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A Latent Contingency Table Approach to Dose Finding for Combinations of Two Agents

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Summary. Two-agent combination trials have recently attracted enormous attention in oncology research. There are several strong motivations for combining different agents in a treatment: to induce the synergistic treatment effect, to increase the dose intensity with nonoverlapping toxicities, and to target different tumor cell susceptibilities. To accommodate this growing trend in clinical trials, we propose a Bayesian adaptive design for dose finding based on latent 2×2 tables. In the search for the maximum tolerated dose combination, we continuously update the posterior estimates for the unknown parameters associated with marginal probabilities and the correlation parameter based on the data from successive patients. By reordering the dose toxicity probabilities in the two-dimensional space, we assign each coming cohort of patients to the most appropriate dose combination. We conduct extensive simulation studies to examine the operating characteristics of the proposed method under various practical scenarios. Finally, we illustrate our dose-finding procedure with a clinical trial of agent combinations at M. D. Anderson Cancer Center.

Key words: Adaptive design; Bayesian estimation; Combining drugs; Gibbs sampling; Maximum tolerated dose; Phase I trial; Synergy; Toxicity.

1. Introduction

A phase I clinical trial is typically conducted to establish the maximum tolerated dose (MTD), which is the dose of a new agent with a toxicity probability closest to the physician's target. In the trial, successive cohorts of patients are adaptively assigned to a set of prespecified doses so that the toxicity profile of the agent under investigation can be determined. Many statistical methods have been developed for single-agent phase I trial designs (for examples, see Storer, 1989; O'Quigley, Pepe, and Fisher, 1990; Goodman, Zahurak, and Piantadosi, 1995; Møller, 1995; Whitehead and Brunier, 1995; Durham, Flournoy, and Rosenberger, 1997; Babb, Rogatko, and Zacks, 1998; Gasparini and Eisele, 2000; Leung and Wang, 2002; Stylianou and Flournoy, 2002; Haines, Perevozskaya, and Rosengberger, 2003; Yuan, Chappell, and Bailey, 2007), among which the continual reassessment method (CRM) is quite popular. CRM relies on a single unknown parameter to determine the shape of the dose–toxicity curve (O'Quigley et al., 1990). Given the physician's prespecified toxicity probability at each dose, CRM updates the posterior estimates of these dose toxicity probabilities using either the exponential or hyperbolic link function. The performance of CRM can be practically improved by introducing a safety stopping rule, limiting each dose escalation to one level and treating patients in cohorts; see Goodman et al. (1995). More recently, Yuan et al. (2007) extended the CRM to incorporate the toxicity grade information. Chevret (2006) and Ting (2006) gave comprehensive reviews and extensive discussions on current dose-finding methods in drug development.

The motivations for combining two agents in medical research are: to induce a synergistic treatment effect, to increase the joint dose intensity with nonoverlapping toxicities, and to target various tumor cell susceptibilities and disease pathways. Unlike the single-agent phase I trial where the agent's toxicity probability can be assumed monotonically increasing with the dose level, it is not reasonable to impose such a monotonic toxicity relationship for combined agents. In particular, one cannot assume that each agent acts independently on the patient. Interactive effects between the two agents often have an enormous impact on the toxicity probabilities of the dose combinations. Consequently, the toxicity ordering in the two-dimensional dose combination space is typically unknown. Without fully understanding the toxicity order, it is difficult to escalate or deescalate the dose correctly during the trial. This difficulty severely limits the application of single-agent dose finding designs for agent combination trials.

Early work related to agent combination studies includes Ashford (1981) and Abdelbasit and Plackett (1982). Simon and Korn (1990) proposed a mathematical model for selecting agents and dosages based on the antitumor activities and organ-specific MTDs of the agents. Their model would serve as a guide for selecting agent combinations from a large number of possibilities worthy of evaluation. Kramar, Lebecq, and Candalh (1999) reported a trial that combined docetaxel and irinotecan to maximize tumor cell eradication within a tolerable toxicity range and prevent the development of new resistant cell lines. To simplify the two-dimensional dose-finding

problem, a selected subset of agent combinations in this trial were assumed to follow a monotonic toxicity order. Lokich (2001) presented a clinical trial that combined four dose levels of topotecan with two dose levels of irinotecan to treat patients with advanced malignancy. Kuzuya et al. (2001) proposed treating ovarian cancer patients by combining paclitaxel and carboplatin, through alternately fixing one agent at a dose level and varying the dose level of the other agent. For a trial of combining gemcitabine and cyclophosphamide in which the doses were continuous, Thall et al. (2003) proposed a six-parameter model for the toxicity probabilities of the dose combinations. In their two-dimensional space, the dose was first escalated along the diagonal direction by increasing the doses of both agents, and then two additional dose combinations were identified using a toxicity equivalence contour. Conaway, Dunbar, and Peddada (2004) distinguished the simple and partial orders of the toxicity probabilities by defining the nodal and nonnodal parameters. Wang and Ivanova (2005) proposed a logistic-type regression for dose combinations that used the doses of the two agents as the covariates. Their primary goal was to find the MTD of one agent while fixing the dose of the other. More recently, Huang et al. (2007) modified the "3 + 3" design for use in the dose-escalation phase of an agent combination trial, and utilized Bayesian posterior probabilities for adaptive randomization. Yin and Yuan (2008) proposed a copula-type model for phase I drug-combination trial designs.

Before the initiation of an agent combination trial, each agent should be carefully studied in advance. The interactive effects between two agents can be complex, which often leads to unforeseen toxicity patterns. To fulfill the needs for designing agent combination trials, we propose a Bayesian adaptive procedure to model the binary toxicity outcomes through a series of 2×2 contingency tables. Cohorts of patients are sequentially assigned to a suitable dose combination as the trial proceeds. Decisions on dose escalation and deescalation can be made using the posterior estimates of the toxicity probabilities of dose combinations.

In Section 2, we present the joint probability model for the toxicity binary outcomes through a 2×2 contingency table for each dose pair. We derive the likelihood function and the posterior distribution for the unknown parameters. In Section 3, we give the dose-finding algorithm, and in Section 4 we present extensive simulation studies to examine the operating characteristics of the new design. We conclude with a brief discussion of our findings in Section 5.

2. Probability Model

2.1 *Bivariate Binary Outcomes*

One goal for the use of agent combinations is to achieve a higher dose intensity by exploiting the nonoverlapping dose-limiting toxicities (DLT) of different agents. The ideal case is that the two agents in the combination have nonoverlapping DLT. This could be achieved by preventing patients from experiencing the agents' common toxicities. For example, in a combination of taxol and cisplatin, if the common toxicities leukopenia and neurotoxicity are prevented by the use of chemoprotective agents such as colony-simulating factors, then these two agents would have nonoverlapping mucosit and renal DLT. In circumstances where the toxicities of the two agents can be explicitly distinguished, we can view the observed outcomes for each dose combination in a 2×2 contingency table.

Let A_j be the jth dose for agent A, $A_1 < \cdots < A_J$, and B_k be the kth dose for agent B, $B_1 < \cdots < B_K$. For a patient treated with the dose combination $(A_j,\ B_k)$, if we observe toxicity from agent A, let $X_{jk} = 1$, otherwise $X_{jk} = 0$; if we observe toxicity from agent B, let $Y_{jk} = 1$, otherwise $Y_{jk} = 0$. This can be represented using the following 2×2 probability table,

$$\begin{array}{r|c|c|} & p_j^{\alpha} & 1-p_j^{\alpha} \\ \hline q_k^{\beta} & \pi_{jk}^{(11)} & \pi_{jk}^{(01)} \\ \hline 1-q_k^{\beta} & \pi_{jk}^{(10)} & \pi_{jk}^{(00)} \\ \hline \end{array}, \tag{1}$$

where $(p_j,\ q_k)$ are the physician-specified marginal probabilities of toxicity associated with the combined agent pair $(A_j,\ B_k)$. To allow for uncertainty in this specification, we incorporate two unknown positive parameters $(\alpha,\ \beta)$ as in the CRM, such that the marginal toxicity probabilities for $(A_j,\ B_k)$ are $(p_j^{\alpha},\ q_k^{\beta})$. We assume a monotonic relationship between the toxicity probability and the dose level for each agent marginally (i.e., $p_1^{\alpha} < \cdots < p_J^{\alpha}$ and $q_1^{\beta} < \cdots < q_K^{\beta}$). In the 2×2 probability table (1), each cell $\pi_{jk}^{(xy)}$ $(x = 0,\ 1;\ y = 0,\ 1)$ represents the joint probability associated with the bivariate binary outcomes.

At each dose combination, we jointly model (1) using the Gumbel model (Murtaugh and Fisher, 1990). Observe that the marginal probability for $X_{jk} = 1$ is p_j^{α}, and the marginal probability for $Y_{jk} = 1$ is q_k^{β}. For $j = 1, \ldots, J$, and $k = 1, \ldots, K$, the joint probability for the bivariate binary outcomes $(X_{jk} = x,\ Y_{jk} = y)$ is

$$\begin{aligned} \pi_{jk}^{(xy)} &= p_j^{\alpha x}\left(1-p_j^{\alpha}\right)^{1-x} q_k^{\beta y}\left(1-q_k^{\beta}\right)^{1-y} \\ &\quad + (-1)^{x+y} p_j^{\alpha}\left(1-p_j^{\alpha}\right) q_k^{\beta}\left(1-q_k^{\beta}\right)\frac{e^{\gamma}-1}{e^{\gamma}+1}, \end{aligned} \tag{2}$$

where the association parameter γ characterizes the agent synergistic effect. If $\gamma = 0$, model (2) reduces to the independent case. Our dose-finding method is not restricted to the Gumbel model, and other models suitable for the bivariate binary outcomes can be used as well.

Suppose that among the n_{jk} patients treated at dose combination $(A_j,\ B_k)$, $n_{jk}^{(11)}$ patients have experienced toxicities from both agents A and B, $n_{jk}^{(10)}$ patients have experienced toxicities only from agent A, $n_{jk}^{(01)}$ patients have experienced toxicities only from agent B, and $n_{jk}^{(00)}$ patients have not experienced any toxicities. Based on the multinomial distribution, the likelihood function under equation (2) is given by

$$\begin{aligned} L(\alpha, \beta, \gamma \,|\, \text{Data}) \propto \prod_{j=1}^{J}\prod_{k=1}^{K} &\left\{\pi_{jk}^{(11)}\right\}^{n_{jk}^{(11)}} \\ &\times \left\{\pi_{jk}^{(10)}\right\}^{n_{jk}^{(10)}} \left\{\pi_{jk}^{(01)}\right\}^{n_{jk}^{(01)}} \left\{\pi_{jk}^{(00)}\right\}^{n_{jk}^{(00)}}. \end{aligned}$$

This likelihood is formulated in an ideal scenario where the two agents in the combination have nonoverlapping toxicities and thus the toxicities for the two agents can always be distinguished.

2.2 *Latent Contingency Tables*

However, the ideal situation in which the two combined agents have nonoverlapping toxicities is rare in practice. A more realistic scenario is that the toxicities from the two agents are partially overlapping. For example, hypertension can only be caused by agent A, elevated lipid levels can only be caused by agent B, and nausea and fatigue are the common toxicities of both agents. Although protection from some common toxicities is possible, typically, most of the toxicities between two agents are common and cannot be completely eliminated. When an overlapping toxicity is observed, it is difficult to determine whether the toxicity is from agent A ($X_{jk} = 1$), agent B ($Y_{jk} = 1$), or both ($X_{jk} = Y_{jk} = 1$). Nevertheless, we can still introduce a latent 2×2 toxicity probability table as in (1) for the combined doses (A_j, B_k). Our strategy here is to collapse the three indistinguishable cells with probabilities $\pi_{jk}^{(11)}$, $\pi_{jk}^{(10)}$, and $\pi_{jk}^{(01)}$ into a single cell with a probability of $\pi_{jk}^{(11)} + \pi_{jk}^{(10)} + \pi_{jk}^{(01)}$ (or, equivalently, $1 - \pi_{jk}^{(00)}$) to represent the probability of *any* toxicity. We can then model the observed data using a binomial distribution. Suppose that among n_{jk} patients treated at the paired dose level of (j, k), $n_{jk}^{(00)}$ patients have not experienced any toxicities. Based on the binomial model, the likelihood is given by

$$L(\alpha, \beta, \gamma \,|\, \text{Data}) \propto \prod_{j=1}^{J} \prod_{k=1}^{K} \left\{1 - \pi_{jk}^{(00)}\right\}^{n_{jk} - n_{jk}^{(00)}} \left\{\pi_{jk}^{(00)}\right\}^{n_{jk}^{(00)}},$$

where $1 - \pi_{jk}^{(00)}$ is the probability of toxicity for the dose combination (A_j, B_k). The rationale is that once a patient has experienced toxicity, regardless of whether the toxicity was caused by agent A, agent B, or the combination of agents A and B, the outcome would fall into the collapsed cell associated with $1 - \pi_{jk}^{(00)}$. Only the cell with probability $\pi_{jk}^{(00)}$ corresponds to the patients with no toxicity, for $j = 1, \ldots, J$ and $k = 1, \ldots, K$.

2.3 *Posterior Computation*

We take the prior distributions of the model parameters to be independent, i.e.,

$$\pi(\alpha, \beta, \gamma) = \pi(\alpha)\pi(\beta)\pi(\gamma),$$

and assign vague prior distributions to α, β, and γ, so that the likelihood dominates the posterior estimation. As α and β are power parameters, we can take $\pi(\alpha) = \pi(\beta) = \text{Unif}(0.2, 2)$, and $\pi(\gamma) = \text{Gamma}(0.1, 0.1)$ with mean one to model the drug synergistic effect. The joint posterior distribution is given by

$$\pi(\alpha, \beta, \gamma \,|\, \text{Data}) \propto L(\alpha, \beta, \gamma \,|\, \text{Data})\pi(\alpha)\pi(\beta)\pi(\gamma),$$

from which the full conditional distributions of the parameters can be easily obtained. Because the toxicity profile for each agent in a combination is usually known, we set (p_j, q_k) at the toxicity probabilities when each agent is administered alone. Based on the cumulated data, we sample from the posterior distributions of the unknown parameters using the Gibbs sampling algorithm (Gilks, Best, and Tan, 1995), and estimate the toxicity probabilities $1 - \pi_{jk}^{(00)}$ by their posterior means based on the posterior samples of (α, β, γ), and model (2). The dose-finding algorithm is guided by $1 - \pi_{jk}^{(00)}$ for $j = 1, \ldots, J; k = 1, \ldots, K$, regardless of the likelihood function resulting from the explicitly observed or the latent 2×2 tables. The computer program to implement the posterior computation was written in `C`, and is available upon request.

3. Dose-Finding Algorithm

At the beginning of a trial, little data have been collected from the patients and the posterior estimates are often unstable. As shown in Figure 1, we initiate a start-up rule by first escalating the dose along the vertical direction (increasing the dose of agent B while fixing agent A at dose level 1) until the first toxicity is observed. We then treat the next cohort of patients at (A_2, B_1) and escalate the dose of agent A along the horizontal direction by fixing agent B at dose level 1 until another toxicity is observed. We estimate the toxicity probabilities for all of the dose combinations based on the collected data, and choose the dose combination with the estimated toxicity probability closest to the target as the starting combination ($A_s, B_{s'}$). After this initial period, the rest of the trial follows the dose-finding algorithm given below.

From a conservative point of view, we restrict each dose escalation or deescalation by one level of change, and prohibit a move along the diagonal line as illustrated in Figure 1. It may be too aggressive to escalate doses along the diagonal direction by increasing the doses of both agents simultaneously. Let ϕ be the physician-specified target toxicity rate, and c_e and c_d be the fixed probabilities for dose escalation and deescalation, respectively. Our Bayesian two-dimensional dose-finding algorithm is described as follows:

(1) Patients in the first cohort are treated at the starting dose combination ($A_s, B_{s'}$).

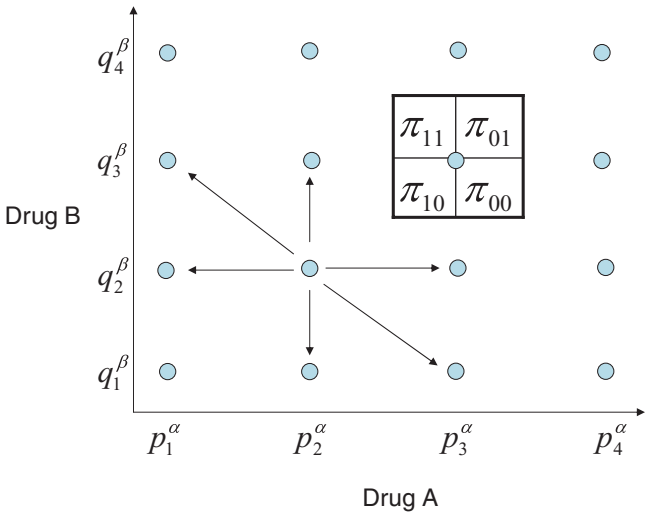

Figure 1. Two-agent combinations with four dose levels for each agent. Given the marginal toxicity probability (p_j^α, q_k^β), we construct a latent 2×2 probability table, and present the dose escalation and deescalation diagram.

(2) If the toxicity probability at the current dose combination, denoted by π_T^{current}, satisfies

$$\Pr\left(\pi_T^{\text{current}} < \phi\right) > c_e,$$

the dose will be escalated to the higher dose combination that has a posterior estimate of the toxicity probability closest to the target ϕ. If the current dose combination is the highest $(A_J,\ B_K)$, the next cohort of patients continue to be treated at that dose combination.

(3) If at the current dose combination,

$$\Pr\left(\pi_T^{\text{current}} > \phi\right) > c_d,$$

the dose will be deescalated to the lower dose combination that has a posterior estimate of the toxicity probability closest to the target ϕ. If the current dose is the lowest $(A_1,\ B_1)$, the trial will be terminated.

(4) Otherwise, the next cohort of patients continue to be treated at the current dose combination.

(5) Once the maximum sample size is reached, the dose combination that has been utilized to treat patients and has a toxicity probability closest to the target ϕ is selected as the MTD combination.

To ensure that the trial has desirable operating characteristics, we can specify the maximum sample size and calibrate c_e and c_d using simulation studies.

4. Numerical Examples

4.1 *Simulation Study*

We examined the operating characteristics of the proposed dose-finding procedure for two-agent combinations by simulating 14 scenarios as shown in Table 1. We used the latent contingency table approach in our simulations to accommodate overlapping toxicities between the two agents. Instead of generating toxicity probabilities from our model, we chose the toxicity probabilities arbitrarily so as to demonstrate the robustness of the proposed design. Scenarios 1 to 8 simulated agent combination trials in which each agent had four dose levels, and scenarios 9 to 14 simulated trials with five dose levels of agent A and three dose levels of agent B. We assumed a target toxicity probability of $\phi = 30\%$, a total sample size of 60, and a cohort size of three.

As a comparison for the proposed design, we also implemented the CRM in which we converted each two-dimensional dose-finding trial into a series of one-dimensional dose-finding trials by fixing the dose of agent B and searching over the

Table 1

Fourteen scenarios for a two-agent combination trial with the target probability of toxicity 0.3. *The MTD combinations are in boldface.*

	Dose level	Agent A									
		1	2	3	4	5	1	2	3	4	5
		Scenario 1					Scenario 2				
	4	**0.30**	0.50	0.60	0.70		0.20	**0.30**	0.45	0.50	
	3	0.15	**0.30**	0.52	0.60		0.16	0.18	**0.30**	0.45	
	2	0.10	0.20	**0.30**	0.55		0.14	0.16	0.20	**0.30**	
	1	0.08	0.14	0.19	**0.30**		0.08	0.13	0.16	0.18	
		Scenario 3					Scenario 4				
	4	**0.30**	0.50	0.55	0.60		0.50	0.55	0.60	0.70	
	3	0.12	**0.30**	0.50	0.55		**0.30**	0.50	0.55	0.60	
	2	0.10	0.15	**0.30**	0.45		0.12	**0.30**	0.50	0.55	
	1	0.08	0.12	0.16	0.18		0.10	0.15	**0.30**	0.45	
		Scenario 5					Scenario 6				
	4	0.48	0.52	0.55	0.58		0.50	0.55	0.60	0.70	
	3	0.42	0.45	0.50	0.52		0.15	**0.30**	0.50	0.60	
	2	**0.30**	0.40	0.48	0.50		0.10	0.12	**0.30**	0.45	
	1	0.15	**0.30**	0.40	0.45		0.06	0.08	0.10	0.15	
		Scenario 7					Scenario 8				
Agent B	4	0.16	0.18	0.20	**0.30**		0.70	0.75	0.80	0.85	
	3	0.13	0.16	0.18	0.20		0.60	0.65	0.70	0.80	
	2	0.12	0.14	0.16	0.18		0.55	0.60	0.65	0.70	
	1	0.10	0.12	0.14	0.16		0.50	0.55	0.60	0.65	
		Scenario 9					Scenario 10				
	3	**0.30**	0.37	0.42	0.47	0.52	0.15	**0.30**	0.50	0.55	0.60
	2	0.15	**0.30**	0.37	0.43	0.48	0.12	0.16	**0.30**	0.50	0.55
	1	0.10	0.12	**0.30**	0.40	0.45	0.06	0.08	0.10	**0.30**	0.50
		Scenario 11					Scenario 12				
	3	0.40	0.43	0.48	0.53	0.58	0.50	0.60	0.70	0.80	0.90
	2	**0.30**	0.40	0.43	0.48	0.53	0.10	**0.30**	0.50	0.70	0.80
	1	0.10	**0.30**	0.40	0.44	0.50	0.06	0.10	0.15	**0.30**	0.50
		Scenario 13					Scenario 14				
	3	0.12	0.15	0.17	0.20	**0.30**	0.55	0.60	0.68	0.75	0.80
	2	0.06	0.08	0.10	0.12	0.16	0.50	0.58	0.65	0.70	0.75
	1	0.02	0.04	0.06	0.09	0.13	0.40	0.50	0.60	0.65	0.68

Table 2
Selection probabilities of the CRM and the proposed two-dimensional design under 14 scenarios

	CRM				Two-dimensional design			
Scenario 1	**14.3**	6.5	0.5	0.0	**19.9**	8.8	0.1	0.0
	5.5	**13.5**	5.0	0.5	5.6	**21.5**	4.6	0.2
	1.8	8.0	**11.5**	3.8	0.3	5.3	**13.3**	3.7
	0.5	2.8	8.0	**14.8**	0.0	0.3	5.7	**10.3**
Scenario 2	6.0	**10.8**	6.0	1.8	4.9	**19.1**	13.2	2.8
	2.3	6.8	**10.3**	5.3	1.0	5.9	**16.2**	11.3
	1.8	4.5	6.3	**12.5**	0.2	0.9	4.7	**15.4**
	0.5	2.0	3.25	19.3	0.0	0.0	0.4	3.1
Scenario 3	**13.8**	6.5	1.0	0.3	**20.0**	9.4	0.8	0.1
	4.0	**14.5**	5.8	0.8	3.9	**19.9**	6.2	1.2
	1.0	6.5	**11.3**	6.3	0.1	3.8	**13.1**	9.9
	0.4	1.8	3.5	19.5	0.0	0.0	2.6	8.6
Scenario 4	8.5	2.0	0.5	0.0	2.5	0.3	0.0	0.0
	14.3	6.0	1.0	0.3	**27.3**	7.3	0.2	0.0
	4.3	**14.5**	5.0	1.0	5.5	**22.9**	6.8	0.2
	1.0	5.5	**12.5**	6.3	0.0	5.6	**17.5**	2.6
Scenario 5	8.8	2.5	1.0	0.3	0.5	0.1	0.0	0.0
	9.5	4.3	1.8	0.8	7.9	1.0	0.2	0.0
	10.5	7.8	2.5	1.0	**27.1**	8.1	1.2	0.1
	4.8	**10.5**	7.0	2.8	4.7	**22.7**	7.3	0.6
Scenario 6	8.8	1.8	0.5	0.0	13.4	1.7	0.1	0.0
	5.5	**13.5**	5.0	0.8	8.9	**24.5**	6.5	0.5
	0.8	5.8	**12.0**	6.5	0.1	1.9	**16.8**	14.6
	0.3	1.0	2.0	22.0	0.0	0.1	1.2	9.8
Scenario 7	2.0	4.3	6.3	**12.3**	0.8	3.6	13.6	**60.5**
	1.5	3.3	4.3	15.8	0.1	1.0	3.6	11.9
	1.3	3.0	3.5	17.3	0.1	0.4	1.3	1.9
	0.8	1.8	2.8	20.0	0.0	0.1	0.2	0.2
Scenario 8	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	4.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0
	7.3	1.0	0.0	0.0	0.0	0.0	0.0	0.0
	8.0	1.8	0.5	0.0	0.2	0.0	0.0	0.0

	CRM					Two-dimensional design				
Scenario 9	**12.0**	10.3	4.7	1.7	0.3	**15.3**	11.0	4.0	1.0	0.2
	5.0	**14.3**	8.3	3.7	1.7	5.5	**18.2**	10.1	3.4	1.0
	0.3	5.3	**15.7**	7.7	4.0	0.0	2.8	**18.2**	6.4	1.5
Scenario 10	5.7	**19.7**	6.7	0.7	0.3	9.7	**22.9**	6.4	0.6	0.1
	1.3	8.0	**17.0**	5.7	1.0	0.0	2.4	**21.8**	9.4	1.0
	0.0	0.3	6.3	**19.7**	6.7	0.0	0.0	2.6	**18.2**	4.9
Scenario 11	12.0	6.3	2.0	0.7	0.3	4.1	1.5	0.4	0.1	0.0
	14.0	8.3	4.3	1.3	0.7	**25.1**	8.5	2.3	0.4	0.0
	2.7	**16.0**	9.7	1.3	1.3	3.8	**29.3**	13.3	1.8	0.2
Scenario 12	9.7	1.3	0.0	0.0	0.0	12.6	0.3	0.1	0.0	0.0
	4.0	**22.7**	6.3	0.0	0.0	4.8	**37.1**	13.9	0.5	0.0
	0.0	1.0	8.3	**17.7**	6.3	0.0	0.5	7.7	**18.6**	3.5
Scenario 13	1.0	2.7	5.3	7.7	**16.3**	0.0	0.2	1.8	14.3	**82.1**
	0.3	0.7	2.3	3.0	27.0	0.0	0.0	0.0	0.2	1.6
	0.0	0.0	0.3	1.3	31.7	0.0	0.0	0.0	0.0	0.0
Scenario 14	6.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	9.3	1.3	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0
	16.0	4.7	0.3	0.0	0.0	1.4	0.7	0.0	0.0	0.0

Table 3

Numbers of patients treated at each dose combination for the CRM and the proposed two-dimensional design under 14 *scenarios*

	CRM				Two-dimensional design			
Scenario 1	**8.2**	4.2	1.2	0.4	**8.1**	4.3	1.1	0.2
	4.4	**6.5**	3.0	1.1	5.6	**7.0**	2.2	0.6
	2.6	4.4	**5.0**	3.0	3.8	2.9	**4.6**	2.2
	1.9	2.7	3.8	**6.7**	3.3	2.9	3.6	**4.0**
Scenario 2	4.5	**5.3**	3.2	1.8	4.3	**6.0**	4.0	2.0
	3.2	3.9	**4.2**	3.6	3.6	3.2	**5.5**	3.5
	2.8	3.3	3.2	**5.7**	3.8	1.0	2.4	**4.8**
	1.8	2.3	2.6	8.2	3.6	3.0	2.6	3.2
Scenario 3	**8.1**	4.1	1.3	0.5	**8.3**	4.4	1.5	0.6
	3.8	**6.5**	3.3	1.3	5.1	**6.7**	2.6	1.3
	2.2	3.8	**4.9**	4.0	3.5	2.0	**4.2**	3.6
	1.8	2.2	2.7	8.4	3.3	2.7	2.9	4.0
Scenario 4	7.6	2.0	0.8	0.3	3.5	0.7	0.1	0.0
	8.1	4.0	1.3	0.6	**10.5**	3.2	0.4	0.1
	3.9	**6.5**	3.1	1.5	7.0	**8.6**	2.7	0.7
	2.2	3.8	**5.1**	3.9	3.8	5.2	**7.1**	2.6
Scenario 5	7.8	2.1	0.9	0.4	1.0	0.2	0.0	0.0
	7.3	2.8	1.3	0.8	4.9	0.9	0.1	0.0
	7.1	4.2	1.7	1.0	**12.4**	3.9	0.8	0.2
	4.1	**5.4**	3.3	2.1	9.5	**10.5**	4.3	0.8
Scenario 6	7.7	1.9	0.8	0.3	5.6	1.7	0.6	0.3
	4.5	**6.2**	3.0	1.2	6.5	**7.5**	2.8	1.7
	2.1	3.6	**5.1**	4.2	3.6	2.1	**5.3**	5.1
	1.5	1.8	2.1	9.6	3.2	2.7	3.0	5.2
Scenario 7	3.0	3.1	3.0	**5.7**	3.9	3.7	5.9	**14.0**
	2.6	2.9	2.7	6.8	3.3	1.2	1.8	4.9
	2.3	2.6	2.5	7.6	3.6	0.5	0.8	2.3
	2.0	2.2	2.3	8.5	3.5	2.6	2.2	2.3
Scenario 8	5.5	0.6	0.1	0.0	0.0	0.0	0.0	0.0
	6.7	1.0	0.2	0.1	0.4	0.0	0.0	0.0
	7.6	1.6	0.4	0.1	3.4	0.0	0.0	0.0
	7.8	1.9	0.6	0.2	6.9	0.7	0.1	0.0

	CRM					Two-dimensional design				
Scenario 9	**8.0**	5.6	2.9	1.4	0.8	**8.0**	4.2	2.4	0.9	0.2
	4.7	**7.4**	4.2	2.1	1.5	6.5	**7.0**	4.3	2.0	0.7
	1.9	4.3	**6.6**	3.9	3.3	3.7	4.9	**7.2**	3.2	1.0
Scenario 10	5.0	**8.8**	4.1	1.3	0.6	5.8	**6.4**	3.9	1.5	0.4
	2.8	5.3	**7.1**	3.3	1.4	3.7	2.1	**6.6**	4.1	1.4
	1.4	1.9	4.2	**7.4**	5.0	3.3	2.7	4.4	**7.5**	3.1
Scenario 11	9.2	3.9	1.7	0.7	0.4	4.2	1.4	0.4	0.1	0.0
	8.9	5.0	2.4	1.2	0.8	**10.4**	4.8	1.6	0.4	0.1
	3.7	**7.8**	4.6	2.3	1.6	8.5	**14.2**	5.7	1.2	0.2
Scenario 12	9.8	2.3	0.5	0.1	0.0	8.0	1.3	0.3	0.0	0.0
	4.2	**10.4**	4.4	0.9	0.2	7.9	**12.5**	3.9	0.6	0.3
	1.5	2.3	4.7	**6.8**	4.8	3.4	3.5	6.6	**6.5**	2.0
Scenario 13	2.5	3.3	3.1	3.7	**7.4**	4.1	1.9	2.6	6.3	**21.8**
	1.6	2.0	2.3	2.4	11.7	3.1	0.1	0.2	0.4	2.5
	1.1	1.3	1.5	2.0	14.1	3.0	2.8	2.6	2.2	3.2
Scenario 14	8.3	1.7	0.5	0.1	0.0	0.6	0.0	0.0	0.0	0.0
	9.3	2.2	0.6	0.2	0.0	4.0	0.2	0.0	0.0	0.0
	10.7	3.9	1.1	0.3	0.1	8.3	2.1	0.2	0.0	0.0

Table 4
Total numbers of observed toxicities for the CRM and the proposed two-dimensional design under 14 *scenarios*

	Scenario													
Method	1	2	3	4	5	6	7	8	9	10	11	12	13	14
CRM	17.9	14.5	16.7	20.0	20.7	16.3	10.5	20.3	18.6	17.7	19.9	18.6	9.1	19.8
Two-dim. design	16.0	14.1	15.8	16.8	15.5	15.9	11.0	6.0	16.2	16.0	16.4	16.6	10.6	6.9

doses of agent A. For example, each 4 × 4 agent combination trial in scenarios 1 to 8 could be converted into four one-dimensional dose-finding trials by fixing agent B at dose levels 1, 2, 3, and 4, respectively. Similarly, each 5 × 3 trial in scenarios 9 to 14 could be converted into three parallel one-dimensional dose-finding trials and conducted using the CRM. For our simulations, 60 patients were equally distributed to the resulting one-dimensional dose-finding trials. For the 4 × 4 trial, we allocated 15 patients to each of the four one-dimensional trials; for the 5 × 3 trial, we allocated 20 patients to each of the three one-dimensional trials. Due to practical needs, we adopted a modified CRM:

(i) each trial always starts at the lowest dose level;
(ii) dose escalation is restricted to one level of change only;
(iii) if Pr(toxicity at the lowest dose $> \phi$) > 0.9, the trial will be terminated for safety.

We specified the prior toxicity probabilities as $(p_1, p_2, p_3, p_4) = (q_1, q_2, q_3, q_4) = (0.075, 0.15, 0.225, 0.3)$ for the 4 × 4 dose combinations; and $(p_1, p_2, p_3, p_4, p_5) = (0.06, 0.12, 0.18, 0.24, 0.30)$ and $(q_1, q_2, q_3) = (0.1, 0.2, 0.3)$ for the 5 × 3 dose combinations. We set $c_e = 0.7$ and $c_d = 0.45$, and simulated 2000 trials under each scenario.

We designed the scenarios to accommodate the commonly encountered situations in which different numbers and locations of target dose combinations may exist in the dose combination space. Table 2 presents the selection probabilities for the MTD combinations, and Table 3 reports the numbers of patients treated at each dose combination averaged over 2000 simulations. In particular, scenario 1 had four MTD combinations in the two-dimensional space, for which the CRM and our design performed comparably. Both designs selected the targets with similar percentages and treated a similar amount of patients at each dose pair. For scenarios 2 to 4, there were three MTD combinations, but located at different positions. The proposed design showed superior performances by increasing the selection percentage more than 15% compared to the CRM. Both designs treated approximately the same number of patients at the MTD combinations in scenarios 2 and 3, while the proposed design treated six more patients in scenario 4. For scenarios 5 and 6, there existed two MTD combinations per scenario, and scenario 7 had only one MTD combination. The CRM performed worse when there were fewer MTD combinations in the dose searching space, and the selection probabilities based on our design were more than doubled as shown in scenarios 5, 6, and 7. The reason is that the CRM allocated the same number of patients to each trial regardless of whether there existed an MTD combination, and no information was borrowed across these parallel trials. More patients in the CRM trials were treated at doses either excessively toxic or far below the MTD. In contrast, our proposed design provided the freedom to move around the entire dose combination space. All the data collected across the two-dimensional dose space would be modeled and integrated together for decision making. Scenario 8 was designed to examine whether the proposed method would terminate the trial early if all the dose combinations were excessively toxic. Both our proposed procedure and the CRM had the ability to stop the trial before a large number of patients were treated at toxic doses. In the 5 × 3 grid with 15 dose pairs, scenarios 9 and 10 contained three MTD combinations each, with our proposed design showing slightly higher selection percentages. Scenarios 11 to 13 had one or two MTD combinations, in which the performance of the CRM again was inferior because information could not be shared across the parallel trials. In scenario 14, all of the dose combinations were excessively toxic, but the CRM selected the overtoxic doses as the MTD with certain percentages. Our design collected all the data to map out the dose combinations' toxicity profile in the whole space, and terminated the trial in scenario 14 much sooner.

Table 4 exhibits the total number of observed toxicities averaged over 2000 simulations. Across these 14 scenarios, our design demonstrated a total of 193.8 observed toxicities, whereas the CRM demonstrated 240.6 toxicities. The gain of our design stems from the freedom to move around the dose combination space to choose the optimal dose combination to treat patients during the trial.

4.2 *Robustness Analysis*

To further examine the robustness of our design, we simulated six scenarios from a logistic regression model by taking the doses of the two agents as covariates. We took the doses for agent A as $Z_A = 0.125$, 0.25, 0.375, and 0.5, and those for agent B as $Z_B = 0.1$, 0.15, 0.2, and 0.25. The joint toxicity probability was given by

$$\pi_{jk} = \frac{\exp(\beta_0 + \beta_1 Z_A + \beta_2 Z_B + \beta_3 Z_A Z_B)}{1 + \exp(\beta_0 + \beta_1 Z_A + \beta_2 Z_B + \beta_3 Z_A Z_B)}, \qquad (3)$$

where (j, k) are the dose levels corresponding to (Z_A, Z_B). We present the six different scenarios generated from model (3) in Table 5, and the selection percentage and the number of patients treated at each dose combination in Table 6. In scenarios 1, 3, and 4, the proposed method selected the target with the highest percentage, while the dose combinations close to the target were also selected with certain percentages. However, in scenarios 2 and 5, our design selected the target dose combination with the second highest percentage, because the toxicity probabilities were very close and the sample size was small. For scenario 6 with all of the doses being overtoxic,

Table 5

Six scenarios generated from a logistic regression model for a 4×4 *two-agent combination trial with the target probability of toxicity* 0.3. *The MTD combinations are in boldface.*

	Dose level	Agent A 1	2	3	4	1	2	3	4
		Scenario 1				Scenario 2			
	4	0.28	0.41	0.55	0.68	0.17	**0.29**	0.45	0.62
	3	0.25	0.35	0.48	0.60	0.14	0.23	0.35	0.50
	2	0.22	**0.30**	0.40	0.51	0.12	0.18	0.27	0.38
	1	0.19	0.26	0.34	0.43	0.09	0.14	0.19	0.27
		Scenario 3				Scenario 4			
	4	0.37	0.72	0.92	0.98	0.04	0.09	0.17	**0.32**
Agent B	3	0.26	0.59	0.85	0.96	0.03	0.06	0.12	0.23
	2	0.18	0.44	0.74	0.91	0.02	0.05	0.09	0.16
	1	0.12	**0.30**	0.59	0.82	0.02	0.03	0.06	0.11
		Scenario 5				Scenario 6			
	4	0.12	0.26	0.48	0.71	0.78	0.94	0.99	1.00
	3	0.09	0.19	0.36	0.57	0.68	0.90	0.97	0.99
	2	0.07	0.14	0.26	0.43	0.57	0.83	0.94	0.98
	1	0.05	0.10	0.18	**0.30**	0.45	0.73	0.90	0.97

Table 6

Robustness analysis: selection probabilities and numbers of patients treated at each dose combination for the proposed two-dimensional design under six scenarios generated from a logistic regression model

	Selection probability				Number of patients			
Scenario 1	6.7	4.3	0.4	0.0	3.3	2.3	0.7	0.2
	9.4	11.5	2.5	0.1	5.8	5.1	1.5	0.3
	6.3	**16.1**	6.4	0.5	8.7	**7.2**	2.9	0.5
	1.2	12.3	8.7	1.4	5.4	6.0	3.7	1.2
Scenario 2	4.0	**13.3**	10.0	1.1	3.7	**5.1**	4.3	2.6
	2.2	8.7	18.1	4.9	3.6	4.3	5.5	2.9
	0.5	1.8	11.2	8.8	3.9	2.3	4.5	3.3
	0.0	0.8	6.3	8.2	3.2	3.0	3.7	3.7
Scenario 3	9.7	0.1	0.0	0.0	3.8	0.6	0.0	0.0
	18.7	2.5	0.0	0.0	9.0	2.1	0.1	0.0
	14.3	15.1	0.2	0.0	13.3	7.6	0.5	0.0
	1.6	**28.8**	2.5	0.0	5.6	**11.8**	2.8	0.3
Scenario 4	0.1	0.1	1.9	**91.5**	3.7	1.2	1.9	**27.9**
	0.0	0.0	0.1	5.4	3.1	0.1	0.2	3.2
	0.0	0.0	0.0	0.7	3.1	0.0	0.1	2.2
	0.0	0.0	0.0	0.5	3.0	3.0	3.2	4.0
Scenario 5	2.7	9.9	10.6	0.5	3.2	4.1	4.2	2.7
	0.9	3.8	19.6	3.3	3.1	2.8	6.1	3.1
	0.1	0.5	13.3	9.4	3.3	1.1	5.6	4.4
	0.0	0.1	10.0	**15.5**	3.0	3.1	4.5	**5.7**
Scenario 6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0
	0.0	0.0	0.0	0.0	4.1	0.1	0.0	0.0
	0.0	0.0	0.0	0.0	8.6	0.7	0.0	0.0

Table 7

Sensitivity analysis: selection probabilities and numbers of patients treated at each dose combination for the two-dimensional design under different prior distributions. The true toxicity probabilities for dose combinations are displayed in scenario 1 *in Table* 1.

Selection probability				Number of patients			
$\alpha, \beta \sim$ Unif(0.2, 2); $\gamma \sim$ Gamma(0.1, 0.1)							
19.9	8.8	0.1	0.0	**8.1**	4.3	1.1	0.2
5.6	**21.5**	4.6	0.2	5.6	**7.0**	2.2	0.6
0.3	5.3	**13.3**	3.7	3.8	2.9	**4.6**	2.2
0.0	0.3	5.7	**10.3**	3.3	2.9	3.6	**4.0**
$\alpha, \beta \sim$ Unif(0.01, 4); $\gamma \sim$ Gamma(0.05, 0.05)							
12.9	7.2	0.5	0.1	**6.4**	3.8	1.3	0.5
6.3	**22.1**	7.4	0.3	5.7	**7.9**	3.0	1.0
0.5	6.7	**17.9**	3.7	3.8	4.0	**5.9**	2.5
0.0	0.7	6.9	**7.1**	3.3	3.0	4.0	**3.8**
$\alpha, \beta \sim$ Unif(0.01, 8); $\gamma \sim$ Gamma(0.01, 0.01)							
10.6	6.6	0.8	0.1	**6.0**	3.6	1.4	0.7
7.8	**21.6**	8.7	0.8	5.8	**7.8**	3.1	1.2
0.7	6.2	**16.1**	3.5	4.1	4.1	**5.4**	2.3
0.0	2.1	7.0	**7.7**	3.1	3.3	4.2	**3.8**
$\alpha, \beta \sim$ Unif(0.01, 16); $\gamma \sim$ Gamma(0.005, 0.005)							
10.3	7.0	1.3	0.2	**5.6**	3.5	1.4	0.8
8.1	**20.9**	9.1	0.7	5.8	**7.5**	3.3	1.2
0.9	6.8	**14.7**	4.0	4.1	4.1	**5.6**	2.2
0.0	2.1	6.7	**7.6**	3.1	3.4	4.5	**3.9**

the proposed design did not select any dose combination. It can be seen that our design still performs reasonably well, even though the underlying true model is so different from our model.

We also conducted a sensitivity analysis to examine the performance of our design using different hyperparameters in the prior distributions. Focusing on scenario 1 in Table 1, we took several different sets of parameter values for the prior distributions of α, β, and γ. From Table 7, we can see that the selection percentages of the MTD combinations and the numbers of patients treated at each dose combination are quite similar under these different prior distributions.

4.3 *Trial Conduct*

We illustrate the proposed method with a renal cell cancer trial design at M. D. Anderson Cancer Center. The trial aimed to investigate the toxicity of 16 dose combinations consisting of four dose levels of an oral, small-molecule inhibitor (agent A) and four dose levels of an intravenous drug (agent B). The target toxicity rate was 30%, and the total number of patients in the trial was 60 with a cohort size of 3. We took $c_e = 0.7$ and $c_d = 0.45$. During the initial phase of the trial, dose combinations of (A_1, B_1), (A_1, B_2), (A_1, B_3), (A_2, B_1), and (A_3, B_1) were administered until two toxicities occurred. Our proposed model was then used to estimate the toxicity probability for each dose combination. The estimated toxicity probability of (A_1, B_3) was closest to the trial's target toxicity rate, and was therefore chosen as the starting dose combination for the formal two-dimensional design, i.e., $(A_s, B_{s'}) = (A_1, B_3)$. Our design assigned the cohorts to the dose combinations in the following sequence: (A_1, B_3), (A_1, B_4), (A_2, B_3), (A_2, B_3), (A_2, B_3), (A_2, B_3), (A_2, B_3), (A_3, B_2), (A_3, B_2), (A_2, B_2), (A_3, B_2), (A_3, B_2), (A_3, B_2), (A_3, B_2), and (A_3, B_2). Correspondingly, the numbers of patients per cohort who experienced toxicity were 0, 2, 0, 1, 1, 2, 1, 1, 2, 0, 0, 0, 1, 2, and 1. Once the outcomes of all the 60 patients were observed and analyzed, (A_3, B_2) was recommended as the MTD combination, with an estimated toxicity probability of 0.302.

5. Concluding Remarks

We have proposed to model the toxicity probabilities of two combined agents by constructing a latent 2×2 contingency table into which the correlation between the bivariate binary outcomes can be easily incorporated. Due to partially overlapping toxicities in agent combinations, we collapsed the three undistinguishable cells in the 2×2 table to derive a binomial likelihood function. Our design utilized all the available data information to efficiently reorder the toxicity probabilities in the entire dose combination space. It escalates and deescalates the dose by moving freely in the two-dimensional dose-finding space, which in turn helps to find the MTD combination faster. The proposed procedure is coherently updated with additional data as more patients enter the trial and more outcomes are observed. Simulation studies showed that our method is rather robust to the model misspecifications.

The key of using the latent 2×2 tables is to model the toxicity probabilities from the two agents and then collapse the three cells with undistinguishable toxicity. Usually, the toxicities of two agents are mostly overlapping. Thus, we cannot recover the information on the common toxicities, i.e., which agent has produced what proportion of the toxicity. Our goal is to use the latent process as a mechanism so that we can easily introduce the correlation and model the joint toxicity probability.

Although several MTDs may exist in a set of dose combinations, our procedure focuses on finding one MTD. The proposed design can be easily adapted for trials in which the goal is to find multiple MTD combinations (i.e., a trial that fixes the dose of one agent and searches over the other agent's doses to find its MTD in the combination). In this situation, we can select the MTD as the dose of agent A that has a toxicity probability closest to the target, while fixing agent B at each prespecified dose.

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