Modeling Two-state Disease Processes with Random Effects

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Abstract. Many chronic medical conditions are manifested by alternating sojourns in symptom-free and symptomatic states. In many cases, in addition to their relapsing and remitting nature, these conditions lead to worsening disease patterns over time and may exhibit seasonal trends. We develop a mixed-effect two-state model for such disease processes in which covariate effects are modeled multiplicatively on transition intensities. The transition intensities, in turn, are functions of three time scales: the semi-Markov scale involving the backward recurrence time for the cyclical component, the Markov scale for the time trend component, and a seasonal time scale. Multiplicative bivariate log-normal random effects are introduced to accommodate heterogeneity in disease activity between subjects and to admit a possible negative correlation between the transition intensities. Maximum likelihood estimation is carried out using Gauss-Hermite integration and a standard Newton-Raphson procedure. Tests of homogeneity are presented based on score statistics. An application of the methodology to data from a multi-center clinical trial of chronic bronchitis is provided for illustrative purposes.

Keywords: bivariate frailty, marginal likelihood, multiple time scales, score test, two-state processes.

1. Introduction

In many chronic diseases, subjects experience symptom-free and symptomatic periods occurring in an alternating fashion. For example, patients with chronic bronchitis experience acute exacerbations of symptoms which typically alternate with periods of good respiratory health (Fietta et al., 1992). Other clinical examples arise from fields such as gastroenterology (Rokkas et al., 1995), infectious disease (Nagelkerke et al., 1990), and psychiatry (Frank et al., 1990). Such chronic conditions are often quite naturally modeled as a two-state stochastic process. The context of the problem will often suggest an appropriate time scale, with the two most obvious being based on Markov or semi-Markov assumptions.

Markov and semi-Markov processes are widely used for the analysis of event history data. For example, Prentice et al. (1981) considered regression models for Markov and semi-Markov processes in the context of point processes arising from recurrent infections, Andersen and Rasmussen (1986) considered Markov and semi-Markov models for a two-state process characterizing hospitalization data, and Andersen (1988) applied a three-state Markov model for a study of nephropathy and mortality in diabetes. Cox (1986) provided a general account of multi-state semi-Markov models for the study of quality of life, and Clayton (1988) reviewed some common models and methods of analysis for event history data. In general, Markov processes are appropriate for degenerative disease conditions in which it is meaningful to model transition intensities with respect to some common time origin. Such degenerative conditions can be said to exhibit time trends. In
contrast, semi-Markov models are appropriate for relatively stable conditions with fairly regular cycles of relapsing and remitting disease activity. Since many chronic conditions exhibit both degenerative trends and relapsing and remitting disease cycles, it is desirable to adopt a general framework which addresses both of these aspects. Cox (1972) introduced modulated renewal and Poisson processes, which accommodate two time scales thereby allowing us to model the trend and renewal (cyclical) behavior simultaneously. Maximum likelihood estimation procedures were suggested by Oakes and Cui (1994) and Lawless and Thiagarajah (1996).

In addition to the use of multiple time scales, extensive subject-to-subject variability in the transition rates often complicates the analysis of event history data arising from chronic diseases. This subject-to-subject variability is termed heterogeneity, or overdispersion, and may be due to latent covariates, or possibly covariates observed with measurement error. To accommodate these additional sources of variability in transitional models, subject-specific random effects, or frailties, are often adopted (Clayton and Cuzick, 1985; Aalen, 1988, 1994; Nielsen et al., 1992; Klein, 1992). In multi-state models of the sort considered here, it is natural to consider multivariate frailties to separately model the heterogeneity across subjects, and the correlation between the transition intensities within a subject. Apart from somewhat restrictive models involving composite frailties (Clayton and Cuzick, 1985; Yashin et al., 1995), this area seems to have received little attention. A notable exception is Aalen (1987), where a variety of mixing distributions are considered for applications to multi-state Markov chains. A model of this sort was also considered by Cook and Ng (1997) for a discrete-time two-state Markov process in which a logistic-bivariate normal model was used to describe heterogeneity in data from an infection field study (Chunge, 1989). In addition, Xue and Brookmeyer (1996) proposed a mixed-effect model for alternating renewal processes using a bivariate log-normal frailty to study in-patient mental health care.

The objective of this article is to present methods for modeling disease activity for chronic conditions which can be characterized by a mixed continuous-time two-state process. The models we consider are quite general in that they accommodate both Markov and semi-Markov structure, as well as heterogeneity in the disease processes. In section 2 we discuss the components of the models, these being the baseline transition intensities and the bivariate mixing distribution. In section 3 we describe the construction of score test statistics for testing the assumption of a homogeneous disease process across subjects. In section 4, we present an application to data from a long-term study of chronic bronchitis. Finally in section 5, we give some concluding remarks and topics for future research.

2. A Mixed Two-state Process

2.1. Model Formulation

Let states 1 and 2 represent symptom-free and symptomatic states respectively. Suppose \( m \) subjects are followed over time to generate data on \( m \) independent two-state processes. We refer to the time since the initiation of the process as the basic (Markov) time scale and denote it by \( t > 0 \). The basic time scale may be, for example, the age of the subject, the time since the diagnosis of the disease, or the time since the first visit to clinic. Let \( N_{ij}(t) \)