CS 6824: Basic Clustering Algorithms for Gene Expression Analysis

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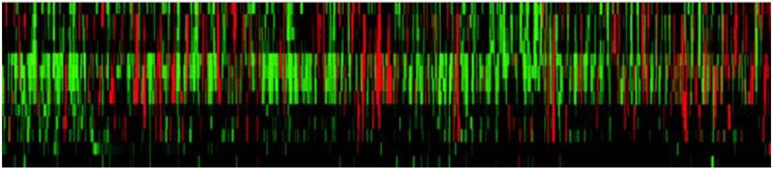
February 14, 2011

Gene Expression Analysis



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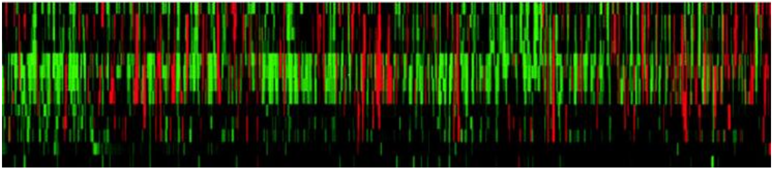

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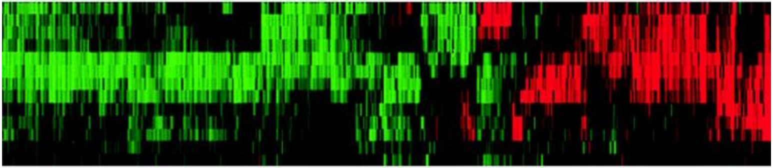

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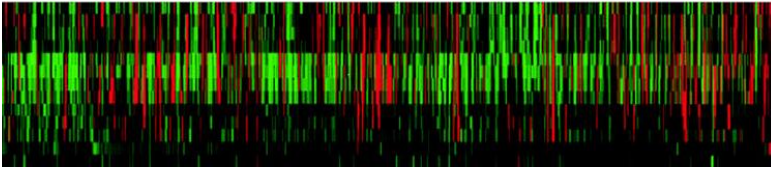

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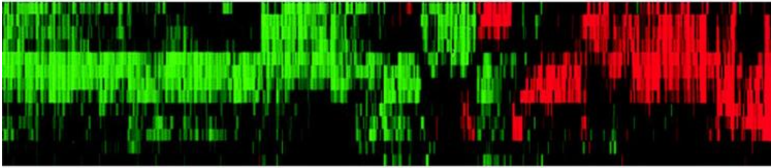
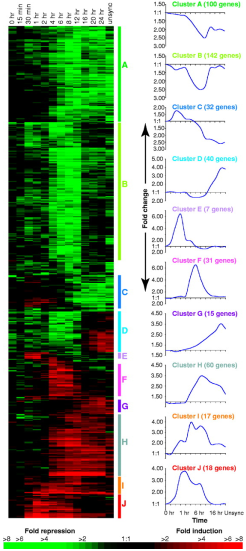


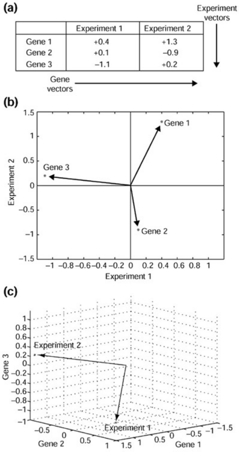
Describe data in terms of clusters of samples and genes that have strong internal similarities.

Example: Iyer and co-authors (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.

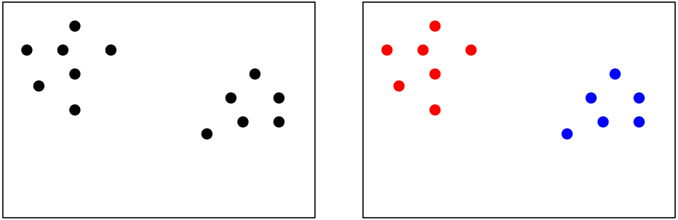


Viewing DNA Microarray Data as Multi-Dimensional Points



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

Definition of Clustering



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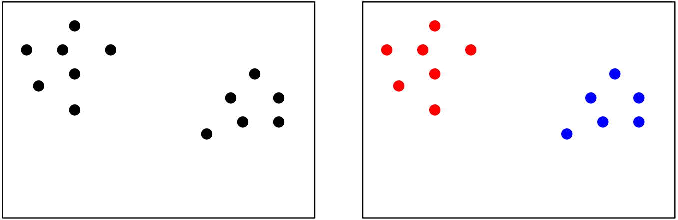

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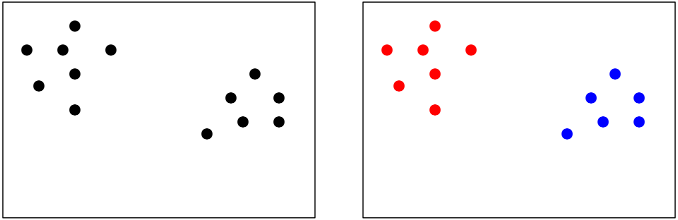

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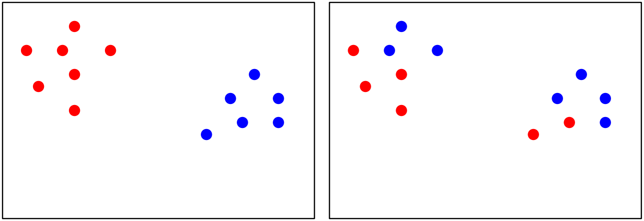

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- How many subsets?
- How do we measure how similar the expression profiles of two genes are?
- How do we compare two different partitions?

Measuring Similarity of Points

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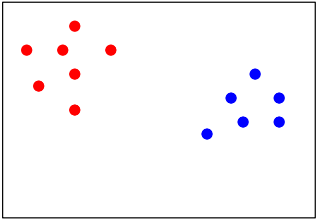
- Other distances: normalised dot product, K-L divergence, relative entropy.
- Metrics obey triangle inequality: $d(p, q) + d(q, r) \geq d(p, r)$.
  - Euclidean, Manhattan distances are metrics.
  - Correlation, dot product are not metrics.

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_is.



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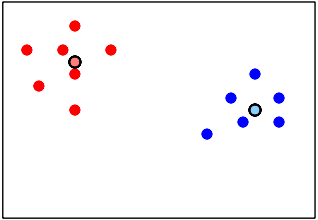

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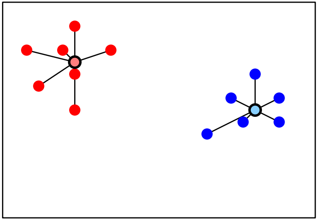


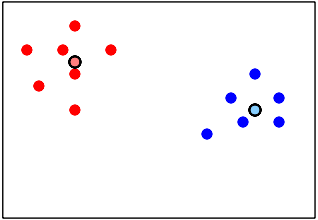
- Sum of squared errors.
  - μ_i = average of points in C_i.
  - $q_i = \frac{1}{n_i} \sum_{p \in C_i} d(p, \mu_i)^2$ = average of squared distance from every point in C_i to q_i.
  - $q(\mathcal{C}) = \sum_i q_i$.

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
   - For each point p, put p in cluster C_i if μ_i is the centre closest to p.
   - Recalculate μ_i's (average of points in C_i).
3. until μ_i's don't change.

Details of k-means algorithm

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- Checking for termination :
  - 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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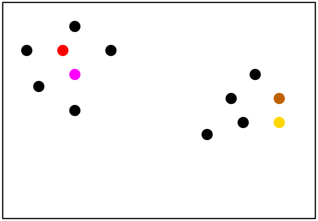
- Algorithm can get stuck in a local minimum.
- Does not work particularly well in very high (≥ 40) dimensions.

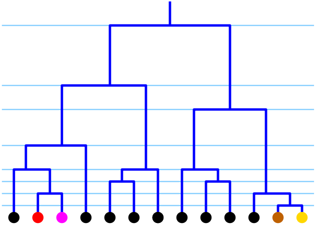
Algorithms

- 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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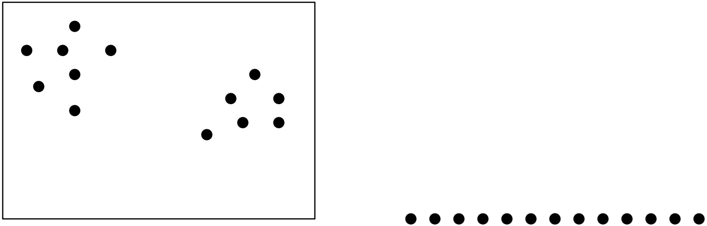

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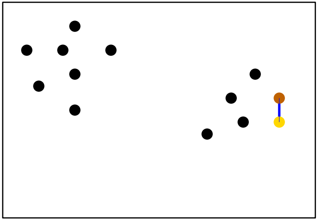

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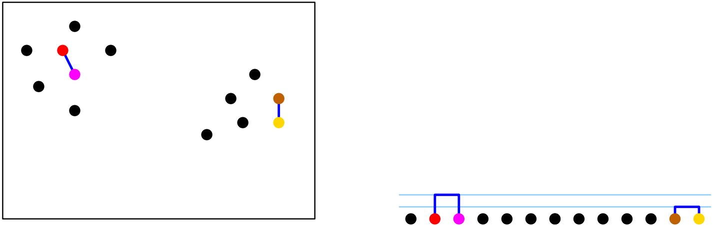

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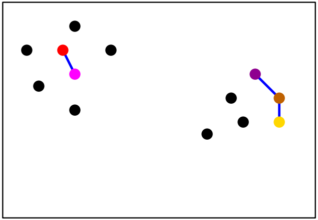

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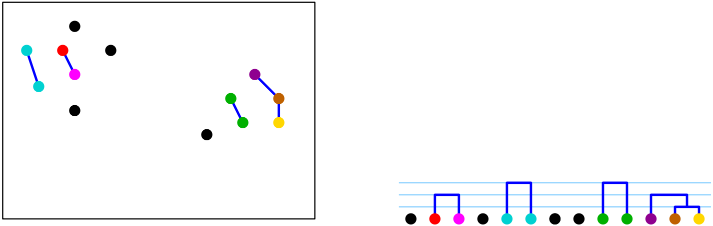

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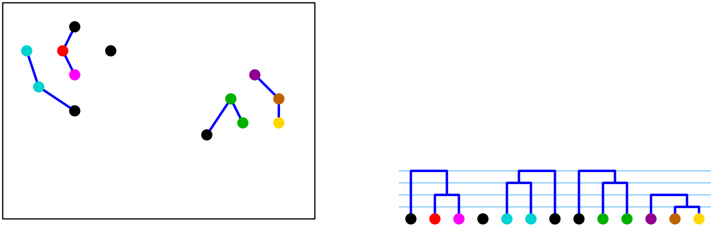

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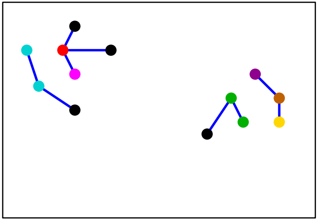

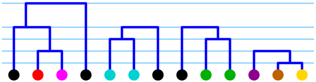

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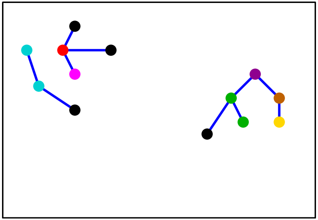

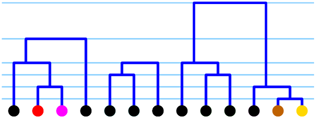

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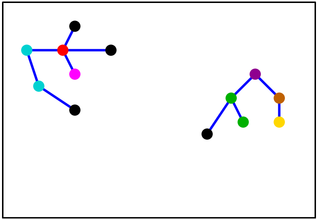

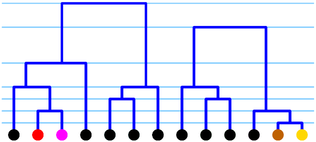

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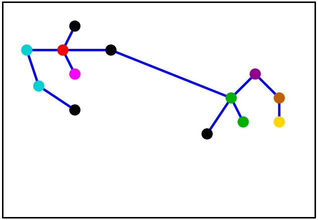
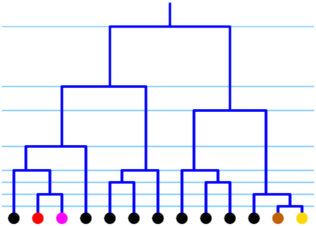
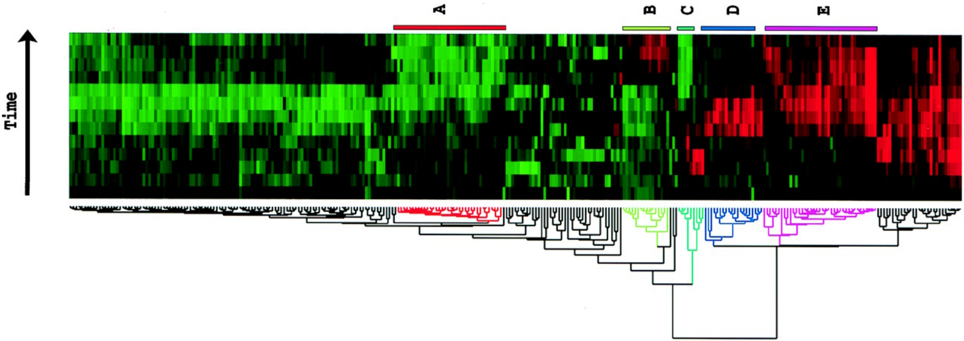
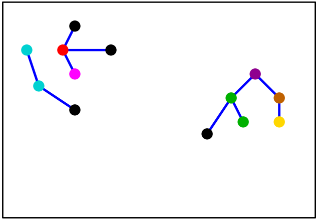


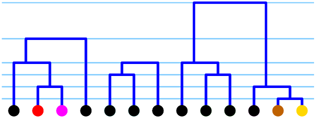


Hierarchical Clustering Result



Measuring Distance between Clusters





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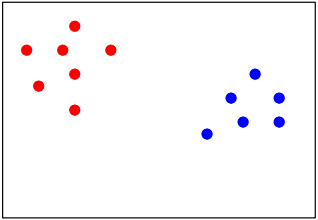

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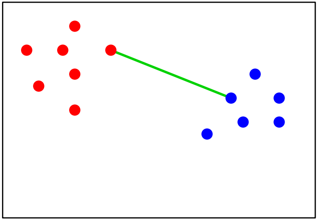

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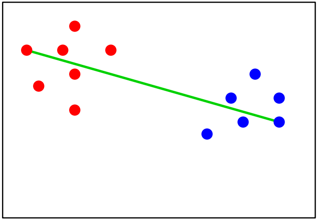

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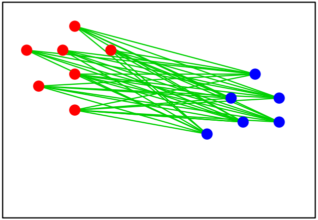

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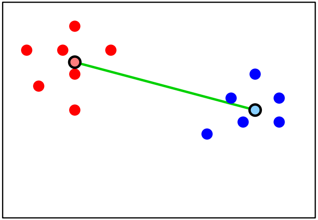

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- Computing $d_{min}, d_{max}, d_{avg}$ takes $O(n_i n_j)$ time.
- Computing d_{mean} takes $O(n_i + n_j)$ time.

Running Time of Hierarchical Clustering

1. Start with every sample (gene) in its own cluster.
2. Repeat
   - Let D_i and D_j be the clusters "nearest" each other.
   - Merge D_i and D_j.
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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.
- Using d_{max}, clusters may not be well separated.
- Other measures try to alleviate this problem.
- In case of d_{min}, tree produced is the minimum spanning tree.
- In other cases, it is difficult to state what properties the partition satisfies.

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- Use χ^2 test or Fisher's exact test.

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- Let u be the number of genes in the gene expression data set.

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$$\sum_{i=c_f}^{\min(c,u_f)} \frac{\binom{u_f}{i}\binom{u-u_f}{c-i}}{\binom{u}{c}}$$

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