Causal Inference

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(updated: 2020-01-08)

Topics

- What is causal effects
- Fundamental Problem of Causal Inference
- Assumptions necessary to identify causal effects
- Matching techniques
- Accessing balance
- Sensitivity analysis to determine the impact of violations of assumptions on conclusions

Brief History

Statisticians started working on causal modeling as far back as the 1920s (Wright 1921; Neyman 1923).

It became its own area of statistical research since about the 1970s.

Some highlights:

- Re-introduction of potential outcomes; Rubin causal model (Rubin 1974)
- Causal diagrams (Greenland and Robins 1986; Pearl 2000)
- Propensity scores (Rosenbaum and Rubin 1983)
- Time-dependent confounding (Robins 1986; Robins 1997)
- Optimal dynamic treatment strategies (Murphy 2003; Robins 2004)
- Targeted learning (van der Laan 2009)

Basic Definitions and Notations

- Treatment: $A = 0, 1$
- Observed Outcome: $Y = 0, 1$
- Potential Outcomes: Y^0, Y^1
- Counterfactural

  If one outcome is Y^a the other one is Y^{1-a}
- Causal Effects: $Y^1 \neq Y^0$

Fundamental Problem of Causal Inference

- It is impossible to observe two outcomes simultaneously.
- However with certain assumptions we can estimate population level (average) causal effects.

Average Causal Effect

- $E(Y^1 - Y^0) = -0.1$
- with 1000 people 100 fewer with treatment A than treatment B

Conditioning vs. Setting

In general

$E(Y^1 - Y^0) \neq E(Y|A = 1) - E(Y|A = 0)$

$E(Y|A = 1)$ is subpopulation who actually had $A = 1$

$E(Y^1)$ means the whole population was actually treated with $A = 1$

Other Causal Effects

$E(Y^1/Y^0)$ Causal relative risk

$E(Y^1 - Y^0|A = 1)$ Causal effect of treatment on treated

$E(Y^1 - Y^0|V = v)$ average causal effect in the subpopulation with covariate $V = v$ heterogeneity treatment effects

Causal Assumptions

- SUTVA stable unit treatment value assumptions
    - No interference:
    - units do not interfere with each other
    - Treatment assignmentof one unit does not affect that outcome of another unit
    - Spillover or contagion are also terms for interference
    - One version of treatment
- Consistency $Y = Y^a$ if $A = a$ for all a
- Ignorability $Y^0, Y^1 \perp\!\!\!\perp A|X$ Among people with the same values of X, we can think of treatment A as being randomly assigned.
- Positivity: for every sef of values for X, treatment assignment was not deterministic: $P(A = a|X = x) > 0$ for all a and x

Observed Data

$$E(Y|A=a, X=x)$$

$$= E(Y^a|A=a, X=x) \text{ (consistency)}$$

$$= E(Y^a|X=x) \text{ (ignorability)}$$

Mean Potential Outcome by standardization

$E(Y^a) = \Sigma_x E(Y|A = a, X = x)P(X = x)$

problem: could be many varibles in X, combinations of variables creat missing values

Confounding

get rid of counfounder by randomization

Matching(one covariate, multiple covariates)

- fine balance
- stochastic balance
- one to one
- one to many
- variable (sometimes one to one, sometimes one to many)
- Distance
  - Mahalanobis
  - robust version (use ranks instead to solve issue of outliers)
- Greedy matching(R package matchit)
  - Caliper (maximum acceptable distance)
- optimal matching (R package optmatch,rcbalance)

Accessing Balance

- Standardized differences (similar means) $smd = \frac{\bar{X}_{treatment} - \bar{X}_{control}}{\sqrt{\frac{S^2_{treatment} + S^2_{control}}{2}}}$
  - <0.1 indicate adequate balance
  - 0.1-0.2 not too alarming
  - >0.2 indicate serious imbalance
- Table 1 (prematching and post-matching balance is compared) + SMD plot

	Unmatched			Matched		
	No RHC	RHC	SMD	No RHC	RHC	SMD
n	3551	2184		2082	2082	
age (mean (sd))	61.8 (17.3)	60.8 (15.6)	0.06	61.6 (16.7)	61.0 (15.8)	0.039
sex = Male (%)	53.9	58.5	0.09	56.9	56.9	0.001
resp = Yes (%)	41.7	28.9	0.27	30.6	30.4	0.005
card = Yes (%)	28.4	42.3	0.30	39.3	39.5	0.004
neuro = Yes (%)	16.2	5.4	0.35	5.3	5.7	0.015

- Hypothesis test and p-values (test for differences in means for each covariate -- two sample t-test)

Analyze Data After Matching

- Randomization test (Permutation test, Exact test) R package (McNemar.test) or t.test for continuous data

Sensitivity analysis

- Possible hidden bias

Propensity Score

Example I

Install and load package

```
#install.packages("tableone")
#install.packages("Matching")

library(tableone)
library(Matching)
```

Example I

Load and view data

```
load(url("http://biostat.mc.vanderbilt.edu/wiki/pub/Main/DataSets/rhc.sav"))
rhc[1:10,1:6]
```

```
##                 cat1          cat2         ca sadmdte dschdte dthdte
## 1               COPD          <NA>        Yes   11142   11151     NA
## 2      MOSF w/Sepsis          <NA>         No   11799   11844  11844
## 3  MOSF w/Malignancy MOSF w/Sepsis        Yes   12083   12143     NA
## 4                ARF          <NA>         No   11146   11183  11183
## 5      MOSF w/Sepsis          <NA>         No   12035   12037  12037
## 6               COPD          <NA>         No   12389   12396     NA
## 7  MOSF w/Malignancy          <NA> Metastatic   12381   12423     NA
## 8                ARF          Coma         No   11453   11487  11491
## 9  MOSF w/Malignancy          <NA>        Yes   12426   12437     NA
## 10               ARF          <NA>        Yes   11381   11400     NA
```

- **swang1**: Treatment variables
- **cat1**: Primary disease category
- **meanbp1**: Mean blood pressure
- **sex, age, death**

Example I

Spread variables

```
head(mydata)
```

```
##   ARF CHF Cirr colcan Coma lungcan MOSF sepsis      age female meanbp1 aps
## 1   0   0    0      0    0       0    0      0 70.25098      0      41  46
## 2   0   0    0      0    0       0    0      1 78.17896      1      63  50
## 3   0   0    0      0    0       0    1      0 46.09198      1      57  82
## 4   1   0    0      0    0       0    0      0 75.33197      1      55  48
## 5   0   0    0      0    0       0    0      1 67.90997      0      65  72
## 6   0   0    0      0    0       0    0      0 86.07794      1     115  38
##   treatment died
## 1         0    0
## 2         1    1
## 3         1    0
## 4         0    1
## 5         1    1
## 6         0    0
```

Example I

Before matching

```
##                       Stratified by treatment
##                        0              1              SMD
##   n                     3551           2184
##   ARF (mean (SD))       0.45 (0.50)    0.42 (0.49)    0.059
##   CHF (mean (SD))       0.07 (0.25)    0.10 (0.29)    0.095
##   Cirr (mean (SD))      0.05 (0.22)    0.02 (0.15)    0.145
##   colcan (mean (SD))    0.00 (0.04)    0.00 (0.02)    0.038
##   Coma (mean (SD))      0.10 (0.29)    0.04 (0.20)    0.207
##   lungcan (mean (SD))   0.01 (0.10)    0.00 (0.05)    0.095
##   MOSF (mean (SD))      0.07 (0.25)    0.07 (0.26)    0.018
##   sepsis (mean (SD))    0.15 (0.36)    0.32 (0.47)    0.415
##   age (mean (SD))      61.76 (17.29)  60.75 (15.63)   0.061
##   female (mean (SD))    0.46 (0.50)    0.41 (0.49)    0.093
##   meanbp1 (mean (SD)) 84.87 (38.87)  68.20 (34.24)   0.455
```

Example I

Match by greedy matching

```
##############################################
#do greedy matching on Mahalanobis distance
##############################################

greedymatch <- Match(Tr=treatment,M=1,X=mydata[xvars],replace=FALSE)
matched<-mydata[unlist(greedymatch[c("index.treated","index.control")]), ]

#get table 1 for matched data with standardized differences
matchedtab1<-CreateTableOne(vars=xvars,
                            strata ="treatment",
                            data=matched,
                            test = FALSE)
```

Example I

After matching

```
print(matchedtab1, smd = TRUE)
```

```
##                       Stratified by treatment
##                        0              1              SMD
##   n                     2184           2184
##   ARF (mean (SD))       0.42 (0.49)    0.42 (0.49)    0.006
##   CHF (mean (SD))       0.10 (0.29)    0.10 (0.29)   <0.001
##   Cirr (mean (SD))      0.02 (0.15)    0.02 (0.15)   <0.001
##   colcan (mean (SD))    0.00 (0.02)    0.00 (0.02)   <0.001
##   Coma (mean (SD))      0.04 (0.20)    0.04 (0.20)   <0.001
##   lungcan (mean (SD))   0.00 (0.05)    0.00 (0.05)   <0.001
##   MOSF (mean (SD))      0.07 (0.26)    0.07 (0.26)   <0.001
##   sepsis (mean (SD))    0.24 (0.43)    0.32 (0.47)    0.177
##   age (mean (SD))      61.53 (16.15)  60.75 (15.63)   0.049
##   female (mean (SD))    0.44 (0.50)    0.41 (0.49)    0.042
##   meanbp1 (mean (SD)) 73.12 (34.28)  68.20 (34.24)   0.144
```

Example I

Outcome analysis by T-test

```
#outcome analysis
y_trt<-matched$died[matched$treatment==1]
y_con<-matched$died[matched$treatment==0]

#pairwise difference
diffy <- y_trt-y_con

#paired t-test
t.test(diffy)
```

```
##
##     One Sample t-test
##
## data:  diffy
## t = 3.9289, df = 2183, p-value = 8.799e-05
## alternative hypothesis: true mean is not equal to 0
## 95 percent confidence interval:
##  0.02706131 0.08099730
## sample estimates:
## mean of x
## 0.0540293
```

Example I

Outcome analysis by McNemar's Chi-squared test:

```
#McNemar test
table(y_trt,y_con)
```

```
##       y_con
## y_trt   0   1
##     0 303 395
##     1 513 973
```

```
mcnemar.test(matrix(c(973,513,395,303),2,2))
```

```
##
##     McNemar's Chi-squared test with continuity correction
##
## data:  matrix(c(973, 513, 395, 303), 2, 2)
## McNemar's chi-squared = 15.076, df = 1, p-value = 0.0001033
```

Example II

Use propensity score for matching

```
##
## Call:
## glm(formula = treatment ~ ARF + CHF + Cirr + colcan + Coma +
##     lungcan + MOSF + sepsis + age + female + meanbp1 + aps, family = binomial(),
##     data = mydata)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -2.0498  -0.9602  -0.6190   1.1289   2.3878
##
## Coefficients:
##               Estimate Std. Error z value Pr(>|z|)
## (Intercept) -1.9460154  0.2321291  -8.383  < 2e-16 ***
## ARF          1.2252930  0.1495511   8.193 2.54e-16 ***
## CHF          1.8905642  0.1735687  10.892  < 2e-16 ***
## Cirr         0.4334062  0.2203366   1.967  0.04918 *
## colcan       0.0481566  1.1242894   0.043  0.96583
## Coma         0.6842545  0.1878333   3.643  0.00027 ***
## lungcan      0.1984600  0.5055005   0.393  0.69461
## MOSF         1.0177797  0.1807159   5.632 1.78e-08 ***
## sepsis       1.8402456  0.1561589  11.784  < 2e-16 ***
## age         -0.0030469  0.0017462  -1.745  0.08101 .
## female      -0.1390768  0.0590139  -2.357  0.01844 *
## meanbp1     -0.0075166  0.0008707  -8.633  < 2e-16 ***
## aps          0.0182356  0.0017286  10.549  < 2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Example II

Do greedy matching on logit(PS) with a caliper

```
logit <- function(p) {log(p)-log(1-p)}
psmatch<-Match(Tr=mydata$treatment,
               M=1,
               X=logit(pscore),
               replace=FALSE,
               caliper=.2)
matched<-mydata[unlist(psmatch[c("index.treated",
                                 "index.control")]), ]
xvars<-c("ARF","CHF","Cirr","colcan","Coma",
         "lungcan","MOSF","sepsis",
         "age","female","meanbp1")
```

Example II

Get standardized differences

```
matchedtab1<-CreateTableOne(vars=xvars,
                            strata ="treatment",
                            data=matched,
                            test = FALSE)
print(matchedtab1, smd = TRUE)
```

```
##                       Stratified by treatment
##                        0              1              SMD
##   n                     1899           1899
##   ARF (mean (SD))       0.47 (0.50)    0.45 (0.50)    0.035
##   CHF (mean (SD))       0.10 (0.30)    0.10 (0.29)    0.012
##   Cirr (mean (SD))      0.03 (0.16)    0.03 (0.16)    0.013
##   colcan (mean (SD))    0.00 (0.00)    0.00 (0.02)    0.032
##   Coma (mean (SD))      0.04 (0.20)    0.05 (0.21)    0.031
##   lungcan (mean (SD))   0.00 (0.06)    0.00 (0.05)    0.027
##   MOSF (mean (SD))      0.08 (0.28)    0.08 (0.27)    0.025
##   sepsis (mean (SD))    0.25 (0.44)    0.27 (0.44)    0.034
##   age (mean (SD))      61.18 (18.04)  61.08 (15.41)   0.006
##   female (mean (SD))    0.44 (0.50)    0.43 (0.49)    0.018
##   meanbp1 (mean (SD)) 71.80 (34.82)  71.55 (34.86)   0.007
```

Example II

Outcome Analysis by T-test

```
y_trt<-matched$died[matched$treatment==1]
y_con<-matched$died[matched$treatment==0]

#pairwise difference
diffy<-y_trt-y_con

#paired t-test
t.test(diffy)
```

```
##
##     One Sample t-test
##
## data:  diffy
## t = 2.1412, df = 1898, p-value = 0.03238
## alternative hypothesis: true mean is not equal to 0
## 95 percent confidence interval:
##  0.002744694 0.062552831
## sample estimates:
##  mean of x
## 0.03264876
```