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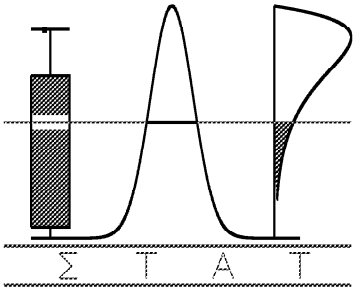
Pseudo-likelihood estimation for a marginal multivariate survival model

F. Tibaldi, G. Molenberghs, T. Burzykowski, and H. Geys



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PSEUDO-LIKELIHOOD ESTIMATION FOR A MARGINAL MULTIVARIATE SURVIVAL MODEL

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TOMASZ BURZYKOWSKI AND HELENA GEYS

Abstract

In this paper, we propose a multivariate Dale model for survival outcomes [1]. A pseudo-likelihood method for the estimation of the parameters is proposed and these ideas are applied to two case studies. The first study is in AIDS where overall survival time and different opportunistic infections in HIV-infected patients are studied. The second study is on adoption data where the association of the survival times within families is modeled, illustrating the use of the proposed methodology for the context of population genetics.

1 INTRODUCTION

Survival models have been used intensively during the past two decades, across a number of application areas. Medical researchers used them extensively, but in many other fields where the main interest is in time-to-event, they became an important tool as well (Fleming and Harrington 1991) [2]. The effect of one or more covariates on the patient's survival can be modeled via the Cox model [3], but we should recall that independence of survival times from one observation to the other is one of the basic assumptions of this model. However, in the last years there has been an increasing interest in frameworks where two or more events per patient or per statistical unit are observed. These statistical units can refer to clusters and hence multivariate survival models should be used, taking into account within-cluster dependencies. The former phenomenon is observed in groups of patients that share common characteristics, such as in family studies where the members share genetic and environmental factors. There are several issues one should take into account when extending the Cox model or other univariate survival model, to the situation where the association needs to be modeled, which is the topic of the current paper.

The paper is organized as follows. Section 2 motivates the problem through two case studies. Section 3.1 gives a description of the Dale model (Molenberghs and Lesaffre 1994) [4] for survival data in the bivariate case. Section 3.2 describes an extension of the model to the case of k correlated survival times and proposes a pseudo-likelihood approach for the estimation of the parameters of the model. Section 5 contains the analysis of the case studies.

2 MOTIVATING CASES

In this section, we will introduce two different studies for which our methodology is of use. The AIDS case study deals with intrasubject correlation, i.e., multiple events per subjects are recorded. The adoption study is an example of a study where clustering, within-cluster dependencies are present.

2.1 The AIDS Study

These data arise from a randomized clinical trial. A total of 1530 patients who participated in two clinical trials sponsored by the AIDS Clinical Trials Group (ACTG): ACTG 116A (Dolin *et al.* 1995) [5] and 116B/117 (Kahn *et al.* 1992) [6] were randomized to compare zidovudine (ZDV) and two doses of didanosine (ddI). Participants either had a diagnosis of AIDS or AIDS related complex (ARC) and/or had CD4 counts of 300 or fewer. The primary outcomes of interest for this analysis were survival and new or recurrent AIDS-defining events. Patients were randomly assigned to receive one of the following three treatments: ddI 750 mg per day, ddI 500 mg per day, or ZDV 600 mg per day. These studies enrolled patients between October 1989 and April 1991; patients were followed for a median of 65 weeks and a maximum of 132 weeks. For illustration, ZDV is compared to any dose of DDI; therefore we use a binary indicator variable for treatment effect. Measures of CD4 for individual patients are included in the model. This choice is supported by the work of Saah *et al.* (1994) [7], who found that CD4 was a laboratory measure in a Cox proportional hazards model which predicted survival after AIDS. There has been

some debate in the literature as to whether such a dichotomization of CD4 can be justified or not. We will use a continuous version of this variable but any other categorization can be considered without substantially having to modify the methodology. Molenberghs, Williams, and Lipsitz (2002) [8] studied the joint modeling of survival and CD4 count on these data.

2.2 The Adoption Study

This study presented in Sørensen *et al.* (1988)[9] was carried out to analyze the impact of environmental and genetic factors on survival of adult adoptees. To this end, dependencies between the survival time of children and biological parents, and between children and adoptive parents are the focus of interest. In this study, families with adoptive children, born between 1924 and 1926, were analyzed. The basic idea is that association between survival times of biological parents and children can be assigned to some extent to genetic factors, while associations between children and adoptive parents can be due only to environmental factors.

These data were studied by Nielsen *et al.* (1992)[10] who proposed a shared gamma frailty model and by Parner (2001)[11] who proposed a composite likelihood method for the estimation of the frailty parameters and the standard deviations. We propose to use a Plackett-Dale model (Burzykowski *et al.* 2001) [12] for correlated survival time data with Weibull margins, as will be described next.

3 MODEL DESCRIPTION

3.1 Bivariate Dale Model for Survival Data

In this section, we will introduce the Dale model for two survival outcomes. Assume that T_1 and T_2 are correlated survival times, then the joint survival function of (T_1, T_2) can be written as

$$S_{T_1T_2}(t_1,\, t_2) = P(T_1 \geq t_1,\, T_2 \geq t_2) = C_{\theta_{12}}\{S_{T_1}(t_1),\, S_{T_2}(t_2)\}, \qquad t_1,\, t_2 \geq 0, \tag{1}$$

where S_{T_1} and S_{T_2} denote marginal survival functions and $C_{\theta_{12}}$ is a copula. An attractive feature of model (1) is that the margins do not depend on the choice of the copula function.

In principle, in model (1) any copula function can be used. For simplicity, we consider primarily one-parameter families; hence the use of a single parameter θ_{12} in (1). Some possible options are the Clayton, Hougaard, and Plackett copulas. Burzykowski *et al.* (2001) studied them in detail within the framework of surrogate endpoints. For the Clayton and Hougaard copulas, model (1) reduces to a proportional frailty model (Oakes 1989)[13] with frailties generated, respectively, by the gamma and the positive stable distributions.

To model the effect of specific covariates on the marginal distributions of T_1 and T_2 in (1) we propose to use the proportional hazard model:

$$S_{T_1}(t_1) = \exp\left\{-\int_0^{t_1} h_{T_1}(x)\exp(\boldsymbol{\beta}_{T_1}\boldsymbol{Z}_1)dx\right\}, \tag{2}$$

$$S_{T_2}(t_2) = \exp\left\{-\int_0^{t_2} h_{T_2}(x)\exp(\boldsymbol{\beta}_{T_2}\boldsymbol{Z}_2)dx\right\}, \tag{3}$$

where h_{T_1} and h_{T_2} are marginal baseline hazard functions and $\boldsymbol{\beta}_{T_1}$ and $\boldsymbol{\beta}_{T_2}$ are vectors of unknown regression parameters corresponding to the covariates $\boldsymbol{Z}$. The hazard functions can be specified parametrically or can be left unspecified as in the classical model proposed by Cox (1972)[3]. When the hazard functions are specified, estimates of the parameters for joint model (1)–(3) can be obtained using the method of maximum likelihood [14]. Alternatively, the two-stage parametric procedure proposed by Shih and Louis (1995)[15] can be used, in which parameters of the marginal survival functions S_{T_1} and S_{T_2} are estimated first (assuming independence), and then θ_{12} is estimated conditional on the estimated values of the marginal parameters.

This one-parameter family is closely related to the Plackett family of bivariate distributions (Plackett 1965) [16]. In this case the dependence can be defined using a *global cross-ratio* at (t_1, t_2) given by

$$\theta_{12}(t_1, t_2) = \frac{F(t_1, t_2)[1 - F_{T_1}(t_1) - F_{T_2}(t_2) + F(t_1, t_2)]}{[F_{T_1}(t_1) - F(t_1, t_2)][F_{T_2}(t_2) - F(t_1, t_2)]}. \tag{4}$$

where F_{T_1} and F_{T_2} are the marginal cumulative density functions. Here, $\theta_{12} = \theta_{12}(t_1, t_2)$ satisfies $0 \leq \theta_{12} \leq \infty$ when $F(t_1, t_2)$ satisfies the Fréchet-Hoeffding (Fréchet 1951)[17] bounds. The components in (4) are the quadrant probabilities in $\mathbb{R}^2$ with vertex at (t_1, t_2). The Plackett distribution is obtained for constant cross-ratio $\theta_{12}(t_1, t_2) \equiv \theta$ (Plackett 1965, Mardia 1970)[16, 18]. The joint distribution $F_{T_1 T_2}$ is defined by means of (4), when F_{T_1}, F_{T_2} and θ_{12} are known.

The values of the Plackett distribution are found as one of the two solutions of the following second degree polynomial equation if the marginal distribution

functions F_{T_1} and F_{T_2}, and the cross-ratio θ_{12} are known:

$$\theta_{12}(F - F_{T_1})(F - F_{T_2}) - F[F - (F_{T_1} + F_{T_2} - 1)] = 0. \tag{5}$$

Dale (1986) and Mardia (1970) gave an explicit solution for (5):

$$F_{T_1,T_2}(t_1, t_2) = \begin{cases} \dfrac{1 + (F_{T_2}(t_2) + F_{T_1}(t_1))(\theta_{12} - 1) - H(F_{T_2}(t_2), F_{T_1}(t_1), \theta_{12})}{2(\theta_{12} - 1)} & \text{if } \theta_{12} \neq 1, \\ F_{T_2}(t_2)F_{T_1}(t_1) & \text{if } \theta_{12} = 1, \end{cases} \tag{6}$$

where

$$H(F_{T_1}, F_{T_2}, \theta_{12}) = \sqrt{(1 + (\theta_{12} - 1)(F_{T_1}(t_1) + F_{T_2}(t_2)))^2 + 4\theta_{12}(1 - \theta_{12})F_{T_1}(t_1)F_{T_2}(t_2)}. \tag{7}$$

Mardia (1970) showed that $F_{T_1,T_2}(t_1, t_2)$ is always a bivariate copula, with θ_{12} in $[0, +\infty]$. Although (6)–(7) was obtained based on the defining equation for the distribution function F, it can be shown that exactly the same copula is obtained for the survival function $S = 1 - F$.

Based upon this distribution function, we can derive a bivariate Plackett *density* function $f_{T_1T_2}(t_1, t_2)$ for two survival times using (6)–(7) by calculating $\partial F_{T_1T_2}(t_1, t_2)/\partial t_1 \partial t_2$ in an appropriate way taking into account censoring.

The parameters of this model and their standard deviations can be estimated by means of the maximum likelihood method. Appendix A details the expression for the log likelihood function, together with the derivatives of the distribution function F.

3.2 Multivariate Dale Model for Survival Data and Pseudo-likelihood Estimation

While the model described in Section 3.1 suffices to analyze bivariate time-to-event outcomes, an extension is needed for applications with more than two times. To this end, consider an experiment involving N subjects or clusters of k time-to-event measurements. Suppose that we also observe a vector of covariates $\boldsymbol{Z}$. A Weibull distribution is assumed for each time T_j with λ_{T_j} and p_{T_j} the scale and shape parameters, respectively. While we focus on Weibull marginals, different researchers may choose to use different univariate marginal survival distributions, implying only relatively small adaptations of the methodology. The information concerning subject i can be expressed in vector format as $(T_{i1}, \ldots, T_{ik}, \Delta_{i1}, \ldots, \Delta_{ik}, z_{i1}, \ldots, z_{in_k})$ so that $\boldsymbol{W}_{ij} = (T_{ij}, \Delta_{ij}, \boldsymbol{Z}_i)$ are the values for a particular subject i and time point j.

While a full multivariate formulation of the Dale model has been done in the context of ordinal data (Molenberghs and Lesaffre 1994, 1999)[4, 19], it poses non-trivial computational complexities. Instead, marginal pseudo-likelihood ideas will be used to keep the amount of computation under control, while enabling to answer relevant research questions (Le Cessie and Van Houwelingen 1994, Geys, Molenberghs, and Lipsitz 1998, Geys, Molenberghs, and Ryan 1999)[20, 21, 22].

The idea behind our pseudo-likelihood function is based on considering all possible pairs $(\boldsymbol{W}_{ir}, \boldsymbol{W}_{il})$ of outcomes on an individual, producing $f_{T_r T_l}(\boldsymbol{W}_{ir}, \boldsymbol{W}_{il})$, rather than the full multivariate density, and then taking the product over them.

The resulting function will be denoted by PL and its log by

$$\ln p\ell(\mathbf{\Phi}) = \sum_{i=1}^{N} p\ell_i, \tag{8}$$

with

$$p\ell_i = \sum_{(s,t)\in S} \ln f_{T_sT_t}(\boldsymbol{W}_{is}, \boldsymbol{W}_{it}, \mathbf{\Phi})$$

where S is the set of indices with all possible pairs of outcomes of interest, $f_{T_sT_t}$ is the value of the function defined in Section 3.1 evaluated in the respective outcomes for subject i, and $\mathbf{\Phi}$ is the vector of parameters. Specifically $\mathbf{\Phi}' = (\boldsymbol{\theta}', \boldsymbol{\beta}_T', \boldsymbol{\lambda}_T', \boldsymbol{p}_T')$ with $\boldsymbol{\theta}$ the subvector of association parameters, $\boldsymbol{\beta}_T$ the subvector of coefficients corresponding to the covariates $\boldsymbol{z}$ and, $\boldsymbol{\lambda}_T$ and $\boldsymbol{p}_T$ subvector of parameters from the Weibull distribution.

The pseudo-likelihood estimator $\widehat{\mathbf{\Phi}}$ is defined as the maximizer of (8). Consistency has been shown by Arnold and Strauss (1991), Le Cessie and Van Houwelingen (1994), and Geys, Molenberghs, and Ryan (1999)[23, 20, 22]. Precisely, it converges in probability to $\mathbf{\Phi}_0$, the true parameter value and $\sqrt{N}(\widehat{\mathbf{\Phi}} - \mathbf{\Phi}_0)$ converges in distribution to $N_q(\mathbf{0}, J(\mathbf{\Phi}_0)^{-1}K(\mathbf{\Phi}_0)J(\mathbf{\Phi}_0)^{-1})$ with $J(\mathbf{\Phi})$ defined by

$$J_{rl} = -\sum_{(s,t)\in S} E_{\mathbf{\Phi}}\left(\frac{\partial^2 \ln f_{T_sT_t}(t_{is}, t_{it})}{\partial\phi_r \partial\phi_l}\right) \tag{9}$$

and $K(\mathbf{\Phi})$ by

$$K_{rl} = -\sum_{(s,t)\in S} E_{\mathbf{\Phi}}\left(\frac{\partial \ln f_{T_s}(t_{is}, t_{it})}{\partial\phi_r}\frac{\partial \ln f_{T_t}(t_{is}, t_{it})}{\partial\phi_l}\right). \tag{10}$$

Similar in spirit to generalized estimating equations (Liang and Zeger 1986)[24] , this asymptotic normality result provides an easy way to estimate consistently

the asymptotic covariance matrix. Indeed, the matrix J is found from evaluating the second derivate of the log $p\ell$ function at the PL estimate. The expectation in K can be replaced by the cross-product of the observed scores. We will refer to J^{-1} as the model based variance estimator, which should not be used as such because it overestimates precision; to K as the empirical correction; and $J^{-1}KJ^{-1}$ as the empirically corrected variance estimator.

A further advantage of the PL approach is the close connection of pseudo-likelihood with likelihood, enabling one to construct pseudo-likelihood ratio and pseudo-score test statistics that have easy-to-compute expressions and intuitively appealing distributions (Aerts *et al.* 2002)[25].

As discussed by Arnold and Strauss (1991), the Cramèr-Rao inequality implies that $J^{-1}KJ^{-1}$ is greater than the inverse of I, corresponding to the Fisher information matrix for the maximum likelihood case, in the sense that $J^{-1}KJ^{-1} - I^{-1}$ is positive semidefinite. Therefore, a PL estimator is always less efficient than the corresponding ML estimator. Aerts *et al.* (2002) show that in many realistic settings efficiency losses are minor.

4 ASSOCIATION MEASURES

The Plackett-Dale model allows us to estimate and interpret the strength of the association between a pair of survival times via global cross ratios (the θ parameters in the model). Therefore, θ may be considered a natural candidate for the measure of association. However, some researchers may feel it is hard

to get a feel for because it ranges throughout the entire real line. Further, different copulas (like the Clayton and Hougaard copulas) carry different and less straightforward association parameters. In such a situation it would be easier to work with a transformation of θ that has the interpretational properties of a correlation coefficient, such as Kendall's τ or Spearman's ρ. These will be discussed in turn.

4.1 Kendall's τ

Kendall's τ can be seen as the difference between the probability of concordance and the probability of discordance of two realizations of (T_1, T_2). This coefficient lies in the $[-1, 1]$ interval and a zero value implies independence between T_1 and T_2. There exists a relationship between Kendall's τ and θ for any copula $C(t_1, t_2, \theta)$ (Genest and MacKay 1986)[26]:

$$\tau(\theta) - 4 \int_0^1 \int_0^1 C_{T_1 T_2}(t_1, t_2, \theta) C_{T_1 T_2}(dt_1, dt_2, \theta) - 1. \tag{11}$$

The marginal distributions of T_1 and T_2 do not affect (11), and hence it follows that τ only depends on the copula function $C_{T_1 T_2}$ (Schweizer and Wolff 1981)[27]. Kendall's τ thus measures the association between both time points after adjustment for the covariates used in the model. Such a relationship is very simple for the Clayton and Hougaard copulas (Burzykowski *et al.* 2001). Precisely, one obtains $\tau = (\theta - 1)/(\theta + 1)$ for Clayton and $\tau = 1 - \theta$ for Hougaard. Estimates and confidence intervals (using the delta method) are accordingly easily obtained. There is no closed form for Kendall's τ in the Plackett-Dale case and an estimate has to be obtained directly from (11). We have developed

a SAS IML 8.02 macro to this effect.

4.2 Spearman's ρ

Spearman's ρ is also based on concordance and discordance, independent of the margins, and belongs to the unit interval. It can be shown that Spearman's ρ equals Pearson's product-moment for grades of a pair of continuous random variables. The relationship between Spearman's ρ and the copula function is

$$\rho(\theta) = 12 \int_0^1 \int_0^1 C_{T_1 T_2}(t_1, t_2, \theta) dt_1 dt_2 - 3. \tag{12}$$

In contrast with the previous case, there is a closed-form expression in the Plackett-Dale case:

$$\rho(\theta) = \frac{\theta + 1}{\theta - 1} - \frac{2\theta . \ln \theta}{(\theta - 1)^2} \tag{13}$$

An estimate follows from $\rho = \rho(\widehat{\theta})$, with delta-method variance

$$\mathrm{Var}(\widehat{\rho}) = \left[\frac{-4(\widehat{\theta} - 1) + 2(\widehat{\theta} + 1) \ln \widehat{\theta}}{(\widehat{\theta} - 1)^3} \right]^2 .\mathrm{Var}(\widehat{\theta}).$$

From (13), the following asymptotic properties are derived: $\rho(\theta) \to 0$ when $\theta \to 1$, $\rho(\theta) \to -1$ when $\theta \to 0$ and $\rho(\theta) \to 1$ when $\theta \to \infty$.

5 CASE STUDIES

We are now in a position to analyze the data from Sections 2.1 and 2.2. Pseudo-likelihood estimates were obtained by using Newton-Raphson with analytical first derivatives and numerical second derivatives, implemented in SAS IML 8.02 and using routine NLPNRR (SAS Institute Inc. 1999–2001). Standard

errors of the parameters were calculated using the inverse of the observed matrix of second derivatives. Although in these two examples a trivariate model is considered, the methodology is fully generally applicable to longer sequences of time-to-event endpoints. Indeed, the structure of the SAS programs allows us to fit any model and any number of outcomes with only minor changes. Using a flexible design matrix structure, a large class of model specifications is possible.

5.1 Analysis of the Adoption Study

We first consider bivariate analyses, selecting pairs out of the three possible survival times of interest. The first aim is to describe the biological associations between mother, father and child, and then to study the environmental effect, e.g., correlations with the adoptive parents. In each case, a trivariate analysis is envisaged. We will start with bivariate analyses and compare these results with those obtained from modeling the trivariate data directly. We will use the abbreviations BM, BF and ACh for biological mother, biological father in the biological models, replacing BM with AM and BF with AF in the adoptive models. The corresponding subscripts are 1, 2, and 3 in each case. All results for the biological families are presented in Table 2, while Table 3 presents estimates for the adoptive families. The marginal distributions are all assumed to be Weibull with parameters λ_j and p_j, $j = 1, 2, 3$, and we consider three different parameters β_1, β_2, and β_3 to adjust for the sex of the child as it was done by Parner (2001). All association parameters are assumed to be constant.

It is clear from the way in which PL is defined that ML estimates are ex-

actly the same when only two outcomes are considered. Although model-based standard errors and empirically corrected standard errors are numerically different, they are of similar magnitudes and no clear ordering is seen between them. The tables reveal that the model based standard errors calculated by means of the information matrix and the empirically corrected ones differ only slightly. Common parameters estimated using two different bivariate models are similar since all models are of a marginal type. For example, $\widehat{\beta}_1 = -0.085$ in model BM–BF as opposed to $\widehat{\beta}_1 = -0.086$ in BM–ACh.

Tables 2 and 3 include all three types of association parameters: not only the log odds ratios θ but also Kendall's τ and Spearman's ρ, as introduced in Section 4. We observe the association is not very strong but nevertheless significantly different from zero in some cases. The τ and ρ parameters are relatively similar but, in spite of them ranging on the same scale, they have a different meaning and they are not directly comparable.

Let us now turn attention to the trivariate situation. Let us consider a model with different association parameters for each pair of outcomes θ_{12}, θ_{13}, and θ_{23} and with different parameters for the covariates corresponding to each outcome β_1, β_2, and β_3. Specific Weibull distributions with different scale and shape parameters for each outcome were used to model the marginals, i.e., p_1, p_2, p_3, λ_1, λ_2, and λ_3. Effectively, this is the trivariate version of the previous bivariate ones. For the trivariate models, only empirically corrected standard errors are given in Tables 2 and 3, since the model-based ones ignore the fact that in using all pairs out of three survival times on a cluster, all outcomes are used

twice, leading to an exaggerated precision. Therefore, model-based standard errors are useless, even if all marginal and association models are correctly specified. We like to point out this feature since it is different from the GEE setting. Other than being a disadvantage, it is merely a "side effect" of the way marginal pseudo-likelihood works. Let us add that obtaining convergence was not different and using different sets of starting values showed stability of the process.

Parameters retain their meaning they had in the bivariate models, with two advantages. First, using the data in a trivariate model is more efficient than using them in three separate models. Second, one avoids the occurrence of double estimates for the marginal parameters (β, λ, and p parameters), in spite of them being not too different between various bivariate models. The same model was applied to the biological and adoptive families, enabling to contrast both sets of dependencies.

Comparisons of our association parameters with the ones given by Parner (2001) cannot be made directly, since they are expressed on different scales. The association in our case is the global odds ratio, while Parner's quantity is based on the mean and variance of the assumed Gamma distribution. Therefore, both sets of association parameters are transformed to Kendall's τ and Spearman's ρ. There is a close agreement between both methods, with of course the added advantage of our approach that it enables consideration of multivariate models.

According to Parner's conclusions, the environmental association between the adoptive child and the mother was significant and negative; the environmen-

tal association between adoptive father and the adoptive mother was significant. In our case, we can see from Table 3 that the estimated Kendall's coefficients are, $\tau_{13} = -0.036$ with a 95% confidence interval $(-0.060, -0.012)$ and $\tau_{12} = 0.052$ with a 95% confidence interval $(0.041, 0.063)$ respectively. These results suggest that the longevity of the mother and the adoptive child were negatively correlated. Thus, we arrived to the same conclusions. The estimates are similar to the estimates obtained using Parner's model as we shown in Table 3. We could also test for equal environmental effects and genetic effects using a Wald type test, but this is not the main goal of this work; details can be found in Parner (2001).

5.2 Analysis of the AIDS Study

In this section, we analyze the data described in Section 2.1. In the original paper by Finkelstein *et al.* (1996)[28] the pattern of the development of opportunistic infections in HIV-infected patients was evaluated, based on a cohort of 1530 patients. For the sake of illustration, we will work with a random sample of 1000 patients. The more common AIDS-defining opportunistic infections are *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV) and systemic mycosis. These authors performed all the analysis adjusted for CD4 count. Without loss of generality, we perform the analysis for three time-to-event outcomes: PCP, CMV and the overall survival time of the AIDS patients (DTH). The main objective is to describe the association between all three outcomes after adjusting by CD4 count

and treatment effect.

Parameters are subscripted with 1, 2, and 3 to refer to CMV, DTH, and PCP, respectively. For the sake of illustration, consider β_T to be the *common* treatment effect and β_1, β_2, and β_3 the outcome-specific parameters associated with the CD4 count. We will assume a Weibull distribution with parameters p_1, p_2, p_3, λ_1, λ_2, and λ_3. Therefore, the vector of parameters to be estimated has 13 components:

$$\boldsymbol{\Phi} = (\theta_{12}, \theta_{13}, \theta_{23}, \beta_T, \beta_1, \beta_2, \beta_3, p_1, p_2, p_3, \lambda_1, \lambda_2, \lambda_3), \tag{14}$$

where θ_{12}, θ_{13} and θ_{23} are the global cross ratios. Using straightforward generalized linear models technology, it is straightforward to construct the overall design matrix $\boldsymbol{X}$, consisting of 13 columns (as many as there are parameters), and $3 \times 7 \times N$ rows. The calculation of the number of rows follows because there are 3 pairs to be formed out of three outcomes, for each pair (i.e., for each bivariate model), there are 7 "natural" parameters (an association parameter, and then a β, λ, and p parameter for each component of the pair). More details on the design matrix are given in Appendix B. Generalization to more than three outcomes is straightforward and the SAS macro we developed carries the general situation. Parameter estimates are summarized in Table 1.

Parameters in common between different bivariate models are generally fairly close, with the exception of β_T, which is even changing signs. While not significant, this is a clear indication that the trivariate model is the more appealing one, in spite of a larger standard error. Note that for some, but not all, parameters the standard error produced by the trivariate model is smaller. The log

global cross ratios θ are quite large, showing a strong association between all pairs of outcomes. Also here, Kendall's τ and Spearman's ρ are calculated to get a better grip on the association. Based on the correlation parameters ρ, a consistent picture of a correlation around 0.5 emerges.

6 CONCLUDING REMARKS

In this paper, we have extended the Plackett-Dale model for survival data to the multivariate case and we have shown that pseudo-likelihood estimation, in the sense of Arnold and Strauss (1991), is a viable and attractive alternative to maximum likelihood in case of multivariate survival data. Maximum likelihood becomes prohibitive for large sequences of times, due to computational requirements. In contrast, the pseudo-likelihood procedure gives quite satisfactory results. In addition, we proposed other association measures and we have shown the link of Spearman's ρ and Kendall's τ to the association parameter of the Plackett-Dale model θ. The method yields consistent and asymptotically normal estimates of the parameters of interest and the computational complexity is manageable.

The choice of the Plackett-Dale model was motivated by the fact that the association parameter θ, has a natural interpretation for this copula. However, other copulas can be considered (Oakes 1989; Shih and Louis 1995; Joe 1997; Nelsen 1999)[13, 15, 29, 30]. To this end, checking the goodness of fit of copulas to bivariate survival data can be done by using the method proposed by Wang

and Wells (2000)[31] and an adaptation of this method to our framework is a topic for future research. It is also worth noting that, while in this work we considered Weibull marginal distributions, it is possible to use other distributional assumptions, or even use a semi-parametric approach with unspecifed baseline hazard functions (Shih and Louis 1995) [15]

The approach we presented gives a flexible tool for modeling any kind of time-to-event data accounting for the association between two or more outcomes. To illustrate our findings we have applied the proposed method in two different situations. Also, we have shown how the standard errors of the parameters need to be corrected in order to account for the lack of independence introduced by the fact that the information of a single subject is used more than once.

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References

[1] Dale, J. R. (1986). Global cross–ratio models for bivariate, discrete, ordered responses. *Biometrics* **42**, 909–917.

[2] Fleming, T. R., Harrington D. P. (1991). *Counting processes and survival analysis* New York: John Wiley.

[3] Cox, D.R. (1972). Regression models in life-tables (with discussion). *Journal of the Royal Statistical Society, Series B* **34**, 187–220.

[4] Molenberghs, G. and Lesaffre, E. (1994). Marginal modelling of correlated ordinal data using a multivariate Plackett distribution. *Journal of the American Statistical Association* **89**, 633–644.

[5] Dolin, R., Amato, D., Fischl, M.A., Pettinelli, C., Beltangady, M., Liou, S., Brown, M.J., Cross, A.P., Hirsch, M.S., Hardy, W.D., Mildvan, D., Blair, D.C., Powderly, W.G., Para, M.F., Fife, K.H., Steigbigel, R.T., Smaldone, L., and the National Institute of Allergy and Infectious Diseases Clinical Trials Group (1995). Zidovudine compared with didanosine in patients with advanced human immunodeficiency virus type I infection and little or no previous experience with zidovudine. *Archives of Internal Medicine* **155**, 961–974.

[6] Kahn, J.O., Lagakos, S.W., Richman, D.D., Cross, A., Petinelli, C., Liou, S., Brown, M., Volberding, P.A., Crumpacker, C.S., Beall, G., Sacks, H.S., Merigan, T.C., Beltangady, M., Smaldone, L., Dolin, R., and the NIAID

AIDS Clinical Trials Group (1992). A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *New England Journal of Medicine*, **327**, 581–587.

[7] Saah, A.J., Hoover, D.R., He, Y., Kingsley, L.A., Phair, J.P., and the Multicenter AIDS Cohort Study (1994). Factors influencing survival after AIDS: Report from the Multicenter AIDS Cohort Study (MACS). *Journal of Acquired Immune Deficiency Syndromes* **7**, 287–295.

[8] Molenberghs, G., Williams, P.L., and Lipsitz, S.R. (2002). Prediction of survival and opportunistic infections in HIV infected patients: a comparison of imputation methods of incomplete CD4 counts. *Statistics in Medicine*, **21**, 000–000.

[9] Sørensen, T.I.A., Nielsen, G.G., Andersen, P.K., and Teasdale, T.W. (1988). Genetic and familial environmental influence on premature death of adults adoptees. *New England Journal of Medicine* **318**, 727–732.

[10] Nielsen, G.G., Gill, R.D., Andersen, P.K., and Sørensen, T.I.A. (1992). A counting process approach to maximum likelihood estimation in frailty models. *Scandinavian Journal of Statistics*, **19**, 25–44.

[11] Parner, E.T. (2001). A composite likelihood approach to multivariate survival data. *Scandinavian Journal of Statistics* **28**, 295–302.

[12] Burzykowski, T., Molenberghs, G., Buyse, M., Geys, H., and Renard, D. (2001). Validation of surrogate endpoints in multiple randomized clinical trials with failure-time endpoints. *Applied Statistics* **50**, 405–422.

[13] Oakes, D. (1989). Bivariate survival models induced by frailities. *Journal of the American Statistical Association* **84**, 487 493.

[14] Lehmann, E.L. (1983). *Theory of Point Estimation.* New York: John Wiley.

[15] Shih, J.H.and Louis, T.A. (1995).Inferences on association parameter in copula models for bivariate survival data. *Biometrics* **51**, 1384–1399.

[16] Plackett, R. L. (1965). A class of bivariate distributions. *Journal of the American Statistical Association* **60**, 516–522.

[17] Fréchet, M. (1951). Sur les tableaux de corrélation dont les marges sont données. *Annals Université de Lyon, Section A, Series 3*, **14**, 143–153.

[18] Mardia, K.V. (1970). *Families of Bivariate Distributions.* London: Griffin.

[19] Molenberghs, G. and Lesaffre, E. (1999). Marginal modelling of multivariate categorical data. *Statistics in Medicine* **18**, 2237–2255.

[20] Le Cessie, S. and Van Houwelingen, J.C. (1994). Logistic regression for correlated binary data. *Applied Statistics* **43**, 95–108.

[21] Geys, H., Molenberghs, G., and Lipsitz, S.R. (1998). A note on the comparison of pseudo-likelihood and generalized estimating equations for marginal odds ratio models. *Journal of Statistical Computation and Simulation* **62**, 45–72.

[22] Geys, H., Molenberghs, G. and Ryan, L. (1999). Pseudo-likelihood modelling of multivariate outcomes in developmental toxicology. *Journal of the American Statistical Association* **94**, 34–745.

[23] Arnold, B.C. and Strauss, D. (1991). Pseudo likelihood estimation: some examples. *Sankhya B* **53**, 233 243.

[24] Liang, K.Y. and Zeger, S.L. (1986).Longitudinal data analysis using generalized linear models. *Biometrika* **50**, 13–22.

[25] Aerts, M., Geys, H., Molenberghs, G., and Ryan, L. (2002). *Topics in Modelling of Clustered Data*. London: Chapman & Hall.

[26] Genest, C. and McKay, J. (1986). The joy of copulas: bivariate distributions with uniform marginals. *American Statistician* **40**, 280–283.

[27] Schweizer, B. and Wolff, E.F. (1981). On nonparametric measures of dependence for random variables. *Annals of Statistics* **9** 879–885.

[28] Finkelstein, D.M., Williams, P.L., nberghs, G., Feinberg, J., Powderly, W., Kahn, J., Dolins, R. and Cotton, D. (1996). Patterns of opportunistic infections in patients with HIV infection. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* **12**, 38–45.

[29] Joe, H. (1997). *Multivariates Models and Dependence Concepts.* London: Chapman and Hall.

[30] Nelsen, R.G. (1999). An introduction to coulas. *Lecture Notes in Statistics,* **139**. New York: Springer-Verlag.

[31] Wang, W. and Wells, M.T. (2000) Model selection and semiparametric inferences for bivariate failure-time data. *Journal of the American Statistical Association*, **95**, 62–76.

APPENDIX A

Log likelihood function for the bivariate Dale model

Let (T_1, T_2) denote paired failures times and (S_1, S_2), (f_1, f_2) the corresponding marginal survival and density functions. Then, the joint survival and density functions of (T_1, T_2) are given by

$$S(t_1, t_2) = F_{T_1 T_2}(S_{T_1}(t_1), S_{T_2}(t_2)), \tag{15}$$

$$f(t_1, t_2) = \frac{\partial^2 S(t_1, t_2)}{\partial t_1 \partial t_2} f_{T_1}(t_1) f_{T_2}(t_2), \tag{16}$$

with t_1, $t_2 \geq 0$.

Let us denote by (C_1, C_2) the paired censoring times. For $i = 1, \ldots, n$, assume that (T_{i1}, T_{i2}) and (C_{i1}, C_{i2}) are independent. For each i we observe $T_{ij} = \min(X_{ij}, C_{ij})$ $j = 1, 2$ then $\Delta_{ij} = I\{X_{ij} = T_{ij}\}$, i.e., indicates whether the lifetime is observed ($\Delta_{ij} = 1$) or not ($\Delta_{ij} = 0$).

We can write now the log likelihood function by combining the following different situations in one expression as follows

Case	Δ_{i1}	Δ_{i2}
I	1	1
II	1	0
III	0	1
IV	0	0

Therefore,

$$\log \ell = \sum_{i=1}^{n} \Delta_{1i}\Delta_{i2} \log(f(t_{i1}, t_{i2})) + \Delta_{i1}(1-\Delta_{i2}) \log\left(-\frac{\partial S(t_{i1}, t_{i2})}{\partial t_1}\right) + (1-\Delta_{i1})\Delta_{i2} \log\left(-\frac{\partial S(t_{i1}, t_{i2})}{\partial t_2}\right) + (1-\Delta_{i1})(1-\Delta_{i2}) \log(S(t_{i1}, t_{i2})) \tag{17}$$

where $S(t_1, t_2)$ and $f(t_1, t_2)$ were defined in (15) and (16), respectively.

Distribution function and its derivatives for $\theta \neq 1$

$$F(u, v, \theta) = \frac{1}{2(\theta-1)} + \frac{u+v}{2} - \frac{H(u, v, \theta)}{2(\theta-1)}$$

$$H(u, v, \theta) = \sqrt{(1+(\theta-1)(u+v))^2 - 4\theta(\theta-1)uv}.$$

$$\frac{\partial H}{\partial u} = \frac{(\theta-1)}{H(u, v, \theta)}[(1+(\theta-1)(u+v)) - 2\theta v]$$

$$\frac{\partial H}{\partial v} = \frac{(\theta-1)}{H(u, v, \theta)}[(1+(\theta-1)(u+v)) - 2\theta u]$$

$$\frac{\partial H}{\partial \theta} = \frac{(1+(\theta-1)(u+v))(u+v) - 2uv(2\theta-1)}{H(u, v, \theta)}$$

$$\frac{\partial^2 H}{\partial u^2} = \frac{\left[(\theta-1)^2 - (\frac{\partial H}{\partial u})^2\right]}{H(u, v, \theta)}$$

$$\frac{\partial^2 H}{\partial v^2} = \frac{\left[(\theta-1)^2 - (\frac{\partial H}{\partial v})^2\right]}{H(u, v, \theta)}$$

$$\frac{\partial^2 H}{\partial \theta^2} = \frac{\left[(u-v)^2 - (\frac{\partial H}{\partial \theta})^2\right]}{H(u,v,\theta)}$$

$$\frac{\partial^2 H}{\partial u \partial \theta} = \frac{\partial H}{\partial u}\left[\frac{1}{\theta-1} - \frac{1}{H(u,v,\theta)}\frac{\partial H}{\partial \theta}\right] + \frac{(\theta-1)(u-v)}{H(u,v,\theta)}$$

$$\frac{\partial^2 H}{\partial v \partial \theta} = \frac{\partial H}{\partial v}\left[\frac{1}{\theta-1} - \frac{1}{H(u,v,\theta)}\frac{\partial H}{\partial \theta}\right] + \frac{(\theta-1)(v-u)}{H(u,v,\theta)}$$

$$\frac{\partial^2 H}{\partial u \partial v} = -\frac{1}{H(u,v,\theta)}\left[\frac{\partial H}{\partial u}\frac{\partial H}{\partial v} + (\theta-1)(\theta+1)\right]$$

$$\frac{\partial F}{\partial u} = \frac{1}{2}\left[1 - \frac{1}{\theta-1}\frac{\partial H}{\partial u}\right]$$

$$\frac{\partial F}{\partial v} = \frac{1}{2}\left[1 - \frac{1}{\theta-1}\frac{\partial H}{\partial v}\right]$$

$$\frac{\partial F}{\partial \theta} = -\frac{H(u,v,\theta)}{\theta-1} + \frac{1}{2(\theta-1)}\left[u+v-\frac{\partial H}{\partial \theta}\right]$$

$$\frac{\partial^2 F}{\partial u^2} = -\frac{1}{2(\theta-1)}\left(\frac{\partial H}{\partial u}\right)^2$$

$$\frac{\partial^2 F}{\partial v^2} = -\frac{1}{2(\theta-1)}\left(\frac{\partial H}{\partial v}\right)^2$$

$$\frac{\partial^2 F}{\partial \theta^2} = -\frac{1}{\theta-1}\left[2\frac{\partial F}{\partial \theta} + \frac{1}{2}\frac{\partial^2 H}{\partial \theta^2}\right]$$

$$\frac{\partial^2 F}{\partial u \partial v} = -\frac{1}{2(\theta-1)}\left[\frac{\partial H}{\partial u}\frac{\partial H}{\partial v} + (\theta-1)(\theta+1)\right]$$

$$\frac{\partial^2 F}{\partial u \partial \theta} = \frac{1}{2H(u,v,\theta)(\theta-1)}\left[\frac{\partial H}{\partial u}\frac{\partial H}{\partial \theta} - (\theta-1)(u-v)\right]$$

$$\frac{\partial^2 F}{\partial v \partial \theta} = \frac{1}{2H(u,v,\theta)(\theta-1)}\left[\frac{\partial H}{\partial v}\frac{\partial H}{\partial \theta} - (\theta-1)(v-u)\right]$$

$$\frac{\partial^3 F}{\partial u^3} = \frac{1}{H(u,v,\theta)}\frac{\partial H}{\partial u}\left[-\frac{\partial^2 F}{\partial u^2} + \frac{1}{\theta-1}\frac{\partial^2 H}{\partial u^2}\right]$$

$$\frac{\partial^3 F}{\partial v^3} = \frac{1}{H(u,v,\theta)}\frac{\partial H}{\partial v}\left[-\frac{\partial^2 F}{\partial v^2} + \frac{1}{\theta-1}\frac{\partial^2 H}{\partial v^2}\right]$$

$$\frac{\partial^3 F}{\partial u^2 \partial v} = \frac{1}{H(u,v,\theta)}\left[-\frac{\partial^2 F}{\partial u^2}\frac{\partial H}{\partial v} + \frac{1}{\theta-1}\frac{\partial^2 H}{\partial v \partial u}\frac{\partial H}{\partial u}\right]$$

$$\frac{\partial^3 F}{\partial u \partial v^2} = \frac{1}{H(u,v,\theta)}\left[\frac{\partial^2 F}{\partial v^2}\frac{\partial H}{\partial u} - \frac{1}{\theta-1}\frac{\partial^2 H}{\partial u \partial v}\frac{\partial H}{\partial v}\right]$$

$$\frac{\partial^3 F}{\partial u^2 \partial \theta} = \frac{1}{\theta-1}\frac{\partial^2 F}{\partial u^2} + \frac{1}{H(u,v,\theta)}\left[-\frac{\partial^2 F}{\partial u^2}\frac{\partial H}{\partial \theta} + \frac{1}{\theta-1}\frac{\partial H}{\partial u}\frac{\partial^2 H}{\partial u \partial \theta}\right]$$

$$\frac{\partial^3 F}{\partial u \partial \theta^2} = -\frac{1}{\theta-1}\frac{\partial^2 F}{\partial u \partial \theta} - \frac{1}{H(u,v,\theta)} - \frac{\partial^2 F}{\partial u \partial \theta}\frac{\partial H}{\partial \theta} + \frac{1}{2H(u,v,\theta)(\theta-1)}\left[\frac{\partial^2 H}{\partial u \partial \theta}\frac{\partial H}{\partial \theta} + \frac{\partial H}{\partial u}\frac{\partial^2 H}{\partial \theta^2} - (u-v)\right]$$

$$\frac{\partial^3 F}{\partial u \partial v \partial \theta} = -\frac{1}{\theta-1}\frac{\partial^2 F}{\partial u \partial v} - \frac{1}{H(u,v,\theta)} - \frac{\partial^2 F}{\partial u \partial v}\frac{\partial H}{\partial \theta} + \frac{1}{2H(u,v,\theta)(\theta-1)}\left[\frac{\partial^2 H}{\partial u \partial \theta}\frac{\partial H}{\partial v} + \frac{\partial H}{\partial u}\frac{\partial^2 H}{\partial v \partial \theta} + 2\theta\right]$$

APPENDIX B

Let us exemplify the construction of a design matrix for the AIDS case study. The contribution of a single individual can be seen in our case as the contribution of three pseudo-likelihood individuals. Thus, $\boldsymbol{X}$ can be written as N blocks,

$$\boldsymbol{X} = \begin{pmatrix} \boldsymbol{X}_1 \\ \boldsymbol{X}_2 \\ \vdots \\ X_N \end{pmatrix},$$

where the block corresponding to subject i is expressed as:

$$\boldsymbol{X}_i = \begin{pmatrix} X_{i12} \\ X_{i13} \\ X_{i23} \end{pmatrix},$$

where

$$\boldsymbol{X}_{i12} = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & trt_i & cd4_i & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & trt_i & 0 & cd4_i & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{pmatrix},$$

$$\boldsymbol{X}_{i13} = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & trt_i & cd4_i & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & trt_i & 0 & 0 & cd4_i & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix},$$

and

$$\boldsymbol{X}_{i23} = \begin{pmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & trt_i & 0 & cd4_i & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & trt_i & 0 & 0 & cd4_i & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}.$$

Table 1: *AIDS study: Maximum likelihood estimates (model based standard errors; empirically corrected standard errors) of bivariate survival times and pseudo-likelihood estimates (standard errors) for trivariate model. For Kendall's τ and Spearman's ρ, estimates and 95% confidence intervals are given.*

Par.	CMV–DTH	CMV–PCP	DTH–PCP	CMV–DTH–PCP
θ_{12}	5.165(2.570;2.401)	–	–	4.369(1.165)
θ_{13}	–	4.434(1.850;2.182)	–	4.466(1.446)
θ_{23}	–	–	3.943(1.023;0.959)	3.691(0.865)
β_T	-0.054(0.020;0.020)	0.183(0.032;0.033)	-0.014(0.019;0.019)	0.016(0.111)
β_1	1.708(1.816;1.681)	1.504(1.892;1.547)	–	1.579(1.095)
β_2	2.160(0.706;0.752)	–	2.010(0.696;0.703)	2.069(0.732)
β_3	–	2.037(1.570;1.845)	2.168(1.487;1.838)	2.109(1.169)
p_1	-0.240(0.137;0.142)	-0.657(0.193;0.184)	–	-0.451(0.350)
p_2	0.341(0.033;0.038)	–	0.353(0.032;0.035)	0.338(0.164)
p_3	–	-1.147(0.257;0.331)	-0.807(0.203;0.270)	-0.958(0.469)
λ_1	1.606(0.033;0.030)	1.406(0.023;0.022)	–	1.487(0.136)
λ_2	1.941(0.015;0.017)	–	1.933(0.015;0.016)	1.940(0.111)
λ_3	–	1.117(0.012;0.014)	1.215(0.014;0.018)	1.161(0.108)
τ_{12}	0.352(0.307,0.397)			0.318(0.292,0.345)
τ_{13}		0.321(0.272,0.370)		0.323(0.291,0.355)
τ_{23}			0.297(0.273,0.322)	0.284(0.260,0.308)
ρ_{12}	0.503(0.269,0.736)			0.459(0.318,0.599)
ρ_{13}		0.462(0.204,0.721)		0.464(0.295,0.634)
ρ_{23}			0.430(0.298,0.563)	0.412(0.283,0.541)

Table 2: *Adoption study: Model for the biological families. Maximum likelihood estimates (model based standard errors; empirically corrected standard errors) of bivariate survival times and pseudo-likelihood estimates (standard errors) for trivariate model. For Kendall's τ and Spearman's ρ, estimates and 95% confidence intervals are given.*

Par.	BM-BF	BM-ACh	BF-ACh	BM–BF–ACh
θ_{12}	1.076(0.128;0.128)	–	–	1.076(0.127)
θ_{13}	–	1.164(0.193;0.187)	–	1.164(0.187)
θ_{23}	–	–	1.176(0.194;0.202)	1.175(0.201)
β_1	-0.085(0.086;0.077)	-0.086(0.086;0.077)	–	-0.084(0.069)
β_2	-0.009(0.078;0.072)	–	-0.010(0.078;0.072)	-0.004(0.036)
β_3	–	-1.066(0.164;0.159)	-1.060(0.164;0.159)	-1.063(0.137)
p_1	0.220(0.017;0.015)	0.219(0.017;0.015)	–	0.220(0.013)
p_2	0.279(0.011;0.010)	–	0.279(0.011;0.010)	0.279(0.006)
p_3	–	0.086(0.054;0.063)	0.085(0.054;0.063)	0.086(0.054)
λ_1	3.818(0.146;0.178)	3.817(0.146;0.179)	–	3.818(0.155)
λ_2	5.568(0.179;0.201)	–	5.568(0.179;0.200)	5.568(0.174)
λ_3	–	2.312(0.175;0.290)	2.313(0.176;0.291)	2.313(0.252)
τ_{12}	0.016(0.003,0.029)			0.016(0.003,0.029)
τ_{13}		0.034(0.016,0.051)		0.034(0.016,0.051)
τ_{23}			0.036(0.018,0.054)	0.036(0.017,0.054)
(Parner) τ_{12}	0.035(0.024,0.045)			
(Parner) τ_{13}		0.050(0.036,0.064)		
(Parner) τ_{23}			0.037(0.023,0.050)	
ρ_{12}	0.024(-0.053,0.102)			0.024(-0.053,0.102)
ρ_{13}		0.051(-0.054,0.155)		0.051(-0.054,0.155)
ρ_{23}			0.054(-0.054,0.162)	0.054(-0.058,0.165)
(Parner) ρ_{12}	0.052(-0.010,0.113)			
(Parner) ρ_{13}		0.075(-0.010,0.165)		
(Parner) ρ_{23}			0.055(-0.027,0.137)	

Table 3: *Adoption study: Model for the biological and adoptive families. Maximum likelihood estimates (model based standard errors; empirically corrected standard errors) of bivariate survival times and pseudo-likelihood estimates (standard errors) for trivariate model. For Kendall's τ and Spearman's ρ, estimates and 95% confidence intervals are given.*

Par.	AM-AF	AM-ACh	AF-ACh	AM–AF–ACh
θ_{12}	1.265(0.132;0.127)	–	–	1.265(0.127)
θ_{13}	–	0.844(0.138;0.133)	–	0.849(0.133)
θ_{23}	–	–	1.237(0.200;0.198)	1.240(0.197)
β_1	-0.015(0.077;0.072)	-0.012(0.077;0.072)	–	-0.029(0.064)
β_2	0.078(0.075;0.074)	–	0.077(0.075;0.074)	0.025(0.034)
β_3	–	-1.066(0.164;0.159)	-1.064(0.164;0.158)	-1.068(0.137)
p_1	0.210(0.009;0.009)	0.210 (0.009;0.009)	–	0.211(0.008)
p_2	0.235(0.008;0.008)	–	0.235(0.008;0.008)	0.241(0.005)
p_3	–	0.085(0.054;0.063)	0.085(0.054;0.063)	0.086(0.055)
λ_1	6.402(0.203;0.218)	6.406(0.203;0.219)	–	6.405(0.189)
λ_2	7.223(0.210;0.220)	–	7.228(0.210;0.022)	7.222(0.191)
λ_3	–	2.312(0.176;0.290)	2.311(0.176;0.291)	2.312(0.252)
τ_{12}	0.052(-0.045,0.150)			0.052(0.041,0.063)
τ_{13}		-0.038(-0.184,0.108)		-0.036(-0.060,-0.012)
τ_{23}			0.047(0.030,0.065)	0.048(0.030,0.065)
(Parner) τ_{12}	0.051(0.040,0.061)			
(Parner) τ_{13}		-0.069(-0.085,-0.052)		
(Parner) τ_{23}			0.041(0.027,0.054)	
ρ_{12}	0.078(-0.501,0.657)			0.078(0.013,0.143)
ρ_{13}		-0.057(-0.931,0.818)		-0.055(-0.198,0.089)
ρ_{23}			0.071(-0.033,0.175)	0.072(-0.034,0.177)
(Parner) ρ_{12}	0.076(0.013,0.140)			
(Parner) ρ_{13}		-0.103(-0.202,-0.004)		
(Parner) ρ_{23}			0.061(-0.021,0.143)	