

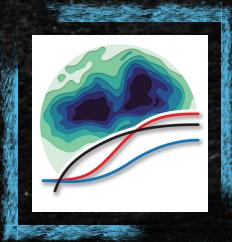
GeoTox and RGCA

Developing Extensible Software for Geospatial Exposure and Risk Assessment of Chemical Mixtures

Kyle P Messier, PhD
Stadtman Tenure Track Investigator

National Institute of Environmental Health Sciences
Division of Translational Toxicology

February 14, 2024



About Us: {SET}group

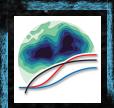
• Spatiotemporal Exposure Mapping

$$y \sim GP(X\beta, \Sigma)$$

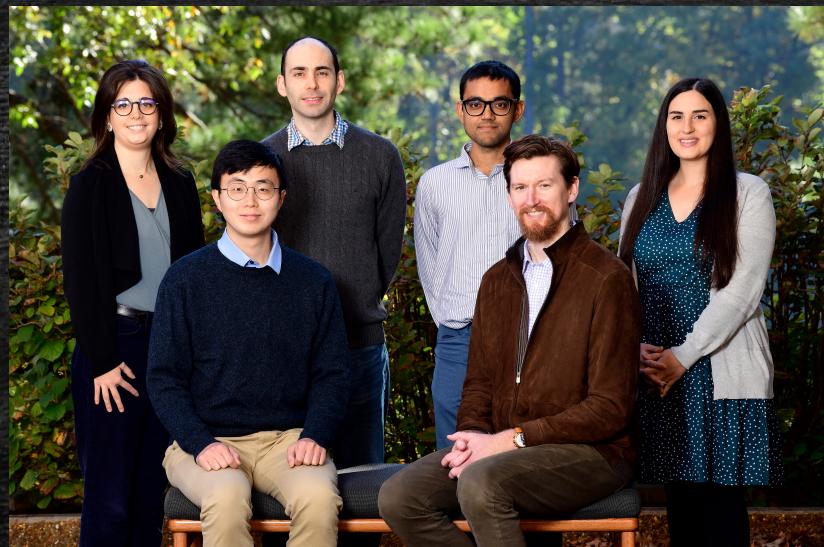
• Chemical and Stressor Mixtures Prediction

$$\frac{[A]}{f_A^{-1}(R)} + \frac{[B]}{f_B^{-1}(R)} = 1$$

Mechanistically Informed Risk Assessment


$$R = f(c|\alpha, \theta, \beta) = \frac{\alpha}{1 + \left(\frac{\theta}{x}\right)^\beta}$$

About Us: {SET}group



Eva Marques

Daniel Zilber

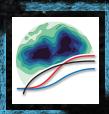
Ranadeep Daw

Mariana Alifa

Insang Song

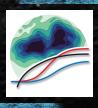
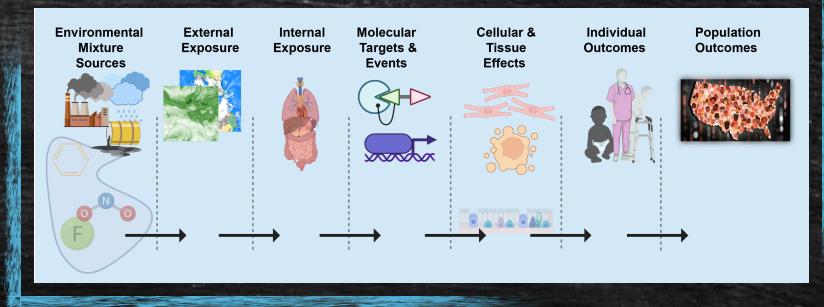
Kyle Messier

Mitchell Manware (Not
Pictured)



A Necessary Cascade for Exogenous Risk Factors

- Exogenous Sources
- External Exposure
- Internal Exposure
- Molecular Targets and Events
- Cellular and Tissue Effects
- Individual Outcomes
- Population Outcomes



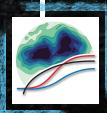
Getting Two Frameworks to Work Together

Aggregate Exposure Pathways

AEP is a comprehensive external analysis of source, media, and transformations

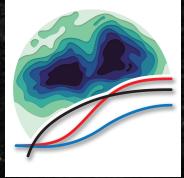
Adverse Outcome Pathway

AOPs provide a linkage specific biological target, pathway or process by a stressor and an adverse outcome(s) considered relevant to risk assessment



Getting Two Frameworks to Work Together

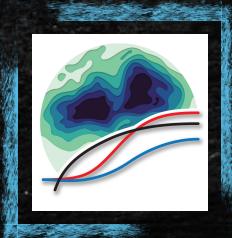
$$GeoTox = AEP + AOP$$



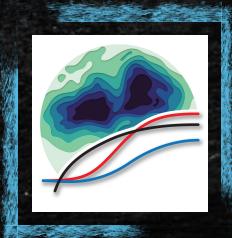
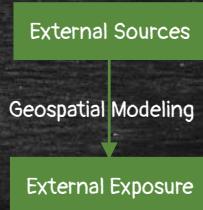
Key Steps of GeoTox

External Sources

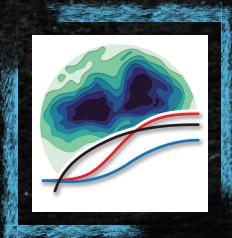
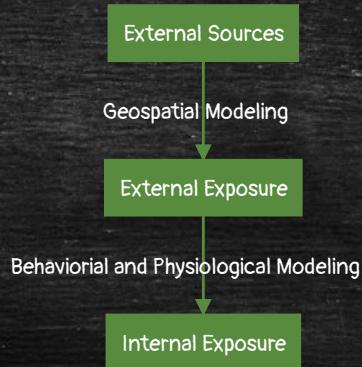
- ◆ A forward, exposure-based approach for mixtures risk modeling
- ◆ Exposure modeling provides a *geospatial* foundation for risk assessment



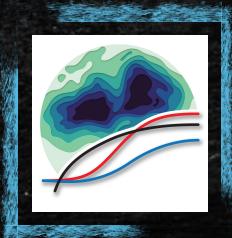
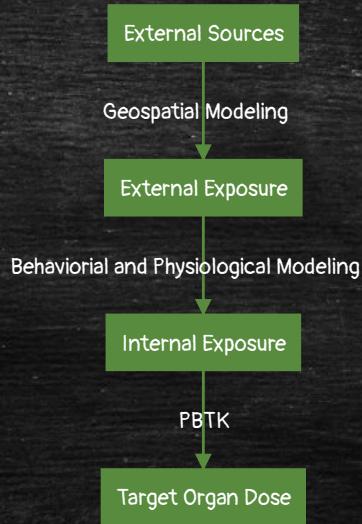
Key Steps of GeoTox



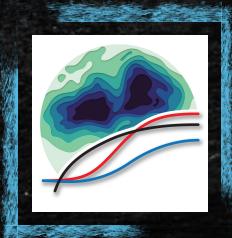
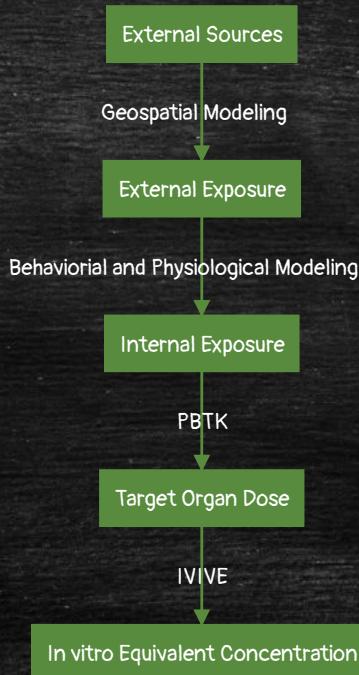
Key Steps of GeoTox



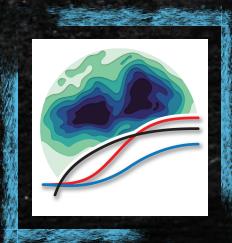
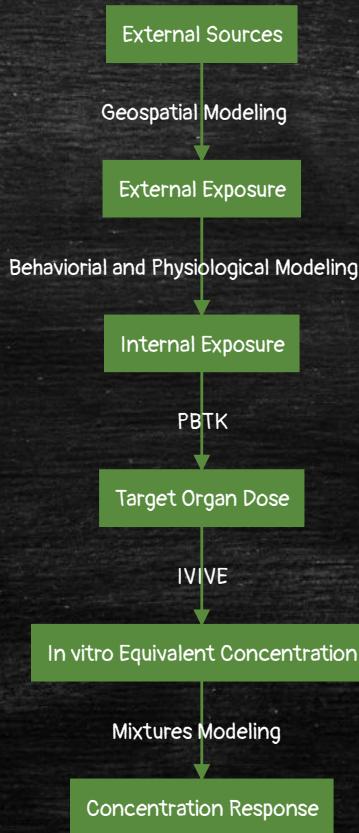
Key Steps of GeoTox



Key Steps of GeoTox



Key Steps of GeoTox



GeoTox Proof of Concept

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journal homepage: www.elsevier.com/locate/scitotenv

Check for updates

A geospatial modeling approach to quantifying the risk of exposure to environmental chemical mixtures via a common molecular target

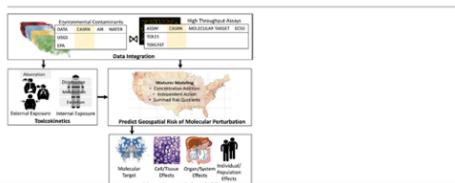
Kristin M. Eccles^a, Agnes L. Karmann^b, Nicole C. Kleinstreuer^a, Fred Parham^a, Cynthia V. Rider^a, John F. Wambaugh^c, Kyle P. Messier^{a,*}

^a National Institute of Environmental Health Science, Division of the Translational Toxicology, Durham, USA
^b Integrated Laboratory Systems, an Iniviv Company, Morrisville, NC, USA
^c United States Environmental Protection Agency, Center for Computational Toxicology and Exposure, Durham, USA

HIGHLIGHTS

- We assess the geographic variation for the joint effect of many chemical exposures.
- This example workflow integrates NIEHS with chemical exposure data.
- The blend of chemicals were heterogeneously distributed across space.
- Exposure concentrations, demographics, and toxicokinetics influence variability.
- We provide methods for modeling the source-exposure-effect continuum.

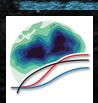
GRAPHICAL ABSTRACT



2022 NIEHS Paper of the Year

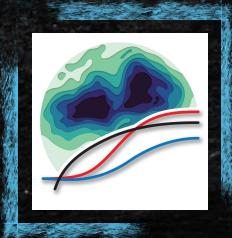


Dr. Kristin Eccles,
Former Visiting Fellow
in DTT and SET, Now
at Health Canada



Making GeoTox F.A.I.R.

- Findable: Publicly available via GitHub, CRAN, NIEHS websites
- Accessible: Open-Source, Easy installation
- Interoperable: Integrate with current and future applications
- Reusable: Documentation and reproducible pipelines



GeoTox Development

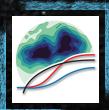
- Currently developing (experimental or not-stable)
- Submitting to CRAN
- Static website hosted via {SET} group website
- Maintained
- Extensible for future development



Dr David Reif, Predictive Toxicology Branch, Senior Scientist and Branch Chief

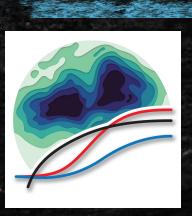


Dr Skylar Marvel, Predictive Toxicology Branch, Bioinformatic Scientist



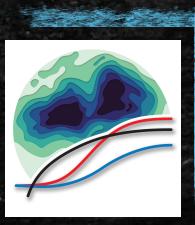
GeoTox: Simulating Data

```
1 # Age  
2 age <- simulate_age(split(geo_tox_data$age, ~FIPS), n = MC_iter)  
3  
4 # Obesity status  
5 obesity <- simulate_obesity(geo_tox_data$obesity, n = MC_iter)  
6  
7 # Inhalation rate  
8 IR <- simulate_inhalation_rate(age)
```



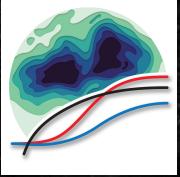
GeoTox: Simulating Data

```
1 # Age  
2 age <- simulate_age(split(geo_tox_data$age, ~FIPS), n = MC_iter)  
3  
4 # Obesity status  
5 obesity <- simulate_obesity(geo_tox_data$obesity, n = MC_iter)  
6  
7 # Inhalation rate  
8 IR <- simulate_inhalation_rate(age)  
9  
10 # External exposure concentration  
11 C_ext <- simulate_exposure(split(geo_tox_data$exposure, ~FIPS), n = MC_iter)  
12  
13 # Sample from pre-simulated steady-state plasma concentration data  
14 C_ss <- sample_Css(geo_tox_data$simulated_css, age, obesity)
```



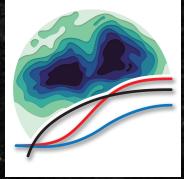
GeoTox: Core Functions

```
1 # Internal dose  
2 D_int <- calc_internal_dose(C_ext, IR, scaling = 1 / 1000)
```



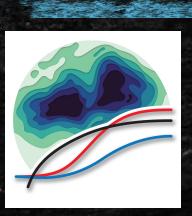
GeoTox: Core Functions

```
1 # Internal dose  
2 D_int <- calc_internal_dose(C_ext, IR, scaling = 1 / 1000)  
3  
4 # in vitro concentration  
5 C_invitro <- calc_invitro_concentration(D_int, C_ss)
```



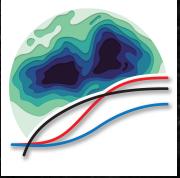
GeoTox: Core Functions

```
1 # Internal dose  
2 D_int <- calc_internal_dose(C_ext, IR, scaling = 1 / 1000)  
3  
4 # in vitro concentration  
5 C_invitro <- calc_invitro_concentration(D_int, C_ss)  
6  
7 # Concentration response  
8 resp <- calc_concentration_response(C_invitro, hill_2_params)
```



GeoTox: Documentation

```
1 # Internal dose  
2 D_int <- calc_internal_dose(C_ext, IR, scaling = 1 / 1000)
```



GeoTox: Documentation

```
1 # Internal dose
2 D_int <- calc_internal_dose(C_ext, IR, scaling = 1 / 1000)
```

GeoTox 0.0.0.9000 Reference Articles ▾

Calculate internal chemical dose

Estimate the internal dose from inhalation of a chemical given inhalation rate, time, and body weight

On this page

Usage Arguments Value Details Examples

Search for

Usage

```
calc_internal_dose(C_ext, IR, time = 1, BW = 1, scaling = 1)
```

Arguments

C_ext
ambient chemical concentration in $\frac{mg}{m^3}$

IR
inhalation rate in $\frac{m^3}{day}$

time
total time in days

BW
body weight in kg

scaling
scaling factor encompassing any required unit adjustments

Value
internal chemical dose in $\frac{mg}{kg}$

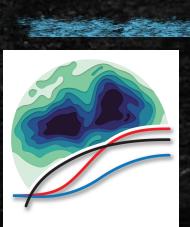
Details
TODO Additional details...

$$D_{int} = \frac{C_{ext} \times IR \times time}{BW}$$

Examples

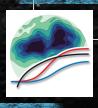
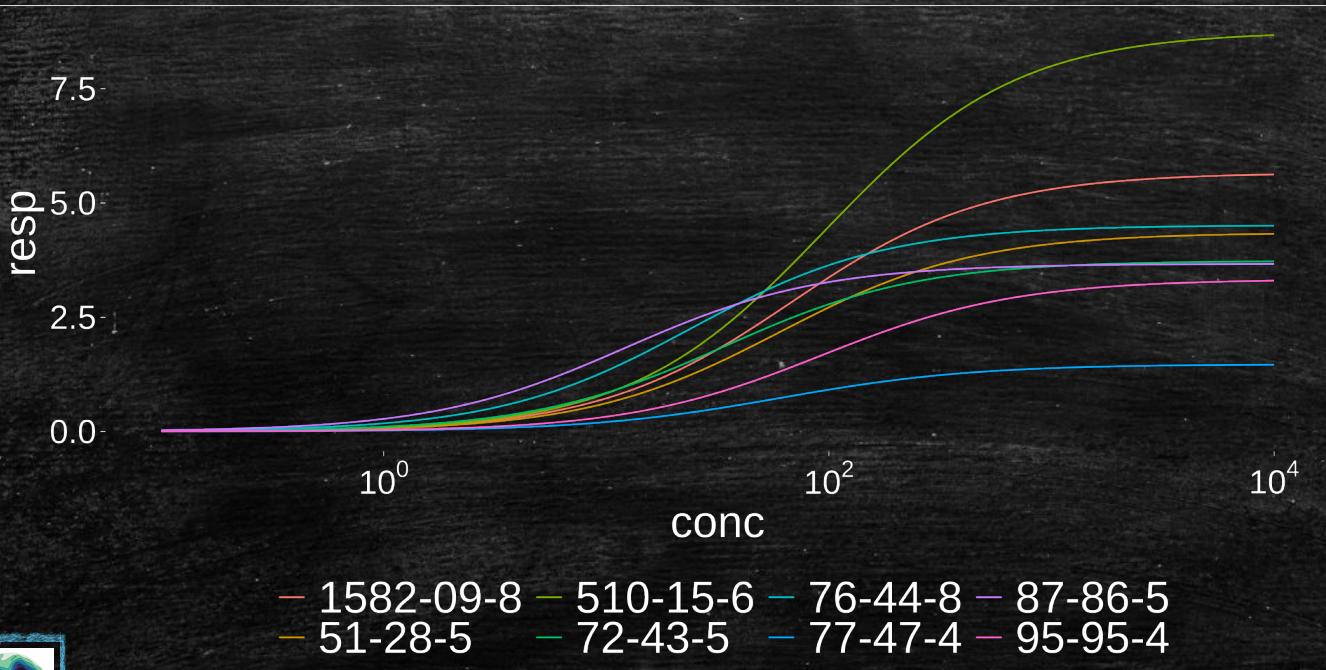
```
n_chem <- 3
n_sample <- 5

# Single population
C_ext <- matrix(runif(n_sample * n_chem), ncol = n_chem)
IR <- runif(n_sample)
calc_internal_dose(C_ext, IR)
#> [1,] 0.015898366 0.09125914 0.171132967
#> [2,] 0.336685183 0.29987215 0.0785395211
#> [3,] 0.038245313 0.01847401 0.002179853
#> [4,] 0.061107128 0.28487219 0.124534354
#> [5,] 0.007218509 0.75363169 0.392490442
```



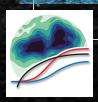
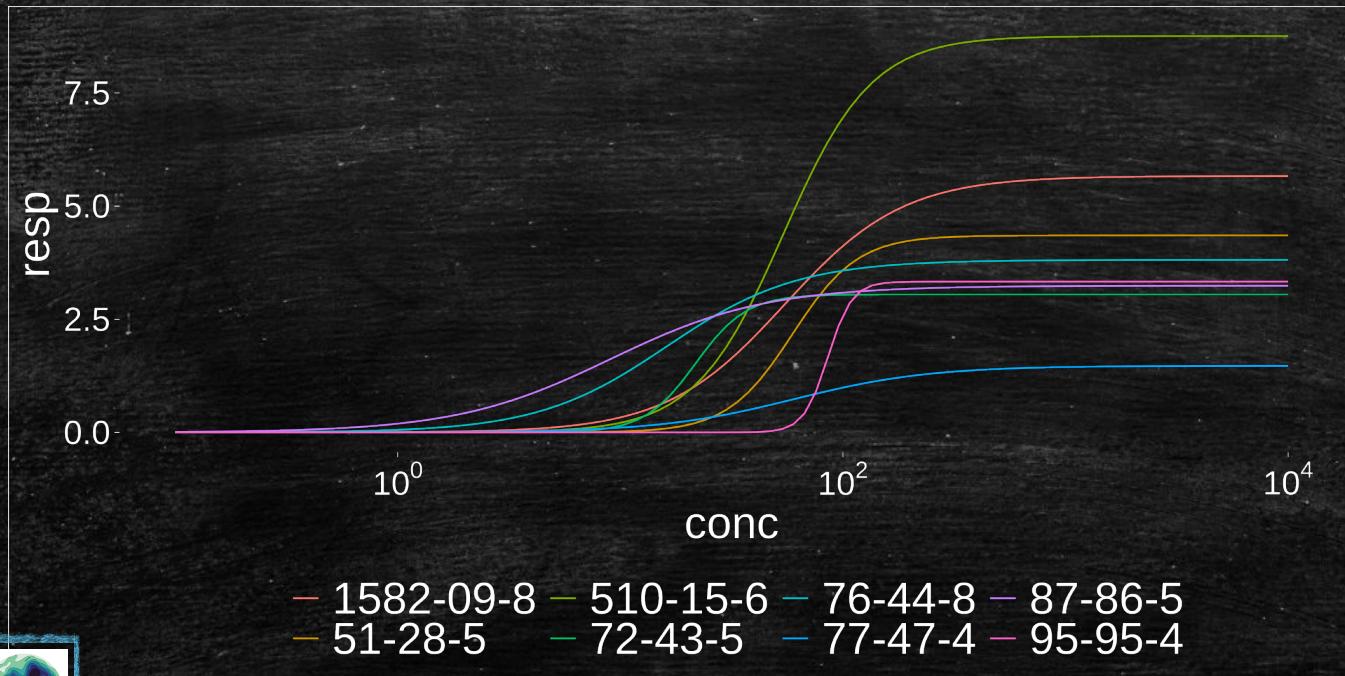
GeoTox: Dose-Response

```
1 hill_2_params <- fit_hill(data)
2 plot_hill(hill_2_params)
```



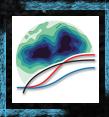
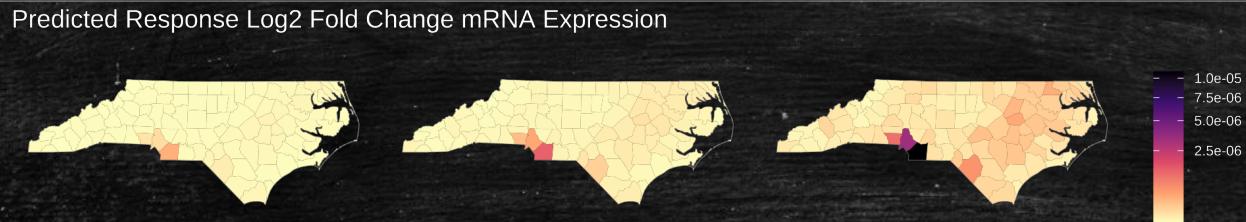
GeoTox: Dose-Response

```
1 hill_3_params <- fit_hill(data, fixed_slope = FALSE)  
2 plot_hill(hill_3_params)
```



GeoTox: Map Visualization

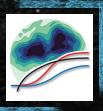
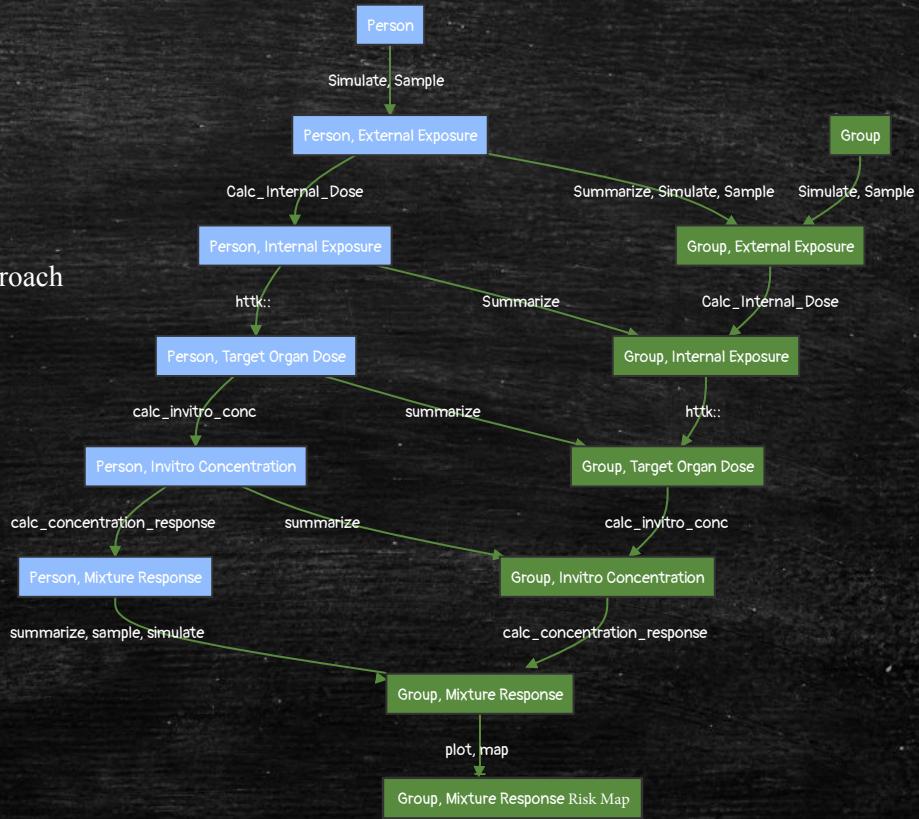
```
1 resp <- resp_df %>% filter(health_measure == "GCA.Eff")  
2 legend_name <- paste("Predicted Response", "Log2 Fold Change", "mRNA Expression", sep = " ")  
3 make_county_heatmap(resp, legend_name)
```



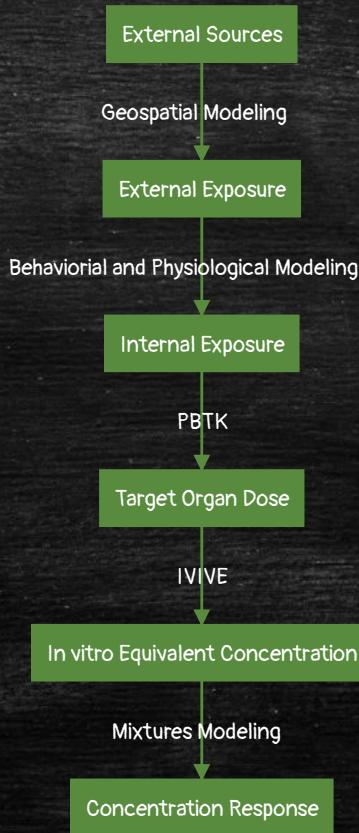
GeoTox: Under Development

lifecycle experimental

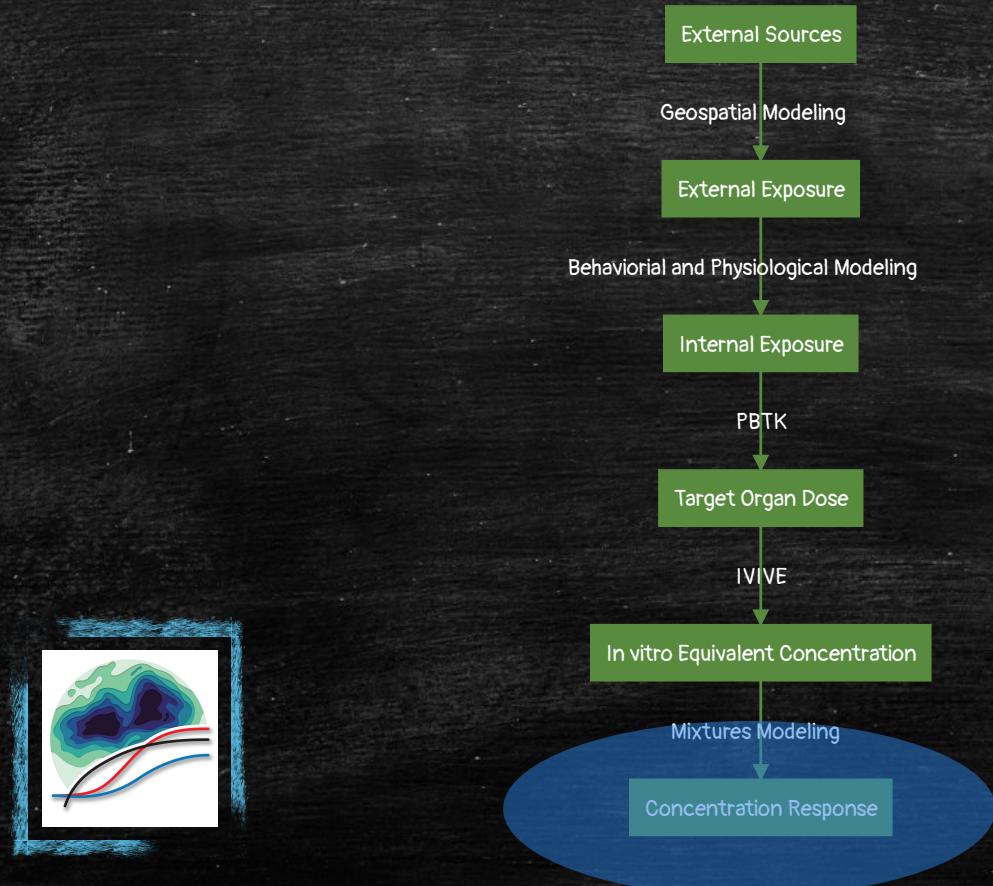
- Individual/Person Level Analysis
- General Grouping or Areal Analysis
- Likely migrating to an object-oriented approach



Revisiting the Steps of GeoTox



Revisiting the Steps of GeoTox

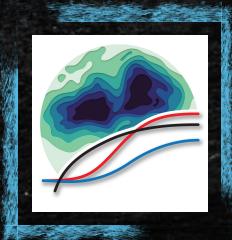


Revisiting the Steps of GeoTox



RGCA Motivation

- ***Infinite Mixture Problem:*** There are infinitely many possible mixtures and we can't test them all
- ***Independent vs Additive:*** No clear approach for general mixtures
- ***Something from Nothing:*** Independently safe chemicals can combine to form a hazardous mixture



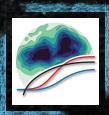
RGCA: Notation

We assume a parametric model for interpretability:

$$r_i(c) = f_i(c|a_i, \theta_i, \beta_i) = \frac{a_i}{1 + \left(\frac{\theta_i}{c}\right)^{\beta_i}}$$

where:

- ◆ r_i : toxic effect or response of chemical i
- ◆ c : concentration of a chemical, later indexed by chemical i
- ◆ a_i : sill or maximum effect parameter
- ◆ θ_i : dissociation constant or EC50 value
- ◆ β_i : slope parameter



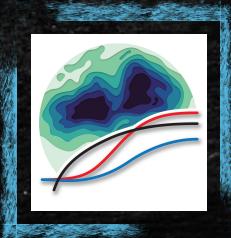
RGCA: Common Mixture Models

- Concentration Addition, CA (Loewe, Isobole): effective total dose adjusted for potency

$$\sum_i \frac{c_i}{EC_i(R)} = 1$$

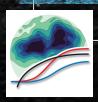
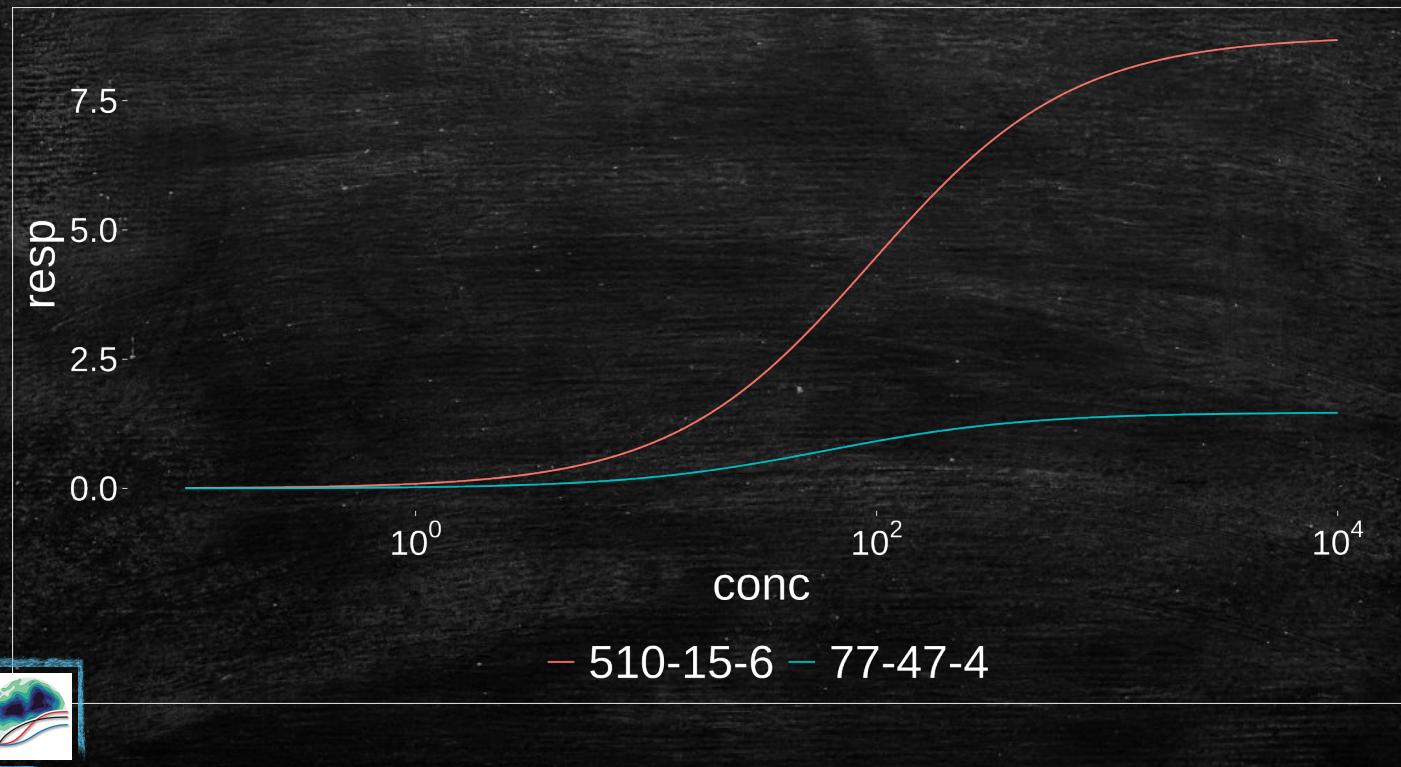
Intuition: ``How much c_2 do I need to get response R under chem 1 given c_1 ''

$$EC_1(R) = c_1 + c_2 \frac{EC_1(R)}{EC_2(R)}$$



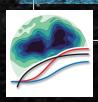
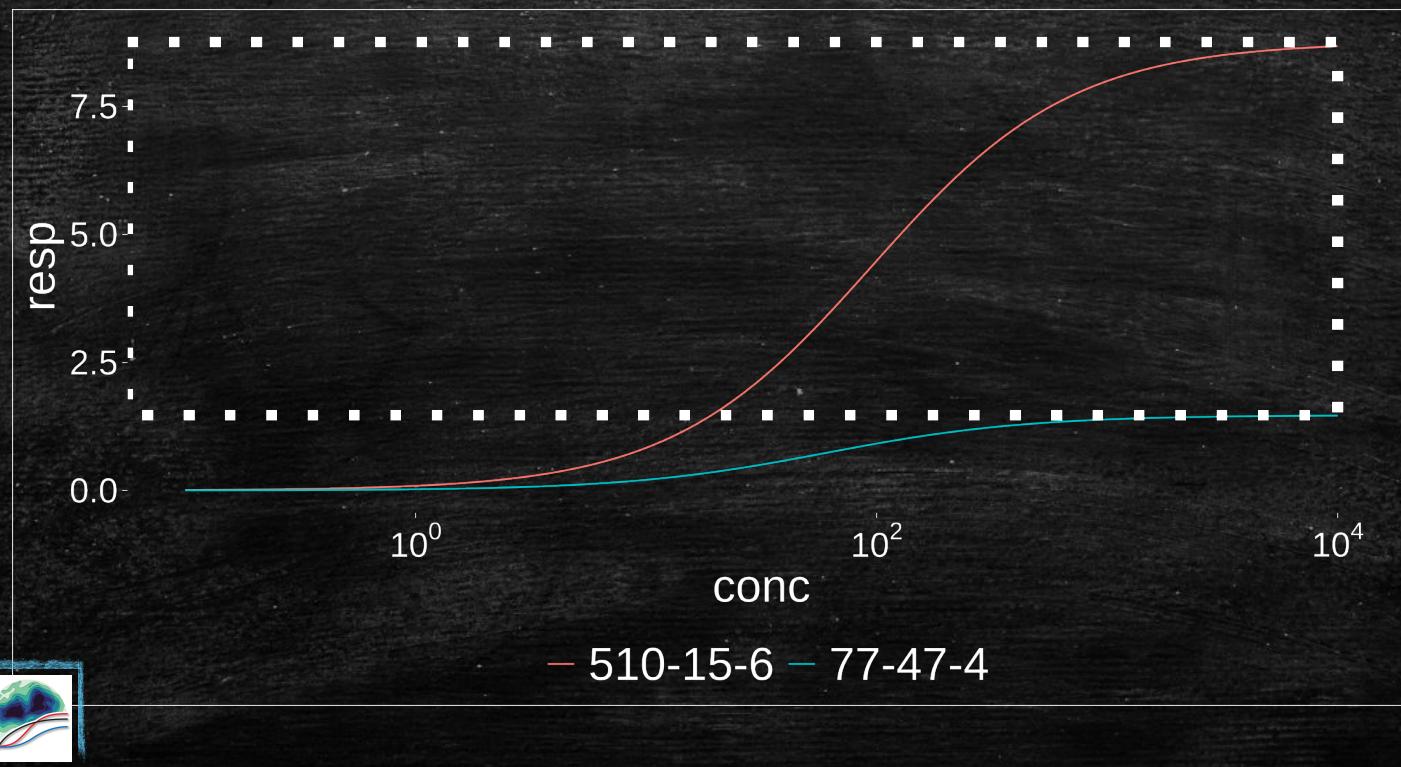
RGCA: Partial Agonists

Partial agonists are the major limitation of traditional CA



RGCA: Partial Agonists

Partial agonists are the major limitation of traditional CA



RGCA: Partial Agonists

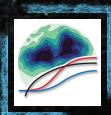
GCA (Howard and Webster, 2009) substitutes $f_i^{-1}(R)$ for $EC_i(R)$ and solves for R to balance the equation given c_i 's:

$$\sum_i \frac{c_i}{f_i^{-1}(R)} = 1$$

- For the Hill model with slope $\beta_i = 1$, we get a hyperbolic function:

$$R = f_i(c) = \frac{a_i}{1 + \left(\frac{\theta_i}{c}\right)^{\beta_i}} = \frac{c \cdot a_i}{c + \theta_i}$$

- So: when $R > a_1, c < 0!$
- A large toxic effect of the mixture requires small concentrations of chemical 1.

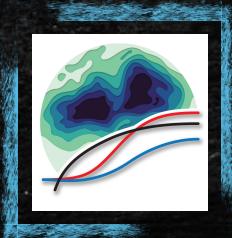


RGCA: Partial Agonists

The GCA trick can be used with $\beta = 1$ because the inverse is still defined for $R > a$:

$$f^{-1}(R) = \frac{\theta}{\left(\frac{a}{R} - 1\right)^{1/\beta}} = \frac{\theta}{\frac{a}{R} - 1}$$

For most β , the inverse at $R > a$ is undefined because it contains a root of a negative value.
We propose a series of reflections to have a well-defined inverse

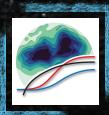


RGCA: Piecewise Inverse Function

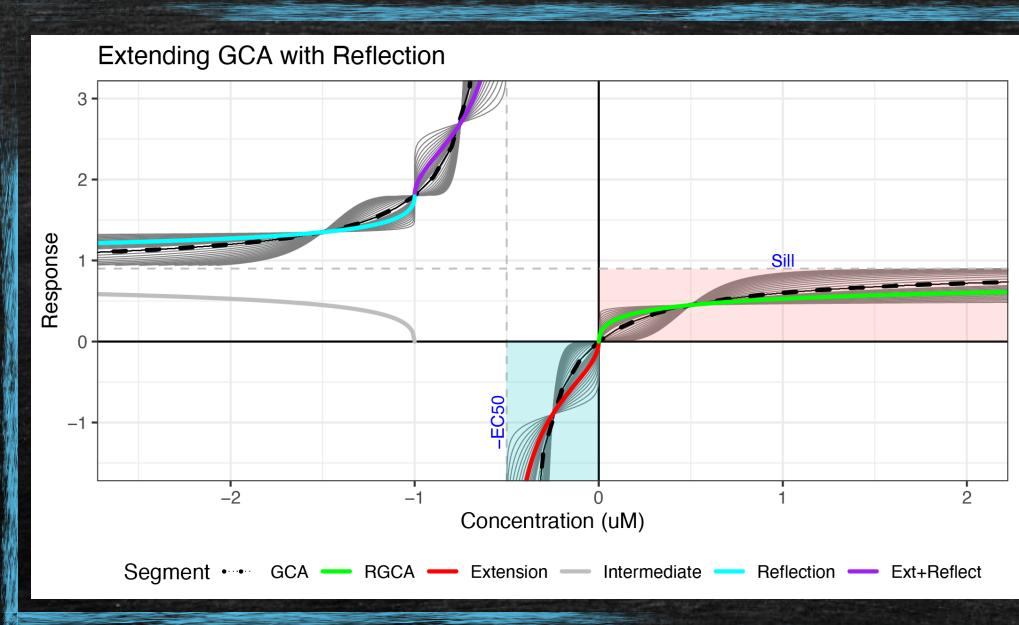


$$f^{-1}(r|\alpha > 0, \theta, \beta > 0) = \begin{cases} \frac{-\theta}{1 + \left(\frac{-\alpha}{r}\right)^{1/\beta}} & r \in (-\infty, 0) \\ \theta \left(\frac{\alpha}{r} - 1\right)^{-1/\beta} & r \in [0, \alpha) \\ -2\theta - \theta \left(\frac{\alpha}{2\alpha - r} - 1\right)^{-1/\beta} & r \in (\alpha, 2\alpha) \\ -2\theta + \frac{\theta}{1 + \left(\frac{\alpha}{r - 2\alpha}\right)^{1/\beta}} & r \in (2\alpha, \infty) \end{cases}$$

Daniel Zilber, PhD,
Postdoctoral Fellow



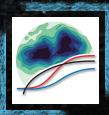
RGCA: Piecewise Inverse Function



This inverse provides a wide enough support to satisfy the invertibility requirements of GCA

RGCA: Summary

- IA and CA represent two extremes of mixture prediction
- GCA extends CA to partial agonists but requires a slope of 1
- We can extend GCA to not require slope 1: RGCA
- Non-unit slope allows for additional post-hoc analyses like clustering on slope, curve, etc.
- Daniel Zilber and Kyle P Messier, *Reflected Generalized Concentration Addition and Bayesian Hierarchical Models to Improve Chemical Mixture Prediction*, PLOS One, In-Press



RGCA: Future Work

Both IA and CA are additive: there is no interaction. One approach is to rescale GCA (Jonker et al. 2005):

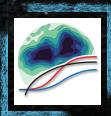
$$\sum \frac{c_i}{f_i^{-1}(R)} = \exp g(Z), \quad g(Z) = a \prod z_i$$

where the z_i is a toxic unit, $z_i = c_i/f_i^{-1}(a/2)$.

We considered the following quadratic version, with a matrix A to be specified by QSAR:

$$g(Z) = -\frac{1}{2} z^\top A z$$

But it is not clear how to determine A from QSAR. Also, this approach is symmetric: there is no dominant chemical.



RGCA: Extensible Software

RGCA 1.0.0.0000 Get started Reference

RGCA

Reflected Generalized Concentration Addition: A geometric, piecewise inverse function for 3+ parameter sigmoidal (e.g. hill) models used in chemical mixture concentration-response modeling

Key Inverse Function:

$$f^{-1}(r|\alpha > 0, \theta, \beta > 0) = \begin{cases} \frac{-\theta}{1 + \left(\frac{-\alpha}{r}\right)^{1/\beta}} & r \in (-\infty, 0) \\ \theta \left(\frac{\alpha}{r} - 1\right)^{-1/\beta} & r \in [0, \alpha) \\ -2\theta - \theta \left(\frac{\alpha}{2\alpha - r} - 1\right)^{-1/\beta} & r \in (\alpha, 2\alpha) \\ -2\theta + \frac{\theta}{1 + \left(\frac{\alpha}{r-2\alpha}\right)^{1/\beta}} & r \in (2\alpha, \infty) \end{cases}$$

This inverse provides a wide enough support to satisfy the invertibility requirements of GCA, but with non-unit slopes. The resulting inverse maintains a coarse hyperbolic shape and continuity and is smooth at the transitions. This procedure is not limited to the Hill function and can be applied to any monotonic dose response function, but the resulting stability may vary. Note that negative slope parameters for the Hill function are not supported.

Abstract:

Environmental toxicants overwhelmingly occur together as mixtures. The variety of possible chemical interactions makes it difficult to predict the danger of the mixture. In this work, the classical two-step model for the cumulative effects of mixtures, which assumes a combination of GCA and independent action (IA). We explore how various clustering methods can dramatically improve predictions. We compare our technique to the IA, CA, and GCA models and show in a simulation study that the two-step approach performs well under a variety of true models. We then apply our method to a challenging data set of individual chemical and mixture responses where the target is an androgen receptor (Tox21 AR-luc). Our results show significantly improved predictions for larger mixtures. Our work complements ongoing efforts to predict environmental exposure to various chemicals and offers a starting point for combining different exposure predictions to quantify a total risk to health.

Links

[Browse source code](#)

License

GPL (>= 2)

Citation

[Citing RGCA](#)

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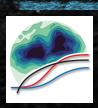
Dev status

 R-CMD-check passing

 lint passing

 codecov 0%

 lifecycle experimental



RGCA: Extensible Software

Simple Application of RGCA

Daniel Zilber

Source: [vignettes/Simple_RGCA.Rmd](#)

Simple Usage of RGCA

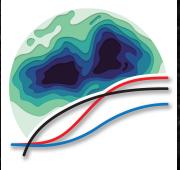
While the method could be generalized to a variety of smooth, monotone dose response functions, our package is designed around the Hill function,

$$f(x|a, b, c) = \frac{a}{1 + \left(\frac{b}{x}\right)^c}$$

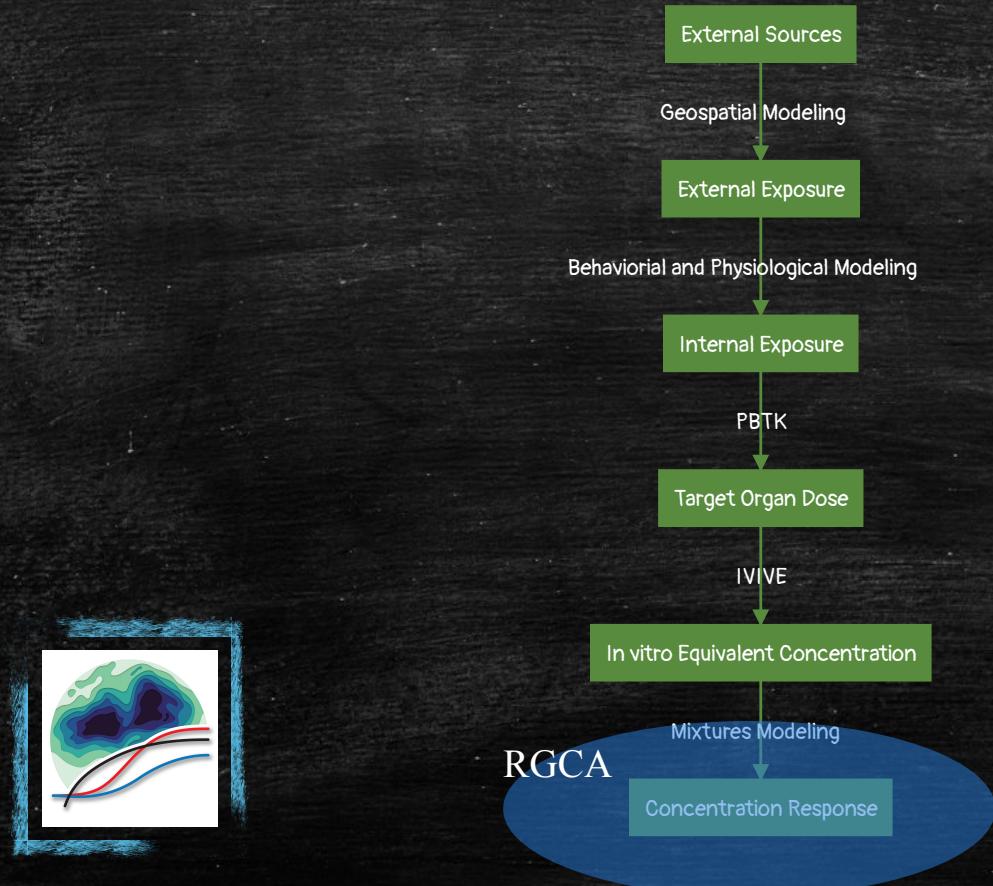
The parameters are the sill (a), the EC50 (b), and the slope (c). Give these parameters and a cluster assignment vector, RGCA can create a calculator that predicts the mixture response given an input dose vector (x_1, \dots, x_n). In the example below, there are three chemicals with known Hill parameters.

```
n_chems <- 3
sills <- c(3, 5, 4)
ec50_vec <- c(1, 0.75, 2.4)
slopes <- c(0.5, 1.1, 2.0)
# Rmax is used to scale IA across clusters, can copy sills
param_matrix <- as.matrix(cbind("a" = sills,
                                 "b" = ec50_vec,
                                 "c" = slopes,
                                 "max_R" = sills))

# specify both chems in cluster 1 of 1
cluster_assign_vec <- c(1, 2, 1)
# create a calculator to predict response given concentration
mix_pred <- mix_function_generator(param_matrix, cluster_assign_vec)
```

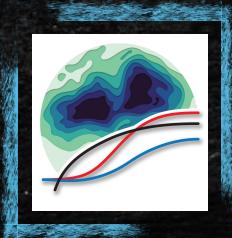


GeoTox + RGCA Integration

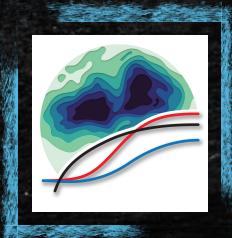
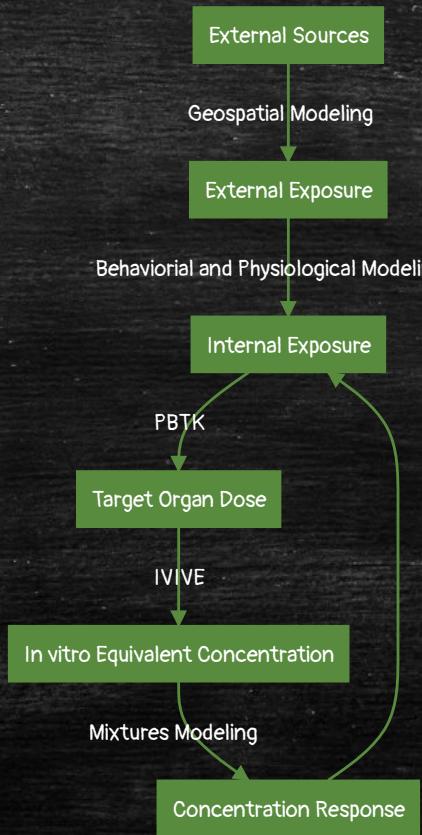


Extensible GeoTox

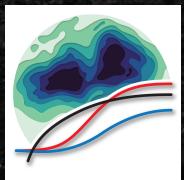
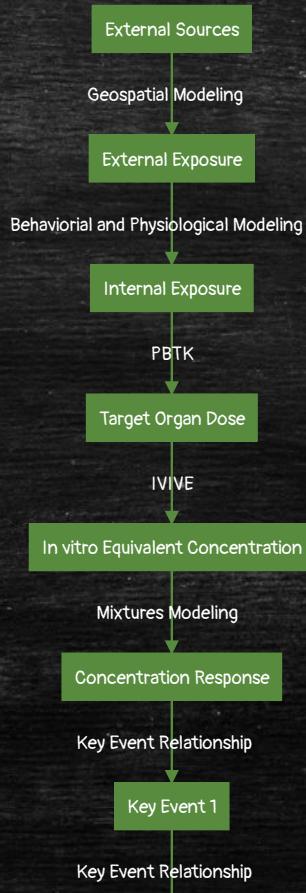
- Looking forward, there are many ways to improve GeoTox mixture risk assessment
- Better handling of *time*
- More and better resolved AOPs!



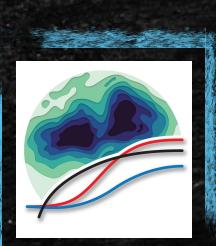
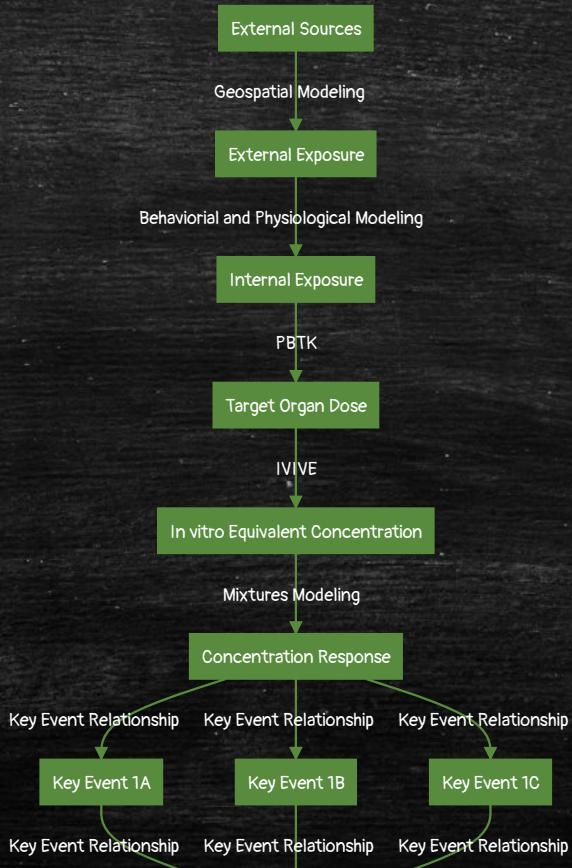
GeoTox: Temporal Feedback



GeoTox: With Complete AOPs

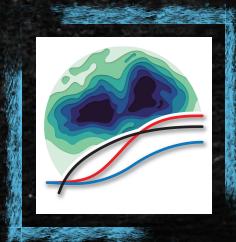


Multiple Assays Informing an AOP



{SET} Summary

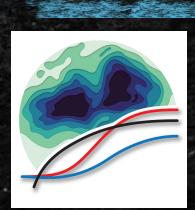
- GeoTox and RGCA code are currently experimental
- Publishing versions 1.0.0. to SET Github and CRAN ASAP
- Many other documented, test-driven, and extensible packages from the SET group on air pollution exposures across the US, download/process GIS environmental data, and scalable GIS operations
- Follow *Spatiotemporal-Exposures-and-Toxicology* on GitHub
- We are fostering a community around best-practices for software in geospatial exposure assessment, risk assessment, and computational toxicology
- email: kyle.messier@nih.gov



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