A competing risks approach for nonparametric estimation of transition probabilities in a non-Markov illness-death model

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Abstract Competing risks model time to first event and type of first event. An example from hospital epidemiology is the incidence of hospital-acquired infection, which has to account for hospital discharge of non-infected patients as a competing risk. An illness-death model would allow to further study hospital outcomes of infected patients. Such a model typically relies on a Markov assumption. However, it is conceivable that the future course of an infected patient does not only depend on the time since hospital admission and current infection status but also on the time since infection. We demonstrate how a modified competing risks model can be used for nonparametric estimation of transition probabilities when the Markov assumption is violated.

Keywords: Left-truncation · Bivariate survival · Nosocomial Infection · Markov assumption · Multi-state model

1 Introduction

A competing risks model considers time to first event and type of first event. In real life, one competing event, say event 1, may be intermediate, and it could be of interest to investigate subsequent occurrence of event 2. This is feasible by extending the competing risks model to an illness-death model. The idea is that all individuals are initially subject to the original competing risks experiment. For those individuals who had a type 1 event as a first

event, a second experiment determines the waiting time between the type 1 event and the type 2 event. See Fine et al. (2001) for a related extension of competing risks.

Both competing risks and illness-death models are, for instance, relevant in hospital epidemiology (Beyersmann et al., 2011): Nosocomial, i.e., hospital-acquired infections are a major healthcare concern, increasing morbidity and mortality, and they are a problem from a health economics perspective. Umscheid et al. (2011) considered preventable nosocomial infections and argued that successful prevention could save up to 53,483 lives a year in the U.S., with up to $23.44 billion annual cost savings to hospitals.

Grambauer et al. (2010) recently demonstrated that estimating the incidence of nosocomial infections must account for end of hospital stay without prior infection as a competing risk, i.e., direct discharge of a patient prevents in-hospital infection. Predicting length of hospital stay for an infected patient or predicting the proportion of infected in-hospital patients is relevant for the planning of hospital resources, but must account for the time-dependency of the infection status as in an illness-death model (Graves et al., 2011). In this model, all patients would share one initial state. Infected patients move into the intermediate illness state at the time of infection, and end of stay is modelled by transitions into the absorbing state.

The canonical nonparametric estimator of the transition probabilities in these models is the Aalen-Johansen estimator (Aalen and Johansen, 1978). The estimator relies on a time-inhomogeneous Markov assumption, which is trivially fulfilled for competing risks, but may be violated in an illness-death model. In the context of nosocomial infections, the assumption does not hold, if the end-of-hospital stay probability of an infected patient depends on the time of infection.

Research for possibly non-Markov models has mostly focused on estimating state occupation probabilities $P(X_t = j)$, where X_t denotes the state occupied at time t and j is a possible state of the model. Under a Markov assumption and assuming one initial state occupied by all individuals at time 0, say $P(X_0 = 0) = 1$, estimation may be based on the Aalen-Johansen estimator of $P(X_t = j \,|\, X_0 = 0)$. In the absence of a common initial state, the Aalen-Johansen estimator of $P(X_t = j \,|\, X_0 = \cdot)$ would need to be multiplied by an estimator of the initial state distribution.

For complete data, Andersen et al. (1993) showed that this approach equals the usual multinomial estimators which do not rely on a Markov assumption. A major breakthrough for data subject to random right-censorship was then obtained by Datta and Satten (2001) and Glidden (2002). Datta and Satten showed that this Aalen-Johansen approach still consistently estimates the state occupation probabilities in the absence of the Markov prop-

erty, and Glidden provided weak convergence results. Earlier work of Pepe et al. (1991) had allowed for estimating the probability of an intermediate condition in a non-Markov illness-death model. Interestingly, Pepe et al. found their estimator to approximately equal the standard Aalen-Johansen estimator, somewhat anticipating the subsequent more general results of Datta and Satten.

Datta and Satten (2002) allowed for non-random censoring by directly modelling the censoring hazard; see also related results by Datta et al. (2000) for the illness-death model. Gunnes et al. (2007) discussed the relative merits of the Aalen-Johansen and the Datta-Satten estimator in terms of bias and mean squared error in the presence of dependent censoring. See Datta and Ferguson (2012) for an overview.

A different line of research that could be applied to non-Markov multistate models is time-multivariate survival analysis. Gill (1992) mentions this possibility and gives an insightful discussion on why nonparametric estimation of a multivariate survival function in the presence of multivariate censoring is a difficult problem, where the usual counting process approach breaks down. Lin and Ying (1993) noted that the difficulties reduce and simpler estimation procedures are feasible, if censoring is univariate. This is the case in a multistate model. Tsai and Crowley (1998) improved on the Lin-Ying estimator, and an overview was given by Prentice et al. (2004).

The aim of the present paper is to use competing risks techniques for nonparametric estimation of transition probabilities in a potentially non-Markov illness-death model without recovery. This aim differs from estimating state occupation probabilities $P(X_t = j)$ in that we do wish to condition on the state occupied at time s, $s \leq t$. There is a connection to time-multivariate survival analysis, because the first estimator that we will derive is algebraically identical to an earlier proposal by Meira-Machado et al. (2006). To the best of our knowledge, the work by Meira-Machado et al. was the first paper which focused on using time-multivariate techniques for estimation of transition probabilities in a non-Markov illness-death model, employing the time-multivariate techniques of Stute (1993).

We develop the Meira-Machado et al. estimator via a different route, which allows for a competing risks explanation on why their estimator works in a non-Markov model. We also give a new inverse probability of censoring weighted (IPCW) representation of the estimator. Using both the new IPCW representation and results of Tsai and Crowley (1998), we derive a new, simpler and theoretically more efficient competing risks-type estimator. The new estimator gives direct access to competing risks methodology, which we demonstrate by also allowing for left-truncation.

The paper is organized as follows: Section 2 introduces competing risks

and illness-death models as stochastic processes. The illness-death model is also re-parametrized via a bivariate time vector and a further competing risks model is derived, which will be crucial for the nonparametric estimation procedures of Section 3. We report simulation results in Section 4 and an analysis of real hospital infection data in Section 5. The closing Section 6 offers a discussion, including an appraisal of the relative merits of the Meira-Machado et al. estimator and the new competing risks estimator. Our conclusion is that both estimators perform comparably, but that the new estimator may be preferred due to its computational simplicity. We also find that the Aalen-Johansen estimator may perform competitively even if the Markov assumption is violated.

2 Competing risks and illness-death models

Consider a stochastic process $(X_u)_{u\in[0,\infty)}$ with state space $\{0,1,2\}$, right-continuous sample paths and initial state 0, $P(X_0 = 0) = 1$. For a competing

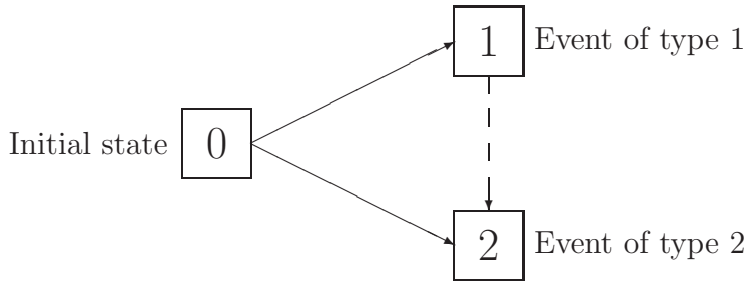

Figure 1: Competing risks model and illness-death model without recovery.

risks model with two competing risks, we model $0 \to 1$ and $0 \to 2$ transitions, and states 1 and 2 are absorbing, i.e., there are no transitions out of the absorbing states. In the context of nosocomial infections, we will consider patients to enter state 0 on admission to hospital. Occurrence of an infection is modelled by a $0 \to 1$ transition, end of hospital stay without prior infection is modelled by a $0 \to 2$ transition.

We may extend this model to an illness-death model without recovery by also allowing for $1 \to 2$ transitions. This is illustrated in Figure 1, where the dashed arrow indicates that $1 \to 2$ transitions are only feasible in the illness-death model. The addendum 'without recovery' means that $1 \to 0$ transitions are not modelled. For nosocomial infections, this entails that $X_u = 1$ is interpreted as 'in hospital at time u, infection has occurred in $(0, u]$'.

This interpretation is in line with the common comparison of infected 'cases' and non-infected 'controls' in hospital epidemiology. The interpretation of $X_u = 2$ is that hospital stay has ended by time u.

Also note that the interpretation of states 1 and 2 differs between the models. For competing risks, the interpretation of state 1 is 'an infection has occurred', while the interpretation of state 2 is 'hospital stay has ended without prior infection'.

Regardless of the model, we may define the time until first event,

$$T_0 = \inf\{u \ : \ X_u \neq 0\}. \tag{1}$$

The type of first event is

$$X_{T_0} \in \{1, 2\}, \tag{2}$$

the state entered by the process at time T_0.

For the illness-death model, we also define the time until absorption (end of hospital stay),

$$T = \inf\{u \ : \ X_u = 2\}. \tag{3}$$

We have $T_0 = T$, if the process makes a direct $0 \to 2$ transition, and $T_0 < T$ otherwise. We assume that the distribution of T has mass on $[0, \infty)$ only. That is, every individual reaches state 2 (spends a finite time in hospital).

In the remainder of the paper, we will take $(X_u)_u$ to be an illness-death model. The aim will be to provide for non-parametric estimation of the transition probabilities

$$P_{lj}(s, t) = P(X_t = j \,|\, X_s = l), \tag{4}$$

where (s, t), $s \leq t$, is a fixed, but arbitrary pair of times, $l \in \{0, 1\}$, $j \in \{1, 2\}$. In (4), we do not assume that conditioning on $X_s = 1$ is tantamount to conditioning on the entire past of the process up to time s. That is, we do not assume that $(X_u)_u$ is Markov.

More specifically and for ease of presentation, we will focus on $P_{01}(s, t)$. In the data example, this is the probability of an infected in-hospital patient at time t given no infection at time s. This quantity can be used for the planning of hospital resources. Our ideas work analogously for the other transition probabilities. We express $P_{01}(s, t)$ in terms of the bivariate time vector (T_0, T),

$$P_{01}(s, t) = \frac{P(X_t = 1, X_s = 0)}{P(X_s = 0)} = \frac{P(s < T_0 \leq t, t < T)}{P(T_0 > s)}. \tag{5}$$

The key to the nonparametric estimation procedures in Section 3 are both (5) and the following competing risks process $(\kappa_{u;s,t})_u = (\kappa_u)_u$, which

is derived from the illness-death process $(X_u)_u$,

$$\kappa_{u;s,t} = \kappa_u = \begin{cases} 0 & : \quad X_u \in \{0,1\}, \\ 1 & : \quad X_u = 2 \text{ and } \mathbf{1}(s < T_0 \leq t, t < T) = 1, \\ 2 & : \quad X_u = 2 \text{ and } \mathbf{1}(s < T_0 \leq t, t < T) = 0, \end{cases} \tag{6}$$

where $\mathbf{1}(\cdot)$ is the indicator function. The competing risks process κ stays in its initial state 0 until time T. At time T, the value of the competing risks mark $\mathbf{1}(s < T_0 \leq t, t < T)$ is known. We have that $P(\kappa_T = 1) = P(s < T_0 \leq t, t < T)$. As a consequence, the numerator of the right hand side of (5) is the limit of the cumulative incidence function for event type 1 of κ,

$$P(s < T_0 \leq t, t < T) = \lim_{u \to \infty} P(T \leq u, \kappa_T = 1). \tag{7}$$

Note that the competing risks process κ depends on the fixed, but arbitrary pair of times (s,t), $s \leq t$, but we are suppressing this in the notation for ease of writing.

3 Nonparametric estimation

We assume that observation of the illness-death process X, or, equivalently, of the random times (T_0, T), is subject to random censorship by C. We also assume that the support of the distribution of T is contained in the support of the distribution of C. This last assumption is needed for estimation of the limit of the cumulative incidence function in (7). It is justifiable for the nosocomial infection example, but may be violated in other settings. In the discussion, we explain how this assumption can be relaxed. We first revisit the estimator of Meira-Machado et al. (2006) in Section 3, revealing that violations of the Markov assumption can be seen to be handled via a competing risks approach and also giving a new IPCW representation of the estimator. These two observations are taken further in Section 3.2, leading to a simpler competing risks-type estimator, which in turn also allows for left-truncated data as explained in Section 3.3.

3.1 The estimator of Meira-Machado et al. revisited

For estimation of (5), we use the usual Kaplan-Meier estimator for estimating the denominator $P(T_0 > s)$, based on the censored observations of T_0. Because of (7), we use the right hand limit of the Aalen-Johansen estimator of $P(T \leq u, \kappa_T = 1)$ for estimation of the numerator. To this end, and for the competing risks process κ, we write N_1 for the counting process of observed

events of type 1, N for the counting process of observed events (of any type), and Y for the at-risk process. We also write N_0 for the counting process of observed replicates of T_0 and Y_0 for the at risk process of the initial state of the illness-death model X. Note that the processes N_1, N and Y depend on the fixed pair of times (s,t) through κ, but N_0 and Y_0 do not depend on (s,t). Then, these estimators are

$$\hat{P}(T_0 > s) = \prod_{v\in[0,s]} \left(1 - \frac{\mathrm{d}N_0(v)}{Y_0(v)}\right) \tag{8}$$

and

$$\hat{P}(s < T_0 \leq t, t < T) = \int_0^\infty \prod_{v\in[0,u)} \left(1 - \frac{\mathrm{d}N(v)}{Y(v)}\right) \frac{\mathrm{d}N_1(u)}{Y(u)}. \tag{9}$$

Recall that the right hand side of (9) depends on (s,t) via N_1, N and Y. In the appendix, we show that the resulting estimator of $P_{01}(s,t)$,

$$\hat{P}_{01}(s,t) = \hat{P}(s < T_0 \leq t, t < T)/\hat{P}(T_0 > s), \tag{10}$$

equals the estimator proposed by Meira-Machado et al. (2006), who derived their estimator via a different route, using Kaplan-Meier integrals. Note that the estimator (10) is, in general, different from the Aalen-Johansen estimator. This is even true for the simple case of $s = 0$. Here, as a function of t, the Aalen-Johansen estimator of $P_{01}(0,t)$ will change its value whenever there is an observed $0 \to 1$ transition in the illness-death model. In contrast, and assuming no ties, the non-Markov estimator will *not* change its value (as a function of t), if the individual at hand is subsequently censored in the intermediate state of the illness-death model. This is so, because N_1 is the counting process of observed events of type 1 of the competing risks process κ. The event times of κ are the waiting times until absorption of the illness-death process.

We now give a new IPCW representation of the estimator, which we will subsequently use to modify and thereby simplify estimation of $P_{01}(s,t)$. The idea is to express (9) in terms of a Kaplan-Meier estimator of the censoring survival function and to then use an observation by Tsai and Crowley (1998), who noted that there is more than one such estimator in bivariate time.

We write N^C for the counting process of censoring events, which have been observed before absorption. We have that

$$\Delta N^C(u) + \Delta N(u) + Y(u+) = Y(u),$$

where Δ indicates the increment of the respective processes. As a consequence,

$$\prod_{v\in[0,u)}\left(1-\frac{\mathrm{d}N(v)}{Y(v)}\right)\cdot\prod_{v\in[0,u)}\left(1-\frac{\mathrm{d}N^C(v)}{Y(v)-\Delta N(v)}\right)=\frac{Y(u)}{Y(0)}, \tag{11}$$

and the estimator in (9) equals

$$\frac{1}{Y(0)}\int_0^\infty\prod_{v\in[0,u)}\left(1-\frac{\mathrm{d}N^C(v)}{Y(v)-\Delta N(v)}\right)^{-1}\mathrm{d}N_1(u). \tag{12}$$

Here, $\prod_{v\in[0,u)}\left(1-\frac{\mathrm{d}N^C(v)}{Y(v)-\Delta N(v)}\right)$ is the Kaplan-Meier estimator of $P(C\geq u)$, based on the censored observations of T.

3.2 A new competing risks-type estimator

Tsai and Crowley (1998) observed that there is more than one Kaplan-Meier-type estimator of $P(C\geq u)$, if a bivariate vector of event times such as (T_0,T) is subject to one censoring variable C. We introduce some additional notation: We write N_0^C for the counting process of censoring events, which have been observed before leaving the initial state of the illness-death model X. We also write ${}_sY$ for the at risk process of the competing risks model κ in the data subset of individuals who were still in the initial state of X and under observation at time s. We analogously define ${}_sN$, ${}_sN_1$ and ${}_sN^C$. Then Tsai and Crowley suggested to use the following Kaplan-Meier-type estimator of $P(C\geq u)$, specialized to our setting with $T_0\leq T$,

$$\prod_{v\in[0,s]}\left(1-\frac{\mathrm{d}N_0^C(v)}{Y_0(v)-\Delta N_0(v)}\right)\cdot\prod_{v\in(s,u)}\left(1-\frac{\mathrm{d}_sN^C(v)}{{}_sY(v)-\Delta_sN(v)}\right). \tag{13}$$

Replacing $\prod_{v\in[0,u)}\left(1-\frac{\mathrm{d}N^C(v)}{Y(v)-\Delta N(v)}\right)$ in (12) by (13) as an estimator of $P(C\geq u)$, we obtain a different estimator of $P(s<T_0\leq t,t<T)$,

$$\begin{aligned}\check{P}(s<T_0\leq t,t<T) &= \frac{1}{Y(0)}\prod_{v\in[0,s]}\left(1-\frac{\mathrm{d}N_0^C(v)}{Y_0(v)-\Delta N_0(v)}\right)^{-1}\cdot\\ &\quad\int_0^\infty\prod_{v\in(s,u)}\left(1-\frac{\mathrm{d}_sN^C(v)}{{}_sY(v)-\Delta_sN(v)}\right)^{-1}\mathrm{d}N_1(u).\end{aligned}$$

Because $Y(0) = Y_0(0)$, $Y_0(s+) = {}_sY(s+)$ and (as a consequence of the definition of κ) $N_1 = {}_sN_1$, this equals

$$\prod_{v\in[0,s]} \left(1 - \frac{\mathrm{d}N_0(v)}{Y_0(v)}\right) \int_s^\infty \prod_{v\in(s,u)} \left(1 - \frac{\mathrm{d}_sN(v)}{{}_sY(v)}\right) \frac{\mathrm{d}_sN_1(u)}{{}_sY(u)}$$

where we have also used an analogous variant of (11) for $\hat{P}(T_0 > s) = \prod_{v\in[0,s]} \left(1 - \frac{\mathrm{d}N_0(v)}{Y_0(v)}\right)$.

The resulting estimator of $P_{01}(s,t)$ is

$$\begin{aligned} \check{P}_{01}(s,t) &= \check{P}(s < T_0 \le t, t < T)/\hat{P}(T_0 > s) \\ &= \int_s^\infty \prod_{v\in(s,u)} \left(1 - \frac{\mathrm{d}_sN(v)}{{}_sY(v)}\right) \frac{\mathrm{d}_sN_1(u)}{{}_sY(u)}. \end{aligned} \tag{14}$$

The estimator in (14) is simple: It is just an estimator of the limit of a cumulative incidence function as in (9), but evaluated in the data subset 'still in the initial state of X and under observation at time s'.

Standard competing risks arguments can be used to derive an estimator of the variance of $\check{P}_{01}(s,t)$ (Andersen et al., 1993, p. 299),

$$\begin{aligned} &\hat{\mathrm{var}}\check{P}_{01}(s,t) = \\ &\int_s^\infty \left\{ \prod_{v\in(s,u]} \left(1 - \frac{\mathrm{d}_sN(v)}{{}_sY(v)}\right) \right\}^2 \left\{1 - \right. \\ &\quad \left. \int_u^\infty \prod_{v\in(u,r)} \left(1 - \frac{\mathrm{d}_sN(v)}{{}_sY(v)}\right) \frac{\mathrm{d}_sN_1(r)}{{}_sY(r)} \right\}^2 \frac{\mathrm{d}_sN_1(u)}{{}_sY(u)} \qquad + \\ &\int_s^\infty \left\{ \prod_{v\in(s,u]} \left(1 - \frac{\mathrm{d}_sN(v)}{{}_sY(v)}\right) \cdot \int_u^\infty \prod_{v\in(u,r)} \left(1 - \frac{\mathrm{d}_sN(v)}{{}_sY(v)}\right) \frac{\mathrm{d}_sN_1(r)}{{}_sY(r)} \right\}^2 \frac{\mathrm{d}_sN_2(u)}{{}_sY(u)}, \end{aligned}$$

where we have also used ${}_sN_2$ for the counting process of observed events of type 2 of the competing risks model κ in the data subset of individuals who were still in the initial state of X and under observation at time s. This variance estimator is motivated by a corresponding asymptotic expression (Andersen et al., 1993, p. 321.).

Theoretically, the new estimator is more efficient than the one of Meira-Machado et al. (2006, Theorem 2). The informal argument is that it uses the full information from the subjects whose illness-death process was right

censored, whereas the Meira-Machado et al. estimator ignores the information in which state the subjects were right censored. This can be seen by comparing the weights used in the construction of the IPCW estimators (this is were information from the censored subjects enters). The new estimator uses the conditional weights given in (13). The first factor of (13) estimates $P(C \geq s \,|\, T_0 > s)$ using all censored times that are less than or equal to time s and where the corresponding illness-death process is *censored in the initial state*. The second factor estimates $P(C \geq u \,|\, T_0 > s, C > s)$ using all the censoring times that are greater than time s and less than or equal to time u for which the corresponding illness-death process is *in the initial state and under observation at time s.* The Meira-Machado et al. estimator uses IPCW weights derived from the marginal Kaplan-Meier estimator $P(C \geq u)$ which uses the censoring times but not the state of the illness-death process at the individual censoring time. There are similar results and a general theory for IPCW (van der Laan and Robins, 2003) which could be used to show formally that $\check{P}_{01}(s,t)$ is asymptotically more efficient as compared to $\hat{P}_{01}(s,t)$. However, our simulation results and data example show comparable small sample performances of both estimates (see Sections 4 and 5).

3.3 Left-truncated data

So far, we have assumed that observation of the illness-death process is subject to random censoring only. We now additionally allow for left-truncation (delayed study entry), which can be handled by the new estimator $\check{P}_{01}(s,t)$ because of general competing risks results (Andersen et al., 1993). To be specific, assume that observation of the random times (T_0, T), is subject to random left-truncation and right-censorship by (L, C), i.e., we assume that the tuples (T_0, T) and (L, C) are independent.

We have to be precise what delayed study entry in this context means, because $\check{P}_{01}(s,t)$ is an estimated cumulative incidence function, estimated in the data subset 'in the initial state of X and under observation at time s'. This entails that only an individual whose left-truncation time L is less than its waiting time T_0 in the initial state can enter the calculation. This is in contrast to standard nonparametric estimation for a time-inhomogeneous Markov model, where an individual may be in any non-absorbing state of the model at the time of study entry.

We now write ${}_sY$ for the at risk process of the competing risks model κ in the data subset of individuals *whose left-truncation times were less than s and* who were still in the initial state of X and under observation at time s. We analogously interpret ${}_sN$, ${}_sN_1$ and ${}_sN_2$. We can then profit from the general fact that counting processes naturally account for left-truncation (Keiding,

1992) and estimate $P_{01}(s,t)$ using

$$\check{P}_{01}(s,t) = \int_s^\infty \prod_{v\in(s,u)} \left(1 - \frac{\mathrm{d}_s N(v)}{{}_sY(v)}\right) \frac{\mathrm{d}_s N_1(u)}{{}_sY(u)}.$$

At the beginning of the section, we had been forced to assume the support of the distribution of T to be contained in that of C, because integrals as on the right hand side of the previous display are being evaluated up to ∞. We now need to additionally account for the presence of left-truncation. Essentially what we need to ensure is that the risk set ${}_sY$ is non-empty on $[s,\infty)$ with asymptotic probability larger than zero. To be precise, we assume that for all $u < \inf\{v : \mathrm{P}(T > v) = 0\}$ there exists a positive function y on $[0,u]$, bounded away from zero, such that

$$\sup_{v\in[s,u]} |{}_sY(v)/{}_sY(s+) - y(v)| \to 0$$

in probability as the 'sample size' ${}_sY(s+)$ goes to infinity (Andersen et al., 1993, Condition (4.1.16)).

4 Simulation Study

We now report results of a limited simulation study, where the aim is to compare the finite sample performance of our new estimator $\check{P}_{01}(s,t)$ from (14) with the more complicated estimator $\hat{P}_{01}(s,t)$ from (10), which is algebraically equal to the estimator of Meira-Machado et al. (2006). We also report results from using the Aalen-Johansen estimator.

We simulated data from a scenario used by Meira-Machado et al., which these authors found to be challenging both in terms of bias and variance. To be specific, we generated replicates of (T_0, X_{T_0}) using an exponential hazard of $0.039 + 0.026$ for simulating T_0 and deciding on $X_{T_0} = 1$ in a binomial experiment with probability $0.039/(0.039 + 0.026)$. If $X_{T_0} = 1$, we set $T = 1.7 \cdot T_0$; as a consequence, the model is not Markov. Random censoring was simulated from an exponential distribution with parameters 0.013 or 0.035. In addition, we also investigated $\check{P}_{01}(s,t)$ when the data were subject to both left-truncation and right-censoring. Left-truncation was simulated from a skew normal distribution (Azzalini, 1985), with location equal to -5, scale equal to 10 and shape equal to 10. Right-censoring was exponentially distributed with hazard 0.013.

We simulated 1000 studies and report the bias (average of the 1000 estimates of $P_{01}(10,t)$ minus true quantity) and the empirical variance of the

	$\check{P}_{01}(10,t)$		$\hat{P}_{01}(10,t)$		Aalen-Johansen	
t	Bias	Variance	Bias	Variance	Bias	Variance
30	1.92e-03	5.07e-03	1.91e-03	5.02e-03	-2.10e-02	3.92e-03
40	4.69e-03	4.46e-03	4.74e-03	4.45e-03	-7.44e-03	3.57e-03
50	-3.33e-03	4.44e-03	-3.21e-03	4.46e-03	-5.75e-03	3.62e-03
60	-6.42e-03	3.86e-03	-6.35e-03	3.88e-03	-3.14e-03	3.08e-03
70	-1.05e-02	3.05e-03	-1.05e-02	3.06e-03	-2.90e-03	2.54e-03
80	-8.47e-03	2.39e-03	-8.49e-03	2.39e-03	1.26e-03	2.17e-03
90	-9.61e-03	1.51e-03	-9.62e-03	1.51e-03	1.71e-03	1.60e-03
100	-7.02e-03	1.11e-03	-7.03e-03	1.11e-03	5.05e-03	1.37e-03

Table 1: Simulation results for censoring hazard 0.013.

estimates. In the presence of right-censoring only, the sample size in each simulated study was 100. With additional left-truncation, the average sample size was 85. The true value $P_{01}(10,t)$ was numerically approximated based on 100 replications of uncensored samples of size 10000 using the usual binomial estimator within the data subset defined by 'in state 0 at time 10', yielding

t	30	40	50	60	70	80	90	100
$P_{01}(10,t)$	0.201	0.162	0.125	0.092	0.067	0.048	0.033	0.023

Tables 1 and 2 give results for the right-censoring scenarios, table 3 displays results for the scenario subject to both left-truncation and right-censoring.

The tables indicate similar performance of both estimators (10) and (14) in terms of bias and variance and in the presence of right-censoring only. Similar results were found for a sample size of 200 (not shown). Interestingly, Tables 1 and 2 find the Aalen-Johansen estimator to perform at least competitively except for the early time point 30. This is somewhat in contrast to the results reported by Meira-Machado et al., who found the Aalen-Johansen estimator to be biased in the absence of the Markov property. The reason is that these authors considered the absolute bias integrated over time, which appears to be dominated by early time points. We find a similar picture when comparing the new estimator and the Aalen-Johansen in the presence of additional left-truncation.

	$\check{P}_{01}(10,t)$		$\hat{P}_{01}(10,t)$		Aalen-Johansen	
t	Bias	Variance	Bias	Variance	Bias	Variance
30	3.31e-03	1.28e-02	2.92e-03	1.27e-02	-1.61e-02	7.27e-03
40	-1.14e-02	1.54e-02	-1.16e-02	1.53e-02	-4.94e-03	9.52e-03
50	-3.35e-02	1.29e-02	-3.36e-02	1.28e-02	-6.03e-03	9.48e-03
60	-3.78e-02	8.93e-03	-3.80e-02	8.82e-03	3.41e-03	8.86e-03
70	-4.14e-02	4.89e-03	-4.15e-02	4.87e-03	9.20e-03	8.55e-03
80	-3.39e-02	2.78e-03	-3.39e-02	2.75e-03	2.04e-02	8.36e-03
90	-2.75e-02	1.03e-03	-2.76e-02	1.01e-03	2.82e-02	7.74e-03
100	-2.08e-02	3.94e-04	-2.08e-02	3.86e-04	3.56e-02	7.58e-03

Table 2: Simulation results for censoring hazard 0.035.

	Aalen-Johansen		$\check{P}_{01}(10,t)$	
t	Bias	Variance	Bias	Variance
30	-2.17e-02	4.00e-03	3.18e-04	5.41e-03
40	-9.38e-03	4.03e-03	2.06e-03	5.24e-03
50	-5.30e-03	3.55e-03	-1.33e-03	4.62e-03
60	-1.38e-03	3.05e-03	-2.79e-03	4.02e-03
70	-4.83e-04	2.42e-03	-6.90e-03	3.02e-03
80	1.25e-03	2.02e-03	-8.43e-03	2.28e-03
90	2.38e-03	1.69e-03	-9.27e-03	1.59e-03
100	3.85e-03	1.38e-03	-9.10e-03	9.97e-04

Table 3: Simulation results for left truncated data and censoring hazard 0.013

5 Real data example

We use a random subsample of 1313 patients from the SIR3 (*S*pread of nosocomial *I*nfections and *R*esistant pathogens) study that has been made publicly available as part of the R-package **kmi** (Beyersmann et al., 2012). The present analyses may therefore be reproduced. SIR3 was a prospective study to assess the occurrence and the impact of hospital-acquired infections in intensive care. Details are reported elsewhere (Beyersmann et al., 2006). Here, we focus on the occurrence of hospital-acquired pneumonia, which is one of the most frequent and most severe nosocomial infections. In an analysis of the full data set of 1876 patients, Allignol et al. (2011) included time of pneumonia as a time-dependent covariate into Cox models for the end-of-stay hazards (distinguishing between competing endpoints alive discharge and hospital death). Because the hazard ratios were approximately equal to one in this informal check of the Markov assumption, these authors concluded that one may assume the data to follow a time-inhomogeneous Markov model. However, because the confidence intervals were marginal, a more robust estimation procedure as in the present paper may be desirable.

Tables 4, 5 and 6 report results on estimating $P_{01}(s,t)$ for $s = 3$, $s = 5$ and $s = 7$, using both $\hat{P}_{01}(s,t)$ and $\check{P}_{01}(s,t)$. These estimates are relevant for planning hospital resources, estimating the probability of future infected intensive care patients among the currently, i.e., at time s uninfected.

The tables also report variance estimates and 95% confidence intervals (CI) computed from 1000 bootstrap samples. We used the bootstrap in order to have one common method for both $\hat{P}_{01}(s,t)$ and $\check{P}_{01}(s,t)$. Section 3 has shown that estimating a cumulative incidence function is at the core of both $\hat{P}_{01}(s,t)$ and $\check{P}_{01}(s,t)$, and recent research has investigated different proposals for estimating the variance of an estimated cumulative incidence function (Braun and Yuan, 2007; Allignol et al., 2010). Because of our representations (10) and (14), the functional delta method justifies both use of the bootstrap and of a normal limit. The tables report CIs both using the 25th and 75th quantiles of the bootstrap estimates distribution and using a normal approximation. Similar to the simulation study in Section 4, we find that $\hat{P}_{01}(s,t)$ and $\check{P}_{01}(s,t)$ perform comparably.

Finally, Table 7 displays the point estimates $\check{P}_{01}(s,t)$ together with the corresponding Aalen-Johansen estimates. Both estimators yield similar results.

	New estimator				Meira-Machado estimator			
t	$P_{01}(s,t)$	Variance	Bootstrap CI	Normal CI	$P_{01}(s,t)$	Variance	Bootstrap CI	Normal CI
5	0.0234	$1.95e-05$	[0.0152; 0.0323]	[0.0147; 0.032]	0.0255	$1.95e-05$	[0.0168; 0.0352]	[0.0162; 0.0347]
6	0.0314	$2.45e-05$	[0.0219; 0.0413]	[0.0217; 0.0411]	0.0342	$2.45e-05$	[0.0244; 0.046]	[0.0236; 0.0448]
7	0.0363	$2.82e-05$	[0.0258; 0.0469]	[0.0258; 0.0467]	0.0395	$2.82e-05$	[0.0286; 0.0517]	[0.0282; 0.0507]
8	0.0396	$3.17e-05$	[0.0288; 0.051]	[0.0285; 0.0506]	0.0431	$3.17e-05$	[0.0315; 0.056]	[0.0313; 0.0549]
9	0.0452	$3.57e-05$	[0.034; 0.0574]	[0.0335; 0.0569]	0.0492	$3.57e-05$	[0.0376; 0.0629]	[0.0366; 0.0618]
10	0.0476	$3.76e-05$	[0.0361; 0.0596]	[0.0356; 0.0596]	0.0518	$3.76e-05$	[0.0392; 0.0655]	[0.0387; 0.0649]
11	0.0502	$4.04e-05$	[0.0379; 0.0631]	[0.0377; 0.0627]	0.0547	$4.04e-05$	[0.0414; 0.0677]	[0.0414; 0.0679]
12	0.0512	$4.04e-05$	[0.0388; 0.0637]	[0.0387; 0.0636]	0.0557	$4.04e-05$	[0.0432; 0.0695]	[0.0424; 0.0691]
13	0.0520	$4.25e-05$	[0.0393; 0.0642]	[0.0392; 0.0648]	0.0566	$4.25e-05$	[0.0441; 0.0708]	[0.0432; 0.07]
14	0.0552	$4.42e-05$	[0.0426; 0.068]	[0.0422; 0.0683]	0.0601	$4.42e-05$	[0.0471; 0.0747]	[0.0464; 0.0739]
15	0.0545	$4.31e-05$	[0.0413; 0.0669]	[0.0416; 0.0673]	0.0593	$4.31e-05$	[0.0468; 0.0739]	[0.0456; 0.073]
20	0.0452	$3.68e-05$	[0.0336; 0.0566]	[0.0333; 0.0571]	0.0492	$3.68e-05$	[0.037; 0.0632]	[0.0365; 0.062]
30	0.0258	$2.09e-05$	[0.0174; 0.0346]	[0.0168; 0.0347]	0.0280	$2.09e-05$	[0.0191; 0.0391]	[0.018; 0.0381]
40	0.0176	$1.60e-05$	[0.0101; 0.0256]	[0.0098; 0.0254]	0.0192	$1.60e-05$	[0.0115; 0.028]	[0.0108; 0.0275]
50	0.0100	$9.03e-06$	[0.0045; 0.0163]	[0.0042; 0.0159]	0.0109	$9.03e-06$	[0.0055; 0.0179]	[0.0046; 0.0173]

Table 4: Estimate of $P_{01}(s,t)$, $s = 3$ using the new estimator and Meira-Machado estimator, along with bootstrap 95% CIs and CIs based on normal approximation

	New estimator				Meira-Machado estimator			
t	$P_{01}(s,t)$	Variance	Bootstrap CI	Normal CI	$P_{01}(s,t)$	Variance	Bootstrap CI	Normal CI
7	0.0167	$1.60e-05$	[0.0091; 0.0243]	[0.0089; 0.0246]	0.0190	$1.60e-05$	[0.0108; 0.0281]	[0.0101; 0.0278]
8	0.0208	$1.95e-05$	[0.0119; 0.0296]	[0.0121; 0.0294]	0.0236	$1.95e-05$	[0.0143; 0.0336]	[0.0137; 0.0334]
9	0.0286	$2.62e-05$	[0.0187; 0.0384]	[0.0186; 0.0386]	0.0324	$2.62e-05$	[0.0217; 0.0443]	[0.021; 0.0438]
10	0.0325	$2.99e-05$	[0.0213; 0.0435]	[0.0218; 0.0432]	0.0369	$2.99e-05$	[0.0255; 0.0498]	[0.0248; 0.049]
11	0.0357	$3.22e-05$	[0.0241; 0.0471]	[0.0246; 0.0468]	0.0405	$3.22e-05$	[0.0281; 0.0535]	[0.0279; 0.0531]
12	0.0379	$3.41e-05$	[0.0262; 0.0494]	[0.0264; 0.0493]	0.0430	$3.41e-05$	[0.0308; 0.0559]	[0.0301; 0.0558]
13	0.0398	$3.56e-05$	[0.0278; 0.0512]	[0.0281; 0.0515]	0.0452	$3.56e-05$	[0.0325; 0.0582]	[0.0321; 0.0583]
14	0.0438	$4.10e-05$	[0.0309; 0.056]	[0.0312; 0.0563]	0.0497	$4.10e-05$	[0.036; 0.0644]	[0.0361; 0.0633]
15	0.0438	$4.17e-05$	[0.0307; 0.0561]	[0.0311; 0.0565]	0.0497	$4.17e-05$	[0.0363; 0.0633]	[0.0359; 0.0635]
20	0.0402	$4.01e-05$	[0.0277; 0.0529]	[0.0278; 0.0526]	0.0456	$4.01e-05$	[0.0324; 0.0593]	[0.032; 0.0593]
30	0.0233	$2.43e-05$	[0.0139; 0.0336]	[0.0136; 0.0329]	0.0264	$2.43e-05$	[0.0157; 0.0374]	[0.0153; 0.0374]
40	0.0174	$1.88e-05$	[0.0096; 0.0264]	[0.0088; 0.0259]	0.0196	$1.88e-05$	[0.0109; 0.0304]	[0.0101; 0.0292]
50	0.0102	$1.16e-05$	[0.0042; 0.0175]	[0.0035; 0.0168]	0.0115	$1.16e-05$	[0.0049; 0.0195]	[0.0042; 0.0187]

Table 5: Estimate of $P_{01}(s,t)$, $s = 5$ using the new estimator and Meira-Machado estimator, along with bootstrap 95% CIs and CIs based on normal approximation

	New estimator				Meira-Machado estimator			
t	$P_{01}(s,t)$	Variance	Bootstrap CI	Normal CI	$P_{01}(s,t)$	Variance	Bootstrap CI	Normal CI
9	0.0165	$2.02e-05$	[0.0087; 0.0266]	[0.0077; 0.0253]	0.0192	$2.02e-05$	[0.01; 0.0304]	[0.0087; 0.0297]
10	0.0215	$2.63e-05$	[0.0119; 0.0329]	[0.0115; 0.0316]	0.0251	$2.63e-05$	[0.0139; 0.0381]	[0.013; 0.0371]
11	0.0269	$3.33e-05$	[0.0167; 0.0398]	[0.0156; 0.0382]	0.0313	$3.33e-05$	[0.0186; 0.0459]	[0.0178; 0.0447]
12	0.0297	$3.61e-05$	[0.0195; 0.0438]	[0.0179; 0.0414]	0.0345	$3.61e-05$	[0.0218; 0.0494]	[0.0206; 0.0484]
13	0.0334	$4.16e-05$	[0.0218; 0.0478]	[0.0208; 0.0461]	0.0389	$4.16e-05$	[0.0248; 0.0546]	[0.024; 0.0538]
14	0.0385	$4.92e-05$	[0.0257; 0.0546]	[0.0248; 0.0523]	0.0448	$4.92e-05$	[0.0301; 0.0617]	[0.0293; 0.0604]
15	0.0398	$5.12e-05$	[0.0267; 0.0554]	[0.0258; 0.0538]	0.0463	$5.12e-05$	[0.0311; 0.0625]	[0.0309; 0.0617]
20	0.0364	$4.70e-05$	[0.0229; 0.0514]	[0.0229; 0.0498]	0.0424	$4.70e-05$	[0.0288; 0.058]	[0.0275; 0.0573]
30	0.0245	$3.28e-05$	[0.0139; 0.0375]	[0.0133; 0.0358]	0.0287	$3.28e-05$	[0.0166; 0.0424]	[0.0161; 0.0413]
40	0.0209	$2.72e-05$	[0.0111; 0.0321]	[0.0107; 0.0311]	0.0244	$2.72e-05$	[0.0135; 0.0383]	[0.0121; 0.0367]
50	0.0130	$1.77e-05$	[0.0057; 0.0222]	[0.0048; 0.0212]	0.0152	$1.77e-05$	[0.0061; 0.0259]	[0.0053; 0.025]

Table 6: Estimate of $P_{01}(s,t)$, $s = 7$ using the new estimator and Meira-Machado estimator, along with bootstrap 95% CIs and CIs based on normal approximation

t	$\check{P}_{01}(3,t)$	Aalen-Johansen	$\check{P}_{01}(5,t)$	Aalen-Johansen	$\check{P}_{01}(7,t)$	Aalen-Johansen
5	0.0234	0.0266				
6	0.0314	0.0359				
7	0.0363	0.0411	0.0167	0.0200		
8	0.0396	0.0446	0.0208	0.0250		
9	0.0452	0.0515	0.0286	0.0343	0.0165	0.01987
10	0.0476	0.0533	0.0325	0.0376	0.0215	0.02498
11	0.0502	0.0559	0.0357	0.0419	0.0269	0.03141
12	0.0512	0.0569	0.0379	0.0440	0.0297	0.03481
13	0.0520	0.0578	0.0398	0.0460	0.0334	0.03813
14	0.0552	0.0612	0.0438	0.0503	0.0385	0.04389
15	0.0545	0.0605	0.0438	0.0505	0.0398	0.04503
20	0.0452	0.0509	0.0402	0.0445	0.0364	0.04218
30	0.0258	0.0292	0.0233	0.0270	0.0245	0.02726
40	0.0176	0.0204	0.0174	0.0196	0.0209	0.02061
50	0.0100	0.0115	0.0102	0.0111	0.0130	0.01165

Table 7: Point estimates $\check{P}_{01}(s,t)$ as in Tables 4–6 and corresponding Aalen-Johansen estimates.

6 Discussion

We have demonstrated how to use competing risks techniques for estimating transition probabilities in a non-Markov illness-death model without recovery. For ease of presentation, we have focused on estimating $P_{01}(s,t)$. Our first estimator, $\hat{P}_{01}(s,t)$ from (10), is algebraically equal to the estimator of Meira-Machado et al. (2006) who derived it using Kaplan-Meier integrals. We have also given a new IPCW representation of the estimator, which we have then used to find a computationally simpler estimator, $\check{P}_{01}(s,t)$ from (14).

To discuss the intrinsic properties of the proposed estimators, it is useful to consider the special case where the process is fully observed for all cases (uncensored data). Then, transition probabilities can be consistently estimated by ratios of crude counts also when the process is non-Markov. In fact, for uncensored data both $\hat{P}_{01}(s,t)$ and $\check{P}_{01}(s,t)$ reduce to

$$\frac{\sum_{i=1}^{n} \mathbf{1}\{X_s^{(i)} = 0, X_t^{(i)} = 1\}}{\sum_{i=1}^{n} \mathbf{1}\{X_s^{(i)} = 0\}}, \tag{15}$$

where the superscript (i) indicates the ith replicate of n i.i.d. copies of the multistate process. This is in analogy to many estimators of the state occupation probabilities which reduce to the usual multinomial estimators for complete data. In (15), each individual contributes with equal weight $1/n$ to the sum in the nominator and in the denominator.

For right-censored data, the status of the process is unknown after the individual end of study time. From an IPCW perspective, the idea underlying $\hat{P}_{01}(s,t)$ is to restrict the summation in (15) to the individuals not lost to follow-up before time t and to re-weight their contributions by the probability of not being lost to follow-up. The weights are based on a Kaplan-Meier estimate of the censoring distribution using the censored observations of T, see (12).

However, some individuals will be lost to follow-up in the initial state and others in the disease state. This information is not used by $\hat{P}_{01}(s,t)$, but $\check{P}_{01}(s,t)$ uses such information, see (13). Theoretically, $\check{P}_{01}(s,t)$ is therefore more efficient, but the simulation results and the practical data example found comparable performance. The practical advantage of $\check{P}_{01}(s,t)$ is that it is computationally simpler.

A further advantage of $\check{P}_{01}(s,t)$ is that, being an Aalen-Johansen estimator of the limit of a certain cumulative incidence function, it gives direct access to competing risks methodology, as we have demonstrated by also allowing for left-truncated data. In the context of hospital-acquired infections, such a delayed study entry may arise if patients are not followed since

admission but conditional on detection of an infectious organism such as Methicillin-Resistant Staphylococcus Aureus as in De Angelis et al. (2011).

So far, a drawback of the estimation procedures as outlined both in the present paper and in Meira-Machado et al. (2006) is that we require the support of the distribution of T to be contained in the support of the distribution of C in order to be able to estimate the limit of a cumulative incidence function, see (7). This is not a restriction for our motivating data situation, but the assumption is often not fulfilled in other medical applications. The problem can be circumvented by 'artificial censoring' black as, e.g., in Quale et al. (2006).

To be specific, consider the fixed, but arbitrary time pair $s \leq t$ and assume that $s, t < \inf\{v : \mathrm{P}\,(C > v) = 0\}$. Then there is a $\tau > t$ with $P(C > \tau) > 0$. The idea is to consider the modified random variables $(\min(T_0, \tau), \min(T, \tau))$ instead of (T_0, T). Their distributions coincide on $[0, \tau) \times [0, \tau)$, which includes the bivariate time point of interest (s, t), and $\min(T, \tau)$ is less than $\inf\{v : \mathrm{P}\,(C > v) = 0\}$ by construction. We can then use the estimation techniques as outlined earlier, but using the modified data. Note that the data do change. E.g., if observation of T is censored after the chosen τ, the modified variable $\min(T, \tau)$ has been observed.

Finally, our limited simulation study indicated that the Aalen-Johansen estimator may competitively estimate transition probabilities in small samples even in the absence of the Markov property. This is not unlike the findings of Gunnes et al. (2007) for estimating state occupation probabilities.

Appendix

The aim of the appendix is to show that our initial estimation procedure based on the competing risks process κ is algebraically identical with the proposal of Meira-Machado et al. (2006). The idea of their estimator is to consider T_0 as a covariate for the event time T and to use Stute's estimator for a Kaplan-Meier integral with a covariate (Stute, 1993).

For the purpose of comparison, note that the formulation of Meira-Machado et al. is based on latent transition times between the states of the illness-death model. These authors then consider censored variants of such latent times, provided they are observable. Meira-Machado et al. then arrive at censored variants of (T_0, T), which will be our starting point. Also note that because T_0 will be considered as a covariate for a Kaplan-Meier integral with respect to T, we will only need an event indicator for the latter. This will further simplify the notation. We will also use that T_0 has been observed, if T has

been observed, because $T_0 \leq T$.

Stute's method requires that the parameter of interest can be formulated as an integral with respect to the joint distribution of (T_0, T),

$$\int \phi(z, y) \, \mathrm{P}^{T_0, T}(\, \mathrm{d}z, \, \mathrm{d}y).$$

Again focussing on $P_{01}(s, t)$ for ease of presentation, the Meira-Machado et al. estimator relies on estimating the above display for $\phi(z, y) = \mathbf{1}(s < z \leq t, t < y)$.

Assume n i.i.d. data $(\tilde{T}_{0i}, \tilde{T}_i, \xi_i)$, $i = 1, \ldots n$, where the tilde indicates a censored observation, e.g., $\tilde{T}_i = \min(T_i, C_i)$, ξ_i is the event indicator $\mathbf{1}(T_i \leq C_i)$, and the index i indicates the ith individual. Stute's method (and the estimator of Meira-Machado et al.) is based on the ordered data $T_{(1)} \leq \ldots \leq T_{(n)}$ with $(\xi_{[i]}, T_{0[i]})$ attached to $T_{(i)}$. Again for ease of presentation, we assume no ties in the data; Stute (1993) discusses how to arbitrarily break ties if present. Note that our formulation of the estimators does allow for ties.

The Meira-Machado et al. estimator of $P(s < T_0 \leq t, t < T)$ is

$$\sum_{i=1}^{n} \prod_{j=1}^{i-1} \left(1 - \frac{\xi_{[j]}}{n - j + 1}\right) \frac{\xi_{[i]}}{n - i + 1} \phi(T_{0[i]}, T_{(i)}).$$

Using the counting process notation introduced earlier, the above display equals

$$\sum_{i=1}^{n} \prod_{j=1}^{i-1} \left(1 - \frac{\Delta N(\tilde{T}_{(j)})}{Y(\tilde{T}_{(j)})}\right) \frac{\Delta N(\tilde{T}_{(i)})}{Y(\tilde{T}_{(i)})} \phi(T_{0[i]}, T_{(i)}).$$

We note two things about the last display: Firstly, because the sum runs over all individuals and because addition and multiplication are each commutative, ordering is not needed. Secondly, if $\Delta N(\tilde{T}_i) = 1$, then $\tilde{T}_i = T_i$ and $\tilde{T}_{0i} = T_{0i}$. Hence, we have $\Delta N(\tilde{T}_i) \cdot \phi(T_{0i}, T_i) = \Delta N_1(\tilde{T}_i)$. As a consequence, the Meira-Machado et al. estimator of $P(s < T_0 \leq t, t < T)$ equals our competing risks-type estimator (9) and hence our estimator (10) equals their estimator of $P_{01}(s, t)$.

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