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The Additive-multiplicative Hazards Model for Multiple Type of Recurrent Gap Times

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Abstract: Recurrent event gap times data frequently arise in biomedical studies and often more than one type of event is of interest. To evaluate the effects of covariates on the marginal recurrent event hazards functions, there exist two types of hazards models: the multiplicative hazards model and the additive hazards model. In the paper, we propose a more flexible additive-multiplicative hazards model for multiple type of recurrent gap times data, wherein some covariates are assumed to be additive while others are multiplicative. An estimating equation approach is presented to estimate the regression parameters. We establish asymptotic properties of the proposed estimators.

Key words: additive-multiplicative hazards model, estimating equation, gap time, multiple recurrent event data, semi-parametric regression model

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1 Introduction

Recurrent event data are frequently encountered in biomedical studies, reliability studies and social sciences when each subject experiences the outcome of interest repeatedly over time. Examples include repeated tumor metastases, multiple infection episodes, recurrent strokes and repeated hospital admissions. A key feature of this type of data is that the different event times within each subject are ordered and thus correlated. Therefore, we can view recurrent event data as a special case of multivariate failure time data.

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Statistical analysis of recurrent event data has received great attention during the last two decades. For example, Prentice *et al.*[1], Anderson and Gill[2] and Zeng and Lin[3] proposed the conditional intensity model approaches; Pepe and Cai[4] and Lin *et al.*[5] proposed the marginal methods based on the mean or rate function; Nielsen *et al.*[6] and Zeng and Lin[7−8] proposed the intensity-based models with random effects. In many applications, multiple type recurrent events may occur where subjects may experience several different but related types of recurrent events. For example, infections in bone marrow transplantation may be classified into bacterial, fungal and viral infections; hematology/oncology patients may suffer from different febrile nonhemolytic transfusion reactions. Many authors have investigated the statistical analysis of multiple type of recurrent event data, for example, see [9–12]. In medical and epidemiology studies, gap time between successive events is often of primary interest. Recently, much effort has been devoted to gap times. Lin *et al.*[13], Wang and Chang[14] and Peña *et al.*[15] have developed nonparametric methods to estimate the common marginal survival function of gap times. Several authors have considered the marginal hazards models to evaluate the effects of covariates on the marginal hazard function of gap times. For example, Huang and Chen[16] and Sun *et al.*[17] assumed that the gap times follow from some renewal process and proposed multiplicative and additive hazard models of gap times, respectively; Schaubel and Cai[18] studied proportional hazards of gap times without specifying the dependent structure between gap times. The frailty models were used to analyze gap times by some authors, such as Fong *et al.*[19] and Huang and Liu[20].

The existing marginal hazards models assume that effects of the covariate on the hazard function are additive or multiplicative. However, these two different types of effects could coexist in the same model. Lin and Ying[21] considered a general additive-multiplicative hazards model, which takes the following form:

$$\lambda(t \mid \boldsymbol{Z}) = g\{\boldsymbol{\beta}_0^{\mathrm{T}}\boldsymbol{W}\} + \lambda_0(t)h\{\boldsymbol{\gamma}_0^{\mathrm{T}}\boldsymbol{X}\}, \tag{1.1}$$

where $\boldsymbol{Z} = (\boldsymbol{W}^{\mathrm{T}},\ \boldsymbol{X}^{\mathrm{T}})^{\mathrm{T}}$ is a column p-vector of covariates and $\boldsymbol{\theta}_0 = (\boldsymbol{\beta}_0^{\mathrm{T}},\ \boldsymbol{\gamma}_0^{\mathrm{T}})^{\mathrm{T}}$ is an unspecified vector of parameters of interest. $g(\,\cdot\,)$ and $h(\,\cdot\,)$ are known link functions and $\lambda_0(\,\cdot\,)$ is an unspecified baseline hazard function. Note that the model (1.1) assumes that the effects of $\boldsymbol{W}$ are additive while those of $\boldsymbol{X}$ are multiplicative. Obviously, the model (1.1) defines a class of important statistical models, which includes the multiplicative hazards model and the additive hazards model as its special cases. In this paper, we are interested in generalizing (1.1) to the multiple type recurrent gap times and making inference about the regression coefficients.

The rest of this paper is organized as follows. In Section 2, we present an estimating equation approach for inference about regression parameters and the cumulative hazard function. The asymptotic properties of the proposed estimators are established in Section 3. The technical proofs are contained in Section 4.

2 Models and Statistical Methods

Assume that there are n subjects and K different types of recurrent events. For each subject i and the event of type k, let T_{ikj} denote the time from the $(j-1)$th occurrence to the jth