

Analysis of Bivariate Survival Data based on copulas with log Generalized Extreme Value marginals

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Abstract

This chapter introduces a novel copula based methodology to analyze right censored bivariate survival data using flexible log-GEV marginals. Copulas are quite popular in high-dimensional data modeling as they allow modeling and estimating the parameters of the marginal distributions separately from the dependence parameter of the copula. The Clayton copula structure has been used to represent the dependency between the log survival times for this chapter. We propose an empirical Bayes method for estimating the dependency parameter which is more efficient than the other existing Bayesian methodologies.

Keywords: Bivariate survival, Clayton copula, DRS, Empirical Bayes, GEV, Importance Sampling, Metropolis Hastings

1 Introduction

During the last two decades, there have been a growing interest in modeling paired data or bivariate survival data which arises primarily from the field of medicine. For example, it has been medically observed that incidence of one disease often increases the risk of another in a patient affected by Human Immunodeficiency Virus. Diabetic retinopathy is the leading cause of blindness in United States. It has been observed that once one eye gets affected, the chances of the other eye contracting

the disease increases many fold. Clayton (1978) and Oakes (1982) were the first to develop a fully parametric approach to model bivariate survival data. In Huster et al. (1989), the authors extended the fully parametric approach to include censored bivariate paired data with covariates. Since then, between year 1985 to year 1999, several methods using both parametric and semiparametric modeling techniques have been introduced and developed by authors such as: Nelson (1986), Oakes (1986), Shih and Louis (1995), Genest and Rivest (1993) and Wang and Wells (2000) among others. Employing copula to model dependency between marginal survival data have been particularly popular since the univariate marginals do not depend on the choice of the dependency structure and can be consequently estimated separately from the dependency parameters.

Bayesian methods to model bivariate survival data started developing since early 20's. In Sahu and Dey (2000), the authors used a Bayesian frailty model to model bivariate survival data with covariates. Chen et al. (2002) introduced a Bayesian model for right censored bivariate survival data with cure fraction. Another interesting work is by Shemyakin and Youn (2000), where the authors develop a Bayesian joint survival model for life insurance data. In Romeo and Tanaka (2006), the authors used a copula based Bayesian framework to model bivariate survival data. Since choosing an appropriate prior for the dependency parameter of any copula is not intuitive, the authors put a β -prior on the Kendall's τ instead. Although these methods are fairly attractive since they are mostly identifiable and produces smooth survival functions, they are not computationally time efficient. Running MCMC algorithm can be expensive especially when for each individual value of selected τ , MCMC chains for the univariate marginal parameters have to be run. In this chapter, we propose a novel empirical Bayes method of estimating the dependency parameter. Unlike previous works, our method requires only two runs of MCMC chain for the marginal parameters. Our goal is to develop a Bayesian framework for inference and estimation of the marginals and the dependence parameter following the approach outlined in Doss (2010) and Roy (2014) using Clayton copula structure and the flexible Generalized Extreme Value (GEV) distribution to model the marginal distributions. The chapter is organized as follows: Section 1 provides a brief introduction to the problem and current methods are outlined including their roadblocks and restrictions. In section 2, the concept of copula, their properties and different types of copulas have been discussed. In section 3, the model settings are described. Our proposed method is outlined in details in section 4. Section 5 provides

background and results of simulation studies. A real data analysis is provided in the section 6. The chapter concludes with future work directions and limitations.

2 A Brief Overview of Copula

Copula “couples” a joint cumulative density function to its marginal distributions and hence the name. Essentially a copula is a bivariate distribution with uniform marginals. The Sklar’s theorem (Nelson (1999), pg:41) defines a copula structure in the following way:

Given a m -dimensional joint cdf F with marginal cdfs F_1, F_2, \dots, F_m , there exists an m -copula C such that,

$$F(x_1, x_2, \dots, x_m) = C(F_1(x_1), F_2(x_2), \dots, F_m(x_m)) \quad (1)$$

for all $(x_1, x_2, \dots, x_m) \in \mathbb{R}^m$. If the marginal distributions are continuous, then C is unique, otherwise C is uniquely determined on $\text{Range } F_1 \times \dots \times \text{Range } F_m$. Conversely, if C is an m -copula and F_1, F_2, \dots, F_m are cdfs, then F defined by (1) is an m -dimensional cdf with marginal cdfs F_1, F_2, \dots, F_m .

Nelson in his book “Introduction to Copulas (1999)” defined the properties of a m -dimensional copula on page 40:

1. For every $u = (u_1, u_2, \dots, u_m) \in [0, 1]^m$, $C(u) = 0$ if at least one element $u_i = 0$.
2. If all coordinates of u are 1, except u_i , then $C(u) = u_i$.
3. For every $a = (a_1, a_2, \dots, a_m), b = (b_1, b_2, \dots, b_m) \in [0, 1]^m$, such that $a_i \leq b_i$ for all $i = 1, 2, \dots, m$,

$$\Delta_{a_m}^{b_m} \Delta_{a_{m-1}}^{b_{m-1}} \dots \Delta_{a_1}^{b_1} C(u) \geq 0, \quad (2)$$

where $\Delta_{a_k}^{b_k}$ defines the first order differences as

$$\Delta_{a_k}^{b_k} C(u) = C(u_1, \dots, u_{k-1}, b_k, u_{k+1}, \dots, u_m) - C(u_1, \dots, u_{k-1}, a_k, u_{k+1}, \dots, u_m).$$

The first and third properties are satisfied if $C(u)$ is a distribution function. The second property is satisfied if the marginal distributions of C are uniform. Using copulas to model dependent bivariate data is advantageous due to many reasons. Copula structure being extremely flexible, allows non-linear dependence between the two associated marginal distributions, or to measure dependence for

heavy tailed distributions. It can be used under fully parametric, semi parametric or non parametric setting and also allows for faster computations. Several families of copula have been studied in details, for example: Gaussian copulas, Clayton copulas, Frank copula, Gumbel copula etc. Copula's are chosen depending on the tail concentrations. In this chapter, Clayton copula is chosen to develop the framework and model the Diabetes Retinopathy Study data, since the copula has a nice relationship with the Kendall's τ . Further, Romeo and Tanaka (2006) have shown that Clayton copula performs reasonably well on the same real data.

3 Marginal Distributions and Bivariate Survival Model

3.1 Generalized Extreme Value Distribution as Marginal

Roy et al. (2013) introduced modeling univariate right censored survival data with a cure fraction using Generalized Extreme Value (GEV) distribution (See also Roy and Dey (2014)). The GEV distribution characterized by three parameters is extremely flexible and also achieves proper posterior distribution with a variety of mild to diffuse priors. Commonly used lifetime distributions such as the Exponential, the Rayleigh and the Weibull are all special cases of the minima Generalized Extreme Value distribution.

If we assume a GEV distribution for $\log T$, where T is a marginal survival time, i.e., $\log T \sim GEV(\mu, \sigma, \xi)$, then the corresponding density and survival functions can be defined respectively as:

$$f(t|\xi) = \begin{cases} \frac{1}{\sigma t} (1 + \xi \frac{(\log t - \mu)}{\sigma})_+^{\frac{1}{\xi} - 1} \exp[-(1 + \xi \frac{(\log t - \mu)}{\sigma})_+^{\frac{1}{\xi}}] & \text{if } \xi \neq 0 \\ \frac{1}{\sigma t} \exp(\frac{\log t - \mu}{\sigma}) \exp[-\exp(\frac{\log t - \mu}{\sigma})] & 0 < t < \infty; \text{if } \xi = 0. \end{cases}$$

$$S(t|\xi) = \begin{cases} \exp[-(1 + \xi \frac{(\log t - \mu)}{\sigma})_+^{\frac{1}{\xi}}] & \text{if } \xi \neq 0 \\ \exp[-\exp(\frac{\log t - \mu}{\sigma})] & \text{if } \xi = 0, \end{cases}$$

where $\mu \in \mathbb{R}$, $\sigma \in \mathbb{R}^+$ and $\xi \in \mathbb{R}$ are the location, scale and shape parameters respectively. The above distribution was called mGEV in Roy et al. (2013).

3.2 Bivariate Model

Let (T_1, T_2) denote failure times of two events for each subject or failure times of members of each group. Marginally we assume that

$$\log T_i \sim \text{GEV}(\mu_i, \sigma_i, \xi_i) \quad (3)$$

for $i = 1, 2$. The joint survival function based on a copula $C_\phi, \phi \in G$ is given by

$$S(\log t_1, \log t_2) = C_\phi(S_1(\log t_1), S_2(\log t_2)), \quad (4)$$

where $S_1(\log t_1)$, and $S_2(\log t_2)$ are the marginal survival functions obtained from (3). The parameter ϕ measures the “intensity” of dependence between the individual failure times. We use the popular bivariate copula from the Clayton family which is given by

$$C_\phi(u_1, u_2) = \max\{(u_1^{-\phi} + u_2^{-\phi} - 1)^{-1/\phi}, 0\}. \quad (5)$$

In this case $G = (-1, \infty) \setminus \{0\}$. One of the major goals while studying bivariate data is to gauge the direction and extent of the association between the two variables. When linear correlation coefficient is not a valid measure of association due to nonlinearity of the association, Kendall’s τ and Spearman’s ρ are two most popular measures of pairwise concordance (Nelson, 1999, chapter 5). Certain families of copula have very nice relationship with Kendall’s τ . For example, in case of Clayton copula family, the Kendall’s τ measure is given by

$$\tau_\phi = \frac{\phi}{\phi + 2} \in (-1, 1).$$

Due to the easy computation and interpretability, Clayton copula remains one of the widely used copula families. For proof of the above relationship, see Nelson (1999), pages 162–163.

3.3 Model Settings

Let T_{ij} (C_{ij}) be the survival (censoring) time of the j th event for the i th subject, $j = 1, 2; i = 1, 2, \dots, n$. We assume (T_{i1}, T_{i2}) and (C_{i1}, C_{i2}) are independent for $i = 1, 2, \dots, n$. We also assume that (T_{i1}, T_{i2}) , are iid with common pdf $f(t_1, t_2)$ and survival time $S(t_1, t_2)$, $i = 1, 2, \dots, n$. The observed data is $(\mathbf{y}_1, \mathbf{y}_2, \boldsymbol{\delta}_1, \boldsymbol{\delta}_2)$, where $\mathbf{y}_1 = (y_{11}, y_{21}, \dots, y_{n1})$, $\mathbf{y}_2 = (y_{12}, y_{22}, \dots, y_{n2})$, $\boldsymbol{\delta}_1 = (\delta_{11}, \delta_{21}, \dots, \delta_{n1})$, and $\boldsymbol{\delta}_2 = (\delta_{12}, \delta_{22}, \dots, \delta_{n2})$, with $y_{ij} = \log(\min(T_{ij}, C_{ij}))$ and $\delta_{ij} = I(y_{ij} =$

$\log T_{ij}$ for $j = 1, 2; i = 1, 2, \dots, n$. Let $\mathbf{y} = (y_1, y_2)$ and $\boldsymbol{\delta} = (\delta_1, \delta_2)$. Let (S_1, S_2) and (f_1, f_2) be the marginal survival and density functions of GEV distribution as given in Section 3. Let $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ be the parameters associated with each of the marginal distribution. So, $\boldsymbol{\theta}_i = (\mu_i, \sigma_i, \xi_i)$, $i = 1, 2$. where μ, σ , and ξ are location, scale and shape parameters respectively of the marginal GEV distributions.

Then the complete data likelihood function (joint distribution) of the parameters $(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \phi)$ can be written as (see also Chen et al. (2012)):

$$\begin{aligned}
L(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \phi | \mathbf{y}, \boldsymbol{\delta}) &= \prod_{i=1}^n (f(y_{i1}, y_{i2}))^{\delta_{i1}\delta_{i2}} \left(\frac{\partial S(y_{i1}, y_{i2})}{\partial y_{i1}} \right)^{\delta_{i1}(1-\delta_{i2})} \left(\frac{\partial S(y_{i1}, y_{i2})}{\partial y_{i2}} \right)^{(1-\delta_{i1})\delta_{i2}} \\
&\quad (S(y_{i1}, y_{i2}))^{(1-\delta_{i1})(1-\delta_{i2})} \\
&= \prod_{i=1}^n (c_\phi(S_{1\boldsymbol{\theta}_1}(y_{i1}), S_{2\boldsymbol{\theta}_2}(y_{i2})) f_{1\boldsymbol{\theta}_1}(y_{i1}), f_{2\boldsymbol{\theta}_2}(y_{i2}))^{\delta_{i1}\delta_{i2}} \\
&\quad \left(-\frac{\partial C_\phi(S_{1\boldsymbol{\theta}_1}(y_{i1}), S_{2\boldsymbol{\theta}_2}(y_{i2}))}{\partial S_{1\boldsymbol{\theta}_1}(y_{i1})} (-f_{1\boldsymbol{\theta}_1}(y_{i1})) \right)^{\delta_{i1}(1-\delta_{i2})} \\
&\quad \left(-\frac{\partial C_\phi(S_{1\boldsymbol{\theta}_1}(y_{i1}), S_{2\boldsymbol{\theta}_2}(y_{i2}))}{\partial S_{2\boldsymbol{\theta}_2}(y_{i2})} (-f_{2\boldsymbol{\theta}_2}(y_{i2})) \right)^{(1-\delta_{i1})\delta_{i2}} \\
&\quad (C_\phi(S_{1\boldsymbol{\theta}_1}(y_{i1}), S_{2\boldsymbol{\theta}_2}(y_{i2})))^{(1-\delta_{i1})(1-\delta_{i2})}, \tag{6}
\end{aligned}$$

where $c_\phi(\cdot, \cdot)$ is the second derivative of the copula function $C_\phi(\cdot, \cdot)$ defined in equation 5.

4 Proposed Methodology

There are mainly two developed approaches to solve the estimation problem. Shih and Louis (1995) proposed a two step procedure. They first assume independence between failure times and estimate the marginals and then estimate the dependency parameter ϕ assuming the estimated marginals are fixed. The Bayesian approach simultaneously estimates $(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \phi)$ from joint posterior distribution. The issue with the first approach is the unnatural assumption of independence to begin with. In the second case finding appropriate prior of ϕ is difficult because of complicated range depending on which copula family is being used. The dependency parameter for Clayton copula, for example, has the range $(-1, \infty) \setminus \{0\}$.

We start by putting appropriate priors on $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$. Let $\pi(\boldsymbol{\theta}_1)$ and $\pi(\boldsymbol{\theta}_2)$ be the priors on $\boldsymbol{\theta}_1$ and

θ_2 . Then for fixed ϕ , the joint posterior density of θ_1 and θ_2 is given by,

$$\pi_\phi(\theta_1, \theta_2 | \mathbf{y}, \delta) = \frac{L(\theta_1, \theta_2, \phi | \mathbf{y}, \delta) \pi(\theta_1) \pi(\theta_2)}{m_\phi(\mathbf{y}, \delta)}, \quad (\theta_1, \theta_2) \in \Theta \quad (7)$$

where $m_\phi(\mathbf{y}, \delta)$ is the normalizing constant given by

$$m_\phi(\mathbf{y}, \delta) = \int_{\Theta} L(\theta_1, \theta_2, \phi | \mathbf{y}, \delta) \pi(\theta_1) \pi(\theta_2) d\theta_1 d\theta_2.$$

Following Roy (2014), we select that value of $\phi \in G$ which maximizes the marginal likelihood of the data $m_\phi(\mathbf{y}, \delta)$. Note that $m_\phi(\mathbf{y}, \delta)$ is not available in closed form and needs to be estimated. Instead of maximizing $m_\phi(\mathbf{y}, \delta)$, we choose to maximize $a \times m_\phi(\mathbf{y}, \delta)$ as it is often easier to estimate. We choose “ a ” as $1/m_{\phi_1}(\mathbf{y}, \delta)$ for a pre fixed value ϕ_1 . Then by ergodic theorem, we have a simple importance sampling consistent estimator of $B_{\phi, \phi_1} := \frac{m_\phi(\mathbf{y}, \delta)}{m_{\phi_1}(\mathbf{y}, \delta)}$.

$$\frac{1}{N} \sum_{l=1}^N \frac{L(\theta_1^{(l)}, \theta_2^{(l)}, \phi | \mathbf{y}, \delta)}{L(\theta_1^{(l)}, \theta_2^{(l)}, \phi_1 | \mathbf{y}, \delta)} \xrightarrow{a.s.} \int_{\Theta} \frac{L(\theta_1, \theta_2, \phi | \mathbf{y}, \delta)}{L(\theta_1, \theta_2, \phi_1 | \mathbf{y}, \delta)} \pi_{\phi_1}(\theta_1, \theta_2 | \mathbf{y}, \delta) d\theta_1 d\theta_2 = \frac{m_\phi(\mathbf{y}, \delta)}{m_{\phi_1}(\mathbf{y}, \delta)}, \quad (8)$$

as $N \rightarrow \infty$ where $\{\theta_1^{(l)}, \theta_2^{(l)}\}_{l=1}^N$ is a single Harris ergodic Markov chain with stationary density $\pi_{\phi_1}(\theta_1, \theta_2 | \mathbf{y}, \delta)$. So one *single* MCMC sample $\{\theta_1^{(l)}, \theta_2^{(l)}\}_{l=1}^N$ from $\pi_{\phi_1}(\theta_1, \theta_2 | \mathbf{y}, \delta)$ is used to estimate B_{ϕ, ϕ_1} for all $\phi \in G$. Once the association parameter is estimated, θ_1 and θ_2 are estimated using Markov Chain (Gibb’s sampler) samples from $\pi_{\hat{\phi}}(\theta_1, \theta_2 | \mathbf{y}, \delta)$.

4.1 A two-stage procedure

Roy (2014) mentioned that the above estimate of B_{ϕ, ϕ_1} although simple is often unstable. To remove this instability introduced due to an arbitrary choice of ϕ_1 , following Doss (2010), Roy (2014) used generalized importance sampling method. Let $\phi_1, \phi_2, \dots, \phi_m \in G$ be m appropriately chosen skeleton points. See Roy et al. (2014) for a discussion on how to choose the skeleton points. Let $\{\theta_1^{(j;l)}, \theta_2^{(j;l)}\}_{l=1}^{N_j}$ be a Markov chain with stationary density $\pi_{\phi_j}(\theta_1, \theta_2 | \mathbf{y}, \delta)$ for $j = 1 \dots, m$. Define $r_k = m_{\phi_k}(\mathbf{y}, \delta)/m_{\phi_1}(\mathbf{y}, \delta)$ for $k = 2, 3, \dots, m$, with $r_1 = 1$. Then B_{ϕ, ϕ_1} is consistently estimated by

$$\hat{B}_{\phi, \phi_1} = \sum_{j=1}^m \sum_{l=1}^{N_j} \frac{L(\theta_1^{(j;l)}, \theta_2^{(j;l)}, \phi | \mathbf{y}, \delta)}{\sum_{k=1}^m N_k L(\theta_1^{(j;l)}, \theta_2^{(j;l)}, \phi_k | \mathbf{y}, \delta) / \hat{r}_k}, \quad (9)$$

where $\hat{r}_1 = 1$, \hat{r}_k , $k = 2, 3, \dots, m$ are consistent estimator of r_k ’s obtained by the “reverse logistic regression” method proposed by Geyer (1994) described in details in the next section.

4.1.1 Estimation of r_k

Following Geyer (1994), \hat{r}_k are estimated by maximizing the quasi-likelihood function,

$$l_n(r) = \sum_{j=1}^m \sum_{l=1}^{N_j} \log p_j(X_{jl}, r), \quad (10)$$

where $X_{jl} = (\boldsymbol{\theta}_1^{(j;l)}, \boldsymbol{\theta}_2^{(j;l)})$, $r = (r_1, r_2, \dots, r_m)$, N_j is the number of MCMC samples with stationary density $\pi_{\phi_j}(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2 | \mathbf{y}, \boldsymbol{\delta})$ corresponding to the skeletal point ϕ_j , $j = 1, 2, \dots, m$ and the function $p_j(\cdot, \cdot)$ is defined below. To avoid identifiability issues, \hat{r}_1 is assumed to be 1. The function $p_j(\cdot, \cdot)$ is defined as,

$$p_j(X_{jl}, r) = \frac{L(\boldsymbol{\theta}_1^{(jl)}, \boldsymbol{\theta}_2^{(jl)}, \phi_j | \mathbf{y}, \boldsymbol{\delta}) e^{r_j}}{\sum_{k=1}^m L(\boldsymbol{\theta}_1^{(jl)}, \boldsymbol{\theta}_2^{(jl)}, \phi_k | \mathbf{y}, \boldsymbol{\delta}) e^{r_k}}, \quad (11)$$

where ϕ_k is the k^{th} skeletal point and $\boldsymbol{\theta}_i^{(jl)} = (\mu_i^{(jl)}, \sigma_i^{(jl)}, \xi_i^{(jl)})$, for $i = 1, 2$ is the l^{th} MCMC sample of the chain with stationary density $\pi_{\phi_j}(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2 | \mathbf{y}, \boldsymbol{\delta})$ corresponding to the skeletal point ϕ_j , $j = 1, 2, \dots, m$ and $l = 1, \dots, N_j$.

Hence the two-stage procedure for estimating B_{ϕ, ϕ_1} and $\hat{\phi}$ are as follows. In the first stage, we run MCMC chains $\{\boldsymbol{\theta}_1^{(j;l)}, \boldsymbol{\theta}_2^{(j;l)}\}_{l=1}^{N_j}$ with invariant density $\pi_{\phi_j}(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2 | \mathbf{y}, \boldsymbol{\delta})$, $j = 1, 2, \dots, m$. We estimate r using these first stage posterior samples using the reverse logistic method as described in section 4.1.1. In the second stage, independent of the first stage samples, we obtain *new* samples $\{\boldsymbol{\theta}_1^{(j;l)}, \boldsymbol{\theta}_2^{(j;l)}\}_{l=1}^{N_j}$ from $\pi_{\phi_j}(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2 | \mathbf{y}, \boldsymbol{\delta})$, $j = 1, 2, \dots, m$ to estimate B_{ϕ, ϕ_1} using equation (9). Finally, the estimate $\hat{\phi}$ where \hat{B}_{ϕ, ϕ_1} attains maximum, can be obtained by an optimization procedure or simply looking at the plot of \hat{B}_{ϕ, ϕ_1} against ϕ .

5 Simulation Study

5.1 Generating data

R package ‘‘Copula’’ was used to generate samples from bivariate distribution with Uniform (0, 1) marginals. The data has dependency according to previously mentioned Clayton copula structure. Next we used ‘‘Inverse Survival Function’’ approach to get survival times generated from bivariate distribution with $GEV(0, 1, \xi)$ marginals. Let $(u_1, u_2) \sim U(0, 1)$. Let t denote the generated survival time.

Case I: $\xi \neq 0$

$$1 - u_i = S(t_i) \tag{12}$$

$$= \exp[-(1 + \xi \log t_i)_+^{\frac{1}{\xi}}]$$

$$\Rightarrow t_i = \exp\left[\frac{-1 + (-\log(1 - u_i))^{\xi}}{\xi}\right]. \tag{13}$$

Case II: $\xi = 0$

$$1 - u_i = S(t_i) \tag{14}$$

$$= \exp(-t_i)$$

$$\Rightarrow t_i = -\log(1 - u_i). \tag{15}$$

Table 1: Naive Importance Sampling: Empirical Estimate of ϕ for Simulated Data

ϕ_1	<i>Param</i>	Estimate
1.00	ϕ	5.2114
2.00	ϕ	5.2116
4.00	ϕ	5.2116
6.00	ϕ	5.2115
8.00	ϕ	5.2117

Table 2: Naive Importance Sampling: Posterior Estimates of Marginal Parameters for Simulated Data

ϕ_1	<i>Param</i>	Estimate[S.E.]	95% HPD
1.00	ξ_1	0.308[0.009]	(0.293, 0.323)
	ξ_2	0.312[0.009]	(0.299, 0.326)
2.00	ξ_1	0.308[0.008]	(0.292,0.322)
	ξ_2	0.312[0.006]	(0.300,0.324)
4.00	ξ_1	0.307[0.008]	(0.291,0.321)
	ξ_2	0.312[0.007]	(0.300,0.321)
6.00	ξ_1	0.308[0.008]	(0.291,0.322)
	ξ_2	0.310[0.009]	(0.294,0.322)
8.00	ξ_1	0.308[0.008]	(0.294,0.322)
	ξ_2	0.310[0.008]	(0.295,0.326)

A random sample of 1000 observations were generated following the above method. We selected true $\xi_1 = \xi_2 = 0.3$ and true $\phi = 5$. The choice of ξ were made keeping in mind that in practical scenarios ξ rarely exceeds $[-0.5, 0.5]$ (See Castillo and Hadi (1997) and Smith (1985)). Censoring percentages in both t_1 and t_2 were taken to be about 12%. 3000 MCMC samples were generated and the first 1000 were discarded as burnin. A uniform prior of $(-0.7, 0.7)$ was considered for ξ . Several initial values of ϕ_1 were tried. The result of the simulation is displayed in table 1 and table 2. Note that due to emirical nature of the estimator, $\hat{\phi}$ has no standard error.

5.2 Estimation of Parameters

Table 3: Generalized Importance Sampling: Empirical Estimates of of ϕ for Simulated Data

<i>Param</i>	Estimate
ϕ	5.212
τ	0.723

Table 4: Generalized Importance Sampling: Posterior Estimates of Marginal Parameters for Simulated Data

<i>Param</i>	Estimate[S.E.]	95% HPD
ξ_1	0.308[0.008]	(0.290, 0.321)
ξ_2	0.311[0.008]	(0.298, 0.326)

In order to use our multi chain importance sampling method, four skeletal points (2, 4, 6, 8) were selected. We simulated 1000 data points following the method described in section 5. The true value of ϕ was 5 and $\xi_1 = \xi_2 = 0.3$. For each of the four ϕ , 3000 MCMC samples were generated. Using the MCMC samples, following Geyer (1994), first r_k , $k = 2, 3, 4$ were estimated (we assume $r_1 = 1$ due to model identifiability issues) and then using them in the second stage, estimate of ϕ was obtained. Finally fixing ϕ as $\hat{\phi}$, ξ_1 and ξ_2 were estimated. Table 3 and table 4 provides the details.

5.3 Note on Monte Carlo Simulation

Since the extreme value distributions have inter dependent parameters, i.e., the criterion: $1 + \xi \frac{\log t - \mu}{\sigma} > 0$ must always hold, when performing Monte Carlo simulations, there is a need to specify bounds for each parameter contained in the likelihood function. When conducting a real data analysis we assume that both the marginal GEV's have three unknown parameters: μ, σ and ξ in order to allow the data to have maximum flexibility. Also more often than not there is one or more associated covariates. Let us assume that there is one covariate Z for simplicity. We introduce the covariate through μ parameter as $\mu = \beta_0 + \beta_1 Z$. So overall we will have 8 parameters in the likelihood function: $\sigma_1, \xi_1, \sigma_2, \xi_2, \beta_{01}$ (intercept for log of survival time y_1), β_{11} (slope for log of survival time y_1), β_{02} (intercept for log of survival time y_2), β_{12} (slope for log of survival time y_2). We define the bounds for each of the parameters in the following way:

For ξ , define $\nu_i = \log y_i - \mu_i$, $i = 1, \dots, n$. We assume n is the sample size and the standard assumption that $\sigma > 0$ also holds. The parameters ξ_1 and ξ_2 will have similar bounds. Then,

$$\max(-1, \max_{1 \leq i \leq n} [-\frac{\sigma}{\nu_i} \mathbb{1}_{\nu_i > 0}]) < \xi < \min(1, \min_{1 \leq i \leq n} [-\frac{\sigma}{\nu_i} \mathbb{1}_{\nu_i < 0}]).$$

For σ , define $\zeta_i = \xi(\log y_i - \mu_i)$, $i = 1, \dots, n$. As before, parameters σ_1 and σ_2 will have similar bounds. Then,

$$\sigma > \max(0, \max_{1 \leq i \leq n}(-\zeta_i)).$$

For the intercept β_0 , we define $A_i = \log y_i + \frac{\sigma}{\xi} - \beta_1 Z_i$. For $\xi > 0$, $\beta_0 \in (-\infty, \min A_i)$. For $\xi < 0$, $\beta_0 \in (\max A_i, \infty)$.

For the slope β_1 , define $B_i = \frac{\log y_i + \frac{\sigma}{\xi} - \beta_0}{Z_i}$. For $\xi > 0$, $\beta_1 \in (-\infty, \min B_i)$. For $\xi < 0$, $\beta_1 \in (\max B_i, \infty)$. Note that these bounds hold for postive Z_i , $i = 1, \dots, n$. Further adjustments are needed in case the covariate can take negative values.

5.4 Note on Implementation of the Algorithm

In practice, often log likelihood function is used instead of likelihood for scaling issues and also to obtain a simplified form of the full data likelihood. While estimating r_k or B_{ϕ, ϕ_1} function in the estimation procedure, using likelihood can be a deterrent due to the large magnitude of the evaluated likelihood. One way around this problem is to deal with log likelihood and consider maximizing:

$$l_n(r) = \sum_{j=1}^m \sum_{l=1}^{N_j} \log p_j(X_{jl}, r) \quad (16)$$

where,

$$\begin{aligned} p_j(X_{jl}, r) &= \frac{1}{\sum_{k=1}^m \frac{e^{L^*(\theta_1^{(jl)}, \theta_2^{(jl)}, \phi_k | \mathbf{y}, \delta)} e^{r_k}}{e^{L^*(\theta_1^{(jl)}, \theta_2^{(jl)}, \phi_j | \mathbf{y}, \delta)} e^{r_j}}} \\ &= \frac{1}{\sum_{k=1}^m \frac{e^{L^*(\theta_1^{(jl)}, \theta_2^{(jl)}, \phi_k | \mathbf{y}, \delta)} e^{r_k}}{e^{L^*(\theta_1^{(jl)}, \theta_2^{(jl)}, \phi_j | \mathbf{y}, \delta)} e^{r_j}}} \\ &= \left[\sum_{k=1}^m e^{L_k^* - L_j^*} e^{r_k - r_j} \right]^{-1}, \end{aligned} \quad (17)$$

where $L_k^* = L^*(\theta_1^{(jl)}, \theta_2^{(jl)}, \phi_k | \mathbf{y}, \delta) = \log L(\theta_1^{(jl)}, \theta_2^{(jl)}, \phi_k | \mathbf{y}, \delta)$. Depending on the converged MCMC chains, the quantity $L_k^* - L_j^*$ should not be overly large and hence the maximization can be carried out. Similar technique can be applied to estimation of maximization of the function B_{ϕ, ϕ_1} while implementing the second stage of the proposed procedure in the log likelihood function.

6 Application to Diabetes Retinopathy Study Data

We consider the well known Diabetes Retinopathy Study (DRS) data for our analyses. This data was first introduced by Huster et al. (1989) in their seminal paper on modeling bivariate data with covariates. The Diabetes retinopathy is the leading cause of blindness in the Unites States under 60 years accounting for approximately 12% of all new cases. It has been shown that 90% of patients who have been diabetic for more than a decade will eventually develop retinopathy, or an ocular manifestation of blindness. The Diabetes Retinopathy Study (DRS) data consists of 197 patients with severe retinopathy affecting the eye. For each patient, the data records a treated eye and a control, untreated eye. Time from detection till blindness is the response variable. One or both eye may be censored. The censoring happens in approximately 79% of the treated eyes and 49% of the untreated eyes. Age at the onset of diabetes is considered as a covariate.

Huster et al. (1989) analyzed the data using a frequentist approach with the Clayton copula family and Weibull marginal distributions. Therneau and Grambsch (2000) considered a random effects frailty model and Sahu and Dey (2000) considered exponential and Weibull bivariate distributions with a Bayesian approach. Romeo and Tanaka (2006) considered copulas to model the dependency of the data and follow the same two step procedures outlined by Shih and Louis (1995).

Let us assume time to blindness for the j^{th} eye of the i^{th} patient, $i = 1, \dots, 197$ is y_{ij} . Then $\log y_{ij} \sim GEV(\mu_{ij}, \sigma_j, \xi_j)$, $j = 1, 2$. The covariate “age at the time of diagnosis” (Z) is included through $\mu_{ij} = \beta_{0j} + \beta_{1j}Z_i$, $j = 1, 2$. For simplicity, independent priors are considered on σ , ξ and β . Since we know from subsection 5.3, that the values of the marginal parameters σ , ξ and β are all interdependent, we adjust for the dependency by restricting the proposed parameter space within the Monte Carlo simulations. Also, we take $\sigma^2 \sim IG(a_\sigma, b_\sigma)$ and $\xi \sim U(-a, a)$. We pick $a = 1$, $a_\sigma = 0.01$, $b_\sigma = 2$. We put diffuse priors for β_{0s} and β_{1s} as $N(0, 100)$. The choices of the hyper parameters are such that the posterior distribution is proper.

For the first step, following the method outlined in section 4, an arbitrary $\phi_1 = 3$ value was chosen. Several initial values of ϕ_1 were tested, however not much difference was observed in the final estimates of the model parameters except the value of ϕ .

Next, using this ϕ_1 , we use the Gibbs sampler with Metropolis-Hastings steps to get the posterior

samples for parameters. For this data set, we have 10,000 MCMC iterations. Convergence was checked using the trace plots, ergodic mean plots and the autocorrelation plots for all the parameters. And we find that 4,000 iterations are adequate as burn-in and every 5th sample was chosen after thinning. Using 1,200 posterior samples, we then estimate the final ϕ value by maximizing B_{ϕ, ϕ_1} . Final estimates and HPD intervals for all 8 parameters were calculated based on the final estimated $\hat{\phi}$. The following table 5 provides us the empirical estimates for the dependency parameter and the estimate of the concordance measure and table 6 provides the consequent posterior estimates of the marginal parameters after the MCMC sampling.

Table 5: Naive Importance Sampling: Empirical Estimate of ϕ and τ for DRS data

<i>Param</i>	Estimate
ϕ	1.065
τ	0.347

Table 6: Naive Importance Sampling: Posterior Estimates of Marginal Parameters for DRS data

<i>Param</i>	Estimate[S.E.]	95% HPD
σ_1	1.012[0.153]	(0.743, 1.323)
ξ_1	0.144[0.165]	(-0.181, 0.426)
σ_2	1.313[0.236]	(0.911, 1.766)
ξ_2	0.148[0.172]	(-0.270, 0.403)
β_{01}	2.644[0.299]	(2.069, 3.229)
β_{11}	0.018 [0.013]	(-0.003, 0.044)
β_{02}	2.650[0.391]	(1.953, 3.454)
β_{12}	0.010[0.017]	(-0.022, 0.042)

However, as figure 1 demonstrates the estimates obtained from the naive importance sampling are not stable and the function B_{ϕ, ϕ_1} achieves it's maximum at different points for differnt initial starting values of ϕ_1 . This unstability becomes more pronounced as higher values of ϕ_1 are used.

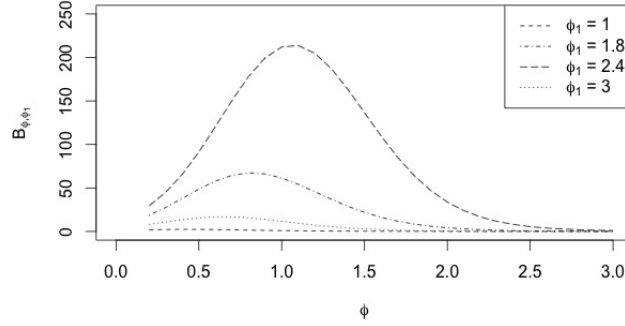


Figure 1: Plot of B_{ϕ, ϕ_1} against ϕ

In order to obtain stable estimates of the model parameters, following the method outlined in subsection 4.1, four skeletal points were chosen as $\phi_1 = 0.2$, $\phi_2 = 0.5$, $\phi_3 = 1$, $\phi_4 = 3$. 10,000 MCMC samples were generated for each skeletal points and 4000 were considered as burn-in after checking for convergence and the chains were thinned every 5^{th} sample. The maximum likelihood estimates of the marginal parameters given the value of skeletal point ϕ were estimated by maximizing the log likelihood function and were considered as initial starting value for the MCMC simulations. Once all the four MCMC chains were obtained, the function (10) was maximized to obtain estimated \hat{r}_j s. The estimated values of \hat{r}_j were quite robust to the change in initial start values. The following table 7 provides the values of \hat{r}_j .

Table 7: Estimated \hat{r}_j for DRS data

r	r_1	r_2	r_3	r_4
\hat{r}	1	0.679	1.445	7.867

Using the estimated \hat{r}_j s, \hat{B}_{ϕ, ϕ_1} was maximized as a function of ϕ and the final estimate $\hat{\phi}$ was obtained. To obtain standard errors of the $\hat{\phi}$ and $\hat{\tau}$, 1000 independent MCMC simulations were conducted and the final $\hat{\phi}$ is the average of the 1000 estimated $\hat{\phi}$ s. Finally, using the estimated $\hat{\phi}$, the marginal parameters were determined using Gibb's sampling algorithm as done before in section 5. Table 8 provides the empirical estimates of the dependency parameter ϕ and the concordance

measure Kendall's τ while table 9 provides the final estimates of the marginal parameters of the model.

Table 8: Generalized Importance Sampling: Empirical Estimate of ϕ and τ for DRS data

<i>Param</i>	Estimate[S.E.]	95% CI
ϕ	2.017[0.042]	(1.945, 2.098)
τ	0.502[0.005]	(0.493, 0.512)

Table 9: Generalized Importance Sampling: Posterior Estimates of Marginal Parameters for DRS data

<i>Param</i>	Estimate[S.E.]	95% HPD
σ_1	1.176[0.196]	(0.830, 1.599)
ξ_1	0.202[0.160]	(-0.139, 0.455)
σ_2	1.524[0.289]	(1.032, 2.082)
ξ_2	0.179[0.188]	(-0.229, 0.486)
β_{01}	2.726[0.351]	(1.983, 3.404)
β_{11}	0.022 [0.015]	(-0.005, 0.054)
β_{02}	2.712[0.454]	(1.754, 3.571)
β_{12}	0.017[0.020]	(-0.017, 0.0561)

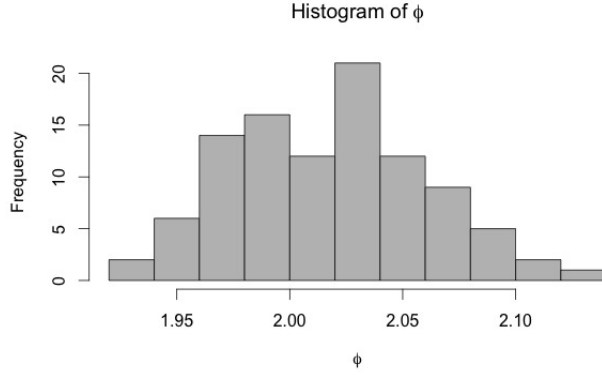


Figure 2: Histogram of $\hat{\phi}$

The final estimate $\hat{\phi}$ is quite different from the simple importance sampling estimator obtained in table 5. The stability of the final estimated ϕ was tested by including one additional $\phi_1 = 4.5$ as a skeletal point. The final estimate of ϕ obtained in the process was quite close to the estimated $\hat{\phi}$ (around 2.49). The standard error of the estimated $\hat{\phi}$ and $\hat{\tau}$ are calculated empirically from 100 independent MCMC simulations. As seen from the figure 2, the final estimates of ϕ are quite robust. In Romeo and Tanaka (2006), the authors found the estimated $\hat{\phi}$ to be approximately 1.061. Our estimated $\hat{\phi}$ is higher but in the same direction. The estimated $\hat{\tau}$ is 0.502. It can be thus concluded that the marginal time to blindness for the patients eyes are indeed positively associated. The estimates of slopes of predictor Age are not significant for both the marginals. This finding agrees with Romeo and Tanaka (2006).

7 Discussion

A new bivariate survival model using copula with flexible log Generalized Extreme Value marginals is proposed in this chapter. Since the construction of appropriate priors for the association parameter of the copula may be difficult, an empirical Bayes methodology is developed for making inference on these parameters by maximizing the marginal likelihood function. The proposed method will work on any bivariate data and is not restricted to survival data or to a particular family of copulas. A future direction of work includes extending the proposed methodology for multivariate responses. If the multivariate copula has many association parameters, use of the proposed methodology for

estimating these parameters seems challenging.

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