# Bayesian Multiplicity Control

## i.e., Bayesian methods of controlling for the 'look elsewhere effect'

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# Outline

- I. Introduction to multiplicity control
  - Introductory examples
  - The Bayesian Ockham's razor is not multiplicity control
  - A pedagogical example and the problem of test statistic dependency
  - Bayesian analysis does not automatically result in multiplicity control
- II. Types of multiplicity control

# I. Introduction to Multiplicity Control

# The need for multiplicity control:

In a recent talk about the drug discovery process, the following numbers were given in illustration.

- 10,000 relevant compounds were screened for biological activity.
- 500 passed the initial screen and were studied in vitro.
- 25 passed this screening and were studied in Phase I animal trials.
- 1 passed this screening and was studied in a Phase II human trial.

This could be nothing but noise, if screening was done based on 'significance at the 0.05 level.'

If no compound had any effect,

- about $10,000 \times 0.05 = 500$ would initially be significant at the 0.05 level;
- about $500 \times 0.05 = 25$ of those would next be significant at the 0.05 level;
- about $25 \times 0.05 = 1.25$ of those would next be significant at the 0.05 level
- the 1 that went to Phase II would fail with probability 0.95.

# The Two Main Approaches to Multiplicity Control

- *Frequentist approach:* A collection of techniques for penalizing or assessing the impact of multiplicity, so as to preserve an overall frequentist accuracy assessment.
  - Perhaps the most basic (and general) frequentist approach is to repeatedly simulate the multiple testing scenario, under the assumption of 'no signal' (e.g., only simulate from the background) and estimate the probability of a false discovery.
    - The problem is that this can be computationally infeasible in modern problems (e.g., detection of gravitational waves?)
  - Another common approach is to ignore the issue, assuming strict standards (e.g. 5-sigma) will cover up such sins.
- *Bayesian approach:* If a multiplicity adjustment is necessary, it is accommodated through prior probabilities associated with the multiplicities. Typically, the more possible hypotheses there are, the lower prior probabilities they each receive.

# An example of the danger of assuming that 'Strict Standards' will cover up multiplicity sins: Genome-wide Association Studies (GWAS)

- A typical GWAS study looks at, say, 20 (related) diseases and 100,000 genes (or SNPs), and attempts to determine which genes are associated with which diseases. (Note: 2,000,000 tests are being done here.)
- GWAS studies from 1997-2007 (about 50,000 published papers) almost universally failed to replicate (estimates of the replication rate are as low as 1%), because they were doing multiple testing at 'strict p-values' on the order of $10^{-3}$ or $10^{-4}$.
- A very influential paper in Nature (2007), by the Wellcome Trust Case Control Consortium, argued for a cutoff of $p < 5 \times 10^{-7}$.
- Later studies in GWAS recommended cutoffs as low as $5 \times 10^{-8}$, and this will be driven lower as the ability to perform more tests increases.
- Note that 5-sigma is a $p$-value of $3 \times 10^{-6}$.

## Bayes argument for the 2007 GWAS cutoff:

- Let $\pi_0$ and $\pi_1 = 1 - \pi_0$ be the prior probabilities at a given location on the genome of not having or having an association, respectively.
- Let $\alpha$ and $(1 - \beta(\theta))$ be the Type I error and power for testing the null hypothesis of no association with a given rejection region $\mathcal{R}$.
- The pre-experimental probability of a false positive is then $\pi_0\alpha$.
- The pre-experimental probability of a true positive is then $\pi_1(1 - \bar{\beta})$, where $(1 - \bar{\beta}) = \int(1 - \beta(\theta))\pi(\theta)d\theta$ is average power wrt the prior $\pi(\theta)$.
- Pre-experimental 'odds of true positive to false positive' $= \frac{\pi_1}{\pi_0} \times \frac{(1-\bar{\beta})}{\alpha}$ .
- For the GWAS study,
  - they choose $\frac{\pi_1}{\pi_0} = \frac{1}{100{,}000}$; $(1 - \bar{\beta}) = 0.5$; and stated that odds of $10 : 1$ in favor of a true positive to a false positive were desired.
  - Solving the above equation yielded a cutoff of $\alpha = 5 \times 10^{-7}$.
  - The key, was the Bayesian prior probability assessment (to control for multiple testing) of odds $\frac{\pi_1}{\pi_0} = \frac{1}{100{,}000}$.

# Bayesian Ockham's Razor is Not Multiplicity Control

- Ockham's razor is attributed to thirteen-century Franciscan monk William of Ockham (Occam in latin)

  *"Pluralitas non est ponenda sine necessitate."*

  (Plurality must never be posited without necessity.)

  *"Frustra fit per plura quod potest fieri per pauciora."*

  (It is vain to do with more what can be done with fewer.)

- Preferring the simpler of two hypothesis to the more complex when both agree with data is an old principle in science.

- Regard $H_0$ as *simpler* than $H_1$ if it makes *sharper predictions* about what data will be observed.

- Models are more complex if they have extra adjustable parameters that allow them to be tweaked to accommodate a wider variety of data.
  - "coin is fair" is a simpler model than "coin has unknown bias $\theta$"
  - $s = a + ut + \frac{1}{2}\,gt^2$ is simpler than $s = a + ut + \frac{1}{2}\,gt^2 + ct^3$

**Example:** *Perihelion of Mercury* (with Bill Jefferys)

In the 19th century it was known that there was an unexplained residual motion of Mercury's perihelion (the point in its orbit where the planet was closest to the Sun) in the amount of approximately 43 seconds of arc per century.

Various hypotheses:

- A planet 'Vulcan' close to the sun.
- A ring of matter around the sun.
- Oblateness of the sun.
- Law of gravity is not inverse square but inverse $(2 + \epsilon)$.

All these hypotheses had a parameter that could be adjusted to deal with whatever data on the motion of Mercury existed.

**Data in 1920:** $X = 41.6$ where $X \sim N(\theta \mid 2^2)$, $\theta$ being the perihelion advance of Mercury.

**Prior (before data) for gravity model $M_G$:** $\pi_G(\theta) = N(\theta \mid 0, 50^2)$.

- Symmetric about 0 (corresponding to inverse square law).
- Decreasing away from zero; normality is convenient.
- Initially, $\tau = 50$, because a gravity effect which would yield $\theta > 100$ would have had other observed effects.
- We will also consider utilization of classes of priors:
  - The class of all $N(\theta \mid 0, \tau^2)$ priors, $\tau > 0$.
  - The class of all symmetric priors that are nonincreasing in $|\theta|$.

**General Relativity (1915) model $M_E$:** Predicted $\theta_E = 42.9$, so no prior is needed. (Thus this is a 'simpler' model.)

**Bayes factor ("evidence" ratio in much of the physics literature):**

$$
\begin{aligned}
B_{EG} &= \frac{f_E(41.6)}{\int f_G(x \mid \theta)\pi_G(\theta)\, d\theta} \\
&= \frac{\frac{1}{\sqrt{8\pi}} \exp\left(-\frac{1}{8}(41.6-\theta_E)^2\right)}{\int \frac{1}{\sqrt{8\pi}} \exp\left(-\frac{1}{8}(41.6-\theta)^2\right) \frac{1}{50\sqrt{2\pi}} \exp\left(-\frac{1}{2\cdot 50^2}\theta^2\right)\, d\theta} \\
&= \frac{\frac{1}{\sqrt{8\pi}} \exp\left(-\frac{1}{8}(41.6-42.9)^2\right)}{\frac{1}{\sqrt{2\cdot 2504\pi}} \exp\left(-\frac{1}{2\cdot 2504}(41.6-0)^2\right)} = 28.6
\end{aligned}
$$

To alleviate worry about the choice of a particular prior, note that the lower bound on the Bayes factor

- over all $N(\theta \mid 0, \tau^2)$ priors is 27.76;
- over all symmetric nonincreasing (in $|\theta|$) priors is 15.04.

**Posterior probability of $M_E$** under the $N(\theta \mid 0, 50^2)$ prior and assuming prior probabilities $P(M_E) = P(M_G) = 1/2$, is

$$
P(M_E \mid x = 41.6) = \frac{1}{1 + (28.6)^{-1}} = 0.97\,.
$$

This is thus an example of the Bayesian Ockham's razor:

- Bayesian analysis automatically favors the simpler model if it explains the data almost as well as the complex model.
- The 'penalty' for the more complex model arises through the prior distribution assigned to its 'extra' parameters.

While this is a penalty favoring simpler models, it is *not* multiplicity control when dealing with multiple testing (or other multiplicities). That only happens through choice of the prior probabilities of models or hypotheses.

**Einstein multiplicity correction:** Apparently, Einstein had several theories of general relativity, and used the Mercury perihilion data to reject at least one of them.

Suppose he had three theories: $M_{E1}$, $M_{E2}$, and $M_{E3}$, and rejected the first two because of the Mercury data.

*Multiplicity correction:* Assign each $M_{Ei}$ prior probability 1/6 and $M_G$ prior probability 1/2. (In a situation where only one of the models can be correct, the model probabilities must sum to one.)

Then the posterior probability that $M_{E3}$ is correct is

$$P(M_{E3} \mid x = 41.6) = \frac{1}{1 + 3(28.6)^{-1}} = 0.91 \quad \text{(instead of the previous 0.97)}\,.$$

**Summary:** While, the more complex $M_G$ was penalized through the prior on $\theta$, the multiple models of Einstein were penalized by each getting only 1/3 of the prior probability assigned to Einstein.

# Pedagogical example: testing exclusive hypotheses and the problem of test statistic dependency

Suppose one is testing mutually exclusive hypotheses $H_i,\ i = 1, \ldots, m$, so that exactly one and only one of the $H_i$ is true.

**Bayesian analysis:** If the hypotheses are viewed as exchangeable, choose $P(H_i) = 1/m$ and analyze the data $\boldsymbol{x}$.

- Let $m_i(\boldsymbol{x})$ denote the marginal density of the data under $H_i$. (The data density integrated over the prior density for unknown parameters under $H_i$.) This is often called the *likelihood* of $H_i$ (or the *evidence* for $H_i$).
- The posterior probability of $H_i$ is

$$Pr(H_i \mid \boldsymbol{x}) = \frac{m_i(\boldsymbol{x})}{\sum_{j=1}^{m} m_j(\boldsymbol{x})} .$$

- Thus the likelihood $m_i(\boldsymbol{x})$ for $H_i$ is 'penalized' by a factor of $O(\frac{1}{m})$, resulting in multiplicity control.

**Null control:** If there is a good possibility of 'no effect' use, e.g.,

- $Pr(H_0) \equiv Pr(\text{no effect}) = 1/2$,
- $Pr(H_i) = 1/(2m)$.

**Example:** 1000 energy channels are searched for the Higgs boson. In each, one observes $X_i \sim N(x_i \mid \mu_i, 1)$, and at most one of $H_i : \mu_i > 0$ is true.

Suppose $x_5 = 3$, and the other 999 of the $X_i$ are standard normal variates.

- If testing in isolation $H_5^0 : \mu_5 = 0$ versus $H_5^1 : \mu_5 > 0$, with prior probabilities of 1/2 each and a standard unit information Cauchy prior on $\mu_i$ under $H_5^1$, then $Pr(H_5^1 \mid x_5 = 3) = \frac{m_5^1(3)}{m_5^1(3)+m_5^0(3)} = 0.96$.
- With multiplicity control, assigning $Pr(H_i) = 1/1000$, this becomes (on average over the 999 standard normal variates)
  $Pr(H_5^1 \mid \boldsymbol{x}) = \frac{m_5(\boldsymbol{x})}{\sum_{j=1}^{1000} m_j(\boldsymbol{x})} = 0.019$ (and 0.38 for $x_5 = 4$; and 0.94 for $x_5 = 5$)
- With null control in addition to multiplicity control, ($Pr(\text{no effect}) = 1/2$ and $Pr(H_i) = 1/(2000)$), this becomes $Pr(H_5^1 \mid \boldsymbol{x}) = 0.019$.
- If null control was employed but *pre-experimentally* the physicist decided to use all of the non-null mass on $H_5$, the answer would have *legitimately* been $Pr(H_5^1 \mid \boldsymbol{x}) = 0.96$.

*An aside:* This is the Bayesian solution regardless of the structure of the data; in contrast, frequentist solutions depend on the structure of the data.

**Example:** For each channel, test $H_{0i} : \mu_i = 0$ versus $H_{1i} : \mu_i > 0$.

*Data:* $X_i, i = 1, ..., m$, are $N(x_i \mid \mu_i, 1, \rho)$, $\rho$ being the correlation.

If $\rho = 0$, one can just do individual tests at level $\alpha/m$ (Bonferroni) to obtain an overall error probability of $\alpha$.

If $\rho > 0$, harder work is needed:

- Choose an overall decision rule, e.g., "declare channel $i$ to have the signal if $X_i$ is the largest value and $X_i > K$."
- Compute the corresponding error probability, which can be shown to be

$$\alpha = \Pr(\max_i X_i > K \mid \mu_1 = \ldots = \mu_m = 0) = E^Z \left[ 1 - \Phi \left( \frac{K - \sqrt{\rho} Z}{\sqrt{1-\rho}} \right)^m \right],$$

  where $\Phi$ is the standard normal cdf and $Z$ is standard normal.

Note that this gives (essentially) the Bonferroni correction when $\rho = 0$, and converges to $1 - \Phi[K]$ as $\rho \to 1$ (the one-dimensional solution).

The advantages here of Bayesian multiplicity control:

- Its implementation depends only on the prior probability assignment, and not on the structure of the data. Hence it is potentially much more computationally feasible.
- It is 'fully powered,' whereas adhoc frequentist procedures which achieve multiplicity control need not be. For instance, in the previous example of correlated data and as $\rho \to 1$,
  - the frequentist procedure with error probability 0.95 declares a discovery if $\max_i X_i > 1.65$, which could be right or wrong;
  - the Bayesian procedure has the rather remarkable property that, for more than two observations, the posterior probability of the true hypothesis goes to 1.

# Bayesian prior probability assignments do not automatically provide multiplicity control

- Suppose $X_i \sim N(x_i \mid \mu_i, 1)$, $i = 1, \ldots, m$, are observed.
- It is desired to test $H_i^0 : \mu_i = 0$ versus $H_i^1 : \mu_i \neq 0$ , $i = 1, \ldots, m$, but any test could be true or false regardless of the others.
- The simplest probability assignment is $Pr(H_i^0) = Pr(H_i^1) = 0.5$, independently, for all $i$.
- This does *not* control for multiplicity; indeed, each test is then done completely independently of the others. Thus $H_1^0$ is accepted or rejected whether $m = 1$ or $m = 1,000,000$.

**1.** The same holds in many other model selection problems such as variable selection: use of equal probabilities for all models does not induce any multiplicity control.

**2.** The above is a proper prior probability assignment. Thus, if these are one's real prior probabilities, no multiplicity adjustment is needed.

## Inducing multiplicity control in this simultaneous testing situation (Scott and Berger, 2006 JSPI; other, more sophisticated full Bayesian analyses are in Gönen et. al. (03), Do, Müller, and Tang (02), Newton et all. (01), Newton and Kendziorski (03), Müller et al. (03), Guindani, M., Zhang, S. and Mueller, P.M. (2007), . . .; many empirical Bayes such as Efron and Tibshirani (2002), Storey, J.D., Dai, J.Y and Leek, J.T. (2007), Efron (2010))

- Suppose $x_i \sim N(x_i \mid \mu_i, \sigma^2)$, $i = 1, \ldots, m$, are observed, $\sigma^2$ known, and test $H_i^0 : \mu_i = 0$ versus $H_i^1 : \mu_i \neq 0$.
- If the hypotheses are viewed as exchangeable, let $p$ denote the common prior probability of $H_i^1$, and *assume $p$ is unknown* with a uniform prior distribution. *This does provide multiplicity control.*
- Complete the prior specification, e.g.
  - Assume that the nonzero $\mu_i$ follow a $N(0, V)$ distribution, with $V$ unknown.
  - Assign $V$ the objective (proper) prior density $\pi(V) = \sigma^2/(\sigma^2 + V)^2$.

- Then the posterior probability that $\mu_i \neq 0$ is

$$p_i = 1 - \frac{\int_0^1 \int_0^1 p \prod_{j \neq i} \left( p + (1-p)\sqrt{1-w}\, e^{w {x_j}^2/(2\sigma^2)} \right) dpdw}{\int_0^1 \int_0^1 \prod_{j=1}^m \left( p + (1-p)\sqrt{1-w}\, e^{w {x_j}^2/(2\sigma^2)} \right) dpdw}.$$

- $(p_1, p_2, \ldots, p_m)$ can be computed numerically; for large $m$, it is most efficient to use importance sampling, with a common importance sample for all $p_i$.

**Example:** Consider the following ten 'signal' observations:
-8.48, -5.43, -4.81, -2.64, -2.40, 3.32, 4.07, 4.81, 5.81, 6.24

- Generate $n = 10, 50, 500,$ and $5000$ $N(0,1)$ noise observations.
- Mix them together and try to identify the signals.

| $n$ | The ten 'signal' observations | | | | | | | | | | #noise |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | -8.5 | -5.4 | -4.8 | -2.6 | -2.4 | 3.3 | 4.1 | 4.8 | 5.8 | 6.2 | $p_i > .6$ |
| 10 | 1 | 1 | 1 | .94 | .89 | .99 | 1 | 1 | 1 | 1 | 1 |
| 50 | 1 | 1 | 1 | .71 | .59 | .94 | 1 | 1 | 1 | 1 | 0 |
| 500 | 1 | 1 | 1 | .26 | .17 | .67 | .96 | 1 | 1 | 1 | 2 |
| 5000 | 1 | 1.0 | .98 | .03 | .02 | .16 | .67 | .98 | 1 | 1 | 1 |

Table 1: The posterior probabilities of being nonzero for the ten 'signal' means.

**Note 1:** The penalty for multiple comparisons is automatic.

**Note 2:** **Theorem:** $E[\#i : p_i > .6 \mid \text{all } \mu_j = 0] \to 0$ as $m \to \infty$, so the Bayesian procedure exerts very strong control over false positives. (In comparison, $E[\#i : \text{Bonferroni rejects} \mid \text{all } \mu_j = 0] = \alpha$.)

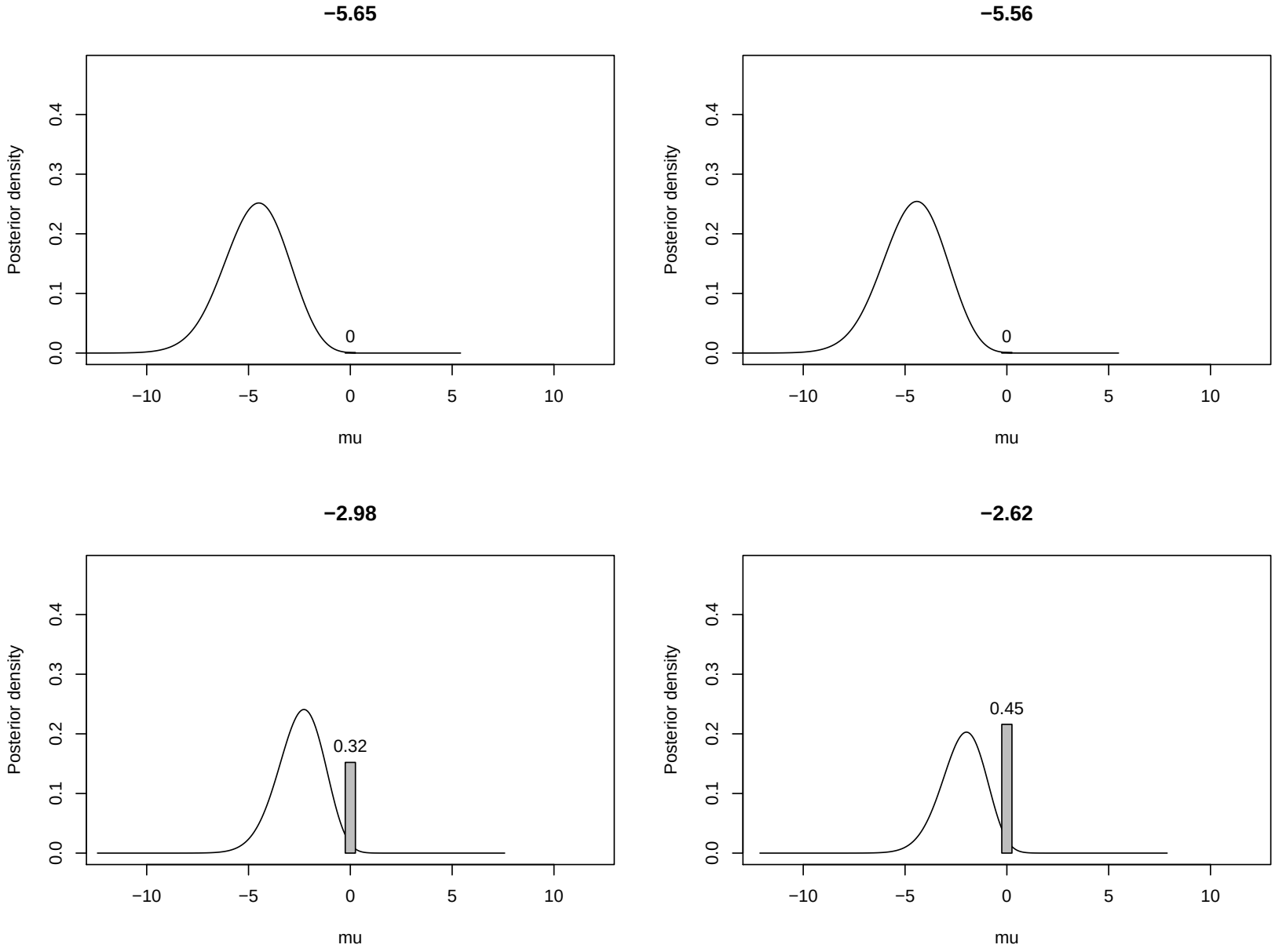



Figure 1: For four of the observations, $1 - p_i = \Pr(\mu_i = 0 \,|\, \boldsymbol{y})$ (the vertical bar), and the posterior densities for $\mu_i \neq 0$ .

## An Aside: Use for Discoveries

- $p_i$ gives the probability that $i$ is a discovery.
- The posterior density for $\mu_i \neq 0$ gives the magnitude of the effect of the possible discovery.
- If claiming $J$ discoveries, with probabilities $p_i$; the probability that *all* are discoveries can be computed from the posterior. (If approximate independence, $\prod_i p_i$.)
- If a discovery is claimed if $p_i > c$, the expected false discovery rate (Bayesian) is

$$\frac{\sum_{\{i:p_i>c\}}(1-p_i)}{\{\#i : p_i > c\}} < 1 - c\,.$$

## Use for Screening (Duncan, 65; Waller and Duncan, 1969)

- Separately specify the cost of a false positive and the cost of missing a true signal. Scott and Berger (06) use

$$L(\text{reject null}, \mu_i) = \begin{cases} 1 & \text{if } \mu_i = 0 \\ 0 & \text{if } \mu_i \neq 0\,, \end{cases}$$

$$L(\text{accept null}, \mu_i) = \begin{cases} 0 & \text{if } \mu_i = 0 \\ c|\mu_i| & \text{if } \mu_i \neq 0\,, \end{cases}$$

  where $c$ reflects the relative costs of each type of error.

- Posterior expected loss is minimized by rejecting $H_{0i}$ when

$$\pi_i > 1 - \frac{c \cdot \int_{-\infty}^{\infty} |\mu_i| \cdot \pi(\mu_i \mid \gamma_i = 1, \boldsymbol{x})\, d\mu_i}{1 + c \cdot \int_{-\infty}^{\infty} |\mu_i| \cdot \pi(\mu_i \mid \gamma_i = 1, \boldsymbol{x})\, d\mu_i}.$$

# Interim Summary

- Bayesian multiplicity control is distinct from the Ockham's razor effect of Bayesian analysis and is implemented through the assignment of prior probabilities of models. Because it enters through the prior probabilities there is never a loss in power when dealing with dependent testing situations, the bane of standard frequentist multiplicity control.
- Bayesian probability assignments can fail to provide multiplicity control. In particular, assigning all models equal prior probability fails in many situations (testing of exclusive hypotheses being an exception).
- A key technique for multiplicity control is to think hierarchically by specifying *unknown* inclusion probabilities for hypotheses or variables, and assigning them a prior distribution.
  - Assigning probability 1/2 to 'no signal' also provides null control, with little cost in power.
  - Any prior specified pre-experimentally is allowed.

# II. Types of Multiplicities

- **Class 1:** Multiplicities not affecting the likelihood function
  - Consideration of multiple (test) statistics or multiple priors
  - Interim or sequential analysis
  - Multiple endpoints
- **Class 2:** Multiplicities affecting the likelihood function
  - Choice of transformation/model
  - Multiple testing
  - Variable selection
  - Subgroup analysis
- **Class 3:** Issues arising from multiple studies of the same situation: meta-analysis, replication, ....

## **Class 1:** Multiplicities Not Affecting the Likelihood

- Consideration of multiple test statistics
  - *Example:* Doing a test of fit, and trying both a Kolmogorov-Smirnov test and a Chi-squared test.
  - Frequentists should either report all tests, or adjust; e.g., if $p_i$ is the p-value of test $i$, base testing on the *statistic* $p_{min} = \min p_i$.
- Consideration of multiple priors: a Bayesian must either
  - have principled reasons for settling on a particular prior, or
  - implement a hierarchical or robustness analysis over the priors.
- Interim analysis (also called optional stopping and sequential analysis)
  - Bayesians do not adjust, as the posterior is unaffected.
  - Frequentists should adjust: 'spending $\alpha$' for interim looks at the data with analysis.

*An example of the effect of Optional Stopping*: Suppose one achieves a $p$-value of 0.08 in a sample of size 20 in testing whether or not a normal mean is zero. Consider the following strategy (ubiquitous in psychology research):

- Take another five observations and stop (and publish) if $p < .05$ for the 25 observations.
- If still $p > 0.05$, take another 5 observations and check $p$ for the 30 observations, stopping if less than 0.05.
- Repeat up to 2 more times if necessary.

*Facts:* Even if the normal mean is 0 (no signal),

**1.** there is a 2/3 chance of ending up with $p < 0.05$ using this strategy;

**2.** if one kept repeating, one would be guaranteed of getting $p$ below 0.05;

**3.** indeed, if one kept repeating, one would be guaranteed of getting a 5-sigma result (at least if the universe lasts long enough).

So a frequentist must account for optional stopping (if used) in computing error probabilities or $p$-values.

*Cool Fact:* Bayesian analysis is not affected by optional stopping; it would be perfectly fine to use the previous optional stopping strategy but stopping when, say, the posterior probability that the mean is zero is less than 0.05.

*The Reason:* For i.i.d data (for simplicity) $X_i$ having density $f(x_i \mid \theta)$, optional stopping alters the data density to be

$$\tau_N(x_1, x_2, \ldots, x_N) \prod_{i=1}^{N} f(x_i \mid \theta)\,,$$

where $N$ is the (random) time at which one stops taking data and $\tau_N(x_1, x_2, \ldots, x_N)$ gives the probability (often 0 or 1) of stopping sampling.

Bayes theorem then yields that the posterior probability of $\theta$ is

$$\begin{aligned} \pi(\theta \mid x_1, x_2, \ldots, x_N) &= \frac{\pi(\theta)\tau_N(x_1, x_2, \ldots, x_N) \prod_{i=1}^{N} f(x_i \mid \theta)}{\int \pi(\theta)\tau_N(x_1, x_2, \ldots, x_N) \prod_{i=1}^{N} f(x_i \mid \theta) d\theta} \\ &= \frac{\pi(\theta) \prod_{i=1}^{N} f(x_i \mid \theta)}{\int \pi(\theta) \prod_{i=1}^{N} f(x_i \mid \theta) d\theta}\,. \end{aligned}$$

## **Class 2:** Multiplicities Affecting the Likelihood

- Choice of transformation/model
- Multiple testing
- Variable selection (later section)
- Subgroup analysis (later section)

## Choice of transformation/model

- Frequentist solutions:
  - Develop the model on part of the data; perform inference on the other part (or do a new experiment).
  - Formal solutions: confidence set after testing, bootstrap
  - *This is often ignored, leading to overconfident inference.*
- Bayesian solution: model averaging.
  - Assign each model/transformation a prior probability.
  - Compute model/transformation posterior probabilities.
  - Perform inference with weighted averages over the models/transformations. (An overwhelmingly supported model/transformation will receive weight near one.)
  - *This is often ignored, leading to overconfident inference.*

## Bayesian Solution: Model Averaging

- Assign probabilities $P(M_i)$ to models; the more models (multiplicities being considered), the less prior probability each model receives.
- Compute the posterior model probabilities $P(M_i \mid data)$
- If, say, inference concerning $\xi$ is desired, it would be based on

$$\pi(\xi \mid data) = \sum_{i=1}^{q} P(M_i \mid data)\ \pi(\xi \mid data, M_i).$$

Note: $\xi$ must have the same meaning across models, as in prediction.

**Example:** From i.i.d. vehicle emission data $\mathbf{X} = (X_1, \ldots, X_n)$, one desires to determine the probability that the vehicle type will meet regulatory standards.

Traditional models for this type of data are Weibull and lognormal distributions given, respectively, by

$$\begin{aligned} M_1 : f_W(x; \beta, \gamma) &= \frac{\gamma}{\beta}\left(\frac{x}{\beta}\right)^{\gamma-1} \exp\left[-\left(\frac{x}{\beta}\right)^{\gamma}\right] \\ M_2 : f_L(x; \mu, \sigma^2) &= \frac{1}{x\sqrt{2\pi\sigma^2}} \exp\left[\frac{-(\log x - \mu)^2}{2\sigma^2}\right]. \end{aligned}$$

Note that both distributions are in the location-scale family (the Weibull being so after a log transformation).

## Model Averaging Analysis:

- Assign each model prior probability 1/2.
- Because of the common location-scale invariance structures, assign the right-Haar prior densities $\pi_W(\beta,\gamma) = 1/(\beta\gamma)$ and $\pi_L(\mu,\sigma) = 1/(\sigma)$, respectively (Berger, Pericchi and Varshavsky, 1998 Sankhyā).
- The posterior probabilities (and conditional frequentist error probabilities) of the two models are then

$$P(M_1 \mid \mathbf{x}) = 1 - P(M_2 \mid \mathbf{x}) = \frac{B(\mathbf{x})}{1 + B(\mathbf{x})}\,,$$

where $z_i = \log x_i$,$\bar{z} = \frac{1}{n}\sum_{i=1}^{n} z_i$, $s_z^2 = \frac{1}{n}\sum_{i=1}^{n}(z_i - \bar{z})^2$, and

$$B(\mathbf{x}) = \frac{\Gamma(n) n^n \pi^{(n-1)/2}}{\Gamma(n-1/2)} \int_0^\infty \left[\frac{y}{n}\sum_{i=1}^{n} exp\left(\frac{z_i - \bar{z}}{s_z y}\right)\right]^{-n} dy\,.$$

- For the studied data set, $P(M_1 \mid \mathbf{x}) = .712$. Hence,

$$\begin{aligned} P(\text{meeting standard}) \quad &= .712\ P(\text{meeting standard} \mid M_1) \\ &\quad +.288\ P(\text{meeting standard} \mid M_2)\,. \end{aligned}$$

# Multiple testing

- Multiple hypothesis testing (earlier Bayesian analysis)
- Multiple multiple testing
  - e.g., plasma samples are sent to separate genomic, protein, and metabolic labs for 'discovery'.
- Serial studies
  - the first three HIV vaccine trials failed
  - all 16 large Phase III Alzheimer's trials have failed

## Multiple multiple testing:

**Example:** Plasma samples are sent to the following labs in a pharmaceutical company:

- a metabolic lab, where an association is sought with any of 200 metabolites;
- a proteomic lab, where an association is sought with any of 2000 proteins;
- a genomics lab, where an association is sought with any of 2,000,000 genes.

The company should do a joint multiplicity analysis.

A Bayesian analysis could give each lab 1/3 of the prior probability of a discovery, with each third to be divided within the lab.

**Serial testing:** In the vaccine example, there were two previous failed trials. Should the third vaccine trial have a multiplicity adjustment? The (exchangeable) Bayesian solution:

- assign each trial common unknown probability $p$ of success, with $p$ having a uniform distribution, and compute the posterior probability that the current trial exhibits no efficacy

$$Pr(H_0 \mid x_1, x_2, x_3) = \left(1 + \frac{B_{01}(x_1)B_{01}(x_2) + B_{01}(x_1) + B_{01}(x_2) + 3}{3B_{01}(x_1)B_{01}(x_2) + B_{01}(x_1) + B_{01}(x_2) + 1} \times \frac{1}{B_{01}(x_3)}\right)^{-1}$$

where $B_{01}(x_i)$ is the Bayes factor of "no effect" to "effect" for trial $i$.

This changes the previous $Pr(H_0 \mid x_3) = 0.20$ to $Pr(H_0 \mid x_1, x_2, x_3) = 0.29$.

**Example:** There have been 16 large Phase III Alzheimer's trials - all failing. (The probability of that is only 0.44.). One cannot do the Bayesian serial testing adjustment should the $17^{th}$ trial succeed, without knowing the Bayes factors in each of the failed trials. But it could be as severe as

$$B_{01}^{adj} = 16 \times B_{01}(x_{17})\,.$$

# III. Variable Selection

**Example:** a retrospective study of a data-base investigates the relationship between 200 foods and 25 health conditions. It is reported that eating broccoli reduces lung cancer ($p$-value=0.02).

- Not adjusting for multiplicity (5000 tests) in this type of situation is a leading cause of 'junk science.'
- There are other contributing problems here, such as the use of $p$-values.

*Frequentist solutions:*

- Bonferonni could be used: to achieve an overall level of 0.05 with 5000 tests, one would need to use a per-test rejection level of $\alpha = 0.05/5000 = 0.00001$.
  - This is likely much too conservative because of the probably high dependence in the 5000 tests.
- Some type of bootstrap could be used, but this is difficult when faced, as here, with $2^{5000}$ models.

*Bayesian solution:*

- Assign prior variable inclusion probabilities.
- Implement Bayesian model averaging or variable selection.

- Options in choosing prior variable inclusion probabilities:
  - Objective Bayesian choices:
    - *Option 1:* each variable has unknown common probability $p_i$ of having no effect on health condition $i$.
    - *Option 2:* variable $j$ has common probability $p_j$ of having no effect on each health condition.
    - *Option 3:* some combination.
  - Main effects may have a common unknown prior inclusion probability $p_1$; second order interactions prior inclusion probability $p_2$; etc.
  - An oversight committee for a prospective study might judge that at most one effect might be found, and so could prescribe that a protocol be submitted in which
    - prior probability 1/2 be assigned to 'no effect;'
    - the remaining probability of 1/2 could be divided among possible effects as desired pre-experimentally. (Bonferonni adjustments can also be unequally divided pre-experimentally.)

# Formal Bayesian Approach to Multiplicity Control in Variable Selection

Problem: Data $\mathbf{X}$ arises from a normal linear regression model, with $m$ possible regressors having associated unknown regression coefficients $\beta_i, i = 1, \ldots m$, and unknown variance $\sigma^2$.

Models: Consider selection from among the submodels $\mathcal{M}_i\,,\ i = 1, \ldots, 2^m$, having only $k_i$ regressors with coefficients $\boldsymbol{\beta}_i$ (a subset of $(\beta_1, \ldots, \beta_m)$) and resulting density $f_i(\mathbf{x} \mid \boldsymbol{\beta}_i, \sigma^2)$.

Prior density under $\mathcal{M}_i$: Zellner-Siow priors $\pi_i(\boldsymbol{\beta}_i, \sigma^2)$.

Marginal likelihood of $\mathcal{M}_i$: $m_i(\mathbf{x}) = \int f_i(\mathbf{x} \mid \boldsymbol{\beta}_i, \sigma^2)\pi_i(\boldsymbol{\beta}_i, \sigma^2)\, d\boldsymbol{\beta}_i d\sigma^2$

Prior probability of $\mathcal{M}_i$: $P(\mathcal{M}_i)$

Posterior probability of $\mathcal{M}_i$:

$$P(\mathcal{M}_i \mid \mathbf{x}) = \frac{P(\mathcal{M}_i)m_i(\mathbf{x})}{\sum_j P(\mathcal{M}_j)m_j(\mathbf{x})}\,.$$

# Common Choices of the $P(\mathcal{M}_i)$

Equal prior probabilities: $P(\mathcal{M}_i) = 2^{-m}$ does not control for multiplicity.

Bayes exchangeable variable inclusion does control for multiplicity:

- Each variable, $\beta_i$, is independently in the model with unknown probability $p$ (called the prior inclusion probability).
- $p$ has a Beta$(p \mid a, b)$ distribution. (We use $a = b = 1$, the uniform distribution, as did Jeffreys 1961.)
- Then, since $k_i$ is the number of variables in model $\mathcal{M}_i$,

$$P(\mathcal{M}_i) = \int_0^1 p^{k_i}(1-p)^{m-k_i}\,\text{Beta}(p \mid a, b)dp = \frac{Beta(a+k_i, b+m-k_i)}{Beta(a,b)}\,.$$

  Note that this can be pre-computed; no uncertainty analysis (e.g. MCMC) in $p$ is needed! (See Scott and Berger, 2008, for discussion.)

Empirical Bayes variable inclusion does control for multiplicities: Find the MLE $\hat{p}$ by maximizing the marginal likelihood of $p$, $\sum_j p^{k_j}(1-p)^{m-k_j} m_j(\mathbf{x})$, and use $P(\mathcal{M}_i) = \hat{p}^{k_i}(1-\hat{p})^{m-k_i}$ as the prior model probabilities.

| | **Equal model probabilities** | | | | **Bayes variable inclusion** | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of noise variables | | | | Number of noise variables | | | |
| Signal | 1 | 10 | 40 | 90 | 1 | 10 | 40 | 90 |
| $\beta_1 : -1.08$ | .999 | .999 | .999 | .999 | .999 | .999 | .999 | .999 |
| $\beta_2 : -0.84$ | .999 | .999 | .999 | .999 | .999 | .999 | .999 | .988 |
| $\beta_3 : -0.74$ | .999 | .999 | .999 | .999 | .999 | .999 | .999 | .998 |
| $\beta_4 : -0.51$ | .977 | .977 | .999 | .999 | .991 | .948 | .710 | .345 |
| $\beta_5 : -0.30$ | .292 | .289 | .288 | .127 | .552 | .248 | .041 | .008 |
| $\beta_6 : +0.07$ | .259 | .286 | .055 | .008 | .519 | .251 | .039 | .011 |
| $\beta_7 : +0.18$ | .219 | .248 | .244 | .275 | .455 | .216 | .033 | .009 |
| $\beta_8 : +0.35$ | .773 | .771 | .994 | .999 | .896 | .686 | .307 | .057 |
| $\beta_9 : +0.41$ | .927 | .912 | .999 | .999 | .969 | .861 | .567 | .222 |
| $\beta_{10} : +0.63$ | .995 | .995 | .999 | .999 | .996 | .990 | .921 | .734 |
| False Positives | 0 | 2 | 5 | 10 | 0 | 1 | 0 | 0 |

Table 2: Posterior inclusion probabilities for 10 real variables in a simulated data set.

# Comparison of Bayes and Empirical Bayes Approaches

**Theorem 1** *In the variable-selection problem, if the null model (or full model) has the largest marginal likelihood, $m(\mathbf{x})$, among all models, then the MLE of $p$ is $\hat{p} = 0$ (or $\hat{p} = 1$.)* (The naive EB approach, which assigns $P(\mathcal{M}_i) = \hat{p}^{k_i}(1-\hat{p})^{m-k_i}$, concludes that the null (full) model has probability 1.)

A simulation with 10,000 repetitions to gauge the severity of the problem:

- $m = 14$ covariates, orthogonal design matrix
- $p$ drawn from $U(0,1)$; regression coefficients are 0 with probability $p$ and drawn from a Zellner-Siow prior with probability $(1-p)$.
- $n = 16$, 60, and 120 observations drawn from the given regression model.

| Case | $\hat{p} = 0$ | $\hat{p} = 1$ |
|---|---|---|
| $n = 16$ | 820 | 781 |
| $n = 60$ | 783 | 766 |
| $n = 120$ | 723 | 747 |

| Covariate | Fully Bayes | Emp. Bayes |
|---|---|---|
| East Asian Dummy | 0.983 | 0.983 |
| Fraction of Tropical Area | 0.727 | 0.653 |
| Life Expectancy in 1960 | 0.624 | 0.499 |
| Population Density Coastal in 1960s | 0.518 | 0.379 |
| GDP in 1960 (log) | 0.497 | 0.313 |
| Outward Orientation | 0.417 | 0.318 |
| Fraction GDP in Mining | 0.389 | 0.235 |
| Land Area | 0.317 | 0.121 |
| Higher Education 1960 | 0.297 | 0.148 |
| Investment Price | 0.226 | 0.130 |
| Fraction Confucian | 0.216 | 0.145 |
| Latin American Dummy | 0.189 | 0.108 |
| Ethnolinguistic Fractionalization | 0.188 | 0.117 |
| Political Rights | 0.188 | 0.081 |
| Primary Schooling in 1960 | 0.167 | 0.093 |
| Hydrocarbon Deposits in 1993 | 0.165 | 0.093 |
| Fraction Spent in War 1960–90 | 0.164 | 0.095 |
| Defense Spending Share | 0.156 | 0.085 |
| Civil Liberties | 0.154 | 0.075 |
| Average Inflation 1960–90 | 0.150 | 0.064 |
| Real Exchange Rate Distortions | 0.146 | 0.071 |
| Interior Density | 0.139 | 0.067 |

Table 3: Exact variable inclusion probabilities for 22 variables in a linear model for GDP growth among a group of 30 countries.

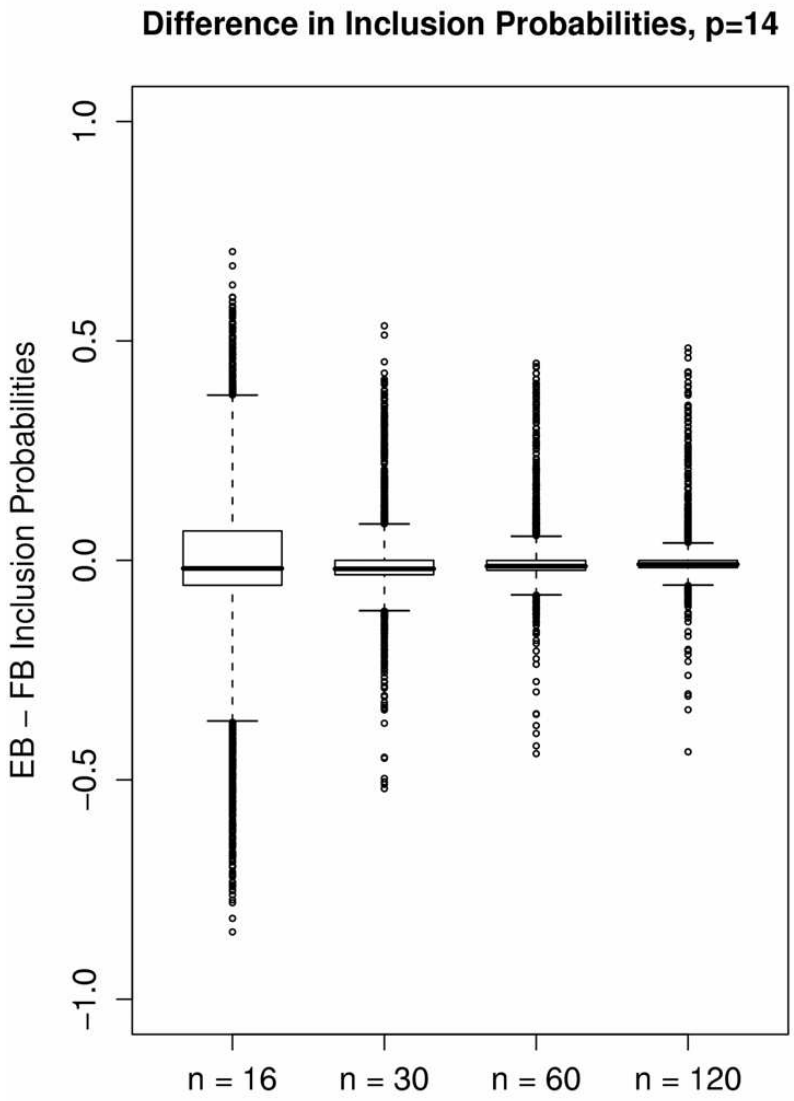



Figure 2: Empirical distribution of difference in inclusion probabilities between EB and FB, 10000 fake data sets with 14 possible covariates in each one, everything drawn from the prior.

## Is empirical Bayes at least accurate asymptotically as $m \to \infty$?

Posterior model probabilities, given $p$:

$$P(\mathcal{M}_i \mid \mathbf{x}, p) = \frac{p^{k_i}(1-p)^{m-k_i} m_i(\mathbf{x})}{\sum_j p^{k_j}(1-p)^{m-k_j} m_j(\mathbf{x})}$$

Posterior distribution of $p$: $\pi(p \mid \mathbf{x}) = K \sum_j p^{k_j}(1-p)^{m-k_j} m_j(\mathbf{x})$

This *does* concentrate about the true $p$ as $m \to \infty$, so one might expect that

$$P(\mathcal{M}_i \mid \mathbf{x}) = \int_0^1 P(\mathcal{M}_i \mid \mathbf{x}, p)\pi(p \mid \mathbf{x})dp \approx P(\mathcal{M}_i \mid \mathbf{x}, \hat{p}) \propto m_i(\mathbf{x})\, \hat{p}^{k_i}(1-\hat{p})^{m-k_i}.$$

This is not necessarily true; indeed

$$\begin{aligned} \int_0^1 P(\mathcal{M}_i \mid \mathbf{x}, p)\pi(p \mid \mathbf{x})dp &= \int_0^1 \frac{p^{k_i}(1-p)^{m-k_i} m_i(\mathbf{x})}{\pi(p \mid \mathbf{x})/K} \times \pi(p \mid \mathbf{x})\, dp \\ &\propto m_i(\mathbf{x}) \int_0^1 p^{k_i}(1-p)^{m-k_i} dp \propto m_i(\mathbf{x}) P(\mathcal{M}_i)\,. \end{aligned}$$

*Caveat:* Some EB techniques have been justified; see Efron and Tibshirani (2001), Johnstone and Silverman (2004), Cui and George (2006), and Bogdan et. al. (2008).

**Theorem 2** *Suppose the true model size $k_T$ satisfies $k_T/m \to p_T$ as $m \to \infty$, where $0 < p_T < 1$. Consider all models $M_i$ such that $k_T - k_i = O(\sqrt{m})$, and consider the optimal situation for EB in which*

$$\hat{p} = p_T + O(\frac{1}{\sqrt{m}}) \quad as \quad m \to \infty \,.$$

*Then the ratio of the prior probabilities assigned to such models by the Bayes approach and the empirical Bayes approach satisfies*

$$\frac{P_B(\mathcal{M}_i)}{P_{EB}(\mathcal{M}_i)} = \frac{\int_0^1 p^{k_i}(1-p)^{m-k_i}\pi(p)dp}{(\hat{p})^{k_i}(1-\hat{p})^{m-k_i}} = O\left(\frac{1}{\sqrt{m}}\right) ,$$

*providing $\pi(\cdot)$ is continuous and nonzero.*

# IV. Subgroup Analysis

## Subgroup Analysis (work in progress)

Our guiding principles:

- Null control and multiplicity control need to be present.
- To maximize power to detect real effects,
  - the subgroups and allowed population partitions need to be restricted to those that are scientifically plausible;
  - allowance for 'scientifically favored' subgroups should be made.
- Full Bayesian analysis is sought. In particular, any inferences should have an interpretation in terms of the actual population.

Allowable subgroups: Subgroups are specified by criteria, denoted by letters. For example, age is A, gender is B, and smoking status is C.

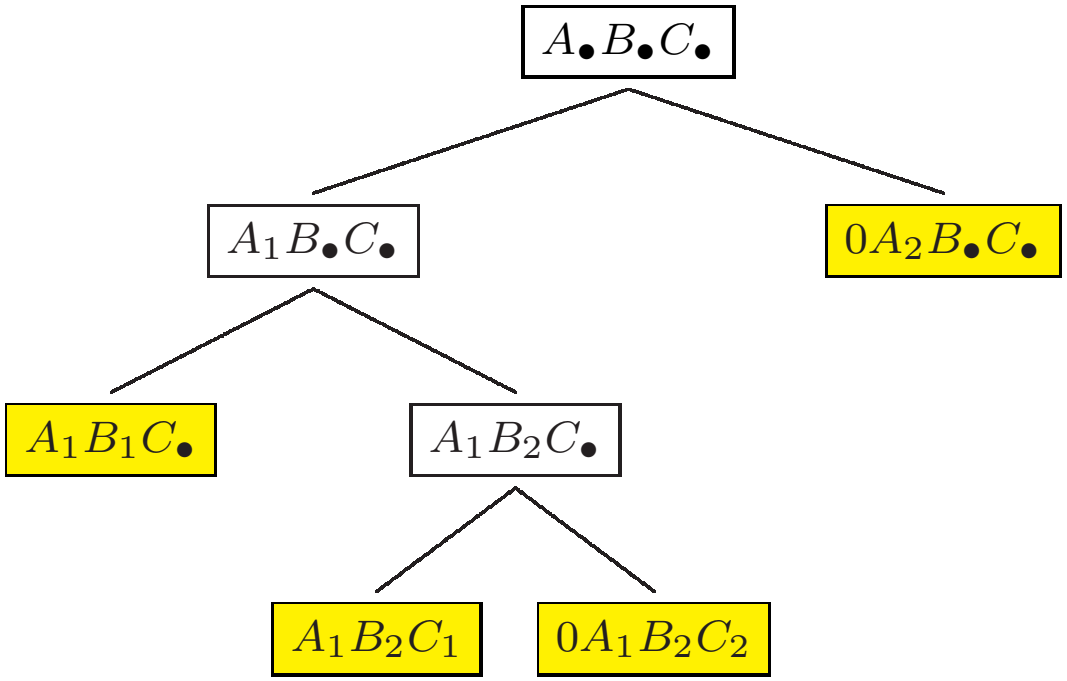
- Young is $A_1$ and old is $A_2$. Male is $B_1$ and female is $B_2$. Smoking is $C_1$ and non-smoking is $C_2$. $A_\bullet$ is any variant of the $A$ factor.
- A subgroup is a concatenation of letters with numbered subscripts; $A_1B_1C_\bullet$ is young males, reflecting the fact that no split has been made according to smoking status. Young male smokers are $A_1B_1C_1$.

Key Fact: Allowing only subgroups of this form is a very strong restriction. For instance, $\{\{\text{male smokers}\} \cup \{\text{female nonsmokers}\}\}$ is not an allowed subgroup.

- For $F$ factors, there are $3^F$ allowable subgroups (81 for F=4).
- For $F$ factors, there are $(2^{2^F} - 1)$ possible subgroups (65,535 for F=4).

Allowed statistical models consist of partitions of the population into allowable subgroups arising from terminal nodes of trees based on factor splits, with possible zero effects, as follows:

- A factor ordering is selected (probabilistically), e.g. $ABC$, $ACB$.
- At each level of the tree, one zero-effect node is possibly assigned by
  - randomly determining if there is to be a zero-effect node at that level; if so, it will be denoted by a '0' in front of the label.
  - then randomly choosing one of the nodes at that level to become the zero-effect node; it then becomes a terminal node.
- The non zero-effect nodes at a given level are possibly split by the factor corresponding to that level.
  - randomly deciding if the node is to be split; if not it becomes a terminal node;
  - if split, creating two new nodes at the next level of the tree.
- The statistical model (population partition) is the collection of terminal nodes (i.e., the last nodes in the branches of the tree).




*Construction Steps*

no 0; split on $A$

0 assigned, terminal; split on $B$

no 0; no split, terminal; split on $C$

0 assigned

Thus the ensuing statistical model $\mathcal{M}$ (population partition) consists of the four yellow nodes, two of which have zero treatment effect and two of which have non-zero and differing treatment effects.

## Motivation for the choice of models (population partitions):

**Why declare a node to be terminal after a failure to split?** Suppose one split on $A$ and then split on $B$ for one branch and $C$ for the other branch, declaring the resulting nodes to be terminal. The resulting partition is {young male, young female, old smoker, old non-smoker}, which does not seem to be a reasonable scientific model (i.e., that the population divides up into these four distinct subgroups, each having differing effects).

**Why allow only one terminal node at each level to be a zero-effect node?** Consider, for instance, the model $\{B_1C_1A_\bullet, 0B_1C_2A_\bullet, 0B_2C_1A_\bullet, B_2C_2A_\bullet\}$, which has two zero effect subgroups at level 2 of the tree. This model would be saying that non-smoking men and smoking women have zero effect, while the others have non-zero effect, which does not seem scientifically plausible.

**There can be multiple zero-effect nodes at a given level that are plausible.** Yes, but then they will have occurred also at a higher level of the tree.

The Elicited Prior contains user specified features, such as

- $k$, the number of factor splits allowed;
- the prior probability of each factor having an effect;
- the prior probability of 'zero effect' for an individual (or this can be left unknown).

The Operational Prior consists of

- probabilities on the factor ordering;
- the tree splitting probabilities;
- the probabilities of assigning 'zero effect' to terminal nodes.

Challenges:

- Choosing the operational prior so that the resulting model probabilities match those from the elicited.
- Determining what is proper societal control for multiplicity and null control.

## Full Bayesian inference:

- Perform a standard Bayesian model uncertainty analysis:
  - Pre-compute the prior model probabilities, including integrating out any unknown multiplicity parameters.
  - Utilize standard objective model parameter priors (e.g., Zellner-Siow).
  - Utilize appropriate stochastic search or other computational strategies if the model space is huge.
- Of primary interest is the posterior probability of an effect for an individual with characteristics $X$:
  - found by summing the posterior probabilities of all models in which individuals with those characteristics were in a subgroup that exhibited an effect;
  - equivalent to the posterior probability of an effect for a last level subgroup.
  - It is hard to make sense of the posterior probability of an effect for a higher level subgroup.

# Illustration: Analysis of data from the Step trial of MRKAd5 vaccine

**Overall Population:** data provided little evidence of any effect, beneficial or harmful

**Uncircumcised men:**

6 HIV cases reported in the 394 individuals receiving placebos

22 HIV cases reported in the 394 individuals receiving the treatment

**Two-sided p-value:** 0.0021.

This was so small that there seemed to be conclusive evidence of harm from the vaccine, and all testing with this vaccine and other variants was stopped.

## Bayesian Analysis: Objective Prior

Let $\theta$ = [P(*HIV under placebo*) - P(*HIV under vaccine*)] in the subgroup.

**Null and alternative hypotheses:**

$$H_0 : \theta = 0 \quad \text{versus} \quad H_1 : \theta \neq 0\,,$$

**Objective prior (to the scientists):**

- Choose $Pr(\theta = 0) = 0.5$, or deal with it by a sensitivity study.
- Give equal weight, to say, the vaccine doubling or halving the infection rate.
- Do this up to an upper (lower) limit of a five-fold increase or five-fold decrease in the infection rate.

**Bayesian answer:** $Pr(\theta = 0 \mid data) = 0.04$ and $Pr(\theta < 0 \mid data) = 0.96$.

Although this is much larger than the $p$-value of 0.0021, it still seems to be strong evidence that the vaccine was harmful to this subgroup.

## Multiple Testing Adjustment for Subgroups:

**Suppose we had initially considered five subgroups:**

- all men
- circumcised men
- uncircumcised men
- men with negative Cd5 count
- men with positive Cd5 count

**The Bayesian multiple testing adjustment** would convert the earlier $Pr(\theta = 0 \mid data)$ from 0.041 to 0.27.

In reality, there were 18 subgroups considered apriori – just among the males – so the adjustment for multiple testing should be even larger.

Note that the Bayesian adjustment can be done posthoc, with information concerning the subgroups considered through the design.

# V. Multiplicities in High-Energy Physics

# A Bayesian Formulation of the Basic HEP Problem

**The statistical model** (following Richard Lockhart's Banff II writeup):

- $N$ is the observed Poisson number of events.
- The events are independent and each has characteristics ('marks' in the Poisson process world) $X_i$, $i = 1, \ldots, N$.
- Under $H_0$: *background only,*
  - the mean of $N$ is $b$,
  - the density of the $X_i$ is $f_b(x) > 0$.
- There may be a signal Poisson process with mean $s$ and density $f_s(x)$.
- Under $H_1$: *background + signal,*
  - the mean of $N$ is $b + s$,
  - the density of the $X_i$ is $(\gamma f_b(x) + (1-\gamma) f_s(x))$, where $\gamma = \frac{b}{(b+s)}$.
- Consider the case where $f_b(x)$ and $f_s(x)$ are known but $b$ and $s$ are unknown.

**Bayes factor of $H_1$ to $H_0$ for priors $\pi_0(b)$ and $\pi_1(b,s) = \pi_0(b)\pi_1(s \mid b)$:**

$$B_{10} = \frac{\int_0^\infty \int_0^\infty (b+s)^N e^{-(b+s)} \prod_{i=1}^N [\gamma f_b(x_i) + (1-\gamma) f_s(x_i)] \pi_1(b,s)\, dsdb}{\int_0^\infty b^N e^{-b} \prod_{i=1}^N [f_b(x_i)]\, \pi_0(b) db}$$

$$= \frac{\int_0^\infty \int_0^\infty b^N e^{-(b+s)} \prod_{i=1}^N \left[1 + \frac{s f_s(x_i)}{b f_b(x_i)}\right] \pi_0(b)\pi_1(s \mid b)\, dsdb}{\int_0^\infty b^N e^{-b}\, \pi_0(b) db} .$$

Note that, if $b$ is known, this becomes

$$B_{10} = \int_0^\infty e^{-s} \prod_{i=1}^N \left[1 + \frac{s f_s(x_i)}{b f_b(x_i)}\right] \pi_1(s \mid b)\, ds .$$

*Priors:* Intrinsic priors are $\pi_0^I(b) = b^{-1/2}$ (note that it is improper) and $\pi_1^I(s \mid b) = b(s+b)^{-2}$ (note that it is proper).

*Note:* Ignoring the densities $f_s$ and $f_b$ and basing the answer solely on $N$ is equivalent to assuming that $f_s \equiv f_b$.

## Multiplicity (look-elsewhere) concerns are automatically handled:

Suppose $N_j$ of the $X_i$ are in bin $B_j$, $j = 1, \ldots, M$, and that we assume we have only densities $f_s(B_j)$ and $f_b(B_j)$. Then

$$B_{10} = \frac{\int_0^\infty \int_0^\infty b^N e^{-(b+s)} \prod_{j=1}^M \left[1 + \frac{s f_s(B_j)}{b f_b(B_j)}\right]^{N_j} \pi_0(b)\pi_1(s \mid b)\, dsdb}{\int_0^\infty b^N e^{-b}\, \pi_0(b) db} .$$

Suppose $f_s(B_j)$ gives probability one to some unknown bin $B$ (the signal could occur in only one bin), with each bin being equally likely. Then

$$\begin{aligned} B_{10} &= \frac{E^B\left[\int_0^\infty \int_0^\infty b^N e^{-(b+s)} \prod_{j=1}^M \left[1 + \frac{s f_s(B)}{b f_b(B_j)}\right]^{N_j} \pi_0(b)\pi_1(s \mid b)\, dsdb\right]}{\int_0^\infty b^N e^{-b}\, \pi_0(b) db} \\ &= \frac{1}{M}\sum_{j=1}^M \frac{\int_0^\infty \int_0^\infty b^N e^{-(b+s)} \left[1 + \frac{s}{b f_b(B_j)}\right]^{N_j} \pi_0(b)\pi_1(s \mid b)\, dsdb}{\int_0^\infty b^N e^{-b}\, \pi_0(b) db} , \end{aligned}$$

so that the results from each $H_j$:*signal in* $B_j$ are downweighted by $1/M$.

# VI. Comparison of Bayesian and Frequentist Approaches to Multiplicity

# Frequentist Approaches: Per-Comparison, Family-wise and FDR error-rates

For $M$ tests, $H_{0i} : \mu_i = 0$ versus $H_{1i} : \mu_i \neq 0$,:

| | accept $H_0$ | Reject $H_0$ | |
|---|---|---|---|
| $H_0$ true | $U$ | $V$ | $M_0$ |
| $H_0$ false | $T$ | $S$ | $M_1$ |
| (observed $\rightarrow$) | $W$ | $R$ | $M$ |

$R =$ total number of rejections (discoveries)

$V = \#$ false discoveries

(There is little concern about $T$ in the non-Bayesian literature, a questionable omission when viewed decision-theoretically.)

| | $d_0$ | $d_1$ | |
|---|---|---|---|
| $H_0$ | $U$ | $\boldsymbol{V}$ | $M_0$ |
| $H_1$ | $T$ | $S$ | $M_1$ |
| | $W$ | $R$ | $\boldsymbol{M}$ |

**Per-Comparison (PCER).** Controls the proportion of false discoveries $\frac{E[V]}{M}$ at level $\alpha$ by testing each $H_{0i}$ at level $\alpha$

'Ignores the multiplicity problem' (too liberal)

**Family-wise (FWER).** Classical Bonferroni: Controls $\Pr(V \geq 1)$ at level $\leq \alpha$ by testing each $H_{0i}$ at level $\frac{\alpha}{M}$.

Results in *very conservative* tests.

... something in between ...

## False Discovery rate (FDR)

| | $d_0$ | $d_1$ | |
|---|---|---|---|
| $H_0$ | $U$ | $\boldsymbol{V}$ | $M_0$ |
| $H_1$ | $T$ | $S$ | $M_1$ |
| | $W$ | $\boldsymbol{R}$ | $M$ |

- focus on $\frac{V}{R}$ instead $\rightsquigarrow$ % of false discoveries (erroneous rejections) among the rejected hypotheses
- Not defined for $R = 0$ (all $M$ nulls accepted), so (Benjamini and Hochberg, 95) propose to control:

$$\text{FDR} = E\left[\frac{V}{\max\{R, 1\}}\right] = E\left[\frac{V}{R} \mid R > 0\right] Pr(R > 0)\,.$$

  with Simes (86) $\alpha$-level multiple comparisons test

- Closely related: Positive FDR: $\text{pFDR} = E\left[\frac{V}{R} \mid R > 0\right]$

## Properties and Comments:

| | accept $H_0$ | reject $H_0$ | |
|---|---|---|---|
| $H_0$ true | $U$ | $\boldsymbol{V}$ | $M_0$ |
| $H_1$ true | $T$ | $S$ | $M_1$ |
| | $W$ | $\boldsymbol{R}$ | $\boldsymbol{M}$ |

- Simes(86) shows control of FWER under null.
- B&H(95) show control of FDR always
- asymptotically FDR $\approx$ pFDR $\approx$ PFP $= \frac{E[V]}{E[R]}$
- Part of the attractiveness of FDR seems to be that, instead of using $\alpha = 0.05$, people use (e.g.)FDR $= 0.15$.
- Genovese and Wasserman(02, 03) observe that FDR is an expected value, and the realized proportion of discoveries, $V/R$ can vary greatly from this expected value; arguing that this variability should be taken into account.

- B&H algorithm controls FDR at level $p\alpha$ (Finner and Roters, 04) $\rightsquigarrow$ use and estimate of $p$ to increase power (keeping control at level $\alpha$); (Benjamini and Hochberg, 2000; Black 04, Storey, Storey et. al., Genovese, Langaas et al. (2005), Cayon, Rice)
- Finner and Roters(01) observe that control of FDR allows 'cheating' "by adding additional hypotheses of no interest which are known to have $p$-values near 0" (the FDR critical value for ranked $p$-values $p_{[i]}$ is $i\,\alpha/m$); for instance, to maximize the chance of rejecting 8 hypotheses of interest while controlling FDR at $\alpha$ one can add 100 'uninteresting' hypothesis with p-values $\approx 0$, so that the 8 'interesting' p-values will have threshold $\geq 101\alpha/108$

# Connections between FDR and Bayes

(Storey, Efron, Tibshirani, Genovese, Wasserman, Rice . . . )

- Frequentists need to estimate $p$ to obtain good power for FDR; this is also key for Bayesians. This hints that there should be some type of exchangeability of hypotheses to apply FDR; this would also address the Finner-Roters objection.
- Genovese and Wasserman (02) have a more Bayesian definition of "Bayesian FDR" $\rightsquigarrow$ focus on *realized* FDR, namely $V/R$, and its posterior distribution, so that uncertainty in $V/R$ can be studied. (They still study frequentist properties.)

- Frequentist analyses that estimate (instead of control) errors, as pFDR, often have same models as Bayesians

$$f(x_i) = pf_0(x_i) + (1-p)f_1(x_i)$$

  - $f_1$ unknown (and often also $f_0$) $\rightsquigarrow$ often frequentist nonparametric estimates (EB needs only estimate the ratio) (Efron&al 01, Efron&Tibshirani 02, Genovese&Wasserman)
  - often $p$ is not estimated, but a lower bound used instead

$$f = pf_0 + (1-p)f_1 \geq pf_0 \rightsquigarrow \ \hat{p} = \min_x \ \frac{\hat{f}(x)}{\hat{f}_0(x)} \, .$$

  - Also full nonparametric Bayes analysis. (Do, Müller, Tang)

- Storey suggests that
  - pFDR has a dual interpretation as a Bayesian and as a frequentist measure because
    $\text{pFDR}(C) = \Pr(H_{0i} \text{ true} \mid X_i \in C) = \frac{E[V]}{E[R]}$ .
    But this is the posterior probability given the data is in 'critical region' $C$, not given the data itself;
  - proposes the $q$-value, defined as

$$q\text{-value}(X_i) = \inf_{\alpha} \Pr(H_{0i} \text{ true} \mid X_i \in C_\alpha)$$

    and calls it a "posterior Bayesian $p$-value," but, again, it depends on a tail region of data, not the data itself.

## Bayesian FDR

Genovese and Waserman (02); Newton et al. (04); Broët et al. (04)

- Recall that pFDR $= \Pr(H_0 \text{ true} \mid \text{reject } H_0)$
- For a 'Bayesian version' of pFDR, compute
$$1 - p_i = \Pr(H_0 \text{ true} \mid x_i)$$
and average over the rejection region
- to 'control Bayesian pFDR' at level $\alpha$, reject the $i$-th null if $p_i > c^*$ where $c^*$ gives the largest rejection region for which the above average $\leq \alpha$
- **But** FDR is taken as a priori being the quantity of interest. Is this reasonable from a Bayesian viewpoint?

# Decision-theoretic Evaluations of FDR

- FDR seems most useful for screening but, in depending only on $p$-values, it seems like it would not reflect typical decision-theoretic screening losses, which depend in part on the magnitude of the effects.
- FDR does not seem good for 'discovery' which corresponds to "0-1" loss; indeed, one cannot derive FDR from this loss. ($E[V]$ and $E[T]$ arise, but not versions of the ratio $V/R$.)
- One could argue that it is a 'global loss' but there are difficulties in interpretation.
- Müller, et. al. (2002) study a variety of losses that include FDR (or variants) *as primitives*, but find problems with doing so.

## Difficulties in interpreting FDR as a loss function

- It could be argued that the Loss for taking decisions $\boldsymbol{d}$ when the truth is $\boldsymbol{H}$ could be directly defined as a linear function of $V/R$; the risk would then be a function of the (expected) FDR.
- Let $d_i = 0$ if $i$-th null is acepted, and $H_i = 0$ if $i$-th null is true. The problem: such a loss function does not depend on $\sum_i H_i$, only on $\sum_i (1 - d_i) H_i$ (and on $\sum_i d_i$)
- This is difficult to justify intuitively (at least for 'scientific' purposes)

- Assume we have $S = 18$ 'true' signals detected and that $FDR = 2/20$ or 1%. We have identical loss if:
  - We only had $M_0 = 2$ noise (*all* noise is declared to be signal)
  - We have $M_0 = 20000$ and hence the procedure is superb in sorting out noise
- In the same situation as before ($R = 20, V = 2$) we have the same loss if
  - In reality there are $M_1 = 18$ signals, so they are all discovered
  - The truth is that there are $M_1 = 1800$ signals so we only 'discover' 1/10000.
- Efforts have been made to define Loss Functions that also take into account the FNR, but this has also problems

## Also bad behaviour:

| | $d=0$ | $d=1$ | |
|---|---|---|---|
| $H_0$ | $U$ | $\boldsymbol{V}$ | $M_0$ |
| $H_1$ | $\boldsymbol{T}$ | $S$ | $M_1$ |
| | $W$ | $R$ | $M$ |

Müller, et. al. (2005) consider minimization of four global (posterior) expected losses

'Univariate' (*expected*) loss functions

- $L_N(\boldsymbol{d}\,) = cE^*[\boldsymbol{V}\,] + E^*[\boldsymbol{T}\,]$
  Bayes rule with $c = k_1/k_0$
- $L_R(\boldsymbol{d}\,) = cE^*[\mathrm{FDR}] + E^*[\mathrm{FNR}]$
  'Bayes rule' for loss function depending on the data
  (suggested by Storey(03) and G&W(02))

| | $d=0$ | $d=1$ | |
|---|---|---|---|
| $H_0$ | $U$ | $\boldsymbol{V}$ | $M_0$ |
| $H_1$ | $\boldsymbol{T}$ | $S$ | $M_1$ |
| | $W$ | $R$ | $M$ |

'Bivariate controlling' (*expected*) loss functions

- $L_{2N}$ 'controls' $(E^*[\boldsymbol{T}\,], E^*[\boldsymbol{V}\,])$
  minimize $E^*[\boldsymbol{T}\,]$ subject to $E^*[\boldsymbol{V}\,] \leq \alpha\, M$ .
- $L_{2R}$ 'controls' $(E^*[\mathrm{FNR}],\ E^*[\mathrm{FDR}])$
  minimize $E^*[\mathrm{FNR}]$ subject to $E^*[\mathrm{FDR}] \leq \alpha$.

  (This is G&W's proposal; it is maybe the most popular)

Their findings:

- All optimal rules are thresholding rules for $p_i$, all of them data-dependent except for the Bayesian $L_N$
- Pathological behavior of $L_{2R}$: Since $E^*[\text{FDR}]$ is 'controlled' as $M$ grows, to achieve the desired (fixed) $E^*[\text{FDR}]$, "we have to knowingly flag some genes as differentially expressed even when $p_i \approx 0$".
- $L_{2N}$ has a similar pathological behaviour (but slower)
- For $L_N$, $E^*[\text{FDR}]$ vanishes as $M \to \infty$
- The loss $L_R$ induces counterintuitive jumps in $E^*[\text{FDR}]$ and is not recommended either

# References

Benjamini, Y. and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, B* **85**, 289–300.

Bickel, D.R. (2003). Error-rate and decision-theoretic methods of multiple testing. Alternatives to controlling conventional false discovery rates, with an application to microarrays. *Tech. Rep*, Office of Biostatistics and Bioinformatics, Medical College of Georgia.

Do, K.A., Müller, P., and Tang, F. (2002). *Tech. Rep*, Department of Bioestatistics, University of Texas.

Dudoit, S., Shaffer, J.P., and Boldrick, J.C. (2003). Multiple hypothesis testing in microarray experiments. *Statistical Science* **18**, 71–103.

DuMouchel, W.H. (1988). A Bayesian model and graphical elicitation model for multi[le comparison. In *Bayesian Statistics 3* (J.M. Bernardo, M.H. DeGroot, D.V. Lindey and A.F.M. Smith, eds.) 127–146. Oxford University Press.

Duncan, D.B. (1965). A Bayesian approach to multiple comparisons. *Technometrics* **7**, 171-222.

Efron, B. (2010). Large-Scale Inference: Empirical Bayes Methods for Estimation, Testing, and Prediction. Institute of Mathematical Statistics Monographs.

Efron, B. and Tibshirani, R. (2002). Empirical Bayes methods and false discovery rates for microarrays. *Genetic Epidemiology* **23** 70–86.

Efron, B., Tibshirani, R., Storey, J.D. and Tusher, V. (2001). Empirical Bayes analysis of

a microarray experiment. *Journal of the American Statistical Association* **96** 1151–1160

Finner, H., and Roters, M. (2001). On the false discovery rate and expected Type I errors. *Biometrical Journal***43**, 895–1005

Genovese, C.R. and Wasserman, L. (2002a). Operating characteristics and extensions of the false discovery rate procedure. *Journal of the Royal Statistical Society* **64** 499–518.

Genovese, C.R. and Wasserman, L. (2002b). Bayesian and frequentist multiple testing. *Tech. Rep.* Department of Statistics, Carnegie-Mellon University.

Morris, J.S., Baggerly, K.A., and Coombes, K.R. (2003). Bayesian shrinkage estimation of the relative abundance of mRNA transcripts using SAGE. *Biometrics*, **59**, 476–486.

Müller, P., Parmigiani, G., Robert, C., and Rouseau, J. (2002), "Optimal Sample Size for Multiple Testing: the Case of Gene Expression Microarrays," Tech. rep., University of Texas, M.D. Anderson Cancer Center.

Newton, M.A., and Kendziorski, C.M. (2003). Parametric empirical Bayes methods for microarrays. In *The analysis of gene expression data: methods and software*, Springer.

Newton, M.A., Kendziorski, C.M., Richmon, C.S., Blattner, F.R., and Tsui, K.W. (2001). On differential variability of expression ratios: improving statistical inference about gene expression changes from microarray data. *Journal of Computational Biology* **8** 37–52.

Scott, G. and Berger, J.O. (2003). An exploration of Bayesian multiple testing. To appear in Volume in honour of Shanti Gupta.

Shaffer, J.P. (1995). Multiple hypothesis testing: a review. *Annual Review of Psychology* **46**, 561–584. Also *Technical Report* # 23, National Institute of Statistical Sciences.

Simes, R.J. (1986). An improved Bonferroni procedure for multiple tests of significance. *Biometrika* **73** 751–754.

Sivaganesan, S., Laud, P.W., Mueller, P. A. (2011). Bayesian subgroup analysis with a zero-enriched Polya urn scheme. Statistics in Medicine, 30(4), 312–323.

Storey J.D. (2002). A direct approach to false discovery rates. *Journal of the Royal Statistical Society B* **64** 479–498.

Storey J.D. (2003). The positive false discovery rate: a Bayesian interpretation and the q-value. *Annals of Statistics*

Storey J.D., Taylor, J.E., and Siegmund, D. (2004). Strong control, conservative point estimation, and simultaneous conservative consistency of false discovery rates: a unified approach. *Journal of the Royal Statistical Society B* **66** 187–205.

Storey J.D. and Tibshirani, R. (2003). Statistical significance for genomewide studies. *PNAS* **100** 9440–9445.

Waller, R.A. and Duncan, D.B. (1969). A Bayes rule for the symmetric multiple comparison problem. *Journal of the American Statistical Association* **64**, 1484-–1503.