

Methodology for Boolean Modeling of Biological Networks Applied to Systems Pharmacology

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OBJECTIVES

Dynamic models are increasingly crucial for understanding biological processes. They can be described using continuous dynamic approaches where the concentrations of the nodes are based on ordinary differential equations, or using discrete dynamic strategies, in which each node can be characterized by only a few discrete states. This project aims to provide an overview of the methodology to perform Boolean modeling (the simplest discrete dynamic modeling) in Systems Pharmacology, describing the required tools and steps for its implementation.

METHODS

Boolean network models are a way to represent biological systems in which the components of the system are represented by nodes and the interactions among them by edges. These causal relationships should be collected from relevant literature. Boolean networks only assumes two states for each component, **ON** or **OFF** (1 or 0). The state of each node is determined by its regulator nodes in the network based on Boolean Functions (BFs), which generally are a combination of **AND**, **OR** and **NOT** operations [1-3].

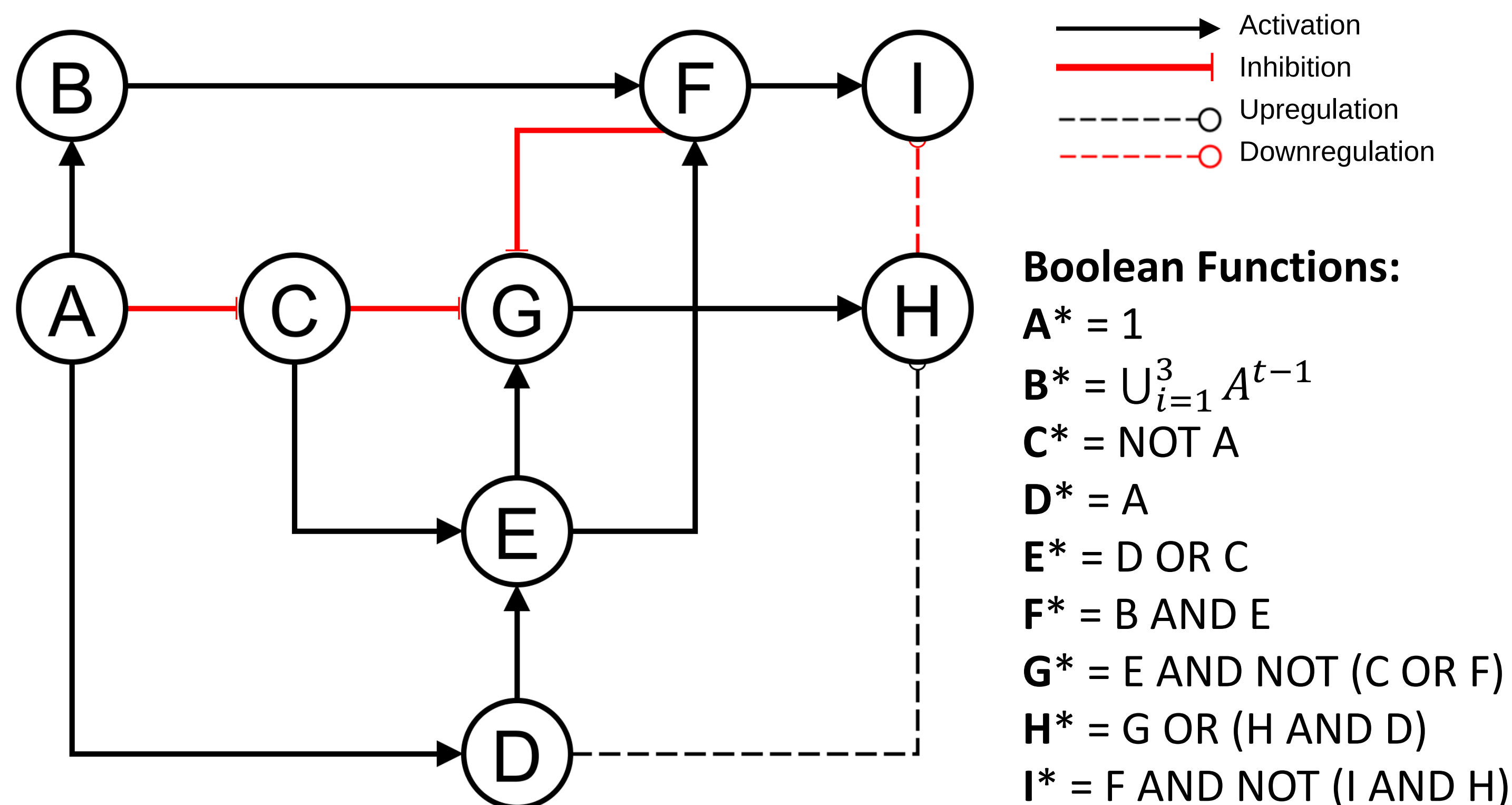


Figure 1. Hypothetical Boolean Network with 9 nodes and 14 interactions and the Boolean transfer functions governing the model. The state of a node in the Boolean functions is represented by the node name. The * denotes the future state of the labeled node. $\bigcup_{i=1}^{A_{max}} A^{t-1}$ notation means that B is active only if node A is activated for A_{max} time steps, in this case 3.

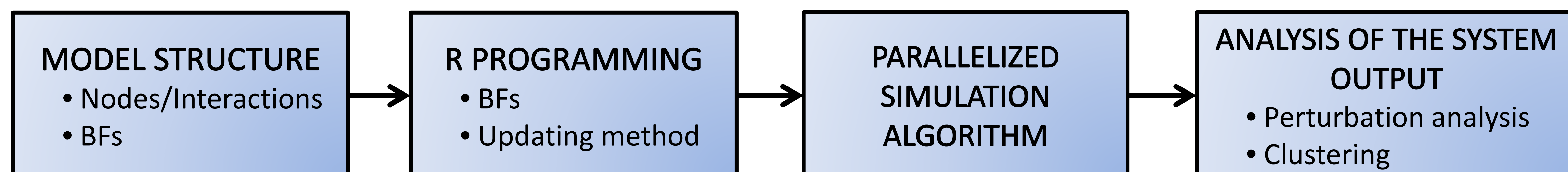
Time variable is considered to be discrete and is referred as time steps, specifying the time needed to update all nodes in the network.

The result of the simulations may differ depending on the random order of updating of the nodes [1-3]. This fact introduces variability to the model.

RESULTS

Our approach entails the following workflow:

FRAMEWORK: **A**uto **I**mmune **T**argeting **O**n **R**



In our models, a system perturbation analysis can be performed in order to see which node knockouts or persistent activations lead to significant changes of the network dynamics.

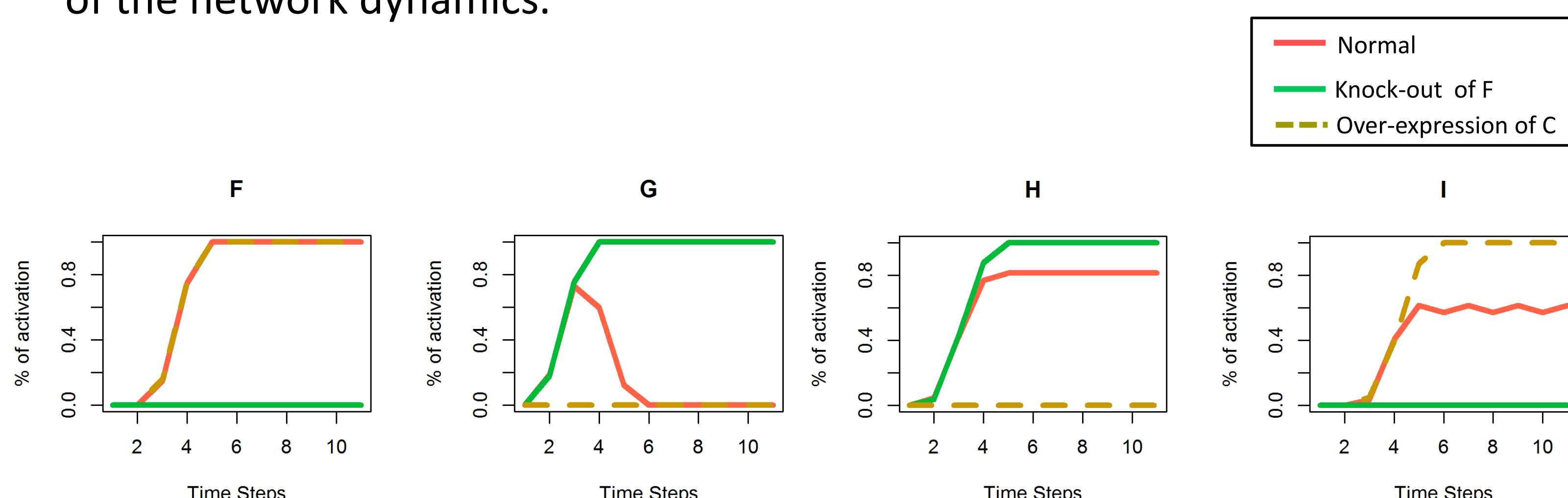


Figure 3. Different perturbations were introduced in the model (knock-out of node F and over-expression of node C) in order to see how the activation profiles of the nodes change.

CONCLUSIONS

Since Boolean models are parameter free, they serve as a starting point for modeling complex pharmacological systems for which a detailed kinetic characterization is not available [1,3]. Applying the proposed tools, simulations of the dynamics of a biological system can be performed, studying the effect of perturbations. The resulting models can be used to analyze signaling networks associated with diseases in order to predict the pathogenesis mechanisms and design potential therapeutic targets.

Implementation of this type of scheme involves running many simulations to obtain the semi-quantitative profile of activation for each node.

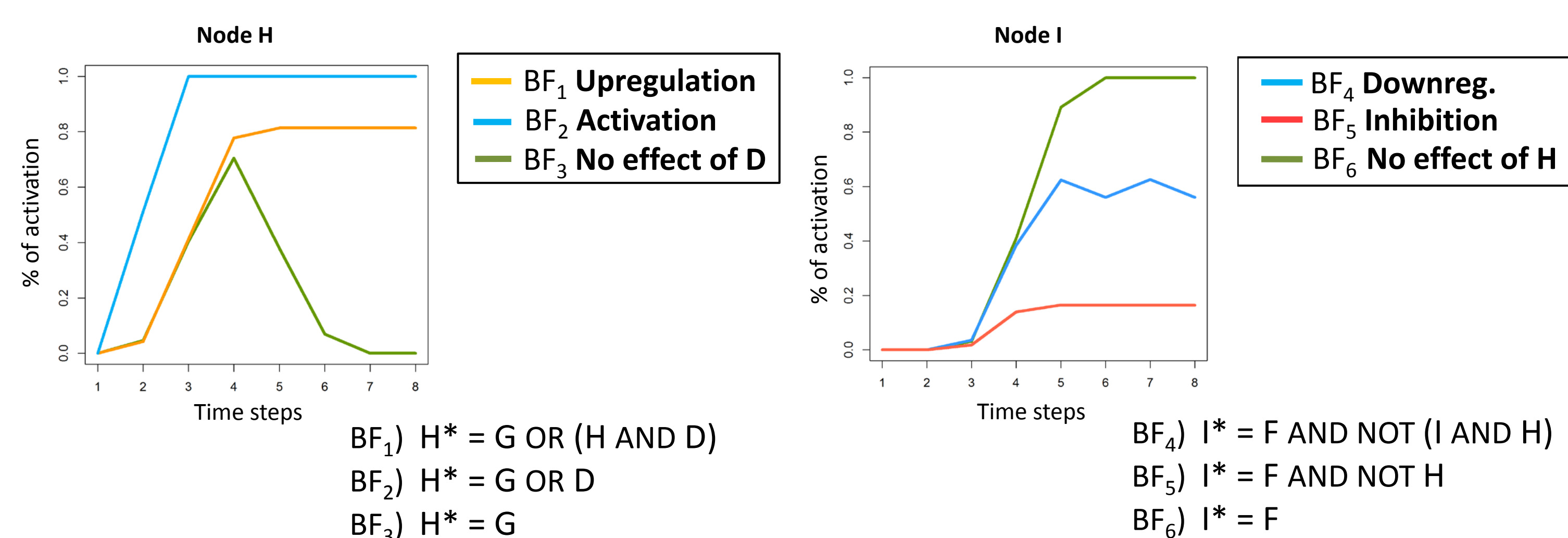


Figure 2. Activation profiles of node H and I with different BFs. The output of the nodes changes when we have an upregulation/downregulation function, a complete activation/inhibition or when the regulator node has no effect on the target node.

How too see the dynamic trajectory of the network in R:

update.m: This matrix shows which nodes has been updated at any time step.

Time steps		1	2	3	...	5	6	...	10
Nodes' states	A	1	1	1	...	1	0	...	0
	B	1	1	1	...	1	0	...	0
	C	1	1	1	...	1	0	...	0
	D	1	1	1	...	1	0	...	0
	E	1	1	1	...	1	0	...	0
	F	1	1	1	...	1	0	...	0
Initial conditions		1	1	1	...	1	0	...	0
Time step 5		1	1	1	...	1	0	...	0
Final state		1	1	1	...	1	0	...	0

pattern.m: This matrix shows the states of the nodes at any time step. It is used to know how the network evolves over time.

Time steps		1	2	3	...	5	6	...	10
Nodes' states	A	1	1	1	...	1	1	...	1
	B	0	0	0	...	1	0	...	0
	C	0	0	0	...	1	0	...	0
	D	0	1	1	...	0	0	...	0
	E	0	0	0	...	1	0	...	0
	F	0	0	0	...	1	0	...	0
Initial conditions		0	0	0	...	0	0	...	0
Time step 5		0	0	0	...	1	0	...	0
Final state		0	0	0	...	1	0	...	0

The Area Under the Curve (AUC) of the nodes usually changes when a single perturbation is introduced in the system.

$$\frac{AUC_{perturbation}}{AUC_{normal}} = \begin{cases} > 1.5 & \text{Upregulation} \\ \sim 1 & \text{No effect} \\ < 0.5 & \text{Downregulation} \end{cases}$$

We can cluster the perturbations that are causing similar effects on the model.

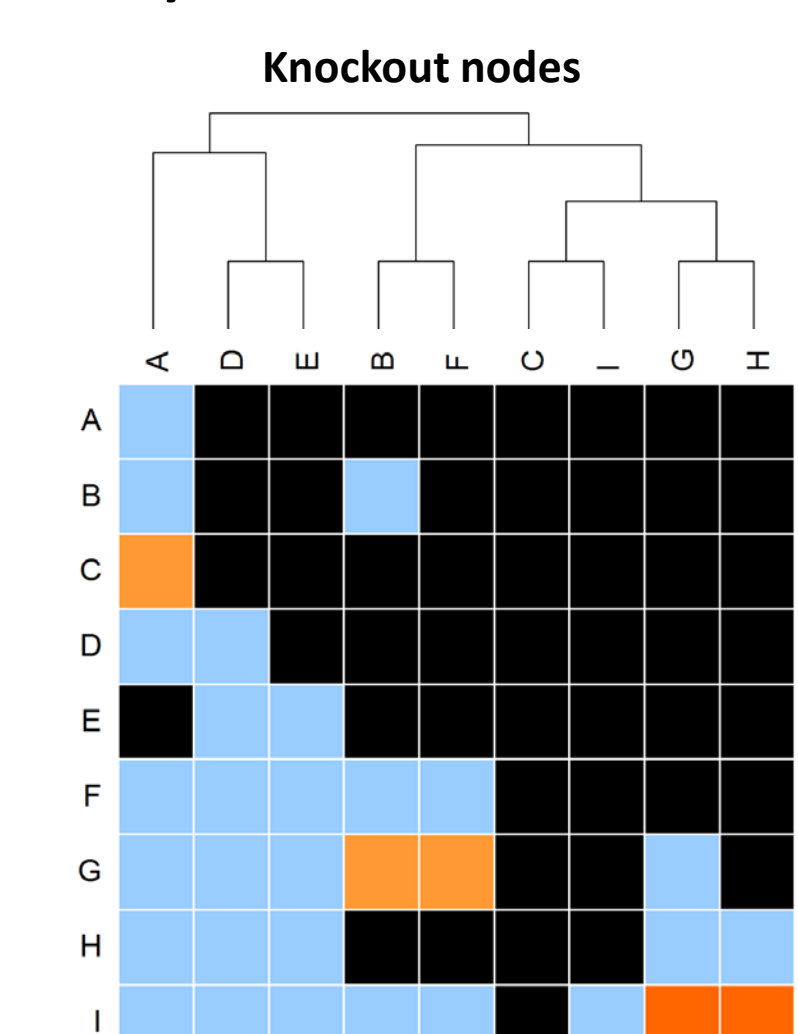


Figure 4. Hierarchical clustering and data matrix showing the effects of the knock-outs of the column nodes in the nodes of the network.

References

1. Saadatpour, A., et al. *Methods* (2013).
2. Thakar, J., et al. *PLoS Comput. Biol.* (2007).
3. Wynn M.L., et al. *Integrative Biology* (2012).