A Biologically Informed Framework for the Analysis of the PPAR Signaling Pathway using a Bayesian Network.

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The US EPA's ToxCast™ program seeks to combine advances in high-throughput screening technology with methodologies from statistics and computer science to develop high-throughput decision support tools for assessing chemical hazard and risk. To develop new methods of analysis of these complex screening data sets, we focused on chemicals that interact with the peroxisome proliferator-activated receptor (PPAR) pathways known to mediate biological processes that are involved with chronic diseases such as diabetes, obesity, atherosclerosis, and hepatotoxicity cancer. The ToxCast assay suite provides broad coverage of the PPAR pathways, including information on events that occur both upstream and downstream of apical chemical-PPAR interactions. We modeled the apical PPARα endpoint using a probabilistic graphical model representative of published PPAR pathways from KEGG and Ingenuity. By integrating data indicative of events occurring both upstream and downstream of the apical endpoint of interest, we have constructed a model that represents the propagation of a signal through the PPAR pathways. Using a Bayesian analytic framework and Markov-Chain Monte Carlo (MCMC) techniques we are able to compute a posterior probability distribution for each observation in our dataset. This allowed for a probabilistic estimation of how likely a compound is to perturb a pathway, instead of relying upon a single endpoint as a sentinel for PPAR activity. This resulted in a more robust assessment of a compound's activity by lessening the impact of individual assay variance. This approach also allowed for assessment of quantities such as assay variance and measurement error, which were previously not able to be estimated in a quantitative way. Together, the model provides a general probabilistic and holistic framework for analyzing how likely a compound is to perturb a given biological pathway. *This abstract does not necessarily reflect Agency policy.*