Clustering through Mixture Models

General references:

Lindsay B.G. (1995), *Mixture models: theory, geometry and applications*, NFS-CBMS Regional Conference Series in Probability and Statistics.

McLachlan G.J., Basford K.E. (1988), *Mixture Models: Inference and Applications to Clustering*, Marcel Dekker, New York.

Fraley C., Raftery A.E. (1998), How Many Clusters? Which Clustering Method? Answers Via Model-Based Cluster Analysis, *The Computer Journal*, **41**, 570--588.

Applications to Microarray data:

Yeung K.Y., Fraley C., Murua A., Raftery A.E. and Ruzzo W. L. (2001),Model-Based Clustering and Data Transformation for Gene Expression Data, *Bioinformatics*, **17** (10) 977-987.

Examples that are joint work with F. Bartolucci, bart@stat.unipg.it Dept. of Statistics University of Perugia, ITALY.

Issues:

- Reliability; arbitrariness (natural “lumpiness” of the data):

  bringing partitions and characteristic patterns within the domain of ***statistical inference***; substitute membership with ***membership probabilities***.

- Multiple and compounding sources of experimental error:

  robustification towards anomalies, while keeping an adequate degree of sensitivity.

- Much is unknown, but some aspects are well known or object of well defined hypotheses:

  integrating ***exploration*** and ***substantive modeling***.

→ An approach based on multivariate normal mixtures and maximum likelihood may provide some answers…

The Mixture Approach: data is a size *N* sample from

$$X \in R^T \quad , \quad X \sim \sum_{c=1}^{C-1} \pi_c N(\mu_c, \Sigma_c) + \pi_C \Gamma \quad , \quad \pi_c \geq 0 \, , \sum_{c=1}^{C} \pi_c = 1$$

…each profile comes from one of *C* alternative components

C; contamination term

Uniform on data range or

sparse and spherical

("absorbs" anomalous profiles)

$$\Gamma = Un(\text{data range}) \quad \text{or}$$

$$\Gamma = N(\mu_C, \sigma_C^2 I) \quad \sigma_C^2 \geq \underline{\sigma}_C^2$$

$$\pi_C \leq \bar{\pi}_C$$

"coverage radius"

"degree of contamination"

c=1…*C*-1; regular components

Model means and within component covariance to various degrees of specificity

$$N(\mu_c, \Sigma_c)$$

$$\mu_c = Z_c \beta_c \; , \; \beta_c \in R^{p_c}$$

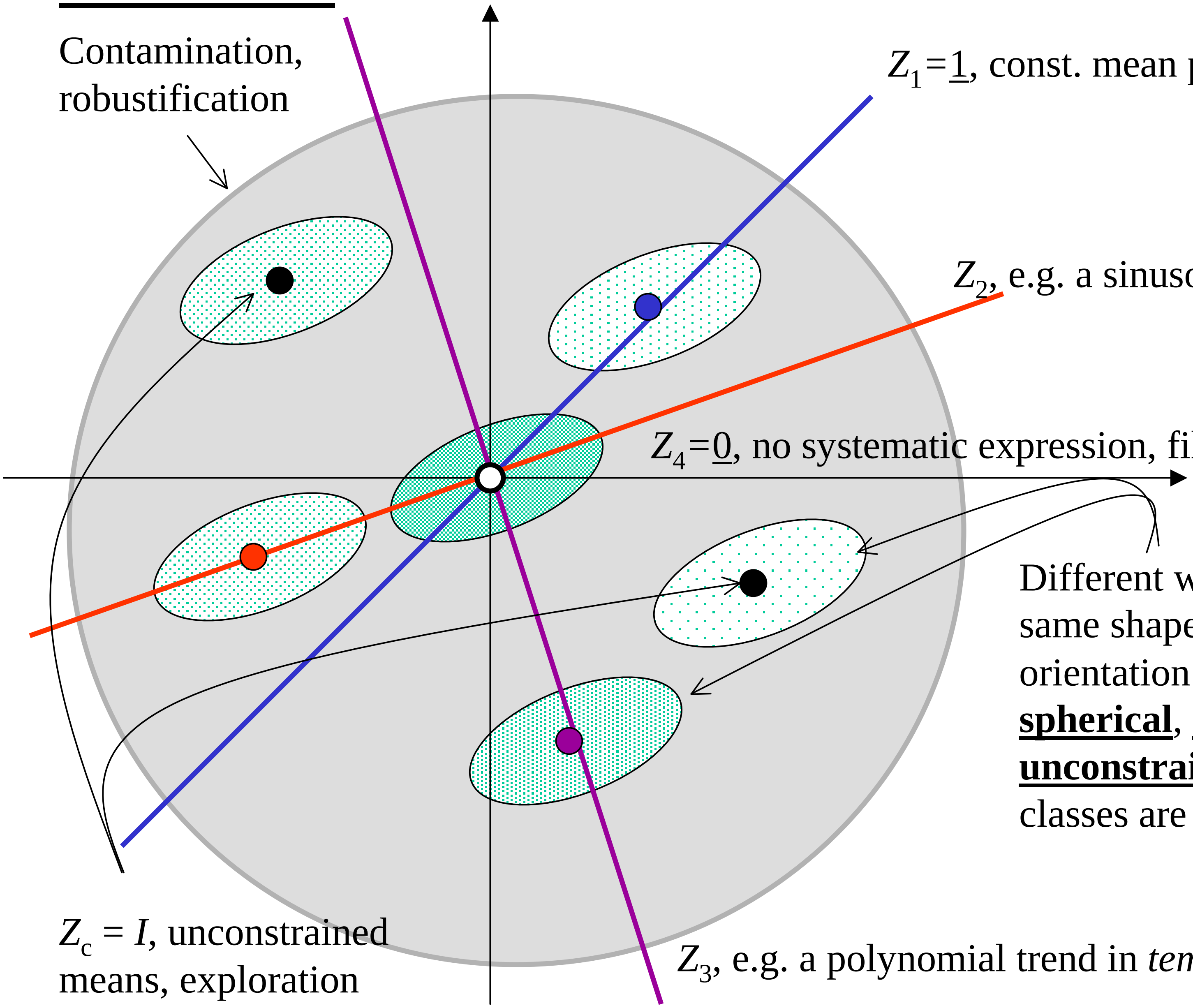
$$\Sigma_c \in S \quad \text{maybe} \quad \Sigma_c = \Sigma \in S$$

Linear re-param of means

Assume equal (better discrimination of within-between variation), and model

A cartoon…

Linear constraints on mean patterns



Contamination, robustification

$Z_1=\underline{1}$, const. mean pattern, filtering

Z_2, e.g. a sinusoidal trend in $time_t$

$Z_4=\underline{0}$, no systematic expression, filtering

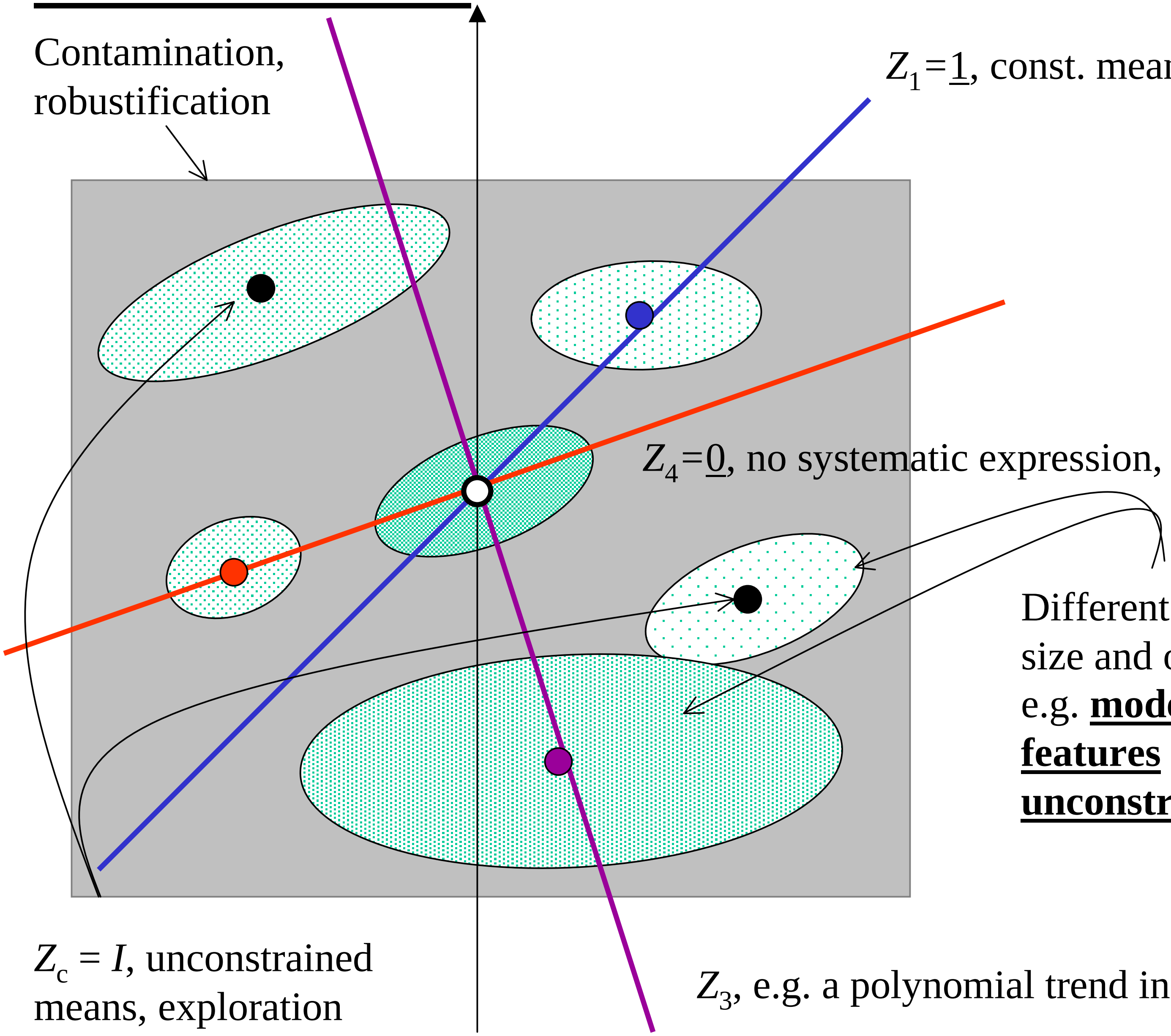
Different weights (π_c), but same shape, size and orientation (Σ) from S. e.g. **spherical**, **diagonal** and **unconstrained**, but other classes are possible.

$Z_c = I$, unconstrained means, exploration

Z_3, e.g. a polynomial trend in $temp_t$

Another cartoon…

Linear constraints on mean patterns



Contamination, robustification

$Z_1=\underline{1}$, const. mean pattern, filtering

$Z_4=\underline{0}$, no systematic expression, filtering

Different weights (π_c), Shape, size and orientation (Σ_c) from *S*. e.g. **modeled to share certain features** (but not others), or **unconstrained**.

$Z_c = I$, unconstrained means, exploration

Z_3, e.g. a polynomial trend in $temp_t$

Log likelihood(s):

Unobserved component membership vectors

$$X_i \in R^T,\ m_i \in \{0,1\}^C\ ,\ i = 1 \ldots N$$

$$\pi = (\pi_1 \ldots \pi_{C1})'$$

T-variate normal density

$$f_i(\tau) = (\varphi(X_i; Z_1\beta_1, \Sigma) \ldots \varphi(X_i; Z_{C-1}\beta_{C-1}, \Sigma), \varphi(X_i; \mu_C, \sigma_C^2 I))'$$

$$l_X(\vartheta) = \sum_{i=1}^{N} \log(\pi' f_i(\tau))$$

"incomplete"

$$l_{X,M}(\vartheta) = \sum_{i=1}^{N} m_i' \log(f_i(\tau)) + \sum_{i=1}^{N} m_i' \log(\pi)$$

"complete"

Important:

in principle, the X's may contain missing values that will end up in the category of unobserved data (not in the incomplete likelihood), and will be imputed by the EM algorithm – next.

Numerical maximization via EM algorithm:

E) Using the current parameter values compute

$$\overline{m}_i = E(m_i \mid X_i) = (\hat{\pi}' f_i(\hat{\tau}))^{-1} diag(\hat{\pi}) f_i(\hat{\tau}) , \quad i = 1 ... N$$

M) Substitute the current parameter values with the maximum of

$$\bar{l}_{X,M}(\vartheta) = E(l_{X,M}(\vartheta) \mid X) = \sum_{i=1}^{N} \overline{m}_i ' \log(f_i(\tau)) + \sum_{i=1}^{N} \overline{m}_i ' \log(\pi)$$

Iterate until convergence.

Initialization: $\overline{m}_i^{(0)}\ , i = 1..N$

memberships from a k-means clustering with *k*=*C*-1. Or other strategies (dependence on initialization is an issue also here)

Outcomes, from the last iteration:

$\hat{\pi}_c \;, c = 1 \ldots C-1$ ← Estimated ***weights***

$\hat{\mu}_c = Z_c \hat{\beta}_c \;, c = 1 \ldots C-1$ ← Estimated ***mean patterns***

$\hat{\Sigma}_c \in S \;, c = 1 \ldots C-1 \;\text{ or }\; \hat{\Sigma} \in S$ ← Estimated ***within-component variability structure(s)***

$\hat{\pi}_C$ and possibly $\hat{\mu}_C \;, \hat{\sigma}^2_C$ ← Estimated ***contamination parameters***

$\hat{p}_i = \overline{m}_i \;, i = 1 \ldots N$

Estimated vectors of conditional prob’s; ***membership probabilities***

Cluster formation:

$$i \in Cluster(c) \quad \leftrightarrow \quad \max\{\hat{p}_{i1} \ldots \hat{p}_{iC}\} = p_i^* = \hat{p}_{ic}$$

or, threshold $\gamma \in (0,1)$

$$i \in Cluster(c) \quad \leftrightarrow \quad \max\{p_i^*; \gamma\} = p_i^* = \hat{p}_{ic}$$

residual $(C+1)$th class for $i : p_i^* < \gamma$

Their distribution’s high end concentration gives interesting info on ***“lumpiness”*** of the data, in the context established by choice of *C* and constraints specification

First application:

Spellman et al., 2000, expression of yeast genes on a time course covering 2+ cell cycles. Log ratios; baseline = unsynchronized culture. Select 800 genes with periodic expression profiles. Halter et al., 2000 restrict attention to T=12 equispaced time points recovering 2 cell cycles, and N=696 profiles without missing values (most of the variability of the data cloud is captured by the first two principal components; data do not appear “lumpy”).

We use this 696 x 12 data matrix, but do not center and standardize by row/gene profile.

- No missing value imputation;
- contamination = spherical normal;
- common within component covariance structure.

Fits in first application:

- K-means, k=8 (initialization for all mixture fits below)
- Mix. Fit A: closest to k-means. *C*-1=8 regular components, plus contamination. Unconstrained mean patterns. Spherical within-comp. cov. structure (var. about mean pattern equal and uncorr. over t's).
- Mix. Fit B: relaxation of A; diagonal within-comp. cov. structure (var. about mean pattern different but uncorr. over t's).
- [Mix. Fit C: relaxation of B; unconstrained within-comp. cov. structure (var. about mean pattern different and freely corr over t's)].
- Mix. Fit D: a restriction of B; mean patterns modeled as

$$\boxed{\mu_{ct} = \underbrace{(\beta_{c1}+\beta_{c2}t)+(\beta_{c3}+\beta_{c4}t)}\sin\left(\frac{(t-shift_c)2\pi}{period}\right) \quad , \quad t=1...12\,, c=1...8}$$

β 's (continuously) optimized by EM

optimized at the outset
over a grid

Second application:

Gasch A.P., Spellman P.T., Kao C.M., Carmel-Harel O., Eisen M.B., Storz G., Botstein D., Brown P.O. (2001), Genomic Expression Programs in the Response of Yeast Cells to Environmental Changes, *Molecular Biology of the Cell* **11** 4241-4257.

N=6152 known and putative genes on over 140 conditions. We concentrate on a T=8 time course for heat shock (25 to 37C, minute 5, 10, 15, 20, 30,40, 60, 80). Log ratios; baseline=pooling equal amounts of all experimental samples. The profiles of 2509 genes (40.78% of the total) have missing values.

We use this 6152x8 matrix, without centering and standardize by row/gene profile.

- Missing value imputation;
- contamination = uniform on data range;
- allow for different within component covariance specifications (also different)

Fits in second application:

- free means, EEE covariances: C-1=7, common within component covariance structure, unconstrained.
- free means and UUE covariances: C-1=7, each component has a common (but not fixed) correlation structure, but differences in overall variability volume and distribution over the time course are allowed.

(many more, also modeling means, not presented)