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A note on assessing agreement for frailty models

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Abstract

Assessing agreement is often of interest in biomedical sciences to evaluate the similarity of measurements produced by different raters or methods on the same subjects. We investigate the agreement structure for a class of frailty models that are commonly used for analyzing correlated survival outcomes. Conditional on the shared frailty, bivariate survival times are assumed to be independent with Weibull baseline hazard distribution. We present the analytic expressions for the concordance correlation coefficient (CCC) for several commonly used frailty distributions. Furthermore, we develop a time-dependent CCC for measuring agreement between survival times among subjects who survive beyond a specified time point. We characterize the temporal pattern in the time-dependent CCC for various frailty distributions. Our results provide a better understanding of the agreement structure implied by different frailty models.

Keywords

Agreement; Frailty models; Concordance correlation coefficient; Bivariate survival times

1. Introduction

The need to assess agreement arises frequently in biomedical science when two raters/methods simultaneously measure an outcome of interest of the same subjects. The similarity between the measurements from the two raters/methods is evaluated to determine whether the two raters/methods are exchangeable or not. For categorical variables, Cohen's kappa statistics with its extensions (Cohen, 1960 and 1968) are the commonly used agreement index.

For correlated continuous outcomes, Lin's (1989) concordance correlation coefficient (CCC) has become a popular measure of agreement. Let X_1 and X_2 denote a pair of continuous outcomes of the same individual assessed by two raters or methods. Lin's (1989) CCC for X_1 and X_2 is defined as

$$\begin{aligned}\rho_c &= 1 - \frac{E[(X_1 - X_2)^2]}{E[(X_1 - X_2)^2 | X_1, X_2 \text{ are independent}]} \\ &= \frac{2\text{cov}(X_1, X_2)}{\text{var}(X_1) + \text{var}(X_2) + [E(X_1) - E(X_2)]^2} = \rho_{\chi a}.\end{aligned}\quad (1)$$

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The CCC can be written as the product of the precision coefficient ρ that measures the strength of association and the accuracy coefficient χ_a that measures the agreement between the two marginal distributions. Here, ρ is the Pearson correlation coefficient and

$\chi_a = \frac{2}{\varpi + \frac{1}{\sigma} + \gamma^2}$ with $\gamma^2 = \frac{(\mu_1 - \mu_2)^2}{\sigma_1 \sigma_2}$ representing the location shift and $\varpi = \sigma_1 = \sigma_2$ representing the scale shift. The CCC ranges from -1 to 1 with a value of 1 representing a perfect agreement, a value of -1 representing a perfect disagreement and a value of 0 representing no beyond chance agreement.

In biomedical sciences, survival times are frequently encountered outcomes. Researchers are often interested in evaluating the agreement between two survival times that are measured on the same subjects. For example, in depression studies, the time of onset of clinical depression are measured using both clinician-administered and patient self-reported scales. Evaluating agreement between the disease onset times is useful in assessing the reliability of patients self-report and identifying an appropriate instrument for diagnosing depression. Special challenges are involved when evaluating agreement with survival times. For example, a common feature of survival data is censoring. A subject's failure time may not be fully observed during the study period due to early dropout or study termination. Most commonly used methods for agreement measures can not accommodate censored observations. Furthermore, survival times are by nature skewly distributed and agreement methods that are based on normal distribution assumption are not appropriate. To solve these issues, Guo and Manatunga (2007 and 2008) have proposed nonparametric estimation methods for agreement measures such as CCC based on estimators of the bivariate survival function.

In this paper, we aim to derive agreement measures for survival times that are modelled with frailty models. Frailty models have been a popular approach to analyze correlated multivariate survival data. In frailty models, the dependence of within-individual survival times is induced by the shared frailty. Common choices for the frailty distribution include the gamma, positive stable and inverse Gaussian. Various frailty distributions generate different dependence structures between bivariate survival times. For example, Oakes (1989) characterized the association between bivariate survival times in terms of a local odds ratio for frailty models. By plotting the estimated odds ratio, one could obtain helpful information in choosing an appropriate frailty distribution. Hougaard (1992) quantified the dependence measures such as the variance of the logarithm of the frailty and Kendall's coefficient of concordance (Kendall's τ) for different frailty distributions. He also found the estimated dependence measures vary significantly across frailty models.

Our objective in this paper is to characterize the strength and structure of agreement between bivariate survival times for commonly used frailty models. We present analytic expressions for Lin's CCC for a class of parametric frailty models. In addition, we propose a time-dependent CCC to describe the agreement between the two survival times among subjects who survive beyond a specified time point. The time-dependent coefficient reflects how the strength of agreement evolves along the time among survivors remaining in the study. The temporal pattern in the time-dependent CCC is derived for various frailty distributions to provide a better understanding of the agreement structure generated by different frailty models.

2. Lin's CCC for frailty models

Let $(T_1; T_2)$ be correlated survival times measured on the same subject with the joint survival function of $S(t_1, t_2) = \Pr(T_1 > t_1, T_2 > t_2)$. Conditional on the shared frailty Y , $T_j, j = 1, 2$ are assumed to follow the Weibull distribution with the survival function,

$$S_j(t_j|Y) = \exp(-\Lambda_j(t_j)Y), \quad j=1, 2,$$

where $\Lambda_j(t_j) = (\eta_j t_j)^Y$ is the conditional cumulative hazard function. Given frailty Y , the survival function $S_j(t_j|Y)$ follows a Uniform(0,1) distribution, which implies $\Lambda_j(t_j)Y$ follows the standard exponential distribution. It then follows

$$T_j|Y \sim \text{Weibull}(Y\eta_j^Y, \gamma), \quad j=1, 2.$$

Let W_1 and W_2 be independent and identically distributed as Weibull(1, γ), the logarithm of the survival times can be written as

$$\log T_j = -\frac{1}{\gamma} \log Y - \log \eta_j + \log W_j, \quad j=1, 2. \quad (2)$$

We can interpret (2) as a linear mixed effects model. The group variation or between-subject variation is represented by the logarithm of the frailty Y . The individual random variation or within-subject variation is represented by $\log W_j$. Note that $\log W_j$ ($j=1, 2$) follow the extreme value distribution. From (2), we have the following results,

$$\begin{aligned} E(\log T_j) &= \frac{1}{\gamma} [\psi(1) - E(\log Y)] - \log \eta_j, & j=1, 2, \\ \text{var}(\log T_j) &= \frac{1}{\gamma^2} [\text{var}(\log Y) + \psi'(1)], & j=1, 2, \text{ and} \\ \text{cov}(\log T_1, \log T_2) &= \frac{1}{\gamma^2} \text{var}(\log Y), \end{aligned}$$

where $\psi(x)$ is the digamma function $\Gamma'(x)/\Gamma(x)$ and $\psi'(x)$ is the trigamma function $d^2 \log \Gamma(x)/dx^2$ with $\psi'(1) = \frac{\pi^2}{6}$. From (1), Lin's CCC for $\log T_1$ and $\log T_2$ is then

$$\rho_c(\log T_1, \log T_2) = \frac{\text{var}(\log Y)}{\text{var}(\log Y) + \psi'(1) + \frac{\gamma^2}{2} (\log \eta_1 - \log \eta_2)^2}. \quad (3)$$

From (3), Lin's CCC depends on the frailty distribution through the variance of the logarithm of the frailty. Note that the CCC is an increasing function of $\text{var}(\log Y)$ which was proposed as a measure of dependence for multivariate survival times from frailty models where larger $\text{var}(\log Y)$ representing stronger association (Hougaard, 2000). As an agreement index, the CCC also measures the difference in the marginal distributions which is represented by the squared difference in the logarithms of η_1 and η_2 in (3).

In Table 1, We present $\text{var}(\log Y)$ for several commonly used frailty distributions: the gamma, positive stable and inverse Gaussian. These three distributions can be united under a three-parameter distribution family called the Power Variance Function (PVF) family (Hougaard, 2000). A distribution belongs to the PVF family if its Laplace transformation $L(s)$ satisfies the following equation,

$$d \log L(s) / ds = -\delta(\theta + s)^{\alpha-1},$$

and is denoted as $PVF(\alpha, \delta, \theta)$. Here, $0 \leq \alpha \leq 1$, $\delta > 0$ and $\theta \geq 0$. The gamma distribution is a special case of the PVF distribution with $\alpha = 0$; the positive stable distribution corresponds to $PVF(\theta=0)$; the inverse Gaussian distribution is $PVF(\alpha=1/2)$. Based on (3) and Table 1, we can derive Lin's CCC for these frailty models.

3. The time-dependent CCC for frailty models

When measuring agreement with survival outcomes, we often need a time-dependent agreement index that conditions on a subject's survival status. For example, in genetic studies, researchers often study twin data to investigate potential genetic influences on life span. But important genetic effects are believed to exist only in old age (Anderson et al., 1992). Hence, research interest in these studies only centers on subjects who survive beyond certain age. A time-dependent measure is also desirable when researchers are interested in the change of agreement across time. We consider a time-dependent CCC for measuring the agreement between $\log T_1$ and $\log T_2$ for subjects whose survival times exceed a specified time point $\underline{t}^0 = (t_1^0, t_2^0)$

$$\begin{aligned} \rho_c(\log T_1, \log T_2 | \underline{T} > \underline{t}^0) &= 1 - \frac{E[(\log T_1 - \log T_2)^2 | T_1 > t_1^0, T_2 > t_2^0]}{E[(\log T_1 - \log T_2)^2 | T_1 > t_1^0, T_2 > t_2^0, T_1, T_2 \text{ are independent}]} \\ &= \frac{2 \text{cov}(\log T_1, \log T_2 | \underline{T} > \underline{t}^0)}{\sum_{j=1}^2 \text{var}(\log T_j | \underline{T} > \underline{t}^0) + [E(\log T_1 | \underline{T} > \underline{t}^0) - E(\log T_2 | \underline{T} > \underline{t}^0)]^2}, \end{aligned}$$

Theorem 1

Define $H_j^0 = \Lambda_j(t_j^0)$ and $e_j = e^{YH_j^0} E_1(YH_j^0)$ ($j=1, 2$) where $E_1(x) = \int_x^\infty t^{-1} e^{-t} dt$ is the exponential integral. We can show the time-dependent CCC is,

$$\begin{aligned} \rho_c(\log T_1, \log T_2 | \underline{T} > \underline{t}^0) &= \frac{2 \text{cov}(e_1, e_2)}{\sum_{j=1}^2 2 \left[E \left[e^{YH_j^0} \int_{YH_j^0}^\infty \log x \frac{e^{-x}}{x} dx \right] - E[\log(YH_j^0)e_j] - \frac{1}{2} \{E(e_j)\}^2 \right] + [\gamma \log \frac{t_1^0}{t_2^0} + E(e_1) - E(e_2)]^2} \end{aligned}$$

where the expectation and covariance functions are evaluated on the conditional frailty distribution $Y | \underline{T} > \underline{t}^0$.

Proof

We can show $S(t_j | \underline{T} \geq \underline{t}^0, Y) = e^{-Y[\Lambda_j(t_j) - \Lambda_j(t_j^0)]}$ for $j = 1, 2$. Because $S(t_j | \underline{T} \leq \underline{t}^0, Y)$ follows Uniform(0,1), we can write that

$$Y(\Lambda_j(t_j) - \Lambda_j(t_j^0)) = Q_j, \quad j=1, 2,$$

where Q_1 and Q_2 are independent and each follows the standard exponential distribution. Therefore, we have the following result given $\underline{T} > \underline{t}^0$ and Y ,

$$\log T_j = -\frac{1}{\gamma} \log Y - \log \eta_j + \log [Q_j + Y \Lambda_j(t_j^0)], \quad j=1, 2. \quad (4)$$

To derive the time-dependent CCC based on (4), we provide the following Lemma,

Lemma 1

Let $Z = \log(Q + a)$ where Q follows a standard exponential distribution and a is a constant. We have the following results,

$$\begin{aligned} E(Z) &= \log a + e^a E_1(a), \\ \text{var}(Z) &= 2e^a \int_a^\infty \log x \frac{1}{x} e^{-x} dx - e^{2a} [E_1(a)]^2 - 2 \log a e^a E_1(a), \end{aligned}$$

From Lemma 1 and (4), we can derive the expressions for $E(\log T_j | \underline{T} > \underline{t}^0)$, $\text{var}(\log T_j | \underline{T} > \underline{t}^0)$ and $\text{cov}(\log T_1, \log T_2 | \underline{T} > \underline{t}^0)$. The time-dependent CCC in Theorem 1 can then be derived through the expectation, variance and covariance functions.

Theorem 1 shows that the time-dependent CCC is evaluated based on the distribution of $Y | \underline{T} > \underline{t}^0$. This conditional distribution represents the updated distribution of the frailty Y among survivors at (t_1^0, t_2^0) . For the three commonly used frailty distributions that belongs to the PVF family, i.e. $Y \sim \text{PVF}(\alpha, \delta, \theta)$ (Table 1), Hougaard (2000) showed the updated distribution of Y given $\underline{T} > \underline{t}^0$ is

$$Y | \underline{T} > \underline{t}^0 \sim \text{PVF}(\alpha, \delta, \theta + \sum_{j=1}^2 \Lambda_j(t_j^0)),$$

which is still in the PVF family.

4. Characterization of temporal patterns in the time-dependent CCC

We evaluate the time-dependent CCC for the three frailty distributions using numerical integration. The conditional distribution for each survival time given the frailty is assumed to be standard exponential, i.e. $\eta_j = 1, \gamma = 1$. To make frailty distributions comparable with respect to the degree of dependence, we followed Hougaard (2000) by choosing parameters in the frailty distributions to produce a Kendall's τ of 0.25. Furthermore, the mean of the frailty $E(Y)$ is set to 1 for the gamma and inverse Gaussian distributions. The positive stable frailty distribution, whose mean $E(Y)$ is infinity by definition, is set at the standard case with $\delta = \alpha$.

We then evaluated $\rho_c(\log T_1, \log T_2 | \underline{T} > \underline{t}^0)$ over the region $(t_1^0, t_2^0) \in (0, 10) \times (0, 10)$ for the three frailty distributions. Results are plotted in Figure 1–3. For all three models, the time-dependent CCC is higher along the diagonal line where $t_1^0 = t_2^0$. As $|t_1^0 - t_2^0|$ increases, the marginal distributions of $\log T_j | \underline{T} > \underline{t}^0 (j = 1; 2)$ become more heterogeneous. Consequently, the time-dependent CCC decreases when (t_1^0, t_2^0) moves away from the diagonal line.

On the diagonal line, the time-dependent CCC remains quite constant for the gamma frailty model but decreases as time increases for both the positive stable and the inverse Gaussian frailty models. More specifically, the CCC decreases very fast in the early period and then levels off at a value close to 0 for the positive stable model. In comparison, the CCC gradually decreases along the time for the inverse Gaussian frailty. The temporal patterns in the diagonal time-dependent CCC for various frailty distributions are consistent with those of the local odds ratio (Oakes, 1989), which is a time-dependent association measure for correlated survival times. Oakes (1989) showed that the odds ratio is constant at all time points for the gamma frailty model but decreases with time for the positive stable and inverse Gaussian frailty models.

Across the region, the time-dependent CCC is generally highest with the gamma frailty model and lowest with the positive stable model. In previous work, Hougaard (1992) had also found the dependence between correlated survival times is usually lower when assuming the positive stable model as compared to other frailty models. The agreement structure of the inverse Gaussian frailty model is intermediate between the gamma and positive stable models.

5. Application

We illustrate the proposed method using the data from a prostate cancer study. Prostate cancer is the most common cancer among US men. Various types of treatments are available where the posttreatment disease free state is defined by different methods for different treatments. All these methods are based on the prostate specific antigen (PSA) with high level PSA indicating cancer relapse. However, different criteria are used to define cancer recurrence (Critz et al., 1996, American Society of Therapeutic Radiation Oncology (ASTRO) consensus criteria, 1997) It is important to assess the agreement between the different definitions of disease free state.

In this study, 1369 men with prostate cancer received simultaneous irradiation by integrating iodine 125 prostate implant with a follow-up external beam radiation. The disease status of all subjects was evaluated every six months after the treatment of the external beam radiation. The posttreatment disease free survival time was defined by two definitions. T_1 is the time elapsed from the end of the irradiation to the time when patients' posttreatment PSA level exceeded the nadir of 0.2ng/ml. T_2 is the time elapsed from the end of the irradiation to the midpoint between the time when the lowest PSA was achieved after irradiation and the time when the first of the three consecutive rises in the PSA level occurred. The two disease recurrence times were subject to independent censoring by the same censoring variable C which represents the end of the follow-up time on a patient.

To select an appropriate frailty distribution for modeling, we first performed an empirical examination of the dependence structure between the two posttreatment disease free survival times. In our previous work (Guo and Manatunga, 2007), we have proposed to estimate the CCC nonparametrically through the bivariate survival function. The nonparametric estimator showed that agreement between the two posttreatment disease free survival times gradually decreases along the time. Following the results of Section 4, the inverse Gaussian frailty is appropriate for describing such time-dependent agreement pattern. Therefore, we fit the inverse Gaussian frailty model with Weibull baseline hazard function. Parameters of our frailty model were estimated using the standard maximum likelihood method. Figure 4 depicts the time-dependent CCC for the two post-treatment disease free survival time based on the estimated inverse Gaussian frailty model. The estimated CCC for all subject is 0.732 which indicates there was substantial agreement between the two survival times. When we considered the agreement among subjects who were free of prostate cancer recurrence for at least one year after the treatment, the estimated time-dependent CCC is 0.494 indicating moderate agreement.

6. Discussion

We investigate the agreement structure for a class of parametric frailty models. Lin's CCC and a time-dependent CCC are derived for several commonly used frailty distributions. Compared to measures of association, agreement measures not only assess the association between the two correlated survival times but also measure the difference in the marginal distributions. In frailty models, the frailty distribution captures the association between the measurements and the difference in the marginal distributions is reflected in the conditional distribution of the survival time given the frailty. Therefore, our estimator involves parameters in both the frailty distribution and the conditional distributions, allowing us to appropriately capture the

agreement structure between bivariate survival times. In comparison, many association measures such as Kendall's τ and Spearman's ρ only depend on the frailty distribution.

The temporal pattern in the time-dependent CCC is considerably different across frailty models. In particular, the agreement of the positive stable model is very high initially but then decreases fast along the time. This is consistent with findings in previous work (Hougaard, 2000) that the positive stable model features a very high early dependence.

We have characterized the agreement structure for a class of parametric frailty model. Our results provide a better understanding of the agreement structures implied by different frailty models and also allow us to readily estimate the time-dependent agreement structure once the frailty model is fitted. Though the parametric model is less flexible as compared to nonparametric approach (Guo and Manatunga, 2007), the proposed methods do have several desirable properties: 1) Since frailty model is commonly used for analyzing correlated survival times, our results offer a convenient tool for quantifying agreement between the survival times; 2) the estimated time-dependent CCC based on the frailty model has a smooth temporal distribution whereas the nonparametric estimates involve step functions that may change abruptly at certain time points. In summary, the proposed methods in the paper provide an estimate of the agreement measures from the frailty modeling perspective which offers a useful alternative to the nonparametric approach in previous work.

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Figure 1.
Plot of the time-dependent concordance correlation coefficient for bivariate standard exponential marginals and gamma frailty, with Kendall's $\tau = 0.25$.

Figure 2.

Plot of the time-dependent concordance correlation coefficient for bivariate standard exponential marginals and positive stable frailty, with Kendall's $\tau = 0.25$.

Figure 3. Plot of the time-dependent concordance correlation coefficient for bivariate standard exponential marginals and inverse Gaussian frailty, with Kendall's $\tau = 0.25$.

Figure 4.
Plot of the time-dependent concordance correlation coefficient for the prostate cancer study
based on inverse Gaussian frailty dependence

Table 1

var(logY) for various frailty distributions.

Frailty model	Laplace transformation of the frailty Y	var(logY)
Gamma	$L(s) = (1 + s/\theta)^{-\delta}$	$\psi'(\delta)$
Positive Stable	$L(s) = \exp(-\delta s^\alpha/\alpha)$	$(\alpha^{-2} - 1)\psi'(1)$
Inverse Gaussian	$L(s) = \exp(-2\delta[(\theta + s)^{1/2} - \theta^{1/2}])$	$\frac{d^2 \log K_\gamma(2\delta\theta^{1/2})}{d\gamma^2} \Big _{\gamma=\frac{1}{2}*}$

$$* K_\gamma(\omega) = \frac{1}{2} \int_0^\infty t^{\gamma-1} \exp\{-\omega(t+1/t)/2\} dt.$$