Mediation analysis when outcome and mediator are semi-competing events with application in health disparities research

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Abstract:
We propose novel methodology for mediation analysis to explain how much of the effect of the exposure on a terminal time-to-event outcome is attributed to a, non-terminal, potentially intermediate, time-to-event. Addressing this question is important in health disparities research when we seek to quantify inequities in timely delivery of treatment and its impact on patients’ survival time.

Rigorous definition of the direct and indirect effects and joint modeling of the outcome and mediator distributions in the presence of semi-competing risks is crucial for valid investigation of mechanisms in continuous time.

We formalize a type of direct and indirect effects using the potential outcome framework in the presence of semi-competing risks. The relationships between exposure, mediator and outcome adjusting for confounding are investigated using a multistate model in continuous time. Simulation based as well as closed form estimators of the causal contrasts are developed.

Mediation analysis that ignores censoring in mediator and outcome time-to-event-processes and/or ignores semi-competing risks may give misleading results.

We employ this novel methodology to investigate the role of delaying treatment uptake in explaining racial disparities in cancer survival in a multicenter cohort study of colorectal cancer patients.