

Model-assisted design for drug combination dose-finding trials

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Drug Combination



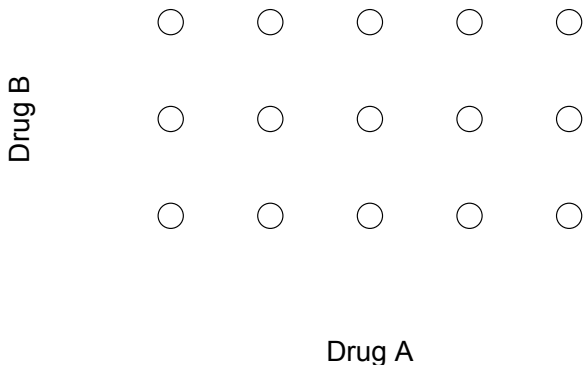
Drug Combination

Synergistic treatment effect!



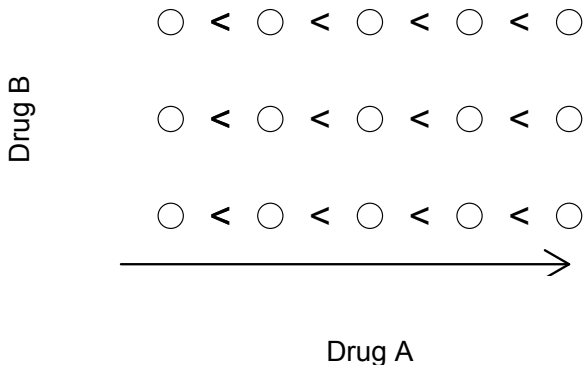
Challenges of drug combination trials

- Larger searching space \implies **larger sample size required!**
- Doses are only partially ordered in toxicity due to complicated drug-drug interaction



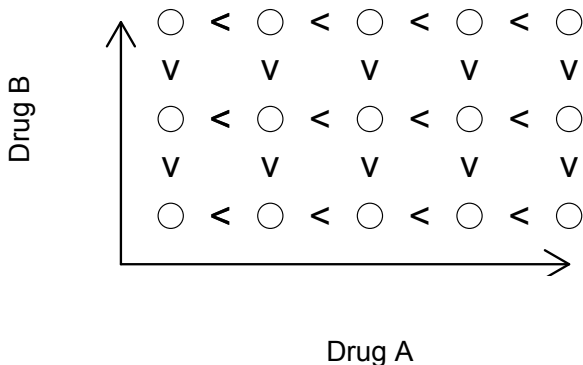
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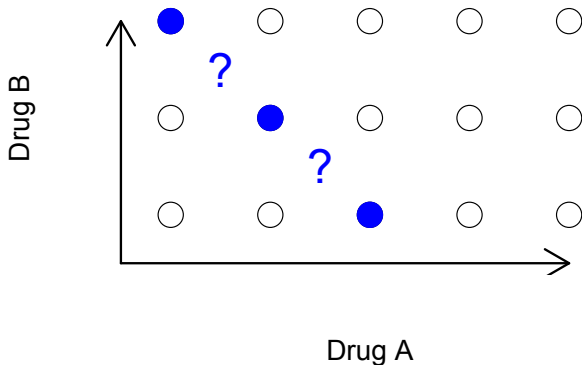
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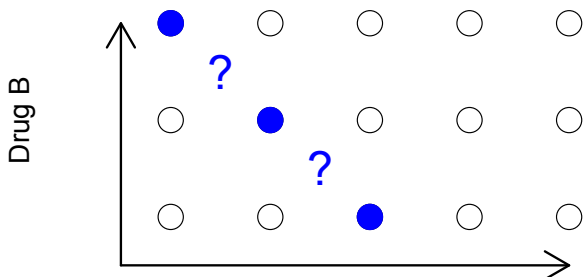
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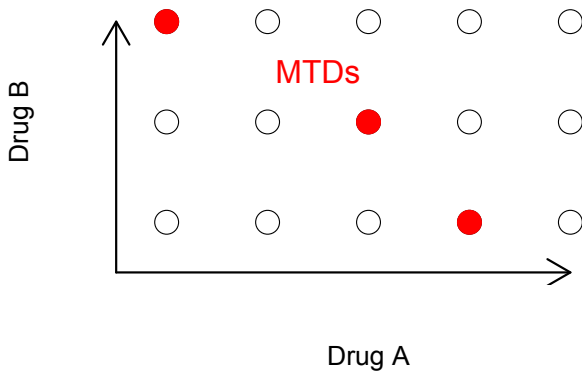
Challenges of drug combination trials

- Larger searching space \implies **larger sample size required!**
- Doses are only partially ordered in toxicity due to complicated drug-drug interaction \implies **single-agent dose-finding methods cannot be directly used for combination trials.**

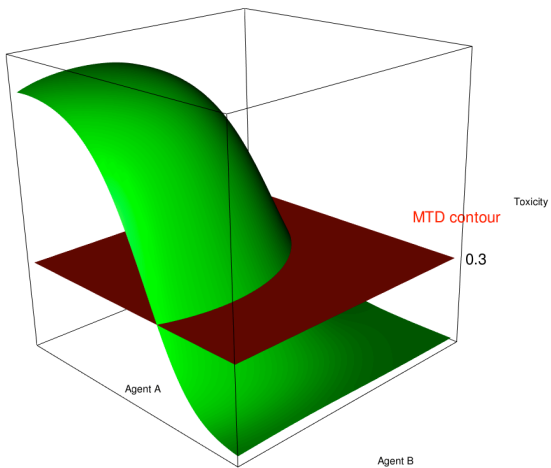


Challenges of drug combination trials

- Multiple MTDs may exist!



MTD contour



A key design question

- A fundamental question when designing a combination trial:

Are we interested in finding **one MTD or the MTD contour (multiple MTDs)?**

- The answer to this question determines the choice of different design strategies.
- This important issue, unfortunately, is largely overlooked in practice.
- We here focus on finding a MTD, refer to Yuan and Zhang (2017) for designs to find the MTD contour.

Three types of design

- Algorithm-based designs
 - Dose transition is based on a set of prespecified rules/algorithm, e.g., 3+3 design or A+B design
 - Transparent, easy to implement, but perform poorly

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- A dose-toxicity model is assumed, and then updated based on accrued data to guide the dose transition, e.g., most existing drug combination trial designs
- Good performance, but less transparent and difficult to implement

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- **Model-assisted designs**

- A class of designs that utilize a model for efficient decision making, similar to the model-based design, but its rule of dose escalation/deescalation can be pretabulated before the onset of the trial in a fashion similar to the algorithm-based design (Yan, Mandrekar and Yuan, 2017)
- Transparent, easy to implement and good performance
- Examples: mtpi (Ji et al., 2007), BOIN (Liu and Yuan, 2015), and keyboard design (Yan, Mandrekar and Yuan, 2017).

Finding a single MTD

- Many novel model-based combination designs have been proposed to find a single MTD (Thall, et al, 2003; Yin and Yuan 2009a, 2009b; Braun and Wang, 2010; Yuan and Yin, 2011; Wage et al., 2011; Riviere, et al., 2014, 2015; ...).
- These designs perform well in simulation, but are rarely used in practice.
 - Statistically and computationally complicated
 - Lack of easy-to-use software
 - Model-based, thus **robustness can be a potential issue** because of complicated two-dimensional dose searching space. In addition, **incoherent dose escalation could be rampant**
- Riviere et al. (2014) reviewed 162 drug-combination phase I trials published 2011-2013, among which 88% used the 3+3 design.

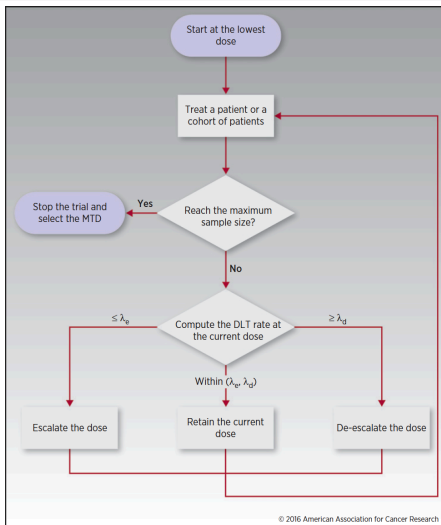
Coherent design

- A design is **coherent** if it will never escalate the dose when the latest treated patient experiences toxicity; and will never deescalate the dose when the latest treated patient does not experience toxicity (Cheung, 2005).
- A design is **long-memory coherent** if it will never escalate the dose when the observed toxicity rate at the current dose is higher than the target toxicity rate; and will never deescalate the dose when the observed toxicity rate at the current dose is lower than the target toxicity rate (Liu and Yuan, 2015).
- Long-memory coherent is a natural requirement in practice.

BOIN drug-combination design

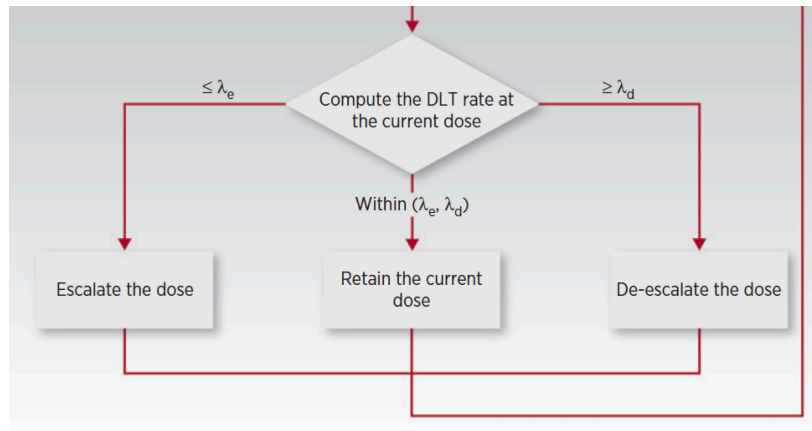
- The Bayesian optimal interval (BOIN) drug-combination design (Lin and Yin, 2016; Yuan and Zhang, 2017) is a **model-assisted design** that is as transparent as the 3+3 design, but yields substantially better performance.
- The BOIN drug-combination design is **long-memory coherent**, which may not be true for most existing model-based drug-combination designs.
- The BOIN drug-combination design is an extension of the BOIN single-agent design (Liu and Yuan, 2015), and makes the decision of dose escalation/de-escalation based on the same rule as the latter.

Bayesian optimal interval (BOIN) design



$$\text{DLT rate at the current dose} = \frac{\text{No. of patients experienced DLT at the current dose}}{\text{No. of patients treated at the current dose}}$$

BOIN dose escalation/deescalation rule



$$\text{DLT rate at the current dose} = \frac{\text{No. of patients experienced DLT at the current dose}}{\text{No. of patients treated at the current dose}}$$

Escalation/de-escalation boundaries

Table: The escalation/de-escalation boundaries (λ_e , λ_d) under the BOIN design for different target toxicity rates*.

boundaries	Target toxicity rate ϕ					
	0.15	0.2	0.25	0.3	0.35	0.4
λ_e	0.118	0.157	0.197	0.236	0.276	0.316
λ_d	0.179	0.238	0.298	0.358	0.419	0.479

* using the default underdosing toxicity rate $\phi_1 = 0.6\phi$ and overdosing toxicity rate $\phi_2 = 1.4\phi$.

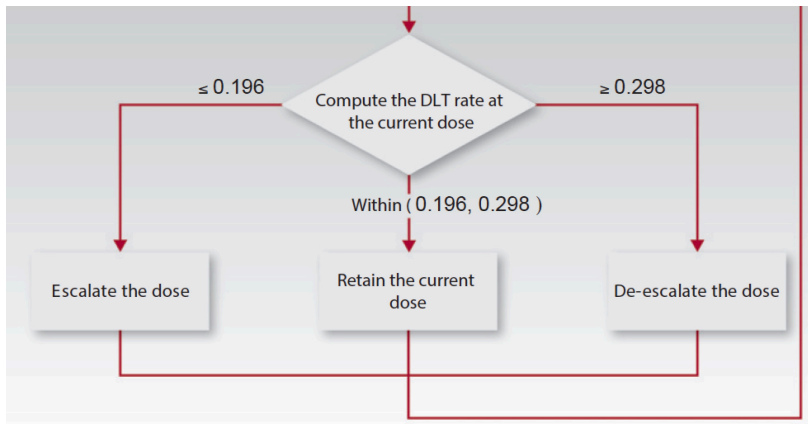
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BOIN design with target toxicity rate of 25%



$$\text{DLT rate at the current dose} = \frac{\text{No. of patients experienced DLT at the current dose}}{\text{No. of patients treated at the current dose}}$$

Statistical principle behind BOIN design

- The BOIN is obtained by minimizing the decision error for dose escalation/deescalation within the whole class of nonparametric designs that do not assume a parametric dose-response curve

A class of nonparametric designs

- 1 The first cohort are treated at the lowest dose level.
- 2 At the current dose level j :
 - if $\hat{\pi}_{T,j} \leq \lambda_{1j}$, escalate
 - if $\hat{\pi}_{T,j} \geq \lambda_{2j}$, deescalate
 - otherwise, i.e., $\lambda_{1j} < \hat{\pi}_{T,j} < \lambda_{2j}$, retain

where $\lambda_{1j} \equiv \lambda_{1j}(n_j, \phi)$ and $\lambda_{2j} \equiv \lambda_{2j}(n_j, \phi)$ denote the dose escalation and deescalation boundaries.

- 3 Repeat step 2 until the maximum sample size is reached.

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- 3 Repeat step 2 until the maximum sample size is reached.

Because λ_{1j} and λ_{2j} can freely vary across the dose levels (i.e., j) and the number of patients treated (i.e., n_j), this class of designs **include ALL possible nonparametric designs** that do not impose a dose-toxicity curve.

Notations and setup

- Specify three point hypotheses

$$H_0 : p_j = \phi$$

$$H_1 : p_j = \phi_1$$

$$H_2 : p_j = \phi_2,$$

- ϕ_1 is the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that dose escalation should be made
- ϕ_2 is the lowest toxicity probability that is deemed overly toxic such that dose deescalation is required
- Example: $\phi = 0.3$, $\phi_1 = 0.2$ and $\phi_2 = 0.4$

Remarks on the hypotheses

- The purpose of specifying three hypotheses, H_0 , H_1 and H_2 , is **NOT** to represent the truth and conduct hypothesis testing.
- H_1 and H_2 , or more precisely $\delta_1 = \phi_1 - \phi$ and $\delta_2 = \phi_2 - \phi$, represent the minimal differences (or effect sizes) of practical interest to be distinguished from the target toxicity rate ϕ (or H_0), under which we want to minimize the average decision error rate for the trial conduct.
- This is analogous to power calculation.

Remarks on the hypotheses

- In practice, we should avoid setting ϕ_1 and ϕ_2 at values very close to ϕ because of the limited power due to small sample sizes of phase I trials.
 - At the significance level of 0.05, we have only 6% power to distinguish 0.35 from 0.25 with 30 patients.
- As default values, we recommend $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$.
 - e.g., when $\phi = 0.25$, $\phi_1 = 0.15$ and $\phi_2 = 0.35$.

Correct and incorrect decisions

- The correct decisions under H_0 , H_1 and H_2 are \mathcal{R} , \mathcal{E} and \mathcal{D} , respectively, where \mathcal{R} , \mathcal{E} and \mathcal{D} denote dose retainment (of the current dose level), escalation and deescalation.
- The incorrect decisions under H_0 , H_1 and H_2 are $\bar{\mathcal{R}}$, $\bar{\mathcal{E}}$ and $\bar{\mathcal{D}}$, where $\bar{\mathcal{R}}$ denotes the decisions complementary to \mathcal{R} (i.e., $\bar{\mathcal{R}}$ includes \mathcal{E} and \mathcal{D}), and $\bar{\mathcal{D}}$ and $\bar{\mathcal{R}}$ are defined similarly.

Decision error rate

- The probability of making an incorrect decision (or decision error rate) at each of the dose assignments is given by

$$\begin{aligned}\alpha &\equiv \text{pr}(\text{incorrect decision on dosing}) \\ &= \text{pr}(H_0)\text{pr}(\bar{\mathcal{R}}|H_0) + \text{pr}(H_1)\text{pr}(\bar{\mathcal{E}}|H_1) + \text{pr}(H_2)\text{pr}(\bar{\mathcal{D}}|H_2)\end{aligned}$$

Decision error rate

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 &= \text{pr}(H_0)\{ \text{Bin}(n_j\lambda_{1j}; n_j, \phi) + 1 - \text{Bin}(n_j\lambda_{2j} - 1; n_j, \phi) \} \\
 &\quad + \text{pr}(H_1)\{ 1 - \text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \} \\
 &\quad + \text{pr}(H_2)\text{Bin}(n_j\lambda_{2j} - 1; n_j, \phi_2)
 \end{aligned}$$

Optimal escalation/deescalation boundaries

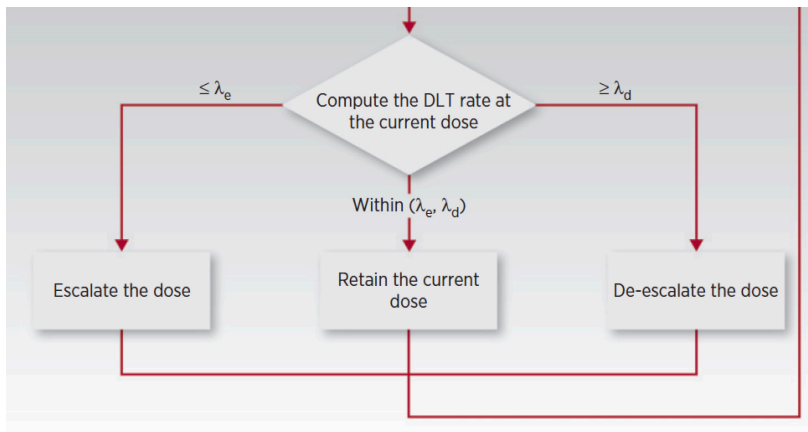
- Assuming the non-informative prior that the current dose has the equal probability of being at, above or below the MTD, the optimal dose escalation/deescalation boundaries that minimize incorrect dose assignment are given by

$$\lambda_{1j} = \log \left(\frac{1 - \phi_1}{1 - \phi} \right) / \log \left(\frac{\phi(1 - \phi_1)}{\phi_1(1 - \phi)} \right)$$

$$\lambda_{2j} = \log \left(\frac{1 - \phi}{1 - \phi_2} \right) / \log \left(\frac{\phi_2(1 - \phi)}{\phi(1 - \phi_2)} \right) .$$

- The optimal escalation/deescalation boundaries **are independent of n_j and j !!**
- This makes the BOIN extremely simple because the same pair of dose escalation/de-escalation boundaries can be used throughout of the trial.

Dose escalation using the BOIN design



$$\text{DLT rate at the current dose} = \frac{\text{No. of patients experienced DLT at the current dose}}{\text{No. of patients treated at the current dose}}$$

Statistical properties of the BOIN

Coherence

The BOIN design is (long-memory) coherent in the sense that the design will never escalate the dose when the observed toxicity rate \hat{p}_j at the current dose is higher than the target toxicity rate ϕ ; and will never deescalate the dose when the observed toxicity rate \hat{p}_j at the current dose is lower than the target toxicity rate ϕ

- Example: suppose target toxicity rate = 30%, if 1/3 has toxicity, the BOIN design will never escalate dose; if 0/3 has toxicity, the design will never deescalate dose.

Consistence

Under the BOIN design, dose allocation and selection converge to the target dose.

BOIN drug-combination design

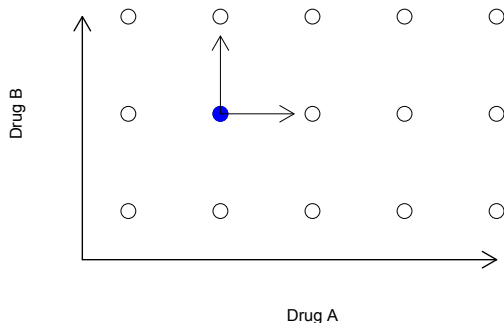
- The BOIN drug-combination design uses the same escalation/de-escalation rule as the BOIN single-agent design
- Thus, the BOIN drug-combination design is **coherent**, **consistent** and **easy to implement** in practice.
- The only difference is that, in combination trials, when we decide to escalate or de-escalate the dose, there are more than one neighbor doses that we can move to.

BOIN drug-combination design

- Let $A_j B_k$ denote the combination of dose level j of agent A with dose level k of agent B.
- Let p_{jk} denote the toxicity rate of $A_j B_k$.
- The BOIN drug-combination design makes its choice based on $\Pr(p_{jk} \in (\lambda_e, \lambda_d) | \text{data})$, which measures how likely the combination has acceptable toxicity given the observed data.

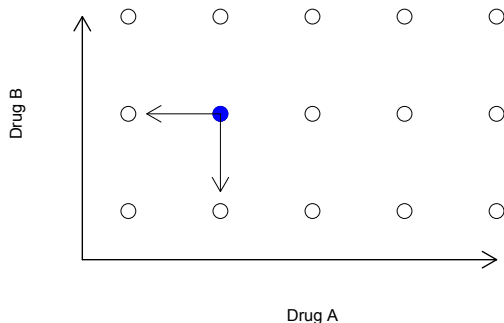
Dose escalation

- When the BOIN rule says escalation, we escalate the dose to $A_{j+1}B_k$ or A_jB_{k+1} , the one that has the largest value of $Pr(p_{j'k'} \in (\lambda_e, \lambda_d) | n_{j'k'}, y_{j'k'})$, where $(j', k') = (j + 1, k)$ or $(j, k + 1)$.



Dose de-escalation

- When the BOIN rule says de-escalation, we de-escalate the dose to $A_{j-1}B_k$ or A_jB_{k-1} , the one that has the largest value of $Pr(p_{j'k'} \in (\lambda_e, \lambda_d) | n_{j'k'}, y_{j'k'})$, where $(j', k') = (j-1, k)$ or $(j, k-1)$.



Software

- Windows desktop program for implementing the BOIN combination design is freely available at MD Anderson Biostatistics software download website

`https://biostatistics.mdanderson.org/
softwaredownload/SingleSoftware.aspx?
Software_Id=99`

- Online app at `http://www.trialdesign.org`
- R package "BOIN" available at CRAN

BOIN Desktop Program

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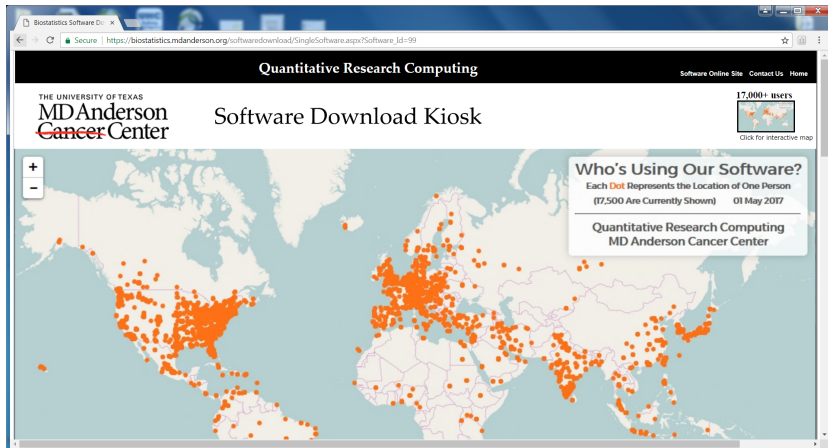
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Last Modified Date	Product Name	Brief Description
2017-06-09	BOIN Design Desktop Program	Bayesian Optimal Interval (BOIN) design for phase I trials to find the maximum tolerated dose (MTD) for both single-agent and drug-combination trials
2017-01-18	One Arm Time to Event Simulator	Design and simulate One-Arm Time-to-Event clinical trials using a Windows GUI
2017-01-13	Adaptive Randomization	Outcome-adaptive randomization for clinical trials
2016-09-14	BMA CRM	Dose-finding software using the Bayesian Model Averaging Continual Reassessment Method, including Data Augmentation
2016-06-28	UARDDET	Phase I/II dose-finding with utility-based adaptive randomization and ordinal efficacy and toxicity.
2016-04-25	CATBUS Design	Categorical Outcome Utility-Based Designs for Randomized Comparative Clinical Trials with Discrete Outcomes (formerly called "BluB Design")
2016-04-20	UZOET	Phase I/II dose-pair-finding based on utilities of 4-level ordinal efficacy and toxicity.
2015-09-23	WPM	Wavelet-based functional mixed model software
2015-02-12	Beta Binomial Distribution Demo	A learning tool to demonstrate a beta-binomial distribution prior being updated to become a posterior distribution
2014-08-27	Pinnacle	A method for detection and quantification of protein spots from 2-D gel electrophoresis images.
2014-05-22	EffTax	Phase I/II dose-finding based on efficacy and toxicity
2014-04-01	Predictive Probabilities	Predictive probability interim analysis of clinical trials
2013-11-26	Inequality Calculator	Calculate the probability of one random variable being larger than another
2013-11-22	Parameter Solver	Solve for distribution parameters for common distributions
2013-07-25	Multi Lean	Monitoring toxicity and efficacy in phase II clinical trials
2013-01-09	Bayes Factor Binary	A Bayesian hypothesis test-based method for clinical trials with single arm binary patient outcomes
2012-12-11	TTEDesignr	Software for designing single arm safety monitoring trials with time-to-event endpoints
2012-10-05	Toxicity Probability Intervals	Dose-finding based on toxicity probability intervals
2012-06-06	BlockARAND	Block adaptive randomization

BOIN Desktop Program



BOIN Desktop Program

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BOIN Design Desktop Program V1.0.4 Date Last Modified: 06/09/2017

File Name	Size	Notes
Download BOIN_V1.0.4.zip	55673 KB	Zip file containing the installer for Windows version

Email Address: Organization: Occupation:

Your email will be used to send you occasional information about software updates. It will NOT be shared with third parties.

Bayesian Optimal Interval (BOIN) Design Desktop Program

The optimal interval design is a novel Bayesian phase I clinical trial design for finding the maximum tolerated dose (MTD) for [single-agent and drug-combination trials](#). It strictly adheres to ethical considerations and optimizes the dose assignment for each patient enrolled into the trial.

Description

The software (i.e., a Windows desktop program called "BOIN") implements the Bayesian optimal interval (BOIN) designs of Liu and Yuan [1] for single-agent trials, of Lin and Yin [3] for drug-combination trials seeking a single MTD, and of Zhang and Yuan [4] for drug-combination trials seeking an MTD contour. The prominent advantage of the BOIN design is that it can be implemented in a simple way similar to the traditional 3+3 design, but yields excellent performance comparable to the more complicated model-based designs, such as the continual reassessment method (CRM). The BOIN design is motivated by the top priority and concern of clinicians, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses.

Inset image: Screenshot of the BOIN software interface showing the Bayesian Optimal Interval (BOIN) Phase I Design window.

BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862); Wersion 1.0.4 *New Input File*

File Help

Model Parameters | Simulation Run | Trial Conduct

Doses

Trial Type

Single Drug Trial

Combination Drug Trial

Drug A Drug B

Number of Doses: 3 5

Starting Dose Level: 1 1

Target Probability

Target Toxicity Probability: $\phi = 0.30$

Use the default alternatives to minimize decision errors (recommended)

Alternatives under which decision errors are minimized:

Underdosing: $\phi_1 = 0.18$ Overdosing: $\phi_2 = 0.42$

Find:

Single MTD MTD Contour

Sample Size

Maximum Sample Size: 30

Cohort Size: 1

Stop trial if # patients assigned to single dose reaches: 15

Safety

Eliminate dose j if:

$$Pr(p_j > \phi(data)) > p_E$$

Use the default cutoff (recommended). $p_E = 0.95$

Check the box to impose a more stringent safety stopping rule. Stop the trial if:

$$Pr(p_1 > \phi(data)) > p_E - \delta$$

where $\delta = 0.05$

Help

Bayesian Optimal Interval (BOIN) Phase I Design

Overview

This application is used to design single-agent or drug-combination phase I clinical trials using the BOIN design. The BOIN design is motivated by the top priority and concern of clinicians, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses. The prominent advantage of the BOIN design is that it can be implemented in a simple way similar to the traditional 3-3 design, but yields excellent performance comparable to the more complicated model-based designs, such as the continual reassessment method (CRM).

Click on the [blue labels](#) to bring up help information on each group. Click on the [background above the Help label](#) to return to this page.

You are strongly encouraged to familiarize yourself with the trial design for the type of trial and methodology you are using. Click on the link for the relevant reference below to retrieve the paper.

Single Drug Study:

[1] Liu S. and Yuan Y. (2015) [Bayesian optimal interval designs for phase I clinical trials](#). *Journal of the Royal Statistical Society: Series C*, ...

BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version 1.0.4 *New Input File*

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Find:

Single MTD MTD Contour

Sample Size

Maximum Sample Size for Subtrial

Subtrial	1	2	3
N	28	16	16

Cohort Size: 1

Stop trial if # patients assigned to single dose reaches: 15

Safety

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BOIN Desktop Program

The screenshot displays the BOIN Desktop Program interface. The window title is "Bayesian Optimal Interval (BOIN) Phase I Design (PID-862), Version 1.0.4 *New Input File*". The interface is divided into several sections:

- File Help**: Standard menu options.
- Model Parameters Simulation Run Trial Conduct**: A set of tabs for navigating between different configuration areas.
- Simulation Setup**: Includes a "Number of Repetitions" field set to 1000.
- Scenarios**: A section with control buttons: "Duplicate Selected Scenario", "Delete Selected Scenario", "Shift Scenario Up", "Add New Scenario", and "Shift Scenario Down". Below these is a table of scenarios.
- Simulation Output Help**: A section with buttons for "Simulate", "Abort", "Output Protocol Document (Word)", "Output Protocol Document (HTML)", and a link for "Simulation Output Help".

The Scenarios table contains the following data:

Scenario Name	Dose B → Dose A	Dose				
		1	2	3	4	5
Scenario 1	1	0.04	0.08	0.11	0.15	0.3
	2	0.06	0.09	0.12	0.3	0.47
	3	0.09	0.11	0.3	0.45	0.59
Scenario 2	1	0.02	0.06	0.09	0.13	0.3
	2	0.07	0.1	0.12	0.3	0.45
	3	0.12	0.3	0.45	0.51	0.57
Scenario 3	1	0.05	0.08	0.11	0.14	0.3
	2	0.1	0.11	0.3	0.47	0.52
	3	0.14	0.3	0.45	0.5	0.55
Scenario 4	1	0.01	0.04	0.08	0.11	0.3
	2	0.14	0.3	0.45	0.49	0.53
	3	0.3	0.46	0.5	0.54	0.58

BOIN Desktop Program

The screenshot displays the BOIN Desktop Program interface. The main window is titled "Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version 1.0.4 *New Input File*". The interface is divided into several sections:

- Simulation Setup:** Includes a "Number of Repetitions" field set to 1000.
- Scenarios:** A table with columns for Scenario Name, Dose B (Dose A), and five dose levels (1-5). Scenarios 1-4 are listed with their respective dose values.
- Simulation Output:** Contains buttons for "Simulate", "Abort", "Output Protocol Document (Word)", "Output Protocol Document (HTML)", and "Simulation Output Help".
- BOIN Simulation Report:** Displays the version and date: "Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version: 1.0.4 Thursday, June 22, 2017 9:16:13 PM (GMT -05:00:00)".
- Trial and Model Specifications:** A table listing parameters and their values.
- Operating Characteristics:** A section for further specifications.

Scenario Name	Dose B (Dose A)	1	2	3	4	5
Scenario 1	1	0.04	0.08	0.11	0.15	0.3
	2	0.06	0.09	0.12	0.3	0.47
	3	0.09	0.11	0.3	0.45	0.59
Scenario 2	1	0.02	0.06	0.09	0.13	0.3
	2	0.07	0.1	0.12	0.3	0.45
	3	0.12	0.3	0.45	0.51	0.57
Scenario 3	1	0.05	0.08	0.11	0.14	0.3
	2	0.1	0.11	0.3	0.47	0.52
	3	0.14	0.3	0.45	0.5	0.55
Scenario 4	1	0.01	0.04	0.08	0.11	0.3
	2	0.14	0.3	0.45	0.49	0.53
	3	0.3	0.46	0.5	0.54	0.58

Parameter	Value
Number of Doses - Drug A	3
Starting Dose - Drug A	1
Number of Doses - Drug B	5
Starting Dose - Drug B	1
Max sample size	30
Cohort size	1
Stop trial if # patients assigned to single dose reaches	15
Target Toxicity Probability	0.3
Acceptable Toxicity - Upper Bound	0.42
Acceptable Toxicity - Lower Bound	0.18
Eliminate Dose Threshold (pE)	0.95
Number of Repetitions	1000

BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862), Version 1.0.4 *New Input File*

File Help

Model Parameters Simulation Run Trial Conduct

Simulation Setup

Number of Repetitions: 1000

Scenarios

Duplicate Selected Scenario Delete Selected Scenario Shift Scenario Up

Add New Scenario Shift Scenario Down

Scenario Name	Dose B → Dose A	Dose Level of Drug A				
		1	2	3	4	5
Scenario 1	1	0.04	0.08	0.11	0.15	0.3
	2	0.06	0.09	0.12	0.3	0.47
	3	0.09	0.11	0.3	0.45	0.59
Scenario 2	1	0.02	0.06	0.09	0.13	0.3
	2	0.07	0.1	0.12	0.3	0.45
	3	0.12	0.3	0.45	0.51	0.57
Scenario 3	1	0.05	0.08	0.11	0.14	0.3
	2	0.1	0.11	0.3	0.47	0.52
	3	0.14	0.3	0.45	0.5	0.55
Scenario 4	1	0.01	0.04	0.08	0.11	0.3
	2	0.14	0.3	0.45	0.49	0.53
	3	0.3	0.45	0.5	0.54	0.58

Simulation Output Help

Simulate Abort Output Protocol Document (Word) Output Protocol Document (HTML) Simulation Output Help

Operating Characteristics

Scenario 1

	Dose Level of Drug B														
	True DLT Rate					Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
1 [†]	0.04	0.08	0.11	0.15	0.30	0.0	0.4	0.9	3.3	6.7	1.3	0.7	0.5	0.8	0.9
2 [†]	0.06	0.09	0.12	0.30	0.47	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7
3 [†]	0.09	0.11	0.30	0.45	0.59	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2

† Dose Level of Drug A

Average Number of Patients: 28.7
 Selection Percentage of MTD: 55.7
 Percentage of Patients Treated at MTD: 33.4
 Percentage of Early Stopping Due to Toxicity: 0.0

Scenario 2

	Dose Level of Drug B														
	True DLT Rate					Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
1	0.02	0.06	0.09	0.13	0.3	0.0	0.4	0.9	3.3	6.7	1.3	0.7	0.5	0.8	0.9
2	0.07	0.1	0.12	0.3	0.45	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7
3	0.12	0.3	0.45	0.51	0.57	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2

BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862), Version 1.0.4 *New Input File*

File Help

Model Parameters Simulation Run Trial Conduct

Simulation Setup

Number of Repetitions: 1000

Scenarios

Duplicate Selected Scenario Delete Selected Scenario Shift Scenario Up

Add New Scenario Shift Scenario Down

Scenario Name	Dose B → Dose A	Dose Level of Drug A				
		1	2	3	4	5
Scenario 1	1	0.04	0.08	0.11	0.15	0.3
	2	0.06	0.09	0.12	0.3	0.47
	3	0.09	0.11	0.3	0.45	0.59
Scenario 2	1	0.02	0.06	0.09	0.13	0.3
	2	0.07	0.1	0.12	0.3	0.45
	3	0.12	0.3	0.45	0.51	0.57
Scenario 3	1	0.05	0.08	0.11	0.14	0.3
	2	0.1	0.11	0.3	0.47	0.52
	3	0.14	0.3	0.45	0.5	0.55
Scenario 4	1	0.01	0.04	0.08	0.11	0.3
	2	0.14	0.3	0.45	0.49	0.53
	3	0.3	0.46	0.5	0.54	0.58

Simulation Output Help

Simulate Abort Output Protocol Document (Word) Output Protocol Document (HTML) Simulation Output Help

Operating Characteristics

Scenario 1

	Dose Level of Drug B														
	True DLT Rate					Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
1 [†]	0.04	0.08	0.11	0.15	0.30	0.0	0.4	0.9	3.3	6.7	1.3	0.7	0.5	0.8	0.9
2 [†]	0.06	0.09	0.12	0.30	0.47	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7
3 [†]	0.09	0.11	0.30	0.45	0.59	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2

† Dose Level of Drug A

Average Number of Patients: 28.7
Selection Percentage of MTD: 55.7
Percentage of Patients Treated at MTD: 33.4
Percentage of Early Stopping Due to Toxicity: 0.0

Scenario 2

	Dose Level of Drug B														
	True DLT Rate					Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
...

BOIN Desktop Program

The screenshot shows the BOIN Desktop Program interface. A "Save data file as..." dialog box is open, showing the file path "System (C) > Users > SYLiu > My Documents > BOIN (PID-862)". The file name is "Protocol Document" and the save as type is "Protocol Document files (*.doc)".

The main application window displays the "Operating Characteristics" section, which includes a table for "Dose Level of Drug B" and "Dose Level of Drug A".

Operating Characteristics

Dose Level of Drug B

DLT Rate	Selection %					# Pts Treated							
	3	4	5	1	2	3	4	5	1	2	3	4	5
0.11	0.15	0.30	0.0	0.4	0.9	3.3	6.7	1.3	0.7	0.5	0.8	0.9	
0.12	0.30	0.47	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7	
0.30	0.45	0.59	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2	

Drug A

of Patients: 28.7

Stage of MTD: 55.7

Patients Treated at MTD: 33.4

Percentage of Early Stopping Due to Toxicity: 0.0

Scenario 2

Dose Level of Drug B

True DLT Rate	Selection %					# Pts Treated							
	1	2	3	4	5	1	2	3	4	5			
...

BOIN Desktop Program

Template for Drug-Combination Protocol Preparation

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Lin and Yin, 2015) to find the MTD. The BOIN design is a novel Bayesian dose-finding method that optimizes patient treatment ethics by minimizing the chance of exposing patients to sub-therapeutic and overly toxic doses. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs. This trial was designed and will be conducted using the BOIN Design Desktop Program v1.0.4 (Venier et al., 2017).

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 1. Let (j, k) denote the combination of j th dose level of agent A and k th dose level of agent B. The trial design is illustrated in Figure 1 and described as follows:

1. Patients in the first cohort are treated at the lowest dose combination $(1, 1)$.
2. Suppose that the current dose is (j, k) . To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 1, which minimizes the probability of incorrect dose assignment with $\phi_1 = 0.18$ and $\phi_2 = 0.42$ designated as the underdosing and overdosing toxicity rates, respectively. Please note the following concerning this table:
 - a. "Eliminate" means the current and higher doses, i.e., the dose set $\{(j^*, k^*); j^* \geq j \text{ and } k^* \geq k\}$, are eliminated from the trial to prevent treating any future patients at these doses because they are overly toxic.
 - b. When a dose is eliminated, the dose is automatically de-escalated as described below. When the lowest dose $(1, 1)$ is eliminated, the trial is stopped for safety. In

BOIN Desktop Program

ProtocolDocument - Microsoft Word

Table Tools

File Home Insert Page Layout References Mailings Review View Design Layout

Print Layout Full Screen Reading Web Layout Outline Draft Ruler Gridlines Navigation Pane Document Views Show Zoom 100% Zoom One Page Two Pages Page Width New Window Arrange All Split View Side by Side Synchronous Scrolling Reset Window Position Window Switch Windows Macros

Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions	The number of patients treated at the current dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if # of DLT \leq	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3
De-escalate if # of DLT \geq	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if # of DLT \geq	NA	NA	3	3	4	4	5	5	5	6	6	7	7	8	8

Start at the prespecified starting dose.

Treat a patient or a cohort of patients

Reach the maximum sample size?

Yes: Stop the trial and select the MTD.

No: Compute the DLT rate* at the current dose.

DLT rate* ≤ 0.236 : Escalate to the next dose.

DLT rate* ≥ 0.359 : De-escalate to the previous dose.

DLT rate* Within (0.236, 0.359): Continue at the current dose.

```

graph TD
    Start([Start at the prespecified starting dose]) --> Treat[Treat a patient or a cohort of patients]
    Treat --> Reach{Reach the maximum sample size?}
    Reach -- Yes --> Stop([Stop the trial and select the MTD.])
    Reach -- No --> Compute{Compute the DLT rate* at the current dose.}
    Compute -- "≤ 0.236" --> Treat
    Compute -- "≥ 0.359" --> Treat
    Compute -- "Within (0.236, 0.359)" --> Treat
  
```

BOIN Desktop Program

The elimination boundaries in Table 1 will be used for toxicity monitoring.

Operating characteristics

Table 2 shows the operating characteristics of the proposed design for this trial with 5 scenarios involving various numbers and locations for the MTDs. These operating characteristics are based on 1000 simulations of the trial using the BOIN Design Desktop Program (Venier et al., 2017). The operating characteristics show that the design selects one of the true MTD(s), if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3.

Table 2. Operating Characteristics of the BOIN design

Scenario 1

	True DLT Rate					Dose Level of Drug B Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
	1 [†]	0.04	0.08	0.11	0.15	0.30	0.0	0.4	0.9	3.3	6.7	1.3	0.7	0.5	0.8
2 [†]	0.06	0.09	0.12	0.30	0.47	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7
3 [†]	0.09	0.11	0.30	0.45	0.59	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2

[†] Dose Level of Drug A

Average Number of Patients: 28.7
Selection Percentage of MTD: 55.7
Percentage of Patients Treated at MTD: 33.4
Percentage of Early Stopping Due to Toxicity: 0.0

Scenario 2

Dose Level of Drug B

BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) - Wersion 1.0.4 - *New Input File*

File Help

Model Parameters Simulation Run Trial Conduct

Patients

Patient ID	Cohort	Dose Level of A	Dose Level of B	Toxicity Outcome	Treatment Date [Decision Date]	Outcome Date or Date Updated	Show Decision

Get Decision
(Add Patient or View the MTD)

Edit Selected Patient

Delete Last Patient

Delete ALL Patients

Help

Combination Trial Conduct

To get a dose decision and add patients to the trial, click the **Get Decision (Add Patient or View the MTD)** button. The Get Decision dialog box will appear giving the trial status (go, wait, ...) and the dose that will be assigned to the new patient along with data used to determine the dose. If the status is Go, you can then add the patient to the trial by clicking the **Add Patient** button to bring up the Patient form. Enter the Patient ID, Outcome Date, and Toxicity Outcome (toxicity, no toxicity, pending) and click **OK** to enter the patient row in the table.

To edit a patient's data after entry, right-click on the row you want to edit and click on the **Edit Selected Patient...** entry on the context menu to bring up the patient dialog box for the selected patient. The context menu can also be used to get a trial conduct decision (and add a patient or view the MTD), or delete patients. Editing the selected patient and deleting patients can also be accomplished by clicking the corresponding buttons below the patient table.

To review the decision details for a specific patient, click on the Show Decision button for that patient. The values shown in the decision dialog reflect the current information in the table that

BOIN Desktop Program

The screenshot shows the BOIN Desktop Program interface. The main window is titled "Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.4: *New Input File*". It has a menu bar with "File" and "Help", and a tabbed interface with "Model Parameters", "Simulation Run", and "Trial Conduct". The "Simulation Run" tab is active, showing a "Patients" table with columns for Patient ID, Cohort, Dose Level of A, and Date of Assessment. A "Get Decision" button is visible at the bottom left, with a sub-label "(Add Patient or View the MTD)".

An "Add New Patient" dialog box is open in the foreground. It contains the following fields and options:

- Patient ID: 1
- Cohort: 1
- Dose Level A: 1
- Dose Level B: 1
- Treatment Date: 6/22/2017
- Outcome Date: 6/22/2017
- Toxicity Outcome: pending

Below the fields, there is a note: "This is the date the outcome was observed (or the date of the last time the patient was assessed for toxicity, if the outcome is pending)." At the bottom of the dialog are "OK" and "Cancel" buttons. The status bar at the bottom of the dialog says "Input Validating Status All the data are valid".

On the right side of the screenshot, there is a yellow sticky note with the following text:

Combination Trial Conduct

and add patients to the trial, click the **Get Patient or View the MTD** button. The Get will appear giving the trial status (go, wait, will be assigned to the new patient along determine the dose. If the status is Go, you can to the trial by clicking the **Add Patient** the Patient form. Enter the Patient ID, Toxicity Outcome (toxicity, no toxicity, to enter the patient row in the table.

After entry, right-click on the row you on the **Edit Selected Patient...** entry on bring up the patient dialog box for the context menu can also be used to get a trial add a patient or view the MTD), or delete selected patient and deleting patients can by clicking the corresponding buttons

For details for a specific patient, click on the for that patient. The values shown in the the current information in the table that

BOIN Desktop Program

The screenshot displays the BOIN Desktop Program interface. The main window has a menu bar (File, Help) and three tabs: Model Parameters, Simulation Run, and Trial Conduct. The 'Trial Conduct' tab is active, showing a 'Patients' table with the following data:

Patient ID	Cohort	Dose Level of A	Dose Level of B	Toxicity Outcome	Treatment Date [Decision Date]	Outcome Date or Date Updated	Show Decision
1	1	1	1	no toxicity	6/22/2017	6/22/2017	Patient ID 1

Below the table are four buttons: 'Get Decision (Add Patient or View the MTD)', 'Edit Selected Patient', 'Delete Last Patient', and 'Delete ALL Patients'.

A 'Help' window is open on the right, titled 'Combination Trial Conduct'. It contains the following text:

Combination Trial Conduct

To get a dose decision and add patients to the trial, click the **Get Decision (Add Patient or View the MTD)** button. The Get Decision dialog box will appear giving the trial status (go, wait, ...) and the dose that will be assigned to the new patient along with data used to determine the dose. If the status is Go, you can then add the patient to the trial by clicking the **Add Patient** button to bring up the Patient form. Enter the Patient ID, Outcome Date, and Toxicity Outcome (toxicity, no toxicity, pending) and click **OK** to enter the patient row in the table.

To edit a patient's data after entry, right-click on the row you want to edit and click on the **Edit Selected Patient...** entry on the context menu to bring up the patient dialog box for the selected patient. The context menu can also be used to get a trial conduct decision (and add a patient or view the MTD), or delete patients. Editing the selected patient and deleting patients can also be accomplished by clicking the corresponding buttons below the patient table.

To review the decision details for a specific patient, click on the Show Decision button for that patient. The values shown in the decision dialog reflect the current information in the table that

BOIN Desktop Program

Bayesian Optimal Interval

Get Decision: Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.4

This decision was made as if the date is: 6/22/2017

Status: GO

The trial should continue and a new patient may be treated at dose level (A, B) of (1, 2).

Details:

The recommended dose combination for the next cohort of patients is (1 , 2)

The number of patients treated at the current dose = 1
 The number of patients experiencing a DLT at the current dose = 0
 Dose escalation boundary: escalate if DLT \leq 0
 Dose de-escalation boundary: de-escalate if DLT $>$ 1

Date for the Decision: 6/22/2017

Add Patient Cancel

BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.4: *New Input File*

File Help

Model Parameters Simulation Run Trial Conduct

Patients

Patient ID	Cohort	Dose Level of A	Dose Level of B
1	1	1	1

Get Decision
(Add Patient or View the MTD)

Edit Selected Patient

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.4: Add New Patient

Patient ID: 2

Cohort: 2

Dose Level A: 1

Dose Level B: 2

Treatment Date: 6/22/2017

Outcome Date: 6/22/2017

This is the date the outcome was observed (or the date of the last time the patient was assessed for toxicity, if the outcome is pending).

Toxicity Outcome: no toxicity

Input Validating Status
All the data are valid

OK Cancel

Combination Trial Conduct

and add patients to the trial, click the **Get Patient or View the MTD** button. The Get Patient or View the MTD button will appear giving the trial status (go, wait, no go). If the status is Go, you can add a patient to the trial by clicking the **Add Patient** button. Enter the Patient ID, Cohort, Dose Level A, Dose Level B, Treatment Date, Outcome Date, and Toxicity Outcome (toxicity, no toxicity, or pending) to enter the patient row in the table.

After entry, right-click on the row you want to edit. The **Edit Selected Patient...** entry on the context menu can also be used to get a trial status, add a patient or view the MTD, or delete a patient and deleting patients can be done by clicking the corresponding buttons.

For details for a specific patient, click on the **Edit Selected Patient...** entry for that patient. The values shown in the table are the current information in the table that

BOIN Desktop Program

Bayesian Optimal Interval

Get Decision: Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.4

This decision was made as if the date is: 6/22/2017

Status: GO

The trial should continue and a new patient may be treated at dose level (A, B) of (2, 2).

Details:

The recommended dose combination for the next cohort of patients is (2 , 2)

The number of patients treated at the current dose = 1
 The number of patients experiencing a DLT at the current dose = 0
 Dose escalation boundary: escalate if DLT <= 0
 Dose de-escalation boundary: de-escalate if DLT >= 1

Date for the Decision: 6/22/2017

Add Patient Cancel

Bayesian Optimal Interval

File Help

Model Parameters Simulation

Patients

Patient ID
1
2

Get Decision
 Add Patient
 View the MT

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BOIN Desktop Program

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version 1.0.4 *New Input File*

File Help

Model Parameters Simulation Run Trial Conduct

Patients

Patient ID	Cohort	Dose Level of A	Dose Level of B	Toxicity Outcome	Treatment Date [Decision Date]	Outcome Date or Date Updated	Show Decision
1	1	1	1	no toxicity	6/22/2017	6/22/2017	Patient ID 1
2	2	1	2	no toxicity	6/22/2017	6/22/2017	Patient ID 2
3	3	2	2	pending	6/22/2017	6/22/2017	Patient ID 3

Get Decision
(Add Patient or View the MTD)

Edit Selected Patient

Delete Last Patient

Delete ALL Patients

Help

Combination Trial Conduct

To get a dose decision and add patients to the trial, click the **Get Decision (Add Patient or View the MTD)** button. The Get Decision dialog box will appear giving the trial status (go, wait, ...) and the dose that will be assigned to the new patient along with data used to determine the dose. If the status is Go, you can then add the patient to the trial by clicking the **Add Patient** button to bring up the Patient form. Enter the Patient ID, Outcome Date, and Toxicity Outcome (toxicity, no toxicity, pending) and click **OK** to enter the patient row in the table.

To edit a patient's data after entry, right-click on the row you want to edit and click on the **Edit Selected Patient...** entry on the context menu to bring up the patient dialog box for the selected patient. The context menu can also be used to get a trial conduct decision (and add a patient or view the MTD), or delete patients. Editing the selected patient and deleting patients can also be accomplished by clicking the corresponding buttons below the patient table.

To review the decision details for a specific patient, click on the Show Decision button for that patient. The values shown in the decision dialog reflect the current information in the table that

Online app

<http://www.trialdesign.org>

An integrated platform for designing clinical trials

Online app

The screenshot displays the trialdesign.org website interface. At the top, there is a navigation bar with links for Home, About Us, and Contact Us. Below this is a banner image with the text "An integrated platform for designing trials®". The main content area is divided into four sections, each with a colored header and several tool cards:

- Sample Size Calculation (Green Header):**
 - Binary Outcome
 - Continuous Outcome
 - Time to Event Outcome
- Phase I Trial Designs (Red Header):**
 - BOIN for Single Agent
 - BOIN for Drug Combination
 - CRM & BMA-CRM
 - Keyboard Design
- Phase II Trial Designs (Light Blue Header):**
 - Simon's Two Stage Design
 - Bayesian Optimal Phase 2 (BOP2) Design
 - Bayesian Efficacy Monitoring with Predictive Probability
- Phase I-II Trial Designs (Dark Blue Header):**
 - Find Optimal Biological Dose for Immunotherapy

At the bottom right of the browser window, there are navigation icons for back, forward, and search.

Online app

The screenshot shows a web browser window displaying the BOIN application. The browser's address bar shows 'bi.indianer.org'. The page header includes the MD Anderson Cancer Center logo and the title 'Bayesian Optimal Interval Design (BOIN) for Drug Combination Trials' by Yanhong Zhou, Suyu Liu, and Ying Yuan, from the Department of Biostatistics, MD Anderson Cancer Center.

The application interface features a navigation menu with tabs: 'Trial Setting', 'Simulation', 'Trial Protocol', 'Next Dose/Subtrial', and 'Select MTD'. The 'Trial Setting' tab is active, showing a section titled 'How to Use the BOIN App for Combination Trial?' with two sub-sections: 'Design Flow Chart' and 'Decision Table'.

The 'Doses' section contains the following settings:

- Number of Doses: Drug A: 3, Drug B: 5
- Starting Dose Level: Drug A: 1, Drug B: 1

The 'Target Probability' section contains the following settings:

- Target toxicity probability ϕ : 0.3
- Use the default alternatives to minimize decision error (recommended).
- Find: Single MTD, MTD Contour

The 'Sample Size' section contains the following settings:

- Number of cohorts: 10
- Cohort size: 3
- Stop trial if the # of patients assigned to the current dose reaches: 15

At the bottom right of the browser window, there are navigation icons for back, forward, and search.

Summary

- The BOIN drug-combination design provides a simple, robust, well-performing approach to find a MTD
- The BOIN design can also be used to find the MTD contour (Zhang and Yuan, 2016)
- Easy-to-use software is freely available to implement the BOIN combination designs
- The R package "BOIN" can also be used to design seamless phase I-II combination trials

References

- Yuan, Y. and Zhang, L. (2017) Designing Early-Phase Drug Combination Trials. *Handbook of Methods for Designing, Monitoring, and Analyzing Dose Finding Trials*, edited by O'Quigley J., Iasonos, A and Bornkamp, B., Chapter 6, p109-p126.
- Yuan, Y., Hess, K., Hilsenbeck, S. and Gilbert M. (2016) Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials *Clinical Cancer Research*, 22, 4291-430.
- Lin R. and Yin G. (2016) Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, *Statistical Methods in Medical Research*, in press
- Zhang, L. and Yuan, Y. (2016) A Practical Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials. *Statistics in Medicine*, 35, 4924-4936.
- Yuan, Y. and Yin, G. (2011) Bayesian phase I/II drug-combination trial design in oncology. *Annals of Applied Statistics*, 5, 924-942.

Thank you !

Backup slides

Finding the MTD contour

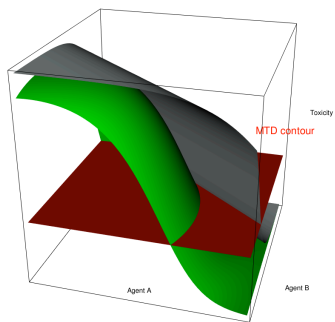
- Finding the MTD contour (or multiple MTDs) is of intrinsic interest to many combination trials.
 - There are multiple MTDs in the dose matrix. Hard to justify a single one as the target.
 - Finding multiple MTDs provides us an opportunity to find the optimal synergistic treatment effect, e.g., identify the MTD with the highest synergistic treatment effect in subsequent phase II trials.

Finding the MTD contour is more challenging

- Much more challenging than finding a single MTD.
- In order to find all MTDs in the dose matrix, we must explore the whole dose matrix using a limited sample size; otherwise, we risk missing some MTDs
- More susceptible to model misspecification

Robustness is an issue

- To find the MTD contour, we must estimate the whole MTD contour correctly.
- In contrast, to find a single MTD, a good local fit to a MTD is adequate.



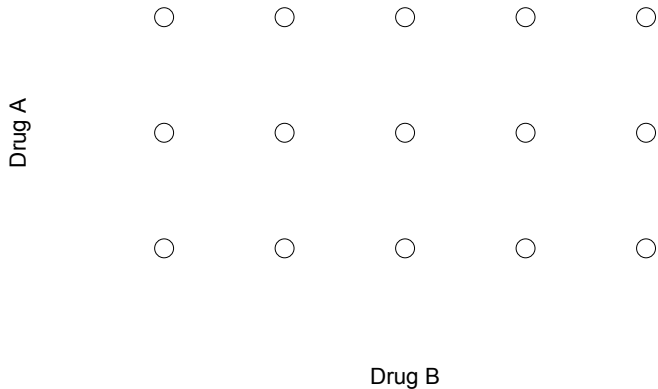
Finding the MTD contour

- Several designs have been proposed to find the MTD contour (e.g., Thall et al. 2003, Yuan and Yin, 2009; Mander and Sweeting, 2015; Zhang and Yuan, 2016).
- We focus on the waterfall design (Zhang and Yuan, 2016), which is well-performing and easy to implement in practice.

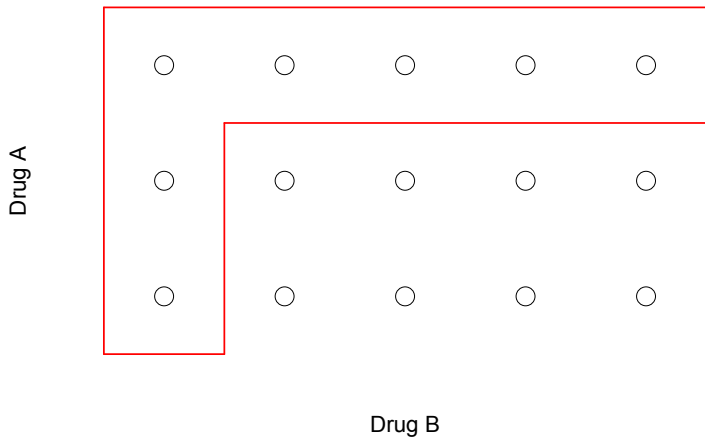
Divide and conquer

- Waterfall design takes the divide and conquer strategy (Yuan and Yin, 2008)
- Partition the dose matrix into a series of blocks (i.e., groups of doses), within which the doses are fully ordered, and then find the MTD within each block.
- Each block is called a “subtrial”
- We conduct each subtrial using the BOIN design

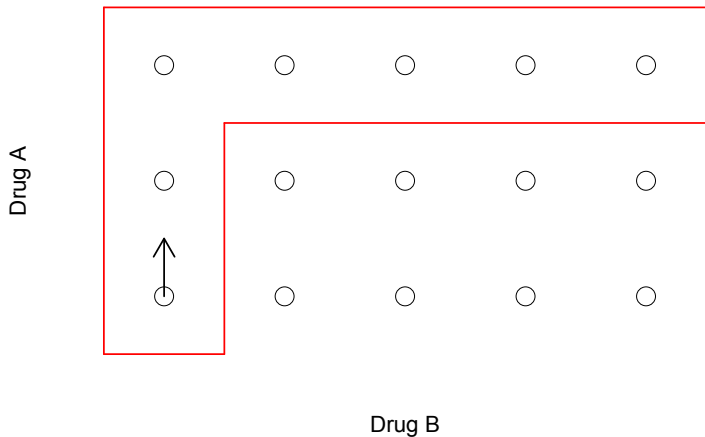
Waterfall design



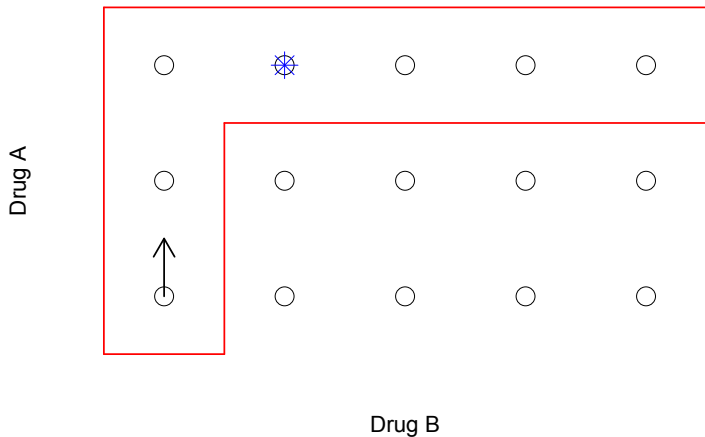
Waterfall design



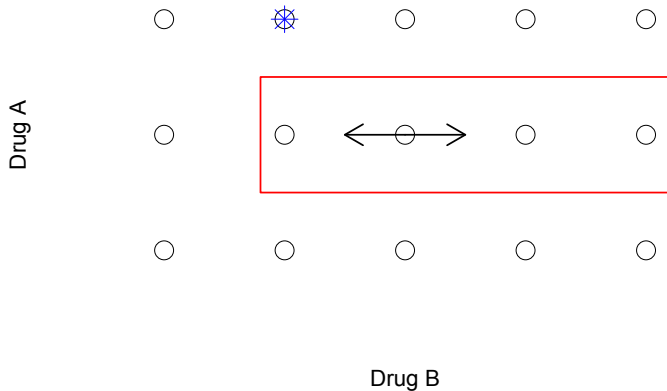
Waterfall design



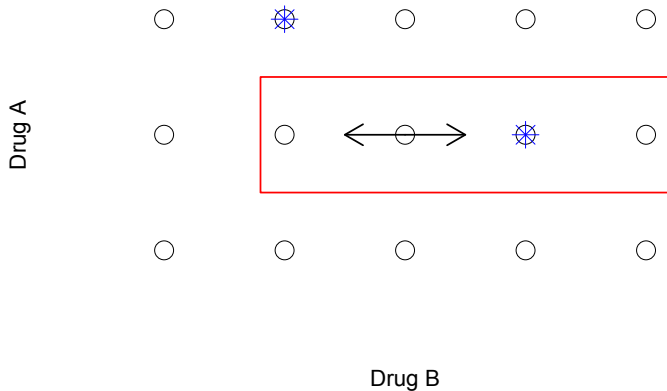
Waterfall design



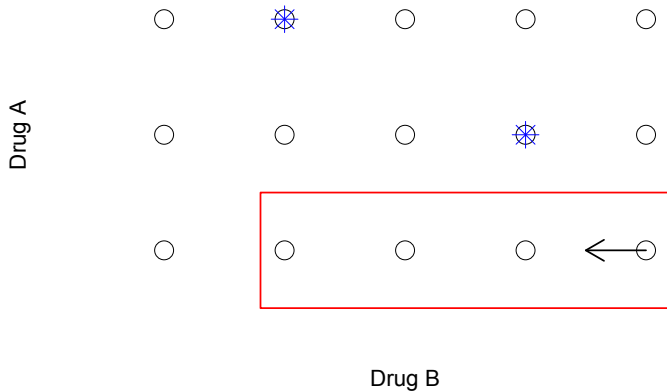
Waterfall design



Waterfall design



Waterfall design



Waterfall design

