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Bivariate survival modeling: a Bayesian approach based on Copulas*

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Abstract

Copula models have been increasingly considered to model multivariate data in general and survival data in particular. In this paper we consider bivariate survival data, review some of the recent work that has been appeared for that type of model and propose a Bayesian modeling. The approach is very flexible with respect to the choice of marginal distributions and, depending on the copula model employed, it is possible to have a large spectrum of variation for the dependence parameter. Since there are several copula models proposed in the literature, we compare some of them using a descriptive method and one procedure proposed by Sahu and Dey (2000) based on predictive distributions. Our methodology is illustrated with the Diabetic Retinopathy Study (1976).

Key-words: association, censoring, predictive selection, copula models, bivariate failure times.

1 Introduction

When dealing with bivariate survival data, the assumption of independence among failure times may not be tenable so that the usual approaches may not be adequate. A well understood example, considered by Huster, Brookmeyer and Self (1989) is the Diabetic Retinopathy study (1976), that deals with diabetic patients submitted to laser therapy in one of the eyes, chosen randomly. The main endpoint is severe visual loss. It is natural to assume that there is an association between the times to event in a given patient and we want to take that into consideration to study the effect of covariates on the responses.

Several approaches have been considered to deal with multivariate survival data and the most popular are the frailty models, where one or more random effects are included in the hazard function in order to take into account the

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dependence among the observations. In this case, the marginal times are considered conditionally independent, given the frailty variable. More details on early developments of such models may be seen in Clayton (1978).

As an alternative, we may model the marginal distributions separately, in a first step, and then consider the association using copula families (marginal model approach).

Schweizer and Sklar (1983), Joe (1997) and Nelsen (1999) deal with copulas in a general framework. For survival analysis, copula based models are considered, for example, by Hougaard (1989), Oakes (1989), Shih and Louis (1995) and Gustafson, Aeschliman and Levy (2003). Given that in a copula model the marginal distributions do not depend on the choice of the dependence structure, the estimation procedure can be performed in two steps. Hougaard (1989) considers, in a first step, the estimation of each marginal using the Nelson estimator for the cumulative risk function, ignoring the dependence among failure times. In a second step a copula model is adopted and a dependence parameter, denoted by $\alpha \in \mathcal{A}$, is estimated considering fixed marginal distributions (estimated in the first step). Shih and Louis (1995) consider the two step procedure for parametric and semi-parametric models, by performing a parametric estimation and a Kaplan-Meier estimation for the marginal distributions. As in Hougaard (1989), they assume independence in this step and include the dependence parameter in the second step. Gustafson, Aeschliman and Levy (2003) apply importance sampling to fit Bayesian survival models. They mention the use of copula models for bivariate survival models considering that the marginal distributions depend on piecewise logarithm risk functions and consider a dependence structure based on Normal copulas. For computational convenience, the authors employ a multivariate Normal prior for the logarithm of the risk function and use a log-normal approximation to the log-gamma distribution.

In this work we develop a systematic modeling of bivariate survival data using copula in a Bayesian environment. We consider the class of Archimedean copulas [Genest and MacKay (1986)] for the association structure. We use either parametric or non parametric margins. The two-steps technique is applied to the already mentioned dataset. In order to compare the copula models we consider a descriptive method based on the cross-ratio function studied by Clayton (1978) and the approach of Sahu and Dey (2000) as a criteria of selection among Bayesian models.

In the next section we present the properties and relationships between bivariate survival data and models based on copulas. The Kendall's tau is included for the sake of comparison of intensity of the association estimated by the models. In Section 3 we develop the methodology of modeling and apply it to the Diabetic Retinopathy Study in Section 4. Section 5 deals with model comparison including the method based on predictive distributions.

2 Frailty models and copulas

The use of copulas is an efficient way to construct multivariate distributions from marginal distributions. In the bivariate case, this can be accomplished in the following way. Let (T_1, T_2) be continuous random variables with survival and density functions given by (S_1, S_2) and (f_1, f_2) respectively. The corresponding joint survival function based on a copula C_α, for some $\alpha \in \mathcal{A}$ can be expressed as

$$S(t_1, t_2) = C_\alpha(S_1(t_1), S_2(t_2)),$$

and the joint density function is

$$f(t_1, t_2) = c_\alpha(S_1(t_1), S_2(t_2))f_1(t_1)f_2(t_2),$$

where $c_\alpha(\cdot, \cdot)$ is a density function related to the copula C_α.

An important family of copulas is the *Archimedean Copula* (see, for example, Genest and MacKay (1986)), where

$$C_\alpha(u_1, u_2) = \phi(\phi^{-1}(u_1) + \phi^{-1}(u_2)), \quad u_1, u_2 \in [0,1], \quad \alpha \in \mathcal{A},$$

with $\phi : [0, +\infty] \to [0,1]$, $\phi(0) = 1$, $\phi' < 0$, $\phi'' > 0$.

Consider that (T_1, T_2) are non-negative random variables, representing bivariate failure times, conditionally independent given a random variable W, i.e., $S(t_1, t_2 \mid w) = S_1(t_1 \mid w)S_2(t_2 \mid w)$. Then,

$$\begin{aligned} S(t_1, t_2) &= E[S(t_1, t_2|W)] \\ &= p[q[S_1(t_1)] + q[S_2(t_2)]], \end{aligned} \tag{1}$$

where $q[S_j(t_j)] = \Lambda_j(t_j)$ corresponds to the cumulative hazard function, conditional to W, $j = 1, 2$. When $p[\cdot]$ is the Laplace transform of W and $q[\cdot]$ is the corresponding inverse, we have the bivariate frailty distribution, that is, the frailty models can be seen as a subclass of Archimedean copula (Oakes, 1989). Hence,

$$S(t_1, t_2) = \phi[\phi^{-1}(S_1(t_1)) + \phi^{-1}(S_2(t_2))].$$

The α parameter measures the "intensity" of the dependence between the failure times. The quantification of dependence can be better understood using the Kendall's tau, given by (Genest e MacKay, 1986)

$$\tau_\alpha(T_1, T_2) = 4 \int_0^1 \frac{\phi^{-1}(t)}{\phi^{-1\prime}(t)} dt + 1. \tag{2}$$

Multivariate extensions for Archimedean copulas are discussed by Joe (1997), Nelsen (1999) and Embrechts, Linskog and McNiel (2001).

Another approach is to consider the *cross-ratio function* defined by Clayton (1978),

$$\theta^*(t_1, t_2) = \frac{S(t_1, t_2)D_1D_2S(t_1, t_2)}{(D_1S(t_1, t_2))(D_2S(t_1, t_2))} = \frac{\lambda(t_1|t_2)}{\lambda(t_1|T_2 > t_2)},$$

where D_j denotes $-\partial/\partial t_j$ and $\lambda(\cdot \mid \cdot)$ are conditional hazard functions. It is a local counterpart of the Kendall's tau coefficient, i.e., it is a local measure of dependence and can be seen as a ratio between a function of the conditional probability of failure for the first component, given that the second failed at t_2 and a function of the conditional probability of a failure for the first component given that the second is at risk in t_2. Clayton (1978) considered this measure as constant in (t_1, t_2), but in most problems it may be more appropriate to assume that this local dependence decreases as time increases (e.g., when T_1 is the time of a recidive of a disease and T_2 the death time, for a given subject).

A more comprehensive discussion on $\theta^*(t_1, t_2)$, including comparisons with other measures of dependence, can be seen in Anderson, Louis, Holm and Harvald (1992).

For Archimedean copulas, Oakes (1989) showed that the cross-ratio function is such that $\theta^*(t_1, t_2) = \theta(S(t_1, t_2))$, where the function θ uniquely defines $p(\cdot)$ given in (1), with

$$q_k(v) = \int_v^1 \exp\left\{\int_z^{1-k} \frac{\theta(y)}{y}\, dy\right\} dz, \tag{3}$$

and

$$\theta(v) = \frac{-vq''[v]}{q'[v]}. \tag{4}$$

Note that in (3) the quantity k is a scale factor, irrelevant for $p(\cdot)$.

Therefore, we have that any multiplicative frailty model for bivariate survival data can be expressed by an Archimedean copula representation. This fact is illustrated for the following three families.

Clayton Family: Clayton (1978) assumes constant cross-ratio function and obtains a gamma frailty model. Considering

$$\theta(v) = \alpha + 1, \ \alpha \in \mathbf{R}^+,$$

we get, from (3) that $q[v] = \alpha^{-1}(v^{-\alpha} - 1)$ and, hence, $p[u] = (1 + \alpha u)^{-1/\alpha}$, corresponding to the Laplace transform of the gamma distribution with both parameters equal to α^{-1}. From (1) we obtain that

$$S(t_1, t_2) = \left(S_1(t_1)^{-\alpha} + S_2(t_2)^{-\alpha} - 1\right)^{-\frac{1}{\alpha}}. \tag{5}$$

Note that as $\alpha \to 0$, we get $S(t_1, t_2) = S_1(t_1)S_2(t_2)$.

The Kendall's tau coefficient evaluated from (2) is given by

$$\tau_\alpha(T_1, T_2) = \frac{\alpha}{\alpha + 2}.$$

Positive stable frailty: Considered by Hougaard (1986a,b), this frailty distribution retains the proportional hazards property of the margins. In this case, $\alpha \in (0, 1)$, is called the stability coefficient and the Laplace transform is $p[u] = \exp(-u^\alpha)$ (see, e.g., Feller, 1971) so that $q[v] = (-\ln v)^{1/\alpha}$. The cross-ratio function obtained from (4) is given by

$$\theta(v) = 1 - \frac{1-\alpha}{\alpha \ln v}.$$

In this case, such function is decreasing in for both t_1 and t_2. The joint survival function is

$$S(t_1, t_2) = \exp\left\{-[(-\ln(S_1(t_1)))^{1/\alpha} + (-\ln(S_2(t_2)))^{1/\alpha}]^\alpha\right\}, \tag{6}$$

and for $\alpha \to 1$, we obtain $S(t_1, t_2) = S_1(t_1)S_2(t_2)$. Kendall's tau is given by

$$\tau_\alpha(T_1, T_2) = 1 - \alpha.$$

For a Bayesian approach of frailty models where the random effect have positive stable distribution we may refer to Ibrahim, Chen and Sinha (2001).

Frank family: This class of distributions is considered by Frank (1979) in the context of probabilistic metric spaces. The statistical properties are studied by Nelsen (1986) and Genest (1987). The distribution function for the Frank family is given by

$$Pr\{T_1 \leq t_1, T_2 \leq t_2\} = \log_\alpha\left(1 + \frac{(\alpha^{t_1} - 1)(\alpha^{t_2} - 1)}{\alpha - 1}\right),$$

for the dependence parameter $\alpha \neq 1$. When this parameter is in $(0, 1)$, the Laplace transform is given by $p[u] = \log_\alpha(1 - (1 - \alpha)e^{-u})$ and its inverse is $q[v] = -\ln\left(\frac{1-\alpha^v}{1-\alpha}\right)$. The cross-ratio function is

$$\theta(v) = -v\frac{\ln \alpha}{1 - \alpha^v},$$

and, hence, $\theta(v) = \theta(S(t_1, t_2))$ is decreasing for t_1 and t_2.

The joint survival function is

$$S(t_1, t_2) = \log_\alpha\left(1 + \frac{(\alpha^{S_1(t_1)} - 1)(\alpha^{S_2(t_2)} - 1)}{\alpha - 1}\right), \tag{7}$$

so that as $\alpha \to 1$, $S(t_1, t_2) = S_1(t_1)S_2(t_2)$. The Kendall's tau is given by

$$\tau_\alpha(T_1, T_2) = 1 + \frac{4}{\ln \alpha}\left(\frac{1}{\ln \alpha}\int_0^{-\ln \alpha} \frac{t}{e^t - 1}\, dt + 1\right).$$

An important property of this family is that if we consider $\alpha = e^{-\gamma}$, with $\gamma \neq 0$, the association can be either positive or negative. This property makes this model very appealing for practical purposes.

The Laplace transform in this case is $p[u] = -(1/\gamma)\ln(1 + (e^{-\gamma} - 1)e^{-u})$, and $q[v] = -\ln\left(\frac{e^{-\gamma v}-1}{e^{-\gamma}-1}\right)$. The cross-ratio function is given by

$$\theta(v) = -v\frac{\gamma}{e^{-\gamma v} - 1}.$$

Note that $\theta(v) = \theta(S(t_1, t_2))$ is decreasing in t_1 and in t_2 if $\gamma > 0$, and increasing for $\gamma < 0$.

The joint survival function is

$$S(t_1, t_2) = -\frac{1}{\gamma} \ln \left(1 + \frac{(e^{-\gamma S_1(t_1)} - 1)(e^{-\gamma S_2(t_2)} - 1)}{e^{-\gamma} - 1} \right),$$

and the Kendall's tau is

$$\tau_\gamma(T_1, T_2) = 1 - \frac{4}{\gamma} \left(1 - \frac{1}{\gamma} \int_0^\gamma \frac{t}{e^t - 1}\, dt \right),$$

so that $\tau_\gamma(T_1, T_2) = -\tau_{-\gamma}(T_1, T_2)$.

3 Estimation

In the previous sections we presented the basic structure of copula models and their relationships to frailty models. Since the choice of the marginal distributions does not depend on a particular choice of a copula, it makes sense to consider the estimation of the margins and the dependence parameters separately.

In Genest, Ghoudi and Rivest (1995), it is considered a classical semi-parametric estimation for the dependence parameter, where a pseudo-likelihood is maximized and the marginal distributions are replaced by empirical distributions.

Censoring is considered by Shih and Louis (1995), and the estimation is considered in two steps: in the first one, it is assumed independence between the failure times and the marginal survival functions are estimated using the Kaplan-Meier estimation. They also consider a parametric family for the margins. In the second step, the association parameter is estimated assuming the estimated margins as fixed.

In order to introduce the estimation procedure, let (T_1, T_2) be bivariate failure times with survival functions (S_1, S_2) and densities (f_1, f_2). Also, let (C_1, C_2) be bivariate censoring times. For $i = 1, \ldots, n$ suppose that (T_{i1}, T_{i2}) and (C_{i1}, C_{i2}) are independent. For each i we have the actually observed quantities represented by random variables $Z_{ij} = \min\{T_{ij}, C_{ij}\}$ and $\delta_{ij} = I[Z_{ij} = T_{ij}]$, $j = 1, 2$.

For a Bayesian parametric estimation in two-steps, suppose that a parametric family of distributions is known for the marginal failure times and let $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ be p-vectors of parameters associated to each one of the marginal distributions. We first propose to estimate the margins separately, assuming independence between the failure times and considering prior distributions for the parameters $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ given by $\pi_j^\theta(\cdot)$, $j = 1, 2$, and the likelihood function

$$L(\boldsymbol{\theta}_j \mid \mathbf{z}_j, \boldsymbol{\delta}_j) = \prod_{i=1}^n f_{j\boldsymbol{\theta}_j}(z_{ij})^{\delta_{ij}} S_{j\boldsymbol{\theta}_j}(z_{ij})^{1-\delta_{ij}}, \qquad j = 1, 2, \tag{8}$$

obtaining the posterior distribution

$$\pi(\boldsymbol{\theta}_j \mid \mathbf{z}_j, \boldsymbol{\delta}_j) \propto L(\boldsymbol{\theta}_j \mid \mathbf{z}_j, \boldsymbol{\delta}_j)\pi_j^{\theta}(\boldsymbol{\theta}_j). \tag{9}$$

If $\widetilde{\boldsymbol{\theta}}_j$ is the estimator of $\boldsymbol{\theta}_j$ obtained from the posterior distribution (9) considering a given loss function, the estimator of α (computed in step 2) is obtained from the "posterior distribution"

$$\pi(\alpha|\mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, \widetilde{\boldsymbol{\theta}}_1, \widetilde{\boldsymbol{\theta}}_2) \propto L(\alpha|\mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, \widetilde{\boldsymbol{\theta}}_1, \widetilde{\boldsymbol{\theta}}_2)\pi^{\alpha}(\alpha), \tag{10}$$

based on the pseudo-likelihood

$$L(\alpha \mid \mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, \widetilde{\boldsymbol{\theta}}_1, \widetilde{\boldsymbol{\theta}}_2) = \prod_{i=1}^{n} f(z_{i1}, z_{i2}; \alpha)^{\delta_{i1}\delta_{i2}} \frac{\partial S(z_{i1}, z_{i2}; \alpha)}{\partial z_{i1}}^{\delta_{i1}(1-\delta_{i2})} \cdot \frac{\partial S(z_{i1}, z_{i2}; \alpha)}{\partial z_{i2}}^{\delta_{i2}(1-\delta_{i1})} S(z_{i1}, z_{i2}; \alpha)^{(1-\delta_{i1})(1-\delta_{i2})}, \tag{11}$$

where $f(\cdot\ ,\cdot)$ is the bivariate density function related to the bivariate survival function $S(\cdot\ ,\cdot)$ and assuming a prior distribution for α given by $\pi^{\alpha}(\cdot)$.

For the semi-parametric Bayesian estimation in two-steps, we estimate in the first step the marginal survival functions assuming independence. As such, let $\widetilde{S}_j$, $j = 1, 2$ be some Bayesian non-parametric estimator[1] of S_j. Then, given $(\mathbf{u}_1, \mathbf{u}_2)$, vectors with elements $(u_{i1}, u_{i2}) = (\widetilde{S}_1(Z_{i1}), \widetilde{S}_2(Z_{i2}))$, $i = 1, \ldots, n$, the estimator of α in step 2 is computed from the following "posterior distribution"

$$\pi(\alpha \mid \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, \mathbf{u}_1, \mathbf{u}_2) \propto L(\alpha \mid \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, \mathbf{u}_1, \mathbf{u}_2)\pi(\alpha), \tag{12}$$

obtained from the copula based pseudo-likelihood function

$$L(\alpha \mid \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, \mathbf{u}_1, \mathbf{u}_2) = \prod_{i=1}^{n} c_{\alpha}(u_{i1}, u_{i2})^{\delta_{i1}\delta_{i2}} \frac{\partial C_{\alpha}(u_{i1}, u_{i2})}{\partial u_{i1}}^{\delta_{i1}(1-\delta_{i2})} \cdot \frac{\partial C_{\alpha}(u_{i1}, u_{i2})}{\partial u_{i2}}^{\delta_{i2}(1-\delta_{i1})} C_{\alpha}(u_{i1}, u_{i2})^{(1-\delta_{i1})(1-\delta_{i2})}. \tag{13}$$

In the case of the joint estimation for the margins and the association parameter under the Bayesian approach, we assume that (T_1, T_2) have marginal survival and density functions $(S_{1\theta_1}, S_{2\theta_2})$ and $(f_{1\theta_1}, f_{2\theta_2})$, respectively. The joint posterior distribution can be written as

$$\pi(\alpha, \boldsymbol{\theta}_1, \boldsymbol{\theta}_2 \mid \mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2) \propto L(\alpha, \boldsymbol{\theta}_1, \boldsymbol{\theta}_2 \mid \mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2)\pi(\alpha, \boldsymbol{\theta}_1, \boldsymbol{\theta}_2), \tag{14}$$

[1]Some examples of such estimators are given in Susarla and Van Ryzin (1976), Hjört (1990) and Salinas-Torres, Pereira and Tiwari (2002).

that is based on the likelihood function

$$L(\alpha,\theta_1,\theta_2 \mid \mathbf{z}_1,\mathbf{z}_2,\delta_1,\delta_2) = \prod_{i=1}^{n} \left(c_\alpha(S_{1\theta_1}(z_{i1}),S_{2\theta_2}(z_{i2}))f_{1\theta_1}(z_{i1})f_{2\theta_2}(z_{i2})\right)^{\delta_{i1}\delta_{i2}}$$
$$\cdot \left(\frac{\partial C_\alpha(S_{1\theta_1}(z_{i1}),S_{2\theta_2}(z_{i2}))}{\partial S_{1\theta_1}(z_{i1})}\cdot(-f_{1\theta_1}(z_{i1}))\right)^{\delta_{i1}(1-\delta_{i2})}$$
$$\cdot \left(\frac{\partial C_\alpha(S_{1\theta_1}(z_{i1}),S_{2\theta_2}(z_{i2}))}{\partial S_{2\theta_2}(z_{i2})}\cdot(-f_{2\theta_2}(z_{i2}))\right)^{(1-\delta_{i1})\delta_{i2}}$$
$$\cdot\, C_\alpha(S_{1\theta_1}(z_{i1}),S_{2\theta_2}(z_{i2}))^{(1-\delta_{i1})(1-\delta_{i2})}. \qquad (15)$$

and prior distribution for $(\alpha,\boldsymbol{\theta}_1,\boldsymbol{\theta}_2)$ given by $\pi(\cdot,\cdot,\cdot)$. Note that for parametric specification of the margins it is possible to introduce covariates in each one of the components, i.e., $\theta_j = \psi(\mathbf{X}_j)$. For simplicity and to avoid restrictions in the parametric space, we consider $\psi(\mathbf{X}_j) = \exp(\mathbf{X}_j^T\boldsymbol{\beta}_j)$, with $\theta_j \in \boldsymbol{\theta}_j$, and $\boldsymbol{\beta}_j$ corresponding to the vector of unknown coefficients, related to the covariates $\mathbf{X}_j$, $j = 1,2$.

4 Application to the Diabetic Retinopathy Study

In this section we consider the copula-based Bayesian approach discussed in the previous sections in the estimation of parameters of interest for a subset of the data from the Diabetic Rethinopaty Study (1976). In particular, we consider the parametric approach in two steps and the joint estimation of margins and dependence parameters. We assume copulas based on the positive stable distribution, Frank and Clayton families to account for the dependence in the data.

The data consist of follow up times for 197 diabetic patients under 60 year of age in the United States with retinopathy. The main endpoint is severe visual loss. The main purpose of the study is to assess the efficacy of photocoagulation treatment for proliferative retinopathy. The treatment was randomly assigned to one eye of each patient. The other eye was considered as control. Therefore, the first component in the vector of times is the time up to visual loss (T_1) for the treatment eye and the second component is time up to visual loss for the control eye (T_2). The subjects could be censored, what happened for 73% of the treated eyes and 49% of the untreated eyes. Age at the onset of diabetes was considered to create 2 groups, at the cutoff point of 20 years (58% of the subjects were less than 20 years old).

Considering a frequentist approach, Huster, Brookmeyer and Self (1989) analyzed the data using the Clayton family with cross-ratio function $\theta(v) = \alpha$, $\alpha > 1$ and Weibull marginal distributions. Therneau and Grambsch (2000) considered random effect models and, from Bayesian approach, Sahu and Dey (2000) considered exponential and Weibull bivariate distributions.

In Figure 1 it is shown the Kaplan-Meier estimates for each eye and age group. There is some indication that the treatment is more effective for older patients.

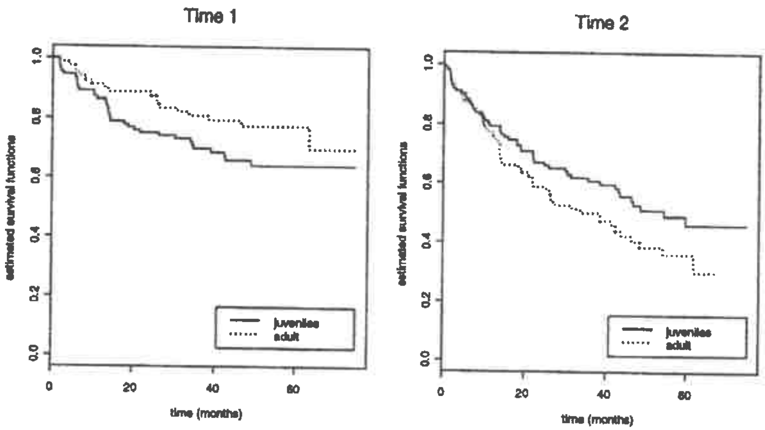

Figure 1: Kaplan-Meier estimates for the Diabetic Retinopathy Study

In order to perform a two-step parametric estimation, consider $T_j \sim$ Weibull (r_j, λ_j), with density function given by

$$f(t \mid r, \lambda) = r\lambda t^{r-1}e^{-\lambda t^r}, \qquad r > 0, \quad \lambda > 0.$$

The covariate is included through $\lambda = \exp(\beta_0 + \beta_1 X)$. Note that this is a proportional hazards model.

As prior distributions to the Weibull parameters, consider $r \sim \exp(0.001)$, $\beta_0 \sim \text{Normal}(0, 100^2)$ and $\beta_1 \sim \text{Normal}(0, 100^2)$, i.e., diffuse or vague priors.

Following Ibrahim *et al.* (2001), the posterior distribution (9), with the prior distributions considered turns out to be log-concave and the adaptative rejection algorithm (Gilks and Wild, 1992) can be used to sample from the posterior distribution, what is implemented in the computer program `WinBugs`, version 1.4 (Spiegelhalter, Thomas and Best, 2003). After a *burn-in* of 1,000 values, the results of the estimation for each time were obtained and are presented in Table 1, considering $n = 2,000$ sample values. In the table, HDP corresponds to the credibility intervals with maximum value for the posterior density that was calculated through the program `BOA`. The convergence criteria for all simulations considered in this paper is the one of Geweke (1992), also implemented in program `BOA`.

From Table 1 it is possible to see that the fit of the Weibull model for each time is satisfactory and the estimates for the parameters are significantly different from 1 and 0, respectively. Note that the effect of age in the time up to visual loss is different depending on the treatment. Also, if we consider only the treated eye the estimate for β_1 is negative, suggesting that those with later age of onset of diabetes may benefit more from the laser therapy.

Table 1: Posterior mean, |standard error| and (95% HDP), Weibull Model.

Time	r	β_0	β_1
1	0.799 |0.099|	-4.003 |0.406|	-0.525 |0.297|
	(0.623; 1.005)	(-4.801; -3.228)	(-1.079; 0.090)
2	0.835 |0.073|	-3.701 |0.306|	0.353 |0.201|
	(0.692; 0.974)	(-4.310; -3.096)	(-0.027; 0.765)

As for the step 2 of the estimation, consider the positive stable copula given in (6) plugged into the pseudo-likelihood (11) so that we get the "posterior distribution" (10) considering as prior $\alpha \sim \text{Beta}(a, b)$. The marginal survival functions to be plugged into (11) are given by Weibull distributions, with the estimators $\widetilde{r}_1$ and $\widetilde{\lambda}_1 = \exp(\widetilde{\beta}_{01}+\widetilde{\beta}_{11}X)$ for T_1, and $\widetilde{r}_2$ and $\widetilde{\lambda}_2 = \exp(\widetilde{\beta}_{02}+\widetilde{\beta}_{12}X)$ for T_2, where $(\widetilde{\theta}_1, \widetilde{\theta}_2) = (\widetilde{r}_1, \widetilde{\beta}_{01}, \widetilde{\beta}_{11}; \widetilde{r}_2, \widetilde{\beta}_{02}, \widetilde{\beta}_{12})$ are given by the corresponding posterior means, in this case, $(0.799, -4.003, -0.525; 0.835, -3.701, 0.353)$.

Therefore, it follows that the pseudo-likelihood (11) can be written as

$$L(\alpha \mid \mathbf{z}_1, \mathbf{z}_2, \delta_1, \delta_2, \widetilde{\theta}_1, \widetilde{\theta}_2) \propto \prod_{i=1}^{n} \alpha^{-\delta_{i1}\delta_{i2}} \widetilde{\lambda}_1^{\delta_{i1}/\alpha} \widetilde{\lambda}_2^{\delta_{i2}/\alpha} \left(z_{i1}^{\widetilde{r}_1\delta_{i1}} z_{i2}^{\widetilde{r}_2\delta_{i2}} \right)^{1/\alpha-1}$$
$$\cdot\, s_{\alpha i}^{\alpha(\delta_{i1}+\delta_{i2}-\delta_{i1}\delta_{i2})-\delta_{i1}-\delta_{i2}} e^{-s_{\alpha i}^{\alpha}} (1-\alpha+\alpha s_{\alpha i}^{\alpha})^{\delta_{i1}\delta_{i2}},$$

where $s_{\alpha i} = (\widetilde{\lambda}_1 z_{i1}^{\widetilde{r}_1})^{1/\alpha} + (\widetilde{\lambda}_2 z_{i2}^{\widetilde{r}_2})^{1/\alpha}$.

It follows that the "posterior distribution" for the dependence parameter is given by

$$\pi(\alpha \mid \mathbf{z}_1, \mathbf{z}_2, \delta_1, \delta_2, \widetilde{\theta}_1, \widetilde{\theta}_2) \propto \alpha^{a-\sum_i \delta_{i1}\delta_{i2}-1}(1-\alpha)^{b-1} \prod_{i=1}^{n} \widetilde{\lambda}_1^{\delta_{i1}/\alpha} \widetilde{\lambda}_2^{\delta_{i2}/\alpha} \tag{16}$$
$$\cdot \left(z_{i1}^{\widetilde{r}_1\delta_{i1}} z_{i2}^{\widetilde{r}_2\delta_{i2}} \right)^{1/\alpha-1} s_{\alpha i}^{\alpha(\delta_{i1}+\delta_{i2}-\delta_{i1}\delta_{i2})-\delta_{i1}-\delta_{i2}}$$
$$\cdot\, e^{-s_{\alpha i}^{\alpha}} (1-\alpha+\alpha s_{\alpha i}^{\alpha})^{\delta_{i1}\delta_{i2}}.$$

Employing this expression as an input in `WinBugs` with $\alpha \sim \text{Beta}(1, 1)$, and using the *slice sampling* method to sample from the posterior (see Neal, 2003), we obtain, after a *burn-in* of 1,000 values and a sample of size 2,000, the posterior mean for the dependence parameter as 0.796, with standard error 0.051 and credibility interval 95% HDP equals to $(0.704, 0.902)$. That implies a Kendall's tau equals to 0.204.

Table 2 presents the results of the two-step estimation for the positive stable copula, in addition to the results for the copulas of Frank (7) and Clayton (5) families. We considered samples of size 2,000 and a *burn-in* of 1,000 values. For the Frank copula, we considered as prior $\alpha \sim \text{Beta}(1,1)$, and for the Clayton copula, $\alpha \sim \text{Gamma}(1, 0.001)$.

Table 2: Posterior mean, [standard error] and (95% HDP), two-steps estimation procedure.

copula	α	τ_α
Positive stable	0.796 [0.051]	0.204 [0.051]
	(0.704; 0.902)	(0.098; 0.296)
Frank	0.153 [0.101]	0.218 [0.060]
	(0.027; 0.358)	(0.106; 0.334)
Clayton	1.061 [0.336]	0.339 [0.073]
	(0.422; 1.718)	(0.187; 0.469)

For the joint estimation procedure we also consider $T_j \sim \text{Weibull}(r_j, \lambda_j)$, with $\lambda_j = \exp(\beta_{0j} + \beta_{1j}X)$, $j = 1, 2$. For the positive stable copula, the likelihood function given in (14) can be written as

$$L(\alpha, r_1, r_2, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2 \mid \mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, X) \propto \prod_{i=1}^{n} \alpha^{-\delta_{i1}\delta_{i2}} e^{(\delta_{i1}/\alpha)(\beta_{01}+\beta_{11}X)} e^{(\delta_{i2}/\alpha)(\beta_{02}+\beta_{12}X)}$$
$$\cdot\, z_{i1}^{\delta_{i1}(r_1/\alpha-1)} z_{i2}^{\delta_{i2}(r_2/\alpha-1)} r_1^{\delta_{i1}} r_2^{\delta_{i2}} s_{\alpha i}^{\alpha(\delta_{i1}+\delta_{i2}-\delta_{i1}\delta_{i2})-\delta_{i1}-\delta_{i2}} e^{-s_{\alpha i}^{\alpha}} (1-\alpha+\alpha s_{\alpha i}^{\alpha})^{\delta_{i1}\delta_{i2}},$$

where $s_{\alpha i} = (z_{i1}^{r_1} e^{(\beta_{01}+\beta_{11}X)})^{1/\alpha} + (z_{i2}^{r_2} e^{(\beta_{02}+\beta_{12}X)})^{1/\alpha}$, and $\boldsymbol{\beta}_j = (\beta_{0j}, \beta_{1j})$.

Considering as priors $\alpha \sim \text{Beta}(a, b)$, $r_j \sim \exp(r_{0j})$, $\beta_{0j} \sim \text{Normal}(c_{0j}, d_{0j}^2)$ and $\beta_{1j} \sim \text{Normal}(c_{1j}, d_{1j}^2)$, it follows that the posterior joint distribution for the parameters $(\alpha, r_1, r_2, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2)$ is

$$\pi(\alpha, r_1, r_2, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2 \mid \mathbf{z}_1, \mathbf{z}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2, X) \propto \alpha^{a-\sum_i \delta_{i1}\delta_{i2}-1}(1-\alpha)^{b-1} \tag{17}$$
$$\cdot\, e^{-r_{01}r_1 - r_{02}r_2} e^{\sum_i (\beta_{01}+\beta_{11}X_i)\delta_{i1}/\alpha - (\beta_{01}^2 - 2\beta_{01}c_{01})/2d_{01}^2 - (\beta_{11}^2 - 2\beta_{11}c_{01})/2d_{11}^2}$$
$$\cdot\, e^{\sum_i (\beta_{02}+\beta_{12}X_i)\delta_{i2}/\alpha - (\beta_{02}^2 - 2\beta_{02}c_{02})/2d_{02}^2 - (\beta_{12}^2 - 2\beta_{12}c_{02})/2d_{12}^2} \prod_{i=1}^{n} z_{i1}^{\delta_{i1}(r_1/\alpha-1)}$$
$$\cdot\, z_{i2}^{\delta_{i2}(r_2/\alpha-1)} r_1^{\delta_{i1}} r_2^{\delta_{i2}} s_{\alpha i}^{\alpha(\delta_{i1}+\delta_{i2}-\delta_{i1}\delta_{i2})-\delta_{i1}-\delta_{i2}} e^{-s_{\alpha i}^{\alpha}} (1-\alpha+\alpha s_{\alpha i}^{\alpha})^{\delta_{i1}\delta_{i2}}.$$

Implementation of the posterior distribution (17) can be performed into `WinBugs`, with $\alpha \sim \text{Beta}(1,1)$, $r_j \sim \exp(0.001)$ and $\beta_{kj} \sim \text{Normal}(0, 100^2)$, $k = 0, 1$, $j = 1, 2$, using the *slice sampling* method and the Metropolis-Hastings algorithm to sample from that distribution. The results are presented in Tables 3 and 4. The estimates were obtained after a *burn-in* of 4,000 values and a sample of size 2,000. The tables also show the estimates for the Frank and Clayton copulas, considering the same specifications for the priors presented in the two-step estimation procedure.

Table 3: Posterior mean, [standard error] and (95% HDP), joint estimation.

copula	β_{01}	β_{11}	β_{02}	β_{12}
Pos.Stable	-3.957 [0.400]	-0.441 [0.278]	-3.641 [0.296]	0.355 [0.197]
	(-4.657, -3.103)	(-0.987, 0.112)	(-4.227, -3.101)	(-0.043, 0.728)
Frank	-4.075 [0.415]	-0.474 [0.293]	-3.709 [0.303]	0.372 [0.197]
	(-4.934, -3.320)	(-1.060, 0.044)	(-4.333, -3.143)	(-0.015, 0.765)
Clayton	-4.051 [0.407]	-0.477 [0.290]	-3.710 [0.311]	0.383 [0.200]
	(-4.942, -3.335)	(-1.071, 0.075)	(-4.352, -3.130)	(-0.018, 0.765)

Table 4: Posterior mean, [standard error] and (95% HDP), joint estimation.

copula	r_1	r_2	α	τ_α
Positive stable	0.782 [0.096]	0.818 [0.071]	0.792 [0.057]	0.208 [0.057]
	(0.604, 0.968)	(0.681, 0.957)	(0.682, 0.902)	(0.098, 0.319)
Frank	0.815 [0.100]	0.834 [0.073]	0.158 [0.103]	0.215 [0.061]
	(0.632, 1.012)	(0.694, 0.985)	(0.018, 0.350)	(0.102, 0.333)
Clayton	0.810 [0.098]	0.833 [0.073]	1.063 [0.352]	0.339 [0.075]
	(0.630, 1.011)	(0.695, 0.981)	(0.352, 1.723)	(0.188, 0.483)

From the previous tables we note that there is a significant positive association between the times up to visual loss. Since the variability of the Kendall's tau obtained from the two-stage estimation, for the three copulas considered, is lesser than the obtained from the joint estimation procedure, we can say that the estimation of association it is better carried out when the margins are extracted and then a copula is assumed.

The covariate has different effects depending on the treatment, as was noted earlier by studying the Kaplan-Meier estimates. In particular, if both estimates for the covariate's effects are compared respect to the estimation procedure, we can see that this effect is subestimated, and with a greater variability, when is assumed independence among the failure times.

We note that the figures presented in Table 3 and 4 for the Clayton copula are similar to those obtained by Huster *et al.* (1989), which assumed that the shape parameters of the Weibull distributions were equal for both times, i.e., $r_1 = r_2 = r$ and, used the Clayton copula with cross-ratio function equals to $\theta(v) = \alpha$, $\alpha > 1$, considering the same covariates as defined in this paper.

5 Model comparison

In the previous sections we considered several copula models to account for the dependence between two failure times. In order to help us to decide which model is more appropriate for the data, we consider a descriptive method based on the cross-ratio function studied by Clayton (1978) and a predictive model selection method discussed in Sahu and Dey (2000).

In Section 2 we presented the cross-ratio function $\theta^*(t_1, t_2)$ as a function of the bivariate survival function for the three copula models under investigation. For the Clayton copula this function is constant and for the two others models (positive stable and Frank), it is decreasing in t_1 and in t_2. With the purpose of getting a better picture of the association varying across the time we examine graphically the posterior cross-ratio function for the three copula models and compare to the nonparametric one. The posterior cross-ratio function is based on a parametric dependency obtained from the two-stage procedure and Kaplan-Meier margins. The nonparametric estimate is based on a discrete version of the cross-ratio function given in Oakes (1989).

Figures 2 to 5 presents the posterior cross-ratio function estimates for each copula and the nonparametric alternative of Oakes (1989). Figures 2 and 3 correspond to adults patients and Figures 4 and 5 to juveniles patients. In each graphics it is shown the estimates of $\theta^*(t_1, t_2)$ as a function of t_j, for selected values of t_k, with $k, j = 1, 2,\ k \neq j$.

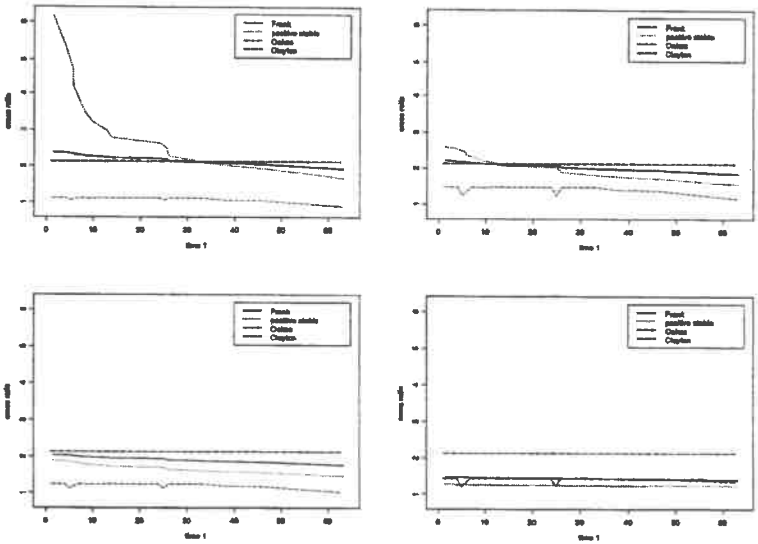

Figure 2: Cross-ratio function estimates for the Diabetic Retinopathy Study, $t = (t_1, t_2 = 1)$ (top left), $t = (t_1, t_2 = 6)$ (top right), $t = (t_1, t_2 = 12)$ (bottom left) and $t = (t_1, t_2 = 48)$ (bottom right), adults patients

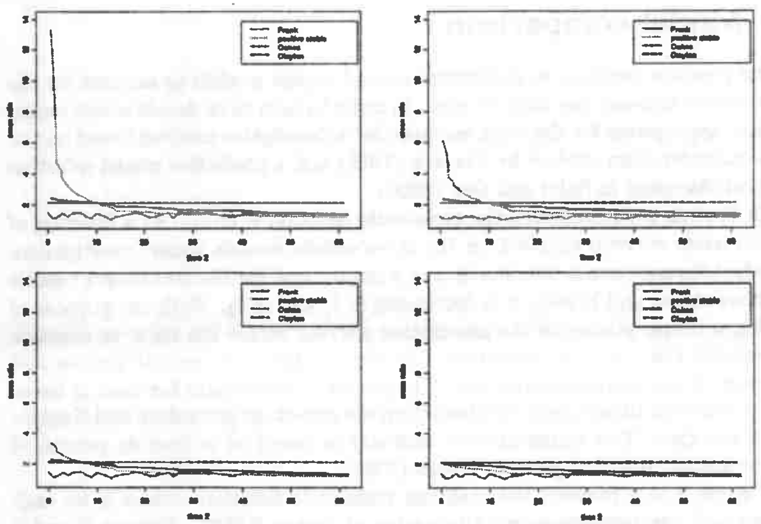

Figure 3: Cross-ratio function estimates for the Diabetic Retinopathy Study, $t = (t_1 = 1, t_2)$ (top left), $t = (t_1 = 6, t_2)$ (top right), $t = (t_1 = 12, t_2)$ (bottom left) and $t = (t_1 = 48, t_2)$ (bottom right), adults patients

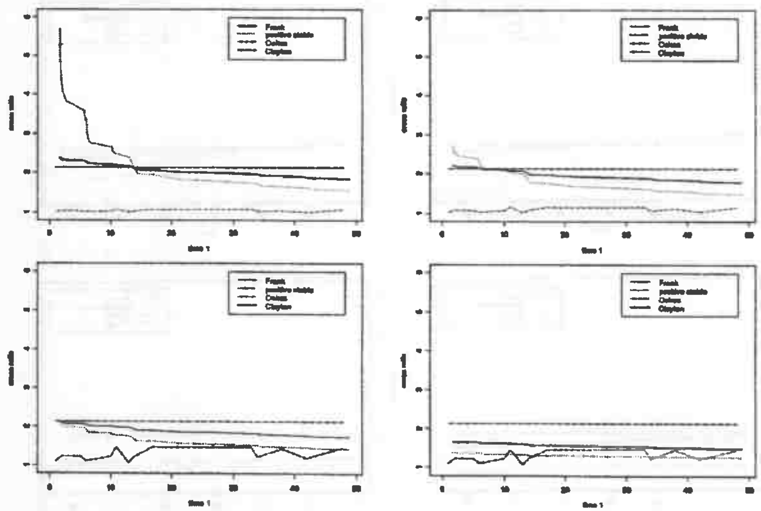

Figure 4: Cross-ratio function estimates for the Diabetic Retinopathy Study, $t = (t_1, t_2 = 1)$ (top left), $t = (t_1, t_2 = 6)$ (top right), $t = (t_1, t_2 = 12)$ (bottom left) and $t = (t_1, t_2 = 48)$ (bottom right), juveniles patients

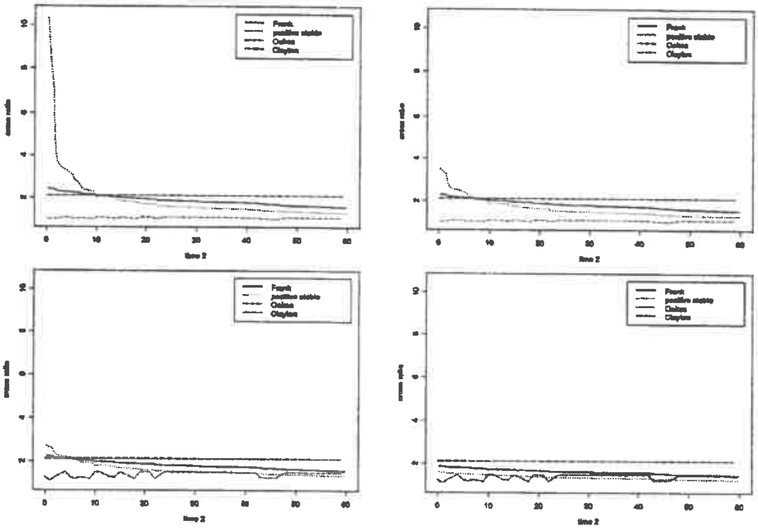

Figure 5: Cross-ratio function estimates for the Diabetic Retinopathy Study, $t = (t_1 = 1, t_2)$ (top left), $t = (t_1 = 6, t_2)$ (top right), $t = (t_1 = 12, t_2)$ (bottom left) and $t = (t_1 = 48, t_2)$ (bottom right), juveniles patients

It is possible to observe from the graphics, as much for the group of adults patients as for juvenile patients, that when the smaller occurrence times are considered (failure times in majority, see Figure 1) the nearest model to the non parametric is the model based in Clayton copula.

If the bigger times are considered (mainly censored times), it is seen that the Frank copula has a better performance regarding to the Oakes's estimator. Finally, in the remaining times, the best performance is given by the estimator obtained from the stable positive copula.

The predictive model selection approach is based on a criteria proposed by Gelfand (1996) and generalized by Sahu and Dey (2000) for censored data. This criteria is given by

$$D = \sum_{i=1}^{n} tr(\Sigma_i) + \sum_{i=1}^{n} (\boldsymbol{\mu}_i - \mathbf{v}_i)^T (\boldsymbol{\mu}_i - \mathbf{v}_i), \tag{18}$$

where $\boldsymbol{\mu}_i$ and $\boldsymbol{\Sigma}_i$ denote the mean and covariance of the predictive posterior distribution of future observations for the considered model and $\mathbf{v}_i$ corresponds to the failure time if the i-th observation is an actual failure, or it is the maximum between the censoring time and $\boldsymbol{\mu}_i$, if the i-th time corresponds to a censoring. This criteria is derived based on the expected value of the predictive distribution,

$$\pi(\mathbf{t}_{rep}|\mathbf{t}_{obs}) = \int \pi(\mathbf{t}_{rep} \mid \theta)\pi(\theta|\mathbf{t}_{obs}),$$

considering the quadratic error loss function

$$L = (\mathbf{t}_{rep} - \mathbf{t}_{obs})^T(\mathbf{t}_{rep} - \mathbf{t}_{obs}),$$

where $\mathbf{t}_{rep}$ denotes a set of future observations for the considered model, and $\mathbf{t}_{obs}$ are the observed failure times.

Table 5 contains the values obtained from (18) for a positive stable, Clayton and Frank copulas. EEPII and WEPII correspond to models with exponential and Weibull margins in a two-step estimation procedure and EEP and WEP correspond to the same marginal models for a joint estimation procedure. Analogously, ECLII, WCLII, ECL, WCL correspond to models based in Clayton copula and EFRII, WFRII, EFR and WFR correspond to models considering the Frank copula. The values of D computed by the same dataset of retinopathy by Sahu and Dey (2000) are also presented. They considered a gamma frailty model with hazard function Weibull (FRL), a bivariate exponential model (EMO) and a bivariate Weibull model (WMO). We refer to Sahu and Dey (2000) for more details on those models.

Table 5: Selection criteria for the retinopathy data

EEPII	WEPII	EEP	WEP
1,166.12	1,537.58	1,181.32	1,604.11
ECLII	WCLII	ECL	WCL
1,165.92	1,560.87	1,171.02	1,559.80
EFRII	WFRII	EFR	WFR
1,170.96	1,563.67	1,173.04	1,520.38
	FRL	EMO	WMO
	1,529.32	1,174.22	1,584.72

From the table we observe that for the exponential models, ECLII has the smallest value of D, followed by EEPII and EFRII models. For the models with Weibull margins the best fit is obtained by WFR, followed by WEPII and WCL. Note that in this particular dataset the two-step procedure estimation has the best fit when considering the D criteria for exponential margins. Hence, we can conclude from the predictive selection criteria and from the Figures 2–5, that the model based on the Clayton copula characterizes better the data, in particular, the failure times data.

6 Discussion

In this paper we present the Bayesian counterpart to the frequentist work of Shih and Louis (1995).

A full estimation procedure was considered for the case in which the main interest is to study the effect of covariates in the presence of dependence among bivariate failure times.

The approach based on copula is very flexible with respect to the choice of the marginal distributions. Further, the class of archimedean copulas leads to an interpretation of the cross-ratio function as a local dependence measure. This interpretability of the cross-ratio function and the predictive selection criteria allows as useful setup for the choice of a particular archimedean copula and marginal distributions.

A full estimation procedure considering nonparametric Bayesian margins and a copula for modeling the dependence structure is an area of current research.

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