Simpson's paradox in survival models

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Abstract

In the context of survival analysis it is possible that increasing the value of a covariate X has a beneficial effect on a failure time, but this effect is reversed when conditioning on any possible value of another covariate Y. When studying causal effects and influence of covariates on a failure time, this state of affairs appears paradoxical and raises questions about the real effect of X. Situations of this kind may be seen as a version of Simpson's paradox.

In this paper we study this phenomenon in terms of the linear transformation model. The introduction of a time variable makes the paradox more interesting and intricate: it may hold conditionally on a certain survival time, that is, on an event of the type $\{T > t\}$ for some but not all t, and it may hold only for some range of survival times.

Key words: Cox model, detrimental covariate, linear transformation model, omitting covariates, positive dependence, proportional hazard, proportional odds model, protective covariate, total positivity.

1 Introduction

Survival analysis data sometimes give rise to situations where a certain covariate X appears to increase the risk of failure in each subgroup defined by the values of another covariate Y, but decreases that risk when there is no conditioning on Y. This may be puzzling, and one may then find it hard to understand the nature of the influence of X on the failure time T. In fact this is an important case of the well-known Simpson's paradox. In this paper we analyze this phenomenon in terms of the linear transformation model, with particular emphasis on the classical Cox regression model, and obtain conditions under which the paradox holds. The time factor which enters in the survival analysis setup makes the paradox more subtle because, as we shall see, it may hold for certain survival times and conditionally on having survived certain times, but not for all such times.

A huge body of literature exists on Simpson's paradox (Simpson, 1951) and related phenomena. An early example concerning survival appears in Cohen & Nagel (1934).

Blyth (1973) gave a simple description of Simpson's paradox in terms of conditional probabilities. Given three events E, F, H, the paradox is the simultaneous occurrence of the following three inequalities

$$\begin{aligned} P(E|F \cap H) &> P(E|F^c \cap H), \\ P(E|F \cap H^c) &> P(E|F^c \cap H^c), \\ P(E|F) &\le P(E|F^c). \end{aligned} \tag{1}$$

Samuels (1993) extended the consideration of the paradox from events to random variables and explained it as a particular case of the *association reversal* or of the *association distortion* phenomena. Aitkin (1998) observed a Simpson's paradox phenomenon in an example related to posterior Bayes factors, and connected it to dependence between covariates. The connection between Simpson's paradox and various dependence concepts has been further exploited by Scarsini & Spizzichino (1999), where an extensive bibliography on the paradox can be found. More recently Rinott & Tam (2003) described conditions under which an instance of the paradox is natural rather than surprising.

We now formalize the paradox for residual failure times. In the whole paper the term increasing (decreasing) means nondecreasing (nonincreasing). Furthermore, when we condition on covariates, we omit the specification "almost surely." Given a failure time T and two covariates X, Y, Simpson's paradox at (t, s) is the simultaneous occurrence of the following two conditions:

$$P(T > t + s | T > t, X = x, Y = y) \text{ is strictly decreasing in } x \text{ for all } y, \tag{2a}$$

$$P(T > t + s | T > t, X = x) \text{ is increasing in } x. \tag{2b}$$

In words, (2a) means that, conditionally on every value of the covariate Y, higher values of X reduce the residual survival probability of s time units given survival at time t (i.e., X is detrimental for T given Y), whereas (2b) means that, unconditionally on Y, the opposite is true (i.e., X is protective for T) for the given values of t and s. In a similar way one may consider situations where the monotonicities are reversed. As we shall see the paradox (2) may hold for certain values of t and s, which we analyze, and not all values, making it more complicated than standard versions of Simpson's paradox.

To see the relation between (2) and (1), define $E = \{T > t + s\}$, $F = \{X = x\}$, $H = \{Y = y\}$, and

$$G = \{X \in \{x, x'\}\} \cap \{Y \in \{y, y'\}\} \cap \ \{T > t\}. \tag{3}$$

The inequalities (1) applied to the conditional probability $P(\cdot|G)$ for all $x' > x$, $y' > y$, become (2). Conditioning on G amounts to treating X and Y as dichotomous, and looking at T only after time t. Indeed the dichotomous case will receive special attention, since the problem essentially reduces to this case.

In the context of survival analysis, it is natural to express Simpson's paradox also in terms of the hazard rate. Since the hazard rate function concerns only the immediate future, the resulting formulation of the paradox is closely related to (2) for small values of s. The conditional hazard rate h is defined by

$$h(t|x,y) := \lim_{s \searrow 0} \frac{P(t+s > T > t | T > t, X = x, Y = y)}{s}, \tag{4a}$$

$$h(t|x) := \lim_{s \searrow 0} \frac{P(t+s > T > t | T > t, X = x)}{s}. \tag{4b}$$

Whenever we talk about hazard rate, we assume that it exists. We say that the hazard-rate Simpson's paradox holds for a given t if

$$h(t|x,y) \text{ is strictly increasing in } x \text{ for all } y, \tag{5a}$$

$$h(t|x) \text{ is decreasing in } x. \tag{5b}$$

In this paper we show that the paradox occurs naturally under certain conditions. We study the range of values of (t, s) for which the paradox (2) holds, and show that under some circumstances it holds for all $s, t > 0$.

It is clear that the classical Simpson's paradox (1) can arise only if the conditioning events exhibit some form of dependence. If F and H are independent, then (1) is impossible. However, our analysis shows that we can have Simpson's paradox even if the covariates X and Y are independent. This surprising phenomenon is due to the fact that, conditioned on the survival history, the covariates may become dependent, and, for suitable values of the parameters, the paradox may arise.

The paper is organized as follows. Section 2 describes the model. Section 3 considers the case of continuously distributed covariates. Section 4 deals with dichotomous covariates.

In Section 5 we consider the paradox in terms of hazard rates. We show the possibility of the paradox for independent covariates in Section 6. Section 7 deals with the issue of omitting relevant covariates. In Section 8 a biomedical example of the paradox is shown within a gene therapy context. Data from failure times of mice are examined conditionally on two covariates that describe properties of the cancer treatment they receive. All proofs are contained in the Appendix.

2 The model

The conditional survival function of T will be assumed to follow the well-known linear transformation model

$$K(T) = -\beta_X X - \beta_Y Y + W, \tag{6}$$

where K is an increasing function and W is a random variable independent of X and Y, supported on the whole real line. The reader is referred to Box & Cox (1964); Cuzick (1988); for a more recent reference see, e.g., Lu & Liang (2006).

We have

$$P(T > t + s | T > t, X = x, Y = y) = \frac{P(T > t + s | X = x, Y = y)}{P(T > t | X = x, Y = y)},$$

where

$$P(T > t | X = x, Y = y) = P(K(T) > K(t) | X = x, Y = y) = \overline{F}_W(K(t) + \beta_X x + \beta_Y y), \tag{7}$$

with $\overline{F}_W(w) := P(W > w)$. To avoid trivialities we will assume throughout that both $\beta_X, \beta_Y \neq 0$. Note that when $\beta_X > 0$ the probability in (7) is decreasing in x for all $t > 0$.

Definition 1. A random variable W is (strictly) IFR if its hazard rate h_W is (strictly) increasing. This is equivalent to assuming that $\log \overline{F}_W$ is (strictly) concave. A random variable is IFR, for instance, when its density is log-concave, such as normal, Gumbel, logistic, or gamma with shape parameter ≥ 1. DFR is defined by replacing increasing with decreasing and concave with convex.

Proposition 1. *Let the model* (6) *hold.*

(i) *Property* (2a) *holds for all* $s, t \geq 0$ *if and only if* $\beta_X > 0$*.*

(ii) *Property* (5a) *holds for a given* t *if and only if* $K'(t) > 0$ *and either* $\beta_X > 0$ *and* W *is strictly IFR, or* $\beta_X < 0$ *and* W *is strictly DFR.*

2.1 The Cox model

A particular case of the model in (6) is the proportional hazards (Cox) model (Cox, 1972)

$$h(t|x, y) = h_0(t)\exp\{\beta_X x + \beta_Y y\}, \tag{8}$$

where h_0 is the underlying baseline hazard rate. We assume that h_0 is a positive function such that $\int_t^\tau h_0(u)\ \mathrm{d}u$ is finite if and only if $\tau < \infty$ for all $t > 0$, that is

$$\infty > \int_t^\tau h_0(u)\ \mathrm{d}u \to \infty \quad \text{as} \quad \tau \to \infty\,. \tag{9}$$

This condition on h_0 corresponds to assuming that the failure time T is finite, but cannot be bounded with probability 1 by any finite constant. The latter assumption is technically useful, since it simplifies the presentation, but can be avoided.

By standard calculations the conditional survival function for the Cox model can be written as

$$P(T > t + s | T > t, X = x, Y = y) = \exp\left\{\left(-\int_t^{t+s} h_0(u)\ \mathrm{d}u\right)\exp\{\beta_X x + \beta_Y y\}\right\}. \tag{10}$$

To see that the Cox model is a particular linear transformation model choose in (7) a Gumbel-type distribution

$$\overline{F}_W(t) = \exp\{-\mathrm{e}^t\}, \quad -\infty < t < \infty. \tag{11}$$

The random variable W in (11) is strictly IFR.

From (11) it follows that

$$\begin{aligned} P(T > t|X = x, Y = y) &= P(K(T) > K(t)|X = x, Y = y) \\ &= P(W - \beta_X x - \beta_Y y > K(t)) \\ &= \exp\{-\exp\{K(t)\}\exp\{\beta_X x + \beta_Y y\}\}, \end{aligned}$$

hence we obtain (10) with $\int_0^t h_0(u)\,\mathrm{d}u = \exp\{K(t)\}$.

2.2 The proportional odds model

Another important example of the linear transformation model is the proportional odds model (see Bennett, 1983a,b; Pettitt, 1984). This model is obtained by considering in (6) a random variable W with a logistic distribution

$$\overline{F}_W(t) = \frac{1}{1+\exp\{t\}}, \quad -\infty < t < \infty. \tag{12}$$

It follows that

$$\frac{P(T > t|X = x, Y = y)}{1 - P(T > t|X = x, Y = y)} = \exp\{\beta_X x + \beta_Y y\}\frac{P(T > t|X = 0, Y = 0)}{1 - P(T > t|X = 0, Y = 0)}. \tag{13}$$

Notice that (13) holds for every choice of K in (6). The random variable W in (12) is strictly IFR.

In the Cox model changing the value of a covariate amounts to multiplying the conditional hazard rate by a constant, whereas in the proportional odds model the same is true for the odds ratio.

3 The paradox for continuous covariates

In order to find conditions for the paradox we need to model the dependence structure of the covariates. We consider now the case of continuous covariates that satisfy the model $Y = \kappa(X) + V$ with X and V independent, for some increasing function κ. In this case

$$f_Y(y|X = x) = f_V(y - \kappa(x)), \tag{14}$$

Theorem 1. *Consider the linear transformation model in* (6)*, and let the covariate Y have a conditional density* (14)*, where both W and V are IFR.*

(i) *Simpson's paradox* (2) *holds for all $t, s > 0$ if*

$$\beta_Y < 0 < \beta_X, \quad \textit{and} \quad \beta_X x + \beta_Y \kappa(x) \textit{ is decreasing in } x. \tag{15}$$

(ii) *If the variables W and V are both strictly IFR, then Simpson's paradox* (2) *holds for all $t, s > 0$ if and only if* (15) *holds.*

The hypothesis that κ is increasing implies that Y is stochastically increasing in X, which is a notion of positive dependence. When V is IFR, the joint density of (X, Y) is TP_2, which is a stronger notion of positive dependence (see, e.g., Joe, 1997); it can be shown that, under (15), this density remains TP_2 given $T > t$ for all $t > 0$, so this strong notion of positive dependence is preserved in time.

Notice that

(a) the function κ quantifies the strength of the dependence between X and Y,

(b) the coefficients β_X and β_Y express the influence of the covariates on T,

(c) condition (15) intertwines (a) and (b); if κ is differentiable, then it becomes $\kappa'(x) > \beta_X/|\beta_Y|$.

We further demonstrate the relation between the parameters of the transformation model and the dependence structure of the covariates in the special case of normal covariates, in which the dependence is simply captured by the correlation coefficient. We will see that the condition required is that the correlation be sufficiently large with respect to the ratio of the β's.

Corollary 1. *Consider the case where the conditional distribution of Y given $X = x$ is normal with mean $\mu + \rho x$ and variance $1 - \rho^2$, which happens for instance when the joint distribution of (X, Y) is bivariate normal with unit variances and correlation ρ. Then Simpson's paradox* (2) *holds for all $t, s > 0$ if and only if $\beta_Y < 0 < \beta_X$, and $\rho > \beta_X/|\beta_Y|$.*

4 The paradox for dichotomous covariates

In this section we assume that the covariates X and Y are dichotomous, each taking values 0 and 1. Although simple, this case is important in biostatistics, where treatment effect is often of interest, and is rich enough to show the salient features of the paradox.

4.1 The Cox Model

In Theorem 2 below we consider the Cox model (8). First we fix t and show that the set of values of s for which the paradox (2) holds, is a single interval. Conditions for this interval to be empty, contain the origin and/or be unbounded, depend on the joint distribution of the covariates and on their relative influence. The last part of the theorem shows that the range of t for which the paradox holds for all $s > 0$ is an upper interval. Define

$$p^t_{y|x} = P(Y = y|T > t, X = x), \quad A = \exp\{\beta_X\}, \quad \text{and} \quad B = \exp\{\beta_Y\}. \tag{16}$$

Notice that, by Proposition 1(i), property (2a) holds for all $s, t \geq 0$ if and only if $\beta_X > 0$, and, when covariates are dichotomous, (2b) is equivalent to

$$P(T > t + s|T > t, X = 0) < P(T > t + s|T > t, X = 1). \tag{17}$$

Therefore the combination of $\beta_X > 0$ and inequality (17) is equivalent to Simpson's paradox. We study (17) in the next theorem.

Theorem 2. *Consider the Cox model* (8) *where the covariates X and Y take only two values,* $0, 1$ *and are not degenerate. Let*

$$\beta_Y < 0 < \beta_X. \tag{18}$$

Then

(i) *There exist some $0 \leq s_1 \leq s_2 \leq \infty$ depending on β_X, β_Y, t, and h_0 such that inequality* (17) *holds if and only if $s \in (s_1, s_2)$. This interval may be empty. A sufficient condition for (s_1, s_2) to be empty is $p^0_{0|0} = 0$.*

Moreover, for s_1, s_2 of (i) *we have:*

(ii) *$s_1 < s_2 = \infty$ if and only if*

$$\beta_X < -\beta_Y \tag{19}$$

and

$$p^0_{1|0} = 0 \tag{20}$$

both hold.

(iii) $0 = s_1 < s_2$ *if and only if*

$$p^t_{1|1} \geq \frac{A-1}{A-AB} + \frac{p^t_{1|0}}{A}. \tag{21}$$

(iv) $s_1 = 0$ *and* $s_2 = \infty$ *if and only if* (20) *and*

$$p^t_{1|1} \geq \frac{A-1}{A-AB} \tag{22}$$

both hold. In this case there exists some $0 \leq t_0 \leq \infty$ *such that* (17) *holds for all* $t \in (t_0, \infty)$ *and all* $s > 0$.

Under condition (20), it can be shown that X and Y exhibit the strongest form of positive dependence: they are comonotone, that is, they are both increasing functions of some latent variable. We will show in the proof of Theorem 2 that $p^0_{1|0} = 0$ if and only if $p^t_{1|0} = 0$ for any $t > 0$, so that condition (20) means that given $X = 0$ then $Y = 0$ at any given time. Therefore, comonotonicity is preserved in time.

It is easy to see that, under (18), condition (21) implies $p^t_{1|1} \geq p^t_{1|0}$, which can be proved equivalent to X and Y being positively correlated.

Remark 1. The paradox does not depend on the coding of the dichotomous covariates. Suppose, for example, that we define $\widetilde{X} = 1 - X$, which amounts to recoding of the variable X. The hazard function (4) can be written as

$$h(t|\widetilde{x}, y) = h_0(t) \exp\{-\beta_{\widetilde{X}}\} \exp\{\beta_{\widetilde{X}}\widetilde{x} + \beta_Y y\},$$

where $\beta_{\widetilde{X}} = -\beta_X$. Now (2a) becomes

$$P(T > t + s|T > t, \widetilde{X} = \widetilde{x}, Y = y) \text{ is strictly increasing in } \widetilde{x} \text{ for all } y,$$

that is, $\widetilde{X}$ is protective for each level of y.

Assume now $\beta_{\widetilde{X}}, \beta_Y < 0$. The analog of Theorem 2 will provide condition for

$$P(T > t + s | T > t, \widetilde{X} = 1) < P(T > t + s | T > t, \widetilde{X} = 0)$$

that is, $\widetilde{X}$ is detrimental.

It is easy to see, for example, that Theorem 2 (iv) which says that the paradox holds for all s, holds under the condition

$$\widetilde{p}^t_{1|0} \geq \frac{\widetilde{A} - 1}{\widetilde{A} - \widetilde{A}B} \tag{23}$$

where

$$\widetilde{p}^t_{y|\widetilde{x}} = P(Y = y | T > t, \widetilde{X} = \widetilde{x}), \quad \widetilde{A} = \exp\{-\beta_{\widetilde{X}}\}, \quad \text{and} \quad B = \exp\{\beta_Y\}.$$

Condition (23) expresses a form of negative dependence among the covariates. So recoding $\widetilde{X} = 1 - X$ trivially yields the same paradox, where protective and detrimental in X are interchanged, and positive dependence of the covariates becomes negative dependence.

Notice that it is essential that Y take only two values, whereas such a restriction is not needed for X; for each pair of values $x_1 < x_2$ we would have an interval of s-values where the inequality $P(T > t + s | T > t, X = x_1) < P(T > t + s | T > t, X = x_2)$ holds. Since the intersection of intervals is itself an interval, we see that the conclusion of the theorem holds without restricting X to be dichotomous.

4.2 The proportional odds model

In the proportional odds model (13) the paradox can happen also on regions that are not intervals. For instance if $A = 7$, $B = .1$, $p^0_{0|0} = .9$, $p^0_{0|1} = .09$ (where the symbols are defined in (16)), then the paradox (2) happens for $t = 0$ on a region for s of the form $(0, s_1) \cup (s_2, \infty)$, with $s_1 \approx 6$ and $s_2 \approx 8$. Figure 1 shows the graph of the function $P(T > t + s|T > t, X = 0) - P(T > t + s|T > t, X = 1)$.

FIGURE 1 ABOUT HERE

5 The paradox for hazard rates

Here we study Simpson's paradox for hazard rates, namely, (5). It is clear from (4) and (5) that the hazard rate paradox is related to the survival paradox (2) with infinitesimal values of s. Proposition 1(ii) characterized (5a). Now we deal with (5b).

Proposition 2. *Let model* (6) *hold. If* (2b) *holds for small values of s, then* (5b) *follows.*

It is easy to see that Proposition 2 follows directly from (4b). Notice that in the Cox model Theorem 2(iii) gives a necessary and sufficient condition for (2b) for small values of s.

In other words Simpson's paradox for immediate survival (small s) implies the hazard-rate Simpson's paradox. The converse can be shown to hold under some technical uniform continuity assumptions, which are left to the reader.

6 Independent covariates

A straightforward calculation in (1) shows that a necessary condition for the existence of Simpson's paradox is that the conditioning events E and F be dependent. Here a necessary condition for the paradox (2) is that given $\{T > t\}$, X and Y be dependent. In particular, for the paradox to hold at $t = 0$ X and Y cannot be independent. Nevertheless it is possible to have the paradox at some time $t > 0$ even when the covariates are independent at time 0, due to the fact that independence is not preserved under conditioning.

Proposition 3. *Suppose the covariates X and Y are independent. There exists a choice of parameters in the Cox model* (10) *such that the paradox* (2) *holds for some $s, t > 0$.*

7 Omitting covariates

The issue of misspecification by omitting covariates in the Cox model has been studied by several authors (see, e.g., Gail et al., 1984; Solomon, 1984; Lagakos & Schoenfeld, 1984, 1986; Bretagnolle & Huber-Carol, 1985, 1988; Morgan, 1986; Struthers & Kalbfleisch, 1986; Lin & Wei, 1989; Anderson & Fleming, 1995; Di Serio, 1997; Gerds & Schumacher, 2001; DiRienzo & Lagakos, 2001a,b; Chen, 2002). Recently Sane & Kharshikar (2001) have connected the issue to Simpson's paradox.

Notice that in the Cox model for all values x_1, y_1, x_2, y_2 the difference

$$P(T > t + s | T > t, X = x_1, Y = y_1) - P(T > t + s | T > t, X = x_2, Y = y_2)$$

cannot change sign as a function of s. This is due to proportionality of the conditional hazard function (8), which implies that changing the value of some covariates moves the whole conditional hazard function up or down, but does not allow any crossing.

On the other hand the difference

$$P(T > t + s | T > t, X = x_1) - P(T > t + s | T > t, X = x_2)$$

can change sign, since the expression

$$P(T > t + s | T > t, X = x) = \int P(T > t + s | T > t, X = x, Y = y) \, \mathrm{d}F_Y(y | T > t, X = x) \tag{24}$$

is not a Cox model, but rather a mixture of Cox models, and mixing destroys proportionality of the hazards. Mixture of Cox models arise in Bayesian statistics (see, e.g., Gouget & Raoult, 1999; Ibrahim et al., 2001).

Therefore it is possible for Simpson's paradox to hold for some s, but not all. Since the class of Cox models is not closed under marginalization, if (10) holds, then

$$\exp\left\{\left(-\int_t^{t+s} h_0(u)\ \mathrm{d}u\right)\exp\{\beta_X x\}\right\}. \tag{25}$$

does not represent $P(T > t + s | T > t, X = x)$.

That misspecification of a model can lead to paradoxes is not entirely surprising. Here we have shown the more subtle fact that a Simpson-type paradox can arise even when the model is perfectly specified, just due to marginalization. As we said above, the proportional hazard feature of the Cox model implies that two conditional survival functions of the form (10), taken at two different values of X, never cross. The same obviously applies to (25). Therefore, misspecification through omission of a covariate can lead only to a a very drastic form of Simpson paradox, namely (10) is decreasing in x, and (25) is increasing in x *for all* s and t.

As already noted, in our model it is possible to have (10) decreasing in x, and (24) increasing in x *for some* values of s and t. Furthermore, the key element of the paradox is the dependence of the covariates X and Y, and this dependence is explicitly modeled via their joint conditional distribution at different times t.

8 Example: survival in gene therapy

Gene therapy is a form of molecular medicine which treats genetic diseases by replacing a defective gene, responsible for the pathology, with a functional one. The basic principle is to introduce a piece of genetic material into cells via a vector, which is typically a virus. The virus integrates with the cell DNA and thus delivers the genetic material into the cell nucleus.

It has been observed that when the virus integrates in certain gene regions (close to the starting point of the transcription), deregulation of the gene transcription may induce insertional mutagenesis. In this case genotoxicity occurs and as a consequence a subject may develop cancer. The integration process is then defined unsafe. Searching for a so called safety vector is now a major goal in gene therapy.

In the application considered here identically inbred mice are made tumor prone by knocking out the oncosuppressor related gene Cdkn2a. These mice develop a variety of tumors with a predictable onset time of 300 days. Bone marrow cells are then extracted from the mice and different vectors are inoculated in them. These cells are transplanted back in the mice, whose survival is then observed. One goal of this study is to investigate the influence of some covariates related to the integration process on the survival of mice. The data was obtained in the context of the study by Montini et al. (2006).

We consider two covariates which are related to how much and where the vector integrates in the genome. These two variables, Y = CIS (common integration sites) and X = NUCLEUS were observed on 60 mice.

The value $Y = 1$ indicates that integration occurred in a low density area, and $Y = 0$ means that integration occurs in a high integration density area, that is, in a genomic region that was targeted twice or more in close proximity.

The value $X = 0$ indicates that integration occurred in a gene which codifies a protein produced within the cell nucleus. This represents a further risk factor for the integration process.

In this data set we consider bone marrow cellular DNA integrations of 60 mice classified with respect to the above two dichotomous variables. Survival time of each mouse is given in days.

The joint distribution of (X, Y) is shown in the following table, indicating that in the present coding they are positively dependent.

TABLE 1 ABOUT HERE

Consider now a Cox Model as in (8). The standard estimation procedure that we use is based on maximizing the partial likelihood as a function of the β parameters and using the Breslow (1972, 1974) estimator for the cumulative baseline hazard function.

The proportionality-of-hazards assumption of Cox model was tested and was not rejected ($p = 0.23$). See Grambsch & Therneau (1994) for details about the test. The β coefficients of the regression were proved significant by the likelihood ratio test ($p = 0.00003$). The estimated coefficients and their 0.95-confidence intervals are

	β	$\exp(\beta)$	Confidence interval for $\exp(\beta)$
β_X	0.405	1.499	$1.01 - 2.91.$
β_Y	-2.01	0.134	$0.056 - 0.321.$

Therefore, condition (18) is met.

Note that condition (21) at time $t = 0$ in Theorem 2 is now satisfied since $P(Y = 1|X = 0) = 13/22 = 0.59$ and

$$P(Y = 1|X = 1) = 0.84 > \frac{\exp(0.405) - 1}{\exp(0.405)(1 - \exp(-2.01))} + \frac{0.59}{\exp(0.405)} = 0.78$$

We next provide the survival plots based on the above estimates. Figures 2 compares $P(T > s|X = 0, Y = 0)$ to $P(T > s|X = 1, Y = 0)$ and $P(T > s|X = 0, Y = 1)$ to $P(T > s|X = 1, Y = 1)$. Figure 3 shows the mixture survival functions (when averaging over CIS): a Cox model was fit with both X and Y and the marginal distributions given $X = x$ were then computed by averaging the fitted model with both X and Y, with respect to the empirical distribution of $(Y|X = x)$ as in (24). Note that in Figures 2 the survival functions do not cross. In Figure 3 they cross at $s = 290$ and therefore the paradox occurs for $s < 290$ (and $t = 0$).

FIGURES 2 AND 3 ABOUT HERE

As explained in Section 7 if a Cox model is assumed for T given X and Y, then the conditional distribution of T given X does not satisfy a Cox model. This implies that the functions $P(T > s|X = 0)$ and $P(T > s|X = 1)$ can cross, and therefore Simpson's paradox can hold when s assumes some values, but not other. Had we simply omitted the covariate Y (by misspecification), then a Cox model would have been imposed on the law of T given X, and the only possible form of Simpson's paradox would have been very drastic, holding for all values of s.

9 Conclusions

Researchers who consider the effect of covariates on survival functions and hazard rates should be aware that the direction of this effect (detrimental or protective) may vary according to the set of conditioning covariates and the survival times. The notions of detrimental and protective are therefore rather subtle and model-dependent. When, for instance, the covariates refer to treatments, the recommendation of a treatment level based on survival analysis with standard models should be done with extreme caution.

We have considered two versions of Simpson's paradox. The first is expressed in terms of survival functions and the second in terms of hazard rates. The survival function version depends on two times: the current survival time t, which determines the conditioning, and a future time $t+s$, for which the survival probability is calculated. The hazard rate paradox at t can be obtained from the previous paradox by looking at infinitesimal values of s. Therefore looking at the survival function allows an extra degree of flexibility in the existence of the paradox, that is not present in the hazard rate formulation.

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Appendix: Proofs

Total Positivity

For the proofs of our results we need some background in Total Positivity. We now provide without proofs the required basic results in this area. The reader is referred to Karlin (1968) and references therein for further definitions, results and proofs, and to Brown et al. (1981) for a useful formulation for statistical applications of the theory.

Definition 2. A function $\phi : \mathbb{R}^2 \to \mathbb{R}$ is said to be SR_k if there exist $\varepsilon_1, \dots, \varepsilon_k \in \{-1, 1\}$ such that for all for $m = 1, \dots, k$ and for all *for all* $x_1 < \cdots < x_m$, $y_1 < \cdots < y_m$ we have

$$\varepsilon_m \det \begin{bmatrix} \phi(x_1, y_1) & \cdots & \phi(x_1, y_m) \\ \vdots & & \vdots \\ \phi(x_m, y_1) & \cdots & \phi(x_m, y_m) \end{bmatrix} \geq 0. \tag{26}$$

The condition simply means that all determinants of the above type of any given order up to k have the same sign. If $\varepsilon_m = 1$ for $m = 1, \dots, k$, then ϕ is said to be TP_k, and RR_k if the sign sequence is $\varepsilon_m = (-1)^{m(m-1)/2}$. SSR_k, STP_k, and SRR_k are defined in the same way with strict inequalities in (26). If ϕ is SR_k for all $k = 1, 2, \dots$, then ϕ is said to be SR. TP, RR, SSR, STP and SRR are defined similarly. In the above SR stands for *sign regular*, TP for *totally positive*, and RR for *reverse rule*, and when S is added these properties are said to hold *strictly*.

Example 1. The function $\psi(x, y) = \exp\{xy\}$ is STP, whereas the function $\phi(x, y) =$

$\exp\{-xy\}$ is SRR. Also, g is a strictly log-concave function if and only if $\phi(x,y) = g(x-y)$ is STP_2.

Proposition 4. *If $\phi(x,y)$ is SSR_k and ζ and ξ are both strictly monotone, then $\phi(\zeta(x),\xi(y))$ is SSR_k.*

If both ζ,ξ are strictly increasing or both strictly decreasing then $\phi(x,y)$ and $\phi(\zeta(x),\xi(y))$ have the same sign sequence, whereas if one is strictly increasing and the other strictly decreasing the sign sequence of $\phi(\zeta(x),\xi(y))$ is obtained from that of $\phi(x,y)$ by multiplying its m-th sign by $(-1)^{m(m-1)/2}$. In this case if $\phi(x,y)$ is STP_k then $\phi(\zeta(x),\xi(y))$ is SRR_k.

Proposition 5 (First composition formula)**.** *If ϕ and ψ are both SSR_k, having sign sequences ε_m and ε'_m, respectively, and σ is a nonnegative σ-finite measure, then the convolution*

$$\zeta(x,y) = \int \phi(x,z)\psi(z,y)\ \mathrm{d}\sigma(z)$$

is SSR_k with sign sequence $\varepsilon_m\varepsilon'_m$ for $m = 1,\ldots,k$.

Proposition 6 (Second composition formula)**.** *Let f and g be nonnegative continuous functions. Define*

$$\overline{F}(x) = \int_x^\infty f(u)\ \mathrm{d}u, \quad \overline{G}(x) = \int_x^\infty g(u)\ \mathrm{d}u.$$

If $\overline{F}$ and $\overline{G}$ are (strictly) log-concave, then

$$\overline{H}(x) = \int \overline{F}(x-u)g(u)\ \mathrm{d}u$$

is (strictly) log-concave.

Definition 3. Let g be a function defined on a totally ordered finite set $\mathcal{X} = \{x_1,\ldots,x_n\} \subset \mathbb{R}$, where $x_1 < x_2 < \cdots < x_n$. Then $S^-(g)$ denotes the number of sign changes of the sequence $g(x_1),\ldots,g(x_n)$, when zeros are deleted; $S^+(g)$ denotes the maximum number of sign changes of the sequence $g(x_1), \ldots, g(x_n)$ that can be obtained by counting zeros as either $+$ or $-$.

If $\mathcal{X}$ is any subset of $\mathbb{R}$, not necessarily finite, then $S^-(g) = \sup_{V \in \mathcal{V}(\mathcal{X})} S^-(g_V)$, where $\mathcal{V}(\mathcal{X})$ is the class of finite subsets of $\mathcal{X}$, and g_V is the restriction of g to V. Analogously for S^+.

The following Proposition is somewhat weaker than Theorem 3.1 p. 233 of Karlin (1968).

Proposition 7 (Variation diminishing property). *Let g be a real valued function defined on $\mathbb{R}$, and let σ be a nonnegative σ-finite measure on $\mathbb{R}$. If ϕ is SSR_k and $S^-(g) \leq k-1$, then $S^+(f) \leq S^-(g)$ where*

$$f(x) = \int g(y)\phi(x,y)\ \mathrm{d}\sigma(y). \tag{27}$$

Proofs of Section 2

Proof of Proposition 1. (i) Obvious.

(ii) The hazard rate of W is

$$h_W(w) = \frac{f_W(w)}{\overline{F}_W(w)},$$

which, by definition is strictly increasing (decreasing) in w if and only if W is strictly IFR (DFR). From (7) we have

$$h_X(t|x,y) = \frac{f_W(K(t) + \beta_X x + \beta_Y y)}{\overline{F}_W(K(t) + \beta_X x + \beta_Y y)} K'(t),$$

and the result follows readily. □

Proofs of Section 3

Proof of Theorem 1. (i) From (7) it is clear that property (2a) holds since $\beta_X > 0$. To see (2b) consider

$$P(T > t + s|T > t, X = x) = \int P(T > t + s|T > t, X = x, Y = y) f_Y(y|T > t, X = x)\ \mathrm{d}y, \tag{28}$$

where

$$f_Y(y|T > t, X = x) = \frac{P(T > t|X = x, Y = y) f_Y(y|X = x)}{\int P(T > t|X = x, Y = y) f_Y(y|X = x)\ \mathrm{d}y}. \tag{29}$$

Using (7), (14), and (29), expression (28) becomes

$$P(T > t + s|T > t, X = x) = \frac{\int \overline{F}_W(K(t + s) + \beta_X x + \beta_Y y) f_V(y - \kappa(x))\ \mathrm{d}y}{\int \overline{F}_W(K(t) + \beta_X x + \beta_Y y) f_V(y - \kappa(x))\ \mathrm{d}y}. \tag{30}$$

The conditional survival $P(T > t + s|T > t, X = x)$ is increasing in x if and only if the denominator of the fraction on the right hand side of (30) is TP_2 in (t, x). To show that this denominator is indeed TP_2, substitute $z = y - \kappa(x)$, and define $\psi(s) := \int \overline{F}_W(s + \beta_Y z) f_V(z)\ \mathrm{d}z$. Since both W and V are IFR, and $\beta_Y < 0$, we have that the function ψ is log-concave by Proposition 6. Therefore, since the function $\beta_X x + \beta_Y \kappa(x)$ is decreasing,

$$\int \overline{F}_W\left(K(t) + \beta_X x + \beta_Y y\right) f_V(y - \kappa(x))\ \mathrm{d}y = \psi(K(t) + \beta_X x + \beta_Y \kappa(x)) \tag{31}$$

is TP_2 in (t, x).

(ii) The above argument shows that now ψ is strictly log-concave. Since we assume that (2b) holds, the discussion of part (i) also shows that $\psi(K(t) + \beta_X x + \beta_Y \kappa(x))$ is TP_2 in (t, x). These two facts can hold together only if $\beta_X x + \beta_Y \kappa(x)$ is decreasing. Moreover, since $\beta_X > 0$, it follows that $\beta_Y < 0$. $\square$

Proofs of Section 4

In the sequel we will use the following notation

$$C_{t,s} = \int_t^{t+s} h_0(u)\ \mathrm{d}u. \tag{32}$$

Proof of Theorem 2. (i) Using (24), (16) and (32) we have

$$P(T > t+s|T > t, X = 0) = p^t_{0|0} \exp\{-C_{t,s}\} + p^t_{1|0} \exp\{-C_{t,s}B\}, \tag{33a}$$

$$P(T > t+s|T > t, X = 1) = p^t_{0|1} \exp\{-C_{t,s}A\} + p^t_{1|1} \exp\{-C_{t,s}AB\}. \tag{33b}$$

For $x, y \in \{0, 1\}$,

$$p^t_{y|x} = \frac{p^0_{y|x} P(T > t|X = x, Y = y)}{p^0_{1|x} P(T > t|X = x, Y = 1) + p^0_{0|x} P(T > t|X = x, Y = 0)}, \tag{34}$$

and, since the support of T is unbounded, we have

$$p^t_{y|x} > 0 \quad \text{if and only if} \quad p^0_{y|x} > 0. \tag{35}$$

By (33), (17) is equivalent to $f(s) < 0$, where

$$f(s) := p^t_{0|0} \exp\{-C_{t,s}\} + p^t_{1|0} \exp\{-C_{t,s}B\} - p^t_{0|1} \exp\{-C_{t,s}A\} - p^t_{1|1} \exp\{-C_{t,s}AB\}. \tag{36}$$

We can write $f(s) = \int g(y)\phi(s, y)\ \mathrm{d}\sigma(y)$, where σ is the measure assigning unit mass to each $y \in \{B, AB, 1, A\}$, $g(y)$ is a function assigning values $p^t_{1|0}$, $-p^t_{1|1}$, $p^t_{0|0}$, $-p^t_{0|1}$ to $y = B, AB, 1, A$, respectively, and $\phi(s, y) = \exp\{-C_{t,s}y\}$. Since $C_{t,s}$ is strictly increasing in s, and $\exp\{-xy\}$ is SRR, it follows by Proposition 4 that $\phi(s, y)$ is SRR, hence SRR_4.

Our goal is to show that the set where $f(s)$ is negative is an interval. Whatever the order in the set $\{B, AB, 1, A\}$, we have $S^-(g) \leq 3$. Using the variation diminishing property of ϕ (see Proposition 7), we conclude that $S^+(f) \leq 3$.

Consider first the case $p^t_{1|0} > 0$. We start by showing that $f(s) > 0$ for large s. Multiply (36) by $\exp\{C_{t,s}B\}$ to obtain the expression

$$p^t_{0|0} \exp\{-C_{t,s}(1-B)\} + p^t_{1|0} - p^t_{0|1} \exp\{-C_{t,s}(A-B)\} - p^t_{1|1} \exp\{-C_{t,s}A(1-B)\}. \quad (37)$$

As $s \to \infty$, since $B < 1 < A$ by (18), and $C_{t,s} \to \infty$ by (9), the expression (37) tends to $p^t_{1|0}$ and therefore $f(s) > 0$ for large s. Using the fact that $f(0) = 0$, we see that if there were two or more disjoint intervals where the function f is negative, then we would have $S^+(f) > 3$, which is a contradiction.

If $p^t_{1|0} = 0$, then clearly $S^-(g) \leq 2$, which implies $S^+(f) \leq 2$. Then it is easy to see that having two disjoint intervals where f is negative would imply $S^+(f) > 2$, which again is a contradiction.

Finally suppose $p^0_{0|0} = 0$ and therefore, by (35), $p^t_{0|0} = 0$, and $p^t_{1|0} = 1$. Since $\exp\{-C_{t,s}B\} > \exp\{-C_{t,s}A\}, \exp\{-C_{t,s}AB\}$, in the present case (36) readily implies $f(s) > 0$ for all $s > 0$.

(ii) The condition $s_2 = \infty$ is equivalent to $f(s) < 0$ for large enough s. Suppose (19) and (20) hold. Clearly (20) implies $p^0_{0|0} = 1$ and, since Y is not degenerate, $p^0_{1|1} > 0$ also follows. By (35) we have $p^t_{0|0} = 1$ and $p^t_{1|1} > 0$, and by (36) we obtain

$$f(s)\exp\{C_{t,s}\} = 1 - p^t_{0|1} \exp\{C_{t,s}(1-A)\} - p^t_{1|1} \exp\{C_{t,s}(1-AB)\}. \quad (38)$$

By (19) we have $AB < 1$ and clearly the expression in (38) goes to $-\infty$ and therefore $f(s) < 0$ as $s \to \infty$.

To prove the converse, suppose $f(s) < 0$ as $s \to \infty$. Note that by multiplying (36) by $\exp\{C_{t,s}B\}$ the expression converges to $p^t_{1|0}$ as $s \to \infty$, and therefore $f(s) < 0$ as $s \to \infty$ implies $p^t_{1|0} = 0$ for all t, and (20) holds. We can now use (38) in a similar way to show that if $f(s) < 0$ as $s \to \infty$, then $AB < 1$, which is (19).

(iii) Consider the function

$$R(C) = (1 - p^t_{1|0}) \exp\{-C\} + p^t_{1|0} \exp\{-CB\} - (1 - p^t_{1|1}) \exp\{-CA\} - p^t_{1|1} \exp\{-CAB\},$$

and note that (17) is equivalent to $R(C_{t,s}) < 0$. At the origin the value of this function is $R(0) = 0$, and its derivative is $R'(0) = -(1 - p^t_{1|0}) - p^t_{1|0}B + (1 - p^t_{1|1})A + p^t_{1|1}AB$. We have

$$R'(0) < 0 \quad \text{if and only if} \quad p^t_{1|1} > \frac{A-1}{A-AB} + \frac{p^t_{1|0}}{A}. \tag{39}$$

Since $C_{t,s}$ is strictly increasing in s and $C_{t,0} = 0$, (39) shows that (17) holds for s in a right neighborhood of the origin if and only if (21) holds. Thus $s_1 = 0$ is equivalent to (21).

(iv) If $s_1 = 0$ and $s_2 = \infty$ then (19), (20), and (21) hold by (ii) and (iii), and (22) follows from (21). To prove the converse note that (22) implies (19), and that (20) and (22) imply (21).

To prove the second part, define

$$D_t = \int_0^t h_0(u)\ \mathrm{d}u. \tag{40}$$

Then

$$\begin{aligned} p^t_{1|1} &= \frac{p^0_{1|1} P(T > t|X = 1, Y = 1)}{p^0_{1|1} P(T > t|X = 1, Y = 1) + p^0_{0|1} P(T > t|X = 1, Y = 0)} \\ &= \frac{p^0_{1|1} \exp\{-D_t AB\}}{p^0_{1|1} \exp\{-D_t AB\} + p^0_{0|1} \exp\{-D_t A\}} \\ &= \frac{p^0_{1|1}}{p^0_{1|1} + p^0_{0|1} \exp\{D_t A(B-1)\}}. \end{aligned}$$

The latter expression is increasing in t since $B < 1$. If (20) holds, then by (35) $p^t_{1|0} = 0$ for all t. Therefore, the right hand side of (21) is constant, while the left hand side is increasing. It is easy to see that this implies that (21) holds for t in some upper interval. $\square$

Proofs of Section 6

Proof of Proposition 3. We will show that the paradox can hold for small values of s by finding parameters in (10) that satisfy (18) and (21) for independent X and Y. The covariates X and Y are independent at time 0 if and only if $p^0_{1|0} = p^0_{1|1} =: p_1$. Hence, using (34), inequality (21) becomes

$$\frac{p_1 P(T > t|X = 1, Y = 1)}{p_1 P(T > t|X = 1, Y = 1) + (1 - p_1)P(T > t|X = 1, Y = 0)} \geq \\ \frac{A - 1}{A - AB} + \frac{1}{A} \frac{p_1 P(T > t|X = 0, Y = 1)}{p_1 P(T > t|X = 0, Y = 1) + (1 - p_1)P(T > t|X = 0, Y = 0)}. \tag{41}$$

By (10), (16), and (40), inequality (41) can be written as

$$\frac{p_1 \exp\{-D_t AB\}}{p_1 \exp\{-D_t AB\} + (1 - p_1) \exp\{-D_t A\}} \geq \frac{A - 1}{A - AB} + \frac{1}{A} \frac{p_1 \exp\{-D_t B\}}{p_1 \exp\{-D_t B\} + (1 - p_1) \exp\{-D_t\}}. \tag{42}$$

An example of values of A, B, D_t , and p_1 that satisfy (42) and (18) is $A = 9$, $B = 0.05$, $p_1 = 0.3$, and any $-\log 0.5 < D_t < -\log 0.3$. $\square$

October 6, 2008

Table 1: Joint distribution of (X, Y)

		X		
		0	1	Total
Y	0	9	6	15
	1	13	32	45
	Total	22	38	60

Figure 1: Proportional odds model of Section 4.2: graph of the function $P(T > t + s|T > t, X = 0) - P(T > t + s|T > t, X = 1)$, when $A = 7$, $B = .1$, $p^0_{0|0} = .9$, $p^0_{0|1} = .09$.

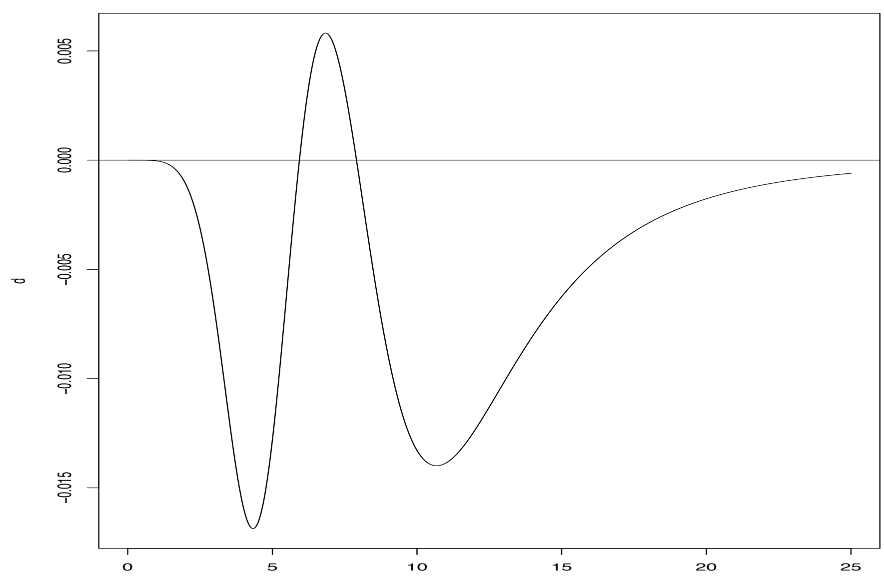

Figure 2: Estimated survival functions $P(T > s|X = 0, Y = 0)$ and $P(T > s|X = 1, Y = 0)$ (left), and $P(T > s|X = 0, Y = 1)$ and $P(T > s|X = 1, Y = 1)$ (right)

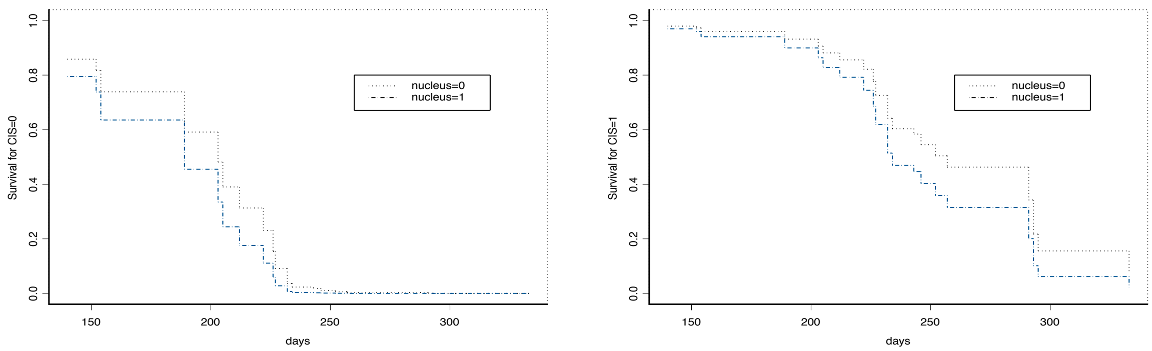

Figure 3: Mixed survival function $P(T > s|X = 0)$ and $P(T > s|X = 1)$