Clustering

Outline

- Microarrays
- Hierarchical Clustering
- K-Means Clustering
- Corrupted Cliques Problem
- CAST Clustering Algorithm

Applications of Clustering

- Viewing and analyzing vast amounts of biological data as a whole set can be perplexing
- It is easier to interpret the data if they are partitioned into clusters combining similar data points.

Inferring Gene Functionality

- Researchers want to know the functions of newly sequenced genes
- Simply comparing the new gene sequences to known DNA sequences often does not give away the function of gene
- For 40% of sequenced genes, functionality cannot be ascertained by only comparing to sequences of other known genes
- Microarrays allow biologists to infer gene function even when sequence similarity alone is insufficient to infer function.

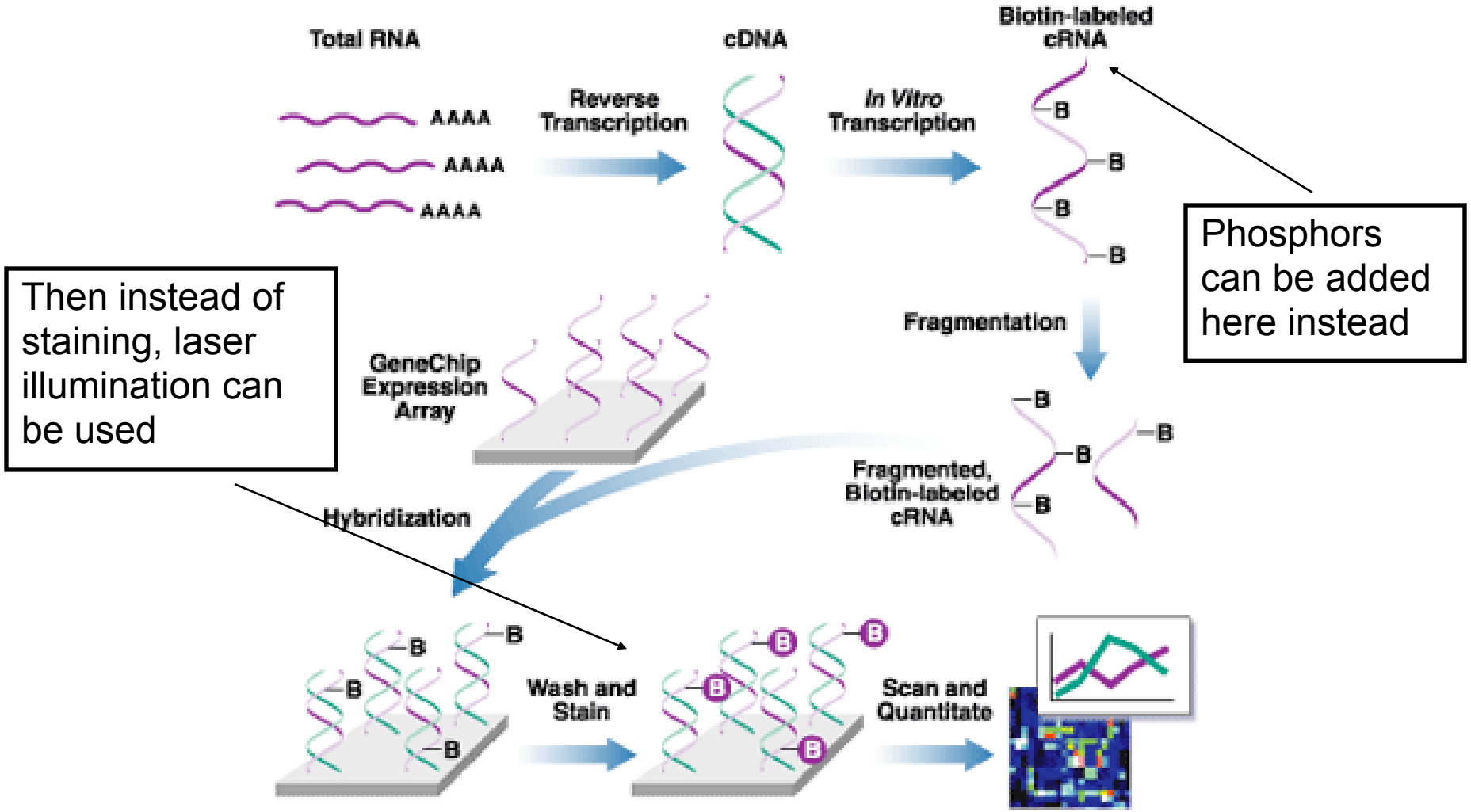
Microarrays and Expression Analysis

- Microarrays measure the activity (expression level) of the genes under varying conditions/time points
- Expression level is estimated by measuring the amount of mRNA for that particular gene
  - A gene is active if it is being transcribed
  - More mRNA usually indicates more gene activity

Microarray Experiments

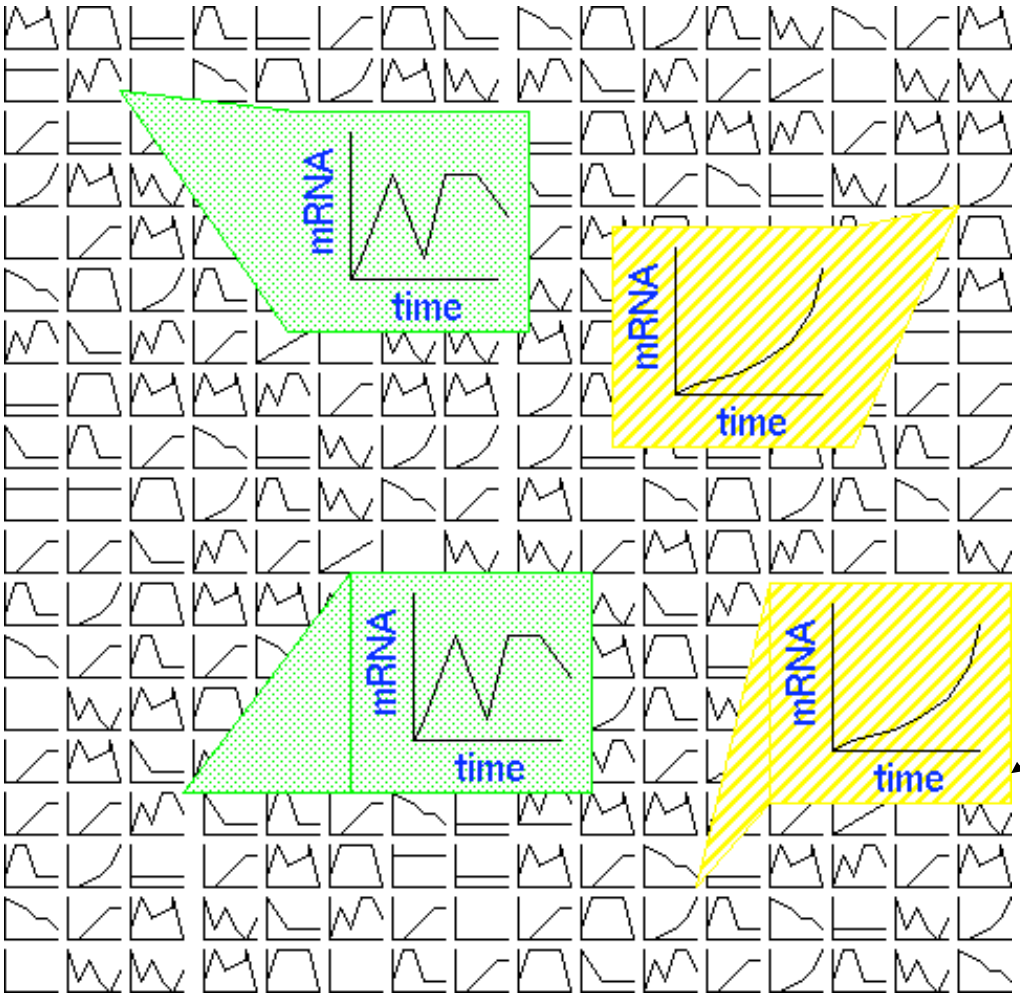
- Produce cDNA from mRNA (DNA is more stable)
- Attach phosphor to cDNA to see when a particular gene is expressed
- Different color phosphors are available to compare many samples at once
- Hybridize cDNA over the micro array
- Scan the microarray with a phosphor-illuminating laser
- Illumination reveals transcribed genes
- Scan microarray multiple times for the different color phosphor's

Microarray Experiments (con't)



www.affymetrix.com

Using Microarrays

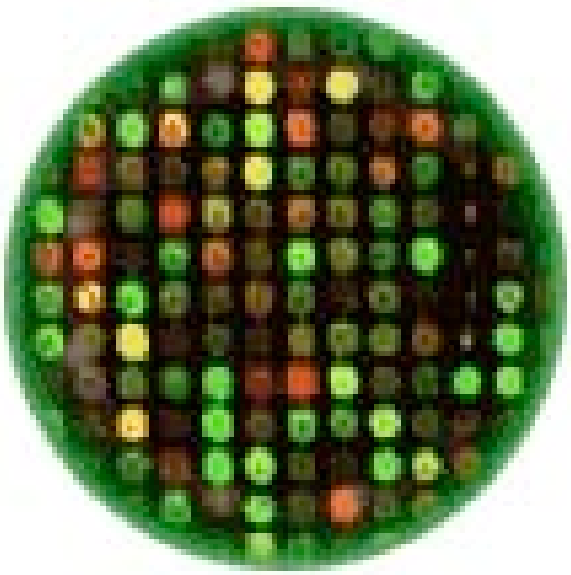


- Track the sample over a period of time to see gene expression over time
- Track two different samples under the same conditions to see the difference in gene expressions

Each box represents one gene's expression over time

Using Microarrays (cont'd)

- **Green**: expressed only from control
- **Red**: expressed only from experimental cell
- **Yellow**: equally expressed in both samples
- **Black**: NOT expressed in either control or experimental cells



Microarray Data

- Microarray data are usually transformed into an intensity matrix (below)
- The intensity matrix allows biologists to make correlations between diferent genes (even if they are dissimilar) and to understand how genes functions might be related

Intensity (expression level) of gene at measured time

Time:	Time X	Time Y	Time Z
Gene 1	10	8	10
Gene 2	10	0	9
Gene 3	4	8.6	3
Gene 4	7	8	3
Gene 5	1	2	3

Clustering of Microarray Data

- Plot each datum as a point in N-dimensional space
- Make a distance matrix for the distance between every two gene points in the N-dimensional space
- Genes with a small distance share the same expression characteristics and might be functionally related or similar.
- Clustering reveal groups of functionally related genes

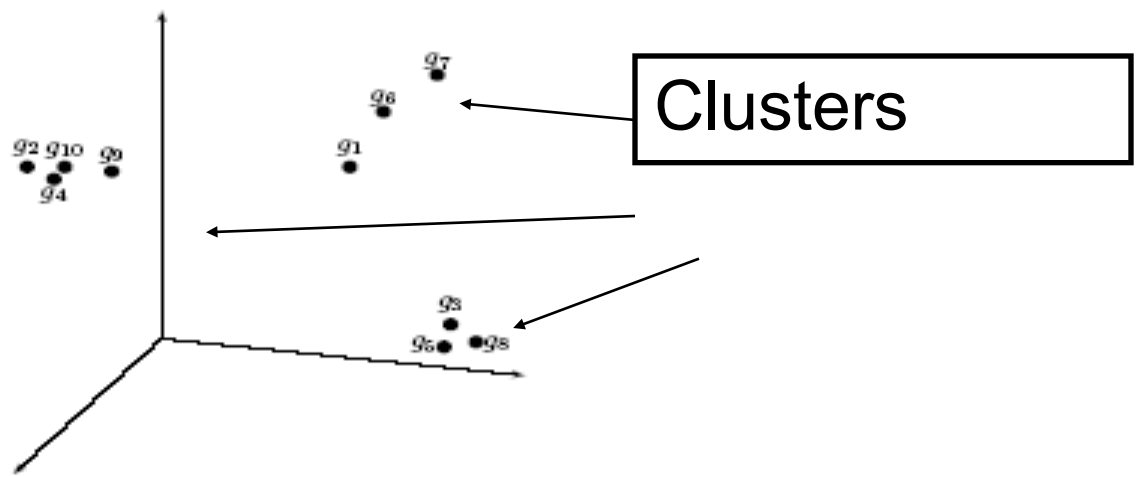
Clustering of Microarray Data (cont'd)

Time	1 hr	2 hr	3 hr
g_1	10.0	8.0	10.0
g_2	10.0	0.0	9.0
g_3	4.0	8.5	3.0
g_4	9.5	0.5	8.5
g_5	4.5	8.5	2.5
g_6	10.5	9.0	12.0
g_7	5.0	8.5	11.0
g_8	2.7	8.7	2.0
g_9	9.7	2.0	9.0
g_{10}	10.2	1.0	9.2

(a) Intensity matrix, I

	g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_8	g_9	g_{10}
g_1	0.0	8.1	9.2	7.7	9.3	2.3	5.1	10.2	6.1	7.0
g_2	8.1	0.0	12.0	0.9	12.0	9.5	10.1	12.8	2.0	1.0
g_3	9.2	12.0	0.0	11.2	0.7	11.1	8.1	1.1	10.5	11.5
g_4	7.7	0.9	11.2	0.0	11.2	9.2	9.5	12.0	1.6	1.1
g_5	9.3	12.0	0.7	11.2	0.0	11.2	8.5	1.0	10.6	11.6
g_6	2.3	9.5	11.1	9.2	11.2	0.0	5.6	12.1	7.7	8.5
g_7	5.1	10.1	8.1	9.5	8.5	5.6	0.0	9.1	8.3	9.3
g_8	10.2	12.8	1.1	12.0	1.0	12.1	9.1	0.0	11.4	12.4
g_9	6.1	2.0	10.5	1.6	10.6	7.7	8.3	11.4	0.0	1.1
g_{10}	7.0	1.0	11.5	1.1	11.6	8.5	9.3	12.4	1.1	0.0

(b) Distance matrix, d

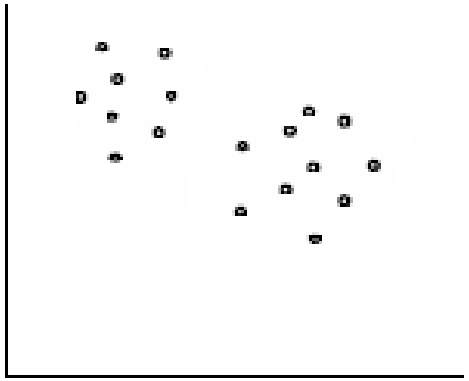


(c) Expression patterns as points in three-dimentsional space.

Homogeneity and Separation Principles

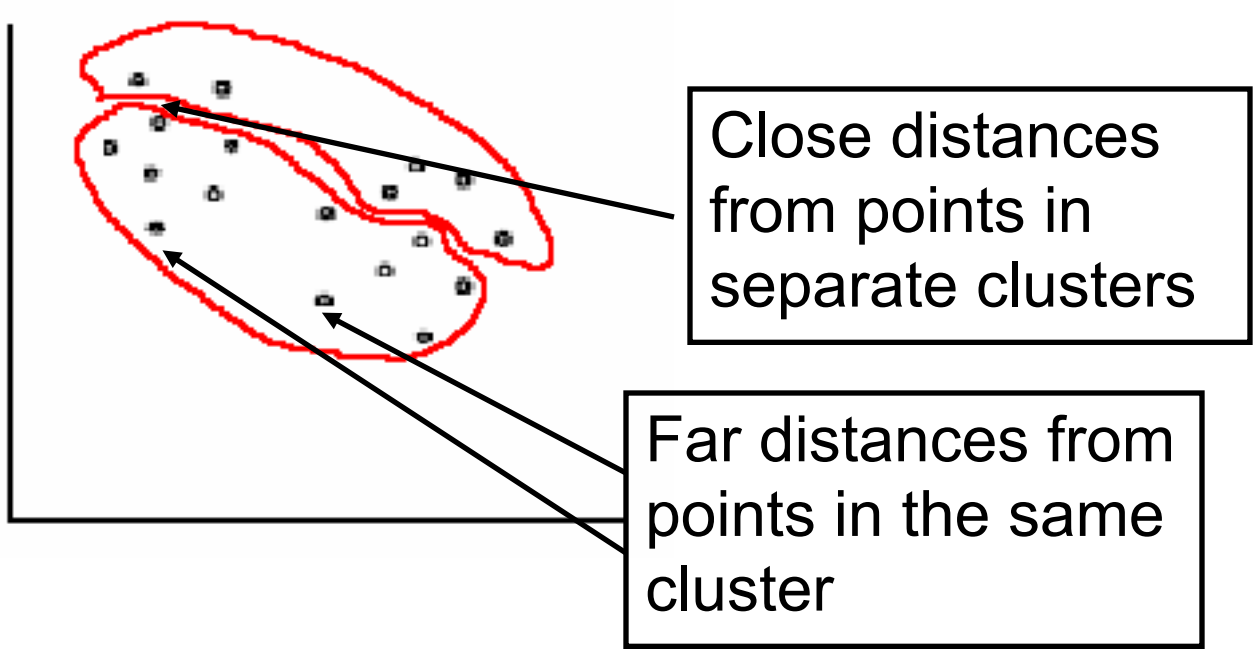
- **Homogeneity:** Elements within a cluster are close to each other
- **Separation:** Elements in different clusters are further apart from each other
- …clustering is not an easy task!

Given these points a clustering algorithm → might make two distinct clusters as follows



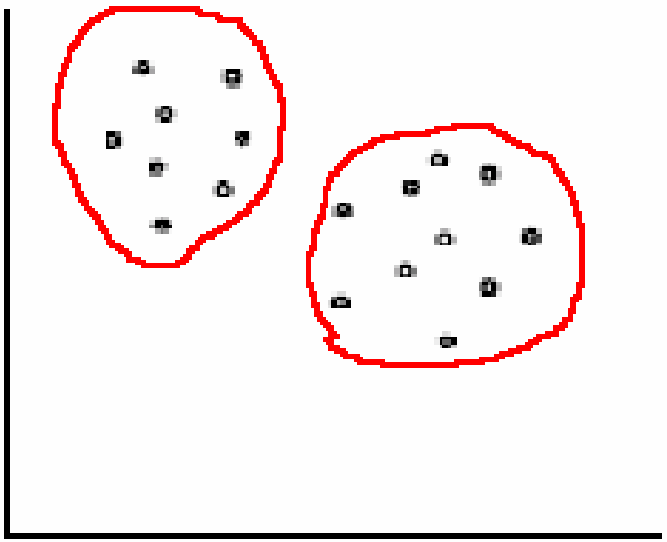
Bad Clustering

This clustering violates both Homogeneity and Separation principles



Good Clustering

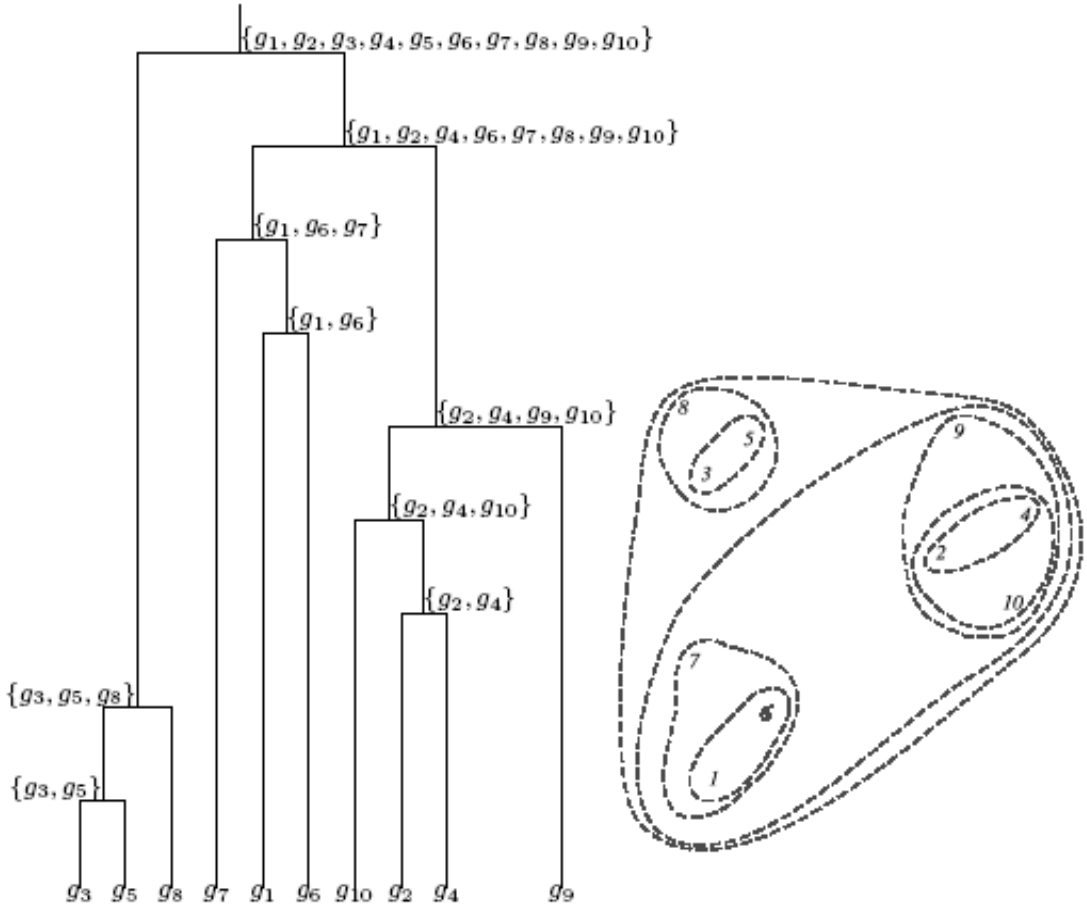
This clustering satisfies both Homogeneity and Separation principles



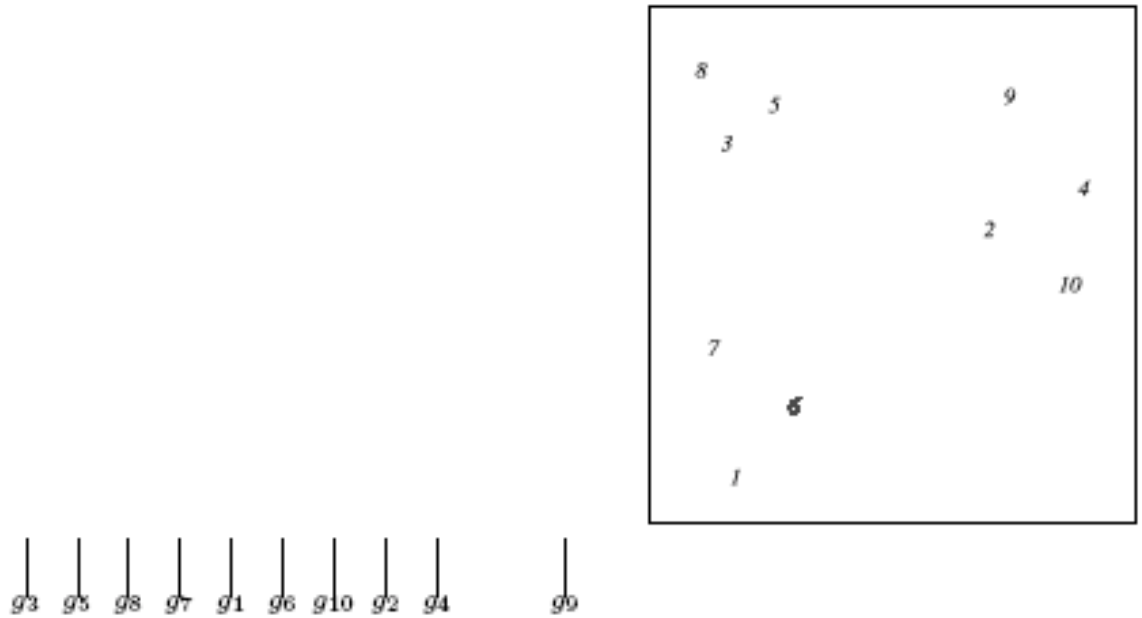
Clustering Techniques

- **Agglomerative:** Start with every element in its own cluster, and iteratively join clusters together
- **Divisive:** Start with one cluster and iteratively divide it into smaller clusters
- **Hierarchical:** Organize elements into a tree, leaves represent genes and the length of the pathes between leaves represents the distances between genes. Similar genes lie within the same subtrees

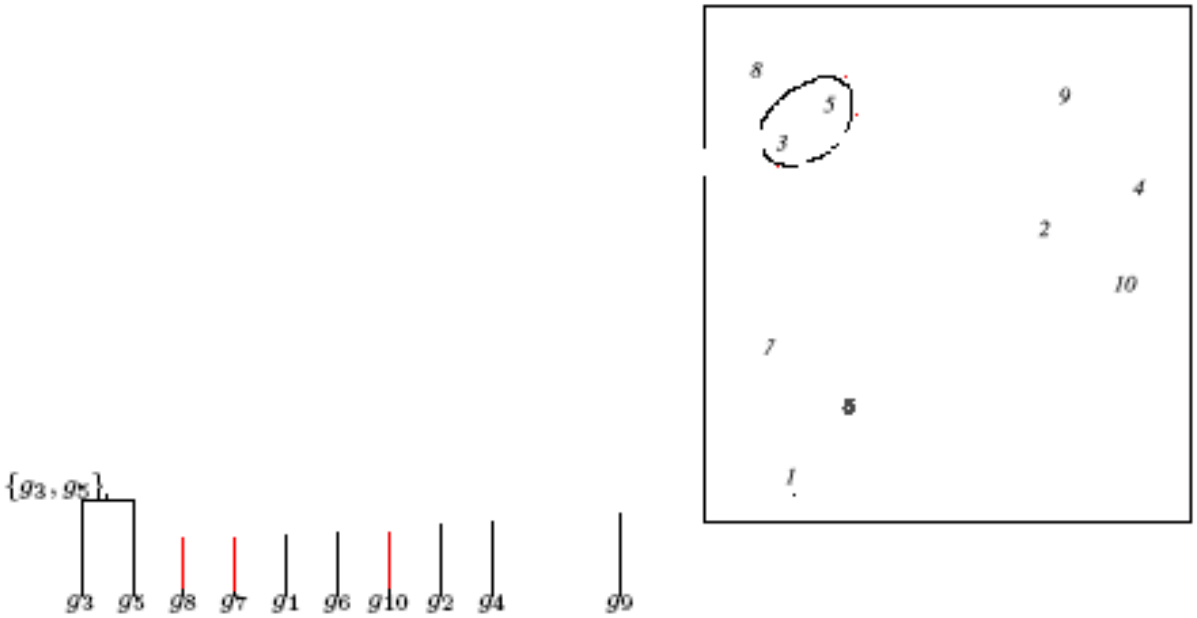
Hierarchical Clustering



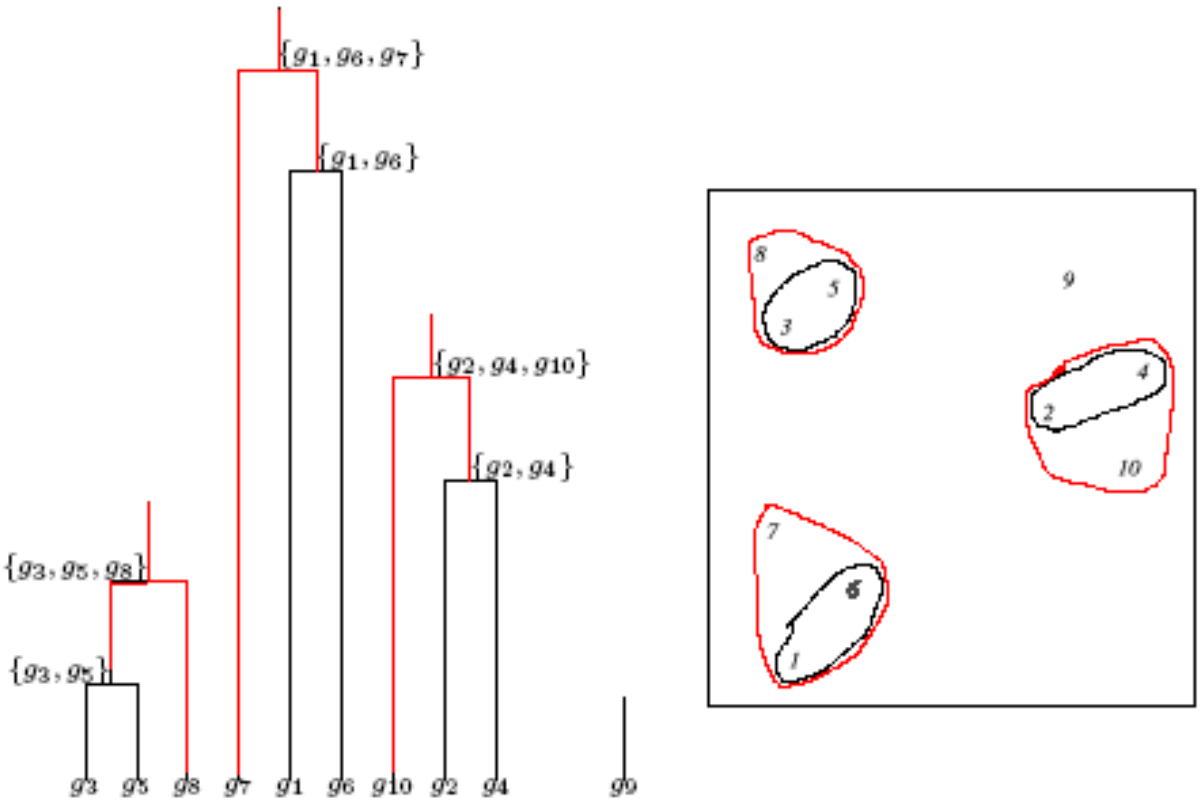
Hierarchical Clustering: Example



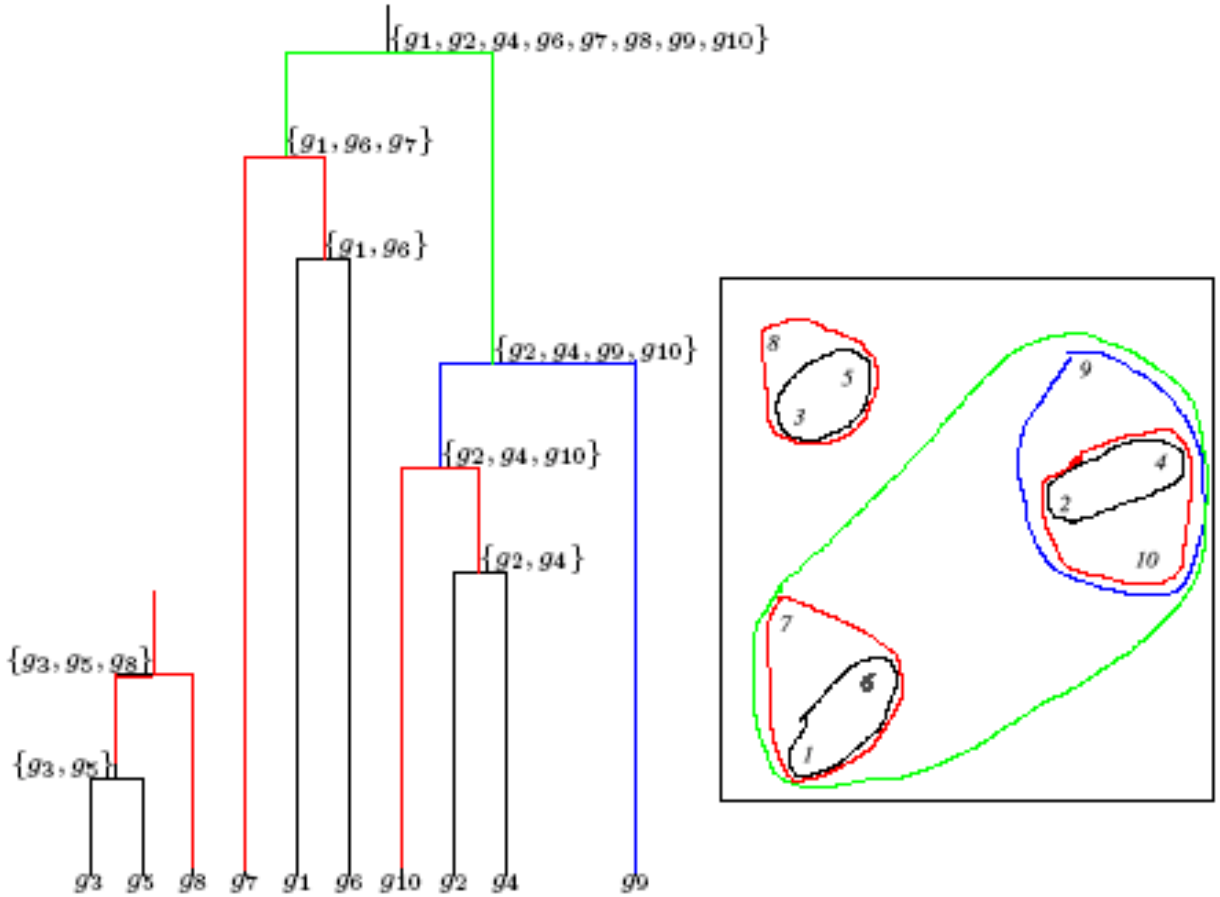
Hierarchical Clustering: Example



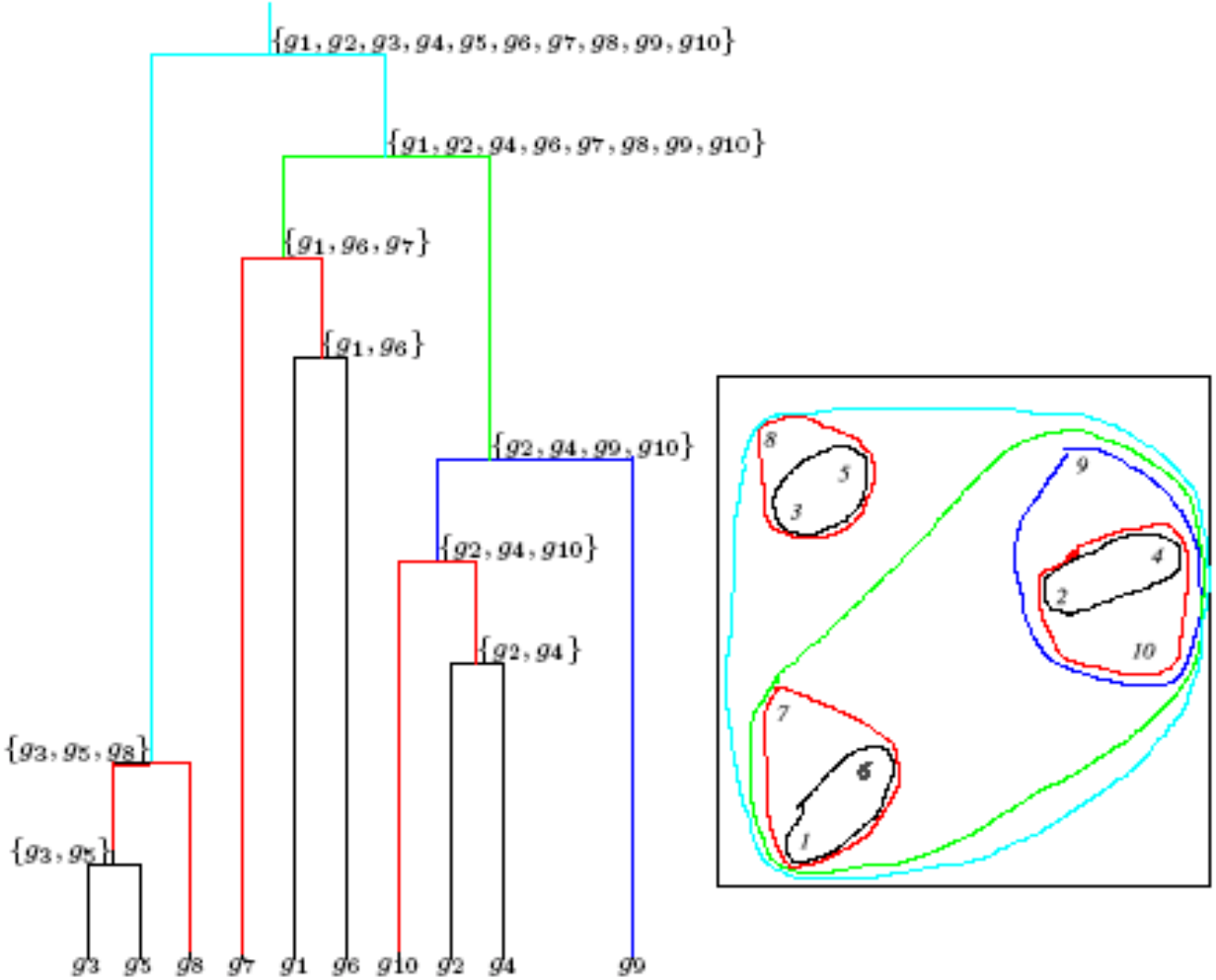
Hierarchical Clustering: Example



Hierarchical Clustering: Example

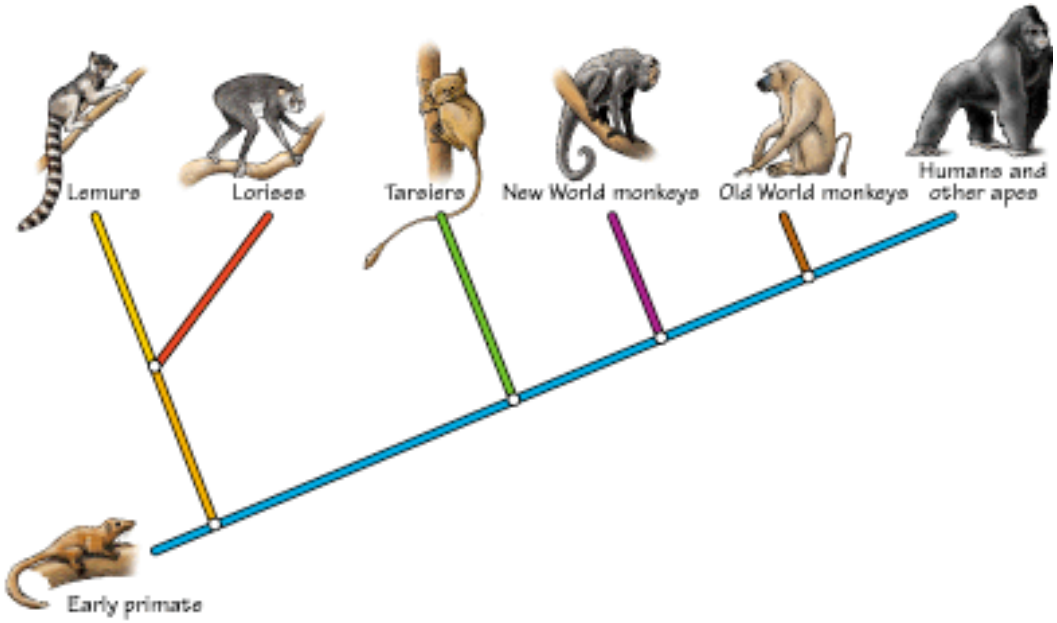


Hierarchical Clustering: Example



Hierarchical Clustering (cont'd)

- Hierarchical Clustering is often used to reveal evolutionary history



Hierarchical Clustering Algorithm

```
Hierarchical Clustering (d , n)
  Form n clusters each with one element
  Construct a graph T  by assigning one vertex to each cluster
  while there is more than one cluster
    Find the two closest clusters C1 and C2
    Merge C1 and C2 into new cluster C with |C1| +|C2| elements
    Compute distance from C to all other clusters
    Add a new vertex C to T and connect to vertices C1 and C2
    Remove rows and columns of d corresponding to C1 and C2
    Add a row and column to d  corrsponding to the new cluster C
  return T
```

The algorithm takes a $n \times n$ distance matrix ***d*** of pairwise distances between points as an input.

Hierarchical Clustering Algorithm

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    Add a new vertex C to T and connect to vertices C1 and C2
    Remove rows and columns of d corresponding to C1 and C2
    Add a row and column to d corrsponding to the new cluster C
  return T
```

Different ways to define distances between clusters may lead to different clusterings

Hierarchical Clustering: Recomputing Distances

- $$d_{min}(C, C^*) = \min \; d(x,y)$$
  $$\textit{for all elements } x \textit{ in } C \textit{ and } y \textit{ in } C^*$$
  - Distance between two clusters is the **smallest** distance between any pair of their elements
- $$d_{avg}(C, C^*) = (1 / |C^*||C|) \sum d(x,y)$$
  $$\textit{for all elements } x \textit{ in } C \textit{ and } y \textit{ in } C^*$$
  - Distance between two clusters is the **average** distance between all pairs of their elements

Squared Error Distortion

- Given a data point ***v*** and a set of points ***X***, define the **distance** from ***v*** to ***X***

$$d(v, \boldsymbol{X})$$

as the (Eucledian) distance from ***v*** to the ***closest*** point from ***X***.

- Given a set of n data points $\boldsymbol{V}=\{v_1 \ldots v_n\}$ and a set of k points ***X***, define the **Squared Error Distortion**

$$d(\boldsymbol{V},\boldsymbol{X}) = \sum d(v_i, \boldsymbol{X})^2 \ / \ n \qquad 1 \leq i \leq n$$

K-Means Clustering Problem: Formulation

- **Input**: A set, ***V***, consisting of *n* points and a parameter *k*
- **Output**: A set ***X*** consisting of *k* points (*cluster centers*) that minimizes the squared error distortion *d(**V**,**X**)* over all possible choices of ***X***

1-Means Clustering Problem: an Easy Case

- **Input**: A set, ***V***, consisting of *n* points
- **Output**: A single points ***x*** (*cluster center*) that minimizes the squared error distortion *d(**V**,**x**)* over all possible choices of ***x***

1-Means Clustering Problem: an Easy Case

- **Input**: A set, ***V***, consisting of *n* points
- **Output**: A single points ***x*** (cluster center) that minimizes the squared error distortion *d(**V**,**x**)* over all possible choices of ***x***

1-Means Clustering problem is easy.

However, it becomes very difficult (NP-complete) for more than one center.

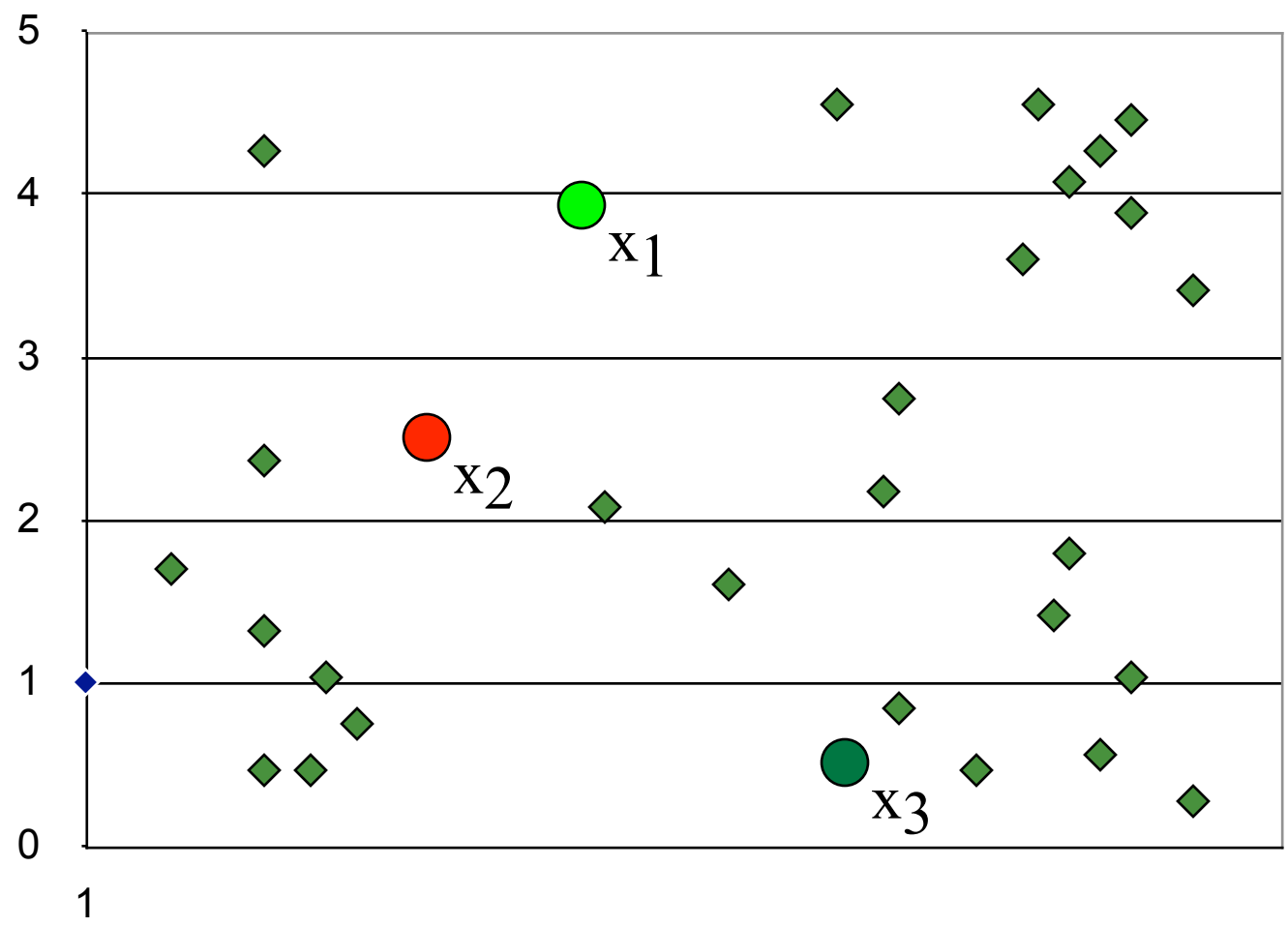
An efficient ***heuristic*** method for K-Means clustering is the Lloyd algorithm

K-Means Clustering: Lloyd Algorithm

1. <u>Lloyd Algorithm</u>
2. Arbitrarily assign the k cluster centers
3. while the cluster centers keep changing
4. Assign each data point to the cluster C_i corresponding to the closest cluster representative (center) $(1 \leq i \leq k)$
5. After the assignment of all data points, compute new cluster representatives according to the center of gravity of each cluster, that is, the new cluster representative is

$$\sum v \backslash |C| \quad \textit{for all } v \textit{ in } C \quad \text{for every cluster } C$$

*This may lead to merely a locally optimal clustering.


5
4
3
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0
1
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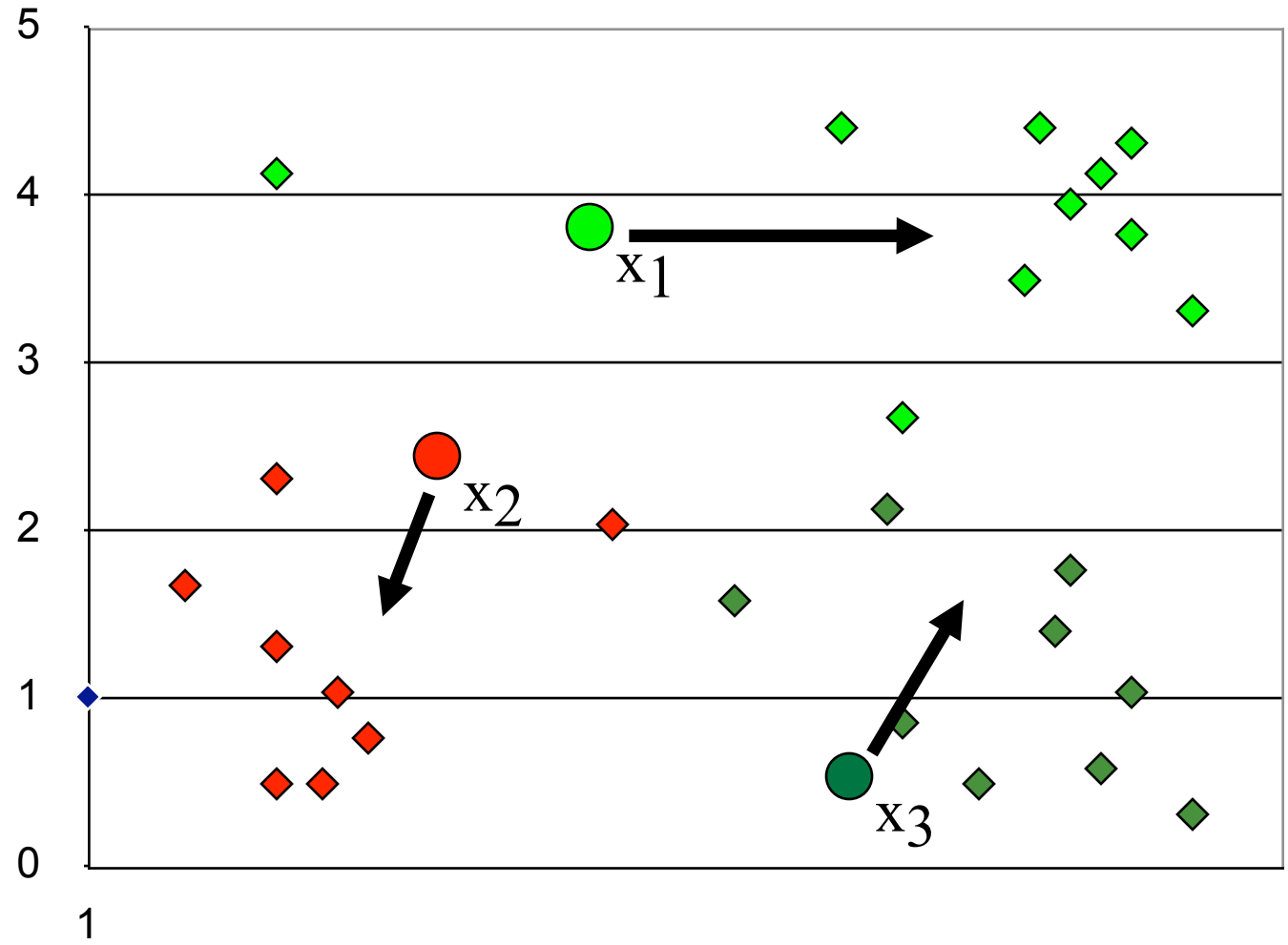
x2
x3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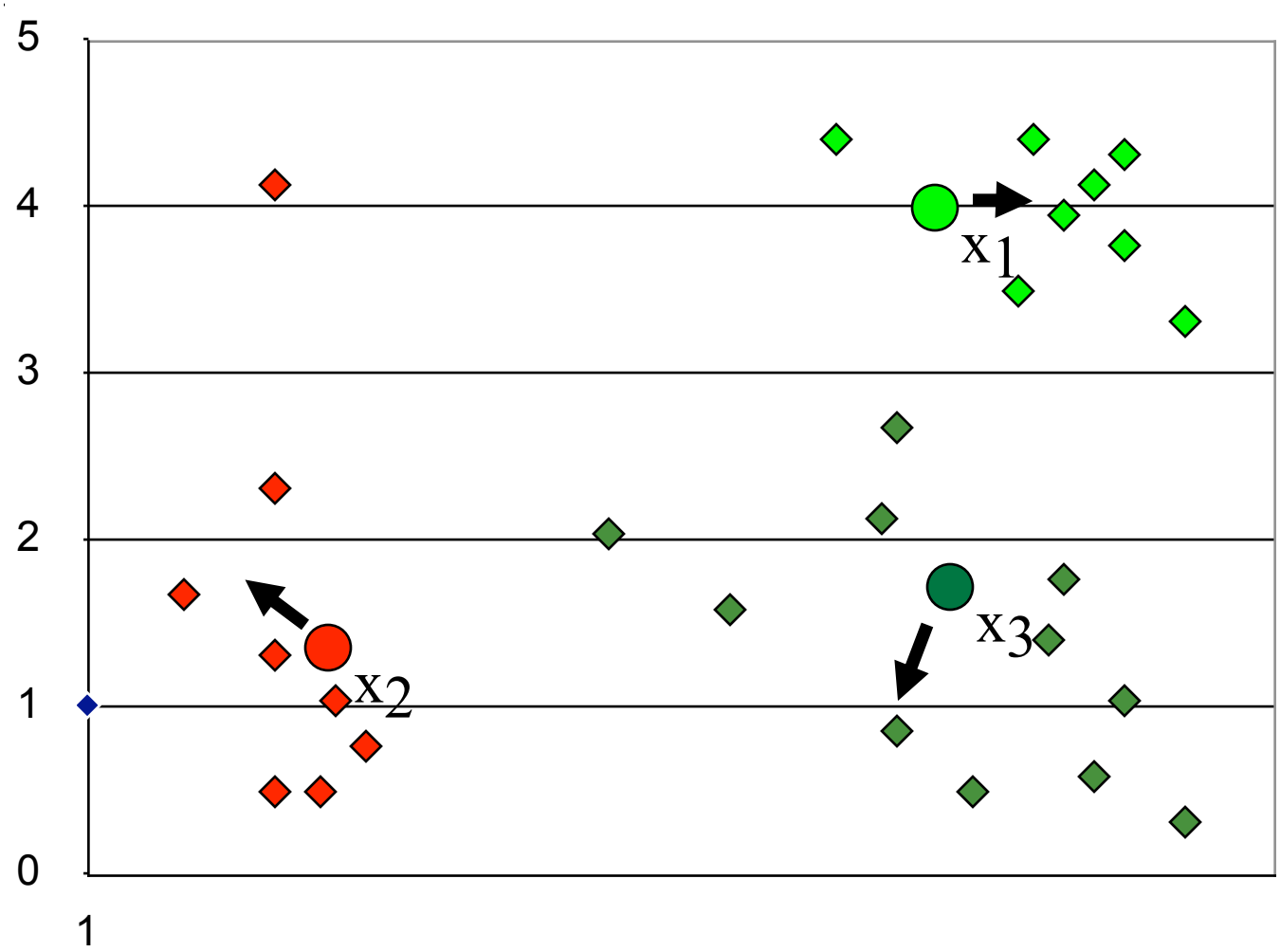
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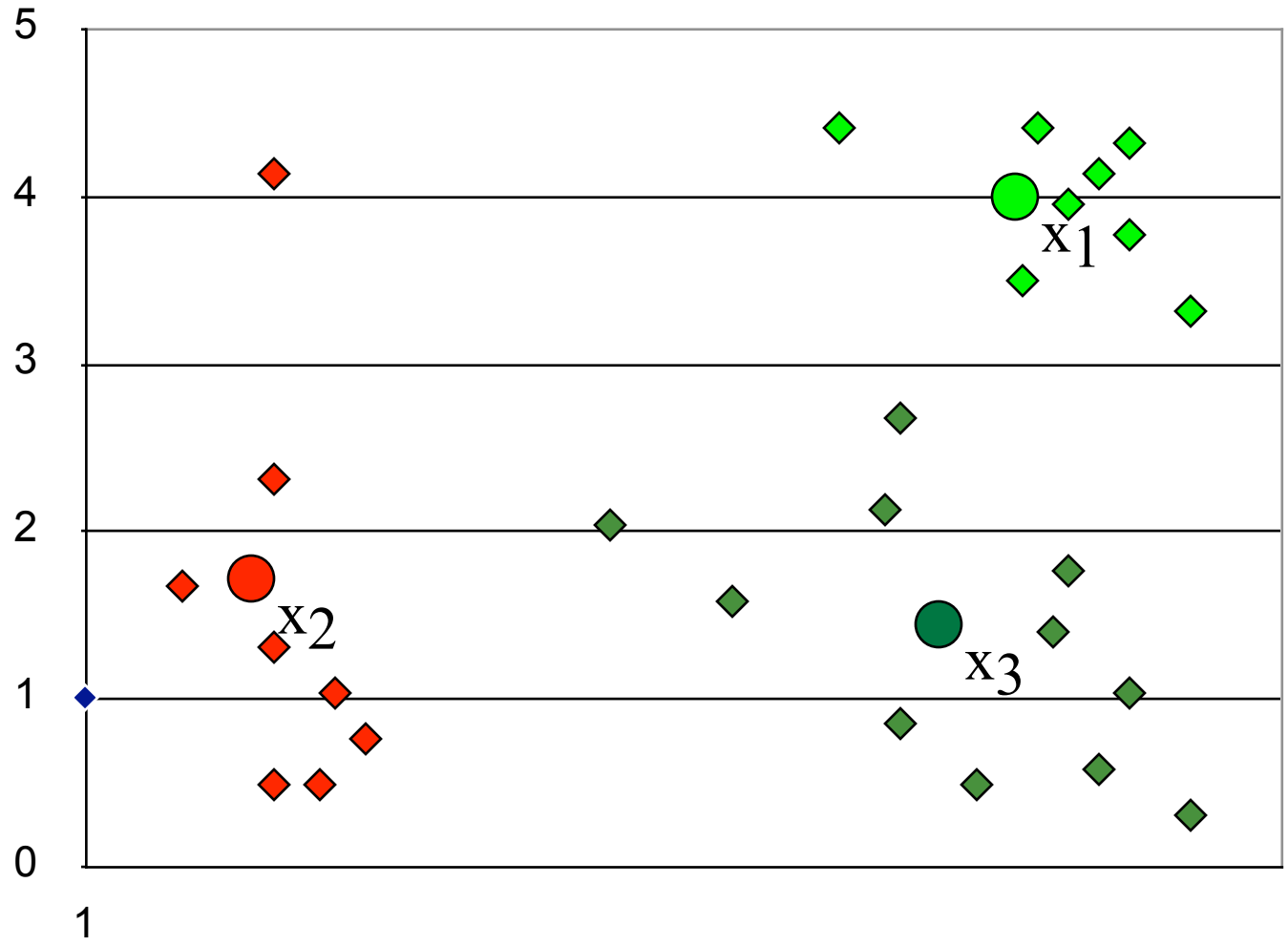

5
4
3
2
1
0
1
x1
x2
x3

Conservative K-Means Algorithm

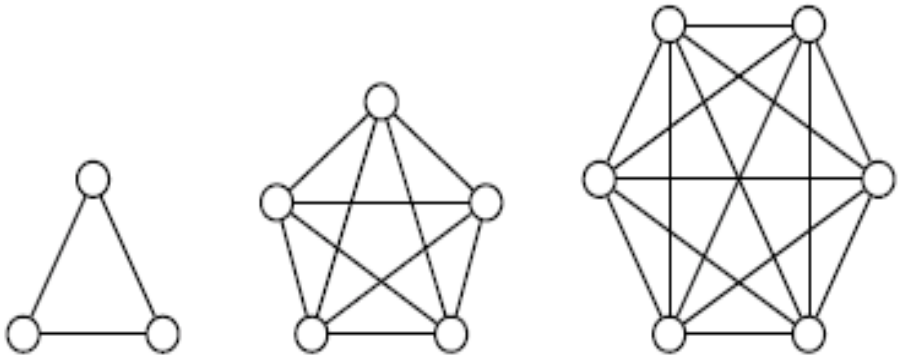
- Lloyd algorithm is fast but in each iteration it moves many data points, not necessarily causing better convergence.
- A more conservative method would be to move one point at a time only if it improves the overall **clustering cost**
  - The smaller the clustering cost of a partition of data points is the better that clustering is
  - Different methods (e.g., the squared error distortion) can be used to measure this clustering cost

K-Means "Greedy" Algorithm

```
ProgressiveGreedyK-Means(k)
Select an arbitrary partition P into k clusters
while forever
   bestChange ß 0
   for every cluster C
      for every element i not in C
         if moving i to cluster C  reduces its clustering cost
            if (cost(P) – cost(P_{i à C}) > bestChange
               bestChange ß cost(P) – cost(P_{i à C})
               i* ß I
               C* ß C
   if bestChange > 0
      Change partition P  by moving i* to C*
   else
      return P
```

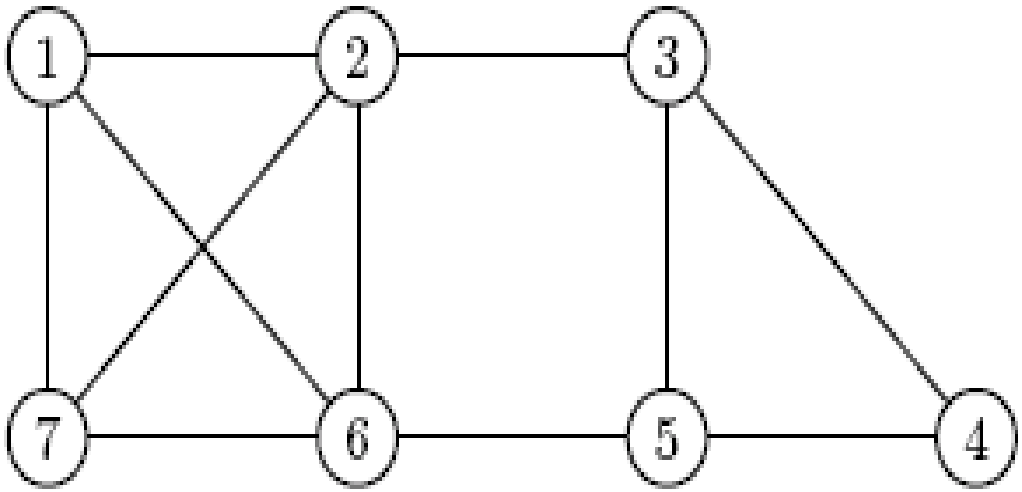
Clique Graphs

- A **clique** is a graph with every vertex connected to every other vertex
- A **clique graph** is a graph where each connected component is a clique



Transforming an Arbitrary Graph into a Clique Graphs

- A graph can be transformed into a clique graph by adding or removing edges



Corrupted Cliques Problem

Input: A graph *G*

Output: The smallest number of additions and removals of edges that will transform *G* into a clique graph

Distance Graphs

- Turn the distance matrix into a distance graph
  - Genes are represented as vertices in the graph
  - Choose a distance threshold θ
  - If the distance between two vertices is below θ, draw an edge between them
  - The resulting graph may contain cliques
  - These cliques represent clusters of closely located data points!

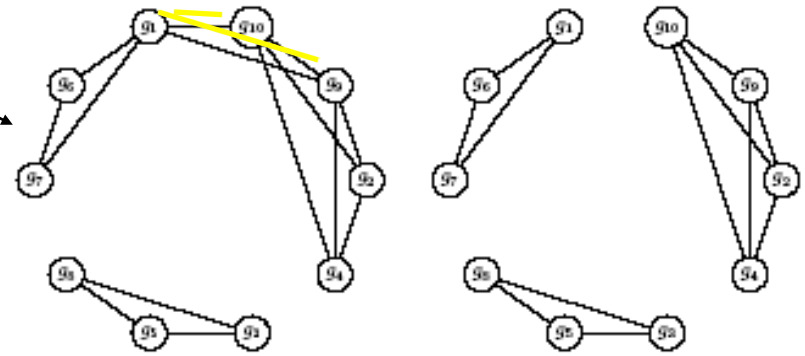
Transforming Distance Graph into Clique Graph

The distance graph (threshold θ=7) is transformed into a clique graph after removing the two highlighted edges

	g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_8	g_9	g_{10}
g_1	0.0	8.1	9.2	7.7	9.3	2.3	5.1	10.2	6.1	7.0
g_2	8.1	0.0	12.0	0.9	12.0	9.5	10.1	12.8	2.0	1.0
g_3	9.2	12.0	0.0	11.2	0.7	11.1	8.1	1.1	10.5	11.5
g_4	7.7	0.9	11.2	0.0	11.2	9.2	9.5	12.0	1.6	1.1
g_5	9.3	12.0	0.7	11.2	0.0	11.2	8.5	1.0	10.6	11.6
g_6	2.3	9.5	11.1	9.2	11.2	0.0	5.6	12.1	7.7	8.5
g_7	5.1	10.1	8.1	9.5	8.5	5.6	0.0	9.1	8.3	9.3
g_8	10.2	12.8	1.1	12.0	1.0	12.1	9.1	0.0	11.4	12.4
g_9	6.1	2.0	10.5	1.6	10.6	7.7	8.3	11.4	0.0	1.1
g_{10}	7.0	1.0	11.5	1.1	11.6	8.5	9.3	12.4	1.1	0.0

(a) Distance matrix, d (distances shorter than 7 are shown in bold).

After transforming the distance graph into the clique graph, the dataset is partitioned into three clusters



(b) Distance graph for $\theta = 7$. (c) Clique graph.

Figure 10.6 The distance graph (b) for $\theta = 7$ is not quite a clique graph. However, it can be transformed into a clique graph (c) by removing edges (g_1, g_{10}) and (g_1, g_9).

Heuristics for Corrupted Clique Problem

- Corrupted Cliques problem is NP-Hard, some heuristics exist to approximately solve it:
- **CAST** (Cluster Affinity Search Technique): a practical and fast algorithm:
  - **CAST** is based on the notion of genes *close* to cluster *C* or *distant* from cluster *C*
  - Distance between gene *i* and cluster *C*:

$d(i,C)$ = average distance between gene *i* and all genes in *C*

Gene *i* is *close* to cluster *C* if $d(i,C) < \theta$ and *distant* otherwise

CAST Algorithm

```
CAST(S, G, θ)
  P ß Ø
  while S ≠ Ø
    V ß vertex of maximal degree in the distance graph G
    C ß {v}
    while a close gene i  not in C or distant gene i in C exists
      Find the nearest close gene i not in C and add it to C
      Remove the farthest distant gene i in C
    Add cluster C to partition P
    S ß S \ C
    Remove vertices of cluster C from the distance graph G
  return P
```

S – set of elements, G – distance graph, θ - distance threshold

References

- http://ihome.cuhk.edu.hk/~b400559/array.html#Glossaries
- http://www.umanitoba.ca/faculties/afs/plant_science/COURSES/bioinformatics/lec12/lec12.1.html
- http://www.genetics.wustl.edu/bio5488/lecture_notes_2004/microarray_2.ppt - For Clustering Example