Extended Abstract

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Partially exact alternatives to regularization in proportional hazards regression models with monotone likelihood

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Abstract:

Proportional hazards regression models are very commonly used to model time to events in the presence of censoring. In some cases, particularly when sample sizes are moderate and covariates are discrete, maximum partial likelihood estimates are infinite. This lack of finite estimators complicates the use of profile methods for estimating and testing the remaining parameters. This presentation provides a method for inference in such cases. The method builds on similar techniques in use in logistic and multinomial regression and avoids arbitrary regularization. The phenomenon of monotone likelihood is observed in the fitting process of a Cox model if the likelihood converges to a finite value while at least one parameter estimate diverges to $\pm\infty$. Monotone likelihood primarily occurs in small samples with substantial censoring of survival times and several highly predictive covariates. Previous options to deal with monotone likelihood have been unsatisfactory. The solution we suggest is an adaptation of a procedure by Firth (1993, Biometrika80, 27–38) originally developed to reduce the bias of maximum likelihood estimates. This procedure produces finite parameter estimates by means of penalized maximum likelihood estimation. Corresponding Wald-type tests and confidence intervals are available, but it is shown that penalized likelihood ratio tests and profile penalized likelihood confidence intervals are often preferable. An empirical study of the suggested procedures confirms satisfactory performance of both estimation and inference. The advantage of the procedure over previous options of analysis is finally exemplified in the analysis of a breast cancer study. Proportional hazards are often used to model event time data subject to censoring. Small samples involving discrete covariates with strong effects can lead to infinite maximum partial likelihood estimates. A methodology is presented for eliminating nuisance parameters estimated at infinity using approximate conditional inference. Conditional higher-order likelihood inference may then be applied to remaining parameter components. In this paper, we introduce a single-index threshold Cox proportional hazard model to select and combine biomarkers to identify patients who may be sensitive to a specific treatment. A penalized smoothed partial likelihood is proposed to estimate the parameters in the model. A simple, efficient, and unified algorithm is presented to maximize this likelihood function. The estimators based on this likelihood function are shown to be consistent and asymptotically normal. Under mild conditions, the proposed estimators also achieve the oracle property. The proposed approach is evaluated through simulation analyses and application to the analysis of data from two clinical trials, one involving patients with locally advanced or metastatic pancreatic cancer and one involving patients with respectable lung cancer. Prognosis plays a pivotal role in patient management and trial design. A useful prognostic model should correctly identify important risk factors and estimate their effects. In this article, we discuss several challenges in selecting prognostic factors and estimating their effects using the Cox proportional hazards model. Although a flexible semi parametric form, the Cox's model is not entirely exempt from model misspecification. To minimize possible misspecification, instead of imposing traditional linear assumption, flexible modeling techniques have been proposed to accommodate the nonlinear effect. We first review several existing nonparametric estimation and selection procedures and then present a numerical study to compare the performance between parametric and nonparametric procedures. We demonstrate the impact of model misspecification on variable selection and model prediction using a simulation study and an example from a phase III trial in prostate cancer.