Enhancing the Robustness of Random Boolean Networks by Epigenetic Regulation

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***Abstract*—Random Boolean Network (RBN) is a type of regulatory network in which the nodes have Boolean values representing their states. The robustness of RBNs against perturbations is a crucial characteristic, and there has been a growing interest in enhancing the network's robustness. In this study, a biologically inspired epigenetic regulation method is proposed to enhance the robustness of the RBNs. A frequency encoding method based on pulse counting is employed to encode the node states within a sliding time window, thereby improving the form of epigenetic regulation. To verify the performance of this method, an antifragility indicator is adopted to measure the robustness of RBNs and yeast cell networks at different scales. The experimental results demonstrate that the networks with epigenetic regulation exhibit excellent robustness, even in the presence of large-scale networks and severe perturbations. This approach provides a new perspective and idea for designing robust RBNs and discrete networks.**

***Index Terms*—Epigenetic regulation, random Boolean network, robustness.**

I. Introduction

REAL-LIFE environments are full of various noises and perturbations. To survive in noisy environments, certain sensitive organisms automatically adjust their internal states, enhancing robustness and maintaining that stability even when damaged. The robustness refers to the ability of an organism or a network to maintain its functionality in a perturbed environment. Perturbations originate from changes in the external environment and internal networks. These perturbations often cause significant fluctuations in network parameters, but the system maintains its behavior through robustness. Therefore, a deep understanding of robustness is an essential precondition for work integrity. Robustness has naturally been the subject of extensive research in various fields: from cellular biological networks [1] to gene regulation networks [2], [43], [44], from networked systems [3] to neural networks [4], [45], and information security [5], [6], [7].

Random Boolean Networks (RBN) are regulatory networks with discrete times and states. RBN with binary node states provides an excellent qualitative analysis model for the regulatory relationship of biological networks [8], [9]. The dynamic behavior of RBNs has been extensively studied [10], [38]. Some of these works have been used to study the network dynamics in biological control mechanisms [11], [12], [39], [40], and to solve machine learning [13] and control tasks [14], [15].

Although much research has been done on the dynamics and applications of RBNs, there is still limited research to improve the robustness of RBNs. Methods to improve network robustness by randomly modifying or adding edges are studied in [3]. It shows that in sufficiently large attacks, moderate randomness can improve network availability and performance, while robustness gradually saturates with edge modification. The approach of [16] proposed an error correction coding method based on information theory to construct robust RBN. But the decoding algorithms may produce false states and even fail if multiple flips in the gene expression vector. The robustness of the networks designed by these methods is limited, and so is the ability to resist large-scale node attacks. The design of a highly robust network should follow two simple principles: first, the target expression state should be highly stable, and second, the initial state can be quickly switched to the target expression state. The topological robustness of a network is also considered to be evolvable, highly robust networks can be reached from networks with lower robustness through gradual evolution [17]. The approach of [2] prompted the utilization of genetic algorithms to build robust gene regulatory networks with specific behaviours. However, this method is computationally intensive regarding network topology evolution and robustness calculation.

Epigenetic regulation is a new way to overcome these problems and improve robustness. It is also suitable for large-scale networks and high-frequency perturbations. Epigenetic regulation is a regulatory mechanism that responds rapidly and precisely to environmental changes, which is also a heritable mechanism by which gene expression changes without altering

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the DNA sequence [41]. Logically and physically, epigenetics can be seen as a dynamic change in gene states in gene regulatory networks [18]. Epigenetic regulation has been used for the control of gene regulatory networks [18], [19] and recurrent neural networks [20], [21] by adding epigenetic control layers. The epigenetic control layer consists of a series of boolean switches that specify which genes are active at each stage of a multistage control task. The impact of epigenetic regulation on network dynamics has also been extensively studied. The adaptation and evolution of epigenetic dynamics to noisy environments are investigated in a simple cellular model with epigenetic feedback regulation [22]. A similar study in [23] introduced epigenetic feedback regulation to enhance the stability of the differentiated state. Epigenetic regulation has also been used to modify expression dynamic thresholds in regulatory networks to study the homeorhesis of epigenetic landscapes [24], [41], [42]. They showed that gene regulatory networks with epigenetic regulation are stable even with the addition of a lot of noise.

Inspired by these methods, we introduce epigenetic mechanisms into RBN to improve robustness. Whereas previous studies on epigenetic regulation are conducted in a continuous model where the variables are real numbers within a certain range, RBNs are discrete models where the variables are represented as finite states. However, our preliminary research found that epigenetics also has good applicability to discrete models. Based on this, a method to improve the robustness of RBNs by epigenetic regulation is proposed in this work. Firstly, epigenetic regulation is employed to alter the expression state of each gene. Positive or negative epigenetic regulation promotes or inhibits gene expression, respectively. Furthermore, the frequency coding method based on pulse counting encodes the node state in a sliding time window to obtain more gene expression information for epigenetic regulation. Besides, antifragility is adopted as the robustness evaluation indicator instead of the attractors or the basin of attractors. The robust performance of epigenetic modifications was tested on RBNs of different sizes, as well as budding yeast cell cycle networks.

The rest of the article structure is organized as follows. The preliminaries are provided in Section II about RBNs, epigenetic regulation, and robustness assessment indicators. The main epigenetic regulation methods of this work are described in Section III. The parametric analysis and related results are listed in Section IV. The summary and future work are given in Section V.

II. Preliminaries

This section introduces the basic principles of RBN, illustrates the background and expression forms of epigenetic regulation, and describes robustness indicators.

A. Random Boolean Network

The RBNs are a classical network of complex dynamical systems. The RBNs capture important phenomena in gene regulatory regulation effectively. RBNs are interesting because their behaviors of RBNs are rich and complex. The RBNs are the gene regulatory networks of discrete state and discrete time, and they work similarly to gene expression patterns in cells [25]. A dynamical model of RBNs consists of nodes and edges, which represent cell genes and the interaction between genes and gene products, respectively. In addition, the boolean state of a node represents a gene's expression state. The state of each node is denoted by a binary variable 0 (OFF) or 1 (ON), which represent non-expressed and expressed states, respectively. The node state variables for N nodes are defined as x_i, $i = 1, 2, \ldots, N$. The Boolean function is defined as $f_i(x_{i1}, \ldots, x_{ik_i})$, where k_i is the number of inputs of node i. The variable f_i is used to update the next moment state of node i.

The Boolean function can be specified by a truth table. For a network with k connections in each node, the number of possible Boolean functions is 2^{2^k}. Each Boolean function is represented as a 2^k-bit binary number, or a decimal number of 0 to 2^{2^k}. The dynamics of RBNs can be studied by using concepts such as state space, trajectories, attractors, and attraction basins. The size of the state space is 2^N in RBNs, where N is the number of nodes. In most cases, since they have a finite number of possible states and they are deterministic, all transients in the network will eventually reach the attractor [26]. A RBN can have one or more attractors. A set of states leading to an attractor forms its basin, the size of which is determined by the number of states in the attractor. Basins of different attractors divide the state space.

B. Epigenetic Regulation

Epigenetic regulation is a structural adjustment at the chromatin level prior to chromosomal transcription. There are multiple epigenetic mechanisms in eukaryotes, of which DNA methylation and histone modification are the main mechanisms [41]. DNA methylation is the addition of a methyl group to a cytosine or adenine base in DNA, and genes with higher methylation are often transcribed at low levels [18]. Histone modification is a process of histone modification, such as methylation and acetylation, under the action of related enzymes. The degree of methylation and acetylation are related to the degree of gene activation. These epigenetic processes regulate chromatin structure and, consequently, control gene expression [37]. There is no clear way to introduce epigenetic processes because the complex and precise molecular processes of histone modifications and DNA methylation are challenging to implement in models of gene expression dynamics [23]. However, the effects of epigenetic processes on expression dynamics were modeled phenomenologically [27]. Epigenetic control factors are mainly determined by the expression levels of the corresponding genes. When a gene is expressed at one moment, it is more likely to be expressed in the next moment. Conversely, it is more likely to be silent when it does not express.

Expression forms of epigenetic regulation proposed by [22] are introduced in this paragraph. A cell is represented as a gene regulatory network composed of multiple genes and is a carrier of epigenetic expression. The expression level of a gene i in a cell is expressed as s_i. The gene expression dynamics of a gene regulatory network can be expressed as

$$\frac{ds_i}{dt} = f\left(\sum_{j=1}^{N} W_{ij}s_j + \theta_i\right) - s_i, \tag{1}$$

where W_{ij} is the regulatory matrix and θ_i is the epigenetic regulation of the gene i. The value of the regulatory matrix W_{ij} represents that gene i is regulated by gene j. The sigmoid function $f(z) = 1/(1 + e^{(-\mu z)})$ is used to represent the update rule for genes, and μ is the gain parameter. We focus on positive self-loops responsible for the up-regulation of their own genes. This mechanism is particularly evident in the differentiation process, where cells, from a stem state, choose a fate towards specific specialised cells [38]. The relationship between expression levels of genes and epigenetic regulation is positive feedback, that is, θ_i increasing with s_i. The dynamics of the epigenetic factor i can be expressed as

$$\frac{d\theta_i}{dt} = v_g(a(s_i - 0.5) - \theta_i) + \eta_i, \tag{2}$$

where a represents the strength of epigenetic control, η_i is a random parameter and can be expressed as Gaussian white noise, v_g is the cell growth rate.

C. Robustness Indicator

The robustness of biological systems is obtained by comparing the system functions before and after perturbation. In RBNs, the robust networks are defined by comparing dynamic attractors before and after network perturbations [28]. The attractors correspond to cell functions demonstrated by numerical and experimental evidence. However, the state space will explode as the network scale expands. It shows that the search for network attractors is very time-consuming and computationally expensive. A novel antifragility that does not require an explicit comparison of attractors was proposed in the research of [29]. Antifragility refers to the ability of the systems to respond to external environmental perturbations and thereby improve system performance [30]. A classic example of antifragility is the immune system, which kills bacteria and acquires new antibodies to boost immunity after exposure to new bacteria. It is an efficient method and suitable for large Boolean networks [31]. In addition, the antifragility measurement can be applied as a control parameter for the construction of robust systems [32]. The network complexity is calculated through the partial state transition of the network so that the antifragility can be calculated relatively quickly. The antifragility measure ($\varnothing$) is defined as

$$\varnothing = -\Delta\sigma * \Delta x, \tag{3}$$

where Δx is the degree of external perturbations, $\Delta\sigma$ is the difference in satisfaction before and after perturbations. The value of antifragility $\varnothing$ is in the interval $[-1, 1]$ and a value close to 0 indicates that RBNs are robust. The external perturbations are obtained by inverting the node states, and the degree of external disturbance can be quantified as

$$\Delta x = \frac{X * \frac{T}{O}}{N * T} = \frac{X}{N * O}, \tag{4}$$

where X is the number of perturbed nodes in the network, N is the scale of the network, T is the simulation time of the network, and O is the perturbed period with a certain time step to increase the disturbance. The degree of perturbation Δx is in the interval $[0, 1]$. The degree of perturbation increases with the number of perturbed nodes and decreases with the increase of the perturbation period.

The variable σ is defined as the degree to which the goal of a node has been reached. The goals of a node can be different in different systems. In RBNs, the goal of a node can be to achieve high complexity. For (3), $\Delta\sigma$ is given as

$$\Delta\sigma = C_1 - C_0, \tag{5}$$

where C_0 is defined as the network complexity before perturbation, C_1 is defined as the network complexity after perturbation. If $\Delta\sigma$ is zero, the network maintains the original complexity in the perturbations. In this case, the network can be considered robust.

The complexity of a network is calculated by evaluating the extent to which the states of nodes in the network are maintained and changed. The complexity implies a balance between order and disorder, which enables the system to adapt robustly to disturbances and changing environments. Order (regularity) preserves useful information that enables an organism or system to survive or maintain its function stably. The change can develop new possibilities in the system, allowing organisms to evolve and adapt to the environment. The equation of complexity C is expressed as

$$C = 4 * E * (1 - E), \tag{6}$$

where coefficient 4 is used to normalize the value of network complexity to the interval $[0, 1]$. The variable E is the number of new states generated over time during the simulation, while $1 - E$ represents how many existing states are maintained. The E is the average of the emergence values for all the nodes, which can be expressed as

$$E = \frac{\sum_{i=1}^{N} - p_0^{(i)} \log_2 p_0^{(i)} + p_1^{(i)} \log_2 p_1^{(i)}}{N}, \tag{7}$$

where $p_0^{(i)}$ is the ratio of the number of states where node i is 0 to the duration of the simulation, $p_1^{(i)}$ is the ratio of the number of states where node i is 1 to the duration of the simulation. For T, the equation uses states with as few transitions as possible from states $T + 1$ to $2T$ time, which results in a more stable ratio by getting states closer to the attractor.

III. Epigenetic Regulation for RBNs

A. Epigenetic Regulation for RBNs

The research done in this paper is about RBNs, where the main content of the research is the robustness of discrete networks with epigenetic modifications. The main reason for investigating the impact of epigenetic regulation as autoregulation in RBN: the robustness of studies of the most widely used RBNs is limited, and a wealth of results on continuous gene regulatory networks are already available. If epigenetic regulation makes continuous gene regulatory networks somehow more adaptive to model differentiation processes, they should be considered in RBNs.

An RBN with N nodes and epigenetic regulation is considered. The node states of the RBN are represented by a vector

$(x_1, x_2, \ldots, x_N)$, where x_i is the expression level of the node i. Each node in the RBN has k inputs. Epigenetic regulation is introduced into each node by fine-tuning the state of the node. The epigenetic regulation is similar to adding a feedback mechanism to a node to monitor the state of the node. Therefore, the state of a node with epigenetic regulation is not arbitrarily changed. The dynamics s_i of a node introduced into epigenetic regulation are expressed as

$$s_i(t+1) = F(f_i(x_{i1}(t), \ldots, x_{ik_i}(t)) + \theta_i), \tag{8}$$

where k_i is the number of inputs to node i, the variable f_i is a logical function of node i for updating the next state, and the θ_i is the epigenetic regulation introduced in the gene expression. The first item on the right represents the actions from regulatory nodes that synergetically determine the expression, while the second item corresponds to the degree of openness of epigenetic regulation. If θ_i is positive, the state of the node is more likely to be 1. Conversely, the state of the node is more likely to be 0 if θ_i is negative. To represent the on-off-type expression of nodes, the function $F(z) = 1/1 + e^{-4\times(z-0.5)}$ is adopted, where the constant 0.5 is to make the function take (0.50.5) as the symmetry center, and the constant 4 scales the main change value of the function in the interval $[0, 1]$. This enables epigenetic regulation to respond to noisy environments more accurately and regulate node states correctly. Since s_i is a continuous value in (8), and the node states of a RBN are Boolean values, it is necessary to discretize the variable s_i. The gene expression dynamics of the RBN are adopted as

$$x_i(t+1) = \begin{cases} 0, & \text{if } s_i(t+1) < 0.5 \\ 1, & \text{if } s_i(t+1) \geq 0.5 \end{cases}, \tag{9}$$

where the constant 0.5 is the threshold that divides the values in the interval $[0, 1]$ into 0 and 1.

The epigenetic change depends on the expression level of gene i. A large number of positive correlations between methylation and gene expression within the promoter regions have been pointed out in [33]. The relationship between histone modifications and genes can be expressed as positive feedback. A classic example is the processivity of Src kinase in signal transduction [34]. From this, a positive feedback process from gene expression to epigenetic modifications is adopted. When a gene is being expressed, it is more likely to be expressed at the next moment under epigenetic modifications, and it is more likely not to be expressed when the gene is not. It is consistent with the stabilization of the epigenetic changes. The form of epigenetic regulation in RBNs is expressed as

$$\theta_i = \begin{cases} -a + b(y_1 - y_0), & \text{if } s_i(t) = 0 \\ a + b(y_1 - y_0), & \text{if } s_i(t) = 1 \end{cases}, \tag{10}$$

where a and b are the positive constants denoting the strength of the epigenetic regulation. In particular, a is the weight of the node state at the last moment, and b is the weight of the difference in the expression level of the node state values in the time window T_w. If the state $s_i(t)$ at the last moment is 0, the first term takes a negative value. If the state at the last moment was 1, the first item takes a positive value. This enables epigenetic regulation of the expression node to promote the expression of the node. The variable y_1 is the ratio of the number of pulses (the node status value is 1) to the time in a specific time interval T_w. Similarly, the variable y_0 is the ratio of the number of no pulses (the node status value is 0) to the time in a specific time interval T_w. It is calculated by the equation $y_0 = 1 - y_1$.

The epigenetic regulation introduced in [22], [24] is based on a continuous dynamic network. The state values of the nodes contain rich information on the node expression level. However, the state values of the nodes are represented as the Boolean values in RBNs. It contains very little information and does not obtain the expression level of the node. Therefore, it is not enough to consider the state of the node at the last moment in RBNs. The time dimension information of Boolean data is exploited to solve the problem. The node states are used and transformed into useful information over time. A coding method based on pulse frequency is used to realize the coding of discrete data into continuous variables to obtain more information on node expression levels. A node whose expression value is 1 can be regarded as an impulse, and a node whose expression value is 0 can be regarded as no impulse. The expression level of the node y_1 is calculated by

$$y_1 = \frac{n_{sp}(T_w)}{T_w}, \tag{11}$$

where T_w is the time window, n_{sp} is the number of pulses in T_w. The encoding method is simple and robust. The larger the time window, the less the effect of noise and disturbance.

B. Robustness Evaluation of the RBNs

Attractor dynamics and epigenetic landscapes are typical ways to measure the robustness of Boolean networks. Expensive computational resources and time are required to search all transient states of the networks. However, antifragility is easily computed by computing the complexity of the network by local state transfer. Therefore, the robustness degree of the RBNs is obtained faster by calculating the antifragility. The closer the antifragility $\emptyset$ is to 0, the better the robustness of the network. Antifragility is determined by the degree of perturbation Δx and the complexity of the network $\Delta\sigma$. The smaller the disturbance period O or the larger the number of disturbance nodes X, the greater the antifragility. The smaller the complexity, the better the robustness of the network. When the emergence E of the network is close to 0, the complexity of the network is close to 0, which means that the dynamics of the network are ordered, regular, and robust.

The robustness of the network is calculated by comparing the network emergence before and after internal perturbations. RBNs and RBNs with epigenetic regulation were investigated for their robustness. To reduce the possibility that epigenetic modifications are only used for networks with specific structures and functions, multiple RBNs are randomly generated for testing. Multiple different initial states are also randomly generated in one RBN. At the same initial state, the state transitions of the RBNs before and after perturbation are calculated at times $T+1$ to $2T$. Random node states are flipped at a fixed period to simulate random disturbances. The greater the random

Algorithm 1: Evaluating the Robustness of RBNs.

Input: parameters $X,\ O,\ a,\ b,\ k$
Output: antifragility $\emptyset$
1 for $t = 1$ to the number of multiple RBNs do
2 initialize an RBN
3 calculate Δx
4 generate multiple different initial states randomly
5 for all elements of initial states do
6 for $i = 1$ to time steps do
7 update the RBN with $a,\ b$
8 calculate y_1
9 compute the value of $E,\ C_0$
10 for $i = 1$ to time steps do
11 if $i \% O == 0$ do
12 select X nodes randomly for perturbation
13 update the RBN with $a,\ b$
14 calculate $y_1,\ E$
15 compute the value of $\emptyset, C$
16 calculate the average of $\emptyset$
17 return $\emptyset$

disturbance, the greater the fragility. The pseudocode for this process is shown in Algorithm 1.

IV. Results

This section presents the parameters and robust analysis of epigenetic regulations in RBNs. The effect of epigenetic parameters on the robustness of RBN was analyzed using the controlled variable approach. Epigenetic regulation is also evaluated through a biological network, the budding yeast cell cycle network. Finally, the robustness of RBNs at different scales with and without epigenetic regulation are compared and analyzed.

A. Analysis of Epigenetic Regulatory Parameters

Parameters in the simulation of RBNs and epigenetic regulation can be divided into environmental parameters, network parameters, and regulatory parameters. The environmental parameters control the changes in the noise environment. The network parameters are used to set the RBN operation. The regulatory parameters are used to control the epigenetic effect. The details of the parameters are shown in Table I. The simulation time of RBNs, the number of different RBNs, and the number of initial states are fixed in all experiments. Specifically, the state transitions were investigated during $2 \times 200 = 400$ time steps. In the last 200 time step, the $\emptyset$ of 10 initial states are computed separately. This subsection examines the regulatory parameters of epigenetic regulation, and subsequent subsections examine the effects of other parameters.

The relationship between the robustness of RBNs with epigenetic regulation and regulation parameters a, b and T_w are studied. They play a decisive role in epigenetic regulation. How these parameters are set to maximize the robustness of the network is analyzed. The RBN is set to 16 nodes with two inputs per node. The number of perturbed nodes X is set as 8. The perturbation frequency O is set as 1. The dependence

TABLE I
Parameters and Settings for Simulation Experiments

Number	Parameter	Meaning	Value
1	N	Number of nodes	-
2	k	Number of inputs per node	-
3	T	Simulation time	200
4	X	Number of perturbed nodes	-
5	O	Perturbation period	-
6	-	Number of different networks	500
7	-	Number of initial states	10
8	a	Weight of the last node state	-
9	b	Weight of the difference in the expression level of the node state values	-
10	T_w	Time window	-

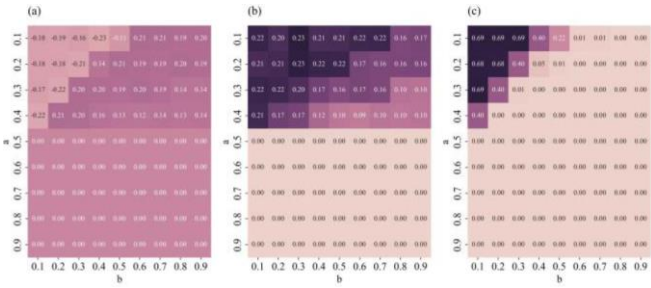

Fig. 1. Phase diagram of results with the weight of the node state a (vertical axis) and b (horizontal axis). (a) The phase diagram with robustness results is affected by regulatory control parameters a and b. (b) The phase diagram of the node emergence E before perturbation is affected by the regulated parameters. (c) The phase diagram of the node emergence E after perturbation is affected by the regulated parameters.

of network robustness on parameters a and b is studied under this perturbed environment and network structure when the time window T_w is set as 8. The phase diagram of robustness and emergence with the weight of the node state a (vertical axis) and b (horizontal axis) is shown in Fig. 1. When $a \geq 0.5$, the node states are dominated by epigenetic regulation. Epigenetic regulation is mainly determined by the states of the previous moment. If the previous moment is 1, there is a very probability that the next moment is also 1. The value of a is too high to focus on the regulatory nodes of the nodes. When the value of a is large, the input noises will not disturb the states of the nodes regardless of b, as shown in Fig. 1(c). Therefore, the robustness of the network is 0 in Fig. 1(a).

When $a < 0.5$, the robustness increases from negative to positive as the b increases. When both a and b are small, the states of the nodes are dominated by the output of the Boolean function and inputs of regulatory nodes. The role of epigenetic regulation is fine-tuning states of the nodes. Affected by noise,

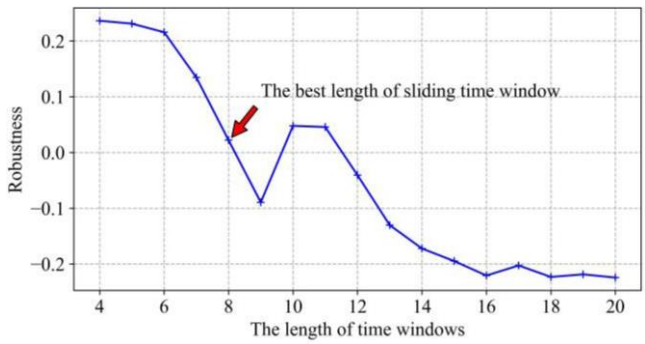

Fig. 2. The effect of time window length on the robustness of RBNs. When $T_w < 8$, the window length is short, the robustness is positive. When $T_w = 8$, $\emptyset$ is closest to 0, and the network robustness is the best. When the length of the time window is long and the disturbance frequency is 1, the robustness gradually decreases, $\emptyset$ is negative.

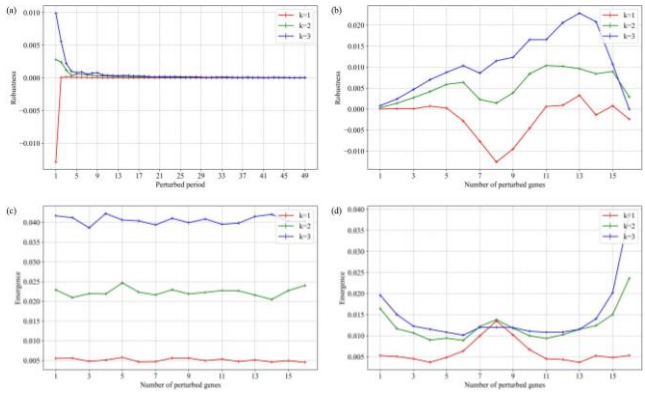

Fig. 3. The effects of epigenetic regulation are on RBNs with k = 1, 2, 3. (a) Influence of perturbation period on the robustness $\emptyset$ of RBN with epigenetic regulation. (b) Influence of perturbed genes on the robustness $\emptyset$ of RBN with epigenetic regulation. (c) The emergence E of RBNs before perturbation varies with the number of perturbed genes. (d) The emergence E of RBNs after perturbation varies with the number of perturbed genes.

the states of the nodes change frequently, and the amount of change in the nodes increases. The emergence of RBN after perturbation in Fig. 1(c) is larger than that before perturbation in Fig. 1(b). Therefore, the robustness of the network is negative in Fig. 1(a). When b is large, the states of the nodes are mainly dominated by the epigenetic regulated node expression level. Thus even with perturbations, the node states within the time window depend only on the previous expression state. In this way, the influence of noise is ignored, the expression states of nodes tend to be regular, and the robustness of the network gradually becomes positive and larger as b increases. To make the network more robust, the selected parameters should make $\emptyset$ close to 0. When a = 0.1 and b = 0.5, the robustness of the network performs better in a noisy environment, as can be seen in Fig. 1.

The time window of epigenetic regulation is an important factor. Shorter time windows are prone to mis-judgment due to insufficient data. The longer the time window, the more information, and the better the suppression effect on outliers (noise). The effect of time window length on the robustness of RBNs is investigated. This result is shown in Fig. 2. When the window length is equal to 8, $\emptyset$ is closest to 0, and the robustness of the network is the best. When $T_w < 8$, the window length is short, which can capture changes and adjust the node state quickly. The states of nodes are fixed quickly, which makes the network emergence reduction and robustness positive. When the length of the time window is long and the perturbation frequency is 1, epigenetic regulation is not enabled until the length of the node data reaches the window length. The data is often perturbed when epigenetic regulation is not enabled, so the factor γ_1 can no longer correctly reflect the node expression level. Therefore, the emergence of the RBNs increases with the length of the time window. The robustness gradually decreases and $\emptyset$ is negative.

B. Robustness of RBNs With Epigenetic Regulation

The experiments in the last section are all carried out under the same noise environment. In order to verify the effect of epigenetic regulation of RBNs in different noise environments, this subsection studies the network robustness and complexity changes under different perturbation periods, as well as the changes in the number of perturbed nodes.

From the experiment results in the last section, it can be seen that the network robustness is better when a = 0.1, b = 0.5, and $T_w = 8$. These parameters are used in the experiments in this section. The robustness $\emptyset$ of ordered (k = 1), critical (k = 2), and chaotic (k = 3) RBNs with epigenetic regulation in different perturbation periods and sizes are studied. The average robustness of RBNs with epigenetic regulation for k = 1, 2, 3 depends on perturbation period O when perturbed node size X = 8 is shown in Fig. 3(a). The dynamics of networks for k = 1, 2, 3 become robust as O increase even if half of the nodes are perturbed. That is, the fewer times a node is perturbed in a period, the higher the robustness. When the perturbation period is 1, the RBN for k = 2 exhibits good robustness of 0.004. It can be seen that the robustness value is very close to 0 when the perturbation period is 10. The trend of robustness is similar for different k in RBNs.

The average robustness of RBNs with epigenetic regulation depending on X when O = 1 is shown in Fig. 3(b). The robustness value $\emptyset$ of the networks with k = 2, 3 increases as the number of perturbed nodes increases. The robustness values are positive numbers, which means that the states of the nodes gradually become the ordered states after the perturbation, and the emergence of the nodes decreases. Under the regulatory parameters a = 0.1 and b = 0.5, the RBNs with k = 2 have good robustness in the number of perturbed nodes X = 8, but are not ideal in other cases. It can be seen that different regulatory parameters of the network are required according to different dynamic characteristics and perturbation environments.

The emergence E before and after node perturbation in different k is shown in Fig. 3(c) and (d). The emergence E of the RBNs with epigenetic regulation before perturbation fluctuated less. In Fig. 3(c), the emergence of networks for k = 1, 2, and 3 are about 0.05, 0.023, and 0.041, respectively. The emergence in Fig. 3(d) first decreased and then increased with the number

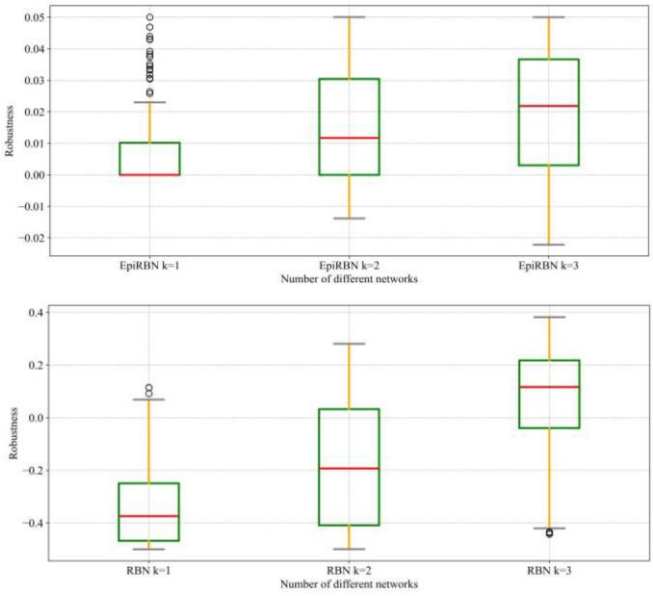

Fig. 4. Robustness of 500 randomly generated networks for k = 1, 2, 3. (a) Robustness of 500 randomly generated RBNs. (b) Robustness of 500 randomly generated RBNs with epigenetic regulation, where EpiRBN represents for RBNs with epigenetic regulation.

of perturbed genes, and the broken lines were axisymmetric about the axis X = 8 roughly. The degree of perturbation Δx is constantly increasing, so the $\varnothing$ in Fig. 3(b) is increasing. When the number of perturbed nodes is 16 and the perturbation period is 1, it is equivalent to adding no perturbation to the network but inverting the node state on each input. Therefore, the emergence and robustness before and after disturbance are very similar.

C Robustness Comparison in RBNs With and Without Epigenetic Regulation

The difference between RBNs with and without epigenetic regulation was investigated by comparing the robustness of generating random networks. The networks are randomly generated for ordered, critical, and chaotic network dynamics. The size of RBNs is set at 16. The perturbation period of the noise environment is O = 1, and the perturbation node X = 8. Epigenetic parameter a is set at 0.1 and b is set at 0.5. The robustness of perturbed RBNs is shown in Fig. 4(a). Their robustness fluctuates widely, meaning that the dynamics of their nodes change frequently over time and the RBNs are susceptible to noise. The robustness of perturbed RBNs with epigenetic modifications is shown in Fig. 4(b). Their robustness is significantly stable and much smaller compared to Fig. 4(a). RBN is affected by noise and its robustness fluctuates in the range of $[-0.4, 0.4]$, while the RBN with epigenetic regulation fluctuates in the range of $[-0.02, 0.05]$ and mainly concentrates on the position where the robustness is 0. The epigenetic regulation mechanism stabilizes the state expression of nodes and makes the expression of nodes more orderly in the figure. Node states are influenced not only by Boolean functions but also by epigenetic regulation based on previous node states.

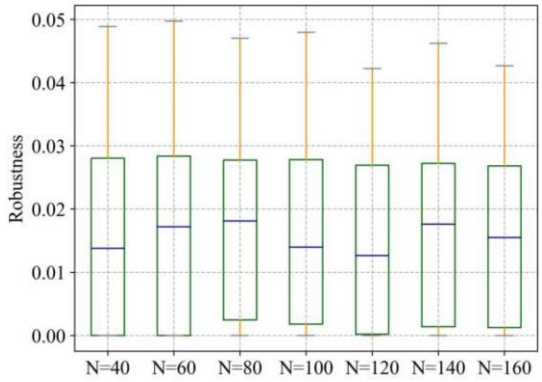

Fig. 5. Robust distribution of RBNs with epigenetic regulation at different network scales. Robustness values for network sizes from 40 to 160 are in the interval [0, 0.05], with an average median of around 0.015. The robustness of large-scale networks is comparable to that of small-scale networks.

Epigenetic regulation corrects the error states of nodes, making the network robust in noisy environments. In the absence of network perturbations, epigenetic regulation makes node states more fixed and stable.

The size of RBNs was 16 in previous experiments, and it is unclear how well epigenetic regulation works in large-scale networks. The RBNs with epigenetic regulation at different network sizes were investigated. The network size is increased from 40 to 160 in steps of 20. The perturbation period of the perturbation environment is O = 1. The number of perturbation nodes is half of the network size (X= N/2). Fig. 5 shows the distribution of robustness of RBNs with epigenetic regulation for k = 2 at different network scales. Robustness values for network sizes from 40 to 160 are in the interval [0, 0.05], with an average median of around 0.015. Even large-scale networks are less affected by noise due to epigenetic regulation, and the network is more orderly, thus possessing robustness comparable to small-scale networks. Therefore, epigenetic regulation is not only applicable to small-scale networks but can also improve the robustness of large-scale networks.

D. Robustness in the Budding Yeast Cell Cycle Network

Epigenetic regulation was applied in budding yeast cell cycle networks to validate performance in biological networks. The budding yeast cell-cycle regulatory network [1] is a discrete Boolean network model that contains 11 nodes and 7 steady states. The proteins of budding yeast cells are the nodes of the Boolean network, and each node is assigned a binary value denoting whether the protein is present or not. In the budding yeast cell cycle network, the strength of protein interaction is not quantified, only described as being activated or inhibited. The protein state $S_i(t+1)$ at the next time is determined by the current protein states via

$$S_i(t+1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > 0 \\ 0, & \sum_j a_{ij} S_j(t) < 0 \\ S_i(t), & \sum_j a_{ij} S_j(t) = 0 \end{cases} \tag{12}$$

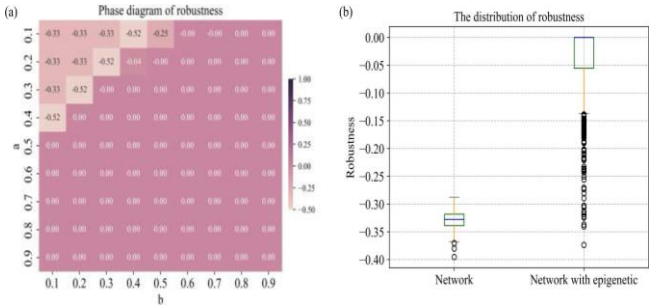

Fig. 6. (a) Phase diagram of regulatory parameters a (vertical axis) and b (horizontal axis) in the budding yeast cell cycle network. (b) Robust distribution and comparison of 1000 random initial states with and without epigenetic regulation.

where a_{ij} represents activation or inhibition from protein j to protein i. It is clear that the regulation rule is not a Boolean function rule, so the epigenetic regulation parameters a and b are re-studied to accommodate different types of Boolean networks. The disturbance frequency of the noise environment is $O = 1$, and the disturbance node $X = 6$. The time window is set as 8. The result is shown in Fig. 6(a). When a>0.5 or b is larger, the robustness is 0 due to the strong epigenetic regulation, but the epigenetic regulation is too strong to have its own regulatory function. When a < 0.5, the robustness transitions from a poorer performance to a better one as b increases. The complexity of the budding yeast cell cycle network before perturbation is zero. When both a and b are relatively large, the order of the perturbed epigenetic regulatory network becomes higher until the network complexity turns to zero. Therefore, it can be seen that the network robustness is 0 for many parameter combinations. The parameters in transition are chosen to exhibit network robustness. In this experiment $a = 0.3$ and $b = 0.4$ were chosen for further experiments. The number of different networks was 1 and 1000 random initial states were generated because the network structure and function of yeast cell cycle networks were fixed. The distribution of robustness after perturbation for 1000 initial states is shown in Fig. 6(b). The median robustness of the budding yeast cell cycle network was approximately -0.33 without epigenetic modifications and 0 with epigenetic modifications. It shows that the epigenetic regulation is an effective way to stabilize the node state and enhance the robustness of the network.

E. Robustness Comparison Between RBN With Epigenetic Regulation and RBN With Memory

The impact on the stability of discrete model systems of gene regulatory networks with memory effects has been studied in literature [35]. The Gene-Protein Boolean Network (GPBN) is an extension of RBN, with (Boolean) entities G nodes and P nodes represent genes and gene products (i.e., proteins or RNAs), respectively. The introduction of a form of memory into the classical RBN model is its basic idea, in terms of synthesis and decay times associated with the entities of the system. The RBNs with epigenetic regulatory were constructed with the same structure as the GBPNs, and the rest of the experimental configurations were consistent with [35]. The epigenetic parameters are set to $a = 0.1$, $b = 0.5$, and the length of sliding time window was set to 8. Fifty different networks were created for each different numbers of node perturbations X. The average of the Hamming distances was calculated and taken. The results are shown in the Table II. The Hamming distance of the RBNs with epigenetic regulation are much smaller than the GPBNs with memory in the table. Epigenetic regulation has a stronger ability to stabilize the network. A longer parameter time for memory means that a greater number of P-nodes have a greater decay time. The node value will be 1 for a greater number of time steps. This effect would force the system toward a configuration of the nodes with a larger fraction of 1's. Epigenetic regulation forces node states towards a stable direction based on their expression values. It is possible to regulate nodes in the direction of 0 or 1, with a larger adjustment range and control ability.

TABLE II
HAMMING DISTANCE FOR DIFFERENT NUMBERS OF PERTURBED NODES

		$X = 1$	$X = 2$	$X = 3$	$X = 4$
GPBN	Ymax=2, bias=0.3	0.92	1.83	2.75	3.63
	Ymax=16, bias=0.7	0.74	1.46	2.19	2.91
RBN	bias=0.3	0.30	0.47	0.84	0.94
	bias=0.7	0.25	0.55	0.68	1.27

V. CONCLUSION AND FUTURE WORK

In this paper, a modified RBN using epigenetic regulation is proposed to improve network robustness. It is a novel improvement strategy for discrete and large-scale networks, with epigenetic regulation as an assisting mechanism at each node. Based on this, the frequency encoding method based on pulse counting is used to encode node states in the sliding time window, and the obtained encoded information is used for epigenetic regulation. The method was validated on randomly generated and different scales of RBNs and on budding yeast cell cycle networks. The method exhibits better robustness than without the regulatory mechanism. The robustness of the 16-node RBN fluctuates in the range of [-0.4, 0.4] under the influence of noise, while the RBN with epigenetic regulation fluctuates in the range of [-0.02, 0.05], which is more robust and stable. The median robustness of budding yeast cell cycle networks with and without epigenetic regulation was 0 and -0.33, respectively. The method is also robust to large-scale networks under epigenetic regulation mechanisms, whose robustness value is close to 0.

Epigenetic regulation is widely used to study adaptation in gene regulatory networks, to model differentiation functions in biology, and to decompose control of complex tasks in artificial networks. It exhibits robust self-regulation and differentiation capabilities in noisy and realistic environments. The introduction of epigenetic regulation improves stability and the ability to adapt to various complex environments. A similar approach has yet to be investigated in RBNs, particularly in terms of

robustness as a fundamental capability against a perturbed environment. The epigenetic regulatory mechanism makes decisions based not only on the current states of the nodes but also on the states over the previous time. It corrects for the effects of perturbations in node flipping. If inputs are perturbed to produce wrong state values, they are corrected based on the expression values at the previous time. If the gene expression values are all expressed as 1 in the previous time, the epigenetic regulation values are also close to 1. The state values at that moment are dominated by epigenetic regulation, which determines the values at the current moment to be 1. The more stable in the state of the node, the less affected by the disturbance at the next moment. Therefore, epigenetic regulatory mechanisms bring the RBNs into a steady state, equivalent to entering the valley of the fitness landscape, and the potential is large enough to take it out of the valley.

Methods to improve the robustness of the RBNs are based on improving the network structure as well as the modulation function [3], [36] of the nodes. They act on some less robust nodes. Epigenetic regulation acts on all nodes, adding a protection mechanism on each node. The vulnerable and stable nodes both are more stable. Some methods screen out robust networks through evolutionary algorithms [2], [17]. For large-scale networks, the search space is relatively large. Therefore, it takes work to develop large-scale and robust RBNs. Epigenetic regulation adds a protective layer to the RBN and applies to networks of various scales. The robustness and stability of RBNs are improved at different levels by determining the control parameters a and b. This work applies epigenetic regulation to RBN, providing a new idea for improving the robustness of large-scale networks. This method can not only be used in the simulation and optimization process of synthetic biology to construct a robust synthetic gene network. Furthermore, the method provides an alternative solution for robust optimization of other discrete networks, such as Hopfield networks. Future work will explore adaptive algorithms for regulation parameters in response to environmental changes.

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