

Biost 517
Applied Biostatistics I
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Lecture 8:
Introduction to Inference

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

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**Role of
Statistical Inference**
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Statistical Goals of Studies
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- 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

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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

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Descriptive Statistics

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

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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?

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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

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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")

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Ex: Estimation of Parameters

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- 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

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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

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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

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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

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Precision of Estimates

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- 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

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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?

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Precision of Continuous Predictions

.....

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

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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?)

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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: $Pr(\text{Healthy among Neg})$

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Ex: Cross-sectional Study

.....

- Hypothetical random sample of 1000 STD patients

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

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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: $Pr(\text{Hlth} | \text{Neg}) = 686 / 716 = 95.8\%$

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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

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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: $\Pr(\text{Hlth} | \text{Neg}) = 479 / 500 = 95.8\%$

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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

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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

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An Aside: A Generalization

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- 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

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Decisions (Hypothesis Testing)

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- 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

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Hierarchy of Experimental Goals

.....

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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

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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

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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

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Statistical Hypotheses

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- 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

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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

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Scientific Importance

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- 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

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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

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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

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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

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Diagnostic Testing

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- 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: $\Pr(- | H)$

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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
 - $\Pr(H | -)$

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Computing Predictive Values

.....

- Bayes' Rule

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

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

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PV+: Relationship to Prevalence

.....

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

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

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

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PV-: Relationship to Prevalence

.....

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

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

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

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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)

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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

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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

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Bottom Line

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- 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

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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”

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Implementation

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- 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)

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Issues

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- 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

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4th Choice: Frequentist Methods

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- 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

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Sampling Distribution

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- 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

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Condition on Hypotheses

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- 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

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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

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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

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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)

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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.

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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?

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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

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Point Estimates

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- 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

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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

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Criteria for Decisions

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- 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

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Quantify Evidence for Decision

.....

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

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

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

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

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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)

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