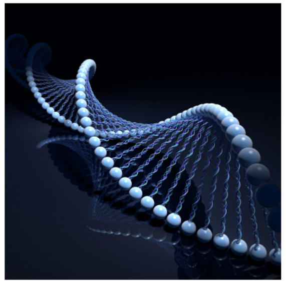
LGBIO2010: Large scale gene expression analysis

Pierre Dupont



UCL – ICTEAM

Outline

1. Introduction
2. Preprocessing
3. Unsupervised gene selection
4. Supervised gene selection
   - Filters
     - Non-specific filtering
     - Fold changes
     - t-Test
     - Mutual information
     - Multivariate filters
   - Wrappers
   - Embedded Methods
     - Classification

Outline

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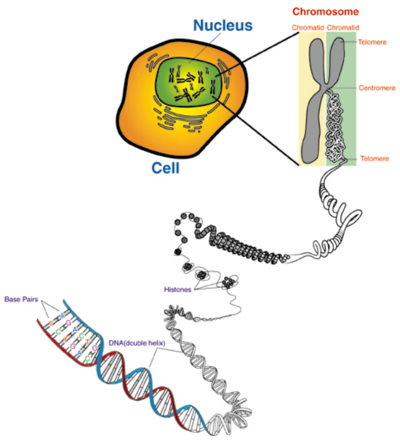
2. Preprocessing
3. Unsupervised gene selection
4. Supervised gene selection

Gene expression



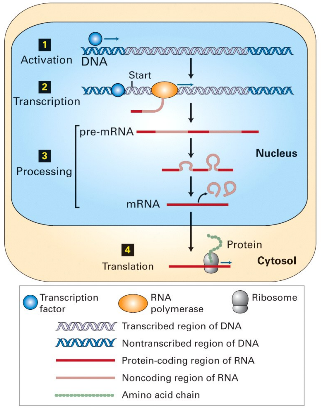
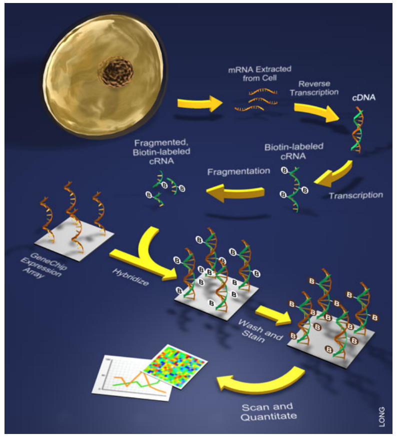


Illustration from Molecular Cell Biology, 5e (© WHFreeman 2004).

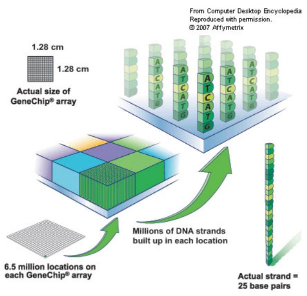
DNA Microarrays

DNA Microarrays measure the level of expression of all genes in a single experiment

1. Data measurements
2. Preprocessing and sample normalization
3. Gene selection and sample classification
4. Diagnosis, prognosis or prediction of the response to a treatment



Affymetrix® technology


1.28 cm
1.28 cm
Actual size of GeneChip® array
6.5 million locations on each GeneChip® array
Millions of DNA strands built up in each location
Actual strand = 25 base pairs

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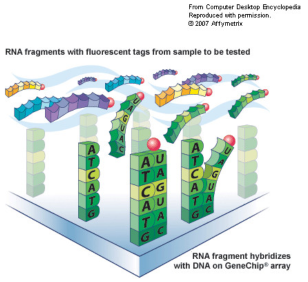
RNA fragments with fluorescent tags from sample to be tested
RNA fragment hybridizes with DNA on GeneChip® array

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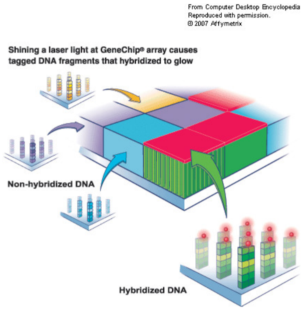
Shining a laser light at GeneChip® array causes tagged DNA fragments that hybridized to glow
Non-hybridized DNA
Hybridized DNA

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Alternative measurement technologies

- Other companies sell DNA chips (Agilent®, . . .)
- Multiplex qPCR (Applied Biosystems®, . . .)
  - larger dynamic range than microarrays
  - limited to ≈ 100 genes
- RNAseq (Illumina®, Ion Torrent®, . . .)
  - fastly evolving
  - scaling effects influence per sample cost

Example: diagnosis

Biomarkers for an early diagnosis of rheumatoid infections

Prediction problem: multi-class feature selection

- Rheumatoid arthritis
- Lupus
- Psoriatic rheumatism
- Microcristalline arthritis
- Inflammatory osteoarthritis

RHEUMAGENE research project with Prof. Lauwerys (UCL/IREC/RUMA)

Example: prognosis

Biomarkers to predict the risk of allergies of newborns

- More than 30% of children are allergic in industrial countries
- Predicting who is more likely to become allergic is a path to prevention and possible treatment

CRISTALL research project with Profs. Sokal and Smets (UCL/IREC/PEDI)

Example: response to treatment prediction

Gene profiling for cancer treatment

Objective

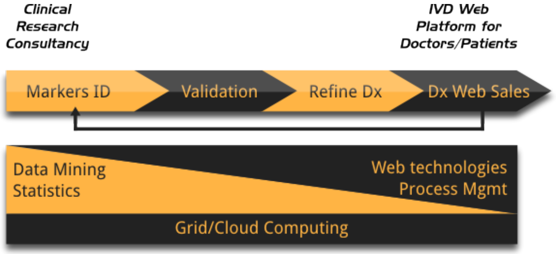
Identify biomarkers for predicting patient response to MAGE-A3 immuno-therapy against melanoma before treatment

In collaboration with GSK Biologicals - WO/2010/029174 (patent).

DNAlytics

Data Mining & IT Solutions for Personalized Medicine

A UCL spin-off



www.dnalytics.com

Supervised selection

	gene 1	gene 2	...	gene p	response
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$	y_1
...	...	...	...	...	...
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$	y_n
test sample	x_1	x_2	...	x_p	?

- The number p of input dimensions (probes, probesets or genes) may be very large ($10^4 \dots 10^6$)
- The number n of samples is typically much smaller ($\approx 50 \dots 100$)
- Each sample is characterized by a vector $\boldsymbol{x}$ of p measurements
- Each training sample has a known response: class label y ($y \in \{-1, 1\}$ or $y \in \mathbb{N}$) or $y \in \mathbb{R}$

Gene selection

Find a small subset of genes, (a.k.a features, attributes or input variables), to predict the response or class y of new samples

Gene selection

Objectives

- Insight into the data and the predictive model
- Link between data analysis and medical expert
- Biological validation on a few genes rather than thousand ones
- Reduction of the financial cost of a diagnosis/prognosis kit (technological constraints)

Difficulties

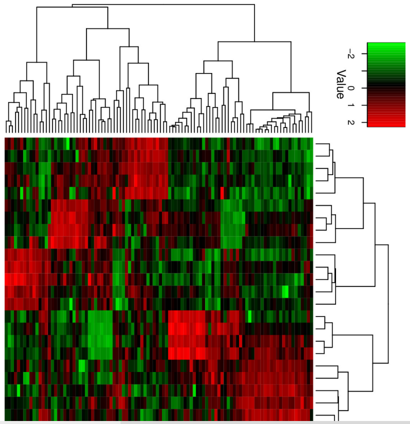
- Measurements are noisy
- Gene expression varies due to many factors (gender, cell type, growth of the organism, chemical environment of the cell, . . .) often not related to the response to be predicted
- Financial cost: $500 \ldots 1,000$ €/experiment
- Small n (e.g. 50), large p (e.g. $50,000$) problems

Unsupervised selection

	gene 1	gene 2	...	gene p	cluster
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$	?
...	...	...	...	...	...
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$	?
cluster	?	?	...	?	

Objective

Find clusters of genes and/or samples that share a similar profile: up or down regulated genes across the same samples



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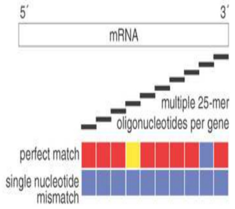
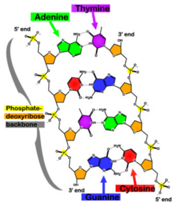
Summarization


5′
3′
mRNA
multiple 25-mer oligonucleotides per gene
perfect match
single nucleotide mismatch



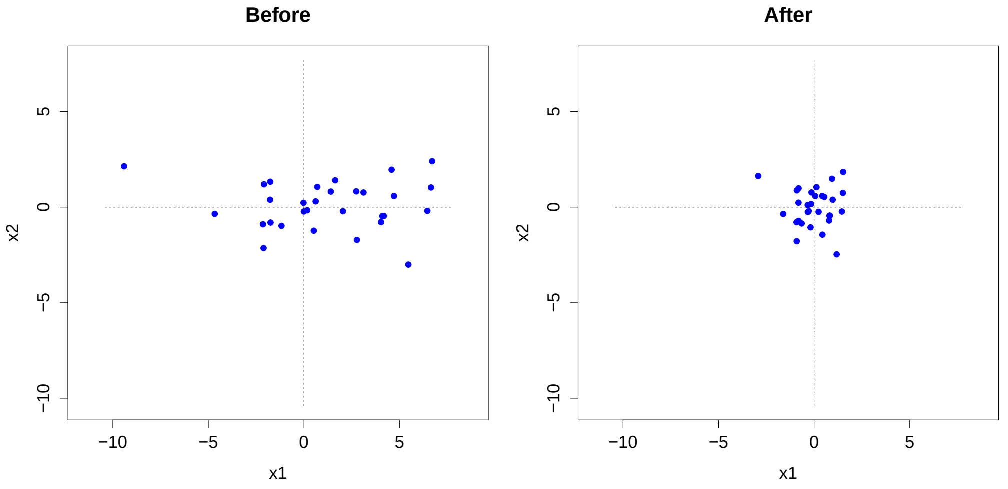
- Define a single probeset expression level from the various probe intensities
- Popular techniques: MAS 5.0, RMA, **GC-RMA**
  1. background adjustment: optical noise correction, probe affinity adjustment (influenced by the GC content), RMA ignores the MM probes
  2. sample normalization: quantiles should be stable across samples, after conversion to log intensities for (GC-)RMA
  3. summarization: median polish

Feature normalization

	gene 1	gene 2	...	gene p
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$
...	...	...	...	...
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$

- Make sure that each gene (probeset) has roughly the same expression range across all samples
- Z-score normalization
  Replace $x_{i,j}$ by $\frac{x_{i,j}-\mu_j}{s_j}$ with μ_j the mean level of expression of probeset j over the training samples and s_j its standard deviation

Feature normalization example



Distance between expression values

	gene 1	gene 2	...	gene p
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$
...	...	...	...	...
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$

Euclidean distance

$$d(\boldsymbol{x}_1, \boldsymbol{x}_2) = \|\boldsymbol{x}_1 - \boldsymbol{x}_2\| = \sqrt{\sum_{i=1}^{n}(x_{i,1} - x_{i,2})^2}$$

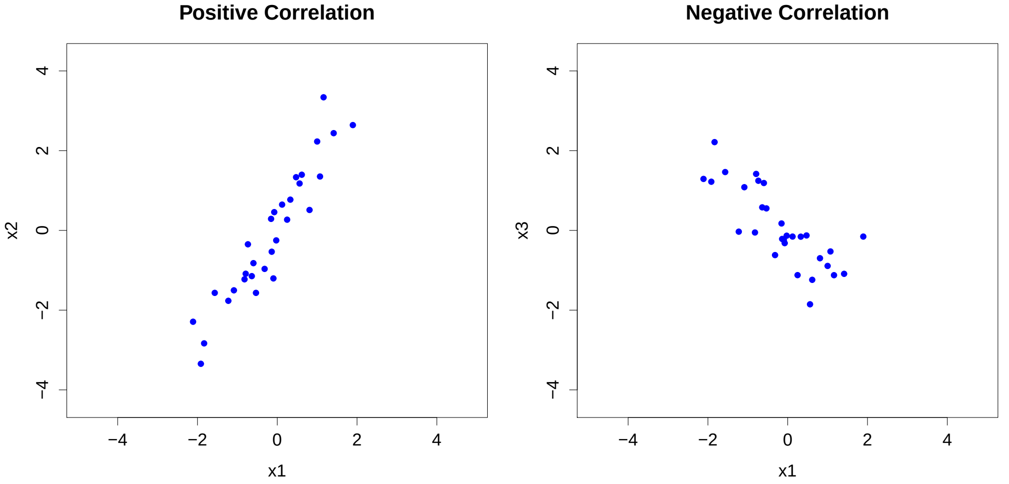
Correlation based distance

$$d(\boldsymbol{x}_1, \boldsymbol{x}_2) = 1 - \frac{1}{2}(1 + \mathrm{corr}(\boldsymbol{x}_1, \boldsymbol{x}_2))$$

Correlation between expression values

Are both genes over/under expressed on the same samples?

Is one gene over-expressed when the other is under-expressed?



Pearson correlation

For two random vectors (*e.g.* gene expression values) $\boldsymbol{x}_1, \boldsymbol{x}_2$ measured over n samples

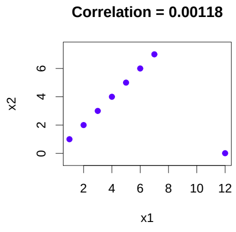
$$\mathrm{corr}(\boldsymbol{x}_1, \boldsymbol{x}_2) = \frac{\sum_{i=1}^{n}(x_{i,1} - \bar{x}_1)(x_{i,2} - \bar{x}_2)}{\sqrt{\sum_{i=1}^{n}(x_{i,1} - \bar{x}_1)^2 \sum_{i=1}^{n}(x_{i,2} - \bar{x}_2)^2}}$$

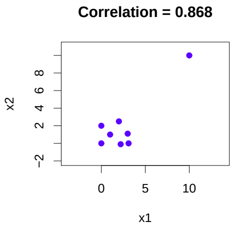
- $\mathrm{corr}(\boldsymbol{x}_1, \boldsymbol{x}_2) = \pm 1$ if $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ are perfectly linearly correlated
- $\mathrm{corr}(\boldsymbol{x}_1, \boldsymbol{x}_2) = 0$ if they are not linearly correlated
- whenever $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ and normalized to zero mean and unit variance:

$$\mathrm{corr}(\boldsymbol{x}_1, \boldsymbol{x}_2) = \sum_{i=1}^{n} x_{i,1} x_{i,2} = \boldsymbol{x}_1^{\top} \boldsymbol{x}_2$$

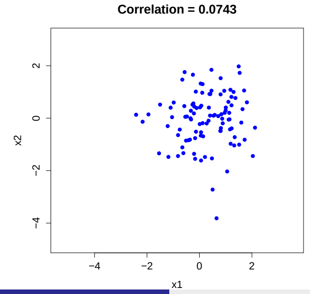
Pitfalls with correlation measures

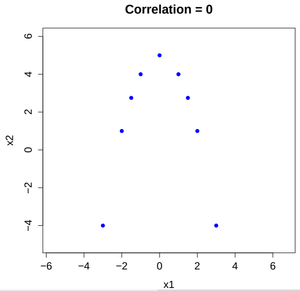
- Correlation is very sensitive to outliers





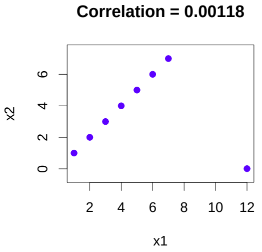
- Correlation measures linear dependence

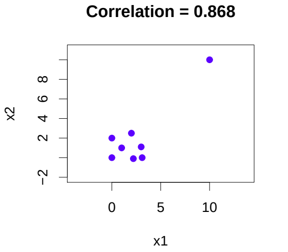


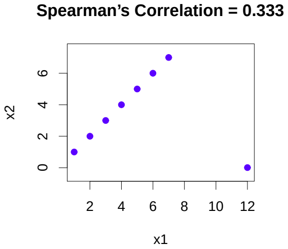


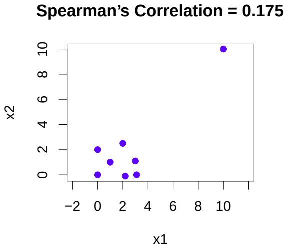
Spearman's rank correlation: less sensitive to outliers

1. Replace feature value by feature value rank across observations
2. Compute Pearson correlation between rank vectors

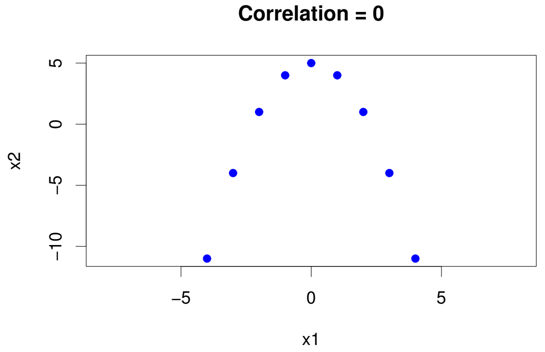








Uncorrelated features are not necessarily independent



- $\mathrm{corr}(\boldsymbol{x}_1, \boldsymbol{x}_2) = 0$ (both Pearson and Spearman correlations)
- $P(\boldsymbol{x}_2 | \boldsymbol{x}_1) \neq P(\boldsymbol{x}_2)$

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2 Preprocessing

3 Unsupervised gene selection

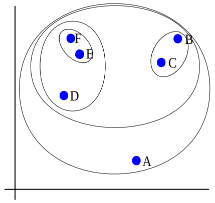
4 Supervised gene selection

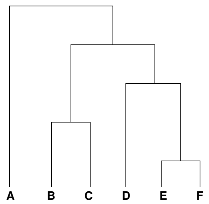
Agglomerative Hierarchical clustering

Each observation represents

either a sample across genes

or a gene across samples





```
Algorithm AGGLOMERATIVEHIERARCHICALCLUSTERING
Input: $D$ a set of observations $\vec{x}_1, \ldots, \vec{x}_m$ ; $d(\vec{x}, \vec{y})$ a distance measure between
         observations
Output: A tree $T$ of subsets of $D$
// Initialize a set $\mathcal{D}$ of clusters $D_1, \ldots, D_m$
$\mathcal{D} \leftarrow \{\{\vec{x}_1\}, \ldots, \{\vec{x}_m\}\}$        // Initial clusters are tree leaves
$T \leftarrow$ a partial tree whose leaves are the $\vec{x}_i$'s
while $|\mathcal{D}| > 1$ do
    Choose pair of clusters $(D_i, D_j)$ in $\mathcal{D}$ such that $Distance(D_i, D_j, d)$ is minimal
    Define a new cluster $D_k = D_i \cup D_j$
    $\mathcal{D} \leftarrow \mathcal{D} \cup D_k - \{D_i, D_j\}$
    Add $D_k$ as parent node of $D_i$ and $D_j$ in the tree $T$
return $T$
```

Distance measure between clusters

Single-link or nearest neighbor rule

$$Distance(D_i, D_j, d) = \min_{\vec{x} \in D_i, \vec{y} \in D_j} d(\vec{x}, \vec{y})$$

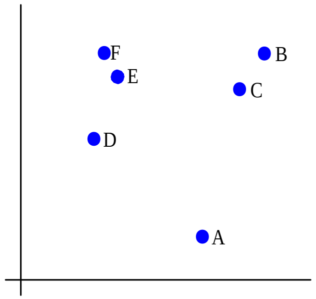
Complete-link or farthest neighbor rule

$$Distance(D_i, D_j, d) = \max_{\vec{x} \in D_i, \vec{y} \in D_j} d(\vec{x}, \vec{y})$$

Average-link rule

$$Distance(D_i, D_j, d) = \frac{1}{|D_i|.|D_j|} \sum_{\vec{x} \in D_i, \vec{y} \in D_j} d(\vec{x}, \vec{y})$$

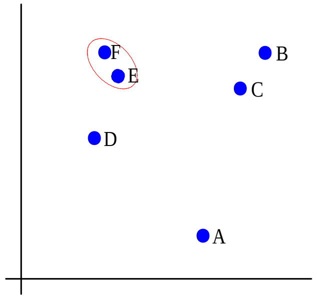
Hierarchical clustering example

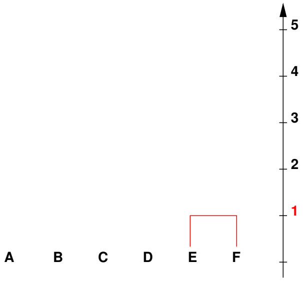


A B C D E F

	A	B	C	D	E	F
A						
B	8					
C	6	2				
D	5	8	6			
E	7	6	4	3		
F	8	6	5	4	1	

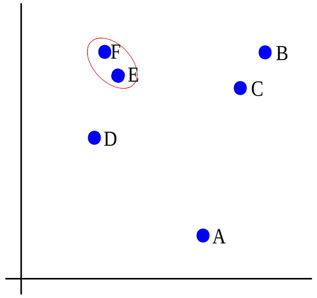
Hierarchical clustering example

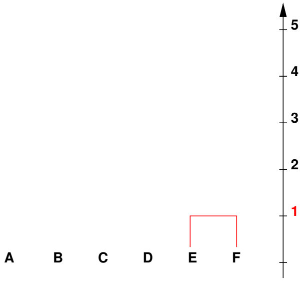




	A	B	C	D	E	F
A						
B	8					
C	6	2				
D	5	8	6			
E	7	6	4	3		
F	8	6	5	4	1	

Hierarchical clustering example

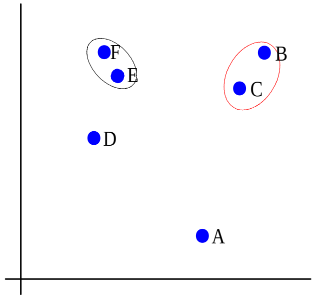


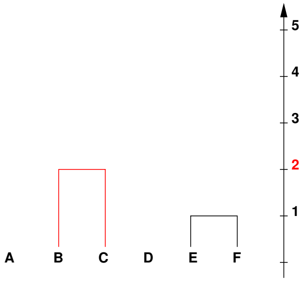


Single-link rule

	A	B	C	D	EF	
A						
B	8					
C	6	2				
D	5	8	6			
E F	7	6	4	3		
	8	6	5	4	1	

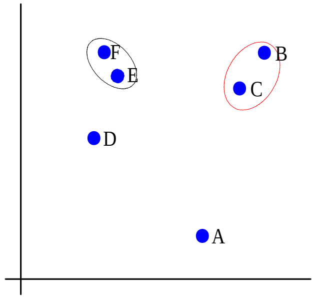
Hierarchical clustering example

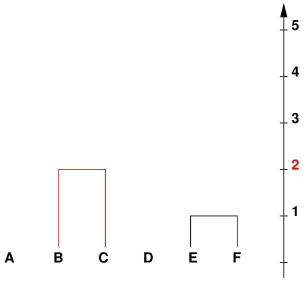




	A	B	C	D	EF
A					
B	8				
C	6	2			
D	5	8	6		
EF	7	6	4	3	

Hierarchical clustering example

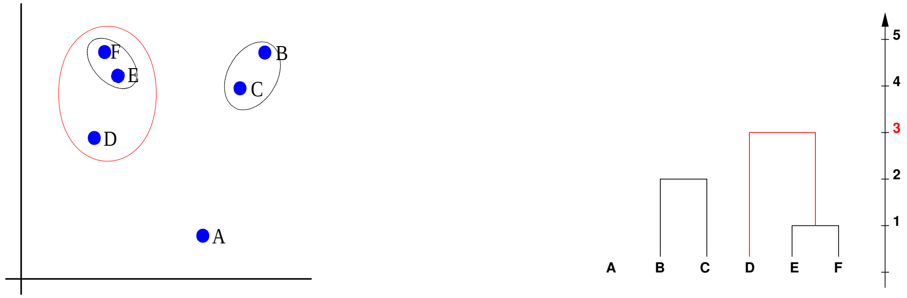




Single-link rule

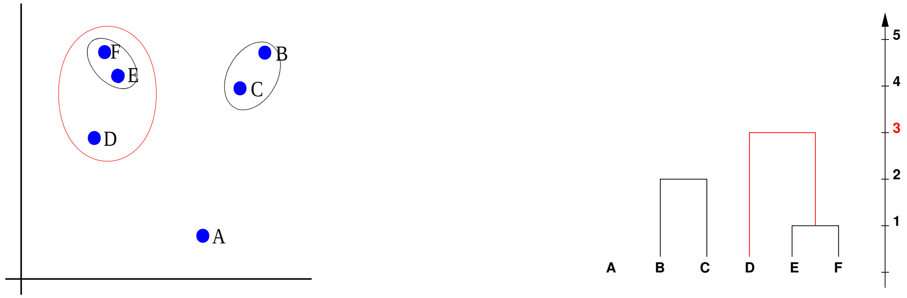
	A	BC		D	EF
A					
BC	8				
	6	2			
D	5	8	6		
EF	7	6	4	3	

Hierarchical clustering example



	A	BC	D	EF
A				
BC	6			
D	5	6		
EF	7	4	3	

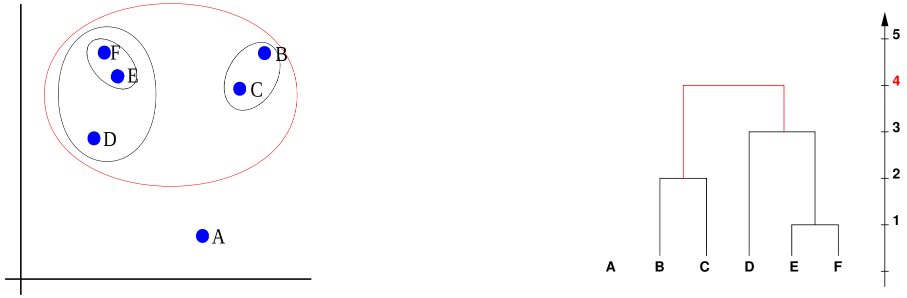
Hierarchical clustering example



Single-link rule

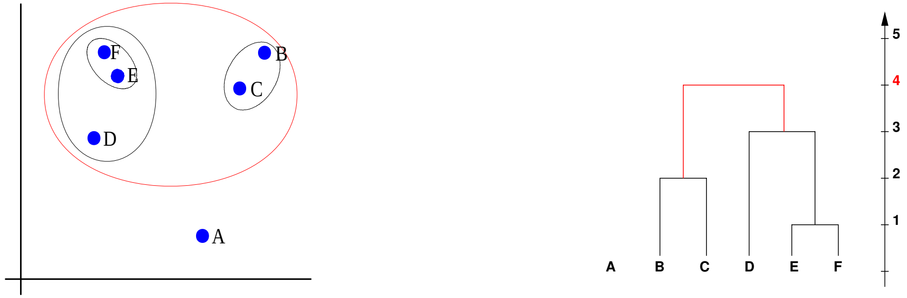
	A	BC	DEF	
A				
BC	6			
DEF	5	6		
	7	4	3	

Hierarchical clustering example



	A	BC	DEF
A			
BC	6		
DEF	5	4	

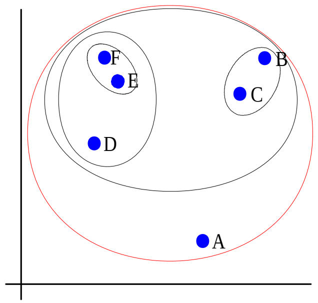
Hierarchical clustering example

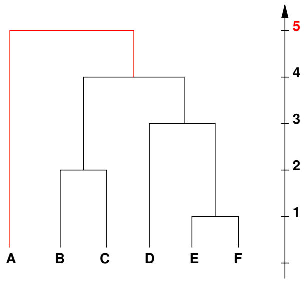


Single-link rule

	A	BCDEF	
A			
BC DEF	6		
	5	4	

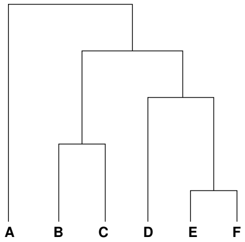
Hierarchical clustering example





	A	BCDEF
A		
BC DEF	5	

A note on phylogeny



This hierarchical clustering algorithm, with the average-link rule, is known as the UPGMA algorithm used in phylogeny

- The observations are (fragments) of sequences representative of some species, called taxa
- The pairwise distance measure is based on alignment scores, generally corrected according to an evolutionary model (*e.g.* Kimura)
- The final tree is interpreted as a phylogenetic tree and the branch length as representative of time

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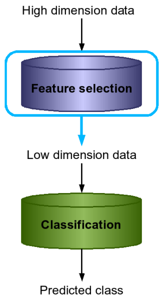
Supervised gene selection

	gene 1	**gene 2**	**...**	**gene p**	**class**
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$	+
sample 2	...	...	...	...	+
...	...	...	...	...	...
sample n-1	...	...	...	...	-
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$	-
test sample	x_1	x_2	...	x_p	?

- we discuss binary classification first:
  e.g. responders (+ or class 1) vs non-responders (- or class 2)
- samples can be indexed by their class label
  - means and variances can be computed on samples of a given class
- find a subset of most discriminating genes for the prediction of the class of any new sample

Feature selection: filters



High dimension data

Feature selection

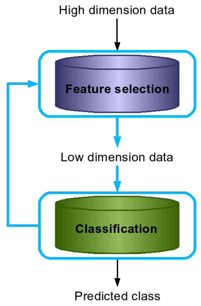
Low dimension data

Classification

Predicted class

- Use only the training data + class labels during the feature selection step
- Standard techniques: fold changes, t-Test, mutual information, . . .
- Train a single classifier taking the selected features as inputs
- The simplest and less computing intensive approach

Feature selection: wrappers



High dimension data

Feature selection

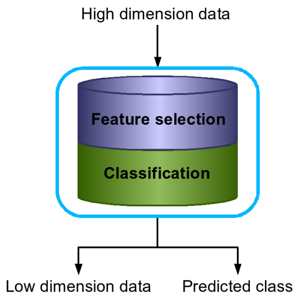
Low dimension data

Classification

Predicted class

- Train a classifier on several subsets of all possible features
  - Exhaustive evaluation of all possible subsets is unfeasible Note: there are $\mathcal{O}(2^p)$ subsets with $p \geq 10,000$
  - Typical solutions: use feature ranking or forward/backward selection
- Select the feature set that optimizes the performance of the trained classifier

Feature selection: embedded approaches



High dimension data

Feature selection

Classification

Low dimension data

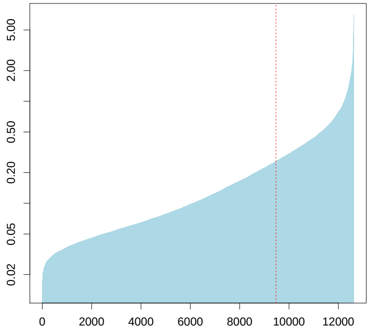
Predicted class

- Define the feature selection and the classifier estimation as a combined optimization process
- Include classifier optimization in the feature selection process
- More elegant/relevant but also more computing intensive than a filter

Non-specific filtering

	gene 1	gene 2	...	gene p	class
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$	+
sample 2	...	...	...	...	+
...	...	...	...	...	...
sample n-1	...	...	...	...	-
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$	-

- genes with a small variance across all training samples are unlikely to be discriminating between classes
- keep only those genes (*e.g.* 25 %) with the larger variances
  - before normalization to unit variance!



Fold changes

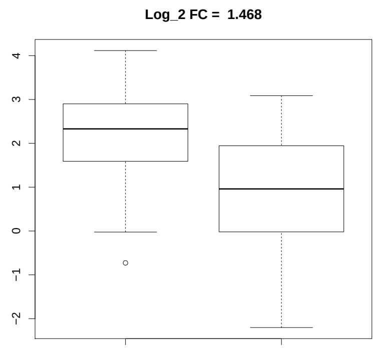
	gene 1	gene 2	...	gene p	class
sample 1	$x_{1,1}$	$x_{1,2}$	...	$x_{1,p}$	+
sample 2	...	...	...	...	+
...	...	...	...	...	...
sample n-1	...	...	...	...	-
sample n	$x_{n,1}$	$x_{n,2}$	...	$x_{n,p}$	-

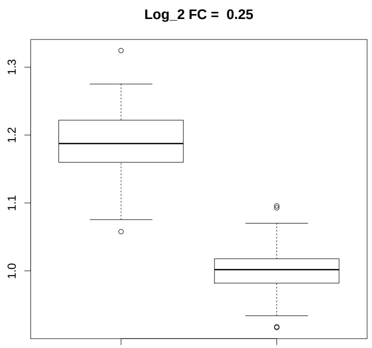
Select genes with the larger fold changes between both conditions

$$\frac{\bar{x}_1}{\bar{x}_2} \text{ or } \log \frac{\bar{x}_1}{\bar{x}_2} = \log \bar{x}_1 - \log \bar{x}_2 \text{ or } \bar{x}_1 - \bar{x}_2$$

Comments on fold changes

- whenever $\bar{x}_1 < \bar{x}_2$, one considers a small value as important
  - $\log_2 \frac{\bar{x}_1}{\bar{x}_2}$ should be ≥ 1 or ≤ -1
- is a two-fold change significant?
  - dependence on the measurement technology
  - dependence on the class conditional variance





t-Test relevance index

- A feature relevance $J(x)$ can be defined according to the distance between the average feature value in each class
- The larger the distance the better, relatively to standard deviations

t-Test statistic (actually Welch t-statistics)

$$J(x) = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{S_1^2/n_1 + S_2^2/n_2}}$$

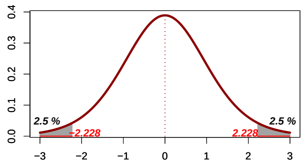
with n_1 (resp. n_2) the number of examples labeled as $+$ (resp. $-$) and the estimated variances in each class $S_i^2 = \frac{1}{n_i - 1} \sum_{j=1}^{n_i} (x_{ij} - \bar{x}_i)^2$

Confidence measure

- The Welch statistics follows a t-distribution with a number of degrees of freedom equal to:

$$\frac{(S_1^2/n_1 + S_2^2/n_2)^2}{(S_1^2/n_1)(n_1-1) + (S_2^2/n_2)(n_2-1)}$$

- p-values assess the significance of the difference between the two class means



- A feature is selected if its associated p-value is below a prescribed threshold (*e.g.* $5\% \Rightarrow |J(x)| \geq 2.228$ when d.f. $= 10$)

The R Project for Statistical Computing

An efficient way of computing *p*-values, and **many** other useful things. . .

http://www.r-project.org/

```
> t.test(x1,x2)
        Welch Two Sample t-test
data:  x1 and x2
t = 0.9183, df = 7.002, p-value = 0.389
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 -0.908216  2.061549
sample estimates:
mean of x mean of y
 1.866667  1.290000
```

where `x1` (resp. `x2`) is the vector of expression values of a given gene from samples labeled as class 1 (resp. class 2)

$p-$value $> 0.05 \Rightarrow$ the difference between the 2 class means is not considered significant for this feature ⇒ discard the feature

Alternatives to a simple t-Test

- Mann-Whitney rank test is an alternative *non-parametric* test
- ANOVA offers a generalization of the t-Test in a multi-class (> 2) setting
- Pairwise t-tests between one class and the others is a common alternative
- Kruskal-Wallis is a generalization of Mann-Whitney to multi-class

The multiple test problem

A microarray experiment to distinguish between patients with a positive or a negative diagnosis

Among 50,000 gene expression values measured in each experiment, only those genes that are differently expressed, with a *p*-value $\leq 0.05 = \alpha$, are selected

The probability of type I error of a statistical test

Conclude that the mean expression values among the 2 classes are significantly different for a given gene while they are not ⇒ the feature is falsely selected with probability α

Test multiplicity

- The test will be performed for each gene ⇒ 50,000 times from the same experiment
- If $\alpha = 0.05$, we are expecting to select wrongly $50,000 \times .05 = 2,500$ genes !!

Multiple test correction

Bonferroni correction

Divide the critical value (e.g. $\alpha = .05$) by the number of tests n_t performed

Example: $\frac{\alpha}{n_t} = \frac{.05}{50,000} = 10^{-6}$

⇒ only genes with associated *p*-values $\leq 10^{-6}$ are selected

Very conservative, often leads to select no feature

False Discovery Rate correction

Benjamini-Hochberg correction

1. Select a confidence level α (*e.g.* 0.05)
2. Rank the p-values (one for each feature) in increasing order $p_1 \leq p_2 \leq \cdots \leq p_{n_t}$
3. Iterate over the n_t features
   ($n_t = p$ with data in $\mathbb{R}^p$, not to be confused with $p-$values)
   - Find the maximal index i such that $\frac{p_i \times n_t}{i} < \alpha$
4. Keep all features up to index i_{max}

Notes:

- If $p_{n_t} < 0.05$ FDR correction leads to select all features
- FDR correction is equivalent to Bonferonni correction whenever a single feature is selected: $p_1 \times n_t < \alpha \Leftrightarrow p_1 < \frac{\alpha}{n_t}$
- Those corrections do not change the relative ranking of features, just the selection threshold
- See R function `p.adjust`

Feature ranking with mutual information

$$I(X;Y) = -\sum_{ij} P(x_i, y_j) \log_2 \frac{P(x_i, y_j)}{P(x_i)P(y_j)}$$

$$= -\sum_{ij} P(x_i, y_j) \log_2 \frac{P(y_j|x_i)}{P(y_j)}$$

- A feature X is more relevant if its mutual information with the class value is higher
- If X tends to bring no information to predict Y then
  $P(y_j|x_i) \approx P(y_j)$ and $I(X;Y) \rightarrow 0$
- $I(X;Y) = 0$ **if and only if** X and Y are independent
- $I(X;Y)$ is invariant under rescaling of the variables X and Y (often rescaled to unit variance)

Univariate versus multivariate filters

- Correlation measures, t-Test (ANOVA), and $I(X;Y)$ are univariate filters
- Mutual information can be used to select several variables at a time $I(X_1, \ldots, X_k; Y)$ **but** MI depends on the distributions $P(X_1, \ldots, X_k, Y)$, $P(X_1, \ldots, X_k)$ and $P(Y)$, which need to be reliably estimated
  - replace the joint problem by an approximation with a greedy selection of features

Maximum relevance minimum redundancy

[Peng et al., 05]

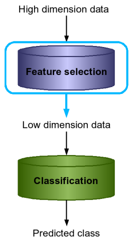
1. Select the feature with maximum mutual information with the response
   - $\hat{X} = \text{argmax}_X \, I(X;Y)$
   - $\Phi = \{\hat{X}\}$ // Initialize the set of selected features
   - $F = \{X_1, \ldots, X_p\} \setminus \{\hat{X}\}$ // The remaining set of features
2. **Repeat**

   $$\hat{X} = \text{argmax}_{X \in F} \left[\underbrace{I(X;Y)}_{\text{maximize relevance}} \underbrace{- \frac{1}{|\Phi|} \sum_{X_j \in \Phi} I(X;X_j)}_{\text{minimize redundancy}} \right]$$

   $\Phi \leftarrow \Phi \cup \{\hat{X}\}$; $F \leftarrow F \setminus \{\hat{X}\}$

   until an appropriate number of features are selected

Filters in a nutshell



High dimension data

Feature selection

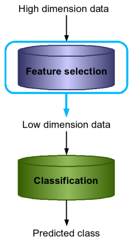
Low dimension data

Classification

Predicted class

- Use only the training data + class labels during selection
- Filters offer interesting baselines which are fast to compute
- Popular univariate filters are based on a t-Test (with multiple test correction) or mutual information
  - they ignore the interactions between genes!
- Maximum relevance minimum redundancy is a popular multivariate extension

Are filters independent from a predictive model?



High dimension data

Feature selection

Low dimension data

Classification

Predicted class

- The two step approach is sometimes considered as a benefit since the features are claimed to be selected independently from the subsequent classifier/regression model
  - Is it really better? (see embedded methods)
  - Is it really the case?

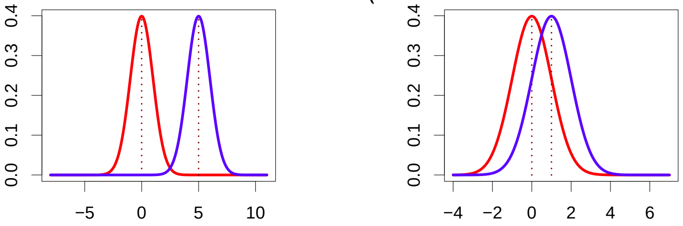
t-Test revisited

t-Test statistic

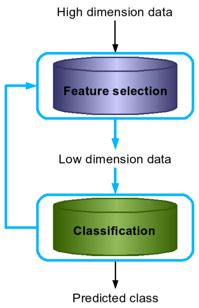
A feature x is selected whenever the difference between the class means is significant (after correction for multiplicity)

$$J(x) = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{S_1^2/n_1 + S_2^2/n_2}}$$

Equivalently, one easily discriminates between the classes using 2 uni-dimensional Gaussian classifiers (with a common variance)



Wrapper principle



High dimension data

Feature selection

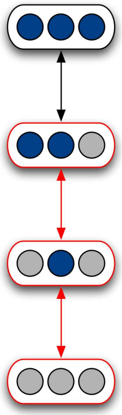
Low dimension data

Classification

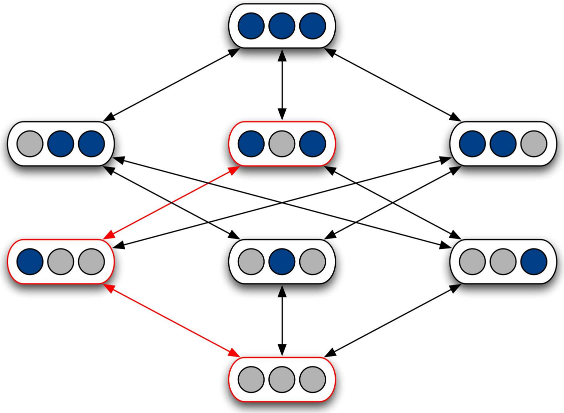
Predicted class

- Estimate a classifier from a given subset of all possible features
- Select the feature subset that optimizes the performance of the classifier (usually on an independent validation set)
  - Feature selection depends on the evaluation protocol of the classifier
  - There are $\mathcal{O}(2^p)$ possible subsets

Univariate feature ranking



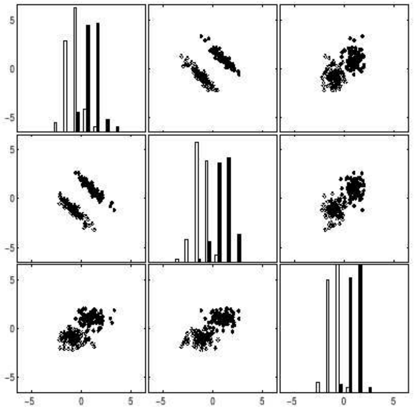
Multivariate Forward/Backward selection



- Forward selection goes bottom-up
- Backward selection goes top-down

Search order matters

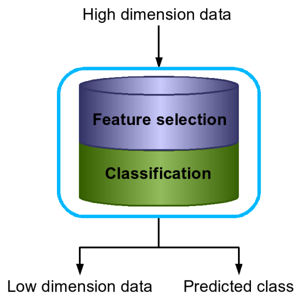
- x_3 alone is better than x_1 or x_2 alone, but x_1 together with x_2 offer the best discrimination
- **2 best features:**
  - Univariate feature ranking selects (x_3, x_2)
  - Forward selection selects (x_3, x_1)
  - Backward selection selects (x_1, x_2)
- **Single best feature:**
  - Forward selection or univariate feature ranking selects x_3
  - Backward selection selects x_2



Wrappers in a nutshell

- A wrapper with **univariate feature ranking** offers a **good baseline**
  - The t-Test statistics can be used to rank features only (no need for multiple test correction nor fixing a confidence measure)
  - Classifier performance is used to decide how many features to keep
  - This can outperform a pure filter approach while not increasing much the computational cost
- A **backward selection** may be preferable over a forward selection, but should not be used to select just a few features (what “a few” means depends on the data. . .)
- More sophisticated search strategies are possible (backward + forward, randomized search, . . .)
- If one can afford the computational cost of a multivariate selection, one should probably consider an embedded approach

Embedded Methods



High dimension data

Feature selection

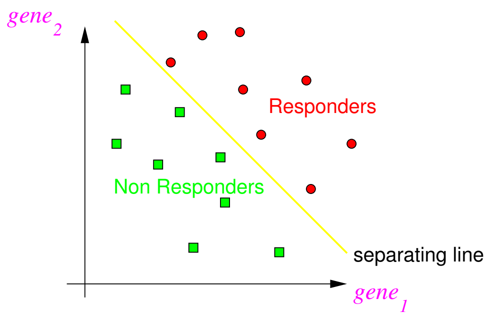
Classification

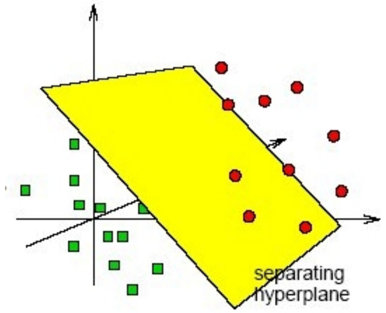
Low dimension data

Predicted class

- Define the feature selection and the classifier estimation as a combined optimization process
- The features are selected as a by-product of the estimated classifier and its parameters

Linear Discriminants

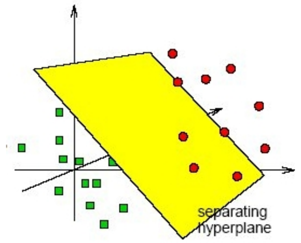




- The actual number of dimensions may be $\approx 10,000$ for microarray classification
- The linear discriminant is a hyperplane in $\mathbb{R}^{\geq 10,000}$
- Decision rule: $\text{sign}\ (\sum_{j=1}^{p} w_j x_j + w_0) = \text{sign}\ (\mathbf{w}^\top \mathbf{x})$ (with $x_0 \triangleq 1$)

  $\Rightarrow |w_j|$ is a measure of the importance of the j^{th} feature

Linear Separability

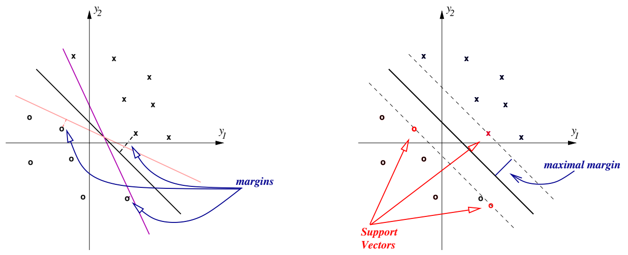


Facts

- The data is linearly separable if the two classes can be perfectly separated by a hyperplane
- A hyperplane in $\mathbb{R}^{10,000}$ can separate perfectly at least $10,001$ (unaligned) points, given any possible 2 class labeling
- There is no problem to find a perfect linear separator of less than 100 points in $\mathbb{R}^{\geq 10,000}$ (*e.g.* for microarray data)
- The problem is that there are many *apparently perfect* models

Linear Support Vector Machines in a nutshell

- When the data is linearly separable the separating hyperplane is not unique but the maximal margin hyperplane separates the data with the largest margin
- For each separating hyperplane, there is an associated set of support vectors



Recursive Feature Elimination [Guyon *et al.* , 02]

Embedded Backward Selection

1. Estimate a SVM on a given set of dimensions (initially p dimensions)
   - Decision rule: sign $(\sum_{j=1}^{p} w_j x_j + w_0)$
2. Consider $|w_j|$ as the relevance of the j^{th} dimension
3. Remove the least relevant dimension(s)
4. Iterate 1 to 3 on a reduced feature set

General Summary

- Feature selection aims at reducing the dimensionality of the data while preserving the interpretation of the original features
- **Filters** methods use only the data + class labels:
  - simple, fast, generally univariate (often an implicit use of a classifier)
- **Wrappers** take the performance of the classifier into account
  - Multivariate as soon as the classifier is multivariate
  - Often computing intensive
- **Embedded methods** take the structure of the classifier into account
  - More elegant and often faster than wrappers, not always better in terms of performance
  - A way to get an insight into a black-box classifier

Further information

- LINGI2262 Machine Learning: classification and evaluation (Semester 2)
- LELEC2870 Machine Learning: regression, dimensionality reduction and data visualization (Semester 1)
- LINGI2369 Artificial Intelligence and Machine Learning Seminar (Semester 1)

Further Reading I

Guyon, I., Gunn, S., Nikarvesh, M. and Zadeh, L.A. (editors) (2006).
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(2nd edition), Springer.

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Bioinformatics, Vol. 26 (3), pp. 392-398.

Bolstad, B.M., Irizarry, R.A., Astrand, M. and Speed, T.P. (2003)
A comparison of normalization methods for high density oligonucleotide array data based on variance and bias
Bioinformatics, Vol. 19 (2), pp. 185-193.

Further Reading II

Guyon, I., Weston, J., Barnhill, S., and Vapnik, V. (2002).
Gene selection for cancer classification using support vector machines.
Machine learning, **46**, 389–422.

Peng, H., Long, F., and Ding, C. (2005).
Feature selection based on mutual information criteria of max-dependency, max-relevance, and min-redundancy.
IEEE Transactions on Pattern Analysis and Machine Intelligence, Vol. 27, N° 8, pp. 1226-1238