

Doubly Robust Methods for Analysis of RCTs

Tim Feeney

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- all errors are mine

Intention to Treat (ITT)

- ITT estimators are unbiased in randomized trials
- Robust property derives from leveraging randomization to assure exchangeability in expectation (in addition to other identifiability conditions)
- ITT is often imprecise due to lack of covariate predictor adjustment
- However, even with covariate adjustment, strong assumptions are made about the relationship between covariates and the outcome

Can we do more?

Background of the AIPW estimator

- 1994 Robins, Rotnitzky and Zhao
- 2006 Tsiatis

$$\hat{\mu}_1 = n_1^{-1} \sum_{i=1}^{n_1} \left[\frac{R_i Y_{1i}}{\pi(W_i, \hat{\gamma}_3)} - \frac{\{R_i - \pi(W_i, \hat{\gamma}_3)\}}{\pi(W_i, \hat{\gamma}_3)} \mu(W_i, \hat{\gamma}_1) \right]$$

- 2011 Jonsson-Funk, Westreich, Wiesen, Sturmer, Brookhart and Davidian

$$\begin{aligned} \hat{\Delta}_{\text{DR}} = & n^{-1} \sum_{i=1}^n \left[\frac{X_i Y_i}{e(\mathbf{Z}_i, \hat{\beta})} - \frac{\{X_i - e(\mathbf{Z}_i, \hat{\beta})\}}{e(\mathbf{Z}_i, \hat{\beta})} m_1(\mathbf{Z}_i, \hat{\alpha}_1) \right] \\ & - n^{-1} \sum_{i=1}^n \left[\frac{(1 - X_i) Y_i}{1 - e(\mathbf{Z}_i, \hat{\beta})} + \frac{\{X_i - e(\mathbf{Z}_i, \hat{\beta})\}}{1 - e(\mathbf{Z}_i, \hat{\beta})} m_0(\mathbf{Z}_i, \hat{\alpha}_0) \right] \end{aligned}$$

Key Points of AIPW for ITT

- Consistent(asymptotically unbiased) under MAR and positivity even if the one of the models is wrong ¹

Under RCT we are guaranteed positivity and exchangeability, and we KNOW one model is right.

- Added bonus: If both models are right then this is the most efficient estimator in its class ¹

¹ Daniel RM. Double Robustness. In: Wiley StatsRef: Statistics Reference Online. 2018. doi:10.1002/9781118445112.stat08068

Simulation/ Proof of concept-Binary

Binary outcome

10000 bootstraps

$n = 1000$

$Y \sim \text{binomial}$

weak, med, strong predictor, error, non predictor $\sim N(0, 1)$

	Estimate	SE	se_ratio
ITT	0.2781	0.0286	1.0000
Non Predictors	0.2509	0.0273	0.9548
Weak Predictors	0.2514	0.0274	0.9579
Strong Predictor	0.2410	0.0217	0.7598
All Predictors	0.2628	0.0198	0.6936

Simulation/ Proof of concept-Continuous

Continuous outcome

10000 bootstraps

$n = 1000$

$Y \sim \text{continuous}$

	Estimate	SE	se_ratio
ITT	4.2836	0.7228	1.0000
null Predictor	4.2836	0.7148	0.9889
non Predictor	4.2838	0.7145	0.9885
Weak Predictor	4.2939	0.7176	0.9929
Medium Predictor	4.1819	0.6606	0.9139
Strong Predictor	5.1438	0.3450	0.4773
All Predictors	5.0600	0.1256	0.1738

Real Data

Reanalysis of ACTG 5202 data based off Sax 2009 NEJM ²

- Phase 3 clinical trial
- Comparing abacavir.lamivudine (ABC/3TC) to emtricitibine/tenofivir (TDF/FTC)
- main outcome was time to virologic failure
- 797 person randomized had $\geq 100,000$ HIV RNA copies/ml, were ≥ 16 years old and had at most 7 days of ART therapy
- primary result was hazard ratio of 2.33 (1.46-3.72) for ABC/3TC versus TDF/FTC

²1 Sax PE et al. Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. N Engl J Med 2009;doi:10.1056/NEJMoa0906768

Real Data-Slightly modified

In this analysis we are approaching categorical and continuous outcome—we have not pursued survival analysis,yet.

- we used data at 48 weeks to define viral supression defined as HIV RNA copies < 200 copies/ml →our binary outcome
- similarly we used data at 48 weeks to define CD4 count, cells/mm² → our continuous outcome
- Use the g-formula as out outcome model; others are potential candidates too
 - predictors included in g-formula are
 - Age(categorized, 16-24, 25-49, 50+)
 - log RNA level at baseline
 - CD4 count at baseline
 - Sex at birth

Confidence Intervals

- Bootstrapping to obtain a standard error; also used closed form solution ³

Also a closed form solution available:

$$\hat{V}(\hat{\mu}) = \frac{1}{n^2} \sum_{i=1}^n \left[\frac{R_i Y_i}{\pi(\mathbf{X}_i; \hat{\alpha})} + \left\{ 1 - \frac{R_i}{\pi(\mathbf{X}_i; \hat{\alpha})} \right\} m(\mathbf{X}_i; \hat{\beta}) - \hat{\mu} \right]^2$$

where $\hat{\mu}$ = AIPW estimate

R code, which I think is a bit easier to read

```
aipw_diff<-(aipw1-aipw0)-aipw_all_est  
  
var_aipw<-(1/(nrow(data)^2))*sum(aipw_diff^2)  
se_aipw<-sqrt(var_aipw)
```

³Learned closed form solution thanks to Paul Zivich

Reanalysis results

	Viral suppression at 48 weeks	SE	SE Ratio
ITT	-0.025 (-0.065,0.016)	0.0205	ref
AIPW	-0.020 (-0.019,0.061)	0.0203	0.99

	CD4 count at 48 weeks (cells/mm ²)	SE	SE Ratio
ITT	-6.85 (-38.92,25.23)	16.34	ref
AIPW	-6.69 (-26.94,13.57)	10.33	0.63

Implications

- Tighter confidence intervals from lower SE around unbiased estimates
- Efficient use of valuable data
- Sample size gains!

Sample Size

RCTs are typically designed with power in mind to make sure that the correct number of people are enrolled to answer a question without enrolling too many people as to make the trial unethical.

- Power typically set at 90% (or higher)

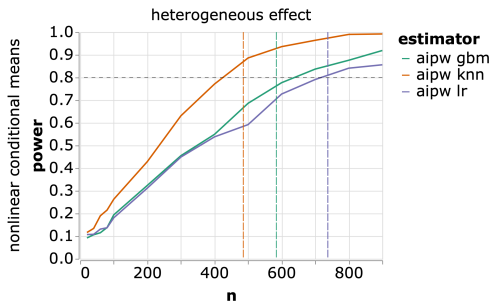
Using AIPW and leveraging the efficiency gains (as evident by the decrease in SE) means you can use less people to answer the same question.

Alternatively, for a study that failed to recruit the appropriate number of participants, AIPW might be a way to recover power

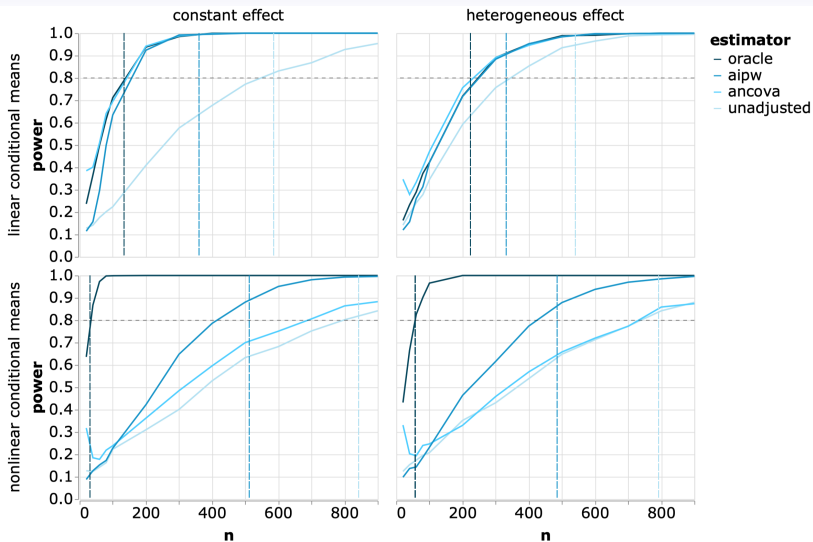
Sample size improvements

As far as I know there are no closed form solutions for calculating sample size 'savings'

Simulation seems to be the best solution so far ⁴, which requires many assumptions about the covariance structure of the data



⁴Schuler A. Designing efficient randomized trials: power and sample size calculation when using semiparametric efficient estimators. arXiv:210410784. 2021.<http://arxiv.org/abs/2104.10784>



Finishing up

As I finish this project I want to make sure I quantify the sample size improvements we should be able to see.

Plan is to evaluate the number of observations I would need to add to my data to achieve the SE of the ITT estimate.

Thank you

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