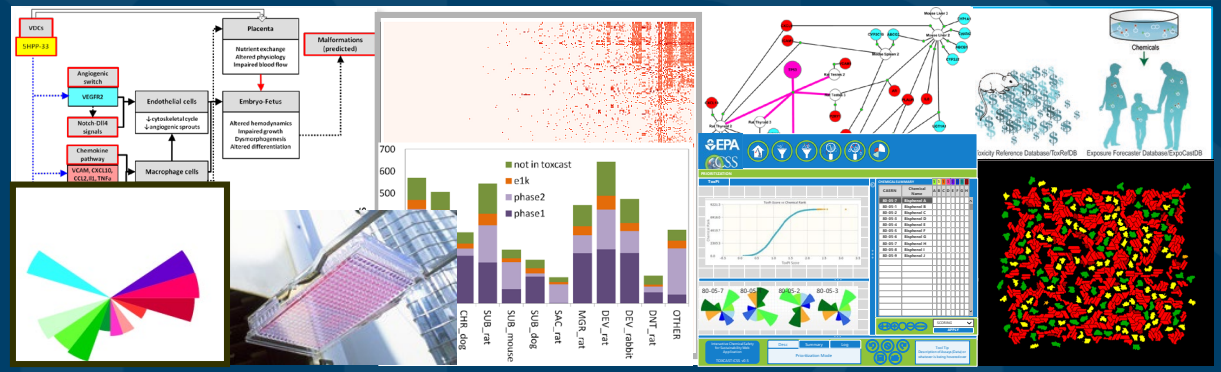
Transitioning GenRA to Quantitative Predictions: A Case Study Using ToxRefDB 2.0



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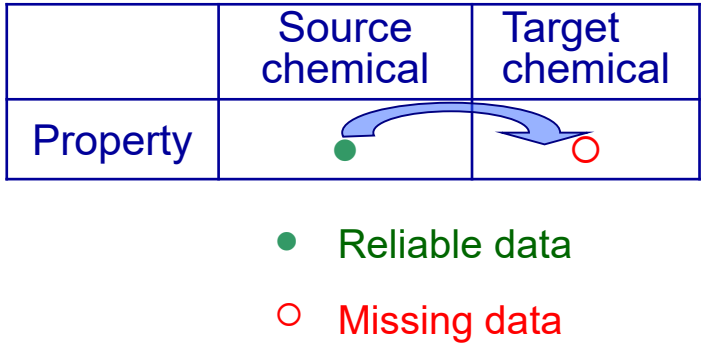
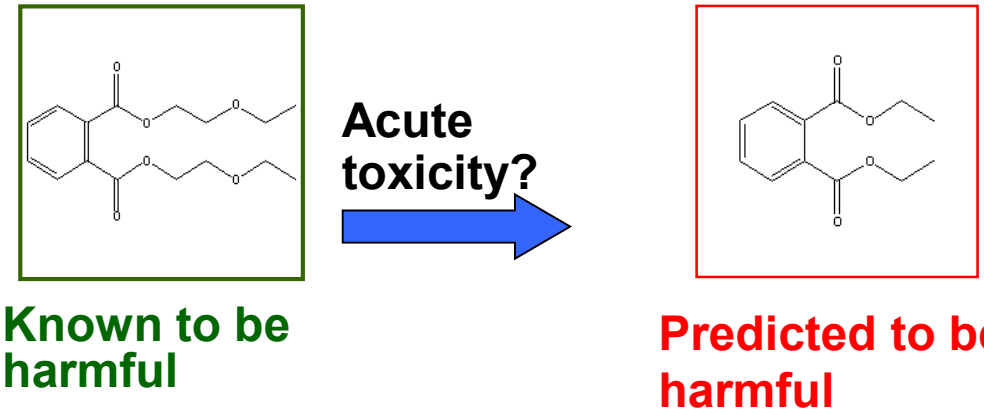
Outline

- Overview of approach
- Summary of ToxRef data
- Analysis
- Evaluation of predictions
- Future work + conclusions

Definitions: Read-across

- Read-across describes the method of filling a data gap whereby a chemical with existing data values is used to make a prediction for a ‘similar’ chemical.
- A target chemical is a chemical which has a data gap that needs to be filled i.e. the subject of the read-across.
- A source analogue is a chemical that has been identified as an appropriate chemical for use in a read-across based on similarity to the target chemical and existence of relevant data.





GenRA - Introduction

- GenRA (Generalized Read-Across) is a “local validity” approach predicting toxicity as a similarity-weighted activity of source analogues based on chemistry and/or bioactivity descriptors. (Shah et al, 2016)

- Generalized version of Chemical-Biological Read-Across (CBRA) developed by Low et al (2013)

- **Goal**: to establish an objective performance baseline for read-across and quantify the uncertainty in the predictions made.

Methods

- GenRA is a similarity-weighted activity score of nearest neighbors

$$y_i = \frac{\sum_j^k s_{ij} x_j}{\sum_j^k s_{ij}}$$

- Similarity calculated using Jaccard distance over Morgan chemical fingerprints
- Search for a maximum of 10 nearest neighbors on entire dataset.
- Use a similarity threshold of 0.5

Original Application

- Underlying data used was taken from ToxRefDB v1, a collection of repeated dose toxicity study types e.g. chronic, multigeneration, developmental, subchronic etc
- Toxicity effects within those study types were recorded as binary outcomes (0 for non-toxic, 1 for toxic)
- Toxicity effects were then predicted as binary outcomes (0 or 1)
- Dataset was clustered into local validity domains to find areas of chemical space where method performs best

Current Application

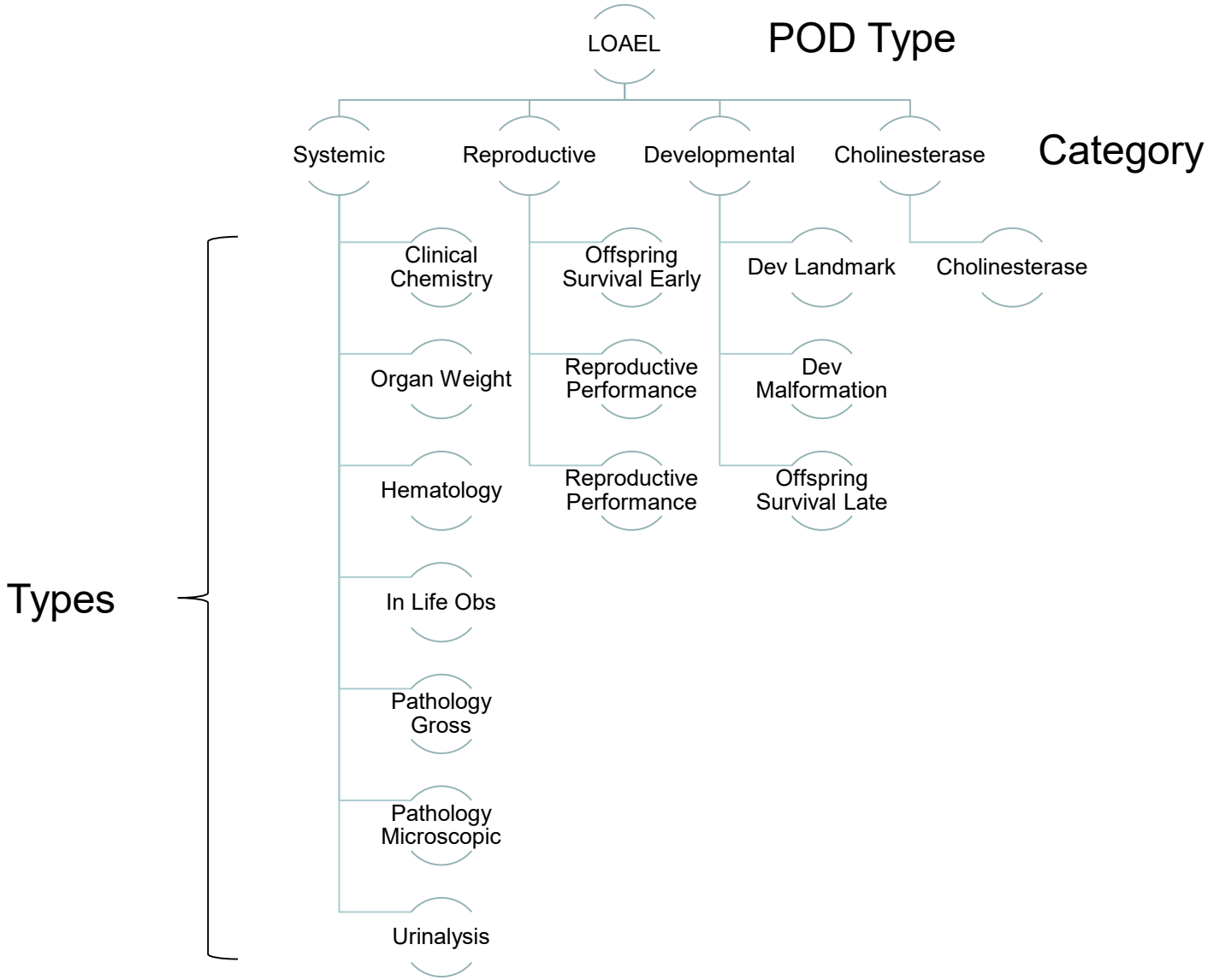
- We would like to test how GenRA performs on non-binary data using POD values from ToxRefDB 2.0.
- POD: Point of departure, or points on a dose-response curve corresponding to an observed effect level or no effect level
- 104,108 chemical level PODs across 1076 substances
- POD types: LOAEL (lowest observed adverse effect level), NOAEL (no observed adverse effect level), LEL (lowest effect level), NEL (no effect level)
- Endpoint categories: cholinesterase, developmental, reproductive, systemic
- 13 endpoint types
- 253 endpoint targets

EPA United States Environmental Protection Agency

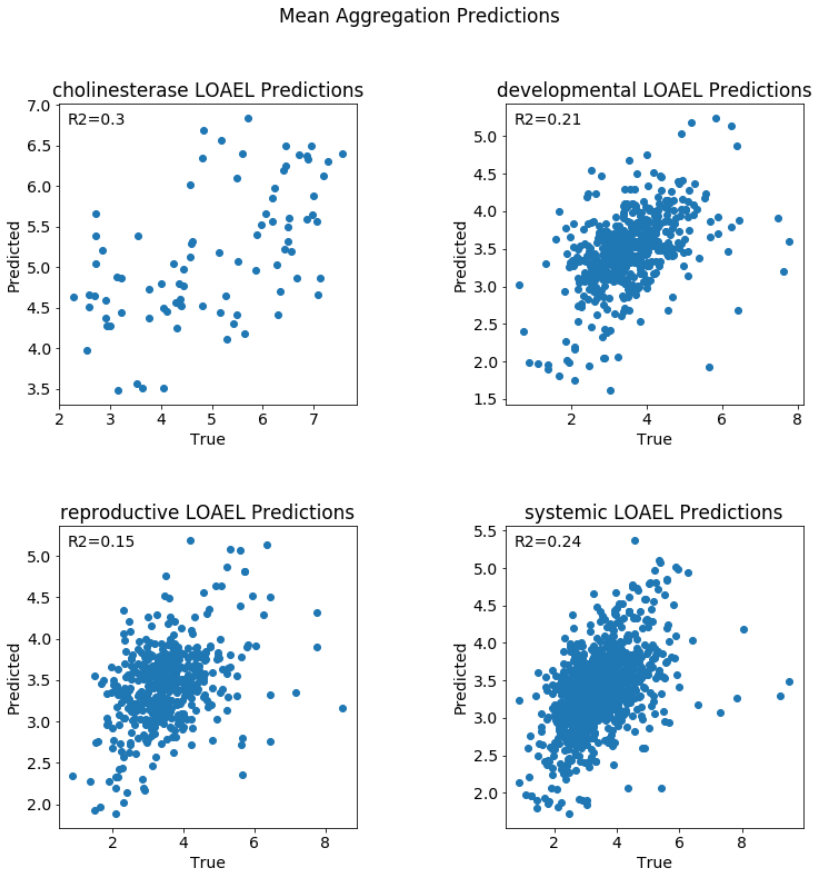
Approach

- We use GenRA to predict LOAEL values using Morgan fingerprints for similarity
- For chemicals that contain multiple LOAEL values, we aggregate them by taking the mean.
- We conduct a grid search over k (number of nearest neighbors) and s (similarity threshold) to find optimal values for R^2
- Cluster analysis was performed to find local neighborhoods of chemicals where approach performs particularly well.

Overview of ToxRef POD types



GenRA Predictions using Morgan fingerprints with k=10 and s=0.05

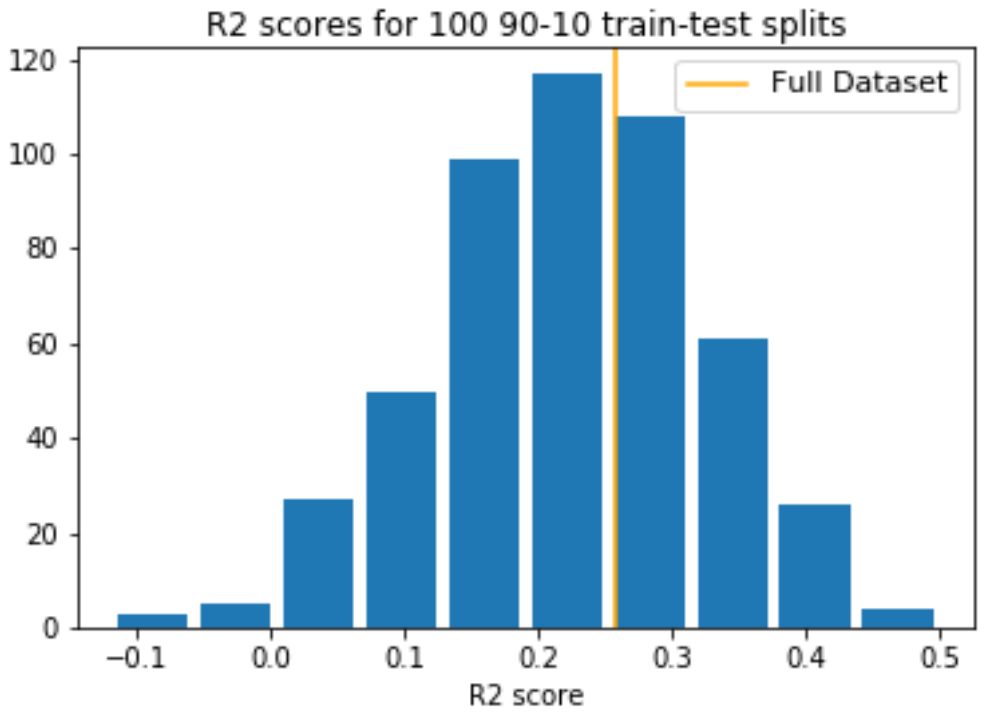


Endpoint Category	R2
Cholinesterase	0.26
Developmental	0.2
Reproductive	0.15
Systemic	0.24

Comparison with Other Methods

- Wignall et al 2018
  - Self-aggregated dataset of chronic toxicity values including RfDs, OSFs, CPVs, RfCs, and IURs for 2261 chemicals
  - Random forest regression
  - $0.2 < Q^2 < 0.45$ (depending on type of toxicity value)
- Helma et al 2018
  - Chronic rat LOAEL values for 826 chemicals
  - Local weighted random forest regression
  - $0.45 < R^2 < 0.47$ (cross validation)
- GenRA
  - LOAEL values for cholinesterase inhibition, developmental, reproductive, and systemic toxicity for 1064 chemicals
  - k-Nearest Neighbors with Morgan fingerprints
  - R2 = 0.24 (k=10, s=0.5, systemic endpoint)

Evaluation of GenRA Predictions



- Cross-validation testing
- Systemic endpoint
- 90-10 train-test splits
- R^2 values range from -0.04 to 0.43

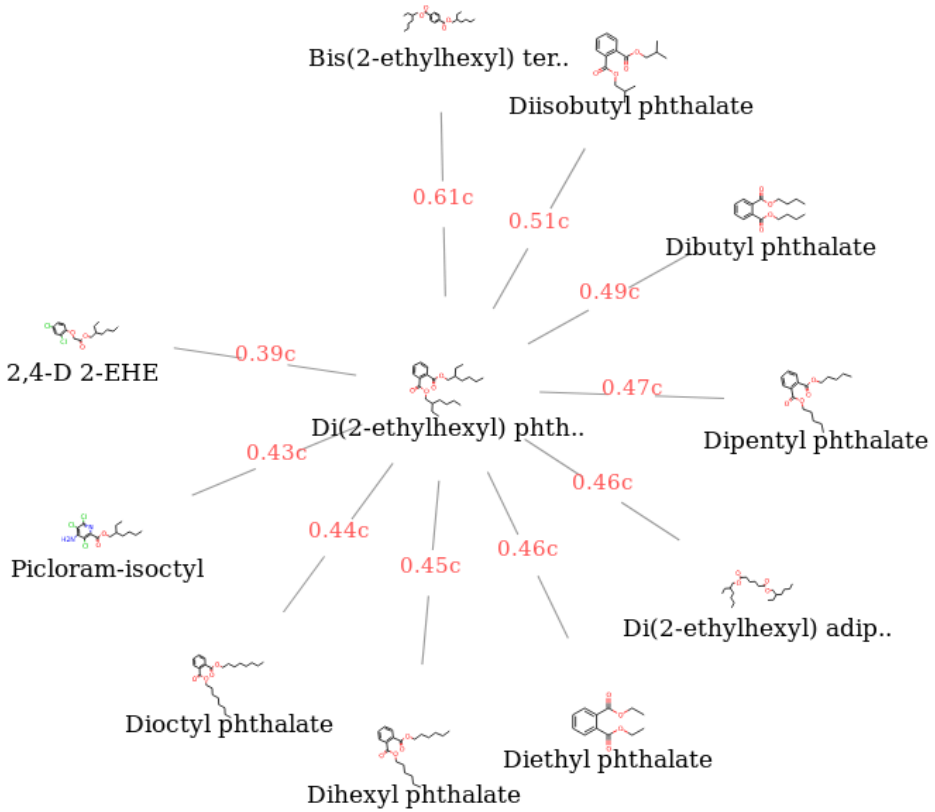
Example Predictions Di(2-ethylhexyl) phthalate

Log Molar (log mol/kg/day)

- Systemic prediction: 2.95
- Systemic measured: 3.00
- Developmental prediction: 2.95
- Developmental measured: 3.00
- Reproductive prediction: 3.04
- Reproductive measured: 3.00

Mg/kg/day

- Systemic prediction: 435.91
- Systemic measured: 388.64
- Developmental prediction: 436.73
- Developmental measured: 391.00
- Reproductive prediction: 359.65
- Reproductive measured: 391.00



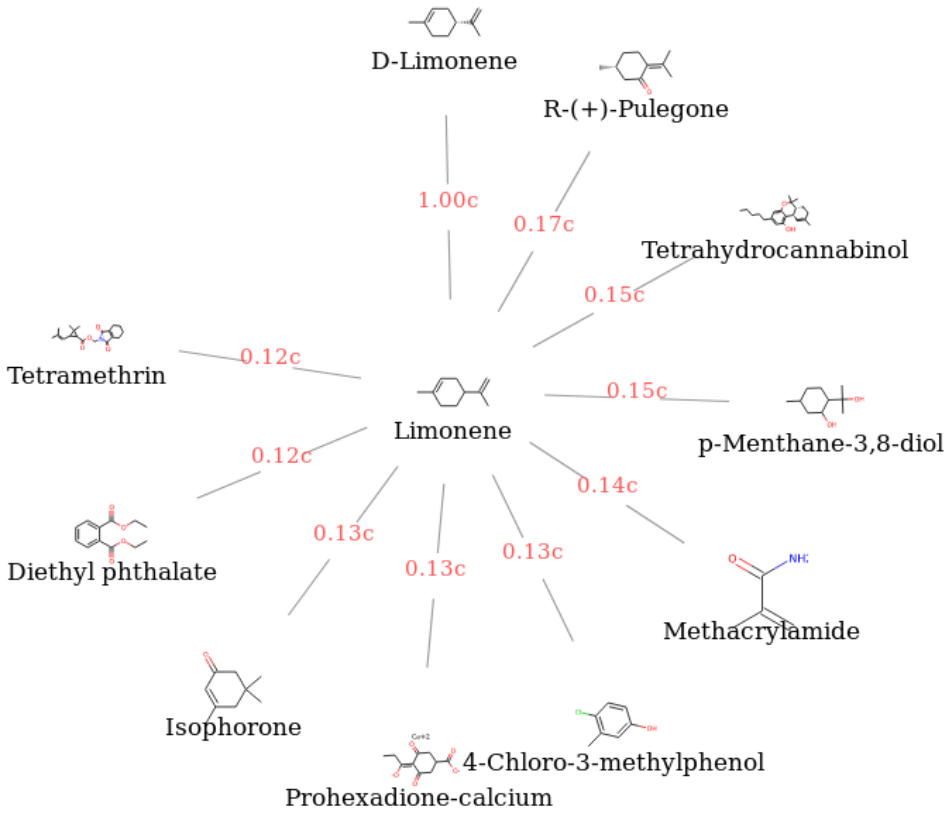
Example Predictions Limonene

Log Molar (log mol/kg/day)

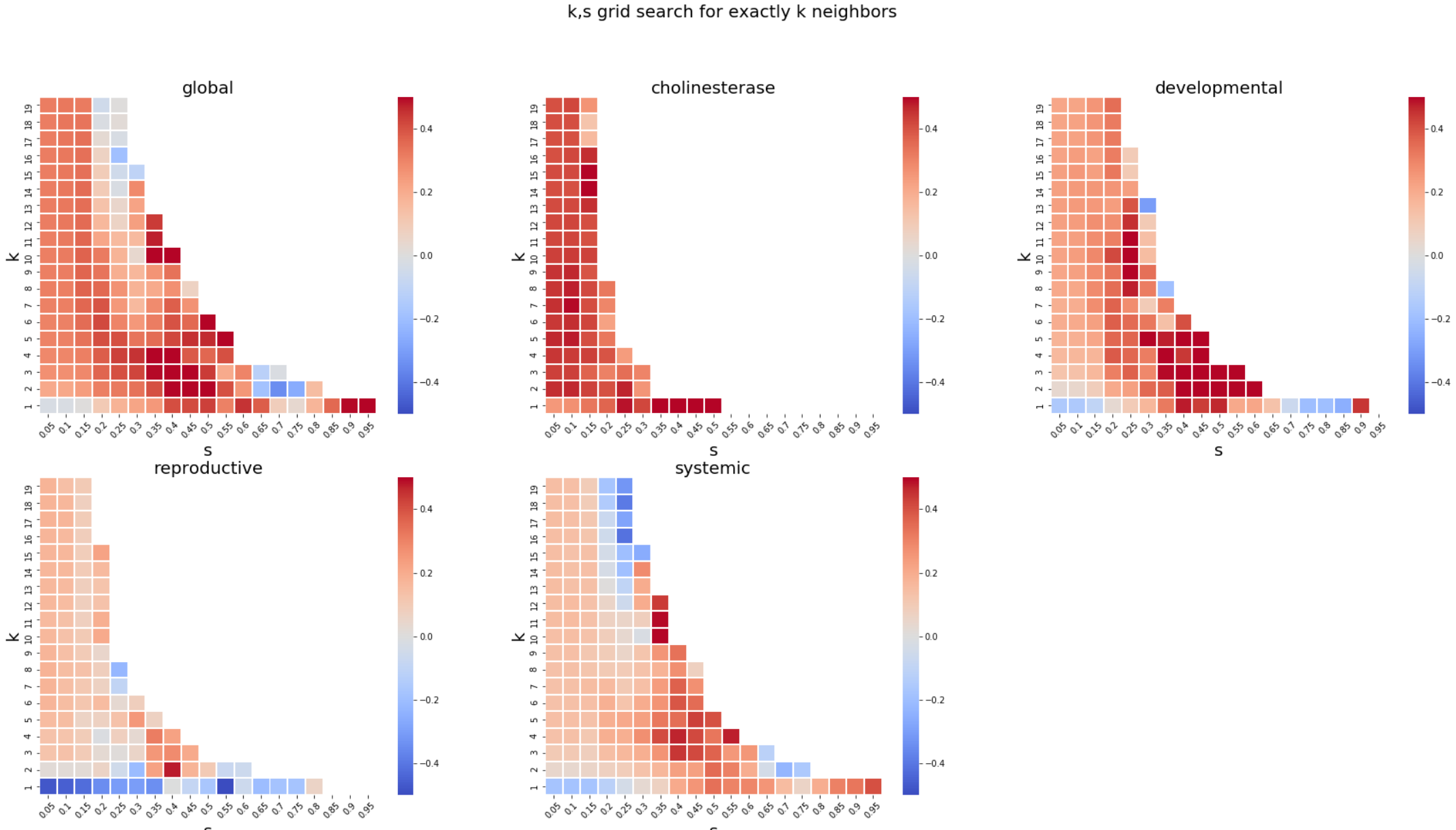
- Systemic prediction: 2.90
- Systemic measured: 2.44
- Developmental prediction: 3.86
- Developmental measured: 2.44

Mg/kg/day

- Systemic prediction: 172.45
- Systemic measured: 500.00
- Developmental prediction: 18.68
- Developmental measured: 500.00



Grid Search over k,s



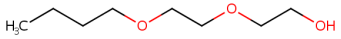
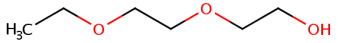
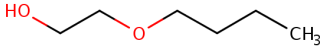
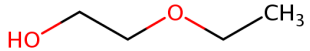
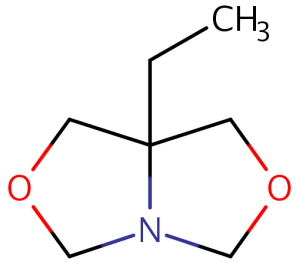
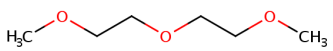
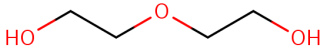
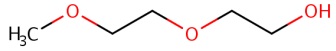
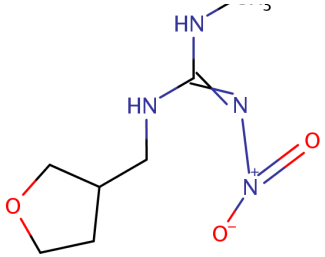
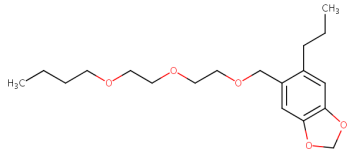
Cluster Analysis

- We try subsetting the data based on the chemical clusters discovered in the original GenRA manuscript in order to find local validity domains where GenRA predicts accurately

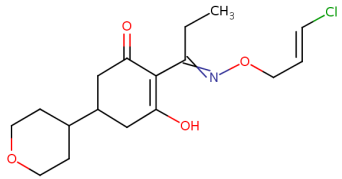
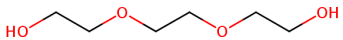
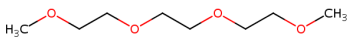
- Clusters discovered by k-means clustering

- We found 36/100 clusters that perform better than the global predictions by 3-fold on average.

Illustrative Example

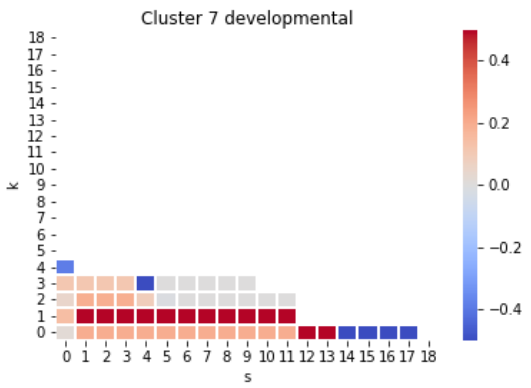
35 chemicals total,
mostly polyols and ethers

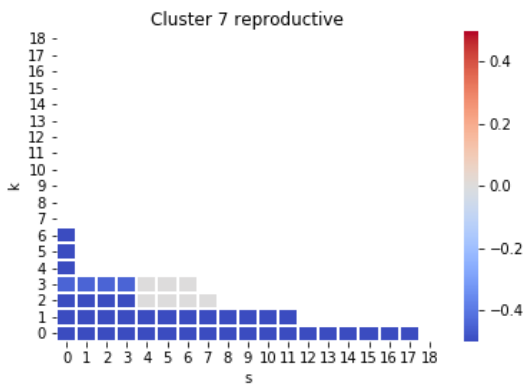




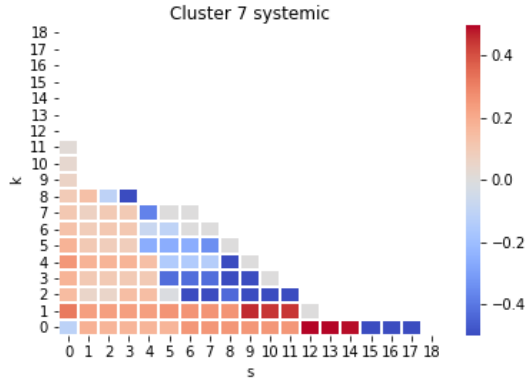
Illustrative example predictions

- Developmental LOAEL range: 120-11260 mg/kg
- Reproductive LOAEL range: 175-5175 mg/kg
- Systemic LOAEL range: 3-2795 mg/kg

- Developmental performance: R2 = 0.95 (k=1, s=0.65)
- Reproductive performance: R2 = 0.76 (k=7, s=0.20)
- Systemic performance: R2 = 0.73 (k=1, s=0.70)







Future Work + Conclusions

- We achieve a reasonable performance compared to other global methods

- Future Work
  - Use of different aggregations for consolidating multiple studies
  - Explore TTC (Threshold of Toxicological Concern) approach