Efficient Estimation of the Marginal Mean of Recurrent Events

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Summary

Recurrent events are often encountered in clinical and epidemiological studies where a terminal event is also observed. With recurrent events data it is of great interest to estimate the marginal mean of the cumulative number of recurrent events experienced prior to the terminal event. The standard nonparametric estimator was suggested in Cook & Lawless (1997) and further developed in Ghosh & Lin (2000). We here investigate the efficiency of this estimator that, surprisingly, has not been studied before. We rewrite the standard estimator as an inverse probability of censoring weighted (IPCW) estimator. From this representation we derive an efficient augmented estimator using efficient estimation theory for right-censored data. We show that the standard estimator is efficient in settings with no heterogeneity. In other settings with different sources of heterogeneity, we show theoretically and by simulations that the efficiency can be greatly improved when an efficient augmented estimator based on dynamic predictions is employed, at no extra cost to robustness. The estimators are applied and compared to study the mean number of catheter-related bloodstream infections in heterogeneous patients with chronic intestinal failure who can possibly die, and the efficiency gain is highlighted in the resulting point-wise confidence intervals.

Some key words: Censoring; Counting processes; Efficiency; Marginal mean; Recurrent events data; IPCW estimator.

1 Introduction

Recurrent events are observed in many clinical and epidemiological studies on individuals who may potentially experience a terminal event such as death. Our motivating study concerns a cohort of patients with chronic intestinal failure who are often treated for long periods, receiving home parenteral support through a central venous catheter. During treatments they experience several recurrent events such as catheter-related bloodstream infections (CRBSI), some patients have a high risk of death and die due to severe failure and comorbidities. This study is characterized by a strong heterogeneity between patients, because of high variability both in the number of CRBSI and in the risk of death, and possible correlation between recurrent events and death. This problem motivated us to explore the efficiency accounting for such data heterogeneity in a nonparametric setting.

A useful analysis of recurrent event data is to compute the marginal mean number of events of a specific type, in the presence of a terminal event, as described in Cook & Lawless (1997), developed further in Ghosh & Lin (2000) and extended to regression models in Ghosh & Lin (2003); Cai & Schaubel (2004). Chen & Cook (2004) considered extensions to deal with multivariate recurrent event processes with focus on making statements about the marginal means for several recurrent event processes jointly. In addition Scheike et al. (2019) considered how to estimate variance and covariance in the context of multivariate recurrent events, still in the presence of a terminal event. A broader discussion of the analysis of recurrent events can be found in Cook et al. (2009); Cook & Lawless (2002).

The aim of this work is to show how the marginal mean of the number of recurrent events can be estimated efficiently, using the theory of efficient estimation for censored data (Tsiatis, 2006; Van der Laan & Robins, 2003; Robins & Rotnitzky, 1992; Bang & Tsiatis, 2000).

The estimator suggested in Cook & Lawless (1997) is simple to compute and its influence function was derived in Ghosh & Lin (2000). We rewrite the estimator into an inverse probability of censoring weighted (IPCW) estimator. Further, based on this representation we can also derive the efficient estimator using the results about efficient estimation for right-censored data. We show how this increment IPCW estimator with an appropriated augmentation term is orthogonal to the nuisance tangent space spanned by the censoring mechanism. The efficiency of the estimator has not been discussed in detail before, and we show that the standard estimator is indeed efficient in some settings and in addition how to improve the efficiency in the settings where this is possible. The improved efficiency can be important, e.g., to extract as much information about treatment effects in clinical trials with recurrent-event endpoints (EMA, 2020).

The rewritten estimator resembles that of Bang & Tsiatis (2000) (BT) that was developed for estimation of medical cost, and the improved efficiency when there is heterogeneity in data comes from a dynamic prediction in contrast to the simple linear prediction used in BT. Moreover, efficiency is gained at no extra cost to robustness, because the augmented procedures remain fully nonparametric even though dynamic "working models" are used to compute the augmentation term.

The paper is structured as follows. In Section 2 the model is formulated, marginal properties of the standard nonparametric estimator are described and an IPCW version of this estimator and of its variance estimator are illustrated. Section 3 presents the efficient estimators and their variance estimators, together with the derivation of the augmentation term: an augmented estimator based on dynamic predictions and an alternative version with non-dynamic predictions. In Section 4 simulation studies show the performance of estimators in small samples under different possible sources of heterogeneity. The example on recurrent events of catheter-related bloodstream infection is illustrated in Section 5. Finally, Section 7 reports a discussion with conclusive remarks.

2 Model formulation

Let D denote the survival time (the terminal event), and let $N^*(t)$ count the number of recurrent events observed over a time-period $[0, t]$, where $t \leq \tau$. Due to the terminal event, we only observe the recurrent event processes up to $\tau \wedge D$, where $a \wedge b = \min(a, b)$, such that $N^*(t) = N^*(t \wedge D)$ because subjects will only have events when still alive. Observations may also be censored, thus only making it possible to observe the processes up to the censoring time C. Let us define $\delta = I(D \leq C)$, $T = D \wedge C$, and let $N(t) = N^*(t \wedge C)$ be the observed number of events and define the at-risk process $Y(t) = I(T \geq t)$. Denote the counting process of the terminal event by $N^D(t)$ and denote its marginal cumulative hazard by $\Lambda^D(t)$. We make the standard assumption that the censoring is independent of D and $N^*(t)$. The observations $\{N_i(t), T_i, \delta_i\}$ are assumed to be independent replicates of $\{N(t), T, \delta\}$ for $i = 1, ..., n$ and any $t \in [0, \tau]$.

2.1 Marginal properties

The mean number of recurrent events up to time t is defined as

$$\mu(t) = E(N^*(t)) = \int_0^t S(s)dR(s), \tag{1}$$

where $S(t) = P(D > t)$ and $dR(t) = E(dN^*(t)|D > t)$ giving the recurrent event rate among the survivors. This marginal mean is justified by the fact that no further recurrent events can be experienced after the terminal event time D, i.e., the number of recurrent events remains constant for any $t > D$, and thus $E\{dN^*(t)\} = E\{dN^*(t \wedge D)) = E(dN^*(t)I(D \geq t)\}$.

Let us define $Y_\bullet(t) = \sum_{i=1}^n Y_i(t)$ and $N_\bullet(t) = \sum_{i=1}^n N_i(t)$. A simple estimator of $\mu(t)$ (Cook & Lawless, 1997) is to consider

$$\hat{\mu}(t) = \int_0^t \hat{S}(s)d\hat{R}(s),$$

where $\hat{S}(t)$ is the Kaplan-Meier estimator and

$$\hat{R}(t) = \int_0^t \frac{1}{Y_\bullet(s)} dN_\bullet(s),$$

is the Nelson-Aalen estimator of $R(t)$. The normalized estimator $n^{1/2}\{\hat{\mu}(t) - \mu(t)\}$ converges weakly to a mean-zero Gaussian process with variance that can be consistently estimated, see Ghosh & Lin (2000) for details. The estimator $\hat{\mu}(t)$ resembles the estimator of the cumulative incidence function and reflects the fact that the number of observed recurrent events depends on both survival and the event rate among the survivors. If $N^*(t)$ reduces to a counting process where the event of interest can occur at most one time, we are in a setting where the terminal event acts as a competing risk and $\hat{\mu}(t)$ coincides with the cumulative incidence estimator for the event of interest.

Let $M_i^D(t) = N_i^D(t) - \int_0^t Y_i(s) d\Lambda^D(s)$ be the martingale associated to the terminal event and let us define $M_i(t) = N_i(t) - \int_0^t Y_i(s) dR(s)$ and $\pi(t) = P(T \geq t)$. Following Ghosh & Lin (2000), the estimator $\hat{\mu}(t)$ can be expanded and written as a sum of i.i.d. zero mean processes $\varphi_i(t)$ as follows

$$n^{1/2}\{\hat{\mu}(t) - \mu(t)\} = n^{-1/2} \sum_{i=1}^{n} \varphi_i(t) + o_P(1),$$

where

$$\varphi_i(t) = \int_0^t \frac{S(s)}{\pi(s)} dM_i(s) - \mu(t) \int_0^t \frac{1}{\pi(s)} dM_i^D(s) + \int_0^t \frac{\mu(s)}{\pi(s)} dM_i^D(s).$$

Let $G_c(t)$ be the survival distribution of C, the right-censoring time, and let $\hat{G}_c(t)$ be the Kaplan-Meier estimator for $G_c(t)$. The estimator can be expressed alternatively as

$$\begin{aligned} \hat{\mu}(t) &= \int_0^t \hat{S}(s) d\hat{R}(s) = \sum_i \int_0^t \hat{S}(s) Y_i(s) \frac{1}{Y_\bullet(s)} dN_i(s) \\ &= \frac{1}{n} \sum_i \int_0^t \frac{Y_i(s)}{\hat{G}_c(s)} dN_i(s) = \frac{1}{n} \sum_i \int_0^t r_i(s) I(D_i \geq s) dN_i(s) \end{aligned} \tag{2}$$

with $r_i(s) = I(C_i \geq s)/\hat{G}_c(s)$ and noting that we can compute $I(C_i \geq s)I(D_i \geq s) = I(T_i \geq s)$, the at-risk indicator, further by using that $Y_\bullet(s) = n\, \hat{S}(s-)\hat{G}_c(s-)$. Thus, this is an increment IPCW estimator, since it is the IPCW sum of increments of the number of recurrent events, $dN_i(s)$, over time in $[0, t]$, and is the limit of the partitioning estimator of Bang & Tsiatis (2000) developed in the context of cumulative medical cost. Using the alternative formulation in (2), in the following we develop an alternative variance estimator for $\hat{\mu}(t)$ and discuss the estimator's efficiency.

We consider the martingale associated to the censoring time, $M_i^C(t) = N_i^C(t) - \int_0^t Y_i(s) d\Lambda_i^C(s)$, with counting process $N_i^C(t) = I(T_i \leq t, \delta = 0)$. Given the identity as in Robins & Rotnitzky (1992), we have that

$$I(D_i > s)\tilde{r}_i(s) = I(D_i > s)\frac{I(s \leq C_i)}{G_c(s)} = I(D_i > s)\left\{1 - \int_0^s \frac{1}{G_c(u)} dM_i^C(u)\right\}.$$

Therefore, the estimator of $\mu(t)$, when $G_c(t)$ is known, can be written as

$$\sum_i \int_0^t \tilde{r}_i(s) I(D_i > s) dN_i(s) = \sum_i \int_0^t \left(1 - \int_0^s \frac{1}{G_c(u)} dM_i^C(u)\right) I(D_i > s) dN_i^*(s)$$
$$= \sum_i \int_0^t I(D_i > s) dN_i^*(s) - \sum_i \int_0^t H_i(s,t) \frac{1}{G_c(s)} dM_i^C(s) \qquad (3)$$

with $H_i(s,t) = \int_s^t I(D_i > u) dN_i^*(u)$, obtained by changing the order of integration. It can be easily shown that this estimator has mean equal to $\mu(t)$ and thus it is unbiased. Note that the first term in (3) is the full-data estimator of $\mu(t) = E\{N^*(t)\}$ when censoring is not present.

Moreover, using the martingale integral representation for the Kaplan-Meier estimator

$$\frac{\hat{G}_c(s) - G_c(s)}{G_c(s)} = -\sum_i \int_0^s \frac{\hat{G}_c(u-)}{G_c(u)} \frac{1}{Y_\bullet(u)} dM_i^C(u) \qquad (4)$$

and following along the lines of Bang & Tsiatis (2000), we get that

$$n^{1/2}(\hat{\mu}(t) - \mu(t)) = n^{-1/2} \left(\sum_i \int_0^t \frac{Y_i(s)}{\hat{G}_c(s)} dN_i(s) - \mu(t) \right)$$

$$= n^{-1/2} \sum_i \left(\int_0^t I(D_i > s) dN_i^*(s) - \mu(t) \right) - n^{-1/2} \sum_i \int_0^t [H_i(s,t) - E(H,s,t)] \frac{1}{G_c(s)} dM_i^C(s) + o_p(1) \tag{5}$$

where $E(H,s,t) = E(H_i(s,t)I(D_i \geq s))/S(s)$. See Appendix A for a detailed derivation.

The normalized estimator in (5) is given as a sum of i.i.d terms. The variance of the estimator $n^{1/2}(\hat{\mu}(t) - \mu(t))$ is

$$E \left(\int_0^t I(D_i > s) dN_i^*(s) - \mu(t) \right)^2 + E \left(\int_0^t [H_i(s,t) - E(H,s,t)]^2 Y_i(s) \frac{1}{G_c^2(s)} d\Lambda_c(s) \right),$$

because conditional on D and $N(\cdot)$, the second term in (5) is still a martingale and therefore has conditional mean 0, given D and $N(\cdot)$. Note that, comparing (3) and (5), the contribution of the Kaplan-Meier estimator for $G_c(s)$ to the influence function is the extra term involving $E(H,s,t)$ in the martingale integral. As a consequence of this, the terms $H_i(s,t)$ are centered with respect to their conditional mean $E(H,s,t)$, and thus the variance of the normalized estimator is reduced, if compared with the variance of the same estimator where the true $G_c(s)$ is used.

The martingale central limit theory can be applied together with the central limit theorem to show that $\hat{\mu}(t)$ is asymptotically normal. We note that the asymptotic arguments here are based on a different expansion compared to Ghosh & Lin (2000). The variance of $\hat{\mu}(t)$ can be estimated by the following IPCW estimator for the two terms

$$\frac{1}{n} \left[\left\{ \hat{E}_2(H,0,t) - \hat{\mu}^2(t) \right\} + \frac{1}{n} \int_0^t \left(\frac{\hat{E}_2(H,s,t)}{\hat{S}(s)} - \bar{H}^2(s,t) \right) \frac{1}{\hat{G}_c^2(s)} dN_\bullet^C(s)) \right] \tag{6}$$

where $N_\bullet^C(s) = \sum_i N_i^C(s)$ and

$$\hat{E}_2(H, s, t) = \frac{1}{n} \sum_i \int_s^t r_i(u) I(D_i > u) f(N_i(u-) - N_i(s)) dN_i(u),$$
$$\bar{H}(s, t) = \frac{1}{n\hat{S}(s)} \sum_i \hat{H}_i(s, t) I(D_i > s), \quad \hat{H}_i(s, t) = \int_s^t \frac{Y_i(u)}{\hat{G}_c(u)} dN_i(u)$$

with $f(k) = (k+1)^2 - k^2$, see Appendix B for further details. Note that the estimators $\hat{E}_2(H, s, t)$ and $\bar{H}(s, t)$ are always computable from data (see remark in Appendix B). Other IPCW estimators could also have been used. The variance estimated by (6) provides an alternative estimator to that of Ghosh & Lin (2000).

3 The efficient estimator

In this section we discuss the efficiency of the increment IPCW estimator, and address how efficiency can be improved by using the efficient estimation theory for missing data (Tsiatis, 2006), building on the semiparametric theory of Robins & Rotnitzky (1992).

We show that an efficient estimator for $\mu(t)$ is given by

$$\tilde{\mu}(t) = \hat{\mu}(t) + \frac{1}{n} \sum_i \int_0^t \frac{L_i^{eff}(s, t)}{\hat{G}_c(s)} d\hat{M}_i^C(s), \tag{7}$$

where the second term is called the augmentation term, and the most efficient estimator is obtained with $L_i^{eff}(s, t) = E(H_i(s, t) | \text{Hist}_i(s), D_i > s)$. This function is the conditional mean of $H_i(s, t)$ given the history of the i^{th} subject up to time s among those that have not experienced the terminal event yet, $D_i > s$. We note that this history shows the number of recurrent events up to s and when they took place. The intuition underlying equation (7) comes from the fact that the augmentation term adds the expected value of the term omitted due to censoring, $E(\int_c^t I(D > s) dN | T > C = c)$, minus its mean (from the compensator of $dN^C(s)$). If $L_i^{eff}(s, t)$ is replaced by any other function, we would still have a consistent estimator. We show in Appendix C that the augmented estimator in (7) is orthogonal to the censoring nuisance space and therefore it is efficient.

When $E(H_i(s,t)|\text{Hist}_i(s), D_i > s)$ does not depend on the individual i, the augmentation term is zero because $\sum_i d\hat{M}_i^C(s) = 0$ and the estimator is efficient. Therefore, importantly, we note that when no heterogeneity is present then the estimator $\hat{\mu}(t)$ is efficient.

The estimator $\tilde{\mu}(t)$ is optimal in the sense that it has the smallest asymptotic variance among the class of regular asymptotically linear (RAL) estimators, and thus its asymptotic variance is equivalent to the semiparametric efficiency bound. However, the conditional expectation $L_i^{eff}(s,t)$ can not be directly computed without any further assumption on the recurrent event process and the death process.

Although the efficiency bound is not reached unless we have the correct conditional mean for the augmentation term, we can construct an estimator in (7) with improved efficiency as compared to the simple increment IPCW estimator in (2). A first approach in this direction is to estimate the conditional expectation by imposing a simple regression model that, even if incorrect, will provide a locally efficient estimator.

3.1 Computation of Augmentation term

In this section we consider some specific models for $L_i^{eff}(s,t)$, by imposing various frailty models, for which we can compute the augmentation term. This gives some insight into the type of augmentation that would give efficiency in specific settings. We consider a scenario with no heterogeneity where both the terminal event and the recurrent events are completely independent (Model 0); a second scenario where the terminal event is independent of the recurrent events, but however, there is heterogeneity (Model 1); finally a setting where both the terminal event and the recurrent events are correlated (Model 2).

In the first model (Model 0) we assume a terminal event rate $\lambda_d(t) = \alpha_d(t)$ and a recurrent event rate $\lambda(t) = \alpha(t)$, such that D is independent of $N^*(t)$ and $N^*(t)$ have independent increments. In this case, $E[dN_i^*(u)|\text{Hist}_i(s), D_i > s] = \lambda(u|D_i > s) = \alpha(u)du$ for any $u > s$ and for all individuals, it is then easy to see that the augmentation term is zero and therefore the estimator $\hat{\mu}(t)$ is efficient.

The second model (Model 1) imposes that $\lambda_d(t) = \alpha_d(t)$ and $\lambda(t|Z) = Z\alpha(t)$, where the frailty variable Z has a Gamma distribution with $E(Z) = 1$ and $Var(Z) = \theta$. Thus the marginal recurrent rate for a survivor at s is $E(dN_i(u)|\text{Hist}_i(s), D_i > s) = \lambda_i(u|\text{Hist}_i(s), D_i > s) = \alpha(u)E[Z_i|\text{Hist}_i(s), D_i > s] = \alpha(u)(1 + \theta N_i(s-))/(1 + \theta A(s))$, for any $u > s$, where $A(s) = \int_0^s \alpha(v)dv$. Therefore we get

$$\begin{aligned} E(H_i(s,t)|\text{Hist}_i(s), D_i > s) &= \int_s^t \exp\left(-\int_s^u \alpha_d(v)dv\right) \frac{1 + \theta N_i(s-)}{1 + \theta A(s)} \alpha(u)du \\ &= \tilde{\alpha}(s,t) + \tilde{\beta}(s,t)N_i(s-), \end{aligned} \tag{8}$$

suggesting that a linear prediction model using $N(s)$ as covariate, is sufficient.

A further more complex model (Model 2) can postulate $\lambda_d(t|Z) = Z\alpha_d(t)$ and $\lambda(t|Z) = Z\alpha(t)$ with the same frailty Z as above. Then, the hazard of D and $N^*(t)$ given the process history $\text{Hist}_i(s)$ and that a subject is still alive at s, will be

$$E(dN_{id}(u)|\text{Hist}_i(s), D_i > s) = \frac{1 + \theta N_i(s-)}{1 + \theta(A(s) + A_d(s))} \alpha_d(u) = \tilde{\alpha}_d(s,u) + \tilde{\beta}_d(s,u)N_i(s-)$$
$$E(dN_i(u)|\text{Hist}_i(s), D_i > s) = \frac{1 + \theta N_i(s-)}{1 + \theta(A(s) + A_d(s))} \alpha(u) = \tilde{\alpha}(s,u) + \tilde{\beta}(s,u)N_i(s-)$$

for any $u > s$ and with $A_d(s) = \int_0^s \alpha_d(v)dv$. Thus we obtain

$$E(H_i(s,t)|\text{Hist}_i(s), D_i > s) = \int_s^t \exp\left(-\int_s^u \tilde{\alpha}_d(s,v) + \tilde{\beta}_d(s,v)N(s-)dv\right)\left[\tilde{\alpha}(s,u) + \tilde{\beta}(s,u)N(s-)\right]du$$
$$= \int_s^t \tilde{A}_d(s,u)\tilde{B}_d(s,u)^{N(s-)}\left[\tilde{\alpha}(s,u) + \tilde{\beta}(s,u)N(s-)\right]du, \tag{9}$$

with $\tilde{A}_d(s,u) = \exp\left(-\int_s^u \tilde{\alpha}_d(s,v)\right)$ and $\tilde{B}(s,u) = \exp\left(-\int_s^u \tilde{\beta}_d(s,v)\right)$.

A possible extension of Models 0,1,2 consists of letting both rates $\alpha(t)$ and $\alpha_d(t)$, or just one of them, depend on some baseline covariates X that could be leveraged to further increase the statistical efficiency of $\tilde{\mu}(t)$. If we assume a proportional hazards form for both rates, then the augmentation term under Model 0 is not null and depends on X_i, but not on $N_i(s)$. For example, under the independence of Model 0 some observed baseline patient's characteristics could be responsible for heterogeneity. Using a regression model for the recurrent event rate, e.g., $\lambda(t|D_i > s, X) = \alpha_0(t)\exp(\beta^T X)$, we get $E(H_i(s,t)|D_i > s, X_i) = \exp(\beta^T X_i)\tilde{\alpha}_0(s,t)$, where $\tilde{\alpha}_0(s,t)$ is the baseline time-varying mean function for $X = 0$. Under Models 1 and 2, results are similar to the scenarios without covariates, with the only difference that the time-varying coefficients given in (8) and (9) depend also on X_i.

3.2 Dynamic prediction based augmentation

The specific optimal augmentation term depends on what information the history contains about the risk of subsequent events, and this will not be known, even though it can be explored by traditional modelling techniques. In the previous section we have illustrated how various simple frailty models lead to different structures for the conditional mean needed in the augmentation term. Bang & Tsiatis (2000) suggested to solve this problem by doing essentially linear regression to approximate the conditional mean with a simple linear model. We here explore this idea and extend this approach to dynamic predictions which turns out to be very important for gaining efficiency with the increment IPCW estimator.

The idea is simply to choose a set of predictors $e(s,t)^T = (e^1(s,t),...,e^J(s,t))$ and regress the $H(s,t)$ onto these predictors. We shall therefore explore how to use the predictions of the conditional mean, $E[H(s,t)|\text{Hist}(s), D > s)]$, on the form $\gamma(s,t)^T e(s,t)$ where $\gamma(s,t)$ is a J-vector function of time-dependent regression coefficients that are then estimated to lower the variance of the estimator. We note that Models 0 and 1 from the previous section indeed can be written on this form, whereas Model 2 can not. Note that here t is considered as fixed. We thus needs to choose the functionals $e^j(s,t)$ that depends on observed data Hist(s) and possibly t, such as for example $(e^1(s), e^2(s)) = (N(s-), \exp(-N(s))$. To simplify the notation we will not necessarily write out explicitly that $e^j(s,t)$ may depend on both s and t, but often just write $e^j(s)$.

With known $\gamma(s,t)$, we can then use the estimator

$$\tilde{\mu}_2(t) = \hat{\mu}(t) + \frac{1}{n}\sum_i \int_0^t \frac{\gamma(s,t)^T(e_i(s) - \bar{e}(s))}{\hat{G}_c(s)} dN_i^C(s), \tag{10}$$

with $\bar{e}(s) = \sum Y_i(s)e_i(s)/Y_\bullet(s)$ being the at risk average of the subject-specific predictors $e_i(s)^T = (e_i^1(s,t),...,e_i^J(s,t))$.

The normalized estimator can be expanded and written as $n^{1/2}(\tilde{\mu}_2(t) - \mu(t)) = n^{-1/2}\sum_i \tilde{\varphi}_i(t) + o_P(1)$ where the influence function is

$$\tilde{\varphi}_i(t) = \left(\int_0^t I(D_i > s) dN_{1i}^*(s) - \mu(t)\right) - y_i(t) + z_i(t), \tag{11}$$

with

$$y_i(t) = \int_0^t [H_i(s,t) - E(H,s,t)] \frac{1}{G_c(s)} dM_i^C(s), \quad z_i(t) = \int_0^t \gamma(s,t)^T [e_i(s) - E(e,s)] \frac{1}{G_c(s)} dM_i^C(s)$$

and $E(e,s) = E(e_i(s)|D_i > s)$.

The variance of $n^{1/2}(\tilde{\mu}_2(t) - \mu(t))$ is

$$E\left(\int_0^t I(D_i > s)dN_i^*(s) - \mu(t)\right)^2 + E\left(\int_0^t P_i^2(s,t)\frac{Y_i(s)}{G_c^2(s)}d\Lambda_c(s)\right) \tag{12}$$

with $P_i(s,t) = [(H_i(s,t) - E(H,s,t)) - \gamma(s,t)^T(e_i(s) - E(e,s))]$. To minimize the variance of the estimator, we need to find an optimal choice of $\gamma(s,t)$ in the second term in (12). This optimal solution is obtained by regressing $(H_i(s,t) - E(H,s,t))Y_i(s)$ on $(e_i(s) - \bar{e}(s))Y_i(s)$. Thus an estimator of the optimal regression coefficient is given as

$$\hat{\gamma}(s,t) = \left(\tilde{\Sigma}(s)\right)^{-1}\hat{G}_c(s)\sum_i \hat{H}_i(s,t)(e_i(s) - \bar{e}(s))Y_i(s),$$

with $\tilde{\Sigma}(s) = \sum_i Y_i(s)(e_i(s) - \bar{e}(s))^{\otimes 2}$. This expression is similar to the classical regression estimator $\hat{\gamma}(s,t) = (Z^TZ)^{-1}Z^TY$, but with $H_i(s,t)$ replaced by $\hat{H}_i(s,t)$. Note that $\sum_i E(H,s,t)(e_i(s) - \bar{e}(s))Y_i(s) = 0$. Note also, by using conditional means, that $E[\tilde{H}_i(s,t)e_i(s)] = E[E(\tilde{H}_i(s,t)e_i(s)|e_i(s))] = E[H_i(s,t)e_i(s)]$, with $\tilde{H}_i(s,t) = \int_s^t (1/G_c(u))I(D_i > u)dN_i(u)$ and that $E[H_i(s,t)e_i(s)Y_i(s)] = G_c(s)E[H_i(s,t)e_i(s)]$. Therefore, with the plug-in of the optimal $\hat{\gamma}(s,t)$ into the expression (10), we obtain the final augmented estimator for $\mu(t)$ with improved efficiency.

Moreover, the estimated variance of the augmented estimator $\tilde{\mu}_2(t)$ is

$$\widehat{\mathrm{var}}(\hat{\mu}(t)) - n^{-2}\int_0^t \hat{\gamma}(s,t)^T\tilde{\Sigma}(s)\hat{\gamma}(s,t)\frac{1}{\hat{G}_c^2(s)Y_\bullet(s)}dN_\bullet^C(s),$$

where $\widehat{\mathrm{var}}(\hat{\mu}(t))$ was given in (6).

Similarly, when $\gamma(s,t)$ is not depending on s, as in Bang & Tsiatis (2000),

$$\hat{\gamma}(t) = \left(\int_0^t \tilde{\Sigma}(s)\frac{1}{G_c^2(s)Y_\bullet(s)}dN_\bullet^C(s)\right)^{-1}\int_0^t \sum_i \hat{H}_i(s,t)(e_i(s) - \bar{e}(s))\frac{Y_i(s)}{\hat{G}_c(s)Y_\bullet(s)}dN_\bullet^C(s),$$

and the estimator is

$$\tilde{\mu}_1(t) = \hat{\mu}(t) + \frac{1}{n}\sum_i \hat{\gamma}^T(t)\int_0^t \frac{(e_i(s) - \bar{e}(s))}{\hat{G}_c(s)} dN_i^C(s). \tag{13}$$

In this case, the estimated variance of the augmented estimator is given as

$$\widehat{\text{var}}(\hat{\mu}(t)) - n^{-2}\hat{\gamma}(t)^T \left[\int_0^t \tilde{\Sigma}(s)\frac{1}{\hat{G}_c^2(s)Y_\bullet(s)} dN_\bullet^C(s)\right]\hat{\gamma}(t)$$

We observe that we thus can improve the performance of our estimator by projecting the optimal augmentation term into a specific augmentation space. In practice, when there is strong heterogeneity, this gain can be quite large if we use the dynamic estimator $\tilde{\mu}_2(t)$ based on $\gamma(s,t)$ as we shall see, while the gain is typically quite small if the simple linear regression estimator $\tilde{\mu}_1(t)$ based on $\gamma(t)$ is used.

The methodology presented in this section still holds and can be applied when heterogeneity is also due to the observed baseline covariates X. In this case, covariates can be included as predictors in the augmentation term of the proposed estimators $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$, with the scope to minimize their variance and thus improve their efficiency. This statement is supported by a simulation study for the simple case $e_i(s) = X$ reported in the next section.

4 Simulations

We considered the three models for which we did the specific calculations to obtain the efficient estimator (see Subsection 3.1). Specifically, we can rewrite these models as Model 0: $\lambda_d(t) = \alpha_d(t)$ and $\lambda_1(t) = k_1\alpha_1(t)$; Model 1: $\lambda_d(t) = \alpha_d(t)$ and $\lambda_1(t) = Zk_1\alpha_1(t)$ with Z being a Gamma variable with mean 1 and variance θ; Model 2: $\lambda_d(t) = Z\alpha_d(t)$ and $\lambda_1(t) = Zk_1\alpha_1(t)$, with the same Z. Here we included a constant k_1 that we varied to obtain different levels of recurrent events. The considered levels were $k_1 = 0.2, 1, 4$. In addition the variance θ of the random effect was assumed to be either 0.3 or 1. For Models 0,1,2, we considered different sample sizes, different levels of censoring, different levels of recurrent events and different levels of dependence via the variance of the random effect.

We simulated data that resemble the data provided by the application in the next section, thus letting $\alpha_d(t)$ and $\alpha_1(t)$ be piecewise linear approximations of the death rate and the event rate among survivors that we saw in the data. This led to a survival rate at around 24 % at 3000 days and an average mean number of events at around 2.3 at 3000 days. The censoring time was exponentially distributed with hazard $\lambda_c = k_c/5000$ with $k_c = 1, 2, 4$, the highest level of censoring thus leading to a censoring proportion of about 81% at 3000 days.

For the three assumed models the number of expected recurrent events are shown in Table 1, where only minor variation across the models and the size of the random effect ($\theta = 0.3$) are studied.

		Time					
k_1	Model	500	1000	1500	2000	2500	3000
0.2	0	0.16	0.24	0.31	0.37	0.42	0.47
0.2	1	0.15	0.22	0.28	0.34	0.38	0.42
0.2	2	0.16	0.24	0.31	0.37	0.42	0.47
1	0	0.79	1.19	1.56	1.88	2.12	2.34
1	1	0.74	1.09	1.42	1.7	1.92	2.11
1	2	0.79	1.19	1.56	1.88	2.13	2.35
4	0	3.18	4.75	6.24	7.53	8.5	9.37
4	1	2.98	4.37	5.68	6.8	7.67	8.45
4	2	3.18	4.77	6.27	7.55	8.52	9.39

Table 1: Mean number of events for different levels of k_1 in assumed Models 0,1,2 with $\theta = 0.3$ in simulations.

We investigated the performance of the two prediction augmented estimators $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$ based on the non-dynamic predictions with coefficient $\gamma(t)$ and the dynamic predictions with $\gamma(s,t)$, respectively (see equations (13) and (10) in Subsection 3.2). We used predictive models of different sizes and based on different covariates. Thus we considered a simple predictor model using only $N_1(s)$ (p-model A1); an extended model with $N_1(s), N_1(s)^2$ (p-model A12); an even larger model with $N_1(s), N_1(s)^2, \exp(-N_1(s))$ (p-model A13); and finally the model with $N_1(s), N_1(s)^2, \exp(-N_1(s)), N_1(s)\exp(-N_1(s))$ (p-model A14). These models are nested and the number of used predictors increases. These settings were studied for both the dynamic prediction model based on $\gamma(s,t)$ and the simple prediction model with constant effects based on $\gamma(t)$. Recall again that t is held fixed.

Simulations results are shown for one of the initial times, $t = 1000$, and the last time $t = 3000$. For prediction model p-model A1 we report the relative efficiency of $\tilde{\mu}_1(t)$, $\tilde{\mu}_2(t)$, computed as ratio between the sampling variances of the augmented estimator and the standard estimator, for the three simulation settings Model 0, Model 1, Model 2, and for all levels of k_c, k_1 and θ (see Table 2). For these scenarios, Table 3 evaluates the coverage probabilities. Tables 4, 5, 6 show the relative mean squared error (rMSE) with respect to the standard estimator, the relative bias (rBias) obtained as the ratio between empirical bias and true mean value, the ratio between the sample mean of estimated standard errors and the empirical standard deviation (RSD). We computed the relative bias to be able to compare settings with a different number of recurrent events that yield mean values for different sizes (see Table 1). Finally, Tables 7, 8 and 9 compare results for the different dynamic prediction models used in the augmentation.

From Tables 2, 3 and 4, we observe that under Model 0, the three estimators performed equally well for all considered settings both in terms of bias, coverage probability and efficiency, and provided nearly equal mean square errors and sampling standard deviations, as seen by all ratios nearly equal to one. Moreover, when using one of the alternative more complex p-models A12, A13, A14 (see Table 7), the estimators $\tilde{\mu}_1(t)$, $\tilde{\mu}_2(t)$ showed no improvements over the standard estimator, similarly to p-model A1.

Since there is no gain when using the proposed augmented estimators, as expected in case of complete independence of recurrent events and no heterogeneity (Model 0), we conclude that in this case the standard estimator $\hat{\mu}(t)$ is efficient and it is the preferable choice.

For all simulation settings, Model 0, Model 1 and Model 2, the estimator of the variance is performing very well, since the ratios between estimated and empirical standard errors (RSD) are approximately one (Tables 4, 5 and 6). We observe a slight underestimation for heavy censoring and the smallest sample size $n = 200$, which however vanishes as the size increases. For this last setting of heavy censoring and the smallest size, under Model 1 and Model 2, we note in Table 3 a slightly lower empirical coverage than the 95% nominal level, but only for the estimator $\tilde{\mu}_1(t)$ based on non-dynamic predictions and only at the latest time $t = 3000$. In all other settings, the coverage probabilities of $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$ are shown to be very good and similar to the standard estimator $\hat{\mu}(t)$.

Different conclusions were obtained under Models 1 and 2 with unobserved heterogeneity. Under these models and when p-model A1 is used, Tables 2 shows that both the augmented estimators perform better than $\hat{\mu}(t)$, with a considerable gain in efficiency, specially if there is strong heterogeneity in the data. In general, the efficiency is larger for highly correlated recurrent events ($\theta = 1$), and even more if Model 2 is assumed where correlation involves both terminal and recurrent events, and thus data are strongly heterogeneous. Indeed, ratios between the empirical variances of the improved estimator and the simple estimator, are below one in most of the cases, with more reductions concentrated at later times (here only $t = 3000$ is shown) where the variance is generally higher. In some settings with small sample size ($n = 200$), the increased efficiency is particularly evident, we observe an empirical variance that is reduced up to 25% for $\tilde{\mu}_2(t)$ and to 11% for $\tilde{\mu}_1(t)$ at the latest time. In addition, simulation results indicate that the efficiency is improved also for large samples, as shown by the case $n = 1600$. We also note that the relative efficiency of $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$ with respect to $\hat{\mu}(t)$, is improved for heavy censoring ($k_c = 4$) and when data present an increasing number of recurrent events ($k_1 = 4$). In these settings, as well as for stronger correlated data, the augmentation procedure is more useful in recovering information on missing data due to censoring and on the conditional mean of the recurrent events process over time via the prediction model. This job in recovering information is more successful for the augmented estimator $\tilde{\mu}_2(t)$, where prediction models are dynamic in time s. This is particularly so when terminal event and recurrent events are both correlated (compare, e.g., Model 1 and Model 2 in Table 2).

Under Model 1 or Model 2, we observe from Tables 5 and 6 that the bias of the augmented estimators is nearly equal to the bias of the standard estimator, with very few exceptions of a negligible inflation when both the sample size is small ($n = 200$) and we have heavy censoring ($k_c = 4$) that is up to 80% at the latest time $t = 3000$. However, this slight increase of bias in this specific setting disappears when the sample size increases. Moreover, simulation results show that the mean squared errors of $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$ are always lower or equal to that of $\hat{\mu}(t)$, as we see from all ratios rMSE being below or equal to one. Similarly to the efficiency discussed above, we note that this MSE reduction is stronger for $\tilde{\mu}_2(t)$ with more heterogeneity, more censoring and more recurrent events.

We shall discuss the optimal choice between the considered prediction models used for computing the augmentation term of $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$. In combination with the p-model A1 with only one predictor, these estimators show simultaneously a higher efficiency and a lower MSE, as compared to $\hat{\mu}(t)$, in all settings that we considered.

When there is heterogeneity between recurrent events (Model 1), Table 8 shows that the optimal choice for the prediction model in the augmentation is p-model A1, because it provided the lowest MSE and improved the efficiency as well as the larger p-models across all settings. The more complex p-models A12, A13, A14 did not bring any additional improvement and in some cases yielded an inflated MSE. This is in agreement with the theoretic considerations that showed that indeed the optimal augmentation, $E(H_i(s,t)|\text{Hist}_i(s), D_i > s)$, was on p-model A1 form.

We note in particular, that for the dynamic estimator, $\tilde{\mu}_2(t)$, p-model A1 showed a clearly advantage over all the alternatives in settings where the sample size is small (about $n = 200$) and with heavy censoring.

From Table 9, when also the terminal event is correlated to the recurrent events (Model 2), we note a different behaviour of the two augmented estimators. For $\tilde{\mu}_1(t)$, p-models A12, A13, A14 were found to produce lower MSE and efficiency as compared to p-model A1 in all settings, with a preference for p-models A12 or A13 when sample size is small. When right censoring is light ($k_c = 1$), also for the estimator $\tilde{\mu}_2(t)$ we found that p-models A12, A13, A14 produced lower MSE and efficiency as compared to p-model A1. However, for $\tilde{\mu}_2(t)$, and with heavy censoring in combination with a small sample ($n \leq 400$), the more complex p-models A13 and A14 that include more predictors, produced still a higher efficiency but at the price of an inflated MSE at latest times, due to a higher bias. This instability is caused by a lower data information in this specific extreme setting, and it was observed to be attenuated at $n = 1600$ where we have a good bias-variance trade-off. In summary, for all settings the optimal choices appear to be p-model A12 or A13 for estimator $\tilde{\mu}_1(t)$, in particular p-model A13 resembles the functional form of covariates $\exp(N(s))$ and $N(s)$ that appears in the assumed model for the expected number of recurrent events (see Model 2 in Subsection 3.1). The same conclusion can be reached for the estimator $\tilde{\mu}_2(t)$. However for this estimator, when censoring is heavy, sample size plays an important role in allowing a more complex p-model in the augmentation procedure.

4.1 Augmentation term with baseline covariates

To illustrate the possible efficiency gain by using only baseline covariates in the augmentation term, we also simulated data where the marginal means depended on covariates. Here, to mimic the worked example in the next section, we considered a baseline covariate with 5 levels with 20 % subjects in each level. The simulated model had proportional means of recurrent events with a proportionality factors given by $k \cdot (0.3, -0.3, 0.3, -0.3)$ with $k = 1, 2$. We still considered independent right censoring that was exponentially distributed with hazard $\lambda_c = k_c/5000$ and $k_c = 1, 2, 4$. Then we computed the dynamic prediction-based estimators $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$ where the augmentation p-model uses only baseline covariates as predictors. Simulations were performed with 10000 replications and for different sample sizes, we computed the bias and variance of the proposed estimators relative to the variance of the standard un-augmented estimator. We found no noticeable bias and an accurate estimator of the variance in all settings and therefore here we only report the relative variances in Table 10. Both the augmented estimators show an improved efficiency as compared to the standard estimator, specially at later time points ($t = 2000, 3000$) and when covariate effect is greater ($k = 2$). The dynamic augmented estimator $\tilde{\mu}_2(t)$ provides a relevant higher efficiency than $\tilde{\mu}_1(t)$, and thus it is the preferable choice when the p-model is based only on covariates.

5 Worked example

Patients with chronic intestinal failure receiving home parenteral support through a central venous catheter can experience several complications during the often long-term treatment periods, see Tribler et al. (2018); Scheike et al. (2019). We consider a cohort of 715 consecutive patients at the University Hospital of Copenhagen, where we here analysed the number of catheter-related bloodstream infections (CRBSI). Some of the patients died due to severe intestinal failure or co-morbidities, while other patients leaved the HPS program alive for different reasons during the around 14 years of follow up. We here studied the mean number of CBRSI's in the first 5000 days of the follow up, where only about 20 % of the patients survived.

All estimators are implemented in the `mets`-package for R and illustrated in a vignette (Holst & Scheike, 2022). For these data, we fitted a conditional regression model for the future events rate, with the current number of recurrent events as a predictor, and, using robust standard errors, we found that this predictor is strongly significant. Thus here there is clear evidence of strong heterogeneity with some subjects having many infections (up to 40 infections). The heterogeneity structure was further described in Scheike et al. (2019). In addition death seems to be related to the number of infections. In fact, the number of infections resulted to be a strong time-dependent predictor for the death rate when for example a Cox model is studied. We also note that the estimated probability $G_c(5000) = 0.14$ thus suggesting that the censoring adjustment do not get unstable. Therefore, we would expect that we can improve the efficiency of the standard estimator quite a bit.

We therefore computed the standard estimator as well as the improved dynamic-prediction estimator using the more complex model (p-model 14) and the model with only one predictor (p-model A1) for the augmentation. The improved estimator was computed only at the time-points, $500, 1000, ..., 5000$. The resulting estimates are shown if Figure 1, together with the estimated marginal mean (solid curve) and standard deviation (SD) of the observed recurrent events (dashed curve) over time. The SD has been computed as in Scheike et al. (2019). The SD and thus also variance is considerably larger than the mean and thus indicates strong overdispersion and heterogeneity between recurrent events. The confidence intervals computed with the improved variance estimator were around 7% narrower at 5000 days using the large prediction model p-model A14, and around 5% narrower using the small prediction model p-model A1. Also at the other time points we observed a substantial narrower confidence interval under the larger p-model A14, as expected because of the strong correlation in these data. The improvement in the size of these confidence intervals is due to the smaller standard errors of the augmentation-based estimator. This is shown in Table 2 where the ratios between the improved standard errors and the standard error of the classical estimator is lower than 1 after around 3000 days.

6 Heterogeneity and choice of prediction models

When studying recurrent events in presence of a terminal events, it is of interest in its own right to explore presence of heterogeneity in data and the possible different sources of this heterogeneity. This knowledge can be very important in general to provide better scientific insight, e.g. for individual risk of disease progression and practical clinical management. In addition, detecting presence and type of data heterogeneity is very useful for choosing the best estimator for the mean number of recurrent events, and in particular for selecting the best prediction model in the augmentation term of $\tilde{\mu}_1$ and $\tilde{\mu}_2$. This last issue has been discussed in the simulation studies and Subsection 3.1, where we assumed, via frailty models, the three different scenarios of no heterogeneity (Models 0), simple heterogeneity between recurrent events (Model 1) and more complex correlation that also involves the terminal event (Model 2).

Heterogeneity between recurrent events can be detected by fitting the frailty model $\lambda(t|Z) = Z\alpha(t)$ for the recurrent event rate, with $Var(Z) = \theta$. Then, a score test of homogeneity can be performed for testing whether the variance θ is equal to zero, see Commenges & Andersen (1995). Based on the conclusions from this test one may choose which of the proposed estimators to use.

An alternative and simple approach to learn if heterogeneity is present in the recurrent events is to fit a conditional regression model where the currently experienced number of events is a predictor for the rate of future events, as for example $\lambda_i(t|Hist_i(t-)) = \alpha_0(t)\exp(\beta N_i(t-))$, see further on such approaches in Cook & Lawless (2007).

More complex heterogeneity where both the terminal event and recurrent events are correlated, can be detected by several procedures. A possible approach is to consider a joint frailty model for the conditional rates of recurrent events and terminal event, with common frailty Z such that $E(Z) = 1$ and $Var(Z) = \theta$, as given in Subsection 3.1. A possible extension is to consider the hazard functions given as, respectively, $\lambda(t|Z) = Z\alpha(t)$ and $\lambda_d(t|Z) = Z^\eta\alpha_d(t)$, see for example Liu et al. (2004). A score test or a likelihood ratio test based on the above model with null hypothesis $H_0 : \eta = 0$ against $H_1 : \eta \neq 0$, allows us to verify whether the terminal event is independent of the recurrent events, and thus heterogeneity concerns only the latter. A correlation score test that does not require the estimation of the joint model has been aslo proposed by Balan et al. (2016). Therefore, if H_0 is rejected, the assumption of a joint model is fulfilled and $\hat{\eta}$ may suggest an equal or different effect of the frailty on the two rates. An alternative approach is to explore the dependence between terminal and recurrent events via a Cox regression model for the terminal event rate, as for example $\lambda_{id}(t|Hist_i(t)) = \alpha_{0d}(t)\exp(\beta N_i(t-))$, with an internal time-dependent covariate that describes the recurrent event history. The recurrent event process can also be studied as a covariate with different functional forms to explore which p-model could be more appropriate in the augmented estimators.

7 Discussion

We have shown how to estimate the marginal mean for recurrent events efficiently in the presence of right censoring. Our work demonstrated that the standard estimator was efficient when no heterogeneity is present, and that the standard estimator can be improved considerably when strong heterogeneity is present in data.

To obtain the efficient estimator, assumptions about the dependence among recurrent events and the dependence between D and $N^*(t)$ were needed. To avoid making these assumptions explicit, we proposed a prediction-based estimator that simply predicts the augmentation term by choosing specific prediction models, and still gave considerable improvements to the standard estimator. Moreover, we presented a version of this efficient augmented estimator where dynamic prediction models with time-varying coefficients are employed in the augmentation term. We found theoretically and via simulations that the efficiency of the estimator can be improved considerable by dynamic prediction when data are heterogeneous, as is often the case. Thus dynamic prediction might play an important role also in general augmented IPCW estimators in other context than the one discussed in the current paper.

Many recent scientific questions, specially in the biopharmacological context and based on randomized clinical trials where baseline confounding is not a concern, focus on estimands for recurrent events in presence of terminal event, and are clearly stated for a period up to a given time point of interest t^*. See, e.g., EMA (2020) and Fritsch et al. (2021), where the need for statistical efficiency is also discussed. In regard of this, it is then of great importance to apply efficient nonparametric estimators for the marginal mean of recurrent events up to the fixed t^*, together with point-wise confidence intervals, as shown in our worked example. In other applications, however, it is desirable to have simultaneous confidence bands, which here could also be obtained for the standard estimators and the proposed augmented ones. These uniform bands rely on the fact that the normalized estimators written as in (5) and (11), are a sum of i.i.d. terms and converge to a zero-mean Gaussian process. Therefore, the idea is to approximate the distribution of the normalized estimators with a zero-mean Gaussian process by a resampling technique. To do so, in the above mentioned equations, the unobservable martingale increments $dM_i^C(s)$ can be replaced with $G_i d\hat{M}_i(s)$, where G_i are independent standard normal variables, and the other unknown quantities are replaced by the respective sample estimates. The resulting process, denoted by $\hat{W}(t)$, can then be used to randomly generate a large number of realizations $\hat{w}_k(t)$, for $k = 1, \ldots, K$, by repeatedly simulating the normal samples $(G_1, \ldots, G_i, \ldots, G_n)$ while keeping fixed the observed data $\{N_i(t), T_i, \delta_i\}$.

When the focus is about studying covariate effects on the marginal mean of recurrent events, in presence of a terminal event, the proposed augmentation methods could also be extended to regression models based on IPCW estimating equations. Ghosh & Lin (2002) presented a semiparametric regression model with multiplicative covariate effects where it is feasible to extend the respective IPCW estimating equation to an augmented form. Moreover, one may also consider a fixed time regression model that simplify the functional form of the augmentation term. However, one particular issue here is that even though an augmented regression estimator is more efficient, it does not correspond to the most efficient estimator. Therefore, it is technically complicated and remains an open question how to build and choose the regression setting that leads to a substantially increased efficiency.

Observed baseline covariates may also be responsible of data heterogeneity. These covariates can be used as predictors in the dynamic augmentation of the proposed estimators, following the same approach of linear regression on $N(t)$. The methodology presented for $\tilde{\mu}_1(t)$, $\tilde{\mu}_2(t)$ still holds and their efficiency is greatly improved also for this setting, as confirmed by the results reported from simulations.

The estimators considered in this paper have all been implemented in the R-package **mets** (Holst & Scheike, 2022) and are demonstrated in a vignette in the package.

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References

Balan, T. A., Boonk, S. E., Vermeer, M. H. & Putter, H. (2016). Score test for association between recurrent events and a terminal event. *Statistics in medicine* **35**, 3037–3048.

Bang, H. & Tsiatis, A. A. (2000). Estimating medical costs with censored data. *Biometrika* **87**, 329–343.

Cai, J. & Schaubel, D. E. (2004). Marginal means/rates models for multiple type recurrent event data. *Lifetime data analysis* **10**, 121–138.

Chen, B. E. & Cook, R. J. (2004). Tests for multivariate recurrent events in the presence of a terminal. event. *Biostatistics* **5**, 129–143.

Commenges, D. & Andersen, P. K. (1995). Score test of homogeneity for survival data. *Lifetime Data Analysis* **1**, 145–156.

Cook, R. J. & Lawless, J. F. (1997). Marginal analysis of recurrent events and a terminating event. *Statistics in medicine* **16**, 911–924.

Cook, R. J. & Lawless, J. F. (2002). Analysis of repeated events. *Statistical Methods in Medical Research* **11**, 141–166.

Cook, R. J., Lawless, J. F. (2007). *The statistical analysis of recurrent events.* Springer Science & Business Media.

Cook, R. J., Lawless, J. F., Lakhal-Chaieb, L. & Lee, K.-A. (2009). Robust estimation of mean functions and treatment effects for recurrent events under event-dependent censoring and termination: Application to skeletal complications in cancer metastatic to bone. *Journal of the American Statistical Association* **104**, 60–75.

EMA (2020). *Qualification Opinion of Clinically Interpretable Treatment Effect Measures Based on Recurrent Event Endpoints that Allow for Efficient Statistical Analyses.* Committee for Medicinal Products for Human Use (CHMP), available at `https://www.ema.europa.eu/en/documents/other/qualification-opinion-clinically-interpretable-treatment-effect-measures-based-recurrent-event_en.pdf`

Fritsch, A., Schlömer, P., Mendolia, F., Mütze, T., Jahn-Eimermacher, A. & Recurrent Event Qualification Opinion Consortium (2021). Efficiency Comparison of Analysis Methods for Recurrent Event and Time-to-First Event Endpoints in the Presence of Terminal Events–Application to Clinical Trials in Chronic Heart Failure. *Statistics in Biopharmaceutical Research*, pages 1–12, published online: 04 Aug 2021.

Ghosh, D. & Lin, D.Y. (2000). Nonparametric analysis of recurrent events and death. *Biometrics* **56**, 554–562.

Ghosh, D. & Lin, D. Y. (2002). Marginal regression models for recurrent and terminal events. *Statistica Sinica* **12**, 663–688.

Ghosh, D. & Lin, D.Y. (2003). Semiparametric analysis of recurrent events data in the presence of dependent censoring. *Biometrics* **59**, 877–885.

Holst, K. K. & Scheike, T. (2022). *mets: Analysis of Multivariate Event Times.* R package version 1.3.0.

Liu, L., Wolfe, R. A. & Huang, X. (2004). Shared frailty models for recurrent events and a terminal event. *Biometrics* **60**, 747–756.

Robins, J. M. & Rotnitzky, A. (1992). Recovery of information and adjustment of dependent censoring using surrogate markers. In *AIDS Epidemiology-Methodological Issues.* Birkhäuser, Boston.

Scheike, T., Eriksson, F. & Tribler, S. (2019). The mean, variance and correlation for bivariate recurrent event data with a terminal event. *Journal of the Royal Statistical Society, Series C (Applied Statistics)* **68**, 1029–1049.

Tribler, S., Brandt, C., Fuglsang, K., Staun, M., Broebech, P., Moser, C., Scheike, T. & Jeppesen, P. (2018). Catheter-related bloodstream infections in patients with intestinal failure receiving home parenteral support: risks related to a catheter-salvage strategy. *American Journal of Clinical Nutrition* **107**, 743–753.

Tsiatis, A. (2006). *Semiparametric theory and missing data.* Springer Verlag.

Van der Laan, M. & Robins, J. (2003). *Unified methods for censored longitudinal data and causality.* Springer Verlag.

Appendix

Appendix A: Derivation of the influence function for the increment IPCW estimator

First we observe that, changing the order of integration and using the identity in (4),

$$\sum_i \int_0^t \frac{Y_i(s)}{\hat{G}_c(s)} \frac{\hat{G}_c(s) - G_c(s)}{G_c(s)} dN_i(s) = -\sum_i \int_0^t \frac{Y_i(s)}{G_c(s)} \sum_j \int_0^s \frac{\hat{G}_c(u-)}{G_c(u) Y_\bullet(u)} dM_j^C(u) dN_i(s)$$
$$= -\sum_j \int_0^t \left(\sum_i \int_s^t \frac{Y_i(u)}{\hat{G}_c(u)} dN_i(u) \right) \frac{\hat{G}_c(s-)}{G_c(s) Y_\bullet(s)} dM_j^C(s) = -\sum_i \int_0^t \hat{E}(H, s, t) \frac{1}{G_c(s)} dM_i^C(s),$$

where

$$\hat{E}(H, s, t) = \frac{\hat{G}_c(s-)}{Y_\bullet(s)} \sum_i \hat{H}_i(s, t) = \frac{1}{n\hat{S}(s)} \sum_i \hat{H}_i(s, t), \qquad \hat{H}_i(s, t) = \int_s^t \frac{Y_i(u)}{\hat{G}_c(u)} dN_i(u),$$

recalling that $Y_\bullet(s) = n\hat{G}_c(s-)\hat{S}(s-)$. Therefore, using the identity in (3), the estimator can be expanded as

$$n^{1/2}(\hat{\mu}(t) - \mu(t)) = n^{-1/2} \sum_i \int_0^t \frac{Y_i(s)}{\hat{G}_c(s)} dN_i(s) - n^{1/2}\mu(t)$$
$$= n^{-1/2} \sum_i \left(\int_0^t \tilde{r}_i(s) I(D_i > s) dN_i(s) - \mu(t) \right) - n^{-1/2} \sum_i \int_0^t \frac{Y_i(s)}{\hat{G}_c(s)} \frac{\hat{G}_c(s) - G_c(s)}{G_c(s)} dN_i(s)$$
$$= n^{-1/2} \sum_i \left(\int_0^t I(D_i > s) dN_i^*(s) - \mu(t) \right) - n^{-1/2} \sum_i \int_0^t [H_i(s, t) - \hat{E}(H, s, t)] \frac{1}{G_c(s)} dM_i^C(s)$$
$$= n^{-1/2} \sum_i \left(\int_0^t I(D_i > s) dN_i^*(s) - \mu(t) \right) - n^{-1/2} \sum_i \int_0^t [H_i(s, t) - E(H, s, t)] \frac{1}{G_c(s)} dM_i^C(s) + o_p(1) \tag{14}$$

where $E(H, s, t) = E(H_i(s, t) I(D_i > s))/S(s)$ and $H_i(s, t) = \int_s^t I(D_i > u) dN_i^*(u)$. Note also that the limit of $\hat{E}(H, s, t)$ is $E(H, s, t)$.

Appendix B: Increment IPCW estimator for the variance of $\hat{\mu}(t)$

The first term of the variance of $n^{1/2}(\hat{\mu}(t)-\mu(t))$ can be written as $E[\int_0^t I(D>s)dN^*(s)-\mu(t)]^2 = E[H(0,t)^2]-\mu(t)^2$, where

$$H(0,t)^2 = [\int_0^t I(D>s)dN^*(s)]^2 = \sum_{k=0}^{\infty}\int_0^t I(D>s)f(k)I(N^*(s-)=k)dN^*(s)$$

with $f(k)=(k+1)^2-k^2$ and its mean is given by

$$E(H(0,t)^2) = \sum_{k=0}^{\infty}\int_0^t S(s)f(k)P(N^*(s-)=k|D>s)E[dN^*(s)|N^*(s-)=k, D>s].$$

See Scheike et al. (2019). An estimator for this quantity is

$$\begin{aligned}\hat{E}_2(H,0,t) &= \sum_{i=1}^{n}\int_0^t \hat{S}(s)\left(\sum_k f(k)I(N_i(s-)=k)\right)\frac{dN_i(s)}{Y_\bullet(s)} = \sum_{i=1}^{n}\int_0^t \hat{S}(s)f(N_i(s-))Y_i(s)\frac{dN_i^*(s)}{Y_\bullet(s)}\\ &= \frac{1}{n}\sum_i\int_0^t \frac{Y_i(s)}{\hat{G}_c(s)}f(N_i(s-))dN_i^*(s) = \frac{1}{n}\sum_i\int_0^t r_i(s)I(D_i>s)f(N_i(s-))dN_i^*(s)\end{aligned}$$

and we clearly obtain an IPCW estimator for the first term of the variance.

The second term of the variance reduces to

$$E\left(\int_0^t [H_i(s,t)-E(H,s,t)]^2\frac{Y_i(s)}{G_c^2(s)}d\Lambda_i^C(s)\right) = \int_0^t \left(E(H_i(s,t)^2)-S(s)E(H,s,t)^2\right)\frac{1}{G_c(s)}d\Lambda_i^C(s).$$

We can write that

$$H(s,t)^2 = [\int_s^t I(D>u)dN^*(u)]^2 = \sum_{k=N^*(s)}^{K}\int_s^t I(D>u)f(k-N^*(s))I(N^*(u-)=k)dN^*(u)$$

and, similarly to above, the mean $E(H(s,t)^2)$ can be estimated by

$$\begin{aligned}\hat{E}_2(H,s,t) &= \sum_{i=1}^{n}\int_s^t \hat{S}(u)f(N_i(u-)-N_i(s))\frac{Y_i(u)}{Y_\bullet(s)}dN_i^*(u)\\ &= \frac{1}{n}\sum_i\int_s^t r_i(u)I(D_i>u)f(N_i(u-)-N_i(s))dN_i^*(u)\end{aligned}$$

Finally, it is easily found that a consistent estimator of $E(H,s,t)$ is $\bar{H}(s,t)$ and $d\Lambda^C(s)$ is estimated by the Nelson-Aalen formula $dN_\bullet^C(s)/Y_\bullet(s)$, then we get

$$\frac{1}{n}\int_0^t\left(\frac{\hat{E}_2(s,t)}{\hat{S}(s)}-\bar{H}(s,t)^2\right)\frac{1}{\hat{G}_c^2(s)}dN_\bullet^C(s).$$

Remark: Note that the estimators $\hat{E}_2(H,s,t)$ and $\bar{H}(s,t)$ are computable for all subjects, even if D is not observed. Indeed, $r_i(u)I(D_i>u)=Y_i(u)$ and the at-risk process can be evaluated at any time; in $\bar{H}(s,t)$, we have that $\hat{H}_i(s,t)I(D_i>s)=\int_s^t I(C_i>u)I(D_i>\max(s,u)dN_i(u)/\hat{G}_c(u)=\int_s^t Y_i(u)dN_i(u)/\hat{G}_c(u)$, which can be also evaluated for all subjects.

Appendix C: Efficient version of nonparametric IPCW increment estimator.

We denote the mean-zero influence function of the full data estimator for $\mu(t)$ and its increment IPCW version, respectively, as

$$\alpha^F(t)=\int_0^t I(D>s)dN^*(u)-\mu(t),\qquad \alpha^{IPCW}(t)=\int_0^t \tilde{r}(s)I(D>s)dN(s)-\mu(t).$$

It follows that, when the model for $H(s,t)$ is known, the observed influence function of the augmented estimator for $\mu(t)$ given in (7), is

$$\alpha^O(t) = \alpha^{IPCW}(t) + L_2 = \alpha^{IPCW}(t) + \int_0^t \frac{L^e(s,t)}{G_c(s)} dM^C(u),$$

where in the augmentation term L_2, the optimal choice is

$$L^{eff}(s,t) = E(H(s,t)|\text{Hist}_i(s), D \geq s)$$

with $H(s,t) = \int_s^t I(D > u)dN(u)$.

Then it follows that the non-parametric estimator in (7) is efficient (Tsiatis, 2006).

Proof

Define an Hilbert space $\mathcal{H}$ of mean-zero random vectors with finite variance, with inner product $< h_1, h_2 >= E(h_1^T h_2)$. Consider the nuisance tangent space $\Lambda \subset \mathcal{H}$.

To obtain an efficient version of the IPCW estimator for $\mu(t)$, we need to find the augmentation term L_2. By using the projection theorem, a unique function L_2 belonging to the nuisance tangent space $\Lambda \subset \mathcal{H}$, is given by the projection onto Λ, i.e., $L_2 = -\Pi(\alpha^{IPCW}(t)|\Lambda)$. This function is closest to $\alpha^{IPCW}(t)$ and such that $\alpha^{IPCW}(t) + L_2$ is an orthogonal projection of $\alpha^{IPCW}(t)$ onto the orthogonal complement space $\Lambda^\perp$, i.e., $< \alpha^{IPCW}(t) + L_2, L >= 0$ for $\forall L \in \Lambda$.

Therefore, we need to show that, with the optimal choice $L^{eff}(s,t) = E(H(s,t)|\text{Hist}_i(s), D \geq s)$, the influence function $\alpha^O(t) = \alpha^{IPCW}(t) + L_2$ is orthogonal to the nuisance censoring space given by $\Lambda = \{\int \alpha_c(t) dM^C(t) | \forall \alpha_c(t)\}$. This can be proved following the arguments as in Tsiatis (2006).

We thus need to show that

$$< \int_0^t \tilde{r}(s) I(D > s) dN(s) - \mu(t) + \int_0^t \frac{L^{eff}(s,t)}{G_c(s)} dM^C(u), \int \alpha_c(u) dM^C(u) >= 0$$

for all $\alpha_c(t)$. Using that $1 - \tilde{r}(t) = \int_0^t 1/G_c(s)dM^C(s)$ and the result in we have the result

$$\int_0^t \tilde{r}(s)I(D > s)dN(s) = \int_0^t I(D > s)dN^*(s) - \int_0^t \frac{H(s,t)}{G_c(s)}dM^C(s)$$

already given in equation (3).

Therefore,

$$\begin{aligned} &\int_0^t \tilde{r}(s)I(D > s)dN(s) - \mu(t) + \int_0^t \frac{L^{eff}(s,t)}{G_c(s)}dM^C(u) = \\ &\alpha^F(t) - \int_0^t \frac{(H(s,t) - E(H(s,t)|\text{Hist}_i(s), D > s))}{G_c(s)}dM^C(s) \end{aligned}$$

See also Appendix A. Due to the linearity of the space $\mathcal{H}$, it is enough to verify that each term on the right-hand side is orthogonal to $\int \alpha_c(u)dM^C(u)$ for all $\alpha_c(t)$. Using conditional independence of C and D, N^*, we have that

$$E\left[\alpha^F(t)\left(\int_0^t \alpha_c(u)dM^C(u)\right)\right] = E\left[\alpha^F(t)E\left[\int_0^t \alpha_c(u)dM^C(u)|D, N^*(\cdot)\right]\right]$$

where the internal conditional expectation is zero because of the mean-zero censoring martingale increments, and thus orthogonality is achieved. Similarly, the second term is also orthogonal to $\int \alpha_c(u)dM^C(u)$, again because of the conditional independence and because $E[(H(s,t) - E(H(s,t)|\text{Hist}_i(s), D > s))I(D > s)] = 0$, by construction.

			$k_c = 1$						$k_c = 4$					
			$k_1 = 0.2$		$k_1 = 1$		$k_1 = 4$		$k_1 = 0.2$		$k_1 = 1$		$k_1 = 4$	
		θ	0.3	1	0.3	1	0.3	1	0.3	1	0.3	1	0.3	1
n	Time	Est	Model 0											
200	1000	$\tilde{\mu}_1$	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
		$\tilde{\mu}_2$	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	3000	$\tilde{\mu}_1$	1.00	-	1.00	-	1.00	-	0.98	-	1.01	-	1.02	-
		$\tilde{\mu}_2$	0.99	-	1.00	-	1.00	-	0.92	-	0.98	-	1.02	-
400	1000	$\tilde{\mu}_1$	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
		$\tilde{\mu}_2$	1.00	-	1.00	-	1.00	-	1.01	-	1.00	-	0.99	-
	3000	$\tilde{\mu}_1$	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.01	-
		$\tilde{\mu}_2$	0.99	-	1.00	-	1.00	-	0.99	-	0.99	-	1.00	-
1600	1000	$\tilde{\mu}_1$	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
		$\tilde{\mu}_2$	1.01	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	3000	$\tilde{\mu}_1$	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
		$\tilde{\mu}_2$	1.01	-	1.00	-	1.00	-	1.01	-	1.01	-	1.00	-
n	Time	Est	Model 1											
200	1000	$\tilde{\mu}_1$	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.00	0.99	0.99	0.98
		$\tilde{\mu}_2$	1.00	1.00	1.00	0.99	1.00	0.98	1.00	1.00	0.99	0.98	0.98	0.96
	3000	$\tilde{\mu}_1$	1.00	0.99	0.99	0.99	0.99	0.98	0.99	0.99	0.97	0.95	0.96	0.89
		$\tilde{\mu}_2$	1.00	0.99	0.98	0.98	0.98	0.94	0.95	0.92	0.92	0.86	0.90	0.78
400	1000	$\tilde{\mu}_1$	1.00	1.00	1.00	0.99	1.00	0.99	1.00	1.00	1.00	0.99	0.99	0.98
		$\tilde{\mu}_2$	1.01	1.00	1.00	0.99	1.00	0.99	1.01	0.99	0.99	0.98	0.98	0.96
	3000	$\tilde{\mu}_1$	1.00	1.00	1.00	0.99	0.99	0.98	0.99	0.99	0.99	0.96	0.96	0.92
		$\tilde{\mu}_2$	1.00	0.99	0.99	0.97	0.98	0.96	0.96	0.94	0.96	0.89	0.91	0.81
1600	1000	$\tilde{\mu}_1$	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.99	0.99	0.98
		$\tilde{\mu}_2$	0.99	1.01	1.00	1.00	1.00	0.99	1.00	0.97	1.00	0.99	0.98	0.95
	3000	$\tilde{\mu}_1$	1.00	1.00	1.00	0.99	0.99	0.98	1.00	1.00	0.98	0.95	0.96	0.90
		$\tilde{\mu}_2$	0.99	1.00	0.99	0.98	0.99	0.97	0.98	0.97	0.97	0.91	0.93	0.80
n	Time	Est	Model 2											
200	1000	$\tilde{\mu}_1$	1.00	1.00	1.00	0.99	0.99	1.00	1.00	1.00	1.00	0.98	0.98	0.96
		$\tilde{\mu}_2$	1.00	1.00	0.99	0.99	0.99	0.98	1.01	1.00	0.99	0.94	0.97	0.91
	3000	$\tilde{\mu}_1$	1.00	1.00	1.00	0.98	0.99	1.06	0.98	0.95	0.97	0.90	0.96	0.95
		$\tilde{\mu}_2$	0.99	0.98	0.98	0.95	0.97	0.96	0.92	0.83	0.89	0.74	0.86	0.71
400	1000	$\tilde{\mu}_1$	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.00	0.98	0.99	0.97
		$\tilde{\mu}_2$	0.99	1.01	1.00	1.00	1.00	0.98	1.00	1.00	0.99	0.96	0.98	0.93
	3000	$\tilde{\mu}_1$	1.00	0.99	1.00	0.98	0.99	1.08	0.99	0.98	0.97	0.94	0.94	0.98
		$\tilde{\mu}_2$	1.00	0.99	0.99	0.96	0.97	0.97	0.96	0.89	0.92	0.82	0.86	0.78
1600	1000	$\tilde{\mu}_1$	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.98	0.99	0.97
		$\tilde{\mu}_2$	1.00	0.99	1.00	0.99	0.99	0.98	1.02	0.98	0.99	0.97	0.97	0.93
	3000	$\tilde{\mu}_1$	1.00	0.99	0.99	0.97	0.98	1.08	1.00	0.98	0.96	0.91	0.94	0.99
		$\tilde{\mu}_2$	1.01	0.98	0.99	0.95	0.97	0.99	0.99	0.97	0.93	0.80	0.86	0.79

Table 2: Efficiency for $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$, computed as ratio between the empirical variances of the augmented estimator and the standard estimator. Simulations with prediction model p-model A1, assuming either Model 0, Model 1 or Model 2 (Model 0 has no assumptions on θ).

			$k_c = 1$						$k_c = 4$					
			$k_1 = 0.2$		$k_1 = 1$		$k_1 = 4$		$k_1 = 0.2$		$k_1 = 1$		$k_1 = 4$	
		θ	0.3	1	0.3	1	0.3	1	0.3	1	0.3	1	0.3	1
n	Time	Est	Model 0											
200	1000	$\hat{\mu}$	0.94	-	0.95	-	0.95	-	0.94	-	0.95	-	0.94	-
		$\tilde{\mu}_1$	0.94	-	0.95	-	0.95	-	0.94	-	0.94	-	0.94	-
		$\tilde{\mu}_2$	0.94	-	0.95	-	0.95	-	0.94	-	0.94	-	0.94	-
	3000	$\hat{\mu}$	0.94	-	0.95	-	0.94	-	0.91	-	0.93	-	0.94	-
		$\tilde{\mu}_1$	0.94	-	0.95	-	0.94	-	0.90	-	0.90	-	0.90	-
		$\tilde{\mu}_2$	0.94	-	0.95	-	0.94	-	0.91	-	0.92	-	0.93	-
400	1000	$\hat{\mu}$	0.95	-	0.94	-	0.95	-	0.95	-	0.94	-	0.95	-
		$\tilde{\mu}_1$	0.95	-	0.94	-	0.95	-	0.95	-	0.94	-	0.95	-
		$\tilde{\mu}_2$	0.95	-	0.94	-	0.95	-	0.95	-	0.94	-	0.95	-
	3000	$\hat{\mu}$	0.94	-	0.94	-	0.94	-	0.93	-	0.94	-	0.95	-
		$\tilde{\mu}_1$	0.94	-	0.94	-	0.94	-	0.92	-	0.92	-	0.93	-
		$\tilde{\mu}_2$	0.94	-	0.94	-	0.94	-	0.93	-	0.93	-	0.94	-
1600	1000	$\hat{\mu}$	0.95	-	0.95	-	0.95	-	0.95	-	0.95	-	0.95	-
		$\tilde{\mu}_1$	0.95	-	0.95	-	0.95	-	0.95	-	0.95	-	0.95	-
		$\tilde{\mu}_2$	0.95	-	0.95	-	0.95	-	0.95	-	0.95	-	0.95	-
	3000	$\hat{\mu}$	0.94	-	0.95	-	0.95	-	0.95	-	0.94	-	0.95	-
		$\tilde{\mu}_1$	0.94	-	0.95	-	0.95	-	0.95	-	0.94	-	0.94	-
		$\tilde{\mu}_2$	0.94	-	0.95	-	0.95	-	0.95	-	0.94	-	0.95	-
n	Time	Est	Model 1											
200	1000	$\hat{\mu}$	0.94	0.94	0.95	0.95	0.95	0.94	0.94	0.93	0.94	0.94	0.95	0.94
		$\tilde{\mu}_1$	0.94	0.94	0.95	0.95	0.95	0.94	0.93	0.93	0.94	0.94	0.95	0.94
		$\tilde{\mu}_2$	0.94	0.94	0.95	0.95	0.95	0.94	0.93	0.93	0.94	0.94	0.95	0.94
	3000	$\hat{\mu}$	0.94	0.94	0.94	0.94	0.94	0.94	0.90	0.90	0.92	0.91	0.92	0.92
		$\tilde{\mu}_1$	0.94	0.94	0.93	0.94	0.94	0.93	0.89	0.89	0.90	0.89	0.90	0.89
		$\tilde{\mu}_2$	0.94	0.94	0.94	0.94	0.94	0.93	0.90	0.90	0.92	0.91	0.92	0.91
400	1000	$\hat{\mu}$	0.95	0.94	0.95	0.94	0.95	0.95	0.95	0.94	0.94	0.94	0.95	0.94
		$\tilde{\mu}_1$	0.95	0.94	0.95	0.94	0.95	0.95	0.95	0.94	0.94	0.94	0.95	0.94
		$\tilde{\mu}_2$	0.95	0.94	0.95	0.94	0.95	0.95	0.95	0.94	0.94	0.94	0.95	0.94
	3000	$\hat{\mu}$	0.95	0.95	0.95	0.95	0.95	0.94	0.93	0.92	0.93	0.93	0.93	0.93
		$\tilde{\mu}_1$	0.95	0.95	0.94	0.94	0.94	0.94	0.92	0.91	0.92	0.92	0.92	0.92
		$\tilde{\mu}_2$	0.95	0.95	0.95	0.94	0.95	0.94	0.92	0.92	0.93	0.93	0.93	0.93
1600	1000	$\hat{\mu}$	0.94	0.94	0.95	0.95	0.95	0.94	0.95	0.94	0.95	0.95	0.96	0.94
		$\tilde{\mu}_1$	0.95	0.94	0.96	0.95	0.95	0.94	0.95	0.94	0.95	0.95	0.96	0.94
		$\tilde{\mu}_2$	0.95	0.94	0.95	0.95	0.95	0.94	0.95	0.94	0.95	0.95	0.96	0.94
	3000	$\hat{\mu}$	0.95	0.95	0.95	0.95	0.95	0.94	0.94	0.94	0.95	0.95	0.95	0.94
		$\tilde{\mu}_1$	0.95	0.95	0.95	0.95	0.96	0.94	0.94	0.94	0.94	0.95	0.94	0.94
		$\tilde{\mu}_2$	0.95	0.95	0.95	0.95	0.95	0.94	0.94	0.94	0.95	0.95	0.95	0.94
n	Time	Est	Model 2											
200	1000	$\hat{\mu}$	0.94	0.93	0.95	0.94	0.94	0.94	0.94	0.92	0.94	0.93	0.94	0.94
		$\tilde{\mu}_1$	0.94	0.93	0.94	0.94	0.94	0.93	0.94	0.92	0.94	0.92	0.94	0.93
		$\tilde{\mu}_2$	0.94	0.93	0.95	0.94	0.94	0.93	0.94	0.92	0.94	0.92	0.94	0.94
	3000	$\hat{\mu}$	0.94	0.93	0.94	0.93	0.95	0.93	0.91	0.88	0.91	0.88	0.92	0.90
		$\tilde{\mu}_1$	0.94	0.93	0.94	0.93	0.95	0.92	0.90	0.85	0.88	0.85	0.88	0.86
		$\tilde{\mu}_2$	0.94	0.93	0.94	0.93	0.95	0.92	0.90	0.87	0.91	0.88	0.91	0.90
400	1000	$\hat{\mu}$	0.95	0.93	0.95	0.94	0.94	0.94	0.95	0.94	0.95	0.94	0.94	0.95
		$\tilde{\mu}_1$	0.95	0.93	0.95	0.94	0.94	0.95	0.95	0.94	0.95	0.94	0.94	0.94
		$\tilde{\mu}_2$	0.95	0.93	0.95	0.94	0.94	0.94	0.95	0.94	0.95	0.94	0.94	0.94
	3000	$\hat{\mu}$	0.95	0.93	0.95	0.94	0.94	0.94	0.93	0.90	0.93	0.92	0.93	0.93
		$\tilde{\mu}_1$	0.95	0.93	0.95	0.94	0.94	0.94	0.92	0.89	0.92	0.90	0.92	0.90
		$\tilde{\mu}_2$	0.95	0.93	0.95	0.94	0.94	0.93	0.92	0.91	0.93	0.92	0.94	0.92
1600	1000	$\hat{\mu}$	0.95	0.94	0.95	0.95	0.95	0.95	0.95	0.94	0.95	0.95	0.95	0.95
		$\tilde{\mu}_1$	0.95	0.93	0.95	0.95	0.95	0.95	0.95	0.94	0.95	0.94	0.95	0.95
		$\tilde{\mu}_2$	0.95	0.93	0.95	0.95	0.95	0.95	0.95	0.94	0.95	0.94	0.95	0.95
	3000	$\hat{\mu}$	0.95	0.94	0.95	0.95	0.95	0.95	0.95	0.93	0.95	0.94	0.94	0.94
		$\tilde{\mu}_1$	0.94	0.94	0.95	0.94	0.95	0.95	0.95	0.92	0.94	0.93	0.94	0.94
		$\tilde{\mu}_2$	0.94	0.94	0.95	0.95	0.95	0.93	0.95	0.93	0.95	0.95	0.94	0.93

Table 3: 95% empirical coverage probability for $\hat{\mu}(t)$, $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$. Simulations with prediction model p-model A1, assuming either Model 0, Model 1 or Model 2 (Model 0 has no assumptions on θ).

			$n=200$						$n=400$						$n=1600$					
			$t=1000$			$t=3000$			$t=1000$			$t=3000$			$t=1000$			$t=3000$		
k_c	k_1	Est	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD
1	0.2	$\hat{\mu}$	1.00	0.00	0.99	1.00	0.01	0.99	1.00	0.00	1.00	1.00	0.01	1.01	1.00	0.00	1.00	1.00	0.01	1.00
		$\tilde{\mu}_1$	1.00	0.00	0.99	1.00	0.01	0.99	1.00	0.00	1.00	1.00	0.01	1.01	1.00	0.00	1.00	1.00	0.01	1.00
		$\tilde{\mu}_2$	1.00	0.00	0.99	0.99	0.01	0.99	1.00	0.00	1.00	0.99	0.01	1.01	1.01	0.00	0.99	1.01	0.01	0.99
	1	$\hat{\mu}$	1.00	−0.00	1.00	1.00	0.00	0.99	1.00	0.00	1.01	1.00	0.00	1.00	1.00	0.00	1.01	1.00	0.00	1.00
		$\tilde{\mu}_1$	1.00	−0.00	1.00	1.00	0.00	0.99	1.00	0.00	1.01	1.00	0.00	1.00	1.00	0.00	1.01	1.00	0.00	1.00
		$\tilde{\mu}_2$	1.00	−0.00	1.00	1.00	−0.00	0.99	1.00	0.00	1.01	1.00	0.00	1.00	1.00	0.00	1.01	1.00	0.00	1.00
	4	$\hat{\mu}$	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	1.00	1.00	0.00	1.00
		$\tilde{\mu}_1$	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	1.00	1.00	0.00	1.00
		$\tilde{\mu}_2$	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	1.01	1.00	0.00	1.00
4	0.2	$\hat{\mu}$	1.00	0.00	1.00	1.00	0.00	0.93	1.00	0.00	0.99	1.00	0.01	0.96	1.00	0.00	1.01	1.00	0.01	0.99
		$\tilde{\mu}_1$	1.00	0.00	1.00	0.98	−0.00	0.92	1.00	0.00	0.99	1.00	0.01	0.95	1.00	0.00	1.01	1.00	0.01	0.99
		$\tilde{\mu}_2$	1.00	−0.00	0.99	0.94	−0.03	0.94	1.01	0.00	0.98	0.98	−0.00	0.95	1.00	0.00	1.01	1.00	0.00	0.99
	1	$\hat{\mu}$	1.00	0.00	0.99	1.00	0.00	0.95	1.00	0.00	1.01	1.00	0.00	1.00	1.00	0.00	0.99	1.00	0.00	0.99
		$\tilde{\mu}_1$	1.00	0.00	0.99	1.01	−0.01	0.93	1.00	0.00	1.01	1.00	0.00	0.99	1.00	0.00	0.99	1.00	0.00	0.99
		$\tilde{\mu}_2$	1.00	−0.00	0.99	1.04	−0.03	0.93	1.00	0.00	1.01	1.00	−0.01	0.99	1.00	0.00	1.00	1.01	−0.00	0.98
	4	$\hat{\mu}$	1.00	−0.00	0.98	1.00	0.00	0.95	1.00	0.00	0.99	1.00	0.00	0.98	1.00	0.00	1.00	1.00	0.00	0.99
		$\tilde{\mu}_1$	1.00	−0.00	0.97	1.03	−0.01	0.93	1.00	0.00	0.99	1.00	0.00	0.97	1.00	0.00	1.00	1.00	0.00	0.99
		$\tilde{\mu}_2$	1.01	−0.00	0.97	1.11	−0.03	0.91	0.99	0.00	0.99	1.03	−0.01	0.97	1.00	0.00	1.00	1.00	−0.00	0.99

Table 4: Relative mean squared error (rMSE) with respect to the standard estimator; relative bias (rBias) with respect to the size of the true mean; ratio between the sample mean of estimated standard errors and the sampling standard deviation (RSD). Simulations with prediction model p-model A1, under complete independence (Model 0).

				$n=200$						$n=400$						$n=1600$					
				$t=1000$			$t=3000$			$t=1000$			$t=3000$			$t=1000$			$t=3000$		
k_c	k_1	θ	Est	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD
1	0.2	0.3	$\hat{\mu}$	1.00	−0.00	0.99	1.00	−0.00	0.99	1.00	0.00	1.01	1.00	0.00	0.99	1.00	−0.00	1.00	1.00	−0.00	1.00
			$\tilde{\mu}_1$	1.00	−0.00	0.99	1.00	−0.00	0.99	1.00	0.00	1.01	1.00	0.00	0.99	1.00	−0.00	1.00	1.00	−0.00	1.00
			$\tilde{\mu}_2$	1.00	−0.01	0.98	1.01	−0.01	0.98	1.01	0.00	1.00	1.00	0.00	0.99	0.99	−0.00	1.01	0.99	−0.00	1.01
		1	$\hat{\mu}$	1.00	−0.01	0.98	1.00	−0.01	0.99	1.00	−0.01	0.99	1.00	−0.00	0.98	1.00	−0.01	0.99	1.00	−0.00	0.99
			$\tilde{\mu}_1$	1.00	−0.01	0.99	1.00	−0.01	0.99	1.00	−0.01	0.99	1.00	−0.00	0.98	1.00	−0.01	0.99	1.00	−0.00	0.99
			$\tilde{\mu}_2$	1.00	−0.01	0.98	0.99	−0.01	0.99	1.00	−0.01	0.99	0.99	−0.01	0.99	1.01	−0.01	0.98	1.00	−0.00	0.98
	1	0.3	$\hat{\mu}$	1.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.99	1.00	−0.00	1.00	1.00	0.00	1.01	1.00	0.00	1.01
			$\tilde{\mu}_1$	1.00	0.00	1.00	0.99	−0.00	1.00	1.00	0.00	0.99	1.00	−0.00	1.00	1.00	0.00	1.01	1.00	−0.00	1.01
			$\tilde{\mu}_2$	1.00	0.00	1.00	0.99	−0.00	1.00	1.00	0.00	0.99	0.99	−0.00	1.00	1.00	0.00	1.00	0.99	−0.00	1.01
		1	$\hat{\mu}$	1.00	−0.00	1.00	1.00	−0.00	0.99	1.00	0.00	1.01	1.00	0.00	1.00	1.00	0.00	1.00	1.00	0.00	0.99
			$\tilde{\mu}_1$	1.00	−0.00	1.00	0.99	−0.00	0.99	1.00	0.00	1.01	0.99	0.00	1.00	1.00	0.00	1.00	0.99	0.00	0.99
			$\tilde{\mu}_2$	0.99	−0.00	1.00	0.98	−0.01	0.99	0.99	0.00	1.01	0.97	−0.00	1.00	1.00	0.00	1.00	0.98	0.00	0.99
	4	0.3	$\hat{\mu}$	1.00	0.00	0.99	1.00	−0.00	0.99	1.00	0.00	1.00	1.00	0.00	0.99	1.00	0.00	1.01	1.00	0.00	1.02
			$\tilde{\mu}_1$	1.00	0.00	0.99	0.99	−0.00	0.99	1.00	0.00	1.00	0.99	0.00	0.99	1.00	0.00	1.01	1.00	0.00	1.02
			$\tilde{\mu}_2$	1.00	−0.00	0.99	0.99	−0.00	0.99	1.00	0.00	1.00	0.98	−0.00	0.99	1.00	0.00	1.01	0.99	−0.00	1.02
		1	$\hat{\mu}$	1.00	−0.00	0.97	1.00	−0.00	1.00	1.00	0.00	1.00	1.00	−0.00	0.98	1.00	0.00	0.99	1.00	−0.00	1.00
			$\tilde{\mu}_1$	0.99	−0.00	0.98	0.98	−0.00	1.00	1.00	0.00	1.00	0.98	−0.00	0.97	1.00	0.00	0.99	0.98	−0.00	1.00
			$\tilde{\mu}_2$	0.98	−0.00	0.98	0.95	−0.01	1.00	0.99	0.00	1.00	0.96	−0.00	0.98	0.99	0.00	0.99	0.97	−0.00	0.99
4	0.2	0.3	$\hat{\mu}$	1.00	0.00	0.99	1.00	0.00	0.92	1.00	0.00	0.99	1.00	0.00	0.97	1.00	−0.00	1.00	1.00	−0.00	0.99
			$\tilde{\mu}_1$	1.00	0.00	0.99	0.99	−0.01	0.91	1.00	0.00	0.99	0.99	−0.00	0.96	1.00	−0.00	1.00	1.00	−0.00	0.99
			$\tilde{\mu}_2$	1.00	−0.00	0.99	0.97	−0.03	0.91	1.01	0.00	0.98	0.97	−0.01	0.97	1.01	−0.01	0.99	0.98	−0.00	1.00
		1	$\hat{\mu}$	1.00	−0.01	0.99	1.00	−0.01	0.94	1.00	−0.01	1.00	1.00	−0.00	0.97	1.00	−0.01	0.99	1.00	−0.01	0.99
			$\tilde{\mu}_1$	1.00	−0.01	0.98	0.99	−0.01	0.93	1.00	−0.01	1.00	0.99	−0.01	0.97	1.00	−0.01	0.99	1.00	−0.01	0.98
			$\tilde{\mu}_2$	1.00	−0.02	0.98	0.95	−0.04	0.94	0.99	−0.01	1.00	0.96	−0.02	0.98	0.98	−0.01	1.00	0.99	−0.01	0.99
	1	0.3	$\hat{\mu}$	1.00	0.00	1.00	1.00	−0.00	0.94	1.00	0.00	1.00	1.00	0.00	0.97	1.00	0.00	1.01	1.00	0.00	1.00
			$\tilde{\mu}_1$	1.00	0.00	1.00	0.98	−0.01	0.94	1.00	0.00	1.00	0.99	−0.00	0.96	1.00	0.00	1.01	0.98	0.00	1.00
			$\tilde{\mu}_2$	0.99	−0.00	1.00	0.98	−0.03	0.95	0.99	0.00	1.00	0.99	−0.02	0.96	1.00	0.00	1.00	0.97	−0.00	1.00
		1	$\hat{\mu}$	1.00	0.00	0.96	1.00	0.00	0.93	1.00	0.00	0.99	1.00	0.00	0.99	1.00	−0.00	1.00	1.00	0.00	0.99
			$\tilde{\mu}_1$	0.99	0.00	0.96	0.95	−0.00	0.93	0.99	0.00	0.99	0.96	−0.00	0.99	0.99	−0.00	1.00	0.95	0.00	0.99
			$\tilde{\mu}_2$	0.99	−0.00	0.96	0.91	−0.03	0.94	0.98	0.00	1.00	0.92	−0.02	1.00	0.99	−0.00	1.00	0.92	−0.01	0.99
	4	0.3	$\hat{\mu}$	1.00	0.00	0.99	1.00	0.00	0.93	1.00	0.00	1.00	1.00	0.00	0.98	1.00	0.00	1.01	1.00	−0.00	0.99
			$\tilde{\mu}_1$	0.99	0.00	0.99	0.96	−0.01	0.93	0.99	0.00	1.00	0.96	−0.00	0.98	0.99	0.00	1.01	0.96	−0.00	0.99
			$\tilde{\mu}_2$	0.98	−0.00	0.99	0.97	−0.03	0.92	0.98	0.00	1.00	0.96	−0.02	0.98	0.98	0.00	1.01	0.95	−0.00	0.99
		1	$\hat{\mu}$	1.00	−0.00	0.98	1.00	−0.00	0.95	1.00	0.00	1.02	1.00	−0.00	0.98	1.00	0.00	0.99	1.00	−0.00	0.98
			$\tilde{\mu}_1$	0.98	−0.00	0.98	0.89	−0.01	0.96	0.98	0.00	1.01	0.92	−0.00	0.98	0.98	0.00	0.99	0.91	−0.00	0.99
			$\tilde{\mu}_2$	0.96	−0.01	0.98	0.87	−0.04	0.95	0.96	−0.00	1.02	0.87	−0.02	0.99	0.95	0.00	0.99	0.81	−0.01	1.00

Table 5: Relative mean squared error (rMSE) with respect to the standard estimator; relative bias (rBias) with respect to the size of the true mean; ratio between the sample mean of estimated standard errors and the sampling standard deviation (RSD). Simulations with prediction model p-model A1, under correlated recurrent events (Model 1).

				$n = 200$						$n = 400$						$n = 1600$					
				$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$		
k_c	k_1	θ	Est	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD	rMSE	rBias	RSD
1	0.2	0.3	$\hat{\mu}$	1.00	0.00	0.98	1.00	0.01	0.97	1.00	0.01	1.00	1.00	0.01	1.00	1.00	0.01	1.00	1.00	0.01	1.01
			$\tilde{\mu}_1$	1.00	0.00	0.98	1.00	0.01	0.97	1.00	0.01	1.00	1.00	0.01	1.00	1.00	0.01	1.00	1.00	0.01	1.01
			$\tilde{\mu}_2$	1.00	0.00	0.98	0.99	0.00	0.97	0.99	0.01	1.00	0.99	0.01	1.00	1.01	0.01	1.00	1.01	0.01	1.00
		1	$\hat{\mu}$	1.00	−0.01	0.99	1.00	−0.01	0.98	1.00	−0.01	0.98	1.00	−0.01	0.97	1.00	−0.01	1.00	1.00	−0.01	1.00
			$\tilde{\mu}_1$	1.00	−0.01	0.99	1.00	−0.01	0.98	1.00	−0.01	0.98	0.99	−0.01	0.97	1.00	−0.01	1.00	0.99	−0.01	1.00
			$\tilde{\mu}_2$	1.01	−0.02	0.99	0.99	−0.02	0.98	1.01	−0.01	0.98	0.99	−0.01	0.97	0.99	−0.01	1.00	0.99	−0.01	1.00
	1	0.3	$\hat{\mu}$	1.00	−0.00	0.99	1.00	−0.00	0.99	1.00	0.00	1.00	1.00	0.00	1.01	1.00	0.00	0.98	1.00	0.00	1.01
			$\tilde{\mu}_1$	1.00	−0.00	0.99	1.00	−0.01	0.99	1.00	0.00	1.00	1.00	−0.00	1.01	1.00	0.00	0.98	0.99	0.00	1.01
			$\tilde{\mu}_2$	1.00	−0.00	0.99	0.99	−0.01	0.99	1.00	0.00	1.00	0.99	−0.00	1.01	1.00	0.00	0.98	0.99	−0.00	1.00
		1	$\hat{\mu}$	1.00	−0.00	1.01	1.00	−0.00	1.01	1.00	−0.00	0.99	1.00	−0.00	0.96	1.00	−0.00	1.01	1.00	−0.00	1.00
			$\tilde{\mu}_1$	0.99	−0.00	1.01	0.98	−0.00	1.01	1.00	−0.00	0.99	0.98	−0.00	0.97	1.00	−0.00	1.02	0.97	−0.00	1.01
			$\tilde{\mu}_2$	0.99	−0.00	1.01	0.95	−0.01	1.01	1.00	−0.00	0.98	0.97	−0.00	0.96	1.00	−0.00	1.01	0.95	−0.00	1.01
	4	0.3	$\hat{\mu}$	1.00	−0.00	1.00	1.00	0.00	1.00	1.00	−0.00	1.00	1.00	0.00	1.00	1.00	−0.00	1.02	1.00	0.00	1.02
			$\tilde{\mu}_1$	1.00	−0.00	1.00	0.99	0.00	1.00	1.00	−0.00	1.00	0.99	0.00	0.99	1.00	−0.00	1.02	0.98	0.00	1.02
			$\tilde{\mu}_2$	0.99	−0.00	1.00	0.97	−0.00	1.00	1.00	−0.00	1.00	0.97	−0.00	0.99	1.00	−0.00	1.02	0.97	0.00	1.02
		1	$\hat{\mu}$	1.00	0.00	1.00	1.00	−0.00	0.99	1.00	0.00	1.00	1.00	−0.00	1.00	1.00	0.00	0.99	1.00	−0.00	1.00
			$\tilde{\mu}_1$	1.00	0.00	1.00	1.07	0.01	0.95	0.99	0.00	1.00	1.10	0.01	0.95	1.00	0.00	0.99	1.15	0.01	0.95
			$\tilde{\mu}_2$	0.98	−0.00	1.00	0.96	−0.01	0.98	0.98	0.00	1.00	0.97	0.00	0.99	0.98	0.00	0.99	1.00	0.00	0.98
4	0.2	0.3	$\hat{\mu}$	1.00	0.00	0.99	1.00	0.00	0.92	1.00	0.01	0.99	1.00	0.01	0.96	1.00	0.00	1.00	1.00	0.01	1.00
			$\tilde{\mu}_1$	1.00	0.00	0.98	0.98	−0.01	0.91	1.00	0.01	0.99	0.99	0.00	0.96	1.00	0.00	1.00	0.99	0.01	0.99
			$\tilde{\mu}_2$	1.01	−0.00	0.97	0.94	−0.03	0.92	1.00	0.01	0.99	0.96	−0.01	0.97	1.02	0.00	0.99	0.99	0.00	0.99
		1	$\hat{\mu}$	1.00	−0.01	1.00	1.00	−0.02	0.89	1.00	−0.02	0.99	1.00	−0.01	0.95	1.00	−0.01	0.98	1.00	−0.01	0.99
			$\tilde{\mu}_1$	1.00	−0.02	1.00	0.96	−0.03	0.89	1.00	−0.02	0.99	0.98	−0.01	0.94	1.00	−0.01	0.98	0.98	−0.01	0.99
			$\tilde{\mu}_2$	1.00	−0.02	1.00	0.91	−0.07	0.91	1.00	−0.02	0.99	0.94	−0.04	0.96	0.98	−0.02	0.99	0.99	−0.02	0.98
	1	0.3	$\hat{\mu}$	1.00	0.00	0.99	1.00	−0.00	0.92	1.00	0.00	0.99	1.00	0.00	0.96	1.00	0.00	1.00	1.00	−0.00	0.99
			$\tilde{\mu}_1$	1.00	0.00	0.99	0.97	−0.01	0.92	1.00	0.00	0.99	0.97	−0.00	0.96	1.00	0.00	1.00	0.97	−0.00	1.00
			$\tilde{\mu}_2$	1.00	−0.00	0.98	0.96	−0.04	0.93	0.99	−0.00	0.99	0.95	−0.02	0.96	0.99	−0.00	1.01	0.95	−0.01	1.00
		1	$\hat{\mu}$	1.00	−0.00	0.97	1.00	0.00	0.90	1.00	−0.00	0.98	1.00	−0.00	0.95	1.00	−0.00	1.01	1.00	0.00	0.99
			$\tilde{\mu}_1$	0.98	−0.00	0.98	0.90	−0.01	0.91	0.98	−0.00	0.98	0.94	−0.00	0.95	0.99	−0.00	1.01	0.91	−0.00	1.00
			$\tilde{\mu}_2$	0.95	−0.01	0.99	0.84	−0.06	0.92	0.97	−0.01	0.98	0.88	−0.03	0.94	0.97	−0.00	1.01	0.83	−0.01	1.00
	4	0.3	$\hat{\mu}$	1.00	−0.00	0.98	1.00	−0.00	0.94	1.00	−0.00	1.02	1.00	0.00	0.99	1.00	−0.00	1.00	1.00	0.00	1.00
			$\tilde{\mu}_1$	0.98	−0.00	0.99	0.97	−0.01	0.92	0.99	−0.00	1.01	0.94	−0.00	0.99	0.99	−0.00	1.01	0.94	−0.00	1.00
			$\tilde{\mu}_2$	0.98	−0.01	0.98	0.96	−0.04	0.92	0.98	−0.00	1.01	0.90	−0.02	0.98	0.98	−0.00	1.01	0.87	−0.01	1.00
		1	$\hat{\mu}$	1.00	0.00	1.00	1.00	−0.00	0.94	1.00	0.00	0.99	1.00	−0.00	0.97	1.00	0.00	0.98	1.00	−0.00	0.99
			$\tilde{\mu}_1$	0.96	0.00	1.01	0.95	−0.00	0.92	0.97	−0.00	0.99	0.98	0.00	0.94	0.97	0.00	0.98	1.00	0.01	0.94
			$\tilde{\mu}_2$	0.91	−0.01	1.01	0.84	−0.06	0.94	0.94	−0.00	0.99	0.85	−0.03	0.94	0.93	0.00	0.98	0.79	−0.00	0.97

Table 6: Relative mean squared error (rMSE) with respect to the standard estimator; relative bias (rBias) with respect to the size of the true mean; ratio between the sample mean of estimated standard errors and the sampling standard deviation (RSD). Simulations with prediction model p-model A1, assuming terminal event and recurrent events both correlated (Model 2).

				$n = 200$						$n = 400$						$n = 1600$					
				$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$		
k_c	k_1	Est	A	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD
1	1	$\tilde{\mu}_1(t)$	1	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.01	1.00	1.00	1.00	1.00	1.00	1.01	1.00	1.00	1.00
			12	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	0.99	1.00	1.00	1.00
			13	1.00	1.00	1.01	1.00	1.00	0.99	1.00	1.00	1.00	1.00	1.00	0.98	1.00	1.00	0.99	1.00	1.00	1.00
			14	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	0.99	1.00	1.00	1.00
		$\tilde{\mu}_2(t)$	1	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.01	1.00	1.00	1.00	1.00	1.00	1.01	1.00	1.00	1.00
			12	1.00	1.00	1.00	0.99	0.99	0.99	1.00	1.00	0.98	0.99	1.00	0.98	1.00	1.00	0.99	1.00	1.00	1.00
			13	1.00	1.00	1.01	1.00	1.00	0.99	1.00	1.00	1.00	1.00	1.00	0.98	1.00	1.00	0.99	0.99	1.00	1.00
			14	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	0.99	0.99	1.00	1.00
	4	$\tilde{\mu}_1(t)$	1	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	1.00	1.00	1.00	1.00
			12	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	1.00	1.00	1.00	1.01
			13	1.00	1.00	1.01	1.00	1.00	0.98	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.02	1.00	1.00	1.00
			14	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	0.99	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	0.99
		$\tilde{\mu}_2(t)$	1	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	0.99	1.00	1.00	0.98	1.00	1.00	1.01	1.00	1.00	1.00
			12	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	0.98	1.00	1.00	1.00	1.00	1.00	1.01
			13	1.00	1.00	1.01	1.01	1.00	0.98	1.00	1.00	1.00	1.00	1.00	0.99	1.00	1.00	1.02	0.99	1.00	1.00
			14	1.00	1.00	1.00	1.02	1.00	0.99	1.00	1.00	0.99	1.00	1.00	0.99	1.00	1.00	0.98	0.99	1.00	0.99
4	1	$\tilde{\mu}_1(t)$	1	1.00	1.00	0.99	1.01	1.01	0.93	1.00	1.00	1.01	1.00	1.00	0.99	1.00	1.00	0.99	1.00	1.00	0.99
			12	1.00	1.00	0.97	1.02	1.02	0.91	1.00	1.00	0.98	1.00	1.00	0.97	1.00	1.00	1.01	1.00	1.00	0.99
			13	1.00	1.00	0.98	1.08	1.07	0.88	1.00	1.00	0.98	1.03	1.02	0.94	1.00	1.00	1.00	1.00	1.01	1.00
			14	1.02	1.02	0.99	1.51	1.50	0.75	1.00	1.00	0.99	1.06	1.06	0.94	1.00	1.00	0.99	1.00	1.01	0.97
		$\tilde{\mu}_2(t)$	1	1.00	1.00	0.99	1.04	0.98	0.93	1.00	1.00	1.01	1.00	0.99	0.99	0.99	1.00	0.99	1.01	1.01	0.98
			12	1.00	1.00	0.97	1.20	0.96	0.90	1.00	1.00	0.98	1.10	0.97	0.96	1.00	1.00	1.01	1.00	0.99	0.99
			13	0.99	0.99	0.99	1.38	0.93	0.88	1.00	1.00	0.98	1.23	0.97	0.94	1.00	1.00	1.00	1.03	0.99	1.00
			14	1.00	0.99	1.00	1.69	0.90	0.89	1.00	0.99	0.99	1.38	0.98	0.93	1.00	1.00	0.99	1.05	0.99	0.97
	4	$\tilde{\mu}_1(t)$	1	1.00	1.00	0.97	1.03	1.02	0.93	1.00	1.00	0.99	1.00	1.01	0.97	1.00	1.00	1.00	1.00	1.00	0.99
			12	1.00	1.00	0.99	1.05	1.05	0.91	1.00	1.00	1.00	1.01	1.01	0.96	1.00	1.00	1.00	1.00	1.01	1.00
			13	1.00	1.00	1.00	1.05	1.05	0.91	1.00	1.00	0.99	1.02	1.02	0.95	1.00	1.00	1.00	1.00	1.00	0.99
			14	1.00	1.00	0.99	1.07	1.06	0.90	1.00	1.00	0.97	1.02	1.02	0.95	1.00	1.00	1.00	1.00	1.00	0.98
		$\tilde{\mu}_2(t)$	1	1.00	1.00	0.97	1.11	1.02	0.91	0.99	0.99	0.99	1.03	1.00	0.97	1.00	1.00	1.00	1.00	1.00	0.99
			12	1.00	0.99	0.99	1.38	1.02	0.88	1.00	1.00	1.00	1.18	1.01	0.94	1.00	1.00	1.00	1.02	1.01	0.99
			13	1.02	1.00	1.00	1.74	1.04	0.85	1.00	0.99	0.99	1.33	1.02	0.93	1.00	1.00	1.00	1.08	1.00	0.98
			14	1.04	0.99	0.98	2.13	1.07	0.82	1.01	1.00	0.97	1.56	1.02	0.91	1.00	1.00	1.00	1.11	1.00	0.97

Table 7: Relative mean squared error (rMSE) and efficiency (Eff), computed as ratios with respect to the standard estimator $\hat{\mu}(t)$; ratio between the sample mean of estimated standard errors and the sampling standard deviation (RSD). Dynamic prediction models A1, A12, A13, A14 for the augmentation term in the estimators $\tilde{\mu}_1(t)$, $\tilde{\mu}_2(t)$ are compared with simulations under complete independence (Model 0).

				$n = 200$						$n = 400$						$n = 1600$					
				$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$		
k_c	k_1	Est	A	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD
1	1	$\tilde{\mu}_1(t)$	1	1.00	1.00	1.00	0.99	0.99	0.99	0.99	0.99	1.01	0.99	0.99	1.00	1.00	1.00	1.00	0.99	0.99	0.99
			12	1.00	1.00	0.99	0.98	0.98	0.98	1.00	1.00	1.01	0.99	0.99	0.99	1.00	1.00	0.99	0.98	0.98	0.99
			13	1.00	1.00	1.00	0.99	0.99	0.99	1.00	1.00	1.00	0.98	0.98	0.99	1.00	1.00	0.99	0.98	0.98	1.00
			14	1.00	1.00	0.99	0.99	0.99	0.99	1.00	1.00	1.00	0.98	0.98	1.00	1.00	1.00	0.99	0.98	0.98	1.00
		$\tilde{\mu}_2(t)$	1	0.99	0.99	1.00	0.98	0.98	0.99	0.99	0.99	1.01	0.97	0.97	1.00	1.00	1.00	1.00	0.98	0.98	0.99
			12	0.99	0.99	0.99	0.97	0.97	0.99	1.00	1.00	1.01	0.98	0.98	0.99	1.00	1.00	0.99	0.98	0.98	0.99
			13	0.99	0.99	1.01	0.98	0.97	0.99	1.00	1.00	1.00	0.98	0.98	0.99	1.00	1.00	0.99	0.99	0.98	1.00
			14	0.99	0.99	0.99	0.99	0.96	0.99	1.00	0.99	1.00	0.99	0.97	1.00	0.99	0.99	0.99	0.98	0.98	1.00
	4	$\tilde{\mu}_1(t)$	1	0.99	0.99	0.98	0.98	0.98	1.00	0.99	0.99	1.00	0.98	0.98	0.97	1.00	1.00	0.99	0.98	0.98	0.99
			12	0.99	0.99	1.00	0.97	0.97	1.00	0.99	0.99	1.00	0.97	0.97	1.01	0.99	0.99	1.01	0.97	0.97	1.02
			13	0.99	0.99	1.00	0.97	0.97	1.00	0.99	0.99	1.00	0.97	0.97	1.00	1.00	1.00	1.00	0.97	0.97	1.00
			14	0.99	0.99	1.00	0.97	0.96	0.98	0.99	0.99	0.98	0.96	0.96	0.98	0.99	0.99	1.00	0.97	0.97	1.01
		$\tilde{\mu}_2(t)$	1	0.98	0.98	0.98	0.95	0.94	1.00	0.99	0.99	1.00	0.96	0.96	0.98	0.99	0.99	0.99	0.97	0.97	0.99
			12	0.99	0.99	0.99	0.95	0.94	1.00	0.99	0.99	1.00	0.95	0.94	1.02	0.99	0.99	1.01	0.96	0.96	1.01
			13	0.98	0.98	1.00	0.96	0.95	1.00	0.99	0.99	1.00	0.96	0.96	1.00	0.99	0.99	1.00	0.97	0.96	1.00
			14	0.99	0.99	1.00	0.96	0.94	0.99	0.98	0.99	0.98	0.96	0.94	0.98	0.99	0.99	1.00	0.97	0.96	1.00
4	1	$\tilde{\mu}_1(t)$	1	0.99	0.99	0.96	0.95	0.95	0.93	0.99	0.99	0.99	0.96	0.96	0.99	0.99	0.99	1.00	0.95	0.95	0.99
			12	0.99	0.99	0.99	0.95	0.95	0.92	0.99	0.99	1.00	0.96	0.96	0.95	0.99	0.99	0.99	0.95	0.95	1.00
			13	0.99	0.99	0.98	0.99	0.98	0.90	0.99	0.99	0.99	0.97	0.96	0.96	0.99	0.99	1.03	0.96	0.96	0.99
			14	1.02	1.02	0.97	1.36	1.35	0.76	0.99	0.99	0.98	1.00	0.99	0.94	0.99	0.99	0.99	0.97	0.97	0.99
		$\tilde{\mu}_2(t)$	1	0.99	0.98	0.96	0.91	0.86	0.94	0.98	0.98	0.99	0.92	0.89	1.00	0.99	0.99	1.00	0.92	0.91	0.99
			12	0.98	0.98	1.00	0.99	0.81	0.93	0.98	0.98	1.00	0.97	0.86	0.96	0.98	0.98	1.00	0.92	0.89	1.01
			13	0.97	0.97	0.98	1.11	0.78	0.93	0.98	0.98	0.99	1.07	0.85	0.97	0.99	0.98	1.03	0.97	0.90	0.99
			14	0.99	0.96	0.99	1.32	0.76	0.91	0.98	0.96	0.99	1.18	0.81	0.97	0.98	0.98	0.99	0.99	0.88	1.00
	4	$\tilde{\mu}_1(t)$	1	0.98	0.98	0.98	0.89	0.89	0.96	0.98	0.98	1.01	0.92	0.92	0.98	0.98	0.98	0.99	0.90	0.90	0.99
			12	0.97	0.97	0.98	0.90	0.89	0.94	0.97	0.97	0.99	0.91	0.91	0.95	0.97	0.97	0.99	0.93	0.92	0.98
			13	0.97	0.97	0.98	0.90	0.89	0.92	0.97	0.97	0.98	0.91	0.90	0.97	0.97	0.97	1.01	0.93	0.93	0.99
			14	0.96	0.96	0.99	0.93	0.92	0.91	0.97	0.97	1.00	0.91	0.90	0.96	0.97	0.97	1.00	0.91	0.91	0.97
		$\tilde{\mu}_2(t)$	1	0.96	0.96	0.98	0.87	0.78	0.95	0.96	0.96	1.01	0.86	0.81	0.99	0.95	0.95	0.99	0.81	0.80	1.00
			12	0.95	0.94	0.98	1.04	0.75	0.93	0.96	0.95	0.99	0.95	0.77	0.96	0.95	0.95	0.99	0.87	0.82	0.99
			13	0.96	0.94	0.98	1.15	0.71	0.92	0.97	0.96	0.98	1.06	0.79	0.96	0.96	0.96	1.00	0.93	0.83	0.99
			14	0.97	0.93	0.99	1.39	0.73	0.91	0.96	0.94	1.01	1.15	0.78	0.95	0.96	0.95	0.99	0.92	0.81	0.97

Table 8: Relative mean squared error (rMSE) and efficiency (Eff), computed as ratios with respect to the standard estimator $\hat{\mu}(t)$; ratio between the sample mean of estimated standard errors and the sampling standard deviation (RSD). Dynamic prediction models A1, A12, A13, A14 for the augmentation term in the estimators $\tilde{\mu}_1(t)$, $\tilde{\mu}_2(t)$ are compared with simulations under correlated recurrent events (Model 1) and $\theta = 1$.

				$n = 200$						$n = 400$						$n = 1600$					
				$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$			$t = 1000$			$t = 3000$		
k_c	k_1	Est	A	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD	rMSE	Eff	RSD
1	1	$\tilde{\mu}_1(t)$	1	0.99	0.99	1.01	0.98	0.98	1.01	1.00	1.00	0.99	0.98	0.98	0.96	1.00	1.00	1.01	0.97	0.97	1.01
			12	0.99	0.99	0.99	0.96	0.96	0.98	1.00	1.00	0.99	0.98	0.98	0.99	1.00	1.00	1.00	0.98	0.98	1.00
			13	1.00	0.99	0.98	0.97	0.97	0.96	1.00	1.00	1.01	0.98	0.97	0.99	1.00	1.00	0.99	0.98	0.98	0.98
			14	0.99	0.99	0.98	0.97	0.96	0.98	1.00	1.00	0.99	0.97	0.97	1.00	0.99	0.99	0.99	0.96	0.96	1.00
		$\tilde{\mu}_2(t)$	1	0.99	0.99	1.01	0.95	0.95	1.01	1.00	1.00	0.98	0.97	0.96	0.96	1.00	0.99	1.01	0.95	0.95	1.01
			12	0.99	0.98	0.99	0.93	0.92	0.99	1.00	0.99	0.99	0.96	0.95	1.00	1.00	0.99	1.00	0.97	0.96	1.00
			13	0.99	0.99	0.98	0.95	0.94	0.97	1.00	0.99	1.01	0.96	0.95	0.99	1.00	0.99	0.99	0.97	0.96	0.98
			14	0.99	0.99	0.98	0.96	0.92	0.99	1.00	0.99	0.99	0.97	0.95	1.00	0.99	0.99	0.99	0.96	0.94	1.00
	4	$\tilde{\mu}_1(t)$	1	1.00	1.00	1.00	1.07	1.06	0.95	0.99	0.99	1.00	1.10	1.08	0.95	1.00	1.00	0.99	1.15	1.08	0.95
			12	0.99	0.99	0.98	0.94	0.94	0.99	0.99	0.99	0.98	0.93	0.93	1.00	0.99	0.99	0.98	0.95	0.94	1.00
			13	0.98	0.98	0.98	0.94	0.94	0.98	0.99	0.99	0.99	0.94	0.94	1.01	0.99	0.99	0.99	0.96	0.95	1.00
			14	0.99	0.99	0.98	0.95	0.95	0.98	0.99	0.99	0.99	0.95	0.94	0.99	0.99	0.99	0.99	0.95	0.95	1.00
		$\tilde{\mu}_2(t)$	1	0.98	0.98	1.00	0.96	0.96	0.98	0.98	0.98	1.00	0.97	0.97	0.99	0.98	0.98	0.99	1.00	0.99	0.97
			12	0.98	0.98	0.99	0.94	0.93	0.97	0.98	0.98	0.98	0.94	0.94	0.98	0.98	0.98	0.98	0.95	0.95	0.98
			13	0.98	0.98	0.98	0.94	0.93	0.96	0.97	0.97	0.99	0.95	0.94	1.00	0.98	0.98	0.99	0.97	0.97	0.98
			14	0.98	0.98	0.98	0.96	0.93	0.97	0.98	0.98	0.99	0.95	0.94	0.98	0.98	0.98	0.99	0.96	0.96	0.98
4	1	$\tilde{\mu}_1(t)$	1	0.98	0.98	0.97	0.90	0.90	0.91	0.98	0.98	0.98	0.94	0.94	0.95	0.99	0.98	1.01	0.91	0.91	1.00
			12	0.98	0.97	1.00	0.90	0.88	0.89	0.98	0.98	1.00	0.90	0.89	0.95	0.98	0.98	0.98	0.93	0.92	0.96
			13	0.98	0.98	0.99	0.94	0.92	0.88	0.98	0.98	1.01	0.92	0.91	0.95	0.98	0.98	1.00	0.91	0.91	0.99
			14	0.98	0.98	0.98	0.99	0.97	0.85	0.99	0.99	0.98	0.91	0.91	0.93	0.98	0.98	1.00	0.92	0.92	0.98
		$\tilde{\mu}_2(t)$	1	0.95	0.94	0.99	0.84	0.74	0.92	0.97	0.96	0.98	0.88	0.82	0.94	0.97	0.97	1.01	0.83	0.80	1.00
			12	0.97	0.95	1.00	1.03	0.69	0.91	0.97	0.96	1.00	0.96	0.74	0.95	0.98	0.97	0.98	0.92	0.82	0.97
			13	0.98	0.95	1.00	1.28	0.70	0.88	0.98	0.96	1.01	1.12	0.74	0.95	0.99	0.97	1.00	0.96	0.79	0.99
			14	0.98	0.93	0.99	1.49	0.68	0.87	0.99	0.96	0.99	1.24	0.74	0.92	0.98	0.96	1.00	1.01	0.80	0.99
	4	$\tilde{\mu}_1(t)$	1	0.96	0.96	1.00	0.95	0.95	0.92	0.97	0.97	0.99	0.98	0.98	0.93	0.97	0.97	0.98	1.00	0.99	0.94
			12	0.95	0.95	1.00	0.88	0.85	0.93	0.96	0.96	0.98	0.87	0.86	0.97	0.96	0.96	0.98	0.87	0.86	0.98
			13	0.95	0.95	1.00	0.88	0.86	0.90	0.94	0.94	1.00	0.88	0.87	0.96	0.96	0.96	0.99	0.88	0.88	0.99
			14	0.93	0.93	0.99	0.87	0.85	0.89	0.95	0.95	1.01	0.89	0.87	0.96	0.95	0.95	1.00	0.88	0.88	0.98
		$\tilde{\mu}_2(t)$	1	0.91	0.91	1.01	0.83	0.71	0.94	0.94	0.93	0.99	0.85	0.78	0.94	0.93	0.93	0.98	0.79	0.79	0.97
			12	0.92	0.90	1.00	1.11	0.68	0.91	0.93	0.92	0.99	0.98	0.72	0.95	0.92	0.92	0.98	0.83	0.75	0.97
			13	0.94	0.90	1.00	1.21	0.66	0.90	0.92	0.91	0.99	1.03	0.72	0.95	0.93	0.93	0.98	0.84	0.76	0.98
			14	0.93	0.88	0.99	1.36	0.66	0.87	0.94	0.91	1.02	1.17	0.72	0.95	0.93	0.93	0.99	0.86	0.75	0.98

Table 9: Relative mean squared error (rMSE) and efficiency (Eff), computed as ratios with respect to the standard estimator $\hat{\mu}(t)$; ratio between the sample mean of estimated standard errors and the sampling standard deviation (RSD). Dynamic prediction models A1, A12, A13, A14 for the augmentation term in the estimators $\tilde{\mu}_1(t)$, $\tilde{\mu}_2(t)$ are compared with simulations under the assumption that the terminal event and recurrent events are both correlated (Model 2), and $\theta = 1$.

		$k_c = 1$				$k_c = 2$				$k_c = 4$			
		$k = 1$		$k = 2$		$k = 1$		$k = 2$		$k = 1$		$k = 2$	
n	Time	$\tilde{\mu}_1(t)$	$\tilde{\mu}_2(t)$	$\tilde{\mu}_1(t)$	$\tilde{\mu}_2(t)$	$\tilde{\mu}_1(t)$	$\tilde{\mu}_2(t)$	$\tilde{\mu}_1(t)$	$\tilde{\mu}_2(t)$	$\tilde{\mu}_1(t)$	$\tilde{\mu}_2(t)$	$\tilde{\mu}_1(t)$	$\tilde{\mu}_2(t)$
400	1000	1.00	0.99	0.99	0.99	1.00	1.00	1.00	0.99	1.00	0.99	0.99	0.99
	2000	1.00	0.98	0.96	0.94	0.99	0.97	0.97	0.95	0.99	0.97	0.97	0.94
	3000	0.99	0.93	0.95	0.89	1.00	0.94	0.96	0.90	0.99	0.94	0.95	0.90
800	1000	1.00	0.99	0.99	0.99	1.00	0.99	0.99	0.99	1.00	0.99	1.00	0.99
	2000	0.99	0.98	0.96	0.95	0.99	0.98	0.97	0.95	0.99	0.98	0.97	0.96
	3000	0.98	0.95	0.95	0.90	0.99	0.96	0.96	0.90	0.99	0.95	0.96	0.91

Table 10: Efficiency of $\tilde{\mu}_1(t)$ and $\tilde{\mu}_2(t)$, computed as ratio between the empirical variances of the augmented estimator and the standard estimator. Prediction model based only on covariates.

Time	$\hat{\mu}(t)$	se	$\hat{\mu}(t) + A14$	se	se-ratio	$\hat{\mu}(t) + A1$	se	se-ratio
500	0.77	0.05	0.77	0.05	1.00	0.77	0.05	1.00
1000	1.16	0.07	1.16	0.07	1.00	1.16	0.07	1.00
1500	1.53	0.09	1.53	0.09	1.00	1.54	0.09	1.00
2000	1.86	0.12	1.86	0.12	0.99	1.86	0.12	0.99
2500	2.11	0.14	2.10	0.14	0.99	2.11	0.14	0.99
3000	2.34	0.16	2.31	0.16	0.98	2.33	0.16	0.98
3500	2.56	0.19	2.51	0.18	0.97	2.54	0.18	0.97
4000	2.76	0.22	2.69	0.21	0.95	2.73	0.21	0.96
4500	2.87	0.23	2.79	0.22	0.94	2.84	0.22	0.96
5000	2.94	0.25	2.85	0.23	0.93	2.91	0.24	0.95

Table 11: Mean number of CRBSI up to death with standard error, augmented with prediction model 14 ($\hat{\mu}(t) + A14$), and with model 1 ($\hat{\mu}(t) + A1$), and relative standard error compared to standard estimator.

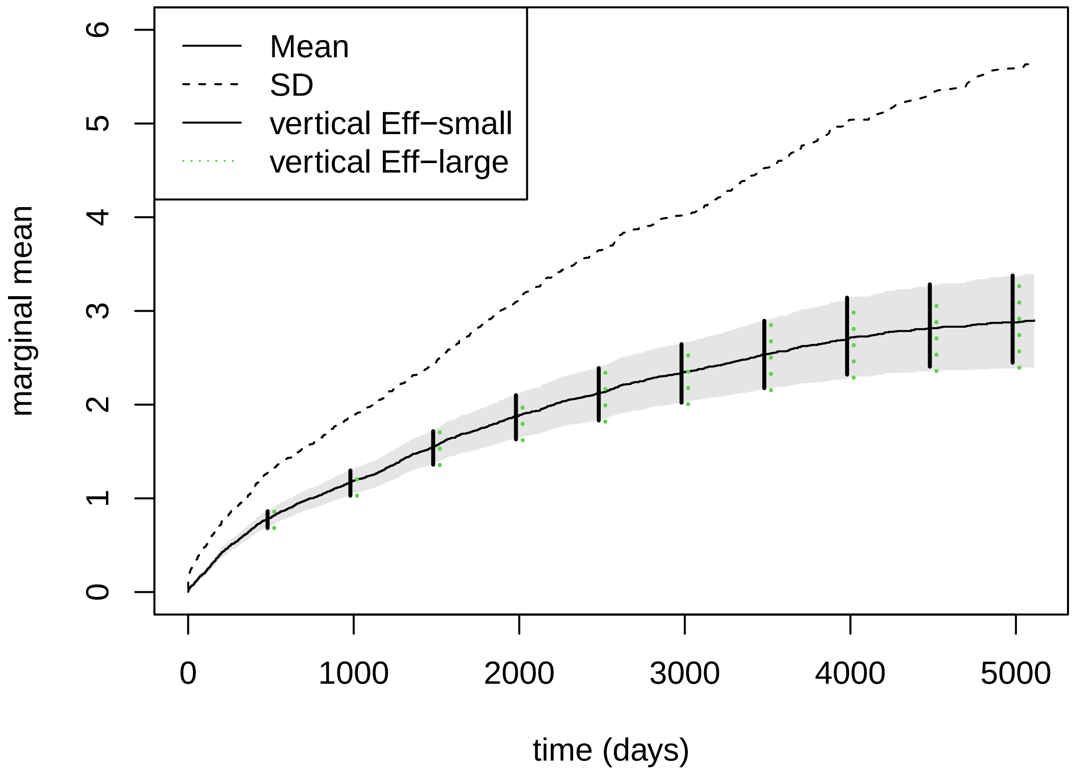

Figure 1: Mean number of CRBSI up to death from the standard estimator (solid curve) with 95 % pointwise confidence intervals (grey area), standard deviation of the observed recurrent events (dashed line) and augmented estimators using dynamic predictions under the small p-model A1 (efficient confidence intervals with vertical black solid lines) and under the large p-model A14 (efficient confidence intervals with vertical green dotted lines).