Copulas and Competing Risks: Applications for Mixture Long-term Survival Models

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Abstract
In terms of competing risks Mixture Long-term Survival Models are widely used for the analysis of individuals may never suffer the considered cause of failure. Under condition of a cured fraction, some individuals will be treated as immune to a specific cause of failure or be defined as long-term survivors. In case of multi- or bivariate cause-specific survival data different dependence structures can be suited with different copula functions. There are two main methodical aspects for the marginal distributions need to account for: first the maximum of flexibility and second the application in case of masked causes. We proposed a bivariate mixture long-term model based on the Farlie-Gumbel-Morgenstern (FGM) copula. Data simulations will be provided with SEER Breast Cancer Data. Otherwise we will discuss optional ideas for this approach in a semi-competing risk setting.

Key Words: Competing Risks, Copula, Long-term Survival, masked causes

1. Background

Competing Risks Models are popular in medical and public health studies. One challenging problem will be the application of cause-specific survival models in case of missing and misclassification in cause of death. Masking is almost present if the information of the considered cause of failure or cause of death is incomplete or only partial identifiable (Flehinger et al. 2002 , Craiu and Lee, 2005, Lu and Liang, 2008 Sen et al. 2010, Roman et al. 2012).
The Mixture Long-term Survival Models have been applied for the analysis of individuals may never suffer the cause of failure under consideration. Under the condition of an unobserved prognostic factor, some individuals will be treated as immune to a certain cause of failure or be defined as long-term survivors (Maller and Zhou, 1996, Roman et al. 2012, Louzada et al. 2012).

The also applied parametric or semi-parametric versions of the Proportional Hazard Model (PH) or the Mixed Proportional Hazard Model (MPH) will be also used in advance on practice. The structure of the properties for these models seems easily to explored but their application to real data is mostly inconvenient. The assumption on the marginal distributions of the latent variables and their dependence structure is restrictive, under some condition not adequate. To prevent such condition researchers assuming indepence structure for their latent variables.

Avoiding independence assumption one can also model the joint dependence structure by means of a copula function (e.g. Escalera and Carrière, 2003, Lo and Wilke, 2009, Wienke, 2011). Many different families of copulas, the model allows for flexible specification of the dependence structure between competing random variables (Nelsen, 2006).

2. The Model

The considered model based on two components mixture model according to Maller and Zhou (1996) with the distinction of one component representing the failure or the survival time of susceptible individuals to a certain and with the other component presenting the not susceptible individuals (see also Francisco et al. 2012, Roman, 2012).

$$S_{popj}(t_j) = p_j S_j(t_j) + (1 - p_j)S_0(t_j)$$

with S_j as the Survival function for the non-susceptible (or cured) individuals, S_0 as the Survival function for susceptible (or non-cured) individuals and p_j the probability (or cured fraction) of an individual to belong to the non-susceptible group.

$$if\ S_j(t_j) = P(T > t) = 1, \forall t \geq 0, then\ S_{popj}(t_j)\ can\ be\ rewritten\ as:$$

$$S_{popj}(t_j) = p_j + (1 - p_j)S_0(t_j)$$

Follow the bivariate Archimedean copula with a single parameter

$$C\left(S_{pop1}(t_1), S_{pop2}(t_2)\right) = S_{pop1}(t_1) + S_{pop2}(t_2) - 1 + \tilde{C}\begin{pmatrix}1 - S_{pop1}(t_1),\\ 1 - S_{pop2}(t_2)\end{pmatrix}$$

can be also applied for Clayton (1978), Ali-Mikhail-Haq (1978), or Frank copula (1979).

In comparison to the alternate mixture approach the bivariate long-term survival model with Farlie-Gumble-Morgenstein distribution (FGM) Copula Model (Conway, 1983) will be defined with the joint survival function of the copula C_φ with the density function c_φ $[0,1]^2$ for $\varphi \in R$. Then, let (T_1, T_2) denoted as the paired failure S_{popj} and f_{popj} denote the marginal long-term survival functions and the marginal long-term density function of $T_{j,j} = 1,2$ (see also Maller and Zhou, 1996, Roman et al. 2012, Louzada et al. 2012)

$$S_{pop}(t_1, t_2) = C_\varphi(S_{pop1}(t_1), S_{pop2}(t_2)), t_1, t_2 > 0$$

$$f_{pop}(t_1, t_2) = c_\varphi(S_{pop1}(t_1), S_{pop2}(t_2)),\ f_{pop1}(t_1) f_{pop2}(t_2) t_1, t_2 > 0$$

Using the Farlie-Gumble-Morgenstern copula (FGM) was first considered by Conway (1983) the application to a Bayesian approach estimates the effect of three copula structures by modeling the dependence effect on the prevalence and performance test parameters (Bairamov and Kotz, 2002, Fisher and Klein, 2007, Amblard and Girard, 2008 and Tovar Cuevas and Archor, 2011).

$$C\varphi(u,v) = uv[1+\varphi(1-u)(1-v)]$$

where $0 \leq u,v \leq 1$ and $-1 \leq \varphi \leq 1$, for $\varphi > 0$ if dependence structure for u and v is positive and $\varphi < 0$ if depence structure for u and v is negative

Consider $(T_{1,}T_{2,})$ for FMG copula the joint long-term survival of $(T_{1,}T_{2,})$ will be given with

$$S_{pop}(t_{1,}t_{2,}) = S_{pop1}(t_1), S_{pop2}(t_2)\left[1+\varphi\left(1-S_{pop1}(t_1)\right)\left(1-S_{pop2}(t_2)\right)\right]$$

Then φ parameter measures the intensity of the dependence between the lifetimes.

If $\varphi = 0$, $S_{pop1}(t_1) = S_{pop2}(t_2)$ is valid then the random variables T_1 and T_2 are independent

Copula functions rely on sophisticated methodical advances because their focus will not be on correlation coefficients but more over on scale invariant measures of association. These measures of association are functions of a measure of dependence between marginals. Then the association parameter can be defined with different values specified on the copula. In comparison to that measures of associations like the Pearson's correlation coefficient are bounded.
Modeling copulas will be arranged with the Gibbs Sampler belonging to the class of the Markov Chain Monte Carlo (MCMC) methodology.
For T_j we assume a Weibull mixture distribution with the parameters α_j and γ_j and

$$p_j = exp(\beta_{0j}+\beta_{1jx})/\left(1+exp(\beta_{0j}+\beta_{1jx})\right)$$

with $\gamma_j \sim Gamma\ (a_j, b_j)$ and $\alpha_j \sim Gamma\ (c_j, d_j)$

3. Data

The mixture long-term survival approach will be applied for Breast Cancer Data provided by the SEER Cancer Statistic Data Base National Cancer Institute, DCCPS, Surveillance Research Program, and Cancer Statistics Branch was released in April 2013.
Information on the incidence by race, gender and age for different period of time are available. We use causespecific mortality data including all cancer. The SEER public use dataset includes the vital status of breast cancer patients from 1992-2010 includes (n=69,990 in Situ).
The mixture cure model define S_0 for susceptible (non-cured) individuals will be identified as breast cancer case and with S_j will be non-breast cancer including all masking cases.

Simulation will be done with OpenBUGS. For more details: see Spiegelhalter et al. 2007

The results from the parameter estimates are presented in table1.

4. Results

Table 1: SEER Breast Cancer Data,
Summary results from the posterior distribution, mean,
standard deviation (SD) and HPD (95%) interval for the FGM copula

	Parameter	Mean	SD	HPD (95%)
Time 1	α_1	1.457	0.158	(1.1089; 1.589)
	λ_1	0.052	0.018	(0.031; 0.073)
	β_{01}	-2.134	0.993	(-4.534; -0.675)
	β_{11}	0.754	0.976	(-1.452; 2.871)
Time 2	α_2	1.564	0.176	(1.286; 1.834)
	λ_2	0.052	0.019	(0.030; 0.074)
	β_{02}	-0.781	0.511	(-1.547; 1.034)
	β_{12}	0.843	0.574	(0.641; 0.984)
Copula	φ	0.673	0.345	(0.031; 0.978)

5. Conclusion

The major gains of this approach yield on the high flexibility to account for different dependence structure. The minor computation problems can be neglected.

The estimates should be realized on a hierarchial two-step procedure:
First the marginals have to be estimated, then in a second step the copula to perform the joint distribution. On the other hand the identification problem of the joint distribution is still present.

Misclassification in cause of failure should be account for because the bias have serious effects on the for estimates and determine lower statistical power type of misclassification also drives the bias: Nondifferential misclassifications have less impact on the estimation bias than systematic misclassification (Sarfati et al. 2010)

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