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Overview and Motivation
Dose-Response Trials Overview

- Key objective: Find a ‘correct’ dose to carry forward
  - Applies at all pre-phase 3 stages

- Key issues to address (Ruberg, JBS1995)
  - Responses related to doses? (Proof of Concept)  Most
  - Dose(s) to carry forward (Target dose selection)  Important
  - Doses producing responses differing from control
  - Form of the dose-response relationship
    - Depends on trial design
    - Not useful for mixture models

- Extensive literature on determining dose-response relationships focuses on modeling or multiple comparisons
Motivation and Objective

- The model in a model-based approach could be wrong

- MCPMod: hypothesis-testing paradigm for including multiple models

- Objective of this presentation

- Determine doses to carry forward by selecting most promising model, or by model averaging

- Use nonlinear regression parameter estimation, multiple comparisons and asymptotic normality assumptions

- Bayesian framework for carrying out multiple model analyses using estimation paradigm
  - Based on actual likelihoods
  - Directly address important issues
  - Definitive graphical displays

- Substantial literature on issues and examples related to optimal model selection and model weighting using Bayesian methods
A simple example: Obvious choice of model

- Data from Ruberg (JBS1995)
- Fitting a selection of models ⇒ EMAX gives best fit
- Dots are observed means

More details later

Any dose-response modeling approach should pick this up quickly
Another Example: Correct model not so obvious

- First-in-man study of immunogenicity and safety of a vaccine in healthy adults
- Response = fold increase in immune response over baseline 14 days after administration
- More later

- Linear Log Dose, Quadratic Log Dose, & EMAX provide good fits -- which to choose?

- Why choose?
Method
Strategy

- **Step 1:** Identify candidate D-R models

- **Step 2:**
  - Fit each model to observed data using conventional MCMC calculations (e.g. STAN, JAGS)
  - Get realizations from posterior distribution of parameters for each model

- **Step 3:**
  - Get posterior distributions of functions of parameters using part 1 results

Discrete or continuous observed outcomes
Use any probability model
Expected outcome for a dose is a function relating response to dose and, possibly, other covariates
Monotonicity not required
Expected & predicted responses at any set of doses
Doses corresponding to a specified target response
Candidate Dose-Response Models

- Work with weighted linear combination of models commonly used in literature:
  1. Linear
     \[ f(d; b) = b_1 + b_2 d \]
  2. Quadratic
     \[ f(d; b) = b_1 + b_2 d + b_3 d^2 \]
  3. Linear log dose
     \[ f(d; b) = b_1 + b_2 \log(d) \]
  4. Quadratic log dose
     \[ f(d; b) = b_1 + b_2 \log(d) + b_3 \log(d)^2 \]
  5. EMAX [Sigmoid]
     \[ f(d, b) = b_1 + b_2 d^{b_4}/(b_3 + d^{b_4}) \]
  6. Exponential
     \[ f(d; b) = b_1 + b_2 (\exp(b_3 d) - 1) \]

- Many other models can be used, e.g., cubic splines, fractional polynomials, nonparametric & semi-parametric models, etc.

- Using a set of models with few parameters ⇒ wt’d average curve has adequate flexibility, can include trials with few doses

- Not clear that including more than 6 models really is necessary, or that fewer than 6 models would be enough
Posterior Distribution of Expected Response

- Example: Linear Log Dose \( f(d; b) = b_1 + b_2 \log(d) \)

- MCMC calculations provide an array of realizations from the posterior dist’n of \((b_1, b_2)\)

- Use this array to produce an array of realizations from posterior dist’n of expected responses to a series of doses \(d_1, \ldots, d_K\)

- Use the expected response array to get summaries of the posterior distribution of the expected response curve, e.g., mean, credible intervals

- Take a weighted linear combination of the arrays corresponding to the candidate models to get the BMA weighted model
Something Different: First Derivatives

• Same Example: Linear Log Dose \( f(d; b) = b_1 + b_2 \log(d) \)

• Look at 1st derivative: \( f'(d; b) = b_2/d \)

• As before, get array of realizations from the posterior dist’n of 1st derivative values at \( d_1, ..., d_K \)

\[
\begin{bmatrix}
\frac{b_1}{d_1} & \cdots & \frac{b_1}{d_K} \\
\vdots & \ddots & \vdots \\
\frac{b_N}{d_1} & \cdots & \frac{b_N}{d_K}
\end{bmatrix}
\]

• Use this array to get summaries of the posterior distribution of the first derivative of the expected response curve

• Since sum of derivatives = derivative of sum, weighted sum of model-specific 1st derivative curves = 1st derivative curve of weighted (BMA) model

• Easy PoC evaluation: lower CI of 1st derivative curve > 0
  o Also easy to see where dose-response flattens
Determining Prior Model Weights

- Clinicians provide explicit weights directly (MCPMod)
- Clinicians provide pairwise ratings of relative preferences for the models (e.g., linear vs EMAX)
  - Construct pairwise preference matrix
  - Weights are elts of eigenvector corresponding to maximum positive eigenvalue. AHP approach uses this method.
- Literature generally assumes uniform weights for models, but this may give undue weights to essentially equivalent models
- Better: Initially assume equal weights for all models, then adjust weights to reflect correlations among predictions provided by each model (Garthwaite et al, ANZJS2010, Bka2012)
- This is the default approach, but explicit specification of weights is an option
Identifying Appropriate Doses

• Two ways to proceed (addressing different questions)

• Lower (or upper) quantiles of posterior distribution of responses given doses
  o “What is the least dose that provides $100\gamma$% posterior probability of a response $R > r$?”

• Posterior distribution of doses given response
  o “Given an observed response $R = r$, what is the posterior modal dose, and what is the corresponding posterior ci for the dose?”
Software

• Calculations proceed in 3 steps
  o Using MCMC to obtain realizations from posterior distributions of model parameters
  o Post-processing the MCMC output to produce summary datasets and tabulations
  o Graphical displays that drive conclusions

• Structure of post-processing software

The driver program for post-processing calculations
Examples
Example 1: Sigmoid Dose-Response
Sigmoid DR Curve (Ruberg JBS1995)

- Data from article (digitized)
- Prior weights
  0.02, 0.02, 0.34, 0.05, 0.35, 0.22
- Posterior weights
  normal
  0, 0, 0, 0, 1, 0

Model likelihoods → ‘correct’ post weights regardless of prior

Expected posterior DR trajectories & 95% CI

EMAX (sigmoid) model provides best fit to data especially with t(3) likelihood
First Derivative of the Optimal Weighted D-R Function

• Posterior distribution of 1\textsuperscript{st} derivatives of weighted dose response function with 95% CI bounds
  ○ Lower 95% bound > 0 ⇒ positive dose-resp relationship
Target Dose (1): Least dose \( \equiv P_{\text{post}}(R > r | \text{dose}) \geq \gamma \)

- Quantiles of posterior dist’n of responses given doses
Target Dose (2): $\text{CDF}_{\text{post}}(\text{Dose} \mid \text{Response})$

- Posterior cdfs of dose as a function of outcome target, either as actual expected response or as expected difference from 0 dose

- $\text{E}($Response$) = 60 \implies 95\%$ post CI for dose $= (2.25, 2.75)$
  - Lower doses are unlikely to give same expected response
  - Higher doses may present an elevated AE risk

- Same calc for AE risk $\rightarrow$ dose choice balances benefit & risk
Example 2: Binary Outcomes
### Summary of Data Source

- **Response** = “pain free 2 hours post dose” from a randomized placebo-controlled trial of a compound for treating acute migraine; 7 active doses [1.usa.gov/28Xd9Hr]

- **Key question**: Which (if any) dose to carry forward?

- **Data summary** (Diff & OR are comparisons with 0 dose)

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>X</th>
<th>(p_{\text{Obs}})</th>
<th>E(p)</th>
<th>(p_{0.025})</th>
<th>(p_{0.975})</th>
<th>(\text{Diff}_{\text{Obs}})</th>
<th>E(Diff)</th>
<th>(\text{Diff}_{0.025})</th>
<th>(\text{Diff}_{0.975})</th>
<th>(\text{OR}_{\text{obs}})</th>
<th>E(OR)</th>
<th>(\text{OR}_{0.025})</th>
<th>(\text{OR}_{0.975})</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>133</td>
<td>13</td>
<td><strong>0.10</strong></td>
<td>0.10</td>
<td>0.06</td>
<td>0.16</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>2.5</td>
<td>32</td>
<td>4</td>
<td><strong>0.12</strong></td>
<td>0.13</td>
<td>0.04</td>
<td>0.27</td>
<td><strong>0.03</strong></td>
<td>0.04</td>
<td>-0.07</td>
<td>0.18</td>
<td><strong>1.3</strong></td>
<td>1.3</td>
<td>0.4</td>
<td>4.1</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>5</td>
<td><strong>0.11</strong></td>
<td>0.11</td>
<td>0.04</td>
<td>0.23</td>
<td><strong>0.02</strong></td>
<td>0.02</td>
<td>-0.08</td>
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<td><strong>1.2</strong></td>
<td>1.2</td>
<td>0.4</td>
<td>3.3</td>
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<tr>
<td>10</td>
<td>63</td>
<td>16</td>
<td><strong>0.25</strong></td>
<td>0.25</td>
<td>0.16</td>
<td>0.37</td>
<td><strong>0.16</strong></td>
<td>0.16</td>
<td>0.05</td>
<td>0.28</td>
<td><strong>3.1</strong></td>
<td>3.2</td>
<td>1.4</td>
<td>7.1</td>
</tr>
<tr>
<td>20</td>
<td>63</td>
<td>12</td>
<td><strong>0.19</strong></td>
<td>0.19</td>
<td>0.11</td>
<td>0.3</td>
<td><strong>0.09</strong></td>
<td>0.10</td>
<td>-0.01</td>
<td>0.21</td>
<td><strong>2.2</strong></td>
<td>2.2</td>
<td>0.9</td>
<td>5.1</td>
</tr>
<tr>
<td>50</td>
<td>65</td>
<td>14</td>
<td><strong>0.22</strong></td>
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<td>0.13</td>
<td>0.32</td>
<td><strong>0.12</strong></td>
<td>0.12</td>
<td>0.01</td>
<td>0.23</td>
<td><strong>2.5</strong></td>
<td>2.6</td>
<td>1.1</td>
<td>5.7</td>
</tr>
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<td>100</td>
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<td>14</td>
<td><strong>0.24</strong></td>
<td>0.24</td>
<td>0.14</td>
<td>0.36</td>
<td><strong>0.14</strong></td>
<td>0.14</td>
<td>0.03</td>
<td>0.26</td>
<td><strong>2.9</strong></td>
<td>2.9</td>
<td>1.3</td>
<td>6.6</td>
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<tr>
<td>200</td>
<td>58</td>
<td>21</td>
<td><strong>0.36</strong></td>
<td>0.36</td>
<td>0.25</td>
<td>0.49</td>
<td><strong>0.26</strong></td>
<td>0.26</td>
<td>0.14</td>
<td>0.40</td>
<td><strong>5.2</strong></td>
<td>5.2</td>
<td>2.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>
Some Posterior Results

- Posterior model weights:

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>0.04</td>
</tr>
<tr>
<td>Quadratic</td>
<td>0.06</td>
</tr>
<tr>
<td>Linear Log Dose</td>
<td>0.36</td>
</tr>
<tr>
<td>Quadratic Log Dose</td>
<td>0.17</td>
</tr>
<tr>
<td>EMAX</td>
<td>0.30</td>
</tr>
<tr>
<td>Exponential</td>
<td>0.07</td>
</tr>
</tbody>
</table>

The diagrams illustrate the dose-response relationships for each model type, showing how the probability of response $P(\text{Resp})$ varies with dose across different scale transformations.
- Posterior expected dose-response fn and 1st derivative ($\times 0.01$)

- There is a monotonic dose-response relationship
- Not much additional effect past doses of 50 or 100
Doses to Consider Carrying Forward

- Posterior distributions of doses as a function of target response

- Target response rate = 0.25 $\Rightarrow$ 95% CI for corresponding dose is (40,150), and interquartile range is (55,100)

- Straightforward to carry out calculation if target response is expressed as difference from zero dose or odds ratio relative to zero dose
Example 3: DR Models with Covariates
Continuous Response, with Covariates

- Response = % chng from bsln in FEV1 after 8 wks of trt in a trial evaluating asthma treatment
- Posterior means & 95% CI for predicted mean response by dose, weighted dose-response curve
- Not much evidence of a dose-response relationship
- Prior weights:
  0.19, 0.19, 0.15, 0.15, 0.15, 0.17
- Posterior weights:
  0.14, 0.18, 0.16, 0.17, 0.19, 0.17

Covariates:
- Age Category (<, ≥ 7) (-2.8, 4.1)
- Bsln FEV1 (-8.5, -3.2)
Derivatives and Doses

- Posterior mean and 95% CI bounds for the 1st derivative of the weighed dose-response curve
  - Not even a monotonic d-r relationship

- Prior probabilities of doses based on expected response

- No dose selection guidance
Example 4: Multiple ‘Adequate’ Models
Multiple Satisfactory Models

- First-in-man study of immunogenicity and safety of a vaccine in healthy adults
- Response = fold increase in immune response over baseline 14 days after administration
- Prior weights
  0.17, 0.16, 0.16, 0.15, 0.19, 0.19
- Posterior weights
  0, 0.06, 0.33, 0.27, 0.34, 0
- Linear log dose, Quadratic log dose, EMAX provide best fits
- Optimal weighted Bayes DR curve is best
Target Dose Selection

- Posterior probabilities of doses, based on

  **Expected response (r)**

  ![Graph of Expected response (r)]

  **Difference from 0 dose**

  ![Graph of Difference from 0 dose]

- **Objective:** 1.4 fold difference from zero dose response
  - Modal dose $\sim 40 \, \mu g$
  - 95% credible interval $\sim (22, 72)$
  - Incorporates posterior variability of responses to zero dose
Example 5: Binary Responses with Random Center Effects
**Ohlssen & Racine (JBS2015)**

- Trial in 3 centers comparing vimpatin vs placebo as adjunct Tx for treating partial-onset epileptic seizures in patients > 15 yrs
- Response = \( \geq 50\% \) reduction in seizure frequency from bsln post 12 wks of maintenance after 4-6 wks forced titration
- O&R used nonparametric monotone regression for analysis
- Summary of data
  - Wider bounds for response prob with random center effect
  - Less pronounced for difference or odds ratio

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>X</th>
<th>( p_{Obs} )</th>
<th>( p_{Exp} )</th>
<th>LB</th>
<th>UB</th>
<th>( p_{Exp} )</th>
<th>LB</th>
<th>UB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>360</td>
<td>81</td>
<td>0.23</td>
<td>0.23</td>
<td>0.18</td>
<td>0.27</td>
<td>0.23</td>
<td>0.16</td>
<td>0.35</td>
</tr>
<tr>
<td>200</td>
<td>267</td>
<td>91</td>
<td>0.34</td>
<td>0.34</td>
<td>0.29</td>
<td>0.40</td>
<td>0.34</td>
<td>0.25</td>
<td>0.49</td>
</tr>
<tr>
<td>400</td>
<td>470</td>
<td>186</td>
<td>0.40</td>
<td>0.40</td>
<td>0.35</td>
<td>0.44</td>
<td>0.41</td>
<td>0.31</td>
<td>0.55</td>
</tr>
<tr>
<td>600</td>
<td>203</td>
<td>80</td>
<td>0.39</td>
<td>0.39</td>
<td>0.33</td>
<td>0.46</td>
<td>0.41</td>
<td>0.31</td>
<td>0.57</td>
</tr>
</tbody>
</table>
Influence of Random Center Effect

No Center Effect

Random Center Effect

Averaged Models
### Posterior Model Weights

<table>
<thead>
<tr>
<th>Prior Weights</th>
<th>Linear</th>
<th>Quadratic</th>
<th>Log</th>
<th>Quadratic Log</th>
<th>EMAX</th>
<th>Exp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garthwaite</td>
<td>0.09</td>
<td>0.25</td>
<td>0.04</td>
<td>0.22</td>
<td>0.35</td>
<td>0.05</td>
</tr>
<tr>
<td>Uniform</td>
<td>0.06</td>
<td>0.21</td>
<td>0.26</td>
<td>0.22</td>
<td>0.21</td>
<td>0.04</td>
</tr>
<tr>
<td>‘Pessimistic’</td>
<td>0.15</td>
<td>0.18</td>
<td>0.22</td>
<td>0.18</td>
<td>0.17</td>
<td>0.11</td>
</tr>
</tbody>
</table>

- Posterior weights not very sensitive to prior weights, weighted log likelihood essentially the same for all prior weight choices.
Response may increase with dose up to about 400 mg, but appears to flatten out thereafter.
What Dose to Pursue?

- Target response rates are (L to R) 0.3, 0.35, 0.4

- Ignoring center effects $\Rightarrow$ 200 mg likely to produce response rate $> 30\%$

- Including center effects $\Rightarrow$ chance of 30% response rate with 200 mg is $\sim 50\%$
Example 6: Covariate Adjustments to All Parameters
‘IBScovars’ data set from MCPmod R package

- Dose-ranging trial of 4 doses (plus pbo) of a compound for treating irritable bowel syndrome

- Posterior model weights:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Linear</th>
<th>Quadratic</th>
<th>Log</th>
<th>Log</th>
<th>EMAX</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>118</td>
<td>0.16</td>
<td>0.18</td>
<td>0.02</td>
<td>0.42</td>
<td>0.04</td>
<td>0.18</td>
</tr>
<tr>
<td>Men</td>
<td>251</td>
<td>0.18</td>
<td>0.28</td>
<td>0.01</td>
<td>0.27</td>
<td>0.06</td>
<td>0.20</td>
</tr>
<tr>
<td>Combined</td>
<td>369</td>
<td>0.13</td>
<td>0.25</td>
<td>0.00</td>
<td>0.45</td>
<td>0.06</td>
<td>0.11</td>
</tr>
</tbody>
</table>

- Weighted dose-response curves
Is There a Monotone Dose – Response Relationship?

- **First Derivatives**

  - Response for women unlikely to increase with dose after Dose 2, but response for men appears to be real, possibly to Dose 4
  - Log likelihoods for weighted models not sensitive to inclusion/exclusion of gender effect or choice of prior model weights
Example 7: Dose Range Limitation
Data and Summary

- ‘biom’ dataset in MCPmd R package
- Posterior model weights
- Posterior weighted dose-response curve and 1st derivatives

<table>
<thead>
<tr>
<th>Linear</th>
<th>Quadratic</th>
<th>Linear</th>
<th>Log</th>
<th>Quadratic</th>
<th>Log</th>
<th>EMAX</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08</td>
<td>0.24</td>
<td>0.13</td>
<td>0.30</td>
<td>0.19</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gutjahr & Bornkamp [Bcs2017] demonstrated significant d-r relationships with linear, exponential, and EMAX models.

- Probably is supportable only for doses < 0.6 given 1st deriv.
Which Doses to Pursue?

- Target response of 0.6 or 0.7 seems to provide reasonable dose selection guidance
Example 8: Slopes from a Random Effects Linear Model
Data and Summary

• Same as Example 4.1 in Pinheiro et al [StatMed2014]

• Evaluate effect of various doses of a new drug on disease rate progression \( \equiv \) slope of linear regn fitted to a patient’s obsns

• 100 patients, 5 functional scale measurement times, treated with 0, 1, 3, 10, or 30 mg

• Step 1: Fit mixed effects linear regns to patients’ sequences, easy to do using lme function in nlme R package to get patient-specific slopes

• Posterior weights for the various models

<table>
<thead>
<tr>
<th>Linear</th>
<th>Quadratic</th>
<th>Linear Log</th>
<th>Quadratic Log</th>
<th>EMAX</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.10</td>
<td>0.02</td>
<td>0.39</td>
<td>0.49</td>
<td>0.00</td>
</tr>
</tbody>
</table>

• Model fit evaluations confirm that quadratic log dose and EMAX provide the best fits
Posterior Summary

- Posterior dose-response function and 1\textsuperscript{st} derivatives

- Pinheiro \textit{et al} estimate dose needed to get 1.4 unit improvement relative to pbo as 2.13 or 2.15

- Better choice might be 5 or 6 units because of variability, to guard against inadequate dose response
Comments and Discussion
The Message

• Bayesian Model Averaging is an efficient and flexible tool for
  o Characterizing dose-response relationships
  o Finding ‘correct’ doses to carry forward

• Key Attributes
  o No need to identify a ‘best’ model
  o Multiplicity adjustments not needed
  o Flexible distributional structure for data likelihood
  o Direct assessment of PoC using small samples
  o Identification of dose range corresponding to specified response targets

• Definitive graphical displays of analysis results simplifies communication

• Software (reasonably user friendly) available for calculations
BMA Analyses Useful for:

• Inferences about the response at each dose level

• Separate objectives: (a) Determining if \( \exists \) a D-R relationship  
   (b) Identifying appropriate dose ranges  
     - Lower quantile of posterior dist’n of 1\(^{st}\) derivative > 0 \( \Rightarrow \)  
       reasonable to conclude a D-R relationship exists  
     - Establish or rule out PoC with modest trials  
     - Use predictive distributions of future responses to inform  
       definitive trials of specific doses

• No need for approximations or assumptions of asymptotic behavior

• Include as many models as are clinically sensible

• Posterior distributions of doses corresponding to target outcomes can be used to determine doses to carry forward
Further Comments

• Just identifying doses that differ significantly from control may not be best dose finding strategy

• Better: quantify the anticipated responses to a set of doses, use results to determine dose range that gives target outcomes
  o High enough to provide target outcome
  o Low enough to minimize toxicity risk

• Determining appropriate dose depends on value of corresponding responses, which depends on
  o Effectiveness
  o Toxicity potential
  o Appeal/convenience of dosage regimen
  o Competition
  o Production cost
## Comparison of Bayes & MCPMod (1)

<table>
<thead>
<tr>
<th>MCPMod</th>
<th>Bayes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical team: decide on the core aspects of the trial design, specify M plausible dose-response models and K doses to include in the trial.</td>
<td>Identify likelihoods &amp; parameters for each model</td>
</tr>
<tr>
<td>Determine model-specific ‘optimal’ dose-response contrasts &amp; sample sizes needed to detect a dose-response relationship</td>
<td>Determine prior model weights (various approaches possible)</td>
</tr>
<tr>
<td>Fit each model to observed data using ANOVA or regression, estimate expected response at each dose, assuming asymptotic normality of parameter estimates</td>
<td>Use MCMC to get realizations from joint posterior distns of each model’s parameters, obtain realizations of functions of the parameters.</td>
</tr>
<tr>
<td>Use ‘optimal’ contrasts to identify dose-response relationships for each model. Overall test uses max of model-specific test statistics, critical values assume multivariate normality</td>
<td>No testing. Estimates of functions of parameters include credible intervals. Could base positive dose-response conclusion on posterior dist’n of first derivatives of D-R functions.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>MCPMod</th>
<th>Bayes</th>
</tr>
</thead>
<tbody>
<tr>
<td>If significant max z value, identify a ‘reference set’ of the models with z-statistics large enough to reject the null hypothesis of zero ‘optimal’ contrast values.</td>
<td>No need to select a 'best' model. Bayesian model averaging → optimum estimate that combines input from all models.</td>
</tr>
<tr>
<td>Use inverse regression based on a ‘best’ model or a weighted average of models to estimate target doses for further development; determine precision using bootstrapping</td>
<td>Determine posterior probabilities of doses corresponding to responses falling in a specified interval. Use with utility functions or other information to guide dose selection.</td>
</tr>
</tbody>
</table>
Post Processing

- N realizations (MCMC) from joint posterior dist’n of parameters for model m (m = 1, ..., M)
  \[ \mathbf{b}^{(m)} = \]

- Look at posterior distributions of functions of the elements of the \( \mathbf{b}_i^{(m)} \)

<table>
<thead>
<tr>
<th>MCMC Realization</th>
<th>Model m Parameter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \mathbf{b}_1^{(m)} )</td>
</tr>
<tr>
<td>2</td>
<td>( \mathbf{b}_2^{(m)} )</td>
</tr>
<tr>
<td>\vdots</td>
<td>\vdots</td>
</tr>
<tr>
<td>N</td>
<td>( \mathbf{b}_N^{(m)} )</td>
</tr>
</tbody>
</table>

- Expected responses at various doses → dose distributions
- Likelihood for obs’ed outcomes → posterior model weights
- Use weights to calculate Bayes averages of model-specific quantities

\[ \mathbf{y}^{(m)} = \text{array with rows } \mathbf{y}_1^{(m)}, ..., \mathbf{y}_N^{(m)} = \text{N realizations from the joint posterior dist’n of functions of the parameters} \]
## Determining Prior Wts using AHP

- Pairwise comparisons of models by relative importance judged by clinicians
  - 1 = equal, 2 = slightly more, 3 = moderately more, 5 = strongly more important

<table>
<thead>
<tr>
<th>MODEL</th>
<th>Linear</th>
<th>Quadratic</th>
<th>Log Linear</th>
<th>Log Quadratic</th>
<th>EMAX</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>1</td>
<td>0.33</td>
<td>0.5</td>
<td>0.33</td>
<td>0.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Quadratic</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Log Linear</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.33</td>
<td>0.2</td>
<td>0.33</td>
</tr>
<tr>
<td>Log Quadratic</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0.2</td>
<td>0.33</td>
</tr>
<tr>
<td>EMAX</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Exponential</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0.2</td>
<td>1</td>
</tr>
</tbody>
</table>

- Model weights: 0.05, 0.09, 0.07, 0.11, 0.48, 0.20
  - Calculate as normalized eigenvector corresponding to maximum positive eigenvalue
Determining ‘Effective’ Doses (details)

- Matrix \( Y^{(m)} \) of functions of MCMC realizations of model parameters

- \( f_d(\vec{b}^{(m)}_i) \equiv \text{expected response to dose } d \text{ given the } i\text{-th realization of the parameters for model } m, \ d = 1, \ldots, S \)

- Also,
  - \( f_y^{(m)}(y; d) = \text{posterior density of } y^{(m)} \text{ (d-th col of } Y^{(m)}\text{)} \)
  - \( R_y = (y \mid y \in (y_L, y_U)) = \text{an interval of response values} \)
  - \( P(R_y \mid d; m) = \int_{y_L}^{y_U} f_y^{(m)}(y; d) dy \rightarrow P_{\text{post}}(y \in R_y \mid d, m) \)

- Hence, \( P(d_j \mid R_y; m) = \frac{\theta_j}{\sum_j \theta_j} P(R_y \mid d_j; m) \)
  - Posterior probability of dose \( d_j \)

\[\begin{array}{l|l}
\text{MCMC} & \text{Functions of Model } m \text{ Parameters} \\
\hline
1 & y_1^{(m)} = f_1(\vec{b}_1^{(m)}), f_2(\vec{b}_1^{(m)}), \ldots, f_S(\vec{b}_1^{(m)}) \\
2 & y_2^{(m)} = f_1(\vec{b}_2^{(m)}), f_2(\vec{b}_2^{(m)}), \ldots, f_S(\vec{b}_2^{(m)}) \\
& \vdots \\
N & y_N^{(m)} = f_1(\vec{b}_N^{(m)}), f_2(\vec{b}_N^{(m)}), \ldots, f_S(\vec{b}_N^{(m)})
\end{array}\]