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Dependent competing risks and summary survival curves

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SUMMARY

In many contexts where there is interest in inferring the marginal distribution of a survival time T subject to censoring embodied in a latent waiting time C , the times T and C may not be independent. This paper presents a new class of nonparametric assumptions on the conditional distribution of T given C and shows how they lead to consistent generalizations of the Kaplan & Meier (1958) survival curve estimator. The new survival curve estimators are used under weak assumptions to construct bounds on the marginal survival which can be much narrower than those of Peterson (1976). In stratified populations where T and C are independent only within strata examples indicate that the Kaplan–Meier estimator is often approximately consistent.

Some key words: Competing risks problem; Cox model; Freund model; Kaplan–Meier estimate; Peterson bounds; Proportional hazards.

1. INTRODUCTION

The classical competing risks problem (Gail, 1975) is to infer the marginal distribution of a waiting time T until failure for lives or devices which are subject to censorship, i.e. removal from observation. For example, T may be the time until death from cancer for a patient entering a cancer clinical trial, in which case censorship occurs if the patient either withdraws from study or dies from a cause other than cancer. The event of censorship from any cause is generally assumed to follow a latent waiting time C , which may or may not depend on T . If $X = \min(T, C)$ and $\Delta = I(T \leq C)$, where $I(\cdot)$ denotes indicator function, the observable data on a single life is simply (X, Δ) . Despite recent criticisms by Elandt-Johnson (1976) and Prentice *et al.* (1978), much survival data analysis depends on inference about the marginal distribution of T from such data (X, Δ) .

If the joint density $f(t, s)$ of (T, C) is not restricted, then data $\{(X_i, \Delta_i): 1 \leq i \leq N\}$ on independent lives are not enough to estimate $S(t) = \text{pr}(T > t)$ consistently (Tsiatis, 1975). The best that can be done generally is to estimate the subsurvival density and crude survival function given by

$$\psi(t) = \int_t^\infty f(t, s) ds, \quad S_X(t) = \text{pr}(T > t, C > t) = \int_t^\infty \int_t^\infty f(u, s) du ds. \quad (1)$$

Peterson (1976) gives sharp bounds in terms of these functions for the marginal survival curve $S(t)$ based on data $\{(X_i, \Delta_i)\}$.

Under the common assumption of ‘identity of forces of mortality’ that the crude

death-specific hazard $\psi(t)/S_X(t)$ is identical to the marginal hazard $h(t) = -S'(t)/S(t)$ of T itself, it is well known that $S(t)$ is consistently estimated by the Kaplan & Meier (1958) survival curve estimator defined by

$$\hat{S}_{\text{KM}}(t) = \prod_{i: X_i \leq t} (1 - \Delta_i/r_i)$$

where $r_i = \sum_j I(X_j \geq X_i)$.

This assumption, which holds in particular when T_i and C_i are independent, is discussed at length by Elandt-Johnson (1976), advocated by Prentice *et al.* (1978) to avoid difficulties in interpreting latent failure times, and proved by Kalbfleisch & MacKay (1979) to be equivalent to the 'constant-sum condition' (Williams & Lagakos, 1977).

The only source of dependence between survival and censoring to have received much attention in the biostatistical literature is the stratification of populations by means of demographic and biological covariables Z . When T and C are assumed conditionally independent given Z , the unconditional joint distribution of T , C in the population under study becomes a mixture of product laws weighted by frequencies of occurrence of the different Z . Hence T and C are dependent, unless either T or C has conditional distribution given Z the same for all values of Z . If Z is a finite-valued random vector, then the distribution of T is readily estimated by a linear combination of stratumwise Kaplan–Meier estimators with weights given by the empirical distribution of covariates. If the conditional hazard of T given Z follows a proportional hazard regression model (Cox, 1972), then the large-sample theory of Tsiatis (1981) gives a consistent estimator of the survival curve. Apart from these two cases, the statistical literature gives no further guidance on how to deal with the unidentifiability of $S(\cdot)$ from data $\{(X_i, \Delta_i, Z_i)\}$.

The present paper first answers the question: what are all the nonparametric assumptions on $f(t, s)$ under which $S(t)$ can be consistently estimated from data $\{(X_i, \Delta_i)\}$? Our §2 shows that for each assumption there is a simple consistent, generalized maximum likelihood estimator of $S(\cdot)$ with a large-sample theory analogous to that proved by Breslow & Crowley (1974) for the product-limit estimator. Next, since the Peterson (1976) upper and lower bounds for $S(\cdot)$ tend to be far apart if there is even a moderate degree of censoring, the new estimators are used to construct much improved bounds under weak nonparametric assumptions. We show in §3 that our assumptions have a natural interpretation in a model of dependence generalizing Freund's (1961) simple bivariate exponential. In §4 we illustrate our bounds on $S(\cdot)$, as well as the often nearly consistent behaviour of $\hat{S}_{\text{KM}}(\cdot)$, on data from stratified populations where T and C are stratumwise but not unconditionally independent.

2. A NEW ASSUMPTION FOR DEPENDENT CENSORING

Our nonparametric assumption on the joint density $f(t, s)$ of (T, C) is

$$\lim_{\delta \rightarrow 0} \frac{\text{pr}(t < T < t + \delta | T > t, C \leq t)}{\text{pr}(t < T < t + \delta | T > t, C > t)} = \rho(t), \quad (2)$$

where $\rho(\cdot)$ is a known function of t . That is, the conditional death hazard at instant t differs by the known factor $\rho(t)$ according as an individual surviving until t is censored before t or after t . A function closely related to $\rho(\cdot)$ has previously been defined in the context of multiple point processes by Cox & Lewis (1972). In terms of the functions $\psi(\cdot)$

and $S_X(\cdot)$ defined in (1) and of the marginal density $f(\cdot)$ of T , (2) can be rewritten:

$$\rho(t) = [\{f(t)/\psi(t)\} - 1][\{S(t)/S_X(t)\} - 1]^{-1} \tag{3}$$

Assumption (2) gives enough information to render $S(\cdot)$, but not the joint law for (T, C) , identifiable from the observable data $\{(X_i, \Delta_i)\}$. Of course each joint law for (T, C) gives rise to a function $\rho(\cdot)$. Conversely, the observable joint distribution of $X = \min(T, C)$ and $\Delta = I(T \leq C)$ is completely summarized by the functions $\psi(\cdot)$ and $S_X(\cdot)$, and assumption (2) on $\rho(\cdot)$ simply relates the marginal distribution of T to ψ and S_X . In fact, rewriting (3) as a differential equation for S , namely

$$\frac{d}{dt}S(t) = -\psi(t)[1 + \rho(t)\{S(t)/S_X(t) - 1\}],$$

with $S(0) = 1$, we find that $S(t)$ has the unique expression

$$S(t) = \exp\left[-\int_0^t \psi(s)\rho(s)\{S_X(s)\}^{-1} ds\right] \left(1 + \int_0^t \psi(s)\{\rho(s) - 1\} \times \exp\left[\int_0^s \psi(u)\rho(u)\{S_X(u)\}^{-1} du\right] ds\right) \tag{4}$$

over the range of $t \geq 0$ such that $S_X(t) > 0$.

Returning to (3), we observe directly that $\rho \equiv 1$ if and only if

$$h(t) \equiv f(t)/S(t) = \psi(t)/S_X(t),$$

that is, if and only if the death hazard is the same as the ‘crude death-specific hazard’ (Prentice *et al.*, 1978). If $\rho(t) > 1$ for all t , we have positive dependence between death and censoring, and if $\rho < 1$ uniformly, we have negative dependence.

When $\rho(\cdot)$ is assumed known, there is a simple consistent estimator of the marginal survival curve $S(\cdot)$ which immediately generalizes the Kaplan & Meier (1958) estimator. Suppose that in the sample $\{(X_i, \Delta_i): 1 \leq i \leq N\}$, the ordered times X_i for which $\Delta_i = 1$ are $X_{(1)} \leq \dots \leq X_{(d)}$ and the number of X_i with $\Delta_i = 0$ between $X_{(j)}$ and $X_{(j+1)}$ is c_j , with c_0 censored before $X_{(1)}$. Let n_j be the number of i with $X_i \geq X_{(j)}$. Then the empirical odds of an uncensored surviving individual’s dying at $X_{(j)}$ is $1:(n_j - 1)$, and by assumption (2) the ‘empirical’ odds of a previously censored surviving individual’s dying at $X_{(j)}$ is $\rho(X_{(j)}):(n_j - 1)$. The product-limit estimator of the probability of being censored before $X_{(j)}$, and surviving through $X_{(j)}$ is therefore

$$N^{-1} \sum_{k=0}^{j-1} c_k \prod_{i=k+1}^j [1 - \rho(X_{(i)})/\{n_i - 1 + \rho(X_{(i)})\}]$$

while the probability of not being censored before $X_{(j)}$ and surviving through $X_{(j)}$ is empirically estimated by $(n_j - 1)/N$. Altogether our product-limit estimator for $S(\cdot)$ based on $\{(X_i, \Delta_i)\}$ is

$$\hat{S}_\rho(t) = N^{-1} \left\{ n(t) + \sum_{k=0}^{d(t)-1} c_k \prod_{i=k+1}^{d(t)} \frac{n_i - 1}{n_i + \rho_i - 1} \right\}, \tag{5}$$

where

$$n(t) = \sum I(X_i > t), \quad d(t) = \sum I(\Delta_i = 1, X_i \leq t), \quad \rho_i = \rho(X_{(i)}).$$

After some algebra with the identities $c_k = n_k - n_{k+1} - 1$, where $n_0 = N + 1$, one finds

$$\hat{S}_\rho(t) = \prod_{i=1}^{d(t)} \frac{n_i - 1}{n_i + \rho_i - 1} + N^{-1} \sum_{k=1}^{d(t)} (\rho_k - 1) \prod_{i=k}^{d(t)} \frac{n_i - 1}{n_i + \rho_i - 1}. \tag{6}$$

In particular when $\rho(\cdot) = 1$, it follows that \hat{S}_ρ is exactly the right-continuous Kaplan–Meier estimator. Moreover, approximating $(n_i - 1)/(n_i + \rho_i - 1)$ by $\exp\{-\rho_i/(n_i - 1)\}$, we find that $\hat{S}_\rho(t)$ is the same as (4) when $\psi(s) ds$ and $S_X(s)$ are replaced by their respective empirical estimators $N^{-1} \sum \delta_{x_i} \Delta_i$ and $\{n(s) - 1\}/N$, where δ_u is the point mass at u .

From the product-limit argument we used to derive $\hat{S}_\rho(t)$, we conclude that $\hat{S}_\rho(t)$ is a generalized maximum likelihood nonparametric estimator for $S(t)$ under assumption (2). When $\rho(\cdot)$ is a continuous function, almost-sure consistency of \hat{S}_ρ follows from the empirical-integral expressions (Breslow & Crowley, 1974); and weak convergence of $N^{1/2}\{\hat{S}_\rho(\cdot) - S(\cdot)\}$ in $C[0, 1]$ as $N \rightarrow \infty$ to a Gaussian process of zero mean follows from the proofs of Theorems 3 and 4 of Breslow & Crowley (1974), together with linearization. Explicit expressions for the asymptotic variance are extremely complicated and we do not present them here.

From (5) it is clear that $\hat{S}_\rho(t)$ is a decreasing function of ρ for fixed t . If $\rho(t)$ is as defined in (2) or (3), then in sufficiently large samples

$$\hat{S}_{\rho_2}(t) \leq S(t) \leq \hat{S}_{\rho_1}(t) \tag{7}$$

if $\rho_1(\cdot) \leq \rho(\cdot) \leq \rho_2(\cdot)$. Under a relatively weak nonparametric assumption, e.g. that $\frac{1}{2} \leq \rho(t) \leq 2$ for all t , (7) can improve dramatically over Peterson’s (1976) general bounds which, as is easy to see from (5), correspond to (7) with $\rho_1(\cdot) = 0$, $\rho_2(\cdot) = \infty$. The primary value of $\hat{S}_\rho(\cdot)$ is in bounding rather than estimating $S(\cdot)$.

3. FREUND MODEL AND COX MODEL

The bivariate model of Freund (1961) assumes that the waiting times T and C are independently subject to constant hazard rates α and β until time $\min(T, C)$. Occurrence of T acts as a shock to change the hazard of C to β' . Likewise, occurrence of C changes the hazard of T to α' . Dropping the assumption of constant hazards, we define a generalized Freund model in which the conditional density $f_C(s)$ of C given $T \leq C$ equals its conditional density given $T > C$:

$$f(t, s) = \begin{cases} f_1(t) f_C(s) & (t \leq s), \\ f_C(s) \frac{S_1(s)}{S_2(s)} f_2(t) & (t > s), \end{cases}$$

where the survival curves $S_i(\cdot)$ for $i = 1, 2$ have densities $f_i(\cdot)$ and hazard intensities $h_i(\cdot) = f_i(\cdot)/S_i(\cdot)$. A straightforward calculation of $\psi(t)$, $S_X(t)$, $f(t)$ and $S(t)$ and use of (3) show that $\rho(t) = h_2(t)/h_1(t)$ for this model, regardless of the form of $f_C(\cdot)$. This model gives an interesting equivalent description of any joint law for (T, C) : every function $\rho(\cdot)$ can be realized within some generalized Freund model. Wherever in specific applications it is possible to give plausible lower and upper bounds $\rho_1(t)$, $\rho_2(t)$ for the ratio of the postcensoring hazard to the precensoring hazard in a hypothetical generalized Freund model, (7) implies corresponding bounds for $S(t)$.

Another sort of dependence between C and T arises from any model with random covariates Z in which T and C are conditionally independent given Z , both with

marginal laws nonconstant in Z . The conditional joint density $f(t, s | Z)$ gives rise to observable functions $\psi(t | Z)$ and $S_X(t | Z)$ as in (1). The assumption of identity of conditional forces of mortality implies that

$$h(t | Z) = \psi(t | Z) / S_X(t | Z), \quad S(t | Z) = \text{pr}(T \geq t | Z) = \exp \left[- \int_0^t \psi(s | Z) \{S_X(s | Z)\}^{-1} ds \right].$$

Equation (3) applied to such a covariate-stratified model implies

$$\rho(t) = \frac{E_Z[\psi(t | Z) \{S(t | Z) / S_X(t | Z) - 1\}] S_X(t)}{E_Z[S_X(t | Z) \{S(t | Z) / S_X(t | Z) - 1\}] \psi(t)}. \tag{8}$$

Since

$$S_X(t | Z) / S(t | Z) = S_C(t | Z) = \text{pr}(C \geq t | Z),$$

equation (8) implies that if $S_C(\cdot | Z) = S_C(\cdot)$ for almost all Z , then $\rho(\cdot) = 1$. Whenever, $\psi(t | Z)$, $S_X(t | Z)$ and $S(t | Z)$ are continuous functions of Z in such a model, the marginal survival curve $S(\cdot)$ is identifiable from large samples of data $\{(X_i, \Delta_i, Z_i)\}$ by (8) and (4) via $\rho(\cdot)$. Formula (8) is useful in estimating the behaviour of $\rho(\cdot)$ in stratified populations, for use in constructing bounds for future studies. Further remarks on how $\rho(\cdot)$ might be bounded are contained in §5.

4. EXAMPLES FROM STRATIFIED SURVIVAL MODELS

Suppose that the conditional hazard $h(t | Z)$ of T at t given Z has the form $\exp(\beta^T Z) h_0(t)$, and T and C are conditionally independent given Z . The large-sample estimates of β , $S_0(\cdot)$, the survival curve with hazard intensity $h_0(\cdot)$, and the distribution of Z , are consistent (Tsiatis, 1981), so that

$$\hat{S}_C(t) = N^{-1} \sum_{i=1}^N \{\hat{S}_0(t)\}^{\exp(\beta^T Z_i)}$$

consistently estimates $S(t)$. The Kaplan–Meier estimator, constructed from the entire nonstratified sample, generally has some other limit, which can be calculated. For example, if Z is discrete taking values $1, \dots, k$ with probabilities p_1, \dots, p_k and if T and C given $Z = j$ are independent exponential variables with parameters λ_j, μ_j , then

$$S(t) = \sum_{j=1}^k p_j \exp(-\lambda_j t), \quad \lim \hat{S}_{KM}(t) = \exp \left[- \int_0^t \{\psi(s) / S_X(s)\} ds \right] \tag{9}$$

as sample size N becomes infinite, where

$$\psi(s) = \sum \lambda_j p_j \exp\{-(\lambda_j + \mu_j) s\}, \quad S_X(s) = \sum p_j \exp\{-(\lambda_j + \mu_j) s\}.$$

We compared $\lim \hat{S}_{KM}(t)$ to $S(t)$ for numerous examples of such stratified populations by applying equations (9). Only for cases which involved both heavy censoring and μ_j varying directly or inversely with λ_j did we see significant discrepancies between $\lim \hat{S}_{KM}(t)$ and $S(t)$. If the magnitudes of the λ_j and μ_j are positively related, $\lim \hat{S}_{KM}(t)$ overestimates $S(t)$. If the magnitudes of the λ_j and μ_j are inversely related, $\lim \hat{S}_{KM}(t)$ underestimates $S(t)$. For example, we calculated $\lim \hat{S}_{KM}(t)$, for various values of t ,

for cases where the population is divided into five equally probable strata with vector of death rates $\lambda = (1, 2, 3, 4, 5)$. If the vector of censorship rates is $\mu = (2, 4, 6, 8, 10)$, the probability of censorship is 0.67, and $\lim \hat{S}_{KM}(t) = 0.557, 0.480$ and 0.312 for $t = S^{-1}(\frac{1}{2}), S^{-1}(0.4)$ and $S^{-1}(0.2)$, respectively. If $\mu = (10, 8, 6, 4, 2)$, the probability of censorship is 0.63, and $\lim \hat{S}_{KM}(t) = 0.441, 0.318$ and 0.087 for the same three values of t .

We also considered examples of the stratified population model where the make-up of the entry population varies over the accrual period, and all censorship is administrative at the end of the study. In this model, if, for example, the patients in the high-risk strata tend to enter late in the accrual period, there will be a positive relation between death and censorship hazard rates. Although it is not hard to construct artificial examples in which time trends in the entering patient population will have an extreme effect on summary survival estimates, we found here as in other stratified population models that only strong trends coupled with heavy censoring leads to noticeable bias.

Table 1 illustrates the close agreement between $\hat{S}_{KM}(\cdot)$ and $\hat{S}_C(\cdot)$ that can be found in typical practice. We used the most recent data for 167 stage III and IV patients from VACURG Study 2 of prostate cancer who died of myocardial infarct, pulmonary embolus,

Table 1. Summary survival curves for 167 patients from VACURG prostate-cancer Study 2 who died from cardiovascular related causes; t_i , months follow-up; r_i , number at risk

t_i	r_i	\hat{S}_{KM}	\hat{S}_C	\hat{S}_0	$\hat{S}_{0.33}$	$\hat{S}_{\frac{1}{2}}$	\hat{S}_2	\hat{S}_5	\hat{S}_∞
4	146	0.897	0.899	0.898	0.898	0.898	0.896	0.893	0.862
12	124	0.788	0.792	0.796	0.793	0.792	0.781	0.764	0.719
20	107	0.701	0.707	0.719	0.712	0.709	0.687	0.661	0.611
30	80	0.577	0.583	0.617	0.602	0.595	0.550	0.506	0.449
38	60	0.475	0.480	0.539	0.514	0.503	0.437	0.388	0.353
51	34	0.310	0.309	0.431	0.379	0.358	0.257	0.207	0.174

One hundred and thirteen died from myocardial infarct, response; 54 from pulmonary embolus or stroke, censoring.

Covariates in model for S_C were: age, indicator of history of pretreatment cardiovascular disease, systolic and diastolic blood pressure, three EKG indicators, and standardized weight.

or cerebro-vascular accident and for whom complete cardiovascular-related covariates were available (Byar, 1973). A proportional hazards model with eight covariates was estimated, using death from myocardial infarct as the response variable and death from the other two competing causes as censorship. The estimators \hat{S}_{KM} and \hat{S}_C are always within 0.006 of one another, even though the Peterson bounds $\hat{S}_\infty(\cdot)$ and $\hat{S}_0(\cdot)$ are quite far apart. Our bounds $\hat{S}_5(\cdot)$ and $\hat{S}_{0.33}(\cdot)$ are somewhat closer, and $\hat{S}_2(\cdot), \hat{S}_{\frac{1}{2}}(\cdot)$ are close enough to give useful information on the sensitivity of \hat{S} to slight dependence between death and censoring. It is worth emphasizing that \hat{S}_C is calculated via the assumption of stratumwise independence of death and censoring, but if there were stratumwise dependence with $\rho(t|Z)$ always between $\frac{1}{2}$ and 2 the curves $\hat{S}_2(\cdot), \hat{S}_{\frac{1}{2}}(\cdot)$ would approximately bracket the true survival function. This set of data was chosen as one where it is plausible to expect dependence between death and censoring times within strata, but such dependence is unidentifiable from the survival data $\{(X_i, \Delta_i, Z_i)\}$, as has been discussed above.

5. CONCLUSIONS

In constructing summary survival curves it has been the rule to assume that the death and censoring hazard rates are independent. The two primary reasons for this are (1)

that the observed $\{(X_i, \Delta_i)\}$, can in no way contradict this assumption, by the nonidentifiability argument, and (2) that the Peterson bounds, in the presence of even modest censoring, are generally too broad to be useful. When covariate information is available, the data $\{(X_i, \Delta_i, Z_i)\}$ can in principle contradict the assumption of independent censoring by yielding an estimated $\rho(\cdot)$ function, via formula (8), not equal to 1. However, unless there is significant censoring and a systematic and pronounced dependence between death and censoring, mediated by the Z_i , the Kaplan–Meier summary survival curve $\hat{S}_{KM}(\cdot)$, calculated under the assumption of independence, will not differ much from the true $S(\cdot)$ or from \hat{S}_C . When systematic dependence is suspected beyond that mediated by the Z_i , i.e. when there is dependent censoring within strata, one can calculate bounds (7) on $S(t)$ in terms of assumed bounds on the $\rho(\cdot)$ function used to define the degree of this dependence. Conceptualizing the $\rho(\cdot)$ function as a hazard ratio within a generalized Freund model should help in determining reasonable bounds. Alternatively, one may use the best available risk-prognostic covariate factors to assess the group differences between the patients lost to follow-up and those remaining and thereby indirectly to guess at bounds for $\rho(\cdot)$. The resulting bounds on $S(\cdot)$ can be much tighter than those of Peterson (1976).

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