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Limit Cycles in Synchronous Boolean Networks

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Introduction

The study of biological systems such as protein-protein are on focus of many scientists who aim to model them by using Boolean modeling. A Boolean network is a qualitative representation of a biological system in which the elements are presented by nodes and the interactions between them are presented by links. The nodes of the network can take only two possible values determined by 1 (ON/Active) or 0 (OFF/Inactive). The future state of each node is determined by some logic functions applied on current states of the nodes. These logic functions, known as Boolean functions are expressed by logic operators such as AND, OR and NOT. Operator NOT is used when a node is regulated by an inhibitor. In this paper we use synchronous Boolean model to analyze the state of the negative feedback loop of S6K inhibition of mTORC1. Synchronous updating is a simple and an attractive way to find and analyze the fixed points of the system. We do such analysis for two different reduced networks derived from the real network in order to see the difference between the fixed points. We are interesting to find fixed points of both reduced networks by using BooleanNet and then analyzing the binary states by using Cytoscape. Considering all possible initial states both networks reach a cycle limit where all the states tend to go and then the system remains there during the whole time. Since we have a feedback loop we find that the system doesn't reach any fixed point but tend to go in a limit cycle, in both cases. If the system enter in this limit cycle it remains there forever, thus we focus more on the limit cycle than in other states of the system. This limit cycle can be described considering Markov chain in which the process starts in one of the cycle's state and move successively from one state to another with a probability p_{ij}, called transition probability.
Moreover, we see the dynamical behavior simulated by BooleSim starting from a state where all nodes are active (ON) and when all of them are inactive (OFF). In the first case we see is once more a cycle limit but in the second case, where the system start from an inactive state it reaches a fixed point after seven iterations. We do this for both reduced networks but we present here just the results of the network with five nodes as the conclusions are the same for both networks.

Network reductions

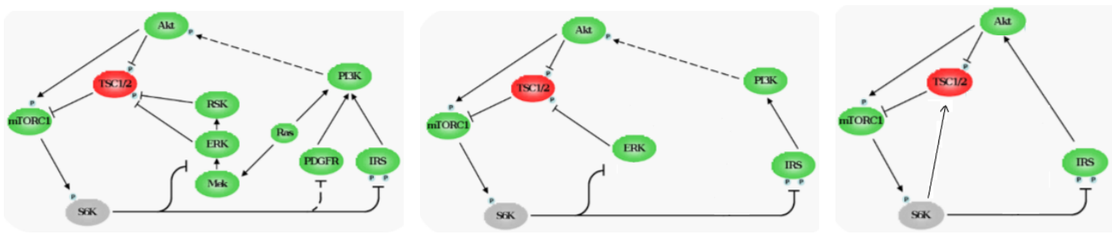

Figure 1: S6K inhibition of mTORC1. **(a)** The real network; **(b)** Network reduced into 7 nodes; **(c)** Network reduced into the 5 most important nodes.

According to Boolean algebra we can reduce the number of the nodes without loosing any important information. For each of these networks we build Boolean rules based on theoretical and/or experimental evidences which are given in Table 1.

Synchronous Boolean Network Analysis

Nodes	Boolean Rules
mTORC1	mTORC1* = Akt or (not TSC1/2)
Akt	Akt* = PI3K
TSC1/2	TSC1/2* = not Akt and (not ERK)
ERK	ERK* = not S6K
S6K	S6K* = mTORC1
PI3K	PI3K* = IRS
IRS	IRS* = not S6K

Nodes	Boolean Rules
mTORC1	mTORC1* = Akt or (not TSC1/2)
Akt	Akt* = IRS
TSC1/2	TSC1/2* = not Akt and S6K
S6K	S6K* = mTORC1
IRS	IRS* = not S6K

Table 1: Boolean Rules of both reduced networks given in Fig. 1

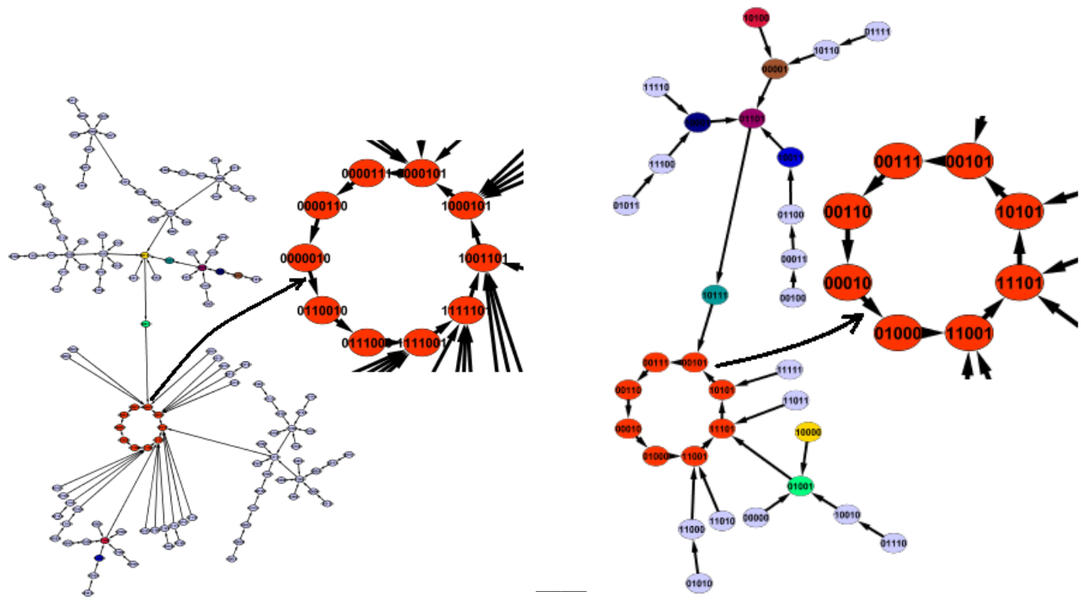

Figure 3: Synchronous Boolean Networks corresponding to Fig.1(b) and Fig. 1(c)

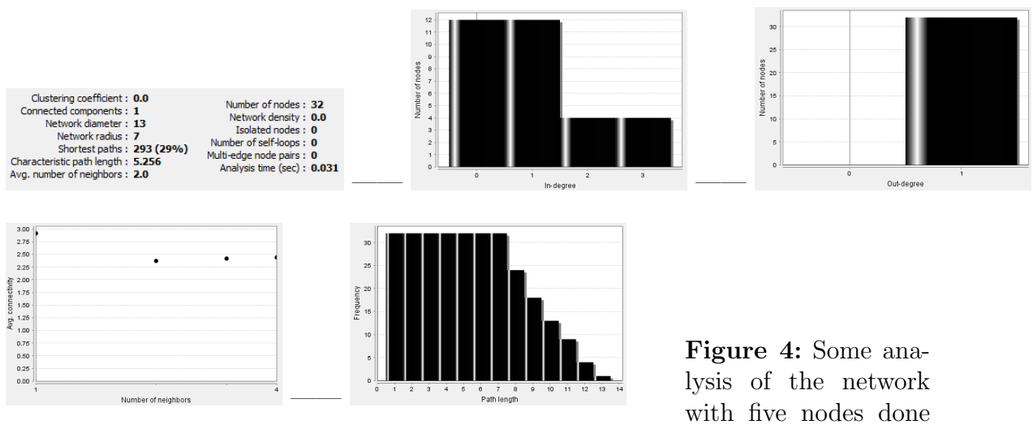

Figure 4: Some analysis of the network with five nodes done with Cytoscape

Cycle Limit State Transition

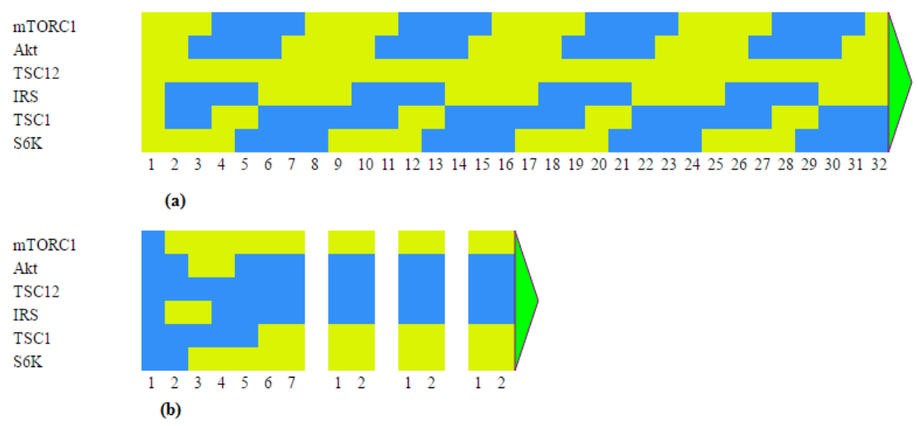

Figure 5: Protein expression pattern corresponding to the cycle limit composed by eight states. **(a)** The initial state is active and the evolution of the system happens in cycle; **(b)** The initial state is inactive and the system reaches a fixed point after seven iterations.

The transition matrix for the cycle limit with eight states is a Markov matrix. The transition probabilities take only two values, 0 or 1, because if the system find itself in one of the states then it has a probability of 1 to go to the successive state since the system moves in a circle. So that, If the system is in the state i then it moves to the state $i+1$ with a probability $p_{i,i+1} = 1$ with only one step. It can't move to the state $i+2$ directly; $p_{i,i+2} = 0$.

$$P = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \end{bmatrix}$$

The transition matrix of the cycle limit is an orthogonal matrix because it is a square matrix which satisfy $P * P^T = I$ and $det(P) = det(P^T)$

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Conclusions

We demonstrated that a feedback loop system tend to a cycle limit starting from any random initial state. We combine different software packages for dynamical simulations and the result was the same. After some iterations the system reach a cycle limit and never get out from there. When we study the evolution of the system starting from a single and fixed initial state the system repeats itself after a fix number of iterations when this initial state is active and the system reaches a fixed point after seven iterations when it is inactive. In this second case, we see that if the system starts moving from this fixed point, then it stops after two iterations because it doesn't reach any other new future state. We saw that the transition matrix is a Markov matrix and it satisfies some mathematical definition of the group theory, as well. In conclusion we must said that Boolean modeling is a proper way to describe and model a not very well known biological system. It is a better solution than quantitative models such as differential equations, especially when we don't have enough kinetic information of the system and other details which should take into account.

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