# Optimal design in population kinetic experiments by set-valued methods

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in collaboration with

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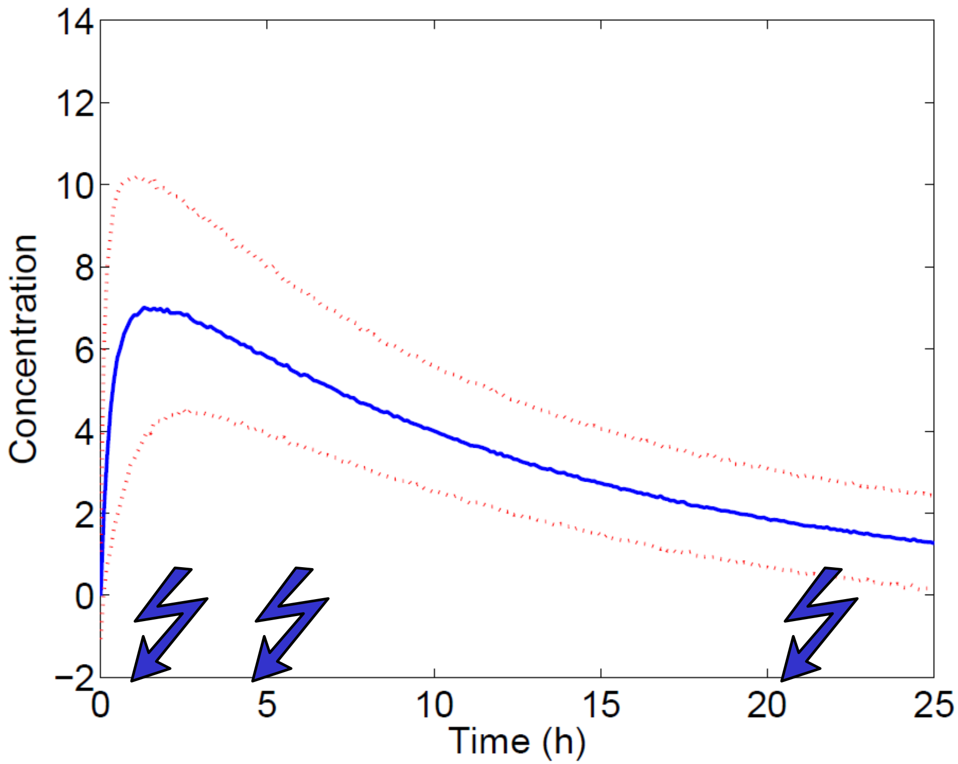
# Optimal experimental design

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




$$k_{21,i} = \beta_1 e^{b_{1,i}}$$

$$k_{02,i} = \beta_2 e^{b_{2,i}}$$

$$Cl_i = \beta_3 e^{b_{3,i}}$$

$$b_i = N(0, D)$$

$$\varepsilon = N(0, \sigma^2)$$

# Optimal design, definition?

# The optimal design problem

**Search domain**, *D*, of possible designs.

**Prior knowledge** of the model structure and parameters.

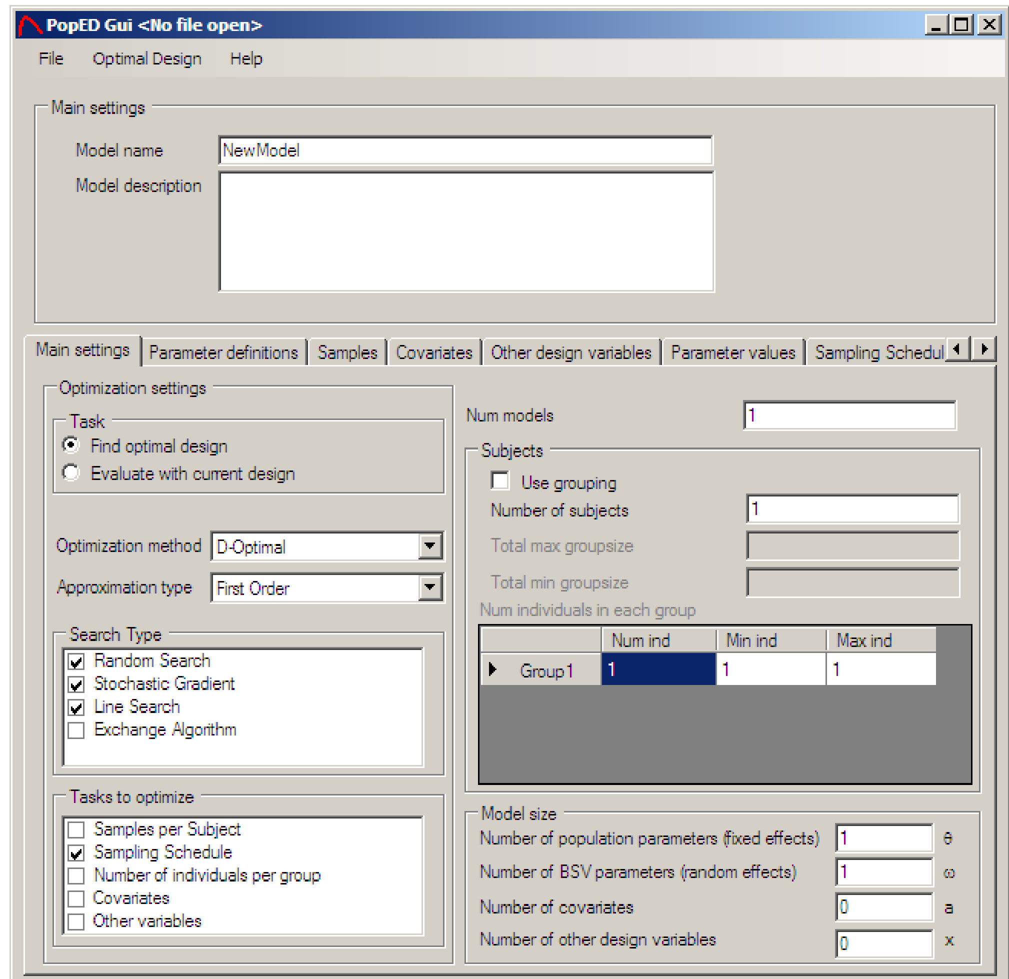
An **objective function**, *f*, that measures the imprecison in the parameter estimates.

$$d^{opt} = \underset{d \in D}{\arg\min} \; f(d)$$

# PopED (Population Experimental Design)

Population optimal design

http://poped.sf.net




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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$$b \in [2,3] \qquad a * b \in [2,6]$$

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

$$b \in [2,3] \qquad a * b \in [2,6]$$

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

# Simple example of constraint propagation

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

Data:

$$f(2) = 4$$

Constraints:

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

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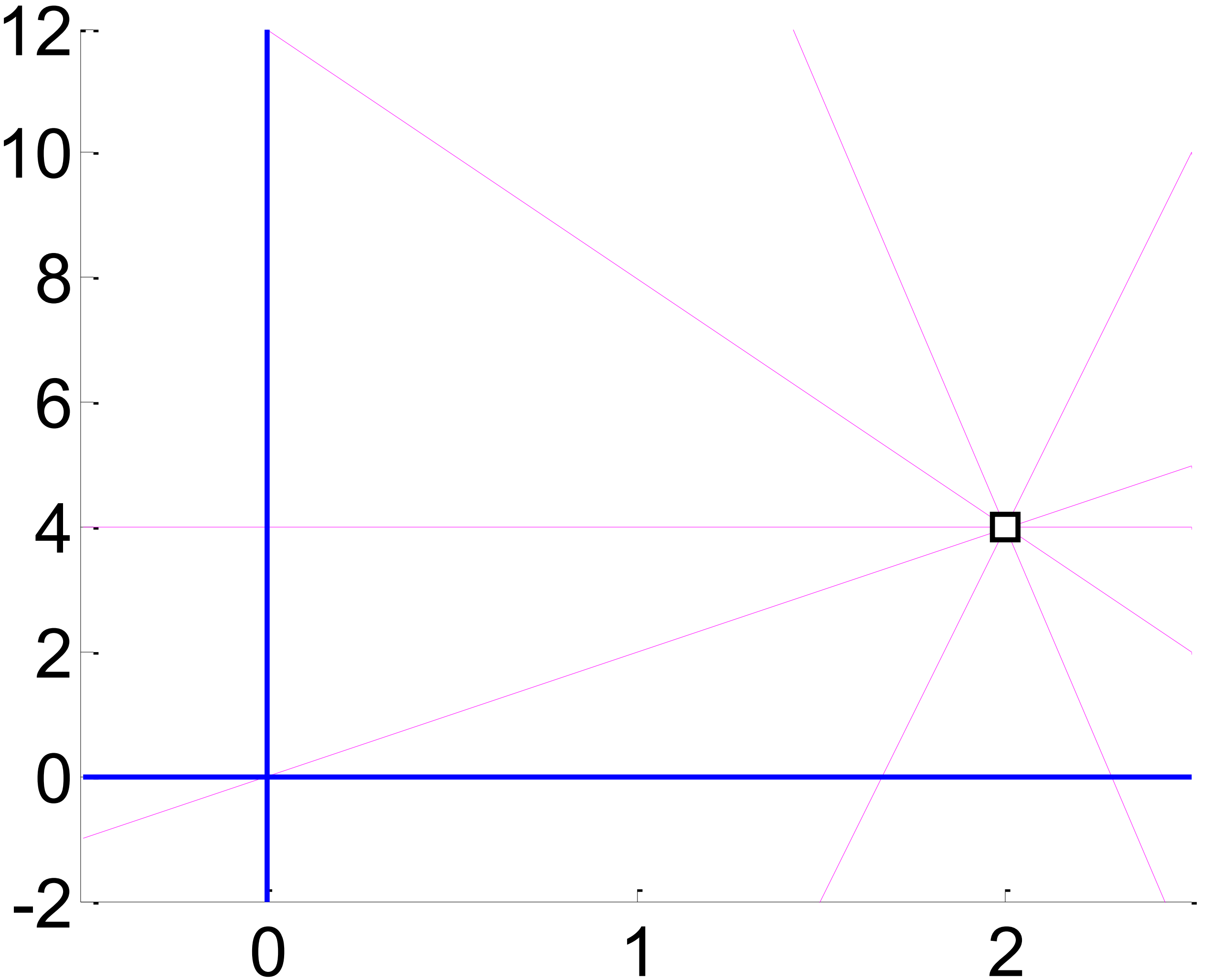

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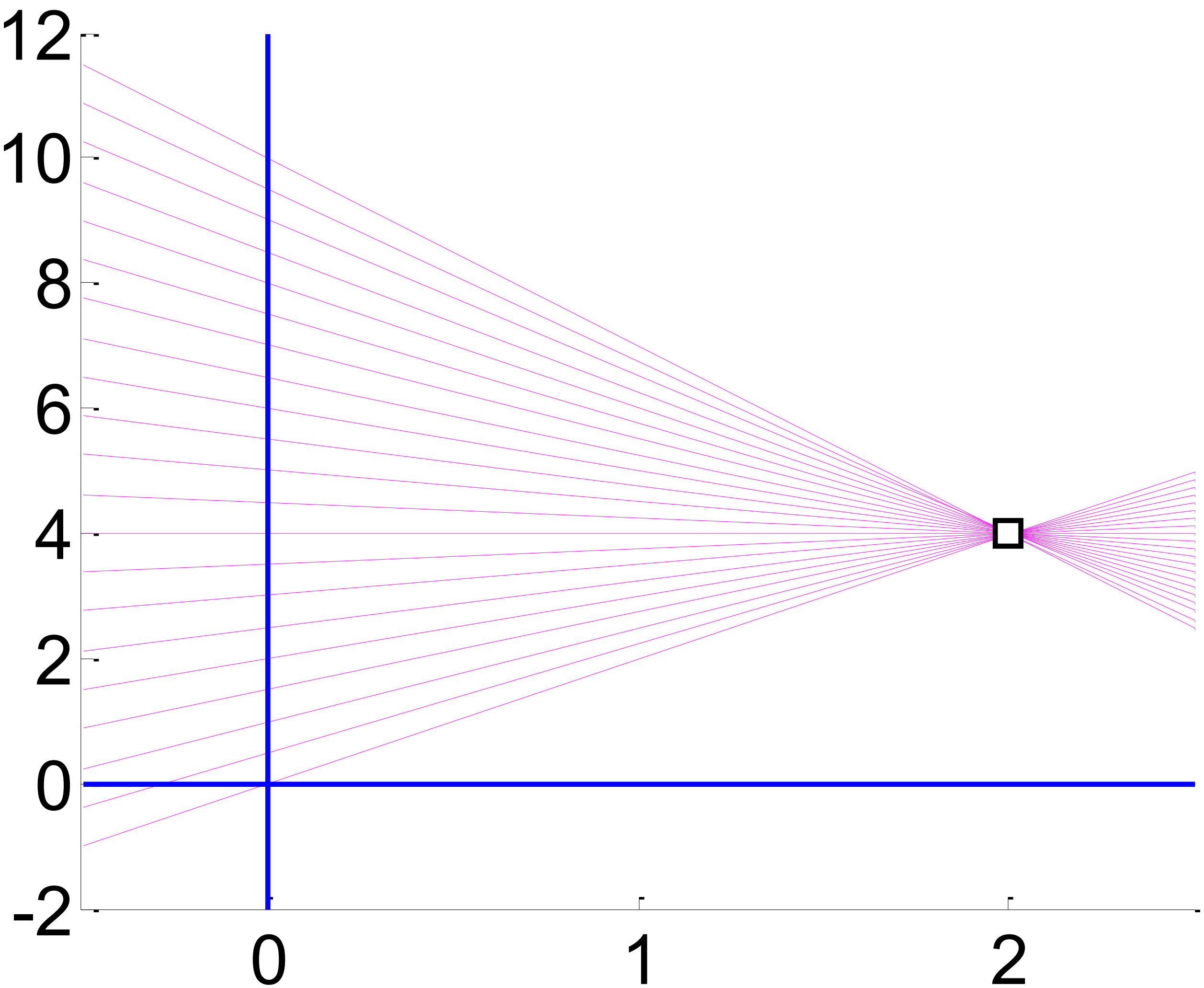

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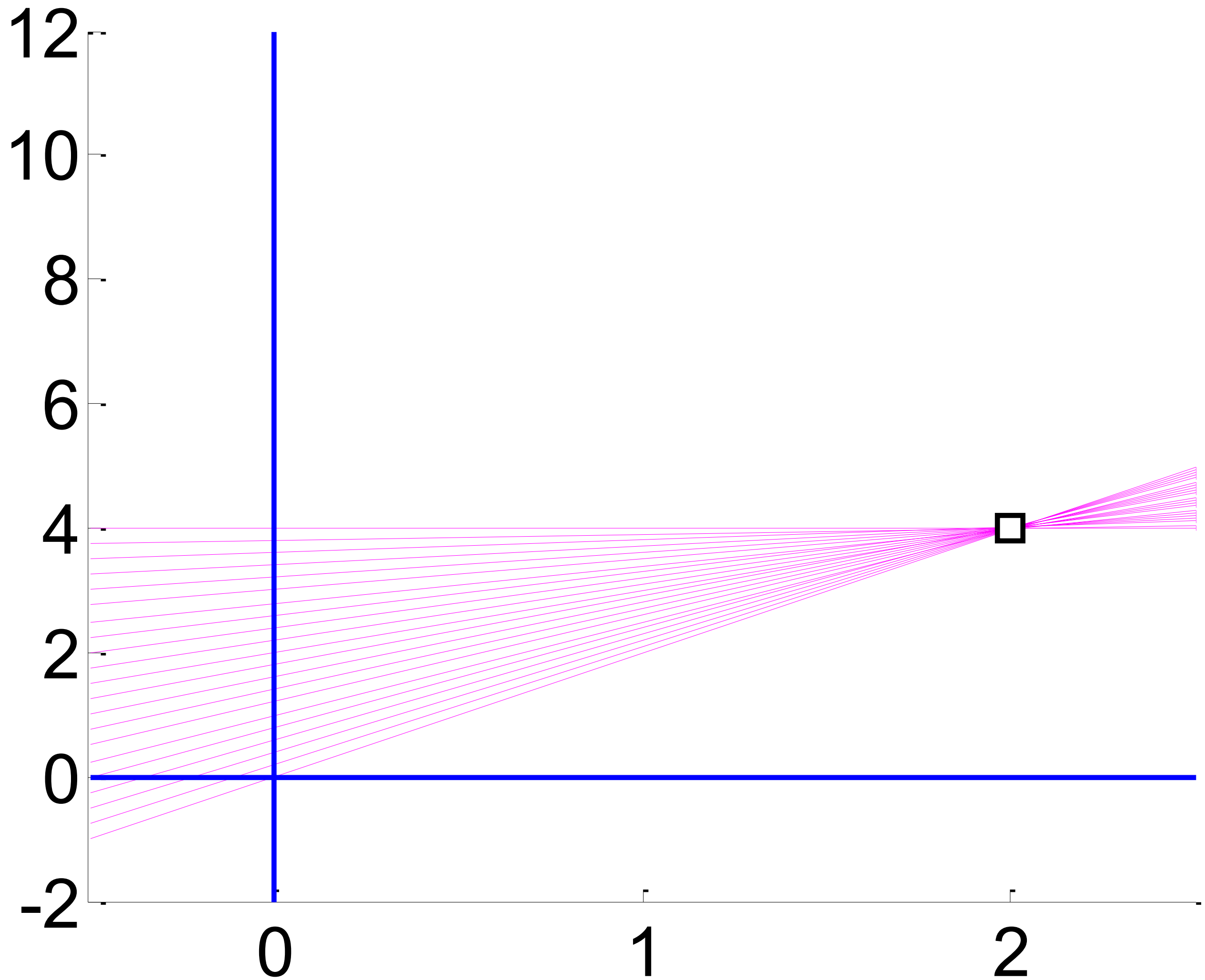

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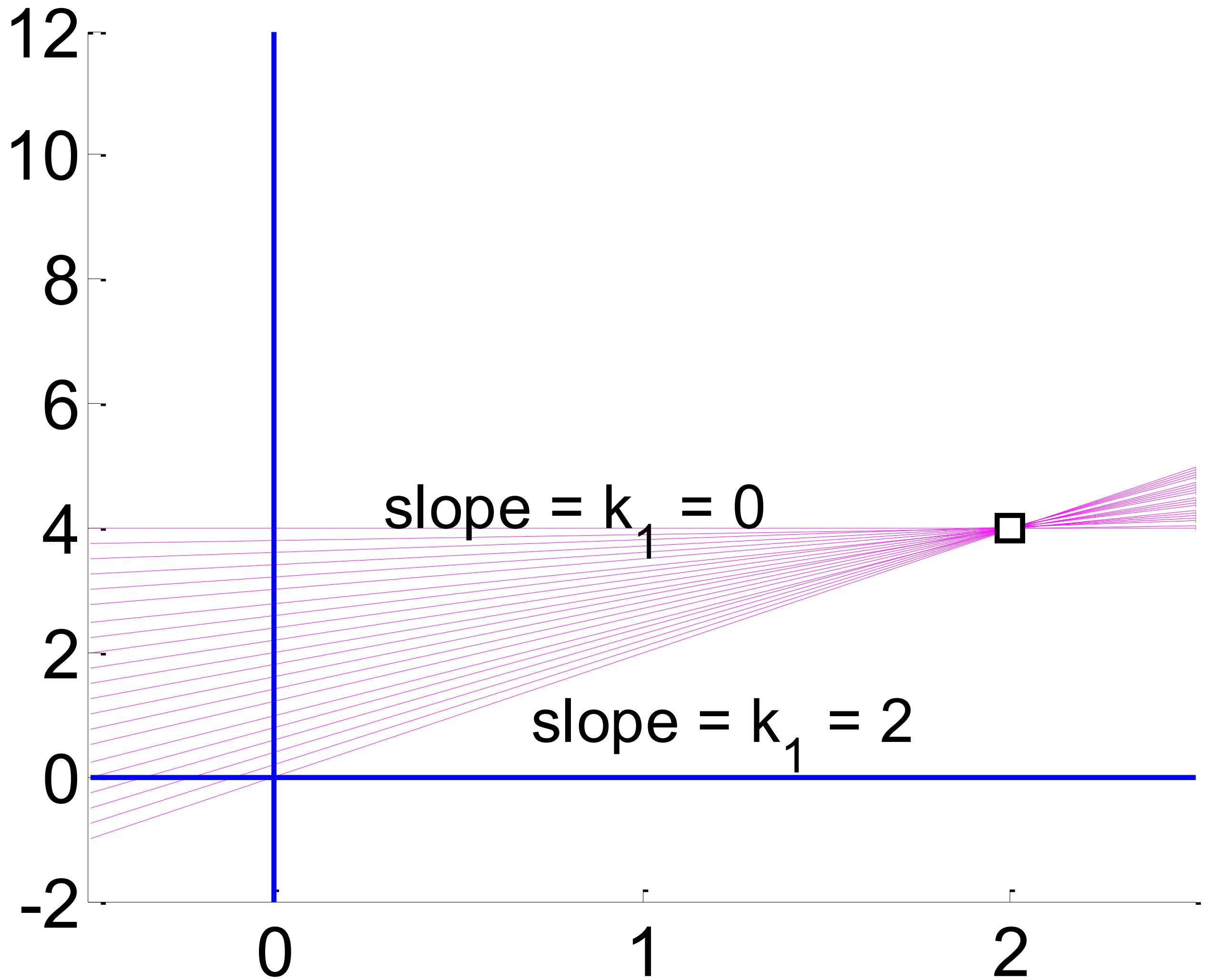

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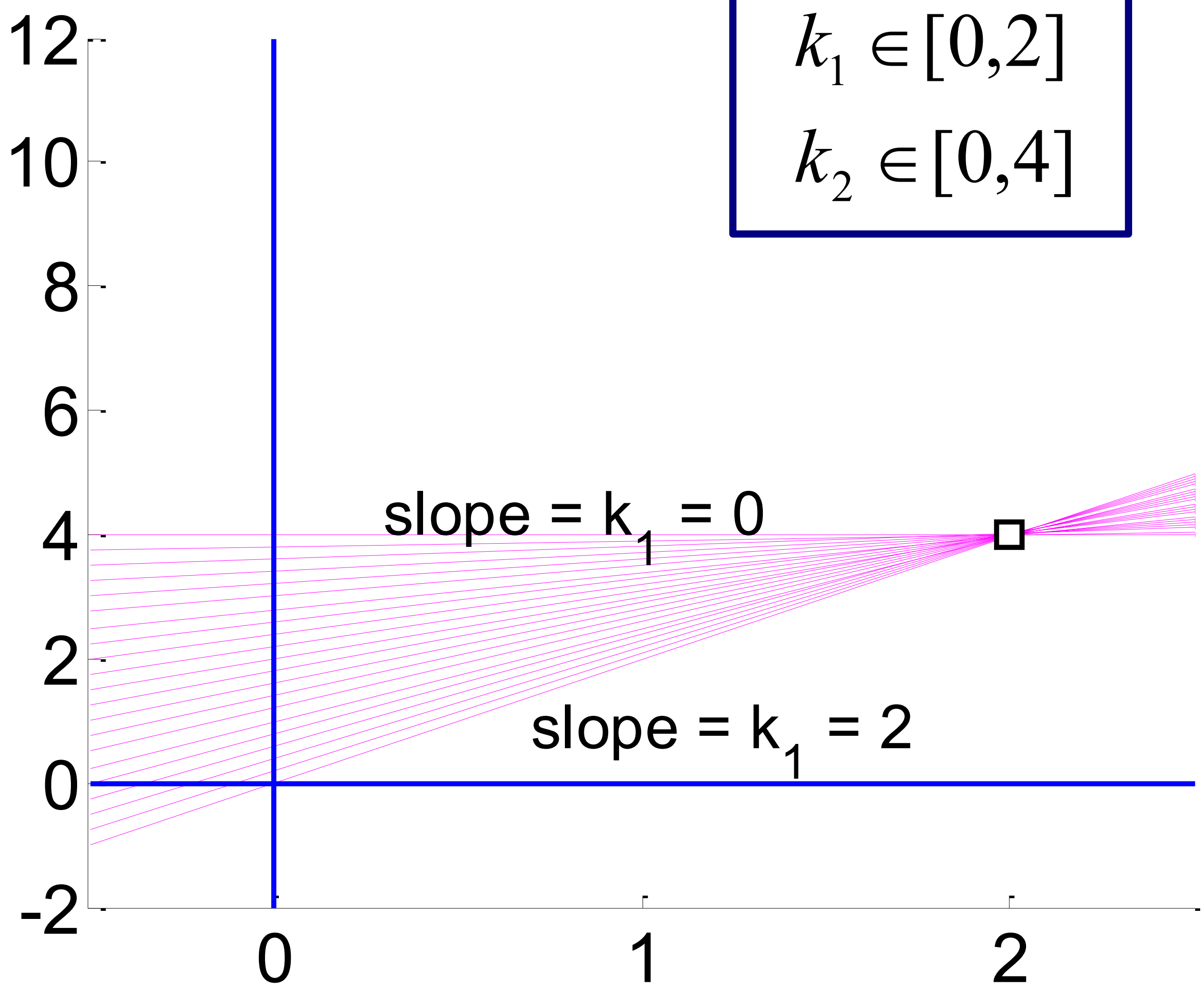


**Solution:**

$k_1 \in [0,2]$

$k_2 \in [0,4]$

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Rearrange the model

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

$$k_2 = f(t) - k_1 t$$

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Propagate constraints

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

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$k_1 \in [0,2]$

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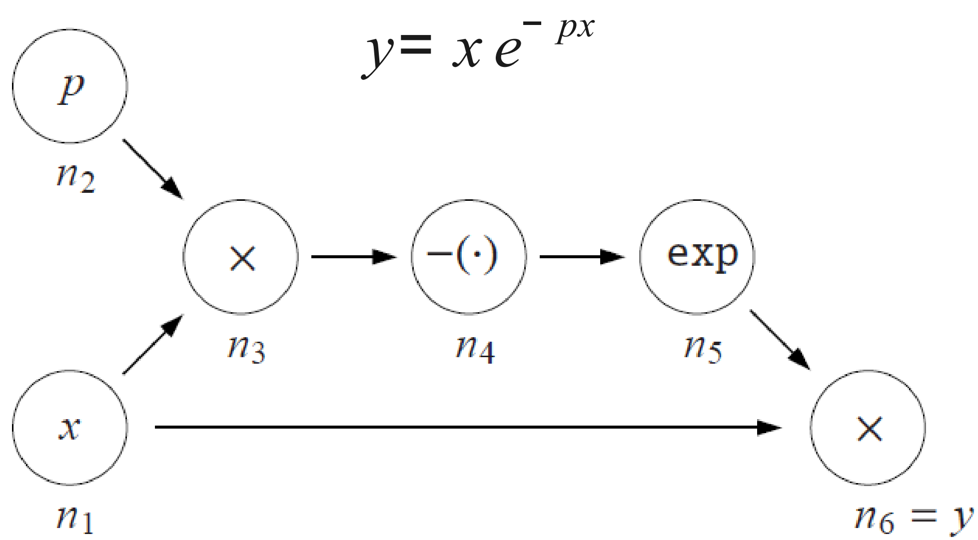
# Constraint propagation

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

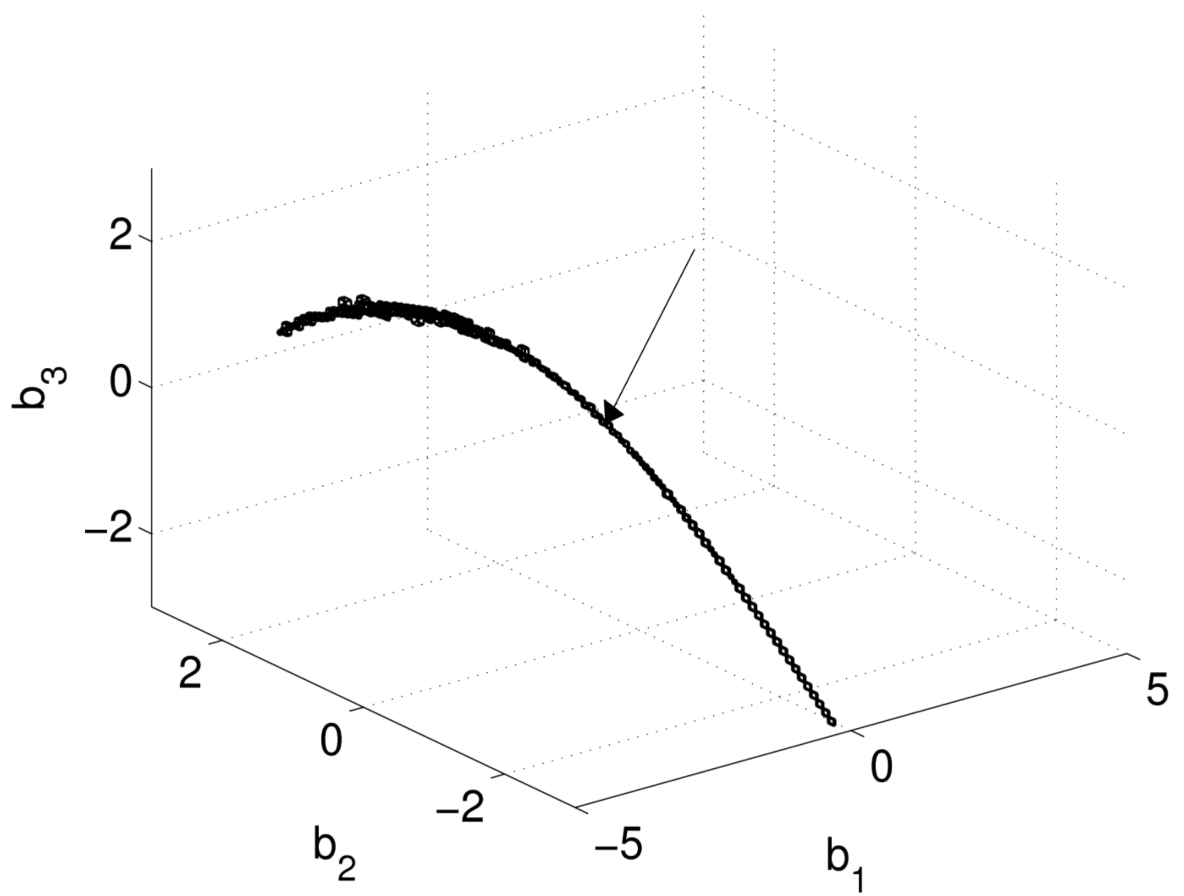
One iterates the constraints and also subdivides the search by partitioning the search space.

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.

$$f(t_i) = a_i \frac{k_{21,i} k_{02,i}}{Cl_i \left(k_{21,i} - k_{02,i}\right)} \left(e^{-k_{02,i}} - e^{-k_{21,i}}\right) + \varepsilon$$

$$k_{21,i} = \beta_1 e^{b_1,i}$$

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

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

$$f = \sum_{i=1}^{N_{boxes}} f_{box}(i)$$

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

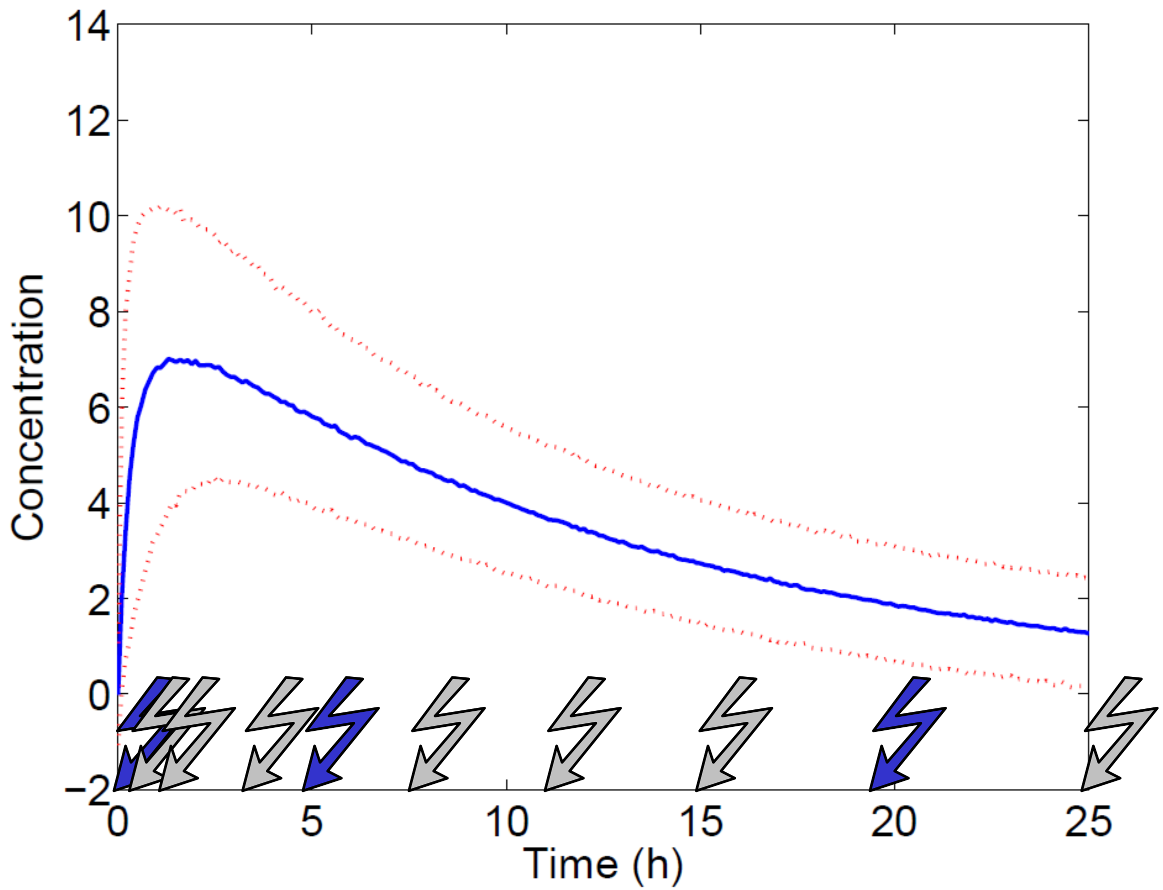
# Basic search method

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

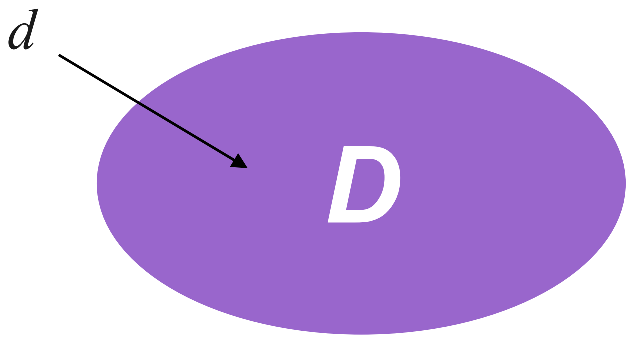
REPEAT
  Try a design from the search space
  Repeat several times:
    Simulate data from the current design
    Compute the set of consistent parameters
    Evaluate objective function *f*
  Monitor mean *f* for the tried design
UNTIL no better design is found

# 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

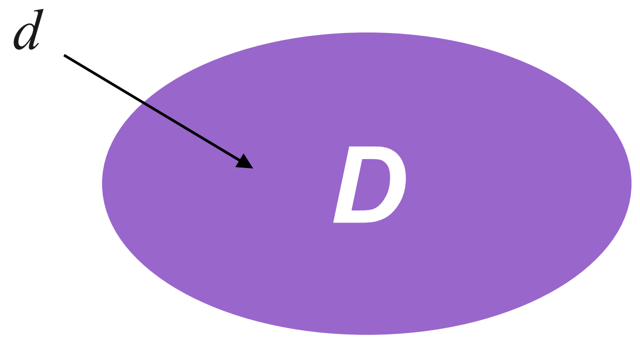
**Global search**
Entire search domain
Decompose the problem into separate groups (same covariates)

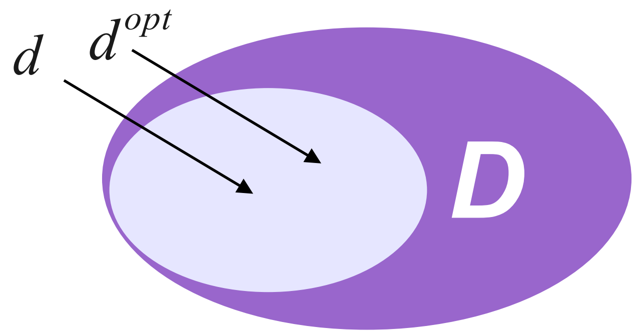
↓

*best solution*

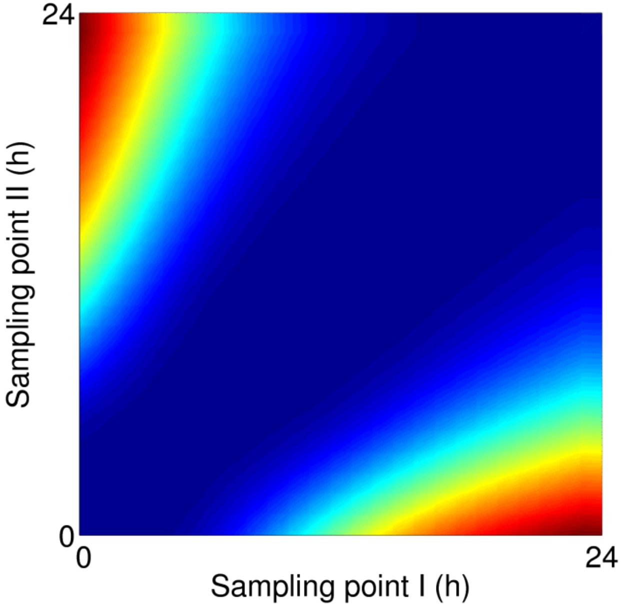
↓

**Local search**
Part of search domain
No decomposition



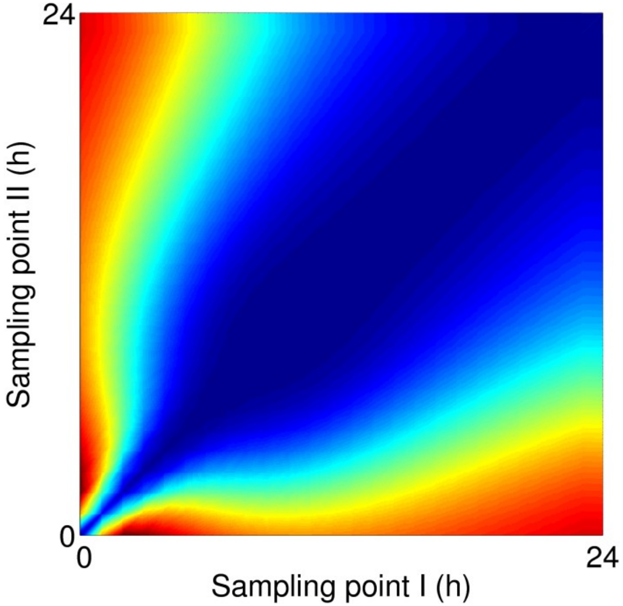



# Example of result



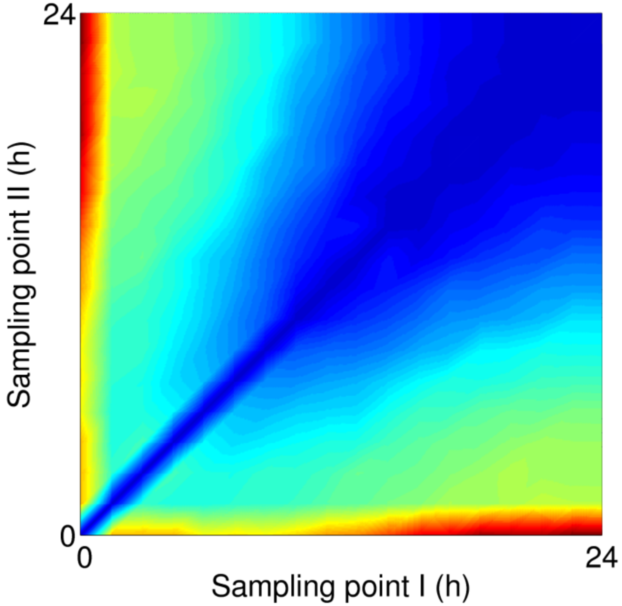

PopED

$$f = \det(FIM)$$




PopED

$$f = tr(1/FIM^{-1})$$




Our method

# A general framework

Covariates like dose and time can be defined as intervals.

Given a dose:

$$\text{dose} \in [4,5]$$

and sampling times with allowed uncertainty

$$t_i \in [t\text{-}\delta, t+\delta]$$

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!

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