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Analysis of Survival Data with Clustered Events

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ABSTRACT

Two methods to analyzing survival data with clustered events are presented. The first method is a proportional hazards model which adopts a marginal approach with a working independence assumption. This model can be fitted by SAS PROC PHREG with the robust sandwich estimate option. The second method is a likelihood-based random effects (frailty) model. In the second model, the baseline hazard could be either a priori determined (e.g., Weibull) or approximated by piecewise constant counterpart. The estimation could be carried out by adaptive Gaussian quadrature method which is implemented in SAS PROC NLMIXED. The advantages, disadvantages, and relevant situations for proper application of each model are demonstrated using the published diabetic retinopathy data.

Keywords: survival analysis, Cox's proportional-hazards model, survival function, frailty model, mixed models, Gaussian quadrature estimation, PROC PHREG, and PROC NLMIXED.

INTRODUCTION

Survival analysis is the phrase used to describe the analysis of data in the form of times from a well-defined "time origin" until the occurrence of some particular event or "end-point" such as death. In this paper we are interested in the analysis of multivariate failure time data. Such data arise when each study subject can potentially experience several events (for instance, multiple infections after surgery) or when there exists some natural or artificial clustering of subjects (for instance, a litter of mice) that induces dependence among the failure times of the same cluster. Data in the former situation are referred to as multiple events data, which include recurrent events data as a special case; data in the latter situation are referred to as clustered data.

Two approaches are generally used in the analysis of correlated failure time data: a marginal model approach (Wei, Lin, and Weissfeld [1], hereafter WLW) and a frailty model approach [2]. In the marginal model, WLW adopts a pseudolikelihood approach with a working independence assumption. They estimated the covariate effect assuming independence among correlated failure times, while adjusting for the correlation by sandwich estimate in estimating the covariance matrix. Frailty model is a random effects proportional hazards model. The random effects could be used to capture the relation of the correlated observations in the clustered or recurrent events data.

There are three SAS procedures available for analyzing survival data: LIFEREG, LIFETEST and PHREG. PROC LIFEREG is a parametric regression procedure to model the distribution of survival time with a set of concomitant variables [3]. PROC LIFETEST is a nonparametric procedure to estimate the survivor function, compare the underlying survival curves of two or more samples [4]. PROC PHREG is a semi-parametric procedure that fits the Cox proportional hazards model [5]. These procedures can not be used directly in modeling correlated survival data. However, with the robust sandwich estimate option, PROC PHREG can be used to perform clustered data analysis or recurrent data analysis, adopting a GEE-like marginal approach. This procedure will be illustrated under Model 1.

In SAS, the estimation in frailty model could be carried out in PROC NLMIXED. The NLMIXED procedure fits nonlinear random effects models using MLE. Both fixed and random effects can be

included the model nonlinearly [6, 7]. These models have a wide variety of applications, e.g., pharmacokinetics and overdispersed binomial data.

PROC NL MIXED fits nonlinear mixed models by maximizing an approximation to the likelihood integrated over the random effects [5, 6]. Different integral approximations are available, the principal ones being adaptive Gaussian quadrature and a first-order Taylor series approximation. A variety of alternative optimization techniques are available to carry out the maximization; the default is a dual quasi-Newton algorithm which updates the Cholesky factor of an approximate Hessian to achieve convergence [6].

Successful convergence of the optimization problem results in parameter estimates along with their approximate standard errors based on the second derivative matrix of the likelihood function. PROC NL MIXED enables the users to apply the estimated model to construct predictions of arbitrary functions by using empirical Bayes estimates of the random effects. The users can also estimate the arbitrary functions of the nonrandom parameters, and PROC NL MIXED computes their approximate standard errors by using the delta method.

SAS PROC NL MIXED enables the user to specify a conditional distribution for the data (given the random effects) having either a standard form (normal, binomial, Poisson) or a general distribution that the user can code using SAS programming statements. The latter feature makes it possible to fit a frailty model with either an a priori (e.g., Weibull) parametric baseline hazard function or a piecewise constant one. We will illustrate these two models under models 2A and 2B, respectively.

SURVIVAL DATA USED

The three models described in this paper are applied to analyze the same dataset to be consistent: the Diabetic Retinopathy Study (DRS) dataset which is available online at <http://www.mayo.edu/hsr/people/therneau/book/data/diabetes.html>. Diabetic retinopathy is the most common and most serious eye complication of diabetes, which may lead to poor vision or even blindness. The DRS was started in 1971 to investigate the efficacy of laser photocoagulation in delaying the onset of severe vision loss. This study enrolled 1742 patients. One eye of each patient was randomly chosen for treatment and the other eye served as an untreated control. Huster et al. [7], Therneau and Grambsch [8] both analyzed a small part of the total data, which is a 50 per cent sample of the high-risk patients (N =197).

Each patient had one eye randomized to laser treatment (laser type 1=xenon, 2=argon) and the other eye received no treatment. For each eye, the event of interest was the time from initiation of treatment to the time when visual acuity dropped below 5/200 two visits in a row (defined as "blindness"). Thus there is a built-in lag time of approximately 6 months (visits were every 3 months). Survival times in this dataset are therefore the actual time to blindness in months, minus the minimum possible time to event (6.5 months). Censoring could be caused by death, dropout, or end of the study. Two covariates are included in the analysis. The Treat covariate indicates an eye received laser treatment. Treat=1 indicates right eye and Treat=2 indicates left eye. The JR covariate indicates the type of diabetes with JR=1 for juvenile (age at diagnosis < 20) and JR=2 for adult. The outcome for the treated eye was compared to the untreated eye for risk groups 6-12 and Status=0 shows censored data and Status=1 shows blindness.

DEMONSTRATION OF MODELS FOR ANALYSIS OF SURVIVAL DATA

MODEL 1: ANALYSIS OF CLUSTERED DATA USING PROC PHREG

1.1 MARGINAL COX MODELS FOR MULTIPLE EVENTS DATA

Suppose there are $i=1,2, \dots, n$ clusters (centers, families, litters, etc.), where each cluster has

$j=1,2,\dots,J$ members. We record the follow-up time X_{ij} for each member, which is the minimum of the failure time D_{ij} and the non-informative censoring time C_{ij} . Denote by $\Delta_{ij} = I(D_{ij} \leq C_{ij})$ the event indicator, where $I(\cdot)$ is the indicator function. For each member there is a covariate vector $Z_{ij}(t)$ for fixed effects at time t .

The marginal Cox model for the j^{th} event and the i^{th} cluster is given by

$$\lambda_j(t; Z_{ij}) = \lambda_{0j} e^{\beta_j' Z_{ij}(t)}, \quad j = 1, \dots, J; i = 1, \dots, n$$

and the j^{th} event-specific partial likelihood is

$$L_j(\beta) = \prod_{i=1}^n \left[\frac{\exp\{\beta' Z_{ij}(X_{ij})\}}{\sum_{l \in R_j(X_{ij})} \exp\{\beta' Z_{il}(X_{ij})\}} \right]^{\Delta_{ij}}$$

Where $\lambda_{0j}(t)$ is an arbitrary baseline hazard function for the j^{th} event and β_j is the (event-specific) column vector of regression coefficients for j^{th} event. WLW estimates β_1, \dots, β_J by the maximum partial likelihood estimates $\hat{\beta}_1, \dots, \hat{\beta}_J$, respectively, and uses a robust sandwich covariance matrix estimate for $(\hat{\beta}'_1, \dots, \hat{\beta}'_J)'$ to account for the dependence of the multiple failure times.

1.2 IMPLEMENTATION IN SAS PROC PHREG

By using a properly prepared input data set, the user can estimate the regression parameters for all the marginal Cox models and compute the robust sandwich covariance estimates in one PROC PHREG invocation. The PHREG procedure uses ODS Graphics to create graphs as part of its output. For example, the ASSESS statement uses a graphical method that uses ODS Graphics to check the model adequacy of the model. PROC PHREG (Version 9.2) also offers a number of important enhanced features. The most noticeable features are the CLASS statement for specifying categorical variables; the CONTRAST statement for estimating and testing linear contrasts; the BAYES statement for performing a Bayesian analysis; and the HAZARDRATIO statement for estimating customized hazard ratios.

A sketch of the SAS program is given in Code Box 1 in the Appendix. The option COVS(AGGREGATE) is specified in the PROC statement to obtain the robust sandwich estimate of the covariance matrix, and the score residuals used in computing the middle part of the sandwich estimate are aggregated over identical ID values. Then, the model is defined including Treat covariate, JR covariate, and interaction term between Treat and JR. The TEST statements can be included in the PROC PHREG code to test various linear hypotheses of the regression parameters based on the robust sandwich covariance matrix estimate.

This method is most appropriate when the main purpose is to estimate the marginal (population) covariate effects. In applications where the estimates of the random effects to capture the correlation between multivariate failure times, frailty models should be used which will be described in the following sections.

MODEL 2A: ANALYSIS OF CLUSTERED DATA WITH KNOWN DISTRIBUTION USING PROC NLMIXED

2A.1 INTRODUCTION TO FRAILTY MODEL

Denote by v_i the unobserved random effect (frailty) for the i th center with a density $f_\theta(\cdot)$, which is often assumed to follow a log-Gamma (hereafter referred to as 'Gamma') or normal distribution, although other distributions have been proposed, e.g. positive stable [9]. Note that here we put the frailty term in the exponential component. Conditional on v_i , a 'simple frailty model' can be written as

$$h_{ij}(t) = h_o(t) \exp(\beta^T Z_{ij}(t) + v_i)$$

where $h_o(t)$ is the unspecified baseline hazard and β is the regression coefficient. The observed data $O_i \equiv \{T_{ij}, \Delta_{ij}, j = 1, \dots, n_i\}$ are i.i.d for distinct center i . The likelihood for O_i is

$$L(O_i) = \int_{-\infty}^{\infty} \prod_{j=1}^{n_i} [h_{ij}(x_{ij})]^{\Delta_{ij}} \exp\left[-\int_0^{x_{ij}} h_{ij}(t) dt\right] f_\theta(v_i) dv_i$$

The diabetic retinopathy data described earlier has a hazard function

$$h_{ij}(t) = h_o(t) \exp(\beta_1 \text{TR}_{ij} + \beta_2 \text{JA}_{ij} + v_i)$$

Using notation previously defined, the contribution for each eye to the log-likelihood is

$$\tilde{l}_{ij} = \Delta_{ij} [\beta_1 \text{TR}_{ij} + \beta_2 \text{JA}_{ij} + v_i + \log \tilde{h}_0(x_{ij})] - \exp(\beta_1 \text{TR}_{ij} + \beta_2 \text{JA}_{ij} + v_i) \tilde{H}_0(x_{ij})$$

2A.2 HOW TO FIND THE RIGHT DISTRIBUTION

The best way to find the right distribution is to fit several frailty models with different distributions for baseline hazard. Then, the model with best loglikelihood can be determined. This approach and related code development is currently ongoing and the results will be presented later. However, for illustration purposes, the PROC LIFEREG can be used to determine the right distribution assuming only fixed effects. The plot of the cumulative baseline hazard estimates from LIFEREG is shown in Figure 1. The -2log likelihood statistics derived from four distributions (Lognormal, Gamma, Exponential, and Weibull) using SAS PROC LIFEREG in Table 1 show that the Gamma distribution is most suited for this data when the random or clustered effects are ignored.

Fit Statistics -2 Log Likelihood	
Lognormal	897.838
Gamma	897.752
Exponential	914.613
Weibull	905.481

Table 1: Comparison of Four Distributions

However, in the presence of random effects, LIFEREG may not reveal the right distribution. The estimated CDF, a line representing the maximum likelihood fit, and point-wise parametric confidence bands are plotted in the Gamma probability Plot using SAS ODS graphics feature. (Please see Code Box 2). The SAS code for estimation of frailty model with Gamma baseline hazard is presented in Code Box 3.

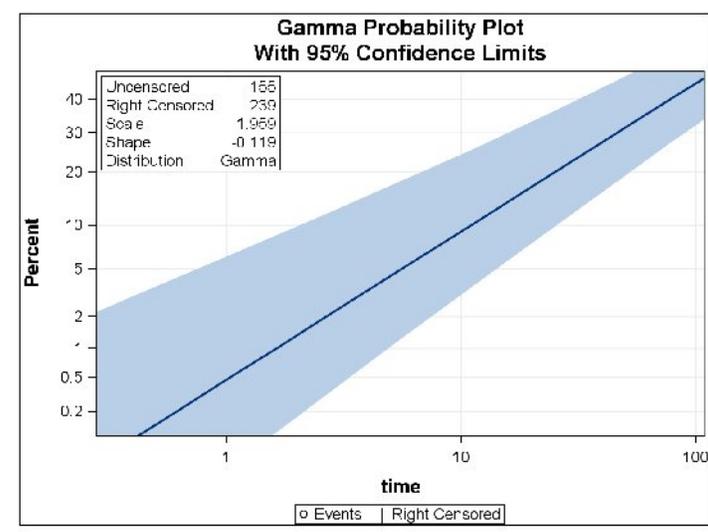


Figure 1: Gamma Probability Plot

MODEL 2B: ANALYSIS OF CLUSTERED DATA WITH UNKNOWN DISTRIBUTION USING PROC NL MIXED

Liu and Huang proposed a novel Gaussian quadrature estimation method for various frailty proportional hazards models [10]. They approximated the unspecified baseline hazard by a piecewise constant one, resulting in a parametric model that can be fitted conveniently by Gaussian quadrature tools in standard software such as SAS PROC NL MIXED. In this model, the estimates for the piecewise constant baseline hazard function are available. Therefore, the user can construct cumulative baseline hazard function (and thus survival function) from these estimates.

They first applied this method to simple frailty models for correlated survival data (e.g. recurrent or clustered failure times), then to joint frailty models for correlated failure times with informative dropout or a dependent terminal event such as death. Simulation studies showed this method compared favorably with the well-received penalized partial likelihood method and the Monte Carlo EM (MCEM) method. A subset of their novel approach will be illustrated in Model 2B.

SIMPLE FRAILTY MODEL FOR DIABETIC RETINOPATHY DATA

A piecewise constant baseline hazard with 10 intervals is used to fit the data by Proc NL MIXED, assuming normal frailty model. The follow-up of the observed event times is divided into 10 intervals by every 10th quantiles. The baseline hazard is

$$\tilde{h}_0(t) = \sum_{k=1}^{10} h_{0k} e_k = \sum_{k=1}^{10} h_{0k} I(Q_{k-1} < t < Q_k)$$

The cumulative baseline hazard is

$$\tilde{H}_0(t) = \sum_{k=1}^{10} h_{0k} e_k = \sum_{k=1}^{10} h_{0k} \max(0, \min(Q_k - Q_{k-1}, t - Q_{k-1}))$$

A sketch of the SAS program is given in Code Box 4 and Code Box 5 in the Appendix. The SAS data set 'diabetes' is prepared so that each patient has multiple data lines, each data line corresponds to the record of the failure time of an eye. In Code Box 4, the first step involves finding 10 knots using quantized intervals. Since the goal is to estimate the 10 knots, PROC UNIVARIATE is used. The next data step shows the estimate for each quantized interval. The duration of each quantization interval is calculated together with the indicator of event in each interval. Then, the frequency of blindness event in each interval is shown (status = 1 means that blindness event has occurred).

In Code Box 5, the parametric model is fitted by Gaussian quadrature tools in PROC NLMIXED using normal distribution. For each record there are 10 variables d_k , $k=1,2, \dots, 10$, for the length within intervals, and 10 variables e_k , $k=1,2, \dots, 10$, for the indicator of the failure happening in intervals 1–10, respectively. \tilde{h}_0 is denoted by 'basehaz' and \tilde{H}_0 by 'cumhaz' in the SAS code.

Each subject has a unique 'ID'. The follow-up time is denoted by 'T' and the event indicator Δ_{ij} by 'status'. The random effect is shown by 'nu'. With normal random effects, the Gaussian quadrature technique can be applied directly. However, some adaption is needed when the random effect has another distribution, e.g. Gamma. Nelson *et al.* (2007) presented a solution by making use of probability integral transformation (PIT). For $a \sim N(0,1)$, $\phi(a) \sim Uniform(0,1)$, where $\phi(\cdot)$ is the standard normal cumulative distribution function (CDF). Likewise, the CDF of a non-normal random variable b is Uniform (0,1), i.e. $f(b) \sim Uniform(0,1)$. Denoting the inverse CDF of b by $F^{-1}(\cdot)$, $b = F^{-1}(\phi(a))$ can be used to generate the non-normal random variable of interest. Liu and Yu (2008) proposed to use a likelihood reformulation method which can be applied to more complicated situations. Their method is often much faster in computation than Nelson *et al.*

The Bounds statement requires that the 10 knots ($h_1 \dots h_{10}$) and variance of the random effect (θ) must be non-negative. The baseline (basehaz) and cumulative hazard (cumhaz) are computed and the model is written with beta1 as the treat covariate, beta2 as the JR covariate, beta3 as the interaction between beta1 and beta2, and 'nu' as the random effect. Random effect has normal distribution with the mean zero and variance θ . Then, the log likelihood for the model for both censoring and non-censoring data is estimated. Finally, the status statement is used to indicate the blindness event and non-event.

This method can handle the unknown distributions for baseline hazard and generate the correct estimates for treatment effects and random effects. It has several advantages. First, piecewise constant baseline hazard gives a close approximation to unspecified baseline hazards. The resulting parametric model is then conveniently maximized by Gaussian quadrature tools as in PROC NLMIXED. This method yields satisfactory results as far as parameter estimation is concerned. Another approach is the Penalized Partial Likelihood (PPL), which was first proposed by McGilchrist and Aisbett [11] for frailty models. Compared with the PPL method, this method has a smaller bias and can provide the standard error estimate (for frailty variance) directly. Furthermore, this method can be easily applied to the joint frailty models while such an extension for the PPL method is not currently available. Compared with the Monte Carlo EM (MCEM) approach, an appealing feature of this method is the ease of implementation, which can greatly enhance the applications of joint frailty models in practice. Monte Carlo MCEM method is often highly computationally intensive and its implementation (programming) is quite difficult and has to be treated on a case-by-case basis. This method also reduces computational time substantially. Finally, this approach is adaptable and can be easily applied to many other settings such as non-proportional hazards models.

RESULTS AND OUTPUTS

Analysis of Maximum Likelihood Estimates									
	PROC PHREG Model 1			PROC NL MIXED Model 2A			PROC NL MIXED Model 2B		
Variable	Par. Est.	Std err	P-value	Par. Est.	Std err	P-value	Par. Est.	Std err	P-value
Treat	-1.27	0.24	<.0001	-1.59	0.30	<.0001	-1.51	0.29	<.0001
JR	-0.34	0.20	0.08	-0.45	0.27	0.10	-0.41	0.26	0.12
Treat*JR	0.85	0.30	0.005	1.04	0.37	0.006	0.98	0.37	0.008
Random Effects				0.13	0.14	0.36	1.03	0.37	0.005

Table 2: Comparison of Outputs from Three Models

Table 2 shows the estimates of covariate effects are close in the three models but slightly higher for the normal frailty model in Model 2A. The standard error estimates are close too. Treatment and JR interaction are significant in the three methods. JR is not significant in all three models based on the 5% significance level. In model 1, there is no estimate for random effects. In comparing Model 2A and Model 2B, the random effect is significant in Model 2B but not significant in Model 2A. This may be caused by the fact that Gamma distribution still does not capture the correct shape of the baseline hazard. The -2log likelihood statistics derived from Model 2A is 1646.0 and from Model 2B is 1629.2. Also, Model 2A has AIC of 1658.0 and BIC of 1677.7, while Model 2B has AIC of 1657.2 and BIC of 1703.1. Therefore, Model 2A should be preferred by BIC while Model 2B should be preferred by AIC.

SUMMARY

Model 1 is a marginal model which can be easily implemented. This model is a pseudolikelihood method which yields a consistent estimate of covariate effects. However, sandwich estimate should be used to obtain a consistent estimate of covariance matrix.

Model 2A is a random effects model which requires an assumption on the distribution for the baseline hazard. The consistency of the estimates depends on the correct assumption of such distribution. Therefore, the researcher should have a good prior knowledge of the baseline survival function.

Model 2B is a random effects model which does not require assuming a distribution for the baseline hazard. Rather it is approximated by a piecewise constant baseline hazard. So this method is more flexible than Model 2A. The performance of this method can be compared with that of Model 2A by AIC or BIC criteria.

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APPENDIX

Code Box 1

```
proc phreg data=diabetes covs(aggregate);
  model Time*Status(0)=Treat JR Interaction;
  Interaction= Treat * JR;
  id ID;
  run;
```

Code Box 2

```
Ods Graphics ON;;
PROC LIFEREG CODE:
proc lifereg data=diabetes;
  title "Lifereg =&distribution ";
  class TREAT JR;
  model Time*Status(0)=treat jr/dist=&distribution;
  probplot / nodata; inset;
  run;
ODS Graphics OFF;
```

Code Box 3

```
Title "Random Frailty Model with Gamma ";
ods output ParameterEstimates=est;
proc nlmixed data=five qpoints=30 noad;
  bounds gamma > 0;
  interaction=treat*JR;
  linp = b0 - b1*(treat)-b2*(JR)-b3*(interaction)+ z;
  alpha = exp(-linp);
  G_t = exp(-(alpha*time)**gamma);
  g = gamma*alpha*((alpha*time)**(gamma-1))*G_t;
  ll = (status=1)*log(g) + (status=0)*log(G_t);
  model time ~ general(ll);
  random z ~ normal(0,exp(2*logsig)) subject=id out=EB;
  predict 1-G_t out=cdf;
  run;
```

Code Box 4

```

proc univariate data=diabetes noprint;
var time;
output out=quant_d pctlpts=0 10 20 30 40 50 60 70 80 90 100 pctlpre=qd;
where status=1;
run;
* Merge data with the quantiles;
data four;
set diabetes;if _n_ =1 then set quant_d;
run;

* Calculate the duration in each quantile interval, together with the indicator of event in
each interval;
data five;
set four;
array quant_d {11} qd0 qd10 qd20 qd30 qd40 qd50 qd60 qd70 qd80 qd90 qd100;

array d {10} d1-d10;

array e {10} e1-e10;

do i=1 to 10;

    d{i}=0;
end;

do i=1 to 10;

    e{i}=0;
end;
do i=2 to 11; /* duration in each death event quantiles */
    if time<=quant_d{i} then do;
        e{i-1}=(status=1); /* indicator of blind event in each interval */
        d{i-1}=time-quant_d{i-1};
        i=11;
    end;
    else d{i-1}=quant_d{i}-quant_d{i-1};
end;

run;

```

Code Box 5

```

proc nlmixed data=five qpoints=5;
Title "Normal frailty with variance theta";
parms h1=1 h2=1 h3=1 h4=1 h5=1 h6=1 h7=1 h8=1 h9=1 h10=1 beta1=1 beta2=-1 theta=1;

bounds h1 h2 h3 h4 h5 h6 h7 h8 h9 h10 theta >= 0;

basehaz=h1*e1+h2*e2+h3*e3+h4*e4+h5*e5+h6*e6+h7*e7+h8*e8+h9*e9+h10*e10;

cumhaz=h1*d1+h2*d2+h3*d3+h4*d4+h5*d5+h6*d6+h7*d7+h8*d8+h9*d9+h10*d10;
interaction=TREAT *JR ;
mu= (beta1 * TREAT) + ( beta2 * JR ) + (beta3 *interaction) + nu;

loglik0=-exp(mu) * cumhaz;

if status=0 then loglik=loglik0; /* log likelihood for censoring */
if status=1 then loglik= log(basehaz) + mu + loglik0; /* for failure */

model Time ~ general(loglik);

random nu ~ normal(0, theta) subject=ID out=eb;

run;

```