SOME RECENT RESULTS IN COMPETING RISKS THEORY

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1. Introduction

The problems of competing risks and complementary risks arise quite naturally in a number of contexts, particularly in problems of survival analysis and reliability theory. The problems, in their simplest form, may be described as follows. Let X_i be a random variable with cumulative distribution function (C.D.F.) $F_i(x)$, $(i = 1,2,\ldots,p)$. We assume that the X_i's are not observable but $U = \min(X_1,\ldots,X_p)$ or $V = \max(X_1,\ldots,X_p)$ is. We would like to determine uniquely the marginal C.D.F.'s, F_i's, from that of U in the competing risks problem or from that of V in the complementary risks problem. We would also consider related inference problems.

As examples of the concepts consider the following:

(a) Let X_i be the time to death (failure) from cause C_i (of component C_i). Here X_i's are not observable but we observe a death time U (or time to series system failure) or a time V at which the last remaining duplicated organ fails (time to failure of a parallel system).

(b) In survival analysis randomly censored data correspond to the situation when $p = 2$, X_1 is the variable of interest and X_2 the censoring variable.

In this report we present results in three areas of competing risks analysis. In Section 2 the problem of identifiability is discussed. In Section 3 we look at dependent competing risks and at techniques for converting dependent models to independent models which preserve the models' properties, in a sense to be discussed later. In Section 4 accelerated life tests in a competing risks framework are considered.

2. Identifiability

2.1 Introduction

Before we can consider the inference problems, we need to resolve the question of identifiability. Basu (1981a,b) has given a survey of the identifiability problem in the parametric case. Consider the following definition of identifiability.

DEFINITION 1: Let U be an observable random variable with C.D.F. F_θ and let $F_\theta \varepsilon \mathcal{F} = \{F_\theta : \theta \varepsilon \Omega\}$, a family of distribution functions indexed by a parameter θ. Here θ could be scaler or vector valued. θ is said to be nonidentifiable by U if there is at least one pair (θ,θ'), $\theta \neq \theta'$, where θ and θ' both are in Ω, such that $F_\theta(u) = F_{\theta'}(u)$ for all u. In the contrary case we shall say θ is identifiable.

In many cases, where θ is not identifiable, there exists a non-constant function $\gamma(\theta)$ which is identifiable. That is, for any $\theta,\theta' \varepsilon \Omega$, $F_\theta(u) = F_{\theta'}(u)$ for all u implies $\gamma(\theta) = \gamma(\theta')$. In this case θ is said to be partially identifiable.

In case θ is not identifiable by U, it may be possible to introduce an additional random variable I so that θ is identifiable by the augmented random variable (U,I). In this case the original identifiability problem is called rectifiable.

EXAMPLE 1: Let X_i be independent random variables with density functions $f_i(x) = \lambda_i \exp(-\lambda_i x)$, $(i=1,2)$. Let $\theta = (\lambda_1, \lambda_2)$. Here θ is not identifiable by U. However, θ is partially identifiable since $\gamma(\theta) = \lambda_1 + \lambda_2$ is identifiable. The problem is also rectifiable since θ is identifiable by (U,I) where $I = i$ if $U = X_i$, $(i = 1,2)$.

Complementary risks is the dual of competing risks since $\max(X_1,\ldots,X_p) = -\min(-X_1,\ldots,-X_p)$. Usually it is sufficient to consider the results in terms of U. However, there are situations when V is analytically simpler to study.

2.2 Independent Random Variables

Assume $X_1,\ldots,X_p$ are independent but not identically distributed random variables. Let $I = k$ if $U = \min(X_1,\ldots,X_p) = X_k$. Let $S_i(x) = P(X_i > x)$ and $S_i^*(x) = P(U > x,\ I = i)$ $(i = 1,\ldots,p)$. Then Berman (1963) has proved the identifiability of the F_i's in the following theorem.

THEOREM 1: (Berman (1963))

$$S_k^*(x) = -\int_x^\infty [\prod_{\substack{j=1 \\ j\neq k}}^{p} S_j(t)]\, dS_k(t)$$

and

$$S_k(x) = \exp[\int_0^x (\sum_{j=1}^{p} S_j^*(t))^{-1} dS_k^*(t)] \quad .$$

Theorem 1 justifies the estimation of parameters in the regression problem of Miller (1976). For $p = 2$, Peterson (1977) extends the result to the case where S_1 and S_2 have no common jump points.

THEOREM 2: (Peterson (1977))

$$S_i(t) = \exp\left\{ \int \frac{dS_1^*(x)}{S_1^*(x) + S_2^*(x)} + \sum_{\substack{s:\text{Jump point of } S_i(\cdot) \\ s \leq t}} \ell n \left[\frac{S_1^*(s^+) + S_2^*(s^+)}{S_1^*(s^-) + S_2^*(s^-)} \right] \right\} .$$

Theorem 2 gives an alternate representation for the survival function and the Kaplan-Meier (1958) estimator. It also helps proving the strong consistency of the Kaplan-Meier estimator.

Next, consider the case of the non-identified minimum. Basu and Ghosh (1980) prove the following result.

THEOREM 3: (Basu and Ghosh (1980))

Let $\mathcal{F}$ be a family of probability density functions (p.d.f.) on R_1 with support on (a,b) which are continuous and are positive to the left of some point A and such that if f and g are any two distinct members of $\mathcal{F}$ then $\lim_{x\to a}\{f(x)/g(x)\}$ is either 0 or ∞. Let X_i be independent with p.d.f. f_i in $\mathcal{F}$ $(i=1,2,\ldots,p)$ and Y_i be independent with p.d.f. $g_j \varepsilon \mathcal{F}$ $(j=1,\ldots,q)$. If $\min(X_1,\ldots,X_p)$ and $\min(Y_1,\ldots,Y_q)$ have identical distributions then $p=q$ and there exists a permutation $(k_1,\ldots,k_p)$ of $(1,\ldots,p)$ such that $q_i = f_{k_i}$ $(i=1,\ldots,p)$.

2.3 Dependent Random Variables

In the case of dependent competing risks Peterson (1976) has obtained bounds on the unobservable marginal survival probabilities $S_i(\cdot)$ in terms of observable crude survival probabilities $S_i^*(\cdot)$, in the case $p=2$. He also obtains a bound on the joint survival function $\bar{F}(x_1,x_2) = P(X_1 > x_1,\ X_2 > x_2)$ in the following theorem.

THEOREM 4: (Peterson (1976))

Let $S_i(x) = P(X_i > x)$, $S_i^*(x) = P(X_i > x,\ \min(X_1,X_2) = X_i)$, $p_1 = P(X_1 < X_2)$, and $p_2 = P(X_2 < X_1)$ then

$$\begin{aligned}\bar{F}(x_1,x_2) &= S_1^*(x_1) + S_2^*(x_2) - P(x_1 < X_1 < X_2 < x_2) \qquad \text{if } x_1 < x_2 \\ &= S_1^*(x_1) + S_2^*(x_2) - P(x_2 < X_2 < X_1 < x_1) \qquad \text{if } x_1 > x_2 \ .\end{aligned}$$

Also

$$S_1^*[\max(x_1,x_2)] + S_2^*[\max(x_1,x_2)] \le \bar{F}(x_1,x_2) \le S_1^*(x_1) + S_2^*(x_2)$$

and

$$S_1^*(x_1) + S_2^*(x_1) \le S_1(x_1) \le S_1^*(x_1) + p_2 \;,$$

$$S_1^*(x_2) + S_2^*(x_2) \le S_2(x_2) \le S_2^*(x_2) + p_2 \;.$$

Basu and Ghosh (1978) prove the following result which can be used in the identifiability problem.

THEOREM 5: (Basu and Ghosh (1978))

Let $\bar{F}_i(x_1,x_2) = \frac{\delta}{\delta x_i} \bar{F}(x_1,x_2)$, $(i=1,2)$ and let $f(x_1,x_2)$ be the joint p.d.f. of (X_1,X_2). Assume that $f(x_1,x_2) > 0$ for all (x_1,x_2) and

$$\int_{-\infty}^{\infty} - \bar{F}_i(z,z)\ (\bar{F}(z,z))^{-1}\ dz = \infty,\ (i=1,2).$$

Define

$$\bar{G}_i(x) = \exp\{- \int_{-\infty}^{x} - \bar{F}_i(z,z)\ (\bar{F}(z,z))^{-1}\ dz\}$$

$$= 1 - G_i(x) \;, \quad (i=1,2) \;,$$

then $G_i(\cdot)$ is a C.D.F. Let Y_i be independent and follow the distribution $G_i(\cdot)$, so that $\bar{G}(x_1,x_2) = \bar{G}_1(x_1)\ \bar{G}_2(x_2)$, then (U,I) has the same distribution whether (X_1,X_2) follow $F(x_1,x_2)$ or (X_1,X_2) follow $G(x_1,x_2)$.

In the case of dependence the identifiability problem makes sense for specified parametric distributions. Basu and Ghosh (1978 and 1980) have results for the bivariate normal distribution and multivariate exponential distributions (c.f. Block and Basu (1974), Marshall and Olkin (1967), Gumbel (1960)). Results for a general p follow readily for the exponential case.

3. Converting Dependent Models to Independent Ones

3.1 Basic Theorems

Implications of the result in Theorem 5 have also been considered by Miller (1977), Tsiatis (1975), Langberg, Proschan and Quinzi (1977,1981), and others. We state some of these results along with their implications.

As in the previous section let $\underline{X} = (X_1,\ldots,X_p)$ be a vector of positive random variables and let $U = \min(X_1,\ldots,X_p)$ be the observable system life. Let $\mathcal{I}$ denote the collection of nonempty subsets of $\{1,\ldots,P\}$. Let $\underline{H}$ be the vector of component life lengths in a series system of (2^P-1) components with system life T where the coordinates of H are indexed lexiographically by $I \in \mathcal{I}$. Define the failure patterns by

$$\xi(\underline{X}) = \begin{cases} I & \text{if } U = X_i \text{ for each } i \in I \text{ and } U \neq X_i \text{ for each } i \notin I \\ \emptyset & \text{otherwise} \end{cases}$$

and

$$\xi^*(\underline{H}) = \begin{cases} I & \text{if } H_I < H_J \text{ for each } J \neq I \\ \emptyset & \text{otherwise} \end{cases} .$$

We say $\underline{X}$ and $\underline{H}$ are equivalent in life length and failure pattern ($\underline{X} \overset{LP}{=} \underline{H}$) if $P(T > t,\ \xi^*(H) = I) = P(X > t,\ \xi(\underline{X}) = I)$, $t \geq 0$, $I \in \mathcal{I}$. When $\underline{X} \overset{LP}{=} \underline{H}$ then the two system lifetimes are identically distributed and corresponding failure patterns have the same chance of occurring.

Langberg et al (1978) give necessary and sufficient conditions for replacing a set of dependent life lengths $\underline{X}$ by a set of independent life lengths $\underline{H}$ such that $\underline{X} \overset{LP}{=} \underline{H}$ in the following theorem.

THEOREM 6: (Langberg et al (1978))

Let $U = \min(X_1,\ldots,X_p)$ denote the life length of a p-component series system, where X_i represents the life length of the i^{th} component, $i = 1,\ldots,p$. Define $\overline{F}_I(u) = P(U > u,\ \xi(\underline{X}) = I)$, $F_I(u) = P(U \leq u,\ \xi(\underline{X}) = I)$, $\overline{F}(u) = P(U > u)$ and $\alpha(F) = \sup\{u: \overline{F}(u) > 0\}$. Then the following statements hold:

(i) A necessary and sufficient condition for the existence of a set of independent random variables $(H_I,\ I \varepsilon \mathcal{I})$ which satisfy $\underline{H} \overset{LP}{=} \underline{X}$ is that the set of discontinuities of F_I be pairwise disjoint on the interval $[0,\alpha(F))$.

(ii) The distribution of $\{H_I,\ I \varepsilon \mathcal{I}\}$ in (i) are uniquely determined on the interval $[0,\alpha(F))$ as follows:

$$\overline{G}_I(t) = P(H_I > t) = \exp[-\int_0^t dF_I^c / \overline{F}] \tag{1}$$

$$\times \prod_{a(I,j) \leq t} \{\overline{F}(a(I,j)) / [\overline{F}(a(I,j)) + f_I(a(I,j))]\}\ ,$$

$0 \leq t < \alpha(F)$, where F_I^c is the continuous part of F_I, $\{a(I,j)\}$ is the set of discontinuities of F_I and $f_I(a(I,j))$ is the size of the jump of F_I at $a(I,j)$.

Langberg et al (1981) show how the marginal survival functions of the dependent system can be recovered from the equivalent in LP independent system. Let $S_I(\cdot)$ denote the marginal survival function of $\underline{X}_I = \{X_i,\ i \varepsilon I\}$.

THEOREM 7: (Langberg et al (1981))

Let $X_1,\ldots,X_p$ be non-negative random variables such that the functions $F(\cdot,\ \xi(\underline{X}) = I)$ have no common discontinuities. Let $I \varepsilon \mathcal{I}$. Then for each $t \varepsilon [0,\alpha(F)]$, $\overline{S}_I(t) = \prod_{J \varepsilon I} \overline{G}_J(t)$ if and only if the following two conditions hold:

$$\frac{S_I(a)}{S_I(a-)} = \begin{cases} \overline{F}(a)/\overline{F}(a-) & \text{for a discontinuity point of } F(\cdot,\xi(\underline{X}) = I) \\ 1 & \text{otherwise} \end{cases} \tag{C1}$$

and

$$P(X_{I'} \geq t \mid X_I = t) = P(X_{I'} > t \mid X_I > t), \tag{C2}$$

where I' is the complement of I in $\mathcal{I}$ and $\overline{G}$ is defined by (1).

EXAMPLE 2: Let $\underline{X} = (X_1, X_2)$ have the bivariate Weibull distribution described by Lee and Thompson (1974) with joint survival function

$$\overline{F}(x_1, x_2) = \exp(-\lambda_1 x_1^{\alpha_1} - \lambda_2 x_2^{\alpha_2} - \lambda_{12}[\max(x_1, x_2)]^{\alpha_{12}}) .$$

Applying Theorem 6 it follows that $\underline{X} \overset{LP}{=} (H_1, H_2, H_{12})$ where the H_i's are independent Weibull random variables with survival functions $\overline{G}_i(t) = \exp(-\lambda_i t^{\alpha_i})$, $i = 1, 2, 12$. The conditions of Theorem 7 are met so that $X_i = \min(H_i, H_{12})$, $i = 1, 2$.

3.2 Constant Sum Models

Let X_1 and X_2 be positive random variables representing the failure time and censoring time of an individual under study. In the random censorship model we observe $U = \min(X_1, X_2)$ and $I = 1$ if $U = X_I$ (a death) or $I = 2$ if $U = X_2$ (a loss). Williams and Lagakos (1977) have examined conditions on the joint distribution of X_1 and X_2 under which the likelihood based on n observations on (U, I) is independent of the censoring distribution of X_2. Let $a(t) = P(I = 1 | t \leq X_1 < t + dt)$ and $dB(t) = P(t \leq U < t + dt, I = 2 | U \geq t)$. A model (X_1, X_2) is said to be a constant sum model if and only if

$$a(t) + \int_0^t dB(y) = 1 \quad .$$

Kalbfleisch and McKay (1979) give an equivalent characterization of the constant sum condition in the following theorem.

THEOREM 8:

A model (X_1, X_2) is constant sum if and only if

$$P(t \leq X_2 < t + dt | U \geq t) = P(t \leq X_1 < t + dt | X_1 \geq t) .$$

We prove a sufficient condition for the constant sum model using the results of Langberg et al (1981).

THEROEM 9: A model (X_1,X_2) is constant sum if the set of discontinuities of $F_I(\cdot)$ are pairwise disjoint for all $I \varepsilon \mathcal{I}$, and ,

$$P(X_1 \geq x | X_2 = x) = P(X_1 > x | X_2 > x) \quad .$$

PROOF:

By Theorems 6 and 7, $(X_1 X_2) \overset{LP}{=} (H_1,H_2,H_{12})$ where the $H_{i's}$ are independent and $U = \min(H_1,H_2,H_{12})$ and $X_1 = \min(H_1,H_{12})$. Now

$$P(t \leq X_1 < t+dt | U \geq t) = P(t \leq X_1 < t+dt,\ U \geq t) \,/\, P(U \geq t)$$

$$= \frac{P(t \leq \min(H_1,H_{12}) < t+dt,\ \min(H_1,H_2,H_{12}) \geq t)}{P(\min(H_1,H_2,H_{12}) \geq t)}$$

$$= \frac{P(t \leq \min(H_1,H_{12}) < t+dt,\ H_1 \geq t,\ H_{12} \geq t)\ P(H_2 \geq t)}{P(H_1 \geq t,\ H_2 \geq t)\ P(H_2 \geq t)}$$

$$= P(t \leq X_1 < t+dt,\ X_1 \geq t) \,/\, P(X_1 \geq t)$$

$$= P(t \leq X_1 < t+dt | X_1 \geq t) \quad .$$

The result now follows by Theorem 8.

3.3 Inference When There is a Dependent Censoring Mechanism

The above result suggests using Theorem 6 to justify standard nonparametric techniques developed for censored data, under the assumption of an independent censoring mechanism, when the censoring mechanism is dependent but satisfies the conditions of Theorem 7. As an example consider the two sample problem. Let (X_1,X_2) and (Y_1,Y_2) be bivariate positive random variables. Suppose the marginal survival function of X_1 is $S_1(t)$ and the marginal survival function of Y_1 is $R_1(t)$ and X_2 and Y_2 are possibly dependent censoring variables. Observations on (X_1,X_2) consist of observing $\min(X_1,X_2)$ and the failure pattern $\xi(X_1,X_2)$. Similarly, for (Y_1,Y_2), we observe $\min(Y_1,Y_2)$ and $\xi(Y_1,Y_2)$. The problem is to test $H_0 : S_1(t) = R_1(t)$, $t \geq 0$ based on n_1 observations on (X_1,X_2) and n_2 observations on (Y_1,Y_2). Suppose the conditions of Theorem 7 hold for both

$\underline{X}$ and $\underline{Y}$. Then $(X_1,X_2) \overset{LP}{=} (H_1,H_2,H_{12})$ and $(Y_1,Y_2) \overset{LP}{=} (K_1,K_2,K_{12})$ where the H_i's and K_i's are independent with survival functions $\overline{G}_i$ and $\overline{M}_i$ $(i=1,2,12)$, respectively. Also $S_1(t) = \overline{G}_1(t)\ \overline{G}_2(t)$ and $R_1(t) = \overline{M}_1(t)\ \overline{M}_{12}(t)$. Hence, testing $S_1(t) = R_1(t)$ is equivalent to testing $H_0{:}\overline{M}_1(t)\ \overline{M}_{12}(t) = \overline{G}_1(t)\ \overline{G}_{12}(t)$. Observations with $\xi(X_1,X_2) = \{1\}$ or $\{1,2\}$ give complete information about $S_1(t)$. Similarly for $R_1(t)$. Those with $\xi(X_1,X_2) = \{2\}$ are censored for testing H_0: $S_1(t) = R_1(t)$ but now from independent censoring distributions. Thus standard nonparametric techniques for independent censoring variables such as Gehan (1965) or Efron (1966) may be used to test this hypothesis.

3.4 Estimating Joint Survival

Theorem 7 can be used to obtain a consistent estimator of the joint survival function, $\overline{F}(x_1,x_2)$, of a bivariate random variable (X_1,X_2). Suppose the conditions of Theorem 7 hold, then $(X_1,X_2) \overset{LP}{=} (H_1,H_2,H_{12})$ and $X_1 = \min(H_1,H_{12})$, $X_2 = \min(H_2,H_{12})$ with H_1,H_2,H_{12} independent. Now

$$\begin{aligned}
\overline{F}(x_1,x_2) &= P(X_1 > x_1,\ X_2 > x_2) \\
&= P(\min(H_1,H_{12}) > x_1,\ \min(H_2,H_{12}) > x_2) \\
&= P(H_1 > x_1,\ H_2 > x_2,\ H_{12} > \max(x_1,x_2)) \\
&= P(H_1 > x_1)\ P(H_2 > x_2)\ P(H_{12} > \max(x_1,x_2) \\
&= \overline{G}_1(x_1)\ \overline{G}_2(x_2)\ \overline{G}_{12}(\max(x_1,x_2)) \quad .
\end{aligned}$$

Let $\hat{\overline{G}}_i(t)$ be a consistent estimator of $\overline{G}_i(t)$ for $i=1,2,12$. A consistent estimator of $\overline{F}(x_1,x_2)$ is given by

$$\hat{\overline{F}}(x_1,x_2) = \hat{\overline{G}}_1(x_1)\ \hat{\overline{G}}_2(x_2)\ \hat{\overline{G}}_{12}(\max(x_1,x_2)) \quad .$$

4. Accelerated Life Testing and Safe Dose Estimation Under Competing Causes of Failure

Accelerated life testing of a product under more severe than normal conditions is commonly used to reduce test time and costs. Data collected at such accelerated conditions are used to obtain estimates of the parameters of a stress translation function. This function is then used to make inference about product life under normal operating conditions.

Klein and Basu (1981a,b,c) have considered the problem of accelerated life tests when the product of interest is a p component series system. Each of the components is assumed to have either exponential distributions or Weibull distributions with different or the same shape parameter.

Klein and Basu considered the following model. Let $X_1,\ldots,X_p$ denote the component life lengths in a p component series system. At a constant application of a stress $V_i (i=1,\ldots,s)$ assume that the j^{th} component has hazard rate given by

$$h_j(x, v_i; \underline{\alpha}_j, \underline{\beta}_j) = g_j(x, \underline{\alpha}_j)\, \lambda_j(V_i, \underline{\beta}_j), \quad i=1,\ldots,s \quad j=1,\ldots,P$$

as introduced in Klein and Basu (1981d). The α_j's may vary from component to component to allow for different component reliabilities. For $\lambda_j(V, \underline{\beta}_j)$ assume a model of the form

$$\lambda_j(V, \underline{\beta}_j) = \exp\Big(\sum_{\ell=0}^{k_j} \beta_{j\ell}\, \Theta_{j\ell}(V)\Big) \tag{2}$$

where $\Theta_{j0}(V)=1$ and $\Theta_{j1}(V),\ldots,\Theta_{jk_j}(V)$ are non-decreasing functions of V. The $\Theta_j(\cdot)$'s may differ from one component to another.

This model includes the standard models, namely, the power rule with $\lambda_j(V, \underline{\beta}_j) = \beta_{j0} V^{\beta_{j1}}$, the Arrhenius reaction rate model with $\lambda_j(V, \underline{\beta}_j) = \exp(\beta_{j0} - \beta_{j1}/V)$, and the Eyring model for a single stress with

$\lambda_j(V, \underline{\beta}_j) = V^{\beta_{j1}} \exp(\beta_{j0} - \beta_{j2}/V)$, as special cases.

The model can be derived from the interpretation of the effects of a carcinogen on a cell as proposed by Armitage and Doll (1961). For details see Klein and Basu (1981d). To produce cancer in a single cell k independent events must occur. The effects of an increased dose of a carcinogen is to increase the rate at which these k events occur. If, for the j^{th} disease, this increase is of the form $\exp(\beta_{j\ell}\Theta_{j\ell}(V))$, $(\ell = 1,\ldots,k_j)$ the model (2) is obtained. If this increase is linear in V the model of Hartley and Sielkin (1977) is obtained. Thus their model is a first order Taylor series approximation to (2). Klein and Basu (1981c) have extended the results of Hartley and Sielkin (1977) to the competing risks model.

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