Hands-on tutorial on Boolean networks – Exercises

C. Müssel, L. Lausser, H. A. Kestler

<target gene 1>, <Boolean function>

Exercise 1: Network modeling

Create a model of the IGF pathway in the *BoolNet* CSV format from the following statements:

Target	Regulatory dependencies
IGF	IGF is considered as an input of the network.
IRS	IGF binds to its tyrosine kinase receptor on the cell membrane, the receptor sequesters IRS (insulin receptor substrate – via Grb and SOS, which are not included in the model). There is a negative feedback loop from S6K to IRS.
PI3K	IRS interacts with a regulatory domain of PI3K (Phosphoinositide 3 Kinase) and activates it. Rho forms an inhibitory feedback loop on PI3K (through ROCK and PTEN, which are not included in the model).
Akt	Akt is activated by PI3K. mTORC2 can also activate Akt independently (to enable intracellular glucose metabolism).
TSC2	Akt phosphorylates and inhibits TSC2 (Tuberous Sclerosis Factor 2), as does mTORC2.
mTORC1	TSC2 inhibits mTORC1 (mammalian Target of Rapamycin complex 1). Rac is needed for mTORC1 activation.
S6K	S6K is one of the substrates of (activated by) mTORC1.
mTORC2	Phosphorylation by PI3K as well as contact with Rac and TSC2 are needed for mTORC2 activation. It is unknown if all or just some factors are needed for activation. We therefore assume that the majority of these factors must be present. S6K inhibits mTORC2 through phosphorylation.
Rac	PI3K, mTORC2 and TSC2 are able to activate Rac (a small GTPase). Rho and Rac inhibit each other and cannot exist in the same compartment at the same time. We therefore require Rho to be absent in the majority of the last three time steps.
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Exercise 2: Network simulation

(a) Load the model into *BoolNet*, and visualize its connections.

(b) Simulate the model using 10 000 randomly generated initial states.

(c) Visualize the attractors of the model.

(d) Visualize the state transition graph.

(e) Specify a sequence of two initial states. Here, TSC2 should be active in both states, and IGF should be active in the second state. Visualize the state transitions from these initial states to the attractor.

Exercise 3: Robustness analysis

(a) Measure the robustness of the network by calculating the average normalized Hamming distance of the successor states of 10 000 randomly generated start states and their perturbed copies. Plot a histogram of the `$stat` component of the result object.

(b) Compare the robustness of your network model to 1000 randomly generated networks that consist of canalyzing functions. As a measure of robustness, use the test function `testTransitionRobustness` that measures the average normalized Hamming distance between the successor states of 500 randomly generated states and their perturbed copies.