Biometrics 61, 344–354
June 2005

DOI: 10.1111/j.1541-0420.2005.00314.x

A Bayesian Approach to Jointly Modeling Toxicity and Biomarker Expression in a Phase I/II Dose-Finding Trial

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Summary. In this article, we propose a Bayesian approach to phase I/II dose-finding oncology trials by jointly modeling a binary toxicity outcome and a continuous biomarker expression outcome. We apply our method to a clinical trial of a new gene therapy for bladder cancer patients. In this trial, the biomarker expression indicates biological activity of the new therapy. For ethical reasons, the trial is conducted sequentially, with the dose for each successive patient chosen using both toxicity and activity data from patients previously treated in the trial. The modeling framework that we use naturally incorporates correlation between the binary toxicity and continuous activity outcome via a latent Gaussian variable. The dose-escalation/de-escalation decision rules are based on the posterior distributions of both toxicity and activity. A flexible state-space model is used to relate the activity outcome and dose. Extensive simulation studies show that the design reliably chooses the preferred dose using both toxicity and expression outcomes under various clinical scenarios.

Key words: Adaptive design; Bayesian inference; Correlated binary-continuous variables; Latent variables; Markov chain Monte Carlo.

1. Introduction

The primary objective of conventional phase I dose-finding trials in oncology is to find the highest dose with tolerable toxicity. This dose is often referred to as the maximum tolerable dose (MTD). Over the past 25 years, statistical algorithms for determining an MTD based only on modeling the probability of toxicity has been an active area of research (e.g., Storer, 1989; O'Quigley, Pepe, and Fisher, 1990; Thall et al., 2003, among others). An implicit assumption of traditional phase I trials is that a monotone increasing relationship between dose and activity exists. Therefore, because most oncology compounds are cytotoxic, the rationale behind traditional phase I trial designs is to find the highest dose that is also safe.

A parallel development in biomedical research has been the increased use of biomarkers as indicators of risk or as surrogate outcomes for activity and efficacy. In an animal study of a new intravesical gene therapy, investigators at the M. D. Anderson Cancer Center found that a protein secreted in the urine is highly correlated with the amount of a therapeutic agent produced by the bladder, and indicates that the compound is biologically active (Benedict et al., 2004). This information can be observed immediately after treatment allowing the investigators to learn about the therapeutic potential of the compound. Because the toxicity profile of the new agent has not been explored in human trials, the investigators are particularly interested in designing a dose-finding trial in which the primary objective is to find a dose with acceptable toxicity as well as high levels of biomarker expression. The objective of this trial differs from conventional phase I trials, in that both biomarker expression and toxicity need to be jointly modeled to determine the best dose.

In this trial, biomarker expression is measured as a continuous variable. We are not aware of any literature that formally incorporates a continuous activity outcome with toxicity into the dose-finding decision criteria in phase I/II clinical trials. Some recent studies in the area of dose-finding methodology have been based on both efficacy and toxicity (Gooley et al., 1994; Thall and Russell, 1998; O'Quigley, Hughes, and Fenton, 2001; Braun, 2002; Thall and Cook, 2004). However, in these previous studies, both outcomes are assumed to be either binary or trinary variables. When the efficacy outcome is a continuous variable, such as the biomarker expression in this example, the existing modeling procedures and decision rules are not applicable without artificially dichotomizing the variable, a procedure that often results in a considerable loss of information.

For example, we consider a trial in which a new compound is to be evaluated using a binary toxicity and a biomarker response, where response is defined as biomarker expression above some threshold. However, higher expression is regarded as better. Among the investigated doses, all patients have expression levels above the threshold but expression increases with dose. Moreover, toxicity is also observed to be increasing with dose but considered to be tolerable for all doses. In this context, if the continuous nature of the biomarker expression data is ignored, then all the doses would be considered equally effective. A rational approach would choose the dose that minimizes toxicity (i.e., the lowest dose).

Although this is an extreme example, it shows how dichotomization in this context can cause substantial loss of information and result in the selection of a less efficacious dose. Thus, there is a pressing need for new dose-finding algorithms that are capable of balancing the benefit of higher biomarker expression against the detrimental effects of toxicity.

This research is motivated by a trial of intravesical gene therapy for the treatment of superficial bladder cancer. The purpose of this report is to describe a Bayesian adaptive dose-finding procedure based on both toxicity and continuous activity (e.g., biomarker expression) data. This method is proposed for use in the context of a single-arm trial in which patients are sequentially accrued and successively treated. Given a range of possible doses, the decision to treat a patient at one of these doses is conditional on the cumulated data for both outcomes. Moreover, a patient's toxicity profile and activity outcome are potentially correlated with each other at a given dose level. We introduce a continuous latent variable, to jointly model the continuous biomarker outcome and the binary toxicity outcome via a bivariate model, as a function of dose, while incorporating dependence between the two outcomes.

We elicit decision criteria from the clinical investigators and use this information in combination with posterior samples from the model to determine which doses are acceptable after observing each patient's outcomes. Among all acceptable doses at each stage, we calculate a "preference score" for each dose. The next patient enrolled in the trial will have a higher probability of assignment to those doses with higher preference scores and vice versa. This added variability in the allocation of patients to different doses increases the probability of correctly selecting the best dose, while sufficiently exploring the potential benefit of other doses.

The remainder of the article is organized as follows. The probability models and the computation of posterior distributions are presented in Section 2; the decision rules for dose finding are discussed in Section 3. We provide an illustrative example and show the method's operating characteristics in Section 4. We conclude with a discussion in Section 5.

2. Probability Models, Priors, and Posteriors

2.1 *Probability Models*

Consider a single-arm trial, in which patients are sequentially accrued and successively treated. Suppose K dose levels will be explored, $d_1, \ldots, d_K$. Let x_i be the dose administered to the ith patient among the set of possible doses and let $\boldsymbol{X}_i = (I(x_i = d_1), \ldots, I(x_i = d_K))$, where $I(B)$ is an indicator function of the event B. The outcome vector for the ith patient is denoted by $Y_i = (W_i, T_i)^{\mathrm{T}}$, which consists of a continuous biomarker variable, W_i, and a binary toxicity variable, T_i. For the binary toxicity outcome, $T_i = 1$ indicates that toxicity is observed, and $T_i = 0$ otherwise.

Because the raw biomarker expression data may be skewed, a transformation, such as the logarithmic, which symmetrizes the raw variable might be appropriate. Without loss of generality let $W_i = h(W_i^*)$, where W_i^* is the raw biomarker expression data. How $h(\cdot)$ is chosen should be made with care, and if the data exist, it should be based on prior biomarker expression data for the same compound or compounds in the same class. In some cases, it may not be possible to know the appropriate transformation prior to the start of the trial. Therefore, we will explore the robustness of the model to violations of the distributional assumptions.

To describe the marginal relationship between dose and biomarker expression, W_i, we use a state-space model, which allows us to borrow strength across doses in a flexible manner (Broemeling, 1985; Congdon, 2001). Assume that W_i follows a normal distribution with mean $\boldsymbol{X}_i\boldsymbol{\beta_W}$ and variance σ^2_W. Let $\boldsymbol{\beta_W} = (\beta_{W,1}, \ldots, \beta_{W,K})^{\mathrm{T}}$ define an unknown vector of parameters, where $\beta_{W,k}$ reflects the mean biologic activity for the kth dose. With the state-space model, a recursive relationship between $\beta_{W,k}$ and $\beta_{W,(k-1)}$ is introduced. Specifically, the relationship between these parameters is given by $\beta_{W,k} = \beta_{W,(k-1)} + u_k$, where $u_k \sim N(0, \sigma^2_{\beta_W})$. This model is quite appropriate in this context because, unlike toxicity, investigators may not want to assume that the mean biomarker expression level increases with dose. In fact, the above recursive relationship is equivalent to assuming a priori that the mean biomarker expression at the kth level, $\beta_{W,k}$, is distributed univariate normal with prior mean $\beta_{W,(k-1)}$ and variance of a fixed constant $\sigma^2_{\beta_W}$. For identifiability, $\beta_{W,1}$ follows a Gaussian distribution with mean $\beta_{W,0}$ and variance $\sigma^2_{\beta_W}$, where $\beta_{W,0}$ is fixed. Furthermore, we assume that $\beta_{W,k}$ given $\beta_{W,(k-1)}$ is conditional independent of the later states. Thus, the joint prior distribution of all K parameters is proportional to

$$\prod_{k=1}^{K} \phi\big(\beta_{W,k}; \beta_{W,(k-1)}, \sigma^2_{\beta_W}\big),$$

where $\phi(\cdot\,; \mu, \sigma^2)$ is the p.d.f. of a random variable distributed $N(\mu, \sigma^2)$.

To describe the marginal relationship between dose and toxicity, T_i, we will use the probit model of Albert and Chib (1993). In particular, we introduce a latent variable Z_i for the ith individual, which follows a normal distribution with mean $\boldsymbol{X}_i\boldsymbol{\beta_Z}$, and variance 1, where $\boldsymbol{\beta_Z} = (\beta_{Z,1}, \ldots, \beta_{Z,K})^{\mathrm{T}}$ is a $K \times 1$ vector of unknown parameters. This latent variable is related to the observed binary toxicity T_i via the condition

$$T_i = \begin{cases} 0 & \text{if } Z_i \in A_0, \\ 1 & \text{if } Z_i \in A_1, \end{cases}$$

where $A_0 = (-\infty, 0]$ and $A_1 = (0, \infty)$. To model the probability of toxicity with dose, we relate the probit binary model on T_i with a normal linear regression on the latent variable, Z_i. The marginal probability distribution of T_i for a patient treated with dose d_k then follows the form

$$\Pr(T_i = 1 \,|\, x_i = d_k) = \Phi(\boldsymbol{X}_i\boldsymbol{\beta_Z}) = \Phi(\beta_{Z,k}),$$

where Φ is the cumulative density function of standard normal variables and $\beta_{Z,k}$ is the regression coefficient that describes the probability of toxicity for the kth dose level. A byproduct of this latent model is that it simplifies numerical computations of the posterior distribution of $\boldsymbol{\beta_Z}$.

The toxicities of most cancer compounds increase with dose. A priori, we use a weakly structured model to reflect a monotone relationship between dose and the probability of toxicity. In particular, we assume a constrained Gaussian prior for $\beta_{Z,k}$, for which the probability density function is proportional to

$$\phi\big(\beta_{Z,k};\mu_{Z,k},\sigma^2_{\beta_Z}\big)I\big(\beta_{Z,(k-1)}<\beta_{Z,k}<\beta_{Z,(k+1)}\big),$$

where $\beta_{Z,0}\equiv-\infty$ and $\beta_{Z,(K+1)}\equiv\infty$. These constrained priors guarantee monotonicity on the probability of toxicity over dose such that $\Phi(\beta_{Z,(k-1)})<\Phi(\beta_{Z,k})<\Phi(\beta_{Z,(k+1)})$.

Given the marginal distributions for biomarker expression and toxicity discussed above, the joint distribution of (W_i, T_i) is assumed to have a bivariate normal distribution with mean $(\boldsymbol{X}_i\boldsymbol{\beta_W}, \boldsymbol{X}_i\boldsymbol{\beta_Z})^{\mathrm{T}}$, and variance/covariance matrix Ω, where

$$\Omega=\begin{bmatrix}\sigma^2_W+\rho^2 & \rho\\ \rho & 1\end{bmatrix}.$$

Here, Ω has the compound symmetric form, which ensures that Ω is positive definite. Note that ρ is the covariance parameter between Z and W, which induces the dependence between toxicity, T, and biomarker, W. Similar models in the literature include Chib and Greenberg's (1998) multivariate probit regression model and Chib's (2003) bivariate continuous-binary variable model. The joint modeling approach to (W, T) is similar to the model first introduced by Chib (2003).

We assume a prior distribution for ρ to be Gaussian, with mean 0 and variance σ_ρ and a prior distribution for σ^2_W to be an inverse gamma Inv-Gamma(γ, ν) with mean $\nu(\gamma-1)^{-1}$ and variance $\nu^2(\gamma-1)^{-2}(\gamma-2)^{-1}$. Some of the priors discussed above should be relatively more informative than others. Specifically, the prior hyperparameters $\mu_{Z,1},\ldots,\mu_{Z,K}$, $\sigma^2_{\beta_Z}$, $\beta_{W,0}$, and $\sigma^2_{\beta_W}$ should be elicited using prior clinical experience. The other priors in the model can be vague. A discussion of the specific choice of priors is found in Section 4.

Given the observed data $y_i=(w_i,\ t_i)$ and $\boldsymbol{X}_i$ for the ith individual, the corresponding likelihood follows

$$f(w_i,t_i\,|\,\boldsymbol{\beta_W},\boldsymbol{\beta_Z},\Omega,\boldsymbol{X}_i)=\prod_{l=0}^{1}\left\{\int_{A_l}\phi_{W,Z}\left(w_i,z_i;(\boldsymbol{X}_i\boldsymbol{\beta_W},\boldsymbol{X}_i\boldsymbol{\beta_Z})^{\mathrm{T}},\Omega\right)dz_i\right\}^{I(t_i=l)},$$

where $\phi_{W,Z}(w,\ z;\ \mu,\ \Sigma)$ denotes a bivariate normal density with mean μ and variance/covariance matrix Σ. The above joint distribution can be expressed as the product of the marginal distribution of W and the conditional distribution of Z given W:

$$\phi_W\left(w_i;\boldsymbol{X}_i\boldsymbol{\beta_W},\sigma^2_W+\rho^2\right)\times\prod_{l=0}^{1}\left\{\int_{A_l}\phi_{Z|W}\left(z_i;\tilde{\mu}_{Z,i},\tilde{\rho}^2\right)dz_i\right\}^{I(t_i=l)},\qquad(1)$$

where $\tilde{\mu}_{Z,i}=\boldsymbol{X}_i\boldsymbol{\beta_Z}+\rho(w_i-\boldsymbol{X}_i\boldsymbol{\beta_W})/(\sigma^2_W+\rho^2)$ and $\tilde{\rho}^2=1-\rho^2/(\sigma^2_W+\rho^2)$.

Alternatively, this joint distribution can be expressed as the product of the marginal distribution of Z and the conditional distribution of W given Z in the derivation of the posteriors:

$$\prod_{l=0}^{1}\left\{\int_{A_l}\phi_Z\left(z_i;\boldsymbol{X}_i\boldsymbol{\beta_Z},1\right)\phi_{W|Z}\left(w_i;\tilde{\mu}_{W,i},\sigma^2_W\right)dz_i\right\}^{I(t_i=l)},\qquad(2)$$

where $\tilde{\mu}_{W,i}=\boldsymbol{X}_i\boldsymbol{\beta_W}+\rho(z_i-\boldsymbol{X}_i\boldsymbol{\beta_Z})$.

2.2 *Posteriors*

At any given point in the trial, the probability that a patient is allocated to a particular dose level is determined by the cumulated data on both toxicity and biomarker expression and the priors. Let $\boldsymbol{\theta}=(\boldsymbol{\beta}^{\mathrm{T}}_{\boldsymbol{Z}},\boldsymbol{\beta}^{\mathrm{T}}_{\boldsymbol{W}},\rho,\sigma_W)^{\mathrm{T}}$ define a vector of all unknown parameters in the model. Conditional on the latent variable Z_i, $\Pr(T_i=l\,|\,\boldsymbol{\theta},\ Z_i)=I(Z_i\in A_l)$, which is similar to the notation in Albert and Chib (1993). Thus, the joint posterior density of the unknown parameters and the latent variable given the observed data for the ith individual is proportional to

$$\phi_W\left(w_i;\boldsymbol{X}_i\boldsymbol{\beta_W},\sigma^2_W+\rho^2\right)\times\phi_{Z|W}\left(z_i,\tilde{\mu}_{Z,i},\tilde{\rho}^2\right)I\left(Z_i\in A_{I(t_i=1)}\right)g(\boldsymbol{\theta}),\qquad(3)$$

where $g(\boldsymbol{\theta})$ is the joint prior distribution for $\boldsymbol{\theta}$.

After each patient's outcomes are observed, we use a Markov chain Monte Carlo (MCMC) algorithm to update the posterior distributions of unknown parameters. Let n be the total number of patients observed at stage n and let N be the maximum number of patients planned for the trial where $n=1,\ldots,N$. At the nth stage, the full conditional distributions of the latent $Z_i^{(n)}$ for $(i=1,\ldots,n)$, and $\boldsymbol{\theta}^{(n)}$ are given in steps 1–5 below. We first generate initial values for $\boldsymbol{\theta}^{(n)}$ from their corresponding priors. We then repeat the steps described below (we omitted the n superscript for the parameters in $\boldsymbol{\theta}^{(n)}$ and the latent variables for notational convenience).

Step 1. Generate latent variable Z_i: For the ith individual, if $T_i=0$ we sample Z_i from the truncated normal distribution $\phi_{Z|W}(Z_i;\tilde{\mu}_{Z,i},\tilde{\rho}^2)I(Z_i\le0)$, with support between negative infinity and 0. If $T_i=1$, Z_i is generated from the full conditional distribution of $\phi_{Z|W}(Z_i;\tilde{\mu}_{Z,i},\tilde{\rho}^2)I(Z_i>0)$, which is a truncated normal distribution with a support between 0 and positive infinity.

Step 2. Conditional on the cumulated data observed up to the nth patient's outcomes, we generate $\boldsymbol{\beta_Z}$ from its corresponding full conditional distribution in (1). This step is complicated by the requirement of $\beta_{Z,k-1}<\beta_{Z,k}<\beta_{Z,(k+1)}$, which results from use of a constrained normal prior. Let $\boldsymbol{\beta}_{Z,-k}$ be a vector with all components of $\boldsymbol{\beta_Z}$ except $\beta_{Z,k}$. For $k=1,\ldots,K$, the full conditional distribution of $\beta_{Z,k}\,|\,Z,\ W,\ \sigma_W,\ \rho,\ \boldsymbol{\beta}_{Z,-k}$ is also a truncated univariate normal, with location parameter equal to $\tilde{\beta}_{Z,k}$ and scale parameter equal to $\tilde{\sigma}_{Z,k}$, which are given by

$$\tilde{\beta}_{Z,k}=\frac{\sigma^2_{\beta_Z}V_k^{(n)}+\left(1-\dfrac{\rho^2}{\sigma^2_W+\rho^2}\right)\mu_{Z,k}}{\displaystyle\sum_{i=1}^{n}I(x_i=d_k)\sigma^2_{\beta_Z}+\left(1-\frac{\rho^2}{\sigma^2_W+\rho^2}\right)},$$

$$\tilde{\sigma}^2_{Z,k}=\frac{\sigma^2_{\beta_Z}\left(1-\dfrac{\rho^2}{\sigma^2_W+\rho^2}\right)}{\displaystyle\sum_{i=1}^{n}I(x_i=d_k)\sigma^2_{\beta_Z}+\left(1-\frac{\rho^2}{\sigma^2_W+\rho^2}\right)},$$

where

$$V_k^{(n)} = \sum_{i=1}^{n} I(x_i = d_k)\left[z_i - \frac{\rho}{\left(\sigma_W^2 + \rho^2\right)}(w_i - \boldsymbol{X}_i\boldsymbol{\beta_W})\right].$$

For brevity of notation, we removed the superscript of n for $\tilde{\beta}_{Z,k}$ and $\tilde{\sigma}_{Z,k}$ in the above notation. We sample observations from this distribution subject to the constraint that $\beta_{Z,k-1} < \beta_{Z,k} < \beta_{Z,k+1}$. It is clear that at any given point, if no patient has been tried at dose level k, $\tilde{\beta}_{Z,k}$ and $\tilde{\sigma}^2_{Z,k}$ reduce to $\mu_{Z,k}$ and $\sigma^2_{\beta_Z}$, respectively, which are the priors for $\beta_{Z,k}$.

Step 3. Similar to Step 2, we generate $\boldsymbol{\beta_W}$ from its corresponding full conditional distribution in (2). For $k = 1, \ldots, (K-1)$, the corresponding log full conditional posterior of $\beta_{W,k}$ is, but for a constant,

$$\frac{\sum_{i=1}^{n} I(x_i = d_k)[w_i - (\beta_{W,k} + \rho(Z_i - \boldsymbol{X}_i\boldsymbol{\beta_Z}))]^2}{2\sigma_W^2} + \frac{(\beta_{W,k} - \beta_{W,(k-1)})^2}{2\sigma^2_{\beta_W}} + \frac{(\beta_{W,(k+1)} - \beta_{W,k})^2}{2\sigma^2_{\beta_W}}.$$

Given the observed data up to the nth patient, the full conditional mean and variance of $\beta_{W,k}$ are given by

$$\tilde{\beta}_{W,k} = \frac{\sigma^2_{\beta_W} U_k^{(n)} + \sigma_W^2(\beta_{(k-1)} + \beta_{(k+1)})}{\sum_{i=1}^{n} I(x_i = d_k)\sigma^2_{\beta_W} + 2\sigma_W^2},$$

$$\tilde{\sigma}^2_{W,k} = \frac{\sigma_W^2\sigma^2_{\beta_W}}{\sum_{i=1}^{n} I(x_i = d_k)\sigma^2_{\beta_W} + 2\sigma_W^2},$$

where

$$U_k^{(n)} = \sum_{i=1}^{n} I(x_i = d_k)[w_i - \rho(z_i - \boldsymbol{X}_i\boldsymbol{\beta_Z})].$$

Note that $\tilde{\beta}_{W,k}$ reduces to $(\beta_{(k-1)} + \beta_{(k+1)})/2$, which is the average of the prior means of the two nearest dose levels, and $\tilde{\sigma}^2_{W,k}$ reduces to $\sigma^2_{\beta_W}$, when there is no patient being evaluated at the kth dose level. At the highest dose level, K, $\beta_{W,K}$ is generated from a similar full conditional distribution where the full conditional mean and variance are given by

$$\tilde{\beta}_{W,K} = \frac{\sigma^2_{\beta_W} U_K^{(n)} + \sigma_W^2\beta_{(K-1)}}{\sum_{i=1}^{n} I(x_i = d_K)\sigma^2_{\beta_W} + \sigma_W^2},$$

$$\tilde{\sigma}^2_{W,K} = \frac{\sigma_W^2\sigma^2_{\beta_W}}{\sum_{i=1}^{n} I(x_i = d_K)\sigma^2_{\beta_W} + \sigma_W^2}.$$

Step 4. Sample σ_W^2 from its full conditional distribution. Because of the compound symmetric structure used for Ω in the likelihood (1), the full conditional distribution of σ_W^2 follows an inverse-Gamma, when σ_W^2 has an inverse-Gamma prior. Specifically, the full conditional distribution of σ_W^2 is proportional to

$$\phi_{W|Z}\left(w_i; \tilde{\mu}_{W,i}, \sigma_W^2\right) g\left(\sigma_W^2\right). \tag{4}$$

Thus, after observing the nth patient, σ_W^2 is distributed with Inv-Gamma$(\tilde{\gamma}, \tilde{\nu})$, where

$$\tilde{\gamma} = (2\gamma + n)/2 \quad \text{and} \quad \tilde{\nu} = \frac{1}{2}\sum_{i=1}^{n}(w_i - \tilde{\mu}_{W,i})^2 + \nu.$$

Step 5. The full conditional distribution of ρ is proportional to

$$\phi_{W|Z}\left(w_i; \tilde{\mu}_{W,i}, \sigma_W^2\right) g_\rho(\rho), \tag{5}$$

where $g_\rho(\rho)$ is the prior distribution of ρ. Because this full conditional distribution cannot be analytically expressed, we will use an independence chain Metropolis–Hastings step (Chib and Greenberg, 1995) to obtain posterior samples for ρ.

3. Decision Rules

Developing sensible decision rules for dose-finding trials when both toxicity and activity outcomes are monitored can be complicated. As described in the introduction, the existing approaches to dose finding are based on either monitoring toxicity alone (disregarding the activity outcome) or bivariate binary outcomes (requiring dichotomization of the activity data). In this article, we propose a different approach to choosing doses that have high expression levels measured by a continuous variable, and also have tolerable toxicities. The decision rule at each stage is based on the data observed up to that point and on the prior information. The posterior probability of toxicity in conjunction with the posterior mean biomarker expression level at each dose are modeled for the purpose of dose finding, as described in Section 2.

Recall the transformation h for the raw biomarker expression data, defined in Section 2. We transform the posterior mean biomarker expression back to its original scale of the observed biomarker by $h^{-1}(\cdot)$. To define a set of acceptable doses, we first elicit from the collaborating investigators a minimally acceptable biomarker expression level, $W^*_{\min}$, and a maximally tolerated toxicity probability, π_t. $W^*_{\min}$ defines the lowest biomarker expression level of clinical interest, while π_t is a maximum acceptable toxicity probability (e.g., values between 20% and 40% are often used in conventional phase I oncology trials).

At the beginning of a trial, we assign the first m patients to the lowest dose, where m is a fixed integer between 1 and 6. Let n_k define the number of patients evaluated at dose d_k. Dose d_k is regarded as *adequately tried*, if at any point in the trial $n_k \geq m$. Let δ_1, δ_2, and δ_3 be the prespecified threshold probabilities. Dose d_k will be declared *acceptable* at any time point if

$$\Pr\left(\left(h^{-1}(\beta_{W,k}\right) > W^*_{\min} \,|\, \text{data}, n_k \geq m\right) > \delta_1 \quad \text{and}$$

$$\Pr(\Phi(\beta_{Z,k}) < \pi_t \,|\, \text{data}, n_k \geq m) > \delta_2$$

or

$$\Pr(\Phi(\beta_{Z,k-1}) < \pi_t \,|\, \text{data}, n_k < m, n_{k-1} \geq m) > \delta_3,$$

where $\Phi(\beta_{Z,k})$ is the probability of toxicity for the kth dose. These rules state that if the kth dose has been adequately evaluated, it will be declared acceptable if the marginal posterior probability that the mean biomarker expression level for the kth dose is greater than $W^*_{\min}$ is greater than δ_1, and the marginal posterior probability that the toxicity rate is less than π_t is greater than δ_2. If the kth dose has not been adequately tried, then it will be acceptable only if there is a high posterior probability that the risk of toxicity for dose $(k-1)$ is less than π_t and if dose $(k-1)$ has been adequately tried. Doses that are not declared acceptable will be *unacceptable*. If at any point in the trial all doses are declared unacceptable, the trial will be terminated and none of the doses will be selected. These rules for defining an acceptable dose are not standard, but they are consistent with the preferences of clinical investigators. Typically, investigators want to try higher doses only after seeing evidence that previous lower doses are safe (i.e., they have been adequately tried). For the intravesical gene therapy, our clinical colleagues believe that a dose should not be considered safe unless at least three patients have been evaluated at that dose.

Once a set of acceptable doses is selected, the next patient will be assigned to one of the acceptable doses probabilistically. The probability of assigning a patient to a given dose in the set of acceptable doses is adaptively calculated in the following manner. At any given point in the trial, let d_1, $d_2, \ldots, d_J$ denote the set of acceptable doses, where $J \leq K$. Define $p_w(d_j) = \mathrm{E}(h^{-1}(\beta_{W,j}) \,|\, \text{data})$ to be the expected posterior mean for the biomarker expression level on its original scale for dose d_j, and let $p_t(d_j) = \mathrm{E}(\Phi(\beta_{Z,j}) \,|\, \text{data})$ be the expected posterior probability of toxicity for dose d_j. We elicit from the investigators a largest possible biomarker expression value, $W^*_{\max}$, and define $(W^*_{\max}, 0)$ to be the *optimal point* on the plane, which corresponds to the maximum activity and zero toxicity. Among the acceptable doses that have been adequately tried, we define e_j as the Euclidean distance of the outcome, $(p_w(d_j),\ p_t(d_j))$, of the acceptable dose d_j to the optimal point, $(W^*_{\max}, 0)$

$$e_j = \sqrt{\left[\frac{W^*_{\max} - p_w(d_j)}{W^*_{\max}}\right]^2 + p_t(d_j)^2}.$$

Note that the support of marginal posterior distribution for random variable $\beta_{Z,j}$ is between $-\infty$ and ∞. Thus, the expected posterior probability of toxicity for a given dose, $p_t(d_j) = \mathrm{E}(\Phi(\beta_{Z,j}) \,|\, \text{data})$ is between 0 and 1. Because the standardized biomarker expression $(W^*_{\max} - p_w(d_j))/W^*_{\max}$ also varies between 0 and 1, the two components in the definition of the distance e_j are on the same scale. In our example, we equally emphasize the two outcomes in the decision rule. However, if the investigators prefer weighing one outcome more than the other, we can assign different weights to the two components that define the distance e_j in our proposed decision rule (Braun, 2002).

Intuitively, a shorter distance to the optimal point indicates better outcomes from the tried dose. Therefore, we let the probability of allocating the next patient among the acceptable doses be proportional to the distance to the optimal point. In particular, let $S_j = 1/e_j$ define a preference score for the jth acceptable dose. We then randomly allocate the next patient to the jth dose with probability

$$\frac{S_j}{\sum_{j=1}^{J} S_j}.$$

For an acceptable dose that has not been adequately tried, we set e_j at an extremely small value (say <0.0001), so that the algorithm will be more likely to assign the next patient to this dose level.

The proposed rules adaptively lead to different decisions depending on the observed data for both toxicity and biomarker expression. Specifically, the algorithm tends to assign patients to a higher dose, which has not been adequately tried if lower doses have been adequately tried and shown to be safe. Furthermore, if the first dose is too toxic, then the algorithm will stop early and not explore higher doses. But if a lower dose has low toxicity and low expression, then the algorithm will proceed to explore higher doses, because it is possible that the higher doses will have higher expression levels with tolerable toxicity.

Although the proposed dose-finding algorithm incorporates dose-limiting toxicities as one of the primary endpoints, any serious adverse events or irreversible toxicities such as death or organ failure should override our algorithm and stop the trial early. As pointed out by the associate editor, the implementation of this additional safety monitoring rule can be especially important in gene therapy trials (Dettweiler and Simon, 2001).

4. Applications and Simulations

Although most patients with superficial bladder cancer are treated with surgery or surgery combined with standard chemotherapy, 50–70% of superficial tumors recur and 20–30% evolve into more aggressive, potentially lethal cancers. The high recurrence rate and the loss of bladder function after surgery have led investigators to search for more effective treatment strategies based on intravesical immunotherapy.

Syn3 is an agent that enhances adenoviral transduction and encodes for the production of a secreted therapeutic protein. Intravesical administration of adenoviral vectors in a Syn3 formulation has the potential to increase transgene expression in both normal urothelium (a transitional layer of epithelium in the wall of the bladder) and in superficial tumors. The therapeutic protein can then be secreted into the urine from both transduced normal urothelium and tumor tissue, resulting in an accumulation and potentially high concentration of the therapeutic protein in the bladder. When exploring the effects of adenoviral transduction within a Syn3 formulation at a given dose, investigators found that the protein secreted in the urine reflects how much of the therapeutic agent is produced. This biomarker is considered a surrogate for therapeutic activity, and has been shown to have a promising effect in animal studies (Benedict et al., 2004). However, the toxicity profile of the Syn3 agent in combination with the adenoviral vector in humans is unknown. The investigators now propose a phase I/II dose-finding trial for the treatment of superficial bladder cancer using Syn3 together with the

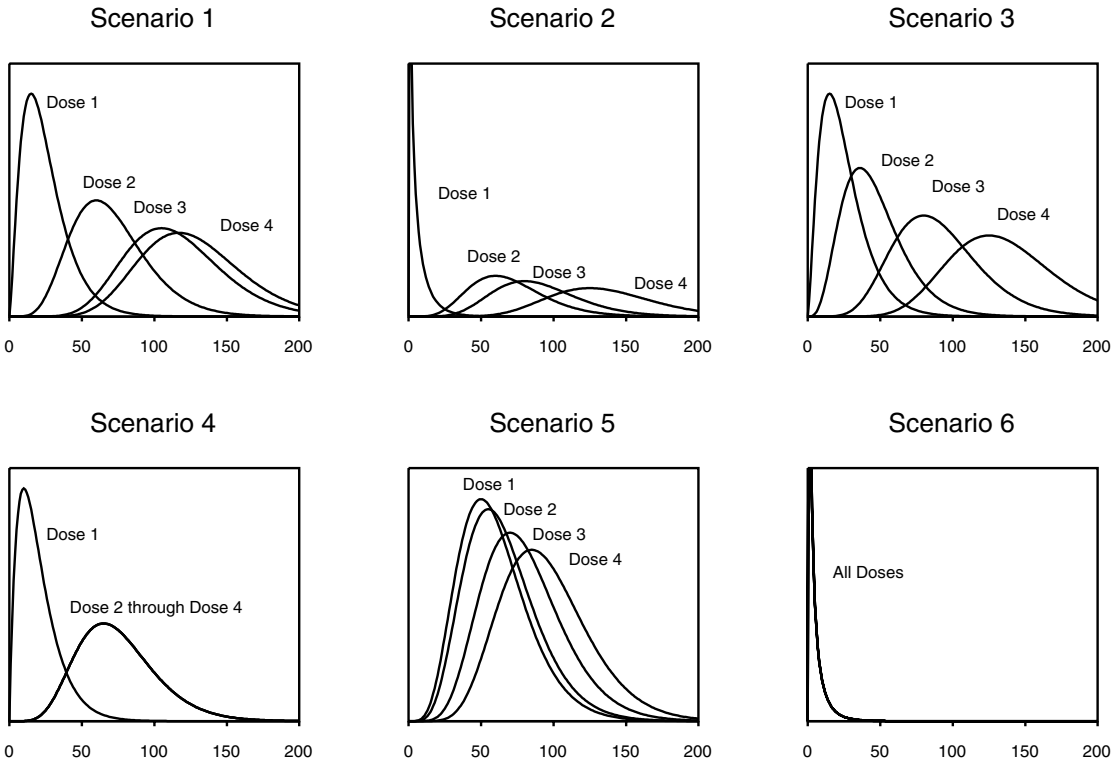

Figure 1. Marginal distribution of biomarker expression used in simulation studies.

appropriate adenoviral vector. The dose-finding scheme should be based on a continuous activity variable and a binary toxicity variable.

To assess the operating characteristics of the proposed method, we perform a series of simulation studies from a wide variety of scenarios. We purposely generate biomarker expression outcomes from a distribution other than the normal to check the sensitivity of our method to deviations from the assumption of normality. Specifically, biomarker expression is generated from a gamma distribution with shape parameter $\tau\lambda_{s,k}$ and scale parameter τ (i.e., mean equal to $\lambda_{s,k}$), for the kth dose of scenario s, where $s = 1, \ldots, 6$ and $k = 1, \ldots, 4$. A total of six scenarios and four dose levels per scenario will be explored. Figure 1 displays the marginal distributions for the simulated biomarker expression data for each of the six scenarios, and each curve corresponds to one of the four dose levels. It is clear that the data are generated from a wide variety of gamma distributions, and some of them have quite large variations and/or skewness. In order to assess the robustness of the model, we will not make any transformation to symmetrize the data in the simulations.

Similarly, we characterize the toxicity rate by $p_{s,k}$ for scenario s at dose level k. For each scenario, the true toxicity and activity at each dose level are displayed in Figure 2. In a given plot, the four points on the plane represent the outcomes for the four dose levels. At each dose level, the probability of toxicity corresponds to the value on the y-axis, and the standardized mean biomarker expression, which is defined as the mean biomarker expression divided by $W^*_{\max}$, corresponds to the value on the x-axis. Within each plot, the horizontal line indicates the maximum acceptable toxicity probability, π_t, which is set at 35%, and the vertical line indicates the standardized minimum biomarker expression level, which is set at 5%.

Because toxicity and biomarker expression are potentially correlated at a given dose, we introduce correlation in our simulations via a copula. We first generate standard bivariate normal random variables $(z_1,\ z_2)$ with a specified correlation coefficient. In each scenario, we use a weak association, 0.25, or a moderate association, 0.5, between the toxicity and biomarker expression. We then obtain a vector of correlated uniform variables, $(u_1,\ u_2) = (\Phi(z_1),\ \Phi(z_2))$. Under the sth scenario with the kth dose level, a patient's toxicity variable is simulated by u_1. Specifically, the patient has toxicity if $u_1 \leq p_{s,k}$, and no toxicity if $u_1 > p_{s,k}$.

We generate biomarker expression data by using the inverse of a gamma cumulative density function (CDF). Let $G^{-1}(\cdot \,|\, \gamma,\ \nu)$ be the inverse CDF of a gamma distribution with mean γ/ν. For each simulated u_2 under the kth dose of scenario s, the biomarker expression outcome w takes the value of $G^{-1}(u_2 \,|\, \tau\lambda_{s,k},\ \tau)$. The values of $(\lambda_{s,k},\ p_{s,k})$ used in each scenario are given in Table 1 and $\tau = 0.10$ for all scenarios.

The prior distributions for the parameters of interest are specified as follows. The prior location parameters for $\beta_{Z,k}$'s, $\mu_{Z,1}, \ldots, \mu_{Z,K}$, are set equal to 0, 1.9, -1, -7.5, which results in prior probabilities of toxicity equal to 0.03, 0.12, 0.21, 0.34. Other priors are used later for sensitivity analyses. The prior variance, σ_{β_Z}, is set equal to 4. To inform the prior distribution for the parameters directly associated with the biomarker expression data, we use $\beta_{W,0} = 5$ with prior variance $\sigma_{\beta_W} = 1000$. Finally, we use vague priors for ρ and σ_W.

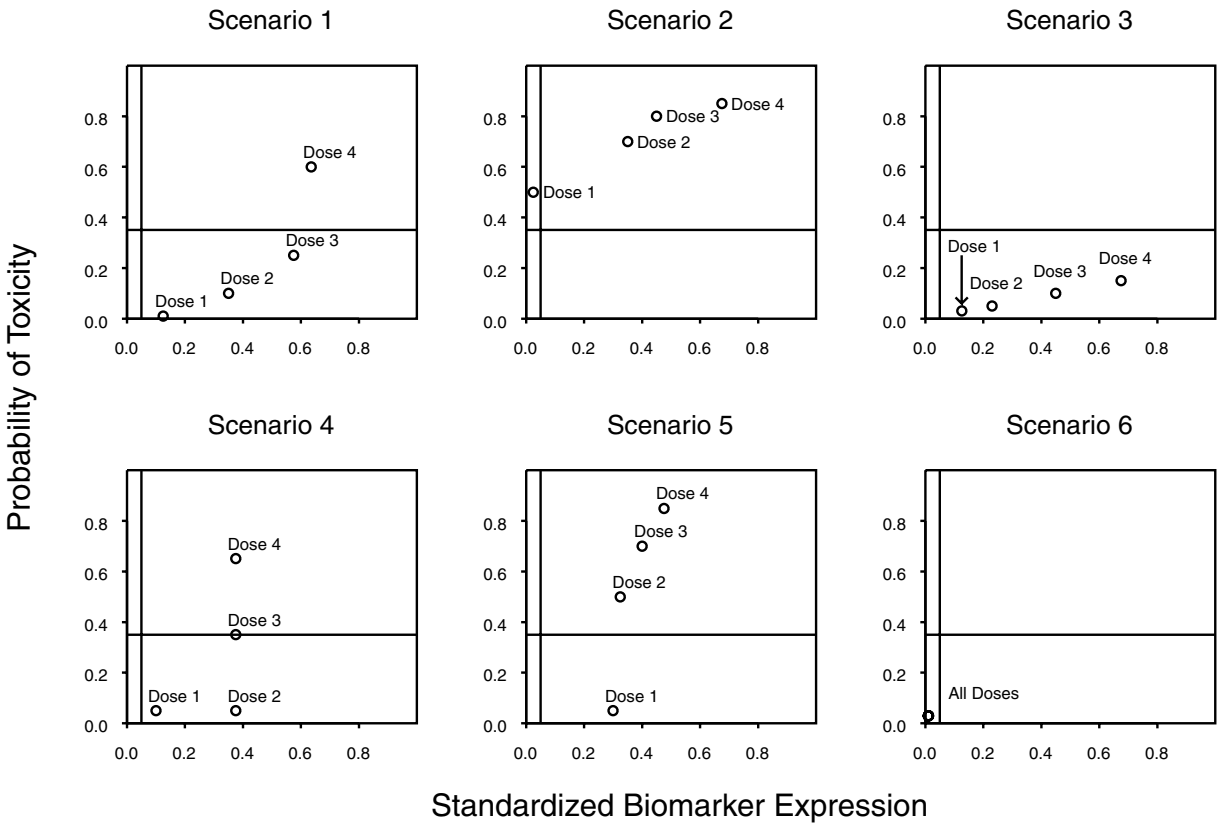

Figure 2. Graphical display of six scenarios evaluated via simulation.

In the preliminary simulation studies, we assessed the MCMC algorithm's convergence using standard diagnostics. Based on these preliminary studies, we decided to use a burn-in of 5000 iterations with a chain of length 5000, retaining every fifth sample. Although the posterior sample size was constrained by computing resources due to the need for many replications in the simulation studies, when conducting the actual trial, we will make inferences based on much larger samples from the posterior distribution of the parameters in the model. We replicated 1000 trials for each scenario. The computer program was written using `Visual Fortran`, and the simulations were carried out on an IBM compatible personal computer with dual 3.06 GHz math coprocessors and 1 GB memory. For each scenario, 1000 simulations were completed in approximately 35 minutes.

Table 1 summarizes the results for the six scenarios with a maximum number of 36 patients. In scenario 1, the third dose is preferred among the three tolerable doses (1, 2, and 3), because dose 4 is too toxic and doses 1 and 2 have lower levels of biomarker expression than dose 3. By using the proposed model and decision rules, the algorithm selects dose 3 with an empirical probability of 95%. Under scenario 2, all four doses are unacceptable due to high toxicity rates. In this scenario, the algorithm does not select any of the four doses in 94% of the trials. Moreover, most of the trials terminate early with an average sample size of 15. Moreover, most of the patients are treated at dose 1, and very few are treated at doses 3 and 4. Thus, our algorithm effectively protects patients from unsafe doses.

Scenario 3 describes an extreme case that shows the limitations of dichotomization to the continuous activity outcome. With the dichotomized activity data, the marginal probability of response (biomarker expression) at each dose is equal to $\Pr(G^{-1}(U \mid \tau\lambda_{3,s}, \tau) > W^*_{\min})$, where U is distributed *uniform*(0, 1). The probability of observing a response at each dose is 0.85, 0.99, 1.0, 1.0 for doses 1, 2, 3, and 4, respectively. The marginal probabilities of toxicity are given in scenario 3 of Table 1, in which all doses are safe. The method of Thall and Cook (2004) chose the first dose 94% of the time, while our method chose the fourth dose 98% of the time. This showed that even an innovative dose-finding algorithm such as that of Thall and Cook (2004) can break down, when continuous data are artificially dichotomized.

As suggested by the associate editor, we also simulated a setting by modifying scenario 3. Specifically, we assume a 20% probability of observing a toxicity at each dose, while biomarker activity has a monotone increasing relationship with dose as in the original scenario 3. The correlation between toxicity and the biomarker expression level is assumed to be zero. The results of the simulation study show that the algorithm selects doses 1–4 with the probabilities of 1.8%, 4.6%, 19.5%, and 74.1%. For this modified scenario we also compared the operating characteristics with a method that uses only toxicity for dose finding, referred to as the continual reassessment method (CRM), and Thall and Cook's (2004) bivariate binary algorithm. Using the CRM, the probability of toxicity at dose k is modeled by $\hat{p}_k^{exp(\alpha)}$, where α is distributed, a priori, $N(0, 1.34)$ and $\hat{p}_k$ is a fixed parameter

Table 1

Simulation results: Percentage that a dose is selected at the end of the trial (P_{sel}), average number of patients at each dose ($\bar{N}_{\text{pat}}$), and the 5th and 95th quantiles for the number of patients at each dose (N_5, N_{95}). ($\lambda_{k,s}$, $p_{k,s}$) are the underlying parameters for biomarker expression mean and toxicity probability for the kth dose and the sth scenario.

Scenario		None	Dose 1	Dose 2	Dose 3	Dose 4
1	True parameters: ($\lambda_{k,s}$, $p_{k,s}$)		(25, 0.01)	(70, 0.10)	(115, 0.25)	(127, 0.60)
	P_{sel}	0.0	0.0	3.3	94.9	1.8
	$\bar{N}_{\text{pat}}$		6.4	10.7	13.5	5.4
	(N_5, N_{95})		(4, 10)	(7, 15)	(9, 18)	(1, 12)
2	True parameters: ($\lambda_{k,s}$, $p_{k,s}$)		(5, 0.50)	(70, 0.70)	(90, 0.80)	(135, 0.85)
	P_{sel}	93.9	5.8	0.3	0.0	0.0
	$\bar{N}_{\text{pat}}$		9.2	5.2	0.3	0.0
	(N_5, N_{95})		(3, 19)	(0, 10)	(0, 1)	(0, 0)
3	True parameters: ($\lambda_{k,s}$, $p_{k,s}$)		(25, 0.03)	(46, 0.05)	(90, 0.10)	(135, 0.15)
	P_{sel}	0.0	0.0	0.1	2.0	97.9
	N_{pat}		5.0	7.5	9.5	14.0
	(N_5, N_{95})		(4, 7)	(6, 9)	(7, 12)	(11, 17)
4	True parameters: ($\lambda_{k,s}$, $p_{k,s}$)		(20, 0.05)	(75, 0.05)	(75, 0.35)	(75, 0.65)
	P_{sel}	0.0	0.0	82.8	17.2	0.0
	N_{pat}		7.7	13.5	10.9	3.9
	(N_5, N_{95})		(6, 9)	(10, 16)	(9, 13)	(2, 6)
5	True parameters: ($\lambda_{k,s}$, $p_{k,s}$)		(60, 0.05)	(65, 0.50)	(80, 0.70)	(95, 0.85)
	P_{sel}	0.0	94.2	5.5	0.3	0.0
	N_{pat}		19.9	13.2	2.8	0.1
	(N_5, N_{95})		(15, 25)	(10, 17)	(0, 5)	(0, 1)
6	True parameters: ($\lambda_{k,s}$, $p_{k,s}$)		(2, 0.03)	(2, 0.03)	(2, 0.03)	(2, 0.03)
	P_{sel}	99.0	0.4	0.4	0.1	0.1
	N_{pat}		3.5	3.6	3.6	3.7
	(N_5, N_{95})		(3, 4)	(3, 4)	(3, 4)	(3, 4)

between 0 and 1, set such that the expected prior probability of toxicity at the kth dose is equal to the probability of toxicity elicited from expert opinion. For the CRM simulations we assume a 20% toxicity rate for all doses, and set the expected prior probability of toxicity at 0.03, 0.12, 0.21, 0.34 for doses 1, 2, 3, and 4, respectively. The resultant selection probabilities from the CRM model are 20%, 22.3%, 26.7%, and 31% for doses 1 through 4, respectively. Using the bivariate binary method of Thall and Cook (2004), the empirical selection probabilities are 95%, 4.5%, 0.5%, and 0% for doses 1 through 4, respectively. As shown from this simulation study, the proposed algorithm is capable of escalating dose appropriately, because it uses information that cannot be fully utilized under the other two dose-finding strategies.

Under scenario 4, doses 1, 2, and 3 have the same biomarker expression level. The first three doses have acceptable toxicities, but dose 3 is much more toxic than doses 1 and 2, while dose 4 is too toxic. We also compare this scenario to the CRM algorithm described above. We used the same marginal probabilities of toxicity used in scenario 4 and the same prior for the CRM described above. Based on the CRM, the probability of correctly selecting the second dose is 3% and the probability of selecting the third dose is 94%. In contrast, using our algorithm dose 2 is selected 83% of the time while dose 3 is selected 17% of the time. Clearly, for this setting, the proposed method is much safer than an algorithm based on toxicity alone. As suggested by one reviewer, we also assessed the algorithm under a modification of scenario 4. Instead of assuming that the biomarker expression levels at doses 2 and 3 were the same, we assumed that the biomarker expression level for dose 3 was 10% greater than that for dose 2. Under this new setting, the second dose is still chosen 69% of the time, while the third dose is selected 31% of the time. It is interesting to note that the algorithm selects dose 2 most of time even when dose 3 has a slightly higher expression level, because the benefit of increased expression at dose 3 is offset by the increased toxicity.

Under scenario 5, only dose 1 is acceptable in terms of toxicity, and it is chosen in 94% of the trials. In scenario 6, all four doses are ineffective and nontoxic. In this case, 99% of the trials do not select any doses, and stop early with an average number of 14 patients like scenario 2. Interestingly, unlike scenario 2 where the patients were observed at lower doses, in this scenario the patients were uniformly distributed across all doses. Based on the proposed algorithm, once lower doses were shown to be safe, higher doses would subsequently be tried. After all doses were tried and no activity was observed, the trials stopped.

We also carried out a large number of sensitivity analyses to evaluate the performance of the model under various conditions. General factors explored include: (1) varying the maximum sample size of a trial ($N = 45$); (2) increasing the correlation coefficient between the toxicity and biomarker expression from mild to moderate; and (3) removing the

Table 2
Sensitivity analyses: Percentage that a dose is selected at the end of the trial under the six scenarios in Table 1 *with a different total sample size, correlation, or allocation rule*

Condition	Scenario	None selected	Dose 1	Dose 2	Dose 3	Dose 4
Sample size ($n = 45$)						
	1	0.0	0.0	3.8	94.7	1.5
	2	97.3	2.7	0.0	0.0	0.0
	3	0.0	0.0	0.0	1.8	98.2
	4	0.0	0.0	87.1	12.9	0.0
	5	0.1	94.8	4.9	0.2	0.0
	6	99.2	0.4	0.3	0.0	0.1
Moderate correlation						
	1	0.0	0.0	3.4	93.3	3.3
	2	92.4	7.3	0.3	0.0	0.0
	3	0.0	0.0	0.0	3.2	96.8
	4	0.0	0.1	93.8	6.1	0.1
	5	0.0	92.1	7.3	0.2	0.0
	6	99.6	0.0	0.0	0.3	0.1
No adaptive allocation						
	1	0.0	0.0	11.6	87.6	0.8
	2	93.9	5.8	0.3	0.0	0.0
	3	0.0	0.3	1.3	11.6	86.8
	4	0.0	0.0	88.4	11.5	0.1
	5	0.0	89.6	10.3	0.1	0.0
	6	99.3	0.2	0.1	0.1	0.3

probabilistic allocation rule based on the preference score. As expected, when the maximum sample size increases from 36 to 45 patients, the probabilities of correctly selecting the preferred doses improve, though the differences are not substantial, as shown in Table 2. With a moderate dependence between the two outcomes and a cohort size of 36, the results in Table 2 do not show appreciable differences in the selection probabilities compared with those under the mild dependence. It is quite interesting to note that the probabilities of selecting the right doses decrease without the random adaptive allocation scheme under scenarios 1, 3, and 5. For example, under scenario 1 more patients are assigned to dose 2,

Table 3
Additional sensitivity analyses: Percentage that a dose is selected at the end of the trial under the six scenarios in Table 1 *with three different sets of priors*

Prior toxicity	Scenario	None selected	Dose 1	Dose 2	Dose 3	Dose 4
(i) All doses very safe						
	1	0.0	0.0	0.2	84.9	14.9
	2	83.3	15.9	0.7	0.1	0.0
	3	0.0	0.0	0.0	0.2	99.8
	4	0.0	0.0	70.5	27.7	1.8
	5	0.0	88.2	9.1	2.6	0.1
	6	99.0	0.2	0.3	0.4	0.1
(ii) All doses too toxic						
	1	0.0	0.1	12.2	87.5	0.2
	2	97.2	2.7	0.1	0.0	0.0
	3	0.1	0.0	1.7	23.4	74.8
	4	0.3	0.0	88.2	11.5	0.0
	5	0.7	95.6	3.7	0.0	0.0
	6	99.3	0.2	0.1	0.4	0.0
(iii) Two doses safe, two toxic						
	1	0.0	0.0	6.7	91.9	1.4
	2	97.2	2.7	0.1	0.0	0.0
	3	0.1	0.0	0.5	9.8	89.6
	4	0.3	0.0	85.8	13.9	0.0
	5	0.2	94.2	5.2	0.4	0.0
	6	99.5	0.2	0.1	0.1	0.1

which is a safe but less effective dose, without the probabilistic allocation scheme. It is plausible that, without adaptive allocation, data observed early in the trial often cause the procedure to "stick" to certain lower doses without sufficiently exploring the potential benefit of other doses.

As requested by one reviewer, we performed additional simulations to assess the sensitivity of the approach to selection of priors in Table 3. Specifically, three additional sets of priors are used to assess the original six scenarios in Table 1: (i) all prior probabilities of toxicity are very low (1%, 4%, 6%, 10%); (ii) all prior probabilities of toxicity are unacceptable (36%, 66%, 87%, 97%); and (iii) the two lowest doses have prior probabilities of toxicity which are acceptable (10%, 31%) and the two highest doses have prior probabilities of toxicity which are unacceptable (62%, 88%). When the prior probabilities of toxicity for all doses are unacceptably high, the proposed algorithm escalates to higher doses much more conservatively under scenario 3. Alternatively, when all doses are thought to be very safe, a priori, the probability of selecting none of the doses is reduced by 10% under scenario 2. In most cases, even for the two extreme sets of priors, the operating characteristics are comparable to those using the original priors. We also examined the effect of varying the prior mean of the biomarker expression variable. The results are similar to the original simulations.

5. Conclusions

This research is motivated by the need to design a new type of dose-finding clinical trial when both toxicity and continuous activity outcomes are available. We have proposed a Bayesian adaptive dose-finding algorithm based on both a continuous variable and a binary toxicity variable. This design could potentially expedite the drug development process by naturally combining phase I and phase II trials with an activity outcome or its surrogate in dose-finding stages. One difficulty in modeling a bivariate toxicity and a continuous activity variable is determining how to induce a correlation between the two different types of outcomes. Albert and Chib (1993) and Chib (2003) introduced the key ideas of using latent variables for computing the posterior distribution and jointly modeling binary and continuous outcomes. By modifying these models and providing decision rules we have developed an algorithm for dose finding in phase I/II clinical trials.

In the earlier phases of new drug development, we may prefer using a flexible model to describe the relationship between the activity outcome and dose. In this article, we apply a flexible state-space model for this purpose, which allows us to borrow strength across doses without imposing stringent model assumptions and model nonlinear relationships between dose and biologic activity. In some applications, biomarker expression levels may be more likely to have a monotone relationship with dose. If it is the case, the model can be modified to reflect such a belief by imposing a more structured model.

One critical step in a dose-finding trial is to elicit hyperparameters from prior clinical experience. The elicitation process should follow a few general guidelines. The prior hyperparameters should be chosen in a way that reflects the physician's prior beliefs, but not be so informative as to dominate the observed data. To ensure appropriate behavior of the algorithm to the chosen priors, we suggest that the operating characteristics be checked via simulations before the initiation of a trial (Thall et al., 2001).

We also show that the use of probabilistic allocation improves the overall operating characteristics of the design. In particular, instead of assigning a patient to a dose with the highest preference score given the accumulated data, we randomly allocate that patient to one of the *acceptable* doses with probabilities calculated from the preference score. A higher preference score for a dose level corresponds to a higher probability of assigning patients to that dose. By comparison, for the standard phase I oncology trial, patient cohorts are successively assigned to the dose whose expected probability of toxicity is closest to some prespecified target probability of toxicity (e.g., 0.33%). Thus, for a given cohort these standard trial designs employ a "winner-take-all" approach to making all other doses inadmissible. Our modification of the traditional approaches allows acceptable doses to have nonzero probabilities of being assigned to the next patient in the dose-finding process.

If there is a desire to use more than one biomarker in a dose-finding trial, in addition to toxicity information, we can generalize the existing bivariate likelihood to a multivariate likelihood and further extend the decision rule to a multidimensional space. It is also worth pointing out that activity variables such as the biomarker expression observed immediately after the treatment may not effectively predict survival or other long-term outcomes of interest. An obvious extension of the method is feasible and of practical interest. After accounting for censoring, the methods can be applied to event-time data, when the event-times of interest can be observed quickly or accrual is slow. In this case, the event-time data accumulated early in the trial combined with toxicity profiles can be used to inform which dose is most appropriate later in the trial. In addition, if time-to-toxicity is one of the primary endpoints of interest, then Albert and Chib's (2001) method may be extended to a bivariate model which includes a time-to-toxicity ordinal outcome and a continuous activity variable.

Acknowledgements

The authors would like to thank Peter Müller and Peter Thall for helpful discussions, and the editor and the referees for their comments, which substantially improved this article. This research was partially supported by National Institutes of Health grant CA 79466 and bladder SPORE CA 091846.

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Received May 2004. *Revised August* 2004.
Accepted September 2004.