

THE TWO-SAMPLE PROBLEM FOR FAILURE RATES DEPENDING ON A CONTINUOUS MARK: AN APPLICATION TO VACCINE EFFICACY

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Abstract: The efficacy of an HIV vaccine to prevent infection is likely to depend on the genetic variation of the exposing virus. This paper addresses the problem of using data on the HIV sequences that infect vaccine efficacy trial participants to 1) test for vaccine efficacy more powerfully than procedures that ignore the sequence data; and 2) evaluate the dependence of vaccine efficacy on the divergence of infecting HIV strains from the HIV strain that is contained in the vaccine. Because hundreds of amino acid sites in each HIV genome are sequenced, it is natural to treat the genetic divergence as a continuous mark variable that accompanies each failure (infection) time. Problems 1) and 2) can then be approached by testing whether the ratio of the mark-specific hazard functions for the vaccine and placebo groups is unity or independent of the mark. We develop nonparametric and semiparametric tests for these null hypotheses, and nonparametric techniques for estimating the mark-specific relative risks. The asymptotic properties of the procedures are established. In addition the methods are studied in simulations and are applied to HIV genetic sequence data collected in the first HIV vaccine efficacy trial.

Key words and phrases: Competing risks, genetic data, mark variable, nonparametric statistics, proportional hazards, survival analysis.

Running title: Continuous Mark-Specific Relative Risks