National Institute of Environmental Health Sciences
Division of Translational Toxicology

Advancing Spatiotemporal Methods for Large-Scale Environmental Exposure and Mechanistically-Informed Risk Assessment

Kyle P Messier, PhD
Stadtman Investigator

Spatiotemporal Exposures and Toxicology (SET) Group

Daniel Zilber

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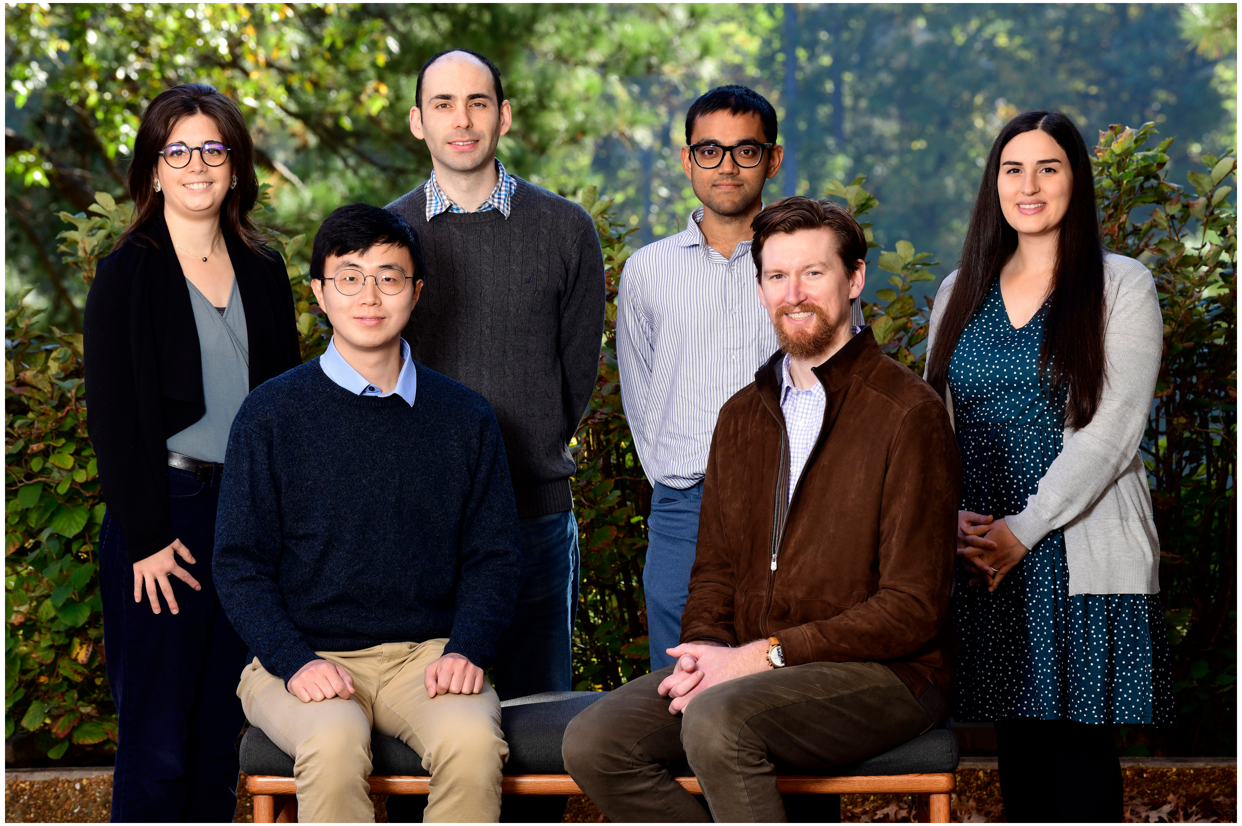


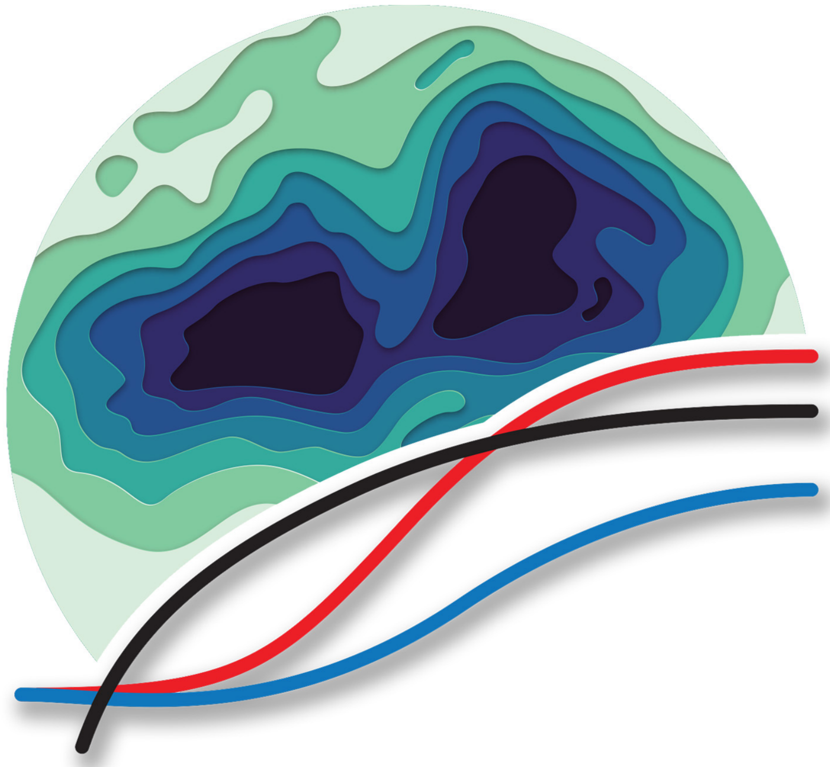
Insang Song

Kyle Messier

Mitchell Manware
(Data Analyst)

Spatiotemporal Exposures and Toxicology Group

- Spatiotemporal Exposure Mapping
- Chemical and Stressor Mixtures Prediction
- Mechanistically Informed Risk Assessment



What drives our health outcomes (i.e. phenotypes)?

Endogenous

Genome	Transcriptome	Proteome	Epigenome	Microbiome	Metabolome

Exogenous

Exposome

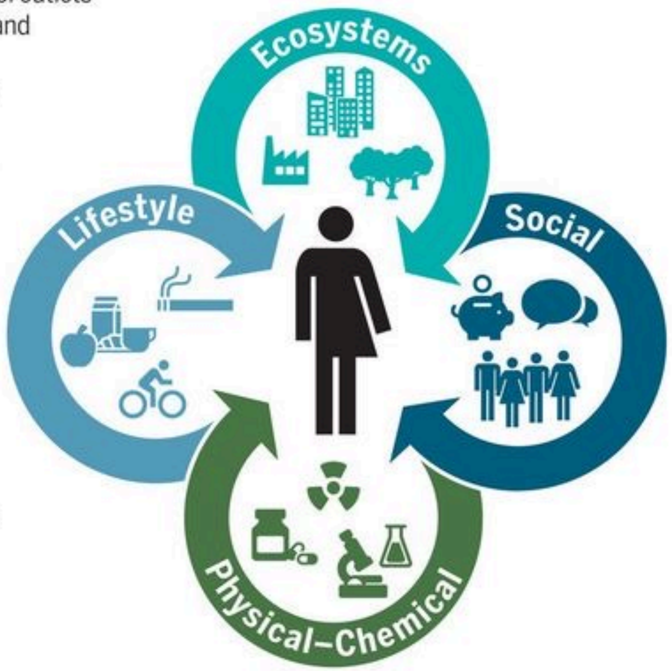
Observed

Phenome

Ecosystems
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

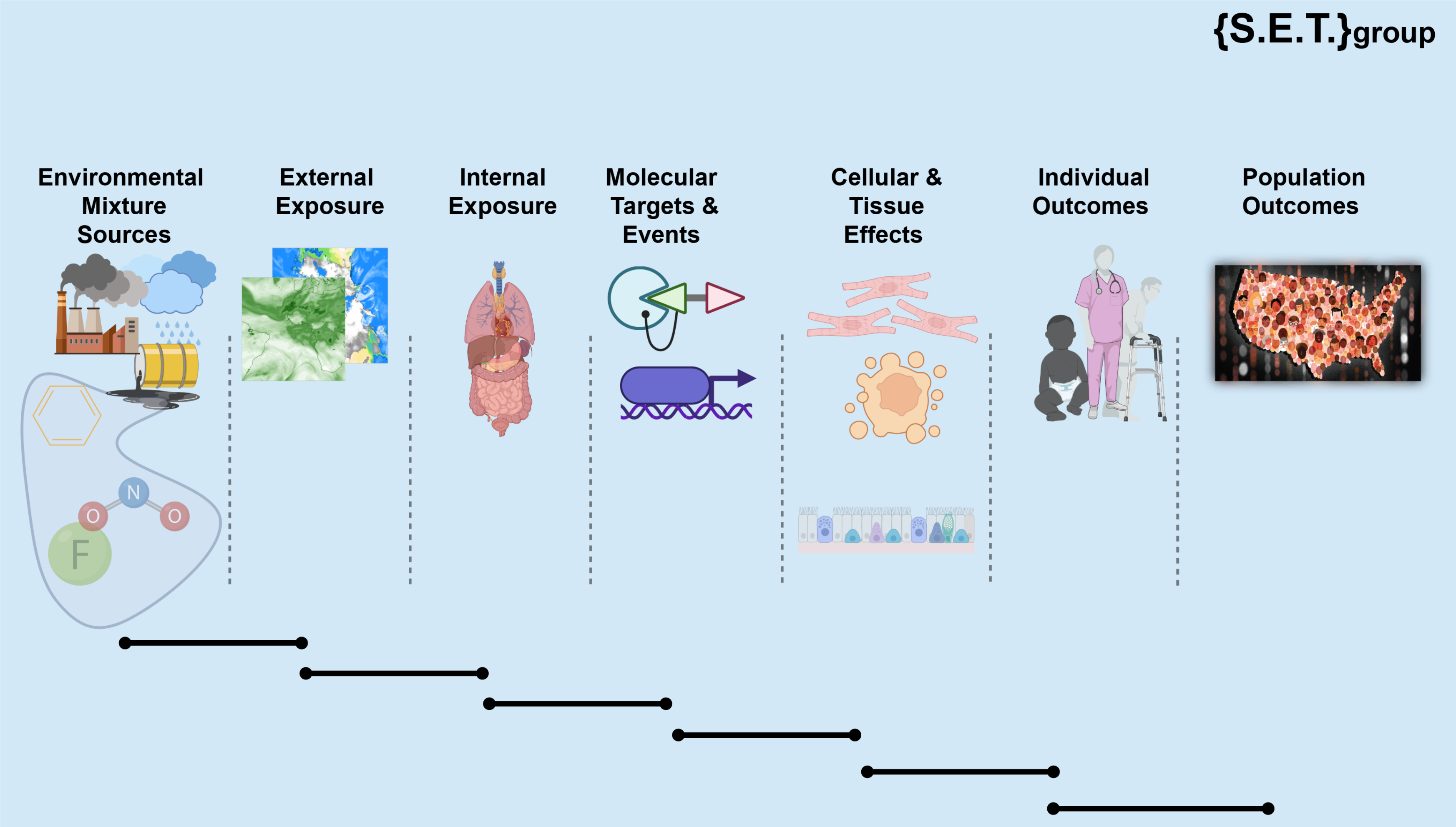
Social
Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress



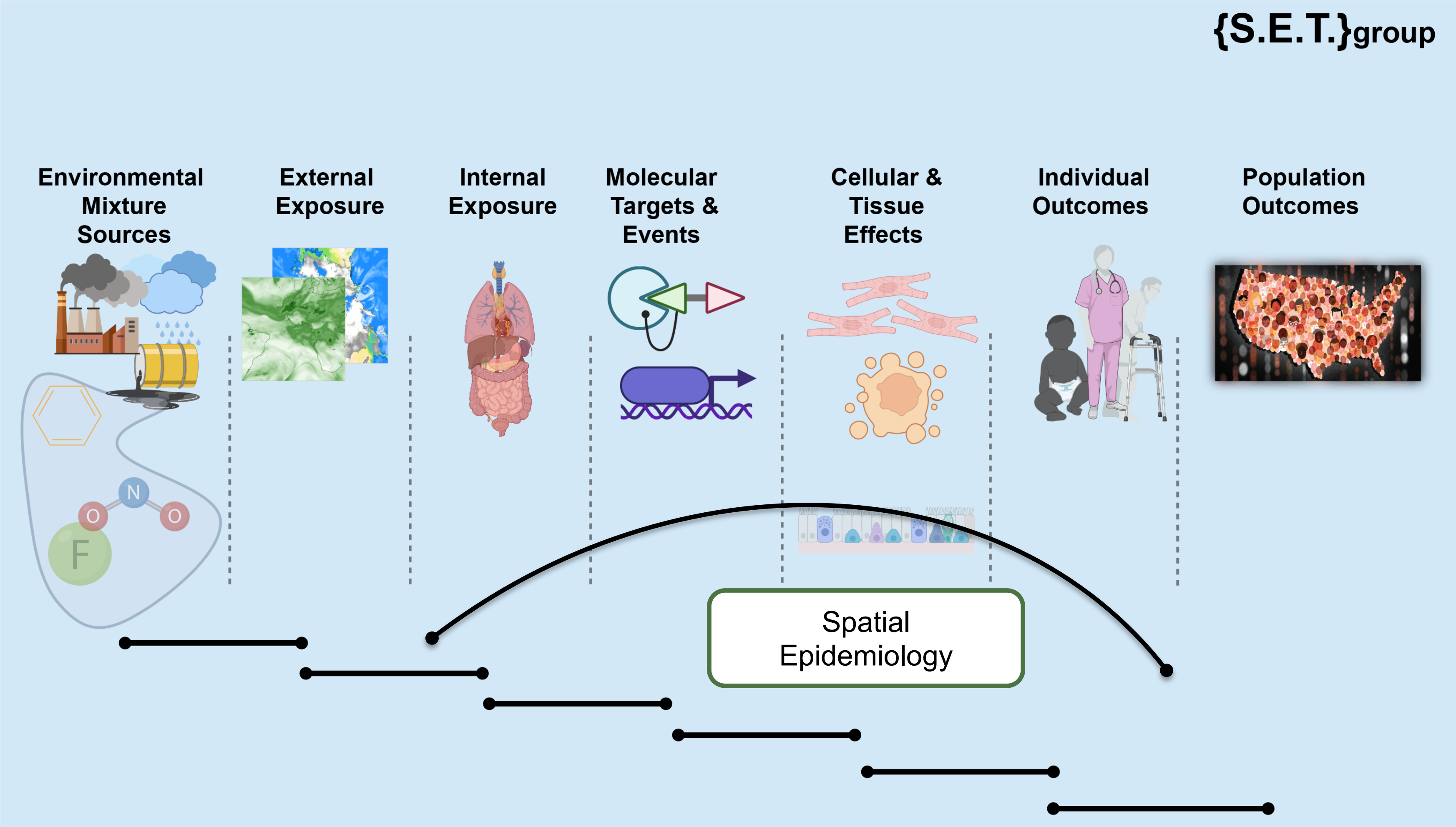
Physical–Chemical
Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g. factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

The exposome and health: Where chemistry meets biology, Volume: 367, Issue: 6476, Pages: 392-396, DOI: (10.1126/science.aay3164)

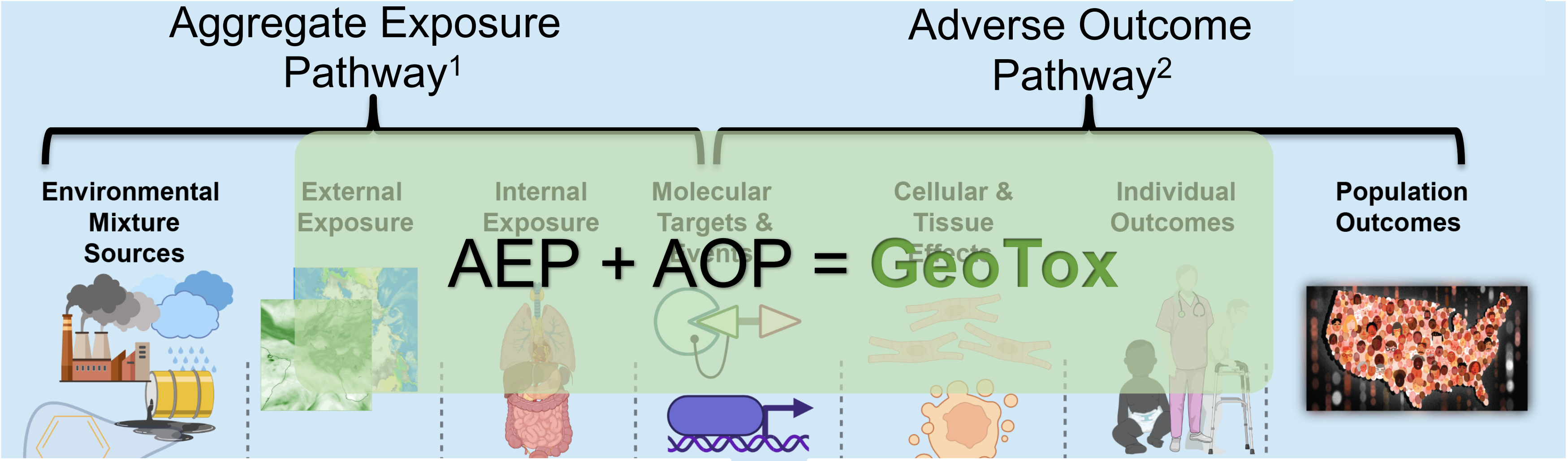
Science | AAAS



A Cascade of Events: The Events MUST Occur In This Order



Bypasses the Mechanisms



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

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

1. Teeguarden JG, Tan YM, Edwards SW, Leonard JA, Anderson KA, Corley RA, Kile ML, Simonich SM, Stone D, Tanguay RL, Waters KM. Completing the link between exposure science and toxicology for improved environmental health decision making: the aggregate exposure pathway framework.

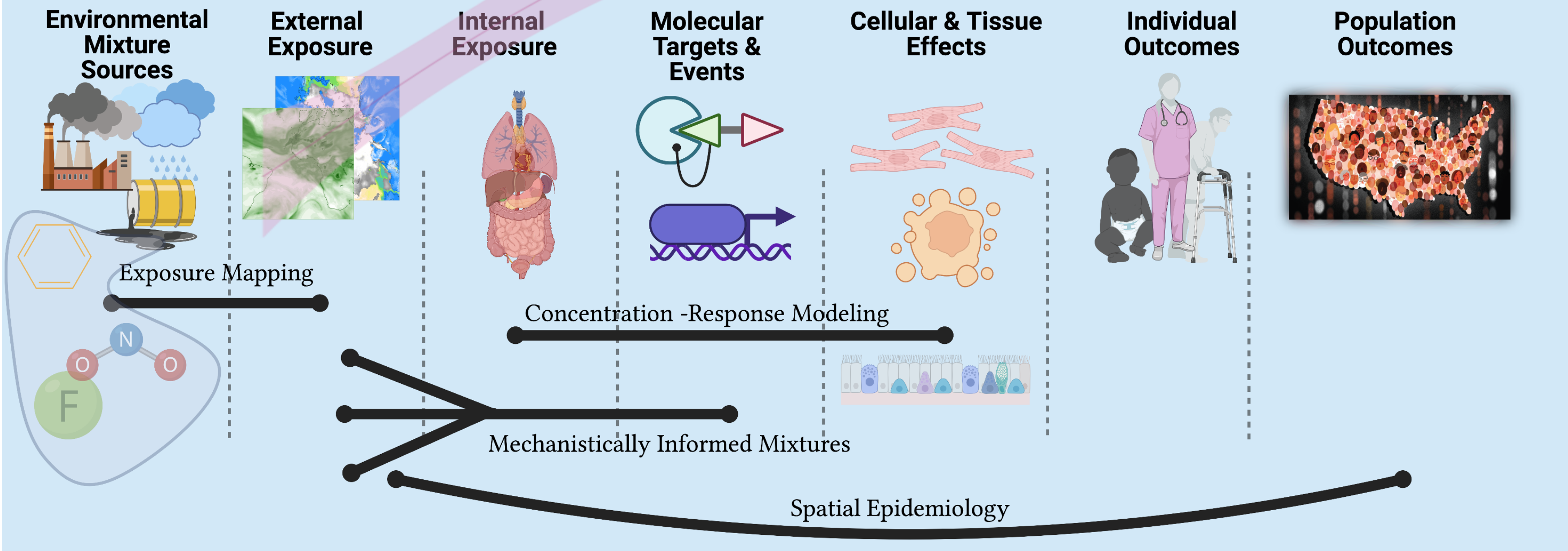
2. http://aop.wiki.org; Society for the Advancement of Adverse Outcome Pathways

Environmental Exposure Assessments and Mechanistically-Informed Mixture Risk Assessments Using Spatiotemporal Statistics

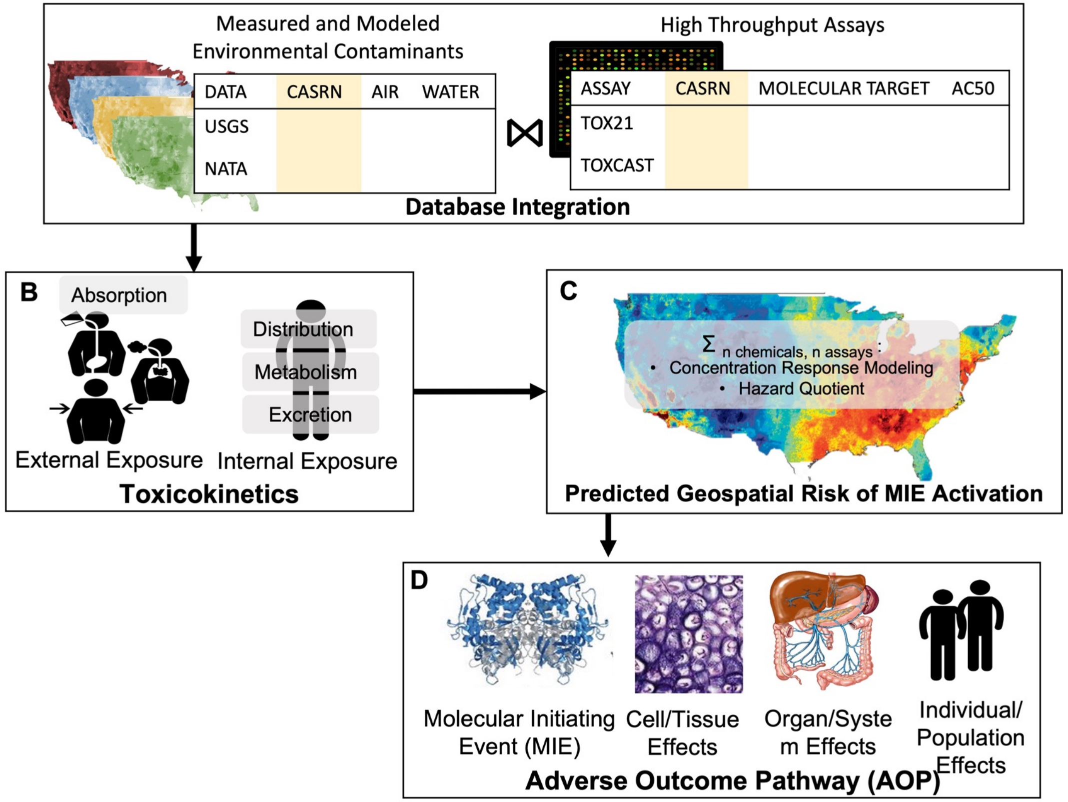
{ S.E.T. }group

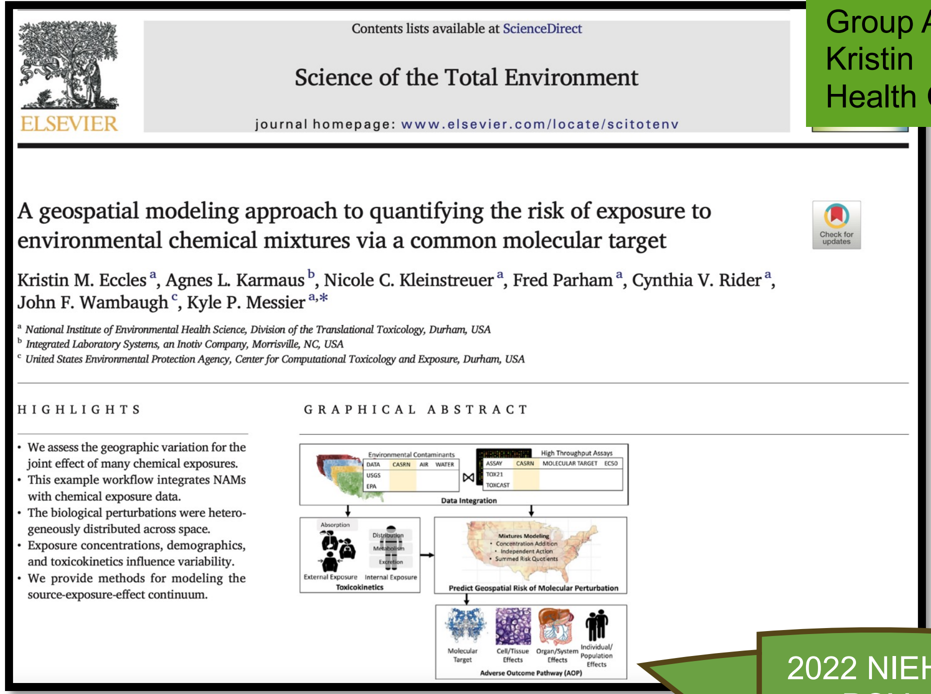
$$\eta \sim GP(\mu, \Sigma)$$

$$\min_{\beta \in \mathbb{R}^p} \left\{ \frac{1}{N} ||y - X\beta||_2^2 + \lambda ||\beta||_1 \right\}$$



GeoTox Proof of Concept





Contents lists available at ScienceDirect

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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

Group Alum:
Kristin Eccles, PhD
Health Canada

2022 NIEHS POY

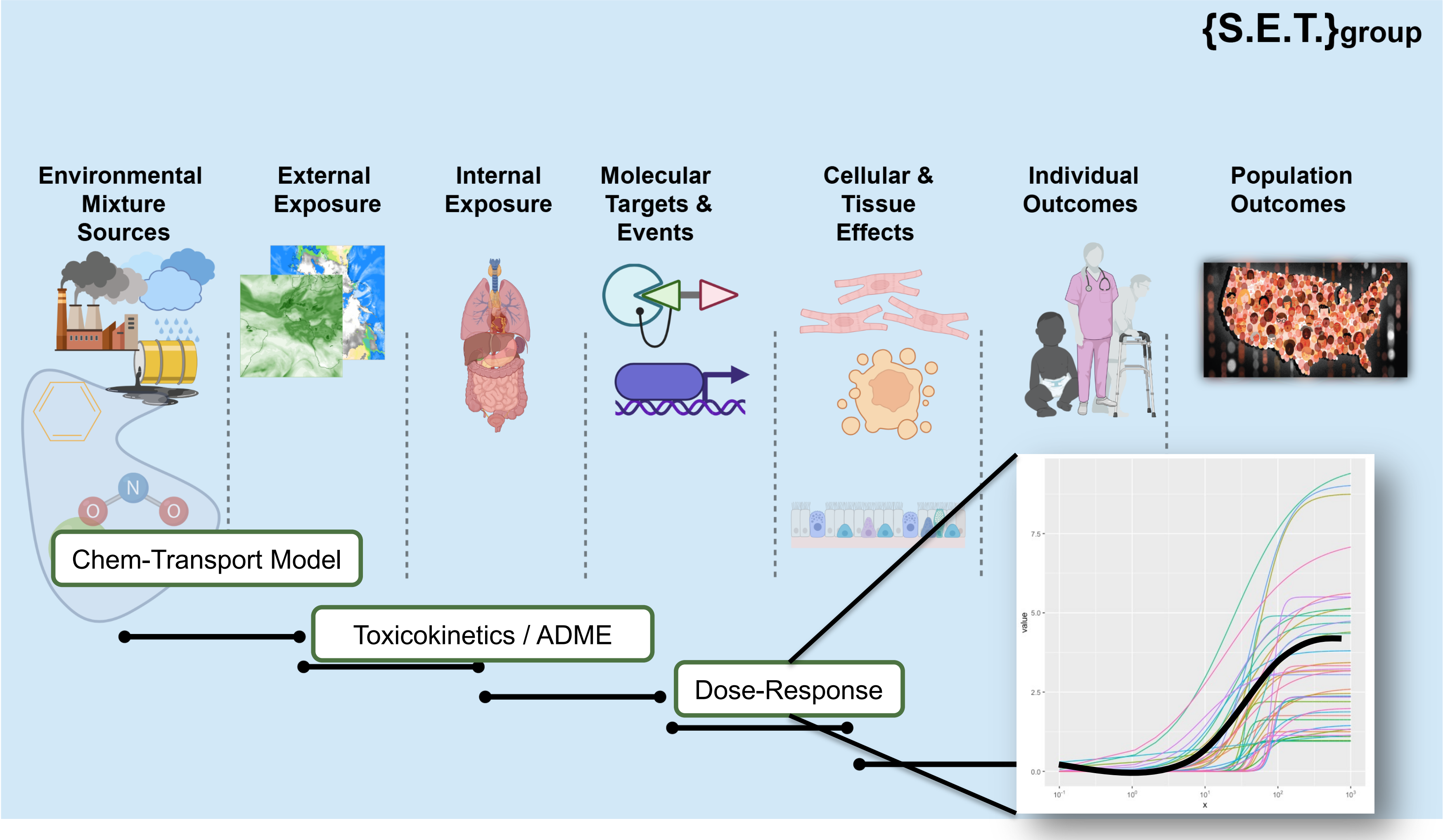
Key Steps in GeoTox Risk Mapping

External Exposure
- Geospatial models:
- Gaussian process, land-use regression, chemical transport

Internal Exposure
- Inhalation, Ingestion, Dermal absorption

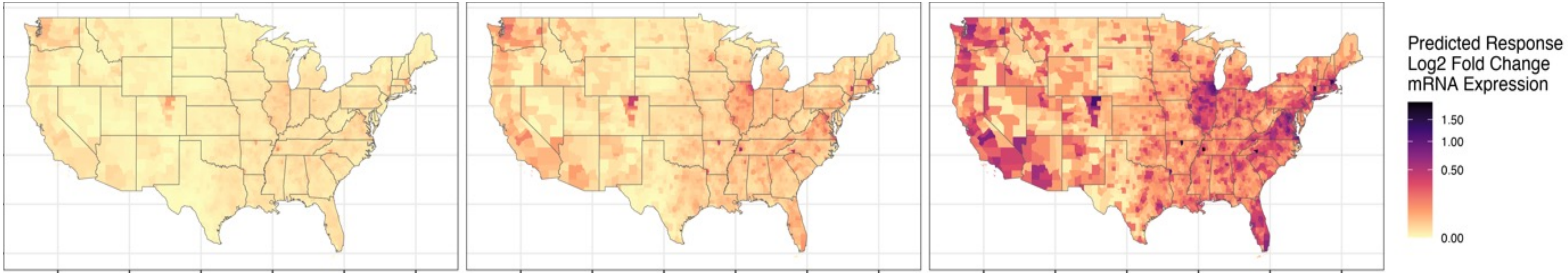
In vitro equivalent dose
- Physiologically Based Toxicokinetic Models
- IVIVE

Dose Response Modeling
- Toxicological Mixtures Predictions
- Generalized Concentration Addition, Independent Action


{S.E.T.}group
Environmental Mixture Sources
External Exposure
Internal Exposure
Molecular Targets & Events
Cellular & Tissue Effects
Individual Outcomes
Population Outcomes
N
O
O
Chem-Transport Model
Toxicokinetics / ADME
Dose-Response
value
x

Mapped Risk of Molecular Perturbation

5th Percentile | Median | 95th Percentile



Current Applications of GeoTox

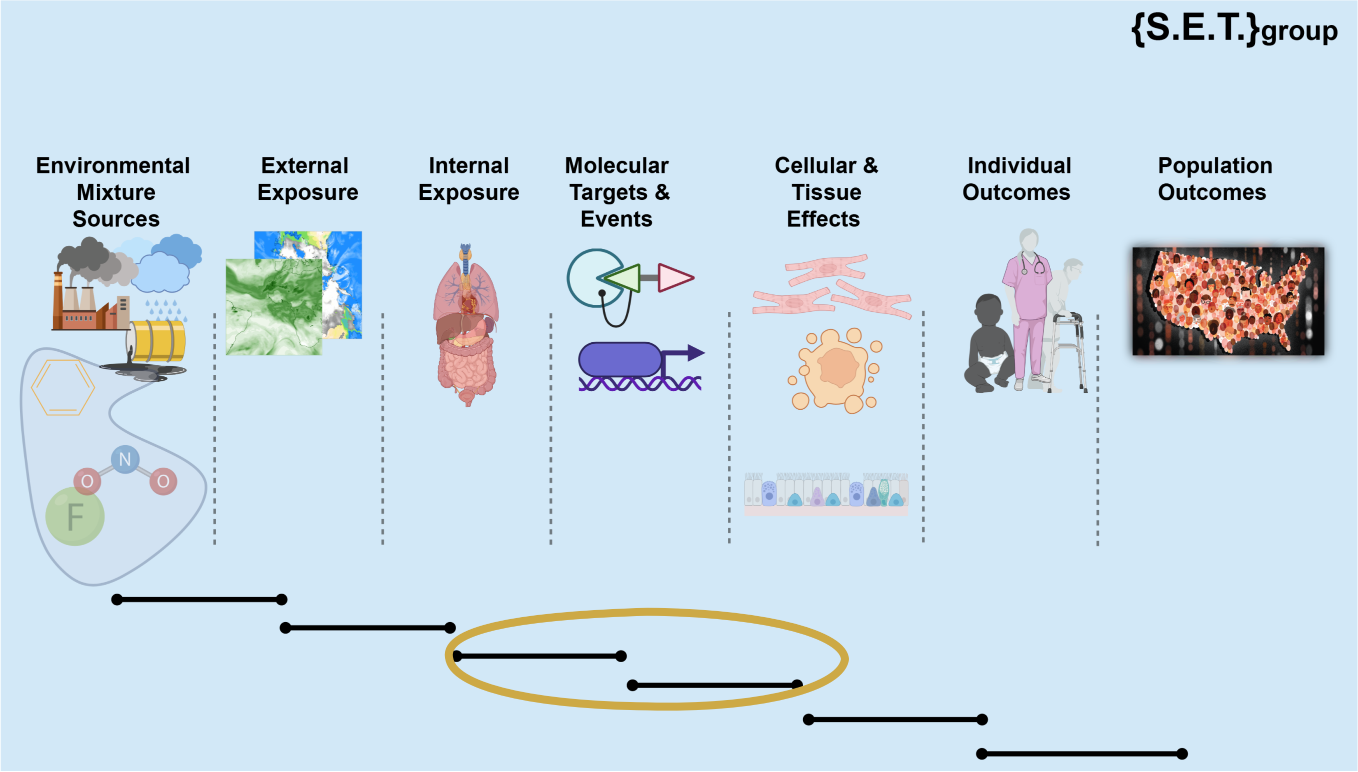
- Ex 1: Air pollution causing impaired mucociliary clearance
- Ex 2: VOC exposures in air and water leading to increased eczema
- Mapped AOP Key Events
- Large Scale Molecular Epidemiology

Some of the Current Limitations of GeoTox

Infinite Mixtures Problem

Geospatial chemical exposure models have a “lamp-post” problem

Improving Chemical Mixture Prediction



Postdoctoral Fellow:
Daniel Zilber, PhD

A little math

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

3 parameter hill model

$$C = f^{-1}(R|\alpha, \theta, \beta) = \frac{\theta}{\left(\frac{\alpha}{R} - 1\right)^{1/\beta}}$$

3 parameter hill model inverse

Parameters $\begin{cases} \alpha & \text{Sill/maximal effect} \\ \theta & \text{Inflection/ Half maximal effect} \\ \beta & \text{Slope at inflection} \end{cases}$

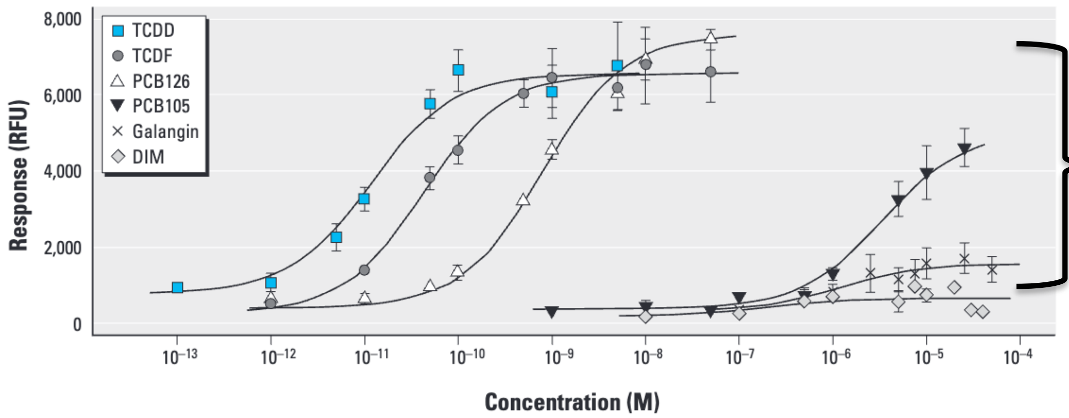
Generalized Concentration Addition (GCA)

- Concentration Addition

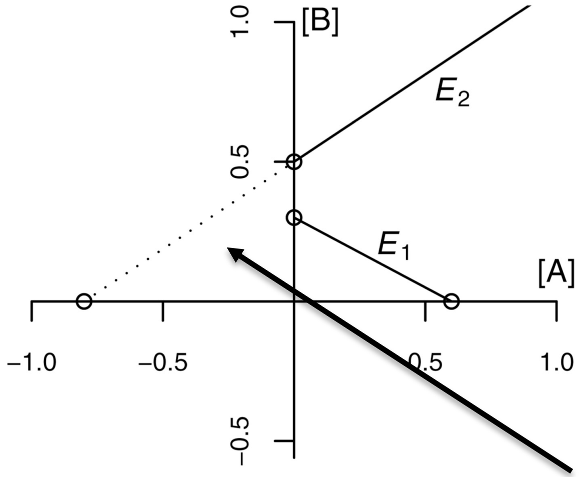
$$\sum_i \frac{c_i}{EC_i(R)} = 1$$

- Generalized Concentration Addition

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



Mixture response can exceed the maximal response (sill) of partial agonists

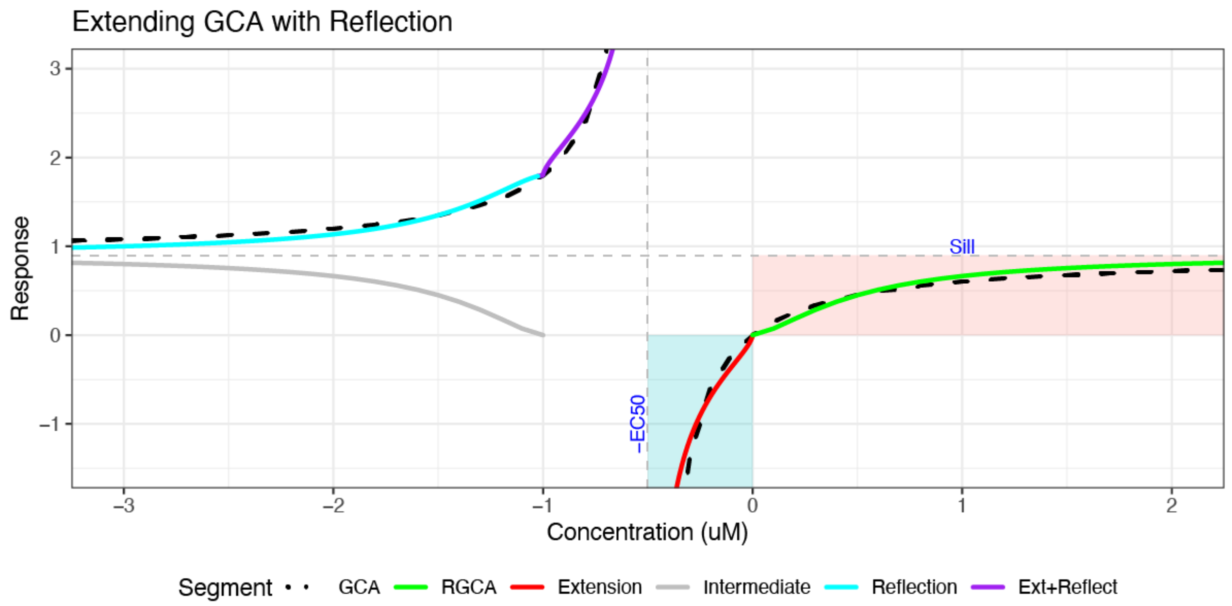


GCA allows for partial agonists to contribute a ”negative” concentration to the mixture response

Reflected Generalized Concentration Addition (RGCA)

- RGCA proposes a geometric technique that piece-wise reflects the inverse function such that it achieves defined inverse functions for 3+ parameter hill (i.e. sigmoidal) models

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



Some of the Current Limitations of GeoTox

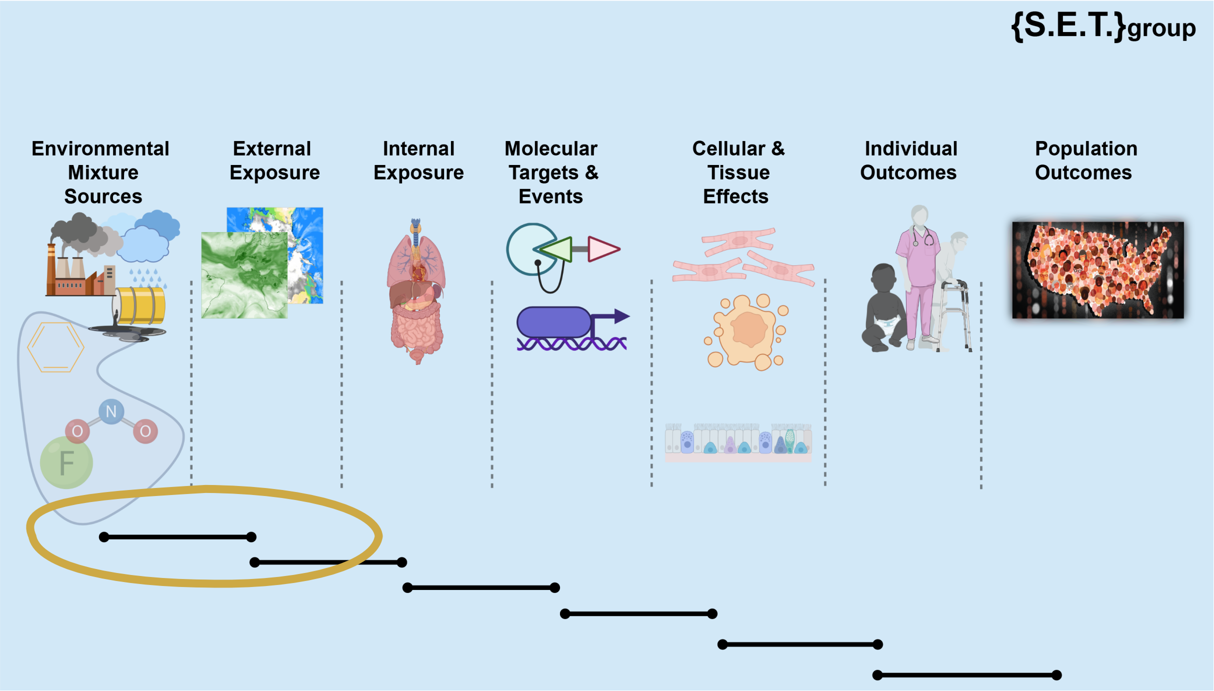
Infinite Mixtures Problem

Geospatial chemical exposure models have a “lamp-post” problem

“Remember who you are”

Please don’t sue me, Disney

Advances in Geospatial Exposure Modeling



1. Modeling Data-Sparse Chemicals
2. Spatially-Explicit Machine Learning Methods
3. Climate Related Exposures
4. Scalable, Interpretable Geospatial Models that deal with censoring
5. Code Development and Accessibility

Modeling Data Sparse Chemicals

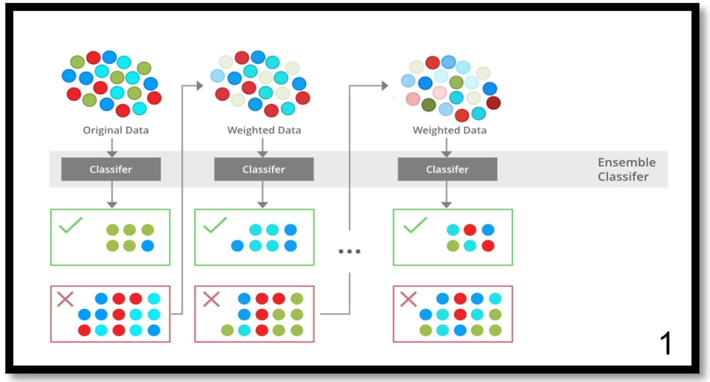
Postdoctoral Fellow:
Mariana Alifa, PhD

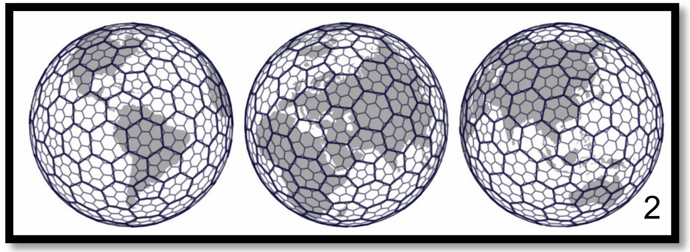
- Toxic Releases and National Emissions Inventory

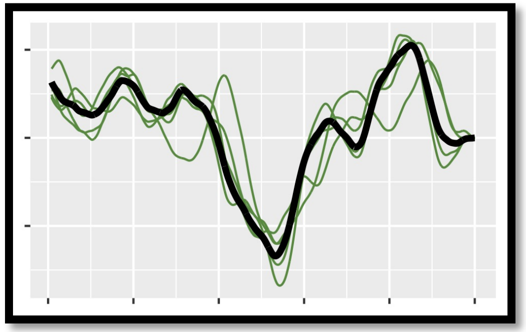
- In-vitro mechanistic and toxicity assays
- Atmospheric Dispersion Model with ML
- Goal: Exposure predictions for 100+ chemicals without information

Spatially-Explicit Machine Learning Methods

Gradient Boosting → Spatiotemporal Random Subsampling → Scalable Gaussian Processes







$$\eta \sim GP(\mu, \Sigma)$$

Postdoctoral Fellow: Ranadeep Daw, PhD

[1]https://www.geeksforgeeks.org/xgboost/# [2]https://www.uber.com/blog/h3/

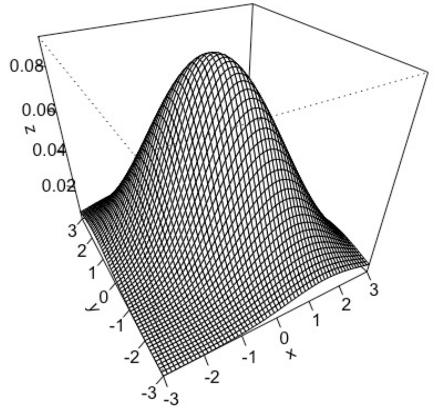
Climate Exposures Modeling

- Data Source Integration: Satellite, Reference Monitoring, Citizen Sensors
- High-Resolution Temperature and Humidity Maps
- Hierarchical Spatiotemporal Model
- Climate Modifications of AEP and AOP
- Epidemiological Relevant Exposure Metrics

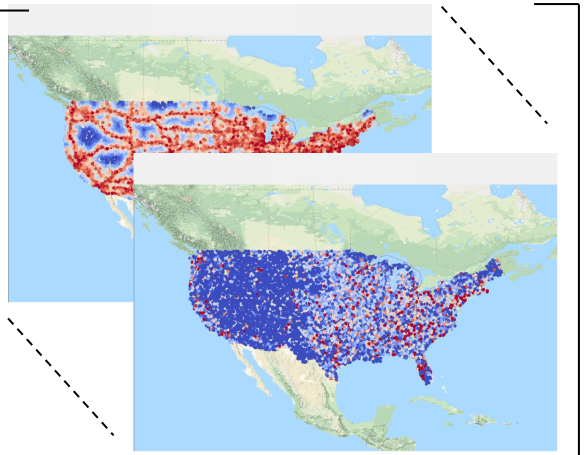
Postdoctoral Fellow:
Eva Marques, PhD

Scalable, Interpretable Geospatial Models with censoring

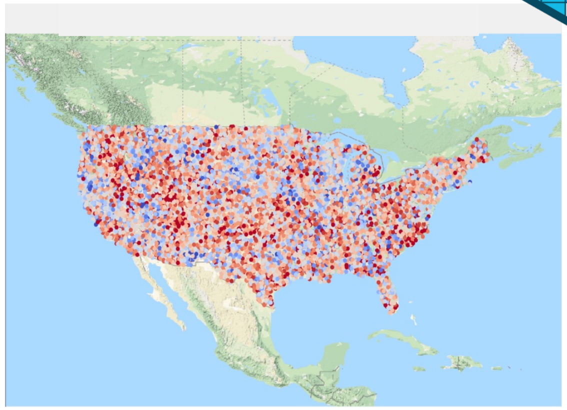
$$Y(s) = X^T(s)\ \beta + \varepsilon(s)$$



$=$



β $+$



$Y(s)$ is assumed Gaussian→ The joint distributions are multivariate normal with mean $X\beta$ and covariance Σ_θ

- GIS Covariates
- Spatial, temporal, spatiotemporal
- Easily 100 to 1000's

- Spatiotemporal error

$$Cov(\varepsilon(s), \varepsilon(s')) = C(\boldsymbol{h}; \boldsymbol{\theta})$$

Penalized Spatiotemporal Regression

$$f(\mathbf{z};\boldsymbol{\beta},\boldsymbol{\theta}) = \mathcal{N}_n(\mathbf{z}|\mathbf{X}\boldsymbol{\beta},\boldsymbol{\Sigma}_{\boldsymbol{\theta}})$$

Multivariate Gaussian Density

$$Q(\boldsymbol{\beta},\boldsymbol{\theta}) = -2\log f(\mathbf{z};\boldsymbol{\beta},\boldsymbol{\theta}) + \lambda\ \mathrm{p}(\boldsymbol{\beta}) = (\mathbf{z}-\mathbf{X}\boldsymbol{\beta})'\boldsymbol{\Sigma}_{\boldsymbol{\theta}}^{-1}(\mathbf{z}-\mathbf{X}\boldsymbol{\beta}) + \log|\boldsymbol{\Sigma}_{\boldsymbol{\theta}}| + \lambda\ \mathrm{p}(\boldsymbol{\beta})$$

Likelihood Density Penalty

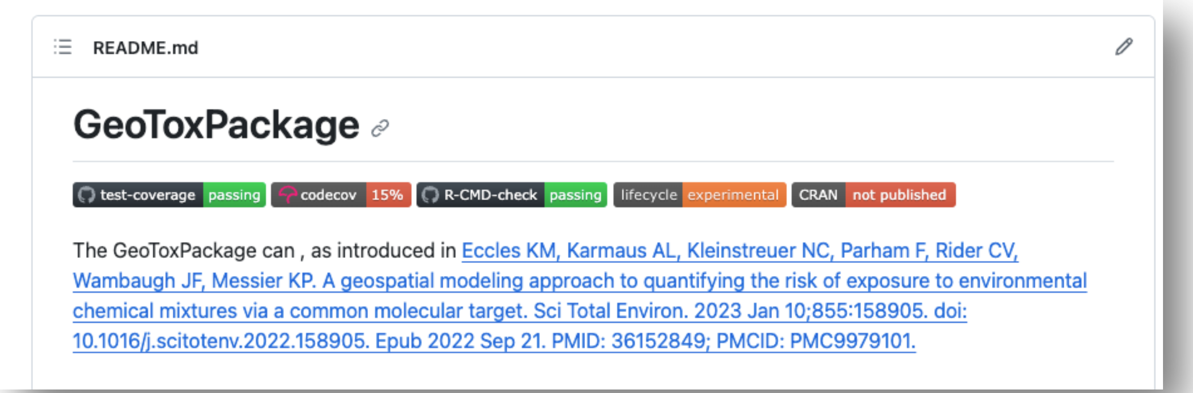
- Simultaneous estimation of covariates and spatiotemporal error parameters
- Computational Scaling via the General Vecchia Approximation
- Model selection via a penalty
- Matérn Cross-Covariances
- Censoring Imputation via Truncated Normal Distribution

Continuous Developments

GeoTox R package

- R package expected by Society of Toxicology meeting (March 2024)
- Increase accessibility and extensibility of GeoTox
- Improve computational speed
- Incorporate time resolution

DTT Staff Scientist:
Skylar Marvel, PhD



README.md

GeoToxPackage

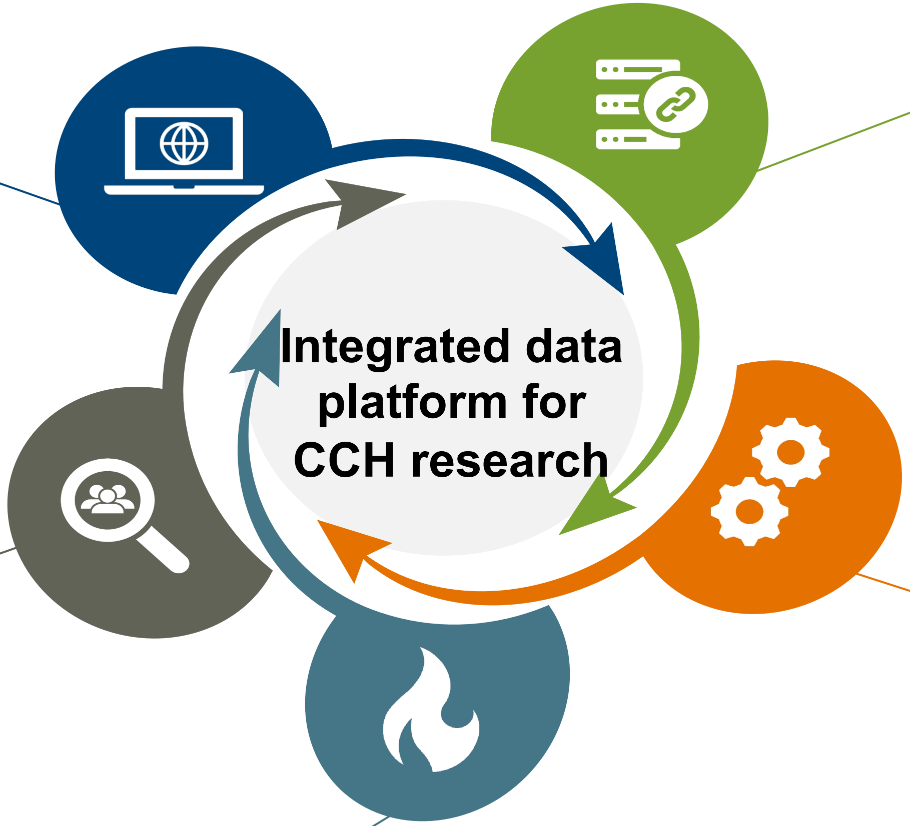
test-coverage passing | codecov 15% | R-CMD-check passing | lifecycle experimental | CRAN not published

The GeoToxPackage can , as introduced in Eccles KM, Karmaus AL, Kleinstreuer NC, Parham F, Rider CV, Wambaugh JF, Messier KP. A geospatial modeling approach to quantifying the risk of exposure to environmental chemical mixtures via a common molecular target. Sci Total Environ. 2023 Jan 10;855:158905. doi: 10.1016/j.scitotenv.2022.158905. Epub 2022 Sep 21. PMID: 36152849; PMCID: PMC9979101.

Mixtures Predictions

- Synergy & Antagonism
- QSAR and Docking Mechanisms

Climate Health Outcomes Research and Data Systems → CHORDS



Objective 1:
Web-based catalog of available resources

Objective 2:
Standardized, linked datasets

Objective 3:
Code and Tools

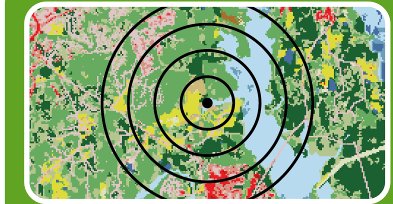
Objective 4:
Evaluation use case

Objective 5:
Addressing end user needs

CCH Data Analyst:
Mitchell Manware, MS

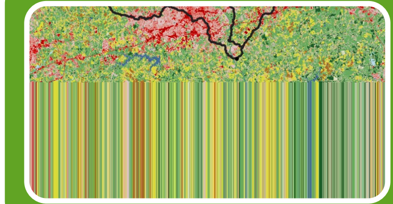
CHORDS Leads:
Aubrey Miller, MD
Charles Schmitt, PhD
Trish Castranio
Kyle Messier, PhD

Scalable GIS Tools for Environment, Climate, and Health



Raster and Vector Processing

- Usable for a laptop
- Blazing fast on high-performance computing

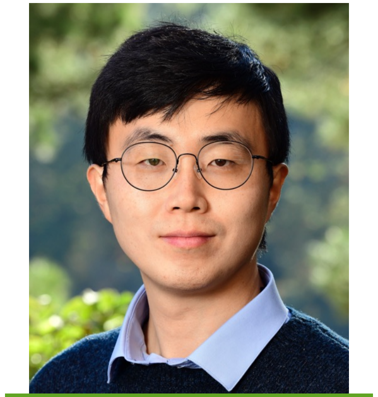


Sophisticated GIS covariates

- Most common GIS covariates for environmental health
- Non-Isotropic buffers
- Mechanistic

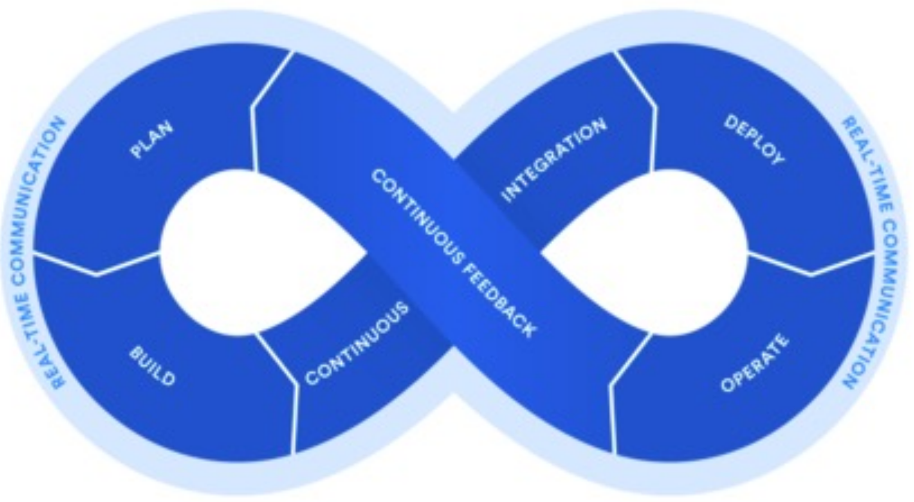
Documented and Tested

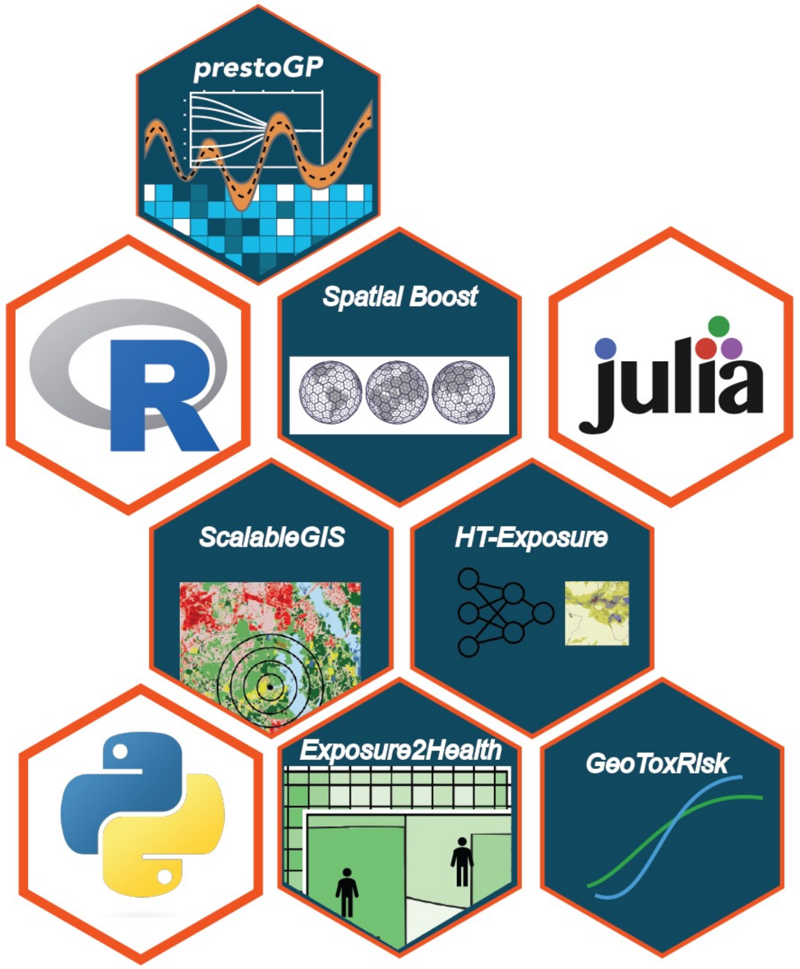
- Documentation
- Vignettes
- Unit Tests
- Build and System Tests



Postdoctoral Fellow:
Insang Song, PhD

FAIR+ Data Science Standards





Documented, Tested, and Open

{SET}group
Spatiotemporal-Exposures-and-Toxicology

Kyle P Messier, PhD Stadtman Investigator -- Geospatial exposure and risk assessment methods with tox data integration. He/Him @NIEHS

Edit profile

5 followers · 2 following

National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina
13:08 (UTC -04:00)
https://www.niehs.nih.gov/research/atniehs/labs/ptb/spatiotemporal/index.cfm

Spatiotemporal-Exposures-and-Toxicology / README.md

{ Spatiotemporal Exposures and Toxicology }

Github for open-source code and projects from {SET}.

Methods Used

- Spatial and Spatiotemporal Statistics
  - Gaussian processes
  - Penalized Regression
- Geographic Information Systems
- Land Use Regression
- Artificial Neural Networks

Software We Use

- R, RMarkdown, RShiny
- Julia
- Python, PyTorch
- Linux
- Jupyter Notebooks

Pinned

NRTAPmodel Public
Near Real Time Air Pollution

R

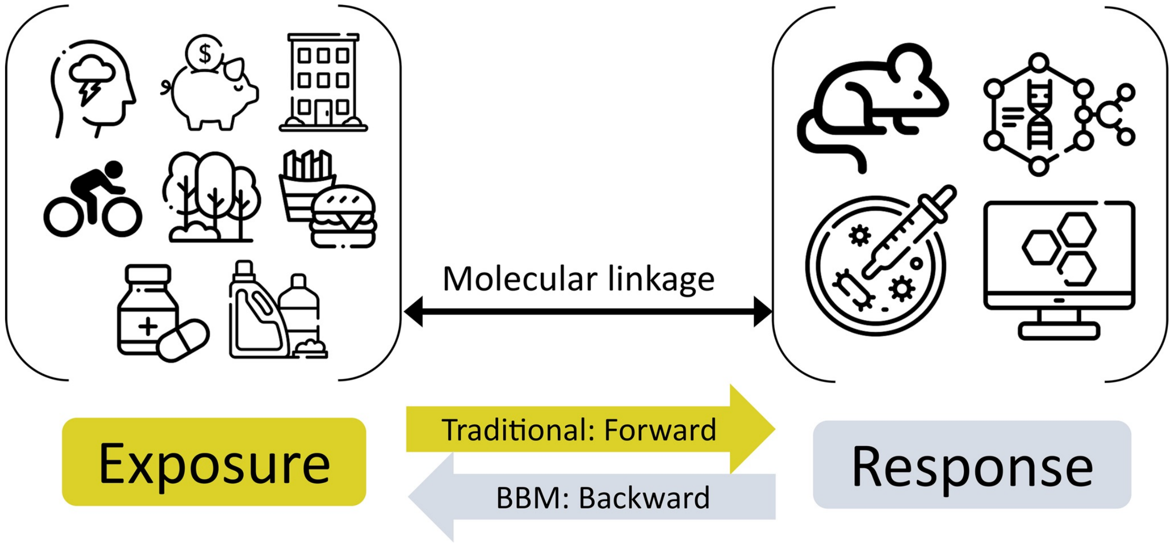
README.md

test-coverage passing | codecov 68% | R-CMD-check passing | lint passing | lifecycle experimental

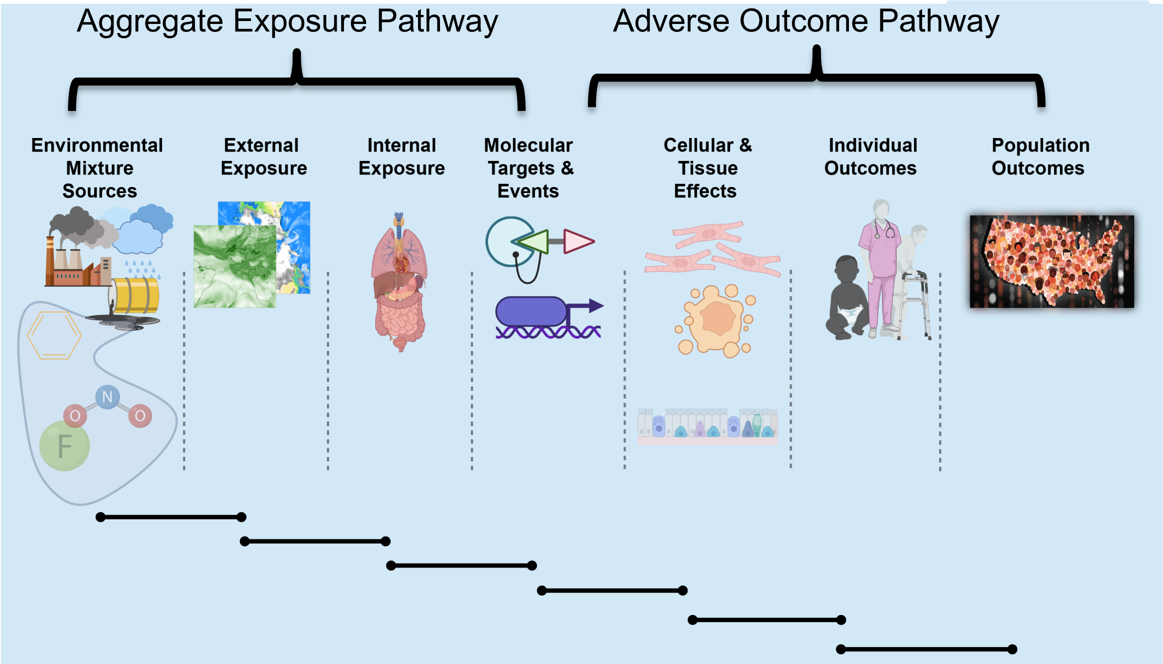
Air Pollution Data for the Masses: An Open-Access, Tested, Updated $PM_{2.5}$ Hybrid Model

Group Project for the Spatiotemporal Exposures and Toxicology group with help from friends 😃 🤠 🌎

Competing and Complementary Ideas



AEP + AOP = GeoTox



[1]Chung et al., EHP, 2021

Acknowledgements

SET group	CHORDS	DTT	Biostatistics and Comp Biology	University of Wisconsin	Sciome

• Daniel Zilber, PhD
• Insang Song, PhD
• Mariana Alifa, PhD
• Ranadeep Daw, PhD
• Eva Marques, PhD
• Alumni:
  • Kristin Eccles, PhD
  • Melissa Lowe, MS
  • Taylor Potter, BA
	• Aubrey Miller, MD
	• Charles Schmitt, PhD
	• Trisha Castranio, MS
	• Ann Liu, PhD
	• Gwen Collman, PhD
	• Mike Conway, PhD
	• Deep Patel, PhD
	• Richard Kwok, PhD
		• David Reif, PhD
		• Skylar Marvel, PhD
		• Kristin Eccles, PhD
		• Cynthia Rider, PhD
		• Nicole Kleinstreuer, PhD
		• Fred Parham, PhD
			• Alison Motsinger-Reif, PhD
			• Matt Wheeler, PhD
				• Matthias Katzfuss, PhD
				• MJ Kang, PhD
					• Ruchir Shah, PhD
					• Eric Bair, PhD
					• Brian Kidd, PhD
					• Deepak Mav, PhD
					• Bekki Elmore, MS