Geospatial Human Health Exposure Science Connections to Toxicology

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Board of Scientific Counselors

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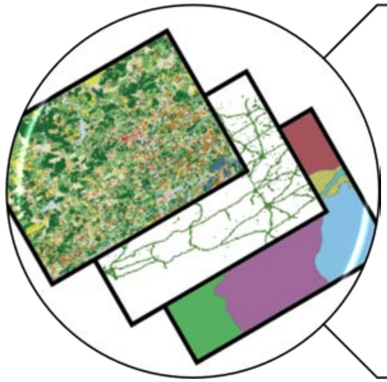
Presentation Theme

“Bridging research in exposure science and disease mechanisms through spatial statistics to protect public health”

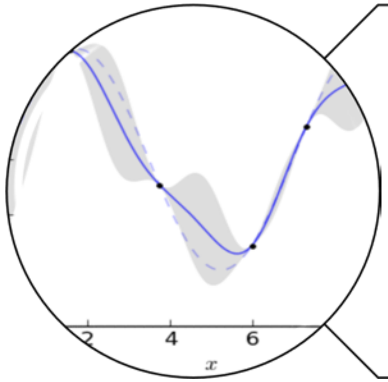
National Toxicology Program Vision

“Spatial statistics for 21st Century Toxicology Research”



Translational

- Maps
- Integrative



Predictive

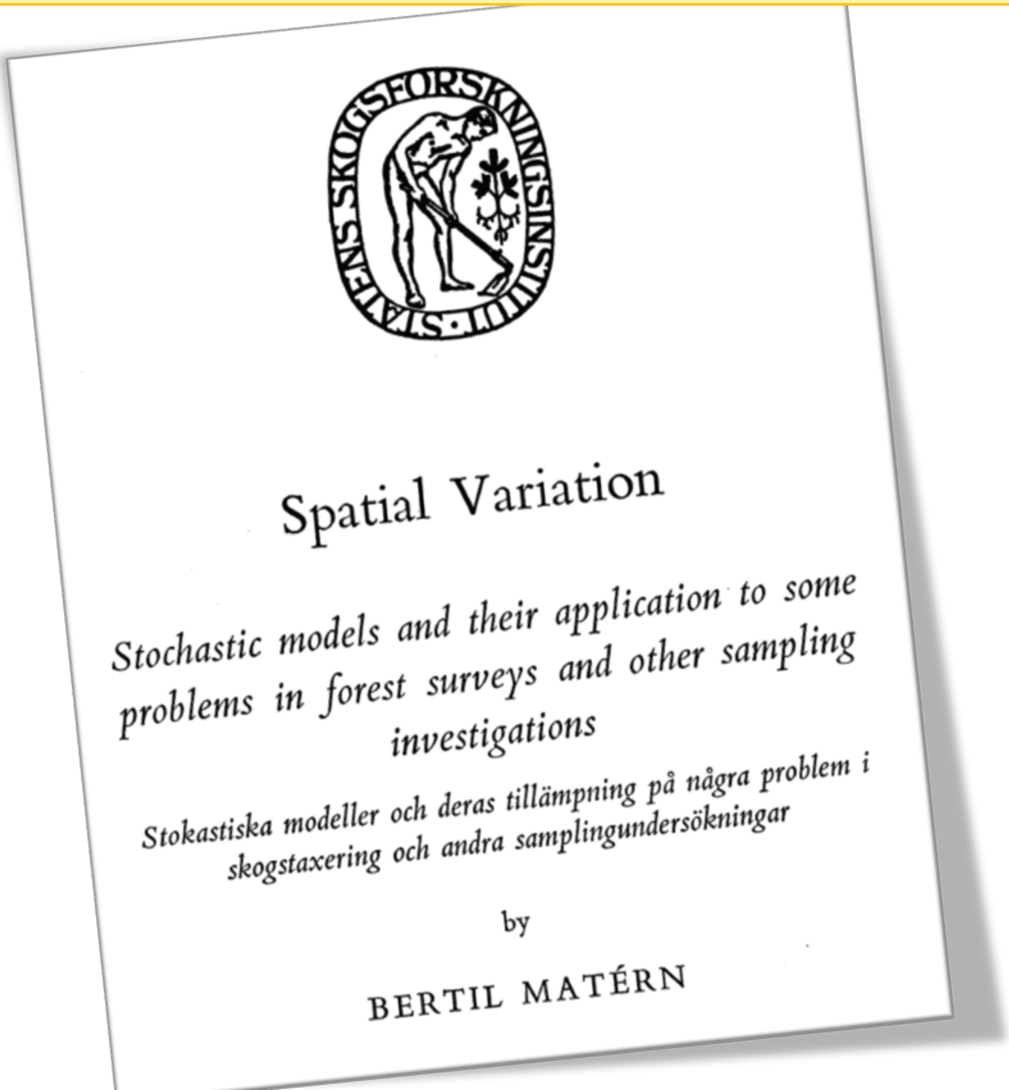
- Interpolation
- Uncertainty

History of Spatial Statistics (a.k.a. Geostatistics)

Mining

- Matheron and Krige
- Developed spatial statistical methods to estimate ore content from core samples

History of Spatial Statistics (a.k.a. Geostatistics)



Spatial Variation

Stochastic models and their application to some problems in forest surveys and other sampling investigations

Stokastiska modeller och deras tillämpning på några problem i skogstaxering och andra samplingundersökningar

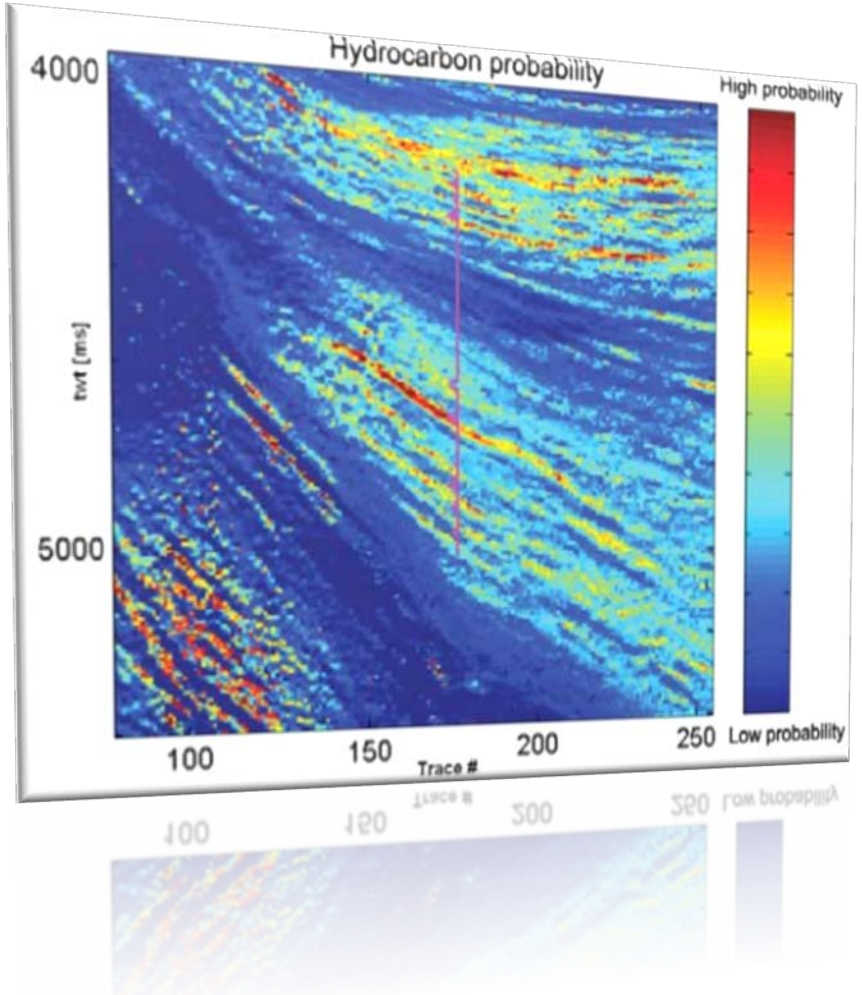
by

BERTIL MATÉRN

Forestry

- Matérn
- Developed correlation models for spatial variation

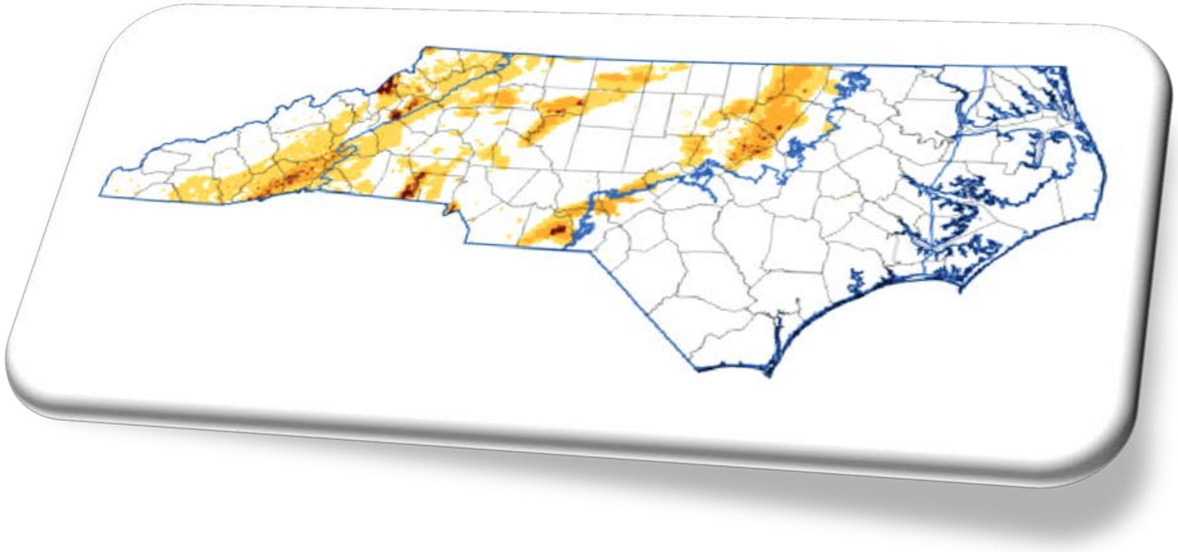
History of Spatial Statistics (a.k.a. Geostatistics)



Petroleum Engineering

- Used to evaluate the oil and gas field reservoirs
- Uses geology and seismic data

History of Spatial Statistics (a.k.a. Geostatistics)



Health Science

- Used in geo and non-geographical applications with correlated variables
- Wide scale adoption for statisticians and engineers in exposure applications

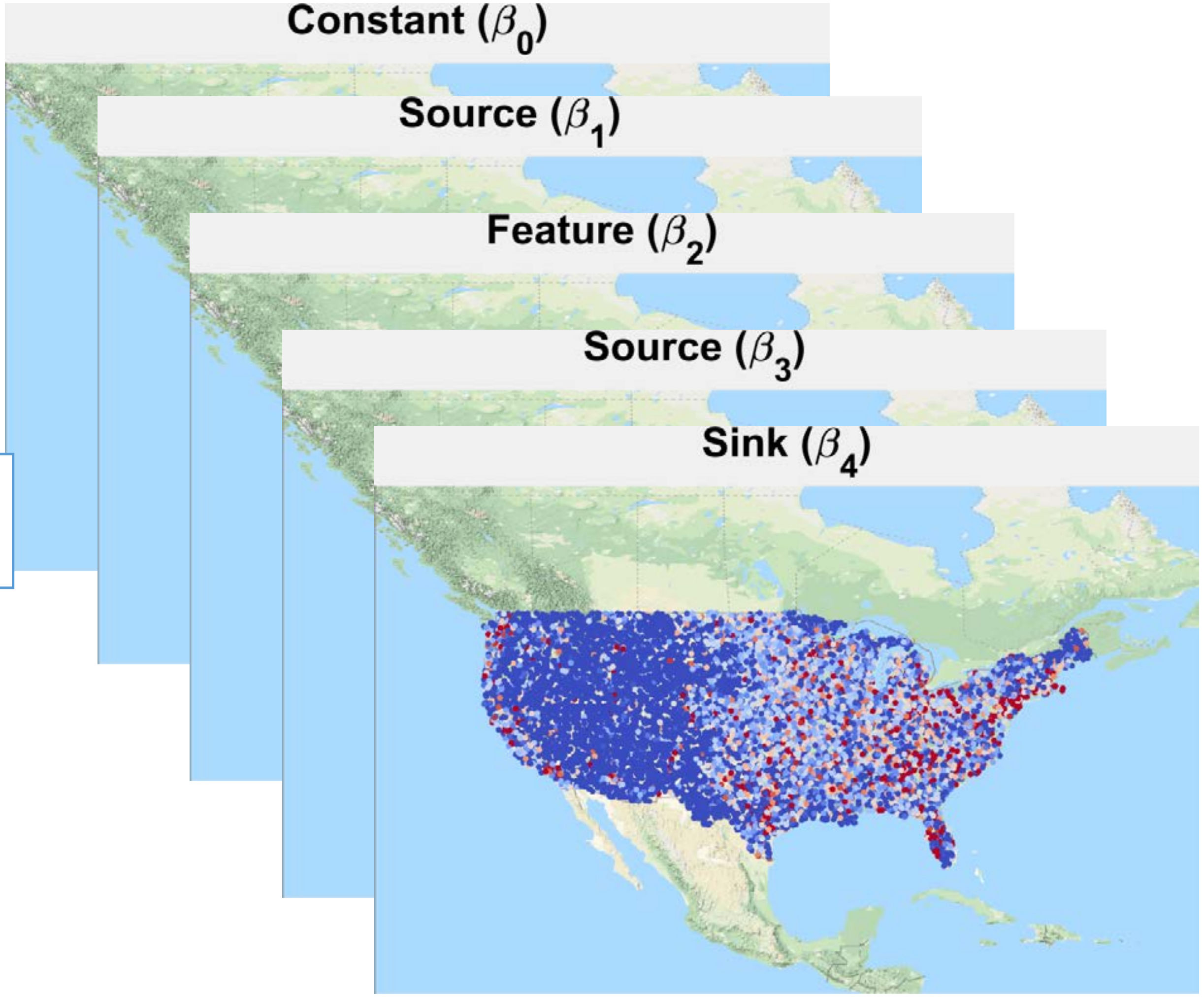
History of Spatial Statistics (a.k.a. Geostatistics)

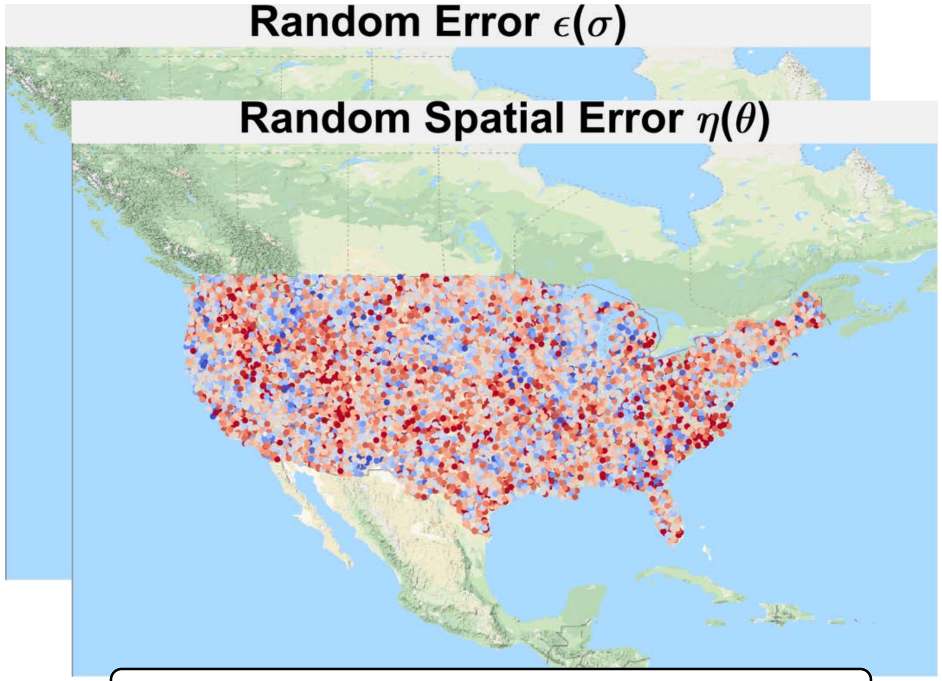
<u>Toxicology</u>

The next frontier for spatial statistics?

Resurrection Trail | © USDA Forest Service Alaskan Region/Flickr

The Power of Spatial Statistics:
(1) estimate relationships accounting for correlation
(2) interpolate at unmonitored locations





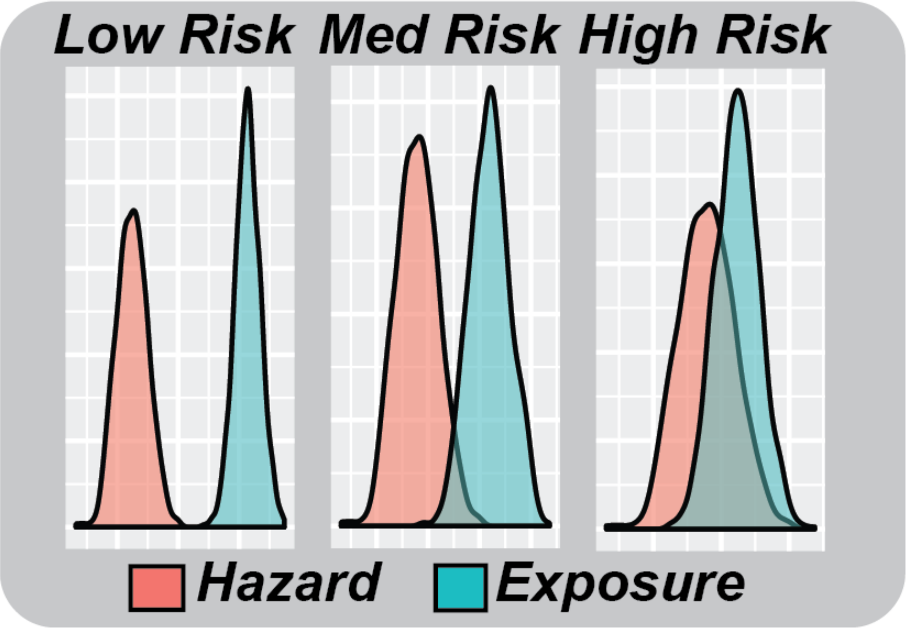
$$Y = \mu(\boldsymbol{s}, t; \beta) + \varepsilon(\boldsymbol{s}, t; \sigma) + \eta(\boldsymbol{s}, t; \theta)$$

Mean trend

i.i.d. error

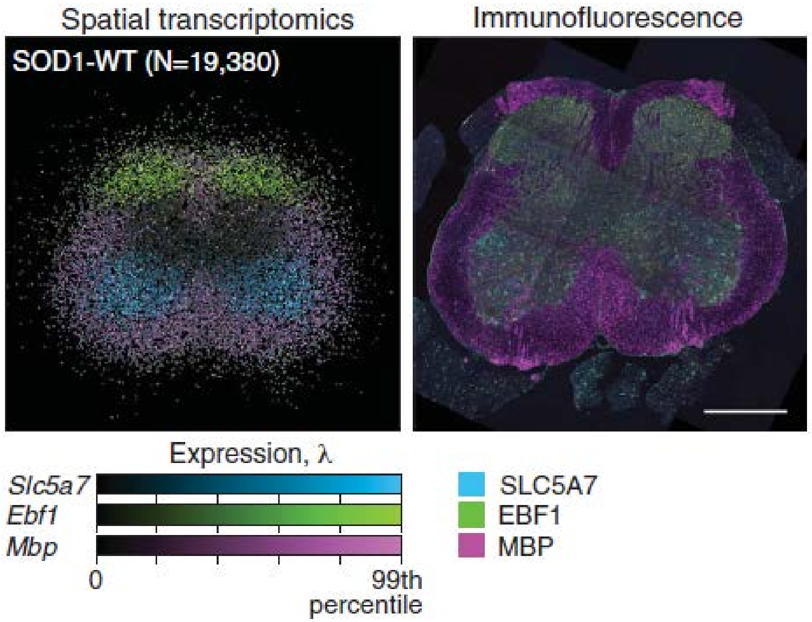
Correlated error

Build upon existing toxicological methods



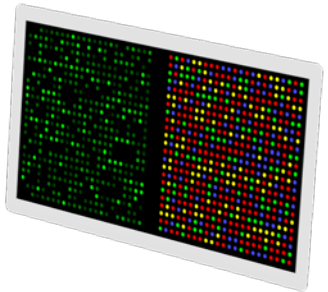
1. Using spatial methods to inform human exposure estimates and uncertainty
2. Risk-based prioritization of chemicals
    - Requires exposure

Expanding upon and developing new spatial methods in toxicology



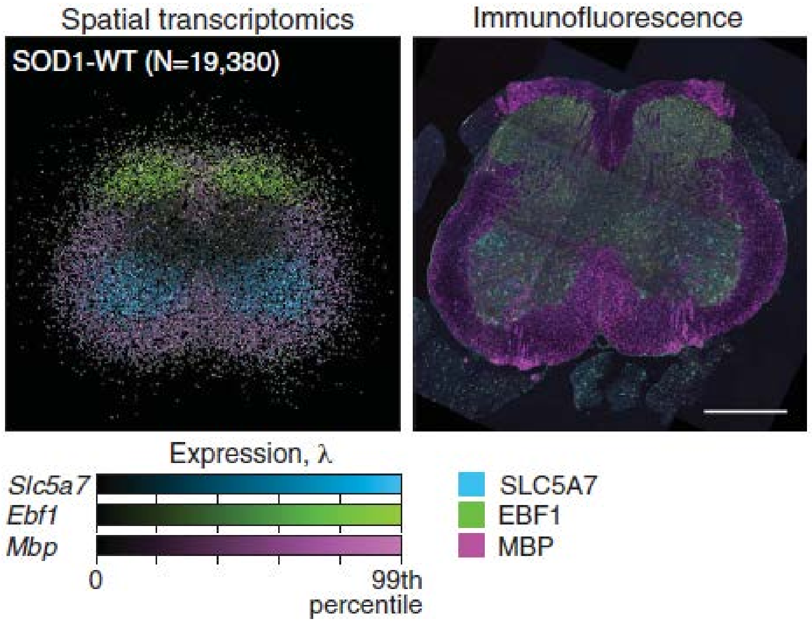
- Expand approaches to toxicology-relevant –omics databases

- Example databases:
  - ArrayExpress
  - Gene Expression Omnibus
  - DrugMatrix
  - TG-Gates



*Maniatis et al. Spatiotemporal Dynamics of Molecular Pathology in Amyotrophic Lateral Sclerosis. *Science.* **2019**, *364*, 89–93.

Expanding upon and developing new spatial methods in toxicology



- Expanding methods in the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP)
- Toxicokinetics / PBPK modeling
- Correlated data
- Multi-stressors

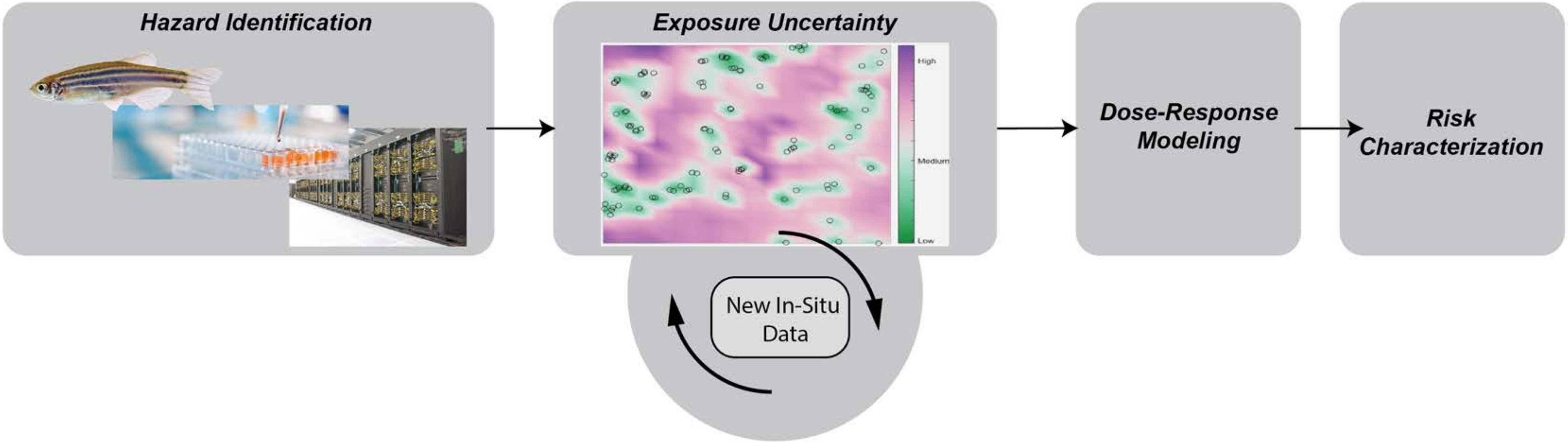
*Maniatis et al. Spatiotemporal Dynamics of Molecular Pathology in Amyotrophic Lateral Sclerosis. *Science.* **2019**, *364*, 89–93.

Vignettes

- Five short, descriptive ideas
- Examples from my own research
- Examples from other published studies

Spatial statistics can be used to explicitly quantify uncertainty in hazard and exposure assessments

Spatial methods can be applied to high-throughput methods to quantify exposure and uncertainty

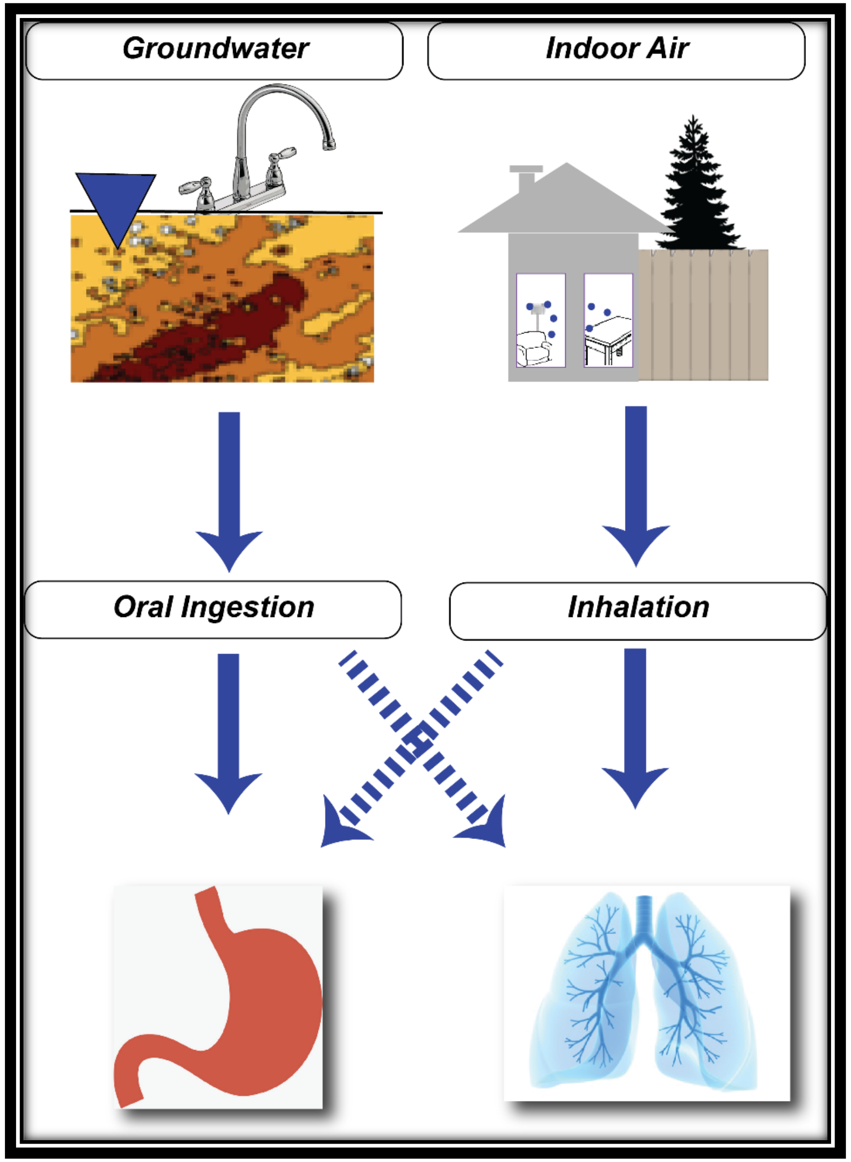


- Alternative models, *in vitro* methods, and *in silico* approaches are rapidly growing
- Provide information on where more *in situ* is needed
- Risk-based Priority Assessment of Chemicals

Case Study: Radon and Cancer

Krewski et al 2006 (Pooled Analysis): "… results provide direct evidence of an association between residential radon and lung cancer risk"

A biokinetic model suggests the stomach may receive a significant dose



Environmental Science & Technology

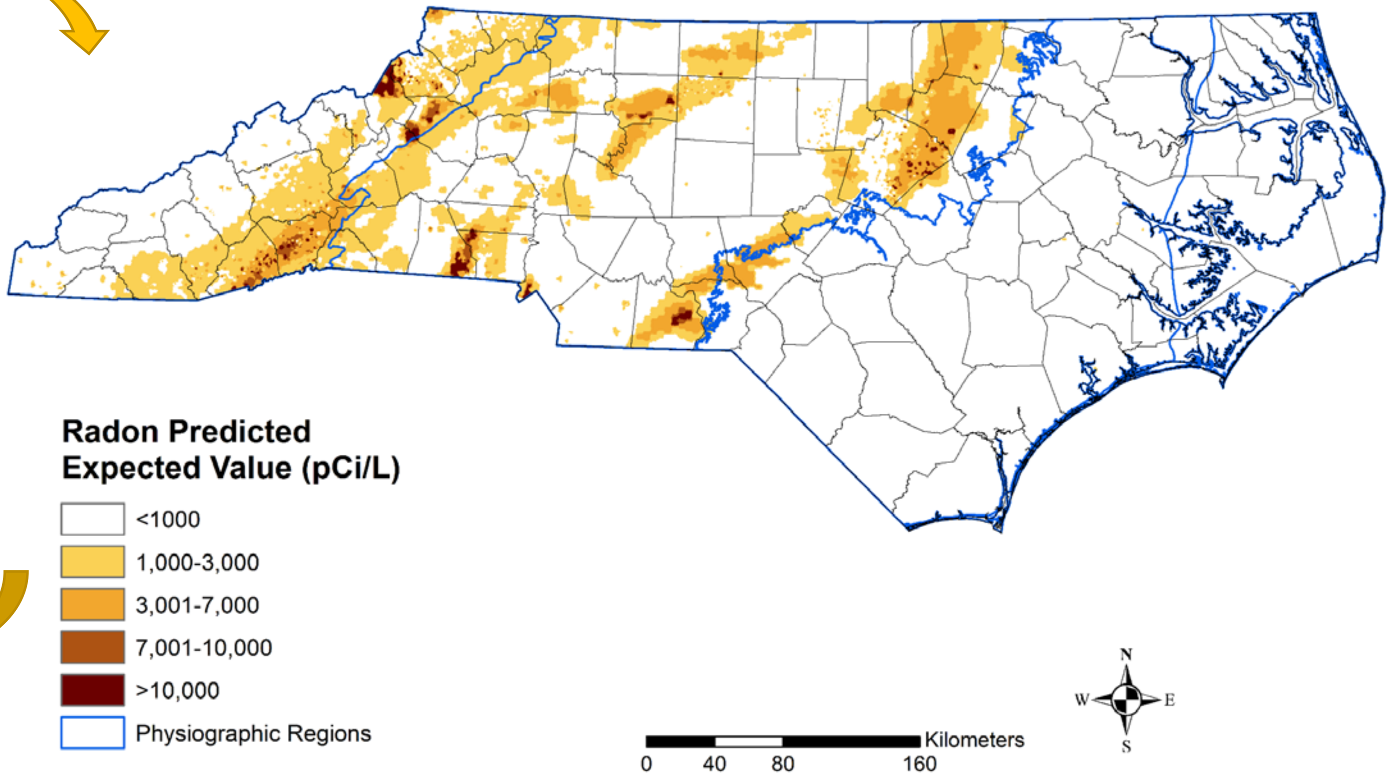
Article

pubs.acs.org/est

Estimation of Groundwater Radon in North Carolina Using Land Use Regression and Bayesian Maximum Entropy

Kyle P. Messier,[*,†] Ted Campbell,[‡] Philip J. Bradley,[§] and Marc L. Serre[†]

- In-situ data was compiled
- **Integrate** three datasets of groundwater radon



Spatial prediction used in exposure assessment

International Journal of Epidemiology, 2017, 676–685
doi: 10.1093/ije/dyw128
Advance Access Publication Date: 16 September 2016
Original article

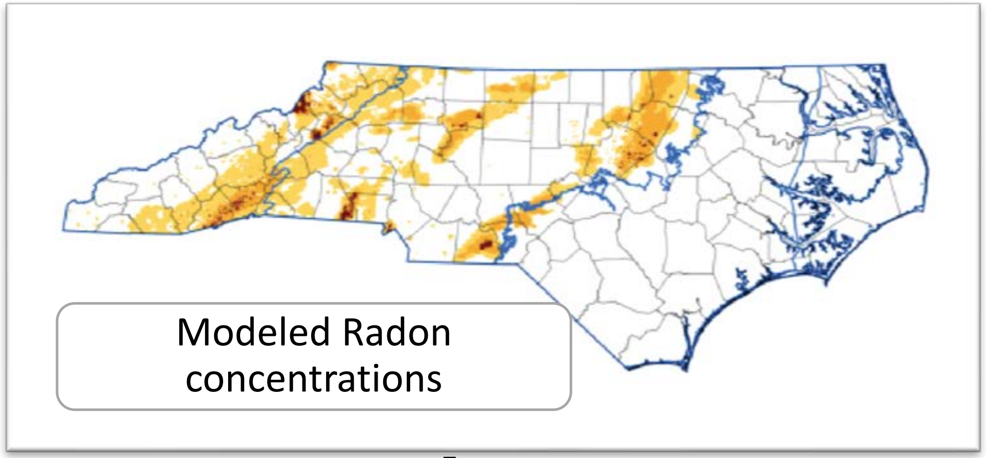
Miscellaneous

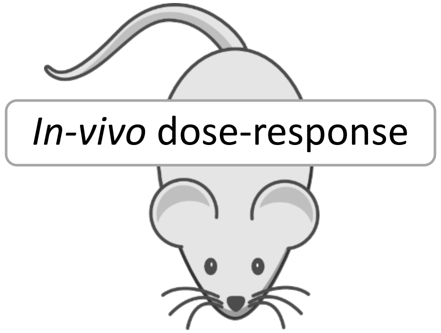
Lung and stomach cancer associations with groundwater radon in North Carolina, USA

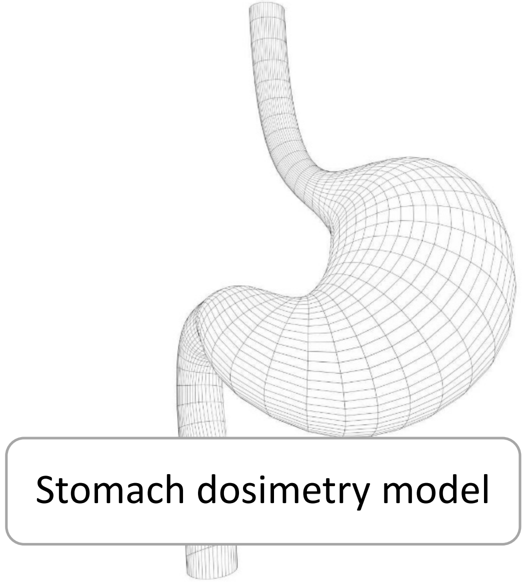
Kyle P Messier and Marc L Serre*

Model	Variable	Crude OR	Age- and Gender Adjusted OR	Fully Adjusted OR
Stomach cancer cluster membership	Groundwater radon (per 100 Bq/L)	1.22 (1.02,1.46)	1.21 (1.01,1.45)	1.24 (1.03,1.49)

Can we improve the risk estimates by including toxicokinetic modeling?





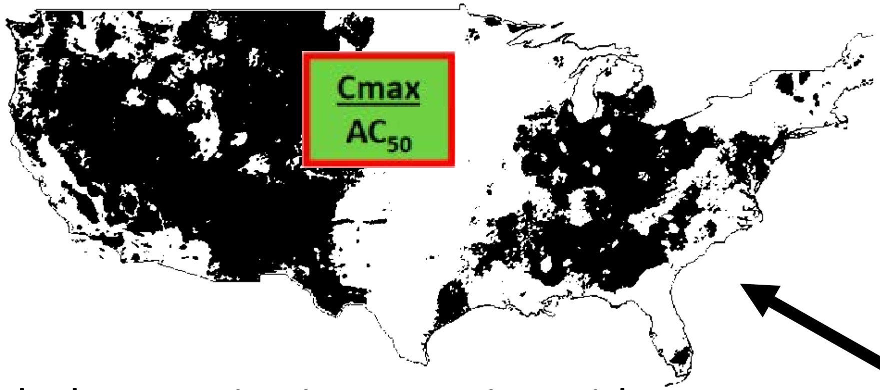


$$\frac{\#\ of\ alpha/beta\ particles}{stomach\ surface\ area}$$

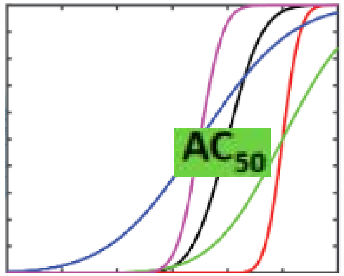
- Uncertainty is introduced at each step
- Spatial methods can quantify the propagation of uncertainty

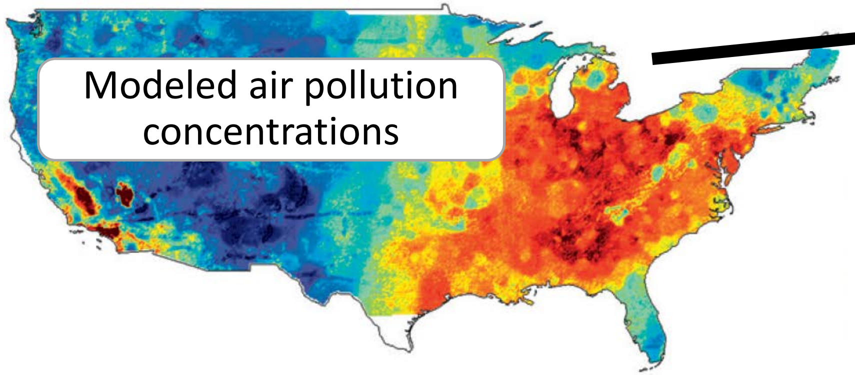
Teeguarden, J.G.; Mikheev, V.B.; Minard, K.R.; Forsythe, W.C.; Wang, W.; Sharma, G.; Karin, N.; Tilton, S.C.; Waters, K.M.; Asgharian, B.; et al. Comparative iron oxide nanoparticle cellular dosimetry and response in mice by the inhalation and liquid cell culture exposure routes. *Part. Fibre Toxicol.* **2014**, *11* (46).

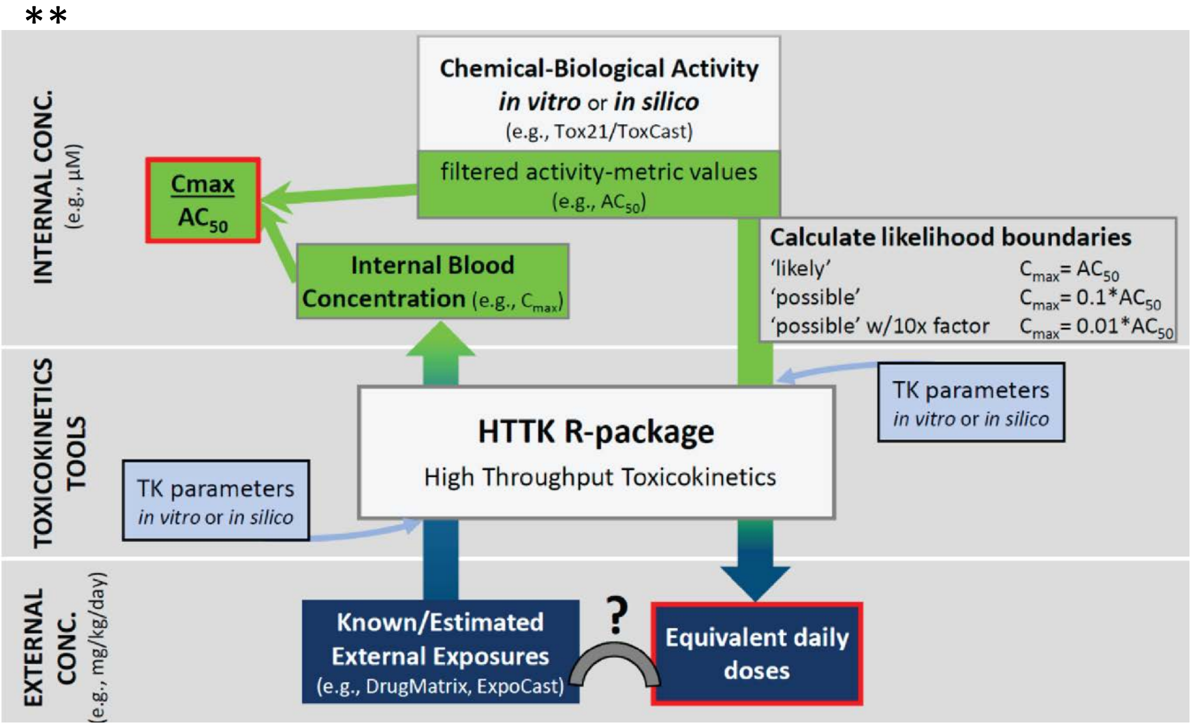
Opportunities to map the likelihood of biological human activity



Risk characterization mapping with direct links to biological activity

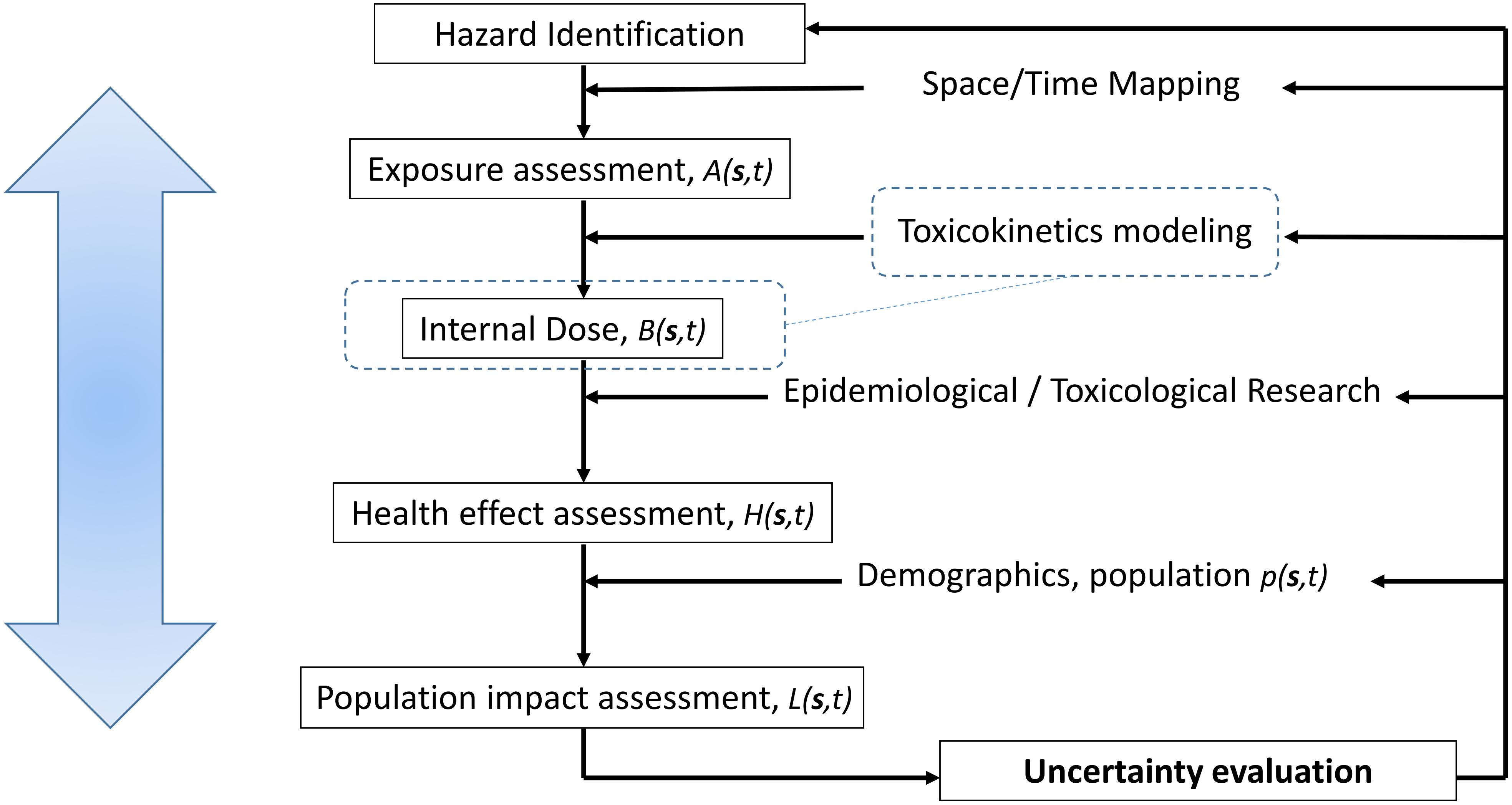






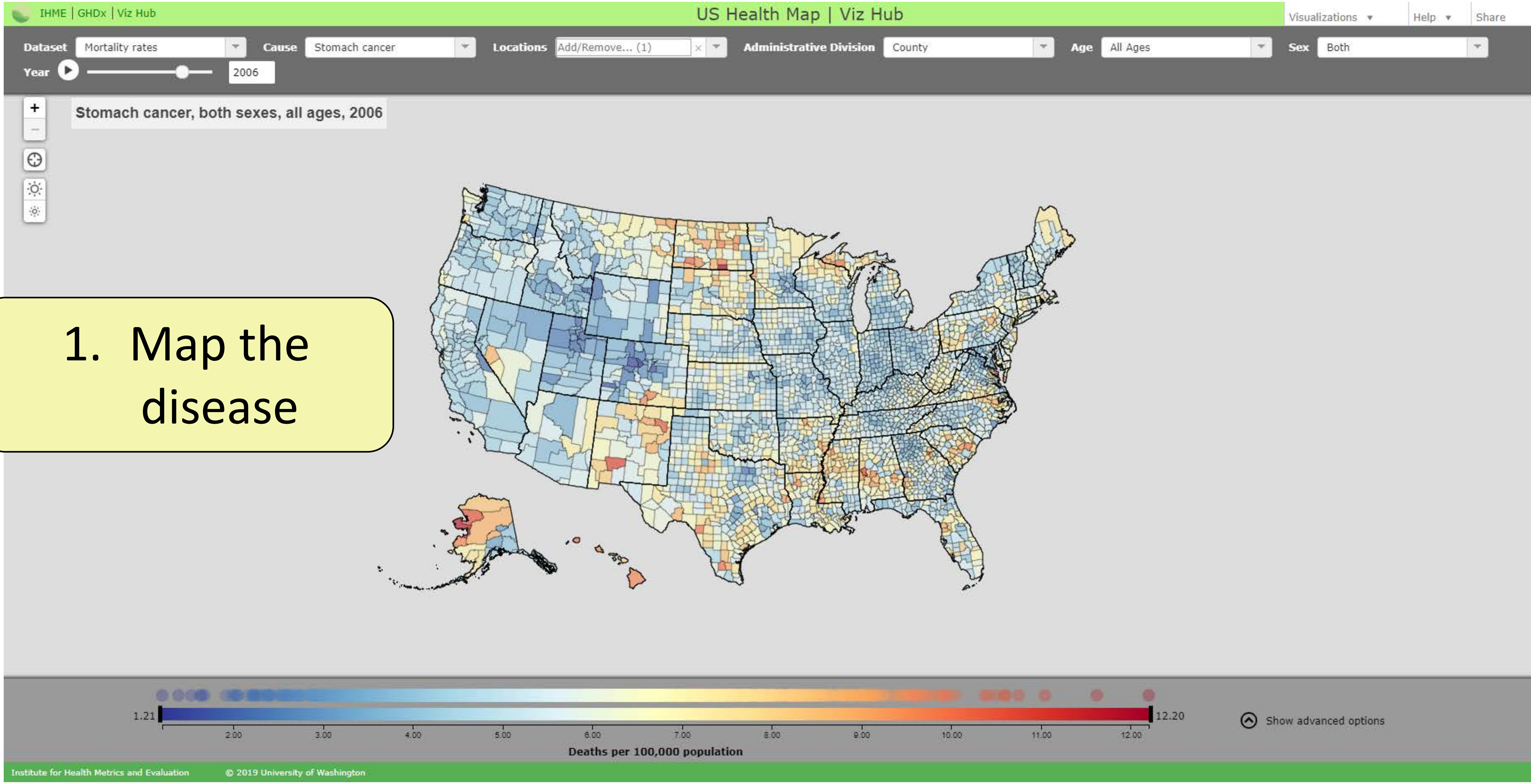
Sipes et al. An Intuitive Approach for Predicting Potential Human Health Risk with the Tox21 10k Library. *Environ. Sci. Technol.* **2017, *51* (18), 786–796.

Spatial model-based health impact assessment framework



Spatial Modeling as an approach to Identify Hazard from Health Outcomes

1. Map the disease



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Original article

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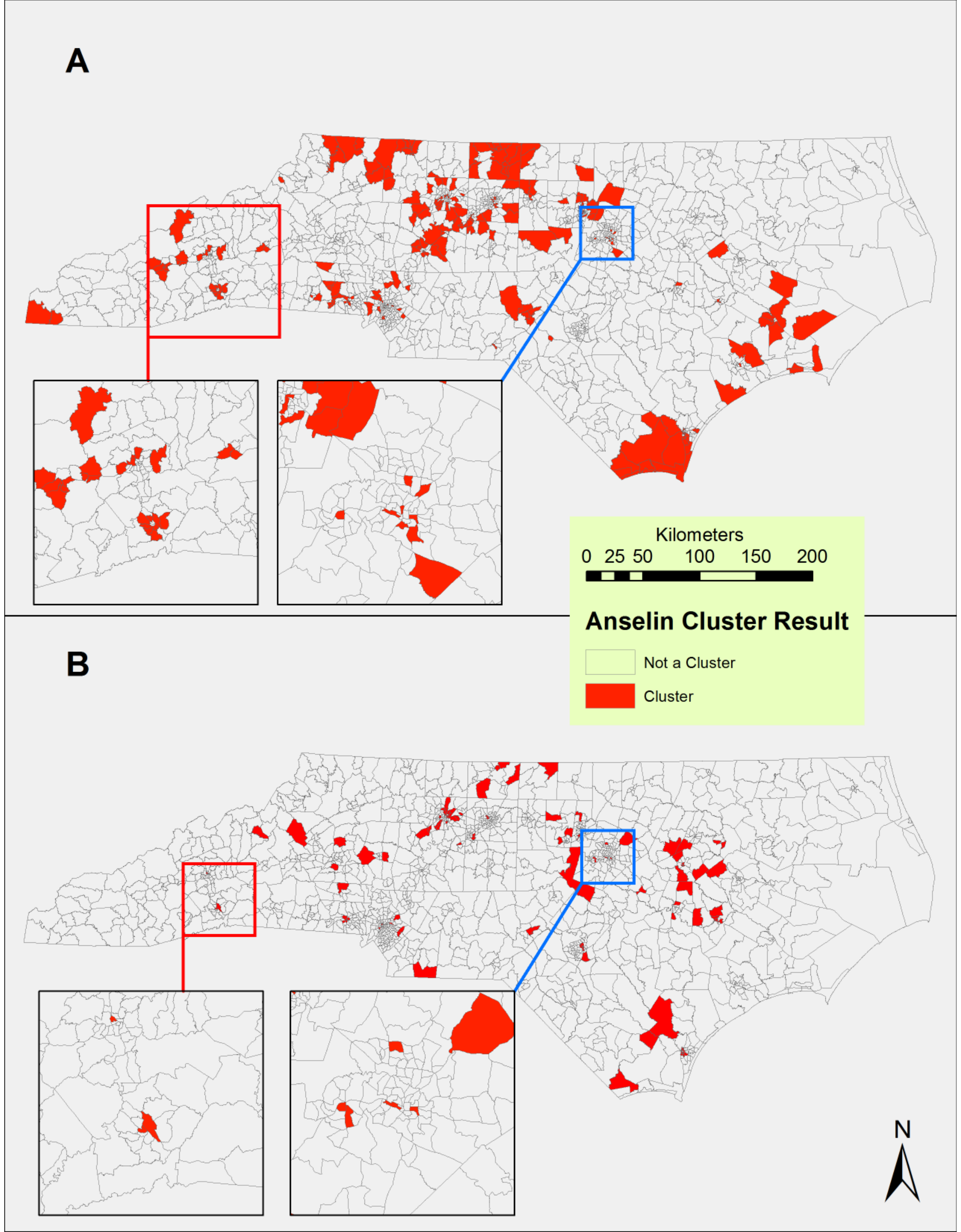
2. Identify "hot-spots" with spatial analysis
3. What exposures are possible, but hazard is unknown?



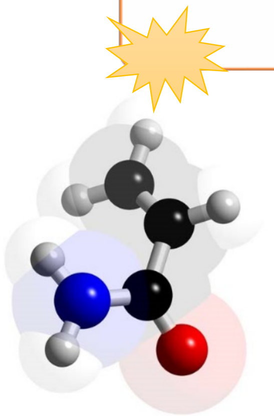
Translating AOPs into human health exposure science research

Implement and Translate Epidemiological Findings into AOP Key Events

Design spatial statistics-based epidemiological studies to inform/test AOPs

Molecular Initiating Event → KER → Key Event → KER → Key Event → KER → Key Event → KER → Adverse Outcome

- Molecular Interactions
- Cellular Responses
- Organ Responses
- Organism Responses
- Population Responses



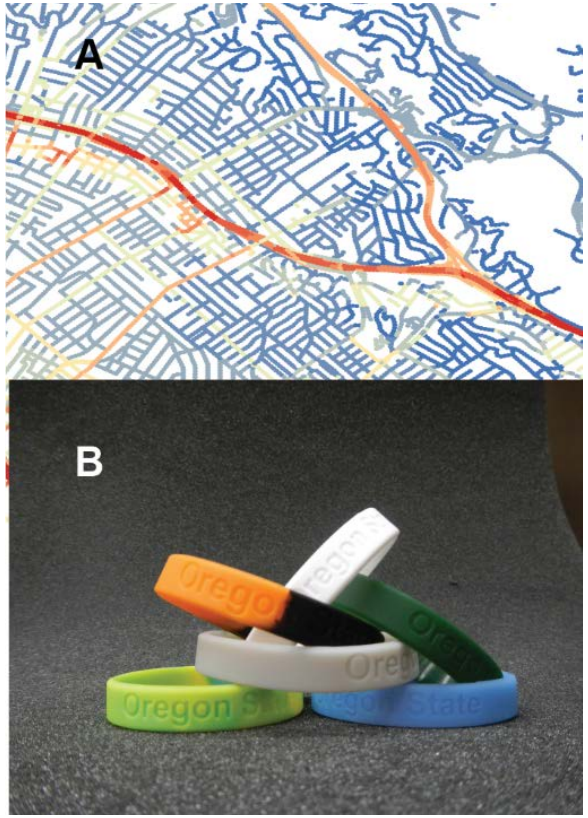
1. Better Statistical Power for Rare Events

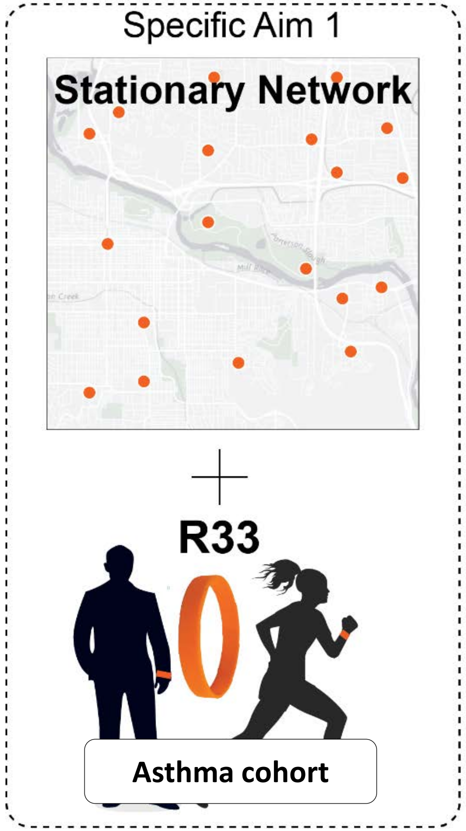
2. Preventative Health

Opportunities for translating AOP in my K99 research

Geospatial model-based exposure assessment

Personal monitor: bioavailable fraction





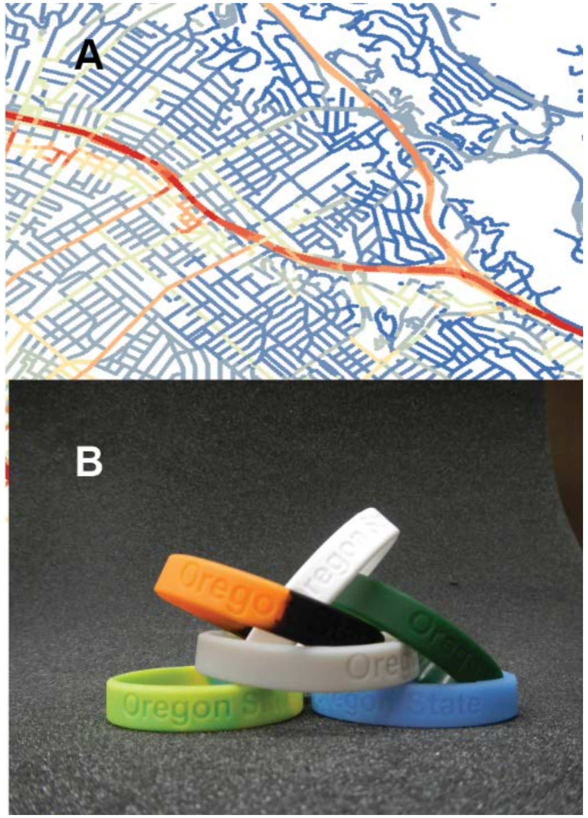
Bioavailable concentration → Molecular Initiating Event → Disease Outcome

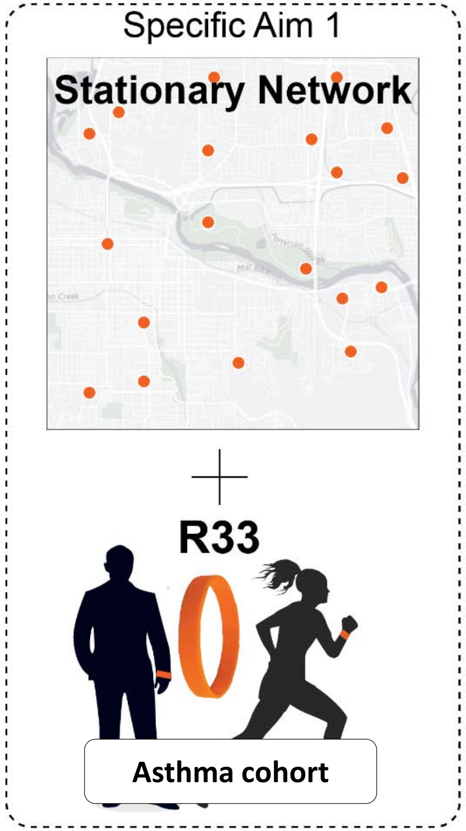
How do personal vs model-based exposure assessments affect dose-response relationships?

Opportunities for translating AOP in my K99 research

Geospatial model-based exposure assessment

Personal monitor: bioavailable fraction





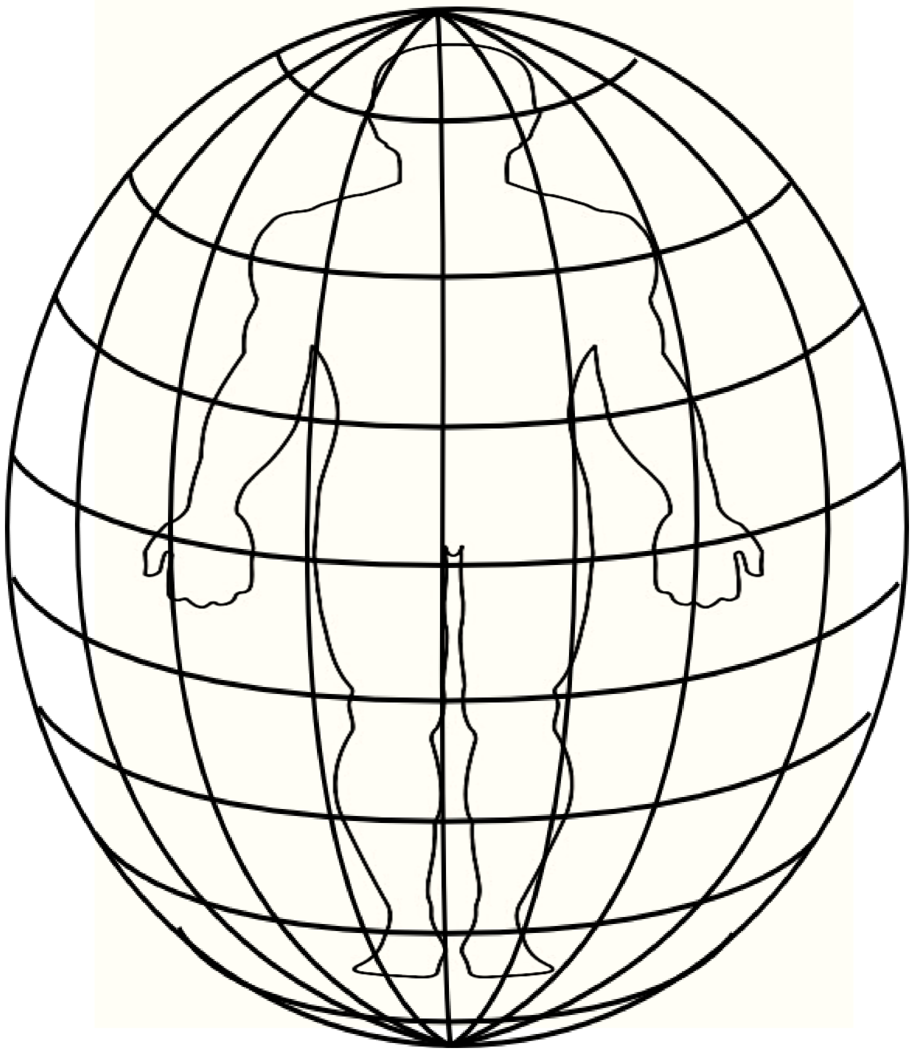
Bioavailable concentration → Molecular Initiating Event → Disease Outcome

Is this an empirical relationship that can be stochastically quantified and transferrable across domains?

e.g., ↑ DNA damage, Epigenetic modifications

Modeling the human body from a spatial statistics perspective to improve toxicokinetics

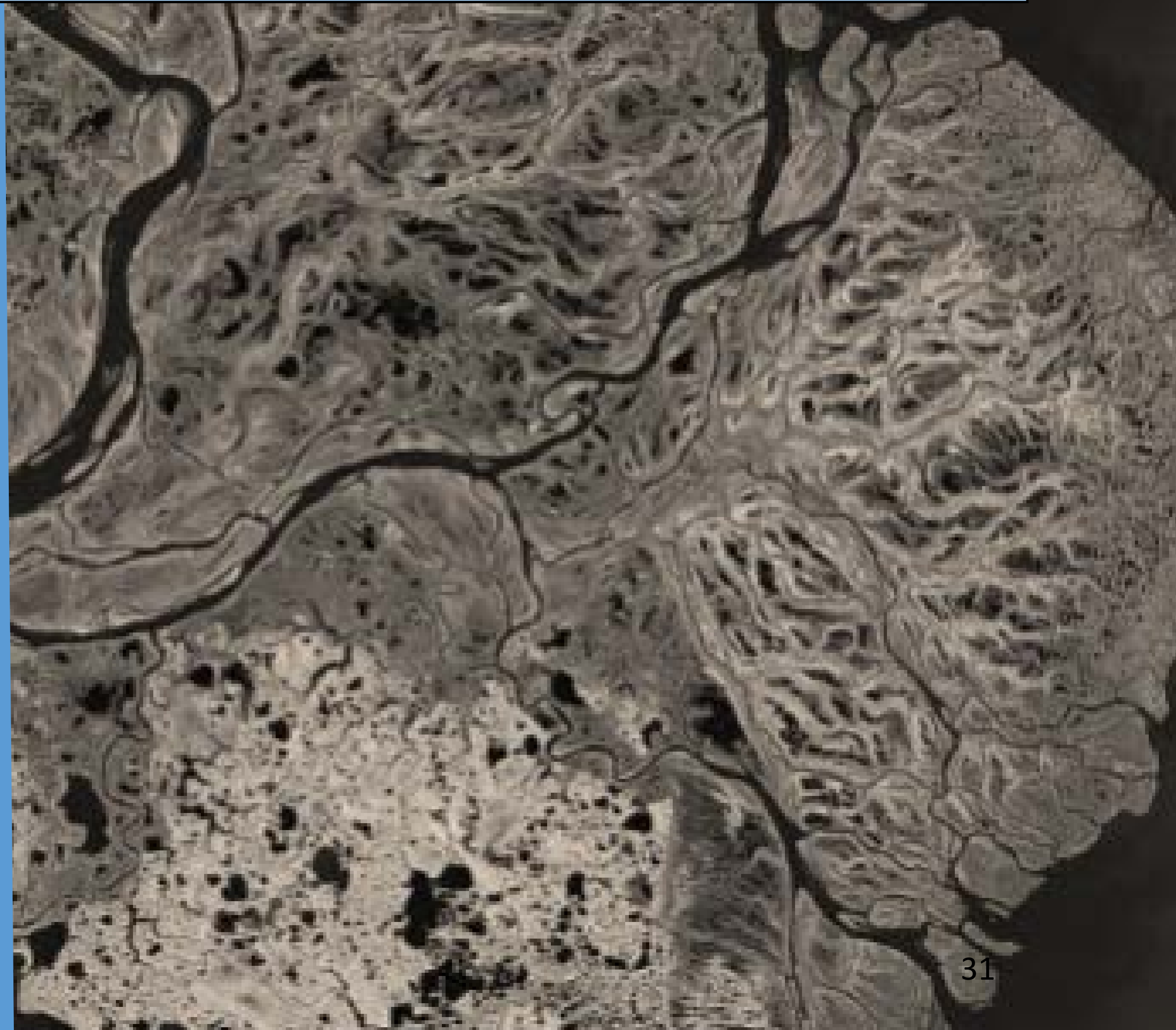
The human body from a spatial statistics perspective



<u>Two Possible Applications</u>

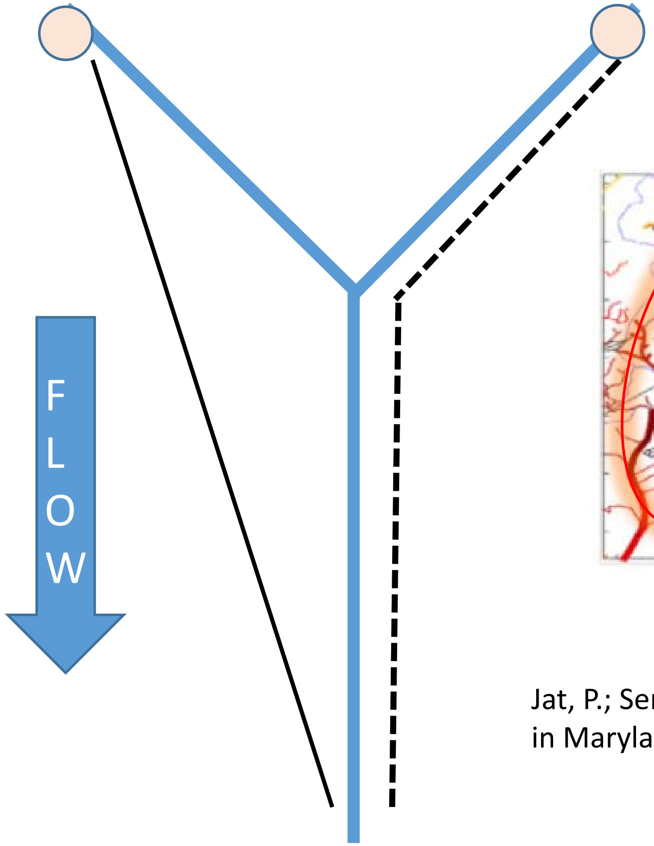
1. Physiologically based pharmacokinetic models
2. Medical Imagery Analysis

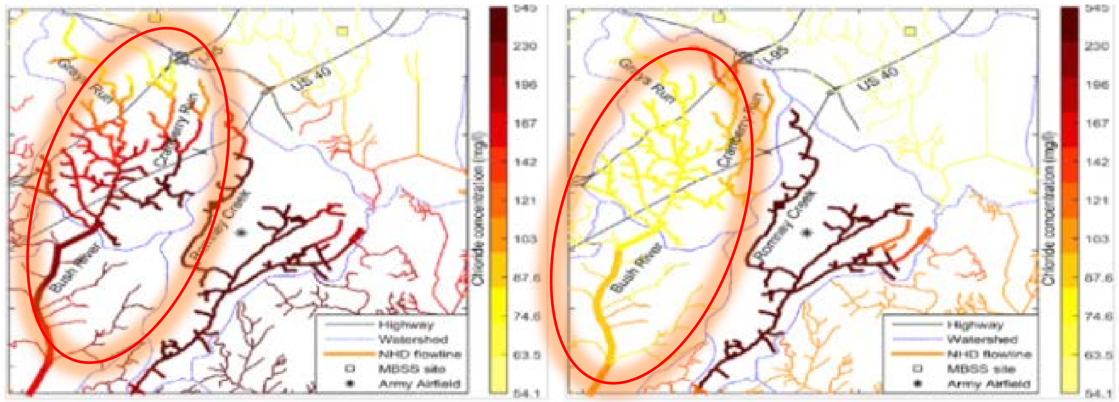
Game Time
River or Blood Vessels?



Covariance functions can include non-Euclidian distance metrics

Geostatistical models used for surface water are amenable to the human body



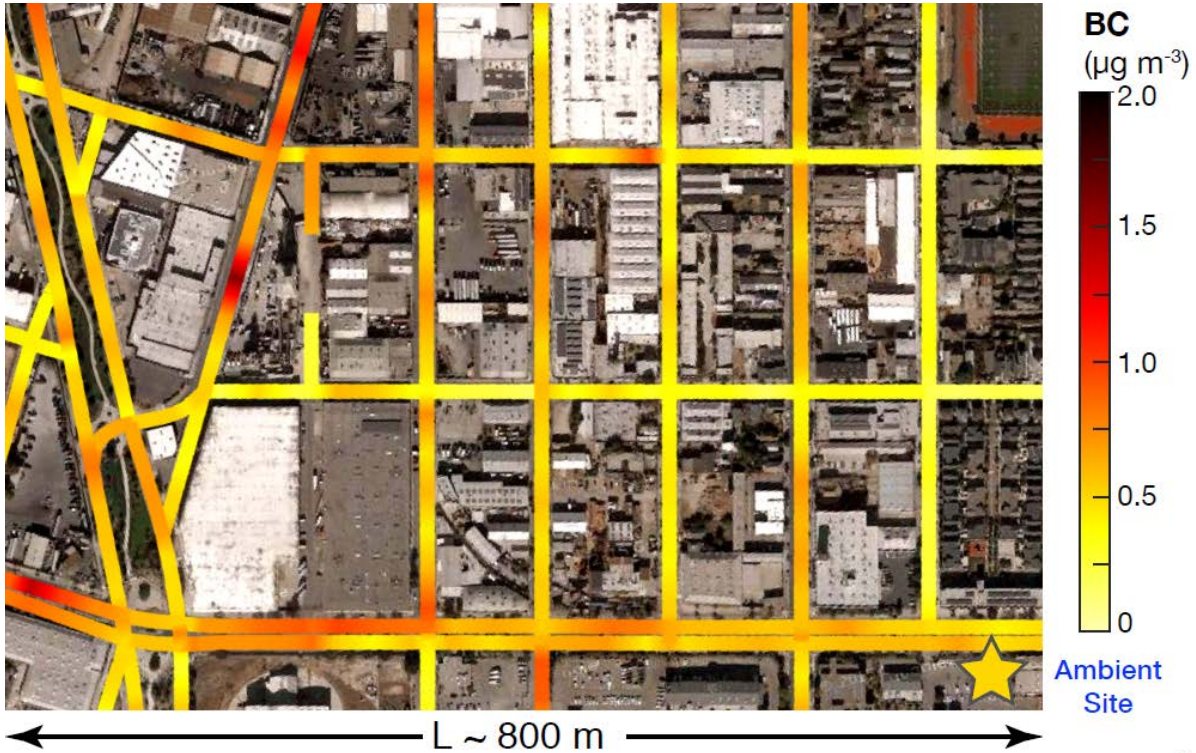


Euclidian distance $\leq$ River distance

Jat, P.; Serre, M. L. Bayesian Maximum Entropy space/time estimation of surface water chloride in Maryland using river distances. *Environ. Pollut.* **2016**, *219*, 1148–1155.

Maps can help improve hazard and risk communication

Mapping Urban Air Pollution at High Resolution with Google Street View Cars



1. Map neighborhood "hot-spots"
2. Connect with local area health outcomes
3. Analyze how local air pollution impacts health

Examples of Improved Risk Communication from Maps

How pollution impacts health in West Oakland

Researchers from EDF and the University of Texas at Austin took our data to the West Oakland Environmental Indicators Project (WOEIP), a community-based organization with recognized leadership in local air pollution issues, to learn more about potential sources of poor air quality.

Explore: Interactive map and points of interest

Black carbon Nitric oxide Nitrogen dioxide

Black carbon particles come from burning fuel, especially diesel, wood and coal. High exposure is associated with heart attacks, stroke and some forms of cancer.

Air quality data from Google/Aclima; analysis by Apte et al / EDF. Colors on the map do not correlate to colors on the Air Quality Index.

Explore this project

Project overview

Health implications

Policy solutions

Methodology and data

About the partnerships

West Oakland partners

Margaret Gordon
Co-Director, West Oakland Environmental Indicators Project

Brian Beveridge
Co-Director, West Oakland Environmental Indicators Project

Media contact

Mica Crouse
(512) 691-3451 (office)
(512) 913-9068 (cell)
Email

Methodology: How we collected data

Data collection

EDF partnered with Google Earth Outreach, the University of Texas at Austin (UT Austin) and Aclima, a San Francisco-based company that specializes in environmental sensor networks, to outfit the cars with mobile sensing equipment and to collect and analyze the data.

The study used two Google Street View cars equipped with Aclima's sensing platform, providing real-time air quality data for the maps. The vehicles drove streets in Oakland, California, on most weekdays between June 2015 and May 2016 (about 150 days). Driving routes, data collection, and processing were managed by software tools designed by Aclima to support large-scale measurement with vehicles. This new method and its results have been published in a peer-reviewed paper for the *Environmental Science & Technology* journal.

The vehicles drove streets in Oakland, California, on most weekdays between June 2015 and May 2016 (about 150 days). Driving took place during daytime hours — typically, between 9:00 am and 6:00 pm — so the dataset is primarily representative of daytime, weekday air quality.

Scientists at UT Austin designed the daily driving plan for cars to ensure that each neighborhood was systematically sampled at different times of the day, week and year. The cars repeatedly measured pollution on every street and highway within a 30 km² area of Oakland. Cars drove in the flow of traffic at normal speeds. Over the course of a year, the team sampled each road in this area (~700 km of roads) an average of 30 times. In total, the cars collected about 3 million unique measurements while driving about 23,000 kilometers. This dataset is one of the largest sets of mobile air pollution measurements ever assembled.

While scientists have measured pollution using mobile technology for about two decades, these studies have generally lasted for a few days or weeks, or only covered select routes within a city.

Explore this project

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Modeling with collected data

About the partnerships

Download the data

The data used to create the visualizations on this is available for download. Get the files »

Our project experts

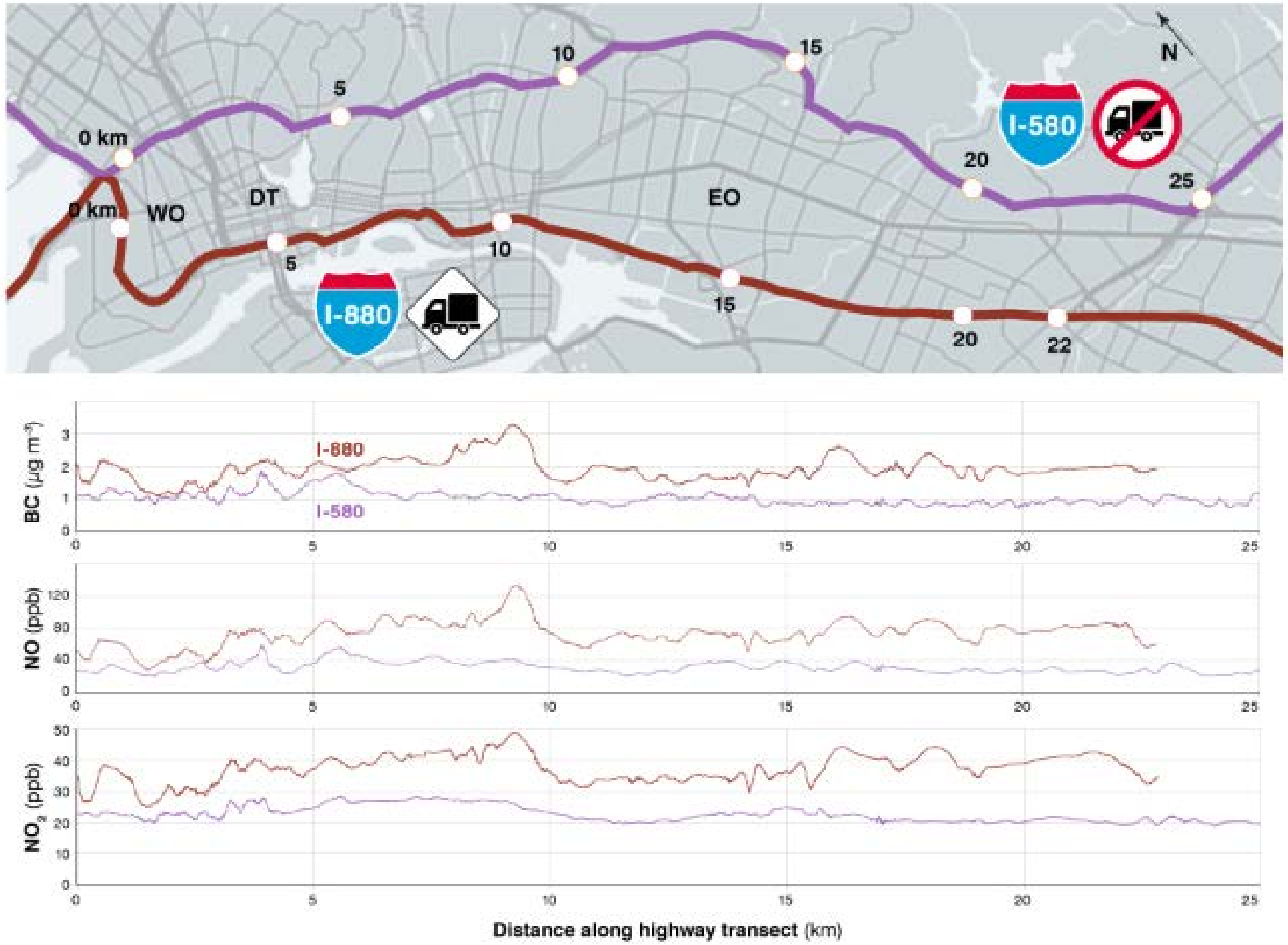
Steven Hamburg
Chief Scientist
Contact

Joshua Apte
Assistant Professor, University of Texas at Austin

Kyle Messier
Former Kravis Post-Doctoral Science Fellow EDF Office of the Chief Scientist

See all health experts »

Maps demonstrating unequitable distribution of hazard and exposure impacts



<u>Tale of Two Freeways</u>

- All measured pollutants were consistently higher on I-880 compared to I-580
- I-580 has a heavy duty truck ban
- Heavy duty trucks are forced onto I-880 to get to the Port of Oakland

Conclusions

Many novel ideas for expanding upon or developing new approaches with spatial statistics for the field of toxicology

- Hazard identification and exposure assessment
- PBPK modeling
- Hazard and Risk Communication
- Adverse Outcome Pathway
- Mixtures studies

Acknowledgements

- NTP/NIEHS
  - Brian Berridge
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- Past Mentors
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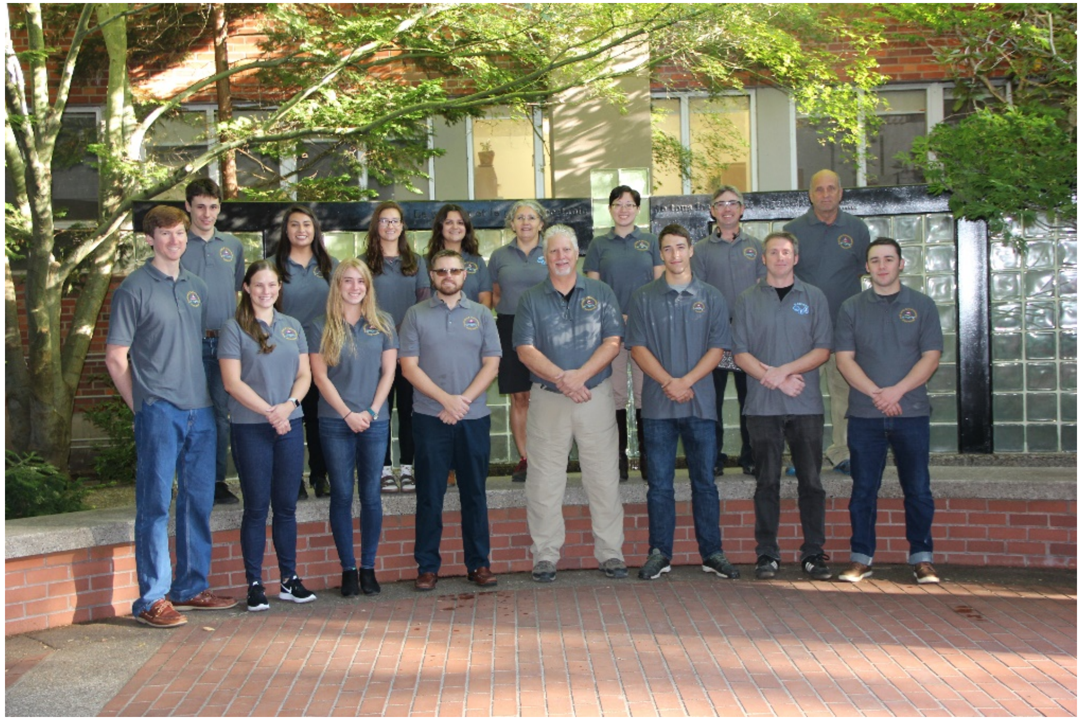
  - Josh Apte, University of Texas
- Current Funding
  - NIEHS 1 K99 ES029523



Food Safety & Environmental Stewardship