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Dependent Hazards in Multivariate Survival Problems

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A new class of bivariate survival distributions is constructed from a given family of survival distributions. The properties of these distributions are analyzed. It is shown that the same bivariate survival function can be derived using two radically different concepts: one involves transformation of the well-known bivariate survival function; the other involves correlated stochastic hazards. The new conditions that guarantee negative associations of life spans are derived. An exponential representation of the survival function for two related individuals is derived in terms of the conditional distribution of the stochastic hazards among survivors. Versions of the multivariate correlated gamma-frailty model are investigated.

AMS 1991 subject classifications: 62P10.

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1. INTRODUCTION

Survival data used in epidemiology, demography, and biostatistics are often censored or truncated. In case of survival data for dependent life spans the problem is even more complicated since one has to consider simultaneous censoring and truncation for several individuals or units. For example, in the case of Swedish (Cederlöf and Lorich, 1978) and Finnish (Kaprio *et al.*, 1978) twin survival data, both twins had to be alive in a certain year in order to be included in the sample. Right censoring occurs when twins are alive at the time of the study or when they are lost from a follow-up study.

The classical approach to the censoring and truncation problem (Kalbfleish and Prentice, 1980) is based on some regularity assumptions

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about the censoring and truncation mechanism (i.e., independent censoring and non-informative censoring). A similar approach may be used for the multivariate situation (Miller, 1981). It turns out that in this case the likelihood of the survival data can be represented in terms of the multivariate survival function $S(x_1, ...x_n) = P(T_1 > x_1, ...T_n > x_n)$ and its partial derivatives. A specification of the multivariate survival model in terms of the survival function therefore eases the computational burden of handling right-censoring and truncation in a maximum likelihood framework.

Let T_1, T_2 be dependent life spans, and let $S_i(x_i) = P(T_i > x_i)$, and $S(x_1, x_2) = P(T_1 > x_1, T_2 > x_2)$ be absolutely continuous univariate and bivariate survival functions, respectively. The hazard rates $\bar{\mu}_i(x) = -d/dx \ln S_i(x)$, $i = 1, 2$ are often used in demography, survival analysis, and biostatistics when analyzing univariate survival data. Two conditional hazards associated with $S(x_1, x_2)$ play an important role in applications related to the analysis of data involving dependent durations. These are $\bar{\mu}_i(x_i, x_j)$, which is the hazard of failure for T_i given $T_j > x_j$; $i, j = 1, 2$; $i \neq j$ defined as

$$\bar{\mu}_i(x_i, x_j) = \lim_{\Delta x \to 0} \frac{1}{\Delta x} P(x_i \leqslant T_i < x_i + \Delta x \mid T_i > x_i, T_j > x_j)$$

$$= -\frac{\partial}{\partial x_i} \ln S(x_i, x_j) \tag{1}$$

$i = 1, 2$; and $\tilde{\mu}_i(x_i; x_j)$, which is the hazard of failure for T_i given $T_j = x_j$,

$$\tilde{\mu}_i(x_i; x_j) = \lim_{\Delta x \to 0} \frac{1}{\Delta x} P(x_i \leqslant T_i < x_i + \Delta x \mid T_i > x_i, T_j = x_j)$$

$$= -\frac{\partial}{\partial x_i} \ln \left(-\frac{\partial}{\partial x_j} S(x_i, x_j) \right) \tag{2}$$

with $i, j = 1, 2$; $i \neq j$. These hazards describe the chances of failure at age x for the ith unit given the failure history of jth unit; hazard (1) uses the condition $\{T_j > x_j\}$, (i.e., the jth unit is functioning at age x_j), and hazard (2) is conditional on $\{T_j = x_j\}$, (i.e., the jth unit fails at age x_j). The deviation of the ratio of these hazards from 1 characterizes the measure of mutual dependence of respective life spans (Oakes, 1989). One way of deriving a bivariate survival model is based on the introduction of relations between these hazards. For example, the condition

$$\tilde{\mu}_i(x_i; x_j) = (1 + \theta)\, \bar{\mu}_i(x_i, x_j) \tag{3}$$

uniquely (up to the marginal distributions) defines a bivariate survival function $S(x_1, x_2)$ (Clayton, 1978; Cox and Oakes, 1984) as

$$S(x_1, x_2) = (S_1(x_1)^{-\theta} + S_2(x_2)^{-\theta} - 1)^{-1/\theta}. \quad (4)$$

An advantage of model (4) is that the value of $(1+\theta)$ has an appealing interpretation, in that it is the relative risk associated with the history of a non-surviving relative or unit.

A different approach used for deriving multivariate survival model is based on the notion of a random hazard. In many applications, chances of failure for related units are described in terms of random hazards and their joint distribution function. Frequently the random hazard structure is induced by dependence of the hazard functions on some unobserved random variables. For example, in genetic epidemiology the random hazard rates $\mu_i(x, Y_i)$, $i=1, 2$, for two related individuals (e.g., twins) depend on "liability" variables Y_i, which follow a bivariate normal distribution (Meyer and Eaves, 1988; Meyer *et al.*, 1991). In this case the relationship between this and marginal hazard $\bar{\mu}_i(x)$ is $\bar{\mu}_i(x) = E(\mu_i(x, Y_i) \mid T_i > x)$, $i=1, 2$. To analyse data on matched-pair experiments in epidemiology and biostatistics, models of gamma-distributed shared frailty with hazards $\mu_i(Z, x) = Z\mu_{0i}(x)$, $i=1, 2$, where Z is called "frailty" and $\mu_{0i}(x)$ is the underlying hazard, are often used (Holt and Prentice, 1974; Clayton, 1978). In genetic studies of aging and longevity, correlated frailty models with hazard rates $\mu_i(Z_i, x) = Z_i\mu_{0i}(x)$ are used (Yashin and Iachine, 1997). In the case of two gamma-distributed frailties with both means equal to one, equal variances $\sigma_1^2 = \sigma_2^2 = \theta$ and correlation coefficient $\rho_z \geqslant 0$, the bivariate survival function is

$$S(x_1, x_2) = S_1(x_1)^{1-\rho_z} S_2(x_2)^{1-\rho_z} (S_1(x_1)^{-\theta} + S_2(x_2)^{-\theta} - 1)^{-\rho_z/\theta}. \quad (5)$$

This is the case of the correlated gamma-frailty model used in the analysis of survival data on related individuals (Yashin and Iachine, 1997). The family of probability distributions characterized by (5) belongs to a large class of distributions determined up to their marginals (e.g., Schweizer and Sklar, 1983). When frailties of related individuals are equal (i.e., $Z_1 = Z_2 = Z$), Eq. (5) represents the survival function for the shared gamma-frailty model. In this case $\rho_z = 1$, and (5) coincides with (4). Thus, there are two derivations of (4) based on radically different concepts: one exploits assumption (3), which concerns proportionality of conditional hazards $\bar{\mu}_i(x_i, x_j)$ and $\tilde{\mu}_i(x_i; x_j)$; the other uses the concept of random hazards with gamma-distributed shared frailty.

An interesting question concerning representation (5) is whether it can be derived without the use of the concept of frailty. To answer this question, a deeper investigation of the relation between the hazards (1), (2) and

the random hazards $\mu_i(Z_i, x)$, $i = 1, 2$, is needed. Another important question is whether equation (5) can determine bivariate survival functions for negative values of ρ_z. (The derivation of (5) based on the idea of correlated frailty involves the condition $\rho \geqslant 0$ (Yashin *et al.*, 1995).) It is also important to have a multivariate extension of (5), which might be applied to the analysis of survival data for more than two related individuals (e.g., genealogical or pedigree data).

The concept of dependent random hazards is important since it provides for a multivariate extension of the traditional univariate demographic models of frailty (Vaupel and Yashin, 1985) and it allows us to take mutual dependence of life spans of related individuals into account in the analysis of survival data. Survival models for dependent life spans are useful since they allow us to address more sophisticated questions about the nature of human aging and mortality processes. Correlated frailty models contain association characteristics of frailty among other model parameters (e.g., correlation coefficients), which makes them convenient for genetic studies of individual susceptibility to disease and death. In particular, questions about the role of genes and the environment in human longevity can be addressed (Yashin and Iachine, 1995a, 1995b). The structure of correlated frailty models makes them convenient for the development of semiparametric estimation algorithms (Iachine, 1995). The models can also be used in the studies of dependent competing risks (Yashin and Iachine, 1996).

In this paper, we derive several new random-effect multivariate survival models. First, we examine a general model of bivariate survival with an arbitrary structure of random hazards. Then we explore the idea of correlated frailties. We give an alternative derivation of (5), which does not make use of the concept of frailty. We also show that representation (5) can describe negative correlations between life spans, for negative ρ_z. Then we investigate multivariate extensions of the correlated frailty model.

2. BIVARIATE SURVIVAL MODELS WITH RANDOM HAZARDS

Survival models utilizing properties of random hazards, known as "heterogeneity," "random effect," "liability," or "frailty" models, have become popular in the demographic and epidemiological literature (Vaupel *et al.*, 1979; Manton *et al.*, 1981; Heckman and Singer, 1984; Hougaard, 1986; Aalen, 1988; Hoem, 1990). Multivariate (bivariate) versions of these models are known as shared relative risk or shared frailty models (Clayton, 1978; Cook and Johnson, 1981; Clayton and Cuzick, 1985; Hougaard, 1987; Marshall and Olkin, 1988; Thomas *et al.*, 1990; Vaupel *et al.*, 1992; Guo and Rodríguez, 1992; Guo, 1993), liability models (Meyer and Eaves, 1988; Meyer *et al.*, 1991), or correlated frailty models (Yashin and Iachine,

1994, 1995a, 1995b, 1995c). Non-parametric estimates of bivariate survival functions are studied by Dabrowska (1988). Some general properties of these models can be analyzed in the framework of the following scheme.

Let T_1, T_2 be two dependent life spans, and $S(x_1, x_2) = P(T_1 > x_1, T_2 > x_2)$ be a bivariate survival function. Any such function can be represented as

$$S(x_1, x_2) = S_1(x_1)\, S_2(x_2)\, e^{A(x_1, x_2)} \tag{6}$$

with $A(x_1, x_2) = \ln(S(x_1, x_2)/S_1(x_1)\, S_2(x_2))$. If a bivariate density distribution function for T_1, T_2 exists, then there is a function $\varphi(u, v)$ such that

$$A(x_1, x_2) = \int_0^{x_1} \int_0^{x_2} \varphi(u, v)\, du\, dv. \tag{7}$$

Representation (6) is called the *exponential representation* of a bivariate survival function. It turns out that in the case of random hazards, the function $\varphi(u, v)$ in (7) can be calculated using the bivariate conditional distribution of these hazards. Let Z_i, $i = 1, 2$ be two random variables. We assume that the survival chances of the ith individual depend on Z_i, i.e., the conditional survival function $S_i(x_i \mid Z_i) = P(T_i > x_i \mid Z_i)$ is

$$S_i(x_i \mid Z_i) = e^{-\int_0^{x_i} \mu_i(Z_i, u)\, du}$$

with individual hazard $\mu_i(Z_i, x)$, $i = 1, 2$. We assume that given Z_1, Z_2 the random variables T_1, T_2 are conditionally independent. Yashin and Iachine (1995c) show that in this case

$$\begin{aligned}\varphi(x_1, x_2) &= Cov(\mu_1(Z_1, x_1), \mu_2(Z_2, x_2) \mid T_1 > x_1, T_2 > x_2) \\ &= E(\mu_1(Z_1, x_1)\, \mu_2(Z_2, x_2) - \bar{\mu}_1(x_1, x_2)\, \bar{\mu}_2(x_1, x_2) \mid T_1 > x_1, T_2 > x_2),\end{aligned} \tag{8}$$

where $\bar{\mu}_i(u, v)$ (defined by (1)) can also be calculated as

$$\bar{\mu}_i(u, v) = E(\mu_i(Z_i, u) \mid T_1 > u, T_2 > v), \qquad i = 1, 2. \tag{9}$$

Remark 1. Representation (8) holds when random variables Z_1, Z_2 in the individual hazards are replaced by stochastic processes, Z_{1t}, Z_{2t}, $t \geqslant 0$, such that conditional mathematical expectations in (8) and (9) exist.

Remark 2. The hazards $\bar{\mu}_i(u, v)$, $i = 1, 2$ in (9), which are associated with the bivariate survival function $S(x_1, x_2)$ by (1), in general differ from the hazards $\bar{\mu}_i(u)$, $i = 1, 2$

$$\bar{\mu}_i(u) = -\frac{d}{du} \ln S_i(u) = E(\mu_i(Z_i, u) \mid T_i > u) = \bar{\mu}_i(u, 0), \qquad i = 1, 2 \tag{10}$$

which are associated with univariate survival function $S_i(u)$ (Vaupel and Yashin, 1985). Both hazards (9) and (10) are conditional means of the same random hazard, but the respective mathematical expectations are calculated under two different conditions. The difference between these hazards will be illustrated in Subsection 2.3, where the correlated gamma-frailty model is discussed.

2.1. *A New Family of Correlated Durations*

An important feature of the correlated hazards model is that using the exponential representation (6) for the bivariate survival function, one can construct a new family of correlated survival times. This result is formulated in the following statement.

THEOREM 1. *Let $S(x_1, x_2)$ be the bivariate survival function of survival times T_1, T_2 given by (6) such that $S_1(x_1)$, $S_2(x_2)$ are the marginal survival functions and $A(x_1, x_2) = \int_0^{x_1} \int_0^{x_2} \varphi(u, v)\, du\, dv$, with $\varphi(x_1, x_2) \geqslant 0$ for all $x_1 \geqslant 0$, $x_2 \geqslant 0$. Then for any $0 \leqslant \gamma \leqslant 1$, the expression*

$$\tilde{S}(x_1, x_2) = S_1(x_1)\, S_2(x_2)\, e^{\gamma A(x_1, x_2)} \tag{11}$$

determines a bivariate survival function for some survival times $\tilde{T}_1$, $\tilde{T}_2$. For each $i = 1, 2$ the marginal distributions of $\tilde{T}_i$ and T_i are identical.

The proof of Theorem 1 is given in the Appendix.

COROLLARY. *Let $S(x_1, x_2)$ be given by (4). Then the exponential representation (6), (7) of this function is characterized by the function $\varphi(x_1, x_2)$ of the form*

$$\varphi(x_1, x_2) = \frac{\theta \bar{\mu}_1(x_1)\, \bar{\mu}_2(x_2)(S_1(x_1)\, S_2(x_2))^{-\theta}}{(S_1^{-\theta}(x_1) + S_2^{-\theta}(x_2) - 1)^2} > 0 \tag{12}$$

and, hence, by Theorem 1, $\tilde{S}(x_1, x_2)$ in (11) is a bivariate survival function with $\tilde{\varphi}(x_1, x_2) = \gamma\varphi(x_1, x_2)$ and $\tilde{S}_1(x_1) = S_1(x_1)$, $\tilde{S}_2(x_2) = S_2(x_2)$. Furthermore, since

$$\tilde{A}(x_1, x_2) = \gamma A(x_1, x_2) = \gamma \ln \left(\frac{S(x_1, x_2)}{S_1(x_1)\, S_2(x_2)} \right)$$

$$= -\frac{\gamma}{\theta} \ln (S_1(x_1)^{-\theta} + S_2(x_2)^{-\theta} - 1),$$

the representation for $\tilde{S}(x_1, x_2)$ *is*

$$\tilde{S}(x_1, x_2) = S_1(x_1)^{1-\gamma} S_2(x_2)^{1-\gamma}(S_1(x_1)^{-\theta} + S_2(x_2)^{-\theta} - 1)^{-\gamma/\theta}. \quad (13)$$

It is clear that (13) *is exactly the survival function corresponding to the bivariate correlated gamma-frailty models* (5) *when* $\gamma = \rho_z$.

Remark 3. Theorem 1 does not, in general, guarantee the existence of random hazards with proportional structure for durations $\tilde{T}_1$ and $\tilde{T}_2$ (i.e., it does not guarantee the existence of random variables $\tilde{Z}_1$, $\tilde{Z}_2$ and hazard functions $\mu_1(x)$, $\mu_2(x)$ such that

$$\tilde{S}(x_1, x_2) = E[\, e^{-\tilde{Z}_1 \int_0^{x_1} \mu_1(u)\, du - \tilde{Z}_2 \int_0^{x_2} \mu_2(u)\, du}]).$$

The new bivariate survival function $\tilde{S}(x_1, x_2)$ obtained in Theorem 1 is a geometric mean of two survival functions; one corresponds to independent survival times, another deals with dependent survival times associated with $S(x_1, x_2)$, i.e., $\tilde{S}(x_1, x_2) = [S_1(x_1)\, S_2(x_2)]^{1-\gamma}\, [S(x_1, x_2)]^{\gamma}$. The parameter γ may be therefore viewed as an association parameter determining the "location" of the survival function $\tilde{S}(x_1, x_2)$ between survival functions $S(x_1)\, S(x_2)$ and $S(x_1, x_2)$.

2.2. *Bivariate Survival Functions with Negatively Correlated Life Spans*

It turns out that transformation (11) may be used to construct bivariate survival functions with negatively correlated life spans.

THEOREM 2. *Let us assume that the conditions of Theorem* 1 *hold. Then for any* γ *satisfying*

$$\max_{x_1, x_2} \left(-\frac{\bar{\mu}_1(x_1)\, \bar{\mu}_2(x_2)}{\varphi(x_1, x_2)} \right) < \gamma < 0 \quad (14)$$

the function $\tilde{S}(x_1, x_2)$ *given by* (11) *determines a bivariate distribution of negatively correlated survival times.*

The proof is given in the Appendix.

The ability to use negative values of γ in (11) is significant for several reasons. First, the models with negatively correlated lifespans can be used in the analysis of any dependent survival times where both positive and negative correlation may occur. In particular, this may be the case for the problem of dependent competing risks (Gavrilov and Gavrilova, 1991) and in the analysis of survival data on adopted children (Nielsen *et al.*, 1992;

Andersen *et al.*, 1992, p. 671). Traditional correlated frailty models based on sums of independent non-negative random variables are only able to produce positive correlations.

Another important reason for allowing $\gamma < 0$ is related to the statistical problem of hypotheses testing. When γ is interpreted as an association parameter (in fact, for the case of gamma-frailty $0 \leqslant \gamma \leqslant 1$ describes the correlation between the frailties) one is frequently interested in testing the null hypothesis H_0: $\gamma = 0$, i.e., whether or not the life spans are dependent. The classical likelihood based approach requires the point $\gamma = 0$ to be an internal point of the parameter space (Azzalini, 1996) in order for the likelihood ratio test statistics to have an asymptotic χ^2-distribution. By allowing $\gamma < 0$ we effectively make the point $\gamma = 0$ an internal point of the parameter space thereby permitting the classical inference methods to be applied.

2.3. *The Bivariate Correlated Gamma-Frailty Model*

Let T_i, $i = 1, 2$ be the life spans of two related individuals, with $\mu(Z_i, x) = Z_i \mu_{0i}(x)$ being their conditional individual hazards given frailties Z_i, $i = 1, 2$, where $\mu_{0i}(x)$, $i = 1, 2$ are the underlying hazards, and let life spans T_1, T_2 be conditionally independent given frailties Z_1, Z_2. The bivariate survival function is then given by

$$S(x_1, x_2) = E\left(\exp\left\{-Z_1 \int_0^{x_1} \mu_{01}(t)\, dt - Z_2 \int_0^{x_2} \mu_{02}(t)\, dt\right\}\right)$$

$$= L\left(\int_0^{x_1} \mu_{01}(t)\, dt, \int_0^{x_2} \mu_{02}(t)\, dt\right),$$

where $L(t_1, t_2)$ is the joint Laplace transform of the distribution of (Z_1, Z_2). The above representation provides a flexible tool for construction of bivariate survival models; assuming a particular parametric family of Laplace transforms for the frailty distribution yields a parametric family of bivariate survival models.

In some applications, it is important to specify different marginal frailty distributions for related individuals (see Remark 7 below). It turns out that in the case of gamma-distributed frailties such a bivariate frailty distribution can be constructed. In this case the frailties of the two related individuals may have different variances σ_1^2, σ_2^2 and correlation coefficient ρ_z. The following statement specifies the form of the respective multivariate survival function.

THEOREM 3. In the case of the proportional hazards model of bivariate survival described above, there exists a bivariate gamma-frailty distribution

with different marginals that allows for representation of the bivariate survival function $S(x_1, x_2)$ as

$$S(x_1, x_2) = S_1(x_1)^{1-(\sigma_1/\sigma_2)\rho_z} S_2(x_2)^{1-(\sigma_2/\sigma_1)\rho_z} \times (S_1(x_1)^{-\sigma_1^2} + S_2(x_2)^{-\sigma_2^2} - 1)^{-\rho_z/\sigma_1\sigma_2} \quad (15)$$

with the correlation coefficient of frailty distribution satisfying

$$0 \leqslant \rho_z \leqslant \min\left(\frac{\sigma_1}{\sigma_2}, \frac{\sigma_2}{\sigma_1}\right).$$

The proof of this statement is provided in Yashin and Iachine (1994, 1997).

Remark 4. When $\sigma_1^2 = \sigma_2^2 = \sigma^2$, the correlated frailty model is characterized by (5), with $\sigma^2 \equiv \theta$. This model has been used in the analysis of survival data on Danish twins (Yashin and Iachine, 1997).

Remark 5. Comparison of (5) and (13) shows that the semiparametric representation (5) can be derived using two radically different concepts; One uses the γ-transformation of the bivariate survival function (4). The other uses the correlated gamma-frailty model.

Remark 6. Let $\tilde{S}(x_1, x_2)$ be defined by (13). Then condition (14) becomes

$$-\frac{1}{\sigma^2} < \gamma < 0, \quad (14')$$

and hence, for such γ, survival function $\tilde{S}(x_1, x_2)$ corresponds to negatively correlated life spans. Thus for $\rho_z > \theta^{-1}$, Eq. (5) determines the bivariate survival function with such life spans. Figure 1 shows three graphs of the probability density function for model (5) with $\theta = 1$, and $\rho_z = 0.99$ (top left panel), $\rho_z = 0$ (bottom right panel), and $\rho_z = -0.99$ (bottom left panel). The effect of different frailty variances on the survival time distribution (model (15)) is shown on the top right panel of Fig. 1 for $\sigma_1 = 1$, $\sigma_2 = 2$, and $\rho_z = 0.5$. In all versions of the model the marginal survival function

$$S(x) = \left[1 + s^2\left(c(x - x_0) + \frac{a}{b}(e^{bx} - e^{bx_0})\right)\right]^{-1/s^2}, \quad (16)$$

with $a = 5 \times 10^{-5}$, $b = 0.1$, $c = 0.003$, $s = 0.3$, $x_0 = 0$ is used. One can see from these graphs that the higher the values of ρ_z, the closer the life spans of related individuals to each other. This effect is further illustrated on Fig. 2, which depicts the dependence of correlation between the life spans on the

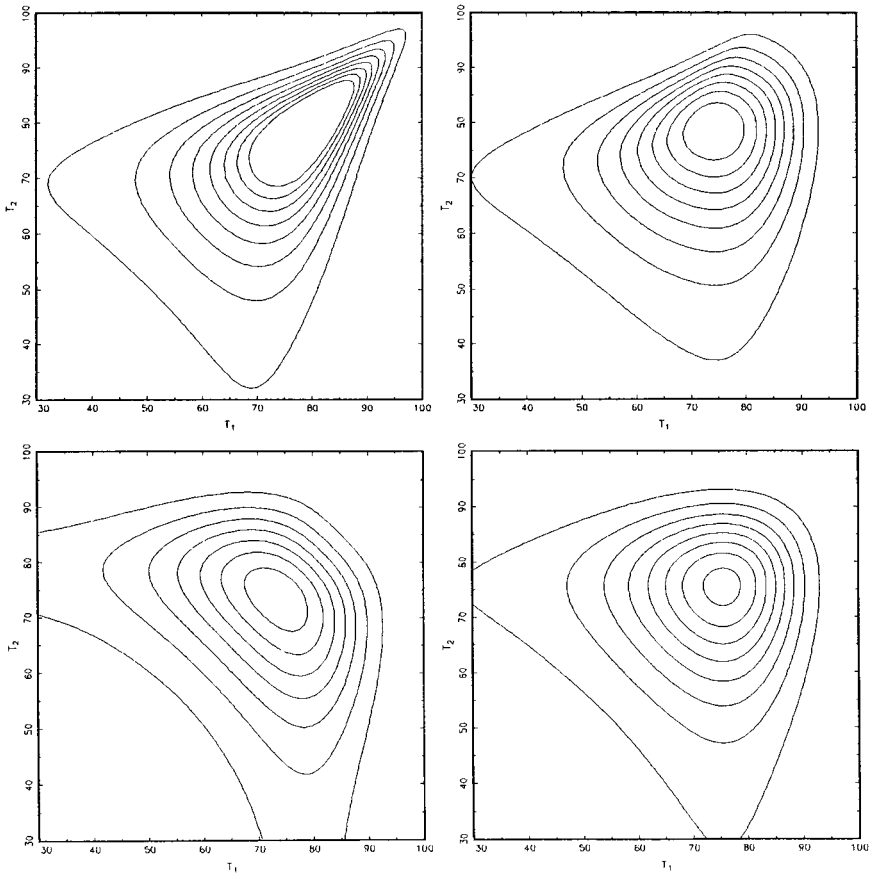

FIG. 1. Contour maps of the bivarite probability density functions corresponding to model (15) where $S(x) = S_1(x) = S_2(x)$ is defined by (16) with $a = S \times 10^{-5}$, $b = 0.1$, $c = 0.003$, $s = 0.3$, $x_0 = 0$. The parameters of the frailty distribution are $\sigma_1 = \sigma_2 = 1$, $\rho_z = 0.99$ (top left panel), $\sigma_1 = \sigma_2 = 1$, $\rho_z = -0.99$ (bottom left panel), $\sigma_1 = \sigma_2 = 1$, $\rho_z = 0$ (bottom right panel), and $\sigma_1 = 1$, $\sigma_2 = 2$, $\rho_z = 0.5$ (top right panel). Each contour line corresponds to a change in the probability density function of 0.0001.

association parameter γ for different values of parameter θ, which in the case $\gamma \geqslant 0$ is equal to the variance of the frailty distribution σ_Z^2. Here we use $a = 2.5 \times 10^{-5}$, $b = 0.11$, $c = 0.002$, $s = 0.3$, $x_0 = 30$ for the marginal distributions. The σ_z parameter is set to 0.5 (thick line), 1.0 (standard thickness line) and 1.5 (thin line) respectively. One can see from these graphs, that there is a monotonic relation between the correlation in lifespans and γ, with $\gamma = 0$ corresponding to zero correlation. Also, the effect of γ on the correlation depends on the value of σ_z, with greater effect for larger values of σ_z.

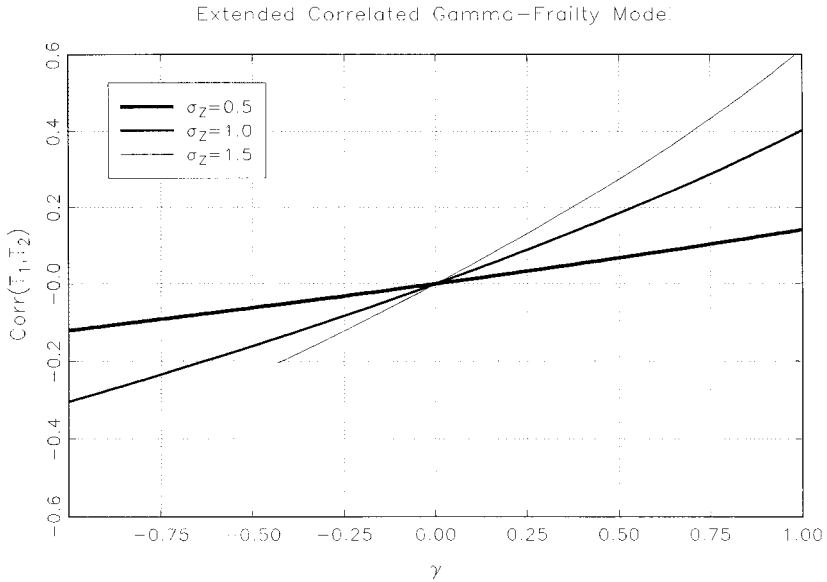

FIG. 2. Graphs of correlation coefficients between the survival times in model (13) as function of parameter γ, where $S(x) = S_1(x) = S_2(x)$ is defined by (16) with $a = 2.5 \times 10^{-5}$, $b = 0.11$, $c = 0.002$, $s = 0.3$, $x_0 = 30$. The ρ_z parameter ($\sigma_z = \theta^{1/2}$) is set to 0.5 (thick line), 1.0 (standard thickness line) and 1.5 (thin line), respectively.

Remark 7. The survival function (15) can be used in the analysis of survival data on unlike-sex twins, brothers and sisters, relatives from different generations, etc. This is because the distribution of individual frailty (susceptibility to death) may be different for males and females, or for individuals taken from different generations.

Remark 8. Using the definitions of hazards $\bar{\mu}_i(x_1, x_2)$ and $\tilde{\mu}_i(x_1, x_2)$ given by (1) and (2) we get in the case of correlated frailty model (15) with $\sigma_1 = \sigma_2 = \sigma$,

$$\bar{\mu}_i(x_1, x_2) = \bar{\mu}_i(x_i)\left(1 - \rho_z \frac{1 - S_j(x_j)^{-\sigma^2}}{1 - S_1(x_1)^{-\sigma^2} - S_2(x_2)^{-\sigma^2}}\right)$$

and

$$\tilde{\mu}_i(x_1; x_2) = \bar{\mu}_i(x_1, x_2) - \bar{\mu}_i(x_i)\,\rho_z\sigma^2 \times \frac{S_1(x_1)^{-\sigma^2} S_2(x_2)^{-\sigma^2}\left((1-\rho_z)(S_i(x_i)^{-\sigma^2} - 1) + S_j(x_j)^{-\sigma^2}\right)^{-1}}{1 - S_1(x_1)^{-\sigma^2} - S_2(x_2)^{-\sigma^2}}$$

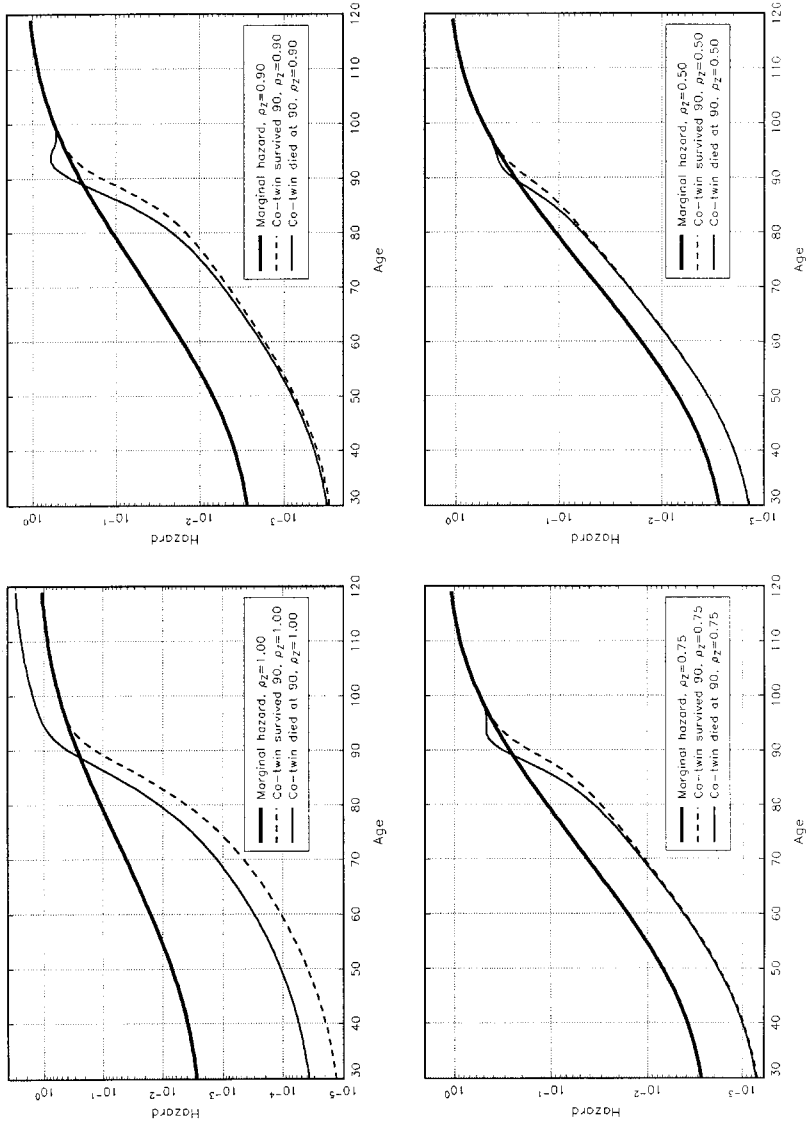

FIG. 3. Plots of marginal and conditional hazards (10), (1) and (2) respectively in the case of the correlated gamma-frailty model (5) where $S(x) = S_1(x) = S_2(x)$ is defined by (16) with $a = 2.5 \times 10^{-5}$, $b = 0.11$, $c = 0.002$, $s = 0.3$, $x_0 = 30$, and $\sigma_1 = \sigma_2 = 1.35$. The correlation coefficients of the frailty distribution are $\rho_z = 1.00$ (top left panel), $\rho_z = 0.90$ (top right panel), $\rho_z = 0.75$ (bottom left panel), and $\rho_z = 0.5$ (bottom right panel). Logarithmic scale is used for the y-axis. The graph of the marginal hazard $\bar{\mu}_1(x)$ is plotted with thick solid line, the graph of the conditional hazard $\bar{\mu}_1(x, 90)$ is plotted with thin dashed line and the graph of the conditional hazard $\tilde{\mu}_1(x, 90)$ is plotted with thin solid line.

$i, j = 1, 2$; $i \neq j$. The graphs of $\ln \bar{\mu}_1(x_1, x_2)$, $\ln \tilde{\mu}_1(x_1; x_2)$ and $\ln \bar{\mu}_1(x_1)$ are shown in Fig. 3 as functions of x_1 for the correlated gamma frailty model (13), with $\gamma = \rho_z$, $\theta = \sigma^2 = 1$, $x_2 = 90$ for four different values of ρ_z: $\rho_z = 1.00$ (top left panel), $\rho_z = 0.90$ (top right panel), $\rho_z = 0.75$ (bottom left panel), and $\rho_z = 0.50$ (bottom right panel). In these graphs, the marginal survival function (16) with parameter values as given in Remark 6 is used. The graphs show how mortality rate of one related individual (e.g., twin) may depend on survival status of other related individual (e.g., co-twin). One can see that when $\rho_z = 1$ (i.e., in the case of the shared frailty model) the distance between $\ln \bar{\mu}_i(x_1, x_2)$ and $\ln \tilde{\mu}_i(x_1; x_2)$ is constant (top left panel). Hence, these hazards are proportional (see Eq. (3)). There is no proportionality between these hazards, however (see three other panels in Fig. 3), when $\rho_z < 1$ (i.e., in the case of correlated frailty model). We see that the differences between the three conditional hazards, as expected, decrease with ρ_z, since lower values of ρ_z correspond to less dependence between the life spans. Also, the fact that one related individual (e.g., co-twin in the twin studies) survived beyond age 90 lowers the conditional hazard for the other twin at lower ages; however, the conditional hazard at ages higher than 90 virtually coincides with the marginal hazard.

3. MULTIVARIATE SURVIVAL FUNCTIONS

Multivariate survival functions for more than two survival times are often used in the analysis of dependent competing risks problem (David and Moeschberger, 1978). They are also important in the analysis of life (health) history data with several events (transitions between health states) and in the survival analysis of related individuals (e.g., twins and their relatives, family members, etc.). For example, the analysis of survival data on adopted children and their biological and adoptive parents requires a five-dimensional survival model (Nielsen *et al.*, 1992). It is clear that this model has to allow for different marginal survival functions for related individuals. For such multivariate situation the gamma frailty models can easily be extended.

3.1. *The Multivariate Correlated Gamma-Frailty Model*

Let T_i, $i = 1, 2, ..., n$, be the life spans of n related individuals, $\mu(Z_i, x) = Z_i \mu_{0i}(x)$ be their conditional individual hazards given frailties Z_i, $i = 1, 2, ..., n$, where $\mu_{0i}(x)$ are the underlying hazards with $H_i(x) = \int_0^x \mu_{0i}(u)\, du$, $i = 1, 2, ..., n$, and let life spans $T_1, ..., T_n$ be conditionally independent given frailties $Z_1, ..., Z_n$. The following statement gives the form of the multivariate survival function in one special case of multivariate frailty distribution.

THEOREM 4. *In the case of the proportional hazards of the n-variate survival model described above, there exists an n-variate frailty distribution with different marginals which allows for representation of the survival function* $S(x_1, x_2, ..., x_n)$ *as*

$$S(x_1, ..., x_n) = \left(1 + \sum_{i=1}^{n} \sigma_i^2 H_i(x_i)\right)^{-\rho_{ij}/\sigma_i\sigma_j} \prod_{i=1}^{n} (1 + \sigma_i^2 H_i(x_i))^{-(1/\sigma_i^2 - \rho_{ij}/\sigma_i\sigma_j)} \tag{17}$$

or in terms of the marginal univariate survival functions

$$S(x_1, ..., x_n) = \left(\sum_{i=1}^{n} S_i(x_i)^{-\sigma_i^2} - n + 1\right) \prod_{i=1}^{n} S_i(x_i)^{1-\sigma_i(\rho_{ij}/\sigma_j)}. \tag{18}$$

Here ρ_{ij} *are the correlation coefficients between* Z_i *and* Z_j, *and* σ_i^2 *are the variances of* Z_i, $i, j = 1, 2, ..., n$; $i \neq j$ *and* $\rho_{ij}/\sigma_i\sigma_j$ *is, in fact, a constant not depending on* i, j.

Remark 9. Representation (15) is a special case of (18) with $n = 2$.

Proof of Theorem 4. Let $Y_0, Y_1, ..., Y_n$ be $n+1$ independent gamma-distributed ($G(k_i, \lambda)$, $i = 0, ..., n$) random variables. Let us define a set of other random variables Z_i, $i = 1, 2, ..., n$ as follows: $Z_i = \alpha_i(Y_0 + Y_i)$, $i = 1, ..., n$, where α_i are positive real numbers with $\alpha_1 = 1$. It is easy to see that all Z_i are gamma-distributed dependent random variables. Let the distribution parameters for Y_i be $k_0 = \rho_{ij}/\sigma_i\sigma_j$, $i, j > 0$, $i \neq j$, $k_i = 1/\sigma_i^2 - \rho_{ij}/\sigma_i\sigma_j$, $i, j > 0$, $i \neq j$, $\lambda = 1/\sigma_1^2$, $\alpha_i = \sigma_i^2/\sigma_1^2$, where $\rho_{ij} \in [0, 1]$ and $\rho_{ij}/\sigma_i\sigma_j = \rho_{kl}/\sigma_k\sigma_l$, $i \neq j, k \neq l$, $i, j, k, l = 1, 2, ..., n$. The it can easily be shown that $E(Z_i) = 1$, $\mathrm{Var}(Z_i) = \sigma_i^2$, $\mathrm{Corr}(Z_i, Z_j) = \rho_{ij}$, $i \neq j$. The requirement $k_i > 0$, $i = 0, ..., n$ implies that $\rho_{ij}/\sigma_j\sigma_j < \min\{1/\sigma_i^2, i = 1, 2, ..., n\}$. Since for each T_i, $i = 1, 2, ..., n$, the conditional survival function given Z_i, $i = 1, 2, ..., n$ is

$$S(x_i \mid Z_i) = e^{-Z_i H_i(x_i)} = e^{-\alpha_i(Y_0 + Y_i) H_i(x)},$$

and T_i, $i = 1, 2, ..., n$ are conditionally independent given Z_i, $i = 1, 2, ..., n$, the multivariate survival function can be calculated as a mathematical expectation

$$\begin{aligned} S(x_1, x_2, ..., x_n) &= E(S(x_1, x_2, ..., x_n \mid Z_1, Z_2, ..., Z_n)) \\ &= E(e^{-\sum_{i=1}^{n} \alpha_i H_i(x)\ Y_0 - \sum_{i=1}^{n} \alpha_i H_i(x)\ Y_i}). \end{aligned}$$

This latter term is a product of the Laplace transforms of independent gamma-distributed random variables:

$$S(x_1, ..., x_n) = \left(1 + \frac{1}{\lambda} \sum_{i=1}^{n} \alpha_i H_i(x_i)\right)^{-k_0} \prod_{i=1}^{n} \left(1 + \frac{1}{\lambda} \alpha_i H_i(x_i)\right)^{-k_i}. \tag{19}$$

After re-parametrization we get (17). Note that each marginal univariate survival function here can be represented as

$$S_i(x_i) = (1 + \sigma_i^2 H_i(x_i))^{-1/\sigma_i^2}. \tag{20}$$

Replacing $H_i(x_i)$ in (17) by the expressions calculated from (20) yields (18).

Remark 10. Note that a relationship between variances and correlation coefficients of vector $Z = (Z_1, Z_2, ..., Z_n)^*$ stems from the fact that the covariance matrix for Z is nonnegative-definite. An additional requirement, $\rho_{ij}/\sigma_i\sigma_j = \rho_{kl}/\sigma_k\sigma_l$, $i, j, k, l = 1, 2, ..., n$, follows from the derivation of (17). Such a requirement may be rather restrictive when estimating life span correlations from real data for $n > 2$. This means that when maximizing the likelihood function of multivariate survival data, one must take into account the constraints, which relate different correlation coefficients and standard deviations of multivariate frailty distribution. One of such constraints is illustrated by the graph in Fig. 4 for the case $n = 2$. This graph shows the maximum allowed correlation coefficient of frailty for different values of σ_1, σ_2. One can see from the graph, that maximum range of the correlation is attained when the standard deviations of frailty have the

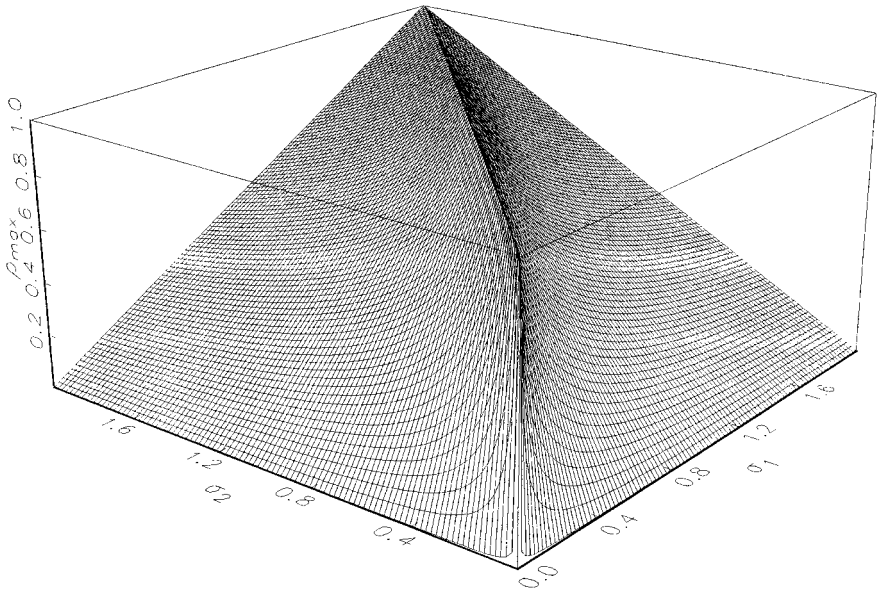

FIG. 4. Three-dimensional plot of the maximal possible value of the correlation coefficient in frailty $\rho_{\max}$ in model (15) as function of standard deviations of frailty σ_1, σ_2, calculated using the equation $\rho_{\max} = \min(\sigma_1/\sigma_2, \sigma_2/\sigma_1)$.

same magnitudes and that this range decreases rapidly when σ_1, σ_2 become different.

Remark 11. When the marginal frailty distributions in model (17) are identical (i.e., $\sigma_i = \sigma, i = 1, ..., n$), and all associations among frailty variables in the multivariate frailty model are described by one parameter ρ_z, representations (17) and (18) become

$$S(x_1, x_2, ..., x_n) = \prod_{i=1}^{n} (1 + \sigma^2 H_i(x_i))^{-(1-\rho_z)/\sigma^2} \left(1 + \sigma^2 \sum_{i=1}^{n} H_i(x_i)\right)^{-\rho_z/\sigma^2} \tag{21}$$

and

$$S(x_1, x_2, ..., x_n) = \prod_{i=1}^{n} S_i(x_i)^{1-\rho_z} \left(\sum_{i=1}^{n} S_i(x_i)^{-\sigma^2} - n + 1\right)^{-\rho_z/\sigma^2}. \tag{22}$$

The frailty model corresponding to the survival function (21) was also considered by Petersen *et al.* (1996) who used an alternative parameterization of the multivariate frailty distribution in terms of the variances of the additive components of frailty. A parameterization in terms of the correlation coefficient ρ_z and total variance σ^2, however, may be more advantageous in genetic studies of longevity, where analysis of correlations plays a crucial role (Yashin and Iachine, 1995b). In particular, representation (21) allows for direct computation of likelihood based confidence intervals for ρ_z.

Remark 12. Formulas (21) and (22) extend the multivariate shared frailty model ($\rho_z = 1$) used by Cook and Johnson (1981) to the correlated frailty case.

The approximations of $S(x_1, ..., x_n)$ for small and large values of σ^2 can be obtained using the following statement.

THEOREM 5. *Assume that in the representation* (22) $\sigma^2 \downarrow 0$. *Then*

$$S(x_1, x_2, ..., x_n) \xrightarrow[\sigma^2 \downarrow 0]{} S_1(x_1)\, S_2(x_2) \ldots S_n(x_n). \tag{23}$$

If $\sigma^2 \uparrow \infty$, *then*

$$S(x_1, x_2, ..., x_n) \xrightarrow[\sigma^2 \uparrow \infty]{} \prod_{i=1}^{n} S_i(x_i)^{1-\rho_z} (\min(S_1(x_1), ..., S_n(x_n)))^{\rho_z}. \tag{24}$$

Proof of Theorem 5. To prove (23), it is enough to show that $\ln S(x_1, x_2, ..., x_n) \xrightarrow[\sigma^2 \downarrow 0]{} \sum_{i=1}^{n} \ln S_i(x_i)$.

We have

$$\ln S(x_1, x_2, ..., x_n) = (1-\rho_z) \sum_{i=1}^{n} \ln S_i(x_i) - \frac{\rho_z}{\sigma^2} \ln \left(\sum_{i=1}^{n} S_i(x_i)^{-\sigma^2} - n + 1 \right).$$

Result (23) follows from applying L'Hôpitale's rule to the term

$$-\frac{\rho_z}{\sigma^2} \ln \left(\sum_{i=1}^{n} S_i(x_i)^{-\sigma^2} - n + 1 \right).$$

Let k be such that $S_k(x_k) \leqslant S_j(x_j)$, $j \neq k$. Then

$$\begin{aligned} &S(x_1, x_2, ..., x_n) \\ &\quad = \prod_{i \neq k}^{n} S_i(x_i)^{1-\rho_z} S_k(x_k) \left(\sum_{i \neq k}^{n} \left(\frac{S_k(x_k)}{S_i(x_i)} \right)^{\sigma^2} - (n-1) S_k(x_k)^{\sigma^2} + 1 \right)^{-\rho_z/\sigma^2} \\ &\quad \xrightarrow[\sigma^2 \uparrow \infty]{} \prod_{i \neq k}^{n} S_i(x_i)^{1-\rho_z} S_k(x_k) \end{aligned}$$

which proves (24).

4. CONCLUSION

Multivariate survival distributions are used in the analysis of dependent durations such as age at onset of diseases or life spans of related individuals, spells of unemployment in economics, dependent competing risks, etc. In a special class of such distributions, multivariate survival functions are represented by their marginals. We show that an important class of such functions can be derived using the concept of random hazards. We suggest a simple transformation of bivariate survival functions which preserves their marginal distributions, and show that the same semiparametric representation of bivariate survival functions can be derived using radically different concepts. Using the suggested transformation we extend the class of models with positive association between the random hazards to allow for negatively correlated survival times. A multivariate extension of the correlated frailty model is derived which can be used in the analysis of survival data for several related individuals. The semiparametric structure of the multivariate survival function allows for the development of semiparametric estimation strategies, and the presence of the correlation coefficients of frailty among the parameters of the models makes such models appropriate for genetic-epidemiological studies of individual susceptibility to disease and death.

APPENDIX

Proof of Theorem 1. If follows from (10) that $\tilde{S}(x_1, 0) = S(x_1)$ and $\tilde{S}(0, x_2) = S(x_2)$, and that $\tilde{S}(x_1, \infty) = \tilde{S}(\infty, x_2) = \tilde{S}(\infty, \infty) = 0$. Hence, $\tilde{A}(x_1, x_2) = \gamma A(x_1, x_2)$. To complete the proof it is enough to show that $\partial^2 \tilde{S}(x_1, x_2)/\partial x_1 \partial x_2 \geqslant 0$. From representation (11) we get

$$\tilde{S}''_{12}(x_1, x_2) = \tilde{S}(x_1, x_2) \times [(\gamma A'_1(x_1, x_2) - \bar{\mu}_1(x_1))(\gamma A'_2(x_1, x_2) - \bar{\mu}_2(x_2)) + \gamma A''_{12}(x_1, x_2)], \tag{25}$$

where

$$\tilde{S}''_{12}(x_1, x_2) = \frac{\partial^2 \tilde{S}(x_1, x_2)}{\partial x_1 \partial x_2}; \qquad A'_i(x_1, x_2) = \frac{\partial A(x_1, x_2)}{\partial x_i}, \qquad i = 1, 2;$$

$$A''_{12}(x_1, x_2) = \frac{\partial^2 A(x_1, x_2)}{\partial x_1 \partial x_2},$$

and $\bar{\mu}_i(x_i) = E(\mu_i(Z_i, x_i) \mid T_i > x_i)$, $i = 1, 2$. The use of representation (6) together with definitions (9) and (10) yields the following relationship between two conditional hazards $\bar{\mu}_i(x_i), \bar{\mu}_i(x_1, x_2)$, $i = 1, 2$, and the partial derivative of $A(x_1, x_2)$;

$$A'_i(x_1, x_2) = \bar{\mu}_i(x_i) - \bar{\mu}_i(x_1, x_2), \qquad i = 1, 2. \tag{26}$$

Note that if $\varphi(x_1, x_2) > 0$, then $\bar{\mu}_i(x_i) > \bar{\mu}_i(x_1, x_2)$.

Taking into account that $A''_{12}(x_1, x_2) = \varphi(x_1, x_2)$, we can rewrite (25) in the form

$$\tilde{S}''_{12}(x_1, x_2) = \tilde{S}(x_1, x_2) \times [(\gamma(\bar{\mu}_1(x_1) - \bar{\mu}_1(x_1, x_2)) - \bar{\mu}_1(x_1)) \times (\gamma(\bar{\mu}_2(x_2) - \bar{\mu}_2(x_1, x_2)) - \bar{\mu}_2(x_2)) + \gamma\varphi(x_1, x_2)]. \tag{27}$$

Note that when $\gamma = 1$ the right hand side of (25) is non-negative for all $x_1, x_2 \geqslant 0$, since

$$(\gamma(\bar{\mu}_1(x_1) - \bar{\mu}_1(x_1, x_2)) - \bar{\mu}_1(x_1))(\gamma(\bar{\mu}_2(x_2) - \bar{\mu}_2(x_1, x_2)) - \bar{\mu}_2(x_2))|_{\gamma=1} = \bar{\mu}_1(x_1, x_2)\, \bar{\mu}_2(x_1, x_2) \geqslant 0 \tag{28}$$

and by the assumption $\varphi(x_1, x_2) \geqslant 0$ in the theorem. For any $0 \leqslant \gamma \leqslant 1$, the terms $\gamma(\bar{\mu}_i(x_1) - \bar{\mu}_i(x_1, x_2)) - \bar{\mu}_i(x_i)$, $i = 1, 2$ are always non-positive. Hence

their product (which appears in formula (25)) is non-negative, which completes the proof of Theorem 1.

Proof of Theorem 2. Note that for any $\gamma < 0$ we have

$$(\gamma(\bar{\mu}_1(x_1) - \bar{\mu}_1(x_1, x_2)) - \bar{\mu}_1(x_1))(\gamma(\bar{\mu}_2(x_2) - \bar{\mu}_2(x_1, x_2)) - \bar{\mu}_2(x_2)) \geqslant \bar{\mu}_1(x_1)\,\bar{\mu}_2(x_2) \geqslant 0$$

and, hence (26) yields

$$\tilde{S}''_{12}(x_1, x_2) \geqslant \tilde{S}(x_1, x_2)[\bar{\mu}_1(x_1)\,\bar{\mu}_2(x_2) + \gamma\varphi(x_1, x_2)].$$

Thus, $\tilde{S}''_{12}(x_1, x_2)$ is non-negative when γ satisfies (14), and hence, for the negative values of γ satisfying (14), $\tilde{S}(x_1, x_2)$ is a bivariate survival function. The covariance of $\tilde{T}_1$, $\tilde{T}_2$ is

$$\mathrm{Cov}(\tilde{T}_1, \tilde{T}_2) = \int_0^\infty \int_0^\infty \tilde{S}(u, v)\,du\,dv - \int_0^\infty \int_0^\infty S_1(u)\,S_2(v)\,du\,dv.$$

Using representation (11) for $\tilde{S}(x_1, x_2)$ we get

$$\mathrm{Cov}(\tilde{T}_1, \tilde{T}_2) = \int_0^\infty \int_0^\infty S_1(u)\,S_2(v)(e^{\gamma A(u, v)} - 1)\,du\,dv.$$

So, if $A(u, v) > 0$, then the sign of $\mathrm{Cov}(\tilde{T}_1, \tilde{T}_2)$ coincides with the sign of γ. This completes the proof of Theorem 2.

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