Principal Stratification

Seen as approach to noncompliance in randomized trials

Now applied more broadly to a wide variety of problems

- Censoring by death
- Mouse toxicity experiments
- Vaccine trials
- Needle exchange evaluations

Will consider

- general formulation
- problems in order; evaluate advantages and problems with approach
- identifying assumptions that have been used with each of the approaches

General Formulation

$\underline{S} \equiv \{S^a; a \in \mathbf{A}\}$

Inference about $f\{Y^a | q(\underline{S})\}$; $q(\cdot)$ some arbitrary function

For randomized trials, if S denotes binary treatment received

Principal strata:

S^0	S^1	name of stratum
0	0	never taker
0	1	complier (cooperator)
1	0	defier
1	1	always taker

Interest may be in effect on compliers: $S^a = A$ $(S^0 = 0, S^1 = 1$

principal strata are based on cross-classification of $S^a, S^{a'}$

For nonbinary treatments, can have princpal strata based on cross-classification of may potential auxiliary outcomes

Can collapse over some of these strata so that even if treatment has many values, can consider cross-classification by 2 (or even 1) potential auxiliary

Censoring by death:

Have some outcome of interest Y

Y not observable/meaningful in subjects who die (S=0)

What would be appropriate measure of effect of exposure on Y?

Two options:

1. Comparison of $f(Y^a|S^a=1)$

What is problematic with this?

What is benefit of approach

Comparing densities for different groups of people

Estimable using usual assumptions:

Ignorability:

$$\{Y^a, S^a\}, \perp A|X \Rightarrow f(Y^a, S^a|X) = f(Y^a, S^a|X, A=a) = f(Y, S|X, A=a)$$

2. Comparison of $f(Y^a|S^0=S^1=1)$

   Effect of treatment on outcome who would live under either treatment

   Individual level effects on mortality only defined for this subset

problems with this approach

subset not identifiable

even proportions in principal strata not identifiable without other assumptions

what assumptions might identify proportion in principal strata? Why?

Monotonicity: $S^1 \geq S^0$

together with randomization or ignorability:

$$pr(S^1=1,S^0=1)=pr(S^0=1)=pr(S=1|A=0)$$

$$pr(S^1=0,S^0=0)=pr(S^1=0)$$

$$pr(S^1=1,S^0=0)=1-pr(S^1=0)-pr(S^0=1)$$

Even though proportions identified, effect in this stratum not identified (unlike noncompliance problem)

Want to identify $f(Y^0|S^1=S^0=1)$, $f(Y^1|S^1=S^0=1)$

Which of these is identified by assumptions above from observable data?

$f(Y^0|S^1=S^0=1)=f(Y^0|S^0=1)=f(Y^0|S^0=1,A=0)=f(Y|S=1,A=0)$

$f(Y^1|S^1=S^0=1)$ not identified

$f(Y|S=1,A=1)$

$=pr(S^0=0|S^1=1)f(Y|S^1=1,S^0=0,A=1)+pr(S^0=1|S^1=1)f(Y|S^1=1,S^0=1,A=1)$

(What is identified in above formula?)

One type of assumption: degree of difference in Y^1 between two principal strata

Can be parametrized as $pr(S^0=1|S^1=0,Y^1)=\alpha_0+\alpha_1 Y^1$

choose α_1; then α_0 identified, as are components of mixture

do sensitivity analysis: see how inference changes as one varies α_1

further discussion of estimand

are principal stratification estimands useful

for decisionmaking?

for understanding processes/explanation?

Decisionmaking

adopt decision theoretic framework

assign utility or loss function to various outcomes

how would one do this?

Let $L_i(S^a, Y^a; a)$ denote cost associated with of particular outcomes for a given individual

How can covariates be incorporated in this model?

Expected loss (given baseline covariates):

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$E\{L_i(S^a, Y^a; a)|X\}$

Make decision to minimize loss:

State implication for three approaches:

joint distribution of outcomes S^a, Y^a

conditional distributions $Y^a|S^a$

principal stratification: $Y^a|\underline{S}$

what role do joint distributions of $\underline{S}, \underline{Y}$ under different treatments play?

joint distribution of outcomes under a: most appropriate

can use conditional distributions and marginal of S^a to obtain joint distribution

joint distributions under different treatments do not influence optimal decision

can obtain marginals from joint distributions; thus, can use principal stratification estimands to obtain marginals; more complicated approach

sometimes modeling joint distribution of potential outcomes can impose additional structure, lead to reduced variance; comes at increased reliance on assumptions

when can one concentrate solely on Y for making decisions?

2 types of conditions:

1. Loss does not depend on S^a:

$$L_i(s,y;a)=L_i(s',y;a)$$

2. Treatment has no effect on S

then require additional condition: e.g., independent influence of S and A on loss: $L_i(S^a,Y^a;a)=q_1(S^a)+q_2(Y^a)$

then, $E\{L_i(S^a,Y^a;a)\}=E\{q_1(S^a)\}+E\{q_2(Y^a)\}=k+E\{q_2(Y^a)\}$

in either case, the difference in expected loss under different treatments solely a function of Y^a

Explanatory uses of analyses

Explanatory uses of principal stratification, alternatives

Principal stratification useful for this purpose:

Only approach considered here which allows consideration of individual level causal effects on Y in isolation

"Among people who would not have died under either treatment or placebo, treatment reduced the rate of cataracts by 20%"

Other approaches:

Joint distribution of Y^a, S^a: consider effects on both

Conditional approach: biased for individual level effects

Vaccine trials

have vaccine that designed to reduce incidence of HIV disease (S); reduce viral load (Y)

viral load (arguably) not of interest for subjects not infected with HIV

interested in effect of vaccine on viral load

structurally, is this problem same as noncompliance or censoring by death?

Structurally similar to censoring by death

effect of interest is for “always takers”: subjects who develop HIV whether or not receive vaccine

why is “exclusion restriction” like condition not relevant here (and in censoring by death)?

Usefulness depended on attributing differences in distribution of *Y* to effect in single stratum

Since *Y* not defined if die/develop HIV, solution doesn't work

Mouse toxicity experiment (Elliott, Joffe, and Chen, 2006 Biometrics)

Give pregnant mice toxin, look at its effect on fetal weight

Multiple fetuses ("pups") per pregnant mouse ("dam")

Toxin may kill some pups

Fewer pups may be associated with better outcomes; each pup is competing with fewer others for mother's resources

Draw DAG

Interested ultimately is in inference for effect of toxin on human pregnancy

What effect is of interest?

Goal is to estimate “direct” effect of toxin on weight

disentangle from “indirect” effect mediated by number of other pups

How can one characterize “direct” effect?

Two levels:

individual pup: effect defined only for those pups which would survive whether or not treated

dam level: interested in effect if hold number of other pups constant

2 ways to do this:

direct effect: consider intervening to keep # of live pups same (e.g., kill extra fetuses *in utero*; hypothetical/unspecified intervention)

principal stratification: consider effects for dams where the number of pups is not affected by the toxin

what is less problematic about principal stratification estimand here than in human studies?

Don’t really care about effect on mice

Not really interested in what would happen to entire population of mice; not real target

Principal stratification estimand represents a direct effect of toxin

assumptions: normality of outcomes within observed groups

mixtures of normal distributions can often be identified

randomization of numbers of pups per litter

adopted Bayesian framework for estimation

needle exchange program evaluation

wanted to estimate the effect of exchanging needles on developing HIV

had various needle exchange centers that were positioned in various places around Baltimore

positioning of exchange centers under the control of investigators

exchanging needles not under the control of investigators

A position of subject relative to exchange cengter

S subject's exchange behavior

Y outcome

wanted to use distance as instrumental variable

principal strata defined by distance

monotonicity assumption: someone who would exchange at greater distance would also exchange at shorter distance

makes principal stratum a scalar quantity: maximum distance would exchange

looked at effect of distance for people within principal stratum

write notation

what might be problems with this approach?

1. Stability assumption:
   effect of position (what is actually intervened on) depends only on distance

2. No notation for causal effect of actually exchanging