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 signalling has led to increasingly accurate models of the complex biochemical networks that regulate cellular function [10, 9, 1]. However, the traditional representation of biochemical networks as static and binary interaction graphs fails to accurately represent an important dynamical feature of these multivariate systems: some pathways propagate control signals much more effectively than others [5] (see Fig. 1A & B). Such heterogeneity of dynamical interactions reflects *canalization*, as the system is robust to interventions in redundant pathways, but responsive to interventions in effective pathways. The simplest way to model such causal, interdependent nonlinear dynamics is with multivariate, discrete dynamical systems; for instance, Boolean Networks (BN) are canonical models of complex systems which exhibit a wide range of dynamical behaviors [2]. BN provide a convenient modelling framework to explore general properties of complex systems, such as self-organization, criticality, causality, canalization, robustness and evolvability [10, 8, 6, 11].

To capture the nonlinear logical redundancy present in biochemical network regulation, signalling, and control, we present the *effective graph*. The effective graph is a weighted, directed graph that statistically integrates all dynamical redundancy present in the BN dynamics, thus revealing the most important interactions in determining state-transitions, as well as very redundant pathways. In this talk we present a summary of key results derived from more than 40 systems biology models analyzed, including that: i) redundant pathways are prevalent in biological models of biochemical regulation (see Fig. 1D & E); ii) the effective graph provides a statistical but precise characterization of multivariate dynamics in a causal graph form (see Fig. 1B & C); and iii) the effective graph provides an accurate explanation of how perturbation and control signals propagate in biochemical regulation, such as those induced by drug therapies on Cancer. See Fig. 1C, and note how cancer drugs (purple nodes) lose their pathway to *Apoptosis* (cell death; green nodes), a desired control outcome in this *ER+* breast cancer model. 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.

All simulations and code to support the findings are freely available in the CANA python package [4].

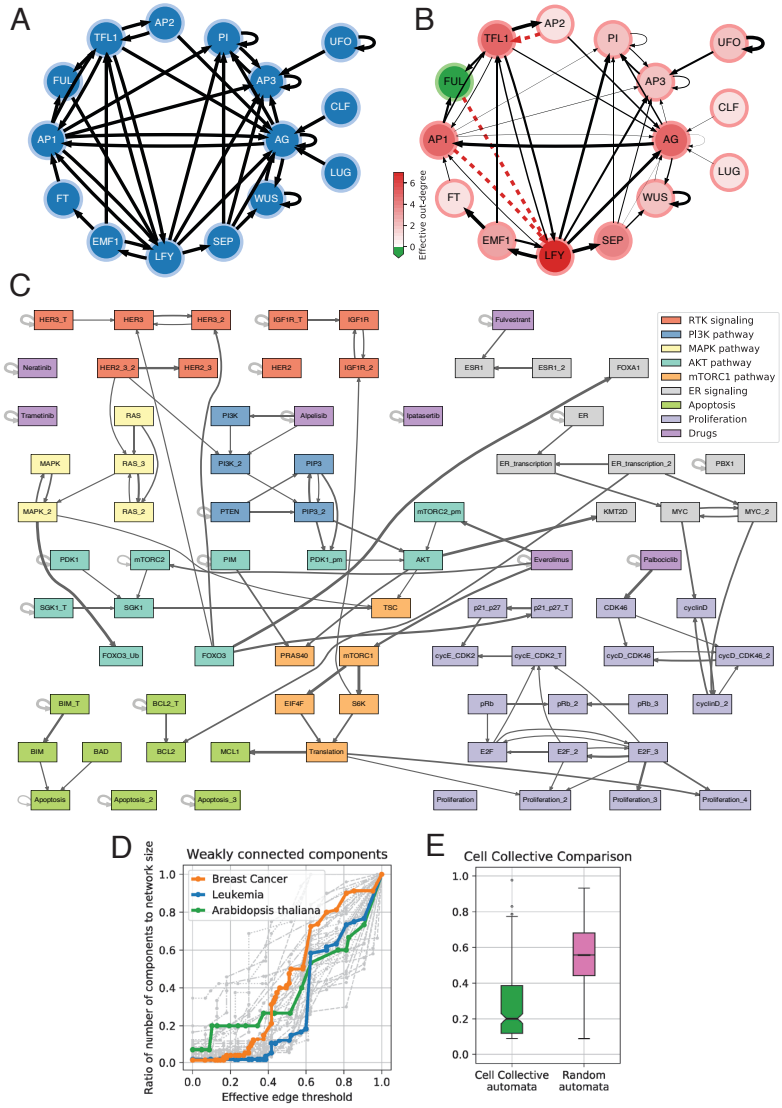

Fig. 1. A. The interaction graph for the *Arabidopsis Thaliana* BN [3]. **B**. The effective graph for the *Arabidopsis Thaliana* BN, in which edge thickness denotes effectiveness, with fully canalized edges shown in dashed red. Node color intensity denotes the node effective out-degree; green nodes denote cases of null effective out-degree. **C**. The effective graph for the BN model of ER+ breast cancer [12], 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* (blue) networks shown highlighted. **E**. Edge effectiveness of the 240 incoming edges (interactions) to 40 automata with degree $k = 6$ in Cell Collective [7] models (green) compared to a bias-matched sample of random Boolean automata (pink).

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