Parametric Empirical Bayes Methods for Microarrays

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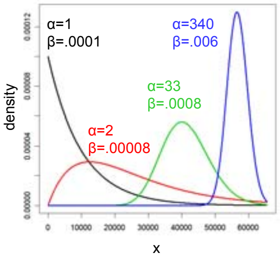
- Kendziorski, C. M., Newton, M. A., Lan, H., Gould, M. N. (2003). On parametric empirical Bayes methods for comparing multiple groups using replicated gene expression profiles. *Statistics in Medicine*. **22**, 3899-3914.
- Newton, M. A. and Kendziorski, C. M. (2003). Parametric empirical Bayes methods for microarrays. Chapter 11 of *The Analysis of Gene Expression Data*. Springer. New York.

The Gamma Distribution

- $X \sim \text{Gamma}(\alpha, \beta)$
- $f(x)=\frac{\beta^{\alpha}}{\Gamma(\alpha)}x^{\alpha-1}e^{-\beta x}$ for $x>0$.
- $E(X)=\alpha / \beta$
- $\text{Var}(X)= \alpha / \beta^2$



A Model for the Data from a Two-Treatment Experiment

- Assume there are J genes indexed by j=1, 2, ..., J.
- Data for gene j is $\mathbf{x}_j = (x_{j1}, x_{j2}, ..., x_{jI})$ where x_{ji} is the normalized measure of expression on the original scale for the jth gene and ith experimental unit.
- Let s_1 denote the subset of the indices {1,...,I} corresponding to treatment 1.
- Let s_2 denote the subset of the indices {1,...,I} corresponding to treatment 2.

The Model (continued)

- Assume that each gene is differentially expressed (DE) with an unknown probability p, and equivalently expressed (EE) with probability 1-p.
- If gene j is equivalently expressed, then

$$x_{j1}, x_{j2}, ..., x_{jI} \overset{\text{i.i.d.}}{\sim} \text{Gamma}(\alpha , \lambda_j) \text{ with mean } \alpha / \lambda_j ,$$

$$\text{where } \lambda_j \sim \text{Gamma}(\alpha_0 , v)$$

The Model (continued)

- If gene j is differentially expressed, then

$$\{x_{ji} : i \text{ in } s_1\} \overset{\text{i.i.d.}}{\sim} \text{Gamma}(\alpha , \lambda_{j1}) \text{ with mean } \alpha / \lambda_{j1} ,$$

$$\text{where } \lambda_{j1} \sim \text{Gamma}(\alpha_0 , v), \text{ and}$$

$$\{x_{ji} : i \text{ in } s_2\} \overset{\text{i.i.d.}}{\sim} \text{Gamma}(\alpha , \lambda_{j2}) \text{ with mean } \alpha / \lambda_{j2} ,$$

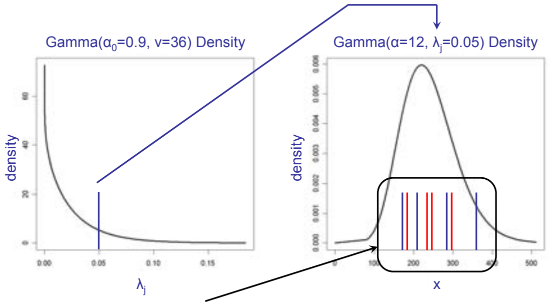
$$\text{where } \lambda_{j2} \sim \text{Gamma}(\alpha_0 , v).$$

- All random variables are assumed to be independent.
- p, α, α_0 , and v are unknown parameters to be estimated from the data.

An example of how the model is imagined to generate the data for the j^{th} gene.

- Suppose p=0.05, α=12, α_0=0.9, and v=36.
- Generate a Bernoulli random variable with success probability 0.05. If the result is a success the gene is DE, otherwise the gene is EE.
- If EE, generate λ_j from Gamma(α_0=0.9, v=36).
- Then generate i.i.d. expression values from Gamma(α=12, λ_j).

If gene is EE…

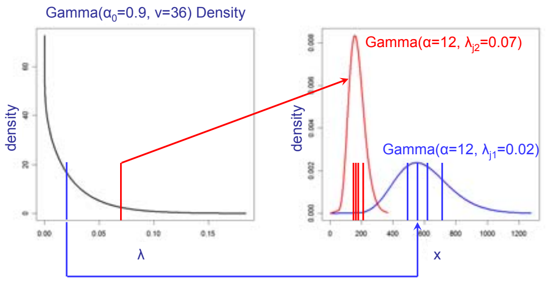


Expression values for the j^{th} gene. Trt 1 and Trt 2

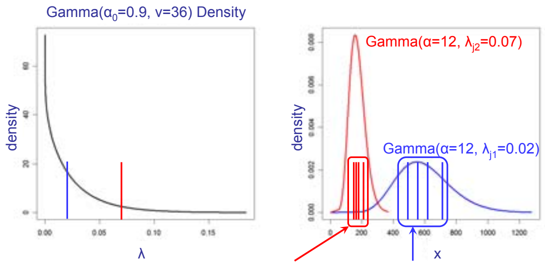
Example Continued

- If the gene is DE, generate λ_{j1} and λ_{j2} independently from Gamma(α_0=0.9, v=36) .
- Then generate treatment 1 expression values i.i.d. from Gamma(α=12, λ_{j1}), and
- generate treatment 2 expression values i.i.d. from Gamma(α=12, λ_{j2}).

If gene is DE…



If gene is DE…



Trt 2 Data Trt 1 Data

Coefficient of Variation is Constant across Gene-Treatment Combinations

- Coefficient of Variation = CV = sd / mean
- Conditional on the mean for a gene-treatment combination, say α / λ_{jk}, the CV for the expression data is the CV of Gamma(α, λ_{jk}).
- CV of Gamma(α, λ_{jk}) is $(\alpha^{1/2}/\lambda_{jk})/(\alpha/\lambda_{jk})=1/\alpha^{1/2}$.
- Note that α is assumed to be the same for all gene-treatment combinations.

Marginal Density for Gene j

$$f(\mathbf{x}_j) = p\, f_{DE}(\mathbf{x}_j) + (1\text{-}p)\, f_{EE}(\mathbf{x}_j)$$

Marginal Likelihood for the Observed Data

$$f(\mathbf{x}_1)\, f(\mathbf{x}_2) \cdots f(\mathbf{x}_J)$$

Use the EM algorithm to find values of p, α, α_0, and v that make the log likelihood as large as possible.

The posterior probability of differential expression for gene j is obtained by replacing p, α, α_0, and v in

$$\frac{p\, f_{DE}(\mathbf{x}_j)}{p\, f_{DE}(\mathbf{x}_j) + (1\text{-}p)\, f_{EE}(\mathbf{x}_j)}$$

with their maximum likelihood estimates.

Software for EBArrays is available at http://www.biostat.wisc.edu/~kendzior.

Extension to Multiple Treatment Groups

- If there are 3 treatment groups, each gene can be classified into 5 categories rather than just the two categories EE and DE:

  a) 1=2=3   b) 1=2≠3   c) 1≠2=3
  d) 1=3≠2   e) 1≠2 , 2≠3, 1≠3.

- Extensions to more than 3 groups can be handled similarly.