

A nonparametric approach to semi-competing risks via causal mediation modeling

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Abstract: The semi-competing risk problem arises when one is interested in the effect of an exposure or treatment on both intermediate (e.g., having cancer) and primary events (e.g., death) where the intermediate event may be censored by the primary event, but not vice versa. Here we propose a nonparametric approach casting the semi-competing risks problem in the framework of causal mediation modeling. We set up a mediation model with the intermediate and primary events, respectively as the mediator and the outcome, and define indirect effect (IE) as the effect of the exposure on the primary event mediated by the intermediate event and direct effect (DE) as that not mediated by the intermediate event. A Nelson-Aalen type of estimator with time-varying weights is proposed for direct and indirect effects where the counting process at time t of the primary event $N_{(2n_1)}(t)$ and its compensator $A_{(n_1)}(t)$ are both defined conditional on the status of the intermediated event right before t , $N_{(1)}(t^-) = n_1$. We show that $N_{(2n_1)}(t) - A_{(n_1)}(t)$ is a zero-mean martingale. Based on this, we further establish the asymptotic unbiasedness, consistency and asymptotic normality for the proposed estimators. Numerical studies including simulation and data application are presented to illustrate the finite sample performance and utility of the proposed method.