Handling positivity violations in longitudinal data

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Abstract

The abstract goes here.

1 Introduction

Background goes here...

The use of causal estimators have become very popular in many fields, from statistics, to the social sciences, to economics. Estimators developed under this framework benefit by combining both the estimation of parameters from a statistical model and causal inference under non-testable assumptions of randomization and positivity. One well known approach for the estimation of these parameters is the inverse probability of treatment weighted (IPTW) estimator. As an estimating equation based estimator the the conditional probability of treatment is required. Normally estimated from the empirical distribution, these propensity scores calculated can then be used in a working marginal structural model, projecting the true dose response curve onto a parametric model. This powerful approach has further been expanded to a longitudinal setting where time dependent confounding may exist. In this setting, a covariate can simultaneously act as both a confounder and as an intermediate. Because bias is introduced by controlling for a variable affected by treatment, more standard classical methods cannot be applied. The longitudinal IPTW avoids this and allows us to control for confounding in an unbiased approach to the estimation of our causal parameter.

define positivity. Valid estimation of these causal parameters rely on three primary assumptions. Consistency assumes that if the treatment is $A = a$ for a given subject, then $Y_a = Y$. This assumption is sometimes known as the counterfactual outcome since it is assumed that under specific treatment regimes, the potential (but unrealized) outcome would equal the observed outcome. Conditional exchangeability (aka the randomization assumption) assumes that there is no unmeasured confounding given data on the covariates L (i.e. $Y_a \coprod A|L$ for all possible values of a and ℓ). Lastly, positivity assumes that if $f_L(\ell) \neq 0$, then $f_{A|L}(a|\ell) > 0$ for all a, where $f_L(\ell) \equiv P(L = \ell)$ is the population marginal probability that L takes the value ℓ and $f_{A|L}(a|\ell) \equiv P(A = a|L = \ell)$ is the conditional probability that A takes the value a among subjects in the population where $L = \ell$ **?**. We define this assumption formally as

$$\inf_{a \in \mathcal{A}} P_0(A = a|L) > 0 \text{ a.e.} \tag{1}$$

where $\mathcal{A}$ is the set of all possible counterfactual treatments. This assumption of positivity is particularly important for IPTW estimators, as these estimators are very sensitive to positivity violations as well as near violations.

Talk about how positivity can arise In realistic clinical care settings, monitoring times can (a) determine the time points at which treatment can change (and are thereby are a source of positivity violation for some treatment regimens), (b) affect the outcome directly (and are also thereby confounders), and (c) affect

when data on a given individual are observed (and thereby the plausibility of the sequential randomization assumption (SRA)). Thus we are faced with a situation where not only is positivity an issue, but that the covariate causing the positivity acts as a confounder and can single handedly threaten the conclusions of our study. In estimating treatment specific counterfactuals, it is required that very careful consideration of both the counterfactual parameter of interest and the positivity violations be given.

Talk about example we'll work with For example, consider the problem in which longitudinal clinical data including clinic visits, time updated CD4 count, and mortality are measured on a sample of HIV patients starting at time of virologic failure of first line antiretroviral therapy (ART). The question of interest is whether a delay in switching off failing ART onto a secondary medication affects mortality. That is, we aim to use data of the described form to estimate how the counterfactual survival or hazard varies as a function of assigned switch time. While some patients may come in to visit frequently, we are faced the inevitability that others will not. It is obvious that for patients that do not come in for clinical visits, the probability of switching off failing ART is 0. We therefore have a serious positivity violation. Additionally, patients who come in more often may have better quality of care, thus affecting the outcome of interest. We also are unable to measure important confounders such as the time updated CD4 count. continued... As a working example for the present paper, we consider a population of subjects with HIV who have failed their primary antiretroviral (ARV) therapy medication. Among these subjects, we are interested in analyzing whether switching to secondary medication results in reduced mortality. More specifically, we are interested in determining whether delays in switching to secondary medication result in different mortality rates. For example, do subjects who switch medication immediately after primary ARV failure experience lower mortality than those who switch at a later time point?

In this paper we use simulations to demonstrate the bias involved if monitoring is either excluded from the adjustment set (due to confounding) or is included (due to positivity). We then demonstrate each of the possible alternatives presented above. Section **??** formally defines the data, our statistical and causal model, and discusses identifiability. Section **??** presents details on each of our approaches, including the exact parameters being estimated. Section **??** investigates the bias incurred by mishandling the monitoring covariate and the performance of each approach presented. Section **??** concludes with some remarks about each of the approaches and advocates for a systematic approach to addressing potential violations in positivity.

We then simulate data such that the positivity violation is present and demonstrate the performance of each approach under this known true probability distribution.

2 Positivity approaches

In response to the positivity violations presented above, we propose several approaches that either target parameters not affected by the violation or modify the target parameter such that there is appropriate support for estimation.

2.1 Selecting appropriate interventions

One can limit the static treatment regimes of interest to only those for which no positivity violations occur. For example, one might simply contrast mortality under a regime that forces patients to switch immediately with one that says never switch. Furthermore, a reasonable approach could be to assume linearity in the dose response curve and to interpolate between the two estimates.

2.2 Dynamic regimes

One might redefine the intervention as a "realistic" dynamic regime. In our example, the intervention of interest would have an assigned switch time, and then force a subject to switch at the first time point he or she is seen after his assigned time.

2.3 Joint interventions

One might chose to intervene jointly on the monitoring times and the treatment (i.e. switch time). We note that whereas the latter two approaches leave the monitoring time to be random, this approach additionally intervenes on the monitoring mechanism itself. This monitoring intervention is less restrictive than, say, forcing patients to come in for clinical visits at all time points, as it forces a patient to come in only at time t during which the patient is forced to switch to secondary medication.

2.4 Excluding covariates

A potential approach is to simply ignore the covariate causing the positivity violation. While this avoids the issue, it can result in noticeable bias depending on whether the covariate directly affects the outcome of interest.

3 Simulations

We approach our simulation under discrete time points in which a subject cannot experience an event in between time t and $t+1$. Subjects are followed up to a fixed time point $K+1$, at which point it is observed whether or not they have experienced an failure. Let our observed data be denoted as

$$O = (L(0), A(0), L(1), A(1), \ldots, L(K), A(K), Y = L(K+1)) \tag{2}$$

where $L(t) = (Y(t), L1(t), L2(t))$, $A(t) = (Z(t), A1(t))$, and $L(0)$ also includes $(W1, W2)$. We describe each of the covariates for the simulation below.

- $W1$ is a baseline continuous covariate.
- $W2$ is a baseline bernoulli covariate.
- $Y(t)$ is an indicator of an event. As a counting process, it jumps to and remains at 1 once a subject experiences a failure.
- $L1(t)$ is a time-varying continuous covariate.
- $L2(t)$ is a time-varying continuous covariate.
- $Z(t)$ is an indicator that the subject has a clinical visit.
- $A1(t)$ is an indicator that the subject switches to secondary medication. As a counting process, this covariate also jumps to and remains at 1 once a subject switches medication.

For the present simulation, the true probability distribution is defined through each individual covariate as a process dependent upon t. That is, we define each covariate to follow the distribution

- $W1 \sim N(0, 1)$
- $W2 \sim Ber(logit^{-1}(.2))$
- $L1(t) \sim N(0.1 + 0.4 \cdot W1 + 0.6 \cdot L1(t-1) - 0.7 \cdot L2(t-1) - 0.45 \cdot A1(t-1), 0.5^2)$
- $L2(t) \sim N(-0.55 + 0.5 \cdot W1 + 0.75 \cdot W2 + 0.1 \cdot L1(t-1) + 0.3 \cdot L2(t-1) - 0.75 \cdot A1(t-1), 0.5^2)$
- $Z(t) \sim Ber(logit^{-1}(2.8 - 0.5 \cdot W1 + 0.6 \cdot W2 + 0.7 \cdot L1(t) + 0.7 \cdot L2(t)))$
- $A1(t) \sim Ber(logit^{-1}(-1.5 - 1.5 \cdot W1 + 0.75 \cdot W2 + 0.8 \cdot L1(t) + 0.8 \cdot L2(t)))$, if $A(t-1) = 0$ & $Z(t) = 1$
- $Y(t) \sim Ber(logit^{-1}(-1.8 + 1.2 \cdot W1 - 2.4 \cdot W2 - 1.6 \cdot L1(t-1) - 1 \cdot L2(t-1) - 1.9 \cdot A1(t-1) - \beta_Z \cdot Z(t-1)))$

where once $Y(t) = 1$, all remaining covariate values become degenerate and are defined as the last value carried forward with probability 1. We define $A1(t)$ such that if $A(t-1) = 1$ or $Z(t) = 0$ then $A(t) = A(t-1)$. Additionally, at time $t = 0$, all covariate values at $t - 1$ are set to be 0. We note that under this model, $A1(t)$ is defined to have a large beneficial effect on the outcome $Y(t)$. That is, observations with $A1(t) = 1$ at lower time points t will have a noticeably lower probability of event $Y(t)$ than those with $A1(t) = 0$.

To analyze how severely option #4 (i.e. ignoring the causing the positivity violation) affects estimates of our target parameter, we undertake two simulations under this specified model, with either $\beta_Z = 1.25$ or $\beta_Z = 0$. The former β_Z accounts for the scenario that clinical visits directly affect the outcome, whilst the latter defines no direct effect on the outcome.

Switch time	$\beta_Z = 1.25$			$\beta_Z = 0$		
	Option 1	Option 2	Option 3	Option 1	Option 2	Option 3
0	0.0811	0.0811	0.0811	0.1998	0.1998	0.1998
1	–	0.1108	0.0998	–	0.2583	0.2555
2	–	0.1326	0.1241	–	0.2974	0.2956
3	–	0.1491	0.1421	–	0.3272	0.3253
4	–	0.1637	0.1573	–	0.3524	0.351
5	–	0.1771	0.1717	–	0.3757	0.3749
6	–	0.1893	0.1845	–	0.3962	0.3952
7	–	0.1992	0.1955	–	0.4122	0.4117
8	–	0.2059	0.2027	–	0.4221	0.4217
9	–	0.2106	0.2087	–	0.4298	0.4287
Never	0.2219	0.2219	0.2219	0.4495	0.4495	0.4495

Table 1: True parameter values ψ_0.

3.1 Target parameter

Formally, a parameter is defined as a mapping Ψ which can be applied to any probability distribution P. The range for this mapping is the parameter space, normally considered to be the real number line $\mathbb{R}$. Here, we define this mapping to be

$$\Psi(P_0^{\bar{a}}) \equiv \mathbb{E}_{P_0^{\bar{a}}} Y. \tag{3}$$

That is, we are interested in the cumulative probability of the event $L(t)$ at the final time point $K+1$ under a fixed treatment value a of the true distribution P_0.

As stated above in Section 2, the fixed treatment value $\bar{a}$ varies depending on the approach taken to address our violation. Therefore, in truth we are estimating different parameters.

3.1.1 True parameter values

Table 1 shows the true parameter values under various switch times. Figure 1 shows the values plotted on the log-odds scale with the resulting interpolated values from option 1 (i.e. selecting appropriate interventions and assuming linearity in the dose response curve).

4 Results

Discuss simulation results.

5 Discussion

Discuss what we just did and implications.

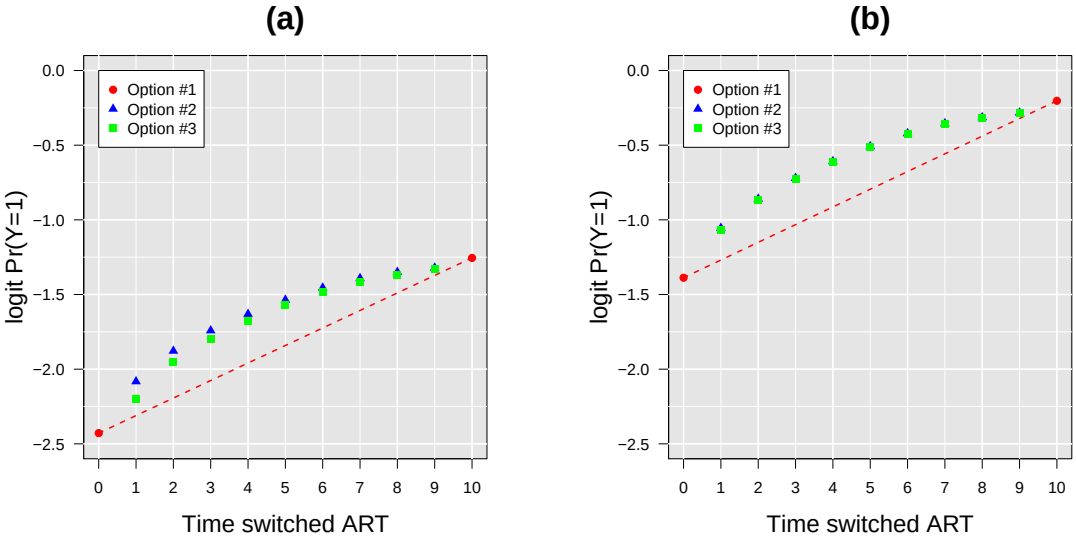

Figure 1: True parameter values with (a) $\beta_Z = 1.25$ and (b) $\beta_Z = 0$ in the log-odds scale.