CAP 5510: Introduction to Bioinformatics

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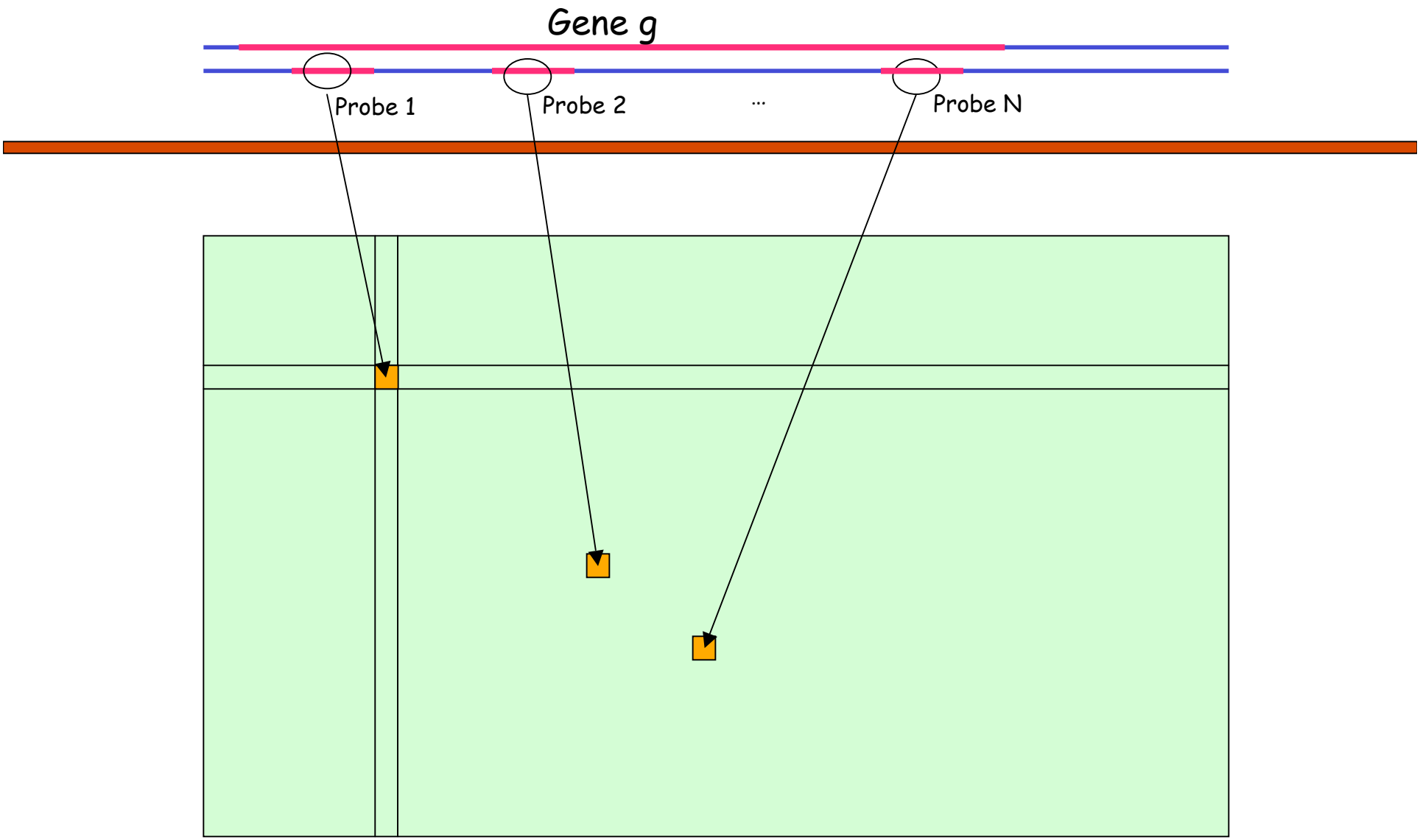
www.cis.fiu.edu/~giri/teach/BioinfS07.html


Gene g
Probe 1
Probe 2
...
Probe N

Microarray Data

Gene	Expression Level
Gene1	
Gene2	
Gene3	
…	

Study effect of treatment over time

Sample

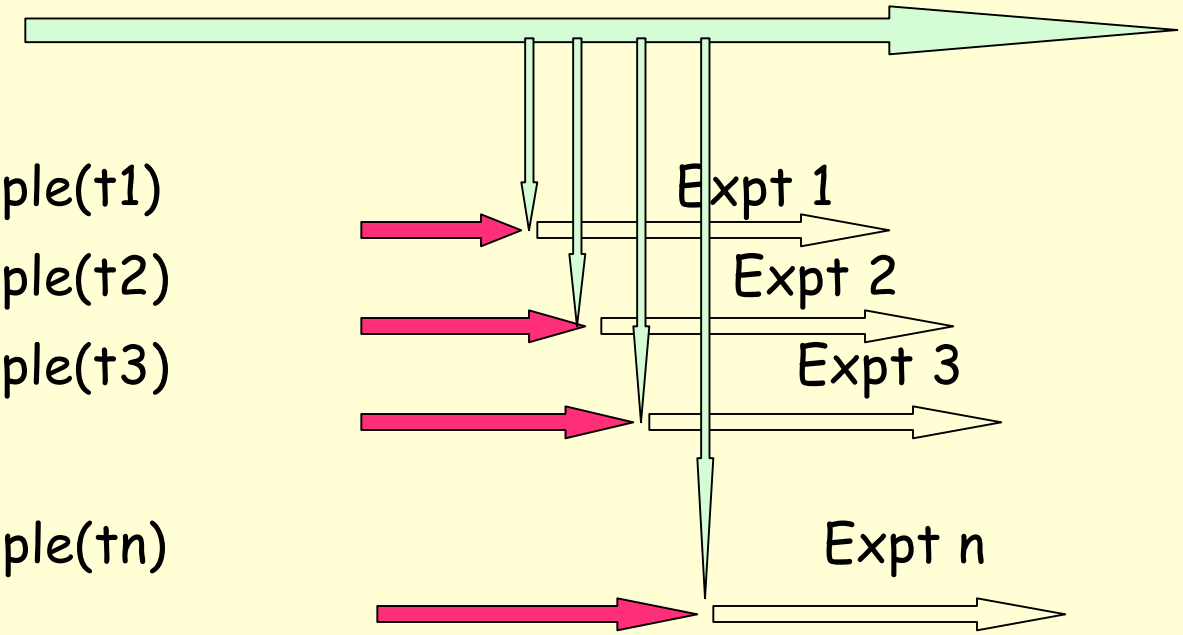
Treated Sample(t1)

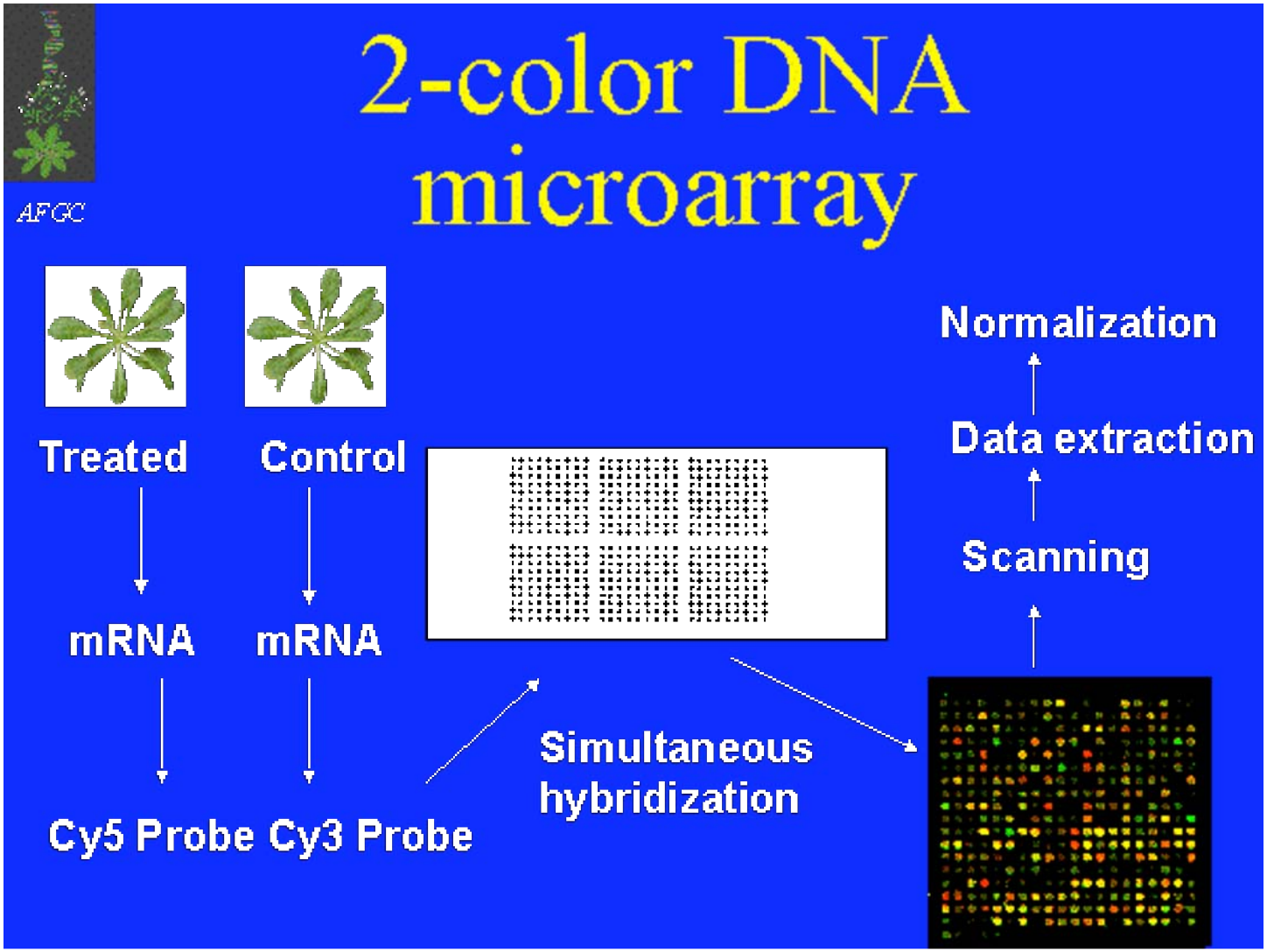
Treated Sample(t2)

Treated Sample(t3)

…

Treated Sample(tn)





http://www.arabidopsis.org/info/2010_projects/comp_proj/AFGC/RevisedAFGC/Friday/

How to compare 2 cell samples with Two-Color Microarrays?

- mRNA from sample 1 is extracted and labeled with a red fluorescent dye.
- mRNA from sample 2 is extracted and labeled with a green fluorescent dye.
- Mix the samples and apply it to every spot on the microarray. Hybridize sample mixture to probes.
- Use optical detector to measure the amount of green and red fluorescence at each spot.

Sources of Variations & Experimental Errors

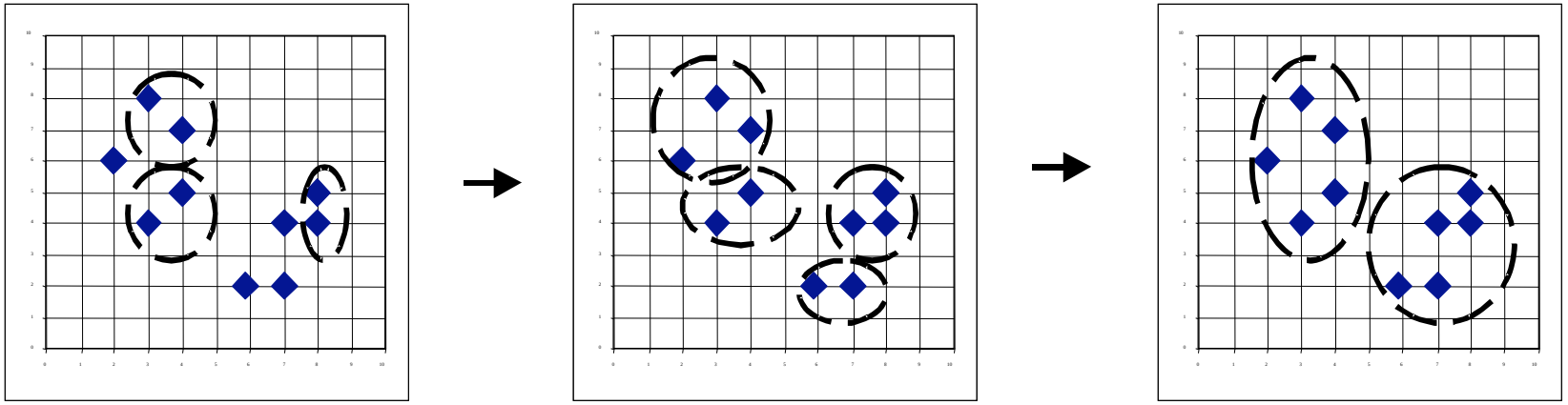
- Variations in cells/individuals
- Variations in mRNA extraction, isolation, introduction of dye, variation in dye incorporation, dye interference
- Variations in probe concentration, probe amounts, substrate surface characteristics
- Variations in hybridization conditions and kinetics
- Variations in optical measurements, spot misalignments, discretization effects, noise due to scanner lens and laser irregularities
- Cross-hybridization of sequences with high sequence identity
- Limit of factor 2 in precision of results
- Variation changes with intensity: larger variation at low or high expression levels

Need to Normalize data

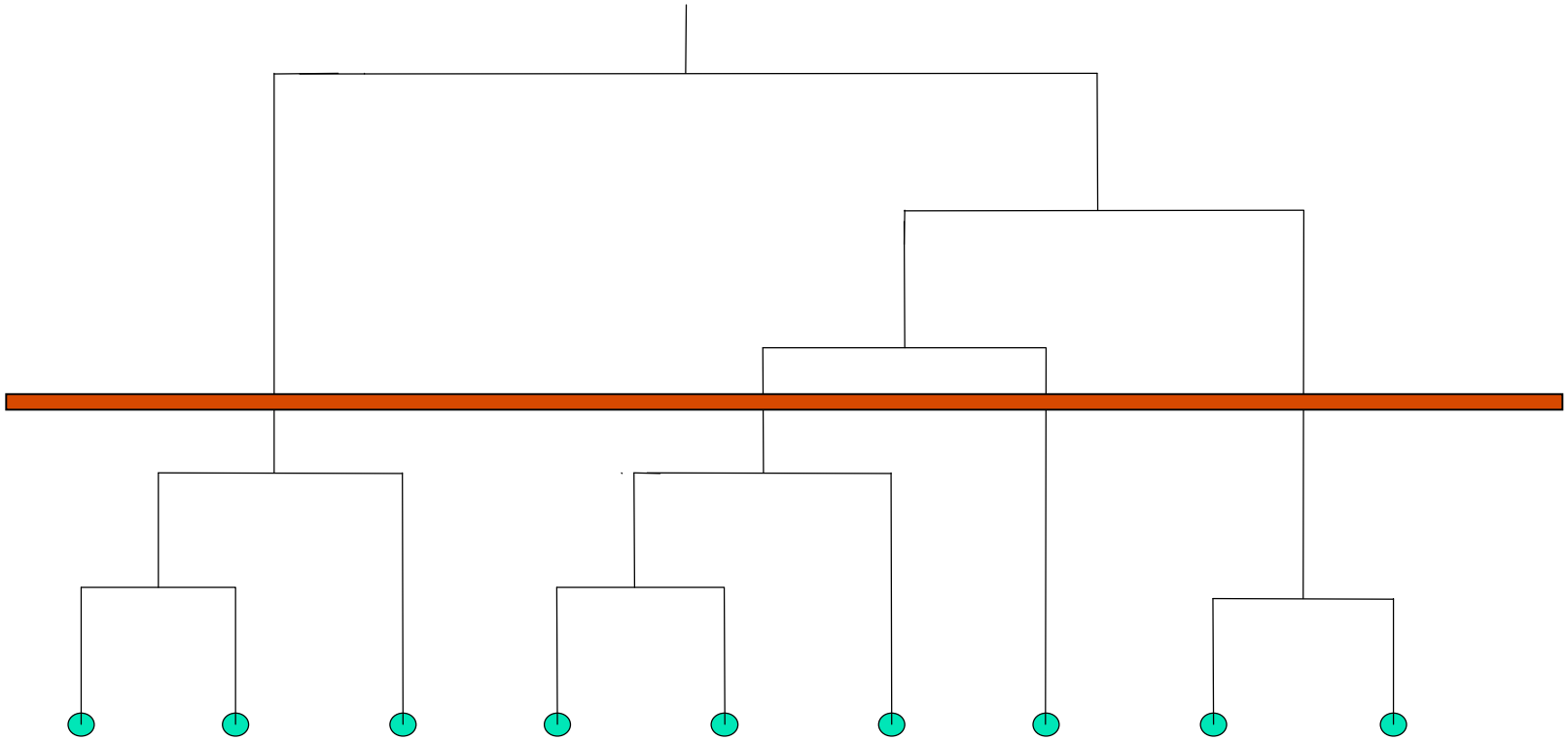
Clustering

- Clustering is a general method to study patterns in gene expressions.
- Several known methods:
  - Hierarchical Clustering (Bottom-Up Approach)
  - K-means Clustering (Top-Down Approach)
  - Self-Organizing Maps (SOM)

Hierarchical Clustering: Example



A Dendrogram



Hierarchical Clustering [Johnson, SC, 1967]

- Given n points in R^d, compute the distance between every pair of points
- While (not done)
  - Pick closest pair of points s_i and s_j and make them part of the same cluster.
  - Replace the pair by an average of the two s_{ij}

Try the applet at:

http://home.dei.polimi.it/matteucc/Clustering/tutorial_html/AppletH.html

Distance Metrics

- For clustering, define a distance function:
  - Euclidean distance metrics

$$D_k(X,Y) = \left[\sum_{i=1}^{d} (X_i - Y_i)^k \right]^{1/k}$$

k=2: Euclidean Distance

  - Pearson correlation coefficient

$$\rho_{xy} = \frac{1}{d} \sum_{i=1}^{d} \left(\frac{X_i - \overline{X}}{\sigma_x} \right) \left(\frac{Y_i - \overline{Y}}{\sigma_y} \right)$$

$-1 \leq \rho_{xy} \geq 1$

EXHIBIT 3.4 *Joint Probability Model for the Ratings of Two People*

(a) $\rho_{XY} = 0$

	y			
x	1	2	3	Total
3	1/9	1/9	1/9	1/3
2	1/9	1/9	1/9	1/3
1	1/9	1/9	1/9	1/3
Total	1/3	1/3	1/3	1

(b) $\rho_{XY} = \frac{1}{2}$

	y			
x	1	2	3	Total
3	1/18	1/18	4/18	1/3
2	1/18	4/18	1/18	1/3
1	4/18	1/18	1/18	1/3
Total	1/3	1/3	1/3	1

(c) $\rho_{XY} = -\frac{1}{2}$

	y			
x	1	2	3	Total
3	4/18	1/18	1/18	1/3
2	1/18	4/18	1/18	1/3
1	1/18	1/18	4/18	1/3
Total	1/3	1/3	1/3	1

(d) $\rho_{XY} = \frac{4}{9}$

	y			
x	1	2	3	Total
3	1/27	2/27	6/27	1/3
2	2/27	5/27	2/27	1/3
1	6/27	2/27	1/27	1/3
Total	1/3	1/3	1/3	1

(e) $\rho_{XY} = -\frac{5}{9}$

	y			
x	1	2	3	Total
3	6/27	2/27	1/27	1/3
2	2/27	5/27	2/27	1/3
1	1/27	2/27	6/27	1/3
Total	1/3	1/3	1/3	1

(f) $\rho_{XY} = \frac{2}{3}$

	y			
x	1	2	3	Total
3	1/36	2/36	9/36	1/3
2	2/36	8/36	2/36	1/3
1	9/36	2/36	1/36	1/3
Total	1/3	1/3	1/3	1

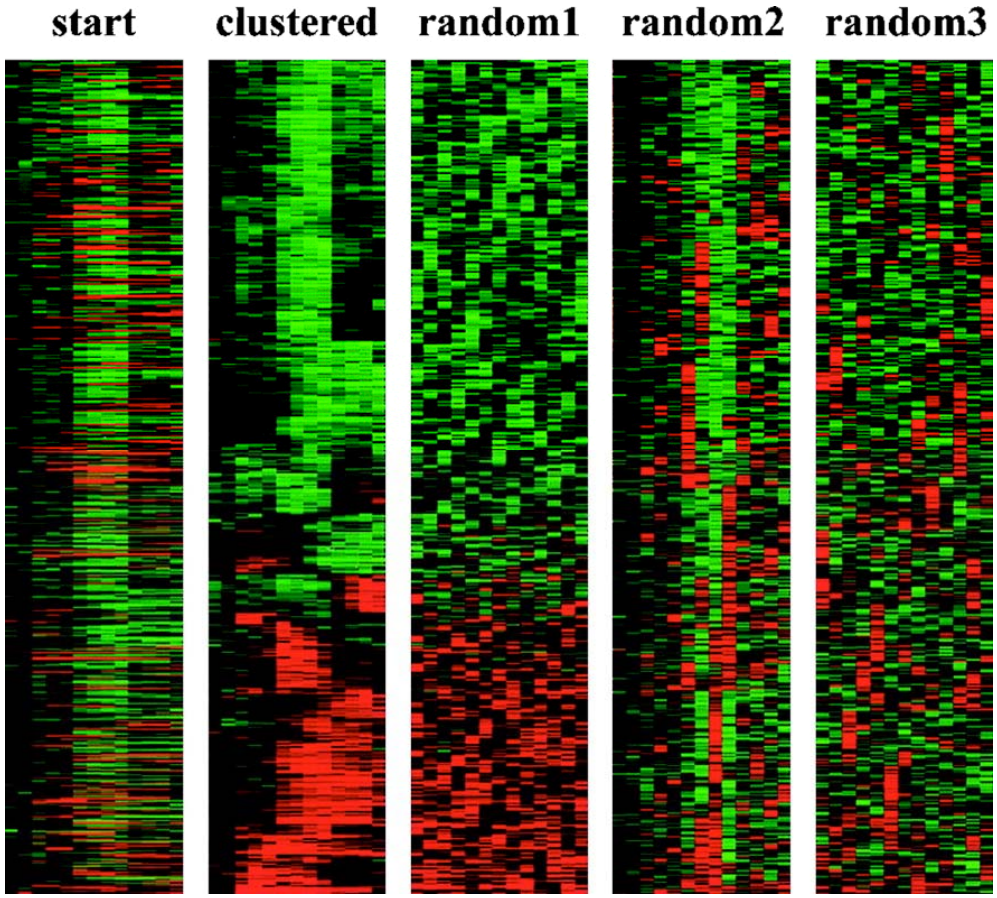
(g) $\rho_{XY} = -\frac{1}{3}$

	y			
x	1	2	3	Total
3	9/36	2/36	1/36	1/3
2	2/36	8/18	2/18	1/3
1	1/36	2/36	9/36	1/3
Total	1/3	1/3	1/3	1

Clustering of gene expressions

- Represent each gene as a vector or a point in d-space where d is the number of arrays or experiments being analyzed.

Clustering Random vs. Biological Data

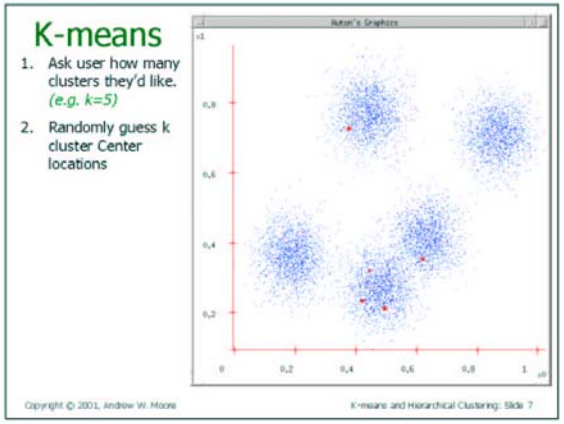


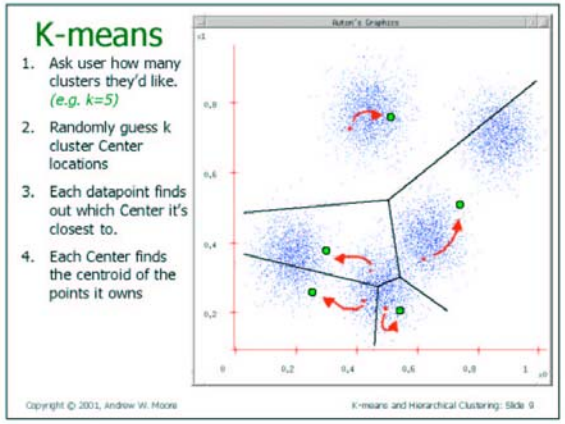
From *Eisen MB, et al, PNAS 1998 95(25):14863-8*

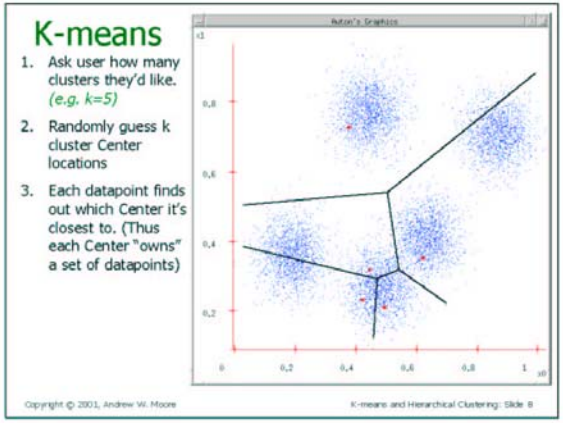
K-Means Clustering: Example

Example from Andrew Moore's tutorial on Clustering.

Start


K-means
1. Ask user how many clusters they'd like. (e.g. k=5)
2. Randomly guess k cluster Center locations
Copyright © 2001, Andrew W. Moore
K-means and Hierarchical Clustering: Slide 7


K-means
1. Ask user how many clusters they'd like. (e.g. k=5)
2. Randomly guess k cluster Center locations
3. Each datapoint finds out which Center it's closest to.
4. Each Center finds the centroid of the points it owns
Copyright © 2001, Andrew W. Moore
K-means and Hierarchical Clustering: Slide 9


K-means
1. Ask user how many clusters they'd like. (e.g. k=5)
2. Randomly guess k cluster Center locations
3. Each datapoint finds out which Center it's closest to. (Thus each Center "owns" a set of datapoints)
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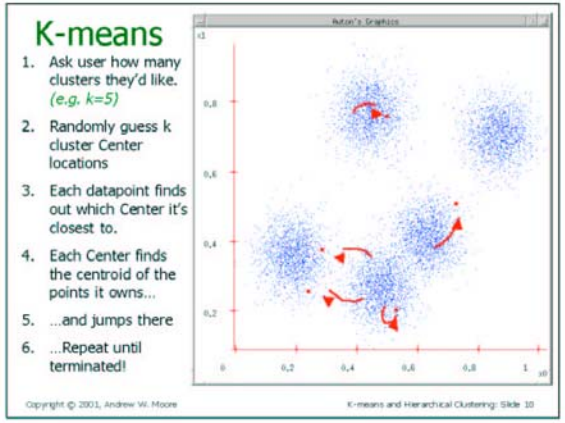
K-means and Hierarchical Clustering: Slide 8


K-means
1. Ask user how many clusters they'd like. (e.g. k=5)
2. Randomly guess k cluster Center locations
3. Each datapoint finds out which Center it's closest to.
4. Each Center finds the centroid of the points it owns...
5. ...and jumps there
6. ...Repeat until terminated!
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K-means and Hierarchical Clustering: Slide 10

4

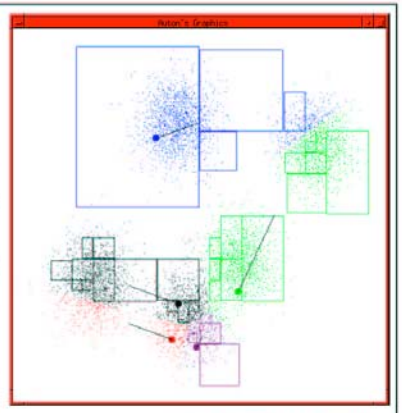
5

K-means Start

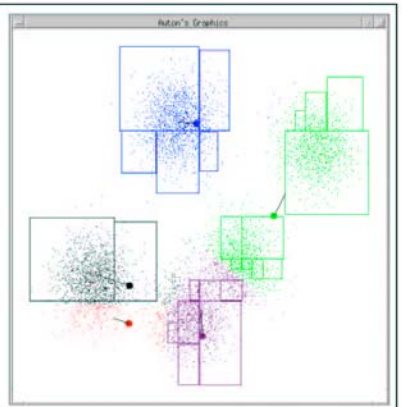
Advance apologies: in Black and White this example will deteriorate

Example generated by Dan Pelleg's super-duper fast K-means system:

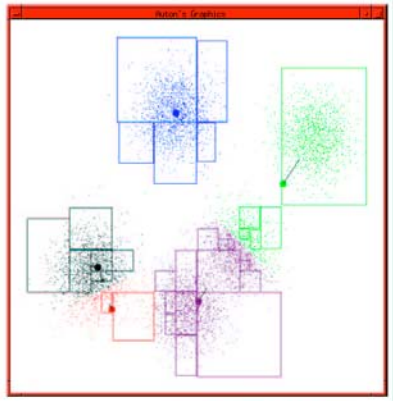
Dan Pelleg and Andrew Moore. Accelerating Exact k-means Algorithms with Geometric Reasoning. Proc. Conference on Knowledge Discovery in Databases 1999, (KDD99) (available on www.autonlab.org/pap.html)



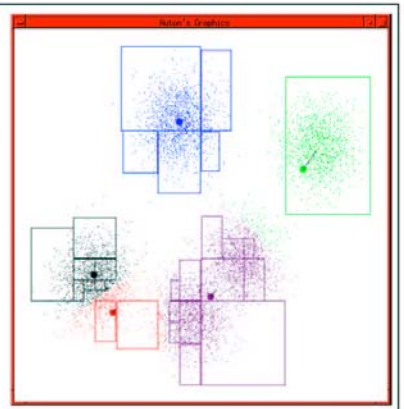
K-means continues ...

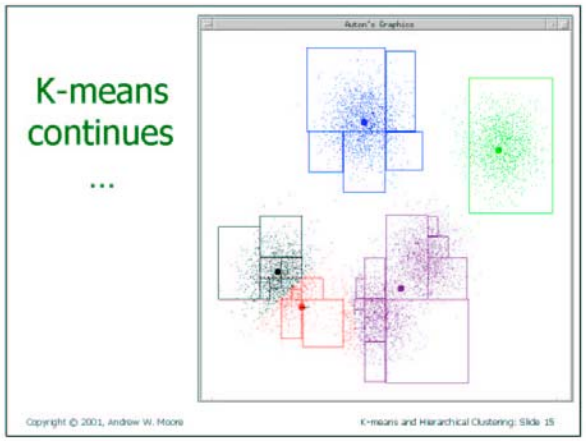


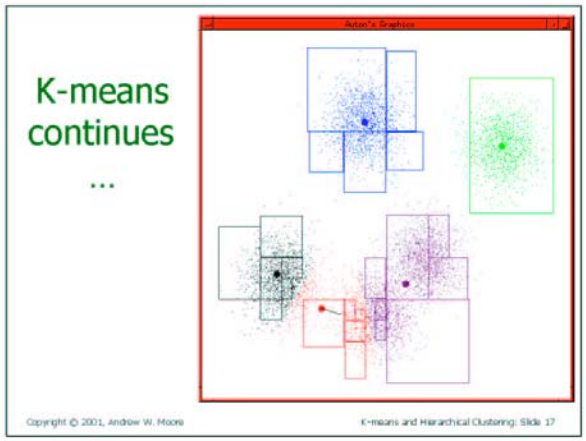
K-means continues ...

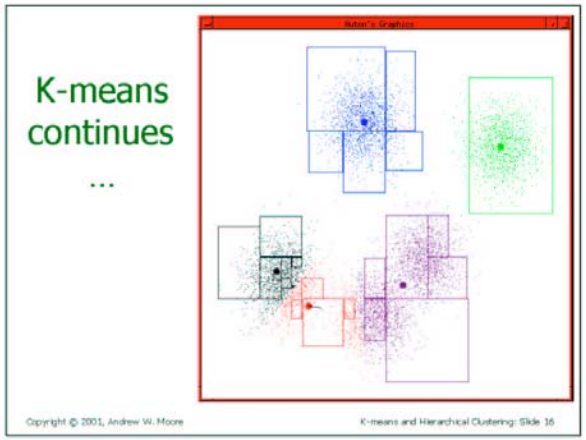


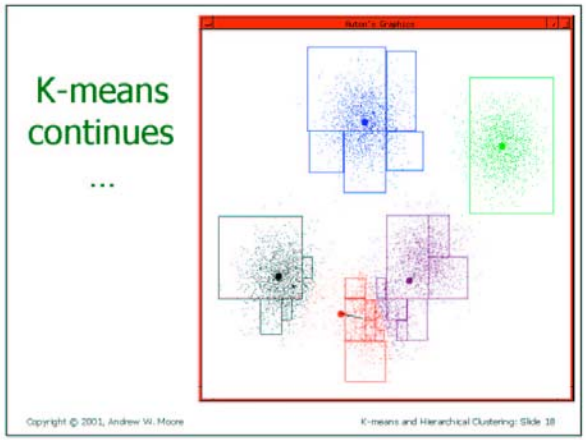
K-means continues ...




K-means
continues
...
Copyright © 2001, Andrew W. Moore
K-means and Hierarchical Clustering: Slide 15


K-means
continues
...
Copyright © 2001, Andrew W. Moore
K-means and Hierarchical Clustering: Slide 17

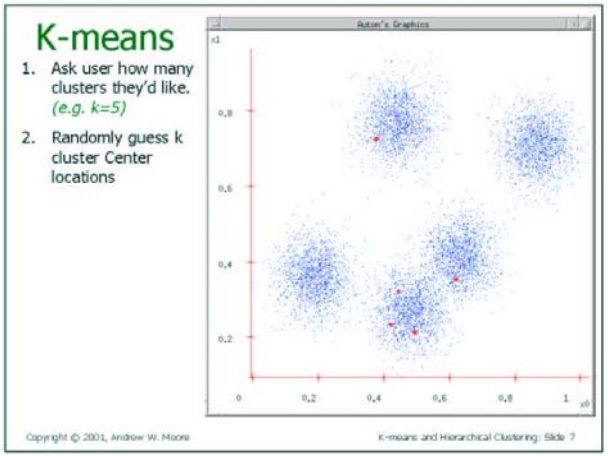

K-means
continues
...
Copyright © 2001, Andrew W. Moore
K-means and Hierarchical Clustering: Slide 16

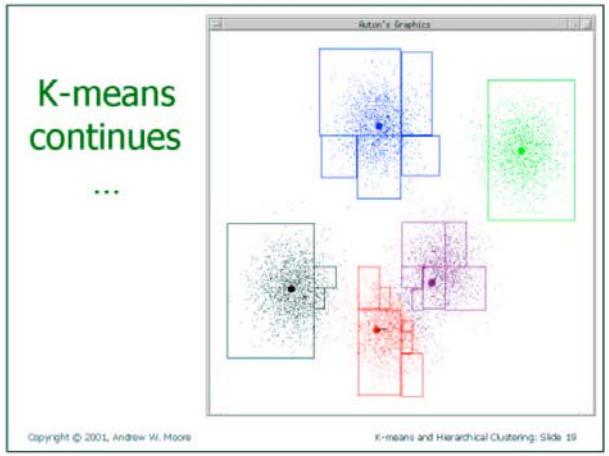

K-means
continues
...
Copyright © 2001, Andrew W. Moore
K-means and Hierarchical Clustering: Slide 18

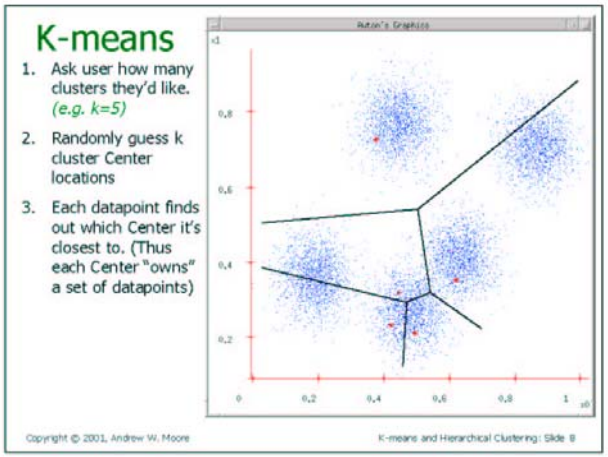
8

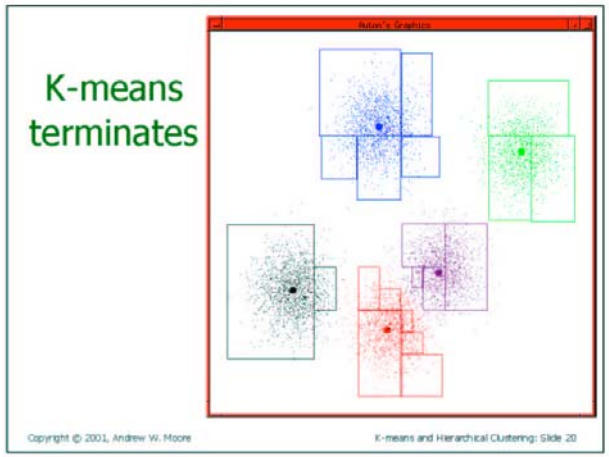
9

Start









End

4

10

K-Means Clustering [McQueen '67]

Repeat

- Start with randomly chosen cluster centers
- Assign points to give greatest increase in score
- Recompute cluster centers
- Reassign points

until (no changes)

Try the applet at:

http://home.dei.polimi.it/matteucc/Clustering/tutorial_html/AppletH.html

Comparisons

- Hierarchical clustering
  - Number of clusters not preset.
  - Complete hierarchy of clusters
  - Not very robust, not very efficient.
- K-Means
  - Need definition of a mean. Categorical data?
  - More efficient and often finds optimum clustering.

Functionally related genes behave similarly across experiments

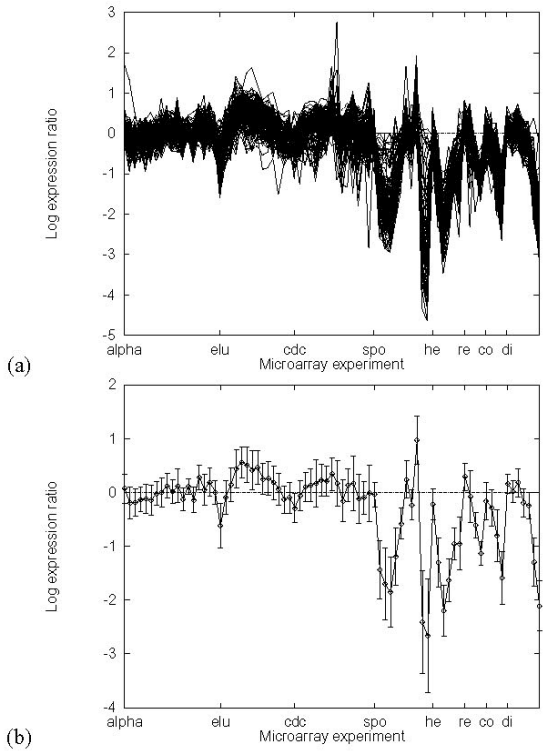


Figure 1: **Expression profiles of the cytoplasmic ribosomal proteins.** Figure (a) shows the expression profiles from the data in [Eisen et al., 1998] of 121 cytoplasmic ribosomal proteins, as classified by MYGD [MYGD, 1999]. The logarithm of the expression ratio is plotted as a function of DNA microarray experiment. Ticks along the X-axis represent the beginnings of experimental series. They are, from left to right, cell division cycle after synchronization with α factor arrest (alpha), cell division cycle after synchronization by centrifugal elutriation (elu), cell division cycle measured using a temperature sensitive *cdc15* mutant (cdc), sporulation (spo), heat shock (he), reducing shock (re), cold shock (co), and diauxic shift (di). Sporulation is the generation of a yeast spore by meiosis. Diauxic shift is the shift from anaerobic (fermentation) to aerobic (respiration) metabolism. The medium starts rich in glucose, and yeast cells ferment, producing ethanol. When the glucose is used up, they switch to ethanol as a source for carbon. Heat, cold, and reducing shock are various ways to stress the yeast cell. Figure (b) shows the average, plus or minus one standard deviation, of the data in Figure (a).

Self-Organizing Maps [Kohonen]

- Kind of neural network.
- Clusters data and find complex relationships between clusters.
- Helps reduce the dimensionality of the data.
- Map of 1 or 2 dimensions produced.
- Unsupervised Clustering
- Like K-Means, except for visualization

SOM Architectures

- 2-D Grid
- 3-D Grid
- Hexagonal Grid

SOM Algorithm

- Select SOM architecture, and initialize weight vectors and other parameters.
- **While** (stopping condition not satisfied) **do** for each input point x
  - winning node q has weight vector closest to x.
  - Update weight vector of q and its neighbors.
  - Reduce neighborhood size and learning rate.

SOM Algorithm Details

- Distance between x and weight vector: $\|x - w_i\|$
- Winning node: $q(x) = \min_i \|x - w_i\|$
- Weight update function (for neighbors):

$$w_i(k+1) = w_i(k) + \mu(k, x, i)[x(k) - w_i(k)]$$

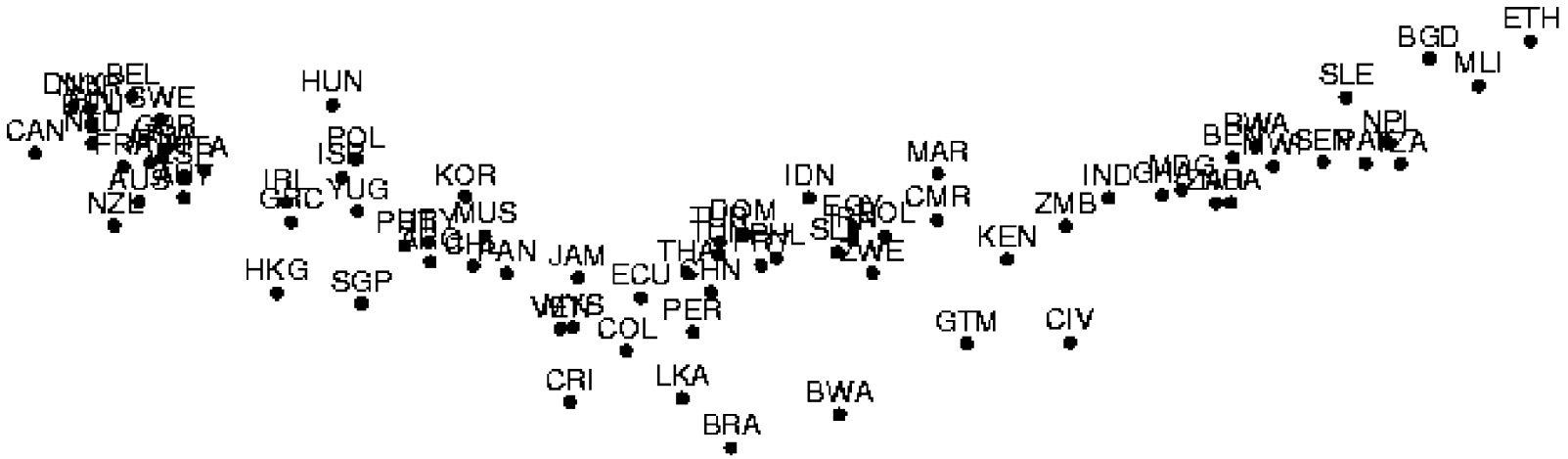
- Learning rate:

$$\mu(k, x, i) = \eta_0(k) \exp\left(\frac{-\|r_i - r_{q(x)}\|^2}{\sigma^2} \right)$$

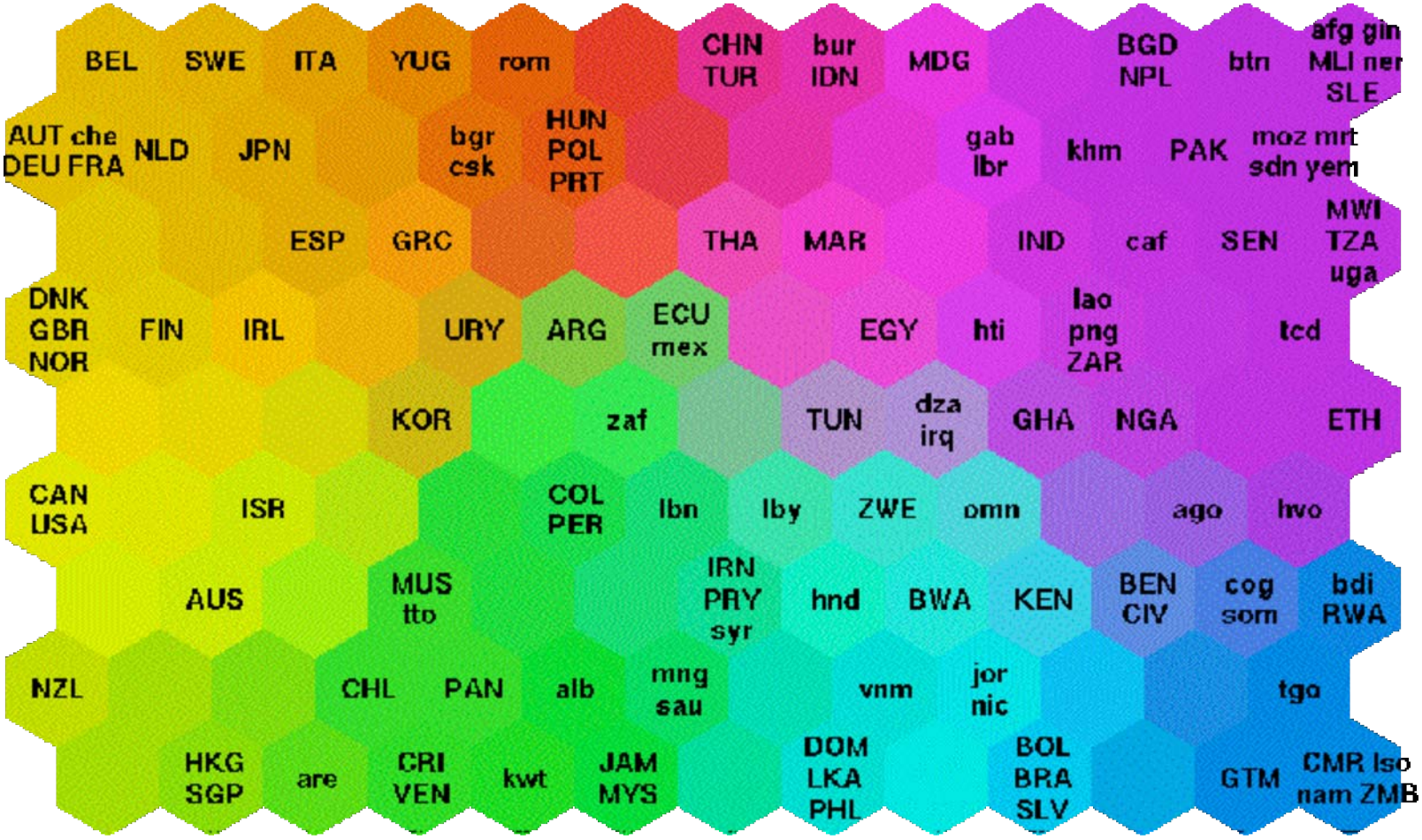
World Bank Statistics

- Data: World Bank statistics of countries in 1992.
- 39 indicators considered e.g., health, nutrition, educational services, etc.
- The complex joint effect of these factors can can be visualized by organizing the countries using the self-organizing map.

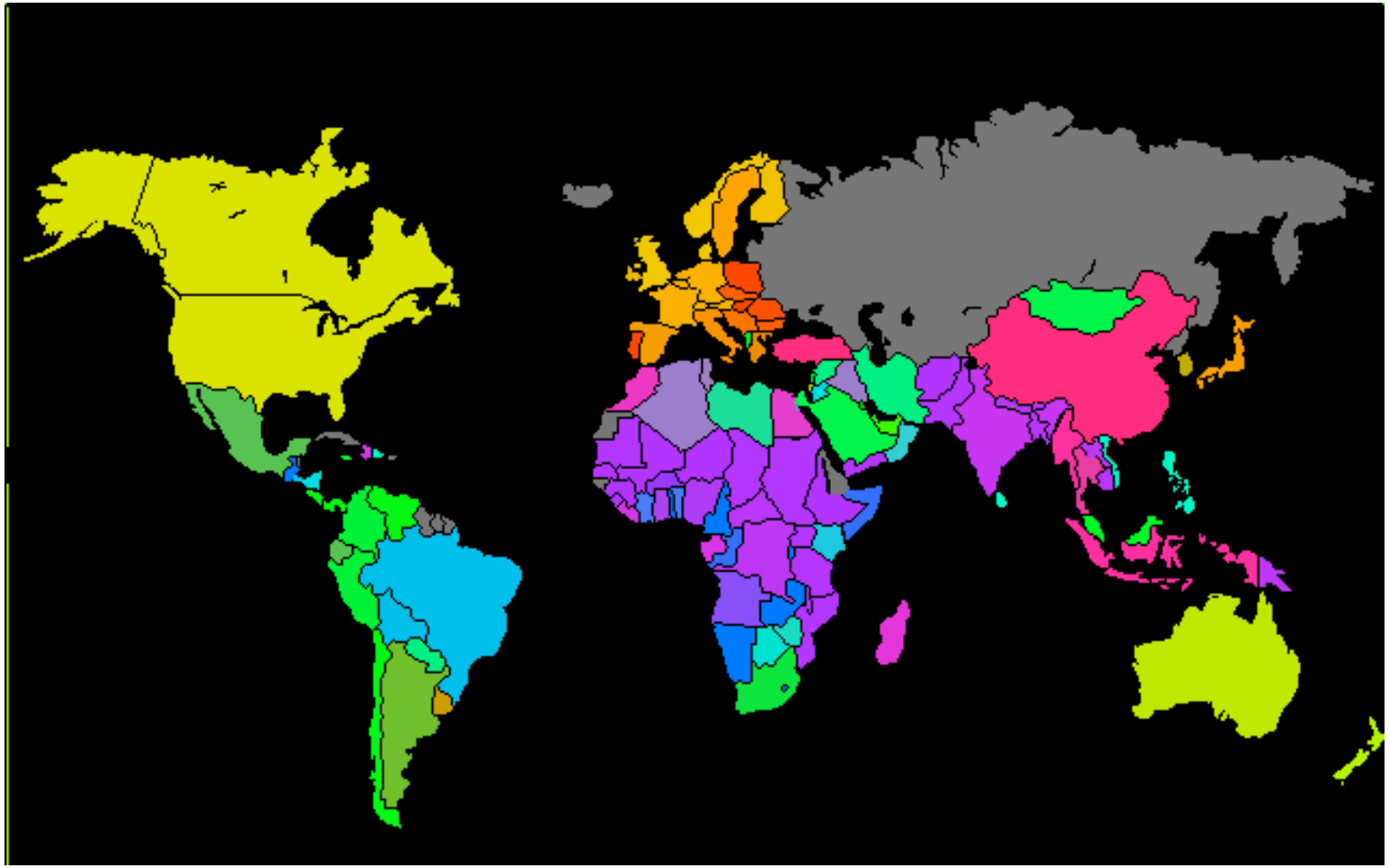
World Poverty PCA

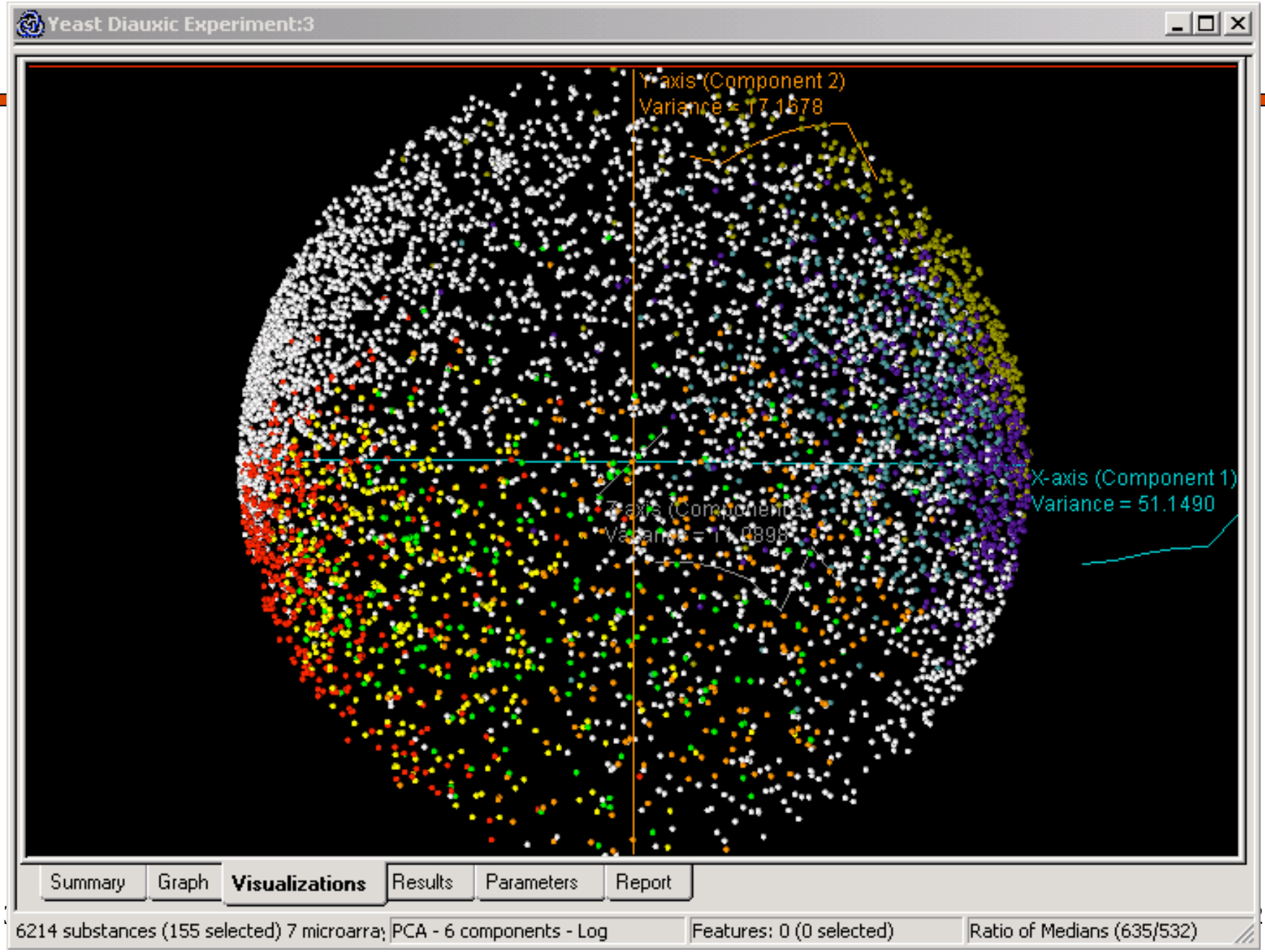


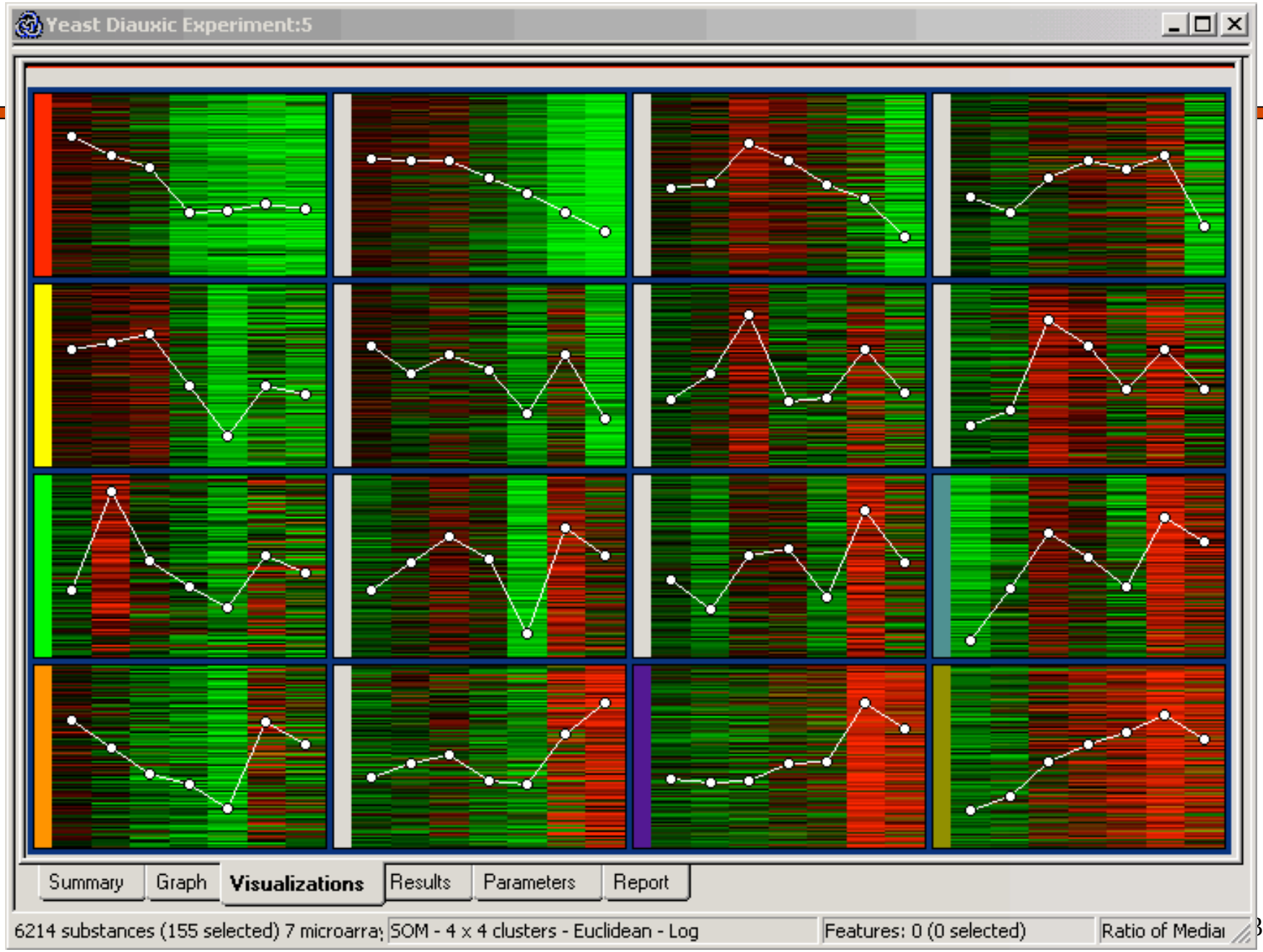
World Poverty SOM



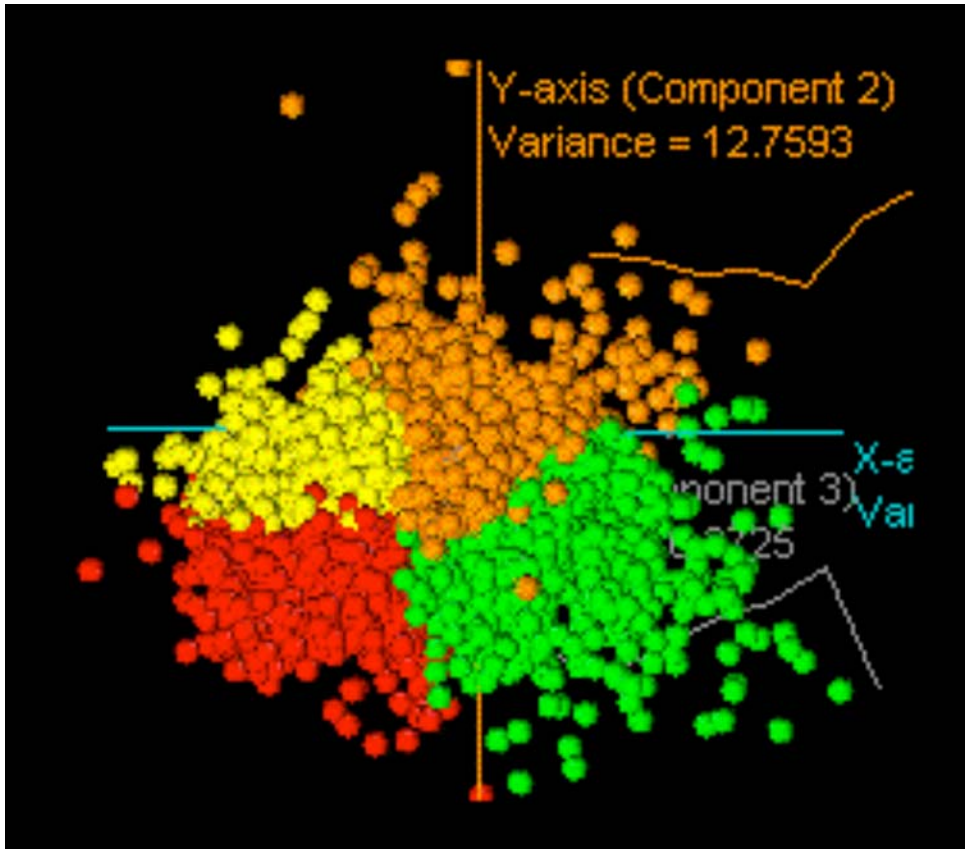
World Poverty Map



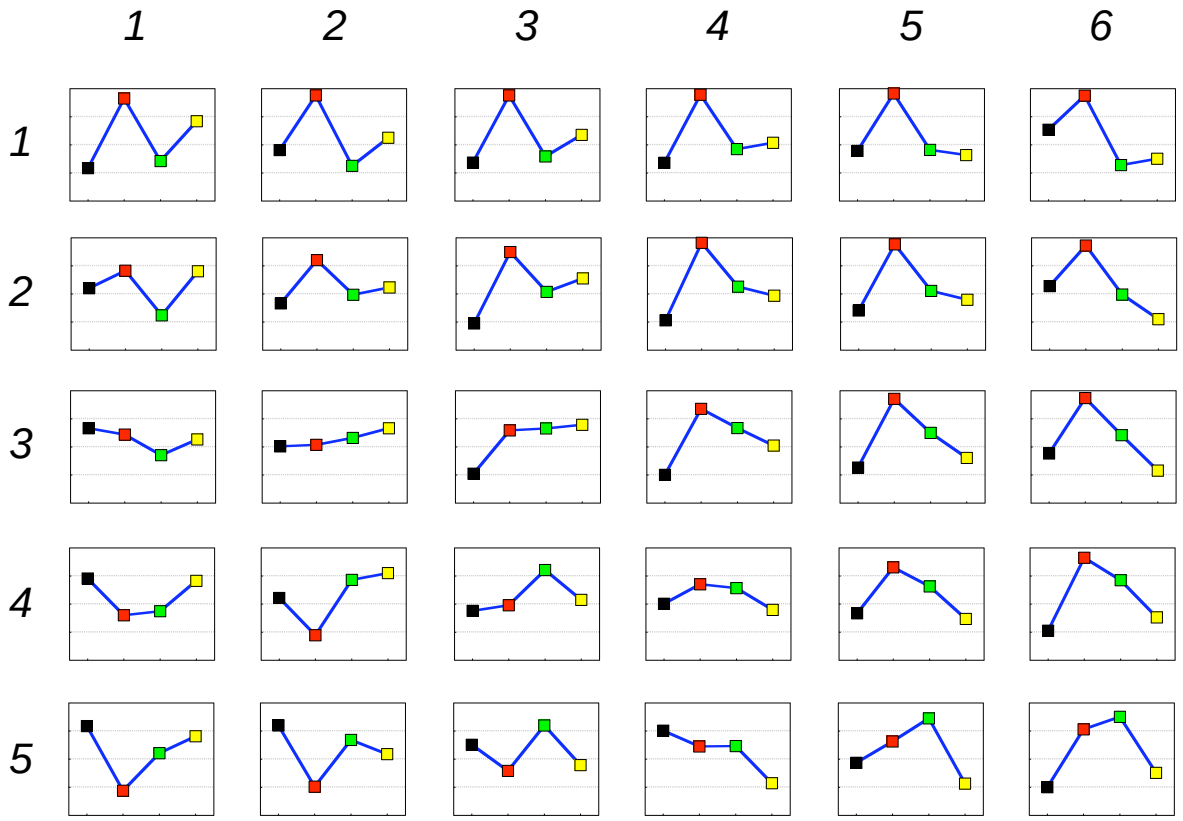

Yeast Diauxic Experiment:3
Y-axis (Component 2)
Variance = 17.1678
X-axis (Component 1)
Variance = 51.1490
Summary
Graph
Visualizations
Results
Parameters
Report
6214 substances (155 selected) 7 microarra
PCA - 6 components - Log
Features: 0 (0 selected)
Ratio of Medians (635/532)


Yeast Diauxic Experiment:5
Summary
Graph
Visualizations
Results
Parameters
Report
6214 substances (155 selected) 7 microarra
SOM - 4 x 4 clusters - Euclidean - Log
Features: 0 (0 selected)
Ratio of Media

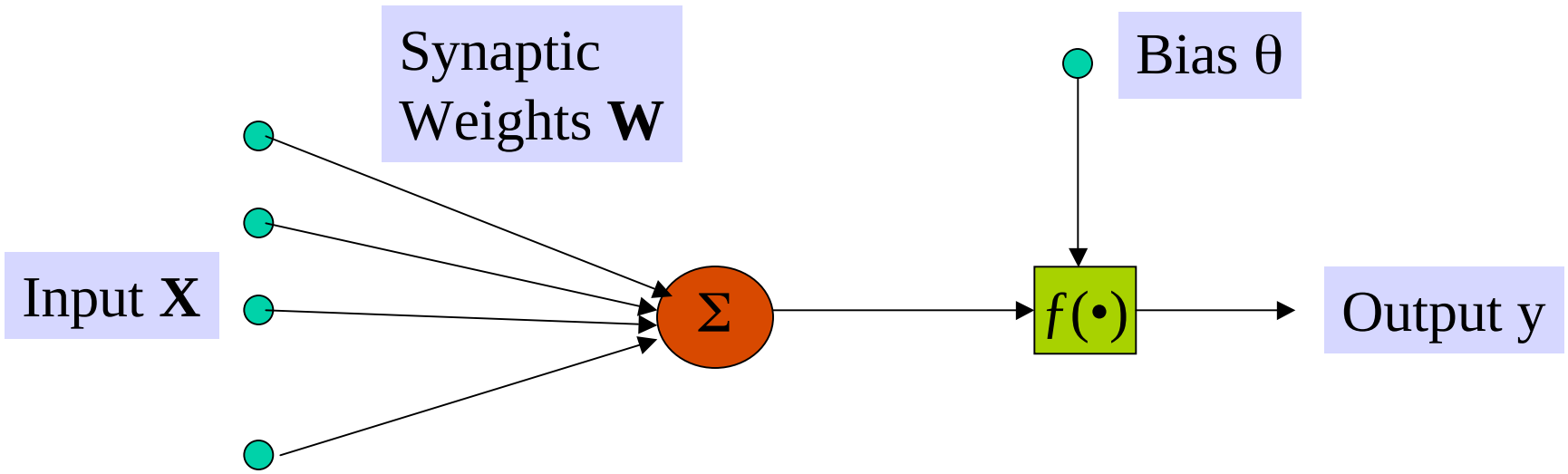
Viewing SOM Clusters on PCA axes



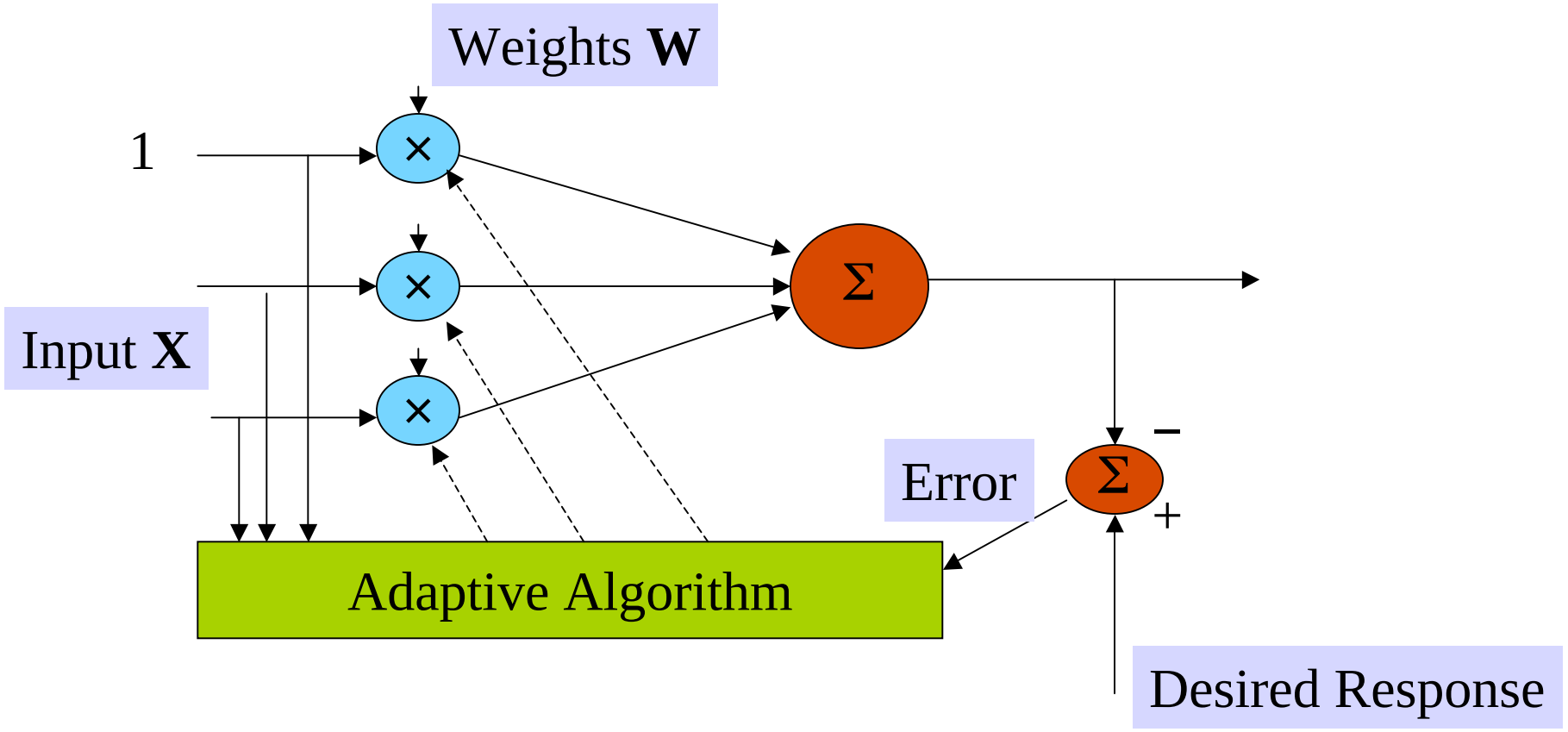
SOM Example [Xiao-rui He]



Neural Networks



Learning NN


Weights W
1
Input X
×
×
×
Σ
Error
Σ
−
+
Adaptive Algorithm
Desired Response

Types of NNs

- Recurrent NN
- Feed-forward NN
- Layered

Other issues

- Hidden layers possible
- Different activation functions possible

Application: Secondary Structure Prediction