Longitudinal Targeted Maximum Likelihood Estimation in Complex HIV Treatment Settings

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Background

HIV treatment research faces multiple challenges when using observational databases to answer questions which are causal in nature: these include long follow-up, gradually declining sample size over time, limited data support for particular interventions of interest, and a high-dimensional set of potential adjustment variables. We evaluate the performance of longitudinal targeted maximum likelihood estimation (LTMLE) in this context, based on simulated data, similar to an IeDEA data set.

Data Generation & Motivating Question

We generated data similar to IeDEA-Southern/West African data from children aged $1-5$ years, for 30 months of follow-up, i.e. region, sex, age as well as baseline CD4 count, CD4%, weight-for-age z-score (WAZ), and height-for-age z-score (HAZ). Follow-up data included antiretroviral therapy (ART), CD4 count, CD4%, WAZ, and HAZ. The outcome of interest was height-for-age z-score (HAZ) after 30 months, under no censoring, for a given ART assignement rule.

Comparison

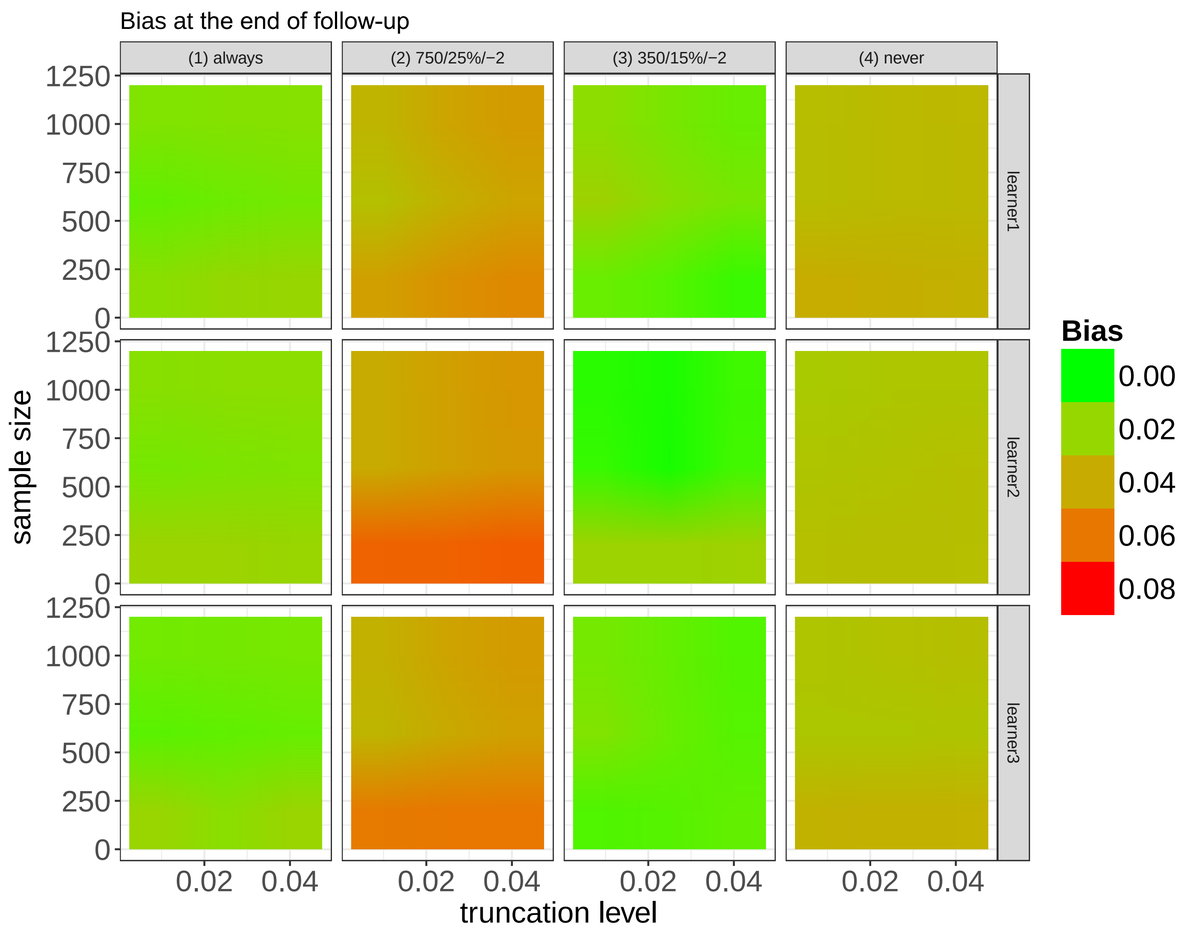
Using LTMLE, we compare bias and coverage, estimated based on 1000 simulation runs, with respect to:

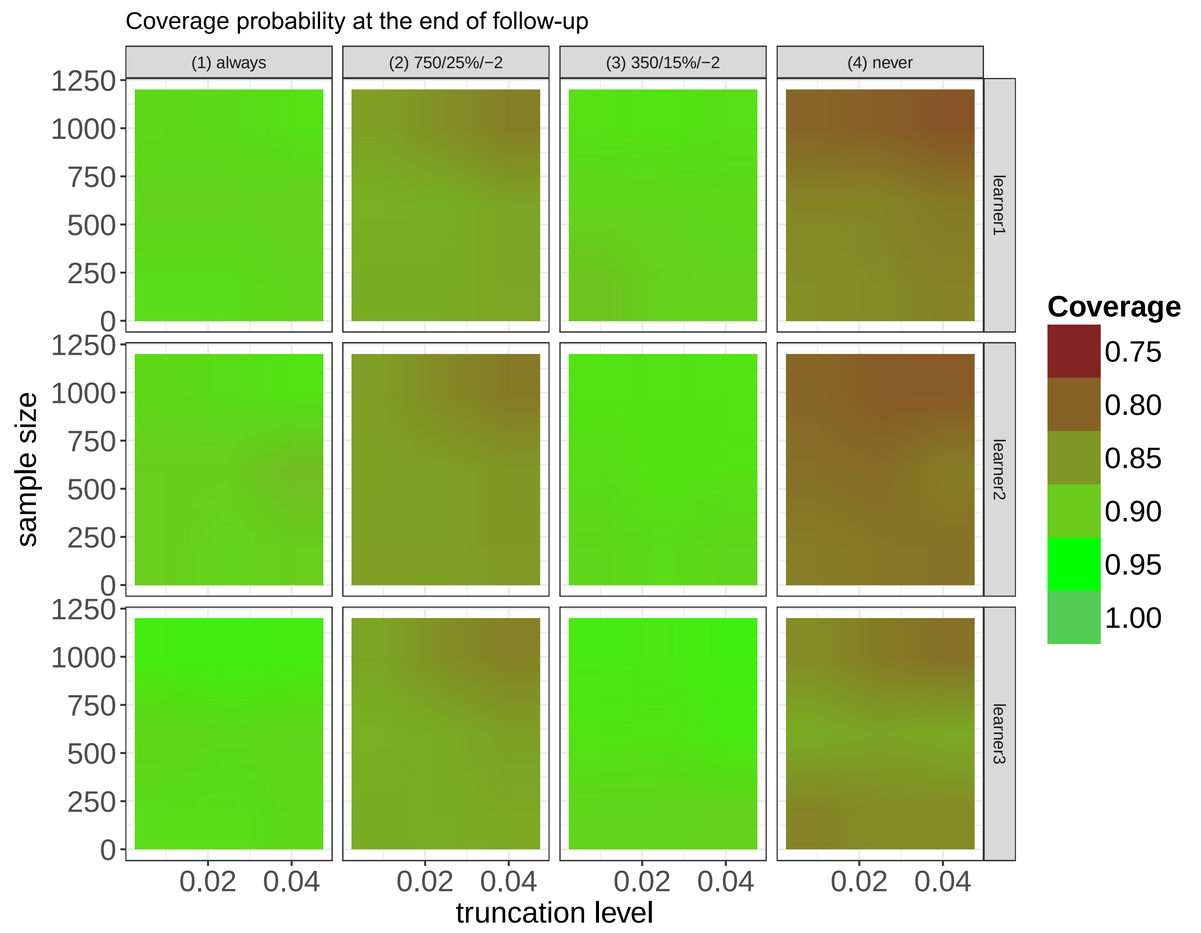
- different ART assignment rules: (1) immediate ART (2) delayed ART until CD4 count<750 cells/μl or CD4%<25% or WAZ<-2 (3) delayed ART until CD4 count$<$350 cells/μl or CD4%$<$15% or WAZ <-2 (4) no ART
- different baseline sample sizes: 200, 600, 1000 patients
- different sets of learners for model specification with machine learning: very simple [learner 1], simple [learner 2], moderate [learner 3]
- different lower bounds for truncation of the estimated cumulative treatment/censoring probabilities: $0.01, 0.025, 0.05$

Results

Descriptive Statistics: Simulated baseline data were: region SA = 75.5%; male sex = 51.2%; mean age = 3.0 years; mean CD4 count = 672.5 cells/μl; mean CD4% = 15.5%; mean WAZ= -1.5; mean HAZ = -2.5. At the end of follow-up the arithmetic mean of CD4 count, CD4%, WAZ and HAZ were 1092 cells/μl, 27.2%, -0.8, -1.5 respectively.

Bias and coverage, as displayed in the two figures, vary substantially with respect to the chosen intervention. However, the level of truncation hardly affected the results. There were gains with greater sample size, as one would expect; it is however worth pointing out that even with small sample sizes results were relatively stable and good.
Learner 3, with the biggest set of learners, typically performs best. Surprisingly, the other two learners also yield good results – which is encouraging given that the data-generating process contains interactions and non-linear associations as well, and this isn't specifically modeled by learner set 1 and learner set 2.





Data support & positivity: Since in the simulation the data-generating process is known, we can estimate the probability (p) of continuing to receive treatment according to the assigned treatment rule, given that a patient has received treatment so far and irrespective of the covariate history. Under the assumption of *positivity*, p should be >0, and not too small. The table lists the proportion of cumulative probabilities which are smaller than 0.01:

Intervention	(1)	(2)	(3)	(4)
% patients for which $p<0.01$	0.1%	0.3%	0.2%	0.8%

The table shows that the highest proportion of small cumulative probabilities is found for the second and fourth intervention, i.e. those interventions which performed worst in the simulations. This highlights the fact that interventions need data support to meet the positivity assumption.

Conclusions

In our setting,

- it could be seen that different interventions may have different support in the data, and that the success of LTMLE therefore varied with respect to the chosen interventions because of practical positivity violations.
- a small sample size, heavy truncation of estimated inverse probabilities, and the inclusion of more complex learning algorithms didn't have a major impact on our results.
- Diagnostics, such as summaries of the data support for each intervention of interest, among others, are inevitable for anyone applying LTMLE.

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