package for the statistical analysis of doubly truncated data: a review

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Abstract

Random double truncation refers a situation in which the variable of interest is observed only when it falls within two random limits. Such phenomenon occurs in many applications of Survival Analysis and Epidemiology, among many other fields. There exist several R packages to analyze doubly truncated data which implement, for instance, estimators for the cumulative distribution, the cumulative incidences of competing risks, or the regression coefficients in the Cox model. In this paper the main features of these packages are reviewed. The relative merits of the libraries are illustrated through the analysis of simulated and real data. This includes the study of the statistical accuracy of the implemented techniques as well as of their computational speed. Practical recommendations are given.

Keywords: biased sampling, interval sampling, survival analysis, random truncation

1 Introduction

Doubly truncated data appear in fields like Astronomy, Survival Analysis, Epidemiology, Engineering or Economics, among others. A random variate $X$ is doubly truncated by a random couple $(U,V)$ when the observations are limited to the triplets $(X,U,V)$ which satisfy $U \leq X \leq V$. In such a setting the variables $U$ and $V$ are called the left and right truncation limits for $X$. Efron and Petrosian (1999) considered the estimation of the cumulative distribution function (cdf) of quasar luminosities (the $X$), which go undetected whenever they fall outside or region $[U,V]$; thus, the $X$ is doubly truncated by $(U,V)$. Double truncation occurs with interval sampling too, which in particular relates the analysis of epidemiological registries. For instance, Moreira and de Uña-Álvarez (2010) estimated the cdf of the age at onset for childhood cancer (the $X$) from the cases diagnosed between two specific dates $d_0$ and $d_1$. Then, the sample consisted of the children with $U \leq X \leq V$, where $V$ is the age by
\( d_1 \) and \( U = V - d_0 \). See also Zhu and Wang (2014), Ye and Tang (2016), Dörre (2017) or Mandel et al. (2018) for more applications with interval sampling.

The double truncation phenomenon can be seen as a generalization of one-sided (left or right) truncation, which has been extensively investigated in the literature, and which requires proper corrections in order to eliminate the sampling bias. However, unlike for one-sided truncation, the nonparametric maximum likelihood estimator (NPMLE) for doubly truncated data has no explicit form and must be computed iteratively. This has motivated the development of software routines which, indeed, have proliferated in the recent years. Specifically for R software (R Core Team, 2017), at the present date at least five different libraries to estimate the cdf of a doubly truncated variable exist; they include some other functionalities too. The methods implemented by these libraries are heterogeneous in both precision and computational speed. A review of these packages is important in order to (i) clearly describe which methods are available in R to analyze doubly truncated data; (ii) how is the relative performance of the several existing libraries in terms of statistical accuracy and execution time; and (iii) give practical recommendations to the scientific community. The aim of this piece of work is to achieve these goals.

The rest of the paper is organized as follows. In Section 2 several algorithms to compute the NPMLE of the cdf of interest and its standard error are reviewed. Estimation approaches for Cox regression are discussed too. Section 3 briefly describes the main features of the existing R packages to analyze doubly truncated data, while Section 4 investigates through simulations their relative merits, including computational speed and statistical accuracy. In Section 5 several illustrative real data applications are given; these concern the age at diagnosis of childhood cancer (together with cumulative incidences for the several cancer types) as well as the age at onset of Parkinson’s disease and its relationship with single nucleotide polymorphisms. A final discussion and some practical recommendations are reported in Section 6.

### 2 Estimation approaches and algorithms

Efron and Petrosian (1999) introduced the NPMLE of the cdf from doubly truncated data, as the maximizer of the conditional likelihood of the \( X_i \)'s given the \((U_i, V_i)\)'s. Here \((X_i, U_i, V_i), 1 \leq i \leq n\), denotes a random sample with the conditional distribution of \((X, U, V)\) given \(U \leq X \leq V\); the variables \(X\) and \((U, V)\) are assumed to be independent. Two iterative procedures to compute the NPMLE were proposed in the aforementioned paper. The first algorithm is based on a self-consistency equation; the second one updates the Lynden-Bell estimator for left-truncated data by improving the hazard rate step by step. Efron and Petrosian (1999) recommended the second algorithm when the right truncation is light due to its relative convergence speed.
Shen (2010) showed that Efron and Petrosian (1999)'s conditional NPMLE indeed maximizes the full likelihood of the \((X_i, U_i, V_i)\)'s. Besides, he proposed a method to jointly estimate the cdf of \(X\), \(F\) say, and that of \((U, V)\), \(K\) say. Specifically, the method iterates by using the couple of equations

\[
\begin{align*}
(S1) & \quad F_n(x) = \sum_{i=1}^{n} w_i(G_n) I(X_i \leq x) / \sum_{i=1}^{n} w_i(G_n), \\
(S2) & \quad K_n(u, v) = \sum_{i=1}^{n} w_i(F_n) I(U_i \leq u, V_i \leq v) / \sum_{i=1}^{n} w_i(F_n),
\end{align*}
\]

where \(w_i(G_n) = G_n(X_i)^{-1}\) with \(G_n(x) = K_n(X_i, \infty) - K_n(X_i, X_i^-)\), and where \(w_i(F_n) = (F_n(V_i) - F_n(U_i^-))^{-1}\). One advantage of (S1)–(S2) is that, unlike the algorithms in Efron and Petrosian (1999), it reconstructs the truncation distribution from the data and, from this, the sampling probabilities for the \(X\)-values \(G(X_i) = P(U \leq X_i \leq V) = K(X_i, \infty) - K(X_i, X_i^-)\) can be evaluated. These sampling probabilities play a critical role in the development of regression methods for doubly truncated data, as it will become clear soon. The asymptotic properties of \(F_n\) were investigated by Shen (2010); the results and proofs in that paper have however some flaws that were corrected only recently, see de Uña-Álvarez and Van Keilegom (2019).

Mandel et al. (2018) and, independently, Rennert and Xie (2018) introduced two different estimation approaches for the Cox model \(h(x|z) = h_0(x) \exp(\beta z)\) under double truncation. The estimator of Mandel et al. (2018) solves the score equation

\[
U(\beta) = \sum_{i=1}^{n} [Z_i - \frac{\sum_{j=1}^{n} Z_j \exp(\beta Z_j) G_n(X_j)^{-1} I(X_j \geq X_i)}{\sum_{j=1}^{n} \exp(\beta Z_j) G_n(X_j)^{-1} I(X_j \geq X_i)}] = 0,
\]

where \(Z_i\) is the covariate vector attached to \((X_i, U_i, V_i)\). On the other hand, Rennert and Xie (2018) investigated an alternative approach in which the \(i\)-th term in \(U(\beta)\) is weighted by \(G_n(X_i)^{-1}\). This extra weighting may introduce more variance in estimation, a fact which is explored in Section 4. Both estimation approaches rely on the independence between the truncation variables and the target \((X, Z)\). The weights \(G_n(X_i)^{-1}\) were used in de Uña-Álvarez (2020) to introduce cumulative incidence functions for competing risks too. The method is consistent when \((U, V)\) is independent of the competing event. When the distribution of \((U, V)\) varies along the competing risks, the sampling probabilities \(G(X_i)\) must be separately estimated from the several groups of events. This however may result in very noisy estimates, particularly when few events are recorded. The theoretical validity of the estimation approaches for both Cox regression and competing risks relies on the asymptotic theory developed in de Uña-Álvarez and Van Keilegom (2019).

One important issue is that of the estimation of standard errors. For \(F_n(x)\), both the simple and the obvious bootstrap have been shown to perform well (Moreira and de Uña-Álvare, 2010). The simple bootstrap was compared to
the Jackknife approach and to an explicit-form variance estimator in Emura et al. (2015); see Section 4.1 below for an independent simulation study. No theoretical, rigorous proof of consistency has been provided so far for any of the existing estimators of the standard error. Also interestingly, Hu and Emura (2015) and Emura et al. (2017) proposed estimation and inference techniques in the setting in which $F$ is assumed to belong to a parametry family of cdf’s. Finally, we mention that a non-iterative approximation to the NPMLE $F_n$ was introduced by de Uña-Álvarez (2018).

3 Existing R packages

In this Section the main features of five existing R packages to analyze doubly truncated data are briefly reviewed. Some of these packages include automatic plots too but such capabilities are not discussed here. The features of the packages are summarized in Table 1.

3.1 Package DTDA

The package DTDA (Moreira et al., 2020) was launched in September 2009, when the statistical community was still quite unaware of the relevance of double truncation. DTDA was the first R library implementing numerical algorithms to compute the NPMLE for doubly truncated data, and it became popular very soon. Last version 2.1-2 (February 2020) introduced some corrections. The main functions in DTDA are efron.petrosian, lynden and shen, implementing respectively the self-consistency algorithm of Efron and Petrosian (1999), the Lynden-Bell-based algorithm, and a numerical solution for the score equations in Shen (2010). By default 95% confidence limits for the marginal cdfs of the variable of interest and (in the case of shen) of the truncating variables are calculated; for this, the simple bootstrap with 500 replicates (default) and the percentile method are used. The obvious bootstrap, which requires the preliminary estimation of the truncation distribution, is available for shen too. The confidence level is an argument of the main functions and therefore its default value of 95% can be changed. See Moreira et al. (2010) for more details.

3.2 Package SurvTrunc

Lior Rennert introduced in July 2018 his package SurvTrunc (Rennert, 2018), including the function cdfDT which implements the solution to Shen (2010)’s score equations. This function allows for the computation standard errors and of 95% confidence limits for the cdf of interest based on the simple bootstrap and the normal approximation method; the confidence level is fixed. Confidence limits for the truncation distribution are not implemented. Package SurvTrunc includes the function CoxDT which allows for Cox regression under double truncation too, based on Rennert and Xie (2018). Finally, the function indeptestDT
performs a test for the quasi-independence between the variable of interest and
the truncating variables, based on the conditional Kendall’s Tau of Martin and
Betensky (2005).

3.3 Package double.truncation
Simultaneously with, and independently of, SurvTrunc, in July 2018 Takeshi
Emura launched the package double.truncation (Emura et al., 2019), im-
plementing several parametric models for likelihood-based inference (Hu and
Emura, 2015; Emura et al., 2017). The package was last updated by January
2019 (version 1.4). For nonparametric inference, the function NPMLE was in-
cluded. This function implements the self-consistency algorithm of Efron and
Petrosian (1999) as well as an explicit-form estimator for the standard error of
the NPMLE introduced in Emura et al. (2015); this standard error does not
require any bootstrapping.

3.4 Package DTDA.cif
In October 2019 a new package to analyse doubly truncated data appeared:
DTDA.cif (de Uña-Álvarez and Soage, 2020). Later updated in February 2020,
DTDA.cif allows for nonparametric estimation of cumulative incidence functions
for competing risks. The main function is DTDAcif, which implements two
different estimators together with standard errors based on the simple bootstrap.
One of the available estimators (method="indep") is recommended when the
truncation variables are independent of the competing events, while the other
one (method="dep") corrects for possible dependences between the truncation
mechanism and the event indicator; see de Uña-Álvarez (2020) for details. When
applied to a single type of event, function DTDAcif returns a numerical solution
to the score equations of Shen (2010) in the spirit of shen{DTDA}. Even in the
standard setting without competing risks, DTDA.cif is of interest, since it offers
computational advantages compared to DTDA. See Section 4.1 for more on this.

3.5 Package DTDA.ni
A non-iterative estimator of the cdf under double truncation was introduced
by de Uña-Álvarez (2018). This is a nonparametric estimator which can be
computed in \( n \) steps (no numerical approximation is needed) and which, in
the simulations studies in the referred article, performs almost as well as the Efron-
Petrosian NPMLE. The non-iterative estimator was implemented in the main
function DTDA.ni of the package DTDA.ni (de Uña-Álvarez and Soage, 2018),
launched in April 2018. The implementation is restricted to interval sampling.
No method to approximate the standard error is available within the package.
Table 1: Summary of features for the several R functions. Focus is on estimation and inference for $F$; other features of the functions/libraries are reported too. Labels indicate availability of point estimates (Est), standard errors (Std.err) and confidence intervals (CI).

| function/library | Est | Std.err | CI | other features |
|------------------|-----|---------|----|----------------|
| efron.petrosian{DTDA} | ✓  | –      | ✓  | simple boot ($B=500$) |
| lynden{DTDA}      | ✓  | –      | ✓  | simple boot ($B=500$) |
| shen{DTDA}        | ✓  | –      | ✓  | simple/obvious boot ($B=500$) estimates for $K$ and $G$ |
| cdfDT{SurvTrunc}  | ✓  | ✓      | ✓  | simple boot ($B=200$) estimate for $K$ |
|                  |     |         |    | Cox model, quasiindep test |
| NPMLE{double.truncation} | ✓  | ✓      | –  | explicit-form std err |
|                  |     |         |    | parametric models |
| DTDAcif{DTDA.cif} | ✓  | ✓      | –  | simple boot ($B=300$) estimate for $G$ |
|                  |     |         |    | cumulative incidences |
| DTDAni{DTDA.ni}   | ✓  | –      | –  | non-iterative estimator |

4 Relative performance of the packages

In this Section the relative performance of the packages listed in Section 3 is investigated through simulated data. More specifically, the focus will be on the execution time when computing the NPMLE (or the non-iterative estimator) and the pertaining standard errors. Also, attention will be paid to the relative accuracy of the two existing estimation approaches for the Cox regression model.

4.1 Computational time for the NPMLE

The execution time for the several existing implementations of the NPMLE is variable, and the differences can be very remarkable. Some of the R functions only compute the estimator for $F$, the cdf of interest; these are efron.petrosian{DTDA}, lynden{DTDA} and NPMLE{double.truncation}. On the other hand, shen{DTDA}, cdfDT{SurvTrunc} and DTDAcif{DTDA.cif} calculate in a simultaneous way the estimator of $F$ and that of the truncation distribution, leading to larger waiting times. Also, when computing standard errors or confidence limits an extra computational effort is needed. This is particularly important for the bootstrap-based methods. Finally, the sample size $n$ may have a role in the relative computational speed too. All these aspects are illustrated now through simulations.

A variable $X$ uniformly distributed on the $(0,1)$ interval was simulated, $X \sim U(0,1)$. Random double truncation was introduced by simulating model (LT)-(RT) in Section 4.2, with $\rho = 1$ or $\rho = 0.5$ and with $\tau = 0.25$. The running
times for the several existing implementations of the NPMLE, as well as for the non-iterative estimator, were computed. To this end, a single sample with size $n \ (n = 250, 500 \text{ or } 1,000)$ was drawn from the model. These execution times are provided in Table 2. For illustration purposes, the resulting estimators for $n = 500$ are displayed in Figure 1; the six R functions which implement the NPMLE report roughly the same result, while the non-iterative estimator returned by DTDAni is only slightly different to the NPMLE.

From Table 2 it is seen that the smallest running times for the computation of the NPMLE correspond to efron.petrosian, the second best being DTDAcif. Function NPMLE is quite competitive, but its results worsen for $n = 1,000$, being about 5 times slower than efron.petrosian. This could be due to the computation of standard errors, which is performed by default and cannot be deactivated. On the other hand, the running time for cdfDT is about 3 times that of DTDAcif. Although the former returns the NPMLE for the truncating distribution, which is not the case for the latter, the function DTDAcif saves the sampling probabilities $G_n(X_i), 1 \leq i \leq n$, which is the essential piece of information on the truncating variables for most applications. Finally, lynden performs badly, particularly for the largest sample size, while the elapsed times for shen are just inadmissible. Summarizing, the fastest option to compute the NPMLE is efron.petrosian, but DTDAcif is recommended when the sampling probabilities are to be computed too. Regarding standard errors, an additional study was performed, including the calculation of bootstrap standard errors (or bootstrap confidence limits) for efron.petrosian, cdfDT and DTDAcif. We took 99 bootstrap resamples in all the cases; obviously, in general the running times in Table 2 will be multiplied by the resampling effort. The main conclusions of this additional study are:

(a) NPMLE is by far the fastest for the computation of standard errors; for example, with $n = 500$, NPMLE took 2 seconds compared to the about 60 seconds of efron.petrosian, which was the quickest option when bootstrapping

(b) there exists a big difference in computational speed among the three functions implementing the bootstrap; for example, with $n = 250$ the execution times were about 11, 65 and 25 seconds for efron.petrosian, cdfDT and DTDAcif, respectively (in agreement with Table 2)

(c) the 95% confidence limits based on the (simple) bootstrap and on the explicit-form standard error implemented in NPMLE(double.truncation) were quite similar for the simulated trials; see Figure 2 for an illustration in the case $n = 500$

One last comment on Table 2 is that the execution time for the non-iterative estimator was very fast compared to the NPMLE. This was somehow expected since the former does not require any iterations.
Figure 1: NPMLE (black line) and non-iterative estimator (red line) computed from a single sample of size $n = 500$ from the simulated model. Left: $\rho = 1$; right: $\rho = 0.5$. The true cdf is uniform on the interval $(0, 1)$.

Figure 2: NPMLE (solid line) and pointwise 95% confidence limits (dashed lines) computed from a single sample of size $n = 500$ from the simulated model. Left: $\rho = 1$; right: $\rho = 0.5$. The true cdf is uniform on the interval $(0, 1)$.
\[
\rho = 1
\]

\[
\rho = 0.5
\]

\[
n = 250 \quad n = 500 \quad n = 1,000 \quad n = 250 \quad n = 500 \quad n = 1,000
\]

| Method         | \( n = 250 \) | \( n = 500 \) | \( n = 1,000 \) | \( n = 250 \) | \( n = 500 \) | \( n = 1,000 \) |
|----------------|---------------|---------------|----------------|---------------|---------------|----------------|
| efron.petrosian| 0.11          | 0.40          | 2.14           | 0.12          | 0.45          | 2.37           |
| lynden        | 6.10          | 12.10         | 52.39          | 2.70          | 10.70         | 65.04          |
| shen          | 8.55          | 90.92         | 565.48         | 8.53          | 112.74        | 587.34         |
| cdfDT         | 0.75          | 2.96          | 6.89           | 0.64          | 3.08          | 6.51           |
| NPMLE          | 0.32          | 1.95          | 10.18          | 0.30          | 2.09          | 10.09          |
| DTDAcif       | 0.15          | 0.81          | 2.63           | 0.12          | 0.86          | 2.69           |
| DTDAni        | 0.02          | 0.14          | 0.61           | 0.03          | 0.20          | 0.88           |

Table 2: Execution time (seconds) for the several existing implementations of the NPMLE and for the non-iterative estimator. One single sample of simulated data with size \( n \).

An interesting issue is that of the statistical accuracy of the standard error implemented in `NPMLE{double.truncation}` relative to the bootstrap standard error reported for instance by `DTDAcif`. Note that the latter requires a quite larger execution time. In Table 3 the bias, standard deviation (SD) and mean squared error (MSE) of the estimated standard error of \( F_n(x) \) along 250 Monte Carlo trials are reported. The distribution of \( X \) was \( U(0,1) \) and the truncation model followed (LT)-(RT) in Section 4.2. The chosen values for \( x \) were the three quartiles of \( X \). The number of bootstrap resamples were 99 and the sample sizes were 50, 100 and 250. The true standard error of \( F_n(x) \) (the target) was approximated by the Monte Carlo standard deviation from an independent experiment with 1,000 trials.

From Table 3 it is seen that the simple bootstrap implemented in `DTDAcif` behaved better than the explicit-form standard error for moderate sample sizes \( (n = 50, 100) \). This was mainly due to the relative smaller standard deviation of the bootstrap. Indeed, the explicit-form estimator reported several outliers, leading to the aforementioned relative large dispersion and to a visible positive bias \( (n = 50) \) too. Relative results were the opposite for \( n = 250 \), although the bootstrap was competitive in this case too. Interestingly, in the case \( n = 250 \) the issue of NPMLE of having outliers just disappeared. The conclusions on the relative mean square error are in agreement with the independent simulation study in Emura et al. (2015).

The method implemented in `NPMLE` reported `NaN` results in a number of trials, with a warning related to `sqrt(V_F)`. For instance, in the case \( n = 100 \) the standard error of \( F_n(x) \) was not available because of this reason for 15 \( (x = x_{0.25}) \), 10 \( (x = x_{0.5}) \) and 8 \( (x = x_{0.75}) \) trials out of the 250. The situation was worse for \( n = 50 \) when, besides, an error in `solve.default(Info)` was declared for 8% of the trials; these trials were eliminated in the summaries of Table 3. Overall, with \( n = 50 \) the percentage cases for which `NPMLE` did not report the standard error ranged from 17% \( (x = x_{0.75}) \) to 28% \( (x = x_{0.25}) \).
| $x$ | $n = 50$ | $n = 100$ | $n = 250$ |
|-----|----------|----------|----------|
|     | Bias     | SD       | MSE      | Bias     | SD       | MSE      | Bias     | SD       | MSE      |
| $x_{25}$ | -0.0416  | 0.0996   | 0.0117   | -0.0001  | 0.0814   | 0.0066   | 0.0338   | 0.0392   | 0.0016   |
| $x_{5}$  | -0.0189  | 0.0719   | 0.0055   | -0.0035  | 0.0530   | 0.0028   | -0.0016  | 0.0211   | 0.0004   |
| $x_{75}$ | -0.0098  | 0.0761   | 0.0059   | -0.0047  | 0.0475   | 0.0023   | 0.0190   | 0.0004   |
| $x_{25}$ | 0.2658   | 1.5794   | 2.5651   | -0.0240  | 0.2762   | 0.0768   | -0.0051  | 0.0354   | 0.0013   |
| $x_{5}$  | 0.1819   | 1.3800   | 1.9376   | -0.0081  | 0.1798   | 0.0324   | -0.0016  | 0.0186   | 0.0004   |
| $x_{75}$ | 0.1239   | 1.2324   | 1.5340   | -0.0065  | 0.1040   | 0.0109   | 0.0002   | 0.0185   | 0.0003   |

Table 3: Bias, standard deviation (SD) and mean squared error (MSE) along 250 trials of estimated standard errors for $F_n(x)$: simple bootstrap based on 99 resamples as computed by DTDAcif, and explicit-form estimator implemented by NPMLE. The chosen values for $x$ are the three quartiles of $X$.

### 4.2 Cox regression

Cox regression with a doubly truncated response can be performed in R by including the estimated, transformed sampling probabilities as an offset in coxph. Specifically, if the $(X_i, Z_i, U_i, V_i)$ are respectively saved in $x, z, u$ and $v$, the code lines

```r
> W <- DTDAcif(x, u, v)$biasf
> coef(coxph(Surv(x) ~ z + offset(-log(W))))
```

return the estimator of the regression coefficients proposed in Mandel et al. (2018). Note that the object $W$ contains the values $G_n(X_i), 1 \leq i \leq n$. As mentioned above, Mandel et al. (2018)'s method is different to the estimator in Rennert and Xie (2018); the latter is implemented in the function coxDT of the package SurvTrunc, and is returned by

```r
> coxDT(Surv(x) ~ z, u, v, data = sim.d, B.SE.np = 2)$results.beta[1]
```

In order to compare both estimation approaches, data with samples sizes $n = 250, 500$ and $1,000$ from a Cox regression model were simulated. The simulated model was

$$h(x|z) = h_0(x) \exp(\beta z)$$  \hspace{1cm} (1)

with baseline hazard $h_0(x) = (1/\sigma) x^{1/\sigma - 1}$ and regression coefficient $\beta = 1/\sigma$, so the conditional distribution of $X$ given $Z = z$ is Weibull with shape parameter $1/\sigma$ and scale parameter $\exp(-z)$. This corresponds to a loglinear regression model $\log(X) = -Z + \sigma \epsilon$, where the error term $\epsilon$ follows a extreme value distribution independent of $Z$. We took $\sigma = 0.1$ so the regression coefficient
was $\beta = 10$. The chosen model for $Z$ was exponential with rate 1. In this scenario the essential support of $X$ falls within the interval $(0, 1.11)$. In order to introduce double truncation, the following model was considered:

(LT) $U = (1 + \tau)\xi^\rho - \tau, \xi \sim U(0, 1), \tau = 0.25, \rho = 0.5$

(RT) $V = U + \tau$

Variables $(U, V)$ were generated independently of the target $(X, Z)$. The model (LT)-(RT) represents a situation with interval sampling and window width 0.25. Note that the supports of $U$ and $V$ are the intervals $(-\tau, 1)$ and $(0, 1 + \tau)$, respectively, so the choice $\tau = 0.25$ is large enough for the identification of $F$, the cdf of $X$. On the other hand, under (LT)-(RT) the sampling probability $G(x) = P(U \leq x \leq V)$ is non constant, see Figure 3; hence, the application of the naive estimator for $\beta$ which ignores the truncation will fail. The truncation rate in the simulations was about 81%.

![Figure 3: NPMLE of the sampling probability $G(x)$ based on a sample of size $n = 1,000$ taken from the simulated Cox model.](image)

In Table 4 the bias, SD and MSE of Mandel et al. (2018)’s and Rennert
and Xie (2018)’s estimators along 250 Monte Carlo trials are reported. For comparison purposes, the benchmark estimator without truncation as well as the naive approach which ignores the double truncation are considered too. From Table 4 it is seen that both estimation approaches are virtually unbiased and consistent, and that the one in Mandel et al. (2018) is better since it reports estimations with smaller variances; the level of improvement of Mandel et al. (2018)’s over Rennert and Xie (2018)’s is larger for small sample sizes. It is also seen that the double truncation results in a loss of efficiency; for example, with $n = 250$ the MSE relative to the benchmark method is 1.67 and 2.10 for $\text{man}$ and $\text{ren}$ approaches, these figures reducing to 1.47 and 1.70 with $n = 1,000$. Finally, Table 4 reveals the systematic bias of the naive estimator which does not correct for truncation.

Table 4: Bias, standard deviation (SD) and mean squared error (MSE) along 250 trials of estimators for regression coefficients: benchmark estimator for no truncation ($\text{ben}$), naive estimator which ignores the truncation ($\text{nai}$), Mandel et al. (2018)’s method ($\text{man}$), and Rennert and Xie (2018)’s method ($\text{ren}$). Cox model. True regression coefficient is $\beta = 1/\sigma = 10$.

|       | $n = 250$ |       | $n = 500$ |       | $n = 1,000$ |
|-------|-----------|-------|-----------|-------|------------|
|       | Bias      | SD    | MSE       | Bias  | SD         | MSE       |
| $\text{ben}$ | 0.0273   | 0.5295 | 0.2811    | -0.0083 | 0.4014   | 0.1612    | 0.0060 | 0.2412 | 0.0582 |
| $\text{nai}$ | 0.4769   | 0.5885 | 0.5737    | 0.4731 | 0.4052   | 0.3880    | 0.4586 | 0.2451 | 0.2704 |
| $\text{man}$ | 0.0842   | 0.6802 | 0.4698    | 0.0601 | 0.4619   | 0.2169    | 0.0508 | 0.2879 | 0.0855 |
| $\text{ren}$ | 0.0455   | 0.766  | 0.5893    | 0.0594 | 0.4928   | 0.2464    | 0.0588 | 0.3087 | 0.0988 |

5 Illustrative data analyses

In this Section applications with real doubly truncated data are provided in order to illustrate the capabilities and relative results of the reviewed packages. Estimation of the marginal cdf of the variable of interest $X$ by parametric and nonparametric methods, cumulative incidences for competing risks, Cox regression analyses and quasi-independence tests are included.

5.1 Estimation of the marginal distribution

In this section we focus on the estimation of the cdf for the age at onset of childhood cancer. The data refer $n = 401$ children diagnosed with cancer in the region of North Portugal between January 1, 1999, and December 31, 2003; see de Uña-Álvarez (2020) for further details. As indicated in the Introduction, the age at onset $X$ is doubly truncated due to the interval sampling; specifically, if $V$ is the age (in days) by December 31, 2003, and $U = V - 1825$, then the available data are restricted to $U \leq X \leq V$. The head of the dataset is as follows:
A test for quasi-independence between $X$ and $U$ was performed with the package `SurvTrunc` by running `indeptestDT(x, u, v)`. Kendall's Tau was $\tau_L = -0.01$ reporting a p-value of 0.952, so the quasi-independence was accepted.

Figure 4 displays the NPMLE of the cdf for the age at cancer diagnosis (black line), together with the non-iterative estimator (red line). The NPMLE was computed by using the six different R functions in the packages `DTDA`, `SurvTrunc`, `double.truncation` and `DTDA.cif` reviewed above; the results overlap. The running time was below 2 seconds except for `lynden` (5.73 seconds) and `shen` (169.78), revealing an inefficient implementation in the latter case. Code lines for Figure 4 were

```r
> ep <- efron.petrosian(x, u, v, boot = FALSE)
> ly <- lynden(x, u, v, boot = FALSE)
> sh <- shen(x, u, v, boot = FALSE)
> st <- cdfDT(x, u, v)
> dt <- NPMLE(u, x, v)
> sh2 <- DTDAcif(x, u, v)
> tau <- (v - u)[1]
> ni <- DTDAni(x, u, tau)
> plot(ep$time, ep$cumulative.df, type = "s", ylab = "cumulative distribution", + xlab = "age at diagnosis (days)")
> lines(ly$time, ly$cumulative.df, type = "s", col = 1)
> lines(sh$time, sh$cumulative.df, type = "s", col = 1)
> lines(st$time, st$F, type = "s", col = 1)
> lines(x[order(x)], dt$F, type = "s", col = 1)
> lines(sh2$data$x, cumsum(sh2$cif.mas), type = "s", col = 1)
> lines(ni$data$x, ni$cumprob, type = "s", col = 2)
> legend(0, 1, legend = c("NPMLE", "Non-iterative"), col = c(1,2), lty = c(1,1))
```

The package `double.truncation` was used to select the special exponential family model with the smallest AIC, which was the one reported by the `PMLE.SEF1.free` function. The corresponding cdf was
\[ F(x; \hat{\eta}) = 1 - \frac{\exp(\hat{\eta} \hat{a}_X) - \exp(\hat{\eta} x)}{\exp(\hat{\eta} \hat{b}_X) - \exp(\hat{\eta} \hat{a}_X)}, \quad \hat{a}_X < x < \hat{b}_X, \quad (2) \]

where \( \hat{a}_X = \min(X_i) = 6, \hat{b}_X = \max(X_i) = 5474, \) and \( \hat{\eta} = -0.00017. \) In Figure 5, the cdf (2) is displayed; for completeness, the NPMLE together with 95% confidence limits (both computed through NPMLE) are included too. The following code was used to generate Figure 5:

```r
> par <- PMLE.SEF1.free(u, x, v)
> tau1 <- min(x)
> tau2 <- max(x)
> cdf <- 1 - (exp(par$eta*tau2) - exp(par$eta*x)) /
+ (exp(par$eta*tau2) - exp(par$eta*tau1))
> plot(x[order(x)], dt$F, type = "s", ylab = "cumulative distribution",
+ xlab = "age at diagnosis (days)"
> lines(x[order(x)], cdf[order(x)], type = "l", col = 2)
> upp <- dt$F - dt$SE*qnorm(.025)
> low <- dt$F + dt$SE*qnorm(.025)
> lines(x[order(x)], upp, type = "s", lty = 2)
> lines(x[order(x)], low, type = "s", lty = 2)
> legend(0, 1, legend = c("NPMLE", "SEF"), lty = 1, col = 1:2)
```

5.2 Estimation of cumulative incidences for competing risks

Several cancer types are present in the childhood cancer registry. Cases were grouped according to the International Classification of Childhood Cancer (ICCC). Specifically, the cancer groups are leukemias (group I, 107 cases), lymphomas (II, 57), central nervous system (III, 94), neuroblastoma (IV, 38), and other less frequently observed cancers that were grouped together (ICCC groups V-XII, 105 cases). In Figure 6, the cumulative incidence for the several ICCC groups are displayed together with 95% pointwise confidence limits based on 99 bootstrap resamples. In order to get estimations with relatively small standard errors the method based on the independence assumption between the truncating variables and the cancer type was used. Here there are the code lines needed to get Figure 6:

```r
> z[z>=5] <- 5
> cr.boot <- DTDAcif(x, u, v, z, method = "indep", boot = TRUE, B = 99)
> plot(cr.boot, ylab = "cumulative incidence",
+ xlab = "age at diagnosis (days)", intervals = TRUE, ylim = c(0, 0.4))
> legend(0, .4, legend = c("group I", "group II",
+ "group III", "group IV", "groups V-XII"), lty = 1, col = 1:5)
```
5.3 Cox regression

In this section Cox regression is applied to investigate the possible influence of two single nucleotide polymorphisms (SNPs) on the risk or age of onset of Parkinson’s disease (PD). The setting is a study of the association of candidate SNPs and age of onset of PD (Clark et al., 2011). Following Clark et al. (2011), the rs8192678 PGC-1α SNP and the A10398G mitochondrial SNP are considered. As indicated by Mandel et al. (2018), in this study the selected patients are the ones with DNA sample taken within eight years of their onset of PD and, besides, the onset was required to be prior to the DNA sample. Therefore, the age of onset \( X \) is right truncated by the age at blood sampling for genetic analysis \( V \), and left truncated by \( U = V - 8 \). We focus on the late onset group of patients (\( n = 100 \)), who had onset ages between 63 and 87 years; the genetic information of these cases is reported in Table 5.

The regression coefficients were estimated by two different methods: the one in Mandel et al. (2018), and the alternative approach proposed by Rennert
Figure 5: Estimators of the age at diagnosis, childhood cancer data: NPMLE with 95% confidence limits (black lines) and parametric estimator based on the special exponential family (red-line).

Table 5: SNP distribution for the Parkinson’s disease data -late onset group.

|        | PGC-1a |
|--------|--------|
|        |        | AG | G |
| SNP10398 | A | 7   | 30 | 36 |
|         | G | 3   | 7  | 17 |

and Xie (2018). For these two approaches standard errors based on the simple bootstrap with 199 bootstrap resamples were obtained, and the corresponding Wald-type two-sided p-values were calculated. The results are displayed in Table 6. The code lines were as follows:

```r
> library(DTDA.cif)
> library(survival)
> library(SurvTrunc)
> late <- read.csv("pdate_8_12_09.csv",header=T,sep="","")
```
Figure 6: Nonparametric estimators of the cumulative incidences for the several ICCC groups, childhood cancer data. Dashed lines correspond to 95% pointwise confidence limits based on 99 bootstrap resamples.

```r
> x <- late[,1]; u <- late[,2]-8; v <- late[,2]
> z1 <- late[,3]
> z2 <- late[,4]
> W <- DTDAcif(x, u, v)$biasf
> res.cox <- coxph(Surv(x) ~ z1 + z2 + offset(-log(W)))
> set.seed(1234)
> n <- length(x)
> B.man <- 199
> beta.man <- matrix(nrow = B.man, ncol = 3)
> for (b in 1:B.man){
+  + i.man <- sample(n, replace = TRUE)
+  + xb <- x[i.man]
+  + ub <- u[i.man]
+  + vb <- v[i.man]
+  + z1b <- z1[i.man]
```


+ z2b <- z2[i.man]
+ Wb <- DTDAcif(xb, ub, vb)$biasf
+ res.coxb <- coxph(Surv(xb) ~ z1b + z2b + offset(-log(Wb)))
+ beta.man[b, ] <- coef(res.coxb)
+
+ }
> se.man <- apply(beta.man, 2, sd)
> p.man <- 2 * pnorm(-abs(coef(res.cox)/se.man))
> res.cox2.199 <- coxDT(Surv(Onset.Age) ~ X10398 +
PGC1A_GLY482SER, Sampling.Age - 8, Sampling.Age,
data = late, B.SE.np = 199)

Table 6: Estimated regression coefficients, bootstrap standard errors and Wald-type two-sided p-values for the Parkinson’s disease data -late onset group. Results correspond to Mandel et al. (2018)’s approach and Rennert and Xie (2018)’s method -figures for the latter in brackets.

| SNP     | Estimate  | Std.err  | p-value  |
|---------|-----------|----------|----------|
| SNP10398 G | 0.5980 (-.1776) | .3061 (.3200) | .0508 (.5789) |
| PGC-1a AG | -1.1926 (.4306) | .8793 (.5684) | .1750 (.4487) |
| PGC-1a G  | -.6383 (-.0419) | .3226 (.3673) | .0478 (.9091) |

From Table 6 it is seen that the results provided by the two estimation approaches are quite different. For example, with Mandel et al. (2018)’s approach, at 5% level SNP10398 almost reaches significance, while one concludes that PGC-1a changes the risk of PD. This is in well agreement with the results in Mandel et al. (2018), Table 4, in which confidence intervals based on the percentile bootstrap are reported. In contrast to this, the application of the method proposed by Rennert and Xie (2018) does not allow to get any significance. This seems to be due not only to the different standard errors, which tend to be larger for Rennert and Xie (2018)’s approach, but also to a shift in the point estimates.

The two estimation approaches in Table 6 require the quasi-independence between the age at onset of PD and the truncating interval, as well as the assumption that the sampling probability $G(x|z) = P(U \leq x \leq V|Z = z)$ is free of the covariate vector $Z$. The application of the indeptestDT{SurvTrunc} reported a Kendall’s Tau of $\tau_L = 0.158$ with p-value 0.103, thus indicating no violation of the quasi-independence condition. On the other hand, in Figure 7 the sampling probabilities for the age at onset of PD along the several groups of individuals are displayed. The curves are close to each other, suggesting that $G(x|z)$ is not strongly influenced by the particular $z$-value.
Figure 7: Sampling probabilities for the age at onset of PD depending on the genetic information - late onset group.

6 Discussion

The statistical analysis of doubly truncated data is non-trivial. Luckily, several R libraries implementing methods for handling the double truncation exist. This facilitates the application of suitable corrections of standard procedures which can remove the potential sampling bias. In particular applications one will come up with a roughly flat curve $G_n(x)$, suggesting that the impact of double truncation is minor. This occurs for example in the childhood cancer data study of Section 5. In such circumstances the user may decide to apply ordinary methods, which will report valid point estimates and standard errors under the null assumption ‘$G(x)$ is constant’. Alternative, he/she may keep the estimator $F_n(x)$ which corrects for double truncation together with its standard error to recognize the initial uncertainty on $G(x)$. In the latter case the variance will be larger and significant features will be more hardly found.

The reviewed packages implement procedures which require the independence (or quasi-independence) between the targeted variable and the truncation couple. A test for the quasi-independence assumption is implemented in SurvTrunc and should be applied as a first step. In case of rejection, alternative procedures which take the dependence structure between X and $(U,V)$ into account are available; see e.g. Moreira et al. (2018). Also, in the regression setting, the function $G(x|z)$ should be free of the specific covariate value $Z = z$. This can be explored by graphically displaying the estimator $G_n$ for several $Z$-groups. No formal test for the independence between $(X,Z)$ and $(U,V)$ has been implemented so far.

The method implemented by DTDAcif computes the solution to the score
equations in Shen (2010), thus allowing for the estimation of \( F \) and of the observational bias \( G \). This follows the spirit of the functions \texttt{shen\{DTDA\}} and \texttt{cdfDT\{SurvTrunc\}}. However, \texttt{DTDAcif} improves the computational speed by reducing the number of targets to a minimum and discarding the construction of automatic plots. Specifically, the simplified algorithm in \texttt{DTDAcif} iterates between the current solutions for \( G_n \) and \( F_n \), by using the couple of equations

\[(i) \quad F_n(x) = \frac{\sum_{i=1}^{n} w_i(G_n) I(X_i \leq x)}{\sum_{i=1}^{n} w_i(G_n)},
(ii) \quad G_n(x) = \frac{\sum_{i=1}^{n} w_i(F_n) I(U_i \leq x \leq V_i)}{\sum_{i=1}^{n} w_i(F_n)}
\]

where \( w_i(G_n) \) and \( w_i(F_n) \) are as in (S1)-(S2), section 2. Unlike for \texttt{shen} and \texttt{cdfDT}, the estimator for the truncation distribution is not returned. More importantly \texttt{DTDAcif} speeds the process up by implementing fast execution modules based on C++. Summarizing, \texttt{DTDA.cif} is the fastest package when both \( F \) and the sampling probabilities are of interest. The execution times of \texttt{DTDAcif} may vary when the analysis includes competing events (\texttt{comp.event} argument) and \texttt{method = "dep"} is selected, since in such a case computations are performed in a slightly different way, more related to the implementations in \texttt{shen\{DTDA\}}.

When the sampling probabilities \( G_n(X_i) \) are not required, the function \texttt{efron.petrosian\{DTDA\}} is recommended because of its computational speed; this function is only beat by \texttt{DTDAni}, which provides a non-iterative approximation to the NPMLE. However, if standard errors are to be computed, \texttt{NPMLE\{double.truncation\}} is quite faster than the functions which implement the bootstrap (like \texttt{efron.petrosian}). Still, the statistical accuracy of the explicit-form standard error in NPMLE can be poor relative to that of the bootstrap, particularly for small sample sizes (\( n \leq 100 \)). Some evidence on this has been provided in Section 4, but more investigation is needed in order to reach general conclusions. For the moment some caution on this regard is indicated. Some errors leading to the non-availability of the standard error were found when running \texttt{NPMLE} too, being particularly frequent in the case \( n = 50 \). So this is an extra drawback of the implementation of the explicit-form standard error which should be taken into account in applications. Regarding Cox regression, the approach in Mandel et al. (2018) is recommended over the one implemented in \texttt{coxDT\{SurvTrunc\}} due to its better statistical precision. The former can be easily performed by including the transformed sampling probabilities as an \texttt{offset} in the function \texttt{coxph\{survival\}}. The reported standard errors must be discarded and recalculated by bootstrapping.

Importantly, we recall that specific techniques may be available in a unique package. This occurs for instance with the cumulative incidences for competing risks (\texttt{DTDA.cif}) or with the estimation of a parametric model for the cdf of \( X \) (\texttt{double.truncation}). Also, we mention that there exist relevant procedures for doubly truncated data which, at the present date, have not been implemented in any software package. This is the case, for example, of the smoothers
for the density and regression functions introduced in Moreira and de Uña-Álvarez (2012) and Moreira et al. (2016) respectively; or of the estimators for the regression coefficients in the accelerated failure time model investigated by de Uña-Álvarez and Van Keilegom (2019). In principle, however, such methods can be applied in an easy way by including the inverse sampling probabilities $G_n(X_i)^{-1}$ in the weights option of the R functions `density`, `loess` or `lm`; when doing so, reported standard errors should be corrected by e.g. bootstrapping to take the random weights into account. The application of procedures which involve the computation of new weights, for instance the one in Moreira et al. (2018) for dependent truncation, is less trivial.

Finally, problems with the possible non-existence or non-uniqueness of the NPMLE were recently pointed out by Xiao and Hudgens (2019). For example, a necessary condition for the existence and uniqueness of $F_n$ is that both $S_{1i} \equiv \sum_{k=1}^{n} I(U_k \leq X_i \leq V_k)$ and $S_{2i} \equiv \sum_{k=1}^{n} I(U_i \leq X_k \leq V_i)$ are strictly greater than 1 for $1 \leq i \leq n$. We have verified that this condition holds for the two real datasets in Section 5. Interestingly, for the childhood cancer registry, it happened $\min_i S_{2i} = 1$ when restricting the analysis to ICCC group III (central nervous system); indeed, `DTDAmcf` fails to report valid estimates when setting `method = "dep"`, because with this option the NPMLE for each cancer group is computed. Other, more sophisticated data checks can be performed following the results in Xiao and Hudgens (2019). To sum up, the issue of non-existence or multiplicity of the NPMLE deserves serious attention in practice.

**Computational details**

The results in this paper were obtained using R 3.6.3. R itself and all packages used are available from the Comprehensive R Archive Network (CRAN) at https://CRAN.R-project.org/.

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