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

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Abstract

Maternal exposure to environmental chemicals during pregnancy can alter birth and children’s health outcomes. Research seeks to identify critical windows, time periods when exposures can change future health outcomes, and estimate the exposure-response relationship. Existing statistical approaches focus on estimation of the association between maternal exposure to a single environmental chemical observed at high temporal resolution (e.g. weekly throughout pregnancy) and children’s health outcomes. Extending to multiple chemicals observed at high temporal resolution poses a dimensionality problem and statistical methods are lacking. We propose a regression tree-based model for mixtures of exposures observed at high temporal resolution. The proposed approach uses an additive ensemble of tree pairs that define structured main effects and interactions between time-resolved predictors and performs variable selection to select out of the model predictors not correlated with the outcome. In simulation, we show that the tree-based approach performs better than existing spline-based methods for a single exposure and can accurately estimate critical windows in the exposure-response relation for mixtures. We apply our method to estimate the relationship between five exposures measured weekly throughout pregnancy and resulting birth weight in a Denver, Colorado birth cohort. We identified critical windows during which fine particulate matter, sulfur dioxide, and temperature are negatively associated with birth weight and an interaction between fine particulate matter and temperature. Software is made available in the R package dlmtree.

Keywords: air pollution, Bayesian additive regression trees, birth outcomes, critical windows, distributed lag models
1 Introduction

Maternal exposure to environmental chemicals during pregnancy is an important public health concern due to potential impact on children’s health. Increased exposure to environmental chemicals has been linked to decreased birth weight, increased risk of asthma, and altered neurological development, among other outcomes (Bosetti et al., 2010; Stieb et al., 2012; Jacobs et al., 2017). Recent research has focused on leveraging exposure data that is observed at high temporal resolution throughout pregnancy to identify critical windows of susceptibility during the gestational process (Wright, 2017; Buckley et al., 2019). Critical windows are periods in time when an exposure can alter a future health outcome and could be as short as a week or span many months. A second equally important goal with regard to environmental mixtures is estimating the exposure-response relationship that accounts for changing levels of susceptibility over the course of the pregnancy. Most studies that leverage temporally-resolved exposure data consider the effects of only a single environmental chemical. While understanding the effects due to a single exposure are essential, considering multiple pollutants is necessary to develop a more realistic picture of the exposure-response relationship (Davalos et al., 2017). The National Institute of Environmental Health Sciences highlighted both identifying susceptible developmental periods, or critical windows, and identifying mixture effects in its strategic plan (NIEHS, 2012). However, estimating critical windows with mixtures has been elusive due to an absence of statistical methods.

A distributed lag model (DLM) is commonly used to estimate the association between a single time-resolved exposure and a health outcome (Schwartz, 2000; Zanobetti et al., 2000; Warren et al., 2012; Wilson et al., 2017a; Gasparrini et al., 2017). A DLM regresses the outcome on the exposure measurements at multiple time points, e.g. regressing birth weight on weekly mean exposure during gestation. Because of high temporal correlation between repeated measures of exposure, a DLM is typically constrained by adding structure so that the exposure-response function varies smoothly over time. Common constraints include splines (Gasparrini et al., 2010), Gaussian processes (Warren et al., 2012) and principal components (Wilson et al., 2017a). Compared to using average exposure over pregnancy or each of the trimesters, the DLM has been shown to reduce bias in estimates as well as improve critical window estimation (Wilson et al., 2017b). To account for multiple exposures, the
DLM can be used additively and extended to include interactions between two time-resolved predictors (Chen et al., 2019; Muggeo, 2007). However, methods to identify critical windows and estimate exposure-time-response functions with mixtures of more than two time-resolved predictors are lacking.

Estimating DLMs with interactions requires flexibility to identify interactions between exposures across time. Interactions at different time points correspond to the the ‘priming’ hypothesis where exposure to a pollutant at one time point changes an individuals’ vulnerability to a different exposure at a later time point or the ‘two hit’ hypothesis where exposure to a pollutant at two different times has an effect that deviates from the additive effect at each time point. Adding flexibility to accommodate time-sensitive interactions poses a challenge of increasing dimensionality in the required parameter space. As the number of exposures and temporal resolution of measurements increase, the number of possible interactions increases at a quadratic rate. In addition, data for mixtures observed at multiple time points typically exhibit high collinearity both over repeated measures and across mixture components at a single time point. A key challenge is, therefore, adding a constraining structure to the model to add stability while allowing for flexibility to accurately estimate the exposure-response relation and identify critical windows.

We propose a regression tree approach to estimate a constrained DLM for a single exposure or mixture of exposures observed at multiple time points. Regression trees are a well-known framework that has been applied in numerous fields including the study of chemical mixtures observed at a single time point in environmental epidemiology (Taylor et al., 2016; Park et al., 2017). Bayesian additive regression trees (BART), introduced by Chipman et al. (2010), has been adapted for a wide variety of data generating situations such as high dimensional prediction (Linero, 2018) or for causal inference (Hahn et al., 2020). While BART is generally focused on out-of-sample prediction, our goal is the adapt this framework to the estimation of distributed lag effects. Applied to exposure observations taken repeatedly over time, current regression tree techniques are lacking in several respects. First, they would treat the measurements for a single exposure at adjacent times as independent predictors. This is equivalent to fitting an unconstrained DLM which has been shown to be unstable due to high collinearity. Second, regression trees would not account for the structure in mix-
ture data where one measurement from each exposure is taken at the same time point. To account for temporal ordering in a single time-resolved predictor, Mork and Wilson (2021) proposed a tree based model to estimate a distributed lag non-linear model that subdivides the time and exposure-concentration dimensions of the exposure-time response surface, but fails to generalize to mixtures of time-resolved exposures.

In this paper, we define the distributed lag mixture model (DLMM), which extends the DLM to estimate the main effects of multiple exposures along with all two-way interactions. We propose regression-tree based methods for estimating both DLM and DLMM. Our DLM method adds structure to regression trees to account for the temporal ordering of the exposure data. The binary trees subdivide the exposure time span into non-overlapping segments. Each segment is defined by a terminal node on the regression tree. We then estimate a linear effect of exposure specific to each terminal node defined by the tree. This both reduces dimensionality by binning exposure measurements and provides constraints necessary for DLMs to make coherent inference with temporal correlation of the measurements.

Our proposed method for estimating the DLMM further builds on the tree literature. We introduce the concept of tree pairs. Each tree in the pair estimates the structured main effects of a time-resolved exposure. The structure both adds stability in the presence of time correlated predictors and adds to the interpretability of the model. The pair also estimates the structured interactions between the two exposures. We develop a computational framework to estimate an additive ensemble of tree pairs that allows for both the tree structures and the exposures to which the tree structures are applied to be stochastically updated in our model. Furthermore, our method conducts exposure selection and effect shrinkage to remove time-resolved predictors or interactions that do not influence the outcome.

We provide a comprehensive simulation of our proposed methods. The simulation demonstrates that our method identifies critical windows in DLMs more precisely than competing methods, accurately estimates the exposure-time-response function accounting for multiple time-resolved exposures and interactions, and performs exposure variable selection. We apply our models to a Colorado-based administrative birth cohort. This analysis investigates changes to birth weight associated with five environmental exposures measured weekly during gestation. We find critical windows for several exposures and an interaction between two
exposures that alludes to a priming effect. Software for the implementation and analysis of our methods is made available in the R package dlmtree available at bit.ly/dlmtree

2 Colorado Birth Cohort Data

We analyze birth weight for gestational age z-score, BWGAZ, using birth vital statistics records from Colorado, USA. BWGAZ is the birth weight adjusted for gestational age and fetal sex using a standard reference table (Fenton and Kim, 2013). The data includes all births from Colorado with estimated conception dates between 2007 and 2015, inclusive. We limit the analysis to the Denver metropolitan area, including the counties Adams, Arapahoe, Broomfield, Denver, Douglas, and Jefferson. Besides birth outcomes, the data includes individual covariate information including mother’s age, weight, height, income, education, marital status, prenatal care habits, smoking habits before and during pregnancy, as well as race and Hispanic designations. Demographic breakdowns are described in Supplemental Section 1.

We are interested in the association between birth weight and a mother’s weekly exposure to particulate matter smaller than 2.5 microns in diameter (PM$_{2.5}$), nitrogen dioxide (NO$_2$), sulfur dioxide (SO$_2$), carbon monoxide (CO), and temperature. PM$_{2.5}$ data was obtained from US Environmental Protection Agency (EPA) CMAQ models. Other exposure measurements came from all available US EPA monitors in the study area. Daily exposure measurements were assigned to each census track based on inverse distance weighting. We then created weekly average exposures for each pregnancy based on the date of conception and census tract of residence. The weekly average PM$_{2.5}$ data was log-transformed to reduce skew. We limited our analysis to singleton, full-term births (≥ 37 weeks) and observations with complete covariate and exposure data, resulting in 195,701 births. This study was approved by the Institutional Review Board of Colorado State University.

3 Model

3.1 Distributed lag mixture models

The single exposure DLM involves estimating the effects of a time-resolved vector of exposures from an individual pollutant on a scalar health endpoint. For a sample $i = 1, \ldots, n$, let $y_i$ denote a continuous response, $x_i = [x_{i1}, \ldots, x_{iT}]'$ represent a vector of exposure
measurements taken at equally spaced times \( t \in \{1, \ldots, T\} \), and \( z_i \) represent a vector of covariates including model intercept. The single exposure DLM is written

\[
y_i = \sum_{t=1}^{T} x_{it} \theta_t + z_i' \gamma + \epsilon_i. \tag{1}
\]

In (1), \( \theta_t \) is the linear effect of exposure at time \( t \); \( \gamma \) is a vector of regression coefficients; and \( \epsilon_i \) represents independent errors distributed \( \mathcal{N}(0, \sigma^2) \).

We consider a model involving \( M \) exposures. Let \( x_{im} = [x_{im1}, \ldots, x_{imT}]' \) represent the vector of measurements for exposure \( m \) corresponding to individual \( i \). A DLMM with pairwise interactions can be written

\[
y_i = \sum_{m=1}^{M} \sum_{t=1}^{T} x_{imt} \theta_{mt} + \sum_{m_1=1}^{M} \sum_{m_2=m_1}^{M} \sum_{t_1=1}^{T} \sum_{t_2=1}^{T} x_{im_1 t_1} x_{im_2 t_2} \theta_{m_1 m_2 t_1 t_2} + z_i' \gamma + \epsilon_i. \tag{2}
\]

Here, \( \theta_{mt} \) is the main effect of exposure to pollutant \( m \) at time \( t \). Interactions are considered at every time combination \( t_1 \) for exposure \( m_1 \) with \( t_2 \) for exposure \( m_2 \) and parameterized by \( \theta_{m_1 m_2 t_1 t_2} \). This includes interactions within the same exposure. Within-exposure interactions at \( t_1 = t_2 \) represents a quadratic main effect. In total, the DLMM requires \( MT + \binom{M+1}{2} T^2 \) parameters, which quickly becomes a ‘large-\( p \)’ problem as the number of exposures grows.

For example, the DLMM in our data analysis involving 5 exposures and 37 time points requires estimating 20,720 parameters.

### 3.2 Treed DLM

We first introduce our proposed method of estimating a DLM for a single exposure with no interactions. In our treed distributed lag model (TDLM), we construct binary trees that partition the entire exposure time span, \( T \), into non-overlapping segments. For a single binary tree, \( \mathcal{T} \), the time partition is encapsulated in a set of \( B \) terminal nodes, denoted \( \eta_b \) for \( b \in \{1, \ldots, B\} \). We estimate the linear relationship, denoted \( \delta_b \), between exposures in each terminal node, \( \eta_b \), and the outcome. The distributed lag effects are, therefore, defined by the terminal nodes and node specific effects as

\[
\theta_t = \delta_b \text{ if } t \in \eta_b. \tag{3}
\]
This represents a piecewise constant DLM such that all times within the same terminal node have the same effect on the outcome.

By keeping the number of terminal nodes small, TDLM introduces a necessary constraint on the distributed lag function to account for temporal correlation by assuming that the effect of exposures within the same terminal node are equal. The piecewise constant nature of this framework also allows for sharp changes in effect estimates across times. For two adjacent exposure times that reside in different terminal nodes the effect estimates can quickly change in magnitude or sign.

We employ an ensemble of $A$ additive trees. Each tree contributes a partial estimate of the DLM. This can allow for smoothness in the DLM as each tree may partition the time span of exposure differently. For tree $T_a$, $a \in \{1, \ldots, A\}$, denote the terminal nodes as $\{\eta_{ab}\}_{b=1}^{B_a}$ with corresponding effects $\{\delta_{ab}\}_{b=1}^{B_a}$. The distributed lag effects are

$$\theta_t = \sum_{a=1}^{A} \sum_{b=1}^{B_a} \delta_{ab} I(t \in \eta_{ab}) \quad (4)$$

where $I(\cdot)$ is the indicator function.

### 3.3 Treed DLMM

The treed distributed lag mixtures model (TDLMM) extends TDLM to multiple time-resolved predictors by using pairs of trees. Each of the trees in a pair partitions a single exposure using a binary tree as described in Section 3.2. The exposures partitioned by a pair may be two different exposures or the same exposure twice. Both the structures of the trees and the exposures that the trees partition are stochastic in our proposed model.

A key feature of the tree pairs is that they parameterize both main effects of each exposure in the pair and interactions between the two exposures. The interactions are structured based on the time partitions of each tree. Exposures in each time-segment of the first tree are interacted with exposures in each time-segment of the second tree. In the case both trees partition the same exposure, we are able to estimate within-exposure interactions as well as potential non-linear effects via quadratic terms created by same-time interactions. A diagram representing the structured regression trees and interaction surface is shown in Figure 1.
Figure 1: Diagram of structured regression trees. Binary tree structures partition the time period for an individual exposure and each terminal node $\eta_{ab}$ corresponds to an estimated effect $\delta_{ab}$ (dashed line). The interaction surface depicts how the tree structures intersect; the intersection of terminal nodes $\eta_{a_1b_1}$ and $\eta_{a_2b_2}$ has corresponding effect $\delta_{a_1b_1a_2b_2}$ (shading).

In TDLMM we use an ensemble of $A$ tree pairs. The ensemble allows for different pairs of exposures to be included in the model, which correspond to the main effects and interactions that may be present. Consider tree-pair $\{T_{a_1}, T_{a_2}\}$ with sets of terminal nodes $\{\eta_{a_1b}\}_{b=1}^{B_{a_1}}$ and $\{\eta_{a_2b}\}_{b=1}^{B_{a_2}}$, respectively. Let $S_{a_1} = m$ if exposure $m$ is partitioned by tree $T_{a_1}$. Similarly $S_{a_2} = m$ if exposure $m$ is partitioned by tree $T_{a_2}$. The main effect of exposure $m$ at time $t$ is

$$\theta_{mt} = \sum_{a=1}^{A} \sum_{b_1=1}^{B_{a_1}} \delta_{a_1b_1} \mathbb{I}(S_{a_1} = m, t \in \eta_{a_1b_1}) + \sum_{b_2=1}^{B_{a_2}} \delta_{a_2b_2} \mathbb{I}(S_{a_2} = m, t \in \eta_{a_2b_2})$$  \hspace{1cm} (5)$$

and the interaction between exposure $m_1$ and $m_2$ at times $t_1$ and $t_2$ is

$$\theta_{m_1m_2t_1t_2} = \sum_{a=1}^{A} \sum_{b_1=1}^{B_{a_1}} \sum_{b_2=1}^{B_{a_2}} \delta_{a_1b_1a_2b_2} \mathbb{I}(S_{a_1} = m_1, S_{a_2} = m_2, t_1 \in \eta_{a_1b_1}, t_2 \in \eta_{a_2b_2})$$  \hspace{1cm} (6)$$

The main effects for terminal nodes $\eta_{a_1b_1}$ and $\eta_{a_2b_2}$ are parameterized by $\delta_{a_1b_1}$ and $\delta_{a_2b_2}$, respectively. The interaction effect between exposures in terminal nodes $\eta_{a_1b_1}$ and $\eta_{a_2b_2}$ is given by $\delta_{a_1b_1a_2b_2}$. This parameterization reduces the $2T$ main effect terms to $B_{a_1} + B_{a_2}$ terms and the $T^2$ interaction terms to $B_{a_1}B_{a_2}$ terms.

TDLMM can be reduced into two simpler models. The first drops within-exposure interaction by fixing these interactions to zero. The second simplification drops all interactions...
which is equivalent to an additive DLM. In the remainder of this paper we refer to these simplifications as TDLMMN (no-self interactions) and TDLMMadd (additive).

4 Prior Specification and Computation

4.1 TDLM priors and posterior computation

The prior for TDLM consists of two parts: a prior on trees and a prior on the regression parameters conditional on the trees. We apply a normal prior to the regression parameters:

$$\delta_{ab} | \tau_a^2, \nu^2, \sigma^2 \sim \mathcal{N}(0, \tau_a^2 \nu^2 \sigma^2).$$

(7)

Here, $\tau_a \sim \mathcal{C}^+(0,1)$ and $\nu \sim \mathcal{C}^+(0,1)$ define the horseshoe-like estimator on tree-specific effects. The additional tree-specific variance component $\tau_a$ allows for the terminal node effects on poor fitting trees to be shrunk. When shrunk, the trees can more easily reconfigure before regaining larger terminal node effects. In practice, we find including this tree-specific variance results in more precise estimates of the distributed lag function. We specify global prior $\sigma \sim \mathcal{C}^+(0,1)$ and $\gamma \sim \text{MVN}(0, \sigma^2 c \mathbf{I})$, where $c$ is fixed at a large value.

The stochastic tree generating process follows Chipman et al. (1998) with adjustments to account for the multivariate nature of each tree’s terminal node effects. The probability a tree splits at node $\eta$ with depth $d_\eta$ equals $p_{\text{split}}(\eta) = \alpha(1 + d_\eta)^{-\beta}$, where hyperpriors $\alpha \in (0,1)$ and $\beta \geq 0$. BART models often utilize four possible tree updates: grow, prune, change and swap. We consider tree structures that split on time only and drop the swap step, which always results in empty terminal nodes. Other deviations from BART include that each exposure observation is contained in multiple terminal nodes and that the model must account for parametric control of confounding variables $z$. To adapt our MCMC algorithm for these changes, we integrate out $\gamma$ and apply Bayesian backfitting to simultaneously estimate node-specific regression parameters. Details in Supplemental Section 2.

4.2 TDLMM priors and posterior computation

For TDLMM with multiple predictors and tree pairs the prior involves three components. The first two, a prior on trees and prior on node specific effects are similar to those used in TDLM. The third, and new, component is the prior on which exposure is divided by each tree. One goal of TDLMM is to shrink or remove exposure and interaction effects that are
uncorrelated with the response. We employ two approaches to do this. First, we add a prior on node specific effects that allows for effects of unique exposures and interactions to be shrunk. Second, we introduce a prior to encourage selection of exposures that are associated with the outcome while excluding other exposures from all trees in the model.

In TDLMM each of the trees in tree-pair \( a \) is defined by a tree structure \( T_a, i \in \{1, 2\} \), and an exposure \( S_{a_i} \) that the tree structure is applied to. The prior on \( T_{a_i} \) is the same as described in Section 4.1 The prior distribution on exposure \( S_{a_i} \) is

\[
S_{a_i | E} \sim \text{Categorical}(E) \quad (8)
\]

\[
E \sim \text{Dirichlet}(\kappa, \ldots, \kappa). \quad (9)
\]

Here, \( E = \{E_m\}_{m=1}^M \), where \( E_m \) is the probability that a tree splits on exposure \( m \) and \( \kappa \) is a hyperprior that controls the sparsity of exposures. This prior is motivated by Linero (2018) but differs in that we select an exposure for the entire tree, while the former selects a variable to split on at a particular node of a tree. Larger values of \( \kappa \) gives a prior probability that many exposures are included into the model while a small value imposes more sparsity. When \( \kappa \) is small and \( A \) is large, the resulting full conditional can concentrate mass on a single exposure. Hence, some care is required in picking an appropriate value or prior for \( \kappa \). In Supplemental Section 2.4 we describe a Bayes factor approach for exposure selection.

Both \( T_{a_i} \) and \( S_{a_i} \) are updated via MCMC. New proposals for the structure of each tree in a tree-pair are the same as in TDLM. We also introduce a new proposal mechanism that switches the exposure, \( S_{a_i} \), considered by a tree. For each tree, we select with equal probability one of four different proposals: grow, prune, change, and switch-exposure. When switch-exposure is the update step we propose a new exposure \( S'_{a_i} \) from (8). The decision to accept any of the four possible moves is made with the MH algorithm. Alternatively, the exposure, \( S_{a_i} \), can be updated with Gibbs sampler but at a high computational cost.

The node-specific priors described in (7) shrinks tree-specific effects, but would apply the same variance parameters for all exposures. We introduce an alternative variance component pertaining to each specific exposure or pair of two exposures. The prior on the node-specific
effect, $\delta_{ab}$, at terminal node $\eta_{ab}$, which splits exposure $S_a$, is defined as

$$\delta_{ab}|\mu_{S_a}^2, \nu^2, \sigma^2 \sim \mathcal{N}(0, \mu_{S_a}^2 \nu^2 \sigma^2).$$

(10)

The prior for an interaction effect between terminal nodes $\eta_{a_1b_1}$ and $\eta_{a_2b_2}$ that split exposures $S_{a_1}$ and $S_{a_2}$, respectively, is

$$\delta_{a_1b_1a_2b_2}|\mu_{S_{a_1}S_{a_2}}^2, \nu^2, \sigma^2 \sim \mathcal{N}(0, \mu_{S_{a_1}S_{a_2}}^2 \nu^2 \sigma^2).$$

(11)

Here, $\mu_m \sim \mathcal{C}^+(0, 1)$ and $\mu_{m_1m_2} \sim \mathcal{C}^+(0, 1)$ represent the variance components for the main effects of exposure $m$ or the interaction of exposures $m_1$ and $m_2$, respectively. Because the same variance components are used in every tree or tree-pair that estimates the same exposure main or interaction effects, it allows the model to separate the main and interaction effect. Priors on $\gamma, \nu,$ and $\sigma$ are the same as in TDLM. Full details on the computation of TDLMM are given in Supplemental Section 2.

Selection and shrinkage are complementary in TDLMM. Shrinkage balances when there is a main effect but no interaction or vice-versa. Selection removes exposures from the model entirely. Furthermore, variable inclusion is hierarchical in that the interaction is included only when both main effects are included. We compare simulation results with and without the exposure and interaction specific shrinkage parameters in Supplemental Material.

4.3 Marginal DLM Effects

Due to the interactions between exposures in TDLMM, the effects of each exposure are dependent on the levels of the other exposures. To estimate the main effect of each exposure $m$ on the outcome while accounting for co-exposures, we marginalize the DLM at specified levels of all exposures. Fixing the levels of all exposures to be $\tilde{x}_1, \ldots, \tilde{x}_M$, the marginal effect of exposure $m$ at time $t$ is defined as

$$\tilde{\theta}_{mt}(\tilde{x}_1, \ldots, \tilde{x}_M) = \theta_{mt} + \sum_{m'=1}^m \sum_{t'=1}^T \tilde{x}_{m't} \theta_{m'mt} + \sum_{m'=m}^M \sum_{t'=1}^T \tilde{x}_{m't} \theta_{mm't}. \quad (12)$$

Marginalization by integrating out other exposure effects amounts to evaluating (12) at the empirical mean of each exposure. Because the within-exposure interaction represents a possible non-linear effect, this can cause interpretation problems when calculating $\tilde{\theta}_{mt}$ (a
linear effect). In this case, estimating a contrast, such as effect due to an inter-quartile range (IQR) change in exposure, is a more reasonable approach.

4.4 Logistic regression

A common application of DLMs is assessing the change in risk of some binary outcome due to time-resolved measures of exposures. We propose a logistic regression method for TDLM and TDLMM by introducing a Pólya Gamma latent variable [Polson et al. 2013]. Details on computation are available in Supplemental Section 2.6.

4.5 Prior selection

For tree structure priors we follow [Chipman et al. 2010] setting $\alpha = 0.95$ and $\beta = 2$. Altering these priors did not improve performance. For both TDLM and TDLMM we set $A = 20$ trees or tree pairs. To set $\kappa$, we consider the prior inclusion probability of exposure $m$. Let $C_m$ be the count of trees using exposure $m$ where $C_m > 0$ indicates that exposure $m$ is included in the model. For $2A$ trees and $M$ exposures,

$$
\Pr(C_m > 0|y) = 1 - \frac{\Gamma(2A + M\kappa) \cdot \Gamma[(M + 1)\kappa]}{\Gamma[2A + (M + 1)\kappa] \cdot \Gamma(M\kappa)}.
$$

(13)

Setting $\kappa = 1.089$ gives a prior inclusion probability of 0.9.

5 Simulation

We considered two simulation scenarios. The first validated TDLM and compared to established DLM methods. The second evaluated the operating characteristics of TDLMM for a mixture of five exposures. In Supplemental Sections 3.1 and 3.2 we provide additional simulations to justify shrinkage components of our models. All simulations can be reproduced with R package dlmmtree.

5.1 Single exposure and binary outcome

We first considered a binary outcome with a single exposure (PM$_{2.5}$) generated by

$$
y_i|p_i \sim \text{Bernoulli}(p_i)$$

(14)

$$
\logit(p_i) = c_1 + 0.1 \cdot [f_1(x_i) + z_i^T \gamma],
$$

(15)

with simulated DLM effect $f_1(x_i) = \sum_{t=s}^{s+7} x_{it}$. This defines a DLM such that $\theta_t = 0.1$ from times $s$ to $s+7$ and zero otherwise. Starting time $s$ was drawn uniformly from $\{1, \ldots, T-7\}$. 

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We set $c_1$ for each simulation replicate such that the mean of $p_i$ is approximately 0.5 or 0.05. In Supplemental Section 3.3 we replicated this simulation using a smooth DLM effect.

We simulated 100 data sets of sample size $n = 5,000$. For each data set we sampled exposure observations from the cohort described in Section 2 with lengths $T = 37$, and centered and scaled all exposure data. We also generated ten covariates (five standard normal, five binomial with probability 0.5) and corresponding regression coefficients from standard normal.

In this scenario, we compared single exposure models TDLM to penalized spline DLM (Zanobetti et al., 2000; Gasparrini et al., 2017) with cubic regression splines and the critical window variable selection (CWVS) method (Warren et al., 2020). In addition, we compared to TDLMM with all 5 exposures from our data analysis. For TDLMM, we included time-resolved measurements of four additional exposures that were not included in any other model and have no effect on the outcome in this design. Using the multi-exposure model in a single exposure setting explored the loss of efficiency that results when only one of five correlated predictors affects the outcome. The results for CWVS are based on the DLM estimation when a critical window is identified (DLM|cw) and when the probability of a critical window is greater than 0.5 ($\Pr(\text{cw}) > 0.5$), as described by Warren et al. (2020). MCMC chains were run for 10,000 iterations after a burn-in period of 5,000 and thinned to every 5th iteration.

The objective of our method is to estimate the distributed lag effect and identify critical windows. We therefore focus our simulation on estimation of these quantities rather than predictive performance, which is the focus of many BART models.

Results from scenario one are given in Table 1. We calculated the marginal DLM RMSE $= \sqrt{\sum_{t=1}^{37} (\hat{\theta}_t - \hat{\theta}_t)^2 / 37}$ and coverage based on the estimated marginal distributed lag effect, $\hat{\theta}_t$. For TDLMM we calculated RMSE and coverage of PM$_{2.5}$ only. We also evaluated the probability that a model detects a true critical window (TP) or places a critical window where the true effect is zero (FP). For TDLMM, FP considered the marginal effects of all exposures. Finally, we evaluated precision of critical window identification, calculated $\text{TP}/(\text{TP} + \text{FP})$.

The tree-based methods were the most accurate in estimating the distributed lag function; they had lowest RMSE and maintained near 95% coverage. The penalized DLM had low RMSE, but poor coverage due to the wiggliness of splines, which also resulted in misclas-
Table 1: Results for simulation scenario one: binary outcome with single exposure DLM effect. The DLM estimation refers to estimation of the active exposure effect only. Effect identification indicates when the DLM 95% CI does not contain zero at correct (TP) or incorrect (FP) time periods and Precision = TP/(TP + FP).

| Model          | DLM Est. | Critical Windows |
|----------------|----------|------------------|
|                | RMSE*    | Cov. | TP     | FP     | Prec.   |
| $\bar{p} = 0.5$ |          |      |        |        |         |
| CWVS: dlm|cw     | 2.10  | 0.97   | 0.99   | 0.03   | 0.97   |
| CWVS: p>0.5   | 2.10     | 0.97   | 0.99   | 0.07   | 0.93   |
| DLMcr          | 1.83     | 0.77   | 1.00   | 0.17   | 0.85   |
| TDLM           | 1.22     | 0.98   | 0.98   | 0.01   | 0.99   |
| TDLMMadd       | 1.31     | 0.97   | 0.99   | 0.02   | 0.98   |
| TDLMMns        | 1.47     | 0.96   | 1.00   | 0.03   | 0.97   |
| TDLMM          | 1.39     | 0.96   | 0.99   | 0.03   | 0.97   |
| $\bar{p} = 0.05$ |         |      |        |        |         |
| CWVS: dlm|cw     | 3.36  | 0.99   | 0.72   | 0.02   | 0.97   |
| CWVS: p>0.5   | 3.36     | 0.99   | 0.94   | 0.11   | 0.90   |
| DLMcr          | 2.64     | 0.72   | 1.00   | 0.21   | 0.83   |
| TDLM           | 2.19     | 0.96   | 0.88   | 0.02   | 0.98   |
| TDLMMadd       | 2.39     | 0.93   | 0.91   | 0.03   | 0.97   |
| TDLMMns        | 2.49     | 0.93   | 0.88   | 0.04   | 0.96   |
| TDLMM          | 2.59     | 0.91   | 0.83   | 0.04   | 0.95   |

*RMSE $\times$ 100
sification of critical windows. The CWVS model maintained high coverage of the distributed lag function, but was not as accurate in estimating the effects as evidenced by RMSE.

In both $\overline{p}$ settings, the mixture models outperformed the single exposure spline-based DLM and CWVS models in terms of RMSE while maintaining near nominal coverage. These are important findings because the cost of including additional exposures into the treed models is minimal in terms of distributed lag function estimation. In TDLMMns when $\overline{p} = 0.5$ the posterior inclusion probability of PM$_{2.5}$ was 1. This decreased slightly (0.89) when $\overline{p} = 0.05$. For other exposures, the posterior inclusion probability was $< 0.01$ in both $\overline{p}$ settings.

Comparing models in terms of critical window detection, TDLM, TDLMM, and CWVS: dlm|cw were the most precise models at identifying critical windows. In the more difficult $\overline{p} = 0.05$ setting, the increased complexity of TDLMM was associated with a slight decrease in TP, but the method retained high precision due to the very low FP rate. CWVS: $p > 0.5$ had higher TP at the cost of higher FP. Spline methods were less precise with higher FP.

Results from the supplemental simulation with a smooth distributed lag function were similar and are presented in Supplemental Section 3.3. In both the current and smooth simulations, TDLM and TDLMM had lower RMSE, closer to nominal coverage, and higher precision in identifying critical windows compared to the spline estimator.

5.2 Multiple exposures and a continuous outcome

We considered a continuous response with an exposure main effect from PM$_{2.5}$ and an interaction effect between PM$_{2.5}$ and NO$_2$. The outcome was generated as

$$y_i = c_2 f_2(x_{i1}, x_{i2}) + z_i^T \gamma + \epsilon$$

(16)

where $c_2$ is a scalar such that the variance of $c_2 f_2$ equals one. The simulated effect was

$$f_2(x_{i1}, x_{i2}) = \sum_{t=s_1}^{s_1+7} x_{i1t} + 0.025 \sum_{t_1=s_1}^{s_1+7} \sum_{t_2=s_2}^{s_2+7} x_{i1t_1} x_{i2t_2}$$

(17)

for starting times $s_1$ and $s_2$ each drawn uniformly from $\{1, \ldots, T-7\}$. This scenario consists of a main effect with a critical window of length eight for the PM$_{2.5}$ exposure and an interaction effect between exposure to PM$_{2.5}$ at times $s_1$ to $s_1 + 7$ and NO$_2$ at times $s_2$ to $s_2 + 7$. 

Table 2: Results for simulation scenario two: main effect of PM$_{2.5}$ with PM$_{2.5}$–NO$_2$ interaction. Estimated marginal distributed lag effects of PM$_{2.5}$ and NO$_2$ were compared to the true simulated marginal effects for RMSE and coverage. Critical window detection was summarized by the probability that the DLM 95% CI does not include zero at a correct (TP) or incorrect (FP) time period.

| Model       | RMSE$^*$ | Coverage | TP       | FP       | Other |
|-------------|----------|----------|----------|----------|-------|
|             | PM  | NO$_2$ | PM  | NO$_2$ | PM  | NO$_2$ | Other |
| $\sigma^2 = 25$ |     |         |       |         |       |       |       |
| TDLMadd     | 3.59 | 4.19   | 0.95  | 0.84   | 0.94 | 0.82  | 0.03  | 0.07 | 0.00 |
| TDLMMns     | 3.57 | 4.27   | 0.97  | 0.96   | 0.91 | 0.63  | 0.02  | 0.03 | 0.00 |
| TDLM        | 3.55 | 4.33   | 0.98  | 0.97   | 0.87 | 0.51  | 0.01  | 0.02 | 0.00 |
| $\sigma^2 = 50$ |     |         |       |         |       |       |       |       |
| TDLMadd     | 4.62 | 4.64   | 0.92  | 0.83   | 0.86 | 0.52  | 0.04  | 0.05 | 0.00 |
| TDLMMns     | 4.61 | 4.75   | 0.96  | 0.97   | 0.76 | 0.31  | 0.02  | 0.02 | 0.00 |
| TDLM        | 4.50 | 4.79   | 0.97  | 0.97   | 0.62 | 0.22  | 0.01  | 0.01 | 0.00 |
| $\sigma^2 = 100$ |    |         |       |         |       |       |       |       |
| TDLMadd     | 5.75 | 5.07   | 0.89  | 0.84   | 0.47 | 0.22  | 0.03  | 0.03 | 0.00 |
| TDLMMns     | 5.85 | 5.21   | 0.93  | 0.95   | 0.29 | 0.10  | 0.02  | 0.01 | 0.00 |
| TDLM        | 5.73 | 5.21   | 0.94  | 0.96   | 0.24 | 0.05  | 0.01  | 0.01 | 0.00 |

$^*$RMSE $\times$ 100

We drew $\epsilon$ independently for each observation from $\mathcal{N}(0, \sigma^2)$ such that $\sigma^2 \in \{25, 50, 100\}$. In this scenario, we compared TDLMM, TDLMMns (no-self interactions) and TDLMMadd (additive DLMs) using all exposure measurements from our data analysis. No other methods are currently available that would offer a direct comparison.

Table 2 compares the marginal DLM RMSE and coverage for active exposures PM$_{2.5}$ and NO$_2$. As in scenario one, we describe TP and FP for critical window detection. We found that all variants of TDLMM had low RMSE for estimating the marginalized effects of PM$_{2.5}$ and NO$_2$. The additive model had below nominal coverage for the marginal effect of NO$_2$ due to lack of appropriate interaction terms. We found that TDLMMns had higher power than full TDLMM. Additive TDLMM had the highest TP rate, but increased FP for NO$_2$. All TDLMM variants show zero FP for nonactive exposures. Overall, the tree-based DLMMs had high precision for identifying critical windows.

Table 3 summarizes exposure and interaction posterior inclusion probabilities averaged across simulation replicates. For the correct exposures, all variants of TDLMM had posterior
Table 3: Exposure and interaction posterior inclusion probabilities. This describes the probability at least one tree or tree-pair in the ensemble estimates the effects for a specific exposure or interaction, respectively. Nonactive exposures or interactions are summarized together as ‘Other’.

| Model       | Posterior Inclusion |          |          |          |          |
|-------------|---------------------|----------|----------|----------|----------|
|             | Main Effect         | Interaction |         |          |          |
|              | PM      | NO₂     | Other    | PM–NO₂  | Other    |
| σ² = 25     |          |          |          |          |          |
| TDLMMadd    | 1.00    | 1.00    | 0.78     | -        | -        |
| TDLMMns     | 1.00    | 1.00    | 0.17     | 0.94     | 0.06     |
| TDLMM       | 1.00    | 0.99    | 0.39     | 0.85     | 0.22     |
| σ² = 50     |          |          |          |          |          |
| TDLMMadd    | 1.00    | 0.99    | 0.82     | -        | -        |
| TDLMMns     | 0.99    | 0.95    | 0.26     | 0.83     | 0.10     |
| TDLMM       | 0.99    | 0.96    | 0.43     | 0.80     | 0.23     |
| σ² = 100    |          |          |          |          |          |
| TDLMMadd    | 0.98    | 0.96    | 0.85     | -        | -        |
| TDLMMns     | 0.88    | 0.81    | 0.38     | 0.61     | 0.15     |
| TDLMM       | 0.89    | 0.85    | 0.52     | 0.58     | 0.25     |

Inclusion probability above the prior inclusion probability (0.9) in low and medium noise settings. For nonactive exposures, the posterior inclusion probability was below that of the correct exposures. The differences were less pronounced in TDLMMadd. Posterior inclusion probabilities for the correct interaction were consistently higher than for other interactions.

6 Analysis of Colorado Birth Cohort Data

We applied TDLMM to BWGAZ for our Denver, CO metro area dataset. The analysis included five exposures and covariates described in Section 2 with $T = 37$ weeks of exposure measurements corresponding to the first 37 weeks of gestation. In addition, our analysis controlled for year and month of conception, census tract elevation, and a county-specific intercept. TDLMM used the prior specification described in Section 4.3. The model ran for 100,000 iterations after 10,000 burn-in and was thinned to every 5th iteration. For this analysis, we used TDLMMns for ease of interpretation of the linear effects. We compared to TDLMM and found few differences (see Supplemental Section 4.2).
6.1 Exposure and interaction selection

Four exposures had posterior inclusion probabilities above the prior inclusion probability (0.9): PM$_{2.5}$ (> 0.99), SO$_2$ (> 0.99), CO (0.989), and temperature (> 0.99). NO$_2$ was included into the model at a much lower rate (0.428). The posterior inclusion probability for the PM$_{2.5}$−temperature interaction was 0.988. The next highest posterior inclusion probabilities for interactions were CO−temperature (0.69) and SO$_2$−CO (0.6). The seven remaining interactions had posterior inclusion probabilities below 0.5.

6.2 Marginal exposure associations with BWGAZ

The top row of Figure 2 shows the estimated marginal distributed lag function of each exposure with other exposures fixed to their empirical means. The results identify critical windows to PM$_{2.5}$ during weeks 6–34, SO$_2$ during weeks 10–29, CO during weeks 9–11 and temperature across the entire pregnancy. The critical windows show that increased exposure is associated with decreased BWGAZ.

Figure 2: Posterior mean distributed lag distributed lag function (black line) for each exposure (columns) with 95% credible interval (grey area) of the effect. The top row shows the estimated marginal effect for an IQR increase in exposure, holding other exposures at their empirical mean. The bottom row shows the estimated change in BWGAZ for a first to third quartile change in one exposure along with the expected changes in all other exposures due to correlation with the exposure of interest.
TDLMM allows us to estimate interactions between time-resolved predictors. Figure 3(a) shows the presence of an interaction between log PM$_{2.5}$ and temperature. This interaction indicates that elevated exposure to PM$_{2.5}$ during weeks 15 – 25 results in an increase in the magnitude of the temperature effect during weeks 19 – 35. These interactions occur at the same times (e.g. weeks 19 – 25) as well as at different times (e.g. log PM$_{2.5}$ in week 20 and temperature in week 30) and hint at the idea of priming, where an early exposure may increase susceptibility to a later exposure. Figure 3(b) shows the marginal distributed lag functions for PM$_{2.5}$ and temperature at varying percentiles of co-exposures. We see a larger effect of PM$_{2.5}$ and changes in critical windows when temperature and other exposures are fixed at a higher percentile. The effect of temperature also shows changes in the magnitude and timing of critical windows at increased levels of other exposures. Additional interaction plots are included in Supplemental Section 4.1 and show no evidence of meaningful interactions.

6.3 Accounting for changes in co-exposures

Due to high correlation among exposures in our analysis (ranging from −0.55 to 0.69 at the same week), a change in any one exposure will likely be accompanied by simultaneous changes in co-exposures. This suggests that the marginal results in Section 6.2, which assumes that co-exposures are held at their empirical means, should only be interpreted in a narrow range. As an alternative, we estimate distributed lag functions that account for simultaneous changes in co-exposures. This provides another way to look at the results from the same model.

Let $x_{m(q)}$ represent the $q^{th}$ quantile of the empirical distribution of exposure $m$. The expected change in the outcome for an IQR change in exposure $m$ at time $t$, conditional on the expected co-occurring changes in all other exposures can be written

$$E \left[ Y \bigg| \tilde{X}_t = E \left\{ X_t \bigg| x_{mt} = x_m(0.75) \right\}, \tilde{X}_{[t]} = \bar{x}, z = z_0 \right] - E \left[ Y \bigg| \tilde{X}_t = E \left\{ X_t \bigg| x_{mt} = x_m(0.25) \right\}, \tilde{X}_{[t]} = \bar{x}, z = z_0 \right].$$

Here, $\tilde{X}_t = \{ \tilde{x}_{1t}, \ldots, \tilde{x}_{Mt} \}$ defines the values of all exposures at time $t$ while $\tilde{X}_{[t]}$ is the collection of exposure measurements at all time points except $t$. We set each element of
(a) PM$_{2.5}$–temperature interaction surface.  
(b) Marginal DLMs showing interaction.

Figure 3: Panel (a) shows the estimated PM$_{2.5}$–temperature interaction effects. The color of each cell indicates the sign and direction of the interaction effect between PM$_{2.5}$ at one time and temperature at another time. The points indicate estimated interactions where the credible interval does not contain zero and the point size represents the credible interval probability. Panel (b) shows the estimated marginal distributed lag function for an IQR increase in the indicated exposure, when all other exposures are fixed at a given percentile (color of lines) of their empirical distributions. Points on each line indicate where the 95% credible interval of the marginal effect does not include zero.

\[ \tilde{X}_{\{q\}} \] equal to the empirical mean for that exposure to isolate the effect only at the time of interest. The value of \( z \) does not does not influence the expected change because it does not interact with exposure measurements. To determine the values of co-exposures at time \( t \), given by \( \mathbb{E}[X_t | x_{mt} = x_{m(q)}] \), we fit penalized spline models (cubic splines with 5 degrees of freedom) between pairs of exposures, estimated using restricted maximum likelihood as described by Wood (2017). Specifically, we considered measurements for exposure \( m \) as the only predictor and fit separate models for each co-exposure (e.g. log PM$_{2.5}$ was used as the predictor for NO$_2$, SO$_2$, CO, and temperature in four separate models). Using the model fits, we predicted all co-exposures at the 25$^{th}$ and 75$^{th}$ percentiles of exposure \( m \). This process was repeated for every \( m \in \{1, \ldots, 5\} \).

The results of this analysis adjusting for changes in co-exposures is shown in the bottom
row of Figure 2. This can be interpreted as the expected change in BWGAZ associated with an IQR change in one pollutant and the expected change in the four other co-exposures at the same time point. Several important takeaways are provided by this analysis technique. First, the shape of estimated distributed lag functions are similar. Second, the confidence intervals take into account the uncertainty in the estimated main effects and interactions of co-exposures. That uncertainty is not included in the estimates presented in the top row of Figure 2 because the level of co-exposures remain fixed. Third, the associations between BWGAZ and exposure to PM$_{2.5}$, SO$_2$ and temperature are persistent after accounting for expected changes in co-exposures.

A change in PM$_{2.5}$ from the 25th to 75th percentile of exposure is an increase from 6.12 to 8.67 µg/m$^3$. Considering the association between PM$_{2.5}$ and BWGAZ after adjusting for co-exposures finds a critical window during weeks 6–33, which is similar to the critical windows found in the marginal distributed lag function. The cumulative effect of PM$_{2.5}$, or the effect of a simultaneous IQR increase in every week of pregnancy, adjusting for co-exposures is associated with an average change in BWGAZ of $-0.064$ (95% CI: $[-0.094, -0.035]$). The cumulative effect of an IQR increase in SO$_2$ (0.94 to 1.90 ppb) is associated with a change in BWGAZ of $-0.049$ (95% CI: $[-0.076, -0.019]$), with a critical window during weeks 9–25.

In terms of birth weight, an IQR increase in PM$_{2.5}$ adjusting for changes in co-exposures amounts to an approximate change of $-27.7$g (95% CI: $[-40.8, -15.0]$). This is approximate because BWGAZ is adjusted for gestational age and sex. An IQR increase in SO$_2$ adjusting for co-exposures corresponds to an approximate change in birth weight of $-20.7$g (95% CI: $[-34.1, -5.9]$).

Our findings of an inverse relationship between PM$_{2.5}$ and birth weight are consistent with a meta-analysis done by Stieb et al. (2012). Similar findings exist for a relationship between SO$_2$ and birth weight (Dugandzic et al., 2006), but are less consistent (Stieb et al., 2012). We note that the majority of comparison studies do not account for effects of co-occurring exposures or interactions over time and no previous study has considered time-resolved measures of five exposures including interactions.
7 Discussion

In this work we propose TDLMM to estimate the association between mixtures of environmental exposures observed at high-temporal resolution on birth and children’s health outcomes. TDLMM, and the reduced version TDLM for a single time-resolved predictor, have several innovative statistical features. The models introduce structured regression trees that account for temporal correlation in the predictors. The mixtures approach, TDLMM, uses an ensemble of tree pairs that parameterize both main effects and pairwise interactions between time-resolved predictors. The MCMC approach for our Bayesian tree ensemble methods includes a new switch-exposure step that allows for exposures not associated with the outcome to be removed from the model.

In a simulation study we demonstrated that our single exposure tree-based DLM outperformed established methods for estimating the DLM in terms of estimation of the exposure-response function and precision in identifying critical windows. Moreover, our tree-based mixture approach, TDLMM, that included additional exposures not associated with the outcome also outperformed the established single exposure methods in the single exposure setting. This is in large part due to the methods’ ability to select out or shrink the effects of exposures that are not associated with the outcome. Using real exposure data, TDLMM identifies critical windows, selects the proper exposures, and estimates the exposure-response function in a simulation scenario with five time-resolved predictors.

We applied TDLMM to analyze associations between Denver, CO area birth weight and five environmental exposures experienced weekly by mothers during gestation. This data set included 195,701 full term births with estimated conception dates from 2007 through 2015. This data analysis to estimate the main and interaction effects due to a mixture of five environmental exposures observed weekly during the first 37 weeks of gestation produced several key takeaways. We identified PM$_{2.5}$, SO$_2$ and temperature effects based on the effect of one exposure conditional on fixed co-exposures and based on a change in one exposure accounting for simultaneous changes in co-exposures. In addition, we found substantial evidence of an interaction between PM$_{2.5}$ and temperature.

Our analysis of five pollutants observed weekly throughout pregnancy and birth weight is the first analysis to identify critical windows to a mixture observed at high-temporal...
resolution within a distributed lag mixture model framework. Previous studies have either estimated critical windows for a mixture observed at high temporal resolution in an additive DLM setting (Figueroa-Romero et al. 2020; Horton et al. 2018) or to a mixture observed at one or a small number of time points (Levin-Schwartz et al. 2019; Chiu et al. 2018; Valeri et al. 2017). Given the sequential nature of fetal development, where changes occur over varying time scales ranging from many months down to a few days, data driven methods that allow for high resolution and precision in identifying critical windows due to environmental mixtures have the potential to open doors to discovery and understanding in biological science (Wright 2017). As the size and resolution of the exposure data available continues to grow, our method fills a critical research gap in statistical methods for epidemiology and environmental health in being able to estimate the effects of time-resolved measures of a mixture on a continuous or binary health outcome.

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Supplementary Materials

Supplemental Sections 1 through 4 are made available to the reader online.

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