Causal Inference with Continuous Exposures

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Abstract

Often, an exposure (treatment, intervention) of interest is continuous and measured over multiple time points. A typical estimand in this case is the longitudinal causal dose-response curve (CDRC). For example, in pharmacoepidemiology, one may be interested in how outcomes of people living with -and treated for- HIV, such as viral failure, would vary for different time-varying exposures such as different antiretroviral drug concentration trajectories (ultimately to determine the therapeutic window for maintaining drug concentrations within an effective and safe range).

A challenge for doing causal inference with continuous exposures is that the so-called positivity assumption is typically violated. The assumption requires positive conditional exposure densities at all time points, at all exposure trajectories of interest. We present 3 possible strategies to address this: 1) using standard g-computation approaches that are used for binary exposures, without any modifications, relying purely on extrapolations; 2) developing projection functions, which reweigh and redefine the CDRC based on functions of the conditional support for the respective exposure strategy: with these functions, we obtain the desired dose-response curve in areas of enough support, and otherwise another estimand that does not require the positivity assumption; 3) an individual, data-adaptive strategy that sticks to the exposure trajectory of interest as long as possible, and uses the closest "most-feasible" exposure value otherwise. We develop g-computation type plug-in estimators for strategies 2 and 3.

Simulations show in which situations a standard g-computation approach (strategy 1) is appropriate, and in which it leads to bias and how then strategy 2 recovers the alternative estimand of interest, and strategy 3 reduces bias (while maintaining interpretability).

All ideas are illustrated with longitudinal data from HIV positive children treated with an efavirenz-based regimen as part of the CHAPAS-3 trial, which enrolled children <13 years in Zambia/Uganda.