Local Control for patient level prediction and heterogeneity of treatment effect

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Abstract

Innovations to the R package LocalControl are presented. The package implements nonparametric approaches to address biases and confounding when comparing treatments or exposures in observational studies. This work illustrates how LocalControl can address the problem of feature selection, and how it can provide bias-corrected insight into what variables modify the difference in outcome from one treatment to another.

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Background

The Local Control method[1-3] provides a powerful and conceptually intuitive approach to statistically addressing biases and confounders in large-scale observational data. It enables estimation of overall treatment effects, as well as estimation of heterogeneity of treatment effect (HTE) in subpopulations. Its theoretical roots are those of propensity scoring, but it provides a tunable, finer-grained matching process for nonparametric treatment comparisons. 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)[4,5]. Figures 1-2 and Tables 1-2 demonstrate bias correction and feature selection on simulated data with the Local Control methodology. This is followed demonstration of HTE analysis.

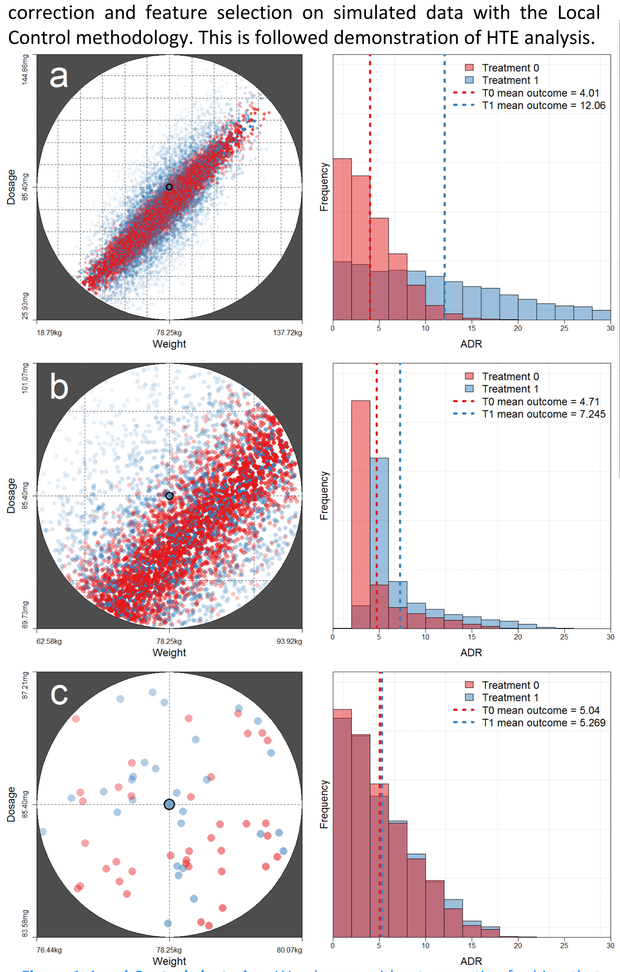

Figure 1: Local Control clustering. We observe without correcting for bias, that the blue T1 outcome average is 8.05 units higher than T1 (top histogram). As the level of correction increases, corresponding to shrinking the radius of near-neighbors (closer weight and dosage), we see that the local estimate approaches the true treatment difference of zero (middle, bottom histograms).

Feature selection

One of the open areas for research in Local Control is how to choose the relevant covariates for bias correction. One approach that is viable for a modest number of covariates is a full factorial regression analysis of how significant each covariate is in modeling the treatment difference. This work describes the full factorial approach, but note that for more variables, a fractional factorial approach could be employed for greater efficiency[4]. A full factorial design of experiments approach first runs all 2^k combinations of including or excluding each of the k covariates in the Local Control model. One can then model with linear regression the outcomes as a function of the binary variables (main effects and interactions) that designate which cluster variables were employed in the Local Control runs.

		T0 + T1	T0	T1	p-value
N		10000	5000	5000	--
Weight (kg)	μ	74.76	74.72	74.80	.804
	σ	14.97	14.99	14.94	0.800
Dosage (mg)	μ	74.77	74.70	74.84	.701
	σ	18.69	15.82	21.18	2.2E-16
ADR (mg)	μ	8.03	4.01	12.06	2.2E-16
	σ	7.86	2.99	9.07	2.2E-16

Table 1: Cross-sectional simulation cohort summary. In this simulation, we introduce a bias where treatment 1 is dosed with a higher variance than treatment 0. The adverse drug reaction (outcome variable) for both treatments is assigned using the same function: ADR = |target_dose – actual_dose|mg, where the optimal dosage is one mg per kg of the patient's weight. We introduce the bias by modifying the variance of treatment dosages between the two groups. This table shows the distribution of weight, and dosage among the simulated patients. Using a t-test, we show that there is no statistical difference between the covariate averages in the two treatment groups. With an F-Test, we compare the variance of the two groups to show the statistical difference between the two.

weight	dosage	noise1	noise2	difs
-1	-1	-1	-1	0.00
1	-1	-1	-1	-0.01
-1	1	-1	-1	0.78
1	1	-1	-1	3.83
-1	-1	1	-1	-0.01
1	-1	1	-1	-0.01
-1	1	1	-1	0.81
1	1	1	-1	3.72
-1	-1	-1	1	0.01
1	-1	-1	1	-0.01
-1	1	-1	1	0.82
1	1	-1	1	3.74
-1	-1	1	1	0.02
1	-1	1	1	0.01
-1	1	1	1	0.95
1	1	1	1	3.72

Table 2. Regression input for full factorial analysis. The difs column shows the average difference in the corrected LTD from the global treatment difference for each of the 16 combinations. A value of -1 for a clustering variable means that it was excluded, while 1 represents including it in the model.

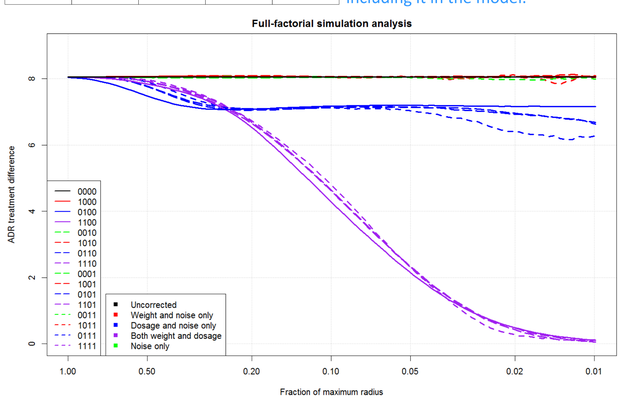

Figure 2: Full factorial Local Control on the cross-sectional sim data. This figure is a graphical representation of the different covariate configurations. Each of the curves on the plot corresponds to one of the rows in Table 2. When both weight and dosage are included in the model (purple), the corrected treatment difference converges to the correct answer of zero. When only one of weight or dosage is used in the model (red or blue), or neither (green), then the biases remain, and the treatment difference estimate is non-zero. Because this simulated data contains no perfect matches, the corresponding section has been omitted from the plot.

Patient-level prediction and heterogeneity of treatment effect

Estimates of bias-corrected treatment differences are useful in making generalizations that one treatment may be safer or more effective than another on average. However, they do not answer the question of what is the expected outcome from a given treatment for a particular patient. Patient level prediction recognizes that there may be heterogeneity of treatment effect, namely that patients can have very different outcomes depending on patient characteristics. Traditional approaches will use regression models or machine learning on patient covariates to predict patient outcomes. While these approaches can provide patient level predictions, the interpretation of such models could be distorted by the biasing variables. Instead, after bias correction, regression or machine learning can be applied to model bias-corrected treatment differences, giving insight into what variables modify the difference in outcome from one treatment to another, unpolluted by variables that govern choice of treatment.

The following example uses data from a study conducted at the Ohio Heart Health Center in 1997, known as the Lindner study[6]. The study examines post-procedure effects of the treatment, Abciximab, plus usual care, compared with outcomes from patients who received usual care alone. Recursive partitioning is used to examine patient subgroups with statistically significant differences in bias-corrected treatment difference as a function of patient covariates, including the clustering variables[2,5,7].

	All patients	Treated	Untreated	p-value
N (patients)	996	698	298	--
female	0.35	0.33	0.39	1.00E-01
height	171.44	171.44	171.45	9.96E-01
stent	0.67	0.70	0.58	3.23E-04
diabetic	0.22	0.2	0.27	3.40E-02
acutemi	0.14	0.18	0.06	4.66E-09
ejecfrac	50.97	50.40	52.29	8.58E-03
ves1proc	1.39	1.46	1.20	4.21E-11
lifepres	11.30	11.42	11.02	1.10E-02
cardbill	15674.16	16126.68	14614.22	9.83E-02

Table 3. Lindner cohort summary. In this example, we focus on the cardbill outcome. This variable represents all cardiac related billing in the 12 months following the procedure.

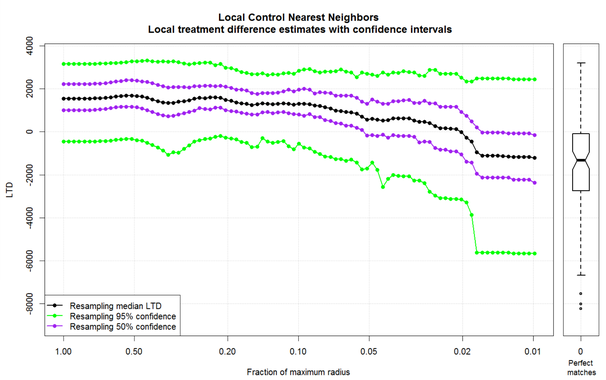

Figure 3. Lindner treatment difference as a function of correction radius. When the maximum radius fraction is 1, the treatment difference is equal to the uncorrected global average. As the fraction decreases (left to right), the treatment difference is drawn from smaller and more similar clusters. The window on the right represents only the perfect matches contained in the data.

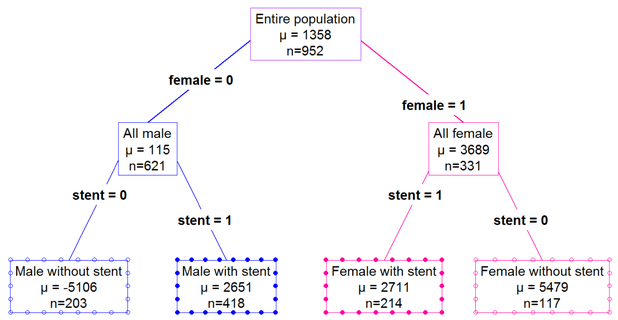

Figure 4. Abciximab recursive partitioning tree. After performing full factorial LocalControl analysis with seven variables, recursive partitioning on the treatment differences identifies four mutually exclusive subgroups: men and women with and without stents.

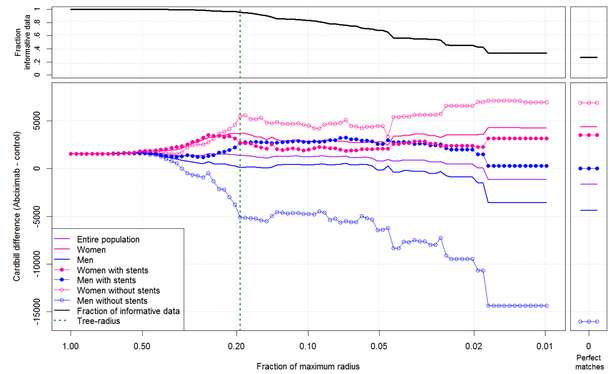

Figure 5. Lindner subgroups. After identifying significant subgroups with recursive partitioning, each of the subgroup treatment differences are graphed together. Observe that the men without stents have a much lower billing cost on Abciximab vs. control than each of the other subgroups. The top two windows display the fraction of data contributing to each of the estimates.

Conclusions

In large data sets it can be true that an "average/overall" effect is meaningless. The answer is that "it depends". For example a drug might work for women, but not for men. When there is treatment response heterogeneity, a recommendation of one-size-fits-all is problematic and even a bias-corrected overall effect is misleading. LocalControl enables the analysis of both the bias-corrected average effect, as well as creates insight into subgroup outcome heterogeneity. This package is vailable on the Central R Archive Network (https://CRAN.R-project.org/package=LocalControl), and on the OHDSI github.

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