Lecture 3
randomized experiments and Fisher's exact p-value

Outline

- Five examples of randomized experiment mechanisms

- Fisher's exact p-value

  - Fisher's original experiment

  - Hypothesis testing

  - Construct confidence intervals

  - Choice of the test statistics

- Suggested reading: Imbens and Rubin Chapter Chapter 4-5, Peng's book

  Chapter Chapter 3

Treatment assignment mechanism

- Assignment vector for binary treatment with N units: $\boldsymbol{W} = (W_1, \cdots, W_N) \in \{0,1\}^N$

- Unconfoundedness property: $P(\boldsymbol{W}|\boldsymbol{X}, \boldsymbol{Y}(0), \boldsymbol{Y}(1)) = P(\boldsymbol{W}|\boldsymbol{X})$
    - Assignment mechanism does not depend unobserved $\boldsymbol{U}$ pretreatment confounders
    - $\boldsymbol{U}$ includes potential outcomes $(Y_i(0), Y_i(1))$
    - We can alternatively understand it as
    $$W_i \perp (Y_i(0), Y_i(1)) \mid \boldsymbol{X}_i$$
    - Make the treatment and control groups "identical"
    $$P(Y_i(0), Y_i(1) \mid \boldsymbol{X}_i, W_i = 0) = P(Y_i(0), Y_i(1) \mid \boldsymbol{X}_i, W_i = 1)$$

    - Identify conditional population average treatment effect under unconfoundedness

Causal estimand that involve the unobserved potential outcomes

$$\tau(\boldsymbol{x}) = \mathbb{E}(Y_i(1) - Y_i(0) \mid \boldsymbol{X}_i = \boldsymbol{x})$$
$$= \mathbb{E}(Y_i(1) \mid \boldsymbol{X}_i = \boldsymbol{x}, W_i = 1) - \mathbb{E}(Y_i(0) \mid \boldsymbol{X}_i = \boldsymbol{x}, W_i = 0)$$
$$= \mathbb{E}(Y_i(W_i) \mid \boldsymbol{X}_i = \boldsymbol{x}, W_i = 1) - \mathbb{E}(Y_i(W_i) \mid \boldsymbol{X}_i = \boldsymbol{x}, W_i = 0)$$
$$= \mathbb{E}(Y_i \mid \boldsymbol{X}_i = \boldsymbol{x}, W_i = 1) - \mathbb{E}(Y_i \mid \boldsymbol{X}_i = \boldsymbol{x}, W_i = 0)$$

Conditional expectations that we can evaluate based on observed data

Common designs of randomized experiments

- Five examples of randomized experiment mechanisms
  - Bernoulli trial
  - Completely randomized experiment
  - Stratified randomized experiment
  - Paired randomized experiment
  - Rerandomization

- The purpose of restricting the assignment mechanism is to eliminate assignment vectors that are less desirable for estimating causal effects
  - Examples: all males get treatment; all females get control

Bernoulli trial

- Simplest Bernoulli experiment tosses a (fair) coin for each unit
  - If the coin is heads, then unit receive treatment
  - Otherwise, the unit receive control

- For each $\boldsymbol{w} \in \{0,1\}^N$, $P(\boldsymbol{W} = \boldsymbol{w}|\boldsymbol{X}) = P(\boldsymbol{W} = \boldsymbol{w}) = 0.5^N$
- $W_1, \cdots, W_N \sim \text{Bernoulli}(0.5)$ and are independent

- More generally, we can toss a specialized coin for each unit depending on its covariates
  - Define propensity score $e(\boldsymbol{X}_i) = P(W_i = 1| \boldsymbol{X}_i)$
  - Assignment property: $P(\boldsymbol{W} = \boldsymbol{w}|\boldsymbol{X}) = \prod_{i=1}^{N}[e(\boldsymbol{X}_i)^{W_i}(1 - e(\boldsymbol{X}_i))^{1-W_i}]$
  - $W_1, \cdots, W_N$ are still independent and each $W_i \sim \text{Bernoulli}(e(\boldsymbol{X}_i))$
  - Example: when trying to induce people with serious disease to enroll for the trial of a promising drug, we give them a higher probability to receive the treatment

- What is the probability that all units receive the same treatment?
  - Any problems? Solution?

Completely randomized experiment

- A fixed number of subjects N_t is assigned to receive the active treatment

- Assignment probability

$$P(\boldsymbol{W} = \boldsymbol{w}|\boldsymbol{X}) = \begin{cases} \binom{N}{N_t}^{-1} & \text{if } \sum_{i=1}^{N} w_i = N_t \\ 0 & \text{otherwise} \end{cases}$$

- Completely randomized experiment guarantees that there are exactly N_t individuals receiving the treatment and $N - N_t$ individuals receiving the control
- $W_1, \cdots, W_N$ are slightly negatively associated

- Assume that half individuals are female
  - What is the probability that all females receive the control?
  - Is that problematic?
- Do we achieve covariates balancing?
  - Randomization guarantee covariates balancing on average
  - For this single experiment, we can get a terrible estimate and wrong judgement
    - Also reflected as large uncertainty in our estimates

Stratified randomized experiment

- Basic procedure:
    1. Blocking (Stratification): create groups of similar units based on pre-treatment covariates, let $B_i \in \{1, \cdots, J\}$ be the block indicator
    2. Block (Stratified) randomization: completely randomize treatment assignment within each group
- Blocking can improve the efficiency by minimizing the variance of the potential outcomes within each strata

"Block what you can and randomize what you cannot"

Box, et al. (2005). Statistics for Experimenters. 2nd eds. Wiley

- Assignment probability

$$P(\boldsymbol{W} = \boldsymbol{w}|\boldsymbol{X}) = \begin{cases} \prod_{j=1}^{J} \binom{N(j)}{N_t(j)}^{-1} & \text{if } \sum_{i:B_i=j}^{N} w_i = N_t(j) \text{ for } j = 1, \cdots, J \\ 0 & \text{otherwise} \end{cases}$$

Examples

- Randomized trial for the Moderna vaccine
  [Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England journal of medicine*, 2020.]
    - Participants were randomly assigned in a 1:1 ratio, through the use of a centralized interactive response technology system, to receive vaccine or placebo.
    - Assignment was stratified into the following risk groups: persons 65 years of age or older, persons younger than 65 years of age who were at heightened risk (at risk) for severe Covid-19, and persons younger than 65 years of age without heightened risk (not at risk).

- Experiment of women policy makers in India
  [Women as policy makers: Evidence from a randomized policy experiment in India. *Econometrica,*2004]
    - Each Gram Panchayat (GP) encompasses 10,000 people in several villages (between 5 and 15)
    - Starting 1993, in a third of the villages in each GP, only women could be candidates for the position of councilor for the area.
    - Random selection: villages are ranked in consecutive order according to an administrative number, every third village is reserved for a woman
    - How is the experiment stratified?

Paired randomized experiment

- Can we keep blocking until we cannot block any further?
- Procedure:
    1. Create $J = N/2$ pairs of similar units
    2. Randomize treatment assignment within each pair

- Example: evaluation of health insurance policy
  [Public policy for the poor? A randomised assessment of the Mexican universal health insurance programme. *The lancet, 2009*.]
    - Seguro Popular, a programme aimed to deliver health insurance, regular and preventive medical care, medicines, and health facilities to 50 million uninsured Mexicans
    - Units: health clusters = predefined health facility catchment areas
    - Randomization within 74 matched pairs of "similar" health clusters
    - Outcome: proportion of households within each health cluster who experienced catastrophic medical expenditure

Rerandomization

[Morgan and Rubin. 2012. Ann. Stat., Li et al. 2018. PNAS]

- The more covariates, the more likely at least one covariate will be imbalanced across treatment groups
- Randomization only eliminate confounding factors and yield unbiased on average (over repeated run of experiments)
- For any particular experiment, covariate imbalance is possible

- Procedure:
    1. Specify the acceptable level of covariate balance
    2. Randomize the treatment and check covariate balance
    3. Repeat until the covariate balance criterion is met
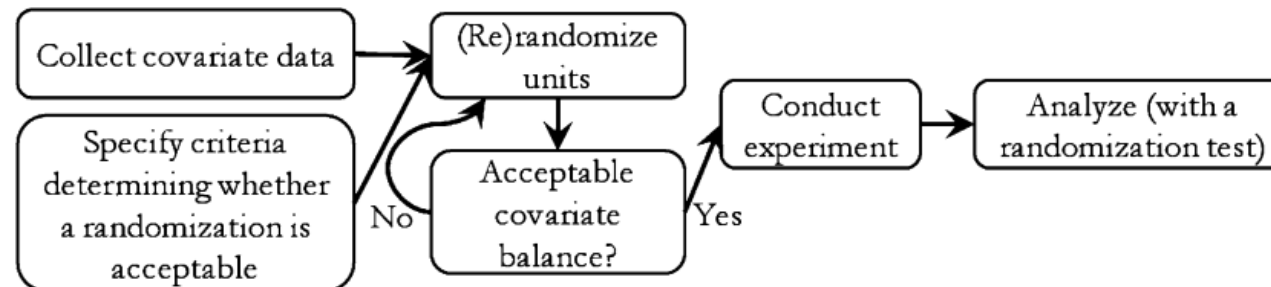
Rerandomization: an example

[Rerandomization to balance tiers of covariates. *Journal of the American Statistical Association,* 2015.]
- The study aim to examine whether observational studies can be analyzed to yield valid estimates of causal effects.
- Undergraduate psychology students at a particular college were randomized to be in one of two arms: a randomized experiment (n_r = 235) or an observational study (n_o = 210).
- In the randomized experiment were randomized to take either a vocabulary or mathematics course
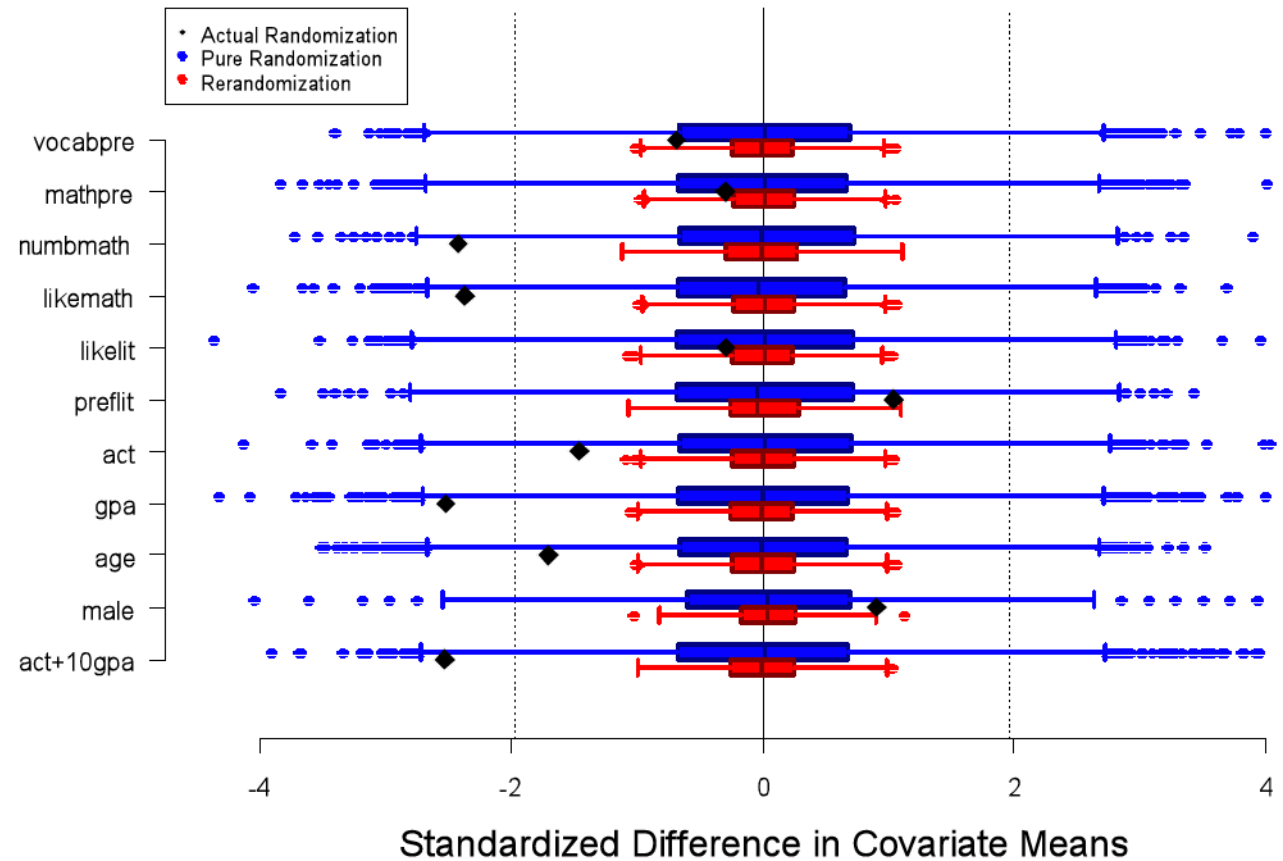
Randomization Inference vs. Model-based Inference

- Randomization as the "reason basis for inference" (Fisher)
- Randomness comes from the physical act of randomization, which then can be used to make statistical inference
- Also called **design-based inference**
- Advantage: design justifies analysis

- model-based inference: assume a distribution for potential outcomes
(at least the i.i.d. assumptions)
- Advantage of model-based inference: flexibility

- Two types of classical randomization inference
  - Fisher's exact p-values
  - Neyman's repeated sampling approach

Fisher's original experiment: Lady tasting tea
[Fisher, 1935]

- The lady in question (Muriel Bristol) claimed to be able to tell whether the tea or the milk was added first to a cup.
- Fisher proposed to give her eight cups, four of each variety, in random order.

- **Null hypothesis:** the lady cannot tell the difference
- How to define the causal effect?
  - whether the tea or the milk was added first has any effect on the lady's guess result
- What is a unit?
- What is the treatment assignment?
  - $W_i = 1$ if tea is added first
- What is $Y_i(0)$ and $Y_i(1)$?
  - The lady's potential guess results

- **Sharp null:** $H_0: Y_i(0) \equiv Y_i(1)$ for all $i = 1, \cdots, 8$

Fisher's original experiment: Lady tasting tea
[Fisher, 1935]

- **Sharp null:** $H_0 : Y_i(0) \equiv Y_i(1)$ for all $i = 1, \cdots, 8$
- **Test statistics:** the number of correctly classified cups
- The lady classified all 8 cups correctly! Did this happen by chance?
- Goal: calculate the distribution of the test statistics under the null

- Completely randomized experiment: $\binom{8}{4} = 70$ possible scenarios with equal probability
- Under the sharp null, the lady will always have the same guesses under all scenarios

	$Y_i(0) = Y_i(1) = Y_i$	W_i	70 possible assignments		
cups	guess	actual	scenarios		...
1	M	M	T	T	
2	T	T	T	T	
3	T	T	T	T	
4	M	M	T	M	
5	M	M	M	M	
6	T	T	M	M	
7	T	T	M	T	
8	M	M	M	M	
correctly guessed		8	4	6	

Null distribution of the test statistics

P-value: 1/70

Number of correctly guessed cups
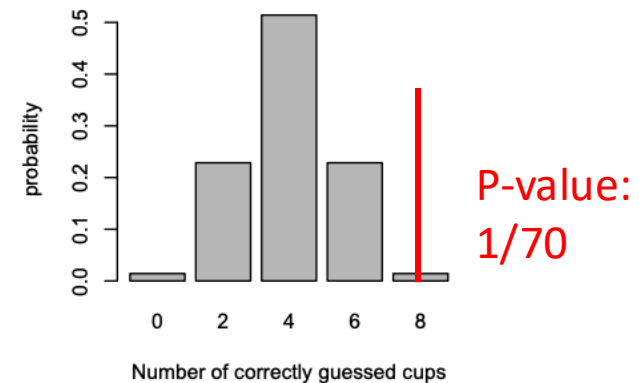
Cough frequency example with 6 units

Table 5.3. *Cough Frequency for the First Six Units from the Honey Study*

Unit	Potential Outcomes		Observed Variables		
	Cough Frequency (cfa)				
	$Y_i(0)$	$Y_i(1)$	W_i	X_i (cfp)	Y_i^{obs} (cfa)
1	?	3	1	4	3
2	?	5	1	6	5
3	?	0	1	4	0
4	4	?	0	4	4
5	0	?	0	1	0
6	1	?	0	5	1

Imputation under the sharp null

	Cough Frequency (cfa)			
	$Y_i(0)$	$Y_i(1)$	Y_i^{obs}	rank(Y_i^{obs})
1	(3)	3	3	4
2	(5)	5	5	6
3	(0)	0	0	1.5
4	4	(4)	4	5
5	0	(0)	0	1.5
6	1	(1)	1	3

- **Sharp null:** $H_0: Y_i(0) \equiv Y_i(1)$ for all $i = 1, \cdots, 6$
  absolutely no causal effect of the treatment
- Test statistics: $|\bar{Y}_t^{obs} - \bar{Y}_c^{obs}|$ or $|\overline{\text{rank}}_t(Y_i^{obs}) - \overline{\text{rank}}_c(Y_i^{obs})|$

Cough frequency example with 6 units

- If following completely randomized experiment: $\binom{6}{3} = 20$ assignments with equal probability

Table 5.5. *Randomization Distribution for Two Statistics for the Honey Data from Table 5.3*

						Statistic: Absolute Value of Difference in Average	
W_1	W_2	W_3	W_4	W_5	W_6	Levels (Y_i)	Ranks (R_i)
0	0	0	1	1	1	−1.00	−0.67
0	0	1	0	1	1	−3.67	−3.00
0	0	1	1	0	1	−1.00	−0.67
0	0	1	1	1	0	−1.67	−1.67
0	1	0	0	1	1	−0.33	0.00
0	1	0	1	0	1	2.33	2.33
0	1	0	1	1	0	1.67	1.33
0	1	1	0	0	1	−0.33	0.00
0	1	1	0	1	0	−1.00	−1.00
0	1	1	1	0	0	1.67	1.33
1	0	0	0	1	1	−1.67	−1.33
1	0	0	1	0	1	1.00	1.00
1	0	0	1	1	0	0.33	0.00
1	0	1	0	0	1	−1.67	−1.33
1	0	1	0	1	0	−2.33	−2.33
1	0	1	1	0	0	0.33	0.00
1	1	0	0	0	1	1.67	1.67
1	1	0	0	1	0	1.00	0.67
1	1	0	1	0	0	3.67	3.00
1	1	1	0	0	0	**1.00**	**0.67**

- P-value based on test statistics $\left|\bar{Y}_t^{obs} - \bar{Y}_c^{obs}\right|: \frac{16}{20} = 0.8$
- P-value based on test statistics
$\left|\overline{rank(Y_t^{obs})} - \overline{rank(Y_c^{obs})}\right|: \frac{16}{20} = 0.8$

- The most extreme p-value we can get: 2/20 = 0.1
- $N = 6$ is too small to obtain statistically significant rejections
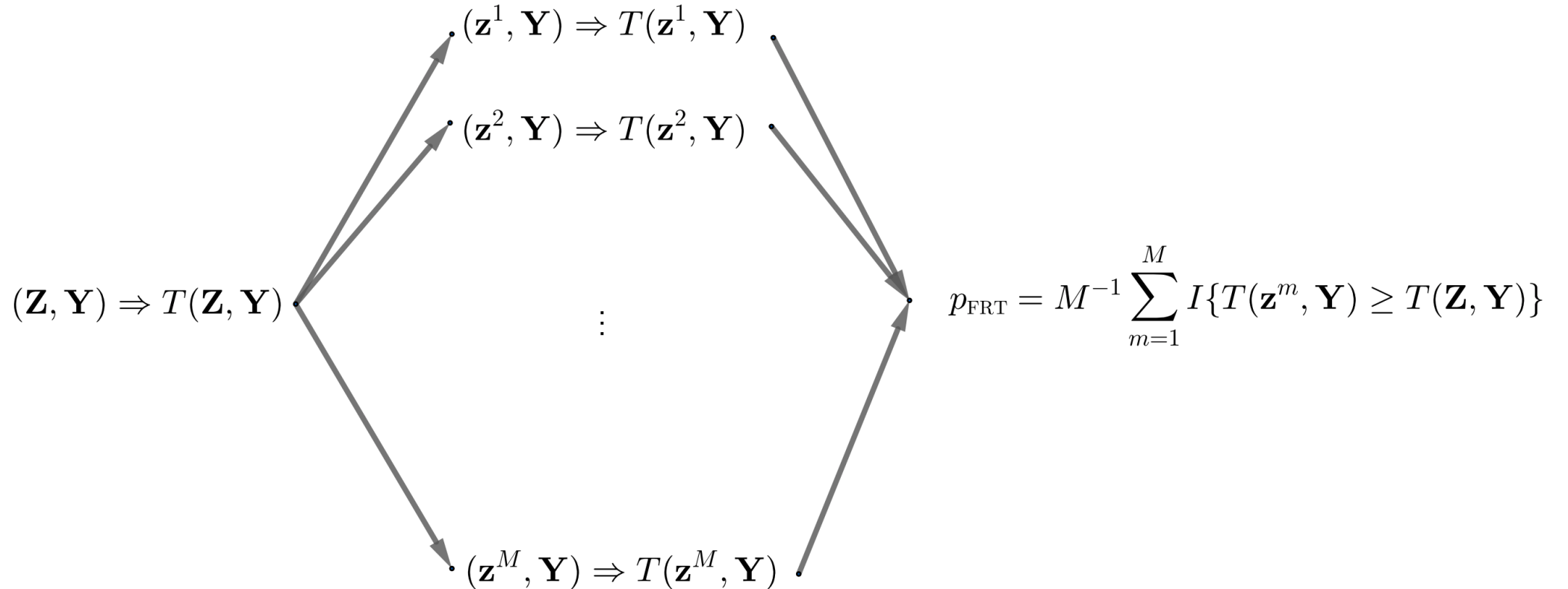
Illustration of Fisher's randomization test

$(\mathbf{z}^1, \mathbf{Y}) \Rightarrow T(\mathbf{z}^1, \mathbf{Y})$

$(\mathbf{z}^2, \mathbf{Y}) \Rightarrow T(\mathbf{z}^2, \mathbf{Y})$

$(\mathbf{Z}, \mathbf{Y}) \Rightarrow T(\mathbf{Z}, \mathbf{Y})$

$\vdots$

$(\mathbf{z}^M, \mathbf{Y}) \Rightarrow T(\mathbf{z}^M, \mathbf{Y})$

$$p_{\mathrm{FRT}} = M^{-1} \sum_{m=1}^{M} I\{T(\mathbf{z}^m, \mathbf{Y}) \geq T(\mathbf{Z}, \mathbf{Y})\}$$

Figure 3.1 of Peng's book

Fisher's exact p-value

- Features
    - Justified by randomization alone: No assumptions about models or asymptotic normality
    - The sharp null may be of little interest
    - P-value is exact for small N
    - Same idea as a permutation test

- Computation of p-value
    - Exact computation is difficult when N is large
    - Monte Carlo approximation
        1. Fill in missing potential outcomes under the sharp null
        2. Sample W_i according to complete randomization
        3. Compute the test statistic to form a reference distribution
    - Approximation can be arbitrarily accurate by increasing number of draws

- Fisher's exact p-value can be calculated for any randomization mechanism
- Analytical approximations when N is large (omitted)

Cough frequency example with $N = 72$

P-value computation with Monte Carlo approximation

Number of Simulations	P-Value	$\widehat{(s.\,e.\,)}$
100	0.010	(0.010)
1,000	0.044	(0.006)
10,000	0.044	(0.002)
100,000	0.042	(0.001)
1,000,000	0.043	(0.000)

Note: Statistic is absolute value of difference in average ranks of treated and control cough frequencies. P-value is proportion of draws at least as large as observed statistic.

Fisher's exact p-value and CI

- Choice of the null hypothesis
    - Sharp null of no treatment effect: $H_0: Y_i(0) \equiv Y_i(1)$ for all $i = 1, \cdots, N$
    - Fisher's approach cannot accommodate a null hypothesis of **zero average effect :** we can not impute the unmeasured potential outcomes

    - Allow more general null hypothesis $H_0: Y_i(0) = Y_i(1) + C_i$ for all $i = 1, \cdots, N$ with pre-defined $(C_1, \cdots C_N)$

- Invert Fisher's exact p-values for confidence intervals of τ_0
    - Assume the constant additive effect model $Y_i(0) - Y_i(1) \equiv \tau_0$
    - We can still impute the missing potential outcomes under the above null with a pre-specified τ_0
    - Collect all null values τ_0 that cannot be rejected by α-level Fisher's exact test
    - Idea: if we cannot reject a null hypothesis with a particular effect size, then the confidence interval should include it

Cough frequency example revisited

- We want to test for the generalized sharp null $H_0 : Y_i(1) - Y_i(0) \equiv 0.5$
  - We need to impute the missing values differently under the new H_0
  - The test statistics is different
    - Based on the mean difference $|\bar{Y}_t^{obs} - \bar{Y}_c^{obs} - 0.5|$
    - Based on the rank: we define the rank of each unit based on $\text{rank}(Y_i(0))$[or equivalently $\text{rank}(Y_i(1))$], instead of $\text{rank}(Y_i^{obs})$

Unit	Potential Outcomes		Actual Treatment	Observed Outcome
	$Y_i(0)$	$Y_i(1)$		
1	(2.5)	3.0	1	3.0
2	(4.5)	5.0	1	5.0
3	(−0.5)	0.0	1	0.0
4	4.0	(4.5)	0	4.0
5	0.0	(0.5)	0	0.0
6	1.0	(1.5)	0	1.0

Cough frequency example with $N = 72$

Hypothesized Treatment Effect	P-Value (level)	P-Value (rank)
-3.00	0.000	0.000
-2.75	0.000	0.000
-2.50	0.000	0.000
-2.25	0.000	0.000
-2.00	0.001	0.000
-1.75	0.006	0.078
-1.50	0.037	0.078
-1.44	0.050	0.078
-1.25	0.146	0.078
-1.00	0.459	0.628
-0.75	0.897	0.428
-0.50	0.604	0.428
-0.25	0.237	0.429
0.00	0.067	0.043
0.06	0.050	0.043
0.25	0.014	0.001
0.50	0.003	0.000
0.75	0.000	0.001
1.00	0.000	0.000

- 95% CI based on statistics $\left|\bar{Y}_t^{obs} - \bar{Y}_c^{obs} - \tau_0\right|$:
  - $[-1.44, 0.06]$

- 95% CI based on statistics $\left|\overline{\text{rank}}_t(Y_i(0)) - \overline{\text{rank}}_c(Y_i(0))\right|$:
  - $[-2, 0]$

Choice of test statistics

- Fisher's exact p-values are valid for any test statistics
  - Choice of test statistic determines "power" to detect a particular alternative hypotheses
  - Choose a test statistics that is sensitive to expected departures from the null hypothesis
    - One principle: test statistics is "centered at 0" under the null

- Examples for test statistics for the sharp null $H_0: Y_i(0) \equiv Y_i(1)$
  - Sample mean difference: $|\bar{Y}_t^{\text{obs}} - \bar{Y}_c^{\text{obs}}|$
  - Sample rank mean difference: $\left|\overline{\text{rank}_t\left(Y_i^{\text{obs}}\right)} - \overline{\text{rank}_c\left(Y_i^{\text{obs}}\right)}\right|$
    [check Imbens and Rubin book page 57 for a formal definition of a normalized rank with ties]

  - Quantile difference (more robust to outliers)
    - Difference in medians: $|\text{med}_t\left(Y_i^{\text{obs}}\right) - \text{med}_c\left(Y_i^{\text{obs}}\right)|$

  - Fisher's exact test statistics for binary outcome: $S = \sum_{i=1}^n W_i Y_i(1) = \sum_{i=1}^n W_i Y_i$
  - Covariate-adjusted statistics

Fisher's exact test for binary outcome

	Treated ($W_i = 1$)	Control ($W_i = 0$)	Total
$Y_i = 1$	$\sum_{i=1}^{n} W_i Y_i(1)$	$\sum_{i=1}^{n} (1 - W_i) Y_i(0)$	m
$Y_i = 0$	$\sum_{i=1}^{n} W_i (1 - Y_i(1))$	$\sum_{i=1}^{n} (1 - W_i)(1 - Y_i(0))$	$N - m$
Total	N_1	N_0	N

- In the tea tasting example, the lady knows that there are 4 cups for each variety, so m is also fixed
- Test statistics: $S = \sum_{i=1}^{n} W_i Y_i(1) = \sum_{i=1}^{n} W_i Y_i$
- Then under complete randomization and the sharp null, S follows a hyper-geometric distribution

$$P(S = s) = \frac{\binom{m}{s} \binom{N - m}{N_1 - s}}{\binom{N}{N_1}}$$

- Under the sharp null $H_0: Y_i(0) \equiv Y_i(1)$, m is always naturally fixed as $Y_i \equiv Y_i(0) \equiv Y_i(1)$ are always fixed

Lady tasting tea revisited: R code

```r
# Data setup: a 2x2 contingency table where rows represent guessed (milk first or tea first),
# and columns represent actual preparation (milk first or tea first).
data <- matrix(c(4, 0, 0, 4), nrow = 2,
               dimnames = list(Guessed = c("Milk First", "Tea First"),
                               Actual = c("Milk First", "Tea First")))
```

```
                   Actual
       Guessed     Milk First  Tea First
       Milk First      4            0
       Tea First       0            4
```

```r
# Perform Fisher's Exact Test
fisher_result <- fisher.test(data, alternative = "greater")
```

```
> print(fisher_result)

        Fisher's Exact Test for Count Data

data:  data
p-value = 0.01429
```

```
> 1/70
[1] 0.01428571
```

The project STAR example

(Mosteller. 1997. Bull. Am. Acad. Arts Sci.)

- The student-Teacher Achievement Ratio Project (1985-1989)
  - More than 10,000 students involved with the cost of $12 million
  - Effects of class size in early grade levels
  - 3 arms: Small class, Regular-sized class, Regular class with aid

- Long-term impact of class size

	Small class	Regular-sized class
Graduate	754	892
Not graduate	148	189
Total	902	1081

- Check by yourself with R
- p-values: 0.28 (one-sided), 0.55 (two-sided)