

Framework for computationally-predicted AOPs

Shannon M. Bell ORISE Fellow at the National Health and Environmental Effects Research Laboratory, US EPA





Given:

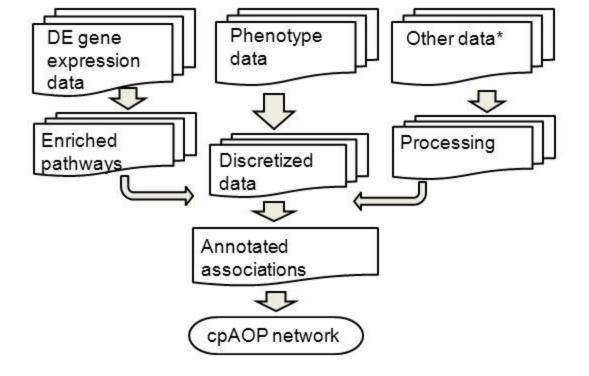
- Large numbers of chemicals we know little to nothing about
- Multiple 'omics' type studies and screening data
- AOPs are useful tools for connecting HTS to regulatory endpoints

Can we:

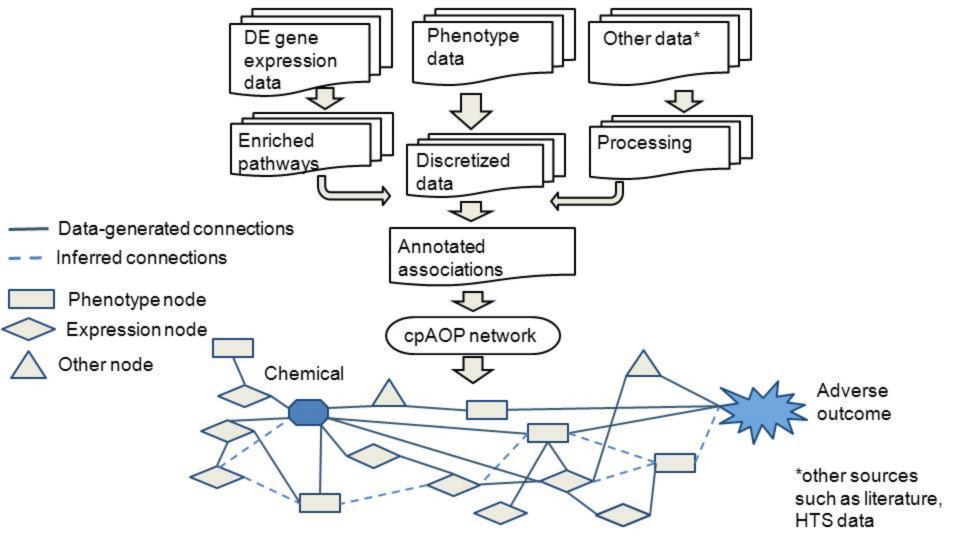
• Create an approach that can identify 100s of putative AOPs using this data

What do we need?

- Methods that can deal with
 - Sparse, categorical, continuous data
 - Missing values and mixed data types
 - Lack of "training set" or gold standards
 - New data streams framework for data integration
- Outputs that are informative and intuitive to biological domain experts
 - This is key for helping evaluate the cpAOPs



*other sources such as literature, HTS data

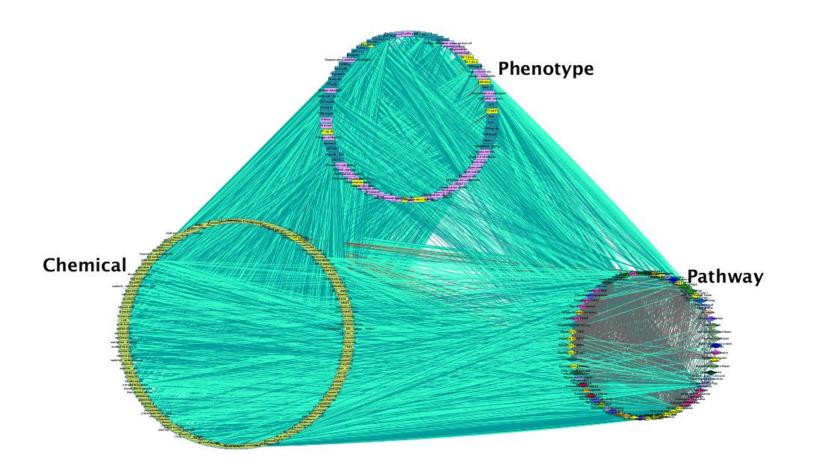


Creating a cpAOP network

• TG GATES data

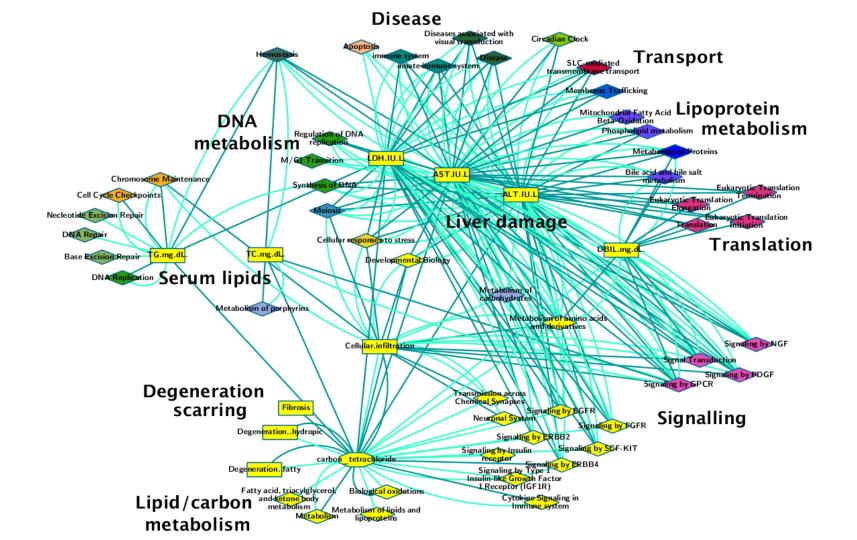
SEPA

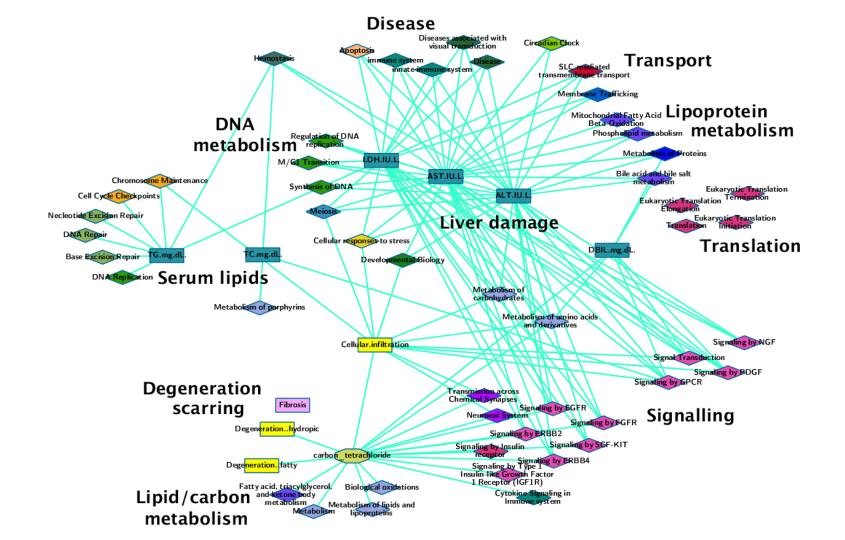
- Large screen of hundreds of chemicals
 - Used only rat liver data
- Includes microarray, clinical chemistry and pathology data
- Resulting network has liver-focused cpAOPs

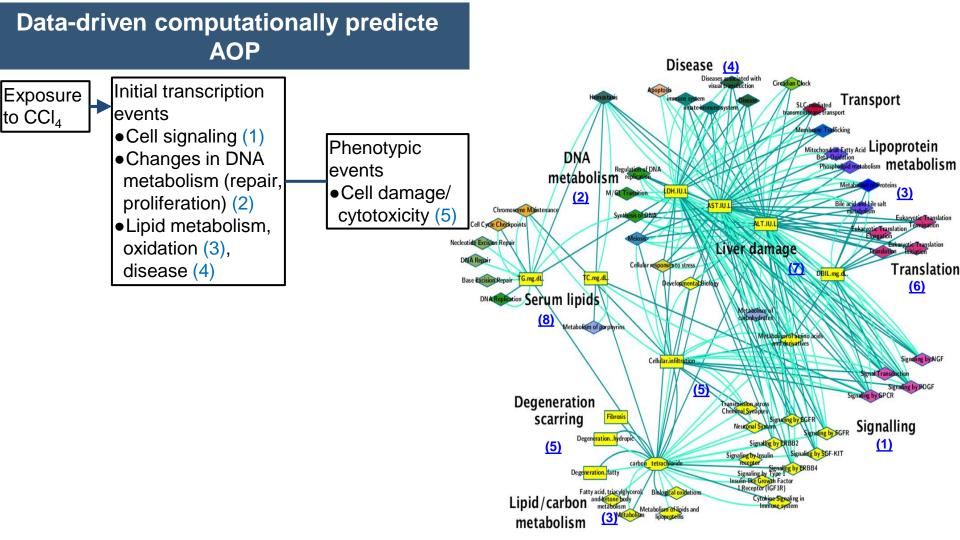


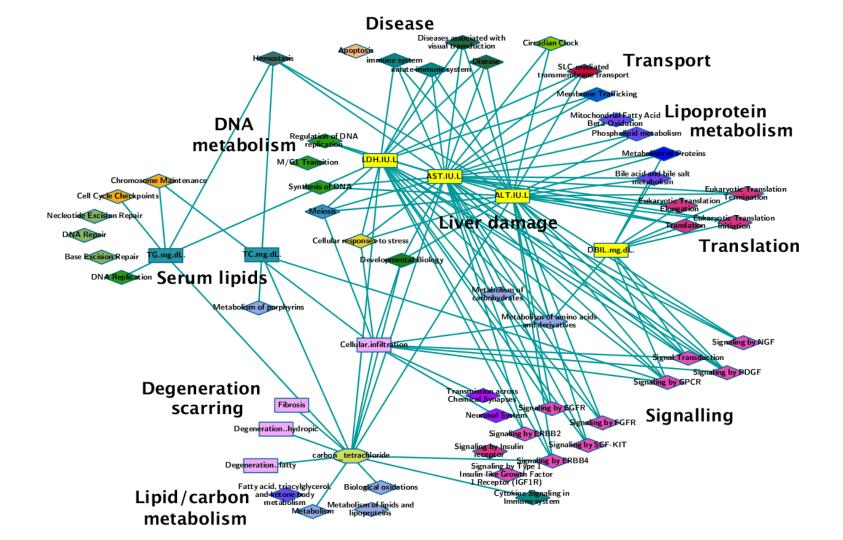
Carbon tetrachloride example

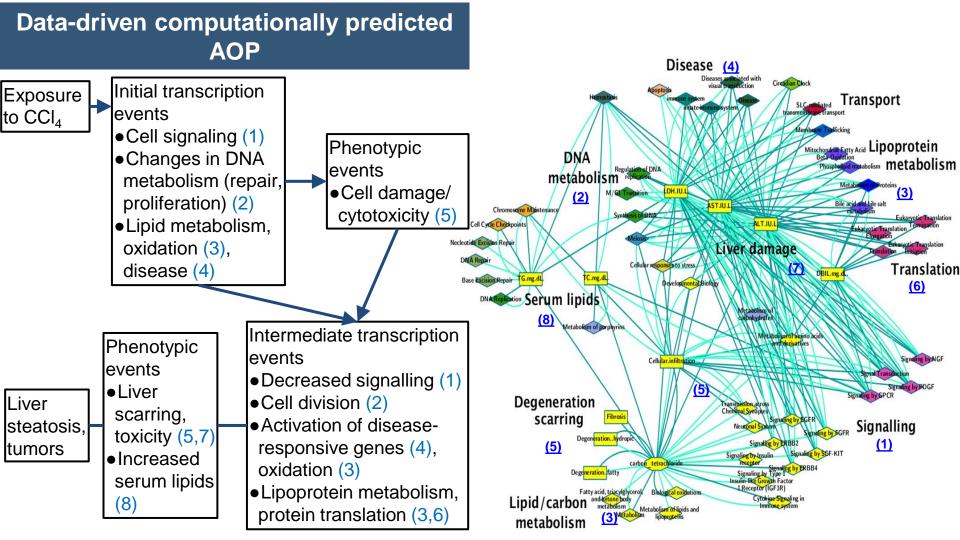
- Given:
 - Large cpAOP network enriched with liver-specific data
- Objective:
 - Probe cpAOPnet to find an adverse outcome pathway associated with CCI₄











Data-driven computationally predicted Hypothesized mode of action adapted from EPA CCL₄ IRIS assessment AOP Chronic Initial transcription Metabolism of CCl₄ Exposure levents exposure by CYP2E1 (3) to CCl₄ to CCl₄ •Cell signaling (1) Phenotypic • Changes in DNA events metabolism (repair, Genetic damage or •Cell damage/ proliferation) (2) alterations cytotoxicity (5) Lipid metabolism, Intermediate Background oxidation (3), events mutations (2) disease (4) Disruption of •Oxidative stress Ca++ (3) homeostasis (1) • Cytotoxicity-Intermediate transcription Lipid induced damage Phenotypic levents peroxidation (3) (4,7)levents Decreased signalling (1) • Liver Liver • Cell division (2) Liver stress scarring, Activation of diseasesteatosis, Hepatocellular toxicity (5,7) Liver responsive genes (4), tumors cytotoxicity (4,5,7) Increased tumors oxidation (3) Hepatocellular serum lipids • Lipoprotein metabolism, regenerative (8) protein translation (3,6)proliferation (2,5,6)

Set EPA

Take home

- Developed a framework for integrating diverse information
 - Framework is flexible to data types using edge properties to hold meta data
- Demonstrated a (manual) way to extract cpAOPs associated with a chemical from the network

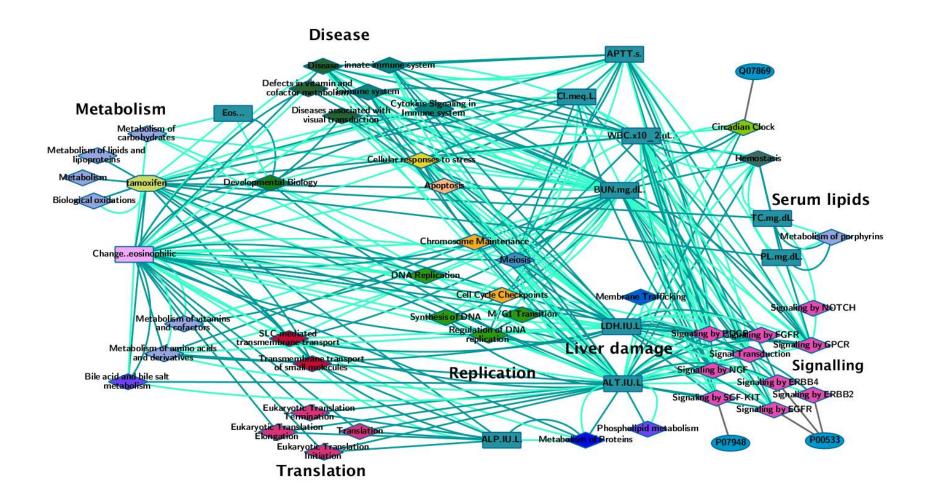
Set EPA

Future work

- Automating the cpAOP identification and ranking
 - Engage domain expertise for model refinement
 - Generate "straw man" cpAOP to serve as a starting point for curation
 - Conform to established AOP definitions
- Integrate Tox21-type data
 - Challenge is in matching names!!

Implications

- Provide AOPs for more HTS assays enhanced interpretation
- cpAOPs can feed AOP development efforts
- Point towards new assay needs







Steve Edwards, US EPA Charles Wood, US EPA Noffisat Oki, ORISE Lyle Burgoon, US EPA