Continuous-time mediation analysis for repeated mediators and outcomes

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Abstract: Mediation analysis focuses on the underlying causal mechanisms between an exposure, an outcome, and an intermediate variable called mediator. Initially developed for cross-sectional studies, it has been extended to the framework of longitudinal data by discretizing the assessment times of mediator/outcome. Yet, processes in play in longitudinal studies are usually defined in continuous time and measured at irregular and subject-specific visits. This is the case in dementia research when interested in causal mechanisms involving neurodegeneration and cognitive functioning.

Our objective was to propose a methodology to estimate the causal mechanisms between a time-fixed exposure (X), a mediator process ($\mathcal{M}_t$) and an outcome (Y_t) both measured repeatedly over time in presence of a time-dependent confounding process ($\mathcal{L}_t$).

We considered two causal estimands, a path-specific effect and a stochastic intervention analogue to natural effect, and defined the identifiability assumptions required to get the estimands estimable. Then, we used a dynamic multivariate model based on differential equations for their estimation.

We applied our method in a population-based cohort of cerebral aging to investigate the causal mechanism between a genetic factor (APOE4) and cognitive functioning potentially mediated by neurodegeneration and confounded by vascular brain lesions.

Key words: Causal Inference; Mediation Analysis; Continuous-time; Longitudinal data ; Dynamic model;