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On penalized likelihood estimation for a non-proportional hazards regression model

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ABSTRACT

In this paper, a semi-parametric generalization of the Cox model that permits crossing hazard curves is described. A theoretical framework for estimation in this model is developed based on penalized likelihood methods. It is shown that the optimal solution to the baseline hazard, baseline cumulative hazard and their ratio are hyperbolic splines with knots at the distinct failure times.

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1. Introduction

The primary goal in analyzing censored survival data is to assess the dependence of survival time on one or more explanatory variables or covariates. The Cox Proportional Hazards (PH) model has become the standard tool for exploring this association (Cox, 1972). Given a vector of possibly time-dependent covariates $\boldsymbol{z}$, the hazard function at time t is assumed to be of the form $\lambda(t|\boldsymbol{z}) = \lambda_0(t)e^{\boldsymbol{\beta}'\boldsymbol{z}}$ where $\lambda_0(t)$ is the baseline hazard function, denoting the hazard under no covariate effect and $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$ is a p vector of regression coefficients. The focus is on inference for $\boldsymbol{\beta}$, with the baseline hazard function $\lambda_0(t)$, the non-parametric part, left completely unspecified. In spite of its attractive semi-parametric feature, the Cox PH model implicitly assumes that the hazard curves corresponding to two different values of the covariates do not cross. Although this assumption may be valid in many experimental settings, it has been found to be suspect in others. For example, if the treatment effect decreases with time, then one might expect the hazard curves corresponding to the treatment and control groups to converge. Other examples that indicate the presence of non-proportional hazards are detailed in Devarajan and Ebrahimi (2002, 2011) and Wu and Hsieh (2009) and references therein.

In order to provide modeling flexibility that accounts for non-proportional hazards, several models have been proposed and investigated in the literature. In this paper, we describe one such semi-parametric generalization of the Cox PH model in which the hazard functions corresponding to different values of covariates can cross (see Devarajan and Ebrahimi, 2011 and references therein). The survival function corresponding to a covariate vector $\boldsymbol{z}$ is assumed to be of the form

$$S(t|\boldsymbol{z}) = \exp(\boldsymbol{\beta}'\boldsymbol{z})\{S_0(t)\}^{\exp(\boldsymbol{\gamma}'\boldsymbol{z})}, \tag{1.1}$$

where $S_0(t)$ is an arbitrary baseline survival function, and $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ are unknown p vectors of parameters. In terms of cumu-

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lative hazard functions, this model takes the form

$$\Lambda(t|\boldsymbol{z}) = e^{\boldsymbol{\beta}'\boldsymbol{z}}\{\Lambda_0(t)\}^{\exp(\boldsymbol{\gamma}'\boldsymbol{z})}. \tag{1.2}$$

The Cox PH model is obtained as a special case of model (1.2) by setting $\boldsymbol{\gamma} = 0$. The conditional hazard function is

$$\lambda(t|\boldsymbol{z}) = \lambda_0(t)\exp[(\boldsymbol{\beta}+\boldsymbol{\gamma})'\boldsymbol{z} + \{e^{\boldsymbol{\gamma}'\boldsymbol{z}} - 1\}\log\{\Lambda_0(t)\}]. \tag{1.3}$$

The hazards ratio corresponding to two different covariate vectors $\boldsymbol{z}_1$ and $\boldsymbol{z}_2$ is

$$\frac{\lambda(t|\boldsymbol{z}_1)}{\lambda(t|\boldsymbol{z}_2)} = \exp\{(\boldsymbol{\beta}+\boldsymbol{\gamma})'(\boldsymbol{z}_1-\boldsymbol{z}_2) + [e^{\boldsymbol{\gamma}'\boldsymbol{z}_1} - e^{\boldsymbol{\gamma}'\boldsymbol{z}_2}]\log[\Lambda_0(t)]\}. \tag{1.4}$$

Since this ratio is a monotone function of t, the model allows the hazards ratio to invert over time. In other words, it allows crossing of hazard curves. For example, when treatment effect decreases or increases over time, model (1.2) can be applied. This model includes, for the two sample problem, the case of two Weibull and two extreme value distributions differing in both scale and shape parameters. An interesting property of this model is that the ratios of hazard to cumulative hazard functions corresponding to two covariate vectors $\boldsymbol{z}_1$ and $\boldsymbol{z}_2$ are proportional. Using (1.2) and (1.3), it can be shown that

$$\frac{\lambda(t|\boldsymbol{z})}{\Lambda(t|\boldsymbol{z})} = \frac{\lambda_0(t)}{\Lambda_0(t)}\exp(\boldsymbol{\gamma}'\boldsymbol{z}). \tag{1.5}$$

Devarajan and Ebrahimi (2011) discussed the unique properties of this model and provided an interpretation of it. In addition, they demonstrated its relationship to the time-dependent coefficient Cox PH model. For small $\boldsymbol{\gamma}$, Eq. (1.2) reduces to

$$\Lambda(t|\boldsymbol{z}) = e^{\boldsymbol{\beta}'\boldsymbol{z}}\{\Lambda_0(t)\}^{1+\boldsymbol{\gamma}'\boldsymbol{z}}. \tag{1.6}$$

For two different covariate vectors $\boldsymbol{z}_1$ and $\boldsymbol{z}_2$, $\log\{\frac{\Lambda(t|\boldsymbol{z}_1)}{\Lambda(t|\boldsymbol{z}_2)}\} = \boldsymbol{\eta}(t)(\boldsymbol{z}_1-\boldsymbol{z}_2)$, where $\boldsymbol{\eta}(t) = [\boldsymbol{\beta} + \log\{\Lambda_0(t)\}\cdot\boldsymbol{\gamma}]'$. This is the Cox PH model with time-dependent coefficients $\boldsymbol{\eta}(t)$ that allows crossing hazard curves. Quantin et al. (1996) and Devarajan and Ebrahimi (2002) used model (1.2) for goodness of fit testing of the Cox PH model. Inference for model (1.2) has been discussed in Devarajan (2000), Devarajan and Ebrahimi (2011), Hsieh (2001) and Wu and Hsieh (2009).

In the following section, we develop a theoretical framework for estimation in this non-proportional hazards model based on penalized likelihood methods. We show that the optimal solution to the baseline hazard, baseline cumulative hazard and their ratio are hyperbolic splines with knots at the distinct failure times. We conclude by briefly discussing the relationship of this approach to prior computational approaches for this model.

2. Maximum penalized likelihood estimation for the non-proportional hazards regression model

The partial likelihood approach of Cox (1972) is the standard inferential method for the Cox PH model. Due to the PH assumption, the baseline hazard, $\lambda_0(t)$, drops out of this partial likelihood and can be left completely unspecified. On the other hand, it is evident from Eqs. (1.3) and (1.4) that the generalized model (1.2) allows crossing hazard curves over time. Due to the non-constant hazards ratio, a factorization of the likelihood into a "partial" likelihood and a nuisance part is not possible. The baseline hazard must be specified in the likelihood or explicitly estimated. For example, Bordes and Breuils (2006) discussed sequential estimation for semi-parametric models with application to the PH model while Wu and Hsieh (2009) adopted the method of sieves and used piecewise constants for estimating the baseline hazard in model (1.2). Devarajan (2000) and Devarajan and Ebrahimi (2011) harnessed the attractive computational properties of *B*-splines and used a set of cubic *B*-spline basis functions to model the baseline hazard. This spline-based approach can be viewed as a generalization of the piecewise constant approach. Here we develop a theoretical framework for estimating the baseline hazard, baseline cumulative hazard and their ratio using penalized likelihood methods. We show that the maximum penalized likelihood estimate of the baseline hazard and the ratio in model (1.2) are hyperbolic splines with knots at the distinct failure times. We briefly discuss the relationship of this approach to prior computational approaches for approximating the baseline hazard in this model.

The maximum penalized likelihood (MPL) approach applies the method of maximum likelihood to curve estimation. Often in survival analysis, one is interested in estimating the hazard function non-parametrically for a group of individuals in a study in the presence of censoring. In many situations, several other concomitant variables are also included in the study, thus giving rise to regression parameters associated with those variables that need to be estimated as well. First, we give a brief introduction to the concept of maximum penalized likelihood estimation in the context of hazard estimation.

The observed data consist of independent observations on the triple $(X, \delta, \boldsymbol{z})$, where X is the minimum of a failure (or survival) and censoring time pair (T, C), $\delta = I(T \leq C)$ is the indicator of the event that a failure has been observed and $\boldsymbol{z} = (z_1, \ldots, z_p)'$ is a p vector of covariates. The random variables T and C denote the failure and censoring times respectively which are assumed to be independent. We are interested in estimating the hazard function in the presence of

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