Modelling Time to Progression
in Multiple Sclerosis

Anneke Neuhaus

Summary

Many questions in medicine but also in other fields require analysis of longitudinal data. Survival analysis provides a powerful tool to handle such data structures. During the collection process of data many mistakes can be made. Incorrect information can be caused by imprecise measurement, retrospectively recording or by an estimation of a single parameter. Ignoring measurement errors could have strong impact on the results of the analyses. Therefore it is necessary to consider information about the error in an analysis.

In 1999 Skinner & Humphreys published an article in which they gave a proposal to handle measurement errors in the response in lifetime data. This publication is based on the Weibull regression model and assumes the independency of time and error. This idea is picked up in this thesis. Several simulation studies are performed to compare the results of the naive Weibull regression model and the adjusted Weibull regression model which considers the information about the measurement error. The superiority of the adjusted estimator over the naive one is shown in a extensive simulation study. It turned out that the superiority increases rapidly with increasing error variance. Furthermore the adjusted estimator is superior for increasing sample size.

To study the results of the naive, the adjusted Weibull regression model and the Cox model a data set of the Sylvia Lawry Centre of Multiple Sclerosis Research is applied. The data set contains different placebo arms of controlled clinical trials. Multiple Sclerosis is a cureless, neurological disease of the central nervous system. Worldwide nearly 2 million people are affected. A central point in the course of the disease is the change to the progressive phase. To predict this point of time it is important to identify covariates affecting this time to progression. The problem which occurs in this question is the uncertainty about this changepoint. This point is estimated on the basis of information about the course of each patient. The underlying model was defined in close collaboration with leading neurologists. The results of the survival regression models are different and depend on the sample of patients. The main statement of the survival analyses is that the risk
of changing in the progressive phase increases with time. Furthermore the number of attacks show in many subgroups a significant effect on time to progression. Patients with a higher number of attacks in the last two years before entering the study stay a longer period in the first phase.

The performed simulation studies and analyses assume the independency of time and error. Since this assumption is debatable in practical applications extensions to model a dependent structure are necessary. Another possibility is the extension of the classic Cox model to data overlayed by an error.