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Heterogeneity and varying effect in hazards regression

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ABSTRACT

In the analysis of survival data, when nonproportional hazards are encountered, the Cox model is often extended to allow for a time-dependent effect by accommodating a varying coefficient. This extension, however, cannot resolve the nonproportionality caused by heterogeneity. In contrast, the heteroscedastic hazards regression (HHR) model is capable of modeling heterogeneity and thus can be applied when dealing with nonproportional hazards. In this paper, we study the application of the HHR model possibly equipped with varying coefficients. An LRR (logarithm of relative risk) plot is suggested when investigating the need to impose varying coefficients. Constancy and degeneration in the plot are used as diagnostic criteria. For the HHR model, a 'piecewise effect' (PE) analysis and an 'average effect' (AE) analysis are introduced. For the PE setting, we propose a score-type test for covariate-specific varying coefficients. The Stanford Heart Transplant data are analyzed for illustration. In the case of degeneration being destroyed by a polynomial covariate, piecewise constancy and/or monotonicity of the LRRs is considered as an alternative criterion based on the PE analysis. Finally, under the framework of the varying-coefficient HHR model, the meanings of the PE and AE analyses, along with their dynamic interpretation, are discussed.

1. Introduction

Although survival data are commonly analyzed by the proportional hazards (PH) model (Cox, 1972), nonproportional hazards among treatments or covariates have also attracted much attention in the past few decades (Breslow et al., 1984; Stablein and Koutrouvelis, 1985; O'Quigley, 1994). Under the assumption of *proportionality*, the ratio of hazard rates (or relative risk) associated with different covariate values or their configurations is a time-invariant constant proportional to the difference; and the relative risk between groups is *homogeneous* over strata. However, this is a rather strong assumption. In real applications, nonproportionality arises in plots of hazard rates which may indicate that 'time' itself can implicitly be a variable of concern. Modeling nonproportionality is appealing because it avoids biased inferences (Wu, 2004). A model commonly used is the PH model with varying coefficients (Murphy and Sen, 1991; Murphy, 1993; Marzec and Marzec, 1997; Martinussen et al., 2002):

$$\lambda_{PH}(t;Z) = \lambda_0(t)\exp\{\beta'(t)Z(t)\}, \tag{1}$$

where $\beta(t)$ denotes the varying effect of Z. Although (1) has the flexibility of modeling 'nonproportionality' over time, it still is a homogeneous model. Basically the Cox-type regression and the partial likelihood inference estimate an *average* effect (AE) at the end of an observational period. When its varying-coefficient setting (1) is used, the covariate effect can theoretically be evaluated at any fixed time, but the effect includes the property of homogeneity (or some kind of 'average') with respect to the

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space spanned by the covariate. When time changes, the average is permitted to differ. In this paper, this property of *variation in time* is termed *nonconstancy*.

The heteroscedastic hazards regression (HHR) model proposed by Hsieh (2001) accommodates the nonproportionality from the perspective of *variation over different subjects* (hereafter termed *heteroscedasticity*):

$$\Lambda^*(t;Z,X) = \{\Lambda_0(t)\}^{\exp(\gamma' X)} \exp(\beta' Z), \tag{2}$$

where X and Z may be two vectors of predictable, time-dependent covariates. In terms of the hazard function, model (2) is written as

$$\lambda(t;Z,X) = \lambda_0(t)\exp(\gamma' X)\{\Lambda_0(t)\}^{\exp(\gamma' X)-1}\exp(\beta' Z). \tag{3}$$

Note that neither (2) nor (3) involves a varying coefficient, but that a 'monotone' time-varying effect can still be calculated due to the power factor $\exp(\gamma' X)$, a device that explicitly model heterogeneity. With the HHR model, accordingly, heterogeneity can be decomposed into nonconstancy (variation in time) and heteroscedasticity (variation across subjects). We can thus ask this question: Is there any other source of heterogeneity? In this regard, a straight inclusion of an *interaction* between 'time' and 'heteroscedasticity' leads to the consideration of time-dependent heteroscedasticity, represented by $\gamma(t)$. So model (3) is extended as follows:

$$\lambda_{HHR}(t;Z,X) = \lambda_0(t)\exp\{\gamma'(t)X\}\{\Lambda_0(t)\}^{\exp\{\gamma'(t)X\}-1}\exp\{\beta'(t)Z\}, \tag{4}$$

where $\exp\{\beta'(t)Z\}$ is referred to as the μ-component or the *risk function*, and $\exp\{\gamma'(t)X\}$ as the σ-component.

Inclusion of a varying-coefficient σ-component is not a simple mathematical generalization. To the authors, applications of the HHR model in several event-history data analyses strongly suggest the need of imposing $\gamma(t)$. For example, data in biological sciences have a rather common feature where a varying mean is often complicated by a different variance. This complication can be suitably captured by $\gamma(t)$. In this paper, we reanalyze the famous Stanford Heart Transplant (SHT) data (Miller and Halpern, 1982), but only consider the covariate 'age' (in order to compare with the analysis of Marzec and Marzec, 1997), to study the varying-coefficient HHR model under two analyses.

In the next section, differences between the PH model and the HHR model are illustrated through several artificial examples by plotting the logarithm of the relative risk (LRR plot). A phenomenon called 'degeneration' can indicate the need for the HHR model, rather than the varying-coefficient PH model. In Section 3, we introduce estimating equations along with the sieve method, under the piecewise effect (PE) analysis. We then offer a companion score-type test for varying heteroscedasticity, in Section 4, with a small simulation study. In Section 5, an analysis of the SHT data is reported. Finally, we briefly discuss the applicability of the HHR model and the implication of its varying-coefficient setting.

2. An illustration of the new model

Survival data collected from organ transplant or clinical trials often appear to be heterogeneous over one or several variables. If the heterogeneity arises from a dichotomous variable, it can be diagnosed simply by plotting the Kaplan–Meier (K–M) estimates of the survivor functions for the two groups or their cumulative hazards, to see if the PH rule is sustained. Notice that a possible result of heterogeneity is nonproportionality between different groups. In some cases, nonproportionality can be modeled by the varying-coefficient PH model (1). However, when the covariate of concern (say, Z) is itself the source of heterogeneity and is a continuous variable, the application of (1) is limited and nonproportionality must be carefully diagnosed. With the HHR model and valid estimates, we suggest plotting the logarithm of the (estimated) relative risk ($\log\{\widehat{\lambda}(t;z_j)/\widehat{\lambda}(t;z_i)\}$), abbreviated as the LRR plot, where z_j and z_i represent two possible strata of Z. Here we give examples in which the LRR plot of the PH model keeps the shape of $\beta(t)$, while the curves under the HHR model are diverse.

Consider a 'univariate' case for model (1) leading to LRR $=\beta(t)(z_j - z_i)$; it has the pattern of $\beta(t)$ except for a scale multiplication representing the difference between strata z_i and z_j. Further consider model (4) when $X(=Z)$ is one-dimensional and continuous. The corresponding LRR consists of two parts:

$$\log\{\lambda(t;z_j)/\lambda(t;z_i)\} = \{\sigma(z_j) - \sigma(z_i)\}\log\Lambda_0(t) + \{\beta(t) + \gamma(t)\}(z_j - z_i), \tag{5}$$

in which $\beta(t)(z_j - z_i)$ is complicated by $\{\sigma(z_j) - \sigma(z_i)\}\log\Lambda_0(t)$ and $\gamma(t)(z_j - z_i)$. Numerical examples summarized in Table 1 illustrate some cases where nonproportional hazards cannot be fully accounted for by model (1). The time interval is selected to be $(0,2)$ for all cases.

Table 1
Specified conditions for the varying-coefficient PH and HHR models.

Parameters	$\Lambda_0(t) = t\exp(t)$ $\beta(t) = \sin(\pi t)$	
Covariate	$z_0 = 0, z_1 = 1, z_2 = 2$	
Case A [Fig. 1(a)]	$\gamma = 0$	Varying-coefficient PH model
Case B [Fig. 1(b)]	$\gamma = \log 2$	HHR model with fixed heteroscedasticity
Case C [Fig. 1(c)]	$\gamma = \log 2 \cdot 1(t > 1)$	HHR model with time-dependent heteroscedasticity

A general formula of the assumed model is: $\lambda(t;Z,X) = \lambda_0(t)\{\Lambda_0(t)\}^{\exp\{\gamma(t)Z\}-1}\exp\{\beta(t)+\gamma(t)\}Z$, in which we choose X and Z to be identical.