Structural Cumulative Survival Models for Robust Estimation of Treatment Effects Accounting for Treatment Switching in Randomized Experiments

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SUMMARY

We propose an instrumental variable estimator to estimate the treatment causal effect when treatment switching is present in a randomized experiment, under a structural cumulative survival model. Our estimator is robust to violation of the exclusion restriction, a commonly adopted assumption for IV methods that is untestable and usually subject to questioning in practice, especially in an open-label randomized trial. We derive large-sample properties of our proposed estimator, along with inferential tools. We apply the estimator to evaluate the treatment effect of Nucleoside Reverse Transcriptase Inhibitors on a safety outcome in the Optimized Treatment That Includes or Omits NRTIs trial.

Some key words: Treatment switching; Open-label; G-estimation; Instrumental variable; Exclusion restriction; Robustness.

1. INTRODUCTION

Treatment switching (also called contamination or crossover) in a randomized controlled trial (RCT) is said to occur when a patient randomized to one treatment arm changes to another arm during the course of follow-up. It might happen at the point of disease progression, where patients in the control arm are switched to the experimental treatment in the hope of improving their prognosis. It can also occur due to changes in treatment guidelines, whereby treatment options might change during the course of follow-up.

The estimated treatment effect on overall survival can be substantially biased after patients switch without appropriate handling because the separation between treatment arms is lost. Treatment switching might also bias the intent-to-treat effect. In fact, in noninferiority/equivalence trials where both arms receive an active treatment and the null hypothesis is that the treatments are equivalently effective against the outcome, non-compliance in either arm due to some patients discontinuing their assigned treatment and either remaining untreated or initiating an external treatment, can lead to bias either towards the null or away from the null. In this case, the intent-to-treat analysis is not valid in the sense that the null hypothesis that the ITT is equal to zero does not necessarily imply the null hypothesis that the assigned treatments are equivalent. This is important for regulators, clinicians, and patients. Inaccurate cost-effectiveness estimates caused by not appropriately handling treatment switching may result, and finite healthcare resources may be wasted.

Although commonly used, conventional methods to deal with treatment switching typically hinge on a key underlying assumption of “no unmeasured confounding (NUC)”, that treatment is randomly assigned through time conditional on baseline or time-varying characteristics, fails to hold. Unfortunately, NUC tends to fail due to dependence upon unknown factors because even under the sharp null hypothesis of no treatment effect, patients who switch treatment tend to have a different overall survival prognosis than patients who remain on their originally assigned treatment. To accommodate unmeasured confounding, a prevailing approach resorts to so-called instrumental variables (IV). An IV is a pre-treatment variable known to be associated with the treatment variable (IV relevance), to only affect the outcome through its
effects on the treatment (IV exclusion restriction), and to otherwise be independent of any unmeasured confounder (IV independence). In randomized trials, the initial randomized treatment assignment can be readily leveraged as an IV since IV relevance and IV independence naturally hold. IV exclusion restriction, on the other hand, may fail to hold, especially under an open-label randomized trial, where patients may change their health-seeking behavior once knowing their initial randomized treatment assignments.

IV approaches include, for instance, the rank-preserving structural failure time model (RPSFTM) of Robins & Tsiatis (1991). A major complication with the estimation of RPSFTM is the need for artificial censoring to address administrative censoring, a technique that analytically treats some subjects for whom failure was actually observed as having been censored. It can further increase bias, aggravate efficiency loss, and render estimation computationally challenging. Shi et al. (2021) proposed an IV estimator under a structural cumulative survival model (SCSM) that accommodates time-varying treatment, which can be readily applied to studies with treatment switching. However, they assumed a constant treatment effect of the time-varying treatment. Recently, Ying & Tchetgen Tchetgen (2021) proposed an estimator of a treatment causal effect for a censored time to event outcome under a SCSM to account for selective treatment switching, which not only avoids administrative censoring but also allows for time-varying treatment effect.

However, all aforementioned IV methods rely heavily on the exclusion restriction for identification. This raises concerns about the validity of all IV methods above, especially in an open-label trial, when site investigators and participants knew the treatment assignments. This is because, one cannot rule out the possibility that study physicians might modify a patient’s treatment course as a result of their randomized treatment assignments in a manner that may in turn directly impact the outcome in view, or patients might change their health-seeking behavior after treatment assignment. These induce an unintended direct effect of the randomized treatment on the outcome, thus violating the exclusion restriction assumption of an IV.

In this paper, we handle treatment switching under a SCSM without assuming exclusion restriction. To that end, we adapt the “no interaction with unmeasured selection” assumption proposed in Tchetgen Tchetgen et al. (2021) to a time-varying treatment. Like Ying & Tchetgen Tchetgen (2021), we propose a recursive estimator that allows for a time-varying treatment effect and further develop an asymptotic framework for inference. We evaluate the proposed estimator’s finite-sample performance via extensive simulations, which, for the sake of space, are postponed into the supplementary materials. The proposed estimator and inferential tools are implemented in the freely available R package “ivsacim” (Ying, 2022) on R CRAN. We apply the proposed approach to evaluate the exposure effect of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) on a key safety outcome (time to first severe or worse sign or symptom) in participants receiving a new antiretroviral regimen that omitted or added NRTIs in the open-label Optimized Treatment That Includes or Omits NRTIs (OPTIONS) trial (Tashima et al., 2015), where treatment switching was present due to possible discontinuation of the NRTIs assignment.

2. Preliminaries

Define

- $T$, a time to event outcome of interest;
- $C$, potential censoring time, we observe $X = \min(T, C)$, a subject’s censored event time;
- $\Delta = 1(T \leq C)$ denotes a subject’s observed event indicator;
- We introduce the counting process notation. We write $N(t) = 1(X \leq t, \Delta = 1)$ and $Y(t) = 1(X \geq t)$ as the observed counting process and the associated at-risk processes;
- We assume that recorded data on treatment do not change except at discrete times $\{1, \cdots, M\}$. Thus the time-varying treatment $D(m) = 1$ if subject $i$ is treated or exposed at time $m$, 0 otherwise, write $D(m) = \{D(l) : 0 < l \leq m\}$. For any $m > X$, $D(m)$ is not observed. We define $D(m) = 0$ for $m > X$, so that the whole treatment process is well defined for each subject even after the outcome event has occurred;
- $Z = D(0)$ denotes the instrumental variable corresponding to the randomized treatment assignment in a randomized trial;
Indeed, under (2) and the no-current treatment value interaction condition, one can readily establish that

- We also introduce the counterfactual outcomes framework for time-varying treatments, $T(d(m), 0, z)$, the potential time to event had possibly contrary to fact, the subject followed the treatment regime $d(m)$ up to time $m$ and and the control treatment thereafter. We make the consistency assumption that $T = T(d(m), 0, z)$ with probability one for individuals with observed $D(m) = d(m)$, $D(l) = 0$, for $l > m$, and $Z = z$. We further assume that intervening on an exposure can only affect survival after the time of that exposure, in other words, the event $T(D(m - 1), 0, Z) \geq m$ occurs if and only if the event $T(D(l), 0, Z) \geq m$ also occurs for all $l \geq m$. It follows that $\{T \geq t\}$ and $\{T(D(m), 0, Z) \geq t\}$ are the same events for $t \in [m, m + 1)$.

We assume a structural cumulative survival model (SCSM),

$$
\frac{\mathbb{P}[T(D(m), 0, Z) > t|\bar{D}(m), Z, L, T \geq m]}{\mathbb{P}[T(D(m - 1), 0, z = 0) > t|\bar{D}(m), Z, L, T \geq m]} = \exp \{-\gamma_m(t; \bar{D}(m), L, Z)\},
$$

(1)

for any $t \geq m$. This model may be interpreted as encoding for individuals still at risk for the outcome at time $m$ with covariates, IV and treatment history $L, Z, \bar{D}(m)$, the ratio of survival probabilities of remaining event-free at time $t \geq m$ upon receiving one final blip of treatment at time $m - 1$ versus at time $m$. This ratio of conditional survival probabilities is modeled by the RHS of (1). For our analysis for the OPTIONS trial where $L = \emptyset$, we choose

$$
\gamma_m(t; \bar{D}(m), L, Z) = \gamma_m(t; D(m), L, Z) = \int_m^{t \wedge (m+1)} D(m)dB_D(s) + ZdB_Z(s),
$$

(2)

which posits that the causal effect of a final blip of treatment at time $m$ is short-lived in the sense that $\gamma_m(t; \bar{D}(m), L, Z) = \gamma_m(t; D(m), L, Z)$ for all $t \geq m + 1$, in other words, only the treatment $D(m)$ at time $m$ can modify the survival between $[m, m + 1)$. This assumption is needed for identification given only one instrument, which was also assumed in [Ying & Tchetgen Tchetgen (2021), Shi et al. (2021)].

Remark 1. Our model specification delivers a convenient summary of the cumulative treatment effect comparing the marginal survival function under the always-treated treatment regime (i.e. the survival curve for $T(1, z = 1)$) versus that of the never-treated treatment regime (i.e. the survival curve for $T(0, z = 0)$) in terms of the function $B_D(t)$, with an additional condition of no-current treatment value interaction [Robins & Greenland (1994)],

$$
\frac{\mathbb{P}[T(D(m - 1), d(m), 0, Z) > t|\bar{D}(m - 1), d(m), Z, L, T \geq m]}{\mathbb{P}[T(D(m - 1), 0, z = 0) > t|\bar{D}(m - 1), d(m), Z, L, T \geq m]} = \frac{\mathbb{P}[T(D(m - 1), d(m), 0, Z) > t|\bar{D}(m - 1), D(m) = 0, Z = 0, L, T \geq m]}{\mathbb{P}[T(D(m - 1), 0, z = 0) > t|\bar{D}(m - 1), D(m) = 0, Z = 0, L, T \geq m]}.
$$

Indeed, under (2) and the no-current treatment value interaction condition, one can readily establish that

$$
\frac{\mathbb{P}[T(1, z = 0) > t]}{\mathbb{P}[T(0, z = 0) > t]} = \exp \left\{-\int_0^t dB_D(s)\right\} = \exp \{-B_D(t)\}.
$$

Therefore our estimator $B_D(t)$ can be interpreted as the difference in the log-marginal cumulative intensity function comparing always-treated versus never-treated regimes up to time $t$, given all subjects are randomized to control. This encodes the causal effect of interest, that is, the causal effect of treatment received. Also, we have

$$
\frac{\mathbb{P}[T(\bar{1}, z = 0) > t]}{\mathbb{P}[T(0, z = 0) > t]} = \exp \left\{-\int_0^t dB_Z(s)\right\} = \exp \{-B_Z(t)\}.
$$

Hence $B_Z(t)$ can be interpreted as the controlled direct effect of treatment assignment on the outcome when the treatment received is set to control throughout an study. The no-current treatment value interaction assumption essentially states that the instantaneous causal effect of one final blip of treatment at time
Among individuals who were treated at time $m$ is equal to that among individuals who were not treated at time $m$ conditional on past history.

**Remark 2.** Ying & Tchetgen Tchetgen (2021); Shi et al. (2021) not only assumed the exclusion restriction, which we will review later among identification assumptions but also set $B_Z(t) \equiv 0$, implicitly imposing the homogeneity, which asserts that the instrument $Z$ does not modify the effect of the treatment $D(m)$ on the outcome $T$ on the multiplicative scale. We, however, do not assume them.

Other possible SCSM variants may be specified, including one which postulates a constant effect for each dose of treatment over time, while allowing the magnitude of the treatment effect to depend on the timing of the final blip of treatment. This equivalent sets $B_D(t) = \beta_{D,m}(t - m)$ and $B_Z(t) = \beta_{Z,m}(t - m)$ for $t \in [m, m + 1)$, and therefore (2) becomes

$$
\gamma_m(t; \bar{D}(m), L, Z) = \beta_{D,m}D(m)(t - m) + \beta_{Z,m}Z(t - m). \quad (3)
$$

A special case of this model may further impose that the treatment effects are constant as a function of the timing of the final treatment blip, that is, further setting $\beta_{D,m} = \beta_D$ and $\beta_{Z,m} = \beta_Z$. In this case, (2) becomes:

$$
\gamma_m(t; \bar{D}(m), L, Z) = \beta_D D(m)(t - m) + \beta_Z Z(t - m). \quad (4)
$$

which later we refer to as the “constant hazards difference model”. This model encodes the SCSM analog of the “common treatment effect” assumption of the rank preserving structural failure time models (Robins & Tsiatis, 1991), which states that the treatment effect is the same for all individuals (with respect to time spent on treatment) regardless of when treatment is received. (4) is typically assumed (Shi et al., 2021), which can be over-smoothing by neglecting time-varying effect of the time-varying treatment. Note that both (3) and (4) are submodels of our model (2). Finally, note that all SCSM described above are guaranteed to be correctly specified under the null hypothesis of no treatment effect, an appealing robustness property of the proposed framework.

Our proposed identification strategy leverages the randomization process as an instrumental variable satisfying two key standard IV assumptions, but not the exclusion restriction:

**Assumption 1 (IV relevance).** The instrument is associated with the exposure at $m$ for individuals still at risk for the event time for all $m$; specifically,

$$Z \perp D(m) | T \geq m, \bar{D}(m - 1), L.$$

IV relevance requires that for subjects who remain at risk for the outcome event at time $m$, the instrument remains predictive of current treatment status even after conditioning on treatment and covariate history. This is typically a reasonable assumption in a randomized trial, given that individuals randomized to the active arm are more likely than the control arm to be treated over time, even upon conditioning on their history.

**Assumption 2 (IV independence).** The instrument is independent of the potential outcome under no treatment, conditional on baseline covariates,

$$Z \perp T(\bar{d} = 0, z = 0) | L.$$

IV independence ensures that the IV itself is unconfounded (conditional on $L$). This assumption is clearly satisfied in a randomized trial as $Z$ is a randomized treatment assignment.

For completeness, here we introduce the exclusion restriction typically assumed in the IV literature. The exclusion restriction assumes that $T(d, z) = T(d)$, which rules out the possibility that randomization itself can impact the outcome via a pathway not involving treatment actually taken. However, this assumption as we mentioned earlier, is inclined to fail in an open-label randomized trial, as the knowledge of assigned treatment may change their health-seeking behavior which in turn influences the outcome. Inspired by Tchetgen Tchetgen et al. (2021), we assume:

**Assumption 3 (IV No Interaction with Unmeasured Confounders).** We assume the treatment process satisfies

$$E(D(t)|Z, L, T(\bar{d} = 0, z = 0)) = \alpha_1(t; Z, L) + \alpha_2(t; L, T(\bar{d} = 0, z = 0)).$$
Note that a linear model for treatment with no interaction between the mean and the empirical mean. In the appendix, we show that requiring that 

\[ C \perp (T, \bar{D}(t), Z) \mid L. \]

Note that although not further pursued here, the above assumption can be relaxed substantially by only assuming in IV literature (Li et al., 2015; Tchetgen Tchetgen et al., 2015; Ying et al., 2019), where they introduced an unknown confounder \( U \) for convenience, playing a similar role here as \( T(d = 0, z = 0) \).

In order to facilitate the exposition, we make a standard conditional independent censoring assumption.

**Assumption 4 (Conditional independent censoring).**

We also propose an estimator under the constant hazards difference model (4), where one may use \( \hat{\beta}_D = \int_0^\tau w(t) d\bar{B}_D(t) \) and \( \hat{\beta}_Z = \int_0^\tau w(t) d\bar{B}_Z(t) \), with \( w(t) = w(t)/\int_0^\tau w(s) ds \) and \( \tau \) denoting time of end of study. Note that although all theorems below are built for \( \hat{\beta}_D(t) \), they can be immediately translated for \( \hat{\beta}_D \) by Slutsky’s theorem and the functional Delta method, which we omit the details.

**Theorem 1.** Under Assumptions 1-4 model (2), and given the technical Assumptions 1 - 3 listed in the appendix, the estimator \( \hat{\beta}_D(t) \) is uniformly consistent for \( B_D(t) \) on \([0, \tau]\), namely,

\[ \sup_{t \in [0, \tau]} \left| \hat{\beta}_D(t) - B_D(t) \right| \rightarrow 0 \text{ a.s.} \]

**Theorem 2.** Under Assumptions 1-4, the model (2), and given the technical Assumptions 1 - 3 listed in the appendix, the normalized process \( \sqrt{n} |\hat{\beta}_D(t) - B_D(t)| \) converges weakly to a zero-mean Gaussian process with variance function that can be consistently estimated by

\[ E_n \hat{\epsilon}(t, \hat{\theta})^2, \]
with \( \hat{e}(t, \hat{\theta}) \) defined in the appendix. We have developed an R package named “ivsacim” (Ying, 2022) available on R CRAN. In addition to implementing inferences based on the estimator \( \hat{B}_D(t) \), the package also provides inferences based on the estimator \( \hat{\beta}_D \) and a goodness-of-fit test for the constant hazards difference model (4) \( (H_0 : B_D(t) = \beta_D t \text{ for all } t) \) and as well as for the causal null hypothesis \( (H_0 : B_D(t) \equiv 0 \text{ for all } t) \), thus effectively extending to the time-varying treatment the analogous test statistic for point treatment SCSMs developed by Martinussen et al. (2017).

4. Real Data Application

The OPTIONS trial was a multi-center, open-label, prospective, randomized, controlled study evaluating the benefits and risks of omitting versus adding NRTIs to a new optimized antiretroviral regimen. For the sake of space, we refer interested readers to (Tashima et al., 2015; Ying, 2022) for a thorough introduction on the data.

Participants were randomly assigned either to omit or to add NRTIs after choosing an optimized regimen and an NRTI regimen. Treatment switching occurred in this trial due to the potential discontinuation of NRTI assignment. This occurred when a participant in the omit-NRTIs group started any NRTI or when a participant in the add-NRTIs group failed to initiate or permanently discontinued all NRTIs (event time was the scheduled week during which the event was recorded). A summary of events and treatment switching in the study can be found in Table 1.

|                      | Add NRTIs (n = 180) | Omit NRTIs (n = 177) | Difference (95% CI), percentage points |
|----------------------|---------------------|----------------------|---------------------------------------|
| First severe or worse sign or symptom | 51 (28.3)           | 35 (19.8)            | 8.6 (-0.8 to 17.9)                    |
| Change in NRTI assignment | 10 (5.3)            | 17 (9.5)             | -4.0 (-10.1 to 2.0)                   |
| Change in NRTI assignment before safety outcome failure | 8 (3.4)             | 9 (2.8)              | -0.6 (-4.4 to 5.4)                   |

Ying & Tchetgen Tchetgen (2021) investigated the treatment effect under their SCSM leveraging initial randomized as an IV, assuming the exclusion restriction. They found a significant time-varying effect of NRTIs on the safety outcome, which revealed possible safety concern of NRTIs. However, a caveat here is that the OPTIONS trial was open-label, that is, site investigators and participants knew the treatment assignments. This might lead to the violation of the exclusion restriction, thus invalidating their analysis. Therefore, we would like to reanalyze the OPTIONS trial without assuming the exclusion restriction.

Using the proposed approach to formally account for treatment switching by leveraging randomized treatment assignment as an IV for treatment actually received which is likely confounded by unmeasured factors, we performed a test of the sharp null hypothesis of no individual causal effect, i.e. \( B_D(t) = 0 \), against which we found nonsignificant statistical evidence, P-value 0.098. Our approach also delivered a nonparametric estimator \( \hat{B}_D(t) \) along with 95% pointwise confidence bands displayed in Figure 1. From the figure, we observe a hazard rate for experiencing the safety outcome severe/worse sign/symptom over time in the add-NRTI group compared to the omit-group. Under a constant hazards difference model, our approach estimated a hazards difference of 0.00167 (-0.003, 0.006), P-value 0.433, though there is significant evidence of a time-varying effect, indicated by our goodness-of-fit test rejecting the constant effect model (P-value 0.005). The test of the null hypothesis of no direct causal effect of the randomization, i.e. \( B_Z(t) = 0 \), reports nonsignificant P-value 0.125.

Ying & Tchetgen Tchetgen (2021) uncovered possible safety concern of NRTIs. Our analysis revealed that such safety concern is mainly caused by the controlled direct effect of unblinded treatment assignment. Therefore it might be explained by possible change of treatment courses by the clinicians or possible health-seeking behavior of treatment-aware patients.
Fig. 1. Kaplan-Meier curves of the time to safety outcome (first severe or worse sign or symptom) between groups, where loss to follow up or end of study are treated as censoring.

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REFERENCES

LI, J., FINE, J. & BROOKHART, A. (2015). Instrumental variable additive hazards models. *Biometrics* **71**, 122–130.
MARTINUSSEN, T., VANSTEELANDT, S., TCHETGEN TCHETGEN, E. J. & ZUCKER, D. M. (2017). Instrumental variables estimation of exposure effects on a time-to-event endpoint using structural cumulative survival models. *Biometrics* **73**, 1140–1149.
ROBINS, J. M. & GREENLAND, S. (1994). Adjusting for differential rates of prophylaxis therapy for pcp in high-versus low-dose azt treatment arms in an aids randomized trial. *Journal of the American Statistical Association* **89**, 737–749.
ROBINS, J. M. & TSIATIS, A. A. (1991). Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Communications in Statistics-Theory and Methods* **20**, 2609–2631.
SHI, J., SWANSON, S. A., KRAFT, P., ROSNER, B., DE VIVO, I. & HERNÁN, M. A. (2021). Instrumental variable estimation for a time-varying treatment and a time-to-event outcome via structural nested cumulative failure time models. *BMC Medical Research Methodology* **21**, 1–12.
TASHIMA, K. T., SMEATON, L. M., FICHTENBAUM, C. J., ANDRADE, A., ERON, J. J., GANDHI, R. T., JOHNSON, V. A., KLINGMAN, K. L., RITZ, J., HODDER, S. et al. (2015). Hiv salvage therapy does not require nucleoside reverse transcriptase inhibitors: a randomized, controlled trial. *Annals of Internal Medicine* **163**, 908–917.
TCHETGEN TCHETGEN, E. J., SUN, B. & WALTER, S. (2021). The genius approach to robust mendelian randomization inference. *Statistical Science* **36**, 443–464.
TCHETGEN TCHETGEN, E. J., WALTER, S., VANSTEELANDT, S., MARTINUSSEN, T. & GLYMOUR, M. (2015). Instrumental variable estimation in a survival context. *Epidemiology (Cambridge, Mass.)* **26**, 402–410.
YING, A. (2022). *ivsacim: Structural Additive Cumulative Intensity Models with IV*. R package version 2.0.0.
YING, A. & TCHETGEN TCHETGEN, E. J. (2021). A new causal approach to account for treatment switching in randomized experiments under a structural cumulative survival model. *arXiv preprint arXiv:2103.12206*.
YING, A., XU, R. & MURPHY, J. (2019). Two-stage residual inclusion for survival data and competing risks—an instrumental variable approach with application to seer-medicare linked data. *Statistics in Medicine* **38**, 1775–1801.

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