Bayesian Two-way Clustering for Gene Expression Data

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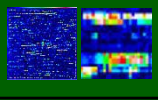
12 July 2003



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Motivation: Obvious potential for Bayesian and EB methods in gene expression analysis: can they be made to work?

BGX project, BBSRC funded

with [illegible], Clare [illegible]ewin and Anne-Mette H[illegible] (Imperial), in collaboration with Helen Causton and Tim Aitman and colleagues (CSC/IC Microarray Centre)

Model-based, flexible approach to gene expression analysis

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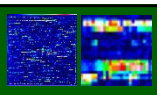
Plan



- Variation and uncertainty in gene expression
- Hierarchical models
- Simultaneous inference
- Common framework, including clustering
- Initial experiments with layer models

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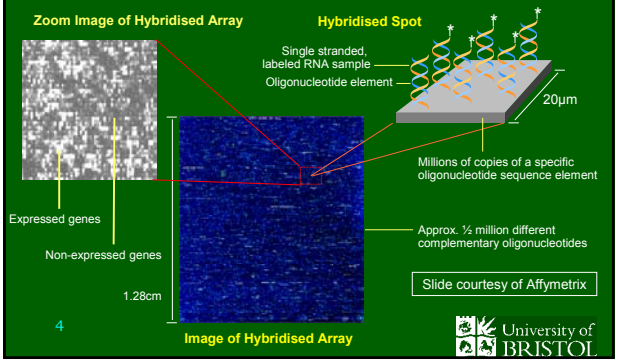
Gene expression using Affymetrix chips



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Variation and uncertainty

Gene expression data (e.g. Affymetrix™) is the result of multiple sources of variability

- condition/treatment
- biological
- array manufacture
- imaging
- technical
- within/between array variation
- gene-specific variability

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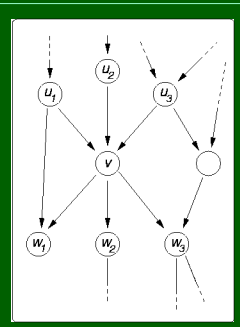
Hierarchical models

Variables at several levels - allows modelling of complex systems



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Bayesian hierarchical models

One of the most important benefits of the Bayesian approach has nothing much to do with having real quantitative prior information

- it has more to do with the structures connecting variables
- especially when there is uncertainty at more than one level

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The Bayes orthodoxy

- Should avoid a plug-in approach -- all sources of variation should be assimilated
- Propagates uncertainty
- 'Borrows strength' - shares out information - according to principle
- Avoids over-optimistic inference

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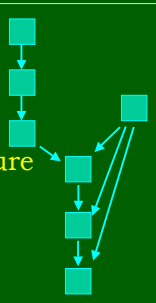
Gene expression is a hierarchical process

- Substantive question
- Experimental design
- Sample preparation
- Array design & manufacture
- Gene expression matrix
- Probe level data
- Image level data



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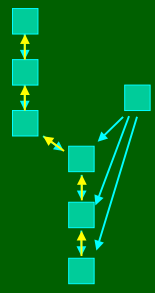
Bayes in hierarchical models

- The arrows represent (top down) model specification, not the order in which operations are performed
- Once specified, model unknowns should be estimated simultaneously
- (We cannot yet claim all of this is practical in gene expression)



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Additive models for (log-) gene expression

The simplest model: gene + sample

$$y_{gs} = \alpha_g + \beta_s + \varepsilon_{gs}$$

g=gene
s=sample/condition

Under standard conditions, the (least-squares) estimates of gene effects are

$$\hat{\alpha}_g = \bar{y}_{g.} - \bar{y}_{..}$$

The model generates the method, and in this case performs a simple form of normalisation

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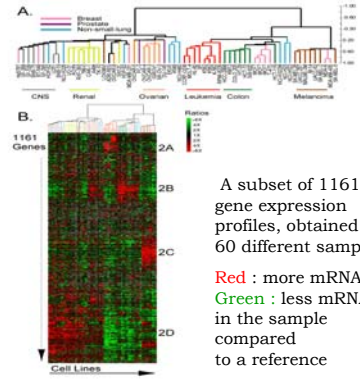
Hierarchical clustering of samples



A subset of 1161 gene expression profiles, obtained in 60 different samples

Red : more mRNA
Green : less mRNA in the sample compared to a reference

The gene expression profiles cluster according to tissue of origin of the samples

Ross et al, Nature Genetics, 2000

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Non-model-based clustering

- Many clustering algorithms have been developed and used for exploratory purposes
- They rely on a measure of 'distance' (dissimilarity) between gene or sample profiles, e.g. Euclidean
- Hierarchical clustering proceeds in an agglomerative manner: single profiles are joined to form groups using the distance metric, recursively
- Good visual tool, but many arbitrary choices → care in interpretation!

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Model-based clustering

- Build the cluster structure into the model, rather than estimating gene effects (say) first, and post-processing to seek clusters
- Bayesian setting allows use of real prior information where it is exists (biological understanding of pathways, etc, previous experiments, …)

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A common framework for specifying gene expression models

For ease of exposition, consider only gene expression matrix y_{gs}

g=gene s=sample/condition

with no structure to samples

(although incorporating experimental structure is a key goal for later)

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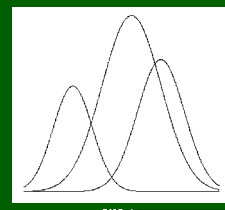
Clustering via additive model

(single sample first!)

$$y_g = \alpha + \varepsilon_g$$

g=gene

$$y_g = \alpha + \gamma_{T_g} + \varepsilon_g$$



T_g= unknown cluster to which gene g belongs
This is a mixture model

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Clustering via additive model

(multiple samples)

$$y_{gs} = \alpha_g + \beta_s + \varepsilon_{gs}$$

s=sample/condition
g=gene

$$y_{gs} = \alpha_g + \beta_s + \gamma_{T_g s} + \varepsilon_{gs}$$

T_g= unknown cluster to which gene g belongs
→ clustering of gene profiles

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Clustering via additive model

$$y_{gs} = \alpha_g + \beta_s + \gamma_{T_g s} + \varepsilon_{gs}$$

T_g=cluster to which gene g belongs

$$y_{gs} = \alpha_g + \beta_s + \delta_{gU_s} + \varepsilon_{gs}$$

U_s=cluster to which sample s belongs

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Two-way Clustering via additive model

$$y_{gs} = \alpha_g + \beta_s + \gamma_{T_g s} + \varepsilon_{gs}$$

$$y_{gs} = \alpha_g + \beta_s + \delta_{gU_s} + \varepsilon_{gs}$$

$$y_{gs} = \alpha_g + \beta_s + \gamma_{T_g s} + \delta_{gU_s} + \varepsilon_{gs}$$

or

$$y_{gs} = \alpha_g + \beta_s + \gamma_{T_g U_s} + \varepsilon_{gs}$$

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Lazzeroni and Owen 'Plaid' model

$$y_{gs} = \alpha_g + \beta_s + \gamma_{T_g s} + \varepsilon_{gs}$$

Now write ρ_{gh}=1 if and only if T_g=h, 0 otherwise

$$y_{gs} = \alpha_g + \beta_s + \sum_h \rho_{gh}\gamma_s^{(h)} + \varepsilon_{gs}$$

h denotes a 'cluster', 'block' or 'layer' - and now we allow them to overlap

.... continued over ....

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'Plaid' model

$$y_{gs} = \alpha_g + \beta_s + \sum_h \rho_{gh}\gamma_s^{(h)} + \varepsilon_{gs}$$

$$y_{gs} = \sum_h \rho_{gh}\kappa_{sh}\gamma_{gs}^{(h)} + \varepsilon_{gs}$$

h denotes a 'cluster', 'block' or 'layer' – pathway?

ρ_{gh}= 0 or 1 and κ_{sh}= 0 or 1

$$\gamma_{gs}^{(h)} = \mu^{(h)} + \alpha_g^{(h)} + \beta_s^{(h)}$$

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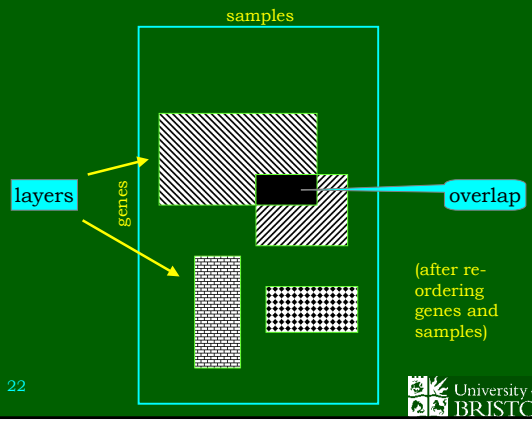

(after re-ordering genes and samples)

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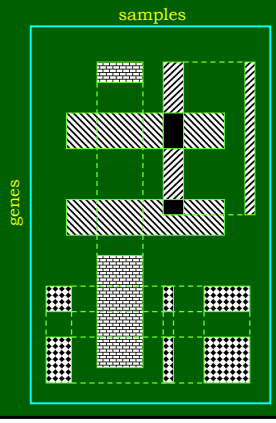

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MacKay and Miskin model

Instead of $$y_{gs} = \sum_h \rho_{gh}\kappa_{sh}\gamma_{gs}^{(h)} + \varepsilon_{gs}$$

where h denotes a 'cluster', 'block' or 'layer';

ρ_{gh}= 0 or 1 and κ_{sh}= 0 or 1

MacKay and Miskin take simply

$$y_{gs} = \sum_h a_s^{(h)} b_g^{(h)} + \varepsilon_{gs}$$

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Markov chain Monte Carlo (MCMC) computation

- Fitting of Bayesian models hugely facilitated by advent of these simulation methods
- Produce a large sample of values of all unknowns, ≈ from posterior given data
- Easy to set up for hierarchical models
- BUT can be slow to run (for many variables!)
- and can fail to converge reliably

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Simultaneous inference

- An important example of the flexibility of MCMC computation in a Bayesian model: inference about several unknowns at once.
- e.g. not only 'which gene has the biggest estimated differential effect?', but also 'how probable is it that this gene has the biggest differential effect?'

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