

CVtreeMLE: Efficient Estimation of Mixed Exposures using Data Adaptive Decision Trees and Cross-Validated Targeted Maximum Likelihood Estimation in R

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Summary

Statistical causal inference of mixed exposures has been limited by reliance on parametric models and, in most cases, by researchers considering only one exposure at a time, usually estimated as a beta coefficient in a regression model (glm). This independent assessment of exposures poorly estimates the joint impact of a collection of exposures in a realistic exposure setting. Non-parametric methods such as decision trees are a useful tool to evaluate combined exposures by finding partitions in the mixture space that best explain the variance in an outcome. However, current methods using decision trees to assess statistical inference for interactions are biased and are prone to overfitting by using the full data to both identify nodes in the tree and make statistical inference given these nodes. The CVtreeMLE R package provides researchers in (bio)statistics, epidemiology, and environmental health sciences with access to state-of-the-art statistical methodology for evaluating the causal effects of a mixed exposure using decision trees. CVtreeMLE builds off the general theorem of cross-validated minimum loss-based estimation (CV-TMLE) which allows for the full utilization of loss-based ensemble machine learning to obtain the initial estimators needed for our target parameter without risk of overfitting. Additionally, CVtreeMLE uses V-fold cross-validation and partitions the full data in each fold into a parameter-generating sample and an estimation sample. Decision trees are applied to a mixed exposure to obtain rules and estimators for our statistical target parameter using the parameter-generating sample. The rules from decision trees are then applied to the estimation sample where the statistical target parameter is estimated. CVtreeMLE makes possible the non-parametric estimation of the causal effects of a mixed exposure producing results that are both interpretable and asymptotically efficient.

Statement of Need

In many disciplines there is a demonstrable need to ascertain the causal effects of a mixed exposure. Advancement in the area of mixed exposures is challenged by real-world joint exposure scenarios where complex agonistic or antagonistic relationships between mixture components can occur. More flexible methods which can fit these interactions are less biased, but results are difficult to interpret which leads many researchers to use more biased methods based on glms. Current software tools for mixtures show minimal performance tests using data that reflect the complexities of real-world exposures. In many instances, new methods are not tested against ground-truth target parameter under various mixture conditions. New areas of statistical research, rooted in non/semi-parametric efficiency theory for statistical functionals, allow for robust estimation of data-adaptive parameters. That is, it is possible to use the data to both define and estimate a target parameter. This is important in mixtures when the most

important set of variables and levels in these variables is unknown and therefore, statistical inference given exposure to these variables are unknown. Thus, the development of asymptotically linear estimators for data-adaptive parameters are critical for the field of mixed exposure statistics. However, the development of open-source software which translates semiparametric statistical theory into well-documented functional software is a formidable challenge. Such implementation requires understanding of causal inference, semiparametric statistical theory, machine learning, and the intersection of these disciplines. The CVtreeMLE R package provides researchers with an open-source tool for evaluating the causal effects of a mixed exposure by treating decision trees as a data-adaptive target parameter to define exposure. The CVtreeMLE package is well documented and includes a vignette detailing semi-parametric theory for data-adaptive parameters, examples of output, results with interpretations under various real-life mixture scenarios, and comparison to existing methods.

Background

In most research scenarios, the analyst is interested in causal inference for an *a priori* specified treatment or exposure. However, in the evaluation of a mixed exposure, such as air pollution or pesticides, it is not possible to estimate the expected outcome given every combination of exposures due to non-identification, violations of the assumption of positivity, and inefficiency. Even still, this approach lacks a pre-specified target parameter. In such a setting, it is helpful to map a set of continuous mixture components into a lower dimensional exposure using a pre-determined algorithm to estimate a target parameter that has easier interpretation. Decision trees provide a useful solution by mapping a set of exposures into a rule which can be represented as a binary vector. This binary vector indicates whether an individual has been exposed to a particular rule estimated by the decision tree. Our target parameter is then defined as the mean difference in counterfactual outcomes for those exposed to the mixture rule compared to those unexposed, or the average treatment effect for the mixture.

CVtreeMLE's Scope

Building on prior work related to data-adaptive parameters (Hubbard et al., 2016) and CV-TMLE (Zheng & Laan, 2010), CVtreeMLE is a novel approach for estimating the joint impact of a mixed exposure by using cross-validated targeted minimum loss-based estimation which guarantees consistency, efficiency, and multiple robustness despite using highly flexible learners to estimate a data-adaptive parameter. CVtreeMLE summarizes the effect of a joint exposure on the outcome of interest by first doing an iterative backfitting procedure, similar to general additive models, by fitting two discrete Super Learning (SL) algorithms, an unrestricted SL for $E(Y|W)$ and a SL restricted to only decision tree learners for $E(Y|A)$, where A is a vector of exposures. After initialization, for every iteration, each algorithm is fit with an offset using predictions from the complementary algorithm; this is done until convergence, when there is no difference in predictions between each model. In this way, we can data-adaptively find the best fitting decision tree model which has the lowest cross-validated model error while flexibly adjusting for covariates. This procedure is done to find rules for the mixture modeled collectively and for each mixture marginal component individually. There are two types of results, 1. an average treatment effect (ATE) comparing those exposed to a mixed exposure of potentially many mixture variables to those unexposed to the mixture rules and 2. the ATE for each data-adaptively identified threshold of an individual mixture component when compared to the lowest identified exposure level. In the marginal space, results are analogous to a dose-response analysis but with data-adaptively identified levels. The CVtreeMLE software package, for the R language and environment for statistical computing (R Core Team, 2020), implements this methodology for deriving causal inference from ensemble decision trees.

CVtreeMLE is designed to provide analysts with both V-fold specific and pooled results for ATE causal effects of a joint exposure determined by decision trees. CVtreeMLE integrates with the [sl3package](#) (Coyle et al., 2020) to allow for ensemble machine learning to be leveraged in the estimation of nuisance parameters.

Availability

The CVtreeMLE package has been made publicly available both [via GitHub](#) and the [Comprehensive R Archive Network](#). Use of the CVtreeMLE package has been extensively documented in the package's README, two vignettes, and its [pkgdown documentation website](#).

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