Inferring Toxicological Responses of HepG2 Cells from ToxCast high-content imaging data

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Understanding the dynamic perturbation of cell states by chemicals can aid in for predicting their adverse effects. High-content imaging was used to measure the state of HepG2 cells over three time points (1, 24, and 72 h) in response to 976 ToxCast chemicals for 10 different concentrations (0.39-200µM). Cell state was characterized by p53 activation, c-Jun activation, phospho-Histone H2A.x, phospho-Histone H3, alpha tubulin, mitochondrial membrane potential, mitochondrial mass, cell cycle arrest, nuclear size and cell number. Dynamic cell state perturbations due to each chemical concentration were utilized to infer coarse-grained dependencies between variables as Boolean networks (BNs). BNs were inferred from data in two steps. First, the data for each state variable were discretized into changed/active (> 1 standard deviation), and unchanged/inactive values. Second, the discretized data were used to learn Boolean relationships between variables. In our case, a BN is a wiring diagram between nodes that represent 10 previously described observable phenotypes. Functional relationships between nodes were represented as Boolean functions. We discovered that inferred BN show that HepG2 cell response is chemical and concentration specific. We observed presence of both single and cycle BN attractors. In addition, there are instances where Boolean functions were not found. We believe that this may be either because our time sample is too small or because our data lack additional cellular features. These results illustrate the utility of Boolean networks in characterizing regulatory networks within biological systems. *This abstract does not necessarily reflect U.S. EPA policy.*