Attractor analysis of Boolean models for Systems Pharmacology Networks

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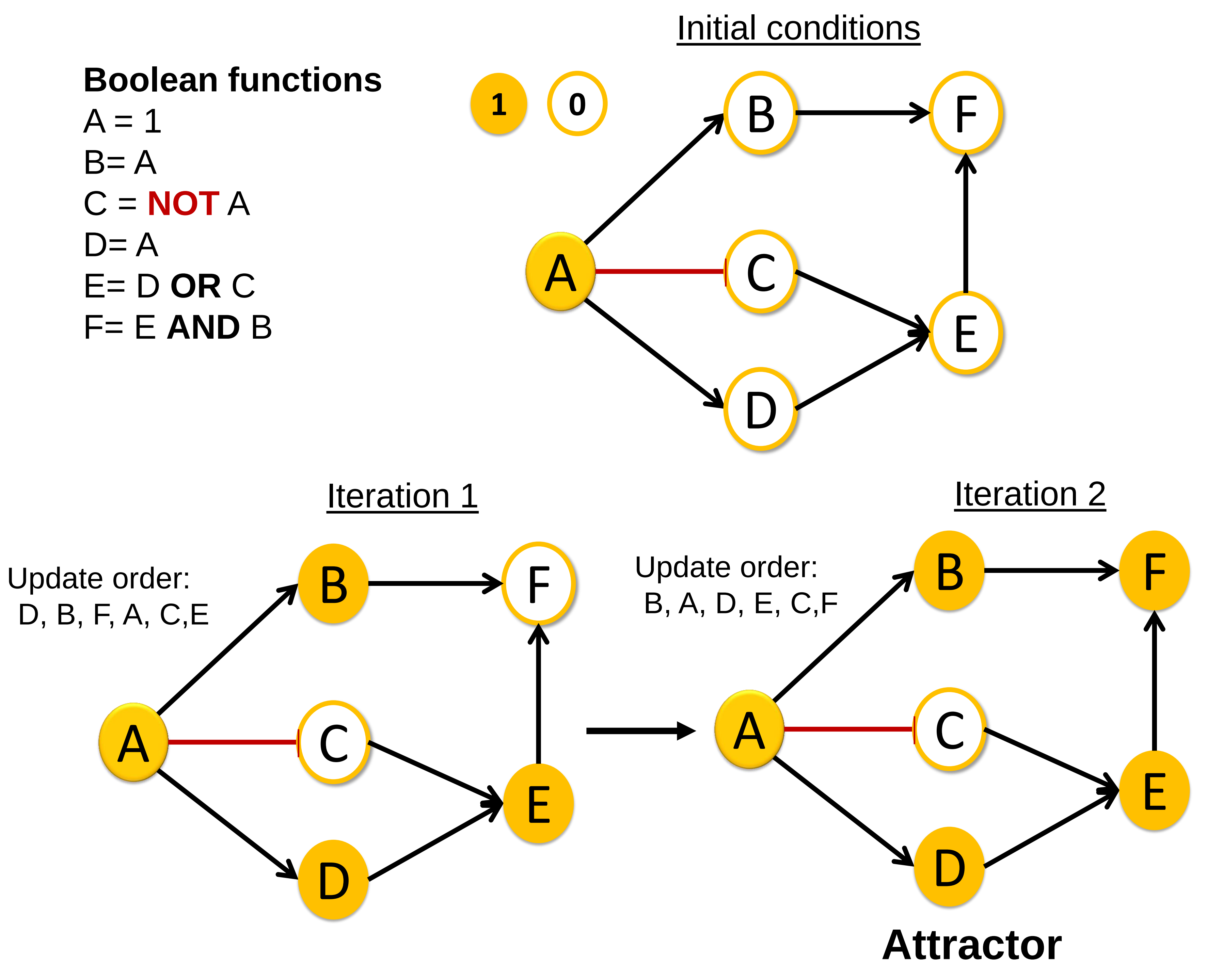
OBJECTIVES

Dynamic models can be described using continuous dynamic approaches where the concentrations of the nodes are based on ordinary differential equations, or using discrete dynamic strategies like Boolean network models, in which each node can be characterized by only two discrete states. This project aims to provide an easy-to-use and efficient methodology to perform attractor analysis on Boolean models of Systems Pharmacology networks, which is the most established method to evaluate the output of this type of models.

METHODS

Boolean network models are the simplest discrete dynamic models in which the components of a system are represented by nodes that assume two possible states, ON or OFF (1 or 0). The state of each node is determined by its regulator nodes in the network based on Boolean functions [1-3]. For any initial condition, Boolean models eventually evolve into a limited set of stable states known as attractors [2-3].



Boolean functions
A = 1
B= A
C = **NOT** A
D= A
E= D **OR** C
F= E **AND** B

Figure 1 . Attractors in Boolean networks . Example with 6 nodes and 7 regulatory edges.

Attractors in moderate size Boolean models are often linked to cellular steady states, cell cycles or to phenotypes.

Attractors fall into three groups:

1. Fixed-points: a single attractor state.
2. Limit cycles: set of states in which the system regularly oscillates.
3. Complex attractors: are set of states in which the system irregularly oscillates.

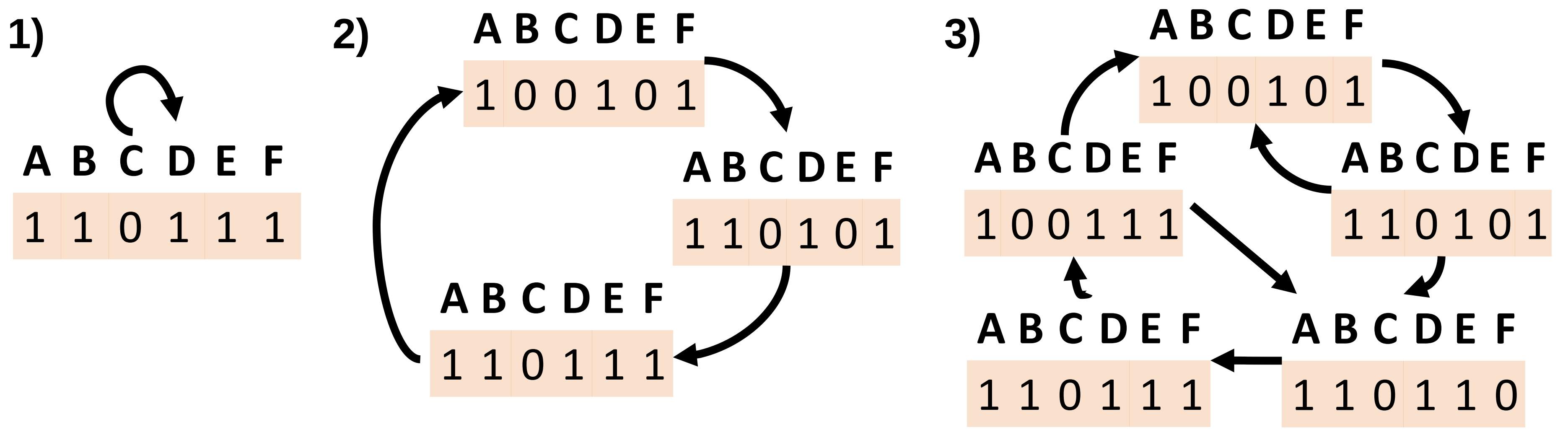
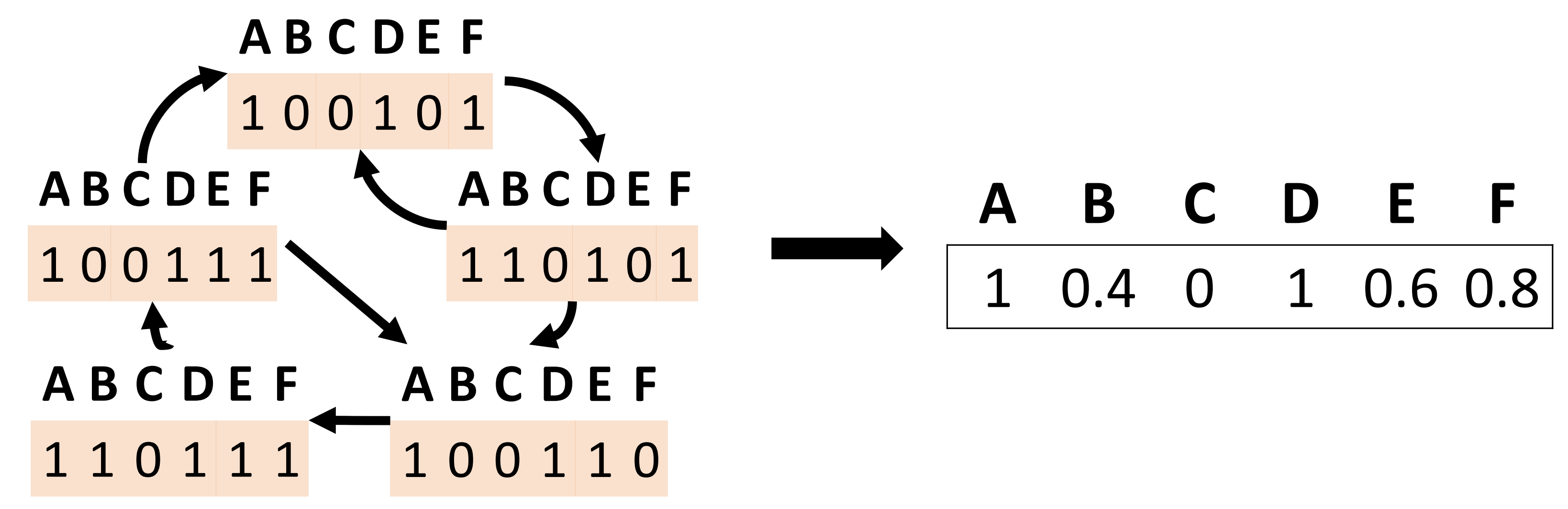


Figure 2. Different types of attractors in Boolean models.

Generally, large-scale or highly interconnected networks converge into complex attractors. In our models we generate the probability that a given node is in ON state inside the complex attractor in order to facilitate its interpretation.



A	B	C	D	E	F
1	0.4	0	1	0.6	0.8

Figure 3. Simpler representation of complex attractors in Boolean models.

RESULTS

In order to minimize the effort to implement Boolean models, run simulations and analyze the results, we developed an R framework called **SPIDDOR** (Systems Pharmacology for effIcient Drug Development On R).

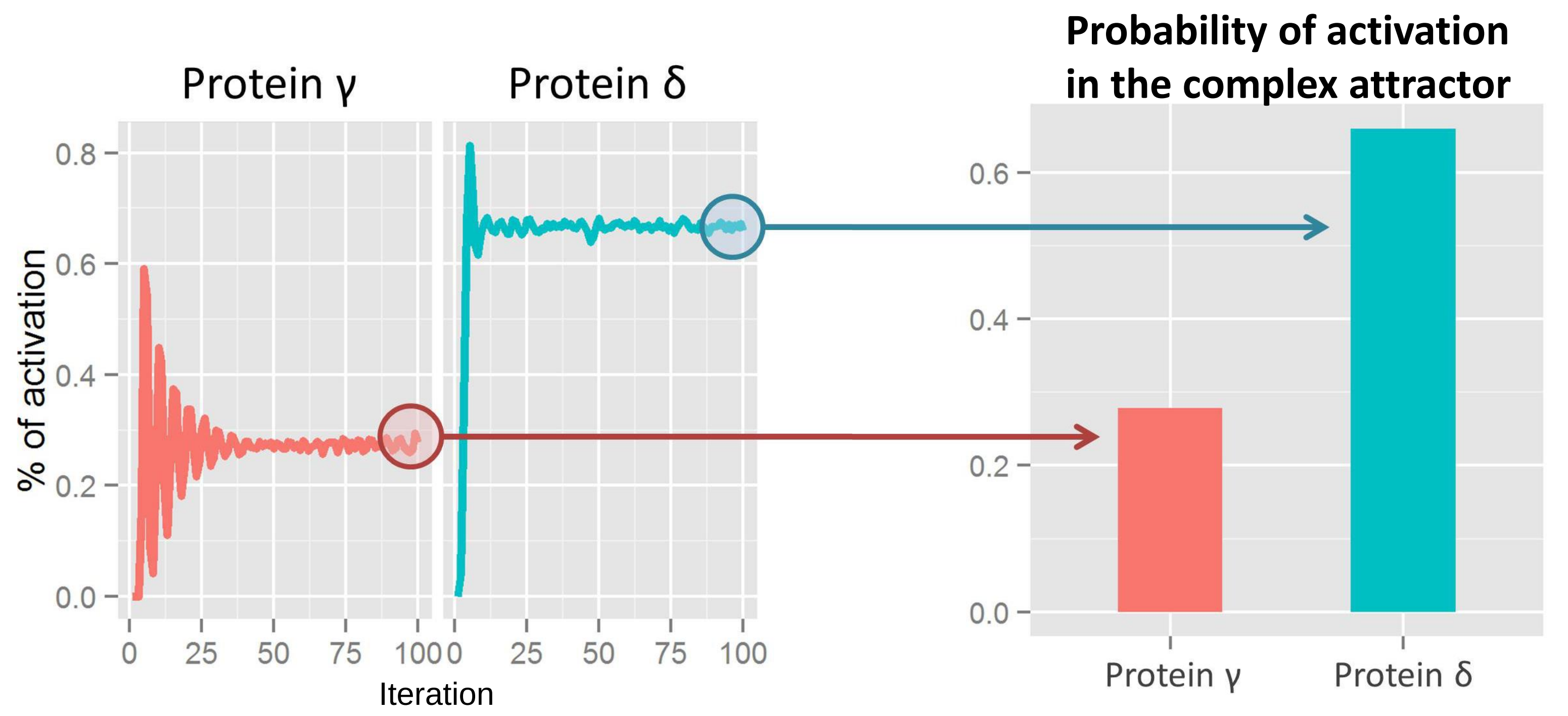


Figure 4. Graphical representation of nodes states in complex attractors. The probability of activation is a way to represent an attractor in Boolean models. Simulations of the network were performed with SPIDDOR framework.

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 attractors.

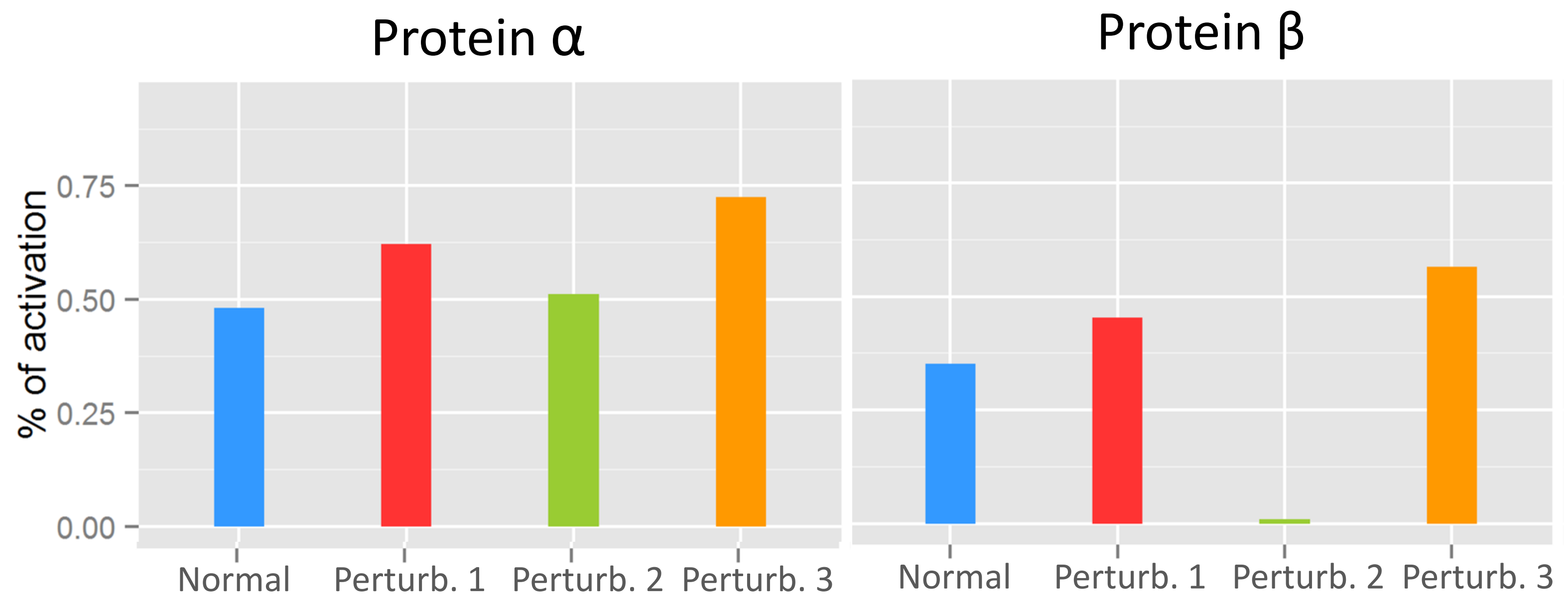


Figure 5. Different perturbations were introduced in the model (knock-outs and over-expressions) in order to see how the attractor states of the nodes change in terms of probability of activation.

$$\frac{Prob_{perturbation}}{Prob_{normal}} = \begin{cases} > 1.25 & \textbf{Higher activation} \\ \sim 1 & \textbf{No effect} \\ < 0.8 & \textbf{Lower activation} \end{cases}$$

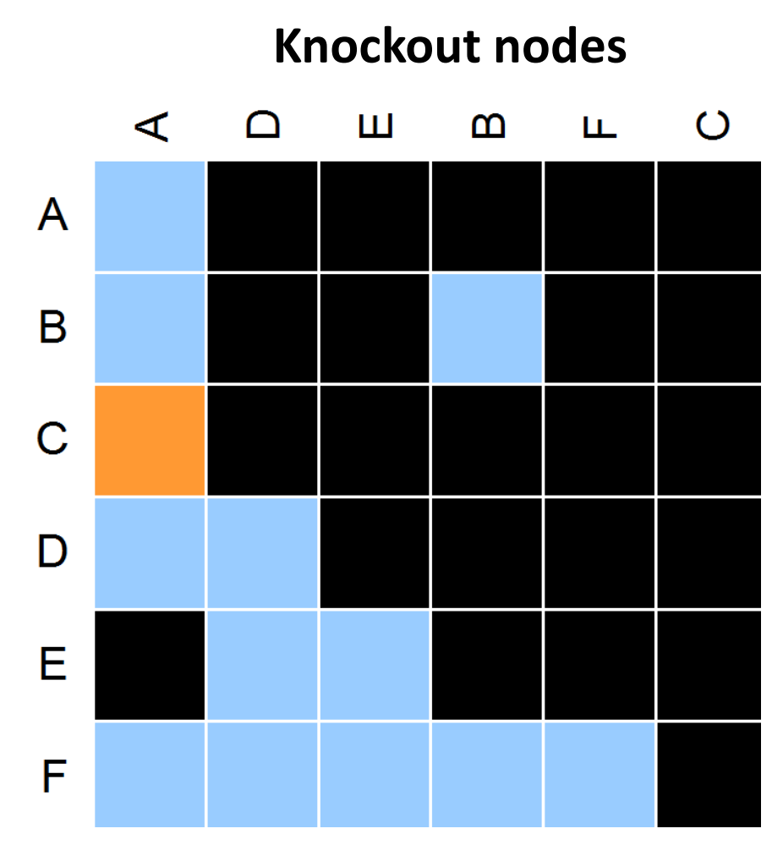


Figure 6. Coloured matrix showing the effects of the knock-outs of the column nodes in the nodes of the network.

CONCLUSIONS

With the tools explained in this methodology, the dynamics of a biological/pharmacological system can be simulated to identify its attractors and therefore understand how perturbations may alter its behavior. 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.

References

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3. Saadatpour, A., et al. *J. Theor. Biol.* (2010).

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