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RANDOM EFFECT BIVARIATE SURVIVAL MODELS AND STOCHASTIC COMPARISONS

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Abstract

In this paper we propose a general bivariate random effect model with special emphasis on frailty models and environmental effect models, and present some stochastic comparisons. The relationship between the conditional and the unconditional hazard gradients are derived and some examples are provided. We investigate how the well-known stochastic orderings between the distributions of two frailties translate into the orderings between the corresponding survival functions. These results are used to obtain the properties of the bivariate multiplicative model and the shared frailty model.

Keywords: Frailty model; environmental effect model; hazard gradient; bivarate multiplicative model; shared frailty model

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1. Introduction

Random effect models have been widely used in the context of linear models. In linear models, the random effect is introduced as the error variable and the distribution of this error variable is reflected in the parameter estimates and other inferential problems. Besides this, the random effect models have been used in survival analysis to model the heterogeneity unexplained by the covariates. In assessing the effect of environmental factors, these models have been used as random environmental models. The dependence structure created by the random effects in survival analysis is quite different than in the linear models. Recently, Rizopoulos *et al.* (2008), using the random effect model, investigated the association structure between a longitudinal response process and the time to an event of interest using the shared parameter framework.

As explained above, random effect models are used in different disciplines. We will present our results in the context of survival analysis or, more specifically, in the context of frailty models where the frailty is modeled as an unobservable random effect. Clayton (1978) and Clayton and Cuzick (1985) introduced the proportional hazard frailty model, where a group of observations is assigned a random effect that acts multiplicatively on the baseline hazard function. The proportional hazard frailty model implies conditional independence—conditional on the frailty terms, the event times are independent. However, unconditionally, they are dependent.

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1.1. Frailty models

As is well known, a particularly useful tool in handling heterogeneity unexplained by the observed covariates is the 'frailty model', introduced in Vaupel *et al.* (1979). The classical frailty model is given by

$$\lambda(t \mid v) = v\lambda_0(t), \qquad t > 0, \tag{1.1}$$

where $\lambda_0(t)$ is the baseline hazard independent of v.

Model (1.1) states that the hazard rate of an individual is the product of the individual specific quantity v and the baseline hazard rate $\lambda_0(t)$ describing the age effect. We consider $v\lambda_0(t)$ to be the conditional failure rate of a random variable T given $V = v$, where V is the frailty or mixing random variable. Frailty models have often been used when groups of subjects have responses that are likely to be dependent in some general way. For example, in an animal carcinogeneity study, the responses of members of the same litter are not likely to be independent. Liang *et al.* (1995) discussed the use of frailty models when multiple events have been observed on the same subject.

It is well known that the choice of frailty distribution strongly affects the estimate of the baseline hazard as well as the conditional probabilities; see Hougaard (1984), (1991), (1995), (2000, pp. 213–262), Heckman and Singer (1984), and Agresti *et al.* (2004). Since different distributions of frailty give rise to different population level distributions of analyzing survival data, it is appropriate to investigate how the comparative effect of two frailties translates into the comparative effect on the resulting distributions. In the shared frailty models, the assumptions about the frailty distributions play an important role in the model's interpretation since the frailty distribution links the two processes of interest. For more discussion, see Rizopoulos *et al.* (2008) and Sargent (1998). In this connection, in the univariate case, Gupta and Kirmani (2006) investigated how well-known stochastic orderings between distributions of two frailties translate into orderings between the corresponding survival functions. More recently, in the univariate case, Gupta and Gupta (2009) studied a similar problem for a general frailty model which includes the classical frailty model (1.1) as well as the additive frailty model. It may be mentioned that, in the univariate setup, the above two papers reached results similar to the ones contained in the present paper.

For model (1.1), the population level hazard function is given by

$$\lambda(t) = -\frac{\mathrm{d}}{\mathrm{d}t} \ln \bar{F}(t),$$

where

$$\bar{F}(t) = \mathrm{P}(T > t) = M_V(-\Lambda_0(t)),$$

$M_V(\cdot)$ denotes the moment generating function of V, and $\Lambda_0(t) = \int_0^t \lambda_0(x)\,\mathrm{d}x$.

The overall population hazard function $\lambda(t)$ is related to the baseline hazard function $\lambda_0(t)$ by the relation

$$\lambda(t) = \lambda_0(t)\,\mathrm{E}(V \mid T > t).$$

Since

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{E}(V \mid T > t) = -\lambda_0(t)\,\mathrm{var}(V \mid T > t)$$

(see Gupta and Gupta (1996)), $\lambda(t)/\lambda_0(t)$ is a decreasing function of t. It can be seen that if $\mathrm{E}(V) \le 1$ then $\lambda(t) \le \lambda_0(t)$, $t > 0$, or, equivalently, $\bar{G}(t)/\bar{F}(t)$ is decreasing on $[0, \infty)$, where $\bar{G}(t)$ is the baseline survival function. In order to avoid identifiability problems, it is generally assumed that $\mathrm{E}(V) = 1$. In the case of gamma frailty, see Hougaard (2000, p. 233).

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In this paper we study a general bivariate frailty model and present some stochastic comparisons using different distributions of the frailty. To this end, we define the bivariate hazard functions as follows.

Let T_1 and T_2 be two dependent random variables having absolutely continuous bivariate survival function $\bar{F}(t_1, t_2) = \mathrm{P}(T_1 > t_1,\ T_2 > t_2)$. Then the hazard (failure) rates, defined as

$$\lambda^{(i)}(t_1, t_2) = -\frac{\partial}{\partial t_i} \ln \bar{F}(t_1, t_2), \qquad i = 1, 2,$$

are often used in demography, survival analysis, and biostatistics when analyzing bivariate survival data. Clearly, $\lambda^{(1)}(t_1, t_2)$ is the hazard rate of T_1 given $T_2 > t_2$. Likewise, $\lambda^{(2)}(t_1, t_2)$ is the hazard rate of T_2 given $T_1 > t_1$. The vector $(\lambda^{(1)}(t_1, t_2), \lambda^{(2)}(t_1, t_2))$ is called the hazard gradient. It is well known that the hazard gradient uniquely determines the survival function. Thus, we consider the general bivariate frailty model

$$\lambda^{(i)}(t_1, t_2 \mid v) = \lambda^{(i)}(t_1, t_2, v), \qquad i = 1, 2, \tag{1.2}$$

where v is the frailty associated with an individual.

As mentioned earlier, our aim in this paper is to develop the properties of the general bivariate frailty model (1.2) and obtain some results for the stochastic comparisons using different frailty distributions. As a special case, we will obtain results for the classical bivariate frailty model and the shared frailty model. The organization of this paper is as follows. After giving the aims and objectives together with the necessary definitions and background, we describe the general bivariate frailty model along with some of the properties in Section 2. In Section 3, our main results lie in seeing how the well-known stochastic orderings between distributions of two frailties translate into the orderings between the corresponding survival functions. These results are used, in Section 4, to investigate the stochastic order properties of the multiplicative model and the shared frailty model. Finally, some conclusions and comments are given in Section 5.

Before proceeding further, we present some definitions and background for various stochastic comparisons.

Definition. Let X and Y be nonnegative absolutely continuous random variables with density functions $f(x)$ and $g(x)$, and survival functions $\bar{F}(x)$ and $\bar{G}(x)$, respectively. Then X and Y can be defined as follows.

(i) X is said to be smaller than Y in the likelihood ratio ordering, written as $X \le_{\mathrm{lr}} Y$, if $f(x)/g(x)$ is nonincreasing in x.

(ii) X is said to be smaller than Y in the failure (hazard) rate ordering, written as $X \le_{\mathrm{fr}} Y$, if $r_F(x) \ge r_G(x)$ for all x, where $r_F(x)$ and $r_G(x)$ are the hazard rates of X and Y, respectively. This means that $\bar{G}(x)/\bar{F}(x)$ increases in x.

(iii) X is said to be smaller than Y in the stochastic ordering, written as $X \le_{\mathrm{st}} Y$, if $\bar{F}(x) \le \bar{G}(x)$ for all x.

(iv) X is said to be smaller than Y in the mean residual life ordering, written as $X \le_{\mathrm{mrl}} Y$, if $\mu_F(x) \le \mu_G(x)$ for all x. Deshpande *et al.* (1990) showed that $X \le_{\mathrm{mrl}} Y$ if and only if $\int_x^\infty \bar{F}(u)\,\mathrm{d}u / \int_x^\infty \bar{G}(u)\,\mathrm{d}u$ is decreasing in x.

(v) Let X and Y be n-dimensional random vectors with hazard gradients

$$(\lambda_X^{(1)}(x), \lambda_X^{(2)}(x), \dots, \lambda_X^{(n)}(x)) \quad \text{and} \quad (\lambda_Y^{(1)}(y), \lambda_Y^{(2)}(y), \dots, \lambda_Y^{(n)}(y)),$$

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respectively. Then $X \leq_{\text{whr}} Y$ (weak hazard rate order) if $\lambda_X^{(i)}(t) \geq \lambda_Y^{(i)}(t)$, $i = 1, 2, \ldots, n$ and $t \in \mathbb{R}^n$; see Shaked and Shanthikumar (2007, p. 271). Note that this condition is weaker than the hazard rate orderings of vectors.

The following relations are well known:

$$\begin{array}{ccccc} X \leq_{\text{lr}} Y & \Longrightarrow & X \leq_{\text{fr}} Y & \Longrightarrow & X \leq_{\text{mrl}} Y \\ & & \Downarrow & & \\ & & X \leq_{\text{st}} Y; & & \end{array}$$

see Shaked and Shanthikumar (2007, p. 271).

2. General bivariate frailty model

Consider a general bivariate frailty model defined by the absolutely continuous joint survival function $\bar{F}(t_1, t_2 \mid v)$, of a two-unit system, where v is the frailty effect associated with the two variables. Define

$$\begin{aligned} \lambda^{(i)}(t_1, t_2 \mid v) &= -\frac{\partial}{\partial t_i} \ln \bar{F}(t_1, t_2 \mid v) \\ &= -\frac{\partial}{\partial t_i} \ln \bar{F}(t_i \mid T_j > t_j, v) \\ &= \frac{f(t_i \mid T_j > t_j, v)}{\bar{F}(t_i \mid T_j > t_j, v)}, \qquad i, j = 1, 2,\ i \neq j. \end{aligned}$$

That is, $\lambda^{(i)}(t_1, t_2 \mid v)$ is the failure rate function of the ith unit with the jth $(i \neq j)$ unit surviving until time t_j, conditional on the frailty variable V.

If $h(v)$ denotes the probability density function (PDF) of the random environmental effect V, then the unconditional joint PDF and the survival function are

$$f(t_1, t_2) = \int_0^\infty f(t_1, t_2 \mid v) h(v) \, \mathrm{d}v$$

and

$$\bar{F}(t_1, t_2) = \int_0^\infty \bar{F}(t_1, t_2 \mid v) h(v) \, \mathrm{d}v,$$

respectively. These functions are known as the population level joint density and survival functions. The population level failure rate functions are defined as

$$\begin{aligned} \lambda^{(i)}(t_1, t_2) &= -\frac{\partial}{\partial t_i} \ln \bar{F}(t_1, t_2) \\ &= -\frac{\partial}{\partial t_i} \ln \bar{F}(t_i \mid T_j > t_j) \\ &= \frac{f(t_i \mid T_j > t_j)}{\bar{F}(t_i \mid T_j > t_j)}, \qquad i, j = 1, 2,\ i \neq j. \end{aligned}$$

In the following, we show that the population level hazard components are the averages of the conditional hazard components.

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Theorem 2.1. *The population level failure rate function of the ith unit in a two-unit system with the jth unit of fixed age t_j is the expected value of $\lambda^{(i)}(t_1, t_2 \mid v)$ with respect to the conditional distribution of the frailty effect V given $T_1 > t_1$ and $T_2 > t_2$. That is,*

$$\lambda^{(i)}(t_1, t_2) = \mathrm{E}_{V \mid \{T_1 > t_1,\, T_2 > t_2\}}(\lambda^{(i)}(t_1, t_2 \mid v)), \qquad i = 1, 2.$$

It is assumed that the conditional distribution of V given $T_1 > t_1$ and $T_2 > t_2$ is absolutely continuous, so that the conditional density exists.

Proof. We first show that

$$h(v \mid T_1 > t_1,\ T_2 > t_2) = \frac{\bar{F}(t_i \mid T_j > t_j, v)h(v)}{\bar{F}(t_i \mid T_j > t_j)}, \tag{2.1}$$

where $h(v \mid T_1 > t_1,\ T_2 > t_2)$ is the conditional density of V among survivors.

We have

$$\begin{aligned}
h(v \mid T_1 > t_1,\ T_2 > t_2) &= \frac{-(\partial/\partial v)\,\mathrm{P}(V > v,\ T_1 > t_1,\ T_2 > t_2)}{\mathrm{P}(T_1 > t_1,\ T_2 > t_2)} \\
&= \frac{-(\partial/\partial v)\,\mathrm{P}(V > v,\ T_i > t_i \mid T_j > t_j)}{\mathrm{P}(T_i > t_i \mid T_j > t_j)} \\
&= \frac{-(\partial/\partial v)\int_v^\infty \int_{t_i}^\infty f(u, x_i \mid T_j > t_j)\,\mathrm{d}x_i\,\mathrm{d}u}{\bar{F}(t_i \mid T_j > t_j)} \\
&= \frac{-(\partial/\partial v)\int_v^\infty \int_{t_i}^\infty f(x_i \mid T_j > t_j, u)h(u)\,\mathrm{d}x_i\,\mathrm{d}u}{\bar{F}(t_i \mid T_j > t_j)} \\
&= \frac{-(\partial/\partial v)\int_v^\infty \bar{F}(x_i \mid T_j > t_j, u)h(u)\,\mathrm{d}u}{\bar{F}(t_i \mid T_j > t_j)} \\
&= \frac{\bar{F}(t_i \mid T_j > t_j, v)h(v)}{\bar{F}(t_i \mid T_j > t_j)}, \qquad i, j = 1, 2,\ i \neq j.
\end{aligned}$$

Therefore,

$$\begin{aligned}
\lambda^{(i)}(t_1, t_2) &= \frac{f(t_i \mid T_j > t_j)}{\bar{F}(t_i \mid T_j > t_j)} \\
&= \frac{\int_0^\infty f(t_i \mid T_j > t_j, v)h(v)\,\mathrm{d}v}{\bar{F}(t_i \mid T_j > t_j)} \\
&= \int_0^\infty \lambda^{(i)}(t_1, t_2 \mid v)\frac{\bar{F}(t_i \mid T_j > t_j, v)h(v)\,\mathrm{d}v}{\bar{F}(t_i \mid T_j > t_j)} \\
&= \int_0^\infty \lambda^{(i)}(t_1, t_2 \mid v)h(v \mid T_1 > t_1, T_2 > t_2)\,\mathrm{d}v,
\end{aligned}$$

using (2.1). Thus, we have shown that

$$\lambda^{(i)}(t_1, t_2) = \mathrm{E}_{V \mid \{T_1 > t_1,\, T_2 > t_2\}}(\lambda^{(i)}(t_1, t_2 \mid v)), \qquad i = 1, 2.$$

Under a very mild condition, the following result addresses the monotonicity of the distribution (survival) function of the random effect as a function of the ages of the two units.

Theorem 2.2. *If $\lambda^{(i)}(t_1, t_2 \mid v)$ is an increasing function of v, $i = 1, 2$, then $H(v \mid T_1 > t_1,\ T_2 > t_2)$ and $\bar{H}(v \mid T_1 > t_1,\ T_2 > t_2)$ are increasing and decreasing functions of t_i, respectively, where*

$$H(v \mid T_1 > t_1,\ T_2 > t_2) = \frac{\int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u}{\bar{F}(t_i \mid T_j > t_j)}, \qquad i, j = 1, 2,\ i \neq j,$$

is the conditional cumulative distribution function of the frailty variable among survivors and $\bar{H} = 1 - H$.

Proof. We have

$$\begin{aligned}
\frac{\partial}{\partial t_i} H(v \mid T_1 > t_1,\ T_2 > t_2) &= \frac{\int_0^v (\partial/\partial t_i)\bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u}{\bar{F}(t_i \mid T_j > t_j)} \\
&\quad - \frac{(\partial/\partial t_i)\bar{F}(t_i, T_j > t_j)}{[\bar{F}(t_i, T_j > t_j)]^2} \int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u \\
&= \frac{\int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u}{\bar{F}(t_i \mid T_j > t_j)} [-A(v) + A(\infty)],
\end{aligned}$$

where

$$A(v) = \frac{\int_0^v \lambda^{(i)}(t_1, t_2 \mid u) \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u}{\int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u}.$$

We now show that $A(v)$ is increasing in $v > 0$. We have

$$\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}v} A(v) &= \frac{1}{(\int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u)^2} \\
&\quad \times \biggl(\biggl(\int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u\biggr) \lambda^{(i)}(t_1, t_2 \mid v) \bar{F}(t_i \mid T_j > t_j, v) h(v) \\
&\qquad - \bar{F}(t_i \mid T_j > t_j, v) h(v) \int_0^v \lambda^{(i)}(t_1, t_2 \mid u) \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u\biggr) \\
&= \frac{\bar{F}(t_i \mid T_j > t_j, v) h(v)}{(\int_0^v \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u)^2} \\
&\quad \times \biggl(\int_0^v \{\lambda^{(i)}(t_1, t_2 \mid v) - \lambda^{(i)}(t_1, t_2 \mid u)\} \bar{F}(t_i \mid T_j > t_j, u) h(u)\,\mathrm{d}u\biggr) \\
&> 0,
\end{aligned}$$

since $\lambda^{(i)}(t_1, t_2 \mid v) > \lambda^{(i)}(t_1, t_2 \mid u)$ for all $u < v$.

Corollary 2.1. *If $\lambda^{(i)}(t_1, t_2 \mid v)$ is an increasing function of v, $i = 1, 2$, then $\mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2)$ is decreasing in t_i, $i = 1, 2$.*

Proof. The hypothesis implies that $\bar{H}(v \mid T_1 > t_1,\ T_2 > t_2)$ is decreasing in $t_i > 0$. Thus,

$$\mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2) = \int_0^\infty \bar{H}(v \mid T_1 > t_1, T_2 > t_2)\,\mathrm{d}v$$

is decreasing in $t_i > 0$, $i = 1, 2$.

Remark 2.1. The statement of Corollary 2.1 is a precise statement of the heuristically obvious fact that the weaker units in the population fail earlier than the others, so the remaining units are more robust than the rest.

Remark 2.2. The condition $\lambda^{(i)}(t_1, t_2 \mid v)$ is an increasing function of v will be satisfied by all the examples considered in the later sections.

The following results compare the frailty distribution of two groups, one with $T_i > t_{i1}$ and $T_j > t_j$, and the other with $T_i > t_{i2}$ and $T_j > t_j$, where $t_{i1} < t_{i2}$, $i, j = 1, 2$, $i \neq j$.

Theorem 2.3. *If $\lambda^{(i)}(t_1, t_2 \mid v)$ is an increasing function of v then*

$$V \mid \{T_i > t_{i2},\ T_j > t_j\} \leq_{\mathrm{lr}} V \mid \{T_i > t_{i1},\ T_j > t_j\}, \qquad 0 < t_{i1} < t_{i2},\ i = 1, 2.$$

Proof. We have

$$\begin{aligned}\frac{h(v \mid T_i > t_{i2},\ T_j > t_j)}{h(v \mid T_i > t_{i1},\ T_j > t_j)} &= \frac{\bar{F}(t_{i2} \mid T_j > t_j, v)h(v)}{\bar{F}(t_{i1} \mid T_j > t_j, v)h(v)} \frac{\bar{F}(t_{i1} \mid T_j > t_j)}{\bar{F}(t_{i2} \mid T_j > t_j)} \\ &= \exp\biggl\{-\int_{t_{i1}}^{t_{i2}} \lambda^{(i)}(t_1, t_2)\,\mathrm{d}t_i\biggr\} \frac{\bar{F}(t_{i1} \mid T_j > t_j)}{\bar{F}(t_{i2} \mid T_j > t_j)}.\end{aligned}$$

Since $\lambda^{(i)}(t_1, t_2 \mid v)$ is an increasing function of $v, h(v \mid T_i > t_{i2},\ T_j > t_j)/h(v \mid T_i > t_{i1},\ T_j > t_j)$ is decreasing in v. This means that the family of random variables $V \mid \{T_i > t_i,\ T_j > t_j\}$ is decreasing in $t_i > 0$ in the sense of the likelihood ratio.

We now present a general result comparing a random variable with its weighted version.

Lemma 2.1. *Let V_1 and V_2 be two random variables with density functions $h_1(\cdot)$ and $h_2(\cdot)$ such that*

$$h_2(v) = \frac{g(v)h_1(v)}{\int_0^\infty g(v)h_1(v)\,\mathrm{d}v},$$

where if $g(v)$ is a decreasing function of v then $V_1 \geq_{\mathrm{lr}} V_2$, and if $g(v)$ is an increasing function of v then $V_1 \leq_{\mathrm{lr}} V_2$.

Proof. Since $h_2(v)/h_1(v)$ is nonincreasing in v, the result follows by definition.

The following result shows how the ordering between two frailties is preserved for surviving individuals.

Theorem 2.4. *Let V_1 and V_2 be two frailty random variables such that $V_2 \leq_{\mathrm{lr}} V_1$. Then $V_2 \mid \{T_1 > t_1,\ T_2 > t_2\} \leq_{\mathrm{lr}} V_1 \mid \{T_1 > t_1,\ T_2 > t_2\}$.*

Proof. We have

$$\begin{aligned}H_2(v \mid T_1 > t_1,\ T_2 > t_2) &= \frac{\int_0^v \bar{F}(t_1, t_2 \mid u)h_2(u)\,\mathrm{d}u}{\int_0^\infty \bar{F}(t_1, t_2 \mid u)h_2(u)\,\mathrm{d}u} \\ &= \frac{\int_0^v \bar{F}(t_1, t_2 \mid u)g(u)h_1(u)\,\mathrm{d}u}{\int_0^\infty \bar{F}(t_1, t_2 \mid u)g(u)h_1(u)\,\mathrm{d}u}.\end{aligned}$$

This means that the distribution of $V_2 \mid \{T_1 > t_1,\ T_2 > t_2\}$ is the weighted version of the distribution of $V_1 \mid \{T_1 > t_1, T_2 > t_2\}$ by weight $g(v)$, a decreasing function of v. By applying Lemma 2.1 we obtain the result.

2.1. Examples

Suppose that

$$\bar{F}(t_1, t_2 \mid v) = \mathrm{e}^{-v\psi(t_1,t_2)},$$

where $\psi(t_1, t_2)$ is a differentiable function in both arguments such that $\bar{F}(t_1, t_2 \mid v)$ is a conditional survival function.

Then

$$\lambda^{(i)}(t_1, t_2 \mid v) = v\frac{\partial}{\partial t_i}\psi(t_1, t_2), \qquad i = 1, 2.$$

This gives (for $i = 1, 2$)

$$\begin{aligned}\lambda^{(i)}(t_1, t_2) &= \mathrm{E}_{v \mid \{T_1>t_1,\, T_2>t_2\}}(\lambda^{(i)}(t_1, t_2 \mid v)) \\ &= \int_0^\infty v\frac{\partial}{\partial t_i}\psi(t_1, t_2)h(v \mid T_1 > t_1,\ T_2 > t_2)\,\mathrm{d}v,\end{aligned}$$

where $h(v \mid T_1 > t_1,\ T_2 > t_2)$ is the PDF of V given $T_1 > t_1$ and $T_2 > t_2$. Thus,

$$\begin{aligned}\lambda^{(i)}(t_1, t_2) &= \frac{\partial}{\partial t_i}\psi(t_1, t_2)\,\mathrm{E}(V \mid T_1 > t_1, T_2 > t_2) \\ &= \lambda_0^{(i)}(t_1, t_2)\,\mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2),\end{aligned}$$

where $\lambda_0^{(i)}(t_1, t_2)$ $(i = 1, 2)$ is the ith component of the hazard gradient without incorporating the frailty effect. Thus,

$$\frac{\lambda^{(i)}(t_1, t_2)}{\lambda_0^{(i)}(t_1, t_2)} = \mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2).$$

It can be verified that

$$\frac{\partial}{\partial t_i}\mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2) = -\lambda_0^{(i)}(t_1, t_2)\,\mathrm{var}(V \mid T_1 > t_1,\ T_2 > t_2).$$

This means that $\lambda^{(i)}(t_1, t_2)/\lambda_0^{(i)}(t_1, t_2)$ is a decreasing function of t_i, $i = 1, 2$.

2.1.1. *Special case.* If T_1 and T_2 are conditionally independent given the frailty, then $\psi(t_1, t_2) = A_1(t_1) + A_2(t_2)$, $\lambda_0^{(1)}(t_1, t_2) = A_1'(t_1)$, and $\lambda_0^{(2)}(t_1, t_2) = A_2'(t_2)$, where the prime denotes the derivative.

The conditional survival function given $V = v$ is

$$\bar{F}(t_1, t_2 \mid v) = \exp\{-v(A_1(t_1) + A_2(t_2))\}.$$

The unconditional survival function is

$$\bar{F}(t_1, t_2) = M_V[-(A_1(t_1) + A_2(t_2))],$$

where $M_V(\cdot)$ is the moment generating function of V.

In the following examples, we use this setup and assume that T_1 and T_2 are independent given the frailty variable.

2.1.2. *Specific examples.*

Example 2.1. Suppose that V has a gamma distribution with PDF

$$h(v) = \frac{1}{\beta^\alpha \Gamma(\alpha)} v^{\alpha-1} \mathrm{e}^{-v/\beta}, \qquad v > 0,\ \alpha > 0,\ \beta > 0.$$

So

$$\bar{F}(t_1, t_2) = [1 + \beta A_1(t_1) + \beta A_2(t_2)]^{-\alpha}.$$

The hazard components are given by

$$\lambda^{(i)}(t_1, t_2) = -\frac{\partial}{\partial t_i} \ln \bar{F}(t_1, t_2) = \frac{\alpha\beta A_i'(t_i)}{1 + \beta A_1(t_1) + \beta A_2(t_2)}, \qquad i = 1, 2.$$

Furthermore,

$$\mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2) = \frac{\alpha\beta}{1 + \beta A_1(t_1) + \beta A_2(t_2)}$$

and

$$\operatorname{var}(V \mid T_1 > t_1,\ T_2 > t_2) = \frac{\alpha\beta^2}{[1 + \beta A_1(t_1) + \beta A_2(t_2)]^2}.$$

The above expressions yield the square of the coefficient of variation of V given $T_1 > t_1$ and $T_2 > t_2$ as $1/\alpha$. It can be verified that a constant value of the coefficient of variation occurs only in the case of gamma frailty.

Example 2.2. Suppose that V has an inverse Gaussian distribution with PDF

$$h(v) = (2\pi a v^3)^{-1/2} \exp\left\{-\frac{(bv-1)^2}{2av}\right\}, \qquad v > 0,\ a > 0,\ b > 0.$$

This gives

$$\bar{F}(t_1, t_2) = \exp\left\{\frac{b}{a}\left(1 - \left(1 - \frac{2a}{b^2}(A_1(t_1) + A_2(t_2))\right)\right)^{-1/2}\right\}.$$

The hazard components are given by

$$\lambda^{(i)}(t_1, t_2) = \frac{A_i(t_i)}{[b^2 + 2a(A_1(t_1) + A_2(t_2))]^{1/2}}, \qquad i = 1, 2.$$

Furthermore,

$$\mathrm{E}(V \mid T_1 > t_1,\ T_2 > t_2) = \frac{1}{[b^2 + 2a(A_1(t_1) + A_2(t_2))]^{1/2}}$$

and

$$\operatorname{var}(V \mid T_1 > t_1,\ T_2 > t_2) = \frac{a}{[b^2 + 2a(A_1(t_1) + A_2(t_2))]^{3/2}}.$$

3. Comparisons of frailty models

There is no firm basis for choosing the probability distribution of the frailty random variable V. It is therefore important to see how the overall survival function of the ith unit, $i = 1, 2$, responds to the change in the probability distribution of V. To be more precise, if the true model for the probability distribution of the frailty random variable is that of V_1 and the adopted model assumes the distribution of V_2, then we would like to know the relationship between the resulting random variables. Our main objective in this section is to see how some of the well-known stochastic orderings between V_1 and V_2 translate into the orderings between the component lifetimes.

Theorem 3.1. *Let $\lambda^{(i)}(t_1, t_2 \mid v)$ be an increasing function of $v > 0$, $i = 1, 2$. If $V_2 \le_{\mathrm{lr}} V_1$ then $(T_{11}, T_{21}) \le_{\mathrm{whr}} (T_{12}, T_{22})$.*

Proof. From (2.1) we have

$$\begin{aligned}
&\lambda^{(i)}_{v1}(t_1, t_2) - \lambda^{(i)}_{v2}(t_1, t_2)\\
&\quad = \int_0^\infty \lambda^{(i)}(t_1, t_2 \mid u) h_1(u \mid T_1 > t_1,\ T_2 > t_2)\,\mathrm{d}u\\
&\qquad - \int_0^\infty \lambda^{(i)}(t_1, t_2 \mid u) h_2(u \mid T_1 > t_1,\ T_2 > t_2)\,\mathrm{d}u\\
&\quad = \lambda^{(i)}(t_1, t_2 \mid u)[H_1(u \mid T_1 > t_1, T_2 > t_2) - H_2(u \mid T_1 > t_1, T_2 > t_2)]_0^\infty\\
&\qquad - \int_0^\infty \frac{\mathrm{d}}{\mathrm{d}u}\lambda^{(i)}(t_1, t_2 \mid u)[H_1(u \mid T_1 > t_1,\ T_2 > t_2) - H_2(u \mid T_1 > t_1,\ T_2 > t_2)]\,\mathrm{d}u\\
&\quad = \int_0^\infty \frac{\mathrm{d}}{\mathrm{d}u}\lambda^{(i)}(t_1, t_2 \mid u)[H_2(u \mid T_1 > t_1,\ T_2 > t_2) - H_1(u \mid T_1 > t_1,\ T_2 > t_2)]\,\mathrm{d}u\\
&\quad > 0.
\end{aligned}$$

The rest of the proof follows by using the fact that $\lambda^{(i)}(t_1, t_2 \mid v)$ is an increasing function of v and $V_2 \le_{\mathrm{lr}} V_1$.

Before presenting the next result, we give the following definition and the composition formula.

Definition 3.1. A real-valued function $f(t, v)$ is said to be RR_2 (reverse rule of order 2) or TP_2 (total positive of order 2) on $[0, \infty) \times [0, \infty)$ if

$$f(t_1, v_1) f(t_2, v_2) \le f(t_1, v_2) f(t_2, v_1)$$

or, respectively,

$$f(t_1, v_1) f(t_2, v_2) \ge f(t_1, v_2) f(t_2, v_1)$$

for all $0 < t_1 < t_2$ and $0 < v_1 < v_2$.

Remark 3.1. The concepts of RR_2 and TP_2 are used to study the dependence between two variables; see Karlin (1968, pp. 11–45).

The following statements are equivalent.

1. A real-valued function $f(t, v)$ is RR_2 on $[0, \infty) \times [0, \infty)$.

2. $f(t, v_1)/f(t, v_2)$ is increasing in $t > 0$ and $0 < v_1 < v_2$.
3. $\partial^2 \ln f(t, v)/\partial t \partial v < 0$.
4. $f(t \mid v)$ or $f(v \mid t)$ is RR_2, where $f(t \mid v)$ and $f(v \mid t)$ are the conditional densities.

Similarly, the following statements are also equivalent.

1. A real-valued function $f(t, v)$ is TP_2 on $[0, \infty) \times [0, \infty)$.
2. $f(t, v_1)/f(t, v_2)$ is decreasing in $t > 0$ and $0 < v_1 < v_2$.
3. $\partial^2 \ln f(t, v)/\partial t \partial v > 0$.
4. $f(t \mid v)$ or $f(v \mid t)$ is TP_2, where $f(t \mid v)$ and $f(v \mid t)$ are the conditional densities.

See Holland and Wang (1987).

We now present the following result.

Theorem 3.2. *Suppose that the conditional joint PDF of T_i and V given $T_j > t_j$, $i, j = 1, 2$, $i \neq j$, is* RR_2. *Then*

(a) *V is stochastically decreasing in the right tail with respect to T_i, that is, $\bar{H}(v \mid T_i > t_i, T_j > t_j, i \neq j)$ is a decreasing function of t_i, $i = 1, 2$;*

(b) *T_i is stochastically decreasing in the right tail with respect to V, that is, $\bar{F}(t_i \mid V > v, T_j > t_j, i \neq j)$ is a decreasing function of v.*

Proof. See Shaked (1977).

We now present the following well-known composition formula, which will be used in the sequel.

Definition. (*Composition formula.*) Let $f(t, v)$ be an RR_2 or TP_2 function in $t \in \mathrm{R}$ and $v \in A$, and let $h_i(v)$ be a TP_2 function on $\{1, 2\} \times A$, where $h_i(v)$ is a probability density function in v for each i. Then

$$\Phi_i(t) = \int_A f(t, v) h_i(v)\, \mathrm{d}v$$

is RR_2 or, respectively, TP_2 on $\{1, 2\} \times \mathbb{R}$. For a proof, see Karlin (1968).

The following result shows how the likelihood ratio ordering of V_1 and V_2 is inherited by T_1 and T_2.

Theorem 3.3. *Suppose that $V_1 \leq_{\mathrm{lr}} V_2$. If $f(t_i \mid v, T_j > t_j)$ is* RR_2 *or* TP_2 *on* $[0, \infty) \times [0, \infty)$, *then*

$$T_{i,v_1} \mid T_j > t_j \geq_{\mathrm{lr}} T_{i,v_2} \mid T_j > t_j \quad \textit{or, respectively,} \quad T_{i,v_1} \mid T_j > t_j \leq_{\mathrm{lr}} T_{i,v_2} \mid T_j > t_j.$$

Proof. The condition $V_1 \leq_{\mathrm{lr}} V_2$ implies that $h_2(v)/h_1(v)$ is increasing in $v > 0$. That is, the map $(k, v) \to h_k(v)$ is TP_2 on $\{1, 2\} \times [0, \infty)$. If $f(t_i \mid v, T_j > t_j)$ is RR_2 or TP_2 in t_i and v then, using the composition formula, the map $(k, t_i) \to f_k(t_i \mid T_j > t_j)$ is RR_2 or, respectively, TP_2 on $\{1, 2\} \times [0, \infty)$, where $f_k(t_i \mid T_j > t_j)$ is given by

$$f_k(t_i \mid T_j > t_j) = \int_0^\infty f(t_i \mid u, T_j > t_j) h_k(u)\, \mathrm{d}u, \qquad k = 1, 2.$$

This implies that $f_2(t_i \mid T_j > t_j)/f_1(t_i \mid T_j > t_j)$ is decreasing or, respectively, increasing

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in $t_i > 0$. Hence, $T_{i,v_1} \mid T_j > t_j \geq_{\mathrm{lr}} T_{i,v_2} \mid T_j > t_j$ or, respectively, $T_{i,v_1} \mid T_j > t_j \leq_{\mathrm{lr}} T_{i,v_2} \mid T_j > t_j$. This completes the proof.

The following result addresses the inheritance of failure rate orderings of V_1 and V_2 by T_1 and T_2.

Theorem 3.4. *Suppose that*

(a) $V_1 \leq_{\mathrm{fr}} V_2$*; and*

(b) $\lambda^{(i)}(t_1, t_2 \mid v_1) \leq \lambda^{(i)}(t_1, t_2 \mid v_2)$ *or* $\lambda^{(i)}(t_1, t_2 \mid v_1) \geq \lambda^{(i)}(t_1, t_2 \mid v_2),\ v_1 < v_2$.

Then

$$T_{i,v_1} \mid T_j > t_j \geq_{\mathrm{fr}} T_{i,v_2} \mid T_j > t_j, \qquad i, j = 1, 2,\ i \neq j,$$

or, respectively,

$$T_{i,v_1} \mid T_j > t_j \leq_{\mathrm{fr}} T_{i,v_2} \mid T_j > t_j, \qquad i, j = 1, 2,\ i \neq j.$$

Proof. Since $V_1 \leq_{\mathrm{fr}} V_2$, $\bar{H}_2(v)/\bar{H}_1(v)$ is increasing in $v > 0$, which is equivalent to the map $(k, v) \to \bar{H}_k(v)$ being TP_2 on $\{1, 2\} \times [0, \infty)$. Condition (b) implies that $\bar{F}(t_i \mid v, T_j > t_j)$ is RR_2 or TP_2 in t_i and v on $[0, \infty) \times [0, \infty)$. Also, (b) implies that

$$\bar{F}(t_i \mid v_1, T_j > t_j) \geq \bar{F}(t_i \mid v_2, T_j > t_j)$$

or, respectively,

$$\bar{F}(t_i \mid v_1, T_j > t_j) \leq \bar{F}(t_i \mid v_2, T_j > t_j)$$

for $v_1 < v_2$. This means that $\bar{F}(t_i \mid v, T_j > t_j)$ is decreasing or, respectively, increasing in v. Define

$$\bar{F}_k(t_i \mid T_j > t_j) = \int_0^\infty \bar{F}_k(t_i \mid u, T_j > t_j) h_k(u)\, \mathrm{d}u.$$

Then the map $(k, t_i) \to \bar{F}_k(t_i \mid T_j > t_j)$ is RR_2 or, respectively, TP_2 on $\{1, 2\} \times [0, \infty)$. Therefore, $\bar{F}_2(t_i \mid T_j > t_j)/\bar{F}_1(t_i \mid T_j > t_j)$ is a decreasing or, respectively, increasing function of $t_i > 0$. Hence, $\lambda^{(i)}_{v_1}(t_1, t_2) \leq \lambda^{(i)}_{v_2}(t_1, t_2)$ or, respectively, $\lambda^{(i)}_{v_1}(t_1, t_2) \geq \lambda^{(i)}_{v_2}(t_1, t_2)$ for all $t_i > 0$. That is,

$$T_{i,v_1} \mid T_j > t_j \geq_{\mathrm{fr}} T_{i,v_2} \mid T_j > t_j$$

or, respectively,

$$T_{i,v_1} \mid T_j > t_j \leq_{\mathrm{fr}} T_{i,v_2} \mid T_j > t_j.$$

The following theorem shows the corresponding result for the stochastic orderings.

Theorem 3.5. *If* $V_1 \leq_{\mathrm{st}} V_2$ *and* $\bar{F}(t_i \mid v, T_j > t_j)$ *is a decreasing function of* v*, then* $T_{i,v_2} \mid T_j > t_j \leq_{\mathrm{st}} T_{i,v_1} \mid T_j > t_j,\ i, j = 1, 2,\ i \neq j$.

Proof. We have

$$\begin{aligned}
&\bar{F}_2(t_i \mid T_j > t_j) - \bar{F}_1(t_i \mid T_j > t_j) \\
&\quad = \int_0^\infty \bar{F}(t_i \mid v, T_j > t_j)[h_2(v) - h_1(v)]\, \mathrm{d}v \\
&\quad = -\bar{F}(t_i \mid v, T_j > t_j)[\bar{H}_2(v) - \bar{H}_1(v)]_0^\infty \\
&\qquad + \int_0^\infty \frac{\mathrm{d}}{\mathrm{d}v} \bar{F}(t_i \mid v, T_j > t_j)[\bar{H}_2(v) - \bar{H}_1(v)]\, \mathrm{d}v \\
&\quad = \int_0^\infty \frac{\mathrm{d}}{\mathrm{d}v} \bar{F}(t_i \mid v, T_j > t_j)[\bar{H}_2(v) - \bar{H}_1(v)]\, \mathrm{d}v.
\end{aligned}$$

Since $\bar{F}(t_i \mid v, T_j > t_j)$ is a decreasing function of v and $H_2(v) \geq H_1(v)$ for all $v > 0$, we have $\bar{F}_2(t_i \mid T_j > t_j) \leq \bar{F}_1(t_i \mid T_j > t_j)$ for all $t_i > 0$. That is, $\mathrm{T}_{i,v_2} \mid T_j > t_j \leq_{\mathrm{st}} T_{i,v_1} \mid T_j > t_j$.

4. Multiplicative model

We now consider the following model as a special case:

$$\lambda^{(i)}(t_1, t_2 \mid v) = v\lambda_0^{(i)}(t_1, t_2), \qquad t_1 > 0,\ t_2 > 0,\ v > 0, \tag{4.1}$$

where $\lambda_0^{(i)}(t_1, t_2)$ is the baseline failure rate of the ith unit without taking into account the frailty effect and is independent of v. In this case

$$\bar{F}(t_1, t_2 \mid v) = [\bar{G}(t_1, t_2)]^v, \qquad v > 0,$$

where $\bar{G}(t_1, t_2)$ is the joint baseline survival function. This gives the unconditional survival function as

$$\bar{F}(t_1, t_2) = \int_0^\infty [\bar{G}(t_1, t_2)]^v h(v)\,\mathrm{d}v, \qquad v > 0,$$

where $h(v)$ is the PDF of the frailty effect V.

We now present the following result.

Theorem 4.1. *For model (4.1), the following statements hold.*

(a) *The ith component of the population level failure rate is given by*

$$\lambda^{(i)}(t_1, t_2) = \lambda_0(t_1, t_2)\,\mathrm{E}_V(V \mid T_1 > t_1,\ T_2 > t_2).$$

(b) *$H(v \mid T_1 > t_1,\ T_2 > t_2)$ is an increasing function of t_i, $i = 1, 2$.*

(c) *$\mathrm{E}_V(V \mid T_1 > t_1,\ T_2 > t_2)$ is decreasing in $t_i > 0$, $i = 1, 2$. Moreover, if $\lambda_0^{(i)}(t_1, t_2)$ is decreasing in $t_i > 0$ then $\lambda^{(i)}(t_1, t_2)$ is decreasing in $t_i > 0$. That is, $T_i \mid T_j > t_j, i, j = 1, 2, i \neq j$, is of decreasing failure rate.*

(d) *$V \mid \{T_i > t_{i2},\ T_j > t_j\} \leq_{\mathrm{lr}} V \mid \{T_i > t_{i1},\ T_j > t_j\}$ for all $t_{i1} < t_{i2}, i, j = 1, 2, i \neq j$.*

(e) *If $V_2 \leq_{\mathrm{lr}} V_1$ then $V_2 \mid \{T_1 > t_1,\ T_2 > t_2\} \leq_{\mathrm{lr}} V_1 \mid \{T_1 > t_1,\ T_2 > t_2\}$.*

Proof. The proof of (a) follows from Theorem 2.1. For parts (b)–(e), since $\lambda^{(i)}(t_1, t_2 \mid v) = v\lambda_0^{(i)}(t_1, t_2)$ is an increasing function of v, Theorems 2.2–2.3 and Corollary 2.1 apply.

We now present the following result, which addresses the monotonicity of the conditional survival function of the ith component given V and the survival of the jth component.

Theorem 4.2. *The random variable T_i is stochastically decreasing in the right tail with respect to V given $T_j > t_j$, $i = 1, 2$. That is, $\bar{F}(t_i \mid v, T_j > t_j)$ is a decreasing function of $v > 0$.*

Proof. We have

$$f(t_i \mid v, T_j > t_j) = \lambda^{(i)}(t_1, t_2 \mid v)\bar{F}(t_i \mid v, T_j > t_j) = v\lambda_0^{(i)}(t_1, t_2)[\bar{G}(t_i \mid T_j > t_j)]^v.$$

If $0 < v_1 < v_2 < \infty$ then

$$\frac{f(t_i \mid v_2, T_j > t_j)}{f(t_i \mid v_1, T_j > t_j)} = \frac{v_2}{v_1}[\bar{G}(t_i \mid T_j > t_j)]^{v_2 - v_1}$$

is a decreasing function of $t_i > 0$. Therefore, the conditional density of T_i given $(v, T_j > t_j)$ is RR_2 in t_i and v on $[0, \infty) \times [0, \infty)$. Hence, the joint PDF of T_i and V given $T_j > t_j$ is RR_2. The result now follows from Theorem 3.2(b).

The following theorem shows how the stochastic comparisons between V_1 and V_2 translate into stochastic comparisons between T_1 and T_2.

Theorem 4.3. *Let* $A \in \{\mathrm{lr}, \mathrm{fr}, \mathrm{st}\}$. *If* $V_1 \leq_A V_2$ *then*

$$T_{i,v_1} \mid T_j > t_j \geq_A T_{i,v_2} \mid T_j > t_j, \qquad i, j = 1, 2,\ i \neq j.$$

Proof. (a) Since $f(t_i \mid v, T_j . t_j)$ is RR_2 in t_i and v, the result for lr follows from Theorem 3.4.

(b) Since $\lambda^{(i)}(t_1, t_2 \mid v) = v\lambda_0^{(i)}(t_1, t_2)$ is an increasing function of v, the result for fr follows from Theorem 3.4.

(c) Since $\bar{F}(t_i \mid v, T_j > t_j) = [\bar{G}(t_i \mid T_j > t_j)]^v$ is decreasing in $v > 0$, the result for st follows from Theorem 3.5.

4.1. Shared frailty model

We now consider the following model, known as the shared frailty model:

$$\lambda^{(i)}(t_1, t_2 \mid v) = v\lambda_{0i}(t_i), \qquad i = 1, 2,$$

where $\lambda_{0i}(t_i)$ is the baseline failure rate of the ith unit, independent of the other unit and of v. In this case

$$\bar{F}(t_1, t_2 \mid v) = [\bar{G}_1(t_1)\bar{G}_2(t_2)]^v, \qquad v > 0,$$

where $\bar{G}_i(t_i)$ is the baseline survival function of the ith unit. Thus,

$$\bar{F}(t_1, t_2) = \int_0^\infty [\bar{G}_1(t_1)\bar{G}_2(t_2)]^v h(v)\,\mathrm{d}v,$$

where $h(v)$ is the PDF of V.

Remark 4.1. It is easily seen that the shared frailty model is a special case of the multiplicative model discussed above, and all the results of Theorems 4.1–4.3 apply.

Remark 4.2. A more general, shared random effect model has been studied in Rizopoulos *et al.* (2008), who investigated the association structure between a longitudinal response and survival processes.

5. Conclusion and comments

In this paper we presented a general bivariate random effect model. Random effect models are used in various disciplines. For example, in survival analysis they are used as frailty models and in problems related to the environment they are used as environmental effect models. We presented our results in the context of frailty models and studied their properties. We also investigated the effect on the survival by using two different frailty distributions. The corresponding results for the multiplicative and shared frailty models were also derived. The two examples presented illustrate the effect on the survival by incorporating the frailty effect. It is hoped that our results will be useful to researchers dealing with random effect models.

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