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

Complement 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}
  - $f(y_{bij}|d_j) = exp\left[y_{bij}\log\left(\frac{p_{ij}}{1-p_{ij}}\right) + \log(1-p_{ij})\right]$
- $y_{cij}|y_{bij}, d_j$ is assumed to be a normal random variable with mean $\mu_{ij} + \tau(y_{bij} - p_{ij})$, variance σ_j^2, truncated to $[0,1]$
  - $f(y_{cij}|y_{bij}, d_j) = \frac{\frac{1}{\sigma_j}\emptyset\left(\frac{y_{cij}-\{\mu_{ij}+\tau(y_{bij}-p_{ij})\}}{\sigma_j}\right)}{\Phi\left(\frac{1-\{\mu_{ij}+\tau(y_{bij}-p_{ij})\}}{\sigma_j}\right) - \Phi\left(\frac{0-\{\mu_{ij}+\tau(y_{bij}-p_{ij})\}}{\sigma_j}\right)}$
    - Where $\emptyset$ and Φ are the PDF and CDF of a standard normal distribution
    - τ determines the correlation between the toxicity and efficacy responses
- The joint distribution function is:
  - $f(y_{bij}, y_{cij}|d_j) = f(y_{bij}|d_j)f(y_{cij}|y_{bij}, d_j)$

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
  - μ_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

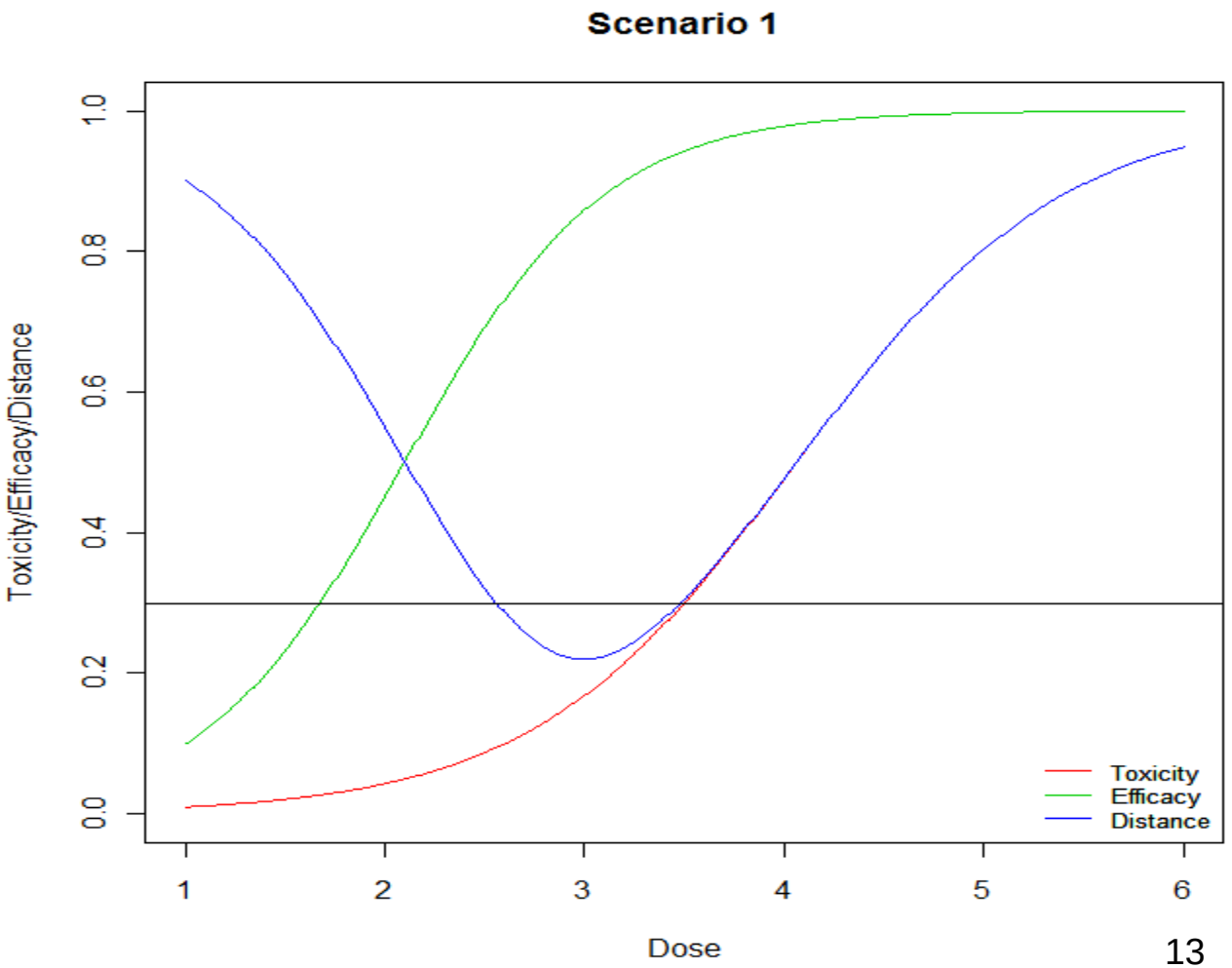
- Maximum number of subjects = 36
- Subjects enrolled in groups of 3
- Toxicity and efficacy limits:
  - No early-stopping for futility
    - $\mu_0 = 0$
  - Toxicity limit of 0.30 targeted
    - p_0 varied from 0.30 to 1.00
    - Setting $p_0 = 0.30$ may be too strict, especially for early dose-allocation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

Simulation Study – Data

Scenario	(p_1, μ_1)	(p_2, μ_2)	(p_3, μ_3)	(p_4, μ_4)	(p_5, μ_5)	(p_6, μ_6)
1	(0.01,0.10)	(0.04,0.45)	**(0.17,0.86)**	(0.48,0.98)	(0.80,0.99)	(0.95,0.99)
2	(0.31,0.50)	(0.37,0.88)	(0.43,0.98)	(0.49,0.99)	(0.55,0.99)	(0.61,0.99)

- 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



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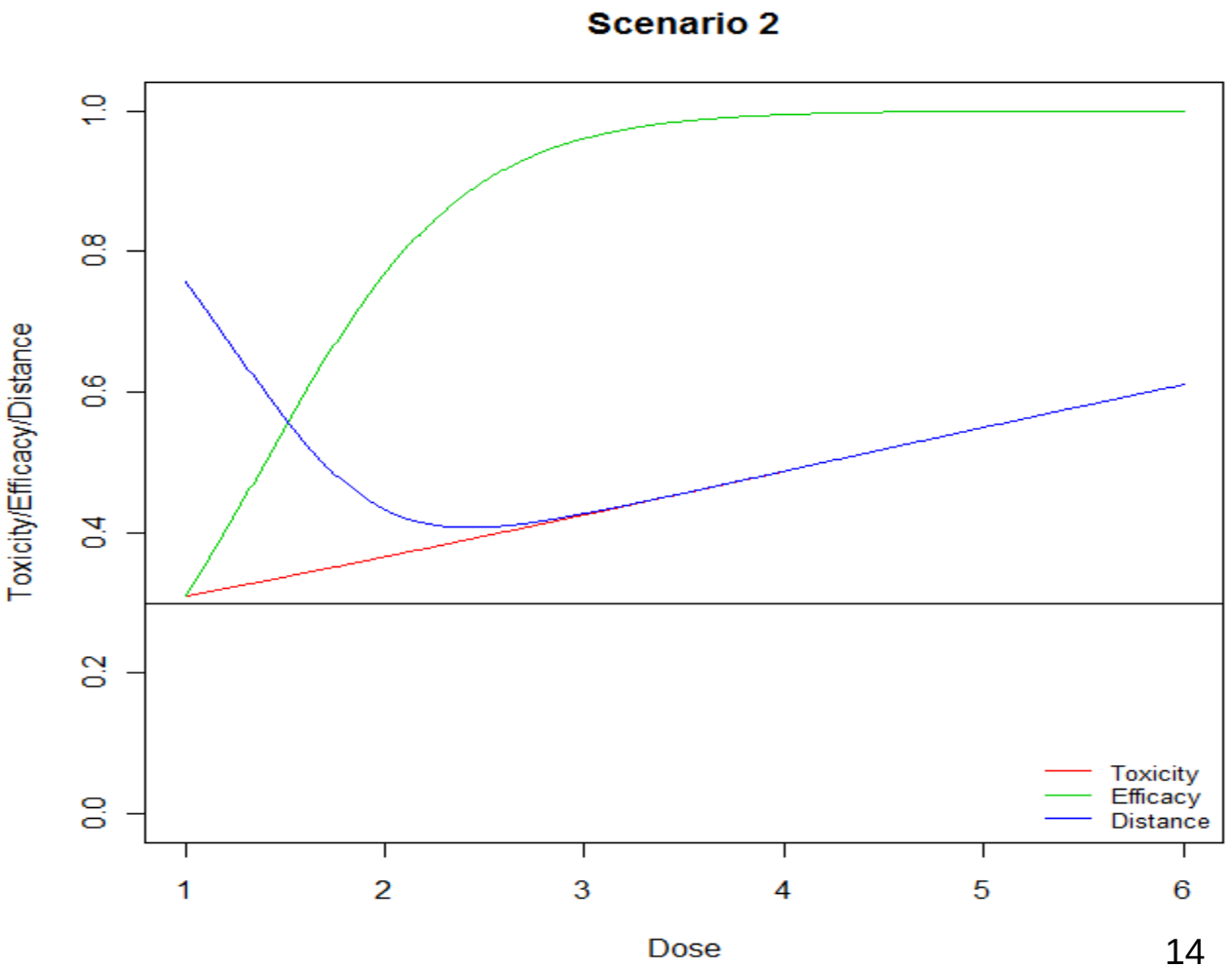

Scenario 1 – Results

Toxicity Limit	Percent Recommended							Sample Size
p_0	None	1	2	**3**	4	5	6	
0.30	0.3	0.3	17.2	**81.4**	0.8	0.0	0.0	28.6
0.35	0.1	0.2	10.9	**87.4**	1.3	0.1	0.0	27.4
0.40	0.0	0.4	6.8	**91.2**	1.6	0.0	0.0	27.6
0.45	0.2	0.2	4.7	**94.6**	0.5	0.0	0.0	27.0
0.50	0.2	0.0	2.7	**96.4**	0.7	0.0	0.0	27.0
1.00	0.0	0.2	2.3	**96.5**	1.0	0.0	0.0	26.8

- 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

Toxicity Limit	Percent Recommended							Sample Size
p_0	None	1	2	3	4	5	6	
0.30	**62.4**	24.3	11.5	1.7	0.1	0.0	0.0	16.3
0.35	**55.8**	24.7	17.3	2.2	0.0	0.0	0.0	16.9
0.40	**52.4**	26.4	19.5	1.7	0.0	0.0	0.0	16.7
0.45	**42.9**	20.7	32.8	3.6	0.0	0.0	0.0	18.5
0.50	**44.7**	24.8	28.0	2.5	0.0	0.0	0.0	20.1
1.00	**28.8**	5.4	53.0	2.5	0.0	0.0	0.0	18.7

- 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?