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MODELING HETEROGENEITY FOR BIVARIATE SURVIVAL DATA BY POWER VARIANCE FUNCTION DISTRIBUTION

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Abstract

We propose a bivariate Weibull regression model with frailty which is generated by power variance function distribution. We assume that the bivariate survival data follow bivariate Weibull of Hanagal (2005a) and distribution of censoring variable is independent of the two life times. There are some interesting situations like survival times in genetic epidemiology, survival times of dental implants of patients and survival times of twin births (both monozygotic and dizygotic) where genetic behavior (which is unknown and random) of patients follows a power variance function frailty distribution. These are the situations which motivate to study this particular model. We propose two stage maximum likelihood estimation procedure for the parameters and develop large sample tests for no frailty and the significance of regression parameters in the proposed model.

Key words: Bivariate Weibull, Parametric regression, Power variance function frailty, Simultaneous failures, Survival times.

1. Introduction

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 environment risk factors the analysis of the clustering is more difficult (Parner, 1998). In a frailty model, it is absolutely necessary to be able to include some known explanatory variables to be able to estimate the aspects of the frailty distribution which represents the effect of unknown covariates. The reason is that the frailty describes the influence of common unknown factors. If some covariates are included in the model, the variation owing to unknown covariates should be reduced. Some covariates are indeed common for all members of the group. For monozygotic twins, examples are gender and any other genetically based covariate. Both monozygotic and dizygotic twins share date of birth and common pre-birth environment. By measuring some potentially important covariates, we can examine the influence of the covariates, and we can examine whether they explain the dependence, that is, whether the frailty has no effect (or more correctly, no variation), when the covariate is included in the model.

There are some situations where the lifetimes of the two components, T_1 and T_2 are dependent, for example, the timing of failure of paired organs like kidneys, lungs, eyes, ears, dental implants, etc. are dependent on each other. The covariates here may be the age of the patient, sex of the patient, smoking or alcoholic habits of the patient, diabetic or no-diabetic conditions of the patient, some specific diseases of the patient, etc. These covariates are risk factors to the paired organs of an individual and are not different for each organ in the same patient and so we have common covariates. There are some situations where we find some non-identical covariates in addition to

identical covariates for paired components in a system, for example, failure times (in months) of a pair of dental implants in a jaw of a patient. Here the identical covariates are age and sex of a patient and non-identical covariates may be (1) different materials (ceramic, metal) of dental implant, (2) different shapes (screw, anchor, pillar, hollow cylinder) of dental implant, (3) dental implants in different locations (front, premolar, molar) of a jaw, (4) dental implants in different jaws (lower, upper).

The regression model is derived conditionally on the shared frailty (Y). Conditionally on Y , the cumulative hazard function of lifetimes (T_1, T_2) is assumed to be of the form

$$Y\, M(t_1,t_2)$$

where $M(t_1,t_2) = -\log S(t_1, t_2)$ is the bivariate cumulative or integrated hazard function of (T_1, T_2) with the bivariate survival function $S(t_1, t_2)$ and that the value of Y is common to several individuals in a group. When there is no variability in the distribution of Y , implies that Y has a degenerate distribution. When the distribution is not degenerate, the dependence is positive. The value of Y can be considered as generated from unknown values of some explanatory variables. Conditional of Y , the bivariate survival function is

$$S(t_1, t_2| y) = \exp\{-yM(t_1, t_2)\} \quad (1)$$

When T_1 and T_2 are independent, $M(t_1, t_2) = M_1(t_1)+M_2(t_2)$, where $M_i(t_i)$, i = 1, 2 are the integrated hazards of T_1 and T_2 respectively. From this, we immediately derive the bivariate survival function by integrating Y out

$$S(t_1, t_2) = E \exp[-YM(t_1, t_2)] = L(M((t_1, t_2))$$

where L(.) is the Laplace transform of the distribution of Y . Thus, the bivariate survivor function is easily expressed by means of the Laplace transform of the frailty distribution, evaluated at the total integrated conditional hazard.

The positive stable model (Hougaard, 1986) is a useful alternative to gamma model, in part because it has the attractive feature that predictive hazard ratio decrease to 1 over time (Oakes, 1989). The property is observed in familial associations of the ages of onset of diseases with etiologic heterogeneity, where genetic cases occur early and longterm survivors are weakly correlated. The positive stable model has the advantage that it fits proportional hazards which means that if the conditional model has proportional hazards, so does the marginal distribution. This is an advantage, when considering the model as a random effects model. Hanagal (2005b, 2006b) also proposed bivariate Weibull (BVW) regression models for the survival data with positive stable and gamma frailty distributions respectively. These BVW models are based on the extension of bivariate exponential of Marshall-Olkin (1967).

The power variance function is a three parameter family uniting gamma and positive stable distributions. That is, gamma and positive stable distributions are sub models of power variance function distribution. In this paper, we study more general distribution as a frailty instead of its sub models.

The most natural parametric distribution to consider is the Weibull model because it allows for both the proportional hazard and the accelerated failure time model. There is no unique natural extension of Weibull distribution in the bivariate or multivariate situations. So, there are different versions of bivariate or multivariate

Weibull distributions, each has its own merits and demerits. These distributions have been derived from the exponential distribution by taking power transformation. Hanagal (2005a) proposed a bivariate Weibull (BVW) distribution which is the Weibull extension of bivariate exponential of Proschan-Sullo (1974). The main feature of this model is that it allows for simultaneous failures of the components and failure of one component changes the failure rate of other component. BVW models of Hanagal (2004) and Hanagal (2006a) are the sub models of BVW of Hanagal (2005a). There are some biometrical applications which motivate to study bivariate Weibull (BVW) regression model in this particular situation. For example, twin births and another example is paired organs in an individual (or patient) as a two component system. It is quit common that simultaneous failures of twin births may occur due to an accident and also simultaneous failures of paired organs within a patient may occur. We are very sorry to say that unfortunately we did not get any suitable data for our present model but in future if someone get a data, the present model which is more general can be applied. In order to compensate the real data, we use simulated data and do the estimation and testing procedures.

The focus of this paper is inference for the power variance function (PVF) frailty parameters with family of paired units following BVW regression model which are randomly censored and estimate the regression parameters and test the significance of the regression parameters. In Section 2, we present PVF distribution. In Section 3, we introduce the BVW regression model with PVF frailty and in Section 4, we obtain estimation of the parameters in the proposed model. In Section 5, we present test procedures for testing no frailty and the significance of regression parameters. In Section 6, we present a simulation study and Section 7 contains some discussions.

2. The Power Variance Function Distribution

The power variance function distribution is denoted PVF(α ,δ ,θ). For α = 0, the gamma distributions are obtained, with same parameterization. Some formulas are valid, but many are others are different in this case. For θ = 0, the positive stable distributions are obtained. For α = 1, a degenerate distribution is obtained. For α = 1/2, the inverse Gaussian distributions are obtained. For α = −1, the non-central gamma distribution of shape parameter zero is obtained.

The parameter set is ($\alpha \leq 1$, $\delta > 0$), with ($\theta \geq 0$ for $\alpha > 0$), and ($\theta > 0$ for $\alpha \leq 0$). The distribution is concentrated on the positive numbers for $\alpha \geq 0$, and is positive or zero for $\alpha < 0$.

In the case $\alpha > 0$, the p.d.f. of PVF is given by [See Hougaard(2000), p. 504].

$$f(y) = \exp\{-\theta y + \delta^{\alpha}/\alpha\}\frac{1}{\pi}\sum_{k=1}^{\infty}\frac{\Gamma(k\alpha+1)}{k!}(-\frac{1}{y})^{\alpha k+1}\sin(\alpha k\pi), \quad y>0 \qquad (2)$$

In the case α <0, the Γ-term in the density is not necessarily defined, and therefore we can use the alternative expression for p.d.f. of PVF as [See Hougaard(2000), p. 504].

$$f(y) = \exp\{-\theta y + \delta^{\alpha}/\alpha\}\frac{1}{y}\sum_{k=1}^{\infty}\frac{(-\delta y^{\alpha}/\alpha)^{k}}{k!\Gamma(-k\alpha)}, \quad y>0 \qquad (3)$$

This expression is valid for all α values, except 0 and 1, with the convention that when the Γ-function in the denominator is undefined (which happens when $k\alpha$ is a positive integer), the whole term in the sum is zero. For α < 0, there is probability $\exp(\delta\theta^{\alpha}/\alpha)$ of the random variable being zero. For $\alpha \geq 0$, the distribution is unimodal. If Y_1 and Y_2 are independent, and Y_i follows PVF(α, δ_i, θ), i = 1, 2 the distribution of $Y_1 + Y_2$ is PVF($\alpha, \delta_1 + \delta_2, \theta$). So, PVF distribution is infinitely divisible. When θ > 0, all (positive) moments exist, and the mean is $\delta\theta^{\alpha-1}$. The variance is $\delta(1-\alpha)\theta^{\alpha-2}$.

The Laplace transform of PVF distribution is

$$L(s) = \exp[-\delta\{(\theta + s)^{\alpha} - \theta^{\alpha}\}/\alpha]$$

In frailty model, it is common to take the mean expectation of the frailty distribution equal to 1 and to limit the parameter space of this distribution in such a way to attain this constraint in order to avoid identifiability problems in the model. In order to avoid this identifiability problem, we assume $\delta = \theta = 1$ and the mean and variance will become 1 and variance $(1-\alpha)$ respectively. The Laplace transform of PVF distribution with the restriction $\delta = \theta = 1$ is

$$L(s) = \exp[-\{(1+s)^{\alpha} - 1\}/\alpha] \quad (4)$$

This model extends both the positive stable and the inverse Gaussian models and thus is useful for testing either of the models. It can also be used as a flexible way to describe dependence.

The unconditional bivariate survival function with PVF frailty is given by

$$S_{\alpha}(t_1, t_2) = \exp[-\{1 + M_1(t_1) + M_2(t_2)\}^{\alpha}/\alpha + 1/\alpha] \quad (5)$$

3. Bivariate Weibull Regression With Power variance Function Frailty

Freund (1961) proposed BVE as a model for failure time distribution of a system with lifetimes (X_1,X_2) operating in the following manner. Initially X_1 and X_2 are independent exponential with failure rates λ_1 and λ_2 respectively, $\lambda_1, \lambda_2, > 0$. The interdependence of the components is such that failure of a component changes the failure rate of other component from λ_1 to λ_{11} (λ_2 to λ_{22}) which is called load sharing. The BVE of Freund (1961) with its joint pdf is given by

$$f(x_1, x_2) = \begin{cases} \lambda_1\lambda_{22}\exp\{-\lambda_{22}x_2 - (\lambda_1 + \lambda_2 - \lambda_{22})x_1\}; & x_1 < x_2 \\ \lambda_2\lambda_{11}\exp\{-\lambda_{11}x_1 - (\lambda_1 + \lambda_2 - \lambda_{11})x_2\}; & x_2 < x_1 \end{cases} \quad (6)$$

where $\lambda_1, \lambda_2, \lambda_{11}, \lambda_{22} > 0$.

Proschan-Sullo (1974) proposed BVE which is the combination of both Marshall-Olkin and Freund models and the two component system operate in the following manner. Initially X_1 and X_2 follow BVE of Marshall-Olkin (1967). When a

component fails the failure of a component changes the failure rate of other component from $\lambda_1+\lambda_3$ to $\lambda_{11}+\lambda_3$ ($\lambda_2+\lambda_3$ to $\lambda_{22}+\lambda_3$) (or load sharing). The BVE of Proschan-Sullo (1974) with its p.d.f. is given by

$$f(x_1,x_2)=\begin{cases}\lambda_1(\lambda_{22}+\lambda_3)\exp\{-(\lambda_{22}+\lambda_3)x_2-(\lambda_1+\lambda_2-\lambda_{22})x_1\}; & x_1<x_2\\ \lambda_2(\lambda_{11}+\lambda_3)\exp\{-(\lambda_{11}+\lambda_3)x_1-(\lambda_1+\lambda_2-\lambda_{11})x_2\}; & x_2<x_1\\ \lambda_3\exp\{-(\lambda_1+\lambda_2+\lambda_3)x\}, & x_1=x_2=x\end{cases} \tag{7}$$

where $\lambda_1,\lambda_2,\lambda_3,\lambda_{11},\lambda_{22}>0.$

Taking transformation $T_1=X_1^c$ and $T_2=X_2^c$, $c>0$ we get bivariate Weibull model (BVW) which was introduced by Hanagal (2005a) with p.d.f. given by

$$f(t_1,t_2)=\begin{cases}\lambda_1(\lambda_{22}+\lambda_3)c^2(t_1t_2)^{c-1}\exp\{-(\lambda_{22}+\lambda_3)t_2^c-(\lambda_1+\lambda_2-\lambda_{22})t_1^c\}; & t_1<t_2\\ \lambda_2(\lambda_{11}+\lambda_3)c^2(t_1t_2)^{c-1}\exp\{-(\lambda_{11}+\lambda_3)t_1^c-(\lambda_1+\lambda_2-\lambda_{11})t_2^c\}; & t_2<t_1\\ \lambda_3\exp\{-(\lambda_1+\lambda_2+\lambda_3)t^c\}, & t_1=t_2=t\end{cases} \tag{8}$$

Reparametrize $\lambda_{11}=\phi_1\lambda_1,\lambda_{22}=\phi_2\lambda_2$ and rewrite the above p.d.f.

$$f(t_1,t_2)=\begin{cases}\lambda_1(\lambda_2\phi_2+\lambda_3)c^2(t_1t_2)^{c-1}\exp\{-(\lambda_2\phi_2+\lambda_3)t_2^c\\ \qquad -(\lambda_1+\lambda_2-\lambda_2\phi_2)t_1^c\}, & t_1<t_2\\ \lambda_2(\lambda_1\phi_1+\lambda_3)c^2(t_1t_2)^{c-1}\exp\{-(\lambda_1\phi_1+\lambda_3)t_1^c\\ \qquad -(\lambda_1+\lambda_2-\lambda_1\phi_1)t_2^c\}, & t_2<t_1\\ \lambda_3\exp\{-(\lambda_1+\lambda_2+\lambda_3)t^c\}, t_1=t_2=t\end{cases} \tag{9}$$

As we know in BVE of Proschan-Sullo (1974), the marginals are weighted combinations of two exponential distributions. Here in the BVW also, the marginals are weighted combinations of two Weibull distributions with same weights. The $\min(T_1,T_2)$ is Weibull with scale parameter $(\lambda_1+\lambda_2+\lambda_3)$ and shape parameter c. When $\lambda_3=0$, the BVW in Eqn (9) reduces to BVW of Hanagal (2006a) and when $\phi_1=\phi_2=1$, it reduces to BVW of Hanagal (2004). When $\phi_1=\phi_2=1$ and $\lambda_3=0$ then T_1 and T_2 are independent.

The probabilities in the three regions are given by

$P[T_1<T_2]=\lambda_1/(\lambda_1+\lambda_2+\lambda_3)$, $P[T_1>T_2]=\lambda_2/(\lambda_1+\lambda_2+\lambda_3)$ and $P[T_1=T_2]=\lambda_3/(\lambda_1+\lambda_2+\lambda_3)$.

The survival function of this BVW is given by

$$S(t_1,t_2)=\begin{cases}\dfrac{\lambda_2(1-\phi_2)e^{-\lambda.t_2^C}+\lambda_1 e^{-\lambda_1+\lambda_2(1-\phi_2)t_1^C-(\lambda_2\phi_2+\lambda_3)t_2^C}}{\lambda_1+\lambda_2(1-\phi_2)}; & t_1<t_2\\ \dfrac{\lambda_1(1-\phi_1)e^{-\lambda.t_1^C}+\lambda_2 e^{-\lambda_2+\lambda_1(1-\phi_1)t_2^C-(\lambda_1\phi_1+\lambda_3)t_1^C}}{\lambda_1+\lambda_2(1-\phi_2)}; & t_2<t_1\end{cases}$$

Where $\lambda=\lambda_1+\lambda_2+\lambda_3$. (10)

Now the conditional survival function of BVW given the frailty (Y=y) is given by

$$S(t_1,t_2\mid y)=\begin{cases}\dfrac{\lambda_2(1-\phi_2)e^{-y\lambda.t_2^C}+\lambda_1 e^{-y[\lambda_1+\lambda_2(1-\phi_2)t_1^C+(\lambda_2\phi_2+\lambda_3)t_2^C]}}{\lambda_1+\lambda_2(1-\phi_2)}; & t_1<t_2\\ \dfrac{\lambda_1(1-\phi_1)e^{-y\lambda.t_1^C}+\lambda_2 e^{-y[\lambda_2+\lambda_1(1-\phi_1)t_2^C+(\lambda_1\phi_1+\lambda_3)t_1^C]}}{\lambda_1+\lambda_2(1-\phi_2)}; & t_2<t_1\end{cases} \quad (11)$$

Assuming Y follows PVF distribution given in (2) and then integrating over Y , we get unconditional survival function and is given by

$$S(t_1,t_2\mid y)=\begin{cases}\dfrac{\lambda_1 e^{-[1+\lambda_1+\lambda_2(1-\phi_2)t_1^C+(\lambda_2\phi_2+\lambda_3)t_2^C]^\alpha/\alpha+1/\alpha}}{\lambda_1+\lambda_2(1-\phi_2)}\\ \quad+\dfrac{\lambda_2(1-\phi_2)e^{-(\lambda.t_2^C)^\alpha/\alpha+1/\alpha}}{\lambda_1+\lambda_2(1-\phi_2)}, & t_1<t_2\\ \dfrac{\lambda_2 e^{-[\lambda_2+\lambda_1(1-\phi_1)t_2^C+(\lambda_1\phi_1+\lambda_3)t_1^C]^\alpha/\alpha+1/\alpha}}{\lambda_1+\lambda_2(1-\phi_2)}\\ \quad+\dfrac{\lambda_1(1-\phi_1)e^{-(\lambda.t_1^C)^\alpha/\alpha+1/\alpha}}{\lambda_1+\lambda_2(1-\phi_2)}, & t_2<t_1\end{cases} \quad (12)$$

Substituting λ_3 = 0 in all the above expressions we get the corresponding expressions for the Weibull extension of BVE of Freund (1961).

The above bivariate survival function (12) has three types of dependencies, one is due to simultaneous failures, the second is due to load sharing, and the third is due to frailty. Now we develop a regression model for the two component system as follows. As we have seen in the univariate Weibull regression, the scale parameter of the univariate Weibull distribution can be expressed in terms of regression coefficients. If λ is the scale parameter of the exponential distribution, then $\lambda=e^{-\beta' z}$ or

$\lambda = e^{\beta' z}$ where β is the vector of regression parameters and z is the vector of regressors or covariates. The exponent term in the above expression, we can take either positive or negative but in either case λ > 0. In the similar manner, the scale parameters $(\lambda_1, \lambda_2, \lambda_3)$ can be expressed in terms of regression parameters in the following way.

$$\begin{aligned} \lambda_1 &= \exp\{-(\beta_0' z_0 + \beta_1' z_1\} \\ \lambda_2 &= \exp\{-(\beta_0' z_0 + \beta_2' z_2\} \\ \lambda_3 &= \exp\{-(\beta_0' z_0 + \beta_1' z_1 + \beta_2' z_2\} \end{aligned} \qquad (13)$$

where

$\beta_0' = (\beta_{01}, ..., \beta_{0p}), \quad -\infty < \beta_0 < \infty \quad z_0' = (z_{01}, ..., z_{op})$

$\beta_1' = (\beta_{11}, ..., \beta_{1q}), \quad -\infty < \beta_1 < \infty \quad z_1' = (z_{11}, ..., z_{oq})$

$\beta_2' = (\beta_{21}, ..., \beta_{2q}), \quad -\infty < \beta_2 < \infty \quad z_2' = (z_{21}, ..., z_{oq})$

$\beta_0' z_0$ corresponds to the term containing identical covariates for both components. $\beta_1' z_1$ corresponds to the term containing covariates for first component and $\beta_2' z_2$ corresponds to the term containing covariates for second component. The parameters $(\beta_0, \beta_1, \beta_2)$ are not the same in $(\lambda_1, \lambda_2, \lambda_3)$. λ_1 which is related to component 1 has combination of (β_0, β_1), λ_2 which is related to component 2 has combination of (β_0, β_2), and λ_3 which is related to the simultaneous failures of both components has combination of $(\beta_0, \beta_1, \beta_2)$. For example, age is common covariate for the two dental implants in an individual. The influence of age is same on both the life times of the implants. Suppose out of the two implants in an individual, one implant is metal and the other is ceramic. Here the influence of two types of materials is different on the life times of implants. Therefore λ_1 contains only (β_0, β_1) which indicates age and metal (for component 1), λ_2 contains only (β_0, β_2) which indicates age and ceramic (for component 2), and λ_3 contains $(\beta_0, \beta_1, \beta_2)$ which indicates age, metal, and ceramic (for both components). We denote this model as power variance function frailty bivariate Weibull (PVFFBVW) regression model with survival function $S(t_1, t_2 \mid Z)$.

4. Estimation of the Parameters

For the bivariate life time distribution, we use univariate censoring scheme given by Hanagal (1992a, 1992b) because the individuals do not enter at the same time and withdrawal or death of an individual or termination of the study will censor both life times of the components. Here the censoring time is independent of the life times of both components. Here the two components may be paired organs or dental implants in an individual and death or withdrawal of an individual censors both the life times of the

organs or dental implants. This is the standard univariate right censoring for both failure times T_1 and T_2. Suppose that there are n independent pairs of components under study and i-th pair of the components have life times (t_{1i}, t_{2i}) and a censoring time (w_i). The life times associated with i-th pair of the components are given by

$$\begin{aligned}(T_{1i}, T_{2i}) &= (t_{1i}, t_{2i}), && \max(t_{1i}, t_{2i}) < w_i \\ &= (t_{1i}, w_i), && t_{1i} < w_i < t_{2i} \\ &= (w_i, t_{2i}), && t_{2i} < w_i < t_{1i} \\ &= (w_i, w_i), && w_i < \min(t_{1i}, t_{2i}).\end{aligned} \tag{14}$$

Discarding factors which do not contain any of the parameters, we want to estimate the parameters in the proposed model. Now the likelihood of the sample of size n is given by

$$L = (\prod_{i=1}^{n_1} f_{1i})(\prod_{i=1}^{n_2} f_{2i})(\prod_{i=1}^{n_3} f_{3i})(\prod_{i=1}^{n_4} f_{41i})(\prod_{i=1}^{n_5} f_{5i})(\prod_{i=1}^{n_6} \overline{F}_i) \tag{15}$$

where

$$f_{1i} = \frac{\mu\lambda_1 c^2[\lambda_1 + \lambda_2(1-\phi_2)](\lambda_2\phi_2 + \lambda_3)(t_{1i}t_{2i})^{c-1} h_1(\underline{\lambda}) S_1(t_{1i}, t_{2i} \mid Z_i)}{[\lambda_1 + \lambda_2(1-\phi_2)]},$$

$$t_{1i} < t_{2i} < w_i$$

$$f_{2i} = \frac{\mu\lambda_2 c^2[\lambda_2 + \lambda_1(1-\phi_1)](\lambda_1\phi_1 + \lambda_3)(t_{1i}t_{2i})^{c-1} h_2(\underline{\lambda}) S_2(t_{1i}, t_{2i} \mid Z_i)}{[\lambda_2 + \lambda_1(1-\phi_1)]},$$

$$t_{2i} < t_{1i} < w_i$$

$$f_{3i} = \mu c\lambda_3 t_i^{c-1}\{1 + \lambda t_i^c\}^{\alpha-1} S(t_{1i}, t_{2i} \mid Z_i), \qquad t_{1i} = t_{2i} = t_i < w_i$$

$$f_{4i} = \frac{\mu\lambda_1 c[\lambda_1 + \lambda_2(1-\phi_2)](t_{1i})^{c-1} h_3(\underline{\lambda}) S_1(t_{1i}, t_{2i} \mid Z_i)}{[\lambda_1 + \lambda_2(1-\phi_2)]}, \quad t_{1i} < w_i < t_{2i}$$

$$f_{5i} = \frac{\mu\lambda_2 c[\lambda_2 + \lambda_1(1-\phi_1)](t_{2i})^{c-1} h_4(\underline{\lambda}) S_2(t_{1i}, t_{2i} \mid Z_i)}{[\lambda_2 + \lambda_1(1-\phi_1)]}, \quad t_{2i} < w_i < t_{1i}$$

$$\overline{F}_i = P[T_{1i} > w_i, T_{2i} > w_i] = S(w_i, w_i \mid Z_i), \qquad w_i < \min(t_{1i}, t_{2i})$$

$$h_1(\underline{\lambda}) = \{1 + [\lambda_1 + \lambda_2(1-\phi_2)]t_{1i}^c + (\lambda_2\phi_2 + \lambda_3)t_{2i}^c\}^{\alpha-2}$$
$$\{(1-\alpha) + \alpha\{1 + [\lambda_1 + \lambda_2(1-\phi_2)]t_{1i}^c + (\lambda_2\phi_2 + \lambda_3)t_{2i}^c\}^{\alpha}\}$$

$$h_2(\underline{\lambda}) = \{1 + [\lambda_2 + \lambda_1(1-\phi_1)]t_{2i}^c + (\lambda_1\phi_1 + \lambda_3)t_{1i}^c\}^{\alpha-2}$$
$$\{(1-\alpha) + \alpha\{1 + [\lambda_2 + \lambda_1(1-\phi_1)]t_{21i}^c + (\lambda_1\phi_1 + \lambda_3)t_{1i}^c\}^{\alpha}\}$$

$$h_3(\underline{\lambda}) = \{1+[\lambda_1+\lambda_2(1-\phi_2)]t_{1i}^c + (\lambda_2\phi_2+\lambda_3)w_i^c\}^{\alpha-1}$$

$$h_4(\underline{\lambda}) = \{1+[\lambda_2+\lambda_1(1-\phi_1)]t_{2i}^c + (\lambda_1\phi_1+\lambda_3)w_i^c\}^{\alpha-1}$$

$$S_1(t_{1i},t_{2i}) = \exp\{-[1+(\lambda_1+\lambda_2(1-\phi_2))t_{1i}^c + (\lambda_2\phi_2+\lambda_3)t_{2i}^c]^{\alpha}/\alpha + 1/\alpha$$

$$S_2(t_{1i},t_{2i}) = \exp\{-[1+(\lambda_2+\lambda_1(1-\phi_1))t_{2i}^c + (\lambda_1\phi_1+\lambda_3)t_{1i}^c]^{\alpha}/\alpha + 1/\alpha$$

$$\underline{\lambda} = (\lambda_1,\lambda_2,\lambda_3,c,\alpha,\phi_1,\phi_2)$$

$$\mu = \exp(1/\alpha)$$

n_1, n_2, n_3, n_4, n_5 and n_6 is the random number of observations observed to fail in the range space corresponding to f_{1i}, f_{2i}, f_{3i}, f_{4i}, f_{5i} and $\overline{F}$ respectively. f_{1i} and f_{2i} are the p.d.f. with respect to Lebesgue measure in R^2 and f_{3i}, f_{4i} and f_{5i} are the p.d.f. with respect to Lebesgue measure in R^1 in their respective regions. $(\lambda_1,\lambda_2,\lambda_3)$ are expressed in terms of regression parameters as in Eq. (13).

The likelihood equations can be obtained by taking first order partial derivatives of the loglikelihood and equating to zero. The likelihood equations are not easy to solve. It may not be possible to obtain maximum likelihood estimators (MLEs) by Newton-Raphson procedure. But we came to know from the simulation study in Section 6, and also from the paper by Hanagal(2005a, 2006a) the likelihood equations sometimes do not converge in the Newton-Raphson procedure and the method of maximum likelihood (ML) fails to estimate all the parameters simultaneously. One can obtain estimates of the parameters by two stage MLE method or conditional MLE method. In the first stage, estimate the parameters ϕ_1,ϕ_2,c,α by ML method under the base line model by conditioning $\beta_0=\beta_1=\beta_2=0$ (which implies $\lambda_1=\lambda_2=\lambda_3=1$) and then in the second stage, estimate the parameters β_0,β_1,β_2 by ML method after substituting MLEs of ϕ_1,ϕ_2,c,α obtained from the first stage. These are conditional MLEs. When (i) it is not possible to obtain MLEs in closed form (ii) iterative procedures fail to converge, one can adopt two stage MLE procedure for estimating the parameters. We are mainly interested in estimating and testing the regression parameters and the other parameters (ϕ_1,ϕ_2,c,α) are involved in the base line model which are here nuisance parameters.

The observed information matrix, I_1 with appropriate second order partial derivatives based on the first stage is

$$I_1 = -\begin{bmatrix} \frac{\partial^2 \log L}{\partial \phi_1^2} & \frac{\partial^2 \log L}{\partial \phi_1 \partial \phi_2} & \frac{\partial^2 \log L}{\partial \phi_1 \partial c} & \frac{\partial^2 \log L}{\partial \phi_1 \partial \alpha} \\ \frac{\partial^2 \log L}{\partial \phi_2 \partial \phi_1} & \frac{\partial^2 \log L}{\partial \phi_2^2} & \frac{\partial^2 \log L}{\partial \phi_2 \partial c} & \frac{\partial^2 \log L}{\partial \phi_2 \partial \alpha} \\ \frac{\partial^2 \log L}{\partial c \partial \phi_1} & \frac{\partial^2 \log L}{\partial c \partial \phi_2} & \frac{\partial^2 \log L}{\partial c^2} & \frac{\partial^2 \log L}{\partial c \partial \alpha} \\ \frac{\partial^2 \log L}{\partial \alpha \partial \phi_1} & \frac{\partial^2 \log L}{\partial \alpha \partial \phi_2} & \frac{\partial^2 \log L}{\partial \alpha \partial c} & \frac{\partial^2 \log L}{\partial \alpha^2} \end{bmatrix} \quad (16)$$

The observed Fisher information matrix I_2 which is of order $(p+2q)\times(p+2q)$ with appropriate second order partial derivatives based on the second stage is

$$I_2 = -\begin{bmatrix} \frac{\partial^2 \log L}{\partial \beta_{0i} \partial \beta_{0j}} & \frac{\partial^2 \log L}{\partial \beta_{0i} \partial \beta_{1j}} & \frac{\partial^2 \log L}{\partial \beta_{0i} \partial \beta_{2j}} \\ \frac{\partial^2 \log L}{\partial \beta_{1i} \partial \beta_{0j}} & \frac{\partial^2 \log L}{\partial \beta_{1i} \partial \beta_{1j}} & \frac{\partial^2 \log L}{\partial \beta_{1i} \partial \beta_{2j}} \\ \frac{\partial^2 \log L}{\partial \beta_{2i} \partial \beta_{0j}} & \frac{\partial^2 \log L}{\partial \beta_{2i} \partial \beta_{1j}} & \frac{\partial^2 \log L}{\partial \beta_{2i} \partial \beta_{2j}} \end{bmatrix} \quad (17)$$

The inverse of the above observed information matrix (I_2) is the observed variance-covariance matrix ($\hat{\Sigma}_{11} = I^{-1}$) of the MLEs $\hat{\beta}' = (\hat{\beta}_{01},....,\hat{\beta}_{0p},\hat{\beta}_{11},....,\hat{\beta}_{1q},\hat{\beta}_{21},.....,\hat{\beta}_{2q})'$ of the parameters $\beta' = (\beta_{01},....,\beta_{0p},\beta_{11},....,\beta_{1q},\beta_{21},.....,\beta_{2q})'$.

Thus $\sqrt{n}(\hat{\beta}-\beta)$ has asymptotic multivariate normal distribution with mean vector zero and variance-covariance matrix Σ_{11}, where Σ_{11} is $(p+2q)x(p+2q)$ variance-covariance matrix of $\hat{\beta}' = (\hat{\beta}_{01},....,\hat{\beta}_{0p},\hat{\beta}_{11},....,\hat{\beta}_{1q},\hat{\beta}_{21},.....,\hat{\beta}_{2q})'$.

5. Large Sample Tests

In this Section, we present asymptotic tests for testing no frailty and also test for regression parameters.

5.1 Tests for no Frailty:

The PVF distribution is degenerate when $\alpha = 1$ that is there is no frailty. We give large sample test procedure for testing frailty based on test statistic, $\hat{\alpha}$, the MLE of α . The hypothesis of no frailty is given by

$H_{01} : \alpha = 1$ versus $H_{11} : \alpha < 1$. The corresponding test statistic is

$$\Lambda_1 = \frac{\hat{\alpha} - 1}{\sqrt{\hat{I}_1^{11}}} \tag{18}$$

Where Λ_1 follows asymptotic N(0, 1) under $H_{01} : \alpha = 1$. $\hat{I}_1^{11}$ is the estimated 1-st diagonal element of $\hat{I}_1^{-1}$ under $H_0 \cup H_1$ and Eqn (18) is studentized test statistic [See Hanagal and Kale (1991, 1992)]. This will solve the problem of the test of parameter value on the boundary of the parameter space. We conclude that there is frailty when $\Lambda_1 < Z_{\alpha'}$ where $Z_{\alpha'}$ is the α' quantile of standard normal variate . These test procedures are carried out without taking into account the fixed covariates.

5.2 Test for Regression Coefficients:

The hypotheses about β can be frequently put in the form $H_0 : \beta_{11} = 0$, with β partitioned as $\beta' = (\beta_{11}, \beta_{22})'$ where β_{11} is $kx1$, ($k < p + 2q$). To test H_{02} against the alternative that $\beta_{11} \neq 0$ one can use

$$\Lambda_2 = \hat{\beta}_{11} \hat{\Sigma}_{22}^{-1} \hat{\beta}_{11} \tag{19}$$

where $\hat{\Sigma}_{22}$ is kxk asymptotic observed variance-covariance matrix of $\hat{\beta}_{11}$. Under H_{02}, Λ_2 is asymptotically chi-square with k d.f.. We conclude that the regression parameters are significant when $\Lambda_2 > \chi^2_{k,1-\alpha'}$ where $\chi^2_{k,1-\alpha'}$ is chi-square variate with k d.f. at the level of significance α'.

6. Simulation study

We generate 1000 samples of sizes n=60, 80 and 100 from BVW model and obtain conditional MLEs of the parameters based on first stage. We observed from the simulation study as in Table 1 that MLEs are very close to the known values of the parameters in BVW model. We also obtain the power of the test statistic for testing no frailty at the level of significance α' = 0.01 and 0.05. In Table 2, we obtain regression parameters and also obtain the power of test statistics based on chi-square test at the levels of significance (α') = .01 and .05. It is observed that the estimates of regression parameters are very close to true values in the second stage also. The following are three hypothesis of the tests discussed in Section 5.

(1) $H_0 : \beta_{01} = 0$ Vs $H_1 : \beta_{01} = .5$

(2) $H_0 : \beta_{11} = 0$ Vs $H_1 : \beta_{11} = .5$

(3) $H_0 : \beta_{21} = 0$ Vs $H_1 : \beta_{21} = .5$

Parameters	α	c	ϕ_1	ϕ_2
values	0.5	0.5	1.5	1.5
	n = 60			
Est.	0.5026	0.5169	1.5214	1.5190
s.e.	0.0295	0.0300	0.0339	0.0350
Power, α' =0.01	0.679			
Power, α' =0.05	0.764			
	n = 80			
Est.	0.5018	0.5120	1.5110	1.5120
s.e.	0.0189	0.0209	0.0249	0.0261
Power, α' =0.01	0.728			
Power, α' =0.05	0.823			
	n = 100			
Est.	0.5009	0.5023	1.5059	1.5053
s.e.	0.0168	0.0120	0.0211	0.0199
Power, α' =0.01	0.821			
Power, α' =0.05	0.880			

Table 1: MLEs of the Parameters in PVFFBVW Model And Power of Test for No Frailty.

Parameters	β_{01}	β_{11}	β_{21}
values	0.5	0.5	0.5
	n = 60		
Est.	0.5133	0.5119	0.5134
s.e.	0.0305	0.0285	0.0309
Power, α =.01	0.669	0.705	0.676
Power, α =.05	0.756	0.779	0.768
	n = 80		
Est.	0.5086	0.5062	0.5053
s.e.	0.0238	0.0252	0.0257
Power, α =.01	0.739	0.766	0.719
Power, α =.05	0.824	0.841	0.837
	n = 100		
Est.	0.5028	0.5014	0.5018
s.e.	0.0173	0.0165	0.0207
Power, α =.01	0.812	0.842	0.832
Power, α =.05	0.917	0.940	0.931

Table 2: Conditional MLEs of the Regression Parameters and Power of the Tests in PVFFBVW Regression Model

The first test is for testing common regression parameter corresponding to both components equal to zero, the second test is for testing the regression parameter corresponding first component equal to zero and the third test is for testing the regression parameter corresponding to second component equal to zero. It is observed

from Table 2 that the tests are very powerful as sample size approaches to 100. The distribution of the censoring time is taken as exponential with failure rate .03.

7. Discussions

I have simulated 1000 samples each of size n = 60, 80 and 100. If I take smaller sample sizes for the simulation, there is a problem of convergence of estimates of the parameters in N-R procedure. In the survival data, one should remember that the number of failures should be less than the sample size. In the simulation process, the percentage of censoring changes from sample to sample for fixed sample size. So the effective sample size for the parametric model is the number of failures. In our case, we have a PVFFBVW model with four parameters under the base line model. The sample sizes 20 and 40 are very small for this model with four parameters and censoring scheme. The efficiency and convergence of estimators depend on three things as follows:

(1) sample size,
(2) percentage of censoring,
(3) number of parameters in the model.

When the sample size is very small and it is highly censored and there are more number of parameters in the model, the probability of convergence of the estimates of the parameters is very less. If we take into account the above things, the power of the tests based on these estimates will perform better.

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