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Correlated Inverse Gaussian Frailty Model

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Abstract

Frailty models are used in the survival analysis to account for the unobserved heterogeneity in individual risks to disease and death. To analyze the bivariate data on related survival times, the shared frailty models were suggested. Shared frailty models are used despite their limitations. To overcome their disadvantages correlated frailty models may be used. In this paper, we introduce the inverse Gaussian correlated frailty models.

Key words: Vivariate survival; Copula; Correlated inverse Gaussian frailty; Cross-ration function; Hazard rate.

1. Introduction

The frailty model is a random effect model for time to event data which is an extension of the Cox's proportional hazards model. Shared frailty models are the most commonly used frailty models in literature, where individuals in the same cluster share a common frailty. Frailty models (Vaupel et al. 1979) are used in the survival analysis to account for the unobserved heterogeneity in the individual risks to disease and death. The frailty model is usually modeled as an unobserved random variable acting multiplicatively on the baseline hazard function. Hanagal and Dabade (2013), Hanagal and Bhambure (2015, 2016) and Hanagal and Pandey (2014a, 2014b, 2015a, 2015b, 2016, 2017a) analyzed kidney infection data and Australian twin data using shared gamma and inverse Gaussian frailty models with different baseline distributions for the multiplicative model. Hanagal and Sharma (2013, 2015a, 2015b, 2015c) analyzed acute leukemia data, kidney infection data and diabetic retinopathy data using shared gamma and inverse Gaussian frailty models for the multiplicative model. Hanagal and Bhambure (2014) developed shared inverse Gaussian frailty model based on the reversed hazard rate for Australian twin data. Hanagal et al.(2017) discussed correlated gamma frailty models for bivariate survival data to analyze kidney infection data and Hanagal and Pandey (2017b) proposed correlated gamma frailty models for bivariate survival data based on reversed hazard rate for Australian twin data. Hanagal (2017) gave extensive literature review on different shared frailty models.

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In a univariate frailty model, let a continuous random variable T be a lifetime of an individual and the random variable Z be frailty variable. The conditional hazard function for a given frailty variable, $Z = z$ at time $t > 0$ is,

$$h(t \mid z) = zh_0(t)e^{\mathbf{X}\boldsymbol{\beta}}, \tag{1}$$

where $h_0(t)$ is a baseline hazard function at time $t > 0$, $\mathbf{X}$ is a row vector of covariates, and $\boldsymbol{\beta}$ is a column vector of regression coefficients. The conditional survival function for given frailty at time $t > 0$ is,

$$S(t \mid z) = e^{-\int_0^t h(x|z)dx} = e^{-zH_0(t)e^{\mathbf{X}\boldsymbol{\beta}}}, \tag{2}$$

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

$$\begin{aligned} S(t) &= \int_0^\infty S(t \mid z) f_Z(z) dz \\ &= \int_0^\infty e^{-zH_0(t)e^{\mathbf{X}\boldsymbol{\beta}}} f_Z(z) dz \\ &= L_Z(H_0(t)e^{\mathbf{X}\boldsymbol{\beta}}), \end{aligned} \tag{3}$$

where $L_Z(.)$ is the Laplace transformation of the distribution of Z. Once we get the survival function at time $t > 0$, of life time random variable for an individual, we can obtain probability structure and make their inferences based on it.

Shared frailty explains correlation's between subjects within clusters. However, it does have some limitations. Firstly, it forces the unobserved factors to be the same within the cluster, which may not always reflect reality. For example, at times it may be inappropriate to assume that all partners in a cluster share all their unobserved risk factors. Secondly, the dependence between survival times within the cluster is based on marginal distributions of survival times. However, when covariates are present in a proportional hazards model with gamma distributed frailty the dependence parameter and the population heterogeneity are confounded (Clayton and Cuzick, 1985). This implies that the joint distribution can be identified from the marginal distributions (Hougaard, 1986). Thirdly, in most cases, a one-dimensional frailty can only induce positive association within the cluster. However, there are some situations in which the survival times for subjects within the same cluster are negatively associated. For example, in the Stanford Heart Transplantation Study, generally the longer an individual must wait for an available heart, the shorter he or she is likely to survive after the transplantation. Therefore, the waiting time and the survival time afterwards may be negatively associated.

To avoid these limitations, correlated frailty models are being developed for the analysis of multivariate failure time data, in which associated random variables are used to characterize the frailty effect for each cluster. Correlated frailty models provide not only variance parameters of the frailties as in shared frailty models, but they also contain additional parameter for modeling the correlation between frailties in each group. Frequently one is interested in construction of a bivariate extension of some univariate family distributions (e.g., gamma). For example, for the purpose of genetic analysis of frailty one might be interested in estimation of correlation

of frailty. It turns out that it is possible to carry out such extension for the class of infinitely-divisible distributions (Iachine 1995a, 1995b). In this case an additional parameter representing the correlation coefficient of the bivariate frailty distribution is introduced.

2. Inverse Gaussian Frailty

The gamma distribution is most commonly used frailty distribution because of its mathematical convenience. Another choice is the inverse Gaussian distribution. The inverse Gaussian makes the population homogeneous with time, whereas for gamma the relative heterogeneity is constant (Hougaard, 1984). Duchateau and Janssen (2008) fit the inverse Gaussian (IG) frailty model with Weibull hazard to the udder quarter infection data. The IG distribution has a unimodal density and is a member of the exponential family. While its shape resembles that of other skewed density functions, such as lognormal and gamma, it provides much flexibility in modeling. Furthermore, there are many striking similarities between the statistics derived from this distribution and those of the normal; see Chhikara and Folks (1986). These properties make it potentially attractive for modeling purposes with survival data. The models derived above are bases on the assumption that a common random effect acts multiplicatively on the hazard rate function.

Alternative to the gamma distribution, Hougaard (1984) introduced the inverse Gaussian as a frailty distribution. It provides much flexibility in modeling, when early occurrences of failures are dominant in a life time 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. Secondly, for the inverse Gaussian distribution, the surviving population becomes more homogeneous with respect to time, where as for gamma distribution the relative heterogeneity is constant. The inverse Gaussian distribution has 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. The inverse Gaussian distribution has a history dating back to 1915 when Schrodinger and Smoluchowski presented independent derivations of the density of the first passage time distribution of Brownian motion with positive drift. Villman et al., (1990) have studied the histomorphometrical analysis of the influence of soft diet on masticatory muscle development in the muscular dystrophic mouse. The muscle fibre size distributions were fitted by an inverse Gaussian law. Barndorff-Nielsen (1994) considers a finite tree whose edges are endowed with random resistances, and shows that, subject to suitable restrictions on the parameters, if the resistances are either inverse Gaussian or reciprocal inverse Gaussian random variables, then the overall resistance of the tree follows a reciprocal inverse Gaussian law. Gacula and Kubala (1975) have analyzed shelf life of several products using the IG law and found to be a good fit. For more real life applications (see Seshadri, 1999).

Consider a continuous random variable Z follows inverse Gaussian distribution with

parameters μ and σ^2 then density function of Z is,

$$f_Z(z) = \begin{cases} \left[\frac{1}{2\pi\sigma^2}\right]^{\frac{1}{2}} z^{-\frac{3}{2}} e^{\frac{(z-\mu)^2}{2z\sigma^2\mu^2}} & ;\ z>0, \mu>0, \sigma^2>0 \\ 0 & ;\ otherwise, \end{cases} \tag{4}$$

and the Laplace transform is,

$$L_Z(s) = exp\left[\frac{1}{\mu\sigma^2} - \left(\frac{1}{\sigma^4\mu^2} + \frac{2s}{\sigma^2}\right)^{\frac{1}{2}}\right]. \tag{5}$$

The mean and variance of frailty variable are $E(Z) = \mu$ and $V(Z) = \mu^3\sigma^2$. For identifiability, we assume Z has expected value equal to one i.e. $\mu = 1$. Under this restriction, the density function and the Laplace transformation of the inverse Gaussian distribution reduces to,

$$f_Z(z) = \begin{cases} \left[\frac{1}{2\pi\sigma^2}\right]^{\frac{1}{2}} z^{-\frac{3}{2}} e^{\frac{(z-1)^2}{2z\sigma^2}} & ;\ z>0, \sigma^2>0 \\ 0 & ;\ otherwise, \end{cases} \tag{6}$$

and the Laplace transform is,

$$L_Z(s) = exp\left[\frac{1-(1+2\sigma^2 s)^{\frac{1}{2}}}{\sigma^2}\right], \tag{7}$$

with variance of Z as σ^2. The frailty variable Z is degenerate at $Z = 1$ when σ^2 tends to zero. Let T_1 and T_2 be failure times of the pair of individuals like kidney, lungs, eyes or any paired organ of an individual or lifetimes of twins. The unconditional bivariate distribution function of lifetimes T_1 and T_2 with inverse Gaussian frailty is,

$$\begin{aligned} L_Z(H_1(t_1) + H_2(t_2)) &= exp\left[\frac{1-(1+2\theta(H_1(t_1)+H_2(t_2)))^{\frac{1}{2}}}{\theta}\right] \\ &= S(t_1, t_2) \end{aligned} \tag{8}$$

where $H_1(t_1)$ and $H_2(t_2)$ are the cumulative baseline hazard functions of the lifetime T_1 and T_2 respectively. Clayton (1978) define cross-ratio function as,

$$\theta^*(t_1, t_2) = \frac{\frac{\partial^2 S(t_1,t_2)}{\partial t_1 \partial t_2} S(t_1, t_2)}{\frac{\partial S(t_1,t_2)}{\partial t_1}\frac{\partial S(t_1,t_2)}{\partial t_2}}$$

The cross ratio function of inverse Gaussian frailty is,

$$\theta^*(t_1, t_2) = 1 + \frac{1}{\frac{1}{\theta} - ln(S(t_1, t_2))}$$

The highest value is obtained at the start and equals $1 + \theta$, and goes to one as the survival function goes to zero. It is decreasing function of t_1, t_2.

The joint bivariate survival functions in (8) can be expressed in terms of survival copula as (see Nelsen (2006) for details)

$$\overline{C}(u,v) = exp\left\{\frac{1-[(1-\theta\log u)^2+(1-\theta\log v)^2-1]^{\frac{1}{2}}}{\theta}\right\}$$

where $u = S_{T_1}(\cdot)$ and $v = S_{T_2}(\cdot)$. This is a new copula and not appeared in the earlier literature.

3. Correlated Frailty

The correlated frailty model is the second important concept in the area of multivariate frailty models. It is a natural extension of the shared frailty approach on the one hand, and of the univariate frailty model on the other. In the correlated frailty model, the frailties of individuals in a cluster are correlated but not necessarily shared. It enables the inclusion of additional correlation parameters, which then allows the addressing of questions about associations between event times. Furthermore, associations are no longer forced to be the same for all pairs of individuals in a cluster. This makes the model especially appropriate for situations where the association between event times is of special interest, for example, genetic studies of event times in families. The conditional survival function in the bivariate case (here without observed covariates) looks like

$$S(t_1,t_2|Z_1,Z_2) = S_1(t_1|Z_1)S_2(t_2|Z_2) = e^{-Z_1H_{01}(t_1)}e^{-Z_2H_{02}(t2)}, \tag{9}$$

where Z_1 and Z_2 are two correlated frailties. The distribution of the random vector (Z_1, Z_2) needs to be specified and determines the association structure of the event times in the model. Integrating the above bivariate survival function over Z_1 and Z_2, we get unconditional bivariate survival function as

$$S(t_1,t_2) \;\; = \;\; E_{Z_1,Z_2}[e^{-Z_1H_{01}(t_1)}e^{-Z_2H_{02}(t2)}] \tag{10}$$

where (Z_1, Z_2) has some known bivariate frailty distribution.

Consider some bivariate event times – for example, the lifetimes of twins, or age at onset of a disease in spouses, time to blindness in the left and right eye, or time to failure in the left and right kidney of patients. In the (bivariate) correlated frailty model, the frailty of each individual in a pair is defined by a measure of relative risk, that is, exactly as it was defined in the univariate case. For two individuals in a pair, frailties are not necessarily the same, as they are in the shared frailty model. We are assuming that the frailties are acting multiplicatively on the baseline hazard function (proportional hazards model) and that the observations in a pair are conditionally independent, given the frailties. Hence, the hazard of the individual $i(i = 1, 2)$ in pair $j(i = j, ..., n)$ has the form

$$h(t|X_{ij},Z_{ij}) = Z_{ij}h_{0i}(t)e^{\beta' X_{ij}}, \tag{11}$$

where t denotes age or time, X_{ij} is a vector of observed covariates, $\boldsymbol{\beta}$ is a vector of regression parameters describing the effect of the covariates X_{ij}, $h_{0i}(.)$ are baseline hazard functions, and

Z_{ij} are frailties. Bivariate correlated frailty models are characterized by the joint distribution of a two-dimensional vector of frailties (Z_{1j}, Z_{2j}). If the two frailties are independent, the resulting lifetimes are independent, and no clustering is present in the model. If the two frailties are equal, the shared frailty model is obtained as a special case of the correlated frailty model with correlation one between the frailties (Wienke(2011)).

In order to derive a marginal likelihood function, the assumption of conditional independence of lifespans, given the frailty, is used. Let δ_{ij} be a censoring indicator for individual $i(i = 1, 2)$ in pair $j(j = 1, ..., n)$. Indicator δ_{ij} is 1 if the individual has experienced the event of interest, and 0 otherwise. According to (2.2), the conditional survival function of the ith individual in the jth pair is

$$S(t|X_{ij}, Z_{ij}) = e^{-Z_{ij}H_{0i}(t)}e^{\beta' X_{ij}}, \tag{12}$$

with $H_{0i}(t)$ denoting the cumulative baseline hazard function. The contribution of individual $i(i = 1, 2)$ in pair $j(j = 1, ..., n)$ to the conditional likelihood is given by

$$\left[Z_{ij}h_{0i}(t)e^{\beta' X_{ij}}\right]^{\delta_{ij}} e^{Z_{ij}H_{0i}(t_{ij})}e^{\beta' X_{ij}}, \tag{13}$$

where t_{ij} stands for observation time of individual i from pair j. Assuming the conditional independence of lifespans, given the frailty, and integrating out the frailty, we obtain the marginal likelihood function

$$\prod_{j=1}^{n} \int_{R\times} \int_{R} \left[u_{1j}h_{01}(t_{1j})e^{\beta' X_{1j}}\right]^{\delta_{1j}} e^{u_{1j}H_{01}(t_{1j})}e^{\beta' X_{1j}}$$
$$\left[u_{2j}h_{02}(t_{2j})e^{\beta' X_{2j}}\right]^{\delta_{2j}} e^{u_{2j}H_{02}(t_{2j})}e^{\beta' X_{2j}} f(z_{1j}, z_{2j})dz_{1j}dz_{2j} \tag{14}$$

where $f(.,.)$ is the probability density function of the corresponding frailty distribution. All these formulas can be easily extended to the multivariate case, but need a specification of the correlation structure between individuals in a cluster in terms of the multivariate density function, which complicates analysis. For more details see (Hanagal(2011, 2019) and Wienke(2011)).

4. Correlated Inverse Gaussian Frailty Model

Let Z be an infinitely divisible frailty variable with Laplace transformation $L_Z(s)$ and $\rho \in [0, 1]$, then there exist random variables Z_1, Z_2 each with univariate Laplace transform $L_Z(s)$ such that the Laplace transform of Z_1, Z_2 is given by:

$$L(s_1, s_2) = L_Z^{\rho}(s_1 + s_2)L_Z^{1-\rho}(s_1)L_Z^{1-\rho}(s_2) \tag{15}$$

If Z has a variance the $Corr(Z_1, Z_2) = \rho$.
The respective bivariate survival model is identifiable under mild regularity conditions on Z provided that $\rho > 0$. The case $\rho = 1$ is known as the shared frailty model.

The above equation can be extended to multivariate case ($\rho > 0$) as below.

$$L(s_1, s_2, ..., s_k) \;=\; L_Z^{\rho}(s_1, s_2, ..., s_k)L_Z^{1-\rho}(s_1)....L_Z^{1-\rho}(s_k).$$

The case $\rho = 1$ leads to shared frailty. If $\rho = 0$, $Z_1, ...Z_k$ are mutually independent.

Let Z_i be the inverse Gaussian distributed with mean 1, variance σ^2, and Laplace transform

$$L(s_i, \sigma^2) = \exp[\frac{1-(1+2\sigma^2 s_i)^{\frac{1}{2}}}{\sigma^2}] \tag{16}$$

The bivariate Laplace transform for the correlated inverse Gaussian frailty model is given by

$$\begin{aligned} L(s_1, s_2, \sigma^2, \rho) &= \exp\left[\rho\frac{1-(1+2\sigma^2(s_1+s_2))^{\frac{1}{2}}}{\sigma^2}\right]\exp\left[(1-\rho)\frac{1-(1+2\sigma^2 s_1)^{\frac{1}{2}}}{\sigma^2}\right] \\ &\quad \exp\left[(1-\rho)\frac{1-(1+2\sigma^2 s_2)^{\frac{1}{2}}}{\sigma^2}\right] \end{aligned} \tag{17}$$

where $Corr(Z_1, Z_2) = \rho$.
The correlated frailty model with inverse Gaussian frailty distribution is characterized by the bivariate survival function of the form:

$$\begin{aligned} S(t,t_{2j}) &= \exp\left[\rho\frac{1-(1+2\sigma^2\eta_j(H_1(t_{1j})+H_2(t_{2j})))^{\frac{1}{2}}}{\sigma^2}\right]\exp\left[(1-\rho)\frac{1-(1+2\sigma^2\eta_j H_1(t_{1j}))^{\frac{1}{2}}}{\sigma^2}\right] \\ &\quad \exp\left[(1-\rho)\frac{1-(1+2\sigma^2\eta_j H_2(t_{2j}))^{\frac{1}{2}}}{\sigma^2}\right] \end{aligned} \tag{18}$$

where $H_{01}(t_{1j})$ and $H_{02}(t_{2j})$ are the cumulative baseline hazard functions of the life time random variables T_{1j} and T_{2j} respectively.

According to different assumptions on the baseline distributions we get different correlated inverse Gaussian frailty models.

5. Likelihood Specification and Bayesian Estimation of Parameters

Suppose there are n individuals under study, whose first and second observed failure times are represented by (t_{1j}, t_{2j}). Let c_{1j} and c_{2j} be the observed censoring times for the j^{th} individual ($j = 1, 2, 3, ..., n$) for first and second recurrence times respectively. We also assume that independence between the censoring time and the life-times of individuals.

The contribution of the bivariate life time random variable of the j^{th} individual in likelihood function is given by,

$$L_j(t_{1j}, t_{2j}) = \begin{cases} f_1(t_{1j}, t_{2j}), & t_{1j} < c_{1j}, t_{2j} < c_{2j}, \\ f_2(t_{1j}, c_{2j}), & t_{1j} < c_{1j}, t_{2j} > c_{2j}, \\ f_3(c_{1j}, t_{2j}), & t_{1j} > c_{1j}, t_{2j} < c_{2j}, \\ f_4(c_{1j}, c_{2j}), & t_{1j} > c_{1j}, t_{2j} > c_{2j}. \end{cases}$$

and the likelihood function is,

$$L(\boldsymbol{\psi}, \boldsymbol{\beta}, \theta) = \prod_{j=1}^{n_1} f_1(t_{1j}, t_{2j}) \prod_{j=1}^{n_2} f_2(t_{1j}, c_{2j}) \prod_{j=1}^{n_3} f_3(c_{1j}, t_{2j}) \prod_{j=1}^{n_4} f_4(c_{1j}, c_{2j}) \tag{19}$$

where θ, $\boldsymbol{\psi}$ and $\boldsymbol{\beta}$ are respectively the frailty parameter $(\sigma_1, \sigma_2, \rho)$, the vector of baseline parameters and the vector of regression coefficients.

The counts n_1, n_2, n_3 and n_4 are the number of individuals for which first and second failure times (t_{1j}, t_{2j}) lie in the ranges $t_{1j} < c_{1j}, t_{2j} < c_{2j}$; $t_{1j} < c_{1j}, t_{2j} > c_{2j}$; $t_{1j} > c_{1j}, t_{2j} < c_{2j}$ and $t_{1j} > c_{1j}, t_{2j} > c_{2j}$ respectively and

$$\begin{aligned} f_1(t_{1j}, t_{2j}) &= \frac{\partial^2 S(t_{1j}, t_{2j})}{\partial t_{1j} \partial t_{2j}} \\ f_2(t_{1j}, c_{2j}) &= \frac{\partial S(t_{1j}, c_{2j})}{\partial t_{1j}} \\ f_3(c_{1j}, t_{2j}) &= \frac{\partial S(c_{1j}, t_{2j})}{\partial t_{2j}} \\ and\ f_4(c_{1j}, c_{2j}) &= S(c_{1j}, c_{2j}) \end{aligned} \tag{20}$$

Usually maximum likelihood estimators can be used to estimate the parameters invloved in the model. Unfortunately computing the maximum likelihood estimators (MLEs) involves solving a fourteen dimensional optimization problem for Model I and Model III and eleven dimensional optimization problem for Model II and Model IV. As the method of maximum likelihood fails to estimate the parameters due to convergence problem in the iterative procedure, so we use the Bayesian approach. The traditional maximum likelihood approach to estimation is commonly used in survival analysis, but it can encounter difficulties with frailty models. Moreover, standard maximum likelihood based inference methods may not be suitable for small sample sizes or situations in which there is heavy censoring (see Kheiri et al. (2007)). Thus, in our problem a Bayesian approach, which does not suffer from these difficulties, is a natural one, even though it is relatively computationally intensive

To estimate parameters of the model, the Bayesian approach is now popularly used, because computation of the Bayesian analysis become feasible due to advances in computing technology [for more details on Bayesian estimation of the parameters and data analysis based on correlated inverse Gaussian frailty model, see Hanagal and Pandey, 2020].

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