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lmtp: An R Package for Non-Parametric Causal Effects Based on Modified Treatment Policies

Nicholas Williams, MPH
Weill Cornell Medicine

Ivan Diaz, PhD
Weill Cornell Medicine

Abstract

The majority of causal inference methods consider treatment effects based on counterfactual outcomes where exposure is deterministically established. When exposure is continuous, deterministic treatment effects may be irrelevant and impossible to bring about. As a solution, modified treatment policies offer a non-parametric alternative to deterministic treatment effects that allow for the study of feasible interventions and offer a safegaurd against positivity violations. The **lmtp** package implements the estimators of Diaz, Williams, Hoffman, and Schenck (2020) for estimating causal effects based on non-parametric modified treatment policies in `R`. The provided methods can be applied to both point-treatment and longitudinal settings, and can account for time-varying exposure, covariates, and right censoring. Additionally, two of the provided estimators can incorporate flexible data-adaptive algorithms for estimation while maintaining valid statistical inference.

Keywords: causal inference, non-parametric, modified treatment policies, R.

1. Introduction

Most modern causal inference methods consider the effects of a exposure on a population mean outcome under interventions that set the treatment value deterministically. For example, the average treatment effect (ATE) considers the hypothetical difference in a population mean outcome if a binary exposure was applied to all observations versus if it was applied to no observations. In the case of a categorical or continuous exposure, it is unlikely any policy could bring this about. In addition, the estimation of causal effects requires the so called positivity assumption which states that all observations have a greater than zero chance of experiencing the exposure levels (Rosenbaum and Rubin 1983). This assumption is often violated when evaluating the effects of deterministic interventions and is usually exacerbated with longitudinal data.

First introduced by Haneuse and Rotnitzky (2013), and building off work by Muñoz and van der Laan (2012), modified treatment policies (MTPs) are stochastic treatment regimes that can be formulated to avoid violations of the positivity assumption. Diaz *et al.* (2020) later extended MTPs to the longitudinal setting with time-varying treatment, covariates, and right-censoring of the outcome.

The package **lmtp** implements four methods for estimating the effects of MTPs. Two of these estimators, a targeted minimum-loss based estimator (TMLE) and a sequentially doubly-robust estimator (SDR), are multiply-robust (Laan and Rose 2011; Laan and Rubin 2006) (NEED TO FIND CITATIONS FOR SDR). In addition to MTPs, the package naturally allows for estimation of the ATE, causal risk ratio, and causal odds ratio and can thus be used for a variety of causal inference problems. In this article we describe how **lmtp** can be used for estimating the causal effects of MTPs and both static and dynamic deterministic treatment effects. The package may be download from CRAN at `cran.r-project.org/package=lmtp`.

2. Notation and modified treatment policies

2.1. Data structure

In this article, we will use the notation of Diaz *et al.* (2020) with slight modification. Let i be the index of an observation from a data set with n total units and t be the index of time for a total time of τ. The observed data for observation Z_i may be denoted as

$$Z_i = (W, L_1, A_1, L_2, A_2, ..., L_\tau, A_\tau, Y_{\tau+1}) \tag{1}$$

where W denotes baseline covariates, L_t denotes time-varying covariates, A_t denotes a vector of exposure variables and Y denotes an outcome at the end of study follow-up. We observe n i.i.d. copies of Z with distribution P. We use $A_t = a_t$ to denote a realization of a random variable. If right-censoring exists, A_t can be adapted so that $A_t = (A_{1,t}, A_{2,t})$ where $A_{1,t}$ equals one if an observation is still in the study at time t and zero otherwise, and $A_{2,t}$ denotes the exposure at time t. We use an overbar to indicate the history of a variable up until time t and an underbar to denote the future of a variable. We then use $H_t = (\bar{L}_t, \bar{A}_{t-1})$ to denote the history of all variables up until just before A_t.

2.2. Modified treatment policies

To formally define our causal effects of interest using our established data structure we will use the potential outcomes framework. We consider a hypothetical policy where in which $\bar{A}$ is set to a hypothetical regime d defined as $A_t^d = d_t(A_t, H_t^d)$, where $H_t^d = (\bar{L}_t, \bar{A}_t^d - 1)$, for a set of user-given regimes $d_t : t \in \{1, ..., \tau\}$. The defining characteristic that makes regime d_t a modified treatment policy is that it depends on the *natural value* of $\bar{A}_t$ and $\bar{L}_t$.

Formally, consider a longitudinal study with loss-to-follow-up. Let $A_t = (A_{1,t}, A_{2,t})$ where $A_{1,t}$ equals one if an observation is still in the study at time t and zero otherwise, and $A_{2,t}$ denote a continuous exposure at time t that can be changed through some intervention. A

modified treatment policy that decreases A_t is then

$$d_t(a_t, h_t) = \begin{cases} (1, a_{2,t} - \delta_t) & \text{if } a_{2,t} > u_t(h_t) + \delta_t \\ (1, a_{2,t}) & \text{if } a_{2,t} \leq u_t(h_t) + \delta_t \end{cases} \tag{2}$$

where $0 < \delta_t < u_t(h_t)$ is a user-defined value and A_t is supported in the data. Notice that the hypothetical exposure after intervention, A_t^d depends on the actually observed exposure, A_t. This is in contrast to a deterministic intervention where A_t^d would be set to a user-defined value with probability one. If right-censoring did not exist in the data, the MTP d would simplify to removing $A_{1,t}$ from the MTP definition. In analogue to Diaz *et al.* (2020), in this article we will focus on estimating the the causal effect of MTP d on outcome Y, using **lmtp**, through the causal parameter

$$\theta = \mathsf{E}\{Y(A^d)\}, \tag{3}$$

where $Y(A^d)$ is the potential outcome in a world, contrary to fact, where $\bar{A}$ was modified according to the MTP d. When Y is continuous, θ is the mean population value of Y under MTP d; when Y is dichotomous, θ is the population proportion of event Y under MTP d. Similarly, when Y is a survival outcome, θ is defined as the cumulative incidence of Y under MTP d.

2.3. Identification

Causal interpretation of θ requires identifying an expression of θ as a function of the data generating distribution P using only the observed data Z. A full review of these identification assumptions is outside the scope of this article. Briefly, the following standard assumptions must hold

Assumption 1 (Consistency) $\bar{A} = \bar{a} \implies Y = Y(\bar{a})$ *for all* $\bar{a} \in \text{supp}\, \bar{A}$

Assumption 2 (Exchangeability) *If* $(a_t, h_t) \in \text{supp}\{A_t, H_t\}$ *then* $(d(a_t, h_t), h_t) \in \text{supp}\{A_t, H_t\}$ *for* $t \in \{1, ..., \tau\}$

Assumption 3 (Positivity) $A_t \perp\!\!\!\perp Y(\bar{a})|H_t$ *for all* $\bar{a} \in \text{supp}\, \bar{A}$ *and* $t \in \{1, ..., \tau\}$

The consistency assumption states that the potential outcome for an observation under their exposure that we observed is the value of the outcome that we did actually observe. Assumption 2, the exchangeability assumption is often also referred to as the no-unmeasured confounding assumption; it is satisfied if all common causes of the exposure and outcome are measured and adjusted for. Of particular importance to this article is the positivity assumption which states that distribution of the exposure under the MTP is supported in the data. In a study with a continuous exposure and loss-to-follow-up, the positivity assumption states that if an observation with covariate history h_t and exposure a_t who was not lost-to-follow-up at time t exists then there is also an observation with covariate history h_t who was not lost-to-follow-up at time t but whose exposure was observed as $d(a_t, h_t)$ that also exists. The

strength of MTPs is that they may be formulated so as to avoid violations of the positivity assumption which is often violated when evaluating continuous exposures.

3. Estimating modified treatment policy effects

3.1. A user's guide

Estimation methods

The **lmtp** package provides four estimation methods: a targeted minimum-loss based estimator (TMLE), a sequentially doubly-robust estimator (SDR), an estimator based on the G-formula, and an inverse probability weighted (IPW) estimator. We will only describe the use of the TMLE, `lmtp_tmle`, and SDR, `lmtp_sdr`, estimators as their use is *strongly* suggested over the G-computation based and IPW methods.

Discuss the difference between TMLE and SDR estimators and when one may have an advantage over the other. All examples in this article will use both the TMLE and SDR estimators.

Required data structure

Data is passed to **lmtp** estimators through the `data` argument. Data should be in wide format with one column per variable per time point under study (i.e., there should be one column for every variable in Z). These columns do not have to be in any specific order and the data set may contain variables that won't be used in estimation. The names of treatment variables, censoring variables, baseline covariates, and time-varying covariates are specified using the `trt`, `cens`, `baseline`, and `time_vary` arguments respectively. The `trt`, `cens`, and `baseline` arguments accept character vectors and the `trt` and `cens` arguments should be ordered according to the time-ordering of the data generating mechanism. The `time_vary` argument accepts an unnamed list ordered according to the time-ordering of the model with each index containing the name of the time-varying covariates for the given time. The outcome variable is specified through the `outcome` argument.

The provided estimators can work with dichotomous, continuous, or survival outcomes. In the case of a dichotomous or continuous outcome, only a single variable name should be passed to the `outcome` argument. For survival outcomes, a vector containing the names of the intermediate outcome and final outcome variables ordered according to time should be passed to the `outcome` argument. Dichotomous and survival outcomes should be coded using zero's and one's where one indicates the occurrence of an event and zero otherwise. The `outcome_type` argument should be set to `"continuous"` for continuous outcomes and `"binomial"` for dichotomous and survival outcomes. If missingness is present in the outcome variable, the `cens` argument must be provided. Censoring indicators should be coded using zero's and one's where one indicates an observation is observed at the next time and zero indicates loss-to-follow-up. Once an observation's censoring status is switched to zero it cannot change back to one. Missing data before an observation is lost-to-follow-up is not allowed.

The `k` argument controls a Markov assumption of the data. With `k = Inf`, the entire history H_t will be used for estimation at time t while `k = 0` will restrict the set of variables in H_t

used for estimation to time-varying covariates at time $t-1$. Baseline confounders are always included in estimation. The user can inspect how estimators will internally use the provided variables during estimation with the `create_node_list` function. The `create_node_list` function uses the same `trt`, `baseline`, `time_vary`, and `k` arguments as **lmtp** estimators and is used internally to create a "node list" that encodes which variables should be used at each time point of estimation. For example, consider a study with the observed data structure

$$Z = (W_1, W_2, L_{1,1}, L_{1,2}, A_1, L_{2,1}, L_{2,2}, A_2, Y_3) \tag{4}$$

We can specify this data structure with

```
R> baseline <- c("W_1", "W_2")
R> trt <- c("A_1", "A_2")
R> time_vary <- list(c("L_11", "L_12"),
R+                   c("L_21", "L_22"))
R> create_node_list(trt = trt, baseline = baseline,
R+                  time_vary = time_vary, tau = 2)


$trt
$trt[[1]]
[1] "W_1"  "W_2"  "L_11" "L_12" "A_1"

$trt[[2]]
[1] "W_1"  "W_2"  "L_11" "L_12" "L_21" "L_22" "A_1"  "A_2"


$outcome
$outcome[[1]]
[1] "W_1"  "W_2"  "L_11" "L_12" "A_1"

$outcome[[2]]
[1] "W_1"  "W_2"  "L_11" "L_12" "A_1"  "L_21" "L_22" "A_2"
```

For this data structure, `create_node_list` returns a list of lists of the names of the variables in H_t to be used for estimation for both the outcome regression and the propensity at every time t. Notice that variables A_1 and A_2 are included for their own estimation. The **lmtp** package recasts the density ratio nuisance parameter estimation into a classification problem based on a $2n$ observations augmented data set where an indicator variable Λ is used as a pseudo outcome (Cheng and Chu 2004; Qin 1998). In the augmented data set, the data structure at time t is redefined as

$$(H_{\lambda,i,t}, A_{\lambda,i,t}, \Lambda_{\lambda,i} : \lambda = 0, 1; i = 1, ..., n) \tag{5}$$

where $\Lambda_{\lambda,i} = \lambda_i$ indexes the duplicate values. For all duplicated observations $i \in \{1, ..., 2n\}$, $H_{\lambda,i,t}$ is the same. While, for $i \in \{1, ..., n\}$ duplicated observations $A_{0,i,t}$ are the observed

exposure values and $A_{1,i,t}$ for $i \in \{n+1, ..., 2n\}$ are the exposure values under the MTP d, A_t^d.

Coding modified treatment policies

Treatment policies are specified using the `shift` argument, which takes a user-defined function that returns a vector of exposure values according the policy of interest. Shift functions should take two arguments, the first for specifying a data set and the second for specifying the current exposure variable. For example, a possible MTP may increase exposure by 2 units if the natural exposure value was below 5 units and do nothing otherwise. A shift function for this MTP would look like

```
R> function(data, trt) {
R+  (data[[trt]] < 5)*(data[[trt]] + 2) + (data[[trt]] >= 5)*data[[trt]]
R+ }
```

This framework is flexible and allows for specifying complex treatment regimes that can also depend on time and covariates. In the case of a binary exposure, two shift functions are installed with the package: `static_binary_on` which sets $A_{i,t} = 1$, and `static_binary_off` which sets $A_{i,t} = 0$.

The estimation engine

An attractive property of multiply-robust estimators is that they can incorporate flexible machine-learning algorithms for the estimation of nuisance parameters while remaining $\sqrt{n}$-consistent. The super learner algorithm is an ensemble learner than incorporates a set of candidate models through a weighted convex-combination based on cross-validation (Laan, Polley, and Hubbard 2007). Asymptotically, this weighted combination of models, called the meta-learner, will outperform any single one of its components.

Access to the super learner is provided by the **sl3** package. To use the super learner, analysts must create **sl3** learner stacks which are then included in estimator calls with the `lrnrs_trt` and `lrnrs_outcome` arguments. The outcome variable type should guide users on selecting the appropriate candidate learners for use with the `lrnrs_outcome` argument. Regardless of whether an exposure is continuous, dichotomous, or categorical, the exposure mechanism is estimated using classification, users should thus only include candidate learners capable of binary classification with the `lrnrs_trt` argument.

Candidate learners specified with `lrnrs_trt` that rely on cross-validation for the tuning of hyper-parameters should support grouped data. Because estimation of the treatment mechanism relies on the augmented $2n$ duplicated data set, duplicated observations must be put into the same fold during sample-splitting.

User's may install **sl3** from https://github.com/tlverse/sl3. Because **sl3** is not available for installation from a standard repository, it is not required to use **lmtp**. Instead, the `lrnrs_trt` and `lrnrs_outcomes` arguments can be set equal to `NULL` and nuisance parameters will be estimated using a generalized linear model (GLM) with the `glm` function from the **stats** package.

Additionally arguments

- Discuss `id`, `folds`, and `bound`

Effect contrasts

Example 1: Longitudinal MTP with no loss-to-follow-up

We have simulated data on $n = 5000$ observations over a 5-month period. Each observation has a continuous exposure (`A_1`, `A_2`, `A_3`, `A_4`) and covariate (`L_1`, `L_2`, `L_3`, `L_4`) recorded at months one through four and a dichotomous outcome (`Y`) at month five. We assume no loss-to-follow-up and no Markov property. This data set is installed with the package and is stored in the object `sim_t4`.

For this example, we are interested in the effect of a longitudinal MTP where at each month an observation's exposure decreases by one only if their observed exposure wouldn't be less than one if modified. Our data structure has no baseline confounders and we will use only GLMs for estimation so the only objects we must specify are the treatment variables, the time-varying covariates, the outcome variable, and the MTP shift function.

```
R> trt <- c("A_1", "A_2", "A_3", "A_4")
R> time_vary <- list(c("L_1"), c("L_2"), c("L_3"), c("L_4"))
R> y <- "Y"
R> shift <- function(data, trt) {
R+   (data[[trt]] - 1) * (data[[trt]] - 1 >= 1) +
R+     data[[trt]] * (data[[trt]] - 1 < 1)
R+ }
R> lmtp_tmle(sim_t4, trt, y, time_vary = time_vary, shift = shift)

LMTP Estimator: TMLE
   Trt. Policy: (shift)

Population intervention effect
      Estimate: 0.2646
    Std. error: 0.019
        95% CI: (0.2274, 0.3019)

R> lmtp_sdr(sim_t4, trt, y, time_vary = time_vary, shift = shift)

LMTP Estimator: SDR
   Trt. Policy: (shift)

Population intervention effect
      Estimate: 0.2608
    Std. error: 0.021
        95% CI: (0.2196, 0.3019)
```

Example 2: Longitudinal MTP, right-censoring, and the super learner

For this example, we have a simulated dataset of $n = 1000$ observations. Data was simulated for three time points with a continuous time-varying exposure at times $t \in \{1, 2\}$ (`A1`, `A2`), a dichotomous time-varying covariate at times $t \in \{1, 2\}$ (`L1`, `L2`), and a dichotomous outcome (`Y`) at time $t = 3$. Loss-to-follow-up is present after time $t = 1$ so the data set contains censoring indicators (`C1`, `C2`). This data is installed with the package and is stored in the object `sim_cens`.

Suppose we are interested in the additive effect of an MTP where exposure is increased by 0.5 at every time point for all observations.

Example 3:

Extra features

4. Reference Manual

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Affiliation:

Nicholas Williams, MPH
Division of Biostatistics
Department of Population Health Sciences
Weill Cornell Medicine
402 East 67th Street, New York, NY 10065
E-mail: niw4001@med.cornell.edu