Nature-Inspired metaheuristic algorithms for finding optimal designs for high dimensional problems

Weng Kee WONG
Department of Biostatistics, UCLA

Meeting the Statistical Challenges in High Dimensional Data and Complex Networks
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Outline

1. Motivation from Optimal Design Problems
3. Optimal Designs via PSO and a Quick Demonstration
4. Closing Thoughts
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- Motivation from Optimal Design Problems
- Why Nature-inspired Meta-heuristic Algorithms?
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  - Standardized maximin optimal designs for enzyme kinetic models
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  - Standardized maximin optimal designs for enzyme kinetic models
  - Extended adaptive 2-stage Simon’s designs
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  - Multiple-objective optimal designs for the 4-parameter logistic model

Closing Thoughts
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An Illustrative Dose Response Example

\[ y = \theta_0 + \theta_1 x + \text{error} = f^T(x)\theta + \text{error}, \quad \theta^T = (\theta_1, \theta_2) \]

\[ \mathbb{E}\text{(error)} = 0 \quad \text{var(error)} = \sigma^2 \quad N \text{ i.i.d. observations} \]

On \( X = [-1, 1] \), what is the optimal design for estimating \( \theta_0 \)?
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- For (2) and (3), take equal number of observations at \( \pm 1 \).
- For (1) answer is any design with \( \bar{x} = 0 \).
1.2 A Typical Setup for a Design Problem

- a given compact design space $X$
- a parametric model with unknown parameters
- errors are \textit{normally and independently} distributed
- observations have with constant variance
- a pre-determined sample size $N$

\textbf{QUESTION}

Given $X$, $f(x)$, $N$ and an optimality criterion $\phi$, how best to select the $N$ points from the design space $X$ to observe the responses $y$?
1.3 Approximate designs (Kiefer, 1958-1982)

**Optimal Approximate Design Problem:** How many points are needed to optimize the criterion? Find \( k \)
Where are the optimal design (or support) points?
Find \( x_1, x_2, \ldots, x_k \in X \)
What is the optimal proportion of the total observations to take at each of these points?
Find \( w_1, w_2, \ldots, w_k \) such that \( 0 < w_i < 1, \ i = 1, 2, \ldots, k \) and \( w_1 + w_2 + \cdots + w_k = 1 \).

The implemented design takes \( n_i = \lfloor Nw_i \rfloor \) observations at \( x_i, \ i = 1, 2, \ldots, k \) and rounded so that \( n_1 + n_2 + \cdots + n_k = N \).
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The implemented design takes $n_i = \lfloor Nw_i \rfloor$ observations at $x_i$, $i = 1, 2, \cdots, k$ and rounded so that $n_1 + n_2 + \cdots + n_k = N$.

- **Optimal Exact Design Problem** finds positive integers $n_i$ directly subject to $n_1 + n_2 + \cdots + n_k = N$. 

Nature-Inspired metaheuristic algorithms for finding optimal designs
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- Does not require an endless list of tables describing optimal design for each model, each N and each type of criterion.
- When the design space $X$ has dimension 1 or 2, a simple way to verify whether a design is optimal among all designs on $X$ is to draw pictures!
1.5 Optimal Approximate Designs on $X = [-1, 1]$

D-optimal designs for estimating model parameters and making inference on the mean response at a given dose level.

<table>
<thead>
<tr>
<th>design</th>
<th>linear model</th>
<th>quadratic model</th>
</tr>
</thead>
<tbody>
<tr>
<td>criterion</td>
<td>$x_i$</td>
<td>$w_i$</td>
</tr>
<tr>
<td>D-optimality</td>
<td>$-1$</td>
<td>$1$</td>
</tr>
<tr>
<td></td>
<td>$1$</td>
<td>$0$</td>
</tr>
<tr>
<td></td>
<td>$1/2$</td>
<td>$1/2$</td>
</tr>
<tr>
<td></td>
<td>$1/2$</td>
<td>$1/2$</td>
</tr>
<tr>
<td></td>
<td>$1/3$</td>
<td>$1/3$</td>
</tr>
<tr>
<td>Extrapolation</td>
<td>$-1$</td>
<td>$1$</td>
</tr>
<tr>
<td>at dose level</td>
<td>$1$</td>
<td>$0$</td>
</tr>
<tr>
<td>$z = 2$</td>
<td>$1/4$</td>
<td>$3/4$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<th>linear model</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>$x_i$ $-1$ 1 $-1$ 0 1</td>
<td>$w_i$ $1/2$ $1/2$ $1/3$ $1/3$ $1/3$</td>
</tr>
<tr>
<td>Extrapolation at dose level</td>
<td>$x_i$ $-1$ 1 $-1$ 0 1</td>
<td>$w_i$ $1/4$ $3/4$ $1/7$ $3/7$ $3/7$</td>
</tr>
</tbody>
</table>

Next, designs for nonlinear models are complicated because they depend on the parameters we want to estimate!
1.6 Locally D-optimal Designs for the Logistic Model on $X = [-1, 1]$ (Ford’s PhD thesis, 1972)

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

\[
\begin{align*}
\{ \theta : \theta_2 - \theta_1 & \geq a \} \\
\{ \theta : \theta_2 - \theta_1 < a, \exp(\theta_1 + \theta_2) & \leq \frac{\theta_2 + 1}{\theta_2 - 1} \} \\
\{ \theta : \exp(\theta_1 + \theta_2) > \frac{\theta_2 + 1}{\theta_2 - 1} \}
\end{align*}
\]

\[
\begin{align*}
\{ \frac{a - \theta_1}{\theta_2}, \frac{-a - \theta_1}{\theta_2}; \frac{1}{2}, \frac{1}{2} \} \\
\{ -1, u^*; \frac{1}{2}, \frac{1}{2} \} \\
\{ -1, 1; \frac{1}{2}, \frac{1}{2} \}
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- Corrected results in Sebastiani and Settimi (JSPI, 1997)
1.7 By Brute Force and Guess Work

Consider the logistic model on a given design space \( X \) given by

\[
\log \frac{\pi(x)}{1 - \pi(x)} = \theta_0 + \theta_1 x,
\]

where \( \theta^T = (\theta_0, \theta_1) \in \Theta \) and \( \Theta \) is known.

**Design Criterion:** Find \( \xi^* = \arg \min_\xi \max_{\theta \in \Theta} \log |M(\xi, \theta)|^{-1} \).
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- There is no known algorithm that is guaranteed to find a minimax optimal design.
- King & Wong (Biometrics, 2002) found minimax D-optimal designs when \( \Theta = [0, 3.5] \times [1, 3.5] \) and \( X \) is unrestricted:

<table>
<thead>
<tr>
<th>( x_i )</th>
<th>( w_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35</td>
<td>0.18</td>
</tr>
<tr>
<td>0.62</td>
<td>0.21</td>
</tr>
<tr>
<td>1.39</td>
<td>0.11</td>
</tr>
<tr>
<td>2.11</td>
<td>0.11</td>
</tr>
<tr>
<td>2.88</td>
<td>0.21</td>
</tr>
<tr>
<td>3.85</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Figure 1. Plot of $\psi(x, \xi^*, \mu^*)$ for example 3.2 with $\Theta = [0, 3.5] \times [1, 3.5]$. 
1.8 Sensitivity Plot of the Generated Design

Figure 1. Plot of $\psi(x, x^*, \mu^*)$ for example 3.2 with $\Theta = [0, 3.5] \times [1, 3.5]$.

- References: Wong (Biometrika, 1992), Wong & Cook (JRSSB, 1993), Berger, King & Wong (Psychometrika, 1994)
1.9 Time required to discretize a 10-dimensional search space with different number of equally spaced points using a Mac laptop 2.6 GHz Intel Core i5

<table>
<thead>
<tr>
<th>number of equally spaced points per covariate space</th>
<th>total number of grid points</th>
<th>CPU time required to generate the grid (secs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>$2^{10} = 1024$</td>
<td>0.0067</td>
</tr>
<tr>
<td>3</td>
<td>$3^{10} = 59049$</td>
<td>0.2302</td>
</tr>
<tr>
<td>4</td>
<td>$4^{10} = 1,048,576$</td>
<td>3.1136</td>
</tr>
<tr>
<td>5</td>
<td>$5^{10} = 9,765,625$</td>
<td>27.5529</td>
</tr>
<tr>
<td>6</td>
<td>$6^{10} = 60,466,176$</td>
<td>172.2832</td>
</tr>
<tr>
<td>7</td>
<td>$7^{10} = 282,475,249$</td>
<td>848.2922</td>
</tr>
</tbody>
</table>
There are immediate implications....
1.10 Implications

- Current design algorithms such as Cocktail-based algorithms: Yu (Stat. & Comp., 2011) and Yang, et al., (JASA, 2014) may not work for high dimensional problems.
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1.11 Mathematistry

In Praise of Simplicity not Mathematistry! Ten Simple Powerful Ideas for the Statistical Scientist

Roderick J. Little

Ronald Fisher was by all accounts a first-rate mathematician, but he saw himself as a scientist, not a mathematician, and he railed against what George Box called (in his Fisher lecture) “mathematistry.” Mathematics is the indispensable foundation of statistics, but for me the real excitement and value of our subject lies in its application to other disciplines. We should not view statistics as another branch of mathematics and favor mathematical complexity over clarifying, formulating, and solving real-world problems. Valuing simplicity, I describe 10 simple and powerful ideas that have influenced my thinking about statistics, in my areas of research interest: missing data, causal inference, survey sampling, and statistical modeling in general. The overarching theme is that statistics is a missing data problem and the goal is to predict unknowns with appropriate measures of uncertainty.

KEY WORDS: Calibrated Bayes; Causal inference; Measurement error; Missing data; Penalized spline of propensity.

1. INTRODUCTION: THE UNEASY RELATIONSHIP BETWEEN STATISTICS AND MATHEMATICS

American Statistical Association President, Sastry Pantula, recently proposed renaming the Division of Mathematical Sciences at the U.S. National Science Foundation as the Division of Mathematical and Statistical Sciences. Opponents, who viewed statistics as a branch of mathematics, questioned why statistics should be singled out for special treatment. Data can be assembled in support of the argument that statistics is different—for example, the substantial number of academic departments of statistics and biostatistics, the rise of the statistics advanced placement examination, and the substantial number of undergraduate statistics majors. But the most important factor for me is that statistics is not just a branch of mathematics. It is an inductive method, defined by its applications to the sciences and other areas of human endeavor, where we try to glean information from data.

The relationship between mathematics and statistics is somewhat uneasy. Since the mathematics of statistics is often viewed as basically rather pedestrian, statistics is rather low on the totem pole of mathematical subdisciplines. Statistics needs its mathematical parent, since it is the indispensable underpinning of the subject. On the other hand, unruly statistics has ambitions to reach beyond the mathematics fold; it comes alive in applications and medicine, and with increasing influence recently on the hard sciences such as astronomy, geology and physics.

The scientific theme of modern statistics fits the character of its most influential developer, the great geneticist, R. A. Fisher, who seemed to revolutionize the field of statistics in his spare time! Fisher’s momentous move to Rothampsted Experimental Station rather than academia underlined his dedication to science. Though an excellent mathematician, Fisher viewed himself primarily as a scientist, and disparaged rivals like Neyman and Pearson as mere “mathematicians.”

George Box’s engaging Fisher lecture focused on the links between statistics and science (Box 1976). He wrote:

My theme then will be first to show the part that [Fisher] being a good scientist played in his astonishing ingenuity, originality, inventiveness, and productivity as a statistician, and second to consider what message that has for us now.

Box attributed Fisher’s hostility to mathematicians to distaste for what he called “mathematistry,” which he defined as [...] the development of theory for theory’s sake, which, since it seldom touches down with practice, has a tendency to redefine the problem rather than solve it. Typically, there has once been a statistical problem with scientific relevance but this has long since been lost sight of. (Box 1976)
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- can help find analytic solution or formula of optimal design for complicated problems
2.3 Usage of Nature-Inspired Metaheuristic Algorithms

- Recent trends indicate rapid growth of nature-inspired optimization in academia and industry. (Whitacre, 2011, Computing, Vol. 93, 121-133.)

- Survival of the flexible: explaining the recent dominance of nature-inspired optimization within a rapidly evolving world. (Whitacre, 2011, Computing, Vol. 93, 135-146.)
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- Recent trends indicate rapid growth of nature-inspired optimization in academia and industry. (Whitacre, 2011, Computing, Vol. 93, 121-133.)

- Survival of the flexible: explaining the recent dominance of nature-inspired optimization within a rapidly evolving world. (Whitacre, 2011, Computing, Vol. 93, 135-146.)

- Can lead in the new frontier of research: solve optimization problems with millions or billions of variables (Foreword by editors in a special issue in Information Sciences, 2015, Vol. 316, 437-439.)
2.4 Metaheuristic Algorithms

From Wikipedia, the free encyclopedia: Metaheuristic

In computer science, metaheuristic designates a computational method that optimizes a problem by iteratively trying to improve a candidate solution with regard to a given measure of quality. Metaheuristics make few or no assumptions about the problem being optimized and can search very large spaces of candidate solutions. However, metaheuristics do not guarantee an optimal solution is ever found. Many metaheuristics implement some form of stochastic optimization.
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- Our interest here is nature-inspired metaheuristic algorithms
- Particle Swarm Optimization (PSO) method is based on animal instincts (Eberhard & Kennedy, IEEE, 1995)
2.5 PSO (Kennedy & Eberhard, 1995)
2.6 PSO: School of Fish
2.7 Basic Equations and Tuning Parameters in PSO

Two defining equations:

\[ v_{i+1} = \omega_i v_i + c_1 \beta_1 (p_i - x_i) + c_2 \beta_2 (p_g - x_i), \]
\[ x_{i+1} = x_i + v_i. \]

\( x_i \) and \( v_i \): position and velocity for the \( i^{th} \) particle
\( \beta_1 \) and \( \beta_2 \): random vectors
\( \omega_i \): inertia weight that modulates the influence of the last velocity
\( c_1 \): cognitive learning parameter
\( c_2 \): social learning parameter
\( p_i \): Best position for the \( i^{th} \) particle (local optimal)
\( p_g \): Best position for all particles (global optimal)

For many applications, \( c_1 = c_2 = 2 \) seem to work well and usually 20 – 50 particles will suffice (Kennedy, IEEE, 1997).
2.8 Other Nature-Inspired Meta-Heuristic Algorithms

- Ant colony (1991)
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- Grey Wolf algorithm (2014, 2016)
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- Glowworm swarm optimization (2009)
- Firefly algorithm (2009, 2010)
- Bat algorithm (2010)
- Grey Wolf algorithm (2014, 2016)
- Bioinspired flower pollination algorithm (2015)
2.9 Cuckoo search (Yang & Deb, 2010)

Cuckoo search is a metaheuristic algorithm inspired by cuckoos’ parasitic breeding behavior.

Figure 1: Balmer, 2009
2.10 Examples of Variants of Particle Swarm Optimization

- Quantum PSO (Evolutionary Computation, 2004)
- Unified PSO (Advances in Natural Computation, 2005)
- Tournament PSO (IEEE Symposium Proceedings, 2007)
- Simplified PSO (Natural Computation, 2010)
- Strength Pareto PSO (Evolutionary Computation, 2010)
- Set-Based PSO (IEEE Transactions on Evol. Comp., 2010)
- Catfish PSO (Artificial Intelligence Research, 2012)
- Compact PSO (Information Sciences, 2013)
- Human Behavior-based PSO (Scientific World Journal, 2014)
- Selectively Informed PSO (Scientific Reports, 2014)
- Competitive Swarm Optimizer (Cybernetika, 2014)
- Fast PSO (Soft Computing, 2015)
- Galactic Swarm Optimization (Applied Soft Computing, 2016)
2.11 Resources for Metaheuristic Optimization and Nature-Inspired Metaheuristic Codes

Scholarpedia, the peer-reviewed open-access encyclopedia: http://www.scholarpedia.org/article/Metaheuristic_Optimization

Xin-She Yang’s 2008 book and updated in 2010:
2.12 Applications of PSO to Find Optimal Designs


Outline

1. Motivation from Optimal Design Problems
3. Optimal Designs via PSO and a Quick Demonstration
4. Closing Thoughts
3.1 Application I: Standardized Maximin Designs

- Locally optimal designs can be sensitive to nominal values.

- The maximin approach assumes a known plausible region $\Theta$ for the model parameters $\theta$. These maximin or minimax optimal designs maximize the minimal efficiency among all $\theta \in \Theta$, see King & Wong (Biometrics, 2000), and Biedermann and Dette (JASA, 2003).

- The standardized maximin $D$-optimal design $\xi_{SM}^*$ maximizes

$$
\psi(\xi) = \min_{\theta \in \Theta} \left\{ \frac{|M(\xi, \theta)|}{\sup_{\gamma} |M(\gamma, \theta)|} \right\}^{1/p},
$$

where $M(\gamma, \theta)$ is the $p \times p$ Fisher Information matrix for the nonlinear model with parameter $\theta$ from design $\gamma$. 

3.2 Application I: Standardized Maximin Designs (cont’d)

- Chen, Chen & Wong (Chemometrics and Intelligent Laboratory System, 2018) applied PSO and found locally standardized maximin D-optimal designs for 4 common inhibit models used in enzyme kinetic studies.

- Contrary to common assumptions, not all locally $D$-optimal designs for these 3 or 4-parameter models with 2 factors are minimally supported.

- Using information of the PSO-generated designs, we were able to derive formulae of such optimal designs for the various inhibit models, including some with 3 nonlinear parameters.
3.3 Application II: Adaptive Designs

In Simon 2-Stage design for Phase II trials, user first selects two efficacy rates of interest $p_0$ and $p_1$ with $p_0 < p_1$.

- Set up hypothesis: $H_0 : p \leq p_0$ versus $H_1 : p > p_1$
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  - number of responders in Stage 1
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- Apply a greedy search to solve the discrete optimization problem relating Binomial probabilities and error rates
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  - number of (additional) responders in Stage 2
- Apply a greedy search to solve the discrete optimization problem relating Binomial probabilities and error rates
- Lin & Shih (Biometrics, 2004) generalized the problem to 2 alternative hypotheses, and we extended it to 3 sets of alternative hypotheses.
3.4 Application II: A Discrete Optimization Problem
Simon’s Two-Stage Designs

- $X$: the number of responders

Stage 1:
Enroll $n_1$ patients

- $X > r_1$?
  - Yes: Move to phase III
  - No: Stop
    - Conclude lack of efficacy

Stage 2:
enroll $n_2$ patients

- $X > r$?
  - Yes: Conclude lack of efficacy
  - No: $\hat{p} \leq p_0$
    - $p_0 < \hat{p} < p_1$
      - Grey zone: Inconclusive
    - $\hat{p} \geq p_1$
      - Move to phase III
Simon’s Two-Stage Designs

- X: the number of responders

Stage 1:
- Enroll $n_1$ patients
- $X > r_1$?
  - No: Stop conclude lack of efficacy
  - Yes: $\hat{p} \leq p_0$

Stage 2:
- Enroll $n_2$ patients
- $X > r$?
  - No: $p_0 < \hat{p} < p_1$
  - Yes: $\hat{p} \geq p_1$
    - Move to phase III
    - Grey zone Inconclusive
    - Conclude lack of efficacy
3.5 Test limits of PSO

Simon’s 2-stage design has 4 parameters and the criterion was to minimize the expected sample size, or minimize the maximum sample size for the whole trial.

Goal: Extend Simon’s 2 stage designs for 3 alternatives target efficacy rates
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**Goal: Extend Simon’s 2 stage designs for 3 alternatives target efficacy rates**

- **Kim & Wong (SMMR, 2018)** applied a modified version of PSO and searched over a constrained 10-dimensional space of positive integers and found optimal designs that a greedy algorithm cannot.
3.6 A 10 Integer-valued Parameters Problem to Optimize

Problem is to optimize $\theta^T = (s_1, r_1, q_1, n_1, s, l, r, m, q, n)$ given error for testing each of the three possible alternative hypotheses rates and the criterion is one of minimizing the maximum (or expected) sample sizes.

The parameters $l, m, n$ are the total number of patients required for the entire trial corresponding to the alternative hypotheses, $H_{11}$: $p > p_1$, $H_{12}$: $p > p_2$, and $H_{13}$: $p > p_3$, respectively.

If true response probability is $p$, similar argument in Simon’s original paper shows the probability of failing to reject $H_0$ is

$$G(\theta|p) = B(s_1, n_1, p) + \sum_{x=s_1+1}^{\min(r_1,s)} b(x, n_1, p)B(s - x, l_2, p) + \sum_{x=r_1+1}^{\min(q_1,r)} b(x, n_1, p)B(r - x, m_2, p) + \sum_{x=q_1+1}^{\min(q,n_1)} b(x, n_1, p)B(q - x, n_2, p),$$
3.7 Application 3: Optimal Designs for GLMs with Mixed Factors

Table 1: The left panel is the theoretical design from Yang, Zhang & Huang (Statistica Sinica, 2011) assuming one continuous factor has an unbounded range. The right panel is the D-optimal design from PSO with a large boundary $[-10, 10]$.

<table>
<thead>
<tr>
<th>$X_1$</th>
<th>$X_2$</th>
<th>$X_3$</th>
<th>$p_i$</th>
</tr>
</thead>
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<tr>
<td>-2</td>
<td>-1</td>
<td>-0.456</td>
<td>0.125</td>
</tr>
<tr>
<td>-2</td>
<td>-1</td>
<td>-2.544</td>
<td>0.125</td>
</tr>
<tr>
<td>-2</td>
<td>1</td>
<td>-1.456</td>
<td>0.125</td>
</tr>
<tr>
<td>-2</td>
<td>1</td>
<td>-3.544</td>
<td>0.125</td>
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<tr>
<td>2</td>
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<td>1.544</td>
<td>0.125</td>
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<tr>
<td>2</td>
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3.8 The PSO-generated design when the continuous factor has a small range $[-2, 2]$ (Lukemire, Mandal & Wong, Technometrics, 2018).
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- When theory is not available, PSO methodology can help. When we restrict the final continuous factor to its natural setting PSO finds the following design.
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<td>-2.000</td>
<td>0.212</td>
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<td>0.075</td>
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3.9 Minimally supported designs for logistic model with 2 additive factors and an intercept term

Minimally supported designs with $\beta_0 = 1$

Minimally supported designs with $\beta_0 = 1.5$
3.10 Application 4: Multiple-objective Optimal Designs

Experiments may have multiple objectives of varying importance. For example, extrapolate and estimate parameters at the same time or estimate parameters but there is model uncertainty (Dette, Melas & Wong, JASA, 2001)
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Want to find a design that delivers user-specified efficiencies under the various objectives with more important objectives having higher efficiencies requirements
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- Want to find a design that delivers user-specified efficiencies under the various objectives with more important objectives having higher efficiencies requirements.

- Cook & Wong (JASA, 1994) proposed a graphical method of constructing a dual-objective optimal design for linear regression problems; Clyde & Chaloner (JASA, 1996) extended the method to several objectives for nonlinear models.
3.11 Dual Objective Optimal Designs

- Constrained Optimal Designs
  i.e. design that satisfies a set of user-specified efficiency requirements; eg. minimize $\phi_2(\xi)$ subject to $\phi_1(\xi) \leq c$. 
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- Compound Optimal Designs
  i.e. design that minimizes a fixed convex combination of convex functionals: $\phi(\xi|\lambda) = \lambda \phi_1(\xi) + (1 - \lambda) \phi_2(\xi)$. 

Nature-inspired metaheuristic algorithms for finding optimal designs.
3.11 Dual Objective Optimal Designs

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- Compound Optimal Designs are equivalent to Constrained Optimal Designs: Plot efficiencies of each compound optimal versus $\lambda$, $\lambda \in [0, 1]$. 
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- Compound Optimal Designs are equivalent to Constrained Optimal Designs: Plot efficiencies of each compound optimal versus $\lambda$, $\lambda \in [0, 1]$.

- Prioritize the importance of the objectives and apply theory for single-objective study (Cook & Wong, JASA, 1994).
Further, using (9), we obtain the values given in the first two lines of Table 1 in Studden (1982).

To connect explicitly the constrained design problems and the compound design problems, the relationship between a constraint expressed as $E_1(\xi) \geq \epsilon_1$ (or $E_1(\xi) \leq \epsilon_2$) and the corresponding value of $\lambda$ must be established. Using results from Fedorov (1980, thm. 1), it can be shown that $\xi_0$ maximizes $\phi(\xi|\lambda)$ if and only if

$$2(1-\lambda)\frac{d_1(x, \xi_0)}{d_1(x, \xi_0)} + \lambda b^T M_1^{-1}(\xi_0) b(x))^2 - 4(1-\lambda) - \lambda b^T M_1^{-1}(\xi_0) b(x) = 0 \quad (11)$$

for all $x$ in $[-1, 1]$. Further (11) becomes an equality at the support points for $\xi_0$. In that case, substituting (9) into (11) yields

$$\lambda = \frac{\epsilon_1^2}{4 + 4(1 - \epsilon_1)^{1/2} - 4\epsilon_1 + \epsilon_1^2}. \quad (12)$$

Figure 1, constructed using (10) and (12), shows the relationship between optimal designs with efficiency constraints and compound optimal designs. For example, a design that maximizes $\phi_2$ subject to the constraint $E_1(\xi) \geq .6$ can be found by maximizing $\phi(\xi|\lambda)$ with $\lambda \approx .1$. Figure 1 contains useful information on the interpretation of $\lambda$ as well. In particular, it might be felt that setting $\lambda = .5$ would yield a design in which equal interest is placed on the two criteria. But from Figure 1, the compound design problem with $\lambda = .5$ is equivalent to the constrained problem in which we maximize $\phi_2$ subject to the constraint that $E_1(\xi) \geq .96$. The resulting constrained design has $E_2(\xi_0) = .78$. In terms of the efficiencies, placing equal interest on the two criteria would seem to require $\lambda = .25$, because at that point $E_1(\xi) = E_2(\xi) = .84$. Finally, reconstructing the plot in Figure 1 so that the horizontal axis is $1 - \lambda$ rather than $\lambda$ provides the corresponding plot for maximizing $\phi_1$, subject to a constraint on $\phi_2$.
3.13 A Quick Demonstration using the Hill’s model

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- We now present a demo to find single and multiple-objective locally optimal approximate designs using different nature-inspired metaheuristic algorithms. The 3 objectives of interest are to estimate the ED50, minimum effective dose (MED) or parameters in a 4-parameter logistic model.
3.13 A Quick Demonstration using the Hill’s model


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- Bayesian optimal approximate designs can likewise be constructed and verified using an equivalence theorem.
3.11 Mean function of the Hill model

Figure 1. Graph of the 4-parameter Hill model. The following parameter values have been assumed: $E_{con} = 100$, $b = 20$, $IC_{50} = 1$, and $m = -1.5$. 

$$ E \gamma = \frac{(E_{con} - b) \left( \frac{D}{IC_{50}} \right)^m}{1 + \left( \frac{D}{IC_{50}} \right)^m} + b $$

$E_{max} = E_{con} - b$

$1/2 E_{max}$

$slope\ m$

$IC_{50}$

CONCENTRATION (Log scale)
3.12 Three-Objective Optimal Designs

Assume nominal values, dose interval and the minimum effect sought $\delta$ are given for the Hill’s model. For a user-selected vector $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ with $\lambda_i \geq 0$, $i = 1, 2, 3$ and $\lambda_1 + \lambda_2 + \lambda_3 = 1$, the sought multiple-objective optimal design is the approximate design that maximizes

$$\lambda_1 \log(\text{Eff}_D(\xi)) + \lambda_2 \log(\text{Eff}_{ED_{50}}(\xi)) + \lambda_3 \log(\text{Eff}_{MED}(\xi))$$

$$= \lambda_1 0.25 \log(|M(\xi, \Theta)|) - \lambda_2 \log(\text{Var}(\hat{ED}_{50})) - \lambda_3 \log(\text{Var}(\hat{MED})).$$

Here $ED_{50}$ and $MED$ are the median effective dose and the user-specified minimum effective dose.
3.12 Three-Objective Optimal Designs

Assume nominal values, dose interval and the minimum effect sought $\delta$ are given for the Hill’s model. For a user-selected vector $\lambda = (\lambda_1, \lambda_2, \lambda_3)$ with $\lambda_i \geq 0, i = 1, 2, 3$ and $\lambda_1 + \lambda_2 + \lambda_3 = 1$, the sought multiple-objective optimal design is the approximate design that maximizes

$$\lambda_1 \log (\text{Eff}_D(\xi)) + \lambda_2 \log (\text{Eff}_{ED_{50}}(\xi)) + \lambda_3 \log (\text{Eff}_{MED}(\xi))$$

$$= \lambda_1 0.25 \log (|M(\xi, \Theta)|) - \lambda_2 \log (\text{Var} (\hat{ED}_{50})) - \lambda_3 \log (\text{Var} (\hat{MED})) .$$

Here $ED_{50}$ and $MED$ are the median effective dose and the user-specified minimum effective dose.

3.13 Sensitivity Plot of a Robust Bayesian Multiple Objective Optimal Design with uniform prior distributions
3.14 Current Work
3.14 Current Work

- Given a fixed time interval, a fixed number of observations, a statistical model and an optimality criterion, design questions for a longitudinal study are
3.14 Current Work

- Given a fixed time interval, a fixed number of observations, a statistical model and an optimality criterion, design questions for a longitudinal study are
  - how many time points is optimal?
3.14 Current Work

Given a fixed time interval, a fixed number of observations, a statistical model and an optimality criterion, design questions for a longitudinal study are:

- how many time points is optimal?
- what are the sampling time points to observe the correlated responses?
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Given a fixed time interval, a fixed number of observations, a statistical model and an optimality criterion, design questions for a longitudinal study are

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- what are the sampling time points to observe the correlated responses?
- do I need replicates and if so how to distribute the replicates?
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- Convergence Issues of PSO
3.14 Current Work

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  - what are the sampling time points to observe the correlated responses?
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- Convergence Issues of PSO

- Finding optimal designs for nonlinear models with many factors and interaction terms (high dimension models)
3.15 A locally $D$-optimal design found by Twice Competitive Swarm Optimizer for a five-factor Poisson model with all pairwise interaction terms (Zhang and Wong, IEEE, 2018, under review)

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<th>$X_1$</th>
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<th>$X_3$</th>
<th>$X_4$</th>
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</tbody>
</table>

With small weights, a large sample is required to implement the design.
3.16 Optimal Discrimination Designs for 2 or 3 multi-factor polynomial models without a null model assumption (Yue, Vanderburgh & Wong, under review)

Figure 1: Plots of the sensitivity functions of two designs found by our algorithm for Example 3 (left) and Example 5 (right) to confirm their optimality.
Outline

1. Motivation from Optimal Design Problems
3. Optimal Designs via PSO and a Quick Demonstration
4. Closing Thoughts
4.1 Closing Thoughts

- Remember the "No Free Lunch Theorem"
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- PSO is a general optimization tool, not limited to minimizing convex functionals or for finding efficient designs
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4.1 Closing Thoughts

- Remember the "No Free Lunch Theorem"
- How to find efficient algorithms for a class of problems of interest?
- PSO is a general optimization tool, not limited to minimizing convex functionals or for finding efficient designs
- Find minimum bias designs, minimum mean-square error (MSE) designs (Stokes, Mandal & Wong, 2017, under prep.)
- Identify parameter redundancy in mixture distributions (Park & Wong, 2017, under prep.)
- Can hybridize with mathematical programming tools and traditional methods (such as simplex methods, Interior Point, etc) and speed up the search for the optimum (Garcia-Rodenas, Fidalgo-Lopez & Wong, 2018, under review)
4.2 PSO for Solving a System of Nonlinear Equations

Let $x^T = (x_1, x_2, \ldots, x_n)$. We want to solve

\[ f_1(x_1, x_2, \ldots, x_n) = 0, \]
\[ f_2(x_1, x_2, \ldots, x_n) = 0, \]
\[ \quad \ldots \]
\[ \ldots \]

and

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$$\vdots$$

and

$$f_r(x_1, x_2, \ldots, x_n) = 0.$$ 

If $x^*$ is the global minimum of $F(x) = \sum_{i=1}^{r} f_i^2(x)$, then $x^*$ solves the above system of equations. (Jabeipour, et al., 2011, Computers and Mathematics with Applications)
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Let \( x^T = (x_1, x_2, \ldots, x_n) \). We want to solve

\[
\begin{align*}
    f_1(x_1, x_2, \ldots, x_n) &= 0, \\
    f_2(x_1, x_2, \ldots, x_n) &= 0, \\
    & \quad \ldots \\
    f_r(x_1, x_2, \ldots, x_n) &= 0.
\end{align*}
\]

and

- If \( x^* \) is the global minimum of \( F(x) = \sum_{i=1}^{r} f_i^2(x) \), then \( x^* \) solves the above system of equations. (Jabeipour, et al., 2011, Computers and Mathematics with Applications)

- Alternatively, assume \( r = n \) and define \( F(x) = \sum_{i=1}^{r} |f_i(x)| \) and find its global minimum. (Wang, et al., 2009, IEEE Xplore)
4.6 Conclusions

- There are many more meta-heuristic algorithms, for example, Imperialist Competitive Algorithm (Masoudi, Holling & Wong, CSDA, 2016)
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- More?

  - Workshop on Particle Swarm Optimization and Evolutionary Computation (20 - 21 Feb 2018) at IMS, NUS (in this room).

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Co-authors:
Anthony Atkinson (The London School of Economics and Political Science, UK)
Ray-Bing Chen, Ping Yang Chen (Dept. of Statistics, National Cheng Kung University, Taiwan)
Holger Dette (Ruhr University, Germany)
Belmiro Duarte (Dept. of Chemical Engineering, University of Coimbra, Portugal)
Ricardo Garcia-Ródenas (Dept. of Mathematics, UCLM, Spain)
Won Hyun (Johnson & Johnson, Irvine, California)
Jozef Kiselak (Institute of Mathematics, Safarik University, Slovakia)
Jesús López-Fidalgo (Institute for Culture and Society, University of Navarra, Spain)
Joshua Lukemire (Dept. of Biostatistics, Emory University)
Abhyudal Mandal (Dept. of Statistics, U of Georgia)
Ehsan Masoudi, Heinz Holling (Dept. of Psychology, Münster University, Germany)
Guanghao Qi (Dept. of Biostatistics, Johns Hopkins University, USA)
Yu Shi, Zizhao Zhao (Dept. of Biostatistics, UCLA)
Milan Stehlik (Dept. of Applied Statistics, Johannes Kepler University, Linz, Austria)
Lieven Vanderburghe (Dept. of Electrical Engineering, UCLA)
Weichung Wang (Dept. of Mathematics, National Taiwan University)
Yuguang Yue (Dept. of Mathematics, Austin, University of Texas)