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3.1 Introduction

In the cancer drug development process, phase I clinical trials focus on identifying the maximum tolerated dose (MTD), which is typically defined as the dose with a toxicity probability closest to the target toxicity rate. Phase I clinical trials are critically important, as the determined MTD will be further investigated in the subsequent Phase II or Phase III trials. Misidentification of the MTD could result in an inconclusive trial, thereby wasting enormous resources, or a trial in which a substantial number of patients would be treated at excessively toxic doses. In addition, if a dose with low toxicity and negligible efficacy is inappropriately selected as the MTD, it may cause researchers to overlook a promising drug.

Many statistical methods have been developed for dose-finding studies, with a basic assumption that toxicity monotonically increases with respect to the dose. The standard 3 + 3 design is an algorithm-based procedure that typically defines the MTD as the highest dose with a toxicity probability less than 33% (Storer 1989). Although the 3 + 3 design is widely used in practice due to its simplicity, the estimates of the toxicity probabilities are not reliable (O’Quigley and Chevret 1991). As an alternative, the model-based continual reassessment method (CRM) proposed by O’Quigley, Pepe, and Fisher (1990) links the true toxicity probabilities and the prespecified toxicity probabilities with a single unknown parameter. During the trial conduct using the CRM, the unknown parameter is continuously updated as more data accumulate. Other related phase I trial designs include the Bayesian decision-theoretic approach by Whitehead and Brunier (1995); random walk rules by Durham, Flournoy, and Rosenberger (1997); dose escalation with overdose control by Babb, Rogatko, and Zacks (1998); and the biased-coin design with an isotonic regression estimator by Stylianou and Flournoy (2002).

Dose finding based solely on toxicity, while ignoring efficacy, may not be the best strategy. There has been increasing research in dose-finding methods that jointly model toxicity and efficacy (Gooley et al. 1994; O’Quigley, Hughes, and Fenton 2001; among others). In particular, Thall and Cook (2004) proposed to partition the two-dimensional toxicity–efficacy probability domain by introducing equivalence contours. However, the trade-off contour was constructed with a polynomial model based on only three physician-specified equivalent points, which might be subjective. Yin, Li, and Ji (2006) developed a toxicity–efficacy odds-ratio contour as a trade-off for dose finding, which is more objective, intuitive, and easily interpretable. Furthermore, Yuan and Yin (2009) extended toxicity–efficacy joint modeling to time-to-event outcomes and constructed the trade-off based on survival curves.

All of the aforementioned methods were developed for single-agent dose-finding trials, and therefore cannot address drug-combination studies, a rapidly growing area of clinical research. Combining different agents can impart the advantages of inducing a synergistic treatment effect, targeting different disease pathways, and achieving a high-dose intensity with nonoverlapping toxicities. However, complex drug–drug interactive effects often lead to an unknown toxicity order (i.e., the usual monotonic toxicity order with respect to the dose is lost). Drug-combination studies can be formulated in a more general framework, that of a trial with several different drugs, each at a prespecified set of doses, or a study of a single agent at a set of doses, adding a change to different administration schedules. Along this direction, Korn and Simon (1993) introduced a tolerable dose diagram to provide guidance in targeting specific MTD combinations. Kramar, Lebecq, and Candalh (1999) proposed searching over a selected subset of drug combinations that still maintains the monotonic order. Kuzuya et al. (2001) proposed fixing one agent at each dose level and varying the other in a trial combining paclitaxel and carboplatin to treat ovarian cancer. Thall et al. (2003) proposed a six-parameter model to define the toxicity probability for the combination of gemcitabine and cyclophosphamide. Conaway, Dunbar, and Peddada (2004) examined the simple and partial orders for drug combinations based on the pool-adjacent-violators algorithm. Wang and Ivanova (2005) studied a logistic regression model with the standardized doses of the two drugs as covariates. Yuan and Yin (2008) developed a sequential CRM for drug-combination trials that uses the partial order of the two-dimensional dose-finding space. By introducing latent $2 \times 2$ contingency tables, Yin and Yuan (2009b) pooled indistinguishable toxicity probabilities together to construct a binomial likelihood for combinations of two agents. Yin and Yuan (2009c, 2010) proposed a copula-type regression to model the joint toxicity probability, which incorporates the prior information on the toxicity probabilities when each drug is administered alone.

Following a phase I drug-combination trial, there may be several MTDs identified, which are carried forward for Phase II testing. Phase II trials typically serve as a drug screening process in terms of efficacy
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or antidisease activities. Simultaneously examining several MTDs naturally leads to a multiarm study, in which adaptive randomization is often used to assign more patients to a more efficacious treatment arm (Yuan and Yin 2010).

To illustrate recent developments in Bayesian approaches for adaptive designs, in this chapter we discuss four innovative Bayesian adaptive designs: the BMA-CRM in phase I dose-finding trials (Yin and Yuan 2009a), jointly modeling toxicity and efficacy in phase I/II trials (Yin, Li, and Ji 2006), copula-type regression in phase I drug-combination trials (Yin and Yuan 2009c), and adaptive randomization in Phase I/II drug-combination trials.

3.2 Bayesian Model Averaging Continual Reassessment Method

3.2.1 Continual Reassessment Method

Let \(d_1, \ldots, d_J\) denote a set of \(J\) prespecified doses for the drug under investigation, and let \(p_1, \ldots, p_J\) be the corresponding prespecified toxicity probabilities, also known as the “skeleton,” satisfying \(p_1 < \ldots < p_J\). Let \(\Phi_T\) be the target toxicity rate. The CRM assumes a working dose–toxicity model,

\[
pr(\text{toxicity at } d_j) = \pi_j(\alpha) = p_j^{\exp(\alpha)}, \quad j = 1, \ldots, J,
\]

where \(\alpha\) is an unknown parameter (O’Quigley and Shen 1996). Parabolic tangent or logistic structures can also be used to model the dose–toxicity curve (O’Quigley, Pepe, and Fisher 1990).

Let \(D\) denote the observed data: \(y_j\) out of \(n_j\) patients treated at dose level \(j\) have experienced the dose-limiting toxicity (DLT). Based on the binomial distribution, the likelihood function is

\[
L(D | \alpha) \propto \prod_{j=1}^{J} \left[ p_j^{\exp(\alpha)} y_j (1 - p_j^{\exp(\alpha)})^{n_j - y_j} \right].
\]

Using Bayes’ theorem, the posterior means of the toxicity probabilities can be computed by

\[
\hat{\pi}_j = \int p_j^{\exp(\alpha)} \frac{L(D | \alpha) f(\alpha)}{\int L(D | \alpha) f(\alpha) d\alpha} d\alpha,
\]

where \(f(\alpha)\) is a prior distribution for \(\alpha\), for example, \(\alpha \sim N(0, \sigma^2)\). After updating the posterior estimates of the dose–toxicity probabilities, the dose recommended for the next cohort of patients is the one that has a toxicity probability closest to the target \(\Phi_T\). That is, a new cohort of patients is assigned to dose level \(j^*\) with \(j^* = \arg \min_{j=1, \ldots, J} |\hat{\pi}_j - \Phi_T|\). The trial continues until the exhaustion of the total sample size, and then the dose with a posterior toxicity probability closest to \(\Phi_T\) is selected as the MTD.

To improve the practical performance of the CRM, the modified version of the CRM (Goodman, Zahurak, and Piantadosi 1995; Møller 1995; Chevret 2006) requires that the cohort size is three; dose escalation is restricted to one level of change only; and if \(pr(\text{toxicity at the lowest dose } > \Phi_T) > 0.9\), the trial is terminated for safety.

3.2.2 Bayesian Model Averaging CRM

Although the practical modifications improve the operating characteristics of the CRM. There is an important unresolved issue: the set of prespecified toxicity probabilities (skeleton) in the CRM is
arbitrary and subjective. Using different skeletons may lead to quite different design properties, and the performance of the CRM can be severely compromised if the elicited toxicity probabilities in the skeleton do not fit the assumed dose–toxicity model. Unfortunately, practitioners usually have no information to justify whether a specific skeleton is reasonable because the underlying true toxicity probabilities are unknown. To overcome the arbitrariness of the skeleton, Yin and Yuan (2009a) proposed the BMA-CRM by using multiple skeletons in the CRM combined with the BMA approach, which provides a better predictive performance than any single model (Raftery, Madigan, and Hoeting 1997; Hoeting et al. 1999).

Let \((M_1, \ldots, M_K)\) be the models corresponding to each set of the prespecified toxicity probabilities \(\{(p_{11}, \ldots, p_{1J}), \ldots, (p_{kJ}, \ldots, p_{kJ})\}\). Model \(M_k\) in the CRM is given by

\[
\pi_k(\alpha_k) = p_{kj}^{exp(\alpha_k)}, \quad j = 1, \ldots, J,
\]

which is based on the \(k\)th skeleton \((p_{1j}, \ldots, p_{kj})\). Let \(pr(M_k)\) be the prior model probability, then the likelihood function under model \(M_k\) is

\[
L(D | \alpha_k, M_k) \propto \prod_{j=1}^J \{p_{kj}^{exp(\alpha_k)}\}^{y_j} \{1 - p_{kj}^{exp(\alpha_k)}\}^{1-y_j}.
\]

The posterior model probability for \(M_k\) is given by

\[
pr(M_k | D) = \frac{L(D | M_k)pr(M_k)}{\sum_{i=1}^K L(D | M_i)pr(M_i)},
\]

where \(L(D | M_k)\) is the marginal likelihood of model \(M_k\),

\[
L(D | M_k) = \int L(D | \alpha_k, M_k) f(\alpha_k | M_k) d\alpha_k,
\]

and \(f(\alpha_k | M_k)\) is the prior distribution of \(\alpha_k\) under model \(M_k\).

The BMA estimate for the toxicity probability at each dose level is

\[
\hat{\pi}_j = \sum_{k=1}^K \hat{\pi}_{kj} pr(M_k | D), \quad j = 1, \ldots, J,
\]

where \(\hat{\pi}_{kj}\) is the posterior mean of the toxicity probability at dose level \(j\) under model \(M_k\),

\[
\hat{\pi}_{kj} = \int p_{kj}^{exp(\alpha_k)} \frac{L(D | \alpha_k, M_k) f(\alpha_k | M_k)}{\int L(D | \alpha_k, M_k) f(\alpha_k | M_k) d\alpha_k} d\alpha_k.
\]
By assigning $\hat{\pi}_{kj}$ a weight of $\text{pr}(M_k \mid D)$, BMA automatically favors the best fitting model, and also provides a coherent mechanism to account for the model uncertainty associated with each skeleton.

### 3.2.3 Dose-Finding Algorithm

Patients in the first cohort are treated at the lowest dose $d_1$, or the physician-specified dose. The dose-finding algorithm of the BMA-CRM is described below.

1. Let $j^{\text{curr}}$ denote the current dose level, and we find dose level $j^*$ that has a toxicity probability closest to $\phi_T$. If $j^{\text{curr}} > j^*$, we de-escalate the dose level to $j^{\text{curr}} - 1$; if $j^{\text{curr}} < j^*$, we escalate the dose level to $j^{\text{curr}} + 1$; otherwise, the dose stays at the same level as $j^{\text{curr}}$ for the next cohort of patients.

2. Once the maximum sample size is reached, the dose that has the toxicity probability closest to $\phi_T$ is selected as the MTD.

In addition, we require an early termination of a trial for safety, if

$$\sum_{k=1}^{K} \text{pr}(\pi_{jk}(\alpha_k) > \phi_T \mid M_k, D) \text{pr}(M_k \mid D) > 90\%.$$  

### 3.2.4 Simulation Study

We investigated the operating characteristics of the BMA-CRM through simulation studies. We considered eight doses and prepared four sets of initial guesses of the toxicity probabilities:

$$(p_1, \ldots, p_8) = \begin{cases} (0.02, 0.06, 0.08, 0.12, 0.20, 0.30, 0.40, 0.50), & \text{skeleton1} \\ (0.01, 0.05, 0.09, 0.14, 0.18, 0.22, 0.26, 0.30), & \text{skeleton2} \\ (0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80), & \text{skeleton3} \\ (0.20, 0.30, 0.40, 0.50, 0.60, 0.65, 0.70, 0.75), & \text{skeleton4}. \end{cases}$$

We refer to the individual CRM using each of these four skeletons as CRM 1, CRM 2, CRM 3, and CRM 4. The target toxic probability was $\phi_T = 30\%$. We took a prior distribution of $\alpha \sim N(0,4)$ and assigned a prior model probability of $1/4$ to each CRM model; that is, $\text{pr}(M_k) = 1/4$ for $k = 1, \ldots, 4$. We took a cohort size of 3, and treated the first cohort of patients at the lowest dose level. The maximum sample size was 30. For each scenario, we carried out 10,000 simulated trials.

In Table 3.1, we summarize the simulation results for three different scenarios. In scenario 1, the seventh dose is the MTD; and the four individual CRMs selected the MTD with quite different probabilities: particularly, CRM 2 had the lowest MTD selection percentage of 30.8%, while incorrectly selected the eighth dose with the highest percentage of 56.9%; and the BMA-CRM had an MTD selection percentage of 51.5%. In scenario 2, for which the MTD is at the sixth dose level, the MTD selection percentage using the BMA-CRM was the second best among all of the five designs. The worst skeleton in Scenario 2 corresponds to CRM 2, which yielded an MTD selection percentage of less than 30%. In Scenario 3, which has the third dose as the MTD, CRM 1 behaved the worst with an MTD selection percentage of less than 50% compared to MTD selection percentages of more than 60% for the others.
We further examined the relationship between the performance of each CRM and the corresponding posterior model probability using the BMA approach. We took 30 cohorts of size 3 and simulated 5000 trials. For each trial, we computed the posterior model probabilities for each CRM after every cohort was sequentially accrued. In Figure 3.1, we present the average of these posterior model probabilities versus the accumulating number of cohorts. Figure 3.1 shows that the posterior model probabilities of the four CRM models started separating after approximately 4–8 cohorts, and eventually stabilized in an order that correctly matches the performance of each CRM. These simulations demonstrated the robustness of the BMA-CRM.

### Table 3.1 Simulation Study Comparing the CRM and BMA-CRM, With a Toxicity Target $\phi_T = 30\%$

<table>
<thead>
<tr>
<th>Design</th>
<th>Recommendation Percentage at Dose Level</th>
<th>Average # Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>CRM 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># patients</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>CRM 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># patients</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>CRM 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># patients</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>CRM 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># patients</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>BMA-CRM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># patients</td>
<td>3.2</td>
<td>3.0</td>
</tr>
</tbody>
</table>

| Scenario 2 | 2 | 6 | 8 | 12 | 20 | 30 | 40 | 50 |                      |
| CRM 1 | 0 | 0 | 0 | 2.9 | 23.9 | 43.6 | 22.7 | 6.9 | 5.9 |
| # patients | 3.2 | 3.1 | 3.2 | 3.6 | 6.3 | 6.6 | 3.0 | 0.8 | 3.9 |
| CRM 2 | 0 | 0 | 0.3 | 4.3 | 17.1 | 28.4 | 25.5 | 24.4 | 6.5 |
| # patients | 3.2 | 3.1 | 3.4 | 3.8 | 4.6 | 4.8 | 3.8 | 3.2 | 3.2 |
| CRM 3 | 0 | 0 | 0.6 | 6.3 | 32.6 | 40.8 | 18.1 | 1.6 | 5.2 |
| # patients | 3.2 | 3.1 | 3.6 | 4.8 | 6.9 | 5.7 | 2.4 | 0.2 | 0.2 |
| CRM 4 | 0 | 0 | 0.4 | 7.5 | 27.8 | 35.3 | 20.7 | 8.2 | 5.5 |
| # patients | 3.2 | 3.1 | 3.6 | 4.9 | 6.4 | 4.8 | 2.9 | 1.0 | 1.0 |
| BMA-CRM | 0 | 0 | 0 | 0.2 | 1.5 | 16.2 | 51.5 | 30.6 | 4.7 |
| # patients | 3.2 | 3.0 | 3.1 | 3.2 | 3.5 | 4.4 | 6.3 | 3.2 | 4.7 |

| Scenario 3 | 6 | 15 | 30 | 55 | 60 | 65 | 68 | 70 |                      |
| CRM 1 | 0.9 | 27.8 | 48.5 | 21.0 | 1.5 | 0.2 | 0 | 0 | 9.1 |
| # patients | 4.3 | 7.4 | 9.7 | 6.5 | 1.9 | 0.2 | 0 | 0 | 0.8 |
| CRM 2 | 0.2 | 22.6 | 60.8 | 15.1 | 1.0 | 0.2 | 0 | 0 | 8.8 |
| # patients | 3.9 | 7.5 | 11.7 | 5.1 | 1.5 | 0.3 | 0 | 0 | 0.8 |
| CRM 3 | 0.3 | 19.6 | 65.1 | 14.4 | 0.6 | 0 | 0 | 0 | 8.4 |
| # patients | 4.1 | 7.2 | 13.0 | 5.0 | 0.6 | 0 | 0 | 0 | 8.4 |
| CRM 4 | 0.4 | 19.3 | 65.6 | 14.2 | 0.5 | 0 | 0 | 0 | 8.5 |
| # patients | 4.1 | 7.2 | 12.7 | 5.2 | 0.7 | 0.1 | 0 | 0 | 8.6 |
| BMA-CRM | 0.3 | 20.6 | 62.0 | 16.1 | 0.9 | 0 | 0 | 0 | 8.6 |
| # patients | 4.1 | 7.2 | 12.2 | 5.6 | 0.8 | 0.1 | 0 | 0 | 8.6 |


Note: MTD is shown in boldface.
3.3 Jointly Modeling Toxicity and Efficacy in Phase I/II Design

3.3.1 Likelihood and Prior

In a typical phase I/II clinical trial, the interest is focused on finding the dose that optimizes the trade-off between toxicity and efficacy. Let \( p_j \) and \( r_j \) be the probabilities of toxicity and efficacy associated with dose level \( j \). We assume a monotonically increasing order of toxicity probabilities with respect to the doses, but no such constraint for efficacy.

Let \( X_{ij} \) denote the binary toxicity outcome for subject \( i \) under dose level \( j \), and let \( Y_{ij} \) denote the binary efficacy outcome of the same subject; that is, \( X_{ij} = 1 \) with probability \( p_j \), or 0 with probability \( 1 - p_j \); and \( Y_{ij} = 1 \) with probability \( r_j \), or 0 with probability \( 1 - r_j \). Following the global cross-ratio model (Dale 1986), at dose level \( j \), we define \( \pi_{xy}^{(j)} = \text{pr}(X_{ij} = x, Y_{ij} = y) \), and \( \theta_j = \frac{\pi_{11}^{(j)}}{\pi_{10}^{(j)} \pi_{01}^{(j)}} / \pi_{00}^{(j)} \). The joint probabilities \( \pi_{xy}^{(j)} \) can be obtained from the association parameter \( \theta_j \) and the marginal probabilities \( p_j \) and \( r_j \):

\[
\pi_{11}^{(j)} = \begin{cases} 
\frac{a_j - \sqrt{a_j^2 + b_j}}{2(\theta_j - 1)} & \theta_j \neq 1 \\
p_j r_j & \theta_j = 1,
\end{cases}
\]

where \( a_j = 1 + (p_j + r_j)(\theta_j - 1) \) and \( b_j = -4\theta_j(\theta_j - 1)p_j r_j \). If \( n_j \) subjects are treated at dose \( d_j \), then the likelihood function is

\[
L(p_1, \ldots, p_J, r_1, \ldots, r_J, \theta_1, \ldots, \theta_J | D) \propto \prod_{j=1}^{J} \prod_{i=1}^{n_j} \prod_{x=0}^{1} \prod_{y=0}^{1} \{ \pi_{xy}^{(j)} \}^{I(X_{ij} = x, Y_{ij} = y)},
\]

where \( I(\bullet) \) is the indicator function.

We apply two different transformations for the \( p \)'s and \( r \)'s in the prior specification with or without incorporating the monotonic ordering constraint. To model toxicity, let

\[
\xi_1 = \log \frac{p_1}{1 - p_1}, \quad \xi_j = \log \left( \frac{p_j - p_{j-1}}{1 - p_j - p_{j-1}} \right), \quad j = 2, \ldots, J,
\]
and then

\[ p_i = \frac{e^{\xi_i}}{1 + e^{\xi_i}}, \quad p_j = \frac{e^{\xi_i + \cdots + \xi_j}}{1 + e^{\xi_i + \cdots + \xi_j}}. \]

Clearly, the \( p_i \)'s satisfy the monotonic toxicity condition. For efficacy, we do not enforce the ordering constraint, and define

\[ \zeta_i = \log \frac{r_i}{1 - r_i}, \quad \zeta_j = \log \left( \frac{r_j}{1 - r_j} \right) - \log \left( \frac{r_{j-1}}{1 - r_{j-1}} \right), \quad j = 2, \ldots, J, \]

and thus,

\[ r_i = \frac{e^{\zeta_i}}{1 + e^{\zeta_i}}, \quad r_j = \frac{e^{\zeta_i + \cdots + \zeta_j}}{1 + e^{\zeta_i + \cdots + \zeta_j}}. \]

For ease of computation, we take the prior distributions for the \( \theta_j \)'s to be independent from a log-normal distribution. Let \( \xi = (\xi_1, \ldots, \xi_J)^T \), and \( \zeta \) and \( \theta \) be defined similarly, then the joint posterior distribution is given by

\[ f(\xi, \zeta, \theta | D) \propto L(\xi, \zeta, \theta | D) f(\xi, \zeta) f(\theta_1) \cdots f(\theta_J), \]

where \( L(\xi, \zeta, \theta | D) \) is the likelihood after reparameterization, and \( f(\xi, \zeta) \) and \( f(\theta) \) are the prior distributions. We typically assign noninformative priors to the model parameters, such that the likelihood dominates the posterior estimation and inference. To implement Gibbs sampling, we derive the full conditional distribution for each model parameter and obtain the posterior samples using the adaptive rejection Metropolis sampling algorithm (Gilks, Best, and Tan 1995).

### 3.3.2 Odds-Ratio Trade-Off

We define a set of admissible doses, \( d_j \in A \), if dose \( d_j \) satisfies

\[ \Pr(p_j < \phi_T) > p^\ast, \quad \Pr(r_j > \phi_E) > r^\ast, \]

where \( \phi_T \) and \( \phi_E \) are prespecified upper toxicity and lower efficacy boundaries, and \( p^\ast \) and \( r^\ast \) are fixed probability cutoffs.

As shown in Figure 3.2, we expect the efficacy and toxicity probabilities \((r_j, p_j)\) of the target dose to be closest to the lower-right corner \((1, 0)\) in the two-dimensional domain. The horizontal and vertical lines crossing point \((r_j, p_j)\) partition the probability space into four rectangles. The toxicity–efficacy odds ratio

\[ \omega_j = \frac{p_j(1 - p_j)}{r_j(1 - r_j)} = \frac{p_j}{r_j}, \]

is exactly the ratio of the areas between the lower-right and the upper-left rectangles. Clearly, a dose with a smaller value of \( \omega_j \) is more desirable. Figure 3.2 also shows the equivalent odds-ratio contours, along which all of the points have the same toxicity–efficacy odds ratio.
We start by treating patients in the first cohort at the lowest dose level, with a restriction that untried doses cannot be skipped during dose escalation. The dose-finding algorithm is described as follows:

1. Let $j^*$ be the highest tried dose level. If $\Pr(p_j^* < \phi_T) > p^*$ for some chosen cutoff probability of escalation, $p^* \geq p^*$, we escalate to dose level $j^* + 1$.

2. Otherwise, the next cohort of patients are treated at the dose with the smallest odds ratio in $\mathcal{A}$. If $\mathcal{A}$ is an empty set, then the trial is terminated and no dose is selected.

3. Once the maximum sample size is reached, the dose with the minimum toxicity–efficacy odds ratio in $\mathcal{A}$ is recommended.

### 3.3.3 Simulation Studies

We conducted simulations to examine the operating characteristics of the Bayesian toxicity–efficacy odds-ratio design. We considered five doses (0.25, 0.5, 0.75, 1, 2); the maximum sample size for each trial was 60; and the cohort size was three. We took $\phi_T = 0.3$, $p^* = 0.25$, $r^* = 0.1$, and $p^* = 0.5$, and for each configuration, we simulated 1000 trials. The bivariate binary outcomes were generated from the Dale model based on prespecified marginal probabilities of toxicity and efficacy with $\theta_j = 1$. After 1000 burn-ins, we recorded every fifth sample out of 5000 iterations to reduce the autocorrelation in the Markov chain.

For comparison, we examined an alternative criterion, which selects the dose with the largest $\pi_{oi}^{(j)} = \Pr(T = 0, E = 1)$ to treat the next cohort of patients. Table 3.2 summarizes the simulation results under four scenarios using the $\omega_0$ and $\pi_{oi}^{(j)}$ criteria, respectively. In Scenario 1, toxicity increases substantially with respect to the dose but efficacy does not change much. The two designs yielded similar dose selection percentages and treated most of the patients at dose level 1. In Scenario 2, efficacy increases dramatically but toxicity does not change much. Both designs selected the fifth dose with the highest percentages. In Scenario 3, the fifth dose is considered overly toxic, and the designs mainly selected the third and fourth doses. In Scenario 4, all of the five doses are excessively toxic and thus none of them should be selected.

By jointly modeling toxicity and efficacy in dose-finding trials, more information can be incorporated into the trial design. Furthermore, seamlessly transiting from Phase I to Phase II eliminates the gap between these two phases, and expedites the drug development process.
3.4 Drug-Combination Trial

3.4.1 Copula-Type Regression

Before several drugs are combined, the toxicity profile of each individual drug needs to be thoroughly investigated. It is important to incorporate this rich prior information in drug-combination trials to improve the efficiency of the design. Considering a drug-combination trial with two agents, say A and B, let \( p_j \) be the prespecified toxicity probability corresponding to \( A_j \), the \( j \)th dose of drug A, \( p_1 < \ldots < p_J \); and \( q_k \) be that of \( B_k \), the \( k \)th dose of drug B, \( q_1 < \ldots < q_K \). Although toxicity monotonically increases with the dose when each drug is administered alone, the ordering of the toxicity probabilities of the combined drugs is less obvious. The maximum dose for each drug in the combination (i.e., \( A_J \) and \( B_K \)) is often the individual MTD that has already been determined in the single-agent trials. The remaining lower doses are some fractions of the MTD. Therefore, the upper bounds \( p_J \) and \( q_K \) are known, and typically given as less than 40%. This shrinks the specification range of the \( p_j \)’s and \( q_k \)’s immensely and thus reduces the variability and arbitrariness of these prespecified probabilities.

As in the CRM, we take \( p_{\alpha}^j \) and \( q_{\beta}^k \) as the true toxicity probabilities for drug A and drug B, respectively, where \( \alpha > 0 \) and \( \beta > 0 \) are unknown parameters with prior means centered at one. A reasonable model to link the joint toxicity probability \( \pi_{jk} \) of \( (A_j, B_k) \) with \( p_j \) and \( q_k \) needs to satisfy the following conditions:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Selection Percentage of Dose (# of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>(15, 55)</td>
</tr>
<tr>
<td>( \omega_j )</td>
<td>.1444</td>
</tr>
<tr>
<td>( \pi_{0i}^j )</td>
<td>.574</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>(1, 5)</td>
</tr>
<tr>
<td>( \omega_j )</td>
<td>.1919</td>
</tr>
<tr>
<td>( \pi_{0i}^j )</td>
<td>.0495</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>(1, 20)</td>
</tr>
<tr>
<td>( \omega_j )</td>
<td>.0404</td>
</tr>
<tr>
<td>( \pi_{0i}^j )</td>
<td>.1980</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>(30, 5)</td>
</tr>
<tr>
<td>( \omega_j )</td>
<td>8.1429</td>
</tr>
<tr>
<td>( \pi_{0i}^j )</td>
<td>.0350</td>
</tr>
<tr>
<td></td>
<td>0 (4.0)</td>
</tr>
</tbody>
</table>


Note: In each scenario, the first row represents the true probabilities \( 100 \times (p_j, r_j) \); the second gives the true values of \( \omega_j \); the third exhibits the dose selection percentages and numbers of treated patients; and the last two rows correspond to the design using \( \pi_{0i}^j \).
Bayesian Approach for Adaptive Design

3-11

i. if \( p^\alpha_j = 0 \) and \( q^\beta_k = 0 \), then \( \pi_{jk} = 0 \);

ii. if \( p^\alpha_j = 0 \) then \( \pi_{jk} = q^\beta_k \) and if \( q^\beta_k = 0 \) then \( \pi_{jk} = p^\alpha_j \);

iii. if either \( p^\alpha_j = 1 \) or \( q^\beta_k = 1 \), then \( \pi_{jk} = 1 \).

We link \( \pi_{jk} \) with \((p^\alpha_j, q^\beta_k)\) through a copula-type regression model \((Nelsen 1999)\),

\[
\pi_{jk} = 1 - (1 - p^\alpha_j)^{-\gamma} + (1 - q^\beta_k)^{-\gamma} - 1 \right)^{1/\gamma},
\]

(3.2)

where the association parameter \( \gamma > 0 \) characterizes the drug–drug interactive effect. Note that \( \lim_{p_j \to 1}(1 - p^\alpha_j)^{-\gamma} = \infty \), and thus \( \pi_{jk} = 1 \) as \( p_j \) goes to 1. Moreover, if only one drug is tested, say \( p_j > 0 \) and \( q_k = 0 \), \( (3.2) \) reduces to the CRM, with \( \pi_j = p^\alpha_j \). In Figure 3.3, we illustrate the joint toxicity probability surface based on \((3.2)\) with \( \alpha = \beta = 2 \) and \( \gamma = 1.5 \) in the two-dimensional probability space. If the target toxicity probability is 40%, as shown by the horizontal plane, there is an intersection curve representing the MTD contour for the two drugs.

We can construct the likelihood function based on the binomial distribution with probabilities \( \pi_{jk} \). If \( y_{jk} \) out of \( n_{jk} \) patients treated at dose levels \((j, k)\) have experienced toxicity, the likelihood is given by

\[
L(\alpha, \beta, \gamma | D) \propto \prod_{j=1}^{J} \prod_{k=1}^{K} \pi_{jk}^{y_{jk}} (1 - \pi_{jk})^{n_{jk} - y_{jk}},
\]

and correspondingly, the posterior distribution is

\[
f(\alpha, \beta, \gamma | D) \propto L(\alpha, \beta, \gamma | D)f(\alpha)f(\beta)f(\gamma),
\]

where \( f(\alpha), f(\beta), \) and \( f(\gamma) \) are gamma prior distributions with mean one.

3.4.2 Dose-Finding Algorithm

Let \( \phi_t \) be the target toxicity rate, and \( c_e \) and \( c_d \) be the fixed probability cutoffs for dose escalation and de-escalation, respectively. Patients are treated in cohorts of size 3. As demonstrated in Figure 3.4, dose escalation or de-escalation is restricted to only one dose level of change, and simultaneously escalating
or de-escalating both agents along the diagonal direction is not allowed. The dose-finding algorithm works as follows:

1. Patients in the first cohort are treated at the lowest dose combination \((A_1, B_1)\).
2. At the current dose combination \((A_j, B_k)\):
   i. If \(pr(\pi_{jk} < \phi_T) > c_e\), the dose is escalated to an adjacent dose combination with the toxicity probability higher than the current and closest to \(\phi_T\). If the current dose combination is \((A_J, B_K)\), the doses stay at the same levels.
   ii. If \(pr(\pi_{jk} > \phi_T) > c_d\), the dose is de-escalated to an adjacent dose combination with the toxicity probability lower than the current and closest to \(\phi_T\). If the current dose combination is \((A_1, B_1)\), the trial is terminated.
   iii. Otherwise, the next cohort of patients continues to be treated at the same dose combination.
3. Once the maximum sample size is reached, the dose combination with the toxicity probability closest to \(\phi_T\) is selected as the MTD combination.

### 3.4.3 Simulation Study

We investigated the Bayesian copula-type dose-finding method through simulation studies under four scenarios, as listed in Table 3.3. Drug A had five dose levels and drug B had four. The target toxicity probability was \(\phi_T = 40\%\), and the sample size was 60, with a cohort size of 3. We set \(c_e = 0.8\) and \(c_d = 0.45\), and took Gamma(2, 2) as the prior distribution for \(\alpha\) and \(\beta\), and Gamma(0.1, 0.1) for \(\gamma\). We simulated 2000 trials under each scenario, and for each simulation, we recorded 2000 posterior samples after 100 burn-in iterations. Because the toxicity rates of the MTDs for Drug A and Drug B when

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Scenario 1**

| 4 | 0.54 | 0.67 | 0.75 | 0.81 | 0.86 | 0.9 | 0.1 | 0 | 0 | 0 |
| 3 | 0.48 | 0.59 | 0.68 | 0.75 | 0.81 | 10.2 | 1.7 | 0.1 | 0 | 0 |
| 2 | **0.40** | 0.45 | 0.59 | 0.67 | 0.74 | **24.9** | 11.6 | 1.7 | 0.1 | 0 |
| 1 | 0.24 | 0.24 | 0.40 | 0.47 | 0.56 | 0.64 | 3.1 | **19.1** | 6.2 | 0.3 |

**Scenario 2**

| 4 | 0.49 | 0.58 | 0.68 | 0.75 | 0.81 | 5.0 | 1.5 | 0 | 0 | 0 |
| 3 | **0.40** | 0.49 | 0.59 | 0.68 | 0.75 | **17.6** | 11.6 | 1.4 | 0.1 | 0 |
| 2 | 0.27 | **0.40** | 0.45 | 0.59 | 0.67 | 7.3 | **19.2** | 9.3 | 1.7 | 0.1 |
| 1 | 0.18 | 0.29 | **0.40** | 0.47 | 0.56 | 0.1 | 5.1 | **11.2** | 5.0 | 0.3 |

**Scenario 3**

| 4 | 0.31 | 0.40 | 0.50 | 0.61 | 0.75 | 3.8 | **11.7** | 8.5 | 1.3 | 0.1 |
| 3 | 0.23 | 0.34 | **0.40** | 0.53 | 0.67 | 0.7 | 5.9 | **12.7** | 8.0 | 1.2 |
| 2 | 0.16 | 0.25 | 0.34 | **0.40** | 0.52 | 0 | 0.7 | 3.5 | **12.0** | 10.3 |
| 1 | 0.09 | 0.16 | 0.18 | 0.22 | **0.40** | 0 | 0 | 0.3 | 3.5 | **15.8** |

**Scenario 4**

| 4 | 0.79 | 0.85 | 0.89 | 0.92 | 0.94 | 0 | 0 | 0 | 0 | 0 |
| 3 | 0.74 | 0.81 | 0.86 | 0.89 | 0.92 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0.67 | 0.76 | 0.81 | 0.86 | 0.89 | 0 | 0 | 0 | 0 | 0 |
| 1 | 0.57 | 0.67 | 0.74 | 0.79 | 0.84 | 0.1 | 0 | 0 | 0 | 0 |

administered alone were 0.4 and 0.3, respectively, we specified the $p_j$’s as (0.08, 0.16, 0.24, 0.32, 0.4) for Drug A; and the $q_k$’s as (0.075, 0.15, 0.225, 0.3) for Drug B.

In the first three scenarios, there are two, three, and four MTDs, respectively. The Bayesian copula-type design selected the MTD combinations with quite high percentages. Scenario 4 examines the situation in which all of the drug combinations are overly toxic. The design successfully terminated 99.9% of the simulated trials early without any selection. The overall performance of the Bayesian copula-type design is satisfactory. The design allows for freedom of dose movement in the two-dimensional space. It continuously updates the posterior estimates of toxicity probabilities for all of the dose combinations based on the accumulated data and efficiently searches for the target across the entire drug-combination space.

### 3.5 Adaptive Randomization with Drug Combinations

#### 3.5.1 Bayesian Adaptive Randomization

In a drug-combination trial, once Phase I dose finding is complete, due to the toxicity equivalence contour as shown in Figure 3.4, we may identify multiple, say $K$, dose combinations that are at a similar toxicity level. These $K$ dose combinations satisfy the same safety requirements, and will be further investigated in a $K$-arm Phase II trial to evaluate their efficacy. Let $(r_1, \ldots, r_K)$ denote the response rates of these $K$ admissible doses. If we observe that $y_k$ out of $n_k$ patients treated in arm $k$ have responded, we can model efficacy using the following Bayesian hierarchical model,

$$y_k \sim \text{Binomial}(n_k, r_k), \quad r_k \sim \text{Beta}(\eta_1, \eta_2),$$

where we assign noninformative gamma prior distributions to $\eta_1$ and $\eta_2$.

In such a randomized multiarm trial, adaptive randomization provides a mechanism to mitigate the problem of randomly assigning patients to inferior treatments by skewing assignment probabilities toward more efficacious treatment arms. A common practice is to take the assignment probability proportional to the estimated response rate of each arm (i.e., $r_k/\sum_{k=1}^{K} r_k$), which, however, does not take into account the variability of the estimated response rates. An alternative is to compare the $r_k$’s to a fixed value, say $r_o$, and take the assignment probability proportional to the posterior probability $p(r_k > r_o | D)$. When two or more $r_k$’s are much higher or lower than $r_o$, the corresponding posterior probabilities

![FIGURE 3.4 Joint toxicity probability surface and MTD contour for the two-drug combinations.](image-url)
Handbook of Adaptive Designs in Pharmaceutical and Clinical Development

pr(r_k > r_0 | D) are either very close to 1 or 0, and thus the superior arm cannot be distinguished. A remedy is to use one arm as the reference, say the first treatment arm, and then randomize patients based on \( R_k / \sum_{k=1}^{K} R_k \) with \( R_k = pr(r_k > r_1 | D) \) for \( k > 1 \), while setting \( R_1 = 0.5 \). Unfortunately, it cannot fully resolve the problem. In a two-arm trial, because \( R_1 = 0.5 \), arm 1 has an assignment probability of at least 1/3 (even if \( R_2 = pr(r_2 > r_1 | D) = 1 \), i.e., treatment 2 is definitely superior to treatment 1), regardless of the efficacy of that treatment.

To overcome these difficulties, we propose a new Bayesian adaptive randomization scheme based on a moving reference instead of fixing the reference as a constant \( r_0 \) or \( r_1 \). Our method simultaneously accounts for the magnitude and uncertainty of the estimated \( r_k \) as follows:

1. Let \( \mathcal{A} \) and \( \mathcal{A} \) denote the sets of treatment arms that have and have not been assigned randomization probabilities, respectively. We start with \( \mathcal{A} = \{1, \ldots, K\} \) and \( \mathcal{A} = \{\} \) an empty set.

2. Take \( \bar{r} = \sum_{k \in \mathcal{A}} r_k / \sum_{k \in \mathcal{A}} 1 \) as the reference to determine \( R_k = pr(r_k > \bar{r} | D) \), for \( k \in \mathcal{A} \), and identify arm \( \ell \) such that \( R_\ell = \min_{k \in \mathcal{A}} R_k \).

3. Assign arm \( \ell \) a randomization probability of \( \pi_\ell \), where

\[
\pi_\ell = \sum_{k \in \mathcal{A}} \frac{R_\ell}{R_k} \left(1 - \sum_{k' \in \mathcal{A}} \pi_{k'}\right),
\]

and then move arm \( \ell \) from \( \mathcal{A} \) to \( \mathcal{A} \).

4. Repeat Steps 2–3 until all of the arms are assigned randomization probabilities, \( (\pi_1, \ldots, \pi_K) \).

As illustrated in Figure 3.5, once an arm is assigned a randomization probability, it will be removed from the admissible set \( \mathcal{A} \). Thus the reference \( \bar{r} \) is moving in the sense that, during the randomization

**FIGURE 3.5** Illustration of the adaptive randomization for a three-arm trial. Based on the posterior distributions of \( r_1, r_2, r_3 \), and \( \bar{r} \), we calculate \( R_k = pr(r_k > \bar{r} | D) \) for \( k = 1, 2, 3 \); and assign the arm with the smallest value of \( R_k \) (i.e., arm 1) a randomization probability \( \pi_1 \). After spending \( \pi_1 \), we remove arm 1 from the comparison set \( \mathcal{A} \) and distribute \( 1 - \pi_1 \) to the remaining two arms in a similar manner.
process, it keeps changing based on the remaining arms in $A$. By doing so, we obtain a zoomed-in comparison and achieve a high resolution to distinguish different treatments. We conducted a Phase II simulation study of randomizing a total of 100 patients to three treatment arms. We used a beta-binomial model to update the posterior estimates of the efficacy rates ($r_1, r_2, r_3$). We simulated 1000 trials under each of the three scenarios given in Table 3.4. The new Bayesian adaptive randomization with a moving reference efficiently allocated the majority of patients to the most efficacious arm, and often performed better than when using Arm 1 as the reference.

In Figure 3.6, we show the randomization probabilities averaged over 1000 simulations with respect to the accumulative number of patients. Using a moving reference, the Bayesian adaptive randomization has a substantially higher resolution to distinguish and separate treatment arms in terms of efficacy compared to using Arm 1 as the reference: for example, in Scenario 1, the curves are well resolved with a moving reference, while using a fixed reference at Arm 1 results in less separation.

### Table 3.4

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Response Probability</th>
<th>Fixed Reference</th>
<th>Moving Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1</td>
<td>Arm 2</td>
<td>Arm 3</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
<td>0.01</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**FIGURE 3.6** Randomization probabilities of the Bayesian adaptive randomization with a moving reference versus a fixed reference at Arm 1.
separated after 20 (using the moving reference) versus 40 patients (using Arm 1 as the reference) were randomized.

### 3.5.2 Phase I/II Design in Drug-Combination Trials

We seamlessly integrated the designs in Phase I and Phase II for combined therapies, as displayed in Figure 3.7. To examine the operating characteristics of the Phase I/II design, we simulated

![Diagram of the Phase I/II trial design for drug-combination trials.](#)

**FIGURE 3.7** Diagram of the Phase I/II trial design for drug-combination trials.
1000 trials with three dose levels of Drug A and two dose levels of Drug B. The sample size was 80 patients: 20 for Phase I and 60 for Phase II. We specified the prior toxicity probabilities of Drug A as (0.05, 0.1, 0.2), and those for Drug B as (0.1, 0.2). The target toxicity upper limit \( \phi_T = 0.33 \), and the target efficacy lower limit \( \phi_E = 0.2 \). We used \( c_r = 0.8 \) and \( c_d = 0.45 \) to direct dose escalation and de-escalation, and \( c_s = 0.45 \) to define the set of admissible doses in Phase I. We applied the toxicity stopping rule of \( \text{pr}(\pi_i < \phi_T) < c_s \) and the futility stopping rule of \( \text{pr}(\pi_i > \phi_E) < c_f \) with \( c_f = 0.1 \) in Phase II. The decisions of dose assignment and adaptive randomization were made after observing the outcomes of every patient. For each simulated trial, we recorded 2000 posterior samples after 100 burn-in iterations.

Under six scenarios in Table 3.5, we report the selection probability and the number of patients treated at each dose combination. Overall, our method performed very well by yielding high selection probabilities of the target dose combinations, and assigning more patients to the more efficacious doses.

### 3.6 Conclusion

We have focused on Bayesian adaptive designs in Phase I and Phase I/II dose-finding trials. The BMA-CRM eliminates the arbitrariness in the specification of the skeleton by incorporating the uncertainties associated with each skeleton into the BMA procedure. It is robust, and straightforward to implement using the Gaussian quadrature approximation or the Markov chain Monte Carlo (MCMC).

Phase I/II trial designs simultaneously evaluate toxicity and efficacy to identify the most appropriate dose using the odds-ratio trade-off. The odds ratio has an objective interpretation of quantifying the relative degree of toxicity versus efficacy. The design efficiently uses all of the available data resources and seamlessly bridges the Phase I and II trials.

To accommodate the enormous need for designing clinical trials with drug combinations, a copula-type model can be used to link the joint toxicity probability with the toxicity probabilities of each drug. The Bayesian copula-type design can fully evaluate the joint toxicity profile of the combined drugs, as well as preserve their single-agent properties. It efficiently reorders the toxicity probabilities of the dose combinations based on the accrued data, so that each newly arrival cohort of patients will receive the most appropriate dose. In a typical drug-combination trial, the doses of each drug are often bounded by the corresponding single-agent MTDs for which the toxicity probabilities are known from previous
studies. Therefore, the prespecified toxicity probabilities of each drug are much more accurate than the usual CRM for single-agent cases in the entire range of \((0, 1)\).

Due to the toxicity equivalence contour in the two-dimensional dose-combination space, multiple MTD combinations with similar toxicity may be identified in Phase I. Thus, Phase II with adaptive randomization is natural and ethical in order to assign more patients to more efficacious doses. The Bayesian MCMC procedure can coherently update the posterior estimates for the model parameters as more patients enter the trial and more outcomes are observed. The Bayesian adaptive designs are flexible, able to incorporate prior knowledge, and achieve the goals of pulling information and borrowing strength from all the aspects of the trial.

References


