Adaptive Experimental Designs for Simultaneous PK and Dose-Selection Studies in Phase I Clinical Trials

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Introduction

Clinical Trials

- Clinical trials are experiments on humans (or living animals) to explore a proposed treatment for a disease and to obtain a licence for the commercial use of the treatment on non-experimental patients.
- Phases of Clinical Trials:
  - Phase I - first in human, small studies to understand PK parameters and to find a dose for further exploration in Phase II.
  - Phase II - larger studies on patients to examine the evidence of a drug effect, compared to placebo.
  - Phase III - very large studies on patients to further refine the dose selection.
  - Phase IV - postmarketing clinical development.

Introduction

Adaptive Designs

"The goal of adaptive designs is to learn from the accumulating data and to apply what is learnt as quickly as possible.

In such trials changes are made "by design" and not on an ad hoc basis;

therefore adaptation is a design feature aimed to enhance the trial, not as a remedy for inadequate planning".
Gallo et al. (2006)

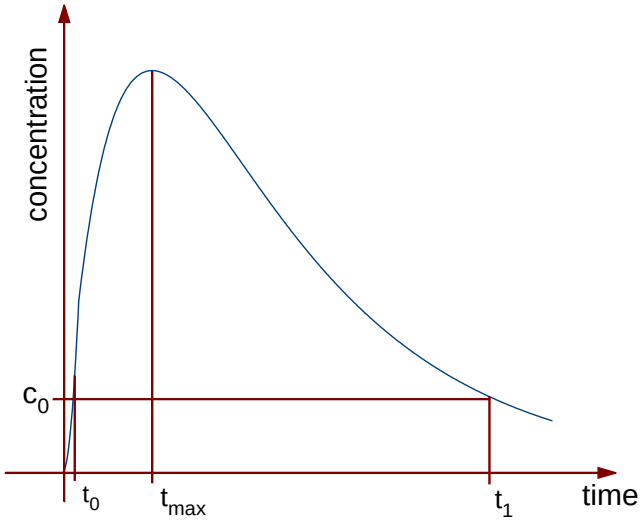
Main features of adaptive designs:

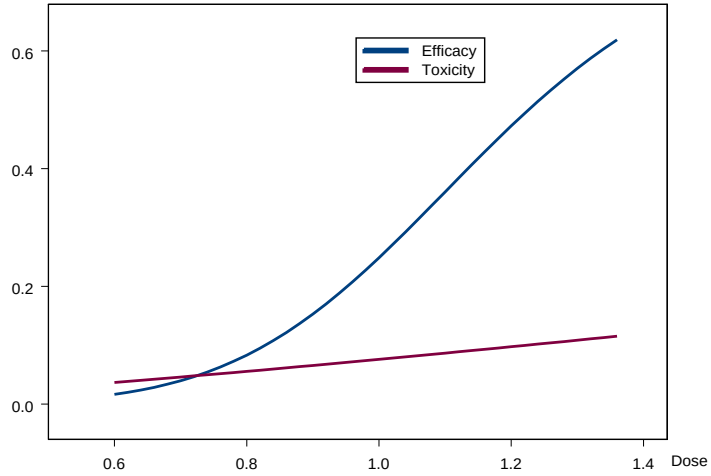
- The information is gathered sequentially.
- After each step of the trial the statistical model is updated.
- Next step of the trial depends on all the results up to date.
- The trial is stopped when the goal of the experiment is achieved (or the resources run out).

Introduction

Phase I Study

- To establish PK parameters.
- To find a safe dose for further studies.





Introduction

Phase I Study

- It is usually assumed that both efficacy and toxicity increase with dose.
- Then the Maximum Tolerated Dose is used for further studies in Phase II.
- Some Medicinal Products do not follow this pattern. For example, when the new treatment stimulates the immune system:
  - large dose may decrease efficacy,
  - dose-efficacy relationship may be unimodal.

Dose-Response Model

After Zhang et al. (2006) we consider three possible responses to a given dose:

y_0 - no efficacy and no severe toxicity ("neutral"),

y_1 - efficacy and no severe toxicity ("success"),

y_2 - severe toxicity ("disaster").

We assign probabilities $\psi_i(x, \vartheta_1)$ to each of the responses, at a given dose x, such that
$\psi_0(x, \vartheta_1)$ - decreases with dose,
$\psi_1(x, \vartheta_1)$ - decreases or is unimodal or increases with dose,
$\psi_2(x, \vartheta_1)$ - increases with dose and

$$\psi_0(x, \vartheta_1) + \psi_1(x, \vartheta_1) + \psi_2(x, \vartheta_1) = 1$$

Dose-Response Model

The Continuation Ratio (CR) model assures such behaviour of the probabilities (Fan and Chaloner (2004))

$$\log\left\{\frac{\psi_1(x;\vartheta_1)}{\psi_0(x;\vartheta_1)}\right\} = \alpha_1 + \beta_1 x$$

$$\log\left\{\frac{\psi_2(x;\vartheta_1)}{1-\psi_2(x;\vartheta_1)}\right\} = \alpha_2 + \beta_2 x$$

where $\vartheta_1 = (\alpha_1, \beta_1, \alpha_2, \beta_2)$ is a set of unknown parameters to be estimated.

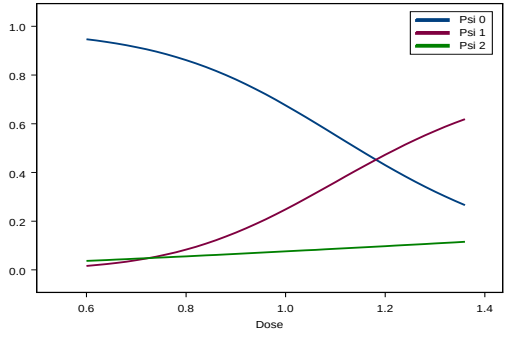
Dose-Response Model

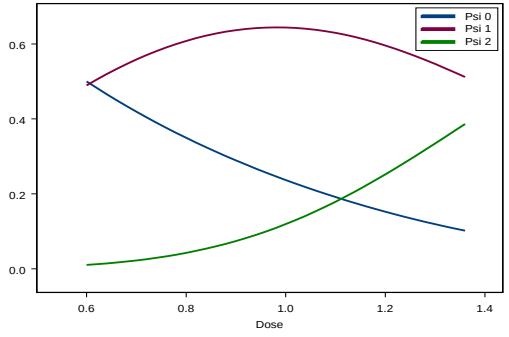
Solving these two equations we obtain three nonlinear functions:

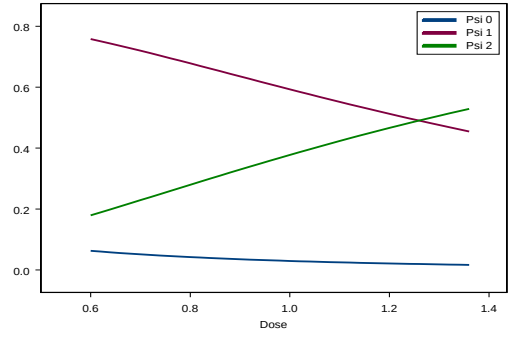
$$\psi_2(x;\vartheta_1) = \frac{\exp(\alpha_2 + \beta_2 x)}{1 + \exp(\alpha_2 + \beta_2 x)}$$

$$\psi_1(x;\vartheta_1) = \frac{\exp(\alpha_1 + \beta_1 x)}{[1 + \exp(\alpha_1 + \beta_1 x)][1 + \exp(\alpha_2 + \beta_2 x)]}$$

$$\psi_0(x;\vartheta_1) = \frac{1}{[1 + \exp(\alpha_1 + \beta_1 x)][1 + \exp(\alpha_2 + \beta_2 x)]}$$







Dose-Response Model

The approach we take here is more relevant when patients rather than healthy volunteers take part in the experiment.

Questions:

- What dose should be recommended for further studies?
- What strategy to take to apply efficacious doses as often as possible and get good estimates of the dose-response model parameters?
- How to incorporate the PK information obtained in the study?

PK Model

Two compartments PK mechanistic model:

$$\begin{cases} \frac{d[B]}{dt} = k_a[A]^{\lambda_1} - k_e[B]^{\lambda_2} \\ \frac{d[A]}{dt} = -k_a[A]^{\lambda_1} + g(t|x) \end{cases}$$

with the initial concentrations $[A] = 0$ and $[B] = 0$.

$\vartheta_2 = (k_a, k_e)$ is a vector of unknown rate of absorption and rate of elimination, respectively.

(λ_1, λ_2) are known orders of the kinetic reaction.

Time t is scaled in hours and $g(t|x)$ is the drug infusion rate:

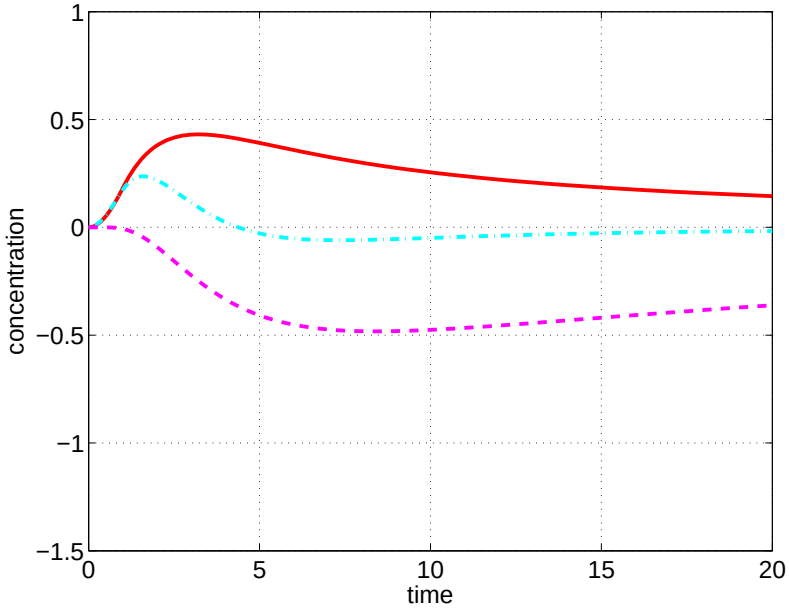
$$g(t|x) = \begin{cases} cx & t \leq 1 \\ 0 & t > 1 \end{cases}$$

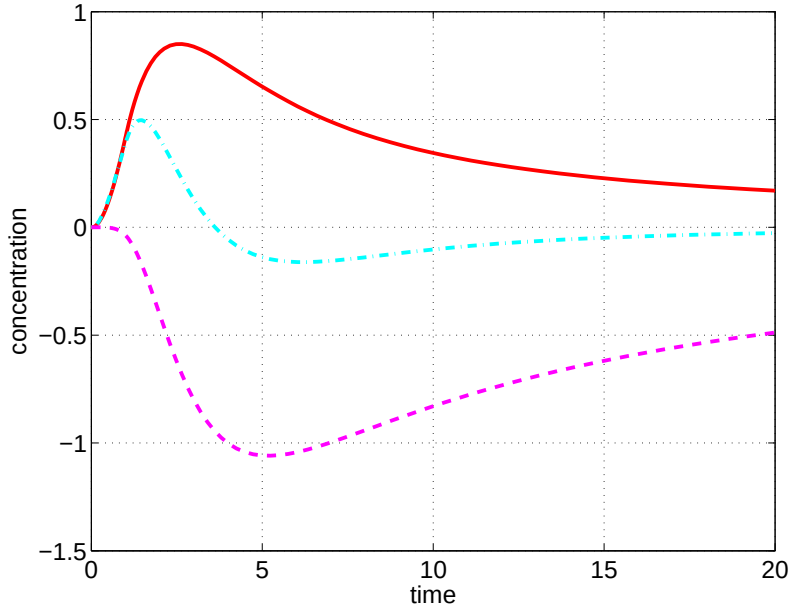
where c is some constant and x is a dose.

We are interested in precise estimation of ϑ_2.

PK Model

Question: What dose to apply and when to measure the concentration to optimally estimate the PK parameters?





Design:

$$\xi(t|x) = \left\{ \begin{array}{ccc} t_1 & \dots & t_s \\ w_1 & \dots & w_s \end{array} \right\}$$

Optimality Criteria

Biologically Optimum Dose

Zhang et al. (2006) propose the following decision functions for finding a BOD:

$$\delta_1(x;\vartheta_1) = I_{[\psi_2(x;\vartheta_1)<\pi_0]},$$
$$\delta_2(x;\vartheta_1) = \psi_1(x;\vartheta_1) - \lambda\psi_2(x;\vartheta_1),$$

where I denotes an indicator function and $\lambda \in [0,1]$.

$\delta_1(x;\vartheta_1) = 1$ means that the toxicity at dose x is smaller than a pre-specified value π_0.

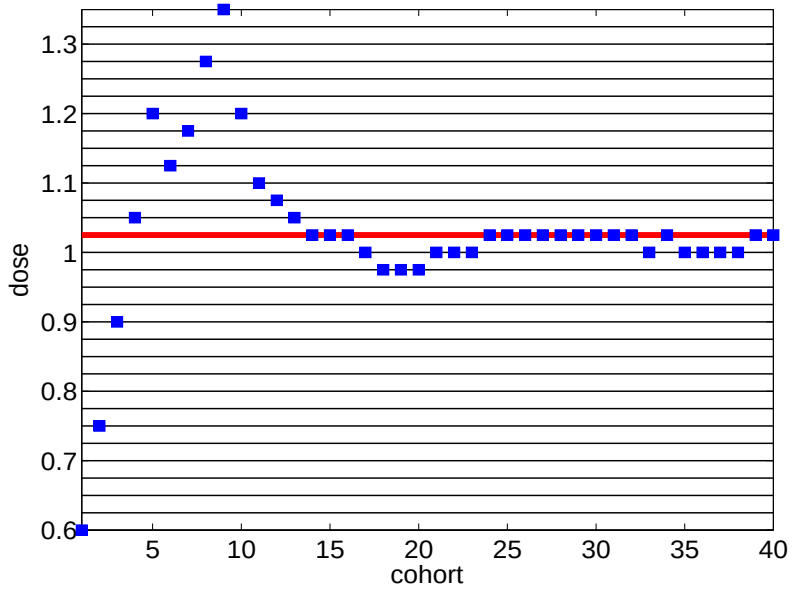
$$x^\star = \arg\max_{C(x)} \delta_2(x;\vartheta_1), \quad C(x) = \{x : \delta_1(x;\vartheta_1) = 1\}$$

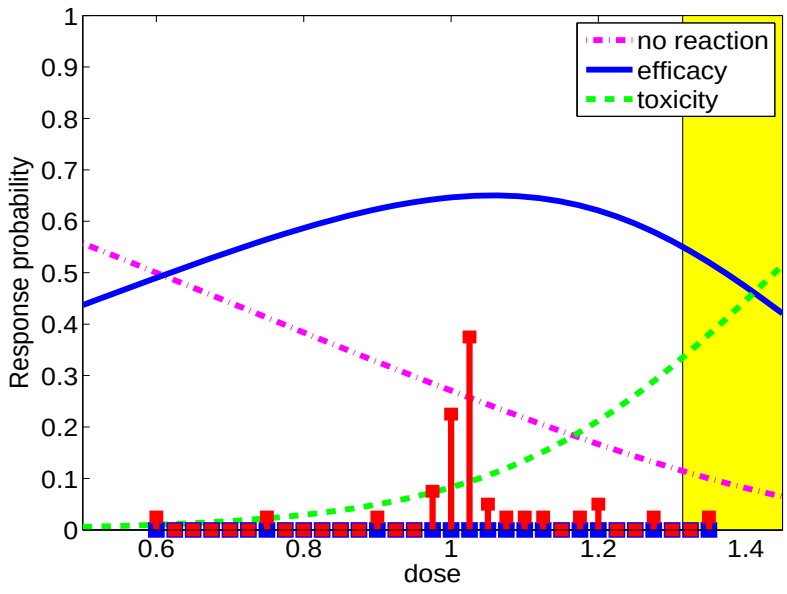
is the recommended BOD for next step of the trial.

Optimality Criteria

Biologically Optimum Dose

An example of a possible Adaptive Design:





Optimality Criteria

Biologically Optimum Dose

At step k of the Adaptive Design:

- dose $x^{\star}_{k-1}$ is applied to cohort k,
- responses are observed,
- parameters of the dose-response model estimated (Bayesian),
- $x^{\star}_{k}$ is calculated,
- stopping rule is checked.

Stopping rules:

- the last cohort of patients is treated, i.e., $n = n_{\max}$,
- the same $x^{\star}$ has been determined minimum m times,

Optimality Criteria

Biologically Optimum Dose

Some technicalities:

- the possible doses were $x = 0.6 + 0.05i, \quad i = 0, 1, \ldots, 16,$
- cohort size was $q = 3$ and maximum number of cohorts was $n_{\max} = 50$,
- the highest tolerable toxicity probability π_0 was assumed to be 0.33 and $\lambda = 0$,
- it was allowed to skip only one dose during the escalation, no restrictions on de-escalations.
- uniform prior distributions for $(\alpha_1, \beta_1, \alpha_2, \beta_1)$ were taken over $[-3, 3]$, $[0, 4]$, $[-13, -7]$, $[3, 9]$, respectively.

Optimality Criteria

Efficiency of PK Estimation

We use the D-optimality criterion for estimating PK parameters $\vartheta_2 = (k_a, k_e)$:

$$\Phi\{M(\xi)\} = \det M(\xi)$$

where $M(\xi)$ is the information matrix for θ_2

and efficiency of the estimation at a given dose x^0 is defined as:

$$E_D(\xi^\star(t|x^0)) = \left\{ \frac{\det M(\xi^\star(t|x^0))}{\max_x \det M(\xi^\star(t|x))} \right\}^{1/p}$$

$p = 2$, is the number of parameters.

Approach 1

BOD Constrained by Toxicity Level and by PK Efficiency

Maximize (over x)

$$\delta_2(x;\vartheta_1) = \psi_1(x;\vartheta_1) - \lambda\psi_2(x;\vartheta_1)$$

subject to

$$\psi_2(x;\vartheta_1) < \pi_0$$

and

$$E_D[\xi^\star(t|x)] \geq \eta$$

Approach 2

PK Efficiency Constrained by Toxicity and Dose Efficacy Levels

Maximize (over ξ)

$$E_D[\xi(t|x^\star)]$$

subject to

$$\psi_2(x^\star;\vartheta_1) < \pi_0$$

and

$$\frac{\delta_2(x;\vartheta_1)}{\max_x \delta_2(x;\vartheta_1)} \geq \varrho$$

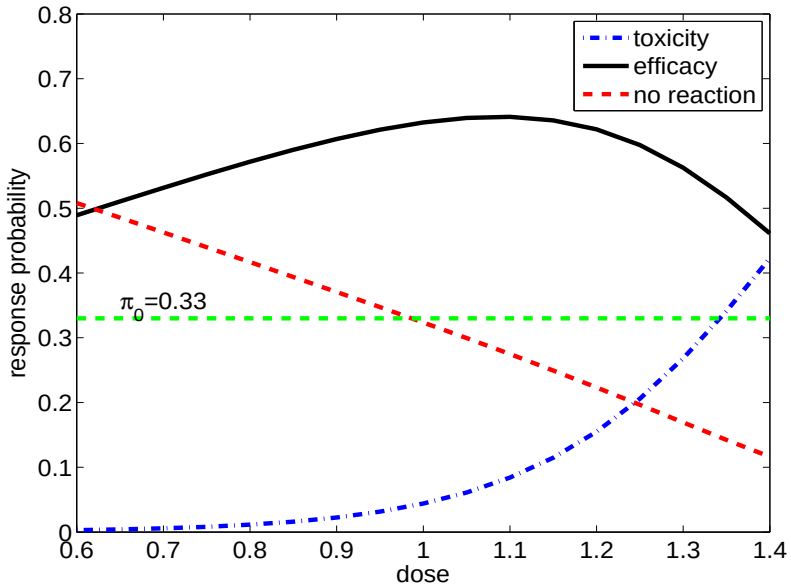
where ϱ is the efficacy coefficient.

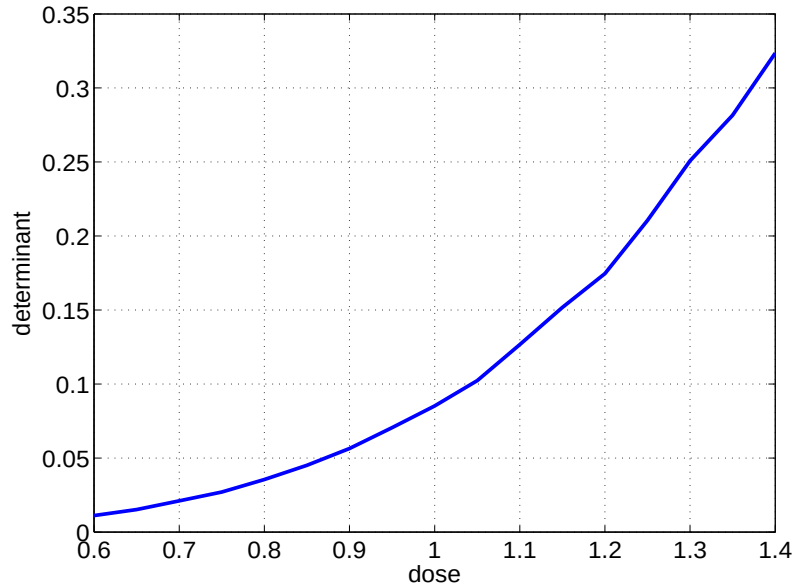
Such a relative efficacy can be considered as an analogy to the efficiency coefficient E_D.

Examples

Approach 1: First Order Kinetics

Probabilities of the responses y_0, y_1, y_2 and $\det M[\xi(t|x)]$ at step k of the Adaptive Design for the parameter estimates $\widehat{\vartheta}_1$ and $\widehat{\vartheta}_2$ obtained in step $k-1$:

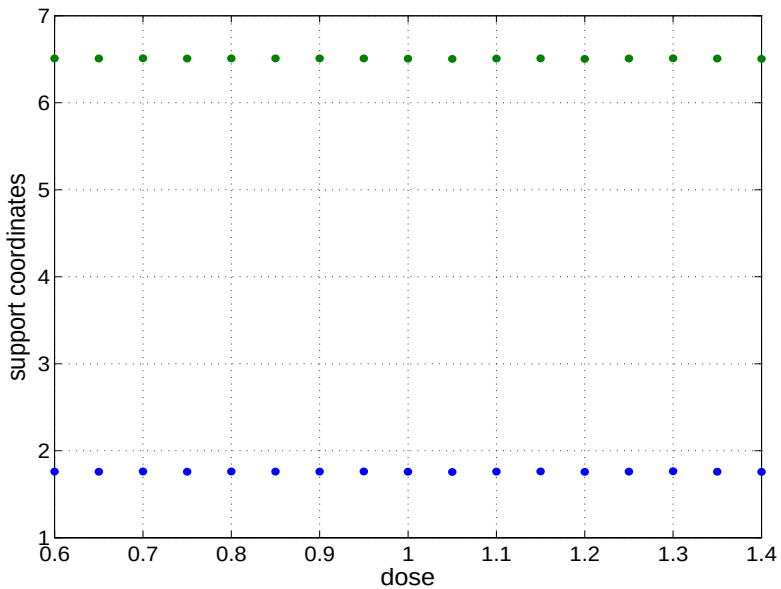


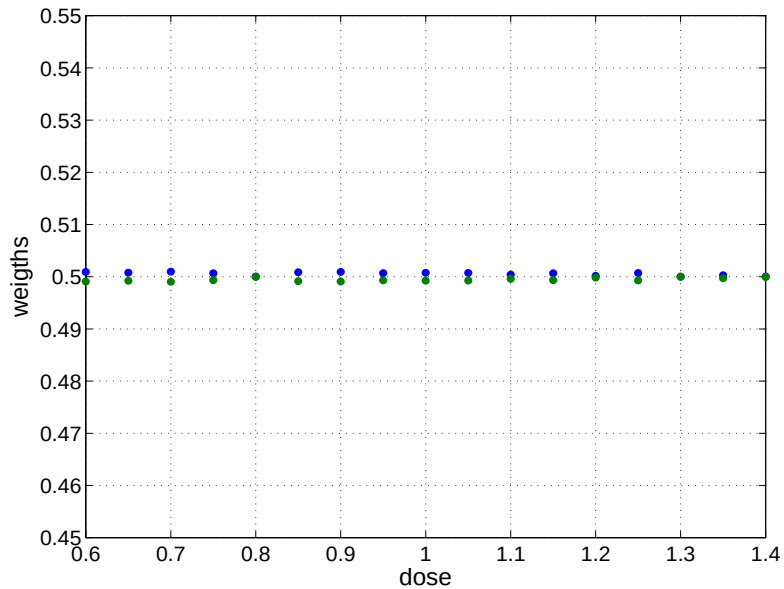


Examples

Approach 1: First Order Kinetics

D-optimum design for estimation of the kinetic parameters $\vartheta_1 = (k_a, k_e)$ does not depend on the dose:



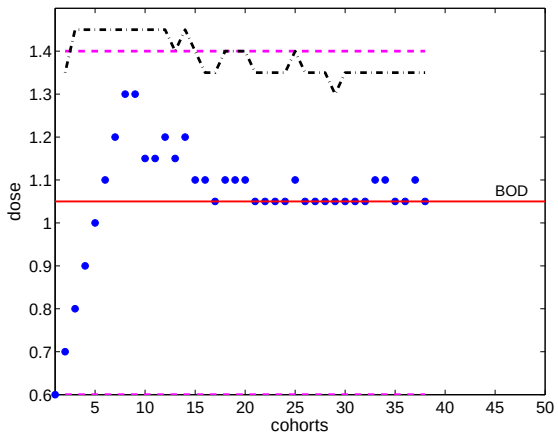


Examples

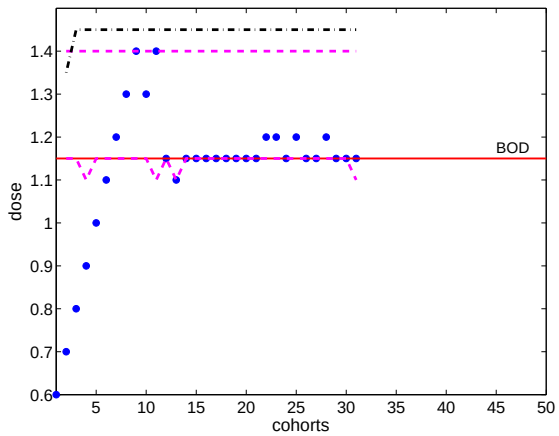
Approach 1: First Order Kinetics

Examples of the trial runs for different levels of PK efficiency.

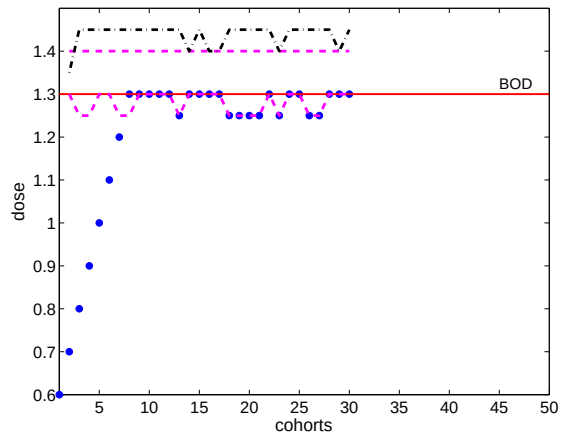
(a) $E_D \leq 40\%$



(b) $E_D \geq 80\%$



(c) $E_D \geq 90\%$



Dashed lines represent the adaptive bounds stemming from the E_D constraint.

The dot-dashed line represents the adaptive upper threshold for non-admissible toxicity.

Examples

Approach 1: First Order Kinetics

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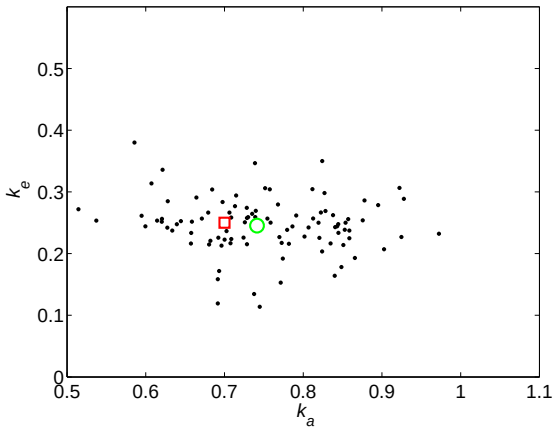

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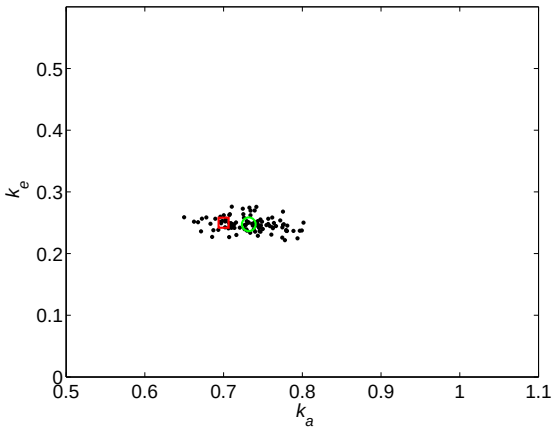

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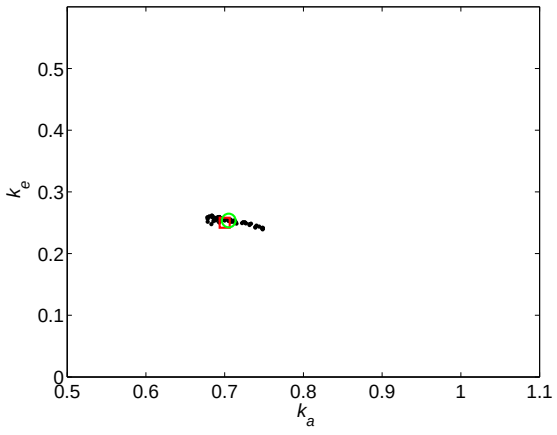


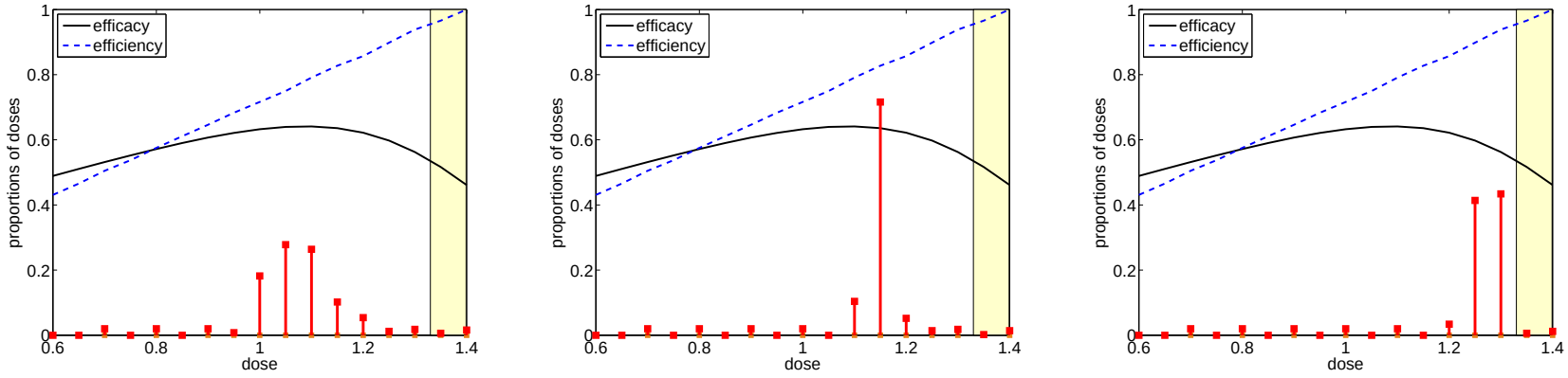
Final estimates of PK parameters from 100 simulations

- red square represents the values assumed for the simulations
- green circle denotes the sample mean

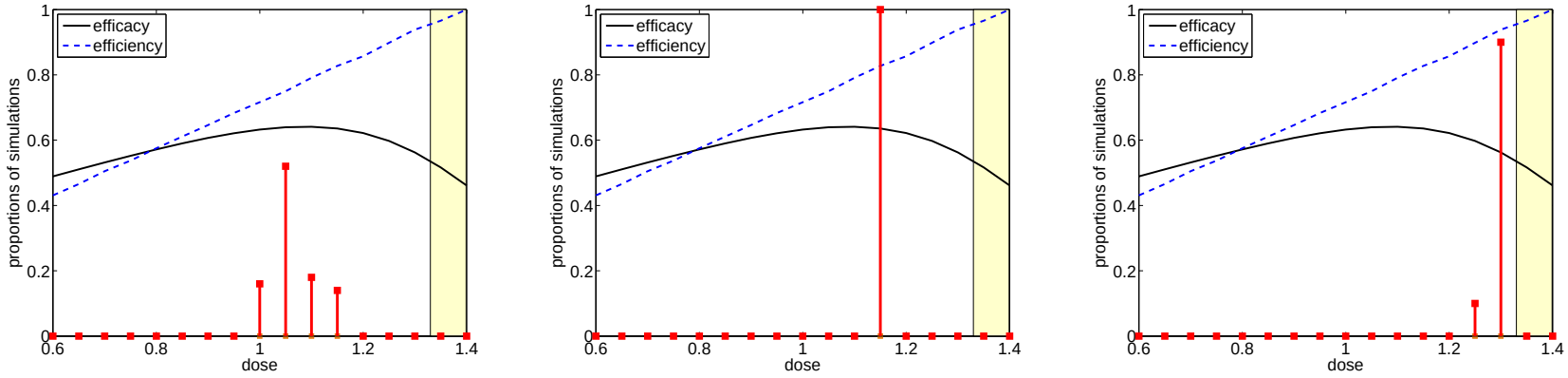
Examples

Approach 1: First Order Kinetics

(a) $E_D \leq 40\%$ (d) $E_D \geq 80\%$ (e) $E_D \geq 90\%$



Dose frequencies averaged over total number of cohorts in 100 simulations.

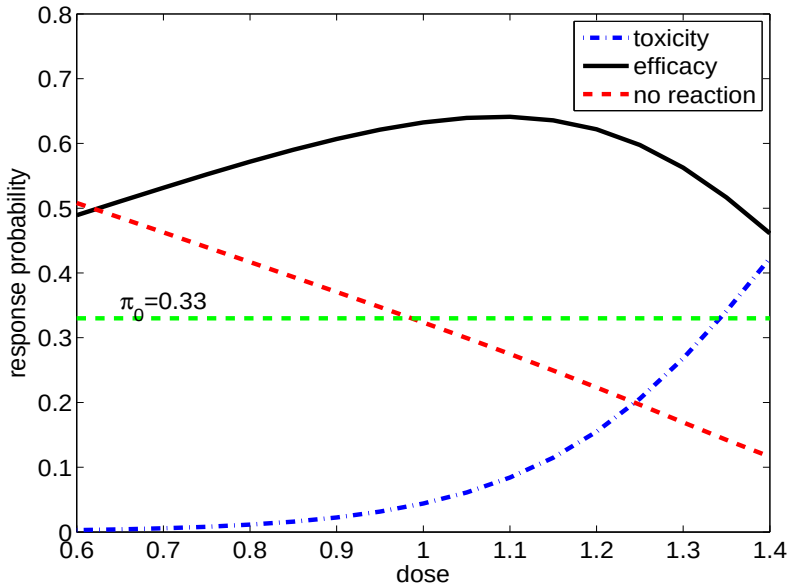


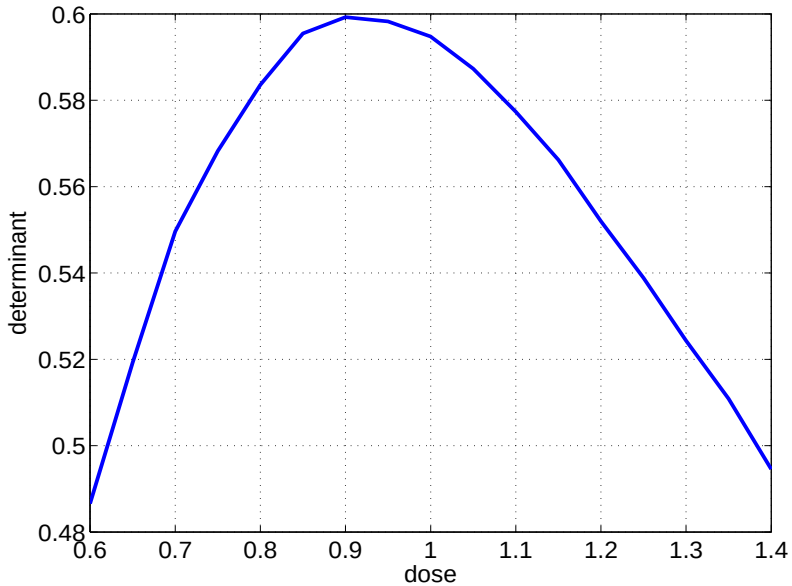
Proportions of the final BOD frequencies in the 100 simulations.

Examples

Approach 1: Second Order Kinetics

Probabilities of the responses y_0, y_1, y_2 and $\det M[\xi(t|x)]$ at step k of the Adaptive Design for the parameter estimates $\widehat{\vartheta}_1$ and $\widehat{\vartheta}_2$ obtained in step $k-1$:

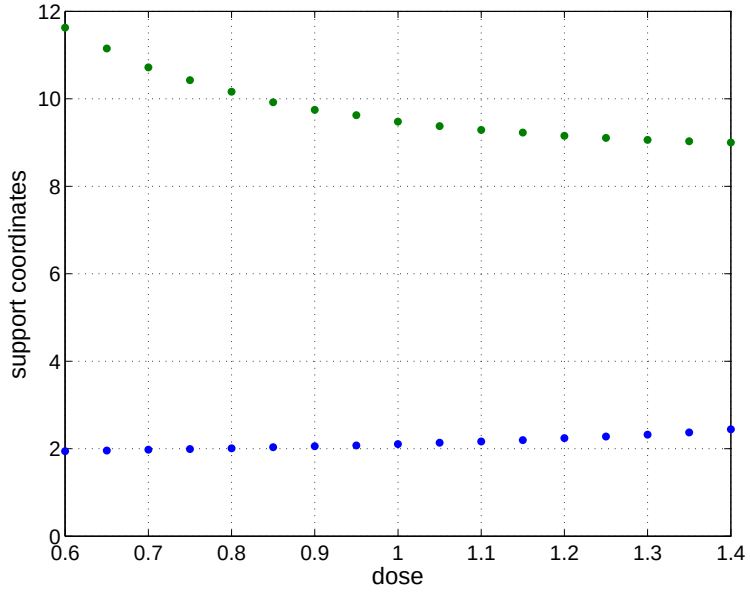


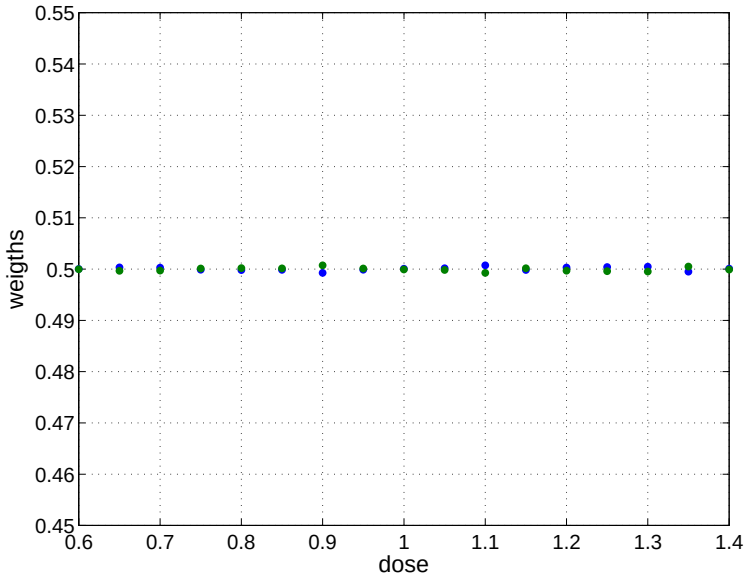


Non-monotonous D-criterion as a function of dose restricts the optimum doses to be in the middle of the dose range.

Examples

Approach 1: Second Order Kinetics





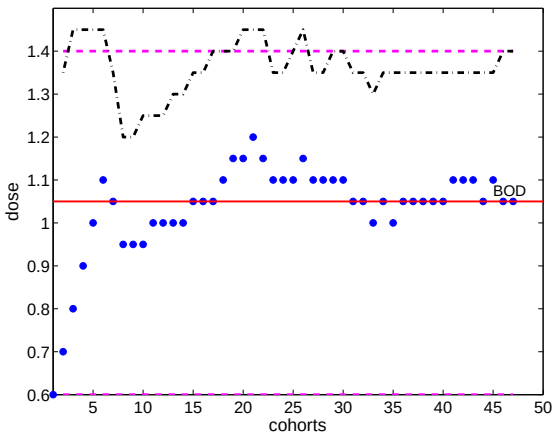
Design support points and weights for different doses, for priors $k_a^0 = 0.8$ and $k_e^0 = 0.3$.

Examples

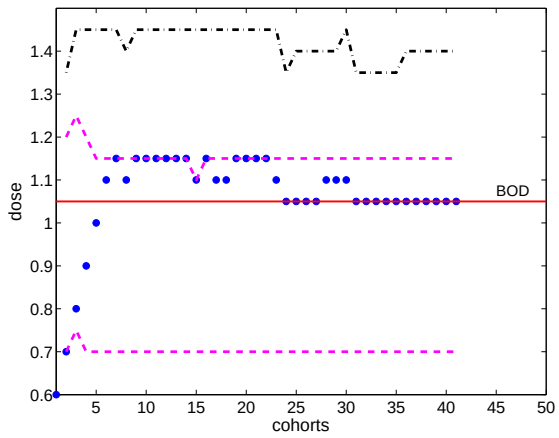
Approach 1: Second Order Kinetics

Examples of the trial runs for different levels of PK efficiency.

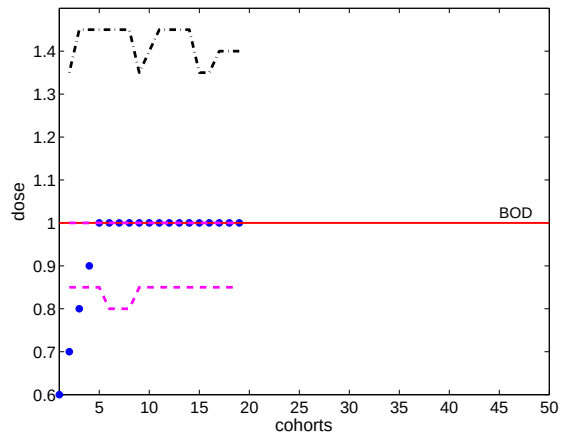
(a) $E_D \leq 75\%$



(b) $E_D \geq 90\%$



(c) $E_D \geq 98\%$



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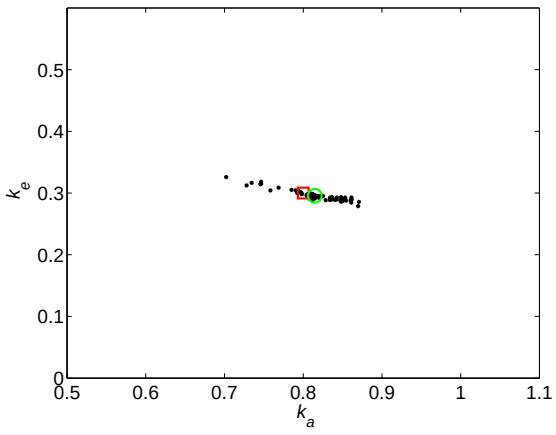

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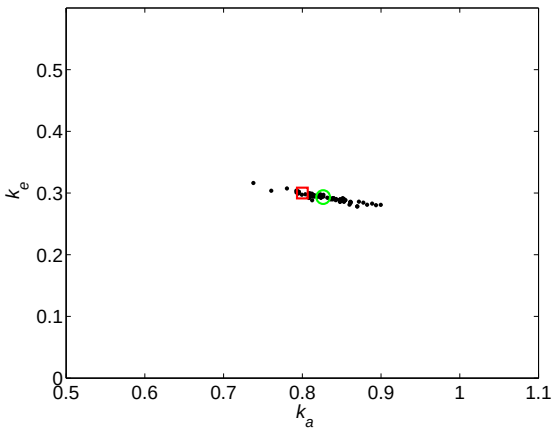

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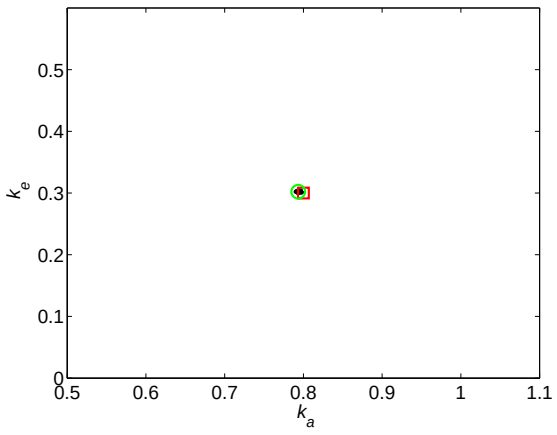

Final estimates of PK parameters from 100 simulations

- red square represents the values assumed for the simulations
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Examples

Approach 1: Second Order Kinetics

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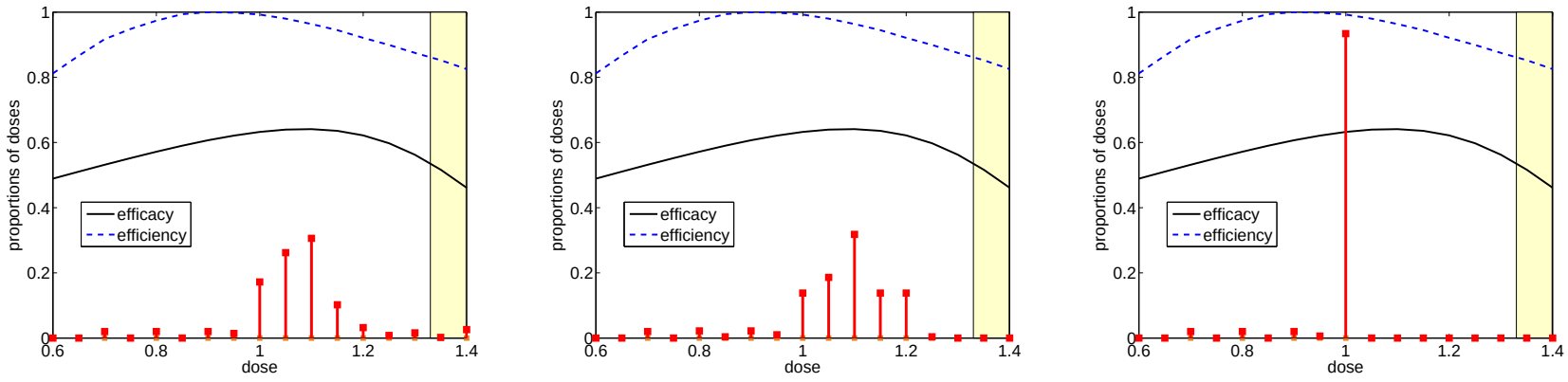
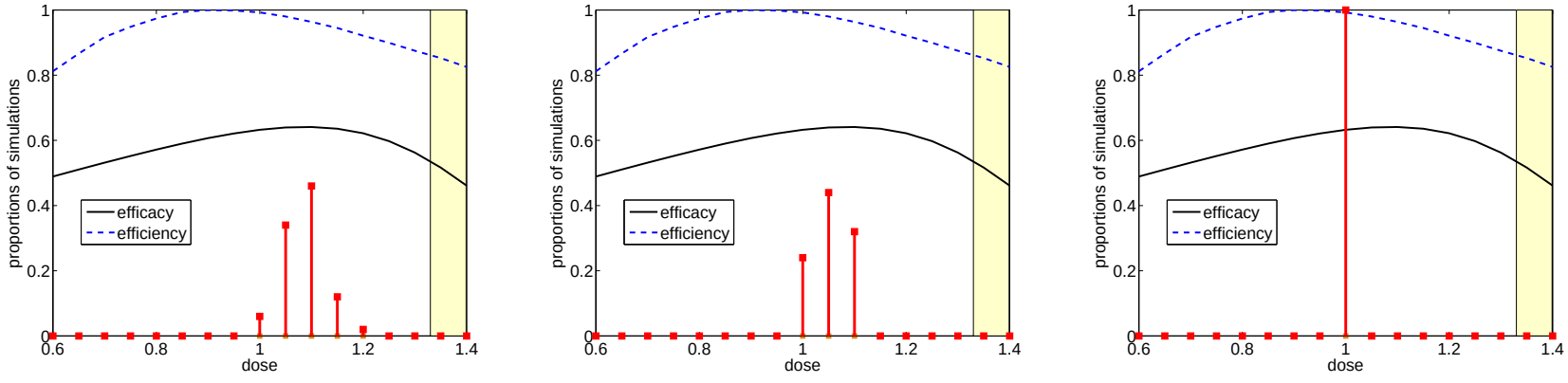


Dose frequencies averaged over total number of cohorts in 100 simulations.



Proportions of the final BOD frequencies in the 100 simulations.

Conclusions I

Approach 1

- Incorporating the constraint on the efficiency of PK estimation into the dose optimization may seriously affect the dose selection design.
- Different orders of the kinetics will differently affect the dose selection design.
- A reasonable E_D constraint may give high quality estimates of PK parameters as well as a good dose determined as BOD.

Conclusions II

Approach 2

- Here we maximize the efficiency of PK estimation with the constraint on the dose efficacy.
- The PK parameters are precisely estimated.
- The selected BODs are pooled towards the optimum region for PK estimation condition.

Conclusions III

- Both Approaches, 1 and 2, are relevant when patients rather than healthy volunteers enter the trial.
- Patients are treated with possibly efficacious doses.
- Some information on the response to BOD is already gathered in Phase I (prior for Phase II).

Also:

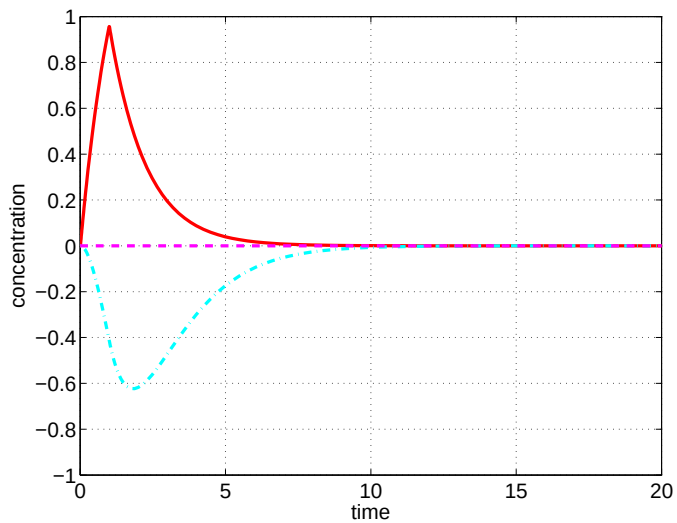
- Approach 1:
  - fewer potentially toxic doses or non-efficacious doses are applied,
  - ensures good efficiency of estimation of the PK parameters,
  - may be considered as a seamless phase I/II, leading to serious saving in resources, both financial and human.
- Approach 2:
  - more relevant when toxicity is a minor issue, in case of first order kinetics,
  - PK parameters are very precisely estimated.

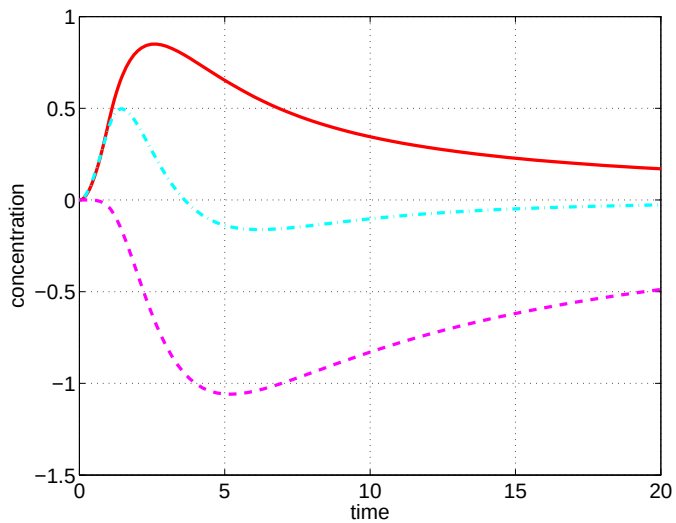
Conclusions IV

- Defining appropriate criteria of optimality, suitable for the purpose of an experiment is paramount.
- Model-based simulation studies may be very useful for making decision about the criteria and foreseeing possible problems.
- Adding PK information, which is collected at Phase I anyway, may improve the dose optimization and lead to serious savings.

Further work

- to consider the kinetics order as unknown parameters,
- to include safety issues into stopping rules,
- to incorporate “safety” parameters into the optimization (time of injection, time between cohorts, toxicity probability).





The concentrations of A and B (solid lines) and their derivatives wrt reaction rates k_a and k_e

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