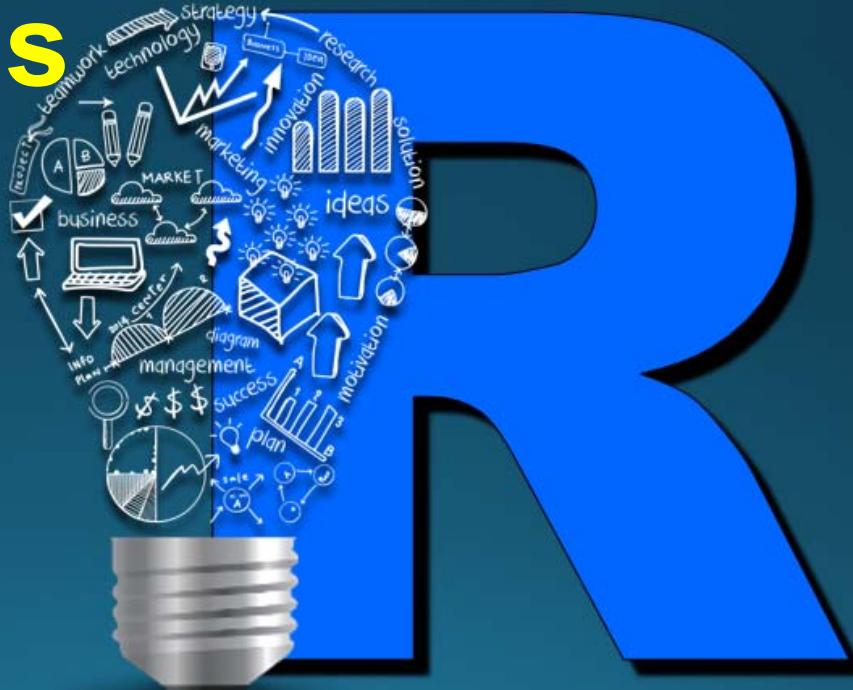


# 群集分析

# Cluster Analysis

吳漢銘  
國立政治大學 統計學系



<https://hmwu.idv.tw>



# Outlines

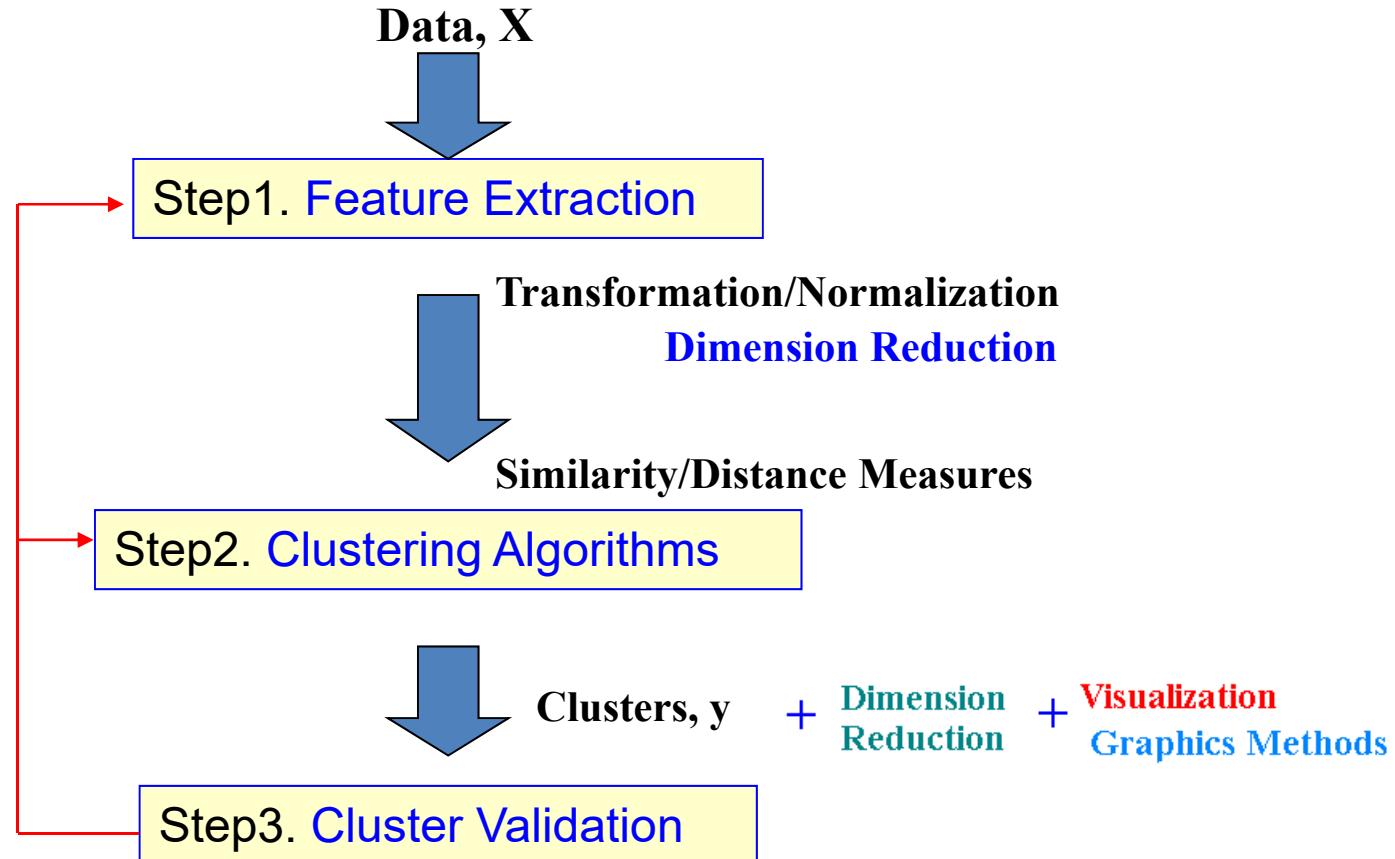
2/122

- Clustering Analysis
- Visualizing Clustering Results (DR, Heat Map)
- Distance and Similarity Measure
- **Clustering Algorithms**
  - K-Means (**K均值法**), On-Line K-Means (**線上K均值法**)
  - kmodes, k-medoid, PAM, CLARA
  - Fuzzy C-Means (**模糊C均值法**)
  - Quality Threshold Clustering (**QT群集法**)
  - Hierarchical Clustering (**階層式分群法**)
  - Self-Organizing Maps (SOM) (**自我組織相關圖**)
  - Generated Association Plots (**廣義相關圖**)
- **How Many Clusters? Cluster Validation**



# Cluster Analysis

**Group a given collection of unlabeled patterns into meaningful clusters.**



**A Good Review Paper:** Dixin Jiang, Chun Tang and Aidong Zhang, (2004), *Cluster analysis for gene expression data: a survey*, *IEEE Transactions on Knowledge and Data Engineering* 16(11), 1370- 1386.

# Hierarchical Clustering

**Hierarchical clustering** can be performed using agglomerative and divisive approaches. The result is a tree that depicts the relationships between the objects.

- **Divisive clustering:**

- begin at step 1 with all the data in one cluster, in each subsequent step a cluster is split off, until there are n clusters.

- **Agglomerative clustering:**

- all the objects start apart.
- There are n clusters at step 0, each object forms a separate cluster.
- In each subsequent step two clusters are merged, until only one cluster is left.

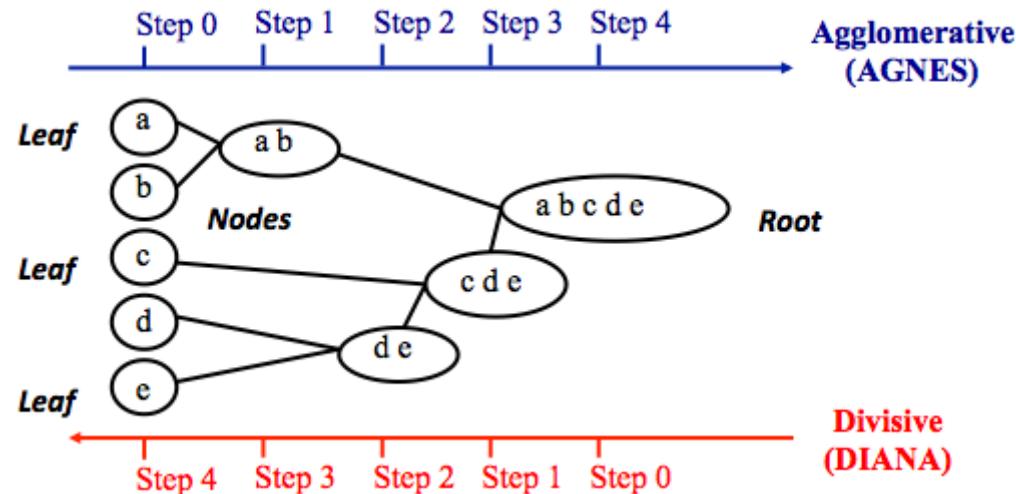


Image Source: <http://www.sthda.com/english/wiki/print.php?id=237>



# Non-Hierarchical Clustering

- 分割演算法 (Partitioning Algorithm)
  - k-means, The EM algorithm, ...
- 密度型演算法 (Density-Based Algorithm)
  - Nearest Neighbor, ...
- NOTES:
  - Only use similarities of instances, without any other requirement of the data.
  - The aim is to find groups such that instances in a group are more similar to each other than instances in different groups.
  - Make sure that all attribute have the same scale.



# After Clustering

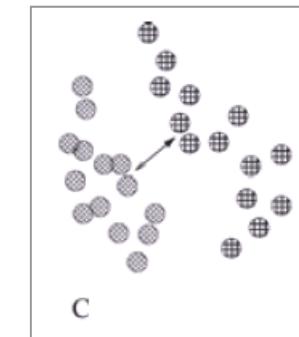
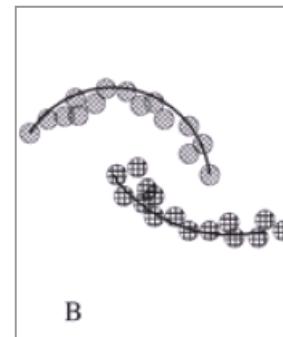
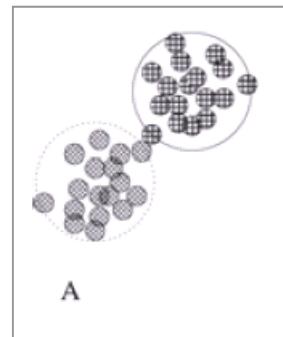
- Supervised learning after clustering
- Dimensionality Reduction vs. Clustering
- The goal of clustering is to determine the intrinsic grouping in a set of unlabeled data.
  - **Marketing**: finding groups of customers with similar behavior given a large database of customer data containing their properties and past buying records;
  - **Biology**: classification of plants and animals given their features;
  - **Libraries**: book ordering;
  - **Insurance**: identifying groups of motor insurance policy holders with a high average claim cost; identifying frauds;
  - **City-planning**: identifying groups of houses according to their house type, value and geographical location;
  - **Earthquake studies**: clustering observed earthquake epicenters to identify dangerous zones;
  - **WWW**: document classification; clustering weblog data to discover groups of similar access patterns.

[http://www.elet.polimi.it/upload/matteucc/Clustering/tutorial\\_html/](http://www.elet.polimi.it/upload/matteucc/Clustering/tutorial_html/)



## Two Important Properties

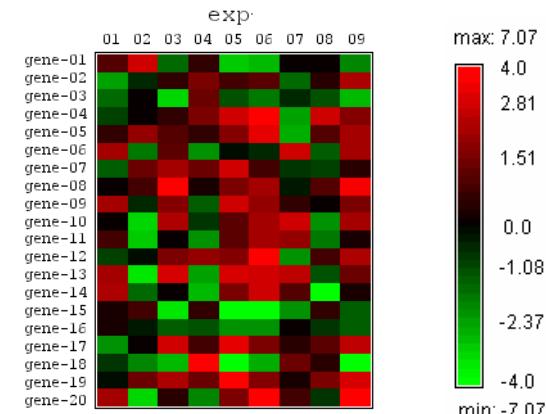
- Most of data has been organized into non-overlapping clusters.
- A good cluster should have a **small within** variance and **large between** variance.



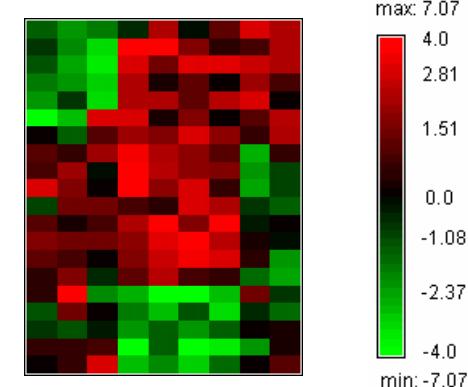
# Visualizing Clustering Results: Heat Map (1/2)



Without ordering



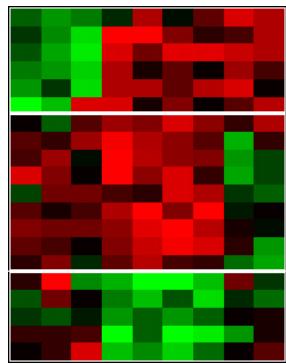
Ordering/Seriation/  
Clustering



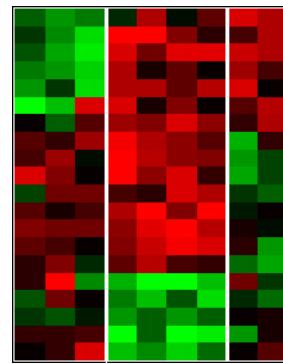
# Visualizing Clustering Results: Heat Map (2/2)



**Gene-based clustering**

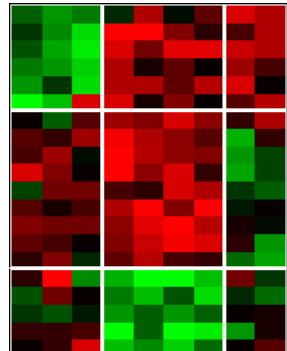


**Sample-based clustering**

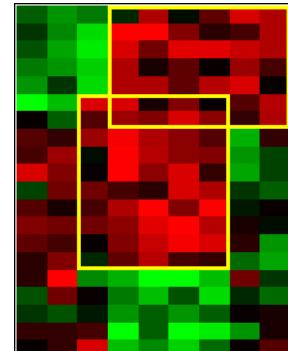


e.g., K-means, SOM, Hierarchical Clustering, Model-based clustering,...

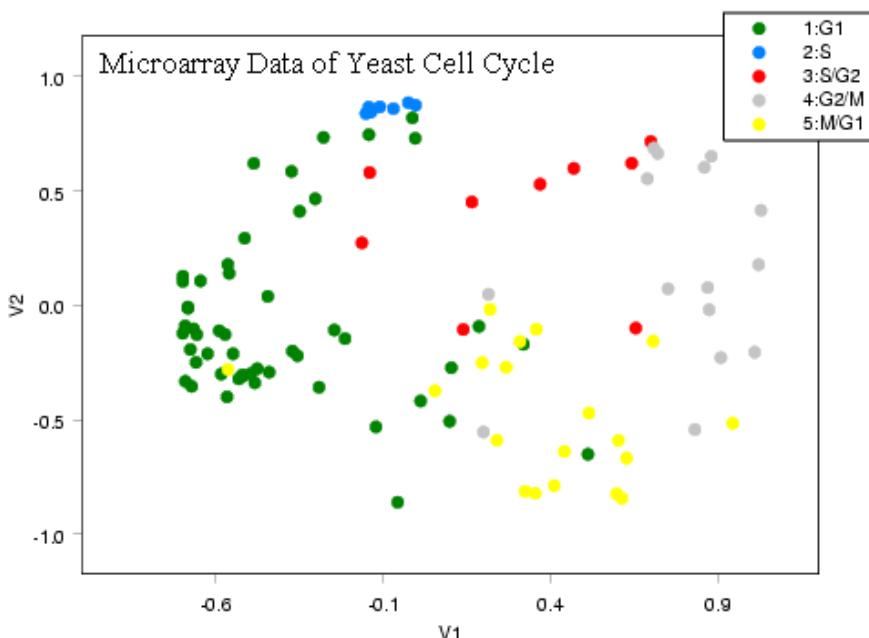
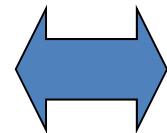
**Two-way-based clustering**



**Subspace clustering**

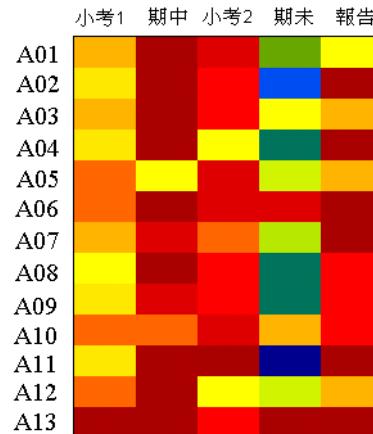


e.g., Bi-clustering

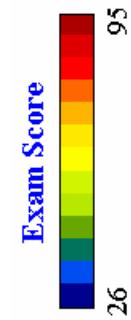


**Dimension Reduction**

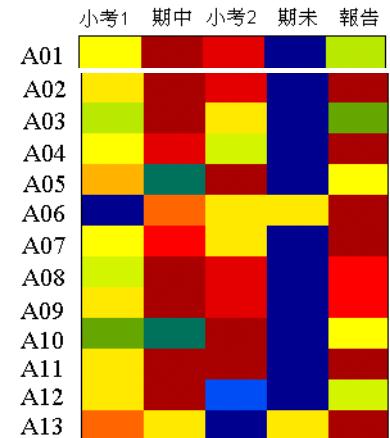
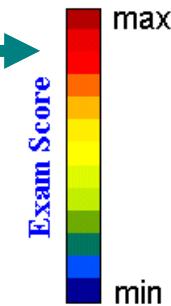
# Heat Map: Data Image, Matrix Visualization



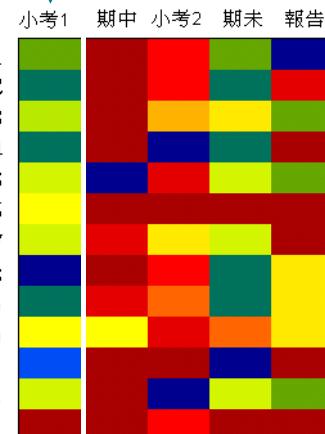
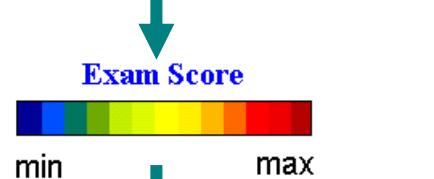
Range Matrix Condition



	A	B	C	D	E	F
1	學號	小考1	期中考	小考2	期末考	報告
2	A01	69	92	85	45	62
3	A02	66	90	83	36	90
4	A03	72	92	80	62	70
5	A04	68	90	60	37	95
6	A05	74	60	86	54	70
7	A06	77	90	88	88	95
8	A07	73	88	77	51	95
9	A08	61	90	84	40	82
10	A09	66	88	82	39	80
11	A10	76	75	87	72	80
12	A11	64	90	90	26	95
13	A12	75	90	60	55	70
14	A13	92	90	83	90	95



Range Row Condition



Range Column Condition

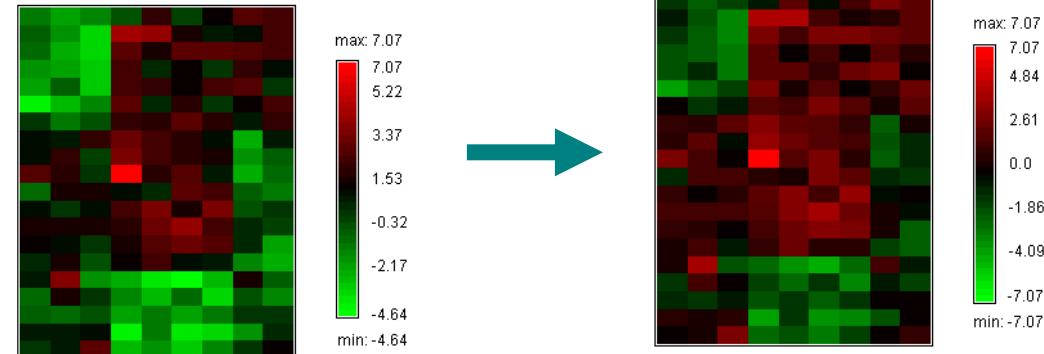
What about this one?



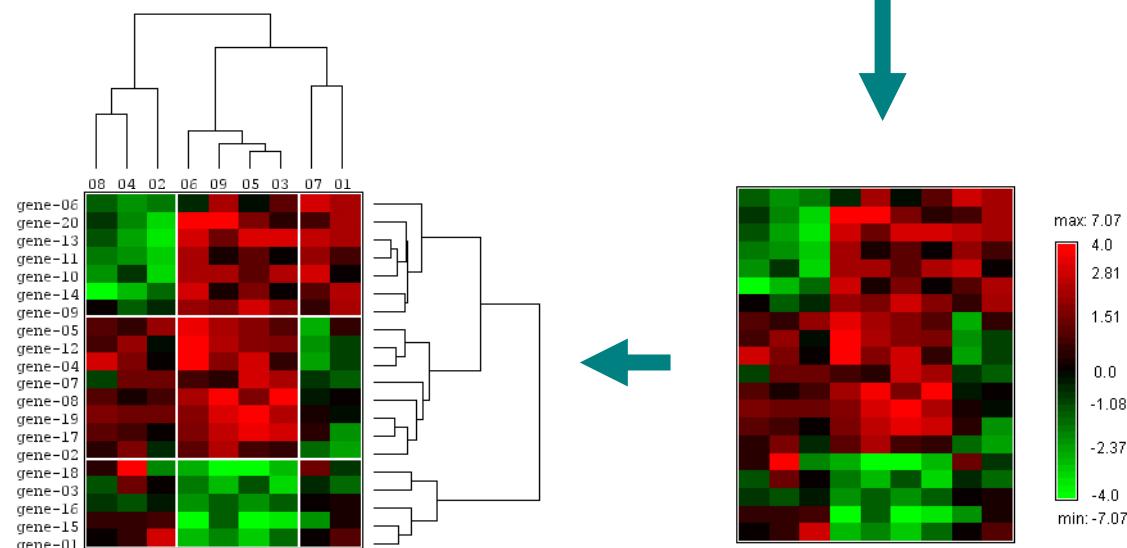


# Heat Map: Display Conditions

	A	B	C	D	E	F	G	H	I
1	-1.37	-2.30	-1.80	-0.55	2.45	-0.13	1.49	3.03	2.48
2	-0.68	-2.11	-3.42	4.67	4.57	1.75	0.61	0.92	2.52
3	-1.19	-2.49	-3.66	3.14	1.70	3.29	3.33	2.92	2.48
4	-1.93	-2.28	-3.16	2.51	0.32	1.49	0.21	2.20	1.03
5	-2.21	-0.79	-3.29	2.55	2.44	1.45	2.68	3.03	0.19
6	-4.14	-2.91	-1.64	3.21	0.37	1.93	0.14	1.27	2.67
7	0.21	-1.36	-0.44	2.22	1.85	3.11	2.03	0.67	2.40
8	1.13	0.79	2.25	3.65	2.52	2.09	1.13	-2.59	0.67
9	0.95	2.33	-0.07	3.89	2.72	2.13	1.75	-2.17	-0.90
10	3.04	1.85	0.21	7.07	2.01	3.05	0.76	-2.58	-1.04
11	-1.02	1.65	1.53	0.95	0.60	3.12	2.52	-0.77	-1.40
12	1.21	0.24	1.04	2.50	3.89	1.81	3.98	-0.33	0.11
13	1.74	1.60	1.70	2.02	3.45	4.46	2.69	0.41	-0.09
14	1.34	1.06	0.06	1.81	2.90	3.64	3.04	0.49	-2.33
15	0.57	1.81	-0.47	1.40	2.70	0.99	0.82	-1.61	-2.56
16	0.61	4.22	-2.03	-2.61	-4.00	-4.64	-2.92	1.55	-0.71
17	-1.13	1.64	0.01	-1.77	-2.85	-1.24	-3.41	-0.59	-1.64
18	-0.86	-1.17	-0.41	-2.20	-1.30	-2.37	-1.41	0.08	0.25
19	0.75	0.66	1.04	-4.26	-1.41	-3.99	-3.53	-2.17	0.34
20	0.15	0.68	3.18	-2.86	-2.01	-3.18	-1.58	0.10	1.28



Center Matrix Condition





# fviz\_cluster {factoextra}

## Visualize Clustering Results

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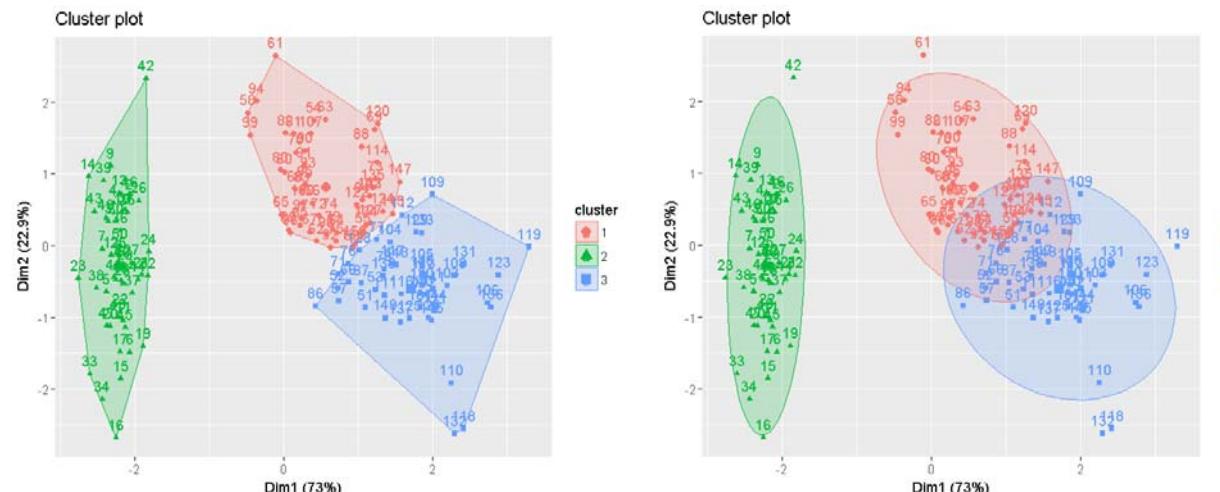
### Usage

```
fviz_cluster(object, data = NULL, choose.vars = NULL, stand = TRUE,
  axes = c(1, 2), geom = c("point", "text"), repel = FALSE,
  show.clust.cent = TRUE, ellipse = TRUE, ellipse.type = "convex",
  ellipse.level = 0.95, ellipse.alpha = 0.2, shape = NULL,
  pointsize = 1.5, labelsize = 12, main = "Cluster plot", xlab = NULL,
  ylab = NULL, outlier.color = "black", outlier.shape = 19,
  ggtheme = theme_grey(), ...)
```

**fviz\_cluster** provides ggplot2-based elegant visualization of partitioning methods including: **kmeans** {stats}; **pam**, **clara** and **fanny** {cluster}; **dbscan** {fpc}; **Mclust** {mclust}; **HCPC** {FactoMineR}; **hkmeans** {factoextra}.

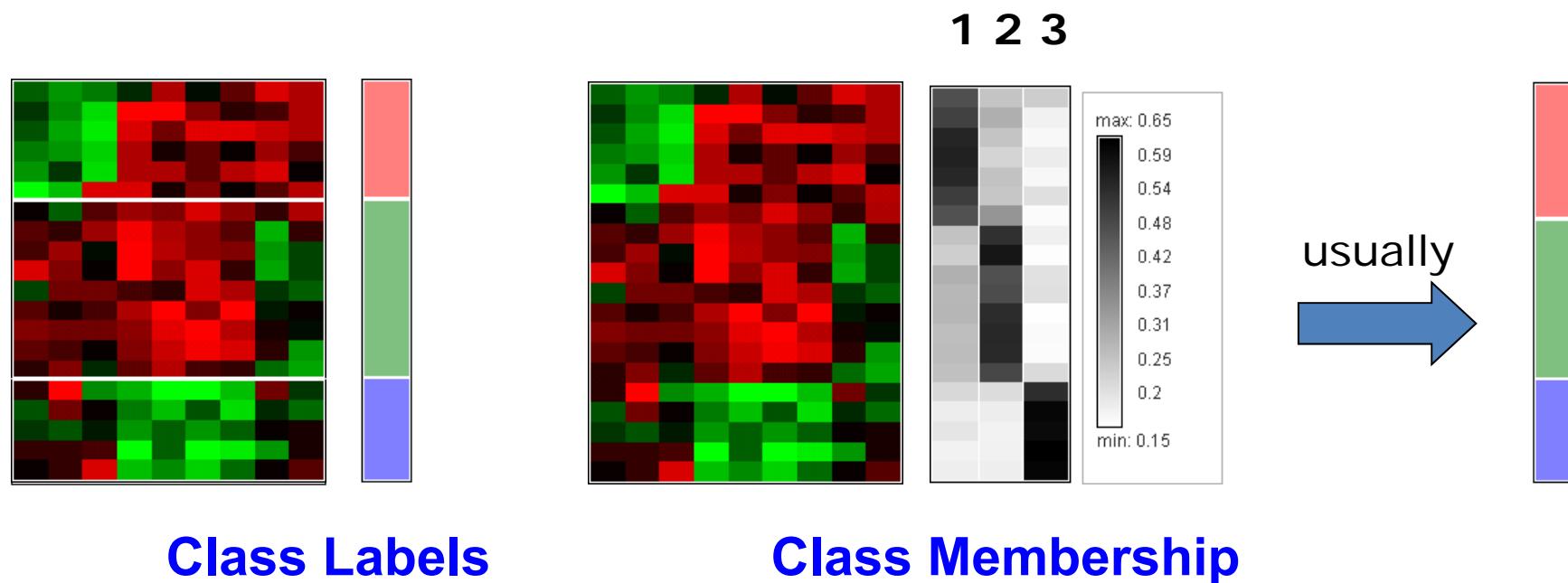
Observations are represented by points in the plot, using **principal components** if `ncol(data) > 2`. An ellipse is drawn around each cluster.

```
> iris.scaled <- scale(iris[, -5])
> iris.km <- kmeans(iris.scaled, centers=3)
> fviz_cluster(iris.km, iris[, -5])
> fviz_cluster(iris.km, iris[, -5], ellipse.type = "norm")
```



# Hard & Soft Clustering

- Hard Clustering: K-means, SOM, Hierarchical Clustering
- Soft Clustering: Fuzzy c-means, model-based clustering, ...





# R functions and packages for cluster analysis

Package	Functions	Description
<i>cclust</i>		Convex clustering methods
<i>class</i>	<i>SOM</i>	Self-organizing maps
<i>cluster</i>	<i>agnes</i> <i>clara</i> <i>diana</i> <i>fanny</i> <i>mona</i> <i>pam</i>	AGglomerative NESting Clustering LARge Applications DIvisive ANAlysis Fuzzy Analysis MONothetic Analysis Partitioning Around Medoids
<i>e1071</i>	<i>bclust</i> <i>cmeans</i>	Bagged clustering Fuzzy C-means clustering
<i>flexmix</i>		Flexible mixture modeling
<i>fpc</i>		Fixed point clusters, clusterwise regression and discriminant plots
<i>hopach</i>	<i>hopach</i> , <i>boothopach</i>	Hierarchical Ordered Partitioning and Collapsing Hybrid
<i>mclust</i>		Model-based cluster analysis
<i>stats</i>	<i>hclust</i> , <i>cophenetic</i> <i>heatmap</i>	Hierarchical clustering Heatmaps with row and column dendograms
	<i>kmeans</i>	<i>k</i> -means

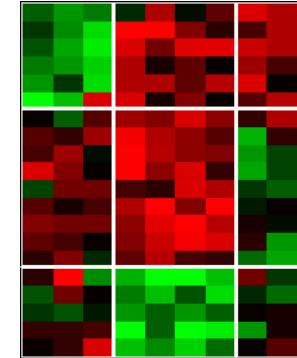
K.S. Pollard, M.J. van der Laan (2005). **Cluster Analysis of Genomic Data with Applications in R**. in *Bioinformatics and Computational Biology Solutions Using R and Bioconductor*, Springer.



# Clustering Analysis in Microarray Experiments

## Goals

- Find natural classes in the data
- Identify new classes/gene correlations
- Refine existing taxonomies
- Support biological analysis/discovery
  
- cluster genes based on samples profiles
- cluster samples based on genes profiles



## Hypothesis:

- genes with similar biological function have similar expression profiles.

## Characteristic of Microarray Data:

- High-throughput (large-scale)
- Noise
- Outliers
- Biological Knowledge

# Distance and Similarity Measure



Cov	x1	x2	x3	x4	x p
x1	1.00	0.48	0.10	-0.10	-0.28
x2	0.48	1.00	0.41	0.22	-0.23
x3	0.10	0.41	1.00	0.36	-0.05
x4	-0.10	0.22	0.36	1.00	0.10
x p	-0.28	-0.23	-0.05	0.10	1.00

Proximity Matrix

Data Matrix

	x1	x2	x3	x4	...	x p
subject01	-0.48	-0.42	0.87	0.92		-0.18
subject02	-0.39	-0.58	1.08	1.21		-0.33
subject03	0.87	0.25	-0.17	0.18		-0.44
subject04	1.57	1.03	1.22	0.31		-0.49
subject05	-1.15	-0.86	1.21	1.62		0.16
subject06	0.04	-0.12	0.31	0.16		-0.06
subject07	2.95	0.45	-0.40	-0.66		-0.38
subject08	-1.22	-0.74	1.34	1.50		0.29
subject09	-0.73	-1.06	-0.78	-0.02		0.44
subject10	-0.58	-0.40	0.13	0.58		0.02
subject11	-0.50	-0.42	0.66	1.05		0.06
subject12	-0.86	-0.29	0.42	0.46		0.10
subject13	-0.16	0.29	0.17	-0.28		-0.55
subject14	-0.36	-0.03	-0.03	-0.08		-0.25
subject15	-0.72	-0.85	0.54	1.04		0.24
subject16	-0.78	-0.52	0.26	0.20		0.48
subject17	0.60	-0.55	0.41	0.45		-0.86
⋮						
subject n	-2.29	-0.64	0.77	1.60		0.55
mean	0.07	-0.04	0.44	0.31	...	-0.21

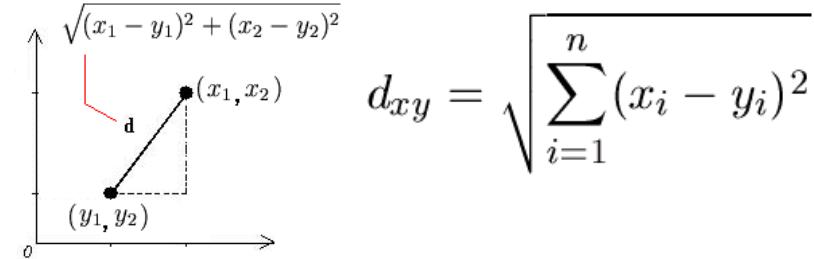
## Pearson Correlation Coefficient

$$r_{xy} = \frac{\sum_{i=1}^n (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^n (x_i - \bar{x})^2} \sqrt{\sum_{i=1}^n (y_i - \bar{y})^2}}$$

$$x = (x_1, x_2, \dots, x_n)$$

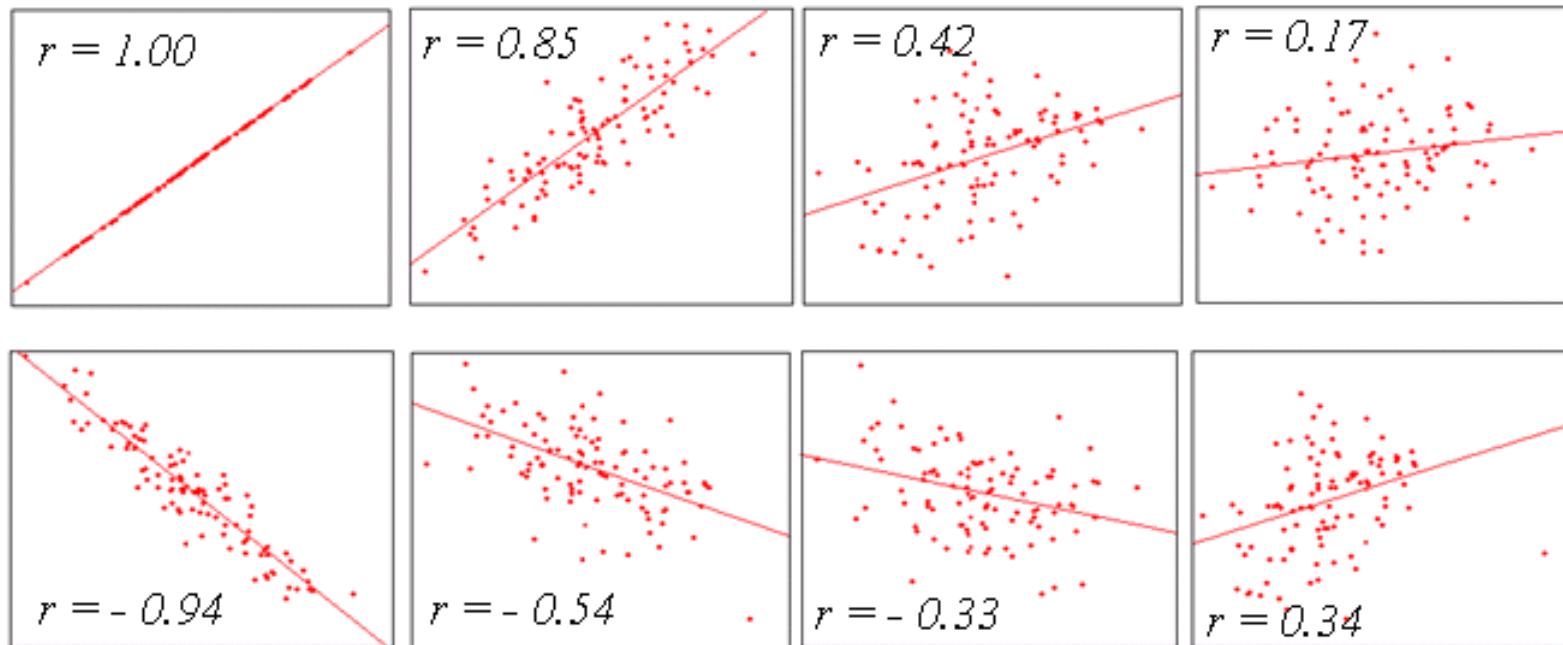
$$y = (y_1, y_2, \dots, y_n)$$

## Euclidean Distance



- The standard transformation from a similarity matrix  $C$  to a distance matrix  $D$  is given by  $d_{rs} = (c_{rr} - 2c_{rs} + c_{ss})^{1/2}$ .
- (Eisen *et al.* 1998)  $d_{rs} = 1 - c_{rs}$
- Other transformations  
(Chatfield and Collins 1980, Section 10.2)

# Pearson Correlation Coefficient



```
dist(x, method = "euclidean", diag = FALSE, upper = FALSE, p = 2)
  method: one of "euclidean", "maximum", "manhattan", "canberra", "binary"
or "minkowski" distance measure.
cor(x, y = NULL, use = "everything",
  method = c("pearson", "kendall", "spearman"))
```



# More Similarity Measures (1/4)

## Dissimilarity/Similarity Measure for Quantitative Data

Similarity	Formula
<b>Pearson correlation</b>	$s(i, j) = \frac{\text{cov}(x_i, x_j)}{\sqrt{\text{var}(x_i) \text{var}(x_j)}}$
<b>Spearman correlation</b> ( $r_i$ is ranked $x_i$ )	$s(i, j) = \frac{\text{cov}(r_i, r_j)}{\sqrt{\text{var}(r_i) \text{var}(r_j)}}$
<b>Kendall's Tau</b>	$s(i, j) = \frac{1}{\binom{p}{2}} \sum_{k \neq k'} \text{sign} [(x_{ik} - x_{ik'}) (x_{jk} - x_{jk'})]$

All indices range from -1 to +1

### Kendall's tau

Two pairs of observation  $(x_i, y_i)$  and  $(x_j, y_j)$

- C: concordant pair:  $(x_j - x_i)(y_j - y_i) > 0$
- D: discordant pair:  $(x_j - x_i)(y_j - y_i) < 0$
- tie:

$E_y$ : extra  $y$  pair in  $x$ 's:  $(x_j - x_i) = 0$

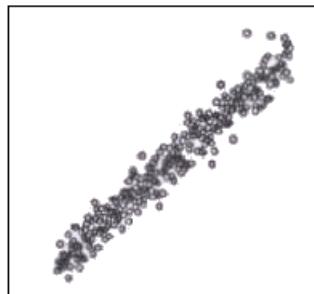
$E_x$ : extra  $x$  pair in  $y$ 's:  $(y_j - y_i) = 0$

$$\tau = \frac{C - D}{\sqrt{C + D - E_y} \sqrt{C + D - E_x}}$$

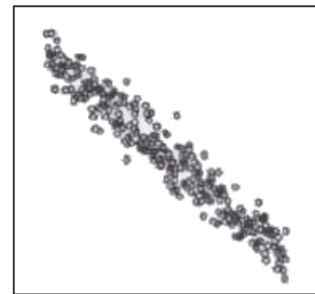


# More Similarity Measures (2/4)

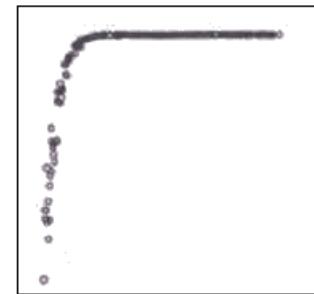
measures the strength of a linear relationship



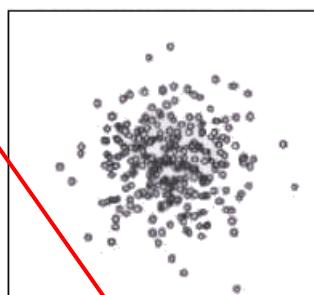
(a) positive linear correlation



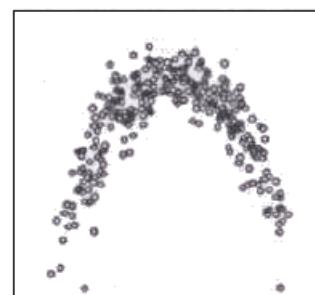
(b) negative linear correlation



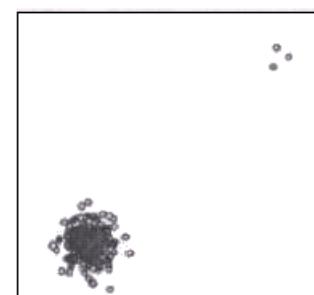
(c) nonlinear relationships



(d) no relationship



(e) nonlinear relationships



(f) no relationship with outliers

measure any monotonic relationship between two variables

non-monotonic, fail to detect the existence of a relationship

Data	Pearson's rho	Spearman's rho	Kendall's tau
(a)	0.98	0.98	0.87
(b)	-0.98	-0.98	-0.87
(c)	0.50	0.99	0.98
(d)	-0.02	-0.03	-0.02
(e)	-0.06	-0.02	-0.02
(f)	0.68	0.00	0.00

more robust



# More Similarity Measures (3/4)

- Pearson's rho measures the strength of a linear relationship [(a), (b)].
- Spearman's rho and Kendall's tau measure any monotonic relationship between two variables [(a), (b) ,(c)].
- If the relationship between the two variables is non-monotonic, all three correlation coefficients fail to detect the existence of a relationship [(e)].
- Both Spearman's rho and Kendall's tau are rank-based non-parametric measures of association between variable X and Y.
- The **rank-based** correlation coefficients are **more robust against outliers**.
- Algorithm they use different logic for computing the correlation coefficient, they seldom lead to markedly different conclusions (Siegel and Castellan, 1988).



# More Similarity Measures (4/4)

Pearson Correlation	Calculate the mean of all elements in vector <b>a</b> . Then subtract that value from each element in <b>a</b> . Call the resulting vector <b>A</b> . Do the same for <b>b</b> to make a vector <b>B</b> . $\text{Result} = \mathbf{A} \cdot \mathbf{B} / (\ \mathbf{A}\  \ \mathbf{B}\ )$
Distance	Distance is not a correlation at all, but a measurement of dissimilarity. Distance is the measurement of Euclidian distance between the expression profile for gene <b>A</b> (defined by its expression values for each point in N-dimensional space, where N is the number of conditions with data in your experiment) and the expression profile for gene <b>B</b> . $\text{Result} =  \mathbf{a} - \mathbf{b}  \text{ divided by the square root of the number of conditions with data}$
Spearman Correlation	Order all the elements of vector <b>a</b> . Use this order to assign a rank to each element of <b>a</b> . Make a new vector <b>a'</b> where the $i^{\text{th}}$ element in <b>a'</b> is the rank of $a_i$ in <b>a</b> . Now make a vector <b>A</b> from <b>a'</b> in the same way as <b>A</b> was made from <b>a</b> in the Pearson Correlation. Similarly, make a vector <b>B</b> from <b>b</b> . $\text{Result} = \mathbf{A} \cdot \mathbf{B} / (\ \mathbf{A}\  \ \mathbf{B}\ )$

Source: Chapter 14, GeneSpring Manual 7.2

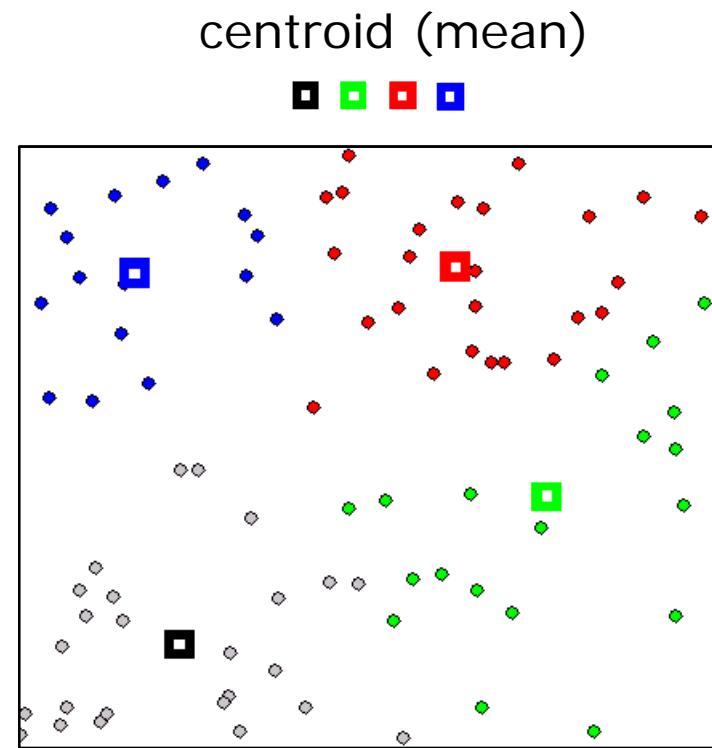
# K-Means Clustering (1/3)

- K-means is a **partition methods** for clustering.
- Data are classified into **k groups** as specified by the user.
- Two different clusters cannot have any objects in common, and the k groups together constitute the full data set.

## The K-Means Algorithm

1. The data points are randomly assigned to one of the K clusters.
2. The position of the K centroids are determined (initial group centroids).
3. For each data point:
  - Calculate the distance from the data point to each cluster.
  - Assign data point to the cluster that has the closest centroid.
4. Repeat the above step until the centroids no longer move.

The choice of initial partition can greatly affect the final clusters that result.



*Converged*



# K-Means Clustering (2/3)

- The best reference vectors are those that minimize the total reconstruction error.
- Distanvatge:
  - a local search.
  - Final  $\mathbf{m}_i$  highly depend on the initial  $\mathbf{m}_i$ .

## (1) initialize

Initialize  $\mathbf{m}_i, i = 1, \dots, k$ , for example, to  $k$  random  $\mathbf{x}^t$

Repeat

## (2) minimize

For all  $\mathbf{x}^t \in \mathcal{X}$

$$b_i^t \leftarrow \begin{cases} 1 & \text{if } \|\mathbf{x}^t - \mathbf{m}_i\| = \min_j \|\mathbf{x}^t - \mathbf{m}_j\| \\ 0 & \text{otherwise} \end{cases}$$

## (3) estimate

For all  $\mathbf{m}_i, i = 1, \dots, k$

$$\mathbf{m}_i \leftarrow \sum_t b_i^t \mathbf{x}^t / \sum_t b_i^t$$

## (4) stabilize

Until  $\mathbf{m}_i$  converge



# K-Means Clustering (3/3)

- When  $X_t$  is represented by  $\mathbf{m}_i$ , there is an **error** that is proportional to the distance.
- Find  $k$  **reference vectors**  $\mathbf{m}_j$  (prototypes/codebook vectors/codewords) which best represent data.
- K-means clustering a special case of the EM algorithm.
- Use nearest (most similar) reference:

$$\|\mathbf{x}^t - \mathbf{m}_i\| = \min_j \|\mathbf{x}^t - \mathbf{m}_j\|$$

- Reconstruction error

$$E(\{\mathbf{m}_i\}_{i=1}^k | \mathcal{X}) = \sum_t \sum_i b_i^t \|\mathbf{x}^t - \mathbf{m}_i\|^2$$

$$b_i^t = \begin{cases} 1 & \text{if } \|\mathbf{x}^t - \mathbf{m}_i\| = \min_j \|\mathbf{x}^t - \mathbf{m}_j\| \\ 0 & \text{otherwise} \end{cases}$$

## K-means for clustering

=> find groups in the data  
=> groups are represented by their centers.

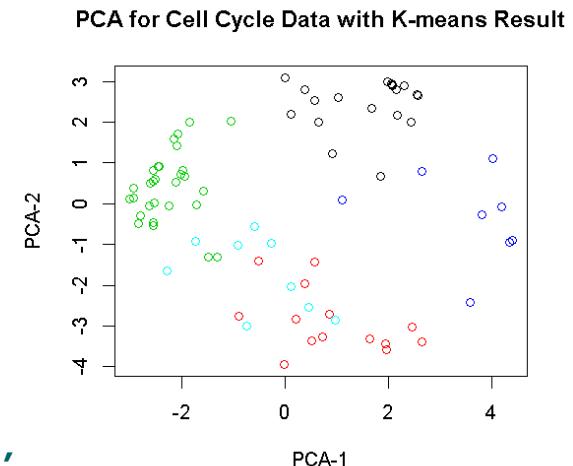
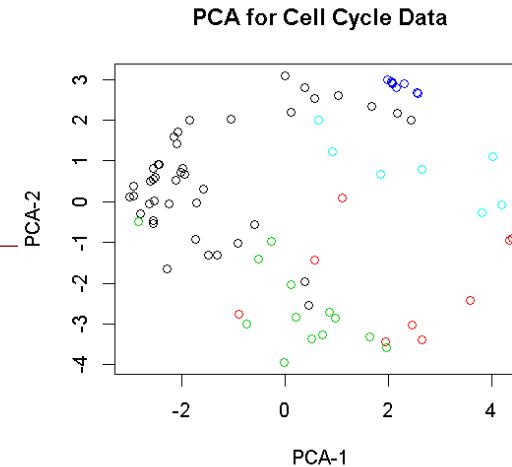


# K-Means' Results Shown on the DR Space

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```
kmeans(x, centers, iter.max = 10, nstart = 1,
        algorithm = c("Hartigan-Wong", "Lloyd", "Forgy",
                      "MacQueen"), trace=FALSE)
## S3 method for class 'kmeans'
fitted(object, method = c("centers", "classes"), ...)
```

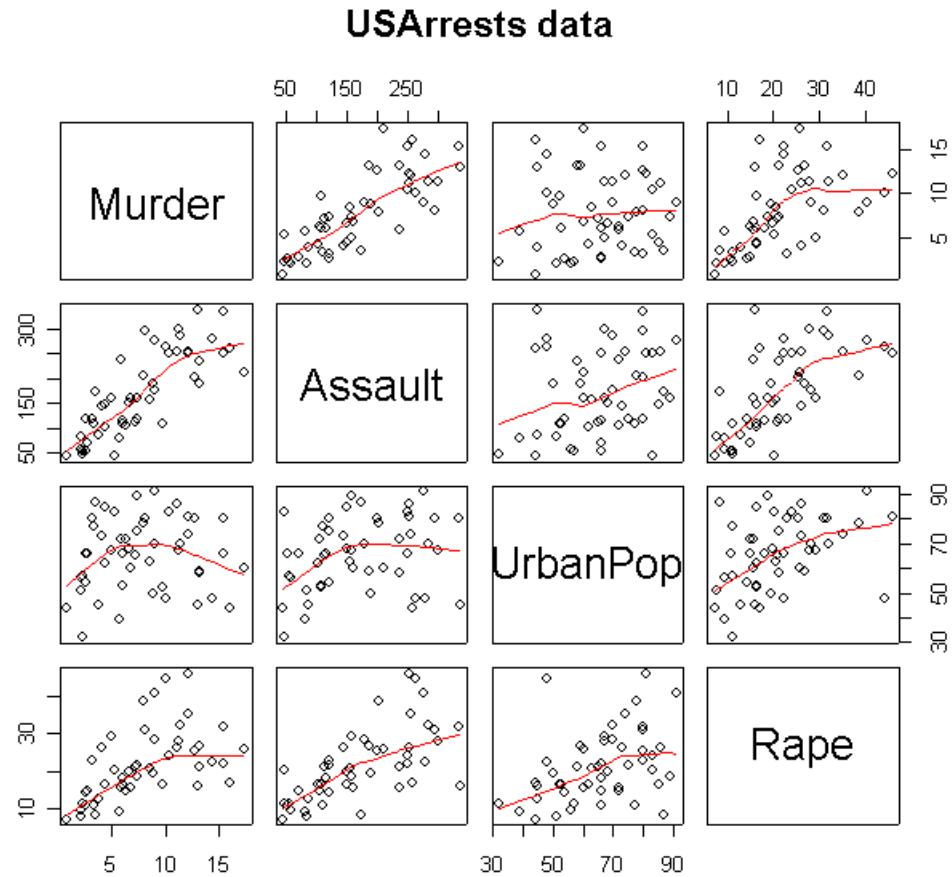
```
> no.group <- 5
> no.iter <- 20
> cell.matrix <- read.table("YeastCellCycle_alpha.txt",
+ header=TRUE, row.names=1)
> n <- dim(cell.matrix)[1]
> p <- dim(cell.matrix)[2]-1
> cell.data <- cell.matrix[,2:p+1]
> gene.phase <- cell.matrix[,1]
> phase <- unique(gene.phase)
> phase.name <- c("G1", "S", "S/G2", "G2/M", "M/G1")
> cell.sdata <- t(scale(t(cell.data)))
>
> cell.kmeans <- kmeans(cell.sdata, no.group, no.iter)
> plot(cell.sdata[,1:4], col = cell.kmeans$cluster)
> ## PCA
> pca.dim <- princomp(cell.sdata)$scores
> plot(pca.dim[,1], pca.dim[,2], main="PCA for Cell Cycle Data",
+ xlab="PCA-1", ylab="PCA-2", col=gene.phase)
> plot(pca.dim[,1], pca.dim[,2], main="PCA for Cell Cycle Data with K-means Result",
+ xlab="PCA-1", ylab="PCA-2", col=cell.kmeans$cluster)
```





# Example: Violent Crime Rates by US State

- This data set contains statistics, in arrests per 100,000 residents for assault, murder, and rape in each of the 50 US states in 1973. Also given is the percent of the population living in urban areas.
- A data frame with 50 observations on 4 variables.
- [,1] Murder arrests (per 100,000)
- [,2] Assault arrests (per 100,000)
- [,3] Percent urban population
- [,4] Rape arrests (per 100,000)



```
data(USArests)
pairs(USArests, panel = panel.smooth, main = "USArests data")
```

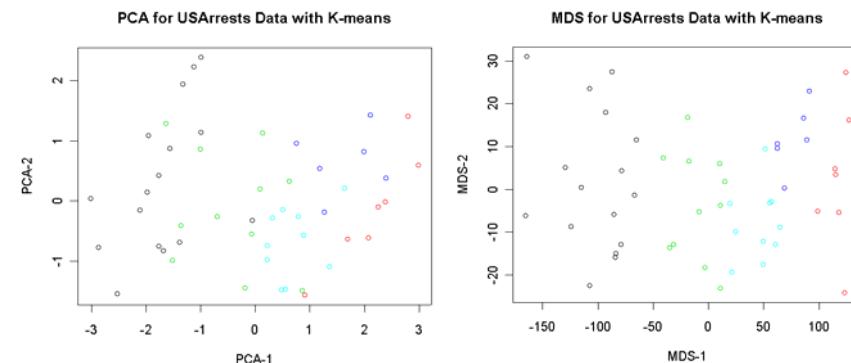
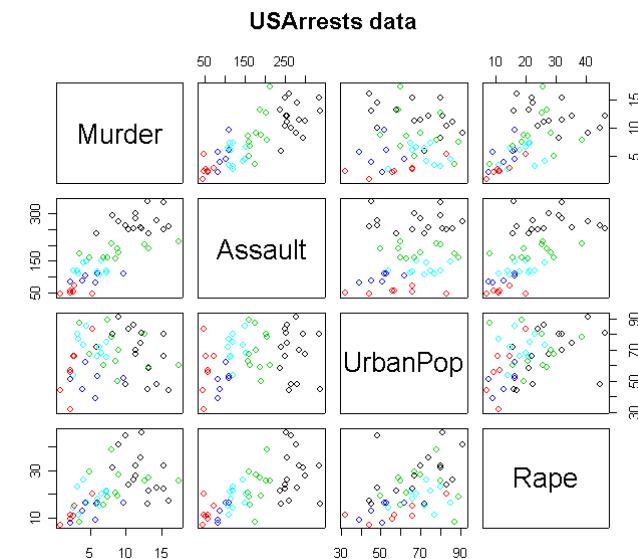


# R: kmeans

```
no.group <- 5
no.iter <- 20
USArrests.kmeans <- kmeans(USArrests, no.group, no.iter)
plot(USArrests, col = USArrests.kmeans$cluster,
     main = "K-means: USArrests data")

## PCA
USArrests.pca <- princomp(USArrests, cor=TRUE, scores=TRUE)
pca.dim1 <- USArrests.pca$scores[,1]
pca.dim2 <- USArrests.pca$scores[,2]
plot(pca.dim1, pca.dim2, main="PCA for USArrests Data
with K-means", xlab="PCA-1", ylab="PCA-2",
     col=USArrests.kmeans$cluster)

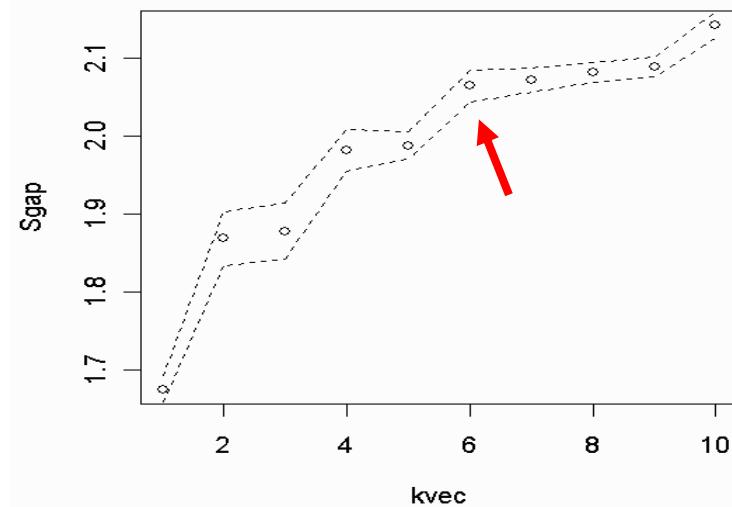
## MDS
USArrests.mds<- cmdscale(dist(USArrests))
mds.dim1 <- USArrests.mds[,1]
mds.dim2 <- USArrests.mds[,2]
plot(mds.dim1, mds.dim2, xlab="MDS-1", ylab="MDS-2", main="MDS for USArrests Data with
K-means", col = USArrests.kmeans$cluster)
```





# Example

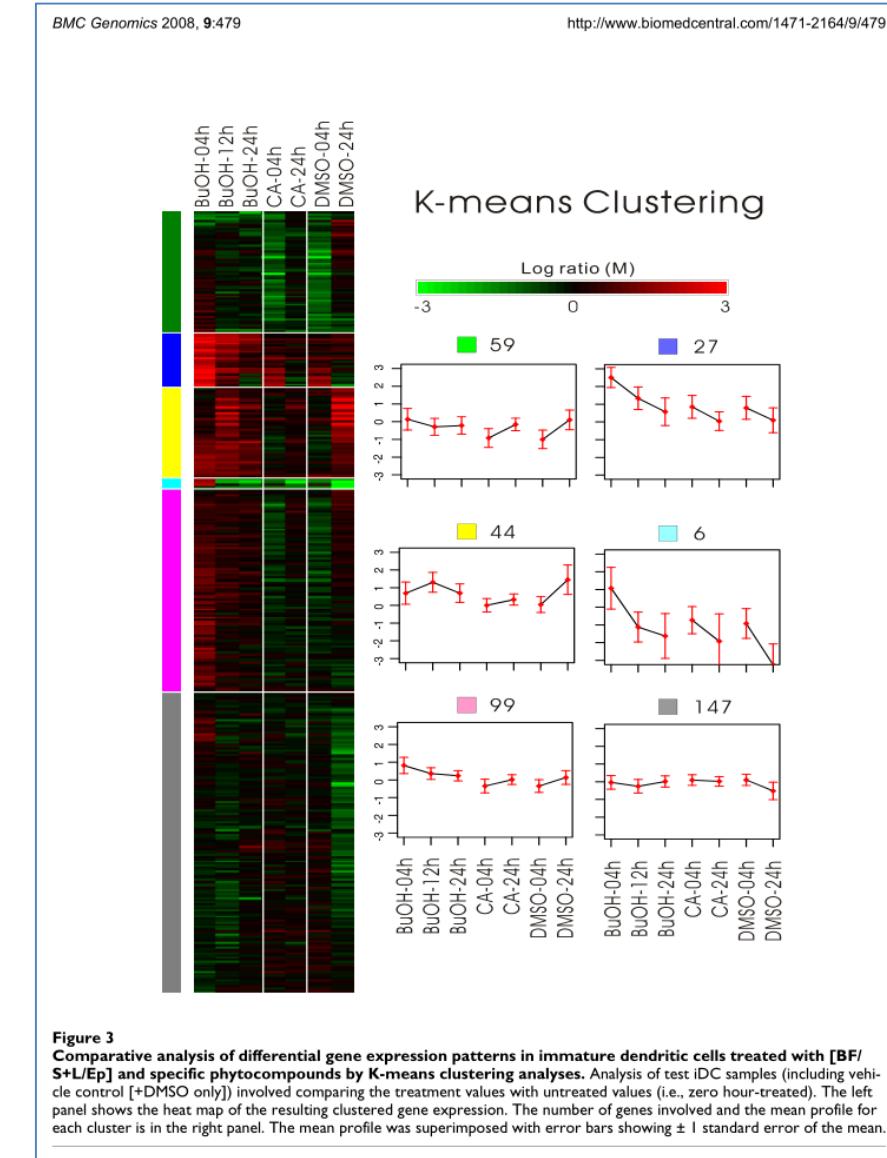
- Data  
Baseline: Culture Medium (CM-00h)  
OH-04h, OH-12h, OH-24h  
CA-04h, CA-24h  
SO-04h, SO-24h
- A set of 359 genes was selected for clustering.



*J. R. Statist. Soc. B (2001)  
63, Part 2, pp. 411–423*

## Estimating the number of clusters in a data set via the gap statistic

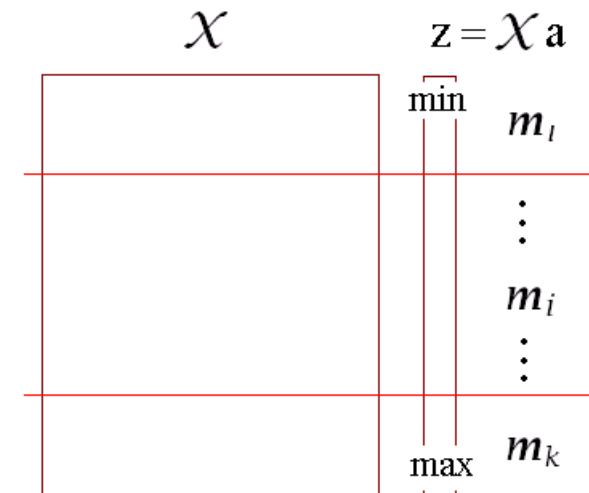
Robert Tibshirani, Guenther Walther and Trevor Hastie  
Stanford University, USA





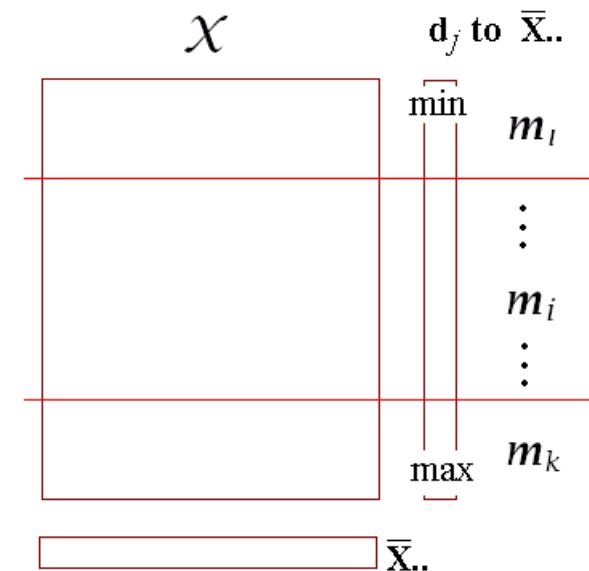
# Initialization of K-means

1. Randomly select k instances from X.
2.  $\text{mean}\{X\} + (\text{small random vector})_i$
3.  $z=Xa$  (PCA).
4. (1) ordering the distances of data points by sample means,  
(2)  $\{1+n(G_i-1)/K\}$ -th point is selected to be the initial cluster centroid.



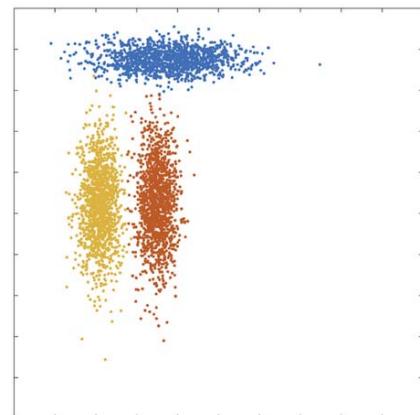
## Leader Cluster Algorithm

- Incremental: an instance far away from existing  $m_i$   
=> new center at that point
- A center covers a large number of instance  
=> split into two centers
- A center cover too few instance  
=> removed

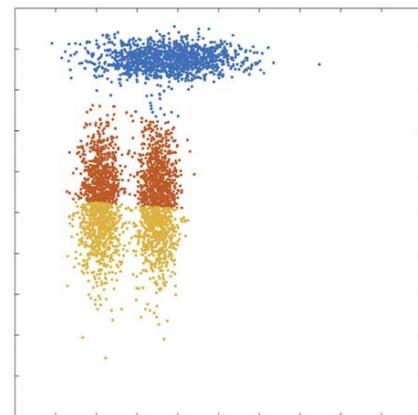
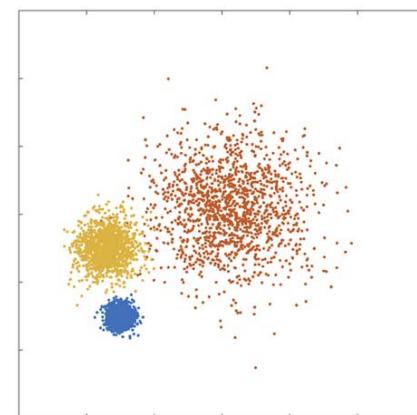


# Properties of K-Means

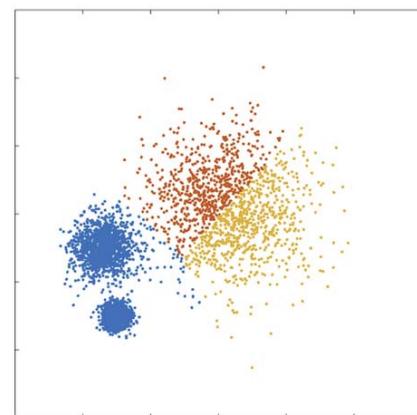
- K-means is by far the most popular algorithm due to its interpretability, easy construction, and appealing computing speed.
- It aims at minimizing the within-cluster variability, given a **pre-specified number of data groups**
- The use of **Euclidean** distances at Step 1 implies that the performance of the algorithm is optimal when clusters have approximately **spherical shapes** and **similar sizes**.



(a) Generated synthetic data

(b) *K*-means

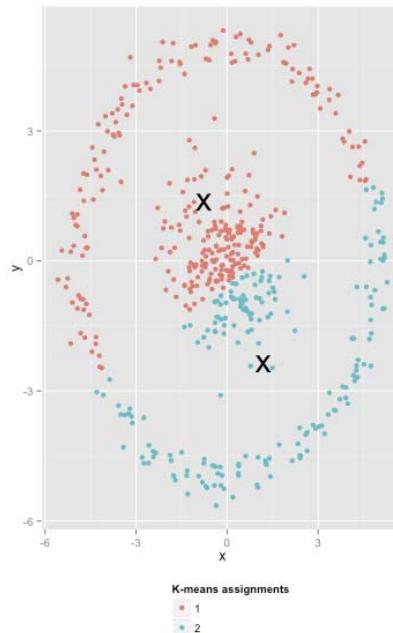
(a) Generated synthetic data

(b) *K*-means

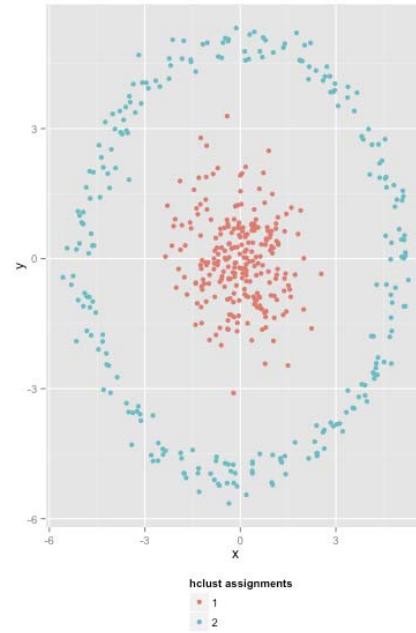


# More examples

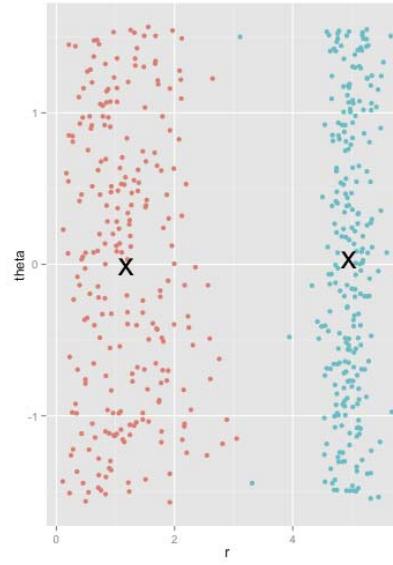
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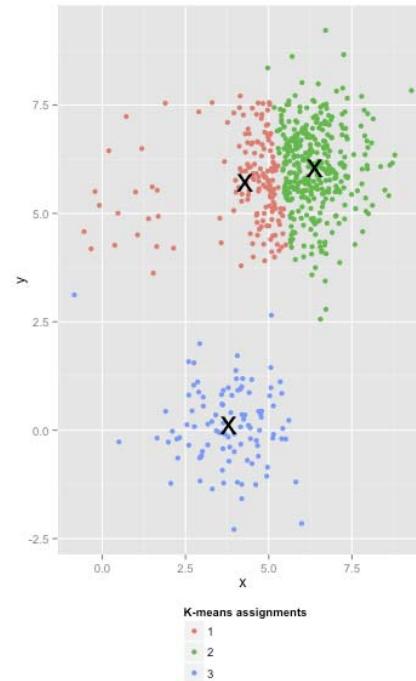
K-means



single-linkage  
hierarchical clustering



K-means  
(polar coordinates)



sizes: 20, 100, 500

<http://varianceexplained.org/r/kmeans-free-lunch/>

Assumptions are where your power comes from!



# Competitive Learning

- **Online learning:**
  - Don't have the whole sample at hand during training.
  - Receive instances **one by one** and update model parameters as we get them.
- **Competitive learning:**
  - **Groups** compete among themselves.
  - **Winner-take-all**: one group wins and gets updated, and the others are not updated at all.
- **Advantage:**
  - Do not need extra memory to store the whole training set.
  - Updates at each step are simple to implement.
  - Model adapts itself to changes of the input distribution automatically.



# Online K-Means

- **Batch algorithm:** all  $\mathbf{m}_j$ ,  $j=1,\dots,k$ , compete and  $\mathbf{m}_i$  wins the competition.
- The calculation of  $\mathbf{b}$  and update of  $\mathbf{m}$  are iterated until convergence.

- Reconstruction error

$$E(\{\mathbf{m}_i\}_{i=1}^k | \mathcal{X}) = \frac{1}{2} \sum_t \sum_i b_i^t \|\mathbf{x}^t - \mathbf{m}_i\|^2$$

$$b_i^t = \begin{cases} 1 & \text{if } \|\mathbf{x}^t - \mathbf{m}_i\| = \min_j \|\mathbf{x}^t - \mathbf{m}_j\| \\ 0 & \text{otherwise} \end{cases}$$

$$\mathbf{m}_i = \frac{\sum_t b_i^t \mathbf{x}^t}{\sum_t b_i^t}$$

- **Online algorithm:** stochastic gradient descent, considering the instances **one by one**, and doing a small update at each step, not forgetting the effect of the previous updates.

- Reconstruction error **for a single instance**

$$\begin{aligned} E(\{\mathbf{m}_i\}_{i=1}^k | \mathbf{x}^t) &= \frac{1}{2} \sum_i b_i^t \|\mathbf{x}^t - \mathbf{m}_i\|^2 \\ &= \frac{1}{2} \sum_i \sum_j b_i^t (x_j^t - m_{ij})^2 \end{aligned}$$

**Update Rule for each instance  $\mathbf{x}^t$**

$$\Delta m_{ij} = -\eta \frac{\partial E^t}{\partial m_{ij}} = \eta b_i^t (x_j^t - m_{ij})$$



# Online K-Means

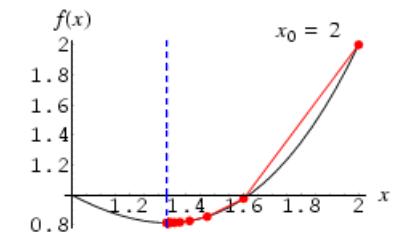
- **Gradient Descent Method:** an algorithm for finding the nearest local minimum of a function which presupposes that the gradient of the function can be computed. Starts at a point  $P_0$  and, as many times as needed, moves from  $P_i$  to  $P_{i+1}$  by minimizing along the line extending from  $P_i$  in the direction of  $-\nabla f(P_i)$ , the local downhill gradient.
- When applied to a 1-dimensional function  $f(x)$ , the method takes the form of iterating

$$x_i = x_{i+1} - \eta f'(x_{i-1})$$

from a starting point  $x_0$  for some small  $\eta > 0$  until a fixed point is reached.

- Reconstruction error **for a single instance**

$$\begin{aligned} E^t(\{\mathbf{m}_i\}_{i=1}^k | \mathbf{x}^t) &= \frac{1}{2} \sum_i b_i^t \|\mathbf{x}^t - \mathbf{m}_i\|^2 \\ &= \frac{1}{2} \sum_i \sum_j^d b_i^t (x_j^t - m_{ij})^2 \end{aligned}$$



**Update Rule for each instance  $\mathbf{x}^t$**

$$\Delta m_{ij} = -\eta \frac{\partial E^t}{\partial m_{ij}} = \eta b_i^t (x_j^t - m_{ij})$$

Initialize  $\mathbf{m}_i, i = 1, \dots, k$ , for example, to  $k$  random  $\mathbf{x}^t$   
Repeat

For all  $\mathbf{x}^t \in \mathcal{X}$  in random order

$$\begin{aligned} i &\leftarrow \arg \min_j \|\mathbf{x}^t - \mathbf{m}_j\| \\ \mathbf{m}_i &\leftarrow \mathbf{m}_i + \eta (\mathbf{x}^t - \mathbf{m}_j) \end{aligned}$$

Until  $\mathbf{m}_i$  converge

- This moves the closest center ( $b_i=1$ ) toward the input by a factor given  $\eta$ .
- The other centers have their ( $b_i=0$ ) equal to 0 and are not updated.



# Handling categorical data: k-modes (Huang 1997)

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k-modes is a variation of the K-Means Method

- Replacing means of clusters with modes.
- Using new dissimilarity measures to deal with categorical objects.  
The simple-matching distance is used to determine the dissimilarity of two objects. It is computed by counting the number of mismatches in all variables.
- Using a frequency-based method to update modes of clusters.
- A mixture of categorical and numerical data: k-prototype method.

```
> # install.packages("vcd")
> library(vcd) # Visualizing Categorical Data
> ?Arthritis # 關節炎Treatment Data
> data(Arthritis)
> str(Arthritis)
'data.frame': 84 obs. of 5 variables:
 $ ID      : int 57 46 77 17 36 23 75 39 33 55 ...
 $ Treatment: Factor w/ 2 levels "Placebo","Treated": 2 2 2 2 2 2 2 2 2 2 ...
 $ Sex      : Factor w/ 2 levels "Female","Male": 2 2 2 2 2 2 2 2 2 2 ...
 $ Age      : int 27 29 30 32 46 58 59 59 63 63 ...
 $ Improved : Ord.factor w/ 3 levels "None"><"Some"><...: 2 1 1 3 3 3 1 3 1 1 ...
> head(Arthritis)
   ID Treatment Sex Age Improved
1 57 Treated Male 27 Some
2 46 Treated Male 29 None
3 77 Treated Male 30 None
4 17 Treated Male 32 Marked
5 36 Treated Male 46 Marked
6 23 Treated Male 58 Marked
```

Huang, Z. (1997) A Fast Clustering Algorithm to Cluster Very Large Categorical Data Sets in Data Mining. in KDD: Techniques and Applications (H. Lu, H. Motoda and H. Luu, Eds.), pp. 21-34, World Scientific, Singapore.



# kmodes {klaR}

```
> # install.packages("klaR")
> library(klaR) # Classification and visualization
> res <- kmodes(Arthritis[,c(2,3,5)], modes=3)
> res
K-modes clustering with 3 clusters of sizes 31, 27, 26
```

Cluster modes:

	Treatment	Sex	Improved
1	Treated	Male	None
2	Treated	Female	Marked
3	Placebo	Female	None

Clustering vector:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	2	1
24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	1	2	2	1	1	1
47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67
1	1	1	1	1	1	3	3	3	3	2	3	3	3	3	3	3	3	3	3	3
70	71	72	73	74	75	76	77	78	79	80	81	82	83	84						
2	3	3	3	3	2	3	3	2	3	3	3	3	3	2						

Within cluster simple-matching distance by cluster:

```
[1] 25 11 7
```

Available components:

```
[1] "cluster"      "size"        "modes"        "withindiff"   "iterations"
[6] "weighted"
```

```
> table(Arthritis[,c(2,3,5)])
, , Improved = None
```

	Female	Male
Placebo	19	10
Treated	6	7

```
, , Improved = Some
```

	Female	Male
Placebo	7	0
Treated	5	2

```
, , Improved = Marked
```

	Female	Male
Placebo	6	1
Treated	16	5



# K-medoid

- A medoid (中心點) can be defined as **the object of a cluster whose average dissimilarity to all the objects in the cluster is minimal.** i.e. it is a most centrally located point in the cluster.
- K-medoid is more robust to noise and outliers as compared to k-means because it **minimizes a sum of pairwise dissimilarities** instead of a sum of squared Euclidean distances.
- PAM uses a greedy search which may not find the optimum solution, but it is faster than exhaustive search.
  - Initialize: select  $k$  of the  $n$  data points as the medoids
  - Associate each data point to the closest medoid.
  - While the cost (**sum of distances of points to their medoid**) of the configuration decreases:
    - For each medoid  $m$ , for each non-medoid data point  $o$ :
    - Swap  $m$  and  $o$ , recompute the cost.
    - If the **total cost** of the configuration increased in the previous step, undo the swap



# Partitioning Around Medoids

## Usage

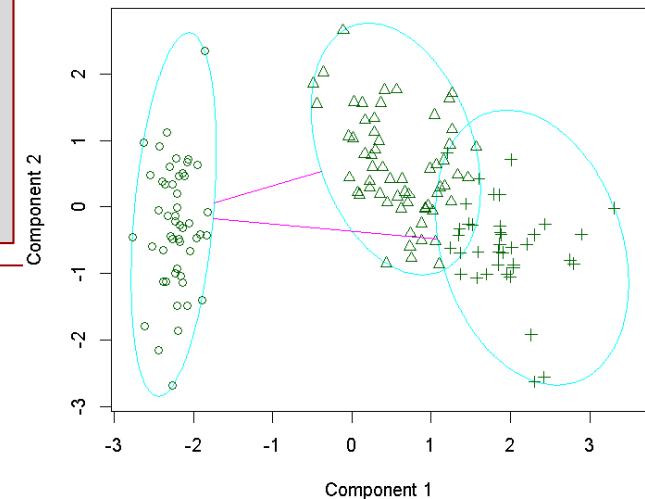
```
pam(x, k, diss = inherits(x, "dist"), metric = "euclidean",
     medoids = NULL, stand = FALSE, cluster.only = FALSE,
     do.swap = TRUE,
     keep.diss = !diss && !cluster.only && n < 100,
     keep.data = !diss && !cluster.only,
     pamonce = FALSE, trace.lev = 0)
```

```
> iris.pam <- pam(iris[,1:4], k=3)
> iris.pam
Medoids:
  ID Sepal.Length Sepal.Width Petal.Length Petal.Width
[1,]   8          5.0        3.4       1.5        0.2
[2,]  79          6.0        2.9       4.5        1.5
[3,] 113          6.8        3.0       5.5        2.1
Clustering vector:
 [1] 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
...
[149] 3 2
Objective function:
  build    swap
0.6709391 0.6542077

Available components:
[1] "medoids"      "id.med"       "clustering"    "objective"    "isolate"
[6] "clusinfo"     "silinfo"      "diss"         "call"        "data"
```

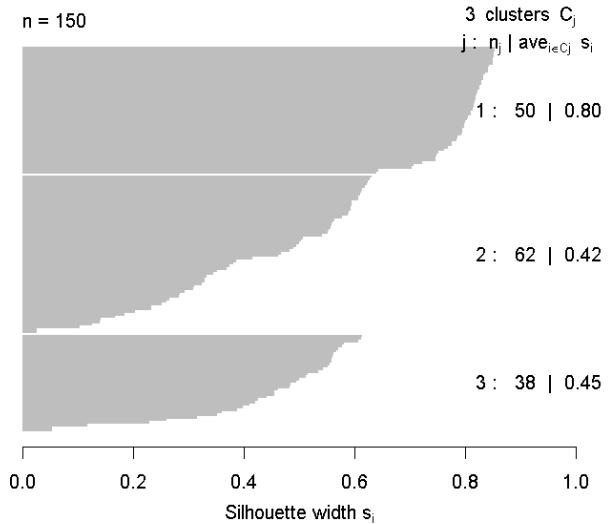
```
> plot(iris.pam)
```

(Kaufman and Rousseeuw, 1990)  
clusplot(pam(x = iris[, 1:4], k = 3))



Component 1  
These two components explain 95.81 % of the point variability.

Silhouette plot of pam(x = iris[, 1:4], k = 3)



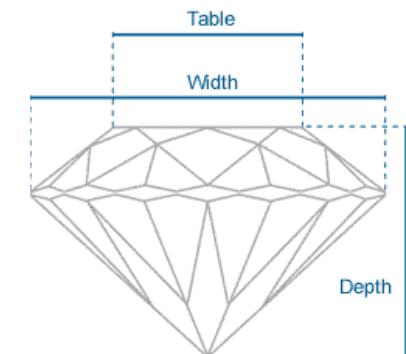
## Clustering Large Applications

- Split randomly the data sets in multiple **subsets** with fixed size (sampsiz)
- Compute **PAM** algorithm on each subset and choose the corresponding ***k*** medoids.
- Assign each observation of the **entire data set** to the closest medoid.
- Calculate the **mean of the dissimilarities** of the observations to their closest medoid.  
(This is used as a measure of the goodness of the clustering.)
- Retain the sub-dataset for which the **mean** is minimal.

### Usage

```
clara(x, k, metric = "euclidean", stand = FALSE, samples = 5,
       sampsiz = min(n, 40 + 2 * k), trace = 0, medoids.x = TRUE,
       keep.data = medoids.x, rngR = FALSE, pamLike = FALSE, correct.d = TRUE)
```

```
> require(ggplot2)
> data(diamonds)
> dim(diamonds)
[1] 53940    10
> head(diamonds)
# A tibble: 6 x 10
  carat      cut color clarity depth table price     x     y     z
  <dbl>     <ord> <ord>   <ord> <dbl> <dbl> <int> <dbl> <dbl>
1 0.23     Ideal     E     SI2    61.5    55    326  3.95  3.98  2.43
2 0.21     Premium   E     SI1     59.8    61    326  3.89  3.84  2.31
3 0.23     Good      E     VS1     56.9    65    327  4.05  4.07  2.31
4 0.29     Premium   I     VS2     62.4    58    334  4.20  4.23  2.63
5 0.31     Good      J     SI2     63.3    58    335  4.34  4.35  2.75
6 0.24 Very Good   J     VVS2    62.8    57    336  3.94  3.96  2.48
```





## Clustering Large Applications

```
> system.time(
+   clara.res <- clara(diamonds[, -(2:4)], k=10, stand=T, samples=500, pamLike=TRUE))
  user  system elapsed
  3.17    0.01   3.20
> clara.res
Call: clara(x = diamonds[, -(2:4)], k = 10, stand = T, samples = 500,      pamLike =
TRUE)
Medoids:
  carat depth table price   x   y   z
[1,]  0.38  61.7     56  1087 4.63 4.66 2.86
[2,]  0.33  61.9     59   579 4.40 4.46 2.74
[3,]  0.53  59.8     60  2542 5.28 5.35 3.18
...
[7,]  1.01  60.1     60  5902 6.46 6.51 3.90
[8,]  1.09  61.9     56  4784 6.61 6.64 4.10
[9,]  1.51  62.6     56  9234 7.32 7.27 4.57
[10,] 2.12  62.3     58 12693 8.25 8.16 5.12
Objective function: 1.410032
Clustering vector: int [1:53940] 1 2 3 2 2 2 2 1 2 3 1 1 2 1 2 2 1 1 ...
Cluster sizes: 10935 5368 4108 6187 6099 5164 4237 5800 3158 2884
Best sample:
 [1] 1052 1556 1866 3298 3359 3811 3917 4379 4531 6145 6412 7057
...
[49] 43265 43851 44593 45306 45472 46776 47279 48835 50549 52598 53314 53607

Available components:
 [1] "sample"      "medoids"      "i.med"        "clustering"   "objective"
 [6] "clusinfo"    "diss"         "call"         "silinfo"      "data"
```



# Fuzzy C-Means Clustering (Bezdek, 1981)

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Minimization of the objective function

$$J_m = \sum_{i=1}^n \sum_{k=1}^K u_{ik}^m \| \mathbf{x}_i - \mathbf{c}_k \|^2$$

$m$ : fuzziness index  
(often  $m=2$ )

$$U = [u_{ik}] \quad \begin{matrix} \text{fuzzy partition matrix} \\ \text{membership degree of } \mathbf{x}_i \text{ to } c_j \end{matrix}$$

$$\mathbf{c}_k = \frac{\sum\limits_{i=1}^n u_{ik} \cdot \mathbf{x}_i}{\sum\limits_{i=1}^n u_{ik}}$$



# Algorithm of FCM

1. Initialize  $U = [u_{ik}]$  matrix,  $U^{(t)}, t = 0$ .
2. At step  $t$ , Compute fuzzy centroids (center vectors)  $C^{(t)} = [\mathbf{c}_k]$  with  $U^{(t)}$

$$\mathbf{c}_k = \frac{\sum_{i=1}^n u_{ik} \cdot \mathbf{x}_i}{\sum_{i=1}^n u_{ik}}, \quad k = 1, \dots, K$$

3. Compute the degree of membership of all data points for all clusters to update the partition matrix, i.e. obtain  $U^{(t+1)}$ , as follows:

$$u_{ik} = \frac{1}{\sum_{j=1}^K \left( \frac{\|\mathbf{x}_i - \mathbf{c}_k\|}{\|\mathbf{x}_i - \mathbf{c}_j\|} \right)^{\frac{2}{m-1}}}$$

4. Repeat step 2 ~ 3 unless  $\| U^{(t+1)} - U^{(t)} \| < \epsilon$ .



## Several Soft Clustering Algorithms in R

- Fuzzy c-means: `cmeans {e1071}`
- Fuzzy Analysis Clustering (Kaufman and Rousseeuw, 1990) : `fanny {cluster}`

$$\sum_{k=1}^K (\sum_{i,j}^n u_{ik}^m u_{jk}^m \| \mathbf{x}_i - \mathbf{x}_j \|^2) / (2 \sum_{j=1}^n u_{jk}^m).$$

- Fuzzy c-shell clustering (Dave, 1996): `cshell {e1071}`

$$J_K = \sum_{i=1}^n \sum_{k=1}^K u_{ik}^m (\| \mathbf{x}_i - \mathbf{v}_k \| - r_k)^2$$

the data point  
 $\mathbf{x}_i$  to a circle  $(\mathbf{v}, r)$ .

- Model-based clustering (Fraley and Raftery, 2002) : `mclust {Mclust}`
- Consensus clustering: `cl_bag {clue}`

# Fuzzy C-Means Clustering

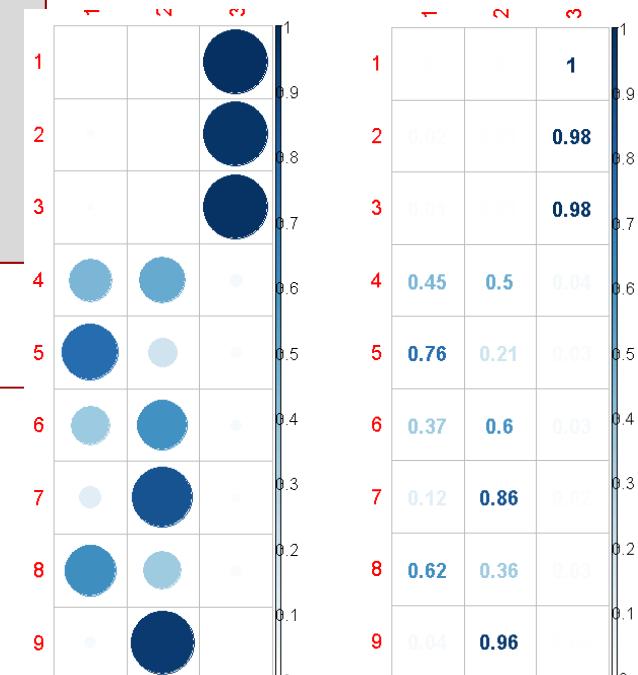
## Usage

```
cmeans (x, centers, iter.max=100, verbose=FALSE,  
        dist="euclidean",  
        method="cmeans", m=2, rate.par = NULL)
```

## Arguments

**centers**: #clusters or initial values for cluster centers  
**dist**: "euclidean"/"manhattan".  
**method**: "cmeans"/"ufcl" (on-line update)

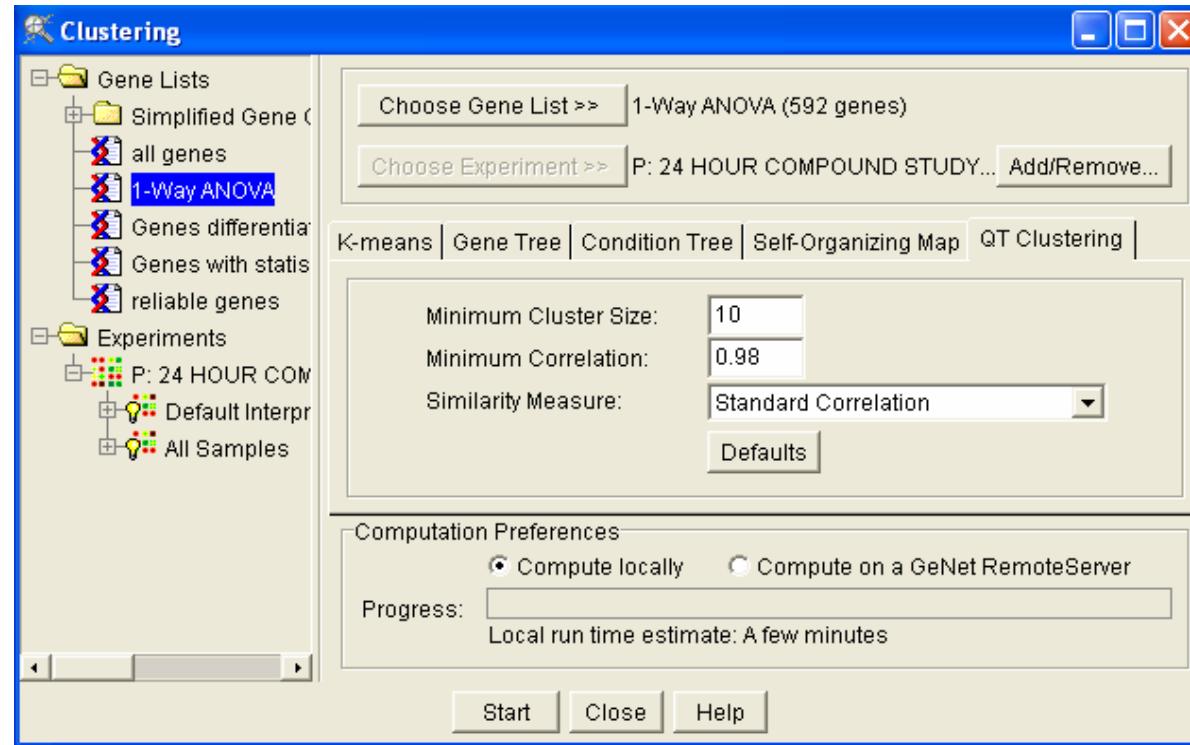
```
> library(e1071)  
> iris.fc <- cmeans(iris[,1:4], centers=3)  
> names(iris.fc)  
[1] "centers" "size" "cluster" "membership" "iter"  
[6] "withinerror" "call"  
> library(corrplot) # A visualization of a correlation matrix  
> id <- c(1:3, 51:53, 101:103)  
> corrplot(iris.fc$membership[id,], is.corr = FALSE)  
> corrplot(iris.fc$membership[id,], method = "number", is.corr = FALSE)  
> iris.fc$cluster  
[1] 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3  
...  
[129] 2 2 2 2 2 1 2 2 2 1 2 2 2 1 2 2 2 1 2 2 2 1
```





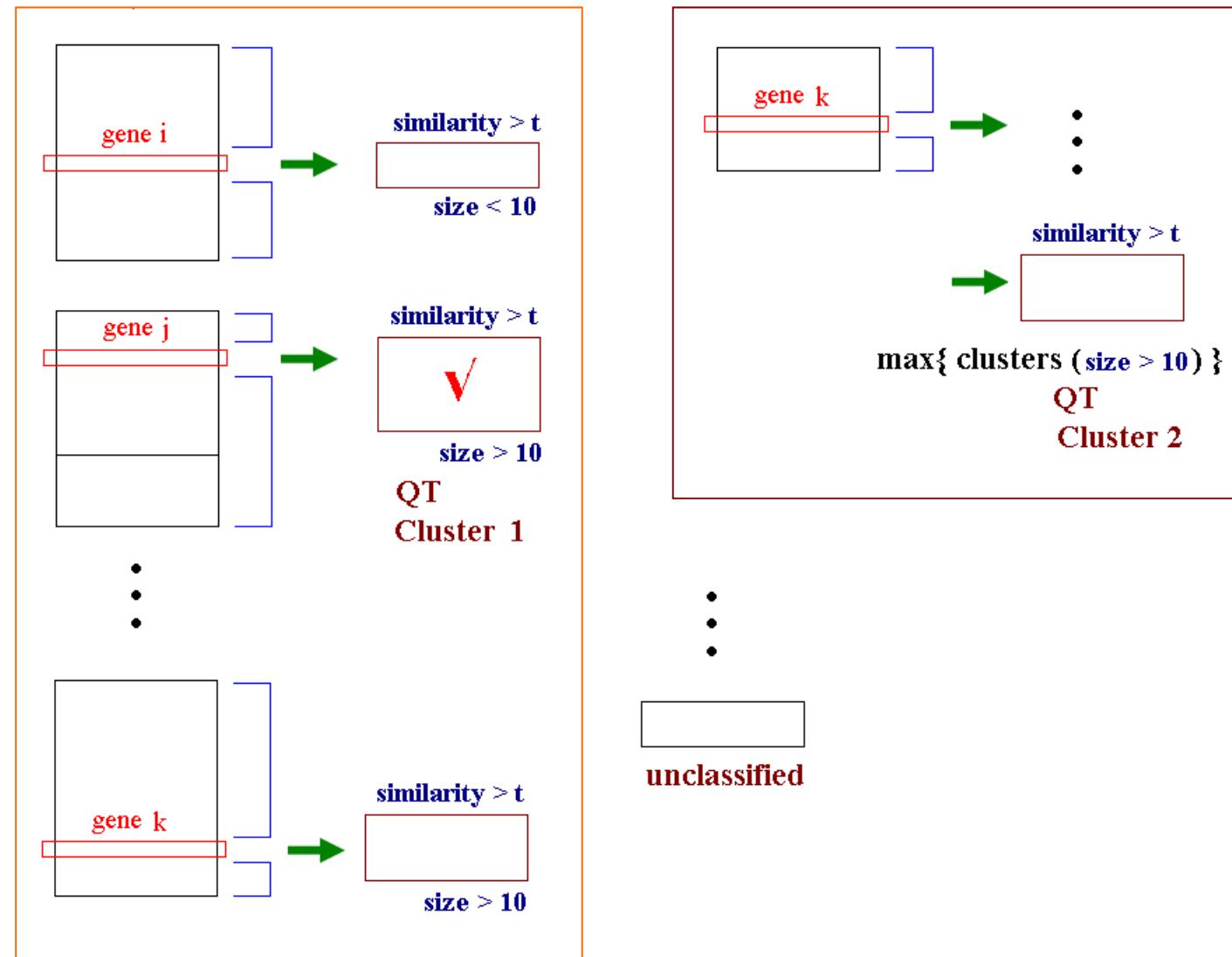
# QT (Quality Threshold) Clustering

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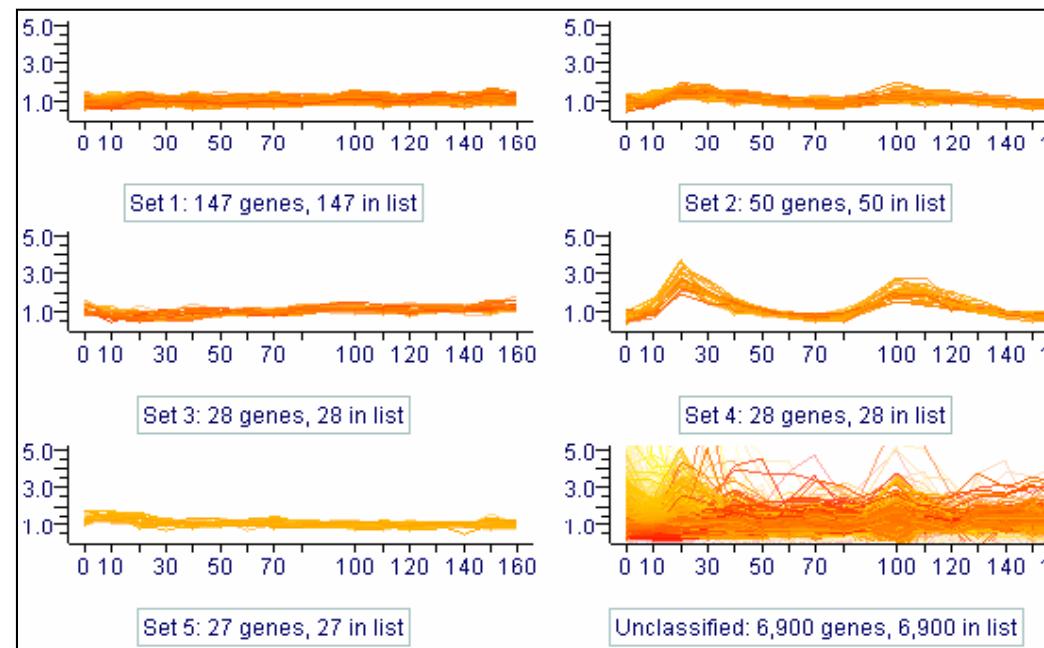
- **Minimum Cluster Size:** Minimum number of genes that you would like to have in each cluster.
- **Minimum Correlation:** Minimum correlation that genes within each cluster must have to one another.
- The diameter is the equivalent of 1 minus the minimum correlation.

# Algorithm of QT Clustering



# Interpreting the Results

- QT Clusters are displayed according to the **cluster size**, from the largest to the smallest.
- All sets will have **at least** the user-defined minimum cluster size and the minimum correlation (diameter).
- For example, all 147 genes in Set 1 below are at least 0.98 correlated to each other.
- Genes that did not meet the minimum quality are grouped under the “unclassified” category.





# QT Clustering: Advantages

## Advantages

- Quality Guarantee
- Number of clusters is not specified a priori
- All possible clusters are considered

## Disadvantages

- Computationally Intensive/Time Consuming

## Main differences between QT clustering and K-means clustering?

	K-means	QT clustering	Consequence
Need to specify cluster number?	Yes	No	K-means: if users specify too few clusters, genes that are not similar will be forced to group together.
Very computationally intensive?	No	Yes	QT clustering: may be too computationally intensive, depending on available RAM and number of genes in starting gene list, for some desktop computer.
Every gene must be clustered?	Yes	No	K-means: every gene on the selected gene list must belong to a cluster. This could potentially group genes that are not very similar into the same cluster. QT clustering: only cluster with user-specified quality will be formed.



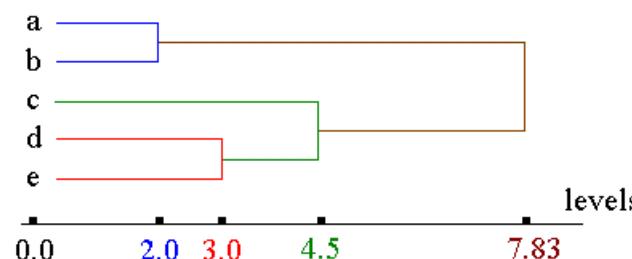
# Hierarchical Clustering and Dendrogram (Agglomerative Nesting, AGNES)

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## Example: Average-Linkage

distance matrix

	a	b	c	d	e
a	0	2	6	10	9
b		0	5	9	8
c			0	4	5
d				0	3
e					0



	{a, b}	c	d	e
{a, b}	0	5.5	9.5	8.5
c		0	4	5
d			0	3
e				0

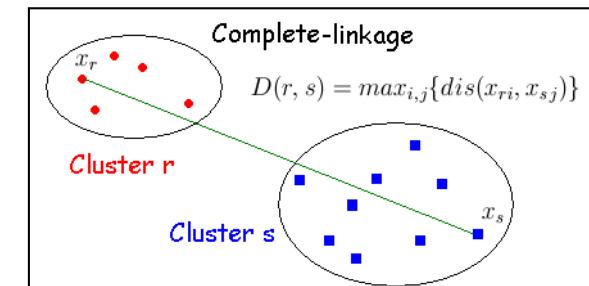
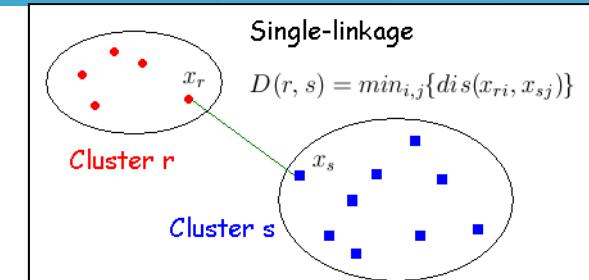
$$D(\{a, b\}, \{c\}) = \frac{1}{2}[D(a, c) + D(b, c)] \\ = \frac{1}{2}(6 + 5) = 5.5$$

	{a, b}	c	{d, e}
{a, b}	0	5.5	9.0
c		0	4.5
{d, e}			0

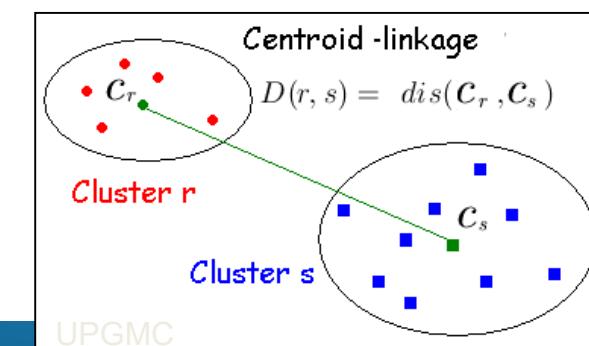
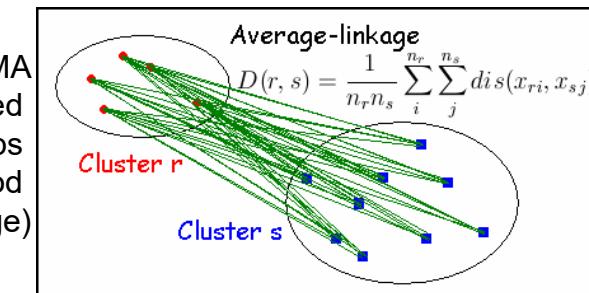
$$D(\{a, b\}, \{d, e\}) \\ = \frac{1}{4}[D(a, d) + D(a, e) + D(b, d) + D(b, e)] \\ = \frac{1}{4}(10 + 9 + 9 + 8) = 9$$

	{a, b}	{c, d, e}
{a, b}	0	7.83
{c, d, e}		0

(Kaufman and Rousseeuw, 1990)



UPGMA  
(Unweighted  
Pair-Groups  
Method  
Average)



UPGMC



# Ward's Method

- The Ward's method forms clusters by maximizing **within-clusters homogeneity**.
- The within-group (i.e., within-cluster) **sum of squares** is used as the measure of homogeneity.
- The within-cluster sums of squares that is minimized is also known as the **error sums of squares (ESS)**.

**Example:**

Charles H. Romesburg (1984)

Toy Data

data	x1	x2
1	10	5
2	20	20
3	30	10
4	30	15
5	5	10

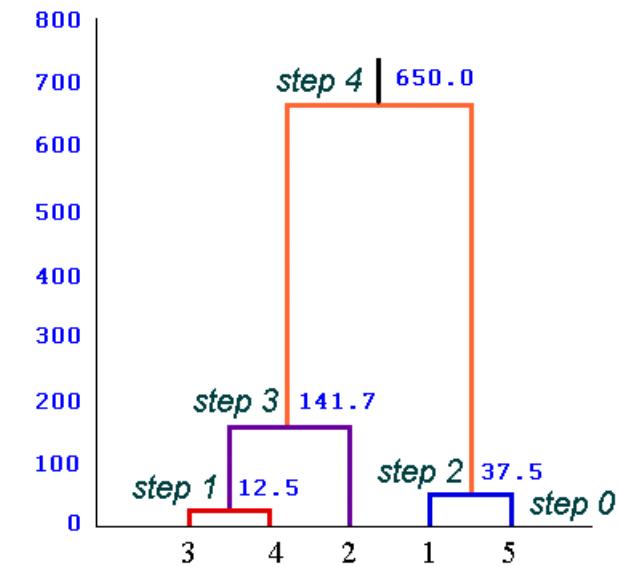
step	Possible Partitions	ESS
1	(12)	?

$$\{\bar{12}\} = [ (10 + 20)/2, (5 + 20)/2 ] \\ = [ 15, 12.5 ]$$

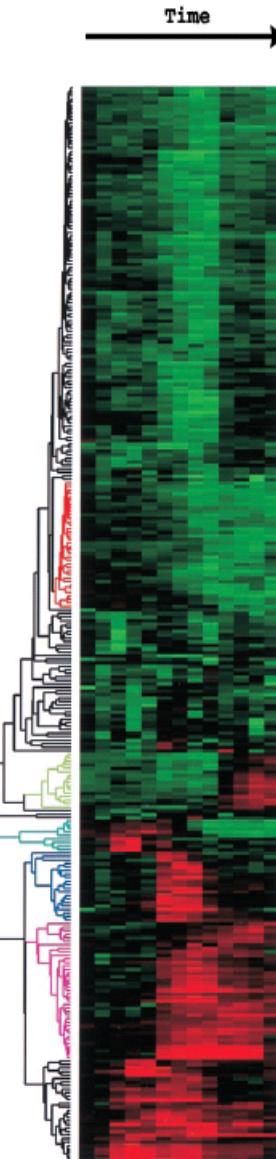
$$\begin{aligned} ESS &= wss\{12\} + wss\{3\} + wss\{4\} + wss\{5\} \\ &= ss(1, \{\bar{12}\}) + ss(2, \{\bar{12}\}) \\ &= (10 - 15)^2 + (5 - 12.5)^2 + (20 - 15)^2 + (2 - 12.5)^2 \\ &= 162.5 \end{aligned}$$

step Possible Partitions

step	Possible Partitions	ESS
1	(12)	162.5
	(13)	212.5
	(14)	250.0
	(15)	25.0
	(23)	100.0
	(24)	62.5
	(25)	162.5
	(34)	12.5*
	(35)	312.5
	(45)	325.0
2	(34)	175.0
	(34)	37.5*
	(34)	175.0
	(134)	316.7
	(234)	116.7
	(345)	433.3
3	(234)	141.7*
	(125)	245.9
	(1345)	568.8
4	(12345)	650.0



# Display of Genome-Wide Expression Patterns



*Proc. Natl. Acad. Sci. USA*  
Vol. 95, pp. 14863–14868, December 1998  
Genetics

## Cluster analysis and display of genome-wide expression patterns

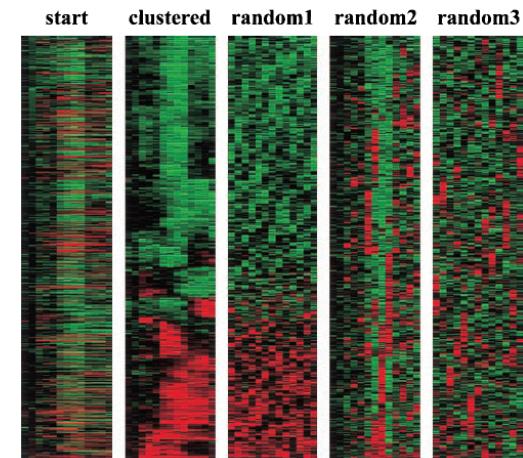
MICHAEL B. EISEN\*, PAUL T. SPELLMAN\*, PATRICK O. BROWN†, AND DAVID BOTSTEIN\*‡

FIG. 1. Clustered display of data from time course of serum stimulation of primary human fibroblasts. Experimental details are described elsewhere (11). Briefly, foreskin fibroblasts were grown in culture and were deprived of serum for 48 hr. Serum was added back and samples taken at time 0, 15 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 8 hr, 12 hr, 16 hr, 20 hr, 24 hr. The final datapoint was from a separate unsynchronized sample. Data were measured by using a cDNA microarray with elements representing approximately 8,600 distinct

human genes. All measurements are relative to time 0. Genes were selected for this analysis if their expression level deviated from time 0 by at least a factor of 3.0 in at least 2 time points. The dendrogram and colored image were produced as described in the text; the color scale ranges from saturated green for log ratios  $-3.0$  and below to saturated red for log ratios  $3.0$  and above. Each gene is represented by a single row of colored boxes; each time point is represented by a single column. Five separate clusters are indicated by colored bars and by identical coloring of the corresponding region of the dendrogram. As described in detail in ref. 11, the sequence-verified named genes in these clusters contain multiple genes involved in (A) cholesterol biosynthesis, (B) the cell cycle, (C) the immediate–early response, (D) signaling and angiogenesis, and (E) wound healing and tissue remodeling. These clusters also contain named genes not involved in these processes and numerous uncharacterized genes. A larger version of this image, with gene names, is available at <http://rana.stanford.edu/clustering/serum.html>.

## Software: Cluster and TreeView

FIG. 3. To demonstrate the biological origins of patterns seen in Figs. 1 and 2, data from Fig. 1 were clustered by using methods described here before and after random permutation within rows (random 1), within columns (random 2), and both (random 3).



# Minimal Spanning Tree

Single-linkage correspond to minimal spanning tree:

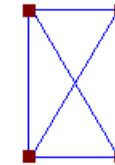
- Consider a weighted, completely connected **graph** with nodes corresponding to instance and **edge** between **nodes** with weights equal to the distances between the instance.

Spanning trees:

- A spanning tree of a graph is just a **subgraph** that contains all the vertices and is a tree. A graph may have many spanning trees; for instance the complete graph on four vertices

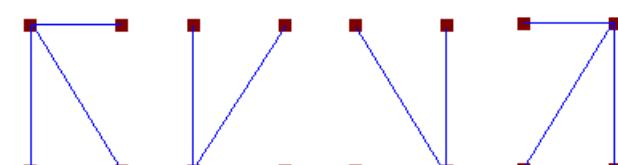
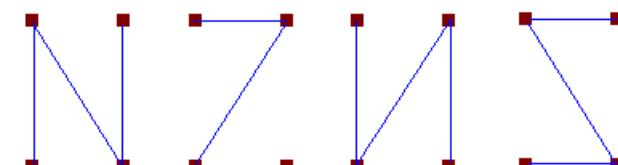
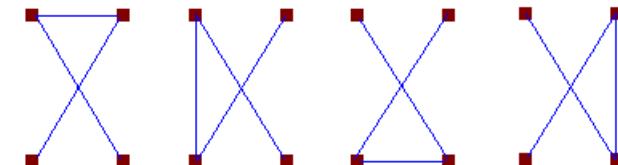
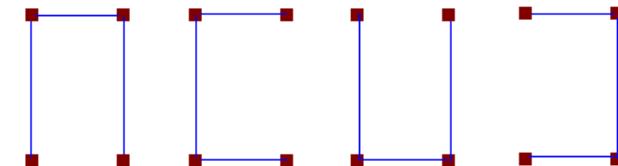
Minimum spanning trees

- Now suppose the edges of the graph have weights or lengths.
- The weight of a tree is just the sum of weights of its edges.
- Different trees have different lengths. **The problem: how to find the minimum length spanning tree?**
- Application: the minimum spanning tree can be used to approximately solve the traveling salesman problem.
- A convenient formal way of defining this problem is to find the shortest path that visits each point at least once.



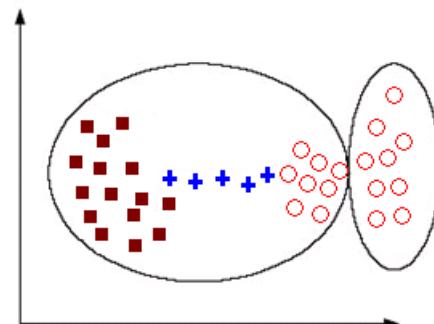
**The complete graph on four vertices**

**Sixteen Spanning Trees**



# Comparisons

- Single-linkage: clusters may be elongated due to the chaining effect.
- Complete-linkage: clusters tend to be more compact.



Method	can be used for clustering cases	useful for clustering variables	different dissimili- arity and similarity measures	agglomera- tion level has a clear interpretation	avoids chaining or dilatation	avoids reversals (d)	invariant to mono- tonic transfor- mation
complete linkage	yes	yes	yes	yes	yes (a)	yes	yes (e)
single linkage	yes	yes	yes	yes	yes (b)	yes	yes (e)
average linkage	yes	yes	yes	no	no	yes	(yes (f))
weighted average linkage	yes	yes	yes	yes	no	yes	no
within average linkage	yes	yes	yes	yes	no	no	no
median Linkage	yes	no	no	no	(no) (c)	no	no
centroid Linkage	yes	no	no	yes	no	no	no
Ward's Linkage	yes	no	no	yes	no	yes	no

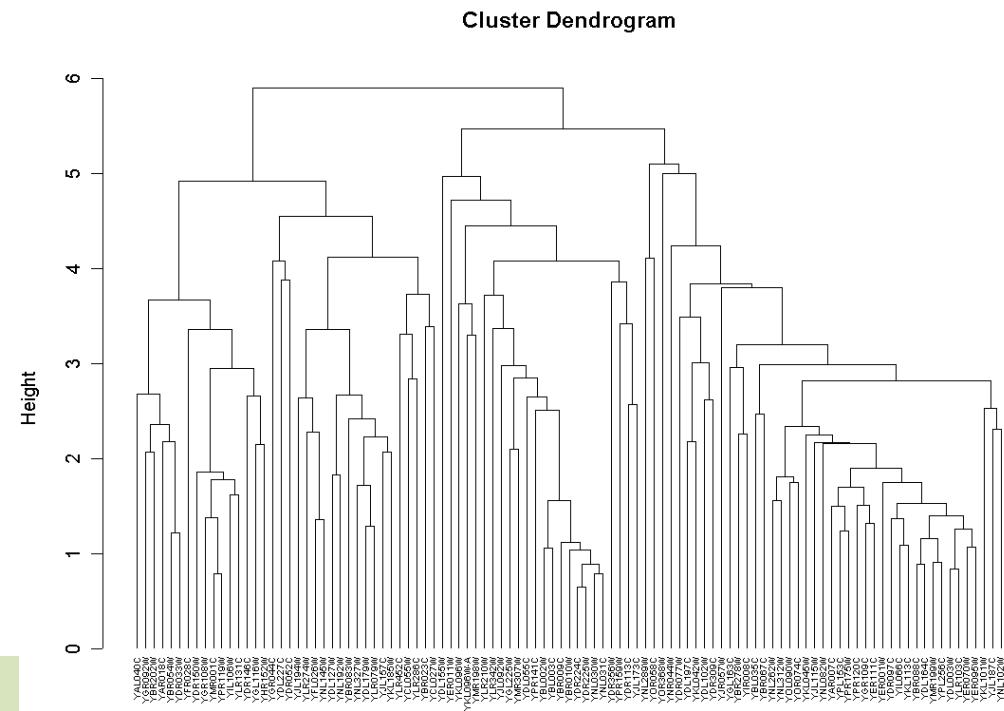
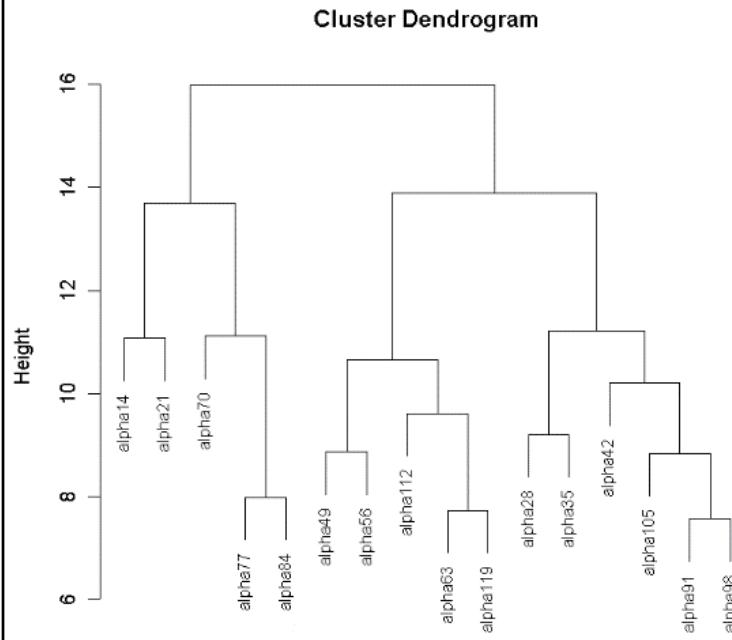
(a) chaining occurs (see text), (b) dilatation occurs (see text), (c) tendency to chaining (Gordon 1999: 67), (d) see text, (e) invariant to monotonic transformation of dissimilarities resp. similarities (Bacher 1996: 146), (f) invariant to linear transformation of dissimilarities resp. similarities (Bacher 1996: 271)



# Hierarchical Clustering

```
> gene.name <- rownames(cell.matrix)                                     See A05: page
## Hierarchical Clustering on genes
> cell.gene.hc.ave <- hclust(dist(cell.sdata), method="ave")
> plot(cell.gene.hc.ave, hang=-1, cex=0.5, labels=gene.name)
## Hierarchical Clustering on experiments
> cell.exp.hc.ave <- hclust(dist(t(cell.sdata))), method="ave")
> plot(cell.exp.hc.ave, cex=0.8)
```

See A05: page 134/172 or C01: page 31/95



*See also:*

**agnes {cluster}**: Agglomerative Nesting (Hierarchical Clustering)

**diana {cluster}**: DIvisive ANAlysis Clustering

# Heatmap (Hierarchical Clustering + Data Image)

```

x <- as.matrix(mtcars)
?heatmap
row.color <- rainbow(nrow(x), start=0, end=.3)
col.color <- rainbow(ncol(x), start=0, end=.3)
hv <- heatmap(x, col = cm.colors(256), scale="column",
               RowSideColors = row.color, ColSideColors = col.color,
               margins=c(5,10),
               xlab = "specification variables", ylab= "Car Models",
               main = "Heatmap(mtcars)(Range Column Condition)")

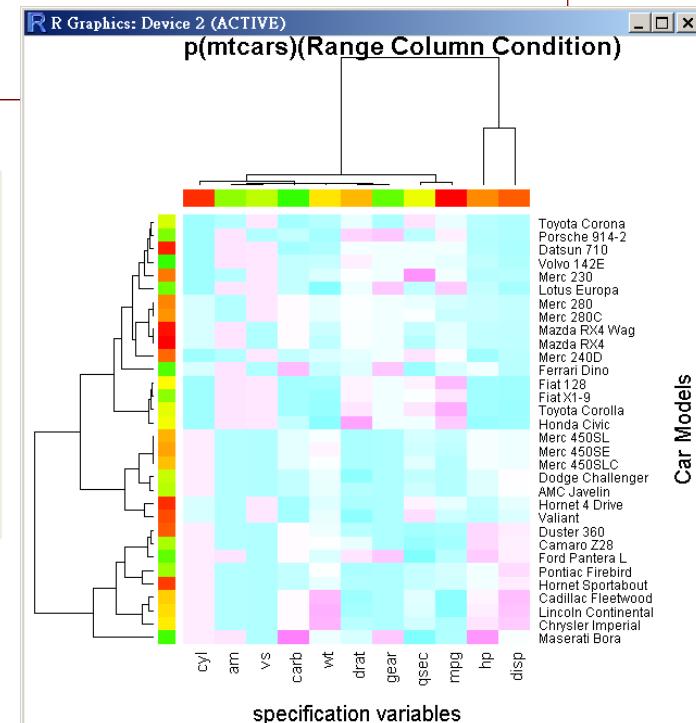
names(hv)
[1] "rowInd" "colInd" "Rowv"    "Colv"

```

```

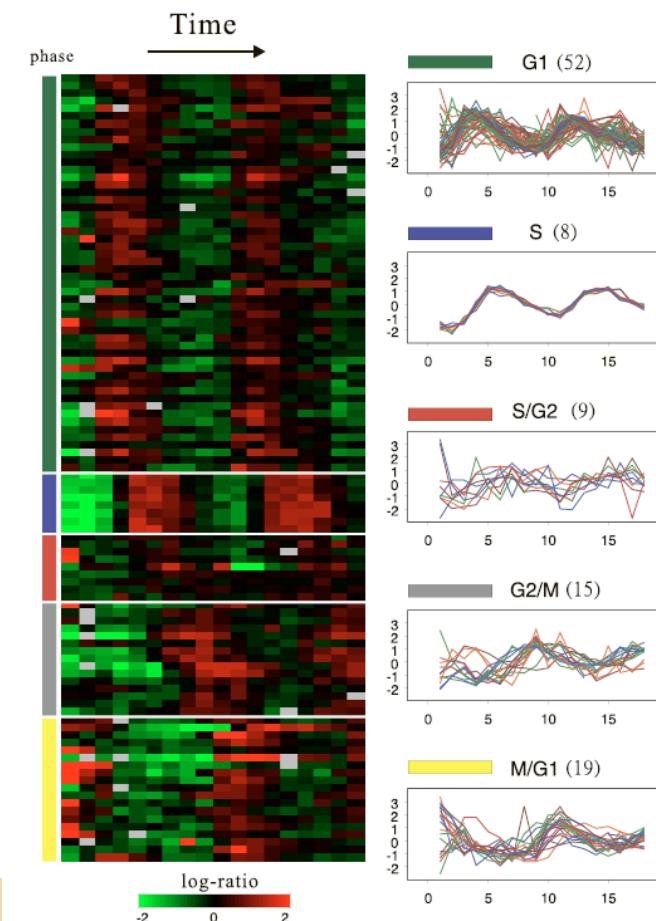
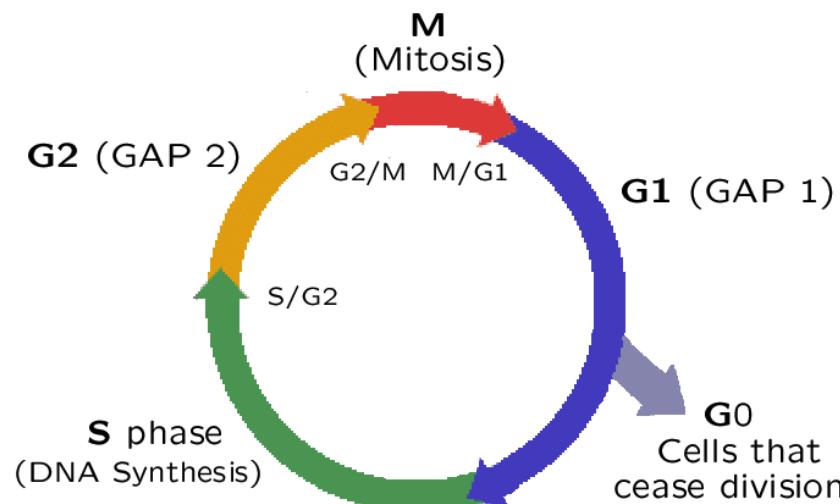
> mtcars
      mpg cyl  disp  hp drat   wt  qsec vs am gear carb
Mazda RX4     21.0   6 160.0 110 3.90 2.620 16.46  0  1    4    4
Mazda RX4 Wag 21.0   6 160.0 110 3.90 2.875 17.02  0  1    4    4
Datsun 710    22.8   4 108.0  93 3.85 2.320 18.61  1  1    4    1
Hornet 4 Drive 21.4   6 258.0 110 3.08 3.215 19.44  1  0    3    1
Hornet Sportabout 18.7   8 360.0 175 3.15 3.440 17.02  0  0    3    2
Valiant       18.1   6 225.0 105 2.76 3.460 20.22  1  0    3    1
Duster 360    14.3   8 360.0 245 3.21 3.570 15.84  0  0    3    4
Merc 240D     24.4   4 146.7  62 3.69 3.190 20.00  1  0    4    2
Merc 230      22.8   4 140.8  95 3.92 3.150 22.90  1  0    4    2
Merc 280      19.2   6 167.6 123 3.92 3.440 18.30  1  0    4    4

```



# 課堂練習: Microarray Data

- Lu and Wu (2010)
  - Time course data: every 7 minutes and totally 18 time points.
  - Known genes: there are 103 cell cycle-regulated genes by traditional method in G1, S, S/G2, G2/M, or M/G1. (Remove NA's: 79.)



*See also:* Using R to draw a Heatmap from Microarray Data

[http://www2.warwick.ac.uk/fac/sci/moac/people/students/peter\\_cock/r/heatmap/](http://www2.warwick.ac.uk/fac/sci/moac/people/students/peter_cock/r/heatmap/)



# 課堂練習: Microarray Data

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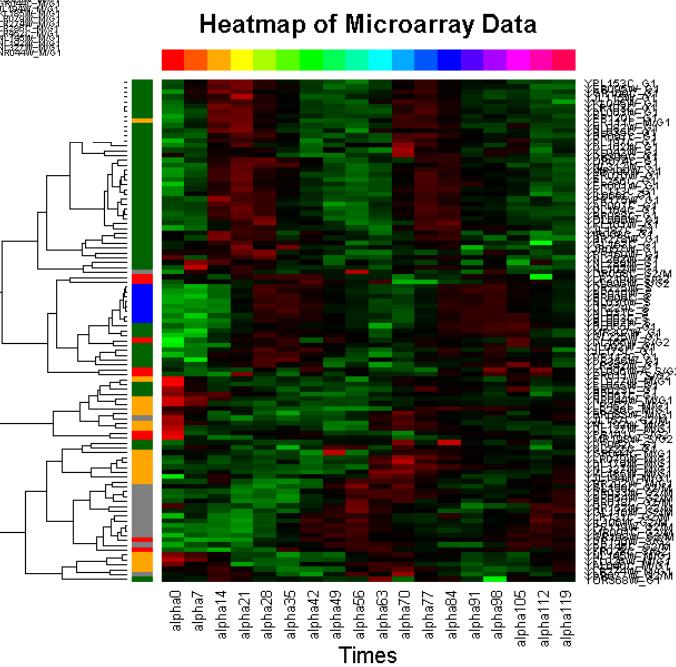
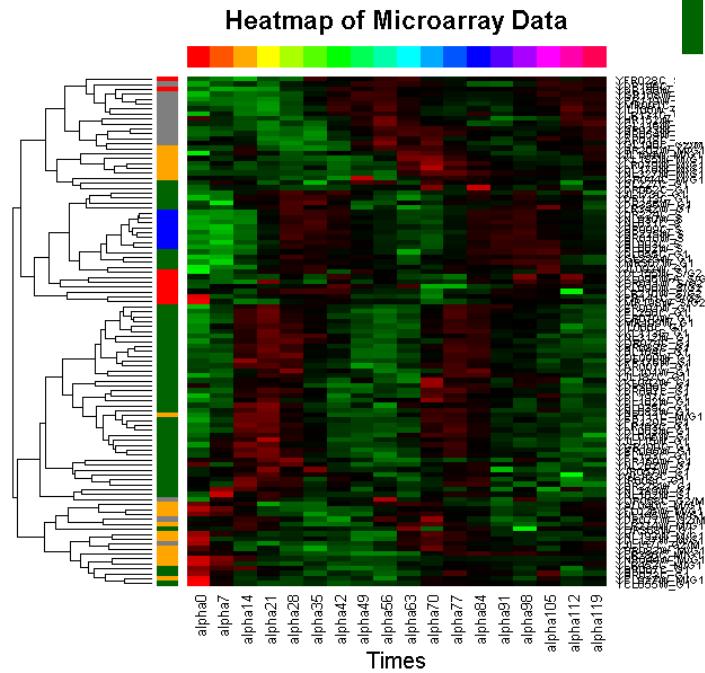
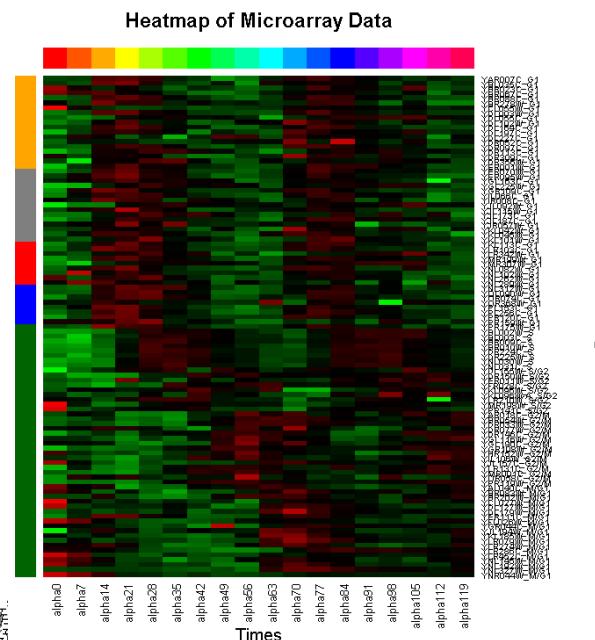
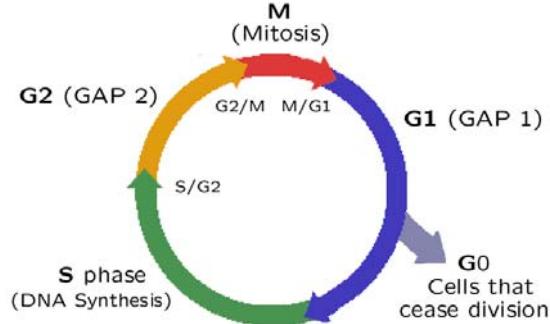
```
# install.packages("fields")
library(fields)
gbr <- two.colors(start="green", middle="black", end="red")
cell.raw <- read.table("trad_alpha103.txt", row.names=1, header=T)
cell.data <- t(scale(t(cell.raw[,2:19]), center=T, scale=T))
n <- nrow(cell.data)
p <- ncol(cell.data)
gene.phase <- cell.raw[,1]
range(cell.data)
cell.data[cell.data > 2.802712] <- 2.802712
cellcycle.color <- c("darkgreen", "blue", "red", "gray50", "orange")
rc <- cellcycle.color[gene.phase+1]
cc <- rainbow(ncol(cell.data))

hv1 <- heatmap(cell.data[n:1,], col = gbr, Colv=NA, Rowv=NA,
                RowSideColors = rc,
                ColSideColors = cc, margins = c(5,10),
                xlab = "Times", ylab = "Genes",main = "Heatmap of Microarray Data")

hv2 <- heatmap(cell.data, col = gbr, Colv=NA, Rowv=NULL,
                RowSideColors = rc,
                ColSideColors = cc, margins = c(5,10),
                xlab = "Times", ylab = "Genes",main = "Heatmap of Microarray Data")

dd <- as.dendrogram(hclust(as.dist(1-cor(t(cell.data)))))
hv3 <- heatmap(cell.data, col = gbr, Colv=NA, Rowv=dd,
                RowSideColors = rc,
                ColSideColors = cc, margins = c(5,10),
                scale = "row",
                xlab = "Times", ylab = "Genes",main = "Heatmap of Microarray Data")
```

# 課堂練習: Microarray Data





# gplots: Heatmap.2

- gplots: Various R programming tools for plotting data

```
> install.packages("gplots")
> library(gplots)
> ?heatmap.2
> library(affy)
> data(SpikeIn)
> pms <- SpikeIn@pm

# just the data, scaled across rows
heatmap.2(pms, col=rev(heat.colors(16)), main="SpikeIn@pm",
           xlab="Relative Concentration", ylab="Probeset",
           scale="row")

# fold change vs "12.50" sample
data <- pms / pms[, "12.50"]
data <- ifelse(data>1, data, -1/data)
heatmap.2(data, breaks=16, col=redgreen, tracecol="blue",
           main="SpikeIn@pm Fold Changes\nrelative to 12.50 sample",
           xlab="Relative Concentration", ylab="Probeset")
```

## More Examples

[http://www2.warwick.ac.uk/fac/sci/moac/currentstudents/peter\\_cock/r/heatmap/](http://www2.warwick.ac.uk/fac/sci/moac/currentstudents/peter_cock/r/heatmap/)



# Self-Organizing Maps (SOM)

60/122

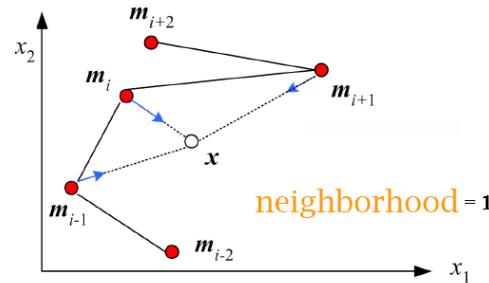
- SOMs were developed by **Kohonen** in the early **1980's**, original area was in the area of speech recognition.
- **Idea:**  
Organise data on the basis of **similarity** by putting entities **geometrically** close to each other.
- SOM is unique in the sense that it combines both aspects:
  - It can be used at the same time both to reduce the amount of data by **clustering**, and
  - to construct a nonlinear projection of the data onto a **low-dimensional display**.



# Self-Organizing Maps (SOM)

61/122

- SOMs were developed by **Kohonen** in the early **1980's**, original area was in the area of speech recognition.
- Idea:** Organise data on the basis of **similarity** by putting entities **geometrically** close to each other.



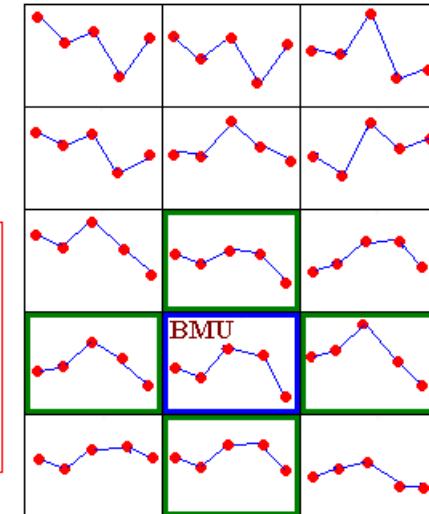
- SOM is unique in the sense that it combines both aspects. It can be used at the same time both to reduce the amount of data by **clustering**, and to construct a nonlinear projection of the data onto a **low-dimensional display**.

Step 0:  
Initialize weights  $\mathbf{w}_i(t)$ .  
Set  $\alpha(t)$  and  $h_{ci}(t)$ .

Learning process:

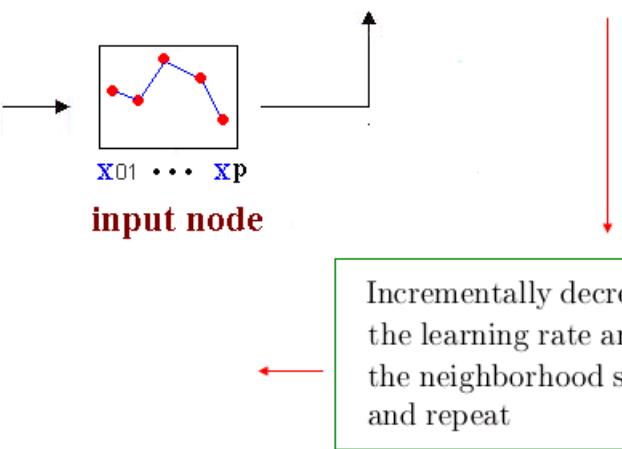
$$\mathbf{w}_i(t+1) = \begin{cases} \mathbf{w}_i(t) + h_{ci}(t)[\mathbf{x}(t) - \mathbf{w}_i(t)] \\ \mathbf{w}_i(t), \text{ o.w.} \end{cases}$$

5 x 3 output node



Data Matrix

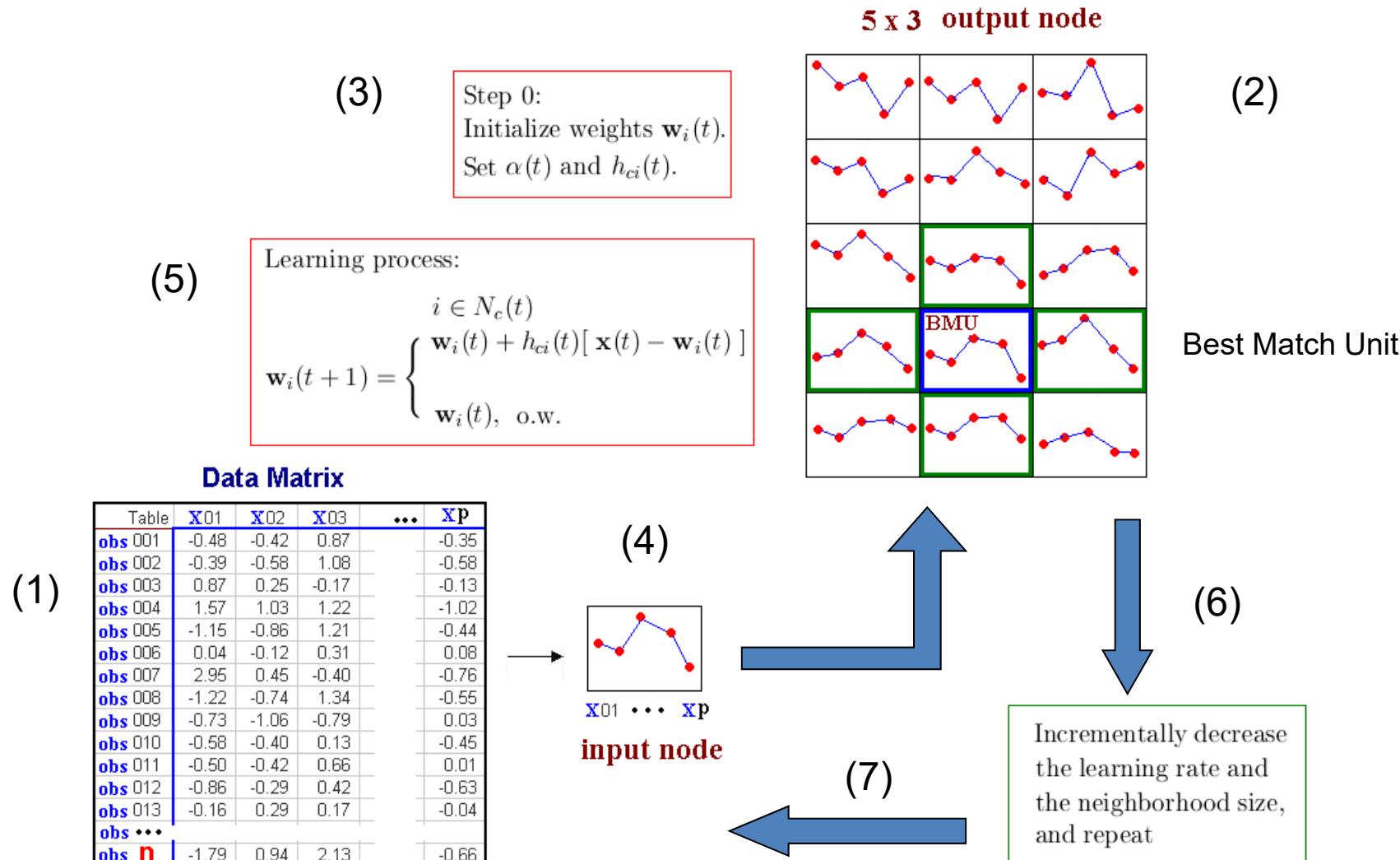
Table	X01	X02	X03	...	Xp
obs 001	-0.48	-0.42	0.87		-0.35
obs 002	-0.39	-0.58	1.08		-0.58
obs 003	0.87	0.25	-0.17		-0.13
obs 004	1.57	1.03	1.22		-1.02
obs 005	-1.15	-0.86	1.21		-0.44
obs 006	0.04	-0.12	0.31		0.08
obs 007	2.95	0.45	-0.40		-0.76
obs 008	-1.22	-0.74	1.34		-0.55
obs 009	-0.73	-1.06	-0.79		0.03
obs 010	-0.58	-0.40	0.13		-0.45
obs 011	-0.50	-0.42	0.66		0.01
obs 012	-0.86	-0.29	0.42		-0.63
obs 013	-0.16	0.29	0.17		-0.04
obs ...					
obs n	-1.79	0.94	2.13		-0.66





# Self-Organizing Maps (SOM)

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# Algorithm of SOM

Step 0: Initialize weights  $\mathbf{w}_i(t)$ .

Set topological neighborhood parameters  $N_c(t)$ .

Set learning rate parameters  $\alpha(t)$  and  $h_{ci}(t)$ .

Step 1: For each input vector  $\mathbf{x}(t)$ , do

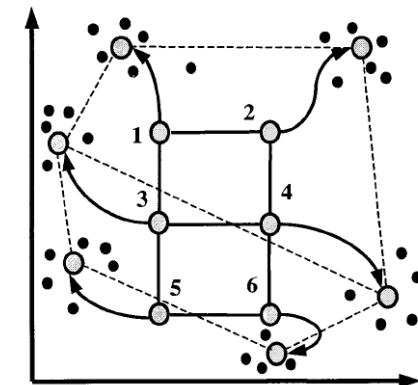
- Finding a BMU:  $\|\mathbf{x}(t) - \mathbf{w}_c(t)\| = \min_i \|\mathbf{x}(t) - \mathbf{w}_i(t)\|$
- Learning process:

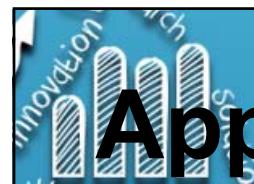
$$\mathbf{w}_i(t+1) = \begin{cases} \mathbf{w}_i(t) + h_{ci}(t)[\mathbf{x}(t) - \mathbf{w}_i(t)], & i \in N_c(t) \\ \mathbf{w}_i(t), & \text{o.w.} \end{cases}$$

- Go to the next unvisited input vector. If there are no unvisited input vector left then go back to the very first one and go to Step 2.

Step 2: Incrementally decrease the learning rate and the neighborhood size, and repeat Step 1.

Step 3: Keep doing Steps 1 and 2 for a sufficient number of iterations.

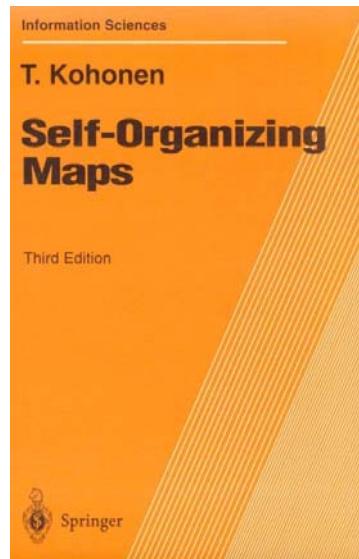




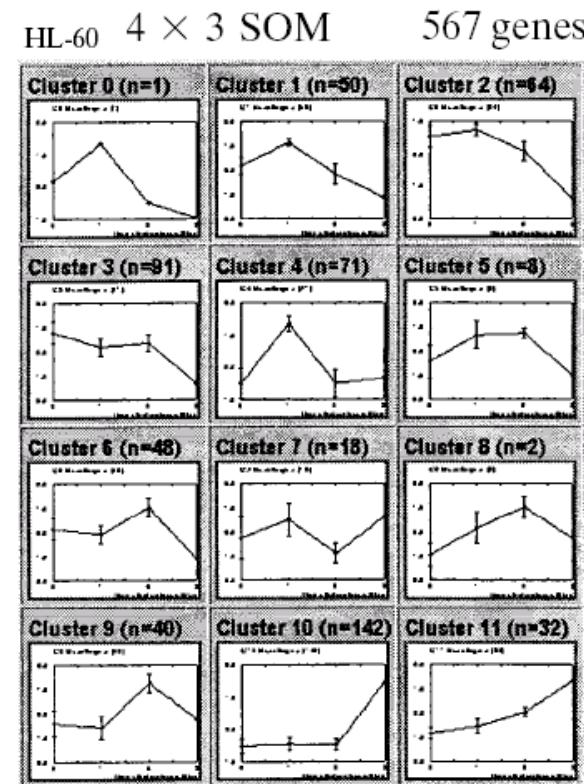
# Apply SOM to Microarray Data

## Macrophage Differentiation in HL-60 cells

Tamayo, P. et al. (1999). Interpreting patterns of gene expression with self-organizing maps: Methods and application to hematopoietic differentiation.  
*Proc Natl Acad Sci* 96:2907-2912.



1995, 1997, 2001



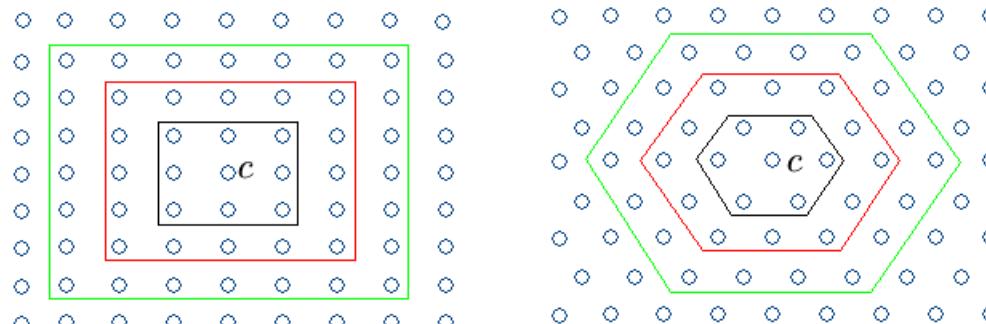
# SOM - Initialization

Step 0: Initialize weights  $\mathbf{w}_i(t)$ .

Set topological neighborhood parameters  $N_c(t)$ .

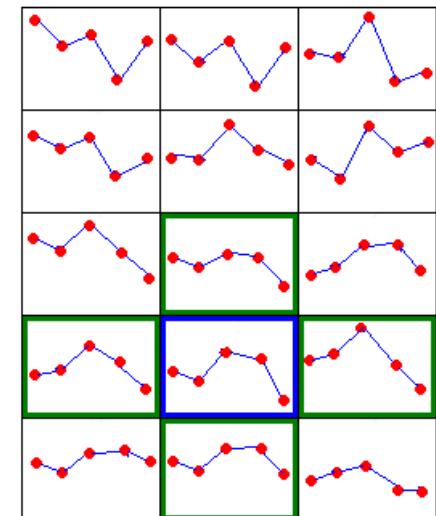
Set learning rate parameters  $\alpha(t)$  and  $h_{ci}(t)$ .

Two examples of topological neighborhood.



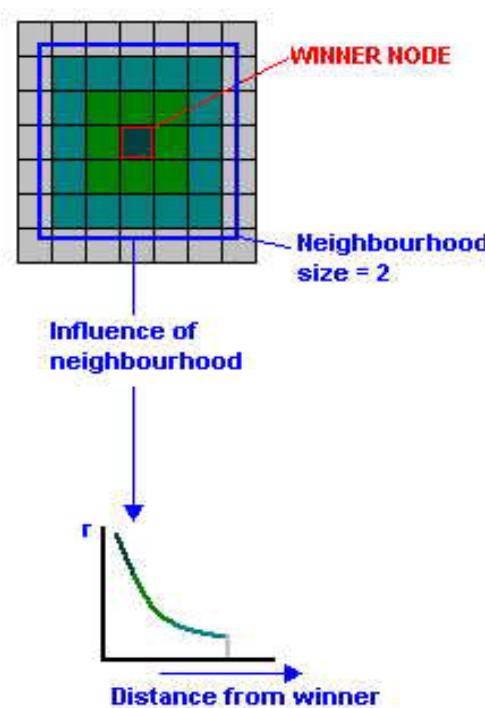
- $N_c(t_1) = 1$ , ■  $N_c(t_2) = 2$ , ■  $N_c(t_3) = 3$ ,  $t_1 < t_2 < t_3$

**5 x 3 output node**





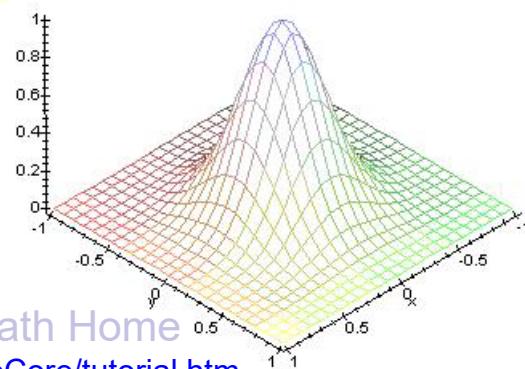
# Neighborhood Functions



The winner node's weight is *modified* such that it becomes even more *similar* to the original input node's vector.

The neighborhood value has a two-fold character - a *size* and a *function of distance to influence*. One could even define a further third character - *the shape* of the neighborhood (in this case, a square - highlighted in blue).

The peak of the Gaussian function would be the location of the *winner node*. As one moves out from that location, the *r* value decreases.

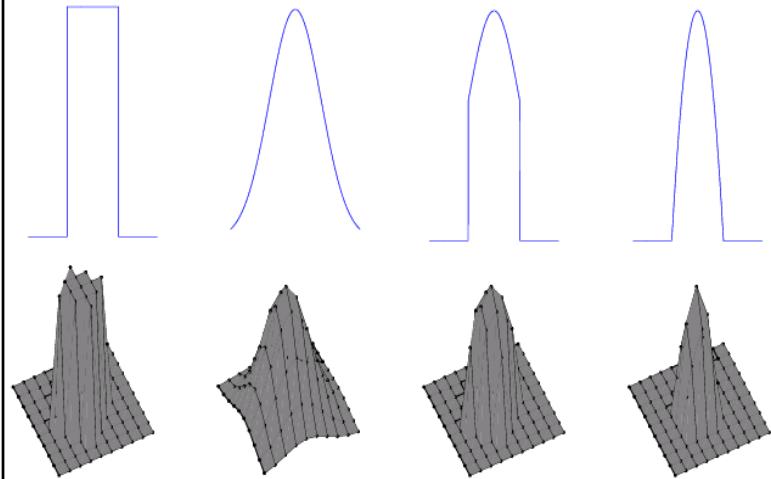


Figures source from: SC/path Home  
<http://www.ucl.ac.uk/oncology/MicroCore/tutorial.htm>



# Neighborhood Functions and Learning Rate

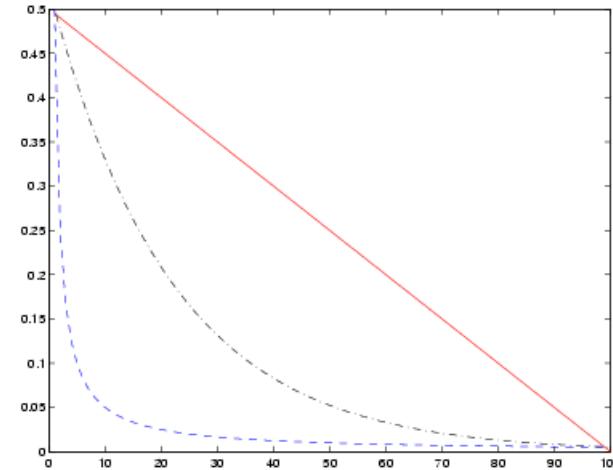
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Different neighborhood functions. From the left  
'bubble',  $h_{ci}(t) = \mathbf{1}(\sigma_t - d_{ci})$ ,  
'gaussian',  $h_{ci}(t) = e^{-d_{ci}^2/2\sigma_t^2}$ ,  
'cutgauss',  $h_{ci}(t) = e^{-d_{ci}^2/2\sigma_t^2} \mathbf{1}(\sigma_t - d_{ci})$ , and  
'ep',  $h_{ci}(t) = \max\{0, 1 - (\sigma_t - d_{ci})^2\}$ , where  
 $\sigma_t$  is the neighborhood radius at time  $t$ ,  
 $d_{ci} = \|\mathbf{r}_c - \mathbf{r}_i\|$  is the distance between map units  $c$  and  $i$  on the map grid  
 $\mathbf{1}(x)$  is the step function:  $\mathbf{1}(x) = 0$  if  $x < 0$  and  $\mathbf{1}(x) = 1$  if  $x \geq 0$ .

The neighborhood radius used is  $\sigma_t = 2$ .

Source from Technical report on SOM Toolbox 2.0 for Matlab.



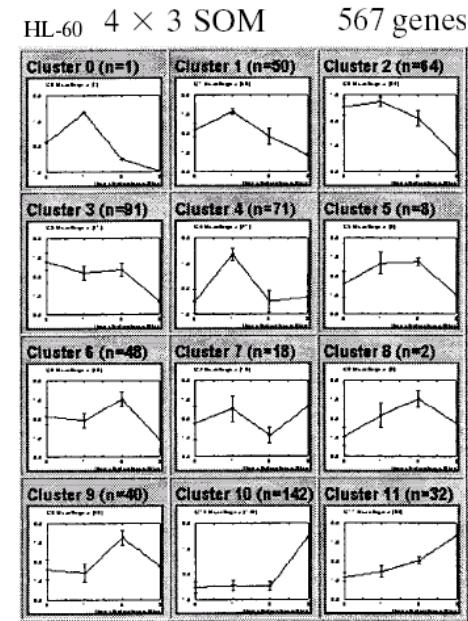
Different learning rate functions:

'linear' (solid line)  $\alpha(t) = \alpha_0(1-t/T)$ ,  
'power' (dot-dashed)  $\alpha(t) = \alpha_0(0.005/\alpha_0)^{t/T}$  and  
'inv' (dashed)  $\alpha(t) = \alpha_0/(1+100t/T)$ , where  $T$  is the training length and  $\alpha_0$  is the initial learning rate.



# Possible Parameters used in SOM

1. Grid dimension: 2D, 3D
2. Grid shape: in 2D → Rectangle, Hexagon, ...
3. Number of node: in 2D Rectangle →  $4 \times 6$ ,  $5 \times 5$ ,  $3 \times 8$ , ...
4. Neighborhood function: Bubble kernel, Gaussian kernel, ...
5. Neighborhood size: radius of  $N_c(t)$
6. Learning rate function:  $\alpha(t)$
7. Initial weights: random, use input vector
8. Order of input vectors: random, ...
9. Ways of learning: number of iteration, ...

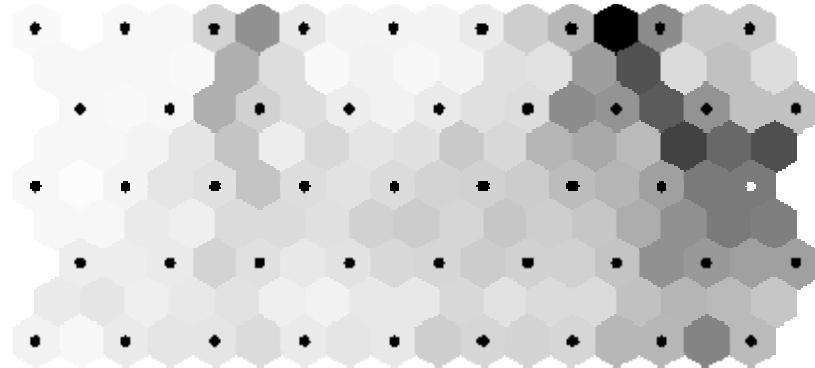


# U-matrix: Unified Matrix Method

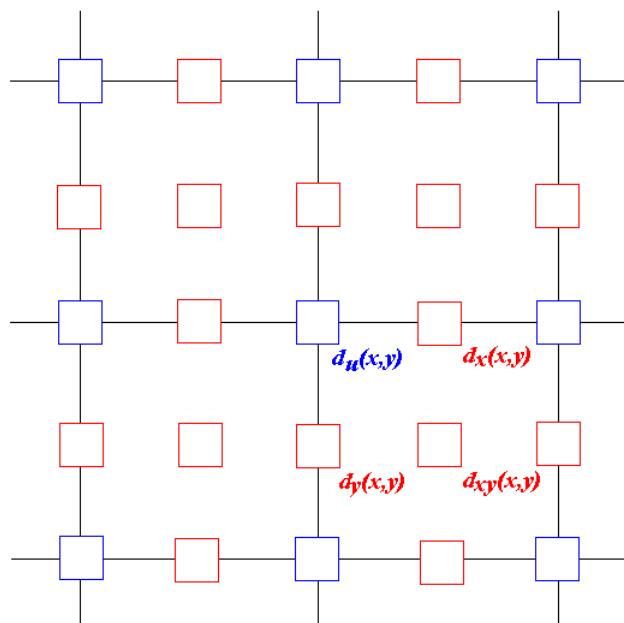
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(Ultsch and Siemon 1989, Ultsch 1993)

U-matrix representation of SOM visualizes the distance between the neurons. The distance between the adjacent neurons is calculated and presented with different colorings between the adjacent nodes.



U-matrix representation of the SOM



$b(x, y)$ : matrix of neurons, of size  $n_x \times n_y$ .

$w_i(x, y)$ : matrix of weights.

$u(x, y)$ : U-matrix of size  $(2n_x - 1) \times (2n_y - 1)$ .

$$d_x(x, y): \|b(x, y) - b(x + 1, y)\| = \sqrt{\sum_i [w_i(x, y) - w_i(x + 1, y)]^2}$$

$$d_y(x, y): \|b(x, y) - b(x, y + 1)\| = \sqrt{\sum_i [w_i(x, y) - w_i(x, y + 1)]^2}$$

$$d_{xy}(x, y): \frac{1}{2} \left[ \frac{\|b(x, y) - b(x + 1, y + 1)\|}{\sqrt{2}} + \frac{\|b(x, y + 1) - b(x + 1, y)\|}{\sqrt{2}} \right]$$

$d_u(x, y)$ : the median of the surrounding elements.



# SOM: iris example

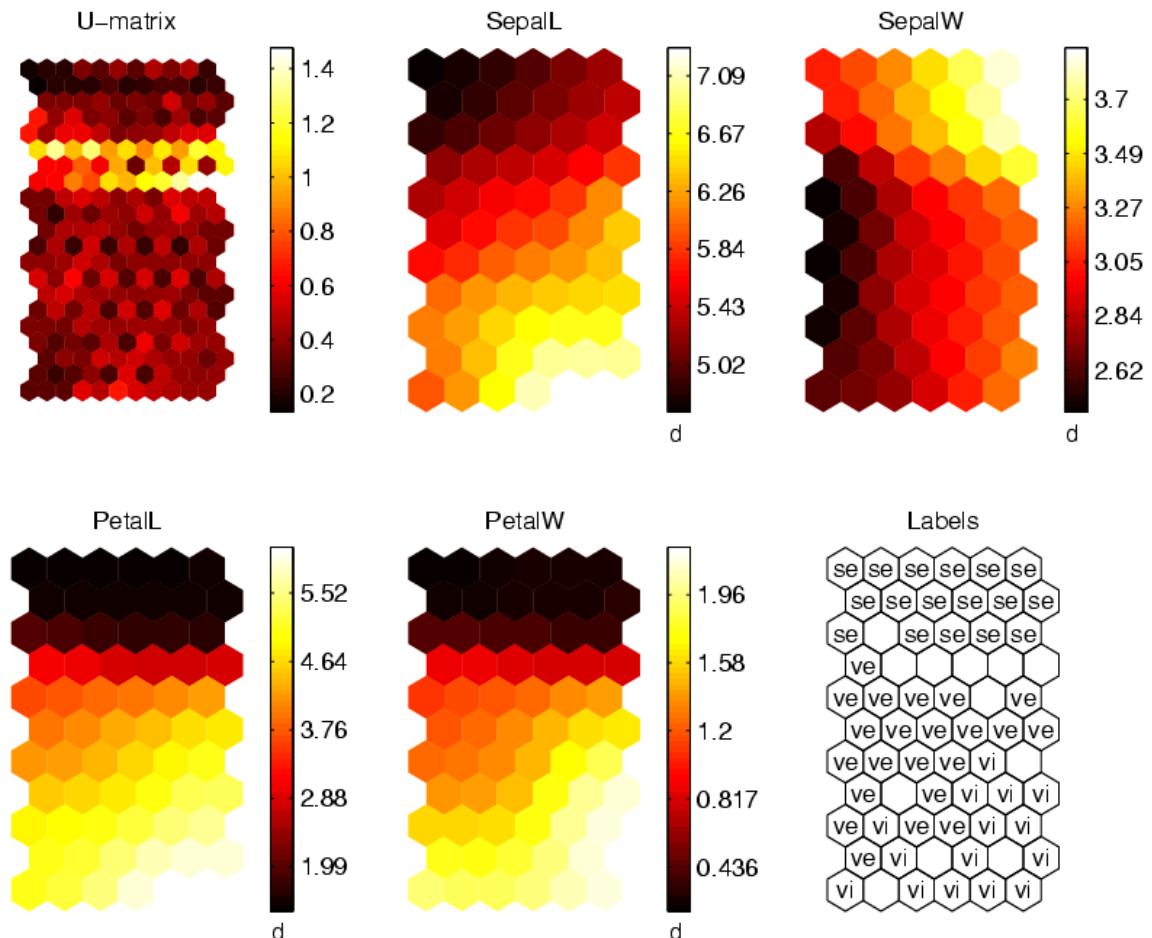
no.	Sepal.Length	Sepal.Width	Petal.Length	Petal.Width	Species
1	5.1	3.5	1.4	0.2	setosa
2	4.9	3.0	1.4	0.2	setosa
3	4.7	3.2	1.3	0.2	setosa
4	4.6	3.1	1.5	0.2	setosa
5	5.0	3.6	1.4	0.2	setosa
			...		
76	6.6	3.0	4.4	1.4	versicolor
			...		
150	5.9	3.0	5.1	1.8	virginica

Iris Flowers



● Iris Setosa    ● Iris Versicolor    ● Iris Virginica

The sepal length, sepal width, petal length, and petal width are measured in centimeters on fifty iris specimens from each of three species, *Iris setosa*, *I. versicolor*, and *I. virginica*. Fisher (1936)



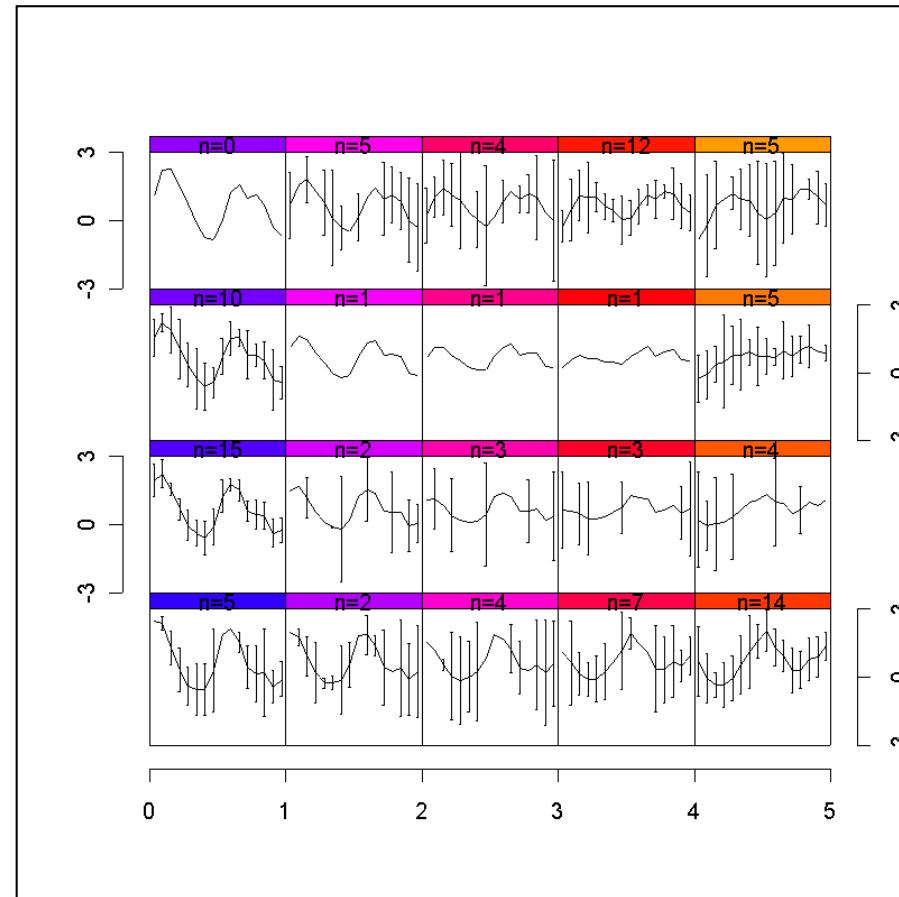
Source from technical Report on SOM Toolbox 2.0 for Matlab

Software: SOM Toolbox 2.0 for Matlab



# R: SOM

```
library(som)
cell.som <- som(cell.sdata, xdim=5, ydim=4, topol="rect", neigh="gaussian")
plot(cell.som)
```



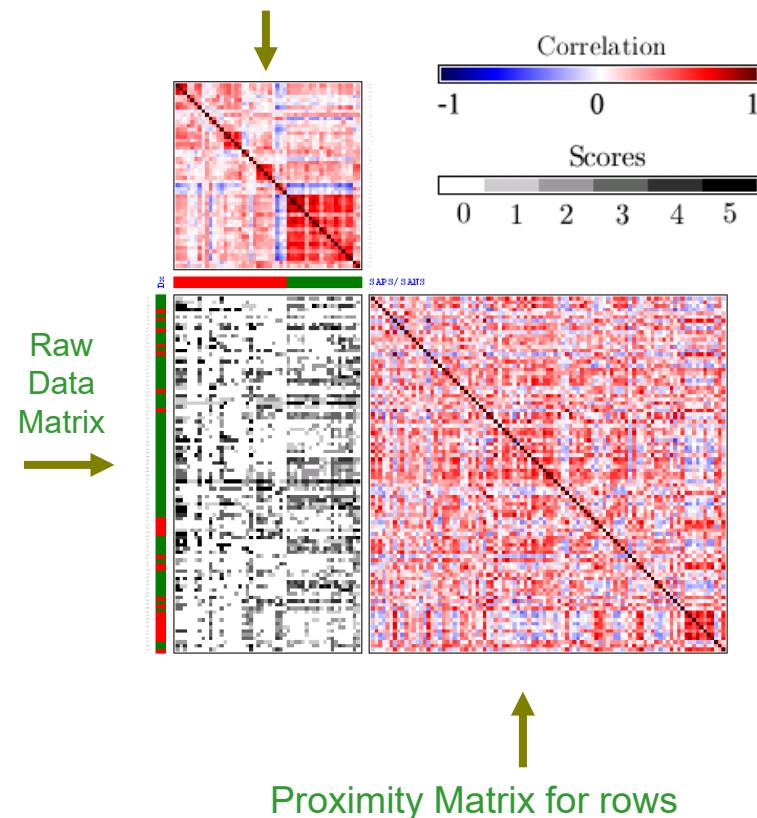


# Generalized Association Plots (GAP) 72/122

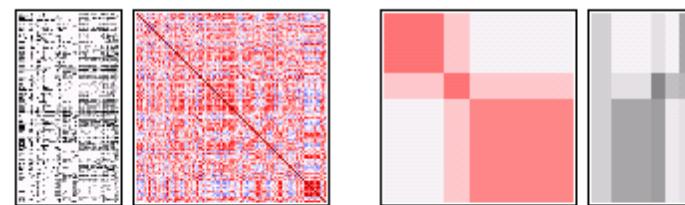
(Chen, 2002)

- 95 patients: 69 schizophrenic and 26 bipolar disorders
- SAPS: 30 items, SANS: 20 items
- Six point scale (0-5).

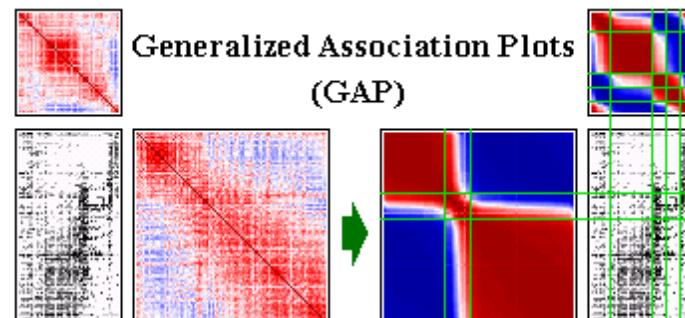
Proximity Matrix for columns



- ① Raw Data Maps  
原始資料與關係  
矩陣之呈現
- ④ Sufficient Data Maps  
充分統計圖



廣義相關圖  
全矩陣式資料視覺化



- ② Sorted Data Maps  
排序後之資料矩陣  
與關係矩陣
- ③ Partitioned Data Maps  
分群後之資料矩陣  
與關係矩陣

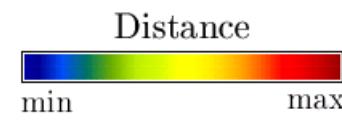
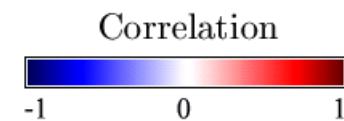
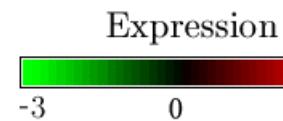
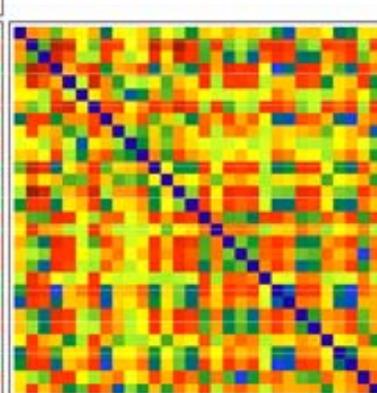
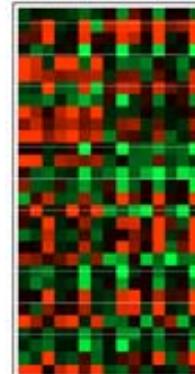
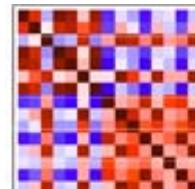


# Presentation of Raw Data Matrix

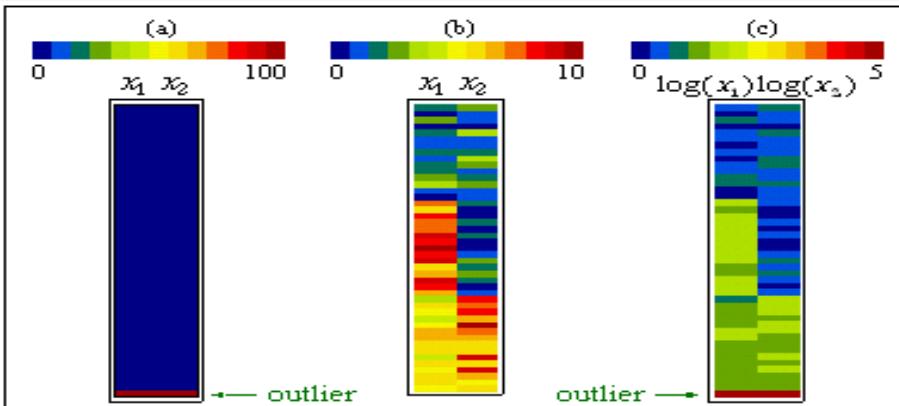
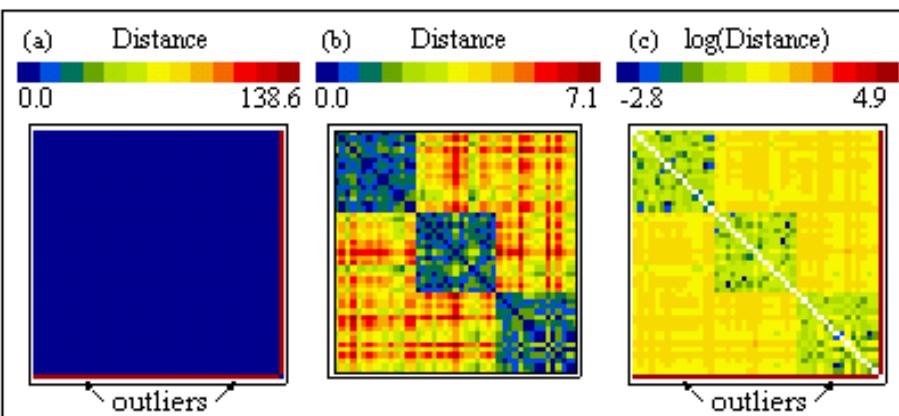
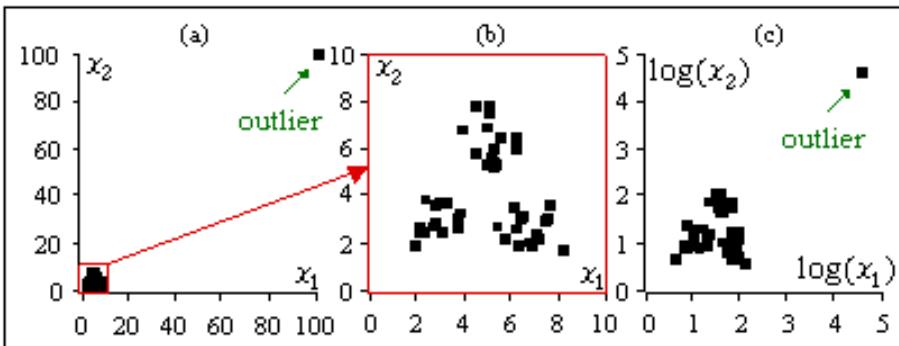
73/122

Image source: Dr. Chen Chun-houh's Slide

1. Color spectrum
2. Variable transformation
3. Selection of proximity



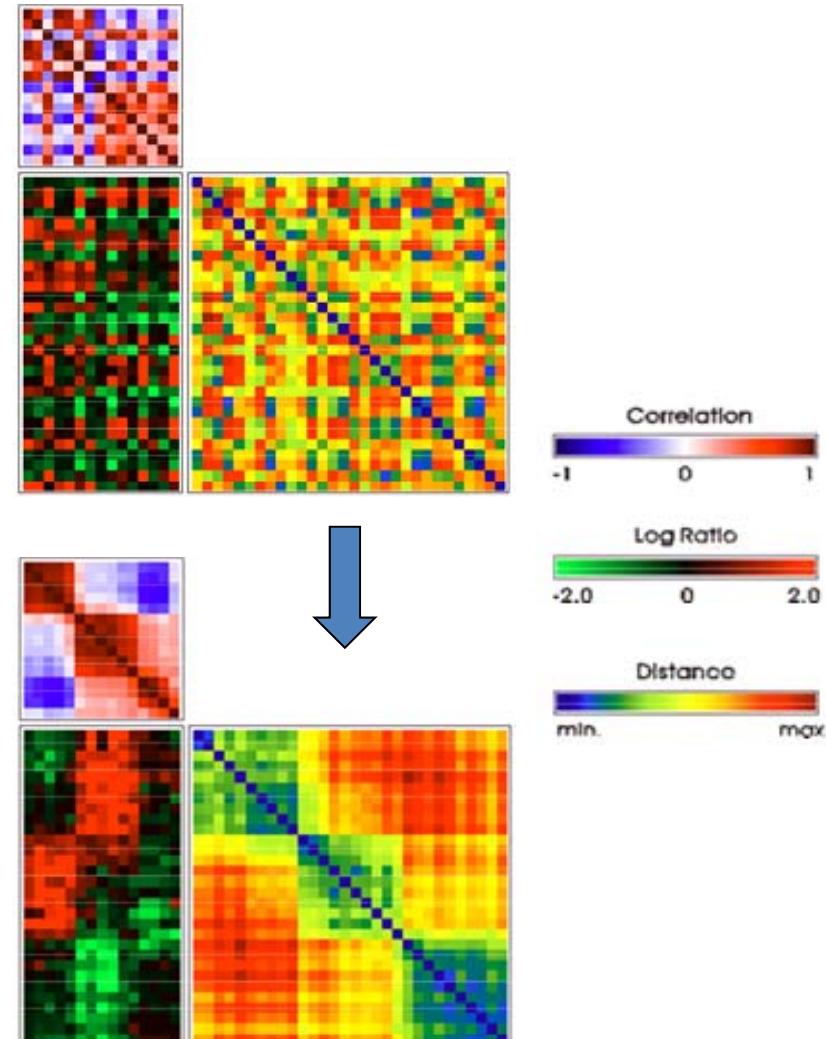
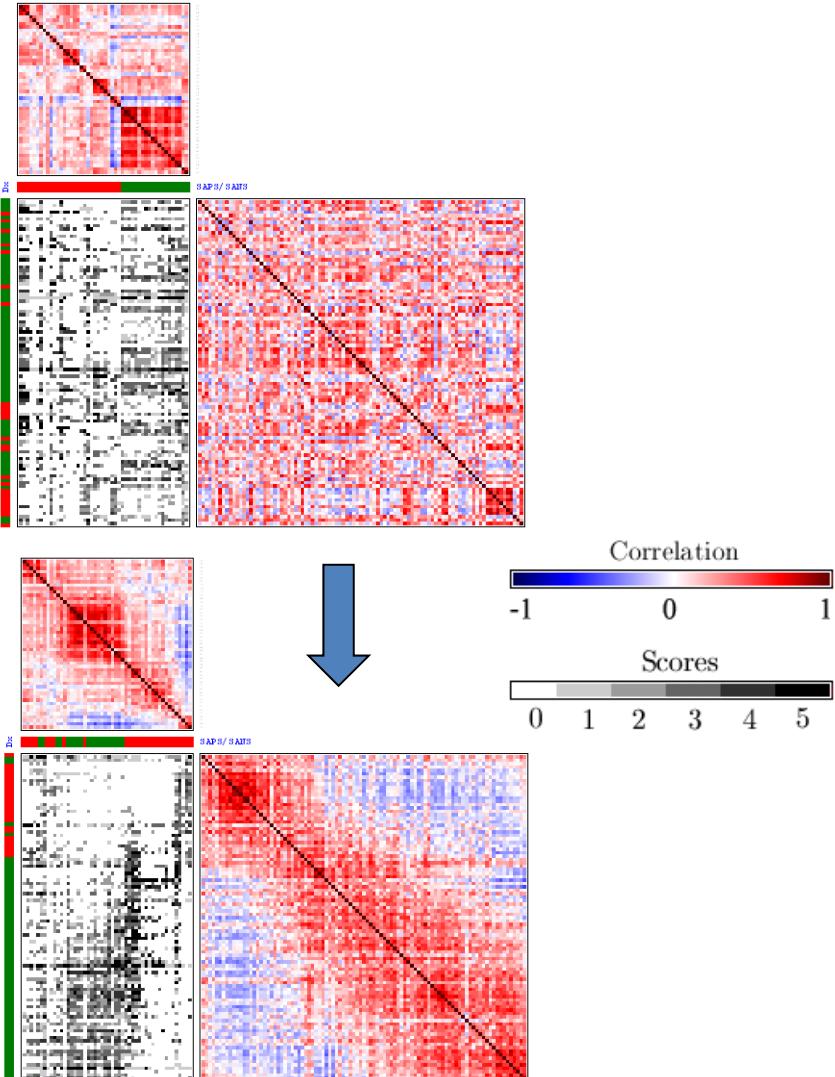
“Resolution”  
of a  
Statistical  
Graph





# Concept of Relativity of a Statistical Graph

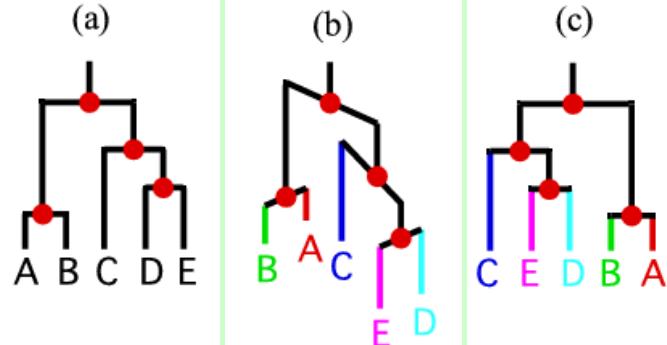
Placing similar (different) objects at closer (distant) positions



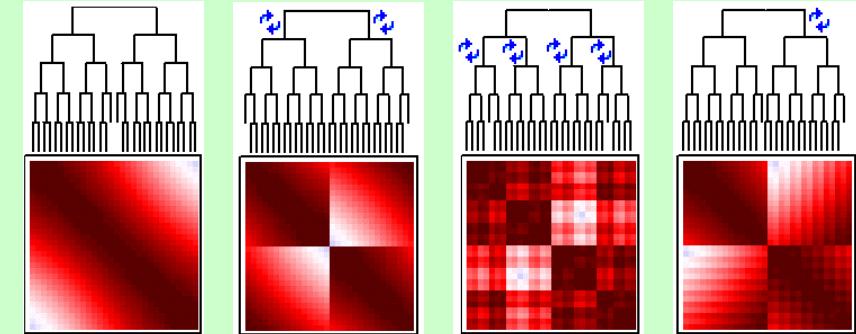
# Seriation Problem for Hierarchical Clustering



Tree seriation

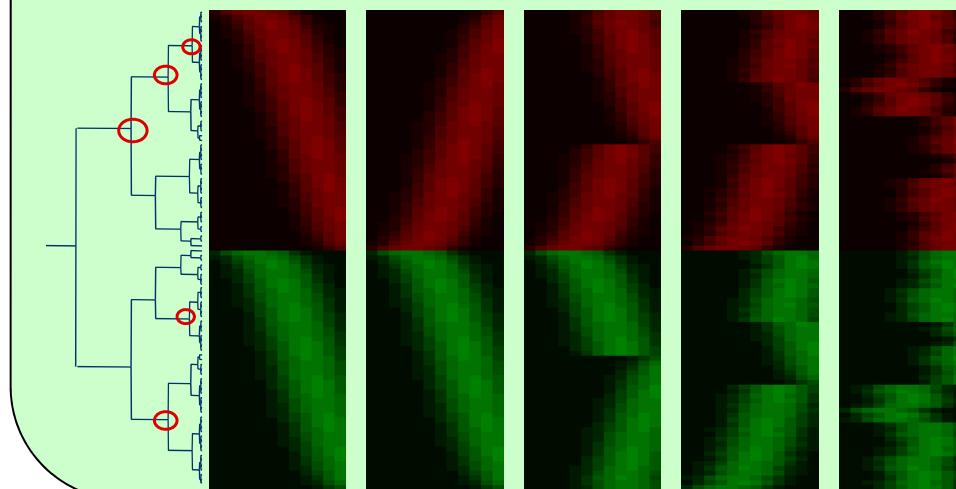


Tree seriation for proximity matrices



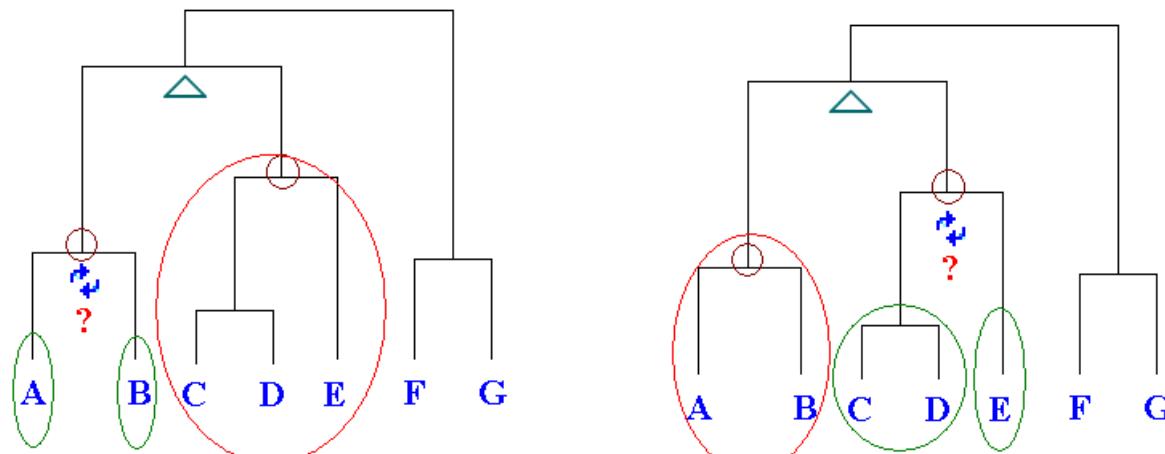
Tree seriation for raw data matrices

ideal model      1 flip      3 flips      5 flips      many flips



Different Seriations  
Generated from Identical  
Tree Structure

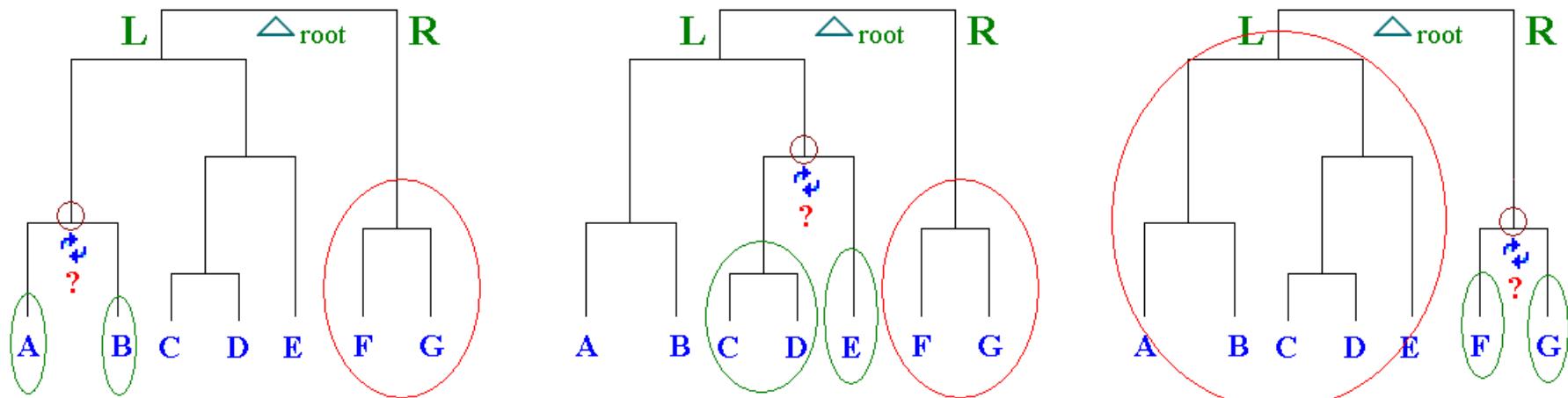
# Internal Tree Flips: Uncle Approach



if  $d(A, \{C, D, E\}) < d(B, \{C, D, E\})$  then flip

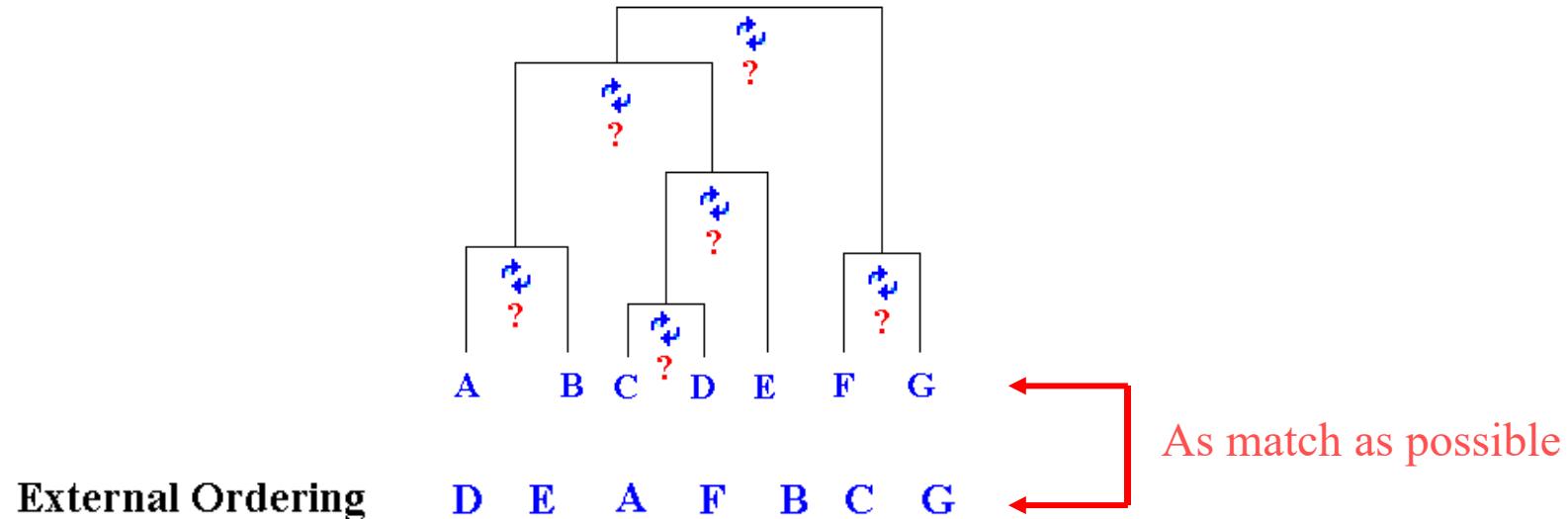
*Further reading:* Ziv Bar-Joseph, David K. Gifford, and Tommi S. Jaakkola, (2001), **Fast Optimal Leaf Ordering** for Hierarchical Clustering. Bioinformatics 17(Suppl. 1):S22–S29.

# Internal Tree Flips: GrandPa Approach



*Further reading:* Ziv Bar-Joseph, David K. Gifford, and Tommi S. Jaakkola, (2001), **Fast Optimal Leaf Ordering** for Hierarchical Clustering. Bioinformatics 17(Suppl. 1):S22–S29.

# External Tree Flips

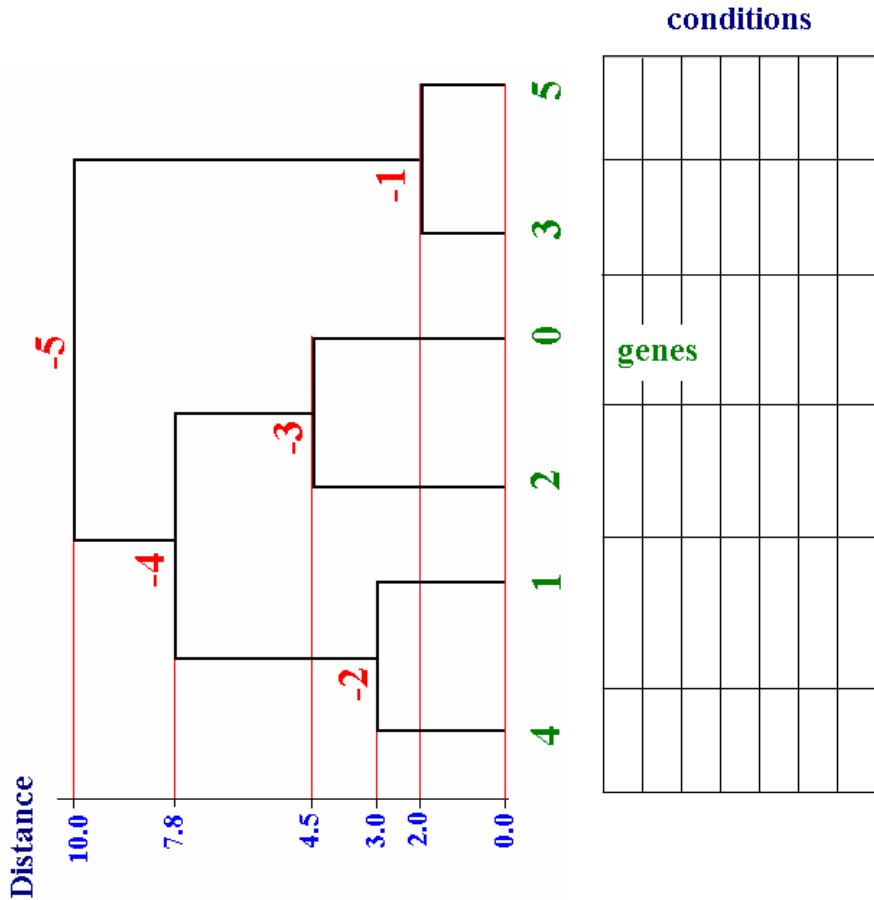


## How to build an external ordering?

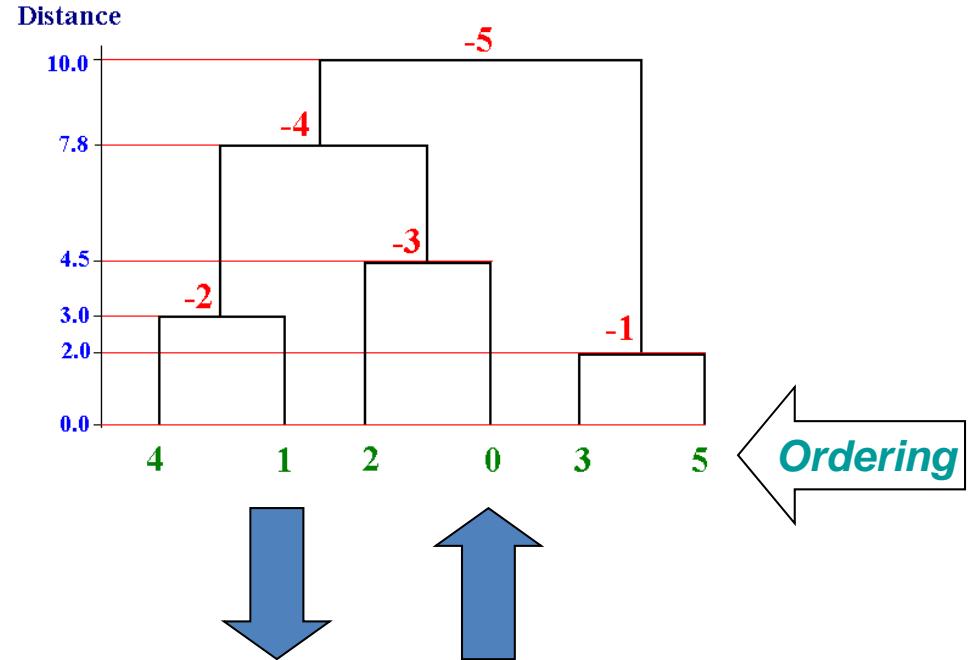
- (1) Based on average expression level (Cluster Software, Eisen et al 1998)
- (2) Using the results of a one-dimensional SOM
- (3) ...

*Further reading:* Tien, Y. J., Lee, Y. S, Wu, H. M. and Chen, C. H. (2006) Integration of clustering and visualization methods for simultaneously identifying coherent local clusters with smooth global patterns in gene expression profiles. BMC Bioinformatics.

# Dendrogram and Tree Storage



*For example:*  
Cluster and TreeView, R

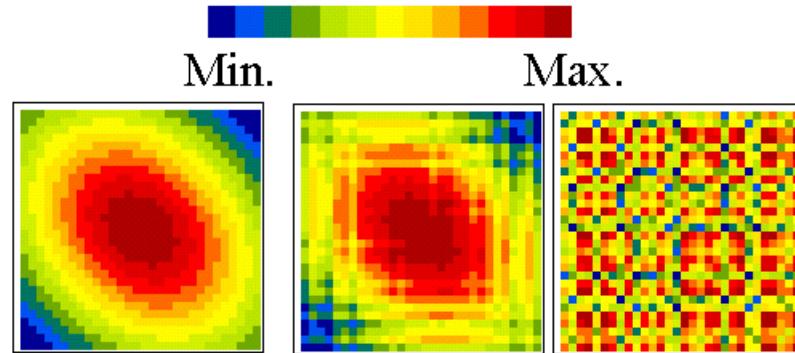


no	NodeID	Left	Right	Distance
0	-1	3	5	2
1	-2	4	1	3
2	-3	2	0	4.5
3	-4	-2	-3	7.8
4	-5	-4	-1	10



# Criteria for a “good” Permutation

80/122



**Robinson**

**pre-Robinson**

**Robinson Form**

	$j$	$k$				
$i$						
$i$						

$$r_{ij} \leq r_{ik} \text{ if } j < k < i, \quad r_{ij} \geq r_{ik} \text{ if } i < j < k$$

When  $T$  is symmetric, we usually want  $T'$  to approximate a Robinson form (Robinson (1951)).

## Global/local Criterion: Anti-Robinson Measurements

permuted matrix,  $D = [d_{ij}]$

$$AR(i) = \sum_{i=1}^p \left[ \sum_{j < k < i} I(d_{ij} < d_{ik}) + \sum_{i < j < k} I(d_{ij} > d_{ik}) \right],$$

$$AR(s) = \sum_{i=1}^p \left[ \sum_{j < k < i} I(d_{ij} < d_{ik}) \cdot |d_{ij} - d_{ik}| + \sum_{i < j < k} I(d_{ij} > d_{ik}) \cdot |d_{ij} - d_{ik}| \right],$$

$$AR(w) = \sum_{i=1}^p \left[ \sum_{j < k < i} I(d_{ij} < d_{ik}) |j - k| |d_{ij} - d_{ik}| + \sum_{i < j < k} I(d_{ij} > d_{ik}) |j - k| |d_{ij} - d_{ik}| \right].$$

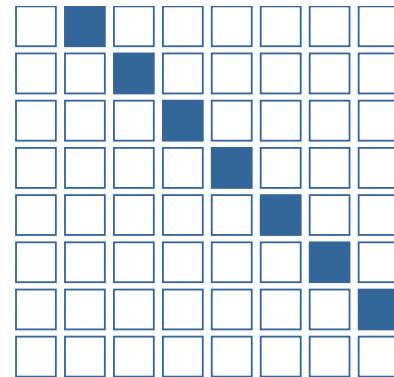


# Criteria for a “good” Permutation

81/122

permuted matrix,  $D = [d_{ij}]$

Local criterion: **Minimal Span Loss Function**

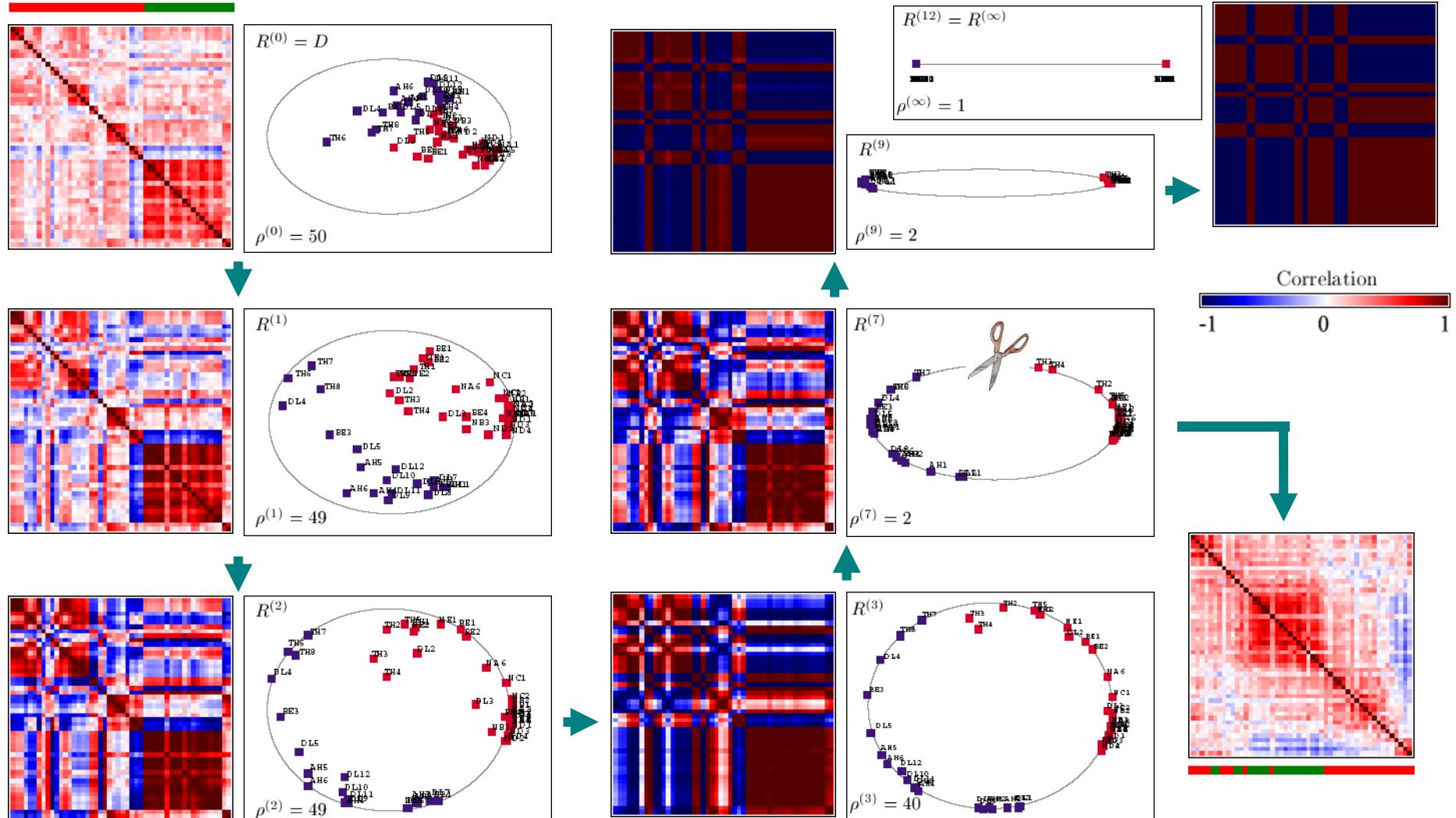


$$MS = \sum_{i=1}^{n-1} d_{i,i+1}$$

*Further Reading:* Michael Friendly , Ernest Kwan, (2003) Effect ordering for data displays, Computational Statistics & Data Analysis, v.43 n.4, p.509-539.

# GAP Rank-Two Elliptical Seriation

- Seriation Algorithms with Converging Correlation Matrices.
- When the sequence reaches an iteration with **rank two**, the  $p$  objects fall on an ellipse and have unique relative position on the ellipse.

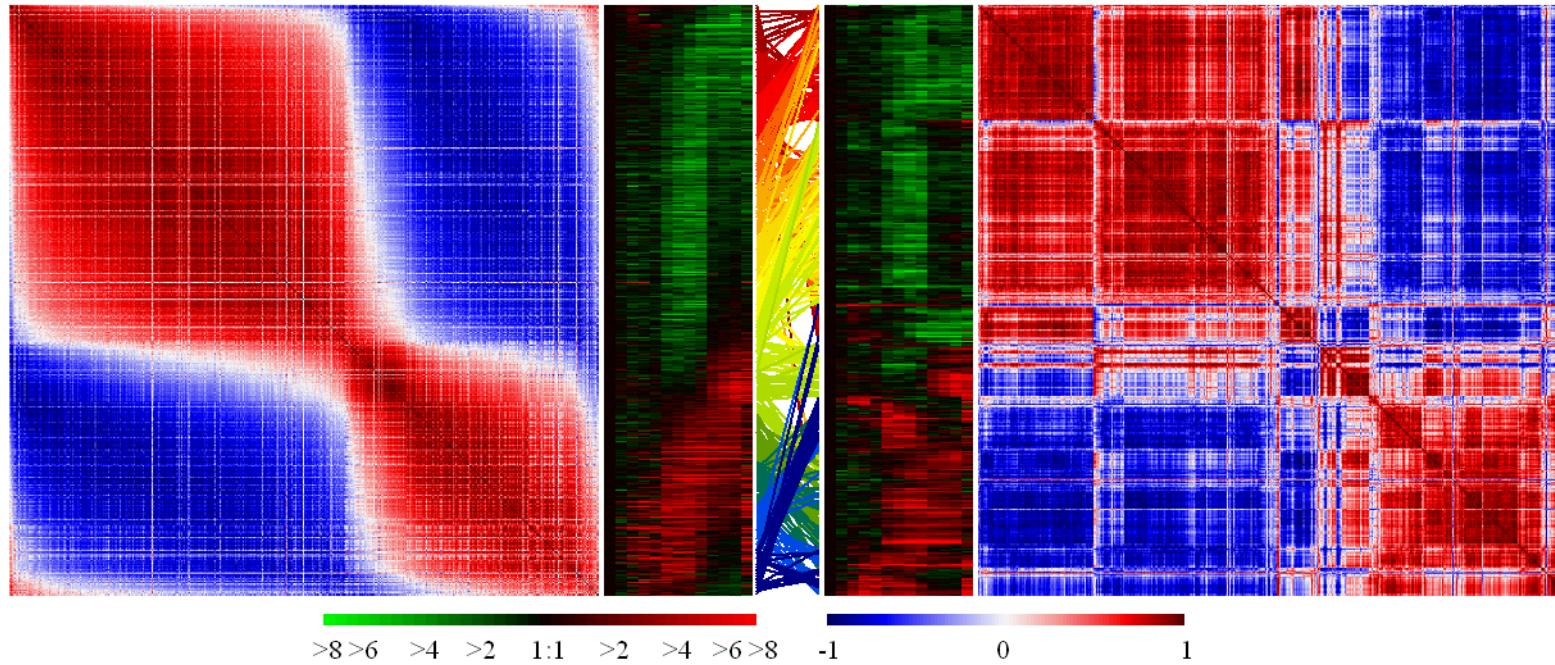


# Global vs Local Seriation

## GAP Elliptical Seriation

An algorithm for identifying global clustering patterns and smoothing temporal expression profiles

GAP Elliptical Seriation



Michael Eisen Tree Seriation

Image source: Dr. Chen Chun-houh's slide

# Sufficient Graph

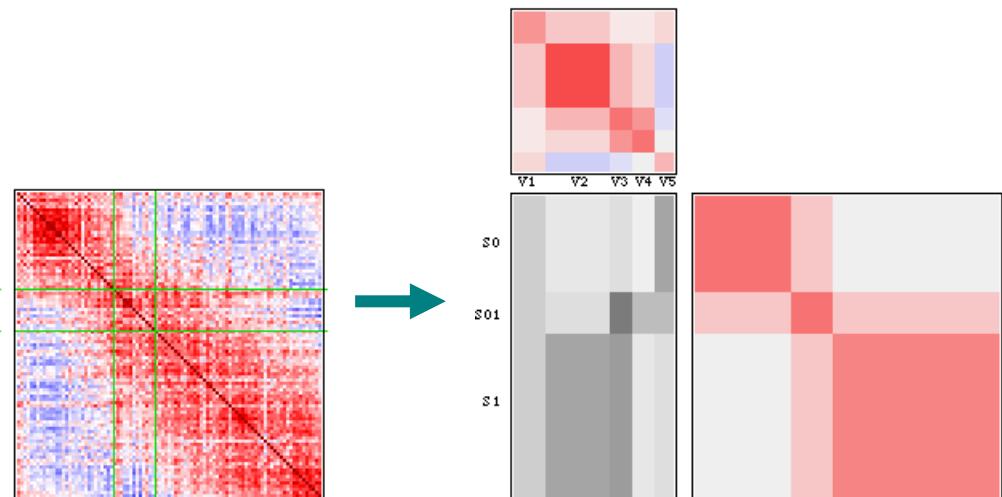
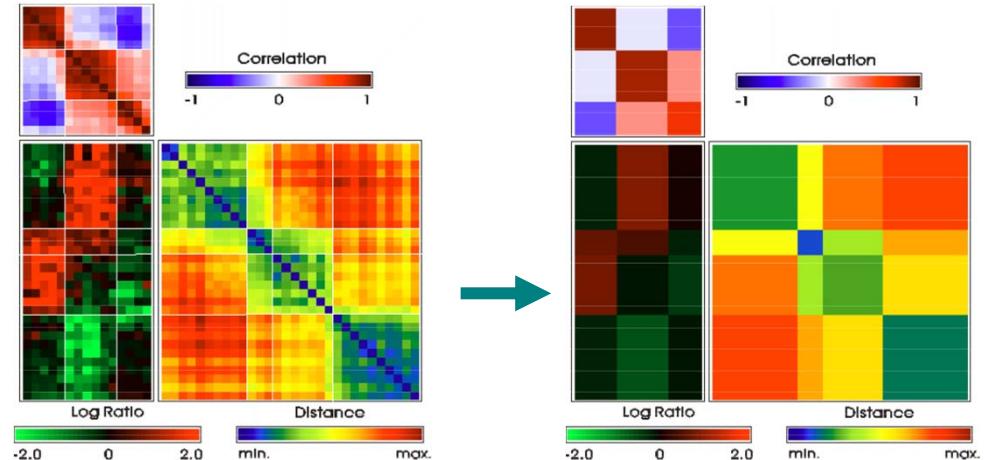
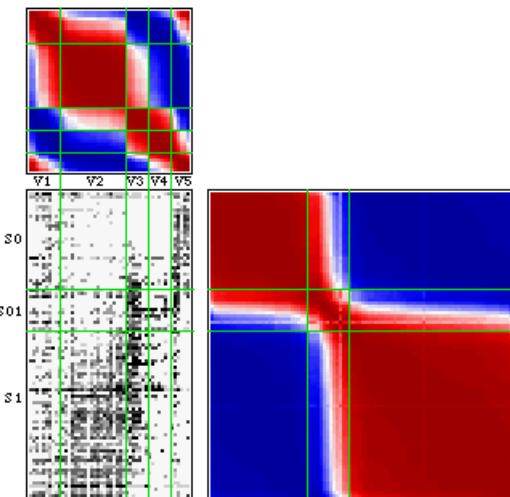


	A	B	C	D	E	F
1	學號	小考1	期中考	小考2	期末考	報告
2	A01	69	92	85	45	62
3	A02	66	90	83	36	90
4	A03	72	92	80	62	70
5	A04	68	90	60	37	95
6	A05	74	60	86	54	70
7	A06	77	90	88	88	95
8	A07	73	88	77	51	95
9	A08	61	90	84	40	82
10	A09	66	88	82	39	80
11	A10	76	75	87	72	80
12	A11	64	90	90	26	95
13	A12	75	90	60	55	70
14	A13	92	90	83	90	95

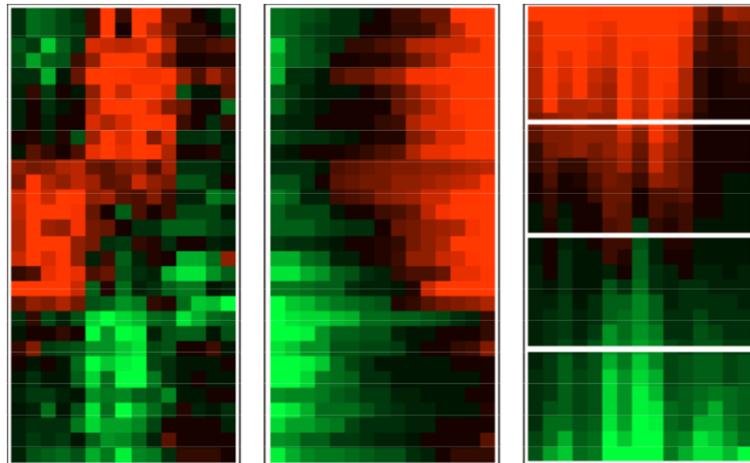
Sufficient  
Statistic

	小考1	期中考	小考2	期末考	報告
平均	71.77	86.54	80.38	53.46	83
低平均	65.67	81.83	73.67	53.67	72
高平均	77.83	90.67	86.67	53.67	94.17

70



Sedimented MV for patients and symptoms.

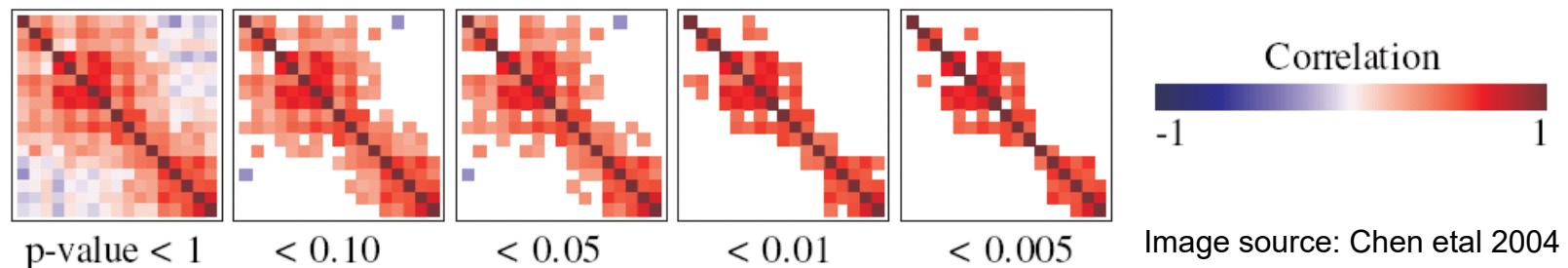


The sediment MV for patients: express severity structure.

The sediment MV for symptoms: this is a side-by-side bar-chart and box-plot which displays the distribution structure for all symptoms simultaneously.

Image source: Chen et al 2004

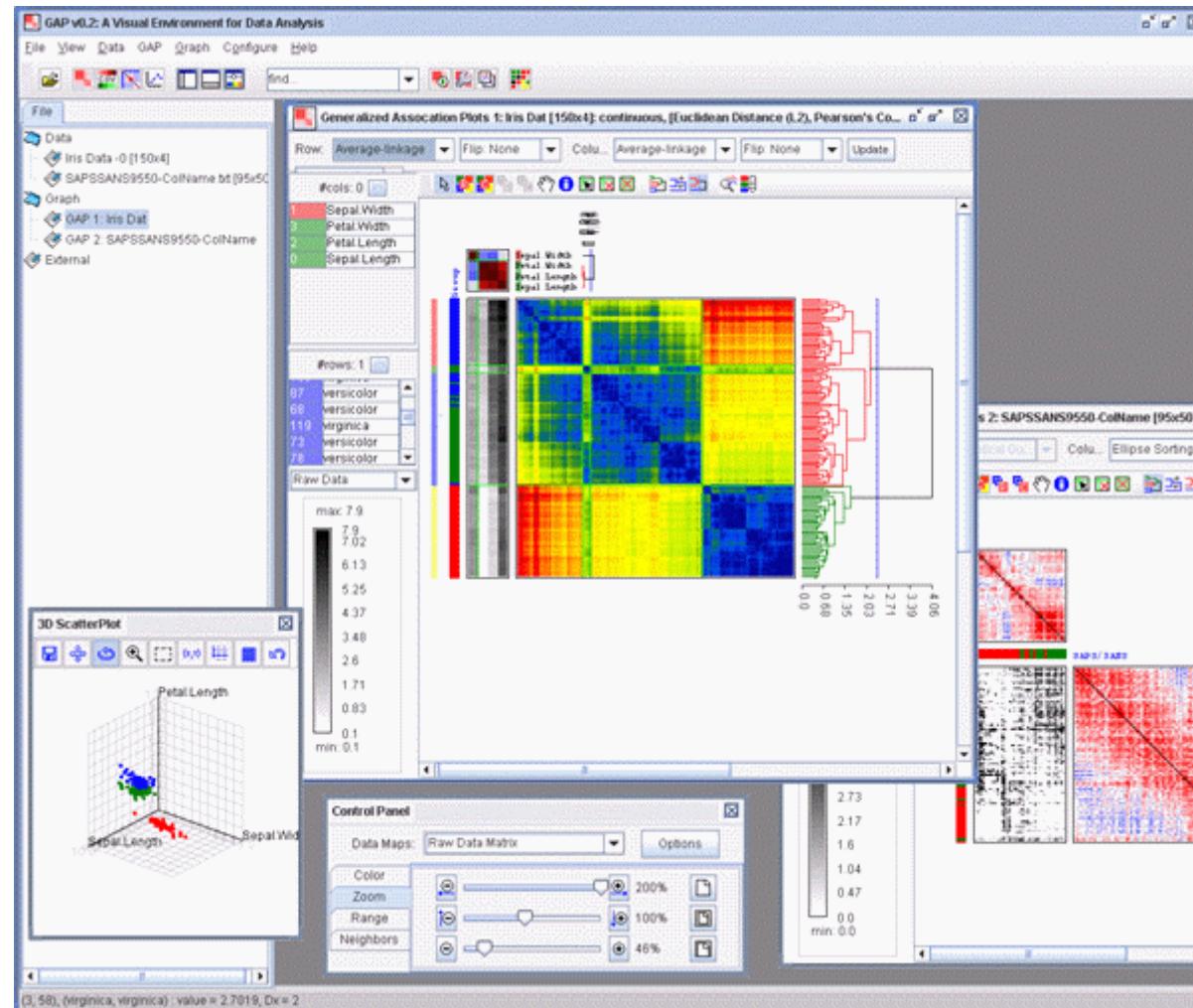
Sectional MV for the permuted correlation coefficient map.



# GAP Software

<http://www.hmwu.idv.tw/GAPSoftware/>

MacOS: <http://gap.stat.sinica.edu.tw/Software/download.htm>



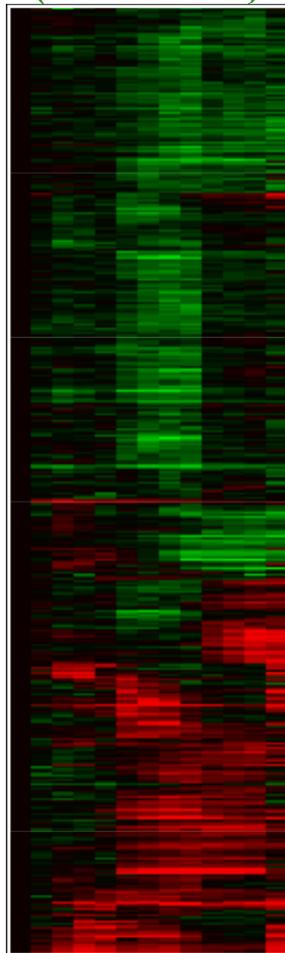
See also:  
R **seriation** package



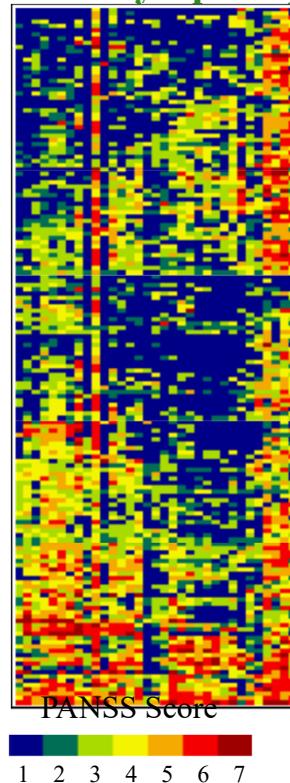
# Visualization of Data Matrices

Simple ← Information Visualization of Data Matrices → Difficult

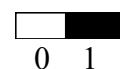
Continuous  
(Gene/Time)



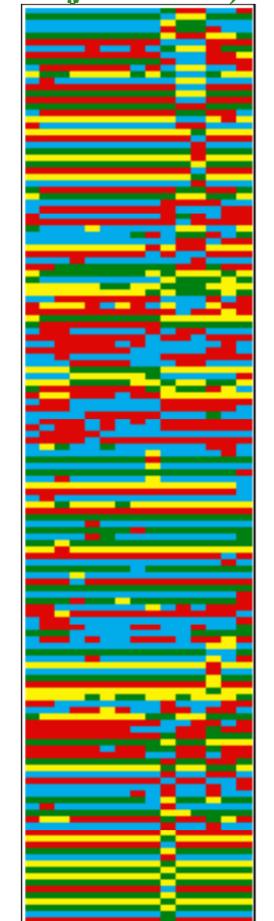
Ordinal  
(Patient/Symptom)



Binary  
(Mouse/Tumor)



Categorical  
(Subject/SNP)



>8 >6 >4 >2 1:1 >2 >4 >6 >8 Log2ratio

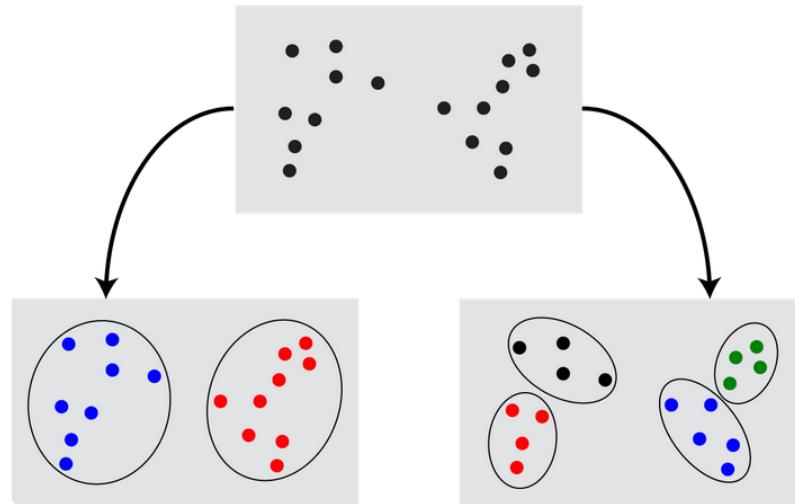
Image source:  
Prof. Chen, Chun-houh's slide



# Choosing the Number of Clusters 88/122

## (1/2)

Are these data better described by 2 or 4 clusters?

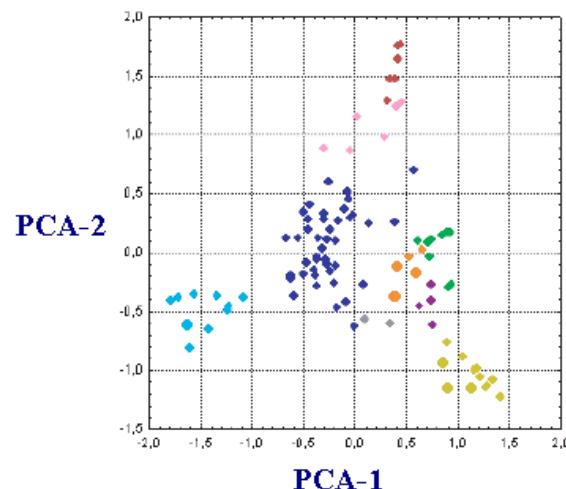


Source: <http://alexhwilliams.info/itsneuronalblog/2015/09/11/clustering1/>

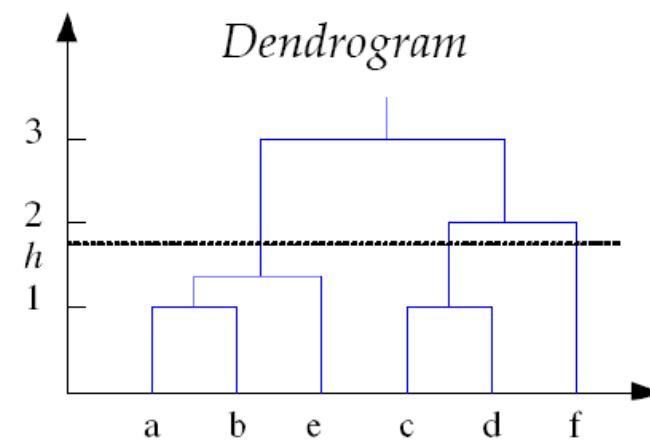
**(1)** K is defined by the application.

Calinski and Harabasz (1974):  $CH(k)$   
Hartigan (1975):  $H(k)$   
Krzanowski and Lai (1985):  $KL(k)$   
Kaufman and Rousseeuw (1990):  $s(i)$

**(2)** Plot the data in two PCA dimensions.



**(3)** Hierarchical clustering:  
look at the difference between  
levels in the tree.

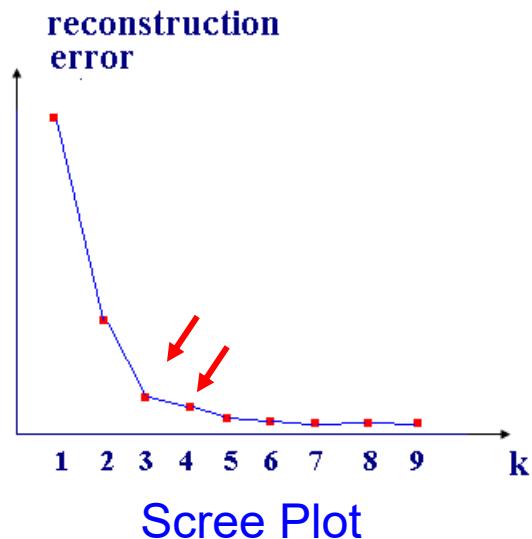




# Choosing the Number of Clusters

(4) Plot the **reconstruction error** or log likelihood as a function of k, and look for the elbow.

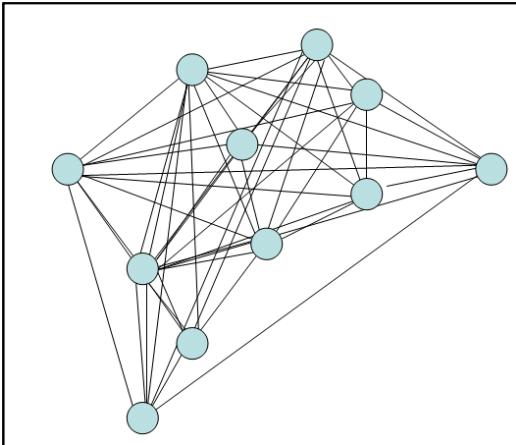
(e.g., k-means: within-cluster sum of squares)



```
> kmeans(iris[, 1:4], 3)
K-means clustering with 3 clusters of sizes 62,
50, 38
...
Within cluster sum of squares by cluster:
[1] 39.82097 15.15100 23.87947
(between_SS / total_SS =  88.4 %)
...
```



# Gap Statistic for Estimating the Number of Clusters

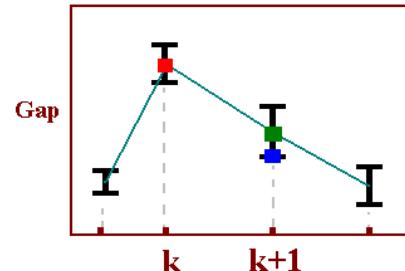


## Computational Implementation

### Within-Cluster Sum of Squares

$$D_r = \sum_{i \in C_r} \sum_{j \in C_r} \|x_i - x_j\|^2$$

$$W_k = \sum_{r=1}^k \frac{1}{2n_r} D_r$$



*J. R. Statist. Soc. B (2001)  
63, Part 2, pp. 411–423*

### Estimating the number of clusters in a data set via the gap statistic

Robert Tibshirani, Guenther Walther and Trevor Hastie  
Stanford University, USA

$$\text{Gap}_n(k) = E_n^* \{\log(W_k)\} - \log(W_k)$$

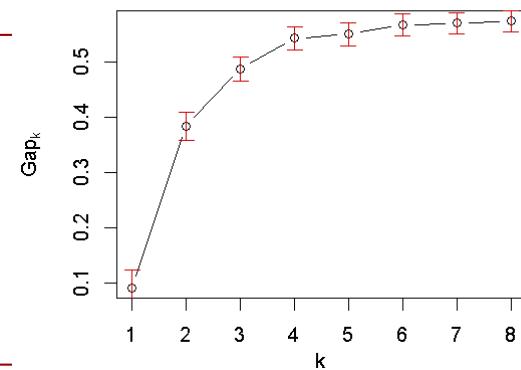
choose the number of clusters via

$\hat{k}$  = smallest  $k$  such that

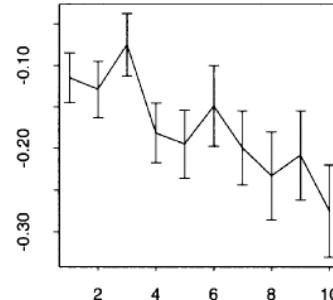
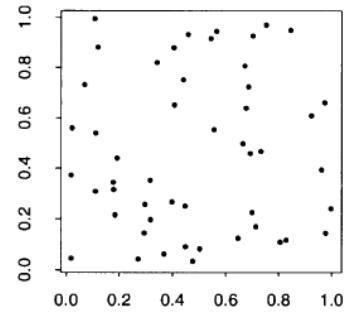
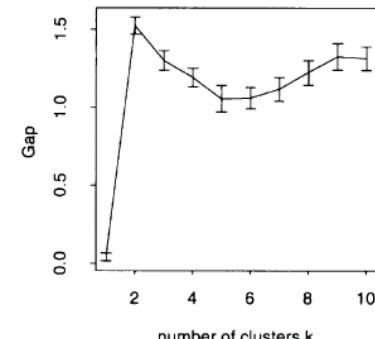
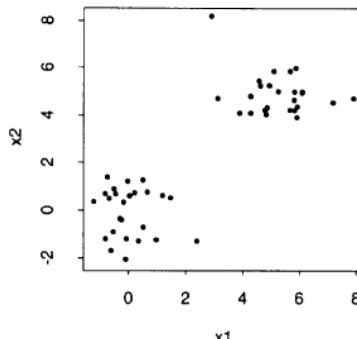
$$\text{Gap}(k) \geq \text{Gap}(k + 1) - s_{k+1}$$

```
> library(cluster)
> x <- iris[, 1:4]
> gskmn <- clusGap(x, FUN = kmeans, nstart = 20, K.max = 8, B = 60)
Clustering k = 1,2,..., K.max (= 8): .. done
Bootstrapping, b = 1,2,..., B (= 60) [one "." per sample]:
..... 50
..... 60
> plot(gskmn, main = "clusGap(., FUN = kmeans, n.start=20, B= 60)")
```

clusGap(., FUN = kmeans, n.start=20, B= 60)

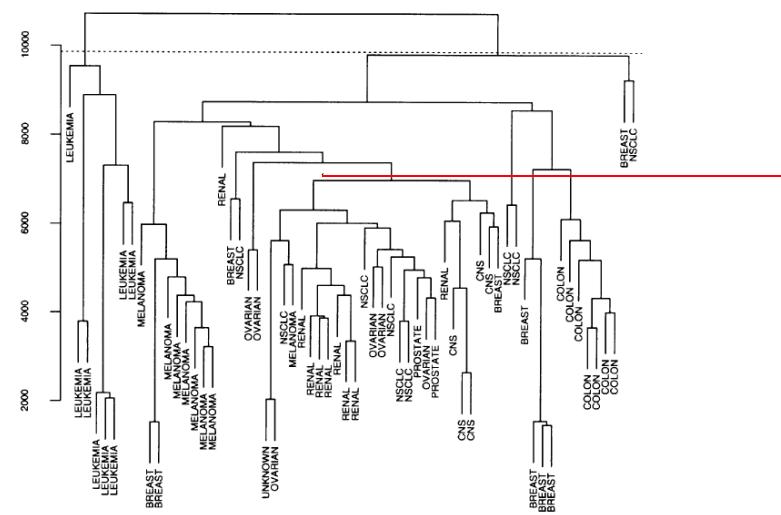


# gap statistics

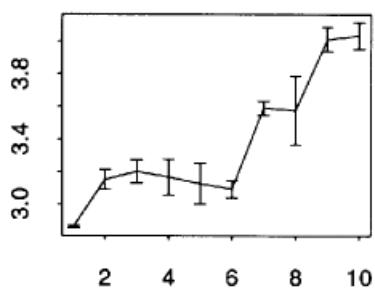


## *application to hierarchical clustering and DNA microarray data*

$6834 \times 64$  matrix



<http://www-genome.stanford.edu/nci60>



*See Also:* [NbClust](#): Determining the Best Number of Clusters in a Data Set

It provides **30 indexes** for determining the optimal number of clusters in a data set and offers the best clustering scheme from different results to the user.



# Cluster Validation

Assess the **quality** and **reliability** of the cluster sets.

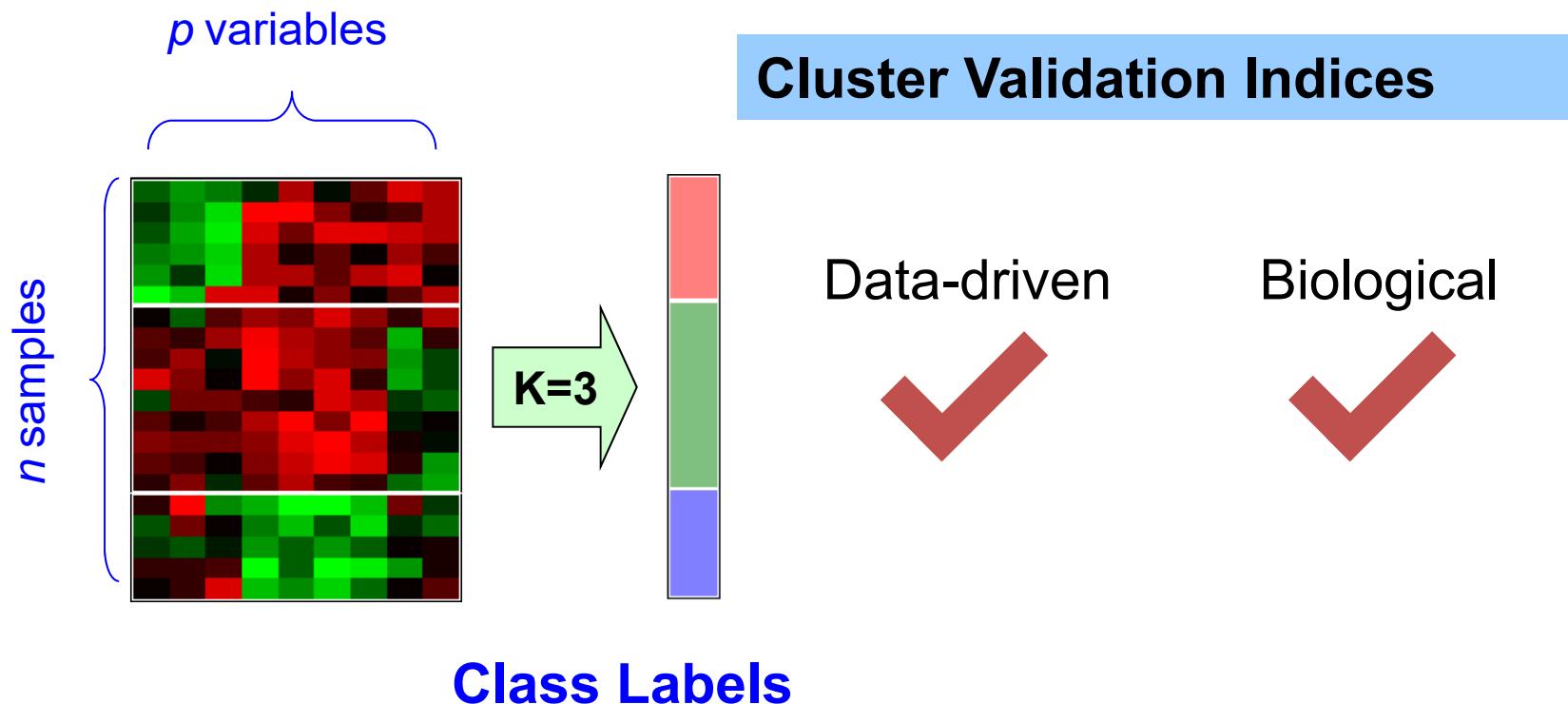
- **Quality:**  
clusters can be measured in terms of **homogeneity** and **separation**.
- **Reliability:**  
cluster structure is not formed by chance.
- **Ground Truth:**  
from domain knowledge.

**NOTE:**

Help to decide the **number of clusters** in the data.

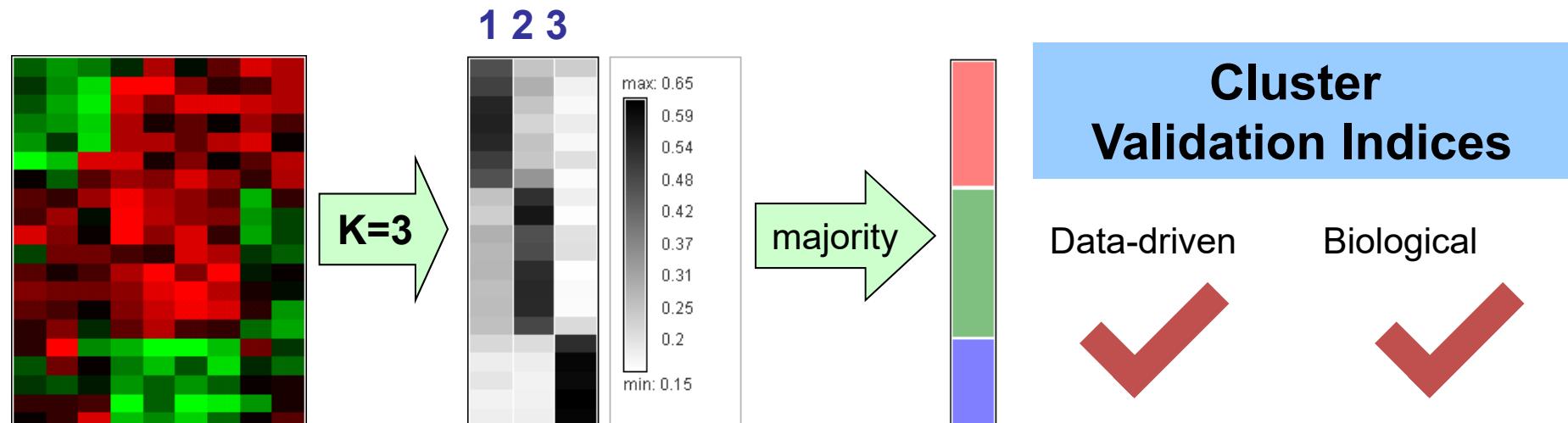
# Validation Indices for Hard Clustering

- K-means, SOM, Hierarchical Clustering,...



# Validation Indices for Soft Clustering

- Fuzzy c-means, Model-based clustering, ...



## Class Membership      Class Labels Cluster Validation Indices

Data-driven



Biological



Wu, H. M.\* (2011), On Biological Validity Indices for Soft Clustering Algorithms for Gene Expression Data, Computational Statistics and Data Analysis, 55(5), 1969-1979.



# Literatures on Cluster Validation (1/2)

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# Literatures on Cluster Validation (2/2)

2007

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- Francisco R. Pinto, João A. Carriço, Mário Ramirez and Jonas S Almeida, (2007), Ranked Adjusted Rand: integrating distance and partition information in a measure of clustering agreement, *BMC Bioinformatics*, 8:44.

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- Susmita Datta and Somnath Datta, (2006), Methods for evaluating clustering algorithms for gene expression data using a reference set of functional classes, *BMC Bioinformatics* 2006, 7:397. [web]
- Anbupalam Thalamuthu, Indranil Mukhopadhyay, Xiaojing Zheng and George C. Tseng, (2006), Evaluation and comparison of gene clustering methods in microarray analysis, *Bioinformatics* 22(19), 2405-2412.
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- Nikhil R Garge, Grier P Page, Alan P Sprague , Bernard S Gorman and David B Allison, Reproducible Clusters from Microarray Research: Whither? *BMC Bioinformatics* 2005, 6(Suppl 2):S10. [web]



# Cluster Validation Index

**Internal Measures**

**Stability Measures**

**Comparing Partitions**

**Biological Measures**

**Cluster Validation**

Internal Measures       Stability Measures

Comparing Partitions       Biological Measures

**Internal Measures**

(1) Dunn Index      (2) Within Cluster Variance  
(3) Silhouette Width      (4) Connectivity

**Stability Measures**

(1) APN: Average Proportion of Non-overlap      (2) AD: Average Distance  
(3) ADM: Average Distance between Means      (4) FOM: Figure of Merit

**Comparing Partitions**

(1) Rand Index      (2) Adjusted Rand Index  
(3) Jaccard Coefficient      (4) Minkowski Index

LungMarkerGene\_68x144-marker.txt ...

**Biological Measures**

(1) BHI: Biological Homogeneity Index      (2) BSI: Biological Stability Index

LungMarkerGene\_68x144-marker.txt ...

**Buttons:** Close   Report

**See:** *clValid*: an R package for cluster validation.



# Statistical Evaluation: Internal Measures

Compactness

Homogeneity

Separation

## Connectivity

$$Conn(\mathcal{C}) = \sum_{i=1}^N \sum_{j=1}^L d_{i,nn_{i(j)}}$$

$d_{i,nn_{i(j)}} = \begin{cases} 0, & \text{for } i \text{ and } j \text{ are in the same cluster,} \\ 1/j, & \text{otherwise.} \end{cases}$

## Dunn index (Dunn, 1974)

$$D(\mathcal{C}) = \frac{\min_{C_k, C_l \in \mathcal{C}, C_k \neq C_l} \left( \min_{i \in C_k, j \in C_l} \text{dist}(i, j) \right)}{\max_{C_m \in \mathcal{C}} \text{diam}(C_m)}$$

## Within-cluster Variance

$$V(\mathcal{C}) = \sqrt{\frac{1}{N} \sum_{C_k \in \mathcal{C}} \sum_{i \in C_k} \text{dist}(i, \mu_k)}$$

## Silhouette Width (Rousseeuw, 1987)

$$S(\mathcal{C}) = \sum_{i=1}^N \frac{S(i)}{N}, \quad S(i) = \frac{b_i - a_i}{\max(b_i, a_i)}$$

the average distance between  $i$  and  
the observations in the closest other cluster

the average distance between  $i$  and  
all other observations in the same cluster.



# Statistical Evaluation: Stability

99/122

- Average Proportion of Non-overlap (APN)
- Average Distance (AD)
- Average Distance between Means (ADM)
- Prediction Strength: Figure of Merit (FOM)

	A	B	C	D	E	F	G	H	I
1	-1.37	-2.30	-1.80	-0.55	2.45	-0.13	1.49	3.03	2.48
2	-0.68	-2.11	-3.42	4.67	4.57	1.75	0.61	0.92	2.52
3	-1.19	-2.49	-3.66	3.14	1.70	3.29	3.33	2.92	2.48
4	-1.93	-2.28	-3.16	2.51	0.82	1.49	0.21	2.20	1.03
5	-0.24	-0.13	-0.14	-0.13	-0.14	-0.14	-0.14	-0.14	-0.14
6	-4.14	-2.91	-1.64	3.21	0.37	1.93	0.14	1.27	2.67
7	0.21	-1.36	-0.44	2.22	1.85	3.11	2.03	0.67	2.40
8	1.13	0.79	2.25	3.65	2.52	2.09	1.13	-2.59	0.67
9	0.95	2.33	-0.07	3.89	2.72	2.13	1.75	-2.17	-0.90
10	3.04	1.85	0.21	7.07	2.01	3.05	0.76	-2.58	-1.04
11	-1.02	1.65	1.53	0.95	0.60	3.12	2.52	-0.77	-1.40
12	1.21	0.24	1.04	2.50	3.69	1.81	3.98	-0.33	0.11
13	1.74	1.60	1.70	2.02	3.45	4.46	2.69	0.41	-0.09
14	1.34	1.06	0.06	1.81	2.90	3.64	3.04	0.49	-2.33
15	0.57	1.81	-0.47	1.40	2.70	0.99	0.82	-1.61	-2.56
16	0.61	4.22	-2.03	-2.61	-4.00	-4.64	-2.92	1.55	-0.71
17	-1.13	1.84	0.01	-1.77	-2.85	-1.24	-3.41	-0.59	-1.64
18	-0.86	-1.17	-0.41	-2.20	-1.30	-2.37	-1.41	0.08	0.25
19	0.75	0.66	1.04	-4.26	-1.41	-3.99	-3.53	-2.17	0.34
20	0.15	0.68	3.18	-2.86	-2.01	-3.18	-1.58	0.10	1.28

Full data ( $n \times p$ )

Compare two clusterings



Repeat: 1,...,p

	A	B	C	D	E	F	G	H
1	-1.37	-2.30	-1.80	-0.55	2.45	-0.13	1.49	3.03
2	-0.68	-2.11	-3.42	4.67	4.57	1.75	0.61	0.92
3	-1.19	-2.49	-3.66	3.14	1.70	3.29	3.33	2.92
4	-1.93	-2.28	-3.16	2.51	0.82	1.49	0.21	2.20
5	-2.21	-0.79	-3.29	2.55	2.44	1.45	2.68	3.03
6	-4.14	-2.91	-1.64	3.21	0.37	1.93	0.14	1.27
7	0.21	-1.36	-0.44	2.22	1.85	3.11	3.11	2.03
8	1.13	0.79	2.25	3.65	2.52	2.09	1.13	-2.59
9	0.95	2.33	-0.07	3.89	2.72	2.13	1.75	-2.17
10	3.04	1.85	0.21	7.07	2.01	3.05	0.76	-2.58
11	-1.02	1.65	1.53	0.95	0.60	3.12	2.52	-0.77
12	1.21	0.24	1.04	2.50	3.69	1.81	3.98	-0.33
13	1.74	1.60	1.70	2.02	3.45	4.46	2.69	0.41
14	1.34	1.06	0.06	1.81	2.90	3.64	3.04	0.49
15	0.57	1.81	-0.47	1.40	2.70	0.99	0.82	-1.61
16	0.61	4.22	-2.03	-2.61	-4.00	-4.64	-2.92	1.55
17	-1.13	1.84	0.01	-1.77	-2.85	-1.24	-3.41	-0.59
18	-0.86	-1.17	-0.41	-2.20	-1.30	-2.37	-1.41	0.08
19	0.75	0.66	1.04	-4.26	-1.41	-3.99	-3.53	-2.17
20	0.15	0.68	3.18	-2.86	-2.01	-3.18	-1.58	0.10

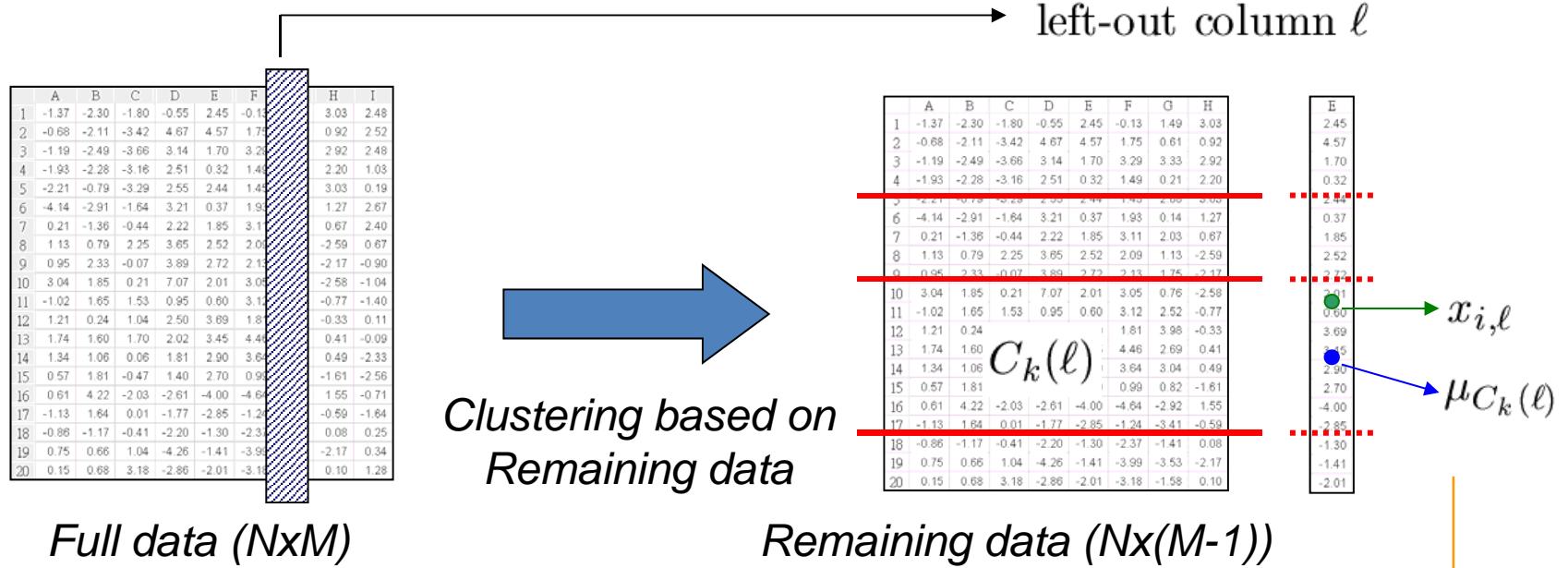
Remaining data ( $n \times (p-1)$ )

left-out column  $\ell$

sample



# Figure of Merit (FOM)





# Agreement with Reference Partition

- Rand index
- Jaccard coefficient
- Minkowski Measure
- Adjusted Rand index

$$\mathcal{U} = \{U_1, \dots, U_K\}$$

$$\mathcal{V} = \{V_1, \dots, V_s\}$$



$$A = \left[ \begin{array}{c|cccc} & O_1 & O_1 & \cdots & O_n \\ \hline O_1 & & & & \\ O_2 & & & & \\ \dots & & & & \\ O_n & & & & \end{array} \right] \quad B = \left[ \begin{array}{c|cccc} & O_1 & O_1 & \cdots & O_n \\ \hline O_1 & & & & \\ O_2 & & & & \\ \dots & & & & \\ O_n & & & & \end{array} \right]$$

$$A_{ij} = I(O_i \in U_k, O_j \in U_k)$$

$$B_{ij} = I(O_i \in V_s, O_j \in V_s)$$

- Rand index, [0, 1], maximum:

$$R(\mathcal{U}, \mathcal{V}) = \frac{n_{11} + n_{00}}{n_{00} + n_{01} + n_{10} + n_{11}}$$

- Jaccard coefficient, [0, 1], maximum:

$$J(\mathcal{U}, \mathcal{V}) = \frac{n_{11}}{n_{11} + n_{10} + n_{01}}$$

- Minikowski measure:

$$M(\mathcal{U}, \mathcal{V}) = \sqrt{\frac{n_{10} + n_{01}}{n_{11} + n_{01}}}$$



$$n_{11} = \#\{(O_i, O_j); I(A_{ij} = 1, B_{ij} = 1)\}$$

$$n_{10} = \#\{(O_i, O_j); I(A_{ij} = 1, B_{ij} = 0)\}$$

$$n_{01} = \#\{(O_i, O_j); I(A_{ij} = 0, B_{ij} = 1)\}$$

$$n_{00} = \#\{(O_i, O_j); I(A_{ij} = 0, B_{ij} = 0)\}$$



# Adjusted Rand index

*May be the most widely used Cluster Validation Index!*

Cluster	$V_1$	$V_1$	$\cdots$	$V_C$	Sums
$A =$	$U_1$	$n_{11}$	$n_{12}$	$\cdots$	$n_{1C}$
	$U_2$	$n_{21}$	$n_{22}$	$\cdots$	$n_{2C}$
	$\cdots$			$\cdots$	$\cdots$
	$U_R$	$n_{R1}$	$n_{R2}$	$\cdots$	$n_{RC}$
Sums	$n_{\cdot 1}$	$n_{\cdot 1}$	$\cdots$	$n_{\cdot C}$	$n$

$$R(\mathcal{U}, \mathcal{V}) = 1 + \frac{\sum_{i=1}^R \sum_{j=1}^C n_{ij}^2 - \frac{1}{2} (\sum_{i=1}^R n_{i\cdot}^2 + \sum_{j=1}^C n_{\cdot j}^2)}{\binom{n}{2}}$$

$$R(\mathcal{U}, \mathcal{V})_{adj} = \frac{\sum_{i=1}^R \sum_{j=1}^C \binom{n_{ij}}{2} - \sum_{i=1}^R \sum_{j=1}^C \binom{n_{i\cdot}}{2} \binom{n_{\cdot j}}{2} / \binom{n}{2}}{\frac{1}{2} [\sum_{i=1}^R \binom{n_{i\cdot}}{2} + \sum_{j=1}^C \binom{n_{\cdot j}}{2}] - \sum_{i=1}^R \sum_{j=1}^C \binom{n_{i\cdot}}{2} \binom{n_{\cdot j}}{2} / \binom{n}{2}}$$

Lawrence Hubert and Phipps Arabie (1985), Comparing partitions, Journal of Classification 2(1), 193-218.



## clValid {clValid}: Validate Cluster Results

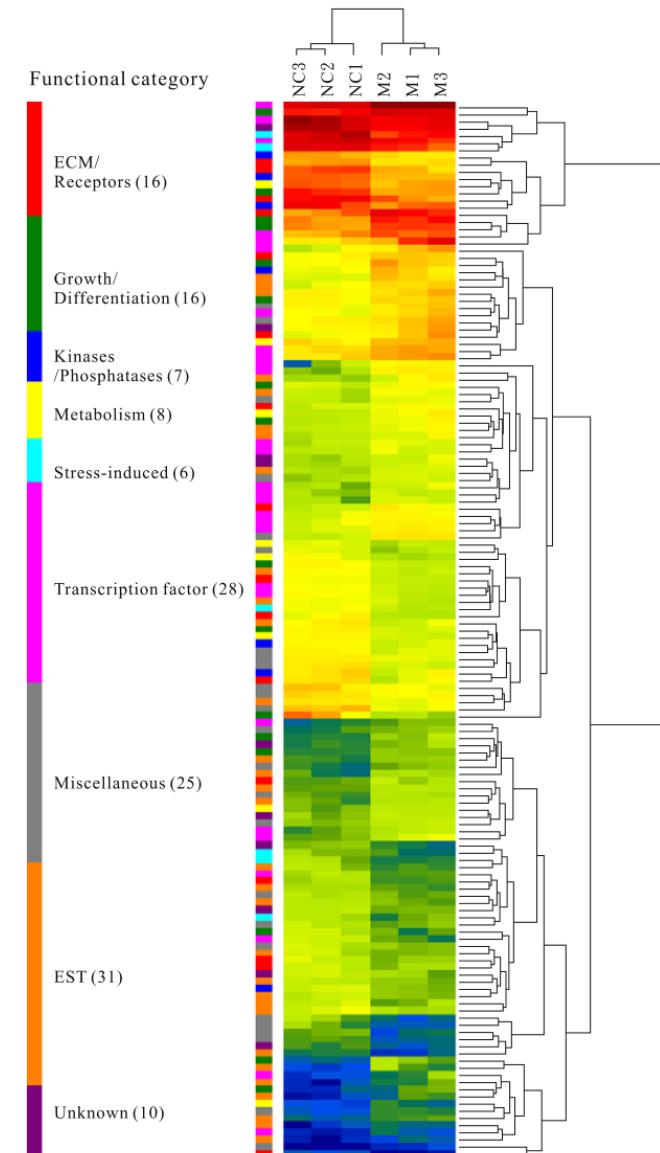
```
clValid(obj, nClust, clMethods = "hierarchical",
        validation = "stability", maxitems = 600,
        metric = "euclidean", method = "average",
        neighbSize = 10, annotation = NULL,
        GOcategory = "all",
        goTermFreq=0.05, dropEvidence=NULL,
        verbose=FALSE, ...)
```

### mouse {clValid} R Documentation

#### Mouse Mesenchymal Cells

##### Description

Data from an Affymetrix microarray experiment (moe430a) comparing gene expression of mesenchymal cells from two distinct lineages, **neural crest (NC)** and **mesoderm (M)** derived. The dataset consists of 147 genes and ESTs which were determined to be significantly differentially expressed between the two cell lineages, with at least a 1.5 fold increase or decrease in expression. There are three samples for each of the neural crest and mesoderm derived cells.





# Example: Mouse Data

```
clMethods = c("hierarchical", "kmeans", "diana", "fanny", "som", "model",
"sota", "pam", "clara", "agnes")
validation = c("internal", "stability", "biological")
```

```
> library(clValid)
> data(mouse)
> head(mouse)
  ID      M1      M2      M3      NC1      NC2      NC3          FC
1 1448995_at 4.706812 4.528291 4.325836 5.568435 6.915079 7.353144 Growth/Differentiation
2 1436392_s_at 3.867962 4.052354 3.474651 4.995836 5.056199 5.183585 Transcription factor
3 1437434_a_at 2.875112 3.379619 3.239800 3.877053 4.459629 4.850978 Miscellaneous
4 1428922_at 5.326943 5.498930 5.629814 6.795194 6.535522 6.622577 Miscellaneous
5 1452671_s_at 5.370125 4.546810 5.704810 6.407555 6.310487 6.195847 ECM/Receptors
6 1448147_at 3.471347 4.129992 3.964431 4.474737 5.185631 5.177967 Growth/Differentiation

> # internal validation
> express <- mouse[1:25,c("M1", "M2", "M3", "NC1", "NC2", "NC3")]
> rownames(express) <- mouse$ID[1:25]
> head(express)
      M1      M2      M3      NC1      NC2      NC3
1448995_at 4.706812 4.528291 4.325836 5.568435 6.915079 7.353144
1436392_s_at 3.867962 4.052354 3.474651 4.995836 5.056199 5.183585
1437434_a_at 2.875112 3.379619 3.239800 3.877053 4.459629 4.850978
1428922_at 5.326943 5.498930 5.629814 6.795194 6.535522 6.622577
1452671_s_at 5.370125 4.546810 5.704810 6.407555 6.310487 6.195847
1448147_at 3.471347 4.129992 3.964431 4.474737 5.185631 5.177967
>
> intern <- clValid(express, 2:6, clMethods=c("hierarchical", "kmeans", "pam"),
+                      validation="internal")
```



# Mouse Data: Internal Measure

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```
> summary(intern) # view results
```

Clustering Methods:

hierarchical kmeans pam

Cluster sizes:

2 3 4 5 6

Validation Measures:

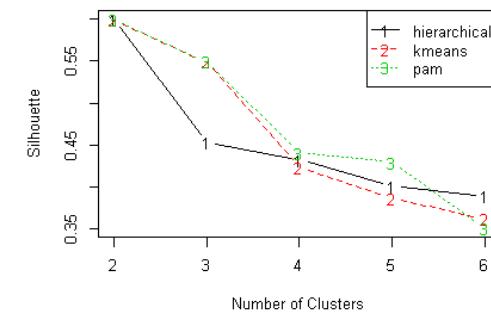
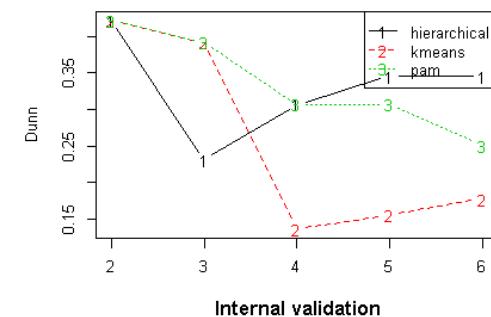
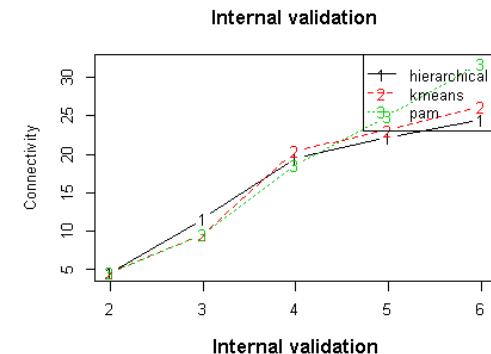
	2	3	4	5	6
--	---	---	---	---	---

	hierarchical	Connectivity	4.6159	11.5865	19.5075	22.2075	24.5044
	Dunn		0.4217	0.2315	0.3068	0.3456	0.3456
	Silhouette		0.5997	0.4529	0.4324	0.4007	0.3891
	kmeans	Connectivity	4.6159	9.5607	20.4774	23.1774	26.2242
	Dunn		0.4217	0.3924	0.1360	0.1556	0.1778
	Silhouette		0.5997	0.5495	0.4235	0.3871	0.3618
	pam	Connectivity	4.6159	9.5607	18.5925	25.0631	31.8381
	Dunn		0.4217	0.3924	0.3068	0.3068	0.2511
	Silhouette		0.5997	0.5495	0.4401	0.4297	0.3506

Optimal Scores:

	Score	Method	Clusters
Connectivity	4.6159	hierarchical	2
Dunn	0.4217	hierarchical	2
Silhouette	0.5997	hierarchical	2

```
> par(mfrow=c(1, 3))
> plot(intern)
```



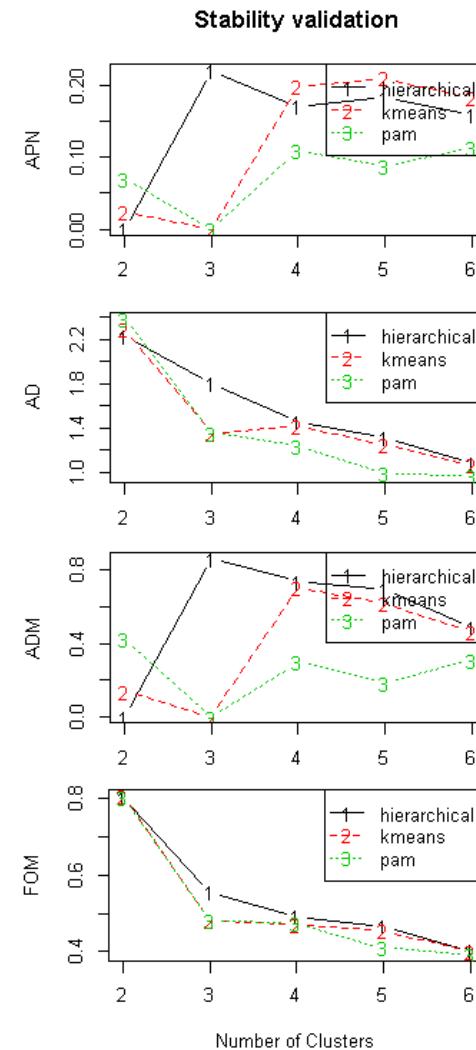


# Mouse Data: Stability Measure

```
> stab <- clValid(express, 2:6, clMethods=c("hierarchical", "kmeans", "pam"),  
+ validation="stability")
```

```
> summary(stab)  
Clustering Methods:  
hierarchical kmeans pam  
Cluster sizes:  
2 3 4 5 6  
Validation Measures:  
          2      3      4      5      6  
hierarchical APN  0.0000 0.2200 0.1702 0.1836 0.1600  
                  AD  2.2328 1.8011 1.4589 1.3174 1.0895  
                  ADM 0.0000 0.8618 0.7372 0.6943 0.4905  
                  FOM 0.8020 0.5545 0.4917 0.4649 0.4021  
kmeans          APN  0.0241 0.0000 0.1983 0.2100 0.1828  
                  AD  2.2861 1.3561 1.4182 1.2525 1.0671  
                  ADM 0.1399 0.0000 0.7050 0.6193 0.4655  
                  FOM 0.8055 0.4809 0.4689 0.4539 0.4007  
pam            APN  0.0698 0.0000 0.1093 0.0867 0.1129  
                  AD  2.3867 1.3561 1.2413 0.9942 0.9642  
                  ADM 0.4236 0.0000 0.3008 0.1845 0.3098  
                  FOM 0.8022 0.4809 0.4731 0.4094 0.3926  
  
Optimal Scores:  
  Score Method Clusters  
APN 0.0000 hierarchical 2  
AD  0.9642 pam       6  
ADM 0.0000 hierarchical 2  
FOM 0.3926 pam       6
```

```
> par(mfrow=c(4, 1))  
> plot(stab)
```





# Biological Evaluation

- Biological Homogeneity Index (BHI)
- Biological Stability Index (BSI)

**Example:**  
**GO (Gene Ontology)**  
**Multiple Functional Categories**

ProbeSet	Clustering	GO-BP Category
38389_at	1	0
1662_r_at	1	0
32607_at	1	0
1582_at	1	0
34699_at	1	0
37890_at	2	0
36008_at	2	1 2 3
36591_at	2	1 2 3 8 10
32081_at	2	1 2 3 4 5 6 7 9 10
668_s_at	2	1 2 3
41535_at	2	1 2 3 4
37666_at	2	1 2 3
40310_at	2	1 2 3 4 5 8 9
34256_at	3	1 2 3
38790_at	3	1
39175_at	3	1 2 3
35819_at	3	1 8
37639_at	3	1 2 3
31508_at	3	1 9
31505_at	4	1 2 3
1882_g_at	4	1 2 3 4 6
33154_at	4	1 2 3
837_s_at	4	1 2 3
35194_at	4	1
38422_s_at	4	1 2 3 4 5
33131_at	4	1 2 3 4 6 7

Susmita Datta and Somnath Datta, (2006), Methods for evaluating clustering algorithms for gene expression data using a reference set of functional classes, BMC Bioinformatics 7:397.

# Biological Evaluation

Susmita Datta and Somnath Datta, (2006), Methods for evaluating clustering algorithms for gene expression data using **a reference set of functional classes**, *BMC Bioinformatics* 7:397.

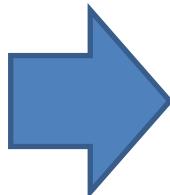
Biological Homogeneity Index (BHI)

Biological Stability Index (BSI)

Generalized indices:

**SBHI, SBSI**

ProbeSet	hard clustering	GO-BP Category
38389_at	1	0
1662_r_at	1	0
32607_at	1	0
37890_at	2	0
36008_at	2	1 2 3
36591_at	2	1 2 3 8 10
32081_at	2	1 2 3 4 5 6 7 9 10
34256_at	3	1 2 3
38790_at	3	1
39175_at	3	1 2 3
35819_at	3	1 8
37639_at	3	1 2 3
•	<b>Multiple Functional Categories</b>	
•		



ProbeSet	soft clustering			GO-BP Category
	1	2	3	
38389_at	0.0543	0.1044	0.8413	0
1662_r_at	0.0175	0.0356	0.9469	0
32607_at	0.0011	0.0023	0.9967	0
37890_at	0.2707	0.7053	0.0240	0
36008_at	0.0834	0.9027	0.0139	1 2 3
36591_at	0.1012	0.8759	0.0229	1 2 3 8 10
32081_at	0.2113	0.7547	0.0339	1 2 3 4 5 6 7 9 10
34256_at	0.9087	0.0830	0.0084	1 2 3
38790_at	0.8908	0.0947	0.0144	1
39175_at	0.8728	0.1074	0.0198	1 2 3
35819_at	0.7601	0.1890	0.0509	1 8
37639_at	0.9062	0.0848	0.0090	1 2 3
•	•	•	•	



# Biological Homogeneity Index (BHI)

a set of biological classes  $\mathcal{B} = \{B_1, \dots, B_F\}$

a statistical hard clustering partition  $\mathcal{H} = \{H_1, \dots, H_K\}$

$B^i$ : the functional class containing gene  $i$

$B^j$ : the function class containing gene  $j$

$$\text{BHI}(\mathcal{H}, \mathcal{B}) = \frac{1}{K} \sum_{k=1}^K \frac{1}{n_k(n_k - 1)} \sum_{i \neq j; i, j \in H_k} \text{I}(B^i = B^j)$$



$$n_k = n(H_k \cap \mathcal{B})$$



# Properties of BHI

- BHI: the **average proportion** of gene pairs belonging to the **same functional classes** that are **clustered together**.
- BHI: ranges from **0 to 1**.
- BHI: **larger** values corresponding to more biologically **homogeneous clusters**.



# Soft BHI (SBHI)

$\mathcal{U} = u_{ik}$ : fuzzy membership matrix

soft clustering:  $u_{ik} = P(y_i \in C_k)$

hard clustering :  $u_{ik} = I(y_i \in C_k)$

a statistical soft clustering partition  $\mathcal{S} = \{S_1, \dots, S_K\}$

$$\text{SBHI}(\mathcal{S}, \mathcal{B}) = \frac{1}{K} \sum_{k=1}^K \frac{1}{\eta_k} \sum_{i \neq j} u_{ik} u_{jk} I(B^i = B^j)$$



$$\eta_k = \sum_{i \neq j} u_{ik} u_{jk} I(\text{genes } i, j \text{ are annotated})$$

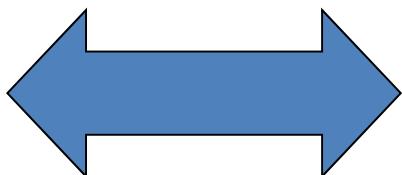


# Evaluation of Stability

	A	B	C	D	E	F	G	H	I
1	-1.37	-2.30	-1.80	-0.55	2.45	-0.13	1.49	3.03	2.48
2	-0.68	-2.11	-3.42	4.67	4.57	1.75	0.61	0.92	2.52
3	-1.19	-2.49	-3.66	3.14	1.70	3.29	3.83	2.92	2.48
4	-1.93	-2.28	-3.16	2.51	0.32	1.49	0.21	2.20	1.03
5	-2.21	-0.79	-3.29	2.55	2.44	1.45	2.68	3.03	0.75
6	-4.14	-2.91	-1.64	3.21	0.37	1.93	0.14	1.27	2.67
7	0.21	-1.36	-0.44	2.22	1.85	3.11	2.03	0.67	2.40
8	1.13	0.79	2.25	3.65	2.52	2.09	1.13	-2.59	0.67
9	0.95	2.33	-0.07	3.89	2.72	2.13	1.75	-2.17	0.00
10	3.04	1.85	0.21	7.07	2.01	3.05	0.76	-2.58	-1.04
11	-1.02	1.65	1.53	0.95	0.60	3.12	2.52	-0.77	-1.40
12	1.21	0.24	1.04	2.50	3.69	1.81	3.98	-0.33	0.11
13	1.74	1.60	1.70	2.02	3.45	4.46	2.69	0.41	-0.09
14	1.34	1.06	0.06	1.81	2.90	3.64	3.04	0.49	-2.33
15	0.57	1.81	-0.47	1.40	2.70	0.99	0.82	-1.61	-2.56
16	0.61	4.22	-2.03	-2.61	-4.00	-4.64	-2.92	1.55	-0.71
17	-1.13	1.64	0.01	-1.77	-2.85	-1.24	-3.41	-0.59	-1.64
18	-0.86	-1.17	-0.41	-2.20	-1.30	-2.37	-1.41	0.08	0.25
19	0.75	0.66	1.04	-4.26	-1.41	-3.99	-3.53	-2.17	0.34
20	0.15	0.68	3.18	-2.86	-2.01	-3.18	-1.58	0.10	1.28

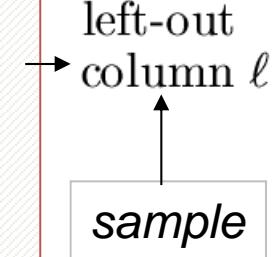
Full data ( $n \times p$ )

Compare these  
two partitions

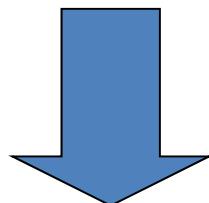


Repeat: 1,...,p

	A	B	C	D	E	F	G	H
1	-1.37	-2.30	-1.80	-0.55	2.45	-0.13	1.49	3.03
2	-0.68	-2.11	-3.42	4.67	4.57	1.75	0.61	0.92
3	-1.19	-2.49	-3.66	3.14	1.70	3.29	3.83	2.92
4	-1.93	-2.28	-3.16	2.51	0.32	1.49	0.21	2.20
5	-2.21	-0.79	-3.29	2.55	2.44	1.45	2.68	3.03
6	-4.14	-2.91	-1.64	3.21	0.37	1.93	0.14	1.27
7	0.21	-1.36	-0.44	2.22	1.85	3.11	2.03	0.67
8	1.13	0.79	2.25	3.65	2.52	2.09	1.13	-2.59
9	0.95	2.33	-0.07	3.89	2.72	2.13	1.75	-2.17
10	3.04	1.85	0.21	7.07	2.01	3.05	0.76	-2.58
11	-1.02	1.65	1.53	0.95	0.60	3.12	2.52	-0.77
12	1.21	0.24	1.04	2.50	3.69	1.81	3.98	-0.33
13	1.74	1.60	1.70	2.02	3.45	4.46	2.69	0.41
14	1.34	1.06	0.06	1.81	2.90	3.64	3.04	0.49
15	0.57	1.81	-0.47	1.40	2.70	0.99	0.82	-1.61
16	0.61	4.22	-2.03	-2.61	-4.00	-4.64	-2.92	1.55
17	-1.13	1.64	0.01	-1.77	-2.85	-1.24	-3.41	-0.59
18	-0.86	-1.17	-0.41	-2.20	-1.30	-2.37	-1.41	0.08
19	0.75	0.66	1.04	-4.26	-1.41	-3.99	-3.53	-2.17
20	0.15	0.68	3.18	-2.86	-2.01	-3.18	-1.58	0.10



Remaining data ( $n \times (p-1)$ )



Summering these comparisons



# Biological Stability Index (BSI)

$C^{i,0}$ : the statistical cluster containing observation  $i$  based on all the data.

$C^{j,\ell}$ : the statistical cluster containing observation  $j$  when column  $\ell$  is removed.

$$\text{BSI}(\mathcal{H}, \mathcal{B}) = \frac{1}{F} \sum_{f=1}^F \frac{1}{n(B_f)(n(B_f) - 1)} \frac{1}{M} \sum_{\ell=1}^M \sum_{i \neq j; i, j \in B_f} \frac{n(C^{i,0} \cap C^{j,\ell})}{n(C^{i,0})}$$

$n(B_f)$  number of genes in the biological category  $B_f$



# Properties of BSI

- BSI: the **average overlap** of the **statistical clusters** obtained based on all of the samples with that of those obtained based on leave-one-out samples for genes that were placed in the **same functional class**.
- BSI: from **0 to 1**.
- BSI: **larger** values corresponding to **more stable** clusters of functionally annotated genes.



# Soft BSI (SBSI)

$$\text{SBSI}(\mathcal{S}, \mathcal{B}) = \frac{1}{F} \sum_{f=1}^F \frac{1}{n(B_f)(n(B_f) - 1)} \frac{1}{M} \sum_{\ell=1}^M \sum_{i \neq j; i, j \in B_f} \frac{\eta(C^{i,0} \cap C^{j,\ell})}{\eta(C^{i,0})}$$

$$\eta(C^{i,0}) = \sum_{k=1}^K \sum_{t=1}^n u_{ik}^{(0)} u_{tk}^{(0)}$$

$$\eta(C^{i,0} \cap C^{j,\ell}) = \sum_{k=1}^K \sum_{h=1}^K \sum_{t=1}^n u_{ik}^{(0)} u_{tk}^{(0)} u_{jh}^{(\ell)} u_{th}^{(\ell)}$$

$u_{ik}^{(0)}$  is the membership for gene  $i$  to cluster  $k$  based on all of the data



# SBHI & SBSI

- SBHI & SBSI can be **reduced** to the BHI and the BSI.
- SBHI & SBSI are close to BHI & BSI when the clustering of a data set is close to being **crisp**.
- SBHI & SBSI consider **multiple statistical cluster** information for each gene and are thus more *reasonable*.



# Mouse Data: Biological Measure

```
> # biological measures (functional classes predetermined)
> fc <- tapply(rownames(express), mouse$FC[1:25], c)
> fc
$`ECM/Receptors`
[1] "1452671_s_at" "1423110_at"    "1439381_x_at" "1450857_a_at"

$EST
[1] "1435327_at"   "1418382_at"    "1439373_x_at"

$`Growth/Differentiation`
[1] "1448995_at"   "1448147_at"    "1421180_at"   "1416855_at"

$`Kinases/Phosphatases`
[1] "1439148_a_at" "1424474_a_at"

$Metabolism
[1] "1449059_a_at"

$Miscellaneous
[1] "1437434_a_at" "1428922_at"    "1449623_at"    "1418486_at"    "1415993_at"
"1452003_at"

$`Stress-induced`
[1] "1422557_s_at" "1456434_x_at"    "1416481_s_at"

$`Transcription factor`
[1] "1436392_s_at" "1424186_at"

$Unknown
NULL
```



# Mouse Data: Biological Measure

```
> fc <- fc[-match( c("EST", "Unknown"), names(fc))]  
> bio <- clValid(express, 2:6, clMethods=c("hierarchical", "kmeans", "pam"),  
+ validation="biological", annotation=fc)  
> summary(bio)
```

Clustering Methods:

hierarchical kmeans pam

Cluster sizes:

2 3 4 5 6

Validation Measures:

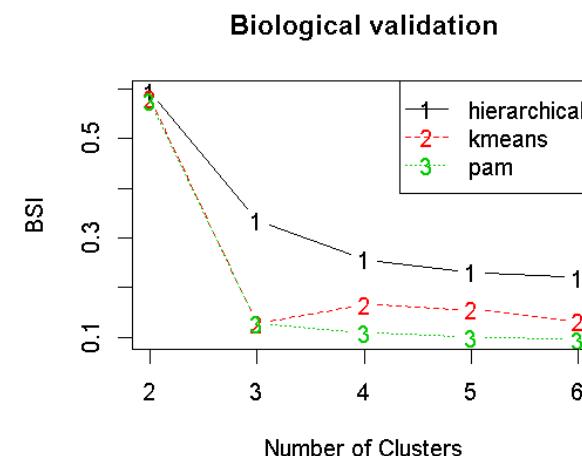
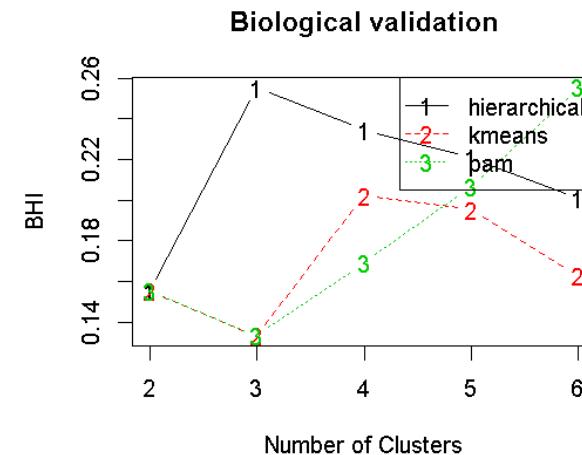
2      3      4      5      6

		2	3	4	5	6
hierarchical	BHI	0.1552	0.2552	0.2345	0.2210	0.2008
	BSI	0.5952	0.3361	0.2574	0.2314	0.2202
kmeans	BHI	0.1552	0.1335	0.2024	0.1952	0.1627
	BSI	0.5818	0.1286	0.1658	0.1557	0.1331
pam	BHI	0.1552	0.1335	0.1690	0.2067	0.2556
	BSI	0.5751	0.1286	0.1094	0.1003	0.0956

Optimal Scores:

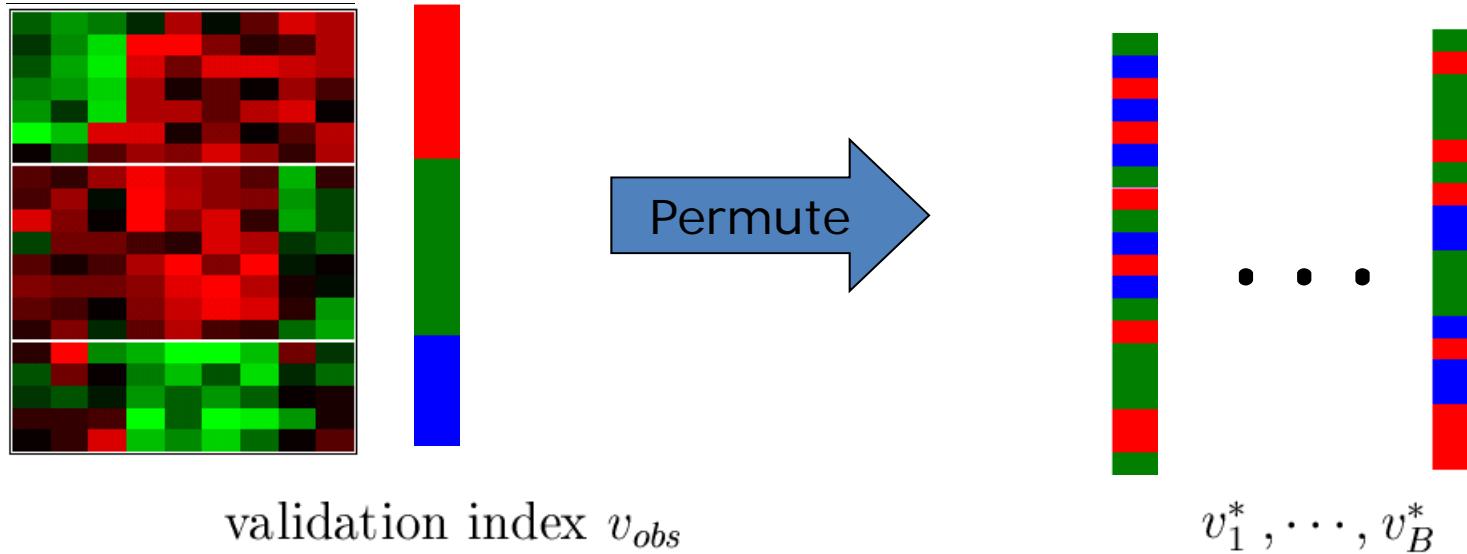
Score	Method	Clusters	
BHI	0.2556	pam	6
BSI	0.5952	hierarchical	2

```
> par(mfrow=c(2, 1))  
> plot(bio)
```





## Significance of the Indices: Permutation Test

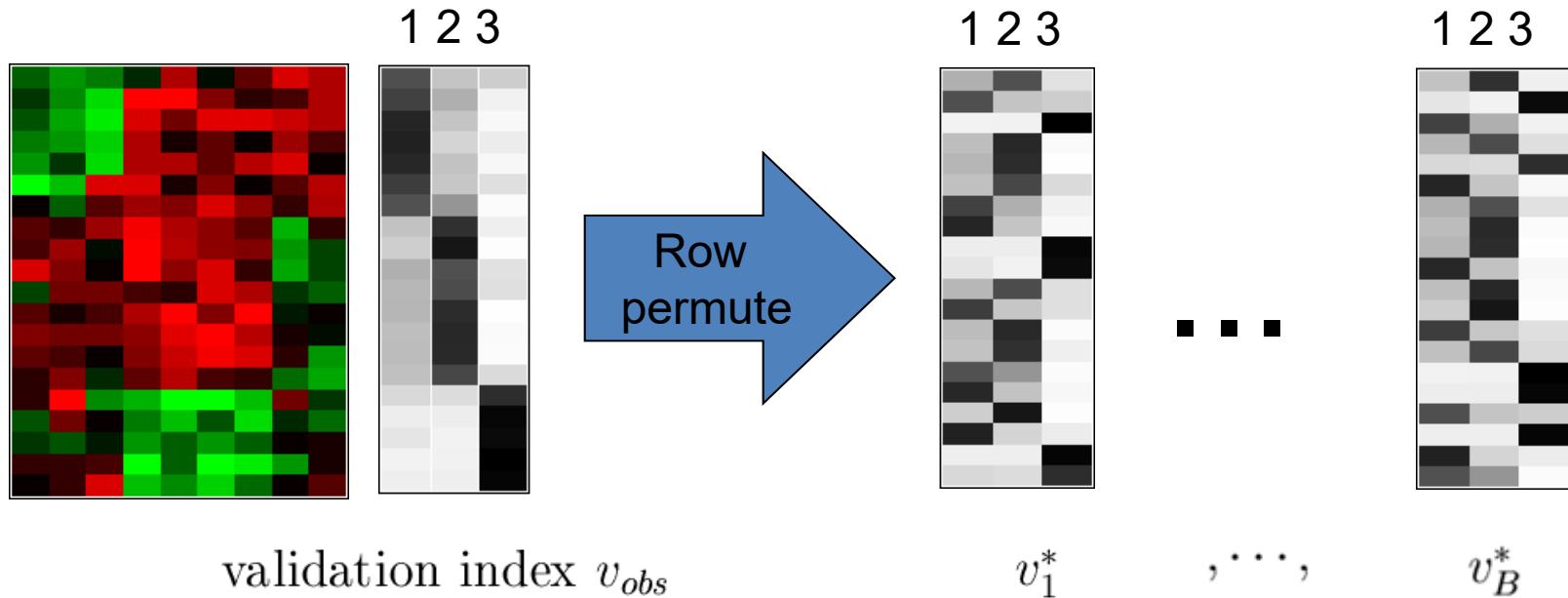


$$p = \frac{1}{B} \sum_{i=1}^B I(v_i^* \geq v_{obs})$$

## Permutation Test for Significance of the Indices

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Functional  
Categories



$$p = \frac{1}{B} \sum_{i=1}^B I(v_i^* \geq v_{obs})$$



# Obtain Functional Categories (Annotation)

## MIPS: the Munich Information Center for Protein Sequences

- <http://mips.gsf.de/>
- MIPS: a database for protein sequences and complete genomes, Nucleic Acids Research, 27:44-48, 1999

The screenshot shows the MIPS homepage. At the top, there's a decorative bar with the word "innovation" and a bar chart graphic. Below it is the main header "mips" with a blue "gsf" logo. The main content area has a banner for "Ustilago maydis". On the left is a sidebar with "Projects" (Fungi, Plants, Structural genomics, Annotation, The Functional Catalogue, Expression analysis, Proteomics, BfAM, cDNA, HNB, BioRGS, GenRE, GAMS, SIMAP, HOBIT) and "Services" (Genomes, Databanks retrieval systems, Analysis tools, Expression analysis, Protein Protein Interactions). The main content area includes a "Welcome to mips" section with news about the genome of Ustilago maydis, a "Anammox in the genes" section, and a "News" section.

The screenshot shows the Gene Ontology Home page. It features a search bar at the top with "Search [ ] gene or protein name [go!]" and a "Gene Ontology Home" heading. Below the search bar is a brief description of the project: "The Gene Ontology project provides a controlled vocabulary to describe gene and gene product attributes in any organism. [Read more about the Gene Ontology...](#)". There's a "Search the Gene Ontology Database" section with a search input field and radio buttons for "gene or protein name" and "GO term or ID". A note says "AmiGO is the official GO browser and search engine. [Browse the Gene Ontology with AmiGO.](#)". The "GO website" section lists links for "GO downloads, including ontology files, annotations and the GO database", "Tools for using GO, including OBO-Edit downloads and AmiGO", "Request new terms or ontology changes via the GO curator requests tracker; help with new term submission is available.", and "Documentation on all aspects of the GO project and the GO FAQ".

## GO: Gene Ontology

- A GO annotation is a Gene Ontology term associated with a gene product.
- <http://www.geneontology.org/>
- The Gene Ontology Consortium. Gene Ontology: tool for the unification of biology. Nature Genet. (2000) 25: 25-29.
- FatiGO (Al-Shahrour et al., 2004)
- FunCat (Ruepp et al., 2004)

# FatiGO

<http://babelomics.bioinfo.cipf.es/index.html>

