Verification of SE Formulas for Mediation Analysis

May 1, 2024

I'm doing some Monte Carlo to verify the new SE formulas. Recall that we're doing mediation analysis, so we've got a response, Y, an exposure, X, and a mediation, M. We also have some number of confounders, which will be grouped together in the matrix W. Broadly speaking, we fit two regression models, one to predict M using X and W, the other to predict Y using M, X and W. We then compute the mediation effect (specifically, the total effect of X on Y) as a function of the coefficients from these two regression models. An asymptotic SE for our mediation effect estimator can then be obtained from the asymptotic standard errors of our fitted regression coefficients using the δ-method.

So far, so simple. There are a few places that things start to get more complicated. First, each of the two regression models can be either linear of logistic depending on whether the corresponding response variable is continuous or binary[1]. Furthermore, we can add random effects to our regression models. In the trust study, we have random effects for the intercept, X and M (naturally, the latter only applies when predicting Y). The problem is slightly simpler with a single confounder (mostly, the bookkeeping is a bit easier), although I don't want to stick to this for long.

We will address each of these extra layers of complexity in turn. First though, we start with the simplest version of the problem.

1 Continuous Response, Continuous Mediation, Fixed-Effects

I set the sample size, n, to 1000. Each regression coefficient is 1 and the residual standard deviation in both regression models is 0.2. I use a single confounder and generate both it, W, and the exposure, X, as iid $N(1,1)$. I generate 1000 datasets, each with different values for X and W.

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[1]In principle, we could have Y and/or M follow any distribution with a suitable GLM formulation. I don't think I've ever seen count data (i.e. Poisson regression) used here, much less anything more exotic.

Empirical	Mean Analytical	Median Analytical
0.00833	0.00896	0.00895

Table 1: Standard errors for estimated mediation effect with continuous response and mediation, fixed-effects.

On each dataset, we fit the two regression models, then extract coefficients and standard errors. Next, we compute our estimate of the mediation effect and its δ-method standard error (see Overleaf for details). After repeating this process 1000 times, we compute the empirical standard error (SD of our estimates), as well as the mean and median estimated standard error. Values are given in Table 1. As you can see, our δ-method formula works very well.

The results are very similar if we use multiple confounders (specifically, I use 3). Henceforth, I will use 3 confounders in my analysis.

2 Continuous Response, Binary Mediation, Fixed-Effects

Here things start getting messier. I will return to documenting the analysis, but first I want to discuss the proposed estimand. Note that the total effect given in Case 2 of Section 1.1, $\gamma(a, \alpha, \beta_1, \beta_2)$ depends on our choice of levels for X and W. If X is binary then its choice is easy since we're computing the effect of a one-unit increase in X. For W however, I don't see any natural choice of reference value. One option is to evaluate γ at each W in the observed dataset and average to "marginalize out" W. I have a few references which discuss doing something along these lines, but it might be worth discussing on Thursday. For now, I'm just going to choose a value of W and study "fixed-confounder" mediation effects.

I repeated the analysis in Section 1, this time with a binary mediator. Datasets are generated with $n = 1000$ observations, 3 confounders. Regression slopes are set to 1, and the intercept is set so that the expected linear predictor is approximately zero (this helps keep the number of 0s and 1s for M approximately balanced). The residual variance for Y is set to 0.2^2.

Following the analysis outlined by Bruno, I use a logistic regression model for the mediator and linear regression for the response. Formulas for the δ-method are messier, but conceptually this case is nearly identical to the continuous response setting. One difference here is that the total mediation effect depends on levels of the covariates, specifically X and W. I report results for $X = 0$ and $W = [1, 1, 1]^T$. This value of X is very natural when the exposure is binary. I have no such reason for choosing this value of W. See the opening paragraph of this section for more on this.

I generated 1000 datasets, fit regression models for M (logistic) and Y (linear), then computed our estimate for the mediation effect. I also evaluated our SE formula on each dataset. Table 2 gives the empirical standard error of our

Empirical	Mean Analytical	Median Analytical
0.0200	0.0203	0.0203

Table 2: Standard errors for estimated mediation effect with continuous response and binary mediation, fixed-effects.

Empirical	Mean Analytical	Median Analytical
0.1060	0.1064	0.1062

Table 3: Standard errors for estimated mediation effect with binary response and mediation, fixed-effects.

total effect estimator, as well as the mean and median analytical SE.

3   Binary Response, Binary Mediator, Fixed-Effects

For my own future reference, I'm going to set out some notation here. a and b are the vectors of regression coefficients in a model for M and Y respectively, whether linear or logistic. We use η and ζ for the linear predictors of M and Y respectively. In my code for Section 2, I used η, but didn't really need ζ. Here I will. I use γ for the total mediation effect. In the previous section (albeit only in my code), I used δ for $\mathbb{E}(M|X = x+1) - \mathbb{E}(M|X = x)$, although here I don't think I will need this quantity.

I had to update Bruno's formulas. It looks like he forgot to include the $\mathbb{P}(Y = 1|X = x, \mathbf{W} = \mathbf{w})$ term in the odds, and thus in the odds ratio. This has been changed now in the Overleaf document. I also worked out all the partial derivatives using Maple, which can produce *Julia* (or *R*, *Python*) code to evaluate these horrendous expressions. All partials were validated against a simple finite difference approximation.

Table 3 gives empirical and analytical SEs when $n = 1000$.

4   Open Questions

How does the standard error decompose between multiple responses with the same fixed covariates (i.e. X and W), versus across replicated covariates? I can imagine how to do this, at least naively: do a bunch of analyses on each of a bunch of sets of covariates. Compute the average "within-covariates" variance and the average total variance. Compute the fraction of total variance due to response replication and, interestingly, one minus this fraction as a naive representation of the variance fraction due to covariate variability. **Every time I've checked this, the difference has been very small. This isn't a priority for me right now.**