Adaptive dose-finding for correlated bivariate data with applications to complement system inhibition studies

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Outline

1. Adaptive dose-finding in phase I/II trials
2. Complement system inhibition studies
3. Method of adaptive dose-finding
4. Simulation study
Adaptive Dose-Finding in Phase I/II Trials

- Adaptive: subject’s dose level is determined using previous subjects’ data
- Phase I/II: Combines the goals of a phase I and phase II trials into a single trial
  - Identifies a dose or group of doses that meet some tolerability and effectiveness criteria
- Properties:
  - First-in-human (often)
  - Small sample size
  - Sequential enrollment
- Often use Bayesian statistical methods
  - Easily incorporates accumulating information
Bivariate Continual Reassessment Method (bCRM)

- Adaptive dose-finding method used in Phase I/II trials
- First bCRM proposed by Braun (2001) for binary toxicity and efficacy responses
- Three elements:
  - Probability distribution of the responses
    - Jointly or separately models the toxicity and efficacy responses
  - Dose-response models
    - Mathematical relationships between the efficacy and toxicity means and dose levels
  - Decision function
    - Function that combines toxicity and efficacy estimates to make decisions
Complement System Inhibition Studies

- The complement system is a part of the innate human immune system.
- Inhibition of this system can provide therapeutic effects for inflammatory diseases.
  - Ex: rheumatoid arthritis.
- Treatments for such diseases may act through inhibition of the complement system.
- Implication for clinical trials:
  - Complement system inhibition is an important surrogate measure for effectiveness.
Compartment System Inhibition
Study Data

- Toxicity response – binary indicator
- Efficacy response – percentage of the complement system inhibited
  - Continuous
  - Bounded on [0,1]
- Options for Phase I/II trials:
  - Dichotomize the efficacy outcome (i.e. drug is successful if inhibition is > 0.50)
    - Lose information
  - Use approaches for continuous data
    - Assume that the data is normal
    - Do not account for bounded data
  - Create bCRM for bounded continuous data
Method—Responses

• For the $ith$ subject, assigned the $jth$ dose let:
  - $y_{bij} = \begin{cases} 
  1, & toxicity \\
  0, & no toxicity 
\end{cases}$
  - $y_{cij}$ be the percentage inhibited
  - $d_j$ be the $jth$ dose level
  - $1 \leq j \leq J, 1 \leq i \leq n_j$
**Method—Distribution**

- $y_{bij}$ is assumed to be a binomial random variable with success probability $p_{ij}$

$$ - f(y_{bij} \mid d_j) = \exp \left[ y_{bij} \log \left( \frac{p_{ij}}{1-p_{ij}} \right) + \log(1 - p_{ij}) \right] $$

- $y_{cij} \mid y_{bij}, d_j$ is assumed to be a normal random variable with mean $\mu_{ij} + \tau (y_{bij} - p_{ij})$, variance $\sigma_j^2$, truncated to $[0,1]$

$$ - f(y_{cij} \mid y_{bij}, d_j) = \frac{1}{\sigma_j} \phi \left( \frac{y_{cij} - (\mu_{ij} + \tau (y_{bij} - p_{ij}))}{\sigma_j} \right) - \phi \left( \frac{0 - (\mu_{ij} + \tau (y_{bij} - p_{ij}))}{\sigma_j} \right) $$

- Where $\phi$ and $\Phi$ are the PDF and CDF of a standard normal distribution
- $\tau$ determines the correlation between the toxicity and efficacy responses

- The joint distribution function is:

$$ - f(y_{bij}, y_{cij} \mid d_j) = f(y_{bij} \mid d_j) f(y_{cij} \mid y_{bij}, d_j) $$
Method—Dose-Response Models

- Linear dose-response models with logit link functions
  - Toxicity
    - $\log \left( \frac{p_{ij}}{1-p_{ij}} \right) = \alpha_0 + \alpha_1 d_j$
  - Efficacy
    - $\log \left( \frac{\mu_{ij}}{1-\mu_{ij}} \right) = \beta_0 + \beta_1 d_j$
Method—Decision Function

• Prior to the trial, set:
  – \( p_0 \): upper bound for unacceptable toxicity
  – \( \mu_0 \): lower bound for unacceptable efficacy
• Dose allocation:
  – Using the Metropolis-Hasting algorithm to estimate posterior means, find estimates \((\hat{p}_j, \hat{\mu}_j)\)
  – Consider doses with \( \hat{p}_j < p_0 \) and \( \hat{\mu}_j > \mu_0 \)
  – Optimally: \((p_j, \mu_j) = (0,1)\)
  – Of the doses under consideration, the dose with the smallest Euclidean distance from \((0,1)\) is the dose allocated
    
    \[ \hat{e}_j = \sqrt{(0 - \hat{p}_j)^2 + (1 - \hat{\mu}_j)^2} \]

• End of study:
  – The dose with the minimum \( \hat{e}_j \) is the recommended dose (RD)
Simulation Study

• Maximum number of subjects = 36
• Subjects enrolled in groups of 3
• Toxicity and efficacy limits:
  – No early-stopping for futility
    • $\mu_0 = 0$
  – Toxicity limit of 0.30 targeted
    • $p_0$ varied from 0.30 to 1.00
    • Setting $p_0 = 0.30$ may be too strict, especially for early dose-allocation
• Vague priors used for all parameters
Simulation Study – Data

<table>
<thead>
<tr>
<th>Scenario</th>
<th>((p_1, \mu_1))</th>
<th>((p_2, \mu_2))</th>
<th>((p_3, \mu_3))</th>
<th>((p_4, \mu_4))</th>
<th>((p_5, \mu_5))</th>
<th>((p_6, \mu_6))</th>
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<tbody>
<tr>
<td>1</td>
<td>(0.01, 0.10)</td>
<td>(0.04, 0.45)</td>
<td><strong>(0.17, 0.86)</strong></td>
<td>(0.48, 0.98)</td>
<td>(0.80, 0.99)</td>
<td>(0.95, 0.99)</td>
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<tr>
<td>2</td>
<td>(0.31, 0.50)</td>
<td>(0.37, 0.88)</td>
<td>(0.43, 0.98)</td>
<td>(0.49, 0.99)</td>
<td>(0.55, 0.99)</td>
<td>(0.61, 0.99)</td>
</tr>
</tbody>
</table>

- Scenario 1: \(d_j = 3\) is the true best dose
  - Dose with smallest distance to \((0,1)\) that has acceptable toxicity
- Scenario 2: All doses are too toxic
  - Examines the effect of varying \(p_0\)
Simulation Study – Data

Scenario 1

Dose

Toxicity/Efficacy/Distance

1 2 3 4 5 6

1.0
0.8
0.6
0.4
0.2
0.0

Toxicity
Efficacy
Distance
Simulation Study – Data

Scenario 2

Toxicity/Efficacy/Distance vs. Dose

- Red: Toxicity
- Green: Efficacy
- Blue: Distance
Scenario 1 – Results

<table>
<thead>
<tr>
<th>Toxicity Limit</th>
<th>Percent Recommended</th>
<th>Sample Size</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>None</td>
<td>1</td>
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<tr>
<td>(p_0)</td>
<td>0.30</td>
<td>0.3</td>
</tr>
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<td></td>
<td>0.35</td>
<td>0.1</td>
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<td></td>
<td>0.40</td>
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- For all values of \(p_0\), greater than 80% correct dose recommendation
- Performs better for increased values of \(p_0\)
- Not much gained by increasing beyond \(p_0 = 0.45\)
Scenario 2 – Results

<table>
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<tr>
<th>Toxicity Limit</th>
<th>Percent Recommended</th>
<th>Sample Size</th>
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<tr>
<td>$p_0$</td>
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<tr>
<td>0.30</td>
<td>62.4</td>
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<td></td>
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<td></td>
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</table>

- For all $p_0$, all doses estimated to be too toxic at least 28% of the time
- As $p_0$ decreases, this percentage increases dramatically
- Values close to $p_0 = 0.30$ are more conservative with respect to toxicity
Conclusions

• This presentation introduced a bCRM for using in complement system inhibition studies
• This method performed well in the scenarios studied
• Simulation performance varies depending on toxicity limit
• Future work: compare results with other bCRMs and examine scenarios in which the dose-response models are misspecified
Questions?