

**Biost 517**  
**Applied Biostatistics I**

.....

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

Lecture 2:  
Statistical Classification  
of Scientific Questions

September 30, 2011

1

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

**Lecture Outline**

.....

- Types of Scientific Questions
  - Clustering cases
  - Clustering variables
  - Quantification of distributions
  - Detecting associations
  - Prediction
- Statistical Tasks

2

**Science**

.....

- Science is about
  - Discovering laws governing the universe
  - Understanding impact / interplay of laws
  - Proving things to people

3

**Statistics**

.....

- Uses numbers to address scientific questions
  - Describe general tendencies and trends
  - Quantifies our knowledge about scientific laws

4

### Scientific Method: Key Elements

.....

- Overall goal
- Specific aims (hypotheses)
- Materials and methods
- Collection of data
- Analysis
- Interpretation

5

### Statistical Tasks

.....

- Understand overall goal
- Refine specific aims (stat hypotheses)
- Materials and methods: Study design
- Collection of data: Advise on QC
- Analysis
  - Describe sample (materials and methods)
  - Analyses to address specific aims
- Interpretation

6

### Statistical Classification of Scientific Questions

.....

My claim:  
All scientific questions addressed with  
statistics are one of 5 types

7

### General Classification

.....

- In order typically used in a new area of science:
  - Clustering of observations
  - Clustering of variables
  - Quantification of distributions
  - Comparing distributions
  - Prediction of individual observations

8

## 1. Cluster Analysis

.....

- Focus is on identifying similar groups of observations
  - Divide a population into subgroups based on patterns of similar measurements
    - Univariate, multivariate
    - Known or unknown number of clusters
  - (All variables treated symmetrically: No delineation between outcomes and groups)

9

## Example: Cluster Analysis

.....

- Potential for different causes for the same clinical syndrome: Glucose in urine
  - Identify patterns of measurements that separate subpopulations of patients with diabetes
    - Age of onset
    - Symptoms at onset (e.g., weight)
    - Auto-antibodies
    - Characteristics of epidemics

10

## Example: Cluster Analysis

.....

- Statistical Tasks:
  - Training sample
    - Measure age, change in weight, auto-antibodies, etc.
  - Statistical analysis
    - Cluster analysis
    - Summarize variable distributions within identified clusters
      - (Attach labels?)

11

## 2. Clustering Variables

.....

- Identifying hidden variables indicating groups that tend to have similar measurements of some outcome
  - Interest in some particular outcome measurement
  - Predictors that imprecisely measure some abstract quality
  - Desire to find patterns in predictors that more precisely reflect the abstract quality

12

### Example: Factor Analysis

.....

- Identifying barriers to patient compliance in clinical trials
  - In the Health Behavior Questionnaire, multiple variables might be used to measure
    - Self-perceived health; social support; depression
  - Desire is to
    - Find subset of questions that would suffice
    - Identify hidden variables that affect compliance

13

### Example: Factor Analysis

.....

- Statistical Tasks:
  - Training sample
    - Measure response to questionnaire
  - Statistical analysis
    - Factor analysis (principal components)
    - Report contribution to factors, factor loadings
      - (Attach labels?)
      - (Draw conclusions about importance of latent variables?)

14

### Example: Genomics/Proteomics

.....

- Combination of clustering cases and variables
  - Measure expression of 10,000 genes on (usually small) number of patients
  - Identify genes that tend to act the same way across patients
    - Pathways?
  - Identify groups of patients that tend to have the same patterns of gene expression
    - Subtypes of disease?

15

### 3. Quantifying Distributions

.....

- Focus is on distributions of measurements within a population
  - Scientific questions about tendencies for specific measurements within a population
    - Point estimates of summary measures
    - Interval estimates of summary measures
      - Quantifying uncertainty
    - Decisions about hypothesized values

16

### Example: Estimate Proportions

.....

- Proportion of women among patients with primary biliary cirrhosis
  - Serious liver disease often leading to liver failure
  - Unknown etiology
    - Characterizing types of people who suffer from disease may provide clues about causes
    - (About 90% of patients with PBC are women)

17

### Example: Estimate Proportions

.....

- Statistical Tasks
  - Sample of patients (from registry?)
    - Measure demographics, etc.
  - Statistical analysis
    - Best estimate of the proportion
    - Quantify uncertainty in that estimate
    - Compare to the known proportion of women in the general population (approximately 50%)?

18

### Example: Estimation of Median

.....

- Median life expectancy of patients newly diagnosed with stage II breast cancer
  - Want to know prognosis
    - Judging public health risks
    - Patients' planning (?really prediction)

19

### Example: Estimation of Median

.....

- Statistical Tasks
  - Sample of patients newly diagnosed with stage II breast cancer
    - Follow for survival time (may be censored)
  - Statistical analysis
    - Best estimate of the median survival (K-M?)
    - Quantify uncertainty in that estimate
    - Compare to some clinically important time range (e.g., 10 years)

20

### 4. Comparing Distributions

.....

- Comparing distributions of measurements across populations
  - 4a. Identifying groups that have different distributions of some measurement
  - 4b. Quantifying differences in the distribution of some measurement across predefined groups (effects or associations)
  - 4c. Quantifying differences in effects across subgroups (interactions or effect modification)

21

### 4a. Identifying Groups

.....

- Identifying groups that have different distributions of some measurement
  - Focus is on some particular outcome measurement
  - Identify groups based on other measurements
    - E.g., quantifying distributions within subgroups
    - E.g., stepwise regression models
  - (cf: Cluster analysis where all measurements are treated symmetrically)

22

### Example: Identifying Groups

.....

- Chromosomal abnormalities associated with ovarian cancer
  - Cytogenetic analysis of dividing cells identifies regions of the chromosomes with defects
    - Cancer is caused by some defects, and cancer causes other defects
    - Approximately 370 identifiable regions
  - Which of the regions are the most promising to explore in more focused studies?

23

### Example: Identifying Groups

.....

- Statistical Tasks:
  - Sample of cancer tissues
    - Measure type of cancer (ovarian, melanoma, etc.)
    - Measure chromosomal defects
  - Statistical analysis
    - Stepwise regression models of chromosomal abnormalities predicting cancer type
      - (Use p values to rank interest in particular regions?)

24

### Example: Identifying Groups

.....

- Risk factors for diabetes
  - Variables most associated with diabetes risk may give clues about etiology and eventual prevention

25

### Example: Identifying Groups

.....

- Statistical Tasks
  - Sample subjects to measure risk factors and disease prevalence
    - Cohort study
    - Case-control study
  - Statistical analysis
    - Stepwise model building
      - (Rank most interesting variables by p value?)

26

### 4b. Detecting Associations

.....

- Associations between variables – distributions of one variable differ across groups defined by another
  - Existence of differences
  - Direction of tendency of effect
  - First, second order relationships in a summary measure
  - Characterization of dose-response in a summary measure

27

### Definition of an Association

.....

- The distributions of two variables are not independent
  - Independence: Equivalent definitions
    - Probability of outcome and exposure is product of
      - Overall probability of outcome, and
      - Overall probability of exposure
    - Distribution of exposure is EXACTLY the same across ALL outcome categories
    - Distribution of outcome is EXACTLY the same across ALL exposure categories

28

### Summary Measures

.....

- Generally we consider some summary measure of the distribution
  - For instance, when we use the mean, we show an association by showing either
    - Mean outcome differs across exposure groups
    - Mean exposure differs across outcome groups

29

### Justification

.....

- This works, because if two distributions are the same, ALL summary measures should be the same
  - If some summary measure is different, then we know the distributions are different
- **HOWEVER:** This means that it is easier to prove an association, than to prove no association

30

### Example: Detecting Association

.....

- Effect of blood cholesterol levels on risk of heart attacks
  - Understanding etiology of heart attacks may lead to prevention and/or treatment strategies

31

### Example: Detecting Association

.....

- Statistical tasks
  - Measure risk factors, MIs on sample
    - Cohort or case-control sample
  - Statistical analysis
    - Regression model (possibly adjusted)
      - Cohort: Incidence of MIs across cholesterol levels
      - Case-control: Cholesterol levels across MI status
      - (Comparison can be at many levels of detail)
    - Quantify estimates, precision, confidence in decisions

32

### 4c. Detecting Effect Modification

.....

- Quantifying differences in effects across subgroups (interactions or effect modification)
  - Existence of interaction
  - Direction of interaction (synergy, antagonism)
  - Quantification of exact relationship of interaction

33

### Example: Effect Modification

.....

- Identifying whether effect of cholesterol on heart attacks differs by sex
  - Comparing association between blood cholesterol level and incidence of heart attacks between sexes
    - Quantify association in men
    - Quantify association in women
    - Compare measures of association

34

### Approach Common to #3 & #4

.....

- Inference based on some summary measure of a distribution
  - #3: Estimate the summary measure
  - #4: Compare and contrast summary measures
- In answering each scientific question, statistics typically provides four numbers
  - Best estimate
    - “Best” can be defined by frequentist or Bayesian criteria
  - Interval describing precision
    - Confidence interval or Bayesian credible interval
  - Quantification of belief in some hypothesis
    - P value or Bayesian posterior probability

35

### Example: Detecting Association

.....

- Association between sex and prevalence of MI in elderly population
  - 59 of 366 males have had MI: 16.1%
  - 32 of 367 females have had MI: 8.7%
  - Association measured by difference
    - Best estimate: Prevalence 7.4% higher in males
    - Interval estimate: Between 2.7% and 12.2%
      - (95% confidence interval)
    - Strength of evidence: P value = 0.002
      - If there were no real difference, the observed data is pretty unlikely: Probability of this data is 0.002

36

### 5. Prediction

.....

- Focus is on individual measurements
  - Point prediction:
    - Best single estimate for the measurement that would be obtained on a future individual
      - Continuous measurements
      - Binary measurements (discrimination)
  - Interval prediction:
    - Range of measurements that might reasonably be observed for a future individual

37

### Example: Continuous Prediction

.....

- Creatinine clearance
  - Creatinine
    - Breakdown product of creatine
    - Removed by the kidneys by filtration
      - Little secretion, reabsorption
  - Measure of renal function
    - Amount of creatinine cleared by the kidneys in 24 hours

38

### Example: Continuous Prediction

.....

- Problem:
  - Need to collect urine output (and blood creatinine) for 24 hours
- Goal:
  - Find blood, urine measures that can be obtained instantly, yet still provide an accurate estimate of a patient's creatinine clearance

39

### Example: Continuous Prediction

.....

- Statistical Tasks:
  - Training sample
    - Measure true creatinine clearance
    - Measure sex, age, weight, height, creatinine
  - Statistical analysis
    - Regression model that uses other variables to predict creatinine clearance
    - Quantify accuracy of predictive model
      - (Mean squared error?)

40

### Example: Discrimination

.....

- Diagnosis of prostate cancer
  - Use other measurements to predict whether a particular patient might have prostate cancer
    - Demographic: Age, race, (sex)
    - Clinical: Symptoms
    - Biological: Prostate specific antigen (PSA)
  - Goal is a diagnosis for each patient

41

### Example: Discrimination

.....

- Statistical Tasks:
  - Training sample
    - “Gold standard” diagnosis
    - Measure age, race, PSA
  - Statistical analysis
    - Regression model that uses other variables to predict prostate cancer diagnosis
    - Quantify accuracy of predictive model
      - (ROC curve analysis?)

42

### Example: Interval Prediction

.....

- Determining normal range for PSA
  - Identify the range of PSA values that would be expected in the 95% most typical healthy males
  - Age, race specific values

43

### Example: Interval Prediction

.....

- Statistical Tasks:
  - Training sample
    - Measure age, race, PSA
  - Statistical analysis
    - Regression model that uses other variables to define prediction interval
      - (Mean plus/minus 2 SD?)
      - (Confidence interval for quantiles?)
    - Quantify accuracy of predictive model
      - (Coverage probabilities?)

44

### Comment About Prediction

.....

- Prediction often requires more understanding about the problem than does detecting associations
  - Relies more heavily on assumptions
- For me to consider a problem to be purely a prediction problem, interest must lie solely in the predicted value, and not in the way that value was obtained
  - E.g., in weather prediction, we might just want to know the weather tomorrow
    - We won't be trying to impress upon our audience the way it should be predicted
  - I do not think this is very often the case

45

### Statistical Tasks

.....

46

### Statistical Tasks

.....

- Statistical considerations come into play in all stages of scientific studies
  - Study Design
  - Data analysis
    - Descriptive statistics
    - Inferential statistics (quantifying precision)
  - Interpretation and reporting of results

47

### Scientific Hypotheses

.....

- Usual statement:
  - The intervention when given to the target population will tend to result in outcome measurements that are

{

higher than,

{

lower than, or

{

about the same as

}

}

{

an absolute standard, or

{

measurements in a comparison group

}

48

### Refining Scientific Hypotheses

.....

- Statistical hypotheses precisely define
  - the intervention
  - the outcome
    - advise on precision of measurement
  - the target population(s)
    - covariates
  - “tend to” (the standards for comparison)
    - summary measures
    - relevance of absolute or relative standards

49

### Study Design: Sampling Plan

.....

- Choosing a method for collecting data
  - Observational vs interventional
  - Cross sectional vs longitudinal
  - Retrospective vs prospective
  - Cohort vs case control
  - Independent vs matched measurements
  - Fixed sample vs sequential
  - Sample size

50

### Treatment of Variables

.....

- Measure and compare distribution across groups (response variable in regression)
- Vary systematically (intervention)
- Control at a single level (fixed effects)
- Control at multiple levels (fixed or random effects)
  - Stratified (blocked) randomization
- Measure and adjust (fixed or random effects)
- Treat as “error”

51

### Statistical Analysis

.....

- Descriptive statistics
  - (Sampling plan)
  - Materials and methods
  - Address scientific question
- Inferential statistics
  - Point estimates
  - Interval estimates (quantify precision)
  - Decision analysis (hypothesis tests)

52