Construction of an Effectiveness Network to Identify Dynamical Interaction of Genes

Maulida Mazaya, Yung-Keun Kwon*
*Dept. of Computer Engineering, University of Ulsan
School of Computer Engineering and Information Technology,
University of Ulsan, 93 Daehak-ro Nam-gu, Ulsan 680-749, Korea

Abstract

Interactions between genes have long been recognized and studied by many researchers, and they formed a large-scale interaction networks. In systems biology, it has been a challenge to investigate the factors to determine network dynamics. Here, we create a new network called an effectiveness network by calculating thy dynamical effectiveness from a node to another node. We found that robust nodes tend to have smaller number of edges than non-robust nodes. This implies that hub nodes are likely to affect the network robustness.

Keywords: effectiveness, gene-gene interaction, robustness, topological network

1. Introduction

Genes' interaction is critical to decide the network dynamics. In perspective on gene interactions, it is important to understand the network structure and the function of genetic pathways because they become essential evolution in genetic systems [1]. Some studies have found the relation of gene-gene interaction with human signaling network, metabolic, disease, and others. The influence of gene-gene interaction also called epistasis [1] or influence of a gene on another gene [2]. Knowing that effects of a gene to other genes, it will help us to know dynamical properties in networks like modularity, robustness, and so on. In reality, gene-gene interaction is more complex than the expectation.

There have been some papers to compute gene-gene interaction by their own method. In modular epistasis [3], they used Prism algorithm to calculate the similarity between interacting genes. In an inference model [2], they used knock-down framework targeting a collection of genes in a network pathways. Moreover, in previous a research [4], genes interaction is used to calculate the effect of feedback loops on disease comorbidity. There can be another interesting parts of gene-gene interaction, one of them is the topology relation.

In this work, we create a new network called an effectiveness network. By using Random Boolean Networks (RBN), we compute effectiveness to represent the quantity of the reciprocal influence of a gene to another gene in terms of the network dynamic. We prove that a node or gene can be very robust if there is no outgoing relation. All simulations are conducted based on PANET [5].

2. Method

To prove our finding, we modified the previous algorithm [4] about mutual-effectiveness in Random Boolean Networks for a pair of genes (nodes) that can be shown on Figure1.

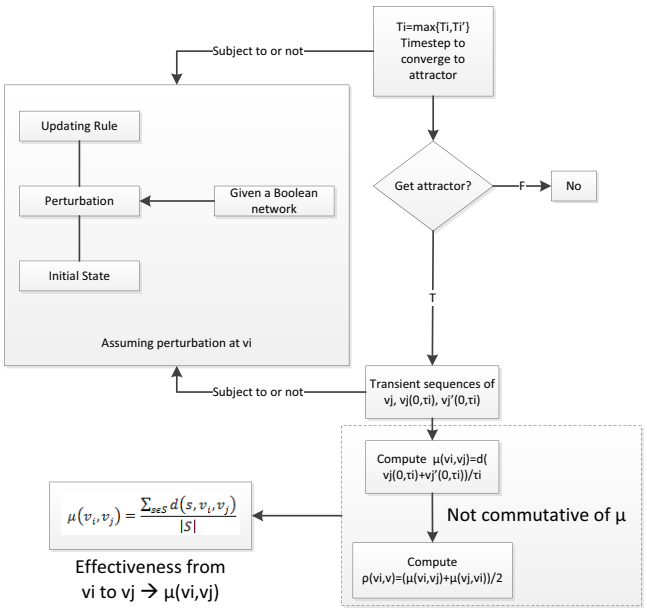

Figure1. Modification of Mutual Effectiveness algorithm**.** Dashed lines represent algorithm modification. Given a random boolean network initialized with $v_1, v_2 \ldots v_n$, the initial-state included at node v_i. The algorithm assumes a perturbation at v_i then define effectiveness on node v_j.

Here, we modified the algorithm by cutting the mutual effectiveness ρ. So we just use the effectiveness μ that represents how largely the trajectory with respect to node v_j was affected by node v_i and compute for all pairs of gene by getting random states from PANET. But, we need to get the result from PANET first like attractor of current and random state and all possible random states in order to compute effectiveness.

Our new method of effectiveness μ can be shown as follows:

$$\mu(v_i, v_j) = \frac{\sum_{s\in S} d(s, v_i, v_j)}{|S|}$$

where v_i is the source node, v_j is the target node. We calculate the summation of distance d (the number of bits

having different values) for each states s dividing by number of random states $|S|$. Trivially, should be in range between 0 and 1. If $\mu = 0$, it means no outgoing link but possible incoming link, so that the node was robust. Figure2 shows an example of effectiveness calculation.

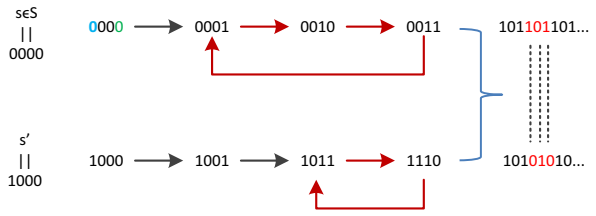

Figure 2 Example of Effectiveness calculation**.** Assume that node perturb v_i in first node (blue) and change v_j in fourth node (green) with starting array is 0. The first line explains the current state distance by calculating attractor (shown by dark red arrows) from right to left with result 101101...; second line explains the random state while the attractor result is 101010… that mean it has three differences (shown by dashed line) from six long array(red).

In Figure2, we got $d(s, v_0, v_3) = \frac{3}{6} = 0.5$ from one random state that compared with the current state. But, we need to compute a distance from all states then divide it with the number of random state to get effectiveness value (μ) as weighted value of network edges. Then, we visualize it by Cytoscape [6].

3. Result

We applied our method using random Boolean network and developed a program in Java for computing effectiveness. First, we tested with a random Boolean network that consists of 10 nodes and 15edges. As shown in Figure3, the result is same between the random Boolean network and effectiveness network. The difference is the interaction. We consider effectiveness value as a weight. So, the edges represent the interaction based on the weight. On Figure4, we tested the real network in yeast cell cycle network (YCCN) with the number of node is same as original network.

On RBN, the lowest effectiveness μ is 0.02173913 and on YCCN μ is 0.0. The lowest μ represents small outgoing link but still possible with incoming edges. If μ=0, it means that the node is very robust in node v_i that assume to be perturb.

The amount of edge colors depends on the number of effectiveness value for each node. It seems to be interesting because effectiveness value both pairs are same. For instance, the effectiveness value for node pair node 0 to node 1 is same with effectiveness value for vice versa. As we can see both on Figure3 and Figure4, each nodes at least has two outgoing link and also effectiveness value will be the same for some relation, though it comes from different source node. Effectiveness value to target node has the same value as shown on Table1.

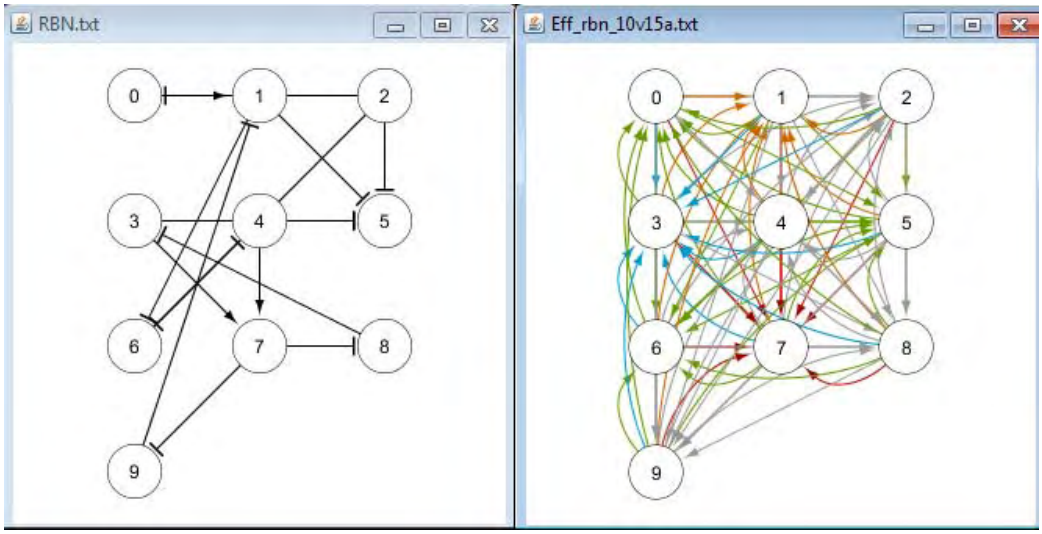

Figure 3. Network Visualization of Random Boolean Network (RBN-left) comparing with effectiveness network of RBN (right). It consists of 10 nodes and 15 edges. The visualization is same both left and right based on node id. In RBN, arrows and bar-headed lines represent positive and negative interactions, respectively, while no headed represents no interaction. On the other hand, the effectiveness network shows the relation between source node and target node. Different color edges represent effectiveness value and arrows represent target node.

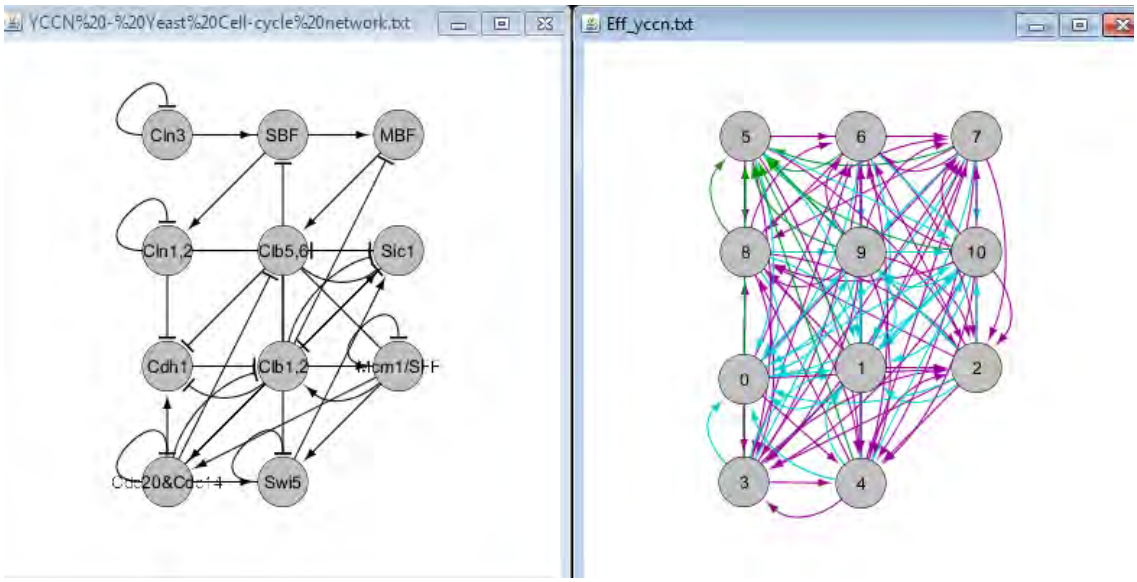

Figure 4. Network Visualization of Yeast Cell Cycle Network (YCCN) consists of 11 nodes and 34 edges. On the left is the original network of YCCN and on the right is the effectiveness network for YCCN. Based on Figure3 above, node that has shown is on the same position as original network. Different color edges represent effectiveness for pair of genes.

Table 1. Effectiveness Value
This table represents effectiveness value for one target node with different source node. Here the result of effectiveness value is same.

Source node	Effectiveness	Target node
0	0	1
2	0	1
3	0	1
4	0	1
5	0	1
6	0	1
7	0	1
8	0	1
9	0	1
10	0	1
1	0	0
2	0	0
3	0	0
4	0	0
0	0.04	2
1	0.04	2
3	0.04	2
4	0.04	2

With this result, we can say that target node with node id 1 and 0 are more robust than others because the effectiveness value is 0, while target node 2 has effectiveness value 0.04 for different source node. However, our effectiveness values used to be the interaction values on Cytoscape for accomplish visualization on Figure3 and Figure4.

4. Discussion

Inference or precedence effect on gene-gene interaction in a biological network has the potential to provide insight into mechanism of genetic phenomenon like metabolic, signaling network, health or disease. However, it has been a little bit difficult to apply in large network since we are not sure that all descendants should been affected. To prove that, we try from small experiment by implementing effectiveness algorithm and create new network called effectiveness network. The most important we used effectiveness value as weight of comparing network edges. From effectiveness network we can find out an interesting property there, such as number of outgoing and ingoing link, node robust based on effectiveness value and shown the same node position as original network. We are currently applying our method to real network not only yeast cycle cell network but also another. While waiting the result and try to implement with larger network based on RBN, we assume that there will be many characteristic of effectiveness network that we can find related with gene-gene interaction. We believe our finding will be helpful to know the interaction between genes and also how the topology of robust node that could be have effect to another node is. However, our validation has limit and imperfect, so that this is still small investigation about gene-gene interaction by creating effectiveness network.

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