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Population optimal experimental design using PopED

(**Pop**ulation optimal **E**xperimental **D**esign)

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Introduction

PopED:

- Written in MATLAB and O-matrix
  - O-Matrix is a faster, less expensive version of MATLAB: http://depts.washington.edu/rfpk/rd/software_popED.html
  - MATLAB version available soon at www.sourceforge.net
- Key points:
  - External GUI that talks to PopED using XML (general method not PopED dependent)
  - Optimization of ‘other’ design variables
  - Optimization of ED-designs
  - Simultaneous optimal design calculations
  - Approximations

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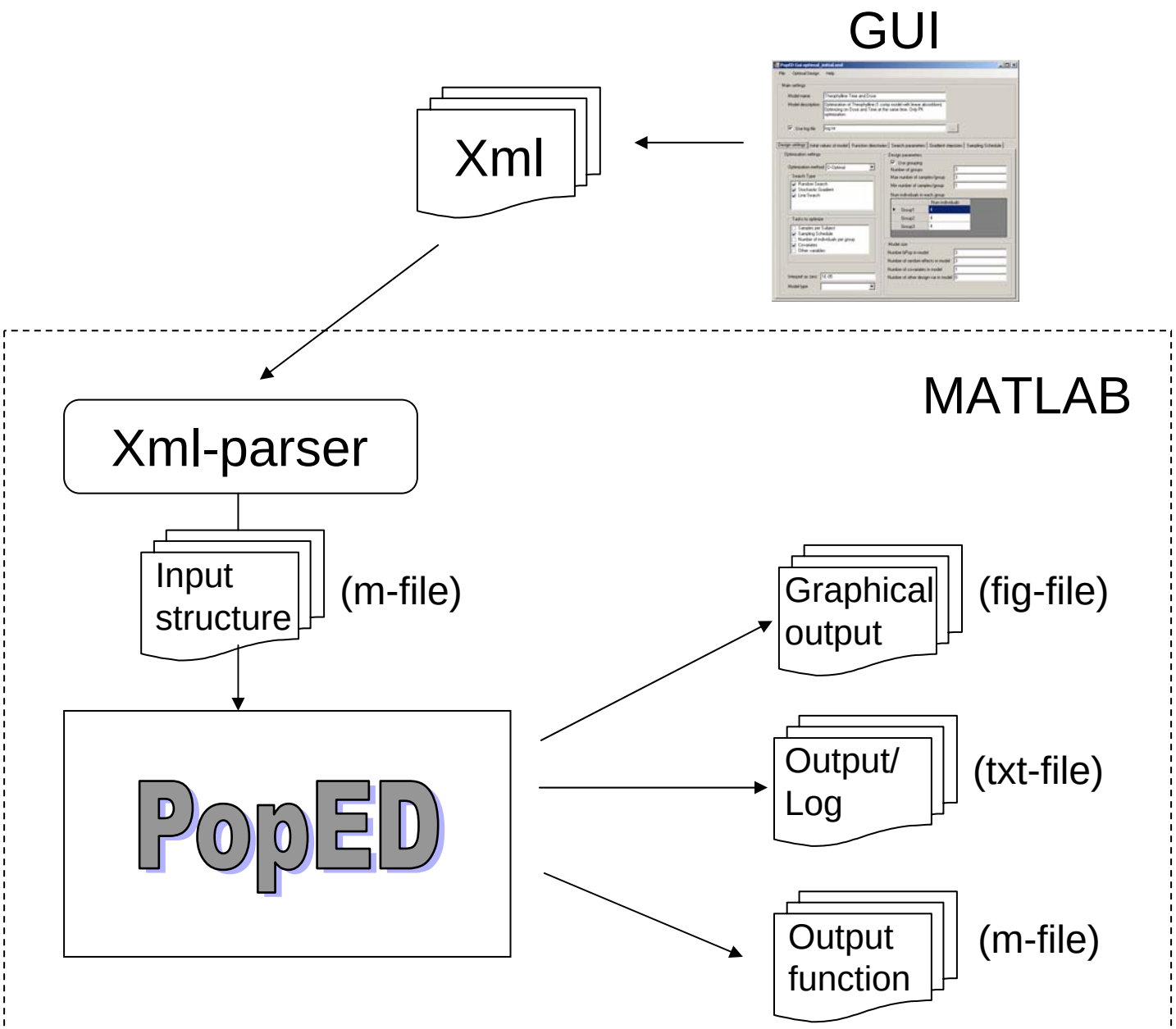

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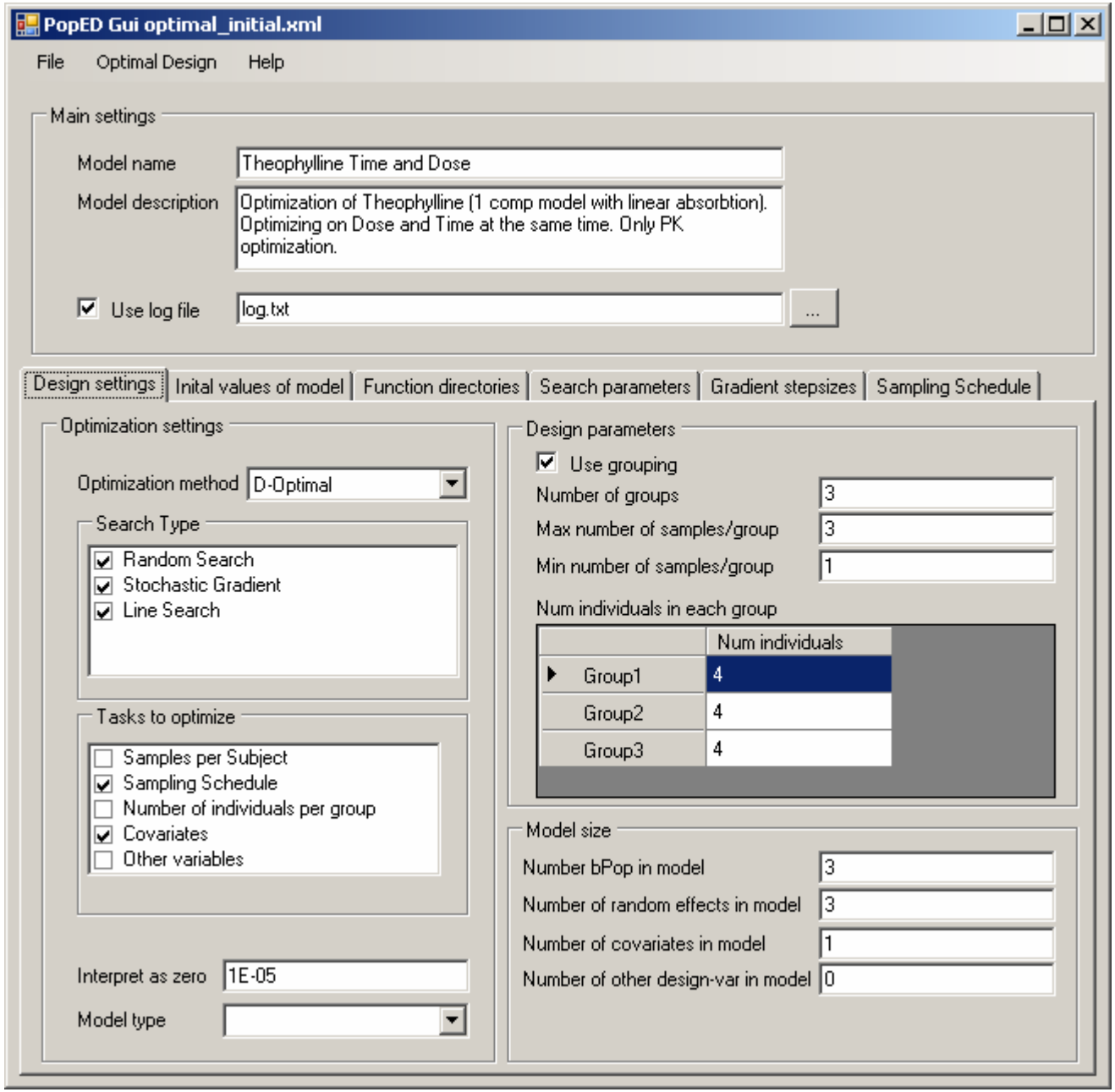

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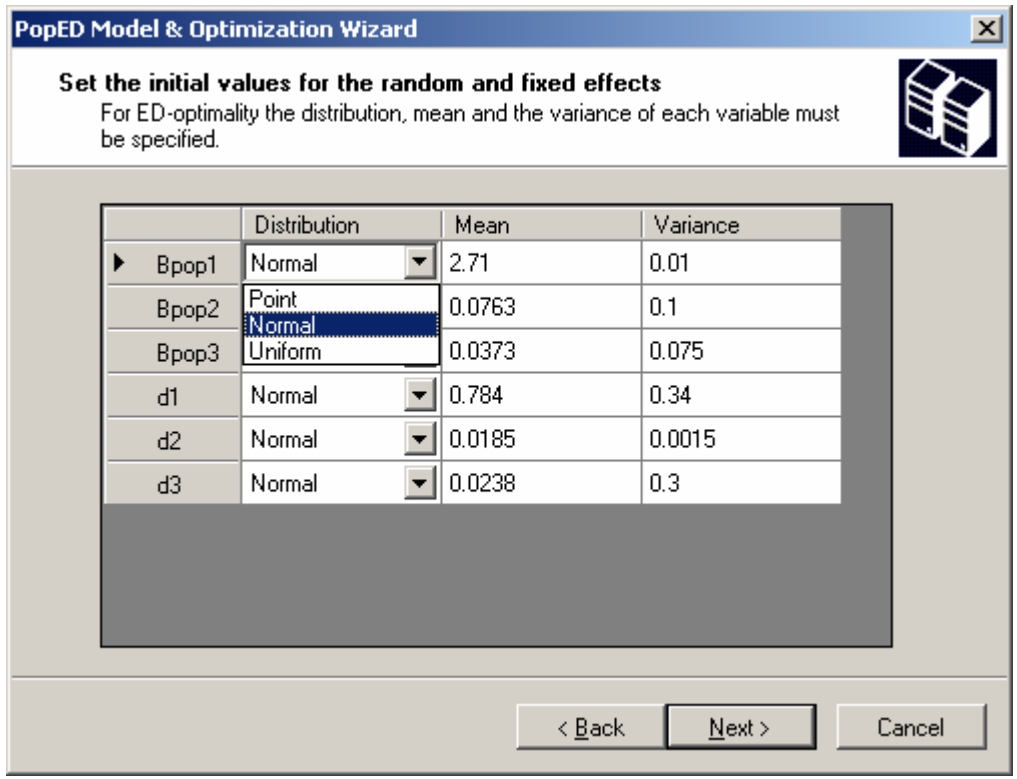

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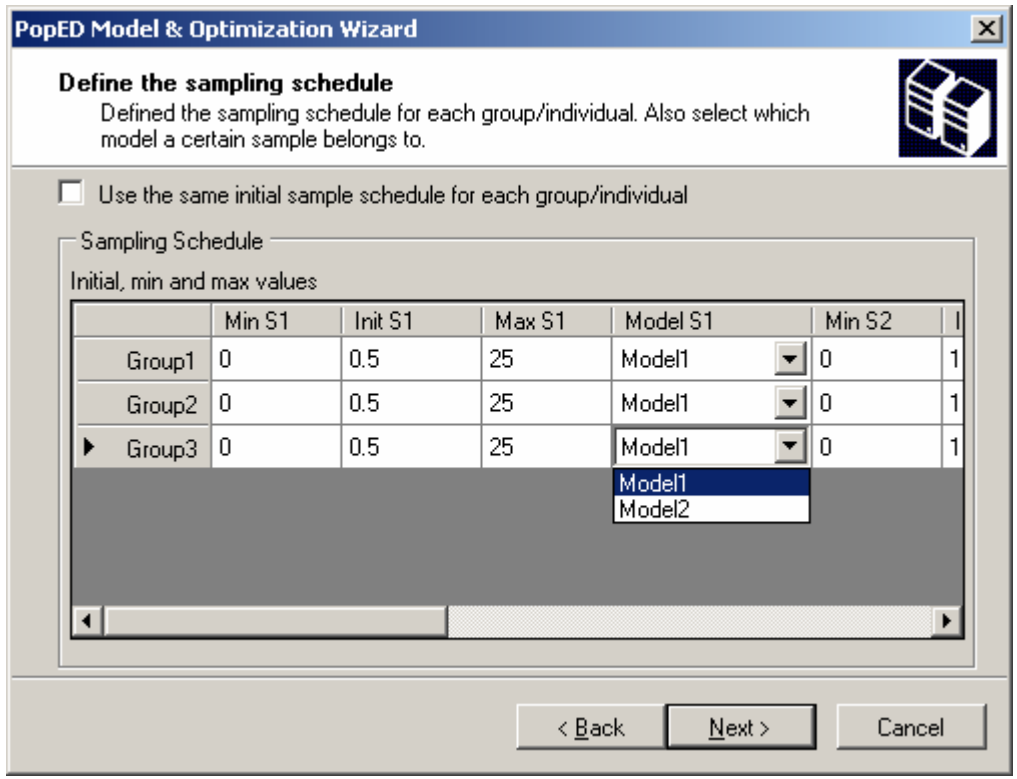

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Optimization variables

PopED can optimize over:

- Sample times
- Number of samples per subject
- Number of individuals per group
- Covariates
- ‘Other’ design variables (e.g. dose!)

These design variables can be optimized sequentially or simultaneously

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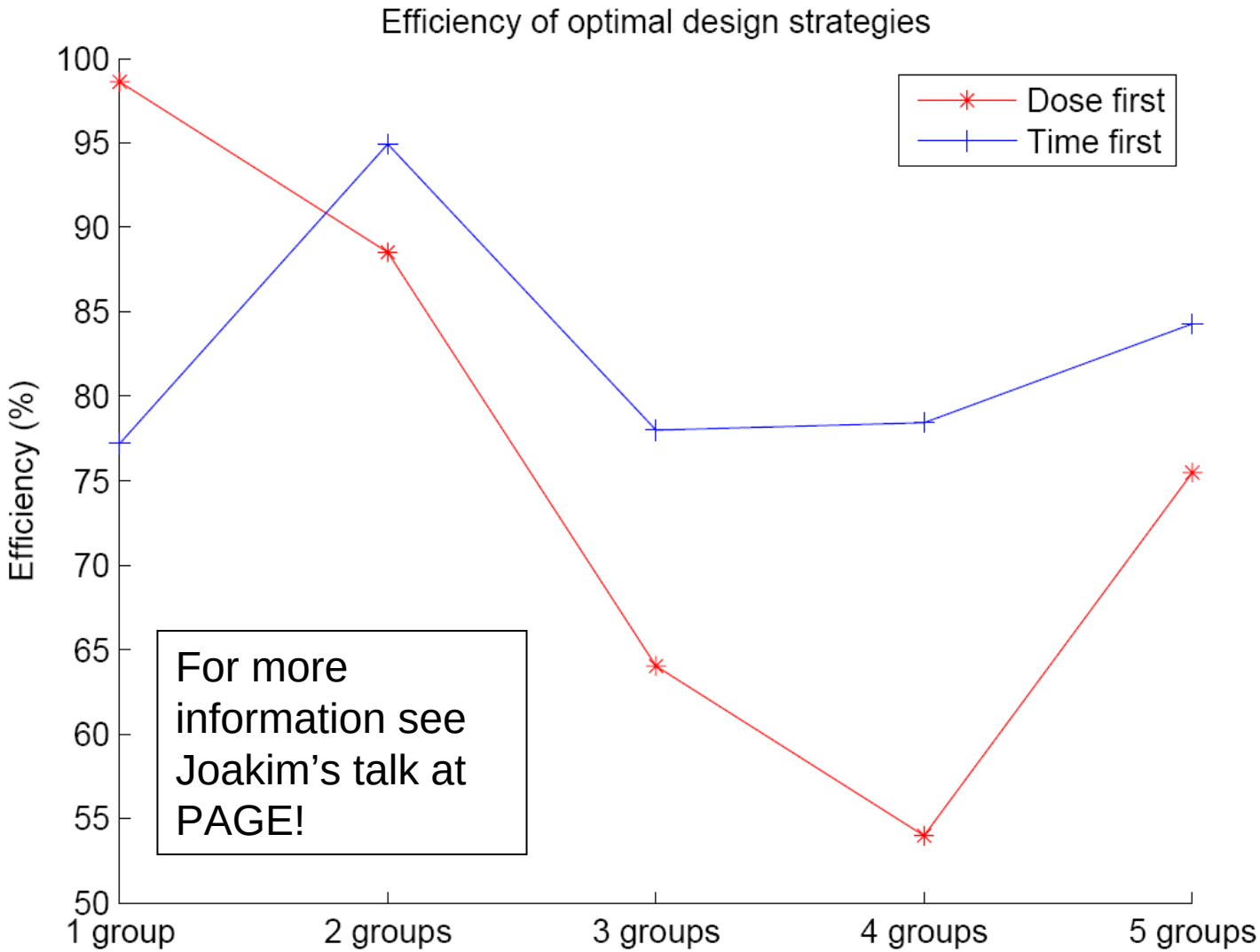
Simultaneous dose and time optimization results in more efficient designs



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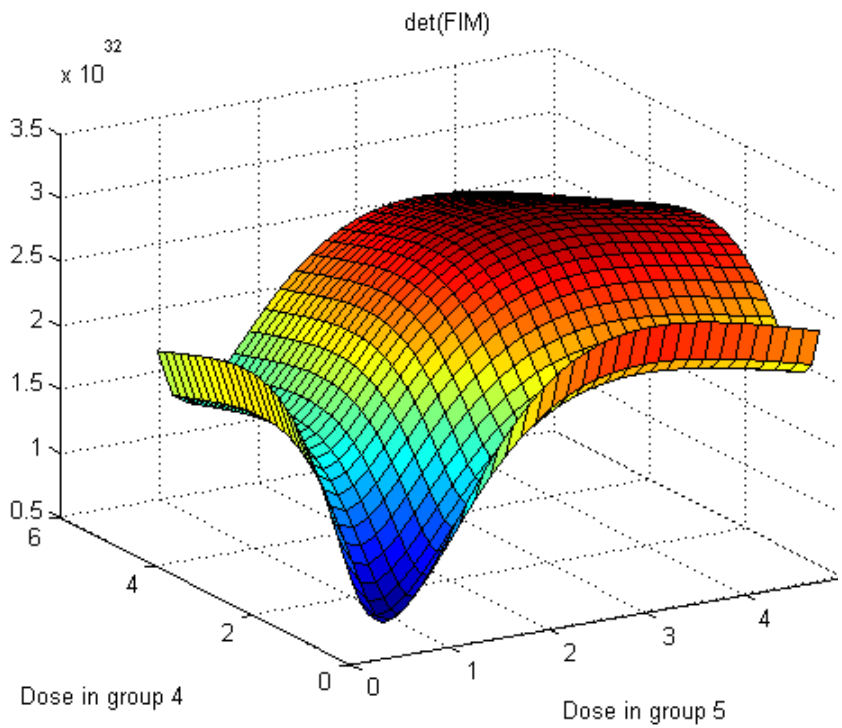
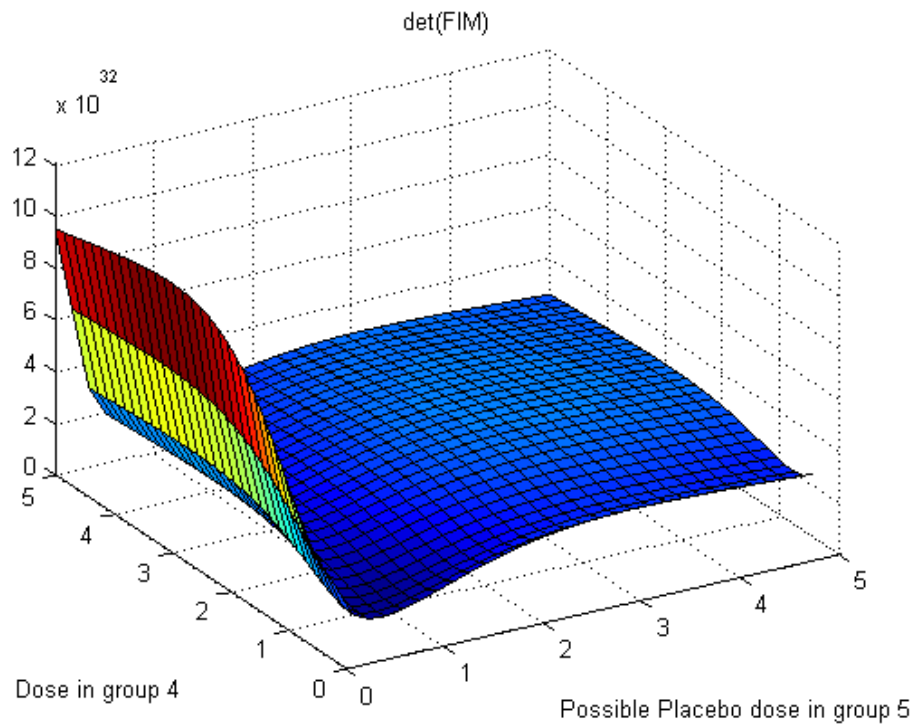
Dose can be an important optimization variable

Without placebo



With Placebo



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Simultaneous optimization of Multiple response models

Simultaneous optimization of multiple response models possible in PopED

- Unbalanced/half-balanced/balanced designs between models and between groups of individuals
- Balanced designs can have different residual variability
- Number of models is unlimited

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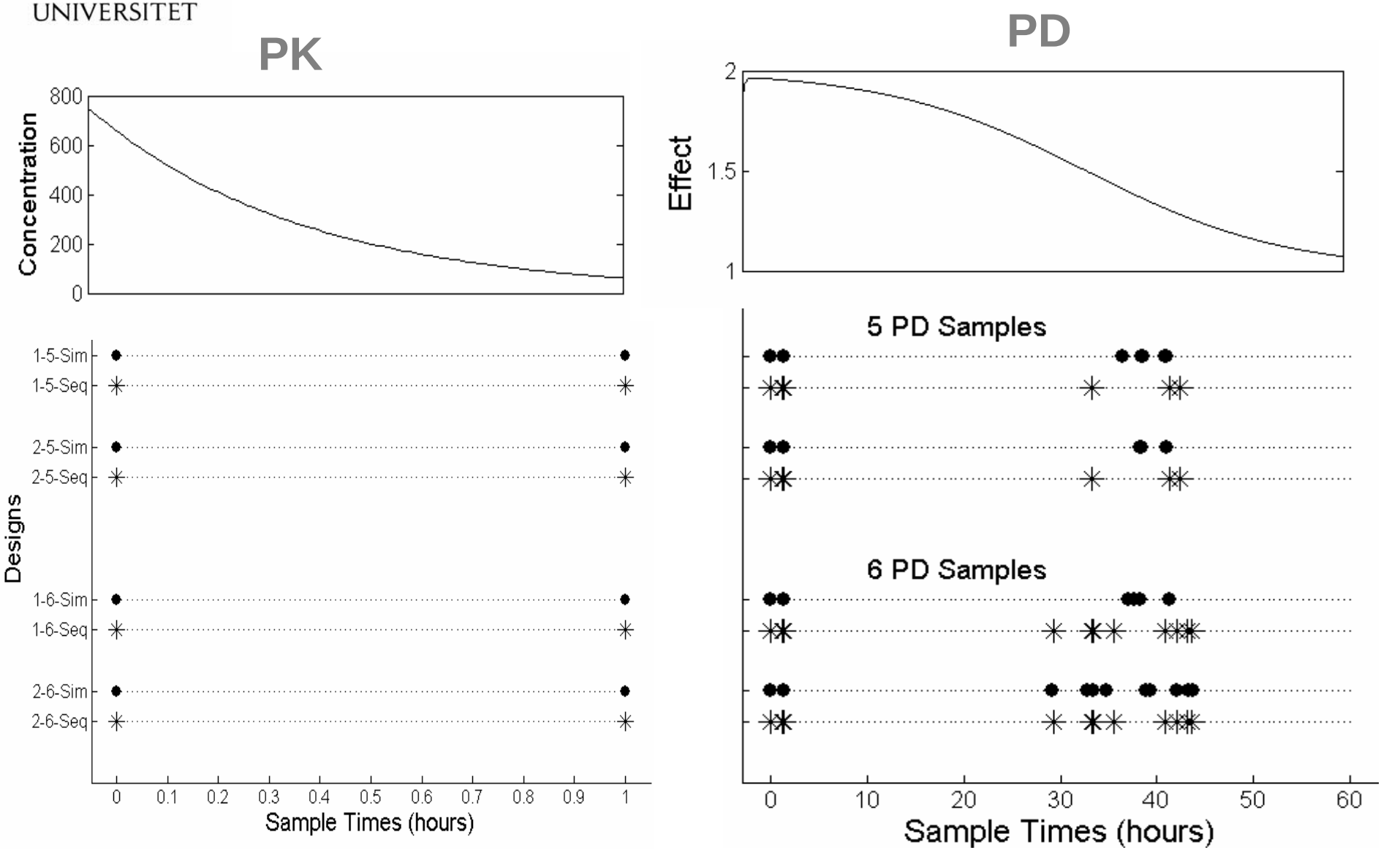
PK-PD optimal designs



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Optimization Methods available in PopED

- D-Optimal

$$\arg\max_x \left(\text{Det} \left[\text{FIM}(x_{design}, \Theta_{\text{best}}) \right] \right)$$

- ED-Optimal

$$\arg\max_x \left(E_\Theta \left[\text{Det} \left[\text{FIM}(x_{design}, \Theta_{\text{best/dist}}) \right] \right] \right)$$

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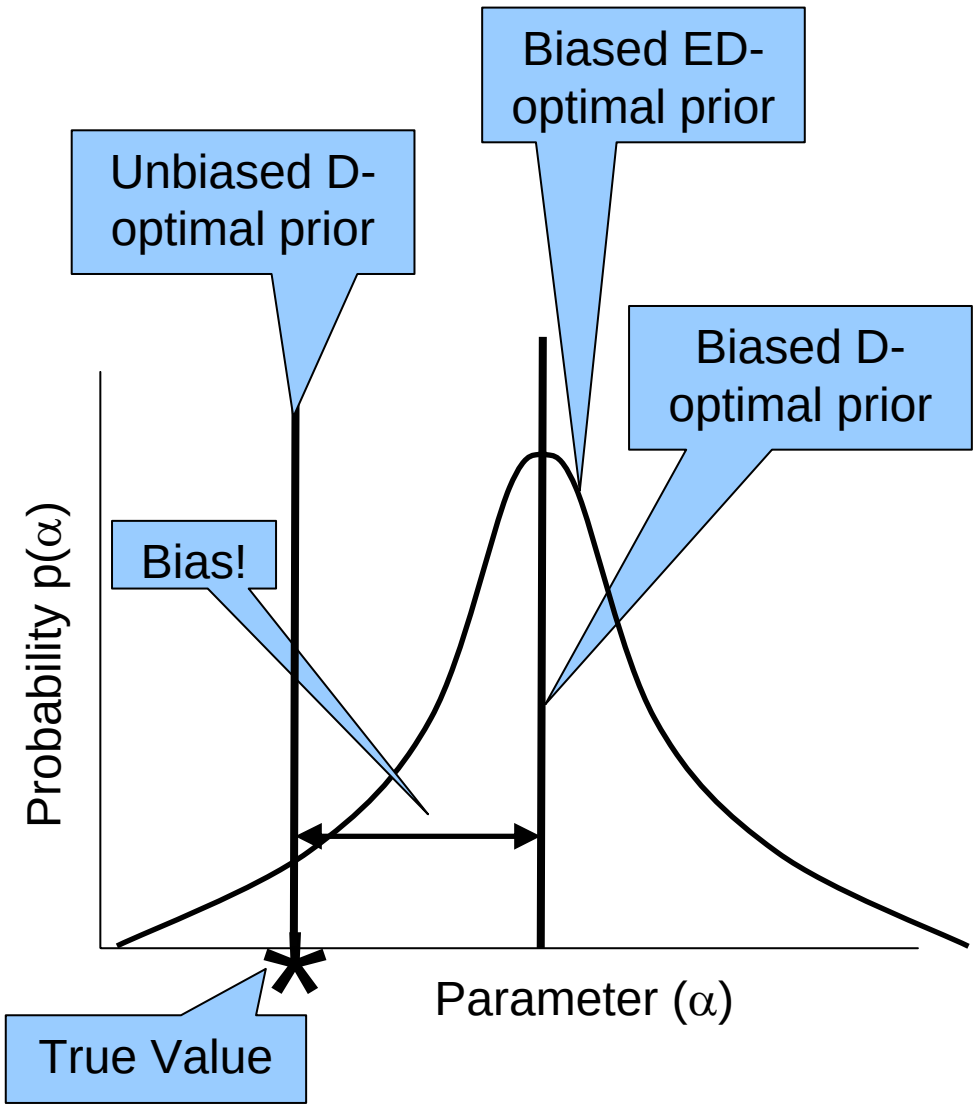
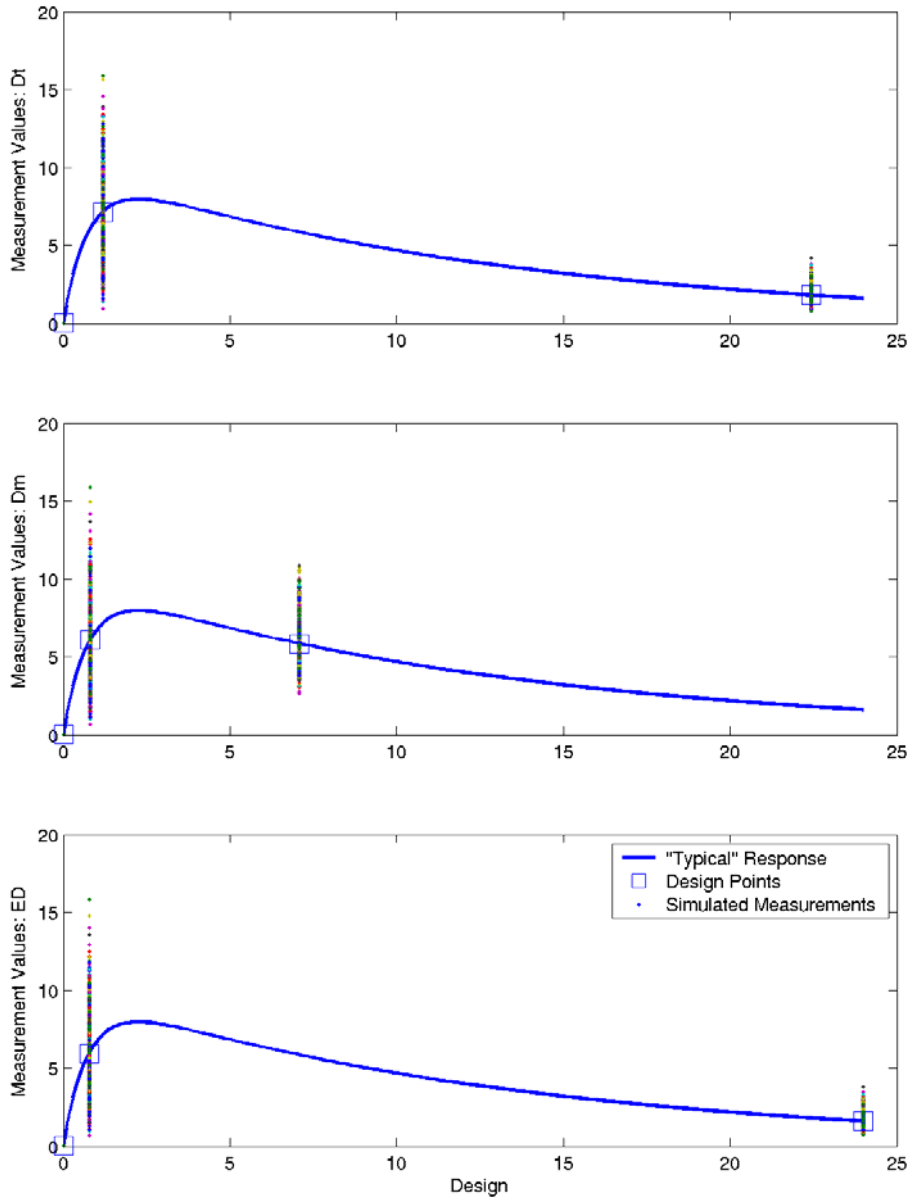
D vs. ED with parameter misspecification





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Optimization algorithms

Continuous variable optimization: a combination of Global optimizers and a local optimizer, used in a loop

- Adaptive random search (global)
- Stochastic gradient (local)
- Line search (global)

Discrete variable optimization: technique is based on an adaptation of an iterative gradient-like algorithm to the discrete domain.

M. Foracchia, A. Hooker, P. Vicini and A. Ruggeri. PopED, a software for optimal experimental design in population kinetics. *Comput Methods Programs Biomed*, 74: 29-46, 2004.

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FIM calculation in practice - approximations

$$\mathbf{y}_i \simeq f(\mathbf{x}_i,\ g(\boldsymbol{\beta}_{pop},\ \mathbf{a}_i,\ \mathbf{0})) + \mathbf{H}(\mathbf{x}_i,\ \boldsymbol{\beta}_{pop},\ \mathbf{a}_i)\mathbf{b}_i + \boldsymbol{\varepsilon}_i$$

$$\begin{aligned} E[\mathbf{y}_i] &\simeq f(\mathbf{x}_i,\ g(\mathbf{x}_i,\ \boldsymbol{\beta}_{pop},\ \mathbf{a}_i,\ \mathbf{0})) \\ Var(\mathbf{y}_i) &\simeq \mathbf{R}_i + \mathbf{H}(\mathbf{x}_i,\ \boldsymbol{\beta}_{pop},\ \mathbf{a}_i)\mathbf{D}\mathbf{H}^T(\mathbf{x}_i,\ \boldsymbol{\beta}_{pop},\ \mathbf{a}_i) \\ &= \mathbf{V}_i(\mathbf{x}_i,\ \boldsymbol{\beta}_{pop},\ \mathbf{a}_i,\ \mathbf{d}) \end{aligned}$$

Note: Both H and V are dependent on fixed effects!

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FIM calculation in practice - approximations

$$\mathbf{FIM}\left(\vec{\theta}\right) = \sum_{i=1}^{m} \mathbf{FIM}_i\left(\vec{\theta}\right) \tag{2.23}$$

$$= \sum_{i=1}^{m} \begin{bmatrix} \mathbf{M}_{1i} & 0 \\ \mathbf{M}_{2i} & \mathbf{M}_{3i} \end{bmatrix}^T \begin{bmatrix} \mathrm{Var}(\vec{y}_i)^{-1} & 0 \\ 0 & \mathbf{M}_{4i}^{-1} \end{bmatrix} \begin{bmatrix} \mathbf{M}_{1i} & 0 \\ \mathbf{M}_{2i} & \mathbf{M}_{3i} \end{bmatrix} \tag{2.24}$$

where

$$\mathbf{M}_{1i} = \frac{\partial f(\vec{x}_i, \vec{\beta}_{pop})}{\partial \vec{\beta}_{pop}} \tag{2.25}$$

$$\mathbf{M}_{2i} = \frac{\partial \mathrm{vec}(\mathrm{Var}(\vec{y}_i))}{\partial \vec{\beta}_{pop}} \tag{2.26}$$

$$\mathbf{M}_{3i} = \frac{\partial \mathrm{vec}(\mathrm{Var}(\vec{y}_i))}{\partial \vec{d}} \tag{2.27}$$

$$\mathbf{M}_{4i} = 2\mathrm{Var}(\vec{y}_i) \otimes \mathrm{Var}(\vec{y}_i) \tag{2.28}$$

Note: M2 is not assumed to be zero!

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Other Points

- ED-objective function:

$$\arg\max_x \left(E_\Theta \left[\text{Det} \left[\text{FIM}(x_{design}, \Theta_{\text{best/dist}}) \right] \right] \right)$$

  - Available with an expectation estimator; the average obtained through Monte Carlo techniques.
  - Soon available using the Laplace approximation to integral (Dodds, Hooker *et al. JPP, 2005*)

- IIV expression is general and does not require a specific form

- Derivatives calculated analytically using MAPLE (in MATLAB) in most cases, otherwise calculated using central differencing

- ODE's solved using MATLAB's solvers (mostly ODE45)