Simple estimator for a shared frailty regression model

Jason P. Fine

University of Wisconsin, Madison, USA

David V. Glidden

University of California, San Francisco, USA

and Kristine E. Lee

University of Wisconsin, Madison, USA

Summary. We propose a simple estimation procedure for a proportional hazards frailty regression model for clustered survival data in which the dependence is generated by a positive stable distribution. Inferences for the frailty parameter can be obtained with output from Cox regression analyses. The computational burden is substantially less than that of the other approaches to estimation. The large sample behavior of the estimator is studied and simulations show the approximations are appropriate for use with realistic sample sizes. The methods are motivated by studies of familial associations in the natural history of diseases. Their practical utility is illustrated with sib-pair data from Beaver Dam, Wisconsin.

Keywords: Cluster effect; Genetic epidemiology; Multiplicative hazards; Partial likelihood; Ratio estimator; Semiparametric; Stratification

1. Introduction

1.1 Frailty models

The shared gamma frailty model was suggested by Clayton (1978) for the analysis of the correlation between clustered survival times in genetic epidemiology. An advantage is that without covariates its mathematical properties are convenient for estimation (Oakes, 1982, 1986). However, when adjusting for environmental risk factors, the analysis of the clustering is more difficult (Parner, 1998). Until recently, a lack of theory and reliable software had prevented widespread use of the model.

In practice, the gamma frailty specification may not fit well (Shih, 1998; Glidden, 1999; Fan, Hsu, and Prentice, 2000). The positive stable model (Hougaard, 1986) is a useful alternative, in part because it has the attractive feature that the predictive hazard ratios decrease to unity over time (Oakes, 1989). The property is often observed in familial associations of onset ages for diseases with low penetrances. The long-term survivors tend to be weakly correlated. The gamma model has predictive hazard ratios which are time invariant and may not be suitable for these patterns of failure.

The focus of this paper is inference for the stable frailty parameter with small clusters, or family units, and individual-level covariates. In cluster i, the complete data consist of failure times T_{ij} and $p \times 1$ covariate vectors Z_{ij} ($i = 1, \ldots, K, j = 1, \ldots, n_i$). There is also an unobserved cluster-level covariate W_i, i.e., a frailty, which induces dependence between members of the cluster. A semiparametric multiplicative model is assumed for the hazard of individual j conditionally on both unobserved and observed factors. That is,

$$\lambda(x|Z_{ij}, W_i) = W_i \lambda_0(x) \exp(\beta^T Z_{ij}), \tag{1}$$

where λ_0 is an unspecified base hazard and β is a $p \times 1$ vector of unknown coefficients.

An issue is that β in (1) is interpreted conditionally on W_i. Integrating out the density of the frailty, $g(w)$, does not generally yield a marginal hazard $\lambda(x|Z_{ij})$ following a proportional hazards model. An exception is when W_i has the positive stable distribution with Laplace transform $E\{\exp(-sW_i)\} = \exp(-s^\alpha), 0 \leq \alpha \leq 1$. In this case,

$$\lambda(x|Z_{ij}) = h_0(x)\exp(\gamma^T Z_{ij}), \tag{2}$$

where $\gamma = \alpha\beta$, $h_0(x) = \alpha\lambda_0(x)\Lambda_0(x)^{\alpha-1}$ and $\Lambda_0(x) = \int_0^t \lambda_0(u)du$. The covariate effects are attenuated by α and the base cumulative hazard is exponentiated by α. Hougaard (2000) has argued that taking g to be positive stable is a convenient parameterisation for clustered data, since α is not identified by (2). Under the assumed model, $\alpha < 1$ is attributable to association, and not to nonproportionality of the marginal hazards, as may occur with gamma W_i.

A joint distribution for $T_{ij}, j = 1, \ldots, n_i$, is ordinarily obtained by positing that the failure times are independent conditionally on W_i and $Z_{ij}, j = 1, \ldots, n_i$. It follows that

$$\Pr(T_{i1} > x_1, \ldots, T_{in_i} > x_{n_i}|Z_{i1}, \ldots, Z_{in_i}) = \int \prod_{j=1}^{n_i} \exp\{-w\Lambda_0(x_j)\exp(\beta^T Z_{ij})\}g(w)dw. \tag{3}$$

However, it is essential to recognize that when g is positive stable the relationship between the conditional hazard (1) and the marginal hazard (2) does not require that (3) holds. That is, there may be residual correlation between failure times which is not explained by the shared frailty. For instance, unobserved covariates other than W_i may vary within clusters and may produce additional dependence. In this scenario, Kendall's τ may not equal $1-\alpha$, as it does under the conditional independence model. Under (3), for independent pairs (T_{11}, T_{12}) and (T_{21}, T_{22}) with $(Z_{11}, Z_{12}) = (Z_{21}, Z_{22})$, $\alpha = 2\Pr(T_{11} > T_{21}, T_{12} < T_{22} \cup T_{11} < T_{21}, T_{12} > T_{22}|Z_{11}, Z_{12}, Z_{21}, Z_{22})$. We consider estimation of the parameter under this assumption.

1.2 *Existing Methods*

Estimation of frailty models with clustered data is complicated by right censoring. The problem is that robust estimating equation methodology (Zhao and Prentice, 1990; Prentice and Zhao, 1991; Zhao, Prentice, and Self, 1992) cannot be used to estimate the parametric aspects of the model separately from the baseline hazard function. Prentice and Hsu (1997) developed analagous estimation functions for the regression coefficients and the frailty parameter in a large class of proportional hazards models, including (3) with g positive stable. The method requires consistent estimators for $H_0(x) = \int_0^x h_0(s)ds$ and is computationally intensive when compared with the partial likelihood for the Cox (1972) model.

Another approach is nonparametric maximum likelihood. Wang, Klein and Moeschberger (1995) employed a likelihood analysis for the positive stable model in (3) using the EM algorithm (Dempster, Laird and Rubin, 1977). The implementation is involved, requiring simultaneous estimation of all unknown parameters, and variance estimation is complicated (Andersen, Klein, Knudsen, and Palacios, 1997). Furthermore, the distributional properties of the maximiser have not been formally established. Numerical studies have shown that the estimator for α may be quite biased with small sample sizes.

A penalized partial likelihood (Therneau and Grambsch, 2000) and a hierarchical likelihood (Ha, Lee, and Song, 2001; Lee and Nelder, 1996) are convenient frameworks for maximum likelihood estimation of (3) with gamma W_i. The frailties are naively treated as fixed effects and the Newton–Raphson technique is used to maximise over the model parameters and the frailties. The special structure of the gamma model is essential for the frequentist validity of these likelihoods. Unfortunately, adaptations for the positive stable frailty do not appear possible in the asymptotic set-up where the number of clusters is increasing and $n_i, i = 1, \ldots, K$, are small. The problem is that there is insufficient information to estimate W_i consistently and this generally leads to biased estimation of the other parameters.

1.3 Outline of Paper

All the existing procedures for α are based on (3). We propose a simple estimator for the frailty parameter which exploits the facts that the conditional model (1) and the marginal model (2) are proportional hazards models. The key point is that the ratio of the coefficients for each covariate in the two models equals α, a property unique to the positive stable frailty. This suggests a closed form estimator which is a function of estimators for β and γ. The estimator and an estimate of its variance may be obtained with output from standard software, e.g., *coxph* in SPLUS. The computational gain relative to the EM algorithm is illustrated in a data analysis in Section 4.

Understanding the theoretical properties of the procedure involves the limiting distributions of the estimators for β and γ. The latter maximises a pseudo partial likelihood (Lee, Wei, and Amato, 1992), while the former maximises a stratified partial likelihood (Holt and Prentice, 1974; Gross and Huber, 1987). These procedures have been studied separately, in the setting where $K \to \infty$ with $n_1, \ldots, n_K$ finite and g unspecified. The results are reviewed in Section 2.1. An optimal linear combination of the ratios of the partial likelihood estimators is provided in Section 2.2. Consistency and asymptotic normality are established, with inferences provided via a derivation of the joint distribution of the ratios across covariates. In Section 2.3, numerical goodness-of-fit tests for homogeneity of the ratios are described.

In Section 3, a simulation study demonstrates that the methods are appropriate for use with realistic sample sizes. The practical utility of the proposal is illustrated with a real data example in Section 4. A discussion is given in Section 5.

2. Estimation

2.1 Regression coefficients

In cluster i, the vector of failure times $\tilde{T}_i = (T_1, \ldots, T_{n_i})$ is subject to right censoring by

$\tilde{C}_i = (C_1, \ldots, C_{n_i})$, where n_i is random and bounded. The observed data are the K independent identically distributed realisations $\{(X_{i1}, \ldots, X_{in_i}, \Delta_{i1}, \ldots, \Delta_{in_i}, Z_{i1}, \ldots, Z_{in_i}, n_i), i = 1, \ldots, K\}$, where $X_{ij} = \min(T_{ij}, C_{ij})$, $\Delta_{ij} = I(T_{ij} \leq C_{ij})$, and $I(\cdot)$ is the indicator function. Random censoring is assumed, where $\tilde{T}_i$ and $\tilde{C}_i$ are independent conditionally on $(Z_{i1}, \ldots, Z_{in_i}, n_i)$.

To estimate γ in (2), we maximise the pseudo partial likelihood under the so-called working independence assumption (Wei, Lin, and Weissfeld, 1989)

$$L(\gamma) = \prod_{i=1}^{K} \prod_{j=1}^{n_i} \left\{ \frac{\exp(\gamma^T Z_{ij})}{\sum_{k=1}^{K} \sum_{l=1}^{n_k} I(X_{kl} \geq X_{ij}) \exp(\gamma^T Z_{kl})} \right\}^{\Delta_{ij}}$$

The information in the correlation amongst observations in clusters is disregarded by L. That is, the dependence structure of $T_{ij}, j = 1, \ldots, n_i$ conditionally on $Z_{ij}, j = 1 \ldots, n_i$, is completely unspecified. Lee, Wei, and Amato (1992) showed that if $\lambda(x|Z_{ij})$ has proportional hazards, then $\hat{\gamma} = \text{argmax}_\gamma L(\gamma)$ is strongly consistent for γ_0, the true value of γ. This is true when W_i in (1) is positive stable but $\alpha \neq 1$, when either the frailty distribution or the form of model (1) is misspecified, and when the conditional independence model (3) fails. That is, if (2) holds, then the estimator is consistent whether or not either (1) or (3) hold.

Lee, Wei and Amato (1992) also showed that $K^{1/2}(\hat{\gamma} - \gamma_0)$ is asymptotically mean zero normal with variance Σ which is consistently estimated by $\hat{\Sigma} = \hat{I}(\hat{\gamma})^{-1} \hat{D} \hat{I}(\hat{\gamma})^{-1}$, where

$$\hat{I}(\gamma) = K^{-1} \frac{\partial^2 L(\gamma)}{\partial \gamma \partial \gamma^T} = K^{-1} \sum_{i=1}^{K} \sum_{j=1}^{n_i} \int_0^\infty \left\{ \frac{S_2(\gamma, u)}{S_0(\gamma, u)} - \frac{S_1(\gamma, u) S_1(\gamma, u)^T}{S_0(\gamma, u)^2} \right\} dN_{ij}(u),$$

$N_{ij}(u) = I(X_{ij} \leq u, \Delta_{ij} = u)$, $S_k(\gamma, u) = K^{-1} \sum_{i=1}^{K} \sum_{j=1}^{n_i} I(X_{ij} \geq u) \exp(\gamma^T Z_{ij}) Z_{ij}^{\otimes k}$, and for vector v, $v^{\otimes 0} = 1, v^{\otimes 1} = v$, and $v^{\otimes 2} = vv^T$ The matrix $\hat{D} = K^{-1} \sum_{i=1}^{K} \hat{\psi}_i(\hat{\gamma})^{\otimes 2}$, where $\hat{\psi}_i(\gamma)$ is

$$\psi_i(\gamma) = \sum_{j=1}^{n_i} \int_0^\infty \{Z_{ij} - E(\gamma, u)\} \, dM_{ij}(\gamma, u)$$

with $M_{ij}(\gamma, u) = N_{ij}(u) - \int_0^u I(X_{ij} \geq x) h_0(x) \exp(\gamma^T Z_{ij}) dx$ replaced by $\hat{M}_{ij}(\hat{\gamma}, u) = N_{ij} -$

$\int_0^u I(X_{ij} \geq u) d\hat{H}(u) \exp(\gamma^T Z_{ij})$ and $E(\gamma, u) = S_1(\gamma, u)/S_0(\gamma, u)$. The quantity

$$\hat{H}(x) = \sum_{i=1}^{K} \sum_{j=1}^{n_i} \int_0^x \frac{dN_{ij}(u)}{S_0(\hat{\gamma}, u)}$$

is a modified Breslow estimator for $H_0(x)$ in which observations within clusters are naively assumed independent. If $T_{ij}, j = 1, \ldots, n_i$ are independent given $Z_{ij}, j = 1, \ldots, n_i$, then the variance of $\hat{\gamma}$ may be estimated with the inverse of the estimated information matrix from L, $\hat{I}(\hat{\gamma})^{-1}$. The "sandwich" variance estimator $\hat{\Sigma}$ allows for arbitrary cluster correlations.

Now, to estimate β in (1) with g unspecified, we use the maximiser $\hat{\beta}$ of the stratified partial likelihood

$$L^*(\beta) = \prod_{i=1}^{K} \prod_{j=1}^{n_i} \left\{ \frac{\exp(\beta^T Z_{ij})}{\sum_{l=1}^{n_i} I(X_{il} \geq X_{ij}) \exp(\beta^T Z_{il})} \right\}^{\Delta_{ij}}.$$

The typical approach to establishing consistency and asymptotic normality of $\hat{\beta}$ is to fix K and let $n_i \to \infty$ $(i = 1, \ldots, K)$. In our setting, the number of clusters is large and the number of observations in each cluster is bounded. Building on Holt and Prentice's (1974) analysis of matched pair designs, Gross and Huber (1987) derived consistency and asymptotic normality of $\hat{\beta}$ for fixed $n_1 = \ldots = n_K = c \geq 2$. The derivations use martingale theory (Andersen and Gill, 1982) which requires that (3) holds, in which case L^* is a proper partial likelihood. Below, we present a straightforward extension to random cluster sizes.

As $K \to \infty$ with $n_1, \ldots, n_K$ bounded, $\hat{\beta}$ is strongly consistent for β_0, the true value of β. Furthermore, $K^{1/2}(\hat{\beta} - \beta_0)$ is asymptotically normal with variance which is consistently estimated by $-\hat{I}^*(\hat{\beta})^{-1}$, where

$$\hat{I}^*(\beta) = K^{-1} \frac{\partial^2 L(\beta)}{\partial \beta \partial \beta^T} = K^{-1} \sum_{i=1}^{K} \sum_{j=1}^{n_i} \int_0^\infty \left\{ \frac{S_{2i}(\beta, u)}{S_{0i}(\beta, u)} - \frac{S_{1i}(\beta, u) S_{1i}(\beta, u)^T}{S_{0i}(\beta, u)^2} \right\} dN_{ij}(u),$$

and $S_{ij}(\gamma, u) = \sum_{k=1}^{n_j} I(X_{jk} \geq u) \exp(\beta^T Z_{jk}) Z_{jk}^{\otimes i}$.

We emphasize that if model (1) is correctly specified and conditional independence is satisfied, then inferences for $\hat{\beta}$ are robust to the distribution of W_i. They continue to hold with W_i replaced by an arbitrary stratum specific baseline hazard, $\lambda_{0i}(t)$, in (1). Of course, to estimate α in model (2), we assume that (1) holds with g positive stable.

2.2 Frailty parameter

Let $\gamma_i, \hat{\gamma}_i, \beta_i$ and $\hat{\beta}_i$ be the i-th components of $\gamma, \hat{\gamma}, \beta$ and $\hat{\beta}$, respectively. Under models (1) and (2) and assuming $|\beta_i| > |\gamma_i| > 0$, $\gamma_i/\beta_i = \alpha$ $(i = 1, \ldots, p)$. This suggests an estimator, $\hat{\alpha}$, which is a weighted average of $\hat{\gamma}_i/\hat{\beta}_i$ $(i = 1, \ldots, p)$. Note that the distribution of the ratio estimators may be heavily skewed. A more stable estimator might transform $\hat{\gamma}_i/\hat{\beta}_i$ and then retransform the average to obtain $\hat{\alpha}$. In general, we propose $\hat{\alpha} = f^{-1}\{\sum_{i=1}^p w_i f(\hat{\gamma}_i/\hat{\beta}_i)\}$, where f is a known, continuously differentiable and invertible function and the weights satisfy $\sum_{i=1}^p w_i = 1$. Assuming $\hat{\gamma}_i \overset{a.s.}{\to} \gamma_{i0}$, $\hat{\beta}_i \overset{a.s}{\to} \beta_{i0}$, and f has bounded derivatives in a neighborhood of $\alpha_0 > 0$, the true value of α, a continuous mapping theorem gives that $\hat{\alpha} \overset{a.s.}{\to} \alpha_0$.

Inferences about α_0 involve the joint distribution of $\{f(\hat{\gamma}_i/\hat{\beta}_i), \ldots, f(\hat{\gamma}_p/\hat{\beta}_p)\}$. A Taylor expansion of the i-th component in $(\hat{\gamma}_i, \hat{\beta}_i)$ around $(\beta_{i0}, \gamma_{i0})$ yields that

$$K^{1/2}[\{f(\hat{\gamma}_1/\hat{\beta}_1), \ldots, f(\hat{\gamma}_p/\hat{\beta}_p)\} - f(\alpha_0)\epsilon]^T \tag{4}$$

is asymptotically equivalent to

$$f'(\alpha_0)\{J(\beta_0)K^{1/2}(\hat{\gamma} - \gamma_0) + J^*(\gamma_0, \beta_0)K^{1/2}(\hat{\beta} - \beta_0)\}, \tag{5}$$

where $J(\beta)$ is a diagonal matrix with β_i^{-1} in the $i, i-$th position, $J^*(\gamma, \beta)$ is a diagonal matrix with $-\gamma_i\beta_i^{-2}$ in the $i, i-$th position, $f'(s) = df(s)/ds$, and ϵ is a $1 \times p$ vector of ones. Using the results from Section 2.1 gives that (5) $\approx K^{-1/2}\sum_{i=1}^n q_i(\alpha_0, \gamma_0, \beta_0)$, where

$$q_i(\alpha, \gamma, \beta) = f'(\alpha)\{J(\beta)I(\gamma)^{-1}\psi_i(\gamma) + J^*(\gamma, \beta)I^*(\beta)^{-1}\psi_i^*(\beta)\},$$

$I(\gamma) = \lim_{K\to\infty} \hat{I}(\gamma)$, $I^*(\beta) = \lim_{K\to\infty} \hat{I}^*(\beta)$, and

$$\psi_i^*(\beta) = \sum_{j=1}^{n_i} \int_0^\infty \{Z_{ij} - S_{1i}(\beta, u)/S_{0i}(\beta, u)\}\, dN_{ij}(u).$$

Asymptotic normality of (4) is obtained with an ordinary central limit theorem. The covariance matrix, Ω, is consistently estimated by

$$\hat{\Omega} = K^{-1} \sum_{i=1}^{K} \hat{q}_i(\hat{\alpha}, \hat{\gamma}, \hat{\beta})^{\otimes 2}, \tag{6}$$

where $\hat{q}_i$ is q_i with I, I^*, and ψ_i replaced by $\hat{I}, \hat{I}^*$, and $\hat{\psi}_i$.

If $w = (w_1, \ldots, w_p)$ converges in probability to a deterministic limit, then Slutsky's lemma implies that $K^{1/2}\{f(\hat{\alpha}) - f(\alpha_0)\}$ is approximately normal for large K with variance which may be estimated by $w\hat{\Omega}w'$. A $100(1-2\nu)$ confidence interval for α is

$$f^{-1}\{f(\hat{\alpha}) \pm z_\nu K^{-1/2}\sqrt{w\hat{\Omega}w'}\}, \tag{7}$$

where z_ν is the upper $\nu-$percentile of the standard normal distribution.

An issue is the optimal choice of w for given f. Standard theory gives $w = K^{-1}(\epsilon\hat{\Omega}^{-1}\epsilon')\hat{\Omega}^{-1}$ ϵ' achieves the minimum asymptotic variance among all estimators with the form of $\hat{\alpha}$. One can show that when using the optimal weights, the limiting variance of $\hat{\alpha}$ does not depend on f. With moderate sample sizes, the ratio estimators may be highly non-normal. The transformation may reduce the skewness of $f(\hat{\gamma}_i/\hat{\beta}_i)$. Simulations show that the choice of f influences the properties of the inferential procedures.

Under model misspecification, $\hat{\gamma}$ and $\hat{\beta}$ converge in probability to γ^* and β^* maximising the limits as $K \to \infty$ of $K^{-1}\log\{L(\gamma)\}$ and $K^{-1}\log\{L^*(\beta)\}$, respectively. If the marginal model is proportional hazards, then $\gamma^* = \gamma_0$. If the conditional model is a frailty model (1) (not necessarily positive stable), then $\beta^* = \beta_0$. In general, the ratios of the estimands in $\gamma^* = (\gamma_1^*, \ldots, \gamma_p^*)^T$ and $\beta^* = (\beta_1^*, \ldots, \beta_p^*)^T$ are not constant. Conceptually, $\alpha_i = \gamma_i^*/\beta_i^*$ ($i = 1, \ldots, p$) is the attentuation (or accentuation) of the covariate parameters due to the cluster effect, which may include both the shared frailty and unobserved covariates which lead to violations of (3). Thus, $\hat{\alpha}$ with $f(u) = u$ may be interpreted as an estimator of a weighted average of these factors. In some applications, this quantity may have meaning outside the context of the positive stable regression model as a summary of the clustering effect.

2.3 Goodness-of-fit

The positive stable frailty implies that the marginal hazard satisfies (2). Graphical and numerical diagnostics based on martingale residuals are popular for evaluating the proportional hazards assumption with univariate data (Schoenfeld, 1980; Barlow and Prentice, 1988; Therneau, Grambsch, and Fleming, 1990; Lin, Wei, and Ying, 1993). Extensions to multivariate failure times are also available (Spiekerman and Lin, 1996). A limitation is that even when proportional hazards holds marginally, the stable frailty regression model may not be true. That is, there may be models other than (1) which generate proportional hazards in the marginal model.

Assuming that proportional hazards holds marginally, it is not possible to check the adequacy of the positive stable frailty with the martingale residuals for the marginal model. A visual comparison of the fitted multivariate distribution and a nonparametric estimate may be useful. With covariates, smoothing may be needed. There has also been work on formal goodness-of-fit testing for the frailty distribution without covariates. Some tests have been proposed for gamma W_i (Shih, 1998; Glidden, 1999). A general model selection procedure is given in Wang and Wells (2000). To our knowledge, there do not exist statistics for assessing the stable frailty regression model.

When any of the model assumptions are invalid, $\hat{\alpha}_i = \hat{\gamma}_i/\hat{\beta}_i$ converges to α_i $(i = 1, \ldots, p)$ and α_i may not equal α_j for some $1 \leq i < j \leq p$. For $p \geq 2$, numerical tests for homogeneity of the ratios can be based on the $(p-1)$ linearly independent contrasts $\hat{\alpha}_i^* = f(\hat{\alpha}_i) - f(\hat{\alpha}_{i+1}), 1 \leq i \leq p-1$. Let $\hat{\alpha}^* = (\hat{\alpha}_1^*, \ldots, \hat{\alpha}_{p-1}^*)^T$ and $\alpha^* = \{f(\alpha_1) - f(\alpha_2), \ldots, f(\alpha_{p-1}) - f(\alpha_p)\}^T$. As $K \to \infty$, $K^{1/2}(\hat{\alpha}^* - \alpha^*)$ has a $(p-1)$-variate normal distribution with covariance matrix $V = e^{*T}\Omega e^*$, where e^* is a $(p-1) \times p$ matrix satisfying $\alpha^* = e^*\tilde{\alpha}$ and

$\tilde{\alpha} = \{f(\alpha_1), \ldots, f(\alpha_p)\}^T$. The matrix V is consistently estimated by $\hat{V} = e^{*T}\hat{\Omega}e^*$ using the formula (6) for $\hat{\Omega}$.

The null hypothesis is $H_0 : \alpha_i = \alpha \, (1 \leq i \leq p)$. Under H_0, $T_1 = K^{-1}\hat{\alpha}^{*T}\hat{V}^{-1}\hat{\alpha}^*$ is a chi-square variate with $(p-1)$ degrees of freedom. We reject H_0 at level ψ when $T_1 > \chi^2_{p-1,1-\psi}$, where $\chi^2_{p-1,1-\psi}$ is the $1-\psi$ percentile of a chi-square distribution with $(p-1)$ degrees of freedom. Note that the choice of the differences in $\hat{\alpha}_*$ has no effect asymptotically, but may in small samples. An omnibus statistic which uses all possible contrasts is $T_2 = \sum\sum_{i<j} |f(\hat{\alpha}_i) - f(\hat{\alpha}_j)|$. The distribution of T_2 is intractable but may be approximated by simulating from that of $(\hat{\alpha}^* - \alpha^*)$. Let $\{G_k, k = 1, \ldots, B\}$ be B independent draws from a mean zero normal random vector with covariance $\hat{\Omega}/K$. Define $T_{2k} = \sum\sum_{i<j} |G_{ki} - G_{kj}|$, where G_{ki} is the i-th component of G_k. Under H_0, the p-value for the goodness-of-fit test using $\{T_{2k}, k = 1, \ldots, B\}$ is $B^{-1}\sum_{k=1}^{B} I(T_{2k} > T_2)$.

The power of the tests depends on the magnitude of $|\alpha_i - \alpha_j|$. The tests are sensitive to a variety of alternatives. Firstly, (1) might be misspecified, that is, the shared frailty model might be inappropriate. If (1) holds, then g may be misspecified, in which case model (2) is incorrect. If both (1) and (2) hold, that is, the distribution of W_i is correctly specified, the condtional independence assumption (3) may be violated, perhaps as a result of other unobserved covariates. Discriminating amongst the alternatives may not be possible using the ratio statistics.

3. Simulation studies

The failure time pair (T_{i1}, T_{i2}) was generated from the joint survivor function

$$\Pr(T_1 > t_1, T_2 > t_2 | Z) = \exp\left(-\left[\sum_{j=1}^{2}\left\{t_j \exp(\gamma^T Z_{ij})\right\}^{\alpha^{-1}}\right]^{\alpha}\right),$$

using the method in Shih and Louis (1995). Independent censoring times C_{i1} and C_{i2} followed a uniform distribution on $[0, 4\exp(-\gamma^T Z_{ij})]$, which yielded approximately 25% censoring in all settings. The number of clusters ($K = 100, 200$) and the strength of association ($\alpha = .75, .50, .25$) were explored. The dimension ($p = 1, 2$) and distribution of the covariates in $Z_{ijk}, i = 1, \ldots, K, j = 1, 2, k = 1, \ldots, p$ were varied. For $k = 1, \ldots, p$, (Z_{i1k}, Z_{i2k}) were independently and identically distributed with $Z_{ijk}, j = 1, 2$ satisfying uniform(0,1) distributions and $\rho = \text{cor}(Z_{i1k}, Z_{i2k}) = -1, 0$, or $.5$. The magnitudes of the covariate effects in $\gamma = (\gamma_1, \ldots, \gamma_p)^T$ were also investigated, with $\gamma_i = \log(5)$ or $\log(15), i = 1, \ldots, p$. In each setting, 5000 simulated datasets were analyzed. Limited results are presented in Table 1.

In each dataset, estimation was based on $\{(X_{i1}, X_{i2}, \Delta_{i1}, \Delta_{i1}, Z_{i1}, Z_{i2}), i = 1, \ldots, K\}$ using the optimal weights from section 2.2. Two estimates were computed. The untransformed estimate was $\hat{\alpha}_u = \sum_{i=1}^{p} \hat{\beta}_i^{-1} \hat{\gamma}_i$. A log-transformed estimate was $\hat{\alpha}_t = \exp\{\sum_{i=1}^{p} \log(\hat{\beta}_i^{-1} \hat{\gamma})\}$. For both cases, a nominal 95% confidence interval was calculated using the formula in (6). The average values of $\hat{\alpha}$ and the model based standard error estimate (5) over the 5000 simulations are given in Table 1. The empirical standard errors and coverage probabilities of the 95% confidence intervals are also given.

The estimators $\hat{\alpha}_u$ and $\hat{\alpha}_t$ are nearly unbiased and the empirical and model based standard errors are in agreement. As $K \to \infty$, the theoretical variances of the estimators are the same. In the simulations, when $p = 1$, $\hat{\alpha}_u = \hat{\alpha}_t$ and their empirical and model based standard errors are identical. When $p = 2$, the estimators and their empirical and model based variances may differ in finite samples. With $K = 100$ or 200, the differences are negligible. The empirical coverage probabilities of the 95% confidence intervals from $\hat{\alpha}_u$ and $\hat{\alpha}_t$ are generally close to the nominal level for $p = 1$. However, when $p = 2$, the coverage based on the untransformed estimator of α may drop below 90%. The intervals using the log-transformation are more reliable. In both cases, the empirical levels improve as K increases.

4. Real example

The Beaver Dam Eye Study is an ongoing population based study of age-related eye diseases.

All people 43-84 years old and living in Beaver Dam, Wisconsin, in 1987-1988 were invited to participate, with 83.2% enrolling. At the baseline examination, demographic information was collected and biological measurements were taken. There was repeated follow-up in 1993-1995 and 1998-2000. Familial clustering has been identified for ophthalmological outcomes, with an adjustment for the baseline risk factors (Lee, Klein, Klein and Fine, 2001; Klein, Klein, Lee, Moore, and Danforth, 2001). In this paper, we explore sib-pair correlations for diabetes onset and incidence of stroke.

At each examination each participant was asked if they had ever been told that they had diabetes and the age at which they were told. They were also asked if a doctor had ever told them that they had had a stroke or brain hemorrhage and the age at which the event occurred. For these analyses, the self-reported information from multiple exams is used to construct a single outcome. Specifically, the age of diagnosis of diabetes and the age of incidence of stroke are defined to be the age reported at the first examination at which the event was reported to have occurred. For those never reporting a history of the event, the age at the last examination was used for the censoring time.

A large number of baseline risk factors are available. The following factors are considered to be scientifically relevant *a priori* and are employed in the analyses: sedentary lifestyle (1 = yes, 0 = no), hypertension (1 = mean diastolic $\geq$ 90, mean systolic $\geq$ 140, or taking medication, 0 = otherwise), smoking (0 = never, 1 = past, 2 = current), gender (1 = male, 0 = female), body mass index (height/weight^2), total serum cholesterol (mg/dL), hematocrit (%), white blood cell count (k/uL), glycated hemoglobin (%), and serum uric acid (mg/dL).

In total, there were 2490 individuals who were members of a family. Of these, 2071 had complete covariate information and are included in the analyses. There are 1289 sibships in the sample with complete covariates: 724 (56%) are singletons, 414 (32%) are sibpairs, 100 (8%) are triples, and 51 (4 %) had four or more sibs with a maximum of eight. There were

227 diabetes events and 122 stroke events reported during the follow-up period.

The selection of covariates for calculating $\hat{\alpha}$ is an important practical issue. For $\hat{\alpha}_u$ and $\hat{\alpha}_t$, including covariates which have zero coefficients in the true model leads to an invalid estimator in large samples. In practice, covariates with small effects are likely to have ratios which are unstable. In some cases the estimated coefficients may have opposite signs. Choosing covariates to estimate α is nonstandard because the fits of models (1) and (2) must be assessed simultaneously.

We adopt a heuristic strategy. The goal is to include covariates which are highly predictive. Firstly, stepwise regression is used to determine the best fitting marginal and conditional models. Next, covariates which are significant at level 0.05 in one of these best fitting models and at level 0.10 in the other best fitting model are used to define a model for estimation of α. Other thresholds may be used. Since the optimal linear combination downweights ratios with larger variances, varying the guidelines does not tend to produce big changes in either the point or the variance estimates.

We begin with diabetes. Glycated hemoglobin is used to define the onset of diabetes and is omitted. Forward and backward selection give a final marginal model with body mass index, white blood cell counts, hematocrit, cholesterol, and hypertension and a final conditional model with body mass index, white blood cell count, and gender. Body mass index and white blood cell count satisfy the criterion for estimation of α and the results for models with these covariates are in Table 2. Obesity is a risk factor for diabetes and elevated white blood cell counts have been correlated with conditions which may be associated with the disease, such as smoking and inflammation (Rimm *et al*, 1993; Schmidt *et al*, 1999).

Omitting covariates from proportional hazards models for independent observations ($n_i = 1, i = 1, \ldots, K$) is known to lessen the effects for those covariates which are correctly included in the model (Struthers and Kalbfleisch, 1986; Schumacher, Olschewski, and Schmoor, 1987;

Bretagnolle and Huber-Carol, 1988). These theoretical results can easily be extended to the analysis of correlated failure times using L. Observe that in our analysis both sets of coefficients exhibit the attentuations. The magnitudes are similar, which is expected under the positive stable model. The untransformed estimate (0.95 confidence interval) for the frailty parameter based on the optimal linear combination is 0.718 (0.453, 0.984). The transformed estimate is 0.717 (0.495, 1.038). This suggests that after adjusting for weight and white blood cell count, there is a moderately strong association between sibs. This may be attributed to the well-known genetic etiology of type II diabetes or to other shared environmental factors (Khoury, Beaty, and Liang, 1988).

Maximum likelihood estimates of γ using an EM implementation (Wang, Klein, and Moeschberger, 1995; Shu and Klein, 1999) are also given in Table 2 and are comparable to those from the pseudo partial likelihood. The estimate of α is 0.943 (0.873, 1.013), which provides some evidence of association, although the magnitude is less than that for $\hat{\alpha}$. Analyses of the 1289 sibships using the SAS macro may require several hours. This contrasts with the new estimator which is calculated in seconds.

The omnibus test statistic T_2 for homogeneity of the ratios is 0.101, with p-value 0.82 obtained by simulating 10,000 multivariate normal random variates with covariance matrix $\hat{\Omega}/1289$. The model fits reasonably well, to the extent that violations of the underlying assumptions have not lead to large differences in the ratios across covariates.

For stroke, forward selection gives smoking and hypertension in the marginal model and white blood cell count in the conditional model. Backward selection picks smoking and hypertension for both models. In the fits for an expanded model with smoking, hypertension, and white blood cell count, smoking and hypertension meet the 0.05/0.10 cut-offs and so are employed in the model for $\hat{\alpha}$. The parameter estimates are in Table 2. The connections between these covariates and stroke are well understood.

In this analysis, the estimated coefficients from the two models are similar. The untransformed estimate of α is 0.873 (0.305, 1.392) and the transformed estimate is 0.866 (0.476, 1.575). This indicates that controlling for smoking and hypertension, correlation in stroke incidence in sibs is not great. Again, the lack-of-fit test is not significant.

The results of the SAS macro are in Table 2. Interestingly, the likelihood is maximised over $\alpha \in [0, 1]$ at $\alpha = 1$. This occurs because the profile likelihood in α is monotone increasing in α. The estimates of γ are identical to those from $L(\gamma)$ which assumes independence within clusters. However, because α is estimated and not fixed at 1, the standard errors from the pseudo partial likelihood are invalid. Since the estimate of α is not an interior point of $[0, 1]$, the usual techniques for deriving variance estimators may not be applicable. Self and Liang (1987) provided the asymptotic properties for the maximum likelihood estimators in parametric models under boundary conditions. It is not clear that the theory can be adapted to our semiparametric set-up. Note that the inferences for $\hat{\alpha}$ do not require $\alpha_0 < 1$.

5. Discussion

The efficiency of our estimator for α is limited by the magnitude of the within-cluster covariate contrasts. That is, the larger is the within-cluster differences in covariates, the more precise is $\hat{\alpha}$. Without covariates, our approach is not applicable. Methods which use direct information on the dependence structure are more efficient. A formal study of the information loss would be worthwhile.

An important consideration is the ease of computation of $\hat{\alpha}$. The new method is most useful with large datasets, like the Beaver Dam Eye Study, where the implementation for maximum likelihood may be impractical. At the least, $\hat{\beta}$, $\hat{\alpha}$, and $\hat{H}$ may serve as starting values for other estimation procedures. The estimators may also be useful in developing inference procedures for more complicated hierarchical models involving residual correlations not captured by (3).

An interesting topic is covariate selection for $\hat{\alpha}$ in real applications. The proposal in Section 4 was based on a covariate being significant in the fits for both models. We conducted a small numerical study to assess the performance of this ad hoc approach. The data was simulated under the set-up in Section 3, with $n = 100$, $p = 2$, and $\beta_i = \log(15)$, for $i = 1, 2$. There was also an additional covariate Z_{3i} generated uniform$(0,1)$ independently of (Z_{1i}, Z_{2i}) with zero coefficients in models (1) and (2). We computed $\hat{\alpha}_u$ and $\hat{\alpha}_t$ using the variable selection procedure described in Section 4 with the same thresholds. For $\alpha = 0.75$, the average, empirical standard error, model based standard error, and coverage, from $\hat{\alpha}_t$ are 0.70, 0.16, 0.15, and 0.91, respectively. For $\alpha = 0.50$, the corresponding values are 0.47, 0.12, 0.11, and 0.92. For $\alpha = 0.25$, the values are 0.23, 0.07, 0.06, 0.93. These numbers are almost identical to those in Table 1, where the ratios for Z_{1i} and Z_{2i} are always included in the estimator and that for Z_{3i} is never used. The results for $\hat{\alpha}_u$ are similar and are omitted. Further investigations are needed into the impact of model selection on the estimation procedure and into other simple estimators which do not require that all covariates have nonzero coefficients.

The shared frailty regression model (1) with g positive stable assumes that the differences in the marginal and conditional hazard ratios originate in a common clustering effect. Neuhaus and Kalbfleisch (1998) argue that such effects may measure different phenomena and may not be equal across covariates, even when (3) holds and there are no additional unmeasured confounders. The goodness-of-fit tests are useful checks for homogeneity of the coefficient ratios and give some indication as to the suitability of the model. Intuitively, under misspecification, the untransformed estimator is a weighted average of the attenuation (or accentuation) factors. This quantity may be meaningful outside the context of the assumed model as an overall clustering effect. It would be helpful to evaluate analytically the behaviour of $\hat{\alpha}$ under various violations of the conditions (1), (2), and (3).

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Table 1. Results of simulation study. In each column, the results for $\hat{\alpha}_u$ are outside the parentheses and the results for $\hat{\alpha}_t$ are inside the parentheses, as needed. Note that when $p = 1$, the means and variances of the estimators are exactly equal.

α	p	γ	ρ	K	Average	Empirical SE	Model Based SE	Coverage
0.75	1	log(5)	-1	100	0.78	0.21	0.20	0.94 (0.96)
				200	0.76	0.13	0.13	0.95 (0.96)
		log(15)	-1	100	0.76	0.16	0.15	0.94 (0.95)
				200	0.75	0.11	0.11	0.95 (0.95)
		log(15)	0	100	0.79	0.26	0.21	0.93 (0.96)
				200	0.76	0.14	0.14	0.95 (0.95)
		log(15)	0.5	100	0.84	0.37	0.33	0.91 (0.96)
				200	0.78	0.22	0.19	0.93 (0.96)
	2	log(15)	-1	100	0.70 (0.70)	0.17 (0.16)	0.15 (0.15)	0.87 (0.92)
				200	0.72 (0.72)	0.11 (0.11)	0.11 (0.11)	0.91 (0.93)
0.50	1	log(5)	-1	100	0.52	0.33	0.20	0.94 (0.97)
				200	0.51	0.11	0.11	0.95 (0.96)
		log(15)	-1	100	0.51	0.12	0.12	0.94 (0.95)
				200	0.50	0.08	0.08	0.94 (0.95)
		log(15)	0	100	0.53	0.20	0.18	0.93 (0.96)
				200	0.51	0.11	0.11	0.94 (0.96)
		log(15)	0.5	100	0.59	0.25	0.25	0.91 (0.97)
				200	0.52	0.16	0.15	0.93 (0.96)
	2	log(15)	-1	100	0.47 (0.47)	0.12 (0.12)	0.11 (0.11)	0.86 (0.91)
				200	0.48 (0.48)	0.08 (0.08)	0.08 (0.08)	0.91 (0.94)
0.25	1	log(5)	-1	100	0.26	0.34	0.21	0.95 (0.97)
				200	0.26	0.08	0.08	0.95 (0.97)
		log(15)	-1	100	0.26	0.08	0.07	0.94 (0.95)
				200	0.25	0.05	0.05	0.94 (0.95)
		log(15)	0	100	0.27	0.15	0.14	0.95 (0.96)
				200	0.26	0.09	0.09	0.95 (0.97)
		log(15)	0.5	100	0.30	0.34	0.32	0.93 (0.97)
				200	0.27	0.12	0.12	0.94 (0.97)
	2	log(15)	-1	100	0.23 (0.23)	0.07 (0.07)	0.06 (0.06)	0.88 (0.92)
				200	0.24 (0.24)	0.05 (0.05)	0.05 (0.05)	0.90 (0.94)

Table 2. Results of Beaver Dam data analysis; NA, not available

	New		EM					
Risk Factor	$\hat{\gamma}$	SE($\hat{\gamma}$)	$\hat{\gamma}$	SE($\hat{\gamma}$)	$\hat{\beta}$	SE($\hat{\beta}$)	$\hat{\alpha}$	SE($\hat{\alpha}$)
				Diabetes				
Body Mass Index	0.092	0.010	0.097	0.010	0.125	0.029	0.740	0.167
White Blood Cells	0.098	0.012	0.101	0.018	0.152	0.092	0.640	0.377
				Stroke				
Smoking	0.507	0.125	0.507	NA	0.629	0.259	0.807	0.293
Hypertension	0.743	0.208	0.743	NA	0.678	0.372	1.096	0.501