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Analysis of Failure Time Data with Mixed-Effects Accelerated Failure Time Model

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In randomized clinical trials or observational studies, subjects are recruited at multiple treating sites. Factors that vary across sites may have some influence on outcomes; therefore, they need to be taken into account to get better results. We apply the accelerated failure time (AFT) model with linear mixed effects to analyze failure time data, accounting for correlations between outcomes. Specifically, we use Bayesian approach to fit the data, computing the regression parameters by Gibbs sampler combined with Buckley-James method. This approach is compared with the marginal independence approach and other methods through simulations and an application to a real example.

Keywords AFT model; Gibbs sampler; Mixed-effects.

Mathematics Subject Classification 62N05; 62P30.

1. Introduction

In randomized clinical trials or observational studies, subjects are sometimes enrolled from multiple treating sites. Site effects potentially lead to correlations between outcomes within the same site. If these effects need to be accounted for, then inferences that ignore the correlations can be seriously biased (Knottnerus, 2002). Appropriate models need to be chosen to incorporate these site effects. This problem is well illustrated by a litter rat tumor study (Lee et al., 1993), in which one of the three rats in each litter was treated by a drug and the other two were controls. When estimating the treatment effects, we need to consider appropriately the correlations between the failure times within litters. In this example, litters are sites.

Two regression models have been studied successfully in failure time analysis. One is the Cox proportional hazards model in which the failure time is modeled through its hazard function (Cox, 1972), and the other is the accelerated failure time (AFT) model, in which the logarithmic scale of the failure time is associated with the covariates through a linear model (Kalbfleisch and Prentice, 1980).

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Here, we focus on the AFT model. Usual AFT model uses the marginal independence approach to ignore the dependence between the outcomes. However, ignoring the dependence generally may lead to bias and inefficiency (Lee et al., 1993). To account for the dependence, Pan and Louis (2000) proposed a mixed effects AFT model in which a random effect is included to carry correlations of failure times. The parameters are estimated by an iterated Monte Carlo expectation-maximization algorithm combined with Buckley-James method, but the algorithm is time-consuming.

We propose a Bayesian model to the censored event data. Treating site effect is a special case of hierarchical model, so the general hierarchical model can be easily generalized here except that we need to deal with the censored data. We can impute the censored times by Buckley-James method, then the parameters can be estimated by Gibbs sampler.

The article is organized as follows. In Sec. 2, the mixed-effects AFT model proposed by Pan and Louis (2000) and their algorithm is described. In Sec. 3, we propose a Bayesian hierarchical model to the censored event data, computing the parameters by Gibbs sampler algorithm. The results are compared with marginal independence model through simulation in Sec. 4. In Sec. 5, we applied the method to a real data set.

2. Notations and Models

Assume that in a study, there are K treating sites. Let n_k be the number of patients in site k, and let $N = \sum_{k=1}^{K} n_k$ be the total sample size. Suppose that T_{ki} is the failure time for subject i in site k. Because of censoring, not all T_{ki}'s are observed. Instead, we observe $T_{ki}^* = T_{ki} \wedge C_{ki}$ and $\delta_{ki} = I(T_{ki} \leq C_{ki})$, where C_{ki} are censoring variable.

The AFT models have been popular and successful in failure time analysis, in which the logarithmic scale becomes a linear model through covariate variables (Miller, 1981). These models have been well studied when the observed failure times are independent. Let $Y_{ki} = \log(T_{ki})$ and $Y_{ki}^* = \log(T_{ki}^*)$. The linear AFT model is frequently used to fit survival data (Miller, 1981),

$$Y_{ki} = X_{ki}'\beta + \varepsilon_{ki},$$

where X_{ki} is the covariate vector, β is the unknown regression coefficient vector of interest, and $\varepsilon_k = (\varepsilon_{k1}, \ldots, \varepsilon_{k,n_k})'$ is the zero mean error vector independent of each other.

The mixed-effects accelerated failure time model is used to account for the correlation structure; see for example, Pan and Louis (2000) and (Lambert et al., 2004). The model is

$$\mathbf{Y_{ki}} = X_{ki}'\beta + b_k + \varepsilon_{ki}, \tag{1}$$

where X_{ki} is the covariate vector and β the unknown regression coefficient vector of interest, and b_k is the random effect of site k causing the possible correlations for the components of $T_k = (T_{k1}, \ldots, T_{k,n_k})'$. Usually, we assume

$$b_k \overset{i.i.d.}{\sim} N(0, \tau^2), \quad \varepsilon_{ki} \overset{i.i.d.}{\sim} N(0, \sigma^2),$$

and β_k and e_{ki} are independent.

Pan and Louis (2000) used Monte Carlo EM algorithm to estimate β. Here is a brief review of their method. When the data are complete, the log likelihood is

$$L_c(\theta \mid Y, X, Z, b) = \sum_{k=1}^{K}\sum_{i=1}^{n_k} \log f(Y_{ki} - X_{ki}\beta - b_k \mid Y_{ki}, X_{ki}, b_k, \theta) + \sum_{k=1}^{K} \log g(b_i \mid \theta), \quad (2)$$

where $\theta = (\beta, \tau, \sigma)$, f and g are the normal densities for ε_{ki} and b_k, $Y = (Y_1', \ldots, Y_k')'$, $X = (X_1', \ldots, X_k')'$, and $b = (b_1, \ldots, b_k)$. In the E-step, compute $E(L_c)$ under the conditional distribution of b_k given Y_k, which could be obtained from a random sample $b_k^{(l)}$, $l = 1, \ldots, L$, from the conditional distribution $b_k \mid (Y_k, \hat{\theta})$. In the M-step, maximizing $E(L_c)$ get the estimator $\hat{\beta}$. When the data are censored, the likelihood has no closed form, then the nonparametric Kaplan-Meier estimator of the distribution function can be applied in Bukley-James method (Miller, 1981) to impute Y_{ki}, and then Monte Carlo Metropolis-Hastings algorithm can be applied to sample the random effects in the E-step.

3. A Bayesian Approach

Since the subjects were collected within different treating sites, it is natural to use a hierarchical model to fit the data. Here, a Bayesian machinery algorithm is used to obtain the estimates of treatment effects and repeated sampling is used to justify it. Here, Bayesian machinary is used to obtain a frequentist result.

3.1. *Estimation with Uncensored Data*

If all the failure times T_{ki} can be observed, then we can have $Y_{ki} = \log(T_{ki})$. The linear mixed-effects AFT model is frequently used to fit failure times (Pan and Louis, 2000),

$$Y_{ki} = X_{ki}\beta + b_k + \varepsilon_{ki},$$

or we can write it as matrix form

$$Y = X\beta + Zb + \varepsilon.$$

In this equation, X and Z are the corresponding design matrices. X has a matrix form $X = (X_1', \ldots, X_K')'$ where $X_k = (X_{k1}, \ldots, X_{kn_k})$, and Z has a simple matrix form $Diag(1_{n_1}, 1_{n_2}, \ldots, 1_{n_k})$. Assume β, σ have noninformative prior distribution $p(\beta, \sigma^2) \propto 1$ and $b = (b_1, \ldots, b_K)$ have prior distribution based on hyperparameters τ, i.e.,

$$b \sim N(0, \tau^2 I_K), \quad (3)$$

and assume σ, τ have non informative prior distributions $p(\sigma^2) \propto 1, p(\tau^2) \propto 1$. Denote $\theta = (\beta, b, \tau^2, \sigma^2)$.

Then the posterior likelihood is proportional to

$$\begin{aligned} p(\theta \mid Y) &\propto p(Y \mid \theta) p(b \mid \tau^2) p(\beta, \sigma^2) p(\tau^2) p(\sigma^2) \\ &= \frac{1}{(\sqrt{2\pi}\sigma)^N} \exp\left\{ \prod_{k=1}^{K}\prod_{i=1}^{n_k} \frac{(Y_{ki} - X_{ki}\beta - b_k)^2}{2\sigma^2} \right\} \times \frac{1}{(\sqrt{2\pi}\tau)^K} \prod_{k=1}^{K} \exp\left\{ \frac{b_k^2}{2\tau^2} \right\}. \quad (4) \end{aligned}$$

We can fit this model using Gibbs sampling algorithm (Gelman et al., 2003). For $k = 1, \ldots, K$, it is easy to get

$$b_k \mid \beta, \tau, \sigma, Y \sim N\left(\frac{n_k \bar{z}_{k.}/\sigma^2}{1/\tau^2 + n_k/\sigma^2}, \frac{1}{1/\tau^2 + n_k/\sigma^2}\right), \tag{5}$$

where $z_{ki} = Y_{ki} - X_{ki}\beta$, and $\bar{z}_{k.} = \frac{1}{n_k}\sum_{i=1}^{n_k} z_{ki}$. Given the other parameters and Y, the conditional distribution of β is

$$\beta \mid b, \sigma^2, \tau, Y \sim N(\hat{\beta}, \sigma^2 V_\beta), \tag{6}$$

where $W = Y - Zb$, $\hat{\beta} = (X'X)^{-1}X'W$, $V_\beta = (X'X)^{-1}$.

Given the other parameters and Y, the conditional distribution of σ^2 is

$$\sigma^2 \mid b, \beta, Y \sim Inv - \chi^2(N-1, s^2), \tag{7}$$

where $s^2 = \frac{\sum_{k=1}^{K}\sum_{i=1}^{n_k}(Y_{ki} - X_{ki}\beta - b_k)^2}{N}$. Similarly,

$$\tau^2 \mid b \sim Inv - \chi^2\left(K-1, \frac{\sum_{k=1}^{K} b_k^2}{K}\right). \tag{8}$$

3.2. *Extension to Censored Data*

When some of the failure times are not observed, Y_{ki}^*'s are available instead. We can use the Buckley-James method to impute the censored time Y_{ki} (Miller, 1981), which are defined pseudo random variables,

$$Y_{ki} = Y_{ki}^*\delta + E(Y_{ki} \mid Y_{ki} > Y_{ki}^*, \beta) \cdot (1-\delta). \tag{9}$$

Since it depends on β, we need to do iterative methods. Here is the algorithm to estimate parameters:

(0) Initiate values.
(1) Impute Y_{ki} based on the initial values.
(2) Estimate θ using Gibbs sampling by the posterior likelihood.
(3) Go to Step 1 until convergence.

4. Simulations for AFT Models

The data were generated through model (Pan and Louis, 2000),

$$\log(T_{ki}) = 2 + X_{ki} + b_k + \varepsilon_{ki}, \tag{10}$$

where $i = 1, 2, 3$, $k = 1, \ldots, K$. Then in this model, $\beta = 1$. We studied two experiments, $K = 50$ and $K = 100$. X_{ki} are generated from Uniform distribution $U(0, 1)$. The random effects b_k and ε_{ki} are generated from normal distribution $N(0, 1)$. In the experiments, 20% of the data are censored which is a moderate low level of censoring.

Do simulations 1,000 times, and results were summarized in Table 1. From Table 1, we can see the performances of the mixed-effects AFT model and the

Table 1
Mean and SD of the estimates of regression coefficient by the three methods

Method	K(number of sites)	MEAN ($\hat{\beta}$)	SD($\hat{\beta}$)
Marginal independence	50	1.02	0.42
	100	1.03	0.36
Monte Carlo EM-Algorithm	50	1.01	0.34
	100	1.01	0.31
Bayesian Gibbs sampler/BJ method	50	1.01	0.32
	100	1.01	0.28

marginal approach accounting for the correlations are close, which is consistent with the conclusions made by Pan and Louis (2000). The performance of Gibbs sampler is a little better in term of the standard deviation than Monte Carlo EM algorithm since it is a gaussian model. The results were based on the two situations here, but similar conclusions were drawn with different designs, sample sizes, and proportions of censoring. This is because the algorithm is based on Buckley–James estimator and Gibbs sampler. Buckley–James estimator has some satisfactory properties such as consistency (Lai and Ying, 1991), and Gibbs sampler gives convergent results of the estimates. The performance of Gibbs sampler is much faster than Monte Carlo EM algorithm, since it does not use iterative method such as Monte Carlo expectation maximization to estimate β when failure times were imputed.

5. Application to the Litter-Matched Tumor Data

We apply the methods to the litter-matched tumor data set (Lee et al., 1993; Pan and Louis, 2000). Only 36 failures were observed among 150 rats in 50 litters; all others were right-censored because of death. We want to estimate the treatment effect accounting for the sites. From Table 2, the estimate of the treatment effect from our approach is very close to the Monte Carlo EM-Algorithm by Pan and Louis (2000), and both estimates are not that different from the marginal independence approach. All bootstrap confidence intervals conclude that there is no strong statistical evidence for a treatment effect. The confidence interval from the method proposed in this article is smaller than the marginal independence approach and the Monte Carlo EM algorithm, and it is less time consuming.

Table 2
Estimates and confidence intervals of treating effect in the Litter Tumor Data

Method	Point estimate	95% CI
Marginal Independence	0.103	(−0.093,0.344)
Monte Carlo EM-Algorithm	0.103	(−0.096,0.326)
Bayesian Gibbs sampler/BJ method	0.102	(−0.087,0.333)

6. Discussion

This article deals with analysis of censored failure time accounting for correlations between outcomes, through statistical concepts and simulations studies, especially the Gibbs sampler is used to estimate the parameters, and compared to some other existing methods. The results from the simulation suggest that a mixed-effects AFT model is more powerful than the marginal independence approach, when the failure times are correlated due to different clusters. The performance of the Gibbs sampler combined with Buckley-James method proposed here is close to the Monte Carlo EM-Algorithm by Pan and Louis (2000), with only a few improvements. As concluded from the simulations, it gave smaller SD of the estimates and it is faster.

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