

Network reachability does not guarantee dynamic perturbation due to multiple positive feedbacks

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Introduction

We distinguish two types of node-to-node reachabilities in network, the *structural* and *dynamic reachability*, based on existence of pathway(s) between the nodes and the response of one node to perturbation in another node, respectively. An intuition is, there is no dynamic reachability without structural reachability. However, it is not intuitive to deduce the dynamic reachability from structural reachability. In this study we apply an *in silico* perturbation approach to investigate the relationship between the two reachabilities and the structural feature underlying the potential discrepancy.

Model and Analysis

A T helper (Th) cell differentiation network^[1] is redrawn to highlight the network backbone, and the feedback and feed-forward interactions (Fig 1A). Perturbations, namely knock-down or over-expression of a node (the *perturber*), at a homogenous and semi-active pre-steady state, are systematically simulated with the GNU Octave software (octave.org). We determined a dynamic reachability with a cutoff of ratio in the change of activity of the target (*perturbee*), and structural reachability is also assigned to each node pair (Fig 1B). Pathway-specific features (Fig 2A) and node-specific features (connection, closeness and feedback, not shown) are compared between dynamically reachable and unreachable (robust) node pairs with structural reachability. For dynamically unreachable edges, conditional perturbations, with feedback or feed-forward interactions blocked from full network or added to backbone network, are simulated to reveal the structural features underlying the robustness (Fig 2B).

Conclusions and discussions

Among the structurally reachable node pairs, less than half also show dynamic reachability. This ratio is slightly lower in the over-expression than the knock-out simulations (Fig 1B). The reachable group has lower shortest and average pathway length than the un-reachable group, but there is no difference in number of possible pathways (Fig 2A), node connections and number of feedback (not shown). Edges lacking dynamic reachability all point towards IFN-g (Fig 1A) and become reachable when the feedback interaction T-bet→IFN-g or STAT3-|IFN-g is blocked from the full network (Fig 2B). Addition of either of these feed-back interactions to the network backbone do not deprive but largely reduce the dynamic reachability of these edges (Fig 2B). The results from *in silico* modeling are in agreement with reported *in vivo* observations.

In conclusion, feedback loops could provide network robustness against perturbation, a mechanism possibly accounting for drug resistance of cancer cells^[2]. A challenge is to design multi-perturbations for both effective treatment and reverse engineering cell networks via perturbation.

Reference

Mendoza and Xenarios, 2006, Theor Biol Med Model, 3: 13.
Misra et al, 2005, J Biol Chem, 280: 20310.

Figure 1: The model and its robustness. (A) The cell differentiation network, modified from Mendoza and Xenarios, 2006. (B) Structural versus dynamical reachability.

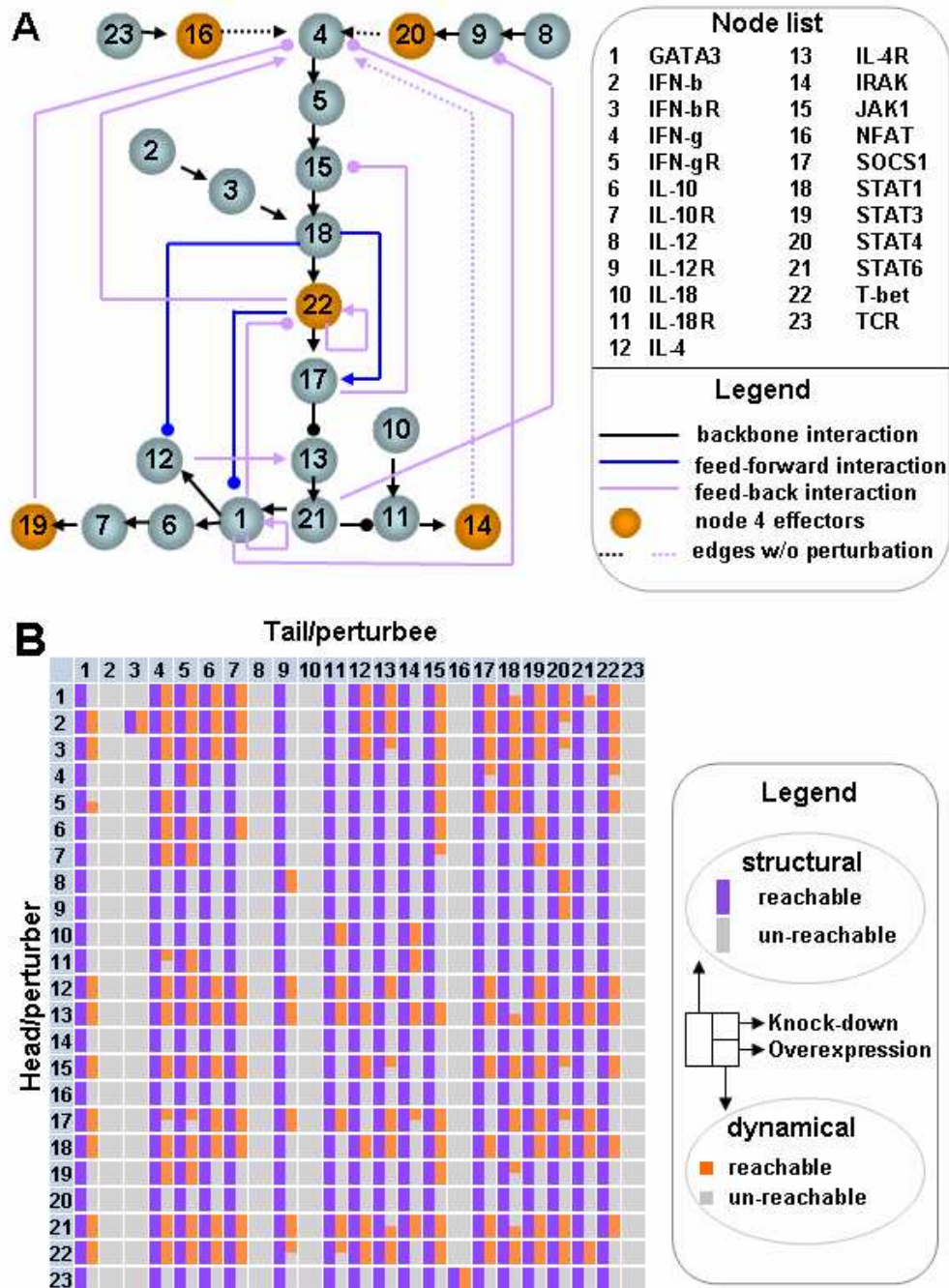
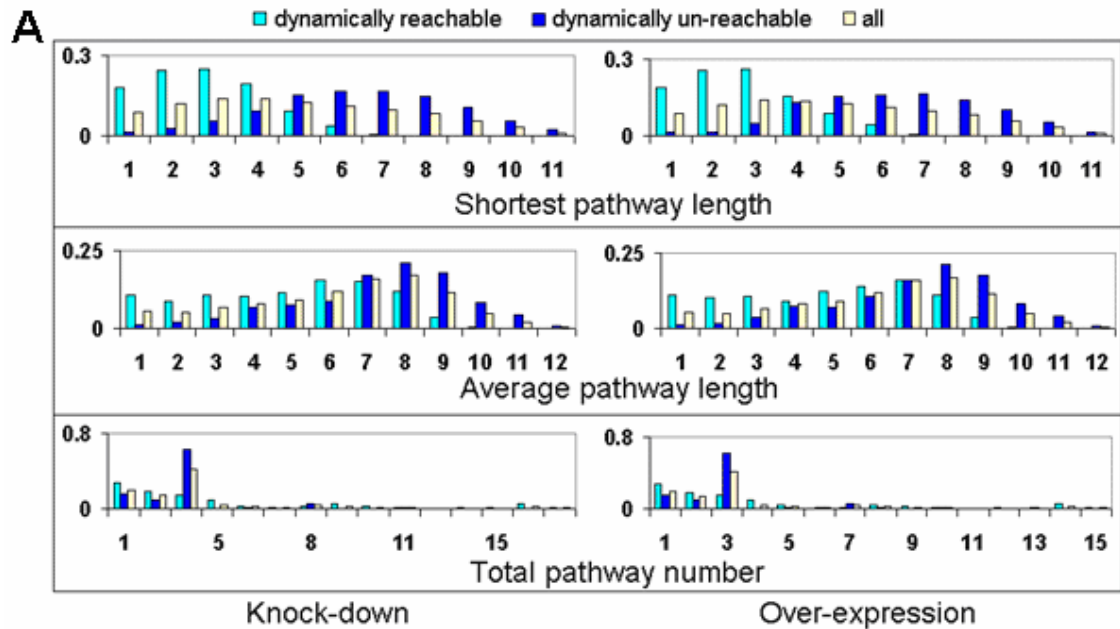


Figure 2: Hunting structural features accounting for robustness. (A) Distribution of pathway-specific features. (B) Single blockage or addition of feed-back or feed-forward interaction from the full network or to the backbone network.



Simulation	condition [*]	perturbation	condition [*]													
			no	feedback interactions										feedforward interactions		
				----	22-4	19-4	12-13	17-15	14-4	1-20	21-9	1-22	1-1	22-22	18-12	22-1
knock-down ^{**}	blockage	14-4	0	1	1	0	0	-	0	0	0	0	1	0	1	0
		16-4	0	1	1	0	0	0	0	0	0	0	1	0	1	0
		20-4	0	1	1	0	0	0	0	0	0	0	1	0	1	0
		Quantity ^{***}	0.52	8.3	4.9	0.53	0.52	0.6	0.5	0.5	0.6	0.52	6.26	0.52	5.52	0.54
knock-down ^{**}	addition	14-4	-	-	-	-	-	1	-	-	-	-	-	-	-	-
		16-4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		20-4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
		Quantity ^{***}	35.1	1.2	11	35.1	35.1	20	120	67	35	35.1	35.1	35.1	35.1	35.1
over-expression ^{**}	blockage	14-4	0	1	1	0	0	-	0	0	0	0	1	0	1	0
		16-4	0	1	1	0	0	0	0	0	0	0	1	0	1	0
		20-4	0	1	1	0	0	0	0	0	0	0	1	0	1	0
		Quantity ^{***}	0.5	7.9	4.3	0.5	0.51	0.6	0.5	0.5	0.6	0.5	5.94	0.5	5.17	0.52
over-expression ^{**}	addition	14-4	-	-	-	-	-	1	-	-	-	-	-	-	-	-
		16-4	1	0	1	1	1	1	1	1	1	1	1	1	1	1
		20-4	1	0	1	1	1	1	1	1	1	1	1	1	1	1
		Quantity ^{***}	26.8	0.9	11	26.8	26.8	17	92	53	27	26.8	26.8	26.8	26.8	26.8

* each interaction (3rd row) is blocked from the full network or added to the backbone network (2nd column).

** 1 and 0 represent perturbation and non-perturbation respectively

*** Ratio of change of node 4 [$\times (-10^{-3})$]