Estimating Perinatal Critical Windows of Susceptibility to Environmental Mixtures via Structured Bayesian Regression Tree Pairs

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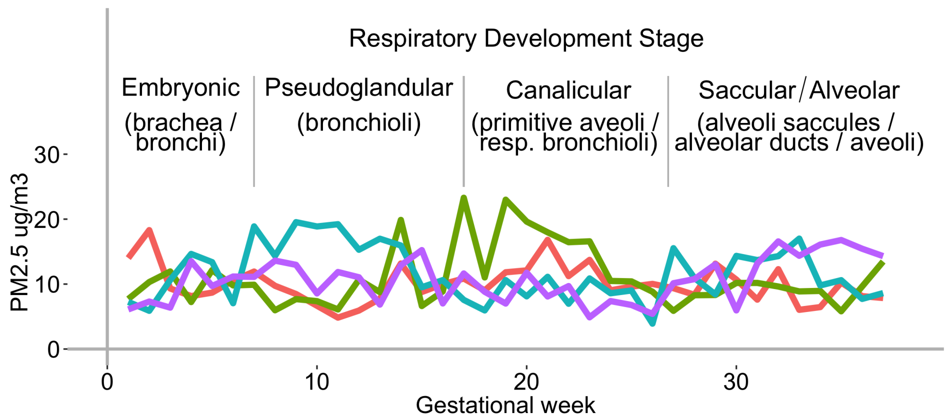
Critical Windows of Susceptibility

Definition

A period in time during which an exposure can alter phenotype.

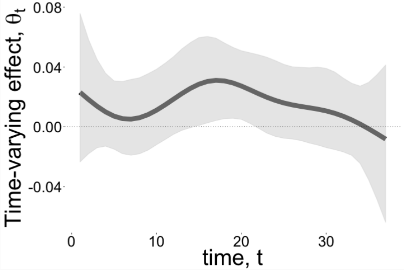


Distributed Lag Model (DLM)

$$y_i = \sum_{t=1}^{T} x_{it}\theta_t + z_i'\gamma + \varepsilon_i$$

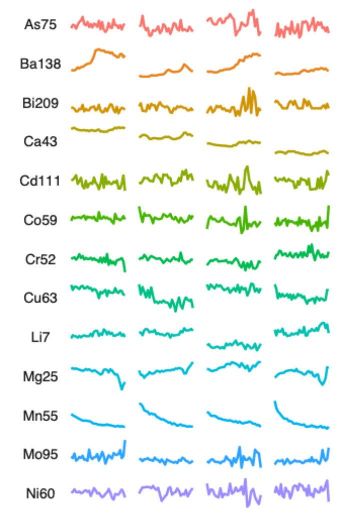
- $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_T)'$ *constrained* to vary smoothly in time (e.g. spline, Gaussian process, ...)
    - adds stability to the model
    - conforms with biological hypothesis that exposure at proximal time points are likely to have similar effects

DLM analysis of $PM_{2.5}$ and asthma among boys in the ACCESS cohort.



[1]Figure source: Wilson et al. (2017a) *Biostatistics*.

Critical Windows with Mixtures



Challenges of Mixtures Assessed at Longitudinally

- High dimensional exposure space
- High correlation between mixture components
- High autocorrelation within each component
- Nonlinear associations
- Interactions between components including time-sensitive interactions (e.g. priming)

Limitations of DLM

- Tendency to over-smooth the distributed lag function
- Lack of DLM methods for mixtures
- This talk: How to use Bayesian additive regression trees (BART) to better estimate a DLM and extend DLM to mixtures

Bayesian Additive Regression Trees (BART)

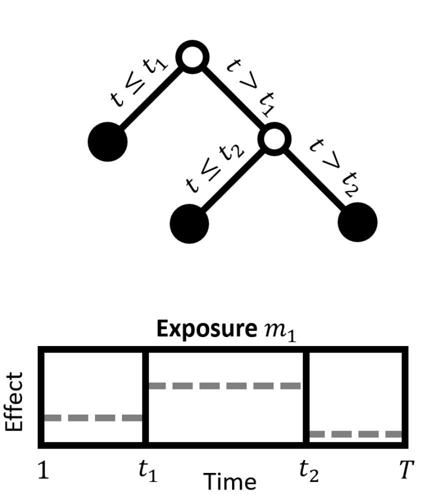
$$y_i = f(\boldsymbol{x}_i) + \varepsilon_i$$

- Proposed by by Chipman, George, McCulloch (1998, *JASA* & 2010, *AOAS*)
- Estimate a general mean function
- State of the art predictive performance
- Allows for coherent Bayesian inference

Treed Distributed Lag Model (TDLM)

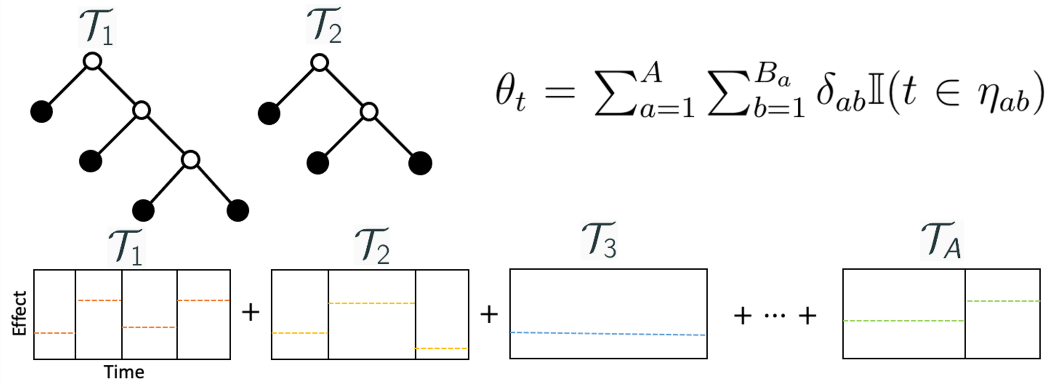
$$y_i = \sum_{t=1}^{T} x_{it}\theta_t + \mathbf{z}_i'\gamma + \varepsilon_i$$

- Apply BART to time ($t = 1, \ldots, T$) to define structure in the lag function $\theta_1, \ldots, \theta_T$
- Constant effect of exposure in each terminal node or time segment

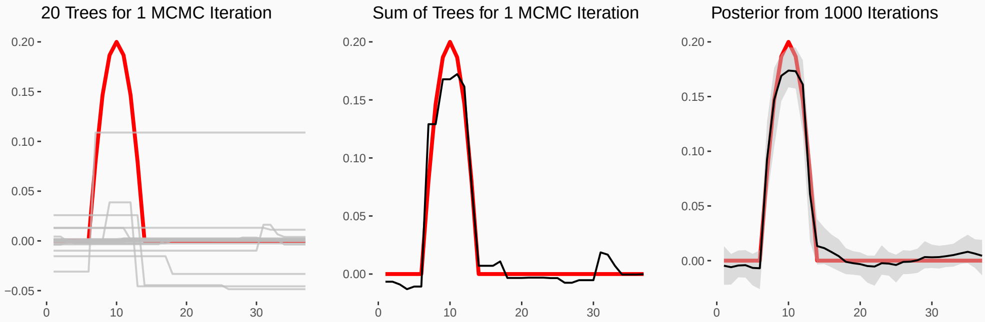


TDLM: Ensemble of Trees

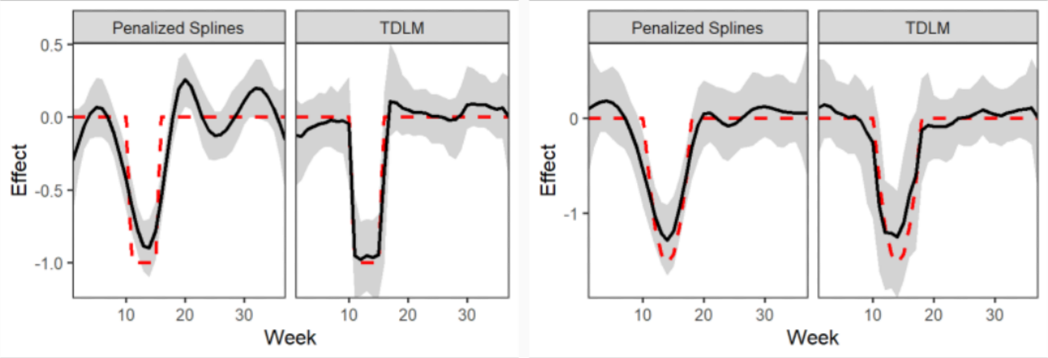
- Use ensemble of A trees
- Adds robustness and can approximate smooth distributed lag functions
- η_{ab} and δ_{ab} is the terminal node and effect for node b on tree a



TDLM: Illustrative Example



TDLM: Illustrative Example

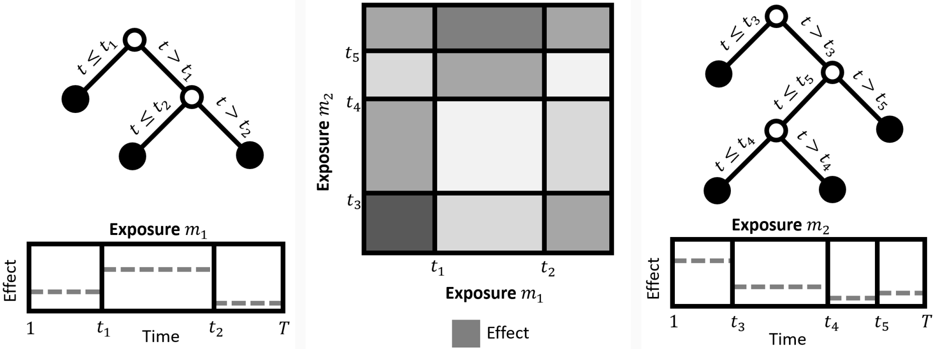


Distributed Lag Mixture Model (DLMM)

$$y_i = \sum_{m=1}^{M}\sum_{t=1}^{T} x_{imt}\theta_{mt} + \sum_{m_1=1}^{M}\sum_{m_2=m_1}^{M}\sum_{t_1=1}^{T}\sum_{t_2=1}^{T} x_{im_1t_1}x_{im_2t_2}\theta_{m_1m_2t_1t_2} + \mathbf{z}_i'\gamma + \varepsilon_i$$

- θ_{mt} is the main effect of exposure m $(m = 1, \ldots, M)$ at time t
- $\theta_{m_1m_2t_1t_2}$ is the interaction among exposures m_1 at time t_1 and m_2 at time t_2
- Includes time-sensitive interactions
- Includes quadratic main effects if we include self interactions
- $MT + \binom{M+1}{2}T^2$ parameters (20,720 in our analysis with $M = 5$ and $T = 37$)

Treed Distributed Lag Mixture Model (TDLMM)



- Structured regression tree pairs add structure to the θ's
- Tree pairs define the main effect and pairwise interaction for two exposures (or a self interaction / quadratic)

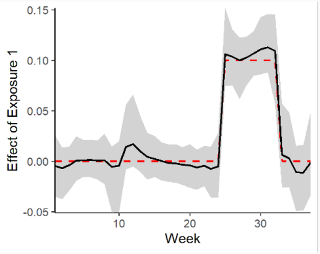
Tree Pairs & Exposure Selection

- Prior on the exposure that each tree is applied to

$$\begin{aligned} S_{aj} &= m \qquad \text{if tree } j \text{ in pair } a \text{ is applied to exposure } m \\ S_{aj}|\mathcal{E} &\sim \text{Categorical}(\mathcal{E}) \\ \mathcal{E} &\sim \text{Dirichlet}(\kappa, \ldots, \kappa) \end{aligned}$$

- New tree proposal update: switch exposure
- If no tree uses exposure m, that exposure is selected out of the model
- Enforces hierarchical variable selection

TDLM Simulation (single pollutant)

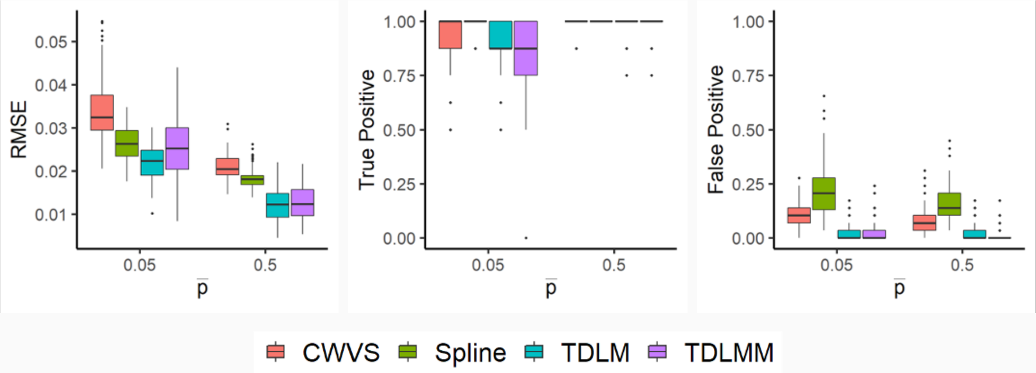


- Scenario 1: Binary outcome, single exposure
- $n = 5000$, two different average probabilities of success (0.05, 0.5)
- Randomly placed, eight-week critical window
- Real Colorado exposure data for $PM_{2.5}$
- Compare:
  - TDLM with a single exposure
  - Penalized cubic regression splines[1]
  - Critical window variable selection (CWVS)[2]
  - TDLMM with four additional exposures in mixture model (NO_2, SO_2, CO, temperature)

[1] Gasparrini et al. (2017) *Biometrics*
[2] Warren et al. (2020) *Biostatistics*

TDLM Simulation (single pollutant)

- Better distributed lag function estimation
- More accurate critical window detection
- Minimal penalty for using TDLMM when only one exposure has a true effect



TDLMM Simulation (mixture with five components)

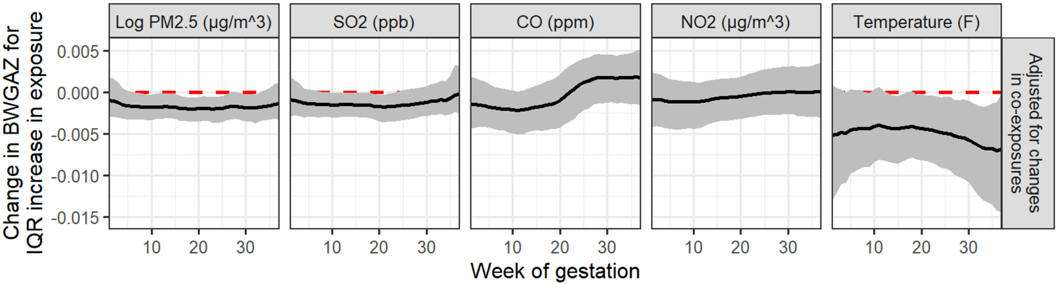
- Second simulation from a mixture with time-sensitive interactions
- Gaussian model
- Overall good performance
    - acceptable RMSE
    - proper 95% interval coverage
    - high precision identifying windows
    - high rate of selecting correct exposures and lower rate of selecting incorrect exposures

Analysis of Colorado Administrative Birth Cohort

- 195,701 full term (37 weeks) births
- Outcome: birth weight z-score (BWGAZ), adjusted for sex, gestational age
- Five exposures assessed weekly during gestation: $PM_{2.5}$, NO_2, SO_2, CO, temperature
- Controlled for: maternal age, weight, income, education, smoking, prenatal care, race, Hispanic, county, elevation, year and month of conception

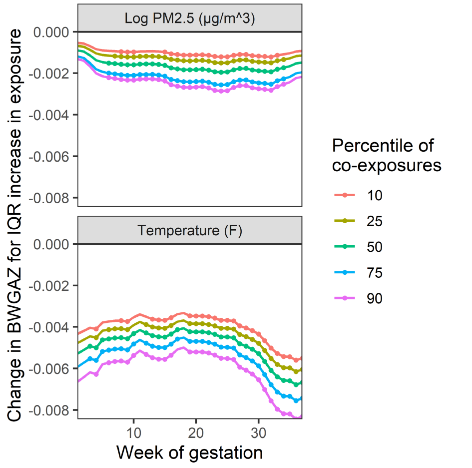
Main Effects

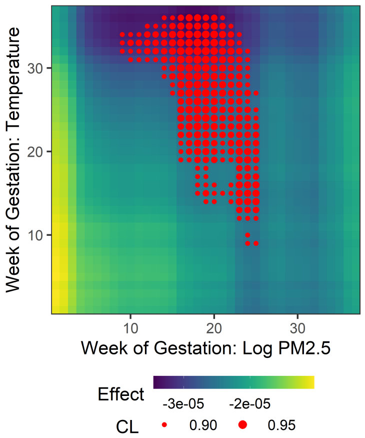
- Many "main effects"
- Here: IQR change of one exposure and the expected corresponding change in the co-exposures



$$E\left[Y\middle|\widetilde{x}_t = E\left\{x_t\middle|x_{mt} = x_{m(0.75)}\right\}, \widetilde{x}_{[t]} = \overline{x}, z = z_0\right]$$
$$- E\left[Y\middle|\widetilde{x}_t = E\left\{x_t\middle|x_{mt} = x_{m(0.25)}\right\}, \widetilde{x}_{[t]} = \overline{x}, z = z_0\right]$$

Temperature-$PM_{2.5}$ Interaction





Summary

- We can add structure to BART to get interpretable estimates of DLMs
- Allows for identifying critical windows
- Tree-pairs allows for mixtures
- Overall good finite sample properties
- Available for linear and logistic regression (zero inflated count data coming soon)
- Similar approach for heterogeneity (Mork et al. 2022, ArXiv:2109.13763)
- Treed distributed lag nonlinear model also available (Mork and Wilson 2021, *Biostatistics*)
- R code available: `github.com/danielmork/dlmtree`

Thank You

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Mork, D., Wilson, A. (In press). Estimating perinatal critical windows of susceptibility to environmental mixtures via structured Bayesian regression tree pairs. *Biometrics*. https://arxiv.org/abs/2102.09071

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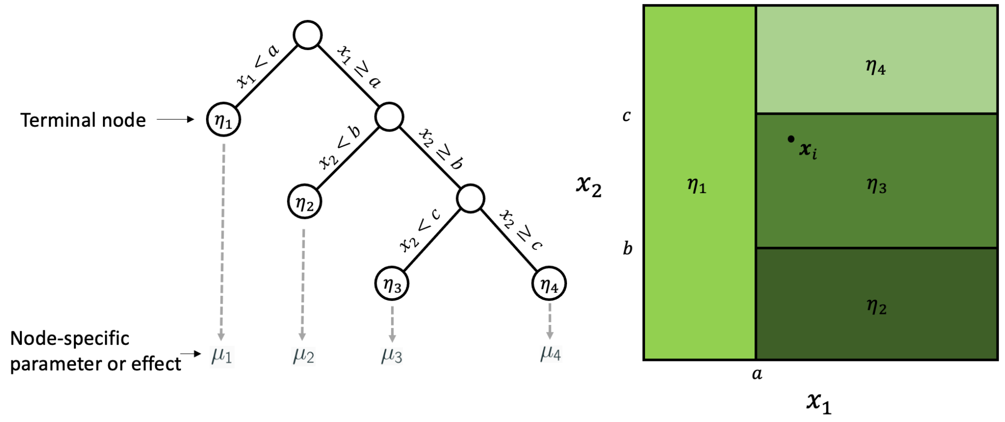
BART

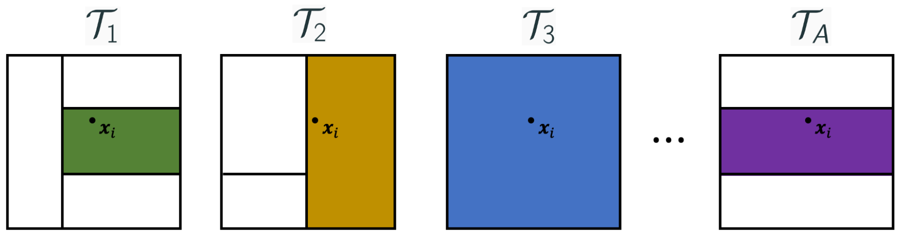
Bayesian Additive Regression Trees (BART)

$$g(\mathbf{x}_i, \mathcal{T}) = \mu_b \qquad \text{if } \mathbf{x}_i \in \eta_b$$

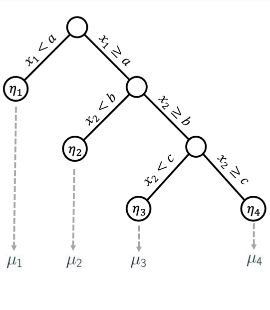


BART

$$f(x_i) = \sum_{a=1}^{A} g(x_i, \mathcal{T}_a)$$



BART Priors

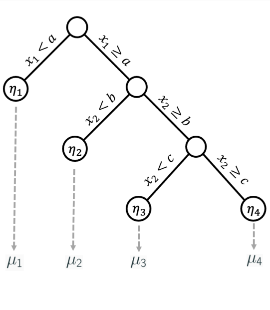


- Implicit prior based on tree generating process
- Three parts:
  - Prior that a node at tree depth d splits
  - Prior on variable that is split at a node (e.g. uniform from all variables)

$$\alpha(1+d)^{-\beta} \qquad \alpha \in (0,1),\ \beta \in [0,\infty)$$

  - Prior on a rule that splits that variable (e.g. uniform breaks in range or uniform of subgroups of categorical variables)
- Independent Gaussian priors on μs

BART Computation



- μs can be integrated out to avoid changing parameter space problem
- Bayesian backfitting updates one tree at a time with Metropolis–Hastings
- Four possible tree-update steps
  - Grow
  - Prune
  - Change splitting rule
  - Swap parent and child node order
- Update other parameters with Gibbs

TDLMM

TDLM Priors

$$
\begin{aligned}
\delta_{ab} | \tau_a^2, \nu^2, \sigma^2 &\sim \mathcal{N}(0, \tau_a^2 \nu^2 \sigma^2) \\
\nu &\sim \mathcal{C}^+(0, 1) \\
\tau_a &\sim \mathcal{C}^+(0, 1) \\
\\
\sigma &\sim \mathcal{C}^+(0, 1) \\
\boldsymbol{\gamma} &\sim \mathcal{MVN}(\mathbf{0}, \sigma^2 c \boldsymbol{I}) \\
\\
\alpha &= 0.95,\ \beta = 2
\end{aligned}
$$

TDLMM Priors

$$
\begin{aligned}
\delta_{ajb} | \mu^2_{S_{aj}}, \nu^2, \sigma^2 &\sim \mathcal{N}(0, \mu^2_{S_{aj}} \nu^2 \sigma^2) \qquad \text{(main effects)} \\
\mu_{S_{aj}} &\sim \mathcal{C}^+(0,1) \\
\zeta_{ab_1 b_2} | \mu^2_{S_{a1} S_{a2}}, \nu^2, \sigma^2 &\sim \mathcal{N}(0, \mu^2_{S_{a1} S_{a2}} \nu^2 \sigma^2) \qquad \text{(interactions terms)} \\
\mu_{S_{a1} S_{a2}} &\sim \mathcal{C}^+(0,1) \\
\nu &\sim \mathcal{C}^+(0,1)
\end{aligned}
$$

$$
\begin{aligned}
\sigma &\sim \mathcal{C}^+(0,1) \\
\boldsymbol{\gamma} &\sim \mathcal{MVN}(\mathbf{0}, \sigma^2 c \boldsymbol{I})
\end{aligned}
$$

$$
\alpha = 0.95, \ \beta = 2
$$

TDLMM Computation

Key modifications to the BART MCMC algorithm:

- Integrate out fixed effect when estimating trees and distributed lag effects
- New proposal step: switch exposure, accepted with Metropolis-Hastings algorithm Simultaneous integration over all distributed lag effects during tree update
- Multivariate draw of tree terminal node and interaction parameters
- Logistic regression method for regression trees using Polya Gamma latent variable (Polson, Scott, Windle, 2013, *JASA*)
- Methods for zero inflated count data coming soon.
- Posterior analysis of tree structures, exposure, and estimates gives distributed lag effects and uncertainty