ASYMPTOTIC THEORY FOR THE GAMMA FRAILTY MODEL WITH DEPENDENT CENSORING

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Abstract. In many clinical studies, there are two dependent event times with one of the events being terminal, such as death, and the other being nonfatal, such as myocardial infarction or cancer relapse. Morbidity can be dependently censored by mortality, but not vice versa. Asymptotic theory is developed for simultaneous estimation of the marginal distribution functions in this semi-competing risks setting. We specify the joint distribution of the event times in the upper wedge, where the nonfatal event happens before the terminal event, with the popular gamma frailty model. The estimators are based on an adaptation of the self-consistency principle. To study their properties, we employ a modification of the functional delta-method applied to Z-estimators. This approach to weak convergence leads naturally to asymptotic validity of both the nonparametric and multiplier bootstraps, facilitating inference in spite of the complexity of the limiting distribution.

Key words and phrases: Bootstrap, dependent censoring, empirical processes, functional delta-method, gamma frailty model, U-statistics, weak convergence, Z-estimators.

1. Introduction

In many clinical studies, there are two dependent event times with one of the events (say Y) being terminal, such as death, and the other being a nonfatal event (say X) such as myocardial infarction or cancer relapse. Often, these studies also have an independent right-censoring time (say U) caused by random loss to follow-up. Because X can be dependently censored by Y but not vice versa, these data pose a semi-competing risks problem. In a recent multi-center clinical trial of allogenic marrow transplants in patients with acute leukemia, the primary endpoint was time to death while an important secondary endpoint was time to relapse (Copelan et al. (1991); Klein and Moeschberger (1997)). An important scientific question is how to estimate the distribution of the relapse times in the presence of the dependent censoring caused by death.

Jiang, Fine, Kosorok and Chappell (2001) (hereafter JFKC) propose a pseudo self-consistency method of estimation under the popular gamma frailty model (Clayton (1978)). However, the details of the asymptotic theory were not provided. The assumed

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model has the form $P(X > x, Y > y) = C_\theta(S_0(x), R_0(y))$, where $S_0$ and $R_0$ satisfy the definition of survival functions, and where, for $\theta \geq 0$ and $u, v \in [0, 1]$, 

$$C_\theta(u, v) \equiv [(u^{1-\theta} + v^{1-\theta} - 1) \vee 0]^{1/(1-\theta)}.$$  

Here we define $C_1(u, v) \equiv \lim_{\theta \to 1} C_\theta(u, v) = uv$ and $C_\infty(u, v) \equiv \lim_{\theta \to \infty} C_\theta(u, v) = u \wedge v$, where $a \vee b$ is the maximum and $a \wedge b$ is the minimum of $a$ and $b$. The model is only on the upper wedge where $x \leq y$. This is weaker than hypothesizing a parametric model for $x > y$, as in traditional competing risks analyses. The pseudo self-consistency methodology proposed in JFKC is insensitive to $P(X > x, Y > y)$ on the lower wedge.  

This robustness is important because the model on the lower wedge is nonidentifiable just as in the case of competing risks data (Tsiatis (1975)). In fact, the parameter $S_0$ is the marginal distribution of $X$ only if $S_0(x) = P(X > x, Y > 0)$. A class of distributions with this property follows. Let $P(X > x, Y > y) = D(S_0(x), R_0(y))$ for $x > y$, where $D(s, r) = P(A > s, B > r)$, $A, B$ are uniform $(0, 1)$ variates with unspecified joint distribution, and $D\{S_0(u), R_0(u)\} = C_\theta\{S_0(u), R_0(u)\}$, for all $u > 0$. Then $P(X > x, Y > y)$ has the same $S_0$ and $R_0$ on both wedges. The copula $D$ is nonparametric and $X, Y$ may be dependent on the lower wedge. Observe that $R_0(y) = P(X > 0, Y > y)$ is the marginal distribution of $Y$, regardless of the model for $x > y$.  

Following Day et al. (1997), $\theta$ in the model on the upper wedge is interpretable as the predictive (Oakes (1989)) hazard ratio. For $x \leq y$, $\lambda(Y | \{X\})/\lambda(y | (x, \infty)) = \theta$, where $\lambda(y | A) = \lim_{\epsilon \to 0} d[P(Y < y + \epsilon | Y \geq y, X \in A)]/d\epsilon$ and $A \subset (0, \infty)$. When $\theta = 1$, $X$ and $Y$ are independent on the upper wedge. Consider the following interpretation of the predictive hazard ratio on the upper wedge in the context of the leukemia example. Take two patients at time $t$: one that has just relapsed and one that has not yet relapsed. There is a $\theta$-fold increase in the probability of death for the relapsed patient relative to the non-relapsed patient at all times $s > t$. This knowledge has clinical implications for disease management. Further details on the interpretation of this model are given in JFKC.  

The basic idea of pseudo self-consistency is to first construct self-consistency equations (Efron (1967)) for $S_0$ and $R_0$ assuming that the association parameter, $\theta_0 \in [1, \infty)$, is known. Next, a consistent estimate of $\theta_0$, $\hat{\theta}_n$, is substituted for $\theta_0$ in these equations and the equations are then solved for the marginal distribution functions. A U-statistic estimating function can be used to estimate $\theta_n$ separately from the marginals (Jiang et al. (1999)). An obvious alternative approach would be to maximize a nonparametric likelihood for the data to estimate $\theta_0$, $S_0$ and $R_0$. The key challenge for establishing consistency would be to demonstrate that the Kullback-Leibler distance uniquely identifies the true parameters (see, for example, Murphy (1994)). Because pseudo self-consistency circumvents estimation of $\theta_0$ via joint maximum likelihood, establishing identifiability of the marginal distributions is simplified. Of course, showing that the equations have a unique solution in the limit is still a formidable task. An added benefit of pseudo self-consistency is that computation of the estimates is relatively straightforward and converges reliably. Furthermore, simulation studies in JFKC demonstrate that the pseudo self-consistency estimates may be more efficient than maximum likelihood estimates for small and moderate sample sizes.  

The fact that the pseudo self-consistency equations contain an estimated parameter precludes the use of existing theory for self-consistency equations (see Tsai and Crowley (1985); and Vardi and Zhang (1992)) and previous asymptotic results for the