
Weng Kee Wong

Department of Biostatistics

Fielding School of Public Health

UCLA
Western Northern American Region (WNAR 2013)
June 16-19 2013
http://www.wnar.org
Two Upcoming Statistics Conferences at UCLA

- Western Northern American Region (WNAR 2013)
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- The 2013 Spring Research Conference (SRC) on Statistics in Industry and Technology
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Beverly Hills, Brentwood, Bel Air, Westwood, Wilshire Corridor
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- Beverly Hills, Brentwood, Bel Air, Westwood, Wilshire Corridor

- Close to the Pacific Ocean
Acknowledgements of Collaborators

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Outline

1 Motivation

2 Metaheuristic algorithms: Particle Swarm Optimization (PSO)

3 Demonstrations using PSO with MATLAB

4 Discussion
1. Motivation

- Derivation of optimal designs for nonlinear models is usually tedious, difficult and method for one model does not usually generalize to another
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- Algorithms are very helpful - available only for some types of optimal designs.

- Issues - proof, speed of convergence, ease of use and availability of software.

- Is there an easy-to-use **and efficient** method for finding optimal designs for different types of optimal designs for any given model?
1.1 Locally D-optimal Designs for the Logistic Model on $X = [-1, 1]$ (from Silvey’s text, 1980)

$$\log \frac{\pi(x)}{1 - \pi(x)} = \theta_1 + \theta_2 x, \quad \theta \in \Theta = \{ (\theta_1, \theta_2) : \theta_1 > 0 \ & \theta_2 > 0 \}.$$
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Let \(a^*\) solve \(\exp(a) = (a + 1)/(a - 1)\) and let \(u^*\) solve

\[
\exp(\theta_1 + \theta_2 u) = \frac{2 + (u + 1)\theta_2}{-2 + (u + 1)\theta_2}.
\]
1.1 Locally D-optimal Designs for the Logistic Model on $X = [−1, 1]$ (from Silvey’s text, 1980)

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

- condition
  
  $\{\theta : \theta_2 - \theta_1 \geq a\}$  
  $\{\theta : \theta_2 - \theta_1 < a, \exp(\theta_1 + \theta_2) \leq \frac{\theta_2 + 1}{\theta_2 - 1}\}$  
  $\{\theta : \exp(\theta_1 + \theta_2) > \frac{\theta_2 + 1}{\theta_2 - 1}\}$

- locally D-optimal design
  
  $\{\frac{a-\theta_1}{\theta_2}, \frac{-a-\theta_1}{\theta_2}; \frac{1}{2}, \frac{1}{2}\}$  
  $\{-1, u^*; \frac{1}{2}, \frac{1}{2}\}$  
  $\{-1, 1; \frac{1}{2}, \frac{1}{2}\}$
1.2 Amended Ford’s results on $X = [-c, c], \ c > 0$

Let $a^*$ solve the equation $e^a = \frac{a + 1}{a - 1}$ \quad (a^* = 1.5434),

let $b^*$ solve the equation $e^{\theta_0 + bc} = \frac{cb + 1}{cb - 1}$

and let $x^*$ solve the equation $e^{\theta_0 + \theta_1 x} = \frac{(x+c)\theta_1 + 2}{(x+c)\theta_1 - 2}$.

\[
\begin{align*}
\text{condition} & \quad \{ \theta : \theta_1 > \frac{1}{c}(\theta_0 + a^*) \} \\
\{ \theta : b^* < \theta_1 \leq \frac{1}{c}(\theta_0 + a^*) \} \\
\{ \theta : 0 < \theta_1 \leq b^* \} \\
\end{align*}
\]

\[
\begin{align*}
\text{locally D-optimal design} & \quad \{ -\frac{a^* - \theta_0}{\theta_1}, \frac{a^* - \theta_0}{\theta_1} ; \frac{1}{2}, \frac{1}{2} \} \\
& \quad \{ -c, x^* ; \frac{1}{2}, \frac{1}{2} \} \\
& \quad \{ -c, c ; \frac{1}{2}, \frac{1}{2} \}.
\end{align*}
\]
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Condition locally D-optimal design
\[
\{ \theta : \theta_1 > \frac{1}{c}(\theta_0 + a^*) \}
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Corrected results when $X = [a, b]$ in Sebastiani and Settimi (JSPI, 1997)
1.2 Amended Ford’s results on $X = [-c, c], \ c > 0$

Let $a^\ast$ solve the equation $e^a = \frac{a+1}{a-1}$ \hspace{1cm} (\(a^\ast = 1.5434\)),

let $b^\ast$ solve the equation $e^{\theta_0 + bc} = \frac{cb+1}{cb-1}$

and let $x^\ast$ solve the equation $e^{\theta_0 + \theta_1 x} = \frac{(x+c)\theta_1+2}{(x+c)\theta_1-2}$.

condition
\[
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locally D-optimal design
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Corrected results when $X = [a, b]$ in Sebastiani and Settimi (JSPI, 1997)

What is the E-optimal design for $X = [3, 6]$?
$y_i = \frac{(E_{con} - b)(\frac{D_i}{IC_{50}})^m}{1 + (\frac{D_i}{IC_{50}})^m} + b + \varepsilon_i = \eta(D_i, \theta) + \varepsilon_i, \varepsilon_i \sim N(0, \sigma(Ey_i)^{2\lambda})$

$D_i =$ dose of a drug assigned to subject $i$

$y_i =$ drug effect of subject $i$

$E_{con} =$ the control effect at zero drug concentration

$b =$ background effect at infinite drug concentration

$IC_{50} =$ inflection point on the curve (a measure of the drug potency)

$= \text{drug concentration that induces a 50\% decrease in the maximal effect } (E_{con} - b)$

$m =$ slope parameter of the curve.
1.4 Selected Plot of the Mean Function

\[ y = \frac{(E_{con} - b) \left( \frac{D}{IC_{50}} \right)^m}{1 + \left( \frac{D}{IC_{50}} \right)^m} + b \]

**EFFECT** (% control)

- **Econ**
- **Emax** = Econ - b
- **1/2 Emax**
- **b**

**CONCENTRATION** (Log scale)

- **IC_{50}**

Slope **m**
1.5 Information matrix for the Hill Model

Let the nominal value for $\theta$ be $\theta_0 = (E_{con}^0, b^0, IC_{50}^0, m^0)^T$ and let

$$f^T(x, \theta_0) = \left( \frac{\partial \eta(x, \theta)}{\partial E_{con}}, \frac{\partial \eta(x, \theta)}{\partial b}, \frac{\partial \eta(x, \theta)}{\partial IC_{50}}, \frac{\partial \eta(x, \theta)}{\partial m} \right)_{\theta_0}$$

where

$$\frac{\partial \eta(x, \theta)}{\partial E_{con}} = \frac{(x/IC_{50})^m}{(1 + x/IC_{50})^m}$$

$$\frac{\partial \eta(x, \theta)}{\partial b} = \frac{1}{1 + (x/IC_{50})^m}$$

$$\frac{\partial \eta(x, \theta)}{\partial IC_{50}} = -\frac{(b - E_{con})(x/IC_{50})^m \log(x/IC_{50})}{(1 + (x/IC_{50})^m)^2}$$

$$\frac{\partial \eta(x, \theta)}{\partial m} = \frac{(b - E_{con})m(x/IC_{50})^m}{IC_{50}(1 + (x/IC_{50})^m)^2}.$$

The total information matrix is proportional to

$$M(\xi, \theta_0) = F^T WF$$

where $F = \left[ f^T(x_1), f^T(x_2), \ldots f^T(x_n) \right]^T$ and $W = \text{diag}(y_1^{-2\lambda}, \ldots, y_n^{-2\lambda})$. 

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October 19, 2012 10 / 50
(a) Recent trends indicate rapid growth of nature-inspired optimization in academia and industry. Computing, Vol. 93, 121-133.
(b) Survival of the flexible: explaining the recent dominance of nature-inspired optimization within a rapidly evolving world. Computing, Vol. 93, 135-146.

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- Compared different types of algorithms based on historical bias, academic bias, conceptual appeal, simplicity of implementation, algorithm utility, flexibility
1.6 Algorithms and Their Usage (Whitacre, 2011)

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- NNIM = \{ greedy randomized adaptive search, great deluge, squeaky wheel optimization, tabu, harmony search, unit-walk, stochastic local search, iterated greedy algorithms, iterated local search, cross entropy method, extremal optimization, stochastic diffusion search, reactive search optimization, random-restart hill climbing, variable neighborhood search \}
1.7 Mathematical Optimization Techniques (MOT) versus Nature-Inspired Metaheuristics (NIM)

- MOT = \{ mathematical programming, constraint programming, quadratic programming, quasi-Newton method, nonlinear programming, interior-point method, goal programming, integer programming, simplex method, branch and bound algorithm, linear programming, dynamic programming, branch-and-cut, exhaustive search, branch and price, convex programming, stochastic programming, quasi-convex programming \}
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- **NIM** = \{ genetic algorithm, evolutionary computation, swarm optimization, ant colony optimization, memetic algorithm, genetic programming, simulated annealing, nature inspired algorithm, bio-inspired optimization, evolitional strategies, *swarm intelligence*, hyper-heuristics, adaptive operator selection, multi-meme algorithms, self generating algorithms, honey bees algorithm, differential evolution \}

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2. Metaheuristic 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 meta-heuristics implement some form of stochastic optimization.
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- Our interest here is nature-inspired meta-heuristic algorithms
- Particle Swarm Optimization (PSO) proposed by Eberhard & Kennedy (IEEE, 1995) models animal instincts.
2.1 Heuristics versus Metaheuristics

Heuristics are often problem-dependent, that is, you define and heuristic for a given problem. Meta-heuristics are problem-independent techniques that can be applied to a broad range of problems. A meta-heuristic knows nothing about the problem it will be applied, it can treat functions as black boxes.

A heuristic exploits problem-dependent information to find a ’good enough’ solution to a specific problem, while meta-heuristics are, like design patterns, general algorithmic ideas that can be applied to a broad range of problems.
How can birds or fish exhibit such a coordinated collective behavior?
Many websites and books provide tutorials, codes and track PSO applications, e.g. http://www.swarmintelligence.org/index.php
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- International Conference on Swarm Intelligence: *Theoretical Advances* and Real world Applications in France on June 2011
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- A journal, Swarm Intelligence, was born in 2007 and another, International Journal of Swarm Intelligence Research, in 2010 - just to keep track of PSO development and applications in the real world. A third is Swarm and Evolutionary Computation (2011)
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- bioinformatics
- reactive power and voltage control in electric power systems
2.5 Recent Papers in Particle Swarm Optimization


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2.6 Main Features of PSO:

Random generation of an initial population

Each particle has a fitness value that depends on the optimum

Population is reproduced based on fitness value

If requirements are met, stop; otherwise each particle updates its fitness value

Shares similarity with genetic algorithm but differs in important ways discussed in numerous sites such as http://www.alife.org or http://www.engr.iupui.edu/ eberhart with tutorials
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PSO comprises a very simple concept, its paradigms can be implemented in a few lines of computer code, requires only primitive mathematical operators and is computationally inexpensive in terms of both memory requirement and speed
2.7 Basic Equations and tuning parameters in PSO

\[ v_i(t + 1) = \omega_i v_i(t) + c_1 \beta_1 (p_i(t) - x_i(t)) + c_2 \beta_2 (p_g(t) - x_i(t)), \]
\[ x_i(t + 1) = x_i(t) + v_i(t + 1). \]

\( x_i \) 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 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)

For many applications, \( c_1 = c_2 = 2 \) seem to work well and usually 20 – 50 particles will suffice (Kennedy, IEEE, 1997).
3 Demonstrations: PSO-generated Optimal Designs

3.1 Locally D-optimal Designs for a 4-parameter Hill Model

3.2 Locally D-Optimal Designs for a Rational Polynomial Model

3.3 Optimal Designs for a Continuation Ratio Model

3.4 Locally c-Optimal Designs for a Compartmental Model

3.5 Locally $D_s$-optimal Designs for the Quadratic Logistic Model
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3.6 Minimax Optimal Designs: Background
   - Locally E-optimal Designs for the Michaelis-Menten Model
   - Minimax D-optimal Designs for the Logistic Model
3.1: PSO-generated designs coincide with the locally D-optimal designs for the Hill model with fixed nominal values $E_{con} = 1.7$, $b = 0.137$, $\lambda = 0.794$ and various nominal values for $IC_{50}$ and $m$ for different drugs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>$IC_{50}$</th>
<th>$m$</th>
<th>support points</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMTX</td>
<td>0.00875</td>
<td>-1.790</td>
<td>0  0.00773 0.02965 8.95</td>
</tr>
<tr>
<td>MTX</td>
<td>0.0223</td>
<td>-2.740</td>
<td>0  0.02056 0.04950 22.3</td>
</tr>
<tr>
<td>AG2034</td>
<td>0.453</td>
<td>-0.825</td>
<td>0  0.32042 5.56703 453</td>
</tr>
<tr>
<td>AG2032</td>
<td>0.0774</td>
<td>-3.490</td>
<td>0  0.07263 0.144756 77.4</td>
</tr>
<tr>
<td>AG2009</td>
<td>111</td>
<td>-1.030</td>
<td>0  53.9007 377.2057 1500</td>
</tr>
<tr>
<td>AG337</td>
<td>0.468</td>
<td>-1.540</td>
<td>0  0.40495 1.93184 468</td>
</tr>
<tr>
<td>ZD1694</td>
<td>0.0429</td>
<td>-1.690</td>
<td>0  0.03761 0.15624 42.9</td>
</tr>
</tbody>
</table>

3.2 Locally D-Optimal Designs for a Rational Polynomial Model

The model is

\[ E(y) = \frac{x + \alpha}{\beta_0 + \beta_1(x + \alpha) + \beta_2(x + \alpha)^2} \]

Examples of the equally weighted locally D-optimal designs:

<table>
<thead>
<tr>
<th>Case</th>
<th>( \alpha )</th>
<th>( \beta_0 )</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
<th>nominal values</th>
<th>support points</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>0.1</td>
<td>1.0</td>
<td>-0.8</td>
<td>1</td>
<td>0</td>
<td>0.384 0.964 2.424</td>
</tr>
<tr>
<td>(ii)</td>
<td>0.5</td>
<td>1.0</td>
<td>0.8</td>
<td>1</td>
<td>0</td>
<td>0.302 1.285 5.470</td>
</tr>
</tbody>
</table>

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

\[
\ln\left[\frac{p_3(\theta, x)}{1 - p_3(\theta, x)}\right] = a_1 + b_1 x, \quad b_1 > 0 \tag{1}
\]

\[
\ln\left[\frac{p_2(\theta, x)}{p_1(\theta, x)}\right] = a_2 + b_2 x, \quad b_2 > 0. \tag{2}
\]
Example 3.3a: Calculus

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

$$g(x, \theta) = b_2(1 + e^{-a_1-b_1x}) - b_1(1 + e^{a_2+b_2x}) = 0.$$
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$$g(x, \theta) = b_2(1 + e^{-a_1-b_1x}) - b_1(1 + e^{a_2+b_2x}) = 0.$$ 

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

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

$$= \begin{pmatrix}
    e^{-a_1-b_1x_{BOD}} / [b_1(e^{-a_1-b_1x_{BOD}} + e^{a_2+b_2x_{BOD}})] \\
    x_{BOD} e^{-a_1-b_1x_{BOD}} / [b_1(e^{-a_1-b_1x_{BOD}} + e^{a_2+b_2x_{BOD}})] \\
    e^{a_2+b_2x_{BOD}} / [b_2(e^{-a_1-b_1x_{BOD}} + e^{a_2+b_2x_{BOD}})] \\
    x_{BOD} e^{a_2+b_2x_{BOD}} / [b_2(e^{-a_1-b_1x_{BOD}} + e^{a_2+b_2x_{BOD}})]
\end{pmatrix}.$$
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$$\left[ \frac{\partial g(x_{BOD}(\theta), \theta)}{\partial x} \right]^{-1} \frac{\partial g(x_{BOD}(\theta), \theta)}{\partial \theta} = \left( \frac{e^{-a_1-b_1x_{BOD}}/[b_1(e^{-a_1-b_1x_{BOD}} + e^{a_2+b_2x_{BOD}})]}{x_{BOD}e^{-a_1-b_1x_{BOD}}/[b_1(e^{-a_1-b_1x_{BOD}} + e^{a_2+b_2x_{BOD}})]} \right).$$

Use standard algorithm to generate the locally optimal design.
### 3.3b Selected BOD- & D-optimal designs and D-efficiencies (Fan & Chaloner, JSPI, 2003)

<table>
<thead>
<tr>
<th>dose</th>
<th>weight</th>
<th>((a_1, b_1, a_2, b_2))</th>
<th>D-efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5.67</td>
<td>0.001</td>
<td>((-3.3, 0.5, 3.4, 1))</td>
<td>-5.67, 0.001</td>
</tr>
<tr>
<td>-0.64</td>
<td>0.800</td>
<td>((-3.3, 0.5, 3.4, 1))</td>
<td>-4.63, 0.292</td>
</tr>
<tr>
<td>4.84</td>
<td>0.199</td>
<td>((-3.3, 0.5, 3.4, 1))</td>
<td>-0.64, 0.800</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.26</td>
<td>0.632</td>
<td>((-1, 0.5, 2, 1))</td>
<td>-1.26, 0.632</td>
</tr>
<tr>
<td>4.11</td>
<td>0.368</td>
<td>((-1, 0.5, 2, 1))</td>
<td>-1.30, 0.549</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.30</td>
<td>0.549</td>
<td>((-1.04, 0.812, 1))</td>
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<tr>
<td>2.37</td>
<td>0.451</td>
<td>((-1.04, 0.812, 1))</td>
<td>-1.30, 0.549</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-14.00</td>
<td>0.100</td>
<td>((0.4, 0.2, 2, 1))</td>
<td>-14.00, 0.100</td>
</tr>
<tr>
<td>-1.14</td>
<td>0.628</td>
<td>((0.4, 0.2, 2, 1))</td>
<td>-13.00, 0.070</td>
</tr>
<tr>
<td>9.99</td>
<td>0.272</td>
<td>((0.4, 0.2, 2, 1))</td>
<td>-13.00, 0.070</td>
</tr>
</tbody>
</table>

Weng Kee Wong (Dept. of Biostatistics) wkwong@ucla.edu
A popular compartmental model with $\theta^T = (\theta_1, \theta_2, \theta_3)$:

$$\eta(x, \theta) = \theta_3 \{ \exp(-\theta_2 x) - \exp(-\theta_1 x) \} \quad \theta_1 \geq \theta_2 \geq 0, \theta_3 \geq 0, \quad x \geq 0.$$  

- Optimality criteria: (i) area under the curve;  
- (ii) time to maximum concentration;  
and  
- (iii) maximum concentration.
3.4 A 3-parameter Compartment Model

A popular compartmental model with \( \theta^T = (\theta_1, \theta_2, \theta_3) \):

\[
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  and (iii) maximum concentration.

- (a) \( AUC = \int_0^\infty \eta(x, \theta) dx = \frac{\theta_3}{\theta_2} - \frac{\theta_3}{\theta_1} = g_1(\theta) \)
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(b) Time to maximum concentration: \( x_{\text{max}} = \frac{\log \theta_1 - \log \theta_2}{\theta_1 - \theta_2} = g_2(\theta) \)
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- (c) Maximum concentration: $\eta(x_{max}, \theta) = g_3(\theta)$
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$$
\eta(x, \theta) = \theta_3 \{ \exp(-\theta_2 x) - \exp(-\theta_1 x) \} \quad \theta_1 \geq \theta_2 \geq 0, \theta_3 \geq 0, \ x \geq 0.
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Optimality criteria: (i) area under the curve; (ii) time to maximum concentration; and (iii) maximum concentration.

- (a) $AUC = \int_0^\infty \eta(x, \theta)dx = \frac{\theta_3}{\theta_2} - \frac{\theta_3}{\theta_1} = g_1(\theta)$
- (b) Time to maximum concentration: $x_{max} = \frac{\log\frac{\theta_2}{\theta_1}}{\theta_1 - \theta_2} = g_2(\theta)$
- (c) Maximum concentration: $\eta(x_{max}, \theta) = g_3(\theta)$

Use nominal values in Atkinson & Donev’s (2004) text:

$\theta_1^0 = 4.29, \theta_2^0 = 0.0589$ and $\theta_3^0 = 21.80$. 
In radiation research, we want to design in vivo multifraction experiments to estimate the $\alpha - \beta$ ratio (Taylor, Radiation Research, 1990).

\[
p(x, \theta) = \frac{1}{1 + \exp\{-a - b(x - m)^2\}} \quad \theta^T = (a, b, m)
\]

Using Elfving’s theorem, Fornius and Nyquist, Communications in Statistics, 2010) used geometrical arguments and reported various $D_s$-optimal designs for estimating different subsets of $\theta$. 
Want to optimally design to, say minimize the maximal variance of the responses over the extrapolated doses.
Want to optimally design to, say minimize the maximal variance of the responses over the extrapolated doses.

Notable References: Kiefer and Wolfowitz (1964a, 1964b, 1965), Levin (1965), Spruill (1984, 1990) assumed homoscedastic polynomial models with $X = [-1, 1]$ and were able to obtain analytical results when $Z = [a, b]$ for selected values of $a$ and $b.$
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Maximizing minimal efficiencies under several objectives in toxicological studies: Dette, Pepelyshev, Shpilev, Wong (Statistics and Its Interface, 2009), Bernoulli Journal (2009, 2010), Dette, Pepelyshev and Wong (Risk Analysis, 2011) and Dette, Pepelyshev and Wong (Journal of Pharmacokinetics and Pharmacodynamics, 2012)
Suppose
\[ y(x) = f^T(x)\theta + e(x)/\sqrt{\lambda(x)}, \quad x \in X \]
where \( f^T(x) \) is a vector of known regression functions, \( \lambda(x) \) is a known efficiency function and \( e(x) \sim N(0, \sigma^2) \). If observations are independent, information matrix is proportional to
\[ M(\xi) = \int_X \lambda(x)f(x)f^T(x)\xi(dx), \]
and the variance of the fitted response at \( x \) using \( \xi \) is proportional to
\[ \nu(x, \xi) = \text{var}_\xi(f^T(x)\hat{\theta}) = f^T(x)M^{-1}(\xi)f(x). \]

**Definition:** \( \xi^* \) is minimax optimal design among all designs on \( X \) if
\[ \xi^* = \arg \min_{\xi} \max_{x \in Z} \nu(x, \xi), \]
where \( Z \) is a user-selected compact set for prediction purposes.
Equivalence Theorem: $\hat{\xi}^*$ is minimax-optimal if and only if there exists a probability measure $\mu^*$ on $A(\hat{\xi}^*)$ such that for all $x \in X$,

$$c(x, \mu^*, \hat{\xi}^*) = \int_{A(\hat{\xi}^*)} \lambda(x)(f^T(x)M(\xi)^{-1}f(a))^2\mu^*(da) - v(a, \hat{\xi}^*) \leq 0,$$

with equality at the support points of $\hat{\xi}^*$. Here,

$$A(\xi) = \{a \in Z | v(a, \xi) = \max_{z \in Z} v(z, \xi)\}.$$
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\]

with equality at the support points of \( \xi^* \). Here,

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A(\xi) = \{ a \in Z | v(a, \xi) = \max_{z \in Z} v(z, \xi) \}.
\]

A proof is in Berger, King & Wong (Psychometrika, 2000), where they applied applied minimax optimal designs for item response models in education testing problems.
3.6b Equivalence theorem for a Minimax-type criterion

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- \( \mu^* \) can be shown to be a maximin probability measure.
3.6b Equivalence theorem for a Minimax-type criterion

Equivalence Theorem: $\xi^*$ is minimax-optimal if and only if there exists a probability measure $\mu^*$ on $A(\xi^*)$ such that for all $x \in X$,

$$c(x, \mu^*, \xi^*) = \int_{A(\xi^*)} \lambda(x) (f^T (x) M(\xi)^{-1} f(a))^2 \mu^*(da) - v(a, \xi^*) \leq 0,$$

with equality at the support points of $\xi^*$. Here,

$$A(\xi) = \{a \in Z | v(a, \xi) = \max_{z \in Z} v(z, \xi)\}.$$

- A proof is in Berger, King & Wong (Psychometrika, 2000), where they applied applied minimax optimal designs for item response models in education testing problems.

- $\mu^*$ can be shown to be a maximin probability measure

- Minimax efficiency lower bound can be directly found for any design using convex theory.
The Michaelis-Menten model for a continuous response is

\[ y = \frac{\theta_1 x}{\theta_2 + x} + \varepsilon, \quad x > 0 \quad \theta^T = (\theta_1, \theta_2), \theta_1 > 0, \theta_2 > 0. \]

If \( \varepsilon \) is normally distributed with mean 0 and constant variance, the
Fisher information matrix for a given design \( \xi \) is

\[ M(\xi, \theta) = \int \left( \frac{\theta_1 x}{\theta_2 + x} \right)^2 \left( -\frac{1}{\theta_1} - \frac{1}{\theta_1(\theta_2 + x)} \right) \, d\xi(x). \]

Let

\[ w = \frac{\sqrt{2}(\theta_1/\theta_2)^2(1 - \tilde{z})\{\sqrt{2} - (4 - 2\sqrt{2})\tilde{z}\}}{2 + (\theta_1/\theta_2)^2\{\sqrt{2} - (4 - 2\sqrt{2})\tilde{z}\}^2} \]

and \( \tilde{z} = \tilde{x}/(\theta_2 + \tilde{x}) \). The locally \( E \)-optimal design has weight \( 1 - w \) at \( \tilde{x} \) and weight \( w \) at \( \{(\sqrt{2} - 1)\theta_2 \tilde{x}\}/\{2 - \sqrt{2}\} \tilde{x} + \theta_2 \).
### Table 1: Locally $E$-optimal designs for the Michaelis-Menten model on $X = [0, 200]$. 

<table>
<thead>
<tr>
<th>$\theta_1$</th>
<th>$\theta_2$</th>
<th>$\xi_{PSO}$</th>
<th>$E$-optimal designs</th>
</tr>
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<tbody>
<tr>
<td>100</td>
<td>150</td>
<td>46.52 (0.693)</td>
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<td>100</td>
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<tr>
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- discrepancy stubbornly remained and did not disappear
- simply calculation error from the formula; PSO gave right answer!
Figure 4: Plot of the maximum eigenvalue of $M(\xi, \theta)^{-1}$ versus the number of PSO iterations.
Figure 5: The movement of particles in the PSO search for the E-optimal design for the Michaelis-Menten model at various stages. The red star in each of the three plots indicates the current best design.
Assume there is a plausible region $\Theta$ for the unknown intercept ($\theta_1$) and slope ($\theta_2$) parameters in the two parameter logistic model, i.e.

$$(\theta_1, \theta_2) \in \Theta.$$  

King & Wong (Biometrics, 2002) found minimax D-optimal designs when the form of $\Theta$ is a cartesian product.

For example, when $\Theta = [0, 3.5] \times [1, 3.5]$ and $X$ is unrestricted:

<table>
<thead>
<tr>
<th>$x_i$</th>
<th>0.35</th>
<th>0.62</th>
<th>1.39</th>
<th>2.11</th>
<th>2.88</th>
<th>3.85</th>
</tr>
</thead>
<tbody>
<tr>
<td>$w_i$</td>
<td>0.18</td>
<td>0.21</td>
<td>0.11</td>
<td>0.11</td>
<td>0.21</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Assume there is a plausible region $\Theta$ for the unknown intercept ($\theta_1$) and slope ($\theta_2$) parameters in the two parameter logistic model, i.e.

$$(\theta_1, \theta_2) \in \Theta.$$

King & Wong (Biometrics, 2002) found minimax D-optimal designs when the form of $\Theta$ is a cartesian product.

For example, when $\Theta = [0, 3.5] \times [1, 3.5]$ and $X$ is unrestricted:

$$x_i = 0.35 \quad 0.62 \quad 1.39 \quad 2.11 \quad 2.88 \quad 3.85$$

$$w_i = 0.18 \quad 0.21 \quad 0.11 \quad 0.11 \quad 0.21 \quad 0.18$$

- Algorithm for finding minimax optimal designs remains elusive.
Figure 6: Plot of the directional derivative of claimed minimax D-optimal design for the logistic model.
Example 3.6f: A minimax D-optimal design for the logistic regression model when we have plausible ranges for the two parameters (King & Wong, Biometrics, 2000)

Consider the logistic model

\[ p(x, \theta) = \frac{1}{1 + \exp(-\theta_2(x - \theta_1))}, \quad \theta^T = (\theta_1, \theta_2). \]

The Fisher information matrix for \( \xi \) is \( M(\xi, \theta) \) given by

\[
\int \begin{pmatrix}
\theta_2^2 p(x, \theta)(1 - p(x, \theta)) & -\theta_2(x - \theta_1)p(x, \theta)(1 - p(x, \theta)) \\
-\theta_2(x - \theta_1)p(x, \theta)(1 - p(x, \theta)) & (x - \theta_1)^2 p(x, \theta)(1 - p(x, \theta))
\end{pmatrix} d\xi(x)
\]

Goal: Find a minimax D-optimal design \( \xi^* \) such that

\[ \xi^* = \arg \min_{\xi} \max_{\theta \in \Theta} \log(\left| M^{-1}(\xi, \theta) \right|). \]

Here \( \Theta \) is a known set containing all plausible values of \( \theta_1 \) and \( \theta_2 \).
Figure 7: Plot of the directional derivatives \( c(x, \xi_{PSO}, \mu^*) \) versus \( x \) for two cases:

(i) \( \Theta = [0, 2.5] \times [1, 3.0] \) on \( X = [-1, 4] \) (left)

(ii) \( \Theta = [0, 3.5] \times [1, 3.5] \) on \( X = [-5, 5] \) (right).

no. of particles for external(internal) optimization: 64(256) 32(512)
no. of iterations for external(internal) optimization: 100(200) 50(100)

Efficiency Lower Bounds of PSO-generated designs are both about 0.9924.
Helpful to have a design website to find tailor-made optimal designs at http://optimal-design.biostat.ucla.edu/optimal/

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- Apply PSO to find optimal exact designs, minimum bias optimal designs and Bayesian Designs? What about optimal designs on a discrete design space? Models with correlated errors?
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- Apply PSO to find optimal exact designs, minimum bias optimal designs and Bayesian Designs? What about optimal designs on a discrete design space? Models with correlated errors?

- Expand website capabilities to find an optimal design for any model and any criterion (?) - hopefully.)
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- Gravitational search algorithm (2009)
- Cuckoo search (Yang & Deb, 2009)
- Firefly algorithm (2009, 2010)
- Bat algorithm (2010)
4.2 Resources for Metaheuristic Optimization and Nature-Inspired Metaheuristic Codes

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

Another is at
http://www.metaheuristic.com/metaheuristic_optimization.php

Xin-She Yang’s 2008 book and updated in 2010:
4.3 Other Methods for Finding Optimal Designs

What about **semi-definite programming (SDP)** and **semi-infinite programming (SIP)**?
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- O’Brien (Journal of Data Science, 2005) noted that the locally $D_s$-optimal design for estimating $\theta_2$ in the 2-compartmental model

$$\eta(x, \theta) = \frac{\theta_1}{\theta_1 - \theta_2} \{ \exp(-\theta_2 x) - \exp(-\theta_1 x) \}$$

found by Hill and Hunter (Technometrics, 1974) over a discretized design space does not satisfy the equivalence theorem.
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found by Hill and Hunter (Technometrics, 1974) over a discretized design space does not satisfy the equivalence theorem.

- Huge memory space is needed especially for finding Bayesian optimal designs for nonlinear models (Duarte and Wong, 2012a)
4.4 Further Minimax Design Problems

(a) Power Logistic Model (Prentice, Biometrics, 1976):

\[ p(x, \theta) = \frac{1}{1 + \exp(\beta(x - \mu))}^s, \quad \theta \in \Theta = \{ (\mu, \beta, s), \mu > 0 \ & \beta > 0 \}. \]

(b) Logistic Model with a nonlinear constraint on the parameter space:

\[ \log \frac{\pi(x)}{1 - \pi(x)} = \beta(x - \mu), \quad \theta \in \Theta = \{ (\mu, \beta), \mu > 0 \ & \beta > 0 \}, \]

i.e. constrained space has a nonlinear relationship in \( \mu \) and \( \beta \).

Duarte and Wong (2012b) used SIP and found minimax D-optimal designs for such problems.
Table 2: Minimax D-optimal designs for the logistic model when the model parameters are functionally dependent inside the plausible region

<table>
<thead>
<tr>
<th>Constraint</th>
<th>$\xi_{op}$</th>
<th>$\xi_{op}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta \geq 2 \mu$</td>
<td>$-0.0680(0.5000)$</td>
<td>$0.2885(0.2796)$</td>
</tr>
<tr>
<td>$\beta \in [0, 3]$</td>
<td>$1.5680(0.5000)$</td>
<td>$1.2678(0.4408)$</td>
</tr>
<tr>
<td>$\beta \leq 2 \mu$</td>
<td>$-0.2997(0.5000)$</td>
<td>$0.1710(0.2606)$</td>
</tr>
<tr>
<td>$\beta \in [0, 3]$</td>
<td>$1.7997(0.5000)$</td>
<td>$1.5000(0.4788)$</td>
</tr>
<tr>
<td>$\beta \geq 2 \mu^2$</td>
<td>$-0.0680(0.5000)$</td>
<td>$0.2498(0.2772)$</td>
</tr>
<tr>
<td>$\beta \in [0, 3]$</td>
<td>$1.5680(0.5000)$</td>
<td>$1.2662(0.4457)$</td>
</tr>
<tr>
<td>$\beta \leq 2 \mu^2$</td>
<td>$-0.6274(0.5000)$</td>
<td>$0.1710(0.2606)$</td>
</tr>
<tr>
<td>$\beta \in [0, 3]$</td>
<td>$2.1274(0.5000)$</td>
<td>$1.5000(0.4788)$</td>
</tr>
</tbody>
</table>
Fig. 8: Plot of the directional derivative $\Psi(x, \xi_{op}, \theta)$ of the SIP-generated design $\xi_{op}$ over $X$ confirms that $\xi_{op}$ is minimax D-optimal for the logistic model with $\beta \leq 2\mu^2$, $\mu \in [0.5, 2.5]$ and $\beta \in [0.0, 3.0]$.
4.3 Tomlab

**LATEST NEWS**

Aug 23rd 2012
TOMLAB 7.9 released. Read more >>

Dec 16th 2011
TOMLAB 7.8 released. Read more >>

Jun 8th 2011
TOMLAB 7.7 released. New versions of CPLEX, GUROBI and KNITRO. Read more >>

Nov 24th 2010
TOMLAB 7.6 released. GUROBI now supports MIQP. Read more >>

Oct 1st 2010
TOMLAB 7.5 released. PROPT now supports binary and integer variables! Read more >>

Mar 24th 2010
TOMLAB 7.4 released. PROPT now has an automated scaling module. Read more >>

Dec 7th 2009
TOMLAB 7.3 released. GUROBI 2.0 released. Several Base Module updates! Read more >>

Aug 18th 2009
TOMLAB 7.2 released. New GUROBI solver now available. Read more >>

Aug 6th 2009
TOMLAB switches to BITROCK for multi-platform installation support. Read more >>

Mar 25th 2009
TOMLAB v7.1 released. Many additional PROPT examples, MINLP support in KNITRO and more. Read more >>

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**TOMLAB /SOL v7.8**
TOMLAB /SOL v7.8 efficiently integrates the well-known solvers developed by the Stanford Systems Optimization Laboratory (SOL) with MATLAB and TOMLAB. The toolbox includes the solvers MINOS, LPOPT, QPOPT, NPSOL, NLSSOL, LSSOL, SNOPT, SQOPT. Read more >> Buy now >>

**TOMLAB /CPLEX v12.2**
Solver package CPLEX 12.2, including Matlab interface. State-of-the-art mixed-integer linear and quadratic programming with quadratic constraints (MILP, MIQP, MIQQ), and large-scale simplex and barrier methods for LP and QP. Read more >> Buy now >>

**TOMLAB /CGO v7.8**
Solver package for costly global optimization. The latest release of the solvers rbfSolve and EGO also handles integer variables. The package is best used in conjunction with TOMLAB /SOL or TOMLAB /OQNLP if integer variables are included. Read more >> Buy now >>
Successes with PSO: nonlinear models up to 6 parameters, cubic mixture models with 8 factors on the regular simplex (185-dimensional optimization problem!) and log contrast mixture models.
4.4 Summary

- successes with PSO: nonlinear models up to 6 parameters, cubic mixture models with 8 factors on the regular simplex (185-dimensional optimization problem!) and log contrast mixture models.

- Recall the **NO FREE LUNCH THEOREM**. For complex problems, need to *hybridize algorithms!*
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PSO methodology offers great promise and I believe represents a leap forward in the field of optimal experimental designs.
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- PSO methodology offers great promise and I believe represents a leap forward in the field of optimal experimental designs.

- Students should be more exposed to different types of optimization techniques - more interdisciplinary training!
Questions/Comments?

Please send them to Weng Kee Wong

( wkwong@ucla.edu )

The support for the entire work on the website was entirely supported by a NIGMS grant award R01GM072876