STATISTICAL METHODS FOR DEPENDENT COMPETING RISKS

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Many biological and medical studies have as a response of interest the time to occurrence of some event, X, such as the occurrence of cessation of smoking, conception, a particular symptom or disease, remission, relapse, death due to some specific disease, or simply death. Often it is impossible to measure X due to the occurrence of some other competing event, usually termed a competing risk. This competing event may be the withdrawal of the subject from the study (for whatever reason), death from some cause other than the one of interest, or any eventuality that precludes the main event of interest from occurring. Usually the assumption is made that all such censoring times and lifetimes are independent. In this case one uses either the Kaplan-Meier estimator or the Nelson-Aalen estimator to estimate the survival function. However, if the competing risk or censoring times are not independent of X, then there is no generally acceptable way to estimate the survival function. There has been considerable work devoted to this problem of dependent competing risks scattered throughout the statistical literature in the past several years and this paper presents a survey of such work.

1. Introduction

A common problem encountered in biological and medical studies (both animal and human) is to estimate the survival function of the time X, from some appropriate starting point, until some event of interest (such as the occurrence of cessation of smoking, conception, a particular disease, remission, relapse, death due to some specific disease, or simply death) occurs. Often it is impossible to measure X due to the occurrence of some other competing event, usually termed a competing risk. For example, this competing event may be the withdrawal of the subject from the study (for whatever reason), death from some cause other than the one of interest or any other eventuality that precludes the main event of interest from occurring. Thus there can be many competing risks, both dependent and independent. With such a competing-risks representation, it is often assumed that the main event time, X, of interest, the competing event times and the censoring times are all independent. This allows for the consistent estimation of the survival function of X, $S(x) = Pr(X \geq x)$. This assumption of independence is made in many competing-risks experiments involving parametric or semi-parametric estimation of the survival function, k-sample testing problems, or regression problems (Cox (1972), Cox and Oakes (1984), and Andersen, et.al. (1993)).

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A standard statistical estimator of the survival function that assumes such competing events (or risks) to be independent is the product-limit estimator of Kaplan and Meier (1958). This estimator is nonparametric and consistent for the class of constant-sum survival models defined by Williams and Lagakos (1977). When the risks are not in this class the product-limit estimator is inconsistent and, in such cases, the investigator may be appreciably misled by assuming independence [see Lagakos and Williams (1978), Lagakos (1979), Moeschberger and Klein (1984), Klein and Moeschberger (1984, 1986, 1987), Slud and Byar (1988) for details]. Of equal importance is an estimator of the cumulative hazard function first proposed by Nelson (1972) in a reliability context and rediscovered by Aalen (1978) who derived the estimator using modern counting process techniques. Again independence of the competing risks and censoring mechanism is crucial for this estimator to be a consistent estimator of the cumulative hazard of X. Of course, there are many reasons which give one confidence in assuming some of the risks to be independent, namely, end of study censoring, patients' moving to another location for reasons unrelated to treatment, accidental deaths, etc.

Unfortunately, there are situations in which such an independence assumption is of questionable validity. Lagakos (1979) mentions the following three situations where censoring indicates an unfavorable prognosis for future survival: a clinical trial in which some patients remove themselves from study for reasons possibly related to therapy and thereby censor their survival time under test conditions, a clinical trial in which those patients experiencing a specific critical event such as metastic spread of disease are, by design, removed from study and no longer followed for survival time, and a clinical trial or animal experiment in which failure times from causes of secondary interest are recorded as censored observations of the failure times from the causes of primary interest. Furthermore, there are conceivable situations where censoring indicates a favorable prognosis for future survival. For example, if a patient in a clinical trial is experiencing success with therapy, then that patient may feel free to move to another location and be considered a drop-out for the study.

Since methods have been extensively worked out for the independent risk situation, we shall restrict our attention only to those risks that are dependent. For simplicity in this discussion, we shall only assume one dependent competing risk whose event time will be denoted by Y. In the competing-risks framework we observe $T = \text{minimum}\,(X, Y)$ and $\delta = I(X < Y)$ is an indicator function which indicates whether or not the main event of interest has occurred. It is well known that the pair (T, δ) provides insufficient information to determine the joint distribution of X and Y. That is, there exists both an independent and one or more dependent models for (X, Y) that produce the same joint distribution for (T, δ). However, these "equivalent" independent and dependent joint distributions may have quite different marginal distributions. More detail on this non-identifiability problem is provided in the next section.

The main dilemma confronting the statistician analyzing data where there may be dependent censoring or competing risks is that, if the independence assumption regarding the pair (X, Y) is suspect, a plausible model for the joint distribution of (X, Y) must be assumed or an approach employing only the estimation of observable quantities must be adopted.

In summary, there are three approaches to dealing with the problem of dependent competing risks and dependent censoring times presented in the literature. The first approach, which assumes some plausible model for the joint distribution of the lifetimes and censoring or competing risk event times is discussed in Section 3. Here maximum likelihood estimators of the parameters may be accomplished which leads one to an estimate of the marginal ("net" or "pure") survival function. The second approach, which attempts to place

bounds on the marginal survival function, is discussed in Section 4. The last approach, involving only observable quantities and thus avoiding the inherent identifiability problem, is presented in Section 5. The interpretation of the results in this case is different than the intrepretations in Sections 3 and 4 and, in many cases, more appropriate.

2. Non-identifiability Issues

The early observation by Cox (1959, 1962) that there was a difficulty in the interpretation of bivariate data in the competing risk context was elucidated and clarified by later authors. Berman (1963) showed explicitly that the distribution of (T, δ) determined that of X, if X and Y are assumed to be independent. Tsiatis (1975) proved a non-identifiability theorem which concluded that a dependent risk model is indistinguishable from some independent risk model and that any analysis of such data should include a careful analysis of biological circumstances. Peterson (1976) argued that serious errors can be made in estimating the survival function in the competing risk problem because one can never know from the data whether X and Y are independent or not.

Crowder (1991) elaborates on the non-identifiability problem when information on the pair (T, δ) and the marginal distribution of X is known. He shows that even when such additional information on the marginal distribution of X is known (as might be the case in controlled experimental situations where it is possible to isolate the causes of equipment failure and study them one at a time) that the joint distribution of (X, Y) is still not identified. He also shows there may be an identifiability problem in engineering systems when breakdown only occurs when r out of p components have failed (as contrasted with the series system when the first failure causes the system to fail).

Heckman and Honore (1989) show, under certain regularity conditions, for both proportional hazards and accelerated failure time models that if there is an explanatory covariate, $\mathbf{Z}$, whose support is the entire real line then the joint distribution of (X, Y) is identifiable from $(T, \delta, \mathbf{Z})$. Slud (1992), in a slightly different vein, shows how the marginal distribution of the survival time X can be nonparametrically identifiable when only the data $(T, \delta, \mathbf{Z})$ are observed, where $\mathbf{Z}$ is an observed covariate such that the competing risk event time, Y, and $\mathbf{Z}$ are conditionally independent given X.

3. Methods Assuming Informative Censoring

One of the earlier attempts to indirectly take into consideration a form of informative censoring was presented by Kimball (1958, 1969), in the context of analyzing grouped failure data, where the probability of death by time t, if one could eliminate the competing risk, could be taken to be $P(T \leq t, \delta = 1|$ elimination of the competing risk$) = P(T \leq t, \delta = 1)/[1 - P(T \leq t, \delta = 0)]$. That is, items which would have failed from the competing risk will now fail from the main event of interest with probabilities related to those obtained before the competing risk was eliminated. As Kimball (1971) points out, the assumption of independent censoring is not required but it is not clear, in the context of individuals subject to a continuous censoring mechanism, what underlying biological or physical process would lead to such an estimate. Furthermore, Chiang (1970) pointed out that this model has an internal inconsistency for grouped data.

Later, a form of censoring which could occur when an individual is removed or removes himself/herself from an experiment because of either deterioration or improvement was provided by Fisher and Kanarek (1974). They assume that for such an individual with

censoring time $C = c$, a survival time $x - c$ after censoring is equivalent to one of $\alpha(x - c)$ if there had been no censoring ($\alpha > 0$). Here being censored occurs at the same time as an event which either "stretches" or "contracts" the survival by an amount associated with a scale parameter α.

More recently, Hoover and Guess (1990) have introduced a response linked censoring model which introduces a positive dependence between censoring time and response time. This model assumes censoring is caused by occurrence of the response or the fact that the response is about to occur. Their model of dependence conditions on different types of covariates, some of which affect the mechanism of informative censoring and some of which affect response.

Two other approaches have been presented when there is no strong reason to believe that censoring is noninformative. The first consists of a latent failure time approach. Moeschberger (1974) suggested this approach for joint lifetimes that may be bivariate Weibull or normal. In such instances, there is not an identifiability problem (see Basu and Klein (1982) for a discussion and references of identifiability of parametric joint distributions for (X, Y)). Gail (1975) adopted a similar approach in a competing risk setting. A detailed discussion of this approach is presented in David and Moeschberger (1978). It should be pointed out that this approach has not been without controversy [see Prentice, et.al. (1978), Slud, et.al. (1988) with rejoinder, and Slud (1992)]. Lagakos and Williams (1978) approached the problem by proposing a model for two censoring functions in terms of an unspecified relative-odds-for-failure function and a scalar which reflects the degree to which censoring affects survival.

A specific type of parametric approach introduced by Clayton (1978) to model association of bivariate lifetables and, later, by Oakes (1982) to model bivariate survival data uses the notion of a common random effect (either environmental or genetic), commonly called frailty. If X_0 and Y_0 denote the potential times to failure from the main event of interest and the competing risk, respectively, then an individual, who lives in an environment where various environmental stresses or biological exposures may produce a random effect W, will have the survival functions of X_0 and Y_0 changed to survival functions raised to the wth power, respectively. Thus a value of w less than 1 implies a joint improvement in the survival probabilities for the two risks, while a value of w greater than 1 implies a joint degradation.

For example, given a frailty, W, distributed as a gamma distribution with probability density function

$$g(w) = \{w^{(1/\alpha - 1)} \exp(-w/\alpha)\}/\Gamma(1/\alpha)\alpha^{1/\alpha}, \alpha \geq 0,$$

the joint distribution of the time until death and censoring, (X, Y) belongs to a family of distributions indexed by a dependence measure α with arbitrary marginals.

For this family, knowledge of α, or equivalently, $\alpha/(\alpha + 2)$ which is the well-known Kendall's τ for this model, along with the observable information, (T, δ), is sufficient to determine uniquely the marginal distributions of X and Y. Other models of the frailty (positive stable, inverse Gaussian, etc.) may be used.

In another approach, recently presented in a series of papers (see Robins, 1993 and Robins, 1992 for details and further references), Robins and coworkers have developed a strategy to study causal patterns of complex survival studies with time-dependent covariates. In particular, it appears that accounting for intermediate variables relating to several competing risk outcomes in the modelling process may impact on methods for analyzing dependent competing risk data.

4. Placing Bounds on the Marginal Survival Function

In light of the consequences of the untestable independence assumption in using the product-limit estimator to estimate the marginal survival function of X, it is important to consider bounds on this function based on the observable random variables (T, δ) and some assumptions on the joint behavior of X and Y. Peterson (1976) has obtained general bounds on the marginal survival function of $X, S(x) = Pr(X \geq x)$, based on the minimal and maximal dependence structure for (X, Y) obtained by Fréchet (1951). Let $P_x(t) = Pr(T \geq t, \delta = 1)$ and $P_y(t) = Pr(T > t, \delta = 0)$ be the crude survival functions of T. The bounds are $P_x(t) + P_y(t) \leq S(t) \leq P_x(t) + P_y(0)$. These bounds allow for any possible dependence structure and can be very wide.

Slud and Rubinstein (1983) have obtained tighter bounds on $S(x)$ in this framework by utilizing some additional information. Their method requires the investigator to bound the function

$$\rho(t) = \{[s(t)/q_x(t)] - 1\}/\{[S(t)/F(t)] - 1\} \tag{4.1}$$

where

$$s(t) = -\frac{dS(t)}{dt}, F(t) = Pr(\min(X, Y) > t),$$

and

$$q_x(t) = \frac{d}{dt} Pr(T < t, X < Y) = -\frac{dP_x(t)}{dt}.$$

Knowledge of the function $\rho(t)$ and the observable information, (T, δ), is sufficient to determine uniquely the marginal distribution of X. The resulting estimators $\widehat{S}_{\rho(x)}$ are decreasing functions of $\rho(\cdot)$. These resulting bounds are obtained by the investigator's specification of two functions, $\rho_i(t)[\rho_1(t) < \rho_2(t)]$ so that if the true $\rho(t)$ function is in the interval $[\rho_1(t) < \rho_2(t)]$, for all t, then $\widehat{S}_{\rho_2(t)} \leq S(t) \leq \widehat{S}_{\rho_1(t)}$.

Klein and Moeschberger (1988) obtain alternative bounds on the marginal survival function utilizing slightly different additional information. They model the joint distribution of (X, Y) in accordance with the gamma frailty model discussed in the previous section. The resulting estimator $\widehat{S}(t)$ is a decreasing function of α so that bounds on $S(t)$ for the family of joint distributions is obtained by specifying a range of possible values for α (or the familiar Kendall's coefficient of concordance).

Dignam, et.al. (1994) compare these bounds for data simulated from two bivariate exponential survival distributions, namely, a bivariate distribution proposed by Clayton (1978) and Oakes (1982) and one proposed by Hougaard (1986). The Peterson bounds were quite wide, as expected. Both the Slud-Rubenstein and Klein-Moeschberger methods performed reasonably well for these two distributions. However, more robustness studies need to be performed as well as more work is needed to develop ways of incorporating information from association or regression methods directly into the estimation of the survival function.

Zheng and Klein (1994a and 1994b) suggest specifying a range of copulas, nonparametric functions that capture the dependence between two random variables. Most nonparametric measures, such as Kendall's τ and Spearman's ρ, are normed distances of the copula of X and Y from the independence copula. Once the copula is specified, they suggest estimating $S(t)$ by either i) a modification of the self-consistency argument used in deriving the Kaplan-Meier estimator, ii) a generalization of the Klein-Moeschberger method which involves solving a system of differential equations, or iii) a graphical method (see the paper by Zheng and Klein (1994c) in this volume).

Link (1989) has suggested that, for situations in which censoring indicates an unfavorable prognosis for future survival, the Kaplan-Meier estimator (which will tend to overestimate the true survival probability) be used as an upper bound and the lower bound be taken by the empirical survival function of the observed random variable T.

5. Crude Incidence Curves

In this section an approach which involves only observable quantities, and thus avoids the inherent identifiability problem, is presented. Let

$$h_x(t) = \lim_{\Delta x \longrightarrow 0} \left[\frac{Pr(t \leq T < t + \Delta t, \delta = 1 | T \geq t)}{\Delta t} \right]$$

be the hazard function of X in the presence of the competing risks and

$$h(t) = \lim_{\Delta x \longrightarrow 0} \left[\frac{Pr(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \right]$$

be the overall hazard rate. Both $h_x(t)$ and $h(t)$ are estimable from the data without making any untestable assumptions.

The first approach, advocated initially by Prentice, et.al. (1978) and Kalbleisch and Prentice (1980), uses the cumulative "incidence" function

$$I_x(t) = P(T < t, \delta = 1) = \int_0^t h_x(u) \exp\left[- \int_0^u h(v) dv \right] du, \tag{5.1}$$

sometimes referred to, when X and Y are continuous, as the crude probability (Chiang (1968)), complement of the subdistribution function (Peterson (1976)), and absolute cause-specific risk (Benichou and Gail (1990)). The latter authors consider a slightly more general case of (5.1), namely, the absolute risk of occurrence of the event in $[t_1, t_2)$ given neither event has occurred by time t_1.

Pepe (1991) and Pepe and Mori (1993) interpret the cumulative incidence function as a "marginal probability". Note that this function is not a true marginal distribution as discussed earlier but rather is the chance of the event of interest occurring prior to time t in a system where an individual is exposed to both risks. Pepe and Mori suggest as an alternative to the cumulative incidence function the "conditional probability" of X, defined by $P(\{X \leq t, X < Y\} | \{Y < t, Y < X\}^c)$ which they interpret as the probability of X occurring in $[0, t)$, given nonoccurrence of Y in $[0, t)$, where A^c denotes the complement of A. While this rough interpretation may be valid when the competing event is a terminal event (as in the context of bone marrow transplantation), the interpretation is open to question when it is possible for X to occur after Y.

Gray (1988) presents a class of k-sample tests for comparing the cumulative incidence of a particular type of failure among different groups for right censored data. The tests are based on comparing weighted averages of the hazards of the subdistribution function for the failure type of interest and do not assume independent underlying processes leading to failures of different types.

Gaynor, et.al. (1993) discuss biases incurred by using the Kaplan-Meier estimator in examples from clinical oncology. In particular, in summarizing the results of using allogeneic bone marrow transplantation in patients with acute leukemia, it is of interest to provide

estimates of the probability of disease relapse, the probability of death without disease due to treatment-related complications, and the probability of disease relapse given that the patient will not die first of transplant-related complications. They provide a variety of other examples where specialized circumstances are present. Also, Korn and Dorey (1992) provide applications of crude incidence curves but hedge on their absolute use in the presence of dependent risks.

6. Summary

This paper has attempted to trace the historical efforts of the development of the statistical methods for dependent competing risks to the present time. As can be seen from the discussion, the earlier efforts were aimed at providing an answer to the question "How would the mortality experience of a population be altered if a specific competing event could be eliminated?" With the advent of the clinical trial, the emphasis shifted to the question "How does one treatment compare to another one in treating a disease?" Accordingly, interest shifted from using the marginal survival function to employing the crude incidence function in the inferential procedure. As is usually true in applying statistical methods, the nature of the scientific question in conjunction with biological understanding determines the statistical method to be used.

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