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# University of Washington

## Computer Science & Engineering

## CSE 527, Au '03: Computational Biology





**Time:** MW 12:00-1:20
**Place:** MGH 284

| | | Office Hours | | Phone |
|---|---|---|---|---|
| **Instructor:** | Larry Ruzzo, ruzzo@cs, | M 1:30 | 554 Allen Center, | 543-6298 |
| **TA:** | Zizhen Yao, yzizhen@cs, | | | |

An introduction to the use of comput
understanding of biological systems
Intended for graduate students in bio
learning about algorithms and compu
graduate students in computer scienc
interested in applications of those fie

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**References:**

The following slides partly from
http://staff.washington.edu/kayee/research.html
Errors are mine.

# Clustering 101

Ka Yee Yeung
Center for Expression Arrays
University of Washington

# Overview

- What is clustering?
- Similarity/distance metrics
- Hierarchical clustering algorithms
  - E.g. [Eisen et al. 1998]
- K-means
  - E.g. [MacQueen, 1965] [Tavazoie et al. 1999]
- Self-organizing map (SOM)
  - E.g. [Tamayo et al. 1999]

# What is clustering?

- Group *similar* objects together
- Objects in the same cluster (group) are more similar to each other than objects in different clusters
- Data exploratory tool

# Clustering Expression Data

- Why cluster gene expression data?
  - Tissue classification } columns
  - Find biologically related genes } rows
  - First step in inferring regulatory networks } rows
  - Look for common promoter elements } rows

  - Hypothesis generation
  - One of the tools of choice for expression analysis

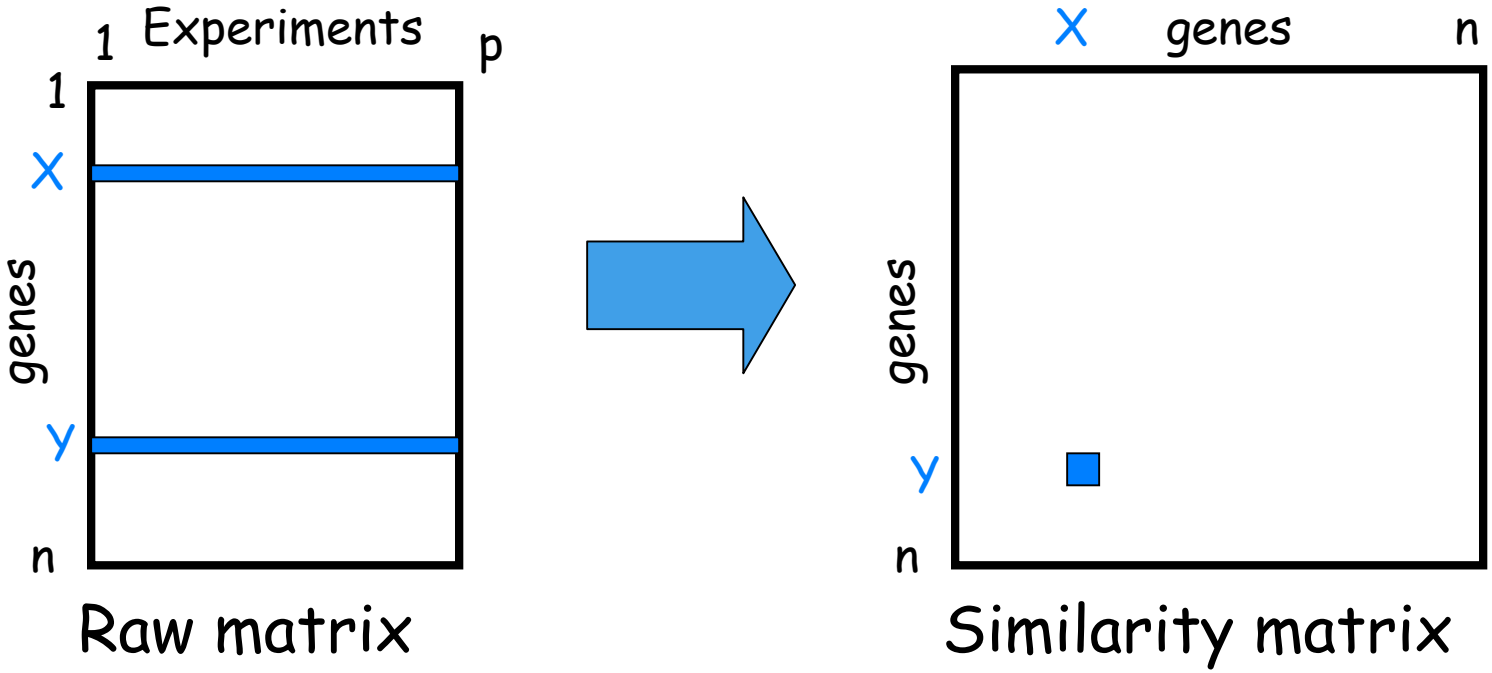
# Clustering Expression Data

- What has been done?
  - Partitional
    - CAST (Ben-Dor et al. 1999)
    - k-means, variously initialized (Hartigan 1975)
  - Hierarchical
    - single-, average-, complete-, centroid-link [Eisen et al. 98]
  - Self Organizing Maps (SOM) [Tamayo et al. 99]
  - Support Vector Machines (SVM) [Grundy et al. 00]
  - etc., etc., etc.

# Clustering Expression Data

- Why so many methods?
  - Clustering is NP-hard, even with simple objectives, data
  - Hard problem: high dimensionality, noise, …
  - ∴ many heuristic, local search, & approximation algorithms
  - No clear winner

# How to define similarity?




- Similarity metric:
  - A measure of pairwise similarity or dissimilarity
  - Examples:
    - Correlation coefficient
    - Euclidean distance

# Similarity metrics

- Euclidean distance

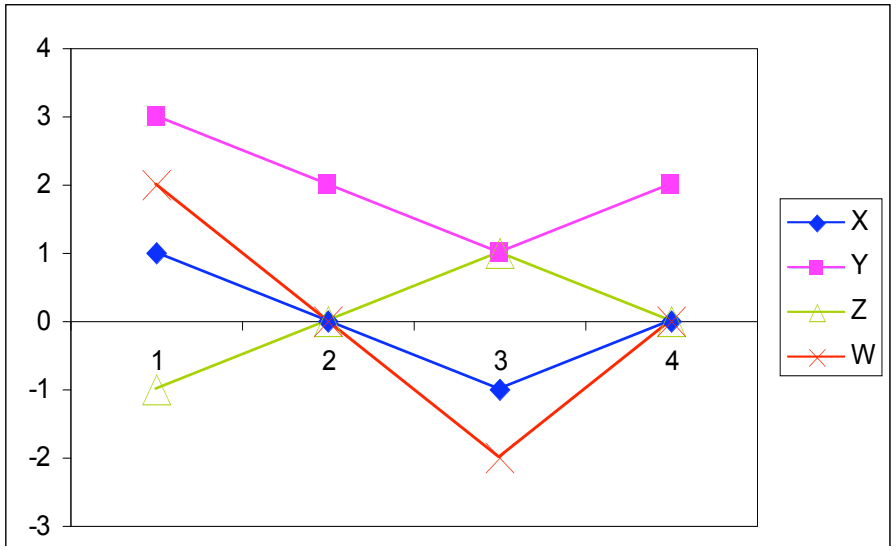
$$\sqrt{\sum_{j=1}^{p}(X[j]-Y[j])^2}$$

- Correlation coefficient

$$\frac{\sum_{j=1}^{p}(X[j]-\overline{X})(Y[j]-\overline{Y})}{\sqrt{\sum_{j=1}^{p}(X[j]-\overline{X})^2\sum_{j=1}^{p}(Y[j]-\overline{Y})^2}}, \quad \textit{where } \overline{X}=\frac{\sum_{j=1}^{p}X[j]}{p}$$

# Example

| | | | | |
|---|---|---|---|---|
| X | 1 | 0 | -1 | 0 |
| Y | 3 | 2 | 1 | 2 |
| Z | -1 | 0 | 1 | 0 |
| W | 2 | 0 | -2 | 0 |




Correlation (X,Y) = 1 Distance (X,Y) = 4

Correlation (X,Z) = -1 Distance (X,Z) = 2.83

Correlation (X,W) = 1 Distance (X,W) = 1.41

# Lessons from the example

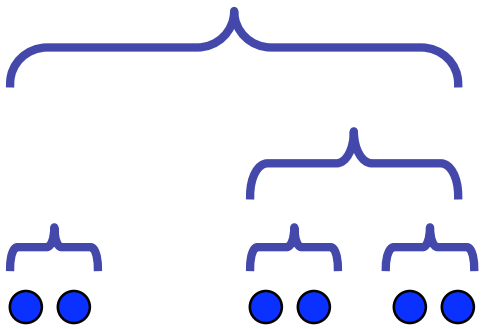
- Correlation – direction only
- Euclidean distance – magnitude & direction
- Min # attributes (experiments) to compute pairwise similarity
  - >= 2 attributes for Euclidean distance
  - >= 3 attributes for correlation
- Array data is noisy ➔ need many experiments to robustly estimate pairwise similarity

# Clustering algorithms

- Inputs:
  - Raw data matrix or similarity matrix
  - Number of clusters or some other parameters
- Many different classifications of clustering algorithms:
  - Hierarchical vs partitional
  - Heuristic-based vs model-based
  - Soft vs hard

# Hierarchical Clustering

[Hartigan 1975]

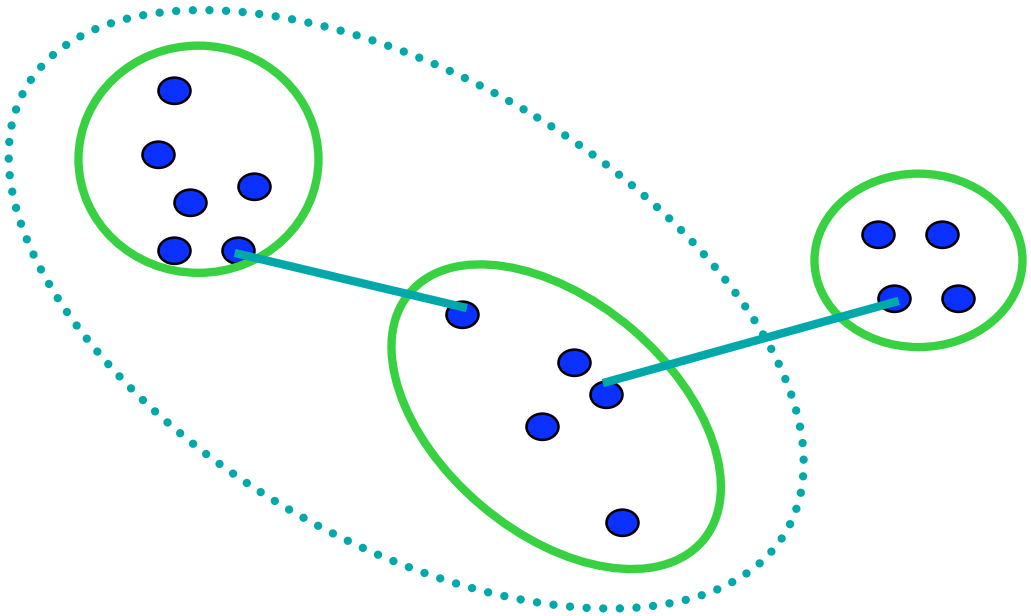


dendrogram

- Agglomerative (bottom-up)
- Algorithm:
  - Initialize: each item a cluster
  - Iterate:
    - select two most similar clusters
    - merge them
  - Halt: when required number of clusters is reached

# Hierarchical: Single Link

- cluster similarity = similarity of two most similar members



- Potentially long and skinny clusters

+ Fast

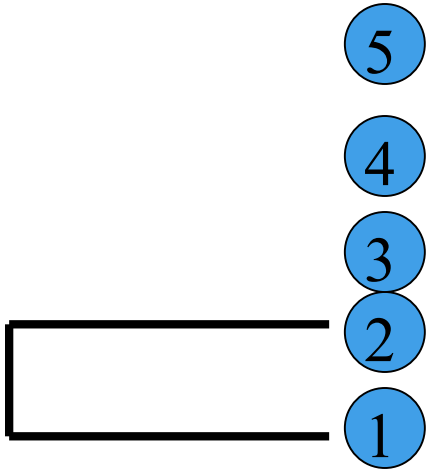
# Example: single link

$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{cccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 3 & 0 & & \\ 9 & 7 & 0 & \\ 8 & 5 & 4 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2),3} = \min\{ d_{1,3}, d_{2,3} \} = \min\{ 6,3 \} = 3$$

$$d_{(1,2),4} = \min\{ d_{1,4}, d_{2,4} \} = \min\{ 10,9 \} = 9$$

$$d_{(1,2),5} = \min\{ d_{1,5}, d_{2,5} \} = \min\{ 9,8 \} = 8$$

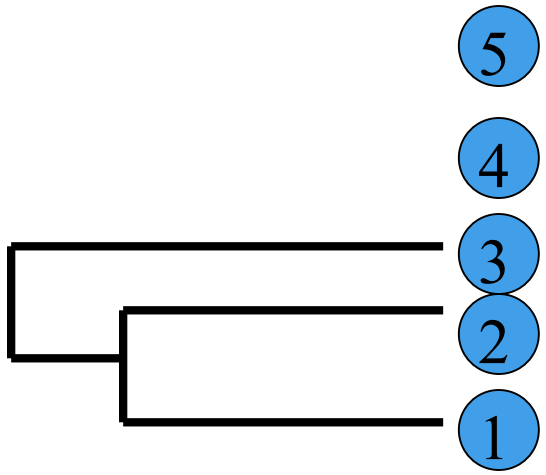


# Example: single link

$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{cccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 3 & 0 & & \\ 9 & 7 & 0 & \\ 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2,3) \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccc} (1,2,3) & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & \\ 7 & 0 & \\ 5 & 4 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2,3),4} = \min\{ d_{(1,2),4}, d_{3,4}\} = \min\{ 9,7\} = 7$$

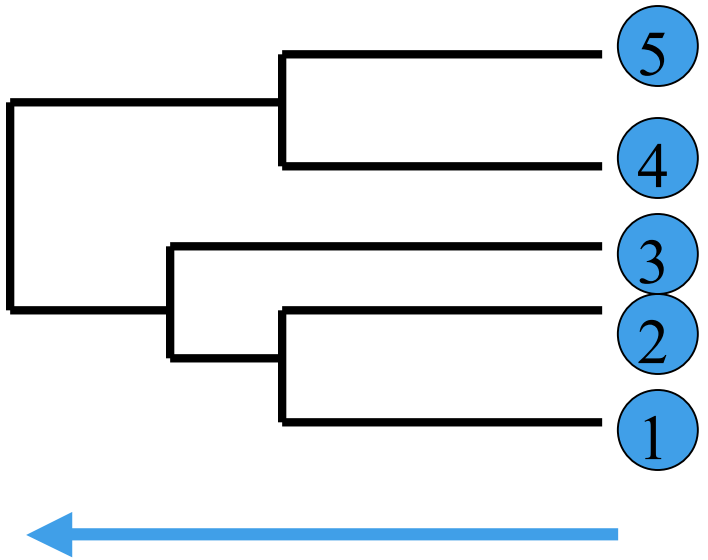
$$d_{(1,2,3),5} = \min\{ d_{(1,2),5}, d_{3,5}\} = \min\{ 8,5\} = 5$$



# Example: single link

$$\begin{array}{c|ccccc} & 1 & 2 & 3 & 4 & 5 \\ 1 & 0 & & & & \\ 2 & 2 & 0 & & & \\ 3 & 6 & 3 & 0 & & \\ 4 & 10 & 9 & 7 & 0 & \\ 5 & 9 & 8 & 5 & 4 & 0 \end{array} \Rightarrow \begin{array}{c|cccc} & (1,2) & 3 & 4 & 5 \\ (1,2) & 0 & & & \\ 3 & 3 & 0 & & \\ 4 & 9 & 7 & 0 & \\ 5 & 8 & 5 & 4 & 0 \end{array} \Rightarrow \begin{array}{c|ccc} & (1,2,3) & 4 & 5 \\ (1,2,3) & 0 & & \\ 4 & 7 & 0 & \\ 5 & 5 & 4 & 0 \end{array}$$

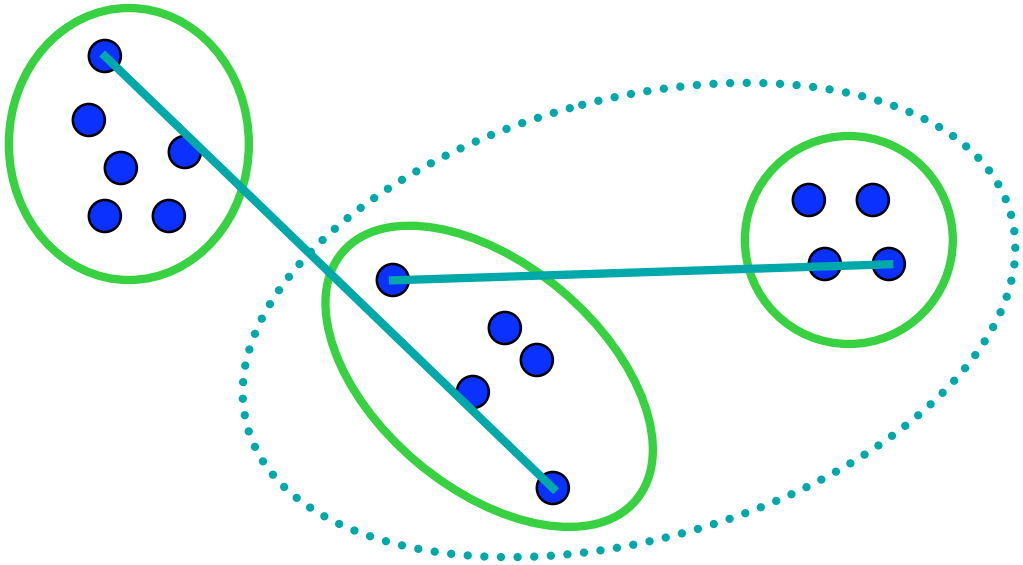
$$d_{(1,2,3),(4,5)} = \min\{ d_{(1,2,3),4}, d_{(1,2,3),5} \} = 5$$




Sometimes drawn to a scale

# Hierarchical: Complete Link

- cluster similarity = similarity of two least similar members



+ tight clusters

- slow

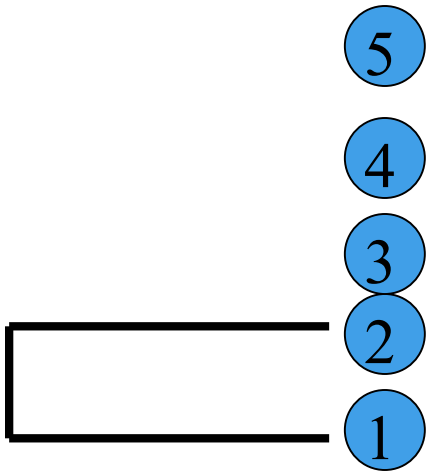
# Example: complete link

$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 6 & 0 & & \\ 10 & 7 & 0 & \\ 9 & 5 & 4 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2),3} = \max\{d_{1,3}, d_{2,3}\} = \max\{6,3\} = 6$$

$$d_{(1,2),4} = \max\{d_{1,4}, d_{2,4}\} = \max\{10,9\} = 10$$

$$d_{(1,2),5} = \max\{d_{1,5}, d_{2,5}\} = \max\{9,8\} = 9$$

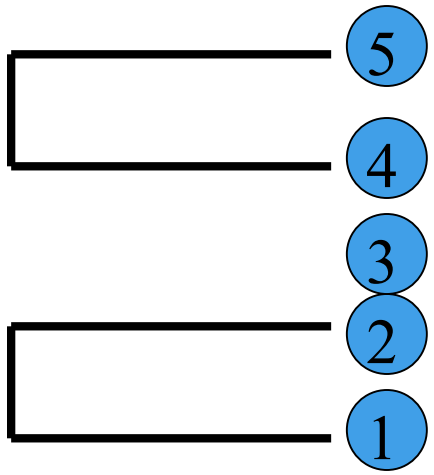


# Example: complete link

$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{cccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 6 & 0 & & \\ 10 & 7 & 0 & \\ 9 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ (4,5) \end{array}\begin{array}{c} \begin{array}{ccc} (1,2) & 3 & (4,5) \end{array} \\ \begin{bmatrix} 0 & & \\ 6 & 0 & \\ 10 & 7 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2),(4,5)} = \max\{d_{(1,2),4}, d_{(1,2),5}\} = \max\{10,9\} = 10$$

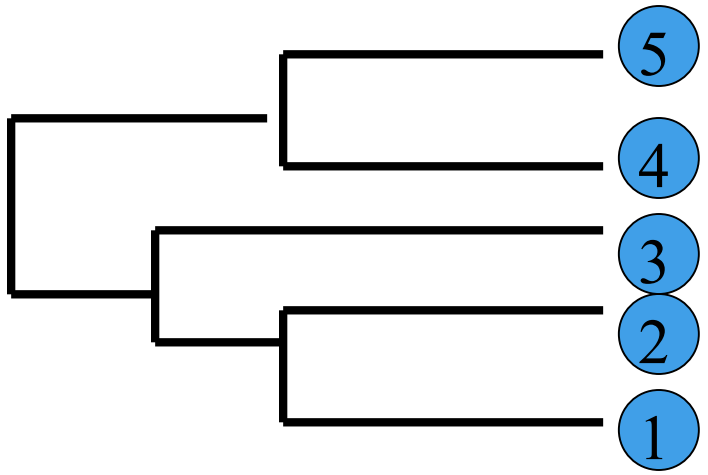
$$d_{3,(4,5)} = \max\{d_{3,4}, d_{3,5}\} = \max\{7,5\} = 7$$



# Example: complete link

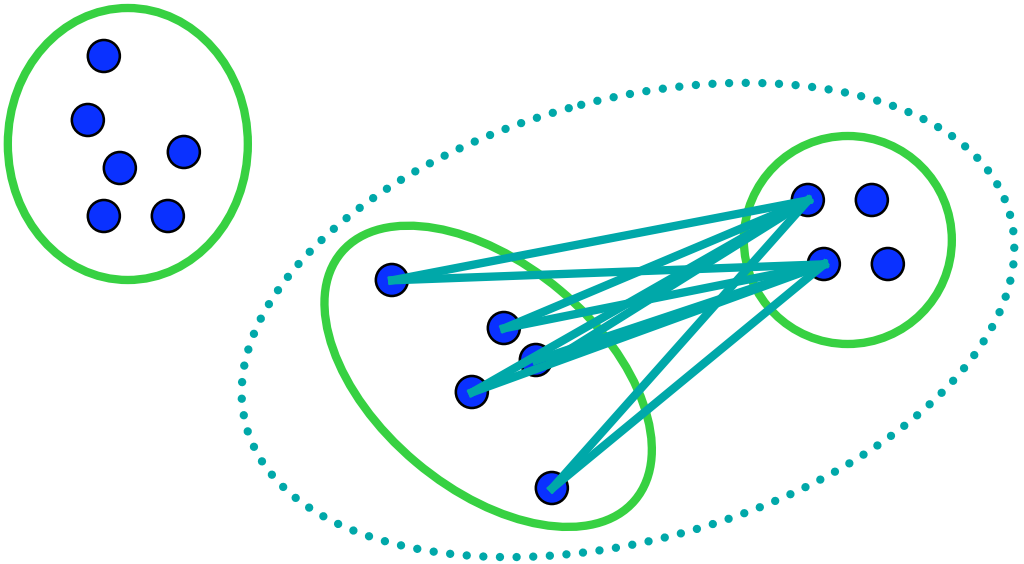
$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \quad \Rightarrow \quad \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{cccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 6 & 0 & & \\ 10 & 7 & 0 & \\ 9 & 5 & 4 & 0 \end{bmatrix} \end{array} \quad \Rightarrow \quad \begin{array}{c} \\ (1,2) \\ 3 \\ (4,5) \end{array}\begin{array}{c} \begin{array}{ccc} (1,2) & 3 & (4,5) \end{array} \\ \begin{bmatrix} 0 & & \\ 6 & 0 & \\ 10 & 7 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2,3),(4,5)} = \max\{ d_{(1,2),(4,5)}, d_{3,(4,5)} \} = 10$$



# Hierarchical: Average Link

- cluster similarity = average similarity of all pairs



+ tight clusters

- slow

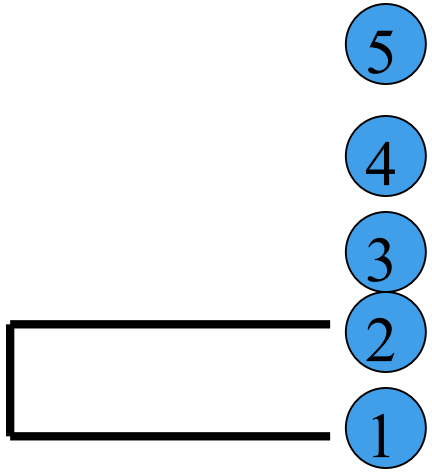
# Example: average link

$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{cccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 4.5 & 0 & & \\ 9.5 & 7 & 0 & \\ 8.5 & 5 & 4 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2),3} = \frac{1}{2}(d_{1,3} + d_{2,3}) = \frac{6+3}{2} = 4.5$$

$$d_{(1,2),4} = \frac{1}{2}(d_{1,4} + d_{2,4}) = \frac{10+9}{2} = 9.5$$

$$d_{(1,2),5} = \frac{1}{2}(d_{1,5} + d_{2,5}) = \frac{9+8}{2} = 8.5$$

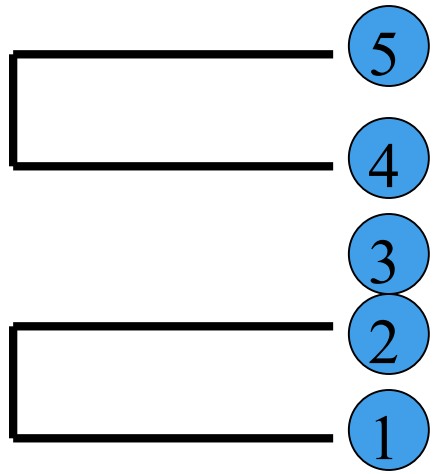


# Example: average link

$$\begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & & \\ 2 & 0 & & & \\ 6 & 3 & 0 & & \\ 10 & 9 & 7 & 0 & \\ 9 & 8 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ 4 \\ 5 \end{array}\begin{array}{c} \begin{array}{cccc} (1,2) & 3 & 4 & 5 \end{array} \\ \begin{bmatrix} 0 & & & \\ 4.5 & 0 & & \\ 9.5 & 7 & 0 & \\ 8.5 & 5 & 4 & 0 \end{bmatrix} \end{array} \Rightarrow \begin{array}{c} \\ (1,2) \\ 3 \\ (4,5) \end{array}\begin{array}{c} \begin{array}{ccc} (1,2) & 3 & (4,5) \end{array} \\ \begin{bmatrix} 0 & & \\ 4.5 & 0 & \\ 9 & 6 & 0 \end{bmatrix} \end{array}$$

$$d_{(1,2),(4,5)} = \frac{1}{4}(d_{1,4} + d_{1,5} + d_{2,4} + d_{2,5}) = 9$$

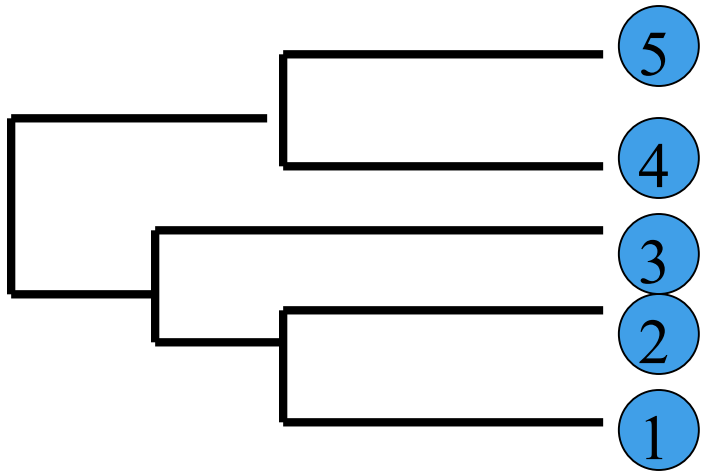
$$d_{3,(4,5)} = \frac{1}{2}(d_{3,4} + d_{3,5}) = 6$$



# Example: average link

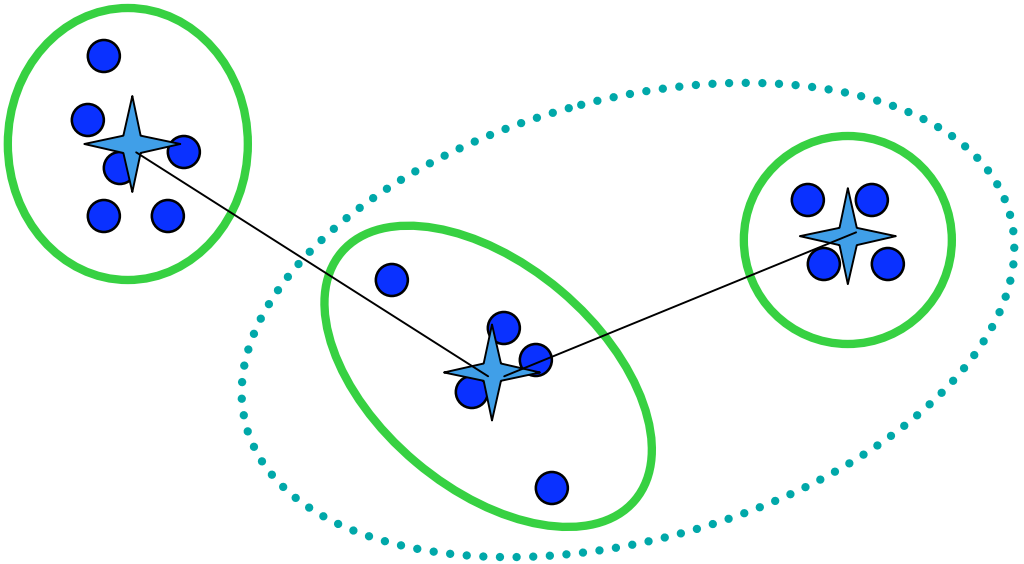
$$\begin{array}{c|ccccc} & 1 & 2 & 3 & 4 & 5 \\ 1 & 0 & & & & \\ 2 & 2 & 0 & & & \\ 3 & 6 & 3 & 0 & & \\ 4 & 10 & 9 & 7 & 0 & \\ 5 & 9 & 8 & 5 & 4 & 0 \end{array} \Rightarrow \begin{array}{c|cccc} & (1,2) & 3 & 4 & 5 \\ (1,2) & 0 & & & \\ 3 & 4.5 & 0 & & \\ 4 & 9.5 & 7 & 0 & \\ 5 & 8.5 & 5 & 4 & 0 \end{array} \Rightarrow \begin{array}{c|ccc} & (1,2) & 3 & (4,5) \\ (1,2) & 0 & & \\ 3 & 4.5 & 0 & \\ (4,5) & 9 & 6 & 0 \end{array}$$

$$d_{(1,2,3),(4,5)} = \frac{1}{6}(d_{1,4} + d_{1,5} + d_{2,4} + d_{2,5} + d_{3,4} + d_{3,5}) = 8$$



# Hierarchical: Centroid Link

- cluster centroid = average of all points
- cluster similarity = distance between centroids



In Expression literature, often called “Average link”

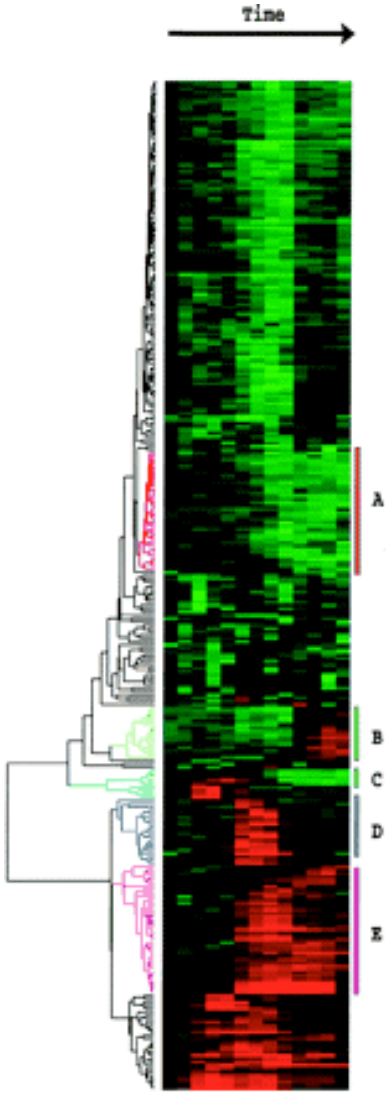
+ faster

- discards shape

# Algorithm Analysis

(see class notes)

# Software: TreeView [Eisen et al. 1998]




- Fig 1 in Eisen's PNAS 99 paper
- Time course of serum stimulation of primary human fibrolasts
- cDNA arrays with approx 8600 spots
- centroid-link
- Free download at: http://rana.lbl.gov/EisenSoftware.htm

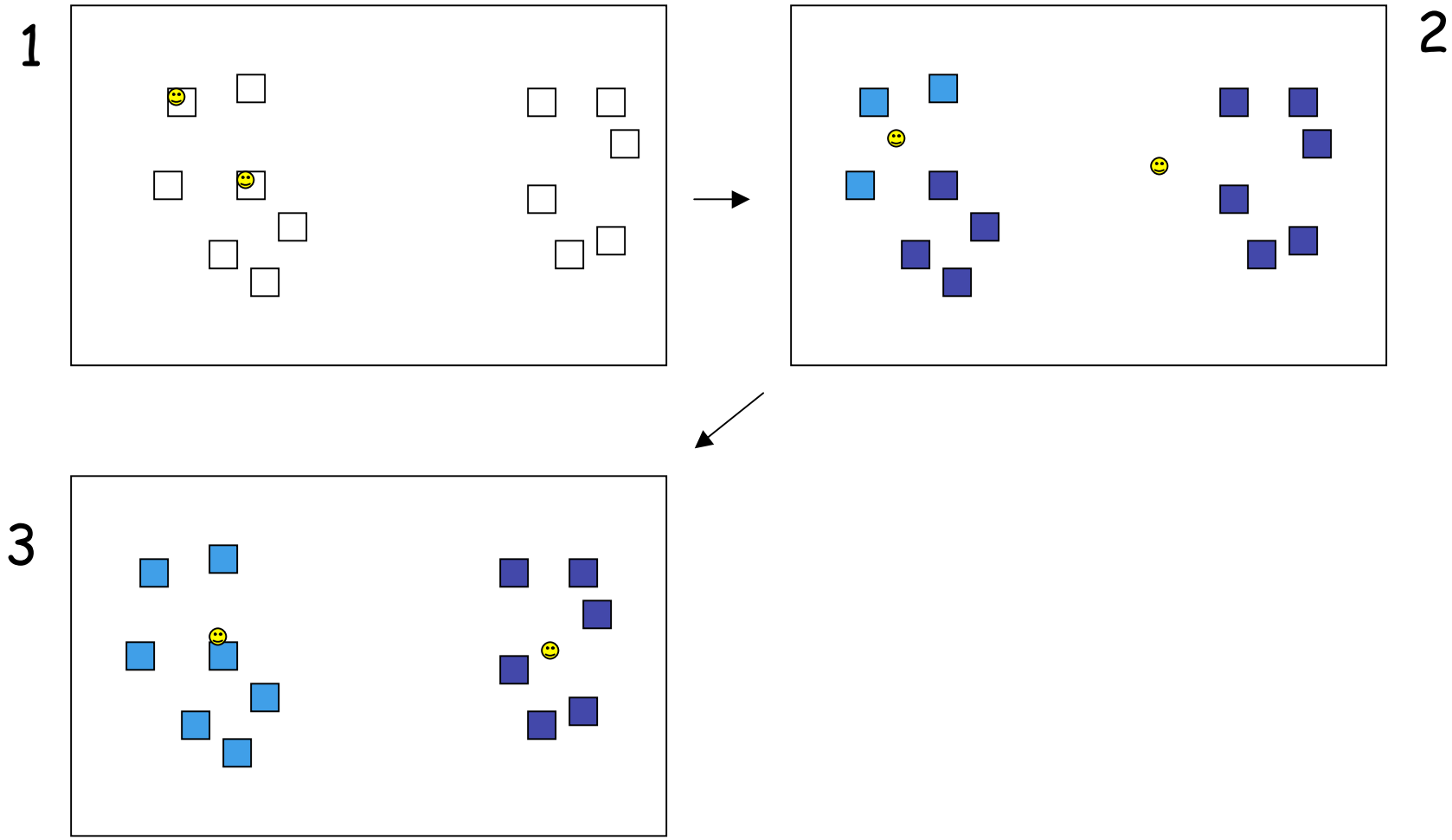
- **Another Good Package: TMEV**
  - http://www.tigr.org/software/tm4/

# Hierarchical divisive clustering algorithms

- Top down
  - Start with all the objects in one cluster
  - Successively split into smaller clusters
- Tend to be less efficient than agglomerative
- Resolver implemented a deterministic annealing approach from [Alon et al. 1999]

# Partitional: K-Means

[MacQueen 1965]



# Details of k-means

- Iterate until converge:
  - Assign each data point to the closest centroid
  - Compute new centroid

**Objective function:**

**Minimize**

$$\sum_{x} \left( x - Centroid(Cluster(x)) \right)^2$$

# Properties of k-means

- Fast
- Proved to converge to local optimum
- In practice, converge quickly
- Tend to produce spherical, equal-sized clusters
- Related to the model-based approach (next lecture)

# Summary

- Definition of clustering
- Pairwise similarity:
  - Correlation
  - Euclidean distance
- Clustering algorithms:
  - Hierarchical (single-, complete-, average-, centroid-ink)
  - K-means
  - SOM
- Different clustering algorithms → different clusters

# Misc Notes

- Greedy algorithms. Can get trapped in local minima. Can be sensitive to addition of new points, order of points,…

+ simple, intuitive algorithms, reasonably fast, ok on simple data, no obvious preconception about structure

- no model of structure; biases unclear