Targeted Maximum Likelihood Estimation for Adaptive Designs: Adaptive Randomization in Community Randomized Trial

Mark J. van der Laan

[1]University of California, Berkeley School of Public Health

laan@berkeley.edu · mayaliv@berkeley.edu
stat.berkeley.edu/∼laan/
works.bepress.com/maya_petersen/

targetedlearningbook.com

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General Adaptive Designs

Full data:

$$\mathbf{X} = (X_1, \ldots, X_n) \; n \text{ i.i.d. full-data } X_i \sim P_{X,0} \in \mathcal{M}^F.$$

Target Quantity: $\psi_0^F = \Psi^F(P_{X,0})$ for some $\Psi^F : \mathcal{M}^F \rightarrow \mathbb{R}$.

Observed data:

$$\mathbf{O} = (O_i = \Phi(X_i, A_i) : i = 1, \ldots, n) \sim P_{P_{X,0},\mathbf{g}_0},$$

for some censored data structure $\Phi(X_i, A_i)$, and, where conditional distribution $\mathbf{g}_0$ of $\mathbf{A} = (A_1, \ldots, A_n)$, given $\mathbf{X}$, is known (or, at least, can be well estimated), and satisfies coarsening at random wr.t. $\mathbf{X}$:

$$\mathbf{g}_0(\mathbf{A} \mid \mathbf{X}) = h_0(\mathbf{O}).$$

The likelihood of $\mathbf{O}$ is given by:

$$P_{P_{X,0},\mathbf{g}_0}(\mathbf{O}) = \prod_{i=1}^{n} P_{X,0}(C(O_i))\mathbf{g}_0(\mathbf{A} \mid \mathbf{X}),$$

where $C(O_i)$ is coarsening of X_i implied by O_i.

Under positivity assumption, the full-data parameter is thus identified from observed data distribution, giving us the statistical target parameter

$$\Psi : \mathcal{M} \rightarrow \mathbb{R}, \text{ with } \mathcal{M} = \{P_{P_X,\mathbf{g}_0} : P_X \in \mathcal{M}^F\}$$

the observed data model. This defines the estimation problem.

Group Sequential Adaptive Randomized Trials

Suppose the individuals are ordered $i = 1, \ldots, n$, and the treatment/action assignment A_i for subject i can also depend on the data $O_1, \ldots, O_{i-1}$, beyond its usual allowed dependence on O_i:

$$g_i = P(A_i \mid \mathbf{X}, \mathbf{A}(i-1)) = h(A_i \mid O_1, \ldots, O_{i-1}, O_i).$$

The adaptive design g_i can be chosen so that it learns/adapts (for $i \rightarrow \infty$) an optimal fixed design $g_{opt}(A \mid X)$.

In van der Laan (2008), and Chambaz, van der Laan (2010a,b), we develop targeted maximum likelihood estimators (TMLE) and statistical inference. The statistical inference is based on Martingale CLT's and tail probability bounds for martingale sum processes.

The limit distribution of the TMLE corresponds with the limit distribution of the TMLE under i.i.d. sampling $P_{P_{X,0},g_\infty}$ under a fixed unknown design g_∞ identified by the limit of the adaptive design g_i.

Adaptive Randomization in Community RCT

Full-data: Let $X_i = (W_i, Y_i^0, Y_i^1) \sim_{i.i.d.} P_{X,0} \in \mathcal{M}^F$ for a nonparametric full-data model $\mathcal{M}^F$, and let $\psi_0^F = E_0\{Y^1 - Y^0\}$ be the additive causal effect of a binary treatment.

Observed data and CAR: Let

$$O_i = (W_i, A_i = (A_i^t, \Delta_i), Y_i = Y_i(A_i^t, \Delta_i) = \Delta_i Y_i^{A_i^t}),$$

where A_i^t denotes treatment, and $1 - \Delta_i$ denotes a missingness indicator. Let $\mathbf{g}_0$ be the conditional distribution of $\mathbf{A}$, given $\mathbf{X}$, which is assumed to only be a function of $\mathbf{W} = (W_1, \ldots, W_n)$.

Likelihood:

$$\mathbf{P}(O_1, \ldots, O_n) = \prod_{i=1}^{n} Q_W(W_i) Q_Y(Y_i \mid W_i, A_i) \mathbf{g}_0(\mathbf{A} \mid \mathbf{W}),$$

where Q_W and Q_Y denote the common marginal distribution of W and the common conditional distribution of Y, given A, W, respectively. We assume

$$\mathbf{g}_0(\mathbf{A} \mid \mathbf{W}) = \prod_{j=1}^{J} g_{0,j}(A(j) : j \in C_j(\mathbf{W}) \mid \mathbf{W}), \quad (1)$$

where $C_1(\mathbf{W}), \ldots, C_J(\mathbf{W})$ is a partitioning of the sample $\{1, \ldots, n\}$ into J clusters deterministically implied by $\mathbf{W}$.

Statistical target: The causal quantity is identified by

$$\Psi(\mathbf{P}_0) = E_{Q_{W,0}}\{\bar{Q}_0(1, W) - \bar{Q}_0(0, W)\},$$

where $\bar{Q}_0(a^t, w) = E_0(Y_i \mid A_i = a^t, \Delta_i = 1, W_i = w)$ (which is constant in i).

Canonical gradient/Efficient Influence Curve:

The statistical parameter Ψ is pathwise differentiable and its canonical gradient at $\mathbf{P}$ is given by

$$\mathbf{D}(\mathbf{P})(\mathbf{O}) = \frac{1}{n}\sum_{i=1}^{n} D(Q,\bar{g})(O_i),$$

where $D(Q,g)$ is the efficient influence curve at $P_{Q,g}$ for the individual level data structure:

$$D(Q,\bar{g})(O_i) = D_W^*(Q)(W_i) + D_Y^*(Q,\bar{g})(O_i)\},$$

$$\begin{aligned} D_W^*(Q)(W_i) &= \bar{Q}(1,W_i) - \bar{Q}(0,W_i) - \Psi(Q) \\ D_Y^*(Q,\bar{g})(O_i) &= \frac{\Delta_i(2A_i^t - 1)}{\bar{g}(A_i \mid W_i)}(Y_i - \bar{Q}(A_i^t, W_i)), \end{aligned}$$

and

$$\bar{g}(a \mid W_i) = \frac{1}{n} \sum_{j=1}^{n} g_j(a \mid W_j = w) \Big|_{w=W_i},$$

$g_{0,j}$ is the conditional distribution of A_j, given W_j, defined by

$$g_{0,j}(a \mid W_j = w) = \sum_{(w_l : l \neq j)} g_{0,j}(a \mid (w_l : l \neq j), W_j = w) \prod_{l \neq j} Q_{W,0}(w_l). \tag{2}$$

Double robustness:

We have

$$E_0\mathbf{D}(\bar{Q}, \bar{g}, \psi) = \psi_0 - \psi \text{ if } \bar{Q} = \bar{Q}_0 \text{ or } \bar{g} = \bar{g}_0, \tag{3}$$

assuming that for all i, $0 < \bar{g}_i(1 \mid W) < 1$ a.e.

Targeted MLE

Let $Y \in \{0,1\}$ be binary or continuous in $(0,1)$. Let $\bar{Q}_n^0$ be an initial estimator of $\bar{Q}_0$, which can be based on the loss-function

$$-L_i(\bar{Q})(O_i) = \Delta_i \left\{ Y_i \log \bar{Q}(W_i, A_i) + (1 - Y_i) \log(1 - \bar{Q}(W_i, A_i)) \right\}.$$

Cross-validation treating sample as i.i.d. based on this loss function is appropriate.

Let $\bar{g}_n = 1/n \sum_i g_{i,n}$ be an estimator of $\bar{g}_0$, which could be based on loss

$$L(\bar{g})(\mathbf{W}, \mathbf{A}) = \sum_i \log \bar{g}(A_i \mid W_i).$$

Cross-validation now has to treat the clusters $C_j(\mathbf{W})$ as unit. If $\mathbf{g}_0$ is known by design, one may/should use plug-in estimator, plugging in empirical distribution $Q_{W,n}$.

As least favorable submodel for fluctuating $\bar{Q}_n^0$ we use logistic regression $\text{Logit}\bar{Q}_n^0(\epsilon) = \text{Logit}\bar{Q}_n^0 + \epsilon H^*_{\bar{g}_n}$, where $H^*_{\bar{g}_n}(A, W) = (2A - 1)/\bar{g}_n(A \mid W)$.

The amount of fluctuation ϵ_n is estimated as

$$\epsilon_n = \arg\min_{\epsilon} \sum_{i=1}^{n} L_i(\bar{Q}_n^0(\epsilon))(O_i).$$

This provides the update $\bar{Q}_n^* = \bar{Q}_n^0(\epsilon_n)$. Let $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$. The TMLE of ψ_0 is the corresponding plug-in estimator

$$\Psi(Q_n^*) = \frac{1}{n} \sum_{i=1}^{n} \{\bar{Q}_n^*(1, W_i) - \bar{Q}_n^*(0, W_i)\}.$$

The TMLE solves

$$0 = \mathbf{D}(\bar{Q}_n^*, \bar{g}_n, \psi_n^*) = \frac{1}{n} \sum_{i=1}^{n} D(\bar{Q}_n^*, \bar{g}_n, \psi_n^*)(O_i).$$

Asymptotics of TMLE for Community RCT's

Theorem: Suppose that for $j = 1, \ldots, J-1$, $C_j(\mathbf{W})$ is a pair whose observations will be denoted with $(O_{1,j}, O_{2,j})$, and one cluster C_J is defined by the units with missingness.

Suppose $g_{0,i}(A_i \mid \mathbf{W}) = g_0(A_i \mid W_i)$, and it is known, so that $\bar{g}_0 = g_0$ is known as well.
Let $\bar{Q}_n^*$ converge to some $\bar{Q}^*$.

The asymptotic variance σ^2 of the standardized TMLE $\sqrt{n}(\psi_n^* - \psi_0)$ can be represented as follows:

$$\begin{aligned}&\sigma^2 = P_{Q_0,g_0}\{D(Q^*, g_0)\}^2 \\ &- \lim_n E_0 \tfrac{1}{J} \textstyle\sum_{j=1}^{J} (\bar{Q}_0 - \bar{Q}^*)(1, W_{1j})(\bar{Q}_0 - \bar{Q}^*)(1, W_{2j}) \\ &- \lim_n E_0 \tfrac{1}{J} \textstyle\sum_{j=1}^{J} (\bar{Q}_0 - \bar{Q}^*)(0, W_{1j})(\bar{Q}_0 - \bar{Q}^*)(0, W_{2j}).\end{aligned}$$

Under the assumption that the covariance-terms are positive, a conservative estimate of σ^2 is thus given by:

$$\sigma_n^2 = \frac{1}{n}\sum_{i=1}^{n}\{D^*(Q_n^*, g_0)(O_i)\}^2.$$

Note: Consistent estimation of true asymptotic variance relies on consistent estimation of $\bar{Q}_0$!

Concluding Remark:

Semiparametric estimation and inference for "**sample size one**" problems is possible and represents an exciting and important area of research.

Further Materials

Targeted Learning Book
Springer Series in Statistics
van der Laan & Rose
targetedlearningbook.com

2012 JSM Short Course
Instructors:
Petersen, Rose & van der Laan