

SYSTEMIC BIOLOGY

Barbara Remic, Metod Škarja, Igor Jerman
Institute Bion, Stegne 21, 1000 Ljubljana
barbara.remic@guest.arnes.si
<http://www.bion.si>

Abstract

Boolean networks with a variable number of inputs per element are very suitable for modeling the dynamics of biological systems. They offer an insight into mathematical laws that govern such complex systems and produce their collective behavior. Analysis of this kind of models will help us understand the spontaneous order in biological systems. In our study we analyzed the perturbations of attractors in the networks and the alterations of the state space that arise due to the changes in their connection matrices. Perturbations of attractors proved to be a very efficient method for exploring the state space of the networks. We introduced the notion of perturbational reciprocity between attractors and information it can give about the structure of the state space. The evaluation and possible applications of network model studies are also discussed.

1. INTRODUCTION

Systemic biology is an area of biology that deals with the system view of biological systems and is trying to understand their general characteristics and laws that govern them. Its methodology bases on the abstract models of complex systems. This kind of theoretical approach is a necessary complement to the present reductionistic paradigm and limited experimental methods. Very useful models are Boolean networks that are used for study of dynamic systems with a multitude of coupled variables.

A Boolean network is composed of N binary elements, connected with directed connections or inputs. Each element has randomly assigned a Boolean function, which determines the value of that element according to its input values. The number of inputs per element (K) is either constant or it varies (this is called a variable K). An element in variable K networks can have many inputs, a few of them or even none. Boolean networks with constant K are not as realistic as networks with variable K .

The connectivity and the Boolean functions are constant for a given network. The initial values of elements are selected at random and then computation of the network begins. During computation the values of elements are synchronously updated, according to the previous state of the network. The network follows a succession of discrete states, which is represented with a trajectory (a curve) in the state space. Eventually all trajectories run into attractors, which are the end-states of network's dynamics. They are either point attractors (static end-states) or cyclic attractors

(periodic end-states). All trajectories that run into the same attractor form a basin of attraction. The number of attractors, their length, their similarity, their basin size and the fraction of frozen elements can indicate the degree of order in the networks.

2. METHODS

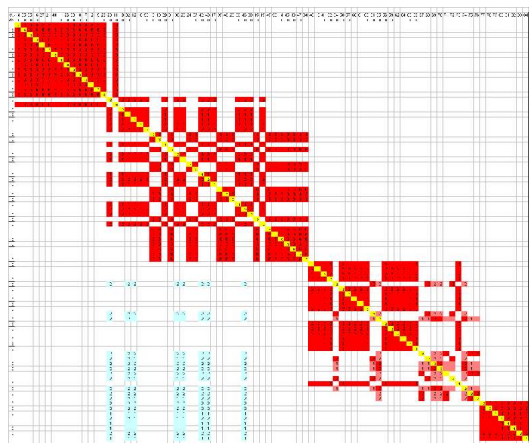
Most of our study is based on computer simulations in Excel. Our networks had 100 elements and 200 connections with a slightly modified binomial distribution. We computed the networks from a number of random initial states and found a certain number of attractors. A perturbation means switching the value of an element. We perturbed the already found attractors and varied the number of perturbed elements. With the perturbations of attractors we found new attractors. We perturbed these new attractors and sometimes found some new attractors again. We repeated the process, until we found no new attractors. We calculated the perturbational reciprocity of attractors over the diagonal. On the diagonal in the perturbation table are the frequencies of returning to itself for each attractor. Symmetrically to the diagonal are the pairs of attractors that fall into each other when perturbed. We compared the frequency of the n -th attractor falling into the m -th attractor and the frequency of the m -th attractor falling into the n -th attractor.

We were curious what alterations of the state space causes a small change in the matrix of connections, so we added an input to a no-input element in networks with one no-input element. The output for an added input was each element of the network, including the no-

input element itself (i.e. self-input). For each connection we applied both active Boolean functions ($0 \rightarrow 1$ and $1 \rightarrow 0$). We calculated the relative frequency of returning into the attractor from which the computation started, the summated relative frequency of old attractors (except the one we started from), the relative portion of new attractors and the summated relative frequency of new attractors.

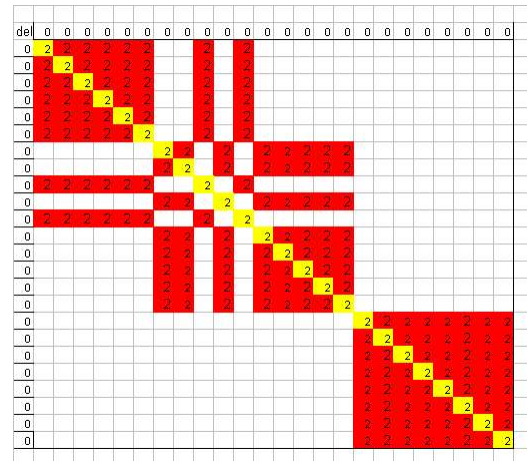
3. RESULTS

When we colored the cells in an attractor perturbation table according to their perturbational reciprocity, we got very interesting patterns. They became even more ordered, when we arranged attractors according to a decreasing size of their basins. The patterns show groups of attractors with a high perturbational reciprocity that are symmetrical over the diagonal. In other modes of perturbation that show no ordered patterns, the perturbational reciprocity is particularly high around the diagonal. It seems that only attractors with similar basin sizes transit reciprocally when perturbed, whereas attractors with different basin sizes do not. Very high perturbational reciprocity in a group of attractors could indicate their proximity and their interrelatedness in the state space.



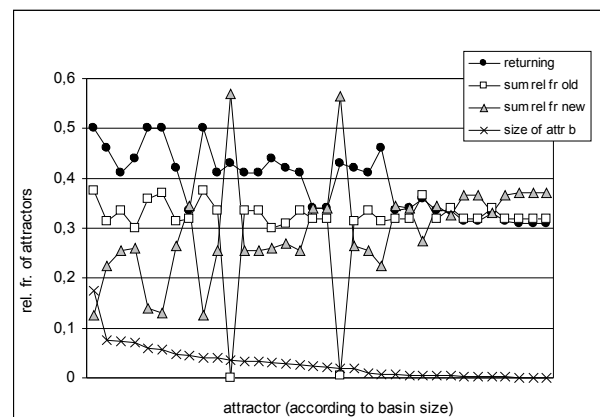
Picture 1: A perturbational table of a network, colored according to the

Perturbations of attractors is efficient complementary method to the random searching, because it sweeps the area around the perturbed attractor and find local small basin attractors. When we perturb these newly found attractors, we usually find some new attractors again. In this way we can find many



Picture 2: A perturbational table of a network, colored according to the perturbational reciprocity of attractors.

new orders of attractors. It seems that most of the small basin attractors form clusters that are not easily accessible from other attractors. The members of such cluster have also a very high perturbational reciprocity. With the perturbations of attractors, we can analyze the structure and complexity of the state space.



Picture 3: The alterations of the state space with the addition of an input. Returning – the relative frequency of the network, returning into the starting point attractor, sum rel fr old – summated relative frequency of old attractors (except returning), sum rel fr new – summated relative frequency of new attractors, size of attr b - size of the attractor basins.

With addition of an input the state space of the networks alters. The alterations are mostly small. The new attractors again turn up in groups. From an attractor we found a certain group of new attractors, but the same group could be found from different attractors. Occasionally there are some major alterations, when the starting-point attractor disappears or even all the old attractors disappear.

4 DISCUSSION AND CONCLUSIONS

Perturbation of attractors is a very efficient method for exploring the state space. Besides the number of attractors, it reveals their location and configuration in the state space and their interrelatedness. The perturbational reciprocity also shows the structure of the state space. The high reciprocity in a group of attractors means that attractor basins are close together and form a separated cluster, or that margins between their basins are lower than between the other attractors.

Addition of a single input alters the state space of the network. Alterations of the state space are mostly small, sizes of attractor basins change and new attractors appear. Occasionally large alterations appear. In this case an attractor or a group of attractors disappears. We cannot predict when the alteration of the state space will be small and when it will be large because there is no rule to that. A large alteration probably happens when the added connection strongly alters the dynamic structure of the network (the portion of frozen, mixed and active component).

The clusters of attractors observed in the perturbations of attractors and in the alterations of the state space could be parts of the same attractor that are separated in a discrete state space but would fuse together in a continuous state space.

5 SYSTEMIC BIOLOGY

Examples of the attractors in biological networks are for instance patterns of gene expression (that reflect in different types of cells and their different physiological states), or associations in succession of ecosystems. A perturbation of elements can divert the network into some other attractor. In genetic interpretation of the model the changes in the matrices are analogous to mutations. A mutation alters the state space of the network and newly formed attractors can be combinations of genes that are not found in normal tissues. The combinations can be anachronistic (the expression of fetal genes). The increased mutability of transformed cells constantly alters their state space, which highly improves their survival strategy.

Modern technologies that base on reductionistic ideas are less efficient than is expected. The problem lies in the fundamental

idea that a cell can be redirected in a desired direction simply by inhibition or activation of one gene or one protein. It is becoming clearer and clearer that it is not an individual element that matters, but the collective dynamics of the interaction network between all the elements. Development of efficient network models is going to be the fundament of systemic technologies, which will enable us to direct the collective dynamics of networks in desired directions. That would mean the control of gene networks, with all its therapeutical and biotechnological applications, the preservation and the restoration of ecosystems, artificial metabolic networks that will be an excellent tool for the discovering of the new therapeutic drugs and prediction of their effects.

Equally important as the development of network models are the researches of actual molecular networks in organisms and the systematization of these data into the databases. Network models will not be precise images of reality but only its abstract approximations that will enable us to predict the behavior of the systems efficiently enough. The models as complicated as real networks would be equally hard to analyze and would demand enormous capacities of computer processing (except if the parallel processing computers are a near future). Masaru Tomita, one of the pioneers in computer modeling of organisms says that computer simulation of an entire cell is one of the great challenges for the 21st century.

6. LITERATURE

Bagley R. J., Glass L. (1996): »Counting and Classifying Attractors in High Dynamical Systems«, J. Theor. Biol. 183, 269-284

Fox J. J., Hill C. C. (2001): »From topology to dynamics in biochemical networks«, Chaos 11, 809-815

Jeong H., Tombor B., Albert R., Oltvai Z. N., Barabasi A. L. (2000): »The large-scale organization of Metabolic Networks«, Nature 406, 651-654

Kauffman S. A. (1993): »Origins of Order: Self-Organization and Selection in Evolution«, Oxford, Oxford University Press

Kauffman S. A. (1996), At Home in the Universe: The Search for the Laws of Self-Organization and Complexity), Oxford, Oxford University Press

Kauffman S. A. (2000): »Investigations«, Oxford University Press, Inc.

Solé R. V., Goodwin B. (2000): »Signs of life«, Basic Books, Member of Perseus Books Group, New York

Szallasi Z. (1999): »Genetic network analysis in light of massively parallel biological data«, Pacif. Symp. on Biocomputing 4:5-16

Škarja M., Remic B., Jerman I. (2004): »Boolean networks with variable number of inputs«, Chaos, vol. 14, p. 205, Jun 2004

Tavazoie S. et al. (1999): »Systematic determination of genetic network architecture«, Nature Genetics 22, 281-285

Wolkenhauer O. (2002): »Mathematical modeling in the post-genome era: understanding genome expression and regulation – a system theoretic approach«, BioSystems 65, p. 1-18, Elsevier Science Ireland Ltd.