Joint estimation of time-dependent and non-linear effects of continuous covariates on survival

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ABSTRACT

In order to yield more flexible models, the Cox regression model, $\lambda(t;x) = \lambda_0(t)\exp(\beta x)$, has been generalized using different non-parametric model estimation techniques. One generalization is the relaxation of log-linearity in x, $\lambda(t;x) = \lambda_0(t)\exp[r(x)]$. Another is the relaxation of the proportional hazards assumption, $\lambda(t;x) = \lambda_0(t)\exp[\beta(t)x]$. These generalizations are typically considered independently of each other. We propose the product model, $\lambda(t;x) = \lambda_0(t)\exp[\beta(t)r(x)]$ which allows for joint estimation of both effects, and investigate its properties. The functions describing the time-dependent $\beta(t)$ and non-linear $r(x)$ effects are modeled *simultaneously* using regression splines and estimated by maximum partial likelihood. Likelihood ratio tests are proposed to compare alternative models. Simulations indicate that both the recovery of the shapes of the two functions and the size of the tests are reasonably accurate provided they are based on the correct model. By contrast, type I error rates may be highly in ated, and the estimates considerably biased, if the model is misspeci ed. Applications in cancer epidemiology illustrate how the product model may yield new insights about the role of prognostic factors.

key words: Cox proportional hazards model; time-dependent e ects; non-linear e ects; regression splines; over-parameterization; hypothesis testing; model selection; residual confounding; bias