Abstract

A causal mediation model with multiple time-to-event mediators is exemplified by the natural course of human disease marked by sequential milestones with a time-to-event nature. For example, from hepatitis B infection to death, patients may experience intermediate events such as liver cirrhosis and liver cancer. The sequential events of hepatitis, cirrhosis, cancer, and death are susceptible to right censoring; moreover, the latter events may preclude the former events. Casting the natural course of human diseases in the framework of causal mediation modeling, we establish a model with intermediate and terminal events as the mediators and outcomes, respectively. We define the interventional analog of path-specific effects (iPSEs) as the effect of an exposure on a terminal event mediated (or not mediated) by any combination of intermediate events without parametric models. The expression of a counting process-based counterfactual hazard is derived under the sequential ignorability assumption. We employ composite nonparametric likelihood estimation to obtain maximum likelihood estimators for the counterfactual hazard and iPSEs. Our proposed estimators achieve asymptotic unbiasedness, uniform consistency, and weak convergence. Applying the proposed method, we show that hepatitis B induced mortality is mostly mediated through liver cancer and/or cirrhosis whereas hepatitis C induced mortality may be through extrahepatic diseases.

Zoom details can be found at: https://stt.natsci.msu.edu/stt-colloquium-zoom-info/