Bayesian Dose-level Finding Methodology

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Abstract

Traditionally, rule-based dose finding methods are adopted for separate phase 1 and 2 trials which aim to find the maximum tolerated dose level and evaluate efficacy of an experimental drug. Johnson and Liu (2016) proposed a single early phase trial model based approach which follows a Bayesian framework that maximizes a utility function. The utility function accounts for desired trade offs between efficacy and toxicity opposed to simply maximizing the dose level until reaching the maximum tolerated dose level. Additionally, we propose a bi-variate probit model to jointly model the binary outcomes of efficacy and toxicity. We conduct extensive simulation studies to examine the operating characteristics of our proposed model versus the Johnson and Liu (2016) model under various practical dose-efficacy and dose-toxicity relationships.

KEY WORDS: Dose finding, Adaptive design, Bayesian models, Bi-variate probit model, Utility

1 Introduction

A primary objective for early phase clinical trials is to identify the maximum tolerated dose level (MTD) of a new drug. The MTD is the dose level where side effects are serious enough to prevent an increase in dose or dose level. Often, for the first phase of a trial, several dose levels are tested to build a toxicity profile of the drug. In the second phase, the drug is administered to a small cohort of patients to build an efficacy profile. With successful results, a third phase begins with a larger cohort of patients. There are some disadvantages to having separate phase one and two trials. The MTD results from a phase one trial are often unreliable due to the often small sample size obtained, thus the results are susceptible to inconsistencies in data collection. As a consequence, MTD can have high variability. Dose adjustments may need to be made for phase two trials if excessive toxicity is reached. Additionally, physicians commonly use rule-based trial designs such as the "3+3" trial design. Rule-based trial designs tend to have limited flexibility, are unable to account for inconsistencies in data, and do not properly utilize previously collected data in further testing, such as information from other dose levels.

An alternative is using a model-based approach under a Bayesian Framework with a singular, early-phase trial aiming to find the optimal dose level of an experimental drug by maximizing a utility function. The utility function accounts for desired trade-offs between efficacy and toxicity rather than simply maximizing the dose level before reaching excessive toxicity. Independent, default prior densities are used to provide information of the expected

efficacy and toxicity which monotonically increase with dose level. Despite the constraint of efficacy and toxicity increasing with dose level, the dose-efficacy and dose-toxicity curves remain fairly malleable, allowing patient results to influence these relationships. Offering model flexibility and accounting for the efficacy and toxicity trade-offs provide important ethical implications, which may be beneficial for patient recruiting.

In our example, we set out to discover the most optimal dose level amongst 5 potential dose levels predetermined for testing by physicians. We compare the Bernoulli probability model from Johnson and Liu (2016) with our proposed bi-variate probit regression model that incorporates dependencies between efficacy and toxicity. For comparison, we simulated efficacy and toxicity from a joint Gumbel distribution for a range of efficacy and toxicity scenarios that may come up during dose-finding trials. We simulated 16 cohorts of 3 patients who received doses in cycles for a total sample size of 48. For the simulations, we assumed very little prior information on the shape of the efficacy and toxicity curves.

2 Johnson and Liu Probability Model

Let y_{Ei} and y_{Ti} represent the binary outcomes for efficacy and toxicity for patient i, where $i = 1, ..., n(t)$, for trial time t. $y_{Ei} = 1$ means the dose given to patient i had an effective response and $y_{Ti} = 1$ means the dose given to patient i showed symptoms resulting from toxicity. Likewise, $y_{Ei} = 0$ and $y_{Ti} = 0$ represent no efficacy or toxicity responses in patient i. For the dose level j, where $j = 1, ..., J$, p_{Ej} and p_{Tj} represent the probability of efficacy and toxicity responses. y_{Ei} and y_{Ti} are modeled with the following Bernoulli distribution,

$$\begin{aligned}
&y_{ki}|d_{[i]} = j \sim Bernoulli(p_{kj}), \;\; k \in \{E, T\}, \\
&p_{kj} = p_{k,j-1} + (1 - p_{k,j-1})\beta_{kj}, \;\; j = 2, ..., J, \\
&p_{k1} = \beta_{k1}, \\
&\beta_{kj} \sim Beta(a_{kj}, b_{kj}).
\end{aligned} \tag{1}$$

In the model, p_{Ej} and p_{Tj} follow a Markov structure, where p_{kj}'s scale through the equation $p_{k,j-1}+(1-p_{k,j-1})\beta_{kj}$, where β_{kj} is a positive variate generated from the Beta distribution. So, we can see that p_{kj} increases with an increase of dose level where $p_{k1} < p_{k2} ... < p_{kJ}$. We can rewrite p_{kj} as $p_{kj} = 1 - (1 - p_{k,j-1})(1 - \beta_{k,j})$, which implies;

$$p_{kj} = 1 - \prod_{r=1}^{j}(1 - \beta_{kr}), \tag{2}$$

Given n patients and J dose levels, where dose $d_{[i]}$ represents the dose chosen for patient i, the model's likelihood function is

$$\begin{aligned}
L(\boldsymbol{\beta_E}, \boldsymbol{\beta_T}|\mathcal{D}_{(t)}) &= \prod_{k=\{E,T\}} \prod_{i=1}^{n(t)} \left\{ 1 - \prod_{r=1}^{d[i]}(1 - \beta_{kr}) \right\}^{y_{ki}} \prod_{r=1}^{d[i]} (1 - \beta_{kr})^{1-y_{ki}} \\
&= \prod_{k=\{E,T\}} \prod_{i=1}^{n(t)} \left\{ 1 - \prod_{r=1}^{d[i]}(1 - \beta_{kr}) \right\}^{y_{ki}} \prod_{r=1}^{d[i]} (1 - \beta_{kr})^{1-y_{ki}}
\end{aligned} \tag{3}$$

where $\boldsymbol{\beta_E} = (\beta_{E1}, ..., \beta_{EJ})$, $\boldsymbol{\beta_T} = (\beta_{T1}, ..., \beta_{TJ})$ and $\mathcal{D}_{(t)} = \{(d_{[i]}, y_{Ei}, y_{Ti}), i = 1, ..., n(t)\}$. The priors for $\boldsymbol{\beta_E}$ and $\boldsymbol{\beta_T}$ which we will define as, $\pi(\boldsymbol{\beta_E})$ and $\pi(\boldsymbol{\beta_T})$, follow Beta distributions, as defined earlier, where

$$\begin{aligned}
\pi(\boldsymbol{\beta_E}) &= \prod_{j=1}^{J} \frac{\Gamma(\alpha_{Ej} + b_{Ej})}{\Gamma(\alpha_{Ej})\Gamma(b_{Ej})} (\beta_{Ej})^{\alpha_{Ej}-1}(1-\beta_{Ej})^{b_{Ej}-1} \\
\pi(\boldsymbol{\beta_T}) &= \prod_{j=1}^{J} \frac{\Gamma(\alpha_{Tj} + b_{Tj})}{\Gamma(\alpha_{Tj})\Gamma(b_{Tj})} (\beta_{Tj})^{\alpha_{Tj}-1}(1-\beta_{Tj})^{b_{Tj}-1}
\end{aligned} \tag{4}$$

Therefore, the posterior distribution, $f(\boldsymbol{\beta_E}, \boldsymbol{\beta_T}|\mathcal{D}_{(t)})$, can be written as

$$\begin{aligned}
f(\boldsymbol{\beta_E},&\boldsymbol{\beta_T}|\mathcal{D}_{(t)}) \propto L(\boldsymbol{\beta_E}, \boldsymbol{\beta_T}|\mathcal{D}_{(t)})\pi(\boldsymbol{\beta_E})\pi(\boldsymbol{\beta_T}) \\
&= \prod_{i=1}^{n(t)} \left\{1 - \prod_{r=1}^{d[i]}(1-\beta_{Er})\right\}^{y_{Ei}} \prod_{r=1}^{d[i]} (1-\beta_{Er})^{1-y_{Ei}} \\
&\quad \left\{1 - \prod_{r=1}^{d[i]}(1-\beta_{Tr})\right\}^{y_{Ti}} \prod_{r=1}^{d[i]} (1-\beta_{Tr})^{1-y_{Ti}} \prod_{j=1}^{J} \frac{\Gamma(\alpha_{Ej} + b_{Ej})}{\Gamma(\alpha_{Ej})\Gamma(b_{Ej})} \\
&\quad (\beta_{Ej})^{\alpha_{Ej}-1}(1-\beta_{Ej})^{b_{Ej}-1} \prod_{j=1}^{J} \frac{\Gamma(\alpha_{Tj} + b_{Tj})}{\Gamma(\alpha_{Tr})\Gamma(b_{Tj})} (\beta_{Tj})^{\alpha_{Tj}-1}(1-\beta_{Tj})^{b_{Tj}-1} \\
&\propto \prod_{i=1}^{n(t)} \left\{1 - \prod_{r=1}^{d[i]}(1-\beta_{Er})\right\}^{y_{Ei}} \prod_{r=1}^{d[i]} (1-\beta_{Er})^{1-y_{Ei}} \left\{1 - \prod_{r=1}^{d[i]}(1-\beta_{Tr})\right\}^{y_{Ti}} \\
&\quad \prod_{r=1}^{d[i]} (1-\beta_{Tr})^{1-y_{Ti}} \prod_{j=1}^{J} (\beta_{Ej})^{\alpha_{Ej}-1}(1-\beta_{Ej})^{b_{Ej}-1}(\beta_{Tj})^{\alpha_{Tj}-1}(1-\beta_{Tj})^{b_{Tj}-1}
\end{aligned} \tag{5}$$

Since y_{Ei} and y_{Ti} are assumed independent, we can model independent full conditionals of $\boldsymbol{\beta_E}$ and $\boldsymbol{\beta_T}$.

$$\begin{aligned}
&f(\boldsymbol{\beta_E}, \boldsymbol{\beta_T}|\mathcal{D}_{(t)}) \propto f(\boldsymbol{\beta_E}|y_{Ei}, d_{[i]})f(\boldsymbol{\beta_T}|y_{Ti}, d_{[i]}) \\
&f(\boldsymbol{\beta_E}|y_{Ei}, d_{[i]}) \propto \prod_{i=1}^{n(t)} \left\{1 - \prod_{r=1}^{d[i]}(1-\beta_{Er})\right\}^{y_{Ei}} \prod_{r=1}^{d[i]} (1-\beta_{Er})^{1-y_{Ei}} \prod_{j=1}^{J} (\beta_{Ej})^{\alpha_{Ej}-1}(1-\beta_{Ej})^{b_{Ej}-1} \\
&f(\boldsymbol{\beta_T}|y_{Ti}, d_{[i]}) \propto \prod_{i=1}^{n(t)} \left\{1 - \prod_{r=1}^{d[i]}(1-\beta_{Tr})\right\}^{y_{Ti}} \prod_{r=1}^{d[i]} (1-\beta_{Tr})^{1-y_{Ti}} \prod_{j=1}^{J} (\beta_{Tj})^{\alpha_{Tj}-1}(1-\beta_{Tj})^{b_{Tj}-1}
\end{aligned} \tag{6}$$

With the full conditional posterior distributions of $f(\boldsymbol{\beta_E}|y_{Ei}, d_{[i]})$ and $f(\boldsymbol{\beta_{Tj}}|y_{Ti}, d_{[i]})$, we aim to obtain posterior samples of β_{Ej} and β_{Tj} through the use of a Monte Carlo Markov Chain (MCMC). We use these values to get the corresponding p_{Ej} and p_{Tj} posterior estimates. The chosen starting values for $\boldsymbol{\beta_E}$ and $\boldsymbol{\beta_T}$ are derived from the prior values of $\tilde{p}_{Ej}$ and $\tilde{p}_{Tj}$ which are discussed in section 2.1 after rearranging equation 2.

2.1 Prior Specification

The hyper-parameter values for a_{kj} and b_{kj}, in the prior Beta distribution, can be derived from prior probability estimates for efficacy and toxicity given from physicians. Let $\tilde{p}_{kj}$ represent the prior probabilities for efficacy and toxicity that are given from physicians for dose j and outcomes $k \in \{E, T\}$. These prior probabilities are values derived from previous studies or physician expectation for a the given dose levels. By re-arranging equation 2, we can solve for B_{kj}:

$$\begin{aligned} \beta_{kj} &= \frac{\tilde{p}_{kj} - \tilde{p}_{k,j-1}}{1 - \tilde{p}_{k,j-1}} \\ \tilde{p}_{k0} &= 0 \end{aligned} \tag{7}$$

Since β_{kj} follows a Beta distribution, we can equate the prior mean of $\beta_{kj} = \frac{a_{kj}}{a_{kj}+b_{kj}}$ to $\frac{\tilde{p}_{kj}-\tilde{p}_{k,j-1}}{1-\tilde{p}_{k,j-1}}$. Additionally, we set a constraint by fixing $a_{kj} + b_{kj} = m$, where m is a constant representing the "effective sample size." A weakly informative prior is achieved by setting m to a low positive value like $m = 1$. With this constraint, we can obtain values for the hyper-parameters.

$$\begin{aligned} a_{kj} &= m\frac{\tilde{p}_{kj} - \tilde{p}_{k,j-1}}{1 - \tilde{p}_{k,j-1}} \\ b_{kj} &= m\frac{1 - \tilde{p}_{kj}}{1 - \tilde{p}_{k,j-1}} \end{aligned} \tag{8}$$

Assuming prior probability for efficacy of $\tilde{p}_{ej} = (0.2, 0.3, 0.4, 0.5, 0.6)$, and prior probability for toxicity of $\tilde{p}_{tj} = (0.05, 0.1, 0.2, 0.3, 0.35)$, we derive α_{kj} and b_{kj} using equation 8 resulting in, $a_{ej} = (0.2, 0.3, 0.4, 0.5, 0.6)$, $b_{ej} = (0.8, 0.7, 0.6, 0.5, 0.4)$, $a_{tj} = (0.05, 0.1, 0.2, 0.3, 0.35)$, and $b_{tj} = (0.95, 0.9, 0.8, 0.7, 0.65)$.

2.2 Posterior Simulation

For the posterior inference of β_{kj}, for $j = 1, ..., J$ and $k \in \{E, T\}$, we use the independent full conditional distributions for β_{Ej} and β_{Tj} to obtain samples. Since β_{Ej}'s and β_{Tj}'s have bounds $[0, 1]$, it is advisable to perform a logit transformation before sampling. Additionally, since sample sizes may vary between dose levels, we recommend using an adaptive Metropolis Hastings for consistent mixing of the chain. With posterior estimates of β_{kj} we can get our posterior p_{kj} estimates using equation 2.

3 Bi-variate Probit Model

For the bi-variate probit model, with our two binary response variables y_{Ei} and y_{Ti}, we define two latent variables $\tilde{y}_{Ei}$ and $\tilde{y}_{Ti}$,

$$\begin{aligned} y_{Ei} &= \begin{cases} 1 \text{ if } \tilde{y}_{Ei} \geq 0 \\ 0 \text{ if } \tilde{y}_{Ei} < 0 \end{cases} \\ y_{Ti} &= \begin{cases} 1 \text{ if } \tilde{y}_{Ti} \geq 0 \\ 0 \text{ if } \tilde{y}_{Ti} < 0 \end{cases} \end{aligned} \tag{9}$$

In this model, $\tilde{y}_{ki}$ follows the bi-variate normal distribution. Additionally, in order to maintain the assumption the efficacy and toxicity monotonically increase with dose level, we define α_{kj}.

$$
\begin{aligned}
&\tilde{\boldsymbol{y}}_{\boldsymbol{i}} = \begin{bmatrix} \tilde{y}_{Ei} \\ \tilde{y}_{Ti} \end{bmatrix} \mid d_{[i]} = j, \Sigma, \boldsymbol{\mu_j} \sim N_2(\boldsymbol{\mu_j}, \Sigma), \\
&\boldsymbol{\mu_j} = \begin{bmatrix} \tilde{\mu}_{Ej} \\ \tilde{\mu}_{Tj} \end{bmatrix}, \\
&\mu_{k1} = \alpha_{k1} \sim N(\bar{\alpha}_{k1}, \tau_{k1}^2), \\
&\mu_{kj} = \mu_{k,j-1} + \alpha_{kj},\ j = 2, ..., J, \\
&\alpha_{kj} \sim N_+(\bar{\alpha}_{kj}, \tau_{k2}^2),\ \alpha_{kj} > 0
\end{aligned}
\tag{10}
$$

We can see that assumption that efficacy and toxicity increases monotonically is maintained with the added variable α_{kj}, so that, $\mu_{k1} \leq \mu_{k2} \leq ... \leq \mu_{kJ}$. Since, $\mu_{k1} = \alpha_{k1}$, it follows that where $d_{[i]} = j$, $\mu_{kj} = \sum_{r=1}^{d_{[i]}} \alpha_{kr}$. The co-variance matrix Σ is,

$$
\begin{aligned}
&\Sigma = \begin{bmatrix} \sigma_E^2 & \rho\sigma_E\sigma_T \\ \rho\sigma_E\sigma_T & \sigma_T^2 \end{bmatrix} = \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix} \\
&\rho = 2 * (\tilde{\rho} - \frac{1}{2}) \\
&\tilde{\rho} \sim \text{Beta}(a_p, b_p)
\end{aligned}
\tag{11}
$$

We use this form of ρ to maintain $\rho \in [-1, 1]$ and we assume $\sigma_E = \sigma_T = 1$. With this model, for dose level $j = 1, ...J$, the probability of efficacy is equal to $p(\tilde{y}_{Ej} > 0)$ and the probability of toxicity is equal to $p(\tilde{y}_{Tj} > 0)$.

3.1 Conditional distributions for Gibbs Sampling

The full joint distribution is,

$$
\begin{aligned}
&\mathcal{D} = \{y_{Ei}, y_{Ti}, d_{[i]}, i = 1, ..., n(t)\} \\
&p(\tilde{y}_{Ei}, \tilde{y}_{Ti}, \alpha_{kj}, \rho | \mathcal{D}) \propto \prod_{k \in \{E,T\}} \prod_{i=1}^{n(t)} p(\tilde{\boldsymbol{y}}_{\boldsymbol{i}} | d_{[i]}, \alpha, \rho) p(\alpha_{kj}) p(\rho) \{1(\tilde{y}_{ki} \geq 0) y_{ki} + 1(\tilde{y}_{ki} < 0)(1 - y_{ki})\}
\end{aligned}
\tag{12}
$$

Following, the full conditional distributions of our random variables are defined in equations 13-18,

$$
\begin{aligned}
p(\tilde{y}_{Ei}|\tilde{y}_{Ti},\mu_{Ej},\mu_{Tj},\tilde{\rho},\mathcal{D}) \propto & \{1(\tilde{y}_{Ei}\geq 0)y_{Ei}+1(\tilde{y}_{Ei}<0)(1-y_{Ei})\} \\
& N(\mu_{Ej}+[2(\tilde{\rho}-\frac{1}{2})]\frac{\sigma_E}{\sigma_T}(\tilde{y}_{Ti}-\mu_{Tj}),\sigma_E^2(1-[2(\tilde{\rho}-\frac{1}{2})]^2) \\
= & \{1(\tilde{y}_{Ei}\geq 0)y_{Ei}+1(\tilde{y}_{Ei}<0)(1-y_{Ei})\} \\
& N(\sum_{r=1}^{d_{[i]}}\alpha_{Er}+(2\tilde{\rho}-1)(\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr}),1-(2\tilde{\rho}-1)^2)
\end{aligned}
$$

$$
\text{If } y_{Ei}=1,\ \ p(\tilde{y}_{Ei}|\tilde{y}_{Ti},\mu_{Ej},\mu_{Tj},\tilde{\rho},\mathcal{D}) \sim N_+(\sum_{r=1}^{d_{[i]}}\alpha_{Er}+(2\tilde{\rho}-1)(\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr}),1-(2\tilde{\rho}-1)^2)
$$

$$
\text{If } y_{Ei}=0,\ \ p(\tilde{y}_{Ei}|\tilde{y}_{Ti},\mu_{Ej},\mu_{Tj},\tilde{\rho},\mathcal{D}) \sim N_-(\sum_{r=1}^{d_{[i]}}\alpha_{Er}+(2\tilde{\rho}-1)(\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr}),1-(2\tilde{\rho}-1)^2) \tag{13}
$$

$$
\begin{aligned}
p(\tilde{y}_{Ti}|\tilde{y}_{Ei},\mu_{Ej},\mu_{Tj},\tilde{p},\mathcal{D}) \propto & \{1(\tilde{y}_{Ti}\geq 0)y_{Ti}+1(\tilde{y}_{Ti}<0)(1-y_{Ti})\} \\
& N(\mu_{Tj}+[2(\tilde{p}-\frac{1}{2})]\frac{\sigma_E}{\sigma_T}(\tilde{y}_{Ei}-\mu_{Ej}),\sigma_E^2(1-[2(\tilde{p}-\frac{1}{2})]^2) \\
= & \{1(\tilde{y}_{Ti}\geq 0)y_{Ti}+1(\tilde{y}_{Ti}<0)(1-y_{Ti})\} \\
& N(\sum_{r=1}^{d_{[i]}}\alpha_{Tr}+(2\tilde{p}-1)(\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er}),1-(2\tilde{p}-1)^2)
\end{aligned}
$$

$$
\text{If } y_{Ti}=1,\ \ p(\tilde{y}_{Ti}|\tilde{y}_{Ei},\mu_{Ej},\mu_{Tj},\tilde{\rho},\mathcal{D}) \sim N_+(\sum_{r=1}^{d_{[i]}}\alpha_{Tr}+(2\tilde{p}-1)(\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er}),1-(2\tilde{p}-1)^2)
$$

$$
\text{If } y_{Ti}=0,\ \ p(\tilde{y}_{Ti}|\tilde{y}_{Ei},\mu_{Ej},\mu_{Tj},\tilde{\rho},\mathcal{D}) \sim N_-(\sum_{r=1}^{d_{[i]}}\alpha_{Tr}+(2\tilde{p}-1)(\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er}),1-(2\tilde{p}-1)^2) \tag{14}
$$

$$
\begin{aligned}
p(\alpha_{Ej}|\tilde{y}_{Ti},\tilde{y}_{Ei},\alpha_{Tj},\tilde{\rho},\mathcal{D},\alpha_{E,-j}) &\propto \prod_{i=1}^{n(t)} p(\tilde{y}_{Ei}|\tilde{y}_{Ti},\mu_{Ej},\mu_{Tj},\tilde{\rho})p(\mu_{Ej})p(\mu_{Tj})p(\tilde{\rho}) \\
&\propto p(\tilde{y}_{Ei}|\tilde{y}_{Ti},\alpha_{Ej},\alpha_{Tj},\tilde{p})p(\alpha_{Ej}) \\
&\quad \text{Let: } I(\tau_E)\begin{cases}\tau_{E1}^2 \text{ if } j=1\\ \tau_{E2}^2 \text{ if } j>1\end{cases} \\
&= \prod_{i=1}^{n(t)} N(\tilde{y}_{Ei};\sum_{r=1}^{d_{[i]}}\alpha_{Er}+(2\tilde{\rho}-1)(\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr}),1-[2\tilde{\rho}-1]^2)N(\alpha_{Ej};\bar{\alpha}_{Ej},I(\tau_E)^2) \\
&\propto \prod_{i=1}^{n(t)} \exp\left\{-\frac{[\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er}-\rho(\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr})]^2}{2(1-[2\tilde{\rho}-1]^2)}\right\}\exp\left\{-\frac{(\alpha_{Ej}-\bar{\alpha}_{Ej})^2}{2I(\tau_E)^2}\right\}
\end{aligned}
$$

$$
\begin{aligned}
&\text{Let, } z_{Ei}=\tilde{y}_{Ei}-\rho(\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr}) \\
&\qquad = \exp\left\{-\sum_{i=1}^{n(t)}\frac{(z_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er})^2}{2(1-[2\tilde{\rho}-1]^2)}\right\}\exp\left\{-\frac{(\alpha_{Ej}-\bar{\alpha_{Ej}})^2}{2I(\tau_E)^2}\right\} \\
&\qquad = \exp\left\{-\sum_{d_{[i]}\geq j}^{n(t)}\frac{(z_{Ei}-\sum_{r=1}^{d_{[i]}}1(r\neq d_{[i]})\alpha_{Er}-\alpha_{Ej})^2}{2(1-[2\tilde{\rho}-1]^2)}\right\}\exp\left\{-\frac{(\alpha_{Ej}-\bar{\alpha_{Ej}})^2}{2I(\tau_E)^2}\right\} \\
&p(\alpha_{Ej}|\tilde{y}_{Ti},\tilde{y}_{Ei},\alpha_{Tj},\tilde{\rho},\mathcal{D},\alpha_{E,-j}) \propto \begin{cases}N(\mu_{\alpha_{E1}},\sigma^2_{\alpha_{E1}})\text{if } j=1\\ N_+(\mu_{\alpha_{Ej}},\sigma^2_{\alpha_{Ej}}) \text{ if } j>1\end{cases}
\end{aligned}
\tag{15}
$$

$$
\begin{aligned}
p(\alpha_{Tj}|\tilde{y}_{Ti},\tilde{y}_{Ei},\alpha_{Ej},\tilde{\rho},\mathcal{D},\alpha_{E,-j}) &\propto \prod_{i=1}^{n(t)} p(\tilde{y}_{Ti}|\tilde{y}_{Ei},\mu_{Ej},\mu_{Tj},\tilde{\rho})p(\mu_{Ej})p(\mu_{Tj})p(\tilde{\rho}) \\
&\propto p(\tilde{y}_{Ti}|\tilde{y}_{Ei},\alpha_{Ej},\alpha_{Tj},\tilde{p})p(\alpha_{Tj}) \\
&\quad \text{Let: } I(\tau_T)\begin{cases}\tau_{T1}^2 \text{ if } j=1\\ \tau_{T2}^2 \text{ if } j>1\end{cases} \\
&= \prod_{i=1}^{n(t)} N(\tilde{y}_{Ei};\sum_{r=1}^{d_{[i]}}\alpha_{Tr}+(2\tilde{\rho}-1)(\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er}),1-[2\tilde{\rho}-1]^2)N(\alpha_{T1};\bar{\alpha}_{T1},I(\tau_T)^2) \\
&\propto \prod_{i=1}^{n(t)} \exp\left\{-\frac{[\tilde{y}_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr}-\rho(\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er})]^2}{2(1-[2\tilde{\rho}-1]^2)}\right\}\exp\left\{-\frac{(\alpha_{Tj}-\bar{\alpha}_{Tj})^2}{2I(\tau_T)^2}\right\}
\end{aligned}
$$

$$
\begin{aligned}
&\text{Let, } z_{Ti}=\tilde{y}_{Ti}-\rho(\tilde{y}_{Ei}-\sum_{r=1}^{d_{[i]}}\alpha_{Er}) \\
&\qquad = \exp\left\{-\sum_{i=1}^{n(t)}\frac{(z_{Ti}-\sum_{r=1}^{d_{[i]}}\alpha_{Tr})^2}{2(1-[2\tilde{\rho}-1]^2)}\right\}\exp\left\{-\frac{(\alpha_{Tj}-\bar{\alpha_{Tj}})^2}{2I(\tau_T)^2}\right\} \\
&\qquad = \exp\left\{-\sum_{d_{[i]}\geq j}^{n(t)}\frac{(z_{Ti}-\sum_{r=1}^{d_{[i]}}1(r\neq d_{[i]})\alpha_{Tr}-\alpha_{Tj})^2}{2(1-[2\tilde{\rho}-1]^2)}\right\}\exp\left\{-\frac{(\alpha_{Tj}-\bar{\alpha_{Tj}})^2}{2I(\tau_T)^2}\right\} \\
&p(\alpha_{Tj}|\tilde{y}_{Ei},\tilde{y}_{Ti},\alpha_{Ej},\tilde{\rho},\mathcal{D},\alpha_{T,-j}) \propto \begin{cases}N(\mu_{\alpha_{T1}},\sigma^2_{\alpha_{T1}})\text{if } j=1\\ N_+(\mu_{\alpha_{Tj}},\sigma^2_{\alpha_{Tj}}) \text{ if } j>1\end{cases}
\end{aligned}
\tag{16}
$$

$$
\begin{aligned}
\mu_{\alpha_{E1}} &= \sigma^2_{\alpha_{E1}} \left\{ \sum_{i|d_{[i]}\geq j}^{n(t)} \frac{(z_{Ei} - \sum_{r=1}^{d_{[i]}} 1(r \neq 1)\alpha_{Er})}{1-(2\tilde{\rho}-1)^2} + \frac{\bar{\alpha}_{E1}}{{\tau_{E1}}^2} \right\} \\
\mu_{\alpha_{Ej}} &= \sigma^2_{\alpha_{Ej}} \left\{ \sum_{i|d_{[i]}\geq j}^{n(t)} \frac{(z_{Ei} - \sum_{r=1}^{d_{[i]}} 1(r \neq j)\alpha_{Er})}{1-(2\tilde{\rho}-1)^2} + \frac{\bar{\alpha}_{Ej}}{{\tau_{E2}}^2} \right\} \\
\sigma^2_{\alpha_{E1}} &= \left\{ \frac{\sum_{i=1}^{n(t)} 1(d[i] > j)}{[1-(2\tilde{p}-1)^2]} + \frac{1}{{\tau_{E1}}^2} \right\}^{-1} \\
\sigma^2_{\alpha_{Ej}} &= \left\{ \frac{\sum_{i=1}^{n(t)} 1(d[i] > j)}{[1-(2\tilde{p}-1)^2]} + \frac{1}{{\tau_{E2}}^2} \right\}^{-1} \\
\mu_{\alpha_{T1}} &= \sigma^2_{\alpha_{T1}} \left\{ \sum_{i|d_{[i]}\geq j}^{n(t)} \frac{(z_{Ti} - \sum_{r=1}^{d_{[i]}} 1(r \neq 1)\alpha_{Tr})}{1-(2\tilde{\rho}-1)^2} + \frac{\bar{\alpha}_{T1}}{{\tau_{T1}}^2} \right\} \\
\mu_{\alpha_{Tj}} &= \sigma^2_{\alpha_{Tj}} \left\{ \sum_{i|d_{[i]}\geq j}^{n(t)} \frac{(z_{Ti} - \sum_{r=1}^{d_{[i]}} 1(r \neq j)\alpha_{Tr})}{1-(2\tilde{\rho}-1)^2} + \frac{\bar{\alpha}_{Tj}}{{\tau_{T2}}^2} \right\} \\
\sigma^2_{\alpha_{T1}} &= \left\{ \frac{\sum_{i=1}^{n(t)} 1(d[i] > j)}{[1-(2\tilde{p}-1)^2]} + \frac{1}{{\tau_{T1}}^2} \right\}^{-1} \\
\sigma^2_{\alpha_{Tj}} &= \left\{ \frac{\sum_{i=1}^{n(t)} 1(d[i] > j)}{[1-(2\tilde{p}-1)^2]} + \frac{1}{{\tau_{T2}}^2} \right\}^{-1}
\end{aligned}
\tag{17}
$$

$$
\begin{aligned}
p(\tilde{\rho}|\tilde{y}_{Ti}, \tilde{y}_{Ei}, \mu_{Ej}, \mu_{Tj}, \mathcal{D}) &\propto p(\tilde{\boldsymbol{y}}_{\boldsymbol{i}}|\mu_{Ej}, \mu_{Tj}, \tilde{\rho}) p(\mu_{Ej}) p(\mu_{Tj}) p(\tilde{\rho}) \\
&\propto p(\tilde{\boldsymbol{y}}_{\boldsymbol{i}}|\alpha_{Ej}, \alpha_{Tj}, \tilde{\rho}) p(\tilde{\rho}) \\
&= \prod_{i=1}^{n(t)} N(\tilde{\boldsymbol{y}}_{\boldsymbol{i}}; \begin{bmatrix} \sum_{r=1}^{d_{[i]}} \alpha_{Er} \\ \sum_{r=1}^{d_{[i]}} \alpha_{Tr} \end{bmatrix}, \begin{bmatrix} 1 & 2\tilde{\rho}-1 \\ 2\tilde{\rho}-1 & 1 \end{bmatrix}) Be(\tilde{\rho}; a_\rho, b_\rho)
\end{aligned}
\tag{18}
$$

3.2 Prior Specification

The hyper-parameter values of $\bar{\alpha}_{Ej}$, $\bar{\alpha}_{Tj}$, τ_{E1}, τ_{T1}, τ_{E2}, τ_{T2}, a_ρ, and b_ρ were determined to match the prior probability estimates for efficacy and toxicity from the JL model. $\bar{\alpha}_{kj}$'s are derived from $\tilde{p}_{kj}$'s, the prior probabilities for efficacy and toxicity proposed by physicians. We set $\tau_{k1} = 0.45$ and $\tau_{k2} = 0.25$. Then we can derive $\bar{\alpha}_{Ej}$ and $\bar{\alpha}_{Tj}$ from $\tilde{p}_{Ej} = p(\tilde{y}_{Ei} > 0|j)$ and $\tilde{p}_{Tj} = p(\tilde{y}_{Ti} > 0|j)$.

$$
\tilde{p}_{kj} = 1 - \Phi(0|\sum_{r=1}^{j} \bar{\alpha}_{kr}, 1) \tag{19}
$$

The prior for $\tilde{\rho}$ follows Beta(a_ρ, b_ρ). We set the prior parameters $a_\rho = b_\rho = 0.5$ to assume no dependence between the probability of efficacy and toxicity with an "effective sample size" of 1.

3.3 Posterior Simulation

We can generate posterior samples from the full conditional distributions for $\tilde{y}_{Ei}, \tilde{y}_{Ti}, \alpha_{Ej}$, and α_{Tj} with Gibbs sampling. Since we can not easily decipher the posterior distribution for $\tilde{\rho}$, we can generate posterior samples with the Metropolis Hastings Algorithm. The posterior probability of efficacy and toxicity, p_{kj} is then calculated as $p(\tilde{y}_{kj} > 0)$ demonstrated in equation 20.

$$p_{kj} = 1 - \Phi(0|\sum_{r=1}^{j} \alpha_{kr}, 1) \tag{20}$$

4 Utility

To determine the trade-off values between efficacy and toxicity, we define utility as:

$$U_j(p_{Ej}, p_{Tj}) = p_{Ej} - w_1 p_{Tj} - w_2 p_{Tj} I(p_{Tj} > \phi_T) \tag{21}$$

Here, p_{Ej} and p_{Tj} are the posterior probabilities of a positive outcome of efficacy or toxicity for dose j calculated from the B_{Ej}'s and B_{Tj}'s . $I(p_{Tj} > \phi_t)$ is the indicator function for when ϕ_t, the upper toxicity threshold determined by physicians, is reached. At a toxicity probability higher than the threshold, an additional penalty is added to the utility function. The non-negative weights, w_1 and w_2, demonstrate the desired trade offs of higher toxicity levels. A more conservative approach would see higher values for the weights, which would put a larger negative affect of toxicity. A high value for w_2 will likely favor dose levels that have toxicity below the toxicity threshold regardless of the efficacy. For example, with a $w_1 = 0.33$ and a $w_2 = 1.09$, we are putting a 33% penalty on dose levels with toxicity below ϕ_t and a $w1 + w2 = 142\%$ penalty on on dose levels with toxicity higher than ϕ_T.

The values of w_1 and w_2 can be directly given by the desires of patients or physicians. Alternatively, they can be determined when given at least three pairs of efficacy and toxicity probabilities that are determined to be equally desirable. With all three pairs (p^*_{Ei}, p^*_{Ti}) having utilities $U^*_1 = U^*_2 = U^*_3$, where $U^*_i = U(p^*_{Ei}, p^*_{Ti})$, we can calculate the weights by minimizing the expression:

$$(w_1, w_2) = \underset{(w_1, w_2)}{\operatorname{argmin}} \sum_{i=1}^{I} (U^*_i - \sum_{i=1}^{I} U^*_i / I) \tag{22}$$

This establishes a contour for the utility values when plotting p_E against p_T. With this contour, we can visually see how the utility responds to the relationship between efficacy and toxicity.

5 Efficacy and Toxicity Simulation

For testing the dose-finding methods, we simulate y_{ki}'s to represent results from patients. We can model y_{Ei} and y_{Ti} jointly, given dose $d_{[i]}$ for patient i, as $\pi_{a,b,j} = \Pr(Y_E = a, Y_T = b|j = d_{[i]})$ for $a, b \in [0, 1]$. The joint distribution of y_{Ei} and y_{Ti} is the Gumbel distribution,

$$\begin{aligned}\pi_{a,b,j} =&(\hat{p}_{Ej})^a(1-\hat{p}_{Ej})^{1-a}(\hat{p}_{Tj})^b(1-\hat{p}_{Tj})^{1-b} \\ &+(-1)^{a+b}\hat{p}_{Ej}(1-\hat{p}_{Ej})\hat{p}_{Tj}(1-\hat{p}_{Tj})(\frac{e^\gamma-1}{e^\gamma+1})\end{aligned} \tag{23}$$

For this equation, a represents a positive efficacy result and b represents a positive toxicity result. We use this probability distribution to produce probability estimates for ([1,1], [1,0], [0,1], [0,0]), with the coordinates structure of [efficacy, toxicity]. $\hat{p}_{Ej}$ and $\hat{p}_{Tj}$ are the true values for probability of efficacy and toxicity for a given dose level. A range of $\hat{p}_{Ej}$ and $\hat{p}_{Tj}$ values were provided to represent a reasonable range of efficacy, toxicity relationships.

6 Trial Conduct

Given the utility function and the data sampling method, the algorithm is as follows:

1. Treat the first cohort at the pre-determined starting dose level (often the lowest dose level)
2. Obtain posterior distribution of β_{kj} to calculate posterior estimates of p_{kj}, and update the posterior U_j's for $j = 1, ..., J$
3. The next cohort is randomly chosen between the the dose of max utility, the preceding dose level, and the following dose level with the probability that $U_j^* = U_{\{\max\}}$.
4. Repeat steps 2-4
5. When the maximum sample size is reached, we determine that the optimal dose level is the dose level with the highest utility amongst the dose levels that have been tested.

As a precaution, a stopping rule is put in place if there is evidence of overly high toxicity or low efficacy. We let ϕ_E be the lower threshold for efficacy and ϕ_T be the upper threshold for toxicity. We remove dose levels from being sampled if they fulfill the at least one of the following inequalities:

$$P(p_{Ej} < \phi_E|D) > 1 - C_E \qquad P(p_{Tj} > \phi_T|D) > 1 - C_T \tag{24}$$

Here, C_E and C_T are predetermined thresholds determined by physicians that require enough p_{Ej} estimates above the lower threshold and enough p_{Tj} estimates below the upper threshold to consider testing a dose level. If these criteria are met, there is evidence that the dose levels may not be beneficial or may even be too dangerous to continue testing. If all of the dose levels fulfill the inequalities, the study is terminated early and no dose is chosen.

7 Numerical Study

For the numerical study, we are studying doses at levels [0.25, 0.5, 0.75, 1.00, 1.25], $j = 1, ..., 5$, over n = 48 patients, with cohorts of size 3. The prior estimates of the efficacy probabilities are $\tilde{p}_{ej} = (0.2, 0.3, 0.4, 0.5, 0.6)$, and the prior estimates for the toxicity probabilities are $\tilde{p}_{tj} = (0.05, 0.1, 0.2, 0.3, 0.35)$. Additionally, we are assuming there is not a

lot of prior information so we use an effective sample size of m=1. Using equation 8, we can get the hyper-parameter values for the JL model, which are $a_{ej} = (0.2, 0.3, 0.4, 0.5, 0.6)$, $b_{ej} = (0.8, 0.7, 0.6, 0.5, 0.4)$, $a_{tj} = (0.05, 0.1, 0.2, 0.3, 0.35)$, and $b_{tj} = (0.95, 0.9, 0.8, 0.7, 0.65)$. For the bi-variate probit model, the hyper parameter variances are $\tau_{k1} = 0.45$ and $\tau_{k2} = 0.25$. $\bar{\alpha_{Ej}}$ and α_{Tj} can be derived from equation 19 resulting in $\bar{\alpha}_E = [-0.84, 0.317, 0.255, 0.255, 0.255]$ and $\bar{\alpha}_T = [-1.645, 0.34, 0.44, 0.31, 0.15]$. We also set $a_\rho = b_\rho = 0.5$. For the utility function we set our thresholds for toxicity and efficacy at $\phi_T = 0.3$ and $\phi_E = 0.2$ with weights, $w_1 = 0.33$ and $w_2 = 1.09$. For the stopping rule, we use $C_E = 0.2$ and $C_T = 0.2$, which were values determined from preliminary studies.

For generating data with the Gumbel model, we use a $\gamma = 3$. We simulated with different true values of p_E and p_T which reflect a range of efficacy and toxicity relationships to see how this dose-finding algorithm works in different circumstances.

7.1 Large scale simulation

The simulation results for scenario 1 is shown in table 1, scenario 2 in table 2, and so on. The tables display the selection percentage of each dose level as the optimal dose level, with the true optimal dose level highlighted in bold. The "None" section identifies the percentage of simulations that were stopped early due to excessive toxicity or inadequate efficacy. The same utility function and trial methodology was used for both models.

In scenario 1, the dose-efficacy curve increased slowly from level 1 to 2 and increased more rapidly thereafter. The dose-toxicity curve, on the other hand, increased rapidly after dose level 1, leaving the optimal dose level to be dose level 1 with excessive toxicity levels on all higher doses. For this scenario, the bi-variate probit model performed better, with a higher selection percentage at the optimal dose level, and fewer instances of an early stopped trial. Likewise, for scenario 2, where the dose-efficacy and dose-toxicity curves scaled fairly linearly, the bi-variate probit model has a higher selection percentage at the optimal dose, fewer early stopped trials, and overall less variability between selected dose levels. In scenario 3 we see the JL model selecting the true optimal dose level more often, but still having more instances of early stopping.

8 Conclusion

Between the two model-based approaches it seems that the bi-variate model tends to result more conservative estimates which prevents a significant margin of early-stopping, and results in a slower climb to testing higher dose levels. In the simulations the bi-variate probit model seems to behave more reliably. The JL model may benefit from adding other conditions to the trial conduct such as removing dose levels from the pool of potential next doses if the individual dose level does not meet the stopping rule criteria. This way, the dose choices may not escalate as quickly towards in-efficacious or toxic dose levels as quickly, thus decreasing the number of early stopped trials.

Test	None	Dose1	Dose2	Dose3	Dose4	Dose5
(p_E, p_T)		**(0.28, 0.15)**	(0.3, 0.32)	(0.44, 0.45)	(0.6, 0.55)	(0.74, 0.62)
U		**0.23**	-0.15	-0.2	-0.18	-0.14
JL	0.17	0.61	0.13	0.08	0.01	0
PR	0.02	0.79	0.19	0	0	0

Table 1: Simulation results for scenario 1 showing the frequency each dose level was chosen as the optimal dose.

Test	None	Dose1	Dose2	Dose3	Dose4	Dose5
(p_E, p_T)		(0.1, 0.04)	**(0.27, 0.18)**	(0.44, 0.37)	(0.58, 0.54)	(0.69, 0.67)
U		0.07	**0.2**	-0.03	-0.02	-0.01
JL	0.13	0.15	0.56	0.15	0.01	0
PR	0.01	0.07	0.86	0.06	0	0

Table 2: Simulation results for scenario 2 showing the frequency each dose level was chosen as the optimal dose.

Test	None	Dose1	Dose2	Dose3	Dose4	Dose5
(p_E, p_T)		(0.05, 0.02)	(0.08, 0.05)	(0.15, 0.07)	(0.28, 0.10)	**(0.43, 0.12)**
U		0.04	0.06	0.13	0.25	**0.39**
JL	0.08	0	0	0.02	0.08	0.82
PR	0.05	0	0.02	0.04	0.12	0.77

Table 3: Simulation results for scenario 3 showing the frequency each dose level was chosen as the optimal dose.

Overall, the Bayesian model-based approaches have the advantage of borrowing information across doses, while not imposing ridged assumptions of the dose-toxicity and dose-efficacy curves.The proposed bi-variate probit model, yields effective results for a variety of dose-efficacy and dose-toxicity curves.

9 Further study

This example assumes that the patients full results are returned before the testing of the next cohort of patients. In practice, this may not be very realistic due to varying response times, patient recruitment, and potential time sensitive needs of the dose testing. A model that incorporates time delay, where p_k values are modeled with a coefficient representing the proportion of time they have been tested versus the necessary time to receive full results can be implemented. This way, patients that have had the necessary time to show responses will be waited more heavily than patients that have not.