Approaches in Modeling Dependence in Bivariate Time-to-Event and Event-History Data

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di GIUSSANI ANDREA
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Abstract

The aim of this thesis is to explore multivariate survival techniques for the analysis of bivariate failure time data under the presence of right-censoring.

In particular, a new family of bivariate frailty model is discussed, and its properties have been widely investigated in both time-to-event and event-history data frameworks. To take into account the correlation between these measurements, the well-known Marshall-Olkin Bivariate Exponential Distribution (MOBVE) is considered for the joint distribution of frailties. The reason is twofold: on the one hand, it allows to model shocks that affect individual-specific frailties; on the other hand, the parameter underlying the Poisson process characterizing the common shock captures completely the dependence between the pair of lifetimes.

Novel approaches for the analysis of bivariate length-biased survival data under the presence of right-censoring are suggested, and both parametric and semi-parametric estimation strategies are discussed.

The proposed methodology is then applied to the investigation of association in dementia onset and death in non-prevalent different-sex couples to the Cache County Study on Memory Health and Aging (CCSMHA) data.

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I am also very grateful to Prof. Masoud Ashgharian, who gave me the fantastic opportunity to visit the Department of Mathematics and Statistics at Mc Gill University as a *Graduate Research Trainee*. He painstakingly introduced me to the length-biased survival analysis, and his vast knowledge has definitely been a positive source of inspiration for the success of this project.

I am indebted to Dr. Maria Norton for having shared with us the *Cache County Study in Memory Health and Aging* dataset, which has been exploited for the analysis of the proposed methodologies.

Last but not least, I would like to thank my girlfriend, Anna, and all my family, especially my parents, for their unconditional love, patience and support during this rewarding four-years period.

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Chapter 1

Introduction

1.1 Overview

Survival data analysis typically deals with time-to-event data, which describe the time elapsed from the time to recruitment into the study to the occurrence of an event, say death or onset of any disease. Such kind of data are basically modelled as a non-negative random variable subject to (right) censoring, due to the fact that the event of interest might not be fully observed. This is the case of many clinical situations, where limited budget and time constraints prevent the researchers to follow every single patient until the occurrence of the event under observation. The ideal scenario to investigate failure time data are the so-called incident studies, where subjects are typically disease-free at the time of recruitment, and then they are followed until censoring or, preferably, the occurrence of the event. Note that censoring may not only happen at the end of the study, but it can also be caused by lost to follow-up, that is patients who decide to drop out of the study, causing an interruption in her clinical record. Figure 1.1 illustrates such a scenario: the first subject is lost at some time in the study, while the third and the bottom one would have been observed, had the study been longer. In this case, standard survival tools, such as the Kaplan Meier estimator, can be applied, since they rely on the assumption that censoring is non-informative about the survival time.

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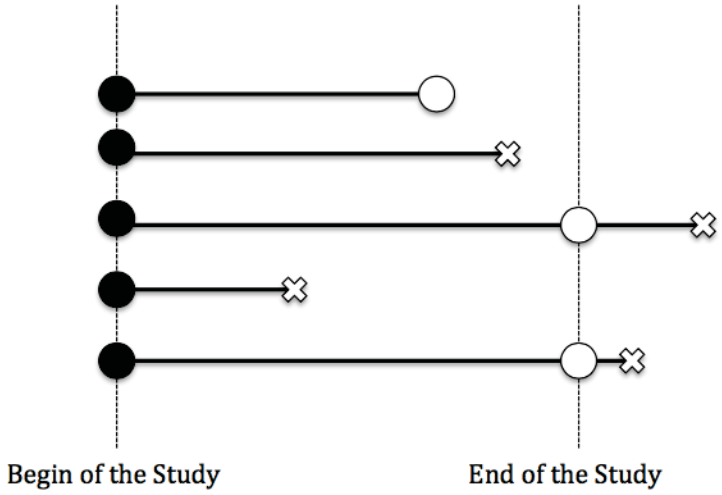

Figure 1.1: Incident Study

In practice, however, we typically estimate the overall survival probability by using data coming from prevalent cohort studies. In such a setting, some of the recruited patients have already experienced the disease before the initiation of the recruitment, and they are followed until failure or censoring. Obviously, this is no longer the ideal setting, as we only observe *the strongest among the weakest*, that is only those who survive among the diseased patients until the day of recruitment is observed. Such patients are called prevalent cases, causing an emerging bias in the sample, which is therefore not representative of the incidence population. As a consequence, using prevalent cases for survival analysis with disease onset as the origin results in overestimation of the survival function, because the time from onset to recruitment is contained in both the full lifetime and censoring time, which is equivalent of saying that the censoring times are informative, and standard survival tools cannot be applied to this case without proper adjustment (Asgharian et al. (2002); Asgharian and Wolfson (2005)).

In many clinical applications, however, some intermediate events can happen before the one of interest, causing a significant change in its hazard. Moreover, more than one event can be of interest, and their occurrence might preclude or be necessary for the occurrence of others. Therefore, it is of vital importance to investigate the association between two consecutive failure times, and multivariate techniques are needed to perform analysis on

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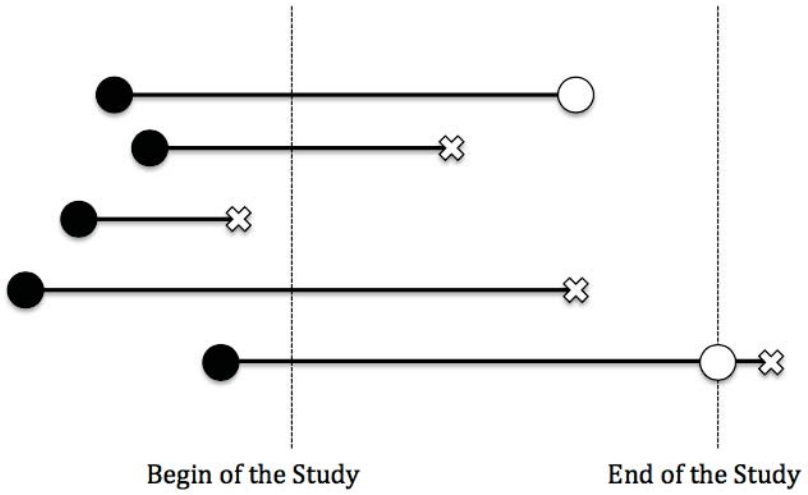

Figure 1.2: Prevalent Case Study

such complex sequence of events.

Among multivariate survival analysis techniques, a multi-state model is the most suitable framework for describing longitudinal failure time data (Hougaard (2000)). In clinical contexts, multi-state models are used to characterize any disease process, and Markov and semi-Markov processes are two fundamental classes of models, with the former being most widely adopted in settings involving progressive conditions (Meira-Machado et al. (2009); Putter et al. (2007)). In the last decade, non-Markov model have been extensively investigated as a natural extension of Markovian multi-state models (Meira-Machado et al. (2006); Allignol et al. (2013)). Under the frequently assumed Markov property, a multi-state model can be seen as a sequence of competing risks models (Beyersmann et al. (2012), and copula-based models may be employed to investigate the dependence across competing-risks events (Diao and Cook (2014); Eryilmaz (2014)). Recently, some authors have integrated frailty into multi-state models in order to study the risk of interrelated events while accounting for unobserved clustering risks factors (Rotolo et al. (2013)). The concept of frailty was firstly introduced by Vaupel (1979) who actually introduced a random effects model to take into account possible heterogeneity in a population due to unobserved covariates. However, the problem of heterogeneity due to unobserved risk

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clustering factor was first addressed by Clayton (1978), and popularized by Oakes (1982) in the context of survival analysis. The integration of frailty and multi-state models can provide powerful survival models to study the risk of many interrelated events while accounting for cluster-related dependence among subjects.

1.2 The Problem

The main problem motivating our research consists in answering clinical questions arising from the investigation of the causes of incidence of Alzheimer's disease, while taking into account both the dependence between subjects and that between individual-related events. Typically, the focus is on the association between dementia onset and death, and measuring its strength can be of clinically importance. Alzheimer's is a chronic degenerative brain disease and the most common cause of dementia among elderly age 65 years and older, with a progressive decline in memory, thinking and learning capacity.

At a population level, both the prevalence and incidence of such disease have astonishingly increased in the last decades, and longer life expectancies will definitively have a profound impact on hastening the number of people suffering from aging-associated diseases. Along these lines, researchers have focused on investigating the factors that may affect the progression of dementia. An alarming discovery is that a subject whose spouse experienced incident dementia onset had a 1.6-fold increase in the hazard for incident dementia compared to subjects whose spouses were dementia free (Norton et al. (2010)). Therefore, not only will national health care systems be hard-pressed to cope, there will also be a growing burden on caregiver families. As a consequence, understanding the natural history of dementia, and more importantly, investigating the evolution of incidence rates among the population is of vital importance.

The Cache County Study on Memory Health and Aging (CCSMHA) is the only population-based longitudinal cohort study attempting, as its primary objective, to estimate the association in dementia onset among 1,221 married couples (Tschanz et al. (2013)). However, no work has exploited such study for the statistical assessment of the association in dementia onset on death in different-sex couples. An interesting fact emerging from the

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CCSMHA is that at the time the study was lunched, 175 patients were recruited as prevalent cases, and presumably excluded from the analysis to avoid the bias that invariably accompanies such studies against shorter survival times. Such bias would emerge because subjects who were diagnosed with dementia in 1994 should have survived long enough to have had a chance of being recruited into the study with respect to the weakest patients who died before recruitment. In such prevalent cohort study setting, the observed survival times are said to be left-truncated, and if the incidence rate is constant, the survival times are termed length-biased. Notwithstanding such emerging bias, these data contain invaluable information, especially if one aims to estimate how long people with dementia survive following onset of their spouse disease, or possibly, death. From a statistical point of view, no methods have been developed for the analysis of bivariate length-biased data in the presence of right-censoring.

Hence, the primary goal of this thesis is to build a statistical framework that permits to take into account the dependence across individual-specific events in a pair. Little has been done to investigate statistical inference procedures for the analysis of dependent bivariate multi-state processes, and frailty models have not been integrated in such context yet. Random effects models will be employed to model the event-related dependence across processes, and the well-known Marshall-Olkin Bivariate Exponential Distribution (MOBVE, Marshall and Olkin (1967)) will be considered for the joint distribution of frailties. The reason is twofold: on the one hand, it allows to model shocks that affect the two individual-specific frailties; on the other hand, the MOBVE is the only bivariate exponential distribution with exponential marginals, which allows to model each marginal multi-state process as a shared frailty model.

1.3 Main Contributions of the Thesis

Firstly, a bivariate frailty survival model has been developed, exploring its identifiability and parametric likelihood inference procedure in presence of right censoring. The contribution here is to model the dependence between members of a pair by employing the

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MOBVE distribution as a bivariate random vector of frailty. Furthermore, we have also investigsted a generalization of the well-know *conditional hazard ratio function* (Oakes (1989)) in the context of ordering, aiming at deriving a summary statistic that permits to compare couples in a stochastic manner. A bivariate MOBVE cure frailty model was also proposed, as its complementary model, to account for the realistic adjustment that a shared of the population never experience the event of interest, say the onset of dementia.
In this thesis, a great deal of attention was given to bivariate frailty models in the context of event-history data analysis, with the derivation of the semi-parametric estimator for the transition probabilities in a simple bivariate illness-death model and, therefore, of the transition-specific hazard, and the corresponding observed data likelihood maximization estimating procedure in presence of right censoring of the association parameter underlying the model.
Finally, a novel approach for the analysis of bivariate length-biased data under right-censoring is proposed. To the best of my knowledge, no work has been proposed for the analysis of such complex sequence of data, and this work aims to fill an important literature gap that has not been deeply researched yet.
Two estimation approaches have been developed and investigated in the thesis: a parametric and a semi-parametric approach. Unfortunately, nonparametric approaches are not available at this stage of the work, though they would have been desirable for both bivariate multi-state models and bivariate length-biased models. On the one hand, fully parametric inference, based on maximum likelihood estimation, is considered in the context of bivariate frailty models, where double integration is needed to obtain the unconditional likelihood; explicit integration is indeed possible in that case, and asymptotic or numerical approximation was not necessary. On the other hand, semi-parametric methods have been investigated in the context of bivariate frailty multi-state models as well as in copula models for the analysis of bivariate length-biased survival data, where two-stages estimation procedures have been considered for potential applications.

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1.4 Structure of the Thesis

Chapter 2 contains a concise review of the main theoretical concepts that will be used throughout the thesis. In Chapter 3, I will firstly discuss a bivariate frailty survival model, focusing on the estimation of the association in time-to-death in different sex-couples from CCSMHA data. A new bivariate cured frailty model is then proposed with the goal of modeling the association in dementia onset, and simulation results are provided.
I will move to the construction of the frailty bivariate multi-state model in Chapter 4, with the derivation of the semi-parametric estimator for the transition probabilities for a bivariate illness-death process and, therefore, of the transition-specific hazard; the corresponding observed data likelihood maximization estimating procedure in presence of right censoring for the association parameter underlying the model is also presented.
Chapter 5 is devoted to the derivation of the bivariate length-biased survival function under the presence of right-censoring; copula models have been employed to take into account the dependence in bivariate length-biased survival data, and likelihood inference procedure in the presence of right-censoring is proposed. More general approaches to model bivariate data from length biased sampling are also proposed.
Finally, Chapter 6 closes with some conclusions and feasible ideas for future work.

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Chapter 2

Background

2.1 Frailty Models

Frailty models extend the well-known Cox model (Cox (1972)) by introducing unobserved random effect into the model. These models assume that the frailty acts multiplicatively on the hazard function, and proportional hazard frailty models can be specified as

$$h\left(t|Z,\boldsymbol{X}\right) = Z\, h_0(t)\, e^{\boldsymbol{\beta}'\boldsymbol{X}} \tag{2.1}$$

where $h_0(t)$ is the baseline hazard function, Z is the unobservable frailty term, and $\boldsymbol{X}$ is a vector of covariates with $\boldsymbol{\beta}$ denoting the regression vector parameters to be estimated. The term *frailty* was firstly introduced by Vaupel (1979), who introduced a random effects model to take into account possible heterogeneity in a population due to unobserved covariates. The crucial assumption underlying frailty models is that the lifetimes are conditionally independent with respect to the frailty term. In this thesis, the focus is on multivariate frailty models, and this section mainly focuses on the bivariate case. In order to have an exhaustive introduction to univariate frailty models, the interested reader is referred to the book by Wienke (2010), which is an up-to-date monograph on frailty models. Another excellent reference is the book by Aalen et al. (2007), which also introduces the reader to different applications to event-history data.

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2.1.1 Bivariate Shared Frailty Models

Let T_1 and T_2 be two non-negative conditionally independent lifetimes with absolutely continuous distribution function given the value z of a frailty Z. It follows that the joint conditional survival function is

$$S\left(t_1, t_2|Z\right) = S_{01}(t_1)^Z S_{02}(t_2)^Z = e^{-Z(\Lambda_{01}(t_1)+\Lambda_{02}(t_2))} \tag{2.2}$$

where $S_{01}(\cdot)$ and $S_{02}(\cdot)$ are baseline survival functions, and $\Lambda_{01}(t_1)$ and $\Lambda_{02}(t_2)$ the cumulative baseline hazard functions of T_1 and T_2, respectively, defined as

$$\Lambda_{0i}(t) = \int_0^t \lambda_{0i}(u)\,\mathrm{du} \quad i = 1, 2$$

with λ_{0i} the two baseline hazards. The marginal survival function is obtained by integrating out the frailty term Z, that is

$$\begin{aligned} S(t_1, t_2) &= \mathbb{E}_Z\left[\mathbb{P}\left(T_1 \geq t_1, T_2 \geq t_2|Z\right)\right] \\ &= \int_{\mathrm{Dom}(z)} S(t_1, t_2|z)\, d\, F(z) \\ &= \mathcal{L}_Z\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2)\right) \end{aligned} \tag{2.3}$$

where $\mathcal{L}_Z(\cdot)$ is the Laplace transform of Z, and $F(\cdot)$ denotes the distribution function of the random variable Z.

In the context of frailty models, a fundamental issue is the choice of the frailty distribution. Following Vaupel (1979) and Oakes (1982), the standard assumption on the frailty distribution is that $Z \sim \mathrm{Gamma}(\frac{1}{\theta}, \frac{1}{\theta})$, so that equation (2.3) becomes

$$\mathcal{L}_Z\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2)\right) = \left(1 + \theta\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2)\right)\right)^{-\frac{1}{\theta}} \tag{2.4}$$

Since it holds that

$$S_i(t_i) = \left(1 + \theta\Lambda_{0i}(t_i)\right)^{-\frac{1}{\theta}} \implies S_i(t_i)^{-\theta} - 1 = \theta\Lambda_{0i}(t_i) \qquad i = 1, 2$$

the well-known *shared frailty model* is easily obtained

$$\mathcal{L}_Z\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2)\right) = \left[S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} - 1\right]^{-\frac{1}{\theta}} \tag{2.5}$$

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In a shared frailty model, Z is typically interpreted as a measure of the relative risk shared by individuals in a cluster. We will refer to couples of individuals when talking about clusters in the following chapters.

Remark 2.1.1. *Under the Gamma shared frailty model, higher values of the dependence parameter θ reflect both a smaller degree of heterogeneity among groups, and a smaller association within groups, with independence as limit, and viceversa for higher values of θ.*

Note that for the marginal survival functions the following holds:

$$S_i(t_i) = \mathbb{E}S_i\left(t_i|Z\right) = \mathcal{L}_Z\left(\Lambda_{0i}(t_i)\right) = \psi\left(\Lambda_{0i}(t_i)\right) \qquad i = 1, 2 \tag{2.6}$$

where $\psi : [0, +\infty) \to [0, 1]$, with $\psi(0) = 1$ and $\psi^{'}$ exists on $(0, +\infty)$, it is non-positive, non-decreasing and concave; if $t^* = \inf\left\{t \geq 0 : \psi(t) = 0\right\}$, we have that ψ is strictly decreasing on $[0, t^*)$, and so its inverse function $\psi^{-1} : (0, 1] \to [0, +\infty)$ is well-defined. Consequently,

$$\Lambda_{0i}(t_i) = \psi^{-1}\left(S_i(t_i)\right) \qquad i = 1, 2$$

from which it follows that the (unconditional) bivariate survival function can by easily expressed in terms of Archimedean copula (Genest and MacKay (1986)), that is

$$S(t_1, t_2) = \psi\left(\psi^{-1}\left(S_1(t_1)\right) + \psi^{-1}\left(S_2(t_2)\right)\right) \tag{2.7}$$

The pioneering paper by Clayton (1978) and the book by Cox and Oakes (1984) pointed out that the bivariate survival function (2.5) can be equivalently derived in terms of conditional hazard functions. Let

$$\lambda\left(t_1|T_2 = t_2\right) = -\frac{\partial \ln S(t_1, t_2)}{\partial t_1} \tag{2.8}$$

and

$$\lambda\left(t_1|T_2 = t_2\right) = -\frac{\partial}{\partial t_1}\left(-\frac{\partial \ln S(t_1, t_2)}{\partial t_2}\right) \tag{2.9}$$

denote the hazard functions for the conditional distributions of T_1 given $T_2 = t_2$ and $T_2 > t_2$, respectively. The cross ratio function of T_1 and T_2 is defined as

$$\tilde{\theta}(t_1, t_2) = \frac{\lambda\left(t_1|T_2 = t_2\right)}{\lambda\left(t_1|T_2 \geq t_2\right)} = \frac{S(t_1, t_2)\partial_{12}S(t_1, t_2)}{\partial_1 S(t_1, t_2)\partial_2 S(t_1, t_2)} \tag{2.10}$$

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Equivalently, Clayton postulated a relation of the form

$$\lambda\left(t_1|T_2=t_2\right)=(1+\theta)\lambda\left(t_1|T_2\geq t_2\right) \tag{2.11}$$

Integrating both sides of Equation (2.11) implies

$$\int_0^{t_1}\frac{\partial}{\partial s}\left(-\frac{\partial \ln S(s,t_2)}{\partial t_2}\right)\,\mathrm{ds}=(1+\theta)\int_0^{t_1}\frac{\partial \ln S(s,t_2)}{\partial t_1}\,\mathrm{ds}$$

or, equivalently,

$$\ln\left(-\frac{\partial S(t_1,t_2)}{\partial t_2}\right)-\ln\left(-\frac{\partial S_2(t_2)}{\partial t_2}\right)=(1+\theta)\left(\ln S(t_1,t_2)-\ln S_2(t_2)\right)$$

Simple calculations leads to

$$\int_{=}^{t_2}\frac{\frac{\partial S(t_1,u)}{\partial t_2}}{S(t_1,u)^{1+\theta}}\,\mathrm{du}=\int_0^{t_2}\frac{\frac{\partial S(u)}{\partial t_2}}{S_2(u)^{1+\theta}}\,\mathrm{du} \tag{2.12}$$

and from a second integration over $(0,t_2)$, the bivariate survival function can be easily obtained

$$S(t_1,t_2)=\left(S_1(t_1)^{-\theta}-S_2(t_2)^{-\theta}-1\right)^{-\frac{1}{\theta}}$$

2.2 Copula Models

2.2.1 Brief Historical Overview

A copula is a function that links together marginal distribution functions to form a joint distribution. Although the first results related to copulas were introduced by Hoeffding in 1940 and Fréchet in 1951, it was Sklar (1959) who first used the term *copula* in his seminal paper. It was chosen to emphasize the manner in which a copula *couples* a joint distribution function to its univariate margins. As noted by Schweizer and Wolf (1981), "...from 1958 to 1976, virtually all the results concerning copulas were obtained in connection with the study and development of the theory of probabilistic metric spaces...". Schweizer and Wolf (1981) were the firsts who highlighted the connection between copulas and measures of dependence from a statistical point of view, but it was the pedagogical piece by Genest and MacKay (1986) which actually contributed to the spreading of the

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concept of copula among statisticians.

In that paper, the two Canadians introduced the well-known class of *Archimedean Copulas*, which still plays a key role in modeling statistical dependence in multivariate survival analysis. Genest and Rivest (1993) have also introduced nonparametric statistical methods for identifying the right copula function by means of the Kendall distribution, which also turns out to be extremely useful while investigating nonparametric ways of estimating the generator of a bivariate Archimedean copula. Shih and Louis (1995) introduced the so-called *rank-based maximum likelihood estimation* technique for dependence parameters, though a similar result was obtained by Genest and Rivest (1995). Copulas have been extensively used in many fileds, from Finance to Biostatistics, and many textbooks have been written in the last decade. The following section is mostly based on the book by Nelsen (2006), which is the main reference for an elementary but exhaustive introduction to copula modeling.

2.2.2 Basic Properties

We define copulas as a certain class of functions with specific properties. We restrict the attention to the bivariate case because that is the object of our empirical work. However, the generalization to the multivaraite case is straightforward.

Definition 2.2.1. *A two-dimensional copula is a function* $C : [0,1]^2 \to [0,1]$ *with the following properties:*

(1) For every $u, v \in [0,1]$, $C(u,0) = C(0,v) = 0$ *and* $C(u,1) = u$ *and* $C(1,v) = v$*;*

(2) For every $u_1, u_2, v_1, v_2 \in [0,1]$ *such that* $u_1 \leq u_2$ *and* $\nu_1 \leq v_2$*,*

$$C(u_2, v_2) - C(u_2, v_1) - C(u_1, v_2) + C(u_1, v_1) \geq 0$$

The first property states that the copula is grounded and has margins, while the second property states that the copula is a 2-increasing function. Copulas are bounded, and the lower and upper bounds are usually given by the following theorem.

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Theorem 2.2.1 (Hoeffding-Fréchet bounds)**.** *Let C be a copula. Then, for every $(u, v) \in [0, 1]^2$*

$$\max(u + v - 1, 0) \leq C(u, v) \leq \min(u, v)$$

The most important theorem of copula theory is the Sklar's theorem. It proves the existence of a copula representation for any joint distribution function. In particular, the copula is unique when the marginal distributions are continuous.

Theorem 2.2.2 (Sklar's Theorem)**.** *Let H be a joint distribution function with margins F and G. Then there exists a copula C such that for all $x, y \in \mathbb{R}$,*

$$H(x, y) = C(F(x), G(y))$$

If F and G are continuous, then C is unique. Conversely, if C is a copula and F and G are distribution functions, then the function H is a joint

In order to characterize the degree of global association between random variables we use nonparametric rank-invariant measures, such as the Kendall's τ and the Sperman's ρ. Let X and Y be continuous random variables whose copula is C. Then, the population version of Kendall's τ and Spearman's ρ for X and Y are given respectively by

$$\tau = 4 \int_0^1 \int_0^1 C(u, v)\, dC(u, v) - 1 \tag{2.13}$$

$$\rho = 12 \int_0^1 \int_0^1 u\, v\, dC(u, v) - 3 \tag{2.14}$$

Interestingly, the Kendall's τ can be interpreted as the expected value of the function $C(U, V)$ of uniform $(0, 1)$ random variables U and V whose joint distribution function is C,

$$\tau = 4\mathbb{E}\left(C(U, V)\right) - 1$$

2.2.3 Archimedean Copulas

Archimedean Copulas (Genest and MacKay (1986)) are the most important class of copulas for multivariate survival analysis because of their wide range of application and nice properties.

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Definition 2.2.2 (Archimedean Copulas)**.** *Let* $\psi : [0,1] \to [0,+\infty]$ *such that* $\psi(1) = 0$, $\psi^{'}(t) < 0$ *and* $\psi^{''}(t) > 0$ *on* $(0,1)$. ψ *is called the generator of the Archimedean copula, and* ψ^{-1} *is its pseudo-inverse.* C *is said to be Archimedean if*

$$C(u,v) = \psi(\psi^{-1}(u) + \psi^{-1}(v))$$

Nelsen (2006) showed that $C(u,v)$ is a copula if and only if ψ is convex.
In general, evaluating the population version of Kendalls τ requires the evaluation of the double integral in (2.13). For an Archimedean copula, the situation is simpler, in that Kendalls τ can be evaluated directly from the generator of the copula, as shown in the following corollary. Indeed, one of the reasons that Archimedean copulas are easy to work with is that often expressions with a one-place function (the generator) can be employed rather than expressions with a two-place function (the copula).

Corollary 1 (Genest and MacKay (1986))**.** *Let* X *and* Y *be random variables with an Archimedean copula* C *generated by* ψ. *The population version of Kendall's* τ *in* X *and* Y *is given by*

$$\tau = 1 + 4\int_0^1 K_C(s)\, ds \tag{2.15}$$

where K_C *is popularly known as the Kendall distribution function of the copula* $C(U,V)$, *with* $U, V \sim$ *Uniform*$(0,1)$, *which has the form*

$$K_C(s) = s - \frac{\psi(s)}{\psi^{'}(s)} \tag{2.16}$$

with associated density function given by

$$k_C(s) = \frac{\psi(s)\psi^{''}(s)}{\psi^{'}(s)^2} \tag{2.17}$$

Remark 2.2.1. *Marshall and Olkin (1988) showed that Archimedean copulas can be generated through mixture models, such as frailty models in survival analysis. In those cases,* ψ^{-1} *is the Laplace transform of frailty distribution so that*

$$C(u,v) = \mathcal{L}^{-1}\left(\mathcal{L}(u) + \mathcal{L}(v)\right)$$

This results suggests that an Archimedean copula can be constructed using the inverse of a Laplace transform as the generator.

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2.2.4 Most Common Archimedean Copula Families

Clayton Copula Model

Let $\psi^{-1}(v) = (1+\theta v)^{-\frac{1}{\theta}}$ be the inverse generator under the assumption that the frailty $Z \sim \text{Gamma}\,(\frac{1}{\theta}, \frac{1}{\theta})$. Then, the associated generator, with $\theta \in [-1, \infty)$, is given by

$$\psi(v) = \frac{v^{-\theta} - 1}{\theta} \tag{2.18}$$

The bivariate survival is then given by

$$\begin{aligned} S(t_1, t_2) &= \left(1 + \theta \left(\frac{v_1^{-\theta} - 1}{\theta} + \frac{v_2^{-\theta} - 1}{\theta}\right)\right)^{-\frac{1}{\theta}} \\ &= \left(v_1^{-\theta} + v_2^{-\theta} - 1\right)^{-\frac{1}{\theta}} \\ &= \left(S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} - 1\right)^{-\frac{1}{\theta}} \end{aligned}$$

The Kendall's distribution is given by

$$K_c(v) = \frac{v(\theta+1) - v^{\theta+1}}{\theta} \tag{2.19}$$

Let $W = C(U, V)$. Then,

$$\tau = 4\,\mathbb{E}\,[W] - 1$$

From (2.17), we have

$$\mathbb{E}\,[W] = \int_0^1 w\, dK_C(w) = 1 - \int_0^1 K_C(w)\, dw$$

It follows that the Kendall's τ under the Clayton model is given by

$$\begin{aligned} \tau &= 4\left(1 - \int_0^1 K_C(w)\, dw\right) - 1 = 3 - 4\int_0^1 \left[w - \frac{\psi(w)}{\psi'(w)}\right] dw \\ &= 1 - 4\int_0^1 \frac{w}{\theta}\, dw + 4\int_0^1 \frac{w^{\theta+1}}{\theta}\, dw = \frac{\theta}{\theta+2} \end{aligned}$$

Gumbel-Hougaard Copula Model

Let $\psi^{-1}(v) = \exp(-s^{\alpha})$ be the inverse generator under the assumption of a positive stable frailty model with scale parameter $\alpha \in (0, 1)$. Then, the associated generator, with $\theta \in [1, \infty)$, is given by

$$\psi(v) = (-\log(s))^{+\frac{1}{\alpha}} \tag{2.20}$$

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The bivariate survival function can be written as:

$$S(t_1, t_2) = \exp\left(-\left((-\log S_1(t_1))^{\frac{1}{\alpha}} + (-\log S_2(t_2))^{\frac{1}{\alpha}}\right)^{\alpha}\right) \tag{2.21}$$

Since

$$\frac{\psi(v)}{\psi^{-1}(v)} = -\frac{\alpha\, v\ (-\log(v))^{\frac{1}{\alpha}}}{(-\log(v))^{\frac{1-\alpha}{\alpha}}}$$

the Kendall's distribution can be written as

$$K_C(v) = v - v\,\alpha\,\log(v) \tag{2.22}$$

It follows that the Kendall's τ under the Gumbel-Hougaard copula is given by

$$\tau = 3 - 4\int_0^1 (v - v\,\alpha\,\log(v))\ dv = 1 - 4\alpha$$

Frank Copula Model

Based on the bivariate distribution proposed by Frank (1979), Genest (1987) introduced the Frank copula with the following generator function

$$\psi(v) = \log\left(\frac{1-\exp(-\alpha)}{1-\exp(-\alpha v)}\right) \tag{2.23}$$

Its inverse can be obtained by means of Laplace transform by assuming the frailty Z follows a log series distribution,

$$\psi^{-1}(v) = -\frac{1}{\alpha}\log\left[1-\exp(-s)(1-\exp(-\alpha))\right]$$

The bivariate survival function is then given by

$$S(t_1, t_2) = -\frac{1}{\alpha}\log\left[\frac{\exp(-\alpha) - 1 + (\exp(-\alpha S_1(t_1)) - 1)(\exp(-\alpha S_2(t_2)) - 1)}{\exp(-\alpha) - 1}\right]$$

The Kendall's distribution and the Kendall's τ are, respectively, given by

$$K_C(v) = v + \frac{1-\exp(-\alpha v)}{\alpha\exp(-\alpha v)}\log\left(\frac{1-\exp(-\alpha)}{1-\exp(-\alpha v)}\right) \tag{2.24}$$

and

$$\tau = 1 + \frac{4\left(\frac{1}{\alpha}\left(\int_0^{\alpha}\frac{t\,dt}{\exp(t)-1}\right) - 1\right)}{\alpha}$$

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2.2.5 Other Common Copula Families

Generalized Cuadras and Augé Family

The following copula family is known as the generalized Cuadras-Augé family, also known as the Marshall and Olkin family because it is obtained from the well-known *Marshall-Olkin Bivariate Exponential Distribution*, which was developed by Marshall and Olkin (1967) to model a two-component system which is subject to shocks, governed by independent Poisson processes $P_1(t, \xi_1)$, $P_2(t, \xi_2)$ and $P_3(t, \xi_3)$, where ξ_i, $i = 1, 2, 3$ denote the parameters of the corresponding Poisson processes. For each $i = 1, 2, 3$, let W_i be independent distributed exponential lifetimes with parameters $\xi_i \geq 0$, and define

$$X = \min(W_1, W_3) \sim \exp(\xi_1 + \xi_3) \tag{2.25}$$

$$Y = \min(W_2, W_3) \sim \exp(\xi_2 + \xi_3) \tag{2.26}$$

The random variables W_1 and W_2 can be interpreted as the arrival time of individual shocks for two different components, whereas W_3 represents the time of arrival of a shock common to both components.
Then, it can be shown that the bivariate survival function of the vector (X, Y), with $x, y \geq 0$, is given by

$$\begin{aligned} \bar{F}(x, y) &= \mathbb{P}(W_1 > x)\ \mathbb{P}(W_2 > y)\ \mathbb{P}(W_3 > \max(x, y)) \\ &= \exp\{-\xi_1 x - \xi_2 y - \xi_3 \max(x, y)\} \end{aligned} \tag{2.27}$$

where the marginal univariate survival functions for X and Y are $\bar{F}(x) = \exp(-(\xi_1+\xi_3)x)$ and $\bar{F}(y) = \exp(-(\xi_2 + \xi_3)y)$. Furthermore, since $\max(x, y) = x + y - \min(x, y)$, we can rewrite (2.27) in terms of uniform representation of the above survival function as follows

$$\begin{aligned} \bar{F}(x, y) &= \exp(-(\xi_1 + \xi_3)x - (\xi_2 + \xi_3)y + \xi_3 \min(x, y)) \\ &= \bar{F}(x)\bar{F}(y) \min(\exp(\xi_3 x), \exp(\xi_3 y)) \end{aligned}$$

Set $u = \bar{F}(x)$ and $v = \bar{F}(y)$, and let $\alpha = \frac{\xi_3}{(\xi_1+\xi_3)}$ and $\beta = \frac{\xi_3}{(\xi_2+\xi_3)}$. Then,

$$u^{-\alpha} = \exp(\xi_3\, x) \qquad v^{-\beta} = \exp(\xi_3\, y)$$

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with the survival copula $\hat{C}$ given by

$$\hat{C}(u,v) = u\,v\,\min(u^{-\alpha}, v^{-\beta}) = \min(u\,v^{1-\beta}, v\,u^{1-\alpha}) \tag{2.28}$$

Since the ξ's are all positive, it follows that α and β satisfy $0 < \alpha, \beta < 1$. Hence, the survival copula for the Marshall and Olkin bivariate exponential distribution yields a two-parameter family of copulas given by

$$C(u,v) = \min(u^{1-\alpha}, v^{1-\beta}) = \begin{cases} u^{1-\alpha}\,v & u^{\alpha} \geq v^{\beta} \\ uv^{1-\beta} & u^{\alpha} \leq v^{\beta} \end{cases} \tag{2.29}$$

Remark 2.2.2. *Muliere and Scarsini (1987) instead derived the extension of the above model by focusing on the class of generator functions for the survival function, that is the cumulative hazard function of the vector of lifetimes W_i, namely*

$$\bar{F}(x,y) = \exp\{-\xi_1 H(x) - \xi_2 H(y) - \xi_3 H(\max(x,y))\} \quad x,y \geq 0 \tag{2.30}$$

A recent result was given by Li and Pellerey (2011), who generalized the one in Muliere and Scarsini (1987) in the following fashion:

$$\bar{F}(x,y) = \exp\{-H_1(x) - H_2(y) - H_3(\max(x,y))\} \quad x,y \geq 0 \tag{2.31}$$

where the right continuous functions H_i are the cumulative hazard functions of the lifetimes W_i.

2.3 Multi-state Models

This section aims to introduce the reader to basic notions for Life-History data modeling. In particular, the aim is to give the basic survival toolkit to understand both probabilistic and inferential aspects in multi-state modeling.

2.3.1 Basic Notions for Life-History Modeling

Multi-state models represent the so-called event-history approach to longitudinal data modelling: individuals can experience several events, taking into account event-related risk

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dependence and possibly individual risk heterogeneity (Andersen and Keiding (2002)). We refer to Hougaard (2000) for a more in-depth treatment of both probabilistic foundations and statistical inference for multi-state models.

A multi-state model is a right-continuous stochastic process $\{X(t) : t \geq 0\}$ taking values in $\mathcal{S} = \{1, \ldots, k\}$, where $X(t)$ denote the state occupied at time $t \geq 0$. Let $Y_k(t) = I(X(t^-) = k)$ indicate that an individual is at risk of transition out of state k at time t. Let $\mathcal{H}_t = \{X(u) : 0 \leq u \leq t\}$ be the σ-field associated to such process. Let $N_{kl}(t)$ denote the number of $k \to l$ transitions over $(0, t]$ for a continuous time process. Assume that two events cannot occur simultaneously. Let also

$$\Delta N_{kl}(t) = N_{kl}\left(t + \Delta t^-\right) - N_{kl}(t^-)$$

count the number of $k \to l$ transitions over $[t, t + \Delta t)$. Let

$$d\, N_{kl}(t) := \lim_{\Delta t \downarrow 0} \Delta\, N_{kl}(t)$$

indicate a $k \to l$ transition at t. For continuous-time process, transition intensities are defined as

$$\lambda_{kl}(t|\mathcal{H}_t) = \lim_{\Delta t \downarrow 0} \frac{\mathbb{P}(X\,(t + \Delta t^-) = l | X\,(t^-) = k, \mathcal{H}_t)}{\Delta t} \tag{2.32}$$

or equivalently in terms of counting processes as

$$\lambda_{kl}(t|\mathcal{H}_{t^-}) = \lim_{\Delta t \downarrow 0} \frac{\mathbb{P}(N_{kl}\,(t + \Delta t^-) - N_{kl}\,(t^-) = 1 | Y_k(t) = 1, \mathcal{H}_{t^-})}{\Delta t} \tag{2.33}$$

which gives the risk of moving to state l out from state k at time t, given all the history $\mathcal{H}_{t^-}$ until time t. For $s < t$, the transition probabilities are defined as:

$$\mathbb{P}_{kl}(s, t|\mathcal{H}_s) = \mathbb{P}\left(X(t) = l | X(s) = k, \mathcal{H}_s\right) \tag{2.34}$$

which describes the probability of being in state l at time t given all the information available until time s.

Remark 2.3.1. *We need to use $\mathcal{H}_{t^-}$ rather than $\mathcal{H}_t$ in order to make the risk set continuous from the left. This formulation makes the models very dynamic, meaning that the course of the process is allowed to depend on everything that has happened.*

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Data from life-history processes are often incomplete since they are observed for a finite period of time. We let $(0, C]$ denote the interval over which $\{X(t) : t \geq 0\}$ is observed. Let $Y(t) = I(t \leq C)$ indicate a process is under observation at time t. We define

$$\begin{aligned}
\overline{Y}_k(t) &= Y(t)Y_k(t) \\
d\overline{N}_{kl}(t) &= \overline{Y}_k(t)dN_{kl}(t) \\
\overline{N}_{kl}(t) &= \int_0^t d\overline{N}_{kl}(s)
\end{aligned}$$

Under the Markov assumption, the transition probabilities are

$$\mathbb{P}_{kl}(s,t) = \mathbb{P}\left(X(t) = l | X(s) = k\right) = \sum_{j \in \mathcal{S}} \mathbb{P}_{kj}(s,u)\mathbb{P}_{jl}(u,t)$$

whereas Markov transition intensities are of the form

$$\lambda_{kl}(t|\mathcal{H}_t) = Y_k(t)\, q_{kl}(t) \tag{2.35}$$

Define $\mathbb{Q}(t) = \{q_{kl}(t)\}$ the $\mathcal{S} \times \mathcal{S}$ transition intensity matrix with off-diagonal elements $q_{kl}(t)$, and diagonal elements $q_{kk}(t) = -\sum_{k \neq l} q_{kl}(t)$. Let $\mathbb{H}(t) = \{\mathbb{H}_{kj}(t)\}$ be a $\mathcal{S} \times \mathcal{S}$ matrix which entries are given by

$$\mathbb{H}_{kl}(t) = \int_0^t q_{kl}(s)\mathrm{ds} \tag{2.36}$$

Let $\mathbb{P}(s,t) = \{\mathbb{P}_{ik}(s,t)\}$ stand for the $\mathcal{S} \times \mathcal{S}$ transition probability matrix. By a general result of product integrals this solution takes the form

$$\mathbb{P}(s,t) = \prod_{(s,t]} (\mathbb{I} + d\mathbb{H}(u)) \qquad s \leq t \tag{2.37}$$

where $\mathbb{I}$ is the $\mathcal{S} \times \mathcal{S}$ identity matrix. With a sample of size n, let

$$d\hat{\mathbb{H}}_{kl}(t) = \frac{\sum_{i=1}^n \overline{Y}_{ik}(t) d\, N_{ikl}(t)}{\sum_{i=1}^n \overline{Y}_{ik}(t)} \qquad k \neq l \tag{2.38}$$

If $D_{kl}(s,t)$ denotes the set of all $k \to l$ transition times over $(s,t]$,

$$\hat{\mathbb{H}}_{kl}(t) = \int_0^t d\,\hat{\mathbb{H}}_{kl}(t) = \sum_{u \in D_{kl}(0,t)} d\,\hat{\mathbb{H}}_{kl}(t) \tag{2.39}$$

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is the Nelson-Allen estimate. If

$$D(s,t) = \{\text{distinct transition times of any type over } (s,t]\}$$

the corresponding Aalen-Johansen estimator (1978) based on the estimated cumulative hazards matrix is

$$\hat{\mathbf{P}}(s,t) = \prod_{(s,t]} \left(\mathbf{I} + d\hat{\mathbf{H}}(u)\right) \tag{2.40}$$

2.3.2 Likelihood Evaluation for Multi-state Models

We now move to the construction of the likelihood function for Markovian multi-state models. Assume K types of events are of interest, and that an individual is observed over $(0, C]$; the end of follow-up time C is assumed independent of the subsequent life history, given the observed past history. Hence, the observed data consist of the last time at which the subject is observed, C, and a set of couples (t_k, s_k) with $k = 1, \ldots, n$ concerning the n transitions into states $s_1, \ldots, s_n$ at time $t_1 < \ldots < t_n$.

The likelihood function for a generic multi-state model can be written as a product integral. Let $g(t)$ be a continuous integrable function over $(a, b]$ (in survival applications, this is the cumulative hazard function), and partition the time interval $(a, b]$ into a number of time intervals $a = t_0 < t_1 < \cdots < t_R = b$, and let $\Delta t_r = t_r - t_{r-1}$. Consider the finite product

$$\prod_{(a,b]} \{1 + g(u)\,\mathrm{d}u\} \tag{2.41}$$

If we let the number R of time intervals increase while their lengths go to zero in a uniform way, that is $\max(\Delta t_r) = \max(t_r - t_{r-1}) \to 0$, the product will approach a limit, which is termed as *product integral*.

$$\prod_{(a,b]} \{1 + g(u)\,\mathrm{d}u\} = \lim_{R\to+\infty} \prod_{r=1}^{R} \{1 + g(u)\,\Delta\, u_r\} \tag{2.42}$$

Here, the product-integral notion $\prod$ is used to suggest a limit of finite products $\prod$, just as the integral $\int$ is a limit of finite sums $\sum$ (Gill and Johansen (1990); Andersen et al. (1993)). Since

$$\log\{1 + g(u)\,\Delta\, u_r\} = g(t_r)\Delta\, t_r + o(\Delta\, t_r)$$

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we see that Equation (2.42) can be written as

$$\prod_{(a,b]} \{1 + g(u)\,\mathrm{du}\} = \exp\left(\int_a^b g(u)\,\mathrm{du}\right) \tag{2.43}$$

Suppose K types of events are of interest. In an event-history process, note that

$$P\left(\text{no events in } (t, t+\Delta t] | \mathcal{H}(t)\right) = 1 - \sum_{k=1}^{K} Y_k(u)\,\lambda_k(u|\mathcal{H}(u))\,\Delta u + o(\Delta\, u)$$

In terms of product integrals,

$$P\left(\text{no events in } (t, t+s] | \mathcal{H}(t)\right) = \exp\left(-\int_t^{t+s} \sum_{k=1}^{K} Y_k(u)\,\lambda_k(u|\mathcal{H}(u))\,\mathrm{du}\right) \tag{2.44}$$

Suppose $X(0) = s_0$ and a life history over $(0, C]$ consists of transitions into states $s_1, \ldots, s_n$ at times $t_1 < \cdots < t_n$. Letting $C = t_{n+1}$, the likelihood can be written as (Hougaard (2000), page 181)

$$\prod_{k=1}^{n} \lambda_{s_{k-1}\,s_k}(t_k|\mathcal{H}(t_k)) \prod_{k=1}^{n+1} \prod_{[t_{k-1},t_k)} \left\{1 - \sum_{l \neq s_{k-1}} \lambda_{s_{k-1},s}(u|\mathcal{H}(u))\,\mathrm{du}\right\} \tag{2.45}$$

$$\prod_{k=1}^{n} \lambda_{s_{k-1}\,s_k}(t_k|\mathcal{H}(t_k)) \prod_{k=1}^{n+1} \exp\left(-\int_{t_{k-1}}^{t_k} \sum_{s \neq s_{k-1}} \lambda_{s_{k-1},s}(u|\mathcal{H}(u))\,\mathrm{du}\right) \tag{2.46}$$

2.4 Length-Biased Survival Data

The Kaplan-Meier estimator is the nonparametric maximum likelihood estimate (NPMLE) for lifetime data with right-censoring, and reduces to the empirical survival function in the case of no censoring. However, the Kaplan-Meier is no longer the efficient estimator for lifetime data in the presence of left-truncation because of informative censoring.

Nonparametric estimation of the survivor function from left-truncated data was firstly investigated by Lynden-Bell (1971). Woodroofe (1985) studied Lynden-Bell estimator thoroughly. It was then Tsai et al. (1987) who extended Lynden-Bells work for estimating the survivor function from left-truncated right-censored data. Wang (1991) pointed out that the Kaplan-Meier estimator can be properly adjusted to accomodate left-truncation

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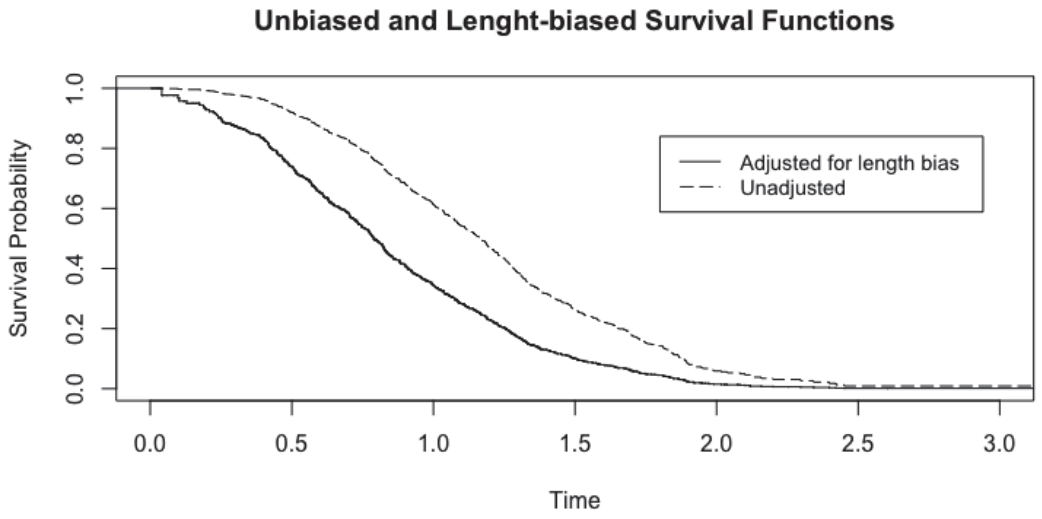

Figure 2.1: Unbiased (solid) vs Length-biased (dashed) Survival Function.

by conditioning upon the truncation time, and it can be referred to as a *conditional approach* to estimation. She also pointed out that when it is possible to make a reasonable, parametric assumption on the truncation distribution, the Tsai et al. (1987) estimator is not asymptotically most efficient after incorporating this information into the estimation procedure, compared to the case where the truncation distribution is completely unknown. However, an unconditional approach to a nonparametric estimation of the survival function for length-biased survival data has been developed by Vardi (1989), but requires the assumption that the truncation times follow (conditionally) a uniform distribution, that is the initiation times of a disease follow a stationary Poisson process. More specifically, Vardi (1989) focused on estimating the prevalent-case survivor function under a special type of censoring which puts mass only at zero and one. He also mentions that from this estimator one can proceed to estimating the incident-case survivor function. However, the theoretical aspects of this estimator was studied by Vardi and Zhang (1992).

The study of the incident-case survivor function under right-censoring and length-biased sampling is due to Asgharian et al. (2002), and the foundations of the work were made in Asgharian and Wolfson (2005), where they highlighted the distinctions between their work and the Vardi's one. The study on density estimation under multiplicative censoring

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is in Asgharian et al. (2012).

Asgharian et al. (2006) and Adonna and Wolfson (2006) have proposed a test for stationarity of the incidence rate in prevalent cohort studies. If this assumption holds, lifetimes sampled from a prevalent cohort are considered to be length-biased. For length-biased lifetimes, the probability of selecting a subject from the target population is directly proportional to their lifetime. As noted by Asgharian et al. (2015), if the stationarity assumption does not hold, the sampled lifetimes are just said to be left-truncated. Generally, left-truncated survival times are length-biased, though they are distinctively used to distinguish between stationary (incidence rate are constant) versus non-stationarity (when the incidence rate changes over time).

Figure 2.1 represents the overall survival probability function estimated nonparametrically from $N = 1000$ length-biased survival times having Weibull$(2, 1)$ baseline; it clearly illustrates how ignoring the length-bias leads to an overestimation of the survival function. When stationarity holds, Asgharian et al. (2002) showed that Vardi's unconditional estimator is more efficient than the modified Kaplan-Meier estimator. Bergeron et al. (2008) have also extended such a framework in the presence of covariates. Before describing Vardi's method of estimation, it is necessary to provide the fundamental tools for length-biased survival data analysis.

Associated to each subject in the target population we have a triple (X, T, C), where X is the failure time, T the truncation time and C the censoring time, all measured from the onset date.

Assumption 1. $X \perp\!\!\!\perp (T, C)$

Assumption 2. *Subjects are observed if* $X \geq T$

Assume that $X \sim F_X(x)$ with density $f_X(x)$, called *unbiased density*, whereas $T \sim G_T(t)$ with density $g_T(t)$, called *truncation density*. The joint distribution of (X, T) given that the subject is in the observed sample is given by

$$f_{X,T}\left(x, t | X \geq T\right) = \frac{f_{X,T}\left(x, t \cap X \geq T\right)}{\mathbb{P}\left(X \geq T\right)} \underbrace{=}_{\text{Assumption 1}} \frac{g_T(t) f_X(x)\, I\left(x \geq t\right)}{\mathbb{P}\left(X \geq T\right)} \tag{2.47}$$

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where

$$\mathbb{P}\left(X \geq T\right) = \int_{t=0}^{+\infty} \mathbb{P}\left(X \geq u | T = t\right)\, g_T(t)\,\mathrm{dt} = \int_{t=0}^{+\infty} S_X(t)\, g_T(t)\,\mathrm{dt}$$

Under the stationary assumption, $g_T(t) \equiv k > 0$, the length-biased density, say $h(\cdot)$, is related to the unbiased density through the equation

$$h(x) = f\left(x | X \geq T\right) = \int_{t=0}^{x} f_{X,T}\left(x, t | X \geq T\right)\,\mathrm{dt} = \frac{G_T(x)\, f_X(x)}{\int_0^{+\infty} S_X(t)\, g_T(t)\,\mathrm{dt}}$$

By the stationarity assumption,

$$h(x) = \frac{x\, f_X(x)}{\int_0^{+\infty} S_X(t)\,\mathrm{dt}} \tag{2.48}$$

This is the length-biased density of $X \sim F_X$ that is observed with probability proportional to its value. Note that if $X \sim f_X$ is a continuous random variable, then the denominator in Equation (2.48) equals the expected value of the random variable X. Indeed,

$$\begin{aligned}
\mu_X = \int_0^{+\infty} \mathbb{P}\left(X \geq x\right)\,\mathrm{dx} &= \int_0^{+\infty} \left(\int_x^{+\infty} f_X(u)\,\mathrm{du}\right)\,\mathrm{dx} \\
&\overset{(=)}{\downarrow} \int_0^{+\infty} f_X(u) \left(\int_0^{u} \mathrm{dx}\right)\,\mathrm{du} \\
&\quad \text{Fubini-Tonelli's Theorem} \\
&= \int_0^{+\infty} u\, f_X(u)\,\mathrm{du} = \mathbb{E}\left[X\right]
\end{aligned}$$

Let $\tilde{X}_1, \ldots, \tilde{X}_k \overset{iid}{\sim} H$, where $\tilde{X}_i = \tilde{T}_i + \min\left(R_i, \tilde{C}_i\right)$, with $\tilde{T}_i$ is the observed time from onset to recruitment, *backward recurrence time*, and R_i is the observed time from recruitment to the event of interest, *forward recurrence time*, and

$$H(x) = \mathbb{P}_X\left(x | X \geq T\right) = \int_x^{+\infty} h(t)\,\mathrm{dt} = \frac{\int_x^{+\infty} t\, f_X(t)\,\mathrm{dt}}{\int_0^{+\infty} S_X(t)\,\mathrm{dt}}$$

Suppose that the W_i's are randomly censored by the C_i's, so that the observed, possibly censored data are $\left\{\left(\tilde{T}_i, \min(R_i, \tilde{C}_i), \delta_i\right), i = 1, \ldots, k\right\}$. Then, one may assume:

Assumption 3. $\left(\tilde{T}_i, \min(R_i, \tilde{C}_i), \delta_i\right) \perp\!\!\!\perp \left(\tilde{T}_j, \min(R_j, \tilde{C}_j), \delta_j\right) \quad i \neq j \in \{1, \ldots, k\}$

Note that the censoring time measured from the initiation $\tilde{T}_i + C_i$ is mechanistically dependent on failure time $\tilde{T}_i + \tilde{R}_i$ even if C_i is independent of $(\tilde{T}_i, R_i)$. Hence, the assumption

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that $\tilde{C}_i \perp\!\!\!\perp (\tilde{T}_i, R_i)$, with $i = 1, \ldots, k$ is not necessary. Asgharian et al. (2006) derived the backward and forward recurrence time density, which are given, respectively, by

$$f_{\tilde{T}}(t) = \frac{g_T(t)\, S_X(t)}{\int_0^{+\infty} g_T(t)\, S_X(t)\, \mathrm{dt}} \tag{2.49}$$

and

$$f_R(r) = \frac{\int_0^{+\infty} g_T(t)\, f_X(t+r)\, \mathrm{dt}}{\int_0^{+\infty} g_T(t)\, S_X(t)\, \mathrm{dt}} \tag{2.50}$$

2.4.1 Vardi's Unconditional NPMLE Approach for Length-Biased Data

Vardi (1989) derived the NPMLE of a length-biased survivor function from multiplicatively censored data. Consider a sample which has m independent complete observations and n independent incomplete observations (which are fixed). The m complete observations $\tilde{X}_1, \ldots, \tilde{X}_m$ are drawn from a length-biased distribution H. Consider, now, the random variable U which is independently selected from a uniform distribution on $(0, 1)$. Then, the n incomplete observations $Z_1, \ldots, Z_n$ are such that $Z_i = Y_i\, U_i$, where Y_i has the same length-biased distribution H as the $\tilde{X}$'s.

Based on the sample of $X_1, \ldots, X_m$ and $Z_1, \ldots, Z_n$, Vardi suggested to estimate H nonparametrically by proposing the likelihood for the observations as

$$L(H) := \prod_{i=1}^{m} H(dx_i) \prod_{i=1}^{n} \int_{y \geq z_i} \frac{1}{y} H(dy) \tag{2.51}$$

To maximize the above likelihood function, EM-algorithm was employed by Vardi because of the presence of incomplete observations (Dempster et al. (1977)). Writing the full failure times as $x_i = t_i + r_i$, for $i = 1, \ldots, m$ and the incomplete times as $y_i = t_{m+i} + T^*$ for $i = 1, \ldots, n$ and some time T^* such that $R_i \leq T^*$ for full observations and $R_i > T^*$ for incomplete observations, the likelihood function for this data can be written as

$$\prod_{i=1}^{m} \frac{f(x_i)}{\mu} \prod_{i=1}^{n} \frac{S(y_i)}{\mu} \tag{2.52}$$

Qin and Shen (2010) and Huang and Qin (2012) have recently proposed alternative estimators for length-biased sampling. The former proposed estimating methods for covariate

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coefficients under the Cox model, whereas the latter proposed a nonparametric estimator which permits to eliminate the lack of a closed-form expression for the asymptotic variance in the Vardi's NPLME.

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Chapter 3

Conditional frailty Marshall-Olkin survival models for bivariate censored failure time data

3.1 Introduction

Among multivariate survival models, the shared frailty (Clayton (1978); Oakes (1982)) assumes that each member of a specific statistical unit (e.g. married couples, twins, paired organs) shares a common unobserved random effect, which acts multiplicatively on the marginal hazard functions, so that the model can be specified as

$$S\left(t_1, t_2 | \boldsymbol{Z}, X\right) = e^{-Z(\Lambda_{01}(t_1)+\Lambda_{02}(t_2))e^{\boldsymbol{\beta}'\boldsymbol{X}}} \tag{3.1}$$

where $\Lambda_{0i}(t_i) = \int_0^{t_i} h_{0i}(s)\,\mathrm{ds}$ $(i = 1, 2)$ is the baseline cumulative hazard function, Z is the unobservable *shared* frailty term, and $\boldsymbol{X}$ is a vector of possibly covariates with $\boldsymbol{\beta}$ denoting a regression vector parameters to be estimated.

Yashin and Iachine (1995) generalize the shared frailty model by allowing each member of the group to have a individual-specific frailty component and only a fraction of Z in common, which induces some dependence among failure times: such model is called correlated frailty model, and its properties have been widely investigated by Parner (1998)

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and Petersen (1998).

The aim of this chapter is to develop a new frailty survival model for examining the association between paired failure times under the presence of right-censoring. To take into account the correlation between these measurements, the well-known Marshall-Olkin Bivariate Exponential Distribution (MOBVE) is considered for the joint distribution of frailties. The reason is twofold: on the one hand, it allows to model shocks that affect individual-specific frailties; on the other hand, the parameter underlying the Poisson process describing the common shock completely captures the dependence between the pair of lifetimes (T_1, T_2).

In order to investigate the association in bivariate right-censored failure time data, several authors have also employed Copula based survival models. Shih and Louis (1995) examined the association of the bivariate data that are both subject to right censoring, through a two-stage semiparametric estimation procedure. Zhang et al. (2010) have also investigated the association of bivariate event times using a copula model. However, they focused on the case where one of the paired event time data is right-censored and the other is observed as current status data. Hanagal and Sharma (2015) proposed a shared gamma frailty regression model under random censoring with Marshall-Olkin distribution as baseline hazard for bivariate survival times. Geerdens et al. (2016) derived a more flexible copula model for examining clustered event times. In a slightly different context, Sutradhar and Cook (2016) have proposed a fully parametric conditional frailty model for examining the association between paired failure times under the presence of interval-truncation.

The proposed methodology is then applied to the investigation of association in dementia onset in different-sex couples to the Cache County Study on Memory Health and Aging (CCSMHA) data (Norton et al. (2010)). Our analysis focuses only on non-prevalent couples, that is couples whose members are dementia-free at the entry of the study.

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3.2 Bivariate Marshall-Olkin Frailty Model

Let $(\mathcal{T}, \mathcal{F})$ and $(Z, \mathcal{B})$ be two measurable spaces, and assume $\mathcal{T} = \prod_{i=1}^{n} \mathcal{T}_i$ and $\mathcal{F} = \bigotimes_{i=1}^{n} \mathcal{F}_i$. Let $\mathcal{P}^* = \prod_{i=1}^{n} \mathcal{P}_i$ be the family of product measures on $(\mathcal{T}, \mathcal{F})$, where $\mathcal{P}_i = \{P_{z_i}, z_i \in Z_i \subseteq \mathbb{R}\}$, with $i = 1, \ldots, r$, such that the mapping $z_i \longmapsto P_{z_i}(A_i)$ is $\mathcal{B}$-measurable for each $A_i \in \mathcal{F}_i$.

Assume $\vec{T} = (T_1, \ldots, T_r)$ to be a vector of r random lifetimes, each with probability measure P_{z_i}. Let P_z^* be a n-variate probability measure on $(\mathcal{T}, \mathcal{F})$ such that

$$P^*(A) = \prod_{i=1}^{r} P_{z_i}(A_i) \tag{3.2}$$

for all $A \in \mathcal{F}$. Suppose that $\tilde{G}$ is any arbitrary r-variate mixing ditribution on Z, and denote the marginals of $\tilde{G}$ by $\tilde{G}_i$, with $i = 1, \ldots, r$. Define

$$S(A) = \int_Z P_z^*(A) \mathrm{d}\tilde{G}(z) \qquad A \in \mathcal{F} \tag{3.3}$$

Then, S is a mixture of the family $\mathcal{P}^* = \prod_{i=1}^{r} \mathcal{P}_i$, and $\tilde{G}$ is called a mixing distribution on Z. Let Λ be the class of all mixing distributions $\tilde{G}$ on $(Z, \mathcal{B})$ and ζ be the corresponding class of mixtures.

In this paper, we focus on the bivariate case, though the r-variate case is, in principle, straightforward; by Equation (3.2) and (3.3) we have that

$$S(t_1, t_2) = \int \int P_{z_1}(t_1) P_{z_2}(t_2) \, \mathrm{d}\, \tilde{G}(z_1, z_2)$$

where the marginals H_1 and H_2 are given by

$$S_i(t_i) = \int_Z P_{z_i}(t_i) \, \mathrm{d}\, \tilde{G}(z_i) \qquad (i = 1, 2) \tag{3.4}$$

Let $\phi_z(\cdot)$ be the Laplace transform of a positive distribution function $\tilde{G}(z)$, with

$$\phi_z(t) = \int_0^{+\infty} e^{-tz} \, \mathrm{d}\, \tilde{G}(z) \quad t \geq 0$$

Marshall and olkin (1988) showed that if

$$P_{z_i}(t_i) = \exp(-\phi_{z_i}^{-1} H_i(t_i)) \qquad (i = 1, 2) \tag{3.5}$$

where $\phi_{z_i}^{-1}$ is the inverse Laplace transform of $\tilde{G}_i$, then S is a bivariate distribution function with marginals S_1 and S_2.

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3.2.1 A result related to Cumulative Hazard Ordering

Let T_1 and T_2 be two non-negative lifetimes with absolutely continuous distribution function, and let $S(t_1, t_2)$ be the bivariate survival function with marginals $S_1(t_1) = S(t_1, 0)$ and $S_2(t_2) = S(0, t_2)$. A natural measure of mutual dependence between two related events is *the conditional hazard ratio function*, which is defined as follows:

$$\tilde{\theta}(t_1, t_2) = \frac{\lambda\left(t_1 | T_2 = t_2\right)}{\lambda\left(t_1 | T_2 \geq t_2\right)} = \frac{S(t_1, t_2)\partial_{12} S(t_1, t_2)}{\partial_1 S(t_1, t_2)\partial_2 S(t_1, t_2)} \tag{3.6}$$

where $\partial_{1,2}$ denote the partial derivative with respect to $T_1 = t_1$ and $T_2 = t_2$, and ∂_i denote the partial derivative with respect to $T_i = t_i$, where $i = 1, 2$.

In its original formulation, such a measure holds for any two events generated under a common gamma frailty, but a natural extension may include the possibility of considering the risk of failure at a given age t_i for the i^{th}-individual, given the information about the status of the other couple-related individual, under an arbitrary frailty model.

Recall that

$$S(t_1 | T_2 > t_2) = \frac{S(t_1, t_2)}{S(t_2)} \qquad\qquad S(t_1 | T_2 = t_2) = \frac{\partial S(t_1, t_2)/\partial t_2}{\partial S(t_2)/\partial t_2}$$

When $z_1 > z_2$, the conditional hazard ratio function is given by

$$\tilde{\theta}_{>}(t_1, t_2) = 1 + \frac{\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2) + \sum_{i=1}^{3} \xi_i\right)\left(\Lambda_{01}(t_1) + \xi_1 + \xi_3\right)}{\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2) + \sum_{i=1}^{3} \xi_i\right)} \tag{3.7}$$

Instead, when $z_1 < z_2$, we have that

$$\tilde{\theta}_{<}(t_1, t_2) = 1 + \frac{\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2) + \sum_{i=1}^{3} \xi_i\right)\left(\Lambda_{02}(t_1) + \xi_1 + \xi_3\right)}{\left(\Lambda_{01}(t_1) + \Lambda_{02}(t_2) + \sum_{i=1}^{3} \xi_i\right)} \tag{3.8}$$

whereas for the singular case, $\tilde{\theta}(t_1, t_2)$ is constant, which is consistent with the assumptions of the shared frailty model in Oakes (1982).

Equation (3.6) can be equivalently written in terms of conditional hazards with respect to a typical history as in Equation (6.B.25) in Shaked and Shanthikumar (2007), that is:

$$\tilde{\theta}(t_1, t_2) = \frac{\frac{f_{T_2|T_1}(t_2|t_1)}{f_{T_2|T_1 \geq t_1}(t_2|T_1 \geq t_1)}}{\frac{S_1(t_1)}{S(t_1, t_2)\, S_2(t_1)}\left[1 - \frac{\int_{t_2}^{t_1} f_{2|1}(u|T_1 = t_1)\, \mathrm{d}u}{\int_{t_2}^{+\infty} f_{2|1}(u|T_1 = t_1)\, \mathrm{d}u}\right]} \tag{3.9}$$

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When $t_1 < t_2$,

$$\begin{aligned}\lambda\left(t_1|T_2 \geq t_2\right) &= \lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\,|T_1 \geq t_1, T_2 \geq t_2\right) \\ &= \lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \geq t_2\right)}{\mathbb{P}\left(T_1 \geq t_1, T_2 \geq t_2\right)} \\ &\underset{\text{since } t_1 < t_2}{\overset{(=)}{\downarrow}} \lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \geq t_1, T_2 \geq t_2\right)}{\mathbb{P}\left(T_1 \geq t_1, T_2 \geq t_2\right)}\end{aligned}$$

Hence,

$$\begin{aligned}&\lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_2 \geq t_2 | T_2 \geq t_1, T_1 \in [t_1, t_1+\Delta t_1)\right) \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1) \cap T_2 \geq t_1\right)}{S\left(t_1, t_2\right)} = \\ &\lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \frac{\left[1 - \mathbb{P}\left(T_2 < t_2 | T_2 \geq t_1, T_1 \in [t_1, t_1+\Delta t_1)\right)\right] \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1) \cap T_2 \geq t_1\right)}{S\left(t_1, t_2\right)}\end{aligned}$$

Since

$$\begin{aligned}&\left[1 - \mathbb{P}\left(T_2 < t_2 | T_2 \geq t_1, T_1 \in [t_1, t_1+\Delta t_1)\right)\right] \\ &= 1 - \frac{\mathbb{P}\left(\{t_1 < T_2 < t_2\}\,|T_1 \in [t_1, t_1+\Delta t_1)\right)}{\mathbb{P}\left(T_2 \geq t_1 | T_1 \in [t_1, t_1+\Delta t_1)\right)} \\ &= 1 - \frac{\mathbb{P}\left(\bigcup_{u=t_1}^{t_2} T_2 \in [u, u+\Delta u)\,|T_1 \in [t_1, t_1+\Delta t_1)\right)}{\mathbb{P}\left(T_2 \geq t_1 | T_1 \in [t_1, t_1+\Delta t_1)\right)} \\ &= 1 - \frac{\int_{t_1}^{t_2} f_{2|1}(u|T_1 = t_1)\,\mathrm{du}}{\int_{t_1}^{+\infty} f_{2|1}(u|T_1 = t_1)\,\mathrm{du}}\end{aligned}$$

holds for every $t_1 < t_2$, and

$$\begin{aligned}&\lim_{\Delta t_1 \downarrow 0} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t) \cap T_2 \geq t_1\right)}{\Delta t_1} \\ &= \lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\right)}{\mathbb{P}\left(T_2 \geq t_1\right)} \\ &= \frac{f_{T_1}(t_1)}{S_1(t_1)} \frac{S_1(t_1)}{S_2(t_1)} = \lambda_1(t_1) \frac{S_1(t_1)}{S_2(t_1)}\end{aligned}$$

then we have that:

$$\lambda\left(t_1|T_2 \geq t_2\right) = \frac{\lambda_1(t_1)}{S\left(t_1, t_2\right)} \left[1 - \frac{\int_{t_1}^{t_2} f_{2|1}(u|T_1 = t_1)\,\mathrm{du}}{\int_{t_1}^{+\infty} f_{2|1}(u|T_1 = t_1)\,\mathrm{du}}\right] \frac{S_1(t_1)}{S_2(t_1)} \tag{3.10}$$

Furthermore, note that

$$\lambda\left(t_1|T_2 = t_2\right) = \lim_{\substack{\Delta t_1 \downarrow 0 \\ \Delta t_2 \downarrow 0}} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\,|T_2 \in [t_2, t_2+\Delta t_2)\right)}{\Delta t_1 \Delta t_2}$$

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Since

$$\begin{aligned}
&\lim_{\substack{\Delta t_1\downarrow 0\\ \Delta t_2\downarrow 0}} \frac{1}{\Delta t_1 \Delta t_2} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \in [t_2, t_2+\Delta t_2)\right)}{\mathbb{P}\left(T_1 \geq t_1, T_2 \in [t_2, t_2+\Delta t_2)\right)} \\
&= \lim_{\substack{\Delta t_1\downarrow 0\\ \Delta t_2\downarrow 0}} \frac{1}{\Delta t_1 \Delta t_2} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1) | T_2 \in [t_2, t_2+\Delta t_2)\right)}{\mathbb{P}\left(T_1 \geq t_1 | T_2 \in [t_2, t_2+\Delta t_2)\right)} \\
&= \lim_{\substack{\Delta t_1\downarrow 0\\ \Delta t_2\downarrow 0}} \frac{1}{\Delta t_1 \Delta t_2} \frac{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2) | T_1 \in [t_1, t_1+\Delta t_1)\right) \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\right)}{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2) | T_1 \geq t_1\right) \mathbb{P}\left(T_1 \geq t_1\right)} \\
&= \lim_{\substack{\Delta t_1\downarrow 0\\ \Delta t_2\downarrow 0}} \frac{1}{\Delta t_1 \Delta t_2} \left[\frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\right)}{\mathbb{P}\left(T_1 \geq t_1\right)}\right] \left[\frac{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2) | T_1 \in [t_1, t_1+\Delta t_1)\right)}{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2) | T_1 \geq t_1\right)}\right]
\end{aligned}$$

and that for any $t_1 < t_2$, it holds that

$$\begin{aligned}
&\lim_{\substack{\Delta t_1\downarrow 0\\ \Delta t_2\downarrow 0}} \frac{1}{\Delta t_2 \Delta t_1} \mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2) | T_1 \in [t_1, t_1+\Delta t_1)\right) \\
&= \lim_{\Delta t_1\downarrow 0} \frac{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2), T_1 \in [t_1, t_1+\Delta t_1)\right)}{\Delta t_2 \Delta t_1 \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\right)} = f_{T_2|T_1}(t_2|t_1)
\end{aligned}$$

It follows that

$$\lambda\left(t_1 | T_2 = t_2\right) = \lambda_{T_1}(t_1) \frac{f_{T_2|T_1}(t_2|t_1)}{f_{T_2|T_1 \geq t_1}(t_2 | T_1 \geq t_1)} \tag{3.11}$$

When $t_2 < t_1$,

$$\begin{aligned}
\lambda\left(t_1 | T_2 \geq t_2\right) &= \lim_{\Delta t_1\downarrow 0} \frac{1}{\Delta t_1} \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1) | T_1 \geq t_1, T_2 \geq t_2\right) \\
&= \lim_{\Delta t_1\downarrow 0} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \geq t_2\right)}{\mathbb{P}\left(T_1 \geq t_1, T_2 \geq t_2\right)} \\
&\underset{\text{since } t_2 < t_1}{\overset{(=)}{\downarrow}} \lim_{\Delta t_1\downarrow 0} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \geq t_2, T_1 \geq t_2\right)}{\mathbb{P}\left(T_1 \geq t_1, T_2 \geq t_2\right)}
\end{aligned}$$

It is easy to see that

$$\begin{aligned}
&\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \geq t_2, T_1 \geq t_2\right) = \\
&\mathbb{P}\left(T_2 \geq t_2 | T_1 \in [t_1, t_1+\Delta t_1), T_1 \geq t_2\right) \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1) \cap T_1 \geq t_2\right)
\end{aligned}$$

where

$$\mathbb{P}\left(T_2 \geq t_2 | T_1 \in [t_1, t_1+\Delta t_1), T_1 \geq t_2\right) = \mathbb{P}\left(\bigcup_{u=t_2}^{t_1} T_2 \in [u, u+\Delta u) | T_1 \in [t_1, t_1+\Delta t_1)\right)$$

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so that

$$\lambda\left(t_1|T_2 \geq t_2\right) = \frac{\left[\int_{t_2}^{t_1} f_{2|1}(u|t_1)\,\mathrm{du}\right] f_{T_1}(t_2)}{S(t_1,t_2)} \tag{3.12}$$

Furthermore,

$$\begin{aligned}
\lambda\left(t_1|T_2 = t_2\right) &= \lim_{\Delta t_1 \downarrow 0} \frac{1}{\Delta t_1} \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\,|T_1 \geq t_1, T_2 \geq t_2\right) \\
&= \lim_{\substack{\Delta t_1 \downarrow 0 \\ \Delta t_2 \downarrow 0}} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1), T_2 \in [t_2, t_2+\Delta t_2), T_1 \geq t_2\right)}{\mathbb{P}\left(T_1 \geq t_1, T_2 \in [t_2, t_2+\Delta t_2)\right)} \\
&\underset{\text{since } t_2 < t_1}{\overset{(=)}{\downarrow}} \lim_{\substack{\Delta t_1 \downarrow 0 \\ \Delta t_2 \downarrow 0}} \frac{1}{\Delta t_1} \frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t)\,|T_2 \in [t_2, t_2+\Delta t_2)\right)}{\mathbb{P}\left(T_1 \geq t_1 | T_2 \in [t_2, t_2+\Delta t_2)\right)}
\end{aligned}$$

Since

$$\begin{aligned}
&\frac{\mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t)\,|T_2 \in [t_2, t_2+\Delta t_2)\right)}{\mathbb{P}\left(T_1 \geq t_1 | T_2 \in [t_2, t_2+\Delta t_2)\right)} = \\
&\frac{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2)\,|T_1 \in [t_1, t_1+\Delta t_1), T_1 \geq t_2\right) \mathbb{P}\left(T_1 \in [t_1, t_1+\Delta t_1)\,|T_1 \geq t_2\right)}{\mathbb{P}\left(T_2 \in [t_2, t_2+\Delta t_2)\,|T_1 \geq t_1\right) \mathbb{P}\left(T_1 \geq t_2\right)}
\end{aligned}$$

it is easy to see that

$$\lambda\left(t_1|T_2 = t_2\right) = \lambda_{T_1}(t_2) \frac{f_{T_2|T_1}(t_2|t_1)}{f_{T_2|T_1 \geq t_2}(t_2|T_1 \geq t_2)} \tag{3.13}$$

Proposition 1. *Let (T_1, T_2) be a bivariate vector of random lifetimes with pdf given by $f(t_i;\theta)$, with $t_i \in \mathcal{T} \subseteq \mathbb{R}$, $\theta = (\theta_1, \ldots, \theta_k) \in \Theta \subseteq \mathbb{R}^k$, $i = 1, 2$. Assume that $(T_1, T_2)^k \leq_{lr} (T_1, T_2)^h$ for all $t_1, t_2 : t_1 < t_2$ and for all $k \neq h \in \{1, 2, \ldots, n\}$.*

If each component of (T_1, T_2) marginally belongs to the exponential family, then

$$(T_1, T_2)^k \leq_{ch} (T_1, T_2)^h \Longrightarrow \tilde{\theta}(t_{1_k}, t_{2_k}) > \tilde{\theta}(t_{1_h}, t_{2_h}).$$

Proof. Assume $(T_1, T_2)^k \leq_{ch} (T_1, T_2)^h$. Then, by Equation (6.C.4) in Shaked and Shanthikumar (2007)

$$\int_{t_1}^{+\infty} \lambda_{2|1}^k(u|T_1 = t_1)\,\mathrm{du} > \int_{t_1}^{+\infty} \lambda_{2|1}^h(u|T_1 = t_1)\,\mathrm{du}$$

Since it holds for all $t_1, t_2 : t_1 < t_2$, we have that

$$\int_{t_1}^{t_2} \lambda_{2|1}^k(u|T_1 = t_1)\,\mathrm{du} > \int_{t_1}^{t_2} \lambda_{2|1}^h(u|T_1 = t_1)\,\mathrm{du}$$

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It follows that

$$\frac{\left[1-\frac{\int_{t_2}^{t_1}\lambda^h_{2|1}(u|T_1=t_1)\,\mathrm{du}}{\int_{t_2}^{+\infty}\lambda^h_{2|1}(u|T_1=t_1)\,\mathrm{du}}\right]}{\left[1-\frac{\int_{t_2}^{t_1}\lambda^k_{2|1}(u|T_1=t_1)\,\mathrm{du}}{\int_{t_2}^{+\infty}\lambda^k_{2|1}(u|T_1=t_1)\,\mathrm{du}}\right]}>1$$

By Theorem (6.C.1) and Theorem (6.B.14) (Shaked and Shanthikumar (2007); pages 289 and 272, respectively), we have that

$$(T_1,T_2)^k \leq_{ch} (T_1,T_2)^h \quad \Rightarrow \quad (T_1,T_2)^k \leq_{st} (T_1,T_2)^h$$

Since $(T_1,T_2)^k \leq_{lr} (T_1,T_2)^h$, it follows that

$$\frac{S^h(t_1,t_2)}{S^k(t_1,t_2)} \text{ is an increasing function in } (t_1,t_2)\in\left\{(t_1,t_2): S^h(t_1,t_2)>0\right\}$$

or equivalently that $(T_1,T_2)^k \leq_{hr} (T_1,T_2)^h$. The desired result follows directly by the Monotone Likelihood Ratio property, which holds under the exponential family assumption for each component of (T_1,T_2); since $(T_1,T_2)^k \leq_{st} (T_1,T_2)^h$, then $\frac{f^h_{T_2|T_1\geq t_2}(t_2|T_1\geq t_2)}{f^k_{T_2|T_1\geq t_2}(t_2|T_1\geq t_2)}$ is increasing in (t_1,t_2), showing that $\lambda^k(t_1|T_2=t_2)>\lambda^h(t_1|T_2=t_2)$, as desired. □

3.2.2 The MOBVE Bivariate Frailty Model

Let T_1 and T_2 be the two time-to-events of the two individuals, whose frailties are Z_1 and Z_2, respectively. The idea is to work directly on the vector of frailties (Z_1,Z_2) to model the dependence across individuals' survival times. In particular, the events are assumed to be conditionally independent given the vector of frailties (Z_1,Z_2). Such assumption directly affects the structure of the model, since the conditional bivariate function of (T_1,T_2) can be written as

$$S(t_1,t_2|z_1,z_2)=S_1(t_1|z_1)S_2(t_2|z_2) \tag{3.14}$$

where $S_i(t_i|z_i)$ is the marginal conditional survival function of T_i given the fixed frailty value $Z_i=z_i$, $i=1,2$.

In particular, we assume that

$$(Z_1,Z_2)\sim \mathrm{MOBVE}(\xi_1,\xi_2,\xi_3) \tag{3.15}$$

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with joint survival function given by

$$\bar{G}(z_1, z_2) = \exp\{-\xi_1 z_1 - \xi_2 z_2 - \xi_3 \max(z_1, z_2)\} \quad z_1, z_2 \geq 0 \tag{3.16}$$

Such distribution was introduced by Marshall and Olkin (1967) to model two-component systems that are subject to shocks, which are governed by independent Poisson processes. Such kind of shock may be fatal to one or both components. Let W_j be independent and identically distributed exponential lifetimes with parameters $\xi_j \geq 0$, $j = 1, 2, 3$. Then, we say the bivariate vector (Z_1, Z_2) follows the Marshall-Olkin model if it admits the following stochastic representation:

$$(Z_1, Z_2) = (Z_1 = \min(W_1, W_3), Z_2 = \min(W_2, W_3)) \tag{3.17}$$

Its associated density function is given by

$$\tilde{g}(z_1, z_2) = \begin{cases} \xi_1(\xi_2 + \xi_3)\,\bar{G}(z_1, z_2) & \text{if} \quad z_1 < z_2 \\ \xi_2(\xi_1 + \xi_3)\,\bar{G}(z_1, z_2) & \text{if} \quad z_2 < z_1 \end{cases} \tag{3.18}$$

whereas $\tilde{g}(z) = \xi_3\,\bar{G}(z)$ when $z = z_1 = z_2$. The conditional probability distribution $P(Z_1 > z_1 | Z_2 = z_2)$ can be obtained as follows:

$$P(Z_1 > z_1 | Z_2 = z_2) = \begin{cases} \xi_2^{-1}(\xi_2 + \xi_3) e^{-\xi_1 z_1 - \xi_3 z_3} & \text{if} \quad z_2 < z_1 \\ e^{-(\xi_2 + \xi_3) z_1} & \text{if} \quad z_1 < z_2 \end{cases} \tag{3.19}$$

One can easily calculate the unconditional bivariate survival function as

$$S(t_1, t_2) = \int \int S(t_1, t_2 | z_1, z_2) \bar{G}(dz_1, dz_2) \tag{3.20}$$

where the integrals range over the domains of the marginal frailty distributions.

Proposition 2. *The unconditional bivariate survival function of the model under* $(Z_1, Z_2) \sim MOBVE(\xi_1, \xi_2, \xi_3)$ *is given by*

$$S(t_1, t_2) = S_>(t_1, t_2) + S_<(t_1, t_2) + S_=(t_1, t_2) \tag{3.21}$$

Proof. We distinguish among three cases:

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(1) when $z_1 > z_2$, we have that

$$\begin{aligned} S_>(t_1,t_2) &= \int_0^{+\infty}\int_0^{z_1} S(t_1,t_2|z_1,z_2)\tilde{g}(z_1,z_2)dz_2dz_1 \\ &= \frac{\xi_2(\xi_1+\xi_3)}{\left(\frac{S_1(t_1)^{-\theta_1}-1}{\theta_1}+\xi_1+\xi_3\right)\left(\frac{S_1(t_1)^{-\theta_1}-1}{\theta_1}+\frac{S_2(t_2)^{-\theta_2}-1}{\theta_2}+\xi_1+\xi_2+\xi_3\right)} \end{aligned}$$

(2) when $z_2 > z_1$, we have that

$$\begin{aligned} S_<(t_1,t_2) &= \int_0^{+\infty}\int_{z_1}^{+\infty} S(t_1,t_2|z_1,z_2)\tilde{g}(z_1,z_2)dz_2dz_1 \\ &= \frac{\xi_1(\xi_2+\xi_3)}{\left(\frac{S_2(t_2)^{-\theta_2}-1}{\theta_2}+\xi_2+\xi_3\right)\left(\frac{S_1(t_1)^{-\theta_1}-1}{\theta_1}+\frac{S_2(t_2)^{-\theta_2}-1}{\theta_2}+\xi_1+\xi_2+\xi_3\right)} \end{aligned}$$

(3) when $z_1 = z_2 = z$, we have that

$$\begin{aligned} S_=(t_1,t_2) &= \int_0^{+\infty} S(t_1,t_2|z)\tilde{g}(z)dz \\ &= \frac{\xi_3}{\left(\frac{S_1(t_1)^{-\theta_1}-1}{\theta_1}+\frac{S_2(t_2)^{-\theta_2}-1}{\theta_2}+\xi_1+\xi_2+\xi_3\right)} \end{aligned}$$

The result directly follows from the above computations. Also, for all t_1 and t_2, $S(t_1,+\infty) = S(+\infty,t_2) = 0$ and $S(t_1,0) = S(t_1)$ and $S(0,t_2) = S(t_2)$. This shows that $S(t_1,t_2)$ is a bivariate survival function. □

Remark 3.2.1. *Interestingly, the MOBVE distribution (3.16) is the only bivariate exponential distribution with exponential marginals, that is having decreasing density and constant hazard functions. However, note that the MOBVE is not absolutely continuous with respect to the Lebesgue measure on* $\mathbb{R}^2$*, as it has a singularity on the diagonal* $x = y$*. Furthermore, since the probability of simultaneous failure is positive, that is*

$$\mathbb{P}(X = Y) = \frac{\xi_3}{\sum_{i=1}^n \xi_i} > 0$$

the dependence between X *and* Y *is totally described by the intensity underlying the Poisson process for the shocks affecting both components.*

Suppose now that (T_1, T_2) is subject to independent right-censoring by the random variable C, and let Q be the survival function for C, $Q(c) = \mathbb{P}(C \geq c)$.

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For each pair $p = 1, \ldots, n$, the observed vector is then $((X_{1p}, \delta_{1p}), (X_{2p}, \delta_{2p}))$ where $X_{ip} = T_{ip} \wedge C$ and $\delta_{ip} = I[T_{ip} \leq C]$, with $i = 1, 2$. The unconditional likelihood of the model can be written as follows:

$$\begin{aligned} &L(\boldsymbol{\vartheta} | (\boldsymbol{X}_1, \boldsymbol{\delta}_1), (\boldsymbol{X}_2, \boldsymbol{\delta}_2)) \propto \\ &= \prod_{p=1}^{n} \left(S(\Delta t_{1p}, \Delta t_{2p})^{\delta_p^{11}} S(\Delta t_{1p}, t_{2p})^{\delta_p^{10}} S(t_{1p}, \Delta t_{2p})^{\delta_p^{01}} S(t_{1p}, t_{2p})^{\delta_p^{00}} \right) \end{aligned} \tag{3.22}$$

where $\boldsymbol{\vartheta} = (\boldsymbol{\xi}, \boldsymbol{\eta})$, with $\boldsymbol{\eta}$ being the set of parameters underlying the distribution of each lifetime T_i, $i = 1, 2$ and $\boldsymbol{\xi}$ the MOBVE parameters. These parameters are estimated via Maximum Likelihood Estimation in a fully parametric setting. Note that $n_p^{11} = \sum_p \delta_p^{\delta_{1p}, \delta_{2p}}$ would denote the number of couples in the sample having the observed configuration $\{X_{1p} = t_{1p}, X_{2p} = t_{2p}, \delta_{1p}, \delta_{2p}\}$.

Remark 3.2.2. *Under a MOBVE conditional frailty model, the conditional joint distribution is integrated out with respect to the unobserved random effect, and the resulting likelihood is perfectly tractable.*

Let us define $\Psi = (\Lambda_{01}(t_1) + \Lambda_{02}(t_2) + \sum_{i=1}^{3} \xi_i)$. The unconditional bivariate survival function can be written as follows:

$$S_{T_1,T_2}^{MO}(t_1, t_2) = \frac{\xi_2(\xi_1 + \xi_3)}{(\Lambda_{01}(t_1) + \xi_1 + \xi_3)\,\Psi} + \frac{\xi_1(\xi_2 + \xi_3)}{(\Lambda_{02}(t_2) + \xi_2 + \xi_3)\,\Psi} + \frac{\xi_3}{\Psi} \tag{3.23}$$

where $\Lambda_{0i}(t_i) = \frac{S_i(t_i)^{-\theta_i} - 1}{\theta_i}$, with $(i = 1, 2)$. Letting $\theta_1 = \xi_1 + \xi_3$ and $\theta_2 = \xi_2 + \xi_3$, the unconditional bivariate density function of the MOBVE Frailty model is given by:

$$S_{T_1,T_2}^{MO}(\Delta t_1, \Delta t_2) = \Psi^{-2}\, S_{T_1}(t_1)^{-\theta_1 - 1} S_{T_2}(t_2)^{-\theta_2 - 1} f_{T_1}(t_1) f_{T_2}(t_2) \left(\Psi_1 + \Psi_2 + 2\,\xi_3\,\Psi^{-1}\right) \tag{3.24}$$

where $S_{T_1,T_2}^{MO}(\Delta t_1, \Delta t_2) = f_{T_1,T_2}^{MO}(t_1, t_2) = \frac{\partial \partial S_{T_1,T_2}^{MO}(t_1,t_2)}{\partial t_1 \partial t_2}$ and

$$\Psi_1 := \xi_2(\xi_1 + \xi_3)(\Lambda_{01}(t_1) + \xi_1 + \xi_3)^{-2} + 2\xi_2(\xi_1 + \xi_3)(\Lambda_{01}(t_1) + \xi_1 + \xi_3)^{-1}\,\Psi^{-1}$$

$$\Psi_2 := \xi_1\,(\xi_2 + \xi_3)(\Lambda_{02}(t_2) + \xi_2 + \xi_3)^{-2} + 2\xi_1(\xi_2 + \xi_3)(\Lambda_{02}(t_2) + \xi_2 + \xi_3)^{-1}\,\Psi^{-1}$$

Since $S_{T_1,T_2}^{MO}(\Delta t_1, t_2) = \frac{\partial S_{T_1,T_2}^{MO}(t_1,t_2)}{\partial t_1}$, we have that

$$S_{T_1,T_2}^{MO}(\Delta t_1, t_2) = -\Psi^{-1} S_{T_1}(t_1)^{-\theta_1 - 1} f_{T_1}(t_1) \left(\Psi_3 + \Psi_4 + \Psi_5 + \xi_3\,\Psi^{-1}\right) \tag{3.25}$$

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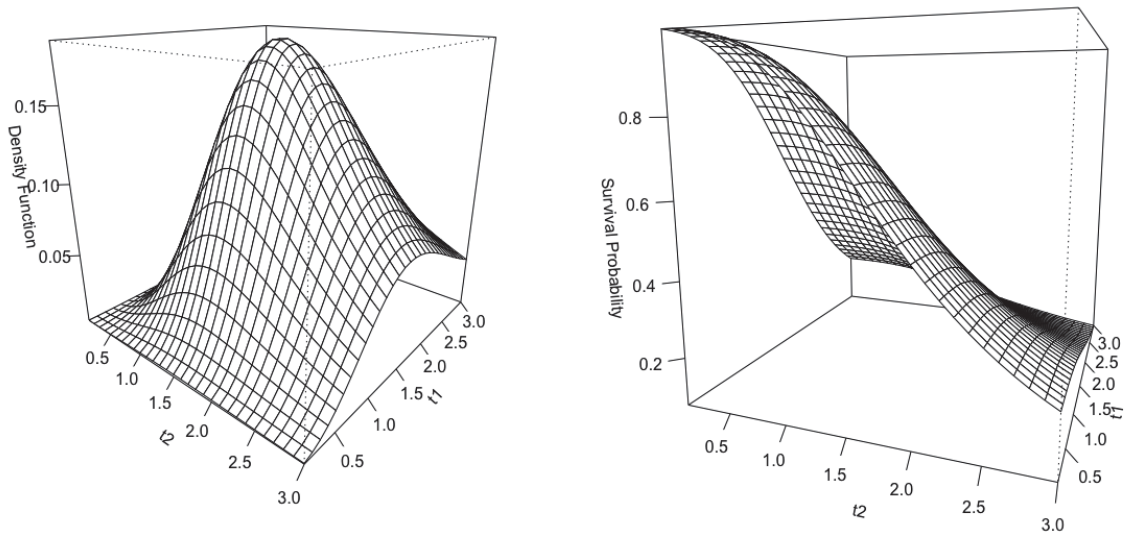

Figure 3.1: Unconditional Bivariate Density and Bivariate Survival Function under the conditional MOBVE frailty model.

where

$$\Psi_3 := \xi_2 \left(\xi_1 + \xi_3\right) \left(\Lambda_{01}(t_1) + \theta_1\right)^{-2}$$
$$\Psi_4 := \xi_2 \left(\xi_1 + \xi_3\right) \left(\Lambda_{01}(t_1) + \theta_1\right)^{-1} \Psi^{-1}$$
$$\Psi_5 := \xi_1 \left(\xi_2 + \xi_3\right) \left(\Lambda_{02}(t_2) + \theta_1\right)^{-1} \Psi^{-1}$$

Finally,

$$S^{MO}_{T_1,T_2}(t_1, \Delta t_2) = -\Psi^{-1} S_{T_2}(t_2)^{-\theta_2 - 1} f_{T_2}(t_2) \left(\Psi_6 + \Psi_7 + \Psi_8 + \xi_3 \Psi^{-1}\right) \tag{3.26}$$

where $S^{MO}_{T_1,T_2}(t_1, \Delta t_2) = \frac{\partial S^{MO}_{T_1,T_2}(t_1,t_2)}{\partial t_2}$ and

$$\Psi_6 := \xi_2 \left(\xi_1 + \xi_3\right) \left(\Lambda_{01}(t_1) + \theta_1\right)^{-1} \Psi^{-1}$$
$$\Psi_7 := \xi_1 \left(\xi_2 + \xi_3\right) \left(\Lambda_{02}(t_2) + \theta_2\right)^{-2}$$
$$\Psi_8 := \xi_1 \left(\xi_2 + \xi_3\right) \left(\Lambda_{02}(t_2) + \theta_2\right)^{-1} \Psi^{-1}$$

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3.2.3 Identifiability Considerations

We now focus on the identifiability of bivariate MOBVE mixture models, showing that their identifiability can be studied from the identifiability of the corresponding marginals. See Prakasa Rao (1992) and references therein for details.

Suppose the distributions functions $F(\boldsymbol{z},\theta)$ and $F(\boldsymbol{z},\tilde{\theta})$ are absolutely continuous with respect to the Lebesgue measure on $\mathbb{R}^2$. Define

$$H(\theta,\tilde{\theta}) = \mathbb{E}_{\tilde{\theta}} \log\left[\frac{f(\boldsymbol{z};\theta)}{f(\boldsymbol{z};\tilde{\theta})}\right] \tag{3.27}$$

Such function is called Kullback-Leibler (KL) divergence between $f(\boldsymbol{z};\theta)$ and $f(\boldsymbol{z};\tilde{\theta})$, which can be denoted as $KL\left(\theta,\tilde{\theta}\right)$, and a general identifiability criterion can be constructed from it.

The next lemma allows to express the MOBVE KL divergence as a function of the KL measures computed on the component-specific conditional distributions, that is the sum of the positive plane and the 45 degree line components.

Lemma 1. *Let $F(\boldsymbol{z},\theta)$ and $F(\boldsymbol{z},\tilde{\theta})$ be two bivariate mixed distribution functions, and assume they follow the MOBVE distribution. The corresponding Kullback-Leibler divergence between $f(\boldsymbol{z};\theta)$ and $f(\boldsymbol{z};\tilde{\theta})$ can be decomposed as follows*

$$\begin{aligned} H\left(\theta,\tilde{\theta}\right) =& \mathbb{E}_{\tilde{\theta}}\left[g_A(\boldsymbol{z};\theta,\tilde{\theta})|\boldsymbol{z}\in A\right]\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A\right) + \\ & \mathbb{E}_{\tilde{\theta}}\left[g_{A^c}(\boldsymbol{z};\theta,\tilde{\theta})|\boldsymbol{z}\in A^c\right]\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A^c\right) \end{aligned}$$

where

$$g_A\left(\boldsymbol{z};\theta,\tilde{\theta}\right) = \log\left[\frac{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\tilde{\theta})}\right] \qquad g_{A^c}\left(\boldsymbol{z};\theta,\tilde{\theta}\right) = \log\left[\frac{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\tilde{\theta})}\right]$$

with $A = \{W_3 > \min(W_1,W_2)\}$ and A^c is its complement, and

$$\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A^c\right) = \frac{\xi_3}{\sum_{h=1}^{3}\xi_h}$$

Proof. By definition, the Kullback-Leibler divergence between $f(\boldsymbol{z};\theta)$ and $f(\boldsymbol{z};\tilde{\theta})$ is defined as follows:

$$H(\theta,\tilde{\theta}) = \mathbb{E}_{\tilde{\theta}}\log\left[\frac{f(\boldsymbol{z};\theta)}{f(\boldsymbol{z};\tilde{\theta})}\right] = \int \log\left(\frac{f_\theta(\boldsymbol{z})}{f_{\tilde{\theta}}(\boldsymbol{z})}\right) f_{\tilde{\theta}}(\boldsymbol{z})\, d\boldsymbol{z}$$

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Let, for ease of notation, $g\left(\boldsymbol{z};\theta,\tilde{\theta}\right)=\log\left[\frac{f(\boldsymbol{z};\theta)}{f(\boldsymbol{z};\tilde{\theta})}\right]$. Then, when $\boldsymbol{z}\in A$, we have that

$$\begin{aligned}H_A\left(\theta,\tilde{\theta}\right)&=\mathbb{E}_{z|z\in A;\tilde{\theta}}\left[g_A\left(\boldsymbol{z};\theta,\tilde{\theta}\right)\right]\\&=\int_A\log\left[\frac{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\tilde{\theta})}\right]\,f_{\boldsymbol{z}|\boldsymbol{z}\in A}(\boldsymbol{z};\tilde{\theta})d\boldsymbol{z}\leq 0\end{aligned}$$

Since

$$f_{\boldsymbol{z}|\boldsymbol{z}\in A}\left(\boldsymbol{z};\theta\right)=\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\theta)I(\boldsymbol{z}\in A)}{\mathbb{P}_\theta\left(\boldsymbol{z}\in A\right)}$$

we have that

$$\begin{aligned}H_A(\theta,\tilde{\theta})&=\int_A\log\left[\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}}(\boldsymbol{z};\tilde{\theta})}\frac{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}\right]\,\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\tilde{\theta})}{\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A\right)}d\boldsymbol{z}\\&=\frac{1}{\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A\right)}\left[\int_A\log\left[\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}}(\boldsymbol{z};\tilde{\theta})}\right]+\log\left[\frac{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}\right]\right]\,f_{\boldsymbol{z}}\left(\boldsymbol{z},\tilde{\theta}\right)\,d\boldsymbol{z}\\&=\frac{1}{\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A\right)}\left[\int_A\log\left[\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}}(\boldsymbol{z};\tilde{\theta})}\right]\,f_{\boldsymbol{z}}\left(\boldsymbol{z};\tilde{\theta}\right)\,d\boldsymbol{z}\right]+\\&+\log\left[\frac{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}\right]\left[\int_A\frac{f_{\boldsymbol{z}}\left(\boldsymbol{z};\tilde{\theta}\right)}{\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A\right)}\,d\boldsymbol{z}\right]\end{aligned}$$

with $\left[\int_A\frac{f_{\boldsymbol{z}}\left(\boldsymbol{z};\tilde{\theta}\right)}{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}\,d\boldsymbol{z}\right]=1$, so that

$$\begin{aligned}0\geq H_A(\theta,\tilde{\theta})&=\int_A\log\left[\frac{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A}}(\boldsymbol{z};\tilde{\theta})}\right]\,f_{\boldsymbol{z}|\boldsymbol{z}\in A}(\boldsymbol{z};\tilde{\theta})d\boldsymbol{z}\\&=\log\left[\frac{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A)}\right]+\frac{1}{\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A\right)}\left[\int_A\log\left[\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}}(\boldsymbol{z};\tilde{\theta})}\right]\,f_{\boldsymbol{z}}\left(\boldsymbol{z};\tilde{\theta}\right)\,d\boldsymbol{z}\right]\end{aligned}$$

The interest reader can easily shows that the same arguments hold for A^c, leading to

$$\begin{aligned}0\geq H_{A^c}(\theta,\tilde{\theta})&=\int_{A^c}\log\left[\frac{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A^c}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}|\boldsymbol{z}\in\boldsymbol{A^c}}(\boldsymbol{z};\tilde{\theta})}\right]\,f_{\boldsymbol{z}|\boldsymbol{z}\in A^c}(\boldsymbol{z};\tilde{\theta})d\boldsymbol{z}\\&=\log\left[\frac{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A^c)}{\mathbb{P}_{\tilde{\theta}}(\boldsymbol{z}\in A^c)}\right]+\frac{1}{\mathbb{P}_{\tilde{\theta}}\left(\boldsymbol{z}\in A^c\right)}\left[\int_A^c\log\left[\frac{f_{\boldsymbol{z}}(\boldsymbol{z};\theta)}{f_{\boldsymbol{z}}(\boldsymbol{z};\tilde{\theta})}\right]\,f_{\boldsymbol{z}}\left(\boldsymbol{z};\tilde{\theta}\right)\,d\boldsymbol{z}\right]\end{aligned}$$

Since both $H_A\left(\theta,\tilde{\theta}\right)$ and $H_{A^c}\left(\theta,\tilde{\theta}\right)$ are at most zero, the identifiability of the model follows. □

Note that for identifiability reasons of the MOBVE parameters we set $\xi_1=\xi_2=1-\xi_3$, which makes the MOBVE distribution a function of ξ_3 only. To show that the parameter

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vector $\boldsymbol{\xi} = \{\xi_1, \xi_2, \xi_3\} \in \Xi$ of the mixing distribution $G_{\boldsymbol{\xi}} \sim$ MOBVE is identifiable if $\xi_1 = \xi_2 = 1 - \xi_3$, consider the following quantities. When $z_2 > z_1$, we have that

$$H_{z_2>z_1}(\theta, \tilde{\theta}) = \int_{\text{supp}(z_2>z_1)} \log\left(\frac{1-\xi_3}{1-\tilde{\xi_3}}\right)(1-\tilde{\xi_3})e^{-z_1(1-\tilde{\xi_3})-z_2}\,\mathrm{d}z_1\,\mathrm{d}z_2 + \int_{\text{supp}(z_2>z_1)} (\xi_3-\tilde{\xi_3})(1-\tilde{\xi_3})z_1 e^{-z_1(1-\tilde{\xi_3})-z_2}\,\mathrm{d}z_1\,\mathrm{d}z_2 \tag{3.28}$$

Similarly, when $z_1 > z_2$, we have that

$$H_{z_1>z_2}(\theta, \tilde{\theta}) = \int_{\text{supp}(z_1>z_2)} \log\left(\frac{1-\xi_3}{1-\tilde{\xi_3}}\right)(1-\tilde{\xi_3})e^{-z_2(1-\tilde{\xi_3})-z_1}\,\mathrm{d}z_1\,\mathrm{d}z_2 + \int_{\text{supp}(z_1>z_2)} (\xi_3-\tilde{\xi_3})(1-\tilde{\xi_3})z_2 e^{-z_2(1-\tilde{\xi_3})-z_1}\,\mathrm{d}z_1\,\mathrm{d}z_2 \tag{3.29}$$

Finally, when $z = z_1 = z_2$,

$$H_z(\theta, \tilde{\theta}) = \int_{\text{supp}(z)} \log(\xi_3)\,\tilde{\xi_3}e^{-z(2-\tilde{\xi_3})}\,\mathrm{d}z - \int_{\text{supp}(z)} (\tilde{\xi_3}-\xi_3)z\tilde{\xi_3}e^{-z(2-\tilde{\xi_3})}\,\mathrm{d}z \tag{3.30}$$

Equation (3.28) can be written as the sum of

$$\begin{aligned}
&\int_0^{+\infty}\int_{z_1}^{+\infty} \log\left(\frac{1-\xi_3}{1-\tilde{\xi_3}}\right)(1-\tilde{\xi_3})\,e^{-z_1(1-\tilde{\xi_3})-z_2}\,\mathrm{d}\,z_2\,\mathrm{d}\,z_1 \\
&= \int_0^{+\infty}\int_{z_1}^{+\infty} \log\left(\frac{1-\xi_3}{1-\tilde{\xi_3}}\right)(1-\tilde{\xi_3})\,e^{-z_1(2-\tilde{\xi_3})}\,\mathrm{d}\,z_1 \\
&= \log\left(\frac{1-\xi_3}{1-\tilde{\xi_3}}\right)\frac{(1-\tilde{\xi_3})}{(2-\tilde{\xi_3})}
\end{aligned}$$

and

$$\begin{aligned}
&\int_0^{+\infty}\int_{z_1}^{+\infty} z_1\left(\xi_3-\tilde{\xi_3}\right)(1-\tilde{\xi_3})\,e^{-z_1(1-\tilde{\xi_3})-z_2}\,\mathrm{d}\,z_2\,\mathrm{d}\,z_1 \\
&= \int_0^{+\infty}\int_{z_1}^{+\infty} z_1\left(\xi_3-\tilde{\xi_3}\right)(1-\tilde{\xi_3})\,e^{-z_1(2-\tilde{\xi_3})}\,\mathrm{d}\,z_2\,\mathrm{d}\,z_1 \\
&= \left(\xi_3-\tilde{\xi_3}\right)(1-\tilde{\xi_3})\left[\int_0^{+\infty}\frac{e^{-z_2\left(2-\tilde{\xi_3}\right)}}{\left(2-\tilde{\xi_3}\right)}\,\mathrm{d}\,z_2\right] \\
&= \frac{\left(\xi_3-\tilde{\xi_3}\right)(1-\tilde{\xi_3})}{\left(2-\tilde{\xi_3}\right)^2}
\end{aligned}$$

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When $z_1 > z_2$, Equation (3.29) can be written as the sum of

$$\begin{aligned}
&\int_0^{+\infty}\int_0^{z_1} \log\left(\frac{1-\xi_3}{1-\tilde{\xi}_3}\right)(1-\tilde{\xi}_3)\, e^{-z_2(1-\tilde{\xi}_3)-z_1}\,\mathrm{d}\,z_2\,\mathrm{d}\,z_1 \\
&= \int_0^{+\infty}\int_0^{z_1} \log\left(\frac{1-\xi_3}{1-\tilde{\xi}_3}\right)(1-\tilde{\xi}_3)\, e^{-z_1}\left[-\frac{e^{-z_2(2-\tilde{\xi}_3)}}{\left(1-\tilde{\xi}_3\right)}\right]_0^{z_1}\mathrm{d}\,z_1 \\
&= \log\left(\frac{1-\xi_3}{1-\tilde{\xi}_3}\right)\left[1+\frac{1}{(2-\tilde{\xi}_3)}\right]
\end{aligned}$$

and

$$\begin{aligned}
&\int_0^{+\infty}\int_0^{z_1} z_2\left(\xi_3-\tilde{\xi}_3\right)\left(1-\tilde{\xi}_3\right)\, e^{-z_2(1-\tilde{\xi}_3)-z_1}\,\mathrm{d}\,z_2\,\mathrm{d}\,z_1 \\
&= \int_0^{+\infty}\left(\xi_3-\tilde{\xi}_3\right)(1-\tilde{\xi}_3)\, e^{-z_1}\left[\int_{z_1}^{+\infty} z_2 e^{-z_2(2-\tilde{\xi}_3)}\,\mathrm{d}\,z_2\right]\mathrm{d}\,z_1 \qquad (3.31)
\end{aligned}$$

Since

$$\int_0^{z_1} z_2\, e^{-z_2\left(1-\tilde{\xi}_3\right)}\,\mathrm{d}\,z_2 = \frac{1-e^{-z_1\left(1-\tilde{\xi}_3\right)}}{\left(1-\tilde{\xi}_3\right)^2} - \frac{z_1\, e^{-z_1\left(1-\tilde{\xi}_3\right)}}{\left(1-\tilde{\xi}_3\right)}$$

Equation (3.31) can be written as

$$\begin{aligned}
&\int_0^{+\infty}\frac{\left(\xi_3-\tilde{\xi}_3\right)}{\left(1-\tilde{\xi}_3\right)}\left[e^{-z_1}-e^{-z_1(2-\tilde{\xi}_3)}\right]\mathrm{d}\,z_1 - \int_0^{+\infty}\left(\xi_3-\tilde{\xi}_3\right)\, z_1\, e^{-z_1(2-\tilde{\xi}_3)}\,\mathrm{d}\,z_1 \\
&= \frac{\left(\xi_3-\tilde{\xi}_3\right)}{\left(1-\tilde{\xi}_3\right)} - \frac{\left(\xi_3-\tilde{\xi}_3\right)}{\left(2-\tilde{\xi}_3\right)} - \frac{\left(\xi_3-\tilde{\xi}_3\right)}{\left(1-\tilde{\xi}_3\right)\left(1-\tilde{\xi}_3\right)}
\end{aligned}$$

Finally, when $z_1 = z_2 = z$, we have that Equation (3.30) can be written as

$$\begin{aligned}
&\int_0^{+\infty}\log\left(\frac{\xi_3}{\tilde{\xi}_3}\right)\tilde{\xi}_3 e^{-z\sum_i\tilde{\xi}_i}\,\mathrm{d}\,z - \int_0^{+\infty}\left(\sum_i\xi_i-\sum_i\tilde{\xi}_i\right)\tilde{\xi}_3 e^{-z\sum_i\tilde{\xi}_i}\,\mathrm{d}\,z \\
&= \log\left(\frac{\xi_3}{\tilde{\xi}_3}\right)\frac{\tilde{\xi}_3}{\sum_i\tilde{\xi}_i} - \frac{\left(\sum_i\xi_i-\sum_i\tilde{\xi}_i\right)\tilde{\xi}_3}{\sum_i\tilde{\xi}_i} = \frac{\tilde{\xi}_3\left(\log\left(\frac{\xi_3}{\tilde{\xi}_3}\right)-\left(\tilde{\xi}_3-\xi_3\right)\right)}{\left(2-\tilde{\xi}_3\right)}
\end{aligned}$$

The case in which

$$H(\theta,\tilde{\theta}) = H_{z_2>z_1}(\theta,\tilde{\theta}) + H_{z_2<z_1}(\theta,\tilde{\theta}) + H_z(\theta,\tilde{\theta}) = 0$$

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is, by definition, true when $\xi_3 = \tilde{\xi_3}$. To prove the result in its general form, we have to show that $H(\theta, \tilde{\theta}) < 0 \Rightarrow \theta \neq \tilde{\theta}$. To accomplish this, let us assume that $\tilde{\xi_3} \neq \xi_3$, and without loss of generalizations, assume that $\tilde{\xi_3} < \xi_3$. Then, from the above calculations, and by Lemma 1, one could prove that

$$H(\theta, \tilde{\theta}) = H_{z_2 > z_1}(\theta, \tilde{\theta}) + H_{z_2 < z_1}(\theta, \tilde{\theta}) + H_z(\theta, \tilde{\theta}) < 0$$

which is sufficient to show the thesis. The reader should be aware of the fact that its proof, unfortunately, is only a partial result. The rather complicated mixed nature of the bivariate random vector $(Z_1, Z_2) \sim \text{MOBVE}(\xi_1, \xi_2, \xi_3)$ does not insure against the possibility of non-negativity of all the KL components.

Remark 3.2.3. *Note that assuming identifiability only through the dependence parameter* ξ_3 *implies that marginally* $Z_1 \sim \exp(\xi_1 + \xi_3) \equiv \exp(1)$ *and* $Z_2 \sim \exp(\xi_2 + \xi_3) \equiv \exp(1)$.

Example 1. *Assume*

$$T_1|z_1 \sim \textit{Weibull}\left(\alpha_1, \frac{\beta_1}{z_1^{1/\alpha_1}}\right) \quad T_2|z_2 \sim \textit{Weibull}\left(\alpha_2, \frac{\beta_2}{z_2^{1/\alpha_2}}\right)$$

where $(Z_1, Z_2) \sim \textit{MOBVE}(\xi_1, \xi_2, \xi_3)$. *Then, the family*

$$\Lambda \equiv \left\{G_\vartheta : \vartheta = (\vartheta_1, \vartheta_2) \in \Theta \subseteq \mathbb{R}^k\right\}$$

is identifiable with respect to $\mathcal{P} = \{\textit{Weibull}(\alpha, \beta), \alpha, \beta \in \mathbb{R}^+\}$. *By Theorem 2.1 in Marshall and Olkin (1988), we have that the bivariate survival function can be written as*

$$S(t_1, t_2) = \int\int P_{\vartheta_1}(t_1) P_{\vartheta_2}(t_2)\, dG(\vartheta_1, \vartheta_2) \tag{3.32}$$

Since

$$P_{\vartheta_1} \equiv \textit{Weibull}\left(\alpha_1, \frac{\beta_1}{z_1^{1/\alpha_1}}\right) \qquad P_{\vartheta_2} \equiv \textit{Weibull}\left(\alpha_2, \frac{\beta_2}{z_2^{1/\alpha_2}}\right)$$

$G_\vartheta \sim \textit{MOBVE}(\xi_1, \xi_2, \xi_3)$ *is identifiable, where* $\vartheta = (\vartheta_1, \vartheta_2)$, *with* $\vartheta_1 = (\xi_3, \eta_1)$ *and* $\vartheta_2 = (\xi_3, \eta_2)$, *and* $\eta_i = (\alpha_i, \beta_i)$ $(i = 1, 2)$ *are nuisance parameters. Then* ϑ_1 *and* ϑ_2 *are identifiable with respect to* $\mathcal{P}_1$ *and* $\mathcal{P}_2$, *respectively. This can be deduced by the fact that* $\Lambda \equiv \Lambda_1 \times \Lambda_2$. *Since each* Λ_i *is identifiable with respect to* $\mathcal{P}_i$ $(i = 1, 2)$, *Corollary 8.6.1 by Prakasa Rao (1992) implies that the class* Λ *is identifiable with respect to* $\mathcal{P}$.

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3.3 A Bivariate Cure MOBVE Frailty Model

So far we have assumed that all individuals in the sample may eventually experience the event of interest, changing their risk of the event of interest (say, death) as well as their partner's risk. However, in many cases, it is reasonable to assume that a fraction of individuals in the sample never experience such event. Therefore, it makes sense constructing a bivariate cure frailty model in order to allow for a *cured* fraction of individuals as well as to take into account the dependence structure when both individuals do experience the event of interest.

Univariate cure rate survival models assume that the reference population can be divided into two subgroups: the susceptible (or non-cured) subjects, and the cured patients, who will always be disease-free. Let $\phi \in (0,1)$ be the fraction of cured patients in the reference population. Since cured individuals do not appear to be affected by the disease even after prolonged follow-up, their failure time is degenerate at infinity. Instead, the proportion $(1-\phi)$ of non-cured patients eventually experience the event of interest according to the conditional survival function $S^{NC}(t)$.

Therefore, the marginal survival function of the entire population is given by

$$S(t) = \phi + (1-\phi)S^{NC}(t)$$

Traditional cure rate models assume that the susceptible individuals are homogeneous in risk (Gray and Tsiatis (1989); Taylor (1995); Maller and Zhou (1996); Lu (2008); Bonetti et al. (2009)). However, a great deal of attention has been given to cure models which allow for heterogeneity among the fraction under risk. Aalen (1992) introduced a cure frailty model by assuming the frailty to be a Poisson compound distribution, extending the well-known Hougaard's model (Hougaard (1986)), and its bivariate extension was introduced in Wienke (2010). A correlated gamma frailty cure model was introduced in Wienke *et al.* (2003), where a cure-mixture model to analyze bivariate time-to-event data was suggested as a natural extension of the cure shared frailty model proposed in Chatterjee and Shih (2001). In this section, we propose a new bivariate frailty cure model by assuming the bivariate random vector of frailty to be MOBVE(ξ_1, ξ_2, ξ_3). We again set

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the MOBVE parameters to be $\xi_1 = \xi_2 = 1 - \xi_3$ for identifiability reasons.
For a pair of individuals, define the binary random variable (ϵ_j, ϵ_k), with $j \neq k$, where

$$\epsilon_j = \begin{cases} 1 & \text{if the } j^{th} \text{ subject } \notin \text{ cured group} \\ 0 & \text{otherwise} \end{cases}$$

and use T_j for the age of onset for the j^{th} individual. Furthermore, let $\pi_j = \mathbb{P}(\epsilon_j = 1)$ and $S_j(t) = \mathbb{P}(T_j > t | \epsilon_j = 1)$ describe the marginal distribution of ϵ_j and the conditional distribution of the failure time T_j for the non cured individuals, respectively.
Let $(T_{11}, T_{12}), \ldots, (T_{n1}, T_{n2})$ be independent and identically distributed nonnegative bivariate vectors of lifetimes, which are assumed to be independently right-censored by pairs of nonnegative random variables $(C_{11}, C_{12}), \ldots, (C_{n1}, C_{n2})$, which are as well assumed to be independent and identically distributed. Similarly to Section 3.2.2, we do assume that $C_{p1} = C_{p2} = C_p$ for each $p = 1, \ldots, n$.
Thus, instead of (T_{p1}, T_{p2}) we only observe $(X_{p1}, X_{p2}, \delta_{p1}, \delta_{p2})$, with $X_{pi} = \min(T_{pi}, C_{pi})$ and $\delta_{pi} = 1(T_{pj} \leq C_{pj})$, with $i = 1, 2$ and $p = 1, \ldots, n$.
Note that, for ease of notation, the following model is specified without the inclusion of any covariate. Dropping the index p to make the notation easier to follow, we can distin-

Table 3.1: Possible scenarios under the Bivariate Fraity Model with Cured Fraction.

	$G = 1$	$G = 2$	$G = 3$	$G = 4$
$(\delta_1 = 0, \delta_2 = 0)$	✓	✓	✓	✓
$(\delta_1 = 1, \delta_2 = 0)$	✘	✘	✓	✓
$(\delta_1 = 0, \delta_2 = 1)$	✘	✓	✘	✓
$(\delta_1 = 1, \delta_2 = 1)$	✘	✘	✘	✓

guish four different scenarios, which are indicated by $G \in \{1, 2, 3, 4\}$: $G = 1$ when both individual are cured, that is $(\epsilon_1 = 0, \epsilon_2 = 0)$; $G = 2$ when only individual two is not cured $(\epsilon_1 = 0, \epsilon_2 = 1)$; $G = 3$ when only individual one is not cured $(\epsilon_1 = 1, \epsilon_2 = 0)$; and $G = 4$ when both members of the pair are not cured $(\epsilon_1 = 1, \epsilon_2 = 1)$. We also assume that C is independent of (T_1, T_2) given the scenario G.

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We now relate the observed data indicator to the four values of G to write the observed data likelihood.

The first situation we have to investigate is when $(\delta_1 = 0, \delta_2 = 0)$, that is when both individuals are censored. As shown in Table 3.1, we might have four different situations that produce such case, depending on which (if any) of the members of the couple have been cured.

Note that the case $(\delta_1 = 0, \delta_2 = 0)$ can only occur with $x_1 = x_2$. Under scenario $G = 1$ we have that both subjects are not cured. Since $(\delta_1 = 0, \delta_2 = 0)$, we have that

$$\begin{aligned}
&\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0 \middle| G = 1\right) \\
&= \mathbb{P}\left(X_1 = x_1, X_2 = x_2, T_1 \geq C, T_2 \geq c \middle| G = 1\right) \\
&= \mathbb{P}\left(\min(T_1, C) = x_1, \min(T_2, C) = x_2, T_1 \geq C, T_2 \geq C \middle| G = 1\right)
\end{aligned}$$

Given that under $G = 1$ we have that $T_1|\text{cured} = +\infty$ and $T_2|\text{cured} = +\infty$ w.p.1, it follows that

$$\begin{aligned}
&\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0 \middle| G = 1\right) \\
&= f_C(x_1)\, S_{T_1,T_2}(x_1, x_2 \,|\, G = 1) = f_C(x_1)
\end{aligned} \tag{3.33}$$

because $S_{T_1,T_2}(x_1, x_2 \,|\, G = 1) = 1$ for all x_1, x_2 when both subjects are cured.

Under the scenario $G = 2$ we have that only individual one is cured, whereas the second individual is not cured. Hence,

$$\begin{aligned}
&\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0 \middle| G = 2\right) \\
&= \mathbb{P}\left(X_1 = x_1, X_2 = x_2, T_1 \geq C, T_2 \geq C \middle| G = 2\right) \\
&= \mathbb{P}\left(\min(T_1, C) = x_1, \min(T_2, C) = x_2, T_1 \geq C, T_2 \geq C \middle| G = 2\right) \\
&= \mathbb{P}\left(T_1 \geq C, T_2 \geq C, x_1 = C, x_2 = C \middle| G = 2\right)
\end{aligned}$$

Given that $T_1|\text{cured} = +\infty$ w.p.1, it follows that

$$\begin{aligned}
&\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0 \middle| G = 2\right) \\
&= f_C(x_1)\, S_{T_1}(x_1)\, S_{\tilde{T}_2}(x_2) = f_C(x_1)\, S_{\tilde{T}_2}(x_2 \,|\, G = 2)
\end{aligned} \tag{3.34}$$

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where we assume that $\tilde{T}_2 \sim \text{Weibull}\,(\alpha_4, \beta_4)$ under the specified cure rate model.
Under scenario $G = 3$, only individual 2 is cured, whereas individual one is not cured. Because of $(\delta_1 = 0, \delta_2 = 0)$, similarly to Equation (3.34), we have that

$$\begin{aligned}&\mathbb{P}\,(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0|\, G = 3)\\ &= f_C(x_1)\, S_{T_2}(x_2 \,|\, G = 3)\, S_{\tilde{T}_1}(x_1 \,|\, G = 3) = f_C(x_1)\, S_{\tilde{T}_1}(x_1 \,|\, G = 3)\end{aligned} \tag{3.35}$$

where $\tilde{T}_1 \sim \text{Weibull}\,(\alpha_3, \beta_3)$.
Finally, under $G = 4$ both subjects are not cured, and we assume the corresponding model to follow the MOBVE frailty model we have discussed in Section 3.2.2. Therefore,

$$\mathbb{P}\,(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0|\, G = 4) = f_C(x_1)\, S^{MO}_{T_1,T_2}(x_1, x_2 \,|\, G = 4) \tag{3.36}$$

where $S^{MO}_{T_1,T_2}(x_1, x_2 \,|\, G = 4)$ is given as in Equation (3.21).
The second possible situation we could encounter is when $(\delta_1 = 0, \delta_2 = 1)$. According to Table 3.1, two scenarios might be observed. On the one hand, when $G = 2$, we have that

$$\begin{aligned}&\mathbb{P}\,(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 1 \,|\, G = 2)\\ &= \mathbb{P}\,(X_1 = x_1, X_2 = x_2, T_1 \geq C, T_2 \leq C \,|\, G = 2)\\ &= \mathbb{P}\,(\min(T_1, C) = x_1, \min(T_2, C) = x_2, T_1 \geq C, T_2 \leq C \,|\, G = 2)\\ &= \mathbb{P}\,(x_1 = C, T_2 = x_2 \,|\, G = 2)\, \mathbb{P}\,(T_1 \geq C, T_2 \leq C|C = x_1, T_2 = x_2, G = 2)\end{aligned} \tag{3.37}$$

By the independence of C from T_2, we have that Equation (3.37) becomes

$$\begin{aligned}&\mathbb{P}\,(T_1 \geq C, T_2 \leq C, C = x_1, T_2 = x_2 \,|\, G = 2)\\ &= \mathbb{P}\,(T_1 \geq C|C = x_1, C = x_2, T_2 \geq c, G = 2)\, \mathbb{P}\,(C = x_1, T_2 = x_2, T_2 \leq C \,|\, G = 2)\end{aligned} \tag{3.38}$$

Note that $\mathbb{P}\,(T_1 \geq C|C = x_1, C = x_2, T_2 \leq C, G = 2)$ is always equal to one, regardless the scenario we might observe. Therefore, when only individual one is cured, Equation (3.38) can be written as

$$\begin{aligned}&\mathbb{P}\,(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 1 \,|\, G = 2)\\ &= \mathbb{P}\,(C = x_1, C = x_2, T_2 \leq C \,|\, G = 2) = f_C(x_1) f_{\tilde{T}_2}(x_2 \,|\, G = 2)\end{aligned} \tag{3.39}$$

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When $(\delta_1 = 0, \delta_2 = 1)$, the second possible scenario we could observe is when both subjects are not cured. In particular, we have that under scenario $G = 4$,

$$\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 1 \,|\, G = 4\right) = \frac{\partial S^{MO}_{T_1,T_2}(x_1, x_2 \,|\, G = 4)}{\partial x_2} \tag{3.40}$$

since we assume that in scenario $G = 4$ the model follows the bivariate MOBVE frailty model defined in Section 3.2.2.

Table 3.1 shows that when $(\delta_1 = 1, \delta_2 = 0)$, we could have two different situations. In particular, we have that

$$\begin{aligned}&\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 1, \delta_2 = 0\right) = \mathbb{P}\left(X_1 = x_1, X_2 = x_2, T_1 \leq C, T_2 \geq C\right)\\ &= \mathbb{P}\left(\min(T_1, C) = x_1, \min(T_2, C) = x_2, T_1 \leq C, T_2 \geq C\right)\end{aligned}$$

It is easy to see that under scenario $G = 3$ we have that

$$\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 1, \delta_2 = 0 \,|\, G = 3\right) = f_C(x_2) f_{\tilde{T}_1}(x_1 \,|\, G = 3) \tag{3.41}$$

where $\tilde{T}_1 \sim \text{Weibull}\,(\alpha_3, \beta_3)$, whereas under scenario $G = 4$ we have that

$$\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 1, \delta_2 = 0 \,|\, G = 4\right) = \frac{\partial S^{MO}_{T_1,T_2}(x_1, x_2 \,|\, G = 4)}{\partial x_1} \tag{3.42}$$

Finally, the case $(\delta_1 = 1, \delta_2 = 1)$ can only be observed when both individuals are not cured. This means that

$$\mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 1, \delta_2 = 1 \,|\, G = 4\right) = f^{MO}_{T_1,T_2}(x_1, x_2 | \, G = 4) \tag{3.43}$$

where $f^{MO}_{T_1,T_2}(x_1, x_2 \,|\, G = 4) = \frac{\partial S^{MO}_{T_1,T_2}(x_1,x_2)}{\partial x_1 \partial x_2}$ is defined according to the MOBVE frailty model.

The likelihood function of the proposed bivariate MOBVE frailty cure model can be written as

$$L(\boldsymbol{\theta} | \boldsymbol{x}_1, \boldsymbol{x}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta_2}) \propto \prod_{p=1}^{n} \left\{ \varpi_1^{\delta_p^{00}} \; \varpi_2^{\delta_p^{10}} \; \varpi_3^{\delta_p^{01}} \; \varpi_4^{\delta_p^{11}} \right\}$$

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where

$$\varpi_1 = \sum_{h=1}^{4} \mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 0 \,|\, G = h\right) \cdot \mathbb{P}\left(G = h\right)$$

$$\varpi_2 = \sum_{h \in \{3,4\}} \mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 1, \delta_2 = 0 \,|\, G = h\right) \cdot \mathbb{P}\left(G = h\right)$$

$$\varpi_3 = \sum_{h \in \{2,4\}} \mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 0, \delta_2 = 1 \,|\, G = h\right) \cdot \mathbb{P}\left(G = h\right)$$

$$\varpi_4 = \mathbb{P}\left(X_1 = x_1, X_2 = x_2, \delta_1 = 1, \delta_2 = 1 \,|\, G = 4\right) \cdot \mathbb{P}\left(G = 4\right)$$

Note that the proportionality of the likelihood permits us to omit the likelihood quantities related to censoring in the above expression of ϖ_d, with $d = 1, 2, 3, 4$, which can be written more specifically as follows

$$\varpi_1 = \phi_{00} + \phi_{01}\, S_{\tilde{T}_2}(t_2) + \phi_{10}\, S_{\tilde{T}_1}(t_1) + \phi_{11}\, S^{MO}_{(T_1,T_2)}(t_1, t_2)$$

$$\varpi_2 = \phi_{10}\, f_{\tilde{T}_1}(t_1) + \phi_{11}\, S^{MO}_{(T_1,T_2)}(\Delta t_1, t_2)$$

$$\varpi_3 = \phi_{01}\, f_{\tilde{T}_2}(t_2) + \phi_{11}\, S^{MO}_{(T_1,T_2)}(t_1, \Delta t_2)$$

$$\varpi_4 = \phi_{11}\, S^{MO}_{(T_1,T_2)}(\Delta t_1, \Delta t_2)$$

where $\phi_{00} = \mathbb{P}\left(\epsilon_1 = 0, \epsilon_2 = 0\right)$, $\phi_{10} = \mathbb{P}\left(\epsilon_1 = 1, \epsilon_2 = 0\right)$, $\phi_{01} = \mathbb{P}\left(\epsilon_1 = 0, \epsilon_2 = 1\right)$ and $\phi_{11} = \mathbb{P}\left(\epsilon_1 = 1, \epsilon_2 = 1\right)$ are the multinomial logit probabilities characterizing the latent cure process.

Simulation Studies

In order to validate our proposed bivariate MOBVE frailty cure rate model, simulations studies were performed. Although the model was specified without the inclusion of any covariate, we do highlight the fact that we also included the covariate Age in the analysis. Such reinforcement not only does directly affect the functions $S^{MO}_{(T_1,T_2)}(t_1, t_2)$, $S_{\tilde{T}_1}(t_1)$ and $S_{\tilde{T}_2}(t_2)$, but also the latent cure process probabilities, that is ϕ_{00}, ϕ_{01}, ϕ_{10} and ϕ_{11}.
Simulated bivariate cure MOBVE frailty model is compared with the bivariate cure shared frailty model, firstly without the inclusion of any covariate and successively with the inclusion of the covariate Age. The R code for replicating such model is available in the

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Appendix. For each specific setting, the observations for each dataset are generated in the following way.

Firstly, we choose the multinomial logit probabilities, characterizing the latent cure process, to be approximately equal for each possible scenario, setting as the reference category $G = 1$, that is when both subjects are cured. This is done by setting $\beta_{01} = 0$, $\beta_{02} = \beta_{03} = 0.5$, and $\beta_{04} = 0.2$. The time-to-event for the i^{th} patient in the p^{th} pair is randomly generated according to the following scheme:

1. If $G = 1$, then $T_1^* = T_2^* = 10000$;
2. If $G = 2$, then $T_1^* \sim \text{Weibull}(\alpha_3, \beta_3)$ and $T_2^* = 10000$;
3. If $G = 3$, then $T_1^* = 10000$ and $T_2^* \sim \text{Weibull}(\alpha_4, \beta_4)$;
4. If $G = 4$, then $T_1^* \sim \text{Weibull}(\alpha_1, \beta_1^*)$ and $T_2^* \sim \text{Weibull}(\alpha_2, \beta_2^*)$, where $\beta_i^* = \frac{\beta_i}{z_i^{1/\alpha_i}}$ for each $i = 1, 2$.

Under the cure shared frailty model, N frailties z's are generated from a Gamma$(\vartheta^{-1}, \vartheta^{-1})$, with $\vartheta = 5$, whereas under the cure MOBVE frailty model, the bivariate random vector of frailties are generated assuming Marshall-Olkin type procedure with intensity of the Poisson process underlying the common shocks equal to $\xi_3 = 0.3$. The censoring time for each subject is randomly generated from an exponential distribution so that approximately 40% censored observations are obtained. Baseline Weibull shape parameters are set to be all equal to $\alpha = 3$, whereas the scale parameters to be equal to $\beta = 2$, for simplicity. However, adjusting by age in both models permits to introduce a better explanation of the dependence structure with respect to covariates. In particular, age of entry in the study for both men and women are generated by taking into account the first moments of the CCSMHA dataset in the following manner:

1. From a graphical assessment with respect to a generic bivariate normal sample, generate ages as $h_i = \sqrt{\text{Age}_i^{\text{CCSMHA}} - 60}$, for each $i = 1, 2$;
2. Construct bivariate Normal random vectors using the first moments of the new generated ages h_i

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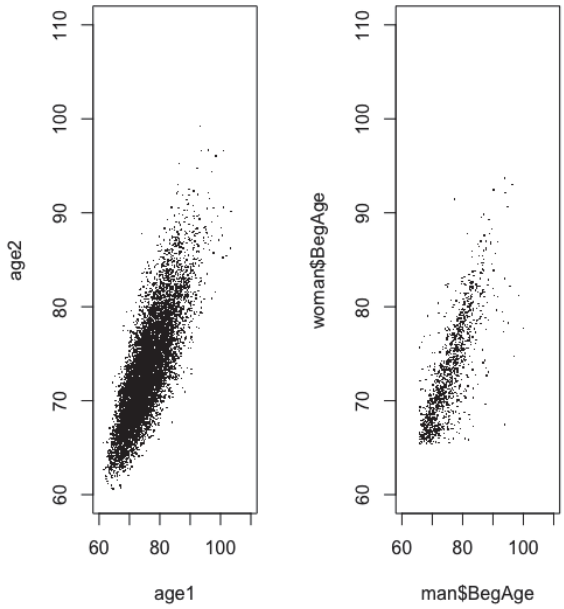

Figure 3.2: Simulated Age of Entry versus Age of Entry in the Study from the CCSMHA

3. For each random vector, obtained a centered value with respect to each subgroup by subtracting the mean subgroup age.

The estimated values from the cure MOBVE frailty model are compared with the bivariate cure shared frailty model proposed by Chatterjee and Shih (2001). Results are shown in the Appendix for the interested reader. In both cases, ten replicates of the $n = 1207$ bivariate vector of the CCSMHA age of entry's are considered. The proposed model was was compared with the cured Shared Frailty model for two reasons. On the one hand, the shared frailty mkodel is known to induce only positive dependence among failure times. In the CCSMHA data, it seems there is a positive age effect for both men and women that affects lifetimes, and therefore the association between their time-to-onset. On the other hand, the cured shared frailty model was the first (multivariate) cured frailty model introduced in the literature, and therefore it was choosen as a benchmark to assess the quality of our model.

Simulation studies confirm the goodness of our methodological framework, which recovers completely all the true parameters in a significant manner.

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Due to the sparcity of available time-to-onset data, we have not implemented the proposed model to the CCSMHA data, though the availability of larger administrative datasets might allow to go beyond to what we have done in this chapter. As a last comment, note that even reducing the dimensionality of the problem by imposing some resctrictions on the parameter space, we have however encountered difficulties in estimating the true model parameters in the cured MOBVE frailty model for samples with $N < 10,000$.

3.4 Analysis of the Cache County Study Data

Our primary goal is to estimate the association in dementia onset and death in different-sex couples followed within the CCSMHA. Our analysis focuses only on non-prevalent couples, that is couples whose members are dementia-free at the entry of the study. Table 3.2 provides descriptive statistics for time-to-onset based on the CCSMHA couples data as provided to us. Figure 3.3 shows the distribution of the age of dementia onset and of the age at entry in the study for both men and women. The times from entry to either death or onset are modelled as Weibull random variables.
Assume $T_1 \sim \text{Weibull}\,(\alpha_1, \beta_1)$ and $T_2 \sim \text{Weibull}\,(\alpha_2, \beta_2)$. Then, we set

$$T_1|z_1 \sim \text{Weibull}\left(\alpha_1, \frac{\beta_1}{z_1^{1/\alpha_1}}\right) \qquad \text{and} \qquad T_2|z_2 \sim \text{Weibull}\left(\alpha_2, \frac{\beta_2}{z_2^{1/\alpha_2}}\right)$$

so that a proportional hazard frailty regression model is therefore obtained as

$$h_i\left(t|z_i\right) = \frac{\alpha_i t^{\alpha_i - 1}}{\left(\beta_i z_i^{-\frac{1}{\alpha_i}}\right)^{\alpha_i}} \qquad (i = 1, 2) \tag{3.44}$$

We now implement the bivariate MOBVE frailty model proposed in Section 3.2.2 to measure the association between the survival times of the two members of the couples in different sex-couples. We perform two analyses: one without covariates and another one with the inclusion of the covariate *Age at entry in the study*, defined as *Age* for ease of notation. In particular, we are interested in capturing its effect on survival times with respect to each subgroup in the study, i.e. men and women, respectively. The associated parameter, γ, captures the effect between the age at entry and the time from entry to

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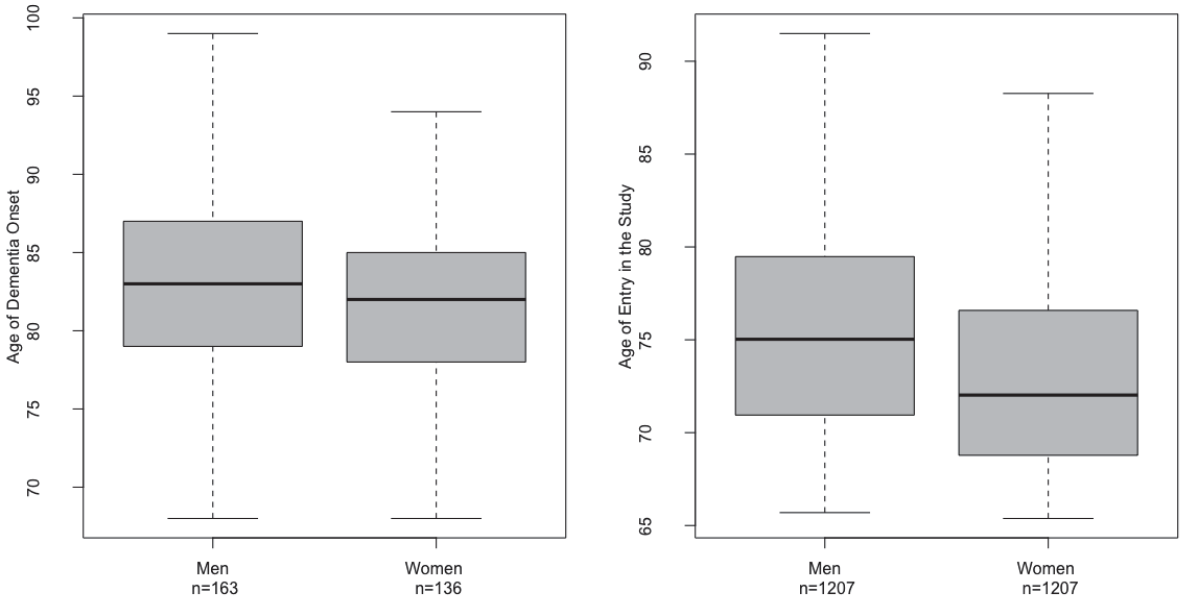

Figure 3.3: Boxplots of Age of Dementia Onset (Left) and of Age at Entry in the Study (Right) for both men and women in the Cache County Study of Memory Health and Aging.

death. It directly affects the frailty term, since the conditional model can be expressed as follows

$$h\left(t_i|z_i, \text{Age}_i\right) = \frac{\alpha_i t_i^{\alpha_i - 1} e^{\gamma_i \text{Age}_i}}{\left(\beta_i z_i^{-\frac{1}{\alpha_i}}\right)^{\alpha_i}} = \alpha_i t_i^{\alpha_i - 1} \left(\beta_i(\text{Age}_i)\right)^{\alpha_i} \quad (i = 1, 2) \tag{3.45}$$

where i indicates the member of the couple (man and woman, respectively), and where

$$\beta_i(\text{Age}_i) = \frac{1}{\beta_i z_i^{-\frac{1}{\alpha_i}} e^{-\frac{\gamma_i}{\alpha_i}\text{Age}_i}}$$

We performed preliminary marginal nonparametric and semiparametric analyses separately for men and women for estimating the time-to-death survival curves. The estimated marginal survival curves under a proportional hazard model with the inclusion of the covariate Age are shown in Figure 3.4. In particular, we estimated the marginal survival curve for a generic individual in the sample with an entry age equal to 70, 75 and 80, for both subgropus, respectively.

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Table 3.2: Descriptive Statistics of the Time from Entry to Onset until the End of the Study. People who do not experience any event are right-censored.

Type of Events	N		Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
Both with Dementia	19	Men	2.032	4.162	5.720	6.476	8.872	11.600
		Women	0.4299	4.5860	6.2450	6.5040	8.9340	12.5300
Only Man with Dementia	144	Men	0.04107	2.49400	6.27500	6.04600	9.16200	12.25000
		Women	0.000	3.458	10.450	8.090	11.260	12.600
Only Woman with Dementia	117	Men	0.000	0.000	3.409	5.231	10.570	11.930
		Women	0.0575	3.4720	6.0400	5.9190	8.5260	12.4400
Nobody with Dementia	927	Men	0.000	0.000	3.321	5.245	10.580	13.820
		Women	0.000	3.123	7.622	6.482	10.880	13.260

Table 3.3 shows the estimation results for the age-at-entry adjusted bivariate model. All parameters are estimated via maximum likelihood estimation. In particular, the estimated age effects for both men and women are strongly significant, and their introduction affects positively the dependence parameter's significativity. Both age effects are positive, though the effect seems to be stronger for women, estimated as being equal to $\hat{\gamma}_2 = 0.1671032$ compared to the one for men, estimated as being equal to $\hat{\gamma}_1 = 0.1359$. Finally, the results under such model also confirm the adjustment for Age in the Weibull scale parameters. The estimated Weibull scale parameters are quite realistic considering the event of interest (death), estimated as being equal to $\hat{\beta}_1 = 10.6270311$ and $\hat{\beta}_2 = 17.0497187$, respectively. Lastly, it seems that the age at entry explains part of the dependence: indeed, the different estimates $\hat{\xi}_3^{\text{no covs}} = 0.7883879$ and $\hat{\xi}_3^{\text{covs}} = 0.3066338$ suggest that when *Age*s are introduced, the residual dependence is indeed reduced.

We also estimated the conditional median survival times for both men and women with respect to the age at entry covariates and conditionally on the partner's death age. Indeed,

$$\mathbb{P}\left(T_1 > t_1 | T_2 \leq t_2, \text{Age}_1, \text{Age}_2\right) = 1 - \mathbb{P}\left(T_1 \leq t_1 | T_2 \leq t_2, \text{Age}_1, \text{Age}_2\right)$$

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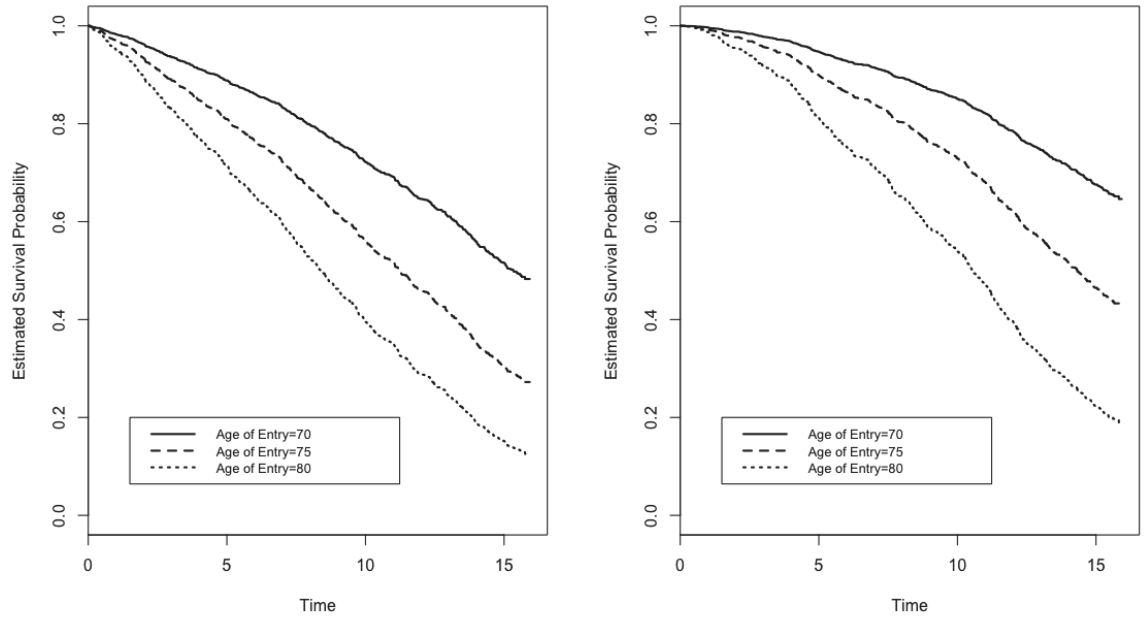

Figure 3.4: Marginal Cox-adjusted Survival Curve for Men (LEFT) and Women (RIGHT) with the inclusion of *Age at Entry in the Study* for the time-to-death.

Table 3.3: Estimation of the Bivariate Frailty MOBVE Model adjusted for Age with respect to death.

Parameter	Estimate	Std. error	t-value	p-value
α_1	1.8047	0.0544	33.1978	< 0.0001
α_2	2.1811	0.0813	26.8193	< 0.0001
β_1	10.6270	0.3022	35.1665	< 0.0001
β_2	17.0497	0.4899	34.8052	< 0.0001
ξ_3	0.3066	0.1019	3.0099	0.0026
γ_1	0.1359	0.0091	14.8924	< 0.0001
γ_2	0.1671	0.0107	15.6001	< 0.0001

with

$$\begin{aligned}\mathbb{P}\left(T_1 \leq t_1 | T_2 \leq t_2, \text{Age}_1, \text{Age}_2\right) &= \frac{\mathbb{P}\left(T_1 \leq t_1, T_2 \leq t_2 | \text{Age}_1, \text{Age}_2\right)}{\mathbb{P}\left(T_2 \leq t_2 | \text{Age}_2\right)} \\ &= \frac{\int_0^{t_1}\int_0^{t_2} f_{12}(u_1, u_2 | \text{Age}_1, \text{Age}_2)\, \mathrm{d}u_2 \mathrm{d}u_1}{\mathbb{P}\left(T_2 \leq t_2 | \text{Age}_2\right)} \end{aligned} \tag{3.46}$$

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and since

$$F_{T_1,T_2}(t_1,t_2) = S_{T_1,T_2}(t_1.t_2) - S_{T_1}(t_1) - S_{T_2}(t_2) + 1$$

conditionally on the covariates Age_1 and Age_2 we have that

$$F(t_1|t_2,\text{Age}_1,\text{Age}_2) = \frac{S_{12}(t_1,t_2|\text{Age}_1,\text{Age}_2) - S_1(t_1|\text{Age}_1) - S_2(t_2|\text{Age}_2) + 1}{1 - S_2(t_2|\text{Age}_1,\text{Age}_2)}$$

where

$$S(t_1,t_2) = \frac{\xi_2(\xi_1+\xi_3)}{(\Lambda_{01}(t_1)+\xi_1+\xi_3)\Psi} + \frac{\xi_1(\xi_2+\xi_3)}{(\Lambda_{02}(t_2)+\xi_2+\xi_3)\Psi} + \frac{\xi_3}{\Psi}$$

where $\Psi = (\Lambda_{01}(t_1) + \Lambda_{02}(t_2) + \sum_{i=1}^{3}\xi_i)$ and $\Lambda_{0i}(t_i) = \frac{S_i(t_i)^{-\theta_i}-1}{\theta_i}$ $(i = 1, 2)$. Finally,

$$\mathbb{P}\left(T_1 > t_1 | T_2 \leq t_2, \text{Age}_1, \text{Age}_2\right) = \frac{S_1(t_1|\text{Age}_1) - S_{12}(t_1,t_2|\text{Age}_1,\text{Age}_2)}{1 - S_2(t_2|\text{Age}_2)} \tag{3.47}$$

Results for the estimated conditional median survival times are shown in Table 3.4 and Table 3.5 for men and women, respectively. The interesting fact emerging from this analysis is the positive dependence between failure times. In particular, the association between the partners' time-to-death is strengthen by the fact that the conditional median lifetime fairly increases as the partner's events is delayed over time.

Figure 3.5 shows the estimated conditional survival function for a generic man in the sample given his partner dies within 1 (solid), 10 (dashed) or 20 (longdash) years from entry, with corresponding estimated confidence intervals, given they enter with ages equal to 10 years after the average sample entry age, where $\hat{A}_m = 75.66$ and $\hat{A}_w = 73.04$ denote the average men and women entry age, respectively. In particular, the top-left figure shows the positive effect on the man's survival curve induced by his partner's survival. His estimated median survival times are estimated as being equal to $\overline{M}_m^1 = 4.43$, $\overline{M}_m^{10} = 4.64$ and $\overline{M}_m^{20} = 4.84$, respectively, showing a positive association between the two lifetimes. In particular, the difference in the two extreme median conditional survival times is approximately 5 months, that is partner's death in one year versus twenty years. Conversely, the top-right and the two bottom figures describe each specific conditional survival function provided in the top-left figure, with the corresponding estimated pointwise confidence intervals. The mathematical details to obtain such confidence intervals as well as more details on the analyses performed on the CCSMHA data, are shown in the Appendix.

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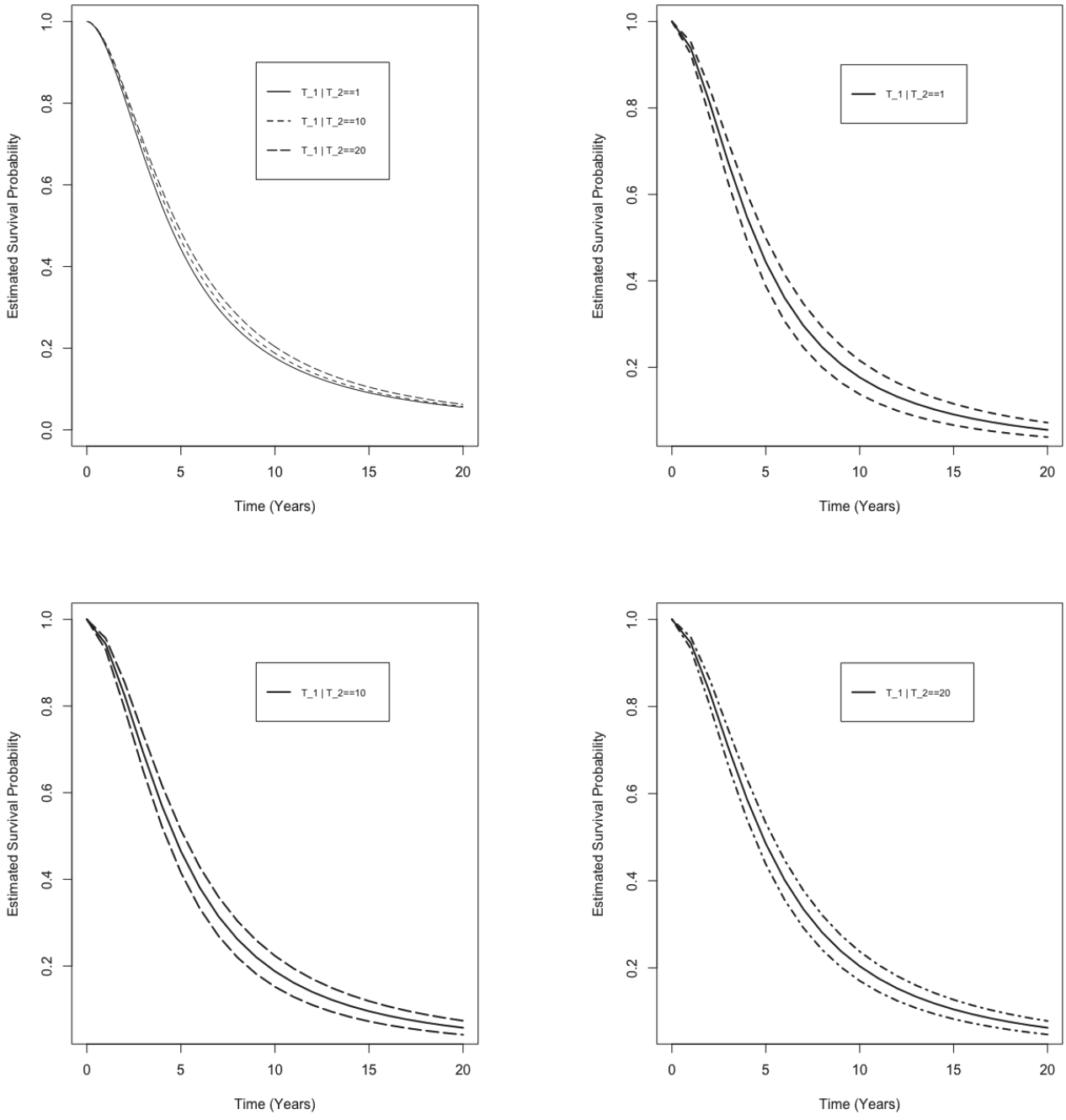

Figure 3.5: Estimated Conditional Survival Function for Men given his (Woman) partner dies within 1 (solid), 10 (dashed) or 20 (longdash) years, with corresponding estimated confidence intervals, given that they both enter with ages equal to 10 years after the average sample entry ages for men and women (i.e. at ages 75.66 and 73.04), respectively.

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Table 3.4: Estimated conditional median survival times for Men

Age_m	Age_w	median$(T_1 \mid T_2 = 1)$	median$(T_1 \mid T_2 = 10)$	median$(T_1 \mid T_2 = 20)$
0	0	9.40	9.53	9.82
10	10	4.43	4.64	4.84
-5	-5	13.71	13.79	14.03
5	5	6.46	6.63	6.90
-5	-3	13.71	13.82	14.12
3	5	7.51	7.70	8.02
-8	-8	17.19	17.25	17.45

Age_m and Age_w are the Age at entry in the study relative to the mean entry age for men and women, respectively.

Table 3.5: Estimated conditional median survival times for Women

Age_m	Age_w	median$(T_2) \mid T_1 = 1$	median$(T_2) \mid T_1 = 10$	median$(T_2) \mid T_1 = 20$
0	0	15.42	15.81	16.27
10	10	7.18	7.58	7.78
-5	-5	22.62	22.95	23.48
5	5	10.52	10.94	11.27
-5	-3	19.40	19.69	20.14
3	5	10.52	10.87	11.20
-8	-8	28.46	28.75	29.28

Age_m and Age_w are the Age at entry in the study relative to the mean entry age for men and women, respectively.

As for the study of association between the two times to dementia onset, we performed preliminary marginal nonparametric and semiparametric analyses for the time to dementia onset for men and women, respectively. Interestingly, the estimated marginal survival functions with the adjustment for Age under the Cox model are approximately replicates of the nonparametric Kaplan-Meier survival curves. The corresponding Cox-adjusted survival curves are shown in Figure 3.6. The bivariate analysis for time to dementia onset was then conducted parametrically via maximum likelihood estimation.

The estimated value for the association parameter among CCSMHA data couples, without the inclusion of any covariates, is $\hat{\xi}_3 = 0.11$, which is however not significant. Furthermore,

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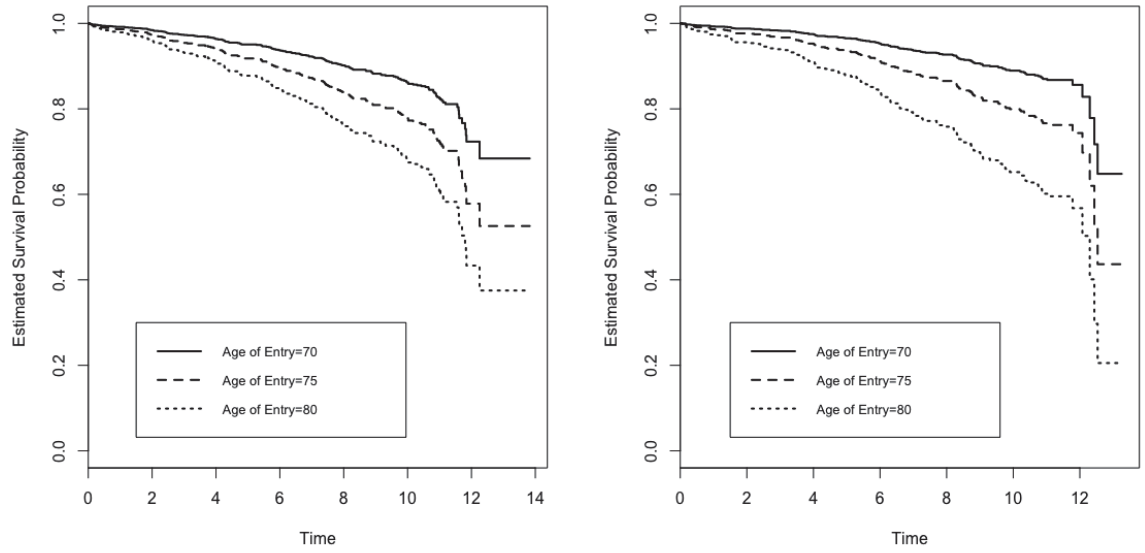

Figure 3.6: Marginal Cox-adjusted Survival Curve for Men (LEFT) and Women (RIGHT) with the inclusion of *Age of Entry in the Study* for the time-to-onset in the two subgroups.

Table 3.6: Estimation of the Bivariate MOBVE Frailty Model with respect to onset with the inclusion of the age effects after the model selection procedure.

Parameter	Estimate	Std. error	t-value	p-value
α_1	1.5529	0.1039	14.9432	< 0.0001
α_2	1.5313	0.1140	13.4369	< 0.0001
β_1	20.9086	1.7980	11.6285	< 0.0001
β_2	30.1470	3.4047	8.8546	< 0.0001
γ_1	0.1030	0.0157	6.5600	< 0.0001
γ_2	0.1487	0.0175	8.5045	< 0.0001

after introducing the two age covariates in the analysis, a similar behaviour as the one discerned with the analysis of survival times, is suggested: in particular, we note a smaller association coefficient (also not significant) after adjusting by age, which is now completely captured by the age effects, so that the residual association effect is even smaller than when no age covariates are inserted. Indeed, compared to the time-to-death analysis, we have fewer onset events, which translates into rather challenging estimation issues.

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We therefore believe that, due to the sparcity of CCSMHA data couples with emerging onsets, fitting the model with both ξ_3 and the age effects γ's is not feasible. We therefore implemented a model selection procedure, and the ξ_3 parameter was further removed. The resulting estimated values are shown in Table 3.6. Our conclusion is that the emerging 1.6 increase in the hazard claimed in Norton *et al.* (2010) is possibly induced by the effect of the ages at entry, implying that no residual association is captured by the dependence parameter ξ_3 once we adjust by the ages at entry.

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Chapter 4

Modeling Dependence in Bivariate Multi-state Processes: a Frailty Approach

4.1 Introduction

Among multivariate survival analysis techniques, a multi-state model is the most suitable framework for describing longitudinal failure time data; such a model is a stochastic process which at any time occupies one of a set of discrete states (Hougaard, 1999): events are seen as transitions from one state to another, taking into account event-related risk dependence and possibly individual risk heterogeneity. More generally, a multi-state model is a continuous-time stochastic process $\{X(t) : t \geq 0\}$ taking values in $\mathcal{S} = \{1, \ldots, k\}$.
In clinical contexts, multi-state models are used to characterize any progressive disease process (Putter et al., 2007), and Markov and semi-Markov processes are two fundamental classes of models with the former being most widely adopted in settings involving progressive conditions (Meira-Machado et al., 2009). Under the frequently assumed Markov property, a multi-state model can be seen as a sequence of competing risks models (Beyersmann et al., 2012), and copula-based models may be employed to model the dependence

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across competing-risks events (Rotolo et al., 2013). Recently, Cook and Lawless (2014) provided an up-to-date review on such issue (please refer to references therein).

Measuring the strength of association between two correlated failures times is crucial in clinical contexts. Several dependence measures have been proposed, such as Kendall's τ coefficient for failure times, but it is the *conditional hazard ratio* function (Oakes, 1982) which has been widely exploited, probably due to its attractive hazard ratio interpretation. Clayton (1978) considered a constant cross-ratio that yields an explicit closed-form bivariate survival function, the Clayton copula model. Reparametrizing the Clayton model, Oakes (1989) analyzed bivariate failure times in the frailty framework, where a common latent variable induces correlation between suvival times. This model is also known as the *shared frailty model*, and it plays a key role in modern survival data analysis modelling. Following the results by Genest and MacKay (1986) and Marshall and Olkin (1988), the shared frailty model model can be also easily expressed in terms of Archimedean copulas. Several extensions of such measure have been proposed in the presence of a competing risks (Bandeen-Roche and Liang, 2002) as well as its time-dependent versions (Hu et al. (2011); Ning and Bandeen-Roche (2014)). However, little has been done to study the dependence between two failures times generated by different processes. To the best of our knowledge, the first attempt in this direction was given by Cheng et al. (2007) in the context of bivariate competing-risks data. A more general proposal was given in the bivariate setting by Aalen et al. (2007), where an intensity-based joint analyses was employed to assess the local dependence between processes. Sutradhar and Cook (2008) investigated multiple recurrent multi-state models under intermittent events. Diao and Cook (2014) proposed a copula-based model which enables joint analysis of multiple progressive multistate process using D-vine copulas. A similar argument is used by Eryilmaz (2014), who employed the Clayton copula to model the global dependence between two multi-state components.

Along these lines, frailty models can be exploited to model the dependence across multi-state models. We aim to incorporate correlated random effects that directly affect the association between two correlated failures times. We will focus on the bivariate case, although the extension to the multivariate case is, in principle, straightforward. We make

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use of the MOBVE distribution for the joint vector of frailty, and the archimedean generalization of the Marshall-Oklin copula is discussed in line with the spirit of Mulinacci (2017).

Finally, the reader should be aware of the fact that this chapter is quite theoretical; nowadays, the area of multiple multistate processes is a quite wild world, which obviously require further investigation. A strong probabilistic background, which might allow to derive a consistent nonparametric estimator for the transition probability matrix of the bivariate model, has not been produced yet, and the lack of asymptotic results does not allow to properly use these models from a practitioner point of view.

4.2 Marginal Multi-state Model as a Shared Frailty Model

Following the idea by Beyersmann et al. (2012), multi-state models can be constructed as a nested sequence of competing risks. In the context of competing risks, Beyersmann et al. (2009) developed a simulation method based on the cause-specific hazards, which can also be extended to multi-state models. However, limitations of such simulation procedure are highlighted by Rotolo et al. (2013), who proposed a more general simulation procedure for multi-state data based on a copula model for each group of competing events. Copulas are frequently employed in multivariate survival analysis, where independence between survival times cannot be assumed. In particular, copula arguments are extremely useful to express any multivariate joint survival function in terms of its marginals (Nelsen (2006), page 18).

Among survival copulas families, Archimedean copulas are perhaps the most suitable and tractable class that easily handle dependence among intermediate failure times and the one of (clinical) interest.

Let us start by recalling the following equation from Chapter 2:

$$S(t_1, t_2) = \left[S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} - 1\right]^{-\frac{1}{\theta}} \tag{4.1}$$

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where $S(t_1, t_2)$ is the absolute continuous joint survival function of two non-negative random variables T_1 and T_2 with (known) marginals $S_i(t_i)$, $i = 1, 2$, and $\theta \in [-1, +\infty)$. Equation (4.1) is the so-called *shared frailty model* (Clayton (1978); Oakes (1982, 1989)) which is a natural tool to model dependence between event-times through the introduction of a clustered-specific random effect, i.e. the frailty. Obviously, the above results in (4.1) can be generalized to the multivariate case, that is

$$S(t_1, \ldots, t_n) = \left[\sum_{i=1}^{n} S_i(t_i)^{-\theta} - (n-1) \right]^{-\frac{1}{\theta}} \tag{4.2}$$

Recall also that for any joint survival function, the following holds:

$$S(t_1, ..., t_n) = S(t_n | t_{n-1}, \ldots, t_1) \cdots S(t_2|t_1) \cdot S(t_1) \tag{4.3}$$

The above representation turns out to be extremely useful when independence among survival times cannot be assumed. From the above shared frailty model, we might be interested in computing its conditional survival function, $S\left(t_2|t_1\right)$, which is derived by differentiating the unconditional bivariate survival function w.r.t. t_1 and divided by the p.d.f. of T_1, that is

$$S\left(t_2|t_1\right) = \frac{\frac{\partial}{\partial t_1} S(t_1, t_2)}{\frac{\partial}{\partial t_1} S(t_1)} = \left[1 + \left(\frac{S_1(t_1)}{S_2(t_2)} \right)^{\theta} - S_1(t_1)^{\theta} \right]^{-\frac{1}{\theta}-1} \tag{4.4}$$

It is not hard to see that the results holds for any $n \geq 2$, that is

$$\begin{aligned} S(t_n | t_1, \ldots, t_{n-1}) &= \frac{\frac{\partial}{\partial t_1 \partial t_2 \cdots \partial t_n} S(t_1, \ldots, t_n)}{\frac{\partial}{\partial t_1 \partial t_2 \cdots \partial t_{n-1}} S(t_1, \ldots, t_{n-1})} \\ &= \left(1 + \frac{S_n(t_n)^{-\theta} - 1}{1 + \sum_{j=1}^{n-1} \left(S_j(t_j)^{-\theta} - 1 \right)} \right)^{1-k-\frac{1}{\theta}} \end{aligned} \tag{4.5}$$

Based on the above considerations, R code for simulating multi-state models as a sequence of competing risks was developed, and it is provided in Appendix B.

Example 2. *Let $\mathcal{S} = \{NED, Mild\ Dem, Sev\ Dem, Death\}$ be the set of states corresponding to No Evidence of Disease, occurrence of mild and severe dementia, and death, respectively. The children sets of the four states are, for example, $\mathcal{C}(NED) = \{Mild, Death\}$,*

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$\mathcal{C}(Mild\ Dem) = \{Sev\ Dem, Death\}$, $\mathcal{C}(Sev\ Dem) = \{Death\}$ *and* $\mathcal{C}(Death) = \{\emptyset\}$.
Let us suppose the process starts at state NED, and suppose that the continuous-time random variable T_{11} *describes the time of transition to state Mild Dem, and* T_{12} *describes the time of transition to state Death. Note that the two events are competing risks events. It follows that*

$$S(t_1, t_2) = \left(S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} + -1\right)^{-\frac{1}{\theta}} \tag{4.6}$$

describes the survival function of the first two transition times. Obviously,

$$S(t_{11}, t_{12}) = S(t_{12}|t_{11})S(t_{11}) \tag{4.7}$$

and each quantity describing equation (4.7) can be easily obtained by using equation (4.5). Say that $\tilde{t}_1 := \min(t_{21}, t_{22})$*; once the process moves to another state, say Mild Dem, then another copula model can be adopted for the incoming transition and all the competing events from the present state are considered, as before. For instance, we may be interested in computing* $S(t_{21}, t_{22})$ *where* T_{21} *describes the transition time to state Sev Dem,* T_{22} *describes the transition time to state Death. Then, by applying the same reasoning as before, we obtain*

$$S(t_{21}, t_{22}|\tilde{t_1}) = S(t_{21}|t_{22}, \tilde{t}_1)S(t_{22}|\tilde{t}_1) \tag{4.8}$$

4.2.1 Marginal Data Analysis based on the CCSMHA

We perform marginal analysis on the two subgroups in the CCSMHA, that is men and women, respectively. We also considered only couples whose members were disease-free at the beginning of the study. Interestingly, only $n_M^{ons} = 163$ and $n_W^{ons} = 136$ were observed experiencing the event Dementia in the sample of $n = 1207$ given couples. A useful way to summarise multi-state data is by means of a frequency table of pairs of consecutive states. This counts the number of times an individual experienced a specific transition from state i to state j over all $n = 1207$ individuals, for each state i and j, $i \neq j \in \{0, 1, 2\}$. The following R output was obtained by firstly using the function **msprep** into the **mstate** package, which creates a long dataset for flexible multi-state modeling. Successively, the function **events** generated the desired frequency table of pairs of consecutive states,

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giving both frequencies and proportions for both subgroups. the following output gives the desired results for men and women, respectively.

```
> head(msmdat.men,10L)
An object of class 'msdata'


Data:
   id from to trans Tstart     Tstop      time status
1   1    1  2     1      0  8.221991  8.221991      0
2   1    1  3     2      0  8.221991  8.221991      1
3   2    1  2     1      0 11.674515 11.674515      0
4   2    1  3     2      0 11.674515 11.674515      1
5   3    1  2     1      0  5.314314  5.314314      0
6   3    1  3     2      0  5.314314  5.314314      1
7   4    1  2     1      0 15.581109 15.581109      0
8   4    1  3     2      0 15.581109 15.581109      0
9   5    1  2     1      0 12.493155 12.493155      0
10  5    1  3     2      0 12.493155 12.493155      1

> events(msmdat.men)
$Frequencies
       to
from     NED Onset Death no event total entering
  NED      0   163   694      350           1207
  Onset    0     0   139       24            163
  Death    0     0     0      833            833


$Proportions
       to
from          NED     Onset     Death  no event
  NED   0.0000000 0.1350456 0.5749793 0.2899751
```

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```
  Onset 0.0000000 0.0000000 0.8527607 0.1472393
  Death 0.0000000 0.0000000 0.0000000 1.0000000


> events(msmdat.wom)
$Frequencies
       to
from     NED Onset Death no event total entering
  NED      0   136   463      608            1207
  Onset    0     0   106       30             136
  Death    0     0     0      569             569

$Proportions
       to
from          NED     Onset     Death  no event
  NED   0.0000000 0.1126761 0.3835957 0.5037283
  Onset 0.0000000 0.0000000 0.7794118 0.2205882
  Death 0.0000000 0.0000000 0.0000000 1.0000000
```

Note that all the above analysis were performed without the inclusion of any covariate, although such extension might be easily accomodate. As a direct consequence of the above outputs, 163 members of the subgroup Men experienced the intermediate event, but only 139 were observed to experience death from the intermediate state, whereas for 694 the direct transition to state 3 (Death) was observed. Moreover, 350 individuals did not experienced any of those events, i.e. they remained healthy for all the investigation period.

Figure 4.1 shows the estimated transition probabilities for Men and Women in the CC-SMHA based on the Aalen-Johansen estimator; it gives the transition probabilities starting from state NED. However, the former plot is definitely more exhaustive if one aims to obtain such probabilities for all possible transitions. For instance, the estimate of the transition probability $p_{00}(1, 10)$, that is the probability for any member of the subgroup

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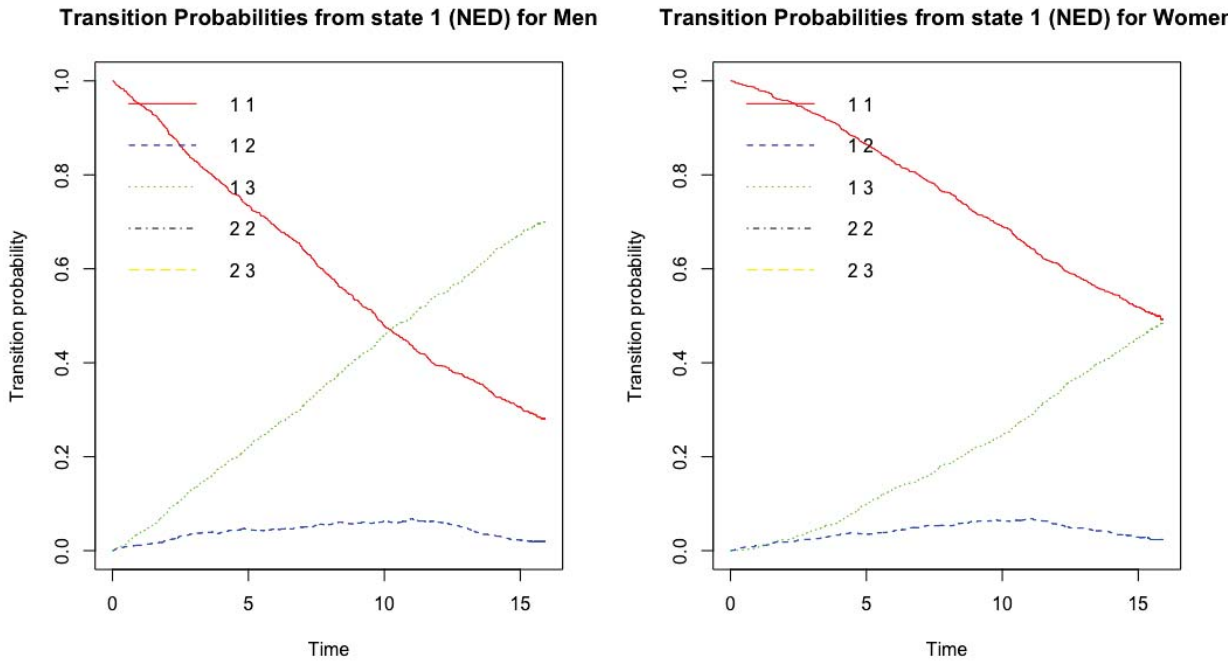

Figure 4.1: NED-specific Transition Probabilities for Men and Women in the CCSMHA based on the Aalen-Johansen Estimator.

Men of moving remaining in state 0 in the time-window $(1, 10)$, is equal to 0.5030514. Similarly, the estimate of the transition probability $p_{12}(1, 10)$ is 0.06364429; the estimate of the transition probability $p_{13}(1, 10)$ is 0.4333043. The estimate of the transition probability $p_{22}(1, 10)$ is 0.1428571, and the estimate of the transition probability $p_{23}(1, 10)$ is 0.8571429. Similar conclusions can be drawn for the subgroup Women.

4.3 A Bivariate Frailty Multi-state Model

Let us now generalize the frailty approach shown in Chapter 3 to the bivariate multi-state case. Without loss of generality, we assume a common state-space, or $\mathcal{S}_1 = \mathcal{S}_2 = \mathcal{S}$. Hence, let $\{X_1(t), X_2(t)\}$ be a bivariate continuous-time random process , where $X_i(t)$ denote the state occupied at time t for process i, taking values in $\mathcal{S}$. Let $\mathcal{H}(t) = (\mathcal{H}_1(t), \mathcal{H}_2(t))$ be the corresponding σ-field, where $\mathcal{H}_1(t)$ and $\mathcal{H}_2(t)$ being, respectively, the marginals for process 1 and 2.

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Our proposal is to employ multiplicative frailty models of the form

$$\lambda_{ij}(t|X_i(t^-)=j,\mathcal{H}(t),z_i)=z_i\lambda_{ij}(t|X_i(t^-)=j,\mathcal{H}(t)) \tag{4.9}$$

Note that each frailty component is process-specific, implying marginally a shared frailty model (Rotolo et al., 2013). For $i=1,2$, the transition-specific hazards are given by

$$\lambda_j\left(t|\mathcal{H}_1(t^-)\right)=\lim_{\Delta t\downarrow 0}\frac{\mathbb{P}_{kj}\left(t,t+\Delta t\right)}{\Delta t} \tag{4.10}$$

and

$$\nu_j\left(t|\mathcal{H}_2(t^-)\right)=\lim_{\Delta t\downarrow 0}\frac{\mathbb{P}_{kj}\left(t,t+\Delta t\right)}{\Delta t} \tag{4.11}$$

where $\lambda_j\left(t|\mathcal{H}_1(t^-)\right)$ and $\nu_j\left(t|\mathcal{H}_2(t^-)\right)$ denote the instantaneous probabilities of moving out from state j at time t for, respectively, process 1 and 2. Our primary interest is on the estimation of such quantities. Let

$$\mathbb{P}_{k_1j_1}(s,t)=\mathbb{P}\left[X_1(t)=j_1|X_1(s)=k_1,z_1,\mathcal{H}_1(s^-)\right] \tag{4.12}$$

and

$$\mathbb{P}_{k_2j_2}(s,t)=\mathbb{P}\left[X_2(t)=j_2|X_2(s)=k_2,z_2,\mathcal{H}_2(s^-)\right] \tag{4.13}$$

be the transition probabilities, that is the probability of being i state j at time t given that the process was in state i at time s. The most common assumption in the multi-state modeling literature is that the process is Markov, that is future developments of the process are independent of the past given the current state. Therefore, we do assume markovianity for each marginal process, though the joint process is not Markov. The Markovian unconditional transition probabilities can be easily obtained by

$$p_{kj}(s,t)=\int\int_{\text{supp}(\mathbf{Z})}p_{k_1j_1}(s,t|z_1)p_{k_2j_2}(s,t|z_2)\overline{F}_{\mathbf{Z}}(d\mathbf{z})$$

where $p_{k_ij_i}$ are the marginal Markovian unconditional transition probabilities for process $i=1,2$.

Let us recall that under the Markov assumption, the likelihood function of every multi-state model can be written as

$$\prod_{m,l\in\mathcal{S}}\prod_{j=1}^{K}\left[\left(\lambda_{ml}(t_j)\right)^{\delta_{ml}(j)}\exp\left(\int_{t_{j-1}}^{t_j}-\sum_{l\neq m}\lambda_{ml}(u)\text{du}\right)\right] \tag{4.14}$$

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where $\delta_{ml}(j) = I\{s_{j-1} = m, s_j = l\}$ be the indicator for the j^{th} transition from state m to state l. At the moment, we assume that the hazard function specific to each transition is defined without the inclusion of covariates.

In our bivariate model, the likelihood can be written as:

$$\prod_{p=1}^{P}\prod_{i=1}^{2}\prod_{m,l}\prod_{j=1}^{K_i}\int\int (\lambda_{m_i l_i}(t_{i,j,p}|Z_{i,p}))^{\delta_{m_i l_i}(i,j,p)}\, S(t_{1,j,p}, t_{2,j,p}|\boldsymbol{z})\, \boldsymbol{G}(\mathbf{dz}) \tag{4.15}$$

This marginal observed data likelihood can be maximized to obtain parameter estimates.

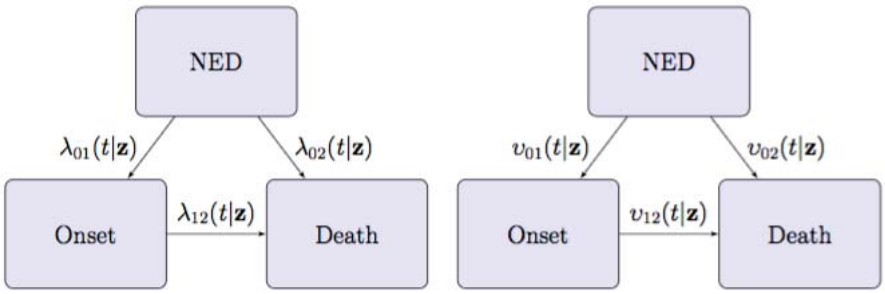

Figure 4.2: Bivariate Illness-death model with the incorporation of correlated individual-specific frailties (NED = No Evidence of Disease).

Example 3 (Bivariate Illness-Death Model). *Consider the well-known Illness-Death model, summarized in Figure 1. Under Markovianity, one can show that the unconditional likelihood for the bivariate Illness-Death model can be written as*

$$L(\boldsymbol{\xi}|\boldsymbol{t}) = \prod_{j\in\{1,2,3\}}\prod_{p,m,l} \lambda_{m_1 l_1}(t_{1_{jp}})^{\delta_{m_1 l_1}(1_{jp})}\alpha_{m_2 l_2}(t_{2_{jp}})^{\delta_{m_2 l_2}(2_{jp})} S(t_{1_{jp}}, t_{2_{jp}}, \Lambda(t_{1_{jp}}), \Upsilon(t_{2_{jp}}), \boldsymbol{\xi}).$$

A semi-parametric procedure for the estimation of ξ_3 and of the transition probabilities can be devised by maximizing :

$$\prod_{j\in\{1,2,3\}}\prod_{p,m,l} \hat{\lambda}_{m_1 l_1}(t_{1_{jp}})^{\delta_{m_1 l_1}(1_{jp})}\hat{\alpha}_{m_2 l_2}(t_{2_{jp}})^{\delta_{m_2 l_2}(2_{jp})} S(t_{1_{jp}}, t_{2_{jp}}, \hat{\Lambda}(t_{1_{jp}}), \hat{\Upsilon}(t_{2_{jp}})),$$

where $\hat{\Lambda}(\cdot)$ and $\hat{\Upsilon}(\cdot)$ are the marginal nonparametrically-estimated cumulative hazards, and $\hat{\lambda}(\cdot)$ and $\hat{\alpha}(\cdot)$ are the estimated transition-specific hazards. The asymptotic behaviour

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of such alternative two-step parameter estimating procedure will be examined in ongoing work.

4.3.1 A Bivariate frailty MOBVE Multi-state Model

Let $p_{ij}(s,t)$ be the unconditional transition probability defined in terms of Laplace transform, that is

$$p_{ij}(s,t) := \int\int p_{ij}\left(s,t|z_1,z_2\right)\, d\,F(z_1,z_2) \tag{4.16}$$

where the bivariate vector (z_1,z_2) follows the bivariate MOBVE distribution with parameter vector given by (ξ_1,ξ_2,ξ_3). Under the Frailty MOBVE model, we have that

$$\begin{aligned} p_{ij}(s,t) := &\int_0^{+\infty}\int_0^{z_1} p_{i_1j_1}\left(s,t|z_1\right)\, p_{i_2j_2}\left(s,t|z_2\right)\, \xi_2\left(\xi_1+\xi_3\right)\, e^{-(\xi_1+\xi_3)\,z_1-\xi_2\,z_2}\,\mathrm{d}z_2\,\mathrm{d}z_1+\\ &\int_0^{+\infty}\int_{z_1}^{+\infty} p_{i_1j_1}\left(s,t|z_1\right)\, p_{i_2j_2}\left(s,t|z_2\right)\, \xi_1\left(\xi_2+\xi_3\right)\, e^{-(\xi_2+\xi_3)\,z_2-\xi_1\,z_1}\,\mathrm{d}z_2\,\mathrm{d}z_1+\\ &\int_0^{+\infty} p_{i_1j_1}\left(s,t|z\right)\, p_{i_2j_2}\left(s,t|z\right)\, \xi_3\, e^{-z(\xi_1+\xi_2+\xi_3)}\,\mathrm{d}z \end{aligned}$$

Assuming the process described in Figure 4.2, the possible transition from state $s_0 = \text{NED}$ are just three. Then, the transition probability of remaining in state (NED,NED) is given by

$$p_{00}(s,t) := \frac{\xi_2\,\left(\xi_1+\xi_3\right)\Phi^*\left(s,t,\boldsymbol{\xi}\right)}{\Phi^*\left(s,t,\boldsymbol{\xi}\right)\,\Psi_1^*\left(s,t,\boldsymbol{\xi}\right)\,\Lambda^*\left(t_1,t_2,\boldsymbol{\xi}\right)} + \frac{\xi_1\left(\xi_2+\xi_3\right)}{\Psi_2^*(s,t,\boldsymbol{\xi})\Lambda^*(s,t,\boldsymbol{\xi})} + \frac{\xi_3}{\Lambda^*(s,t,\boldsymbol{\xi})}$$

where $\Phi^*\left(s,t,\boldsymbol{\xi}\right) := (\Lambda_{01}^2(s,t)+\Lambda_{02}^2(s,t)+\xi_2)$, $\Psi_i^*\left(s,t,\boldsymbol{\xi}\right) := (\Lambda_{01}^i(s,t)+\Lambda_{02}^i(s,t)+\xi_1+\xi_3)$, $(i=1,2)$ and

$$\Lambda^*\left(s,t,\boldsymbol{\xi}\right) := \left(\Lambda_{01}^2(s,t)+\Lambda_{02}^2(s,t)+\Lambda_{01}^1(s,t)+\Lambda_{02}^1(s,t)+\sum_{i=k}^{3}\xi_k\right)$$

Note that $\Lambda_{ij}^1(s,t)$ and $\Lambda_{ij}^2(s,t)$ stands for the unconditional transition-specific cumulative hazard function related to process one and two, respectively, which can be estimated nonparametrically via the Aalen-Johansen estimator.

Since

$$p_{01}\left(s,t|(z_1,z_2)\right) := p_{00}(s,t|z_1)\,p_{01}(s,t|z_2)$$

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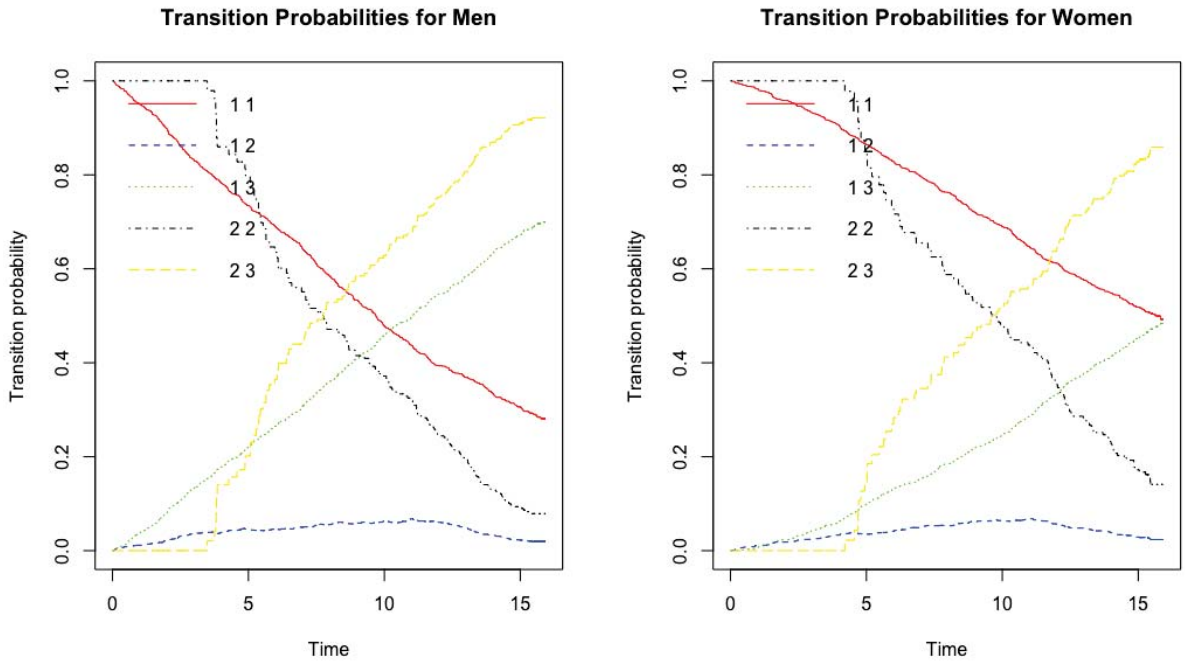

Figure 4.3: Transition Probabilities for Men and Women in the CCSMHA based on the Aalen-Johansen Estimator.

with

$$p_{01}\left(s,t|z_2\right)=\frac{\hat{\lambda}_{01}(s,t)}{\hat{\lambda}_{01}(s,t)+\hat{\lambda}_{02}(s,t)-\hat{\lambda}_{12}(s,t)}\left[e^{-z_2\hat{\Lambda}_{12}(s,t)}-e^{-z_2(\hat{\Lambda}_{01}(s,t)+\hat{\Lambda}_{02}(s,t))}\right]$$

the unconditional transition probability to state $(\text{NED}, \text{Onset})$ is given by

$$p_{01}(s,t):=h(s,t,\boldsymbol{\xi})+l(s,t,\boldsymbol{\xi})+m(s,t,\boldsymbol{\xi})$$

where

$$\begin{aligned}h(s,t,\boldsymbol{\xi}) &:= h\left(\hat{\Lambda}^2_{01}(s,t),\hat{\Lambda}^2_{02}(s,t),\hat{\Lambda}^2_{12}(s,t),\Lambda^1_{01}(s,t),\Lambda^1_{02}(s,t)\right)\\ l(s,t,\boldsymbol{\xi}) &:= l\left(\hat{\Lambda}^2_{01}(s,t),\hat{\Lambda}^2_{02}(s,t),\hat{\Lambda}^2_{12}(s,t),\Lambda^1_{01}(s,t),\Lambda^1_{02}(s,t)\right)\\ m(s,t,\boldsymbol{\xi}) &:= m\left(\hat{\Lambda}^2_{01}(s,t),\hat{\Lambda}^2_{02}(s,t),\hat{\Lambda}^2_{12}(s,t),\Lambda^1_{01}(s,t),\Lambda^1_{02}(s,t)\right)\end{aligned}$$

are respectively defined as

$$\begin{aligned}h(s,t,\boldsymbol{\xi})=\mathbf{f}(s,t,\boldsymbol{\xi})\Bigg\{&\left[\frac{1}{\hat{\omega}^*_2(s,t,\boldsymbol{\xi})\,\Psi^*_1(s,t,\boldsymbol{\xi})}\right]-\left[\frac{1}{\hat{\omega}^*_2(s,t,\boldsymbol{\xi})\,\Upsilon^*(s,t,\boldsymbol{\xi})}\right]-\\&\left[\frac{1}{\omega^*_2(s,t,\boldsymbol{\xi})\,\Psi^*_1(s,t,\boldsymbol{\xi})}\right]+\left[\frac{1}{\omega^*_2(s,t,\boldsymbol{\xi})\,\Lambda^*(s,t,\boldsymbol{\xi})}\right]\Bigg\}\end{aligned}$$

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$$l(s,t,\boldsymbol{\xi}) := \mathbf{g}(s,t,\boldsymbol{\xi}) \left\{ \left[\frac{1}{\hat{\varsigma}_2^*(s,t,\boldsymbol{\xi})\,\Upsilon^*(s,t,\boldsymbol{\xi})} \right] - \left[\frac{1}{\varsigma_2^*(s,t,\boldsymbol{\xi})\Upsilon^*(s,t,\boldsymbol{\xi})} \right] \right\}$$

$$m(s,t,\boldsymbol{\xi}) := \mathbf{h}(s,t,\boldsymbol{\xi}) \left\{ \left[\frac{1}{\Upsilon^*(s,t,\boldsymbol{\xi})} \right] - \left[\frac{1}{\Lambda^*(s,t,\boldsymbol{\xi})} \right] \right\}$$

with

$$\Upsilon^*(s,t,\boldsymbol{\xi}) := \left(\Lambda_{01}(s,t,\boldsymbol{\xi}) + \Lambda_{02}(s,t,\boldsymbol{\xi}) + \hat{\Lambda}_{12}(s,t,\boldsymbol{\xi}) + \sum_{k=1}^{3} \xi_k \right)$$

$$\mathbf{f}(s,t,\boldsymbol{\xi}) := \frac{\hat{\lambda}_{01}^2(s,t)\,\xi_2\,(\xi_1+\xi_3)}{\hat{\lambda}_{01}^2(s,t) + \hat{\lambda}_{02}^2(s,t) - \hat{\lambda}_{12}^2(s,t)}$$

$$\mathbf{g}(s,t,\boldsymbol{\xi}) := \frac{\hat{\lambda}_{01}^2(s,t)\,\xi_1\,(\xi_2+\xi_3)}{\hat{\lambda}_{01}^2(s,t) + \hat{\lambda}_{02}^2(s,t) - \hat{\lambda}_{12}^2(s,t)}$$

$$\mathbf{h}(s,t,\boldsymbol{\xi}) := \frac{\hat{\lambda}_{01}^2(s,t)\,\xi_3}{\hat{\lambda}_{01}^2(s,t) + \hat{\lambda}_{02}^2(s,t) - \hat{\lambda}_{12}^2(s,t)}$$

and

$$\omega_2^*(s,t,\boldsymbol{\xi}) := \left(\hat{\Lambda}_{01}(s,t) + \hat{\Lambda}_{02}(s,t) + \xi_2 \right) \quad \hat{\omega}_2^*(s,t,\boldsymbol{\xi}) := \left(\hat{\Lambda}_{12}(s,t) + \xi_2 \right)$$

$$\varsigma_2^*(s,t,\boldsymbol{\xi}) := \left(\hat{\Lambda}_{01}(s,t) + \hat{\Lambda}_{02}(s,t) + \xi_2 + \xi_3 \right) \quad \hat{\varsigma}_2^*(s,t,\boldsymbol{\xi}) := \left(\hat{\Lambda}_{12}(s,t) + \xi_2 + \xi_3 \right)$$

Finally, the unconditional transition probability to state $(\text{NED}, \text{Death})$ is given by

$$p_{02}(s,t) := q(s,t,\boldsymbol{\xi}) + w(s,t,\boldsymbol{\xi}) + t(s,t,\boldsymbol{\xi})$$

where

$$q(s,t,\boldsymbol{\xi}) := q\left(\hat{\Lambda}_{01}^2(s,t), \hat{\Lambda}_{02}^2(s,t), \Lambda_{01}^1(s,t), \Lambda_{02}^1(s,t), \Lambda_{12}^1(s,t) \right)$$

$$w(s,t,\boldsymbol{\xi}) := w\left(\hat{\Lambda}_{01}^2(s,t), \hat{\Lambda}_{02}^2(s,t), \Lambda_{01}^1(s,t), \Lambda_{02}^1(s,t), \Lambda_{12}^1(s,t) \right)$$

$$t(s,t,\boldsymbol{\xi}) := t\left(\hat{\Lambda}_{01}^2(s,t), \hat{\Lambda}_{02}^2(s,t), \Lambda_{01}^1(s,t), \Lambda_{02}^1(s,t), \Lambda_{12}^1(s,t) \right)$$

are respectively defined as

$$q(s,t,\boldsymbol{\xi}) = \mathbf{q}(s,t,\boldsymbol{\xi}) \left\{ \left[\frac{1}{\varrho_1^*(s,t,\boldsymbol{\xi})} \right] - \left[\frac{1}{\Psi_1^*(s,t,\boldsymbol{\xi})} \right] - \left[\frac{1}{\Phi^*(s,t,\boldsymbol{\xi})} \right] + \left[\frac{1}{\hat{\Phi}^*(s,t,\boldsymbol{\xi})} \right] \right\}$$

$$w(s,t,\boldsymbol{\xi}) = \mathbf{w}(s,t,\boldsymbol{\xi}) \left\{ \left[\frac{1}{\Phi^*(s,t,\boldsymbol{\xi})} \right] + \left[\frac{1}{\hat{\Phi}^*(s,t,\boldsymbol{\xi})} \right] \right\}$$

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$$t(s,t,\boldsymbol{\xi}) = \mathbf{t}(s,t,\boldsymbol{\xi}) \left\{ \left[\frac{1}{\Phi^*(s,t,\boldsymbol{\xi})} \right] + \left[\frac{1}{\hat{\Phi}^*(s,t,\boldsymbol{\xi})} \right] \right\}$$

where

$$\mathbf{q}(s,t,\boldsymbol{\xi}) := \frac{\lambda_{01}(s,t,\boldsymbol{\xi})\xi_2(\xi_1+\xi_3)}{(\lambda_{01}(s,t,\boldsymbol{\xi}) + \lambda_{02}(s,t,\boldsymbol{\xi}) - \lambda_{12}(s,t,\boldsymbol{\xi}))\,\omega_2^*(s,t,\boldsymbol{\xi})}$$

$$\mathbf{w}(s,t,\boldsymbol{\xi}) := \frac{\lambda_{01}(s,t,\boldsymbol{\xi})\xi_1(\xi_2+\xi_3)}{(\lambda_{01}(s,t,\boldsymbol{\xi}) + \lambda_{02}(s,t,\boldsymbol{\xi}) - \lambda_{12}(s,t,\boldsymbol{\xi}))\,\varsigma_2^*(s,t,\boldsymbol{\xi})}$$

$$\mathbf{t}(s,t,\boldsymbol{\xi}) := \frac{\lambda_{01}(s,t,\boldsymbol{\xi})\xi_3}{(\lambda_{01}(s,t,\boldsymbol{\xi}) + \lambda_{02}(s,t,\boldsymbol{\xi}) - \lambda_{12}(s,t,\boldsymbol{\xi}))}$$

with $\varrho_1^*(s,t,\boldsymbol{\xi}) := (\Lambda_{12}(s,t,\boldsymbol{\xi}) + \xi_1 + \xi_2)$, and

$$\Phi^*(s,t,\boldsymbol{\xi}) := \left(\hat{\Lambda}_{01}(s,t,\boldsymbol{\xi}) + \hat{\Lambda}_{02}(s,t,\boldsymbol{\xi}) + \Lambda_{12}(s,t,\boldsymbol{\xi}) + \sum_{k=1}^{3} \xi_k \right)$$

$$\hat{\Phi}^*(s,t,\boldsymbol{\xi}) := \left(\hat{\Lambda}_{01}(s,t,\boldsymbol{\xi}) + \hat{\Lambda}_{02}(s,t,\boldsymbol{\xi}) + \Lambda_{01}(s,t,\boldsymbol{\xi}) + \Lambda_{02}(s,t,\boldsymbol{\xi}) + \sum_{k=1}^{3} \xi_k \right)$$

Similar results can be obtained for the transitions p_{10} and p_{20}, which are not reported here due to the symmetry of the model.

Remark 4.3.1. *Note that a full treatment of the parameters identifiability of the bivariate mixture MOBVE multistate model requires separate work that is beyond the scope of this thesis. However, it is worth to point out that in oder to have marginal shared frailty processes as individual multistate processes, the same requirements we used in Chapter 3 still apply here. In other words, we still require that Z_1 and Z_2 are exponential with parameters one, or equivalently that $\xi_1 = \xi_2 = 1 - \xi_3$. This conditions allows the marginal shared frailty models to be identifiable.*

4.4 Bivariate Multi-state models in terms of Archimedean Generalized Marshall-Olkin copula

At the core of this thesis, there was also the interesting idea to employ copula-based models to model the dependence among multiple multi-state processes, similarly as Eryilmaz

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(2014) and Diao and Cook (2014). However, differently from them, the objective was to employ Generalized Marshall-Olkin type copula. The Generalized Marshall-Olkin type distribution was introduced by Li and Pellerey (2011), following the work by Muliere and Scarsini (1987). The main idea was to obtain a more flexible copula family that allowed to model the marginal process as a shared frailty model. With this argument in mind, I try to investigate the conditions for which a Generalized Marshall-Olkin copula function can be written in terms of Archimedean copulas. Such idea was also investigated by Mulinacci (2017), although with a different approach.

The well-known Marshall Olkin distribution (Marshall and Olkin (1967)) was developed to model two-component systems which are subject to shocks, governed by independent Poisson processes. Such kind of shock may be fatal to one or both components. Let S_i, $i = 1, 2, 3$, be independent and identically distributed exponential lifetimes with parameters $\lambda_i \geq 0$, $i = 1, 2, 3$, and define

$$(T_1, T_2) = (T_1 = \min(S_1, S_3), T_2 = \min(S_2, S_3))$$

Then, it can be shown that

$$\bar{F}(t_1, t_2) = \exp\{-\lambda_1 t_1 - \lambda_2 t_2 - \lambda_3 \max(t_1, t_2)\} \quad t_1, t_2 \geq 0 \tag{4.17}$$

Muliere and Scarsini (1987) instead derived the extension of the above model by focusing on the class of generator functions for the survival function, that is the cumulative hazard function of the vector of lifetimes S_i, namely

$$\bar{F}(t_1, t_2) = \exp\{-\lambda_1 H(t_1) - \lambda_2 H(t_2) - \lambda_3 H(\max(t_1, t_2))\} \quad t_1, t_2 \geq 0 \tag{4.18}$$

A recent result was given by Li and Pellerey (2011), who generalized the one in Muliere and Scarsini (1987) in the following fashion:

$$\bar{F}(t_1, t_2) = \exp\{-H_1(t_1) - H_2(t_2) - H_3(\max(t_1, t_2))\} \quad t_1, t_2 \geq 0 \tag{4.19}$$

where the right continuous functions H_i are the cumulative hazard functions of the lifetimes S_i.

The objective is to generalize (4.19) in the following fashion:

$$\boxed{\bar{F}(t_1, t_2) = \psi\left(H_1(t_1) + H_2(t_2) + H_3(\max(t_1, t_2))\right) \quad t_1, t_2 \geq 0}$$

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This can be accomplished if one consider a more general class generating Marshall-Olkin type distributions where $\psi : [0, +\infty) \to [0, 1]$ with $\psi(0) = 1$ and $\psi(+\infty) = 0$ is strictly decreasing on $[0, \psi^{-1}(0)]$ and concave function, with $\psi^{-1}(x) = \inf\{u : \psi(u) \leq x\}$.

Example 4. *Obviously, by setting $\psi(a) = e^{-a}$, we immediately get the same family as in the case of Li and Pellerey (2011).*

Following exactly the same argument by Li and Pellerey (2011), we have that

$$\begin{aligned}\bar{F}(t_1, t_2) &= P(T_1 > t_1, T_2 > t_2) \\ &= P(S_1 > t_1, S_2 > t_2, S_3 > \max\{t_1, t_2\}) \\ &= \psi(H_1(t_1) + H_2(t_2) + H_3(\max(t_1, t_2)))\end{aligned} \tag{4.20}$$

Letting

$$\tilde{H}_1(t_1) = H_1(t_1) + H_3(t_1) \qquad \text{if} \quad t_1 > t_2$$

$$\tilde{H}_2(t_2) = H_2(t_2) + H_3(t_2) \qquad \text{if} \quad t_2 > t_1$$

we obtain the marginal survival functions as follows:

$$\bar{F}_1(t_1) = P(T_1 > t_1) = \psi\left(\tilde{H}_1(t_1)\right) = u \tag{4.21}$$

$$\bar{F}_2(t_2) = P(T_2 > t_2) = \psi\left(\tilde{H}_2(t_2)\right) = v \tag{4.22}$$

Then,

$$\bar{F}_1^{-1}(u) = \tilde{H}_1\left(\psi^{-1}(u)\right) = t_1 \tag{4.23}$$

$$\bar{F}_2^{-1}(v) = \tilde{H}_2\left(\psi^{-1}(v)\right) = t_2 \tag{4.24}$$

Using Sklar's theorem, we have that the survival copula of the vector (T_1, T_2) is defined as

$$C(u, v) = \psi\left(H_1\left(\bar{F}_1^{-1}(u)\right) + H_2\left(\bar{F}_1^{-1}(v)\right) + H_3\left(\max\left\{\bar{F}_1^{-1}(u), \bar{F}_2^{-1}(v)\right\}\right)\right)$$

1. If $\bar{F}_1^{-1}(u) \leq \bar{F}_2^{-1}(v)$,

$$\begin{aligned}C(u, v) &= \psi\left(H_1\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) + H_2\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right) + H_3\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right)\right) \\ &= \psi\left(\tilde{H}_2\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right) + H_1\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right)\right) \\ &= \psi\left(\psi^{-1}(v) + H_1\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right)\right) \\ &= \psi\left(\psi^{-1}(v) + \psi_*^{-1}(u)\right)\end{aligned} \tag{4.25}$$

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2. If $\bar{F}_1^{-1}(u) > \bar{F}_2^{-1}(v)$,

$$\begin{aligned} C(u,v) &= \psi\left(H_1\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) + H_2\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right) + H_3\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right)\right) \\ &= \psi\left(\tilde{H}_1\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) + H_2\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right)\right) \\ &= \psi\left(\psi^{-1}(u) + H_2\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right)\right) \\ &= \psi\left(\psi^{-1}(u) + \psi_*^{-1}(v)\right) \end{aligned} \tag{4.26}$$

If we allow C to belong to the Archimedean family, then I may be in position to define it as follows:

$$C(u,v) = \psi\left\{\psi^{-1}(u) + \psi^{-1}(v)\right\} \quad (u,v) \in [0,1]^2 \tag{4.27}$$

where $\psi^{-1} : [0,1] \to [0,\infty]$ is defined as the inverse of $\psi : [0,+\infty] \to [0,1]$.
Which condition should I give to $\psi_*^{-1}(\cdot)$ in order 4.20 to be satisfied? In order words, I would like $\psi_*^{-1}(\cdot)$ to be the inverse of the generator ψ, and more importantly, to be a convex function, since it holds that (see Nelsen (2006))

C is Archimedean if and only if ψ^{-1} is convex

Let us analyze the intrinsic properties of ψ_*^{-1}.Recall that for $\bar{F}_1^{-1}(u) > \bar{F}_2^{-1}(v)$ we have that

$$\psi_*^{-1}(v) = H_2 \circ \bar{F}_2^{-1}(v) = H_2 \circ (H_2 + H_3)^{-1}\left(\psi^{-1}(v)\right)$$

Obviously, it holds that

$$\begin{aligned} \tilde{H}_1^{-1}\left(\psi^{-1}(u)\right) &> \tilde{H}_2^{-1}\left(\psi^{-1}(v)\right) \\ H_2\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) &> H_2\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right) \end{aligned}$$

Since $H_2 = \tilde{H}_2 - H_3$, then it follows that

$$\tilde{H}_2\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) - H_3\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) > \psi^{-1}(v) - H_3\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right)$$

from which we have that

$$\psi^{-1}(v) < \tilde{H}_2\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right) + H_3\left(\tilde{H}_2^{-1}\left(\psi^{-1}(v)\right)\right) - H_3\left(\tilde{H}_1^{-1}\left(\psi^{-1}(u)\right)\right)$$

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In order $\psi_*^{-1}(u)$ to be convex, note that

$$\begin{aligned} H_1 \circ (H_1 + H_3)^{-1} \left(\psi^{-1}(u)\right) = \psi^{-1}(u) & \\ \iff (H_1 + H_3)^{-1} = H_1^{-1} & \\ \iff H_3 = 0 & \end{aligned}$$

which, however, seems a quite restrictive condition if one aims to induce dependence via such copula family.

Remark 4.4.1. *Mulinacci (2017) imposed some conditions on* $\tilde{H}^{-1}\left(\psi^{-1}\left(u\right)\right)$ *which allows to obtain an Archimedean-based Marshall Olkin Copula. However, such class is a distorted class, that is it depends on the either* $\tilde{H}_1^{-1}\left(\psi_1^{-1}\left(u\right)\right) \geq \tilde{H}_2^{-1}\left(\psi_2^{-1}\left(u\right)\right)$ *or* $\tilde{H}_1^{-1}\left(\psi_1^{-1}\left(u\right)\right) \leq \tilde{H}_2^{-1}\left(\psi_2^{-1}\left(u\right)\right)$*. She elegantly derived some properties of this distorted copula class, such as the Kendall's* τ *and tail dependence.*

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Chapter 5

Modeling bivariate length-biased right-censored failure time data using Archimedean Copulas

5.1 Introduction

Let X be a non negative random variable standing for failure time with probability density function $f(x)$ and T be the left-truncation time with density $g(t)$. Suppose that X and T are independent, and we also assume that subjects are observed only if $X \geq T$. It follows that the joint distribution of (X, T) given $X \geq T$ is given by

$$f_{X,T}(x, t|X \geq T) = \frac{g_T(t) f_X(x)}{\mu_X} \tag{5.1}$$

where $\mu_X := \int_0^{+\infty} g_T(w) S_X(w)\,\mathrm{du}$ is the mean failure time. Assuming uniform truncation on the positive real line, that is $g_T(t) \equiv k > 0$, we have that Equation 5.1 can be written as:

$$f_{X,T}(x, t|X \geq T) = \frac{f_X(x)}{\int_0^{\infty} S_X(w)\,\mathrm{du}} \tag{5.2}$$

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For now on, we always write $\mu_X := \int_0^\infty S_X(w)\,\mathrm{du}$. The marginal biased density (Asgharian et al. (2002)) is then given by

$$f_{LB}(x) = f_X(x|X \geq T) = \int_0^x f_{X,T}(x,t|X \geq T) = \frac{x f_X(x)}{\mu_U} \tag{5.3}$$

The study on the incident-case survivor function under right-censoring and length-biased sampling is due to Asgharian et al. (2002), and the foundations of the work were made in Asgharian and Wolfson (2005), where they highlighted the distinctions between their work and the Vardi (1989) and Vardi and Zhang (1992) works. We aim to investigate the association between two related lifetimes when bivariate length-biased right-censored data are available by using Archimedean Copula models (Nelsen (2006)).

A copula C is said to be Archimedean if it can be expressed as

$$C_\theta(u,v) = \psi_\theta\left(\psi_\theta^{-1}(u) + \psi_\theta^{-1}(v)\right) \qquad 0 < u, v < 1 \tag{5.4}$$

where $\psi_\theta : (0,1] \to [0,+\infty)$ such that $\psi_\theta(1) = 0$ θ is a convex, strictly decreasing function called the copula generator such that $\frac{d\psi_\theta(u)}{d\,u} = \psi'_\theta(u) < 0$ and $\frac{d^2\psi_\theta(u)}{d\,u^2} = \psi''_\theta(u) > 0$. Taking $\psi_\theta(u) = (1+u)^{\frac{1}{\theta}}$ as geneator, we obtain the well-known Clayton copula,

$$C_\theta(u,v) = \left(u^{-\theta} + u^{-\theta} - 1\right)^{\frac{1}{\theta}} \qquad \theta > 1 \tag{5.5}$$

The popularity of employing copula methods has definitely increased thanks to Sklar's theorem Sklar (1959): it basically states that copulas allow to model the marginal distributions and the association separately. A semi-parametric strategy is employed for the estimation of the association parameter θ, following the standard procedure proposed by Shih and Louis (1995), who examined the association of the bivariate data that are both subject to right censoring, through a two-stage semi-parametric estimation procedure. To select the adequate copula, goodness-of-fit tests for censored copula models have been investigated by Wang and Wells (2000), among others.

Under the Archimedean copula, there exists a one-to-one relationship between the association parameter θ and the Kendall's τ,

$$\theta \overset{1:1}{\iff} \tau = 4\int\int C_\theta(u,v)\,\mathrm{du}\,\mathrm{dv} - 1 \tag{5.6}$$

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Manatunga and Oakes (1996) have also proposed a measure of association for bivariate frailty distributions for left truncated and right-censored data, assuming the truncation times are fixed. Recently, Shen (2016) investigated the problem of estimating the association between two related survival variables when they follow a copula model and bivariate left-truncated and right-censored data are available.

5.2 The Bivariate Model

Let $p = 1, \ldots, n$ be the pairs in the sample. Consider a sample $\tilde{X}_1, \ldots, \tilde{X}_n$ of independent random variables with cdf F_{LB}. We may regard $\tilde{X}_i$ as being of the form $\tilde{X}_i = T_i + R_i$, where T_i is the truncation variable (backward recurrence time) and R_i the observed residual lifetime (forward recurrence time). These correspond, respectively to the observed "onset" to the date of the cross sectional survey, and the observed time from the recruitment until "failure". For each individual, we assume that there is an independent random censoring variable C_{ip} such that under a right censoring scheme, the observed quantities are given by $\{(W_{ip}, \delta_{ip}), i = 1, 2, p = 1, \ldots, n\}$ where

$$\begin{aligned} W_{ip} &= \tilde{X}_{ip} \wedge C_{ip} \\ \delta_{ip} &= I(R_{ip} \leq C_{ip}) \end{aligned} \tag{5.7}$$

The likelihood of the model can be written as

$$\begin{aligned} L(\theta|\mathcal{R}) = \prod_{i=1}^{p} & \left\{ \left(c_\theta(S^1_{LB}(x_1), S^2_{LB}(x_2)) f^1_{LB}(x_1) f^2_{LB}(x_2) \right)^{\delta_{1p}\delta_{2p}} \right\} \\ & \times \left\{ -\frac{\partial C_\theta(S^1_{LB}(x_1), S^2_{LB}(x_2))}{\partial S^1_{LB}(x_1)} \frac{\partial S^1_{LB}(x_1)}{\partial X_{1p}} \right\}^{\delta_{1p}(1-\delta_{2p})} \\ & \times \left\{ -\frac{\partial C_\theta(S^1_{LB}(x_1), S^2_{LB}(x_2))}{\partial S^2_{LB}(x_2)} \frac{\partial S^2_{LB}(x_2)}{\partial X_{2p}} \right\}^{\delta_{2p}(1-\delta_{1p})} \\ & \times \left\{ C_\theta(S^1_{LB}(x_1), S^2_{LB}(x_2)) \right\}^{(1-\delta_{1p})(1-\delta_{2p})} \end{aligned} \tag{5.8}$$

where $\mathcal{R}_i = (x_{1p}, x_{2p}, \delta_{1p}, \delta_{2p})$ denote the observed data, and $c_\theta(\cdot)$ denotes the copula density, whereas $f^i_{LB}(x_i)$ denotes the length-biased density $(i = 1, 2)$.

In particular, the following result holds for all copulas belonging to the Archimedean family.

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Lemma 2. *The bivariate unbiased survival function can be written as*

$$S_U(x_1, x_2) = \psi_\theta \left(\psi_\theta^{-1}(S_U^1(x_1)) + \psi_\theta^{-1}(S_U^2(x_2)) \right) \tag{5.9}$$

where $S_U^i(x_i)$ denote the marginal unbiased survival function $(i = 1, 2)$, and θ denote the association copula parameter.

Proof. The bivariate length-biased survival function under the Archimedean copula is given by

$$S_{LB}(x_1, x_2) = \psi_\theta \left(\psi_\theta^{-1}(S_{LB}^1(x_1)) + \psi_\theta^{-1}(S_{LB}^2(x_2)) \right) \tag{5.10}$$

where $S_{LB}^i(x_i)$ denote the marginal length-biased survival function $(i = 1, 2)$. Since it holds that

$$S_{LB}(x_1, x_2) = S_{LB}^1(x_1) + S_{LB}^2(x_2) - 1 + C\left(1 - S_{LB}^1(x_1), 1 - S_{LB}^2(x_2)\right)$$

where C is a copula function, the result follows from the fact that

$$S_{LB}(x) = \frac{\int_x^\infty w \, \mathrm{d}S_U(w)}{\int_0^\infty w \, \mathrm{d}S_U(w)} \quad \overset{1:1}{\Longleftrightarrow} \quad S_U(x) = \frac{\int_x^\infty w^{-1} \, \mathrm{d}S_{LB}(w)}{\int_0^\infty w^{-1} \, \mathrm{d}S_{LB}(w)} \tag{5.11}$$

□

Lemma 3. *For a sample of bivariate length-based survival data $\{(x_{ip}, \delta_{1p}), (x_{2p}, \delta_{2p})\}$ $(p = 1, \ldots, n)$, the contribution of pair i to the Archimedean copula likelihood can be written as*

$$\int_0^\infty \prod_{i=1}^{2} e^{-z\psi_\theta^{-1}(S_{LB}^i(x_{ip}))} \left[\frac{-z f_{LB}^i(x_{ip})}{\psi_\theta'(\psi_\theta^{-1}(S_{LB}^i(x_{ip})))} \right]^{\delta_{ip}} dH_\theta(z) \tag{5.12}$$

Proof. In order to avoid heavy notation, we denote by $X_i = X_{ip}$ $(i = 1, 2)$ the length-biased random variables, and by $\delta_1 = \delta_{1p}$ and $\delta_2 = \delta_{2p}$. We distinguish among four different possible cases:

(1) If both subjects are censored, that is $\delta_1 = \delta_2 = 0$, then

$$\begin{aligned} L(0,0) = S_{LB}(x_1, x_2) &= C_\theta \left(S_{LB}^1(x_1), S_{LB}^2(x_2) \right) \\ &= \psi_\theta \left(\psi_\theta^{-1}(S_{LB}^1(x_1)) + \psi_\theta^{-1}(S_{LB}^2(x_2)) \right) \\ &= \int_0^{+\infty} e^{-z\left(\psi_\theta^{-1}(S_{LB}^1(x_1)) + \psi_\theta^{-1}(S_{LB}^2(x_2))\right)} dH_\theta(z) \end{aligned}$$

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(2) If only the first subject experienced the event of interest, then

$$\begin{aligned} L(1,0) &= -\frac{\partial S(X_1,X_2)}{\partial X_1} = -\psi^{'}\left(\psi_\theta^{-1}(S_{LB}(x_1)+\psi_\theta^{-1}(S_{LB}(x_2))\right)\frac{\partial \psi^{-1}(S_{LB}(x_1))}{\partial x_1} \\ &= -\psi^{'}\left(\psi_\theta^{-1}(S_{LB}(x_1)+\psi_\theta^{-1}(S_{LB}(x_2))\right)\frac{f_{LB}(x_1)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_1)))} \\ &= \int_0^{+\infty} e^{-z\left(\psi_\theta^{-1}(S^1_{LB}(x_1))+\psi_\theta^{-1}(S^2_{LB}(x_2))\right)}\left[\frac{z f_{LB}(x_1)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_1)))}\right]^{\delta_1} dH_\theta(z) \end{aligned}$$

(3) Similarly, if only the second subject experienced the event of interest,

$$\begin{aligned} L(0,1) &= -\frac{\partial S(X_1,X_2)}{\partial X_2} = -\psi^{'}\left(\psi_\theta^{-1}(S_{LB}(x_1)+\psi_\theta^{-1}(S_{LB}(x_2))\right)\frac{\partial \psi^{-1}(S_{LB}(x_2))}{\partial x_2} \\ &= -\psi^{'}\left(\psi_\theta^{-1}(S_{LB}(x_1)+\psi_\theta^{-1}(S_{LB}(x_2))\right)\frac{f_{LB}(x_2)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_2)))} \\ &= \int_0^{+\infty} e^{-z\left(\psi_\theta^{-1}(S^1_{LB}(x_1))+\psi_\theta^{-1}(S^2_{LB}(x_2))\right)}\left[\frac{z f_{LB}(x_2)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_2)))}\right]^{\delta_2} dH_\theta(z) \end{aligned}$$

(4) Finally, if both subjects experienced the event of interest, that is $\delta_1 = \delta_2 = 1$, then

$$\begin{aligned} L(1,1) &= \psi^{''}\left(\psi_\theta^{-1}(S_{LB}(x_1)+\psi_\theta^{-1}(S_{LB}(x_2))\right)\frac{\partial \psi^{-1}(S_{LB}(x_1))}{\partial x_1}\frac{\partial \psi^{-1}(S_{LB}(x_2))}{\partial x_2} \\ &= \psi^{''}\left(\psi_\theta^{-1}(S_{LB}(x_1)+\psi_\theta^{-1}(S_{LB}(x_2))\right)\frac{f_{LB}(x_1)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_1)))}\frac{f_{LB}(x_2)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_2)))} \end{aligned}$$

which equals

$$\int_0^{+\infty} e^{-z\left(\psi_\theta^{-1}(S^1_{LB}(x_1))+\psi_\theta^{-1}(S^2_{LB}(x_2))\right)}\left[\frac{z f_{LB}(x_1)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_1)))}\right]^{\delta_1}\left[\frac{z f_{LB}(x_2)}{\psi'(\psi_\theta^{-1}(S_{LB}(x_2)))}\right]^{\delta_2} dH_\theta(z)$$

□

5.3 Estimation

We aim to estimate the dependence parameter θ by employing the two-step semi-parametric procedure proposed by Shih and Louis (1995) but with length-biased data which might be subject to right-censoring. It basically goes as follows: in the first step, the marginal unbiased survival functions of X_1 and X_2 can be estimated nonparametrically via the Vardi's NPMLE for length-biased right-censored data (Vardi (1989)).

As pointed out by Asgharian et al. (2015), using the standard Kaplan-Meier as the

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NPMLE of the length-biased survivor function would lead to a distorted estimator because censoring for length-biased data obtained from a prevalent cohort study with follow-up is informative. In the second step, the dependence parameter θ of a copula function is estimated by maximizing the pseudo likelihood function, that is

$$\max_{\theta\in\Theta} \hat{L}(\theta|\mathcal{R}) = \max_{\theta\in\Theta} \prod_{p=1}^{n} \hat{L}_i(\theta|\mathcal{R}) \tag{5.13}$$

where $L_i(\theta|\mathcal{R})$ has the form as in Equation 5.8 for each $p = 1, \ldots, n$, and we plug in the estimates for $\hat{S}^i_{LB}(x_i)$, $i = 1, 2$ obtained in the first step. Using a copula approach, we also need the estimates of the density functions, $\hat{f}_{LB}(x_i)$ for each $i = 1, 2$. This could be done by using a kernel smoothing estimation for the hazards, and then using the relationship

$$\hat{f}_{LB}(x) = \hat{\lambda}_{LB}(x)\, \hat{S}_{LB}(x)$$

to obtain the desired estimates for the length-biased density. Note that the proposed two-step procedure requires further, future investigations, especially for the asymptotic properties of the semi-parametric estimates.

5.3.1 Bivariate length-biased Weibull-Gamma Model

Recall the bivariate unconditional survival function obtained from the shared frailty model

$$S(x_1, x_2) = (1 + \theta\,(\Lambda_{01}(x_1) + \Lambda_{02}(x_2)))^{-\frac{1}{\theta}} = \left(S(x_1)^{-\theta} + S^{-\theta}(x_2) - 1\right)^{-\frac{1}{\theta}}$$

where

$$S(x_i) := \int e^{-z\Lambda_{0i}(x_i)}\, v(z)\, \mathrm{dz} \qquad i = 1, 2$$

We would like to employ a two-stage estimation procedure for the estimation of the bivariate survival function $S(x_1, x_2)$. For the sake of notation, set $S(x_i) = S_X(x)$.
Let X be any absolute continuous non-negative random variable. Recall that under the multiplicative frailty approach, the unconditional survival function can be written as

$$S_X(x) := \int e^{-z\Lambda_0(x)}\, g_Z(z)\, \mathrm{dz}$$

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where $\Lambda_0(x) = \int_0^x \lambda(u)\,\mathrm{du}$ is the cumulative hazard function, and $g_Z(z)$ is the probability density function of a continuous random effect Z. The conditional survival of $X|Z$ is defined through the Lehmann family construction

$$S_{X|Z}(x|z) = [S_0(x)]^z = \left[e^{-\Lambda_0(x)}\right]^z$$

based on a multiplicative effect of the frailty term on the baseline cumulative hazard function $\Lambda_0(x)$. Under the assumption that $Z \sim \text{Gamma}(\theta^{-1}, \theta^{-1})$, one can show that the unconditional marginal survival function is given by

$$S_X(x) = \left(\frac{1}{1+\theta\,\Lambda_0(x)}\right)^{\frac{1}{\theta}} = (1+\theta\,\Lambda_0(x))^{-\frac{1}{\theta}} \tag{5.14}$$

where $\Lambda_0(x) = \left(\frac{x}{\beta}\right)^{\alpha}$. In particular, under the above shared frailty model, the marginal density function can be obtained from (5.14) as

$$f_X(x) = \frac{\alpha\,x^{\alpha-1}\,(1+\theta\,\Lambda_0(x))^{-\left(\frac{\theta+1}{\theta}\right)}}{\beta^{\alpha}} \tag{5.15}$$

The length-biased bivariate shared frailty density is obtained as

$$f_{LB}(x) = \frac{x\,f_X(x)}{\mu_X} \tag{5.16}$$

where $\mu_X := \int_0^{+\infty} S_X(u)\,du$ denotes the mean failure time. Let $X|z \sim \text{Weibull}(\alpha, \beta^*)$, where $\beta^* := \beta\,z^{-\frac{1}{\alpha}}$. Note that we can write

$$\mu_X = \mathbb{E}_Z\left[\mathbb{E}_X\left(X|Z=z\right)\right] \tag{5.17}$$

For our choice of $X|Z$ one has

$$\mathbb{E}\left(X|Z=z\right) = \int_0^{+\infty} \frac{\alpha\,x^{(\alpha+1)-1}\,e^{-(\frac{x}{\beta^*})^{\alpha}}}{(\beta^*)^{\alpha}}\,\mathrm{dx}$$

and after having substituted $u = x^{\alpha}$, or equivalently, $x = u^{\frac{1}{\alpha}}$, with $\mathrm{dx} = \frac{u^{(\frac{1}{\alpha}-1)}\,\mathrm{du}}{\alpha}$, we obtain

$$\mathbb{E}\left(X|Z=z\right) = \int_0^{+\infty} \frac{u^{(1+\frac{1}{\alpha})-1}\,e^{-\frac{u}{(\beta^*)^{\alpha}}}}{(\beta^*)^{\alpha}}\,\mathrm{du}$$

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By substituting $y = \frac{u}{(\beta^*)^\alpha}$, or $u = y(\beta^*)^\alpha$, with $du = (\beta^*)^\alpha\, dy$, we obtain

$$\mathbb{E}\left(X|Z=z\right) = \frac{(\beta^*)^{\alpha\left(\frac{1}{\alpha}+1\right)}}{(\beta^*)^\alpha} \int_0^{+\infty} y^{\left(1+\frac{1}{\alpha}\right)-1}\, e^{-y}\, \mathrm{dy}$$

where we recognize the gamma function

$$\Gamma(a) = \int_0^{+\infty} t^{a-1}\, e^{-t}\, \mathrm{dt}$$

so that

$$\mathbb{E}\left(X|Z=z\right) = \beta^*\, \Gamma\left(\frac{1}{\alpha}+1\right) = \beta\, z^{-\frac{1}{\alpha}}\, \Gamma(1+\frac{1}{\alpha})$$

Let us denote by

$$g_z(z) = \frac{\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} z^{\frac{1}{\theta}-1} e^{-\frac{z}{\theta}}$$

the density function of the random effect $Z \sim \Gamma\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$. We have that

$$\begin{aligned}
\mu_X = \mathbb{E}\left[X\right] = \mathbb{E}_Z\left[\mathbb{E}_X\left(X|Z=z\right)\right] &= \int_0^{\infty} \beta^* \Gamma\left(\frac{1}{\alpha}+1\right) g_Z(z)\, \mathrm{dz} \\
&= \Gamma\left(1+\frac{1}{\alpha}\right)\, \beta\, \mathbb{E}_Z\left(z^{-\frac{1}{\alpha}}\right) \\
&= \frac{\Gamma\left(1+\frac{1}{\alpha}\right) \beta \left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma\left(\frac{1}{\theta}\right)} \int_0^{+\infty} z^{-\frac{1}{\alpha}}\, z^{\frac{1}{\theta}-1}\, e^{-\frac{z}{\theta}}\, \mathrm{dz} \\
&= \frac{\beta\, \left(\frac{1}{\theta}\right)^{\frac{1}{\alpha}}\, \Gamma\left(\frac{1}{\alpha}+1\right)\, \Gamma\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)}{\Gamma\left(\frac{1}{\theta}\right)} \qquad (5.18)
\end{aligned}$$

with the requirement that $\theta \leq \alpha$ for the mean to be non-negative. Note that by means of the results in Bhattacharjee and Mukhopadhyay (2010) as well as in Mukhopadhyay and Son (2016), we have that

$$\lim_{\theta \downarrow 0} \frac{\left(\frac{1}{\theta}\right)^{\frac{1}{\alpha}}\, \Gamma\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)}{\Gamma\left(\frac{1}{\theta}\right)} = 1$$

so that

$$\lim_{\theta \downarrow 0} \mathbb{E}_X\left[X\right] = \beta\, \Gamma\left(1+\frac{1}{\alpha}\right) \qquad (5.19)$$

which is the same as $\mathbb{E}\left[X\right]\left(X|Z=1\right)$. Indeed, $z \xrightarrow{d} z^* \equiv 1$ w.p.1 when $\theta \downarrow 0$, so that no frailty effect occurs. As for the unconditional length-biased survival function, we have

$$S_{LB}(x) = \frac{\int_x^{+\infty} t\, f_X(t)\, \mathrm{dt}}{\mu_X}$$

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where $\mu_X := \int_0^\infty S_X(u)\,\mathrm{du}$. We have that

$$S_{LB}(x) = \int_x^{+\infty} w\, f_X(w)\,\mathrm{dw} = \int_{\mathbb{R}^+}\int_x^{+\infty} w\, f_{X|Z}(w)\,\mathrm{dw}\, g_z(z)\,\mathrm{dz}$$
$$= \frac{1}{\mu_X}\int_{\mathbb{R}^+} \frac{\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}\beta}{\Gamma\left(\frac{1}{\theta}\right)}\left[\int_{\frac{x^\alpha\theta}{\beta^\alpha}}^{+\infty} y^{(1+\frac{1}{\alpha})-1}\, e^{-y}\,\mathrm{dy}\right] z^{\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)-1}\, e^{-\frac{z}{\theta}}\,\mathrm{dz} \tag{5.20}$$

The integral

$$\Gamma(a,t) := \int_t^{+\infty} y^{a-1}\, e^{-y}\,\mathrm{dy}$$

is the Incomplete Gamma Function, which is equal to $\Gamma(a)\,[1 - P(a,t)]$, where

$$P(a,t) := \frac{1}{\Gamma(a)}\int_0^t y^{a-1}\, e^{-y}\,\mathrm{dy}$$

Since

$$\Gamma\left(\left(\frac{1}{\alpha}+1\right), \frac{x^\alpha z}{\beta^\alpha}\right) = \Gamma\left(\frac{1}{\alpha}+1\right)\left[1 - \frac{1}{\Gamma\left(\frac{1}{\alpha}+1\right)}\int_0^{\frac{x^\alpha z}{\beta^\alpha}} y^{\left(\left(\frac{1}{\alpha}+1\right)-1\right)} e^{-y}\, dy\right] \tag{5.21}$$

equation (5.20) can be therefore rewritten as

$$\frac{1}{\mu_X}\int_{\mathbb{R}^+} \frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} z^{\frac{1}{\theta}-\frac{1}{\alpha}-1}\, e^{-\frac{z}{\theta}}\left(\Gamma\left(\frac{1}{\alpha}+1\right)\left[1 - \frac{1}{\Gamma\left(\frac{1}{\alpha}+1\right)}\int_0^{\frac{x^\alpha z}{\beta^\alpha}} y^{\left(\left(\frac{1}{\alpha}+1\right)-1\right)} e^{-y}\, dy\right]\right)\mathrm{dz}$$

which is equivalent to

$$\frac{1}{\mu_X}\int_{\mathbb{R}^+} \frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} z^{\frac{1}{\theta}-\frac{1}{\alpha}-1}\, e^{-\frac{z}{\theta}}\Gamma\left(\frac{1}{\alpha}+1\right)\mathrm{dz} +$$
$$- \frac{1}{\mu_X}\int_{\mathbb{R}^+} \frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} z^{\frac{1}{\theta}-\frac{1}{\alpha}-1}\, e^{-\frac{z}{\theta}}\left(\int_0^{\frac{x^\alpha z}{\beta^\alpha}} y^{\left(\left(\frac{1}{\alpha}+1\right)-1\right)} e^{-y}\, dy\right)\mathrm{dz}$$

Finally, using (5.18),

$$S_{LB}(x) = 1 - \frac{1}{\mu_X}\int_{\mathbb{R}^+} \frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} z^{\frac{1}{\theta}-\frac{1}{\alpha}-1}\, e^{-\frac{z}{\theta}}\left(\int_0^{\frac{x^\alpha z}{\beta^\alpha}} y^{\left(\left(\frac{1}{\alpha}+1\right)-1\right)} e^{-y}\, dy\right)\mathrm{dz} \tag{5.22}$$

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By substituting $y = zw$, then $dy = zdw$, it follows that Equation (5.22) can be written as

$$= 1 - \frac{1}{\mu_X}\left[\int_{\mathbb{R}^+} \frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})}\, z^{\frac{1}{\theta}-\frac{1}{\alpha}-1}\, e^{-\frac{z}{\theta}} \left(\int_0^{\frac{x^\alpha z}{\beta^\alpha}} y^{\left((\frac{1}{\alpha}+1)-1\right)} e^{-y}\, dy\right) \mathrm{dz}\right]$$

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} \int_{\mathbb{R}^+}\int_0^{\frac{x^\alpha}{\beta^\alpha}} z^{\frac{1}{\theta}}\, e^{-z\left(\frac{1}{\theta}+w\right)} w^{\left(\frac{1}{\alpha}+1\right)-1}\, \mathrm{dw}\,\mathrm{dz}\right]$$

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} \int_{\mathbb{R}^+}\int_0^{\frac{x^\alpha}{\beta^\alpha}} z^{\frac{1}{\theta}}\, e^{-z\left(\frac{1}{\theta}+w\right)} w^{\left(\frac{1}{\alpha}+1\right)-1}\, \mathrm{dw}\,\mathrm{dz}\right]$$

By substituting $z = \frac{u}{\left(w+\frac{1}{\theta}\right)}$ with $\mathrm{dz} = \frac{\mathrm{du}}{\left(w+\frac{1}{\theta}\right)}$, with $u = z\,\left(w+\frac{1}{\theta}\right)$, we have that

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} \int_0^{\left(\frac{x}{\beta}\right)^\alpha} \left[\int_{\mathbb{R}^+} \left(\frac{u}{w+\frac{1}{\theta}}\right)^{\frac{1}{\theta}} e^{-u}\, w^{\frac{1}{\alpha}} \left(\frac{1}{w+\frac{1}{\theta}}\right) \mathrm{du}\right] \mathrm{dw}\right]$$

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}}{\Gamma(\frac{1}{\theta})} \int_0^{\left(\frac{x}{\beta}\right)^\alpha} \left(\frac{1}{w+\frac{1}{\theta}}\right)^{\frac{1}{\theta}+1} w^{\frac{1}{\alpha}} \left[\int_{\mathbb{R}^+} u^{(1+\frac{1}{\theta})-1}\, e^{-u}\, \mathrm{du}\right] \mathrm{dw}\right]$$

so that Equation (5.22) is equal to

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}\,\Gamma\left(1+\frac{1}{\theta}\right)}{\Gamma(\frac{1}{\theta})} \int_0^{\left(\frac{x}{\beta}\right)^\alpha} w^{\frac{1}{\alpha}} \left(\frac{1}{w+\frac{1}{\theta}}\right)^{-\frac{1}{\theta}-1} \mathrm{dw}\right]$$

Now, we make another substitution by letting $w = \frac{t}{\theta}$, with $\mathrm{dt} = \theta\,\mathrm{dw}$, from which it follows that

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\theta}}\,\Gamma\left(1+\frac{1}{\theta}\right)}{\Gamma(\frac{1}{\theta})} \int_0^{\theta\left(\frac{x}{\beta}\right)^\alpha} \left(\frac{t}{\theta}\right)^{\frac{1}{\alpha}} \left(\frac{t+1}{\theta}\right)^{-\frac{1}{\theta}-1} \frac{\mathrm{dt}}{\theta}\right]$$

$$= 1 - \frac{1}{\mu_X}\left[\frac{\beta\,\left(\frac{1}{\theta}\right)^{\frac{1}{\alpha}}\,\Gamma\left(1+\frac{1}{\theta}\right)}{\Gamma(\frac{1}{\theta})} \int_0^{\theta\left(\frac{x}{\beta}\right)^\alpha} \left(\frac{t^{\frac{1}{\alpha}}}{(1+t)^{1+\frac{1}{\theta}}}\right) \mathrm{dt}\right]$$

Hence, Equation (5.22) is equal to

$$S_{LB}(x) = 1 - \frac{\Gamma\left(1+\frac{1}{\theta}\right)}{\Gamma\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)\Gamma\left(1+\frac{1}{\alpha}\right)} \int_0^{\theta\left(\frac{x}{\beta}\right)^\alpha} \frac{t^{\frac{1}{\alpha}}}{(1+t)^{1+\frac{1}{\theta}}}\,\mathrm{dt} \tag{5.23}$$

Alternatively, one might obtain the same result given in equation (5.23) by noting that

$$S_{LB}(x) = \int_x^{+\infty} \frac{u\, f_X(u)}{\mu_X}\,\mathrm{du} = 1 - \frac{\mu_X(x)}{\mu_X}$$

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where $\mu_X(t) = \int_0^x u\, f_X(u)\,\mathrm{du}$ is the restricted mean of the r.v. X. Under our assumptions, the length-bias adjustment to Equation (5.15) produces the observed data density function

$$f_{LB}(x) = \frac{x f_X(x)}{\mu_X} \propto x^{\alpha}\left[1+\theta\left(\frac{x}{\beta}\right)^{\alpha}\right]^{-\left(1+\frac{1}{\theta}\right)}$$

Let $X = \beta\left(\frac{R}{\theta}\right)^{\frac{1}{\alpha}}$; then, $R = \left(\frac{X}{\alpha}\right)^{\alpha}\theta$ with $\frac{\mathrm{dx}}{\mathrm{dr}} = \frac{\beta\, r^{\frac{1}{\alpha}-1}}{\theta^{\frac{1}{\alpha}}}$ implies that

$$f_R(r) \propto \frac{r^{\frac{1}{\alpha}}}{(1+r)^{1+\frac{1}{\theta}}} \tag{5.24}$$

We note that this is a two-parameter Pearson's type VI distribution with parameters $\nu_1 = 2\left(1+\frac{1}{\alpha}\right)$ and $\nu_2 = 2\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)$ (Johnson et al., 1995, page 248). The Pearson Type VI distribution, also known as a beta-prime distribution, is defined as

$$f_{K_{\nu_1,\nu_2}} := \frac{1}{\mathrm{B}\left(\frac{\nu_1}{2},\frac{\nu_2}{2}\right)}\frac{k^{\frac{\nu_1}{2}-1}}{(1+k)^{\frac{\nu_1+\nu_2}{2}}} \quad k>0$$

so we have

$$f_R(r) = \frac{\Gamma\left(1+\frac{1}{\theta}\right)}{\Gamma\left(1+\frac{1}{\alpha}\right)\Gamma\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)}\frac{r^{\frac{1}{\alpha}}}{(1+r)^{1+\frac{1}{\theta}}} \tag{5.25}$$

In particular, note again that $\theta \le \alpha$ must hold, and that the distribution of R is almost the F_{ν_1,ν_2} density function, as $f_R(r)$ can be obtained as the distribution of the ratio of two independently χ^2-distributed random variables X_1 and X_2 with ν_1 and ν_2 degrees of freedom, respectively, so

$$\begin{aligned}
F_{LB}(x) &= \mathbb{P}_{LB}\left(X \le x\right)\\
&= \mathbb{P}_{LB}\left(R \le \left(\frac{x}{\beta}\right)^{\alpha}\theta\right)\\
&= \mathbb{P}_{LB}\left(\frac{\nu_2}{\nu_1}R \le \frac{\nu_2}{\nu_1}\left(\frac{x}{\beta}\right)^{\alpha}\theta\right)\\
&= \mathbb{P}_{LB}\left(F_{\nu_1,\nu_2} \le \frac{\nu_2}{\nu_1}\left(\frac{x}{\beta}\right)^{\alpha}\theta\right)
\end{aligned}$$

Indeed, since the density function of the F_{ν_1,ν_2} random variable is

$$f_{\nu_1,\nu_2}(x) = \frac{\Gamma\left(\frac{\nu_1+\nu_2}{2}\right)}{\Gamma\left(\frac{\nu_1}{2}\right)\Gamma\left(\frac{\nu_2}{2}\right)}\left(\frac{\nu_1}{\nu_2}\right)^{\frac{\nu_1}{2}} x^{\frac{\nu_1}{2}-1}\left(1+\left(\frac{\nu_1}{\nu_2}\right)x\right)^{-\left(\frac{\nu_1+\nu_2}{2}\right)} \tag{5.26}$$

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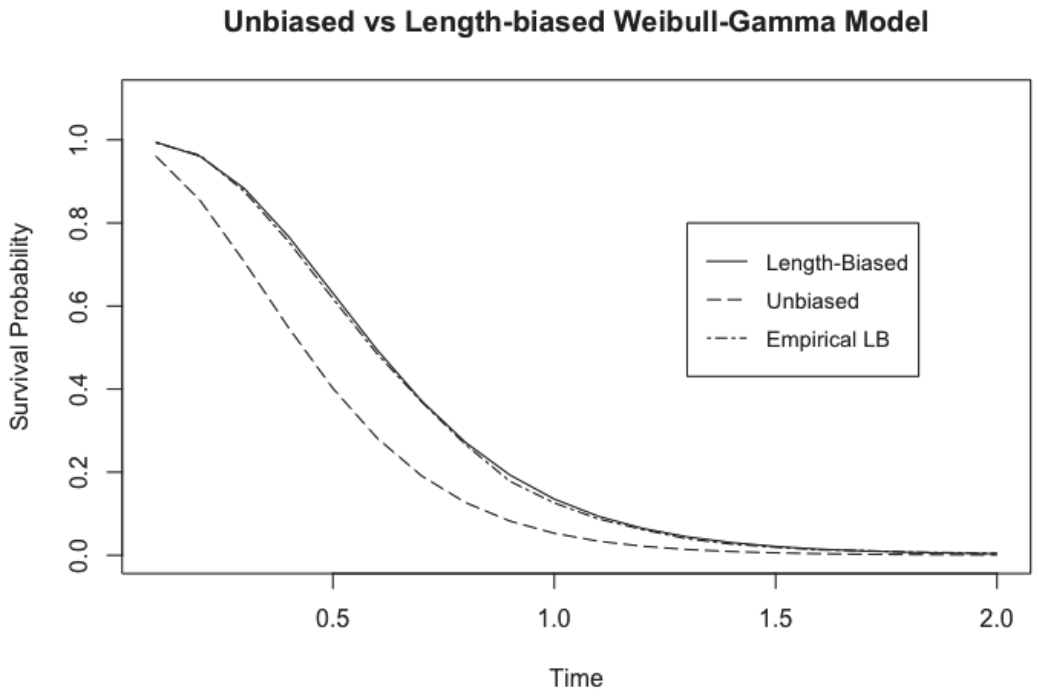

Figure 5.1: Underlying Unbiased (dashed) vs theoretical (solid) and empirical (dot-dashed) Length-biased Survival Function under the Weibull-Gamma Model.

we recover equation (5.22) as

$$\begin{aligned} S_{LB}(x) = 1 - F_{LB}(x) &= 1 - \mathbb{P}\left(F_{\nu_1,\nu_2} \leq \frac{\nu_2}{\nu_1}\left(\frac{x}{\beta}\right)^{\alpha}\theta\right) \\ &= 1 - \frac{\Gamma\left(1+\frac{1}{\theta}\right)}{\Gamma\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)\Gamma\left(1+\frac{1}{\alpha}\right)}\int_0^{\theta\left(\frac{x}{\beta}\right)^{\alpha}} \frac{t^{\frac{1}{\alpha}}}{(1+t)^{1+\frac{1}{\theta}}}\,\mathrm{dt} \end{aligned} \tag{5.27}$$

Notably, the length-biased sampling process has the effect of producing, from $S_X(x)$, an observed data distribution such that the transformed random variable $R = \theta\left(\frac{X}{\beta}\right)^{\alpha}$ has a post-sampling distribution that belongs the same family as its pre-sampling distribution, with a change in the parameter values (ν_1, ν_2) from $\left(2, \frac{2}{\theta}\right)$ to $\left(2\left(1+\frac{1}{\alpha}\right), 2\left(\frac{1}{\theta}-\frac{1}{\alpha}\right)\right)$.
Figure 5.1 was obtained by simulating $N = 100000$ observations from a Weibull-Gamma model with baseline $X \sim \text{Weibull}(\alpha, \beta)$, with $\alpha = 2, \beta = 0.5$, and a multiplicative Gamma frailty $Z \sim \text{Gamma}\left(\frac{1}{\theta}, \frac{1}{\theta}\right)$, with $\theta = 0.2$. Because of length-biased sampling, only $N^* < N$ individuals were selected, that is only if they were still alive at recruitment. The empirical survival function computed based on one such sample is also shown, which

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basically coincides with the theoretical one.

One might observe that the length-biased sampling process produces the expected excess of larger survival times. Inference on the parameters of the underlying marginal survival distribution S_x (i.e. α, β, θ) can be performed by maximizing the length-bias observed data likelihood function (typically, with right-censored data), thus obtaining the maximum likelihood estimators.

5.4 Generalized bivariate length-biased survival function: a first attempt

Let $S(x_1, x_2) = \mathbb{P}(X_1 > x_1, X_2 > x_2)$ be the joint survival function of (X_1, X_2), and let $S_1(x_1) = \mathbb{P}(X_1 > x_1)$ and $S_2(x_2) = \mathbb{P}(X_2 > x_2)$ be the marginal survival functions of X_1 and X_2 respectively.

We are interested in studying the bivariate survival function of two lifetimes that are subject to left truncation. Assuming independence between (X_1, X_2) and (T_1, T_2), we have

$$S_{LB}(x_1, x_2 | X_1 \geq T_1, X_2 \geq T_2) = \frac{G(t_1, t_2) S_U(x_1, x_2)}{\mathbb{P}(X_1 \geq T_1, X_2 \geq T_2)} \tag{5.28}$$

where $G(\cdot)$ denote the distribution function of the random vector of positive truncation times (T_1, T_2). At the denominator, we have

$$\mathbb{P}(X_1 \geq T_1, X_2 \geq T_2) = \int\int \mathbb{P}(X_1 \geq t_1, X_2 \geq t_2 | T_1 = t_1, T_2 = t_2)\, G(dt_1, dt2)$$

Assuming constant rate of incidence of disease (e.g. patients enter uniformly in the study through time), we have

$$\mathbb{P}(X_1 \geq T_1, X_2 \geq T_2) = \int\int \kappa \mathbb{P}(X_1 \geq t_1, X_2 \geq t_2)\; dt_1\, dt_2 = \int\int \kappa S_{x_1,x_2}(dt_1.dt_2)$$

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Hence,

$$\begin{aligned}\int\int \mathbb{P}\left(X_1 \geq t_1, X_2 \geq t_2\right)\, dt_1\, dt_2 &= \int\int \left[\int_{t_2}^{+\infty}\int_{t_1}^{+\infty} f_{X_1,X_2}(u,v)\, du\, dv\right] dt_1\, dt_2 \\ &= \int\int \left[\int_{t_1}^{+\infty}\int_{t_2}^{+\infty} f_{X_1|X_2}(u|v) f_{X_2}(v)\, dv\, du\right] dt_1\, dt_2 \\ &= \int\int \left[\int_{t_2}^{+\infty} f_{X_2}(v) \int_{t_1}^{+\infty} f_{X_1|X_2}(u|v)\, du\, dv\right] dt_1\, dt_2 \\ &= \int\int \left[\int_{t_2}^{+\infty} f_{X_2}(v) S_{X_1|X_2=v}(t_1)\, dv\right] dt_1\, dt_2\end{aligned}$$

A simple application of Fubini-Tonelli's theorem leads to

$$\begin{aligned}&\int\int \left[\int_0^{v} f_{X_2}(v) S_{X_1|X_2=v}(t_1)\, dt_2\right] dv\, dt_1 \\ &= \int\int v f_{X_2}(v) S_{X_1|X_2=v}(t_1)\, dt_1\, dv \\ &= \int v f_{X_2}(v) \int S_{X_1|X_2=v}(t_1)\, dt_1\, dv \\ &= \mathbb{E}_{X_2}\left[v\mathbb{E}\left[X_1|X_2=v\right]\right] = \mathbb{E}\left[X_1 X_2\right]\end{aligned}$$

Therefore,

$$S_{LB}(x_1, x_2|X_1 \geq T_1, X_2 \geq T_2) = \frac{S^*(x_1,x_2)}{\mathbb{E}\left[X_1 X_2\right]} \tag{5.29}$$

where

$$S^*(x_1,x_2) = \int_{x_1}^{+\infty}\int_{x_2}^{+\infty} x_1\, x_2\, f_U(x_1,x_2)\, dx_2\, dx_1 \tag{5.30}$$

Proposition 3. *The unbiased bivariate survival function is given by*

$$S_U(x_1,x_2) = \frac{\int_{u_1=x_1}^{+\infty}\int_{u_2=x_2}^{+\infty} \frac{f_{LB}(u_1,u_2|U_1\geq T_1, U_2\geq T_2)}{u_1 u_2}\, du_1\, du_2}{\int_{u_1=0}^{+\infty}\int_{u_2=0}^{+\infty} \frac{f_{LB}(u_1,u_2|U_1\geq T_1, U_2\geq T_2)}{u_1 u_2}\, du_1\, du_2} \tag{5.31}$$

where $f_{LB}(\cdot)$ is the bivariate length-biased density function.

Proof. Under the assumption that (X_1, X_2) is independent of (T_1, T_2), it is also possible to derive the bivariate length-biased density as follows:

$$\begin{aligned}f_{LB}(x_1,x_2|X_1\geq T_1, X_2\geq T_2) &= \int_{t_1=0}^{x_1}\int_{t_2=0}^{x_2} f(x_1,t_1,x_2,t_2|X_1\geq T_1, X_2\geq T_2)\, \mathrm{d}t_2\, \mathrm{d}t_1 \\ &= \int_{t_1=0}^{x_1}\int_{t_2=0}^{x_2} \frac{f(x_1,x_2) g_{T_1,T_2}(t_1,t_2)}{\mathbb{P}\left(X_1\geq T_1, X_2\geq T_2\right)}\, dt_2\, dt_1\end{aligned}$$

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Assuming that $g_{T_1,T_2}(t_1,t_2)=k>0$, we have that

$$f_{LB}(x_1,x_2|X_1\geq T_1,X_2\geq T_2)=\frac{x_1x_2f_U(x_1,x_2)}{\mathbb{E}\left(X_1X_2\right)} \tag{5.32}$$

where $f_U(x_1,x_2)$ is the unbiased density function, which can be written as

$$f_U(x_1,x_2)=\frac{\mathbb{E}\left(x_1x_2\right)\ f_{LB}(x_1,x_2|X_1\geq T_1,X_2\geq T_2)}{x_1x_2} \tag{5.33}$$

Since $\mathbb{E}\left(x_1x_2\right)$ is a constant, it is possible to show that

$$\int_0^{+\infty}\int_0^{+\infty}\frac{f_{LB}(x_1,x_2|X_1\geq T_1,X_2\geq T_2)}{x_1x_2}\,\mathrm{d}x_2\,\mathrm{d}x_1=\left[\mathbb{E}\left(x_1x_2\right)\right]^{-1} \tag{5.34}$$

being

$$\int_0^{+\infty}\int_0^{+\infty}f_U(x_1,x_2)\,\mathrm{d}x_2\,\mathrm{d}x_1=1$$

Hence,

$$f_U(x_1,x_2)=\frac{\frac{f_{LB}(x_1,x_2|X_1\geq T_1,X_2\geq T_2)}{x_1x_2}}{\int_0^{+\infty}\int_0^{+\infty}\frac{f_{LB}(x_1,x_2|X_1\geq T_1,X_2\geq T_2)}{x_1x_2}\,\mathrm{d}x_1\,\mathrm{d}x_2} \tag{5.35}$$

from which the result follows easily. □

For each pair $p=1,\ldots,n$, the observed vector is given by $\left(\left(\tilde{X}_{1p},\delta_{1p}\right),\left(\tilde{X}_{2p},\delta_{2p}\right)\right)$, where $\tilde{X}_i$ can be regarded as being of the form $\tilde{X}_i=T_i+R_i$, where T_i is the truncation variable (backward recurrence time) and R_i the observed residual lifetime (forward recurrence time). These correspond, respectively to the observed "union formation of the couple" to the date of the cross sectional survey, and the observed time from the recruitment until "failure". For each individual, we assume that there is an independent random censoring variable C_{ip} such that under a right censoring scheme, the observed quantities are given by $\{(W_{ip},\delta_{ip}),i=1,2,p=1,\ldots,n\}$ where

$$\begin{aligned}W_{ip}&=\tilde{X}_{ip}\wedge C_{ip}\\ \delta_{ip}&=I(R_{ip}\leq C_{ip})\end{aligned} \tag{5.36}$$

The likelihood of the model can be written as

$$\begin{aligned}L(\boldsymbol{\theta}|\mathcal{R})=\prod_{i=1}^{p}&\left\{\left(\frac{\partial^2S_{LB}(X_{1p},X_{2p})}{\partial X_{1p}\partial X_{2p}}\right)^{\delta_{1p}\delta_{2p}}\right\}\times\left\{-\frac{\partial S_{LB}(X_{1p},X_{2p})}{\partial X_{1p}}\right\}^{\delta_{1p}(1-\delta_{2p})}\\&\times\left\{-\frac{\partial S_{LB}(X_{1p},X_{2p})}{\partial X_{2p}}\right\}^{\delta_{2p}(1-\delta_{1p})}\times\left\{S_{LB}(X_{1p},X_{2p})\right\}^{(1-\delta_{1p})(1-\delta_{2p})}\end{aligned} \tag{5.37}$$

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where $\mathcal{R}_i = (x_{1p}, x_{2p}, \delta_{1p}, \delta_{2p})$ denote the observed data, and $\boldsymbol{\theta}$ denotes the set of parameters underlying the distribution of each lifetime X_i, $i = 1, 2$. These parameters are estimated via Maximum Likelihood Estimation in a fully parametric setting.

5.4.1 Simulation Study

The validation of the proposed bivariate length-biased survival model was done via simulation studies. Without loss of generality, simulation studies were performed without the inclusion of any covariate.

We assumed that the bivariate random vector of lifetimes (X_1, X_2) follows a Gumbel bivariate exponential distribution, which cdf is given by

$$F_{X_1,X_2}(x_1, x_2) = F_{X_1}(x_1)\, F_{X_2}(x_2)\, [1 + \alpha\, (1 - F_{X_1}(x_1))\, (1 - F_{X_2}(x_2))] \tag{5.38}$$

with $-1 \leq \alpha \leq 1$. Such distribution was introduced by Gumbel (1960), and it is widely discussed by Kotz et al. (1994). In particular, $X_i \sim \exp(1)$, with $i = 1, 2$. Hence, Equation 5.38 becomes

$$F_{X_1,X_2}(x_1, x_2) = \left(1 - e^{-x_1}\right)\, \left(1 - e^{-x_2}\right)\, \left[1 + \alpha\, \left(1 - e^{-(x_1+x_2)}\right)\right] \tag{5.39}$$

with pdf given by

$$f_{X_1,X_2}(x_1, x_2) = e^{-(x_1+x_2)}\, \left(1 + \alpha\, \left(2\, e^{-x_1} - 1\right)\, \left(2\, e^{-x_2} - 1\right)\right) \tag{5.40}$$

Since we are in the lenght biased sampling framework, we observe $(X_1, X_2) \in \mathbb{R}^2$ if and only if both $X_1 \geq T_1$ and $X_2 \geq T_2$. In our setting, it is reasonable to assume that $T_1 \equiv T_2$ w.p. 1, which implies that a generic couple is observe if and only if $\min(X_1, X_2) \geq T$. We proceed as follows:

1. Generate N births (union formations) from a Uniform$(-20, 20)$, and denoted as b;
2. Generate N lifetimes $X_1 = x_1$ from a standard Exponential;
3. Using the inverse transform sampling method, we want to generate N samples from $F_{X_2|X_1=x_1}(x_2|x_1)$ in the following manner:

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(a) Generate a random number $U = u$ from a standard Uniform distribution;

(b) Compute x_2^* such that

$$\mathbb{P}\left(X_2 \leq x_2^* | X_1 = x_1\right) = u$$

that is $x_2^* = \text{argmin}_{x_2 \in \mathbb{R}^+}\left[h(x_2^*; x_1)\right]$, with

$$h(x_2^*; x_1) = \left[\mathbb{P}\left(X_2 \leq x_2^* | X_1 = x_1\right) - u\right]^2$$

4. We select only couples whose birth occurred before the start of the study *and* both individuals are still alive at the time of recruitment.

Furthermore, we assume that patients are observed if $(x_i < t^* - b)$, with $i = 1, 2$, where t^* denote the calendar time of the end of the study, whereas b denote the birth union formation time. For simplicity, the time at which the study begins is set up as equal to zero, whereas $t^* = 1.2$. The simulation seed was set equal to one.
We firstly set $\alpha = 0.6$, and we generate $N = 500000$ couples. However, only $N^* < N$ were observed at the beginning of the study, and the inference was made on such sample.
Note that when $T_1 \equiv T_2$ w.p.1, the bivariate Gumbel length-biased density is given by

$$f_{LB}(x_1, x_2) = \frac{\min\left(x_1, x_2\right) e^{-x_1} e^{-x_2} \left(1 + \alpha \left(2e^{-x_1} - 1\right)\left(2e^{-x_2} - 1\right)\right)}{\left(0.5 + \frac{\alpha}{12}\right)} \tag{5.41}$$

where $\mathbb{E}\left(X_1 X_2\right) = 0.5 + \frac{\alpha}{12}$, which is not anymore equal to $1 + \frac{\alpha}{4}$ as in the standard bivariate Gumbel distribution setting because of the $\min(x_1, x_2)$. As for the bivariate Gumbel survival distribution, we have that it can be written as

$$S_{LB}(x_1, x_2) = \begin{cases} \int_{x_2}^{+\infty} \left[\int_{x_1}^{u_2} u_1 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_1 + \int_{u_2}^{+\infty} u_2 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_1\right] \mathrm{d}u_2 & x_1 \leq x_2 \\ \int_{x_1}^{+\infty} \left[\int_{x_2}^{u_1} u_2 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_1 + \int_{u_1}^{+\infty} u_1 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_1\right] \mathrm{d}u_2 & x_1 > x_2 \end{cases}$$

where by tedious, long computations, each component is equal to

$$\begin{aligned} S_{LB}^{x_2<x_1}(x_1, x_2) &= \int_{x_1}^{+\infty} \left[\int_{x_2}^{u_1} u_2 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_2 + \int_{u_1}^{+\infty} u_1 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_2\right] \mathrm{d}u_1 \\ &= \frac{1}{\left(0.5 + \frac{\alpha}{12}\right)} \left[\frac{e^{-2(2x_1+x_2)}}{12}\left(-6e^{2x_1+x_2}\left(e^{x_2} - 2e^{x_1}(1 + x_2)\right)\right) + \alpha\Psi(x_1, x_2)\right] \end{aligned}$$

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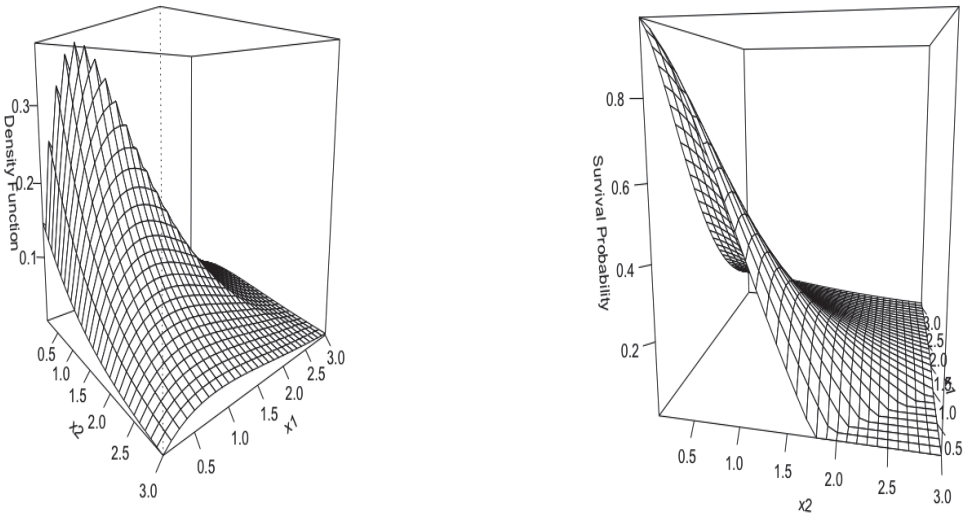

Figure 5.2: Bivariate Density and Bivariate Survival Function under the Length-Biased Gumbel model when $T_1 \equiv T_2$ with probability 1.

when $x_1 > x_2$, and when $x_2 \geq x_1$ we have that

$$S_{LB}^{x_2 \geq x_1}(x_1, x_2) = \int_{x_2}^{+\infty} \left[\int_{x_1}^{u_2} u_1 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_1 + \int_{u_2}^{+\infty} u_2 f_{X_1,X_2}(u_1, u_2)\, \mathrm{d}u_1 \right] \mathrm{d}u_2$$
$$= \frac{1}{\left(0.5 + \frac{\alpha}{12}\right)} \left[\frac{e^{-2(x_1+2x_2)}}{12} \left(6e^{x_1+2x_2} \left(-e^{x_1} + 2e^{x_2}(1 + x_1) \right) \right) + \alpha \Phi(x_1, x_2) \right]$$

where

$$\Psi(x_1, x_2) = = \big(-3e^{2x_2} - 6e^{2(x_1+x_2)} + 10e^{x_1+2x_2} - 12e^{2x_1+x_2} + 12e^{3x_1+x_2}(1 + x_2)$$
$$+6e^{2x_1}(1 + 2x_2) - 6e^{3x_1}(1 + 2x_2) \big)$$

and

$$\Phi(x_1, x_2) = \big(-3e^{2x_1} - 6e^{2(x_1+x_2)} + 10e^{2x_1+x_2} - 12e^{x_1+2x_2}(1 + x_1) + 12e^{x_1+3x_2}(1 + x_1)$$
$$+6e^{2x_2}(1 + 2x_1) - 6e^{3x_2}(1 + 2x_1) \big)$$

The (only) parameter α was recovered by employing maximum likelihood estimation, and results are shown in Table 5.1.

Finally, note that only when T_1 and T_2 are different for each specific individual in the

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Table 5.1: Simulation study performed on the bivariate Gumbel length-biased model.

	$N = 2E6$			$N = 2E5$		
α	Estimate	Std. error	t value	Estimate	Std. error	t value
0.6	0.6150	0.0162	37.88	0.62	0.0523	11.85
	(***)			(***)		
0.2	0.2145	0.0151	14.15	0.2261	0.0490	4.614
	(***)			(***)		
-0.2	-0.1884	0.0135	-13.96	-0.1911	0.0433	-4.412
	(***)			(***)		
-0.6	-0.5910	-0.0112	-52.73	-0.5844	0.0362	-16.14
	(***)			(***)		

couple, then the bivariate survival function can be written as

$$S_{LB}(x_1, x_2) = \frac{(e^{-x_1}(x_1+1))\ (e^{-x_2}(x_2+1)) + \alpha\left((e^{-x_2}a(x_1,x_2))\,(e^{-x_1}b(x_1,x_2))\right)}{\left(1+\frac{\alpha}{4}\right)} \quad (5.42)$$

with $a(x_1, x_2) = \left(x_2 e^{-x_2} + \frac{e^{-x_2}}{2} - x_2 - 1\right)$ and $b(x_1, x_2) = \left(x_1 e^{-x_1} + \frac{e^{-x_1}}{2} - x_1 - 1\right)$.

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Chapter 6

Conclusions and Further Directions

At the core of this thesis, multivariate survival techniques, such as multivariate frailty models, have been deeply investigated, especially under the proposed MOBVE frailty model.

Our proposed methodology aims to model the dependence between pairs of lifetimes. To take into account the association between these measurements, bivariate frailty have been considered. The main advantage on using such methodology relies on the dependence structure of the model, which allows to exploit tractable fully parametric likelihood functions, as well as capturing the dependence structure in a very systematic way. Extensions of and alternatives for the proposed mixture model could also be taken into account: for instance, one might employ the class of Cuadras-Augé Copula to model the association between pairs of failure times; such class has the Marshall-Olkin copula as its special case, which can be showned to be derived from the bivariate survival function that has been exploited in work. However, this familiy of copulas does not belong to the well-known Archimedean class, which is statistical appealing for inference procedure.

In order to illustrate and validate our approach we used the CCSMHA data as a benchmark for analysis and simulations. We also proposed a cure MOBVE frailty model to take into account the fraction of individuals who do not ever experience the event of interest, as the onset of dementia. Due to the sparcity of time-to-onset data from the CCSMHA, we faced challenging estimating issues for the association in dementia onset

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in married different-sex couples couples. In particular, we faced difficulties when dealing with datasets with size $N < 10000$; in order to solve this problem, we tried to reduce the dimensionality of the problem by imposing some restrictions on the parameter space. However, even by resorting to this strategy, we were not able to obtain the true values unless we used samples with size $N > 10000$. We do believe that both methodologies might be successfully applied to population and epidemiological studies of rare events because the lack of real data application for this model is just due to a small sample of couples who both experience dementia in the CCSMHA.

Identifiability issues of the MOBVE were addressed by means of Kullback-Leibler divergence; other approaches as the one proposed by Iachine (2004) might be interesting to be investigated, but this is beyond the scope of this work.

In order to understand the impact of low to medium violation of the assumptions we made in this work, one might try different baseline survival distributions, which indeed require a full, new formulation of the proposed models, and compare the obtained results. Alternatively, one might employ different covariates (or combination of them) to understand the behaviour of the model. However, in both cases, it is necessary to point out that the maximum likelihood estimates are not consistent if the model is wrong; since our MOBVE frailty model was parametrically estimated, this always can be checked easily. Finally, note that the assumptions we made regarding the baseline survival distributions validity in the model were assessed by employing goodness-of-fit; if one aims to study the impact of different assumptions on the model ,one might compare the predicted (empirical) survival distributions versus the observed KM estimates within strata defined by the covariates values. However, such methodology is typically employed in nonparametric settings.

To our knowledge, the CCSMHA is the only population-based longitudinal cohort study attempting, as its primary objective, to estimate the association in dementia onset among 1,207 married couples. However, no work has specifically focused on the statistical assessment of the association among dementia onsets and deaths within different-sex couples. As a natural extension, bivariate multi-state models can be employed to investigate such dependence, extending the proposed MOBVE conditional frailty model into the multi-

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state framework.

Bivariate multi-state models have also been investigated, with particular interest to the bivariate illness-death intensity-based joint multi-state model (Aalen et al. (2007)). Their main advantage consists of being a very flexible framework to investigate the event-history of a patient, taking into account the influence of intermediate events on the one of interest. In our framework, we try to investigate such dependence not only within a subject-specific event-history, but also between couple's members-specific events by employing a MOBVE frailty model in the same spirit as Chapter 3. We discussed the construction of the frailty bivariate multi-state model, with the corresponding observed data likelihood maximization estimating procedure in presence of right censoring. The proposed model was not implemented neither to real or simulated data. The motivation is simple: just a few papers tried to investigate theoretical properties of multiple MSMs, and most of them relied on copula modeling (Diao and Cook (2014); Eryilmaz (2014)), which is statistical appealing for its properties. However, the goal of this work was to directly work with transition probabilities, but a multivariate counterpart of the well-known Aalen-Johansesn estimator for transition probability matrix built on a generic bivariate product space is not available at the time this thesis was written; such generalization is not obvious at all, and its solution is, in my honest opinion, far from being formalized in a suitable form. Therefore, the need of such probabilistic framework is indeed crucial for the study of asymptotic properties of the estimators, and implementing the proposed model would have not given any statistical direction of the results.

Note that a semi-parametric strategy for the estimation of the dependence parameter in the MOBVE framework has been considered, though its asymptotic properties will be examined in future works, based on Generalized Estimating Equations (GEE) for semi-parametric models and asymptotic theory.

Finally, we proposed a new, bivariate survival model for modelling the dependence between length-biased right-censored failure time data; this work aims to fill an important literature gap for multivariate prevalent cohort survival models, and it turns out to be extremely appealing for the investigation of the association in dementia onset.

Archimedean copulas were exploited to address the problem of modeling dependence be-

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tween pair of length-biased data, in the same spirit of Manatunga and Oakes (1996) and Shen (2016). Note that, differently from them who assumed a given truncation time, we assume that the truncation time is a uniform random variable. The assumption of uniform truncation is reasonable in our case, since we aimed to study the association in dementia onset in different-sex couples. However, it would not be extremely realistic if one aims to study, say, an infectious disease who has a seasonality components as well as other clinical events which are extremely random in times, e.g. strokes.

We ended the chapter with a generalization of the univariate framework in Asgharian et al. (2002) to the bivariate case in a fully parametric setting, which provides important relationships among relevant quantities. Likelihood implementation was done via simulation study because of the lack of prevalent cohort data at the time this thesis was written. Note that we used a simple setting for our simulation study, and the Gumbell distribution was choosen to model the bivariate vector of lifetimes. However, more general model can be used, such as the one introduced by Freund (1961), though it seems to have heavy calculations for its length-biased generalization. Finally, notice that this result might be worth to be investigated in a nonparametric setting, though its derivation is far from being simple.

6.1 Feasible Extensions and Developments

As natural developments of this work, I would like to highlight the need for a more formal construction of the above two-stages estimator for the dependence parameter in the multi-state framework. In particular, a two-stages Generalized Estimating Equation type procedure for the estimation of the dependence parameter should be carefully developed, as well as the study of its asymptotic properties.

Furthermore, in a semi-Markov setting, the likelihood seems to be intractable due to the fact that not only each transition depends on the current state, but also on the time of entry in the current state. Therefore, numerical algorithms might be proposed for univariate semi-Markov multi-state models, and Approximate Bayesian Computation (ABC) might be reasonably used to adress this problem.

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As for the ordering issues showed in Chapter 3, one might be interested in trying to investigate the promising relationship between the cumulative hazard order, defined in Shaked and Shanthikumar (2007) and conditional hazard ratio function, defined in Oakes (1982) to construct a general dependence index, as the one proposed. in this work. However, a reformulation of that result is necessary if one aims to use a different multivariate order, such as the multivariate likelihood ratio order, which however is not an order in the usual sense.

Little as been done in the context of bivariate length-biased survival models with right-censoring. Therefore, a further development of the proposed model requires the investigation of nonparametric methods. However, a more feasible, and realistic objective is the extension of the univariate length-biased framework to multi-state processes, which in turns require adjustments for the estimation of the transition-specific Aalen-Johansen probabilities. Finally, developing a comprehensive R package that would allow both statisticians and practitioners to use these models would definetely extend the available survival toolkit. As a last note, it is worth to point out that the R copula package is not flexible with respect to user-defined functions; that was a big challange when trying to implement the length-biased shared frailty model in a copula setting. It would be desirable to work on an extension of copula packages which allows the use of user-defined functions.

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Appendix A

Supplementary Material for the Conditional frailty Marshall-Olkin survival model for bivariate censored failure time data

A.1 Censoring Distribution under the CCSMHA.

As for the all CCSMHA time-to-deaths, we assume that the censoring C is uniformly distributed over the intervals (c_L, c_{cut}) and (c_{cut}, c_U), that is

$$f_C(c) = \begin{cases} k_1 & \text{if } c_L \leq c \leq c_{cut} \\ k_2 & \text{if } c_{cut} \leq c \leq c_{c_U} \\ 0 & \text{else} \end{cases}$$

Note that

$$\mathbb{P}\left(c_L \leq c \leq c_{cut}\right) = \int_{c_L}^{c_{cut}} k_1 \, d\, c = \left(c_{cut} - c_L\right) k_1 \tag{A.1}$$

and

$$\mathbb{P}\left(c_{cut} \leq c \leq c_U\right) = \int_{c_{cut}}^{c_U} k_2 \, d\, c = \left(c_U - c_{cut}\right) k_2 \tag{A.2}$$

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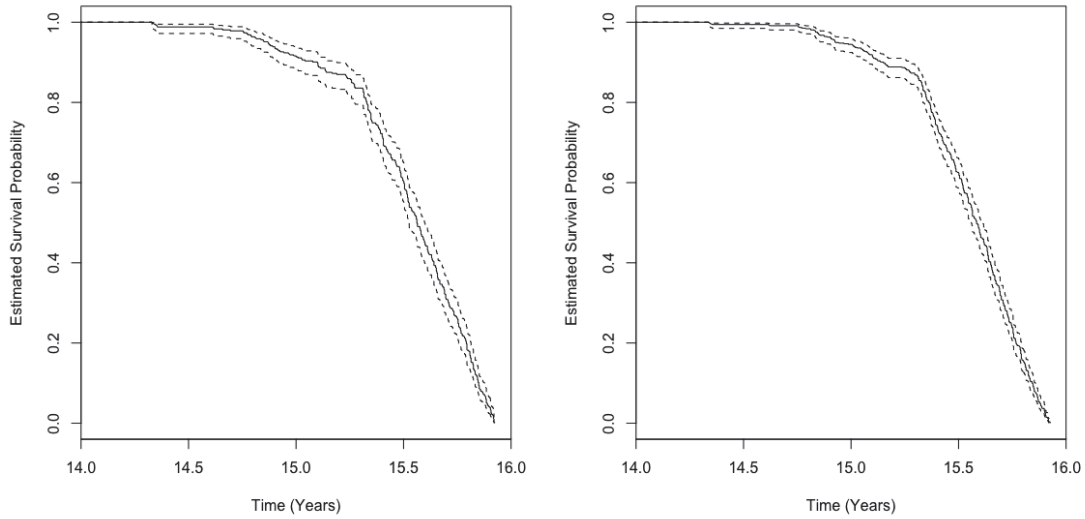

Figure A.1: Estimated Survival Distribution Function for Censored Observations for Men (LEFT) and Women (RIGHT).

Its distribution function can be written as

$$F_C(c) = \begin{cases} 0 & \text{if } c \leq c_L \\ k_1 (c - c_L) & \text{if } c_L \leq c \leq c_{cut} \\ (c_{cut} - c_L) k_1 + k_2 (c - c_{cut}) & \text{if } c_{cut} \leq c \leq c_{c_U} \\ 1 & \text{if } c \geq c_U \end{cases}$$

If $U \sim \mathcal{U}(0,1)$, it is easy to see that

$$\begin{aligned} c =& I\left(0 \leq u \leq (c_{cut} - c_L) k_1\right) \left(\frac{u}{k_1} + c_L\right) + \\ & I\left((c_{cut} - c_L) k_1 \leq u \leq 1\right) \left(c_{cut} + \frac{u - (c_{cut} - c_L) k_1}{k_2}\right) \end{aligned} \tag{A.3}$$

where $I(\cdot)$ is the indicator function.

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A.2 Delta Method to Construct Confidence Intervals for Conditional Survival Functions computed for Survival Times with the CSSMHA data

The conditional survival function derived in Chapter 3 is defined as

$$S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)=\frac{S_1(t_1|\text{Age}_1)-S_{12}(t_1,t_2|\text{Age}_1,\text{Age}_2)}{1-S_2(t_2|\text{Age}_2)}$$

We would like to compute its confidence intervals by applying the delta method. We firstly need to compute the vector of partial derivatives with respect to the vector parameter $\boldsymbol{\theta}=(\alpha_1,\alpha_2,\beta_1,\beta_2,\xi_3,\gamma_1,\gamma_2)$, evaluating them at the MLEs, and then calculating the variance of this functional as being equal to

$$\text{Var}\left(J(\hat{\boldsymbol{\theta}})\right)=\frac{\partial J(\hat{\boldsymbol{\theta}})}{J(\hat{\boldsymbol{\theta}})}\,\text{Var}\left(\boldsymbol{\theta}\right)\,\left[\frac{\partial J(\hat{\boldsymbol{\theta}})}{J(\hat{\boldsymbol{\theta}})}\right]^T \tag{A.4}$$

where $\text{Var}\left(\hat{\boldsymbol{\theta}}\right)$ is the main diagonal of the Hessian MLEs matrix, with

$$\left[\frac{\partial J(\hat{\boldsymbol{\theta}})}{J(\hat{\boldsymbol{\theta}})}\right]^T=\begin{bmatrix}S_{1|2}^{\alpha_1} & S_{1|2}^{\alpha_2} & S_{1|2}^{\beta_1} & S_{1|2}^{\beta_2} & S_{1|2}^{\xi_3} & S_{1|2}^{\gamma_1} & S_{1|2}^{\gamma_2}\end{bmatrix}^T \tag{A.5}$$

where

$$\begin{aligned}
S_{1|2}^{\alpha_1}&:=\frac{\partial S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)}{\partial\alpha_1}\\
S_{1|2}^{\alpha_2}&:=\frac{\partial S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)}{\partial\alpha_2}\\
S_{1|2}^{\beta_1}&:=\frac{\partial S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)}{\partial\beta_1}\\
S_{1|2}^{\beta_2}&:=\frac{\partial S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)}{\partial\beta_2}\\
S_{1|2}^{\xi_3}&:=\frac{\partial S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)}{\partial\xi_3}\\
S_{1|2}^{\gamma_1}&:=\frac{\partial S_{1|2}\left(t_1|T_2=t_2,\mathbf{Age}\right)}{\partial\gamma_1}
\end{aligned}$$

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$$S_{1|2}^{\gamma_2} := \frac{\partial S_{1|2}\left(t_1|T_2 = t_2, \mathbf{Age}\right)}{\partial \gamma_2}$$

We have that

$$\begin{aligned}
S_{1|2}^{\alpha_1} = &-\frac{e^{\gamma_1 a_1 - \gamma_2 a_2}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\log\left(\frac{t_1}{\beta_1}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)^2} + \\
&\frac{e^{\gamma_1 a_1 - \gamma_2 a_2}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}(1-\xi_3)\log\left(\frac{t_1}{\beta_1}\right)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)^2} + \\
&\frac{e^{\gamma_1 a_1 - \gamma_2 a_2}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\log\left(\frac{t_1}{\beta_1}\right)(1-\xi_3)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)^2} + \\
&\frac{e^{\gamma_1 a_1 - \gamma_2 a_2}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\log\left(\frac{t_1}{\beta_1}\right)(1-\xi_3)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)^2\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)} + \\
&\frac{e^{\gamma_1 a_1 - \gamma_2 a_2}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\log\left(\frac{t_1}{\beta_1}\right)\xi_3}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)^2}
\end{aligned}$$

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$$
\begin{aligned}
S_{1|2}^{\alpha_2} = & \frac{\log\left(\frac{t_2}{\beta_2}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} - \frac{e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\log\left(\frac{t_2}{\beta_2}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} + \\
& \frac{(1-\xi_3)\log\left(\frac{t_2}{\beta_2}\right)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)^2} + \\
& \frac{\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)(1-\xi_3)\log\left(\frac{t_2}{\beta_2}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)^2} - \\
& \frac{(1-\xi_3)\log\left(\frac{t_2}{\beta_2}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)} + \\
& \frac{e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}(1-\xi_3)\log\left(\frac{t_2}{\beta_2}\right)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)} + \\
& \frac{e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)(1-\xi_3)\log\left(\frac{t_2}{\beta_2}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)} + \\
& \frac{\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\xi_3\log\left(\frac{t_2}{\beta_2}\right)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)^2} - \\
& \frac{\xi_3\log\left(\frac{t_2}{\beta_2}\right)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)} + \\
& \frac{e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\xi_3\log\left(\frac{t_2}{\beta_2}\right)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}+2-\xi_3\right)}
\end{aligned}
$$

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$$
\begin{aligned}
S_{1|2}^{\beta_1} = & \frac{\alpha_1\, e^{\gamma_1 a_1 - \gamma_2 a_2}\, t_1 \left(\frac{t_1}{\beta_1}\right)^{\alpha_1 - 1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)}{\beta_1^2 \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)^2} - \\
& \frac{\alpha_1\, e^{\gamma_1 a_1 - \gamma_2 a_2}\, t_1 \left(\frac{t_1}{\beta_1}\right)^{\alpha_1 - 1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} (1 - \xi_3)}{\beta_1^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} - \\
& \frac{\alpha_1\, e^{\gamma_1 a_1 - \gamma_2 a_2}\, t_1 \left(\frac{t_1}{\beta_1}\right)^{\alpha_1 - 1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1 - \xi_3)}{\beta_1^2 \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right) \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} - \\
& \frac{\alpha_1\, e^{\gamma_1 a_1 - \gamma_2 a_2}\, t_1 \left(\frac{t_1}{\beta_1}\right)^{\alpha_1 - 1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1 - \xi_3)}{\beta_1^2 \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} - \\
& \frac{\alpha_1\, e^{\gamma_1 a_1 - \gamma_2 a_2}\, t_1 \left(\frac{t_1}{\beta_1}\right)^{\alpha_1 - 1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) \xi_3}{\beta_1^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2}
\end{aligned}
$$

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$$
\begin{aligned}
S_{1|2}^{\beta_2} = &- \frac{\alpha_2}{\beta_2 \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} + \frac{\alpha_2 e^{-\gamma_2 a_2} t_2 \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2 - 1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)}{\beta_2^2 \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} - \\
&\frac{\alpha_2 (1 - \xi_3)}{\beta_2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} - \\
&\frac{\alpha_2 \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1 - \xi_3)}{\beta_2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2 \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} + \\
&\frac{\alpha_2 (1 - \xi_3)}{\beta_2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right) \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} - \\
&\frac{\alpha_2 e^{-\gamma_2 a_2} t_2 \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2 - 1} (1 - \xi_3)}{\beta_2^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} - \\
&\frac{\alpha_2 e^{-\gamma_2 a_2} t_2 \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2 - 1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1 - \xi_3)}{\beta_2^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right) \left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} - \\
&\frac{\alpha_2 \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) \xi_3}{\beta_2^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} + \\
&\frac{\alpha_2 \xi_3}{\beta_2^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
&\frac{\alpha_2 e^{-\gamma_2 a_2} t_2 \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2 - 1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) \xi_3}{\beta_2^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)}
\end{aligned}
$$

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$$
\begin{aligned}
S_{1|2}^{\xi_3} = & - \frac{e^{-\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2-1} (1-\xi_3)}{\left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} - \\
& \frac{e^{-\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2-1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1-\xi_3)}{\left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right) \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} + \\
& \frac{e^{-\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2-1}}{\left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} - \\
& \frac{e^{-\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2-1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)}{\left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
& \frac{e^{-\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2-1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)}{\left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right) \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} - \\
& \frac{e^{-\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2-1} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) \xi_3}{\left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} -
\end{aligned}
$$

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$$
\begin{aligned}
S_{1|2}^{\gamma_1} = &- \frac{a_1\, e^{\gamma_1 a_1 - \gamma_2 a_2} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)}{\left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)^2} + \\
&\frac{a_1\, e^{\gamma_1 a_1 - \gamma_2 a_2} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} (1 - \xi_3)}{\left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} + \\
&\frac{a_1\, e^{\gamma_1 a_1 - \gamma_2 a_2} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1 - \xi_3)}{\left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right) \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} + \\
&\frac{a_1\, e^{\gamma_1 a_1 - \gamma_2 a_2} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) (1 - \xi_3)}{\left(1 + e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)^2 \left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
&\frac{a_1\, e^{\gamma_1 a_1 - \gamma_2 a_2} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} \left(\frac{t_2}{\beta_2}\right)^{-\alpha_2} \left(1 + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right) \log\left(\frac{t_1}{\beta_1}\right) \xi_3}{\left(e^{\gamma_1 a_1} \left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2} \left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2}
\end{aligned}
$$

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$$
\begin{aligned}
S_{1|2}^{\gamma_2} = & \frac{a_2}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} - \frac{a_2\, e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)} + \\
& \frac{(1-\xi_3)\, a_2}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} + \\
& \frac{a_2\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)(1-\xi_3)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} - \\
& \frac{a_2\,(1-\xi_3)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
& \frac{a_2\, e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}(1-\xi_3)}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
& \frac{a_2\, e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)(1-\xi_3)}{\left(1+e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1}\right)\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
& \frac{a_2\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\xi_3}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)^2} - \\
& \frac{a_2\,\xi_3}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)} + \\
& \frac{a_2\, e^{-\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{-\alpha_2}\left(1+e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2}\right)\xi_3}{\left(e^{\gamma_1 a_1}\left(\frac{t_1}{\beta_1}\right)^{\alpha_1} + e^{\gamma_2 a_2}\left(\frac{t_2}{\beta_2}\right)^{\alpha_2} + 2 - \xi_3\right)}
\end{aligned}
$$

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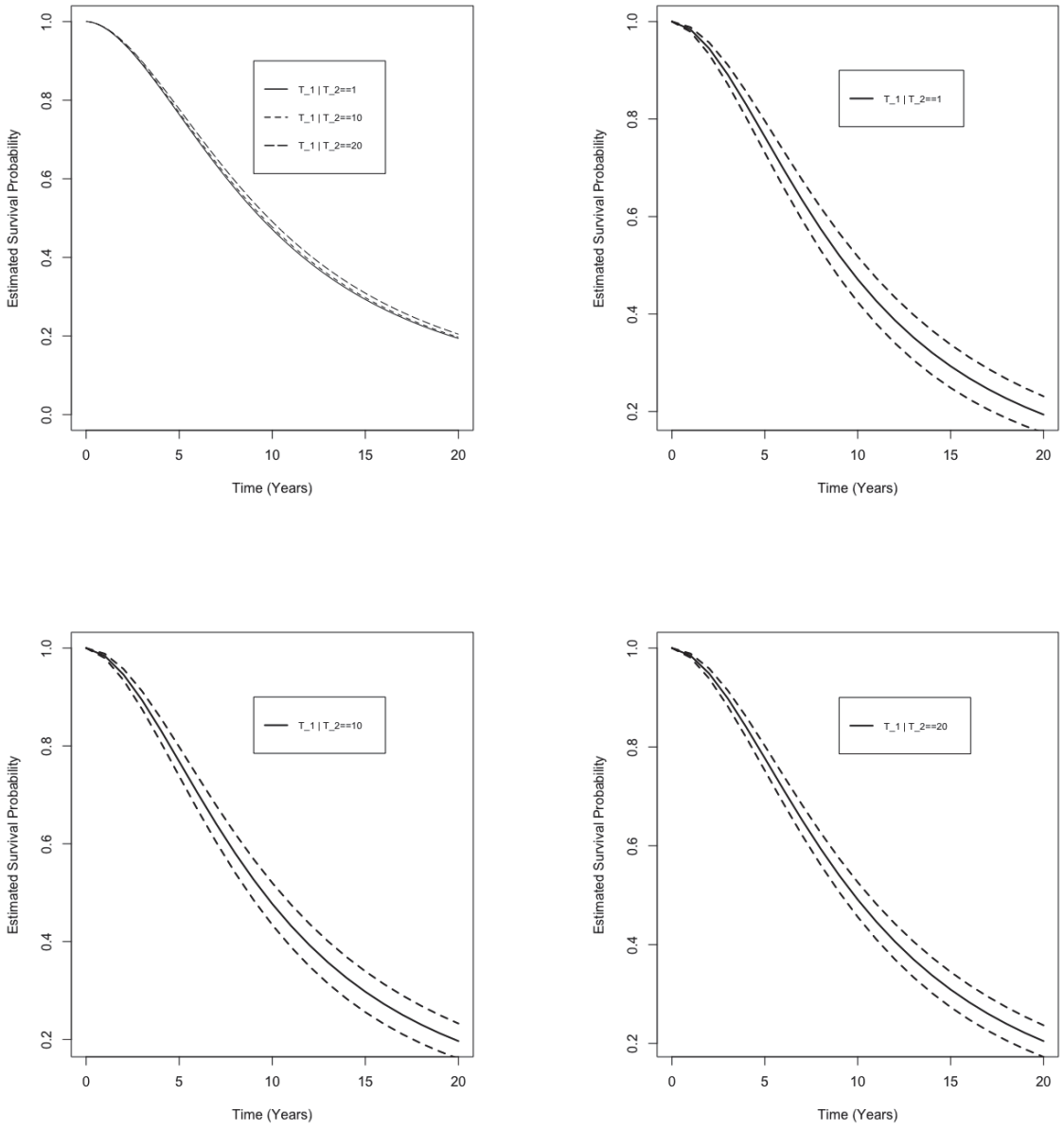

Figure A.2: Estimated Conditional Survival Function for Men given his (Woman) partner dies after 1 (solid), 10 (dashed) or 20 (longdash) years, with corresponding estimated confidence intervals, given they enter with age equal to the average sample entry age.

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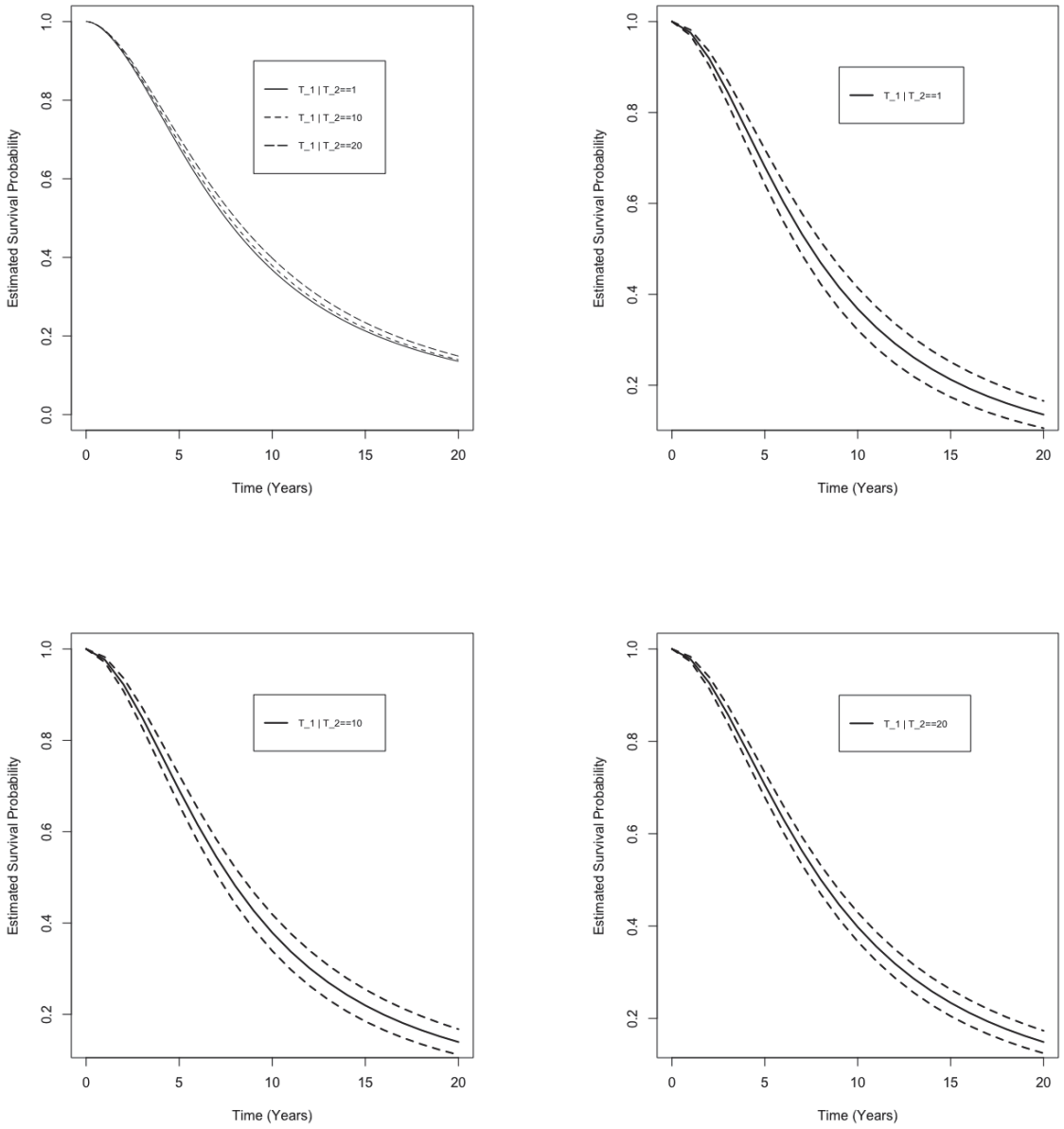

Figure A.3: Estimated Conditional Survival Function for Men given his (Woman) partner dies after 1 (solid), 10 (dashed) or 20 (longdash) years, with corresponding estimated confidence intervals, given the man enters with age equal to 3 years after the men average sample entry age, and she enters with age equal to 5 years after the women average sample entry age

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A.3 R code for Simulating the Bivariate MOBVE Cure Frailty Model

The following R codes is reported for the sake of replicability of the cured MOBVE Frailty Model. The interested reader should, however, note that only the code without covariates is given. The case with covariates directly is just an extension of it, so that it has been omitted in this manuscript.

```
set.seed(123987)
beta03 <- beta02 <- 0.5
beta04 <- 0.2
# beta01 reference category hence must be equal to zero!
n <- 12000
vec <- rep(1,n)
beta01 <- 0
pi4 <- function(beta02,beta03,beta04){
  ( vec*exp(beta04)/( exp(beta04) + exp(beta03) + exp(beta02) +1)  ) #exp
     (0)=1 !
}
pi3 <- function(beta02,beta03,beta04){
  ( vec*exp(beta03)/( exp(beta04) + exp(beta03) + exp(beta02) + 1)  )
}
pi2 <- function(beta02,beta03,beta04){
  ( vec*exp(beta02)/( exp(beta04) + exp(beta03) + exp(beta02) + 1)  )
}
pi1 <- function(beta02,beta03,beta04){
  ( (1-pi4(beta02,beta03,beta04)-pi3(beta02,beta03,beta04)-pi2(beta02,
     beta03,beta04)) )
}

phi4 <- pi4(beta02,beta03,beta04)
phi3 <- pi3(beta02,beta03,beta04)
phi2 <- pi2(beta02,beta03,beta04)
phi1 <- pi1(beta02,beta03,beta04)
```

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```
# set baseline and MOBVE frailty parameters
alpha1 <- alpha2 <- alpha3 <- alpha4 <- 3
beta1 <- beta2 <- beta3 <- beta4 <- 2
xi3 <- .3
xi1 <- 1-xi3
xi2 <- 1-xi3
w1 <- rexp(n, rate=xi1)
w2 <- rexp(n, rate=xi2)
w3 <- rexp(n, rate=xi3)
z1 <- pmin(w1, w3)
z2 <- pmin(w2, w3)
t1ast <- rep(NA,n)
t2ast <- rep(NA,n)

# latent group generation
gengroup <- rep(NA,n)
for(i in 1:n){
  gengroup[i] <- sample(1:4, 1, replace=F,c(phi1[i],phi2[i],phi3[i],phi4[i
      ]))
}
gengroup
table(gengroup)/n
for(i in 1:n){
  if(gengroup[i]==1)
  {
    t1ast[i] <- 10000
    t2ast[i] <- 10000
  }
  if(gengroup[i]==2)
  {
    t1ast[i] <- 10000
    t2ast[i] <- rweibull(1,alpha4, beta4)
  }
  if(gengroup[i]==3)
  {
    t1ast[i] <- rweibull(1,alpha3,beta3)
```

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```
    t2ast[i] <- 10000
  }
  if(gengroup[i]==4)
  {
    #t1ast[i] <- rweibull(1,shape=alpha1, scale=beta1 )
    #t2ast[i] <- rweibull(1,shape=alpha2, scale=beta2 )
    t1ast[i] <- rweibull(1,shape=alpha1, scale= ( beta1/(z1[i]^(1/alpha1))
        ))
    t2ast[i] <- rweibull(1,shape=alpha2, scale= ( beta2/(z2[i]^(1/alpha2))
        ))

  }
}
par(mfrow=c(1,1))
plot(t1ast[gengroup==4],t2ast[gengroup==4])

# censoring
cens_time_new.mast <- rexp(n,rate=.02)
cens_time_new.wast <- rexp(n,rate=.02)
x1ast <- pmin(t1ast,cens_time_new.mast) #obs times for individual 1
x2ast <- pmin(t2ast,cens_time_new.wast) #obs times for individual 2
cens_1c <- ifelse((t1ast>cens_time_new.mast), 0, 1) # create censoring for
    Men
cens_2c <- ifelse((t2ast>cens_time_new.wast), 0, 1) # create censoring for
    Women
datframec <- data.frame(gengroup,cens_1c,cens_2c)
xtabs(~ gengroup+cens_2c,datframec)
censoring11 <- ifelse((cens_1c==1)&(cens_2c==1),1,0) #create indicator both
     experienced event
n11 <- sum(censoring11)
censoring10 <- ifelse((cens_1c==1)&(cens_2c==0),1,0) # create indicator
    only 1 experienced event
n10 <- sum(censoring10)
censoring01 <- ifelse((cens_1c==0)&(cens_2c==1),1,0)# create indicator only
     2 experienced event
n01 <- sum(censoring01)
```

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```
censoring00 <- ifelse((cens_1c==0)&(cens_2c==0),1,0) # create indicator
    nobody experienced event
n00 <- sum(censoring00)

# Define Functions (same functions used for the standard bivariate MOBVE
    Frailty Model)
 # (unconditional) marginal survival of T1
S1 <- function(t1,alpha1,beta1,par1,par2,par3){
  ( par1/( (t1/beta1)^(alpha1) + par1+par2+par3 )) +
    ( par3/( (t1/beta1)^(alpha1) + par1+par2+par3 )) +
    ( (par1+par3) /( (t1/beta1)^(alpha1) + par1+par3 )) -
    ( (par1+par3)/( (t1/beta1)^(alpha1) + par1+par2+par3 ))
}
# (unconditional) marginal survival of T2
S2 <-function(t2,alpha2,beta2,par1,par2,par3){
  (par2+par3) / ( (par2+par3) + (t2/beta2)^(alpha2))
}
# (unconditional) cumulative hazard of T1
Lambda01<- function(t1,alpha1,beta1,par1,par2,par3){
  (((S1(t1,alpha1,beta1,par1,par2,par3))^(-par1-par3)-1)/(par1+par3) )
}
#(unconditional) cumulative hazard of T2
Lambda02 <- function(t2,alpha2,beta2,par1,par2,par3){
  (((S2(t2,alpha2,beta2,par1,par2,par3))^(-par2-par3)-1)/(par2+par3))
}
# (unconditional) marginal density function of T1
f1 <- function(t1,alpha1,beta1,par1,par3){
  (-(par1+par3)*(alpha1*t1^(alpha1-1))/ ( (beta1^(alpha1))*(par1+par3+(t1/
      beta1)^(alpha1))^2 ) )
}
#(unconditional) marginal density function of T2
f2 <-function(t2,alpha2, beta2,par2,par3){
  (-(par2+par3)*(alpha2*t2^(alpha2-1))/ ( (beta2^(alpha2))*(par2+par3+(t2/
      beta2)^(alpha2))^2 ) )
}
# Joint Survival MOBVE model
```

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```
S12 <- function(t1,t2,alpha1,alpha2,beta1,beta2,par1,par2,par3){
  fun0 <-  ( (par2*(par1+par3)) / ( (Lambda01(t1,alpha1,beta1,par1,par2,
      par3)+par1+par3)*( Lambda01(t1,alpha1,beta1,par1,par2,par3) +
      Lambda02(t2,alpha2,beta2,par1,par2,par3) + par1+par2+par3)))  +
    ( (par1*(par2+par3)) / ( (Lambda02(t2,alpha2,beta2,par1,par2,par3)+par2
        +par3)*( Lambda01(t1,alpha1,beta1,par1,par2,par3) +  Lambda02(t2,
        alpha2,beta2,par1,par2,par3) + par1+par2+par3)))  +
    ( (par3)/(Lambda01(t1,alpha1,beta1,par1,par2,par3) + Lambda02(t2,alpha2
        ,beta2,par1,par2,par3) + par1+par2+par3))
  return(pmax(rep(0.00000001,length(t1)),fun0))
}
# joint density MOBVE model
density12 <-function(t1,t2,alpha1,alpha2,beta1,beta2,par1,par2,par3){
  fun1 <- ((Lambda01(t1,alpha1,beta1,par1,par2,par3) + Lambda02(t2,alpha2,
      beta2,par1,par2,par3) + par1+par2+par3)^(-2))*(S1(t1,alpha1,beta1,par1
      ,par2,par3)^(-par1-par3-1))*(S2(t2,alpha2,beta2,par1,par2,par3)^(-par2
      -par3-1))*f1(t1,alpha1,beta1,par1,par3)*f2(t2,alpha2,beta2,par2,par3)*
      (
    (par2*(par1+par3))*((Lambda01(t1,alpha1,beta1,par1,par2,par3) + par1+
        par3)^(-2)) + (2*par2*(par1+par3))*((Lambda01(t1,alpha1,beta1,par1,
        par2,par3) + par1+par3)^(-1))*((Lambda01(t1,alpha1,beta1,par1,par2,
        par3)+Lambda02(t2,alpha2,beta2,par1,par2,par3) + par1+par2+par3)
        ^(-1))
    + (par1*(par2+par3))*((Lambda02(t2,alpha2,beta2,par1,par2,par3) + par2+
        par3)^(-2)) + (2*par1*(par2+par3))*((Lambda02(t2,alpha2,beta2,par1,
        par2,par3)+par2+par3)^(-1))*((Lambda01(t1,alpha1,beta1,par1,par2,
        par3) +Lambda02(t2,alpha2,beta2,par1,par2,par3) + par1+par2+par3)
        ^(-1))
    + (2*(par3))*((Lambda01(t1,alpha1,beta1,par1,par2,par3) +Lambda02(t2,
        alpha2,beta2,par1,par2,par3)+par1+par2+par3)^(-1)))
  return(pmax(rep(0.00000001,length(t1)),fun1))
}
#partial derivative wrt t1 of S(t1,t2)
chunk2 <- function(t1,t2,alpha1,alpha2,beta1,beta2,par1,par2,par3){
  fun2 <-    -(((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2,alpha2
      ,beta2,par1,par2,par3) + par1+par2+par3)^(-1))*(S1(t1,alpha1,beta1,
```

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```
      par1,par2,par3)^(-par1-par3-1))*(f1(t1,alpha1,beta1,par1,par3)))*(
    (par2*(par1+par3))*(Lambda01(t1,alpha1,beta1,par1,par2,par3)+par1+par3)
        ^(-2) +
      (par2*(par1+par3))*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+par1+
          par3)^(-1))*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2
          ,alpha2,beta2,par1,par2,par3)+par1+par2+par3)^(-1)) +
      (par1*(par2+par3))*((Lambda02(t2,alpha2,beta2,par1,par2,par3)+par2+
          par3)^(-1))*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2
          ,alpha2,beta2,par1,par2,par3)+par1+par2+par3)^(-1)) +
      (par3)*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2,alpha2,
          beta2,par1,par2,par3)+par1+par2+par3)^(-1)))
  return(pmax(rep(0.00000001,length(t1)),fun2))
}
#partial derivative wrt t2 of S(t1,t2)
chunk3 <- function(t1,t2,alpha1,alpha2,beta1,beta2,par1,par2,par3){
  fun3 <-  -(((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2,alpha2,
      beta2,par1,par2,par3) + par1+par2+par3)^(-1))*(S2(t2,alpha2,beta2,par1
      ,par2,par3)^(-par2-par3-1))*(f2(t2,alpha2,beta2,par2,par3)))*(
    (par2*(par1+par3))*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+par1+par3
        )^(-1))*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2,
        alpha2,beta2,par1,par2,par3)+ par1+par2+par3)^(-1)) +
      (par1*(par2+par3))*((Lambda02(t2,alpha2,beta2,par1,par2,par3)+par2+
          par3)^(-2)) + (par1*(par2+par3))*((Lambda02(t2,alpha2,beta2,par1,
          par2,par3)+par2+par3)^(-1))*((Lambda01(t1,alpha1,beta1,par1,par2,
          par3)+Lambda02(t2,alpha2,beta2,par1,par2,par3)+par1+par2+par3)
          ^(-1)) +
      (par3)*((Lambda01(t1,alpha1,beta1,par1,par2,par3)+Lambda02(t2,alpha2,
          beta2,par1,par2,par3)+par1+par2+par3)^(-1)))
  return(pmax(rep(0.0000001,length(t1)),fun3))

}
summary.optim <- function ( optim.fit ){

  Estimate = optim.fit$par
  cov.mat = solve(optim.fit$hessian)
  Std.Error = sqrt( diag(cov.mat) )
```

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```
  t.value = Estimate/Std.Error
  p.value = 2*( 1-pnorm(abs(t.value)) )

  ds.out = cbind(Estimate, Std.Error, t.value, p.value)
  colnames(ds.out) <- c('Estimate', 'Std Error', 't value', 'p value')

  ds.out
}

# relevant likelihood functions for the cure MOBVE model
chunk1c <- function(t1,t2,alpha1,alpha2,alpha3,alpha4,beta1,beta2,beta3,
    beta4,par1,par2,par3,beta02,beta03,beta04){
  sd1 <- pi1(beta02,beta03,beta04)[censoring00==1]+
    pi2(beta02,beta03,beta04)[censoring00==1]*exp(-(t2/beta4)^(alpha4)) +
    pi3(beta02,beta03,beta04)[censoring00==1]*exp(-(t1/beta3)^(alpha3)) +
    pi4(beta02,beta03,beta04)[censoring00==1]*S12(t1,t2,alpha1,alpha2,beta1
        ,beta2,par1,par2,par3)
  return(pmax(rep(0.0000001,length(t1)),sd1))
}
chunk2c <- function(t1,t2,alpha1,alpha2,alpha3,alpha4,beta1,beta2,beta3,
    beta4,par1,par2,par3,beta02,beta03,beta04){
  sd2 <- pi3(beta02,beta03,beta04)[censoring10==1]*((alpha3*t1^(alpha3-1)*
      exp(-(t1/beta3)^(alpha3)))/(beta3^(alpha3))) +
    pi4(beta02,beta03,beta04)[censoring10==1]*chunk2(t1,t2,alpha1,alpha2,
        beta1,beta2,par1,par2,par3)
  return(pmax(rep(0.0000001,length(t1)),sd2))
}
chunk3c <- function(t1,t2,alpha1,alpha2,alpha3,alpha4,beta1,beta2,beta3,
    beta4,par1,par2,par3,beta02,beta03,beta04){
  sd3 <- pi2(beta02,beta03,beta04)[censoring01==1]*((alpha4*t2^(alpha4-1)*
      exp(-(t2/beta4)^(alpha4)))/(beta4^(alpha4))) +
    pi4(beta02,beta03,beta04)[censoring01==1]*chunk3(t1,t2,alpha1,alpha2,
        beta1,beta2,par1,par2,par3)
  return(pmax(rep(0.0000001,length(t1)),sd3))
}
```

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```
chunk4c <- function(t1,t2,alpha1,alpha2,alpha3,alpha4,beta1,beta2,beta3,
    beta4,par1,par2,par3,beta02,beta03,beta04){
  sd4 <- pi4(beta02,beta03,beta04)[censoring11==1]*density12(t1,t2,alpha1,
      alpha2,beta1,beta2,par1,par2,par3)
  return(pmax(rep(0.0000001,length(t1)),sd4))
}

# Likelihood Function
likefun <- function(theta){
  alpha1 <- theta[1]
  alpha2 <- theta[2]
  alpha3 <- theta[3]
  alpha4 <- theta[4]
  beta1 <- theta[5]
  beta2 <- theta[6]
  beta3 <- theta[7]
  beta4 <- theta[8]
  xi3 <- theta[9]
  xi1 <- 1-xi3
  xi2 <- xi1
  beta02 <- theta[10]
  beta03 <- theta[11]
  beta04 <- theta[12]
  loglike <- sum(log(chunk1c(x1ast[censoring00==1],x2ast[censoring00==1],
      alpha1,alpha2,alpha3,alpha4,beta1,beta2,beta3,beta4,xi1,xi2,xi3,beta02
      ,beta03,beta04))) +
    sum(log(chunk2c(x1ast[censoring10==1],x2ast[censoring10==1],alpha1,
        alpha2,alpha3,alpha4,beta1,beta2,beta3,beta4,xi1,xi2,xi3,beta02,
        beta03,beta04))) +
    sum(log(chunk3c(x1ast[censoring01==1],x2ast[censoring01==1],alpha1,
        alpha2,alpha3,alpha4,beta1,beta2,beta3,beta4,xi1,xi2,xi3,beta02,
        beta03,beta04))) +
    sum(log(chunk4c(x1ast[censoring11==1],x2ast[censoring11==1],alpha1,
        alpha2,alpha3,alpha4,beta1,beta2,beta3,beta4,xi1,xi2,xi3,beta02,
        beta03,beta04)))
  return(-loglike)
```

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```
}
theta_start_sim <- c(1,1,1,1,1,1,1,1,0.8,0.1,0.1,0.1)
mle.sim <- optim(theta_start_sim, likefun, method="L-BFGS-B", lower=c
    (0,0,0,0,0,0,0,0,0,-Inf,-Inf,-Inf), upper=c(Inf, Inf, Inf, Inf, Inf, Inf, Inf,
    Inf,1, Inf, Inf, Inf), hessian=TRUE)

summary.optim(mle.sim)
```

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A.4 Example of Simulation Results for the Bivariate MOBVE Frailty Cure Model

Table A.1: Estimated MOBVE Frailty Cure Model, with adjustment for Age, using simulated data (N=12070)

Parameter	True	Estimate	Std. error	t-value	p-value	p-value for $H_0 : \theta_j = \theta_j^*$
α_1	3.00	3.0191	0.0769	39.2318	< 0.0001	0.8038
α_2	3.00	3.0356	0.0780	38.8905	< 0.0001	0.6481
α_3	3.00	2.9623	0.0673	44.0349	< 0.0001	0.5753
α_4	3.00	3.0145	0.0708	42.5727	< 0.0001	0.8377
β_1	2.00	2.0194	0.0491	41.1355	< 0.0001	0.6928
β_2	2.00	1.9930	0.0499	39.9548	< 0.0001	0.8884
β_3	2.00	2.0064	0.0248	80.8244	< 0.0001	0.7963
β_4	2.00	2.0001	0.0243	82.4427	< 0.0001	0.9967
ξ_3	0.30	0.2878	0.0828	3.4743	0.0005	0.8828
γ_1	0.10	0.1002	0.0083	12.0614	< 0.0001	0.9808
γ_2	0.10	0.1083	0.0092	11.7330	< 0.0001	0.3670
β_{02}	0.500	0.4943	0.0691	7.1475	< 0.0001	0.9342
β_{03}	0.500	0.5698	0.0676	8.4234	< 0.0001	0.3018
β_{04}	0.200	0.2225	0.0652	3.4099	0.0006	0.7300
β_{12}	0.050	0.0474	0.0154	3.0814	0.0021	0.8659
β_{13}	0.050	0.0423	0.0153	2.7595	0.0058	0.6148
β_{14}	0.100	0.1023	0.0152	6.7143	< 0.0001	0.8797
β_{22}	0.030	0.0355	0.0191	1.8611	0.0627	0.7734
β_{23}	0.030	0.0446	0.0186	2.3984	0.0165	0.4325
β_{24}	0.200	0.1969	0.0180	10.9646	< 0.0001	0.8633

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Table A.2: Estimated Shared Frailty Cure Model, with adjustment for Age, using simulated data (N=12070)

Parameter	True	Estimate	Std. error	t-value	p-value	p-value for $H_0 : \theta_j = \theta_j^*$
α_1	3.00	3.0008	0.1068	28.0858	< 0.0001	0.9940
α_2	3.00	2.9999	0.1057	28.3867	< 0.0001	0.9992
α_3	3.00	2.9161	0.0611	47.7223	< 0.0001	0.1697
α_4	3.00	2.8391	0.0605	46.8845	< 0.0001	0.0078
β_1	2.00	2.1095	0.0858	24.5702	< 0.0001	0.2019
β_2	2.00	2.0254	0.0882	22.9530	< 0.0001	0.7734
β_3	2.00	2.0119	0.0226	88.9505	< 0.0001	0.5985
β_4	2.00	2.0258	0.0242	83.5257	< 0.0001	0.2864
ϑ	5.00	4.5463	0.3661	12.4186	< 0.0001	0.2152
γ_1	0.10	0.0914	0.0122	7.4938	< 0.0001	0.4809
γ_2	0.10	0.0876	0.0137	6.3750	< 0.0001	0.3654
β_{02}	0.500	0.5627	0.1074	5.2374	< 0.0001	0.5593
β_{03}	0.500	0.5699	0.1068	5.3360	< 0.0001	0.5128
β_{04}	0.200	0.1071	0.1481	0.7235	0.4694	0.5305
β_{12}	0.050	0.0699	0.0179	3.8924	< 0.0001	0.2662
β_{13}	0.050	0.0780	0.0179	4.3631	< 0.0001	0.1177
β_{14}	0.100	0.1231	0.0232	5.2940	< 0.0001	0.9957
β_{22}	0.030	0.0329	0.0222	1.4822	0.1383	0.8961
β_{23}	0.030	0.0124	0.0223	0.5554	0.5786	0.4300
β_{24}	0.200	0.2231	0.0274	8.1377	< 0.0001	0.3992

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Appendix B

R Code for Simulating Multi-state Models as a Sequence of Competing Risks under a MOBVE Frailty Model

```
########## create MOBVE frailties ##########
n=1000
xi3 <- 0.5
xi1 <- 1-xi3
xi2 <- 1-xi3
w1 <- rexp(n, rate=xi1)
w2 <- rexp(n, rate=xi2)
w3 <- rexp(n, rate=xi3)
z1 <- pmin(w1, w3)
z2 <- pmin(w2, w3)
        ########## first competing block ###############
u1 <- runif(n)
T1<- rep(NA,n) #time from state 1 (NED) to state 2 (onset)
```


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```
for(i in 1:n){
  T1[i] <- (-log(u1[i]))^(1/alpha1) / (beta1*z1[i]^(1/alpha1))
}
u2 <- runif(n)
arg2 <- rep(NA,n)
T2 <- rep(NA,n) #time from state 1 (NED) to state 3(death)
for(i in 1:n){
  arg2_m[i] <- ( (u2[i]^(-(theta)/(theta+1))-1)*exp(theta*(z1[i])*beta1*T1[
      i]^(alpha1)) +1 )^(1/theta)
  T2[i] <- (log(arg2[i]))^(1/alpha1) / (beta1*(z1[i])^(1/alpha1))
}
cens0 <- rexp(100,.5)
T1_obs <- pmin(T1,T2,cens0)
# which values are censored?
cen <- rep(NA,n)
for(i in 1:n){
if(T1_obs[i]== cens0[i]) {cen[i]<-cens0[i]}
}
# When did T1 happen?
event1 <- rep(NA,n)
for(i in 1:n){
  if(T1_obs[i]== T1[i]) {event1[i]<-T1[i]}
}
event1_count <- sapply(event1, function(y) sum(length(which(!is.na(y)))))
sum(event1_count)
trans1stat <- ifelse((T1_obs==T1),1,0)
trans2stat <- ifelse((T1_obs==T2),1,0)
            ########## second competing block  ###############
u3 <- runif(100)
arg3 <- rep(NA,100)
T3 <- rep(NA,100)
for(i in 1:n){
  if(T1_obs[i]==T1[i]){
      arg3[i] <- ( (u3[i]^(-(theta)/(theta+1))-1)*exp(theta*(z1[i])*beta1*
          T1_obs[i]^(alpha1)) +1 )^(1/theta)
      T3[i] <- (log(arg3[i]))^(1/alpha1) / (beta1*(z1[i])^(1/alpha1))
```

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```
  }
}
T3[is.na(T3)] <- 0

event1 <- rep(NA,n)
for(i in 1:n){
  if(T1_obs[i]== T1[i]) {event1[i]<-T1[i]}
}
event1[is.na(event1)] <- 0#
cens1 <- rep(0,n)
  for(i in 1:n){
    if(event1[i]!=0){
      cens1[i] <- cens0[i]-T1[i]
    }
  }
cens1[which(cens1==0)] = NA #set again NA's
T3[which(T3==0)] = NA
event1[which(event1==0)] = NA
T2_obs <- pmin(T3,cens1)
trans3stat <- ifelse((T2_obs==T3),1,0)
trans3stat [is.na(trans3stat)] <- 0
demons_stat <- trans1stat
death_stat <- trans2stat+ trans3stat

            ######## Dementia Onset time #########
dem <- rep(NA,n)
for(i in 1:n){
  if(T1_obs[i]==T1[i]) {
    dem[i] <- T1[i]
    }
  if( (T1_obs[i]==T2[i]) || (T1_obs[i]==cens0[i]) )    {
    dem[i] <- cens0[i]
    }
}
            ####### Overall Failure Time #######
```

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```
T2_obs[is.na(T2_obs)] <- 0
cens1[is.na(cens1)] <- 0
T3[is.na(T3)] <- 0
srv <- rep(NA,n)
for(i in 1:n){
  if( (T1_obs[i]==T1[i])&((T2_obs[i]!=0)==(T3[i]!=0)) ){
    srv[i]<- T1[i]+ T3[i]
  }
  if((T1_obs[i]==T1[i])&((T2_obs[i]!=0)==(cens1[i]!=0))){
    srv[i]<- cens0[i]
  }
  if((T1_obs[i]==T2[i])){
    srv[i]<- T2[i]
  }
  if((T1_obs[i]==cens0[i])){
    srv[i]<- cens0[i]
  }
}
srv_stat <- death_stat
T3[which(T3==0)] = NA # set again NA's
cens1[which(cens1==0)] = NA
T2_obs[which(T2_obs==0)] = NA
```

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