Framework for computationally-predicted AOPs

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Objective

Given:

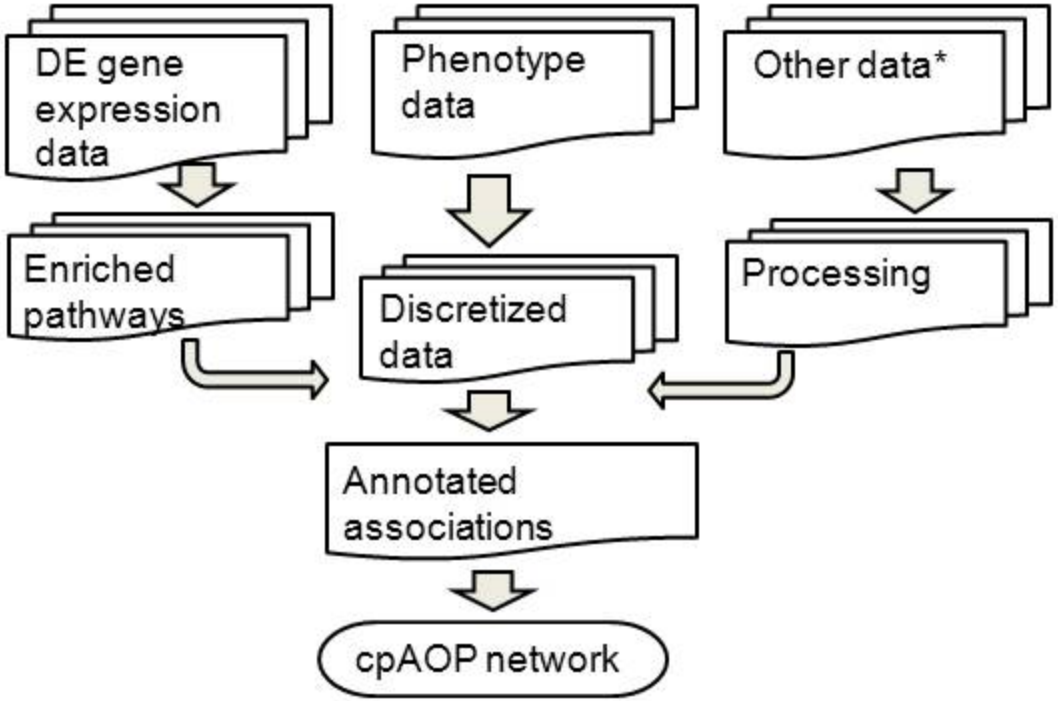
- **Large numbers of chemicals we know little to nothing about**
- **Multiple ‘omics’ type studies and screening data**
- **AOPs are useful tools for connecting HTS to regulatory endpoints**

Can we:

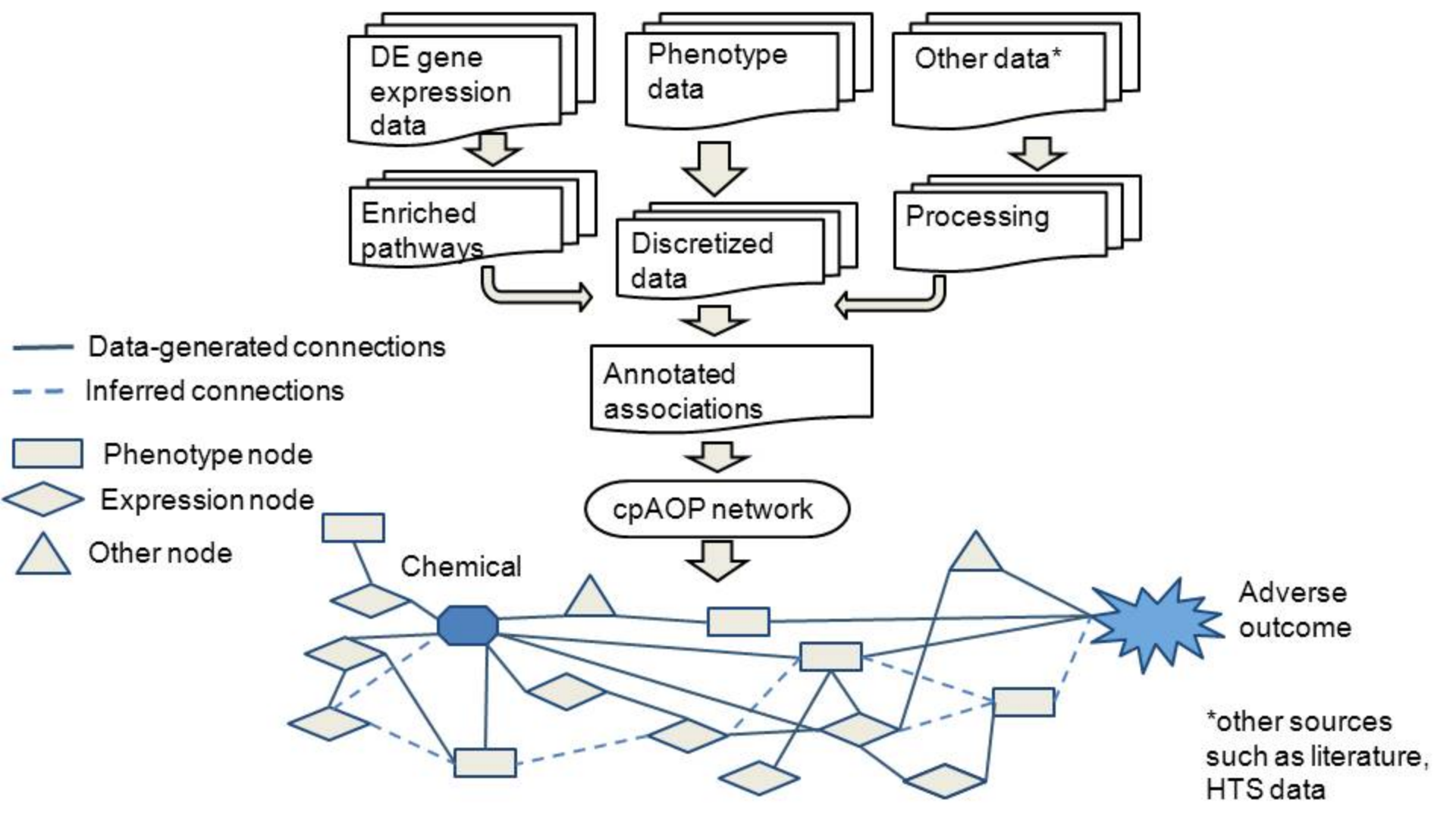
- **Create an approach that can identify 100s of putative AOPs using this data**

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

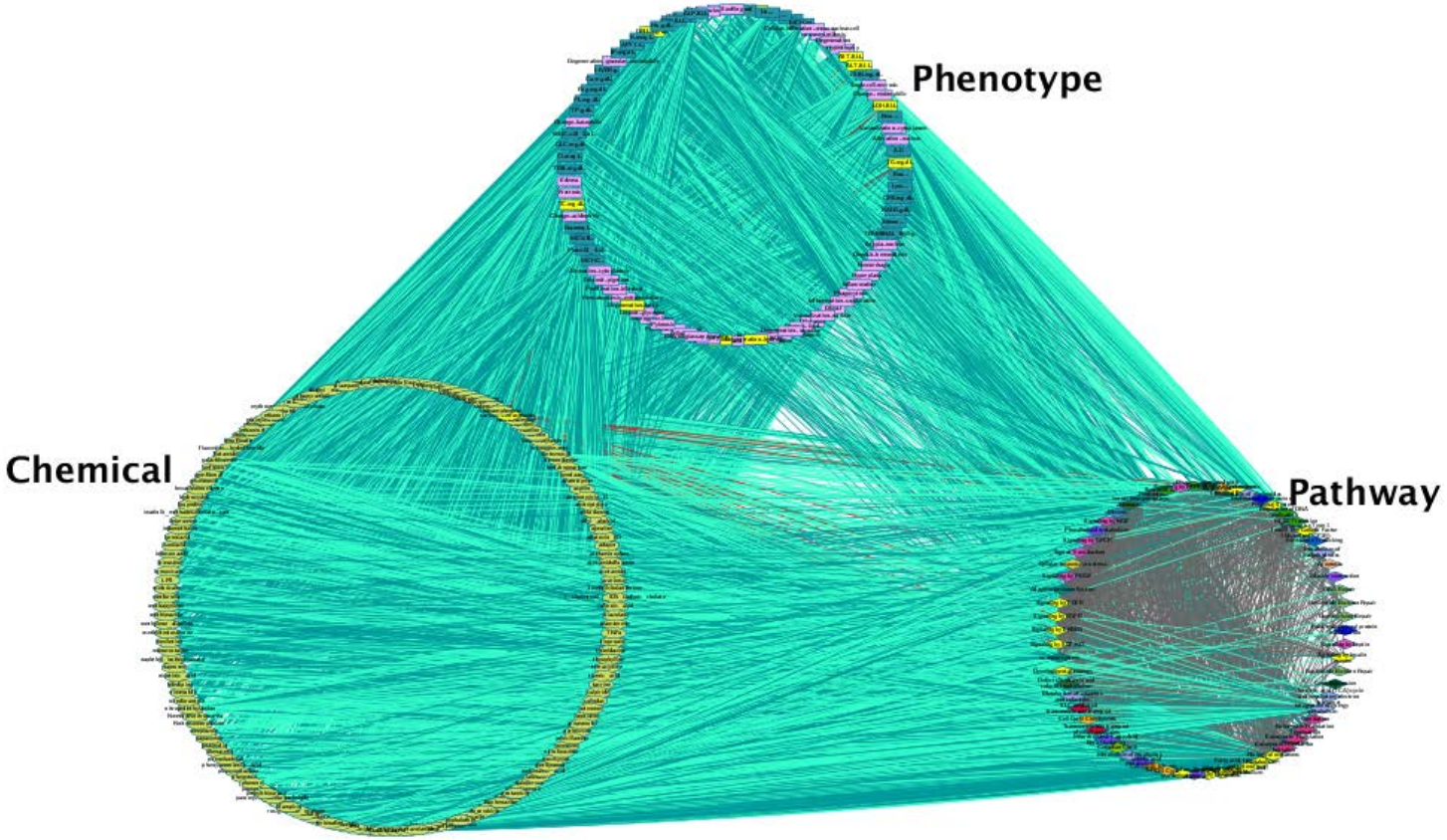


*other sources such as literature, HTS data


DE gene expression data
Phenotype data
Other data*
Enriched pathways
Discretized data
Processing
Annotated associations
cpAOP network
Chemical
Adverse outcome
Data-generated connections
Inferred connections
Phenotype node
Expression node
Other node
*other sources such as literature, HTS data

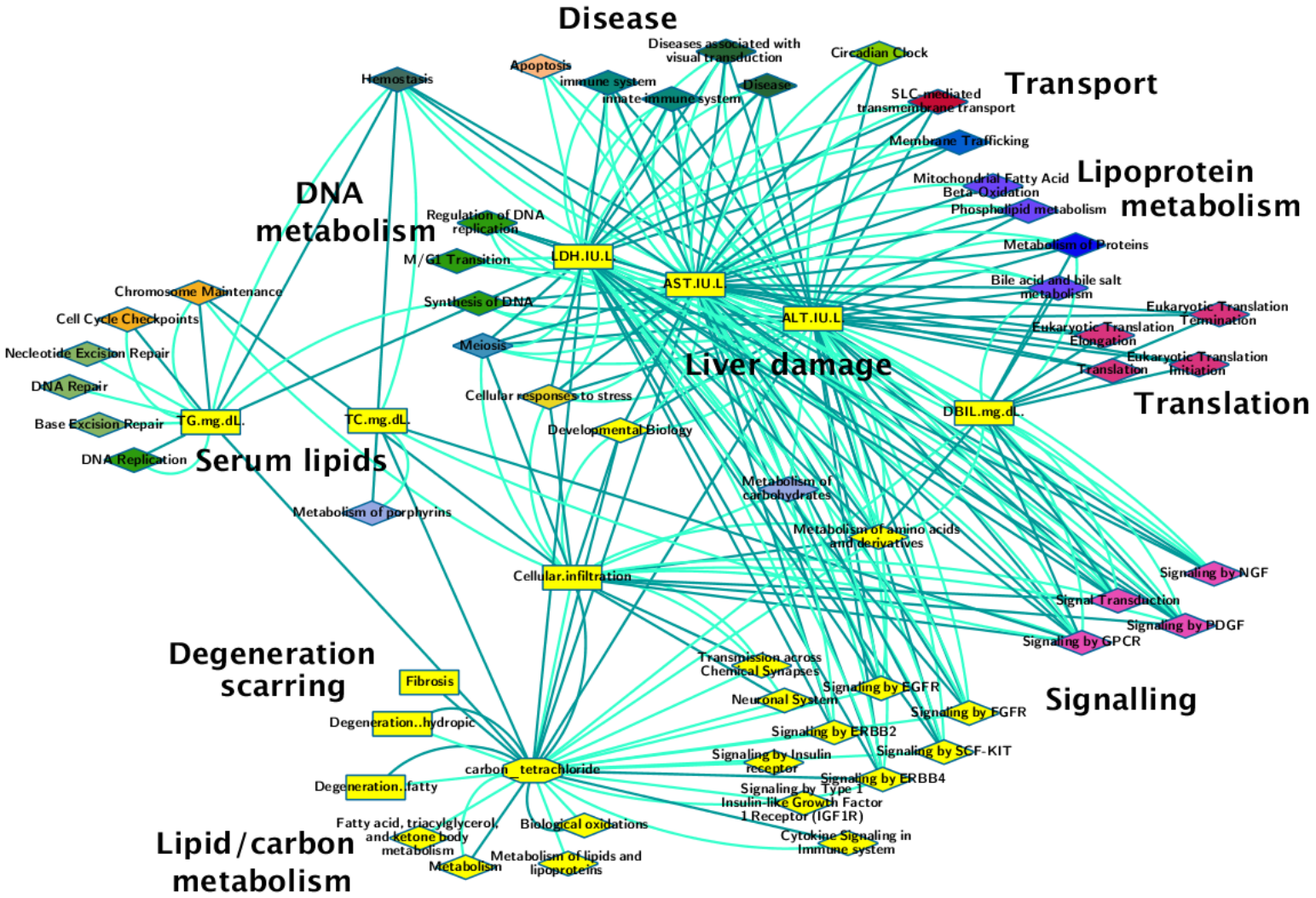
Creating a cpAOP network

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


Phenotype
Chemical
Pathway

Carbon tetrachloride example

- **Given:**
  - **Large cpAOP network enriched with liver-specific data**
- **Objective:**
  - **Probe cpAOPnet to find an adverse outcome pathway associated with CCl_4**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Diseases associated with visual transduction
Circadian Clock
Apoptosis
Hemostasis
immune system
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Disease
Transport
SLC-mediated transmembrane transport
Membrane Trafficking
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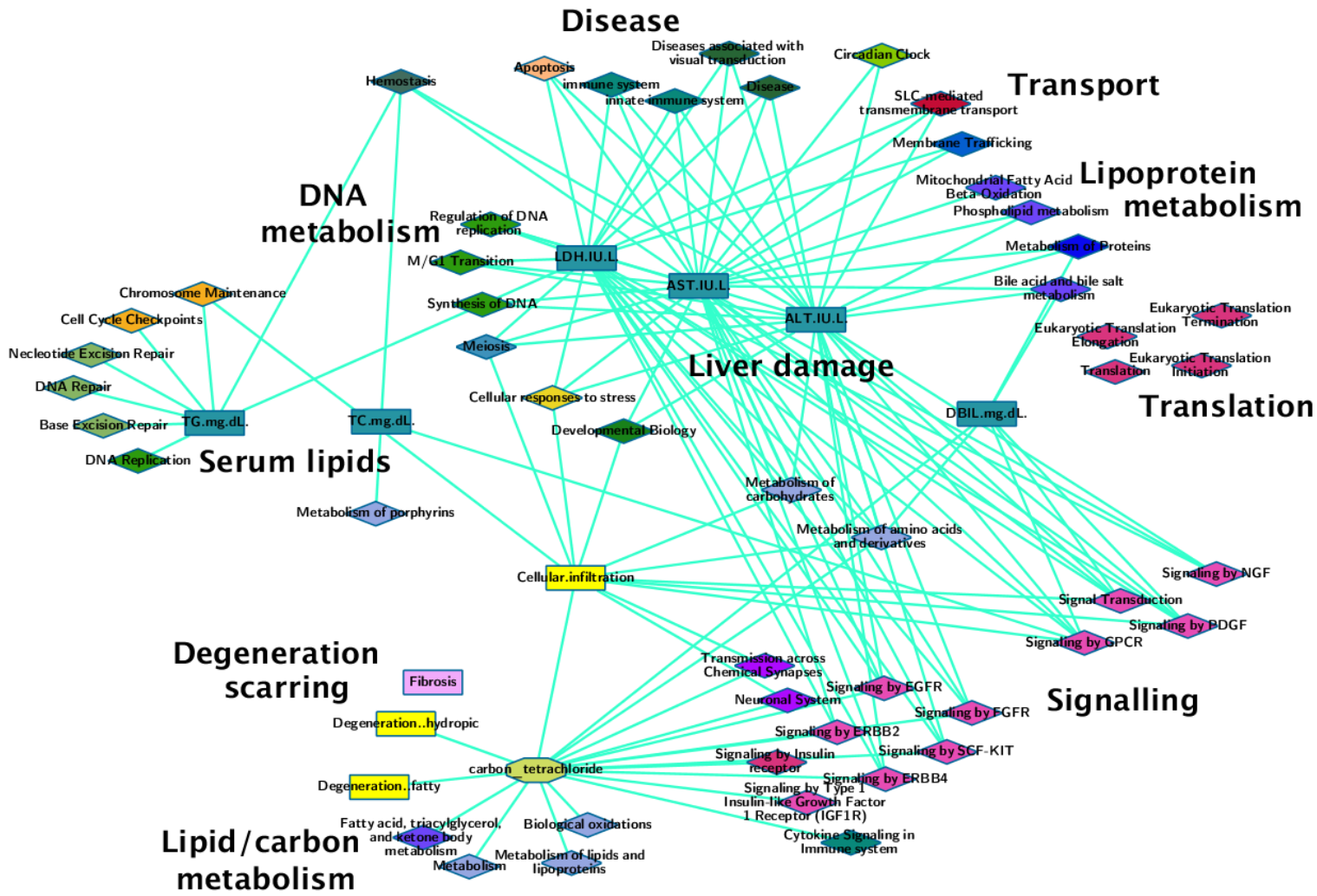
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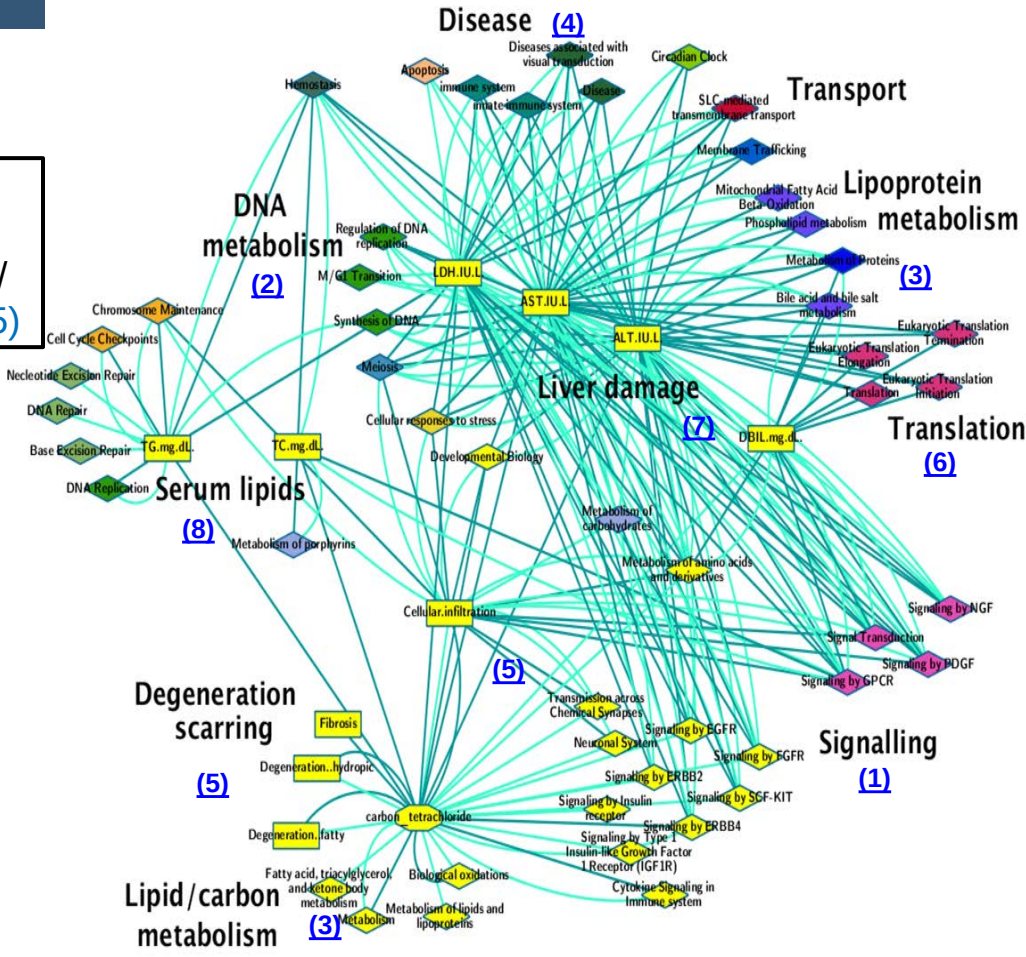
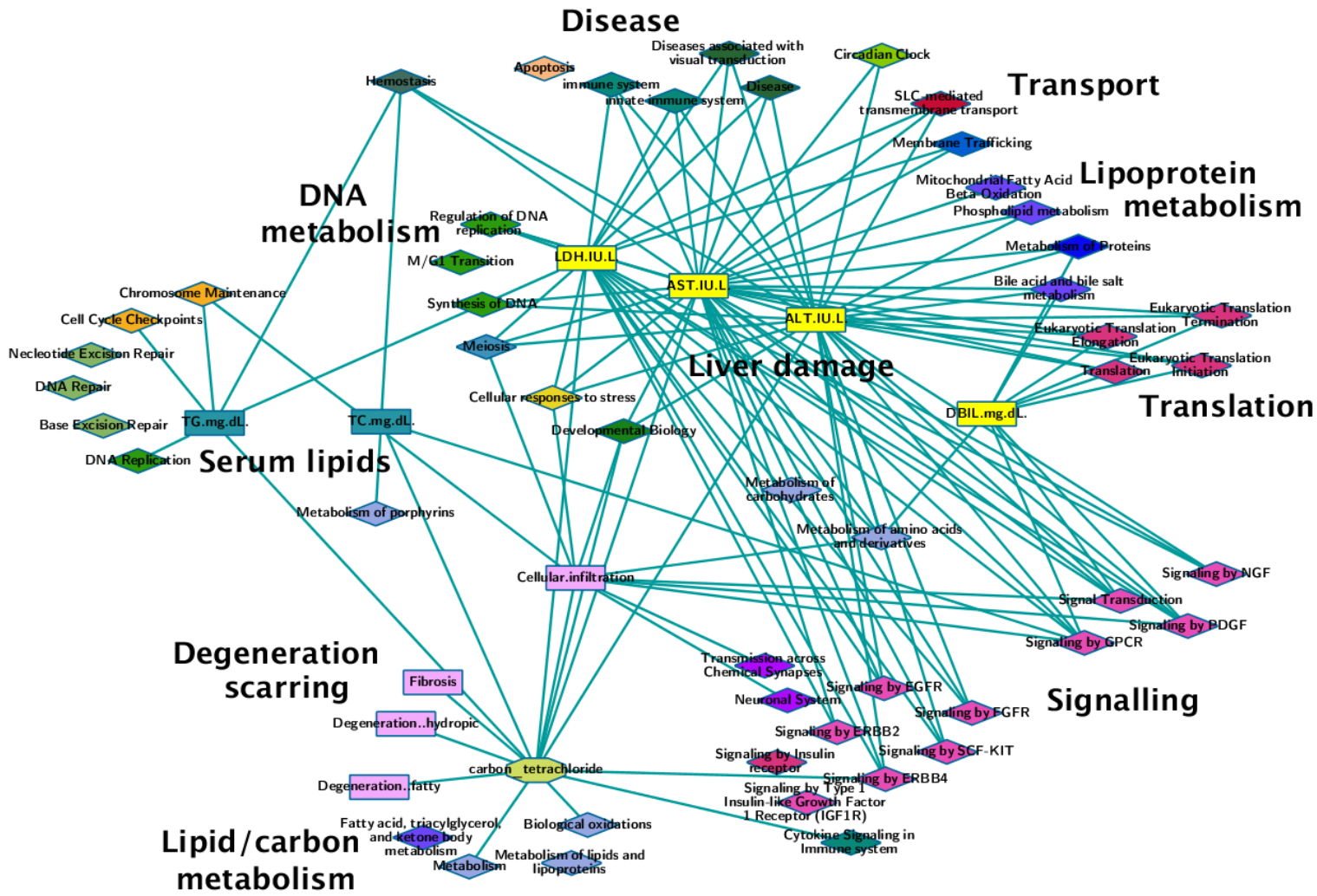
Data-driven computationally predicte AOP

Exposure to CCl_4

Initial transcription events
- Cell signaling (1)
- Changes in DNA metabolism (repair, proliferation) (2)
- Lipid metabolism, oxidation (3), disease (4)

Phenotypic events
- Cell damage/ cytotoxicity (5)

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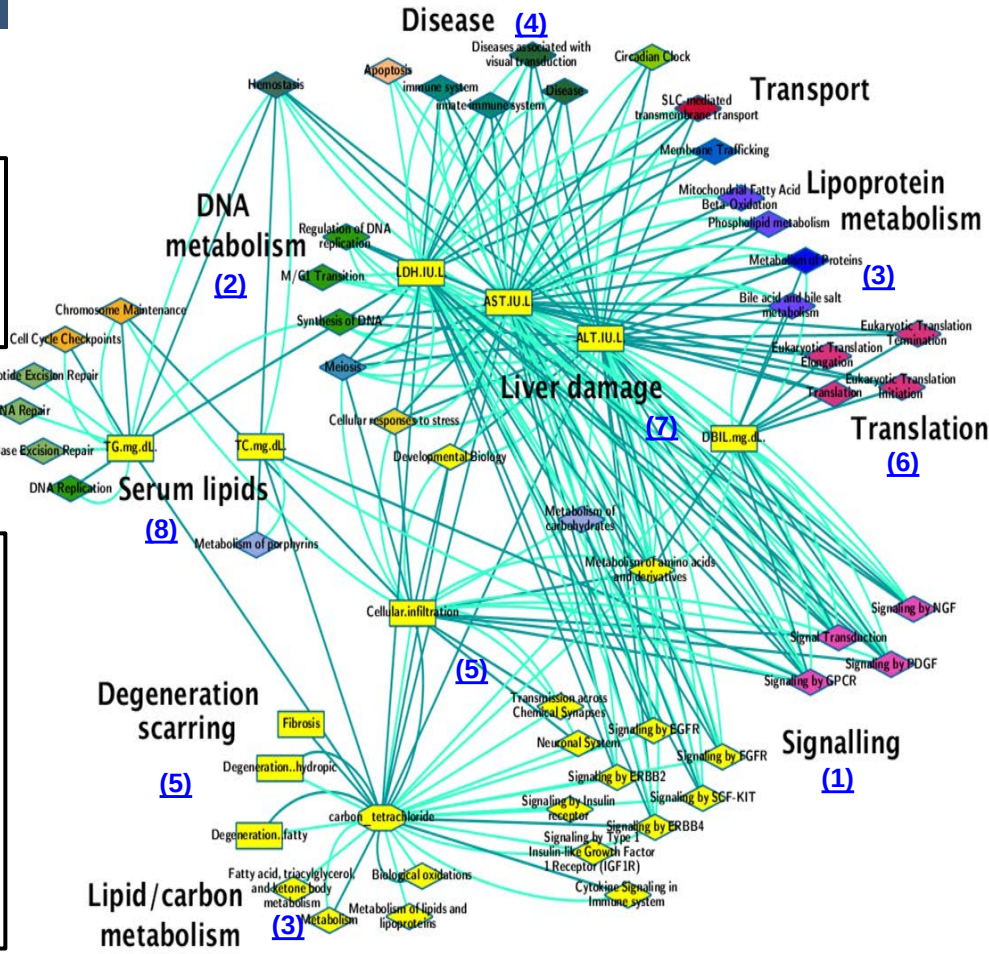
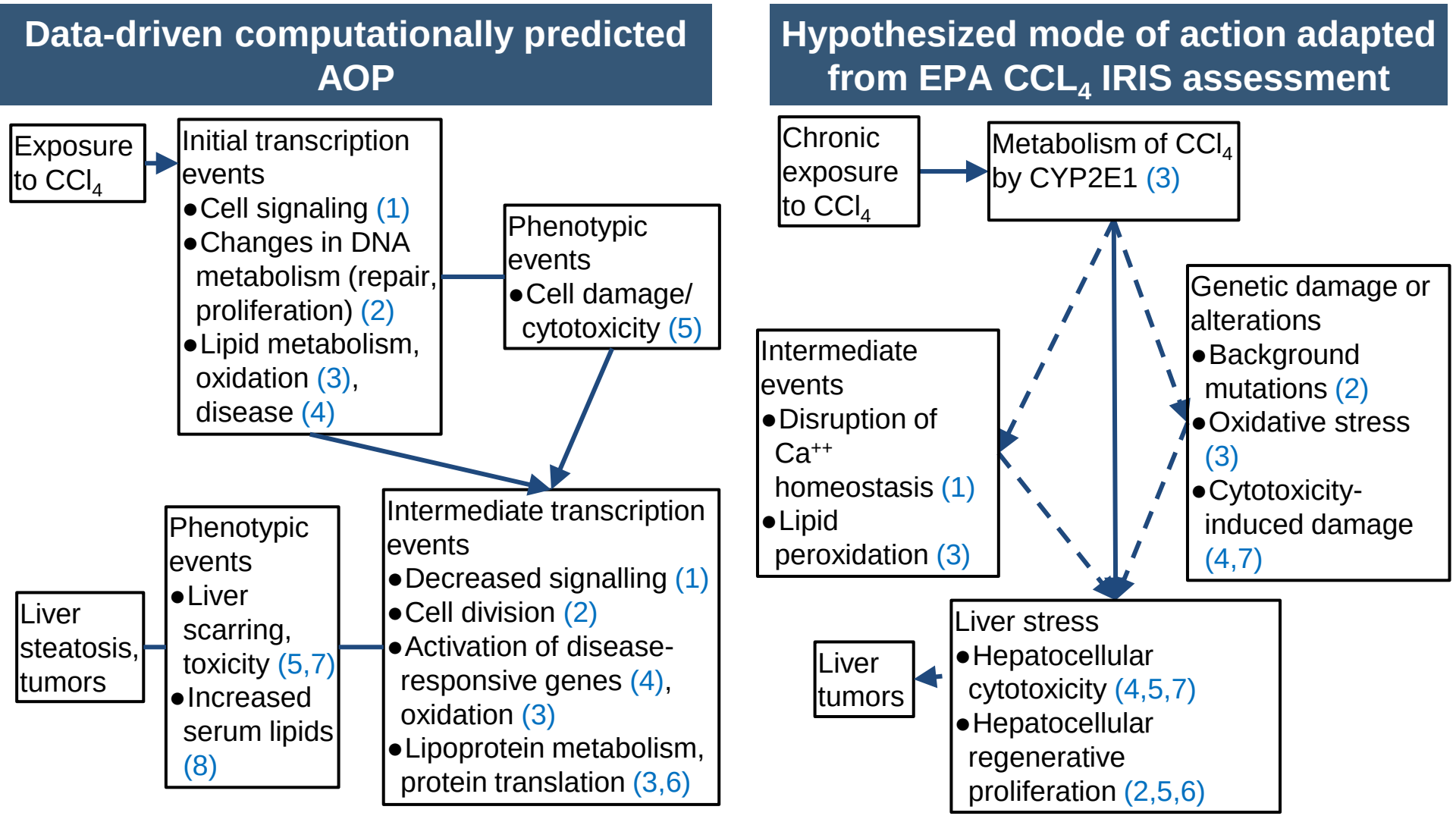
Intermediate transcription events
- Decreased signalling (1)
- Cell division (2)
- Activation of disease-responsive genes (4), oxidation (3)
- Lipoprotein metabolism, protein translation (3,6)

Phenotypic events
- Liver scarring, toxicity (5,7)
- Increased serum lipids (8)

Liver steatosis, tumors

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Liver steatosis, tumors
Hypothesized mode of action adapted from EPA CCL_4 IRIS assessment
Chronic exposure to CCl_4
Metabolism of CCl_4 by CYP2E1 (3)
Intermediate events
●Disruption of Ca^{++} homeostasis (1)
●Lipid peroxidation (3)
Genetic damage or alterations
●Background mutations (2)
●Oxidative stress (3)
●Cytotoxicity-induced damage (4,7)
Liver stress
●Hepatocellular cytotoxicity (4,5,7)
●Hepatocellular regenerative proliferation (2,5,6)
Liver tumors

Take home

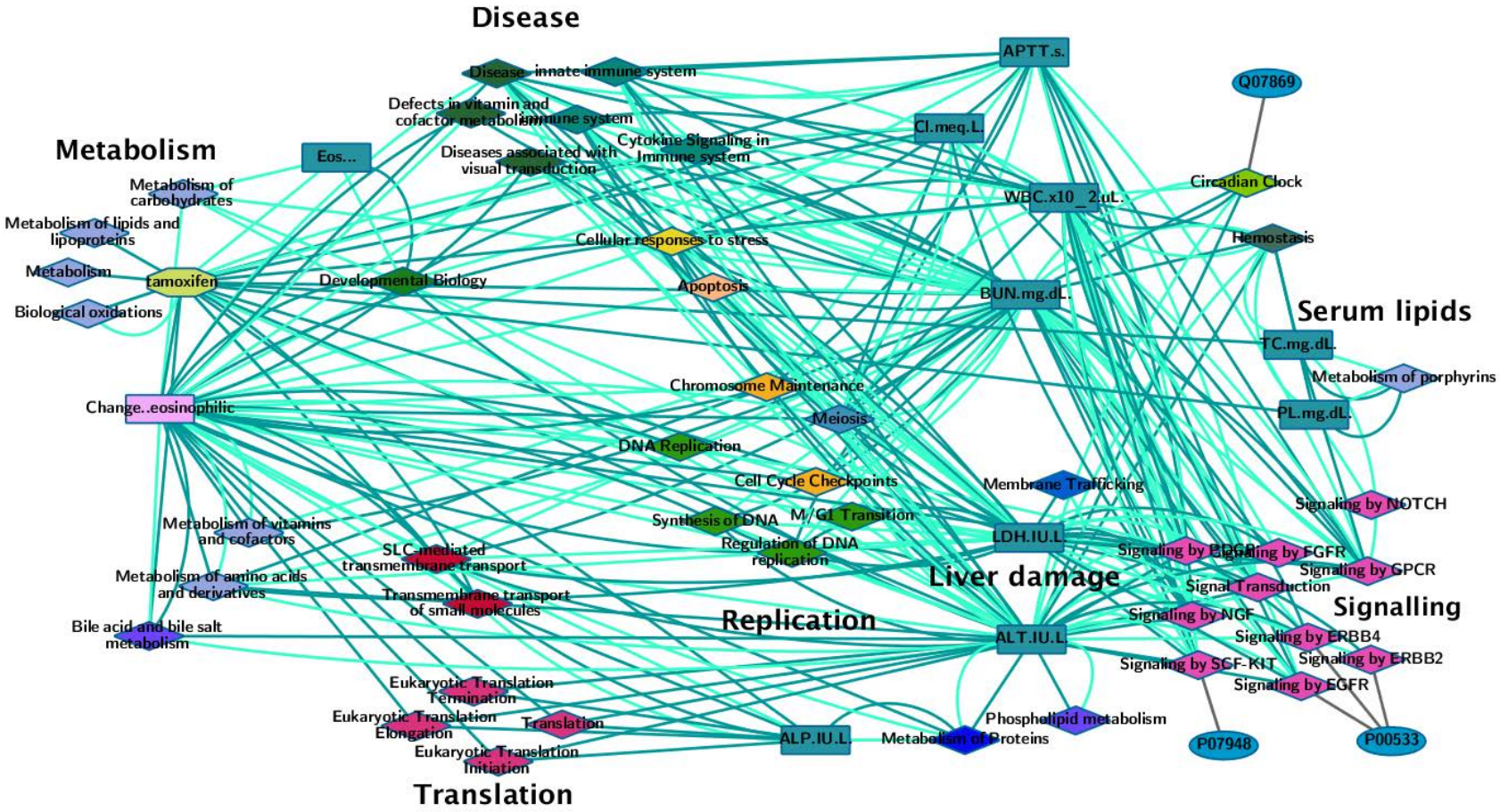
- Developed a framework for integrating diverse information
  - Framework is flexible to data types using edge properties to hold meta data
- Demonstrated a (manual) way to extract cpAOPs associated with a chemical from the network

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**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P07948
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Thank you

Steve Edwards, US EPA

Charles Wood, US EPA

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Lyle Burgoon, US EPA