

Modelling the Disease Course of Multiple Sclerosis with Mixed Effects (Diploma Thesis, Claudia Lamina)

This thesis was aimed at finding new statistical methods for analyzing and predicting the clinical progression of MS patients within clinical trials. The available data were those from 17 placebo-controlled clinical trials provided by the first releases of the SLCMSR database from spring 2002.

The common statistical tools used in the MS community focus on “time to event” as endpoints, for example time to worsening, defined by an increase of 1 point in EDSS. However, a lot of available information is lost. To take advantage of the repeated measures on MS patients participating in a clinical study, the dataset has been analyzed longitudinally and change in EDSS has been taken as the interesting response variable. Then, the modified covariance structure was to be taken into account by introducing an additional random effect within a mixed model. This subject-specific effect can also be thought of explaining unobserved heterogeneity, which is a crucial point in MS disease progression.

Several covariates were available for analysis, such as age at disease onset, gender, the EDSS value at the first observation in the study, duration of the disease, the disease course and the time from first observation. To ensure, that all relationships between covariates and the response variable were detected, metric variables were modelled with smooth functions: Bayesian P-Splines.

The analysis of the data showed, that random effects explain a substantial part of the variance in the data. To assess the heterogeneous disease progression adequately, the introduction of subject-specific intercepts, slopes and quadratic slopes was necessary. That is, the model accounts for a different disease progression of each patient in addition to an “average” disease profile. Overall, the entry EDSS appears to be of big influence on the change in EDSS within the timeframe of a clinical trial. Patients enrolled in a study with an EDSS lower than 2 or bigger than 5.5 can be expected to experience a higher increase in disability as patients in between. The effects of duration of disease, age at onset and gender are neglectable. However, there is a “positive” time trend: The more time elapses, the higher is the change in EDSS. The course of the disease also emerged as a predictive factor: The disability of patients, which are categorized in one of the progressive courses, increases more compared to a relapsing-remitting disease course.

The proposed mixed model within a Bayesian framework emerged as a reasonable tool for analyzing heterogeneous longitudinal data as in MS clinical trials. In any case, it proves useful to leave common paths of statistical analysis in MS research to approach the goal of a “virtual patient”.