FRAILTY MODELS FOR MULTIPLE EVENT TIMES

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ABSTRACT. In some clinical, epidemiologic and animal studies multiple events, possibly of different types, may occur to the same experimental unit at different times. Examples of such data include times to tumor detection, times from remission to relapse into an acute disease phase, and times to discontinuation of an experimental medication. Methods for the statistical analysis of such data need to account for heterogeneity between subjects. This can be achieved by incorporation of additional unobserved random effects into standard survival models. We concentrate on models including frailties - unobserved random proportionality factors applied to the time-dependent intensity function. In this paper we survey some such models, exhibit connections with extensions of the standard Andersen-Gill (1982) model for multiple event times that are reminiscent of the classical results of Greenwood and Yule (1920) on "accident - proneness", and discuss methods of inference about the frailty distribution and regression parameters. The methods are illustrated by application to some animal tumor data of Gail, Santner and Brown (1980) and to data from a recently completed large multicenter clinical trial.

1. Introduction

Often in clinical studies the primary response variable is the time to some event, generically called a "failure", such as the detection of a new visible tumor, recurrence of disease after treatment, or death. Usually interest centers on the dependence of this "survival time" on explanatory variables such as diet, initial disease stage or treatment administered. The survival times of those subjects who remain failure free at the end of the period of observation will be right censored. Conventional methods for the analysis of such data using Cox's (1972a) proportional hazards model - see for example Kalbfleisch and Prentice (1980) or Cox and Oakes (1984) - assume that any subject experiences failure at most once, and that failure times of different study subjects are independent. These assumptions are violated if a study subject can experience multiple failures, or if there is some natural or artificial matching of the subjects that induces a correlation between the survival times of related individuals.

In this paper we focus on issues that arise when multiple failures may be observed on each subject. The models we discuss are generally appropriate when there are a fairly small number of failures on each of a large number of study subjects. Examples of such data abound. Gail, Santner and Brown (1980) give data on times to occurrence of mammary tumors in 48 rats injected with a carcinogen and subsequently randomized to either retinoid prophylaxis treatment or to a control. The numbers of new tumors detected for each animal in a uniform 182 days of follow-up ranged from zero to 13, with means (standard deviations) of 2.65 (1.95) for the treated group and 6.04 (3.94) for the control group. In

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the recently completed multicenter diltiazem post-infarction trial (Multicenter Diltiazem Post-Infarction Trial Research Group, 1988) a double-blind, placebo controlled clinical trial of diltiazem therapy for post-infarction patients, the primary analysis was based on the time to the first recurrent cardiac event (death or nonfatal reinfarction) an event which by definition can occur at most once for each subject. It is of interest to explore the extra information regarding treatment effects provided by the second and subsequent recurrent events. Also in this trial, records were kept of drug initiations and discontinuations for each subject. We can view drug discontinuations as a secondary outcome variable because they may be prompted by side effects of the treatment or by a general decline in clinical status. This example differs from the previous one in two respects. First, the length of follow-up varies from subject to subject (1-3 years) and secondly, regarding the discontinuation analysis, patients cannot be at risk for discontinuation of medication unless they are at that time on study medication.

Several methods have been proposed to allow for the possibility of multiple events per subject. Andersen and Gill (1982) proposed a simple extension of Cox's (1972a) model to allow for multiple events and extended Cox's (1975) partial likelihood to this situation. Their model makes the assumption that the risk of an event for a given subject is unaffected by any earlier events that occurred to the same subject, unless terms that capture such dependence are included explicitly in the model as covariates. An interesting and potentially very useful extension of this class of models can now be fitted using the "time-dependent stratification" option recently introduced into the program BMDP2L (Dixon et al, 1988). These models allow the baseline hazard functions to depend arbitrarily on the number of previous events. As in Andersen and Gill's model, time is always measured from the start of follow-up, so that sojourn times to the j'th event, other than to the first, are subject to left-truncation (Cox and Oakes, 1984, p178) as well as right-censorship. Other authors, for example Lagakos, Sommer and Zelen (1978), have proposed Markov and semi-Markov models for transitions between states defined by the number and type of previous events. Here the time clock is reset to zero at each transition. Such models have many parameters and can be hard to interpret. Also the dependence implied by the Markov structure decays rapidly as the number of intermediate transitions increases. An intriguing class of models, modulated renewal processes (Cox, 1972b) has not been widely used, perhaps because of the difficulty of obtaining an appropriate estimate of the asymptotic covariance matrix of the parameter estimates (Oakes, 1981). However it should be noted that recent unpublished simulation studies by Lu Cui, a doctoral student at the University of Rochester, have given encouragement to the use of second derivative of the log-likelihood in the usual way, even though the partial likelihood justification for this approach is lacking.

2. Frailty Models

Our approach to the analysis of multiple event times is via the concept of frailty introduced by Vaupel, Manton and Stallard (1979). Briefly, a frailty is an unobserved random proportionality factor which applies to the hazard function for each subject. So if

$$b(t) = \lim_{\delta \to 0} \frac{1}{\delta} \, pr(T \leq t + \delta | T > t, W = 1)$$

is the so-called baseline hazard for a subject whose frailty is $W = 1$ the hazard for a subject whose frailty is $W = w$ is $wb(t)$. Frailties for different subjects are supposed independent and identically distributed according to a distribution $dF(w)$ with Laplace transform $p(s) = E(e^{-sW}) = \int e^{-sw} dF(w)$.

Aalen (1988) gives an authoritative survey and many new results. As he notes, the introduction of heterogeneity effects via frailties leads to severe problems of identifiability when only one event can be observed for each subject. For it is easily seen that the unconditional distribution of the survival time T is

$$S(t) = \int \exp\{-wB(t)\}dF(w) = p\{B(t)\},$$

where $B(t) = \int_0^t b(u)du$ is the integrated baseline hazard function. If only the unconditional ("marginal") distribution of T is observed then it is clearly impossible to recover the two unknown functions p(.) and B(.) from data only on S(.).

Oakes (1989) showed that the identifiability problem is radically different for bivariate frailty models, that is when data are available on pairs of individuals where the two members of a pair have the same value of the frailty W and their survival times T_1 and T_2 are assumed to be conditionally independent given W. For, writing $t = (t_1,t_2)$ for the bivariate survival time, the observable joint survivor function is

$$S(t) = \int \exp[-w\{B(t_1) + B(t_2)\}]dF(w) = p\{B_1(t_1) + B_2(t_2)\},$$

where $B_1(.)$ and $B_2(.)$ are the baseline integrated hazard functions for T_1 and T_2. It turns out that the function p(.) is uniquely determined by S(.) up to a scale factor, through the inverse function, q(.) of p(.) which satisfies the equation

$$\frac{q''(v)}{q'(v)} = -\frac{\theta(v)}{v},$$

which may be integrated directly. Here $\theta(v)$ is the cross-ratio function $S_{11}(t)S(t)/\{S_{01}(t)S_{10}(t)\}$ where $v = S(t)$ and the subscripts denote the order of the derivatives in the two components of t.

Introduction of fixed covariate effects into a frailty model leads to one immediate conceptual issue. The action of the fixed effects on the failure time may be specified either conditionally on the value of the frailty W or unconditionally in terms of the observable distributions of survival time. In standard linear Gaussian models, for example mixed model ANOVA, the two specifications are equivalent, but this is not true for frailty models. If the conditional action of a covariate is governed by the proportional hazards model, its unconditional action will not be in general. The conditional specification is more naturally related to underlying mechanisms, but the unconditional specification leads to simpler methods of analysis. For example, a "working independence model" (Huster, Brookmeyer and Self, 1989) which simply ignores the existence of the random effects will typically lead to inefficient but consistent estimates of the fixed effects under an unconditional model. Under a conditional specification these estimates will not be consistent.

Hougaard (1986) noted that the conditional and unconditional specifications can be reconciled if and only if the frailty follows a positive stable distribution (Feller, 1971, p170) which has Laplace transform $p(s) = \exp(-s^\alpha)$, $(0 < \alpha \leq 1)$. Then if the unconditional action of a covariate, representing say the log-hazard ratio for treated and untreated subjects

having the same value of W is β its unconditional action, representing the log-hazard ratio for treated and untreated subjects having different values of W, is $\alpha\beta$. The effect of the random term is to shrink the regression coefficient towards zero, but the proportional hazards model itself is still preserved. Were the frailty to have, say, a gamma distribution, the proportional hazards model could not hold both conditionally and unconditionally.

When there are no covariates, Andersen and Gill's (1982) model for multiple events reduces to a simple non-stationary Poisson process in which the intensity function $b_{ij}(t)$ for the time $T_{i,j+1}$ to the j+1'th event to the i'th subject, conditional on previous events occurring to that subject at times $0 < t_1,...,t_j < t$ is

$$b_{ij}(t) = \lim_{\delta \to 0} \frac{1}{\delta} \, pr(T_{i,j+1} \leq t + \delta | T_{i1} = t_1,..., T_{ij} = t_j, T_{i,j+1} > t) = b(t).$$

The total number $D_i(t)$ of events for subject i over any time interval (0,t) then follows a Poisson distribution with mean $B(t) = \int_0^t b(u)du$.

3. Frailty Models for Multiple Events

Suppose now that a subject-specific random frailty is introduced into the Andersen-Gill model. Then the intensity function above becomes, conditionally on the value w_i of this frailty, $b_{ij}(t|w) = w_i b(t)$. This is, of course, the defining property of a so-called mixed Poisson process (c.f. Karr (1991, p7)). Still conditioning on w_i, the total number $D_i(t)$ of events to the i'th subject over the interval (0,t) follows a Poisson distribution with mean $w_i B(t)$. Integration over the distribution of the unobserved frailty w_i converts this into a mixed Poisson distribution.

The modified Andersen-Gill model, still without covariates, allows the intensity function to depend on the number of previous events experienced by the subject, so that $b_{ij}(t) = b_j(t)$ for some functions $b_j(.)$. Survivor functions corresponding to each $b_j(.)$ can then be estimated using the well-known modification of Kaplan and Meier's (1958) estimator for data that are subject to left truncation as well as right censorship. To include the effects of covariates z_i in this model we may write $b_{ij}(t) = \phi_i b_{0j}(t)$, where $\phi_i = \exp(\beta z_i)$ and $b_{0j}(t)$ are the intensity functions corresponding to $z_i = 0$. This model may be fitted, using the "time-dependent stratification" option in the program BMDP2L.

There is an interesting and useful relationship between the mixed Poisson (subject-specific frailty) model and the modified Andersen-Gill model. Although reminiscent of the classic "accident-proneness" models of Greenwood and Yule (1920) - see Neyman and Scott (1972) - it has not been fully exploited in the recent survival analysis literature.

Let $h_j(t|t_1,...,t_j) = E(Wb(t)|T_1 = t_1,...,T_j = t_j)$ denote the observable intensity function at t in the subject-specific frailty model, still conditioning on the times $t_1,...,t_j$ of the j previous events in (0,t) but integrating over the distribution of the unobserved frailty W. We drop the subscript i for notational convenience. It is easily shown (c.f. Karr (1991, p274)) that given the number D(t) = j of events in (0,t) their locations $T_1,...,T_j$ are independent of W so that D(t) carries all the available predictive information from the "past" of the process about its future. This implies that $h_j(.|.)$ is a function of its first argument only, which is precisely the definition of the modified Andersen-Gill model.

We can derive an expression for $H_j(t) = \int_0^t h_j(u)du$ in terms of the baseline integrated hazard $B(t) = \int_0^t b(u)du$ and the Laplace transform p(.) of the frailty distribution. We find that

$$H_j(t) = -\log[p^{(j)}\{B(t)\}/p^{(j)}(0)].$$

An immediate consequence of Muntz's theorem (Feller (1971, p430)) is that in the subject-specific frailty model the distribution of the frailty W is identifiable up to a scale factor as $n \to \infty$ from the observed data on n subjects over any period (0,t) even when the baseline intensity function b(.) is unknown. A different characterization can be given in terms of the two intensity functions $h_0(.)$ and $h_1(.)$. Their ratio is given by

$$\frac{h_1(t)}{h_0(t)} = \frac{p''\{B(t)\}p\{B(t)\}}{[p'\{B(t)\}]^2} .$$

Written as a function of $v = \exp\{- H_0(t)\} = p\{B(t)\}$ this becomes

$$\theta(v) = - \frac{vq''(v)}{q'(v)} .$$

This is the equation that Oakes (1989) derived for the bivariate frailty model, so that the results of that paper also apply here. In particular the function $\theta(.)$ characterizes the distribution of W up to a scale factor. In the sequel we shall take this scale factor to be unity. Of special interest is the case $\theta(v) = c > 1$ a constant intensity ratio, which yields $p(s) = (1+ \kappa s)^{-1/\kappa}$ where $c = 1+ \kappa$, the Laplace transform of a gamma distribution with index $1/\kappa$, unit mean and variance κ.

It follows immediately that all the intensity ratios $h_j(t)/h_0(t)$ are constant, with values $1+j\kappa$.

Gail, Santner and Brown (1980) mention an "m-site model" for the tumor data. According to this model, the total number of tumors that would occur in any animal over the interval $(0,\infty)$ is fixed, say at m. The times at which they actually occur are independent and identically distributed random variables, say with density g(t) and hazard function $h_g(t)$. It is easily seen that the m-site model also yields a modified Andersen-Gill model, with $h_j(t) = (m - j)h_g(t)$. However in this model the occurrence of each event reduces the risk of subsequent events to the same individual, since the total number of events is fixed. A natural generalization of this model is to allow m to be the realization of a random variable M. It is easily seen that if M has a Poisson distribution with mean μ then a *simple* Andersen-Gill model with intensity $h_j(t) = \mu g(t)$ is obtained (c.f. Neyman and Scott (1972)). Finally if we multiply μ by the random variable W, so that M has a mixed Poisson distribution, we obtain the frailty model just discussed. One advantage of this representation is that the latent (unobserved) random variable W which usually has a continuous distribution, can be replaced by a discrete random variable M. This could be helpful in computational work, for example involving the E-M algorithm or the Gibbs sampler.

Incorporation of covariates into models that include frailties can be achieved in several ways. As before, in the subject-specific frailty model the conditional specification, in which the action of the covariates on the baseline intensity function b(t) is specified conditionally on the frailty, and the unconditional specification can both give proportional intensities only if the frailty distribution is positive stable. Even in this case the proportionality would hold only among the $h_{i0}(t)$ not among the $h_{ij}(t)$ $(j > 0)$. Also, since the positive stable distribution has infinite mean, the expected number of events in any interval would be infinite. A possible way to avoid this unappealing property is to condition on there being no events in some prior interval $(-\delta_n,0)$ (c.f. Crowder (1989)) and consider a sequence of models in which both $\delta_n \to 0$ and the baseline hazard function

$b_n(t) \to 0$ at appropriate rates. In general however, the gamma distribution is more attractive than the positive stable in this context, in which case different models are obtained with the conditional and unconditional regression specifications.

4. Marginal Model For Covariates With Gamma Frailties

In the remainder of this paper we focus on a model with a gamma distribution of frailties and in which the covariates act on the marginal intensities through a proportional intensity model. Lawless (1987) and Abu-Libdeh, Turnbull and Clark (1990) consider models with covariates acting on the baseline intensities. Since the gamma frailty model ensures that the intensities $h_{ij}(t)$, $j = 0,1,...$ for a a given subject i are proportional, by taking proportionality between subjects for a single j say $j = 0$ we force proportionality among all the functions $h_{ij}(t)$, $i = 1,2,...$, $j = 0,1,...$. It is easily seen that the proportionality factor among the $h_{ij}(.)$ for fixed j does not depend on j so that the modified Andersen-Gill model holds and the standard software, which works with the product of the partial likelihoods over each time-dependent stratum, may be used to estimate the covariate effects. However, a more efficient procedure is to form a single partial likelihood which allows the joint estimation of the frailty parameter κ and the covariate effects. We have

$$h_{ij}(t) = (1 + j\kappa)\phi_i h_0(t),$$

where $\kappa = \text{var}(W)$ and $\phi_i = \exp(\beta z_i)$ is the proportionality factor among the hazard functions for a common value of j. For simplicity we shall ignore the possibility of ties and write d(i) for the observed number of failures experienced by the i'th subject, with the conventions that $T_{i0} = 0$ and $T_{i,d(i)+1}$ denotes that subject's censoring time. The partial likelihood (actually now a conditional likelihood if the censoring times are prespecified) in the regression coefficients β and frailty parameter κ is

$$\text{lik}(\beta,\kappa) = \prod_{i=1}^{n} \prod_{j=1}^{d(i)} \frac{\{1 + (j - 1)\kappa\}\phi_i}{\sum_{k \in R(i,j)} \{1 + j'(k)\kappa\}\phi_k}$$

where $R(i,j) = \{k : \exists\ j'(k);\ T_{k,j'(k)} < T_{ij} < T_{k,j'(k)+1}\}$ and this expression serves also to define j'(k).

Note that if κ were known, there is an appealing interpretation of partial likelihood in terms of each event resulting in an augmentation of subsequent risk sets by a further κ individuals with the same covariate values and event and censoring times as the individual who experienced the event.

5. Examples

The model of the previous section was fit to the tumor data of Gail, Santner and Brown (1980), with a single binary covariate to indicate group membership. The parameter estimates and their standard errors were $\hat{\kappa} = 0.329$ (s.e. 0.125), $\hat{\phi} = 0.566$ (s.e. 0.091). There is thus strong evidence that $\kappa \neq 0$ and that $\phi \neq 1$. For comparison we also fitted the simple Andersen-Gill model, that is with $\kappa = 0$. It is easy to show that in this case, the uniform follow-up time for all animals gives a simple closed form for the estimate, namely

$$\hat{\phi} = \frac{d_1 n_0}{d_0 n_1},$$

where d_0, n_0 and d_1, n_1 are the total numbers of events and animals in the control and treatment groups. We obtained $\hat{\phi}_{\kappa=0} = 0.4391$. Allowance for the frailty has attenuated this simple estimate. The likelihood ratio test of the hypothesis $\kappa = 0$ gives a chi-square on one degree of freedom of 2(-793.37 - (-804.54)) = 22.3, again giving strong evidence against the simple Andersen-Gill model.

Notice that under the full model, ϕ represents the ratio of intensity functions for the two groups, conditionally on there being exactly j prior failures in each group. It does not represent either the unconditional ratio of the two intensities, or the conditional ratio given W. Under our model both these ratios would depend on t

Our second example is the multi-center diltiazem post-infarction trial, which enrolled 2466 patients from 34 centers. The primary analysis (Multi-Center Diltiazem Post-infarction Trial Research Group, 1988) showed no significant overall effect of diltiazem therapy on the primary outcome variable (first recurrent cardiac event), but gave strong evidence of a "bidirectional" (qualitative) interaction between diltiazem therapy and pulmonary congestion on X-ray, a measure of left ventricular dysfunction. Diltiazem therapy appeared to have beneficial effects among the majority (80%) of patients without pulmonary congestion, but harmful effects among the minority (20%) of patients with pulmonary congestion on X-ray. Subsequent exploratory analyses of the data supported this finding (Moss et al, 1989). To illustrate our methodology we fit the frailty model to the subgroup of patients with pulmonary congestion. There were 97 recurrent events among the 248 patients assigned to active treatment in this subgroup, compared with 79 events among the 242 subjects assigned to placebo. We found strong evidence of heterogeneity, with $\hat{\kappa} = 1.96$ (s.e. 0.57). The estimated log-relative risk associated with diltiazem therapy was $\hat{\beta} = 0.297$ (s.e. 0.152). A similar analysis restricted to the first recurrent event, gave $\hat{\beta} = 0.183$ (s.e. 0.166). This differs from the analysis reported in the primary paper, because the latter included (prespecified) adjustments for three baseline covariates and was also stratified by center.

For a larger example we fit the same model to data on drug discontinuations in MDPIT. Only discontinuations prior to the end of the study or to the first recurrent cardiac event, the primary outcome measure for the trial, were included in this analysis. The numbers of discontinuations in the two groups followed Poisson distributions quite closely, with means 0.738 and 0.799 and standard deviations 0.834 and 0.898 respectively. However the fit of the frailty model showed substantial and significant heterogeneity, $\hat{\kappa} = 0.59$ (s.e. 0.074). The log-relative risk was estimated as $\hat{\beta} = 0.038$ (s.e. 0.048). For comparison, the simple Andersen-Gill model gave $\hat{\beta} = 0.064$ (s.e. 0.046), so for this analysis allowance for heterogeneity has attenuated the treatment effect. In neither analysis however, was this difference significant. Separate analyses for patients with and without pulmonary congestion revealed no interaction with treatment in this example.

One further issue remains to be addressed in this example. As mentioned earlier, patients are not at risk of discontinuation of medication at any time when they are already off medication. Strictly speaking the proposed model is therefore inappropriate and should

be replaced by one in which the intensity for a discontinuation is zero in the interval between a discontinuation and a subsequent initiation. Such models can certainly be formulated and fitted - however the connection between the simple frailty model and the Andersen-Gill model is lost. For the present data, lengths of time that subjects were off medication were typically quite short, so these more complex models were not considered.

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