The effective graph: a weighted graph that captures nonlinear logical redundancy in biochemical systems

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The ability to map causal interactions underlying genetic control and cellular signaling has led to increasingly accurate models of the complex biochemical networks that regulate cellular function. These network models provide deep insights into the organization, dynamics, and function of biochemical systems,for example by revealing genetic control pathways involved in disease. However, the traditional representation of biochemical networks as binary interaction graphs fails to accurately represent an important dynamical feature of these multivariate systems: some pathways propagate control signals much more effectively than do others. Such heterogeneity of interactions reflects *canalization*—the system is robust to dynamical interventions in redundant pathways, but responsive to interventions in effective pathways. Here, we introduce the *effective graph*, a weighted graph that captures the nonlinear logical redundancy present in biochemical network regulation, signaling, and control. Using 78 experimentally-validated models derived from systems biology, we demonstrate that: (a) redundant pathways are prevalent in biological models of biochemical regulation, (b) the effective graph provides a probabilistic but precise characterization of multivariate dynamics in a causal graph form, and (c) the effective graph provides an accurate explanation of how dynamical perturbation and control signals, such as those induced by cancer drug therapies, propagate in biochemical pathways. Overall, our results indicate that the effective graph provides an enriched description of the structure and dynamics of networked multivariate causal interactions. We demonstrate that it improves explainability, prediction, and control of complex dynamical systems in general, and biochemical regulation in particular [1].

References

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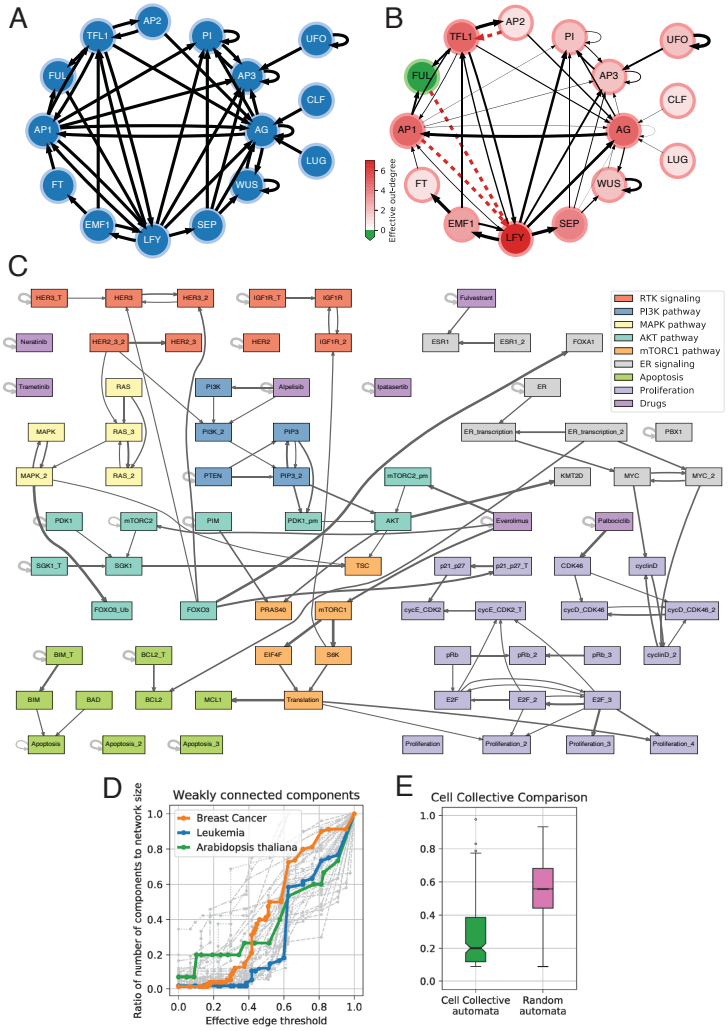

Fig. 1. A. The interaction graph for the *Arabidopsis Thaliana* BN [2]. **B**. The effective graph for the *Arabidopsis Thaliana* BN, in which edge thickness denotes effectiveness, with fully canalized edges shown in dashed red. Node color intensity denotes the node effective out-degree; green nodes denote cases of null effective out-degree. **C**. The effective graph for the BN model of ER+ breast cancer [4], in which edge thickness denotes its effectiveness, thresholded to show only effectiveness edges $e_{ij} > 0.4$ for $e_{ij} \in [0,1]$. **D**. Ratio of the number of weakly connected components to network size in relation to the effective edge threshold for a variety of biochemical BN. The *ER+* breast cancer (orange), leukemia (blue), and *Arabidopsis thaliana* (green) networks shown highlighted. **E**. Edge effectiveness of the 240 incoming edges (interactions) to 40 automata with degree $k = 6$ in Cell Collective [3] models (green) compared to a bias-matched sample of random Boolean automata (pink).