Rapid Computation and Interpretation of Boolean Attractors in Biological Networks

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Biological networks comprise myriad interactions between signalling molecules, genes and proteins. Information is transmitted and processed through such networks decide cellular fate. Determining if certain cellular fates are correlated to disease conditions has important bearing in biological and clinical research but the complexity is overwhelming. As recourse, biological networks may be represented as Boolean networks and analyzed by computational methods. The on (0) or off (1) state of a vertex, for example, indicates if a gene is active or inactive, and the stables states or singleton attractors of the network denotes cell fate. However, determination of singleton attractors is a NP-hard problem and limits detection of singleton attractors of biological Boolean networks (BBN) to sizes of about 20 vertices.

We developed a sequential subgraph (SSG) algorithm that identifies all singleton attractors of a biological network and reduces the number of computations to do so by several orders of magnitude compared to explicit enumeration while retaining accuracies. The SSG algorithm deconstructs the biological network into subgraphs of sizes equal to their in-degrees. For each subgraph, the states constituting singleton attractors are computed separately and then stitched together according to a computed sequence to obtain the complete set. We applied this algorithm to determine the attractors of the γ-secretase network consisting of 146 vertices and 193 edges, a near impossible task by explicit enumeration. For this network, we also simulated the effect of gain of function of PSEN1 observed in Alzheimer's patients, and compared the differences in the 550 attractors with those obtained for normal PSEN1 activity. The proteins exhibiting differential activity were segregated and categorized into apoptosis, Ca^{2+} signalling, amyloidosis, Notch signalling, oxidative stress, MAPK cascade, cell cycle, and proliferation clusters. By segregating proteins in this manner from the attractor states, it was possible to elucidate the metabolic impact of PSEN1 mutation in Alzheimer's disease. The SSG algorithm can rapidly detect singleton attractors of BBNs, and may be applied to understand other diseases.