
Estimation of the Hypothetical Estimands using Longitudinal version of the TMLE

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01 Introduction

- RCTs are the gold standard for conducting clinical trials to extract the pure treatment effect, by randomizing participants into treatment-no-treatment groups and balancing the other factors (demographics, external factors) across groups.
- However , there might be events that occur post-randomization that can alter the outcome of interest or the corresponding interpretation, leading to biased treatment effects estimates. These events are called Intercurrent events (ICEs).
- According to ICH E9(R1), it is necessary to define an appropriate estimand for clinical question of interest, to handle these ICE. One of the strategies defined in the addendum is Hypothetical Strategy, in which we estimate the treatment effect in a hypothetical scenario in which ICE does not occur at all.
- This presentation introduces a causal method called Longitudinal Targeted Maximum Likelihood Estimator (LTMLE), to estimate the parameter of interest, that is, the pure treatment effect in a scenario when no ICE occur.

02. Hypothetical Strategy

- According to the ICH E9(R1) addendum, an estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective, that summarizes what the outcome would be in the same patients under the different treatment conditions being compared, at a population level.
- Under the hypothetical strategy for estimand to handle the ICE, a hypothetical world is envisaged in which the ICE is considered to have not occurred at all.
- Our outcome of interest in this case is the outcome that would have been if the ICE had not occurred. These outcomes would not be observed for the patients with ICE and these need to be predicted or imputed.
- The causal estimand under this strategy is the effect of treatment on an outcome when the entire population is given the treatment and when it is not, provided there was no occurrence of ICE.

03 Causal Inference

Causal Inference helps us to identify and quantify the causal effect of one variable over the other, while controlling the *confounding factors* that are the unmeasured variables having an influence over the relationship of the variables under study (treatment and outcome), causing potential bias in the estimation of treatment effect.

Causal methods help to extract the pure treatment effect over the outcome of interest by balancing/controlling the external effects of the confounding factors. Causal methods can be used in observational studies as well as RCTs (randomized clinical trials) where there are occurrences of ICEs.

Causal concepts work on the idea of potential outcome framework introduced by Rubin-Neyman. Before person given or not given a treatment, they have two possible outcomes (outcome when treatment is given and outcome when treatment is not given). However, in real world, only one of the two possible outcomes is observed, leading to a biased estimate. The aim of causal methods is to estimate the other potential outcome for every individual in the study.

Causal Assumptions

Due to this imbalance in the two groups and the problem of being able to observe only one potential outcome in observational studies, it becomes important to make these two groups comparable by controlling for the confounders in order to get the unbiased estimate for the ATE. For observational studies suffering from confounders the estimation of the causal effect from the observed data the following assumptions are sufficient:

Consistency:

Potential outcome of a subject is exactly the same as the outcome observed under the given treatment for that subject.

$$Y^{A=a} = Y|A = a, \text{ for } a = 0, 1.$$

Positivity:

The probability of a patient receiving treatment or placebo, for any level of confounder X lies in the interval $(0, 1)$.

$$0 < P(A = a | X = x) < 1, \text{ for any } x, a \in \{0, 1\}.$$

Conditional Exchangeability:

The potential outcome of a patient (corresponding to any treatment) is independent of the treatment assignment. In other words, the potential outcomes corresponding to the treatment or placebo for any patient shall remain same no matter whether the patient is assigned to treatment or the placebo group.

$$Y^{A=a} \perp\!\!\!\perp A \text{ for } a = 0, 1.$$

04. Causal Estimators

Causal Estimand: Expected Difference in the outcome when treatment is given and when it is not.

$$E[Y^{A=1} - Y^{A=0}]$$

To estimate the above parameter, we have single robust estimators, like g-computation and Inverse probability of treatment weighting (IPTW), which uses treatment probability model and the former uses outcome model over covariates and treatment.

But, the estimates from above methods are biased and unreliable if the model is not correctly specified, and extreme treatment probabilities lead to high variance, making the estimate highly sensitive.

Similarly, we have double robust estimators, that use both outcome and treatment probability models, so the estimate is unbiased and consistent if either of the model is correctly specified, and efficient if both are correctly specified. For e.g. AIPTW and TMLE.

Targeted Maximum Likelihood Estimator

Targeted Maximum Likelihood Estimation, is another double robust estimator that can be used to estimate the average treatment effect.

It is a semiparametric method of estimation that relies on machine learning to avoid making unrealistic parametric assumptions about the underlying distribution of the data.

TMLE Algorithm –

1) Estimating the Outcome Mechanism:

$$\begin{aligned}\bar{Q}^0(A, X) &= \text{logit}[P(Y|A, W)] = \beta_0 + \beta_1 A + \beta_2 X \\ \bar{Q}^0(0, X) &= \text{expit}(\hat{\beta}_0 + \hat{\beta}_1 0 + \hat{\beta}_2 X) \\ \bar{Q}^0(1, X) &= \text{expit}(\hat{\beta}_0 + \hat{\beta}_1 1 + \hat{\beta}_2 X)\end{aligned}$$

2) Estimating Probability of Treatment

$$\begin{aligned}\text{logit}[P(A = 1|X)] &= \alpha_0 + \alpha_1 X \\ PS = \hat{g}(1, W) &= \text{expit}(\hat{\alpha}_0 + \hat{\alpha}_1 X)\end{aligned}$$

PS is the propensity scores that are used as weights.

3) Clever covariates and fluctuation parameter

$$H(1, X) = \frac{A}{\hat{g}(1, X)}, \quad H(0, X) = \frac{1 - A}{1 - \hat{g}(1, X)}$$

$$E[Y = 1|A, X](\epsilon) = \frac{1}{1 + \exp(-\log \frac{\bar{Q}^0(A, X)}{(1 - \bar{Q}^0(A, X))} - \epsilon_0 H(0, W) - \epsilon_1 H(1, W))}$$

(ϵ_0 and ϵ_1 are the fluctuation parameters)

4) Updating the estimates

$$\begin{aligned}\bar{Q}^1(0, X) &= \text{expit}[\text{logit}(\bar{Q}^0(0, X)) + \hat{\epsilon}_0 / (1 - \hat{g}(1, X))] \\ \bar{Q}^1(1, X) &= \text{expit}[\text{logit}(\bar{Q}^0(1, X)) + \hat{\epsilon}_1 / \hat{g}(1, X)]\end{aligned}$$

5) ATE

$$\hat{ATE}_{tmle} = \frac{1}{n} \sum_{i=1}^n \bar{Q}^1(1, X) - \frac{1}{n} \sum_{i=1}^n \bar{Q}^1(0, X)$$

* The standard error of the TMLE can be computed using the influence function.

05. Causal Inference in Hypothetical Strategy

Parameter of Interest : Expected Difference in the outcome when treatment is given and when it is not, when no intercurrent event (ICE) occurs.

$$E[Y^{A=1,E=0} - Y^{A=0,E=0}]$$

The idea is to apply the causal inference concepts to estimate the treatment effects when there are occurrences of intercurrent events post randomized treatment arm allotment, using the hypothetical strategy, under which we envisage such a hypothetical world where the ICE had not been occurred.

In accordance with the potential outcome framework, the patients for whom ICE does not occur post randomized treatment allotment, their outcome corresponds to the outcome of interest. However, for those patients, for whom ICE did occur, their potential outcome of interest (i.e., the outcome when no ICE occurs) is missing.

Using causal tools, these potential outcomes can be estimated under the causal assumptions and the unbiased estimate of treatment effect with no ICE can be computed.

LTMLE FOR HYPOTHETICAL STRATEGY

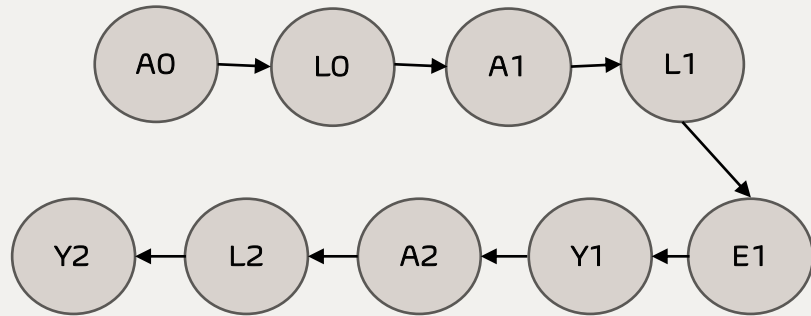
TMLE can be further used in longitudinal data when the causal effect of interest is the some static/dynamic treatment at different time points with covariates and outcome recorded at every time points.

LTMLE involves finding initial estimates by outcome model and updating it at the target step using the treatment probability model. This process is done for every time point, starting from the final time point and back iterating it till the first time point.

The updated estimates at the first time point after back iteration, is the LTMLE estimate of the treatment intervention of interest.

In case of hypothetical strategy, we predict our estimates by plugging in treatment regime of interest and plugging in the ICE as zero.

Implementation



Average Treatment Effect of interest:

$$E[Y^{a0=1, a1=1, a2=1, e1=0, e2=0} - Y^{a0=0, a1=0, a2=0, e1=0, e2=0}]$$

Step 1: Creating the new data incorporating treatment regime of interest and no ICE

From the data we have, we plug in the treatment regime of interest and no ICE, to get new dataset to predict our models over.

Step 2: Computing propensity scores and clever covariates.

Model the probability of ICEs over the past treatment, covariate and past ICE, using a binomial model, at every time point ($t = 1, 2$).

$$P(E_t = 1 | \bar{L}_t, \bar{A}_{t-1}, \bar{E}_{t-1})$$

Further, using these models, predict the probability of ICE and assign weights as the inverse of the product of probabilities for $t, t-1, \dots, 1$. for time point t .

These weights are assigned at every time point, for the subset of the subjects having no ICE, for the other subjects the weights are zero.

$$W_t = \frac{1}{\prod_1^t P(E_t=1 | \bar{L}_t, \bar{A}_{t-1}, \bar{E}_{t-1})}$$

Step 3: Outcome modelling

Starting from the final timepoint, we model the outcome (normalised by min-max method if continuous) over the treatment history, covariate history, ICE history and past outcomes. We then use this model to predict the outcomes by plugging the treatment of interest and no ICE.

$$E(Y_T | \bar{A}_T, \bar{L}_T, \bar{E}_T, \bar{Y}_{T-1})$$

Step 4: Updating step

Now, we model the outcome from the final timepoint over the offset and logit of the predicted outcome value from step2 and weights computed in step1. Then, using this model, predict the outcome for the treatment regime of interest and no ICE.

$$Y_t \sim -1 + \text{offset}\left(q\logis(\hat{Y}_t)\right) + w_t$$

Step 5: Repeat steps 2 and 3 for other timepoints $t \dots, 2, 1$.

Next, we use the updated outcomes from final timepoint in time point $T-1$, and repeat the steps 2-3, using the corresponding weights from step1. This back-iteration is repeated until we get updated outcomes at time $t=1$.

Step 6: ATE

All of the above steps are performed for both new data, "treatment-given" and "treatment-not-given" groups to get the final values $A1$ and $A0$. The final Average treatment effect is computed as the mean difference of the updated outcome $A0$ and $A1$ at time $t=1$, over the treatment given or not.

$$ATE = \text{mean}(A1 - A0)$$

Summary

From the above simulations, the true ATE being 0.5, we can see that the use of LTMLE gives an estimate near to 0.44, with bias reducing further as sample size increases.

The procedure that LTMLE uses incorporates information both from the outcome model as well as treatment model, also not dropping any observations as “missing” due to occurrence of intercurrent events (ICEs).

LTMLE being a semi-parametric method can also use machine-learning methods, reducing data assumptions and model misspecification, making the estimate consistent and efficient than the other methods.

It is important to note that this is a general idea of using causal methods like LTMLE and further research on different scenarios like longer follow-ups, decreasing sample sizes and different intercurrent events should be explored.

00 References.

- Luque-Fernandez MA, Schomaker M, Rachet B, Schnitzer ME. (2018) Targeted maximum likelihood estimation for a binary treatment: A tutorial. *Stat Med*.
- Olarte Parra, C., Daniel, R. M., & Bartlett, J. W. (2023). Hypothetical Estimands in Clinical Trials: A Unification of Causal Inference and Missing Data Methods. *Statistics in Biopharmaceutical Research*, 15(2), 421–432
- Schomaker M, Luque-Fernandez MA, Leroy V, Davies MA. (2019) Using longitudinal targeted maximum likelihood estimation in complex settings with dynamic interventions. *Stat Med*. 30