Estimation of separable direct and indirect effects in continuous time

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\begin{abstract}
Many research questions involve time-to-event outcomes that can be prevented from occurring due to competing events. In these settings, we must be careful about the causal interpretation of classical statistical estimands. In particular, estimands on the hazard scale, such as ratios of cause-specific or subdistribution hazards, are fundamentally hard to interpret causally. Estimands on the risk scale, such as contrasts of cumulative incidence functions, do have a clear causal interpretation, but they only capture the total effect of the treatment on the event of interest; that is, effects both through and outside of the competing event. To disentangle causal treatment effects on the event of interest and competing events, the separable direct and indirect effects were recently introduced. Here we provide new results on the estimation of direct and indirect separable effects in continuous time. In particular, we derive the nonparametric influence function in continuous time and use it to construct an estimator that has certain robustness properties. We also propose a simple estimator based on semiparametric models for the two cause-specific hazard functions. We describe the asymptotic properties of these estimators and present results from simulation studies, suggesting that the estimators behave satisfactorily in finite samples. Finally, we reanalyze the prostate cancer trial from Stensrud et al. (2020).

\textbf{Keywords}
competing events, hazard functions, influence function, separable effects, survival analysis
\end{abstract}

\section{Introduction}

In survival analysis, the event of interest can be prevented from occurring due to a competing event. The presence of competing events requires us to be careful about the interpretation of classical statistical estimands (Robins, 1986; Young et al., 2020). In particular, it is well-established that estimands on the hazard scale, such as cause-specific hazard or subdistribution hazard ratios, do not have a causal interpretation unless we impose strong assumptions that usually are unreasonable (Robins, 1986; Hernán, 2010; Martinussen et al., 2020; Young et al., 2020). Yet the cumulative incidence function, which is defined on the risk scale (Andersen et al., 2012), has a causal interpretation as the total effect on the event of interest (Young et al., 2020).

However, the total effect, that is, the conventional cumulative incidence function, does not inform us about the mechanisms by which the treatment exerts effects on the event of interest. To illustrate this, suppose that we perfectly executed a randomized experiment in which 1000 patients received a cancer drug and 1000 patients received control. Five years after randomization, 250 patients died in the treatment arm and 500 died in the control arm,
and therefore the drug was successfully shown to reduce mortality after 5 years. However, the drug was excreted by the kidneys and to study a potential side effect the investigators did an additional analysis in which kidney failure was the primary outcome. They found 250 kidney failures in the treatment arm and 100 kidney failures in the placebo arm 5 years after randomization (in individuals who possibly died after getting kidney failure). Two scientists debated the treatment effect on kidney events. As the drug was known to be excreted by the kidneys, the first scientist suspected that the increase in kidney events was a biological side effect. The second scientist doubted this explanation and claimed that the increase in kidney events occurred because the drug reduced mortality, and hence more subjects were at risk of developing kidney events in the treatment arm. Thus, even though the scientists could identify the cumulative incidences of mortality and kidney events, they were unable to agree on the causal mechanism by which treatment causes kidney events.

It has sometimes been suggested that the marginal distribution function, also called the net risk, can be used to assess the causal effect of treatment on the event of interest outside of its effect on the competing event. However, interpreting this estimand requires us to consider a hypothetical intervention to prevent the competing event. In particular, this creates direct effect.

The paper is organized as follows. In Section 2, we describe the observed data structure, establish notation that will be used in subsequent sections, and define the separable effects in continuous time. In Section 3, we derive the nonparametric influence function of the separable direct effect in continuous time, propose an estimator based on the influence function, and define its robustness to model misspecification. In Section 4, we study the asymptotic properties of the so-called plug-in estimator when Cox proportional hazard models are used for estimation. We also describe the asymptotic properties of the one-step estimator that is based on the efficient influence function. In Section 5, we give the efficient influence function of the separable indirect effect. In Section 6, we assess the performance of the estimators in a simulation study and reanalyze the prostate cancer data from Stensrud et al. (2020). In Section 7, we provide a discussion. Detailed calculations are given in the Supporting Information.

2 | DATA STRUCTURE AND NOTATION

Suppose that we observe data from a study in which \( i = 1, \ldots, n \) individuals receive a dichotomous treatment \( A_i \). For each individual \( i \), we measure data on a vector of covariates, \( W_i \), before treatment assignment, and each \( i \) has an event time \( T_i \) of type \( \varepsilon_i \in \{1, 2\} \), where \( \varepsilon_i = 1 \) denotes the event of interest \( Y \) and \( \varepsilon_i = 2 \) the competing event \( D \). We will hereby suppress the individual \( i \) subscript, because the random vector for each individual is assumed to be drawn independently from a distribution common to all subjects. Because of loss to follow-up, we only observe \( \Delta = I(T \leq C) \) and \( T = \min(T, C) \), where \( C \) denotes the right censoring time. We assume that \( (T, \varepsilon) \) and \( C \) are conditionally independent given \( (A, W) \). To focus on the main ideas of this work and simplify the derivations, we initially develop the theory without censoring. Thus, we first assume that data for a given individual consist of the vector \( Z = (T, \varepsilon, A, W) \). However, the results immediately extend to settings with censoring, where the censoring may depend on \( A \) and \( W \), as we describe in more detail in Section 3.
2.1 Treatment decompositions

To define our estimands of interest—the separable effects—we consider a decomposition of $A$ into two dichotomous components, $A_Y$ and $A_D$, inspired by Robins and Richardson (2010). Analogous to Stensrud et al. (2020), we suppose that the $A_Y$ component exerts all its effects on the event of interest ($Y$) outside of the competing event ($D$), and $A_D$ exerts all its effect on $Y$ through $D$. This assumption is denoted full isolation (Stensrud et al., 2021).

In the observed data, the treatment components are deterministically related in each individual, $A = A_Y = A_D$, but we will conceive a hypothetical experiment in which these components are assigned different values. This decomposition assumption motivates the definition of our separable direct and indirect effects. However, the separable effects can still be meaningful, even if a physical decomposition of the treatment is not possible, for example, if we can conceive a modified treatment that operates in the same way as the $A_Y$ component of $A$, but does not exert effects on $D$ (Stensrud et al., 2020, 2021).

2.2 Definition of separable effects

We use superscripts to denote counterfactuals, such that $T^a$ is the event time when, possibly contrary to fact, $A$ is set to $a$, and $e^a$ indicates whether an event of interest $Y(e^a = 1)$ or a competing event $D(e^a = 2)$ occurred at $T^a$. Similarly, $T^{a_Y,a_D}$ and $e^{a_Y,a_D}$ denote counterfactual values under an intervention that sets $A_Y$ to $a_Y$ and $A_D$ to $a_D$.

We will consider the cumulative incidence function under an intervention that sets $A_Y$ to $a_Y$ and $A_D$ to $a_D$,

$$P_1(t, a_Y, a_D) \equiv P(T^{a_Y,a_D} \leq t, e^{a_Y,a_D} = 1).$$

Similar to the results in Stensrud et al. (2020) in discrete time, we can now define the separable direct effect of treatment $A$ at the time $t$ as

$$P_1(t, 1, a_D) \text{ vs. } P_1(t, 0, a_D) \text{ for } a_D \in \{0, 1\}.$$

At the time $t$, the separable direct effect quantifies the effect of treatment $A$ on the event of interest $Y$ not mediated by its effect on the competing event. In our introductory example on kidney failure, the separable direct effect $P_1(t, 1, 1)$ versus $P_1(t, 0, 1)$ could correspond to a comparison of the original cancer drug and a modified cancer drug that is metabolized in the liver and thus does not have any side effects on the kidneys.

The separable indirect effect is defined as

$$P_1(t, a_Y, 1) \text{ versus } P_1(t, a_Y, 0) \text{ for } a_Y \in \{0, 1\}.$$

At the time $t$, the separable indirect effect quantifies the treatment effect on the event of interest only through its effect on the competing event.

Note that pairs of separable direct and indirect effects sum to the total effect, which is equal to the classical cumulative incidence function, that is,

$$\{P_1(t, 1, a) - P_1(t, 0, a)\} + \{P_1(t, 1 - a, 1) - P_1(t, 1 - a, 0)\} = P_1(t, 1, 1) - P_1(t, 0, 0),$$

for $a \in \{0, 1\}$.

2.3 Identifiability conditions

Consider the additive separable direct effect,

$$\delta_1(t, a_D) = P_1(t, 1, a_D) - P_1(t, 0, a_D) \text{ for } a_D \in \{0, 1\}.$$

To identify $\delta_1(t, a_D)$ from the observed data, where $A$ and the components $A_Y$ and $A_D$ are deterministically related, we impose the following conditions, which are continuous time analogues to the conditions in Stensrud et al. (2020); see also Robins and Richardson (2010).

We assume conditional exchangeability, that is,

$$(T^a, e^a) \perp A \mid W \text{ for } a \in \{0, 1\},$$

which is a classical exchangeability condition that is expected to hold when treatment $A$ is randomly assigned.

Second, we assume consistency, such that if an individual has observed treatment $A = a$, then

$$(T^a, e^a) = (T, e),$$

for $a \in \{0, 1\}$. The consistency assumption ensures that the observed outcome is equal to the counterfactual outcome for any individual who has observed data history consistent with a counterfactual scenario.

Third, positivity such that

$$f_W(w) > 0 \Rightarrow \Pr(A = a \mid W = w) > 0 \text{ for } a \in \{0, 1\},$$

(1)
where \( t^* \) denotes the end of follow-up and \( f_W(\cdot) \) is the density of \( W \). Note that (1) is the usual positivity condition under interventions on \( A \) and (2) ensures that among those event-free through each follow-up time, there exist individuals with \( A = 1 \) and individuals with \( A = 0 \) that are uncensored.

Finally, we impose dismissible component conditions, which are key conditions for identification of the separable effects (Robins et al., 2020; Stensrud et al., 2020, 2021). To introduce these conditions, let \( \Lambda_j(t|A = a, W = w) \) denote the conditional cause-specific hazard function with \( j = 1, 2 \), denoting the \( j \)th cause, and let \( \Lambda_j(t|A = a, W = w) = \int_0^t \Lambda_j(s|A = a, W = w) \, ds \) be the corresponding cumulative conditional cause-specific hazard function. Similarly, let \( \lambda_j^a(t|W = w) \) and \( \lambda_j^{a,D}(t|W = w) \) be the counterfactual conditional cause-specific hazard functions under interventions on \( A \) and joint interventions on \( A_Y \) and \( A_D \), respectively. Then, the dismissible components conditions are

\[
\Delta 1 : \lambda_1^{a,Y,a_D = 1}(t|W = w) = \lambda_1^{a,Y,a_D = 0}(t|W = w),
\]

\( a_Y \in \{0, 1\} \),

at all \( t \), which states that a counterfactual hazards functions of the event of interest \( (j = 1) \) are equal under all values of \( A_D \), and

\[
\Delta 2 : \lambda_2^{a,Y = 1,a_D}(t|W = w) = \lambda_2^{a,Y = 0,a_D}(t|W = w),
\]

\( a_D \in \{0, 1\} \),

at all \( t \), which states that counterfactual hazards functions of the competing event \( (j = 2) \) are equal under all values of \( A_Y \). Although these two conditions are formulated using cause-specific hazard functions, we do not require any causal interpretation of these hazard functions. As a matter of fact, such an interpretation is in any case subtle as it is distorted by selection effects because of the intrinsic conditioning on \( T^{a_Y,a_D} \geq t \). The dismissible component conditions put restrictions on the distribution of \( T^{a_Y,a_D} \) given \( T^{a_Y,a_D} \geq t \), but how the population, obtained by this conditioning, is formed does not matter. This also has some resemblance to the definition of organic interventions in Lok (2016). Note that the dismissible component conditions can be empirically tested (falsified) in a future four-arm trial in which both \( A_Y \) and \( A_D \) are randomly assigned (Robins and Richardson, 2010; Robins et al., 2020, 2021).

### 2.4 Functionals of counterfactual and observed data

Let

\[
P_1(t, a_Y, a_D, w) = \int_0^t e^{-\Lambda_1(s|A = a_Y, w) - \Lambda_2(s|A = a_D, w)} \, d\Lambda_1(s|A = a_Y, w),
\]

\[
\delta_1(t, a_D, w) = P_1(t, 1, a_D, w) - P_1(t, 0, a_D, w).
\]

Under the treatment decomposition assumption and the identification conditions in Section 2.3, the cumulative incidence function for \( Y \) under treatment \( a \) conditional on \( W = w \) is given by \( P_1(t, a, a, w) \), which is also denoted by \( P_1(t|a, w) \). Then a continuous-time equivalent to the G-formula (Robins, 1986) in Stensrud et al. (2020) is

\[
P(T^{a_Y,a_D} \leq t, e^{a_Y,a_D} = 1) = E \{P(T^{a_Y,a_D} \leq t, e^{a_Y,a_D} = 1|W)\}
\]

\[
= \int P_1(t, a_Y, a_D, w) f_W(W = w) \, dw,
\]

because of \( \Delta 1 \) and \( \Delta 2 \). The G-formula given in the latter display allows us to identify our parameter of interest, \( \delta_1(t, a_D) = E[\delta_1(t, a_D, W)] \), from the observed data.

### 2.5 Estimation using classical regression models

Suppose we were willing to postulate (semi)parametric models for the cause-specific hazard functions, such as Cox proportional hazards models. Then it would be straightforward to estimate \( \delta_1(t, a) \) using

\[
\hat{\delta}_1(t, a) = \hat{P}_1(t, 1, a) - \hat{P}_1(t, 0, a),
\]

where

\[
\hat{P}_1(t, 1, a) = n^{-1} \sum_i \left\{ \int_0^t e^{-\Lambda_1(s|A = 1, W_i)} - \Lambda_2(s|A = a, W_i) \, d\Lambda_1(s|A = 1, W_i) \right\},
\]

\[
\times d\Lambda_1(s|A = 1, W_i),
\]

\[
\hat{P}_1(t, 0, a) = n^{-1} \sum_i \left\{ \int_0^t e^{-\Lambda_1(s|A = 0, W_i)} - \Lambda_2(s|A = a, W_i) \, d\Lambda_1(s|A = 0, W_i) \right\},
\]

\[
\times d\Lambda_1(s|A = 0, W_i).\]
because the terms in $P_1(t, 1, a)$ and $P_1(t, 0, a)$ can easily be estimated using Cox models for the two cause-specific hazard functions. That is, if $\lambda_j(t | a, w) = \lambda_{j0}(t)e^{\beta_j^Tz}$, with $l = (a, w^T)^T$, then $\hat{\lambda}_j(s | l)$ is obtained from $\hat{\lambda}_{j0}(t)e^{\beta_j^Tz}$, which can be estimated from a Cox regression analysis. Asymptotic properties can also be derived using the approach of Chen et al. (2010), which we return to in Section 4.1. This type of estimator is usually referred to as a plug-in estimator (Fisher and Kennedy, 2020).

However, using such semiparametric regression models for the cause-specific hazard functions may lead to biased results if these models are misspecified. Therefore we will provide more general results, based on semiparametric theory (van der Vaart, 2000; van der Laan and Robins, 2003), which leads us to estimators with desirable properties such as semiparametric efficiency and certain kinds of robustness (Bang and Robins, 2005) that generally make them more attractive than plug-in estimators (Fisher and Kennedy, 2020). The primary tool to finding these estimators is to derive the so-called efficient influence function (see van der Vaart, 2000), which we do in Section 3.

## 3 THE EFFICIENT INFLUENCE FUNCTION AND ESTIMATION OF THE SEPARABLE DIRECT EFFECT

In this section, we give the efficient influence function for the target parameter

$$\psi_1(P) = \delta_1(t, 1) = E\{P_1(t, 1, 1, W)\} - E\{P_1(t, 0, 1, W)\},$$

where we use $P$ to denote the probability measure from which we observe $Z = (T, \varepsilon, A, W)$. We remind the reader that $\psi_1(P)$ is an (additive) separable direct effect: it is the effect of the component $A_\varepsilon$ when $A_\delta$ is set to 1. As discussed in Section 2.2, this separable effect is often of substantial interest. It could, for example, correspond to a comparison of the original cancer drug and a modified cancer drug that does not affect the kidneys.

Note that it is possible to recode the treatment variable $A$, that is, interchanging the two levels 0 and 1, and thus we can restrict our attention to $\delta_1(t, 1)$ without loss of generality. The corresponding separable indirect effect is $P_1(t, 0, 1) - P_1(t, 0, 0)$, which we describe in more detail in Section 5.

We impose no structure on $P$ and show in the Supporting Information that the efficient influence function is

$$\psi(t, Z) = \left\{ N_1(t) - P_1(t, 1, 1, W) \right\} \frac{I(A = 1)}{P(A = 1 | W)}$$

$$- \left\{ \int_0^t e^{-\Lambda_2(s | 1, W)} dN_1(s) - P_1(t, 0, 1, W) \right\}$$

$$\times \frac{I(A = 0)}{P(A = 0 | W)}$$

$$- \int_0^t \left\{ P_1(t, 0, 1, W) - P_1(u, 0, 1, W) \right\}$$

$$\times \left[ \frac{dM_1^T(u | 0, W)}{P(T > u | 0, W) P(A = 0 | W)} \right]$$

$$\left[ \frac{dM_1^T(u | 1, W)}{P(T > u | 1, W) P(A = 1 | W)} \right]$$

$$- \frac{dM_2^T(u | 1, W)}{P(T > u | 1, W) P(A = 1 | W)} I(A = 1)$$

$$+ \delta_1(t, 1, W) - E\{ \delta_1(t, 1, W) \},$$

where $N_j(t) = I(T \leq t, \varepsilon = j)$ is the $j$th specific counting process and $M_j^T(t | a, w)$ is the corresponding counting process martingale given $A = a, W = w$, that is, $M_j^T(t | a, w) = N_j(t) - \int_0^t I(s \leq t) d\Lambda_j(s | a, w)$. We can further rewrite the efficient influence function in terms of the counting process martingales (see the Supporting Information for further details),

$$\psi(t, Z) = \int h_1(s, t, A, W) dM_1^T(s | A, W)$$

$$+ \int h_2(s, t, A, W) dM_2^T(s | A, W)$$

$$+ \delta_1(t, 1, W) - E\{ \delta_1(t, 1, W) \},$$

where

$$h_1(s, t, A, W) = I(s \leq t) g(A, W) e^{-\Lambda_2(s | 1, W)}$$

$$\times \left\{ 1 - \frac{\{F_1(t | A, W) - F_1(s, | A, W)\}}{P(T > s | A, W)} \right\},$$

$$h_2(s, t, A, W) = I(s \leq t) g(A, W) P(T > s | A, W)$$

$$\times \left\{ P_1(t, 0, 1, W) - P_1(s, 0, 1, W) \right\}$$

$$\times \frac{e^{-\Lambda_2(s | 1, W)}}{e^{-\Lambda_2(s | A, W)}} \left\{ F_1(t | A, W) - F_1(s, | A, W) \right\},$$

$$g(A, W) = \frac{A}{P(A = 1 | W)} - \frac{1 - A}{P(A = 0 | W)}.$$
imposed no structure on \( P \) (Tsiatis, 2006, formula 10.76): the efficient influence function based on the observed data \( O = (T, \Delta, \Delta \epsilon, A, W) \) is given by

\[
\psi(t, O) = \frac{\hat{\psi}(t, Z)\Delta}{K_C(T|A, W)} + \int_0^\infty \frac{L(s, A, W)}{K_C(s|A, W)} dM_C(s|A, W),
\]

(4)

where we let \( K_C(s|A, W) = \int_0^s \lambda_C(u|A, W) du \) denote the cumulative censoring hazard function, \( K_C(s|A, W) = e^{-\Lambda_C(s|A, W)} \) is the corresponding survival function for the censoring process, and

\[
M_C(t|A, W) = N_C(t) - \int_0^t I(s \leq \tilde{T})d\Lambda_C(s|A, W)
\]

is the martingale associated with the censoring counting process \( N_C(t) = I(T \leq t, \Delta = 0) \) using the filtration where we include \( A \) and \( W \). In (4),

\[
L(s, A, W) = E\{\hat{\psi}(t, Z)|T > s, A, W\}.
\]

Following Lemma A.2 of Lu and Tsiatis (2008), which is easily generalized to the competing risk setting considered here (see the Supporting Information for details), we can express (4) in terms of the counting process martingales based on the observed data. We get that the efficient influence function based on the observed data can be written as

\[
\psi(t, O) = \phi(t, O) + \delta_1(t, 1, W) - E\{\delta_1(t, 1, W)\},
\]

(6)

where

\[
\phi(t, O) = \int \frac{h_1(s, t, A, W)}{K_C(s|A, W)} dM_1(s|A, W)
\]

\[
+ \int \frac{h_2(s, t, A, W)}{K_C(s|A, W)} dM_2(s|A, W)
\]

and where \( M_j(t|a, w), j = 1, 2 \), are the cause-specific observed counting process martingales given \( A = a, W = w \), that is, for \( j = 1, 2 \),

\[
M_j(t|a, w) = \Delta I(T \leq t, \epsilon = j) - \int_0^t I(s \leq \tilde{T})d\Lambda_j(s|a, w).
\]

The one-step estimator \( \hat{\delta}_{1e}(t, 1) \) based on the efficient influence function is thus given by

\[
\hat{\delta}_{1e}(t, 1) = n^{-1} \sum_{i=1}^n \{ \hat{\delta}_1(t, 1, W_i) + \hat{\phi}(t, O_i) \},
\]

(7)

where \( \hat{\delta}_1(t, 1, W_i) \) is defined analogously to \( \delta_1(t, 1, W_i) \), except that the unknown quantities are replaced with estimated counterparts, and similarly for \( \hat{\phi} \). This part requires working models, and in Section 3.1 we describe how robust the resulting estimator is to misspecification of these working models. Note also that the one-step estimator is equal to the simple plug-in estimator \( \hat{\delta}_1(t, 1) \) plus an augmentation term.

### 3.1 Robustness

We argue now that the estimator \( \hat{\delta}_{1e}(t, 1) \) given in (7) has certain robustness properties unlike the initial estimator \( \hat{\delta}_1(t, 1) \) based on Cox models for the cause-specific hazard functions. Consider first the setting where there is no censoring, that is, we are then basing estimation on the efficient influence function \( \hat{\psi}(t, Z) \) given in (3). Let \( H \) denote the unknown parameters that go into the efficient influence function \( \hat{\psi}(t, Z) \), that is, \( H = \{\Lambda_1(\cdot|A, W), \Lambda_2(\cdot|A, W), P(A = 1|W)\} \). Our estimator in this case is then the solution to 0 = \( n^{-1} \sum_i \hat{\psi}(t, Z_i, H_n) \), where \( H_n \) is an estimator of \( H \). We show in the Supporting Information that the resulting estimator is consistent if two out of the three possible working models are correctly specified. Now consider the setting where we allow for censoring. Let \( G \) denote the unknown parameters that go into the efficient influence function, that is, \( G = \{\Lambda_1(\cdot|A, W), \Lambda_2(\cdot|A, W), P(A = 1|W), \Lambda_C(\cdot|A, W)\} \) so there are now four models, which we denote (i)–(iv) in the order indicated in the definition of \( G \). We show in the Supporting Information that \( \hat{\delta}_{1e}(t, 1) \) is consistent if the following models are correctly specified: (i) and (ii), or (i), (iii), and (iv), or (ii), (iii), and (iv). Hence, in a randomized study with the censoring being independent of \( W \) then we obtain consistency if one of the two cause-specific hazard models is correctly specified, but not necessarily both.

### 4 LARGE SAMPLE PROPERTIES

#### 4.1 Properties under proportional cause-specific hazards

In this subsection, we assume that the cause-specific hazard functions are of Cox proportional hazards form, that is, that these models are correctly specified. Specifically, let

\[
\Lambda_j(t|a, w) = \Lambda_{0j}(t)e^{\beta_j a + \beta_{0j} w}, \quad j = 1, 2,
\]
and
\[ P_1(t, a_Y, a_D) = n^{-1} \sum_i P_i(t, a_Y, a_D, W_i), \]
where \( P_i(t, a_Y, a_D, W_i) \) is calculated using the estimates from fitting separate Cox regression models with the event of interest and the competing event as a dependent variable. We show in the Supporting Information that
\[ n^{1/2} \{ \hat{P}_1(t, a_Y, a_D) - P(t, a_Y, a_D) \} = n^{-1/2} \sum_i \xi_i(t, a_Y, a_D) + o_p(1), \]
where \( \xi_i(t, a_Y, a_D) \) are zero-mean independently and identically distributed terms (i.e., the influence function) so that \( \hat{P}_1(t, a_Y, a_D) \) is a regular asymptotically linear (RAL) estimator (Tsiatis, 2006) as long as the specified Cox proportional hazards models for the cause-specific hazard functions are correctly specified. In the Supporting Information, we also give further details on how to estimate the influence function facilitating estimation of the variance of the estimator.

### 4.2 Nonparametric properties

Let
\[ \hat{\phi}(t, O, G) = \delta_1(t, 1, W, G) + \phi(t, O, G), \]
so that the efficient influence function \( \psi(t, O, G) \) is reexpressed as \( \hat{\phi}(t, O, G) - \delta_1(t, 1) \) with \( G \) being defined in Section 3.1 (see, e.g., (6)). If \( G \) is known then
\[ 0 = n^{-1} \sum_i \{ \hat{\phi}(t, O_i, G) - \hat{\delta}_{1e}(t, 1) \} = n^{-1} \sum_i \{ \phi(t, O_i, G) - \delta_1(t, 1) \} - \{ \hat{\delta}_{1e}(t, 1) - \delta_1(t, 1) \}, \]
from which we see that \( \hat{\delta}_{1e}(t, 1) \) has the influence function \( \psi(t, O, G) \), that is, the efficient influence function. Thus, in this case, \( \hat{\delta}_{1e}(t, 1) \) is a semiparametrically efficient RAL estimator (Tsiatis, 2006). In reality, \( G \) is not known and needs to be estimated. Let \( G_n \) be such an estimator of \( G \). The proposed estimator \( \hat{\delta}_{1e}(t, 1) \) solves
\[ 0 = n^{-1} \sum_i \{ \hat{\phi}(t, O_i, G_n) - \hat{\delta}_{1e}(t, 1) \}, \]
and, therefore,
\[ n^{1/2} \{ \hat{\delta}_{1e}(t, 1) - \delta_1(t, 1) \} \]

### 5 THE EFFICIENT INFLUENCE FUNCTION OF THE SEPARABLE INDIRECT EFFECT

Analogous to the results in Section 3, we get the efficient influence function for the separable indirect effect, \( P_1(t, 0, 1) - P_1(t, 0, 0) \), which can be written as a function of the observed data,
\[ \psi^l(t, O) = \phi^l(t, O) + P_1(t, 0, 1, W) - P_1(t, 0, 0, W) \]
\[ - \{ P_1(t, 0, 1) - P_1(t, 0, 0) \}, \]
where
\[ \phi^l(t, O) = \int h_1^l(s, t, A, W) \frac{dM_1(s|A, W)}{K_C(s|A, W)} \]
\[ + \int h_2^l(s, t, A, W) \frac{dM_2(s|A, W)}{K_C(s|A, W)}, \]
with
\[ h_1^l(s, t, A, W) \]
\[ = I(s \leq t)g(A, W) \left\{ 1 - \frac{e^{-\Lambda_2(s|A, W)}}{e^{-\Lambda_2(s|A, W)}} \right\} \]
\[
\left\{ 1 - \frac{\{ F_1(t|A, W) - F_1(s, |A, W) \}}{P(T > s|A, W)} \right\},
\]

\[
h_2(s,t,A,W) = I(s \leq t) \frac{g(A, W)}{P(T > s|A, W)} \times \left[ P_1(t,0,1,W) - P_1(s,0,1,W) \right] \left\{ 1 - \frac{1}{e^{-\Delta_2(s,1,W)}} \right\} \left\{ F_1(t|A,w) - F_1(s,|A, W) \right\},
\]

and \( M_j(t|a,w), j = 1, 2 \), are the cause-specific observed counting process martingales given \( A = a, W = w \).

6 | SIMULATIONS

6.1 | Performance of \( \hat{\delta}_1(t,1) \)

We first consider the performance of the estimator \( \hat{\delta}_1(t,1) \) that is based on using Cox-proportional hazards models for the two cause-specific hazard functions. Clearly, this estimator is only consistent if the proportional cause-specific hazards models are correctly specified. To generate data, we used the cause-specific hazard functions

\[
\lambda_1(t|A = a, W = w) = \lambda_{10}(t)e^{\beta_1 A + \beta_W W} \\
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_2 A + \beta_W W}
\]

with \( \lambda_{10}(t) = 0.05, \beta_1 A = -\log(2), \beta_W = 0.5 \log(2) \), and with \( \lambda_{20}(t) = 0.1, \beta_2 A = -0, \beta_W = 0.5 \log(2) \). The treatment indicator \( A \) was generated with \( P(A = 1) = 0.5 \), and the covariate \( W \) was uniform on \((0,1)\). Censoring was generated according to the minimum of 7 and an exponential distribution with a mean of 12. We then calculated the estimators \( \hat{P}_1(t,1,1), \hat{P}_1(t,0,1) \) and \( \hat{\delta}_1(t,1) = \hat{P}_1(t,1,1) - \hat{P}_1(t,0,1) \) and their corresponding standard error estimators, all calculated at time points 2, 4, and 6. Results are summarized in Table 1. Each entry in the table is based on 1000 replicates.

Both the estimators and their corresponding standard error estimators behave satisfactorily (Table 1). At the early time points, the coverage is slightly less than the nominal level for \( P_1(t,1,1) \) and \( P_1(t,0,1) \) when \( n = 400 \) but improves for \( n = 800 \).

6.2 | Performance of the estimator \( \hat{\delta}_{1e}(t,1) \)

We now assess the performance of the estimator \( \hat{\delta}_{1e}(t,1) \) given in (7), which is derived from the efficient influence function. We investigate the robustness properties of this estimator. We also report results for the simple estimator \( \hat{\delta}_{1e}(t,1) \). The exposure \( A \) is binary, and the covariate \( W \) is uniform on \((0,1)\). To be able to compute \( \hat{\delta}_{1e}(t,1) \), we need working models for the two cause-specific hazard models, the propensity score and the censoring hazard function. We used Cox proportional hazard models for the two cause-specific hazard models with main effects of \( A \) and \( W \), a logistic regression model with main effects of \( W \) for the propensity score, and a Cox proportional hazards model for the censoring hazard function with the effect of \( A \) only. Let \( L = I(W > 1/2) \), \( \lambda_{10}(t) = 0.05, \lambda_{20}(t) = 0.1, \beta_{1A} = -\log(5), \beta_{2A} = 0, \beta_W = \log(2) \beta_{2W} = 0.5 \log(2) \). Censoring times were generated as \( C = \min(C,12) \), where \( C \) was generated using the hazard function \( \lambda_C(t|A,W) \) specified below. We used a sample size of \( n = 400 \) and simulated data from the following different scenarios:

\[
A1 \quad \text{All models are correctly specified.}
\]

\[
\lambda_1(t|A = a, W = w) = \lambda_{10}(t)e^{\beta_1 A + \beta_W W}, \\
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_2 A + \beta_W W} \\
\lambda_C(t|A,W) = \lambda_{20}(t)e^{\beta_2 A + \beta_W W}
\]

\[
P(A = 1|W) = \expit(\log(2)(W - 0.5)), \\
\lambda_C(t|A,W) = 12.
\]

\[\text{TABLE 1} \quad \text{Simulation results concerning the estimators} \]

\[
\begin{array}{ccccccccc}
\hline
\text{n} & \text{t} & \text{t} & \text{t} & \text{t} & \text{t} & \text{t} & \text{t} & \text{t} \\
\text{200} & \text{4} & \text{6} & \text{2} & \text{4} & \text{6} \\
\text{True} P_1(t,1,1) & 0.052 & 0.089 & 0.118 & 0.052 & 0.089 & 0.118 \\
\text{Mean} \hat{P}_1(t,1,1) & 0.052 & 0.089 & 0.118 & 0.052 & 0.089 & 0.118 \\
\text{sd} (\hat{P}_1(t,1,1)) & 0.013 & 0.020 & 0.025 & 0.009 & 0.014 & 0.018 \\
\text{95% CP}(\hat{P}_1(t,1,1)) & 0.924 & 0.934 & 0.945 & 0.939 & 0.938 & 0.942 \\
\text{True} \hat{\delta}_1(t,1) & 0.100 & 0.170 & 0.219 & 0.100 & 0.170 & 0.219 \\
\text{Mean} \hat{\delta}_1(t,1) & 0.099 & 0.169 & 0.218 & 0.100 & 0.170 & 0.219 \\
\text{sd} (\hat{\delta}_1(t,1)) & 0.020 & 0.027 & 0.032 & 0.014 & 0.019 & 0.023 \\
\text{95% CP}(\hat{\delta}_1(t,1)) & 0.929 & 0.952 & 0.952 & 0.948 & 0.954 & 0.956 \\
\text{95% CP}(\hat{\delta}_{1e}(t,1)) & 0.946 & 0.951 & 0.952 & 0.956 & 0.957 & 0.956 \\
\hline
\end{array}
\]
A2 All models are correctly specified except the censoring model.
\[
\lambda_1(t|A = a, W = w) = \lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w},
\]
\[
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_A^2 a + \beta_W^2 w},
\]
\[
P(A = 1|W) = \expit(\log(2)(W - 0.5)),
\]
\[
\lambda_C(t|A, W) = 12e^{0.2W}.
\]

B1 The cause-specific hazard models and the censoring model are correctly specified, but the propensity score model is not.
\[
\lambda_1(t|A = a, W = w) = \lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w},
\]
\[
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_A^2 a + \beta_W^2 w},
\]
\[
P(A = 1|W) = 0.7L + 0.1(1 - L),
\]
\[
\lambda_C(t|A, W) = 12.
\]

B2 The cause-specific hazard models are correctly specified, but the propensity score model and the censoring model are not.
\[
\lambda_1(t|A = a, W = w) = (1 - a)\lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w} + a\lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w - \beta_A^1 L - \beta_W^1 (1 - L) + \beta_W^1 w},
\]
\[
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_A^2 a + \beta_W^2 w},
\]
\[
P(A = 1|W) = \expit(0 + \log(2)(W - 0.5)),
\]
\[
\lambda_C(t|A, W) = 12e^{0.2W}.
\]

C1 \(\lambda_2(t|A = a, W = w)\) is a proportional hazard, but \(\lambda_1(t|A = a, W = w)\) is not. The propensity score model and the censoring model are correctly specified:
\[
\lambda_1(t|A = a, W = w) = (1 - a)\lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w} + a\lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w - \beta_A^1 L - \beta_W^1 (1 - L) + \beta_W^1 w},
\]
\[
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_A^2 a + \beta_W^2 w},
\]
\[
P(A = 1|W) = \expit(0 + \log(2)(W - 0.5)),
\]
\[
\lambda_C(t|A, W) = 12.
\]

C2 \(\lambda_2(t|A = a, W = w)\) is a proportional hazard, but \(\lambda_1(t|A = a, W = w)\) is not. The propensity score model is correctly specified, but the censoring model is not
\[
\lambda_1(t|A = a, W = w) = (1 - a)\lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w} + a\lambda_{10}(t)e^{\beta_A^1 a + \beta_W^1 w - \beta_A^1 L - \beta_W^1 (1 - L) + \beta_W^1 w},
\]
\[
\lambda_2(t|A = a, W = w) = \lambda_{20}(t)e^{\beta_A^2 a + \beta_W^2 w},
\]
\[
P(A = 1|W) = \expit(0 + \log(2)(W - 0.5)),
\]
\[
\lambda_C(t|A, W) = 12e^{0.2W}.
\]

We used 250 bootstrap replicates to calculate the bootstrap estimate of the variability of \(\hat{\delta}_1(t, 1)\). We also calculated an estimator of the variability based on the squared efficient influence function.

The results are summarized in Table 2, where each entry in the table is based on 1000 replicates. We see that both estimators are consistent under scenarios A1 and A2, and that the simple estimator is slightly more efficient, as expected since both cause-specific hazard functions are proportional. In Scenario B1 and B2, where the two cause-specific hazards models are correctly specified but the propensity score model is misspecified, both estimators are consistent. Under scenario C1, where only \(\lambda_2(t|A, W)\) is a proportional hazard, the simple estimator is biased whereas the one based on the efficient influence function is still consistent, as both the censoring and propensity score models are correctly specified. Under scenario C2, where the censoring model is misspecified, the estimator based on the efficient influence function is now slightly biased, while the plug-in estimator suffers from more severe bias.

### 6.3 Prostate cancer data

To illustrate the new estimators, we used data from a randomized trial on prostate cancer therapy (Byar and Green, 1980), which were also analyzed in Stensrud et al. (2020). Data and R-code can be found in the Supporting Information. We restricted our analysis to the patients who received placebo (127 patients) and high-dose diethylstilbestrol (DES) (125 patients).

We included baseline measurements of daily activity function (binary), age (centered around its mean), hemoglobin level (centered around its mean), and previous cardiovascular disease (binary) in our analysis. We considered death due to prostate cancer as the event of interest and death due to other causes (consisting primarily of cardiovascular deaths) as the competing event.

The events were recorded in monthly intervals from randomization. We used Cox proportional hazards models to obtain the following hazard ratio estimates of the two cause-specific hazards (comparing treatment to placebo):

| Event | Hazard Ratio (95% CI) |
|-------|----------------------|
| Primary event | 0.74 (0.45, 1.21) |
| Competing event | 1.17 (0.90, 1.52) |

However, these hazard ratio estimates cannot be interpreted causally...
TABLE 2 Simulation results concerning the simple estimator $\delta_i(t, 1)$ and the one-step estimator based on the efficient influence function, $\delta_i(t, 1)$. We let $\text{se}_{\text{v}}$ denote the average (over the sample) standard error estimate based on the squared efficient influence function and $\text{se}_{\text{v}}$, denotes the average (over the sample) standard error estimate based on 250 bootstrap replicates. Each entry in the table is based on 1000 replicates.

| A1 | $t = 1$ | $t = 3$ | $t = 5$ | $t = 7$ | $t = 9$ |
|----|---------|---------|---------|---------|---------|
| True $\delta_i(t, 1)$ | -0.052 | -0.128 | -0.178 | -0.210 | -0.231 |
| Mean $\delta_i(t, 1)$ | -0.052 | -0.128 | -0.177 | -0.209 | -0.229 |
| Mean $\delta_i(t, 1)$ | -0.052 | -0.128 | -0.178 | -0.209 | -0.229 |
| sd ($\delta_i(t, 1)$) | 0.014 | 0.024 | 0.029 | 0.032 | 0.034 |
| sd ($\delta_i(t, 1)$) | 0.020 | 0.029 | 0.033 | 0.035 | 0.036 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.020 | 0.030 | 0.035 | 0.037 | 0.038 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.020 | 0.029 | 0.033 | 0.035 | 0.036 |

| A2 | $t = 1$ | $t = 3$ | $t = 5$ | $t = 7$ | $t = 9$ |
|----|---------|---------|---------|---------|---------|
| True $\delta_i(t, 1)$ | -0.052 | -0.128 | -0.178 | -0.210 | -0.231 |
| Mean $\delta_i(t, 1)$ | -0.052 | -0.127 | -0.176 | -0.208 | -0.228 |
| Mean $\delta_i(t, 1)$ | -0.052 | -0.127 | -0.176 | -0.207 | -0.227 |
| sd ($\delta_i(t, 1)$) | 0.015 | 0.028 | 0.034 | 0.039 | 0.042 |
| sd ($\delta_i(t, 1)$) | 0.020 | 0.033 | 0.038 | 0.042 | 0.044 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.020 | 0.032 | 0.038 | 0.042 | 0.046 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.020 | 0.031 | 0.038 | 0.042 | 0.044 |

| B1 | $t = 1$ | $t = 3$ | $t = 5$ | $t = 7$ | $t = 9$ |
|----|---------|---------|---------|---------|---------|
| True $\delta_i(t, 1)$ | -0.052 | -0.128 | -0.178 | -0.210 | -0.231 |
| Mean $\delta_i(t, 1)$ | -0.052 | -0.126 | -0.176 | -0.207 | -0.227 |
| Mean $\delta_i(t, 1)$ | -0.052 | -0.126 | -0.176 | -0.207 | -0.227 |
| sd ($\delta_i(t, 1)$) | 0.014 | 0.025 | 0.031 | 0.034 | 0.037 |
| sd ($\delta_i(t, 1)$) | 0.024 | 0.036 | 0.041 | 0.043 | 0.046 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.024 | 0.037 | 0.043 | 0.046 | 0.048 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.023 | 0.035 | 0.040 | 0.043 | 0.044 |

| C1 | $t = 1$ | $t = 3$ | $t = 5$ | $t = 7$ | $t = 9$ |
|----|---------|---------|---------|---------|---------|
| True $\delta_i(t, 1)$ | 0.065 | 0.120 | 0.120 | 0.11 | 0.092 |
| Mean $\delta_i(t, 1)$ | 0.054 | 0.093 | 0.113 | 0.121 | 0.124 |
| Mean $\delta_i(t, 1)$ | 0.064 | 0.114 | 0.118 | 0.105 | 0.091 |
| sd ($\delta_i(t, 1)$) | 0.030 | 0.040 | 0.042 | 0.041 | 0.041 |
| sd ($\delta_i(t, 1)$) | 0.030 | 0.041 | 0.043 | 0.044 | 0.043 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.030 | 0.040 | 0.042 | 0.042 | 0.042 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.030 | 0.040 | 0.042 | 0.042 | 0.042 |

| C2 | $t = 1$ | $t = 3$ | $t = 5$ | $t = 7$ | $t = 9$ |
|----|---------|---------|---------|---------|---------|
| True $\delta_i(t, 1)$ | 0.065 | 0.120 | 0.120 | 0.110 | 0.092 |
| Mean $\delta_i(t, 1)$ | 0.054 | 0.111 | 0.134 | 0.144 | 0.147 |
| Mean $\delta_i(t, 1)$ | 0.066 | 0.117 | 0.122 | 0.111 | 0.099 |
| sd ($\delta_i(t, 1)$) | 0.032 | 0.043 | 0.047 | 0.049 | 0.050 |
| sd ($\delta_i(t, 1)$) | 0.031 | 0.044 | 0.048 | 0.051 | 0.052 |
| $\text{se}_{\text{v}}$($\delta_i(t, 1)$) | 0.030 | 0.043 | 0.048 | 0.050 | 0.051 |

(Stensrud et al., 2020; Young et al., 2020). We could use the hazard models to estimate the net risk of prostate cancer mortality. As emphasized in the Introduction, this is not desirable because we would need to conceptualize a hypothetical intervention to prevent death from other causes. This is an ill-defined and implausible intervention, which is not of scientific interest.

Whereas the confidence intervals are wide and cover null effects, the point estimates of the cumulative incidence curves suggest that the treatment reduces the risk of death to prostate cancer (Figure 1, left display), but increases the risk of death due to other causes (Figure 1, right display).

To disentangle the causal treatment effect on the risk of dying from prostate cancer and competing events, we estimated the separable direct $\delta_i(t, 0)$ using the proposed $\delta_i(t, 0)$ (Figure 2, left display). The point estimates suggest a beneficial separable direct effect of the prostate cancer therapy (although the confidence intervals mostly cover 0). It is seen that the separable direct effect after 40 months is estimated to be approximately −0.09, that is, $\delta_i(t = 40, 0) = −0.09$ (95% CI: −0.17, −0.01), suggesting that a component of treatment reduces the risk of death due to prostate cancer. As discussed in Stensrud et al. (2020), this is supported by the biological argument that DES prevents the male testicles from producing testosterone, which, in turn, may prevent prostate cancer cells from replicating. On the other hand, the separable indirect effect (Figure 2, right display) is estimated to be approximately −0.01 (95% CI: −0.05, 0.03) at $t = 40$. The point estimate of the indirect effect suggests that some individuals died due to side effects of DES, but the confidence intervals are wide. The simple plug-in direct effect estimator $\delta_i(t, 0)$ was very similar to the one-step estimator, for example, $\delta_i(t = 40, 0) = −0.5$.

Given that our identifiability conditions hold, the point estimates of the direct and indirect effect suggest that DES mainly is beneficial, but some individuals are harmed by the treatment. Thus, based on the point estimates, we would conclude that there is potential for improving the prostate cancer treatment by providing a new (modified) drug that does not exert effects on death due to other causes. Finally, we note that such modified treatments, which can be conceived as combinations ($A_Y = 1, A_D = 0$), exist today: Luteinizing hormone releasing hormone antagonists and orchidectomy (castration) are now frequently used to suppress testosterone production in prostate cancer patients. Unlike DES, these treatments do not contain estrogen. Indeed, DES is rarely used today because it increases the risk of cardiovascular events (Turo et al., 2014; Dobbs et al., 2019). The sample size in our data
FIGURE 1 Results from the prostate cancer data example. The curves describe the cumulative incidence of prostate cancer death (left panel) and death due to other causes (right panel). The full curves denote the placebo arm, while the dotted curves denote the treatment arm; along with the curves are also shown 95% confidence bands.

FIGURE 2 Separable effects in the prostate cancer data application. The left panel shows the estimator for the direct effect \( \hat{\delta}_{1e}(t, 0) \) (on prostate cancer death, full curve) against time (months) with dashed lines showing 95% confidence bands using the nonparametric bootstrap. The right panel shows the corresponding separable indirect effect (on death from other causes, full curve) with dashed lines showing 95% confidence bands using the nonparametric bootstrap.

example is small, and therefore our estimates have wide confidence intervals. Nevertheless, it is seen that estimates (and confidence intervals) of separable effects and classical statistical estimands are different, both in terms of interpretation and magnitude.

7 CONCLUDING REMARKS

The separable direct and indirect effects clarify the causal interpretation of treatment effects in competing event settings (Stensrud et al., 2020), which are ubiquitous
in medicine and epidemiology. Our new results enable researchers to estimate these effects using classical statistical models for survival analysis, such as Cox proportional hazards models. Moreover, by deriving the nonparametric efficient influence function, we have obtained a one-step estimator of the separable effects. Alternatively, one may estimate the parameter using targeted maximum likelihood estimation (TMLE); see van der Laan and Rubin (2006) and van der Laan and Rose (2011). In the Supporting Information, we give calculations to carry out TMLE for the specific parameters considered in this paper.

The estimator derived from the efficient influence function has certain desirable robustness properties, allowing some of the working models to be misspecified. It is, however, not straightforward to estimate the variance of the resulting estimator, because it depends on the working models that may contribute to the variability of the estimator. This is a well-known problem; see, for instance, Moore and van der Laan (2009) and van der Laan and Rose (2011). In this article, we use the nonparametric bootstrap to estimate the variance. Alternatively, one may follow the more complicated route outlined in Benkeser et al. (2017) that gives a detailed description of the asymptotic linearity of a similar estimator, although in a simpler setting than the one considered in this paper. Extending the method of Benkeser et al. (2017) to the setting considered in the present paper is a topic for future research.

DATA AVAILABILITY STATEMENT

The prostate cancer data analyzed in this paper are available in the Supporting Information.

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**SUPPORTING INFORMATION**

Web Appendices referenced in Sections 3, 4 and 7 are available with this paper at the Biometrics website on the Wiley Online Library. Available is also the prostate-data and some R-code performing the proposed estimation for the prostate-data.

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