Statistical methods for frailty models: studies on old-age mortality and recurrent events

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Summary

Frailty models continue to play an important role in the analysis of time-to-event data. Introducing a positive random effect, the frailty, that affects the risk of experiencing the event of interest can account for unobserved heterogeneity between individuals. In studies of multivariate survival data, frailties can also be used to account for the dependence between observations on the same individual or on different units belonging to a cluster. A variety of frailty models have been proposed in different contexts, ranging from frailty proportional hazards models for univariate survival data, to shared frailty models for clustered survival data, to joint frailty models in which two or more event processes are modeled simultaneously. Although considerable advances have been made in this field in recent decades, further developments of the methodology are often needed to handle specific applications.

In this thesis, we extend the available statistical techniques for inference in two distinct frailty models. In the first part, we focus on a frailty proportional hazards model for studying human adult mortality. With the aim of identifying methods that allow for a reliable assessment of the mortality trajectory at advanced ages, we discuss aspects of parameter estimation, hypothesis testing, and study design in this model, as well as model selection. The second part is concerned with inference in a joint frailty model for recurrent events and a terminal event in settings in which there is delayed entry, or in which the recurrence process is observed only intermittently. In the following, we provide a more detailed overview of the individual chapters.

Chapter 1 gives a brief introduction to frailty modeling of time-to-event data in general, and provides some background information on the models and the methods we study in the two following parts of the thesis.

In the first part of the thesis, which consists of Chapters 2 to 4, we examine different aspects of statistical studies on a demographic phenomenon known as mortality deceleration. This slowing down of the death rates at advanced ages is analyzed in the framework of the gamma-Gompertz model. In this frailty proportional hazards model, the deceleration arises as an effect of selection, because the group of survivors to older ages is made up of the more robust individuals with lower mortality risks. The competing situation without mortality deceleration occurs if the frailty variance takes the value of zero. The model is then simplified to the Gompertz model. However, in this case, the frailty variance lies on the boundary of its parameter space. This non-standard condition of a 'boundary parameter' requires adjustments of the statistical methods used for detecting the potential

deceleration of the death rates. Moreover, conducting empirical investigations of old-age mortality can be challenging due to the scarcity of data at the tail of the survival distribution. In addition, as a scientific validation of the ages at death is often compulsory, but is naturally subject to time and cost constraints, samples may be restricted to cover only survivors beyond a certain age. In light of these challenges, we study and compare different approaches for assessing mortality deceleration in the first part of the thesis.

Chapter 2 examines the asymptotic properties of likelihood inference in the gamma-Gompertz model, as well as the Akaike information criterion (AIC) for this model. Due to the boundary parameter, the standard results of likelihood theory for regular problems do not hold in this setting. Our derivations are based on a framework of local alternatives. We find that the maximum likelihood estimator in the gamma-Gompertz model asymptotically follows a mixture distribution if the underlying frailty variance is small. Similarly, the test statistic of a likelihood ratio test for a zero frailty variance asymptotically has a mixture distribution. An explicit formula for the approximate local power of this test to detect a positive frailty variance is presented. Moreover, we prove that the standard formula for the AIC does not apply to the gamma-Gompertz model, but gives a biased estimate of the corresponding Akaike information.

In Chapter 3, we discuss issues of study design for old-age mortality studies based on the gamma-Gompertz model, and introduce information measures for evaluating such designs. The design aspects we consider include the choice of the age range covered by a sample and the sample size. Drawing on the theory of optimal design, we define different information measures as scalar functions of the Fisher information matrix of the gamma-Gompertz model. Interpretations of these measures are provided, including with regard to the non-standard condition of the boundary parameter. We demonstrate how the proposed measures can be used to appraise different study designs. The approach is complemented by calculations of the power of a likelihood ratio test to detect a deceleration in the death rates in specific design settings. We find that in the scenarios we consider, the information carried by the data and the power of the test are markedly reduced if only survivors to increasingly high ages are included in a study. In an application of the proposed methods to mortality data of French-Canadians born in the late 19^{th} century, we investigate the potential benefits for the statistical analysis if information on deaths at ages 85-89 could be added to an existing data set on survivors beyond age 90.

In Chapter 4, we introduce focused model selection as a new method for assessing mortality deceleration. A focused information criterion (FIC) evaluates the model performance for a specific parameter of interest, the focus parameter, and therefore allows us to address model performance at the advanced ages for which mortality deceleration is most evident. We derive formulas of a FIC for choosing between two candidate models that differ only by a boundary parameter. In a simulation study, we investigate how this new version of the FIC performs when selecting between the gamma-Gompertz model and the Gompertz model depending on the choice of the focus parameter. We find that compared to a modified version of the AIC that includes a bias correction term based on the results of Chapter 2, the FIC is a more reliable tool for detecting a deceleration in the

death rates. Model selection using the new information criteria is also illustrated with the French-Canadian mortality data.

The second part of the thesis, which consists of Chapters 5 and 6, deals with the study of recurrent events in the presence of a terminal event. A joint frailty model is applied to account for the potential dependent censoring of the recurrence process by the terminal event. The model incorporates an additional association parameter that governs whether and, if so, to what extent higher recurrence rates imply that there is a higher or a lower hazard of experiencing the terminal event. Up to now, inference in this joint frailty model has been studied mainly in ideal situations in which the recurrence times are known exactly, and individuals are observed from the moment they become at risk of experiencing the events of interest. We adapt the statistical methods to two other common observational settings. In the first setting, only interval counts of the recurrent events, which give the numbers of recurrences in specific time intervals, are available. In the second setting, individuals are included in the study only after the processes have started, resulting in left truncation. In both settings, parameter estimation is based on the marginal likelihood, which is approximated using Gaussian quadrature. For the baseline rates, we adopt piecewise constant models.

In Chapter 5, we present the studies with interval counts of recurrent events in a general setting in which the observation intervals can vary across individuals. Apart from the estimation method, we also adjust a score test to the setting with interval counts, which allows us to assess the association between the recurrent events and the terminal event before estimating the joint model. Both the estimation and the testing procedure perform well on simulated data. We apply the methods to determine whether asexual reproduction and mortality in the marine organism *Eleutheria dichotoma* are related.

In Chapter 6, we address the issue of delayed entry into recurrent event studies with a terminal event. In such cases, individuals can be included in the study only if the terminal event has not yet occurred for them at the start of the study. If the recurrence rates and the hazard of the terminal event are associated, this selection can lead to differences between the frailty distributions in the sample and the underlying population. In simulation studies, we demonstrate that neglecting the selection effects on the frailty distribution in the construction of the likelihood can bias the estimation results. Furthermore, we show how different observation schemes, and corresponding patterns of incomplete information, affect the performance of the estimation procedure. The proposed method enables us to study recurrent urinary tract infections in an elderly population while using age as the main time scale.