Discovering and assessing the quality of emergent Adverse Outcome Pathway knowledge

AOP-Wiki 3.0 Idea Generation and Discussion Workshop

August 16th, 2023

Nate Pollesch, PhD
USEPA Office of Research and Development - Duluth, MN

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Extracting and benchmarking emerging adverse outcome pathway knowledge *ToxSci* 2019
- Pollesch, NL; Villeneuve, DL; O'Brien, JM

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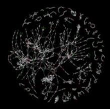
- Pollesch, NL; Olker, JH; Wang, R-L

Discovering emergent A O P



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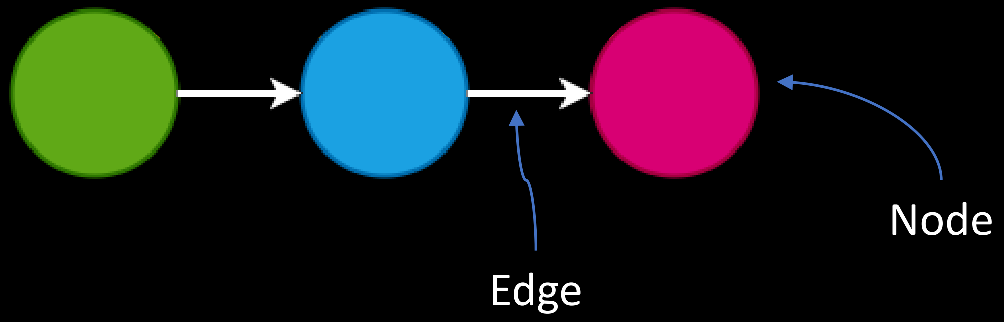

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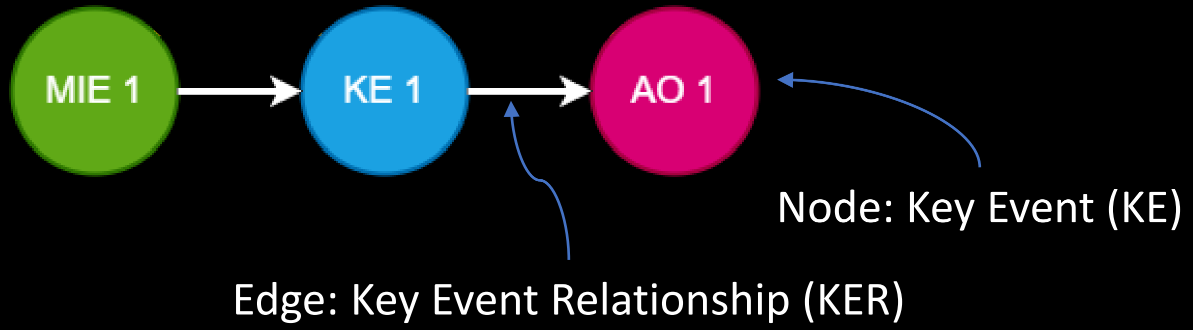

MIE: Molecular Initiating Event
KE: Key Event
AO: Adverse Outcome

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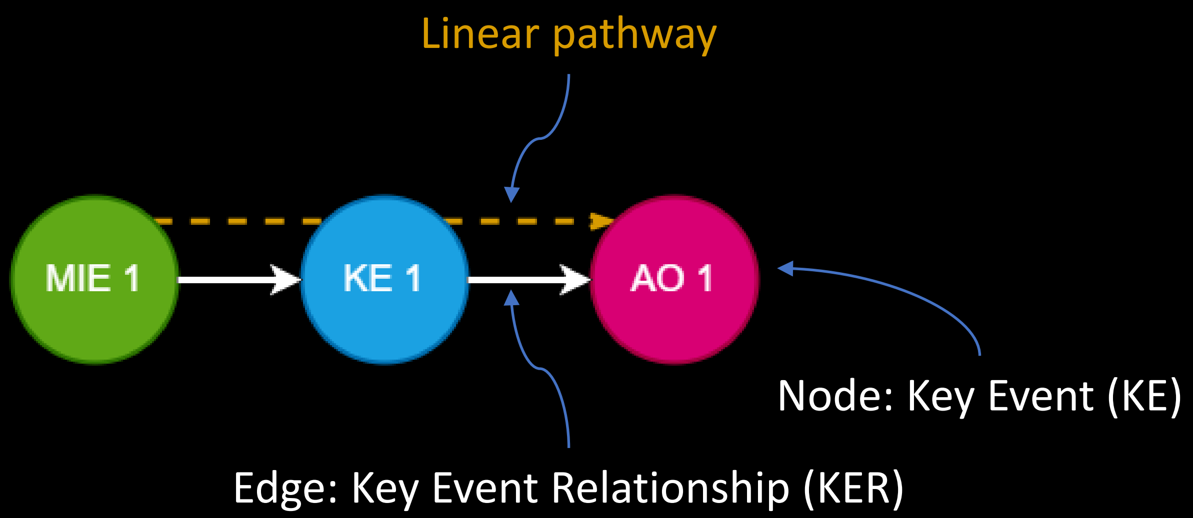

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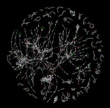
- Building the Network
  - Key event relationship info was downloaded from AOPwiki.org and was used to create an edge list
  - The edge list was converted to a graph using *igraph* package in R Studio



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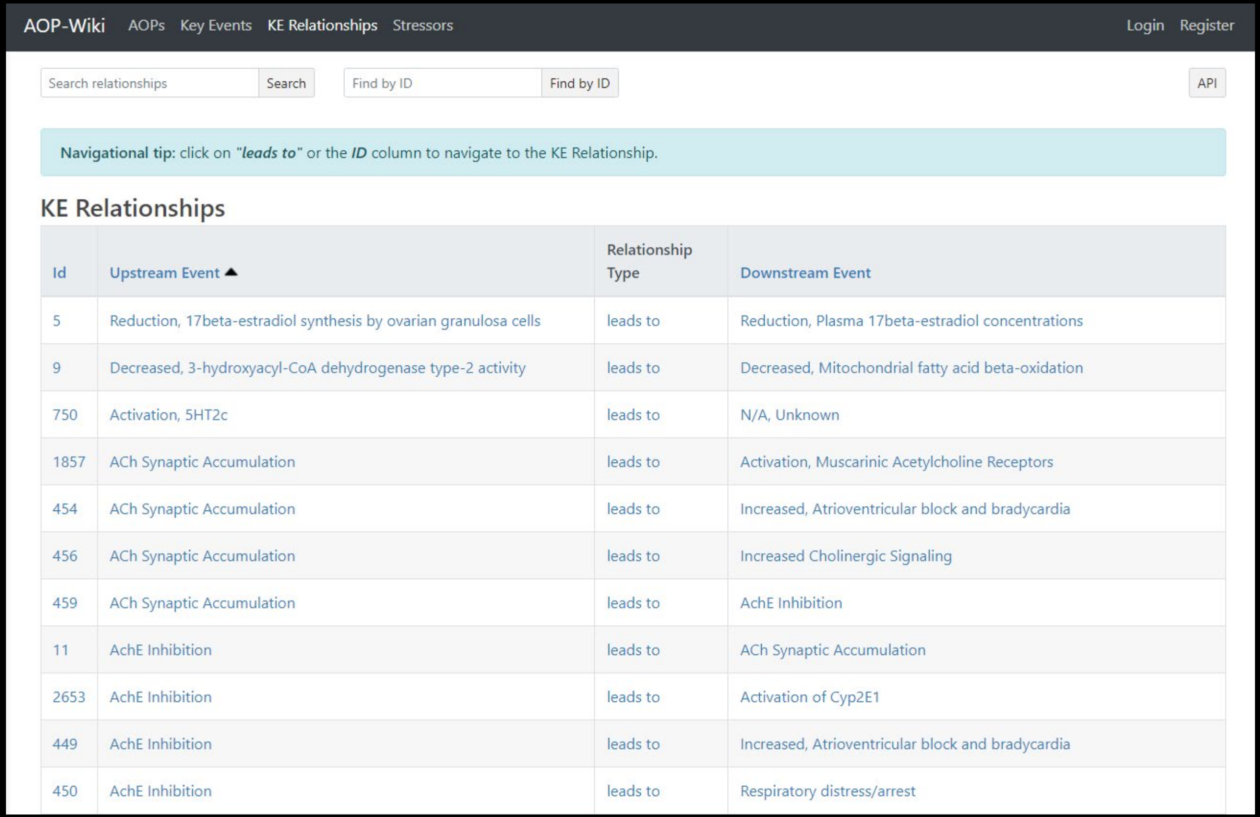
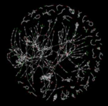

AOP-Wiki AOPs Key Events KE Relationships Stressors Login Register

Search relationships Search Find by ID Find by ID API

Navigational tip: click on "***leads to***" or the ***ID*** column to navigate to the KE Relationship.

KE Relationships

Id	Upstream Event ▲	Relationship Type	Downstream Event
5	Reduction, 17beta-estradiol synthesis by ovarian granulosa cells	leads to	Reduction, Plasma 17beta-estradiol concentrations
9	Decreased, 3-hydroxyacyl-CoA dehydrogenase type-2 activity	leads to	Decreased, Mitochondrial fatty acid beta-oxidation
750	Activation, 5HT2c	leads to	N/A, Unknown
1857	ACh Synaptic Accumulation	leads to	Activation, Muscarinic Acetylcholine Receptors
454	ACh Synaptic Accumulation	leads to	Increased, Atrioventricular block and bradycardia
456	ACh Synaptic Accumulation	leads to	Increased Cholinergic Signaling
459	ACh Synaptic Accumulation	leads to	AchE Inhibition
11	AchE Inhibition	leads to	ACh Synaptic Accumulation
2653	AchE Inhibition	leads to	Activation of Cyp2E1
449	AchE Inhibition	leads to	Increased, Atrioventricular block and bradycardia
450	AchE Inhibition	leads to	Respiratory distress/arrest



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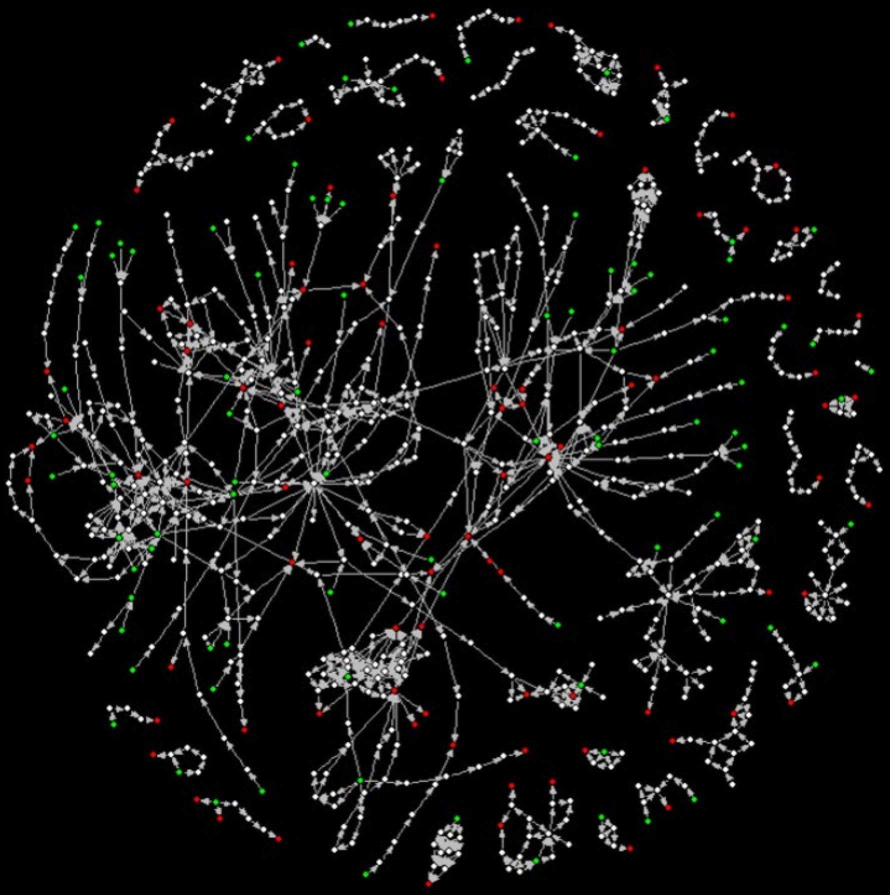

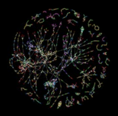

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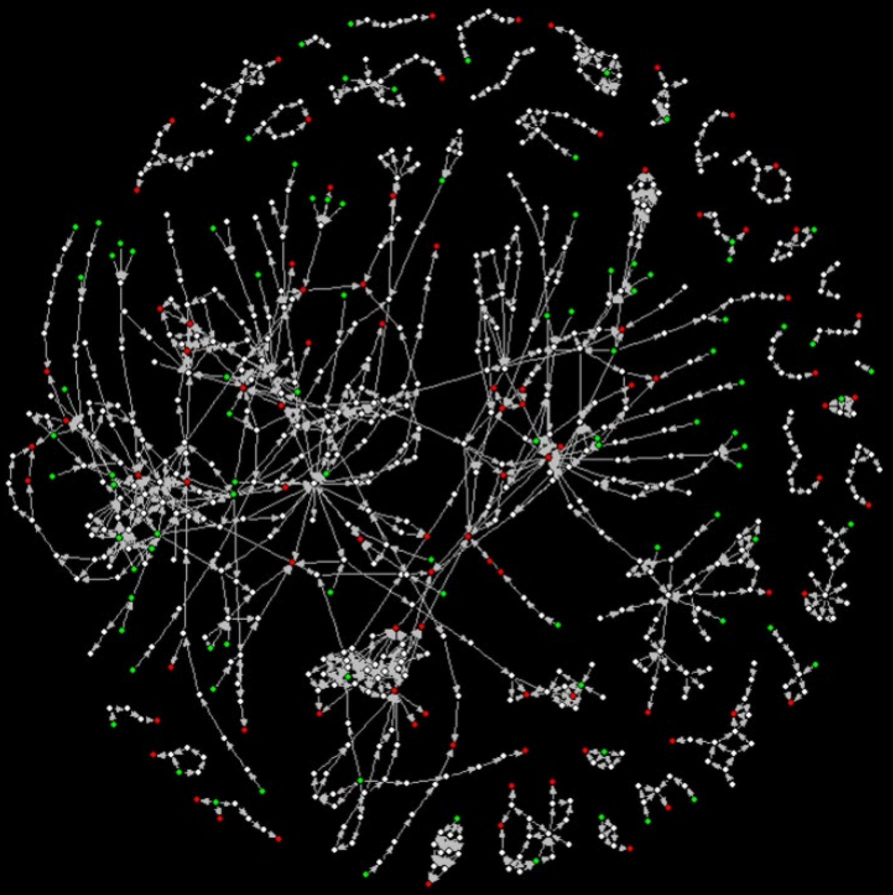
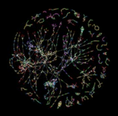
A little about the methods:

- Graph attributes assigned to each KE and KER
  - KE: KE ID, AOP ID, designator (MIE, KE, AO), and Level of biological organization (LOBO)
  - KER: KER ID, AOP ID, weight of evidence (WOE), and quantitative understanding (QE)





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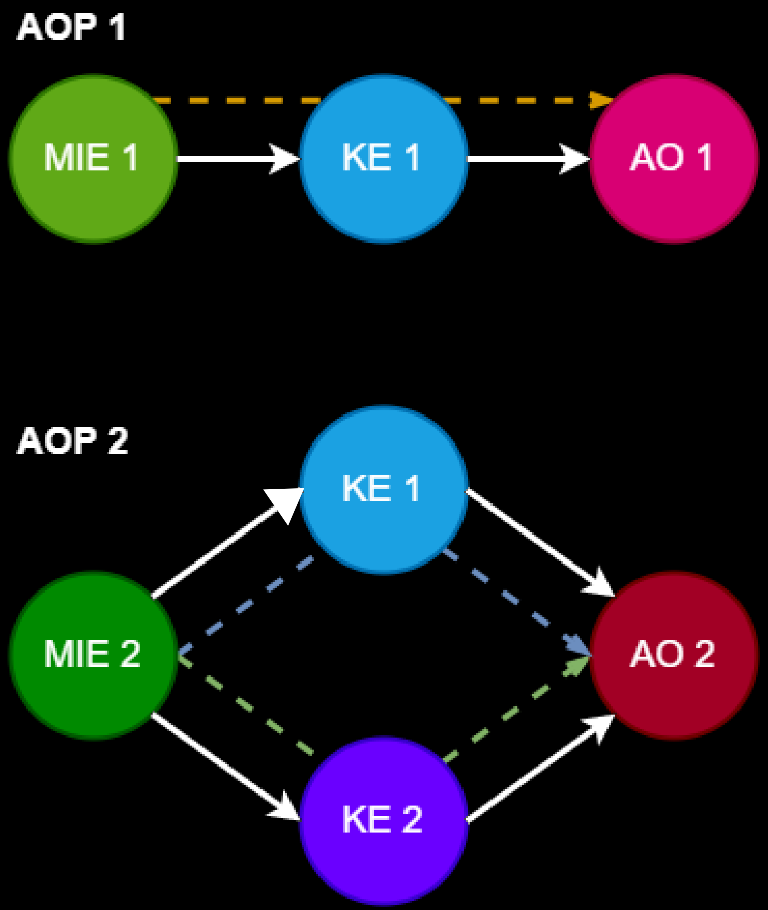

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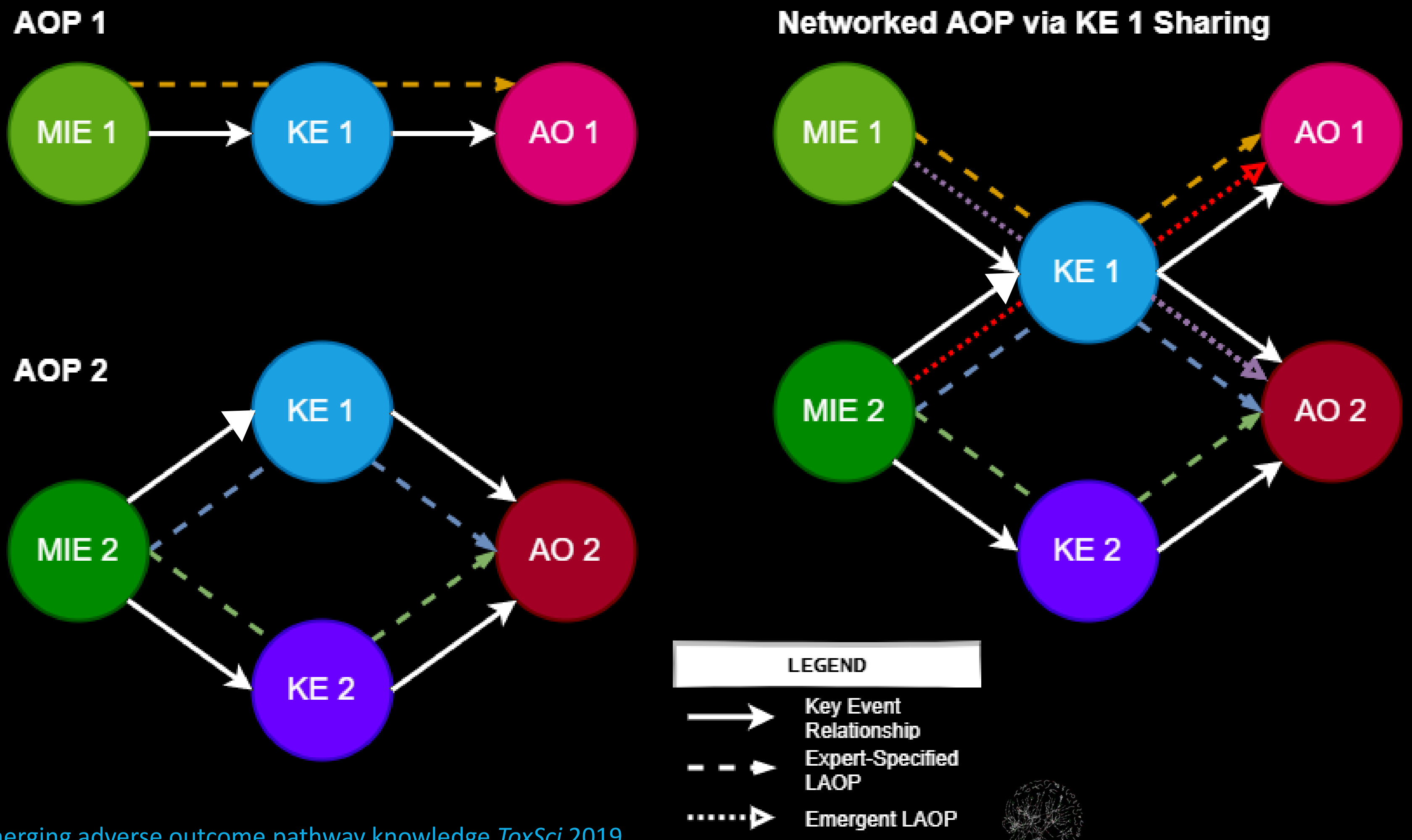

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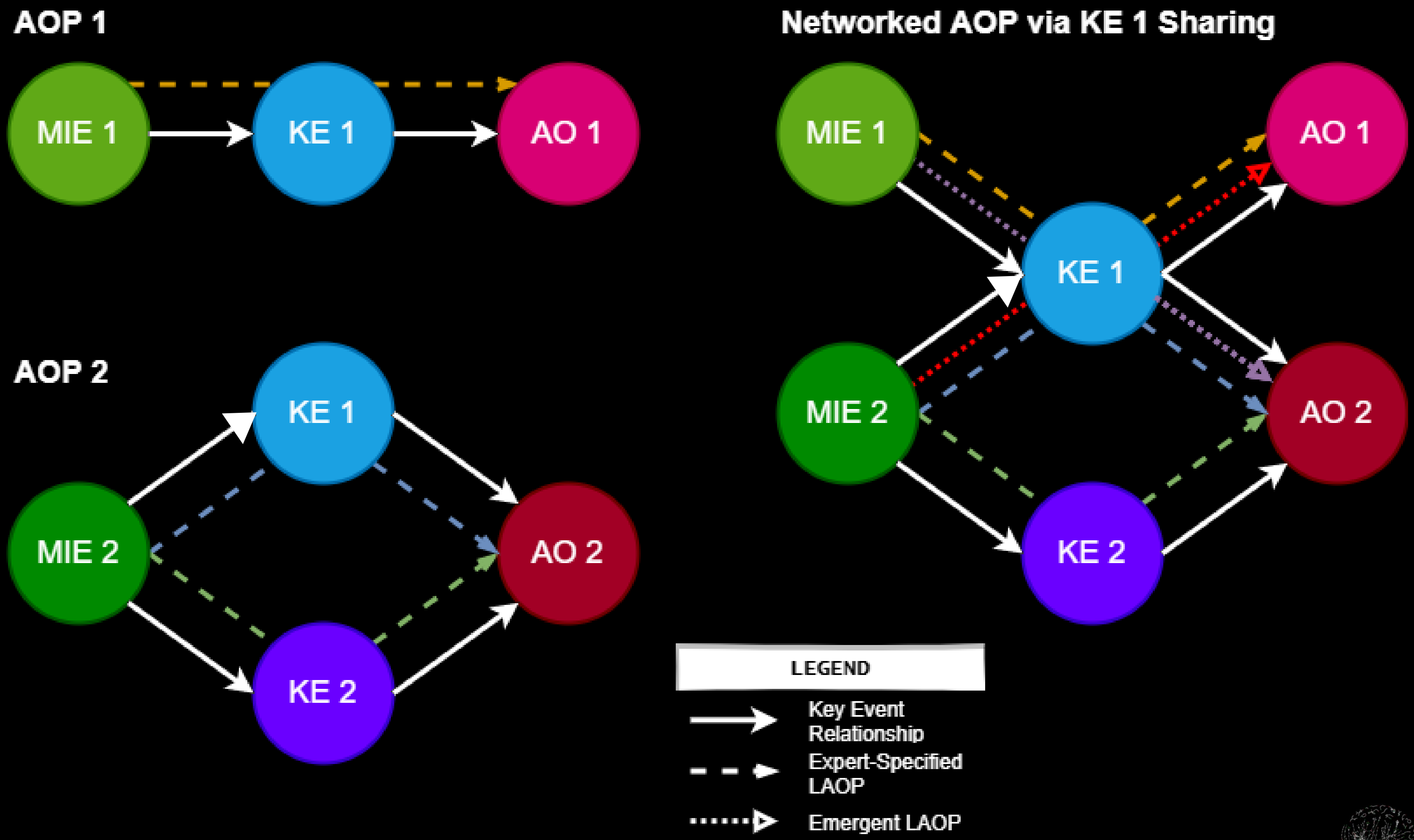

This KE sharing example had

- 2 AOPs
- 3 unique expert-specified linear AOPs
- 2 unique emergent AOPs

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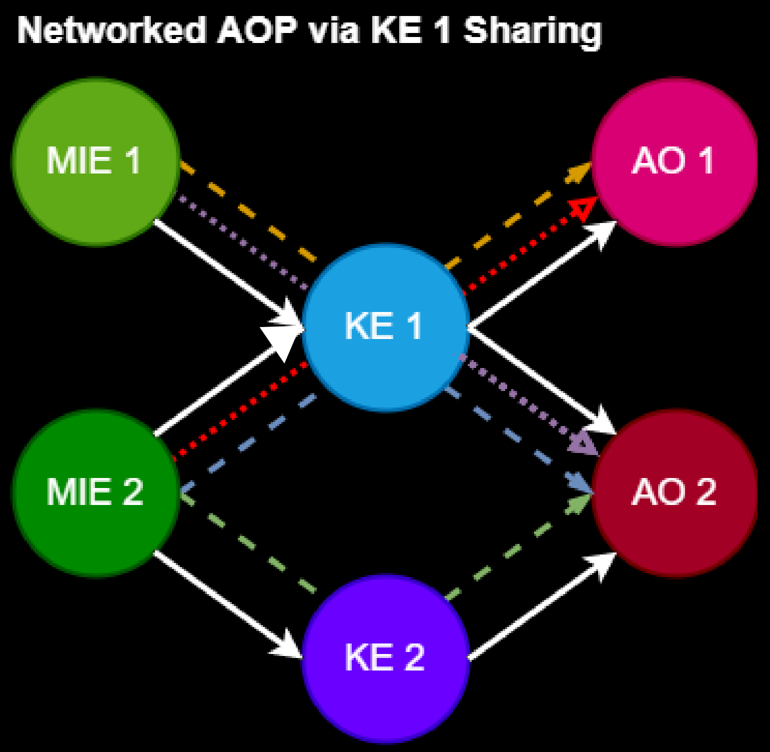

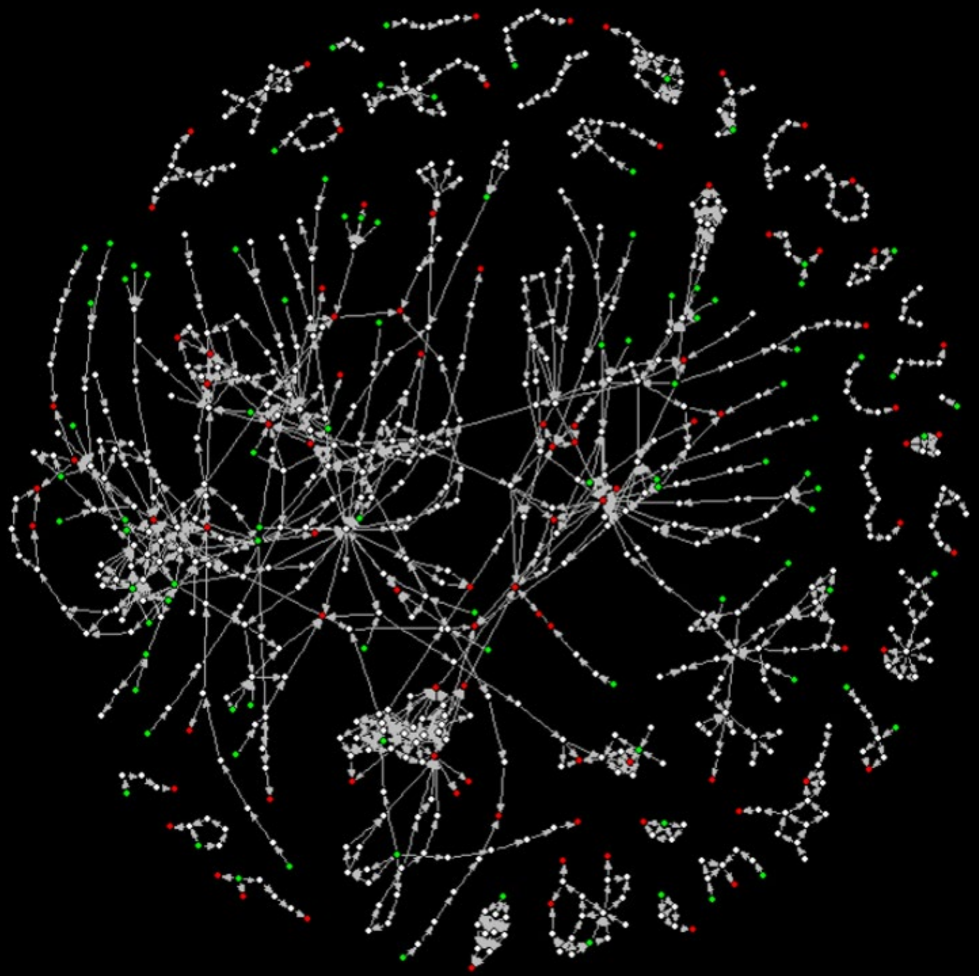

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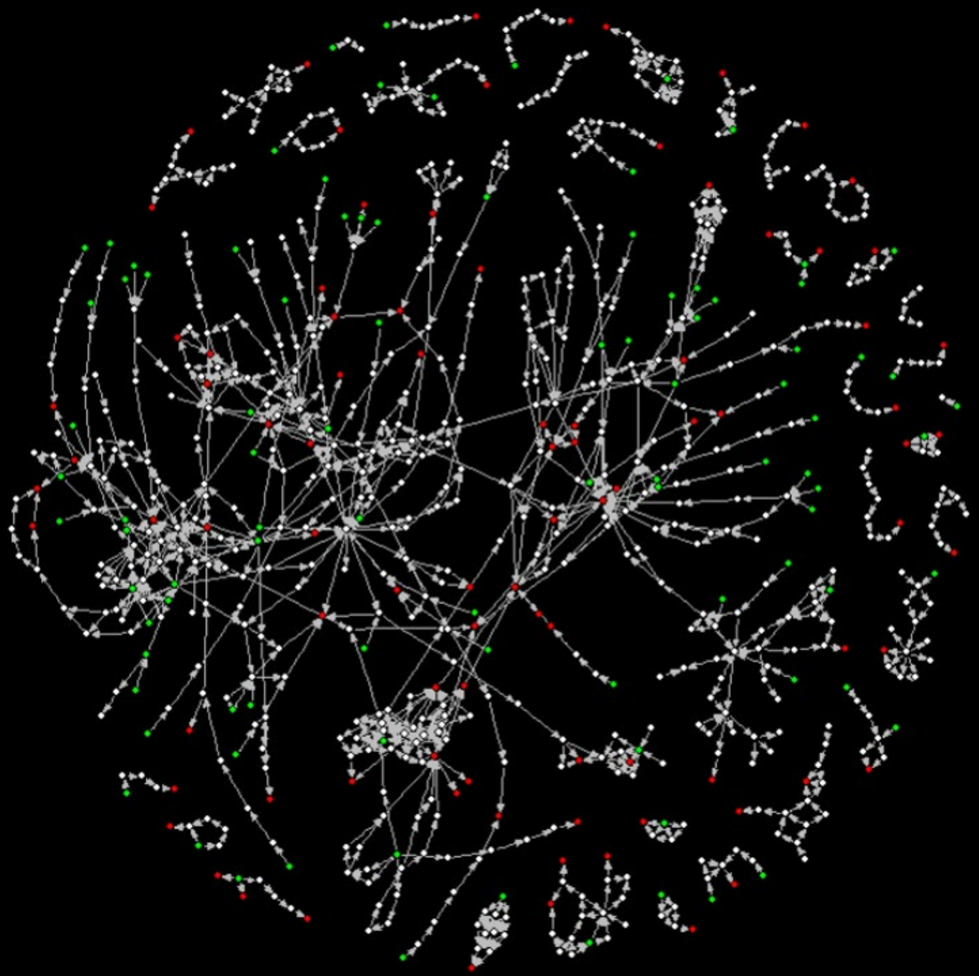
Discovering emergent A O P

Our Analysis showed that the AOP-Wiki had

- 187 AOPs
- 471 unique expert-specified linear AOPs
- 9405 unique emergent linear AOPs



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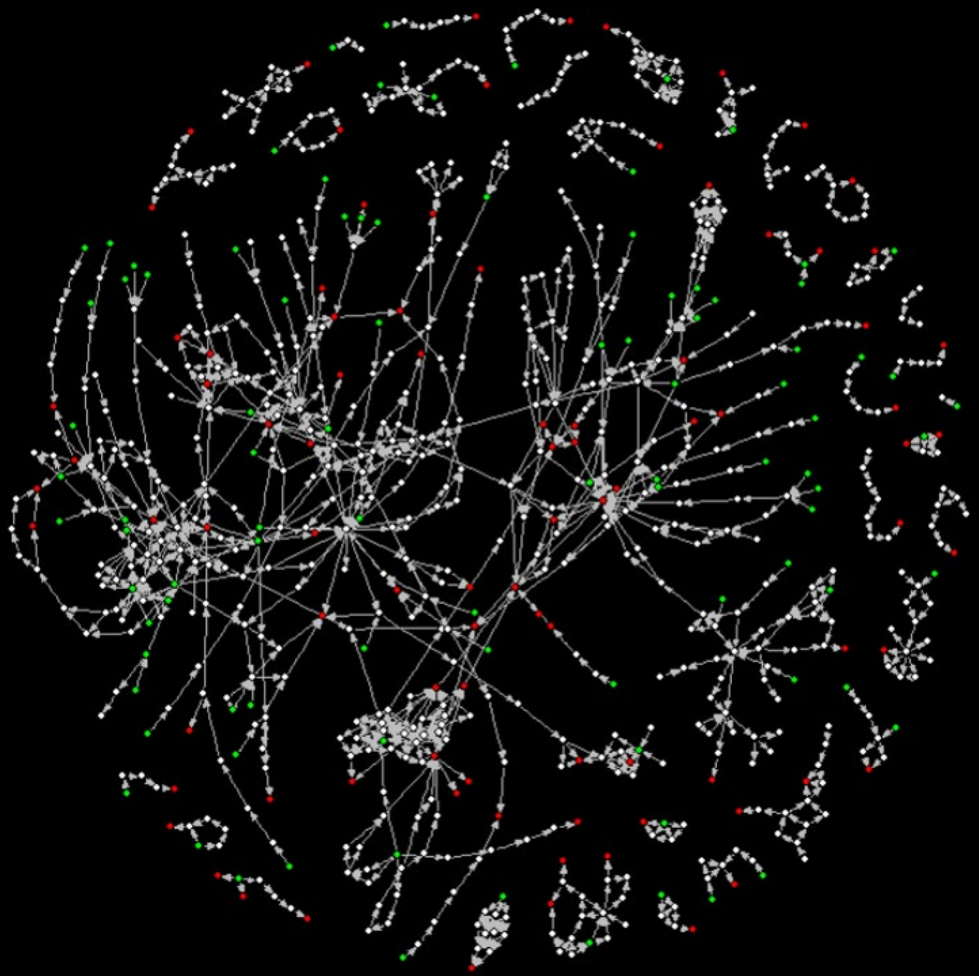

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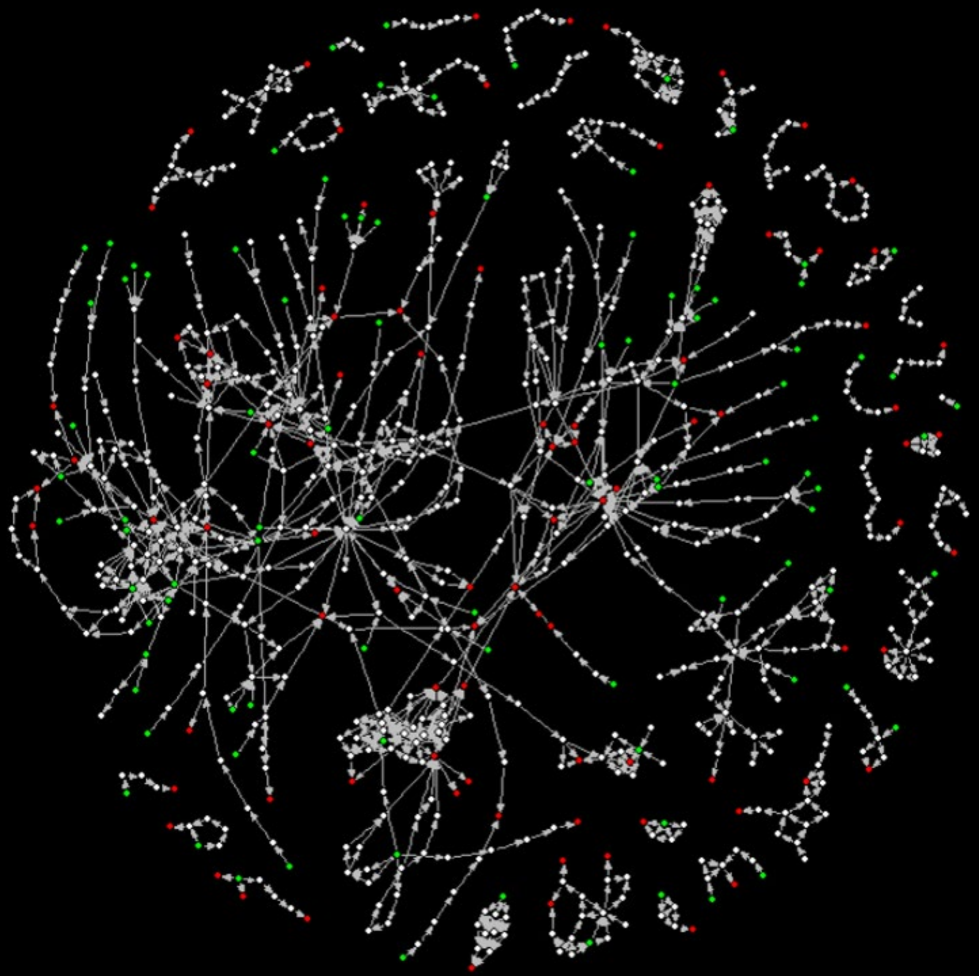

We found them, but are they useful?

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In 2020, Rong-Lin Wang (CCTE/GLTED) showed that semantic analysis provides a method for quantifying the quality of AOPs based on semantic coherence

Aquatic Toxicology 222 (2020) 105478

Contents lists available at ScienceDirect

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Semantic characterization of adverse outcome pathways

Rong-Lin Wang*

Great Lakes Toxicology & Ecology Division, Center for Computational Toxicology & Exposure, U.S. Environmental Protection Agency, Cincinnati, OH, 45268, USA

Check for updates

Assessing the quality of emergent AOP knowledge

In 2020, Rong-Lin Wang (CCTE/GLTED) showed that semantic analysis provides a method for quantifying the quality of AOPs based on semantic coherence

This is a method of converting expressions into logical definitions and looking at similarity/closeness of those definitions to one another based on their structured content

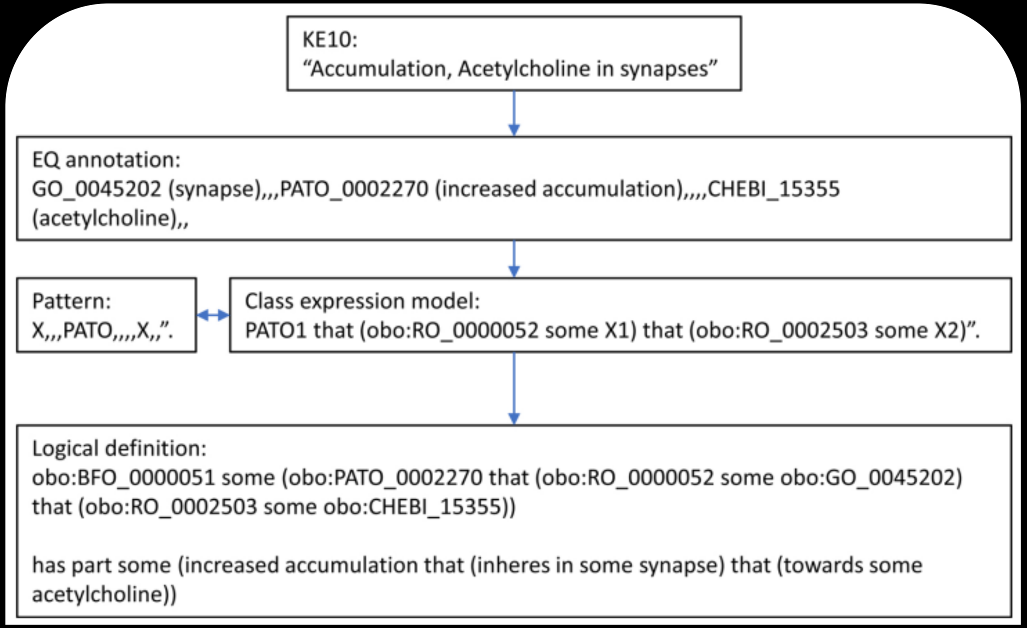
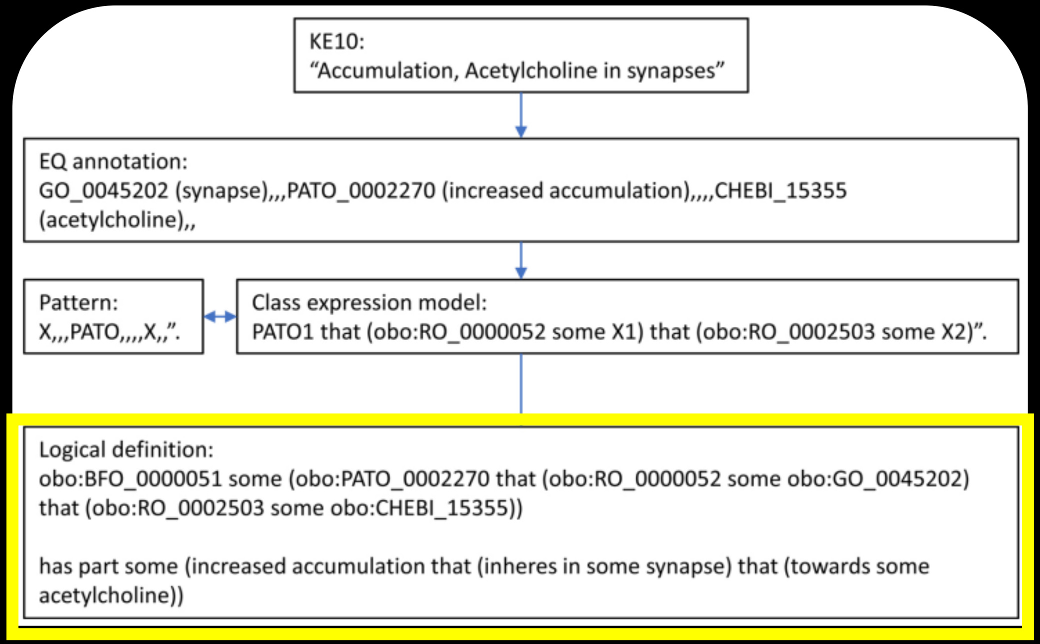


Figure 1b: Creation of logical definitions from KEs (Wang, 2020)

Assessing the quality of emergent AOP knowledge

From Wang, (2020)

- *A logical definition here is defined as several phenotypic expressions composed of more atomic terms from multiple reference ontologies and linked together by appropriate object properties from the Relations Ontology.*



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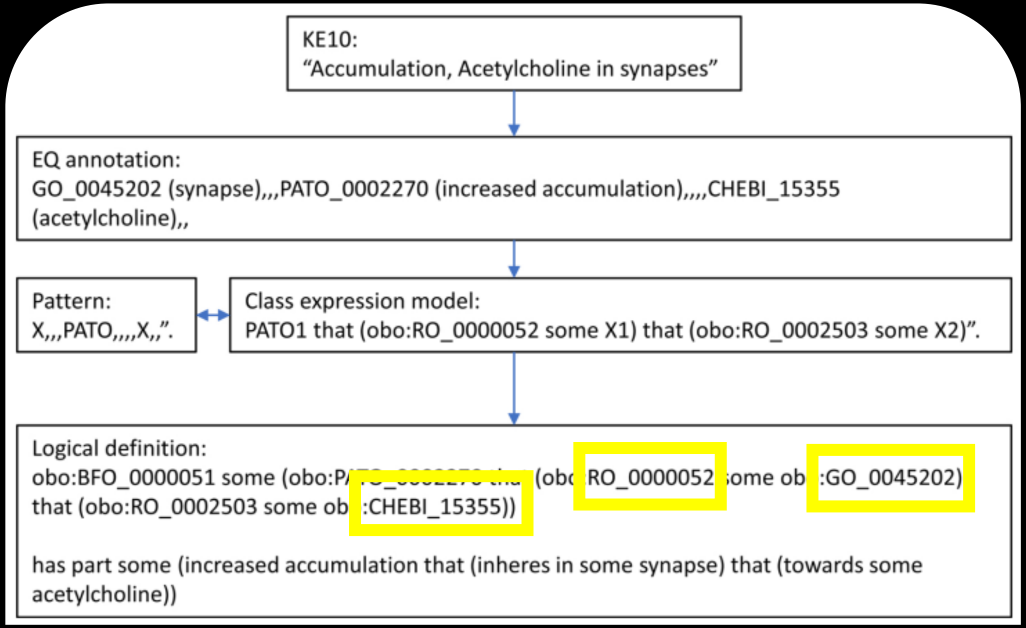
- *There are many reference domain ontologies developed thus far, such as the Gene Ontology, Chemical Entities of Biological Interest Ontology, Cell Ontology, Phenotype and Trait Ontology, and various anatomy ontologies (http://obofoundry.org/).*



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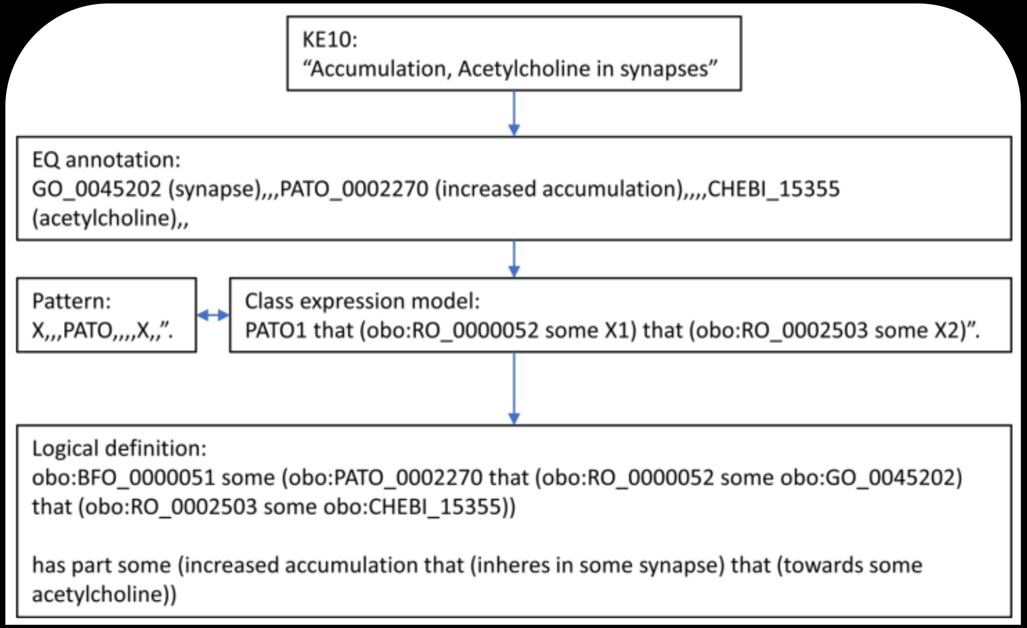

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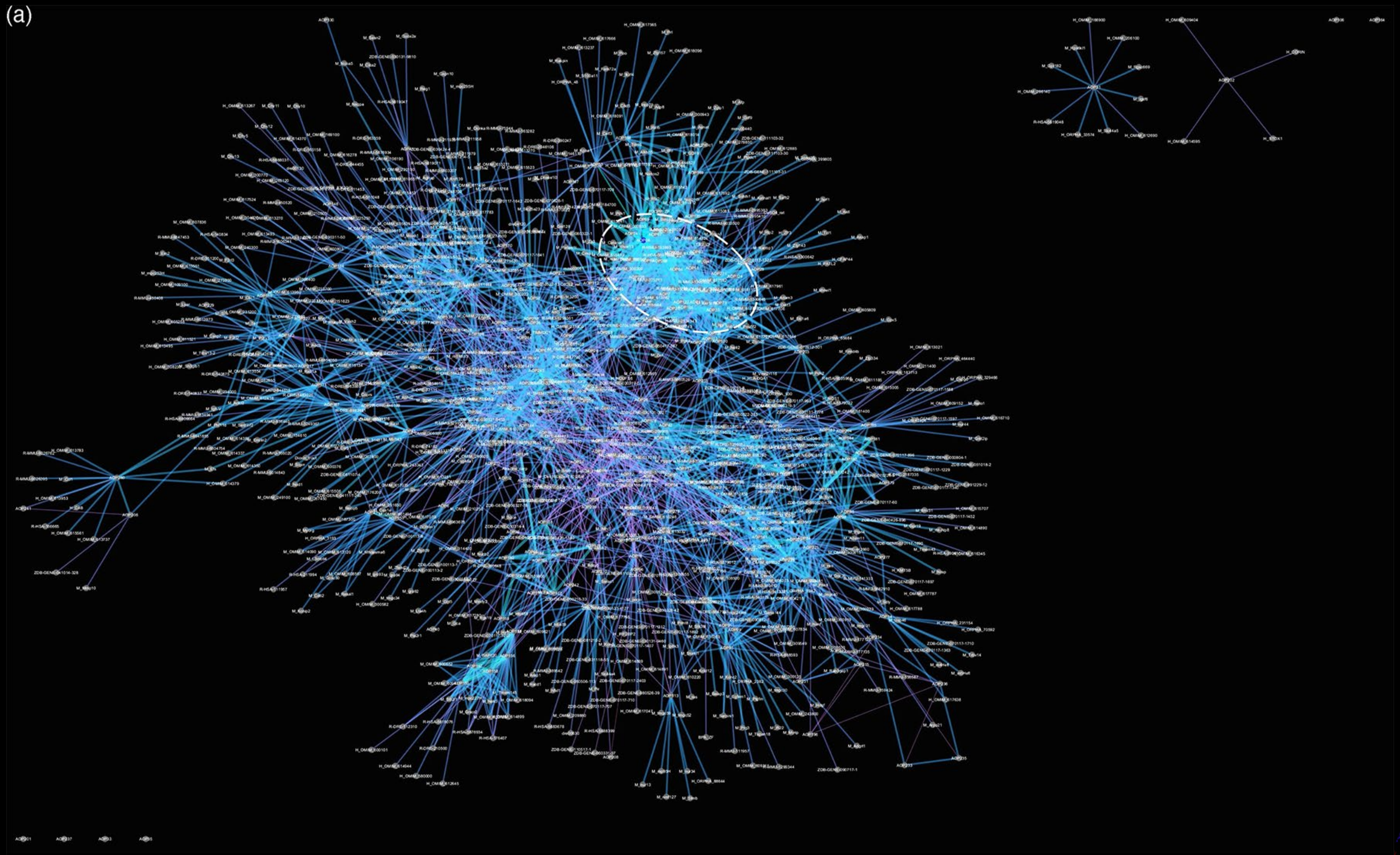
Semantic similarity networks of AOPs, CSPPs, genes, pathways, and diseases (Wang, 2020)



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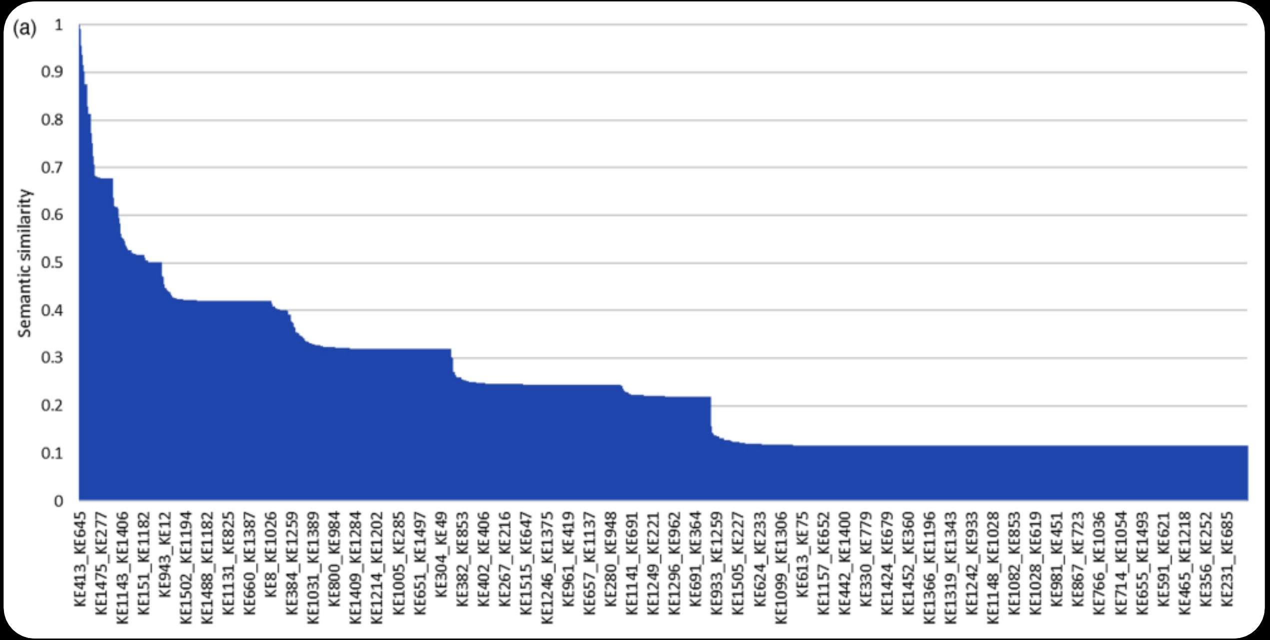

Figure 2a: Pairwise similarities of logical KE definitions (Wang, 2020)

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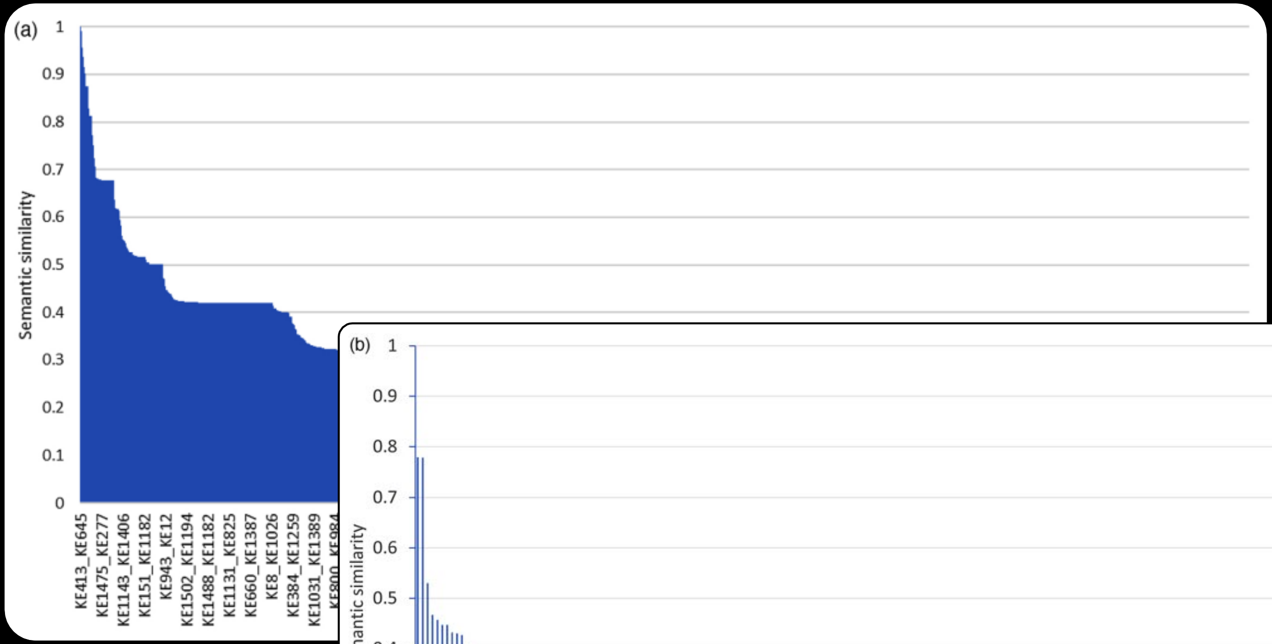

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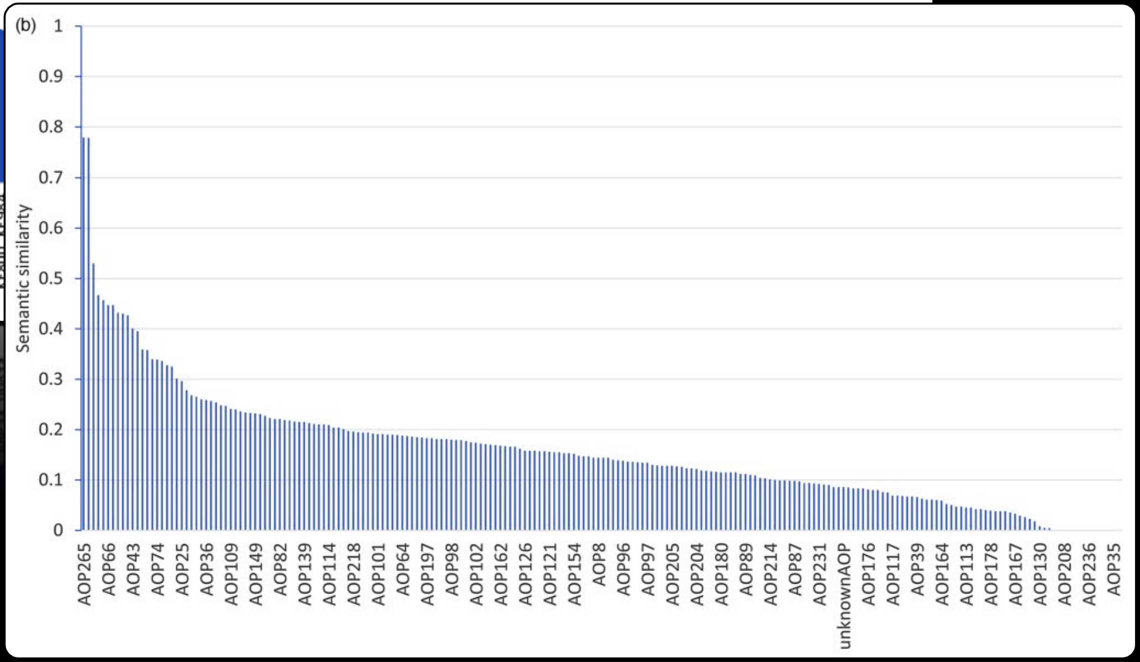

Figure 2b: Mean pairwise similarity within AOPs (Wang, 2020)

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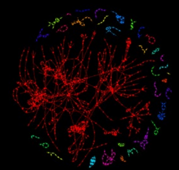
20 of 471 expert-specified LAOPs identified in Pollesch et al., (2019)

	A	B	C	D	E	F	G	H	I	J
1	1	2	3	4	5	6	7	8	9	10
2	888	887	177	889	890	896				
3	888	887	177	890	896					
4	103	1264	1265	988	1266	1267	1268	993	990	351
5	998	1000	858	859	860	861	862	863	864	
6	998	1000	858	860	861	862	863	864		
7	998	1000	858	861	862	863	864			
8	408	3	219	405						
9	408	3	219	405	406					
10	667	64	669	682	616	613				
11	201	195	52	381	55	188	352			
12	201	195	52	381	55	188	352	341		
13	201	195	52	381	382	385	386	341		
14	201	195	52	381	383	385	386	341		
15	201	195	52	381	55	385	386	341		
16	97	155	185	336						
17	97	185	336							
18	97	336								
19	12	10	444	351						
20	12	10	39	445	351					
21	12	351								



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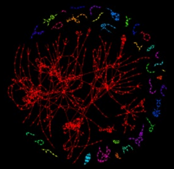
20 of 9408 emergent LAOPs identified in Pollesch et al., (2019)



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Semantic analysis metrics

For an AOP with N KEs, $AOP_N = KE_1 \rightarrow KE_2 \rightarrow \cdots \rightarrow KE_N$, and with $SS\left(KE_x, KE_y\right) \in [0,1]$ as the semantic similarity between KEs x and KE y:

- $SSS_{Mean}(AOP_N) = \frac{1}{N-1} \sum_{i=1}^{N-1} SS(KE_i, KE_{i+1})$
- $SSS_{Min}(AOP_N) = \min_{i=1,\ldots,N-1} SS(KE_i, KE_{i+1})$
- $PSS_{Mean}(AOP_N) = \frac{1}{\binom{N}{2}} \sum_{i<j} SS\left(KE_i, KE_j\right) \; for \; i,j \in \{1, \ldots, N\}$

Where KE_1 is the MIE and KE_N is the AO. Each metric captures different AOP semantic qualities

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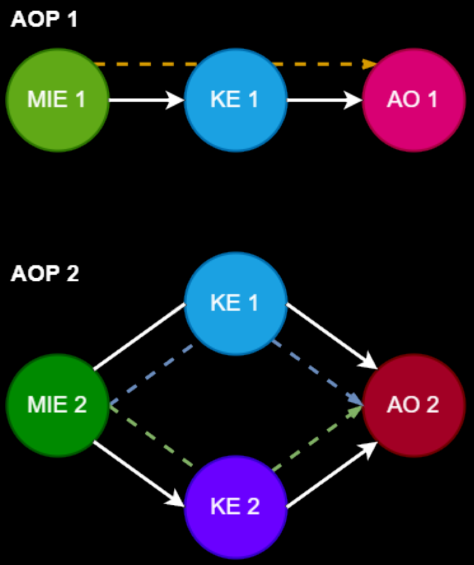

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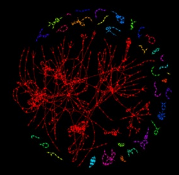
- $SSS_{Min}(AOP_N) = \min_{i=1,\ldots,N-1} SS(KE_i, KE_{i+1})$
- $PSS_{Mean}(AOP_N) = \frac{1}{\binom{N}{2}}\sum_{i<j} SS\left(KE_i, KE_j\right)\ for\ i,j \in \{1,\ldots,N\}$

Where KE_1 is the MIE and KE_N is the AO. Each metric captures different AOP semantic qualities

Results

	SSS_{Mean}	SSS_{Min}	PSS_{Mean}
AOP: Mean (n=236) • Max (ID)	0.153[a] • 0.553 (66)	.025 • 0.421 (41)	0.151[b] • 0.391 (66)
EAOP: Mean (n=9408) • Max (ID)	0.144[a] • 0.409 (9402)	.007 • 0.319 ([c])	0.141[b] • 0.424 (9403)

[a,b] Difference in means not statistically significant ($\alpha = 0.05$)
[c] 12 EAOPs tied for the maximum SSS_{Min} value: 6761, 6762, 6766, 6767, 6768, 6772, 6778, 6784, 9401, 9402, 9403, 9404. *Note: EAOP IDs were assigned for analysis purposes and details of specific EAOPs can be shared upon request*



Assessing quality of emergent adverse outcome pathways *Work in Progress*
- Pollesch, NL; Olker, JH; Wang, R-L

Assessing the quality of emergent AOP knowledge

He agreed and ran the analyses on the nearly 10000 LAOPs I sent

The results from the first round of analyses are exciting

Semantic analysis metrics

For an AOP with N KEs, $AOP_N = KE_1 \to KE_2 \to \cdots \to KE_N$, and with $SS(KE_x, KE_y) \in [0,1]$ as the semantic similarity between KEs x and KE y:

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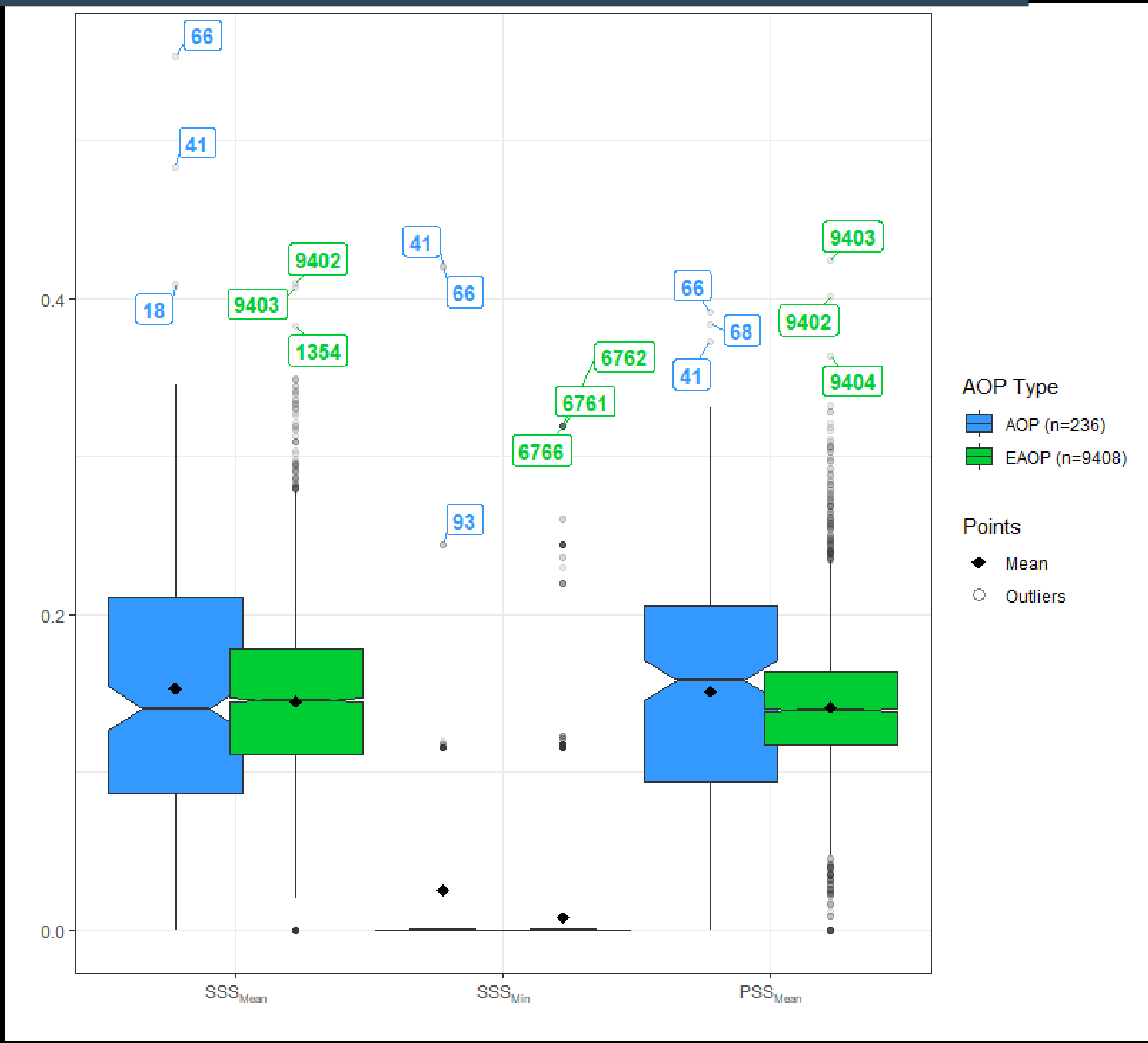
Semantic similarity metrics for AOPs and EAOPS



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Assessing the quality of emergent AOP knowledge

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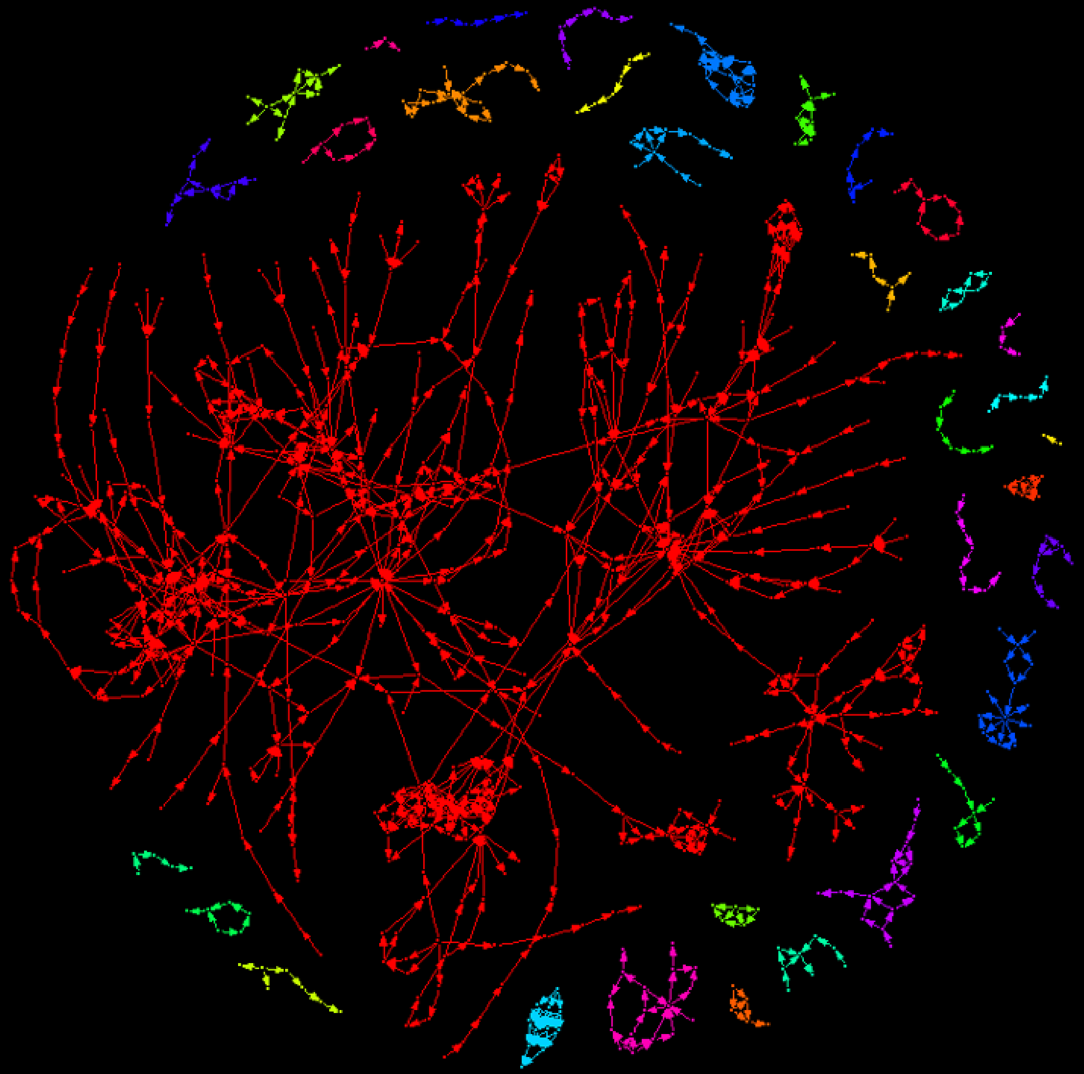
Why?

If these results hold up, that means that we have computationally identified (likely to be thousands of) unique emergent AOPs that are of high semantic quality



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Assessing the quality of emergent AOP knowledge

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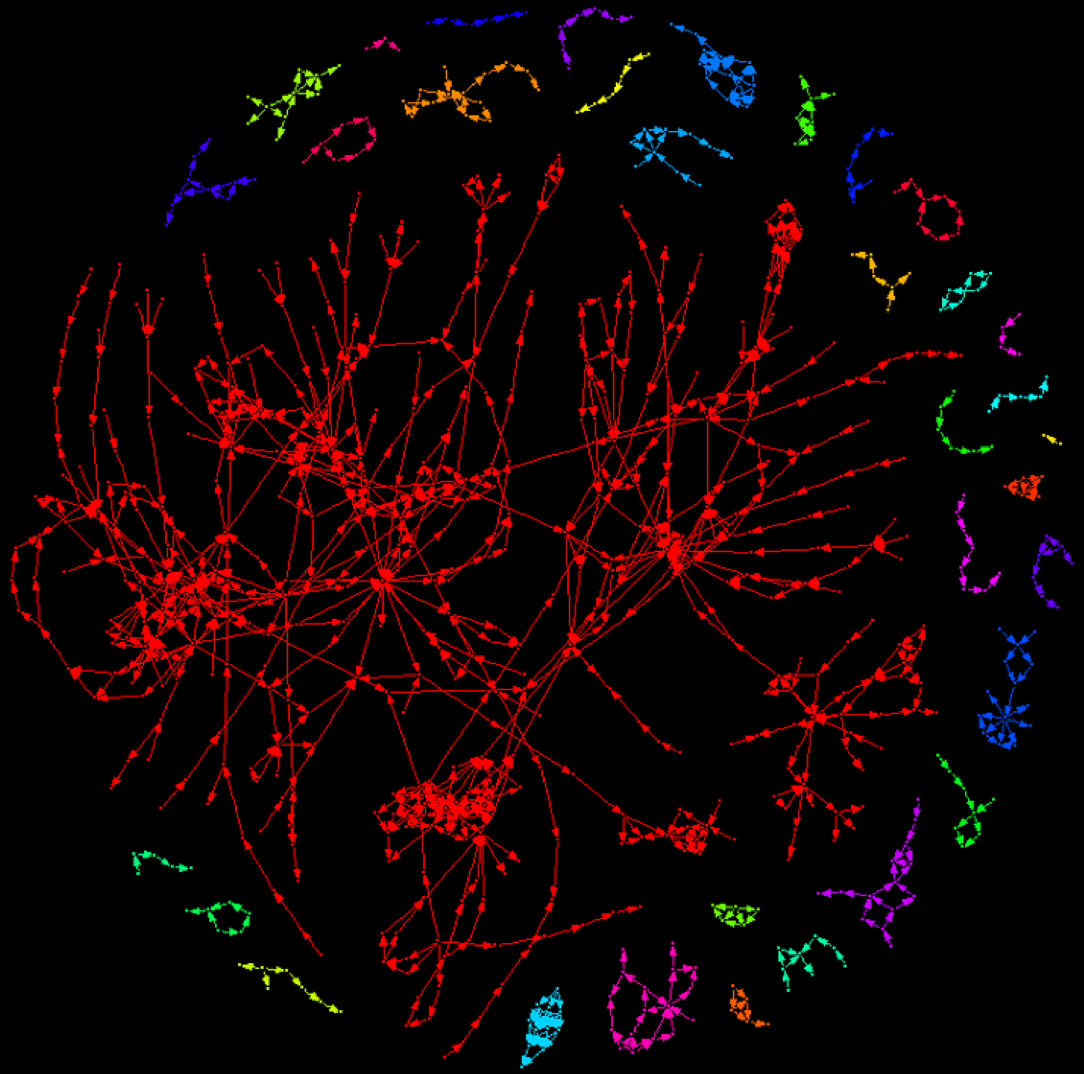

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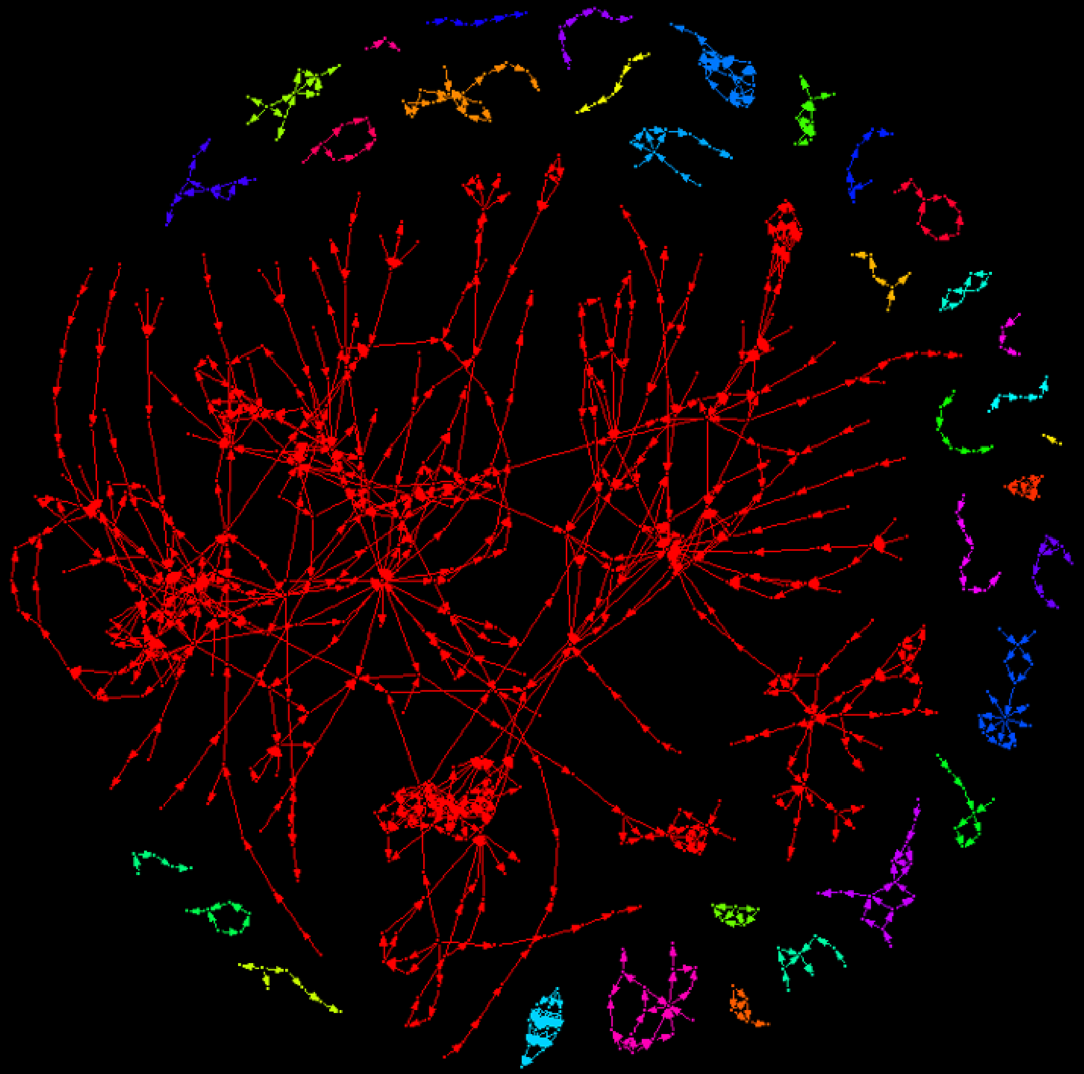
Assessing the quality of emergent AOP knowledge

So, what is next?

- Manual inspection of computational results
  - Are there patterns in highly coherent LAOPs
  - Do these results pass the sniff test?
  - Identifying a few of the outstanding emergent LAOPs to use as case studies



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Assessing the quality of emergent AOP knowledge

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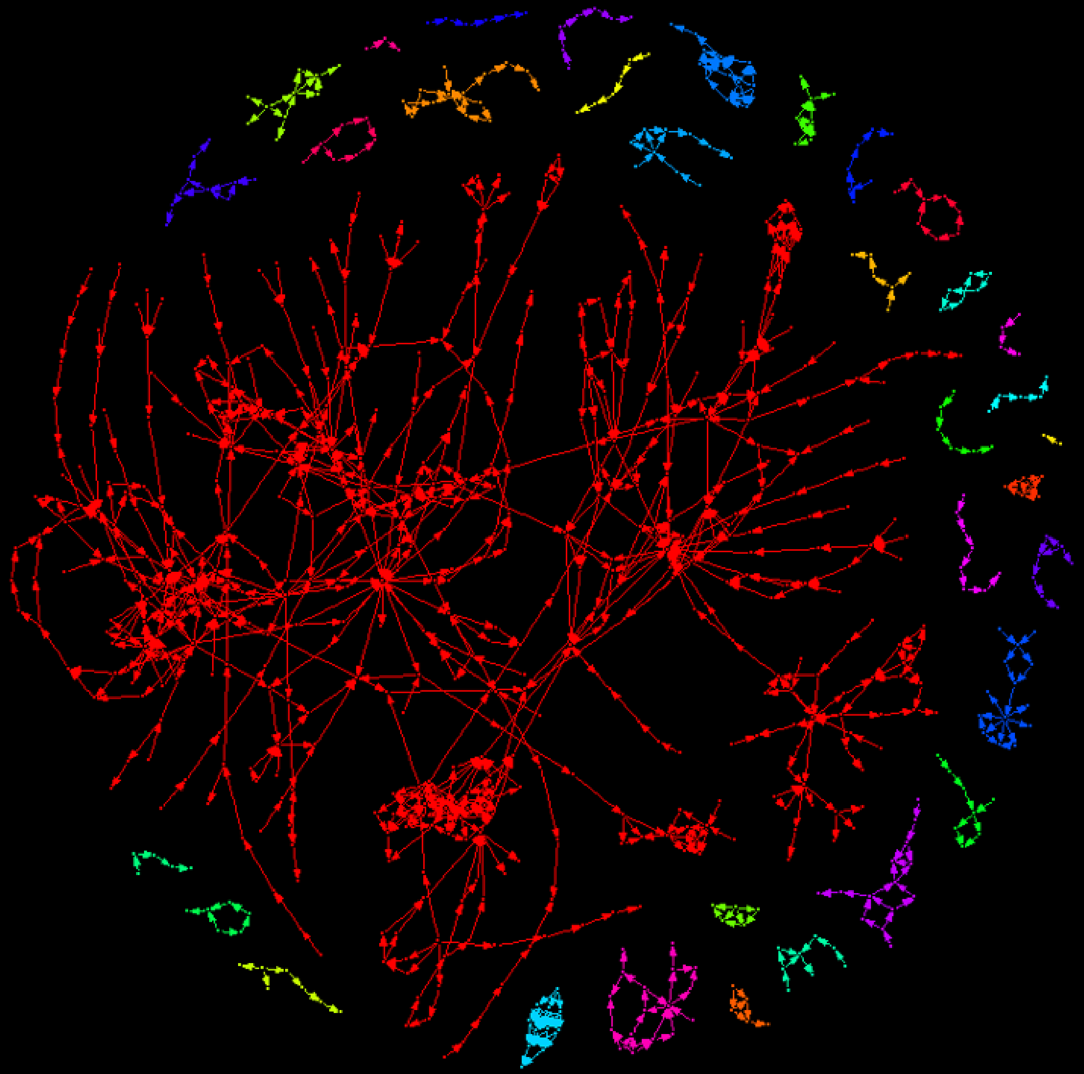
We are also comparing how other metrics of quality compare to semantic quality metrics



Assessing quality of emergent adverse outcome pathways *Work in Progress*
 - Pollesch, NL; Olker, JH; Wang, R-L

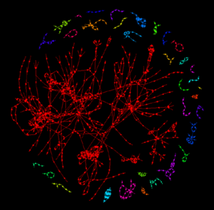
Assessing the quality of emergent AOP knowledge

What aspects of the AOP-Wiki enabled these analyses?

Emergent AOP:

Graph attributes assigned to each KE and KER

- KE: KE ID, AOP ID, and designator (MIE, KE, AO)
- KER: KER ID, AOP ID, weight of evidence (WOE), and quantitative understanding (QE)



Assessing the quality of emergent AOP knowledge

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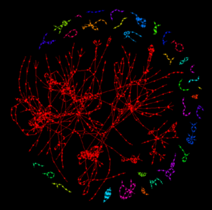
Semantic Analysis:

KE descriptions and supplementary information on applicability



Assessing the quality of emergent AOP knowledge

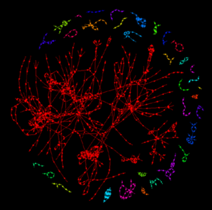
What aspects of these analyses could be useful in the AOP-Wiki?

Emergent AOP:

- How involved are KEs in emergent AOPs? (We calculated this)
- High quality emergent AOPs could be identified, evaluated for quality, and added explicitly to the AOP-Wiki

Semantic Analysis:

- Semantic Similarity Scores for all KERS *and* for any pair of KEs in the WIKI
- Semantic similarity metrics for all AOPs
- Suggested KEs for developers (based on high SS scores)



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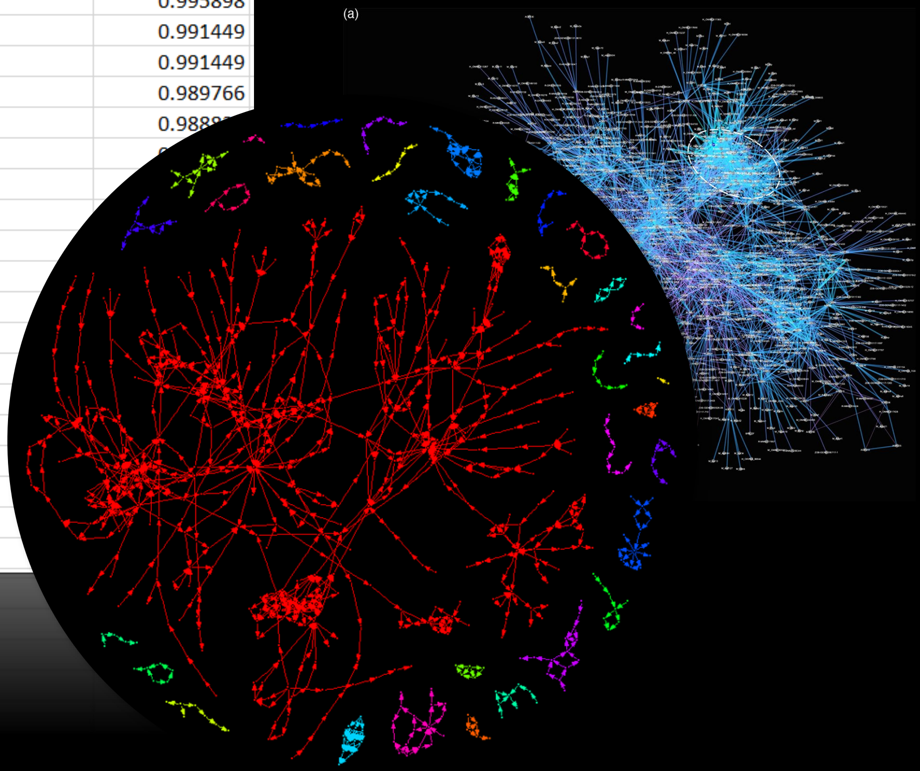
Discovering and **Assessing the quality** of emergent Adverse Outcome Pathway knowledge

If you have questions

262	AOP158	AOP155	0.995898
263	userAOP94	AOP18	0.991449
264	userAOP95	AOP18	0.991449
265	userAOP23	AOP23	0.989766
266	userAOP112	AOP216	0.9888
267	EmergingAOP1814	AOP216	
268	userAOP33	AOP25	
269	EmergingAOP6816	AOP216	
270	userAOP348	AOP6	
271	userAOP143	AOP42	
272	EmergingAOP6812	AOP216	
273	userAOP113	AOP238	
274	userAOP163	AOP54	
275	EmergingAOP1815	AOP238	
276	userAOP171	AOP134	
277	userAOP160	AOP7	
278	AOP238	AOP268	
279	AOP268	AOP238	
280	EmergingAOP1869	AOP42	



Please reach out to me at Pollesch.Nathan@epa.gov with any questions.

EXTRA:
So, what can we do with AOP networks?

- That depends on the network, in particular:
  - The structure of the network
  - The data available to describe the relationships
- Some network analyses:
  - Shortest path analyses
  - Topological sorting for visualization
- From a quantitative modeling standpoint, it also depends on the network, in particular:
  - The structure of the network
  - The data available to describe the relationships

Perkins et al describe how qAOP can utilize networks of increasing specificity

Bayesian networks are coming under increasing use in ecotoxicology.

IEAM special issue, Burgoon et al, Landis et al

Petri nets (Edhlund et al)