

# 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 dose-toxicity and dose-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 choose the best dose using both toxicity and expression outcomes under various clinical scenarios.

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# 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 a MTD based on modeling the probability of toxicity alone 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 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 (Tao 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 the 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,

Martin, Fisher and Pettinger, 1994; Thall and Russell, 1998; O'Quigley, Hughes and Fenton, 2001; Braun, 2002; and 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, a procedure that often results in a considerable loss of information.

For example, we can imagine 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 expressions 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 existing algorithms selecting a less efficacious dose. There is thus 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 the 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. At a given dose level, a patient's toxicity profile and activity outcome are potentially correlated with each other. We introduce a continuous latent variable, to jointly

model the continuous biomarker outcome and the binary toxicity outcome via a bivariate regression 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 paper is organized as follows. The probability models and the computation of posterior distributions are presented in Section 2; the decision rules in 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

### 3.1 Probability Models

Consider a single-arm trial, in which patients are sequentially accrued, and successively treated. Suppose  $K$  dose levels will be explored,  $d_1, \dots, d_K$ . Let  $x_i$  be the dose administered to the  $i$ th patient among the set of possible doses and let  $\mathbf{X}_i = (I(x_i = d_1), \dots, I(x_i = d_K))$ , where  $I(B)$  is an indicator function of the event  $B$ . The outcome vector for the  $i$ th patient is denoted by  $Y_i = (W_i, T_i)^T$ , 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.

Since 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 exists, 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  $\mathbf{X}_i\boldsymbol{\beta}_W$  and variance  $\sigma_W^2$ . Let  $\boldsymbol{\beta}_W = (\beta_{W,1}, \dots, \beta_{W,K})^T$  define a unknown vector of parameters, where  $\beta_{W,k}$  reflects the mean biologic activity for the  $k$ th 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  $u_k \sim N(0, \sigma_{\beta_W}^2)$ . This model is quite appropriate in this context because, unlike toxicity, one does 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 of the mean biomarker expression at the  $k$ th level,  $\beta_{W,k}$ , is distributed univariate normal with prior mean  $\beta_{W,(k-1)}$  and variance of a fixed constant  $\sigma_{\beta_W}^2$ . For identifiability,  $\beta_{W,1}$  follows a Gaussian distribution with mean  $\beta_{W,0}$  and variance  $\sigma_{\beta_W}^2$ , 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

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

where  $\phi(\cdot; \mu, \sigma^2)$  is the pdf of  $N(\mu, \sigma^2)$ .

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  $i$ th individual, which follows a normal distribution with mean  $\mathbf{X}_i\boldsymbol{\beta}_Z$ , and variance 1, where  $\boldsymbol{\beta}_Z = (\beta_{Z,1}, \dots, \beta_{Z,K})^T$  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 regression 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

$$Pr(T_i = 1 \mid x_i = d_k) = \Phi(\mathbf{X}_i\boldsymbol{\beta}_Z) = \Phi(\beta_{Z,k}),$$

where  $\Phi$  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  $k$ th dose level. A by-product 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

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

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  $(\mathbf{X}_i\boldsymbol{\beta}_W, \mathbf{X}_i\boldsymbol{\beta}_Z)^T$ , and variance/covariance matrix  $\Omega$ , where

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

Here,  $\Omega$  has the compound symmetric form, which ensures that  $\Omega$  is positive definite. Note that  $\rho$  is the covariance parameter between  $Z$  and  $W$ , which induces the dependence between toxicity,  $T$ , and biomarker,  $W$ .

We assume a prior distribution for  $\rho$  to be Gaussian, with mean 0 and variance  $\sigma_\rho$  and a prior distribution for  $\sigma_W^2$  to be an inverse gamma Inv-Gamma( $\gamma, \nu$ ) with mean  $\nu(\gamma - 1)^{-1}$  and variance  $\nu^2(\gamma - 1)^{-2}(\gamma - 2)^{-1}$ . Some of the priors discussed above should be informative. Specifically, the prior hyper-parameters  $\mu_{Z,1}, \dots, \mu_{Z,K}, \sigma_{\beta_Z}^2, \beta_{W,0}$ , and  $\sigma_{\beta_W}^2$  should be elicited using prior clinical experience. The other priors in the model can be vague.

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

$$\begin{aligned} & f(w_i, t_i | \boldsymbol{\beta}_W, \boldsymbol{\beta}_Z, \Omega, \mathbf{X}_i) \\ &= \prod_{l=0}^1 \left\{ \int_{A_l} \phi_{W,Z}(w_i, z_i; (\mathbf{X}_i\boldsymbol{\beta}_W, \mathbf{X}_i\boldsymbol{\beta}_Z)^T, \Omega) dz_i \right\}^{I(t_i=l)}, \end{aligned}$$

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

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

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

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:

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

where  $\tilde{\mu}_{W,i} = \mathbf{X}_i \boldsymbol{\beta}_W + \rho(z_i - \mathbf{X}_i \boldsymbol{\beta}_Z)$ .

### 3.2 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  $\boldsymbol{\theta} = (\boldsymbol{\beta}_Z^T, \boldsymbol{\beta}_W^T, \rho, \sigma_W)^T$  define a vector of all unknown parameters in the model. Conditional on the latent variable  $Z_i$ ,  $Pr(T_i = l \mid \boldsymbol{\theta}, Z_i) = I(Z_i \in A_l)$ , 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  $i$ th individual is proportional to

$$\phi_W(w_i; \mathbf{X}_i \boldsymbol{\beta}_W, \sigma_W^2 + \rho^2) \phi_{Z|W}(z_i; \tilde{\mu}_{Z,i}, \tilde{\rho}^2) I(Z_i \in A_{I(t_i=1)}) g(\boldsymbol{\theta}), \quad (3)$$

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

After each patient's outcomes are observed, we use an 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 patient planned for the trial where  $n = 1, \dots, N$ . At the  $n$ th stage, the full conditional distributions of the latent  $Z_i^{(n)}$  for  $(i = 1, \dots, n)$ , and  $\boldsymbol{\theta}^{(n)}$  are given in steps 1 through 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  $i$ th individual, if  $T_i = 0$  we sample  $Z_i$  from the truncated normal distribution  $\phi_{Z|W}(Z_i; \tilde{\mu}_{Z,i}, \tilde{\rho}^2) I(Z_i \leq 0)$ , 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  $n$ th 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  $k = 1, \dots, K$ , the full conditional distribution of  $\beta_{Z,k} \mid Z, W, \sigma_W, \rho, \boldsymbol{\beta}_{Z,-k}$  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

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

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

where

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

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  $\tilde{\sigma}_{Z,k}^2$  reduce to  $\mu_{Z,k}$  and  $\sigma_{\beta_Z}^2$ , 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  $k = 1, \dots, (K-1)$ , the corresponding log full conditional posterior of  $\beta_{W,k}$  is, but for a constant,

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

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

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

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

where

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

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  $\tilde{\sigma}_{W,k}^2$  reduces to  $\sigma_{\beta_W}^2$ , when there is no patient being evaluated at the  $k$ th dose level. For the highest dose level,  $k = K$ ,  $\beta_{W,K}$  is generated from a similar full conditional distribution where the full conditional mean and variance are given by

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

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

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

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

Thus, after observing the  $n$ th patient,  $\sigma_W^2$  is distributed with  $\text{Inv-Gamma}(\tilde{\gamma}, \tilde{\nu})$ , 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  $\rho$  is proportional to,

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

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

### 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 paper, we propose a different approach that chooses 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,  $\pi_t$ .  $W_{min}^*$  defines the lowest biomarker expression level of clinical interest, while  $\pi_t$  is a maximum acceptable toxicity probability (e.g., values between 20% to 40% are often used in conventional phase I oncology trials).

Let  $n_k$  be the number of patients evaluated at dose  $d_k$ . Dose  $d_k$  is regarded as *adequately tried*, if at any point in the trial  $n_k \geq m$ , where  $m$  is a fixed integer between 1 and 6. Let  $\delta_1$ ,  $\delta_2$ , and  $\delta_3$  be pre-specified threshold probabilities. Dose  $d_k$  will be declared *acceptable* at any time point if

$$Pr((h^{-1}(\beta_{W,k}) > W_{min}^* | \text{data}, n_k \geq m) > \delta_1 \quad \text{and} \quad Pr(\Phi(\beta_{Z,k}) < \pi_t | \text{data}, n_k \geq m) > \delta_2$$

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  $k$ th dose. These rules state that if the  $k$ th dose has been adequately evaluated, it will be declared *acceptable* if the marginal posterior probability that the mean biomarker expression level for the  $k$ th dose is greater than  $W_{min}^*$  is greater than  $\delta_1$ , and the marginal posterior probability that the toxicity rate is less than  $\pi_t$  is greater than  $\delta_2$ . If the  $k$ th 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  $\pi_t$  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. 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  $d_1, d_2, \dots, d_J$  denote the set of acceptable doses, where  $J \leq K$ . Define  $p_w(d_j) = E(h^{-1}(\beta_{W,j}) \mid \text{data})$  to be the expected posterior mean for the biomarker expression level on its original scale for dose  $d_j$ , and let  $p_t(d_j) = E(\Phi(\beta_{Z,j}) \mid \text{data})$  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,  $(p_m(d_j), p_t(d_j))$ , of the acceptable dose  $d_j$  to the *optimal point*,  $(W_{max}^*, 0)$

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

where the second component for the biomarker expression is standardized to the same scale as the toxicity rate in the definition of the distance. 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  $j$ th acceptable dose. We then randomly allocate the next patient to the  $j$ th 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 less than 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.

## 4 Applications and Simulations

Although most patients with superficial bladder cancer are treated with surgery or surgery combined with standard chemotherapy, 50 to 70 percent of superficial tumors recur and 20

to 30 percent 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 immuno-therapy.

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, which has shown a promising effect in animal studies (Tao 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 appropriate adenoviral vector. The dose-finding schemes 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  $\tau$  (i.e., mean equal to  $\lambda_{s,k}$ ), for the  $k$ th dose of scenario  $s$ , where  $s = 1, \dots, 6$  and  $k = 1, \dots, 4$ . 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

1. A total of four dose levels will be explored per scenario. 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,  $\pi_t$ , which is set at 35%, and the vertical line indicates the standardized minimum biomarker expression level, which is set at 5%.

Figure 2 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.

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  $s$ th scenario with the  $k$ th 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  $\gamma/\nu$ . For each simulated  $u_2$  under the  $k$ th 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  $\lambda_{s,k}$  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,  $\mu_{Z,1}, \dots, \mu_{Z,K}$ , 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 (These prior toxicity probabilities were found to be reasonable by the investigators). The prior variance,  $\sigma_{\beta_Z}$  is set equal to 4. To inform the prior distribution for the parameters directly associated with the biomarker expression data, we use  $\beta_{W,0} = 50$  with prior variance  $\sigma_{\beta_W} = 1000$ . Lastly, we use vague priors for  $\rho$  and  $\sigma_W$ .

In the simulation study, we use a MCMC algorithm with the standard convergence diagnostics. After a burn-in of 5000 iterations with a chain of length 5000, we retain every 5th sample. Although the posterior sample size is 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.

Table 3 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, 94% of the trials do not select any of the 4 doses. The trials are terminated early and the average sample size is 15. Moreover, most of the patients are treated at doses 1, and very few are treated at doses 3 and 4. Thus, our algorithm is effective to protect patients from unsafe doses.

Scenario 3 describes an extreme case to show 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  $Pr(G^{-1}(U | \tau \lambda_{3,s}, \tau) > W_{min}^*)$ , 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. Based on 1000

simulations for this scenario, 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.

Under scenario 4, doses 1, 2 and 3 have the same biomarker expression. 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 include this scenario to compare the proposed algorithm with the continual reassessment method (CRM), a method that only uses the toxicity outcome. Using the CRM, the probability of toxicity at dose  $k$  is modeled by  $\hat{p}_k^{exp(\alpha)}$ , where  $\alpha$  is distributed, *a priori*,  $N(0, 1.34)$  and  $\hat{p}_k$  is a fixed parameter between 0 and 1, set such that the expected prior probability of toxicity at the  $k$ th dose is equal to the probability of toxicity elicited from expert opinion. With the same marginal probabilities of toxicity given for scenario 4, the expected prior probability of toxicity for the CRM is set at 0.03, 0.12, 0.21, 0.34 for doses 1, 2, 3, and 4, respectively. Based on 1000 simulations, the probability of correctly selecting the second dose is 3% and the probability of selecting the third dose is 94% using the CRM. In contrast, using our algorithm dose 2 is selected 83% of the time while dose 3 is selected 17% of the time. Clearly, the proposed method is much safer than an algorithm based on toxicity alone, for this setting.

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 non-toxic. 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 algorithm stopped.

We also carried out sensitivity analyses on scenarios 1 through 6 to evaluate the per-

formance of the model under various conditions. The 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 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, which is a safe but less effective dose, without the probabilistic allocation scheme. It is plausible that 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 without this random allocation scheme.

## 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. Such the design also has great potential to 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) introduced a key idea of using latent

variables for computing the posterior distribution. By extending their method, we can relate the binary toxicity variable to a continuous latent variable with an underlying normal regression structure. A bivariate model is thus naturally introduced to connect this latent continuous variable with the continuous activity variable.

In earlier phases of new drug development, we often prefer using a flexible model to describe the relationship between the activity outcome and dose. In this article, we apply the flexible state-space model for this purpose, which allows us to borrow strength across doses without imposing stringent model assumptions. Simulation studies show that the model is robust to deviations from the underlying distributional assumptions, and various correlation coefficients between toxicity and biomarker expression. Furthermore, we 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 pre-specified 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 doses with preference scores close to the highest preference score to have non-zero probabilities of being assigned to the next patient in the dose-finding process.

It is 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.

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**Table 1.** *Percent Selected  $P_{sel}$  and Avg. Number of Patients  $N_{pat}$  at Each Dose Syn3 trial*

Scenario	Tot. Pats.		None Selected	Dose 1	Dose 2	Dose 3	Dose 4
1	36.0	$(\lambda_{k,s}, 100p_{k,s})$		(25,1)	(70,10)	(115,25)	(127,60)
		$P_{sel}$	0.0	0.0	3.3	94.9	1.8
		$N_{pat}$		6.4	10.7	13.5	5.4
2	14.8	$(\lambda_{k,s}, 100p_{k,s})$		(5,50)	(70,70)	(90,80)	(135,85)
		$P_{sel}$	93.9	5.8	0.3	0.0	0.0
		$N_{pat}$		9.2	5.2	0.3	0.0
3	36.0	$(\lambda_{k,s}, 100p_{k,s})$		(25,3)	(46,5)	(90,10)	(135,15)
		$P_{sel}$	0.0	0.0	0.1	2.0	97.9
		$N_{pat}$		5.0	7.5	9.5	14.0
4	36.0	$(\lambda_{k,s}, 100p_{k,s})$		(20,5)	(75,5)	(75,50)	(75,65)
		$P_{sel}$	0.0	0.0	82.8	17.2	0.0
		$N_{pat}$		7.7	13.5	10.9	3.9
5	36.0	$(\lambda_{k,s}, 100p_{k,s})$		(60,5)	(65,50)	(80,70)	(95,85)
		$P_{sel}$	0.0	94.2	5.5	0.3	0.0
		$N_{pat}$		19.9	13.2	2.8	0.1
6	14.4	$(\lambda_{k,s}, 100p_{k,s})$		(2,3)	(2,3)	(2,3)	(2,3)
		$P_{sel}$	99.0	0.4	0.4	0.1	0.1
		$N_{pat}$		3.5	3.6	3.6	3.7

**Table 2.** *Sensitivity Analyses for Probability of Correct Selection*

Condition	Scenario	None Selected	Dose I	Dose II	Dose III	Dose IV
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 Adapt. Alloc.	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

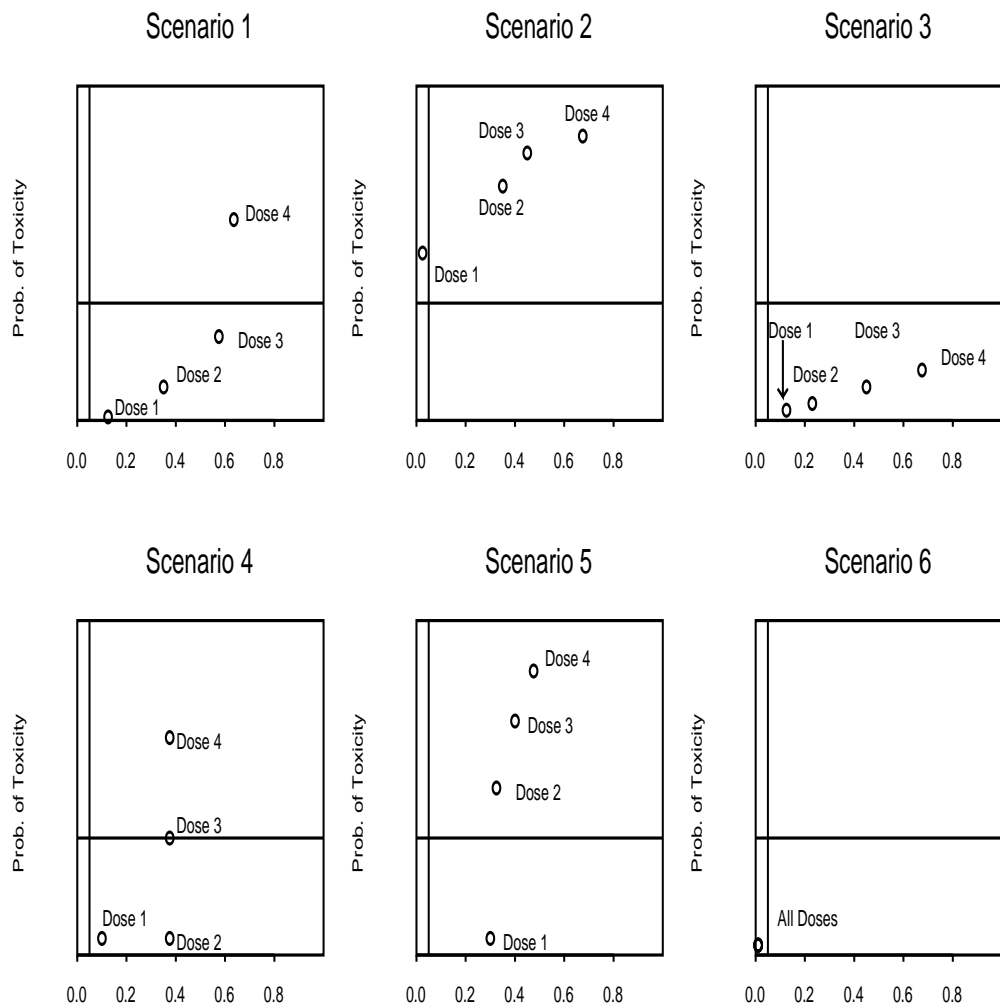


Figure 1: Graphical Display of Six Scenarios Evaluated Via Simulation

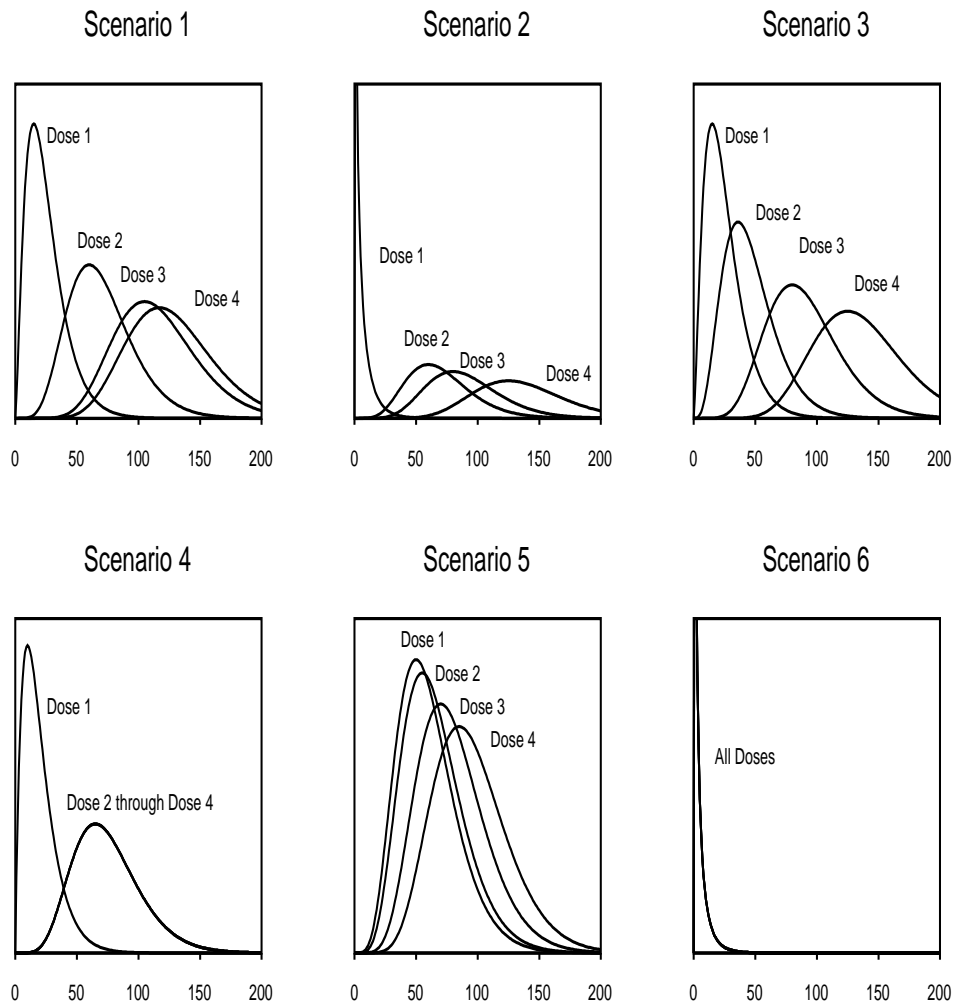


Figure 2: Marginal Distribution of Biomarker Expression Used in Simulation Studies