Mixture of Gompertz Regression Model with Different Frailty Distributions

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Abstract: **In this article we present a parametric approach to standard mixture model with frailty in the presence of covariates. The problem of analyzing parameters of Gompertz mixture distribution with shared frailty is of interest and the focus of this paper. We propose frailty regression models in Gompertz mixture distributions and assume the distribution of frailty as gamma or inverse Gaussian or positive stable or power variance function distribution. There are some interesting situations like survival times in genetic epidemiology, dental implants of patients and twin births (both monozygotic and dizygotic) where genetic behavior (which is unknown and random) of patients follows a known frailty distribution. These are the situations which motivate to study this particular model. We give estimation procedures and develop test for frailty and the significance of regression parameters. A search of the literature suggests there is currently no work has been done for Gompertz mixture regression model with frailty.**

Keywords: **Frailty, Gamma, Gompertz distribution, Inverse Gaussian, Mixture distribution, Parametric regression, Positive stable, Power variance function, Survival times.**

1. INTRODUCTION

Parametric survival models are regression models in which the distribution of the response is chosen to be consistent with what one would see if the response is time-to failure. In particular, the distribution of the response should have positive support. Examples of such distributions are the exponential, Weibull, log-normal, log-logistic, Gompertz, and the generalized gamma, among others. Here, we consider Gompertz distribution as baseline distribution. The Gompertz distribution is one of the most important growth models. It has many applications in, for example, medical, biological, and actuarial studies. This distribution was first introduced by Gompertz (1825).

Survival models also differ from standard regression models in their ability to account for censoring and truncation. For purposes of interpretability, the distribution of time-to-failure is often times characterized by the hazard function, which is the ratio of the probability density function to one minus the cumulative density function. Hazard functions also provide a convenient means to adjust for regressors, either by assuming that the covariates serve to multiplicatively shift the hazard function (proportional hazards) or by assuming that the covariates serve to accelerate or decelerate the effect of time (accelerated failure time).

A frailty model is a generalization of a survival regression model. In addition to the observed regressors, a frailty model also accounts for the presence of a latent multiplicative effect on the hazard function. This effect, or frailty, is not directly estimated from the data, but instead is assumed to have unit mean and finite variance, which is estimated. In cases where the frailty is greater than one, subjects experience an increased hazard (or risk) of failure and are said to be more frail than their cohorts. In this way, frailty models can provide a useful alternative to a standard survival model when the standard model fails to adequately account for all the variability in the observed failure times.

The notion of frailty provides a convenient way to introduce random effects, association and unobserved heterogeneity into models for survival data. In its simplest form, a frailty model is a random effects model for survival data.

A natural extension of the univariate frailty model would be a multivariate survival model where individuals are allowed to share the same frailty value. The shared frailty model is used with multivariate survival data where the unobserved frailty is shared among groups of individuals, and thus a shared frailty model may be thought of as a random effects model for survival data. In the following, we will restrict our considerations to the bivariate case. Sharing a frailty value also generates dependence between those individuals who share frailties, whereas conditional on the frailty those individuals are independent.

Let a continuous random variable T be the lifetime of an individual and the random variable U be the frailty variable. The conditional hazard function for a given frailty variable $U = u$ at time $t > 0$ is,

$$h(t|u) = uh_0(t)e^{X'\beta} \qquad (1.1)$$

where $h_0(t)$ is a baseline hazard function at time $t > 0$. X is a column vector of covariates and β is a column vector of regression coefficients. The conditional survival function for given frailty at time $t > 0$ is,

$$S(t|u) = e^{-\int_0^t h(y|u)dy} = e^{-uH_0(t)e^{X'\beta}} \quad (1.2)$$

where $H_0(t)$ is cumulative baseline hazard function at time $t > 0$. Integrating over the range of frailty variable U having density $f(u)$, we get marginal survival function as

$$\begin{aligned} S(t) &= \int_0^\infty S(t|u)f(u)du \\ &= \int_0^\infty e^{-uH_0(t)e^{X'\beta}} f(u)du \\ &= E\left[e^{-uH_0(t)e^{X'\beta}}\right] \\ &= L_U(H_0(t)e^{X'\beta}) \end{aligned} \quad (1.3)$$

where $L_U(.)$ is a Laplace transformation of the distribution of U.

Once we have survival function at time $t > 0$ of lifetime random variable of an individual one can obtain probability structure and can base their inference on it.

2. GENERAL SHARED FRAILTY MODEL

The shared frailty model is relevant to event time of related individuals, similar organs and repeated measurements for example, if the timing of failure of paired organs like kidneys, lungs, eyes, ears, dental implants etc. are considered. In this model individuals from a group share common covariates. For monozygotic twins, examples are sex and any other genetically based covariates. Both monozygotic and dizygotic twins share date of birth and common pre birth environment. Also for human lifetime, natural disasters and accidents lead to the death of several persons at the same time or in the infectious diseases, two or more family members might visit an infected person and all of them become infected.

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 (see Oakes, 1982, 1986). However, when adjusting for environment risk factors the analysis of the clustering is more difficult (see Parner, 1998). Until recently, a lack of theory and reliable software had prevented widespread use of this model. In a frailty model, it is absolutely necessary to be able to include explanatory variables. The reason is that the frailty describes the influence of common unknown factors. If some common 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 sex 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. The regression model is derived conditionally on the shared frailty (U).

Suppose n individuals are observed for the study and let a bivariate random variable (T_{i1}, T_{i2}) be the first and second survival times of i^{th} individual ($i = 1,2,3,\ldots n$). Also suppose that there are k observed covariates collected in a vector $X_i = (X_{i1},\ldots..X_{ik})'$ for i^{th} individual where X_{ia} ($a = 1,2,3,\ldots..\ k$) represents the value of a^{th} observed covariate for i^{th} individual. Here, we assume that the first and second survival times for each individual share the same value of the covariates. Let U_i be shared frailty for i^{th} individual. Assuming that the frailties are acting multiplicatively on the baseline hazard function and both the survival times of individuals are conditionally independent for given frailty, the conditional hazard function for i^{th} individual at j^{th} ($i = 1,2$) survival time $t_{ij} > 0$ for given frailty $U_i = u_i$ has the form,

$$h(t_{ij}|u_i, X_i) = u_i h_0(t_{ij}) e^{X_i'\beta} \quad (2.1)$$

where $h_0(t_{ij})$ is baseline hazard at time $t_{ij} > 0$ and β is a column vector of order k of regression coefficients.

The conditional cumulative hazard function for i^{th} individual at j^{th} survival time $t_{ij} > 0$ for given frailty $U_i = u_i$ is,

$$H(t_{ij}|u_i, X_i) = u_i H_0(t_{ij})\eta_i \quad (2.2)$$

where $\eta_i = e^{X_i'\beta}$ and $H_0(t_{ij})$ is cumulative baseline hazard function at time $t_{ij} > 0$.

The conditional survival function for i^{th} individual at j^{th} survival time $t_{ij} > 0$ for given frailty $U_i = u_i$ is,

$$\begin{aligned} S(t_{ij}|u_i, X_i) &= e^{-H(t_{ij}|u_i, X_i)} \\ &= e^{-u_i H_0(t_{ij})\eta_i} \end{aligned} \quad (2.3)$$

Under the assumption of independence, bivariate conditional survival function for given frailty $U_i = u_i$ at time $t_{i1} > 0$ and $t_{i2} > 0$ is,

$$\begin{aligned} S(t_{i1}, t_{i2}|u_i, X_i) &= S(t_{i1}|u_i, X_i)S(t_{i2}|u_i, X_i) \\ &= e^{-u_i(H_{01}(t_{i1})+H_{02}(t_{i2}))\eta_i} \end{aligned} \quad (2.4)$$

Unconditional bivariate survival function at time $t_{i1} > 0$ and $t_{i2} > 0$ can be obtained by integrating over frailty variable U_i having the probability function $f(u_i)$, for i^{th} individual.

$$S(t_{i1}t_{i2}|X_i) = \int_{U_i} S(t_{i1}t_{i2}|u_i)f(u_i)du_i$$

$$= \int_{U_i} e^{-u_i(H_{01}(t_{i1})+H_{02}(t_{i2}))\eta_i} f(u_i)\, du_i$$

$$= L_{U_i}\left[\left(H_{01}(t_{i1}) + H_{02}(t_{i2})\right)\eta_i\right] \quad (2.5)$$

where $L_{U_i}(.)$ is Laplace transform of frailty variable of U_i for i^{th} individual.

Thus, unconditional bivariate survival function for i^{th} individual at time $t_{i1} > 0$ and $t_{i2} > 0$ is,

$$S(t_{i1}t_{i2}|X_i) = L_{U_i}\left[\left(H_{01}(t_{i1}) + H_{02}(t_{i2})\right)\eta_i\right] \quad (2.6)$$

Here onwards we represent $S(t_{i1}t_{i2}|X_i)$ as $S(t_{i1}t_{i2})$.

Once we have unconditional survival function of bivariate random variable ($T_{i1,}$ T_{i2}) we can obtain likelihood function and estimate the parameters of the model.

3. FRAILTY REGRESSION MODEL IN MIXTURE DISTRIBUTION

The mixture distribution in terms of survival function is

$$S(t) = \phi S_1(t) + (1-\phi)S_2(t) = \phi exp[-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)] + (1-\phi)exp[-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)] \quad (3.1)$$

There are two ways of obtaining frailty models. The first one is

$$S_M(t|U) = \phi S_1(t|U) + (1-\phi)S_2(t|U) = \phi exp[-u\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)] + (1-\phi)exp[-u\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)] \quad (3.2)$$

This is called mixture of frailty models or mixture frailty. The second one is

$$S_F(t|U) = exp\left[ulog[\phi exp\{-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\} + (1-\phi)\exp\{-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)\}]\right] \quad (3.3)$$

This is called frailty of the mixture distributions in order to make the distinction between the two types. The same technique can be generalized to mixture of more than two distributions. When we integrate with respect to frailty (U), we get survival function of mixture distribution in terms of frailty parameter. The scale parameters λ_1 and λ_2 in the Gompertz mixtures can be expressed in terms of regression parameters in the following way:

$$\lambda_1 = \exp(\beta' X)$$
$$\lambda_2 = \exp(\beta' X) \quad (3.4)$$

where $\beta = (\beta_0, \beta_1, \beta_2, \ldots\ldots, \beta_p)'$ and X= $(1, X_1, \ldots\ldots X_p)'$. If we want to make a distinction between the two scale parameters, one can express λ_1 and λ_2 as

$$\lambda_1 = \theta_1\exp(\beta' X)$$
$$\lambda_2 = \theta_2\exp(\beta' X) \quad (3.5)$$

After substituting λ_1 and λ_2 in (3.2) and (3.3), we get frailty regression models in Gompertz mixtures.

4. GAMMA FRAILTY MODEL

We consider frailty distribution as gamma distribution because the gamma distribution fits well to failure data from a computational and analytical point of view and it is easy to derive the closed form expression of survival and hazard function. Gamma distributions have been used for many years to generate mixtures in exponential and Poisson models. The gamma distribution (we use notation Gamma (α, κ) for the two parameter distribution with shape parameter α and scale parameter κ) is one of the most commonly used distributions to model variables that are necessarily positive.

Let a continuous random variable U follows gamma distribution with shape parameter α and scale parameter κ then density function of U is,

$$f_U(u) = \frac{\kappa^{\alpha}u^{\alpha-1}\exp(-\kappa u)}{\Gamma(\alpha)}; \quad (4.1)$$

where $\boldsymbol{u} > 0, \alpha > 0, \kappa > 0$

To make the model identifiable, although we consider two parameter gamma distribution, we restrict that expectation of the frailty equal to 1, variance be finite and scale parameter = shape parameter, so that only one parameter needs to be estimated.

Thus the mathematical convenient choice for the distribution of the frailty U is the one parameter ($\alpha = \kappa = \theta^{-1}$) gamma distribution i.e.

$$U \sim \text{Gamma}(\theta^{-1}, \theta^{-1}) \quad (4.2)$$

with the corresponding density function

$$f_U(u) = \frac{u^{\theta^{-1}-1}\exp(-u/\theta)}{\theta^{\frac{1}{\theta}}\Gamma(1/\theta)};\ u > 0, \theta > 0 \quad (4.3)$$

The Laplace transform of gamma distribution and unconditional survivor function are respectively as follows.

$$L(s) = (1+s\theta)^{-1/\theta} \quad (4.4)$$

The unconditional bivariate survival function expressed as the Laplace transform of the frailty distribution, evaluated at the cumulative baseline hazard for i^{th} individual at time $t_{i1} > 0$ *and* $t_{i2} > 0$ is,

$$S_\theta(t_1, t_2) = [1 + \theta\{H_1(t_1) + H_2(t_2)\}]^{-1/\theta} \quad (4.5)$$

where $H_i(t_i)$ is cumulative baseline hazard functions of lifetime random variables T_i.

4.1 Gamma Frailty in Gompertz Mixture

Assuming the distribution of frailty variable, U as gamma and and integrating Eq. (3.2) over U, we get Gompertz mixture model with gamma mixture frailty, given by

$$S_M(t) = \phi[1 + \theta\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)]^{-1/\theta} + (1 - \phi)[1 + \theta\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)]^{-1/\theta} \quad (4.6)$$

The density function corresponding to $S_M(t)$ is

$$f_M(t) = \phi\lambda_1 e^{\gamma_1 t} {S_{M_1}}^{(1+\theta)} + (1 - \phi)\lambda_2 e^{\gamma_2 t} {S_{M_2}}^{(1+\theta)} \quad (4.7)$$

where $S_{M_1}(t) = [1 + \theta\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)]^{-1/\theta}$

and $S_{M_2}(t) = [1 + \theta\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)]^{-1/\theta}$ (4.8)

Assuming the distribution of frailty variable, U as gamma and and integrating Eq. (3.3) over U, we get Gompertz mixture model with gamma frailty, given by

$$S_F(t) = [1 - \theta\log[\phi exp\{-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\} + (1 - \phi)\exp\{-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)\}]]^{-1/\theta} \quad (4.9)$$

The pdf corresponding to above survival function $S_F(t)$ is

$$f_F(t) = \frac{\phi\lambda_1 e^{\gamma_1 t} S_1 + (1-\phi)\lambda_2 e^{\gamma_2 t} S_2}{\phi S_1 + (1-\phi) S_2} S_F^{(1+\theta)} \quad (4.10)$$

where $S_1(t) = \exp[-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)]$

$$S_2(t) = \exp[-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)] \quad (4.11)$$

Here λ_1 and λ_2 are functions of regression parameters.

5. INVERSE GAUSSIAN FRAILTY MODEL

In shared frailty models gamma distribution is the most commonly used frailty distribution because of its mathematical convenience. However, it has drawbacks (see Kheiri et al. (2007)), for example, it may weaken the effect of covariates. As an alternative to the gamma distribution, the inverse Gaussian (inverse normal) distribution was introduced by Hougaard (1984) and has been used, for example, by Manton et al. (1986), Klein et al. (1992), Keiding et al. (1997), Price and Manatunga (2001), Kheiri et al. (2007) and Duchateau and Janssen (2008).

Hougaard (1984) remarked that survival models with gamma and inverse Gaussian frailties behave very differently, noting that the relative frailty distribution among survivors is independent of age for the gamma, but becomes more homogeneous with time for the inverse Gaussian. The inverse Gaussian distribution has many similarities to standard Gaussian distribution. Furthermore, it provides much flexibility in modeling, when early occurrences of failures are dominant in a lifetime distribution and its failure rate is expected to be non-monotonic. In such situations the inverse Gaussian distribution might provide a suitable choice for the lifetime model. Also inverse Gaussian is almost an increasing failure rate distribution when it is slightly skewed and hence is also applicable to describe lifetime distribution which is not dominated by early failures.

Similar to the gamma frailty model, simple closed-form expressions exist for the unconditional survival and hazard functions, this makes the model attractive. The inverse Gaussian distribution has unimodal density and is the member of exponential family. While its shape resembles the other skewed density functions, such as log-normal and gamma. These properties of inverse Gaussian distribution motivate us to use inverse Gaussian as frailty distribution.

Let a continuous random variable U follows inverse Gaussian distribution with parameters μ and α then density function of U is,

$$f(u) = \begin{cases} \left[\frac{\alpha}{2\pi}\right]^{\frac{1}{2}} u^{-\frac{3}{2}} e^{-\frac{\alpha(u-\mu)^2}{2u\mu^2}} ; u > 0, \mu > 0, \alpha > 0 \\ 0 \ ; otherwise \end{cases} \quad (5.1)$$

and Laplace transform is,

$$L_U(s) = exp\left[\frac{\alpha}{\mu} - \left(\frac{\alpha^2}{\mu^2} + 2\alpha s\right)^{1/2}\right] \quad (5.2)$$

with expectation and variance

$$E(U) = \mu, Var(U) = \frac{\mu^3}{\alpha}$$

For identifiability, we assume U has expected value equal to one i.e. μ = 1.

Now the distribution of the frailty U is the one parameter ($\alpha = \theta^{-1}$) inverse Gaussian distribution i.e.

$$U \sim IG(1, \theta^{-1}) \quad (5.3)$$

Under the restriction, density function and Laplace transformation of inverse Gaussian distribution result in the following simplified form,

$$f(z) = \begin{cases} \left[\frac{1}{2\pi\theta}\right]^{\frac{1}{2}} u^{-3/2} e^{-\frac{(u-1)^2}{2u\theta}} ; u > 0, \theta > 0 \\ 0 \ ; otherwise \end{cases} \quad (5.4)$$

and

$$L_U(s) = exp\left[\frac{1-(1+2\theta s)^{1/2}}{\theta}\right] \quad (5.5)$$

with variance of U is $\theta = 1/\alpha$. Note that there is heterogeneity if $\theta > 0$. The unconditional bivariate survival function expressed as the Laplace transform of the frailty distribution, evaluated at the cumulative baseline hazard for i^{th} individual at time $t_{i1} > 0$ *and* $t_{i2} > 0$ is,

$$S_\theta(t_1, t_2) = exp\left[\frac{1-(1+2\theta\{H_1(t_1)+H_2(t_2)\})^{1/2}}{\theta}\right] \quad (5.6)$$

where $H_i(t_i)$ is cumulative baseline hazard functions of lifetime random variables T_i.

5.1 Inverse Gaussian Frailty in Gompertz Mixture

Assuming the distribution of frailty variable, U as inverse Gaussian and integrating Eq. (3.2) over U, we get Gompertz mixture model with inverse Gaussian mixture frailty, given by

$$S_M(t) = \phi exp\left[\theta^{-1}\left\{1 - \left(1 + 2\theta\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\right)^{\frac{1}{2}}\right\}\right] + (1 - \phi)exp\left[\theta^{-1}\left\{1 - (1 + 2\theta\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1))^{1/2}\right\}\right] \quad (5.7)$$

Then pdf corresponding to above survival function $S_M(t)$ is

$$f_M(t) = \frac{\phi\lambda_1 e^{\gamma_1 t} S_{M_1}}{\left[1+2\theta\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\right]^{\frac{1}{2}}} + \frac{(1-\phi)\lambda_2 e^{\gamma_2 t} S_{M_2}}{\left[(1+2\theta\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)\right]^{1/2}} \quad (5.8)$$

where

$$S_{M_1}(t) = exp\left[\theta^{-1}\left\{1 - \left(1 + 2\theta\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\right)^{\frac{1}{2}}\right\}\right]$$

and

$$S_{M_2}(t) == exp\left[\theta^{-1}\left\{1 - (1 + 2\theta\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1))^{\frac{1}{2}}\right\}\right] \quad (5.9)$$

Assuming the distribution of frailty variable, U as inverse Gaussian and integrating Eq. (3.3) over U, we get Gompertz mixture model with inverse Gaussian frailty, given by

$$S_F(t) = exp\left[\theta^{-1}\left[1 - \{1 - 2\theta\log\left[\phi exp\{-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\} + (1 - \phi)\exp\{-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)\}\right]\right]^{1/2}\right] \quad (5.10)$$

The pdf corresponding to above survival function $S_F(t)$ is

$$f_F(t) = S_F[1 - 2\theta\log(\phi S_1 + (1 - \phi)S_2)]^{-1/2} * \frac{\phi\lambda_1 e^{\gamma_1 t} S_1 + (1 - \phi)\lambda_2 e^{\gamma_2 t} S_2}{\phi S_1 + (1 - \phi)S_2} \quad (5.11)$$

where $S_1(t) = \exp\left[-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\right]$

$$S_2(t) = \exp\left[-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)\right] \quad (5.12)$$

Here λ_1 and λ_2 are functions of regression parameters.

6. POSITIVE STABLE FRAILTY MODEL

In practice, the gamma frailty specification may not fit well (Shih, 1998; Glidden, 1999; Fan et al., 2000). The positive stable model (Hougaard, 1986) is a useful alternative, in part because it has the attractive feature that predictive hazard ratio decreases 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 long-term survivors are weakly correlated. The gamma model has predictive hazard ratios which are time invariant and may not be suitable for these patterns of failures (Fine et al., 2003). Although this replacement helps us to avoid problems induced by the identifiability of the univariate gamma-frailty model i.e. the univariate positive stable-frailty model with observed covariates is non-identifiable.

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.

The pdf of positive stable distribution with two parameters α and δ is given by

$$f(u) = \frac{-1}{\pi u}\sum_{n=1}^{\infty}\frac{\Gamma(n\alpha + 1)}{\mathrm{n!}}\left(-u^{-\alpha}\frac{\delta}{\alpha}\right)^n \sin(\alpha n\pi); \quad u > 0, 0 < \alpha < 1 \quad (6.1)$$

with Laplace transform

$$L_U(s) = E[e^{-su}] = exp\left[\frac{-\delta s^\alpha}{\alpha}\right] \quad (6.2)$$

(see Hougaard, 2000, p. 503).

For α=δ, the pdf of positive stable distribution is given by

$$f(u) = \frac{-1}{\pi u}\sum_{n=1}^{\infty}\frac{\Gamma(n\alpha+1)}{\text{n!}}(-u)^{-\alpha n}\sin(\alpha n\pi); \tag{6.3}$$

Thus,

$$f(u) = \frac{-1}{\pi}\sum_{n=1}^{\infty}\frac{\Gamma(n\alpha+1)}{\text{n!}}(-u)^{-(\alpha n+1)}\sin(\alpha n\pi);$$

$$u > 0, 0 < \alpha < 1 \tag{6.4}$$

with Laplace transform

$$L_U(s) = E[e^{-su}] = exp[-s^{\alpha}] \tag{6.5}$$

The unconditional bivariate survival function expressed as the Laplace transform of the frailty distribution, evaluated at the cumulative baseline hazard for i^{th} individual at time $t_{i1} > 0$ *and* $t_{i2} > 0$ is,

$$S_{\alpha}(t_1, t_2) = exp[-\{H_1(t_1) + H_2(t_2)\}^{\alpha}] \tag{6.6}$$

where $H_i(t_i)$ is cumulative baseline hazard functions of lifetime random variables T_i.

6.1 Positive Stable Frailty in Gompertz Mixture

Assuming the distribution of frailty variable, *U* as positive stable and integrating Eq. (3.2) over *U*, we get Gompertz mixture model with positive stable mixture frailty, given by

$$S_M(t) = \phi exp[-\{\lambda_1\gamma_1^{-1}(e^{\gamma_1 t} - 1)\}^{\alpha}] +$$

$$(1-\phi)exp[-\{\lambda_2\gamma_2^{-1}(e^{\gamma_2 t} - 1)\}^{\alpha}] \tag{6.7}$$

Then pdf corresponding to above survival function $S_M(t)$ is

$$f_M(t) = \alpha\big[\phi\lambda_1^{\alpha}\gamma_1^{1-\alpha}e^{\gamma_1 t}(e^{\gamma_1 t}-1)^{\alpha-1}S_{M_1} + (1-\phi)\lambda_2^{\alpha}\gamma_2^{1-\alpha}e^{\gamma_2 t}(e^{\gamma_2 t}-1)^{\alpha-1}S_{M_2}\big] \tag{6.8}$$

where $S_{M_1}(t) = \exp[-\{\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)\}^{\alpha}]$

and $S_{M_2}(t) = \exp[-\{\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)\}^{\alpha}]$ (6.9)

Assuming the distribution of frailty variable, *U* as positive stable and integrating Eq. (3.3) over *U*, we get Gompertz mixture model with positive stable frailty, given by

$$S_F(t) = exp[-[-log\{\phi exp\langle-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)\rangle + (1-\phi)exp\langle-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)\rangle\}]^{\alpha}] \tag{6.10}$$

The pdf corresponding to above survival function is

$$f_F(t) = \frac{\alpha[-\log\langle\phi S_1+(1-\phi)S_2\rangle]^{\alpha-1}[\phi\lambda_1 e^{\gamma_1 t}S_1+(1-\phi)\lambda_2 e^{\gamma_2 t}S_2]}{\phi S_1+(1-\phi)S_2}S_F \tag{6.11}$$

where $S_1(t) = \exp[-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)]$

$$and\ S_2(t) = \exp[-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)] \tag{6.12}$$

7. POWER VARIANCE FRAILTY MODEL

This distribution is a three-parameter family uniting gamma and positive stable distributions. The distribution is denoted as PVF(α,δ,θ).

For α = 0, the gamma distributions are obtained with same parametrization.

For α = 1/2, the inverse Gaussian distributions are obtained.

For α = −1, the non-central gamma distribution of shape parameter zero is obtained.

For α = 1, a degenerate distribution is obtained.

For α = 0, the positive stable distributions are obtained.

The parameter set is $(\alpha \le 1, \delta > 0)$, with $(\theta \ge 0\ for\ \alpha > 0)$, and $(\theta > 0\ for\ \alpha \le 0)$. The distribution is concentrated on the positive numbers for $\alpha \ge 0$, and is positive or zero for $\alpha < 0$. In the case $\alpha > 0$, the pdf of PVF is given by (see Hougaard, 2000, p. 504)

$$f(u) = exp\left\{-\theta u + \delta\frac{\theta^{\alpha}}{\alpha}\right\}\frac{1}{\pi}\sum_{n=1}^{\infty}\frac{\Gamma(n+1)}{\text{n!}}\left(-\frac{1}{u}\right)^{(\alpha n+1)}\sin(\alpha n\pi);\ u > 0 \tag{7.1}$$

If α<0, the Γ-term in the density is not necessarily defined, and therefore we can use the alternative

expression for pdf of PVF as (see Hougaard, 2000, p. 504)

$$f(u) = exp\left\{-\theta u + \delta\frac{\theta^{\alpha}}{\alpha}\right\}\frac{1}{u}\sum_{n=1}^{\infty}\frac{\left(-\left(\delta\frac{u^{\alpha}}{\alpha}\right)\right)^{n}}{\text{n!}\Gamma(-n\alpha)} \tag{7.2}$$

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 $n\alpha$ is a positive integer), the whole term in the sum is zero. For $\alpha < 0$, there is

probability $exp(\delta\frac{\theta^{\alpha}}{\alpha})$ of the random variable being zero. For $\alpha \geq 0$, the distribution is unimodal.

If U_1 and U_2 are independent, and U_i follows PVF(α,δ_i,θ); i =1, 2 the distribution of $U_1 + U_2$ is PVF(α,δ_1 ,δ_2,θ).

So, PVF distribution is infinitely divisible. When $\theta > 0$, all (positive) moments exist, and the mean of Y is $\delta\theta^{\alpha-1}$and its variance is $\delta(1-\alpha)\theta^{\alpha-2}$.

The Laplace transform of PVF distribution is

$$L_U(s) = exp\left[-\frac{\delta\{(\theta+s)^{\alpha}-\theta^{\alpha}\}}{\alpha}\right] \quad (7.3)$$

The unconditional bivariate survival function expressed as the Laplace transform of the frailty distribution, evaluated at the cumulative baseline hazard for i^{th} individual at time $t_{i1} > 0$ *and* $t_{i2} > 0$ is,

$$S_{\alpha,\delta,\theta}(t_1,t_2) = exp\left[\frac{\delta\theta^{\alpha}}{\alpha}\right] exp\left[-\frac{\delta\{(\theta+H_1(t_1)+H_2(t_2))^{\alpha}\}}{\alpha}\right] \quad (7.4)$$

where $H_i(t_i)$ is cumulative baseline hazard functions of lifetime random variables T_i.

7.1 Power Variance Frailty in Gompertz Mixture

Assuming the distribution of frailty variable, U as PVF and integrating Eq. (3.2) over U, we get Gompertz mixture model with PVF mixture frailty, given by

$$S_M(t) = \mu\begin{bmatrix} \phi exp\left[-\frac{\delta\{\theta+\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)\}^{\alpha}}{\alpha}\right] + \\ (1-\phi)exp\left[\frac{-\delta\{\theta+\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)\}^{\alpha}}{\alpha}\right] \end{bmatrix} \quad (7.5)$$

where $\mu = exp\left(\delta\frac{\theta^{\alpha}}{\alpha}\right)$

Then pdf corresponding to above survival function $S_M(t)$ is

$$f_M(t) = \mu\left[\phi\delta\{\theta+\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)\}^{\alpha-1}\lambda_1 e^{\gamma_1 t}S_{M_1} + (1-\phi)\delta\{\theta+\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)\}^{\alpha-1}\lambda_2 e^{\gamma_2 t}S_{M_2}\right] \quad (7.6)$$

where $S_{M_1}(t) = exp\left[-\frac{\delta\{\theta+\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)\}^{\alpha}}{\alpha}\right]$

and $S_{M_2}(t) = exp\left[-\frac{\delta\{\theta+\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)\}^{\alpha}}{\alpha}\right]$ (7.7)

Assuming the distribution of frailty variable, U as PVF and integrating Eq. (3.3) over U, we get Gompertz mixture model with PVF frailty, given by

$$S_F(t) = \mu exp\left[\frac{-\delta}{\alpha}\{\theta - log[\phi exp\{-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)\} + (1-\phi)exp\{-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)\}]\}^{\alpha}\right] \quad (7.8)$$

The pdf corresponding to above survival function is

$$f_F(t) = \frac{\delta\mu[\theta-\log\langle\phi S_1+(1-\phi)S_2\rangle]^{\alpha-1}[\phi\lambda_1 e^{\gamma_1 t}S_1+(1-\phi)\lambda_2 e^{\gamma_2 t}S_2]}{\phi S_1+(1-\phi)S_2}S_F \quad (7.9)$$

where $S_1(t) = \exp[-\lambda_1\gamma_1^{-1}(e^{\gamma_1 t}-1)]$

$$and\ S_2(t) = \exp[-\lambda_2\gamma_2^{-1}(e^{\gamma_2 t}-1)] \quad (7.10)$$

8. ESTIMATION OF THE PARAMETERS

Some of the lifetimes may be censored, because it is not possible to wait until failure of all individuals in the sample. We consider the censoring time (W) being of the right censoring type which is independent of lifetime (T). We first give estimation procedure for the Gompertz mixture frailty model for different frailty distributions, where a similar estimation procedure holds for frailty model of mixtures. The likelihood based on a sample of size n is given by:

$$L = (\prod_{i=1}^{r} f_M(t_i))(\prod_{i=1}^{n-r} S_M(\omega_i)) \quad (8.1)$$

where r is the number of failed individuals and (n-r) the number of censored individuals in the sample of size n.

We can then maximize the marginal log-likelihood with respect to $\underline{\zeta} = (\gamma_1,\gamma_2,\eta_1,\eta_2,\theta,\beta,\phi)'$ where $\beta = (\beta_0,\beta_1,\beta_2,\ldots\ldots,\beta_p)'$. The likelihood equations can be obtained by taking first order partial derivatives of the log-likelihood and equating them with zero. The likelihood equations are not easy to solve. One may obtain maximum likelihood estimates (MLEs) by applying the Newton-Raphson procedure. The second order partial derivatives of the log-likelihood can also be obtained. The observed information matrix, I is of order (p + 7) x (p + 7) with appropriate second order partial derivatives as follows:

$$I = \begin{bmatrix} \frac{\partial^2 logL}{\partial\gamma_1^2} & \frac{\partial^2 logL}{\partial\gamma_1\partial\gamma_2} & \frac{\partial^2 logL}{\partial\gamma_1\partial\eta_1} & \frac{\partial^2 logL}{\partial\gamma_1\partial\eta_2} & \frac{\partial^2 logL}{\partial\gamma_1\partial\theta} & \frac{\partial^2 logL}{\partial\gamma_1\partial\beta_0} & & \frac{\partial^2 logL}{\partial\gamma_1\partial\beta_p} \\ \frac{\partial^2 logL}{\partial\gamma_1\partial\gamma_2} & \frac{\partial^2 logL}{\partial\gamma_2^2} & \frac{\partial^2 logL}{\partial\gamma_2\partial\eta_1} & \frac{\partial^2 logL}{\partial\gamma_2\partial\eta_2} & \frac{\partial^2 logL}{\partial\gamma_2\partial\theta} & \frac{\partial^2 logL}{\partial\gamma_2\partial\beta_0} & \cdots\cdots & \frac{\partial^2 logL}{\partial\gamma_2\partial\beta_p} \\ \frac{\partial^2 logL}{\partial\gamma_1\partial\eta_1} & \frac{\partial^2 logL}{\partial\gamma_2\partial\eta_1} & \frac{\partial^2 logL}{\partial\eta_1^2} & \frac{\partial^2 logL}{\partial\eta_1\partial\eta_2} & \frac{\partial^2 logL}{\partial\eta_1\partial\theta} & \frac{\partial^2 logL}{\partial\eta_1\partial\beta_0} & & \frac{\partial^2 logL}{\partial\eta_1\partial\beta_p} \\ \frac{\partial^2 logL}{\partial\gamma_1\partial\eta_2} & \frac{\partial^2 logL}{\partial\gamma_2\partial\eta_2} & \frac{\partial^2 logL}{\partial\eta_1\partial\eta_2} & \frac{\partial^2 logL}{\partial\eta_2^2} & \frac{\partial^2 logL}{\partial\eta_2\partial\theta} & \frac{\partial^2 logL}{\partial\eta_2\partial\beta_0} & & \frac{\partial^2 logL}{\partial\eta_2\partial\beta_p} \\ \frac{\partial^2 logL}{\partial\gamma_1\partial\theta} & \frac{\partial^2 logL}{\partial\gamma_2\partial\theta} & \frac{\partial^2 logL}{\partial\eta_1\partial\theta} & \frac{\partial^2 logL}{\partial\eta_2\partial\theta} & \frac{\partial^2 logL}{\partial\theta^2} & \frac{\partial^2 logL}{\partial\theta\partial\beta_0} & \cdots\cdots & \frac{\partial^2 logL}{\partial\theta\partial\beta_p} \\ \frac{\partial^2 logL}{\partial\gamma_1\partial\beta_0} & \frac{\partial^2 logL}{\partial\gamma_2\partial\beta_0} & \frac{\partial^2 logL}{\partial\eta_1\partial\beta_0} & \frac{\partial^2 logL}{\partial\eta_2\partial\beta_0} & \frac{\partial^2 logL}{\partial\theta\partial\beta_0} & \frac{\partial^2 logL}{\partial\beta_0^2} & & \frac{\partial^2 logL}{\partial\beta_0\partial\beta_p} \\ & & \vdots & \vdots & \vdots & \ldots\ldots & \vdots & \\ \frac{\partial^2 logL}{\partial\gamma_1\partial\beta_p} & \frac{\partial^2 logL}{\partial\gamma_2\partial\beta_p} & \frac{\partial^2 logL}{\partial\eta_1\partial\beta_p} & \frac{\partial^2 logL}{\partial\eta_2\partial\beta_p} & \frac{\partial^2 logL}{\partial\theta\partial\beta_p} & \frac{\partial^2 logL}{\partial\beta_0\partial\beta_p} & \cdots\cdots & \frac{\partial^2 logL}{\partial\beta_p^2} \end{bmatrix} \quad (8.2)$$

The inverse of the observed Fisher information matrix (8.2) is the observed variance-covariance matrix (Σ=I^{-1}) of the MLE

$\hat{\underline{\zeta}} = (\hat{\gamma}_1, \hat{\gamma}_2, \hat{\eta}_1, \hat{\eta}_{2,} \hat{\theta}, \hat{\beta}, \hat{\phi})'$ of the parameter $\underline{\zeta} = (\gamma_1, \gamma_2, \eta_1, \eta_2, \theta, \beta, \phi)'$ where $\beta = (\beta_0, \beta_1, \beta_2, \ldots\ldots, \beta_p)'$.

Thus, $\sqrt{n}(\hat{\beta} - \beta)$ has an asymptotic multivariate normal distribution with mean vector zero and variance-covariance matrix Σ_{11}, where Σ_{11} is (p+1) x (p+1) variance-covariance matrix of $\beta = (\beta_0, \beta_1, \beta_2, \ldots\ldots, \beta_p)'$.

9. LARGE SAMPLE TESTS

We present test procedure based on large sample which is asymptotically normally distributed.

9.1 Test for Regression Coefficients

The hypotheses about β can be frequently put in the form $H_0 : \beta_{11} = \beta_{11}^0$ with β partitioned as $\beta = (\beta_{11}, \beta_{22})'$ where β_{11} is of dimension k x 1, (k < p + 1) and β_{11}^0 consists of fixed and known values of the corresponding regression parameters of β_{11}. To test H_0 against the alternative that is $H_1 : \beta_{11} \neq \beta_{11}^0$ one can use

$$\Lambda_1 = (\hat{\beta}_{11} - \beta_{11}^0)' \hat{\Sigma}_{22}^{-1} (\hat{\beta}_{11} - \beta_{11}^0) \qquad (9.1)$$

where $\hat{\Sigma}_{22}$ is k x k asymptotic observed variance-covariance matrix of $\hat{\beta}_{11}$. Under H_0, Λ_1 is asymptotically chi-square with *k* d.f.

If $\Lambda_1 > \chi^2_{k,1-\alpha}$, the corresponding regression coefficients are significant at the level of significance α, where $\chi^2_{k,1-\alpha}$ is the chi-square variate with *k* d.f. at level of significance α.

When $\beta_{11}^0 = 0$, it will lead to the test for regression coefficients equal to zero.

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