GeoTox and RGCA

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

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Division of Translational Toxicology
February 14, 2024

About Us: $\{SET\}_{group}$

- Spatiotemporal Exposure Mapping

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

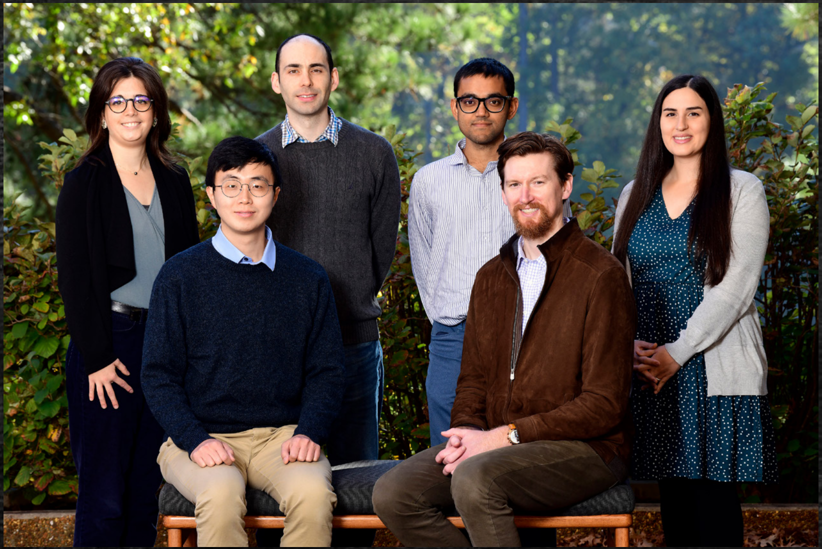
- Chemical and Stressor Mixtures Prediction

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

Mechanistically Informed Risk Assessment

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

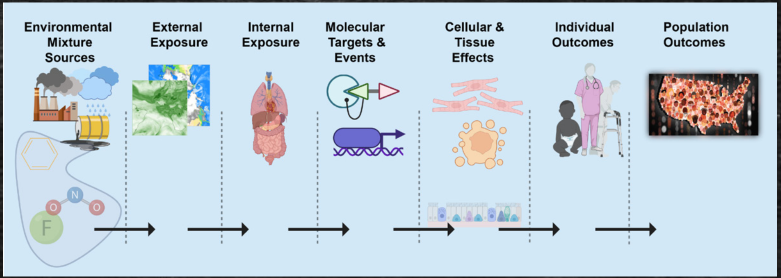
About Us: {SET}$_{group}$



- Eva Marques
- Daniel Zilber
- Ranadeep Daw
- Mariana Alifa
- Insang Song
- Kyle Messier
- Mitchell Manware (Not Pictured)

A Necessary Cascade for Exogoneous 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

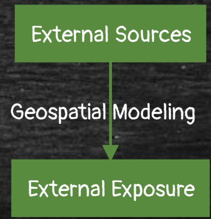
$$GeoTox = AEP + AOP$$

Key Steps of GeoTox

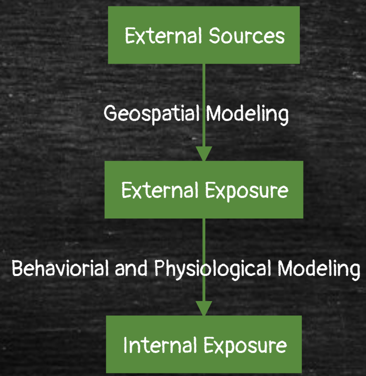
External Sources

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

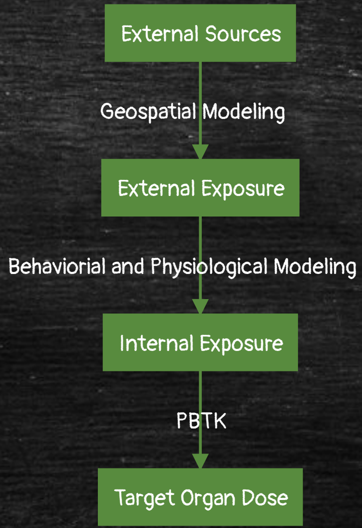
Key Steps of GeoTox



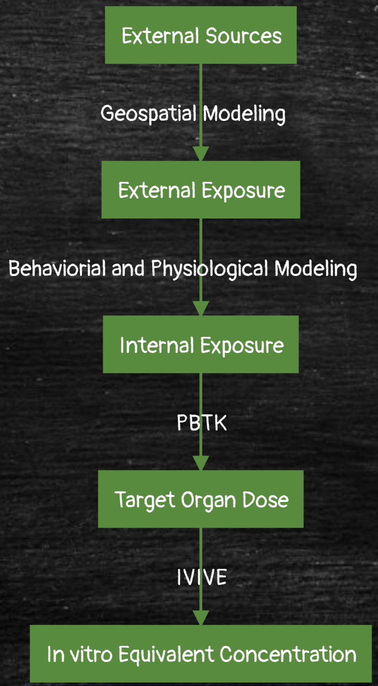
Key Steps of GeoTox



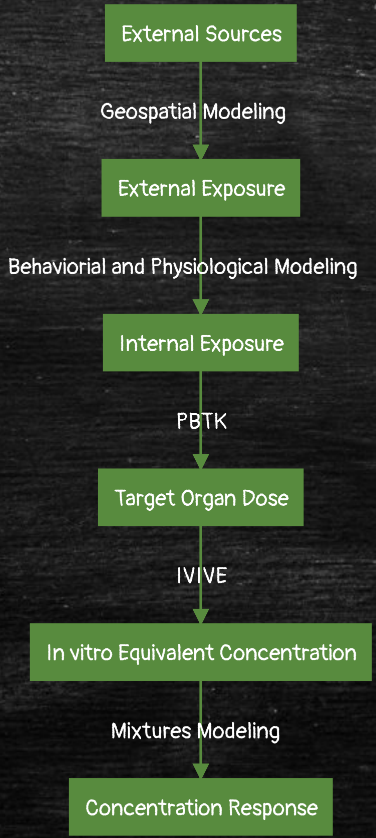
Key Steps of GeoTox



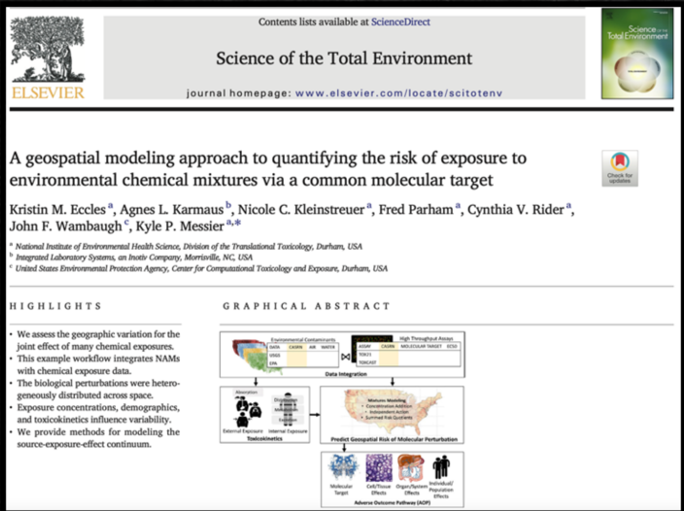
Key Steps of GeoTox



Key Steps of GeoTox



GeoTox Proof of Concept



Contents lists available at ScienceDirect

Science of the Total Environment

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

ELSEVIER

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. Karmaus [b], Nicole C. Kleinstreuer [a], Fred Parham [a], Cynthia V. Rider [a], John F. Wambaugh [c], Kyle P. Messier [a,*]

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HIGHLIGHTS

- We assess the geographic variation for the joint effect of many chemical exposures.
- This example workflow integrates NAMs with chemical exposure data.
- The biological perturbations 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

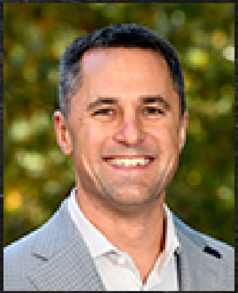
Dr. Kristin Eccles, Former Visiting Fellow in DTT and SET, Now at Health Canada

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

```r
# Age
age <- simulate_age(split(geo_tox_data$age, ~FIPS), n = MC_iter)

# Obesity status
obesity <- simulate_obesity(geo_tox_data$obesity, n = MC_iter)

# Inhalation rate
IR <- simulate_inhalation_rate(age)
```

GeoTox: Simulating Data

```
# Age
age <- simulate_age(split(geo_tox_data$age, ~FIPS), n = MC_iter)

# Obesity status
obesity <- simulate_obesity(geo_tox_data$obesity, n = MC_iter)

# Inhalation rate
IR <- simulate_inhalation_rate(age)

# External exposure concentration
C_ext <- simulate_exposure(split(geo_tox_data$exposure, ~FIPS), n = MC_iter)

# Sample from pre-simulated steady-state plasma concentration data
C_ss <- sample_Css(geo_tox_data$simulated_css, age, obesity)
```

GeoTox: Core Functions

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

GeoTox: Core Functions

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

# in vitro concentration
C_invitro <- calc_invitro_concentration(D_int, C_ss)
```

GeoTox: Core Functions

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

# in vitro concentration
C_invitro <- calc_invitro_concentration(D_int, C_ss)

# Concentration response
resp <- calc_concentration_response(C_invitro, hill_2_params)
```

GeoTox: Documentation

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

GeoTox: Documentation

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

GeoTox 0.0.0.9000 Reference Articles Search for

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

Usage

```r
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...

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

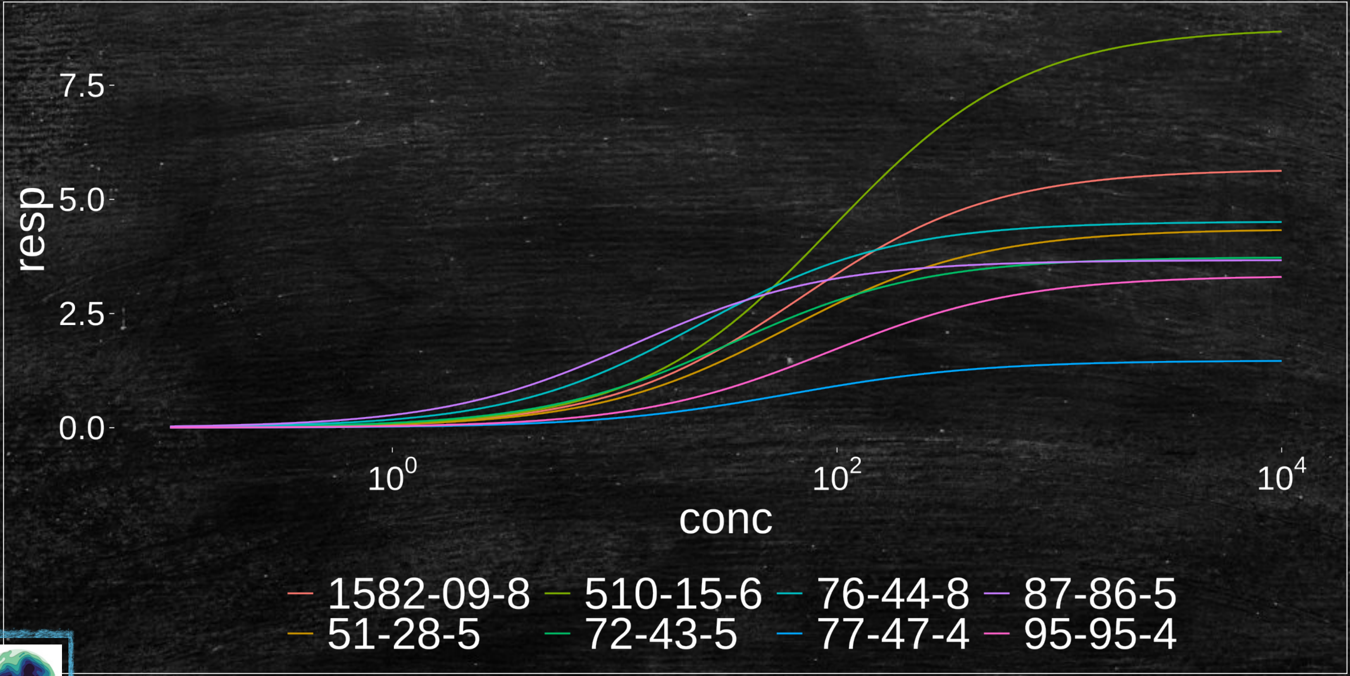
Examples

```r
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]       [,2]        [,3]
#> [1,] 0.015800366 0.09125914 0.171132967
#> [2,] 0.336685183 0.20087215 0.070595211
#> [3,] 0.038245313 0.01844701 0.002179853
#> [4,] 0.061107128 0.28487219 0.124534354
#> [5,] 0.007218509 0.75363169 0.392490442
```

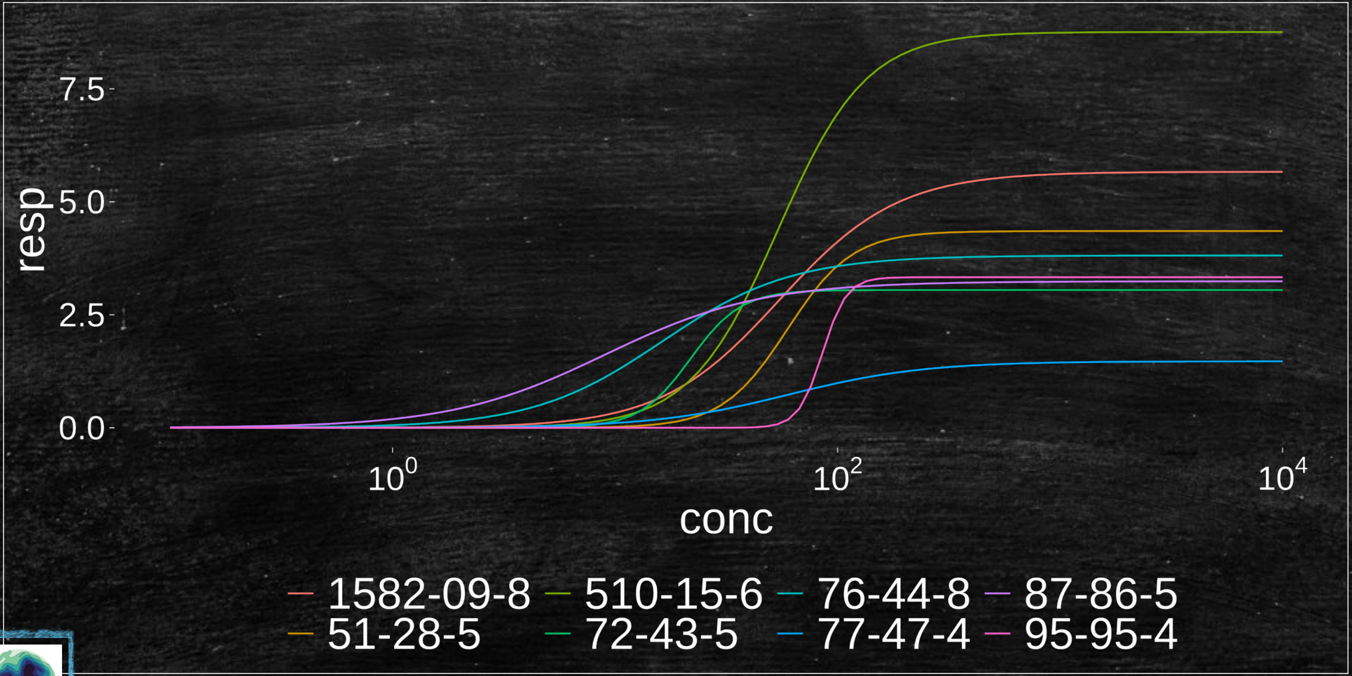
GeoTox: Dose-Response

```r
hill_2_params <- fit_hill(data)
plot_hill(hill_2_params)
```



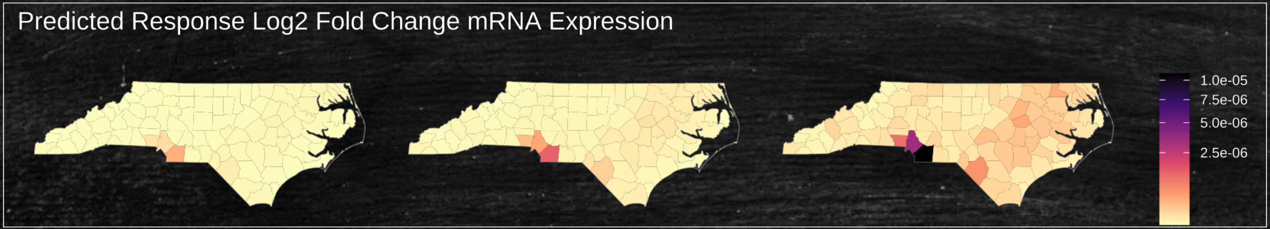
GeoTox: Dose-Response

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



GeoTox: Map Visualization

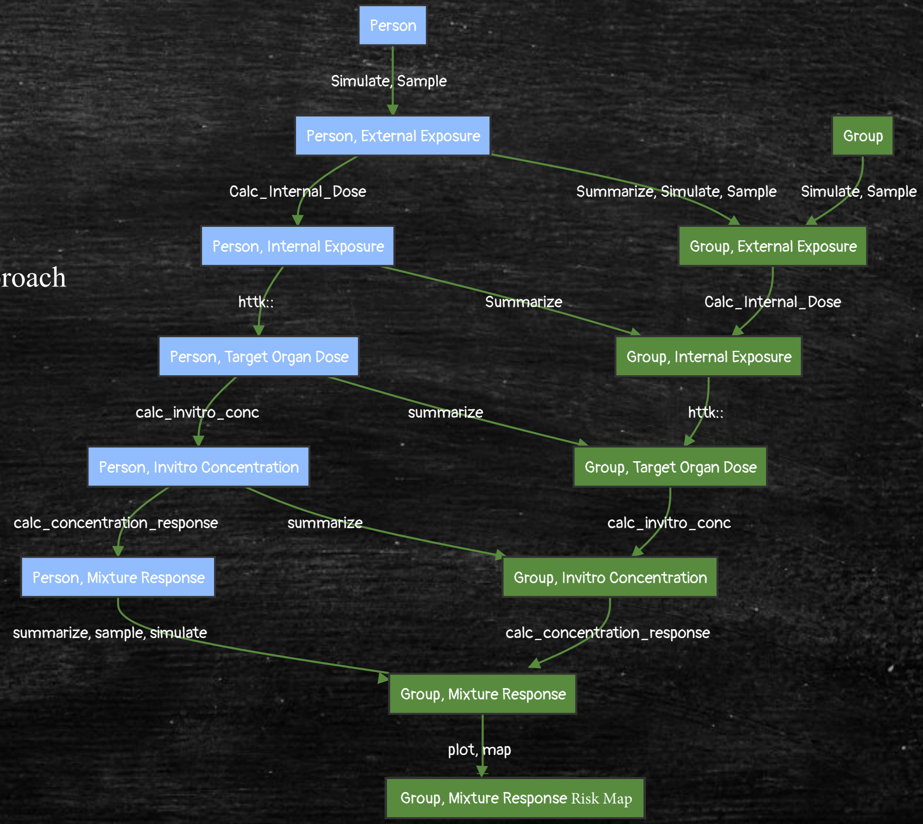
```r
resp <- resp_df %>% filter(health_measure == "GCA.Eff")
legend_name <- paste("Predicted Response", "Log2 Fold Change", "mRNA Expression",sep = " ")
make_county_heatmap(resp, legend_name)
```



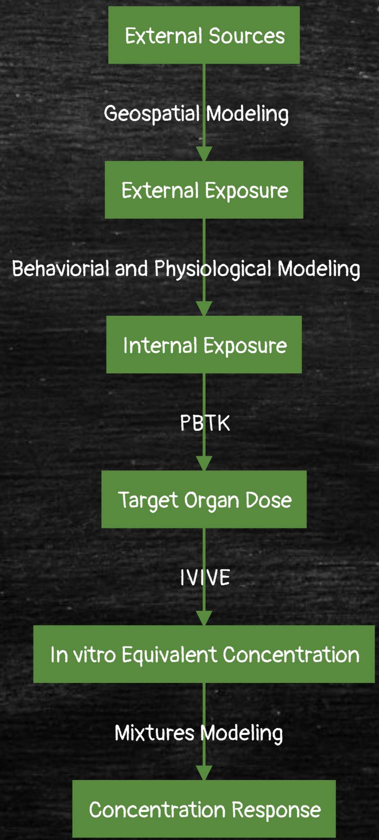
GeoTox: Under Development

lifecycle experimental

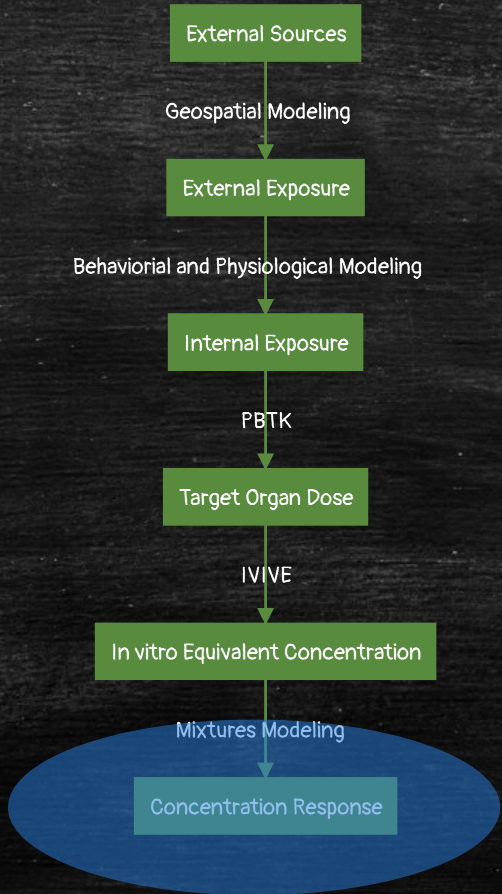
- Individual/Person Level Analysis
- General Grouping or Areal Analysis
- Likely migrating to an object-oriented approach



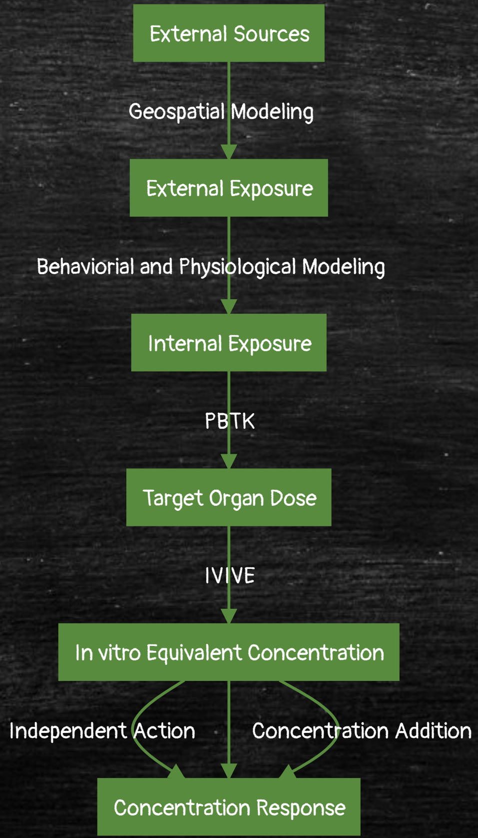
Revisiting the Steps of GeoTox

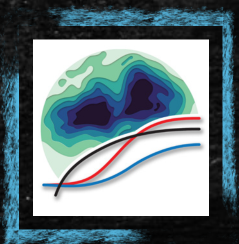


Revisiting the Steps of GeoTox



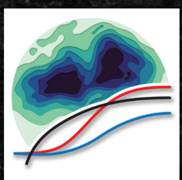
Revisiting the Steps of GeoTox





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

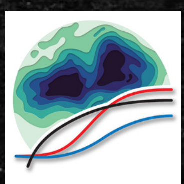
RGCA: Common Mixture Models

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

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

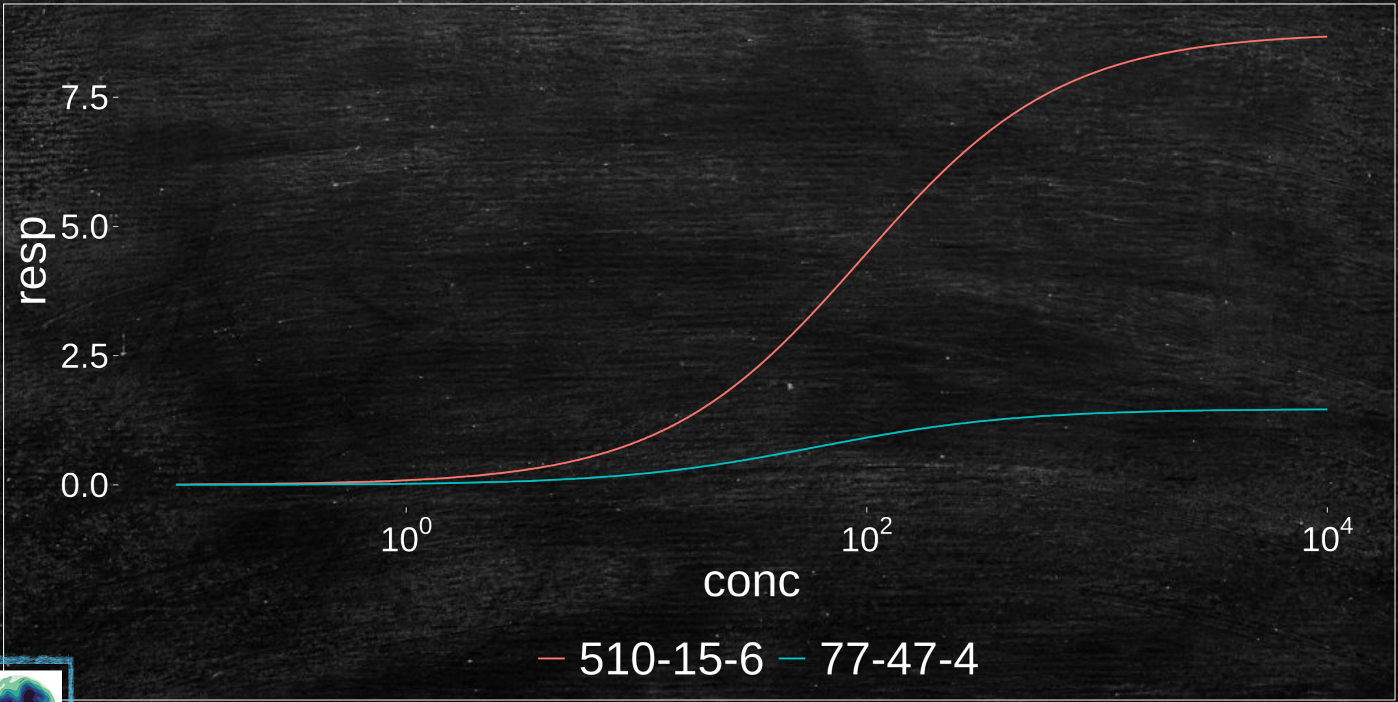
Intuition: ``How much c_2 do I need to get response R under chem 1 given c_1"

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



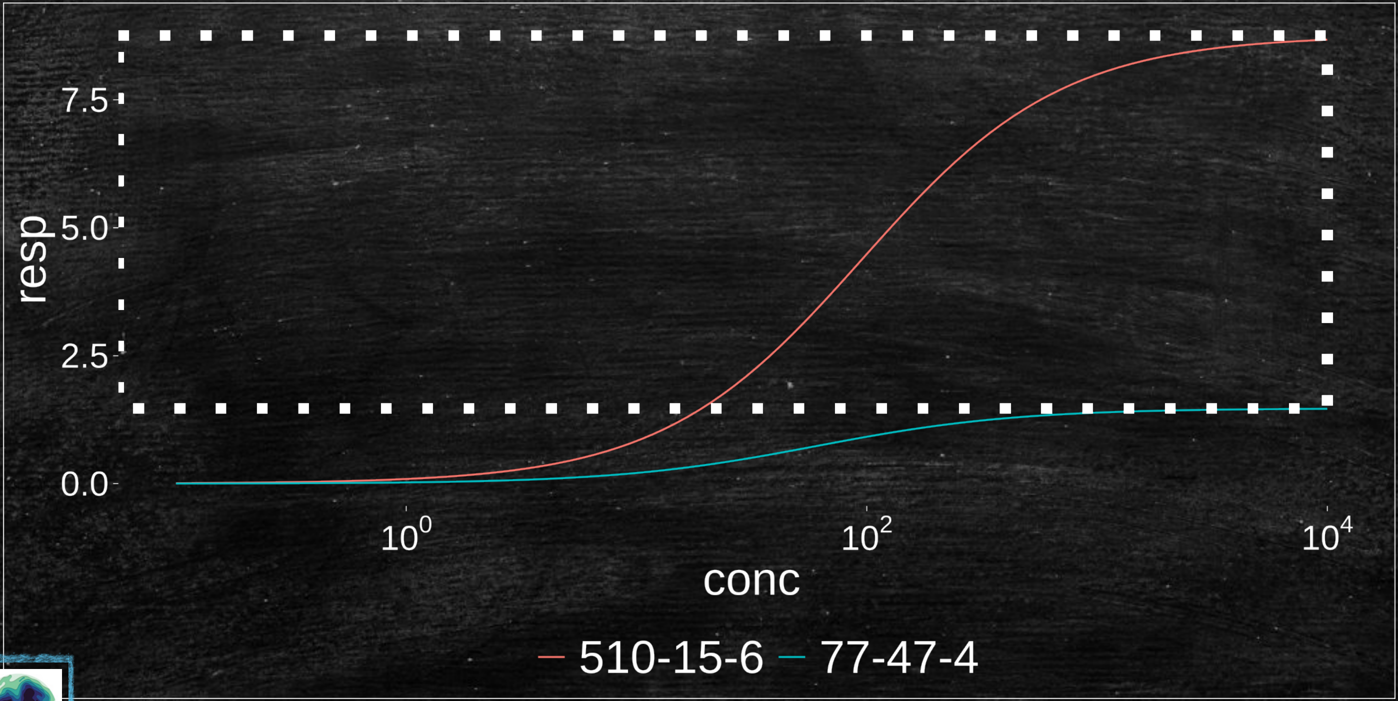
RGCA: Partial Agonists

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.

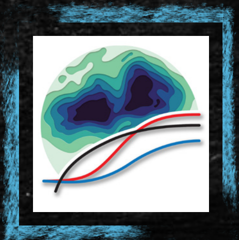
RGCA: Partial Agonists

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

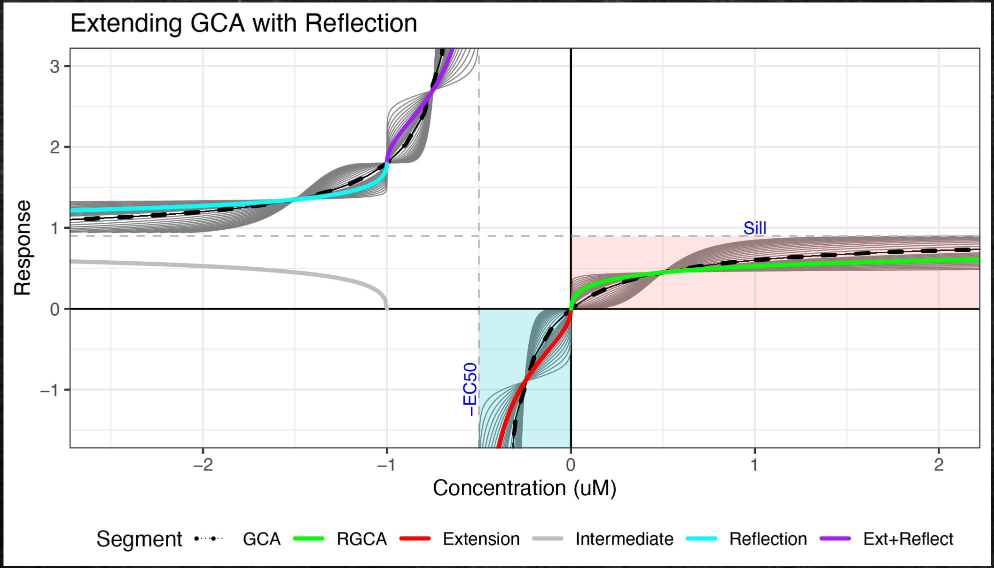


RGCA: Piecewise Inverse Function

Daniel Zilber, PhD,
Postdoctoral Fellow

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

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 \hl{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

Developers

Daniel Zilber
Author, maintainer

Kyle Messier
Author

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

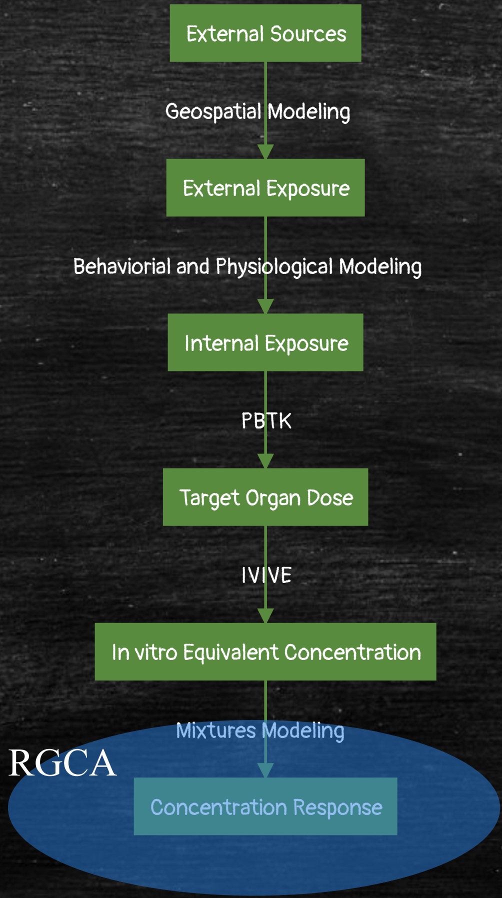
While the method could be generalize to a variety of smooth, monotone dose response functions, our package is designed around the Hill function,

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

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 $(x_1, \ldots, x_n)$. 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)
```

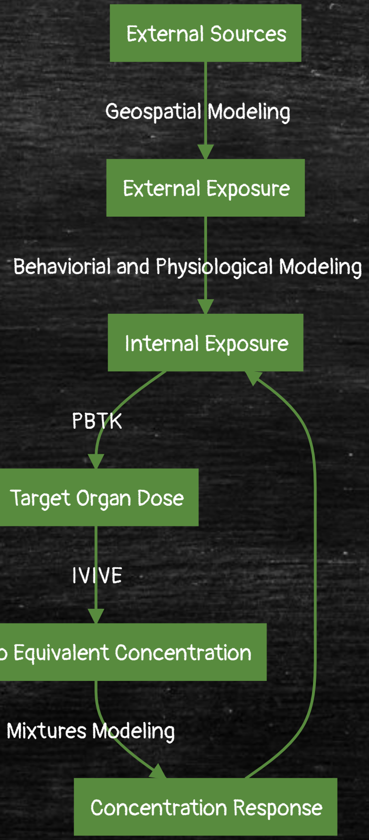
GeoTox + RGCA Integration

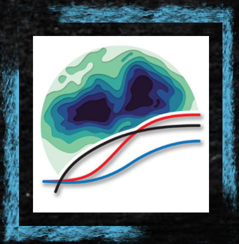


Extensible GeoTox

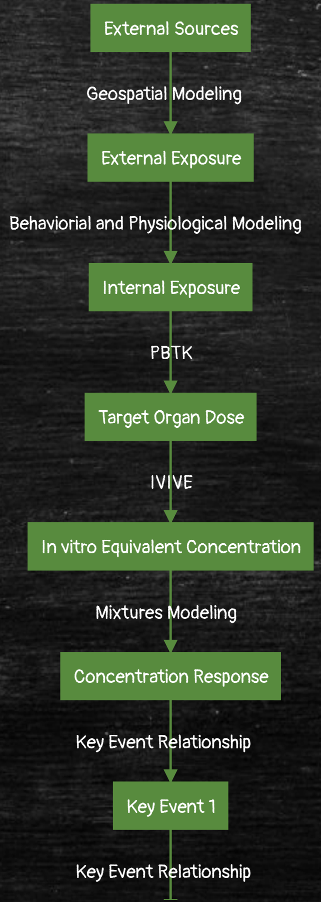
- Looking forward, there are many ways to improve GeoTox mixture risk assessment
- Better handling of ***time***
- More and better resolved AOPs!

GeoTox: Temporal Feedback

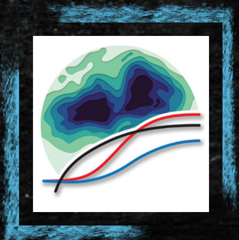




GeoTox: With Complete AOPs



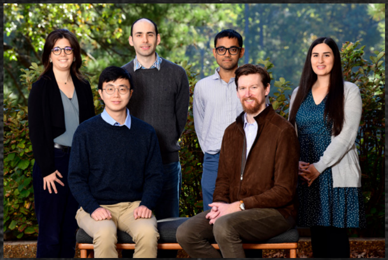
Multiple Assays Informing an AOP



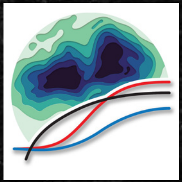
{SET} Summary

- 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

Acknowledgements



SET group in October 2023: Eva Marques, Daniel Zilber, Ranadeep Daw, Mariana Alifa Kassien, Insang Song



- Mitchell Manware
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- Fred Parham
- Cynthia Rider
- Melissa Lowe
- Taylor Potter
- John Wambaugh
- Mike DeVito
- Andy Shapiro
- Julia Rager
- Alison Motsinger-Reif
- David Reif
- Aubrey Miller
- Charles Schmitt
- Trisha Castranio
- Ann Liu
- Richard Kwok