Antifragility of Random Boolean Networks

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Abstract

Antifragility is a property that enhances the capability of a system in response to external perturbations. Although the concept has been applied in many areas, a practical measure of antifragility has not been developed yet. Here we propose a simply calculable measure of antifragility, based on the change of “satisfaction” before and after adding perturbations, and apply it to random Boolean networks (RBNs). Using the measure, we found that ordered RBNs are the most antifragile. Also, we demonstrate that seven biological systems are antifragile. Our measure and results can be used in various applications of Boolean networks (BNs) including creating antifragile engineering systems, identifying the genetic mechanism of antifragile biological systems, and developing new treatment strategies for various diseases.

Introduction

Antifragility suggested by Taleb is defined as a property to enhance the capability of a system in response to external stressors [1]. It is beyond resilience or robustness. While the resilient/robust systems resist stress and stay the same, antifragile systems not only withstands stress but also benefit from it. The immune system is a representative example of antifragile systems. When exposed to diverse germs at an early age, our immune system strengthens and thus overcomes new diseases in the future.

The concept of antifragility has been actively applied in numerous areas such as risk analysis [2, 3], physics [4], molecular biology [5, 6], transportation planning [7, 8], engineering [9, 10, 11], aerospace and computer science [12-15]. However, a practical measure of antifragility has not been developed yet. Here we propose a novel measure for antifragility based on the change of complexity before and after adding perturbations. We will use random Boolean networks (RBNs) as a case study to illustrate our measure.

BNs have a wide range of applications from biochemical systems [16-20], to economic systems [21]; from social networks, [22, 23] to robots [24]. Our antifragility measure can be
utilized in various applications of BNs. For instance, one could create antifragile engineered systems or identify the genetic mechanisms of antifragile biological systems.

The rest of our article is structured as follows. In the section of “Measurement of Antifragility in RBNs”, we describe RBNs, complexity of RBNs, perturbations to RBNs, and how to assess antifragility in RBNs. In the section “Experiments”, methods and parameter setting for simulations are explained. In the section of “Results and Discussion”, the results of the antifragility of RBNs and several biological BNs are presented and analyzed. The section of “Conclusions” summarizes and closes the article.

Measurement of Antifragility in RBNs

Random Boolean Networks

RBNs were proposed as models of gene regulatory networks by Kauffman [25, 26]. A RBN consists of \( N \) nodes representing genes. Each node can take either 0 (off, inhibited) or 1 (on, activated) as its state. The node state is determined by the states of input nodes and Boolean functions assigned to each node. Every node has \( K \) input nodes (or input links). Self-inputs are allowed. The links are wired randomly, and the Boolean functions are also randomly assigned. Once the links and the Boolean functions set up, they remain fixed.

In Figure 1(a) and (b), the left plots show how randomly chosen initial states are updated over time. Because the plots are simulated until \( T = 40 \), they present only part of state spaces. A state space refers to the set of all the possible configurations \( (2^N) \) and all the transitions among them. Being deterministic, classic RBNs have one and only one successor for each state. When states repeat, it implies that an attractor (stationary or periodic). States that lead to attractors are part of their basin of attraction. Depending on the structure of the state space, there are three dynamical regimes in RBNs: ordered, chaotic, and critical. The first two are phases, while the critical regime lies at the phase transition. The dynamical regimes can be varied by \( K \). For RBNs with internal homogeneity \( p = 0.5 \), \( K = 1 \) is ordered, \( K = 2 \) is critical, and \( K > 2 \) is chaotic, on average [27]. Other properties of RBNs can be used to regulate dynamical regimes [28]

Complexity of RBNs

Using our previous approach, we can measure the complexity of RBNs [29]. The complexity is calculated based on Shannon’s information entropy. Its equation is as follows:

\[
E_i = -(p_0 \log_2 p_0 + p_1 \log_2 p_1)
\]

\[
C = 4 \times \bar{E} \times (1 - \bar{E})
\]

where \( E_i \) is the “emergence” of node \( i \), \( p_j \) is the probability that the state of the node is \( j \) \((j = 0, 1)\), \( C \) \((0 \leq C \leq 1)\) is the complexity of the network, and \( \bar{E} \) \((0 \leq \bar{E} \leq 1)\) is the average of the emergence values for all the nodes. Specifically, \( p_0 \) \((p_1)\) is calculated by counting the number of 0s \((1s)\) in node \( i \) until simulation time \( T \). For example, in the left plot of Figure 1(b), \( p_0 \) and \( p_1 \) of the last node are \( \frac{1}{40} \) and \( \frac{39}{40} \), respectively.

The complexity reaches maximum when the emergence \( \bar{E} \) is 0.5 \((\bar{E} = 0.5 \rightarrow C = 1)\). It is when the expression of any one of the two states is highly probable, i.e., \( p_0 \) or \( p_1 \approx 0.89 \) [30, 31]. Meanwhile, \( C \) becomes 0 when the two states are evenly distributed \((p_0 = p_1 = 0.5; \bar{E} = 1)\) or only one state has maximum probability \((p_0 \) or \( p_1 = 1; \bar{E} = 0)\).
Complexity represents a balance between regularity and change [26], which allows systems to adapt robustly. The regularity ensures that useful information survives, while the change enables the systems to explore new possibilities essential for adaptability [32]. Living organisms or computer systems need not only stability to survive or to maintain information but also flexibility to evolve and adapt to their environment. In RBNs, high complexity means an optimal balance between keeping and changing the states of the network. As shown in Figure 1(a), the antifragile network maintains original states overall, and simultaneously explores new states by means of perturbations. On the other hand, Figure 1(b) shows that most of the states in the fragile network change with perturbations, which indicates that the network does not maintain information in a noisy environment.

![Figure 1: Schematic diagrams showing state transitions of (a) critical and (b) chaotic RBNs with $N = 20, X = 2$, and $O = 1$. The left side is the network without perturbations and the right one is the network with perturbations with the same initial states. Each square represents the state of a node (white = 0, black = 1). The state transitions were calculated from the initial states at the top to states at the bottom during $T = 40$. (a) $K = 2$ (critical), $\dot{\phi} = -0.0519$. (b) $K = 3$ (chaotic), $\dot{\phi} = 0.0401$.](image)

**Network Perturbations**

We “mutate”, “disturb” or “perturb” the nodes of a RBN by changing current states. We flip the states of $X$ nodes randomly chosen, where the perturbations are added with frequency $O$ during simulation run time $T$. In other words, the perturbations are added whenever the time step $t$ is divisible by $O$ ($t \mod O = 0$). For example, $X = 2, O = 3$, and $T = 99$ mean that the states of two nodes randomly chosen in each configuration are flipped every three time steps until the simulation run time becomes 99. By comparing the state transitions of the original network and its perturbed network, we can observe how the perturbations propagate over time (Figure 1).

In our study, the degree of perturbations is defined as follows:

$$\Delta x = \frac{X \times \frac{T}{O}}{N \times T} \quad (3)$$

where $0 \leq \Delta x \leq 1$.  

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Antifragility of RBNs

We define fragility $\hat{f}$ as:

$$\hat{f} = -\Delta \sigma \times |\Delta x|$$  (4)

where $\Delta \sigma$ is the difference of “satisfaction” before and after perturbations, while $\Delta x$ is the degree of perturbations. The satisfaction can be measured differently depending on the particular systems, e.g. performance, value, fitness. If the satisfaction is decreased with perturbations, then the system is fragile. If the satisfaction does not change, then the system is robust. If the satisfaction increases with perturbations, then the system is antifragile. Antifragility is simply $1 - \hat{f}$. Notice that $\Delta \sigma$ and $\Delta x$ should be normalized to the interval [-1, 1].

The perturbations $\Delta x$ for RBNs were defined in the previous section. We can define the “satisfaction” of a RBN based on its complexity. Since a high complexity offers a balance between robustness and adaptability, we can arbitrarily prefer RBNs with a high complexity.

Using the complexity measure presented previously, $\Delta \sigma$ is calculated by the following equation:

$$\Delta \sigma = C - C_0$$  (5)

where $C_0$ is complexity of a network before adding perturbations, and $C$ is complexity of the network after adding perturbations. The same initial states are used at $t = 0$. Because the value of complexity is between 0 and 1, $-1 \leq \Delta \sigma \leq 1$.

Negative values of $\hat{f}$ mean that the RBN is antifragile and positive values mean that the RBN is fragile. Values close to zero indicate that the RBN is robust. As shown in equation (4), $\hat{f}$ has the opposite sign of $\Delta \sigma$. Hence, the negative values of $\hat{f}$ indicate that $C$ is larger than $C_0$ (i.e., the complexity of a system is improved by external perturbations), while the positive values represent that $C_0$ is greater than $C$ (i.e., the complexity is exacerbated by the perturbations). The value of 0 refers to the complexity does not change before and after perturbations, which represents that the RBN is robust.

Experiments

We performed two sets of experiments: one for RBNs, and the other for biological BNs.

First, to measure antifragility of RBNs, we generated ordered, critical and chaotic RBNs composed of 100 nodes ($K = 1$ (ordered), 2 (critical), 3, 4, 5 (chaotic)) with internal homogeneity $p = 0.5$ [27]. For each RBN, we randomly chose 10 different initial states and then examined their state transitions until simulation time $T = 200$, respectively. For the same RBN taking the same initial states, varying perturbed node size $X$ and perturbation frequency $O$, we obtained the state transitions of the perturbed RBN until $T = 200$. By comparing complexity before and after perturbations, we calculated mean of antifragility for the 10 initial states. The measured values shown in the plots are average calculated from 50 different RBNs per $K$. 
Secondly, to measure antifragility of biological BNs, we used the following seven biological network models:

- **CD4+ T cell differentiation and plasticity** [33] \((N = 18)\). It is a model representing how CD4+ T cells orchestrate immune responses depending on environmental signals and immunological challenges.
- **Mammalian cell-cycle** [34] \((N = 20)\). It is a model explaining the mechanism of action of the cell cycle checkpoints in mammalian cells.
- **Cardiac development** [35] \((N = 15)\). It is a model referring to how the first heart field (FHF) and second heart field (SHF) are formed by differential expression of transcription and signaling factors during cardiac developmental processes.
- **Metabolic interactions in the gut microbiome** [36] \((N = 12)\). It is a model describing interactive host-microbiota metabolic processes.
- **Death receptor signaling** [37] \((N = 28)\). It is a model related to the activation of death receptors (TNFR and Fas) that determine either survival or cell death.
- **Arabidopsis thaliana cell-cycle** [38] \((N = 14)\). It is a model explaining the mechanism of plant cell-cycle and cell differentiation in \(A.\ thaliana\).
- **Tumor cell invasion and migration** [39] \((N = 32)\). It is a model representing the mechanism and interplays between pathways that are involved in the process of metastasis.

For each network, we randomly chose 1000 different initial states and then investigated their state transitions until \(T = 200\). Changing \(X\) and \(O\), we computed antifragility. Specifications of parameters for the simulation follows Table 1. Our simulator for antifragility was implemented in Python\(^1\).

| Figure | \(N\) | \(T\) | \(X\) | \(O\) | # of different networks | # of initial states |
|--------|-------|-------|-------|-------|------------------------|-------------------|
| 2(a)   | 100   | 200   | 1..50 | 1     | 50                     | 10                |
| 2(b)   | 100   | 200   | 40    | 1..50 | 50                     | 10                |
| 3(a)   | 100   | 2000  | 0     | 0     | 1000                   | 1                 |
| 3(b)   | 100   | 200   | 1..50 | 1     | 50                     | 10                |
| 3(c)   | 100   | 200   | 1..50 | 1     | 50                     | 10                |
| 4      | \(N\) | 200   | 1..N  | 1     | 1                      | 1000              |
| 5      | 100   | 200   | 1..100| 1..30 | 50                     | 10                |
| 6      | \(N\) | 200   | 1..N  | 1..20 | 1                      | 5000              |

\(^1\) The source code is available at https://github.com/Okarim1/RBN.git

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Results and Discussion

Antifragility in RBNs

Figure 2 shows average fragility of ordered \((K = 1)\), critical \((K = 2)\), and chaotic RBNs \((K = 3, 4, 5)\) depending on perturbed node size \(X\) and perturbation frequency \(O\). The ordered and critical RBNs had negative values (antifragility) in certain ranges of \(X\) and \(O\), while the chaotic RBNs all had zero or positive values in the given ranges. This means that the ordered and critical RBNs can be antifragile if they have the “right” amount of perturbations. However, chaotic RBNs are just robust or fragile against perturbations.

As shown in Figure 2(a), the ordered and critical RBNs became gradually antifragile as \(X\) increased but their antifragility decreased beyond certain \(X\) values, and even the critical RBNs changed from antifragile to fragile \((X>20)\). From this, we found that neither too large nor too small, but a moderate level of perturbations can induce more antifragility. These dynamics are similar to the slower-is-faster effect, where a moderate individual efficiency leads to a better systemic performance [40].

![Average Fragility of ordered, critical, chaotic RBNs depending on X and O.](image)

Meanwhile, in Figure 2(b), antifragility of the ordered and critical RBNs decreased overall as \(O\) grew (i.e., the period of adding perturbations became longer and longer). Furthermore, all the RBNs were robust in the case of that the perturbations were not added frequently although the perturbed nodes were 40 \((X = 40)\). From these results, we found that the more frequently perturbations are added, the more antifragile a system is, particularly for the ordered RBNs. Moreover, how often perturbations are added has a greater effect on antifragility than how many nodes are perturbed. Thus, it is essential that moderate perturbations are added frequently in order to obtain maximal antifragility.

Based on Figure 2, we are able to see that the ordered RBNs are the most antifragile. Figure 3 clearly accounts for the reason. In Figure 3(a), the complexity before adding perturbations was lowest at \(K = 1\). However, as shown in Figure 3(b), the complexity after adding perturbations increased most greatly and the value was also largest except for the early range of \(X\) at \(K = 1\). Therefore, the difference was largest at \(K = 1\) (Figure 3(c)), which led the ordered RBNs to be most antifragile.
Our result for complexity before perturbations is the same as previous studies showing that critical RBNs have the most appropriate balance between regularity and change [29, 30, 41]. In Figure 3(a), for low $K$, the complexity was low, which represents that the ordered RBNs have high robustness and few changes. That is, there is few or no information emerging. For high $K$, the complexity was also low, which reflects that the chaotic RBNs have high variability and many changes. Almost all the nodes carry novel emergent information. For medium connectivities ($2 < K < 3$), there was a balance between regularity and change, leading to a high complexity. This is consistent with the dynamics of critical RBNs, where criticality is found theoretically at $K = 2$ (when $N \rightarrow \infty$) and for finite systems at $2 < K < 3$ [30] due to a finite-size effect.

However, the result is changed by adding perturbations. In Figure 3(b), the ordered RBNs had the biggest complexity excluding the early range of $X$, which means that the ordered RBNs show the most efficient transition of information with optimal balance between regularity and change in the presence of noise. This illustrates that systems can exhibit different properties in accordance with the presence of external stressors. Such phenomenon was recently observed in a neural network as well [42]. The onset of chaotic activity occurs at different transition thresholds depending on the presence of time-varying inputs.

![Figure 3: Initial and final complexity for $K = 1, 2, 3, 4, 5$ with $N = 100$. The error bars represent the standard error of measurements for 50 different networks at 10 different initial states run by 200 steps. (a) Complexity before adding perturbations. (b) Complexity after adding perturbations. (c) Difference of complexity before and after perturbations.](image)

**Antifragility in Biological BNs**

Boolean networks have been extensively used as models of genetic or cellular regulation in the fields of computational and systems biology [33-39], because they can capture interesting features of biological systems despite their simplicity. Using seven biological Boolean network models, we measured the (anti)fragility of biological systems.

We first consider a volatile environment where perturbations are added every time step ($O = 1$). Figure 4 shows that for this high level of noise, the network of *A. thaliana* cell-cycle is fragile, the networks of death receptor signaling and tumor cell invasion and migration are robust in a certain range of $X$ and fragile in the rest of the range, and the networks of CD4+ T cell differentiation and plasticity, mammalian cell-cycle, cardiac development, and metabolic interactions in the gut microbiome are antifragile against perturbations. When comparing with Figure 2(a), we found that antifragility of the biological networks except for *A. thaliana* cell-cycle is similar to that of ordered or critical RBNs.
Figure 4: Fragility of biological Boolean networks. The error bars represent the standard error of measurements for 1000 different initial states run by 200 steps.

Figure 5: Probability of generating antifragile networks depending on $X$ and $O$ for ordered, critical, chaotic RBNs with $N = 100$, $T = 200$, $p = 0.5$. 50 different networks were used. 10 different initial states were randomly chosen for each network. (a) $K = 1$. (b) $K = 2$. (c) $K = 3$. (d) $K = 4$.

To obtain more generalized dynamics, we investigated the probability of generating antifragile networks in a diverse range of $X$ and $O$. Figure 5 is a heat map showing the probability for RBNs. As shown in the figure, the ordered and critical RBNs can produce antifragile networks. However, if too large perturbations are added in a volatile environment (i.e., $O = 1$), both of them do not exhibit antifragile dynamics. In the case of the chaotic RBNs, they cannot produce antifragile networks in any range of $X$ and $O$.

Figure 6 is a heat map for the seven BNs. They all show antifragile dynamics like the ordered or critical RBNs. Among the heat maps, the most interesting networks are *A. thaliana cell-cycle* and *CD4+ T cell differentiation and plasticity*. We found that *A. thaliana cell-cycle*
repeatedly produces antifragile networks at regular intervals depending on the values of \( O \). Based on many studies demonstrating living organisms are ordered or critical \([43-46]\), we can infer that \( A. thaliana \) might have been evolved in the environments where perturbations with \( X \) and \( O \) generating antifragile networks are added. We also found that \( CD4^+ T \text{ cell differentiation and plasticity} \) is the most antifragile of the ones studied, probably because it has the most variable environment. It indicates that our antifragility measure successfully captures the property of the immune system mentioned as a representative example of antifragile systems.

**Conclusions**

In this study, we proposed a new measure of (anti)fragility and applied to RBNs. We found that ordered and critical RBNs show antifragile dynamics, and especially ordered RBNs are most antifragile. Also, biological systems show antifragile dynamics. It might be that antifragility characterizes better the properties of biological systems compared to criticality.

In addition to the findings, we gained a meaningful insight to external stressors. Firstly, systems can exhibit different properties in accordance with the presence of perturbations. Secondly, systems show fragile, robust or antifragile dynamics depending on the degree of perturbations, and furthermore maximum antifragility can be obtained by a moderate level of perturbations added very frequently. One result of our antifragility study is that its “optimal” value depends on the precise variability of the environment. How can systems be antifragile or robust for varying levels of noise? Which mechanisms can be used to adjust the internal variability depending on the external variability? These questions demand further studies, but possible answers are already being explored based on the results presented here.

Based on the findings and insight, by adjusting the size and frequency of perturbations, we can control system properties from fragile through robust to antifragile dynamics. It may help to understand dynamical behaviors of biological systems depending on environmental conditions and develop new treatment strategies for various diseases including cancer or AIDS, *e.g.* how can we decrease the antifragility of cancer cells or pathogens? This should reduce their adaptability and potentially improve treatments.

Here we focused on antifragility of RBNs at single cell level. For further study, we plan to measure antifragility of our multilayer gene regulatory network (GRN) model \([47]\). Our multilayer GRN model consists of an intercellular layer and an intracellular layer. A network in an intercellular layer represents interactions between cells, and a network in an intracellular layer indicates interactions between genes. All the cells have identical RBNs as intracellular GRNs. We will investigate antifragility of the multilayer GRNs, and check if there are differences between the antifragile dynamics at a single cell and multicellular level.
Figure 6: Probability of generating antifragile networks depending on $X$ and $O$ for different biological Boolean networks with $T = 200$. 5000 different initial states were used for each network. (a) CD4+ T cell differentiation and plasticity. (b) Mammalian cell-cycle. (c) Cardiac development. (d) Metabolic interactions in the gut microbiome. (e) Death receptor signaling. (f) A. thaliana cell-cycle. (g) Tumor cell invasion and migration.

**Data Availability**

Our simulator and data are available at [https://github.com/Okarim1/RBN.git](https://github.com/Okarim1/RBN.git).

**Conflicts of Interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

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