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# Goodness-of-fit test of the stratified mark-specific proportional hazards model with continuous mark

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ABSTRACT

Motivated by the need to assess HIV vaccine efficacy, previous studies proposed an extension of the discrete competing risks proportional hazards model, in which the cause of failure is replaced by a continuous mark only observed at the failure time. However the model assumptions may fail in several ways, and no diagnostic testing procedure for this situation has been proposed. A goodness-of-fit test procedure for the stratified mark-specific proportional hazards model in which the regression parameters depend nonparametrically on the mark and the baseline hazards depend nonparametrically on both time and the mark is proposed. The test statistics are constructed based on the weighted cumulative mark-specific martingale residuals. The critical values of the proposed test statistics are approximated using the Gaussian multiplier method. The performance of the proposed tests is examined extensively in simulations for a variety of the models under the null hypothesis and under different types of alternative models. An analysis of the 'Step' HIV vaccine efficacy trial using the proposed method is presented. The analysis suggests that the HIV vaccine candidate may increase susceptibility to HIV acquisition.



## 1. Introduction

In preventive HIV vaccine efficacy trials, the study cohort is exposed to many genetic types of circulating HIVs but the vaccine only contains HIV antigens based on one or a few types, and the vaccine protection is likely to be lower against the infecting types that are not in the vaccine construct (Gilbert et al., 1999). The similarity/dissimilarity between two HIV viruses can be measured by the genetic distance or 'mark' defined as the weighted percent mismatch of amino acids between two aligned HIV sequences. Since this distance may be unique for all infected subjects, it is natural to consider it as a continuous mark variable. A partially efficacious vaccine would likely provide better protection against infecting HIV types close to the type(s) in the vaccine construct than against infecting HIV types with greater genetic distance. Inferences about how vaccine protection varies with the mark influences the iterative development of efficacious vaccines.

Because the mark is only available for trial participants who become infected with HIV, Gilbert et al. (2004) investigated this problem under a competing risks model, where the cause of failure, a term used in the classical competing risks model,

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is replaced by the continuous mark. Gilbert et al. (2004) developed statistical methods to evaluate the dependence of the mark-specific hazard rate on the mark defined as the divergence of infecting HIV types from an HIV type(s) contained in the vaccine. Also for a continuous mark variable, Gilbert et al. (2008) developed statistical methods for assessing mark-specific HIV vaccine efficacy. Sun et al. (2009) extended this work to assess continuous mark-specific HIV vaccine efficacy adjusting for covariate effects. The methods were applied to analyze the first HIV vaccine efficacy trial conducted by VaxGen Inc. from 1998 to 2003 in North America and the Netherlands.

The competing risks model with continuous marks also has applications in other situations. In the development of flu vaccines, the endpoint is clinically significant infection with flu and the mark of interest is the genetic distance between the infecting flu virus and the virus represented in the vaccine. It is well known for flu vaccines that moderate genetic mismatch between an exposing flu virus and the virus represented in the vaccine causes vaccine failure, which has necessitated development of a new vaccine each year that is closely matched to the contemporary circulating flu strains. In studies of quality-adjusted lifetime (Olschewski and Schumacher, 1990), the lifetime medical cost is a mark variable measured at death. In another example (Huang and Louis, 1998), the endpoint is onset of a disease and the mark is the incubation period between infection and disease onset. Recent competing risks failure time research in CSDA includes Han and Balakrishnan (2010), Cramer and Schmiedt (2011), and Feizjavadian and Hashemi (2015).

Let $T$ be the failure time, $V$ a continuous mark variable, and $Z(t)$ a time-dependent $p$-dimensional covariate. The conditional mark-specific hazard function is defined as $\lambda(t, v|z) = f(t, v|Z(t) = z)/S(t|Z(t) = z)$, where $f(t, v|Z(t) = z)$ is the conditional density of $(T, V)$ at $(t, v)$ given $Z(t) = z$ and $S(t|Z(t) = z)$ is the conditional survival function of $T$ at $t$ given $Z(t) = z$. Let $\lambda_k(t, v|z)$ be the conditional mark-specific hazard function at time $t$ with mark $v$ for a subject in stratum $k$ with covariate $z$. We assume that the mark $V$ takes value in the interval $[0, 1]$, rescaled if necessary. The stratified mark-specific proportional hazards (PH) model posits that

$$\lambda_k(t, v|z) = \lambda_{0k}(t, v) \exp\{\beta^T(v) z(t)\}, \quad \text{for } t \geq 0,\ 0 \leq v \leq 1, \tag{1}$$

for $k = 1, 2, \ldots, K$, where $K$ is the number of the strata, $\lambda_{0k}(t, v)$ is an unspecified baseline mark-specific hazard function for stratum $k$, $z(t)$ is a $p$-dimensional possibly time-dependent covariate and $\beta(v)$ is a $p$-dimensional vector of regression functions.

Sun et al. (2009) developed an estimation method for model (1) when $K = 1$. In practice, different key subgroups (e.g., men and women; subjects living in different geographic regions) typically have different baseline mark-specific hazards of HIV infection. Model (1) is a generalization of the mark PH model of Sun et al. (2009), allowing different baseline functions for different strata. Sun and Gilbert (2012) and Gilbert and Sun (2014) developed estimation and hypothesis testing procedures respectively for assessing mark-specific vaccine efficacy defined as one minus the mark-specific hazard ratio (vaccine/placebo) of infection. The methods were used to analyze the RV144 HIV vaccine efficacy trial in Thailand, which was the first trial to demonstrate partial efficacy of an HIV vaccine (Rerks-Ngarm et al., 2009).

However, the usefulness of the statistical procedures for model (1) relies on the validity of the model. The model (1) may fail in three ways: (i) the time invariance of the hazard ratio does not hold; (ii) the exponential form of the link function for the hazard ratio is inappropriate; (iii) the functional forms of individual covariates in the exponent of the model are misspecified. The model misspecification can have detrimental effects on the validity and efficiency of the partial likelihood inference for the proportional hazards model (Lagakos and Schoenfeld, 1984; Struthers and Kalbfleisch, 1986; Lagakos, 1988; Lin and Wei, 1989).

This paper develops a goodness-of-fit testing procedure for the stratified mark-specific PH model with continuous marks. Following the development of the goodness-of-fit tests of Lin et al. (1993) for the Cox model, the proposed test statistics are constructed based on weighted cumulative mark-specific martingale residual processes. However, the theoretical development of the goodness-of-fit tests for model (1) is more challenging because of the nonparametric regression function $\beta(v)$ of the model. The weak convergence of the weighted mark-specific martingale residual processes is investigated. The asymptotic distributions of the proposed test statistics are derived. The performance of the proposed tests is examined extensively in simulations for a variety of the models under the null hypothesis and under different types of alternative models. The simulation study shows that the proposed goodness-of-fit test procedure works well. We present an analysis of the 'Step' HIV vaccine efficacy trial using the stratified mark-specific proportional hazards model and the model checking is conducted using the proposed method. Our analysis suggests that the Merck Adenovirus 5 vaccine may increase susceptibility to HIV acquisition.

The rest of the paper is organized as follows. The goodness-of-fit test procedure for the stratified mark-specific PH model is presented in Section 2. A simulation study is conducted to examine the finite sample performance of the proposed method in Section 3. The proposed method is applied to the Step trial in Section 4. Proofs of the main results are placed in the online Supplementary material (see Appendix B).

## 2. Goodness-of-fit test

Let $n_k$ be the number of observations in the $k$th stratum. For an individual in the $k$th stratum, let $T_k$ be the failure time, $V_k$ the mark observed at the time of failure with support on $[0, 1]$, and $Z_k(\cdot) = \{Z_k(t), 0 \leq t \leq \tau\}$ the associated $p$-dimensional covariate process. Suppose that $(T_k, V_k, Z_k(t))$ follows model (1). Under right censoring, the observed random variables are