response dynamics to any input, including unforeseen ones, showed remarkable resemblance. These reflected cooperative behavior among the different inputs as well as among the different ML-genes. Although each input gene directly activated or inhibited a limited number of ML-genes as the network was sparse, almost all ML-genes subsequently responded through the entangled network with LEGI; some showed input specific responses, but most genes behaved independently of the input types. For the Direct and FF-network types, however, there were almost no such similarities among the different input signals that were observed, and only a small number of ML-genes exclusively responded to each input.

Dynamic mode decomposition of response dynamics

To investigate the origin of the resemblances of the response dynamics more closely, we analyzed the dynamics with dynamic mode decomposition (DMD) [35]. DMD decomposes time-series data with a large degree of freedom into a small number of dominant modes [36–40]. It corresponds to a principle component analysis (PCA) for temporal sequence data.

First, from a data series $\{\mathbf{x}_0, \mathbf{x}_1, \dots, \mathbf{x}_t\}$, we defined two time-series matrices $X = (\mathbf{x}_0, \mathbf{x}_1, \dots, \mathbf{x}_{t-1})$ and $Y = (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_t)$ and assumed a relationship of $Y = AX$ with an operator A . We calculated the eigenvalues and eigenvectors of A by utilizing the singular value decomposition. When the dimension of each time sample $\mathbf{x}_i$ was D_0 , A was a square matrix of size D_0 and had D_0 pairs of eigenvalues and eigenvectors by definition. If only a small number (r) of singular values of X had much larger values than others that were close to 0, the singular value decomposition could be truncated to include only those r modes. The r modes dominantly influenced the dynam-

FIG. 6: Similarity in response dynamics against different inputs. Resemblance of the response dynamics of all ML-genes with each input signal calculated using dynamic time warping (DTW). Inputs $I_1 \sim I_5$ are original evolutionary conditions and $I_6 \sim I_{10}$ correspond to unforeseen inputs. Each square at the intersection shows the similarity of the ML-gene expression against I_i and I_j . For each square, there are the number of ML-genes pixels and each pixel represents the distance between the ML-gene's responses upon I_i and I_j measured by DTW. Yellow indicates a complete correspondence (i.e., the responses of the gene upon I_i and I_j agree), purple indicates disagreement, and black indicates that when the gene shows no response to I_i and I_j . (a) Direct type with $y_T = 0.5$ and $\beta = 10^{1.75}$, (b) FF-network type with $y_T = 1.0$ and $\beta = 10^{1.5}$, (c) Cooperative type with $y_T = 0.5$, and $\beta = \sqrt{10}$.

ics of the data among the D_0 eigenvectors of A . These dominant eigenvectors corresponded to the primary axes in the PCA.

How the number of dominant modes (r) differed according to the network type was investigated first (see Fig 7 (a)). For the Direct type, the number of dominant modes was almost the same as the number of respond-

ing ML-genes with each input. For the FF-network type, most ML-genes showed no responses to the unforeseen inputs, and hence $r = 1$ truncation was just an artifact. In contrast, the Cooperative type showed responses that were represented by a smaller number of dominant modes. Its behavior could be described with fewer modes, although a larger number of ML-genes responded

S1 Fig. Time course in re-evolutionary process. Changes in fitness (ordinate) over a re-evolutionary course with an unforeseen input against the generation (abscissa). The networks are evolved to select a larger response to the new target gene corresponding to the unforeseen input. The averaged fitness from 125 different trials are plotted for each parameter set. Networks are re-evolved keeping the number of total paths from the fitted structure after the original evolution (a) or from its core structure (b).

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- [1] Mangan S, Alon U. Structure and function of the feed-forward loop network motif. *Proc Natl Acad Sci USA*. 2003;100:11980–11985.
 - [2] Alon U. *An Introduction to Systems Biology: Design Principles of Biological Circuits*. Chapman and Hall/CRC; 2006.
 - [3] Karlebach G, Shamir R. Modelling and analysis of gene regulatory networks. *Nat Rev Mol Cell Biol*. 2008;9:770–780.
 - [4] Ma HW, Kumar B, Ditges U, Gunzer F, Buer J, Zeng AP. An extended transcriptional regulatory network of *Escherichia coli* and analysis of its hierarchical structure and network motifs. *Nucleic Acids Res*. 2004;32:6643–6649.
 - [5] Jimenez A, Cotterell J, Munteanu A, Sharpe J. A spectrum of modularity in multi-functional gene circuits. *Mol Syst Biol*. 2017;13:925.
 - [6] Kaneko K. *Life: An Introduction to Complex Systems Biology. Understanding Complex Systems*. Springer-Verlag Berlin Heidelberg; 2006.
 - [7] Ciliberti S, Martin OC, Wagner A. Innovation and robustness in complex regulatory gene networks. *Proc Natl Acad Sci USA*. 2007;104:13591–13596.
 - [8] Kaneko K. Evolution of robustness to noise and mutation in gene expression dynamics. *PLoS One*. 2007;2:e434.
 - [9] Wagner A. *Robustness and Evolvability in Living Systems*. Princeton University Press; 2007.
 - [10] Nagata S, Kikuchi M. Emergence of cooperative bistability and robustness of gene regulatory networks. *PLoS Comput Biol*. 2020;16:e1007969.
 - [11] Elowitz MB, Levine AJ, Siggia ED, Swain PS. Stochastic gene expression in a single cell. *Science*. 2002 Aug 16;297:1183–1186.
 - [12] Furusawa C, Suzuki T, Kashiwagi A, Yomo T, Kaneko K. Ubiquity of log-normal distributions in intra-cellular reaction dynamics. *Biophysics (Nagoya-shi)*. 2005;1:25–31.
 - [13] Hashimoto M, Nozoe T, Nakaoka H, Okura R, Akiyoshi S, Kaneko K, et al. Noise-driven growth rate gain in clonal cellular populations. *Proc Natl Acad Sci USA*. 2016;113:3251–3256.
 - [14] Swain PS, Elowitz MB, Siggia ED. Intrinsic and extrinsic contributions to stochasticity in gene expression. *Proc Natl Acad Sci USA*. 2002;99:12795–12800.
 - [15] Eldar A, Elowitz MB. Functional roles for noise in genetic circuits. *Nature*. 2010;467:167–173.
 - [16] Taniguchi Y, Choi PJ, Li GW, Chen H, Babu M, Hearn J, et al. Quantifying *E. coli* proteome and transcriptome with single-molecule sensitivity in single cells. *Science*. 2010;329:533–538.
 - [17] Braun E. The unforeseen challenge: from genotype-to-phenotype in cell populations. *Rep Prog Phys*. 2015;78:036602.
 - [18] Stolovicki E, Dror T, Brenner N, Braun E. Synthetic gene recruitment reveals adaptive reprogramming of gene regulation in yeast. *Genetics*. 2006;173:75–85.
 - [19] David L, Stolovicki E, Haziz E, Braun E. Inherited adaptation of genome-rewired cells in response to a challenging environment. *HFSP J*. 2010;4:131–141.
 - [20] David L, Ben-Harosh Y, Stolovicki E, Moore LS, Nguyen M, Tamse R, et al. Multiple genomic changes associated with reorganization of gene regulation and adaptation in yeast. *Mol Biol Evol*. 2013;30:1514–1526.
 - [21] Inoue M, Kaneko K. Cooperative reliable response from sloppy gene-expression dynamics. *Europhys Lett*. 2018;124:38002.
 - [22] Becskei A, Kaufmann BB, van Oudenaarden A. Contributions of low molecule number and chromosomal positioning to stochastic gene expression. *Nat Genet*. 2005;37:937–944.
 - [23] Rosenfeld N, Young J, Alon U, Swain P, Elowitz M. Gene regulation at the single-cell level. *Science*. 2005;307:1962–1965.
 - [24] Dekel E, Alon U. Optimality and evolutionary tuning of the expression level of a protein. *Nature*. 2005;436:588–592.
 - [25] Kim HD, O’Shea EK. A quantitative model of transcription factor-activated gene expression. *Nat Struct Mol Biol*. 2008;15:1192–1198.
 - [26] GLASS L, KAUFFMAN S. The logical analysis of continuous, non-linear biochemical control networks. *J Theor Biol*. 1973;39:103–129.
 - [27] Mjolsness E, Sharp DH, Reitsnitz J. A connectionist model of development. *J Theor Biol*. 1991;152:429–453.

- [28] Salazar-Ciudad I, Newman S, Sole R. Phenotypic and dynamical transitions in model genetic networks I. Emergence of patterns and genotype-phenotype relationships. *Evol Dev.* 2001;3:84–94.
- [29] Furusawa C, Kaneko K. A generic mechanism for adaptive growth rate regulation. *PLoS Comput Biol.* 2008;4.
- [30] Inoue M, Kaneko K. Cooperative adaptive responses in gene regulatory networks with many degrees of freedom. *PLoS Comput Biol.* 2013;9:e1003001.
- [31] Levchenko A, Iglesias P. Models of eukaryotic gradient sensing: Application to chemotaxis of amoebae and neutrophils. *Biophys J.* 2002;82:50–63.
- [32] Donald JB, James C. Using dynamic time warping to find patterns in time series. in *Proceedings of the 3rd International Conference on Knowledge Discovery and Data Mining.* 1994;AAAIWS'94:359–370.
- [33] Eamonn JK, Michael JP. Derivative Dynamic Time Warping. in *Proceedings of the SIAM International Conference on Data Mining.* 2001; p. 1–11.
- [34] Keogh E, Ratanamahatana CA. Exact indexing of dynamic time warping. *Knowl Inf Syst.* 2005;7:358–386.
- [35] Schmid PJ. Dynamic mode decomposition of numerical and experimental data. *J Fluid Mech.* 2010;656:5–28.
- [36] Rowley CW, Mezic I, Bagheri S, Schlatter P, Henningson DS. Spectral analysis of nonlinear flows. *J Fluid Mech.* 2009;641:115–127.
- [37] Budisic M, Mohr R, Mezic I. Applied Koopmanism. *Chaos.* 2012;22:047510.
- [38] Mezic I. Analysis of fluid flows via spectral properties of the Koopman operator. *Annu Rev Fluid Mech.* 2013;45:357–378.
- [39] Tu JH, Rowley CW, Luchtenburg DM, Brunton SL, Kutz JN. On dynamic mode decomposition: Theory and applications. *J Comput Dyn.* 2014;1:391–421.
- [40] Brunton SL, Proctor JL, Kutz JN. Discovering governing equations from data by sparse identification of nonlinear dynamical systems. *Proc Natl Acad Sci USA.* 2016;113:3932–3937.
- [41] Kaneko K, Furusawa C, Yomo T. Universal Relationship in Gene-Expression Changes for Cells in Steady-Growth State. *Phys Rev X.* 2015;5:011014.
- [42] Furusawa C, Kaneko K. Formation of dominant mode by evolution in biological systems. *Phys Rev E.* 2018;97:042410.
- [43] von Neumann J. Probabilistic logics and the synthesis of reliable organisms from unreliable components. *Automata Stud.* 1956;34:43–98.
- [44] Gasch A, Spellman P, Kao C, Carmel-Harel O, Eisen M, Storz G, et al. Genomic expression programs in the response of yeast cells to environmental changes. *Mol Biol Cell.* 2000;11:4241–4257.
- [45] Causton HC, Ren B, Koh SS, Harbison CT, Kanin E, Jennings EG, et al. Remodeling of yeast genome expression in response to environmental changes. *Mol Biol Cell.* 2001;12:323–337.
- [46] Stern S, Dror T, Stolovicki E, Brenner N, Braun E. Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge. *Mol Syst Biol.* 2007;3:106.
- [47] Jozefczuk S, Klie S, Catchpole G, Szymanski J, Cuadros-Inostroza A, Steinhäuser D, et al. Metabolomic and transcriptomic stress response of *Escherichia coli*. *Mol Syst Biol.* 2010;6:364.
- [48] Gerashchenko MV, Lobanov AV, Gladyshev VN. Genome-wide ribosome profiling reveals complex translational regulation in response to oxidative stress. *Proc Natl Acad Sci USA.* 2012;109(43):17394–9.
- [49] Ho YH, Shishkova E, Hose J, Coon JJ, Gasch AP. Decoupling yeast cell division and stress defense implicates mRNA repression in translational reallocation during stress. *Curr Biol.* 2018;28:2673–2680.
- [50] Isalan M, Lemerle C, Michalodimitrakakis K, Horn C, Beltrao P, Raineri E, et al. Evolvability and hierarchy in rewired bacterial gene networks. *Nature.* 2008;452:840–845.
- [51] Baumstark R, Hanzelmann S, Tsuru S, Schaeferli Y, Francesconi M, Mancuso FM, et al. The propagation of perturbations in rewired bacterial gene networks. *Nat Commun.* 2015;6:10105.
- [52] Takeda K, Shao D, Adler M, Charest PG, Loomis WF, Levine H, et al. Incoherent feedforward control governs adaptation of activated Ras in a eukaryotic chemotaxis pathway. *Sci Signal.* 2012;5:ra2.
- [53] Wang CJ, Bergmann A, Lin B, Kim K, Levchenko A. Diverse sensitivity thresholds in dynamic signaling responses by social amoebae. *Sci Signal.* 2012;5:ra17.
- [54] Nakajima A, Ishihara S, Imoto D, Sawai S. Rectified directional sensing in long-range cell migration. *Nat Commun.* 2014;5:5367.
- [55] Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D, Alon U. Network motifs: Simple building blocks of complex networks. *Science.* 2002;298:824–827.
- [56] Shen-Orr S, Milo R, Mangan S, Alon U. Network motifs in the transcriptional regulation network of *Escherichia coli*. *Nat Genet.* 2002;31:64–68.
- [57] Ma W, Trusina A, El-Samad H, Lim WA, Tang C. Defining Network Topologies that Can Achieve Biochemical Adaptation. *Cell.* 2009;138(4):760–773.