05
JAN.
2016

de 12h15 à 13h45

SÉMINAIRE

Flexible modeling of the cumulative effects in Marginal Structural Proportional Hazards model

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Longitudinal studies of disease progression and treatment increasingly involve time-varying treatments. Many such treatments may have cumulative effects, where the risk of the outcome does depend not only on the current or most recent treatment status or dose but also on the history of the past treatment. One important analytical challenge in such studies concerns the need to specify an 'etiologically correct exposure metric' that summarizes the impact of treatment/exposure history on the current hazard. Flexible modeling of a weighted cumulative exposure (WCE), where the exposure metric is defined as a weighted sum of past treatments, has been proposed to address this challenge and the WCE model has been shown to incorporate conventional simpler exposure models as its special cases. Another important challenge in assessing the causal effects of time-varying treatments occurs if the treatment both affects (future) and depends on (past) values of a time-varying risk factor. Such risk factor will act then as both a confounder and a mediator of the estimated treatment effect. Marginal Structural Models (MSM) have been developed and demonstrated to provide un-biased treatment effect estimates in the presence of such time-varying confounders/mediators. We propose, and validate in simulations, a new, flexible model that combines the MSM and the WCE methodologies. The new model is a flexible extension of the weighted Cox MSM, with inverse-probability of treatment (IPT) weights. To estimate the cumulative effect of the past treatments, we use use cubic regression splines to estimate the marginal weight function, which estimates the relative importance weights assigned to the past exposures, depending on the time elapsed since the exposure. The new WCE model is implemented by inserting the artificial time-dependent (TD) covariates into the Cox model. Stabilized IPT TD weights are employed to control for TD confounders / mediators of the treatment effect. Simulations demonstrate that our MSM WCE estimates well capture the total causal effect of time-varying treatments i.e. the sum of (i) its direct effect on the hazard, and (ii) its indirect effect, mediated through changes in the TD confounder/mediator. Furthermore, if the indirect effect is moderate or strong, the estimated marginal cumulative treatment effect may be substantially stronger than the effect estimate from the conventional (un-weighted) 'conditional' WCE model. Xiao Y, Abrahamowicz M, Moodie EEM, Weber R, Young J. Flexible Marginal Structural Models for Estimating the Cumulative Effect of a Time-Dependent Treatment on the Hazard: Reassessing the Cardiovascular Risks of Didanosine Treatment in the Swiss HIV Cohort Study. Journal of the American Statistical Association. Jan 2014; Epub Merci de me confirmer votre présence avant le jeudi 17 décembre 2015 en raison des congés de fin d'année Cordialement.