Nature-Inspired Meta-Heuristic Algorithms for Constructing Efficient Designs for Clinical Trials

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Optimizing Dose Selection Across the Clinical Trials Spectrum

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Outline

- 1 Preamble/Motivation
- 2 Nature-inspired Metaheurstic Algorithms
- 3 Sample Applications to Find Efficient Designs for Clinical Trials:
  - 3.1 Extended Simon Two-stage response-adaptive designs for Phase II trials;
  - 3.2 Dose-finding adaptive optimal designs for the continuation-ratio (CR) models;
  - 3.3 Preliminary applications to enhance flexibility of Bayesian Optimal Phase 2 Designs (BOP2).
- 4 Summary

1 Motivation

- Model-based designs seem to be increasingly helpful and used for more precise statistical inference at minimal cost

  Reference:

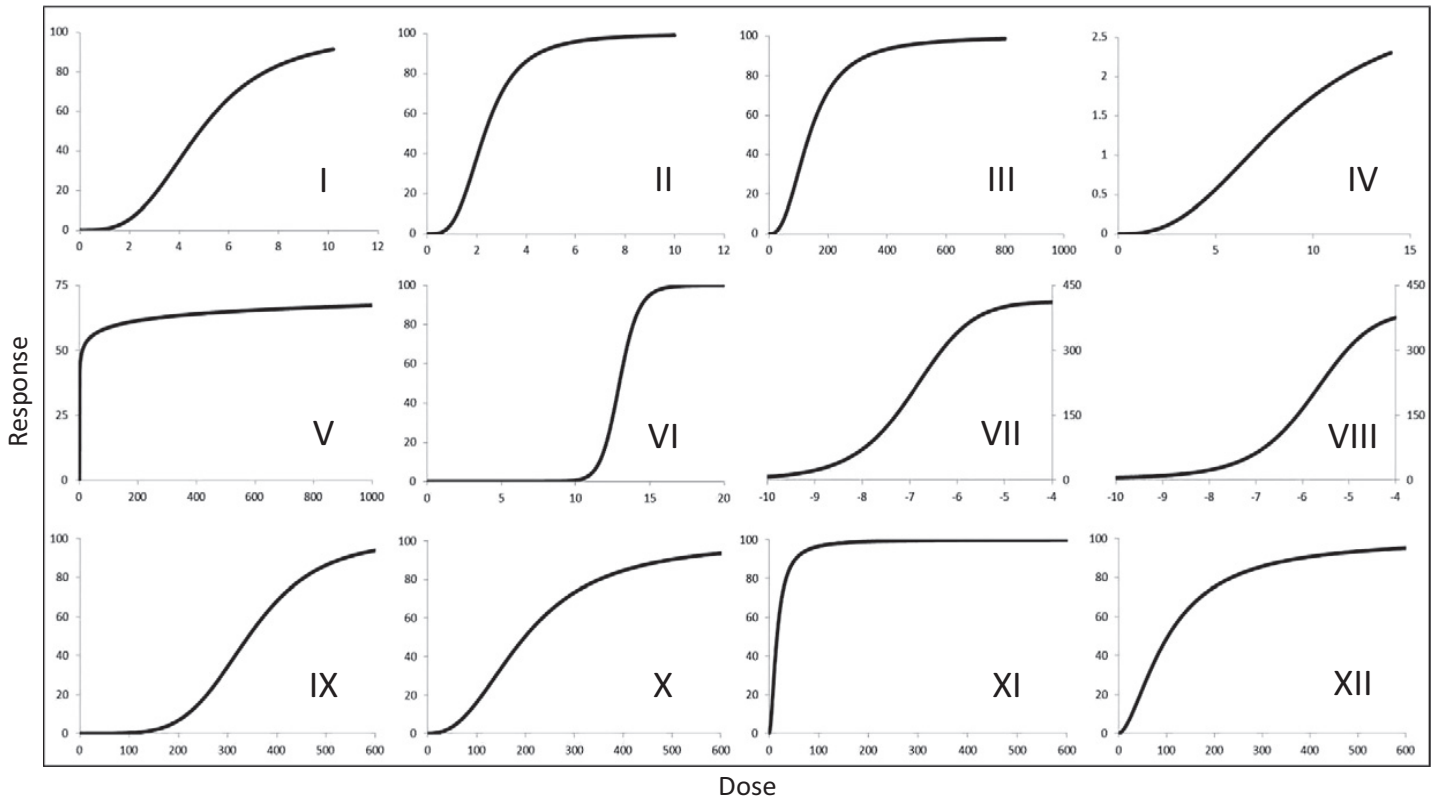
  Love, et al. (2017) Embracing model-based designs for dose-finding trials. British Journal Cancer.

  Pierrillas, P. B. (2018). Model-Based Adaptive Optimal Design (MBAOD) Improves Combination Dose Finding Designs: an Example in Oncology. The AAPS Journal.

  Yuan, Y., el at. (2019). Model-Assisted Designs for Early-Phase Clinical Trials: Simplicity Meets Superiority. Journal of Clinical Oncology, Precision Oncology.

- Given a regression model on a design interval X and a design criterion, find a design that optimizes the criterion (or criteria with possibly unequal interest in them).

1.1 Shapes of a continuous response (in toxicology)



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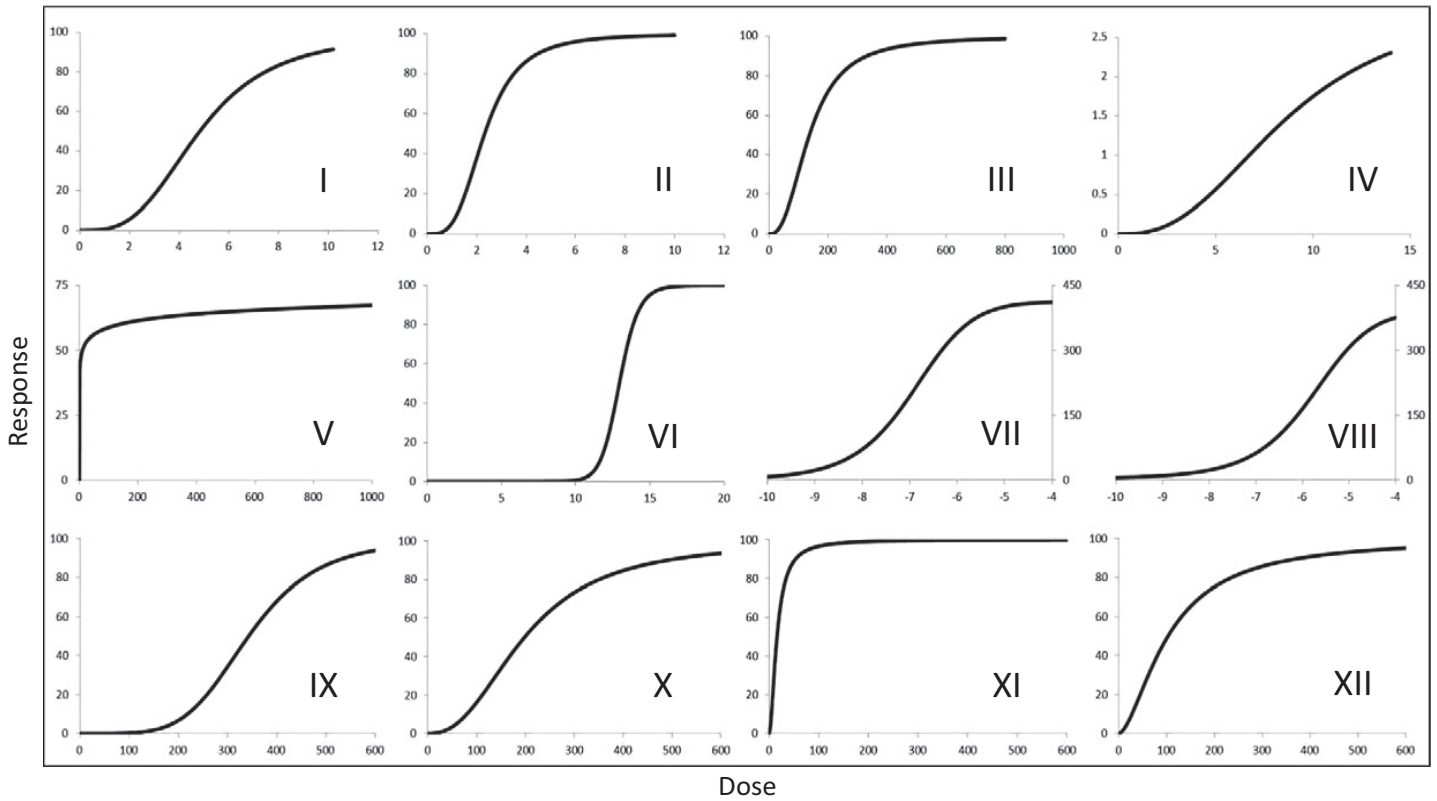

- Reference: Gadagkar, S. R. and Call, G. B. (2015). Computational tools from fitting the Hill equation to dose-response curves Journal of Pharmacological and Toxicologoical Methods.

1.2 Two Types of Optimal Designs

For a given regression model and a design criterion, determine

- Exact optimal designs: If N is a pre-selected sample size, find optimal number of doses (k), where the optimal doses are $(x_i's)$ and the optimal number of subjects $(n_i's)$ to assign at each x_i such that $n_1 + n_2 + \ldots + n_k = N$.
- Continuous optimal designs (Kiefer, 1959-1980): Determine the optimal number (k) of doses required, where these optimal doses $(x_i's)$ are and the optimal proportion of subjects $(p_i's)$ to assign to each x_i such that $p_1 + p_2 + \ldots + p_k = 1$.
- Continuous designs assume sample size is large. When the design criterion is a convex function of the information matrix, the design problem is a convex optimization problem and convex analysis results can be used to **find and confirm** optimality of a continuous design via an equivalence theorem.
- No unified theory for finding optimal exact designs. They are much more difficult to find and are especially useful when the sample size is small.

1.3 Locally D-optimal Designs for the Logistic Model on $X = [-1, 1]$ (Result from a PhD thesis,1976)

$$log\ \frac{\pi(x)}{1-\pi(x)} = \theta_1 + \theta_2 x, \quad \theta^T = (\theta_1, \theta_2), \quad \theta_1 > 0 \ \ \& \ \ \theta_2 > 0.$$

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- Let a solve $exp(z) = (z+1)/(z-1)$ and let u^* solve

$$exp(\theta_1 + \theta_2 u) = \frac{2 + (u+1)\theta_2}{-2 + (u+1)\theta_2}.$$

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condition	locally D-optimal design
$\{\theta : \theta_2 - \theta_1 \geq a\}$	$\{\frac{a-\theta_1}{\theta_2}, \frac{-a-\theta_1}{\theta_2}; \frac{1}{2}, \frac{1}{2}\}$
$\{\theta : \theta_2 - \theta_1 < a, exp(\theta_1+\theta_2) \leq \frac{\theta_2+1}{\theta_2-1}\}$	$\{-1, u^*; \frac{1}{2}, \frac{1}{2}\}$
$\{\theta : exp(\theta_1+\theta_2) > \frac{\theta_2+1}{\theta_2-1}\}$	$\{-1, 1; \frac{1}{2}, \frac{1}{2}\}$

1.4 Need for Efficient Algorithms

- Derivation of optimal designs for nonlinear models is usually tedious, difficult and method for one model invariably does not generalize to another;
- Formulae for optimal designs rarely exist and if they do, they are complicated and frequently unhelpful to the practitioners;
- Algorithms are very helpful - available only for finding some types of optimal designs;
- Criteria of good algorithms: Proof of convergence, speed, ease of use and availability of software/codes;
- Is there an easy-to-use and efficient method for finding optimal designs for different types of optimal designs for different types of models including those with multiple interacting factors?

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- Is there an easy-to-use and efficient method for finding optimal designs for different types of optimal designs for different types of models including those with multiple interacting factors?
- Are there effective general purpose optimization tools for solving any type of optimization problems without requiring technical assumptions???

2 Meta-heuristic Algorithms

From Wikipedia, the free encyclopedia: Meta-heuristic

In computer science, meta-heuristic designates a computational method that optimizes a problem by iteratively trying to improve a candidate solution with regard to a given measure of quality. Meta-heuristics make few or no assumptions about the problem being optimized and can search very large spaces of candidate solutions. However, meta-heuristics do not guarantee an optimal solution is ever found. Many have stochastic components in them (to get the algorithm out of a local optimum) and they have tuning parameters (that user may have to input);

- Perhaps Simulated Annealing and Genetic Algorithms are most familiar to statisticians, but there are many others;
- Generally, they seem relatively under-utilized in statistical research.

2.0 Our interest is nature-inspired meta-heuristic algorithms

Particle swarm optimization: Origins

How can birds or fish exhibit such a coordinated collective behavior?

2.1 Some Applications of PSO proposed by Eberhard and Kennedy (IEEE, 1995)

- artificial neural network training
- K-means cluster analysis mathematical finance
- social networks
- data mining
- foraging techniques
- intrusion detection
- resources allocation problems
- course+exam scheduling in real time
- designing ideotypes for sustainable product systems in genetics
- prediction of stock market indices using hybrid genetic algorithm and PSO with a perturbed term
- bioinformatics
- reactive power and voltage control in electric power systems
- COVID19 prevention and control, monitoring and prediction

2.2 Main Features of meta-heuristics:

- Random generation of an initial population
- Each particle has a fitness value (design criterion value or objective function value);
- The population moves or reproduces itself based on their fitness values; the former is swarm based and the latter is evolutionary;
- An exemplary swarmed based algorithm is Particle Swarm Optimization (PSO) and an exemplary evolutionary algorithm is Differential Evolution (DE). Both are very widely used.
- If requirements are met, stop; otherwise each particle updates its fitness value and iteratively searches for the optimum;
- They are general purpose optimization algorithms,virtually assumptions free, and they search by exploring and exploiting the domain based on animal instincts or behavior.

2.3 Basic Equations and Tuning Parameters in PSO

$$v_{i+1} = \omega_i v_i + c_1 \beta_1 (p_i - x_i) + c_2 \beta_2 (p_g - x_i), \quad (1)$$

$$x_{i+1} = x_i + v_i. \quad (2)$$

- x_i and v_i: position and velocity for the i^{th} particle β_1 and β_2: random vectors
- ω_i: inertia weight that modulates the influence of the former velocity
- c_1 and c_2: cognitive learning parameter and social learning parameter
- p_i and p_g: Best position for the i^{th} particle (local optimal) and for all particles (global optimal)

2.4 Standardized Maximin D-optimal Designs

Let Θ be a user-specified set of all plausible values of θ. The standardized maximin D-optimal design ξ^*_{SM} maximizes the minimal D-efficiency among all subsets θ of Θ, i.e.,

$$\xi^*_{SM} = \arg\max_{\xi} \min_{\theta \in \Theta} \left\{ \frac{|I(\xi, \theta)|}{\sup_{\gamma} |I(\gamma, \theta)|} \right\}^{1/m}, \tag{3}$$

where $m = \dim(\theta)$ and the denominator is the criterion value of the locally D-optimal design for the specific θ.

Here, nested PSOs were used to solve the three-layer optimization problem. In the inner loop, PSO was used to find the locally D-optimal design for each θ. Then the worst value of the D-efficiency was determined via another PSO. Finally, PSO was used a third time to identify the best design among all designs ξ on X that maximizes the minimum D-efficiency across all $\theta \in \Theta$. (Chen, Chen & Wong, Chemo. and Intell. Lab. Sys., 2018)

Recent Use of Meta-heuristics for Finding Optimal Designs

Masoudi, E., ... and Wong, W. K. (2019). Meta-heuristic Adaptive Cubature Based Algorithm to Find Bayesian Optimal Designs for Nonlinear Models. JCGS

Liu, X., ... and Wong, W. K. (2021). G-optimal Designs for Hierarchical Linear Models: an Equivalence Theorem and a Nature-inspired Meta-heuristic Algorithm. Soft Computing

Kim, S., ... and Wong, W. K. (2021). Meta-heuristics for Pharmacometrics. Pharmacometrics and Systems Pharmacology.

Chen, P. Y., ... and Wong, W. K. (2023). Particle Swarm Optimization for Finding Efficient Longitudinal Optima Exact Designs for Nonlinear Models. NEJSDS

Stokes, Z., ... and Wong, W. K. (2024). Metaheuristic Solutions to Order-of-Addition Design Problems. JCGS.

Schepps, M., ... and Wong, W. K. (2024). Optimizing Patient Enrollment in Global Clinical Trials by Metaheuristics. Statistics in Biopharmaceutical Research.

2.5 Locally c-optimal Designs for a Nonlinear Model

Given a nonlinear model with mean function $f(x, \theta)$, we want to find a design to estimate a nonlinear function $g(\theta)$. Assuming θ is 3-dimensional, the sought design ξ^* minimizes

$$c^T(\theta) M(\xi, \theta)^{-1} c(\theta)$$

over all designs ξ on the dose interval X, where

$$c(\theta) = \nabla g(\theta) = \left(\frac{\partial g(\theta)}{\partial \theta_0}, \frac{\partial g(\theta)}{\partial \theta_1}, \frac{\partial g(\theta)}{\partial \theta_2}\right)^T$$

and $M(\xi, \theta)$ is the information matrix from design ξ. Assume nominal values for θ are available. Then, a continuous design ξ^* is c-optimal if and only if

$$\{f^T(x, \theta) M(\xi^*, \theta)^{-1} c(\theta)\}^2 - c(\theta)^T M(\xi^*, \theta)^{-1} c(\theta) \leq 0 \quad \forall x \in X,$$

with equality at the optimal doses of ξ^* (Berger and Wong, Intro. to Optimal Designs, 2016). We apply this result to find Biological Optimal Dose (BOD) or Most Successful Dose (MSD). Wong (Biometrika, 1992) considers non-differentiable criteria.

3 Sample Applications of PSO

To find efficient clinical trials

- for a 2-stage adaptive phase II trials with 3 target alternatives
  - Simon (Controlled Clinical Trials, 1989),
  - Lin and Shih (Biometrics, 2004).
  - Kim and Wong (Stat. Methods in Med. Research, 2018) ;

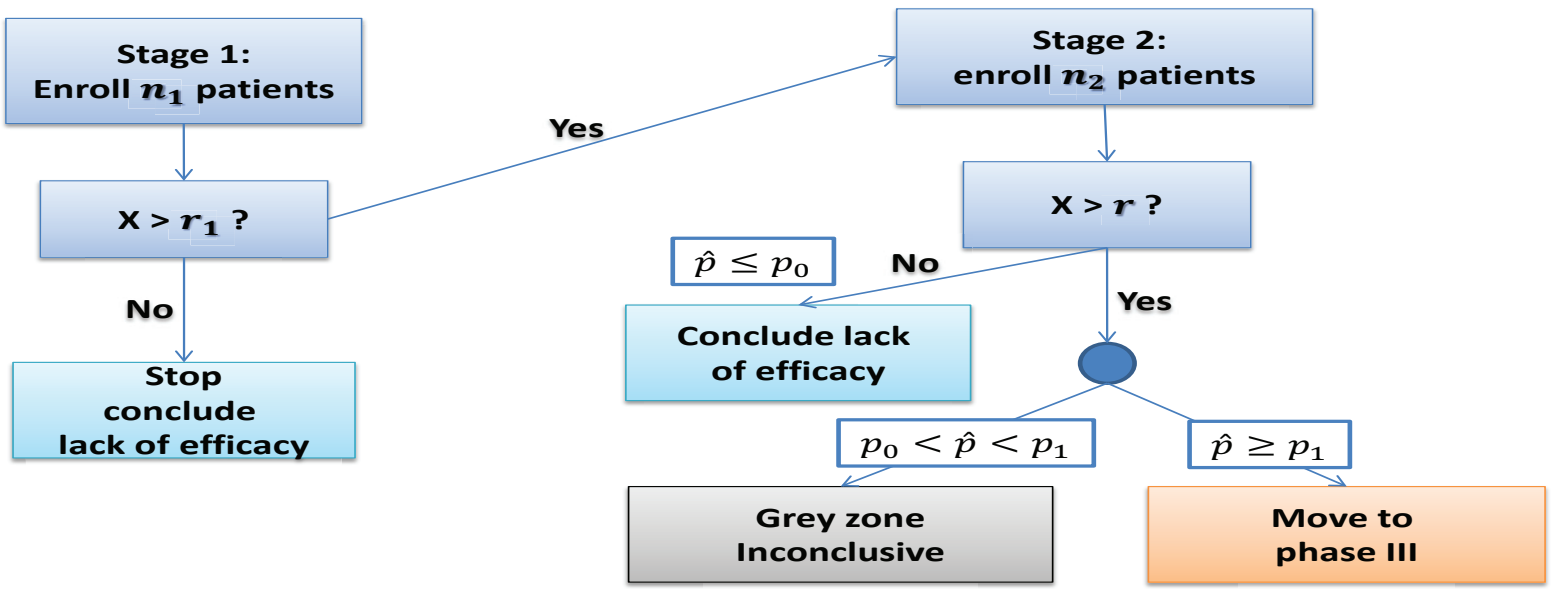
- for estimating the Biologically Optimal Dose (BOD) for a Continuation Ratio (CR) model
  - Fan and Chaloner (J. Stat. Plan. Inference, 2004)
  - Marshall, el at. (J. of Clinical Oncology, 20212) - Optimum Biologic Dose (??)
  - Qiu and Wong (New Eng. J. of Stat. & Data. Sc., 2023)

- for enhancing capabilities of Bayesian optimal designs for a phase II trial (BOP2)
  - Zhao, el at. (Stat. In Med., 2016)
  - Zhao, el at. (Stat. Biopharm, Stat., 2022)

3.2 Application 1: Simon 2-stage Phase II Designs

Simon's Two-Stage Designs

- X: the number of responders



3.3. Simon's 2-stage Adaptive Phase II Trials

Review of Simon's Design (Controlled Clinical Trials, 1989)

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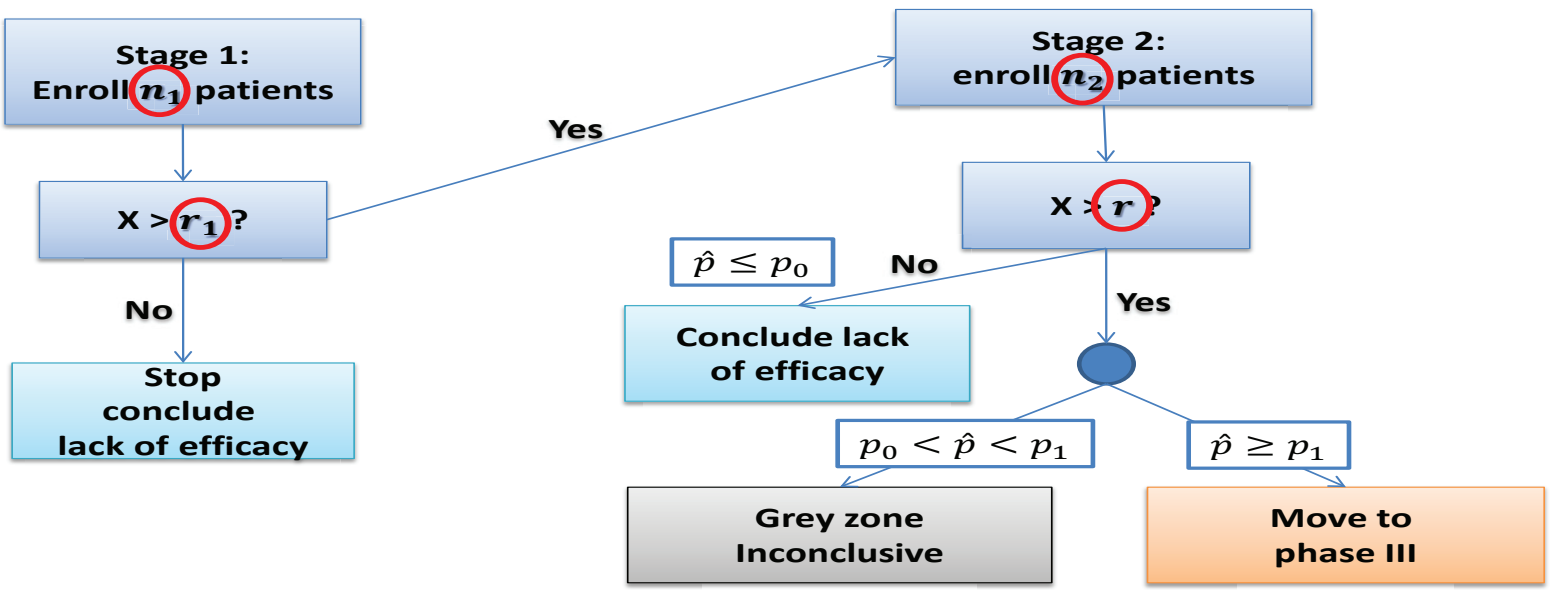

3.4 Various adaptive 2-stage optimal designs with 1 target response when $\alpha = 0.05$ and $\beta = 0.20$.

p_0	p_1	Optimal criteria	Method	s_1/n_1	s/n	$1-\alpha$	β	$E(N\|p_0)$	$E(N\|p_1)$	CPU time (mins)
0.05	0.20	C1	GS	0/10	3/29	0.953	0.199	17.624	26.960	0.09
			G-DPSO	1/15	4/40	0.968	0.197	19.274	35.822	2.51
		C2	GS	0/11	3/28	0.956	0.199	18.330	26.540	0.1
			G-DPSO	0/11	3/28	0.956	0.199	18.330	26.540	2.32
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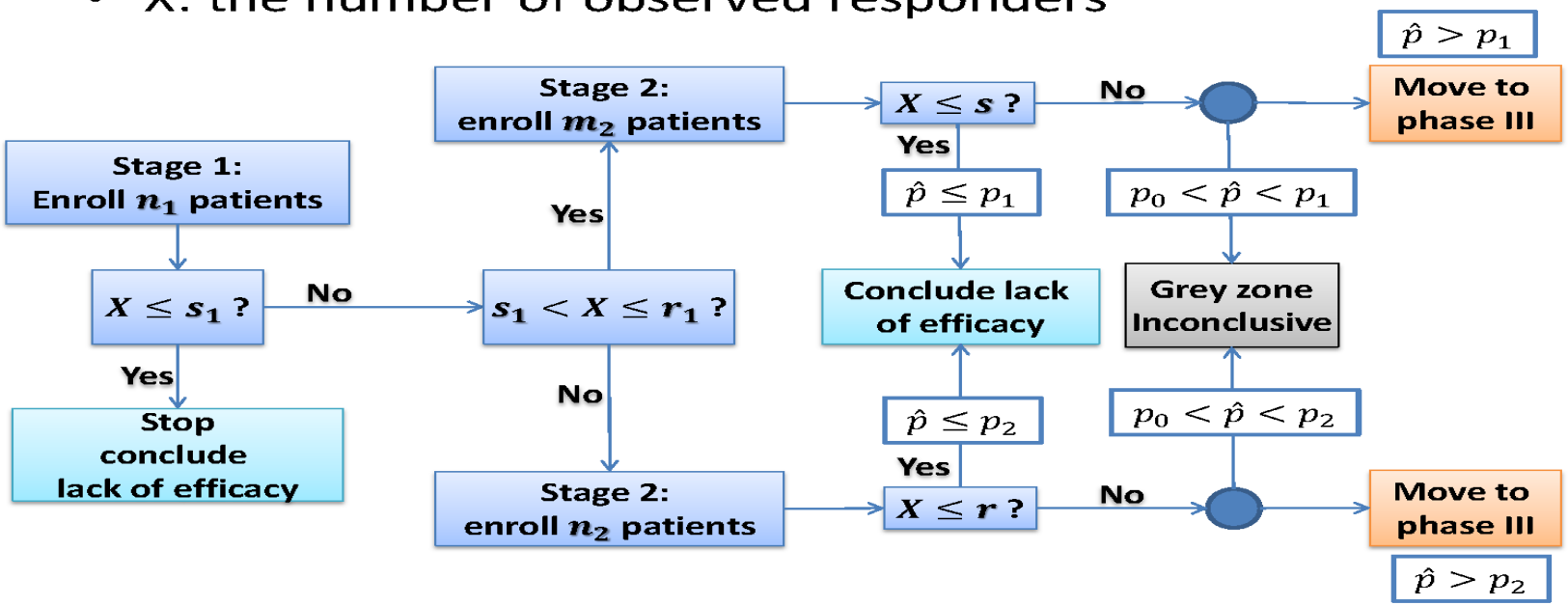
- C1 and C2 are Simon's original optimality criteria
- Note: When $p_1 = 0.20$ and $p_2 = 0.35$, there many more possible solutions compared to the case when $p_1 = 0.05$ and $p_2 = 0.20$. The computation time for greedy search depends on the size of the set of possible solutions, while PSO generally does not.

3.5 A Discrete Optimization Problem: Extended 2-stage Adaptive Phase II Trials with Two Targeted Alternatives (Lin and Shih, Biometrics, 2004)

Lin and Shih (2004)

- X: the number of observed responders



Depending on quality of Stage 1 results, one of the 2 alternative hypotheses is tested to target p_1 more accurately.

3.6 Extended 2-stage Adaptive Phase II Trials (cont'd)

Lin and Shih (2004)

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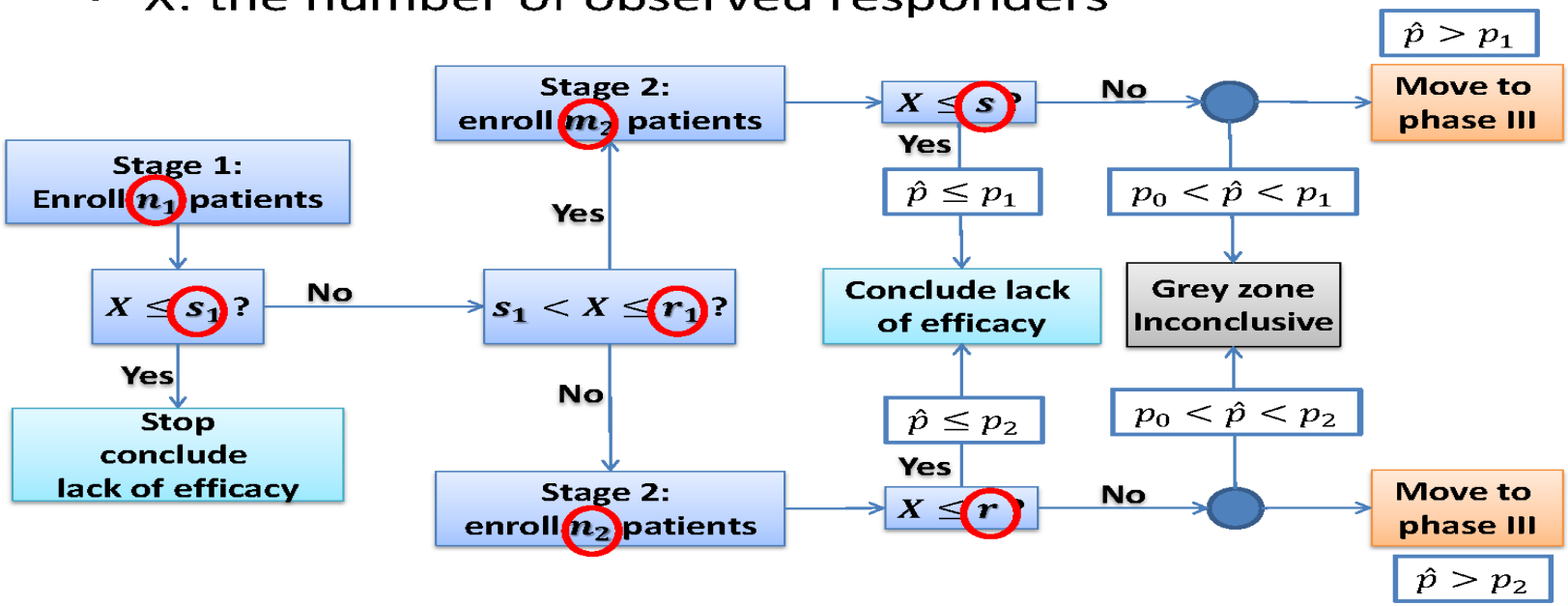
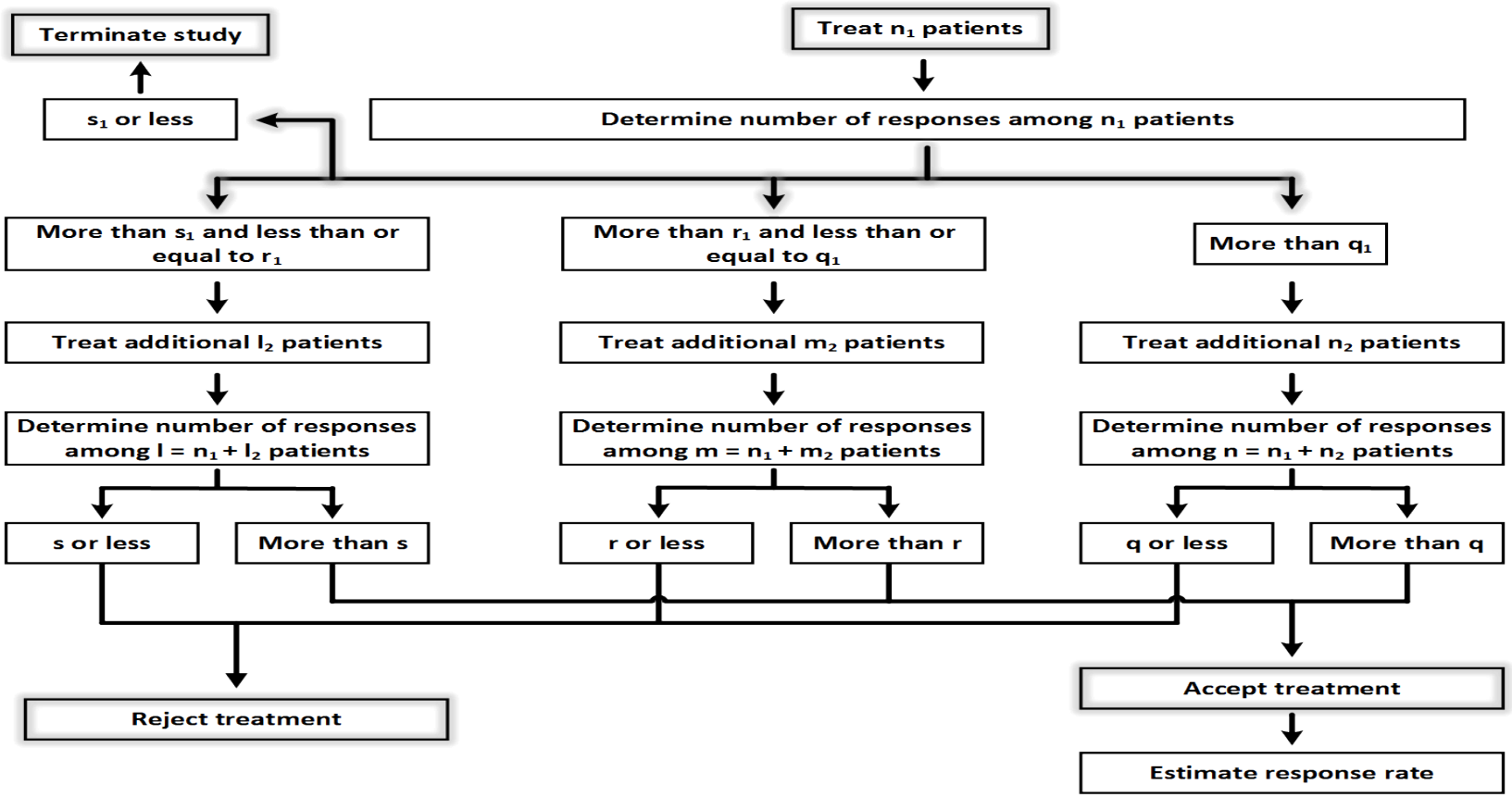


Depending on quality of Stage 1 results, the next scenario tests one of 3 alternative hypotheses to target p_1 more accurately.

3.8 Extended 2-stage Adaptive Phase II Trials for 3 Targeted Alternatives (cont'd)



Kim, S. and Wong, W. K. (Stat. Meth. in Med. Res., 2016) used a modified version of PSO to solve the 10-integer valued optimization problem with multiple nonlinear constraints.

3.9 Application 2: Find Biological Optimal Dose (BOD) for an Early Phase Clinical Trial

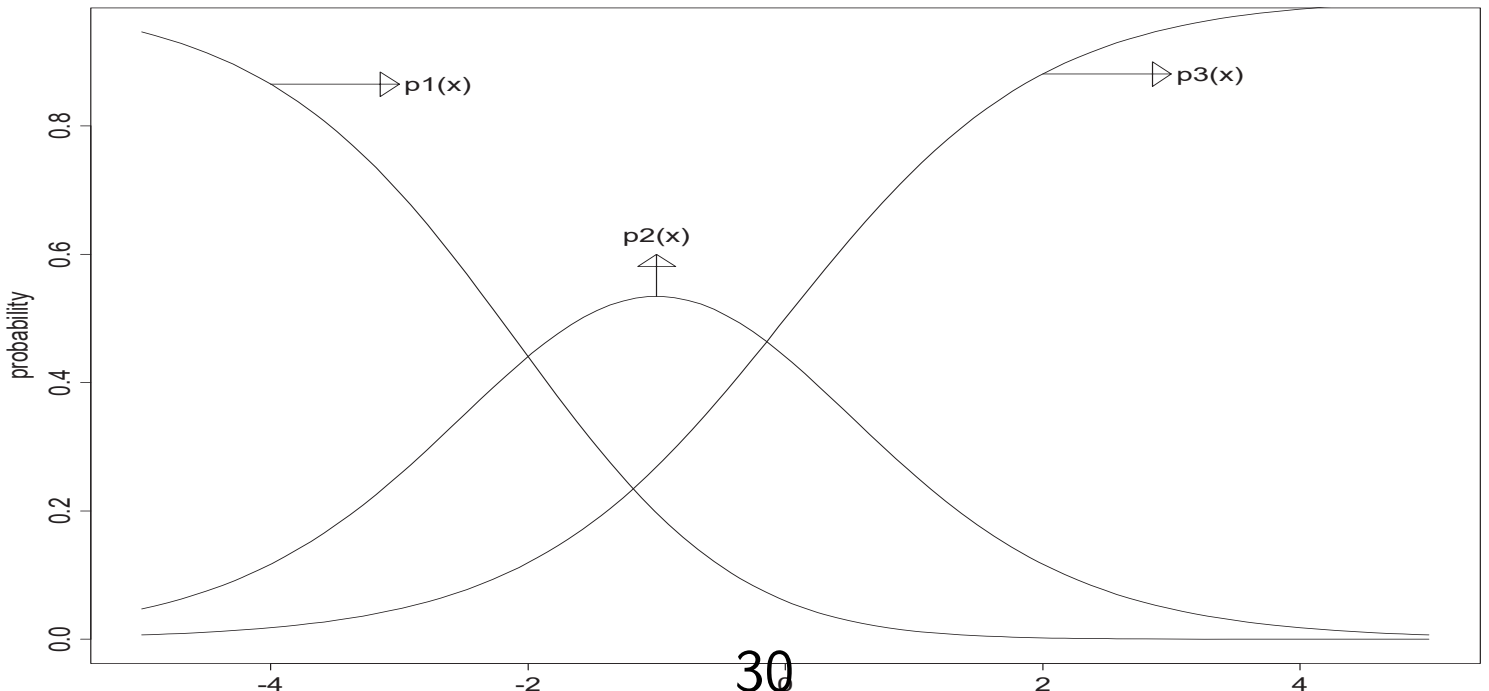
The Continuation Ratio Model relates probabilities of no response (p_1),efficacy and no severe toxicity (p_2) and severe toxicity (p_3) by:

$$\ln[p_3(\theta, x)/(1 - p_3(\theta, x))] = a_1 + b_1 x, \quad b_1 > 0 \quad (4)$$

and

$$ln[p_2(\theta, x)/p_1(\theta, x)] = a_2 + b_2 x, \quad b_2 > 0, \quad (5)$$

where $\theta^T = (a_1, b_1, a_2, b_2)$.



3.10 Calculus (Fan & Chaloner, JSPI, 2003)

The biologically optimal dose x_{BOD} depends on $\theta^T = (a_1, b_1, a_2, b_2)$ and solves

$$g(x, \theta) = b_2(1 + e^{-a_1 - b_1 x}) - b_1(1 + e^{a_2 + b_2 x}) = 0.$$

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- By the implicit function theorem, the gradient of the solution to the above equation is

$$\left[\frac{\partial g(x_{BOD}(\theta), \theta)}{\partial x}\right]^{-1} \frac{\partial g(x_{BOD}(\theta), \theta)}{\partial \theta}$$

$$= \begin{pmatrix} e^{-a_1 - b_1 x_{BOD}} / [b_1(e^{-a_1 - b_1 x_{BOD}} + e^{a_2 + b_2 x_{BOD}})] \\ x_{BOD} e^{-a_1 - b_1 x_{BOD}} / [b_1(e^{-a_1 - b_1 x_{BOD}} + e^{a_2 + b_2 x_{BOD}})] \\ e^{a_2 + b_2 x_{BOD}} / [b_2(e^{-a_1 - b_1 x_{BOD}} + e^{a_2 + b_2 x_{BOD}})] \\ x_{BOD} e^{a_2 + b_2 x_{BOD}} / [b_2(e^{-a_1 - b_1 x_{BOD}} + e^{a_2 + b_2 x_{BOD}})] \end{pmatrix}.$$

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- Use standard algorithm to generate the locally optimal design

3.11 Selected BOD- & D-optimal designs and BOD-efficiencies

dose	weight	(a_1, b_1, a_2, b_2)	dose	weight	BOD-efficiency
-5.67	0.001	$(-3.3, 0.5, 3.4, 1)$	-4.63	0.292	56%
-0.64	0.800		-1.32	0.416	
4.84	0.199		4.19	0.056	
			8.64	0.236	
-1.26	0.632	$(-1, 0.5, 2, 1)$	-3.54	0.366	67%
4.11	0.368		-0.59	0.403	
			4.80	0.231	
-1.30	0.549	$(-1.04, 0.81.2, 1)$	-2.67	0.370	77%
2.37	0.451		0.00	0.398	
			2.88	0.232	
-14.00	0.100	$(0.4, 0.2, 2, 1)$	-13.00	0.070	62%
-1.14	0.628		-4.11	0.400	
9.99	0.272		-0.77	0.372	

3.12 Optimal Adaptive Designs for Finding BOD

- Above design strategy is not adaptive;
- Merging optimal design ideas and research in adaptive designs is helpful since many latter designs do not incorporate optimal design techniques;
- For example, adaptive ideas from the below paper for the CR model can be integrated into the the proposed strategy via meta-heuristics just described.

Reference: Alam, et al. (2019). Combined criteria for dose optimisation in early phase clinical trials (using a CR model). Stat. in Medicine.

3.13 Application 3: Strategies to Enhance BOP2 designs

These are Bayesian optimal phase II designs proposed by (Zhou,et al. SIM, 2017)

Website for Finding Bayesian Optimal Designs for Phase II (BOP2) Trials:

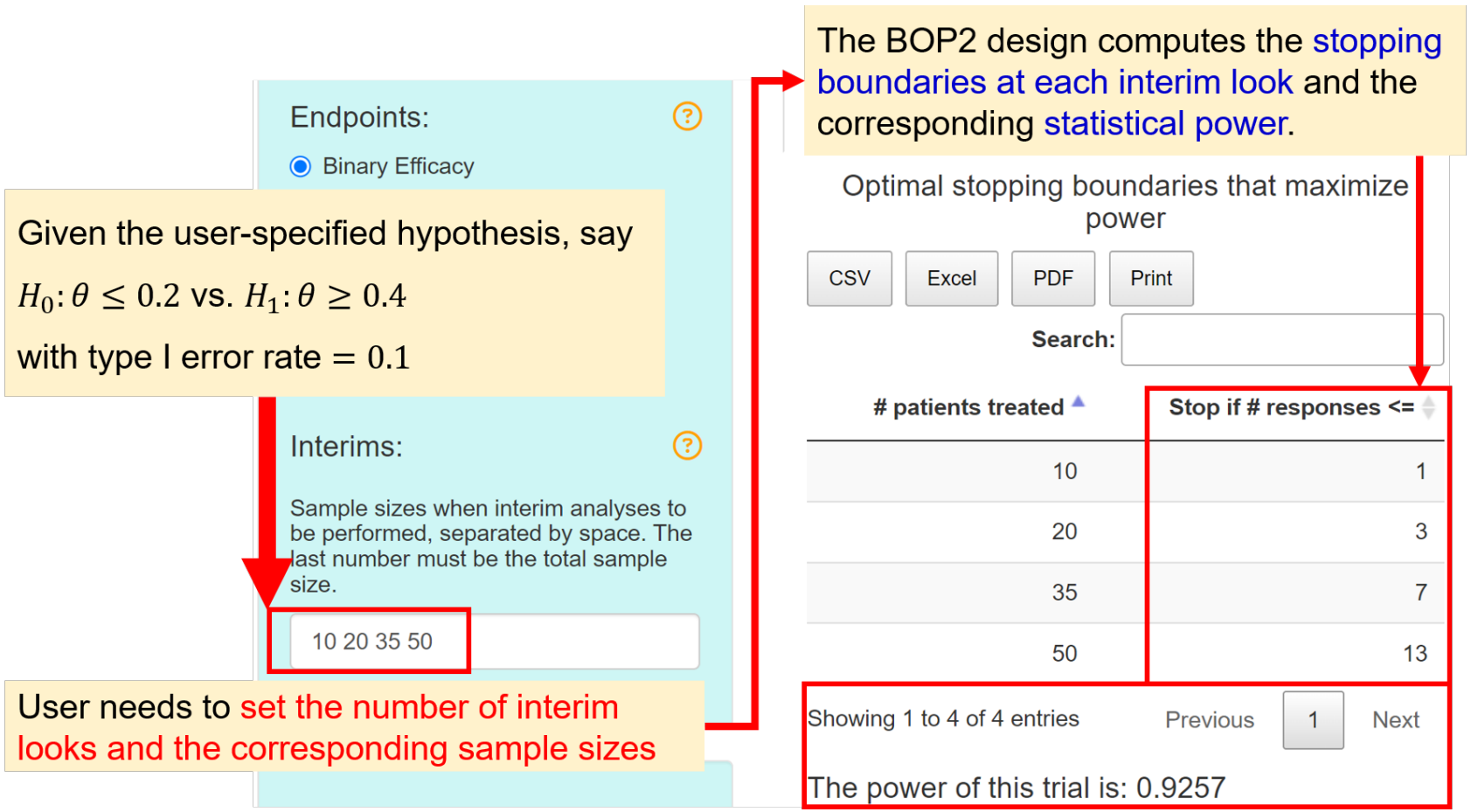
`https://trialdesign.org/one-page-shell.html#BOP2`

3.14 Requirements of Generating a BOP2 Design

Currently, to generate a BOP2 design, the user has to pre-specify:

(1) The total sample size, N, and, the number of interim looks, R;

(2) the number of patients at each interim look, $n_1 < \ldots < n_{R-1}$.



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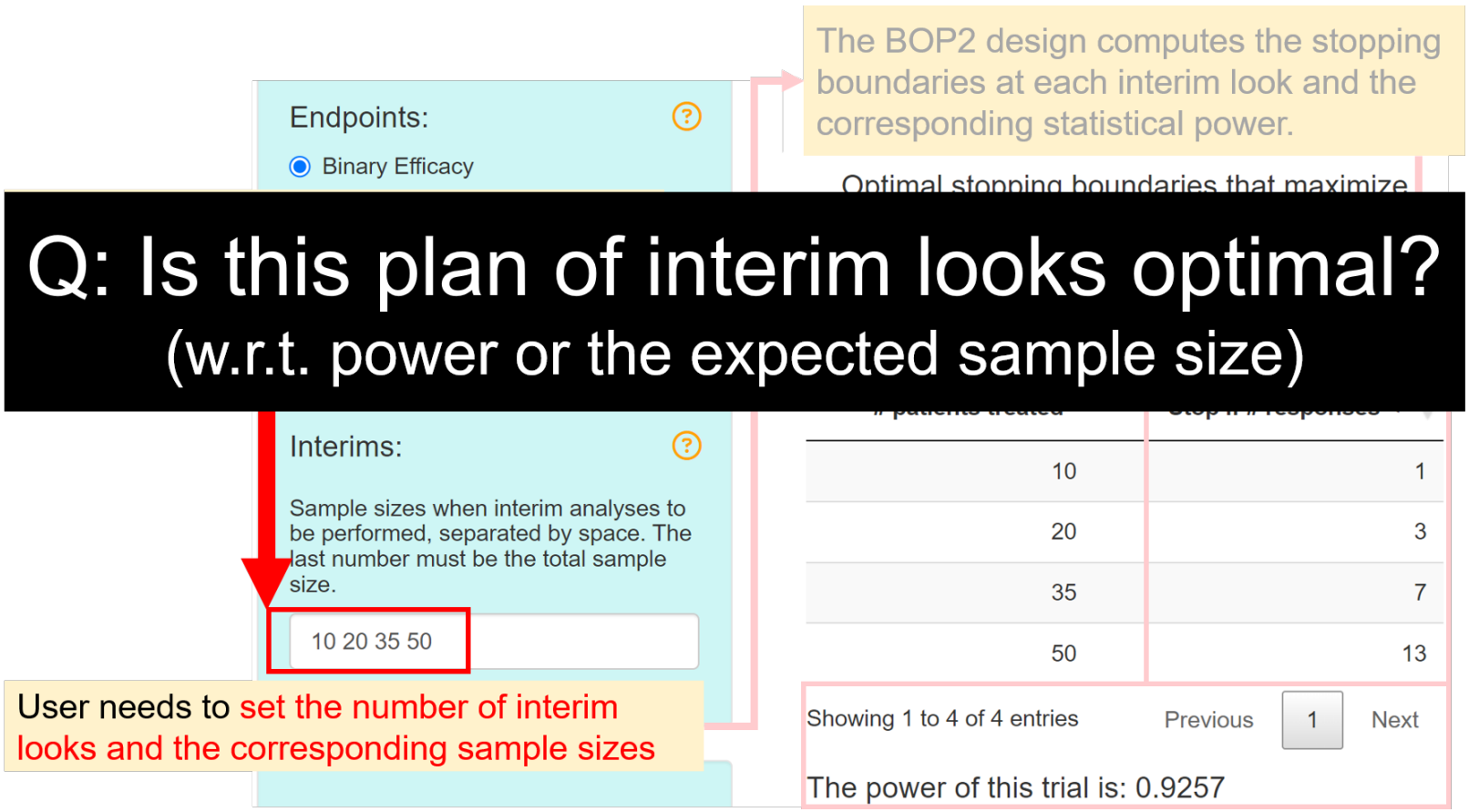
- The total sample size, N, and, the number of interim looks, R;
- the number of patients at each interim look, $n_1 < \ldots < n_{R-1}$.



3.16 Optimize the BOP2 Design

We investigate how PSO can additionally optimize the setup by

(1) Optimizing the total sample size, N, and, the number of interim looks, R;

(2) Optimizing the sample size at each interim look, $n_1 < n_2 < \cdots < n_{R-1}$.

through the objective function

$$\max_{N,R} \left\{ \max_{n_1<n_2<\cdots<n_{R-1}} \text{Power} \right\}$$

or a compound criterion considering both maximizing power and minimizing expected sample size with a pre-specified weigh α

$$\max_{N,R} \left\{ \max_{n_1<n_2<\cdots<n_{R-1}} \alpha \times \text{Power} - (1-\alpha) \times \frac{1}{N} E(N \mid H_0) \right\}$$

3.17 Preliminary Results

- If power dominates the objective function, the resulting best BOP2 design would be no interim look (test only once when all patients are enrolled).
- Thus, let $\alpha = 0.4$ for the compound criterion. Below are the current results of PSO-generated BOP2 designs based on the fixed design requirements:
  (0) $H_0 : \theta \leq 0.2$ vs. $H_1 : \theta \geq 0.4$ and Type I error rate $= 0.1$.
  (1) Fix $N = 50$

R	PSO-BOP2 Design	Crit. Value	Power	$E(N \mid H_0)$	CPU Time (seconds)
3	4, 35, 50	0.8657	0.8505	43.8	15.0
6	4, 9, 43, 45, 48, 50	0.8449	0.8289	42.8	400.2

4 Summary

Other Nature-Inspired Algorithms:

- Differential evolution (1995)
- Bees algorithm (2006)
- Invasive weed optimization (2006)
- Artificial bee colony algorithm (2007)
- Monkey search (2007)
- Imperialist competitive algorithm (2007)
- Intelligent water drops algorithm (2009)
- Glowworm swarm optimization (2009)
- Cuckoo search (Yang & Deb, 2009, Journal of Mathematical Modeling and Numerical Optimization)
- Firefly algorithm (2009, 2010)
- Bat algorithm (2010)

and the list goes on and on...

4.1 Conclusions

- PSO methodology offers great promise and I believe represents a leap forward in the field of optimal experimental designs;
- Optimal designs should be more accessible now and hopefully optimal design ideas will be more widely used in practice, but not religiously;
- Nature-inspired meta-heuristic algorithms are assumptions free and general purpose optimization tools;
- Did I oversell nature-inspired metaheuristic algorithms?

4.1 Conclusions

- PSO methodology offers great promise and I believe represents a leap forward in the field of optimal experimental designs;
- Optimal designs should be more accessible now and hopefully optimal design ideas will be more widely used in practice, but not religiously;
- Nature-inspired meta-heuristic algorithms are assumptions free and general purpose optimization tools;
- Did I oversell nature-inspired metaheuristic algorithms?
- Nature-inspired algorithms are not problems free, but they are very appealing for both academicians and practitioners on many fronts.....

4.2 Acknowledgement of collaborators:

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