Semiparametric Transformation Models for Interventional Path-Specific Effects with Multiple Time-to-Event Mediators

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Abstract

Disease progression is often characterized by a sequence of time-to-event milestones subject to right censoring and structural dependence, where terminal events may preclude the subsequent occurrence or observation of intermediate events. For example, in the progression from hepatitis B infection to death, patients may experience intermediate events such as liver cirrhosis and hepatocellular carcinoma. Quantifying causal effects along specific pathways is scientifically important but methodologically challenging, because multiple time-to-event mediators are correlated and constrained by an event-ordering structure.

Although recent nonparametric approaches have addressed interventional path-specific effects in this context, they often rely on stratification to adjust for confounding, which may lead to substantial efficiency loss, particularly when confounders are continuous or high-dimensional. To balance robustness and efficiency, we adopt a semiparametric transformation-model family that allows data-adaptive model selection while adjusting for confounders through covariate inclusion. Simulation studies show that the proposed approach achieves substantially smaller variance than the nonparametric estimator and accurately recovers the target interventional path-specific effects when the selected transformation model is well specified. In an analysis of the motivating clinical dataset, our conclusions are consistent with prior nonparametric results but are supported by smaller standard errors and stronger statistical evidence.