Synergistic Interaction Detection

Shounak Chattopadhyay
Duke University

Ongoing work with Prof. David Dunson

Background

- We focus on modeling dose response surfaces in the presence of interaction.
- Most joint modeling approaches cannot incorporate prior information regarding interactions.
- Prior information present in terms of synergistic or antagonistic interactions between exposures.

Formulation

- Continuous response y and exposures $x_1, \dots, x_p \in [0,1]$ along with covariates z.
- Our model is

$$y = z'\alpha + \sum_{j=1}^{p} f_j(x_j) + \sum_{u=1,v=1}^{p} \sum_{u<v} \gamma_{uv}\, h_{uv}(x_u, x_v) + \epsilon$$

- Here, $\gamma_{uv} \in \{-1, 1\}$. Assume $\epsilon \sim N(0, \sigma^2)$. All the $h_{uv} \geq 0$.
- Fix an arrangement of γ_{uv} beforehand based on prior information about interaction to be synergistic (+1) or antagonistic (-1).
- Can also estimate them assuming they are unknown, but time consuming.

Model Specification

- f_j is the j-th main effect of the exposure x_j and $h_{uv}(x_u, x_v)$ is the absolute interaction between x_u and x_v.
- To ensure identifiability and smooth estimates, we enforce $\int f_j(x_j)\, dx_j = 0$ for $j = 1, \ldots, p$ and $h_{uv}(x_u, 0) = 0$ for all x_u and $h_{uv}(0, x_v) = 0$ for all x_v.
- B-spline expansion for f_j with coefficient $\beta_j \sim N\left(0, \frac{\sigma^2 \Sigma}{\lambda_j}\right), \lambda_j \sim G(0.5, 0.5)$.
- We model $h_{uv} = H_{uv}^2$ and model H_{uv} with a tensor product spline B-spline expansion with coefficient $\psi_{uv} \sim N\left(0, \frac{\sigma^2 \tau^2 S}{\delta_{uv}}\right), \delta_{uv} \sim C^+(0,1), \tau^2 \sim G(0.5, 0.5)$.
- Σ and S are known covariance matrices as suggested in Lang and Brezger (2004).
- τ^2 signifies shared information across interactions and δ_{uv} signifies interaction-specific effects which are given heavy-tailed prior to allow shrinkage to zero.
- Finally, $\sigma^2 \sim IG(0.5, 0.5)$. We sample from the posterior using a Metropolis Adjusted Langevin Algorithm (MALA)-within-Gibbs approach.

Key Goals

- Our model incorporates prior information about possible synergistic or antagonistic reactions.
- The interaction is shrunk to be close to 0 by the heavy-tailed prior on the coefficient δ_{uv} if there is an absence of interaction.

- Goal 1: Identify whether there are synergistic / antagonistic interactions according to prior belief.
- Goal 2: If such interactions are present, provide a point estimate along with accurate uncertainty quantification.

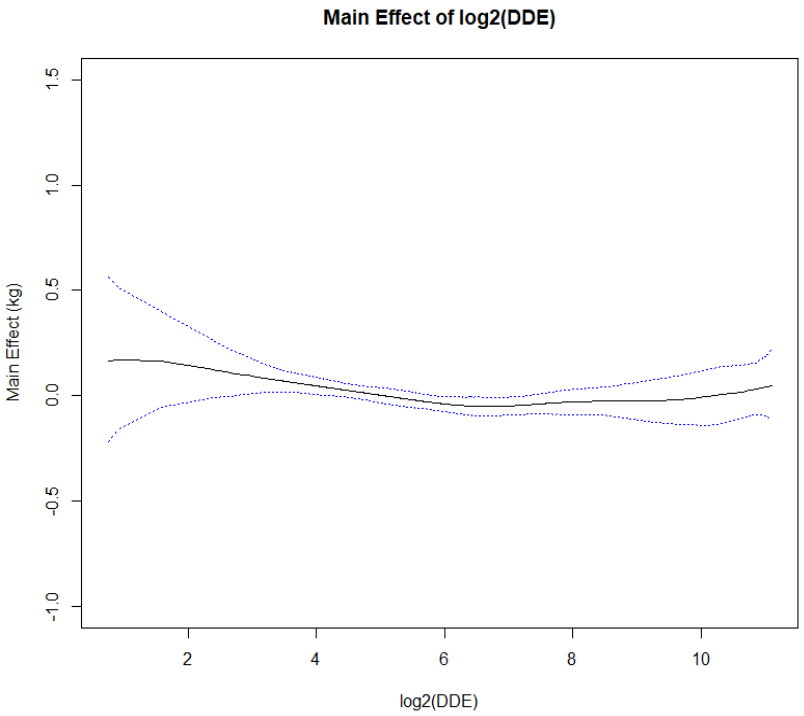
Exposome Dataset

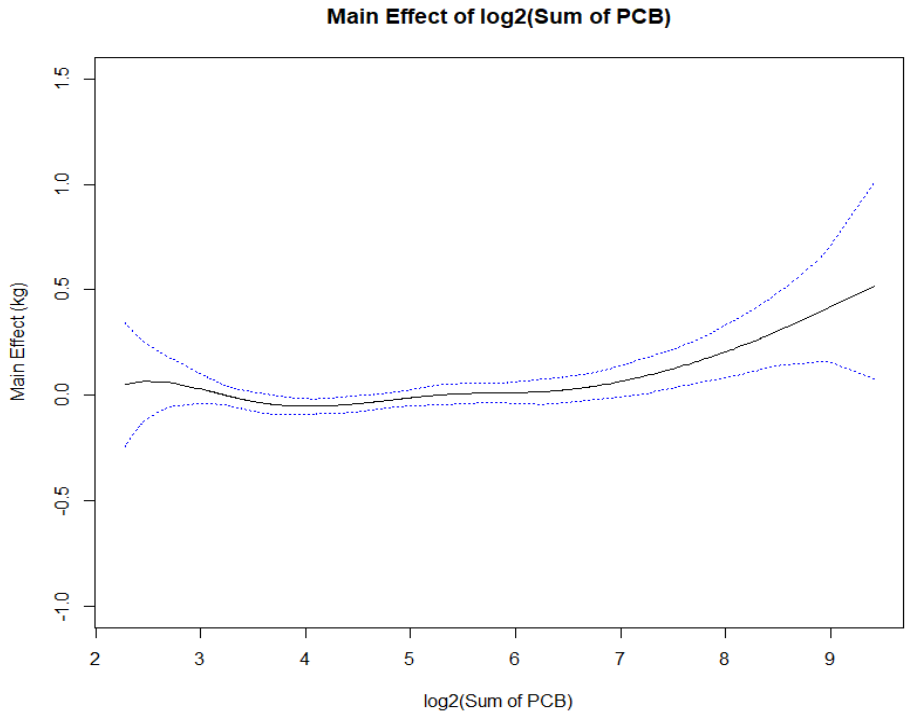
- We consider the effect of exposures and covariates on the response birth weight, which appeared reasonably Gaussian from a Q-Q plot.
- We took only those subjects with gestational period ≥ 37 weeks as our data. The sample size is then $n = 1234$.
- The covariates were taken to be pre-pregnancy BMI, maternal weight gain during pregnancy, gestational age at birth, maternal age, alcohol usage (0/1) and smoking status (0/1).
- The exposures were (all in $\log_2$ scale) sum of PCBs (Polychlorinated biphenyl), DDE (Dichlorodiphenyldichloroethylene), and PFOA (Perfluorooctanoate). So $p = 3$.
- Of interest are the interactions which reduce weight at birth.
- We standardized the data prior to fitting the model and ensured each exposure was in the interval [0,1]. All the interactions were fitted with -1 sign.

Summary of Results

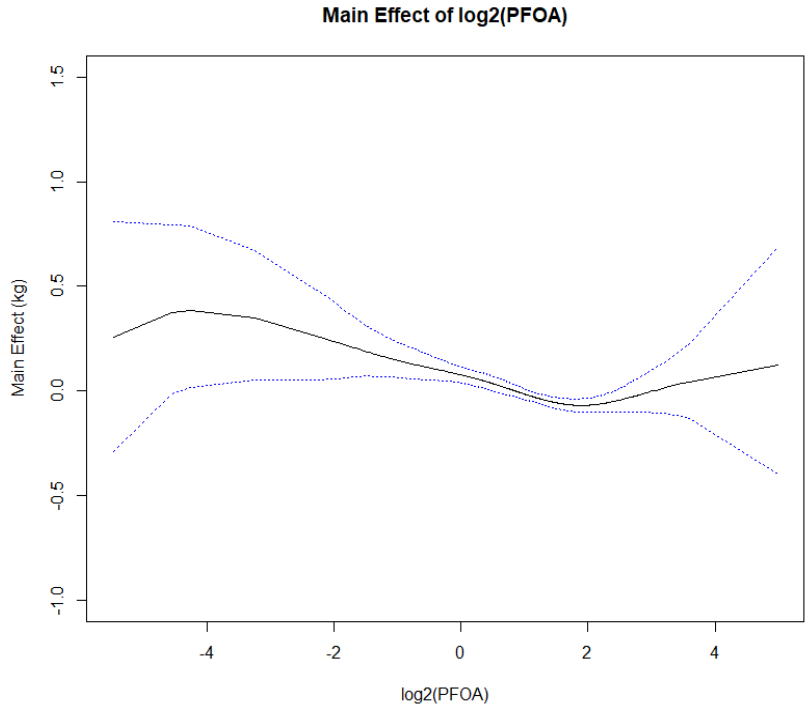
- The covariates pre-pregnancy BMI, maternal weight gain and gestational age at birth had positive effects on birth weight.
- Smoking had a negative effect on birth weight.
- Sum of PCBs have a slight positive effect on birth weight in the range [8, 9] in $\log_2$ scale.
- Exposure to PFOAs in the range [0, 2] in $\log_2$ scale have a negative effect on birth weight.
- Only the sum of PCBs and PFOA seem to have a strong interaction for large values of sum of PCBs and moderate-to-large values of PFOA.
- Sum of PCBs and DDE had a slight estimated interaction for high values of both but otherwise there seemed to be a lack of interaction.
- Estimated variance was $\widehat{\sigma^2} = 0.77$ with a 95% credible interval [0.72, 0.84].

Plots – Main Effects

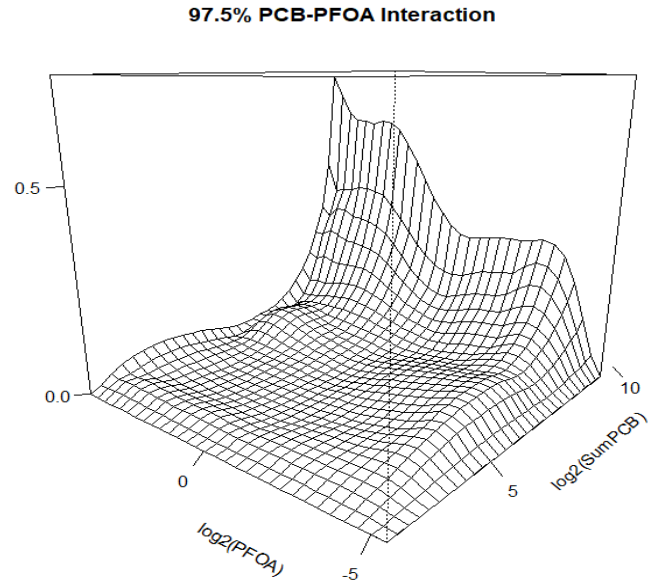


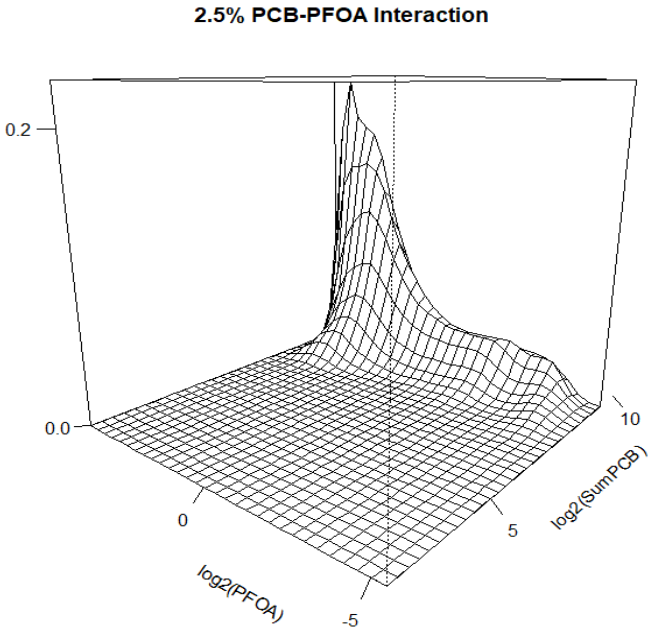


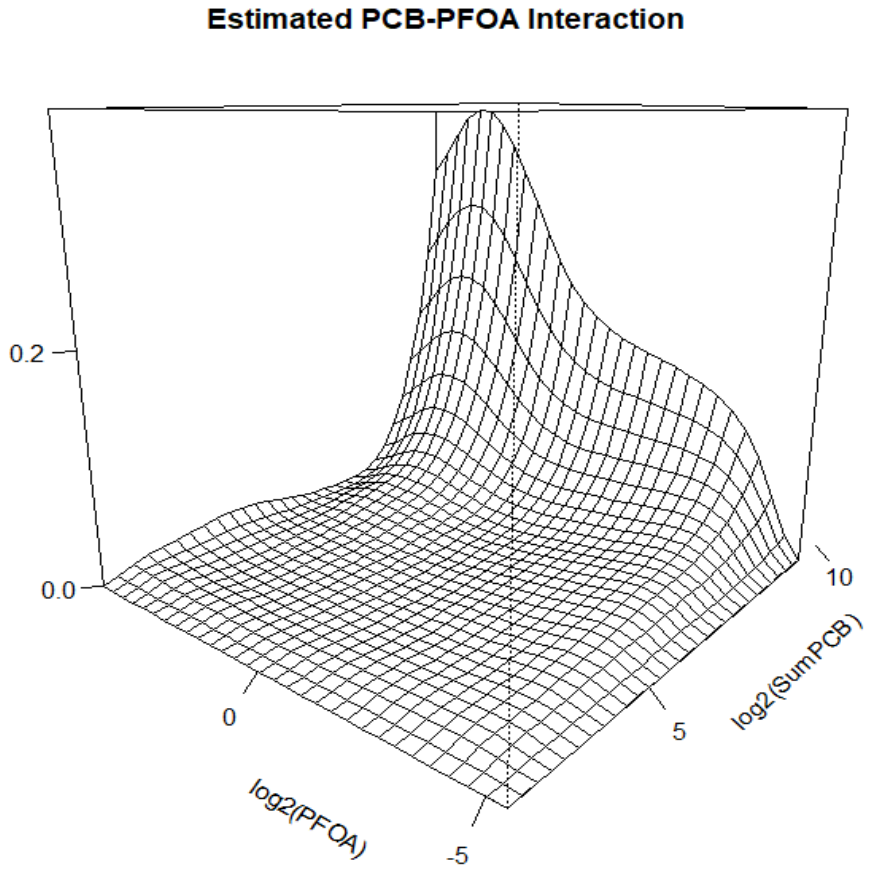
Estimated main effect in black and
95% credible bands are in dotted blue



PCB-PFOA Interaction







- Negative of the interactions plotted.
- Maximum estimated interaction value is 0.38 with a 95% credible interval of [0.23, 0.73].
- Suggests possibility of a negative interaction between sum of PCBs and PFOA, especially for large values of sum of PCBs.