Estimation of Nonlinear Interactions in Cox Regression

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Cox's proportional hazards (PH) model is frequently used in medical biostatistics to analyze survival outcomes. For continuous prognostic factors, the standard definition of the PH model assumes a linear relationship with the log hazard. Nonlinear effects of continuous prognostic factors could be accommodated, e.g., by the use of fractional polynomials (FP) or restricted cubic splines. The FP method selects so-called 'powers' to create nonlinear transformations of the original variable, which lead to the best fit in a subsequent Cox regression. Due to the optimal selection, confidence intervals of log hazard ratios have to be estimated by the bootstrap, repeating the selection process in resampled data sets. Here, we consider estimating the interaction of a binary prognostic factor, such as type of treatment or sex, with a continuous prognostic factor, such as haematocrit level. We further assume, as is often seen in practice, that the continuous factor could exhibit different types of nonlinear effects on survival time in both levels of the binary factor. In this context, we explored Firth´s bias corrective (FC) approach for estimating the parameters of the Cox model (Firth, Biometrika 1993, 80: 27-38). The likelihood penalization imposed by FC not only prevents the occurrence of infinite parameter estimates in case of monotone likelihood, but it also provides more accurate estimates in small- or moderately-sized samples without monotone likelihood (Heinze and Schemper, Biometrics 2001, 57: 114-119). Using a newly developed R package for PH regression combining the FC and FP approaches, we performed a comparative analysis of a medical study inferring the gender-specific effect of haematocrit levels on the risk of recurrence of deep vein thrombosis. We also report on a simulation study investigating properties of FC/FP point and interval estimates of nonlinear interaction effects. We conclude that confidence interval estimation for nonlinear interaction effects can be improved by using FC. In the real data analysis, this improvement was most obvious when monotone likelihood occurred frequently in bootstrap resamples.