On change in length of stay associated with an intermediate event: estimation within multi-state models and large sample properties.

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Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 General introduction to this thesis

This thesis is on the impact of an intermediate on a terminal event. More precisely, it is concerned with quantifying such an impact in terms of (expected) change in length of stay until occurrence of the terminal and associated with the intermediate event. Essentially, we will treat the situation as a random time interval problem, with length of the time interval (possibly zero) equal to the time spent in the intermediate state. We will suggest and study functionals quantifying change in length of stay. Our approach applies quite generally to functionals summarizing the impact of an intermediate on a terminal event.

The motivating application comes from clinical research: Here, length of hospital stay (LOS) is used at large to assess the utilization of hospital resources, the costs and the general impact of a disease, cf., e. g., Li (1999) and Lee et al. (2003) for recent references. Consequently, physicians would like to use information on change in LOS to assess the impact and the costs of an intermediate event during the course of a patient's disease. A prominent example are nosocomial, i. e. hospital-acquired infections. Since a nosocomial infection represents an additional complication during a patient's hospital stay, physicians reckon with an extra time needed to treat that patient. As recent references, consider, e. g., Mahieu et al. (2001), Mylotte et al. (2001), Orsi et al. (2002) and Olaechea et al. (2003). Other examples include adverse drug events, cf., e. g., Classen et al. (1997), Bates et al. (1997) and Vargas et al. (2003). Generally speaking, information on change in LOS is considered in particular when assessing complications that occur after admission to hospital, cf., e. g., Epstein et al. (2000) and Harbrecht et al. (2002) for further recent examples.

When investigating the question of change in LOS, it is crucial to account for the timing of events: The intermediate event can only have an effect on LOS, once the event has occurred. It cannot have an effect on the time spent in hospital before. On the contrary, a long time in hospital without having experienced the intermediate event may even be considered a 'reason' for finally experiencing it: The patient has been under risk, i. e. in hospital, 'long enough' for the intermediate event to finally occur. Usually, applied analyses do not adequately account for this. We will elaborate a bit more on this in the following Section 1.2. The major difficulty stems from the fact that the occurrence of nosocomial infection is time-dependent on the one hand. On the other hand, hazard-based methods do not straightforwardly supply us with an estimate of the *summary* change in LOS. At this point, we should note that while our methods will allow for independent censoring, the key issue for our motivating data problem is not censoring (which could be avoided, time being counted in days rather than years), but the temporal dynamics by which information on infection status becomes available.

Our approach will be based on multi-state models (Andersen, Borgan, Gill, and Keiding 1993). This is illustrated in Figure 1.1. Figure 1.1 also

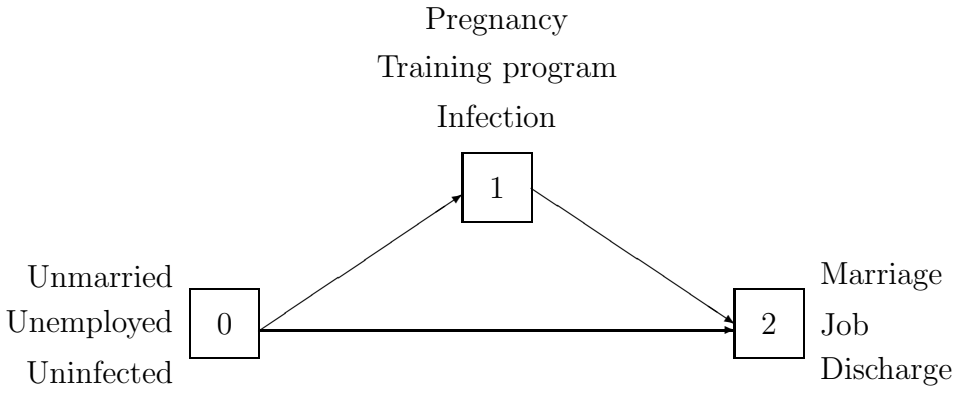

Figure 1.1: The so-called illness-death model without recovery for the occurrence of an intermediate event together with possible interpretations of the states. Possible transitions are indicated by arrows.

shows that the question of change in LOS is not restricted to hospital stay alone. Blossfeld and Rohwer (2002) give a lot of possible interpretations that do not come from biometry. Since our data examples are on nosocomial infections, we will often speak of 'nosocomial infection' representative of 'intermediate event' for linguistic ease and in order to make the presentation

more vivid. For examples of recent research related to the other interpretations of Figure 1.1 see Utikal et al. (2003) and Abbring and van den Berg (2003).

The thesis is organized as follows:

- The remainder of this introduction discusses previous work by Schulgen and Schumacher (1996), the scope of this thesis and introduces the data examples.
- In Chapter 2, we define and estimate quantities describing change in LOS within the three-state model.
- Large sample properties of the latter estimates are investigated in Chapter 3.
- Chapter 4 extends the results of the preceding two chapters to two competing absorbing endpoints. This is, for instance, relevant in the infection example if we want to distinguish the effect of an infection on discharge and death, respectively.
- A discussion is offered in Chapter 5. In particular, we discuss analysing the effect of an intermediate event in a bivariate time setting. We argue that the methodology presented in this thesis constitutes a quite general framework of describing and analysing the impact of an intermediate event.
- Appendix A introduces an R-program to estimate change in LOS.
- Appendix B lists symbols and abbreviations.

1.2 Temporal dynamics, previous work and scope of this thesis

Ad hoc approaches of analysing change in LOS due to a nosocomial infection retrospectively stratify patients into those who have and into those who have not experienced the intermediate event. By doing so, they do not adequately account for the timing of events. In particular, they cannot account for an effect on LOS an early occurrence of the intermediate event may have as compared to a late one. This is even true for matched analyses where 'controls' (uninfected patients) still have to be in hospital the day the 'case' acquires an infection. The main reason is that even with such a matching procedure one needs to define on day 0 the group of 'cases' and the group of 'controls'.

This information is simply not available on admission. A more mathematical formulation of this has it that the information on future infection status is not contained in the filtration generated by the observable counting processes (e. g. Andersen et al. (1993), Chapter II). A filtration represents the available information (or: data) up to some time point. It is generally agreed upon in the applied literature that such ad hoc approaches tend to overestimate the effect of a nosocomial infection on LOS, see for instance Irala-Estévez et al. (2001). A major reason for overestimation is that ad hoc approaches cannot distinguish between long LOS due to an infection and long LOS leading to an infection. Still, such analyses are almost exclusively used in the applied literature.

Schulgen and Schumacher (1996) proposed methods based on multi-state models in order to appropriately account for the timing of events. A non-technical presentation of their ideas can be found in Schulgen et al. (2000), together with a detailed comparison with ad hoc techniques. In particular, Schulgen et al. (2000) drive home the point why matching is no cure.

Multi-state models provide an appropriate framework to study the effect of an intermediate event. A prominent example is the occurrence of graft-versus-host disease in bone marrow transplantation patients, cf. Klein and Shu (2002) for an overview. Multi-state models are discussed in detail by Andersen et al. (1993), and an overview is given by Andersen and Keiding (2002). These models are usually assumed to be Markovian; see, however, Remark 3.16 for relaxing this assumption within our framework.

Of the estimation techniques proposed by Schulgen and Schumacher (1996), their 'approach B' relied on observable quantities only. Our approach is based on the ideas of 'approach B', but not identical to it. We revisit their approach in Chapter 2, formulating it in a rigorous way, in the course of which we offer some refinements. In particular, we consider different weighting schemes; the latter issue is connected with the basic methodological question of how to weight group differences observed over the course of time, if group membership (uninfected/infected) only becomes definite as time progresses. Differences are discussed in detail in Chapter 2.3.3. In a reanalysis of the data used by Schulgen and Schumacher (1996) in Chapter 2.7.4, we show that these refinements do make a difference in practice. In addition, we consider the special case of constant transition intensities which facilitates the mathematical treatment considerably, but shows a bad fit at least for one data set. We also briefly discuss further quantities of interest, namely 'median change' in LOS and a comparison between avoidable and unavoidable intermediate events.

Schulgen and Schumacher (1996) did not consider more theoretical properties of their estimates. Large sample results are given in Chapter 3, which

allow for constructing asymptotic confidence intervals.

In Chapter 4, we then take up a critique frequently brought forward against the concept of change in LOS — often a prolongation of hospital stay — due to an intermediate event: While such an event may prolong hospital stay for a patient eventually discharged, one might suspect it to even expedite death for a patient who eventually dies in hospital. This calls for distinguishing the effect an intermediate event has on two competing, absorbing events. We will do so in the sense of a 'cumulative incidence function'. We also give large sample properties.

A major theme is that change in LOS is a summary to judge the effect of an intermediate on the occurrence of a terminal event as opposed to a hazard-oriented analyses. In our data analyses, we will also consider nosocomial infection as a time-dependent covariate in a proportional hazards model. Such an analysis can be used to decide whether there is an effect on LOS at all. It cannot, at least not straightforwardly, be used to estimate the extra time in hospital associated with a nosocomial infection, say, because the model is not formulated in these terms. Schulgen and Schumacher (1996) make this point very clear. First of all, one has to define what it is meant by change in LOS in stochastic terms.

Multi-state models display a complex stochastic behaviour. Summaries are therefore considered to make an interpretation more accessible than from an hazard-based analysis alone. Such difficulties are for instance illustrated in our proportional hazards-analysis of the competing events discharge and death in Chapter 4.4. In the discussion presented in Chapter 5.1, we will argue that our treatment of change in LOS provides for a framework of defining and analysing such summaries in general, not just specifically change in LOS.

An implementation of the methods discussed in this work is illustrated in Appendix A using the open source statistical computing language R (R Development Core Team 2004). We comment on computational issues and data representation intimately connected with the mathematical theory, and the code is extensively annotated.

At this point, we would like to stress that while our treatment starts from the summaries suggested in 'approach B' by Schulgen and Schumacher (1996), we do not claim that the functionals we will be investigating are the only possible ones to study change in LOS. In fact, our consideration of different weighting schemes in Chapter 2 already supports this point of view. Of course, the major difficulty is that it is not straightforward to actually define in (observable) stochastic terms what change in LOS associated with an intermediate event is. To the best of our knowledge, this thesis makes the first attempt — based on the previous work by Schulgen and Schumacher

(1996) — to rigorously define this. We should also like to to stress that alternative suggestions may be studied along the lines presented in this thesis.

1.3 Data examples

We consider two data examples in this work.

Our major data example will be the SIR 3 (*S*pread of nosocomial *i*nfections and *r*esistant pathogens) cohort study initiated in 2000 at the Charité university hospital in Berlin with prospective assessment of data to examine the effect of nosocomial infections, cf. Grundmann et al. (2005). All patients admitted to one medical, two interdisciplinary, one surgical and one neurosurgical intensive care unit (ICU) during the 18 month-period from February 2000 to July 2001, and who stayed on the unit for more than 48 hours, entered the study. Altogether, 1876 admissions were included in the cohort.

341 (18.2%) of these 1876 admissions acquired at least one nosocomial infection. Overall, 214 (11.4%) patients died. Of the admissions who acquired nosocomial infection, 65 (19.1%) died. 30 (1.6%) observations were censored, i. e. still on ICU as the study was finished. Eleven of these 30 censored observations had acquired a nosocomial infection.

We will exemplarily focus on nosocomial pneumonia, a both frequent and grave nosocomial infection. 158 (8.4%) admissions acquired nosocomial pneumonia. Of these, 33 (20.9%) died. Seven admissions were censored after having acquired nosocomial pneumonia.

The mean duration of ICU stay was estimated as 15.6 ($\pm$ standard error 1.0) days, the median duration was estimated as 9 days (95%-confidence interval: $[9, 10]$).

As a second example we will use the data originally considered by Schulgen and Schumacher (1996). We will offer a brief reanalysis of these data in Sections 2.3.3 and 2.7.4. The data were collected at one anesthesiological and one medical ICU at the university hospital Freiburg from July 1991 to June 1993. 756 admissions with an ICU stay of more than 48 hours were included, for all of which complete follow-up information is available. 191 (25.3%) patients died. 124 (16.4%) patients acquired nosocomial pneumonia, of which 34 (27.4%) patients died. The mean duration of ICU stay was estimated as 10.5 ($\pm$ standard error 0.37) days, the median duration was estimated as 7 days (95%-confidence interval: $[7, 8]$).

Chapter 2

Change in length of stay associated with an intermediate event

In this chapter, we describe the possible occurrence of an IE by a multistate model and derive a functional for (expected) change in length of stay associated with the intermediate event.

2.1 A multistate model for change in LOS

Let $(X_t)_{t\in[0,\infty)}$ be a nonhomogeneous, continuous-time stochastic process with state-space $\{0, 1, 2\}$ and right-continuous sample paths. We will often simply write X_t for the stochastic process, if the meaning is clear from the context. The state-space together with its possible transitions is illustrated in Figure 2.1 for the example of nosocomial infections.

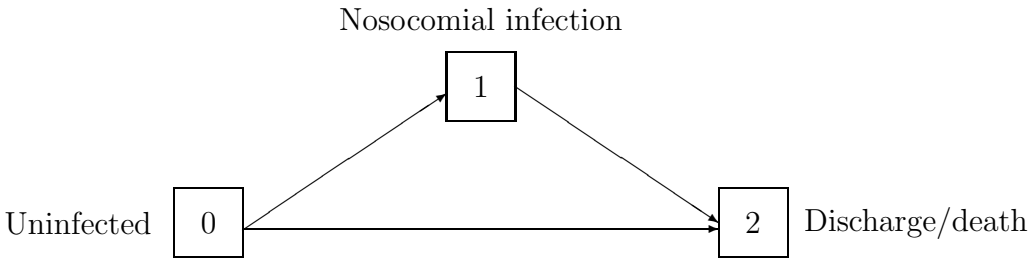

Figure 2.1: Potential states and transitions for occurrence of nosocomial infection.

Define transition probabilities

$$P_{hj}(s,t) := P\left(X_t = j \mid X_s = h\right) \text{ for } h,j \in \{0,1,2\},\ s \leq t. \tag{2.1}$$

The transition matrix is then given as

$$\mathbf{P}(s,t) := \Big(P_{hj}(s,t)\Big)_{hj}. \tag{2.2}$$

As depicted in Figure 2.1, we do not model backward transitions, i. e. $P_{hj}(s,t) = 0$ for $j < h$. We do not do so, because once an individual has experienced the intermediate event, (s)he has become a 'case'. We elaborate on this point in the following two Sections 2.2 and 2.3. We also assume the initial distribution of X_t to be degenerated at state 0, i. e. $P(X_0 = 0) = 1$. Corresponding to the transition probabilities, define transition intensities

$$\alpha_{hj}(t) := \lim_{\Delta t \to 0} \frac{P_{hj}(t, t+\Delta t)}{\Delta t}, \tag{2.3}$$

which we assume to exist. Moreover, define integrated transition intensities

$$A_{hj}(t) := \int_0^t \alpha_{hj}(u)\,\mathrm{d}u. \tag{2.4}$$

In this chapter, we derive quantities within the multistate framework to describe change in LOS associated with the intermediate state 1. In our study on large sample properties of the respective estimators in Chapter 3, we will assume that X_t occupies one of the transient states 0 or 1 with positive probability on a finite time interval only. Thus, let

$$\tau := \sup\{t :\ P(X_t \neq 2) > 0\}; \tag{2.5}$$

we assume τ to be finite. For $\tau \leq s \leq t$ let $P_{00}(s,t) = P_{11}(s,t) = 1$ (and $\mathbf{P}(s,t)$ be the unit matrix). As a consequence, we have

$$\sup\{u :\ \int_0^u \alpha_{hj}(t)\,\mathrm{d}t < \infty,\ h \neq j\} = \infty. \tag{2.6}$$

In addition, X_t is usually assumed to be Markovian, if censored observations occur. For ease of presentation, we will make this assumption in Chapter 3.3. See Remark 3.16 for a detailed discussion on this and how the Markov assumption may be dropped even in the censored case. Also recall that for the question of change in length of hospital stay, hospital stay being counted in days, censoring is not a central issue, but the temporal dynamics by which information on infection status becomes available are.

We interpret the multistate model for the nosocomial infection example in the following way: A patient enters the initial state 0 on admission (time $t = 0$). His or her time of hospital stay is terminated by reaching the absorbing state 2. The individual moves to the intermediate state 1, once a nosocomial infection has occurred.

Let us finally define two waiting times connected with the multistate model. We are interested in the time of hospital stay; it can be defined as the waiting time in the sub-state-space $\{0, 1\}$:

$$T := \inf \{t \geq 0 : \ X(t) \notin \{0, 1\}\}. \tag{2.7}$$

More specifically, we are interested in how a nosocomial infection affects the time of hospital stay T. Obviously, the timing of the intermediate event is crucial. We may rephrase our question as: 'How does the time to nosocomial infection affect the time of hospital stay?' This formulation is somewhat ambiguous, since a patient need not acquire a nosocomial infection. We consider the closely connected waiting time in the initial state 0,

$$T_0 := \inf \{t \geq 0 : \ X(t) \neq 0\}, \tag{2.8}$$

which is well defined and finite for every patient. Note that a patient acquires an infection by time T_0, if (and only if) $T_0 < T$. Otherwise $T_0 = T$, and the patient is directly discharged without prior nosocomial infection. The process X_t may equivalently be described in terms of T and T_0:

$$\left\{ \begin{array}{lcl} X_t = 0 & \Longleftrightarrow & t < T_0 \\ X_t = 1 & \Longleftrightarrow & T_0 \leq t < T \\ X_t = 2 & \Longleftrightarrow & T \leq t \end{array} \right\}. \tag{2.9}$$

One can think of the pair of waiting times (T_0, T) in terms of the *random time interval* $[T_0, T]$ denoting the time span spent in the intermediate state. (This formulation is a little imprecise, since at time T the process enters the absorbing state.) If the random time interval is degenerated, its length being 0, the patient has not passed through the intermediate state.

In competing risks terminology, the random variable X_{T_0} (with $X_{T_0}(\omega) := X_{T_0(\omega)}(\omega)$) denotes the cause (either 1 or 2) for leaving the initial state 0; the mapping $[0; \infty) \ni t \mapsto P(T_0 \leq t, X_{T_0} = 1)$ is often called the cumulative incidence function for cause 1, e. g. Crowder (2001). (Note that for some stochastic process $\tilde{X}$ and some stopping time $\tilde{T}$ measurability of $\tilde{X}_{\tilde{T}}$ need not be immediately clear. This is, however, of no concern in our context, e. g. Andersen et al. (1993), p. 62.) We assume that both state 1 and state 2 are entered with positive probability at T_0:

$$P(X_{T_0} = 1) \cdot P(X_{T_0} = 2) > 0. \tag{2.10}$$

Finally, we denote the joint distribution function of (T_0, T) by F: For $s \geq 0$ and $t \geq 0$ let

$$F(s,t) := P\left(T_0 \leq s \text{ and } T \leq t\right). \tag{2.11}$$

In the following, we will use both 'waiting time notation' in terms of (T_0, T) and 'stochastic process notation' in terms of X_t whatever appears to be more intuitive. In our study on large sample properties in Chapter 3, we will study large sample properties of our estimated quantities of interest as functionals of an empirical counterpart of F.

2.2 Expected change in LOS given status at time s

Let us think of infected patients as 'cases' and of uninfected patients as 'controls'. The key idea of 'approach B' in (Schulgen and Schumacher 1996) was that, while one could not unambiguously distinguish between 'cases' and 'controls' over the complete course of time, one might very well do so for some fixed, but otherwise arbitrary time s. Our approach will be based on this idea, but is not identical with 'approach B' of Schulgen and Schumacher (1996); differences will be discussed in Section 2.3.3 and highlighted in a data reanalysis in Section 2.7.4.

Consider some time $s > 0$ such that

$$P\left(X_s = 1\right) > 0 \text{ and } P\left(X_s = 0\right) > 0 \tag{2.12}$$

and define

$$\phi(s) := \mathrm{E}\left(T \,|\, X_s = 1\right) - \mathrm{E}\left(T \,|\, X_s = 0\right). \tag{2.13}$$

The assumption in (2.12) stipulates that, at time s, there are two groups to compare, namely patients who have acquired a nosocomial infection up to time s, and patients who are still free of it. The quantity $\phi(s)$ then compares the expected time of hospital stay between these two groups. In doing so, it allows to account for two aspects inherent in the temporal character of the situation at hand: First, it allows for the impact of a nosocomial infection to depend on the time by which the infection has been acquired. (This aspect is illustrated in Figures 2.3 and 2.6 in the data examples to follow.) Second, it takes care of changes in group membership: An individual who is still free of nosocomial infection by time s contributes to $\mathrm{E}\left(T \,|\, X_s = 0\right)$. He or she may become a 'case' for some later time s', $s' > s$, though, i. e. acquire a nosocomial infection in the time interval $(s,\, s']$. The individual will then contribute to $\mathrm{E}\left(T \,|\, X_{s'} = 1\right)$.

The difference of two conditional expectations in Equation (2.13) can be considered as the expected change in LOS due to nosocomial infection present at time s. We have

$$\begin{aligned}\phi(s) &= \mathrm{E}\left(T \mid X_s = 1\right) - \mathrm{E}\left(T \mid X_s = 0\right) \\ &= \int \mathbf{1}\left(X_s = 1\right) \cdot \frac{1}{P(X_s = 1)} \cdot T - \mathbf{1}\left(X_s = 0\right) \cdot \frac{1}{P(X_s = 0)} \cdot T \,\mathrm{d}P.\end{aligned} \tag{2.14}$$

The integrand on the right-hand side of Equation (2.14) has an interpretation: Basically, the integrand consists of the time of hospital stay T. However, T is assigned a positive sign, if a nosocomial infection has been acquired up to time s, and a negative sign, if the individual is still infection-free, but in hospital. In order to compare these two addends, they are weighted by the inverse of the probabilities of being in state 1 and state 0, respectively, by time s. Note that in a Markovian framework, $\phi(s)$ can even be interpreted as the expected change in LOS due to nosocomial infection acquired at time s.

In the following Section 2.3, we will aim at arriving at a summary to quantify the impact of a nosocomial infection on LOS. In order to do so, we need to define $\phi(s)$ if assumption (2.12) is violated. If $P(X_s = 1) = 0$, but $P(X_s = 0) > 0$, say, there is no group of 'cases'. As a consequence of that, we cannot ascribe a change in LOS at time s to nosocomial infection and set $\phi(s) := 0$ in this situation. We deal with $P(X_s = 1) > 0$, $P(X_s = 0) = 0$ and $P(X_s = 1) = 0$, $P(X_s = 0) = 0$ likewise and define

$$\phi(s) := \begin{cases} \mathrm{E}\left(T \mid X_s = 1\right) - \mathrm{E}\left(T \mid X_s = 0\right) & P(X_s = 0) \cdot P(X_s = 1) > 0 \\ & \text{if} \\ 0 & \text{else} \end{cases} \tag{2.15}$$

Note that, although meaningful, setting $\phi(s)$ equal to 0 in the discussed situation is somewhat arbitrary, since $\mathrm{E}(T \mid X_s)$ is only P^{X_s}-a. s. defined.

2.3 Expected change in LOS

2.3.1 A summary quantity

The notion of change in LOS due to nosocomial infection recalls the idea of a classical two-group comparison: A patient either acquires a nosocomial infection ('case') or remains free of it during his or her stay in hospital ('control'). Among patients discharged, we expect a patient to stay longer in hospital, if he or she acquires a nosocomial infection. Unlike the classical two-group

comparison, however, every patient starts as a 'control'. Only as time progresses do some patients become a 'case', i. e. acquire a nosocomial infection, while others remain a 'control', i. e. free of nosocomial infection, until the end of hospital stay. This temporal aspect of the data has been, e. g., emphasized by Klein et al. (2001) in the context of bone marrow transplants and the occurrence of graft-versus-host disease, and by Schulgen et al. (2000) in the context of nosocomial infection.

In the previous Section 2.2, we compared 'cases' and 'controls' with respect to some fixed time s. A meaningful weighting of the difference $\phi(s)$ between groups at time s is now given by the distribution of the time until group membership becomes definite. Group membership becomes definite at the random time T_0, when a patient leaves the initial state 0. The expected change in LOS associated with an IE is then given as

$$\mathrm{E}_{P^{T_0}}(\phi) = \int_{\{s\,:\,P(X_s=0)\cdot P(X_s=1)>0\}} \mathrm{E}_P(T \mid X_s = 1) - \mathrm{E}_P(T \mid X_s = 0)\ \mathrm{d}P^{T_0}(s), \tag{2.16}$$

where we write $\mathrm{E}_{P^{T_0}}(\phi)$ for $\mathrm{E}(\phi)$ etc. in order to make integration unambiguous.

In the following Section 2.3.2, we will discuss alternative weightings of ϕ. For the time being, note that $\mathrm{E}_{P^{T_0}}(\phi)$ can be thought of as an 'overall summary', with every patient of a study cohort contributing to the weighting of the weighted average (ignoring, for the moment, possibly censored observations). We will emphasize this weighting scheme. It can be given further interpretation on the individual level in a Markovian framework: It is exactly the waiting time in the initial state when a patient directly discharged may ask how many days in hospital he or she has been spared by avoiding a nosocomial infection. And it is a point in time when an infected patient may ask how many extra days in hospital he or she has to reckon with, now that a nosocomial infection has been acquired. The respective mean number of days is given by ϕ.

2.3.2 Alternative weightings and discussion

To the expected change in LOS patients who acquire a nosocomial infection and patients who are discharged or die without a prior nosocomial infection contribute in the following way:

$$\mathrm{E}_{P^{T_0}}(\phi) = P(X_{T_0} = 1)\cdot \mathrm{E}_{P^{T_0\mid X_{T_0}=1}}(\phi) + P(X_{T_0} = 2)\cdot \mathrm{E}_{P^{T_0\mid X_{T_0}=2}}(\phi)\,. \tag{2.17}$$

As said at the end of the previous Section 2.3.1, $\mathrm{E}_{P^{T_0}}(\phi)$ can be understood as an 'overall' summary. On the other hand, the quantity $\mathrm{E}_{P^{T_0|X_{T_0}=1}}(\phi)$, e. g., gives the expected change in LOS due to nosocomial infection given a nosocomial infection is acquired. It thus assumes the viewpoint of a patient who becomes infected at some time during his or her hospital stay. Consequently, only patients who acquire a nosocomial infection contribute to the weighting. Analogously, $\mathrm{E}_{P^{T_0|X_{T_0}=2}}(\phi)$ assumes the viewpoint of a patient who remains free of nosocomial infection throughout.

Note that the effect a nosocomial infection has on the time of hospital stay may differ between infected and non-infected patients. That is to say, if hospital stay is prolonged by k days given an infection is acquired, hospital stay need not necessarily be reduced by k days given discharge or death without prior infection. This peculiarity is illustrated in the example in Section 2.7. It is an immediate consequence of the temporal characteristic of the data: By the definition of $\phi(s)$, we have allowed for an impact of nosocomial infection that depends on the time by which the infection has been acquired, or by which the individual is still infection-free, respectively. Now, on the right-hand side of Equation (2.17), we weight $\phi(s)$ according to the distribution of the onset of nosocomial infection given an infection is acquired, $P^{T_0|X_{T_0}=1}$, or according to $P^{T_0|X_{T_0}=2}$, the distribution of the time of hospital stay given no infection is acquired. There is no reason for these two distributions to be identical; i. e. there is no reason why nosocomial infections should be acquired in the same way patients are directly discharged (or die).

We will see in Section 2.7 that the respective point estimates differ at most by about one day for our data example. One may, however, think of at least two situations where the difference may be more pronounced. First, consider a very common (hypothetical) nosocomial infection. 'Controls' at time s are potential future 'cases' and, in the situation under consideration, will very likely become 'cases'. This possibly leads to the somewhat paradoxical situation that the change in LOS expressed in terms of $\mathrm{E}_{P^{T_0}}(\phi)$ may get smaller the more frequent the infection is. This, of course, limits the interpretation of change in LOS in terms of 'How many days could be saved by the hypothetical prevention of the infection?' This difficulty is not restricted to change in LOS alone, but may arise for other quantities, too. An example is the innovation gain, cf. Arjas and Eerola (1993), which could here be used to contrast the probabilities of death given infection or given being infection-free at time s, say. For an example of the use of the innovation gain in analysing the effect of an intermediate event cf. Klein and Shu (2002). The bottom line here is that the effect of an infection is hard to tell if virtually everyone gets infected. However, a let-out may exist in our situation by explicitly assuming the viewpoint of a definite 'control'. If the times of

infection and the times of direct discharges or deaths are rather distinct, weighting $\phi(s)$ by $P^{T_0|X_{T_0}=2}$ might tell us more about the days potentially to be saved even in the situation of a very common infection.

A second situation where the change in LOS might become 'paradoxically' small is this: Consider an infection that arises during two distinct and short time intervals (due to a very specific hygiene problem, say) and quickly leads to death. Then $\phi(s)$ will often equal zero, because the 'case'-group is often empty, and $\mathrm{E}_{P^{T_0}}(\phi)$ may consequently be close to zero. While this would reflect the situation of many patients, one would consider the effect of the infection, once it has occurred, to be a pronounced reduction in LOS. The latter effect might be analysed weighting $\phi(s)$ by $P^{T_0|X_{T_0}=1}$. Note that a distinctive feature of this situation is that the group of 'cases' would be non-empty only for two short time intervals. This distinguishes the situation in question from one where an infection that typically arises rather late is studied, say. In the latter situation one might think of excluding all patients who left hospital before the first (late) infection arises. However, this is no solution in the general case as the original situation shows: We cannot exclude patients who leave hospital before the second time interval with a non-empty 'case'-group.

2.3.3 Differences to Schulgen and Schumacher (1996)

In their original paper, Schulgen and Schumacher (1996) suggested to look at the quantity (2.13), i. e. $\mathrm{E}(T \mid X_s = 1) - \mathrm{E}(T \mid X_s = 0)$, which played the key role in their 'approach B'. (However, they did not give the interpretation of Equation (2.14) as *expected change* and did not discuss assumption (2.12).) While we have based our approach on this idea, there are two major differences: First, Schulgen and Schumacher (1996) used a different multi-state model. Their exemplary intermediate event of interest was nosocomial pneumonia, and they introduced a second intermediate event 'sepsis', since the occurrence of sepsis is often fatal. They treated patients who acquired sepsis after pneumonia as 'cases', but patients who acquired sepsis without a preceding pneumonia dropped out of the 'control'-group. Contrary to this, we have chosen to still treat patients with sepsis (or some other major complication), but without preceding intermediate event of interest as 'controls'. We believe this leads to a more 'balanced' analysis, since patients with sepsis after pneumonia are still compared to patients with only sepsis. Second, Schulgen and Schumacher (1996) suggested to weight ϕ by $P^{T_0|X_{T_0}=1}$. (And in a model studying the effect of pregnancy on time to marriage, Utikal et al. (2003) considered analogous weighting according to the time to pregnancy. However, the functional by which Utikal et al. (2003) judge the effect differs from

ϕ.) We emphasize weighting according to P^{T_0}, since it has (in an uncensored situation) every patient of a study cohort contribute to the weighting. We also considered weights according to $P^{T_0|X_{T_0}=2}$ and explained the relationship between weights according to P^{T_0} on the one hand and weights according to $P^{T_0|X_{T_0}=1}$ and $P^{T_0|X_{T_0}=2}$ on the other hand in the previous Section 2.3.2.

We will illustrate these differences in a data example in Section 2.7.4.

2.4 A parametric approach: constant transition intensities

If a parametric form may be assumed for the distribution of X_t, our analysis may be considerably easier. In particular, we may hope for a lesser variation of the estimator of the expected change in LOS in the data examples to follow. A natural candidate for a parametric approach is a homogeneous Markov model assuming constant transition intensities, cf. e. g. Kijima (1997). We derive formulas for the cumulative incidence function and for change in LOS in this model; they will be applied to the SIR 3 data in Section 2.7. Interestingly, we will see that cumulative incidence functions may reasonably well be described by this parametric model, while this need not be the case for change in LOS.

Assume the process X_t introduced Section 2.1 to be a homogeneous Markov process with constant transition intensities α_{01}, α_{02} and α_{12}, i. e. $\alpha_{01}(t) = \alpha_{01} = \text{const.}$ for all $t \geq 0$ etc.. The probability that the process enters state 1 or state 2, respectively, at the random time T_0 can be expressed in terms of the transition intensities,

$$\begin{aligned} P\left(X_{T_0} = 1\right) &= \frac{\alpha_{01}}{\alpha_{01} + \alpha_{02}}, \\ P\left(X_{T_0} = 2\right) &= \frac{\alpha_{02}}{\alpha_{01} + \alpha_{02}}, \end{aligned}$$

and the waiting time distribution in state 0 is given by means of

$$P\left(T_0 > t\right) = e^{-(\alpha_{01}+\alpha_{02})\cdot t}$$

for all $t \geq 0$. Since, in the present set up, the waiting time T_0 in state 0 and the cause X_{T_0} for leaving this state are independent, e. g. Elandt-Johnson (1976), we have for the cumulative incidence function:

$$\begin{aligned} P\left(T_0 \leq t,\, X_{T_0} = 1\right) &= P\left(X_{T_0} = 1\right) - P\left(T_0 > t,\, X_{T_0} = 1\right) \\ &= P\left(X_{T_0} = 1\right) - P\left(T_0 > t\right) \cdot P\left(X_{T_0} = 1\right) \\ &= \frac{\alpha_{01}}{\alpha_{01} + \alpha_{02}} \cdot \left(1 - e^{-(\alpha_{01}+\alpha_{02})\cdot t}\right). \end{aligned} \tag{2.18}$$

We can now derive an expression for the expected prolongation of hospital stay due to nosocomial infection. Introduce

$$\begin{aligned} \mu_0 &:= \frac{1}{\alpha_{01} + \alpha_{02}}, \\ \mu_1 &:= \frac{1}{\alpha_{12}}. \end{aligned}$$

μ_0 is equal to the expected waiting time in state 0. Given the process enters state 1, μ_1 is equal to the expectation of the respective waiting time in state 1. Following from this, we have for the change in LOS $\phi(s)$ at time s, cf. Equation (2.13):

$$\begin{aligned} \phi(s) &= \mathrm{E}\left(T \mid X_s = 1\right) - \mathrm{E}\left(T \mid X_s = 0\right) \\ &= \mu_1 - \left[P\left(X_{T_0} = 1\right)\left(\mu_0 + \mu_1\right) + P\left(X_{T_0} = 2\right)\mu_0\right] \\ &= P\left(X_{T_0} = 2\right)\mu_1 - \mu_0 \\ &= \left(\frac{\alpha_{02}}{\alpha_{12}} - 1\right) \cdot \frac{1}{\alpha_{01} + \alpha_{02}} \qquad (2.19) \\ &=: \phi. \end{aligned}$$

Note that the functional $\phi(\cdot)$ does not depend on s anymore, since the Markov process X_t is assumed to be homogeneous. The expected change in LOS is therefore equal to ϕ in this model. Equation (2.19) has the intuitive interpretation that hospital stay is prolonged by an infection, if (and only if) the transition intensity α_{12} out of the intermediate state 1 is less than the 'direct discharge' intensity α_{02}.

An estimator of $P(T_0 \leq t, X_{T_0} = 1)$ as well as of ϕ may now be derived by using the usual maximum likelihood estimator for the transition intensities, cf. e. g. Hougaard (2000).

2.5 Other quantities of interest

We will make in Chapter 4 the important distinction what the effect on LOS is for patients discharged and patients deceased. Obviously, while for the former LOS may be prolonged, an infection may even expedite death for the latter. In this section we briefly consider other quantities of interest which will not be further considered in the remainder of this thesis.

2.5.1 Comparison between avoidable and unavoidable intermediate events

A major goal of the SIR 3 study was to detect so-called transmission-associated nosocomial infections, where the causative organism has been acquired in hospital, cf. Grundmann et al. (2005). Only these infections are considered to be truly avoidable (by preventing the nosocomial transmission of the causative organism); for short, we will call them exogenous nosocomial infections. In contrast to this, infections where the causative organism is already carried on admission by the respective patient are called endogenous nosocomial infections. The medical reasoning here is that such a patient is already that weak due to his or her illness that the infection eventually breaks out. A healthier patient may also carry such an organism, but may avoid the infection. One may then be specifically interested in comparing exogenously infected patients (the new 'cases') with endogenously infected patients (the new 'controls'). I. e., the question now is: What change in LOS is associated with exogenous nosocomial infection as compared to endogenous nosocomial infection?

In order to deal with this question, we have to distinguish the intermediate event 1 of our old model (Figure 2.1) into two intermediate events 1a and 1b as depicted in Figure 2.2.

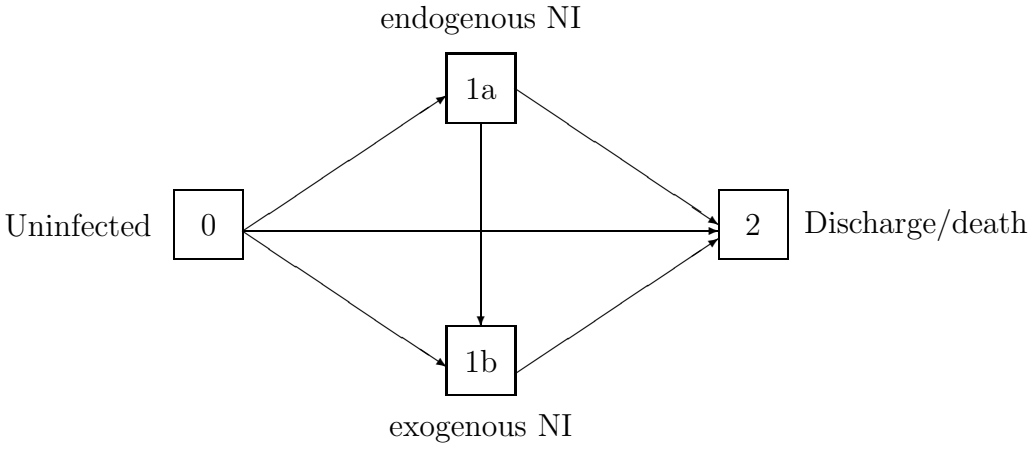

Figure 2.2: Potential states and transitions for the occurrence of exogenous as compared to endogenous nosocomial infection.

Note that we are not interested in modelling acquiring an endogenous nosocomial infection that follows an exogenous nosocomial infection, since,

once a exogenous infection has been acquired, the respective patient has become a 'case'.

For the present problem, let $(X_t)_{t\in[0,\infty)}$ be a (nonhomogeneous, continuous-time) stochastic process with state-space $\{0, 1a, 1b, 2\}$. The time of hospital stay is now given by

$$T := \inf\{t \geq 0 : \ X(t) \notin \{0, 1a, 1b\}\}.$$

For fixed time points s, we are interested in the difference

$$\mathrm{E}(T \mid X_s = 1b) - \mathrm{E}(T \mid X_s = 1a). \tag{2.20}$$

It less evident than in Section 2.3 how to weight the quantity of (2.20), since no patient starts out as a 'control'. In fact, many patients will neither become 'control' or 'case' but move directly to the absorbing state 2. A weighting scheme that immediately transfers from the previous situation is weighting according to the time until one becomes a 'case', i. e. acquires an exogenous infection. Denote the waiting in the sub-state-space $\{0, 1a\}$ by $T_{\{0,1a\}}$,

$$T_{\{0,1a\}} := \inf\{t \geq 0 : \ X(t) \notin \{0, 1a\}\}.$$

The role played by $\mathrm{d}P^{T_0|X_{T_0}=2}$ in Section 2.3.2 is now played by $\mathrm{d}P^{T_{\{0,1a\}}|X_{T_{\{0,1a\}}}=1b}$.

2.5.2 'Median change' in LOS

Motivated by applied work, we have chosen to look at expected (change in) LOS. Typically, data on LOS will be (positively) skewed, which may raise concerns whether it is appropriate to look at the expectation. While this is indeed often overlooked in data analyses (and the data sometimes implicitly assumed to be Gaussian), one established way to deal with this is looking at the logarithm of (possibly trimmed) LOS. A recent discussion is given by Lee et al. (2003). Note that for estimation purposes we will rely on T to be nonnegative, computing $\mathrm{E}(T)$ as an integral over the survival function of T. While $\ln(T)$ will not be nonnegative in general, this need not be of any practical consequence here. Typically, LOS data in studies on complications will be greater than one. E. g., a usual requirement in studies on nosocomial infection is that patients have been in hospital for at least 48 hours.

Alternatively, one might want to look at the median rather than the expectation. Thus, instead of Equation (2.13), one might consider

$$\begin{aligned}\tilde{\phi}(s) \ := \ & \inf\{t \geq 0 : \ P(T > t \mid X_s = 1) \leq 0.5\} - \\ & \inf\{t \geq 0 : \ P(T > t \mid X_s = 0) \leq 0.5\}.\end{aligned}$$

The discussion on weighting schemes in Section 2.3 now applies analogously (as will the estimation techniques). However, an interpretation as in Equation (2.14) does not seem to be as obvious.

2.6 Estimation based on the Aalen-Johansen estimator of the transition matrix.

We will base estimation mainly on the Aalen-Johansen or Product-Limit estimator $\widehat{\mathbf{P}}(s,t)$ of the transition matrix $\mathbf{P}(s,t)$ for nonhomogeneous Markov processes with a finite state-space. The Aalen-Johansen estimator $\widehat{\mathbf{P}}(s,t)$ is given as a finite matrix product, one matrix for every observed transition time in $(s,t]$. For any such matrix, non-diagonal entries (h,j), $h \neq j$, are given as the number of observed transitions from state h to state j, divided by the number of individuals in state h just prior to the transition time in question. The diagonal elements are chosen such that the sum of each row equals 1. Thus, non-diagonal entries are equal to the increments of the respective Nelson-Aalen estimators. If no transitions were observed in $(s,t]$, $\widehat{\mathbf{P}}(s,t)$ is estimated by the the unit matrix, as is $\widehat{\mathbf{P}}(s,s)$. This formulation of the Aalen-Johansen estimator allows for right-censoring and tied observations. The Aalen-Johansen estimator and the Nelson-Aalen estimator are considered in detail by Andersen et al. (1993).

We have seen by the system of equations (2.9) that the process X_t is fully determined by the pair of waiting times (T_0, T). In fact, we will, in Chapter3, study ϕ and $\mathrm{E}(\phi)$ as functionals of the joint distribution F of (T_0, T). Therefore, we now firstly write F in terms of the transition matrix $\mathbf{P}$ and secondly write our quantities of interest in terms of F. We then estimate by plugging in $\widehat{\mathbf{P}}$ for $\mathbf{P}$. We also give perhaps more intuitively appealing representations of ϕ and $\mathrm{E}(\phi)$ in terms of the transition probabilities and transition intensities, respectively, at the end of Section 2.6.2.

2.6.1 Estimating the joint distribution function F of (T_0, T)

Recall that T_0 denotes the waiting time in the initial state 0 and T denotes the waiting time in the sub-state-space $\{0,1\}$. The initial distribution of the process X_t is degenerated at state 0. It suffices to consider times $0 < s \leq$

$t < \infty$. We have:

$$\begin{aligned} F(s,t) &= P\left(T_0 \leq s, T \leq t\right) \\ &= P\left(X_s \in \{1,2\}, X_t = 2\right) \\ &= P\left(X_s = 1, X_t = 2\right) + P\left(X_s = 2, X_t = 2\right) \\ &= P\left(X_s = 1\right) \cdot P\left(X_t = 2 \,|\, X_s = 1\right) + P\left(X_s = 2\right) \\ &= P_{01}\left(0,s\right) \cdot P_{12}\left(s,t\right) + P_{02}\left(0,s\right). \end{aligned} \tag{2.21}$$

Note that we can make (2.21) also work for $s > t$ by setting it to

$$F(s,t) = P_{01}\left(0,s\right) \cdot P_{12}\left(s,t\right) + P_{02}\left(0, \min(s,t)\right), \tag{2.22}$$

since then $P_{12}\left(s,t\right) = 0$. The plug-in estimator of F is now given as

$$\widehat{F}(s,t) := \widehat{P}_{01}\left(0,s\right) \cdot \widehat{P}_{12}\left(s,t\right) + \widehat{P}_{02}\left(0, \min(s,t)\right). \tag{2.23}$$

If we have complete data, the estimator $\widehat{F}$ coincides with the usual empirical distribution function. The argument runs completely analogous to the respective result for the Kaplan-Meier estimator.

Remark 2.1. From a multistate point of view, it is natural to consider the matrix of transition probabilities, which is why we have based estimation of F on the Aalen-Johansen estimator, see also Schulgen and Schumacher (1996). In particular, the single ingredients of Equation 2.23 are meaningful and interpretable in terms of the multistate model of Figure 2.1. Alternatively, we could have based estimation of F on one of the available estimators of bivariate survival, see Chapter 3 and Chapter 5.1 for a detailed discussion. Here, we note that estimation based on the Aalen-Johansen estimator is not of the inverse probability of censoring weighted (IPCW) type. A number of IPCW estimators for the bivariate survival function have been proposed, if the pair of failure times is subject to only one censoring variable (so-called univariate censoring): The bivariate survival function is estimated by the empirical survival function of the observable data divided by an estimator of one minus the censoring distribution function (Lin and Ying (1993), Tsai and Crowley (1998), Kosorok (2002), van der Laan et al. (2002)). To see that our approach is not of this type, note that the bivariate survival function $P(T_0 > s, T > t)$ can be written as

$$P_{00}(0, \max(s,t)) + P_{00}(0,s) \cdot P_{01}(s,t), \tag{2.24}$$

The estimator of the bivariate survival function based on Equation (2.24) and the Aalen-Johansen estimator is not an IPCW estimator: This is easily

shown by modifying the multistate model such that state 2 becomes 'discharge/death or censored'. The Aalen-Johansen estimate of the analogue of Equation (2.24) then equals the empirical survival function of the observable data; however it does not factor to the IPCW-type. To see this, note that the risk sets in state 0 and state 1 as well as the state 0 to state 1-transitions remain unaffected by modifying the multistate model. Compare the estimates at some (s,t), such that s is less than the first observed 0 to 1-transition time and t is equal to the second one. Consider different censoring patterns, e. g. assume that only a censoring event in state 1 has happend between these two transition times.

2.6.2 Estimating $\phi(s)$ and $\mathrm{E}(\phi)$

We will rely on the fact that the expectation of a non-negative random variable may be (through integration by parts) computed as the integral over its survival function, i. e. one minus its distribution function. This argument leads, inter alia, to the usual estimator of mean live as the area under the Kaplan-Meier curve, see e. g. Gill (1983).

Recall that we assume the process X_t to be unequal the absorbing state 2 on the finite time interval $[0,\tau)$ only, cf. (2.5). We first consider (see the definition of ϕ in (2.15))

$$\begin{aligned} P\left(X_s = 0\right) &= P\left(T_0 > s\right) \\ &= 1 - F(s,\tau) \end{aligned} \tag{2.25}$$

and

$$\begin{aligned} P\left(X_s = 1\right) &= P\left(T_0 \leq s < T\right) \\ &= P\left(T_0 \leq s, T \leq \tau\right) - P\left(T_0 \leq s, T \leq s\right) \\ &= F(s,\tau) - F(s,s). \end{aligned} \tag{2.26}$$

Let us now consider the conditional expectations of T. We have

$$\begin{aligned} \mathrm{E}\left(T \mid X_s = 0\right) &= \int \mathbf{1}\left(X_s = 0\right) \cdot \frac{1}{P(X_s = 0)} \cdot T \,\mathrm{d}P \\ &= \int \mathbf{1}\left(T_0 > s\right) \cdot \frac{1}{1 - F(s,\tau)} \cdot T \,\mathrm{d}P \\ &= \int \mathbf{1}\left(u > s\right) \cdot \frac{1}{1 - F(s,\tau)} \cdot v \,\mathrm{d}F(u,v), \end{aligned} \tag{2.27}$$

where we identify, as usual, integration with respect to the distribution function with integration with respect to the corresponding probability measure.

Analogously, we have

$$\begin{aligned} \mathrm{E}\left(T \mid X_s = 1\right) &= \int \mathbf{1}\left(X_s = 1\right) \cdot \frac{1}{P(X_s = 1)} \cdot T \,\mathrm{d}P \\ &= \int \mathbf{1}\left(0 < u \leq s < v\right) \cdot \frac{1}{F(s,\tau) - F(s,s,)} \cdot v \,\mathrm{d}F(u,v). \end{aligned} \tag{2.28}$$

We may now estimate $\phi(s)$ by plugging in $\widehat{F}$ for F. Also, we may estimate integrals over ϕ: P^{T_0} is a marginal distribution from F, and we have $P^{T_0 \mid X_{T_0}=1} = P^{T_0 \mid T_0<T}$ and $P^{T_0 \mid X_{T_0}=2} = P^{T_0 \mid T_0=T}$.

Additionally, we now give representations of ϕ and $\mathrm{E}(\phi)$ in terms of the transition probabilities and transition intensities, respectively. Obviously, we have $P\left(X_s = 0\right) = P_{00}(0,s)$ and $P\left(X_s = 1\right) = P_{01}(0,s)$, respectively. The conditional expectations of T can be written as

$$\begin{aligned} \mathrm{E}\left(T \mid X_s = 1\right) &= \int_0^\tau P^{T \mid X_s=1}\left((t,\tau]\right) \,\mathrm{d}t \\ &= s + \int_s^\tau P^{T \mid X_s=1}\left((t,\tau]\right) \,\mathrm{d}t \\ &= s + \int_s^\tau P_{11}(s,t) \,\mathrm{d}t, \end{aligned}$$

and

$$\mathrm{E}\left(T \mid X_s = 0\right) = s + \int_s^\tau P_{00}(s,t) + P_{01}(s,t) \,\mathrm{d}t,$$

respectively. Considering the (conditional) waiting time distributions in the initial state 0, we first note that $P\left(T_0 \leq t\right) = 1 - P_{00}(0,t)$. Secondly, we exemplarily consider $P^{T_0 \mid X_{T_0}=1}$. We rely on a Kolmogorov forward differential equation describing the relationship between transition probabilities and transition intensities, cf. Andersen et al. (1993), Chapter II.6, and write for the cumulative incidence function for state 1:

$$P\left(T_0 \leq t,\, X_{T_0} = 1\right) = \int_0^t P_{00}(0,u-) \cdot \alpha_{01}(u) \,\mathrm{d}u. \tag{2.29}$$

Analogously, we get

$$\begin{aligned} P\left(X_{T_0} = 1\right) &= P\left(T_0 \leq \tau,\, X_{T_0} = 1\right) \\ &= \int_0^\tau P_{00}(0,u-) \cdot \alpha_{01}(u) \,\mathrm{d}u. \end{aligned}$$

2.7 Examples

The data are briefly introduced in Section 1.3. All analyses were done using the statistical computing language R (R Development Core Team 2004).

We computed bootstrap standard errors based on the bootstrap distribution of the respective nonparametric estimators, using 2000 bootstrap samples and the function `bootstrap()` of the R package `bootstrap`. We will report these results as ± standard error (SE) in this section. Later, in Chapter 3, we will show that 'the bootstrap works' for our quantities of interest and that confidence intervals can be constructed by Gaussian approximation.

2.7.1 Analysis of the SIR 3 data

Before estimating change in LOS, we analysed nosocomial pneumonia as a time-dependent covariate in a proportional hazards model. While this approach does not directly lead to an estimate of change in LOS, it can be used for a first evaluation whether there is an effect on the combined intensity of dying or being discharged, i. e. on the time spent in hospital at all. The effect of nosocomial pneumonia as a time dependent covariate in a proportional hazards model was significant (Wald test: $p < 0.0001$). Nosocomial pneumonia significantly reduced the hazard of (the combined end point of) death or discharge ($\widehat{\mathrm{HR}} = 0.65$; 95%-CI=$[0.54, 0.77]$), i. e. prolonged ICU stay. This analysis may be refined, distinguishing between competing endpoints discharge and death, cf., e. g., Therneau and Grambsch (2000), and we will do so in Chapter 4.4.

Estimates of $\phi(s)$ are illustrated in Figure 2.3. They are weighted by the respective distributions illustrated in Figure 2.4. Time points with an empty 'case'-group were 1, 2 and 184; there were no time points with an empty 'control'-group. The noticeable low value at 6.5 days for the distributions depicted in Figure 2.4 results from a patient who both acquired pneumonia and died on the seventh day after admission to hospital; we treated this case of pneumonia as having occurred after 6.5 days. We estimated the expected change in LOS, i. e. $\int \phi(s)\,\mathrm{d}P^{T_0}(s)$, due to nosocomial pneumonia as 4.9 (±2.9) days. The expected change in LOS $\int \phi(s)\,\mathrm{d}P^{T_0|X_{T_0}=1}$ due to nosocomial pneumonia given the infection was acquired at some time during hospital stay was estimated as 6.2 (±2.6) days. The expected change in LOS $\int \phi(s)\,\mathrm{d}P^{T_0|X_{T_0}=2}$ due to nosocomial pneumonia given the infection was not acquired was estimated as 4.8 (±3.0) days.

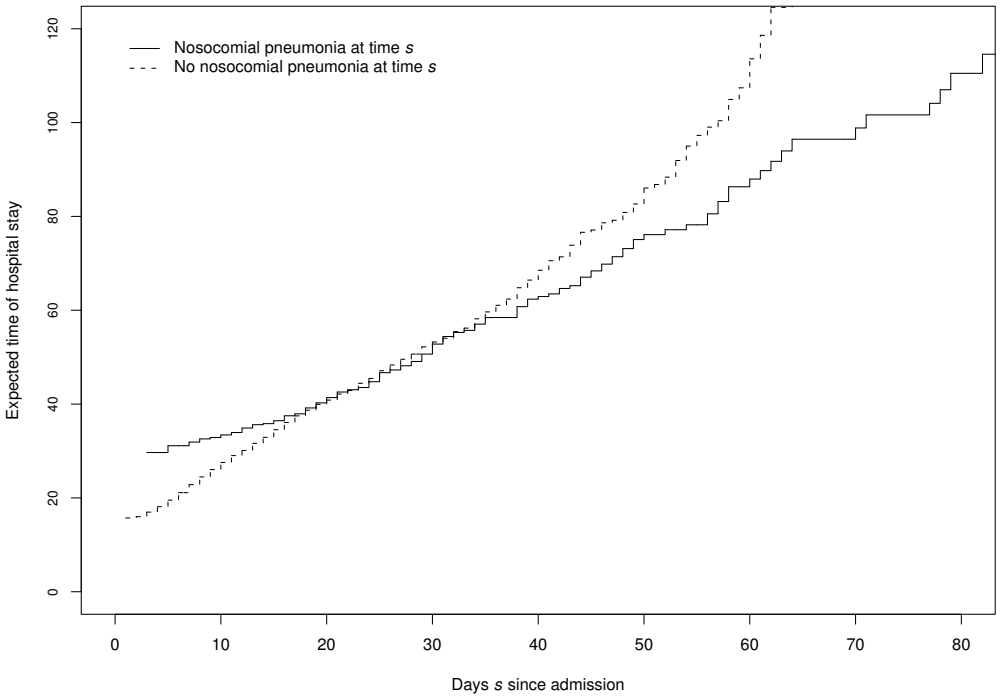

Figure 2.3: Estimated expected change in LOS due to nosocomial pneumonia at time s: The solid curve indicates the estimated expected time of hospital stay, given nosocomial pneumonia has been acquired by time s. The broken curve indicates the respective time, given still being free of nosocomial pneumonia by time s. The estimates of the expected change $\phi(s)$ at time s equal the vertical difference between the two curves. Note that the solid curve starts on day 3, the first day with a non-empty 'case'-group.

2.7.2 Comparison with ad hoc approaches

The different concepts of change in LOS due to an intermediate event introduced in Section 2.3 adequately account for the timing of events. They thus avoid the pitfalls of retrospective stratification used in ad hoc analyses that, in the majority of cases, will overestimate the effect, cf. Schulgen et al. (2000). In the following, we contrast the approach based on multi-state models with two-group comparison and confounder and time matching.

Admissions who did not acquire nosocomial pneumonia stayed on ICU for a mean duration time of 13.3 ($\pm$0.6) days. Admissions who acquired nosocomial pneumonia stayed on average for 35.1 ($\pm$3.6) days. The extra time spent on ICU attributable to nosocomial pneumonia would consequently

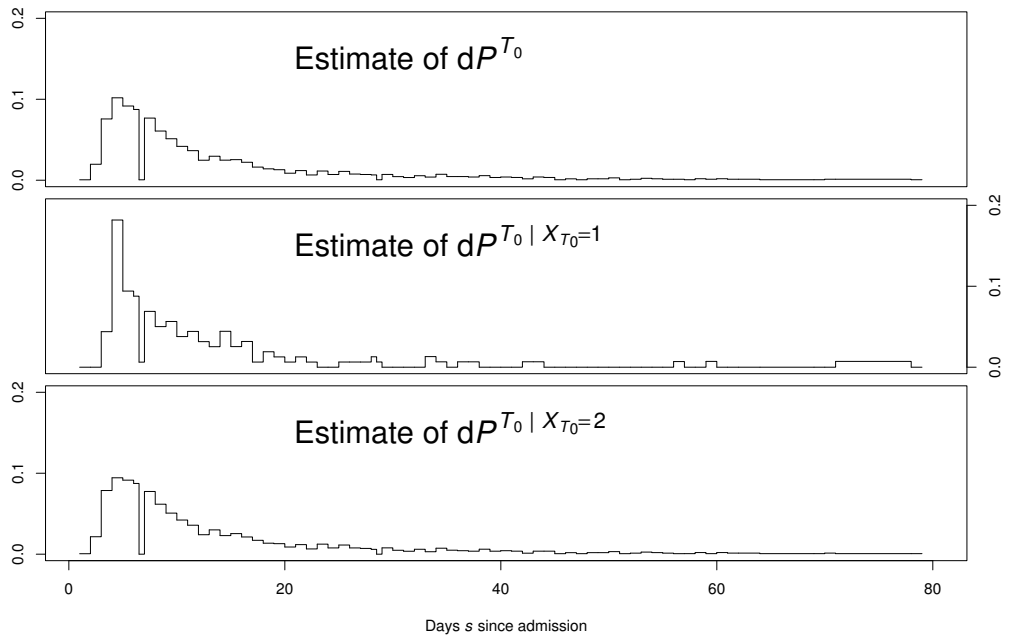

Figure 2.4: Estimated densities of the (conditional) distributions of the waiting time T_0 in the initial state 0.

have been overestimated by a simple two-group comparison as an extra time of 21.8 ($\pm$3.5) days.

In order to lessen overestimation, a matched two-group comparison is often considered. We exemplarily matched for age, sex and time to manifestation of nosocomial pneumonia for the cases. Matching for time to manifestation implied that admissible controls were still on ICU when infection was diagnosed for the case; Schulgen et al. (2000) argue the latter to be the single most important matching factor. We allowed for a maximum of five controls per case, using a SAS macro courtesy of Bergstrahl et al. of the Mayo Medical Center, cf. (Bergstrahl, Kosanke, and Jacobsen 1996). Matching yielded an estimate of 15.8 ($\pm$3.6) days of prolongation of hospital stay due to nosocomial pneumonia. Note that matching cannot capture the effect an early nosocomial pneumonia has on LOS as compared to a late occurrence of nosocomial pneumonia.

2.7.3 Constant transition intensities

We have seen in Section 2.4 that a model assuming constant transition intensities can facilitate the analysis considerably. In fact, such a model seems to offer a reasonable fit judged by the cumulative incidence function $t \mapsto P(T_0 \leq t, X_{T_0} = 1)$: Figure 2.5 contrasts the parametric with the nonparametric estimates. The parametric estimate has been derived from Equation (2.18), the nonparametric estimate from Equation (2.29).

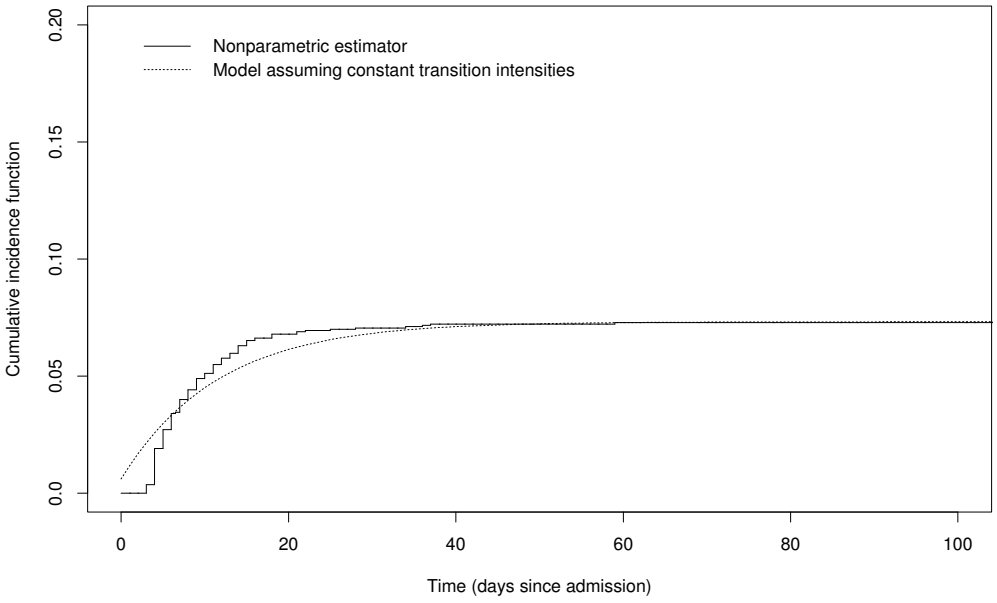

Figure 2.5: Nonparametric and parametric estimates of the cumulative incidence function for nosocomial pneumonia.

Table 2.1 lists both the nonparametric and the parametric estimates of the change in LOS due to nosocomial pneumonia, but also due to nosocomial infection in general and due to the most frequent type of nosocomial infection, urinary tract infection.

Looking at nosocomial pneumonia, the reason for the substantial difference between the nonparametric and the parametric estimate can be seen to be twofold.

In the model assuming constant transition intensities, the extra time spent in hospital due to nosocomial infection does not depend anymore on the time by which the nosocomial infection has been acquired, cf. Equation (2.19). Speaking in terms of the expected time of hospitalization, this im-

	Estimate	
	Nonparametric	Parametric
First acquired nosocomial infection	5.2	16.1
Nosocomial pneumonia	6.1	19.7
Nosocomial urinary tract infection	-0.2	18.6

Table 2.1: Selected nonparametric and parametric estimates of change in LOS due to nosocomial infection.

plies that nosocomial pneumonia prolongs hospital stay by the same amount ϕ on any day s in hospital compared to still being free of nosocomial pneumonia on that day. As a consequence of that, lines illustrating the conditional expected duration of ICU stay given the state of an admission would run parallel, their vertical distance being ϕ. However, contradictory to the homogeneous Markov model, the lines illustrating the nonparametric estimates in Figure 2.3 cross.

Closely related to the assumed constant effect of nosocomial pneumonia in the parametric model is another point why we observe a substantial difference between the nonparametric and the parametric estimate of the extra time spent in hospital. The nonparametric estimate usually emphasizes early differences in the conditional expected times of hospitalization, cf. Figure 2.4. Unlike the parametric estimate, the nonparametric estimate weights these differences according to the empirical waiting time distribution in the initial state. More than 60% of the mass of the empirical distribution lie within the first 10 days, nearly 90% of the mass lie within the first 20 days. Judged by Figure 2.5, though, the fit of the parametric model is not best for early, but for late times of hospitalization.

Following from this, we get the impression that the assumption of an underlying homogeneous Markov process with constant transition intensities describes the cumulative incidence as depicted in Figure 2.5 fairly well overall. However, it does not appear to be an adequate model for the specific issue in question. As a consequence of that, a more complex parametric model would have to be considered in order to estimate the extra time spent in hospital due to nosocomial infection. Yet, it seemed difficult to find a parametric model suitable for the analysis of all types of nosocomial infection, which was the aim of the original analysis.

2.7.4 Reanalysis of the data originally considered by Schulgen and Schumacher (1996)

We estimated the expected change in LOS, i. e. $\int \phi(s)\,\mathrm{d}P^{T_0}(s)$, due to nosocomial pneumonia as 2.0 ($\pm$1.2) days. The expected change in LOS $\int \phi(s)\,\mathrm{d}P^{T_0|X_{T_0}=1}$ due to nosocomial pneumonia given the infection was acquired at some time during hospital stay was estimated as 2.1 ($\pm$1.2) days. The expected change in LOS $\int \phi(s)\,\mathrm{d}P^{T_0|X_{T_0}=2}$ due to nosocomial pneumonia given the infection was not acquired was estimated as 2.0 ($\pm$1.1) days. The first day with a non-empty 'case'-group was day 3. Only one further day with an empty 'case'-group was observed (day 78); there was no day with an empty 'control'-group.

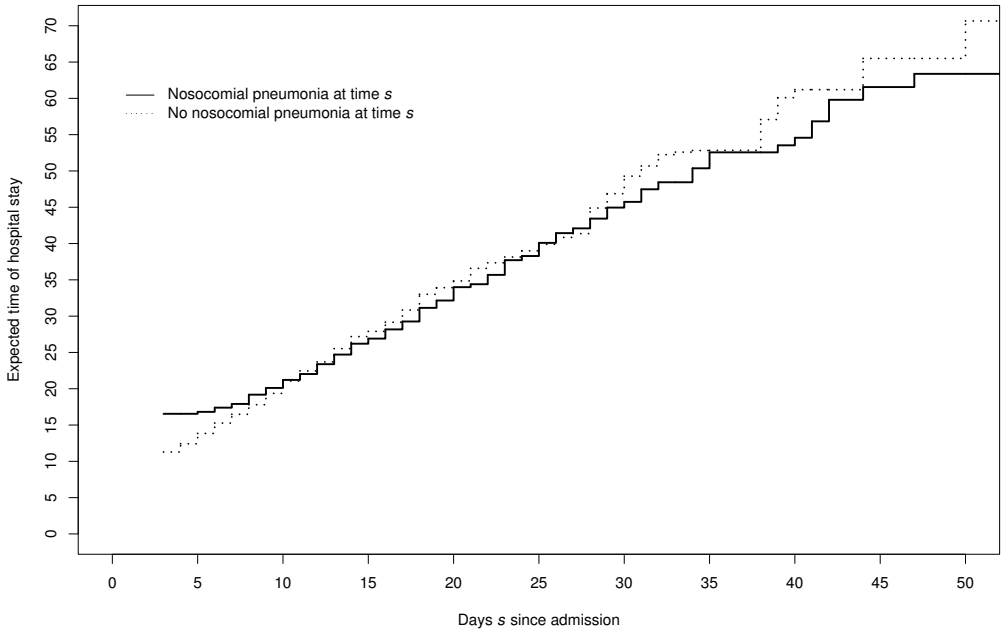

Figure 2.6: Estimated expected change in LOS due to nosocomial pneumonia at time s for the data originally used by Schulgen and Schumacher (1996). The limits of the x- and y-axis are chosen as in Schulgen and Schumacher (1996), Figure 4. We have drawn both curves starting with day 3, the first day with a non-empty 'case'-group.

Estimates of $\phi(s)$ are illustrated in Figure 2.6. They are weighted by the respective distributions illustrated in Figure 2.7.

For their version of ϕ, weighted by $\mathrm{d}P^{T_0|X_{T_0}=1}$, Schulgen and Schumacher

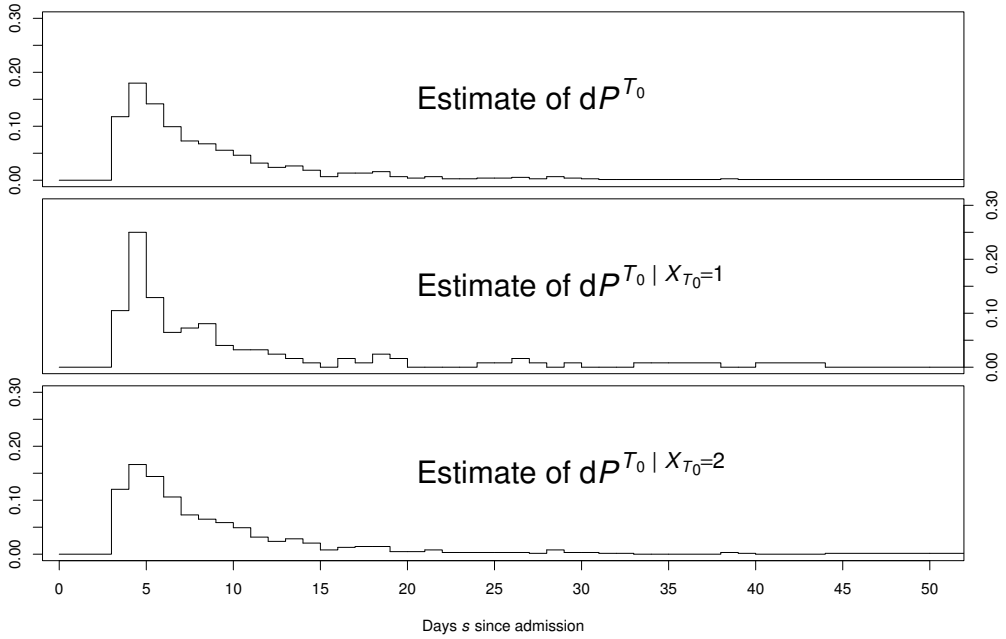

Figure 2.7: Estimated densities of the (conditional) distributions of the waiting time T_0 in the initial state 0 for the data originally used by Schulgen and Schumacher (1996).

(1996) reported an estimate of 3.4. Since there are very few days with one of the groups of 'cases' or 'controls' being empty, and since our different weighted summaries of ϕ do not differ substantially, the main reason for the difference between our result and the one of Schulgen and Schumacher (1996) is seen to lie in the use of different multi-state models. In fact, the residual hospital stay increases within the 'control'-group, if patients with nosocomial sepsis, but no preceding nosocomial pneumonia are still counted as 'controls'. This supports our belief that the 3-state model leads to a more balanced analysis, cf. Section 2.3.3.

Chapter 3

Large sample properties for change in length of stay associated with an intermediate event

In this chapter, we consider $s \mapsto \phi(s)$ and the different summaries $\mathrm{E}.(\phi)$ as functionals of $P^{(T_0,T)}$. Given an estimator $\widehat{P^{(T_0,T)}}$ of the joint distribution of (T_0, T), we want to study the asymptotic expansion of the plug-in estimators. If we know weak convergence of $\sqrt{n}\left(\widehat{P^{(T_0,T)}} - P^{(T_0,T)}\right)$ as the sample size increases, we may deduce weak convergence of our functionals by means of the delta method. In order to make the delta method work, we need to show that our functionals can be approximated at $P^{(T_0,T)}$ by a linear functional; this is done by showing Hadamard-differentiability. This will also give us asymptotic correctness of the bootstrap.

We will consider convergence of $\widehat{P^{(T_0,T)}}$ in the (to be defined) space $D([0,\tau]^2)$ of bivariate cadlag (continu à droite, limité à gauche) functions on $[0,\tau]^2$, endowed with the supremum norm and the Borel σ-field, which is generated by all open sets. However, a function $x \mapsto \sup_f |f(x)|$, the supremum taken over a class of measurable, real-valued functions f, need not itself be measurable (e. g. Billingsley (1968), Chapter 3.18). As a consequence, a new weak convergence theory has been established that only requires asymptotic measurability. We will use this theory as presented in the book by van der Vaart and Wellner (1996), which we also use as our main reference on Hadamard-differentiability and the delta method. We shall, however, not be further concerned with the technicalities and simply write $\xrightarrow{\mathcal{D}}$ for weak convergence: Our functionals will take values in the space

$D([0,\tau])$ of univariate cadlag functions on $[0,\tau]$ (or even in the space $\mathbb{R}$ of real numbers), and our limiting processes will have continuous sample paths, i. e. are elements of $C([0,\tau])$, the subset of continuous functions in $D([0,\tau])$. In this case, weak convergence in the 'old' sense of the Skohorod metric (e. g., Billingsley (1968)) and in the 'new' sense of the supremum norm coincide, see, e. g., the discussion of Præstgaard of Gill (1989). Note that Gill (1989) tackles the issue of measurability of suprema by looking at the ball σ-field on $D([0,\tau])$, generated by all open balls. The ball σ-field is smaller than the Borel σ-field, and they coincide on separable spaces. $D([0,\tau])$ endowed with the supremum norm is not separable, but $C([0,\tau])$ is. Van der Vaart and Wellner (1996), Chapter 1.7, show that the weak convergence theory for ball measurable maps is a special case of the more general theory discussed in their book, see also the discussion of Wellner of Gill (1989) and Gill's reply. We will leave these issues aside from now on.

This chapter is organized as follows: In Section 3.1, we briefly comment on the use of the bivariate time scale (T_0, T). This needs some explanation, since, in general, bivariate survival analysis is much more difficult than univariate survival analysis. We will see, however, that our situation is essentially easier than bivariate survival analysis in general, as (T_0, T) derives from a multi-state model. We then study the uncensored situation in Section 3.2. We do so for several reasons: Of course, our motivating data example being on length of hospital stay, counted in days, such a situation is practically feasible and therefore relevant. More important for our presentation, our large sample result will hold for $\int_q^r \phi \, \mathrm{d}P^{T_0}$, with $0 < q < r < \tau$ such that X_t fullfills some boundness assumptions on $[q,r]$. We will see that these assumptions are fullfilled, if $P(X_s = 0) \cdot P(X_s = 1) > c > 0$ for all $s \in [q,r]$. For applications, such a result suffices. In this respect, it is comparable to early results on restricted mean survival (e. g. Fleming (1978)); however, the reason for the restriction to $[q,r]$ in our case stems from the multi-state model, not from some outward censoring mechanism. To clarify this issue, we have chosen to present the uncensored case first. It also simplifies the presentation a bit and allows us to defer assuming the process X_t to be Markovian to Section 3.3. (See, however, Remark 3.16 for relaxing the Markov assumption even in the censored case.) Section 3.5 concludes this chapter with a discussion.

3.1 Bivariate time scale (T_0, T)

The reason for using a bivariate time scale is essentially this: We are looking at a *series* of differences $\mathrm{E}(T \mid X_s = 1) - \mathrm{E}(T \mid X_s = 0)$. For some fixed s, the difference depends on the later time of discharge (or death), which gives

us one time dimension. A second one comes into play by letting s vary, i. e. by looking at the series of differences. In Chapter 2.1, we have seen by the system of equations (2.9) that our multi-state model may equivalently be described by the stochastic process $(X_t)_{t\in[0,\tau]}$ or by the pair of waiting times (T_0, T). So far, we have used the waiting time T to determine, of course, length of stay, and the waiting time T_0 to determine time until group membership ('case'/'control') becomes definite and to thus motivate meaningfully weighted summaries. Finding expressions suitable for plug-in estimation in Section 2.6.2, we have given such expressions both in terms of transition probabilities and transition intensities and in terms of the joint distribution of (T_0, T). In the following two sections 3.2 and 3.3, we will find that the asymptotic expansion of our estimators follows rather straightforwardly from the respective knowledge on estimators of the joint distribution of (T_0, T). In addition, we will argue in Section 5.1 that the question of the impact of an intermediate on a terminal event can be formulated unambiguously and straightforwardly in the setting of the random time interval $[T_0, T]$. Here, $[T_0, T]$ essentially denotes the time span spent in the intermediate state. (See also page 17.)

The bivariate situation is illustrated in Figure 3.1 for two patients l and m: Let $(T_0^{(i)}, T^{(i)})$, $i = 1, \ldots, n$ denote n i. i. d. replicates of (T_0, T). Patient l has $T_0^{(l)} < T^{(l)}$; (s)he reaches the intermediate state by time $T_0^{(l)}$ and leaves hospital by time $T^{(l)}$. Contrary to patient l, patient m does not pass through the intermediate state, but leaves hospital directly at time $T_0^{(m)} = T^{(m)}$. The distribution of (T_0, T) has mass only on the upper rectangle $\{(s,t) \in (0,\tau]^2 : s \leq t\}$, with positive mass on the diagonal $\{(s,t) \in (0,\tau]^2 : s = t\}$. Recall that τ has been defined in Equation (2.5) as the supremum over all times with positive probability of being in one of the transient states 0 or 1, and that we assume τ to be finite.

Using the bivariate time scale (T_0, T) comes with a certain price: Perhaps most palpable, we lose our usual concept of future and past. This is illustrated for patient l in Figure 3.1: Two dashed lines run through the bivariate time point $(T_0^{(l)}, T^{(l)})$, marking four time regions. The upper right rectangle clearly is future, and the lower left rectangle clearly is past, but this concept gets blurred looking at the remaining two rectangles. Looking at the upper left rectangle (all bivariate times (s,t) such that $s < T_0^{(l)}$ and $t > T^{(l)}$), these time points are 'past' with respect to the waiting time in the initial state, but 'future' with respect to the waiting time until reaching the absorbing state. Gill (1992a) argues that the upper left and lower right rectangles are rather 'past' and further explains the connected problems of multivariate survival analysis. One problem that follows is that there are now many pathes in

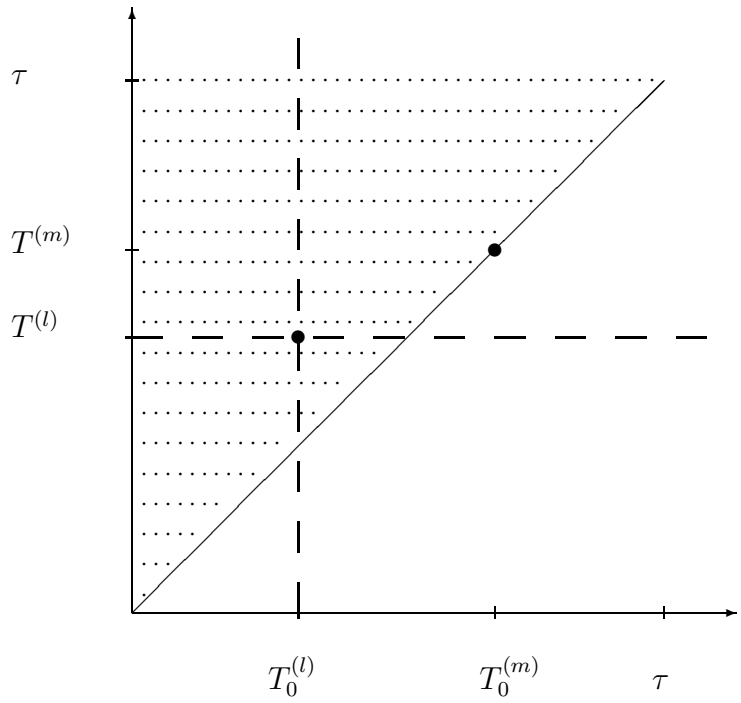

Figure 3.1: Pair of waiting times for two exemplary patients l and m. The waiting time in the initial state is plotted on the x-axis, length of stay is plotted on the y-axis. Patient l passes through the intermediate state, while patient m does not. The distribution of (T_0, T) has mass only on the dotted area.

bivariate time to move from one time point to another one, and, as one consequence, in general martingale methods don't work anymore. Fortunately, our case is much easier, since the pair of waiting times (T_0, T) derives from the multi-state model. In particular, we have only one outward censoring mechanism. The multi-state model also implies that we may think of (T_0, T) as the random time interval $[T_0, T]$, its length being equal to the time spent in the intermediate state. We will get back to this notion in Section 3.3, studying weak convergence of the estimator $\widehat{F}$ from Equation (2.23), where we will use results from Gill and Johansen (1990) on differentiability of the product integral, taking *interval functions* as an argument. (An interval function is a bivariate function only taking arguments where the first entry of its argument is less than or equal to the second entry.)

3.2 Uncensored situation

We first define the space of bivariate cadlag functions on $[0, \tau]^2$, following Neuhaus (1971) (see also Ren and Sen (1995) for a more recent reference), and then restate the usual weak convergence result for bivariate empirical distribution functions. We write $f(s+, t)$ for $\lim_{s_n \to s, s_n > s} f(s_n, t)$ etc..

Definition 3.1 (Bivariate cadlag function space). *Let $D([0, \tau]^2)$ be the vector space of bivariate functions $f : [0, \tau]^2 \to \mathbb{R}$ for which all limits $f(s-, t-)$, $f(s-, t+)$, $f(s+, t-)$ and $f(s+, t+)$ exist and which are 'continuous from above':*

$$f(s+, t+) = f(s, t).$$

We call $D([0, \tau]^2)$ the space of bivariate cadlag functions on $[0, \tau]^2$.

Remark 3.2. Note that we have defined $D([0, \tau]^2)$ for τ as defined in Equation (2.5). For the definition of a bivariate cadlag function space in general there is nothing special about τ, however, and it may be replaced by some other positive real number.

Also note that the limits which are assumed to exist in the previous definition correspond to the four time regions illustrated in Figure 3.1 for the bivariate time point $(T_0^{(l)}, T^{(l)})$. Neuhaus (1971) calls these limits 'quadrant limits'.

By Neuhaus (1971), Corollary 1.6, every bivariate cadlag function on $([0, \tau]^2)$ is bounded. We consider $D([0, \tau]^2)$ as a subspace of the space $l^\infty([0, \tau]^2)$ of all bounded functions on $[0, \tau]^2$: Let

$$||f|| := ||f||_{[0,\tau]^2} := \sup_{[0,\tau]^2} |f(s, t)| \tag{3.1}$$

be the supremum norm for bivariate real-valued functions f on $[0,\tau]^2$, and let

$$l^\infty\left([0,\tau]^2\right) := \{f : [0,\tau]^2 \to \mathbb{R} \,:\, ||f|| < \infty\}. \tag{3.2}$$

We can now consider $D\left([0,\tau]^2\right)$ and $l^\infty\left([0,\tau]^2\right)$ as metric spaces, equipped with the metric induced by the supremum norm. The respective Borel σ-fields are the smallest σ-fields containing the open sets. We may now restate the usual weak convergence result for bivariate empirical distribution functions: As before, let $(T_0^{(i)}, T^{(i)})$, $i = 1,\ldots,n$ denote n i. i. d. replicates of (T_0, T). In (2.11), we have defined the bivariate distribution function F of (T_0, T), which we have estimated by an plug-in estimator $\widehat{F}$ in (2.23) derived from the Aalen-Johansen estimator. For complete observations we have

$$\widehat{F}(s,t) = \left|\left\{i \in \{1,\ldots,n\} :\, T_0^{(i)} \leq s \text{ and } T^{(i)} \leq t\right\}\right| /n, \tag{3.3}$$

i. e. the proportion of observations in the lower left rectangle defined by the upper right time point (s,t), $(s,t) \in (0,\tau]^2$. We consider $\widehat{F}$ as a stochastic process with index set $[0,\tau]^2$. For notational ease we have suppressed the dependence of $\widehat{F}$ on the sample size n. We now have the following theorem:

Theorem 3.3 (CLT for bivariate edf's). *For $\widehat{F}$ as in (3.3) and F as in (2.11) we have*

$$\sqrt{n}\left(\widehat{F} - F\right) \xrightarrow{\mathcal{D}} G \text{ as } n \to \infty, \tag{3.4}$$

where G is a mean zero Gaussian process, also with index set $[0,\tau]^2$, and covariance function

$$\mathrm{Cov}\left(G(s,t), G(u,v)\right) = F\left(\min(s,u), \min(t,v)\right) - F(s,t)\cdot F(u,v). \tag{3.5}$$

For a proof of the preceding theorem, see for instance Wellner (1992), p. 252. The theorem follows from more general results in van der Vaart and Wellner (1996), see also van der Vaart (1998), Chapter 19. The general theory is developed for much larger index sets than $[0,\tau]^2$, but for our purposes the 'usual' index set $[0,\tau]^2$ suffices. The limit process G is called a F-Brownian bridge process.

3.2.1 Hadamard-differentiability and weak convergence for expected change in LOS given status at time s

Introduce for $r \in (0,\tau)$, $s \in [0,\tau]$ and functions $G \in D\left([0,\tau]^2\right)$

$$\iota(G,s,r) = \mathbf{1}(s < r)\cdot \mathbf{1}\left(1 - G(s,\tau) > 0\right)\cdot \mathbf{1}\left(G(s,\tau) - G(s,s) > 0\right). \tag{3.6}$$

Note that

$$\iota(F,s,r)\cdot\big(\mathrm{E}\,(T\,|\,X_s=1)-\mathrm{E}\,(T\,|\,X_s=0)\,\big)=\phi(s),$$

if $s<r$, cf. Equation (2.15) and Equations (2.25) and (2.26). We first show Hadamard-differentiability of the functional corresponding to $\mathrm{E}\,(T\,|\,X_s=0)$, but restricted to a certain time interval $[0,r)\subsetneqq[0,\tau]$.

Lemma 3.4. *Let $r\in(0,\tau)$ be fixed, such that $\iota(F,s,r)/(1-F(s,\tau))$ is bounded away from infinity, i. e. $\iota(F,s,r)/(1-F(s,\tau))<b(r)$, $0<b(r)<\infty$ for all $s<r$ (with $0/0:=0$). Then the mapping $\psi_0:\{G\in D\,([0,\tau]^2):$ G is a bivariate distribution function.$\}\to D\,([0,\tau])$, $G\mapsto\psi_0(G)$ with*

$$\psi_0(G)(s):=\int\frac{\iota(G,s,r)\cdot\mathbf{1}(s<u)\cdot v}{1-G(s,\tau)}\,\mathrm{d}G(u,v)$$

is Hadamard-differentiable in F with derivative $\psi'_{0,F}:D\,([0,\tau]^2)\to D\,([0,\tau])$, $G\mapsto\psi'_{0,F}(G)$ with

$$\begin{aligned}\psi'_{0,F}(G)(s)\;:=\;&\int\frac{\iota(F,s,r)\cdot\mathbf{1}(s<u)\cdot v}{1-F(s,\tau)}\,\mathrm{d}G(u,v)\\&+\int\frac{\iota(F,s,r)\cdot\mathbf{1}(s<u)\cdot v\cdot G(s,\tau)}{(1-F(s,\tau))^2}\,\mathrm{d}F(u,v),\end{aligned}$$

where the first integral on the right hand side in the last display is defined via integration by parts, if G is not of bounded variation.

Remark 3.5. Note that ψ_0 evaluated at F gives the mapping $s\mapsto\mathbf{1}(s<r)\cdot\mathbf{1}(P(X_s=0)>0)\cdot\mathbf{1}(P(X_s=1)>0)\cdot\mathrm{E}\,(T\,|\,X_s=0)$.

For a bivariate version of the integration by parts-formula, which we use to define integrals with respect to some $G\in D([0,\tau]^2)$ of unbounded variation, see van der Laan (1995), Lemma 6.1.

Proof of Lemma 3.4. Define $F_t:=F+t\cdot G_t$ with $t\to0$ and $G_t\to G$, such that F_t is in the domain of ψ_0. We have to show

$$\frac{1}{t}\left(\psi_0(F_t)-\psi_0(F)\right)\to\psi'_{0,F}(G)$$

in $D([0,\tau])$ endowed with the supremum norm. For $s \in [0,\tau]$ consider

$$\begin{aligned}
&\frac{1}{t}\left(\psi_0(F_t) - \psi_0(F)\right)(s) \\
&\quad = \frac{1}{t}\left(\int \frac{\iota(F_t,s,r)\cdot \mathbf{1}(s<u)\cdot v}{1-F_t(s,\tau)}\,\mathrm{d}(F+t\cdot G_t)(u,v)\right. \\
&\qquad \left. - \int \frac{\iota(F,s,r)\cdot \mathbf{1}(s<u)\cdot v}{1-F(s,\tau)}\,\mathrm{d}F(u,v)\right) \\
&\quad = \int \frac{\iota(F_t,s,r)\cdot \mathbf{1}(s<u)\cdot v}{1-F_t(s,\tau)}\,\mathrm{d}G_t(u,v) \\
&\qquad + \frac{1}{t}\left(\int \mathbf{1}(s<u)\cdot v\cdot\left(\frac{\iota(F_t,s,r)}{1-F_t(s,\tau)} - \frac{\iota(F,s,r)}{1-F(s,\tau)}\right)\mathrm{d}F(u,v)\right)
\end{aligned} \tag{3.7}$$

We first consider the first addend on the right hand side of (3.7). For every $\epsilon > 0$ there is t_ϵ such that G_t is only ϵ away from G for all t with $|t| < |t_\epsilon|$ and with respect to the uniform metric. Thus, we get as an upper bound:

$$\int \frac{\iota(F_t,s,r)\cdot \mathbf{1}(s<u)\cdot v}{1-F_t(s,\tau)}\,\mathrm{d}G_(u,v) + 2\epsilon \sup_{(u,v)\in[0,\tau]^2}\left(\frac{\iota(F_t,s,r)\cdot \mathbf{1}(s<u)\cdot v}{1-F_t(s,\tau)}\right)$$

The supremum in the latter display will eventually be bounded for $|t|$ small enough. As a consequence, the second addend can be made arbitrarily small by choice of ϵ. Now substract from the first addend in the latter display the supposed limit and consider

$$\begin{aligned}
&\sup_{s\in[0,\tau]}\left|\int\left(\frac{\iota(F_t,s,r)}{1-F_t(s,\tau)} - \frac{\iota(F,s,r)}{1-F(s,\tau)}\right)\cdot \mathbf{1}(s<u)\cdot v\,\mathrm{d}G(u,v)\right| \\
&\quad \leq \sup_{s\in[0,\tau]}\left|\frac{\iota(F_t,s,r)}{1-F_t(s,\tau)} - \frac{\iota(F,s,r)}{1-F(s,\tau)}\right|\cdot \sup_{s\in[0,\tau]}\left|\int \mathbf{1}(s<u)\cdot v\,\mathrm{d}G(u,v)\right|
\end{aligned}$$

The integral on the right hand side of the latter display is bounded via the integration by parts formula. (Note that G itself is uniformly bounded and the limits of integration are finite.) The first supremum on the right hand side of the latter display converges to 0 by construction of F_t. An lower bound of the first addend on the right hand side of (3.7) may be treated analogously.

For the second addend on the right hand side of (3.7), it suffices to consider

$$\left|\frac{1}{t}\left(\frac{\iota(F_t,s,r)}{1-F_t(s,\tau)} - \frac{\iota(F,s,r)}{1-F(s,\tau)}\right) - \frac{\iota(F,s,r)\cdot G(s,\tau)}{(1-F(s,\tau))^2}\right|,$$

which does not depend on the integration variables u and v. The latter display is equal to

$$\left| \frac{1}{t} \cdot \frac{\iota(F_t, s, r) \cdot (1 - F(s,\tau)) - \iota(F, s, r) \cdot (1 - F(s,\tau)) + \iota(F, s, r) \cdot t \cdot G_t}{(1 - F_t(s,\tau)) \cdot (1 - F(s,\tau))} - \frac{\iota(F, s, r) \cdot G(s,\tau)}{(1 - F(s,\tau))^2} \right| ,$$

which uniformly in s converges to 0.

Note that the proof shows that $\psi'_{0,F}$ as stated in the lemma is continuous. □

In the same manner one shows an analogous result for $\mathrm{E}\,(T \mid X_s = 1)$, but now restricted to a certain time interval $(q, r) \subsetneqq (0, \tau)$. The reason for the new restriction on left side of the time interval stems from the fact that the initial distribution of the process X_t is degenerated in state 0. As a consequence, we have to wait until the intermediate state is occupied with positive probability. Introduce for $q, r \in (0, \tau)$, $q < r$, $s \in [0, \tau]$ and functions $G \in D\,([0, \tau]^2)$

$$\tilde{\iota}(G, s, q, r) = \mathbf{1}(q < s < r) \cdot \mathbf{1}\,(1 - G(s,\tau) > 0) \cdot \mathbf{1}\,(G(s,\tau) - G(s,s) > 0)\,. \tag{3.8}$$

We have the following lemma:

Lemma 3.6. *Let $q < r \in (0, \tau)$ be fixed, such that $\tilde{\iota}(F, s, q, r)/(F(s,\tau) - F(s,s))$ is bounded away from infinity, i. e. $\tilde{\iota}(F, s, q, r)/(F(s,\tau) - F(s,s)) < b(q, r)$, $0 < b(q, r) < \infty$ for all $s \in (q, r)$ (with $0/0 := 0$). Then the mapping $\psi_1 : \{G \in D\,([0, \tau]^2) :\ G$ is a bivariate distribution function.$\} \to D\,([0, \tau])$, $G \mapsto \psi_1(G)$ with*

$$\psi_1(G)(s) := \int \frac{\tilde{\iota}(G, s, q, r) \cdot \mathbf{1}(0 < u \le s < v) \cdot v}{G(s,\tau) - G(s,s)}\, \mathrm{d}G(u, v)$$

is Hadamard-differentiable in F with derivative $\psi'_{0,F} : D\,([0, \tau]^2) \to D\,([0, \tau])$, $G \mapsto \psi'_{1,F}(G)$ with

$$\begin{aligned} \psi'_{1,F}(G)(s) \;:=\; & \int \frac{\tilde{\iota}(F, s, q, r) \cdot \mathbf{1}(0 < u \le s < v) \cdot v}{F(s,\tau) - F(s,s)}\, \mathrm{d}G(u, v) \\ & + \int \frac{\tilde{\iota}(F, s, q, r) \cdot \mathbf{1}(0 < u \le s < v) \cdot v \cdot (G(s,s) - G(s,\tau))}{(F(s,\tau) - F(s,s))^2}\, \mathrm{d}F(u, v), \end{aligned}$$

where the first integral on the right hand side in the last display is defined via integration by parts, if G is not of bounded variation.

We now get Hadamard-differentiability of the functional corresponding to $s \mapsto \phi(s)$ on a true subinterval of $(0, \tau)$.

Lemma 3.7. *Let $q < r \in (0, \tau)$ be fixed, such that the boundness assumptions of Lemma 3.4 and of Lemma 3.6 are fullfilled. Then $\psi : \{G \in D([0,\tau]^2) : G$ is a bivariate distribution function.$\} \to D([0,\tau])$, $\psi(G)(s) := \psi_1(G)(s) - \psi_0(G)(s) \cdot \tilde{\iota}(G,s,q,r)/\iota(G,s,r)$, is Hadamard-differentiable in F with derivative $\psi'_F : D([0,\tau]^2) \to D([0,\tau])$, $\psi'_F(G)(s) := \psi'_{1,F}(G)(s) - \psi'_{0,F}(G)(s) \cdot \tilde{\iota}(G,s,q,r)/\iota(G,s,r)$. (With $0/0 := 0$.)*

Proof of Lemma 3.7. The lemma follows immediately from Lemma 3.4 and Lemma 3.6 together with, e. g., Flett (1980), Theorem 4.2.3. Note that replacing ι by $\tilde{\iota}$ in Lemma 3.4 is of no consequence. □

Weak convergence of our estimator of expected change in LOS given status at time s, restricted to a proper subinterval of $(0, \tau)$ and properly standardized, towards a Gaussian limit now follows:

Theorem 3.8. *Let $q < r \in (0, \tau)$ be fixed, such that the boundness assumptions of Lemma 3.4 and of Lemma 3.6 are fullfilled. Let $\widehat{F}$ denote the bivariate empirical distribution function as in (3.3) and let G denote the Gaussian limit process of Theorem 3.3. Then*

$$\sqrt{n}\left(\psi(\widehat{F}) - \psi(F)\right) \xrightarrow{\mathcal{D}} \psi'_F(G) \text{ as } n \to \infty$$

on $D([0,\tau])$. Moreover,

$$\sqrt{n}\left(\psi(\widehat{F}) - \psi(F)\right) \text{ and } \psi'_F\left(\sqrt{n}(\widehat{F} - F)\right)$$

are asymptotically equivalent. The limit variable $\psi'_F(G)$ is a mean zero Gaussian process.

Proof of Theorem 3.8. The first assertion follows from Hadamard-differentiability of ψ at F, i. e. Lemma 3.7 and the delta method, e. g. van der Vaart and Wellner (1996), Theorem 3.9.4. The second assertion also follows from the delta method and the fact that the derivative ψ'_F is defined on the whole of $D([0,\tau]^2)$, rather than just on the subset of all bivariate distribution functions. Finally, the assertion that the limit is Gaussian follows from van der Vaart and Wellner (1996), Chapter 3.9.2. □

Remark 3.9. In the situation of Theorem 3.8, we also get asymptotic correctness of the bootstrap process. A precise statement of this assertion can be found in van der Vaart and Wellner (1996), Chapter 3.9.3, see also Gill

(1989). We rely on this, computing bootstrap standard errors in our data examples.

Note that the boundness assumptions of Lemma 3.4 and of Lemma 3.6 are fullfilled if we assume both $P(X_s = 0)$ and $P(X_s = 1)$ to be greater than some constant $c > 0$ on a proper subset of $(0, \tau)$. This is a reasonable assumption for our motivating data example. In fact, $s \mapsto P(X_s = 0)$ is decreasing with $P(X_0 = 0) = 1$. Recall that $\tau := \sup\{t : \ P(X_t \neq 2) > 0\}$, see (2.5). It also reasonable to assume that $P(X_s = 0) > 0$ for $s \in (0, \tau)$, i. e. a patient does not inescapably acquire a nosocomial infection, even if (s)he stays in hospital very long. Moreover, Figures 2.4 and 2.7 loosely suggest that we may assume $s \mapsto P(X_s = 1)$ to be first increasing and then decreasing. We will get back to this issue in Section 3.4 when looking at the data.

3.2.2 Hadamard-differentiability and weak convergence for expected change in LOS

In this section, we aim at showing Hadamard-differentiability for functionals corresponding to weighted summaries of ϕ. We first consider weighting according to $\mathrm{d}P^{T_0}$. More precisely, we want to show Hadamard-differentiability at $\psi(F)$ for a functional corresponding to $\int \mathbf{1}(q < s < r)\phi(s)\,\mathrm{d}P^{T_0}(s)$ with q and r as in Lemma 3.7. The composition of such a functional and ψ will also be Hadamard-differentiable according to the chain rule for Hadamard-differentiability, e. g. van der Vaart and Wellner (1996), Lemma 3.9.3. For such a result, we need not only know $\psi(F)$, but we also have to remember F. The following lemma is useful:

Lemma 3.10. *Let ψ be as in Lemma 3.7 and define $\widetilde{\psi} : \{G \in D([0,\tau]^2) :$ G is a bivariate distribution function.$\} \to D([0,\tau]) \times D([0,\tau])$,*

$$G \mapsto \widetilde{\psi}(G) := (\psi(G), G)\,,$$

where $D([0,\tau]) \times D([0,\tau])$ is endowed with the maximum supremum norm, i. e.:

$$\text{For } (x,y) \in D([0,\tau]) \times D([0,\tau]) : \ ||(x,y)|| := \max\{||x||, ||y||\}\,.$$

Then $\widetilde{\psi}$ is Hadamard-differentiable at F under the assumptions of Lemma 3.7 with derivative $\widetilde{\psi}'_F : D([0,\tau]^2) \to D([0,\tau]) \times D([0,\tau])$, $\widetilde{\psi}'_F(G) := (\psi'_F(G), G)$.

Proof of Lemma 3.10. Follows from the definition of Hadamard-differentiability and Lemma 3.7. □

Moreover, we have

Lemma 3.11. *Define for fixed $c > 0$ the mapping $\varphi : D([0,\tau]) \times \{G \in D([0,\tau]^2) : G$ is a bivariate distribution function, its total variation bounded by $c.\} \to \mathbb{R}$,*

$$(f, G) \mapsto \varphi(f, G) := \int f(x)\mathbf{1}\left(y \in [0,\tau]\right) \, \mathrm{d}G(x, y).$$

Then φ is Hadamard-differentiable at each (f, G) in the domain of φ with f of bounded variation. The derivative $\varphi'_{(f,G)} : D([0,\tau]) \times D([0,\tau]^2) \to \mathbb{R}$ is given as

$$\varphi'_{(f,G)}(a, b) := \int f(x)\mathbf{1}\left(y \in [0,\tau]\right) \, \mathrm{d}b(x, y) + \int a \, \mathrm{d}G,$$

where the first integral on the right hand side of the latter display is defined via integration by parts, if b is not of bounded variation.

Proof of Lemma 3.11. The proof runs completely analogous to the proving the 'usual' result on integration for functionals on $D([0,\tau]) \times \{G \in D([0,\tau]) :$ total variation of G bounded by some constant $c\}$, e. g. van der Vaart and Wellner (1996), Lemma 3.9.17. It is of no consequence that G is a bivariate distribution function, since integration is only carried out with respect to the marginal distribution corresponding to the first argument of G. ($\mathbf{1}\left(y \in [0,\tau]\right)$ is constantly equal to 1.) □

Remark 3.12. Note that, for some suitable constant c, we have:

$$\begin{aligned} \varphi\left(\widetilde{\psi}(F)\right) &= \int \psi(F)(s) \cdot \mathbf{1}\left(t \in [0,\tau]\right) \, \mathrm{d}F(s, t) \\ &= \int \mathbf{1}(q < s < r) \cdot \phi(s) \, \mathrm{d}P^{T_0}(s), \end{aligned}$$

which is the expected change in LOS associated with an IE as defined in (2.16), but *restricted* to some time interval $(q, r) \subsetneq (0, \tau)$. In Section 3.4, we will discuss for our data example that we may assume q and r to be close to left and right limit, respectively, of the support of the distribution of T_0S.

Weak convergence of our estimator of expected change in LOS (as weighted by the waiting time distribution in the initial state), restricted to a proper subinterval of $(0, \tau)$ and properly standardized, towards a Gaussian limit now follows. Also, the remark made on the correctness of the bootstrap in Remark 3.9 still holds.

Theorem 3.13. *Let $q < r \in (0, \tau)$ be fixed, such that the boundness assumptions of Lemma 3.4 and of Lemma 3.6 are fullfilled. Denote by $\widehat{\phi}$ and by $\widehat{P^{T_0}}$ the empirical counterparts of ϕ and P^{T_0}, respectively, which are derived as plug-in estimators from the bivariate empirical distribution function $\widehat{F}$ of (3.3). The plug-in procedure is described in Section 2.6.2. Also, let G denote the Gaussian limit process of Theorem 3.3. Then*

$$\sqrt{n}\left(\int \mathbf{1}(q < s < r) \cdot \widehat{\phi}(s)\, \mathrm{d}\widehat{P^{T_0}}(s) - \int \mathbf{1}(q < s < r) \cdot \phi(s)\, \mathrm{d}P^{T_0}(s)\right)$$

$$\xrightarrow{\mathcal{D}} \varphi'_{\psi_F, F} \circ (\psi'_F(G), G) \text{ as } n \to \infty$$

on $\mathbb{R}$. Moreover,

$$\sqrt{n}\left(\int \mathbf{1}(q < s < r) \cdot \widehat{\phi}(s)\, \mathrm{d}\widehat{P^{T_0}}(s) - \int \mathbf{1}(q < s < r) \cdot \phi(s)\, \mathrm{d}P^{T_0}(s)\right)$$

and

$$\varphi'_{\psi_F, F} \circ \left(\psi'_F(\sqrt{n}(\widehat{F} - F)), \sqrt{n}(\widehat{F} - F)\right)$$

are asymptotically equivalent. The limit variable $\varphi'_{\psi_F, F} \circ (\psi'_F(G), G)$ is a mean zero Gaussian process.

Proof of Theorem 3.13. The argument is analogous to the proof of Theorem 3.8 together with the chain rule for Hadamard-differentiability, e. g. van der Vaart and Wellner (1996), Lemma 3.9.3, and lemmas 3.10 and 3.11. □

We finally comment on the alternative weightings introduced and discussed in Section 2.3.2. We exemplary discuss weighting according to $\mathrm{d}P^{T_0|X_{T_0}=1}$. The assertions of Theorem 3.13 will hold in an analogous manner, if a variant of Lemma 3.10 holds, with the second entry, i. e. G, of the image of $\widetilde{\psi}(G)$ is replaced by a univariate 'conditional version'. Lemma 3.11 would then have to be slightly modified (φ would only take univariate distributions as a second argument), but this is of no consequence, cf. the proof of Lemma 3.11. Note that we have assumed that both state 1 and state 2 are entered with positive probability at T_0, cf. (2.10), and consider

$$\begin{aligned} P^{T_0|X_{T_0}=1}([0, s]) &= \frac{P(T_0 \le s, X_{T_0} = 1)}{P(X_{T_0} = 1)} \\ &= \frac{P(T_0 \le s, T_0 < T)}{P(T_0 < T)} \\ &= \frac{\int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}F(x, y)}{\int \mathbf{1}(x < y)\, \mathrm{d}F(x, y)} \end{aligned}$$

It suffices to consider the following lemma.

Lemma 3.14. *Let* $\rho : \{G \in D([0,\tau]^2) : G \text{ is a bivariate distribution function.}\} \to D([0,\tau])$, $G \mapsto \rho(G)$ *with*

$$\rho(G)(s) := \frac{\int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}G(x,y)}{\int \mathbf{1}(x < y)\, \mathrm{d}G(x,y)}$$

Then ρ *is Hadamard-differentiable in* F *with derivative* $\rho'_F : D([0,\tau]^2) \to D([0,\tau])$ *given as*

$$\begin{aligned}\rho'_F(G)(s) \;:=\; & \frac{\int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}G(x,y)}{\int \mathbf{1}(x < y)\, \mathrm{d}F(x,y)} \\ & - \frac{\int \mathbf{1}(x < y)\, \mathrm{d}G(x,y) \cdot \int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}F(x,y)}{\left(\int \mathbf{1}(x < y)\, \mathrm{d}F(x,y)\right)^2},\end{aligned}$$

where integrals with respect to G *are defined via integration by parts, if* G *is not of bounded variation.*

Proof of Lemma 3.14. As in the proof of Lemma 3.4 define $F_t := F + t \cdot G_t$ with $t \to 0$ and $G_t \to G$, such that F_t is in the domain of ρ. Consider

$$\begin{aligned}&\frac{1}{t} \cdot \left(\frac{\int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}F_t(x,y)}{\int \mathbf{1}(x < y)\, \mathrm{d}F_t(x,y)} - \frac{\int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}F(x,y)}{\int \mathbf{1}(x < y)\, \mathrm{d}F(x,y)} \right) \\ &= \frac{\int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}G(x,y)}{\int \mathbf{1}(x < y)\, \mathrm{d}F_t(x,y)} + \frac{1}{t} \cdot \int \mathbf{1}(x \le s) \cdot \mathbf{1}(x < y)\, \mathrm{d}F(x,y) \\ &\qquad \cdot \left[\frac{1}{\int \mathbf{1}(x < y)\, \mathrm{d}F_t(x,y)} - \frac{1}{\int \mathbf{1}(x < y)\, \mathrm{d}F(x,y)} \right]\end{aligned}$$

It suffices to consider the term in square brackets in the latter display times $1/t$. It is equal to

$$\frac{1}{t} \cdot \frac{-t \cdot \int \mathbf{1}(x < y)\, \mathrm{d}G_t(x,y)}{\int \mathbf{1}(x < y)\, \mathrm{d}F(x,y) \cdot \mathbf{1}(x < y)\, \mathrm{d}F_t(x,y)}$$

and the desired result now follows. □

3.3 Censored situation

In the censored situation, we essentially need a censored variant of Theorem 3.3 stating weak convergence of an estimator of the censored bivariate distribution function. The remainder of Section 3.2 then carries over without further ado. By 'censored situation' we mean: The data are subject to

independent right-censoring, see Andersen et al. (1993), Chapter III.2.2 for a formal definition.

Indeed, such weak convergence results exist for general bivariate survival, most prominent, perhaps, on the Dabrowska estimator (Dabrowska 1989). However, the general bivariate survival set-up is difficult, where little can be assumed about the two waiting times except for them *not* being independent. (Think of twins, for instance.) Our situation is much easier, where the relationship between the two waiting times T_0 and T can be described in terms of the multi-state model. Consequently, we want to study estimation based on the Aalen-Johansen estimator of the transition matrix. Recall that by Equation (2.22)

$$F(s,t) = P_{01}(0,s) \cdot P_{12}(s,t) + P_{02}(0, \min(s,t))$$

for $(s,t) \in [0,\tau]^2$. Equation (2.23) defines the plug-in estimator we want to study:

$$[0,\tau]^2 \ni (s,t) \mapsto \widehat{F}(s,t) := \widehat{P}_{01}(0,s) \cdot \widehat{P}_{12}(s,t) + \widehat{P}_{02}(0, \min(s,t)),$$

where $\widehat{P}_{\cdot\cdot}$ are the respective entries of the Aalen-Johansen estimator $\widehat{\mathbf{P}}$ described in Section 2.6. In order to show weak convergence of $\widehat{F}$ we first discuss weak convergence of

$$\left\{(s,t) \in [0,\tau]^2 : \ s \leq t\right\} \ni (s,t) \mapsto \widehat{\mathbf{P}}(s,t).$$

We then show that $\widehat{F}$ can be expressed as an image of $\widehat{\mathbf{P}}$ under an Hadamard-differentiable functional; the desired result then follows again by the delta method. Note that the restriction to $s \leq t$ in the latter display is of no consequence, since this is where F and every $\widehat{F}$ have mass only.

Note that we do need convergence of $(s,t) \mapsto \widehat{\mathbf{P}}(s,t)$ as a *bivariate* function. In their original paper on the estimator named after the authors, Aalen and Johansen (1978) show convergence of $t \mapsto \widehat{\mathbf{P}}(0,t)$ using a martingale central limit theorem, as does the detailed treatment of the Aalen-Johansen estimator by Andersen et al. (1993), Chapter IV.4, see in particular their Theorem IV.4.2. The latter authors also offer a proof based on writing the transition matrix $\mathbf{P}$ as a product integral with respect to the matrix of integrated transition intensities $\mathbf{A}(t) := (A_{hj}(t))$, i. e.

$$\mathbf{P}(s,t) = \prod_{(s,t]} (\mathbf{I} + \mathrm{d}\mathbf{A}(u)),$$

where we write $\mathbf{I}$ for the identity matrix and $\prod$ for the product integral. They then use Hadamard-differentiability of the product integral and the

respective convergence result on the Nelson-Aalen estimator of $\mathbf{A}$ to show the desired result. See Andersen et al. (1993), Chapter II.6 as well as Gill and Johansen (1990) and Gill (1994) for details on product integration. We may hope for the desired result on convergence for $(s,t) \mapsto \widehat{\mathbf{P}}(s,t)$ along the latter lines, if we have Hadamard-differentiability of the product integral taking *interval* functions as an argument. In fact, such a result is shown to hold by Gill and Johansen (1990), Theorem 8. Gill and Johansen (1990) also envisage the desired application (on page 1542), but then turn to more probabilistic issues.

We now first state the convergence result for $(s,t) \mapsto \widehat{\mathbf{P}}(s,t)$ in a manner analogous to Andersen et al. (1993), Theorem IV.4.2. We then derive the convergence result for $(s,t) \mapsto \widehat{F}(s,t)$ by means of the delta method. To do so, we need counting process notation. Let $(X_t^{(1)})_t, (X_t^{(2)})_t, \ldots, (X_t^{(n)})_t$, $i = 1, \ldots, n$, denote n stochastic processes, all with initial distribution degenerated in state 0 and right-continuous sample paths, that are independent replicates of $(X_t)_t$. The relationship to the observations $(T_0^{(i)}, T^{(i)})$, $i = 1, \ldots, n$ of the uncensored case, cf. Section 3.2, is given by means of

$$T^{(i)} := \inf \left\{ t \geq 0 : \, X_t^{(i)} \notin \{0,1\} \right\}.$$

and

$$T_0^{(i)} := \inf \left\{ t \geq 0 : \, X_t^{(i)} \neq 0 \right\},$$

cf. Equations (2.7) and (2.8). Closely following Andersen et al. (1993), Chapter VI.4, define the 3-variate counting process $\mathbf{N}(t) := (N_{hj}; h \neq j)\,(t)$, where $N_{hj}(t)$ counts the number of observed transitions from state h to state j in $[0,t]$, i. e.

$$\begin{aligned} N_{hj}(t) \;:=\; & \Big| \Big\{ i \in \{1, \ldots, n\} : \text{There is } u \in [0,t] \text{ such that } X_{u-}^{(i)} = h \text{ and} \\ & X_u^{(i)} = j \Big\} \Big| \end{aligned} \tag{3.9}$$

Note that the multi-state model of Figure 2.1 allows three possible transition types and no backward transitions. Let $Y_h(t)$ denote the number of sample paths observed to be in state h just prior to time t, i. e.

$$Y_h(t) := \left| \left\{ i \in \{1, \ldots, n\} : X_{t-}^{(i)} = h \right\} \right|, \tag{3.10}$$

and let $J_h(t)$ denote whether there are sample paths observed to be in state h at all just prior to time t, i. e.

$$J_h(t) := \mathbf{1}\left(Y_h(t) > 0\right). \tag{3.11}$$

As usual, we understand $J_h(t)/Y_h(t)$ to be zero, if $Y_h(t)$ is zero. Also, define the intensity process $\boldsymbol{\lambda} := (\lambda_{hj}; h \neq j)$, where

$$\lambda_{hj}(t) := Y_h(t) \cdot \alpha_{hj}(t). \tag{3.12}$$

Note however that Andersen et al. (1993) make different use of the letter 'τ' in their Chapter VI.4 on the Aalen-Johansen estimator. We have defined τ as $\tau := \sup\{t : \ P(X_t \neq 2) > 0\}$ and assume τ to be finite, cf. Section 2.1. Andersen et al. (1993) use the letter for $\sup\{u : \ \int_0^u \alpha_{hj}(t)\,\mathrm{d}t < \infty,\ h \neq j\}$ and show properties of the Aalen-Johansen estimator on time intervals with right limits less than this supremum. Since in our setting the supremum is equal to infinity, see Equation 2.6, such properties hold for $[0, \tau]$. Also note that the processes N_{hj}, Y_h, J_h and λ_{hj} depend on the sample size n, but we have suppressed this in the notation.

As stated at the beginning of this section, we assume our observations to be subject to *independent* right-censoring. Intuitively, this is to say that the intensity process $\boldsymbol{\lambda}$ at time t is not altered by knowing about the right-censoring times up to $t-$.

We are now ready to state the convergence result for $(s,t) \mapsto \widehat{\mathbf{P}}(s,t)$.

Theorem 3.15. *Let the process $(X_t)_t$ as defined in Section 2.1 be Markovian. Assume the assumptions of Andersen et al. (1993), Theorem IV.1.2 on weak convergence of the multivariate Nelson-Aalen estimator to hold, i. e.: Assume that there exist non-negative functions y_h with domain $[0, \tau]$ such that α_{hj}/y_h is integrable over $[0, \tau]$ for all $h \neq j$. Let*

$$\sigma_{hj} := \int_0^t \frac{\alpha_{hj}(u)}{y_h(u)}\,\mathrm{d}u$$

for $h \neq j$ and assume the following conditions (A)–(C) to hold:
(A) For every t in $[0, \tau]$ and all $h \neq j$:

$$n \int_0^t \frac{J_h(u)}{Y_h(u)} \cdot \alpha_{hj}(u)\,\mathrm{d}u \xrightarrow{P} \sigma_{hj}(t) \ \text{as } n \to \infty.$$

(B) For all $\epsilon > 0$ and all $h \neq j$:

$$n \int_0^\tau \frac{J_h(u)}{Y_h(u)} \cdot \alpha_{hj}(u) \cdot \mathbf{1}\left(\left|\sqrt{n} \cdot \frac{J_h(u)}{Y_h(u)}\right|\right) \mathrm{d}u \xrightarrow{P} 0 \ \text{as } n \to \infty.$$

(C) For all $h \neq j$:

$$\sqrt{n} \cdot \int_0^\tau (1 - J_h(u)) \cdot \alpha_{hj}(u)\,\mathrm{d}u \xrightarrow{P} 0 \ \text{as } n \to \infty.$$

Furthermore, let $U = (U_{hj})$ *be a* 3×3 *matrix valued process, such that the non-diagonal elements* U_{hj}, $h \neq j$ *are independent Gaussian martingales with* $U_{hj}(0) = 0$ *and* $\mathrm{Cov}(U_{hj}(t_1), U_{hj}(t_2)) = \sigma_{hj}(\min(t_1, t_2))$, *and diagonal elements* $U_{hh} := -\sum_{j \neq h} U_{hj}$. *Then we have*

$$(s,t) \mapsto \sqrt{n} \cdot \left(\widehat{\mathbf{P}}(s,t) - \mathbf{P}(s,t) \right) \xrightarrow{\mathcal{D}} (s,t) \mapsto \int_s^t \mathbf{P}(s,u) \, \mathrm{d}U(u) \mathbf{P}(u,t)$$

on the space of 3×3*-matrix valued, bivariate cadlag functions with domain* $[0,\tau]^2$, *where the norm of a matrix* (M_{hj}) *is defined as* $||(M_{hj})|| := \max_h \sum_j ||(M_{hj})||$.

Proof of Theorem 3.15. The proof runs completely analogous to the proof of Andersen et al. (1993), Theorem IV.4.2 based on the delta method (a martingale-based proof is also presented), but with the slightly more general result on Hadamard-differentiability for product integration offered in Gill and Johansen (1990), Theorem 8: The assumptions (A)–(C) imply convergence of $\sqrt{n}(\hat{\mathbf{A}} - \mathbf{A})$, see Andersen et al. (1993), Theorem IV.1.2, where $\hat{\mathbf{A}}$ denotes the Nelson-Aalen estimator of the integrated transition intensities $\mathbf{A}$. Since $\mathbf{P}(s,t) = \prod_{(s,t]} (\mathbf{I} + \mathrm{d}\mathbf{A}(u))$ is an Hadamard-differentiable functional of the integrated transition intensities, the assertion of the theorem follows via the delta method. □

Remark 3.16. The validity of the assumptions of Theorem 3.15 for finite-state Markov processes is discussed by Andersen et al. (1993), Example IV.1.9. The Markov assumption itself may be relaxed: Datta and Satten (2001) discuss the Aalen-Johansen estimator to be consistent for non-Markovian data, and claim that an asymptotic distribution theory is feasible. Glidden (2002) appears to be the first to offer such results, also using Hadamard-differentiability of product integration. Aalen et al. (2001), in a paper on covariate adjustment for the Aalen-Johansen estimator, discuss that consequently the Markov assumption may be less essential than thought earlier, but point out that it is not clear how to apply the lines of Datta and Satten (2001) and Glidden (2002) to the treatment of covariates (then available to the authors in form of technical reports). We have chosen to stay in the more classical framework of Markov processes for a straightforward presentation of the results, with the book by Andersen et al. (1993) as a ready reference. Of particular importance to us is the immediate connection to the work of Gill and Johansen (1990) on product integration and interval functions, since we have been treating the impact of the intermediate on the terminal event as a random time interval situation. Starting out from a multistate point of view, we have based estimation on the Aalen-Johansen estimator of the transition matrix, which is a natural to consider in a multistate

framework. Alternatively, we could have chosen to use one of the available estimators for bivariate survival and associated results on weak convergence (in particular Dabrowska (1989) and Lin and Ying (1993)), which do not require to assume X_t to be Markovian. The remainder of our treatment would remain unaffected. We discuss the connection to bivariate survival in greater detail in Chapter 5.1, see in particular Chapter 5.1.3.

We should note that for our motivating data problem (for which the Markov assumption may be questioned) the temporal dynamics by which the intermediate event occurs is the key issue, less so censoring and consequently the Markov assumption.

To derive a convergence result for $\widehat{F}$ we first need a result on differentiability:

Lemma 3.17. *Let us call a bivariate, real-valued function an* interval function *on $[0,\tau]^2$, if it only takes arguments $(s,t) \in [0,\tau]^2$ with $s \leq t$. Consider a functional ρ with domain*

$$\left\{ f : f : [0,\tau] \supseteq [s,t] \mapsto \big(f_{hj}(s,t)\big)_{h,j=1,2,3} \text{ with } \sup_{(s,t)} |f_{hj}(s,t)| < \infty \right\}$$

into the set of all interval functions on $[0,\tau]^2$ with

$$\rho(f)(s,t) := f_{01}(0,s) \cdot f_{12}(s,t) + f_{02}(0,s).$$

Endow the set of interval functions with the supremum norm and the domain of ρ with the induced matrix norm $||(f_{hj})|| := \max_h \sum_j ||(f_{hj})||$. Then ρ is Hadamard-differentiable in $[s,t] \mapsto \mathbf{P}(s,t)$ with derivative $\rho'_{\mathbf{P}}$ given as

$$\rho'_{\mathbf{P}}(f)(s,t) := f_{01}(0,s) \cdot P_{12}(s,t) + f_{12}(s,t) \cdot P_{01}(0,s) + f_{02}(0,s).$$

Proof of Lemma 3.17. Consider $t \to 0$ and $f_t \to f$ such that $\mathbf{P} + t \cdot f_t$ is in the domain of ρ. Consider

$$\begin{aligned}
&\frac{1}{t} \cdot \big(\rho(\mathbf{P} + t \cdot f_t) - \rho(\mathbf{P})\big)(s,t) = \\
&\quad \frac{1}{t} \cdot \big(P_{01}(0,s) \cdot t \cdot f_{t,12} + P_{12}(s,t) \cdot t \cdot f_{t,01}(0,s) + t^2 \cdot f_{t,01}(0,s) \cdot f_{t,12}(s,t) \\
&\quad + t \cdot f_{t,02}(0,s)\big)
\end{aligned}$$

The assertion of the lemma now follows considering each addend in the preceding display separately. □

Since $\rho(\mathbf{P}) = F$, we can now invoke the delta method and get from Theorem 3.15 together with Lemma 3.17 the following theorem:

Theorem 3.18. *Let U be as in Theorem 3.15 and define*

$$Z(s,t) := \int_s^t \mathbf{P}(s,u)\,\mathrm{d}U(u)\mathbf{P}(u,t)$$

for $s \leq t \in [0,\tau]$. Assume the assumptions of Theorem 3.15 to hold. Then with ρ, $\rho'_{\mathbf{P}}$ as in Lemma 3.17 we have

$$\sqrt{n}\left(\widehat{F} - F\right) \xrightarrow{\mathcal{D}} \rho'_{\mathbf{P}}(Z).$$

on the set of all interval functions on $[0,\tau]^2$, endowed with the supremum norm. Moreover,

$$\sqrt{n}\left(\widehat{F} - F\right) \text{ and } \rho'_{\mathbf{P}}\left(\sqrt{n}(\widehat{\mathbf{P}} - \mathbf{P})\right)$$

are asymptotically equivalent. The limit variable $\rho'_{\mathbf{P}}(Z)$ is a mean zero Gaussian process.

Remark 3.19. The result of the preceding Theorem 3.18 can be immediately extended to the 'complete' index set $[0,\tau]^2$ by noting that for $s > t \in [0,\tau]$ we have $F(s,t) = F(t,t)$ and $\widehat{F}(s,t) = \widehat{F}(t,t)$, see also Section 2.6.1.

3.4 Examples

Applying the results of this chapter to the data examples of Section 2.7.1 and Section 2.7.4 in order to compute confidence intervals, we essentially need to be concerned whether the the boundness assumptions of Lemma 3.4 and of Lemma 3.6 are fullfilled. In Remark 3.9, we have discussed that these assumptions are fullfilled if both $P(X_s = 0)$ and $P(X_s = 1)$ are greater than some constant $c > 0$ on a proper subset of $(0,\tau)$. In particular, we have discussed that $s \mapsto P(X_s = 0)$ is decreasing on $[0,\tau]$ and can be assumed to be strictly positive on $[0,\tau)$. Figures 3.2 and 3.3 show $s \mapsto \widehat{P}(X_s = 1) = \widehat{P}_{01}(0,s)$ for the SIR 3 data and the data used by Schulgen and Schumacher (1996). The curves agree with assuming $P(X_s = 1)$ to be greater than some $c > 0$ on a proper subset of $(0,\tau)$. They even suggest that $s \mapsto P(X_s = 1)$ may be assumed to be first increasing and then decreasing on $[0,\tau]$. In Remark 3.9, we argued that we may assume that a patient does not inescapably acquire a nosocomial infection, even if (s)he stays in hospital very

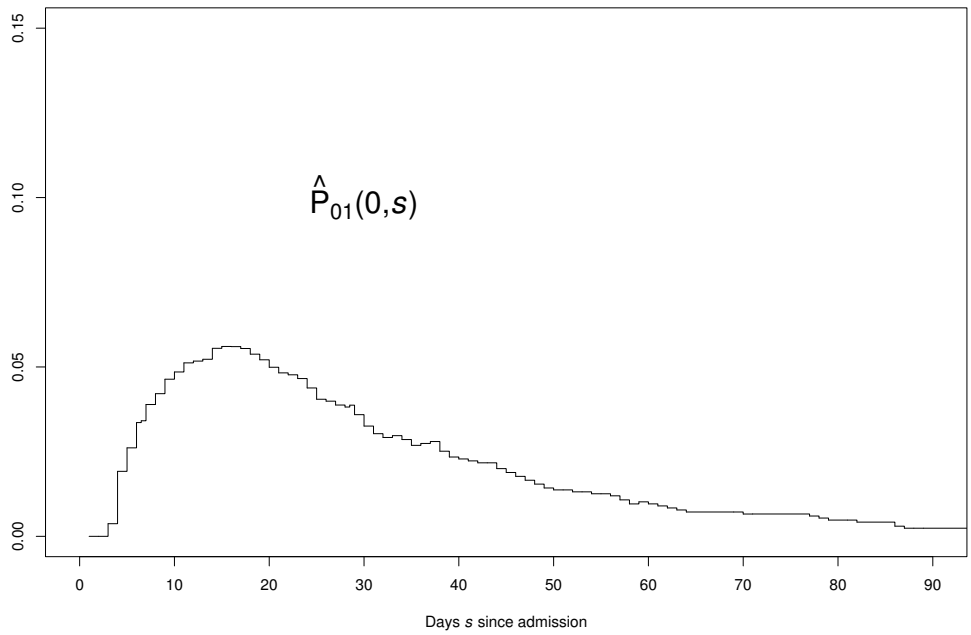

Figure 3.2: Aalen-Johansen estimator of $P(X_s = 1)$ for the SIR 3 data.

long. The assumptions is still reasonable the other way round: Of course, we can assume that a patient is not necessarily free of a a nosocomial infection, even if (s)he stays in hospital very long. Consequently, we may assume $P(X_s = 1)$ to be strictly positive close to (but unequal to) τ. Thus, we may assume the boundness assumptions to hold on some proper subinterval (q, r), where r can be chosen arbitrarily close to τ. In order to determine possible choices of q, note that a usual requirement in studies on hospital-acquired infections is that patients have been in hospital for at least 48 hours. Infections occurring before that time are rarely considered nosocomial due to lack of a sufficiently long incubation period, but infections occurring after that time usually are. Consequently, we may assume q to be arbitrarily close to (but greater than) 2. Table 3.1 displays results for the estimates of Section 2.7, where we now reinterpret the point estimates as estimates of appropriately weighted integrals of $\mathbf{1}(q < s < r) \cdot \phi(s)$. We have argued in this section, that the difference between an appropriately weighted integral of $\phi(s)$ and of $\mathbf{1}(q < s < r) \cdot \phi(s)$, respectively, is of no practical importance, since the results may be assumed to hold for any interval $(q, r) \subsetneqq [2, \tau]$.

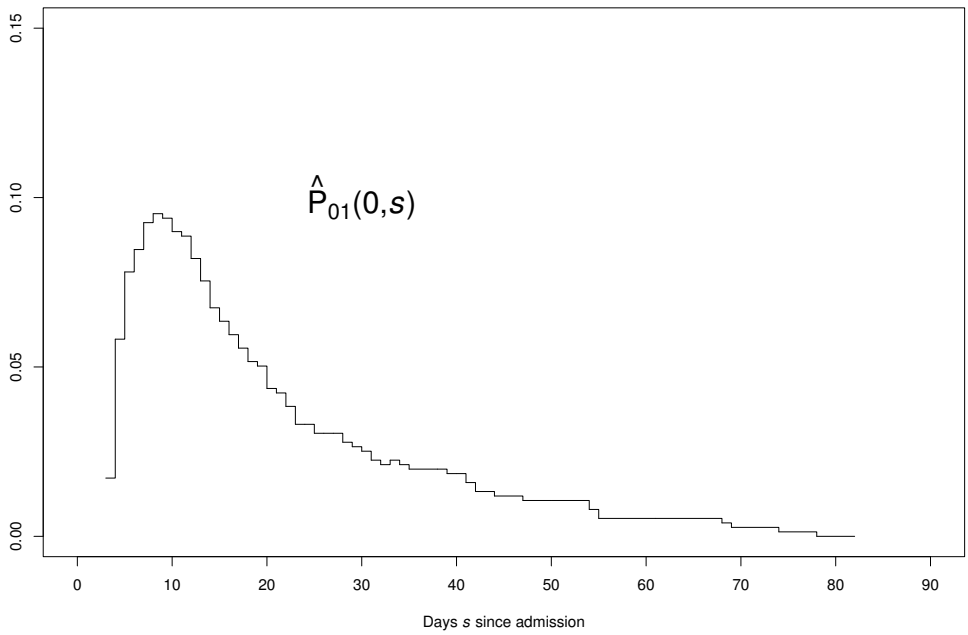

Figure 3.3: Aalen-Johansen estimator of $P(X_s = 1)$ for the data originally used by Schulgen and Schumacher (1996).

3.5 Discussion

In Chapter 5, we will argue that the program pursued in this chapter constitutes a meaningful and general framework to discuss intermediate events and their impact on some terminal event.

We have used a multi-state model to describe the occurrence of the intermediate event. Since multi-state models can be thought of as a generalization of survival analysis in terms of states rather than time dimensions, it is however not immediately clear why one should not apply a martingale limit theorem to get the desired results. In particular, a martingale-based proof may be more instructive than a proof on Hadamard-differentiability. We therefore briefly discuss problems in applying the martingale central limit theorem (Rebolledo 1980) as presented in Andersen et al. (1993), Chapter II.5.1. We will see that these difficulties pertain to two essential issues of the situation at hand, namely the timing of events and the question whether its fruitful to adopt a time-bivariate view.

To simplify things, we only consider the uncensored case. We use counting process notation as in Section 3.3. In addition, let us denote by $N_{0\bullet}(t) :=$

weighting	point estimate	95%-confidence interval
	SIR 3 study	
$\mathrm{d}P^{T_0}$	4.9	$[-0.7, 10.6]$
$\mathrm{d}P^{T_0\mid X_{T_0}=1}$	6.2	$[1.1, 11.3]$
$\mathrm{d}P^{T_0\mid X_{T_0}=2}$	4.8	$[-1.0, 10.6]$
	Data used by Schulgen and Schumacher (1996)	
$\mathrm{d}P^{T_0}$	2.0	$[-0.3, 4.2]$
$\mathrm{d}P^{T_0\mid X_{T_0}=1}$	2.1	$[-0.3, 4.5]$
$\mathrm{d}P^{T_0\mid X_{T_0}=2}$	2.0	$[-0.3, 4.2]$

Table 3.1: Point estimates with confidence intervals for restricted change in LOS as explained in Section 3.4.

$N_{01}(t)+N_{02}(t)$ the number of transitions out of the initial state 0 in the time interval $[0,t]$. Our estimator of $\int \phi \,\mathrm{d}P^{T_0}$ equals a weighted sum of differences of arithmetic means:

$$\frac{1}{n}\int \sum_{i=1}^{n}\left(\frac{\mathbf{1}(X_s^{(i)}=1)}{Y_1(s+)}-\frac{\mathbf{1}(X_s^{(i)}=0)}{Y_0(s+)}\right) J_0(s+)\cdot J_1(s+)\cdot T^{(i)}\,\mathrm{d}N_{0\bullet}(s),$$

where the sample size is n. To make Rebolledo's theorem work, we need the integrand in the latter display to be predictable with respect to the self-exciting filtration of the three-variate counting process $(N_{01}, N_{02}, N_{12})(t)$, i. e. with respect to $\sigma((N_{01}, N_{02}, N_{12})(s) : s \le t)$. It is not: Right from the start, we will need to know $T^{(i)}$, $i = 1, \ldots, n$. This issue touches upon the temporal dynamics of the data: So far, we have argued that accounting for the timing of the events is crucial: an infection can only have an effect once it has occurred.

We may rewrite the estimator: Rather than counting transitions out of the initial state, we count transitions into the absorbing state. At $T^{(i)}$ those $T_0^{(j)}$'s are known at which the i-th patient was in state 0 and at which (s)he was in state 1. It is as straightforward exercise that our estimator equals

$$\frac{1}{n}\sum_{i=1}^{n}\left(\sum_{\{j:\,T_0^{(i)}\le T_0^{(j)}<T^{(i)}\}}\frac{J(T_0^{(j)}+)}{Y_1(T_0^{(j)}+)}\;-\sum_{\{j:\,T_0^{(j)}<T_0^{(i)}\}}\frac{J(T_0^{(j)}+)}{Y_0(T_0^{(j)}+)}\right)\cdot T^{(i)}.$$

We may now aim at rewriting the sum with index i in the latter display as an integral with respect to a counting process $N_{\bullet 2} := N_{02}+N_{12}$, counting the

transitions into the absorbing state. The integrand, however, will depend on the individual waiting time $T_0^{(i)}$ in the initial state. We would therefore have to rewrite the latter display in terms of *patient-individual* counting processes. If in such a setting the conditions of Rebolledo's theorem can be verified, we do not know. The major difficulty is this: By having to consider individual rather than aggregated counting processes and by integrating with respect to a counting measure that informs us about LOS, but not about the waiting time in the initial state, we are left with the impression that not 'enough randomness' is 'aggregated' in the counting measure. This touches upon the second crucial issue: It would be nice to have a counting process that informs us both about the waiting time in state 0 and about the waiting time in the sub-state-space $\{0, 1\}$ at the moment of 'click'. This leads us to adopting a time-bivariate view. However, we then loose our intuitive notion of past and future as briefly described in Section 3.1.

Chapter 4

Change in length of stay associated with an intermediate event, distinguished for competing endpoints ‘death’ and ‘discharge’

Looking at length of stay as such does not distinguish whether a patient has been discharged or died, although the individual implications are contrarian. In terms of change in LOS, a nosocomial infection may prolong the time in hospital among patients discharged. But one can imagine a severe infection to even expedite death among patients deceased. In this chapter, We discuss how to distinguish between patients discharged and patients deceased in terms of change in LOS. Note that this question is not only of importance to the hospital example: If we are interested, say, in how pregnancy affects time to marriage for unmarried couples, we may want to account for the competing event that the couple splits. If we study the effect of some training program on the time of unemployment, say, we will possibly need to account for retirement as a competing event. We will, in the following, term the competing events ‘discharge’ and ‘death’ for linguistic ease. We first need to make some adjustments to the underlying stochastic process.

4.1 A multistate model with competing endpoints

Let $(X_t)_{t\in[0,\infty)}$ be a nonhomogeneous, continuous-time stochastic process with right-continuous sample paths as in Chapter 2.1, but with state-space $\{0, 1, 2, 3\}$. The state-space together with its possible transitions is illustrated in Figure 4.1 for the example of nosocomial infections.

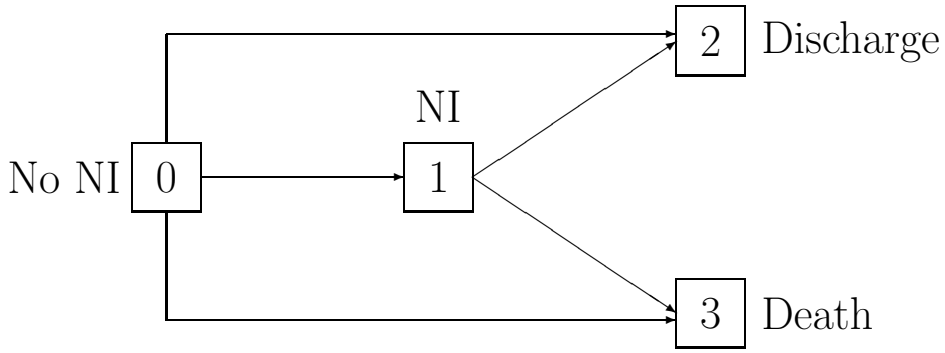

Figure 4.1: Potential states and transitions for occurrence of nosocomial infection (labelled 'NI') with competing absorbing states 'discharge' and 'death'.

The interpretations of states 0 and 1 remain the same, but we now distinguish two absorbing states, 'discharge' (state 2) and 'death' (state 3). We need to make few modifications of the quantities defined in Chapter 2.1. Transition probabilities $P_{hj}(s,t)$ and transition intensities $\alpha_{hj}(t)$ are now defined for $h, j \in \{0, 1, 2, 3\}$. Equation (2.5) now becomes

$$\tau := \sup\{t : \ P(X_t \notin \{2, 3\}) > 0\}. \tag{4.1}$$

(This is not a major modification; we could have originally defined τ as $\sup\{t : \ P(X_t \in \{0, 1\}) > 0\}$.) The definitions of the waiting time T_0 in the initial state and the waiting time T in the sub-state space $\{0, 1\}$, respectively, carry over without modification. However, knowing (T_0, T) does not suffice anymore to completely determine the state of the stochastic process X_t at any time t. We additionally need the 'mark' X_T telling us, which absorbing

state is entered at the random time T:

$$\left\{ \begin{array}{lcl} X_t = 0 & \Longleftrightarrow & t < T_0 \\ X_t = 1 & \Longleftrightarrow & T_0 \leq t < T \\ X_t = 2 & \Longleftrightarrow & T \leq t \text{ and } X_T = 2 \\ X_t = 3 & \Longleftrightarrow & T \leq t \text{ and } X_T = 3 \end{array} \right\}. \tag{4.2}$$

We assume that both state 2 and state 3 are entered with positive probability at T:

$$P(X_T = 2) \cdot P(X_T = 3) > 0. \tag{4.3}$$

Finally, we define for $s \geq 0$, $t \geq 0$ and $i = 2, 3$

$$F(s, t, i) := P(T_0 \leq s,\, T \leq t \text{ and } X_T = i), \tag{4.4}$$

a 'marked' variant of the joint distribution function of (T_0, T). Slightly abusing parlance, we will call F the *joint distribution function of* (T_0, T, X_T). (Although we have not defined $F(s, t, i)$ as $P(T_0 \leq s,\, T \leq t,\, X_T \leq i)$, but an order on the mark space $\{2, 3\}$ would be arbitrary anyways.) We also write

$$F(s, t, \{2, 3\}) := P(T_0 \leq s, T \leq t).$$

4.2 Expected change in LOS given status at time s, distinguished for competing endpoints 'death' and 'discharge'

In the present subsection, we again look at a fixed, but arbitrary time $s > 0$, as we did in Chapter 2.2. Weighting with respect to s will then carry over in a manner analogous to Chapter 2.3. Let us assume that s is such that

$$P(X_s = 1) > 0 \text{ and } P(X_s = 0) > 0.$$

Note that this is the assumption of (2.12) of Chapter 2.2.

The situation at hand is one of competing events or 'competing risks'. The time T of hospital stay is terminated by either reaching state 2 (discharge) or state 3 (death). The occurrence of these events is mutually exclusive. Thus, the state of the process at the random time T, i. e. X_T, denotes, in competing risks terminology, the 'cause' for leaving hospital.

In competing risks, one often looks at the cumulative incidence function in order to consider different 'causes' (or absorbing states), cf., e. g., Andersen et al. (2002) for a recent reference. In our situation, the cumulative

incidence function is the joint distribution of the time T of hospital stay and the reason X_T for leaving hospital being discharge or death, respectively. This suggests to decompose $\phi(s)$ as follows:

$$\begin{aligned}\phi(s) &= \mathrm{E}\left(T \,|\, X_s = 1\right) - \mathrm{E}\left(T \,|\, X_s = 0\right) \\ &= \sum_{i=2,3} \mathrm{E}\big(T \cdot \mathbf{1}\left(X_T = i\right) | X_s = 1\big) - \mathrm{E}\big(T \cdot \mathbf{1}\left(X_T = i\right) | X_s = 0\big)\end{aligned} \tag{4.5}$$

However, this will not serve our purpose. To see this, consider a situation where an infection at time s is virtually lethal, while being uninfected at time s is 'protective', i. e. an uninfected patient is very likely to be eventually discharged. The latter might, e. g., be the case if the lethal infection is rare. The addend from Equation (4.5) for patients who eventually die is:

$$\begin{aligned}&\mathrm{E}\big(T \cdot \mathbf{1}\left(X_T = 3\right) | X_s = 1\big) - \mathrm{E}\big(T \cdot \mathbf{1}\left(X_T = 3\right) | X_s = 0\big) \\ &= \int \underbrace{\frac{\mathbf{1}\left(X_s = 1\right)}{P(X_s = 1)} \cdot T \cdot \mathbf{1}\left(X_T = 3\right)}_{(\star)} - \underbrace{\frac{\mathbf{1}\left(X_s = 0\right)}{P(X_s = 0)} \cdot T \cdot \mathbf{1}\left(X_T = 3\right)}_{(\star\star)} \,\mathrm{d}P\end{aligned} \tag{4.6}$$

In the situation just described, the integrand of the right-hand side of Equation (4.6) would mainly consist of terms $(\star)$, while terms $(\star\star)$ would almost vanish. Thus the integral would be positive. However, it need not hold true that the few patients uninfected at time s who die have a shorter LOS than those infected at time s (of which most die).

Alternatively, we seek to decompose

$$\phi(s) = \sum_{i=2,3} \int \frac{\mathbf{1}\left(X_s = 1\right)}{P(X_s = 1)} \cdot T \cdot \mathbf{1}\left(X_T = i\right) - a_i(s) \cdot \frac{\mathbf{1}\left(X_s = 0\right)}{P(X_s = 0)} \cdot T \,\mathrm{d}P \tag{4.7}$$

with nonrandom coefficients $a_i(s)$, $a_1(s) + a_2(s) = 1$, such that, e. g., in the hypothetical situation mentioned above the addend

$$a_3(s) \cdot T \cdot \mathbf{1}\left(X_s = 0\right) / P(X_s = 0)$$

does not 'vanish'. We propose to use

$$a_i(s) = P\left(X_T = i \,|\, X_s = 1\right), \quad i = 2, 3. \tag{4.8}$$

Before we give an interpretation, we note that, in the hypothetical situation above, the proposed choice of the a_i's performs more meaningful: With an

infection at time s being virtually lethal, $a_3(s) = P(X_T = 3 \mid X_s = 1)$ will be close to one. Thus, there will 'always' be a comparison term for the addend ($\star$) from Equation (4.6). On the other hand, both respective terms will almost vanish for $X_T = 2$.

For an interpretation, we rewrite Equation (4.7) for the proposed choice of the a_i's:

$$\begin{aligned}\phi(s) &= \sum_{i=2,3} \mathrm{E}\big(T \cdot \mathbf{1}(X_T = i) \,|X_s = 1\big) - P(X_T = i \mid X_s = 1) \cdot \mathrm{E}(T|X_s = 0) \qquad (4.9)\\ &= \sum_{i=2,3} P(X_T = i \mid X_s = 1) \cdot \big[\mathrm{E}(T \mid X_T = i, X_s = 1) - \mathrm{E}(T \mid X_s = 0)\big] \qquad (4.10)\end{aligned}$$

The term in square brackets of Equation (4.10) compares, for $i = 3$, the expected LOS for patients infected at time s, who eventually die, with the expected LOS for patients still uninfected at time s. The contribution to $\phi(s)$ then depends on how many of the infected patients eventually die. Note that it is meaningful that only the expectation for those infected is further conditioned on the endpoint type: It thus acknowledges that the particular endpoint, 'death' in the case of $i = 3$, may be a consequence of the infection.

As stated earlier, the weighting discussed in Chapter 2.3 now carries over for the addends on the right-hand side of Equation (4.7). We will refer to the addends of the right-hand side of Equation (4.10) as $\phi_i(s)$, $i = 2, 3$. If the assumption of (2.12) is violated, i. e. if s is such that

$$P(X_s = 1) \cdot P(X_s = 0) = 0,$$

then we define $\phi_i(s) := 0$, $i = 2, 3$, which is in agreement with (2.15).

The quantity $\phi_3(s)$, e. g., can be interpreted as the contribution to the expected change in LOS at time s by patients infected up to time s who eventually die. Note, however, that we may not conclude from $\mathrm{E}_{P^{T_0}}(\phi_2) > \mathrm{E}_{P^{T_0}}(\phi_3)$, say, that LOS is prolonged more for infected and discharged patients than for infected and deceased patients. This is in analogy to a cumulative incidence function. Because the cumulative incidence function for failure type 1 runs beneath the respective function for failure type 2, say, this need not mean that one is less likely to fail if failure will be of type 1. It could also mean that failure type 1 is much less frequent. As stated following Equation (4.10), the contributions of $\phi_2(s)$ and of $\phi_3(s)$ to the expected change $\phi(s)$ depend on how many of those infected up to time s are discharged or die. If one is

specifically interested in what the effect on LOS would be for infected patients that are eventually discharged, say, Equation (4.10) suggests to pursue $\mathrm{E}\left(T \,|\, X_T = 2, X_s = 1\right) - \mathrm{E}\left(T \,|\, X_s = 0\right)$.

4.3 Estimation

The techniques are essentially as in Chapter 2.6. We exemplarily consider ϕ_2. Let us first consider an estimator of the joint distribution function F of (T_0, T, X_T). For $s \leq t$ consider

$$\begin{aligned} F(s,t,2) &= P\left(T_0 \leq s, T \leq t, X_T = 2\right) \\ &= P\left(X_s \neq 0, X_t = 2\right) \\ &= P\left(X_s = 1, X_t = 2\right) + P\left(X_s = 2, X_t = 2\right) \\ &= P\left(X_s = 1\right) \cdot P\left(X_t = 2 \,|\, X_s = 1\right) + P\left(X_s = 2\right) \\ &= P_{01}\left(0, s\right) \cdot P_{12}\left(s, t\right) + P_{02}\left(0, s\right). \end{aligned} \tag{4.11}$$

Note that the preceding lines follow the same argumentation as the ones leading to (2.21) in the model with state-space $\{0, 1, 2\}$. Note, however, that space 2 has different meanings. Here, we explicitly use — and need to do so — the information, that the process cannot enter state 3, if $X_T = 2$. For arbitrary $(s, t) \in [0, \tau]^2$ and $i \in \{2, 3\}$ we have

$$\begin{aligned} F(s,t,i) &= \mathbf{1}(i=2) \cdot \Big(P_{01}\left(0, s\right) \cdot P_{12}\left(s, t\right) + P_{02}\left(0, \min(s,t)\right) \Big) \\ &\quad + \mathbf{1}(i=3) \cdot \Big(P_{01}\left(0, s\right) \cdot P_{13}\left(s, t\right) + P_{03}\left(0, \min(s,t)\right) \Big) \end{aligned} \tag{4.12}$$

The plug-in estimator $\widehat{F}$ of F is now given by plugging in the empirical counterparts of the transition probabilities from the Aalen-Johansen estimator in (4.12).

We now give representations of the addends of $\phi_2(s)$ for times s, where both state 1 and state 2 are occupied with positive probability, in terms of F. We have

$$\begin{aligned} &\mathrm{E}\big(T \cdot \mathbf{1}\left(X_T = 2\right) | X_s = 1\big) \\ &= \int \frac{1(X_s = 1)}{P(X_s = 1)} \cdot T \cdot \mathbf{1}\left(X_T = 2\right) \, \mathrm{d}P \\ &= \int \frac{\mathbf{1}(0 < u \leq s < v)}{F(s, \tau, \{2,3\}) - F(s, s, \{2,3\})} \cdot v \cdot \mathbf{1}(i=2) \, \mathrm{d}F(u, v, i) \end{aligned} \tag{4.13}$$

In order to rewrite the second addend of $\phi_2(s)$ note that

$$\begin{aligned} P\left(X_T = 2 \,|\, X_s = 1\right) &= \frac{P\left(X_T = 2 \text{ and } X_s = 1\right)}{P(X_s = 1)} \\ &= \frac{P\left(X_T = 2 \text{ and } T_0 \leq s < T\right)}{P(T_0 \leq s < T)} \\ &= \frac{F(s,\tau,2) - F(s,s,2)}{F(s,\tau,\{2,3\}) - F(s,s,\{2,3\})} \end{aligned} \tag{4.14}$$

The second addend of $\phi_2(s)$ may then be written as

$$\begin{aligned} P\left(X_T = 2 \,|\, X_s = 1\right) \cdot \mathrm{E}\left(T | X_s = 0\right) = \\ \frac{F(s,\tau,2) - F(s,s,2)}{F(s,\tau,\{2,3\}) - F(s,s,\{2,3\})} \cdot \frac{1}{1 - F(s,\tau,\{2,3\})} \cdot \\ \int \mathbf{1}\left(u > s\right) \cdot v \, \mathrm{d}F(u,v,\{2,3\}) \end{aligned} \tag{4.15}$$

We additionally give somewhat nicer representations of the addends of $\phi_2(s)$ directly in terms of the transition probabilities and transition intensities, respectively. We have

$$\begin{aligned} \mathrm{E}\big(T \cdot \mathbf{1}\left(X_T = 2\right) | X_s = 1\big) &= \int_s^\tau P\left(T > t,\, X_T = 2 \,|\, X_s = 1\right) \, \mathrm{d}t \\ &= \int_s^\tau P\left(X_T = 2 \,|\, X_s = 1\right) \\ &\quad - P\left(T \leq t,\, X_T = 2 \,|\, X_s = 1\right) \, \mathrm{d}t \\ &= \int_s^\tau P\left(X_T = 2 \,|\, X_s = 1\right) - P_{12}(s,t) \, \mathrm{d}t, \end{aligned}$$

where

$$P\left(X_T = 2 \,|\, X_s = 1\right) = \int_s^\tau P_{11}(s, u-) \cdot \alpha_{12}(u) \, \mathrm{d}u.$$

4.4 Example

We consider the SIR 3 data. Before turning to the actual analysis, let us consider a number of plots illustrating the problem at hand. Figure 4.2 recalls the situation of the preceding chapters, where we considered the combined endpoint 'discharge/death'. The estimator $s \mapsto \widehat{\phi}(s)$ can be thought of as a series of differences between the area under Kaplan-Meier curves. This is

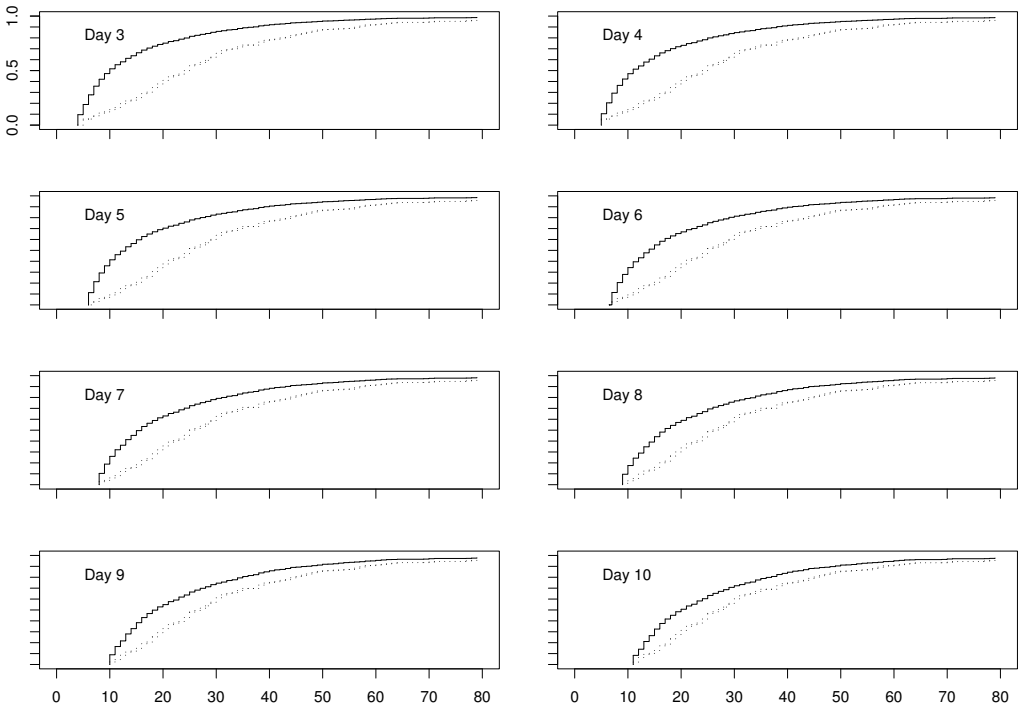

Figure 4.2: One minus Kaplan-Meier curves (combined event discharge/death) given $X_s = 0$ (solid line) and given $X_s = 1$ (dotted line): Plots are presented for $s \in \{3, 4, \ldots, 9, 10\}$.

illustrated in Figure 4.2 for $s \in \{3, 4, \ldots, 9, 10\}$. Prolonged LOS for patients infected up to day s is illustrated by delayed increase of the respective one minus Kaplan-Meier curve. The decreasing differences between these curves correspond to the plot of $\widehat{\phi}(s)$ in Figure 2.3. The Kaplan-Meier curves of Figure 4.2 are split into cumulative incidence functions in Figures 4.3 and 4.4. These cumulative incidence functions display the mixing of effects for infected patients both in possibly prolonged LOS and in increased proportion of patients deceased, which we have discussed in Section 4.2. The cumulative incidence functions for death — of particular interest, because one may suspect that an infection leads to earlier death — are redisplayed in Figure 4.5 at a larger scale. From Figure 4.5, we get the impression that hospital stay may even be prolonged for patients eventually deceased.

We now turn to the actual analysis of the contributions of patients discharged and patients deceased, respectively, to $\int \phi(s)\, \mathrm{d}P^{T_0}$. As in Chapter 2.7, we also analysed nosocomial pneumonia as a time-dependent covariate in a proportional hazards model, this time distinguishing between the competing endpoints discharge and death. We allowed for different baseline

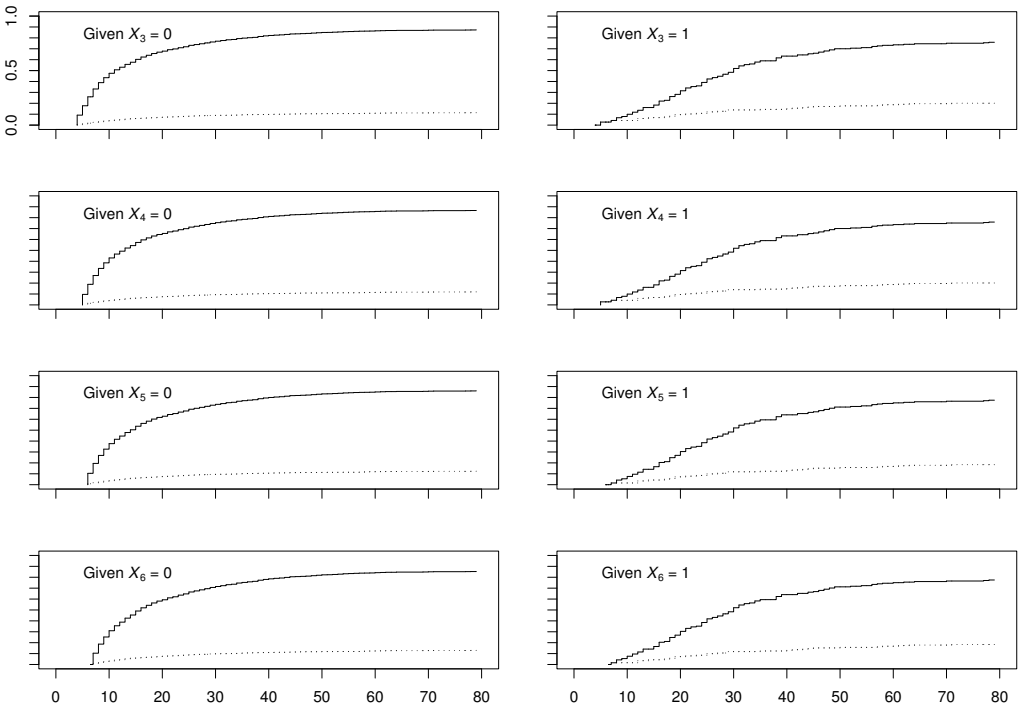

Figure 4.3: Cumulative incidence functions for discharge (solid line) and death (dotted line) given infection status on day s. Plots are presented for $s \in \{3, 4, 5, 6\}$.

hazards per endpoint and for endpoint-specific effects of the covariate. Also, the admission-ID was entered as a `cluster`-term to the function `coxph` of the R-package `survival`. This leads to a 'robust' variance estimation, which is desirable, since, technically, each admission is entered twice into the analysis. For uncensored admissions, the entry corresponding to the endpoint which was *not* reached is treated as censored. See Therneau and Grambsch (2000) for a detailed discussion on these issues. We found for the death hazard $\widehat{\text{HR}} = 0.91$ (95%-CI=$[0.62, 1.35]$, Wald test: $p = 0.65$) and for the discharge hazard $\widehat{\text{HR}} = 0.59$ (95%-CI=$[0.51, 0.69]$, Wald test: $p < 0.0001$). Note that we may not conclude from the fact that nosocomial pneumonia reduces the death hazard (looking, for the moment, only at the point estimates of the respective hazard ratios) that a patient is less likely to die after having acquired pneumonia. This is a consequence of the competing risks situation: Nosocomial pneumonia reduces the discharge hazard much more than it reduces the death hazard. A particularly easy and intriguing example of this peculiarity has been given by Gray (1988). The analysis, however, shows that LOS may even be prolonged for infected patients who eventually

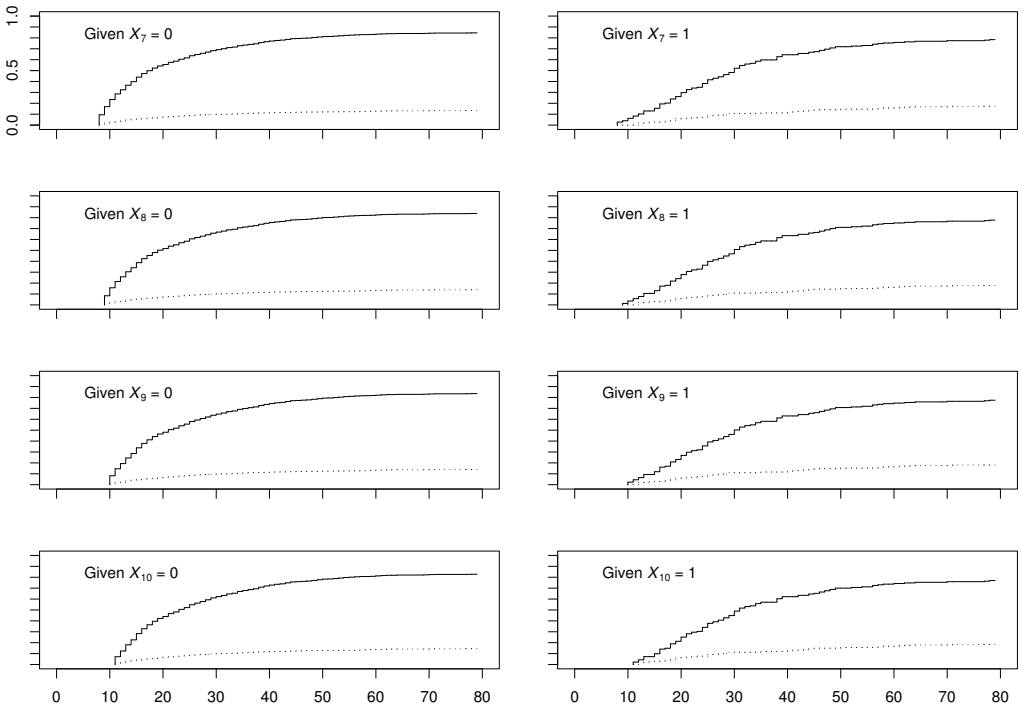

Figure 4.4: Cumulative incidence functions for discharge (solid line) and death (dotted line) given infection status on day s. Plots are presented for $s \in \{7, 8, 9, 10\}$.

die. To the estimated expected change in LOS of 4.9 ($[-0.7, 10.6]$) days due to nosocomial pneumonia, 2.9 ($[-1.4, 7.3]$) days were contributed by patients infected and discharged, and 2.0 ($[-0.16, 4.1]$) days were contributed by patients infected and deceased. Note that the latter two estimates add up to 4.9 days, cf. Equation (4.9). In anticipation of the results of Section 4.5, where we will study large sample properties, we have given 95%-confidence intervals obtained by Gaussian approximation. As in chapter 3.4, these results are to be interpreted as change in LOS restricted to some interval $(q, r) \subsetneqq [2, \tau]$. It is interesting to note that the contribution of patients infected and deceased is larger than one would perhaps expect from the proportional hazards analysis. We have to keep in mind, however, that this analysis can only be used to decide whether there is an effect on LOS at all. The estimates of the contributions to change in LOS given status at time s are illustrated in Figure 4.6. The Figure shows that daywise change in LOS evolves slightly differently for patients discharged and patients deceased, which is also why the contribution of patients deceased is larger than perhaps expected: The LOS-curve for uninfected patients runs underneath the one for infected patients ('pro-

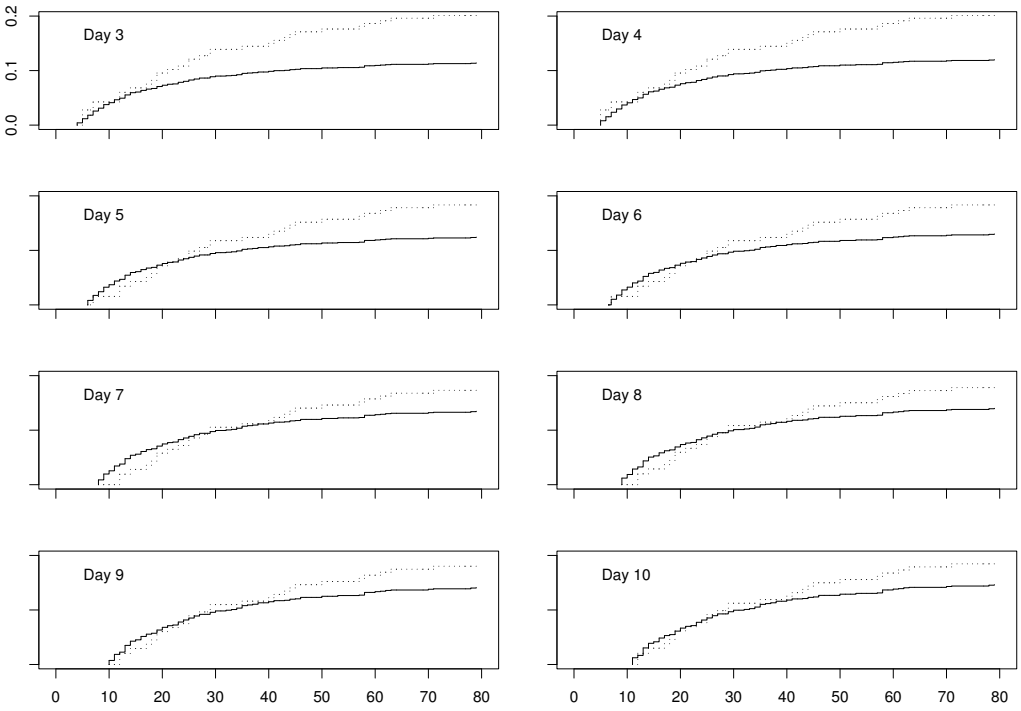

Figure 4.5: Cumulative incidence function for death given $X_s = 0$ (solid line) and given $X_s = 1$ (dotted line): Plots are presented for $s \in \{3, 4, \ldots, 9, 10\}$.

longation') for both patients discharged and patients deceased and for early times of hospital stay. These are the days where most weighting is put on, see Figure 2.4. The curves cross in both cases, but do so at different points in time. While the difference in LOS between infected and non-infected patients is more pronounced for early days in hospital for patients discharged, the curves already cross on day 15. The respective difference is less pronounced for patients deceased, but the curves cross as late as day 38.

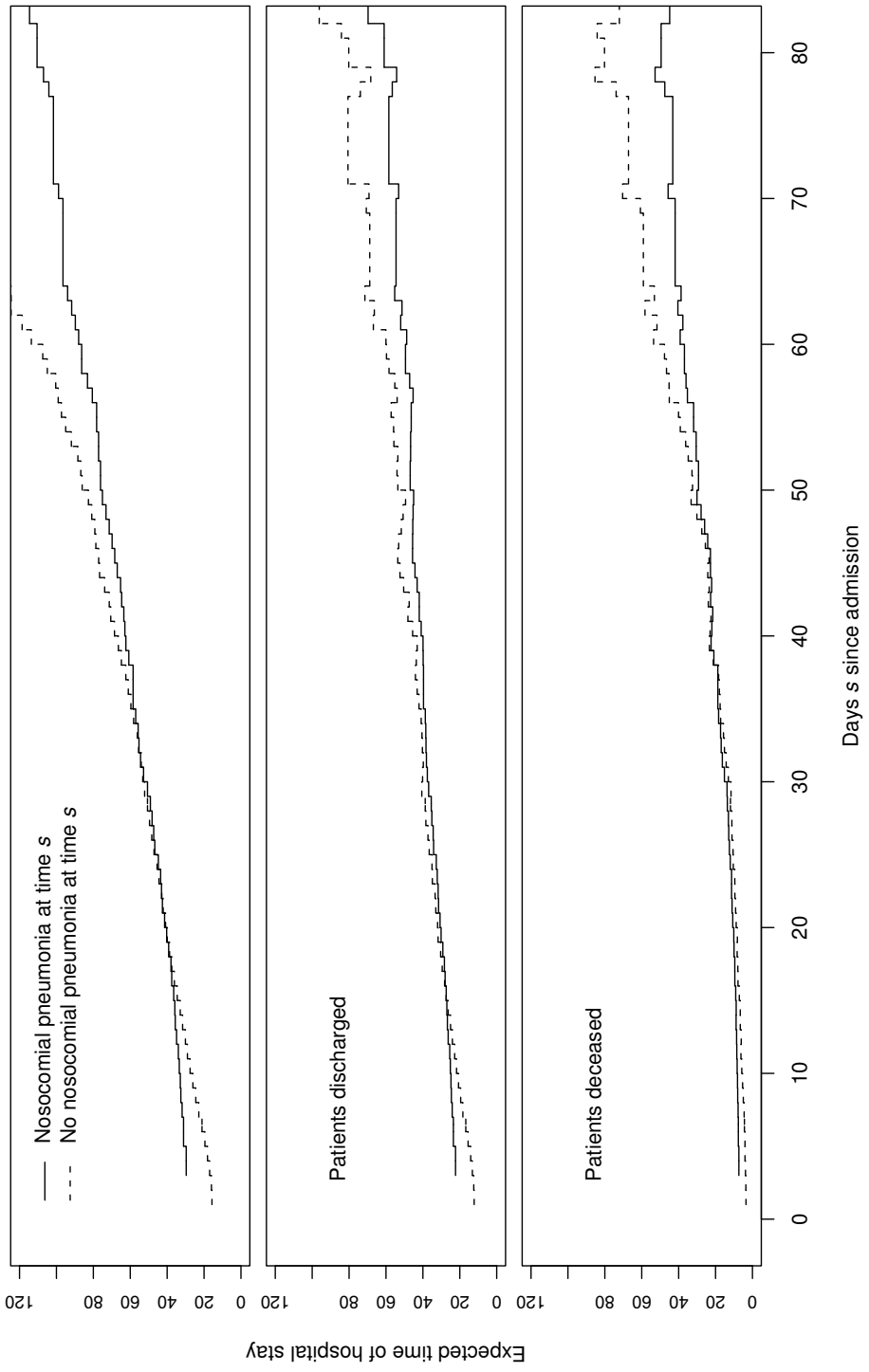

Figure 4.6: Estimated expected change in LOS given status at time s and distinguished for competing endpoints 'discharge' and 'death': The upper plot is the same as in Figure 2.3. Note that the solid lines and the dashed lines, respectively, in the two lower plots add up to the respective lines in the upper plot.

4.5 Large sample properties

We now study large sample properties of our estimators the way we did in Chapter 3. Essentially, we need analogous results to Theorem 3.3 and Theorem 3.18 on weak convergence of our estimator of the joint distribution function of (T_0, T, X_T) and an result analogous to Lemma 3.7. Having laid out in detail the line of argumentation in Chapter 3, we now directly consider the censored case. We note, however, that a weak convergence result for the empirical joint distribution function of (T_0, T, X_T) follows immediately by the lines of, e. g., Wellner (1992), see also our brief discussion following Theorem 3.3. Essentially, one has to note that the index set of the empirical process does not get too large by moving from $[0,\tau]^2$ to $[0,\tau]^2 \times \{2,3\}$. Technically speaking, $[0,\tau]^2 \times \{2,3\}$ is still a Vapnik-Červonenkis class. Let us now consider estimation based on Aalen-Johansen estimator. We will see that a weak convergence result follows rather straightforwardly. The reason for this is that the Aalen-Johansen estimator has essentially been formulated in the language of marked point processes with finite mark space corresponding to the transitions of the multi-state model. See Andersen et al. (1993), Chapter II.4.1.1 for a concise discussion on this.

Recall that we have defined

$$F(s,t,i) := P\left(T_0 \leq s,\, T \leq t \text{ and } X_T = i\right)$$

in (4.4) for $s \geq 0$, $t \geq 0$ and $i = 2, 3$. For $s \leq t$ our estimator of F is given as

$$\begin{aligned} \widehat{F}(s,t,i) &= \mathbf{1}(i=2) \cdot \left(\widehat{P}_{01}(0,s) \cdot \widehat{P}_{12}(s,t) + \widehat{P}_{02}(0,s) \right) \\ &\quad + \mathbf{1}(i=3) \cdot \left(\widehat{P}_{01}(0,s) \cdot \widehat{P}_{13}(s,t) + \widehat{P}_{03}(0,s) \right) \\ &, \end{aligned} \tag{4.16}$$

We first state an result analogous to Lemma 3.17:

Lemma 4.1. *Consider a functional ρ with domain*

$$\left\{ f :\ f : [0,\tau] \supseteq [s,t] \mapsto \left(f_{hj}(s,t)\right)_{h,j=1,2,3,4} \text{ with } \sup_{(s,t)} |f_{hj}(s,t)| < \infty \right\}$$

into

$$\{ g : \{(s,t) \in [0,\tau]^2\} \times \{2,3\} \to \mathbb{R} :\ g(\cdot,i) \text{ is an interval function for } i = 2,3 \}$$

with

$$\begin{aligned}\rho(f)(s,t,i) &:= \mathbf{1}(i=2)\cdot\big(f_{01}(0,s)\cdot f_{12}(s,t)+f_{02}(0,s)\big)\\ &\quad+\mathbf{1}(i=3)\cdot\big(f_{01}(0,s)\cdot f_{13}(s,t)+f_{03}(0,s)\big).\end{aligned}$$

Endow the domain of ρ with the matrix norm $||(f_{hj})|| := \max_h \sum_j ||(f_{hj})||$ induced by the supremum norm on the set of interval functions. Endow the range of ρ with the supremum norm. Then ρ is Hadamard-differentiable in $[s,t] \mapsto \mathbf{P}(s,t)$ with derivative $\rho'_{\mathbf{P}}$ given as

$$\begin{aligned}&\rho'_{\mathbf{P}}(f)(s,t,i)\\ &:= \mathbf{1}(i=2)\cdot\big(f_{01}(0,s)\cdot P_{12}(s,t)+f_{12}(s,t)\cdot P_{01}(0,s)+f_{02}(0,s)\big)\\ &\quad+\mathbf{1}(i=3)\cdot\big(f_{01}(0,s)\cdot P_{13}(s,t)+f_{13}(s,t)\cdot P_{01}(0,s)+f_{03}(0,s)\big)\end{aligned}$$

Proof of Lemma 4.1. As the proof of Lemma 3.17. □

Since $\rho(\mathbf{P})$ equals the marked joint distribution function, we can now invoke the delta method and get from Theorem 3.15 together with Lemma 4.1 the following theorem:

Theorem 4.2. *Let Z be as in Theorem 3.18 and let $\widehat{F}$ be as in (4.16). Assume the assumptions of Theorem 3.15 to hold. Then with ρ, $\rho'_{\mathbf{P}}$ as in Lemma 4.1 we have*

$$\sqrt{n}\left(\widehat{F}-F\right) \xrightarrow{\mathcal{D}} \rho'_{\mathbf{P}}(Z).$$

with respect to the supremum norm. Moreover,

$$\sqrt{n}\left(\widehat{F}-F\right) \text{ and } \rho'_{\mathbf{P}}\left(\sqrt{n}\big(\widehat{\mathbf{P}}-\mathbf{P}\big)\right)$$

are asymptotically equivalent. The limit variable $\rho'_{\mathbf{P}}(Z)$ is a mean zero Gaussian process.

We finally need a result on Hadamard-differentiability analogous to Lemma 3.7:

Lemma 4.3. *Let $q < r \in (0,\tau)$ be fixed, such that the boundness assumptions of Lemma 3.4 and of Lemma 3.6 are fullfilled. Consider ψ with domain*

$$\begin{aligned}\{G : G \text{ a function with domain } [0,\tau]^2\times\{2,3\} \text{ such that } G(\cdot,i) \text{ is a}\\ \text{bivariate distribution function on } D([0,\tau]^2 \text{ for } i=2,3\}\end{aligned}$$

and range $D([0,\tau])$ with

$$\begin{aligned}\psi(G)(s) := \tilde{\iota}\big(G(\cdot,\{2,3\}),s,q,r\big)\cdot\Big(\int \frac{\mathbf{1}(0<u\le s<v)\cdot v\cdot\mathbf{1}(i=2)}{G(s,\tau,\{2,3\})-G(s,s,\{2,3\})}\,\mathrm{d}G(u,v,i)\\ -\int\frac{G(s,\tau,2)-G(s,s,2)}{G(s,\tau,\{2,3\})-G(s,s,\{2,3\})}\cdot\frac{\mathbf{1}(u>s)\cdot v}{1-G(s,\tau,\{2,3\})}\,\mathrm{d}G(u,v,\{2,3\})\Big).\end{aligned}$$

Then ψ is Hadamard-differentiable in F. Its derivative ψ'_F has domain

$$\{G : G \text{ a function with domain } [0,\tau]^2 \times \{2,3\} \text{ such that } G(\cdot, i) \in D([0,\tau]^2) \text{ for } i = 2,3\}$$

and range $D([0,\tau])$. For G in the domain of ψ'_F and $s \in [0,\tau]$ define

$$\begin{aligned}\alpha(G,s) \;:=\; & \big(G(s,\tau,2) - G(s,s,2)\big) \cdot \big(F(s,\tau,\{2,3\}) + F(s,s,\{2,3\})\big) \\ & - \big(F(s,\tau,2) - F(s,s,2)\big) \cdot \big(G(s,\tau,\{2,3\}) + G(s,s,\{2,3\})\big).\end{aligned}$$

Then ψ'_F is given via

$$\begin{aligned}&\psi'_F(G)(s) := \tilde{\iota}(F(\cdot,\{2,3\}), s, q, r) \cdot \\ &\Bigg(\int \frac{\mathbf{1}(0 < u \le s < v) \cdot v \cdot \mathbf{1}(i=2)}{F(s,\tau,\{2,3\}) - F(s,s,\{2,3\})} \,\mathrm{d}G(u,v,i) \\ &+ \int \frac{\mathbf{1}(0 < u \le s < v) \cdot v \cdot \mathbf{1}(i=2) \cdot (G(s,s,\{2,3\}) - G(s,\tau,\{2,3\}))}{(F(s,\tau,\{2,3\}) - F(s,s,\{2,3\}))^2} \,\mathrm{d}F(u,v,i) \\ &- \int \frac{F(s,\tau,2) - F(s,s,2)}{F(s,\tau,\{2,3\}) - F(s,s,\{2,3\})} \cdot \frac{\mathbf{1}(u > s) \cdot v}{1 - F(s,\tau,\{2,3\})} \,\mathrm{d}G(u,v,\{2,3\}) \\ &- \int \frac{\mathbf{1}(s < u) \cdot v \cdot \alpha(G,s)}{(F(s,\tau,\{2,3\}) - F(s,s,\{2,3\}))^2 \cdot (1 - F(s,\tau,\{2,3\}))^2} \,\mathrm{d}F(u,v,\{2,3\}) \Bigg),\end{aligned}$$

where integrals with respect to G are defined via integration by parts, if G is not of bounded variation.

Proof of Lemma 4.3. Essentially as for Lemma 3.4 and Lemma 3.6. The term $\alpha(G,s)$ is a result of lengthy algebraic computations. □

Since $\psi(F) = \phi_2$, we can once again invoke the delta method. Moreover, we can also follow the route of Chapter 3.2.2 in order to get the desired weak convergence result for our estimator of $\int \phi_2 \,\mathrm{d}P^{T_0}$. Since this is rather technical, but otherwise straightforward, we refrain from doing so. Instead, we emphasize the importance of asymptotic correctness of the bootstrap as one result of the delta method. Obviously, the analytic evaluation of the limit variable becomes increasingly involved, as is clear from the form of the Hadamard-derivative in the preceding Lemma.

Chapter 5

Discussion

5.1 The occurrence of an intermediate event as a time-bivariate or random time interval situation

A defining characteristic and therefore intrinsic problem in analysing the effect of an intermediate event is this: The potential effect depends on the random time of occurrence of the intermediate event. Hence, we want to consider the stochastic properties of the intermediate event, in particular the distribution of the random time of occurrence. However, an intermediate event *need not* occur. This is where we run into trouble if we want to look at the distribution of the random time of occurrence, since it is not, without further ado, clear what we mean by this.

This problem already occurs in the simpler competing risks situation. We will first discuss this situation before turning to the random time interval $[T_0, T]$, because our approach of writing the data as a pair of waiting times (T_0, T) is closely related to what is called a cumulative incidence function in competing risks. We will argue that our treatment of change in LOS actually constitutes a general program to analyse the effect of an intermediate on a terminal event. The program does not rely on hypothetical quantities.

5.1.1 Competing Risks

Reconsider the three-state model of Figure 2.1. Ignoring the transition from the intermediate to the absorbing state for the moment, i. e. only considering the state reached on leaving the initial state 0, this is the simplest competing risks situation, with just two competing absorbing states. This situation is illustrated in Figure 5.1. Within our framework, the stochastic behaviour

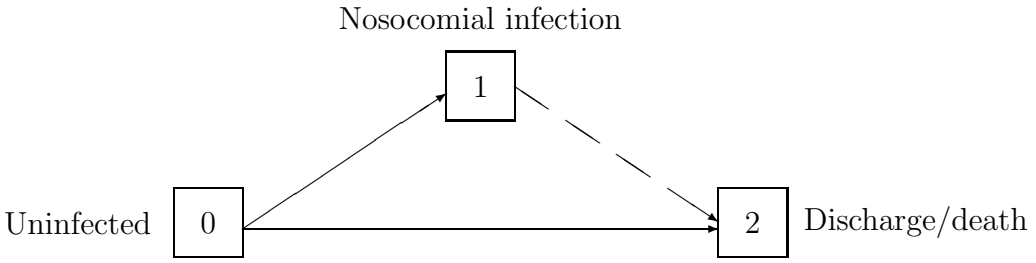

Figure 5.1: The three-state model turns into a competing risks model if we only consider the first event that occurs, i. e. ignore the transition between states 1 and 2.

of a multi-state model is perfectly determined by the transition intensities, see for instance Andersen et al. (1993), Chapter II.6. However, their interpretation is less straightforward than in the two-state model 'alive' and 'dead' of classic survival analysis: Some dichotomous baseline covariate may reduce both transition intensities, say, but may reduce the discharge/death-hazard much more than the infection-hazard. Firstly, this will lead to an increased waiting time in the initial state, and secondly, to an eventually higher proportion of infected patients. For a more accessible interpretation, one would therefore like to talk about (the distribution of) the random time of occurrence of a competing event. Once again, we run into the trouble that a certain competing event need not occur (and the other one will, competingly). One approach to deal with this has been the so-called latent failure time approach: Here, one associates one waiting time with each transition out of the initial state 0. The observable waiting time in the initial state is then modelled as the minimum of the two supposed latent waiting times. There has been a long and controversial discussion about how meaningful this approach is, see for instance Crowder (2001) for a recent and sedate discussion. For instance, it can be considered meaningful to assume a lifetime of its own for a light bulb in a light bulb chain, say. This is less clear for latent lifetimes of organs whose failure is lethal: A light bulb may exist without the chain, but an organ does not usually 'live' without the rest of the human body. Latent waiting times may be even more debatable in our context: There is no such thing as a hospital-acquired infection, after one has been discharged from hospital. (We would need to reinterpret the intermediate state as simply 'infection'.) There are also genuinely statistical problems (e.g. Crowder (2001)): We cannot infer from the observable data on the dependence structure of the supposed latent waiting times. A quantity

generally agreed upon to deal with this situation is the so-called cumulative incidence function. For the competing event 'nosocomial infection' it is given as

$$t \mapsto P(T_0 \leq t, X_{T_0} = 1) = P_{01}(0, t), \tag{5.1}$$

see for instance Andersen et al. (2002) and Crowder (2001). Without going into the technical details, this quantity is identifiable, since the corresponding data are observable (except for independent right-censoring). The notion of a cumulative incidence function is closely related to our writing of the data as a pair of waiting times (T_0, T). We have

$$T_0 \leq t \text{ and } X_{T_0} = 1 \iff T_0 \leq t \text{ and } T_0 < T.$$

Figure 5.2 plots the observed pairs of waiting times (T_0, T) for the data originally used by Schulgen and Schumacher (1996). This data set is complete, without right-censored observations. For any t, $P(T_0 \leq t, X_{T_0} = 1)$ may be estimated by the number of non-diagonal dots in the square $[0, t] \times [0, \infty]$ divided by the total number of individuals. Counting the diagonal dots gives an estimator of $P(T_0 \leq t, X_{T_0} = 2)$.

It is the essential idea of a cumulative incidence function to *consider the observable data only.* Essentially, this has also been our approach for analysing the effect of an intermediate event. (We do not think, however, that models going further than the data cannot be helpful.)

Finally, before we turn to the 'full' three-state model and the random time interval $[T_0, T]$, let us briefly comment on the term 'cumulative incidence function' and the discussion thereon. One might wonder why there is such a discussion at all, and why the cumulative incidence function deserves a name in its own right: After all, it can be explained, at least for discrete finite time spans, by elementary means and is essentially a transition probability for the simplest multi-state model other than the two-state model without backward transition. We believe this is less a question of mathematical but of interpretational difficulty: A nice way to think of the cumulative incidence function is in terms of how a probabilist would likely define the random time of occurrence of an event, which may, but need not occur: If the event occurs at time t, we define the random time as t. If it does not occur, i. e. if there is no *finite* occurrence time t, we define it as infinity. This is, for instance, the way Shiryaev (Shiryaev 1995) does it in his book on probability (e. g. on page 559.)[1]. Let us denote the latter random time $\widetilde{T}_0$. Then we have:

$$\left\{ \begin{array}{lcl} \widetilde{T}_0 = t & \iff & T_0 = t < T \\ \widetilde{T}_0 = \infty & \iff & T_0 = T \end{array} \right\}. \tag{5.2}$$

[1] We will use this notion in Appendix A, where we introduce an R-program, for a concise and intuitive representation of the collected data.

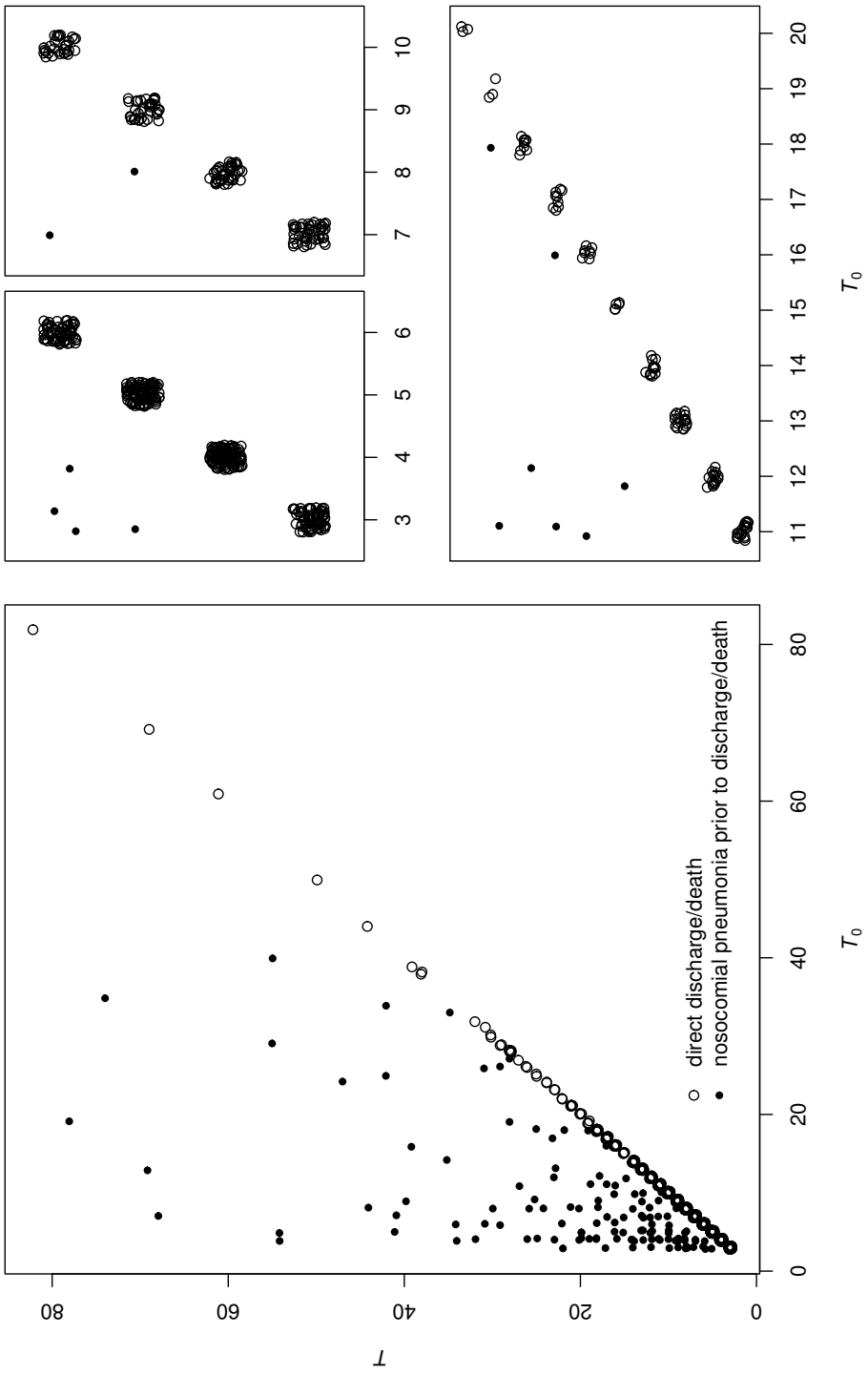

Figure 5.2: Observed pairs of waiting times (T_0, T) for the data originally used by Schulgen and Schumacher (1996). Note that the data have been jittered, i. e. a small random noise has been added in order to better separate ties for plotting. The three plots on the right magnify certain regions of the left plot. The range of the x- and of the y-axis are always the same within one plot, but the scaling is different within the lower right plot.

Note that $\widetilde{T}_0$ is completely determined by (T_0, T). The distribution function for $\widetilde{T}_0$ on $[0, \infty)$ now equals the cumulative incidence function for state 1:

$$P(\widetilde{T}_0 \leq t) = P(T_0 \leq t, X_{T_0} = 1),\ t \in [0, \infty).$$

In a paper on a regression model for cumulative incidence functions, Fine and Gray (1999) call $\widetilde{T}_0$ an 'improper random variable'. The mass that the cumulative incidence function lacks to be a proper distribution function is $P(\widetilde{T}_0 = \infty) = P(X_{T_0} = 2)$. (This is why, for instance, Crowder (2001) or Fine and Gray (1999) call the cumulative incidence function a subdistribution function.) Intuitively, it appears to be an uncomfortable notion that the distribution of a waiting time has positive mass at infinity. In fact, the name 'cumulative incidence function' itself can be regarded as being representative of these interpretational difficulties, since it is, somewhat misleadingly, not an integrated transition intensity in the sense of

$$A_{0j}(t) = \int_0^t \alpha_{0j}(u)\,\mathrm{d}u,\ j = 1, 2,$$

cf. Equation (2.4). These difficulties reappear in our analysis of state 1 as an intermediate state, since we want to compare patient groups defined by their infection status. These difficulties are further complicated, since we want to compare the groups in terms of some future outcome, namely LOS.

5.1.2 The random time interval $[T_0, T]$ and summaries

Two cornerstones of the discussion in the literature on competing risks play a key role in our treatment of the impact of an intermediate on a terminal event: Firstly, while the stochastic behaviour of the multi-state model is essentially determined by the transition intensities, we aim at summaries for interpretational purposes. Secondly, our treatment shall be based on modelling the observed data.

Multi-state models display a complex stochastic behaviour. In fact, already the transition matrix $\mathbf{P}$ is often a called a summary, not only functionals thereof, e. g. Keiding et al. (2001) or Glidden (2002). This work has dealt with a rather involved summary, change in length of stay associated with an intermediate event. This summary is being used by clinical researchers, because it obviously makes sense to them, but we have found it somewhat involved to settle on a formal definition. An intrinsic problem is that there is no immediate way of formalizing what the distribution of the time until the intermediate event occurs is, since it may, but need not occur. In fact, such a distribution is sometimes used in the literature without

explicitly stating what is meant by it. To deal with this problem we have introduced the waiting time T_0 in the initial state 0 and the waiting time T in the sub-state-space $\{0, 1\}$. The pair of waiting times (T_0, T), interpretable as the random time interval $[T_0, T]$, has all the ingredients we desire: Firstly, it is important to note that the state of the stochastic process X_t (with state space $\{0, 1, 2\}$ and initial distribution degenerated in state 0) at time t is completely determined by (T_0, T), cf. Equation (2.9): There is no way to learn more from the data than knowledge of $P^{(T_0,T)}$. Secondly, we have argued that the time the intermediate event occurs — if it occurs — is crucial, since it cannot have an effect on the occurrence of the terminal event before. This is perfectly mirrored by the random time interval $[T_0, T]$. Its length denotes the random time span spent in the intermediate state, possibly zero. If its length is positive, its left limit denotes the time the intermediate event has occurred. It is meaningful and unambiguous to consider the joint distribution of (T_0, T). The data according to (T_0, T) are observable except for independent right-censoring, no hypothetical quantities are involved. Thirdly, and important for applications, the meaning of the random time interval $[T_0, T]$ can be communicated to practioners without being overtly technical. One may speak of it as the random time span spent in the intermediate state until discharge/death. (This is only a little imprecise, as at time T the individual reaches the absorbing state.)

We have shown in Equation (2.22) that the joint distribution function can be expressed as functional of the transition matrix $\mathbf{P}$. We may think of the joint distribution of (T_0, T) as a summary of $\mathbf{P}$, the way $\mathbf{P}$ is a summary of the transition intensities. However, an analysis of the impact of an intermediate event will not likely stop with estimating $P^{(T_0,T)}$. An empirical joint distribution for the data used by Schulgen and Schumacher (1996) is displayed in Figure 5.2. Fortunately, the data are complete, so that the picture is not complicated by right-censored observations. Still, it is hard to judge on grounds of this figure whether an infection prolongs hospital stay, say, and if so, for how many days. Further summaries are needed. Figure 5.3 illustrates one step of how we have computed a summary from the empirical distribution of Figure 5.2: The data are split according to infection status on day 5. One gets the impression that the average LOS within the uninfected group is lower, mainly because of the large number of observations on the lower left part of the diagonal. Our summary considers a series of plots like Figure 5.3, so to speak, and eventually computes a weighted average of differences of average LOS gathered from these plots. The weights are much harder to grasp from a plot like Figure 5.2, and Figures 2.6 and 2.7 offer a much nicer graphical presentation of the summary. Still, Figures 5.2 and 5.3 show how a summary evolves from the joint distribution of (T_0, T).

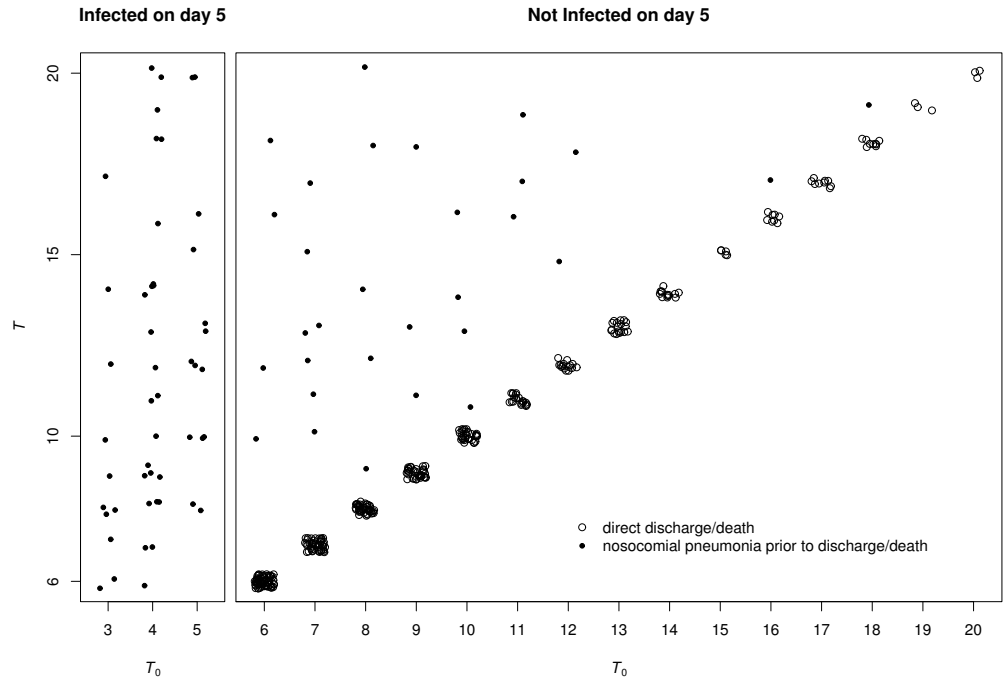

Figure 5.3: Observed pairs of waiting times (T_0, T) for the data originally used by Schulgen and Schumacher (1996) for individuals who were still in hospital on day 5 (i. e. with $T > 5$). The left plot corresponds to the 'cases' on day 5, i. e. patients infected on day 5 ($T_0 \leq 5$). The right plot corresponds to the 'controls' on day 5 ($T_0 > 5$). Note that the y-axis has been truncated at day 20 to better separate points on the diagonal for plotting. Also, the data have again been jittered as in Figure 5.2. Confer Figure 5.2 for a plot with untruncated axes.

We have shown that weak convergence of an estimator of $P^{(T_0,T)}$ can be derived from weak convergence of the Aalen-Johansen estimator of $\mathbf{P}$, and that weak convergence also carries over to a plug-in estimator of the summary measure, if the latter can be written as an Hadamard-differentiable functional of $P^{(T_0,T)}$. This constitutes a general approach to analyse the impact of an intermediate on a terminal event:

- Write the data as a pair of waiting times (T_0, T).
- Quantify the impact of the intermediate event as functional of $P^{(T_0,T)}$.
- Show Hadamard-differentiability of the functional.
- Estimate $P^{(T_0,T)}$ via the Aalen-Johansen estimator.

- Plug in the estimate of $P^{(T_0,T)}$ in order to estimate the summary.

We have seen that summaries may be rather involved. It is therefore an important surplus of this program that by Hadamard-differentiability of the summary and the delta method we get asymptotic correctness of the bootstrap.

5.1.3 Bivariate approaches in the literature

We have stated in Chapter 3.1 that the general bivariate case is essentially more difficult than ours. Still, there has been some related work: Most recently, Jiang and coworkers in a series of articles (Fine et al. (2001), Kosorok et al. (2002), Jiang et al. (2003), Jiang et al. (2004)) as well as Wang (2003a) have considered the so-called semi-competing risks model. This model is closely related to both our three-state model and the latent failure time model for competing risks: The waiting time in the initial state is modelled as the minimum of two latent failure times. Unlike the classical competing risks setting, however, both latent failure times can be observed, if first the intermediate event occurs and then the absorbing state is entered. Otherwise the time until the intermediate event is said to be (possibly dependently) censored by the time to the absorbing state. Interest focuses on the dependence structure between the latent failure times, which is modelled by a so-called copula, and on estimating the marginal distribution of the latent failure time until the occurrence of the intermediate event. The copula function also serves the purpose of reducing estimating the bivariate distribution to estimating the marginals. For related work on (then explicitly called:) dependent competing risks see, e. g., Moeschberger and Klein (1995) and Rivest and Wells (2001). For related work explicitly interested in measuring the dependence structure of bivariate failure times see, e. g., Fan et al. (2000) and Fan and Prentice (2002). Another line of research models that a fraction of the population in the initial state is not susceptible to experiencing a certain event, infection, say. See Wang (2003b) for a recent application to semi-competing risks.

The scope of semi-competing risks models somewhat differs from ours: Firstly, it has been an essential feature of our approach to model the observable data only. Secondly, our interest has laid less on the marginal distribution of the time until nosocomial infection or on explicitly modelling the dependence between that time and the discharge time, but rather on the effect of the intermediate event on the residual time to discharge. Studying the relationship between semi-competing risks models and the approach suggested in this work promises to be interesting research.

For general bivariate survival analysis, the most famous estimator of the joint distribution function is probably the Dabrowska-estimator (Dabrowska (1988) and Dabrowska (1989)). (See Prentice and Kalbfleisch (2003) for an overview on recent work in this area and also Prentice et al. (2004) for recent work on bivariate survival function estimation.) The difficulties encountered in bivariate survival reduce to a certain degree if there is only one outward censoring mechanism, i. e. if both failure times are censored by one common censoring variable, see Lin and Ying (1993), Tsai and Crowley (1998), Kosorok (2002) and van der Laan et al. (2002). It has been noted in the literature that bivariate survival under univariate censoring can be described as a multi-state model (e. g. Hougaard (2000), Chapter 14 as well as Figures 5.12–5.14); we do not know, however, of any explicit use of the Aalen-Johansen estimator to estimate the bivariate distribution function like we have done following Equation (2.21) in our (admittedly even more restricted) multi-state setting . Lin and Ying (1993) mention, inter alia, an example which would be a classic for multi-state modelling — development of AIDS and time to death among HIV-infected persons —, but then pursue different techniques (as does the other aforementioned work), see Remark 2.1. Still, the time-bivariate aspect, which has played such a prominent role in our treatment of an intermediate event within the three-state model, has at least been present in form of an 'undercurrent' in the literature on multi-state models and the Aalen-Johansen estimator. Very importantly, Gill and Johansen (1990) have treated product integration as a functional between spaces of interval functions, see Chapter 3.1. In his seminal paper on multivariate survival analysis (Gill (1992a), Gill (1992b)), Gill mentions 'Markov [...] models for modeling the different stages in an individual's life history' as one example for a time-univariate analysis, where the general problem is time-multivariate. The use of the Aalen-Johansen estimator to study bivariate survival under univariate censoring certainly deserves further research.

5.2 General

Based on previous work by Schulgen and Schumacher (1996), we have studied expected change in LOS associated with an intermediate event using multi-state models, thereby adequately accounting for the timing of events. We have refined and rigorously formulated the approach of Schulgen and Schumacher (1996). The refinements are seen to make a difference in concrete analyses. We have extended their approach to distinguishing the effect of an intermediate event on two competing endpoints, which is of interest not only in the nosocomial infection example. Large sample properties have

been given, and the program constitutes a general framework for analysing summaries that quantify the impact of an intermediate event. There are, however, numerous points worthwhile of further research. Areas connected to bivariate survival have been mentioned in the previous section. A number of points are essentially on the work in this thesis:

- Our large sample properties hold for some true subinterval (q, r) of $[0, \tau]$. Usually, as in our motivating data examples, it should be possible to choose (q, r) large enough to suffice for applications. Still, it would be more pleasing to get rid of this restriction. A related issue is considering the multi-state model on $[0, \infty)$ rather than on the finite interval $[0, \tau]$.

- The confidence intervals of Table 3.1 leave something to be desired. Intuitively, we think that zero 'should not' be included, i. e. we are a priori sure that a nosocomial infection prolongs hospital stay. We have used bootstrap standard errors based on the bootstrap distribution of the respective nonparametric estimators and the normal limit results to compute the confidence intervals. We should note however that there is not one single way to apply bootstrap methods to this problem. Empirical comparisons appear to be worthwhile. We refer to Davison and Hinkley (1997), Chapter 5, for a detailed discussion.

- An analytical evaluation of the limit variables will also be of interest, in particular in connection with the latter item, although very likely burdensome.

There are, of course, further issues:

- We have built on what Schulgen and Schumacher (1996) called 'approach B', which did not use hypothetical quantities. In addition, Schulgen and Schumacher (1996) have considered alternative methods. One approach, in a kind of sensitivity analysis, varied the transition intensity α_{01} of acquiring a nosocomial infection by factors between zero and one. Future applications of this approach could possibly account for dependence between intensities by means of frailty models, cf. Hougaard (2000). In a third approach, Schulgen and Schumacher (1996) used structural nested failure time models, cf. Robins et al. (1992), considering counterfactual lengths of hospital stay, had the individual patient (not) acquired a nosocomial infection. Interestingly, all three approaches considered by Schulgen and Schumacher (1996) provided comparable results. Future research on these approaches might consider the connection to the framework of this thesis. One interesting question is how the different weighting schemes of Chapter 2.3 fit into

the alternative suggestions of Schulgen and Schumacher (1996). As another worthwhile problem, one might study these alternative quantities as functionals of the joint distribution of (T_0, T).

- Apart from the aforementioned alternative quantities considered by Schulgen and Schumacher (1996), there may be further functionals of interest. One interesting research question would be how to incorporate (and account for) length of stay so far in the intermediate state into our notion of change in LOS given status at some fixed time. This information is contained in the pair (T_0, T). (Note that the functional $\int \phi \, \mathrm{d}P^{T_0}$ implicitly takes the time spent in the intermediate state into account, since one contributes the longer to this weighted average, the longer one has been in the intermediate state.)

- An area completely neglected in this work, but very important is that of regression models. An incorporation of discrete covariates would be straightforward by means of Equation (2.13); here, the expectation of T could be further conditioned on the discrete covariates. Also, one might seek to model the influence of covariates on the transition probabilities and to move on thence. Aalen et al. (2001) and Andersen et al. (2003) have put forward recent proposals how to adjust transition probabilities for covariate values directly. Another line of research deals with 'functional mean models', see Fine et al. (2004) for a recent reference.

- Yet another important issue is that of efficiency (in some appropriate asymptotic sense). See Wellner (1992) for a brief overview on empirical processes and efficiency, for connections to Hadamard-differentiability see van der Vaart (1991) and Gill and van der Vaart (1993). Van der Laan (1995) considers the case of bivariate survival; see also van der Laan and Gill (1999) for a more recent reference.

Appendix A

An R-program to compute change in LOS

In this section, we briefly introduce an R-program to estimate $\int \phi \, \mathrm{d}P^{T_0}$, $\int \phi \, \mathrm{d}P^{T_0|X_{T_0}=1}$ and $\int \phi \, \mathrm{d}P^{T_0|X_{T_0}\neq 1}$. So far, we have emphasized the importance of the bootstrap in our setting, and it is consequently important to have a fast program to do the computations in practice. Our R-function `cLOS()` makes heavy use of R's ability to perform calculations on arrays to achieve this. One run only took about 2–3 seconds on a multi-user Linux PC for the SIR 3 data encompassing 1876 admissions, whereas generating 2000 bootstrap replicates of the data lasted for about one and a half hours. We make a short comment on some computational issues as well as on the data structure. For the latter, note that R allows ∞ as a numerical value which we will use to provide for a concise and intuitive representation of the data. This data structure has one row per patient and is therefore well suited to be bootstrapped.

A.1 Some computational issues

Denote the observed event times by $t_1, t_2, \ldots, t_n$, where experiencing a complication, being discharged and death are considered an 'event'. In addition, let $\hat{\tau}$ denote the largest observed time. This may be a pure censoring time and $\hat{\tau} > t_n$; otherwise, if the largest observed time was an event time, $\hat{\tau} = t_n$. We will need to estimate expected times of hospital stay given status at time t_i, $i = 1, \ldots, n$. We will rely on the fact that the expectation of a non-negative random variable may be computed as the integral over its survival

function, see Chapter 2.6.2. Thus, the following equations hold:

$$\begin{aligned}
\widehat{\mathrm{E}}\left(T \,|\, X_{t_i} = 1\right) &= t_{i+1} + (t_{i+2} - t_{i+1}, t_{i+3} - t_{i+2}, \ldots, \tau - t_n) \cdot \\
&\quad \left(\widehat{P}_{11}(t_i, t_{i+1}), \widehat{P}_{11}(t_i, t_{i+2}), \ldots, \widehat{P}_{11}(t_i, t_n)\right)^\top \\
\widehat{\mathrm{E}}\left(T \,|\, X_{t_i} = 0\right) &= t_{i+1} + (t_{i+2} - t_{i+1}, t_{i+3} - t_{i+2}, \ldots, \tau - t_n) \cdot \Big(\widehat{P}_{00}(t_i, t_{i+1}) \\
&\quad + \widehat{P}_{01}(t_i, t_{i+1}), \widehat{P}_{00}(t_i, t_{i+2}) + \widehat{P}_{01}(t_i, t_{i+2}), \ldots, \widehat{P}_{00}(t_i, t_n) + \widehat{P}_{01}(t_i, t_n)\Big)^\top
\end{aligned}$$

To compute these terms, we will need the Aalen-Johansen estimator which was introduced at the beginning of Chapter 2.6 as a finite product of matrices $\widehat{\mathbf{P}}(t_i-, t_i)$. It will be convenient to have the Aalen-Johansen estimates necessary for computing $\widehat{\mathrm{E}}\left(T \,|\, X_{t_{i+1}} = \cdot\right)$ available when computing $\widehat{\mathrm{E}}\left(T \,|\, X_{t_i} = \cdot\right)$, since

$$\begin{aligned}
\widehat{\mathbf{P}}\left(t_i, t_{i+1}\right) &= \widehat{\mathbf{P}}(t_{i+1}-, t_{i+1}), \\
\widehat{\mathbf{P}}\left(t_i, t_{i+2}\right) &= \widehat{\mathbf{P}}(t_{i+1}-, t_{i+1}) \cdot \widehat{\mathbf{P}}\left(t_{i+1}, t_{i+2}\right), \\
&\vdots \\
\widehat{\mathbf{P}}\left(t_i, t_n\right) &= \widehat{\mathbf{P}}(t_{i+1}-, t_{i+1}) \cdot \widehat{\mathbf{P}}\left(t_{i+1}, t_n\right).
\end{aligned}$$

This backward algorithm has been explicitly mentioned by Aalen and Johansen (1978) in their original paper on the estimator $\widehat{\mathbf{P}}$. One easily verifies that $\widehat{\mathrm{E}}\left(T \,|\, X_{t_{n-1}} = \cdot\right) = \tau$. Our R-program therefore starts with computing $\widehat{\mathrm{E}}\left(T \,|\, X_{t_{n-2}} = \cdot\right)$ and moves 'down' to $\widehat{\mathrm{E}}\left(T \,|\, X_{t_1} = \cdot\right)$.

A.2 Data structure and running the program

Our R-function `cLOS` to compute change in LOS due to an intermediate event requires a data frame (of the data on LOS) passed to the argument `my.data`. A second argument, a vector `x`, is only required for bootstrapping the computed change in LOS. To run `cLOS`, the package `survival` has to be loaded.

Assume the data set on LOS is named `los.data`. It should be a data frame, which can be achieved by help of the R function `data.frame`. Usually, data sets in R will already be data frames. `los.data` should have one row per patient and should include the variables `j.01`, `j.02`, `j.03`, `j.12`, `j.13` and `cens`. The variables starting with 'j' will hold the time when a respective transition (or '*j*ump') was observed within the state space depicted in Figure 4.1. E. g., if a patient experiences a complication 7 days after admission to hospital and is being discharged 23 days after admission, the variable

`j.01` will be equal to 7, and the variable `j.12` will be equal to 23. Entries for non-observed transitions have to be set to infinity, which is represented in R by `Inf`. In the example, the variables `j.02`, `j.03` and `j.13` would be set to `Inf`. Note that setting transitions that do not occur to infinity recalls the idea of what we have termed $\widetilde{T}_0$ in Equation (5.2).

In addition, if a patient is censored, i. e. still in hospital by the end of the study, the variable `cens` is set to the time when censoring occurred. If the patient is not censored, it is set to `Inf`. This is the case in our example. The exemplary patient would yield the following entry to `los.data`:

```
 j.01  j.02  j.03  j.12  j.13  cens
   7   Inf   Inf    23   Inf   Inf
```

These variables fully describe the patients' movements within the state space depicted in Figure 4.1. The mechanism is best illustrated by an example: E. g., the number of patients who experienced a complication is given by:

```
los.data[is.finite(los.data$j.01),]
```

and the number of patients censored without having experienced a complication yet is given by:

```
los.data[is.infinite(los.data$j.01) & is.finite(los.data$cens),]
```

The change in LOS can now be computed as:

```
los.result <- cLOS(my.data=los.data)
```

`los.result` will be a list with the following arguments:

`cLOS`	change in LOS
`times`	time points $t_1, t_2, \ldots, t_n$
`e.given.1`	estimates $\mathrm{E}\left(T \mid X_{t_i} = 1\right)$, $i = 1, \ldots n$
`e.given.0`	estimates $\mathrm{E}\left(T \mid X_{t_i} = 0\right)$, $i = 1, \ldots n$
`weights`	weights for the weighted average w. r. t. $\mathrm{d}P^{T_0}$
`matrices`	matrices $\widehat{\mathbf{P}}(t_1-, t_1), \widehat{\mathbf{P}}(t_2-, t_2), \ldots, \widehat{\mathbf{P}}(t_n-, t_n)$

Weights for the alternative weighting schemes are also provided for in the code below, although not returned in the list above in order to save on computational resources. The code is easily altered accordingly.

In addition, the function `cLOS` provides a straightforward way to compute bootstrap variances based on the bootstrap distribution of the estimator. Note that a number of R packages provide bootstrap functions. For instance, after the R package `bootstrap` has been loaded, this may be done (with, e. g., 2000 bootstrap samples) by means of:

```
los.var <- bootstrap(x=1:length(los.data[,1]), nboot=2000,
theta=function(x){y <- cLOS(x); return(y$cLOS)}, func=var)
```

The bootstrap standard error is now given by:

```
sqrt(los.var$func.thetastar)
```

A.3 Code for `cLOS()`

The following code is extensively documented. Comments are preceded by one or more characters #.

```
"cLOS" <- function(x=NA, my.data)
  {
    ## This program is published under the terms of the GNU General
    ## Public License. The terms of GNU General Public License can be
    ## obtained at http://www.gnu.org/copyleft/gpl.html.  The program
    ## is free software and comes with absolutely no warranty. It may
    ## be redistributed under the conditions of the GNU
    ## General Public License.

    ## Author: Jan Beyersmann, jan@fdm.uni-freiburg.de

    ## need package survival
    require(survival)

    ## need x for bootstrapping, e. g.:
    ## library(bootstrap)
    ## result <- bootstrap(x=1:length(los.data[,1]), nboot=50,
    ## theta=function(x){y <- cLOS(x); return(y$cLOS)}, func=var)
    if(is.na(x[1])){## war bis 19.9.04: if(is.na(x)){
      x <- 1:length(my.data[,1])
    }
    my.data <- my.data[x,]

    ## compute variables cens.0 for admissions censored in the
    ##  initial state 0 and cens.1 for admissions censored in state 1

    my.data$cens.0 <- my.data$cens
    my.data$cens.0[is.finite(my.data$j.01)] <- Inf

    my.data$cens.1 <- my.data$cens
    my.data$cens.1[is.infinite(my.data$j.01)] <- Inf


    ## compute 'transition matrix' for every jump time

    jump.times <- sort(unique(c(my.data$j.01, my.data$j.02,
                        my.data$j.03, my.data$j.12, my.data$j.13)))
    jump.times <- jump.times[is.finite(jump.times)]
```

```
jump.matrices <- array(0, c(4,4,length(jump.times)))

for(i in 1:length(jump.times)){

  ## compute number of jumps
  jump.matrices[1,2,i] <- length(my.data$j.01
                  [my.data$j.01==jump.times[i]]) ## jump 0->1
  jump.matrices[1,3,i] <- length(my.data$j.02
                  [my.data$j.02==jump.times[i]]) ## jump 0->2
  jump.matrices[1,4,i] <- length(my.data$j.03
                  [my.data$j.03==jump.times[i]])
                                                        # etc.
  jump.matrices[2,3,i] <-
              length(my.data$j.12[my.data$j.12==jump.times[i]])
  jump.matrices[2,4,i] <-
              length(my.data$j.13[my.data$j.13==jump.times[i]])

  ## divide by number at risk
  ## (only necessary, if risk set is not empty)
  risk.0 <- length(my.data[,1]) - length(
  c(my.data$j.01, my.data$j.02, my.data$j.03, my.data$cens.0)
  [c(my.data$j.01, my.data$j.02, my.data$j.03, my.data$cens.0)
                        < jump.times[i]])

  risk.1 <- length(my.data$j.01[my.data$j.01 < jump.times[i]])
  - length(c(my.data$j.12, my.data$j.13,my.data$cens.1)
  [c(my.data$j.12, my.data$j.13, my.data$cens.1)
   < jump.times[i]])

  if(risk.0 > 0) jump.matrices[1,,i]
                  <- jump.matrices[1,,i]/risk.0

  if(risk.1 > 0) jump.matrices[2,,i]
                  <- jump.matrices[2,,i]/risk.1

  ## compute diagonal elements; sum over each row should be 1.

  jump.matrices[,,i] <- jump.matrices[,,i] + diag(1,4,4) -
    diag(apply(jump.matrices[,,i], 1, sum))

}## end of compute transition matrices
```

```
## compute expected LOS given the state at every observed
## transition time _except for_ the greatest observed time
## (which may be a censoring time)

## is there a censoring time greater than the last observed
## transition time?  my.times <- sort(unique(c(jump.times,
## max(my.data$cens[is.finite(my.data$cens)], jump.times))))

los <- matrix(data=rep(my.times,3), ncol=3, byrow=FALSE,
              dimnames=list(NULL, c("Time", "Given in state 1",
                                    "Given in state
0"))) los[length(my.times)-1,2:3] <- rep(max(my.times), 2)

## last two rows in los already correct. compute the rest,
## starting with the last but two row (which corresponds to the
## third greatest time in my.times)

## will need to temporarily store Aalen-Johansen estimates aj <-
## array(NA, c(4,4,1)) aj[,,1] <- diag(1,4,4)

## will need function that does matrix multiplication running
## thru the 'slices' of array aj "my.function" <-
## function(x,y){x%*%aj[,,y]}

for(i in (length(my.times)-2):1){

  ## compute time differences diffs <-
  ## diff(my.times[(i+1):length(my.times)])

  ## find 'transition matrix' that corresponds to my.times[i +
  ## 1]...  my.matrix <-
  ## jump.matrices[,,length(jump.times[jump.times <= my.times[
  ## i + 1]])]

  ## ...and multiply it with Aalen-Johansen estimates of the
  ## previous loop

  aj <- array(apply(X=diag(1:dim(aj)[3]), 1, my.function,
                    x=my.matrix), c(4,4,dim(aj)[3]))

  ## LOS given in state 1 at time my.times[i] los[,2][i] <-
  ## my.times[i+1] + matrix(diffs, nrow=1) %*%
  ## matrix(aj[2,2,],ncol=1)
```

```
  ## LOS given in state 0 at time my.times[i] los[,3][i] <-
  ## my.times[i+1] + matrix(diffs, nrow=1) %*% matrix((aj[1,1,]
  ## + aj[1,2,]),ncol=1)

  ## stack identity matrix on top for the next loop

  aj <- array(c(diag(1,4,4), aj), c(4,4, (dim(aj)[3] + 1)))

}


## compute distribution to weight differences in LOS

## need waiting time distribution in initial state 0.
## create a survival object and fit it.
## event: left state 0.  T0 <-
## Surv(apply(as.matrix(my.data[, c("j.01","j.02",
## "j.03","cens")]), 1, min), 1-is.finite(my.data$cens.0))
## T0.fit <- survfit(T0)
## Only need 'time' and 'surv' for non-censoring
## events: T0.fit$time <- T0.fit$time[T0.fit$n.event!=0]
## T0.fit$surv <- T0.fit$surv[T0.fit$n.event!=0]

## weight by waiting time distribution in initial state 0
## need mass for each event time my.weights[i] corresponds
## to T0.fit$time[i] my.weights <- diff(c(0,1-T0.fit$surv))

## compute estimate estimate <-
## matrix((los[,2]-los[,3])[is.element(los[,1], T0.fit$time)],
## nrow=1) %*% matrix(my.weights, ncol=1)

## return results my.return <- list(cLOS=estimate,
## times=jump.times, e.given.1=c(los[,2]), e.given.0=c(los[,3]),
## weights=my.weights, matrices=jump.matrices)

return(my.return)


## 2nd: waiting time distribution in initial state 0
## given cause for leaving is state 1

pr.cause1 <-
```

```
  matrix(c(1, T0.fit$surv[1:length(T0.fit$surv)-1]),nrow=1) %*%
  matrix(jump.matrices[1,2,][is.element(jump.times,T0.fit$time)]
                                                    , ncol=1)

  ## my.weights.1[i] corresponds to T0.fit$time[i] my.weights.1
  ## <- diag(diag(c(1, T0.fit$surv[1:length(T0.fit$surv)-1]))
  ##  %*% diag(jump.matrices[1,2,]
  ## [is.element(jump.times, T0.fit$time)]))/ pr.cause1

  estimate.1 <- matrix((los[,2]-los[,3])[is.element(los[,1],
  T0.fit$time)], nrow=1) %*% matrix(my.weights.1, ncol=1)

  ## 3rd: waiting time distribution in initial state 0 given
  ## cause for leaving are states 2 or 3

  pr.cause23 <- matrix(c(1,
  T0.fit$surv[1:length(T0.fit$surv)-1]),nrow=1) %*%
  matrix((jump.matrices[1,3,] + jump.matrices[1,4,])
      [is.element(jump.times, T0.fit$time)], ncol=1)

  ## my.weights.23[i] corresponds to
  ## T0.fit$time[i] my.weights.23 <-
  ## diag(diag(c(1, T0.fit$surv[1:length(T0.fit$surv)-1])) %*%
  ## diag((jump.matrices[1,3,] +
  ## jump.matrices[1,4,])[is.element(jump.times, T0.fit$time)])) /
  ## pr.cause23

  estimate.23 <- matrix((los[,2]-los[,3])[is.element(los[,1],
  T0.fit$time)], nrow=1) %*% matrix(my.weights.23, ncol=1)


  ## return results my.return <- list(overall=estimate,
  ## given.1=estimate.1, given.no1=estimate.23)

  return(my.return)

}## end of function
```

Appendix B

Symbol index and list of abbreviations

The symbol index lists symbols in the order in which they appear in the thesis. Symbols that are only used in the immediate context in which they have been defined are not listed. In Chapter 4, some symbols are adapted to the new four-state model. For instance, the transition matrix becomes a 4×4- instead of 3×3-matrix. The adaptions are made in Chapter 4.1 and Chapter 4.5, respectively. Since the symbols' essential meaning does not change and they are only used in the described way in Chapter 4, they have not been listed twice.

Symbol index

$\mathbf{1}(\cdot)$	indicator function
$(X_t)_t$	stochastic process with finite state-space
$P_{hj}(s,t)$	transition probability, see (2.1)
$\mathbf{P}(s,t)$	transition matrix, see (2.2)
$\alpha_{hj}(t)$	transition intensity, see (2.3)
$A_{hj}(t)$	integrated transition intensity, see (2.4)
$\mathbf{A}(t)$	matrix of integrated transition intensities, see page 53
τ	finite time defined as $\sup\{t : X_t \neq$ absorbing state$\}$, see (2.5)
T	length of stay (LOS), see (2.7)
T_0	waiting time in initial state, see (2.8)
F	distribution function of (T_0, T), see (2.11)
$\phi(s)$	change in LOS given status at time s, see (2.15)

Symbol index (cont.)

$\widehat{\mathbf{P}}(s,t)$	Aalen-Johansen estimator of the transition matrix
$\widehat{F}$	estimator of the distribution function F of (T_0, T), see (2.23)
$\xrightarrow{\mathcal{D}}$	weak convergence, see p. 39
$D([0,\tau]^2)$	bivariate cadlag functions on $[0,\tau]^2$, see Definition 3.1
$D([0,\tau])$	univariate cadlag functions on $[0,\tau]$, see p. 39
$C([0,\tau])$	univariate continuous functions on $[0,\tau]$, see p. 40
$(T_0^{(i)}, T^{(i)}),\ i = 1,\ldots,n$	n i. i. d. replicates of (T_0, T), see page 41
$f(s+,t)$	$\lim_{s_n \to s, s_n > s} f(s_n, t)$, see p. 43
$\|\|f\|\|$, $\|\|f\|\|_{[0,\tau]^2}$	supremum norm for function f on $[0,\tau]^2$, see (3.1)
$l^\infty([0,\tau]^2)$	uniformly bounded functions on $[0,\tau]^2$, see (3.2)
$\iota(G,s,r)$	see (3.6)
ψ_0, $\psi'_{0,F}$	see Lemma 3.4
$\tilde{\iota}(G,s,q,r)$	see (3.8)
ψ_1, $\psi'_{1,F}$	see Lemma 3.6
ψ, ψ'_F	see Lemma 3.7
$\widetilde{\psi}$, $\widetilde{\psi}'_F$	see Lemma 3.10
φ, φ'	see Lemma 3.11
$\mathbf{I}$	identity matrix, see page 53
$\prod\!\!\!\!\int$	product integral, see page 53
$(X_t^{(i)})_t,\ i = 1,\ldots,n$	n i. i. d. replicates of $(X_t)_t$, see page 54
$\mathbf{N}(t) := (N_{hj}; h \neq j)(t)$	counting process, see (3.9)
$Y_h(t)$	risk set process, see (3.10)
$J_h(t)$	defined as $\mathbf{1}(Y_h(t) > 0)$, see (3.11)
$\boldsymbol{\lambda} := (\lambda_{hj}; h \neq j)$	intensity process, see (3.12)
ρ, $\rho'_{\mathbf{P}}$	see Lemma 3.17

Abbreviations

cadlag	continu à droite, limité à gauche
edf	empirical distribution function
HR	hazard ratio
ICU	intensive care unit
IE	intermediate event
NI	nosocomial infection
SE	standard error

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