Statistical Basics for Microarray Studies

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Outline

- Microarray Basics
- Description or Inference - Why Statistics?
- Some useful graphics
- Numerical Summaries
- Populations and samples
- Statistical hypothesis testing
- Parametric, Non-parametric testing
- Power, false discovery, false nondiscovery
- Frequentist and Bayesian paradigms
- Clustering (time permitting)
Microarrays

Construction of Microarrays
- DNA clones
  - Human
  - Virus
  - Control

Sample Preparation
- Mock
- Hela-Cells
- Adenovirus infected

Data Analysis
- Composed image
  - Up-regulated
  - Equal expressed
  - Down-regulated

PCR amplification

Reverse Transcription
- Cy3-dUTP
- Cy5-dUTP

cDNA

Hybridization

Scanning

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"Spotted" arrays

The spot material may be a cDNA, or an oligo - generally 50-70 codons long.

Some commercial arrays use only a single dye.

"Spotted" refers to the print technology. Arrays with similar format may have oligos synthesized directly on the array surface.

A gene may be represented by several spots or oligos
The data are preprocessed to remove as much noise as possible before other analyses (sometimes signal is also removed!)

There are 2 samples on the array (red and green).

The data for a single gene for each sample are highly correlated - often the $\log_2(\text{red/green})=M$ is used for analysis, but the individual channels can also be used.
Affymetrix Array

- Each "probe set" is 16-20 pairs of oligos
- Each oligo is 25 nucleotides
- Each gene is represented by a "probe set"
- Usually the probe set information is combined to form a single expression summary for each gene
- The preprocessing usually is designed to remove as much noise as possible.
Data Used for this Talk

Data:

Golub et al (1999) demonstrated that microarray gene expression could be used to distinguish among human leukemia types: acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).

There are 72 Affymetrix Hgu6800 microarrays (47 ALL, 25 AML), with data on the expression of 7129 genes.

The data were preprocessed to reduce array to array variability.

The entire dataset is available from www.bioconductor.org. We use a subset that is available in R when you load the affy package.
Data Used for this Talk

Data: (e.g. 5 probe-sets, 19 randomly selected cases from golubMergeSub in R)

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</table>

It usually pays to have a quick look at the numerical values of your data. e.g. in this data set, we have some negative expression values (which is not biologically supportable).
Any standard statistical package (and probably Excel) can do the plots and analyses I will show.

I will use R because:
- Free from [www.bioconductor.org](http://www.bioconductor.org)
- Available: Windows, Mac, Unix, Linux
- Programmable
- Great graphics
- Bioconductor Project for genomics
- Lots of resources (R + Splus communities)

But: the learning curve for R is steep.
Why use statistics?

Statistical methods are used to:

Describe what was observed.

Make inference to what was not observed.

Determine how to collect the data appropriately.
Description versus inference

Statistical methods are used both to:

Describe what was observed:
  requires data

Make inference to what was not observed:
  requires data collected using statistical methods such as randomization and replication.
Describing the Data

Graphically
- Histogram
- Density Plot
- Boxplot
- Scatterplot

Numerically
- Quantiles
- Averages
- Variance, Standard Deviation
- Correlation
Some R commands

library(affy)
data(golubMergeSub)
golubMergeSub
gExprs=exprs(golubMergeSub)
gPheno=pData(golubMergeSub)

# Load software and data
# get data
# see what is in the data
# extract expression values
# extract variables describing samples

gExprs[1:5,]
gPheno[1:5,]
Looking at the data:

Here are 4 of the genes, aggregated over the 72 arrays.

The "shapes" of the distributions vary.

Most of the data for L38500_at are negative.

We have combined ALL and AML data.
Looking at the data:

Here are 2 of the genes, aggregated over the 72 arrays with histograms organized by cancer type.

There are some obvious features, (e.g. outlier) but it is hard to compare the AML and ALL samples because the x-axes differ and even the bin widths are not the same.
Looking at the data:

Here we have used the same x-axis for both cancer types (but varying by gene).

We can see that the AML patients tend to be higher on L38503, but there is not much difference for L37378.

```r
for (i in c(1,11)) {
  low=min(golubExprs[i,])-1
  high=max(golubExprs[i,])+1
  b=seq(low,high,length.out=20)
  hist(golubExprs[i,ALL.AML=="ALL"],
       main=paste(rownames(golubExprs)[i],"ALL"),
       xlab="Expression",breaks=b)
  hist(golubExprs[i,ALL.AML=="AML"],
       main=paste(rownames(golubExprs)[i],"AML"),
       xlab="Expression",breaks=b)
}
```
Looking at the data:

Here we have used the same x-axis for both cancer types (but varying by gene).

We can see that the AML patients tend to be higher on L38503, but there is not much difference for L37378.
The red line is the median, the blue are the 25\textsuperscript{th} and the 75\textsuperscript{th} quantiles.

A boxplot emphasizes the central 50\% of the data and the outliers and is extremely useful for comparisons.
The "whiskers" on the plot extend to the furthest data value that is no more than 1.5 boxwidths from the edge of the box. Any values beyond are denoted by a circle.

We can see immediately that L38503 is differentially expressed.

As well, L37868_s is more variable in the AML group, which is not useful for detecting AML, but may have some biological meaning.
Statisticians love to use logarithms

Because:

1. Right skewed data become more symmetric.
2. If the variance of the data increases with the size, logs equalize variance.
3. $\log(x/y) = \log(x) - \log(y)$

Note that $\log_b(x) = \log_c(b) \log_c(x)$ so we statisticians don't really care what base is used.

In microarray analysis, many people use $\log_2$. In these units a "2-fold" difference ($x/y=2$) is $\log(x/y)=1$. 
Why we use $\log_2(\text{expression})$.
Scatterplots give us the opportunity to plot 2 quantities and color coding adds information.

We can clearly see that even using both genes, we cannot completely separate the AML and ALL patients.
Scatterplots are the most useful tool for quality control. I always plot log(expression) of each array against other arrays. Even when the arrays come from different conditions, we should get a diagonal "cloud".

Note array X5523 which was a dud. (These are from a plant project at Penn State.)
Golub Data
Scatterplots for 2-channel arrays

\[ A = \frac{\log_2(\text{Red}) + \log_2(\text{Green})}{2} \]

\[ M = \log_2(\text{Red}) - \log_2(\text{Green}) \]
LO(W)ESS Trend Curves

It is sometimes useful to add a trend line to a scatterplot (and this is an integral part of the "normalization" process).

A plot is worth 50,000 numbers

- Most people are far to eager to get to a "p-value" or fold-change
- Look at the data table
- Plot everything you can
Numerical Summaries

Measuring the Center

Mean=average= $\bar{Y}$

Median=$50^{th}$ quantile

Mode=highest point on histogram or density

Geometric mean=antilog(mean(log(data)))
Numerical Summaries

Measuring the Spread

Variance = average squared deviation from the mean

\[ \text{Variance} = \frac{\sum (Y_i - \bar{Y})^2}{n-1} \]

Standard deviation = \( \sqrt{\text{var}} \)

Interquartile range = length of boxplot box

\[ = 75^{\text{th}} \text{quantile} - 25^{\text{th}} \text{quantile} \]
Numerical Summaries

Measuring Linearity

Correlation: $-1 \leq r \leq 1$

If $r=0$ there is no linear relationship

If $r>0$, the relationship is increasing.

If $r<0$ the relationship is decreasing.

All 4 plots to the left have the same correlation $= .8$
Populations and Statistical Inference

What do we mean when we state:

Gene X expresses (or differentially expresses)?

Sepals are more similar to petals than to leaves?
Populations and Statistical Inference

What do we mean when we state:

Gene X expresses (or differentially expresses)?

Sepals are more similar to petals than to leaves?

The population is the general class of organisms for which we want to make an inferential statement.
If we could observe the entire population with no measurement error, we would not need inferential statistics.

Alternatively, if all the members of the population are identical and there is no measurement error, we would not need inferential statistics.
Populations and Statistical Inference

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Alternatively, if all the members of the population are identical and there is no measurement error, we would not need inferential statistics.

Statistical inference is used to make a statement about the population in the presence of error because we observe only a sample from a varying population and there is measurement error.
Samples and replication

A sample is the set of observed items from the population.

Generally, for statistical inference we need information about how variable these items are.

If there is also measurement error, we might want to make multiple measurements on the same individual, because averaging these reduces the measurement error.
Hypotheses

Classical statistical tests are based on comparing 2 hypotheses

$H_0$: the null hypothesis (which we hope to disprove)

$H_A$: the alternative hypothesis (which we accept if there is evidence to reject the null hypothesis)

e.g.

$H_0$: the gene does not express

$H_A$: the gene expresses

$H_0$: the gene does not differentially express

$H_A$: the gene differentially expresses
Classical hypothesis testing

Hypotheses are statements about the population:

e.g.

\( H_A : \text{the gene expresses in leaf guard cells} \)

Means that the average expression level over some population of leaf guard cells is positive.

Since there is both measurement error and biological variability from leaf to leaf, plant to plant, etc., we need to:
What goes into a hypothesis test?

1. Determine the population of cells, leaves, plants … for which we want to make the inference.

2. Ensure that the sample represents the population of interest, not just one member of the population.

This has 2 implications:
Essential data for hypothesis testing

We need to sample several individuals from our population.

We need to estimate the biological variability of our population (using the sample).

Sampling should be done at random.
Tests about the population average.

The usual tests require that the data are independent and have the same variability.

Same variability – take logarithms

Independent – dependence is induced by taking multiple measurements of the same object - e.g. organism, RNA sample, microarray
Tests of one sample mean or median

- t-test
- Wilcoxon test
- Permutation and bootstrap tests
Tests about the population average.

Hypotheses about expression levels are usually treated as hypotheses about population averages (t-test) or population medians (Wilcoxon test).

We want to make a guess about the value of the red line, but we do not get to measure the entire population.
Tests about the population average.

Hypotheses about expression levels are usually treated as hypotheses about population averages (t-test) or population medians (Wilcoxon test).

We want to make a guess about the value of the red line, but we do not get to measure the entire population.

We estimate the parameter from the data and then see if it is too far from the hypothesized value to be plausible.
An important aside:

The population variance is $\sigma^2$.
The population mean is $\mu$.

If we take independent samples of size $n$, the variance of $\overline{Y}$ is $\sigma^2/n$.

We denote the variance of the sample by $S^2_Y$. 
Classical testing is based on the distribution of the test statistic when the null hypothesis is true.

This depends on the original population, but may be the sample average, sample "t" value, etc.

The distribution of the test statistic is computed through statistical theory or simulation, or by "resampling" from the data (bootstrap and permutation methods).
2 simple ideas for tests

If the population mean is $\mu$, then the sample mean should be close to $\mu$.

$t$-test, permutation test, bootstrap test

If the population median is $\mu$, then about 50% of the observations should be above $\mu$ and 50% below.

Sign and Wilcoxon test
Classical Inference: P-values

We assume that the NULL distribution is true. The test statistic then has a distribution that is either known or can be simulated under this assumption.

The p-value is the probability of observing a value of the test statistic more extreme than the observed value.

The test is 2-sided if the null hypothesis proposes equality of 2 values. Then we consider the absolute value of the test statistic.
The t-test is the usual example and is based on estimating \( \mu \) with the sample mean, and determining the “size” of estimate – \( \mu_0 \).

If the null hypothesis is true, the distribution is given by one of the curves on the plot.
Fail to reject: this is a typical value if $\mu \leq \mu_0$

since we expect the estimate to be smaller than $\mu_0$
Reject: this is not a typical value if $\mu = \mu_0$
Some Questions of Interest

Does gene\textsubscript{i} express under this condition?

Does the expression level of gene\textsubscript{i} differ under these 2 (or more) conditions?

Do gene\textsubscript{i} and gene\textsubscript{j} have similar patterns of expression under several conditions?
Some Questions of Interest

Does gene \( i \) express under this condition?

\[ H_0: \mu_i = 0 \quad \text{H}_A: \mu_i > 0 \]

Since we measure intensity, which is always non-negative, we cannot test this. We use a small constant (how small?) and do a one-sided test.

This is often considered to be inaccurate - PCR is often used to check at least some of the conclusions.
Some Questions of Interest

Does the expression level of gene_\text{i} differ under these 2 (or more) conditions?

\[ H_0 : \mu_{ij} = \mu_{ik} \quad \quad H_A : \mu_{ij} \neq \mu_{ik} \]

This is considered the most appropriate setting for microarray data.
Some Questions of Interest

Do gene_i and gene_j have similar patterns of expression under several conditions

We need to know what we mean by "pattern". Equality of means under the conditions can be determined by statistical testing. Other types of pattern similarity are generally developed by heuristic methods such as clustering.
tests of means:

1. Is the population mean $\mu_0$? (2-sided) $\leq, \geq$ (1-sided).

2. Is there a difference in population means? (usually 2-sided)
   
   (Paired) Is the mean difference equal 0? (usually 2-sided)
Some necessary assumptions

1. The observations are independent.
2. The observations are a random sample from a known population.
3. If there are 2 populations, the population histograms have the same shape.
t-test

\[ H_0: \mu = \mu_0 \]

\[ H_A: \mu \neq \mu_0 \]

\[ t^* = \frac{\bar{Y} - \mu_0}{S_Y / \sqrt{n}} \]

We obtain the p-value from a table or our software (d.f. = n-1)

RNA was spiked into the sample so that the expression level for the oligo should have been \(2^4\). Was this level achieved?
A $1-\alpha$ confidence interval for the mean is all the hypothesized values that would not be rejected by doing the 2-sided test at level $\alpha$.

Looking at the test statistic, we can readily see that this is

$$\bar{Y} \pm t_{1-\alpha/2,n-1} s / \sqrt{n}$$
Example:

$H_0: \mu = 4$

Sample average = 3.6, $n=49$

Sample variance = 0.041

One Sample t-test

data: R.gene1.array1

t = -13.5428, df = 48, p-value < 2.2e-16

alternative hypothesis: true mean is not equal to 4

95% confidence interval 3.517, 3.682
What is required for a one sample t-test?

The data should be independent. (This is essential.)

The data histogram should be symmetric and unimodal (i.e. the data should be "bell-shaped, although normality is not essential").
Testing the difference in means

If $X_1 \ldots X_n$ and $Y_1 \ldots Y_m$ are independent samples, another form of the t-test can be used to test if there is a difference in the mean. (e.g. to test differential expression)

$H_0: \mu_X = \mu_Y$
2-sample t-test

We now test:

$H_0$: difference in populations averages is 0

$H_A$: difference in population averages is not 0

\[
t^* = \frac{\bar{X} - \bar{Y}}{\sqrt{\frac{S^2_X}{n} + \frac{S^2_Y}{m}}}\]

Again we use the t-table, with d.f. $\approx n+m-2$
2-sample t-test

e.g. Do genes L37868 and L38503 differentially express between ALL and AML patients (a test for each gene).

L37868
t = -0.4401, df = 64.69, p-value = 0.6613
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval: 0.9250874 0.5910186
sample estimates:
mean in group ALL 7.283753 mean in group AML 7.450787

L38503
t = -4.9775, df = 64.913, p-value = 5.021e-06
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval: -1.8834056 -0.8047853
sample estimates:
mean in group ALL 10.03113 mean in group AML 11.37522
Some notes:

Notes:

1. Statistical significance is not the same as practical significance.
2. There is an alternative form of the denominator of the test if we assume that 2 populations have the same spread.
3. We need to be careful about the independence of the samples.
Another example:

$H_0$: Gene 1 was spiked into the red and green samples at the same level (2-color array).

Problem: We have already seen that red and green on the same spots are correlated.

Solution: Do a 1-sample t-test using the spot differences. (This is called the paired t-test.)

The spread need not be the same, as we use the variance of the differences.
Another example:

**H₀**: Gene 1 was spiked into the red and green samples at the same level on array 1.

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<th>Paired t-test</th>
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<td>( t = -4.3212, \text{df} = 48, p-value = 7.768e-05 )</td>
</tr>
<tr>
<td>alternative hypothesis: true mean is not equal to 0</td>
<td>alternative hypothesis: true difference in means is not equal to 0</td>
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<tr>
<td>sample estimates: mean of x</td>
<td>sample estimates: mean of the differences</td>
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<td>-0.1558204</td>
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Alternatives to the t-test

The t-test is not the only choice for testing hypotheses about average expression levels. These methods require equal variance and independence, but not bell-shaped

Permutation test
Bootstrap test
Wilcoxon test
Permutation test (2-sample)

Compute t* as usual, but do not use t table.

Instead: Make one big sample \( X_1 \ldots X_n Y_1 \ldots Y_m \)

For all possible choices of selection \( n \) items 
(or a sample, if this is too many)

Select \( n \) observations at random to be the X’s; 
the remainder are the Y’s.
Compute \( T^* \) for each selection.
Permutation test (2-sample)

The p-value is based on where $t^*$ is in the histogram of $T^*$

For a 2-sided test, consider the values to the left of $-T^*$
Compute $t^*$ as usual, but do not use $t$-table.

Instead: Make one big sample $X_1 \ldots X_n Y_1 \ldots Y_m$

For all possible choices of selection $n$ items with replacement to be the $X$’s and $m$ items with replacement to be the $Y$’s.

Proceed as for the permutation test.
The Wilcoxon test (2-sample) aka Mann-Whitney test

Make one big sample $X_1 \ldots X_n Y_1 \ldots Y_m$

Rank the observations from lowest (1) to highest (n)

$W^* = \Sigma \text{rank}(X’s) - \Sigma \text{rank}(Y’s)$

The p-value is computed by the permutation test, (and these are available in tables based on n and m).
Note:

There are 1-sample and paired sample versions of these tests.

The Wilcoxon test is often used instead of the t-test. The Wilcoxon p-value is usually very close to the t-test p-value when the t-test is appropriate, and is more accurate when the t-test is not appropriate. On the other hand, the Wilcoxon test does not readily generalize to the more powerful analyses based on Bayesian methods.
Power, False Discovery, Nondiscovery

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<tr>
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<td>$R$</td>
<td>$m$</td>
</tr>
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</table>

Power – probability of rejecting when $H_0$ false

$FDR = \frac{V}{R}$

$FNR = \frac{T}{(m-R)}$
Multiple Comparisons Problem

e.g. Pick 1 person from the class. What is the probability that the person > 72 inches tall?

Pick 10 people from the class. What is the probability that at least one selected person > 72 inches tall?

The more tests we do at a selected p-value, the greater the probability of falsely rejecting at least one - the multiple comparisons problem.
The p-value is the probability of rejecting the null hypothesis when it is true.

Under the alternative:

We can see that \( t^* \) will be larger when – the difference between the means is larger, the variance is smaller or \( n \) is larger.

The only item under our control is the sample size.
For fixed $p$-value at which we declare statistical significance, increasing the sample size:

- Increases power
- Reduces FDR
- Reduces FNR
For fixed FDR at which we declare statistical significance, increasing the sample size:

Reduces FNR

The sample size in most microarray studies is too small.

This leads to large FNR – which needs to be considered when known genes are not found to be statistically significant.
Improving Power

Besides increasing the sample size we can:

1. Pick the best tests. (Generally t-test and Wilcoxon are more powerful than resampling when appropriate.)
2. Use (Empirical) Bayes tests (SAM, LIMMA, …)
Bayes Methods

We have lots of genes.

Gene $i$ has mean $\mu_i$ and variance $\sigma_i^2$.

Bayesian methods assume that the means and variances come from known distributions (the priors).

Empirical Bayes methods assume that the means and variances have distributions that are estimated from the data.
Empirical Bayes Methods

Most focus is on the distribution of the variances.

SAM – add a constant based on a quantile of the distribution of the $S^2$ over all the genes. (SAM also uses permutation tests.)

LIMMA – more formal eBayes analysis
- results in replacing gene variances by a weighted average of the gene variance and the mean variance of all genes.
True Bayes

Combine prior information (in the form of assumed distribution) with the data.

Instead of p-values, we obtain the posterior odds ratio of the hypothesis being true.
Increasing power

Classical methods are known to be less powerful than eBayes and Bayes methods.

For complicated experiments, it can be difficult to develop correct Bayesian methods. For many microarray experiments, these methods are available.
Multiple comparisons problem

The problem with p-values is that:

If we declare significance when \( P < \alpha \) then \( \alpha m_0 \) of the genes are false detections (e.g. \( \alpha = 0.01, m_0 = 20,000 \rightarrow 200 \) false detections)

The 2 main methods for handling this are controlling the family-wise error rate (FWER) the probability of at least one false detection and controlling the false detection rate FDR the percentage of all detections which are false.

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<td>( m-m_0 )</td>
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<tr>
<td>total</td>
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<td>( R )</td>
<td>( m )</td>
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</table>
Clustering Samples

We may wish to cluster samples with similar expression profiles, or classify a new sample based on expression profiles.
Clustering Genes

Log Expression Profile  Z-score Profile

Log Expression Profile  Z-score Profile

Log Expression Profile  Z-score Profile

Log Expression Profile  Z-score Profile