

Biost 517

Applied Biostatistics I

.....

Scott S. Emerson, M.D., Ph.D.
Professor of Biostatistics
University of Washington

Lecture 8: Introduction to Inference

October 25, 2006

1

© 2002, 2003, 2005 Scott S. Emerson, M.D., Ph.D.

Lecture Outline

.....

- Statistical Inference
 - Role of Statistical Inference
 - Hierarchy of Experimental Goals
 - Statistical Criteria for Evidence

2

Role of Statistical Inference

.....

3

Statistical Goals of Studies

.....

- Clustering of measurements across variables
- Clustering of variables
- Quantify summary measures of distributions
- Comparison of distributions across groups
 - Interactions
- Prediction of values
 - Single best estimate; interval estimates

4

Use of Samples

- Data is sampled from a population
 - Sampling schemes
 - Observational studies
 - Cross-sectional; cohort; case-control
 - Interventions
 - Time of observation
 - Single point in time
 - Longitudinal

5

Descriptive Statistics

- Purpose of descriptive statistics
 - Detection of errors
 - Materials and methods
 - Validity of methods used in analysis
 - Estimates of association, etc.
 - Hypothesis generation

6

Statistical Inference

- Use the sample to make inference about the entire population
 - Inferential estimates
 - Quantify the uncertainty in the estimates computed from the sample
 - To what extent does the random variation inherent in sampling affect our ability to draw conclusions?

7

Statistical Role

- Experimental results are subject to variability
 - Statistics provides
 - Framework in which to describe general trends
 - Estimates of treatment effect
 - Framework in which to describe our level of confidence in the conclusions drawn from the experiment
 - Measures of the precision of our estimates
 - Estimates of the generalizability of the results

8

Point Estimates

.....

- Optimal estimates of population summary measures (parameters) or future observations
 - Single best estimate: “Point estimate”
 - Prediction
 - Categorical data: Discrimination, classification
 - Continuous data
 - Population parameters
 - E.g., mean, median, etc.
 - (We must define what we mean by “best”)

9

Ex: Estimation of Parameters

.....

- Prognosis in prostate cancer
 - “Parameter” is some summary measure of the population’s distribution
 - A descriptive statistic for the entire population
 - E.g., mean, median, proportion above threshold
- Usually use a sample summary measure to estimate the population parameter
 - E.g., Kaplan-Meier estimate of median

10

Ex: Categorical Prediction

.....

- Diagnosis of disease based on laboratory values
 - Type of disease is a categorical variable
 - Use laboratory values to classify patients according to their type of disease
 - (Discriminate between diseases)
 - Obtain training sample in which both type of disease and laboratory values are known
 - Derive a prediction (classification, discrimination) rule

11

Ex: Continuous Prediction

.....

- Creatinine clearance from more easily measured laboratory values
 - Creatinine clearance is a continuous variable
 - Use a single patient’s laboratory values to estimate that patient’s creatinine clearance
 - Obtain a training sample in which both true creatinine clearance and other laboratory values are known
 - Derive a prediction rule base on mean or median within groups defined by lab values

12

Ex: Prediction Intervals

.....

- Normal range of time delay until arrival of Somatosensory Evoked Potential (SEP)
 - “Normal range” might be defined as the central 95% of the distribution of measurements for a healthy population
 - Goal is to estimate two population parameters
 - 2.5th percentile
 - 97.5th percentile

13

Precision of Estimates

.....

- Choose “best” method for estimation
- Determine how good we were now
 - Quantify confidence/uncertainty in estimates
- Methods will depend upon the type of inference
 - Estimation of population parameters
 - Prediction of individual measurements
 - Categorical
 - Continuous

14

Precision of Parameter Estimates

.....

- Two approaches
 - “Frequentist”
 - What is the variability of the estimate across repeated experiments?
 - Standard error = standard deviation of an estimate
 - Confidence interval = range of values leading to data like this
 - “Bayesian”
 - What is the probability that the true value is in some range?

15

Precision of Continuous Predictions.....

- “Frequentist”
 - Average absolute error
 - Average squared error
- “Bayesian”
 - Probability of being within a certain tolerance

16

Precision of Classification

- The probability of making an error
 - Overall error rate
 - Proportion of subjects incorrectly classified
 - Depends on frequency of each category
 - Estimated from cross-sectional study?
 - Conditional error rates
 - For each category, proportion of subjects incorrectly classified
 - By disease status (from case-control studies?)
 - By test status (from cohort studies?)

17

Ex: Syphilis and VDRL

- Overall error rate
 - Proportion of subjects incorrectly classified
 - $\Pr(\text{Pos and Healthy}) + \Pr(\text{Neg and Syphilis})$
- Conditional error based on diagnosis
 - False Positives: $\Pr(\text{Pos among Healthy})$
 - “Specificity” is $1 - \text{False Positive rate}$
 - False Negatives: $\Pr(\text{Neg among Diseased})$
 - “Sensitivity” is $1 - \text{False Negative rate}$
- Conditional error based on test result
 - Positive Predictive Value: $\Pr(\text{Disease among Pos})$
 - Negative Predictive Value: $\Pr(\text{Healthy among Neg})$

Ex: Cross-sectional Study

- Hypothetical random sample of 1000 STD patients

		Syphilis		Tot
		Yes	No	
VDRL	Pos	270	14	284
	Neg	30	686	716
Total		300	700	1000

19

Ex: Cross-sectional Study

- Valid estimates for inference from cross-sectional study:
 - Prevalence of syphilis (at that clinic): 30.0%
 - Overall error rate: 4.4%
 - Sensitivity: $\Pr(\text{Pos} | \text{Dis}) = 270 / 300 = 90.0\%$
 - Specificity: $\Pr(\text{Neg} | \text{Hlth}) = 686 / 700 = 98.0\%$
 - Pred Val Pos: $\Pr(\text{Dis} | \text{Pos}) = 270 / 284 = 95.1\%$
 - Pred Val Neg: $\Pr(\text{Hlth} | \text{Neg}) = 686 / 716 = 95.8\%$

20

Ex: Sampling by Test Result

- Sample 500 positive subjects and 500 negative subjects at STD clinic (cohort study?)

		<u>Syphilis</u>		
		Yes	No	Tot
VDRL	Pos	475	25	500
	Neg	21	479	500
Total		496	504	1000

21

Ex: Sampling by Test Result

- Valid estimates for inference from study based on sampling according to test result:

- Prevalence of syphilis (at that clinic): NA
- Overall error rate: NA
- Sensitivity: $\Pr(\text{Pos} | \text{Dis}) =$ NA
- Specificity: $\Pr(\text{Neg} | \text{Hlth}) =$ NA
- Pred Val Pos: $\Pr(\text{Dis} | \text{Pos}) = 475 / 500 = 95.0\%$
- Pred Val Neg: $\Pr(\text{Hlth} | \text{Neg}) = 479 / 500 = 95.8\%$

22

Ex: Sampling by Disease Status

- Sample 500 subjects with syphilis and 500 healthy subjects (case-control?)

		<u>Syphilis</u>		
		Yes	No	Tot
VDRL	Pos	450	10	460
	Neg	50	490	540
Total		500	500	1000

23

Ex: Sampling by Disease Status

- Valid estimates for inference from study based on sampling according to disease status:

- Prevalence of syphilis (at that clinic): NA
- Overall error rate: NA
- Sensitivity: $\Pr(\text{Pos} | \text{Dis}) = 450 / 500 = 90.0\%$
- Specificity: $\Pr(\text{Neg} | \text{Hlth}) = 490 / 500 = 98.0\%$
- Pred Val Pos: $\Pr(\text{Dis} | \text{Pos}) =$ NA
- Pred Val Neg: $\Pr(\text{Hlth} | \text{Neg}) =$ NA

24

An Aside: A Generalization

.....

- The previous example had a decision rule based on a binary variable (VDRL)
- With a continuous variable, we usually define a threshold
 - E.g., PSA > 4 for prostate cancer diagnosis
- Sensitivity, specificity will depend on threshold
 - Receiver operating characteristic (ROC) curves consider all possible thresholds

25

Decisions (Hypothesis Testing)

.....

- We often use a statistical analysis to make a binary (yes / no) decision about a hypothesis
 - Precision of our decision is measured by conditional error rates
 - Analogy with categorical prediction

26

Hierarchy of Experimental Goals

.....

27

Ideal: Deterministic Results

.....

- Determine the exact value of a measurement or population parameter
 - Prediction: What will the value of a future observation be?
 - Comparing groups: What is the difference between response across two populations?
- Problem: In the real world, we do not observe the same outcome for all subjects
 - Hidden (unmeasured) variables
 - Inherent randomness

28

2nd Choice: Describe Tendency

.....

- Probability model for response with summary measure for outcomes
 - Phrase scientific question in terms of summary measure
 - Prediction: What is the probability that a future observation will be some value?
 - Within groups: What is the average response within the group?
 - Comparing groups: What is the difference in average response between groups

29

Choice of Summary Measure

.....

- Often we have many choices
 - Example: Treatment of high blood pressure
 - Average
 - Geometric mean
 - Median
 - Percent (or odds) above 160 mm Hg
 - Mean or median time until blood pressure below 140 mm Hg
 - Hazard function

30

Statistical Hypotheses

.....

- Upon choosing a summary measure, the scientific question is stated in terms of the summary measure
 - E.g., Larger mean response might be regarded as “superiority” of a new treatment

31

Criteria for Summary Measure

.....

- Consider (in order of importance)
 - Current state of knowledge about treatment effect
 - Scientific (clinical) relevance of summary measure
 - Plausibility that treatment would affect the summary measure
 - Statistical precision of inference about the summary measure

32

Scientific Importance

- Summary measure for comparison should most often be driven by scientific issues
 - Thresholds may be most important clinically
 - Means allow estimates of total costs/benefits
 - Medians less sensitive to outliers
 - Sometimes clinical importance is not proportional to magnitude of measurements
 - But sometimes, the effect we are trying to detect is greatest on outliers

33

Scientific Importance

- Sometimes choice of summary measure is more arbitrary
 - Types of scientific questions
 - Existence of an effect on the distribution
 - Direction of effect on the distribution
 - Linear approximations to effect on summary measure
 - Quantifying dose-response on summary measure
 - Only last two need dictate a choice of summary measure

34

2nd Choice: Problem

- The distribution (or summary measure) for the outcome is not directly observable
 - Use a sample to estimate the distribution (or summary measure) of outcomes
 - Such an estimate is thus subject to sampling error
 - We want to quantify our uncertainty

35

3rd Choice: Bayesian Methods

- Use the sample to estimate the probability that the hypotheses are true
 - Probability of hypotheses given the observed data
- Such a Bayesian approach is analogous to the problem of diagnosing disease in patients using a diagnostic procedure

36

Diagnostic Testing

.....

- We most often characterize the sensitivity and specificity of a diagnostic test
 - Sensitivity of test: Positivity in diseased
 - Sample a group of subjects with the disease
 - Estimate the proportion who have a positive test result: $\Pr(+ | D)$
 - Specificity of test: Negativity in healthy
 - Sample a group of healthy subjects
 - Estimate the proportion who have a negative test result: $\Pr(- | H)$

37

Predictive Values

.....

- We are actually interested in the diagnostic utility of the test
 - Predictive value of a positive test: Probability of disease when test is positive
 - $\Pr(D | +)$
 - Predictive value of a negative test: Probability of health when test is negative
 - $\Pr(H | -)$

38

Computing Predictive Values

.....

- Bayes' Rule

$$\Pr(D | +) = \frac{\Pr(+ | D)\Pr(D)}{\Pr(+ | D)\Pr(D) + \Pr(+ | H)\Pr(H)}$$

$$\Pr(H | -) = \frac{\Pr(- | H)\Pr(H)}{\Pr(- | H)\Pr(H) + \Pr(- | D)\Pr(D)}$$

39

PV+: Relationship to Prevalence

.....

- Need to know sensitivity, specificity, AND prevalence of disease

$$\Pr(D | +) = \frac{\Pr(+ | D)\Pr(D)}{\Pr(+ | D)\Pr(D) + \Pr(+ | H)\Pr(H)}$$

$$PVP = \frac{Sens \times Prev}{Sens \times Prev + (1 - Spec) \times (1 - Prev)}$$

40

PV-: Relationship to Prevalence

- Need to know sensitivity, specificity, AND prevalence of disease

$$\Pr(H | -) = \frac{\Pr(- | H)\Pr(H)}{\Pr(- | H)\Pr(H) + \Pr(- | D)\Pr(D)}$$

$$PVN = \frac{Spec \times (1 - Prev)}{Spec \times (1 - Prev) + (1 - Sens) \times Prev} \quad 41$$

Ex: Syphilis and VDRL

- Typical study: Sample by disease
 - Sensitivity of test: Probability of positive in diseased
 - 90% of subjects with syphilis test positive
 - (Actually depends on duration of infection)
 - Specificity of test: Probability of negative in healthy
 - 98% of subjects without syphilis test negative
 - (Actually depends on age and prevalence of certain other diseases)

42

Ex: PV+, PV- at STD Clinic

- Ex: 1000 patients at STD clinic
 - Prevalence of syphilis 30%
 - PV+: 95% with positive VDRL have syphilis

		Syphilis		
		Yes	No	Tot
VDRL	Pos	270	14	284
	Neg	30	686	716
Total		300	700	1000

43

Ex: PV+, PV- in Marriage License

- Ex: Screening for marriage license
 - Prevalence of syphilis 2%
 - PV+: 48% with positive VDRL have syphilis

		Syphilis		
		Yes	No	Tot
VDRL	Pos	18	20	38
	Neg	2	960	962
Total		20	980	1000

44

Bottom Line

.....

- Predictive value of a diagnostic test depends heavily on the prevalence of the disease
 - In typical study (sampling by disease status) we need to use Bayes' Rule to obtain predictive values
 - Prevalence estimated from another study

45

Analogy to Bayesian Inference

.....

- Statistical analysis “diagnoses” an association between variables
 - Association is the true value of parameter
 - Analogous to disease status
 - Estimate association from sample
 - Analogous to the diagnostic test result
 - Compute the probability of hypotheses
 - Analogous to predictive values
 - Need to know prevalence= “prior probability”

46

Implementation

.....

- A generalization of the diagnostic testing situation
 - The estimate of treatment effect is continuous, rather than just positive or negative
 - The parameter measuring a beneficial treatment is continuous, rather than just healthy or diseased
 - Prior distribution is thus an entire distribution (a probability for every possible value of the treatment effect)

47

Issues

.....

- How to choose the prior distribution?
 - As we have seen, the predictive values are very sensitive to the choice of prior distribution
 - Possible remedies:
 - Use data from previous experiments
 - Use subjective opinion or consensus of experts
 - Do a sensitivity analysis over many different choices for the prior distribution
 - Use frequentist approaches

48

4th Choice: Frequentist Methods

.....

- Estimate the behavior of methods over conceptual replications of experiment
 - Calculate the probability of observing data such was obtained in the experiment under the hypotheses
 - Not affected by subjective choice of prior distributions
 - But not really answering the most important question

49

Sampling Distribution

.....

- Frequentist methods consider the “sampling distribution” of statistics over (conceptual) replications of the same study
 - If we were to repeat the study a large number of times (under the exact same conditions) what would be the distribution of the statistics computed from the samples obtained

50

Condition on Hypotheses

.....

- Knowing the true sampling distribution requires knowledge of the parameter
 - We can often guess what would happen under specific hypotheses
 - Frequentists characterize the sampling distribution under specific hypotheses
 - Compare the observed data to what might reasonably have been obtained if that hypothesis were true

51

Bayesian vs Frequentist Poker

.....

- Example: When playing poker, I get 4 full houses in a row
 - Bayesian:
 - Knows the prior probability that I might be a cheater before observing me play
 - Knows the probability that I would get 4 full houses for every level of cheating that I might engage in
 - Computes the posterior probability that I was cheating (probability after observing me play)
 - If that probability is high, calls me a cheater

52

Bayesian vs Frequentist Poker

- Example: When playing poker, I get 4 full houses in a row
 - Frequentist:
 - Hypothetically assumes I am not a cheater
 - Knows the probability that I would get 4 full houses if I were not a cheater
 - If that probability is sufficiently low, calls me a cheater

53

Tradeoffs

- Bayesian: A vague (subjective) answer to the right question
 - How could the Bayesian know my propensity to cheat?
- Frequentist: A precise (objective) answer to the wrong question
 - (The frequentist would give the same answer even if it were impossible that I were a cheater)

54

Tradeoffs

- In fact, there is no real reason to regard tradeoffs as necessary.
- Both approaches contribute complementary information about the strength of statistical evidence.
- It is valid to consider both measures.

55

Bayesian vs Frequentist

- Bayesian inference:
 - How likely are the hypotheses to be true based on the observed data (and a presumed prior distribution)?
- Frequentist inference:
 - Are the data that we observed typical of the hypotheses?

56

Statistical Criteria for Evidence

- At the end of the study analyze the data to provide
 - Estimate of the treatment effect
 - Single best estimate
 - Range of reasonable estimates
 - Decision for or against hypotheses
 - Binary decision
 - Quantification of strength of evidence

57

Point Estimates

- Frequentist methods: using the sampling density for the data
 - Find estimates which minimize bias
 - Difference between true value and average estimate across replicated trials
 - Find estimates with minimal variance
 - Find estimates which minimize mean squared error
- Bayesian methods
 - Use mean, median, or mode of posterior distribution of θ based on some prespecified prior

58

Interval Estimation

- Frequentist confidence intervals
 - Find all values of θ such that it is not unusual to obtain data as extreme as that which was observed
- Bayesian interval estimates
 - Find a range of θ values such that the posterior probability that θ is in that range is high

59

Criteria for Decisions

- Frequentist hypothesis tests
 - Reject hypothesis that $\theta < \theta_0$ if the probability of obtaining the observed data (or more extreme) is low when that hypothesis is true
- Bayesian hypothesis tests
 - Reject hypothesis that $\theta < \theta_0$ if the posterior probability of that hypothesis is low when the observed data is obtained

60

Quantify Evidence for Decision

- Hypothesis testing
 - Based on a statistic T which tends to be large for large θ and an observed value $T = t$

$$\Pr(T \geq t | \mathcal{G}_0)$$

- Bayesian Methods
 - Based on a presumed prior distribution for θ and the observed observed statistic $T = t$

$$\Pr(\mathcal{G} < \mathcal{G}_0 | T = t)$$

61

Statistical Criteria for Evidence

- A threshold must be defined for what constitutes a “low” probability
 - Often 5% when considering both too high or too low (a “two-sided” test)
 - Often 2.5% when considering only one direction (a “one-sided” test)

62