Today’s agenda

• Reminder about deadlines
• Some quick i>clicker questions about the readings
• X on the reading
• Probability density distributions (pdf’s)
• More in depth on the readings
First draft deadline is in 3 weeks: Monday October 26

- Needs to be at least a mockup of your paper
- With sections that include complete sentences
- At least one table or figure produced and discussed
- Be sure that the 3 sentences from your topic appear in the draft, whether verbatim or updated

1. Question you’re asking
2. Data
3. Answer you expect
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Current events: 2015 Nobel Prize in Medicine

• Shared by 3 researchers for work on parasites (1/2) and malaria (1/2)

• Malaria: Youyou Tu, born 1930, is the first scientist citizen of the People’s Republic of China to win

• According to the NY Times:
  - Mao Zedong initiated a military project to help North Vietnam treat its soldiers for malaria
  - Skilled in Chinese and Western medicine, Youyou Tu isolated artemisinin
  - A recipe written more than 1,600 years ago in a text titled “Emergency Prescriptions Kept Up One’s Sleeve” — soak one bunch of wormwood in water and then drink the juice.
i>clicker question 6.1

James Lind was known for what?

A. Treating malaria aboard a British ship
B. Treating dysentery aboard a British ship
C. Treating scurvy aboard a British ship
D. Dying while on a British ship
What was unique about Lind’s scurvy experiment?

A. He administered separate treatments to groups
B. He tried giving lemons & oranges to sick sailors
C. In his trial, sailors actually got better
D. The admiralty actually paid attention to his results
Suppose I flipped 10 coins. Then I did it again, and again, and again for like a day. What would the distribution of the number of heads look like?

A.  
B.  
C.  
D.  
E.  

Answer: E.
For context, some historical events:

- 1000: Variolation is practiced in China
- 1579: Jamestown, VA, settled
- 1607: Sir Francis Drake visits Pt. Reyes during his circumnavigation
- 1607: James Lind conducts scurvy experiments
- 1747: John Snow maps cholera to a public water pump in London's Soho
- 1777: Washington orders army variolated
John Snow maps cholera to a public water pump in London’s Soho
An outcome $y$ is a function $f(\cdot)$ of lots of things

$$y = f(x_1, x_2, x_3, x_4)$$
Good health in particular depends on lots of related things

friends → f(x₁, x₂, x₃, x₄) → Good health
education →
exercise →
smoking →
The inter-relationships are part of the issue

friends  
education  
exercise  
smoking  

\[ f(x_1, x_2, x_3, x_4) \]  

Good health
Before the germ theory of disease, people fixated on bad smells and bad air, bad diet

bad air or “miasma”

sewage

rats

bad diet

$g(x_1,x_2,x_3,x_4)$

Bad health
When the x’s are inter-related, how do you tell which one is important?

bad air or “miasma”

sewage

rats

bad diet

$g(x_1,x_2,x_3,x_4)$

Bad health
The setup

- Objective: to determine the effect on $x_1$ on $y = f(\cdot)$

- With calculus, this is $\partial f/\partial x_1$ with other things constant

- When $x_1$ is a dichotomous 0/1 kind of treatment, we can also look at

  $$f(x_1, \overline{x}_2, \overline{x}_3, \overline{x}_4) - f(0, \overline{x}_2, \overline{x}_3, \overline{x}_4)$$

- Here, we evaluate $f(\cdot)$ at the averages of the other $x$'s
treatment − control

\[ f(x_1, \bar{x}_2, \bar{x}_3, \bar{x}_4) − f(0, \bar{x}_2, \bar{x}_3, \bar{x}_4) \]

- You could pick any x’s that you like as long as they were the same across treatment and control
- Picking the averages means the experiment is valid for the average individual, which is handy
- You could also measure the average outcome \( E[\cdot] \) over groups that have varying x’s

\[ E[ f(x_1, x_2, x_3, x_4) ] − E[ f(0, x_2, x_3, x_4) ] \]
treatment  –  control

\[ f(x_1, \bar{x}_2, \bar{x}_3, \bar{x}_4) - f(0, \bar{x}_2, \bar{x}_3, \bar{x}_4) \]

- It’s best to have a control group or “business as usual” with which to compare

- But merely observing a suffering group is dicey at best

- **James Lind** picked 12 sailors with scurvy out of 30 or 40 and specified 6 treatments, 2 sailors for each

- “Their cases were so similar as I could have them” “They lay together in one place … and had one diet common to all”

  He’s trying to control for the other x’s
Lind’s scurvy experiments

• There were many theories about why scurvy afflicted sailors, and citrus fruit was one of the common remedies

• Lind’s 6 treatments included
  - Cider
  - Elixir of vitriol: sulfuric acid, alcohol, aromatics
  - Vinegar
  - Sea water
  - Oranges and lemons
  - Purgative mixture: maybe sodium sulfate, a laxative
The setup & the outcome

• 8 weeks after leaving port, May 20th, 1747, *HMS Salisbury* was patrolling the French coast, part of the War of the Austrian Succession

• 10% of the crew had scurvy! *But the roll call showed nobody sick*

• We now know that scurvy is caused by a deficiency of vitamin C

• Sailors who received the oranges and lemons grew healthier by the end of May
The context & aftermath

• The Royal Navy didn’t adopt citrus rations until 1795, a year after James Lind died

• For us, Lind’s scurvy experiment is convincing; it fits our thinking

• But at the time:
  - Deaths onboard were commonplace, illnesses were overlooked (Sutton)
  - Other diseases like dysentery could be more debilitating & deadly
  - There was no way to know why citrus (i.e., vitamin C) should work any more than anything else; differentiation between food types was elusive
  - Lind himself thought highly of the navy diet and hypothesized that digestion and evacuation were impeded onboard (Bartholomew’s)
Why was Lind’s experiment noteworthy?

• One of the few early studies we know of in which there were “control groups”

• An ideal control group resembles the treated in every way except receives no treatment

• Here, Lind isolated 6 treatments across 12 sailors (but also observed other sick sailors? Maybe)

• In other cases of scurvy prevention, multiple treatments were overlaid, impeding inference
How do you know which $x$ is important?

- citrus fruit
- fresh provisions
- cleanliness
- no eating copper

$$f(x_1, x_2, x_3, x_4)$$

No scurvy
• Is it right to observe a control group without providing an intervention?

• What about actively denying interventions?

• Tuskegee syphilis experiment in the U.S.
  - Begun in 1932 as an observational comparison of African American males with and without syphilis
  - No participants were ever told their status
  - By the 1940s, penicillin was known to cure it, but researchers kept it and other treatments from the participants
  - The study continued until 1972, when a whistleblower took it to the media. The CDC and the AMA had colluded to keep it going
  - In years since, its legacy has motivated human subjects protections and institutional review boards (IRBs)
Domain of IRBs protecting human subjects

- Government-funded studies that have traditionally been undertaken at research universities
- Other studies at research universities
- Research labs receiving government funds
- What’s missing?
  - Big Data adventures. Facebook. Google
Challenges for RCTs

• When participants suspect that a treatment is going to improve their conditions,

• And if they know they’re in a control group, not receiving the treatment,

• Members of the control group may seek the treatment and “contaminate” the experiment

• In medical studies, researchers use placebos; in other studies, vigilance