ADDRESSING BIAS FROM UNMEASURED DISPOSITIONS IN OBSERVATIONAL STUDIES

PAUL R. ROSENBAUM

Abstract. An unmeasured general disposition or an unmeasured generic bias is an unmeasured covariate that promotes several different treatments in an analogous way. Unmeasured generic biases may invalidate treatment-versus-control comparisons, without invalidating the differential comparison of two treatments. This possibility is explored in theory, in several models, in several examples, and in a sensitivity analysis that examines the possibility that the unmeasured bias is not, in fact, generic.

1. Notation

Observed covariate x and **unobserved covariate** u. There are S strata or matched sets defined by observed covariates, $s = 1, \ldots, S$. There are n_s people in stratum s, $i = 1, \ldots, n_s$. $x_{si} = x_{sj}$ for all strata and people, but possibly $u_{si} \neq u_{sj}$.

There are **two treatments**, each of which may be given or withheld, making a 2×2 factorial design. Treatment 1: $Z_{si} = 1$ if the i^{th} person in stratum s received the first treatment, $Z_{si} = 0$ otherwise. Treatment 2: $Z^{'}_{si} = 1$ if the i^{th} person in stratum s received the second treatment, $Z^{'}_{si} = 0$ otherwise. Four possible combinations: $\left(Z_{si}, Z^{'}_{si}\right) = (1,1)$ or $(1,0)$ or $(0,1)$ or $(0,0)$.

Main effect of first treatment compares $Z_{si} = 1$ to $Z_{si} = 0$, ignoring $Z^{'}_{si}$. **Adjusting** the main effect of the first treatment for the second treatment means comparing $Z_{si} = 1$ to $Z_{si} = 0$ adjusting for $Z^{'}_{si}$, but this adjusts for the treatment $Z^{'}_{si}$ as if it were a covariate, not for u_{si}. The **differential comparison** is the comparison of one treatment in lieu of the other, $\left(Z_{si}, Z^{'}_{si}\right) = (1,0)$ to $\left(Z_{si}, Z^{'}_{si}\right) = (0,1)$.

Each person si has **four potential outcomes** for the four potential treatment combinations, $\left(Z_{si}, Z^{'}_{si}\right) = (1,1)$ or $(1,0)$ or $(0,1)$ or $(0,0)$, namely $(r_{11si}, r_{10si}, r_{01si}, r_{00si})$, and we observe one of these; see Neyman (1923) and Rubin (1974). The differential effect is $r_{10si} - r_{01si}$. It requires care and thought in picking Z' so that $r_{10si} - r_{01si}$ is of interest.

Treatment assignment probabilities: $\pi_{absi} = \Pr\left(Z_{si} = a, Z^{'}_{si} = b \,\middle|\, r_{11si}, r_{10si}, r_{01si}, r_{00si}, x_{si}, u_{si}\right)$ for $a = 0,1$ and $b = 0,1$ with $1 = \pi_{11si} + \pi_{10si} + \pi_{01si} + \pi_{00si}$. For distinct people in the population, treatment assignments are conditionally independent given $(r_{11si}, r_{10si}, r_{01si}, r_{00si}, x_{si}, u_{si})$.

Treatment assignment is **ignorable** given the strata s if $0 < \pi_{absi} = \zeta_{abs} < 1$ varies with s but not with i for $a = 0,1$ and $b = 0,1$. (Recall $x_{si} = x_{sj}$ for all s, i, j.) Equivalently, treatment assignment is ignorable given the observed covariates x_{si} if π_{absi} varies with x_{si} but not with $(r_{11si}, r_{10si}, r_{01si}, r_{00si}, u_{si})$. If treatment assignment were ignorable given observed covariates x_{si} or the strata, then appropriate adjustments for x_{si} or the strata would yield correct causal inferences for all of the factorial effects (Rosenbaum and Rubin 1983).

2. Key definition

Let $\rho_{si} = \pi_{10si}/\pi_{01si}$.

Definition 1. *There are only generic unobserved biases if ρ_{si} varies with s but not with i, that is, if*

$$\rho_{si} = \frac{\pi_{10si}}{\pi_{01si}} = \lambda_s \text{ with } 0 < \lambda_s < 1 \tag{2.1}$$

for all s, i.

Note carefully that (2.1) may be true when π_{10si} and π_{01si} each vary with i while their ratio does not. There are *differential biases* if (2.1) is false.

Basic fact. If there are only generic unobserved biases, so $\rho_{si} = \pi_{10si}/\pi_{01si} = \lambda_s$ does not depend upon i, then $\Pr\left(Z_{si} = 1 \,|\, Z_{si} + Z'_{si} = L_{si},\, r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, x_{si},\, u_{si}\right) = 0$ if $L_{si} = 0$, or $= 1$ if $L_{si} = 2$, or $= \pi_{10si}/\left(\pi_{10si} + \pi_{01si}\right) = \lambda_s/\left(1 + \lambda_s\right)$ if $L_{si} = 1$. That is, if there are only generic unobserved biases, then a differential comparison of $\left(Z_{si}, Z'_{si}\right) = (1,0)$ or $(0,1)$ has treatment assignment probabilities that depends only on x_{si} or the strata. Here, $\lambda_s/\left(1 + \lambda_s\right)$ is the **differential propensity score**.

Equivalently, if there are only generic unobserved biases, then

$$\left(Z_{si}, Z'_{si}\right) \perp\!\!\!\perp \left(r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, u_{si}\right) \Big| \left(x_{si},\, Z_{si} + Z'_{si}\right)$$

even when treatment assignment is not ignorable given observed covariates.

If there are only generic unobserved biases, so $\rho_{si} = \pi_{10si}/\pi_{01si} = \lambda_s$ does not depend upon i, then the conditional distribution of $(Z_{s1}, \ldots, Z_{s,n_s})$ given $Z_{s+} = \sum_{i=1}^{n_s} Z_{si}$, $Z'_{s+} = \sum_{i=1}^{n_s} Z'_{si}$ and $\left(Z_{si} + Z'_{si},\, r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, x_{si},\, u_{si}\right)$, $i = 1, \ldots, n_s$ is **a known permutation/randomization distribution**. Conditioning also on Z_{s+} and Z'_{s+} eliminates the unknown nuisance parameter λ_s.

3. Many treatments, some unobserved

Suppose I have not 2 but K treatments, Z_{ksi}, $k = 1, \ldots, K$, where Z_{ksi}, $k = 3, \ldots, K$, are not be observed, but they are all promoted by the same generic bias u_{si}. Write $\mathbf{P}_{si}$ for all the 2^K potential outcomes. Model for treatment assignment is a latent variable model with unmeasured u_{si}:

$$\Pr\left(Z_{ksi} = z_{ksi},\, k = 1, \ldots, K \,|\, \mathbf{P}_{si},\, x_{si}, u_{si}\right) = \prod_{k=1}^{K} \psi_{ks}\left(u_{si}\right)^{z_{ksi}} \left\{1 - \psi_{ks}\left(u_{si}\right)\right\}^{1-z_{ksi}}$$

$$\frac{\psi_{1s}\left(u_{si}\right)}{1 - \psi_{1s}\left(u_{si}\right)} = \lambda_s \frac{\psi_{2s}\left(u_{si}\right)}{1 - \psi_{2s}\left(u_{si}\right)}$$

or an IRT model where the first two treatments, Z_{1si} and Z_{2si}, have proportional odds. Then

$$\left(Z_{1si},\, Z_{2si}\right) \perp\!\!\!\perp \left(\mathbf{P}_{si},\, u_{si},\, Z_{3si}, \ldots, Z_{Ksi}\right) \Big| \left(x_{si},\, Z_{1si} + Z_{2si}\right)$$

so that, by overadjusting for Z_{2si} you have adequately adjusted for the disposition u_{si}.

4. Differential biases

There are **differential biases** if (2.1) is false because $\rho_{si} = \pi_{10si}/\pi_{01si}$ does depend upon i. A model for sensitivity analysis limits the degree to which $\rho_{si} = \pi_{10si}/\pi_{01si}$ varies from person to person within the same stratum: for a specific $\Gamma \geq 1$

$$\frac{1}{\Gamma} \leq \frac{\rho_{si}}{\rho_{si'}} = \frac{\pi_{10si}\,\pi_{01si'}}{\pi_{10si'}\,\pi_{01si}} \leq \Gamma \text{ for all } s,\ i,\ i'.$$

With a little work, one finds that the sensitivity analyses I have proposed for treatment-control comparisons (Rosenbaum 2002, §4) now govern the differential comparison, $(Z_{1si}, Z_{2si}) = (1, 0)$ versus $(0, 1)$. The analysis is parallel, but the interpretation has changed.

5. Time dependent generic biases

Based on Zubizarreta, Small and Rosenbaum (2014), whose example came from Angrist and Evans (1998). Treatments are assigned by a marked point process. Marks indicate the specific treatment received. Timing of treatments is biased by unobservables, but conditionally given that a treatment is received at time t, the assignment of one treatment rather than the other is not biased by unobservables. There are only time-dependent generic biases if the hazard of at least one treatment at time t is biased by unobservables, but the ratio of hazards for two different treatments is not biased by unobservables. Angrist and Evans (1998) asked: Does having twins rather than a single child affect workforce participation? There are only generic unobserved biases if: unobserved biases may affect the timing of pregnancies, but not the twin-versus-single-child treatment conditionally given a pregnancy.

References

Angrist, J. D. & Evans, W. (1998). Children and their parent's labor supply: Evidence from exogenous variation in family size. *Am. Econ. Rev.* **88** 450–477. Time dependent example in Zubizarreta et al. (2014).

Cornfield, J. et al. (1959) Smoking and lung cancer. *J. Nat. Cancer Inst.* **22** 173-203. First sensitivity analysis in an observational study.

Evans, L. (1986) Effectiveness of safety belts in preventing fatalities. *Accid. Anal. Prevent.* **18** 229-41. Original version of the seat belt example.

Fatal Accident Reporting System. Data source for the 2010/2011 seat belt example.

Fisher, R. A. (1935) *Design of Experiments*, Edinburgh: Oliver & Boyd.

Holland, P. W. and Rosenbaum, P. R. (1986) Conditional association and unidimensionality in monotone latent variable models. *Ann. Statist.* **14** 1523-1543. Proof of the claim that adjustments for a manifestation of a latent disposition always underadjust for the disposition.

in 't Veld, B. A., et al. (2002) Pharmacologic agents associated with a preventive effect on Alzheimer's disease. *Epidemiol. Rev.* **24** 248-268. Review related to the Alzheimer's example.

Neyman, J. (1923, 1990) On the application of probability theory to agricultural experiments. *Statist. Sci.* **5** 463-480. Neyman-Rubin notation for causal effects.

Rasch, G. (1961) On general laws and the meaning of measurement in psychology. *Berkeley Symposium on Mathematical Statistics and Probability* **4** 321-333, University of California Press. Discusses the Rasch model.

Rosenbaum, P. R. and Rubin, D. B. (1983) The central role of the propensity score in observational studies for causal effects. *Biometrika* **70** 41-55. Adjustments for observed covariates under ignorable treatment assignment.

Rosenbaum, P. R. (1987) Sensitivity analysis for certain permutation inferences in matched observational studies. *Biometrika*, **74** 13-26. Sensitivity analysis.

Rosenbaum, P. R. (1987) Comparing item characteristic curves. *Psychometrika* **52** 217-233. With proportional latent odds, discusses independence of other items/treatments from two items given their total.

Rosenbaum, P. R. (2002) *Observational Studies* NY: Springer. Sensitivity analyses.

Rosenbaum, P. R. (2006) Differential effects and generic biases in observational studies. *Biometrika* **93** 573-586. Proposes use of differential effects to remove generic biases.

Rosenbaum, P. R. and Silber, J. H. (2009) Amplification of sensitivity analysis in matched observational studies. *JASA* **104** 1398-1405. Interprets Γ in terms of two odds ratios, one (Λ) linking treatment and unobserved covariate, the other (Δ) linking outcome and unobserved covariate via $\Gamma = (\Lambda\Delta + 1) / (\Lambda + \Delta)$. `amplify` function in `R` package `sensitivitymv.`

Rosenbaum, P. R. (2013) Using differential comparisons in observational studies. *Chance* **26** #3 18-25. Elementary discussion of differential effects and the NHANES example.

Rosenbaum, P. R. (2015) How to see more in observational studies. *Annual Review of Statistics and Its Application* **2** 21-48. Brief discussion of generic biases.

Rosenbaum, P. R. (2015) Some counterclaims undermine themselves in observational studies. *JASA* **110** 1389-1398. Much more about the seat-belt example.

Rosenbaum, P. R. (2017) Biases from general dispositions. Chapter 12 of *Observation and Experiment*, Cambridge, MA: Harvard University Press.

Rubin, D. B. (1974) Estimating causal effects of treatments in randomized and nonrandomized studies. *J. Educ. Psych.* **66** 688-701. Neyman-Rubin notation for causal effects.

Tjur, T. (1982) A connection between Rasch's item analysis model and a multiplicative Poisson model. *Scand. J. Statist.* **9** 23-30. Last sections discuss conditional independence conditions related to the Rasch model.

Zandi, P. P., et al. (2002) Reduced incidence of AD with NSAID but not H_2 receptor antagonists. *Neurology* **59** 880-886. Alzehiemer's example.

Zubizarreta, J. R., Small, D. S. and Rosenbaum, P. R. (2014) Isolation in the construction of natural experiments. *Ann. App. Statist.* **8** 2096-2121. Extends the concept of differential effects and generic biases to time-dependent treatments, where the generic disposition may vary with time.

Zubizarreta, J. R., Small, D. S. and Rosenbaum, P. R. (2018) A simple example of isolation in building a natural experiment. *Chance*, to appear. A simple example of the time-dependent version of differential effects.

Relevant R packages

Sensitivity analysis: `sensitivitymv`, `sensitivitymult`, `sensitivity2x2xk`, `senstrat`.

Department of Statistics, Wharton School, University of Pennsylvania, Philadelphia, PA 19104 US
E-mail address: `rosenbaum@wharton.upenn.edu`
URL: `http://www-stat.wharton.upenn.edu/~rosenbap/`