Dose-Finding Based on Bivariate Efficacy-Toxicity Outcome Using Archimedean Copula

Yuxi Tao\textsuperscript{1,2,3}, Junlin Liu\textsuperscript{1,2,3}, Zhihui Li\textsuperscript{1,2,3}, Jinguan Lin\textsuperscript{4}, Tao Lu\textsuperscript{1,2,3,4*}, Fangrong Yan\textsuperscript{1,2,3,4*}

\textsuperscript{1} State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing, China, \textsuperscript{2} Research Center of Biostatistics and Computational Pharmacy, China Pharmaceutical University, Nanjing, China, \textsuperscript{3} Department of Mathematics, China Pharmaceutical University, Nanjing, China, \textsuperscript{4} Department of Mathematics, Southeast University, Nanjing, China

\begin{abstract}

In dose-finding clinical study, it is common that multiple endpoints are of interest. For instance, efficacy and toxicity endpoints are both primary in clinical trials. In this article, we propose a joint model for correlated efficacy-toxicity outcome constructed with Archimedean Copula, and extend the continual reassessment method (CRM) to a bivariate trial design in which the optimal dose for phase III is based on both efficacy and toxicity. Specially, considering numerous cases that continuous and discrete outcomes are observed in drug study, we will extend our joint model to mixed correlated outcomes. We demonstrate through simulations that our algorithm based on Archimedean Copula model has excellent operating characteristics.

\end{abstract}

\section{Introduction}

The fundamental objective of drug development is to find a dose, or dose range, of a new drug. It is believed by many that the high attrition rate currently observed in phase III is largely driven by inadequate dose selection [1]. In most common dose-finding designs and methods, Phase I trials are designed to study the safety of the test drug, and maximum tolerable dose(MTD) is determined only based on toxicity. Efficacy outcomes are observed but not used. In Phase II trials, efficacy of the test drug is studied [2,3]. However, under a variety of circumstances, adverse events may lead to the early termination of drug development before efficacy outcome is observed, and there is a probable correlation between efficacy and toxicity. Besides that, valuable information may be lost if the efficacy outcome is ignored in Phase I.

Therefore, it is necessary to establish joint model for toxicity and efficacy to choose optimal dose and analyze their correlation. A number of joint modeling strategies have been studied in the literature [4,5]. In the context of an HIV trial, O’Quigley, Hughes, and Fenton [6] proposed model \( p(d) = \pi_{E|T}(d,\theta)(1 - \pi_{F}(d,\theta)) \) to describe the relationship of dose and success rate. In 1998, Peter F. Thall and Kathy E. Russell [7] combined the toxicity and efficacy into a single trinomial variable, then used a proportional odds regression (PO) model for the relationship of dose and the single trinomial variable. Afterwards, Wei Zhang, Daniel J.Sargent [8] adopted continuation-ratio(CR) model instead of PO model. In 2002, Braun [9] provided a bivariate distribution for correlated binary outcomes. This distribution contains a parameter \( \psi \) to represent the association between two outcomes. In 2005, Vladimir Dragalin, Valerii Fedorov [10] modeled the distribution of bivariate binary endpoint using either Gumbel bivariate logistic regression or Cox bivariate binary model. Moreover, Valerii Fedorov [11,12,13] provided a bivariate probit model in 2007. Most joint modeling methods above are only suitable for binary endpoint, and model the relationship of dose and probability. However, continuous outcomes are also observed in clinical trials. For example, shrinkage in a solid tumor, changes in blood pressure, or changes of glomerular filtration rate. In 2010, Aiyang Tao [14] studied bivariate continuous outcomes by bivariate normal distribution, and use AMCP-MOD method which is a fixed design with pre-determined randomization strategy to find optimal dose for phase III.

In our article, we propose Archimedean Copula joint model to evaluate efficacy and toxicity simultaneously. We mainly focus on two cases: bivariate continuous outcome and a mixture of continuous and categorical outcomes. Compared with other joint models, Archimedean Copula joint model has four main advantages: 1) The Copula joint model has no restrictions on probability distributions of efficacy and toxicity. 2) Marginal parameters in Copula joint model for both efficacy and toxicity are meaningful; 3) Copula joint model has few limitation of data type. 4) Archimedean Copula has explicit joint distribution formula. Bivariate mixed outcome is one of most analytically difficult cases, because they do not follow an obvious multivariate distribution. Based on this nice property of Archimedean Copula, we can easily structure the joint distribution via marginal distribution of continuous outcome and the conditional distribution of discrete outcome. In addition, Archimedean Copula is not restricted to radial symmetry. Take three popular Archimedean Copulas as examples. The Clayton Copula is an asymmetric Archimedean

\begin{figure}

\caption{Example Figure}

\end{figure}

\begin{table}

\caption{Example Table}

\end{table}

\section{Methodology}

Archimedean Copula is a multivariate distribution on the unit square. The copula function \( C(u_1, u_2; \theta) \) for Archimedean Copula is linked to the Archimedean generator \( \rho(u) \) by the following relationship:

\( C(u_1, u_2; \theta) = \rho^{-1}(\rho(u_1; \theta) + \rho(u_2; \theta)) \)

where \( \rho(u) \) is an Archimedean generator, \( u \) is the uniform distribution on the unit interval [0,1], and \( \theta \) is the parameter connecting the copula to the generator.

There are many Archimedean generators which have been used in clinical trials. Two popular Archimedean generators are the Clayton generator and the Gumbel generator.

**Clayton Copula**

The Clayton copula is defined as:

\( C(u_1, u_2; \theta) = \left( \frac{u_1^{-\theta} + u_2^{-\theta} - 1}{\theta - 1} \right)^{-\frac{1}{\theta}} \quad (\theta > 0) \)

where \( \theta \) is the parameter which controls the dependence structure. The Clayton copula is a decreasing function of \( \theta \), meaning that the dependence increases as \( \theta \) increases. The Clayton copula has marginal distributions:

\( F_{\theta}(u) = (\frac{u}{\theta})^{-\frac{1}{\theta}} \quad (0 < u < 1) \)

\( G_{\theta}(u) = (u^{-\theta} - 1)^{-\frac{1}{\theta}} \quad (0 < u < 1) \)

**Gumbel Copula**

The Gumbel copula is defined as:

\( C(u_1, u_2; \theta) = e^{-(\frac{u_1^{-\theta} + u_2^{-\theta}}{\theta})} \quad (\theta > 0) \)

where \( \theta \) is the parameter which controls the dependence structure. The Gumbel copula is an increasing function of \( \theta \), meaning that the dependence decreases as \( \theta \) increases. The Gumbel copula has marginal distributions:

\( F_{\theta}(u) = 1 - e^{-u^{-\theta}} \quad (0 < u < 1) \)

\( G_{\theta}(u) = 1 - e^{-u^{-\theta}} \quad (0 < u < 1) \)

In this article, we propose a joint model for correlated efficacy-toxicity outcome constructed with Archimedean Copula. We extend the continual reassessment method (CRM) to a bivariate trial design in which the optimal dose for phase III is based on both efficacy and toxicity. Specially, considering numerous cases that continuous and discrete outcomes are observed in drug study, we will extend our joint model to mixed correlated outcomes. We demonstrate through simulations that our algorithm based on Archimedean Copula model has excellent operating characteristics.
Copula, exhibiting greater dependence in the negative tail than in the positive. The Frank Copula is a symmetric Archimedean Copula. The Gumbel Copula is an asymmetric Archimedean Copula, exhibiting greater dependence in the positive tail than in the negative. According to different situations, we can choose corresponding Archimedean Copula. In fact, Archimedean Copula has another merit that they allow modeling dependence in arbitrary high dimensions with only one parameter. However, we mainly focus on bivariate efficacy–toxicity outcome in this article, so this merit is not obvious.

Continuous reassessment method (CRM) [15] is a popular algorithm in Phase I cancer clinical trials which is proposed to select maximum tolerated dose (MTD) [16,17,18]. It is also an adaptive design which means design is guided by examination of the accumulated data at an interim point in the clinical trial. It aims to (1) keep to a minimum number of patients treated at unacceptable high toxic dose levels, (2) keep to a minimum number of undertreated patients (3) respond quickly to errors in initial estimates, rapidly escalating in the absence of indication of drug activity and rapidly de-escalating in the presence of unacceptable high levels of observed toxicity (4) come to an early closure if there is no appropriate dose. According to its good character, we adopt CRM approach and extend it to bivariate trials to select the optimal dose for phase III in our article.

The remainder of the paper is organized as follows. In ‘Methods’ section, we propose Copula joint model for bivariate efficacy-toxicity outcome in detail, and dose-finding design is also discussed here. ‘Results’ section provides simulations to illustrate the performance of proposed model and algorithm. Finally, a conclusion is made in the part of “Discussion”.

Motivating Example

**Bivariate continuous outcomes.** ACE inhibitors/inhibitors of angiotensin-converting enzyme are used primarily in treatment of hypertension and heart failure. However, renal impairment is a significant adverse effect of all ACE inhibitors. The reason for this is still unknown. Some suggest that it is associated with their effect on angiotensin II-mediated homeostatic functions such as renal blood flow. Renal blood flow may be affected by angiotensin II because it vasoconstricts the efferent arterioles of the glomeruli of the kidney, thereby increasing glomerular filtration rate (GFR). Hence, by reducing angiotensin II levels, ACE inhibitors may reduce GFR, a marker of renal function. In one clinical trial an ACE inhibitor (an inhibitor of angiotensin-converting enzyme) are used primarily in treatment of hypertension and heart failure. However, renal impairment is a possible side effect. Some suggest that it is associated with their effect on angiotensin II-mediated homeostatic functions such as renal blood flow. Renal blood flow may be affected by angiotensin II because it vasoconstricts the efferent arterioles of the glomeruli of the kidney, thereby increasing glomerular filtration rate (GFR). Hence, by reducing angiotensin II levels, ACE inhibitors may reduce GFR, a marker of renal function. In one clinical trial an ACE inhibitor is used to treat hypertension. The efficacy endpoint is the change of sitting blood pressure from baseline. Decreasing GFR is the undesirable effect and the main toxicity measure is the change of GFR from baseline.

**Bivariate mixed outcomes.** Anticoagulants are pivotal agents for the prevention and treatment of thromboembolic disorders. The efficacy of Anticoagulant is to lower the VTE (venous thromboembolism) incidence rate. Unfortunately, such an effect can be accompanied by an increase in major bleeding, especially postoperative, during the treatment. Therefore, when choosing the optimal dose, we should consider the VTE incidence rate and bleeding event simultaneously.

**Methods**

**Archimedean Copula for Bivariate Correlated Efficacy–toxicity Outcome**

Copula is recently popular strategy for joint modeling in statistical applications. The history of Copula may begin with Frechet [19], who studied the problem in low-dimension. In 1959, Sklar researched in-depth in this respect, by introducing the notion, and the name, of a Copula, and proving the theorem that now bears his name [20]. Sklar’s theorem states that a multivariate cumulative distribution function of n random variables can be written as

\[ F_{X_1, \ldots, X_n}(x_1, \ldots, x_n) = C[F_{X_1}(x_1), \ldots, F_{X_n}(x_n)|\Gamma], \]

where \( C \) is a Copula, and \( F_{X_i}(x_i) = P[X_i < x_i] \).

In our study, Let \( X_i \) and \( Y_i \) respectively denote the efficacy and toxicity outcomes obtained from \( j \) subject within fixed dose group \( j(i = 1, \ldots, n_f; f = 1, \ldots, n) \). For each dose \( d \), we assume \( X_i \sim F_{X_i} \), and \( Y_i \sim F_{Y_i} \). The marginal distributions can be arbitrary continuous distributions. To specify the marginal models, let \( \mu_1 \) and \( \mu_2 \) be suitable link models chosen from common candidate models like Emax, Exponential, logit, etc.

**E(\( X_i \)) = \mu_1(d, \alpha), E(\( Y_i \)) = \mu_2(d, \beta),**

here, \( \alpha \) and \( \beta \) are marginal model parameter vectors.

For Archimedean Copula, the Copula function \( C \) is defined as:

\[ C(u_1, u_2) = \begin{cases} \varphi^{-1}[\varphi(u_1) + \varphi(u_2); z] & \sum_{i=1}^{2} \varphi(u_i) \leq \varphi(0), \\ 0 & \text{otherwise} \end{cases} \]

where \( \varphi \) is the so-called generator, \( u_i = F_{X_i}, \mu_2 = F_{Y_i} \), and \( z \) is the association parameter measuring dependence between efficacy and toxicity. Some popular Archimedean Copulas, their corresponding generators and association parameters are listed in Table 1.

| Copula      | \( u_1, u_2; z \)                          | \( z \) | \( \varphi(u; z) \) |
|-------------|-------------------------------------------|--------|------------------|
| Frank       | \(- \frac{1}{2} \log[1 + \frac{1}{1 - \exp(-z \cdot u_1)}], \frac{1}{e^{-z} - 1} \) | \(- \infty, \infty \) | \( 0 \) |
| Gumbel      | \( \exp(-[-(\ln u_1)^{1/z}] + [(\ln u_2)^{1/z}]) \) | \( [1, \infty] \) | \( - \log(u_1)^z \) |
| Clayton     | \( \max(u_1^{z}, u_1^{-1})_{-1/2, z} \) | \( (-1, \infty) \) | \( \frac{1}{2} (u_1 - 1)^{1/z} \) |

Table 1. Archimedean Copula, generator and association parameter.

\[ \text{doi:10.1371/journal.pone.0078805.t001} \]
where $f_x$ and $f_y$ represent corresponding marginal density function.

When the margins appear to be mixed outcomes, we adopt another strategy to build joint model. Assume efficacy $X_{ij}$ is continuous and toxicity $Y_{ij}$ is categorical. Similarly, let $u_1 = F_{X_{ij}}$ and $u_2 = F_{Y_{ij}}$, but $u_2$ is discrete distribution here. Let

$$C_1^{u_1}(u_1,u_2) = \frac{\partial C_1^{u_1}(u_1,u_2)}{\partial u_1}, C_2^{u_2}(u_1,u_2) = \frac{\partial C_2^{u_2}(u_1,u_2)}{\partial u_1},$$

where $u_2 -$ is the left-hand limit of $u_2$. Then, the joint density is given by

$$f_{X_{ij},Y_{ij}}(x,y; z) = f_{X_{ij}}(x)(C_1^{u_1} - C_2^{u_1}).$$

Take Frank Copula for example, the joint distribution $F_{X_{ij},Y_{ij}}$ determined by Frank Copula takes the form

$$f_{X_{ij},Y_{ij}}(x,y; z) = f_{X_{ij}}(x)|\frac{e^{-zu_2}(e^{-zu_2} - 1)}{(e^{-z} - 1) + (e^{-zu_1} - 1)(e^{-zu_2} - 1)} - \frac{e^{-zu_1}(e^{-zu_2} - 1)}{(e^{-z} - 1) + (e^{-zu_1} - 1)(e^{-zu_2} - 1)}.$$

Copula is popular in statistical applications as it allows one not only to conveniently build joint regression model, but also to easily estimate the parameters in joint regression model by using Copula density function. Once we get the Copula joint density function, we can use maximum likelihood estimation, which has come to be quite mature and be integrated in many softwares.

**Decision Rules**

**Dose-finding criteria.** After the Copula joint model is established and successfully fitted to data, the optimal dose(s) to be carried into Phase III still remains unresolved. We calculate the minimum effective dose (MED) and the maximum tolerated dose (MTD) first.

| Table 2. Operating characteristics under scenario 1-3. |
|-------------------------------------------------------|
| scenario | Copula joint model | Tao’s joint model | Separate model |
|----------|---------------------|-------------------|----------------|
|          | 1       | 2       | 3       | 1       | 2       | 3       | 1       | 2       | 3       |
| Trials where correct dose found (%) | 0.594  | 0.610  | 0.890  | 0.494  | 0.703  | 0.860  | 0.585  | 0.705  | 0.856  |
| Average number subjects given dose under inefficacy (%) | 0.349  | 0.114  | 0.744  | 0.373  | 0.121  | 0.729  | 0.356  | 0.114  | 0.745  |
| Average number subjects given dose under toxicity (%) | 0.138  | 0.133  | 0.256  | 0.164  | 0.166  | 0.271  | 0.141  | 0.142  | 0.255  |

**Figure 1. Dose-response curves in first three scenarios.**

doi:10.1371/journal.pone.0078805.g001
Following Ruberg [21], the MED is defined as the smallest dose, which shows a clinically relevant and a statistically significant effect. Let $D_E$ denotes the clinically relevant difference with respect to the smallest dose (often placebo $d_1$). Note that $D_E$ does not depend on the particular dose-response model under consideration, but only depend on the objectives of the guidelines or clinicians. Given a marginal model $f(\cdot, \theta)$ for efficacy, $f(d_1, \theta) + D_E$ is the clinically relevant effect, and

$$\text{MED} = \text{argmin} \{f(d, \theta) > f(d_1, \theta) + D_E\}.$$ 

Similar, MTD is defined as the maximum dose which shows clinically acceptable toxicity. Let $D_T$ denotes the clinically acceptable difference, that is, that largest toxicity acceptable difference, by which we expect a dose to be not too worse than placebo. A marginal model $g(\cdot, \theta)$ for toxicity is given as follow:

$$\text{MTD} = \text{argmax} \{g(d, \theta) \leq g(d_1, \theta) + D_T\}.$$ 

If the interval [MED, MTD] called therapeutic range exists, we can select the final optimal dose based on the following utility function [22]. The utility function is

$$F(d) = \text{eff}(d) - k \times \text{saf}(d).$$

The final dose is determined by maximizing the utility function. Here, $k > 0$ represents the weight for the discounted toxicity from efficacy.

For example, we expect efficacy outcome $x$ would increase, and toxicity outcome $y$ would not decrease heavily after take medicine. Then

$$\text{eff}(d) = p(x > a|d), \text{saf}(d) = p(y > b|d),$$

where $a$ and $b$ are the desired efficacy threshold and toxicity threshold. In general, $a$ and $b$ are tightened than clinical acceptable threshold to increase the success rates in phase III. Other situations can be solved by changing the operator in above expression.

**Dose finding design.** We adopt CRM approach and extend it to bivariate response to select the optimal dose for phase III in our article. Due to safety and ethics concerns, the up and down design [3] will be used until the first toxicity is observed. The trial is carried out as follows.

![Dose-response curves in last three scenarios.](doi:10.1371/journal.pone.0078805.g002)

**Table 3. Operating characteristics under scenario 4–6.**

| scenario     | Copula model | Separate model |
|--------------|--------------|----------------|
|              | 4            | 5              | 6              | 4            | 5    | 6    |
| Trials where correct DOSE found(%) | 0.664 | 0.784 | 1 | 0.593 | 0.745 | 1 |
| Average number subjects given dose under inefficacy(%) | 0.344 | 0.265 | 0.987 | 0.345 | 0.264 | 0.974 |
| Average number subjects given dose under toxicity(%) | 0.202 | 0.192 | 0.013 | 0.217 | 0.213 | 0.026 |

![Figure 2. Dose-response curves in last three scenarios.](doi:10.1371/journal.pone.0078805.g002)
1. Treat subjects in cohorts of size $c$, up to maximum of $N$ subjects. Dose-response (efficacy) model and dose-response (toxicity) model are assumed. Set fixed dose groups.

2. Define the clinically acceptable difference $\Delta$ for efficacy and toxicity, and define the desired thresholds for efficacy and toxicity in utility function.

3. The up and down design will be used for the first cohort and will be stopped after the first observed toxicity.

4. Collect the efficacy and toxicity responses to fit joint models, and calculate the initial therapeutic range [MED, MTD].

5. If MTD is smaller than MED, our trial is stop and there is no appropriate dose for phase III. If MTD is larger than MED, fixed dose groups in the Therapeutic range are delivered for next cohort. Then, return to the step4.

6. Once the predetermined fixed sample size is reached, the final dose is selected by utility function.

**Sample size.** An optimal sample size can be derived through simulation. Under a scenario where the efficacy at the selected dose $d^*$ equals the MED, specially, MED = $f(d^*,0)$. For given sample size $N$, and interval width $\Delta t$, simulations can determine the probability $\Pr(MED - \delta \leq MED \leq MED + \delta)$. Then we can choose the sample size $N$ based on following formula. Here, target probability is pre-specified as

$$N = \arg \min \{ \Pr(MED - \delta \leq MED \leq MED + \delta) > \text{target probability} \}$$

In our following simulations, we set $\delta = 0.1 \times$ MED, and target probability is 0.7. Note that marginal model for continuous outcome often contains many parameters. When we decide the size of cohort, this point need to be considered.

**Results**

**Simulation**

We examine the operating characteristics of our algorithm in a study seeking for optimal dose for phase III. We simulate six different scenarios here, allowing the evaluation of the methods under a wide range of scenarios likely to be observed in clinical practice.

**Example of bivariate continuous outcomes.** We examine the operating characteristics of Archimedean Copula in the ACE inhibitors study through simulations. The performance is illustrated under three possible scenarios, which are shown in Figure 1, and the true optimal dose indicated by arrows.

We assume efficacy outcome—the decreased DBP from baseline $X$ follows normal distribution and Emax model,

$$X_i \sim \text{normal}(f(d_i, a), \sigma^2),$$

$$f(d_i, a) = E_0 + E_{\text{max}} \cdot d_i/(ED50 + d_i).$$

The toxicity outcome—the decreased GFR from baseline $Y$ follows exponential distribution and exponential model,

$$Y_i \sim \text{exponential}(\exp\{g(d_i, b)\}), g(d_i, b) = \beta_0 + \beta_1 \cdot d_i,$$

here, $a = (E_0, E_{\text{max}}, ED50), b = (\beta_0, \beta_1)$.

We select Gumbel Copula as our joint model. The modeling approach and dose-finding algorithm can easily extended to other Archimedean Copula models with similar process. We assume association parameter $\rho = 1.67$ which represents a moderate correlation between two outcomes. The sample size of subjects is 175, and cohort size $c = 20$/dose. We have a fixed dose group $DOSE = \{0.05, 0.2, 0.4, 0.6, 0.8\}$. To adequately estimate the operating characteristics of our algorithm, 1000 simulations are conducted for each scenario. The data is generated using the mvdC function in the “copula” library in R software.

To illustrate the advantages of Copula joint model, we compare its performance with Tao’s joint model [14]. Considering that both outcomes in Tao’s joint model must follow normal distribution, we assume toxicity outcome

$$Y_i \sim \text{normal}(1/\exp\{g(d_i, b)\}), g(d_i, b) = \beta_0 + \beta_1 \cdot d_i.$$
The efficacy outcome is the lowered VTE incidence rate \( X \), which follows normal distribution and linear model,

\[ X \sim \text{normal}(f(d_i,a),\sigma^2) \quad f(d_i,a) = E_0 + E_{\text{max}} \times d_i. \]

The toxicity outcome is having major bleeding event \( Y \) with 1 representing occurrence and 0 representing no occurrence. \( Y \) follows the Bernoulli distribution and logistic model.

\[ Y \sim \text{bernoulli}(g(d_i,\beta)), \quad g(d_i,\beta) = 1/(1 + \exp(-\beta_0 - \beta_1 \times d_i)), \]

where, \(\beta = (E_0,E_{\text{max}})\), and \(\beta = (\beta_0,\beta_1)\).

We also select Gumbel Copula as our joint model. Sample size of subjects is 225, and cohort size \( c = 20/\text{dose} \). We have a fixed dose group \( \text{DOSE} = 0.05, 0.2, 0.4, 0.6, 0.8 \). The association parameter \( z = 20 \) represents a highly correlation between two outcomes. To adequately estimate the operating characteristics of our algorithm, 1000 simulations are conducted for each scenario. The performance of Copula model is shown in Table 3.

The performance of our algorithm under last three scenarios is shown in Table 3. Copula model performs better than separate model in these three scenarios. In scenario 4, 66.4% simulations select the right dose based on Copula joint model. Similarly, it is the lowest value among last three scenarios because of the narrow therapy range. In scenario 5, Copula model correctly identifies the dose in 784 of the 1000 simulations. In scenarios 6, the accuracy rate of dose selection is up close to 1, and only 58.1% subjects enter clinical trial. In addition, in scenarios 4–5, the average number of subjects under toxicity is about 20%, and average number of subjects under inefficacy is about 30%.

**Discussion**

Assessment of dose-response profiles for efficacy and toxicity outcomes is the key to reliable evaluations of the risk-benefit profile of a drug as well as the selection of final doses to be carried into clinical trials. In this article, we develop Archimedean Copula joint model for bivariate efficacy-toxicity outcome of new drug. We study in detail two situations: one for bivariate continuous variates, and the other for bivariate mixed outcome. Simulation results indicate that Copula joint model provides better design performance than separate model in both cases.

Actually, lots of remaining interesting issues are unresolved. The following directions are considered as important potential study directions in the future. 1) There are many useful Archimedean Copulas. Obviously, if one knows the “right” Copula, the Copula-based regression analysis is more effective. But which one is “right”? In this article, we take the Gumbel as example, but we can use AIC or other model selection method [23] to select optimal Copula model. Actually, we had intended to add model selection into simulation. Weigh the practicability and the amount of calculation, we present the current design. 2) We assume throughout the paper that efficacy and toxicity responses have no relation with covariates; however, many observations in the drug study are affected by covariates, such as age, gender, etc. Extending our methodology to allow for individual characteristics in the data is meaningful. 3) To address different objectives, a number of different dose-finding approaches have been developed. Simulation and comparison of their character based on Copula joint model will be the focus of our study in the future.

**Acknowledgments**

The authors gratefully acknowledge the Editor, Associate Editor, and referees for their valuable comments and suggestions that substantially improved the paper.

**Author Contributions**

Conceived and designed the experiments: FY TL. J. Liu. Performed the experiments: YT. Analyzed the data: ZL. FY. Contributed reagents/materials/analysis tools: J. Liu. Wrote the paper: YT FY.

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