



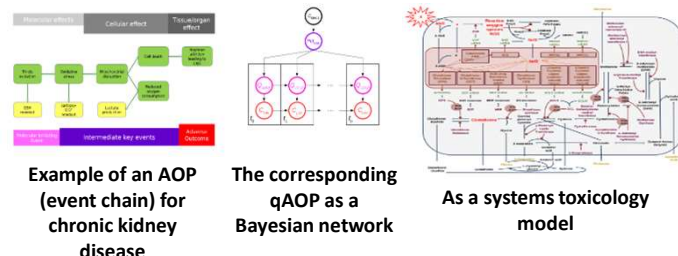
J. Beltman, F. Bois, B. Hardy, O. Taboureau



Coordinated by: Certara

Background Information

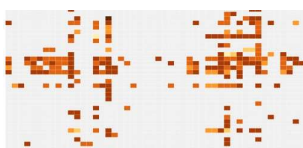
Adverse outcome pathways (AOPs) help knowledge management and data integration for toxicity hazard or risk assessment. We developed quantitative AOPs to help forecast the potential effect of chemicals in humans on the basis of *in vitro* and computational chemistry methods (NAMs).



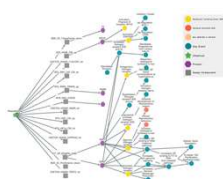
Technology:

Big data mapping, Bayesian networks, Systems toxicology

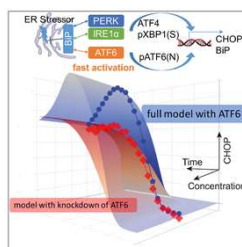
Heatmap: 5290 chemicals mapped to 82 AOPs



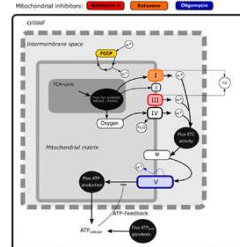
Webserver for AOPs: <http://saop.cpr.ku.dk/>



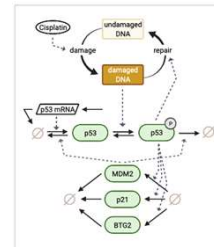
Unfolded protein toxicity model



Mitochondrial respiration toxicity



DNA damage model



Applications – Lessons learned

- For the unfolded protein toxicity model, ATF6 is an early-responding regulator of CHOP, which is an important predictor of adverse outcomes.
- Upon exposure to specific compounds, the mitochondrial toxicity response terminated quickly due to compound decay.
- In the DNA damage toxicity, the relation between p53 and MDM2 complicates extrapolation from HepG2 cells to primary human hepatocytes.
- However, systems toxicology models are more precise and offer a mechanistic understanding of the data and toxicity mechanisms. They have better predictive power than Bayesian networks, even though these were simpler to develop.

