The influence of network topologies in drug treatments

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An accurate prediction of the outcome of a given drug treatment requires quantitative data of all parameters and concentrations involved as well as a detailed characterization of the network of interactions where the target molecule is embedded. This is especially relevant if nonlinearities and feedback interactions are involved in the signaling pathway.

Here we present a high-throughout *in silico* screening of all potential networks of three nodes to study the effect of the initial conditions of the network in the efficiency of drug treatment.

To characterize the effect of the network topology, we compare the dose-response curves of the same drug treatment starting from two different initial conditions in the activity of the network [see Fig. 1 (right)].

Our analysis reveals that the initial conditions affect the efficiency of the treatment in most network topologies of three nodes. This dependence is translated into modifications in the dose-response curves and changes in the *EC50* as well as in the overall effect of the inhibitor.

Moreover, we found network configurations that show a novel behavior characterized by the inversion of the steady states respect to the initial conditions. In some conditions, this "inverse bistability" of the target node can also result in "inverse hysteresis loops", where the reduction of the efficiency of the treatment also occurs when the concentration of inhibitor is varied gradually. An example of a network topology inducing inverse hysteresis and its corresponding dose-response curve is shown in Fig. 1.

Finally, our study shows that most of the topologies that present this inverse bistability and hysteresis behaviors contain core motifs of four links, composed by a positive feedback and a negative regulation. These results were represented in an atlas (Fig. 2) that correlates topologies by their architecture.

Our results illustrate how the dependence of the drug effect on the initial state of the network may be affecting the reproducibility of drug studies and clinical trials.

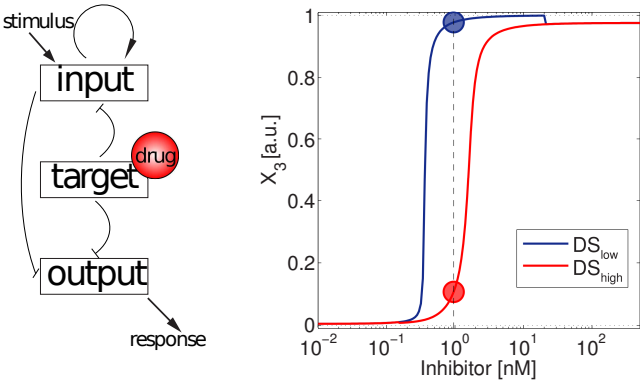

Fig. 1. (Left) Example of a network architecture that induces inverse hysteresis. (Right) Dose-response curves DS_{low} (blue) and DS_{high} (red) for initial conditions IC_{low} and IC_{high}, respectively.

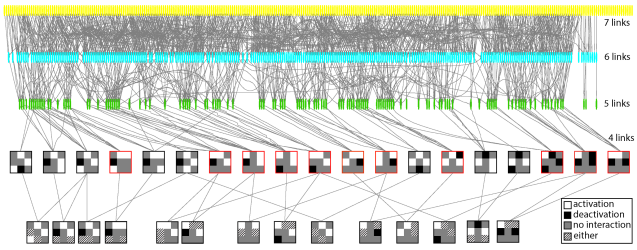

Fig. 2. Atlas for all network topologies that induce "inverse bistability" and "inverse hysteresis loops". Circles represent each of the topologies where our screening has shown inverse bistable response to drug treatment.