CS 5984: Basic Clustering Algorithms for Gene Expression Analysis

T. M. Murali

January 25 and 30, 2007
# Project Choices

<table>
<thead>
<tr>
<th>Project</th>
<th>1st choice</th>
<th>2nd choice</th>
<th>3rd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypes of <em>C. elegans</em> genes</td>
<td>D. Badger</td>
<td>Chris</td>
<td>Mike</td>
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<td>microRNA biological processes</td>
<td>Chris, D. Badger</td>
<td>William</td>
<td>Mike</td>
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<tr>
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<td>D. Beck</td>
<td>Song</td>
<td>Ying</td>
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<td>Bicluster-based classifiers</td>
<td>Henry</td>
<td>Ying</td>
<td>D. Badger</td>
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<td>Song</td>
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<td>D. Beck</td>
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<td>Biclustering epidemic transmission</td>
<td>Bryan, Mike</td>
<td></td>
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<tr>
<td>Matrix factorisation for active networks</td>
<td>D. Beck</td>
<td>Arjun</td>
<td>Zhuo</td>
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<tr>
<td></td>
<td>Mike</td>
<td></td>
<td>Henry</td>
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<tr>
<td>CDM of c-Myc targets</td>
<td>Arjun</td>
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<td>Henry</td>
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<td></td>
<td>Mahima, Srinivas</td>
<td></td>
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<tr>
<td>Predict PPIs</td>
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<td>William</td>
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<td><em>A. thaliana</em> interactions</td>
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<td>Chris</td>
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- Project meeting times:
  - Mondays: 10am–12pm, 3pm–6pm.
  - Fridays: 11am–12pm.
Gene Expression Analysis

- How do we automatically extract meaning from so much microarray data?
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Gene Expression Analysis

How do we automatically extract meaning from so much microarray data?

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

- $d$ genes and $n$ samples.

- **Figure (b)**
  - Gene $\equiv$ point: $d$ points
  - Condition $\equiv$ dimension: $n$-dimensional space
  - Expression level $\equiv$ coordinate.

- **Figure (c)**
  - Sample $\equiv$ point: $n$ points.
  - Condition $\equiv$ dimension: $d$-dimensional space.
  - Expression level $\equiv$ coordinate.

- For a point $p$, $p_i$ is its $i$th coordinate.
Definition of Clustering

Given a set of \( n \) genes whose expression levels are measured across \( d \) 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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- How many subsets?
- How do we measure how similar the expression profiles of two genes are?
Definition of Clustering

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

- 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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- Distance between two points $p$ and $q$ is $d(p, q)$.
- Euclidean metric: $d(p, q) = \sqrt{\sum_i (p_i - q_i)^2}$. 
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- Pearson correlation coefficient:
  \[
  \frac{1}{d} \sum_i \left( \frac{p_i}{\mu(p)} \right) \left( \frac{q_i}{\mu(q)} \right)
  \]

- 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.
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  \frac{1}{d} \sum_i \left( \frac{p_i - \mu(p)}{\sigma(p)} \right) \left( \frac{q_i}{\sigma(q)} \right)
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  - $\mu(p)$: average of $p$’s coordinates,
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- Metrics obey triangle inequality: $d(p, q) + d(q, r) \geq d(p, r)$.
  - Euclidean, Manhattan distances are metrics.
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Quality of a Partition

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

- Sum of squared errors.
  - $\mu_i = $ average of points in $C_i$. 

$\mu_i = \frac{1}{n_i} \sum_{p \in C_i} d(p, \mu_i)^2$.
Quality of a Partition

- Partition points into $k$ clusters $C = \{C_1, C_2, \ldots, C_k\}$.

- Define quality $q_i$ of a cluster $C_i$ and define quality $q(C)$ in terms of $q_i$s.

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

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Algorithms

- $k$-means algorithm.
- Hierarchical clustering.
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
$q(C) = \sum_i \sum_{p \in C_i} \| p - \mu_i \|^2$ over all possible partitions of $S$ into $k$ clusters.
**k-means algorithm**

Partition $S$ into $k$ clusters that minimise the sum of squared errors

$$q(C) = \sum_i \sum_{p \in C_i} \|p - \mu_i\|^2$$

over all possible partitions of $S$ into $k$ clusters.

1. Initialise centres $\mu_1, \mu_2, \ldots \mu_k$.
2. Repeat
   - For each point $p$, put $p$ in cluster $C_i$ if $\mu_i$ is the centre closest to $p$.
   - Recalculate $\mu_i$’s (average of points in $C_i$).
3. until $\mu_i$’s don’t change.
Details of $k$-means algorithm

1. Initialise centres $\mu_1, \mu_2, \ldots \mu_k$.

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- Initialisation:
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- Initialisation: random $\mu_i$’s or “well-separated” $\mu_i$’s.
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3. until $\mu_i$’s don’t change.

▶ Initialisation: random $\mu_i$’s or “well-separated” $\mu_i$’s.
▶ Checking for termination:
   ▶ use thresholds to avoid numerical errors.
   ▶ check if sets in the partition do not change.
Properties of $k$-means

1. Initialise centres $\mu_1, \mu_2, \ldots \mu_k$.
2. Repeat
   - For each point $p$, put $p$ in cluster $C_i$ if $\mu_i$ is the centre closest to $p$.
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- Each iteration takes time.
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- Each iteration takes $O(dkn)$ time.
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- Each iteration takes $O(dkn)$ time.
- $q(C)$ does not increase.
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   - Algorithm can get stuck in a local minimum.
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- Each iteration takes $O(dkn)$ time.
- $q(C)$ does not increase.
- Algorithm can get stuck in a local minimum.
- Does not work particularly well in very high ($\geq 40$) dimensions.
Introduction

- $k$-means
- Hierarchical clustering

Algorithms

- $k$-means and $k$-median.
- 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.
Hierarchical Clustering Algorithm

- Bottom-up clustering algorithm.
Hierarchical Clustering Algorithm

- Bottom-up clustering algorithm.

1. Start with every sample (gene) in its own cluster.
Hierarchical Clustering Algorithm

- Bottom-up clustering algorithm.

1. Start with every sample (gene) in its own cluster.
2. Repeat
   - Let $C_i$ and $C_j$ be the clusters “nearest” each other.
   - Merge $C_i$ and $C_j$. 
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![Diagram of hierarchical clustering]
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   - Let $C_i$ and $C_j$ be the clusters “nearest” each other.
   - Merge $C_i$ and $C_j$.
3. until all the samples (genes) are in one cluster.
Measuring Distance between Clusters

- \( d_{min}(D_i, D_j) \) = distance between closest pair of points.
- \( d_{max}(D_i, D_j) \) = distance between farthest pair of points.
- \( d_{avg}(D_i, D_j) \) = average of distances between all pairs of points.
- \( d_{mean}(D_i, D_j) = d(\mu_i, \mu_j) \).

Computing \( d_{min}, d_{max}, d_{avg} \) takes \( O(n_i n_j) \) time.

Computing \( d_{mean} \) takes \( O(n_i + n_j) \) time.
Measuring Distance between Clusters

- $d_{\text{min}}(D_i, D_j) =$ distance between closest pair of points.
- $d_{\text{max}}(D_i, D_j) =$ distance between farthest pair of points.
- $d_{\text{avg}}(D_i, D_j) =$ average of distances between all pairs of points.
- $d_{\text{mean}}(D_i, D_j) = \overline{d}(\mu_i, \mu_j)$.

Computing $d_{\text{min}}$, $d_{\text{max}}$, $d_{\text{avg}}$ takes $O(n_i n_j)$ time.
Computing $d_{\text{mean}}$ takes $O(n_i + n_j)$ time.
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- Computing \(d_{\text{min}}, d_{\text{max}}, d_{\text{avg}}\) takes \(O(n_i n_j)\) time.
- Computing \(d_{\text{mean}}\) 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 $D_j$.
3. until all the samples (genes) are in one cluster.
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   - Store all $O(n^2)$ inter-point distances.
   - At each iteration, compute distance between every pair of clusters: takes $O(dn^2)$ time in total.
   - There are $n$ iterations, so overall running time is $O(dnn^2) = O(dn^3)$. 
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.