# Basic Clustering Algorithms for Gene Expression Analysis

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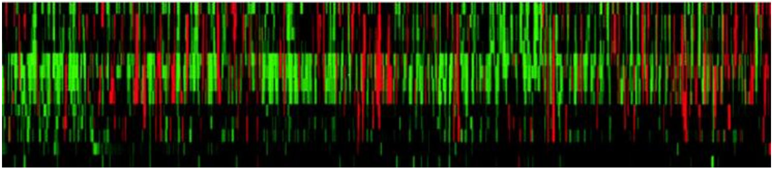
# Gene Expression Analysis



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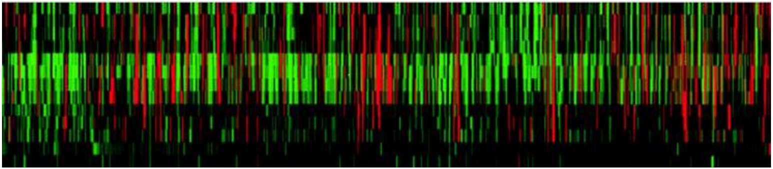

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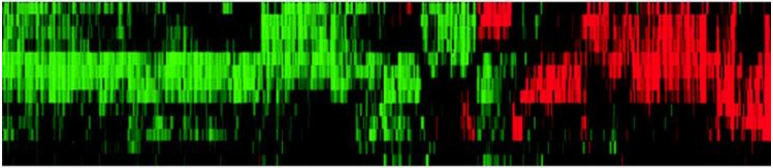

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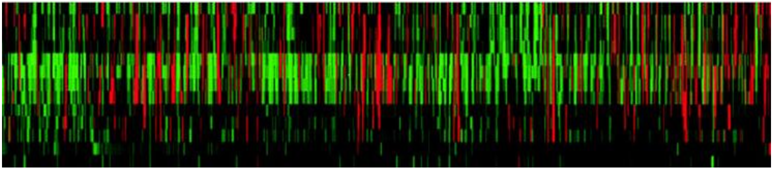

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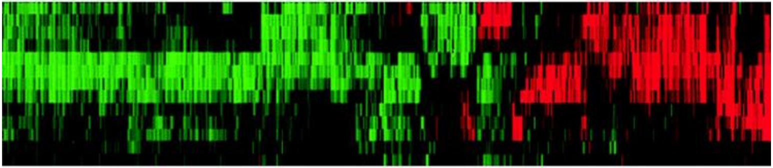
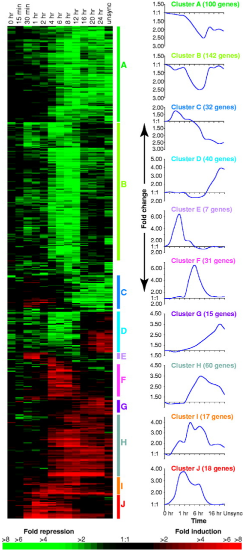


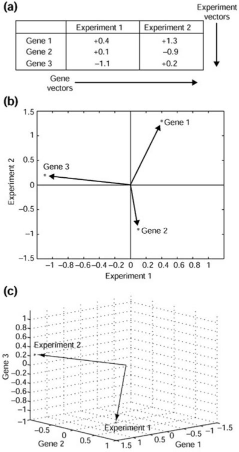
*Describe data in terms of clusters of samples and genes that have strong internal similarities.*

# Example: Iyer et al. (Science 1999)

- Measure temporal expression profiles of 8600 human genes in fibroblasts in response to serum addition.
- Over 200 previously unknown genes with specific temporal expression profiles.
- Based on known genes in cluster, authors assign putative functions to these genes.



# Viewing DNA Microarray Data as Multi-Dimensional Points

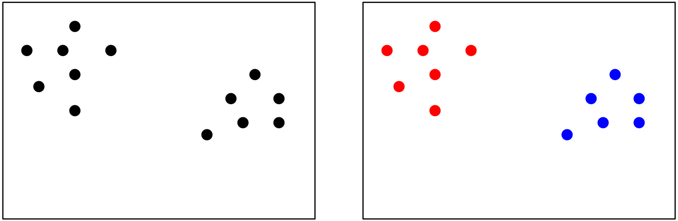


(a)

| | Experiment 1 | Experiment 2 |
|---|---|---|
| Gene 1 | +0.4 | +1.3 |
| Gene 2 | +0.1 | −0.9 |
| Gene 3 | −1.1 | +0.2 |

- $m$ genes and $n$ samples.
- Figure (b)
  - Gene ≡ point: $m$ points
  - Condition ≡ dimension: $n$-dimensional space
  - Expression level ≡ coordinate.
- Figure (c)
  - Sample ≡ point: $n$ points.
  - Condition ≡ dimension: $m$-dimensional space.
  - Expression level ≡ coordinate.
- For a point $p$, $p_i$ is its $i$th coordinate.

# Definition of Clustering



*Given a set of m genes whose expression levels are measured across n conditions, find the best partition of the genes into subsets such that each subset contains genes whose expression profiles are similar to each other.*

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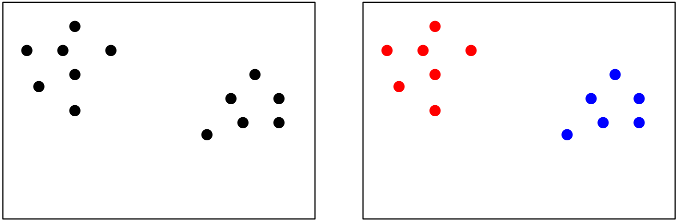

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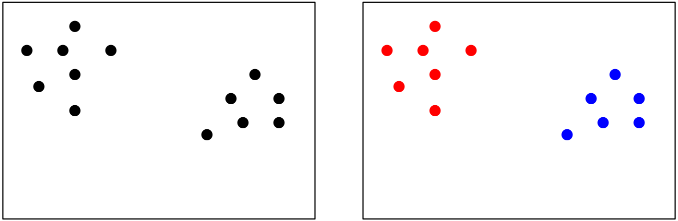

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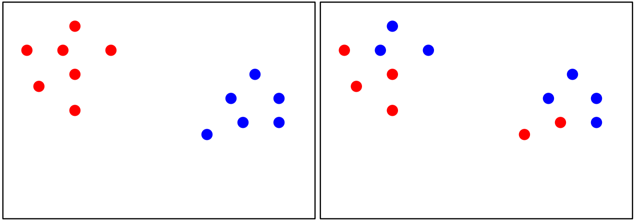

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- How many subsets?
- How do we measure how similar the expression profiles of two genes are?
- How do we compare two different partitions?

# Measuring Similarity of Points

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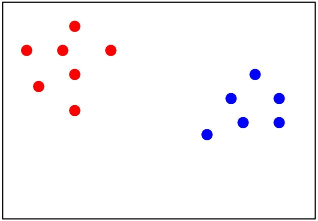
- Other distances: normalised dot product, K-L divergence, relative entropy.
- Metrics obey triangle inequality: $d(p, q) + d(q, r) \geq d(p, r)$.
  - Euclidean, Manhattan distances are metrics.
  - Correlation, dot product are not metrics.

# Quality of a Partition

- Partition points into $k$ clusters $\mathcal{C} = \{C_1, C_2, \ldots, C_k\}$.
- Define quality $q_i$ of a cluster $C_i$ and define quality $q(\mathcal{C})$ in terms of $q_i$s.



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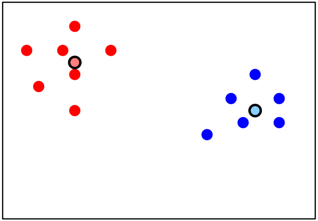

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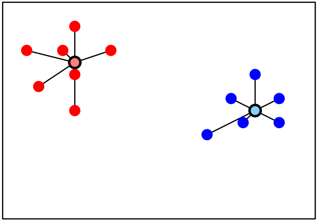


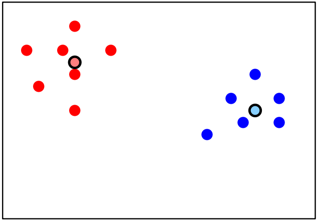
- Sum of squared errors.
  - $\mu_i =$ average of points in $C_i$.
  - $q_i = \frac{1}{n_i} \sum_{p \in C_i} d(p, \mu_i)^2 =$ average of squared distance from every point in $C_i$ to $q_i$.
  - $q(\mathcal{C}) = \sum_i q_i$.

# Algorithms

- *k*-means algorithm.
- Hierarchical clustering.

# Algorithms

- *k*-means: find *k* cluster "centres" and form clusters by assigning a point to the closest cluster centre.



# $k$-means algorithm

*Partition $S$ into $k$ clusters that minimise the sum of squared errors $q(\mathcal{C}) = \sum_i \sum_{p \in C_i} \|p - \mu_i\|^2$ over all possible partitions of $S$ into $k$ clusters.*

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2. Repeat
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    - use thresholds to avoid numerical errors.
    - check if sets in the partition do not change.

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- Each iteration takes time.

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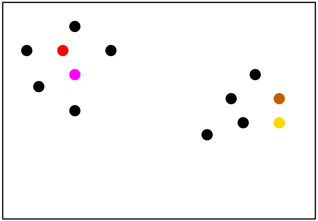
- Algorithm can get stuck in a local minimum.
- Does not work particularly well in very high ($\geq 40$) dimensions.

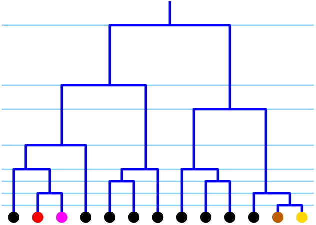
# Algorithms

- *k*-means algorithm.
- Hierarchical clustering.

# Hierarchical Clustering

- Attempt to recursively find sub-clusters within clusters.
- Natural way to “zoom into” areas of interest.
- Represent using a tree or dendrogram.





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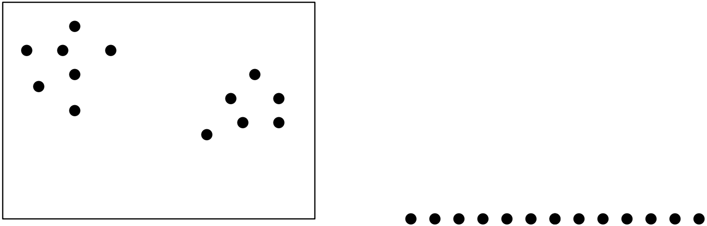

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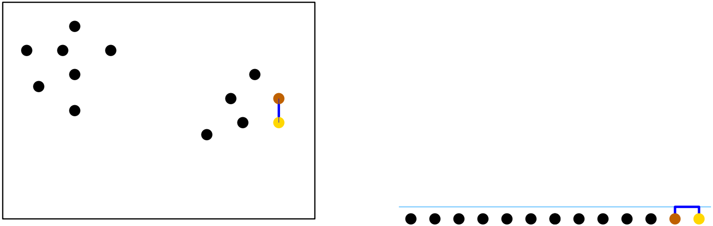

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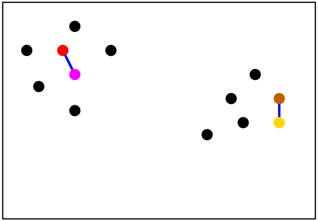

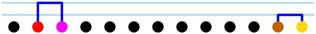

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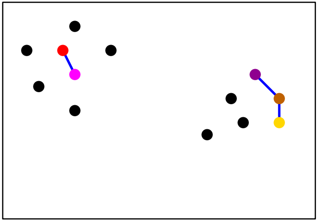

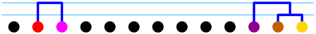

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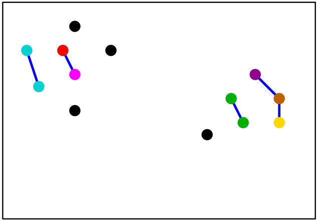

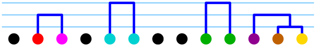

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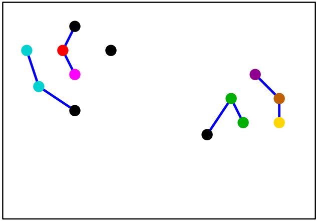

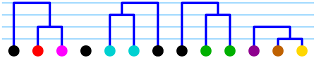

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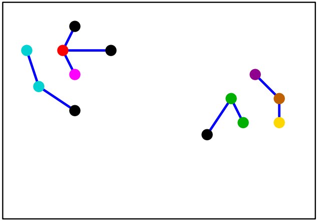

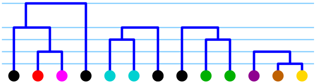

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2. Repeat
   - Let $C_i$ and $C_j$ be the clusters “nearest” each other.
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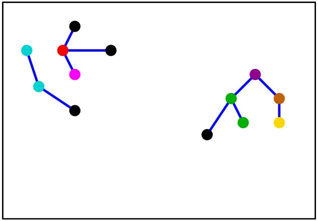

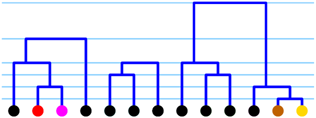

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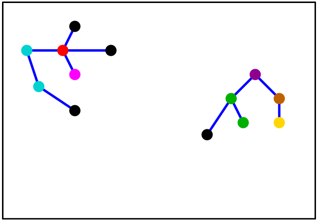

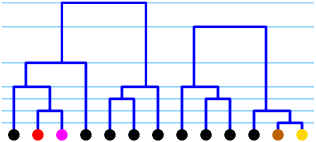

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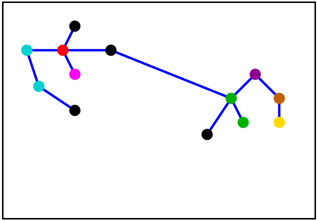
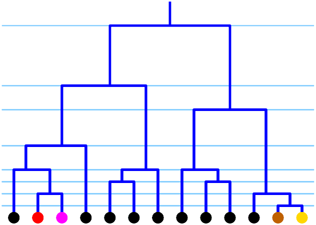
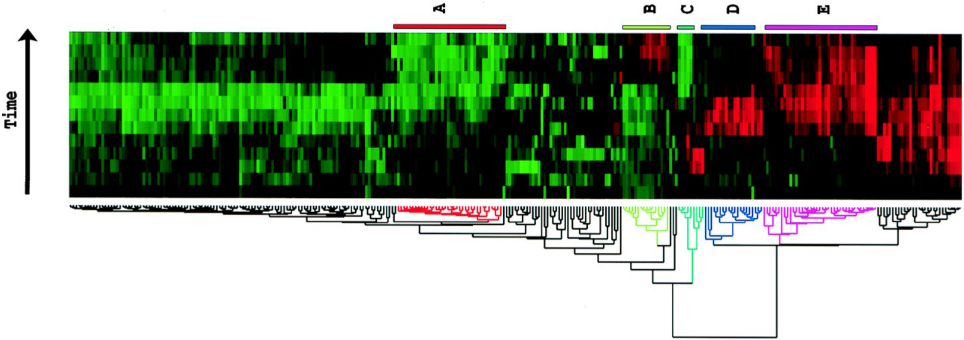
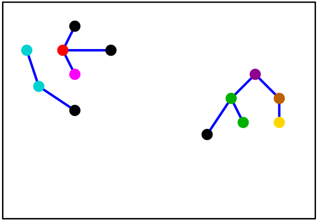


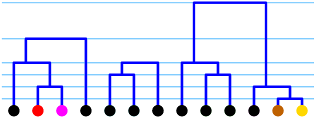


# Hierarchical Clustering Result



# Measuring Distance between Clusters





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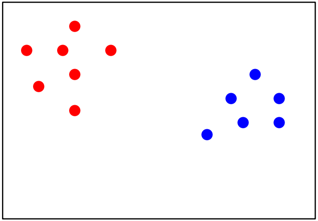

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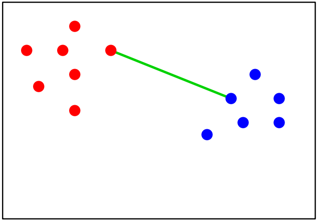

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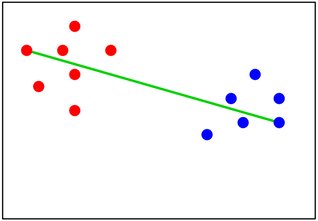

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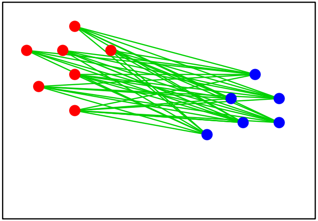

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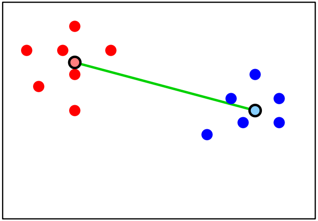

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- Computing $d_{min}, d_{max}, d_{avg}$ takes $O(n_i n_j)$ time.
- Computing $d_{mean}$ takes $O(n_i + n_j)$ time.

# Running Time of Hierarchical Clustering

1. Start with every sample (gene) in its own cluster.
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- Store all $O(m^2)$ inter-point distances.
- At each iteration, compute distance between every pair of clusters: takes $O(nm^2)$ time in total.
- There are $n$ iterations, so overall running time is $O(nmm^2) = O(nm^3)$.

# Properties of Hierarchical Clustering

- Using $d_{min}$, tree tends to look like an elongated chain.
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- Other measures try to alleviate this problem.
- In case of $d_{min}$, tree produced is the minimum spanning tree. Exercise.
- In other cases, it is difficult to state what properties the partition satisfies.

# Evaluating Cluster Quality

- How can measure the "useful" biological knowledge that a cluster contains? Exercise.