OPTIMUM DESIGNS FOR NONLINEAR MIXED EFFECTS MODEL IN THE PRESENCE OF COVARIATES

Barbara Bogacka

Queen Mary, University of London

Joint work with M. Latif, S.G. Gilmour and K. Youdim within the EPSRC grant EP/C54171/1

Introduction

Drug-drug Interaction

- Drug-Drug Interactions (DDIs) fall into two major classes: PK and PD interactions.
- This work is related to PK DDI (changes in the adsorption, distribution, metabolism and elimination of the drug).
- PK DDIs can be largely attributed to the induction (stimulation) or inhibition (suppression) of the cytochrome P450 enzymes (CYPs).
- Most enzymes are located in the liver, which is regarded as the primary site of drug metabolism.
- The first step of an enzyme kinetic study involves characterizing the metabolism reaction in human liver microsomes (Michaelis-Menten Model). These are *in vitro* studies.

Standard Model, Design and Data

Enzyme Kinetics Model

In a typical enzyme kinetics reaction enzymes bind substrates and turn them into products. The binding step is reversible while the catalytic step irreversible:

$$S + E \longleftrightarrow ES \rightarrow E + P,$$

S, E and P denote substrate, enzyme and product, respectively.

Standard Model, Design and Data

Enzyme Kinetics Model

The reaction rate is represented by the Michaelis-Menten model

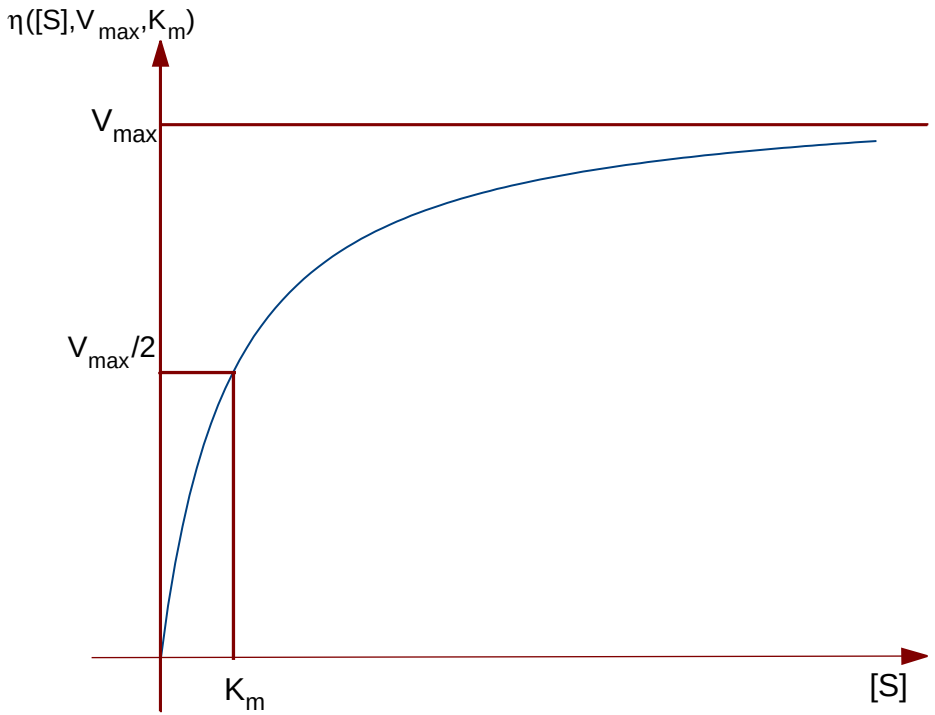
$$v = \frac{V_{\max}[S]}{K_{\mathrm{m}} + [S]},$$

where $[S]$ is the concentration of the substrate and $V_{\max}$ and K_{m} are the model parameters:

- $V_{\max}$ denotes the maximum velocity of the enzyme and
- K_{m} is Michaelis-Menten constant, it is the value of $[S]$ at which half of the maximum velocity $V_{\max}$ is reached.

Standard Model, Design and Data

Enzyme Kinetics Model



Michaelis-Menten Model. The response function: $\eta\left([S]; V_{\max}, K_{\mathrm{m}}\right)$ for the point priors $V^0_{\max} = 1, K^0_{\mathrm{m}} = 1$.

Standard Model, Design and Data

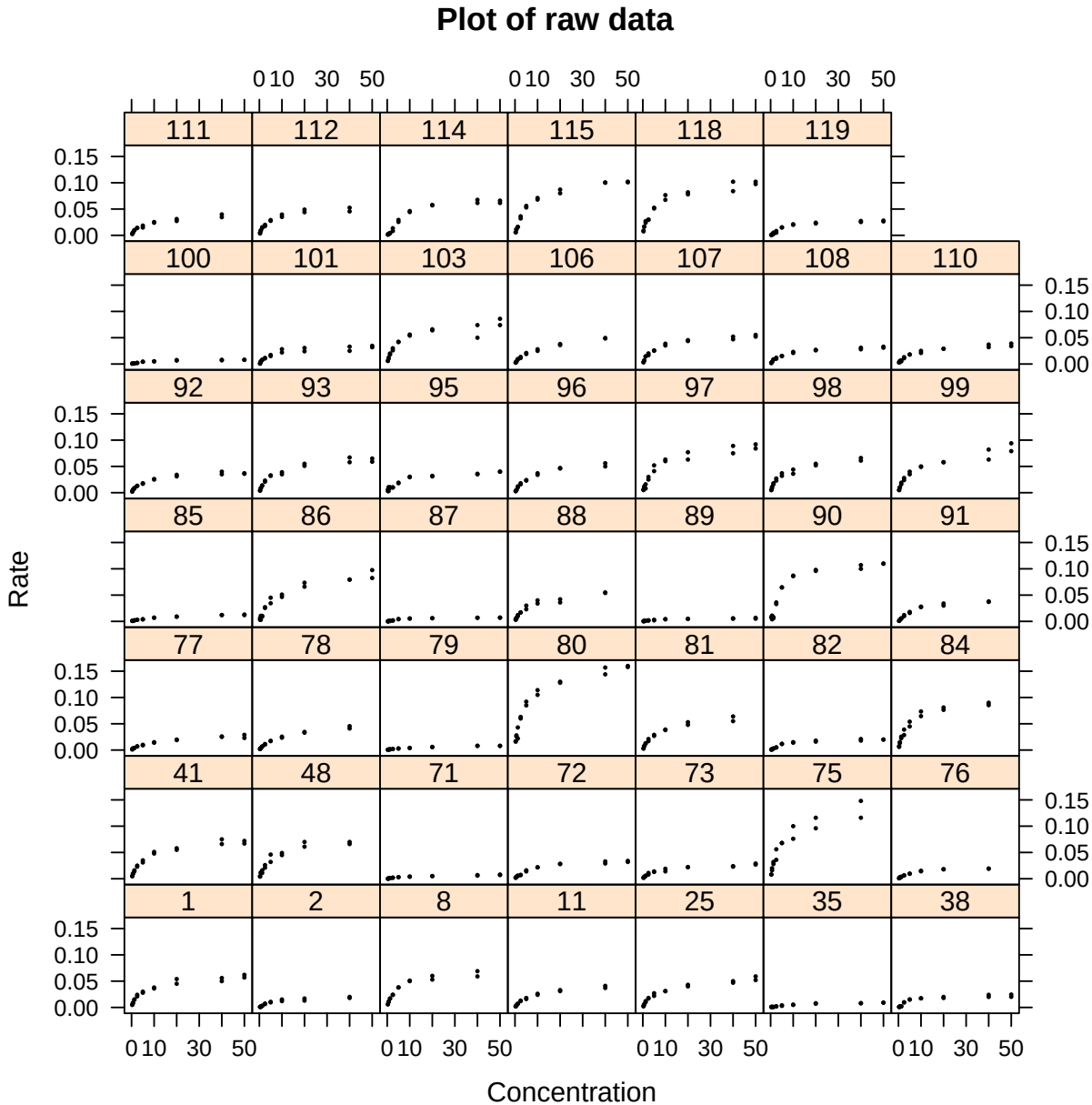
Design

- Human liver microsomal preparations are 'subjects'.
- Concentration levels of a probe substrate are design points.
- A typical design consists of several concentration levels, same for all subjects.
- We have data from an experiment on 47 liver preparations and 9 substrate concentration levels, two observations per each combination ($= 423 \times 2$).
- The concentration levels were

$$\{0.3,\ 0.6,\ 1.2,\ 2.5,\ 5.0,\ 10.0,\ 20.0,\ 40.0,\ 50.0\}.$$

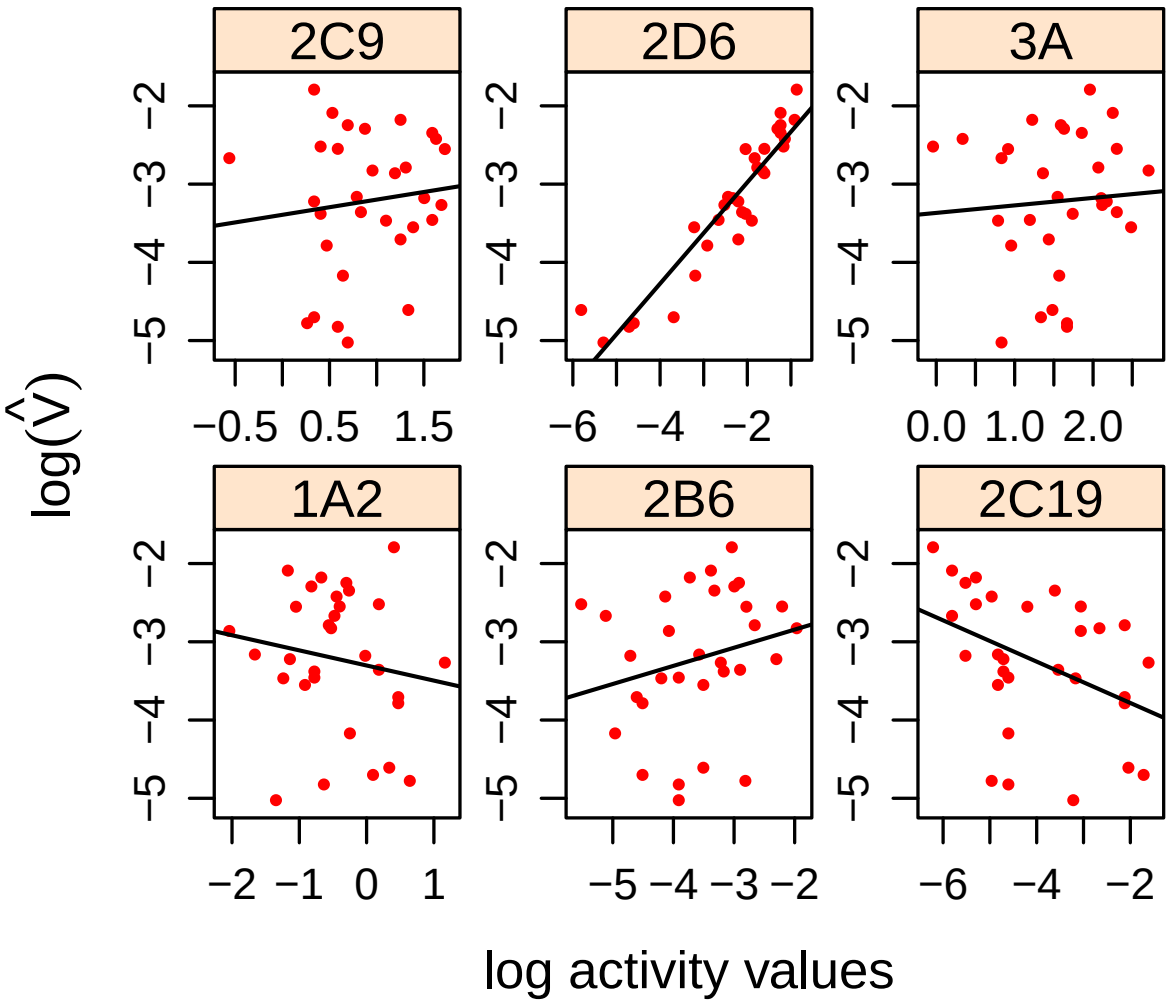
Standard Model, Design and Data

Data



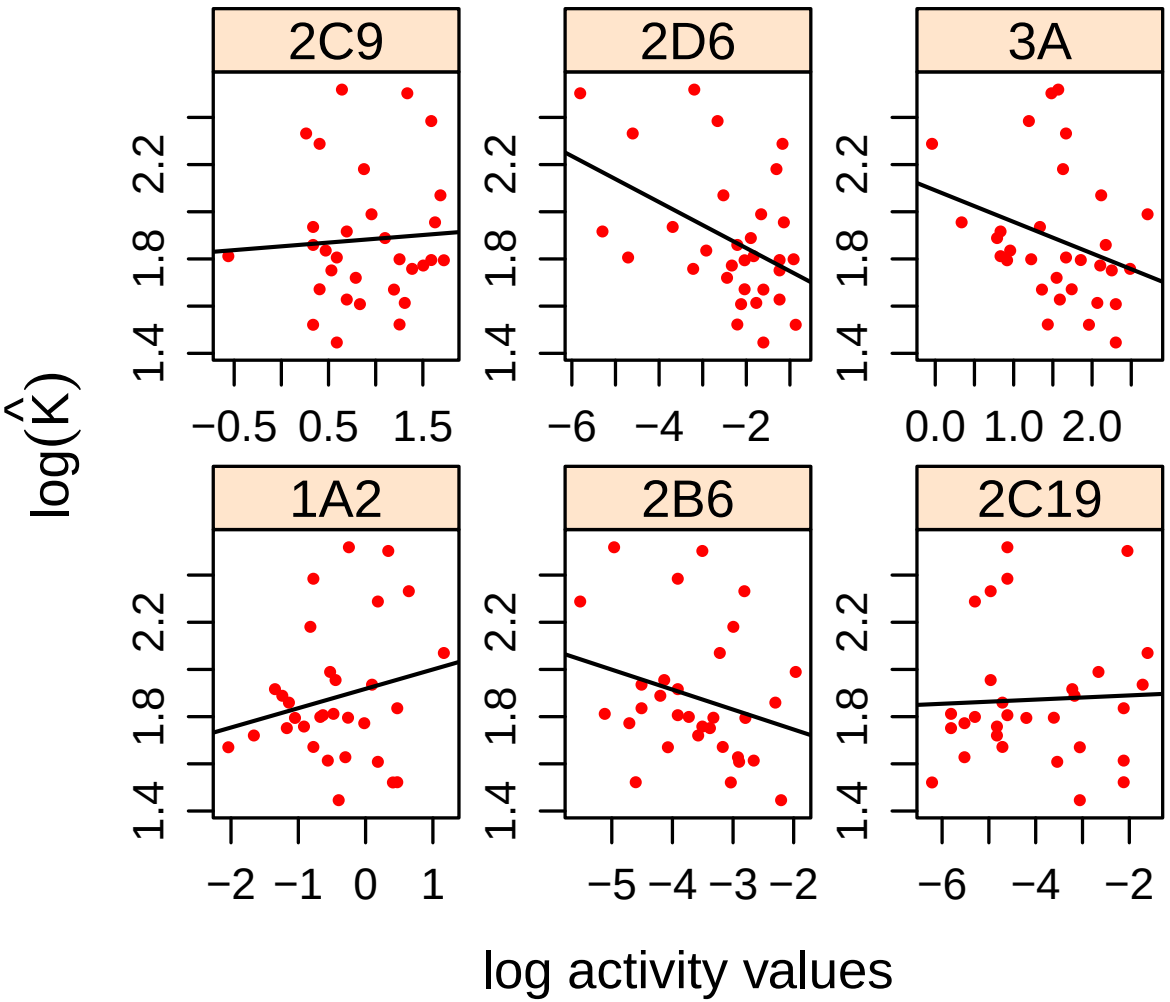
Standard Model, Design and Data

Correlation with Enzyme Activity



Standard Model, Design and Data

Correlation with Enzyme Activity



Population Approach - Modelling

Inter-Subject Variability

- The inter-subject variability may be related to the enzyme activity.

Population Approach - Modelling

Inter-Subject Variability

We express the inter-subject variability by the following relation between the parameter $V_{\max}$ and the enzyme activity:

$$\log V_{\max} = \beta_0 + \beta_1 z + b,$$

where z denotes the log-activity value and b is a random variable expressing uncontrolled sources of the variability.

We assume that $b \sim \mathcal{N}(0, \sigma_V^2)$.

Similar approach to modelling is shown in
Belle et al (2000). A population approach to enzyme characterization and Identification: Application to Phenacetin O-Deethylation. Pharmaceutical Research, vol. 17, No 12, 1531–1536.

Population Approach - Modelling

Model

$$y_{ij} = \frac{V_{\max} x_i}{K + x_i} + \epsilon_{ij} = \frac{e^{\beta_0 + \beta_1 z_j + b_j} x_i}{e^{\beta_2} + x_i} + \epsilon_{ij},$$

where i is the index of concentration level, j index of the enzyme activity,

$$\begin{aligned}
\theta &= (\beta_0, \beta_1, \beta_2, \sigma_V^2)^{\mathrm{T}} \\
x_i &\in (0, x_{\max}] \\
z_j &\in (0, z_{\max}] \\
b_j &\sim \mathcal{N}(0, \sigma_V^2), \quad \epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)
\end{aligned}$$

Population Approach - Modelling

Transformation

Box-Cox transformation

$$h(y,\lambda) = \begin{cases} \frac{y^{\lambda}-1}{\lambda}, & \text{when } \lambda \neq 0; \\ \log y, & \text{when } \lambda = 0. \end{cases}$$

applied to both sides gives

$$h(y_{ij},\lambda) = h\left(\frac{e^{\beta_0+\beta_1 z_j+b_j}x_i}{e^{\beta_2}+x_i},\lambda\right)+\varepsilon_{ij}$$

Population Approach - Modelling

Transformation

To find an estimate of the transformation parameter we apply the ANOVA method

Latif, M. and Gilmour, S.G. (2011). Transform-both-sides nonlinear models for randomized experiments. Submitted.

$$h(y_{ijk}, \lambda) = \tau_{ij} + e_{ijk},$$

where τ_{ij} is the mean response corresponding to 'treatment' ij, $e_{ijk} \sim \mathcal{N}(0, \sigma_e^2)$.

MLE$(\lambda) = \widehat{\lambda}$ is then used to transform the model.

Population Approach - Designing

Definition and Design Region

Here we have two design variables:

- x - concentration of the substrate
- z - enzyme activity (covariate)

$$\xi = \left\{ \begin{array}{c} \begin{pmatrix} x_i \\ z_j \end{pmatrix} \\ w_{ij} \end{array} \right\}_{i,j}$$

Design Region is $\mathcal{D} = (0, x_{\max}] \times (0, z_{\max}]$.

Population Approach - Designing

Optimality Criterion

- We are interested in precise estimation of the transformation parameter and of the Michaelis-Menten parameters.
- We combined the information coming from the data through two models:
  - the ANOVA model

$$h(y_{ijk}, \lambda) = \tau_{ij} + e_{ijk}$$

  - the transformed MM model

$$h(y_{ijk}, \widehat{\lambda}) = h\left(\frac{e^{\beta_0+\beta_1 z_j+b_j} x_i}{e^{\beta_2} + x_i}, \widehat{\lambda}\right) + \varepsilon_{ijk}$$

Population Approach - Designing

Optimality Criterion

The combined criterion is

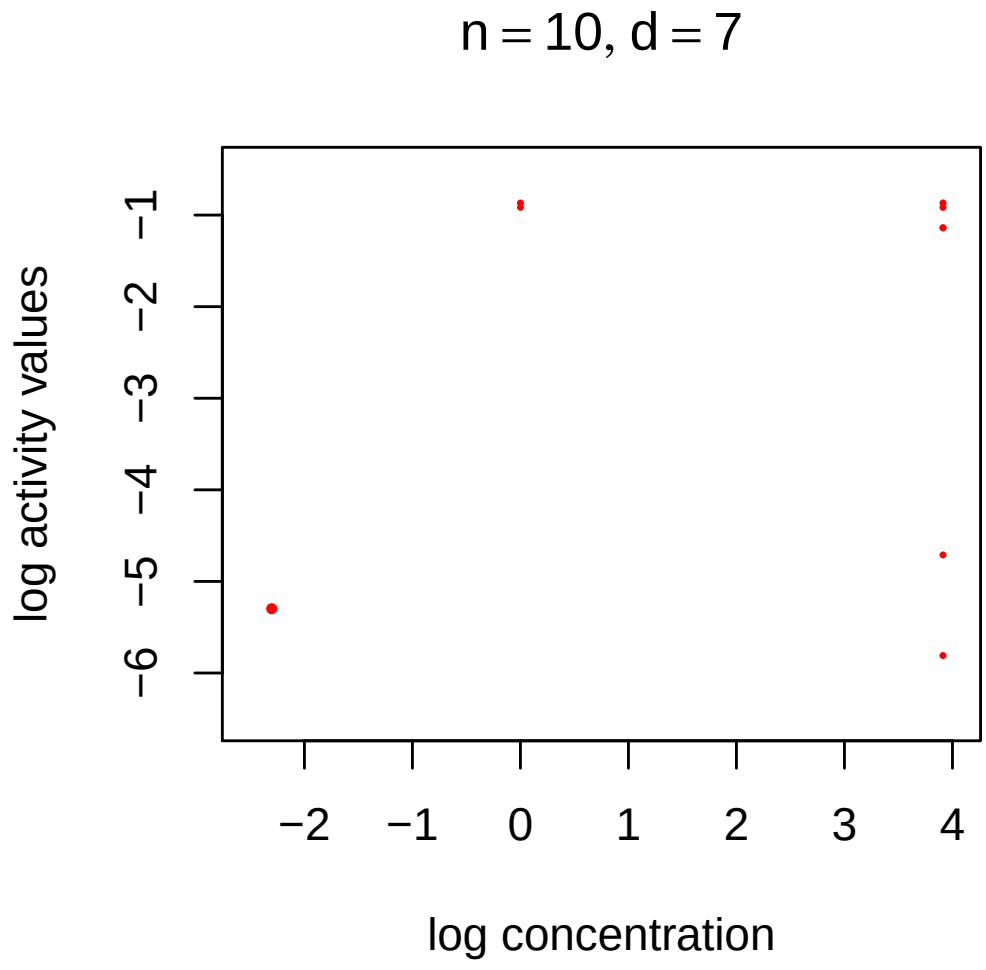
$$\Psi(x, z; \theta, \lambda) = \Psi_1(x, z; \theta, \lambda) + \Psi_2(x, z; \theta, \widehat{\lambda}),$$

where

$$\Psi_1(x, z; \theta, \lambda) = -\log c^{\mathrm{T}} M_\lambda^{-1} c$$
$$\Psi_2(x, z; \theta, \lambda) = \log \det M_\theta$$

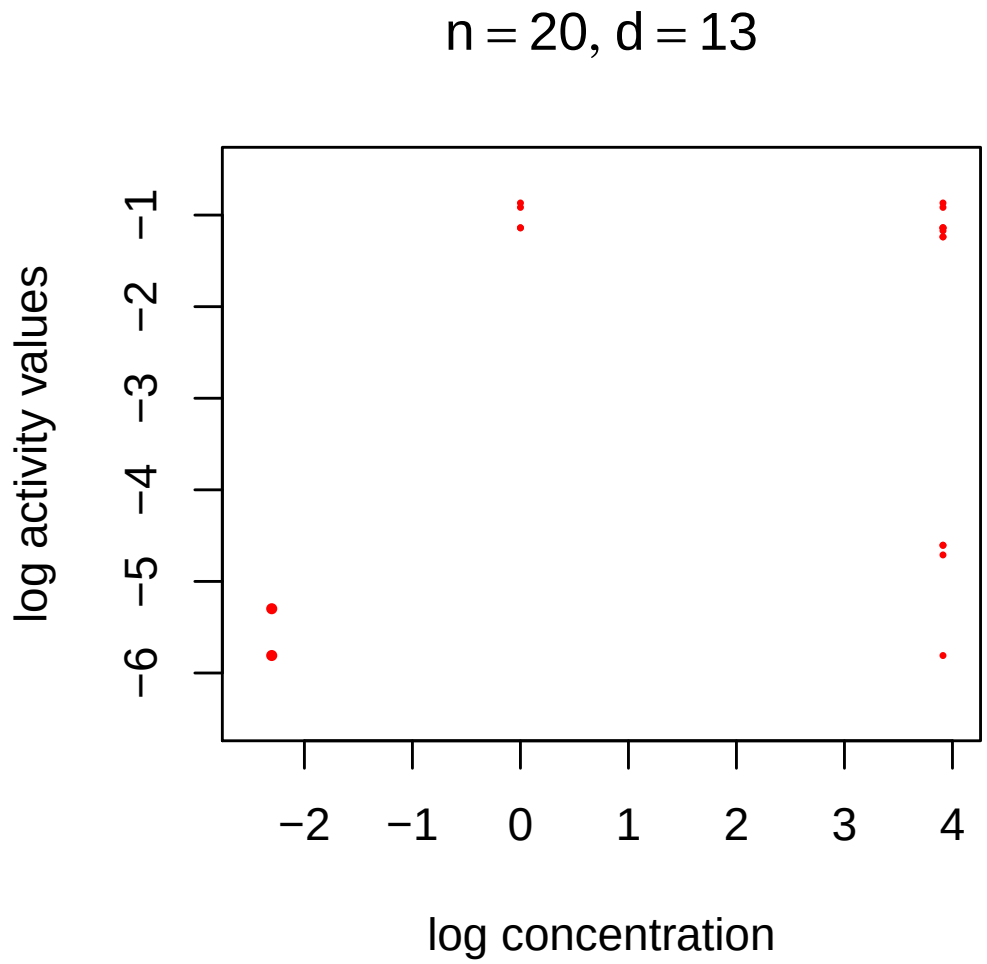
Population Approach - Designing

Optimum Designs



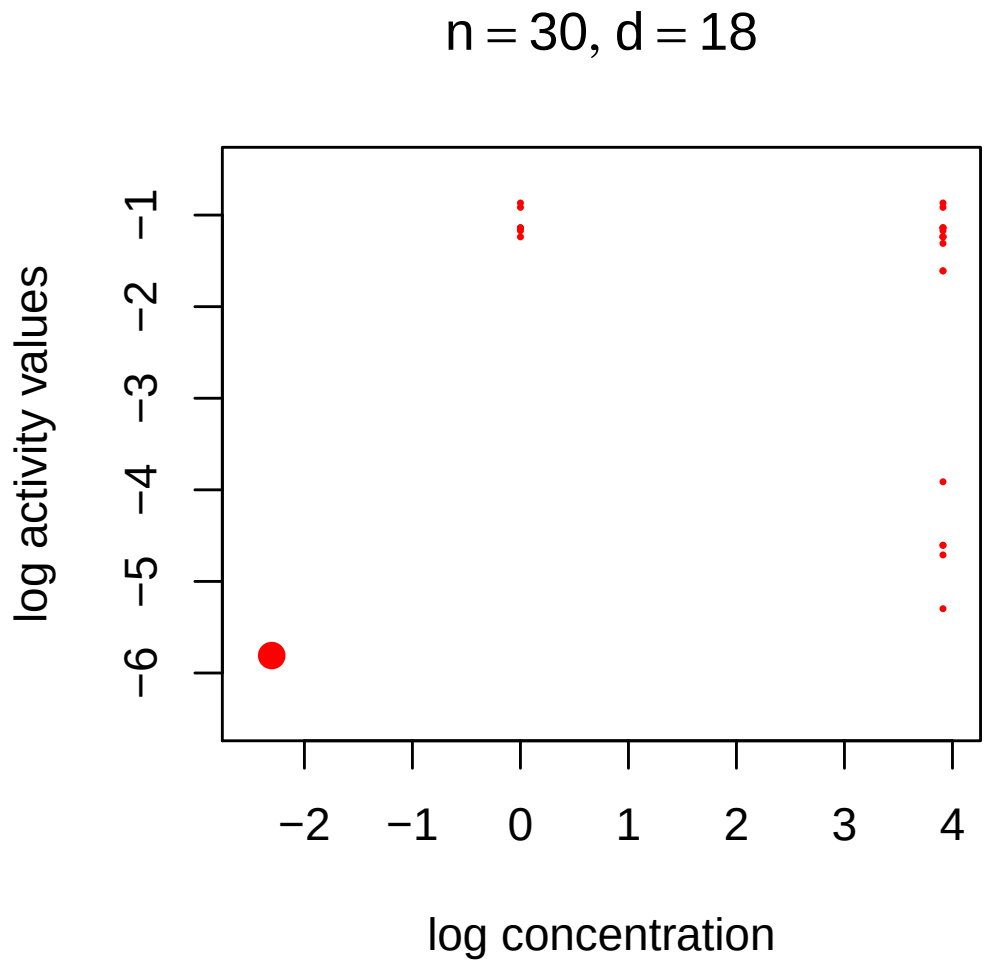
Population Approach - Designing

Optimum Designs



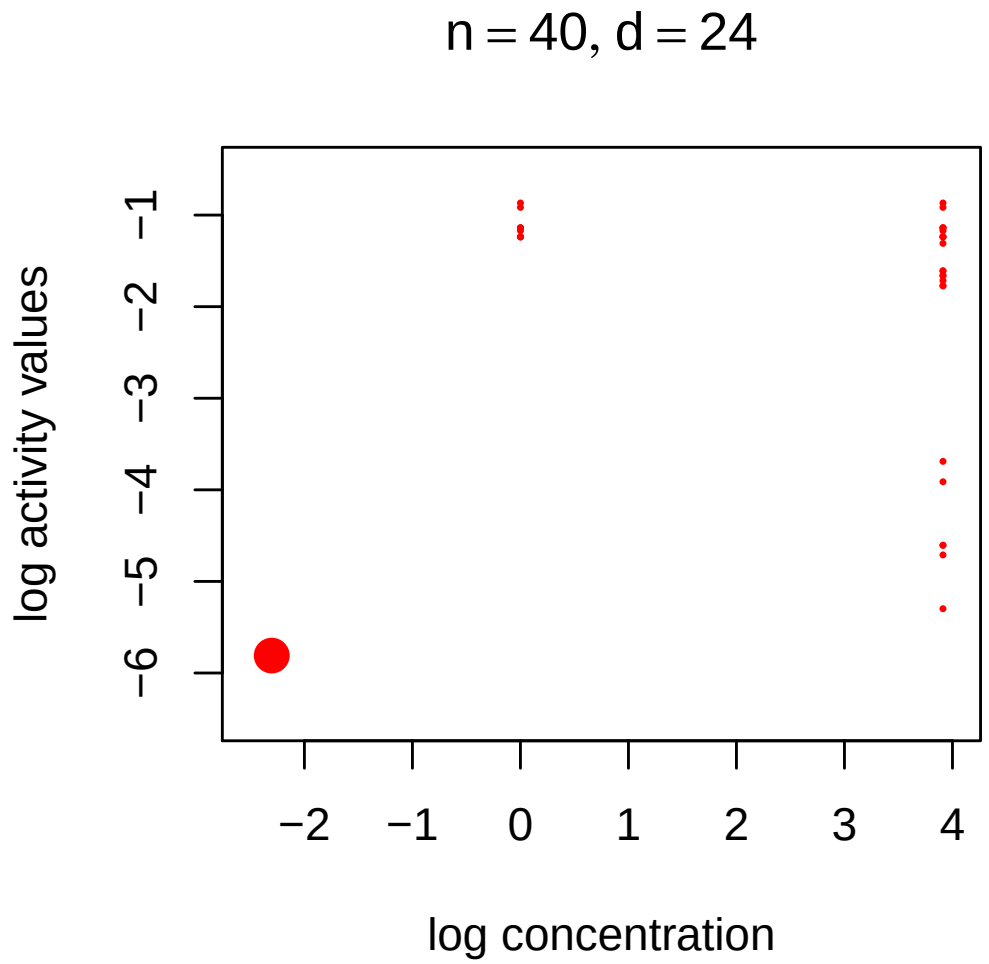
Population Approach - Designing

Optimum Designs



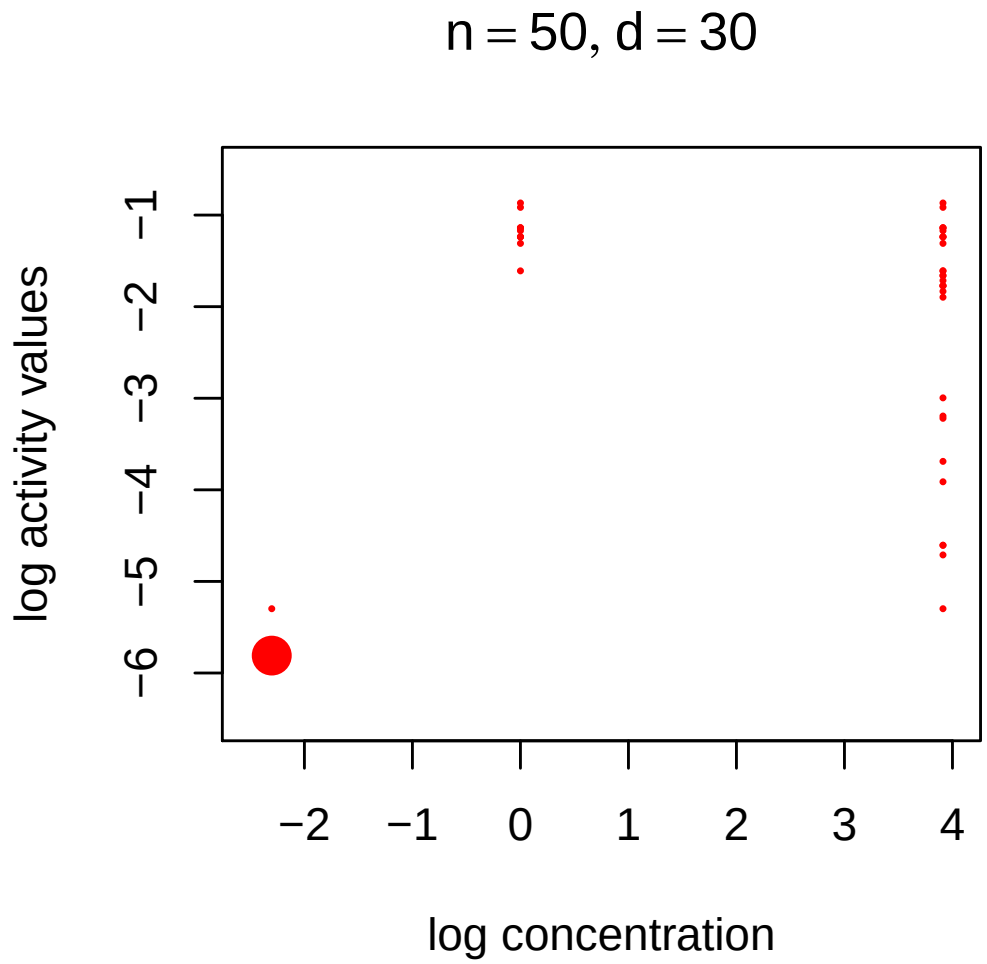
Population Approach - Designing

Optimum Designs



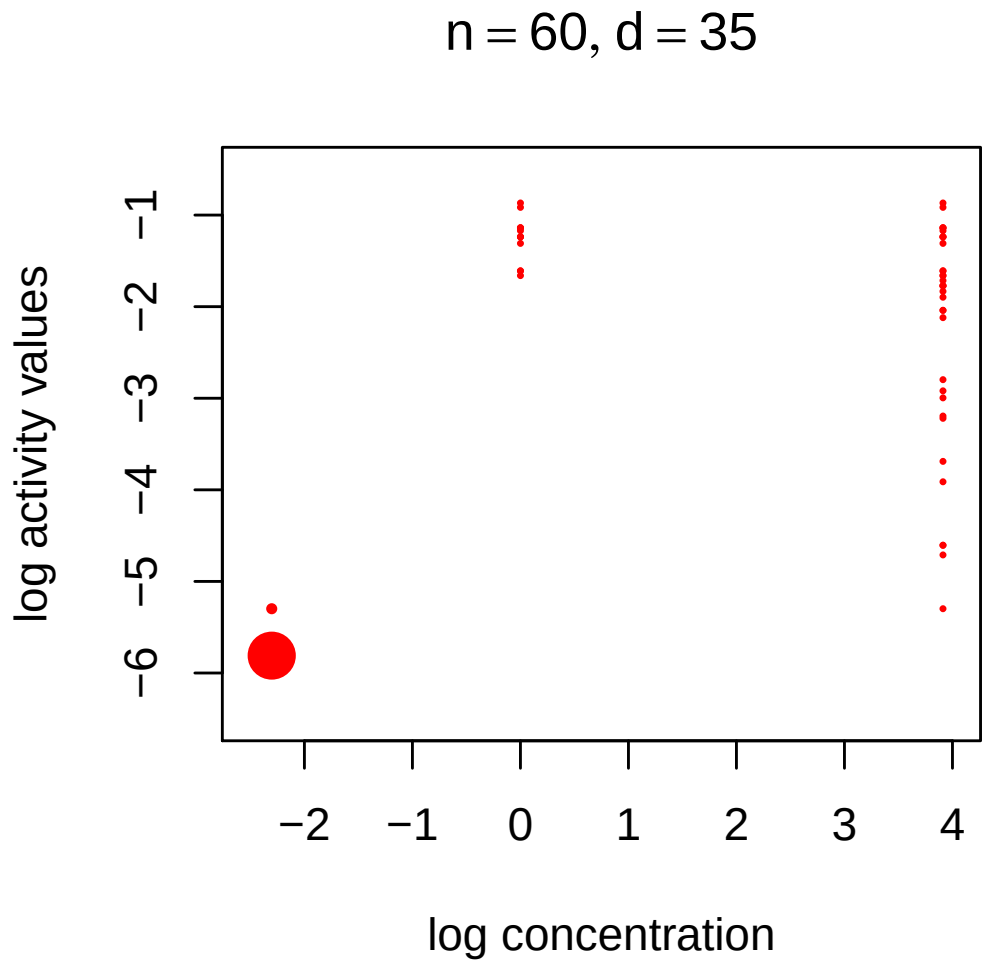
Population Approach - Designing

Optimum Designs



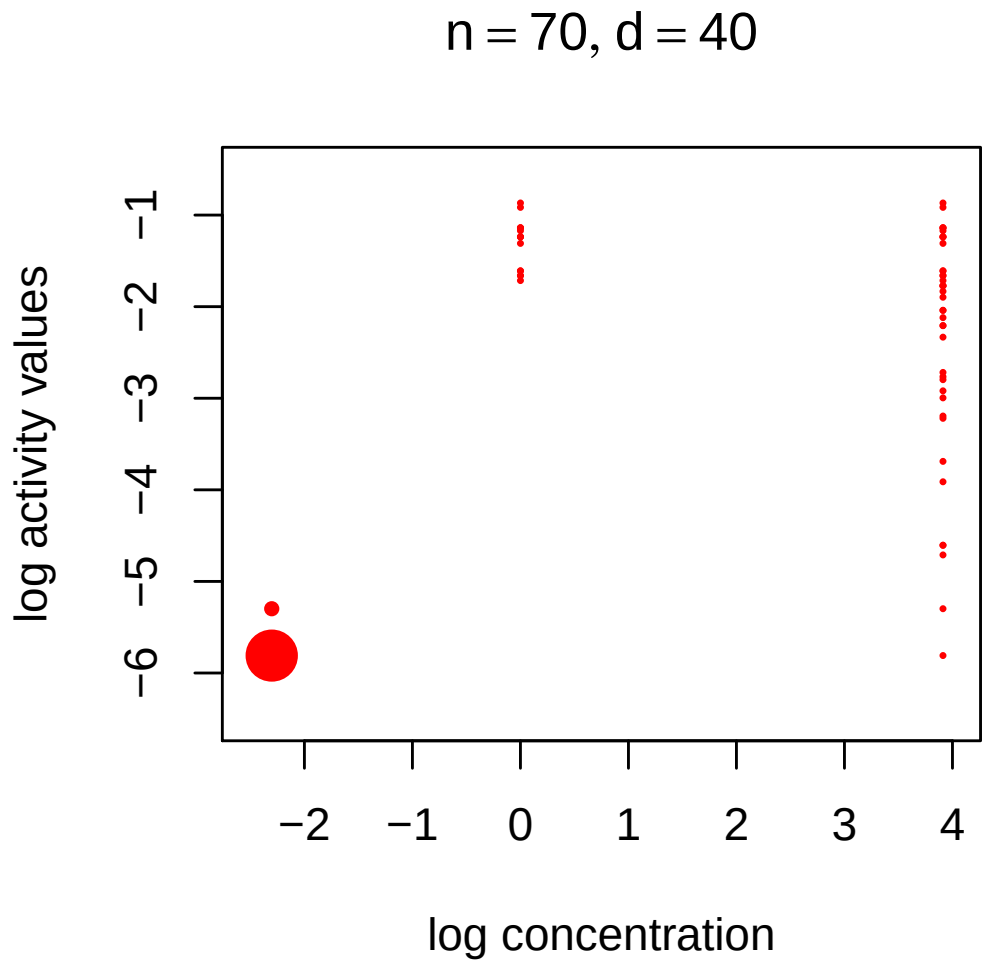
Population Approach - Designing

Optimum Designs



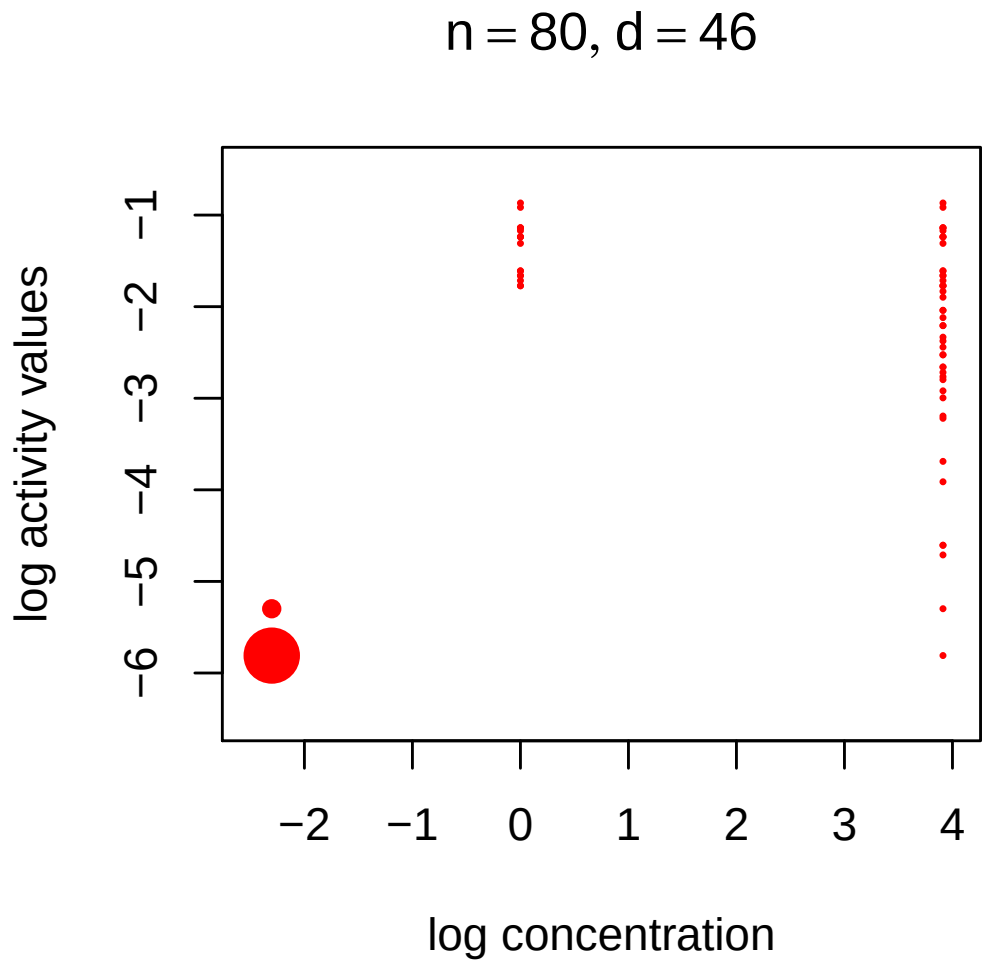
Population Approach - Designing

Optimum Designs



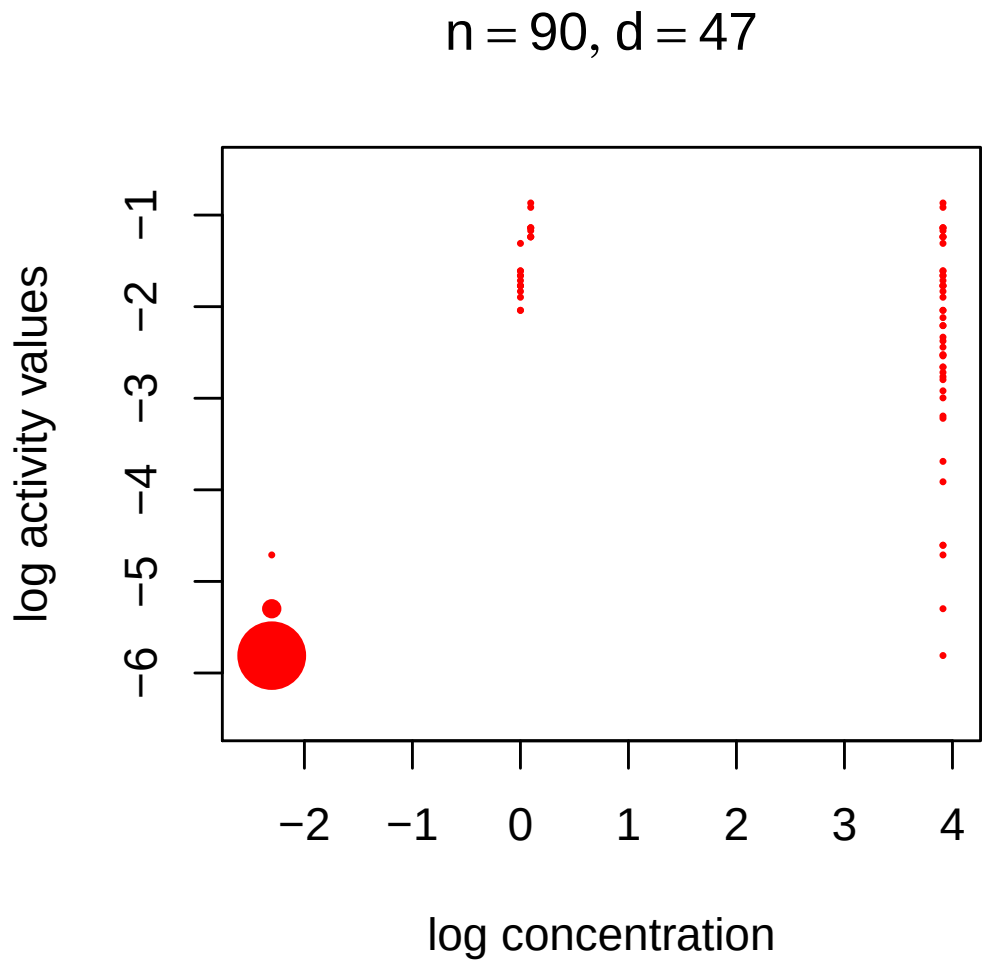
Population Approach - Designing

Optimum Designs



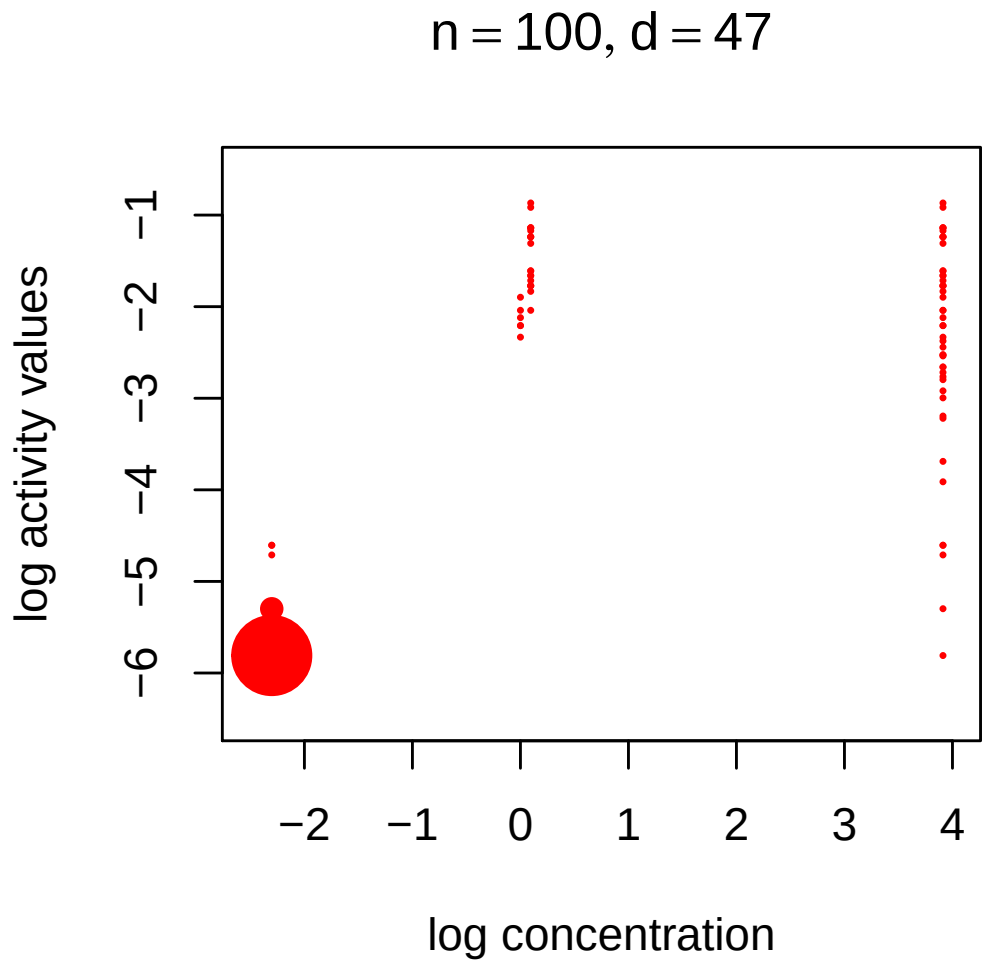
Population Approach - Designing

Optimum Designs



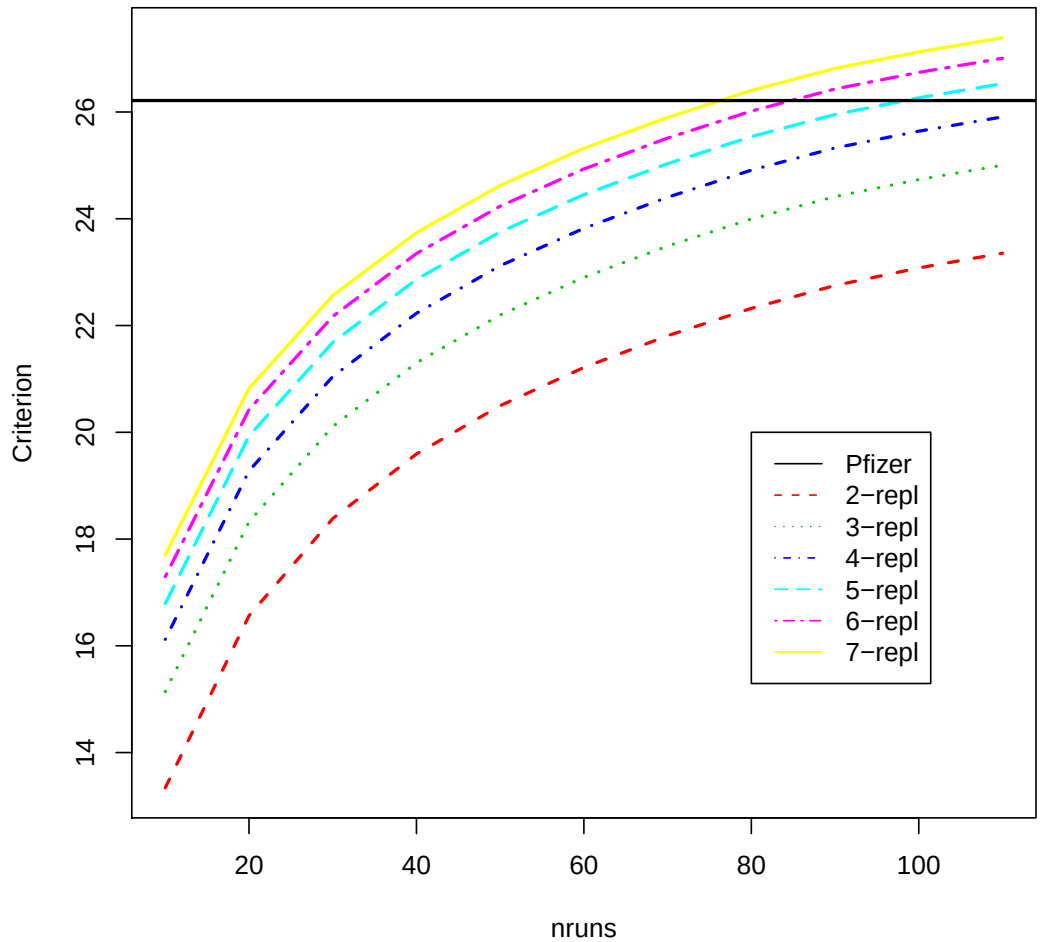
Population Approach - Designing

Optimum Designs



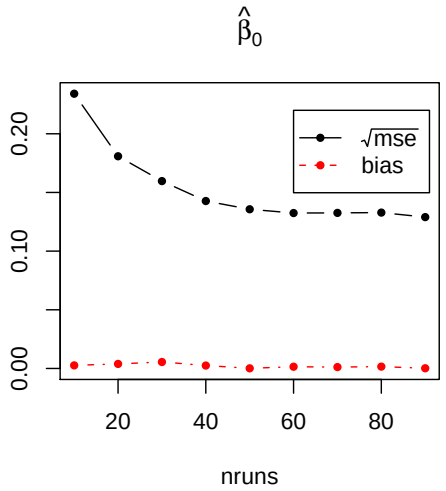
Population Approach - Designing

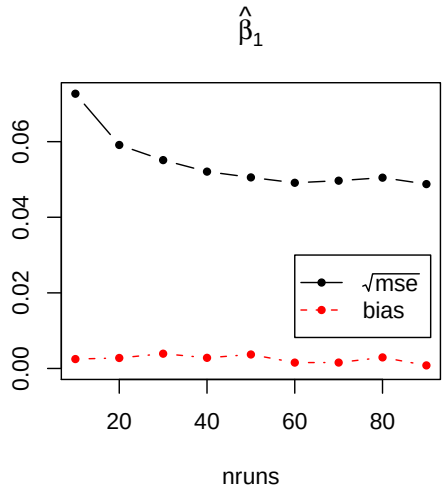
Values of the Optimality Criterion for Various Design Replications

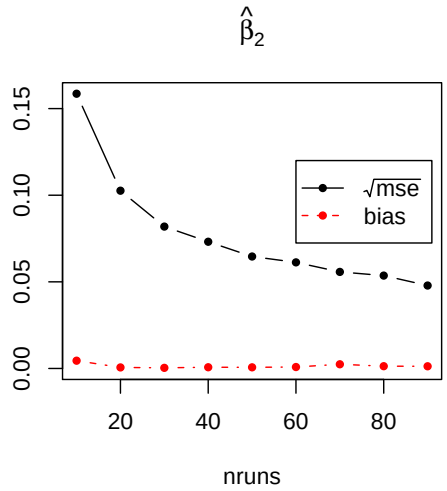


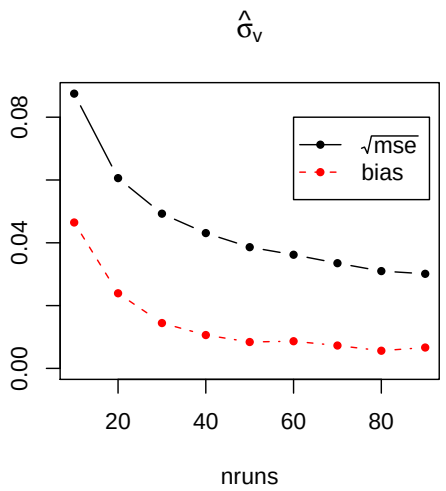
Some Simulations

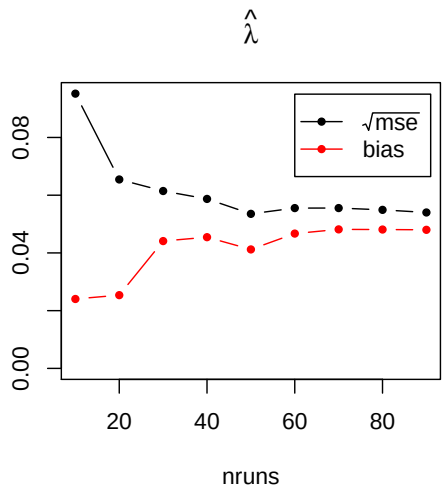
Parameter Estimates











Conclusions

- Including enzyme activity into the model helps to get good designs for precise estimation of the population enzyme kinetic parameters as well as for assessing the correlation with the enzyme activity.
- The experiments are substantially smaller than in the traditional approach.

THANK YOU