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ASSOCIATION MEASURES IN THE BIVARIATE CORRELATED FRAILTY MODEL

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Abstract:

- This paper deals with a general bivariate correlated frailty model. This includes the multiplicative as well as the additive frailty effect. The association parameter is studied for the shared as well as the general correlated model. The results for the gamma, the inverse Gaussian and the stable frailty models are derived.

Key-Words:

- *survival function; failure rate; Clayton's association measure; gamma distribution; inverse Gaussian distribution; positive stable distribution.*

AMS Subject Classification:

- 62H20, 62N99.

1. INTRODUCTION

Cox (1972) proportional hazard model (PHM) is commonly used to model survival data as a function of the covariates. Sometimes the observed source of variation in the explanatory variables fail to account for the true differences in risk. That is,in addition, there are other important but omitted unobserved variables present. These unobserved random effects are modeled by introducing a frailty variable Z. More precisely we assume that (T, Z) is a pair of non-negative random variables such that for each z in the support of the distribution of Z, the conditional distribution of T given $Z = z$ is absolutely continuous with hazard rate $\lambda(t|z)$ given by

$$\lambda(t|z) = z\lambda_0(t), \quad t > 0, \tag{1.1}$$

where $\lambda_0(t)$ is the base line hazard rate independent of z. It will be helpful to think of T as the age at death and $\lambda(t|z)$ as the hazard rate at age t for a person with frailty Z, see Vaupel *et al.* (1979).

The model (1.1) states that the hazard rate of an individual is the product of the specific quantity z and the base line hazard $\lambda_0(t)$ describing the age.

In addition to introducing the unobserved random effects in a multiplicative manner, various other forms have been studied in the literature in the context of random effect models. More recently, there has been an interest in studying additive frailty models. Tomazalla *et al.* (2006) have analyzed recurrent event data considering a homogeneous Poisson process with additive frailty intensity. Silva and Amaral Turkman (2004) have considered Bayesian analysis of an additive survival model with frailty. Yin and Ibrahim (2005) presented a class of Bayesian shared Gamma frailty models with multivariate failure time data.

In this paper, we shall study a very general frailty model where the conditional failure rate $\lambda(t|z) = \lambda(t, z)$, is an appropriate general function of t and z. Obviously, the multiplicative (proportional hazards) as well as the additive model can be studied under this umbrella.

A basic problem in a frailty model is the modeling of the probability distribution of Z. The choice of the frailty distribution strongly affects the estimate of the base line hazard as well as that of the conditional probabilities, see Hougaard (1984, 19991, 1995, 2000), Heckman and Singer (1984) and Agresti *et al.* (2004). Agresti *et al.* (2004) have demonstrated that a considerable loss of efficiency can result from assuming a parametric distribution for a random effect that is substantially different from that of the true population.These authors observed that the misspecification of random effect has the potential for a serious drop of efficiency in the prediction of random effects and the estimation of other parameters. In the absence of a theoretical basis for selecting the distribution of

frailty, the choice of the distribution of Z is often made on the basis of mathematical tractability and the nice properties of the resulting distributions. For this reason, frailty distributions having a tractable Laplace transform are natural choices. The gamma distribution, the inverse Gaussian distribution and the family of stable distributions are popular choices for modeling the distribution of Z. Some researchers propose nonparametric modeling of the frailty distribution, see Heckman and Singer (1984) and Anderson *et al.* (1992).

Hougaard (2000) provides some guidelines for choosing an appropriate frailty distribution.The comparison is made in three directions:

(**1**) Theoretical comparison describing the nice properties of the frailty distribution. For example, the gamma distribution and the inverse Gaussian distribution are easibly tractable.

(**2**) Comparison of fit: The fit and the flexibility of the models are important factors in comparison. The stable frailty distribution implies high early dependence, whereas the gamma frailty model describes high late dependence.

(**3**) Various measures of dependence: The measures of dependence depend on the frailty distribution. The expressions for various dependence measures depend on the frailty distribution. For some frailty distributions, it is simple to evaluate these measures.

For more discussion, see Hougaard (2000).

Since different level distributions of frailty give rise to different population level distribution for analyzing survival data, it is appropriate to investigate how the comparative effect of two frailties translates into the comparative effect on the survival distribution. The stochastic orderings on various characteristics of the model can be studied by using the general results contained in Gupta and Gupta (2009, 2010). Also see Gupta and Kirmani (2006).

The aim of this paper is to study a general bivariate correlated frailty model and the association measure due to Clayton (1978). The bivariate correlated model and its derivatives have been studied in the literature in the context of twin's survival, see for example Yashin and Iachine (1995a, 1995b) and Yashin *et al.* (1995). The idea of using the shared relative risk in bivariate survival models was first discussed by Clayton (1978) who suggested an approach to the analysis of association between two survival times based on the limiting properties of certain contingency tables. Later this approach was followed by Oakes (1989) in the proportional hazards shared frailty model. He introduced the notion of the local association measure which characterizes the limiting behaviour of the odds ratio statistics for the dependent life spans. The properties of this measure were studied by Anderson *et al.* (1992).

We obtain a general expression for the population level survival function. The proportional hazards as well as the additive hazards case is studied. General expressions for the Clayton's(1978) association measure are obtained.The results are illustrated for the gamma frailty model and the inverse Gaussian frailty model.

The organization of this paper is as follows: Section 2 contains the general bivariate correlated frailty model and an expression for the population level survival function. Explicit expressions are obtained for the bivariate gamma correlated model. The Clayton's association measure is studied in Section 3. Results are derived for the multiplicative as well as the additive frailty models. Several examples are provided. It also contains the results for the shared frailty model. Section 4 contains some practical examples from the literature. Finally, some conclusions and comments are provided in Section 5.

2. BIVARIATE CORRELATED FRAILTY MODEL

Let T_i and Z_i, $i = 1, 2$ be the life spans and frailty variables for the two related individuals with dependent individual hazards $\mu_i(x_i, Z_i)$, $i = 1, 2$. The functional form of $\mu_i(x_i, Z_i)$ is assumed to be the same for both individuals. We assume that the life spans T_1 and T_2 are conditionally independent given Z_1 and Z_2. Also the joint, conditional and marginal distributions are absolutely continuous.

Then the joint conditional survival function of T_1 and T_2 is given by

$$S(x_1, x_2|z_1, z_2) = \exp\big\{-\big(H_1(x_1, z_1) + H_2(x_2, z_2)\big)\big\},$$

where

$$H_i(x_i, z_i) = \int_0^{x_i} \mu_i(u_i, z_i) du_i, \quad i = 1, 2.$$

The unconditional survival function is given by

$$S(x_1, x_2) = \iint \exp\big\{-\big(H_1(x_1, z_1) + H_2(x_2, z_2)\big)\big\}\, g(z_1, z_2)\, dz_1\, dz_2,$$

where $g(z_1, z_2)$ is the joint probability density function (pdf) of (Z_1, Z_2).

This gives

$$\begin{aligned} S_i(x_1, x_2) &= \frac{\partial}{\partial x_i} S(x_1, x_2) \\ &= -E_{Z_1,Z_2}\big[\mu_i(x_i, Z_i) \exp\big\{-\big(H_1(x_1, Z_1) + H_2(x_2, Z_2)\big)\big\}\big], \quad i = 1, 2, \end{aligned}$$

and

$$\begin{aligned} f(x_1, x_2) &= \frac{\partial^2}{\partial x_1 \partial x_2} S(x_1, x_2) \\ &= E_{Z_1,Z_2}\big[\mu_1(x_1, Z_1)\, \mu_2(x_2, Z_2) \exp\big\{-\big(H_1(x_1, Z_1) + H_2(x_2, Z_2)\big)\big\}\big]. \end{aligned}$$

Thus

$$\begin{aligned}\frac{f(x_1,x_2)}{S(x_1,x_2)} &= \frac{1}{S(x_1,x_2)}\iint \mu_1(x_1,z_1)\,\mu_2(x_2,z_2)\\ &\quad\times \exp\big\{-\big(H_1(x_1,z_1)+H_2(x_2,z_2)\big)\big\}\,g(z_1,z_2)\,dz_1\,dz_2\\ &= \iint \mu_1(x_1,z_1)\,\mu_2(x_2,z_2)\,g\big(z_1,z_2\,|\,T_1>x_1,T_2>x_2\big)\,dz_1\,dz_2 \qquad (2.1)\\ &= \rho_{\mu_1,\mu_2}(x_1,x_2)\,\sigma_{\mu_1}(x_1,x_2)\,\sigma_{\mu_2}(x_1,x_2)+\overline{\mu_1}(x_1,x_2)\,\overline{\mu_2}(x_1,x_2),\end{aligned}$$

where

$$\overline{\mu_i}(x_1,x_2) = E\big[\mu_i(x_i,Z_i)\,|\,T_1>x_1,T_2>x_2\big],\quad i=1,2,$$

$\rho(.,.)$ is the conditional correlation coefficient and $\sigma_{\mu_{ii}}|\,T_1>x_1,\,T_2>x_2$, $i=1,2$ is the conditional standard deviation.

Also

$$g\big(z_1,z_2\,|\,T_1>x_1,T_2>x_2\big) = \frac{\exp\big\{-\big(H_1(x_1,z_1)+H_2(x_2,z_2)\big)\big\}}{S(x_1,x_2)}\;g(z_1,z_2)$$

is the conditional pdf of Z_1,Z_2 given $T_1>x_1,T_2>x_2$.

The hazard components are given by

$$\begin{aligned}h_i(x_1,x_2) &= -\frac{\partial}{\partial x_i}\ln S(x_1,x_2)\\ &= -\iint \mu_i(x_i,z_i)\,g\big(z_1,z_2\,|\,T_1>x_1,T_2>x_2\big)\,dz_1\,dz_2\\ &= -E\big[\mu_i(x_i,Z_i)\,|\,T_1>x_1,T_2>x_2\big] = -\overline{\mu_i}(x_1,x_2),\quad i=1,2.\end{aligned}$$

Note that the expectations are taken with respect to the conditional distribution of the joint distribution of the frailty given $T_1>x_1,T_2>x_2$.

Define

$$\begin{aligned}\phi(x_1,x_2) &= \frac{\partial^2}{\partial x_1\partial x_2}\ln S(x_1,x_2)\\ &= \frac{f(x_1,x_2)}{S(x_1,x_2)} - h_1(x_1,x_2)\,h_2(x_1,x_2)\\ &= E\big[\mu_1(x_1,Z_1)\,\mu_2(x_2,Z_2)\,|\,T_1>x_1,T_2>x_2\big]\\ &\quad - E\big[\mu_1(x_1,Z_1)\,|\,T_1>x_1,T_2>x_2)\big]\big[E\big[\mu_2(x_2,Z_2)\,|\,T_1>x_1,T_2>x_2\big]\big]\\ &= Cov\big[\mu_1(x_1,Z_1),\mu_2(x_2,Z_2)\,|\,T_1>x_1,T_2>x_2\big]\\ &= \rho\big[\mu_1(x_1,Z_1),\mu(x_2,Z_2)\,|\,T_1>x_1,T_2>x_2\big]\\ &\quad\times\big[\sigma_{\mu_1(x_1,Z_1)}\,|\,T_1>x_1,T_2>x_2\big]\big[\sigma_{\mu_2(x_2,Z_2)}\,|\,T_1>x_1,T_2>x_2\big].\end{aligned}$$

Let

$$A(x_1,x_2) = \int_0^{x_2}\int_0^{x_1}\phi(u_1,u_2)\,du_1\,du_2.$$

Thus

$$\ln S(x_1, x_2) \;=\; \int_0^{x_2}\!\int_0^{x_1} \phi(u_1, u_2)\, du_1\, du_2 \;-\; \int_0^{x_1} \psi_1(u)\, du \;-\; \int_0^{x_2} \psi_2(u)\, du,$$

for some appropriate functions $\psi_1(.)$ and $\psi_2(.)$.

Finally,

$$\begin{aligned} S(x_1, x_2) \;&=\; \exp\Big\{ \int_0^{x_2}\!\int_0^{x_1} \phi(u_1, u_2)\, du_1\, du_2 \;-\; \int_0^{x_1} \psi_1(u)\, du \;-\; \int_0^{x_2} \psi_2(u)\, du \Big\} \\ &=\; S_1(x_1)\, S_2(x_2)\, \exp\{A(x_1, x_2)\}, \end{aligned}$$

where

$$S_i(x_i) \;=\; \exp\Big\{ -\int_0^{x_i} \psi_i(u)\, du \Big\}, \quad i = 1, 2.$$

We now present a bivariate gamma correlated frailty model.

2.1. Bivariate Gamma Correlated Frailty Model

Suppose Y_0, Y_1 and Y_2 are independent random variables and $Z_1 = Y_0 + Y_1$, $Z_2 = Y_0 + Y_2$. Then Z_1 and Z_2 are correlated since they contain the common part Y_0. This constitutes one of the ways of constructing bivariate distributions, see Marshall and Olkin (1988). Let

$$S(x_1, x_2 | z_1, z_2) \;=\; \exp\big\{ -\big(H_1(x_1) z_1 + H_2(x_2) z_2 \big) \big\}, \tag{2.2}$$

i.e., given Z_1 and Z_2, the life spans T_1 and T_2 are independent. This is the proportional hazards bivariate correlated model. The unconditional distribution is given by

$$\begin{aligned} S(x_1, x_2) \;=\; &\iiint \exp\big\{ -\big((y_0 + y_1)\, H_1(x_1) + (y_0 + y_2)\, H_2(x_2) \big) \big\} \\ &\times\, g_0(y_0)\, g_1(y_1)\, g_2(y_2)\, dy_0\, dy_1\, dy_2, \end{aligned} \tag{2.3}$$

where $g_0(.)$, $g_1(.)$ and $g_2(.)$ are the *pdf's* of Y_0, Y_1 and Y_2. Denoting by $L_{Y_0}(.)$, $L_{Y_1}(.)$ and $L_{Y_2}(.)$ the Laplace transform of Y_0, Y_1 and Y_2, it can be seen that

$$S(x_1, x_2) \;=\; L_{Y_0}\big[H_1(x_1) + H_2(x_2) \big]\, L_{Y_1}[H_1(x_1)]\, L_{Y_2}[H_2(x_2)]. \tag{2.4}$$

We shall now derive the correlated frailty model of Yashin *et al.* (1995); see also Korsgaard and Anderson (1998).

Let Y_0, Y_1, Y_2 have independent gamma distribution with parameters (α_0, β_0), (α_1, β_1) and (α_2, β_2) having *pdf's*

$$g_i(y_i) = \frac{1}{\beta_i^{\alpha_i} \Gamma(\alpha_i)}\; e^{-y_i/\beta_i}\, y_i^{\alpha_i - 1}, \qquad y_i > 0, \quad i = 0, 1, 2. \tag{2.5}$$

To ensure that Z_1 and Z_2 are gamma distributed, we make the assumption (on the scale parameters) that $\beta_0 = \beta_1 = \beta_2 = \beta$ (say). Note that this assumption is not a restriction for population of unrelated individuals since gamma distributed variables $Z_i, i = 1, 2$ can be decomposed this way. Thus

$$E(Z_1) = (\alpha_0 + \alpha_1)\beta, \qquad E(Z_2) = (\alpha_0 + \alpha_2)\beta,$$
$$Var(Z_1) = (\alpha_0 + \alpha_1)\beta^2, \qquad Var(Z_2) = (\alpha_0 + \alpha_2)\beta^2.$$

We now assume that Z_1 and Z_2 have the same gamma distribution. To do this, we assume that $\alpha_1 = \alpha_2 = \alpha$ (say). This condition is relevant in twin studies when there is no reason to assume different distributions of frailty for the twins.

The correlation coefficient between Z_1 and Z_2 is

$$\rho_Z = \frac{Var(Y_0)}{\sqrt{Var(Z_1)Var(Z_2)}} = \frac{\alpha_0}{\alpha_0 + \alpha}.$$

This implies that $\alpha_0 = \alpha\rho_Z/(1 - \rho_Z)$.

We now use the standard assumption that the mean frailty of the individuals is 1. This condition is typical for proportional hazards models which do not contain a frailty term, but covariates. This will imply that $Var(Z_1) = Var(Z_2) = \beta = \sigma_Z^2$ (say) and hence $\alpha_0 = \rho_Z/\sigma_Z^2$. Note that the formulated assumptions significantly restrict the class of frailty models which we propose here. However, this class is still wide enough to include individual frailty models and shared frailty models with gamma distributed random effects as particular cases.

Noting that $L_{Y_0}(t) = (1 + \beta t)^{-\alpha_0}$, $L_{Y_1}(t) = L_{Y_2}(t) = (1 + \beta t)^{-\alpha}$, it can be verified that

$$\begin{aligned} S(x_1, x_2) \;=\; & \big[1 + \sigma_Z^2\big(H_1(x_1) + H_2(x_2)\big)\big]^{-\rho_Z/\sigma_Z^2} \\ & \times \big[\big(1 + \sigma_Z^2(H_1(x_1))\big)\big(1 + \sigma_z^2(H_2(x_2))\big)\big]^{-(1-\rho_Z)/\sigma_Z^2}. \end{aligned} \tag{2.6}$$

Shared Frailty Model

In the shared frailty model, the two shared components are identical and, therefore, $\rho_Z = 1$. The survival function is given by

$$S(x_1, x_2) \;=\; \big[1 + \sigma_Z^2\big(H_1(x_1) + H_2(x_2)\big)\big]^{-(1/\sigma_Z^2)}. \tag{2.7}$$

Remark 2.1. Recently Hanagal and Dabade (2015) have considered four shared frailty models. These models have been illustrated with real life bivariate survival data related to kidney infection.

3. CLAYTON'S ASSOCIATION MEASURE

In the context of bivariate survival models induced by frailties, Oakes (1989) studied the following association measure

$$\theta(x_1, x_2) = \frac{SS_{12}}{S_1 S_2},$$

where $S = S(x_1, x_2)$ is the survival function, $S_{12} = \partial^2 S(x_1, x_2)/\partial x_1 \partial x_2$, $S_1 = \frac{\partial}{\partial x_1} S(x_1, x_2)$ and $S_2 = \frac{\partial}{\partial x_2} S(x_1, x_2)$; see also Clayton (1978).

Clayton (1978) presented the above association measure, deriving from the Cox model, in a study of the association between the life spans of fathers and their sons.

It can be easily seen that

$$\theta(x_1, x_2) = \frac{r(x_1 | T_2 = x_2)}{h_1(x_1, x_2)}.$$

The numerator is the hazard rate for sons at time x_1 given that their fathers died at x_2. The denominator is the hazard rate for sons at time x_1 given that their fathers live past x_2. Also

$$r(x_1 | T_2 = x_2) = -S_{12}/S_2 \qquad \text{and} \qquad h_1(x_1, x_2) = -S_1/S.$$

For the bivariate frailty model considered before, we have from (2.1)

$$\frac{f(x_1, x_2)}{S(x_1, x_2)} = \rho_{\mu_1,\mu_2}(x_1,x_2)\, \sigma_{\mu_1}(x_1,x_2)\, \sigma_{\mu_2}(x_1, x_2) + \overline{\mu_1}(x_1, x_2)\, \overline{\mu_2}(x_1, x_2),$$

and

$$\frac{S_1(x_1, x_2)}{S(x_1, x_2)} \frac{S_2(x_1, x_2)}{S(x_1, x_2)} = \overline{\mu_1}(x_1, x_2)\, \overline{\mu_2}(x_1, x_2).$$

Thus

$$\begin{aligned} \theta(x_1, x_2) &= 1 + \frac{\sigma_{\mu_1}(x_1,x_2)\, \sigma_{\mu_2}(x_1, x_2)}{\overline{\mu_1}(x_1, x_2)\, \overline{\mu_2}(x_1, x_2)}\, \rho_{\mu_1,\mu_2}(x_1,x_2) \\ &= 1 + [CV_{\mu_1}(x_1, x_2)]\, [CV_{\mu_2}(x_1, x_2)]\, \rho_{\mu_1,\mu_2}(x_1,x_2), \end{aligned} \tag{3.1}$$

where $CV_{\mu_i}(x_1, x_2)$ is the coefficient of variation, $i = 1, 2$.

Note that all expectations are taken with respect to the conditional distribution of (Z_1, Z_2) given $T_1 > x_1, T_2 > x_2$.

It is, therefore, clear that

$$\begin{aligned} \theta(x_1, x_2) > 1, &\quad \text{if } \rho_{\mu_1,\mu_2}(x_1,x_2) > 0 \\ < 1, &\quad \text{if } \rho_{\mu_1,\mu_2}(x_1,x_2) < 0 \\ = 1, &\quad \text{if } \rho_{\mu_1,\mu_2}(x_1,x_2) = 0. \end{aligned}$$

It is also clear that

$$\begin{aligned} \theta(x_1, x_2) > 1, &\quad \text{if } \phi(x_1,x_2) > 0 \\ < 1, &\quad \text{if } \phi(x_1, x_2) < 0 \\ = 1, &\quad \text{if } \phi(x_1,x_2) = 0. \end{aligned}$$

3.1. Proportional Hazards Bivariate Correlated Frailty Model

In this case

$$\begin{aligned} \mu_1(x_1, Z_1) &= Z_1 \mu_1(x_1), \\ \mu_2(x_2, Z_2) &= Z_2 \mu_2(x_2). \end{aligned}$$

It can be verified that

$$\begin{aligned} \rho_{\mu_1,\mu_2}(x_1,x_2) &= \frac{Cov\big(\mu_1(x_1, Z_1), \mu_2(x_2, Z_2)\big)}{\sqrt{Var(\mu_1(x_1, Z_1))\, Var(\mu_2(x_2, Z_2))}} \\ &= \frac{\mu_1(x_1)\, \mu_2(x_2)\, \rho_{Z_1,Z_2}(x_1, x_2)\, \sigma_{Z_1}(x_1, x_2)\, \sigma_{Z_2}(x_1, x_2)}{\mu_1(x_1)\, \mu_2(x_2)\, \sigma_{Z_1}(x_1, x_2)\, \sigma_{Z_2}(x_1, x_2)} \\ &= \rho_{Z_1,Z_2}(x_1, x_2). \end{aligned}$$

Also

$$CV_{\mu_i}(x_1, x_2) = CV_{Z_i}(x_1, x_2), \quad i = 1, 2.$$

Hence

$$\theta(x_1, x_2) = 1 + \rho_{Z_1,Z_2}(x_1, x_2)\, CV_{Z_1}(x_1, x_2)\, CV_{Z_2}(x_1, x_2). \tag{3.2}$$

Shared Bivariate Frailty Model

In this case $Z_1 = Z_2 = Z$ (say) and $\rho_{Z_1,Z_2}(x_1, x_2) = 1$, giving

$$\theta(x_1, x_2) = 1 + CV_Z^2(x_1, x_2).$$

We now try to give an explicit expression for $\theta(x_1, x_2)$.

The conditional survival function of T_1 and T_2 given $Z = z$ is

$$S\big(x_1, x_2|Z=z\big) \;=\; \exp\big\{-z\big(H_1(x_1) + H_2(x_2)\big)\big\}.$$

The unconditional survival function is given by

$$\begin{aligned} S(x_1, x_2) \;&=\; \int_0^\infty \exp\big\{-z\big(H_1(x_1) + H_2(x_2)\big)\big\}\, g(z)\, dz \\ &=\; L_Z\big(H_1(x_1) + H_2(x_2)\big), \end{aligned}$$

where $L_Z(.)$ is the Laplace transform of Z.

Thus, the conditional density of Z given $T_1 > x_1, T_2 > x_2$ is given by

$$g\big(z|\, T_1 > x_1, T_2 > x_2\big) \;=\; \frac{\exp\big\{-z\big(H_1(x_1) + H_2(x_2)\big)\big\}}{L_Z\big(H_1(x_1) + H_2(x_2)\big)}\; g(z).$$

It can be verified that

$$E\big[Z\,|\,T_1 > x_1, T_2 > x_2\big] = \frac{-L_Z^{'}\big(H_1(x_1) + H_2(x_2)\big)}{L_Z\big(H_1(x_1) + H_2(x_2)\big)}$$

and

$$E\big[Z^2\,|\,T_1 > x_1, T_2 > x_2\big] = \frac{L_Z^{''}\big(H_1(x_1) + H_2(x_2)\big)}{L_Z\big(H_1(x_1) + H_2(x_2)\big)}.$$

Hence

$$Var\big[Z\,|\,T_1 > x_1, T_2 > x_2\big] = \left[\frac{L_Z^{''}\big(H_1(x_1) + H_2(x_2)\big)}{L_Z\big(H_1(x_1) + H_2(x_2)\big)}\right] - \left[\frac{L_Z^{'}\big(H_1(x_1) + H_2(x_2)\big)}{L_Z\big(H_1(x_1) + H_2(x_2)\big)}\right]^2.$$

Using the above expressions, one can obtain $\theta(x_1, x_2)$.

We now consider some examples

Example 3.1. Z has a gamma distribution with probability density function (*pdf*)

$$g(z) = \frac{1}{\beta^\alpha \Gamma(\alpha)}\; e^{-z/\beta}\, z^{\alpha-1}, \qquad z > 0, \quad \alpha > 0, \quad \beta > 0. \tag{3.3}$$

The Laplace transform of Z is given by

$$L_Z(t) \;=\; \frac{1}{(1+\beta t)^\alpha}.$$

This gives

$$\frac{L_Z^{'}(t)}{L_Z(t)} = \frac{-\alpha\beta}{1+\beta t}$$

and

$$\frac{L_Z^{''}(t)}{L_Z(t)} = \frac{\alpha\beta^2(\alpha+1)}{(1+\beta t)^2}.$$

It can be easily verified that in this case

$$\theta(x_1, x_2) = 1 + \frac{1}{\alpha}. \tag{3.4}$$

Note that, in this case, $\theta(x_1, x_2)$ is independent of (x_1, x_2); see Hanagal (2011, page 83) Wienke (2010) and Duchateau and Janssen (2008).

Example 3.2. Z has an inverse Gaussian distribution with pdf

$$g(z) = \left(\frac{1}{2\pi a z^3}\right)^{1/2} \exp\left[-(bz-1)^2/(2az)\right], \qquad z, a, b > 0. \tag{3.5}$$

The Laplace transform of Z is given by

$$L_Z(t) = \exp\left[\frac{b}{a}\left(1 - \left(1 + \frac{2a}{b^2}\,t\right)^{1/2}\right)\right].$$

This gives

$$\frac{-L_Z^{'}(t)}{L_Z(t)} = \frac{1}{(b^2+2at)^{1/2}}$$

and

$$\frac{L_Z^{''}(t)}{L_Z(t)} = \frac{1 + a(b^2+2at)^{-1/2}}{b^2+2at}.$$

It can be verified that, in this case

$$\theta(x_1, x_2) = 1 + \frac{a^2}{\left[b^2 + 2a\left(H_1(x_1) + H_2(x_2)\right)\right]^{1/2}}. \tag{3.6}$$

Remark 3.1. Recently Hanagal and Bhanbure (2016) considered inverse Gaussian distribution as frailty distribution and three baseline distributions. They applied these three models to the analysis of kidney infection data.

Example 3.3. Z has a positive stable distribution with *pdf*

$$f_Z(z) = -\frac{1}{\pi z}\sum_{k=1}^{\infty}\frac{\Gamma(k\alpha+1)}{k!}\,(-z^{-\alpha})^k\sin(\alpha k\pi), \quad z>0,\ \ 0<\alpha<1, \tag{3.7}$$

see Duchateau and Janssen (2008) for more explanation and justification of this distribution as frailty distribution. Note that this density has infinite mean. Therefore, the variance is undetermined.

The Laplace transform of Z is given by

$$L_Z(t) = e^{-t^{\alpha}}, \quad 0<\alpha<1,$$

whose derivatives are given by

$$L_Z^{'}(t) = -\alpha t^{\alpha-1}L_Z(t)$$

and

$$L_Z^{''}(t) = L_Z(t)\left[\alpha^2 t^{2\alpha-2} - \alpha(\alpha-1)t^{\alpha-2}\right].$$

It can be verified that

$$\theta(x_{1,}x_2) = 1 + \frac{(1-\alpha)}{\alpha\left[H_1(x_1+H_2(x_2)\right]^{\alpha}}. \tag{3.8}$$

Bivariate Gamma Correlated Proportional Hazards Model

We follow the notations and assumptions given in section 2.1. The conditional survival function is given by

$$S\big(x_1,x_2|Z_1=z_1,Z_2=z_2\big) = S\big(x_1,x_2\,|\,z_1,z_2\big) = \exp\big\{-\big(H_1(x_1)z_1+H_2(x_2)z_2\big)\big\}.$$

Here Z_1 and Z_2 have been taken with the same marginal distribution, but correlated. This means that $Var(Z_1)=Var(Z_2)=\sigma_Z^2$ (say). Also the correlation coefficient between Z_1 and Z_2 will be denoted by ρ_Z.

We have

$$\rho_{Z_1,Z_2}(x_1,x_2) = \frac{Var_{Y_0}(x_1,x_2)}{\sigma_{Z_1}(x_1,x_2)\,\sigma_{Z_2}(x_1,x_2)}.$$

Under our assumptions

$$\alpha_0 = \rho_Z/\sigma_Z^2, \quad \alpha=(1-\rho_Z)/\sigma_Z^2, \quad \beta=\sigma_Z^2,$$

$$Var_{Y_0}(x_1,x_2) = \frac{\alpha_0\,\sigma_Z^4}{\left[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\right]^2} = \frac{\rho_Z\,\sigma_Z^2}{\left[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\right]^2},$$

$$Var_{Y_i}(x_1,x_2) = \frac{\alpha\sigma_Z^4}{\big[1+\sigma_Z^2 H_i(x_i)\big]^2} = \frac{(1-\rho_Z)\sigma_Z^2}{\big[1+\sigma_Z^2 H_i(x_i)\big]^2}, \qquad i=1,2.$$

These give

$$\begin{aligned} Var_{Z_i}(x_1,x_2) &= Var_{Y_o}(x_1,x_2) + Var_{Y_i}(x_1,x_2) \\ &= \frac{\rho_Z\sigma_Z^2\big[1+\sigma_Z^2 H_i(x_i)\big]^2 + (1-\rho_Z)\,\sigma_Z^2\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]^2}{\big[1+\sigma_Z^2 H_i(x_i)\big]^2\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]^2}, \\ & \qquad\qquad i=1,2. \end{aligned}$$

Thus

$$\begin{aligned} &\rho_{Z_1,Z_2}(x_1,x_2) = \\ &= \frac{Var_{Y_0}(x_1,x_2)}{\sigma_{Z_1}(x_1,x_2)\,\sigma_{Z_2}(x_1,x_2)} \\ &= \frac{\rho_Z\big[1+\sigma_Z^2 H_1(x_1)\big(1+\sigma_Z^2 H_2(x_2)\big)\big]}{\Big[\prod_{i=1}^{i=2}\Big\{\rho_Z\big[1+\sigma_Z^2 H_i(x_i)\big]^2 + (1-\rho_Z)\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]^2\Big\}\Big]^{1/2}}, \end{aligned} \tag{3.9}$$

Now

$$\begin{aligned} &E\big(Z_i|\,T_1>x_1, T_2>x_2\big) = \\ &= E\big(Y_0|\,T_1>x_1, T_2>x_2\big) + E\big(Y_i|\,T_1>x_1, T_2>x_2\big) \\ &= \frac{\rho_Z\big[1+\sigma_Z^2 H_i(x_i)\big] + (1-\rho_Z)\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]}{\big[1+\sigma_Z^2 H_i(x_i)\big]\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]}, \quad i=1,2. \end{aligned} \tag{3.10}$$

Using the above expressions, the $\mathrm{CV}_{Z_i}(x_1,x_2)$ is given by

$$\begin{aligned} &\big[CV_{Z_i}(x_1,x_2)\big]^2 = \\ &= \frac{\rho_Z\sigma_Z^2\big[1+\sigma_Z^2 H_i(x_i)\big]^2 + (1-\rho_Z)\,\sigma_Z^2\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]^2}{\big\{\rho_Z\big[1+\sigma_Z^2 H_i(x_i)\big] + (1-\rho_Z)\big[1+\sigma_Z^2\big(H_1(x_1)+H_2(x_2)\big)\big]\big\}^2}, \\ & \qquad\qquad i=1,2. \end{aligned} \tag{3.11}$$

Using the expressions of $\rho_{Z_1,Z_2}(x_1,x_2)$, $CV_{Z_1}(x_1,x_2)$ and $CV_{Z_2}(x_1,x_2)$, $\theta(x_1,x_2)$ can be obtained.

Remark 3.2. Eriksson and Scheike (2015) have mentioned a similar formula, in the competing risk set up, in a more complex form. See also Gorfine and Hsu (2011) where they provide a new class of frailty based competing risk model for clustered failure time data.

Shared Frailty Model

In this case $\rho_Z = 1$ and hence $\rho_{Z_1,Z_2}(x_1,x_2) = 1$ and the expression for $\theta(x_1,x_2)$ simplifies to

$$\theta(x_1,x_2) = 1+\sigma_Z^2.$$

3.2. Additive Bivariate Correlated Frailty Model

In this case

$$\mu_1(x_1, Z_1) = Z_1 + \mu_1(x_1),$$
$$\mu_2(x_2, Z_2) = Z_2 + \mu_2(x_2).$$

It can be verified that

$$\begin{aligned}\rho_{\mu_1,\mu_2}(x_1,x_2) &= \frac{Cov\big(\mu_1(x_1, Z_1), \mu_2(x_2, Z_2)\big)}{\sqrt{Var(\mu_1(x_1, Z_1))\, Var(\mu_2(x_2, Z_2))}} \\ &= \rho_{Z_1,Z_2}(x_1, x_2).\end{aligned}$$

Also

$$CV_{\mu_i}(x_1, x_2) = \frac{\sqrt{Var_{Z_i}(x_1, x_2)}}{\mu_i(x_i) + E\big(Z_i|\, T_1 > x_1, T_2 > x_2\big)}, \quad i = 1, 2.$$

Hence

$$\begin{aligned}\theta(x_1, x_2) \;=\; & 1 + \rho_{Z_1,Z_2}(x_1, x_2)\, \frac{\sqrt{Var(Z_1|\, T_1 > x_1, T_2 > x_2)}}{\big(\mu_1(x_1) + E(Z_1|\, T_1 > x_1, T_2 > x_2)\big)} \\ & \times \frac{\sqrt{Var(Z_2|\, T_1 > x_1, T_2 > x_2)}}{\big(\mu_2(x_2) + E(Z_2|\, T_1 > x_1, T_2 > x_2)\big)}.\end{aligned} \tag{3.12}$$

Shared Additive Bivariate Frailty Model

In this case $Z_1 = Z_2 = Z$ (say) and $\rho_{Z_1,Z_2}(x_1, x_2) = 1$, giving

(3.13)
$$\begin{aligned}\theta(x_1, x_2) \;&= \\ &= 1 + \frac{Var\big(Z\,|\, T_1 > x_1, T_2 > x_2\big)}{\big[\mu_1(x_1) + E\big(Z|T_1 > x_1, T_2 > x_2\big)\big]\big[\mu_2(x_2) + E\big(Z|T_1 > x_1, T_2 > x_2\big)\big]}.\end{aligned}$$

We now try to give an explicit expression for $\theta(x_1, x_2)$.

The conditional survival function of T_1 and T_2 given $Z = z$ is

$$S(x_1, x_2|Z = z) \;=\; \exp\big\{-\big(\Lambda_1(x_1) + \Lambda_2(x_2) + z(x_1 + x_2)\big)\big\}$$

where $\Lambda_1(x_1)$ and $\Lambda_2(x_2)$ are the integrated hazards.

The unconditional survival function is given by

$$\begin{aligned} S(x_1, x_2) &= \int_0^\infty \exp\big\{-\big(\Lambda_1(x_1) + \Lambda_2(x_2) + z(x_1 + x_2)\big)\big\}\, g(z)\, dz \\ &= H_1(x_1)\, H_2(x_2)\, L_Z(x_1 + x_2), \end{aligned}$$

where $H_1(x_1) = e^{-\Lambda_1(x_1)}$, $H_2(x_2) = e^{-\Lambda_2(x_2)}$ and $L_Z(.)$ is the Laplace transform of Z.

Thus, the conditional density of Z given $T_1 > x_1, T_2 > x_2$ is given by

$$g\big(z|\, T_1 > x_1, T_2 > x_2\big) \;=\; \frac{\exp\big\{-z(x_1 + x_2)\big\}}{L_Z(x_1 + x_2)}\; g(z).$$

It can be verified that

$$E\big[Z \,|\, T_1 > x_1, T_2 > x_2\big] = \frac{-L_Z^{'}(x_1 + x_2)}{L_Z(x_1 + x_2)}$$

and

$$E\big[Z^2 | \, T_1 > x_1, T_2 > x_2\big] = \frac{L_Z^{''}(x_1 + x_2)}{L_Z(x_1 + x_2)}.$$

Hence

$$Var\big[Z \,|\, T_1 > x_1, T_2 > x_2\big] = \frac{L_Z^{''}(x_1 + x_2)}{L_Z(x_1 + x_2)} - \left(\frac{L_Z^{'}(x_1 + x_2)}{L_Z(x_1 + x_2)}\right)^2.$$

The above expressions yield

$$\theta(x_1, x_2) \;=\; 1 + \frac{\frac{L_Z^{''}(x_1+x_2)}{L_Z(x_1+x_2)} - \left(\frac{L_Z^{'}(x_1+x_2)}{L_Z(x_1+x_2)}\right)^2}{\left[\mu_1(x_1) - \frac{L_Z^{'}(x_1+x_2)}{L_Z(x_1+x_2)}\right]\left[\mu_2(x_2) - \frac{L_Z^{'}(x_1+x_2)}{L_Z(x_1+x_2)}\right]}. \tag{3.14}$$

We now present some examples

Example 3.4. Suppose Z has a gamma distribution with *pdf* given by (3.3). Also its Laplace transform and its derivatives are given in Example 3.1.

It can be verified that

$$\theta(x_1, x_2) \;=\; 1 + \frac{\alpha\beta^2}{\big[1+\beta(x_1+x_2)\big]^2}\left[A(x_1, x_2) + \left\{\frac{\alpha\beta}{\big[1+\beta(x_1+x_2)\big]}\right\}^2\right]^{-1}, \tag{3.15}$$

where

$$A(x_1, x_2) \;=\; \mu_1(x_1)\, \mu_2(x_2) + \frac{\alpha\beta}{\big[1+\beta(x_1+x_2)\big]}\, \big(\mu_1(x_1) + \mu_2(x_2)\big).$$

Thus $\theta(x_1, x_2) > 1$. Also as $x_1 \to \infty$ or $x_2 \to \infty$, $\theta(x_1, x_2) \to 1$. It is symmetric in x_1 and x_2 and is a decreasing function of x_1 or x_2.

Remark 3.3. Note that, in the multiplicative case, the value of $\theta(x_1, x_2)$ is independent of x_1 and x_2; see Hanagal (2011, page 83).

Example 3.5. Suppose Z has inverse Gaussian distribution with *pdf* given by (3.5). Also its Laplace transform and its derivatives are given in Example 3.2

It can be verified that

$$\theta(x_1, x_2) \;=\; 1 + \frac{a\big[b^2 + 2a\,(x_1 + x_2)\big]^{-3/2}}{A(x_1, x_2) + \big[b^2 + 2a\,(x_1 + x_2)\big]^{-1/2}}, \tag{3.16}$$

where

$$A(x_1, x_2) \;=\; \mu_1(x_1)\,\mu_2(x_2) + \big[b^2 + 2a\,(x_1 + x_2)\big]^{-1/2}\big(\mu_1(x_1) + \mu_2(x_2)\big).$$

Thus $\theta(x_1, x_2) > 1$. Also as $x_1 \to \infty$ or $x_2 \to \infty$, $\theta(x_1, x_2) \to 1$. It is symmetric in x_1 and x_2 and is a decreasing function of x_1 or x_2.

Example 3.6. Suppose Z has positive stable distribution with *pdf* given by (3.7). Also its Laplace transform and its derivatives are given in Example 3.3

It can be verified that

$$\theta(x_1, x_2) \;=\; 1 + \frac{\alpha(1-\alpha)\,(x_1 + x_2)^{\alpha-2}}{A(x_1 + x_2) + \alpha^2(x_1 + x_2)^{2\alpha-2}}, \tag{3.17}$$

where

$$A(x_1, x_2) \;=\; \mu_1(x_1)\,\mu_2(x_2) + \alpha(x_1 + x_2)^{\alpha-1}\big(\mu_1(x_1) + \mu_2(x_2)\big).$$

Thus $\theta(x_1, t_2) > 1$. Also as $x_1 \to \infty$ or $x_2 \to \infty$, $\theta(x_1, x_2) \to 1$. It is symmetric in x_1 and x_2 and is a decreasing function of x_1 or x_2.

Bivariate Gamma Correlated Additive Hazards Rate Model

Suppose Y_0, Y_1 and Y_2 are independent random variables and $Z_1 = Y_0 + Y_1$, $Z_2 = Y_0 + Y_2$. Then Z_1 and Z_2 are correlated.

The conditional survival function is given by

$$S\big(x_1, x_2 | Z_1 = z_1, Z_2 = z_2\big) \;=\; H_1(x_1)\,H_2(x_2)\,e^{-(z_1x_1 + z_2x_2)}.$$

We follow the notations and assumptions given in section 2.1. Here Z_1 and Z_2 have been taken with the same marginal distribution, but correlated.

This means that $Var(Z_1) = Var(Z_2) = \sigma_Z^2$ (say). Also the correlation coefficient between Z_1 and Z_2 will be denoted by ρ_Z.

We have

$$\rho_{Z_1,Z_2}(x_1,x_2) = \frac{Var_{Y_0}(x_1,x_2)}{\sigma_{Z_1}(x_1,x_2)\,\sigma_{Z_2}(x_1,x_2)}.$$

Under our assumptions

$$\alpha_0 = \rho_Z/\sigma_Z^2, \quad \alpha = (1-\rho_Z))/\sigma_Z^2, \quad \beta = 1/\sigma_Z^2,$$

$$Var_{Y_0}(x_1,x_2) = \frac{\alpha_0\sigma_Z^2}{\big[1+\sigma_Z^2(x_1+x_2)\big]^2} = \frac{\rho_Z\,\sigma_Z^2}{\big[1+\sigma_Z^2(x_1+x_2)\big]^2},$$

$$Var_{Y_i}(x_1,x_2) = \frac{\alpha\sigma_Z^2}{\big[1+\sigma_Z^2 x_i)\big]^2}, \quad i=1,2.$$

These give

$$\begin{aligned} Var_{Z_i}(x_1,x_2) &= Var_{Y_o}(x_1,x_2) + Var_{Y_i}(x_1,x_2) \\ &= \frac{\rho_Z\sigma_Z^2\big[1+\sigma_Z^2(x_i)\big]^2 + (1-\rho_Z)\,\sigma_Z^2\big[1+\sigma_Z^2(x_1+x_2)\big]^2}{\big[1+\sigma_Z^2(x_i)\big]^2\big[1+\sigma_Z^2(x_1+x_2)\big]^2}, \quad i=1,2. \end{aligned}$$

Thus

$$\begin{aligned} \rho_{Z_1,Z_2}(x_1,x_2) &= \frac{Var_{Y_0}(x_1,x_2)}{\sigma_{Z_1}(x_1,x_2)\,\sigma_{Z_2}(x_1,x_2)} \\ &= \frac{\rho_Z\big[\big(1+\sigma_Z^2(x_1)\big)\big(1+\sigma_Z^2(x_2)\big)\big]}{\Big[\prod_{i=1}^{i=2}\big\{\rho_Z[1+\sigma_Z^2(x_i)]^2 + (1-\rho_Z)[1+\sigma_Z^2(x_1+x_2)]^2\big\}\Big]^{1/2}}. \end{aligned} \tag{3.18}$$

Now

$$\begin{aligned} &E\big(Z_i|\,T_1>x_1, T_2>x_2\big) = \\ &\quad = E\big(Y_0|\,T_1>x_1,T_2>x_2\big) + E\big(Y_i|\,T_1>x_1,T_2>x_2\big) \\ &\quad = \frac{\rho_Z\big[1+\sigma_Z^2(x_i)\big] + (1-\rho_Z)\big[1+\sigma_Z^2(x_1+x_2)\big]}{\big[1+\sigma_Z^2(x_i)\big]\big[1+\sigma_Z^2(x_1+x_2)\big]}, \quad i=1,2. \end{aligned} \tag{3.19}$$

Using the above expressions, the $\mathrm{CV}_{Z_i}(x_1,x_2)$ is given by

$$\big[CV_{Z_i}(x_1,x_2)\big]^2 = \frac{\rho_Z\sigma_Z^2\big[1+\sigma_Z^2(x_i)\big]^2 + (1-\rho_Z)\,\sigma_Z^2\big[1+\sigma_Z^2(x_1+x_2)\big]^2}{\Big\{\rho_Z\big[1+\sigma_Z^2(x_i)\big] + (1-\rho_Z)\big[1+\sigma_Z^2(x_1+x_2)\big]\Big\}^2}, \quad i=1,2. \tag{3.20}$$

Using the expressions of $\rho_{Z_1,Z_2}(x_1,x_2)$, $CV_{Z_1}(x_1,x_2)$ and $CV_{Z_2}(x_1,x_2)$, $\theta(x_1,x_2)$ can be obtained.

Shared Frailty Model

In this case $\rho_Z = 1$ and hence $\rho_{Z_1,Z_2}(x_1, x_2) = 1$ and the expression for $\theta(x_1, x_2)$ simplifies to

$$\theta(x_1, x_2) = 1 + \sigma_Z^2.$$

4. SOME APPLICATIONS

In medical and epidemiological studies, the primary object is to study the effect of concomitant information on the time to event such as death or recurrence of a disease. Cox proportional hazard model is commonly used in the analysis of survival time data.

As has been indicated earlier, there is some amount of unobserved heterogeneity among individuals that is not accounted for by the Cox model. Failing to account this form of heterogeneity between individuals may lead to distorted results. Models, which account for this form of unobserved heterogeneity, are known as frailty models. The models are formulated based on the idea that individuals who are most frail will experience the event of interest earlier than others.

Price and Manatunga (2000) analyzed the leukemia patients data. In this data, leukemia patients receive either an allogenic transplant or an autologous transplant. Patients are followed and time to recurrence is recorded. They applied, cure models, frailty models and frailty mixture models to analyze this data. Specifically, the cure models, gamma frailty, gamma frailty mixture, inverse Gaussian frailty, inverse Gaussian mixture and compound Poisson models are utilized to model the data.

Xue and Ding (1999) applied the bivariate frailty model to inpatients mental health data. One frailty is used to represent heterogeneity across all hospital stays and another to represent heterogeneity across all community stays. These two frailties are jointly distributed. They show that this model offers much more flexibility than the univariate frailty model in modelling heterogeneity for the analysis of bivariate survival times.

Hens *et al.* (2009) considered multisera data on hepatitis A and B. They applied the bivariate correlated gamma frailty model for type I interval censored data. They showed that applying a shared rather than a correlated frailty model to this cross-sectionally collected serological data on hepatitis A and B leads to biased estimate for the baseline hazards and variance parameters. Weinke *et al.* (2003) point out that the shared frailty explains correlation within clusters. However, it does have some limitations.

Wienke *et al.* (2003) applied the correlated gamma frailty model to fit bivariate time to event (occurrence of breast cancer) data. They fitted the model for left truncated and right truncated censored data and the analysis accounts for heterogeneity as well as insusceptible (cure fraction) in the study population. This approach includes the shared gamma frailty model as a special case. The correlated gamma model provides a specific parameter for correlation between the two frailties. They also observed that individual frailties in twin pairs could not be observed, but their correlation could be estimated by application of the gamma frailty model.

Weinke *et al.* (2006) used three correlated frailty models to analyze survival data by assuming gamma, log-normal and compound Poisson distributed frailty. All approaches allow to deal with right censored data and account for heterogeneity as well as non susceptible (cure fraction) in the study population. Breast cancer incidence data of Swedish twin pairs illustrate the practical relevance of the models, which are used to estimate the cure fraction and the correlation between the frailties of the twin partners.

We have described some applications of frailty models and correlated frailty models. For more applications, the reader is referred to the bibliography in these papers and the books on frailty models.

5. SOME CONCLUSION AND COMMENTS

Multivariate survival distributions are used in the analysis of life spans of related individuals. An important class of such distributions can be derived by using the concept of random hazards. The randomness is modeled as a frailty random variable having an appropriate distribution. This paper presents a general bivariate correlated frailty model and unifies various results available in the literature. A bivariate gamma correlated frailty model is studied. Clayton's association measure is derived for the general model under study. Proportional hazards as well as additive hazards bivariate frailty model is investigated along with several examples. We hope that the results presented here will be found useful for researchers dealing with various problems involving frailty.

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