Optimal design in population kinetic experiments by set-valued methods





Peter Gennemark

(Mathematical sciences, Göteborg, Dept. of Mathematics, Uppsala)

in collaboration with

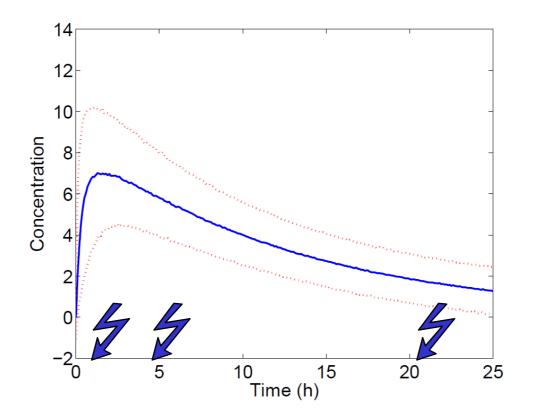
Warwick Tucker, Alexander Danis (Dept. of Mathematics, Uppsala)

Andrew Hooker, Joakim Nyberg

(Dept. Of Pharmaceutical Biosciences, Pharmacometrics, Uppsala)

Optimal experimental design

$$f(t_{i,j}) = a_i \frac{k_{21,i} k_{02,i}}{Cl_i (k_{21,i} - k_{02,i})} \left(e^{-k_{02,i} t_{i,j}} - e^{-k_{21,i} t_{i,j}} \right) + \mathcal{E}_{i,j}$$



$$k_{21,i} = \beta_1 e^{b_1,i}$$
$$k_{02,i} = \beta_2 e^{b_2,i}$$
$$Cl_i = \beta_3 e^{b_3,i}$$
$$b_i = N(0,D)$$
$$\varepsilon = N(0,\sigma^2)$$

Optimal design, definition?



The optimal design problem

Search domain, *D*, of possible designs.

Prior knowledge of the model structure and parameters.

An **objective function**, *f*, that measures the imprecison in the parameter estimates.

$$d^{opt} = \arg\min_{d \in D} f(d)$$

PopED (Population Experimental Design)

Population optimal design

http://poped.sf.net

▶ PopED Gui <no file="" open=""></no>	
File Optimal Design Help	
Main settings	
Model name NewModel	
Model description	
Main settings Parameter definitions Samples Covaria	tes Other design variables Parameter values Sampling Schedul
Optimization settings	
Task	Num models 1
Find optimal design	Subjects
C Evaluate with current design	Use grouping
	Number of subjects
Optimization method D-Optimal	Total max groupsize
Approximation type First Order	Total min groupsize
- Crank Tara	Num individuals in each group
Search Type	Num ind Min ind Max ind
Stochastic Gradient	Group1 1 1
Line Search Exchange Algorithm	
Tasks to optimize	
Samples per Subject	Model size
✓ Samples per Sabjeet	Number of population parameters (fixed effects)
Number of individuals per group	Number of BSV parameters (random effects)
Covariates Other variables	Number of covariates 0 a
	Number of other design variables 0 x

Nyberg J., Ueckert S., Karlsson M.O., Hooker A.C., Uppsala University

Our optimal design approach

We pioneer the use of set-valued methods based on **interval analysis** and **constraint propagation** to estimate parameters in NLME models.

We use this for optimal experimental design.

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$a \in [1,2]$	$a + b \in [3,5]$
$b \in [2,3]$	$a * b \in [2, 6]$

Our optimal design approach

We pioneer the use of set-valued methods based on **interval analysis** and **constraint propagation** to estimate parameters in NLME models.

We use this for optimal experimental design.

 $a \in [1,2] \qquad a+b \in [3,5]$ $b \in [2,3] \qquad a^*b \in [2,6]$ $f(x) = 3x + 2 \qquad f(a) \in 3^*[1,2] + 2 = [5,8]$

Consider the model $f(t) = k_1 t + k_2$

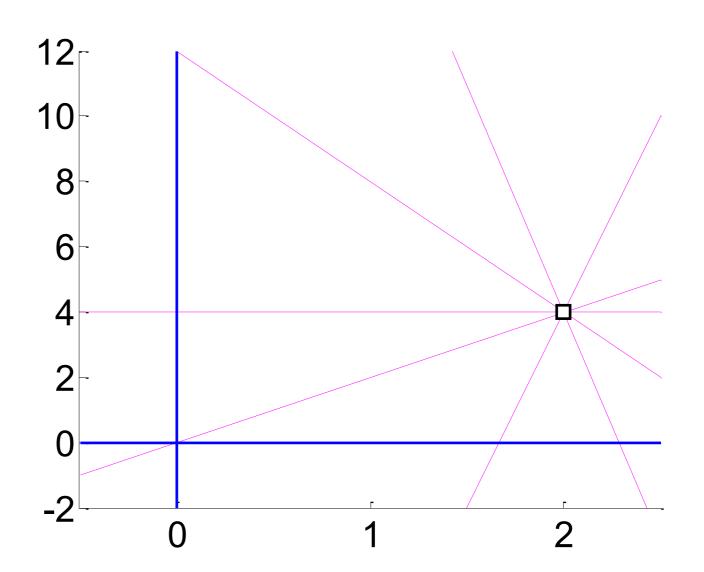
Data:
$$f(2) = 4$$

Constraints:

Consider the model $f(t) = k_1 t + k_2$

Data: f(2) = 4

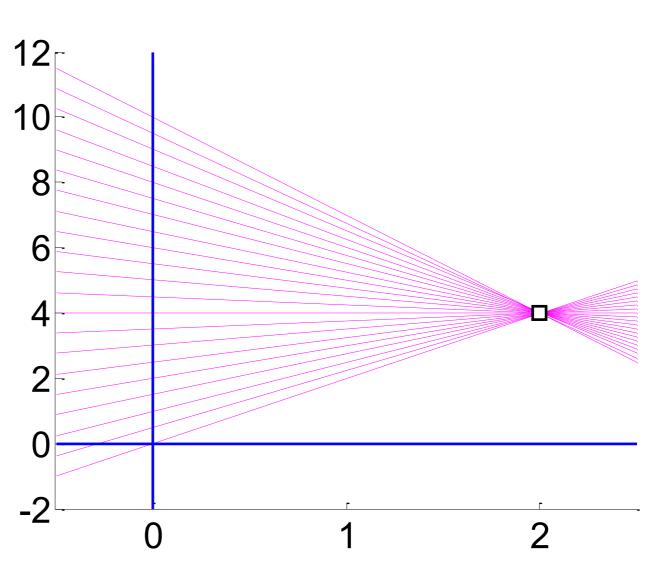
Constraints:



Consider the model $f(t) = k_1 t + k_2$

Data: f(2) = 4

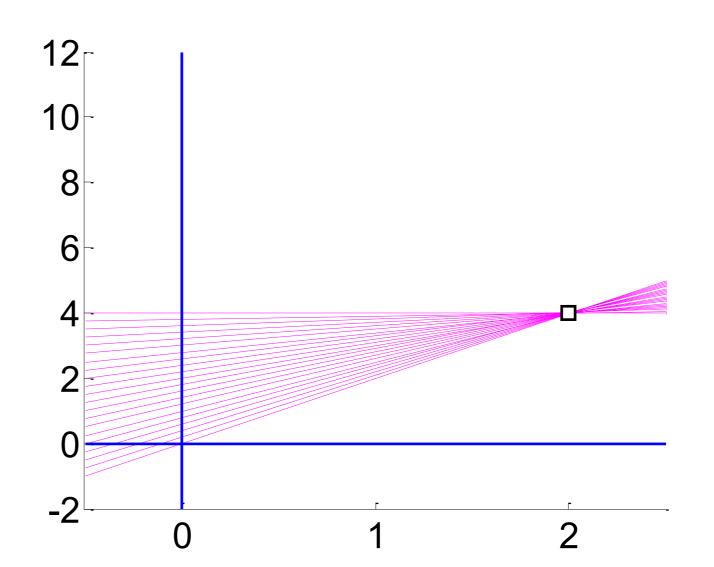
Constraints:



Consider the model $f(t) = k_1 t + k_2$

Data: f(2) = 4

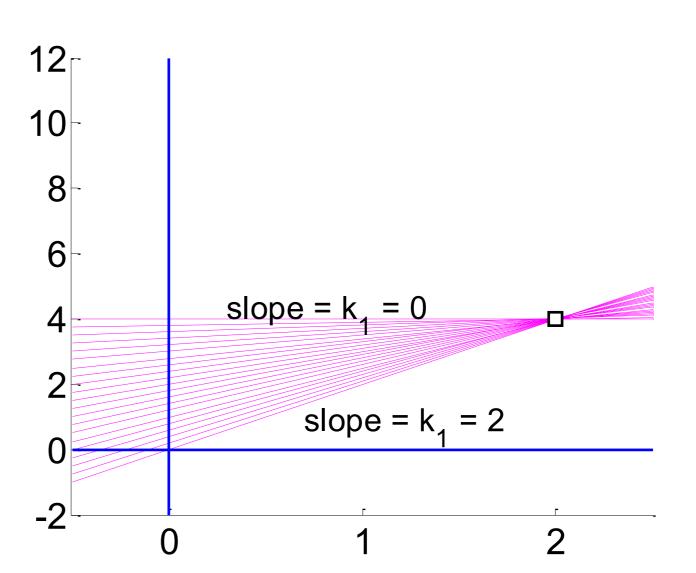
Constraints:



Consider the model $f(t) = k_1 t + k_2$

Data: f(2) = 4

Constraints:



Consider the model $f(t) = k_1 t + k_2$ Solution: $k_1 \in [0,2]$ $k_2 \in [0,4]$ 12 Data: 10 f(2) = 48 **Constraints:** 6 $k_1, k_2 \in [0, 10]$ slope = $k_1 = 0$ 4 2 slope = $k_1 = 2$

2

Consider the model $f(t) = k_1 t + k_2$

Data:
$$f(2) = 4$$

Constraints:

Consider the model $f(t) = k_1 t + k_2$

Rearrange the model

Constraints:

f(2) = 4

Data:

$$k_1 = \frac{f(t) - k_2}{t}$$
$$k_2 = f(t) - k_1 t$$

Consider the model $f(t) = k_1 t + k_2$

Rearrange the model f(t) - k

Constraints:

f(2) = 4

Data:

 $k_1 = \frac{f(t) - k_2}{t}$ $k_2 = f(t) - k_1 t$

 $k_1, k_2 \in [0, 10]$

Propagate constraints

$$k_1 \in [0,10] \cap \frac{4 - [0,10]}{2} = [0,10] \cap \frac{[-6,4]}{2} = [0,10] \cap [-3,2] = [0,2]$$

Consider the model $f(t) = k_1 t + k_2$

Rearrange the model

1

 $\mathcal{C}(A)$

Constraints:

f(2) = 4

Data:

 $k_1, k_2 \in [0, 10]$

$$k_1 = \frac{f(t) - k_2}{t}$$
$$k_2 = f(t) - k_1 t$$

Solution: $k_1 \in [0,2]$ $k_2 \in [0,4]$

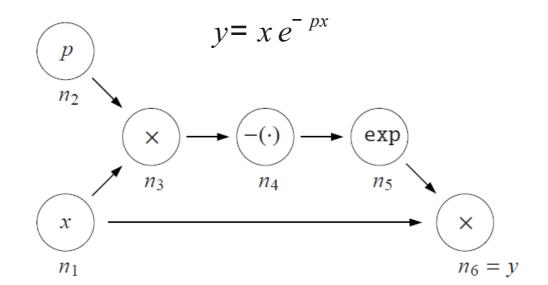
Propagate constraints $k_1 \in [0,10] \cap \frac{4 - [0,10]}{2} = [0,10] \cap \frac{[-6,4]}{2} = [0,10] \cap [-3,2] = [0,2]$

Constraint propagation

In general, many parameters, data-points and constraints.

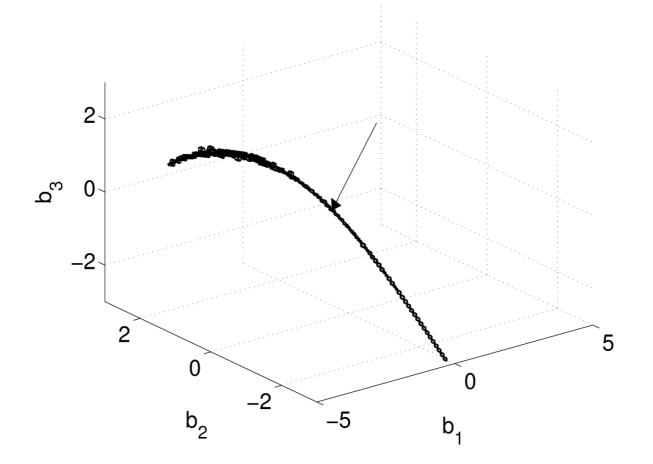
One iterates the constraints and also subdivides the search by partitioning the search space.

Implemented by directed acyclic graphs (DAG's).



Danis A., Hooker A.C., Tucker W. Proc. Int. Symp. on Nonlinear Theory and its Applications 67-70, 2010.

Set-valued parameter estimation



Output consists of boxes that cover the solution.

The optimal design problem

Search domain, *D*, of possible designs.

Prior knowledge of the model structure and parameters.

An **objective function**, *f*, that measures the imprecison in the parameter estimates.

$$d^{opt} = \arg\min_{d \in D} f(d)$$

The optimal design problem

Search domain, *D*, of possible designs.

Discrete

Prior knowledge of the model structure and parameters.

$$f(t_{i}) = a_{i} \frac{k_{21,i} k_{02,i}}{Cl_{i} (k_{21,i} - k_{02,i})} (e^{-k_{02,i}} - e^{-k_{21,i}}) + \varepsilon$$

$$k_{21,i} = \beta_{1} e^{b_{1},i}$$

$$k_{02,i} = \beta_{2} e^{b_{2},i}$$

$$Cl_{i} = \beta_{3} e^{b_{3},i}$$

An **objective function**, *f*, that measures the imprecison in the parameter estimates.

$$d^{opt} = \arg\min_{d \in D} f(d)$$

$$f = \sum_{i=1}^{N_{boxes}} f_{box}(i)$$
$$f_{box} = \frac{1}{N_p} \sum_{j=1}^{N_p} \frac{width(p_j)}{mid(p_j)}$$

Basic search method

Try a design from the search space Repeat several times:

Simulate data from the current design Compute the set of consistent parameters Evaluate objective function *f* Monitor mean *f* for the tried design

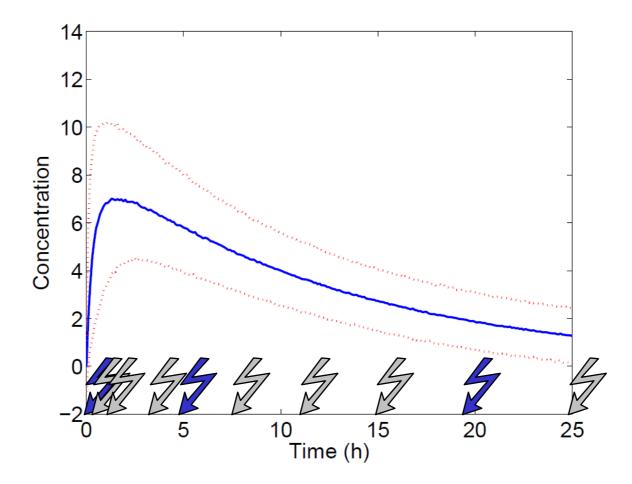
Basic search method

REPEAT

Try a design from the search space Repeat several times:

Simulate data from the current design Compute the set of consistent parameters Evaluate objective function *f* Monitor mean *f* for the tried design UNTIL no better design is found

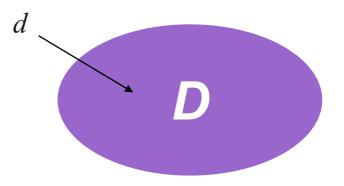
Exhaustive search suggests optimal sampling times



A heuristic search

Global search

Entire search domain Decompose the problem into separate groups (same covariates)



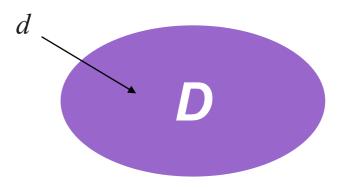
A heuristic search

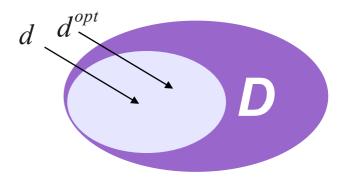
Global search

Entire search domain Decompose the problem into separate groups (same covariates)

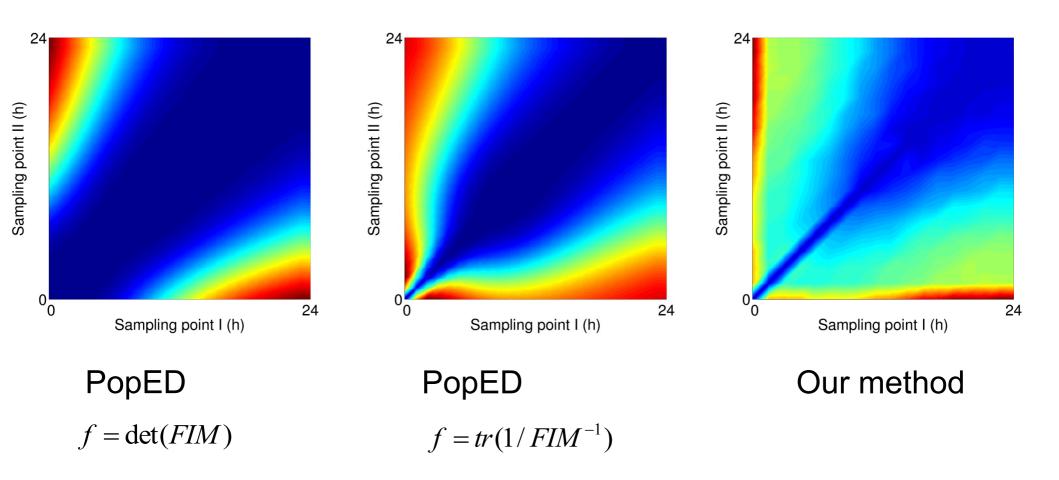
best solution

Local search Part of search domain No decomposition





Example of result



A general framework

Covariates like dose and time can be defined as intervals.

Given a dose:

dose \in [4,5]

and sampling times with allowed uncertainty

 $t_i \in [t - \delta, t + \delta]$

What is the optimal design?

Conclusions

No prior information in form of point estimates for the parameters is required (as in local optimal design).

Any covariate can be represented by an interval.

Problems with local minima and model linearisation are avoided in the parameter estimation.

Thanks for your attention!





Peter Gennemark

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