

Model-based clustering and data transformations of gene expression data

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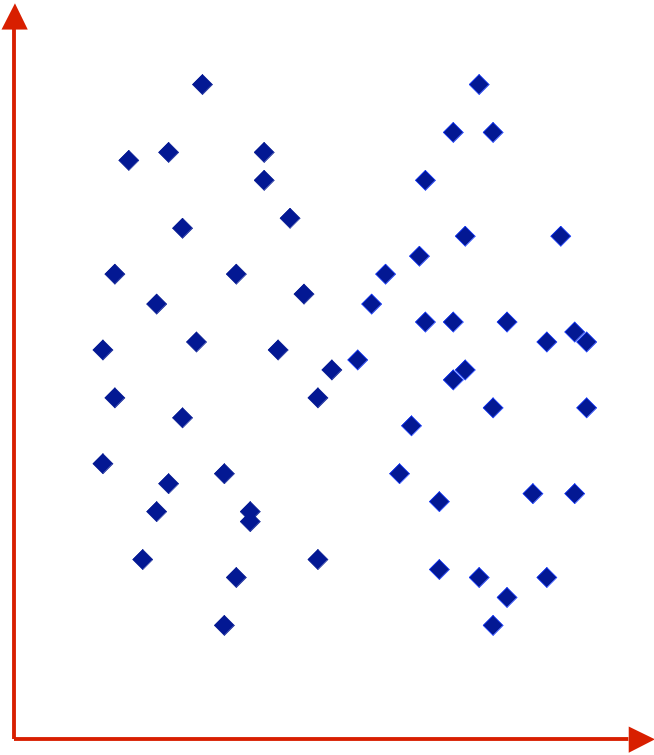


UW CSE Computational Biology Group

Overview

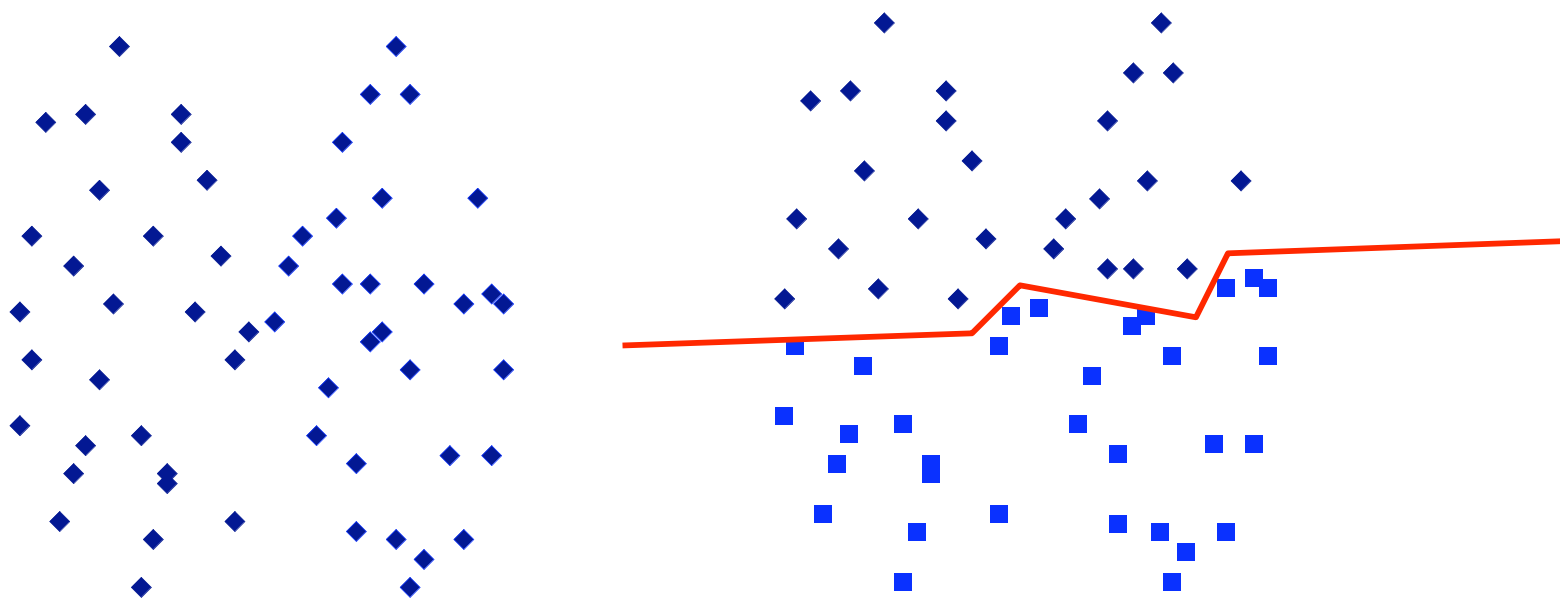
- Motivation
- Model-based clustering
- Validation
- Summary and Conclusions

Toy 2-d Clustering Example

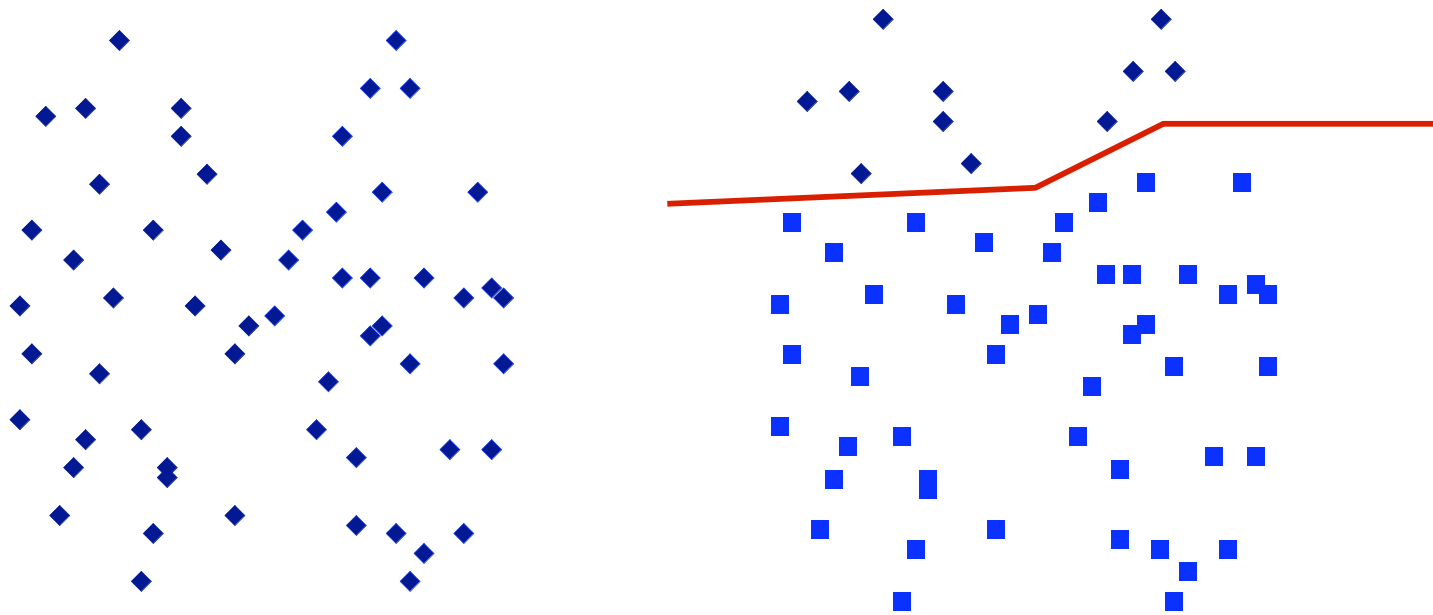


?

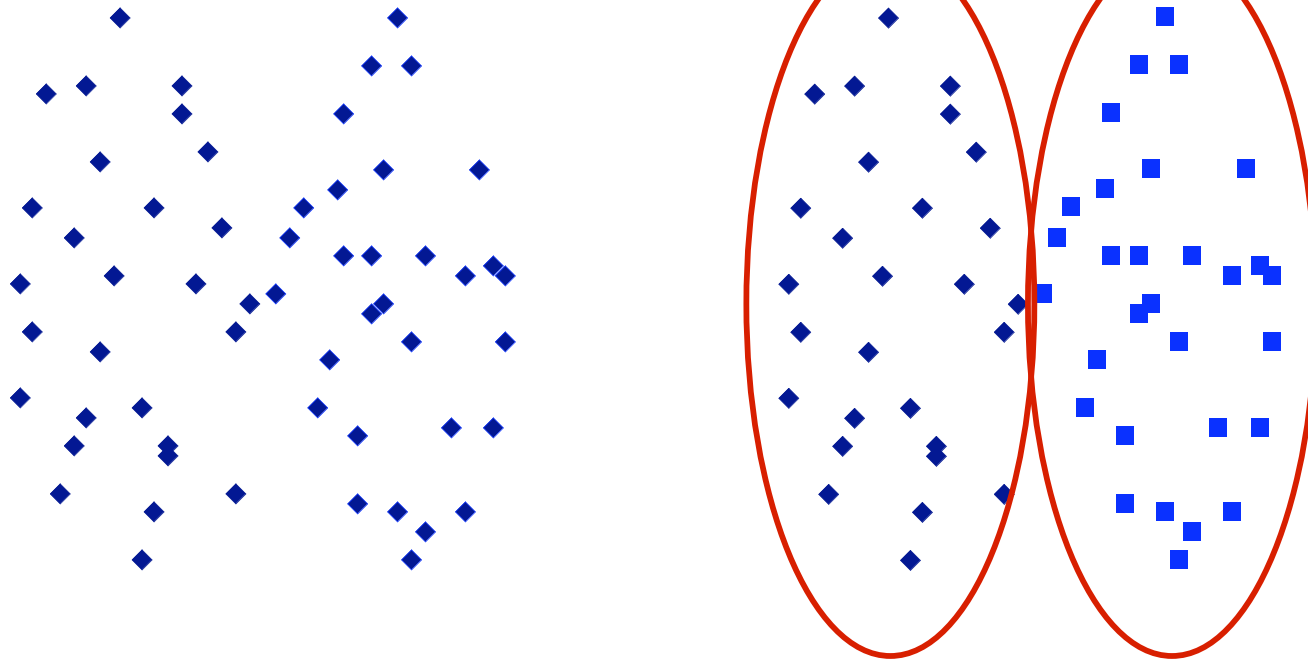
K-Means




Hierarchical Average Link



Model-Based (If You Want)



Overview

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-  • Model-based clustering
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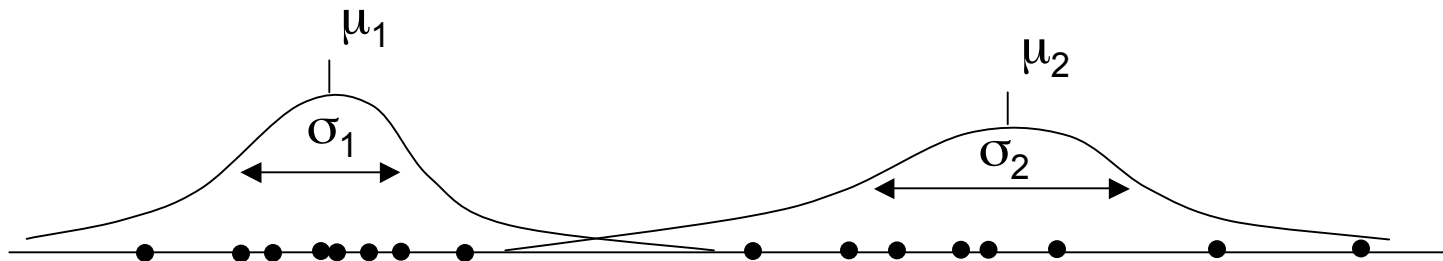
Model-based clustering

- Gaussian mixture model:
 - Assume each cluster is generated by a multivariate normal distribution
 - Cluster k has parameters :
 - Mean vector: μ_k
 - Covariance matrix: Σ_k



Model-based clustering

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Variance & Covariance

- Variance

$$\text{var}(x) = E((x - \bar{x})^2) = \sigma_x^2$$

- Covariance

$$\text{cov}(x, y) = E((x - \bar{x})(y - \bar{y}))$$

- Correlation

$$\text{cor}(x, y) = \frac{\text{cov}(x, y)}{\sigma_x \sigma_y}$$

Gaussian Distributions

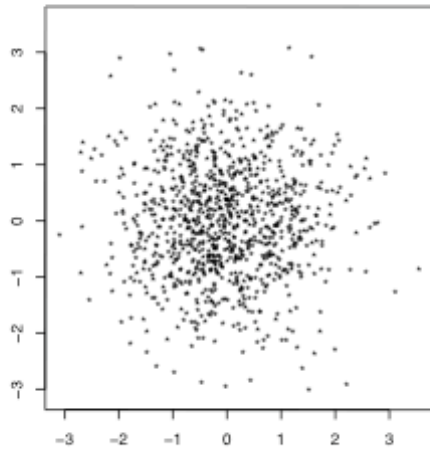
- Univariate $\frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{2}(x-\bar{x})^2/\sigma^2}$
- Multivariate $\frac{1}{\sqrt{(2\pi)^n |\Sigma|}} e^{-\frac{1}{2}(x-\bar{x})^T (\Sigma^{-1})(x-\bar{x})}$

where Σ is the variance/covariance matrix:

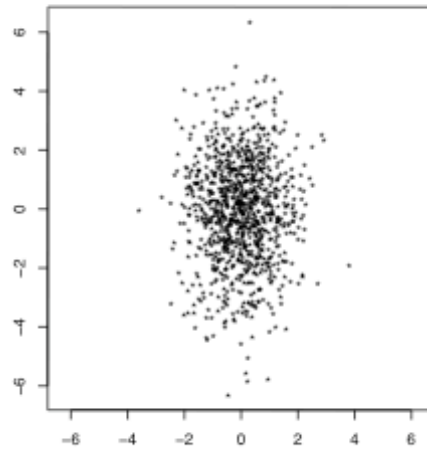
$$\Sigma_{i,j} = E((x_i - \bar{x}_i)(x_j - \bar{x}_j))$$

Variance/Covariance

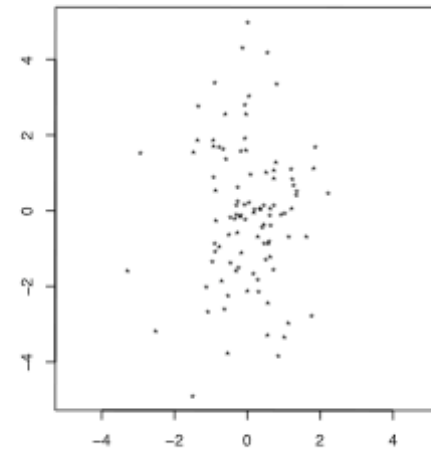
$\text{var}(x)=1, \text{var}(y)=1, \text{cov}=0, n=1000$



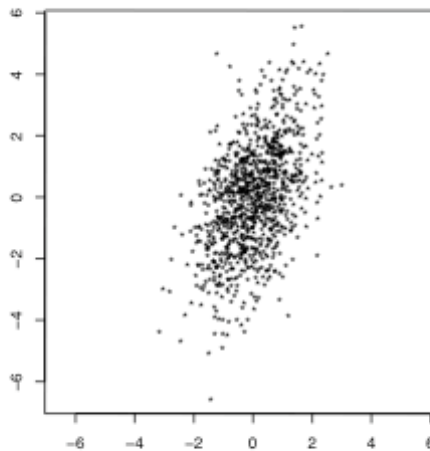
$\text{var}(x)=1, \text{var}(y)=3, \text{cov}=0, n=1000$



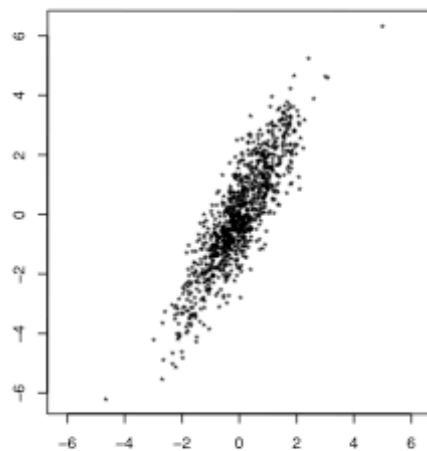
$\text{var}(x)=1, \text{var}(y)=3, \text{cov}=0, n=100$



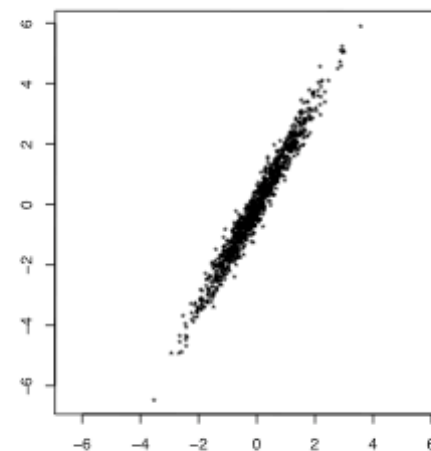
$\text{var}(x)=1, \text{var}(y)=3, \text{cov}=0.8, n=1000$



$\text{var}(x)=1, \text{var}(y)=3, \text{cov}=1.5, n=1000$



$\text{var}(x)=1, \text{var}(y)=3, \text{cov}=1.7, n=1000$



Covariance models

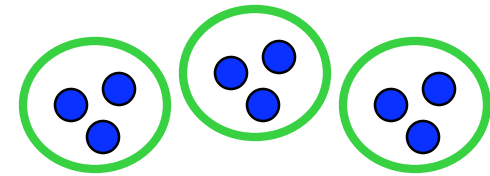
(Banfield & Raftery 1993)

- Equal volume spherical model (EI): \sim kmeans

$$\Sigma_k = \lambda I$$

$$\Sigma_k = \lambda_k D_k A_k D_k^T$$

volume shape orientation



Covariance models

(Banfield & Raftery 1993)

$$\Sigma_k = \lambda_k D_k A_k D_k^T$$

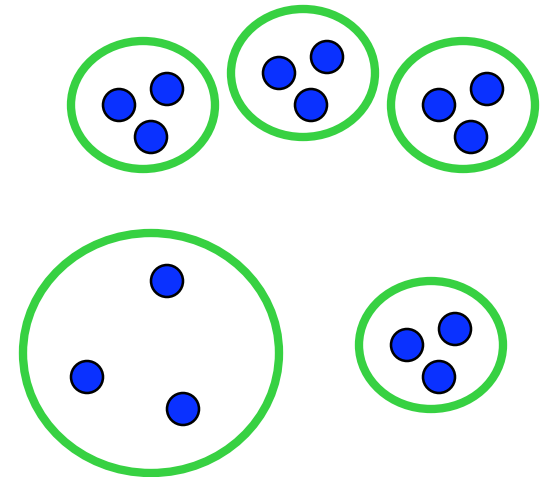
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- Equal volume spherical model (EI): \sim kmeans

$$\Sigma_k = \lambda I$$

- Unequal volume spherical (VI):

$$\Sigma_k = \lambda_k I$$



Covariance models

(Banfield & Raftery 1993)

$$\Sigma_k = \lambda_k D_k A_k D_k^T$$

volume shape orientation

- Equal volume spherical model (EI): \sim kmeans

$$\Sigma_k = \lambda I$$

- Unequal volume spherical (VI):

$$\Sigma_k = \lambda_k I$$

- Diagonal model:

$$\Sigma_k = \lambda_k B_k, \text{ where } B_k \text{ is diagonal, } |B_k|=1$$

- EEE elliptical model:

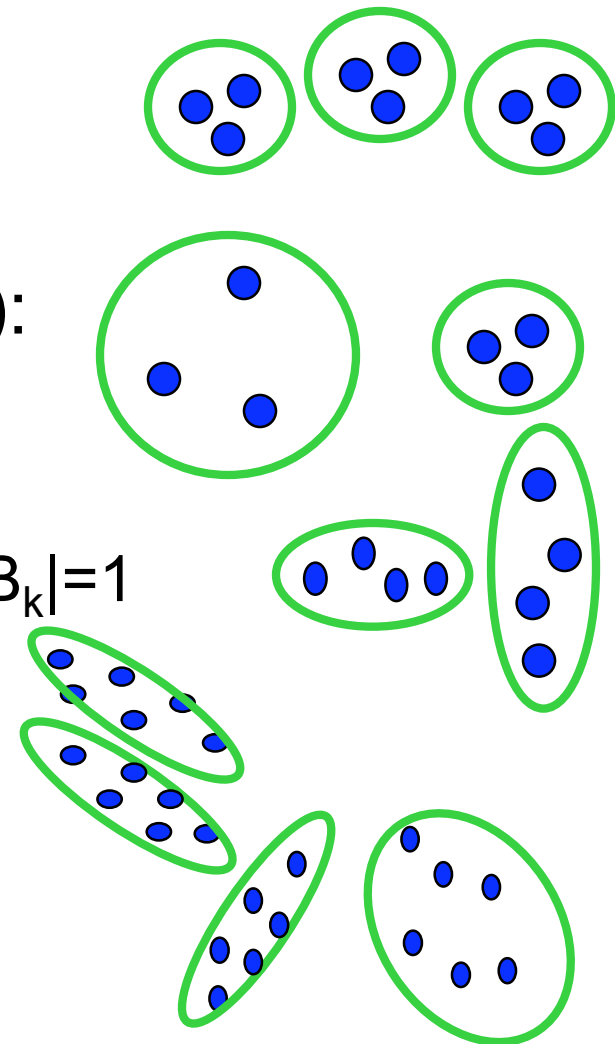
$$\Sigma_k = \lambda D A D^T$$

- Unconstrained model (VVV):

$$\Sigma_k = \lambda_k D_k A_k D_k^T$$

More flexible

But more parameters



EM algorithm

- General approach to maximum likelihood
- Iterate between E and M steps:
 - E step: compute the probability of each observation belonging to each cluster using the current parameter estimates
 - M-step: estimate model parameters using the current group membership probabilities

Advantages of model-based clustering

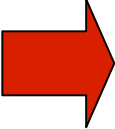
- Higher quality clusters
- Flexible models
- Model selection – **A principled way to choose right model and right # of clusters**
 - Bayesian Information Criterion (**BIC**):
 - Approximate Bayes factor: posterior odds for one model against another model
 - Roughly: data likelihood, penalized for number of parameters
 - A large BIC score indicates strong evidence for the corresponding model.

Definition of the BIC score

$$2\log p(D | M_k) \approx 2\log p(D | \hat{\theta}_k, M_k) - v_k \log(n) = BIC_k$$

- The integrated likelihood $p(D|M_k)$ is hard to evaluate,
where D is the data, M_k is the model.
- BIC is an approximation to $\log p(D|M_k)$
- v_k : number of parameters to be estimated in model M_k

Overview

- Motivation
- Model-based clustering
-  Validation
 - Methodology
 - Data Sets
 - Results
- Summary and Conclusions

Validation Methodology

- Compare on data sets with *external criteria* (BIC scores do **not** require the external criteria)
- To compare clusters with external criterion:
 - Adjusted Rand index (Hubert and Arabie 1985)
 - Adjusted Rand index = 1 → perfect agreement
 - 2 random partitions have an expected index of 0
- Compare quality of clusters to those from:
 - a leading heuristic-based algorithm: CAST (Ben-Dor & Yakhini 1999)
 - k-Means (EI).

Gene expression data sets

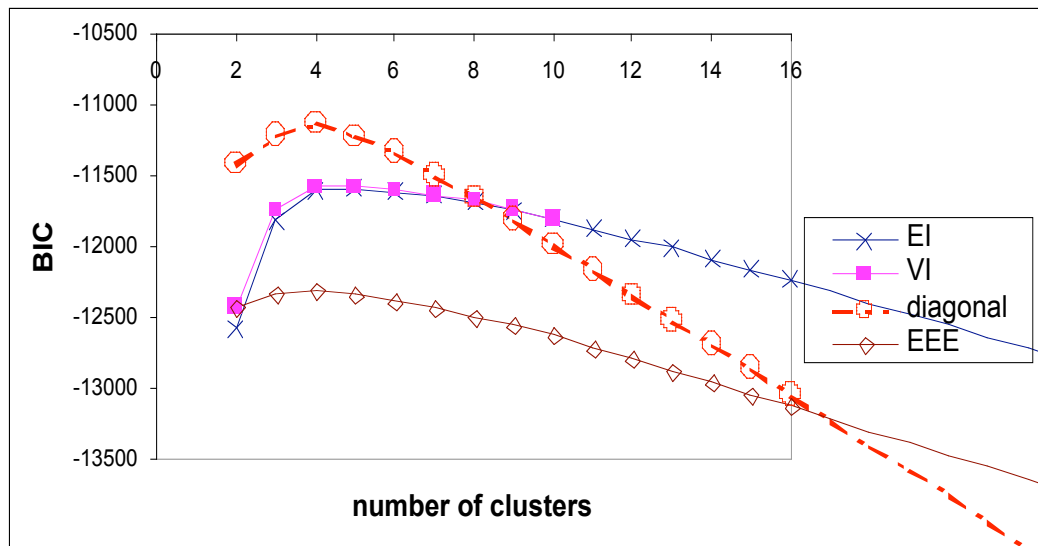
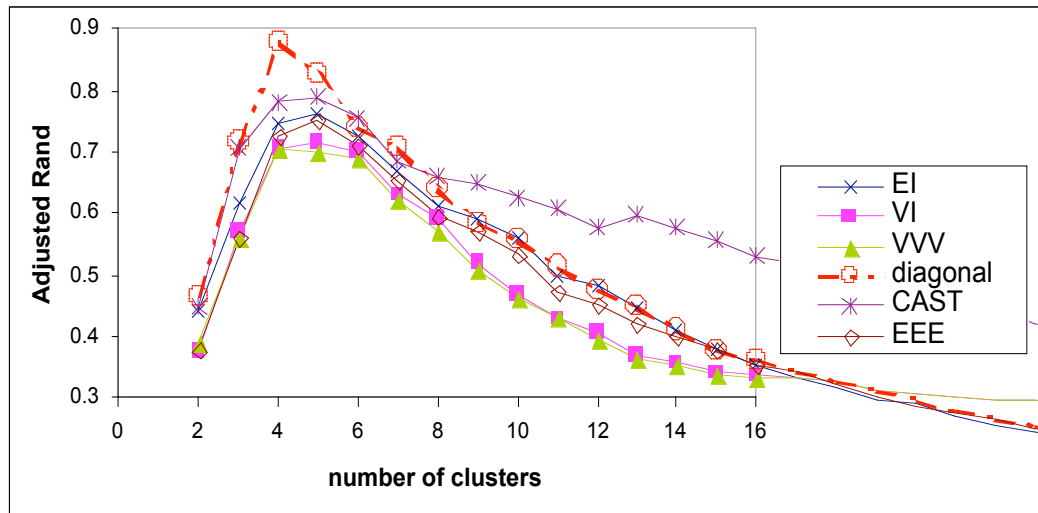
- Ovarian cancer data set
(Michel Schummer, Institute of Systems Biology)
 - Subset of data: 235 clones
24 experiments (cancer/normal tissue samples)
 - 235 clones correspond to 4 genes
- Yeast cell cycle data (Cho *et al* 1998)
 - 17 time points
 - Subset of 384 genes associated with 5 phases of cell cycle

Synthetic data sets

Both based on ovary data

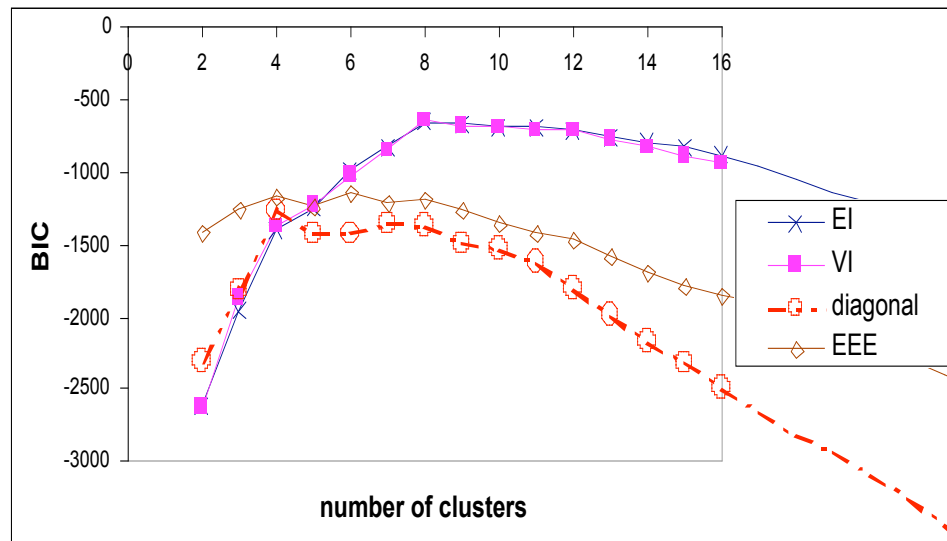
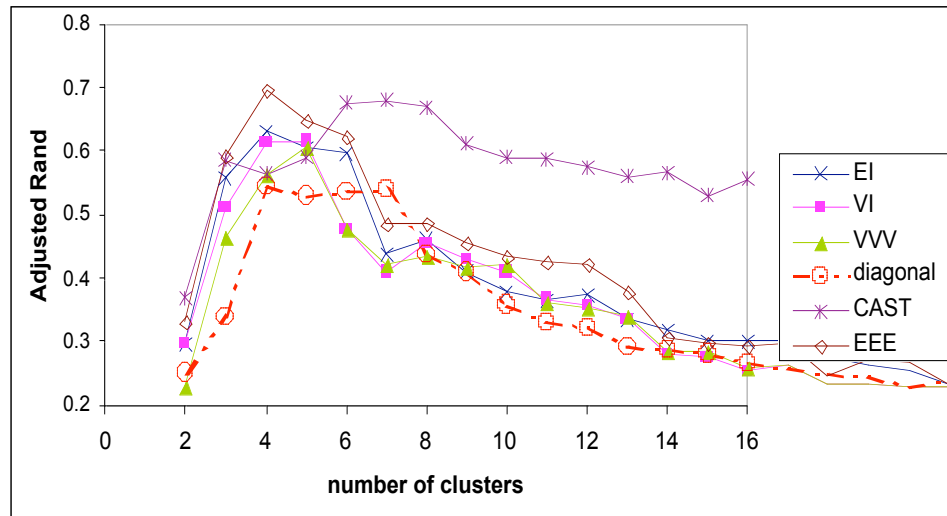
- Randomly resampled ovary data
 - For each class, randomly sample the expression levels in each experiment, independently
 - Near diagonal covariance matrix
- Gaussian mixture
 - Generate multivariate normal distributions with the sample covariance matrix and mean vector of each class in the ovary data

Results: randomly resampled ovary data



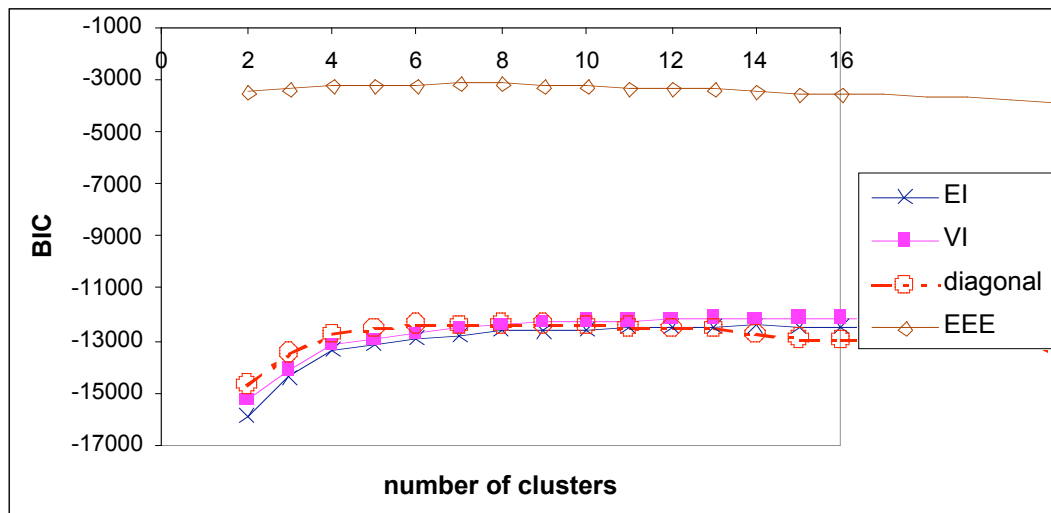
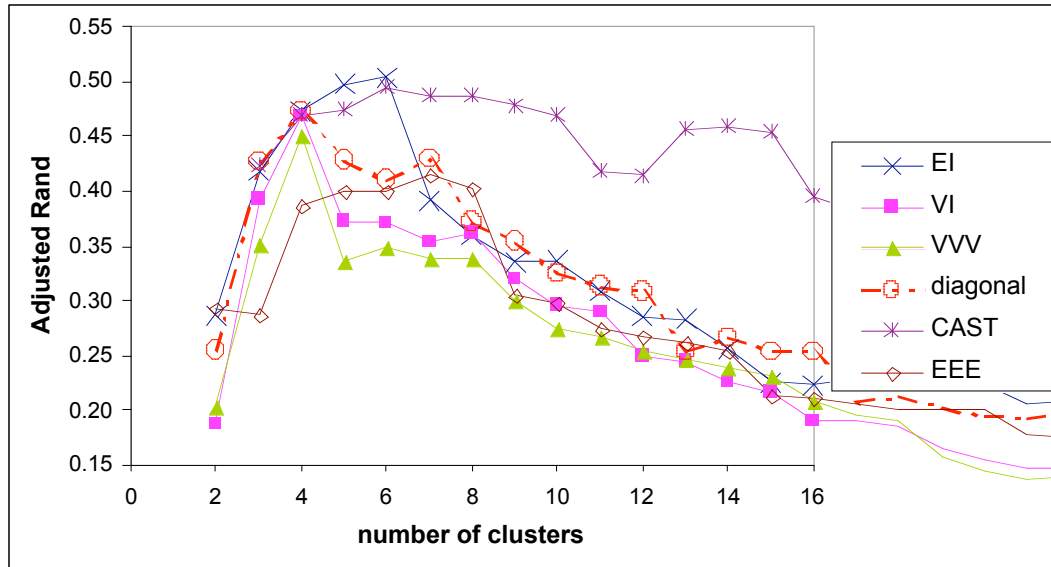
- Diagonal model achieves max BIC score (~expected)
- max BIC at 4 clusters (~expected)
- max adjusted Rand
- beats CAST

Results: square root ovary data



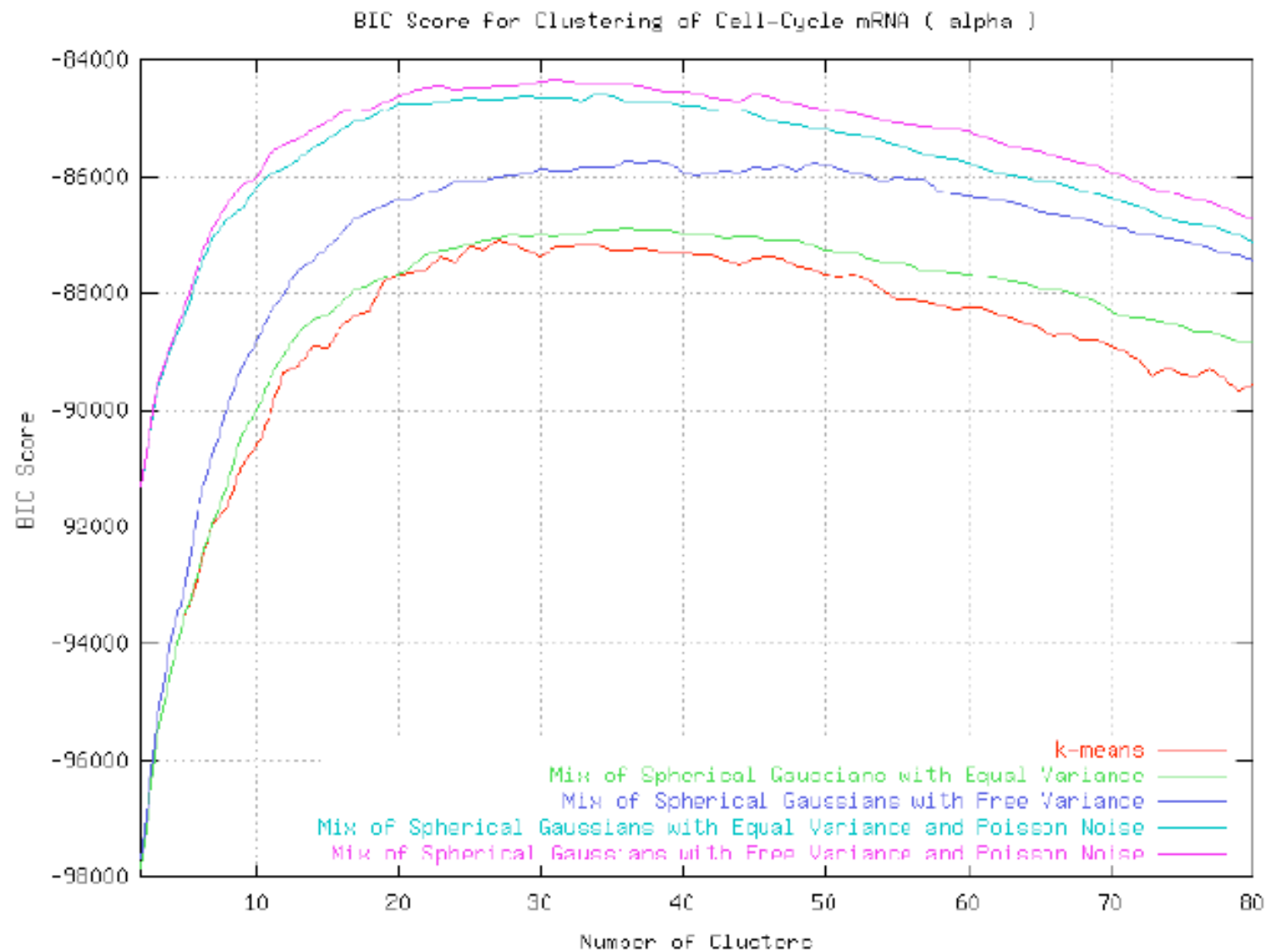
- Adjusted Rand: max at EEE 4 clusters (> CAST)
- BIC analysis:
 - EEE and diagonal models → local max at 4 clusters
 - Global max → VI at 8 clusters (8 ≈ split of 4).

Results: standardized yeast cell cycle data

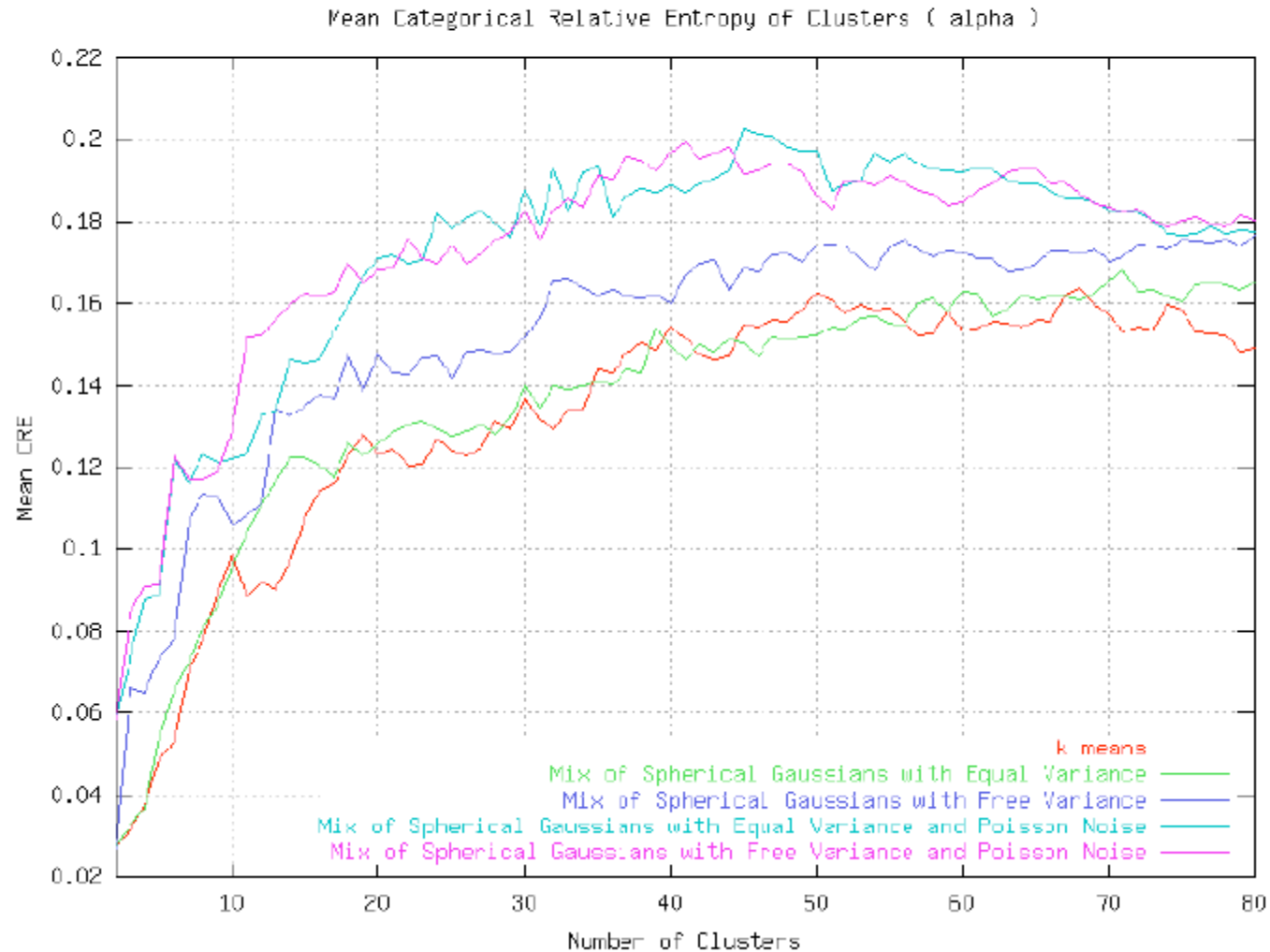


- Adjusted Rand: EI slightly $>$ CAST at 5 clusters.
- BIC: selects EEE at 5 clusters.

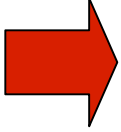
BIC Scores for Clustering of Alpha-Factor Data with Noise Mixture Models



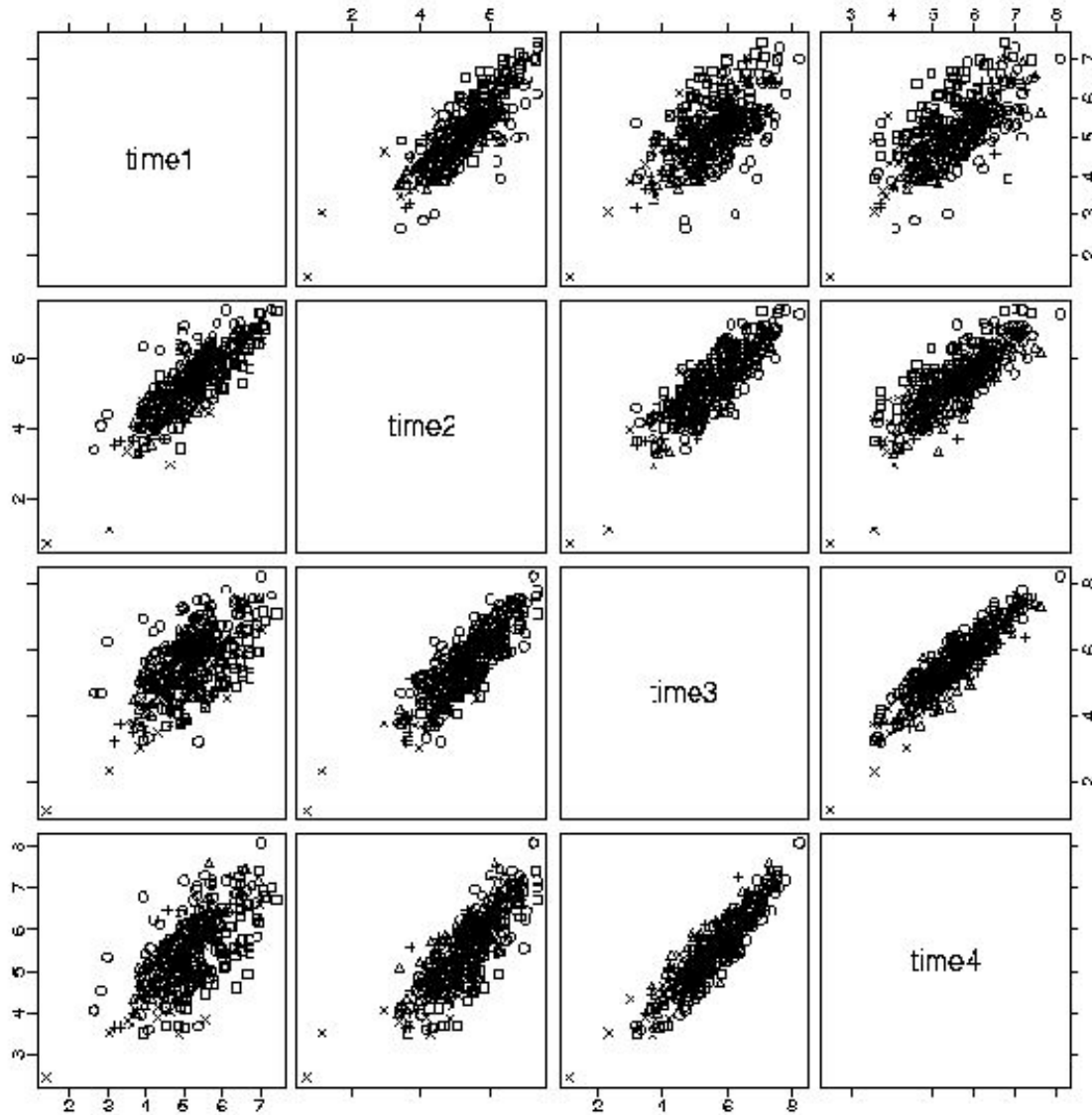
CRE Scores for Clustering of Alpha-Factor Data with Noise Mixture Models



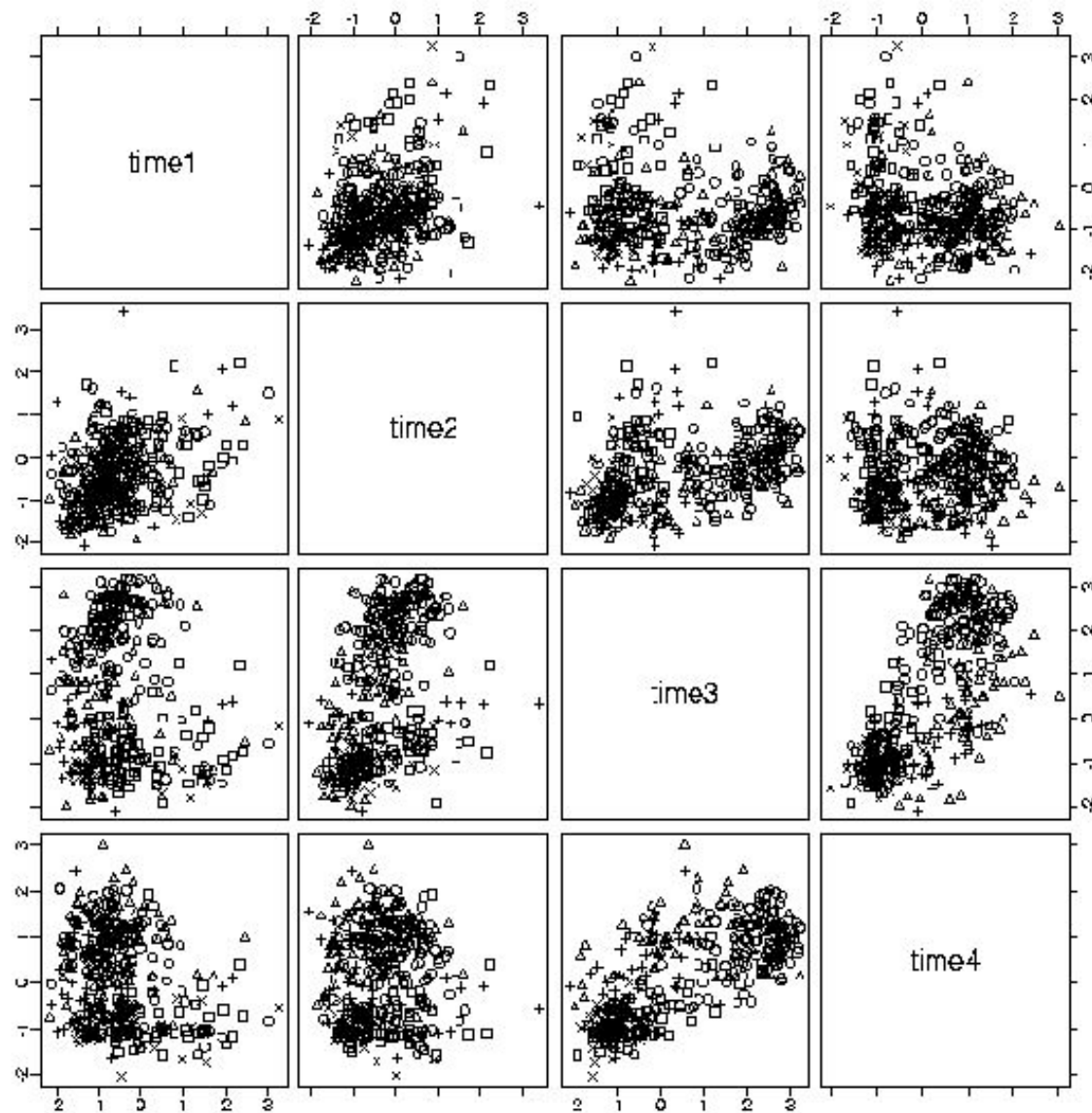
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-  • Importance of Data Transformation
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log yeast cell cycle data

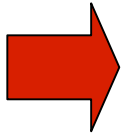


Standardized yeast cell cycle data



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Summary and Conclusions

- Synthetic data sets:
 - With the correct model, model-based clustering better than a leading heuristic clustering algorithm
 - BIC selects the right model & right number of clusters
- Real expression data sets:
 - Comparable adjusted Rand indices to CAST
 - BIC gives a good hint as to the number of clusters
- Appropriate data transformations increase normality & cluster quality (See paper & web.)

Acknowledgements

- Ka Yee Yeung¹, Chris Fraley^{2,4},
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- Michèle Schummer⁵ – the ovary data
- Jeremy Tantrum² – help with MBC software (diagonal model)
- Chris Saunders³ – CRE & noise model

¹Computer Science & Engineering

²Statistics

³Genome Sciences

⁴Insightful Corporation

⁵Institute of Systems Biology

More Info

<http://www.cs.washington.edu/homes/ruzzo>



Adjusted Rand Example

	c#1(4)	c#2(5)	c#3(7)	c#4(4)
class#1(2)	2	0	0	0
class#2(3)	0	0	0	3
class#3(5)	1	4	0	0
class#4(10)	1	1	7	1

$$a = \binom{2}{2} + \binom{3}{2} + \binom{4}{2} + \binom{7}{2} = 31$$

$$b = \binom{4}{2} + \binom{5}{2} + \binom{7}{2} + \binom{4}{2} - a = 43 - 31 = 12$$

$$c = \binom{2}{2} + \binom{3}{2} + \binom{5}{2} + \binom{10}{2} - a = 59 - 31 = 28$$

$$d = \binom{20}{2} - a - b - c = 119$$

$$Rand, R = \frac{a + d}{a + d + c + d} = 0.789$$

$$Adjusted\ Rand = \frac{R - E(R)}{1 - E(R)} = 0.469$$