The effective graph captures canalizing dynamics and control in Boolean network models of biochemical regulation

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Boolean Networks (BN) are useful models of biochemical regulation in systems biology, capturing the qualitative dynamics of genetic control, cell signalling, metabolism, etc[1]. An important aspect of these models is the ability to model both the structure and dynamics of multivariate interactions. However, the underlying interaction graph (the structure of the network) fails to accurately represent the variable effectiveness of pathways in propagating control signals—a consequence of logical redundancy in the dynamical transition rules of BN. This way, the dynamics is said to be *canalized*, as it is robust to interventions in redundant pathways, but responsive to interventions in effective pathways[2]. Here we introduce the *effective graph*, a weighted subgraph of the original BN interaction graph, where edge strength reflects a statistical measure of nonlinear redundancy based on schema redescription and the Quine–McCluskey algorithm[3]. The effective graph is thus a more parsimonious representation of how variables truly interact in a given BN, integrating both structure and dynamics. Using simple network motifs, random ensembles, and systems biology models, we show that the effective graph captures the canalizing dynamics of BN better than the original interaction graph. Specifically, we show that the effective graph: 1) is better at capturing the spread of perturbations after flipping a node's state, such as those induced by drug therapies or gene knockouts; 2) helps understand how control operates and propagates in BN, including revealing how structure-only methods under- or over-estimate the set of required control variables. Overall, our results indicate that the effective graph provides a valuable enriched description of multivariate interactions in BN that can improve our understanding, prediction, and control of complex systems in general and biochemical regulation in particular.

References

1. Bornholdt, S. (2008) Boolean network models of cellular regulation: prospects and limitations.Journal of Royal Society Interface 5, S85–S94
2. Kauffman, S., Peterson, C., Samuelsson, B. & Troein, C. (2004) Genetic networks with canalyzing Boolean rules are always stable. PNAS 101, 17102–17107
3. Marques-Pita, M. & Rocha, L. M. (2013) Canalization and control in automata networks: body segmentation in Drosophila melanogaster. PloS one 8, e55946

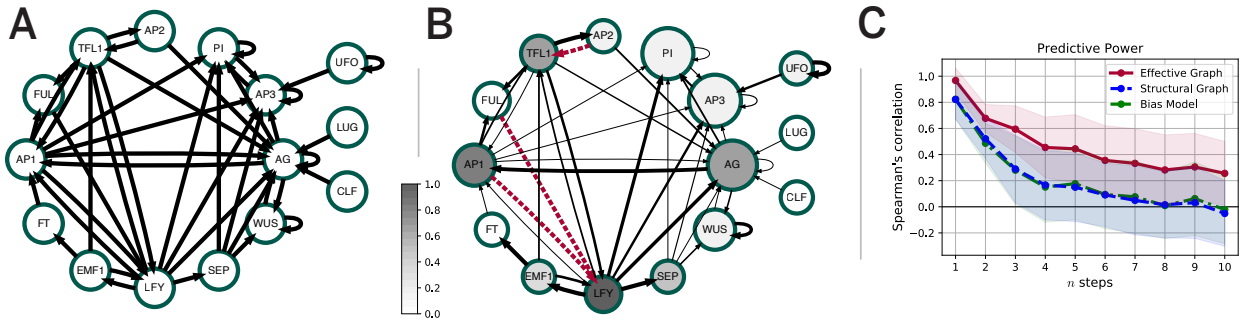

Figure 1. The variable interaction structure *Arabidopsis Thaliana* biological model can be represented by **(A)** its interaction graph, or **(B)** its effective graph. For the effective graphs, edge thickness denotes the effective connectivity, with fully redundant edges shown in dashed red in B; node size denotes the effective connectivity; and gray shading denotes its effective out-degree (see legend). **(C)**, The effective graph captures the spread of perturbations in random BN as evidenced by the Spearman correlation between the dynamical impact of a bit-flip after n-steps and the approximations based on the structural graph (blue), structural graph with bias (green), and the effective graph (red).