8

Classical Regression Models for Competing Risks

Jan Beyersmann

Freiburg University Medical Center and Ulm University

Thomas H. Scheike

University of Copenhagen

CONTENTS

8.1 Introduction

Analysing time until death is the archetypical example of a survival analysis, hence the name. In practice, however, time-to-event endpoints are often composites. Common examples in oncology include progression-free survival, disease-free survival and relapse-free survival (Mathoulin-Pelissier et al., 2008). Relapse-free survival is the time until relapse or death, whatever occurs first. Death can also be considered to be a composite, if we distinguish between disease-specific death, say, and death from other causes (Cuzick, 2008). In other words, the "survival time" is typically the time until the first of a number of possible events. It is often tacitly understood that sooner or later every individual experiences at least one of these events. Then the distribution of the survival time will approach one as time progresses. For instance, the cumulative event probabilities of disease-specific death and of death from other causes, respectively, add up to the cumulative all-cause mortality distribution. The latter will ultimately approach one.

Competing risks are the single components of such a composite time-to-event endpoint.

A competing risks model as discussed in this chapter considers time-until-first-event *and* type-of-first-event (Putter et al., 2007). A competing risks analysis therefore provides for more specific results, e.g., in that it allows to study a treatment effect on relapse (but not death) and the treatment effect on death without prior relapse.

Because survival data are often incompletely observed as a consequence of left truncation and right censoring, survival analysis is based on hazards. The concept of hazards is amenable to competing risks. There will now be as many hazards — often called "cause-specific or event-specific hazards" — as there are competing risks. The sum of all cause-specific hazards equals the usual hazard corresponding to the time until any first event.

It will be a key theme of the present chapter that virtually any regression model for a "usual" survival hazard can straightforwardly be used for the cause-specific hazards, too. However, interpretation of the results in terms of probabilities will be complicated by their dependence on all cause-specific hazards. This is so, because the sum of all cause-specific hazards equals the all-cause survival hazard, which in turn determines the survival distribution. As a consequence, regression models of the cumulative event probabilities of a competing risk have emerged since the late 1990s.

A classical textbook reference for competing risks in general and for Cox regression of the cause-specific hazards is the first edition of Kalbfleisch and Prentice (2002) from 1980. A rigorous mathematical treatment of semiparametric multiplicative models and nonparametric additive models for the cause-specific hazards using counting process theory is contained in Andersen et al. (1993). Applied texts include Andersen et al. (2002), Putter et al. (2007) and Beyersmann et al. (2012), the latter two putting an emphasis on using R. The overview paper Andersen and Perme (2008) includes a discussion on inference for cumulative event probabilities of a competing risk.

8.2 The competing risks multistate model

8.2.1 The multistate model

We disregard covariates for the time being. Consider competing risks data arising from a multistate model as depicted in Figure 8.1 for two competing risks. Boxes in the figure indicate states which an individual may occupy. At time 0, all individuals are in the initial

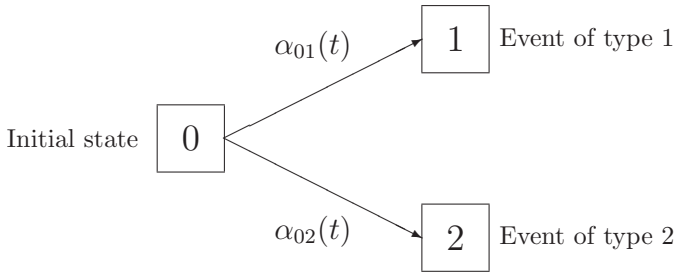

FIGURE 8.1
Competing risks multistate model for two competing risks with cause-specific hazards $\alpha_{0j}(t)$, $j = 1, 2$.

state 0. Events are modelled as transitions between the states. A competing risks model only models transitions out of the initial state, indicated by the arrows in the figure. An individual's event time can be envisaged as the waiting time in state 0. Occurrence of a competing risk of type j is modeled by making a transition from 0 to j at this time.

More formally, consider the competing risks process $(X_t)_{t\geq 0}$, with state space $\{0, 1, 2, \dots J\}$. The competing risks process moves out of the initial state 0, $P(X_0 = 0) = 1$, at time T,

$$T = \inf\{t > 0 \,|\, X_t \neq 0\}.$$

As usual, we assume $(X_t)_{t\geq 0}$ to be right-continuous. The competing risks process is then in one of the competing event states $1, 2, \dots J$ at time T. The type of the first event, often called "cause of failure," therefore is

$$X_T \in \{1, 2, \dots J\},$$

the state the process enters at time T.

The stochastic behaviour of the competing risks process is completely determined by the cause-specific hazards

$$\alpha_{0j}(t)\mathrm{d}t = P(T \in \mathrm{d}t, X_T = j \,|\, T \geq t),\ j = 1, 2, \dots J,$$

which we assume to exist. Here we have written $\mathrm{d}t$ both for the length of the infinitesimal interval $[t, t + \mathrm{d}t)$ and the interval itself. We also write $A_{0j}(t)$ for the cumulative cause-specific hazards, $A_{0j}(t) = \int_0^t \alpha_{0j}(u)\mathrm{d}u$, $j = 1, 2$.

The cause-specific hazards can be thought of as momentary forces of transition, moving along the arrows in Figure 8.1. They generate competing risks data as follows (Gill and Johansen, 1990; Allignol et al., 2011b). The sum of all cause-specific hazards yields the usual all-cause survival hazard $\alpha_{0\cdot}(t)$ corresponding to the distribution of T,

$$\alpha_{0\cdot}(t) = \sum_{j=1}^{J} \alpha_{0j}(t),\ A_{0\cdot}(t) = \sum_{j=1}^{J} A_{0j}(t).$$

Say, $T = t_0$. Then the competing event type is j with probability $P(X_{t_0} = j | T = t_0) = \alpha_{0j}(t_0)/\alpha_{0\cdot}(t_0)$.

The survival function of T is $P(T > t) = \exp(-A_{0\cdot}(t))$ and the cumulative event probabilities of the competing risks — often called "cumulative incidence functions"— are

$$F_j(t) = P(T \leq t, X_T = j) = \int_0^t P(T > u-)\, \alpha_{0j}(u)\, \mathrm{d}u,\ j = 1, 2, \dots J.$$

We note that $P(T > t) + \sum_{j=1}^{J} F_j(t) = 1$. Both the survival function and, via $P(T > u-)$, the cumulative incidence functions depend on all cause-specific hazards.

8.2.2 Advantages over the latent failure time model

Competing risks data are sometimes considered to arise from risk-specific latent times. Restricting ourselves to two competing risks for ease of presentation, the latent failure time model postulates the existence of random variables $T^{(1)}, T^{(2)} \in [0, \infty)$. The connection to the multistate data is

$$T = \min\left(T^{(1)}, T^{(2)}\right) \quad \text{and} \quad X_T = 1 \iff T^{(1)} < T^{(2)}.$$

The times $T^{(1)}, T^{(2)}$ are latent, because, say, $T^{(2)}$ in general remains unobserved, if $X_T = 1$. This is unlike the data (T, X_T) arising from the multistate model, which are observable save for left truncation and right censoring.

One difficulty of the additional latent failure time structure is that one has to specify the dependence of $T^{(1)}$ and $T^{(2)}$, which, however, is empirically non-identifiable, see, e.g., Chapter 17 of Crowder (2012) and the references therein.

We do not use the latent failure time model because nothing is gained from superimposing this additional structure, as, in particular, Aalen (1987) forcefully argues. As we will see below, the (cumulative) cause-specific hazards are empirically identifiable. Knowledge of these does suffice because they generate the competing risks data (T, X_T) as described in Section 8.2.1.

Two remarks are in place before dropping the subject: Firstly, an analysis of $\alpha_{01}(t)$, say, coincides with an analysis of the hazard corresponding to the distribution of $T^{(1)}$, *if* one assumes $T^{(1)}$ and $T^{(2)}$ to exist and to be independent. This is sometimes misinterpreted in the sense that the aim of analysing $\alpha_{01}(t)$ is to learn about the distribution of $T^{(1)}$. This is not the case.

Secondly, there persists an attraction towards the latent failure time approach. The reason probably lies in the fact that it suggests a way to answer "what if" questions. The distribution of $T^{(1)}$ is often interpreted as the survival distribution in a hypothetical world where the competing risk of type 2 no longer occurs. The value of such hypothetical considerations has been questioned (Andersen and Keiding, 2012), but they are feasible without the additional latent failure time structure simply by modifying the cause-specific hazards, potentially equating them with zero.

Both such hypothetical consideration and the theory of competing risks are typically traced back to Daniel Bernoulli's 18th century argument in favour of vaccination against smallpox; see, e.g., Section 3.3 of Beyersmann et al. (2012) or Appendix A of David and Moeschberger (1978). Bernoulli did not use latent times but (time-constant) hazards and he hypothesized that vaccination would equate the smallpox hazard with zero.

8.3 Nonparametric estimation

It is instructive to recapitulate nonparametric estimation in the presence of competing risks before considering regression models. The appealingly simple Nelson-Aalen estimator of the cumulative cause-specific hazards highlights in which sense competing risks act as censoring, an issue which has led to quite some confusion. The nonparametric estimators also provide a template for prediction based on regression models for the cause-specific hazards; the approach will be to replace the Nelson-Aalen estimator by its model-based counterparts.

We consider n individuals under study. Their individual competing risks data are assumed to be i.i.d. replicates of $(X_t)_{t\geq 0}$, where observation of $(X_t)_{t\geq 0}$ is subject to independent right censoring/left truncation as in Andersen et al. (1993) and Aalen et al. (2008). We aggregate the data over all individuals. In counting process notation, let

$$\begin{aligned} Y(t) &= \#\text{ Individuals observed to be in state 0 just before } t,\\ N_{0j}(t) &= \#\text{ Individuals with observed } 0 \to j\text{-transition in } [0,t],\ j = 1, 2, \dots J,\\ N_{0\cdot}(t) &= \sum_{j=1}^{J} N_{0j}(t) = \#\text{ Individuals with an observed event in } [0,t]. \end{aligned}$$

We also write $\Delta N_{0j}(t)$ for the increment $N_{0j}(t) - N_{0j}(t-)$, i.e., the number of type j events observed exactly at time t, and $\Delta N_{0\cdot}(t) = \sum_{j=1}^{J} \Delta N_{0j}(t)$.

The Nelson-Aalen estimator $(\hat{A}_{01}(t), \hat{A}_{02}(t), \ldots \hat{A}_{0J}(t))$ of the cumulative cause-specific hazards has jth entry

$$\hat{A}_{0j}(t) = \sum_{s \le t} \frac{\Delta N_{0j}(s)}{Y(s)},$$

where the sum is taken over all observed event times s, $s \le t$. The Nelson-Aalen estimator of the cumulative all-cause hazard is $\hat{A}_{0\cdot}(t) = \sum_{j=1}^{J} \hat{A}_{0j}(t)$.

Note that for computation of $\hat{A}_{01}(t)$, say, the numerator $\Delta N_{01}(s)$ only counts observed type 1 events, while the denominator $Y(s)$ handles right-censored event times and observed competing events of type j alike, $j \neq 1$. This implies that for computing $\hat{A}_{01}(t)$ in some statistical software package, we may *code* both the usual censoring events and observed competing events other than type 1 as a censoring event.

However, these roles change when computing $\hat{A}_{02}(t), \ldots \hat{A}_{0J}(t)$. For $\hat{A}_{02}(t)$, only observed type 2 events are counted in the numerator, while the denominator $Y(s)$ handles right-censored event times and observed competing events other than type 2 alike. Only the usual censoring events would *always* be coded as a censoring event.

We will encounter this principle again when considering regression models for the cause-specific hazards. A formal justification can be found in Chapter III of Andersen et al. (1993).

The usual Kaplan-Meier estimator of $P(T > t)$ is a deterministic function of $\hat{A}_{0\cdot}(t)$ and, hence, of all cause-specific Nelson-Aalen estimators,

$$\hat{P}(T > t) = \prod_{s \le t} \left(1 - \Delta \hat{A}_{0\cdot}(s)\right),$$

where we have written $\Delta \hat{A}_{0\cdot}(s)$ for the increment $\hat{A}_{0\cdot}(s) - \hat{A}_{0\cdot}(s-)$.

The Aalen-Johansen estimator of the cumulative incidence functions can be derived from the Kaplan-Meier estimator recalling that the cumulative incidence functions add up to the all-cause distribution function. Considering the increments $\widehat{P}(T \le t) - \widehat{P}(T < t)$, one sees that

$$1 - \hat{P}(T > t) = \sum_{s \le t} \hat{P}\big(T > s - \big) \cdot \Delta \hat{A}_{0\cdot}(s).$$

The interpretation of $\hat{P}(T > s-) \cdot \Delta \hat{A}_{0\cdot}(s)$ is that it estimates the probability to have an event at time s. Using $\hat{A}_{0\cdot}(t) = \sum_{j=1}^{J} \hat{A}_{0j}(t)$ yields the Aalen-Johansen estimator of the cumulative incidence functions,

$$\hat{P}(T \le t, X_T = j) = \sum_{s \le t} \hat{P}\big(T > s - \big) \cdot \Delta \hat{A}_{0j}(s),\ j = 1, 2, \ldots J.$$

The interpretation of the summands now is that they estimate the probability to have an event *of type* j at time s. The Aalen-Johansen estimator can also be obtained by plugging the Kaplan-Meier estimator and the Nelson-Aalen estimator into the representation of $P(T \le t, X_T = j)$ given at the end of Section 8.2.1.

A detailed discussion of the Nelson-Aalen, Kaplan-Meier and Aalen-Johansen estimators is in Chapter IV of Andersen et al. (1993) and in Chapter 3 of Aalen et al. (2008).

8.4 Data example (I)

We consider a random subsample of 1,000 patients from ONKO-KISS, a surveillance program of the German National Reference Centre for Surveillance of Hospital-Acquired Infections. The dataset is part of the R package `compeir`, which is available at `http://cran.r-project.org`. The patients in the dataset have been treated by peripheral blood stem-cell transplantation, which has become a successful therapy for severe hematologic diseases. After transplantation, patients are neutropenic; that is, they have a low count of white blood cells, which are the cells that primarily avert infections. Occurrence of bloodstream infection during neutropenia is a severe complication.

The dataset contains information on the event time, i.e., a patient's time of neutropenia until occurrence of bloodstream infection, end of neutropenia or death, whatever occurs first, and on the event type. Transplants are either autologous (cells are taken from the patient's own blood) or allogeneic.

The dataset contains 564 patients with an allogeneic transplant. Of these, 120 acquired bloodstream infection. End of neutropenia, alive and without prior infection, was observed for 428 patients. These numbers are 83 and 345, respectively, for the remaining 436 patients with an autologous transplant. There were few cases of death without prior infection and few censoring events.

Figure 8.2 displays the Nelson-Aalen estimates of the cumulative cause-specific hazards within transplantation group. For ease of presentation, we have used a combined competing endpoint "end of neutropenia, alive or dead, without prior bloodstream infection," because there were few such death cases. We have also omitted pointwise confidence intervals in order not to further complicate the figure; Beyersmann et al. (2012) explain how to add such confidence intervals in practice.

The figure illustrates that the cause-specific hazard for end of neutropenia is the major hazard in both transplant groups. We also find that both cause-specific hazards are reduced by allogeneic transplants, the major effect being on the hazard for end of neutropenia. Thinking of the cause-specific hazards as momentary forces of transition, this means that the all-cause "force" is reduced for patients undergoing allogeneic transplant, and that the relative magnitude of the cause-specific forces changes in favour of infection. The interpretation is that events of *any* type are delayed for allogeneic transplants. During this prolonged time of event-free neutropenia, patients are exposed to an only slightly reduced infection hazard. As a consequence, there will *eventually* be more infections in the allogeneic group.

The figure also illustrates the importance to analyse *all* competing risks. For instance in epidemiology, researchers sometimes only compute the infection incidence density or incidence rate, i.e., an estimate of the cause-specific hazard of infection under the assumption that the hazard is constant over time. Because of Figure 8.2 (right), such an analysis would be incomplete and miss a key point if not complemented by an analysis of the other competing risk.

Figure 8.3 displays the corresponding Aalen-Johansen estimates. The figure confirms our previous conclusion that events of any type are delayed within the group of allogeneic transplants, but that there will eventually be more infections for this group. We have again omitted pointwise confidence intervals for ease of presentation and refer to Beyersmann et al. (2012) for a practical textbook account.

One may ask whether we are over-interpreting the difference of the curves in the left panel of Figure 8.3. Hieke et al. (2013) investigated this question in the full dataset and found the early difference between the cumulative incidence functions to be significant based

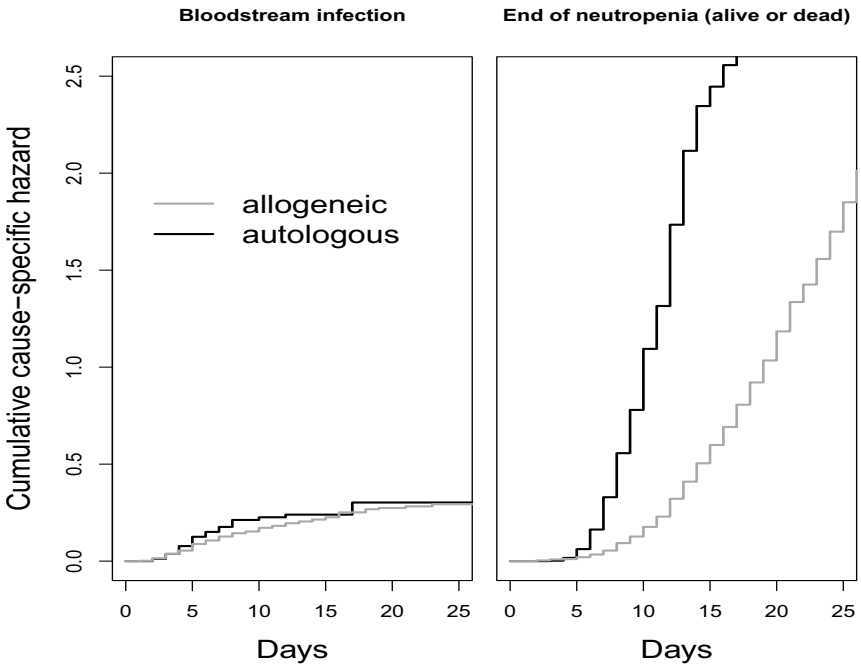

FIGURE 8.2
Nelson-Aalen estimates of the cumulative cause-specific hazards within a transplantation group.

on simultaneous confidence bands. They also discussed medical literature on why allogeneic transplants are expected to increase the proportion of infected patients.

8.5 Regression models for the cause-specific hazards

The aim is to relate the cause-specific hazards to a vector of covariates Z_i for individual i, $i = 1, \ldots, n$, known at time origin. A hazard regression model can also be formulated for time-dependent covariates, but the interpretation often becomes more difficult, see, e.g., Chapters 4, 8, and 9 of Aalen et al. (2008). Results from regression models for all cause-specific hazards and with only baseline covariates can be interpreted in terms of probabilities and can, e.g., be used to predict cumulative incidence functions. In general, this is not possible anymore with time-dependent covariates. A simple binary time-dependent covariate can be modelled by introducing an additional transient state $\tilde{0}$ into the multistate model of Figure 8.1. Transitions between states 0 and $\tilde{0}$ would reflect changes of the time-dependent covariate. Occurrence of a competing risk would still be modelled by transitions into one of the two absorbing states 1 and 2. A regression model including this time-dependent covariate and for the cause-specific hazard of event j, $j \in \{1, 2\}$, would compare the hazard of the $\tilde{0} \to j$ transition with the hazard of the $0 \to j$ transition. However, probabilities

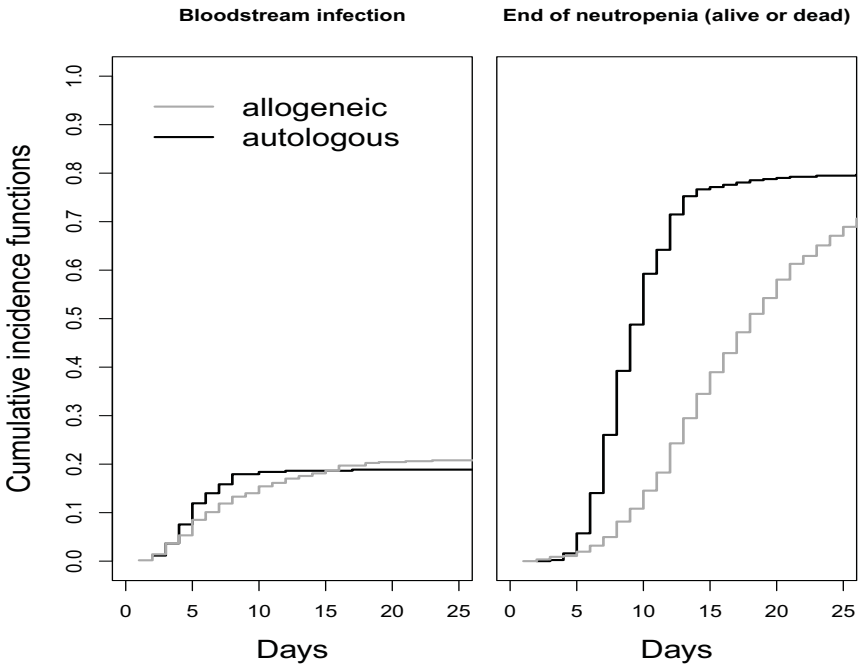

FIGURE 8.3
Aalen-Johansen estimates of the cumulative incidence functions within a transplantation group.

would also depend on the $\tilde{0} \leftrightarrow 0$ transitions, which are not modelled in this approach. The problem persists in the absence of competing risks.

We restrict ourselves to baseline covariates for ease of presentation. Particular attention to time-dependent covariates in the presence of competing risks has been given by Cortese and Andersen (2010) and Beyersmann et al. (2012), Section 11.2.

We will also assume that covariates have cause-specific, i.e., different effects on the cause-specific hazards. Models are also feasible where one covariate has a common effect on all cause-specific hazards, while another covariate has different effects on these hazards. However, these models are rarely used in practice for competing risks. They do lead to more parsimonious models, which is one reason why they are attractive for more complex multistate models. Readers are referred to Chapter VII of Andersen et al. (1993) for an in-depth treatment and to Lunn and McNeil (1995) and Andersen and Keiding (2002) for practical accounts.

Assuming cause-specific effects, virtually any hazard regression model can easily be fitted to a cause-specific hazard by coding the other competing events as censoring, as stated earlier. The data example in Section 8.4 illustrated that this approach should typically be applied to each cause-specific hazard in turn, because one might otherwise miss important aspects of the data.

Cox's proportional hazards model is one of the most common choices with competing risks and will be discussed in Section 8.5.1. A drawback of the model in the competing risks setting is that assuming all cause-specific hazards to follow Cox models usually precludes the all-cause hazard to comply with the proportional hazards assumption. If, as is common

in oncology, one uses the Cox model to analyse both the composite time-to-event endpoint and the competing risks, this may lead to inconsistencies. Klein (2006) therefore argued in favour of Aalen's additive hazard model. The reason is that the cause-specific hazards add up to the all-cause hazard of the composite. We discuss the Aalen model in Section 8.5.2.

8.5.1 Cox's proportional hazards model

Proportional cause-specific hazards models assume that

$$\alpha_{0j;i}(t; Z_i) = \alpha_{0j;0}(t) \cdot \exp\left(\beta_{0j} \cdot Z_i\right), \; j = 1, 2, \ldots J, \; i = 1, \ldots, n,$$

where β_{0j} is a $1 \times p$ vector of regression coefficients, Z_i is a $p \times 1$ vector of covariates for individual i, and $\alpha_{0j;0}(t)$ is an unspecified, non-negative baseline hazard function. We also write

$$A_{0j;0}(t) = \int_0^t \alpha_{0j;0}(u)\mathrm{d}u \quad \text{and} \quad A_{0j;i}(t; Z_i) = \int_0^t \alpha_{0j;i}(u; Z_i)\mathrm{d}u$$

for the respective cumulative cause-specific hazards.

Andersen and Borgan (1985) used counting processes and the results of Andersen and Gill (1982) to study multivariate Cox models, including the present competing risks case; see Andersen and Borgan (1985) for earlier references and Chapter VII.2 of Andersen et al. (1993) for a textbook account. They derived a partial likelihood which is a product over all observed event times, all individuals and all competing risk types. Assuming cause-specific effects β_{0j}, $j = 1, 2, \ldots J$, the partial likelihood factors into J parts. The jth part is algebraically identical to the partial likelihood that one obtains by treating observed competing events of type $\tilde{\jmath}$, $\tilde{\jmath} \in \{1, 2, \ldots J\} \setminus \{j\}$, as censoring.

As a consequence, we can use any Cox routine of a statistical software package to fit a Cox model to the jth cause-specific hazard by coding both the usual censoring events and the other observed competing events as a censoring event. One analogously obtains the Breslow estimator $\hat{A}_{0j;0}(t)$ of the cumulative cause-specific baseline hazard. Writing $\hat{\beta}_{0j}$ for the estimator of β_{0j} obtained by maximizing the partial likelihood, the predicted cumulative cause-specific for a covariate vector equal to z is

$$\hat{A}_{0j}(t; z) = \hat{A}_{0j;0}(t) \cdot \exp\left(\hat{\beta}_{0j} \cdot z\right).$$

We reiterate that a Cox analysis in the presence of competing risks remains incomplete as long as this approach has not been applied to all competing risks in turn. Readers are also warned that a Cox routine of a statistical software package may additionally return Kaplan-Meier-type survival probabilities. This information, however, is typically without use because probabilities will depend on all cause-specific hazards.

Survival probabilities and cumulative incidence functions may be predicted by replacing the increments of the cause-specific Nelson-Aalen estimators in Section 8.3 with their predicted counterparts. The predicted survival probability is

$$\hat{P}(T > t \,|\, z) = \prod_{s \le t} \left(1 - \Big(\sum_{j=1}^{J} \Delta\hat{A}_{0j}(s; z)\Big)\right),$$

where as before Δ indicates an increment and the index s runs over all observed event times s, $s \le t$. The predicted cumulative incidence functions are

$$\hat{P}(T \le t, X_T = j \,|\, z) = \sum_{s \le t} \hat{P}(T > s- \,|\, z) \cdot \Delta\hat{A}_{0j}(t; z).$$

These predictions have been implemented in SAS Macros (Rosthøj et al., 2004) and in the R packages `mstate` (de Wreede et al., 2010, 2011) and `riskRegression` (Gerds et al., 2012). One nice property of these predictions is that they ensure non-decreasing cumulative hazards and that $\hat{P}(T > t \mid z) + \sum_j \hat{P}(T \leq t, X_T = j \mid z) = 1$.

Readers are referred to Chapter VII of Andersen et al. (1993) for a careful discussion of the properties of multivariate Cox regression and subsequent prediction.

8.5.2 Aalen's additive hazards model

Additive hazards models assume that

$$\alpha_{0j;i}(t; Z_i) = \alpha_{0j;0}(t) + \beta_{0j}(t) \cdot Z_i,\ j = 1, 2, \ldots J,\ i = 1, \ldots, n,$$

where $\beta_{0j}(t)$ is a $1 \times p$ vector of regression coefficient functions, Z_i is a $p \times 1$ vector of covariates for individual i, and $\alpha_{0j;0}(t)$ is an unspecified, non-negative baseline hazard function. The cumulative cause-specific hazards can then be computed as $A_{0j;0}(t) + Z_i B_{0j}(t)$ where

$$A_{0j;0}(t) = \int_0^t \alpha_{0j;0}(u)\mathrm{d}u \quad \text{and} \quad B_{0j}(t) = \int_0^t \beta_{0j}(u)\mathrm{d}u.$$

This model has been introduced by Aalen (1980) and has been studied in further details in a large number of papers. The model can be fitted using the R-packages `addreg`[1], `survival`, or `timereg`.

In the context of the competing risks setting one important property of the model as pointed out by for example Klein (2006) is that it is closed under addition. Therefore if the cause-specific hazards are additive, the total hazard of dying $\sum_{j=1}^{J} \alpha_{0j;i}(t; Z_i)$ is still additive. The standard least squares estimator of the cumulative hazards has the nice property that if the covariates are the same for all causes then the estimator of the total hazard for mortality is equivalent to the sum of the estimators of the cause specific hazards. The model is very flexible but has the problem that the standard fitting procedures does not enforce the condition that the cumulative hazard is non-decreasing.

Given the standard least-squares estimators of $A_{0j;0}(t)$ and $B_{0j}(t)$, that we denote as $\widehat{A}_{0j;0}(t)$ and $\widehat{B}_{0j}(t)$, we can predict the cumulative cause-specific hazards for a covariate vector equal to z as

$$\hat{A}_{0j}(t; z) = \hat{A}_{0j;0}(t) + z\hat{B}_{0j}(t).$$

Subsequently this model can also be used to predict survival probabilities and cumulative incidence functions by again replacing the increments of the cause-specific Nelson-Aalen estimators in Section 8.3 with their predicted counterparts. The predicted survival probability then becomes

$$\hat{P}(T > t \mid z) = \prod_{s \leq t} \left(1 - \Big(\sum_{j=1}^{J} \Delta \hat{A}_{0j}(s; z) \Big) \right).$$

The predicted cumulative incidence functions are

$$\hat{P}(T \leq t, X_T = j \mid z) = \sum_{s \leq t} \hat{P}(T > s - \mid z) \cdot \Delta \hat{A}_{0j}(t; z).$$

These predictions have been implemented in `addregmc` (Aalen et al., 2001); see the same web page as for `addreg`.

[1] `www.med.uio.no/imb/english/research/groups/causal-inference-methods/software`

8.6 Data example (II)

We revisit the ONKO-KISS data of Section 8.4 and illustrate using standard Cox regression for the cause-specific hazards. Fitting separate Cox models to the competing risks outcomes as described above, we find that allogeneic transplants decrease the cause-specific hazard of bloodstream infection by an estimated hazard ratio of 0.77 (95% confidence interval $[0.58, 1.03]$). The analysis of the competing cause-specific hazard finds that allogeneic transplants decrease it by an estimated hazard ratio of 0.27 ($[0.23, 0.31]$).

The interpretation is as before: Allogeneic transplants decrease both cause-specific hazards. Therefore, they also decrease the all-cause hazard and events of any type are delayed in this group. However, the decrease as measured by the cause-specific hazard ratio is much more pronounced for the hazard for end of neutropenia. Allogeneic transplants therefore change the relative magnitude of the cause-specific hazards in favour of infection. As a consequence, there are eventually more infections in this group.

Note that this reasoning has neglected the fact that the hazard for end of neutropenia is also the major cause-specific hazard as illustrated in Figure 8.2. Computing the Breslow estimators and subsequent predictions would capture this aspect. Briefly speaking, the very same cause-specific hazard ratio is the more important the more pronounced the corresponding cause-specific baseline hazard is. Readers are referred to Allignol et al. (2011b) who discussed this aspect via simulations from the empirical law of baseline group data.

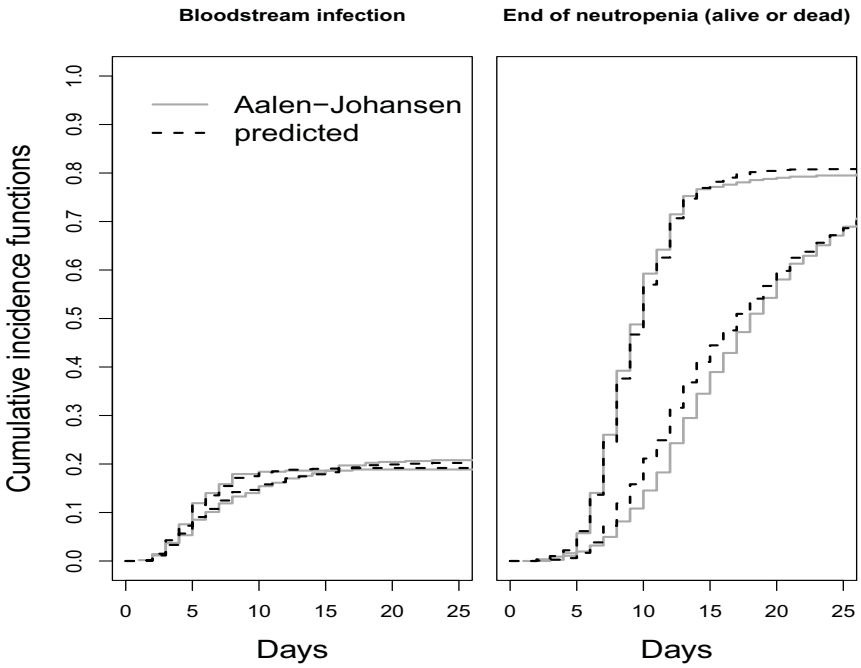

FIGURE 8.4
Aalen-Johansen estimates (dark-grey) as in Figure 8.3 and predicted cumulative incidence functions (black) based on Cox models for the cause-specific hazards.

The predicted cumulative incidence functions are compared with the Aalen-Johansen estimates in Figure 8.4. We find that the fit is reasonable, although it is not perfect for the cumulative incidence function for end of neutropenia. The reason is a time-varying effect of allogeneic transplants on the cause-specific hazard for end of neutropenia, cf. Figure 8.2 (right), which is not captured by the present Cox model with time-invariant regression coefficients.

8.7 Regression models for the cumulative incidence functions

The data example illustrated that a covariate effect on the cause-specific hazard scale does not translate without further ado into an effect on the cumulative incidence functions scale. This has motivated efforts to *directly* model the cumulative incidence functions. Gray (1988) considered a K-sample test for cumulative incidence functions, which directly makes inference about the cumulative incidence functions. This work was later extended into a regression setting where the effects were further quantified in the Fine-Gray model (Fine and Gray, 1999).

The Fine-Gray model assumes that the cumulative incidence for cause j and subject i is given by

$$F_j(t; Z_i) = 1 - \exp\left\{-\Lambda_0(t) \cdot \exp\left(\beta_{0j} \cdot Z_i\right)\right\}, \; i = 1, \ldots, n,$$

where β_{0j} is a $1 \times p$ vector of regression coefficients, related to the j'th cause, Z_i is a $p \times 1$ vector of covariates for individual i, and $\Lambda_0(t)$ is an unspecified, non-decreasing baseline with $\Lambda_0(0) = 0$. This model has some resemblance with Cox's regression and was motivated as a Cox-type model for the subdistribution hazard that we get back to later.

We note that the $\beta_{0j,k} > 0$ implies that the cumulative incidence increases with $Z_{i,k}$, and $\beta_{0j,k} < 0$ implies that the cumulative incidence decreases with $Z_{i,k}$. The interpretation on the cumulative incidence scale is such that

$$\log(-\log(1 - F_j(t; Z_i))) = \log(\Lambda_0(t)) + \beta_{0j} \cdot Z_i$$

and if we compare $X = (x_1, \ldots, x_p)$ with $\tilde{X} = (x_1 + 1, x_2, \ldots, x_p)$ we get a constant of $\beta_{0j,1}$. Clearly this is a somewhat indirect and difficult interpretation in terms of $1 - F_j(t; Z_i)$. The advantage of the model is that it is a very flexible model that inherits many of the useful properties of Cox's regression model. The ability to make useful predictions and to capture the main features of the cumulative incidence functions as well as being implemented in R (package `cmprsk`) and Stata have made the Fine-Gray model the most popular approach in practice. There has recently been considerable interest in providing the model with various Goodness-of-fit procedures to validate the "proportionality" of the model (Scheike and Zhang, 2008; Andersen and Perme, 2010).

More generally if interest is on accessing covariate effects directly on the cumulative incidence function we can consider any link-function (with nice properties)

$$F_j(t; Z_i) = h(\Lambda_0(t), \beta_{0j}, Z_i), i = 1, \ldots, n,$$

and estimate a non-decreasing baseline $\Lambda_0(t)$ and regression coefficients β_{0j}. The Fine-Gray model is then given by the link $h_{\text{fg}}(a, b, z) = 1 - \exp(a \exp(bz))$.

Various other link functions, known from binary data, that aim at making the interpretation of the regression coefficients easier have been suggested. Notably, one may use the logistic link-function, $h_{\text{logistic}}(a, b, z) = \exp(a + bz)/(1 + \exp(a + bz))$, absolute,

$h_{\text{absolute}}(a, b, z) = a + bz$, or relative risk measures, $h_{\text{relative}}(a, b, z) = a \exp(bz)$, as described and advocated in Fine (2001); Ambrogi et al. (2008); and Gerds et al. (2012).

We also note that the Fine and Gray model, although custom-made for one cumulative incidence function, is often used to model all cumulative incidence functions, which will typically imply that at least one of these models is misspecified, see, e.g., Section 5.3.4 in Beyersmann et al. (2012). In addition, when fitting models separately, the regression models will not satisfy the natural constraint that $\hat{P}(T > t \,|\, z) + \sum_j \hat{P}(T \leq t, X_T = j \,|\, z) = 1$. Grambauer et al. (2010) found that a misspecified Fine and Gray analysis still has a quantitative interpretation in that it informs on the plateau of the cumulative incidence functions.

The direct regression models of this section are typically estimated using inverse probability of censoring weighted (IPCW) score equations or related techniques, for example the subdistribution based approach, the pseudo-value approach, see Chapter 10, or the binomial regression approach, see Chapter 11. The Fine-Gray model is typically best fitted using the subdistribution hazard that we present briefly in the next section. Ruan and Gray (2008) suggested a multiple imputation approach.

One key point that adds additional complexity to the estimation of these models is the underlying IPCW model. The typical assumption is that the IPCW is independent of covariates and then the censoring distribution can be estimated by a simple and non-parametric Kaplan-Meier estimator, but if the censoring distribution depends on covariates included in the model then one needs to correctly model this association. This point is often forgotten in practical work.

The Fine-Gray model has been extended to handle left truncation in recent work (Geskus, 2011; Zhang et al., 2011; Shen, 2011). Further methodological developments include stratified models (Zhou et al., 2011), frailties (Katsahian et al., 2006; Katsahian and Boudreau, 2011; Dixon et al., 2011; Scheike et al., 2010), marginal modeling (Scheike et al., 2010; Chen et al., 2008), time-dependent covariates (Beyersmann and Schumacher, 2008), parametric regression (Jeong and Fine, 2007), sample size calculation (Latouche and Porcher, 2007) and joint modeling (Deslandes and Chevret, 2010). Fine (2001) considered linear transformation models of the cumulative incidence function, covering both the Fine and Gray model and a proportional odds model. Sun et al. (2006) proposed a combination of Aalen's additive hazards model and the Cox model for the subdistribution hazard.

8.7.1 Subdistribution hazard

We now briefly describe the subdistribution hazard that can be used for making estimating equations for the parameters of the model. These estimating equations become an IPCW version of a Cox type score equation.

The approach of Fine and Gray (1999) was to consider a "subdistribution time" until occurrence of a certain competing risk, say, type 1,

$$\tilde{T} = \inf\{t > 0 \,|\, X_t = 1\}$$

which equals the real life event time T, if and only if $X_T = 1$. Otherwise, the subdistribution time equals infinity. Then, the distribution of the subdistribution time equals $P(T \leq t, X_T = 1)$ for $t \in [0, \infty)$. Fine and Gray now suggested to fit a Cox model to the corresponding subdistribution hazard $\lambda(t)$,

$$\lambda(t) = -\frac{\mathrm{d}}{\mathrm{d}t} \log\left(1 - P(T \leq t, X_T = 1)\right) = \frac{P(T > t)}{1 - P(T \leq t, X_T = 1)}\, \alpha_{01}(t). \tag{8.1}$$

Because $P(T \leq t, X_T = 1) = 1 - \exp(-\int_0^t \lambda(u)\, \mathrm{d}u)$, the result measures a direct effect on the cumulative incidence function of type 1 events.

The technical difficulty of the Fine and Gray model stems from the *observed* competing events. Their subdistribution times equal infinity, such that their *censored* subdistribution times equal the censoring times. Because observation often stops at the real life event time, these censoring times are in general unknown. In other words, the risk sets associated with the subdistribution hazard approach will be unknown for observed competing events after their real life event times. The main technical achievement of Fine and Gray (1999) was to approximate these risk sets by directly modeling the censoring distribution. They also used empirical process arguments to study the asymptotic properties of the model. In practice, one typically assumes random censoring, i.e., censoring does not depend on covariates, and uses the Kaplan-Meier estimator of the censoring survival function.

To be specific, assume i.i.d. data $(\min(T_i, C_i), X_{T_i}, Z_i)_{i=1,\ldots n}$ with random censorship following the survival function $G(t) = P(C \geq t)$. Consider the "complete data" processes $\tilde{N}_i(t) = \mathbf{1}(T_i \leq t, X_{T_i} = 1)$ of type 1 events with at-risk process $\tilde{Y}_i(t) = 1 - \tilde{N}_i(t-)$. Note that $\tilde{Y}_i$ is only the usual "complete data" at-risk process in the absence of competing risks. These functions are in general unknown, but their products with an indicator function $r_i = \mathbf{1}(C_i \geq \min(T_i, t))$ denoting knowledge of vital status are computable from the observable data.

Writing $\hat{G}$ for the Kaplan-Meier estimator of G, Fine and Gray suggested to use the weights $w_i(t) = r_i(t)\hat{G}(t)/\hat{G}(\min(t, T_i, C_i))$ in the "complete data" score function,

$$U(\beta_{01}) = \sum_{i=1}^{n} \int_0^\infty \left(Z_i - \frac{\sum_{j=1}^n w_j(s)\tilde{Y}_j(s)Z_j \exp\{\beta_{01}Z_j\}}{\sum_{j=1}^n w_j(s)\tilde{Y}_j(s)\exp\{\beta_{01}Z_j\}} \right) w_i(s)\mathrm{d}\tilde{N}_i(s). \tag{8.2}$$

This score function reduces to a standard score function for the Cox model in the absence of competing risks, i.e., if only type 1 events are feasible. However, if there are competing risks, the reason to use (8.2) is that the "subdistribution risk set" $\mathbf{1}(\min(\tilde{T}_i, C_i) \geq t)$ is in general unknown after T_i, if $X_{T_i} \neq 1$ and $T_i \leq C_i$. The rationale is that $w_j(t)\tilde{Y}_j(t)$ approximates this subdistribution risk set. Fine and Gray also derived an estimator of the subdistribution baseline hazard along analogous lines. One considers the usual Breslow estimator for complete subdistribution data $(\tilde{N}_i, \tilde{Y}_i)$ and then introduces weights as above.

The *interpretational* difficulty of the subdistribution model also stems from the observed competing events, because, conceptually, these are kept in the subdistribution risk set *after* their real life event times. This has led to somewhat controversial views on the subdistribution hazard concept. For instance, Pintilie (2007) and Lim et al. (2010) stressed that keeping the observed competing events in the risk set accounts for or incorporates the presence of competing risks. On the other hand, Andersen and Keiding (2012) argued that regarding individuals at risk after the real life failure times compromises interpretability of the subdistribution hazard as a hazard, i.e., as an instantaneous risk of failure.

8.8 Data example (III)

We begin with a Fine and Gray analysis of the cumulative incidence function of bloodstream infection. Allogeneic transplants increase the risk of bloodstream infection by a ratio of $\log(1 - F_1(t; \text{allogeneic}))/\log(1 - F_1(t; \text{autologous}))$ at 1.09 ([0.83, 1.44]). The result is obviously different from the Cox analyses of the cause-specific hazards as illustrated in Table 8.1.

Interpreting the result, we first note that the Aalen-Johansen estimators in Figure 8.3 (left) cross, violating the proportional subdistribution hazards assumption. This can be

TABLE 8.1
Results of the data analyses of Sections 8.6 and 8.8: The left panel displays cause-specific hazard ratios. The Fine-Gray result is a subdistribution hazard ratio, logistic link yields an odds ratio. The numbers in square brackets denote 95% confidence intervals.

Cox models for the cause-specific hazards		Direct regression models for the cumulative infection probability	
infection	competing event	Fine-Gray	logistic link
0.77 ([0.58, 1.03])	0.27 ([0.23, 0.31])	1.09 ([0.83, 1.44])	1.07 ([0.78, 1.46])

formally validated by considering goodness-of-fit procedures, see for example Scheike and Zhang (2008). As a consequence, the subdistribution hazard ratio must be interpreted as a time-averaged effect on the scale of the cumulative incidence function (Claeskens and Hjort, 2008). But how the time-average is constructed depends on for example the censoring pattern, so this makes the interpretation difficult. The qualitative interpretation is that the subdistribution hazard ratio of 1.09 reflects that the plateau of the cumulative incidence function is increased for allogeneic transplants. Readers are referred to Beyersmann et al. (2007) for an extensive analysis of the full ONKO-KISS dataset. We here note that censoring was entirely administrative and did not depend on the type of transplant which is an underlying assumption.

A Fine and Gray analysis of $P(T \leq t, X_T = 1)$ and a Cox analysis of $\alpha_{01}(t)$ sometimes lead to comparable or numerically almost identical results, a fact which has led to some confusion in its own right. Grambauer et al. (2010) found that the results are comparable if a covariate has no effect on the other cause-specific hazards or if censoring is heavy. The reason for the latter fact is that the difference between $\alpha_{01}(t)$ and $\lambda(t)$ is small for early times; see (8.1). These findings also suggest an indirect and hence limited way to quantitatively interpret the subdistribution hazard ratio.

Using the `timereg` or `riskRegression` packages of R we also fitted a logistic link model to describe the effect of allogeneic transplants, and conclude that the allogeneic transplants have a increased risk of infection with an odds ratio of 1.07 ([0.78, 1.46]).

The results from all regression models are tabulated in Table 8.1. Finally, we compared the predicted cumulative incidence functions of bloodstream infection based on a Fine-Gray model with the Aalen-Johansen estimates of Figure 8.3. Because of the model misspecification discussed above, the predicted curves cannot capture the crossing of the Aalen-Johansen estimates, but they do capture their plateaus.

8.9 Other regression approaches

We have focused on the two main regression approaches in competing risks. Because hazards are the key quantities in survival analysis, it is both natural and straightforward to fit hazard regression models to the cause-specific hazards. The data example illustrated that it is via the cause-specific hazards that one understands how the cumulative event probabilities evolve, but that there is also a need for direct regression models for the cumulative incidence functions.

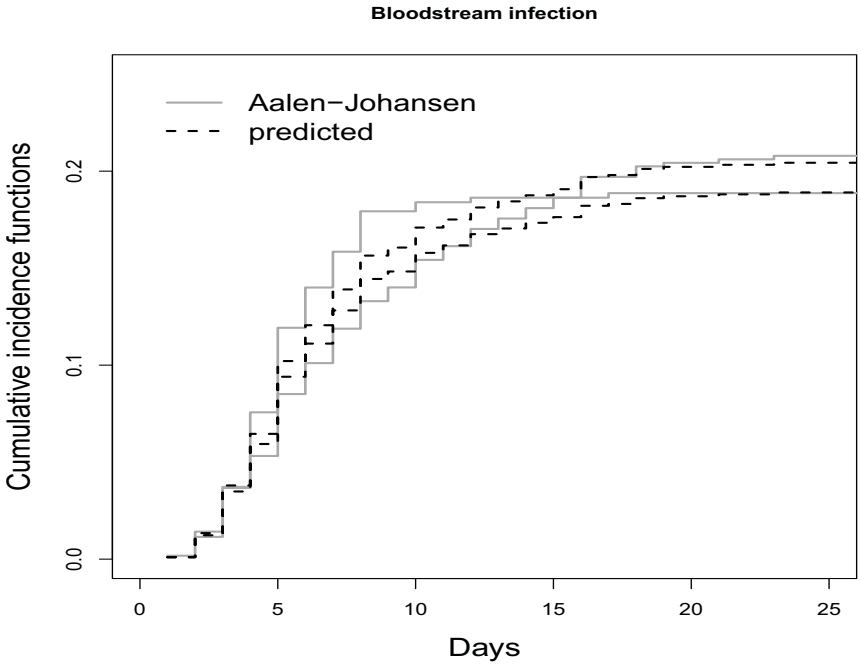

FIGURE 8.5
Aalen-Johansen estimates (dark-grey) as in Figure 8.3 (left) and predicted cumulative incidence functions (black) based on a Fine-Gray model for the outcome bloodstream infection.

There are further regression approaches. Larson and Dinse (1985) considered the decomposition

$$P(T \leq t, X_T = j) = P(T \leq t \,|\, X_T = j)P(X_T = j)$$

and suggested separate regression models for the two probabilities on the right-hand side of the above display, see also Hernandez-Quintero et al. (2011) and the references therein. One important technical difficulty of the approach is that $P(X_T = j) = \lim_{t\to\infty} P(T \leq t, X_T = j)$ will not be identifiable with many survival data. Fine (1999) therefore considered

$$P(T \leq \min(t, \tau), X_T = j) = P(T \leq t \,|\, T \leq \tau, X_T = j)P(T \leq \tau, X_T = j)$$

for a fixed time point τ inside the support of $\min(T, C)$; see also Shen (2012) and the references therein. The interpretational difficulty is that this mixture approach considers a lifetime distribution conditional on the failure cause, which is in general unknown before the event (Andersen and Keiding, 2012).

In contrast, Nicolaie et al. (2010) considered so-called "vertical modeling" via the decomposition

$$P^{T,X_T} = P^T P^{X_T \,|\, T},$$

which follows the prospective algorithm of Section 8.2.1. Similar to the decomposition used by Larson and Dinse, Nicolaie et al. used a standard survival model for P^T and a multinomial logistic regression model for the (conditional) distribution of the failure type. Because the prospective point of view considers these probabilities conditional on the event time, the

technical challenge is that such a model is needed as a function of time. In their data analysis, Nicolaie et al. used splines for this purpose.

Further regression approaches include Allignol et al. (2011a) who used "temporal process regression" (Fine et al., 2004) for the so-called conditional probability function of Pepe and Mori (1993), which is defined for type 1 events as

$$P(T \leq t, X_T = 1 \,|\, T > t \text{ or } \{T \leq t, X_T = 1\}) = P(X_t = 1 \,|\, X_t \in \{0, 1\}).$$

Pepe and Mori advocated this quantity, because it is a monotone increasing function, starting at 0 and reaching 1, just like a distribution function. The interpretational difficulty is that it is not the distribution function of an obvious random variable of the competing risks setting. Andersen and Keiding (2012) argue that this function only becomes useful, if the more complex illness-death multistate model applies.

We finally mention Fiocco et al. (2005) who started from Cox models as in Section 8.5.1 in situations with many regression parameters (many competing risks and/or many covariates) but relatively few events. The idea is to decompose the matrix of all regression coefficients into two matrices. One matrix aggregates the covariates into prognostic scores and is estimated based on all events. The other matrix contains the cause-specific effects of the prognostic scores.

8.10 Further remarks

We have assumed that the data are replicates of (T, X_T), subject to independent left truncation and right censoring. This implies that the event type is known for individuals with an observed event time. Sometimes, only the time, but not the event type is known. If these data are missing completely at random, they may be removed from the analysis. Alternatively, one may introduce "event type unknown" as an additional competing risk, which would preserve the risk sets. More sophisticated methods have been discussed by, e.g., Nicolaie et al. (2011) and Lee et al. (2011); see also the references in these papers.

Earlier, we have referred to Andersen et al. (1993) for a careful mathematical treatment of hazard regression models. The asymptotic distribution of predictions may then be studied using the functional delta method, which can be used to derive pointwise confidence intervals. Simultaneous confidence bands, however, are typically based on resampling methods, see Martinussen and Scheike (2006) for a textbook account.

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