

The effect of negative feedback loops on the dynamics of Boolean networks

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Introduction

An understanding of the organizing principles of biochemical networks, such as gene regulatory, metabolic, or intra-cellular signaling networks is a central concern of systems biology; in particular, the intricate interplay between network topology and resulting dynamics is crucial to our understanding of such networks. A topological feature of central interest is the existence of positive and negative feedback loops (see, e.g., [1, 3]). We focus here on Boolean network (BN) models, introduced originally in [2].

Goal

This work has as its goal a computational study of the effect of independent negative feedback loops on network dynamics, based on an appropriately defined measure of *distance to positive-feedback*. The notion of a positive-feedback network is related to the notion of a monotone network. We study the effect of PF distance on features of the network dynamics, namely the number and length of limit cycles. In [3] it was conjectured that “small distance to monotone” should correlate with more ordered behavior. Partial confirmation this conjecture was provided in [4].

Terminology

Definition. Let F be a Boolean network. Then

1. F is a *positive-feedback* network (PF) if it does not contain any odd parity directed cycles.
2. The *PF-distance* of F is the smallest number of edge signs that need to be changed to obtain a PF network. We denote this number by $|F|$.

The Experiment

For a random unsigned directed graph G on n nodes. Consider 10 Boolean networks chosen at random with G as their dependency graph. If G has m directed edges, then there are 2^m possible sign assignments.

1. For each one of the signed graphs, compute its PF-distance. Let $D > 0$ be less than or equal to the maximal PF-distance of G .
2. For $0 \leq d \leq D$, let G_d be a signed graph associated to G with distance d .
 - (a) For each one of the ten networks,
 - i. modify the network such that G_d is the signed dependency graph of that network.
 - ii. Compute the number and lengths of all limit cycles.
 - (b) Compute the average number N of limit cycles for the 10 Boolean networks as well as their average length L .
3. Compute the slopes s_N (resp. s_L) of the best fit-line of the N 's (resp. L 's).

We illustrate this process with an example in Figure 1.

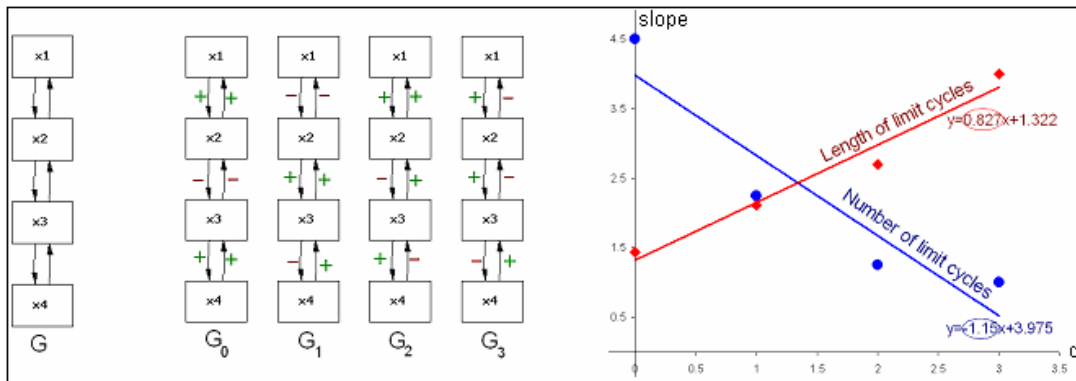


Figure 1. Random network (left), G_0, G_1, G_2, G_3 (middle), average length and number of cycles vs. d (right).

Results

We generated 40000 experiments. 99.99% (99.98%) of the experiments had positive (negative) slope for the average length (number) of limit cycles (Figure 2). This means that the length (number) of limit cycles increases (decreases) as PF-distance increases.

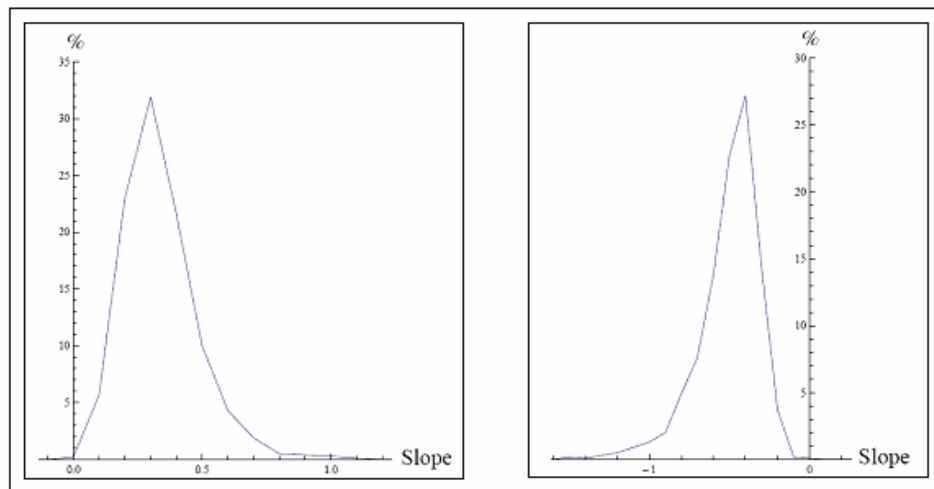


Figure 2. Histogram of the slopes for the average length (left) and number (right) of limit cycles.

Conclusion

The experiments show that, as the number of independent negative feedback loops increases, the number (length) of limit cycles tends to decrease (increase). These conclusions are consistent with the fact that certain natural biological networks exhibit generally regular behavior and have fewer negative feedback loops than randomized networks with the same numbers of nodes and connectivity.

References

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