Exposure to Chemical Mixtures and ADHD-Related Behaviors Near the New Bedford Harbor Superfund Site

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Superfund Research Program

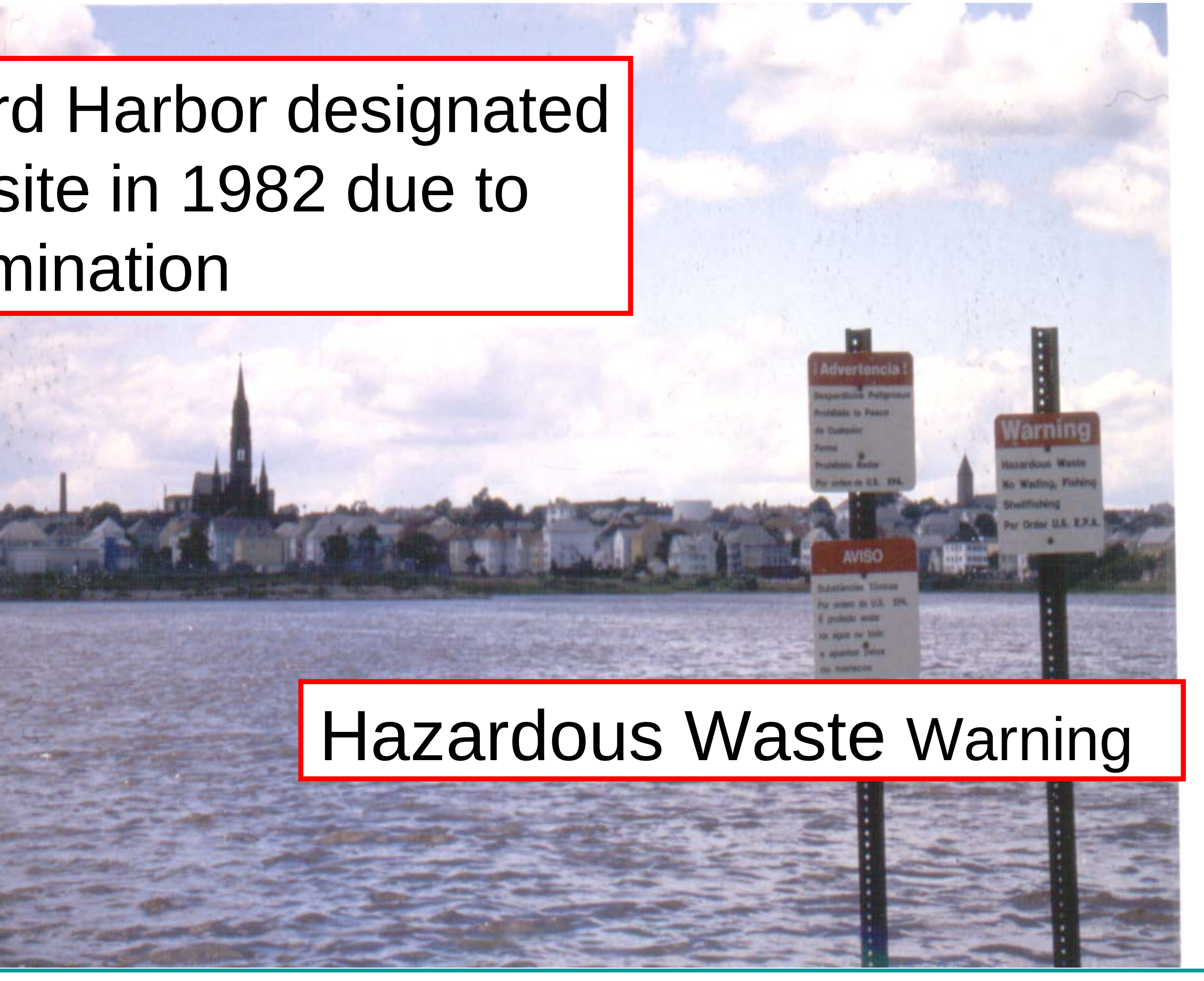
- NIEHS SRP funds university-based multidisciplinary research on human health and environmental issues related to hazardous substances
- Currently 19 Multiproject Research Centers (P42) across the U.S.
- Project Leader: Analyzing Patterns in Epidemiologic and Toxicologic Data

Outline

- Motivation for Mixtures Analyses
  - Community of New Bedford, Massachusetts
- Generalized Additive Models (GAMs)
  - Predict risk by smoothing exposure
  - Spatial Confounders, Hypothesis Testing
- New Bedford Cohort Study (Dr. Korrick, Harvard SRP)
  - Example of real-world exposures
  - Mapping risk of ADHD-related behavior based on exposure to chemical mixtures
- Conclusions and Future Research

Motivating Problem

- New Bedford Harbor designated Superfund site in 1982 due to PCB contamination



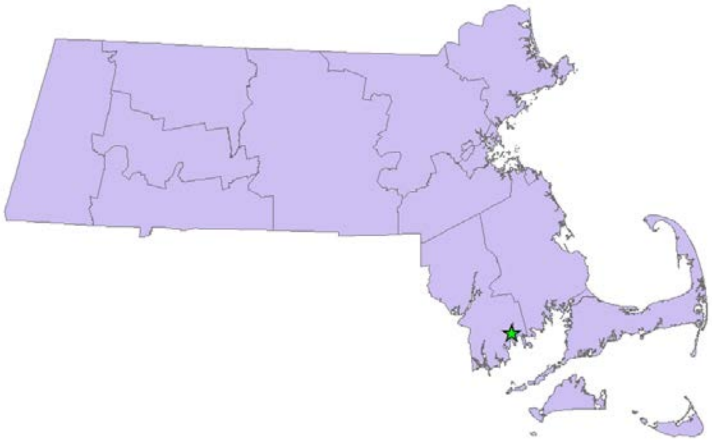
Hazardous Waste Warning

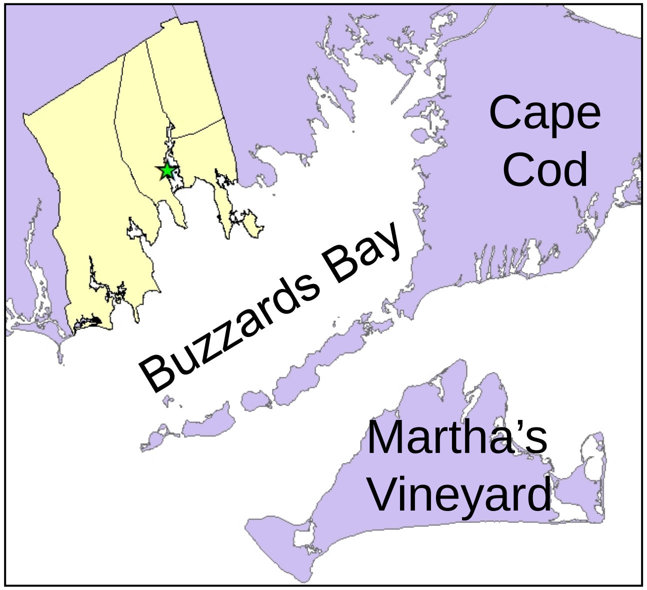
Acushnet river estuary

Photo: S. Korrick, 1998

New Bedford Harbor Timeline

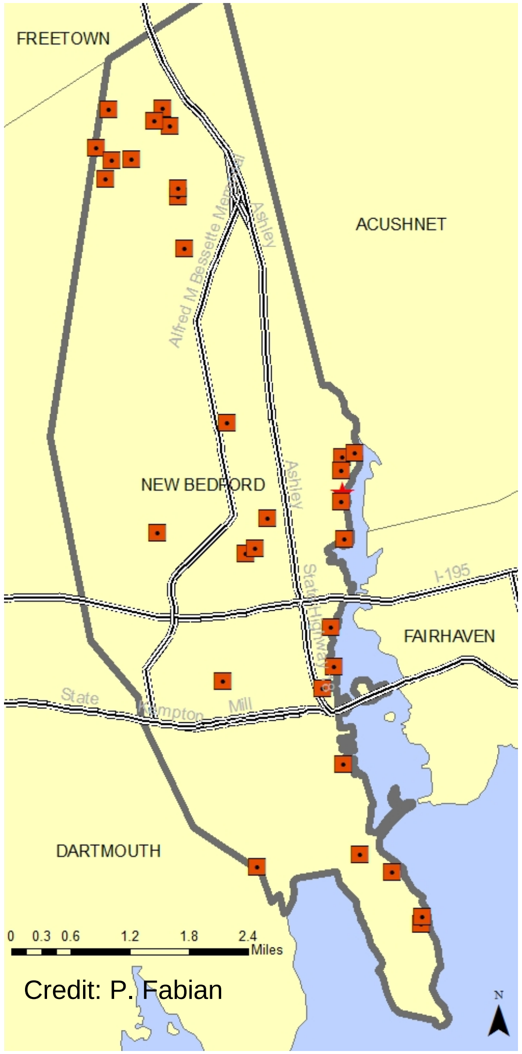
1940s-1970s	Discharge of PCB-laden waste
1970s	Contamination discovered in NBH
1977	PCB production banned in the U.S.
1979	Harbor closed to fishing
1982	NBH listed on EPA National Priority List





New Bedford Community

- Other pollutant sources
  - hazardous waste sites
  - heavy industry
  - nearby major roadways
- 52% of children live in high-poverty neighborhoods (vs. 14% statewide)



New Bedford Cohort (NBC)

- 1993-1998 enrolled 788 newborns (Korrick et al. 2000) from 4 nearby towns
- Aim is to assess relation of prenatal OC and metal exposures with neurodevelopment
- Extensive questionnaire data, medical record abstraction, home assessments, longitudinal neurocognitive and behavioral assessments
- 573 eight-year old children with data on both exposure and outcome

Attention Deficit Hyperactivity Disorder (ADHD)

- ADHD is a problem with inattentiveness, over-activity, impulsivity
- Affects about 6 - 12% of school aged children, diagnosed more often in boys
- ADHD-related behavior assessed using the Conners' Rating Scale for Teachers (CRS-T)
- Scales include Conners' ADHD index, DSM-IV total, DSM-IV hyperactive, DSM-IV inattentive

ADHD-Related Behaviors

New Bedford Cohort Conners' Rating Scales (n=573)

	Mean (SD)	Median	Range
Conners' ADHD Index	53.19 (11.07)	50	41-90
DSM-IV Inattentive	53.51 (10.74)	50	40-90

- Raw scores converted to *T*-scores, scaled for age and gender with a mean (SD) = 50 (10)
- Higher score $\longrightarrow$ more adverse behavior
- Mean of NBC (53) shifted from general population
- Spearman Correlation Coefficient = 0.89
- Case status dichotomized at 86th percentile

Environmental Exposures

Umbilical Cord Serum Levels in ng/g serum

	Mean (SD)	Median	Range
$\sum PCB_4$ *	0.26 (0.31)	0.19	0.01 - 4.41
p,p'-DDE	0.50 (1.04)	0.31	0.00 - 14.93

* Sum of 4 prevalent PCB congeners: 118, 138, 153, and 180

- PCBs and p,p'-DDE have been shown to cross the placenta and have been associated with neurobehavioral effects in children
- Spearman Correlation Coefficient = 0.64

Aims

- Map underlying risk patterns for Conners' ADHD Index and DSM-IV Inattention associated with a mixture of exposure:

  $\sum PCB_4$ and *p,p*'-DDE

- Assess how risk patterns change after adjustment for known risk factors (e.g. maternal age and smoking)

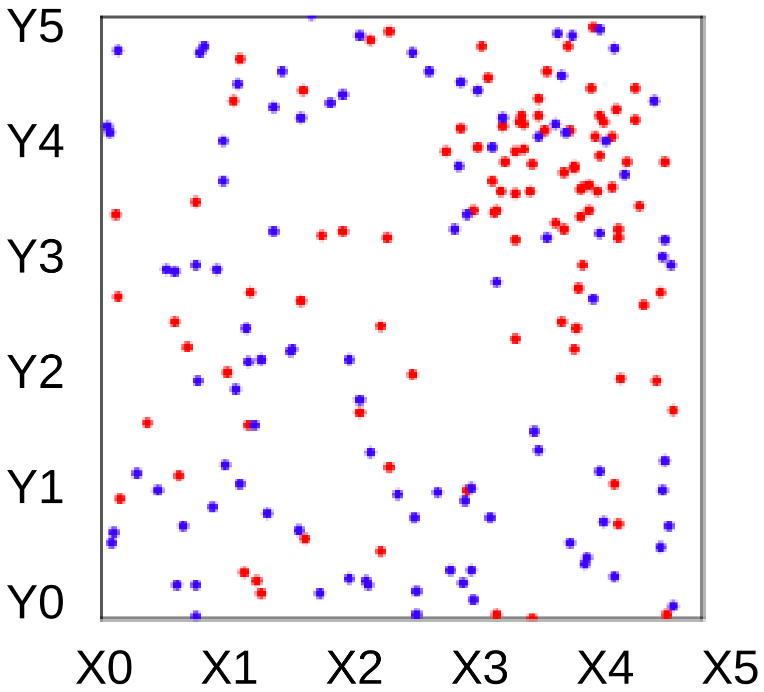
Overview of “Exposure Space”

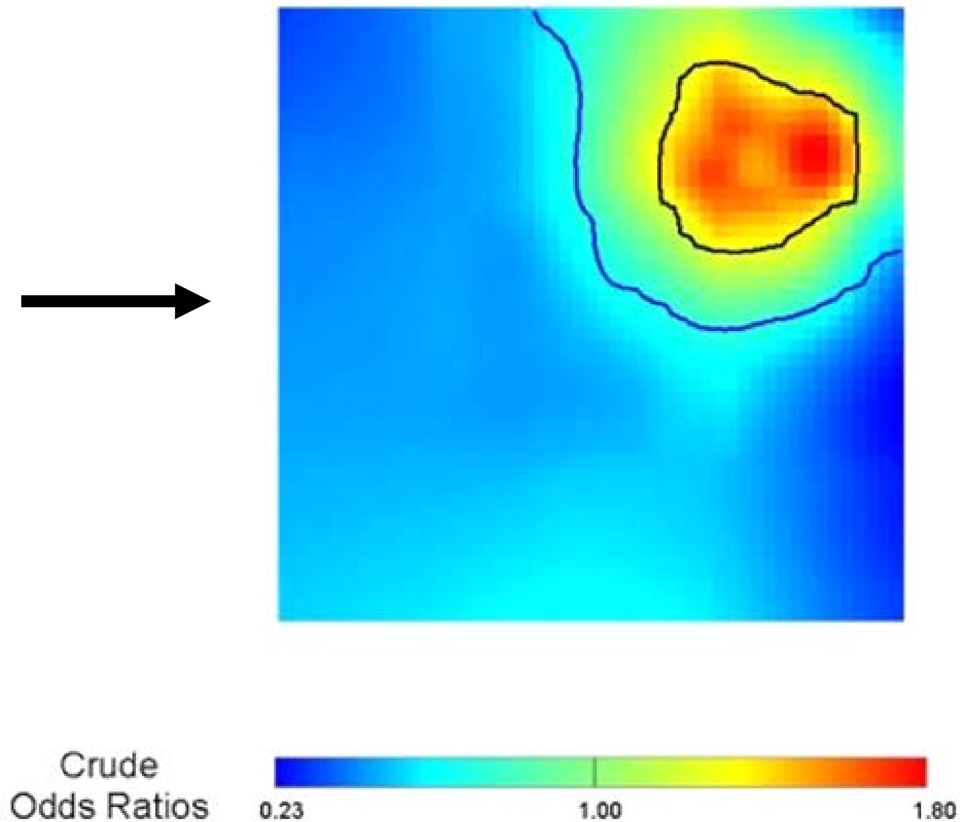
- Data can be “mapped” in 2-D using chemical concentrations as the X, Y axis instead of traditional measures of location (i.e., longitude and latitude)
- In environmental epidemiology, we’re interested in whether risk varies at different locations in exposure space (i.e., different combinations Chemical A + B)

Exposure Space Smoothing (ESS)

Binary ADHD outcome
Red=cases, Blue=noncases

Bivariate-smoothed surface of risk using GAMs



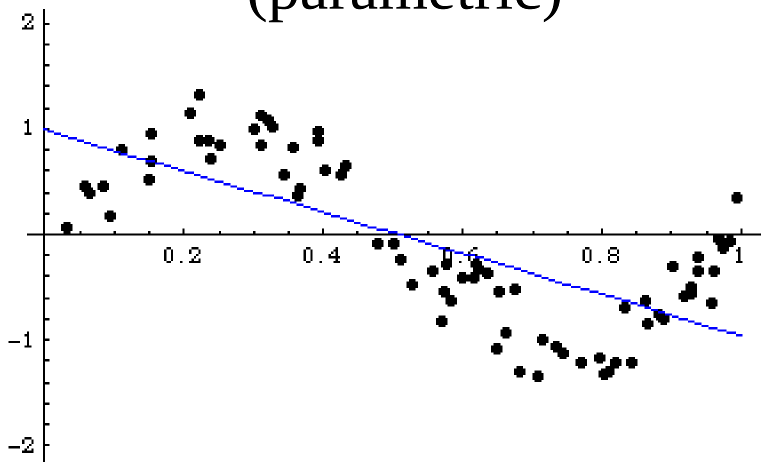


mapped by exposure
X-axis: PCB levels
Y-axis: DDE levels

Smoothing in 1 Dimension

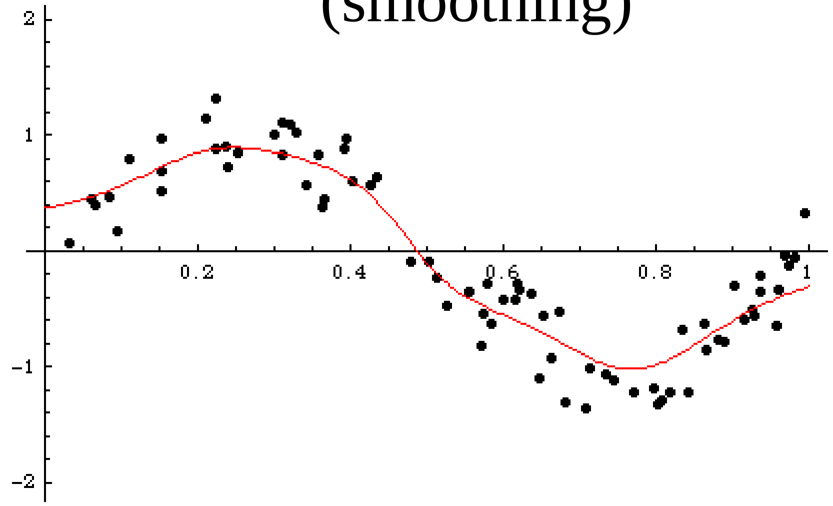
Allows non-linear associations between predictors and outcomes

ordinary linear regression (parametric)



$y = \alpha + \beta x + \varepsilon$

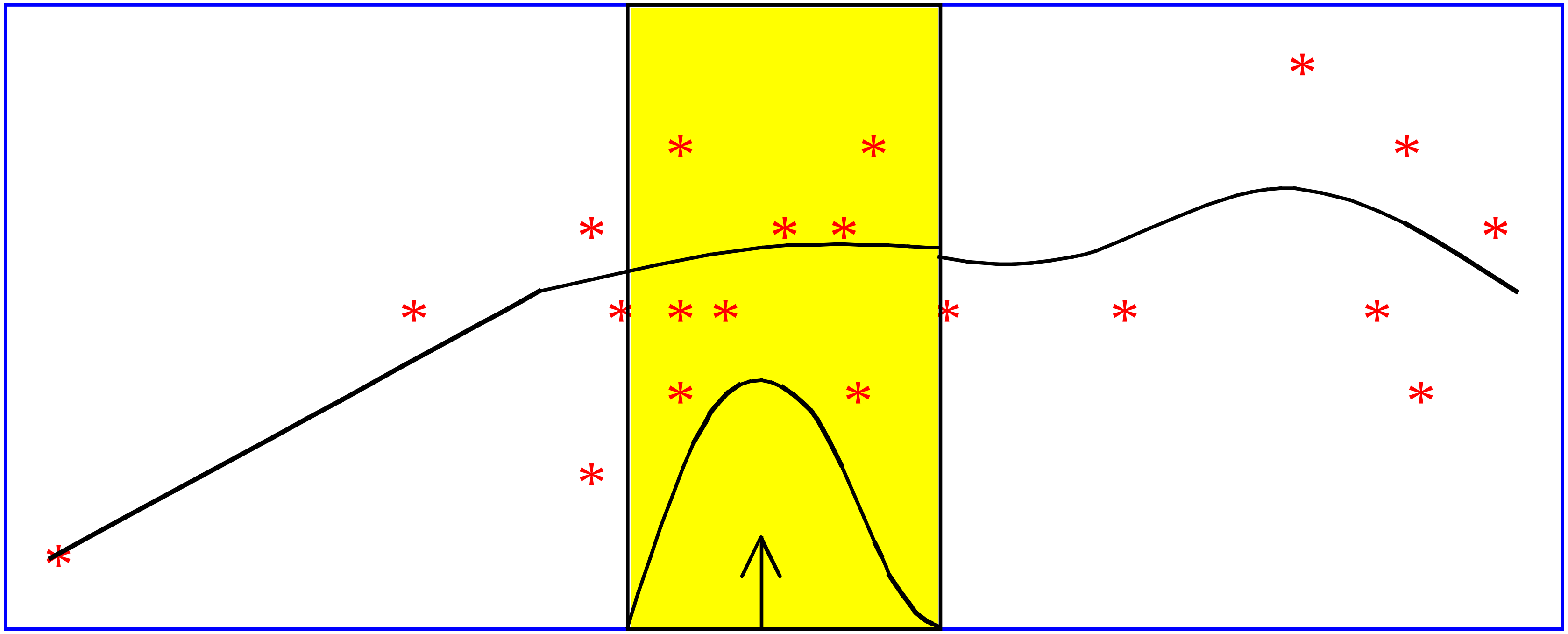
nonparametric regression (smoothing)



$y = S(x) + \varepsilon$

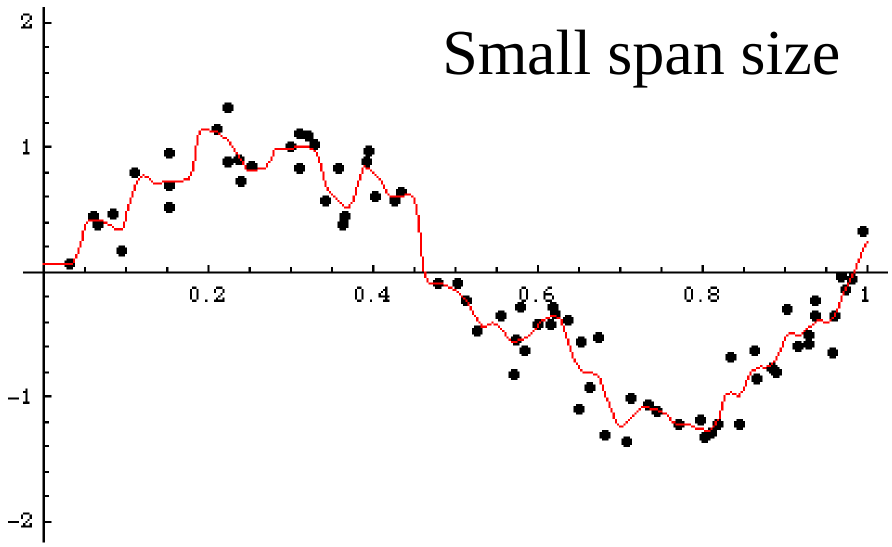
Loess Smoother

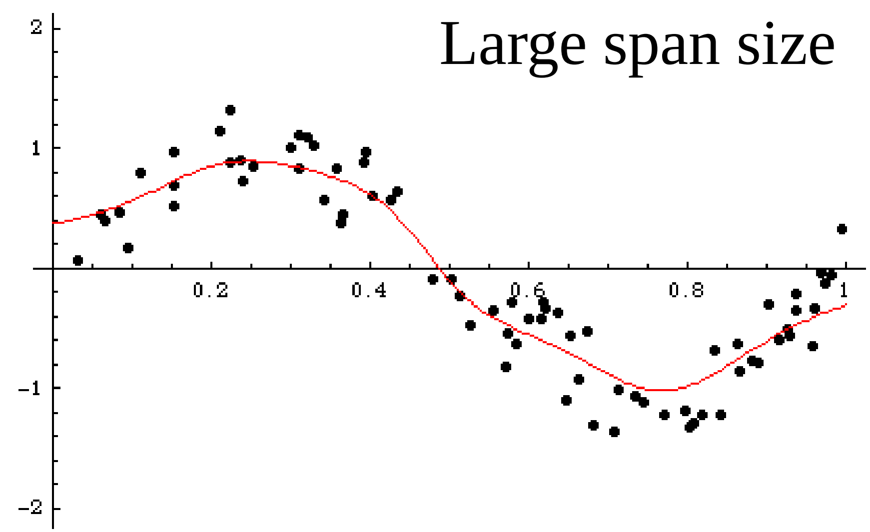
- Locally weighted straight line smoother combines advantages of nearest neighbor & fixed kernel
- Percent of points in dataset included in the *k* nearest neighbors is called the ***span***



Optimal Span Size

- Apply a range of possible span sizes
- Span that minimizes AIC statistic is the “Optimal Span Size”





Generalized Additive Model (GAM)

Binary Outcome

$$\text{logit}[p(x_1,x_2)] = S(x_1,x_2) + \gamma z$$

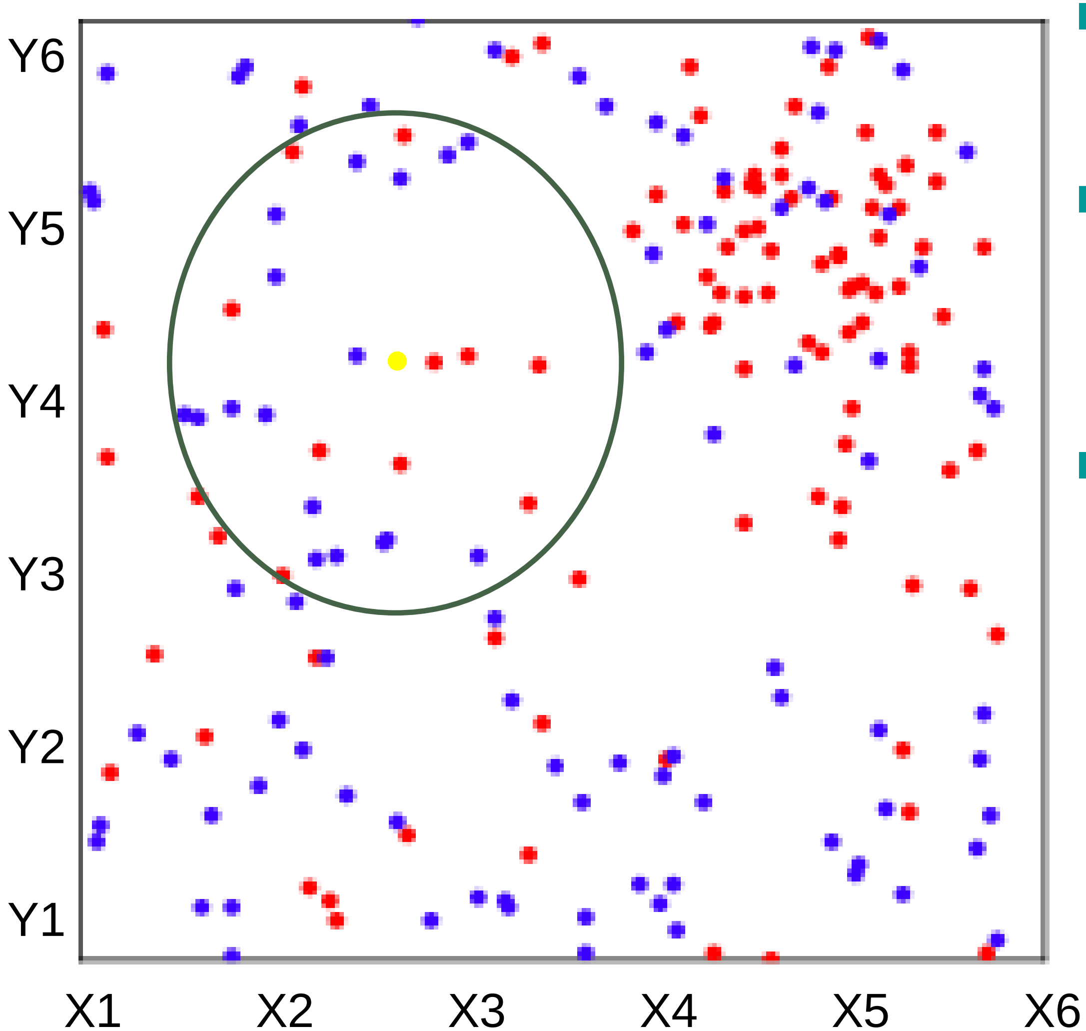
log disease odds at chemical (x_1,x_2)

bivariate smoothing function of location

adjust for covariates

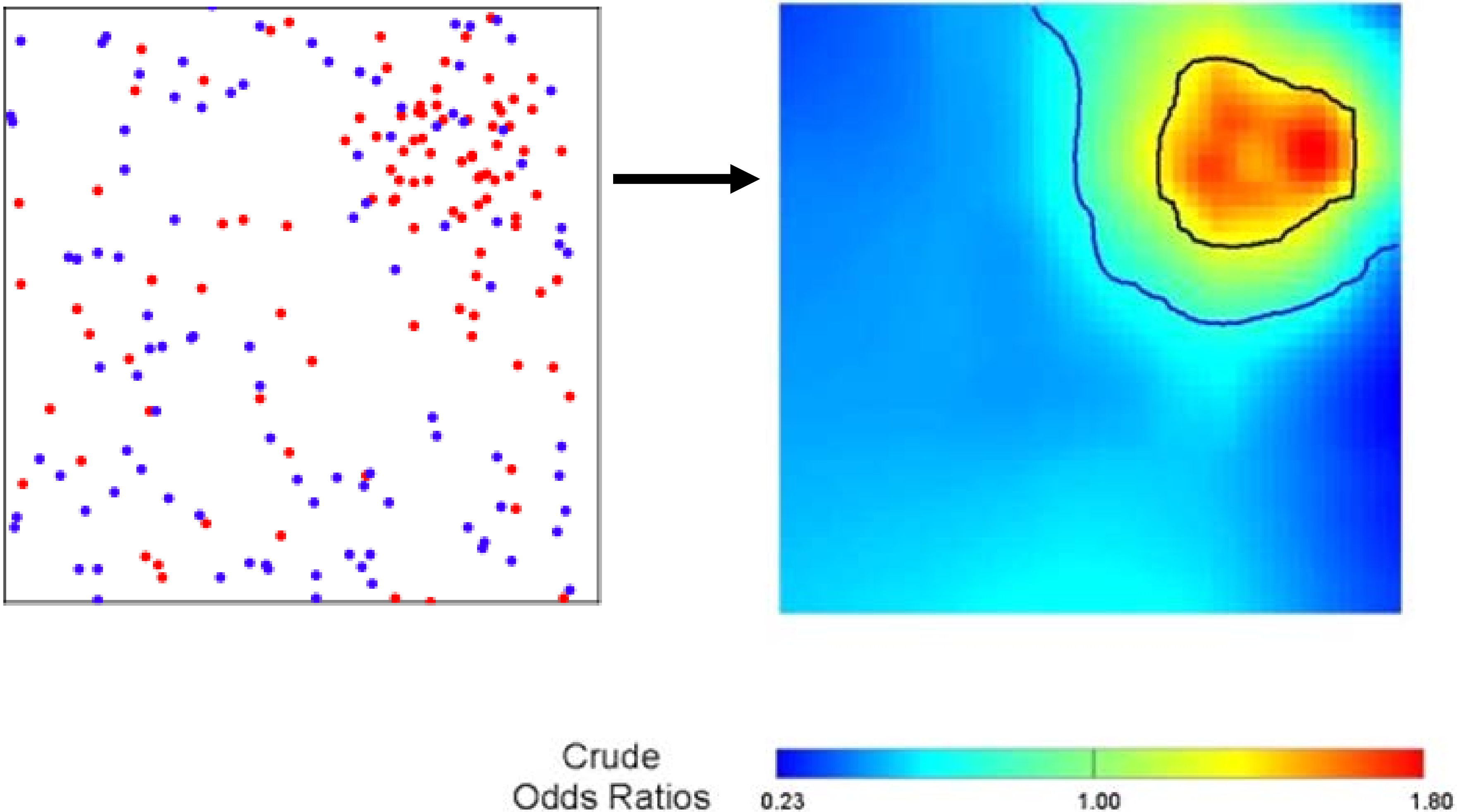
- A generalization of Generalized Linear Models, so can also be applied to continuous outcomes
- Allows simultaneous smoothing and adjustment for covariates
- Can smooth multivariate mixtures and then 2-D cross sections are mapped

GAM in 2 Dimensions



- Cases (red) = 125
  Controls (blue) =125
- For span=0.10, 10% of the data (25 pts) is included in smooth
- To predict the odds ratios at point (X, Y), the #cases/controls in the smooth is divided by #cases/control in the entire study area: (9/16)/(125/125)

From Points to Smoothed Surface



Traditional Disease Mapping

ID	CASE	LONG	LAT	SMOKING
1	0	-81.7	39.0	1
2	1	-79.4	38.3	0
3	1	-84.2	41.1	0
4	0	-88.3	42.9	1
5	0	-83.4	39.4	1

…

Model 1: CASE ~ lo(LONG, LAT, span=0.1)+ SMOKING, family=binary(logit)

ESS with Binary Outcome Data

ID	CASE	$\sum PCB_4$	*p,p'*-DDE	SMOKING
1	0	0.26	0.50	1
2	1	0.57	1.54	0
3	1	0.19	0.31	0
4	0	0.01	0.01	1
5	0	4.41	14.93	1

…

Model 2: CASE~lo($\sum PCB_4$, *p,p'*-DDE, span=0.1)+ SMOKING, family=binary(logit)

ESS With Continuous Outcome

ID	T-score	$\sum PCB_4$	*p,p*’-DDE	SMOKING
1	90	0.26	0.50	1
2	41	0.57	1.54	0
3	53	0.19	0.31	0
4	82	0.01	0.01	1
5	37	4.41	14.93	1

…

Model 3: T-score~lo($\sum PCB_4$, *p,p*’-DDE, span=0.1)+ SMOKING, family=gauusian

Analysis Steps

- Fit GAM to epidemiologic data
- Use GAM to predict risk for every possible combination of exposure levels while keeping covariates constant (prediction grid)
- Hypothesis testing for significance of risk areas and drawing of contour lines if applicable

Prediction Grid for Location

LONG	LAT	SMOKING
-84.2	38.3	0
-84.2	38.4	0
-84.2	…	0
-84.2	42.9	0
-84.1	38.3	0
-84.1	38.4	0
-84.1	…	0
-84.1	42.9	0
…	…	0
-79.4	42.9	0

Prediction Grid for Exposure

$\sum PCB_4$	*p,p*'-DDE	SMOKING
0.01	0.01	0
0.01	0.02	0
0.01	…	0
0.01	14.93	0
0.02	0.01	0
0.02	0.02	0
0.02	…	0
0.02	14.93	0
…	…	0
4.41	14.93	0

Hypothesis Testing

- Global Hypothesis Testing

  H_0: There is no association between smoothed location or smoothed exposure and outcome

  H_A: There is an association between smoothed location or smoothed exposure and outcome

- Unconditional Permutation Test:
  1. Rank the deviance statistic of the observed model and 999 permutations of the smoothed model
  2. For nominal significance level of 0.05, if observed statistic falls in top 5% of the permutation distribution, then reject H_0

Locating Areas of Significance

- Performed if global null hypothesis was rejected
- Produce point-wise predictions from models applied to observed and permuted datasets
- For each point:
  - Compare predictions to permutation distribution of predictions
  - If observed data value falls in the upper/lower 2.5% of the distribution, the point is located in an area where the outcome is significantly increased or decreased

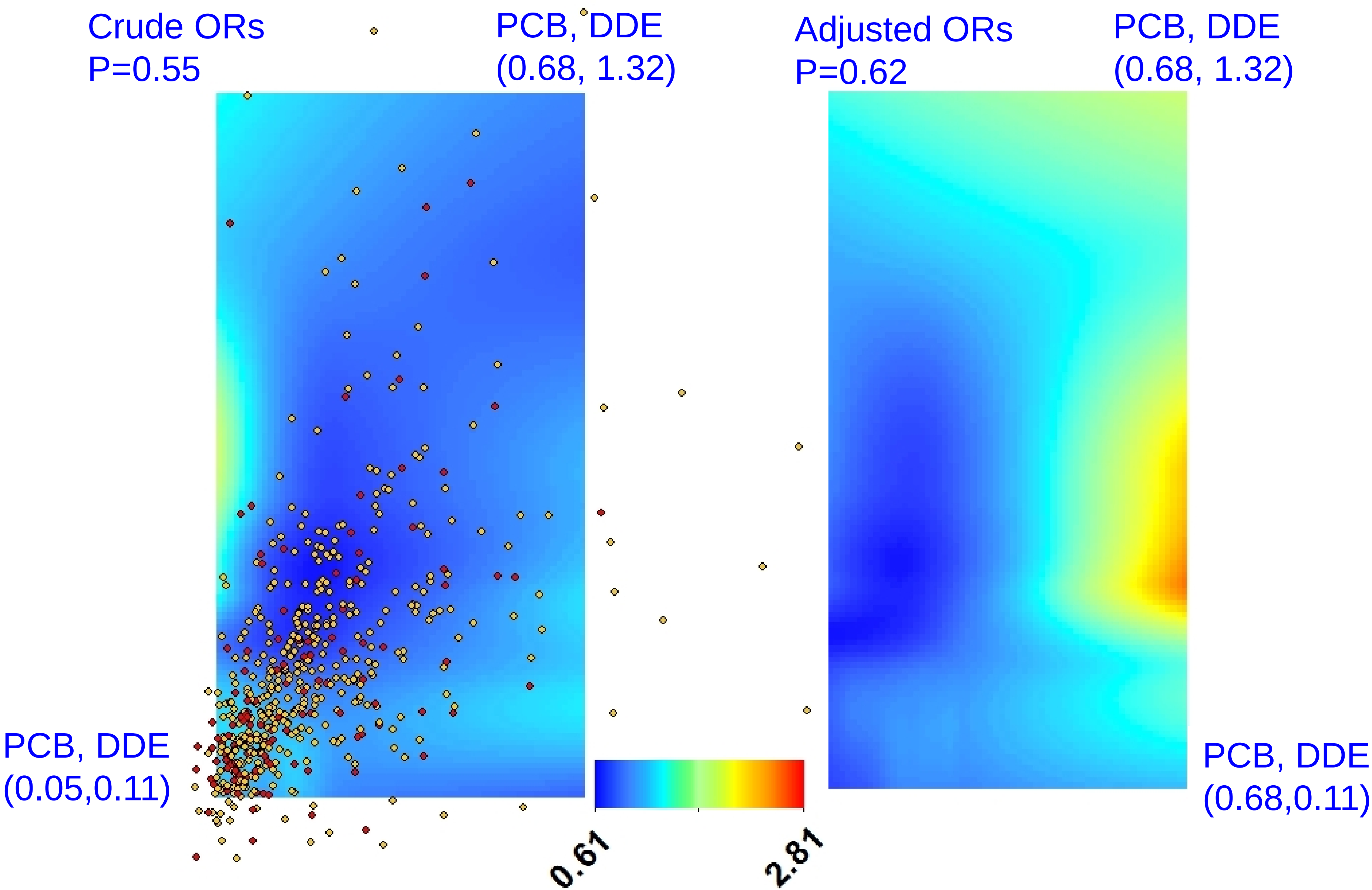
Statistical Analyses (1)

- Dichotomized outcomes at the 86th percentile (*T*-score 61) represents mildly to markedly atypical scores indicative of a possible or significant problem
- Conners' ADHD Index: Cases = 132; Controls = 441
- DSM-IV Inattention: Cases = 139; Controls = 434

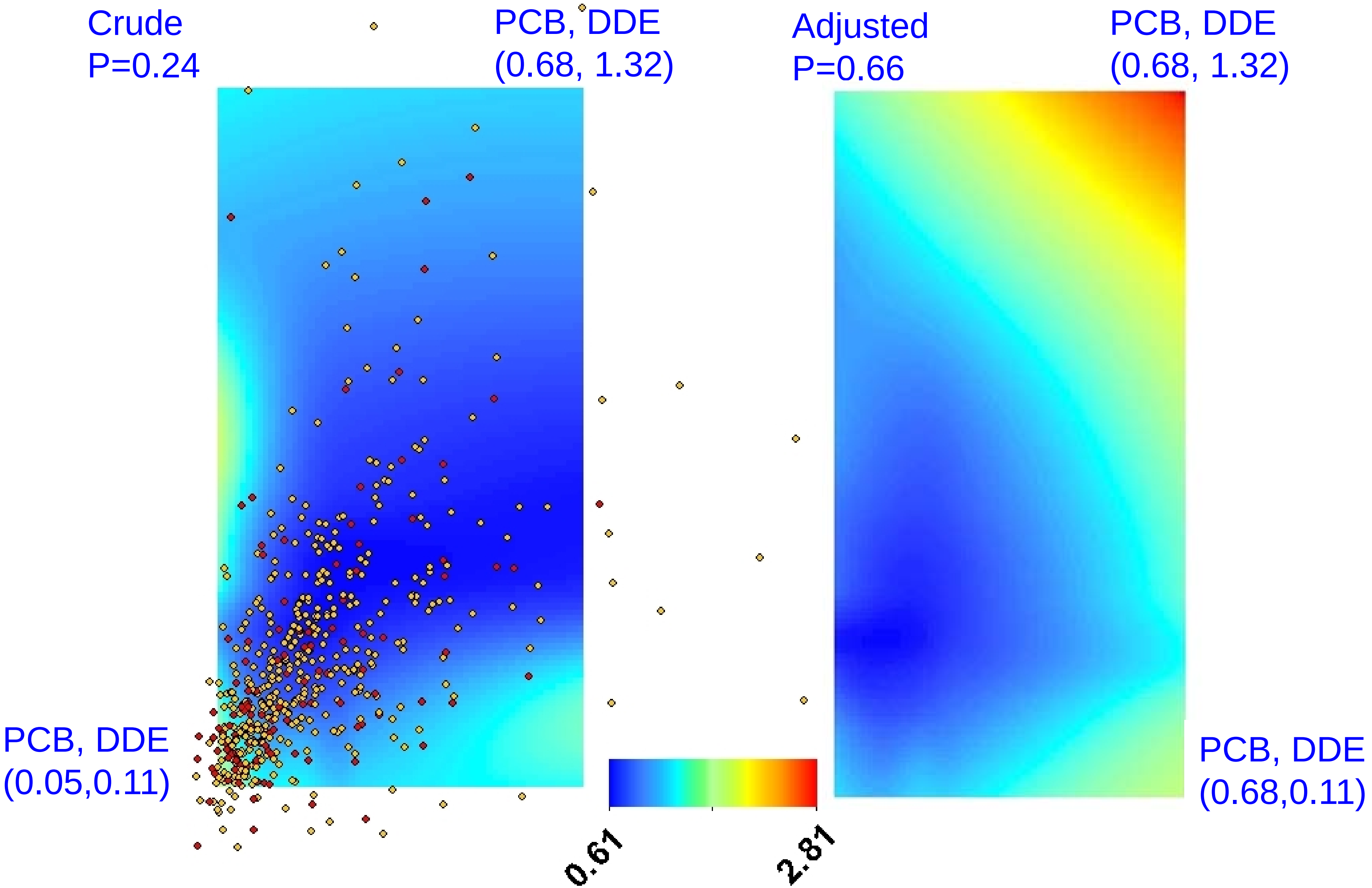
Statistical Analyses (2)

- Exposures ng/g umbilical cord serum
- Controlled for child's age, sex; maternal age, marital status, education, income; smoking, alcohol consumption, local fish consumption, and illicit drug use during pregnancy

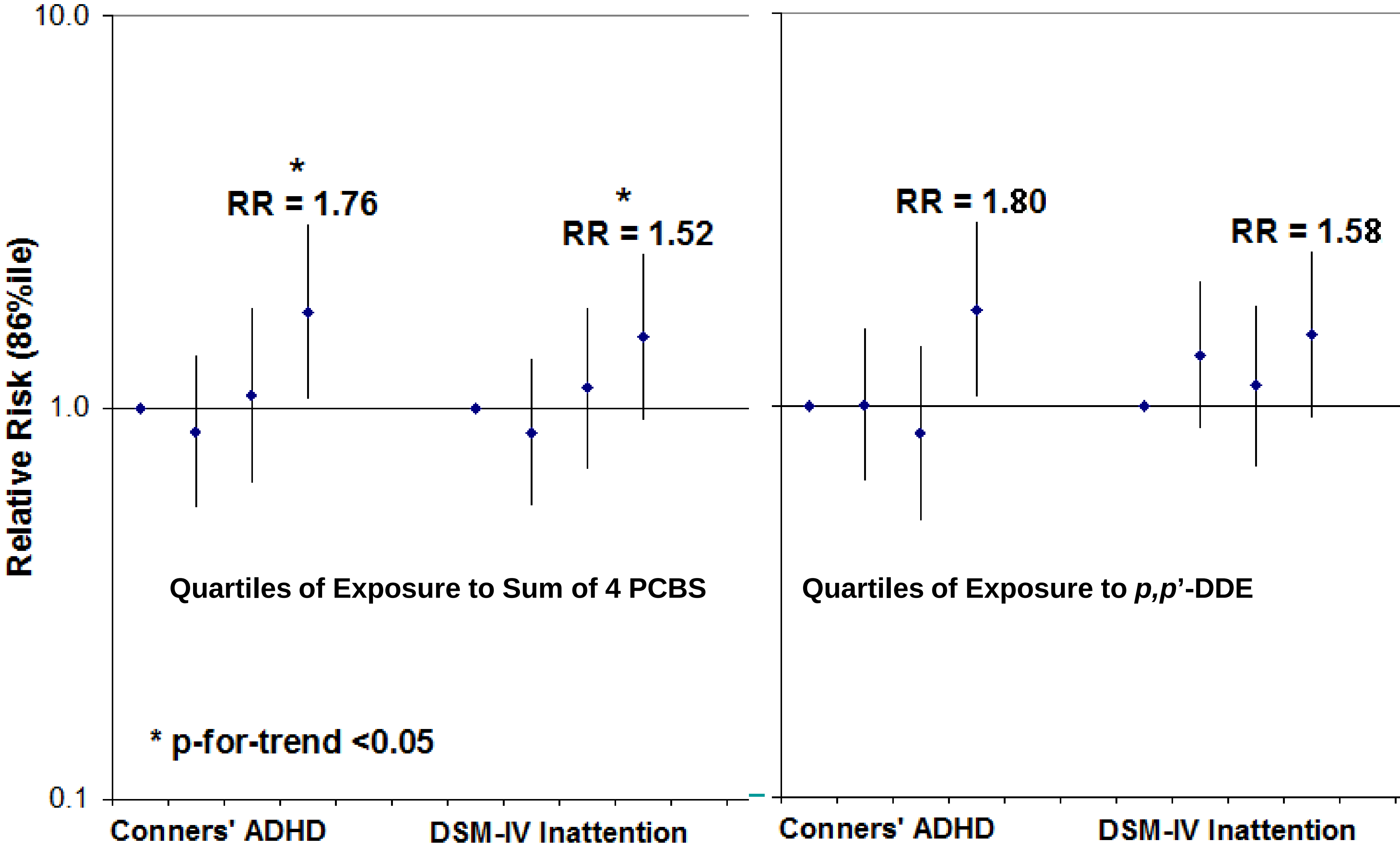
Results – DSM-IV Inattention



Results – ADHD Index



Single Exposure Results



Conclusions

- GAMs are an effective method for detecting patterns in epidemiologic data
- Commonly used for location, bivariate smooth can also be used to analyze chemical mixtures
- Smoothed analysis of PCB and DDE exposures shows increased risk for Conners' ADHD Index at higher concentrations

MapGAM R package

- To download, go to: http://cran.r-project.org/web/packages/MapGAM/
- Data and code also at Boston University SRP Project 2: http://www.bu.edu/sph/research/research-landing-page/superfund-research-program-at-boston-university/

Future Research

- Improve methods to address GAM limitations
  - sparse data
  - edge effects
  - different units
- Examine other Conners' scales (DSM-IV total, DSM-IV hyperactive) and exposures (lead, mercury, other PCBs)
- Consider other pollutant sources (living nearby major roadways) and risk factors generated through an ongoing cumulative risk assessment study in New Bedford

NIEHS Mixtures Workshop, 2015

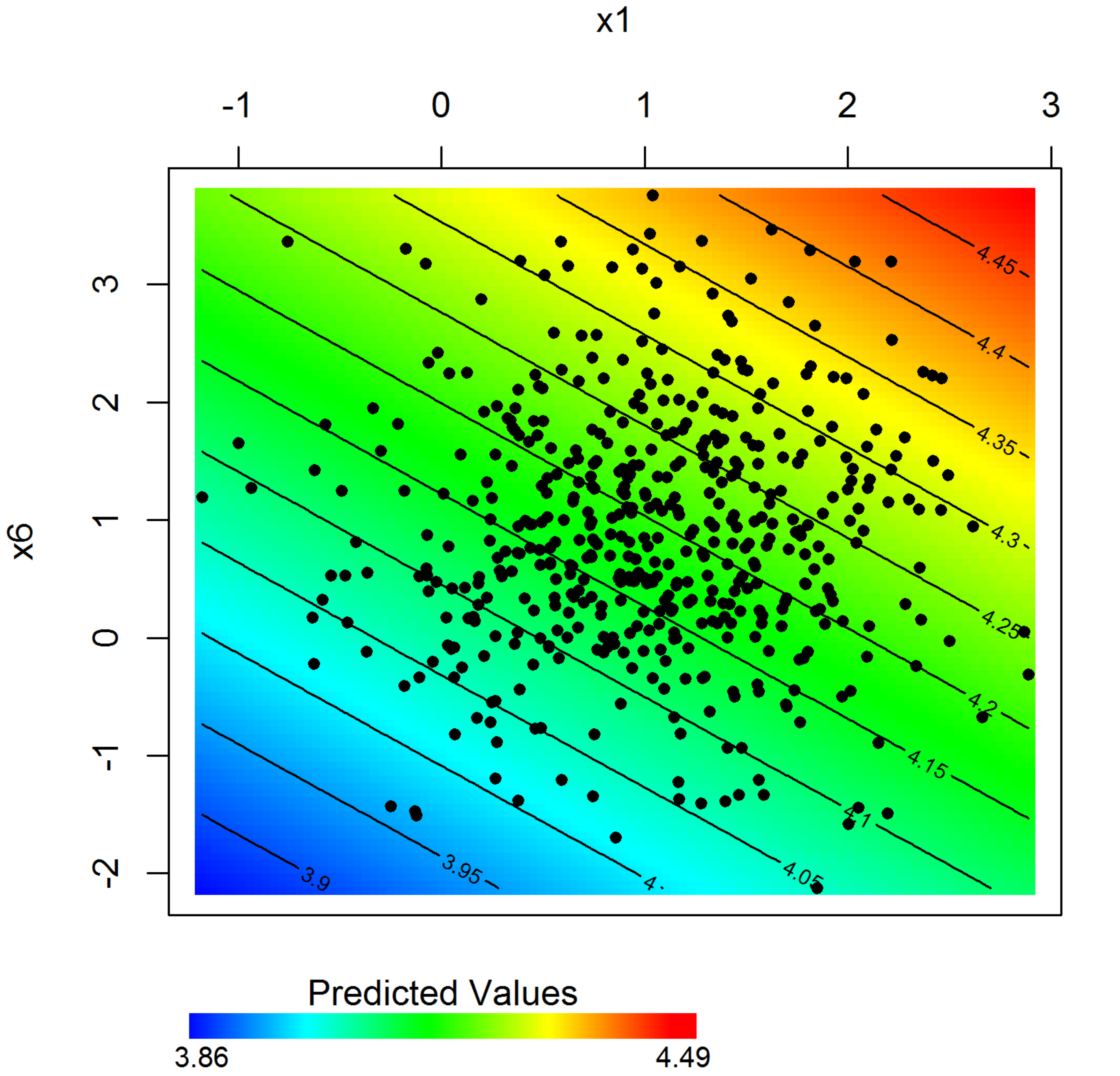
- **Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies**

- http://www.niehs.nih.gov/about/visiting/events/pastmtg/2015/statistical/

ESS and Isoboles (1)

- Work led by Tom Webster, BUSPH
- Isobole shapes are informative about toxicologic “interactions” relative to concentration addition.
- Parallel straight line isoboles (usually of negative slope) imply that the variables can be modeled using toxic equivalent factors (TEFs).

TEF

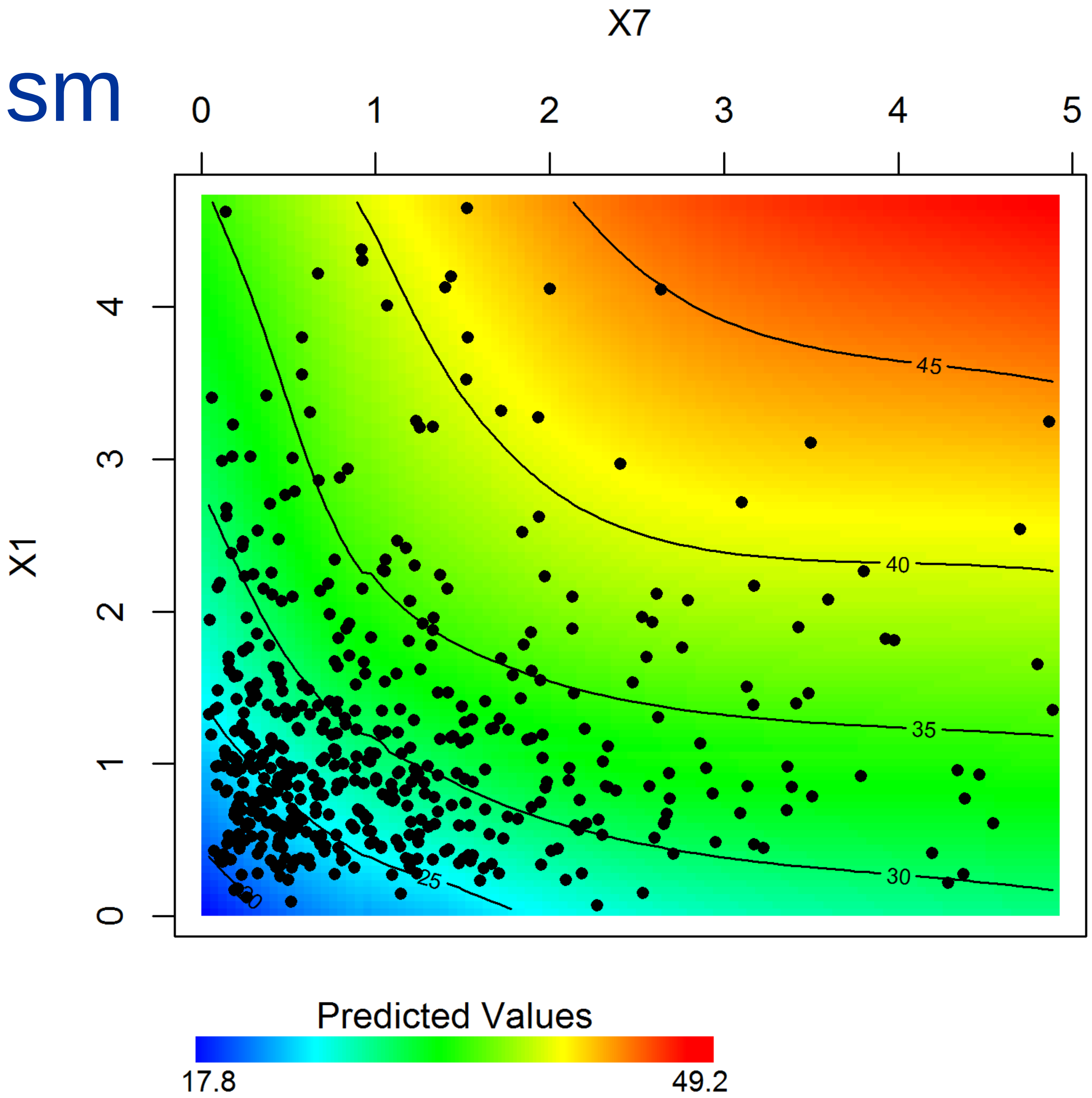


x1
-1
0
1
2
3
x6
3
2
1
0
-1
-2
4.45
4.4
4.35
4.3
4.25
4.2
4.15
4.1
4.05
4
3.95
3.9
Predicted Values
3.86
4.49

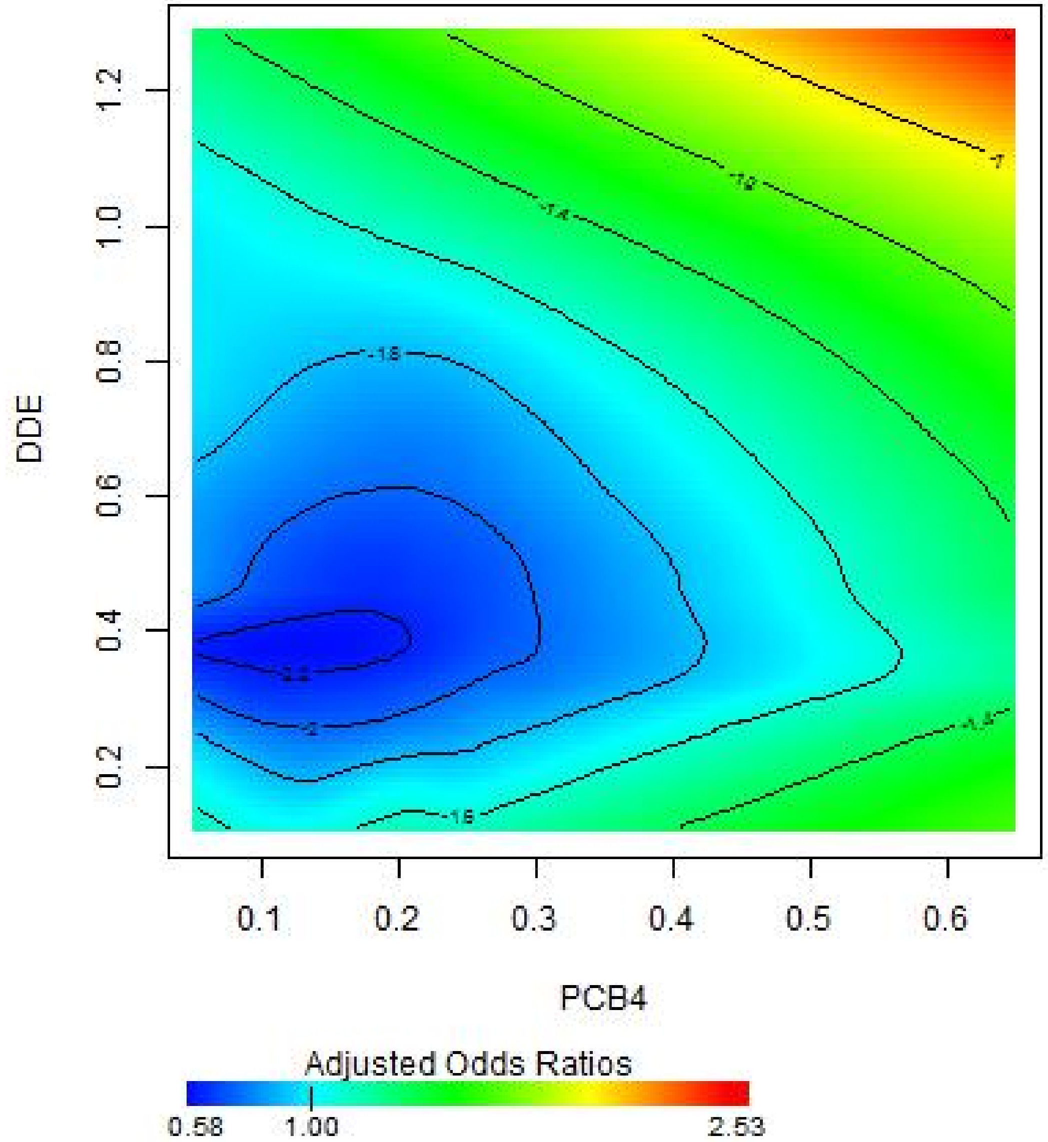
ESS and Isoboles (2)

- Negatively sloped isoboles that bow downward (positive second derivative) are supra-linear (“synergistic”) relative to concentration addition.
- Positively sloped isoboles (straight or curved) are types of “antagonism” where the compounds are acting in opposite directions. There are other types.

Synergism



Real World NBC Analysis



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More information on NBH

- http://www2.epa.gov/new-bedford-harbor