Sensitivity Analysis

Have assumed that ignorable treatment assignment holds

Except in randomized trials, justification flimsy

What can be done when this is not believed?

Compute nonparametric bounds

tend to be wide, uninformative

Methods based on other assumptions: e.g., instrumental variables

also based on (different) conditional independence assumptions

Sensitivity analysis; look for departures from ignorability/comparability

How can one look for departures from ignorability?

Consider different ways of parametrizing

Typical ways:

Directly

in terms of association of potential outcomes with treatment assignment

Indirectly

in terms of third, unmeasured variable associated with exposure and outcome

Historically, which came first? Why?

Sensitivity analysis in terms of third, unmeasured variable came earlier

Potential outcome model, methods explicitly based on it not available

Came out of debate on smoking and lung cancer

Several studies found that smoking/tobacco associated with elevated rates of lung cancer

Those who felt association not causal posited that there could be some unmeasured factor that was associated with smoking, lung cancer that could explain away association

Cornfield responded by sensitivity analysis

posited factor U possibly associated with smoking, lung cancer

specify strength of associations

what is strength of associations are required to explain association of smoking and lung cancer?

concluded that, for a binary factor U, required very strong associations with both to explain smoking-lung cancer association

implausible for any factor people could think of

still no plausible candidate

sketch method for binary outcome, covariate, exposure

Consider binary exposure, binary outcome, binary covariate

Have information on marginal frequencies and associations:

$pr(A)$, $pr(Y|A)$

need information on covariate: overall prevalence, associations with exposure and outcome

assume $pr(Y^a|U,A)=pr(Y^a|U)$
(Latent ignorability: not identifiable assumption: no restrictions on observable data)

specify model for $pr(U|A,Y)$

for binary variables, how many parameters are there in this model (without additional constraints)?

for binary variables, 4 parameters to specify (various ways to do this)

can add additional constraints:

- common effect (e.g., odds ratio) for effect of exposure on outcome (if analysis is to solve for this)
- information on marginal probability of U, $pr(U)$
- information on association of U with outcome or exposure ($pr(U|Y)$ or $pr(U|A)$)

can then compute measure of association for A and Y, controlling for U

- marginal measures
- conditional measures

what approach is taken in Greenland paper?

Marginal measures

what is needed in $pr(U|A,Y)$ to produce bias?

Conditions of confounder: under ignorability $pr(U|A) \neq pr(U)$,
$pr(U|A,Y) \neq pr(U|A)$

How would one do sensitivity analysis?

Vary some or all of the unknown aspects of $pr(U|A,Y)$

what is potential problem here (in general)?

In simplest case, 4 parameters that may vary

In complex case, many more possible

May want to restrict sensitivity to departures in specified directions

Could summarize with worst-case scenarios

e.g., let $pr(U|A,Y) = \beta_0 + A\beta_1 + Y\beta_2$

specify β_1, β_2, search over β_0 for largest or smallest effect of A on Y

Alternate approach: specify in terms of conditional associations of potential outcomes and exposures

How can this be done? (At least 2 ways)

1. Model exposure assignment

$pr(A|X,\underline{Y})$

make explicit dependence of A on some component of potential outcomes

e.g., $logit\{pr(A=1|X,Y^{a})\} = X\beta + Y^{a}\gamma$

posit value for γ

2. Model potential outcomes

e.g., $E(Y^a | X, A = a) - E(Y^a | X)$

or $E(Y^a | X, A = a) - E(Y^a | X, A = 0)$

or $E(Y^a | X, A = a) - E(Y^a | X, A = 1 - a)$ (For binary treatment)

discuss meaning of different parameters, model parameterize degree of bias

$$E(Y^a|X,A=a)-E(Y^a|X,A=1-a)=c(a,X)$$

implications for overall bias in estimating $E(Y^1|X)-E(Y^0|X)$:

$$E(Y^a\mid X)=E(Y^a\mid X,A=a)\,pr(A=a)+E(Y^a\mid X,A=1-a)\,pr(A=1-a)$$

$$=E(Y^a\mid X,A=a)\,pr(A=a)+\{E(Y^a\mid X,A=a)-c(a,X)\}\,pr(A=1-a)$$

$$=E(Y^a\mid X,A=a)-c(a,X)\,pr(A=1-a)$$

$$=E(Y\mid X,A=a)-c(a,X)\,pr(A=1-a)$$

overall:

$$E(Y^1|X)-E(Y^0|X)=E(Y|X,A=1)-E(Y|X,A=0)-\{c(1,X)pr(A=0|X)-c(0,X)pr(A=1|X)\}$$

what is bias for estimating effect of treated on treated (untreated)?

For treated:

$$E(Y^1|X,A=1)-E(Y^0|X,A=1)=E(Y|X,A=1)-\{E(Y|X,A=0)-c(0,X)\}$$
$$=\{E(Y|X,A=1)-E(Y|X,A=0)\}+c(0,X)$$

untreated:

$$E(Y^1|X,A=0)-E(Y^0|X,A=0)=\{E(Y|X,A=1)-c(1,X)\}-E(Y|X,A=0)$$
$$=\{E(Y|X,A=1)-E(Y|X,A=0)\}-c(1,X)$$

can parameterize $c(a,X)$ in various ways:

$$c(a,X) = \alpha(2a-1)$$

$$c(1,X) = -c(0,X)$$

$$E(Y^1|X,A=1) - E(Y^1|X,A=0) = E(Y^0|X,A=1) - E(Y^0|X,A=0) = \alpha$$

difference between treatment or exposure groups is same for both potential outcomes

add $E(Y^1|X,A=0)$ and subtract $E(Y^0|X,A=1)$ from both sides of equation

$$E(Y^1|X,A=1) - E(Y^0|X,A=1) = E(Y^1|X,A=0) - E(Y^0|X,A=0)$$

i.e., treatment effects are same for treated and untreated

is this reasonable?

Depends on setting

in randomized trials, clearly reasonable (here $\alpha = 0$)

requires assumption

- expected benefits play little role in treatment decisions, or
- decisionmakers' idea of benefit not correlated with true benefits

in general, disbelieved in econometrics

more often believed in biomedical research

why the difference?

In medical care, mechanism of action of treatment, whether treatment is working poorly understood by decisionmakers

In economic decisions, people typically have better idea of these things

In general, need to evaluate on a case-by-case basis

$$c(a,X)=\alpha a$$

$$E(Y^1|X,A=1)-E(Y^1|X,A=0)=\alpha$$

$$E(Y^0|X,A=1)-E(Y^0|X,A=0)=0$$

interpret:

potential outcome Y^1 associated with treatment decisions, not Y^0

expected treatment benefit associated with decisions, but baseline expectation not associated

$$E(Y^1 - Y^0 | X, A = 1) - E(Y^1 - Y^0 | X, A = 0) = \alpha$$

$$c(a, X) = \alpha$$

$$E(Y^1 | X, A = 1) - E(Y^1 | X, A = 0) = \alpha$$

$$E(Y^0 | X, A = 0) - E(Y^0 | X, A = 1) = \alpha$$

interpret:

subjects with higher outcomes on treatment Y^1 preferentially selected for treatment (for $\alpha > 0$)

subjects with higher outcomes on control Y^1 preferentially selected for control (for $\alpha > 0$)

rules out constant treatment effect model

effect modification:

add equations together:

$$\begin{array}{r} E(Y^1|X,A=1) - E(Y^1|X,A=0) = \alpha \\ \underline{E(Y^0|X,A=0) - E(Y^0|X,A=1) = \alpha} \\ E(Y^1 - Y^0|X,A=1) - E(Y^1 - Y^0|X,A=0) = 2\alpha \end{array}$$

effect of treatment more positive in treated (for $\alpha > 0$)

estimation:

$$E(Y^a \mid X, A = a) = E(Y \mid X, A = a)$$

$$E(Y^a \mid X, A = 1 - a) = E(Y^a \mid X, A = a) - c(a, X)$$
$$= E(Y \mid X, A = a) - c(a, X)$$

estimate desired outcome by subtracting off $c(a,X)$ from outcome in observed group (or from each individual)

so, estimate of effect in given treatment group:

$$E(Y^a \mid X, A = a) - E(Y^{1-a} \mid X, A = a)$$
$$= E(Y \mid X, A = a) - E(Y \mid X, A = 1 - a) + c(a, X)$$

effect in group as a whole:

$$E(Y^1|X) - E(Y^0|X) = E(Y|X,A=1) - E(Y|X,A=0) - \{c(1,X)pr(A=0|X) - c(0,X)pr(A=1|X)\}$$

Practical implementation:

Replace each observation Y by $Y^{\alpha} \equiv Y - c(A,X)pr(1-A|X)$

do naive estimation using this approach:

$$E(Y^{\alpha}|X,A=a) = E(Y|X,A) - c(a,X)pr(A=1-a|X) = E(Y^{a}|X)$$

previous estimation assumed that possible to estimate stratum-specific expectations from data; won't work well if sparse data

can use inverse probability of treatment weights (IPTWs), with data $Y^{\alpha}, V, A, w(X)$

where $w(X)$ are weights derived before ($q(A,V)/pr(A|X)$; what is $q(A,V)$ for simple weights, stabilized weights?)

Can one use estimated IPTWs to get conservative estimate of variance? Why or why not?

Write likelihood for data (including latent variables/potential outcomes):

$pr(X)pr(\underline{Y}|X)pr(A|\underline{Y},X)$

where do MSM/treatment effects parameters reside?

If treatment assignment ignorable, only in model for causal effects (i.e, in $pr(\underline{Y}|X)$)

Otherwise, both in $pr(\underline{Y}|X)$ and in $pr(A|\underline{Y},X)$

parameters for treatment effects do not factorize from parameters in selection model

thus, $pr(A|\underline{Y},X)$ not ancillary

inference not conservative

can use bootstrap, more complex methods to get variance

what if $V=X$ and using stabilized weights (i.e., standard modeling)?

Weights all identically 1

Can then presumably use naive variance from model

Aside: how might one write likelihood for MSMs in terms of V and X?

$$pr(\underline{Y}|X) = pr(\underline{Y}|X,V) = \frac{pr(\underline{Y},X|V)}{pr(X|V)} = pr(\underline{Y}|V)\frac{pr(X|V,\underline{Y})}{pr(X|V)}$$

put back into likelihood for data

In MSMs, estimating effect of treatment on outcomes in combined group (all exposure levels)

required sensitivity parameters for confounding for each potential outcome

for binary treatment, require sensitivity parameters for both potential outcomes to get causal effect for exposure in aggregate

what if interested in estimating effect of treatment in treated?

Require only 1 set of sensitivity parameters comparison of approaches: formulating unmeasured confounding in terms of unmeasured confounder, directly in terms of potential outcome

advantages and disadvantages

in general, formulating in terms of single variable unrealistic; doesn't usually result from plausible story/account

occasional exceptions

e.g., Multicenter AIDS Cohort Study

large cohort study of subjects infected with HIV

interested in effect of AZT/ZDV

exposure A measured refers to that received over a 6 month interval

exposure over period influenced by CD4 counts over period

CD4 count associated with outcome

thus confounder

measure CD4 at beginning, end of period

CD4 count at end of period influenced by AZT received over period

variable affected by exposure; not appropriate for simple control (will discuss in much more detail later)

if knew CD4 count used to make decisions in middle of period, would want to control for it

use CD4 count at end as proxy for CD4 in middle

but, poor proxy

subtract out effect of AZT during period on CD4 at end to obtain guess at CD4 at end

don't know exact effect of AZT on CD4 count create model: $CD4_1^0 = CD4_1 - A\Phi$

$CD4_1^0$: CD4 count that would have been observed at end had no treatment been provided

if guess correctly, $CD4_1^0(\Phi)$ is not affected by treatment, and

$$E(Y^a | X, CD4_1^0, A) = E(Y^a | X, CD4_1^0)$$

analysis due to Rosenbaum (1984); extended to time-varying covariates in Joffe et al. (1998?)

In model for CD4, require rank preservation; different from discussion of structural nested distribution models, where rank preservation is useful heuristic

In sensitivity analysis using potential outcomes, can also parametrize departures from ignorability in terms of dependence of treatment assignment on outcomes:

e.g., $pr(A=1|X,Y^0)$ may be parametrized as a logistic model

$$logit\{pr(A=1|X,Y^0)\} = \alpha + X\beta + \gamma Y^0$$

here, dependence is expressed in terms of single potential outcome

consider structural nested model, estimated by G-estimation

$$g\{E(Y^A|X,A)\} - g\{E(Y^0|X,A)\} = g\{E(Y|X,A)\} - g\{E(Y^0|X,A)\}$$

need only express dependence on single potential outcome, as above, to estimate effect of treatment received to estimate effect of treatment on all subjects, must make assumptions about other potential outcomes

$$[g\{E(Y^1|X,A=1)\}-g\{E(Y^0|X,A=1)\}]-[g\{E(Y^1|X,A=0)\}-g\{E(Y^0|X,A=0)\}]$$

describe what is being compared here

Current treatment interaction

comparing effect of treatment for treated to potential effect for untreated

in G-estimation, first obtain estimate of parameters Ψ, with selection bias parameters framed in terms of Y^0

then, obtain estimates of Y^1, using current treatment interaction parameters (not estimable

method is asymmetric: requires choosing baseline value of treatment a

Can do sensitivity analysis for

p-values (see Rosenbaum)

Estimates (point and interval)

Bayesian alternative: specify

put prior on selection bias parameter

how can one summarize over multiple sources of bias (e.g., multiple unmeasured confounders; multiple sensitivity parameters)?

Look at all values of parameters

Worst-case scenarios

Bayesian averaging