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ESTIMATING GLOBAL AND LOCAL MEASURES OF ASSOCIATION FOR BIVARIATE INTERVAL CENSORED DATA WITH A SMOOTH ESTIMATE OF THE DENSITY.

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Estimating global and local measures of association for bivariate interval censored data with a smooth estimate of the density.

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Abstract

Measures of association for bivariate interval censored data have not yet been studied extensively. Betensky and Finkelstein (1999, *Statistics in Medicine* **18**, 3101–3109) proposed to calculate Kendall's coefficient of concordance using a multiple imputation technique, but their method becomes computer intensive for moderate to large data sets. We suggest a different approach consisting of two steps. Firstly, a bivariate smooth estimate of the density of log-event times is determined. The smoothing technique is based on a mixture of Gaussian densities fixed on a grid with weights determined by a penalized likelihood approach. Secondly, given the smooth approximation several global and local measures of association can be estimated readily.

The performance of our method is illustrated by an extensive simulation study and is applied to tooth emergence data of 7 permanent teeth measured on 4468 children from the Signal-Tandmobiel®study.

Key words: Bivariate survival; interval-censored; Kendall's tau; Spearman's correlation; cross ratio function.

1 Introduction

Measures of association are well studied and often applied to data that are completely observed. Some measures have been extended to right censored data (e.g. Oakes [1982], Dabrowska [1986], Clayton [1978]). However for interval censored data, association measures have not yet been studied extensively.

In the absence of censoring, Kendall's tau (τ) is estimated from scores assigned to each pair of bivariate observations, say $(X_1, Y_1), (X_2, Y_2)$ to measure the concordance between the two observations. More specifically, (X_1, Y_1) and (X_2, Y_2) are said to be concordant if $X_1 > X_2$ and $Y_1 > Y_2$ or if $X_1 < X_2$ and $Y_1 < Y_2$ and they are discordant if $X_1 > X_2$ and $Y_1 < Y_2$ or if $X_1 < X_2$ and $Y_1 > Y_2$. Concordant pairs are assigned a score of 1, discordant pairs are assigned a score of -1, and pairs in which there is equality among either variable are assigned a score of 0. Kendall's tau is then estimated by the average of these scores over all pairs of observations and in this way it estimates the difference between the probability of concordance and the probability of discordance. In the presence of censoring, things are more complicated. Oakes [1982] proposed to estimate Kendall's tau for bivariate right censored data by assigning zero to pairs of observations that cannot be compared. Following Oakes's approach, Betensky and Finkelstein [1999] suggested to calculate Kendall's tau in the presence of interval censoring using a multiple imputation

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strategy. However, their approach is quite computer intensive for moderate to large data sets.
Our approach is based on 2 steps. First we approximate the bivariate density of the log of the event times by a smoothing technique. The smoothing technique is an extension of the approach used by Ghidey et al. [2004] for smoothing the random effects distribution in a linear mixed model and by Komárek et al. [2005] for smoothing the distribution of the error term in an accelerated failure time model. More specifically the smooth density is a mixture of Gaussian densities fixed on a bivariate grid with weights determined by a penalized likelihood approach. In the second step, the estimated smoothed bivariate cumulative distribution function $\widehat{F}$ is plugged into the expression $\tau = 4\int FdF - 1$, which is the population's version of Kendall's tau. The same approach can be used to estimate other measures of association like Spearman's rank correlation, the cross ratio function and a conditional version of Kendall's tau. Spearman's correlation is a global measure of association like Kendall's tau, the latter two are local measures of association.
The next section describes the smoothing procedure and its mathematical properties. The calculation and properties of the measures of association are described in Section 3. An overview of alternative approaches is described in Section 4. A simulation study is presented in Section 5. The application to tooth emergence data of the Signal Tandmobiel®study is described in Section 6. Concluding remarks are found in Section 7.

2 Smooth estimate of the bivariate density

2.1 Smoothing Method

A detailed description of the smoothing method can be found in Bogaerts and Lesaffre [2003]. Briefly, let (T_1, T_2) represent a positive valued bivariate random vector with density f. Let T_1 and T_2 be interval censored in the rectangle $(t_{1l}, t_{1r}] \times (t_{2l}, t_{2r}]$ by an independent censoring process. We also include here the special cases, i.e. left ($t_l = 0$) and right censoring ($t_r = \infty$). The smoothing procedure is an extension of the approach of Ghidey et al. [2004] and Komárek et al. [2005]. The bivariate density g of $U_1 \equiv \log(T_1)$ and $U_2 \equiv \log(T_2)$ is modelled as a weighted sum of bivariate normal distributions with zero correlation over a (fixed) fine grid of size $k_1 \times k_2$ with means equal to the gridpoints of the grid and variances equal but fixed. Let $(\mu_i, \nu_j), i = 1 \ldots, k_1$ and $j = 1 \ldots, k_2$ denote the locations of the gridpoints. Thus, we assume that

$$\begin{pmatrix} U_1 \\ U_2 \end{pmatrix} \sim \sum_{i=1}^{k_1}\sum_{j=1}^{k_2} c_{ij}\mathcal{N}((\mu_i, \nu_j)^T, \begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{bmatrix}) \tag{1}$$

where $c_{ij} > 0, \forall i, j$ and $\sum_{i=1}^{k_1}\sum_{j=1}^{k_2} c_{ij} = 1$. The aim is to estimate the weights $c_{ij} (i = 1, \ldots, k_1, j = 1, \ldots, k_2)$. Note that this involves a constrained maximum likelihood procedure in the $k_1 \times k_2$ weight parameters. Unconstrained maximum likelihood estimation is obtained by introducing parameters a_{ij} as $c_{ij} = e^{a_{ij}} \Big/ \sum_{i,j} e^{a_{ij}}$, with, say $a_{11} = 0$ to ensure identifiability.
Following the work of Eilers and Marx [1996] a penalty term is used to smooth our ap-

proximation to the true density g. The penalty term equals to

$$p = \frac{\lambda_1}{2} \sum_{j=1}^{k_2} \sum_{i=k}^{k_1} (\nabla_1^k a_{ij})^2 + \frac{\lambda_2}{2} \sum_{i=1}^{k_1} \sum_{j=k}^{k_2} (\nabla_2^k a_{ij})^2 \tag{2}$$

where λ_1 (> 0) and λ_2 (> 0) are "smoothing" parameters. ∇_d^k is the k^{th} order difference operator in the d-th dimension ($d = 1, 2$) which is iteratively defined for the first dimension as $\nabla_1^k a_{ij} = \nabla_1^{k-1} a_{ij} - \nabla_1^{k-1} a_{i-1,j}$ for $k > 0$ and $\nabla_1^0 a_{ij} = a_{ij}$ and analogously defined for the second dimension.
Given λ_1, λ_2, let l_n denote the loglikelihood for a sample of size n and p the penalty defined in (2). Maximizing the penalized loglikelihood $l_{P,n} = l_n - p$ with respect to $\mathbf{a} = (a_{11}, \dots, a_{k_1 k_2})^T$, yields estimates $\widehat{a}_{ij} (i = 1, \dots, k_1, j = 1, \dots, k_2)$.
The parameters λ_1 and λ_2 are assumed to be given, they determine the smoothness of the density, i.e. the larger λ_1 and λ_2 the smoother the density will be. The optimum λ_1 and λ_2 correspond to a minimum Akaike's Information Criterium (AIC) (Akaike [1974]) defined as $AIC = -2 \times$log-likelihood$+2 \times$"effective number of parameters". The "effective number of parameters" can be determined (Gray [1992]) as $trace \left[H_{L_P}^{-1} H_L \right]$ where $H_L = -\frac{\partial^2 l_n}{\partial \mathbf{a} \partial \mathbf{a}^T}$ and $H_{L_P} = -\frac{\partial^2 l_{P,n}}{\partial \mathbf{a} \partial \mathbf{a}^T}$. The optimum λ_1 and λ_2 can be found by a grid search or a parabolic interpolation search.

2.2 Statistical Properties

2.2.1 Consistency

When parameters $\mathbf{a}_0$ exist such that the truth can be written like (1), it can be shown that the parameters are consistently estimated (Ghidey et al. [2004]). So, $\widehat{\mathbf{a}}_n \to \mathbf{a}_0$. However, in general the true distribution can not be written as a weighted sum of normal distributions with means at a pre-specified grid. Using White's theory (White [1982]), one can show that all the parameter estimates asymptotically converge to a function that minimizes the Kullback-Leibler distance. From limited simulations (results are not reported) we observed that the Kullback-Leibler distance indeed goes to zero for a fine enough grid and a large sample size.

2.2.2 Asymptotical Normality

Under the same conditions as in 2.2.1 it can also be shown that the estimated parameters are asymptotically normally distributed. Namely, $\sqrt{n}(\widehat{\mathbf{a}}_n - \mathbf{a}_0) \to \mathcal{N}(\mathbf{0}, \Sigma)$ where Σ can be consistently estimated by

$$n H_{L_P}^{-1}(\widehat{\mathbf{a}}_n) H_L^{-1}(\widehat{\mathbf{a}}_n) H_{L_P}^{-1}(\widehat{\mathbf{a}}_n).$$

3 Measures of association

3.1 General concept

Our approach consists in replacing the true density function, cumulative distribution function, survival function, etc. by their estimated counterparts determined from the bivariate smoothed function in the expression of the association measure. Two global dependence measures: Kendall's tau and Spearman's rho, and two local dependence measures: the

cross ratio function and the conditional version of Kendall's tau are estimated using our approach in the following subsections. A SAS macro (version 8.2) has been written and can be downloaded from http://www.med.kuleuven.be/biostat/index.htm.
Because of the promising results of our smoothing procedure (see Bogaerts and Lesaffre [2003]), it might be expected that our plug-in estimates also have good properties.
Let f and g represent the bivariate densities of (T_1, T_2) and $(U_1, U_2) \equiv (\log(T_1), \log(T_1))$ respectively. $F(t_1, t_2)$ and $G(u_1, u_2)$ denote the bivariate cumulative distribution functions of f and g, respectively. Let $F_1(t_1)$ and $F_2(t_2)$ denote the univariate marginal distributions corresponding to $F(t_1, t_2)$. Analogously, $G_1(u_1)$ and $G_2(u_2)$ represent the univariate marginal distributions corresponding to $G(u_1, u_2)$. Finally, let $S_F(t_1, t_2)$ and $S_G(u_1, u_2)$ denote the bivariate survival functions corresponding to F and G respectively.

3.2 Kendall's tau

The association between two survival times can be expressed by Kendall's tau (Hougaard [2000]), which is equal to

$$\begin{aligned} \tau &= 4 \cdot \int F(t_1, t_2) \mathrm{d}F(t_1, t_2) - 1 \\ &= 4 \cdot \int G(u_1, u_2) \mathrm{d}G(u_1, u_2) - 1. \end{aligned} \tag{3}$$

Our approach consists in replacing G by the cumulative distribution of the bivariate smoothed function in expression (3). This leads to the following expression for the estimate of τ (see Appendix):

$$\widehat{\tau} = 4 \cdot \sum_{i=1}^{k_1} \sum_{j=1}^{k_2} \sum_{k=1}^{k_1} \sum_{l=1}^{k_2} \widehat{c}_{ij} \widehat{c}_{kl} \Phi\left(\frac{\mu_i - \mu_k}{\sqrt{2}\sigma_1}\right) \Phi\left(\frac{\nu_j - \nu_l}{\sqrt{2}\sigma_2}\right) - 1 \tag{4}$$

where $\widehat{c}_{ij}$ and $\widehat{c}_{kl}$ are the estimated coefficients and Φ denotes the univariate cumulative standard normal distribution. Clearly, given the coefficients $\widehat{c}_{ij}$, the calculation of $\widehat{\tau}$ is readily done.
Based on the variance-covariance matrix of $\widehat{\mathbf{a}}$ (see Section 2.2.2) and using the delta method, one can easily derive the asymptotic variance and a (95%) confidence interval for $\widehat{\tau}$. Further, for $\widehat{\tau_1}$ and $\widehat{\tau_2}$ estimated from two independent groups of subjects a two-sample Z-test can be derived to test $H_0 : \tau_1 = \tau_2$ (see Appendix for details).

3.3 Spearman's rho

The population measure of Spearman's correlation (Joe [1997]) is defined as $\rho_s = 12 \cdot \int\int F_1(t_1)F_2(t_2)\mathrm{d}F(t_1, t_2) - 3$. Alternatively on the log scale, $\rho_s = 12 \cdot \int\int G_1(u_1)G_2(u_2)\mathrm{d}G(u_1, u_2) - 3$. As for Kendall's tau, one can derive that ρ_s is estimated by

$$\widehat{\rho_s} = 12 \cdot \sum_i \sum_j \sum_k \sum_l \sum_p \sum_q \widehat{c}_{ij} \widehat{c}_{kl} \widehat{c}_{pq} \Phi\left(\frac{\mu_i - \mu_p}{\sqrt{2}\sigma_1}\right) \Phi\left(\frac{\nu_k - \nu_q}{\sqrt{2}\sigma_2}\right) - 3. \tag{5}$$

Given the coefficients $\widehat{c}_{ij}$, the calculation of $\widehat{\rho_s}$ is again readily done but is computationally harder than the calculation of $\widehat{\tau}$ due to the extra summation. Similar as for Kendall's tau, one can derive the asymptotic variance, a (95%) confidence interval for $\widehat{\rho_s}$ and a significance test for $H_0 : \rho_{s1} = \rho_{s2}$.

3.4 Cross ratio function

The cross ratio function suggested by Clayton [1978] and Oakes [1989] is a local measure of association. It evaluates the degree of dependence at a single time point. It is defined as

$$\theta(t_1,t_2) = S_F(t_1,t_2)\cdot\frac{\partial^2 S_F(t_1,t_2)}{\partial t_1\partial t_2}\Big/\left[\frac{\partial S_F(t_1,t_2)}{\partial t_1}\cdot\frac{\partial S_F(t_1,t_2)}{\partial t_2}\right] \quad (6)$$

$$= S_G(u_1,u_2)\cdot\frac{\partial^2 S_G(u_1,u_2)}{\partial u_1\partial u_2}\Big/\left[\frac{\partial S_G(u_1,u_2)}{\partial u_1}\cdot\frac{\partial S_G(u_1,u_2)}{\partial u_2}\right]. \quad (7)$$

The cross ratio function has a very natural interpretation in conditional hazard rates (Oakes [1989]), namely

$$\theta(t_1,t_2) = \frac{\lambda_1(t_1\mid T_2=t_2)}{\lambda_1(t_1\mid T_2\geq t_2)} = \frac{\lambda_2(t_2\mid T_1=t_1)}{\lambda_2(t_2\mid T_1\geq t_1)},$$

where λ_1 and λ_2 are the hazard functions for T_1 and T_2 respectively.
To illustrate this interpretation, suppose we are analyzing the time to death for the elements of a married couple. Let X and Y represent the time to death for the wife and husband respectively, then $\theta(x,y)$ is the ratio of the mortality risk for wifes of age x whose husband died at the age of y, compared to the mortality risk for wifes of age x whose husband was still alive at age y.
Our approach consists in replacing $S(u_1,u_2)$ by the estimated survivor function of the bivariate smoothed function in expression (7) and leads to the following expression for the estimate of $\theta(t_1,t_2)\equiv\theta(u_1,u_2)$

$$\widehat{\theta}(t_1,t_2)\equiv\widehat{\theta}(u_1,u_2) = \frac{\sum_i\sum_j\widehat{c}_{ij}\Phi(-\frac{u_1-\mu_i}{\sigma_1})\Phi(-\frac{u_2-\nu_j}{\sigma_2})\times\sum_i\sum_j\widehat{c}_{ij}\phi(\frac{u_1-\mu_i}{\sigma_1})\phi(\frac{u_2-\nu_j}{\sigma_2})}{\sum_i\sum_j\widehat{c}_{ij}\Phi(-\frac{u_1-\mu_i}{\sigma_1})\phi(\frac{u_2-\nu_j}{\sigma_2})\times\sum_i\sum_j\widehat{c}_{ij}\phi(\frac{u_1-\mu_i}{\sigma_1})\Phi(-\frac{u_2-\nu_j}{\sigma_2})}, \quad (8)$$

where ϕ denotes the univariate standard normal density. When (8) is evaluated at the values of the grid, the evaluation of $\widehat{\theta}(t_1,t_2)$ can be done quite efficiently.
Based on the variance-covariance matrix of $\widehat{\mathbf{a}}$ (see Section 2.2.2) and using the delta method, one can easily derive the asymptotic variance of the cross ratio function on the logarithmic scale and correspondingly a (95%) confidence interval for $\widehat{\theta}$.

3.5 Conditional version of Kendall's tau

Oakes [1989] proposed to use a conditional version of Kendall's tau as a local measure of dependence. It can be defined in function of the cross ratio function as

$$\tau(t_1,t_2) = \frac{\theta(t_1,t_2)-1}{\theta(t_1,t_2)+1}.$$

Given the cross ratio function, estimation of $\tau(t_1,t_2)$ is readily done. For more details about the conditional version of Kendall's tau, we refer to the article of Oakes [1989].

4 Alternative approaches of estimating measures of association

4.1 Midpoint method

In principle the problem of interval censored data is overcome by approximating the event time by the midpoint of the interval. However, it has been reported by several authors that this approach can induce serious bias (e.g. Odell et al. [1992], Law and Brookmeyer [1992]). The midpoint method was implemented for the simulation study using the following algorithm: an interval or left censored observation was replaced by the midpoint of the interval, a right censored observation was left unchanged. Kendall's tau was then estimated for these adjusted data according to the method of Oakes [1989].

4.2 Approach of Betensky and Finkelstein

The method of Betensky and Finkelstein [1999] starts with modelling the bivariate survivor function, either in a parametric or a non-parametric way. The parametric approach has the obvious drawback that it is hard to choose the correct distribution, especially with interval censored observations. For the non-parametric fit, there are two drawbacks. First, the non-parametric maximum likelihood estimate (NPMLE) is not necessarily unique for bivariate interval censored data. Unfortunately, Betensky and Finkelstein [1999] do not describe how this affects their estimator. Secondly, although some recent progress in the computation of the NPMLE (e.g. Bogaerts and Lesaffre [2004], Maathuis [2005]) has been made, the estimation of the NPMLE is still quite computationally intensive for moderate to large data sets. This implies for the analysis of emergence times of the Signal-Tandmobiel®study that the calculation of the NPMLE for a pair of teeth is impossible with the current computing power due to an excessive large number of regions of possible support. The procedure of Betensky and Finkelstein [1999] can therefore even not be performed with the NPMLE as starting point.
Further, for right censored data, Wang and Wells [2000] reported that the estimator of Oakes [1982] is not consistent when the true value of τ is not equal to zero. The bias even increases as the degree of dependence increases. As the estimator of Betensky and Finkelstein [1999] is based on Oakes's approach, it is likely that their estimator is also biased when the true value of τ is not equal to zero. In their simulations, Betensky and Finkelstein [1999] only examine a situation where the true τ equals 0.224. For this setting, the mean bias was limited to 0.01. Situations with a true higher association were not examined. We performed for our simulations also the method of Betensky and Finkelstein [1999], but only for a sample size of 100 since for higher sample sizes the method becomes prohibitively computer intensive, e.g. for $n = 500$ estimating Kendall's tau takes more than 2 hours.

5 Simulation Study

A simulation study was set up where independent failure times were simulated from a bivariate log-normal distribution (scenario 1, $\tau = 0$) and a bivariate log t-distribution with 3 degrees of freedom (scenario 2, $\tau = 0$). In addition, failure times were simulated from scenarios with τ different from zero (scenarios 3 to 8): 1) a bivariate log-normal distribution ($\tau = 0.41$), 2) an equal mixture of two bivariate log-normal distributions with the same variance ($\tau = 0.63$), 3) an equal mixture of two bivariate log-normal distributions with different variances ($\tau = 0.49$), 4) an unequal mixture ($\pi_1 = 0.3, \pi_2 = 0.7$) of two bivariate log-normal distributions with the same variance and with two modes for both marginal distributions ($\tau = 0.54$), 5) an unequal mixture ($\pi_1 = 0.4, \pi_2 = 0.6$) of two bivariate log-normal distributions with the same variance but with only one mode for one marginal and two modes in the other marginal ($\tau = 0.26$) and 6) a bivariate log t-distribution with 3 degrees of freedom ($\tau = 0.48$).

Four different independent censoring schemes were applied to the (uncensored) data: 1) about 10% left, 70% interval and 20% right censoring; 2) about 10% left, 50% interval and 40% right censoring; 3) about 5% left, 20% interval and 75% right censoring and 4) about 75% left, 20% interval and 5% right censoring. This was done by generating 6 visit times and a drop out process both independently of the failure times.

The sample sizes were 100 and 500. Two gridsizes were examined i.e. 10×10 and 20×20, but the 10×10 grid was not always satisfactory and is therefore not further considered here. For each setting 1000 simulations were performed. For the smoothing parameters, a grid search with 10 values ranging from 0.001 to 500 in both dimensions was performed in order to choose the smoothing parameters. For $N = 100$, both smoothing parameters were assumed to be equal to each other ($\lambda_1 = \lambda_2$) since without this restriction many simulations had computational problems during the grid search. An explanation for this is that the amount of information for $N = 100$ is rather low. Third order differences were used in the penalty. The variances σ_1^2 and σ_2^2 of expression (1) were set to the square of 2/3 of the gridsize (see Bogaerts and Lesaffre [2003]).

For each setting, both Kendall's tau and Spearman's correlation and their corresponding variances were calculated. As a benchmark, Kendall's tau and Spearman's correlation was also estimated for the uncensored failure times using the standard expressions.

For scenarios 1 and 2 we investigated the type I error, after applying a Fisher transformation, for testing $H_0 : \tau = 0$ and $H_0 : \rho_s = 0$. Only the results for Kendall's tau will be discussed in detail because similar conclusions can be drawn for Spearman's correlation. For the two more reasonable censoring schemes 1 and 2, our results showed that the probability of the type I error was inflated for sample size 100 (mean 7.2%, range 5.4%-8.8%). However for sample size 500, it approached the nominal level (mean 5.1%, range 3.9%-5.5%). For the extreme censoring schemes 3 and 4, our results showed a serious inflation in the probability of the type I error for sample size 100 (mean 16.8%, range 14.3%-21.9%). And even for sample size 500, the probability on a type I error was still almost doubled (mean 9.0%, range 7.1%-10.2%). But in an additional simulation for scenario 1 with a sample size of 1000, the probability on a type I error was further reduced to 4.8% and 8.0% for censoring schemes 3 and 4 respectively.

Figures 1 and 2 display a box plot of the difference between Kendall's tau calculated using our method and the true population Kendall's tau from which data was simulated for the sample sizes 100 and 500, respectively. The median bias for censoring schemes 1 and 2 is already very small for sample size 100. For censoring schemes 3 and 4, the median bias is much larger and increases as the true τ is larger. In general the median bias reduces if the sample size is increased to 500. Only for censoring schemes 3 and 4, the median bias remains important in some settings. The variability for censoring schemes 3 and 4 is also substantially larger than for censoring schemes 1 and 2. Also the difference between Kendall's tau calculated using our method for the censored observations and using the standard formulae for the uncensored observations was examined. A similar conclusion as for the difference with the true population value can be made and therefore the results

Table 1: Simulation study: Median difference of $\widehat{\tau}_i - \tau$ ($i = 1, \ldots, 1000$), where $\widehat{\tau}_i$ is given by our method ($B\&L$), the midpoint method (MID) and the method of Betensky & Finkelstein ($B\&F$) in the simulated data sets of size 100 and τ is the true Kendall's tau. $\lambda_1 = \lambda_2$ was imposed for $B\&L$.

		Censoring 10% left 70% interval 20% right			Censoring 10% left 50% interval 40% right			Censoring 5% left 20% interval 75% right			Censoring 75% left 20% interval 5% right		
sc.	τ	B&L	MID	B&F	B&L	MID	B&F	B&L	MID	B&F	B&L	MID	B&F
1	0	−0.00	0.03	−0.00	−0.01	−0.00	−0.01	−0.02	−0.00	0.03	−0.02	0.26	0.05
2	0	0.00	0.04	0.01	−0.01	0.01	−0.00	−0.03	0.02	0.04	−0.04	0.32	0.06
3	0.41	0.01	−0.09	0.03	0.00	−0.18	0.02	−0.01	−0.31	−0.05	−0.07	0.14	−0.04
4	0.63	0.00	−0.12	0.02	−0.01	−0.19	0.02	−0.08	−0.45	−0.17	−0.16	0.03	−0.27
5	0.49	0.02	−0.07	−0.03	−0.02	−0.19	−0.01	−0.07	−0.40	−0.22	−0.03	0.21	−0.13
6	0.54	−0.01	−0.13	0.02	−0.01	−0.17	0.00	−0.09	−0.36	−0.23	−0.12	0.12	−0.18
7	0.26	0.00	−0.02	0.01	0.00	−0.10	−0.00	−0.03	−0.19	−0.08	−0.04	0.24	−0.07
8	0.48	−0.03	−0.07	0.05	0.00	−0.16	−0.00	−0.02	−0.32	−0.15	−0.07	0.12	−0.10

Table 2: Simulation study: Mean Squared error ($\times 10^3$) of $\widehat{\tau}_i$ according to our method ($B\&L$), the midpoint method (MID) and the method of Betensky & Finkelstein ($B\&F$) from the 1000 simulated data sets of size 100. $\lambda_1 = \lambda_2$ was imposed for $B\&L$.

		Censoring 10% left 70% interval 20% right			Censoring 10% left 50% interval 40% right			Censoring 5% left 20% interval 75% right			Censoring 75% left 20% interval 5% right		
sc.	τ	B&L	MID	B&F	B&L	MID	B&F	B&L	MID	B&F	B&L	MID	B&F
1	0	7.4	4.4	11.8	7.1	2.1	9.0	32.7	0.9	12.8	52.3	75.6	25.3
2	0	9.4	7.2	15.2	10.0	3.5	9.9	35.1	1.4	12.4	44.0	112.4	28.5
3	0.41	5.3	10.9	9.4	4.9	33.8	6.4	29.6	94.2	18.5	44.0	26.5	25.9
4	0.63	1.8	16.8	4.5	1.9	39.6	2.6	16.2	202.5	37.1	60.7	7.0	83.3
5	0.49	7.2	8.3	12.8	4.2	40.3	4.2	32.3	160.1	56.0	26.6	48.9	26.8
6	0.54	3.0	20.2	4.0	3.5	30.8	3.7	34.2	133.0	57.3	49.6	18.9	42.9
7	0.26	9.4	4.1	5.9	10.0	12.8	6.8	35.1	35.6	13.6	44.0	62.7	14.5
8	0.48	8.0	9.2	21.8	6.1	28.7	12.2	23.3	105.6	34.6	34.0	21.1	36.3

are not shown.

In addition to our method, both the midpoint approach and the method of Betensky and Finkelstein [1999] have been applied to the simulated data of sample size 100. Tables 1 and 2 show the median bias and Mean Squared Error for the three methods. Except for the midpoint method under censoring scheme 4, all the three methods show a very small bias under all censoring schemes for the scenarios with $\tau = 0$. However, when there is dependence (scenarios 3 to 8), the midpoint method induces a severe bias. For censoring schemes 1 and 2, both the method of Betensky and Finkelstein [1999] and our method show a very low median bias. In general, our method performs somewhat better when when looking at the MSE. For censoring schemes 3 and 4, the median bias using the method of Betensky and Finkelstein [1999] is larger than with our method. However, also our method underestimates the true dependence substantially for some settings. More specifically, the median bias increases as the true dependence is larger. The conclusion for the MSE is less clear. For the lower values of τ the method of Betensky and Finkelstein [1999] has a lower MSE, whereas for the higher values of τ our method has the lower MSE.

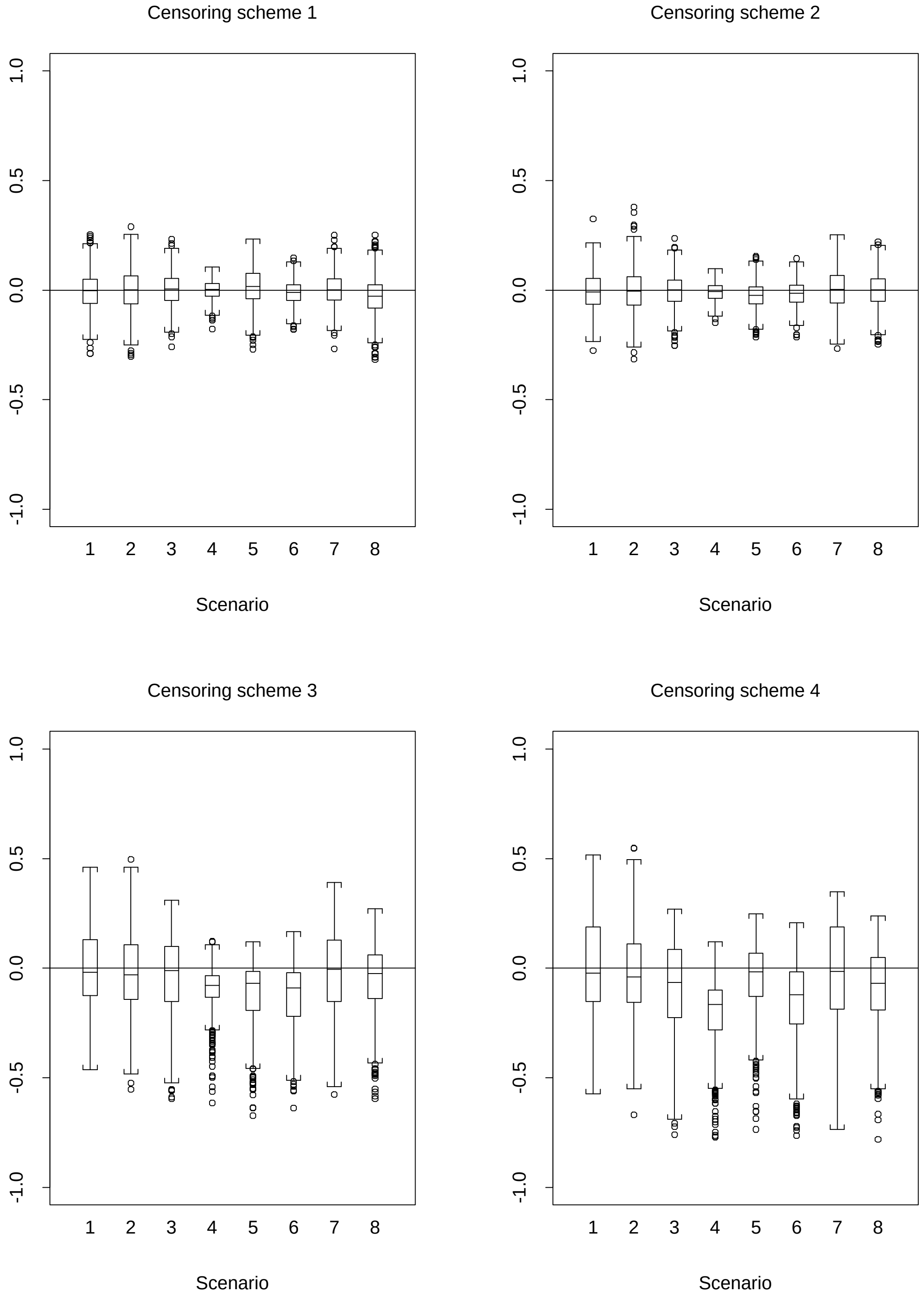

Figure 1: Simulation study: Box plot of $\widehat{\tau}_i - \tau$ $(i = 1, \ldots, 1000)$, where $\widehat{\tau}_i$ is given by (4) in the simulated data set of size 100 and τ is the true Kendall's tau. $\lambda_1 = \lambda_2$ was imposed. The Box plot was created using the function "boxplot" from S-plus version 6.0.

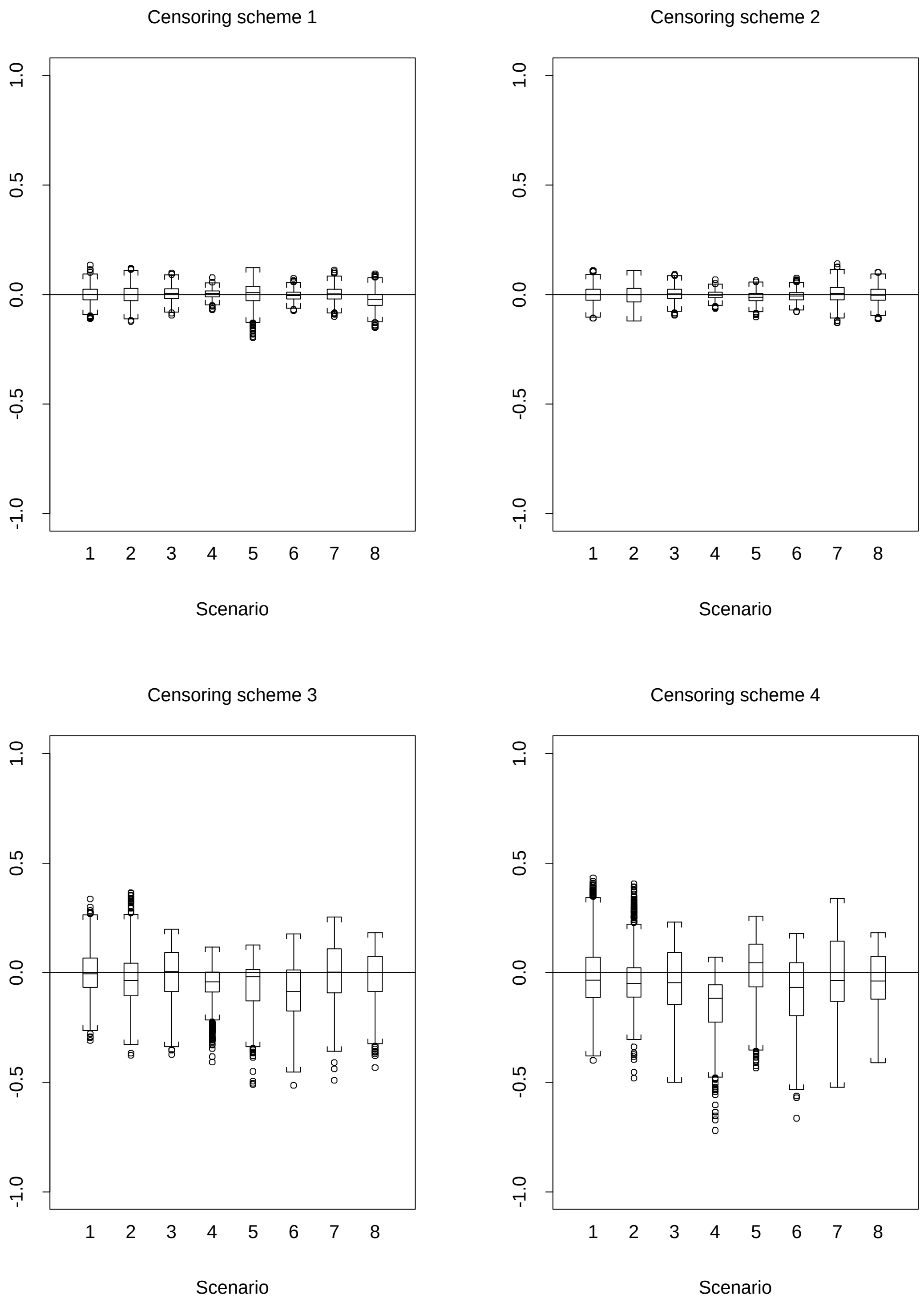

Figure 2: Simulation study: Box plot of $\widehat{\tau}_i - \tau$ ($i = 1, \ldots, 1000$), where $\widehat{\tau}_i$ is given by (4) in the simulated data set of size 500 and τ is the true Kendall's tau. The Box plot was created using the function "boxplot" from S-plus version 6.0.

Table 3: Signal-Tandmobiel®study: Median emergence times and censoring distribution for the teeth of the right side of the upper jaw for boys and girls.

Tooth number	Tooth name	Boys (N=2315) Median (years)	% censoring left	interval	right	Girls (N=2153) Median (years)	% censoring left	interval	right
11	Central incisor	7.08	49	45	6	6.85	62	34	4
12	Lateral incisor	8.25	9	77	14	7.84	21	68	11
13	Canine	11.53	0	39	61	10.91	0	56	44
14	First premolar	10.73	1	56	43	10.31	0	68	32
15	Second premolar	11.62	1	37	62	11.26	0	47	53
16	First molar	6.31	83	15	2	6.14	89	10	1
17	Second molar	12.27	0	19	81	11.95	0	29	71

6 Application to Signal Tandmobiel®Study

The emergence age of a tooth is the chronological age of a child at which that tooth appears in the mouth. Not only the timing, but also the association pattern of (permanent) tooth emergence is of interest to dentists.
The Signal-Tandmobiel®study is a prospective longitudinal survey, which collected dental and oral health behaviour data from a representative sample (N=4468) of Flemish children born in 1989. A detailed description of the Signal-Tandmobiel®project can be found in Vanobbergen et al. [2000]. The children were examined annually on pre-scheduled visits (from the age of 7 to the age of 12) by 16 trained dentist-examiners in a mobile dental clinic on the school premises. The ages at examination over the six years ranged from 6.1 to 12.5 years. Tooth emergence was recorded at each examination by direct inspection. Each permanent tooth was scored according to its clinical eruption stage (adapted from Carvalho et al. [1989]). However, for the present analysis, the status of tooth eruption was dichotomized: not emerged versus emerged. As the children were examined annually, the emergence times are interval-censored. However, since a tooth can emerge before the first or after the last visit also left and right censored emergence times are encountered.
In Europe, the teeth are numbered with a two digit number as follows: the first digit represents the quadrant numbered from 1 to 4 (the upper right quadrant is “1”, upper left “2”, lower left “ 3” and lower right “4”), the second digit refers to the place within the quadrant starting from the midline towards the back of the mouth. The last molar (tooth 18, a wisdom tooth) emerges (if it emerges) at the age of 17 years or later. Since its emergence time could not be recorded in our study we discarded that tooth here. Based on data obtained from the Signal-Tandmobiel®study the distribution of the emergence times for each of the 28 permanent teeth separately were determined for Flemish children from 7 to 12 years of age (Leroy et al. [2003]). Table 3 displays the median emergence times and the censoring distribution for teeth 11 to 17 for for the 2315 boys and 2153 girls of the Signal-Tandmobiel®study, separately. The median emergence times were estimated by fitting a log-logistic model to the data.

As an illustration we measured the association between the emergence times by means of Kendall’s tau for each pair of the first quadrant. A 20×20 grid and a third order difference penalty was applied. The results are presented in Table 4. The highest association for both boys and girls was observed between the two incisors (teeth 11 and 12) and the two premolars (teeth 14 and 15). The lowest association was 0.28, between the second premolar and first molar for boys. From Figure 3 the following trend can be observed for boys: the closer the median emergence times, the higher the correlation. A similar

Table 4: Signal-Tandmobiel®study: Kendall's tau for the teeth of the right side of the upper jaw compared to the results of Parner et al. [2002] (within parentheses). On each second line the 95% confidence interval of the true value of τ based on our method is given within parentheses. Results for boys and girls are presented in the upper and lower part, respectively.

	11	12	13	14	15	16	17
11	1	0.53(0.56)	0.45(0.48)	0.38(0.42)	0.42(0.39)	0.43(0.39)	0.42(0.39)
		(0.50-0.56)	(0.40-0.50)	(0.34-0.41)	(0.38-0.46)	(0.36-0.50)	(0.35-0.48)
12	0.52(0.55)	1	0.46(0.46)	0.32(0.39)	0.35(0.38)	0.33(0.36)	0.35(0.36)
	(0.48-0.55)		(0.43-0.50)	(0.29-0.35)	(0.31-0.39)	(0.25-0.41)	(0.30-0.41)
13	0.43(0.47)	0.46(0.46)	1	0.49(0.57)	0.49(0.48)	0.39(0.39)	0.35(0.39)
	(0.39-0.47)	(0.43-0.49)		(0.45-0.52)	(0.41-0.57)	(0.31-0.47)	(0.27-0.44)
14	0.36(0.43)	0.35(0.41)	0.48(0.57)	1	0.57(0.60)	0.33(0.38)	0.38(0.41)
	(0.32-0.4)	(0.32-0.39)	(0.45-0.51)		(0.53-0.60)	(0.24-0.41)	(0.29-0.47)
15	0.35(0.39)	0.34(0.37)	0.42(0.46)	0.56(0.59)	1	0.28(0.40)	0.35(0.44)
	(0.31-0.4)	(0.31-0.38)	(0.38-0.47)	(0.52-0.60)		(0.23-0.33)	(0.26-0.43)
16	0.40(0.39)	0.36(0.36)	0.42(0.36)	0.33(0.38)	0.34(0.39)	1	0.35(0.62)
	(0.24-0.57)	(0.25-0.48)	(0.32-0.52)	(0.15-0.51)	(0.25-0.42)		(0.19-0.50)
17	0.36(0.39)	0.32(0.36)	0.39(0.38)	0.38(0.40)	0.44(0.44)	0.48(0.60)	1
	(0.30-0.41)	(0.27-0.38)	(0.32-0.45)	(0.33-0.43)	(0.38-0.50)	(0.39-0.57)	

pattern is found for the girls. This relates to the two emergence phases that are observed in Table 3. Namely, there is an early emergence phase for the first molar and the two incisors around 7 years and a later emergence phase for the canine, the two pre-molars and the second molar around 11 and 12 year. Although the emergence times of girls are significantly earlier than those of boys (Leroy et al. [2003]), no significant difference in association could be shown between boys and girls using a two-sample Z-test (see Appendix). The width of the confidence interval is apparently related with the proportion of left, right or interval censored data. Namely, the larger the proportion of left or right censored data, the wider the confidence interval is. This can be explained by the fact that an interval censored observation contains more information about the event time than a left or right censored observation.
In addition, we also calculated the cross ratio function for tooth 14 given that tooth 12 emerged at 8 years. The results are displayed in Figure 4. On the y-axis one can see the ratio of the risk on emergence of tooth 14 for children of a specific age (see X-axis) whose tooth 12 was emerged at 8 years, compared to children of the same age whose tooth 12 was not yet emerged at 8 years. From around 8.5 years the ratio is significantly larger than 1 and keeps increasing over time until 10 years. Afterwards the ratio levels out.

Parner et al. [2002] fitted a bivariate normal distribution to tooth emergence data of Danish children born in 1978. More than 12,000 children were analyzed for both boys and girls. The children were examined annually from 3 to 18 years old. They reported Pearson correlations for all pairs of teeth. For a bivariate normal distribution there exists a relation between Kendall's tau and Pearson's correlation (ρ), namely $\tau = 2sin^{-1}(\rho)/\pi$. When transforming the Pearson correlations reported by Parner et al. [2002] to Kendall's tau's, our correlations were somewhat lower than those of Parner. However, with the exception for 4 and 6 associations for girls and boys respectively, the estimates of Parner et al. [2002] always lie within our 95% confidence intervals. Several reasons can explain the discrepancy. Parner's assumption of a bivariate normal distribution for the emergence times is perhaps not fulfilled. Furthermore, Parner's population is different from ours.

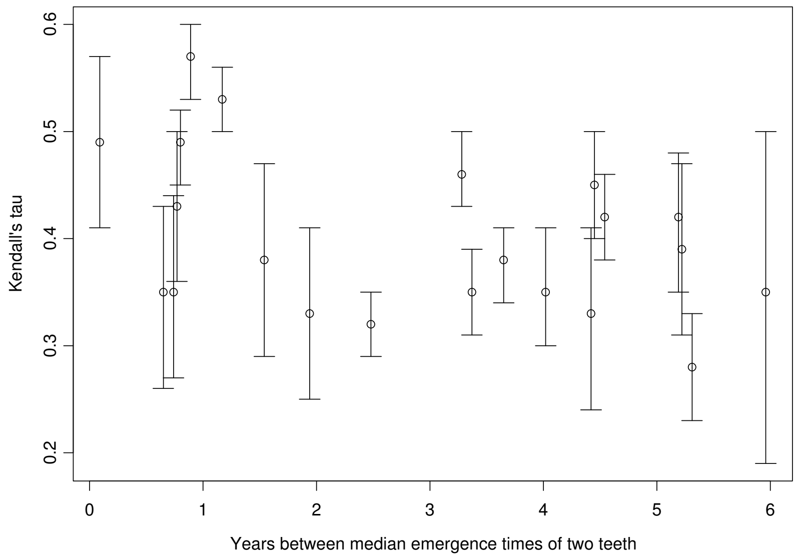

Figure 3: Signal-Tandmobiel®study: $\widehat{\tau}$ with a 95% confidence interval versus the time between median emergence times of two teeth of the right side of the upper jaw for boys.

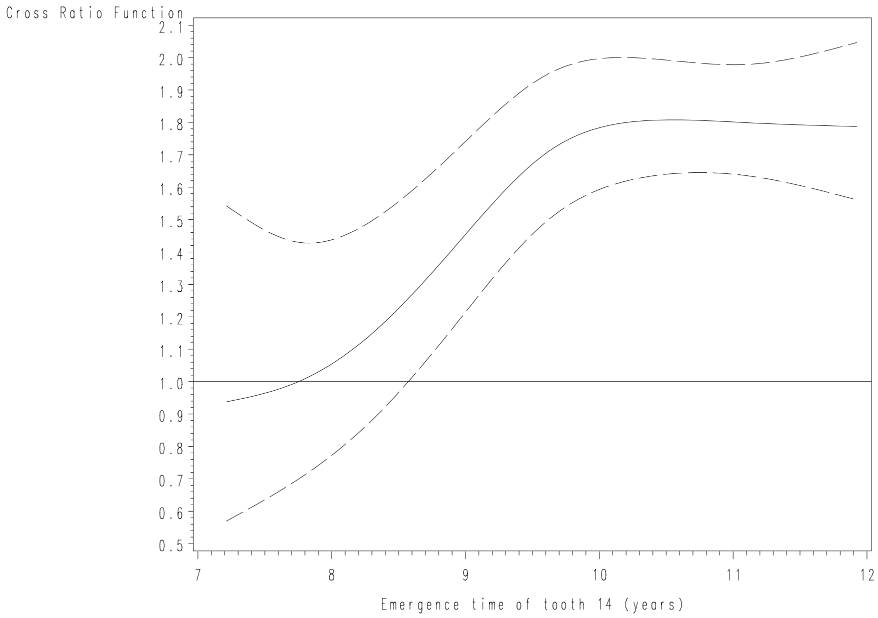

Figure 4: Signal-Tandmobiel®study: The estimated cross ratio function for tooth 14 given tooth 12 emerged at 8 years for boys. The dotted lines represent the pointwise 95% confidence interval.

Indeed, as argued by Leroy et al. [2003], emergence standards should be derived from the population in which they are to be applied since factors related to emergence may vary considerably. Closer inspection of the results show that the discrepancy between our results and those of Parner et al. [2002] was primarily observed for those teeth with extreme right or left censoring (up to 89%) in our study. In order to measure the effect of potential bias in such a case of extreme censoring, an additional simulation study with 1,000 repetitions was performed on a bivariate log-logistic model with a true τ equal to 0.40 (a value observed by Parner et al. [2002]) and on a sample of size 2223. One tooth was about 75% left censored, the other tooth about 75% right censored. The mean difference between the estimated τ's and the true τ was found to be -0.25. Thus, the size of this bias can explain the difference found between our results and the results of Parner et al. [2002]. Indeed, because the Danish children have been followed up over a longer period of time, the proportion of left and right censored observations was much less and therefore the association measure is estimated probably with more precision in Parner's study.
As a conclusion, we can state that the results for the teeth that are highly left or right censored should be interpreted with great caution due to the potential bias on the estimates. However, the observed bias is mostly negative indicating that the true dependence is potential higher than observed.

7 Concluding remarks

It is important to note that our smoothing method is not a classical mixture problem. Indeed, only the mixing weights are estimated because the means and variances of the bivariate standard normal densities are fixed.
The penalty was defined in the parameters a_{ij}. On first sight, it seems more natural to define the penalty in the parameters c_{ij}. However, the computation in c_{ij} implied a significantly higher computation time with more numerical instability. The same was true when the penalty was expressed in terms of c_{ij} but the computations were done in a_{ij}.
In all our settings, a 20×20 grid provided good results. In practice, one can fit several increasing grid sizes to the data. If the results remain similar, this would indicate that a good fit is obtained. Given the grid, calculating the measures of association using our macro is done in a fairly automated way. On an AMD Opteron 244 (1.8 GHz), calculation of the measures of the measures of association for a data set of size 100 and 500 in our simulations without restriction on the smoothing parameters took on average 12 and 26 minutes respectively. However, for smaller data sets like with $N = 100$ and with both smoothing parameters not restricted to be equal to each other, there can be computational difficulties in the grid search. Manually adaption of the values used in the grid search or better starting values can resolve the problems.
We also investigated how sensitive the estimation of Kendall's tau is w.r.t. the choice of the smoothing parameters λ_1 and λ_2. For this purpose, we looked at the estimated τ's from the fit with the next best AIC value. Only very small differences in the estimated τ's were observed.
Considering the quite large bias the midpoint approach can produce, it should be avoided. The method of Betensky and Finkelstein [1999] performs well for small studies and small values of τ but becomes impractical for moderate to large data sets due to an excessive computation time.
In conclusion, we provide a relative easy method for estimating a measure of association for bivariate interval censored data. It performs well for reasonable censoring schemes (up

to 40% right censoring). For heavily right or left censored data, caution must be taken as the estimate can be severely biased for all methods.

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Appendix

Calculation of Kendall's Tau and Spearman's correlation in terms of the coefficients c

The population measure of Kendall's tau for a cumulative distribution function F is defined as $\tau = 4 \cdot \int\int F(t_1, t_2)\mathrm{d}F(t_1, t_2) - 1$. Note that working on the logarithmic scale yields a similar expression, namely $\tau = 4 \cdot \int\int G(u_1, u_2)\mathrm{d}G(u_1, u_2) - 1$ where $G(u_1, u_2)$ is the cumulative distribution function of the log of the event times (u_i =log$(t_i), i = 1, 2$). Denote by $\Phi_2((\mu_i, \nu_j)^T, \Sigma)$ the cumulative bivariate normal distribution with mean $(\mu_i, \nu_j)^T$ and variance-covariance matrix $\Sigma = \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$ and let $\phi_2((\mu_i, \nu_j)^T, \Sigma)$ denote the corresponding density. When we replace G by the cumulative distribution of our smooth estimate in the expression of τ, so $\widehat{G} = \sum_i \sum_j \widehat{c}_{ij} \Phi_2((\mu_i, \nu_j)^T, \Sigma)$, then we obtain

$$\begin{aligned}
\widehat{\tau} &= 4 \cdot \int\int \sum_i \sum_j \widehat{c}_{ij} \Phi_2((\mu_i, \nu_j)^T, \Sigma) \cdot \sum_k \sum_l \widehat{c}_{kl} \phi_2((\mu_k, \nu_l)^T, \Sigma)\mathrm{d}x\mathrm{d}y - 1 \\
&= 4 \cdot \sum_i \sum_j \sum_k \sum_l \widehat{c}_{ij} \widehat{c}_{kl} \int\int \Phi_2((\mu_i, \nu_j)^T, \Sigma) \cdot \phi_2((\mu_k, \nu_l)^T, \Sigma)\mathrm{d}x\mathrm{d}y - 1
\end{aligned}$$

These integrals can be simplified using the fact that in the variance-covariance matrix Σ zero correlation is assumed. Thus

$$\begin{aligned}
&\int\int \Phi_2((\mu_i, \nu_j)^T, \Sigma) \cdot \phi_2((\mu_k, \nu_l)^T, \Sigma)\mathrm{d}x\mathrm{d}y = \\
&\quad \int_{-\infty}^{\infty} \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi} \cdot \sigma_1} \exp\left[-\frac{1}{2}\left(\frac{z - \mu_i}{\sigma_1}\right)^2\right] \mathrm{d}z \cdot \frac{1}{\sqrt{2\pi} \cdot \sigma_1} \exp\left[-\frac{1}{2}\left(\frac{x - \mu_k}{\sigma_1}\right)^2\right] \mathrm{d}x \times \\
&\quad \int_{-\infty}^{\infty} \int_{-\infty}^{y} \frac{1}{\sqrt{2\pi} \cdot \sigma_2} \exp\left[-\frac{1}{2}\left(\frac{z - \nu_j}{\sigma_2}\right)^2\right] \mathrm{d}z \cdot \frac{1}{\sqrt{2\pi} \cdot \sigma_2} \exp\left[-\frac{1}{2}\left(\frac{y - \nu_l}{\sigma_2}\right)^2\right] \mathrm{d}y
\end{aligned}$$

Using transformations these integrals can be converted to integrals of bivariate standard normal densities with zero correlation, i.e.

$$\begin{aligned}
&\int_{-\infty}^{\infty} \int_{-\infty}^{\frac{t\sigma_1 + \mu_i - \mu_k}{\sigma_1}} \frac{1}{\sqrt{2\pi}} \exp\left[-\frac{1}{2}z^2\right] \mathrm{d}z \cdot \frac{1}{\sqrt{2\pi}} \exp\left[-\frac{1}{2}t^2\right] \mathrm{d}t \times \\
&\int_{-\infty}^{\infty} \int_{-\infty}^{\frac{t\sigma_2 + \nu_j - \nu_l}{\sigma_2}} \frac{1}{\sqrt{2\pi}} \exp\left[-\frac{1}{2}z^2\right] \mathrm{d}z \cdot \frac{1}{\sqrt{2\pi}} \exp\left[-\frac{1}{2}t^2\right] \mathrm{d}t
\end{aligned}$$

By taking advantage of the symmetry of the bivariate standard normal distribution, we can rewrite this product of bivariate integrals as a product of univariate cumulative standard normal distributions.

Hence, finally

$$\widehat{\tau} \;=\; 4 \cdot \sum_i \sum_j \sum_k \sum_l \widehat{c}_{ij}\widehat{c}_{kl}\Phi(\frac{\mu_i - \mu_k}{\sqrt{2}\sigma_1})\Phi(\frac{\nu_j - \nu_l}{\sqrt{2}\sigma_2}) - 1.$$

The derivation for Spearman's rho is done analogously and leads to

$$\widehat{\rho}_s \;=\; 12 \cdot \sum_i \sum_j \sum_k \sum_l \sum_p \sum_q \widehat{c}_{ij}\widehat{c}_{kl}\widehat{c}_{pq}\Phi(\frac{\mu_i - \mu_p}{\sqrt{2}\sigma_1})\Phi(\frac{\nu_k - \nu_q}{\sqrt{2}\sigma_2}) - 3.$$

Comparing Kendall's tau or Spearman's rho between two independent groups

Assume we have two independent groups. Let τ_1 and τ_2 denote the true Kendall's tau's in both groups. For a large sample sizes (n_1 and n_2) in both groups, we have that $\widehat{\tau}_i \sim \mathcal{N}(\tau_i, \sigma_i^2/n_i)$ for i=1,2. Therefore we can test $H_0 : \tau_1 = \tau_2$ by a simple two-sample Z-test, i.e. $Z = (\widehat{\tau}_1 - \widehat{\tau}_2)/\sqrt{\sigma_1^2/n_1 + \sigma_2^2/n_2}$.
The derivation for Spearman's rho is done analogously.

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