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Local Control for bias correction of time-to-event observational studies

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Abstract

We present to the OHDSI community the R package LocalControl, which implements novel nonparametric approaches to address biases and confounding when comparing treatments or exposures in observational studies. LocalControl is an open-source tool for researchers whose aim is to generate high quality evidence using observational health records. The package releases a family of methods for nonparametric bias correction when comparing treatments in cross-sectional, case-control, and survival analysis settings, including competing risks with censoring.

Introduction

We all envision a day when high-quality safety and effectiveness evidence is continuously generated, scrutinized, and updated within a culture of reproducible research, and deployed at point-of-care to improve patient outcomes. A major challenge in making treatment comparisons in observational data is biases and confounders.

One approach to address biases is to model their effects as covariates in linear models. While widely accepted and useful, regression methods have difficulty modeling nonlinearity, have convergence problems when analyzing correlated covariates, and are problematic when multiple mechanisms drive the outcome. Propensity scoring approaches have gained wide use in correcting treatment biases[1], and on average, outperform alternative methods, including regression in large scale patient records analyses[2,3]. However, a weakness of propensity scoring is that there is no guarantee about patient similarity with respect to their biasing variables, rather they only have a similar probability of treatment. Thus, if a 99-year old female had the same propensity for treatment as a 24-year old male, they might be grouped for comparison, even though this makes very little biological sense.

Often it is more appropriate in observational studies to employ survival analysis to model time to events of interest. While visually intuitive, Kaplan-Meier curves do not address biases. Methods that do, include linear survival models like Cox regression, and competing risks regression[4]. In recent years, propensity scoring has also been extended to a survival framework and evaluated[5,6]. However, these approaches suffer from the same limitations in a survival setting as enumerated earlier for cross-sectional and case-control settings.

The Local Control method[7-9] provides a powerful, nonparametric, and conceptually intuitive approach to statistically addressing biases and confounders in large-scale observational data. It enables the estimation of overall treatment effects, and provides a framework for investigating heterogeneity of treatment effect in subpopulations. It has been successfully used to compare treatments for major depressive disorder[8,10], and to evaluate the effect of air quality on mortality[11]. The key idea behind local control is to form many homogeneous patient clusters within which one can compare alternate treatments, statistically correcting for *measured* biases and confounders, analogous to a randomized block design within a randomized controlled trial (RCT). Local Control can be used alongside, or as an alternative to other methods of treatment comparisons, such as regression, or propensity scoring. Prior to our work, the Local Control methodology was developed only for case/control and cross-sectional studies. We introduce our new R LocalControl package, which implements survival/time-to-event analysis, including competing risks.

Local Control

While similar methods depend on perfect or near-perfect matches, Local Control creates neighborhoods of similar patients along a continuum. Each of the patients are clustered for similarity on variables that are thought to be sources of bias and confounding. We have made the innovation of using the nearest neighbors to a given patient, instead of using a clustering without replacement approach where patients reside in only a single cluster. Each patient has a unique set of near-neighbors, and the approach becomes more akin to a non-parametric density estimate using similar patients within a covariate hypersphere of a given radius. With this radius as a parameter, users have direct control over the degree of patient similarity within clusters. The radius can assume all real values in the range between zero, where clusters contain only perfect matches, and the maximum diameter of the covariate-space, building only clusters which contain the entire population.

For this package, we have extended the functionality of the Local Control method to support longitudinal data analysis. For case/control and cross-sectional studies, Local Control calculates the global treatment difference as the average of the treatment differences across each of the neighborhoods. Because one cannot simply average survival curves, the transition to longitudinal analysis required further innovation. We first devised an approach of weighting the failure events from each treatment in a cluster so that they sum to one, resulting in an equal contribution from all of the clusters. We then sum the series of events from all clusters, producing a global estimate which can be used with the Kaplan-Meier and Competing Risk counting processes. We found in communicating results of Local Control that people struggle to intuitively grasp the

notion that they are looking at a difference between treatments. With that in mind, rather than presenting survival curve differences, we created visualizations of the separate treatments before and after bias correction (Figure 1).

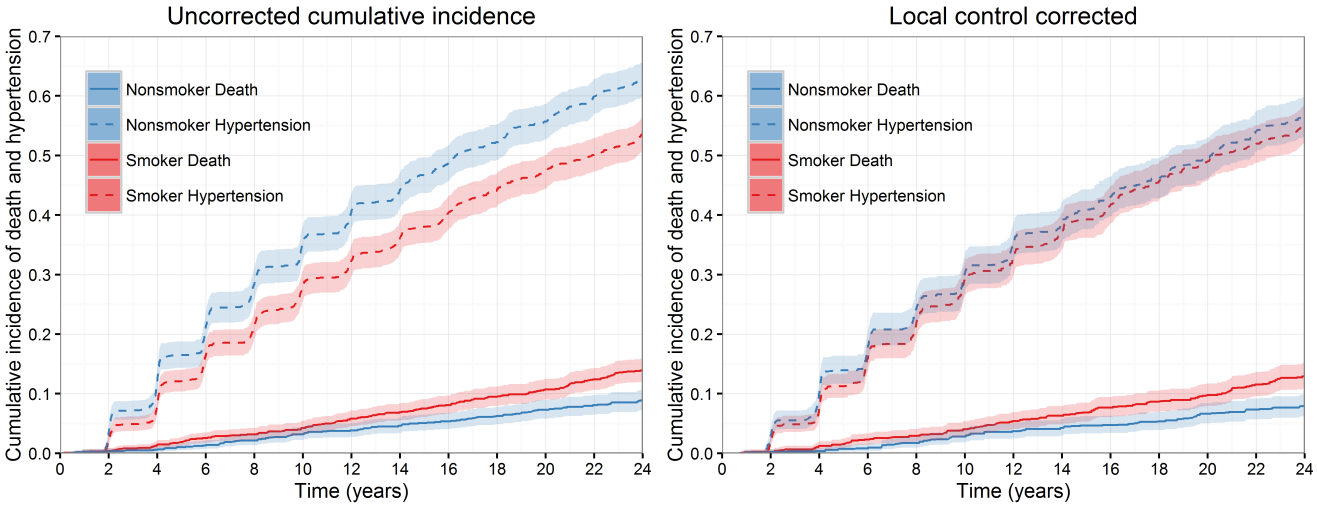

Figure 1. Framingham Heart Study: Competing risks of hypertension and death among smokers and nonsmokers. These plots use data from the Framingham Heart Study[12] to demonstrate CompetingRisksLocalControl. The plot on the left was created prior to correcting for any comorbidities. This plot suggests that while smokers have worse survival than nonsmokers, they are experiencing hypertension at a lower rate. The right plot displays the results from Local Control after correcting for gender, cholesterol, age, BMI, heart rate, and blood glucose level. The bias-corrected curves show us that, among comparable patients, there is almost no difference in the rate of hypertension over time.

Conclusion

With LocalControl, we introduce a new open-source tool for the correction of bias and confounding to the OHDSI and R communities. Preliminary studies on real and simulated data with known answers have shown that LocalControl effectively corrects for measured biases in both case/control and survival/time-to-event settings.

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