

Microarray Data Analysis

Clustering and Visualization (II)

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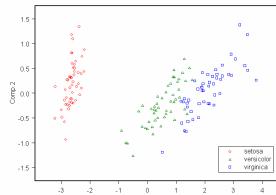
Outlines

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- Heat Map
- Hierarchical Clustering
 - ◆ Dendrogram
 - ◆ Single-linkage, complete-linkage, average-linkage, centroid-linkage, Ward's Method
- How Many Clusters?
- Generalized Association Plots (GAP)
- Generalization and Flexibility
- Visualization of Data Matrices
- Software: GAP

Dimension Free Data Visualization

全矩陣式資料視覺化



Data visualization techniques that can simultaneously visualize high dimensional (thousands) data structure without dimension reduction

No.	iris	Sepal.Length	Sepal.Width	Petal.Length	Petal.Width
1	setosa	5.1	3.5	1.4	0.2
2	setosa	4.9	3	1.4	0.2
3	setosa	4.7	3.2	1.3	0.2
4	setosa	4.6	3.1	1.5	0.2
5	setosa	5	3.6	1.4	0.2
...					
50	setosa	5	3.3	1.4	0.2
51	versicolor	7	3.2	4.7	1.4
52	versicolor	6.4	3.2	4.5	1.5
53	versicolor	6.9	3.1	4.9	1.5
54	versicolor	6.5	2.3	4	1.3
55	versicolor	6.5	2.8	4.6	1.5
...					
50	versicolor	5.7	2.8	4.1	1.3
101	virginica	6.3	3.3	6	2.5
102	virginica	5.8	2.7	6.1	1.9
103	virginica	7.1	3	5.9	2.1
104	virginica	6.3	2.9	5.6	1.8
...					
150	virginica	5.9	3	5.1	1.8

Data/Information Visualization

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What is Visualization?

- ◆ To visualize = to make visible, to transform into pictures.
- ◆ Making things/processes visible that are not directly accessible by the human eye.
- ◆ Transformation of an abstraction to a picture.
- ◆ Computer aided extraction and display of information from data.

Data/Information Visualization

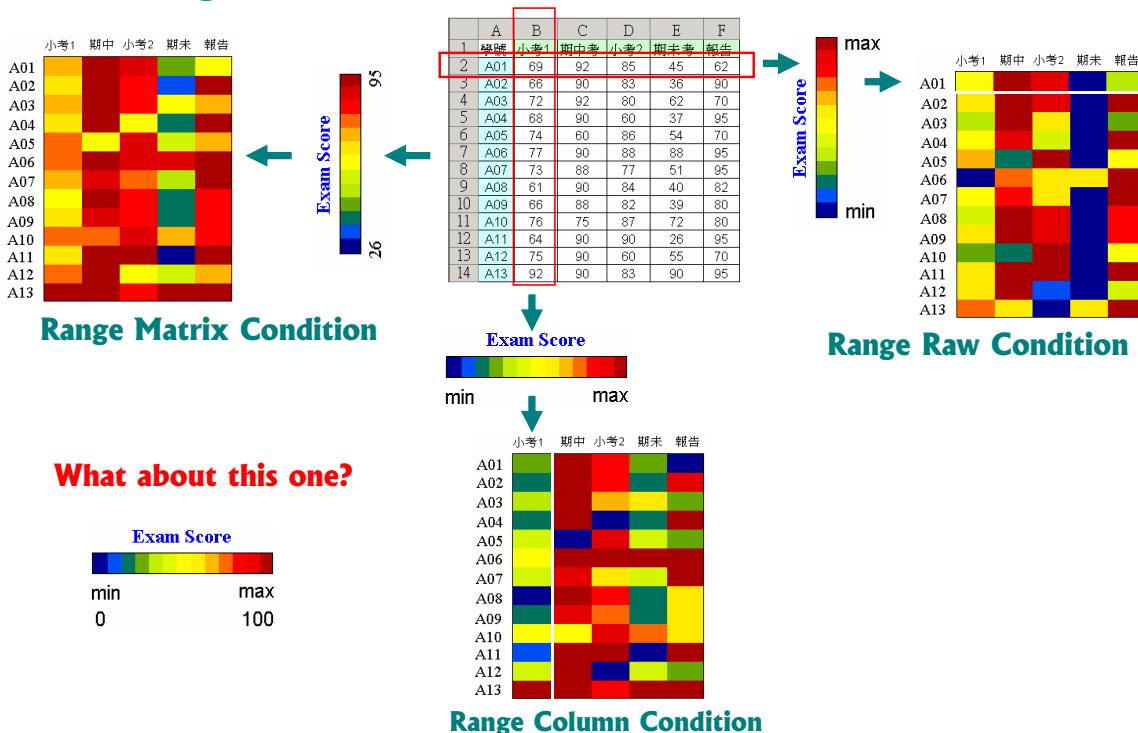
- ◆ Exploiting the human visual system to extract information from data.
- ◆ Provides an overview of complex data sets.
- ◆ Identifies structure, patterns, trends, anomalies, and relationships in data.
- ◆ Assists in identifying the areas of interest.

Visualization = Graphing for Data + Fitting + Graphing for Model

Tegarden, D. P. (1999). Business Information Visualization. Communications of AIS 1, 1-38.

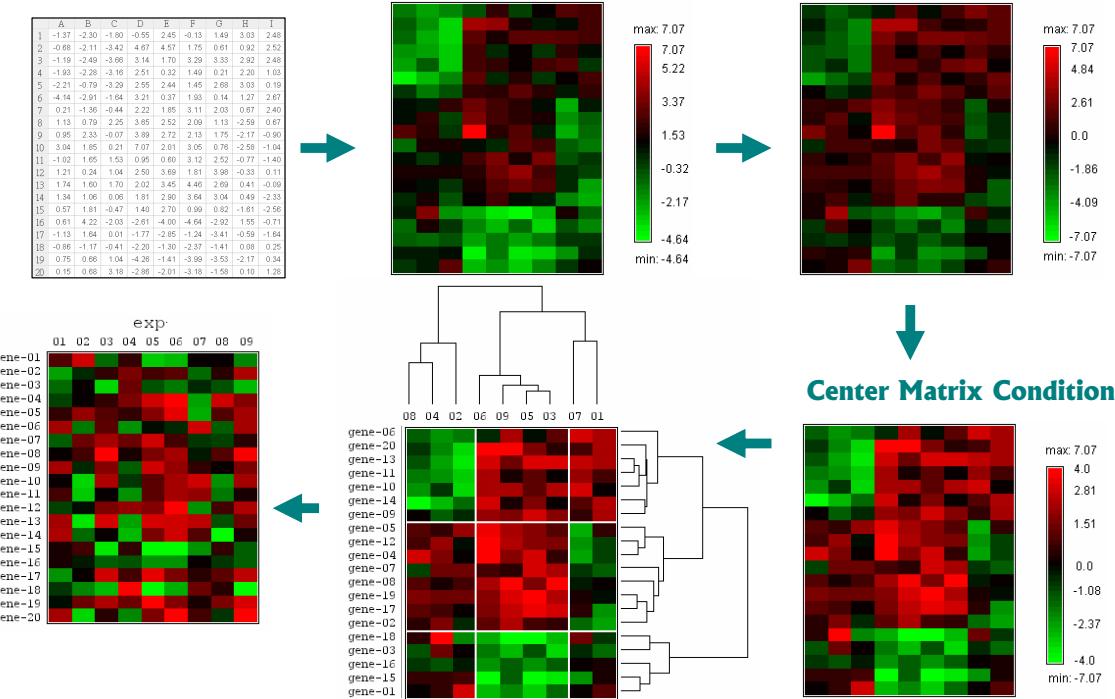
Heat Map (Data Image, Matrix Visualization)

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Heat Map (cont.)

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Hierarchical Clustering

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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.

Non-Hierarchical clustering

- ◆ k-means
- ◆ The EM algorithm
- ◆ Nearest Neighbor
- ◆ ...

Hierarchical Clustering and Dendrogram

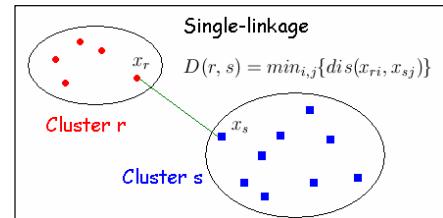
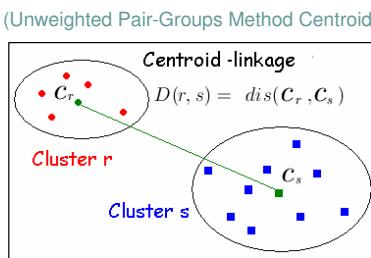
(Kaufman and Rousseeuw, 1990)

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Example:

Average-Linkage

	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



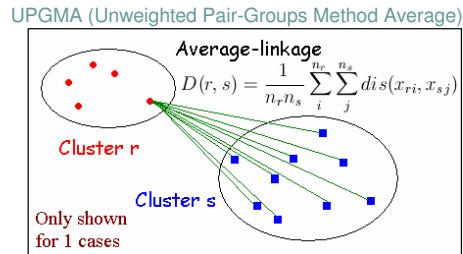
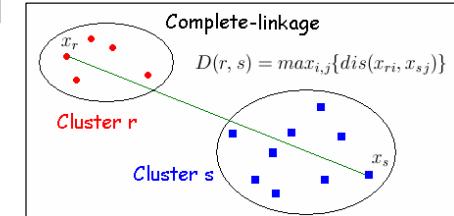
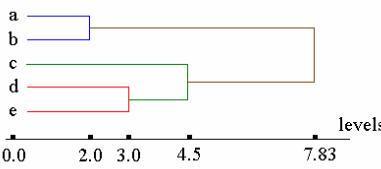
$$D(\{a, b\}, \{c\}) = \frac{1}{2}[D(a, c) + D(b, c)]$$

$$= \frac{1}{2}(6 + 5) = 5.5$$

$$D(\{a, b\}, \{d, e\})$$

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

$$= \frac{1}{4}(10 + 9 + 9 + 8) = 9$$

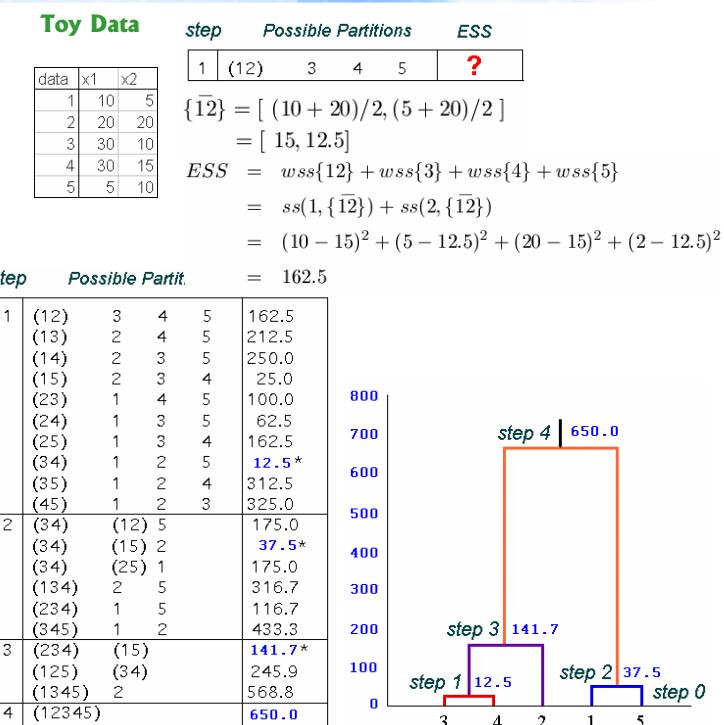


Ward's Method

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- The Ward's method does not compute distances between clusters.
- It 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 Ward's method tries to minimize the total within-group or within-cluster sum of squares.
- Clusters are formed at each step such that the resulting cluster solution has the fewest within-clustersums of squares.
- The within-cluster sums of squares that is minimized is also known as the error sums of squares (ESS).

Example:
Charles H. Romesburg (1984)



Exercise

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Toy Data

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

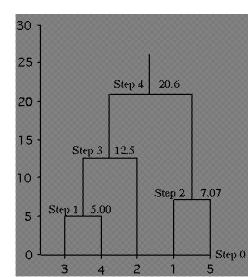
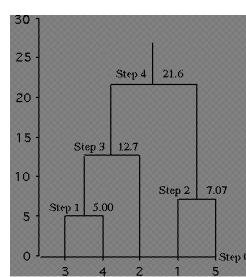
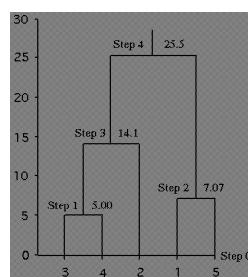
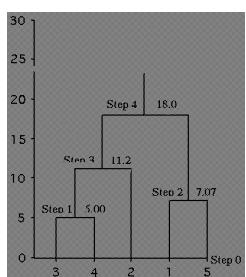
0.00				
18.00	0.00			
20.60	14.10	0.00		
22.40	11.20	5.00	0.00	
7.07	18.00	25.00	25.50	0.00

Single-Linkage

Complete-Linkage

Average-Linkage

Centroid-Linkage



Display of Genome-Wide Expression Patterns

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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*‡

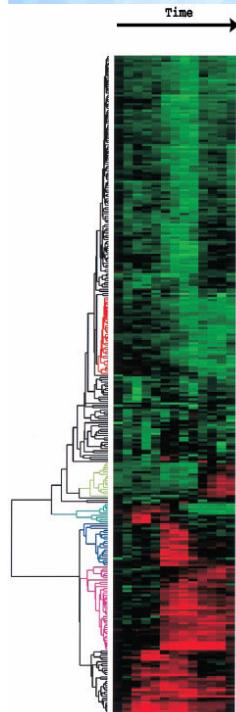
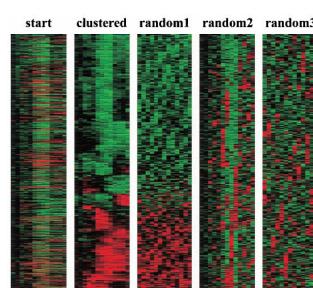


FIG. 1. Clustered display of data from time course of serum stimulation of primary human fibroblasts. Experimental details are described elsewhere (11). Briefly, foreskin fibroblasts were grown in culture and were deprived of serum for 48 hr. Serum was added back and samples taken at time 0, 15 min, 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).



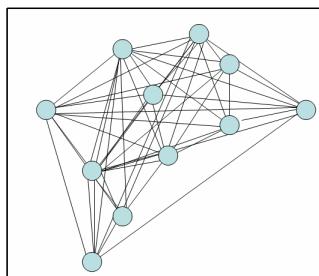
How Many Clusters?

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

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

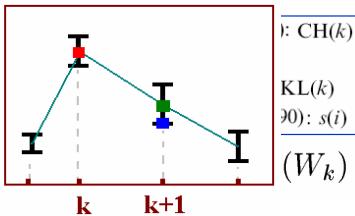


Within-Cluster Sum of Squares

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

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

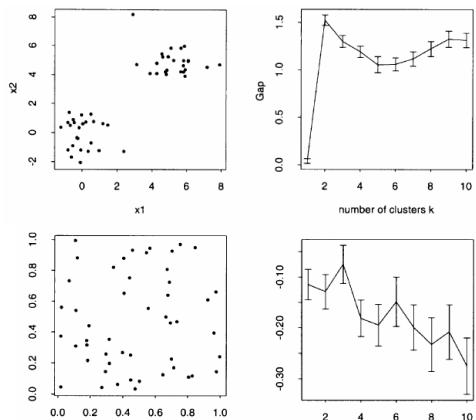
Gap_n(l)



Computational Implementation choose the number of clusters via
Implementation \hat{k} = smallest k such that

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

application to
hierarchical clustering
and DNA microarray data
 6834×64 matrix



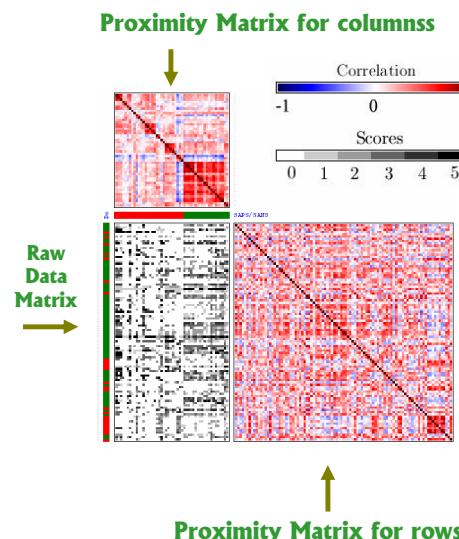
<http://www-genome.stanford.edu/nci60>

Generalized Association Plots (GAP)

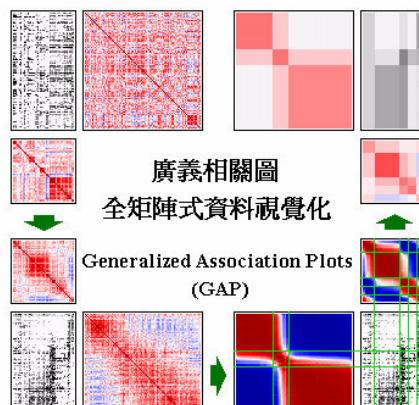
(Chen, 2002)

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



- 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

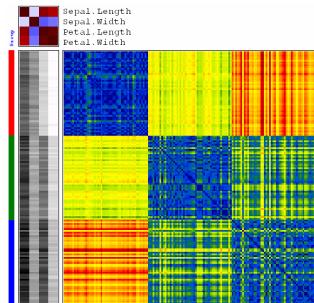


- ② Generalized Association Plots (GAP)
- ③ Partitioned Data Maps 分群後之資料矩陣與關係矩陣

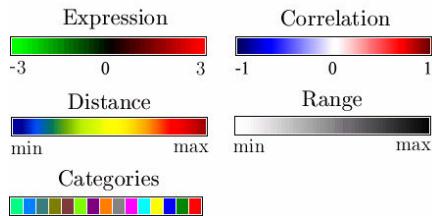
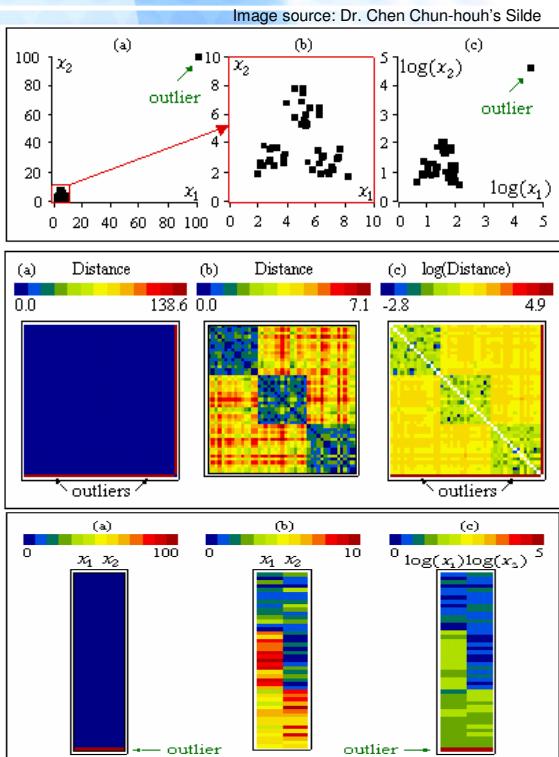
Presentation of Raw Data Matrix

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1. Color spectrum
2. Variable transformation



“Resolution” of a Statistical Graph



Selection of Proximity Measures

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Dissimilarity/Similarity Measure for Quantitative Data

Dissimilarity	Formula
Minkowski	$d(i, j) = \left(\sum_k x_{ik} - x_{jk} ^p \right)^{1/p}$
Canberra	$d(i, j) = \sum_k \frac{ x_{ik} - x_{jk} }{ x_{ik} + x_{jk} }$
Soergel	$d(i, j) = \sum_k x_{ik} - x_{jk} / \sum_k \max(x_{ik}, x_{jk})$
Divergence	$d(i, j) = \sum_k (x_{ik} - x_{jk})^2 / \sum_k$
Bary-Curtis	$d(i, j) = \text{Similarity}$
Wave-Hedges	$d(i, j) = \text{Pearson correlation}$
Bhattacharyya	$d(i, j) = \text{Spearman correlation}$
	$s(i, j) = \text{Kendall's Tau}$

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

Kendall's tau

• C: concordant pair: $(x_j - x_i)(y_j - y_i) > 0$

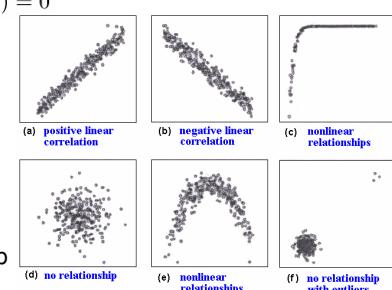
• D: discordant pair: $(x_j - x_i)(y_j - y_i) < 0$

• tie:

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

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

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



- 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.

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

Algorithm they use different logic for computing the correlation coefficient, they seldom lead to markedly different conclusions (Siegel and Castellan, 1988).

Concept of Relativity of a Statistical Graph

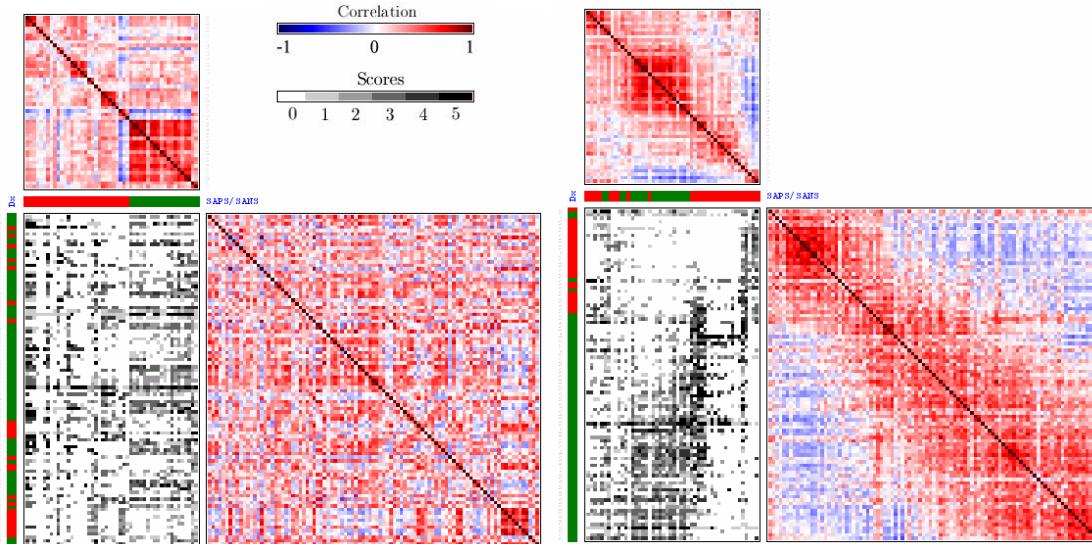
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Placing similar (different) objects at closer (distant) positions

Statistica Sinica 12(2002), 7-29

GENERALIZED ASSOCIATION PLOTS:
INFORMATION VISUALIZATION VIA ITERATIVELY
GENERATED CORRELATION MATRICES

Chun-Hou Chen



Seriation Problem

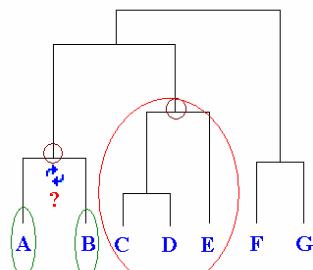
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Cluster Software (Eisen et al 1998):

- (1) Based on average expression level
- (2) Using the results of a one-dimensional SOM

Alon et al (1999):

Based on similarity to their parent's siblings

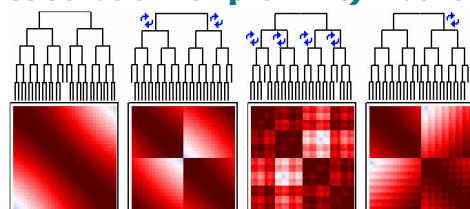


if $d(A, \{C, D, E\}) < d(B, \{C, D, E\})$ then flip

Bar-Joseph et al (2001)

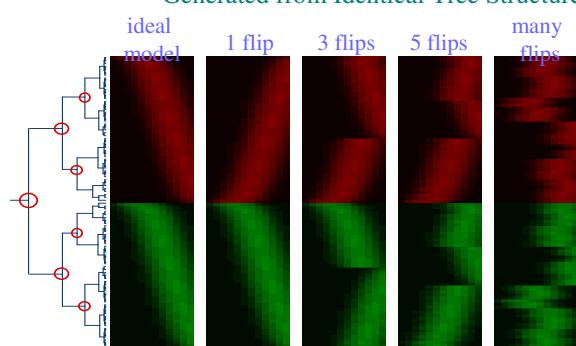
Ziv Bar-Joseph, David K. Gifford, and Tommi S. Jaakkola, (2001), **Fast Optimal Leaf Ordering** for Hierarchical Clustering, Bioinformatics 17(Suppl. 1):S22-S29.

Tree seriation for proximity matrices



Different Seriations

Generated from Identical Tree Structure

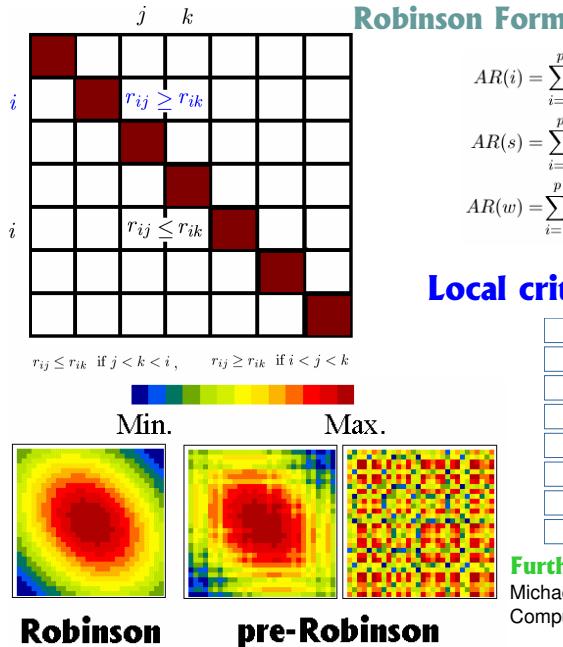


Tree seriation for raw data matrices

Criteria for a “good” Permutation

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



Global/local Criterion: Anti-Robinson Measurements

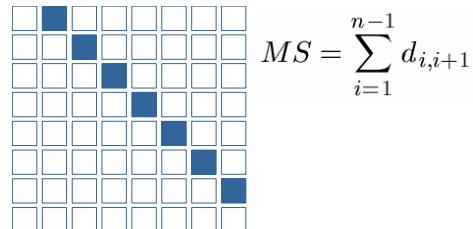
permuted matrix, $D = [d_{ij}]$

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

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

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

Local criterion: Minimal Span Loss Function



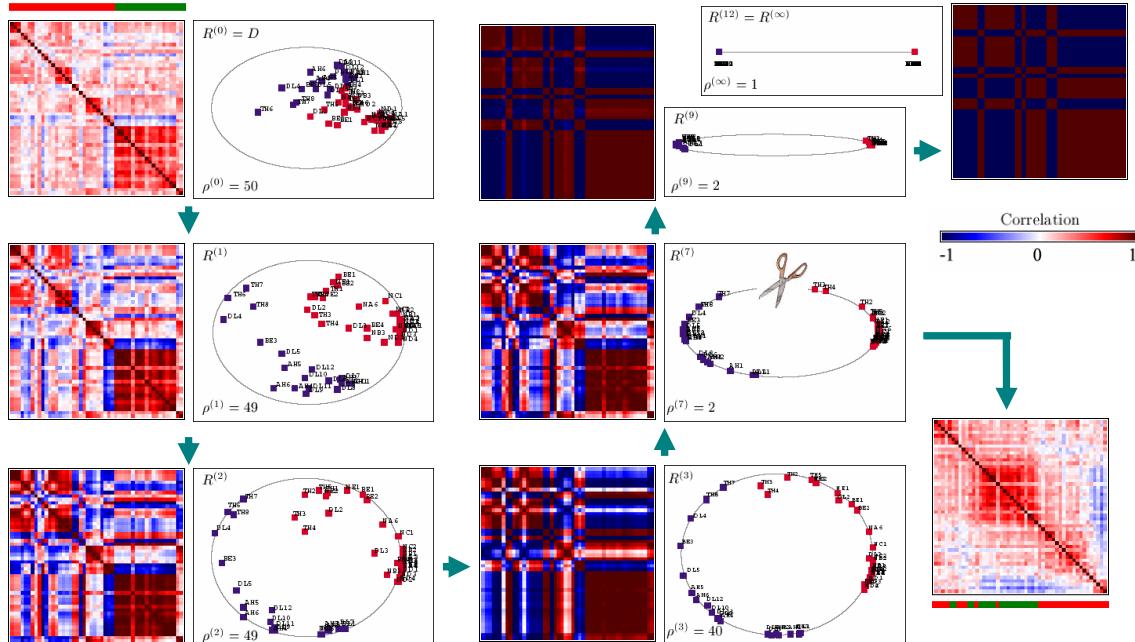
Further Reading

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

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- 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.



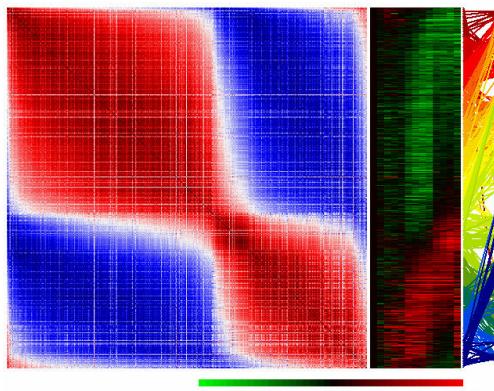
Global vs Local Seriation

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GAP Elliptical Seriation

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

GAP Elliptical Seriation



Michael Eisen Tree Seriation

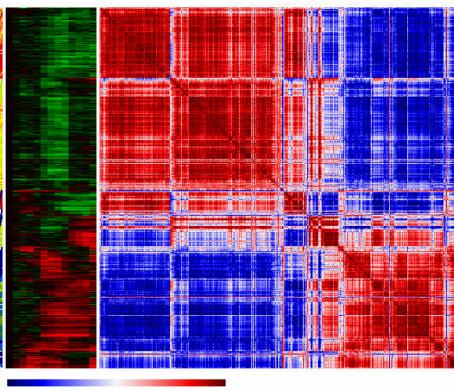
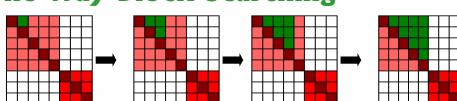


Image source: Dr. Chen Chun-houh's slide

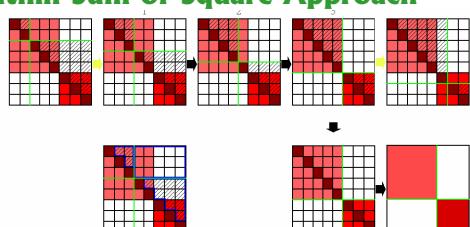
Partitions of Permuted Matrix Maps

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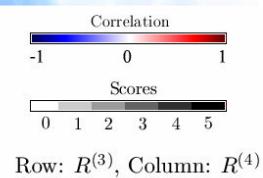
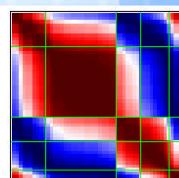
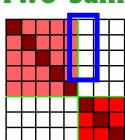
One-Way block Searching



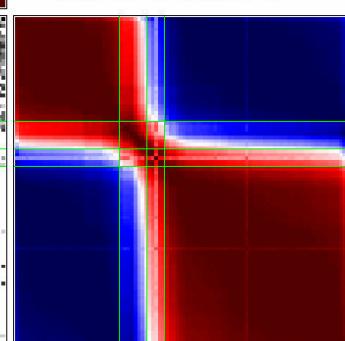
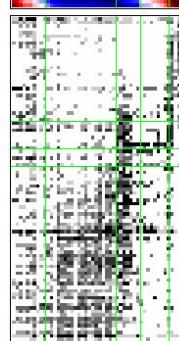
Within-Sum-of-Square Approach



Two-Sample Problem



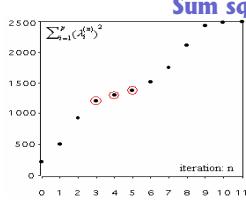
Row: $R^{(3)}$, Column: $R^{(4)}$



Sum squared eigenvalues (sum squared correlations)

Further Reading

J. A. Hartigan. Direct clustering of a data matrix. Journal of the American Statistical Association, 67(337):123-129, March 1972.
Duffy, D. & Quiroz, A. (1991), 'A permutation-based algorithm for block clustering', J. of Classification 8, 65–91.



Sufficient Graph

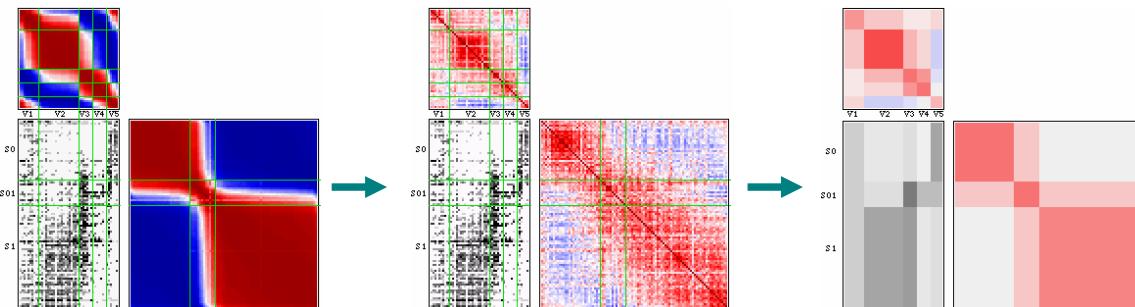
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	A	B	C	D	E	F	報告
1	學號	小考1	期中考	小考2	期末考		
2	A01	69	92	85	45	62	
3	A02	66	90	83	36	90	
4	A03	72	92	80	62	70	
5	A04	68	90	60	37	95	
6	A05	74	60	86	54	70	
7	A06	77	90	88	88	95	
8	A07	73	88	77	51	95	
9	A08	61	90	84	40	82	
10	A09	66	88	82	39	80	
11	A10	76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

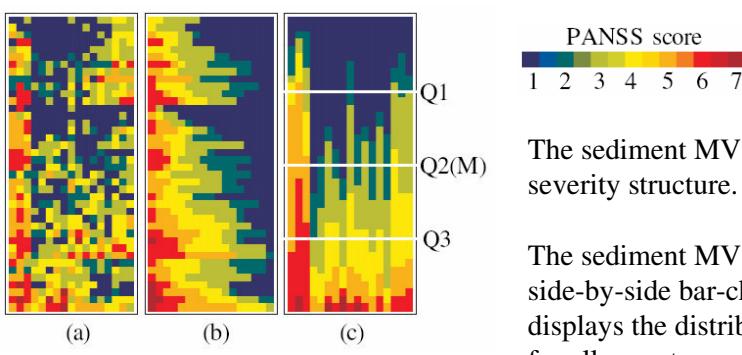
70	低平均	65.67	81.83	73.67	53.67	72
	高平均	77.83	90.67	86.67	53.67	94.17



Generalization and Flexibility

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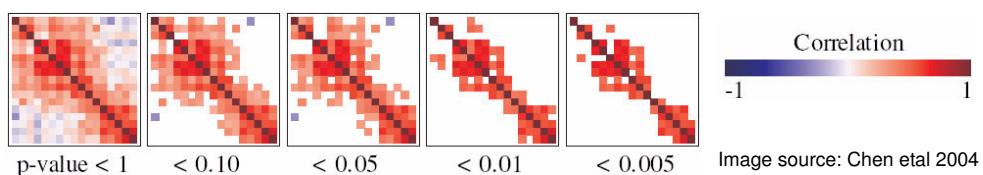
Sedimented MV for patients and symptoms.



The sediment MV for patients: express severity structure.

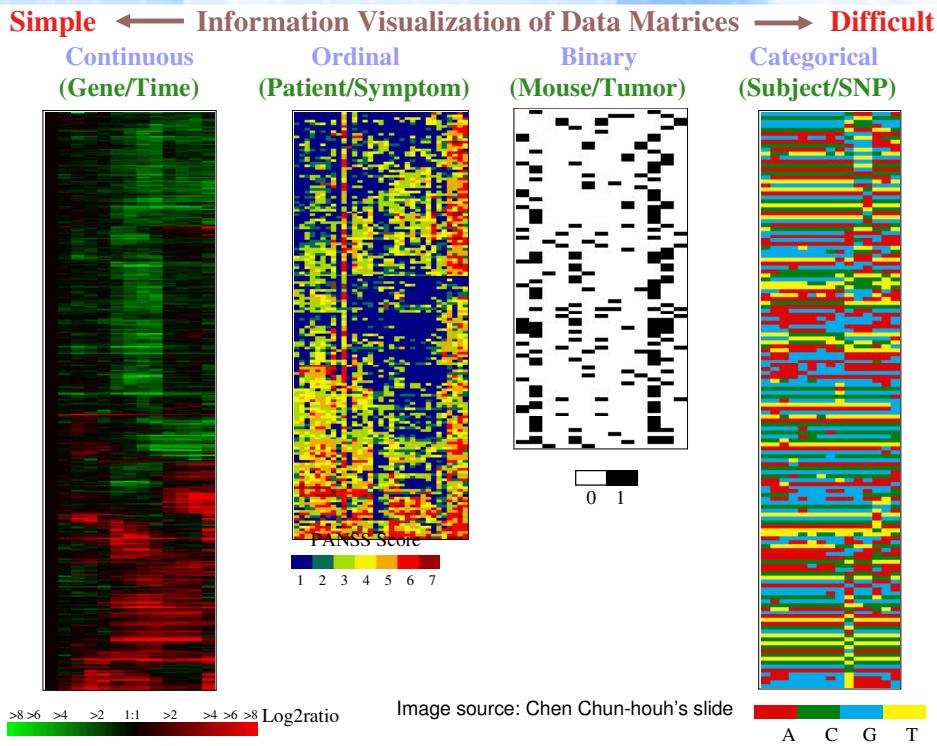
The sediment MV for symptoms: this is a side-by-side bar-chart and box-plot which displays the distribution structure for all symptoms simultaneously.

Sectional MV for the permuted correlation coefficient map.



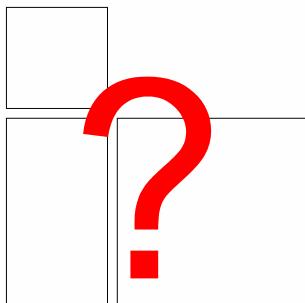
Visualization of Data Matrices

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Chen's Lab for Information Visualization

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- 類別型 (categorical) 資料之全矩陣視覺化
- 條件式 (變項校正) 全矩陣視覺化
- 全矩陣視覺化之遺漏值 (missing value) 處理
- 多時點 (相同變項) 資料之全矩陣視覺化
- 多條件 (不同變項) 資料之全矩陣視覺化
- 相依 (dependent) 或群集 (clustered) 資料之全矩陣視覺化
- 巨量資料之全矩陣視覺化

Web site

<http://gap.stat.sinica.edu.tw>

The screenshot shows the homepage of the Chen's Lab for Information Visualization. The header includes the lab's name, the researcher's name (Chun-houh Chen), and the Institute of Statistical Science, Academia Sinica. The main content area is divided into several sections:

- Information Visualization**: Includes links to Generalized Association Plots (GAP), Sliced Inverse Regression (SIR), and Multidimensional Scaling (MDS).
- Psychiatry Research**: Includes links to Psychiatry and Bioinformatics.
- Bioinformatics**: Includes links to Microarray Data Analysis and SNPs.
- Talks/Seminar**: Includes links to Lecture Notes and Posters.
- News/Conference**: Includes links to various conferences and events.

On the right side, there is a diagram illustrating the process of Dimension Free Data Visualization, showing four steps: Raw Data Maps, Sorted Data Maps, Partitioned Data Maps, and Sufficient Data Maps, leading to Generalized Association Plots (GAP). Below the diagram, there is a link to the handbook of Computational Statistics (Volume III): Data Visualization.

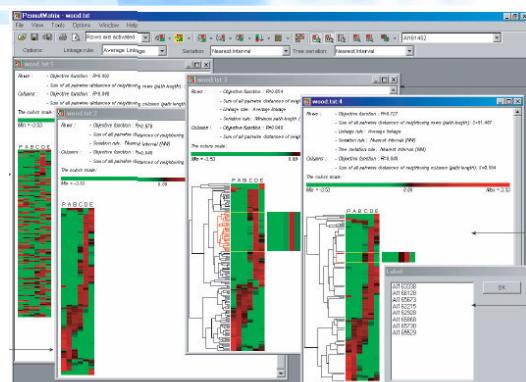
Software

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■ PermutMatrix

<http://www.lirmm.fr/~caraux/PermutMatrix>

Caraux, G., and Pinloche, S. (2005), "Permutmatrix: A Graphical Environment to Arrange Gene Expression Profiles in Optimal Linear Order," *Bioinformatics*, 21, 1280-1281.

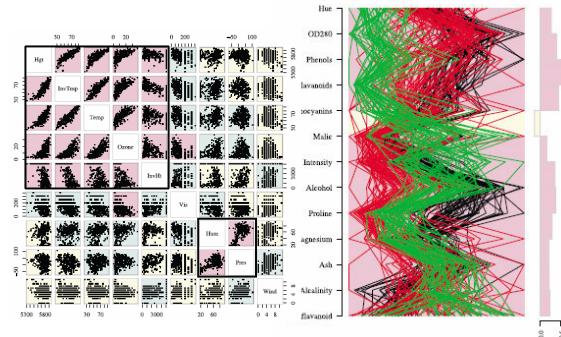


■ gclus: Clustering Graphics

(R package)

<http://cran.r-project.org/src/contrib/Descriptions/gclus.html>

Catherine B. Hurley, (2004), Clustering Visualizations of Multidimensional Data, *Journal of Computational & Graphical Statistics*, Vol. 13, No. 4, pp.788-806



Software: GAP

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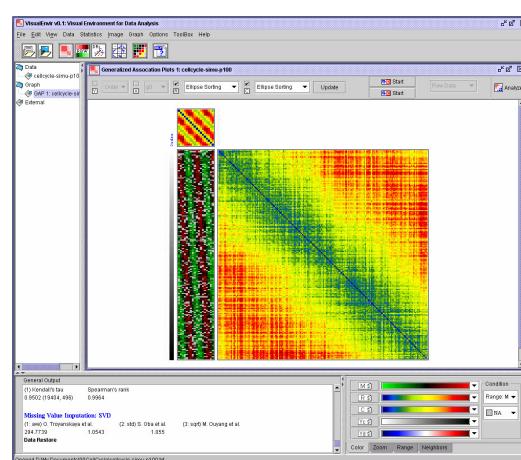
- Generalized Association Plots
 - ◆ Various seriation algorithms (Clustering Analysis)
 - ◆ Various display conditions
- GAP with a Covariate Adjusted
 - ◆ Within And Between Analysis (WABA).
 - ◆ Partial Correlation Analysis.
- GAP with Nonlinear Association Analysis
 - ◆ ISOMAP
 - ◆ Kernel Transformation
- GAP with Missing Values Imputation
 - ◆ Row means, Columns means
 - ◆ Regression methods
 - ◆ KNN (KNNImpute)
 - ◆ SVD (SVDImpute)
 - ◆ GAPImpute
- Statistical Plots
 - ◆ Histogram, 2D Scatterplot, 3D Scatterplot (Rotatable)

<http://gap.stat.sinica.edu.tw/Software/GAP>

Expected to release on 15th Dec, 2005.



Dec. 15-17, 2005 (IASC-ARS 2005)
The 5th Asian Conference on Statistical Computing, IASC
The University of Hong Kong, Hong Kong



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