



Some Ideas for Causal Inference with Continuous Multiple Time Point Interventions

Michael Schomaker

(Department of Statistics, LMU Munich)

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Causal inference for multiple time-point interventions has received considerable attention in the literature over the past few years: if the intervention of interest is binary, popular estimation approaches include inverse probability of treatment weighting approaches, g-computation estimators and longitudinal targeted maximum likelihood estimation. However, suggestions on how to estimate treatment effects of variables that are continuous and measured at multiple time points are limited, particularly when the true dose-response relationship should be described as closely as possible (i.e., the research question should not be changed). These situations may, however, be of interest: for example, in pharmacoepidemiology, one may be interested in how counterfactual outcomes of people living with -and treated for- HIV, such as viral failure, would vary for time-varying treatments (i.e., interventions) such as different drug concentration trajectories. One issue with continuous interventions is that the so-called positivity assumption, which is the requirement that individuals have a positive probability of continuing to receive treatment according to the assigned treatment rule, given that they have done so thus far and irrespective of the covariate history, is often violated. To tackle such positivity violations, we develop different projection functions, which reweigh and redefine the estimand of interest based on functions of the actual data support for the respective interventions, i.e. concentration trajectories. With these functions, we get the desired dose-response curve in areas of enough support, and otherwise a meaningful estimand that does not require the positivity assumption. We develop g-computation type plug-in estimators for this case. Those are contrasted with using g-computation estimators in a naïve manner, i.e. applying it to continuous interventions without specifically addressing positivity violations. The ideas are illustrated with longitudinal data from HIV+ children treated with an efavirenz-based regimen as part of the CHAPAS-3 trial, which enrolled children < 13 years in Zambia/Uganda.