Robust and Efficient Estimation in the Parametric Cox Regression Model under Random Censoring

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Abstract

Cox proportional hazard regression model is a popular tool to analyze the relationship between a censored lifetime variable with other relevant factors. The semi-parametric Cox model is widely used to study different types of data arising from applied disciplines like medical science, biology, reliability studies and many more. A fully parametric version of the Cox regression model, if properly specified, can yield more efficient parameter estimates leading to better insight generation. However, the existing maximum likelihood approach of generating inference under the fully parametric Cox regression model is highly non-robust against data-contamination which restricts its practical usage. In this paper we develop a robust estimation procedure for the parametric Cox regression model based on the minimum density power divergence approach. The proposed minimum density power divergence estimator is seen to produce highly robust estimates under data contamination with only a slight loss in efficiency under pure data. Further, they are always seen to generate more precise inference than the likelihood based estimates under the semi-parametric Cox models or their existing robust versions. We also sketch the derivation of the asymptotic properties of the proposed estimator using the martingale approach and justify their robustness theoretically through the influence function analysis. The practical applicability and usefulness of the proposal are illustrated through simulations and a real data example.

Keywords: Minimum Density Power Divergence Estimator; Cox Regression; Parametric Survival Models; Robustness; Influence Function; Random Censoring; Counting Process Martingale.

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1 Introduction

Randomly censored lifetime data frequently occur in many applications like medical science, biology, reliability studies, etc., which need to be analyzed properly to make correct inference and suitable research conclusions. The data are often right censored because it is not possible to observe the patients or the items under study till their death or patients may withdraw during the study period. Mathematically, if $t_1, \ldots, t_n$ denote the actual life-times of $n$ independent patients (or items) under study, in reality we only observe $x_i = \min\{t_i, c_i\}, i = 1, \ldots, n$, where $c_1, \ldots, c_n$ are their respective censoring times. It is generally assumed that $\{t_i\}, \{c_i\}$ and $\{x_i\}$ are separately independent and identically distributed (IID) realizations of the true lifetime variable $T$, the censoring variable $C$ and the observed lifetime variable $X$, respectively, having distribution functions $G_T$, $G_C$, and $G_X = 1 - (1 - G_T)(1 - G_C)$. Generally the censoring information is available, so that we know $\delta_i = I(t_i \leq c_i)$ for each $i = 1, \ldots, n$, which can also be thought of as IID realizations of the random variable $\delta = I(T \leq C)$. Here $I(E)$ denotes the indicator function for the event $E$. In the absence of other relevant data, one needs to do inference about the true life-time distribution $G_T$ from $\{(X_i, \delta_i), i = 1, \ldots, n\}$. The Kaplan-Meier product limit (KMPL) estimator (Kaplan and Meier, 1958) is commonly used to non-parametrically estimate $G_T$. However, a more efficient inference procedure can be derived through the parametric approach where one assumes a parametric model for the density $g_T$ of the life-time distribution $G_T$ or the corresponding hazard rate $\lambda(t) = g_T(t)/(1 - G_T(t))$. These parametric assumptions are often based on previous experiences (e.g., similar drugs or similar diseases may have been studied in the past); some commonly used examples are exponential, Weibull, log-normal, log-logistic, gamma, etc. Such parametric inference procedures under randomly censored data (without any additional covariates) are well-studied in the literature; see Borgan (1984), Andersen and Borgan (1985) and Hjort (1986) for the classical maximum
likelihood procedures and Basu et al. (2006), Cherfi (2012), Ghosh et al. (2017), etc. for more recent robust inference procedures. The robust procedures are much more stable in the presence of data contamination; hence they are more useful in practical applications which are prone to data contamination.

In complex real life scenarios, the life-time variables often depend on several associated factors which need to be modelled properly for better insight generation. For example, lifetime of patients in a medical study always depends on patients’ age, sex, demography, and other conditions, along with the treatments, hospital conditions, socio-economic factors, etc. In such scenarios, we need to model the life-time variable $T$ given the values of other available covariates, say $Z \in \mathbb{R}^p$, through an appropriate regression structure. Among others, the Cox proportional hazard regression model (Cox, 1962) is widely used in medical and biological applications which assumes that the covariate effects on the life-time hazard rate $\lambda(t)$ are multiplicative and independent over time $t$. In particular, assuming that $z_i$ denotes the covariate value of the $i$-th patient, her hazard rate is modeled by the semi-parametric relation

$$
\lambda_i(t) = \lambda(t|Z = z_i) = \lambda_0(t)e^{\beta^T z_i}, \quad i = 1, \ldots, n,
$$

where $\lambda_0$ is the unknown baseline hazard in the absence of any covariates and $\beta \in \mathbb{R}^p$ is the unknown regression coefficients. These unknowns are estimated based on the observed data $\{(x_i, \delta_i, z_i) : i = 1, \ldots, n\}$ through maximum, partial or conditional likelihood approach; see, e.g., Cox (1972, 1975), Andersen and Gill (1982) and Kalbfleisch and Prentice (2011).

However, as noted earlier, a properly specified parametric approach always yields more efficient inference than any non-parametric or semi-parametric approach. As discussed by Hosmer et al. (2008, ch. 8), a fully parametric model has several important advantages including (i) greater efficiency, (ii) more meaningful estimates having simple interpretations, (iii) precise prediction, etc. Their successful application can be found in Cox and Oakes.
among others. Further, Hjort (1992) noted that such a parametric model “would lead to more precise estimation of survival probabilities and related quantities and concurrently contribute to a better understanding of the survival phenomenon under study” (Hjort, 1992, p. 375). Therefore, for greater efficiency, a direct parametric extension of the Cox model (1) can be considered by assuming a parametric form for the unknown baseline hazard \( \lambda_0(t) \), i.e., we assume the fully parametric regression structure

\[
\lambda_{i, \theta}(t) = \lambda_\theta(t | Z_i) = \lambda(t, \gamma)e^{\beta^T Z_i}, \quad i = 1, \ldots, n, \quad \theta = (\gamma^T, \beta^T)^T \in \mathbb{R}^{q+p},
\]

where \( \lambda(t, \gamma) \) is a known parametric function involving the unknown \( \gamma \in \mathbb{R}^q \). Common examples of \( \lambda(t, \gamma) \) could be the hazard rate of the standard lifetime distributions like exponential, Weibull, log-normal, etc. or the piece-wise constant hazard. Then, the full parameter vector \( \theta = (\gamma^T, \beta^T)^T \) can be estimated efficiently based on the observed data \( \{(x_i, \delta_i, Z_i) : i = 1, \ldots, n\} \) through the maximum likelihood approach on which the subsequent inference can be based. See Borgan (1984), Hjort (1992) and Kalbfleisch and Prentice (2011) for detailed properties and applications of the likelihood based inference under the parametric Cox regression model.

Although asymptotically efficient, a major drawback of this maximum likelihood approach, used in estimating the Cox regression model, is its high instability under data contamination (Reid and Crepeau, 1985; Hjort, 1992). As outliers are not uncommon in modern complex datasets in many applications including medical and biological studies, a robust approach under the parametric Cox regression model would be highly useful to provide the best trade-off between the efficiency and robustness of the deduced inference. However, although a few robust alternatives for the semi-parametric Cox regression model exist (Bednarski, 1993; Sasieni, 1993a,b; Bednarski, 2007; Farcomeni and Viviani, 2011), the literature has
paid little attention to developing robust estimators under their fully parametric version \(^{(2)}\). This paper fills this gap in the literature by developing a robust estimation approach for parametric Cox regression in presence of random censoring.

Among several possible approaches to robust inference, we consider the minimum divergence approach where the unknown parameter is estimated by minimizing a suitable discrepancy measure between the observed data and the postulated model. In particular, we consider the density power divergence (DPD) measure originally introduced by \(\text{Basu et al. (1998)}\) for complete IID data. The DPD, a generalization of the Kullback-Leibler divergence (KLD), is given by

\[
d_{\alpha}(g, f) = \int \left[ f^{1+\alpha} - \left( 1 + \frac{1}{\alpha} \right) f^{\alpha} g + \frac{1}{\alpha} g^{1+\alpha} \right] d\mu, \quad \alpha \geq 0, \tag{3}
\]

for any two densities \(g\) and \(f\) with respect to some common dominating measure \(\mu\). As the tuning parameter \(\alpha \to 0\), the DPD measure tends to the KLD measure \(d_0(g, f) = \int g \log(g/f) d\mu\), whereas \(d_1\) coincides with the squared \(L_2\) distance. Note that, the MLE is a minimizer of the KLD measure between the data and the model. Therefore the minimum DPD estimator (MDPDE), obtained as the minimizer of the DPD measure between the empirical data density and the assumed model density, yields a robust generalization of the MLE; it coincides with the non-robust MLE at \(\alpha = 0\) and becomes more robust as \(\alpha > 0\) increase. Due to several nice properties (see, e.g., \(\text{Basu et al., 2011}\)), along with its simplicity in construction and computation (we have a simple unbiased estimating equation as a generalization of the likelihood score equation), the MDPDE has also been extended successfully to several types of models. In parametric survival analysis, the MDPDE has been developed and successfully applied by \(\text{Basu et al., 2006}\) and \(\text{Ghosh and Basu, 2017}\) for randomly censored variables without covariates and a parametric accelerated failure time model, respectively.
In this paper, we develop the MDPDE for the fully parametric Cox regression model \(^2\) based on the randomly censored observations \(\{(x_i, \delta_i, z_i) : i = 1, \ldots, n\}\). The asymptotic properties of this new MDPDE including its consistency and asymptotic normality are derived using the martingale approach. Its robustness is illustrated theoretically through the influence function analysis and numerically through appropriate simulation studies. The superior efficiency and robustness of the proposed MDPDE under the fully parametric model \(^2\) compared to the existing robust estimators under the semi-parametric formulation \(^1\) are clearly visible in all our illustrations. The applicability of the proposed methodology is illustrated with some real data and the paper ends with a short concluding discussion.

2 Estimation in Parametric Cox Regression Models

2.1 The Maximum Likelihood Estimator

For better understanding of the proposed estimator, we start by recalling the maximum likelihood estimator (MLE) under the fully parametric Cox regression model \(^2\). Throughout this paper, we will make the standard assumption that the observed data \((x_i, \delta_i, z_i)\), for \(i = 1, \ldots, n\), are IID realizations of the random variables \((X, \delta, Z)\) having true joint distribution \(H\) on \([0, \infty) \times \{0, 1\} \times \mathbb{R}^p\), deduced from \(G_T, G_C\) and the true distribution \(G_Z\) of \(Z\). This IID assumption holds, for example, under random censoring schemes and random covariates. For each individual \(i\), define the counting process \(N_i\) and the at-risk process \(Y_i\) as \(dN_i(s) = I \{x_i \in [s, s + ds], \delta_i = 1\}, Y_i(s) = I \{x_i \geq s\}\), so that the process \(M_i(t) = N_i(t) - \int_0^t Y_i(s) \lambda_i(s) ds\) is a martingale. When the data are IID, the sequence \(\{(N_i, Y_i, M_i) : i = 1, \ldots, n\}\) also becomes IID and we can apply martingale limit theorems under standard regularity conditions (see, e.g., [Billingsley, 2013]). Note that, \(M_i\) involves the true hazard rate \(\lambda_i\) of \(i\)-th individual and not the model hazard rate \(\lambda_{i, \theta}\). We wish to model
this true conditional hazard $\lambda_i$ by the parametric Cox regression model (2). However, as in usual practice, we will not assume any model for the covariate distribution $G_Z$ and work with the conditional densities given the covariate values.

Now, under the model hazard rate given by (2), the model survival function of $T$ given $Z = z_i$ has the form $S_{i, \theta}(t) = S_{\theta}(t|Z = z_i) = \exp \left[ -\Lambda_{\gamma}(t)e^{\beta^T z_i} \right]$, where $\Lambda_{\gamma}(t) = \int_0^t \lambda(s, \gamma)ds$ is the (model) cumulative baseline hazard. Therefore, for each $i$, the model (partial) likelihood of the observed data-point $(x_i, \delta_i)$ given the covariate value $Z = z_i$ has the form [Andersen et al. 1992]

$$f_{i, \theta}(x, \delta) = f_{\theta}(x, \delta|Z = z_i) = \left[ \lambda(x, \gamma)e^{\beta^T z_i}Y_i(x) \right]^{1-\delta} \exp \left[ -\Lambda_{\gamma}(x)e^{\beta^T z_i} \right],$$

(4)

where the parameter of interest is $\theta = (\gamma^T, \beta^T)^T$. Note that, in this set-up with given covariate values, the observations $(X_i, \delta_i)$ are independent but non-homogeneous having true densities $g_i(x, \delta) = g(x, \delta|Z = z_i)$, which we wish to model by the density $f_{i, \theta}$ in (4).

The MLE of $\theta$ is defined as the maximizer of the likelihood function $L_n = \prod_{i=1}^n f_{i, \theta}(x_i, \delta_i)$, or equivalently as the maximizer of the log-likelihood function $\frac{1}{n} \log L_n(\theta)=\frac{1}{n} \sum_{i=1}^n \log f_{i, \theta}(x_i, \delta_i) = \text{Constant} - \frac{1}{n} \sum_{i=1}^n d_0(\hat{g}_i, f_{i, \theta})$, where $\hat{g}_i$ is the empirical estimate of $g_i$ and $d_0$ is the KLD measure. Under standard differentiability assumptions, the MLE can be obtained as a solution to the score equation $\frac{1}{n} \sum_{i=1}^n u_{i, \theta}(x_i, \delta_i) = 0_{p+q}$, where $0_{p+q}$ is the zero vector of length $(p + q)$ and the $i$-th score function $u_{i, \theta}(x, \delta) = \left( u_{i, \theta}^{(1)}(x, \delta)^T, u_{i, \theta}^{(2)}(x, \delta)^T \right)^T = \left( \frac{\partial}{\partial \gamma} \log f_{i, \theta}(x, \delta), \frac{\partial}{\partial \beta} \log f_{i, \theta}(x, \delta) \right)$ given the covariate value $Z = z_i$ has the form

$$u_{i, \theta}^{(1)}(x, \delta) = \left\{ \psi_{\gamma}(x) - \Psi_{\gamma}(x)e^{\beta^T z_i} \right\}I(\delta = 1) - \Psi_{\gamma}(x)e^{\beta^T z_i}I(\delta = 0),$$

(5)

$$u_{i, \theta}^{(2)}(x, \delta) = z_i \left\{ 1 - \Lambda_{\gamma}(x)e^{\beta^T z_i} \right\}I(\delta = 1) - z_i \Lambda_{\gamma}(x)e^{\beta^T z_i}I(\delta = 0),$$

(6)

with $\psi_{\gamma}(x) = \frac{\partial}{\partial \gamma} \log \lambda(x, \gamma)$ and $\Psi_{\gamma}(x) = \int_0^x \frac{\partial}{\partial \gamma} \lambda(s, \gamma)ds = \int_0^x \psi_{\gamma}(s)\lambda(s, \gamma)ds$. 

6
The asymptotic distribution of this MLE at the model and outside the model can be found in Andersen and Gill (1982), Borgan (1984), Andersen and Borgan (1985), Lin and Wei (1989) and Hjort (1992). The main idea is to write down the objective function and the estimating equations in terms of the counting processes $N_i$ and $Y_i$ as given by

$$\frac{1}{n} \log L_n(\theta) = \frac{1}{n} \sum_{i=1}^{n} \int_0^T \left[ \log \lambda_i(s) I(\delta_i = 1) + \log S_i(s) \right] I(x_i \in [s, s + ds]) ds,$$

$$= \frac{1}{n} \sum_{i=1}^{n} \int_0^T \left[ (\log \lambda(s, \gamma) + \beta^T z_i) dN_i(s) - Y_i(s)\lambda(s, \gamma)e^{\beta^T z_i} ds \right], \quad (7)$$

$$u_{i,\theta}(x_i, \delta_i) = \int_0^T \psi(\gamma(s)) \left[ dN_i(s) - Y_i(s)\lambda(s, \gamma)e^{\beta^T z_i} ds \right],$$

$$u_{i,\theta}(x_i, \delta_i) = \int_0^T z_i \left[ dN_i(s) - Y_i(s)\lambda(s, \gamma)e^{\beta^T z_i} ds \right],$$

where it is assumed that the process is observed in the time-interval $[0, T]$ and then use appropriate limit theorems for these processes and the associated martingale $M_i$ (Billingsley 1961, 2013, Gill 1984). However, the major drawback of this MLE is that it has an unbounded influence function (Hampel et al., 1986) as illustrated by Reid and Crepeau (1985), Lin and Wei (1989) and Hjort (1992) among others, which implies its non-robust nature against outliers. Any inference based on this MLE is then also non-robust.

### 2.2 The Proposed Minimum DPD Estimator

We are now in a position to define the MDPDE for the parametric Cox regression model (2). Since the observed data-points $(x_i, \delta_i)$, given their respective covariate values $z_i$, are non-homogeneous under (2), we cannot directly apply the Basu et al. (1998) definition of MDPDE for IID data. An extended definition of the MDPDE under the general non-homogeneous data (without censoring) has been developed by Ghosh and Basu (2013), who obtain the MDPDE as the minimizer of the average of the DPD measures between different estimated
true densities and the respective model densities. We follow this extended approach to define the MDPDE under the parametric Cox model as the minimizer of \( \frac{1}{n} \sum_{i=1}^{n} d_{\alpha}(\hat{g}_i, f_{i,\theta}) \) with respect to \( \theta = (\gamma^T, \beta^T)^T \) for any fixed \( \alpha \geq 0 \).

This objective function given by the average DPD measure also has another justification as a generalization of the MLE objective function. Note that, the MLE is also the minimizer of the average (over the unknown covariate distributions) KLD measures between conditional empirical and model model densities. Since the DPD is a generalization of the KLD, it is intuitive to construct a generalization of the MLE by minimizing the average DPD measure \( \frac{1}{n} \sum_{i=1}^{n} d_{\alpha}(\hat{g}_i, f_{i,\theta}) \) with respect to the parameter of interest. Also, whenever the covariates are stochastic, this quantity gives (in probability limit) the empirical estimate of the expected population divergence \( E_{G_{\alpha}} [d_{\alpha}(g(\cdot | Z), f_{\theta}(\cdot | Z))] \); this is again an intuitive quantity to minimize for estimating the model parameter \( \theta \).

Now, using the form of DPD measure given in (3), we note that the third term has no contribution in the minimization with respect to \( \theta \) and hence the MDPDE can equivalently be obtained by minimizing the simpler objective function

\[
H_{n,\alpha}(\theta) = \frac{1}{n} \sum_{i=1}^{n} \left[ \int f_{i,\theta}^{1+\alpha} - \frac{1 + \alpha}{\alpha} \lambda_{i,\theta}(x_i)^{\alpha \delta_i S_{i,\theta}(x_i)^{\alpha}} \right]
\]

(8)

It is straightforward to verify that \( H_{n,\alpha}(\theta) + \frac{1}{\alpha} \) tends to \( -\frac{1}{n} \log L_n(\theta) \), as \( \alpha \to 0 \); thus the MDPDE at \( \alpha = 0 \) is nothing but the usual MLE. Under standard differentiability assumptions, we can alternatively obtain the MDPDE by solving the system of estimating equations

\[
\left( u_{n}^{(1,\alpha)}(\theta)^T, u_{n}^{(2,\alpha)}(\theta)^T \right)^T := -\frac{1}{1+\alpha} \left( \frac{\partial}{\partial \gamma^T} H_{n,\alpha}(\theta), \frac{\partial}{\partial \beta^T} H_{n,\alpha}(\theta) \right)^T = 0_{p+q}.
\]

Some algebra based
on (8) lead to the simpler form of these estimating equations as given by

\[ u_n^{(1,\alpha)}(\theta) = \frac{1}{n} \sum_{i=1}^{n} \left\{ \psi_{\gamma}(x_i)\lambda_i,\theta(x_i)^\alpha S_i,\theta(x_i)^\alpha - (\lambda_i,\theta(x)^\alpha - 1) \Psi_{\gamma}(x_i)e^{\beta^Tz_i}S_i,\theta(x_i)^\alpha \right\} I(\delta_i = 1) \]

\[ - \psi_{\gamma}(x_i)e^{\beta^Tz_i}S_i,\theta(x_i)^\alpha - \xi_i^{(1,\alpha)}(\theta) = 0_q, \]  

(9)

\[ u_n^{(2,\alpha)}(\theta) = \frac{1}{n} \sum_{i=1}^{n} \left\{ \lambda_i,\theta(x_i)^\alpha S_i,\theta(x_i)^\alpha - (\lambda_i,\theta(x)^\alpha - 1) \Lambda_{\gamma}(x_i)e^{\beta^Tz_i}S_i,\theta(x_i)^\alpha \right\} z_i I(\delta_i = 1) \]

\[ - z_i\Lambda_{\gamma}(x_i)e^{\beta^Tz_i}S_i,\theta(x_i)^\alpha - \xi_i^{(2,\alpha)}(\theta) = 0_p, \]  

(10)

where \( \xi_i^{(j,\alpha)}(\theta) = \int u_i,\theta f_{1+\alpha} \), for \( j = 1, 2 \). Again, it follows that \( \xi_i^{(j,0)}(\theta) = 0 \) and \( u_n^{(j,0)}(\theta) = \frac{1}{n} \sum_{i=1}^{n} u_i,\theta(x_i, \delta_i) \) for each \( j = 1, 2 \). Thus, the above MDPDE estimating equations (9)–(10) are indeed a generalization of the MLE score equations in order to achieve greater robustness. They are also unbiased at the model distribution as shown in the next section.

3 Asymptotic Properties of the MDPDE

In order to derive the asymptotic properties of the proposed MDPDEs, we adopt the martingale approach of Andersen and Gill (1982). For simplicity in presentation, we here discuss the main asymptotic properties of our MDPDE in a simpler language with easier assumptions; further basic sufficient conditions for our assumptions can be obtained along the lines of Bor- gan (1984), Andersen and Borgan (1985), Hjort (1986) or Andersen et al. (1992). However, we develop these asymptotic results under a general class of underlying true distributions beyond only the model family, which is defined through the following assumption.

**Assumption (A):** The true hazard rate, given covariate value \( Z = z_i \), is of the form \( \lambda_i(s) = \lambda_0(s)h_0(z_i) \) for some positive functions \( \lambda_0 \) and \( h_0 \). Denote \( \Lambda_0(t) = \int_0^t \lambda_0(s)ds \).

Let us rewrite the left-hand sides of the MDPDE estimating equations (9)–(10) in terms of the processes \( (N_i, Y_i, M_i) \) as \( u_n^{(j,\alpha)}(\theta) = \frac{1}{n} \sum_{i=1}^{n} u_n^{(j,\alpha)}(\theta) \), for each \( j = 1, 2 \), where
In terms of these quantities, we can rewrite
\[
\mathbf{u}_{n,i}^{(1,\alpha)}(\theta) = \left[ \int_0^T \left\{ \psi_{\gamma}(s)\lambda(s, \gamma)^\alpha e^{\alpha\beta z_i}S_i,\theta(s)^\alpha - \left( \lambda(s, \gamma)^\alpha e^{\alpha\beta z_i} - 1 \right) \Psi_{\gamma}(s)e^{\beta T z_i}S_i,\theta(s)^\alpha \right\} dN_i(s) 
\right.
\]
\[
- \int_0^T \Psi_{\gamma}(s)e^{\beta T z_i}S_i,\theta(s)^\alpha I(x_i \in [s, s + ds]) - \xi_{i}^{(1,\alpha)}(\theta) \right] , \tag{11}
\]
\[
\mathbf{u}_{n,i}^{(2,\alpha)}(\theta) = \left[ \int_0^T \left\{ \lambda(s, \gamma)^\alpha e^{\alpha\beta z_i}S_i,\theta(s)^\alpha - \left( \lambda(s, \gamma)^\alpha e^{\alpha\beta z_i} - 1 \right) \Lambda_{\gamma}(s)e^{\beta T z_i}S_i,\theta(s)^\alpha \right\} z_i dN_i(s) 
\right.
\]
\[
- \int_0^T z_i \Lambda_{\gamma}(s)e^{\beta T z_i}S_i,\theta(s)^\alpha I(x_i \in [s, s + ds]) - \xi_{i}^{(2,\alpha)}(\theta) \right] . \tag{12}
\]

In order to study their limits, we need some additional notations; for each \( j = 0,1 \) and \( \alpha_1, \alpha_2 \geq 0 \), let us denote \( dG_{n,\alpha_1,\alpha_2}^{(j)}(s) = \frac{1}{n} \sum_{i=1}^{n}(z_i)^j e^{\alpha_1 \beta T z_i}S_i,\theta(s)^{\alpha_2}dN_i(s) \), \( dH_{n,\alpha_1,\alpha_2}^{(j)}(s) = \frac{1}{n} \sum_{i=1}^{n}(z_i)^j e^{(\alpha_1+1)\beta T z_i}S_i,\theta(s)^{\alpha_2}Y_i(s) \),
\( r_{\alpha_1,\alpha_2}^{(j)}(s) = E \left[ (Z)^j I(X \geq s)e^{\alpha_1 \beta T Z}S_0(s)Z)^{\alpha_2}h_0(Z) \right] \), \( q_{\alpha_1,\alpha_2}^{(j)}(s) = E \left[ (Z)^j I(X \geq s)e^{(\alpha_1+1)\beta T Z}S_0(s)Z)^{\alpha_2} \right] \).

In terms of these quantities, we can rewrite \( \mathbf{u}_{n}^{(j,\alpha)}(\theta) \), \( j = 1,2, \) as
\[
\mathbf{u}_{n}^{(1,\alpha)}(\theta) = \left[ \int_0^T \left\{ \psi_{\gamma}(s)\lambda(s, \gamma)^\alpha dG_{n,\alpha_1,\alpha_2}^{(0)}(s) - \lambda(s, \gamma)^\alpha \Psi_{\gamma}(s)dG_{n,\alpha_1,\alpha_2}^{(0)}(s) + \Psi_{\gamma}(s)dG_{n,1,\alpha_2}^{(0)}(s) \right\} 
\right.
\]
\[
- \int_0^T \Psi_{\gamma}(s)dH_{n,1,\alpha_2}^{(0)}(s) - \xi_{i}^{(1,\alpha)}(\theta) \right] , \tag{13}
\]
\[
\mathbf{u}_{n}^{(2,\alpha)}(\theta) = \left[ \int_0^T \left\{ \lambda(s, \gamma)^\alpha dG_{n,\alpha_1,\alpha_2}^{(1)}(s) - \lambda(s, \gamma)^\alpha \Lambda_{\gamma}(s)dG_{n,\alpha_1,\alpha_2}^{(1)}(s) + \Lambda_{\gamma}(s)dG_{n,1,\alpha_2}^{(0)}(s) \right\} 
\right.
\]
\[
- \int_0^T \Lambda_{\gamma}(s)dH_{n,1,\alpha_2}^{(1)}(s) - \xi_{i}^{(2,\alpha)}(\theta) \right] . \tag{14}
\]

Now, let us assume the following limiting results, along with Assumption (A).

**Assumption (B):** As \( n \to \infty \), \( dG_{n,\alpha_1,\alpha_2}^{(j)}(s) \overset{P}{\to} r_{\alpha_1,\alpha_2}^{(j)}(s)\lambda_0(s)ds \), \( Q_{n,\alpha_1,\alpha_2}^{(j)}(s) \overset{P}{\to} q_{\alpha_1,\alpha_2}^{(j)}(s) \), and \( dH_{n,\alpha_1,\alpha_2}^{(j)}(s) \overset{P}{\to} r_{\alpha_1,\alpha_2}^{(j)}(s)\lambda_0(s)ds + q_{\alpha_1,\alpha_2}^{(j)}(s)ds \).

Note that Assumption (B) holds under mild boundedness conditions on the parametric baseline hazard and the covariate values by using the limit theorems for empirical processes
Further, under Assumptions (A) and (B), the quantities $u_n^{(j,\alpha)}(\theta)$ converges in probability to $u_0^{(j,\alpha)}(\theta)$, for each $j = 1, 2$, respectively, where

$$u_0^{(1,\alpha)}(\theta) = \int_0^T \left\{ \psi_\gamma(s)\lambda(s, \gamma) a r_{a,0}^{(0)}(s) - \lambda(s, \gamma) a \Psi_\gamma(s) r_{a+1,0}^{(0)}(s) \right\} \lambda_0(s) ds - \int_0^T \Psi_\gamma(s) q_{0,0}^{(0)}(s) ds - \xi_0^{(1,\alpha)}(\theta),$$

$$u_0^{(2,\alpha)}(\theta) = \int_0^T \left\{ \lambda(s, \gamma) a q_{a,0}^{(1)}(s) - \lambda(s, \gamma) a \Lambda_\gamma(s) r_{a+1,0}^{(1)}(s) \right\} \lambda_0(s) ds - \int_0^T \Lambda_\gamma(s) q_{0,0}^{(1)}(s) ds - \xi_0^{(2,\alpha)}(\theta),$$

and $\xi_0^{(j,\alpha)}(\theta) = \lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^n \xi_i^{(j,\alpha)}(\theta) = E \xi_i^{(j,\alpha)}(\theta)$ for $j = 1, 2$. Further calculations yield

$$\xi_0^{(1,\alpha)}(\theta) = \int_0^T \left\{ \psi_\gamma(s)\lambda(s, \gamma) a q_{a,0}^{(0)}(s) - \lambda(s, \gamma) a \Psi_\gamma(s) q_{a+1,0}^{(0)}(s) - \Psi_\gamma(s) q_{0,0}^{(0)}(s) \right\} ds,$$

$$\xi_0^{(2,\alpha)}(\theta) = \int_0^T \left\{ \lambda(s, \gamma) a q_{a,0}^{(1)}(s) - \lambda(s, \gamma) a \Lambda_\gamma(s) q_{a+1,0}^{(1)}(s) - \Lambda_\gamma(s) q_{0,0}^{(1)}(s) \right\} ds,$$

where $q_{a1,02}^{(j)}(s) = E \left[ (Z)^j e^{(a1+1)Z s} S_\theta(s) | Z_{a2+1} \right]$. Substituting in Eqs. (15)–(16), we get

$$u_0^{(1,\alpha)}(\theta) = \int_0^T \left[ \psi_\gamma(s)\lambda(s, \gamma) a \left\{ r_{a,0}^{(0)}(s) \lambda_0(s) - \tilde{q}_{a,0}^{(0)}(s) \lambda(s, \gamma) \right\} - \Psi_\gamma(s) \left\{ q_{0,0}^{(0)}(s) - \tilde{q}_{0,0}^{(0)}(s) \right\} \right] ds,$$

$$u_0^{(2,\alpha)}(\theta) = \int_0^T \left[ \lambda(s, \gamma) a \left\{ r_{a+1,0}^{(1)}(s) \lambda_0(s) - \tilde{q}_{a+1,0}^{(1)}(s) \lambda(s, \gamma) \right\} - \Lambda_\gamma(s) \left\{ q_{0,0}^{(1)}(s) - \tilde{q}_{0,0}^{(1)}(s) \right\} \right] ds,$$

Now, if the parametric Cox regression model [2] is indeed true, i.e., $\lambda_i(t) = \lambda(t, \gamma_0) e^{\theta_0^T z_i}$ for all $i$ and some parameter value $\theta_0 = (\gamma_0^T, \beta_0^T)^T$, then $\lambda_0(t) = \lambda(t, \gamma_0)$ and $h_0(Z) = e^{\theta_0^T Z}$ and hence $r_{a1,02}^{(j)}(s) = q_{a1,02}^{(j)}(s) = \tilde{q}_{a1,02}^{(j)}(s)$ for each $j = 0, 1$ and $a_1, a_2 \geq 0$. Therefore, we
get \( u_0^{(1,\alpha)}(\theta_0) = 0 \) and \( u_0^{(2,\alpha)}(\theta_0) = 0 \) leading to the following result.

**Theorem 3.1** Suppose the observed data \((x_i, \delta_i, z_i)\), for \( i = 1, \ldots, n \), are IID realizations of the random variables \((X, \delta, Z)\) satisfying the assumed parametric model \((\mathcal{M})\). Then, under Assumptions (A)-(B), the MDPDE estimating equations \((9)-(10)\) are asymptotically unbiased at the model and the resulting MDPDE is Fisher consistent.

Whenever the model \((\mathcal{M})\) does not hold exactly, we assume that there exists a unique solution \( \theta^g \) to the asymptotic estimating equations of the MDPDE given by

\[
\begin{align*}
0 &= u_0^{(1,\alpha)}(\theta) = 0 \\
0 &= u_0^{(2,\alpha)}(\theta) = 0
\end{align*}
\]

leading to the following result.

**Assumption (C):** There exists a neighborhood \( \Theta_0 \) of \( \theta^g \) such that for every \( \theta \in \Theta_0 \),

\[
-K_n = \max_{1 \leq j,k,l \leq p+q} \sup_{\theta \in \Theta_0} \left| \frac{1}{n} \sum_{i=1}^{n} \frac{\partial^2}{\partial \theta_j \partial \theta_l} u_{n,i,j}^{(\alpha)}(\theta) \right|
\]

is stochastically bounded, where \( \theta_j \) and \( u_{n,i,j}^{(\alpha)}(\theta) \) denote the \( j \)-th element of \( \theta \) and \( u_{n,i,j}^{(\alpha)}(\theta) = (u_{n,i,j}^{(1,\alpha)}(\theta), u_{n,i,j}^{(2,\alpha)}(\theta))^T \), respectively.

**Assumption (D):** There exists a neighborhood \( \Theta_0 \) of \( \theta^g \) such that the quantity

\[
K_n = \max_{1 \leq j,k,l \leq p+q} \sup_{\theta \in \Theta_0} \left| \frac{1}{n} \sum_{i=1}^{n} \frac{\partial^2}{\partial \theta_j \partial \theta_l} u_{n,i,j}^{(\alpha)}(\theta) \right|
\]

is stochastically bounded, where \( \theta_j \) and \( u_{n,i,j}^{(\alpha)}(\theta) \) denote the \( j \)-th element of \( \theta \) and \( u_{n,i,j}^{(\alpha)}(\theta) = (u_{n,i,j}^{(1,\alpha)}(\theta), u_{n,i,j}^{(2,\alpha)}(\theta))^T \), respectively.

Note that, one can choose the neighborhood in Assumptions (C) and (D) to be the same (otherwise choose the smaller one). Further, these assumptions can also be verified under mild boundedness regularity conditions in the line of Borgan (1984, Theorem 1). In the same vein, an application of martingale central limit theorem also yields the following condition.
Assumption (E): $\sqrt{n}u_n^{(\alpha)}(\theta^g) \xrightarrow{D} N_{p+q}(0_{q+p},K_\alpha(\theta^g))$, where $K_\alpha(\theta) = Var \begin{bmatrix} u_{n,i}^{(1,\alpha)}(\theta) \\ u_{n,i}^{(2,\alpha)}(\theta) \end{bmatrix}$.

Finally, Assumptions (C) and (E) can be used directly to derive the asymptotic distribution of the MDPDE. Consider a Taylor series expansion of $u_n^{(\alpha)}(\theta) = \left(u_n^{(1,\alpha)}(\theta)T, u_n^{(2,\alpha)}(\theta)T\right)^T$ at the MDPDE, say $\hat{\theta}_{n,\alpha}$, around the best fitting parameter value $\theta^g$ to get

$$0 = u_n^{(\alpha)}(\hat{\theta}_{n,\alpha}) = u_n^{(\alpha)}(\theta^g) + \nabla u_n^{(\alpha)}(\tilde{\theta}) \left(\hat{\theta}_{n,\alpha} - \theta^g\right),$$

$$\Rightarrow \sqrt{n} \left(\hat{\theta}_{n,\alpha} - \theta^g\right) = \left[-\nabla u_n^{(\alpha)}(\tilde{\theta})\right]^{-1} \sqrt{n} u_n^{(\alpha)}(\theta^g),$$

where $\tilde{\theta}$ lies between $\hat{\theta}_{n,\alpha}$ and $\theta^g$. Now using the consistency of $\hat{\theta}_{n,\alpha}$ for $\theta^g$ and applying Assumptions (C) and (E), we get the asymptotic distribution of the MDPDE $\hat{\theta}_{n,\alpha}$; all these are summarized in the following theorem.

**Theorem 3.2** Suppose the observed data $(x_i, \delta_i, z_i)$, for $i = 1, \ldots, n$, are IID realizations of the random variables $(X, \delta, Z)$ having true joint distribution $H$ and there exists unique best fitting parameter $\theta^g$. Then, under Assumptions (A)–(D), there exists MDPDE $\hat{\theta}_{n,\alpha}$ as a solution to the estimating equations (9)–(10), which is consistent for $\theta^g$. Also, if additionally Assumption (E) holds, $\sqrt{n} \left(\hat{\theta}_{n,\alpha} - \theta^g\right) \xrightarrow{D} N_{p+q}(0_{q+p},J_\alpha(\theta^g)^{-1}K_\alpha(\theta^g)J_\alpha(\theta^g)^{-1})$.

The next theorem presents a consistent estimate of the asymptotic variance matrix of the MDPDE which can be used for estimating their standard errors and for developing robust significance testing procedures based on these MDPDEs. The proof follows from martingale inequalities and uniform convergence in probability arguments; see Hjort (1991, 1992) for a similar argument in case of the MLE.

**Theorem 3.3** Under the assumptions of Theorem 3.2, a consistent estimate of the asymptotic variance of the MDPDE $\hat{\theta}_{n,\alpha} = \left(\hat{\gamma}_{n,\alpha}^T, \hat{\beta}_{n,\alpha}^T\right)^T$ is given by $\frac{1}{n} \hat{J}_{n,\alpha}^{-1} \hat{K}_{n,\alpha} \hat{J}_{n,\alpha}^{-1}$, where $\hat{J}_{n,\alpha}$ and $\hat{K}_{n,\alpha}$ are consistent estimates of the matrices $J_\alpha(\theta^g)$ and $K_\alpha(\theta^g)$, respectively, given by
\[ J_{n,\alpha} = -\nabla u_n^{(\alpha)}(\hat{\theta}_{n,\alpha}), \quad \text{and} \quad K_{n,\alpha} = \frac{1}{n} \sum_{i=1}^{n} \begin{pmatrix} \hat{L}_{1,\alpha,i} \hat{L}_{1,\alpha,i}^T & \hat{L}_{1,\alpha,i} \hat{L}_{2,\alpha,i}^T \\ \hat{L}_{2,\alpha,i} \hat{L}_{1,\alpha,i}^T & \hat{L}_{2,\alpha,i} \hat{L}_{2,\alpha,i}^T \end{pmatrix}, \quad (20) \]

with \( \hat{S}_i(x_i) = \exp \left[ -\Lambda(x_i, \hat{\gamma}_{n,\alpha}) e^{\hat{e}_{n,\alpha}^T z_i} \right] \) and

\[
\hat{L}_{1,\alpha,i} = \left\{ \psi_{\hat{\gamma}_{n,\alpha}}(x_i) \lambda(x_i, \hat{\gamma}_{n,\alpha}) e^{\hat{\beta}_{n,\alpha}^T z_i} \hat{S}_i(x_i)^\alpha \right. \\
- \left( \lambda(x_i, \hat{\gamma}_{n,\alpha}) e^{\hat{\beta}_{n,\alpha}^T z_i} - 1 \right) \Psi_{\hat{\gamma}_{n,\alpha}}(x_i) e^{\hat{\beta}_{n,\alpha}^T z_i} \hat{S}_i(x_i)^\alpha \bigg\} \delta_i \\
- \Psi_{\hat{\gamma}_{n,\alpha}}(x_i) e^{\hat{\beta}_{n,\alpha}^T z_i} \hat{S}_i(x_i)^\alpha - \zeta_i^{(1,\alpha)}(\hat{\theta}_{n,\alpha}) \right], \quad (21)
\]

\[
\hat{L}_{2,\alpha,i} = \left\{ \lambda(x_i, \hat{\gamma}_{n,\alpha}) e^{\hat{\beta}_{n,\alpha}^T z_i} \hat{S}_i(x_i)^\alpha \\
- \left( \lambda(x_i, \hat{\gamma}_{n,\alpha}) e^{\hat{\beta}_{n,\alpha}^T z_i} - 1 \right) \Lambda_{\hat{\gamma}_{n,\alpha}}(x_i) e^{\hat{\beta}_{n,\alpha}^T z_i} \hat{S}_i(x_i)^\alpha \\
- z_i \lambda_{\hat{\gamma}_{n,\alpha}}(x_i) e^{\hat{\beta}^T z_i} \hat{S}_i(x_i)^\alpha - \zeta_i^{(2,\alpha)}(\hat{\theta}_{n,\alpha}) \bigg\} z_i \delta_i. \quad (22)
\]

**Remark 3.1** At \( \alpha = 0 \), the MDPDE coincides with the MLE and hence our Theorems 3.2 and 3.3 yield the asymptotic properties of the MLE as a special case, which coincide with the earlier results in Theorem 6.1 of [Hjort, 1992]. In particular, our matrices \( J_{\alpha} \) and \( K_{\alpha} \) at \( \alpha = 0 \) coincide with the matrices \( J \) and \( K \) of [Hjort, 1992, p. 377].

### 4 Robustness: Influence Function Analysis

We now study the robustness of the proposed MDPDE theoretically through the classical influence function analysis [Hampel et al., 1986]. In the context of censored data, the concept of influence function (IF) has been extended by [Reid, 1981], [Reid and Crepeau, 1985] and [Hjort, 1992] among others. In particular, [Hjort, 1992] derived the IF of the MLE of the parameters in the Cox regression model (2) and argued that it is unbounded indicating the
denotes a degenerate distribution. Here we derive the IF of the proposed MDPDE at \( \alpha > 0 \).

Note that the MDPDE functional at any \( \alpha \geq 0 \), say \( T_\alpha(H) = \theta^0 \), at the true distribution \( H \) of the triplet \( (X, \delta, Z) \) can be defined as the solution to the asymptotic estimating equations \( u_0^{(1,\alpha)}(\theta) = 0 \) and \( u_0^{(2,\alpha)}(\theta) = 0 \). Now, let us consider a point mass contamination at the point \( (x_t, \delta_t, z_t) \) and the contaminated density \( H_\epsilon = (1 - \epsilon) H + \epsilon \Lambda_{(x_t, \delta_t, z_t)} \) where \( \Lambda \) denotes a degenerate distribution. Then, the IF of the proposed MDPDE is defined as

\[
IF((x_t, \delta_t, z_t); T_\alpha, H) = \lim_{\epsilon \downarrow 0} \frac{T_\alpha(H_\epsilon) - T_\alpha(H)}{\epsilon} = \frac{\partial}{\partial \epsilon} T_\alpha(H_\epsilon) \bigg|_{\epsilon = 0}.
\]

In order to derive this IF, we substitute \( T_\alpha(H_\epsilon) \) and \( H_\epsilon \) in place of \( T_\alpha(H) \) and \( H \), respectively, in the asymptotic estimating equations and then differentiate with respect to \( \epsilon \) at \( \epsilon = 0 \). Collecting terms, after some lengthy but routine algebra, the IF of the MDPDE becomes

\[
IF((x_t, \delta_t, z_t); T_\alpha, H) = J_\alpha(\theta^0)^{-1} \begin{bmatrix}
\dot{i}_{1,\alpha}((x_t, \delta_t, z_t); \theta^0) \\
\dot{i}_{2,\alpha}((x_t, \delta_t, z_t); \theta^0)
\end{bmatrix},
\]

where

\[
\dot{i}_{1,\alpha}((x_t, \delta_t, z_t); \theta) = -\Psi_\gamma(x_t) e^{\beta^T z_t} S_t(x_t)^\alpha - \xi_t^{(1,\alpha)}(\theta)
\]

\[
+ \left\{ \psi_\gamma(x_t) \lambda(x_t, \gamma)^\alpha e^{\alpha \beta^T z_t} S_t(x_t)^\alpha - \left( \lambda(x_t, \gamma)^\alpha e^{\alpha \beta^T z_t} - 1 \right) \Psi_\gamma(x_t) e^{\beta^T z_t} S_t(x_t)^\alpha \right\} \delta_t,
\]

\[
\dot{i}_{1,\alpha}((x_t, \delta_t, z_t); \theta) = -z_t \Lambda_\gamma(x_t) e^{\beta^T z_t} S_t(x_t)^\alpha - \xi_t^{(2,\alpha)}(\theta)
\]

\[
+ \left\{ \lambda(x_t, \gamma)^\alpha e^{\alpha \beta^T z_t} S_t(x_t)^\alpha - \left( \lambda(x_t, \gamma)^\alpha e^{\alpha \beta^T z_t} - 1 \right) \Lambda_\gamma(x_t) e^{\beta^T z_t} S_t(x_t)^\alpha \right\} z_t \delta_t.
\]

Note that, due to the presence of the terms \( \lambda(x_t, \gamma)^\alpha \), \( e^{\alpha \beta^T z_t} \) and \( S_t(x_t)^\alpha \), the above IF of the MDPDE remains bounded over contamination points at any \( \alpha > 0 \). This implies the claimed robustness properties of the MDPDEs with \( \alpha > 0 \).

Further, a diagnostic measure for the \( i \)-th observation can be obtained from this IF as

\[
\hat{i}_i = IF((x_i, \delta_i, z_i); T_\alpha, \hat{H}_n) = \hat{J}_{n,\alpha}^{-1} \begin{bmatrix}
\hat{L}_{1,\alpha,i} \\
\hat{L}_{2,\alpha,i}
\end{bmatrix} = \hat{J}_{n,\alpha}^{-1} \begin{bmatrix}
\dot{i}_{1,\alpha}((x_i, \delta_i, z_i); \hat{\theta}_{n,\alpha}) \\
\dot{i}_{2,\alpha}((x_i, \delta_i, z_i); \hat{\theta}_{n,\alpha})
\end{bmatrix},
\]

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where $\hat{H}_n$ is the empirical distribution of the observed data $(x_i, \delta_i, z_i), i = 1, \ldots, n$. Larger values of $\hat{I}_i$ indicate greater influence of the $i$-th observations in computing the MDPDEs and hence it tends to be an outlying observation.

5 Simulation Studies

Here we present a few interesting findings from some simulation studies in order to examine the finite sample properties of the proposed MDPDE. Consider the exponential baseline hazard in the parametric Cox regression model (2) given by $\lambda(t, \gamma) = \gamma \in [0, \infty)$. Here our parameter of interest is the $p + 1$ dimensional vector $(\gamma, \beta^T)$. We simulate samples of size $n$ from this model with the covariates being generated from standard normal distributions; uniform random censoring with censoring proportions 5% or 10% are applied to these data. We report the results for the specific case with $p = 2$ where the true parameter values are taken as $\gamma_0 = 1$ and $\beta_0 = (2, -2)^T$. To study the effect of contaminations, $100\epsilon\%$ of each sample is contaminated by replacing the covariate values by IID observations from $N(1, 4)$ distribution. We then compute the MDPDEs of the three parameters $(\gamma, \beta_1, \beta_2)^T$ for different $\alpha \geq 0$ ($\alpha = 0$ generates the MLE) based on each simulated sample. The whole process is repeated over 1000 samples to compute the empirical biases and MSEs of the MDPDEs in all cases, which are reported in Tables 1–2 for $n = 50$ and 100. For comparison, we also report the empirical bias and MSE of the partial likelihood estimator (PLE) of Cox (1975) and the popular robust estimator of Bednarski (1993) (BRE) for $\beta = (\beta_1, \beta_2)^T$ with the semi-parametric Cox model (1) for the same sets of simulated data; these PLE and BRE are computed using the R package ‘coxrobust’ (Bednarski and Borowicz 2006).

It is clear from the tables that both the parametric MLE (MDPDE at $\alpha = 0$) and the semi-parametric MLE (PLE) are highly non-robust against any amount of contamination in data. Under pure data, the parametric MLE has the least bias and MSE in all cases and
the empirical bias and MSE of the MDPDEs increase as $\alpha$ increases. However, the loss in efficiency under pure data is not very significant for the MDPDEs with small $\alpha > 0$; for most $\alpha$ they are, in fact, still smaller than the semi-parametric PLE and its existing robust version BRE. In other words, if the parametric model is correctly specified without contamination, the MDPDEs with small $\alpha > 0$ yield the least (insignificant) loss in efficiency among other existing robust estimators when compared to the fully efficient (but non-robust) MLE.

On the other hand, when there is some amount of contamination in the data, the bias and the MSE of the parametric MLE increase significantly, but those of the MDPDEs remain more stable at $\alpha > 0$. In particular, as $\alpha$ increases, both bias and MSE of the MDPDEs initially have a substantial decrease under data contamination but then increase again at larger $\alpha$ values (due to their low efficiency in pure data). From the tables, one can see that the MDPDEs with $\alpha \in (0.2, 0.4)$ give the least bias and MSE under contamination and these are lower than the same for the existing robust estimator (BRE) with semi-parametric modeling. Considering their pure data performance, the MDPDEs with $\alpha \in (0.2, 0.4)$ yield the best trade-off between the efficiency and robustness for estimating the parameters under the Cox regression model. This parametric formulation also makes it possible to estimate the baseline hazard function through robust and efficient estimation of the underlying parameter $\gamma$. These clearly illustrate the advantages of the proposed MDPDE under the parametric Cox regression model for more precise and robust estimation in the cases where data may be prone to outlying observations.

6 Real Data Applications

We will now apply the proposed parametric Cox regression model to analyze two interesting survival data examples in the context of medical science. Both examples are seen to produce incorrect results, when analyzed using the usual semi-parametric Cox models using the R
package ‘coxrobust’ (Bednarski and Borowicz, 2006), due to the presence of a few outliers. For brevity, we will not present these detailed semi-parametric analysis and illustrate the advantages of our proposal by fitting a suitable parametric Cox regression model with only the significant covariates obtained from the semi-parametric full model analysis. The parametric baseline hazards are chosen individually for each dataset from the plot of the cumulative baseline hazard estimated from semi-parametric analysis and the corresponding Cox-Snell residual plot is used to identify the outliers (see Figure 1). The MLE and the MDPDE of all the parameters are compared for data with and without these outliers, which clearly exhibits significantly better stability of the proposed MDPDEs compared to the MLE.

6.1 Myeloma Data

The first example is the survival data of 65 multiple myeloma patients obtained from Heritier et al. (2009), where the associated significant covariates are the logarithms of blood urea nitrogen (BUN), serum calcium at diagnosis (CALC) and hemoglobin (HGB) of the patients. Further, the survival times of only 48 patients are observed and that for the other 17 patients are right censored; so the censoring proportion in the data is quite high, approximately 26%.

As mentioned above, the usual semi-parametric Cox model is initially fitted and the resulting Cox-Snell residuals based on the deviance method, presented in Figure 1a reveal three outlying points in the dataset having deviance values outside the 95% tolerance range \([-2, 2]\). Further, the corresponding estimate of the cumulative baseline hazard function is plotted in the log-scale in Figure 1a. It is clearly evident from the figure that the cumulative baseline hazard closely resembles a \(y = x\) straight line in the log scale; this particular form corresponds to the exponential hazard function \(\lambda(t, \gamma) = \gamma\), for a constant \(\gamma > 0\). So, we fit the parametric Cox regression model \((2)\) with the above exponential baseline hazard and the previously mentioned three covariates (BUN, CALC and HGB). Under this fully parametric
set-up, we compute the estimates of the regression coefficients and the parameters $\gamma$ in the hazard function using the MLE and the proposed MDPDEs with different $\alpha > 0$; these are reported in Table 3. However, due to the presence of the outliers, the MLE gets affected significantly. To demonstrate this, we re-compute the MLE and the MDPDEs after removing the three outlying observations from the dataset which are also reported in Table 3. One can clearly see that the MDPDEs remain much more stable in the presence of outliers compared to the MLE under the fully parametric Cox regression model. In particular the MDPDEs at $\alpha = 0.3, 0.4$ and $0.5$ show excellent stability. Additionally, this parametric version gives us the flexibility to estimate the baseline hazard in a more rigorous parametric form.

6.2 Breast and Ovarian Cancer Data

Our second example is from a large Breast and Ovarian cancer trial with 1619 patients’ suffering either from breast or ovarian cancer; the corresponding number of patients in the two types of cancer are 1044 and 575, respectively. These data are obtained from a recent R-package *survminer*, after filtering out the erroneous observations of zero and negative lifetimes. In total, the lifetime of 401 patients are not observed exactly, yielding a censoring proportion of approximately 24%. We want to get an idea about the difference in patient’s lifetimes between the two types of cancer; this can be achieved through a Cox type modeling with only one indicator covariate (say “Type”) which we take to be one for breast cancer.

Again, we first apply the standard semi-parametric Cox model; the resulting Cox-Snell residuals based on the deviance method and the estimate of the cumulative baseline hazard function are presented Figure 1b. Note that, 19 observations have residual values outside the 95% tolerance range $[-2, 2]$ and are identified as outliers. Further, the cumulative baseline hazard can be well approximated by a straight line in the log scale, which leads to the Weibull hazard function given by $\lambda(t, \gamma) = \gamma_1 \gamma_2 t^{\gamma_2 - 1}$, for $\gamma = (\gamma_1, \gamma_2)^T \in [0, \infty)^2$. Therefore, we apply
the proposed MDPDE, along with MLE, to fit the parametric Cox regression model (2) with the above Weibull baseline hazard function and only one covariate “Type” (of cancer). The parameter estimates obtained under the full data and the outlier deleted data are reported in Table 4. Once again, it is clearly observed that the MDPDEs with larger $\alpha > 0$ are far more stable than the MLE. However it may be noted that these MDPDEs are not necessarily close to the outlier deleted MLE. This is an outcome of the fact that the outlier detection based on the Cox-Snell residuals is far too liberal a process in this case and identifies too few outliers relative to the robust MDPDE procedure. The situation changes if the trimming proportion is increased. For example, trimming 15% of the extreme residuals (in absolute values) pushes the outlier deleted MLE to the neighborhood of the full data MDPDE at $\alpha = 0.3$. On the whole it is obvious that the MDPDE gives good and stable inference, even under the full data, in this example.

7 Concluding Remarks

This paper presents a fully parametric alternative to the semi-parametric Cox model for more precise and efficient inference under randomly censored responses. Due to the non-robust nature of the existing maximum likelihood approach under data contamination, we here develop a robust generalization, namely the robust technique using the minimum density power divergence estimator (MDPDE), which provides better trade-off between efficiency and robustness under the fully parametric Cox regression model. In particular, we have illustrated that the MDPDEs with tuning parameter $\alpha \in (0.2, 0.4)$ generate highly robust estimators in the presence of contamination while there is no significant loss in their efficiency under pure data. Therefore, these MDPDEs can be used in practice to get better and stable inference in analyzing different practical datasets which are prone to the presence of outlying observations. We have also derived in brief the asymptotic properties of the
proposed MDPDE under the fully parametric Cox regression model to show its consistency and asymptotic normality. We also provide a consistent estimate of the asymptotic variance matrix of the MDPDEs which can be used to estimate their standard errors in any practical applications.

There could be several extensions of this work with interesting real life applications. The asymptotic variances of the MDPDEs and their estimates can later be used to develop robust hypothesis testing or model selection procedures under the fully parametric Cox regression model. The concept of efficient parametric formulations and robust estimation using the MDPDEs can also be extended to many different applications involving the semi-parametric or non-parametric counting process models with or without censoring. Finally, although some empirical suggestions are made for $\alpha$ providing best trade-offs, a data driven choice of this MDPDE tuning parameter $\alpha$, along the lines of [Warwick and Jones (2005)] and [Ghosh and Basu (2015)], would be really helpful for practitioners from applied sciences to use the proposed procedure. Further, in our second example, the limitation of the Cox-Snell residual approach in identifying all the outliers in a contaminated dataset is clearly observed and hence a new robust version of the Cox-Snell residual, possibly based on the proposed MDPDEs, will be more helpful and effective for outlier detection. We hope to pursue some of these extensions in our future research.

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Figure 1: Residual plots (left) and the empirical estimate of the cumulative hazard $\Lambda(t)$ (right) for the two real datasets
Table 1: Empirical biases of the estimates of $\beta = (\beta_1, \beta_2)^T$ and $\gamma$ for $n = 50$ and 100 and different contamination proportion $\epsilon$

| Cens. Prop. | $\epsilon$ | Parametric MDPDE with $\alpha$ | Semi-parametric |  
|------------|-------------|-------------------------------|-----------------|
|            |             | $\beta_1$ | $\beta_2$ | $\gamma$ | $\beta_1$ | $\beta_2$ | $\gamma$ | $\beta_1$ | $\beta_2$ | $\gamma$ | $\beta_1$ | $\beta_2$ | $\gamma$ |
| $n = 50$   |             | $0.05$    | $0.1$    | $0.2$    | $0.3$    | $0.4$    | $0.5$    | $0.5$    | $0.5$    |
| 5%         | 0           | $-0.011$  | $-0.011$ | $-0.034$ | $-0.064$ | $0.115$  | $0.200$  | $0.060$  | $0.212$  |
|            | $\beta_2$  | $0.000$   | $0.011$  | $-0.021$ | $-0.045$ | $-0.078$ | $-0.119$ | $-0.190$ | $-0.073$ |
|            | $\gamma$   | $-0.014$  | $-0.024$ | $-0.035$ | $-0.059$ | $-0.089$ | $-0.121$ | $-0.150$ | $-$     |
| 0.05       | $\beta_1$  | $-0.704$  | $-0.401$ | $-0.166$ | $-0.086$ | $-0.108$ | $-0.144$ | $-0.137$ | $-0.928$ |
|            | $\beta_2$  | $0.254$   | $0.104$  | $0.019$  | $-0.014$ | $-0.035$ | $-0.067$ | $-0.186$ | $0.706$  |
|            | $\gamma$   | $-0.397$  | $-0.211$ | $-0.091$ | $-0.061$ | $-0.063$ | $-0.045$ | $-0.008$ | $-$     |
| 0.1        | $\beta_1$  | $-0.888$  | $-0.558$ | $-0.240$ | $-0.150$ | $-0.190$ | $-0.259$ | $-0.296$ | $-1.193$ |
|            | $\beta_2$  | $0.551$   | $0.253$  | $0.098$  | $0.045$  | $0.025$  | $0.018$  | $-0.064$ | $1.050$  |
|            | $\gamma$   | $-0.515$  | $-0.289$ | $-0.112$ | $-0.054$ | $-0.030$ | $0.025$  | $0.101$  | $-$     |
| $n = 100$  |             | $0.05$    | $0.1$    | $0.2$    | $0.3$    | $0.4$    | $0.5$    | $0.5$    | $0.5$    |
| 5%         | 0           | $-0.006$  | $0.000$  | $0.007$  | $0.021$  | $0.041$  | $0.067$  | $0.128$  | $0.029$  |
|            | $\beta_2$  | $-0.001$  | $-0.014$ | $-0.032$ | $-0.068$ | $-0.104$ | $-0.167$ | $-0.232$ | $-0.083$ |
|            | $\gamma$   | $-0.071$  | $-0.087$ | $-0.105$ | $-0.145$ | $-0.189$ | $-0.234$ | $-0.260$ | $-$     |
| 0.05       | $\beta_1$  | $-0.745$  | $-0.439$ | $-0.178$ | $-0.081$ | $-0.115$ | $-0.158$ | $-0.152$ | $-0.967$ |
|            | $\beta_2$  | $0.274$   | $0.105$  | $0.021$  | $-0.021$ | $-0.038$ | $-0.083$ | $-0.182$ | $0.733$  |
|            | $\gamma$   | $-0.445$  | $-0.276$ | $-0.162$ | $-0.140$ | $-0.152$ | $-0.154$ | $-0.126$ | $-$     |
| 0.1        | $\beta_1$  | $-0.934$  | $-0.561$ | $-0.274$ | $-0.151$ | $-0.193$ | $-0.244$ | $-0.259$ | $-1.219$ |
|            | $\beta_2$  | $0.586$   | $0.275$  | $0.105$  | $0.024$  | $0.010$  | $-0.024$ | $-0.078$ | $1.063$  |
|            | $\gamma$   | $-0.534$  | $-0.331$ | $-0.185$ | $-0.142$ | $-0.141$ | $-0.110$ | $-0.055$ | $-$     |
| 10%        | 0           | $-0.007$  | $0.008$  | $0.023$  | $0.053$  | $0.080$  | $0.112$  | $0.160$  | $0.028$  |
|            | $\beta_2$  | $-0.003$  | $-0.017$ | $-0.032$ | $-0.061$ | $-0.090$ | $-0.136$ | $-0.216$ | $-0.037$ |
|            | $\gamma$   | $-0.079$  | $-0.092$ | $-0.107$ | $-0.141$ | $-0.179$ | $-0.219$ | $-0.248$ | $-$     |
| 0.05       | $\beta_1$  | $-0.801$  | $-0.215$ | $-0.069$ | $-0.026$ | $-0.059$ | $-0.112$ | $-0.154$ | $-1.057$ |
|            | $\beta_2$  | $0.452$   | $0.070$  | $0.008$  | $-0.036$ | $-0.053$ | $-0.078$ | $-0.095$ | $0.894$  |
|            | $\gamma$   | $-0.492$  | $-0.201$ | $-0.139$ | $-0.144$ | $-0.161$ | $-0.152$ | $-0.113$ | $-$     |
| 0.1        | $\beta_1$  | $-1.169$  | $-0.466$ | $-0.169$ | $-0.109$ | $-0.193$ | $-0.321$ | $-0.430$ | $-1.412$ |
|            | $\beta_2$  | $0.823$   | $0.230$  | $0.070$  | $0.020$  | $0.034$  | $0.067$  | $0.041$  | $1.257$  |
|            | $\gamma$   | $-0.642$  | $-0.311$ | $-0.165$ | $-0.137$ | $-0.124$ | $-0.057$ | $0.042$  | $-$     |
Table 2: Empirical MSEs of the estimates of $\beta = (\beta_1, \beta_2)^T$ and $\gamma$ for $n = 50$ and 100 and different contamination proportion $\epsilon$

| Cens. Prop. $\epsilon$ | Parametric MDPDE with $\alpha$ 0 (MLE) 0.05 0.1 0.2 0.3 0.4 0.5 | Semi-parametric PLE BRE |
|------------------------|-----------------------------------------------------------|-------------------------|
| **n = 50**             |                                                           |                         |
| 5%                     |                                                           |                         |
| 0 $\beta_1$           | 0.025 0.026 0.030 0.045 0.095 0.291 0.822                | 0.103 0.215             |
| $\beta_2$              | 0.026 0.028 0.032 0.050 0.119 0.267 0.762                | 0.116 0.227             |
| $\gamma$               | 0.022 0.023 0.024 0.030 0.048 0.087 0.160                | - -                     |
| 0.05 $\beta_1$        | 0.862 0.433 0.165 0.120 0.207 0.369 0.855                | 1.206 0.326             |
| $\beta_2$              | 0.371 0.180 0.077 0.077 0.154 0.334 1.344                | 0.762 0.266             |
| $\gamma$               | 0.289 0.126 0.051 0.041 0.071 0.173 0.380                | - -                     |
| 0.1 $\beta_1$         | 1.182 0.652 0.251 0.166 0.246 0.485 0.923                | 1.672 0.676             |
| $\beta_2$              | 0.701 0.308 0.132 0.102 0.205 0.482 1.455                | 1.307 0.647             |
| $\gamma$               | 0.415 0.183 0.071 0.048 0.068 0.186 0.445                | - -                     |
| **n = 100**            |                                                           |                         |
| 5%                     |                                                           |                         |
| 0 $\beta_1$           | 0.012 0.012 0.014 0.021 0.042 0.096 0.394                | 0.046 0.078             |
| $\beta_2$              | 0.011 0.011 0.013 0.020 0.042 0.111 0.576                | 0.045 0.082             |
| $\gamma$               | 0.012 0.012 0.013 0.017 0.028 0.056 0.112                | - -                     |
| 0.05 $\beta_1$        | 1.021 0.184 0.042 0.032 0.075 0.190 0.494                | 1.387 0.205             |
| $\beta_2$              | 0.548 0.106 0.030 0.027 0.060 0.211 0.537                | 1.017 0.206             |
| $\gamma$               | 0.341 0.068 0.020 0.017 0.029 0.083 0.232                | - -                     |
| 0.1 $\beta_1$         | 1.639 0.422 0.099 0.069 0.140 0.304 0.569                | 2.143 0.611             |
| $\beta_2$              | 1.026 0.202 0.053 0.039 0.079 0.188 0.537                | 1.713 0.588             |
| $\gamma$               | 0.533 0.130 0.032 0.022 0.033 0.108 0.341                | - -                     |
| 10%                    |                                                           |                         |
| 0 $\beta_1$           | 0.013 0.013 0.016 0.025 0.048 0.110 0.433                | 0.050 0.087             |
| $\beta_2$              | 0.013 0.014 0.017 0.027 0.051 0.186 0.604                | 0.046 0.083             |
| $\gamma$               | 0.017 0.019 0.022 0.033 0.050 0.085 0.138                | - -                     |
| 0.05 $\beta_1$        | 0.992 0.188 0.060 0.037 0.079 0.183 0.473                | 1.381 0.198             |
| $\beta_2$              | 0.565 0.096 0.038 0.028 0.066 0.275 0.456                | 1.028 0.195             |
| $\gamma$               | 0.366 0.087 0.040 0.034 0.049 0.091 0.189                | - -                     |
| 0.1 $\beta_1$         | 1.622 0.468 0.124 0.077 0.154 0.324 0.622                | 2.115 0.589             |
| $\beta_2$              | 1.047 0.230 0.071 0.038 0.083 0.201 0.736                | 1.711 0.577             |
| $\gamma$               | 0.567 0.170 0.058 0.037 0.048 0.098 0.261                | - -                     |
Table 3: Parameter estimates for the Myeloma data

|         | Parametric MDPDE with $\alpha$ | Semi-parametric |
|---------|-------------------------------|-----------------|
|         | 0 (MLE) 0.05 0.1 0.2 0.3 0.4 0.5 | PLE  BRE        |
| Full Data With Outliers |                            |                 |
| BUN     | 0.016 0.016 0.016 0.016 0.016 0.016 | 0.023 0.025     |
| CALC    | 0.137 0.155 0.173 0.207 0.234 0.253 0.265 | 0.165 0.298     |
| HGB     | -0.059 -0.065 -0.073 -0.091 -0.110 -0.128 -0.141 | -0.137 -0.180   |
| $\gamma$ | 0.012 0.010 0.009 0.007 0.006 0.006 | – –             |
| Without 3 outlying observations |                            |                 |
| BUN     | 0.016 0.016 0.016 0.015 0.015 0.015 0.015 | 0.027 0.025     |
| CALC    | 0.247 0.251 0.254 0.261 0.267 0.273 0.278 | 0.370 0.344     |
| HGB     | -0.123 -0.128 -0.133 -0.145 -0.156 -0.166 -0.175 | -0.235 -0.218   |
| $\gamma$ | 0.009 0.009 0.009 0.009 0.008 0.008 | – –             |

Table 4: Parameter estimates for the Breast and Ovarian Cancer data

|         | Parametric MDPDE with $\alpha$ | Semi-parametric |
|---------|-------------------------------|-----------------|
|         | 0 (MLE) 0.05 0.1 0.2 0.3 0.4 0.5 | PLE  BRE        |
| Full Data With Outliers |                            |                 |
| Type    | -1.585 -2.372 -2.583 -2.979 -3.390 -3.886 -4.894 | -1.570 -1.770   |
| $\gamma_1$ | 0.136 0.131 0.060 0.011 0.002 1.84e^{-4} 1.14e^{-5} | – –             |
| $\gamma_2$ | 1.361 0.087 0.175 0.336 0.467 0.572 0.662 | – –             |
| Without 19 outlying observations |                            |                 |
| Type    | -1.762 -2.389 -2.608 -3.048 -3.507 -4.047 -4.645 | -1.840 -1.800   |
| $\gamma_1$ | 1.6e^{-5} 0.001 0.060 0.011 0.002 1.73e^{-4} 1.1e^{-5} | – –             |
| $\gamma_2$ | 1.497 0.879 0.176 0.345 0.485 0.597 0.686 | – –             |

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