American Journal of Epidemiology

Vol. 173, No. 7
DOI: 10.1093/aje/kwq475
Advance Access publication:
March 16, 2011

Response to Invited Commentary

Rose et al. Respond to ''G-Computation and Standardization in Epidemiology''

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Initially submitted November 29, 2010; accepted for publication December 2, 2010.

Abbreviation: TMLE, targeted maximum likelihood estimator.

We thank Vansteelandt and Keiding (1) for their commentary on our article (2), in which we implemented G-computation, a maximum likelihood-based substitution estimator of the G-formula. The goals of that article included 1) translating G-computation into the applied epidemiology literature by using a point-treatment example and marginal parameter, 2) drawing connections between traditional regression and G-computation, 3) demonstrating G-computation in a simple simulated data set, and 4) briefly presenting related topics, such as super learning (3, 4). Their commentary provides valuable background on G-computation that was outside the scope of our article. Standardization was addressed, albeit briefly, in our article, and we disagree that our chosen presentation of G-computation was divorced from the literature. We respond to their remaining commentary via a road map for effect estimation (4), which can be a useful component of epidemiologic analysis and can guide investigators to address issues raised by Vansteelandt and Keiding (1).

The road map for effect estimation we follow includes definition of the research question, the estimator, and inference (not discussed here) (4). Defining the research question involves describing the data, model, and target parameter. Suppose the data are n i.i.d. observations of the random variable O, where O has probability distribution P. A statistical model is the set of possible probability distributions, and the model is the statistical model augmented with possible additional causal assumptions. The target parameter is a specific feature of P.

Vansteelandt and Keiding (1) discussed near violation of the positivity assumption and the problem of extrapolation when using G-computation. Near violations of the positivity assumption should be addressed for all estimators. Positivity is a testable statistical assumption, part of the statistical model in the road map, and we refer readers to the article by Petersen et al. (5) for information regarding diagnosis of and response to violations of this assumption. Vansteelandt and Keiding (1) also discussed marginal versus conditional parameters. If a conditional parameter is most appropriate for the research question, this fact will be translated into the statistical question when defining the target parameter in the road map.

The second step in the road map is the choice and implementation of an estimator. Vansteelandt and Keiding (1) discuss inverse probability-of-treatment weighting estimators (6, 7) and ''doubly robust standardization'' (8, 9). Inverse probability-of-treatment weighting estimators are not asymptotically efficient and can lead to problems in finite samples (4, 10, 11). Doubly robust standardization is a substitution estimator that relies on weighting and a parametric regression statistical model. Robins et al. (9) describe situations in which this estimator may not perform well.

The targeted maximum likelihood estimator (TMLE) (4, 12–14) is a doubly robust efficient loss-based substitution estimator with appealing asymptotic and finite sample properties. One first obtains an estimator of the data-generating distribution and then defines a parametric working submodel to fluctuate the initial estimator in a step targeted toward making the optimal bias-variance trade-off for the target parameter. Estimator comparisons involving TMLEs have been presented elsewhere (4, 15–19).

The doubly robust estimator of Scharfstein et al. (20), which is a special case of a TMLE (21), and the TMLE with linear fluctuation function (12) were also examined in the article by Robins et al. (9) that was referenced by Vansteelandt and Keiding (1). For discussion of these estimators, we refer to previous publications (18, 21). A valid TMLE for continuous outcomes has been recently presented

(18), and it demonstrates that the previously observed sensitivity of these 2 estimators to the positivity assumption was due to those specific implementations.

G-computation is an important estimator and building block for other estimators. Our article (2) was designed to illustrate implementation of G-computation for an epidemiologic audience. We agree with Vansteelandt and Keiding (1) that, before analysis, epidemiologists should consider additional estimators based on their asymptotic and finite sample properties.

ACKNOWLEDGMENTS

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Conflict of interest: none declared.

REFERENCES

1. Vansteelandt S, Keiding N. Invited commentary: G-computation: lost in translation? *Am J Epidemiol*. 2011;173(7):739–742.
2. Snowden JM, Rose S, Mortimer KM. Implementation of G-computation on a simulated data set: demonstration of a causal inference technique. *Am J Epidemiol*. 2011;173(7):731–738.
3. van der Laan MJ, Polley EC, Hubbard AE. Super learner. *Stat Appl Genet Mol Biol.* 2007;6(1):article 25. (doi: 10.2202/1544-6115.1309).
4. van der Laan MJ, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. New York, NY: Springer Publishing Company. In press.
5. Petersen ML, Porter KE, Gruber S, et al. Diagnosing and responding to violations in the positivity assumption [published online ahead of print on October 28, 2010]. *Stat Methods Med Res*. (doi: 10.1177/0962280210386207).
6. Robins JM. Marginal structural models versus structural nested models as tools for causal inference. In: Halloran ME, Berry D, eds. *Statistical Models in Epidemiology: The Environment and Clinical Trials*. New York, NY: Springer Publishing Company; 1999:95–134.
7. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology.* 2000;11(5):561–570.
8. Kang JDY, Schafer JL. Demystifying double robustness: a comparison of alternative strategies for estimating a population mean from incomplete data. *Stat Sci.* 2007;22(4):523–539.
9. Robins JM, Sued M, Lei-Gomez Q, et al. Comment: performance of double robust estimators when "inverse probability" weights are highly variable. *Stat Sci.* 2007;22(4):544–559.
10. Neugebauer R, van der Laan M. Why prefer double robust estimators in causal inference? *J Stat Plan Inference*. 2005;129(1-2):405–426.
11. Ertefaie A, Stephens DA. Comparing approaches to causal inference for longitudinal data: inverse probability weighting versus propensity scores. *Int J Biostat*. 2010;6(2):14.
12. van der Laan MJ, Rubin DB. Targeted maximum likelihood learning. *Int J Biostat*. 2006;2(1):article 11. (doi: 10.2202/1557-4679.1043).
13. van der Laan M. Targeted maximum likelihood based causal inference: part I. *Int J Biostat*. 2010;6(2):article 2. (doi: 0.2202/1557-4679.1211).
14. van der Laan M. Targeted maximum likelihood based causal inference: part II. *Int J Biostat*. 2010;6(2):article 3. (doi: 10.2202/1557-4679.1241).
15. Rose S, van der Laan MJ. Simple optimal weighting of cases and controls in case-control studies. *Int J Biostat*. 2008;4(1):article 19. (doi: 10.2202/1557-4679.1115).
16. Gruber S, van der Laan MJ. An application of collaborative targeted maximum likelihood estimation in causal inference and genomics. *Int J Biostat*. 2010;6(1):article 18. (doi: 10.2202/1557-4679.1182).
17. Stitelman OM, van der Laan MJ. Collaborative targeted maximum likelihood for time to event data. *Int J Biostat*. 2010;6(1):article 21. (doi: 10.2202/1557-4679.1249).
18. Gruber S, van der Laan MJ. A targeted maximum likelihood estimator of a causal effect on a bounded continuous outcome. *Int J Biostat*. 2010;6(1):article 26. (doi: 10.2202/1557-4679.1260).
19. Wang H, Rose S, van der Laan MJ. Finding quantitative trait loci genes with collaborative targeted maximum likelihood learning [published online ahead of print on November 11, 2010]. *Stat Prob Lett*. (doi: 10.1016/j.spl.2010.11.001).
20. Scharfstein DO, Rotnitzky A, Robins JM. Adjusting for nonignorable drop-out using semiparametric non-response models (with discussion). *J Am Stat Assoc.* 1999;94:1096–1146.
21. Rosenblum M, van der Laan MJ. Targeted maximum likelihood estimation of the parameter of a marginal structural model. *Int J Biostat*. 2010;6(2):article 19. (doi: 10.2202/1557-4679.1238).