

Modeling Dose-response Trends in Microarray Experiments: Hierarchical Bayesian Approach

Abstract

Keywords: Dose-response curve; Microarray; Hierarchical Bayesian Models; Isotonic regression; Deviance information criterion.

1 Introduction

A common experiment in early drug development is a dose-response study that is set up to assess the biological activity of a chemical compound. In such a study, the response of primary interest is measured at several increasing dose levels. Typically, the first dose level is a control group with zero dose. In recent years, dose-response studies were extended to the microarray setting, in which the arrays are administered to measure intensities of thousands of genes simultaneously. The goal of the experiment is to identify genes, whose expression is affected by dose.

In the context of dose-response microarray experiments, Hu *et al.* (2005) proposed to use the so called M statistics based on isotonic regression, in order to test the null hypothesis against ordered restricted alternatives, i.e,

$$\begin{array}{l} H_0 : \mu_0 = \mu_1 = \mu_2 = \mu_3 \\ H_1^{up} : \mu_0 \leq \mu_1 \leq \mu_2 \leq \mu_3 \end{array} \quad \text{or} \quad \begin{array}{l} H_0 : \mu_0 = \mu_1 = \mu_2 = \mu_3 \\ H_1^{dn} : \mu_0 \geq \mu_1 \geq \mu_2 \geq \mu_3 \end{array} \quad (1)$$

with at least one equality. All the possible models under the ordered alternative hypothesis for dose-response microarray experiments with four doses are presented in Table 1. Note that for dose-response microarray experiment with K , there exist finite number of monotone trends under both direction.

Table 1: The set of seven possible monotonic dose-response models for an experiment with four dose levels. μ_i is the mean response of dose level i , where $i = 0, 1, \dots, K - 1$

| Model | Up: Mean Structure | Down: Mean Structure |
|-------|---------------------------------|---------------------------------|
| g_1 | $\mu_0 = \mu_1 = \mu_2 < \mu_3$ | $\mu_0 = \mu_1 = \mu_2 > \mu_3$ |
| g_2 | $\mu_0 = \mu_1 < \mu_2 = \mu_3$ | $\mu_0 = \mu_1 > \mu_2 = \mu_3$ |
| g_3 | $\mu_0 < \mu_1 = \mu_2 = \mu_3$ | $\mu_0 > \mu_1 = \mu_2 = \mu_3$ |
| g_4 | $\mu_0 < \mu_1 = \mu_2 < \mu_3$ | $\mu_0 > \mu_1 = \mu_2 > \mu_3$ |
| g_5 | $\mu_0 = \mu_1 < \mu_2 < \mu_3$ | $\mu_0 = \mu_1 > \mu_2 > \mu_3$ |
| g_6 | $\mu_0 < \mu_1 < \mu_2 = \mu_3$ | $\mu_0 > \mu_1 > \mu_2 = \mu_3$ |
| g_7 | $\mu_0 < \mu_1 < \mu_2 < \mu_3$ | $\mu_0 > \mu_1 > \mu_2 > \mu_3$ |

Lin *et al.* (2007) discussed several testing procedures, namely, the likelihood ratio test, Williams (1972), Marcus (1976)), M and the modified M statistics. Lin *et al.* (2009) used a multiple-contrast test in order to test the hypothesis above. Note that it is important in these methods to first decide on the direction of the monotone trends before investigating dose-response relationship between gene expression and doses. However, for microarray experiments, the direction of the monotone trends is unknown for each gene. As a result, Lin *et al.* (2007) proposed to determine the likelihood of each gene under both the upward and downward monotone trends. Then, assign each gene to a direction where its likelihood is the maximum. Conditioning on the direction of monotone trends, the existing frequentists methods (the likelihood ratio test, the M and the modified M statistics) can then be used to establish the dose-response relationship. Note that these frequentists methods seek evidence in the data to reject or not to reject the null hypothesis of no dose-response relationship.

In this paper, we focus on a hierarchical Bayesian modeling approach for dose-response microarray experiments. The Bayesian approach seeks evidence in the data under both the null and alternative hypotheses. This is made possible by fitting all possible competing

models under both the null and alternative hypotheses and select the most suitable model for each gene using deviance information criteria (DIC) suggested by Spiegelhalter *et al.* (1998) and Spiegelhalter *et al.* (2002). The deviance information criterion has been used extensively in literature for the purpose of model selection. Erkanli *et al.* (1999), Rahman *et al.* (1999) and Gelfand *et al.* (2000) used it for model selection within the Bayesian framework. In the context of hierarchical models, Berg *et al.* (2004) applied the DIC for model selection in stochastic volatile model. Zhu and Carlin (2000) applied the DIC to model selection for hierarchical models in medical applications. And Green and Richardson (2002) use DIC as a model selection tool in an application involving hierarchical modeling of the spatial heterogeneity of the rare count data arising in disease mapping. Recently, a modification of the DIC for model selection in missing data context was proposed and applied by McGrory and Titterton (2007).

The estimation of dose effects on gene expression under the monotone constraint are obtained by imposing the constraint on the prior distribution of dose specific parameters in the Bayesian approach. In particular, Gelfand *et al.* (1992) suggested to assign a zero value to the posterior distribution of the parameters whenever the posterior draw does not fulfill the order constraint. However, this makes equality constraints between parameters impossible, as this can not be observed from the posterior distribution of a continuous distribution. To circumvent this problem, we considered two approaches within the Bayesian framework. Our first approach is to consider the null model as a model with one parameter μ , that is, $\mu_0 = \mu_1 = \mu_2 = \mu_3 = \mu$ and considered $\mu_0 < \mu_1 < \mu_2 < \mu_3$ and $\mu_0 > \mu_1 > \mu_2 > \mu_3$ as the direction specific alternative models. This first approach replaces the equalities between parameters in the alternative models with small nonnegative value. For example, consider a model whose true dose-response relationship is $\mu_0 = \mu_1 < \mu_2 < \mu_3$. This model can be fitted as $\mu_0 < \mu_1^* < \mu_2 < \mu_3$, where $\mu_1^* = \mu_0 + \delta$ and δ is a nonnegative value. Note that this approach may favour the null model, because monotone genes with at least one equality constraint may receive more penalty than its gain in likelihood. In the second approach, we considered all the possible models under the ordered restricted alternatives hypothesis. A gene is considered to have no dose-response relationship if the value of DIC using the null

model is smaller than the minimum value of DIC using the alternative models.

The rest of this paper are organized as follows: after introduction of the data used for the analysis, we formulate the dose-response hierarchical Bayesian model in Section 3. In particular, we discuss constrain prior distribution in Section 3.1 and the model selection criteria in section 3.2. Section 4 is devoted to the data analysis; while in Section 5, we discuss the results and end with discussion and conclusion in Section 6

2 Data

The case study data used in this paper come from an experiment where the human epidermal squamous carcinoma cell line A431 was grown in Dulbecco's modified Eagle's medium, supplemented with L-glutamine (20mM), Gentamycin (5 mg/ml) and 10% fetal bovine serum. The cells were pretreated with three different compounds. RNA was harvested using RLT buffer (Qiagen). In total of 12 microarrays were used under four conditions (three higher doses and one control) with three arrays per group and 16,998 genes on each array. All microarray-related steps including the amplification of total RNAs, labeling, hybridization and scanning were carried out as described in the GeneChip Expression Analysis Technical Manual, Rev.4 ((Affymetrix, 2004)). Biotin-labeled target samples were hybridized to human genome arrays U133 A 2.0 containing probe sets interrogation approximately 22,000 transcripts from the UniGene database (Build 133). Hybridization was performed using 15 μ g of cRNA for 16 h at 45⁰C under continuous rotation at 60rpm. Arrays were stained in Affymetrix Fluidics stations using streptavidin/phycoerythrin staining. Thereafter, arrays were scanned with the Affymetrix scanner 3000, and images were analyzed using the GeneChip Operating System v1.1 (GCOS, Affymetrix). The collected data was quantile normalized in two steps: first within each sample group, and then across all sample groups. (Bolstad *et al.*, 2002).

3 Hierarchical Bayesian Dose-response Models

3.1 Model Formulation

We consider a dose-response microarray experiment described in Section 2. The first dose level is a control (zero dose). For each gene, the following linear model is considered

$$Y_{ij} = \mu_i + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2), \quad i = 0, 1, 2, \dots, K - 1, \quad j = 1, 2, 3, \quad (2)$$

where Y_{ij} is the gene expression at the i th dose level for sample j . μ_i is the average gene expression level at dose level i . We further assume that gene expression increases or decreases with doses, although not necessarily in a linear fashion. In the present study, we use hierarchical Bayesian models to estimate the parameters in the dose-response model in (2). Note that, since we assume that the dose-response relationship is monotone, we wish to estimate a model in which $\mu_0 \leq \mu_1 \leq \mu_2 \leq \dots \leq \mu_{K-1}$. The monotone constraints can be achieved by constraining the parameter space of μ . We assume that μ is a right-continuous nondecreasing function defined on $[0, d_i]$ where d_i is the highest dose level. We do not assume any deterministic relationship between μ_i and dose i but instead we specify a probabilistic model for μ_i at each distinct level of dose i .

The problem is to estimate μ under the order restrictions, $\mu_0 \leq \mu_1 \leq \dots \leq \mu_{K-1}$. Thus, the K dimensional parameter vector is constrained to lie in a subset S^K of R^K , where R^K is the parameter space for all possible values of dose specific parameters and S^K is a subset of R^K that satisfies the monotone constraints. The constrained set S^K is determined by the order among the components of μ . It is natural to incorporate the constraints into the specification of the prior distribution. Gelfand *et al.* (1992) show that (for a binary case) the posterior distribution of μ given the constraints is the unconstrained posterior distribution normalized such that

$$P(\mu|\mathbf{y}) \propto \frac{P(\mathbf{y}|\mu)P(\mu|\eta, \tau)}{\int_{S^K} P(\mathbf{y}|\mu)P(\mu|\eta, \tau)d\mu}, \quad \mu \in S^K. \quad (3)$$

Let $S_j^K(\mu_j, j \neq i)$ be a cross section of S^K defined by the constraints for the component

μ_i at a specified set of μ_i , where $j \neq i, j = 0, 1, 2, \dots, K - 1$. In our setting, $S_j^K(\pi_j, j \neq i)$ is the interval $[\mu_{i-1}, \mu_{i+1}]$. It follows from (3) that the posterior distribution for μ_i is given by

$$\begin{cases} P(\mu_i|y, \eta, \tau, \mu_{-i}) \propto P(y|\mu)P(\mu|\eta, \tau) & \mu_i \in S_j^K(\mu_j, j \neq i), \\ 0, & \mu_i \notin S_j^K(\pi_j, j \neq i). \end{cases} \quad (4)$$

Here, $\mu_{-i} = (\mu_1, \dots, \mu_{i-1}, \mu_{i+1}, \dots, \mu_K)$. Hence, when the likelihood and the prior distribution are combined, the posterior conditional distribution of $\mu_i|\mathbf{y}, \eta, \tau, \mu_{-i}$ is the standard posterior distribution restricted to $S_j^K(\mu_j, j \neq i)$ restricted to the interval $[\mu_{i-1}, \mu_{i+1}]$ (Gelfand and Kuo, 1991 for the binary case). This means that during the MCMC simulation the sampling from the full conditional distribution can be reduced to interval restricted sampling from the standard posterior distribution (Gelfand *et al.*, 1992).

The hierarchical model we consider is given by

$$\begin{aligned} y_i &\sim N(\mu_i, \tau_1^2) && \text{likelihood} \\ \mu_i &\sim N(\eta_{\mu_i}, \tau_{\mu_i})I(\mu_{i-1}, \mu_{i+1}) && \text{prior,} \end{aligned} \quad (5)$$

where $I(\mu_{i-1}, \mu_{i+1})$ an indicator variable which takes the value of 1 if $\mu_{i-1} \leq \mu_i \leq \mu_{i+1}$ and zero elsewhere. Note that η_{μ_i} and τ_{μ_i} are the prior mean and precision respectively for average gene expression level at dose i . In order to complete the specification of the hierarchical model in (5) we need to specify a hyper prior distributions for η_{μ_i} and τ_{μ_i} and τ_1^2 . We assume vague hyper prior distributions at the third level of the model, $\eta_{\mu_i} \sim N(0, 10000)$ and $\tau_1^{-2}, \tau_{\mu_i}^{-2} \sim \text{gamma}(1000, 1000)$.

Alternatively, suppose μ_0 is the smallest dose for the upward monotone trends, the order constrains can be incorporated for other parameters in the model using the following definition for the mean structure:

$$\mu_k = \mu_0 + \sum_{i=1}^k \delta_i \quad ; \quad \delta_i \geq 0. \quad (6)$$

The constraints on the parameter space can be incorporated in the hierarchical model by assuming truncated normal distributions for the components of $\boldsymbol{\delta} = (\delta_1, \delta_2, \dots, \delta_{K-1})$.

$$\delta_i \sim \text{truncated } N(\eta_{\delta_i}, \tau_{\delta_i}) \quad i = 1, 2, \dots, K - 1.$$

Here, the normal prior distribution is left truncated at 0 to ensure that $\delta_i \geq 0$. To complete the specification of the probability model, we assume flat hyper prior distributions

at the third level of the model, i.e. $\eta_{\delta_i} \sim N(0, 10000)$, $\tau_{\delta_i}^{-2} \sim \text{gamma}(1000, 1000)$ and $\mu_0 \sim N(\eta_0, \tau_0^{-2})$, with $\eta_0 \sim N(0, 10000)$ and $\tau_0^{-2} \sim \text{gamma}(1000, 1000)$

Let \mathbf{X}_1 and \mathbf{X}_2 be two design matrix given by

$$\mathbf{X}_1 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \end{pmatrix} \quad \text{and} \quad \mathbf{X}_2 = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 0 \\ 1 & 1 & 1 & 0 \\ 1 & 1 & 1 & 0 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{pmatrix}$$

Hence, in matrix notation the mean of the i^{th} dose level in models (5) and (6) are given by $\boldsymbol{\mu} = \mathbf{X}_1(\mu_0, \mu_1, \dots, \mu_{K-1})$ and $\boldsymbol{\mu}_i = \mathbf{X}_2(\mu_0, \boldsymbol{\delta})$, respectively.

It is relatively straight forward to incorporate constraints in Markov Chain Monte Carlo (MCMC) analysis of Bayesian models. Gelfand *et al.*, 1992 suggest first choosing a prior density without considering the constraint and discarding draws inconsistent with the constraint. For example, suppose we want to compare two models

$$\begin{aligned} g_0 : \mu_0 = \mu_1 = \mu_2 = \mu_3 \\ g_7 : \mu_0 < \mu_1 < \mu_2 < \mu_3 \end{aligned} \tag{7}$$

with normal priors on the model parameters. Gibbs sampling algorithm for posterior computation can then proceed by sampling from the unconstrained full conditional posterior density, with draws inconsistent with the constraint discarded. However, this implies that we already assigned probability 1 to g_7 and probability 0 to g_0 . Because except that the parameters $[\mu_0, \mu_1, \mu_2, \mu_3]$ are discrete, we can never sample values having $\mu_0 = \mu_1 = \mu_2 = \mu_3$.

However, we can formulate model g_0 as a model with 1 parameter. that is, $\mu_0 =$

$\mu_1 = \mu_2 = \mu_3 = \mu$ and model g_7 as a model with 4 ordered parameters. The models can therefore be evaluated based on how well the model describes the observed data relative to the complexity of the model.

Based on this reasoning, we propose in this paper an hierarchical Bayesian approach to model dose-response microarray data. First, we identify the direction of the dose-response relationship by fitting for each gene the models in 8. The direction of a gene is assigned based among the two models which has a smaller DIC value

$$\begin{aligned} g_{up} : \mu_0 < \mu_1 < \mu_2 < \mu_3 \\ g_{dn} : \mu_0 > \mu_1 > \mu_2 > \mu_3 \end{aligned} \tag{8}$$

3.2 Model Selection

A model selection procedure is needed in order to compare between the ordered constrained linear models (an example for dose-response microarray data with four dose levels is presented in Table 1). Goodness-of-fit and complexity of the models were assessed by using the DIC as proposed by ?. They suggested to measure the effective number of parameters (the complexity) in a model by the difference between the posterior expectation of the deviance and the deviance evaluated at the posterior expectation of μ , that is

$$P_D = E_{\boldsymbol{\mu}|\mathbf{y}}(D) - D(E_{\boldsymbol{\mu}|\mathbf{y}}(\boldsymbol{\mu})) = \bar{D} - D(\bar{\boldsymbol{\mu}}), \tag{9}$$

with deviance given by $D(\bar{\boldsymbol{\mu}}) = -2 \log P(\mathbf{y}|\bar{\boldsymbol{\mu}}) + 2 \log(f(\mathbf{y}))$. The second term in the deviance is a standardizing factor which does not depend on $\boldsymbol{\mu}$. We use -2 log likelihood of the saturated model, i.e treating the doses as a class variable. Hence, for the models described in 5 and 6 the deviance for normally distributed data is given by

$$D(\bar{\boldsymbol{\mu}}) = N \log(2\pi\hat{\sigma}^2) + \frac{\sum_{i=1}^K \sum_{j=1}^3 (Y_{ij} - \hat{\mu}_i)^2}{\hat{\sigma}^2} \tag{10}$$

In practice, $D(\bar{\boldsymbol{\mu}})$ and $\boldsymbol{\mu}$ can be monitored during the MCMC runs, \bar{D} is the sample mean of $D(\boldsymbol{\mu})$; while $D(\bar{\boldsymbol{\mu}})$ is the deviance evaluated at the posterior mean. For model selection,

Spiegelhalter *et al.* (1998, 2002) suggested to use the *Deviance Information Criterion (DIC)*:

$$DIC = \bar{D} + P_D = D(\bar{\boldsymbol{\mu}}) + 2P_D. \quad (11)$$

Smaller values of the *DIC* indicate a better fitting model. Unlike the frequentist approach, Bayesian approach favors model selection as an alternative to the classical testing of hypotheses. It seeks evidence in the data to support both the null and alternative hypotheses in order to establish an evidence for the choice of better model. It computes posterior probabilities distribution over a set of hypotheses or models in terms of relative support from the data.

4 Application to the Data

4.1 Direction of Dose-response Relationship

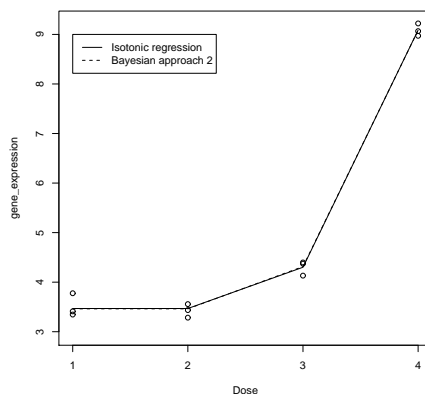
Order restricted inference for dose-response microarray data requires that the direction of order restriction be known. As a result, Lin *et al.* (2007) used global likelihood method (\hat{E}^2) to assign each gene to either upward or downward trends. This they achieved by maximizing the likelihood twice under both directions and assign a direction with the maximum likelihood for each gene. In the present paper, we consider using the DIC to assign direction of increasing or decreasing trends to each gene. A direction with the minimum DIC is assigned to each gene. Out of the 16998 genes, 16419 (97%) genes were assigned the same directions by both the DIC and the (\hat{E}^2). But the methods differ in the directions of 579 genes.

4.2 Establishing Dose-response Relationship

The interest in the analysis of dose-response microarray data is to establish a relationship between gene expression measurements and doses of a therapeutic compound. We formulate this problem as a set of competing models, among which the the best model is selected based on the DIC value. Due to the high dimensionality of the microarray data, it is not feasible to check the convergence of the Bayesian models for every models fitted. We therefore, assume

sufficiently large samples of 20,000 iterations, with the first 10,000 discarded as a burn-in part.

In our first approach, we considered strict inequality constraints (g7). The null model has smaller DIC values for 16,165 genes. This implies that only 833 genes will be selected as genes with dose-response relationship using this approach. When we compared the result with that of \hat{E}^2 , only 172 out of 833 genes were declared significant based on this frequentist approach. In our second approach, we compared all the possible 7 order restricted models described in Table 1. Genes for which the null model has the smallest DIC value are considered as non-interesting genes. There are 13,111 genes assigned to g0 and 3,887 genes assigned to the monotone models. Based on the frequentist approach by using \hat{E}^2 (Lin *et al.*, 2007), there are 13,499 genes whose null hypothesis of no dose-response relationship is not rejected, and 3,499 whose null hypothesis are rejected. We observed that for the interesting genes, the \hat{E}^2 and the DIC agreed only on 806 genes. But all 833 genes obtained from our first Bayesian approach are subset of the 3887 obtained from the second approach. We present in Figure 1 the plot of the isotonic regression, Bayesian estimates and the observed data. Both the estimates from the isotonic regression and Bayesian approach seem to closely follow the observed data.



(a)

Figure 1: Bayesian estimates under upward monotone constraints, the isotonic means and the observed data

5 Discussion

A dose response microarray experiment is increasingly gaining attention due to its ability to monitor gene expression measurements of thousands of genes under increasing doses of a therapeutic compound. The objective of such study is to establish dose response relationship between gene expression measurement and doses of a therapeutic compound.

In this paper, we considered Bayesian approach for the modeling of dose response microarray data and formulate the problem as a set of competing models. In order to establish dose-response relationship under monotone constraints, we propose to first assign a direction to each genes using the DIC. Specific to each direction, there are eight possible models. Seven of which are model with monotone trends but with different order of constraints and consequently with different shapes. These models are denoted with g1 - g7, where g7 is a model with strict inequality and g1 - g6 are models with at least one equality for dose specific means. We implemented the constrains on each model in their priors. The null model is a model with flat means. This model is denoted with g0 and correspond to no dose-response relationship.

Within the Bayesian framework, we first approximate the equality constrain between parameters of a monotone model with a small nonnegative value and therefore compare only between g0 and g7 under each direction. This approach results in 833 genes selected as genes with dose-response relationship. In our second approach, we compared between the null model and the every possible models under the alternative hypothesis. We only assigned gene to the null model if its DIC value under the null model is smaller than its minimum DIC values under the alternatives models. This results in 3,887 genes selected as genes with dose-response relationship. The difference in the result between the two approaches considered seems to confirm our reservation about the first approach. That is, it is likely to favour the null model. Note that genes obtained from the first approach are subset of genes from the second approach. We compared the results from the Bayesian models with the results obtained based on a frequentist approach using \hat{E}^2 . However, the results from the two method agreed only on 833 genes out of the 3,887 genes obtained from the Bayesian

approach and 3,499 from the frequentist approach. The models presented in this paper can be implemented with Winbugs or R packages ; R2Winbugs and Brugs.

References

- Affymetrix (2004) Genechip expression analysis. *Tech. rep.*, Affymetrix Santa Clara, CA.
- Berg, A., Meyer, R. and Yu, J. (2004) Deviance information criterion for comparing stochastic volatility models. *Journal of Business and Economic Statistics*, **22**, 107–119.
- Bolstad, B., Irizarry, R. A., Astrand, M. and Speed, T. (2002) A comparison of normalization methods for high density oligonucleotide array data based on bias and variance. *Bioinformatics*, **19**, 185–193.
- Erkanli, A., Soyer, R. and Costello, E. (1999) Bayesian inference for prevalence in longitudinal two-phase studies. *Biometrics*, **55**, 1145–1150.
- Gelfand, A., Ecker, M., Christiansen, C., Mclaughlin, T. and Soumerai, S. (2000) Conditional categorical response with application to treatment of acute myocardial infraction. *Applied Statistics*, **49**, 171–186.
- Gelfand, A. and Kuo, L. (1991) Nonparametric bayesian bioassay including ordered polytomous. *Biometrika*, **78**, 657–666.
- Gelfand, A., Smith, A. and Lee, T. (1992) Bayesian analysis of constrained parameters and truncated data using gibbs sampling. *Journal of the American Statistical Associations*, **87**, 523–532.
- Green, P. and Richardson, S. (2002) Hidden markov models ad disease mapping. *Journal of the American Statistical Associations*, **97**, 1055–1070.
- Hu, J., Kapoor, M., Zhang, W., Hamilton, S. and Coombes, K. R. (2005) Analysis of dose response effects on gene expression data with comparison of two microarray platforms. *Bioinformatics*, **21(17)**, 3524–3529.

- Lin, D., Shkedy, Z., Burzykowski, T., Gömann, H., De Bondt, A., Perera, T., Geerts, T. and Bijmens, L. (2009) Classification of trends in dose response microarray experiments using information theory selection methods. *Open Informatics*, **xx**, xx.
- Lin, D., Shkedy, Z., Yekutieli, D., Burzykowski, T., Gömann, H., De Bondt, A., Perera, T., Geerts, T. and Bijmens, L. (2007) Testing for trend in dose-response experiments: comparison of several testing procedures, multiplicity, and resampling-based inference. *Statistical Application in Genetics and Molecular Biology*, **6(1)**, article 26.
- Marcus, R. (1976) The powers of some tests of the equality of normal means against an ordered alternative. *Biometrika*, **63**, 177–183.
- McGrory, C. and Titterton, D. (2007) Variational approximation for bayesian model selection for finite mixture distribution. *Computational Statistics and Data Analysis*, **51(11)**, 5352–5367.
- Rahman, H., Wakefield, J., Stephens, D. and Falcoz, C. (1999) The bayesian analysis of pivotal pharmacokinetic study. *Statistics methods in medical research*, **8**, 195–216.
- Speigelhalter, D., Best, N. and Carlin, B. (1998) Bayesian deviance, the effective number of parameters, and the comparison of arbitrarily complex model. *Research Report 98-009, Division of Biostatistics, University of Minisota*.
- Speigelhalter, D., Best, N., Carlin, B. and Van de Linde, A. (2002) Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society, B.*, **64**, 1–34.
- Williams, D. (1972) The comparison of several dose levels with a zero dose control. *Biometrics*, **28**, 519–531.
- Zhu, L. and Carlin, B. (2000) Comparing hierarchical models for spatio-temporally misaligned data using teh deviance information criterion. *Statistics in medicine*, **19**, 2265–2278.