DOSE SELECTION INCORPORATING PK/PD INFORMATION IN EARLY PHASE CLINICAL TRIALS

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Introduction

Clinical Trials

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  - Phase IIB: Definite dose range finding study in patients with efficacy as primary endpoint

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- **Phase IV** - postmarketing clinical development.

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Observed:

- Concentration of the drug candidate in plasma (PK, continuous)
- Response to the drug candidate
  - toxicity, efficacy (binary)
  - markers, surrogates (PD, continuous)

Adaptive Designs

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- Next step of the trial depends on all the results up to date.
- The trial is stopped according to pre-specified stopping rules.

Modelling

Dose-Response Model

Modelling

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Zhang et al (2006), Stats in Medicine

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 (“failure”).

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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 increases with dose or has a proper extremum,

$\psi_2(x, \vartheta_1)$ - increases with dose and

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

Modelling

Dose-Response Model

S.K.Fan, K.Chaloner (2004), JSPI

The Continuation Ratio (CR) model assures such behaviour of the probabilities

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

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

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

Modelling

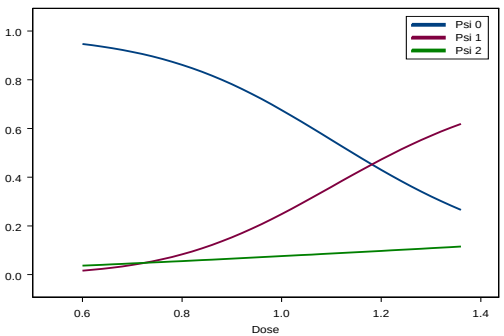
Dose-Response Model

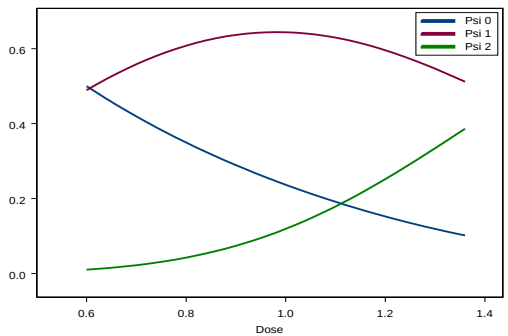
Solving these equations we obtain the nonlinear functions:

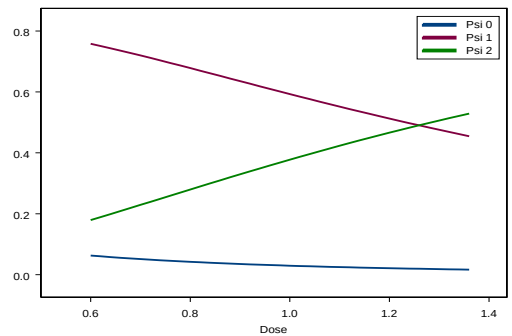
$$\psi_2(x;\vartheta_1) = \frac{\exp(\alpha_2 + \beta_2 x)}{1 + \exp(\alpha_2 + \beta_2 x)}$$

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

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







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Questions:

- What strategy to take to apply efficacious doses as often as possible and get a good estimate of the doses to recommend for further studies?
- How to incorporate the PK/PD information obtained in the study?

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PK mechanistic model:

$$\begin{cases} \frac{d[B]}{dt} = k_a[A]^{\lambda_1} - k_e[B]^{\lambda_2} \\ \frac{d[A]}{dt} = -k_a[A]^{\lambda_1} \end{cases}$$

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

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λ_1 and λ_2 - known orders of the kinetic reaction.

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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.

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We are interested in precise estimation of (k_a, k_e).

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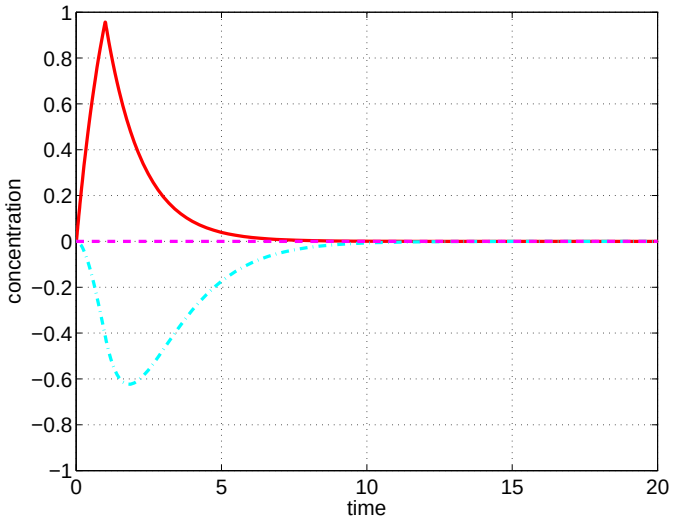
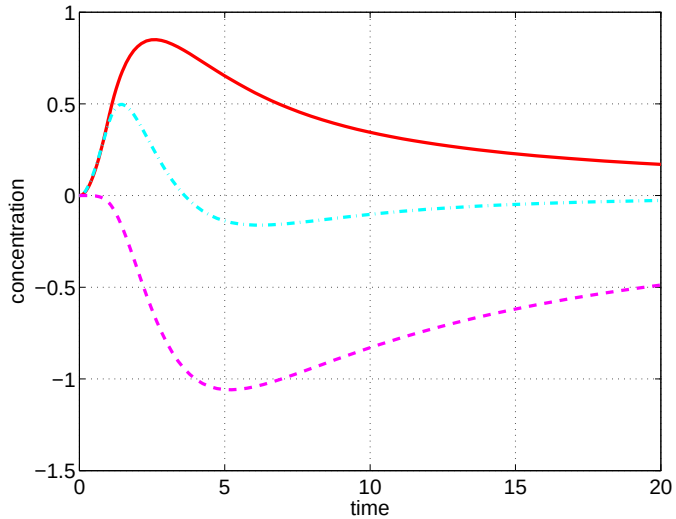


$[A](t|x)$



$[B](t|x)$

Here we assumed $\lambda_1 = 1, \lambda_2 = 2$ and took $k_a^0 = 0.8, k_e^0 = 0.3$ as prior parameter values.

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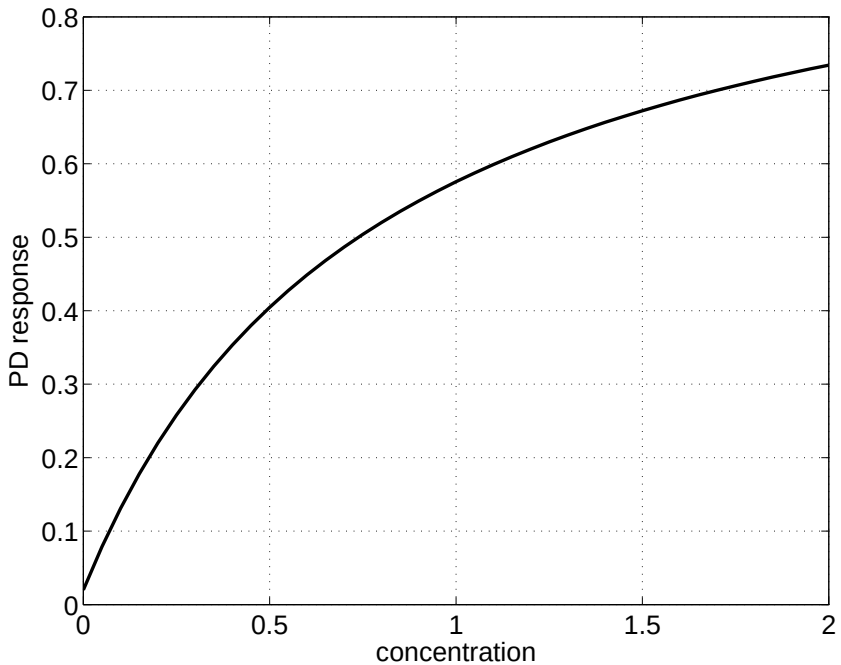

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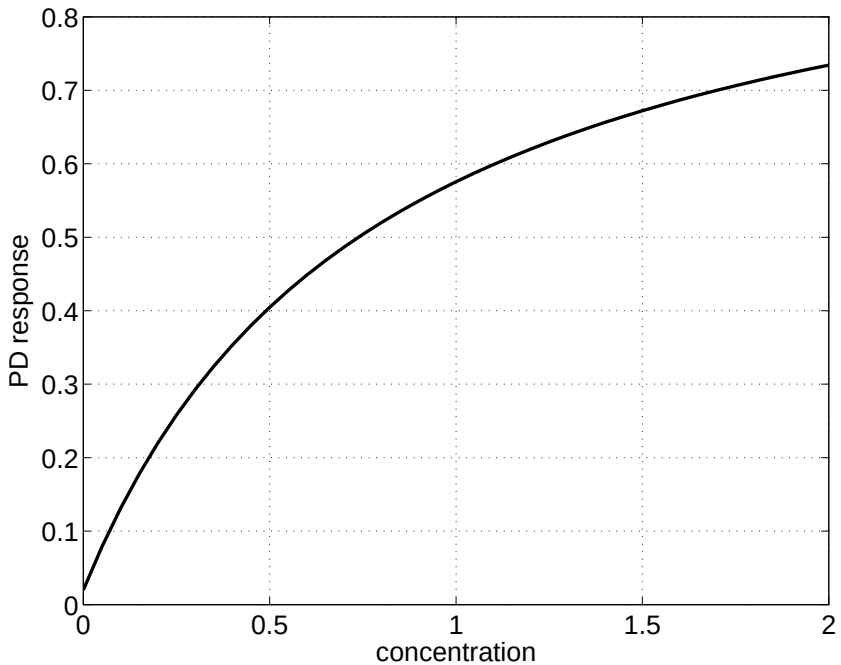

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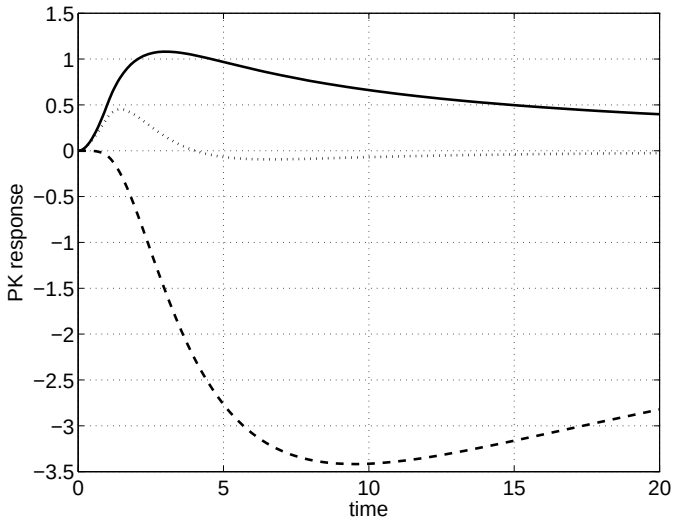
PK/PD Model



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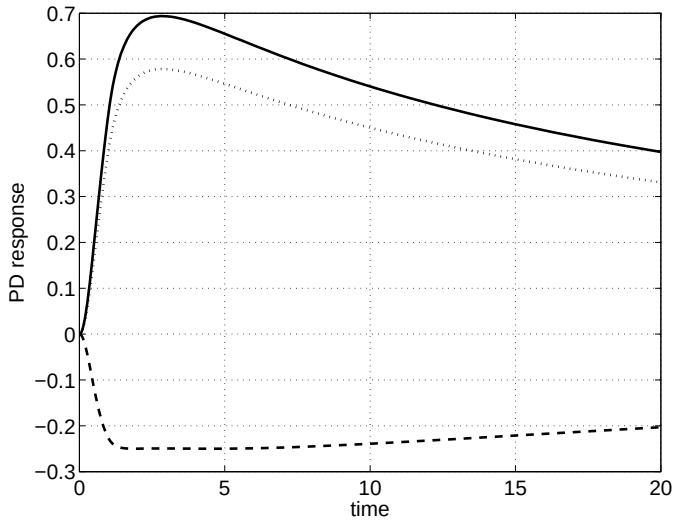

$$\frac{E_{\max}[B](t|x)}{EC_{50}+[B](t|x)}$$

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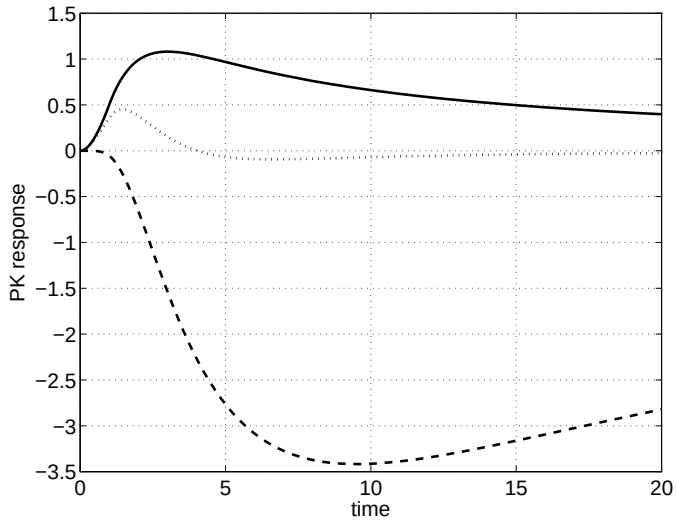
PK/PD Model



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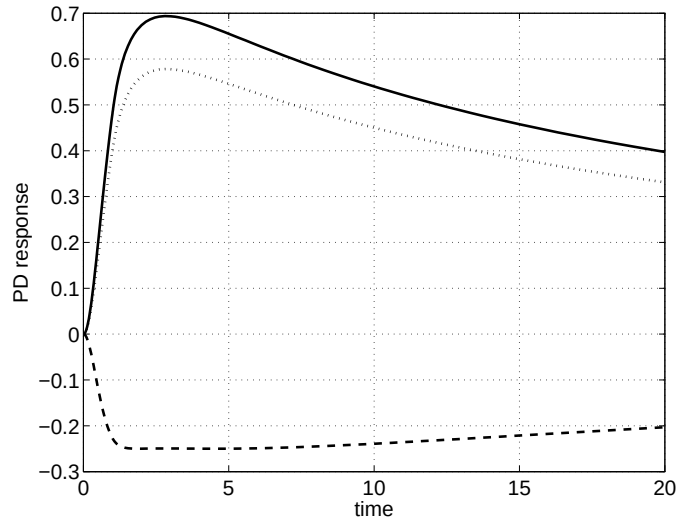

$$\frac{E_{\max}[B](t|x)}{EC_{50}+[B](t|x)}$$

PK/PD design for a given dose x

$$\xi = \left\{ \begin{array}{ccc} t_1 & \dots & t_s \\ w_1 & \dots & w_s \end{array} \right\}$$

k-th Step Design

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For a given dose x we observe the following responses:

$$y_{pk} = [B](t|x) + \varepsilon_{pk}, \qquad \varepsilon_{pk} \underset{iid}{\sim} \mathcal{N}(0, \sigma^2_{pk})$$

$$y_{pd} = \frac{E_{\max}[B](t|x)}{EC_{50} + [B](t|x)} + \varepsilon_{pd}, \quad \varepsilon_{pd} \underset{iid}{\sim} \mathcal{N}(0, \sigma^2_{pd})$$

and the trinomial dose-response (y_0, y_1, y_2).

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The k-th step design is

$$(x^\star_{k-1}, \xi^\star_{k-1})$$

Optimality Criteria

Biologically Optimum Dose

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We use the following decision functions for finding a BOD:

Zhang et al (2006), Stats in Medicine

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

where I denotes an indicator function (=1 or 0) and $\gamma \in [0,1]$.

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

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

is the recommended BOD for next step of the trial.

Optimality Criteria

Efficiency of PK Estimation

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We use the D-optimality criterion for estimating PK/PD parameters $\vartheta_2 = (k_a, k_e, E_{\max}, EC_{50})$:

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

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

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

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

p is the number of parameters; here $p = 4$.

Optimality Criteria

BOD Constrained by Toxicity and by PK/PD Efficiency

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Maximize (over x)

$$\delta_2(x;\vartheta_1) = \psi_1(x;\vartheta_1)$$

subject to

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

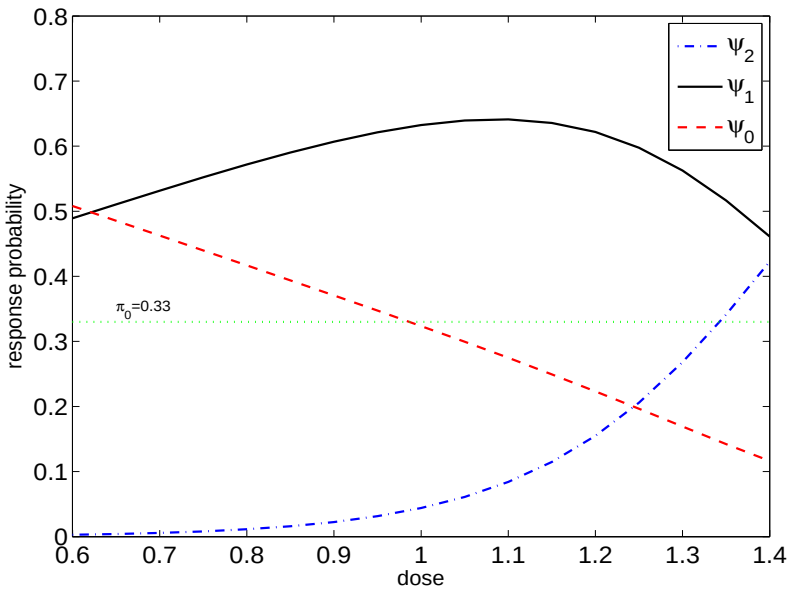
and

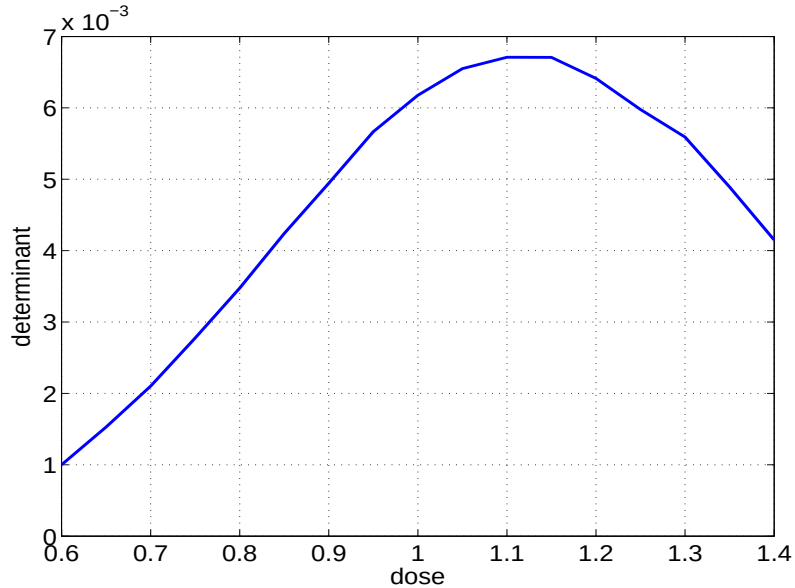
$$E_D(\xi^\star|x) \geq \eta$$

Optimality Criteria

BOD Constrained by Toxicity and by PK/PD Efficiency

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



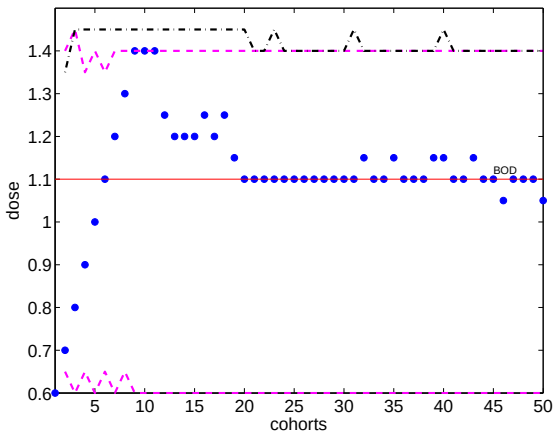


Non-monotonic D-criterion as a function of dose restricts the optimum doses to be in the middle of the dose range.

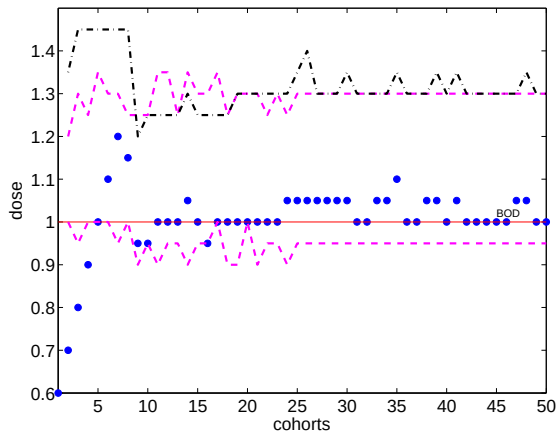
Adaptive Optimum Design

Examples of the trial runs for different levels of D-efficiency of PK/PD parameters

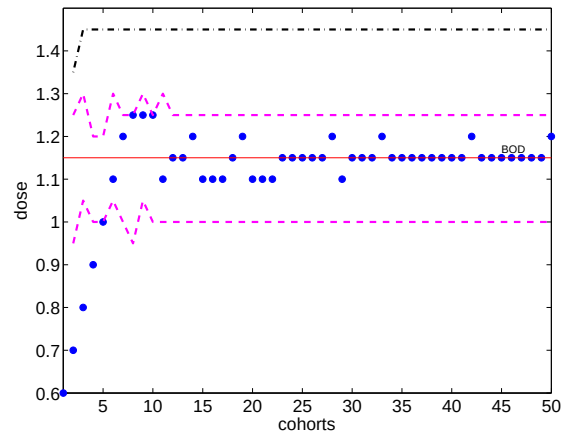
(a) $E_D \geq 60\%$



(b)$E_D \geq 80\%$



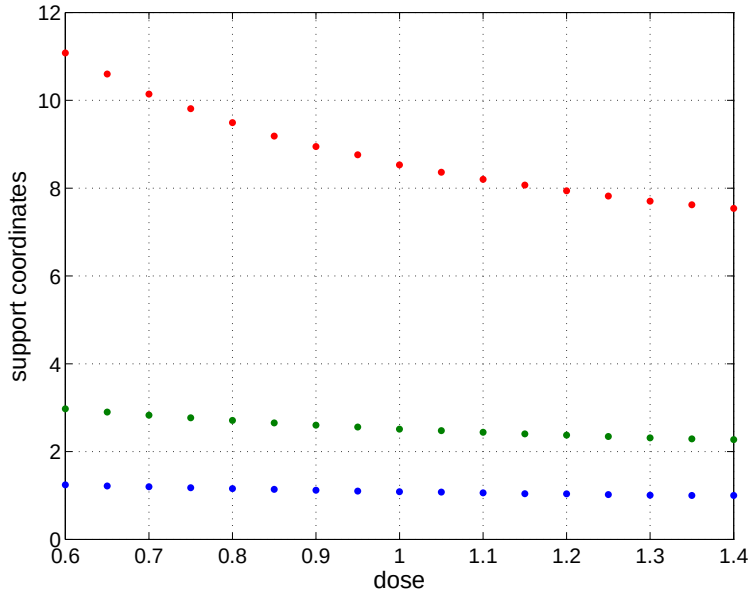
(c) $E_D \geq 95\%$



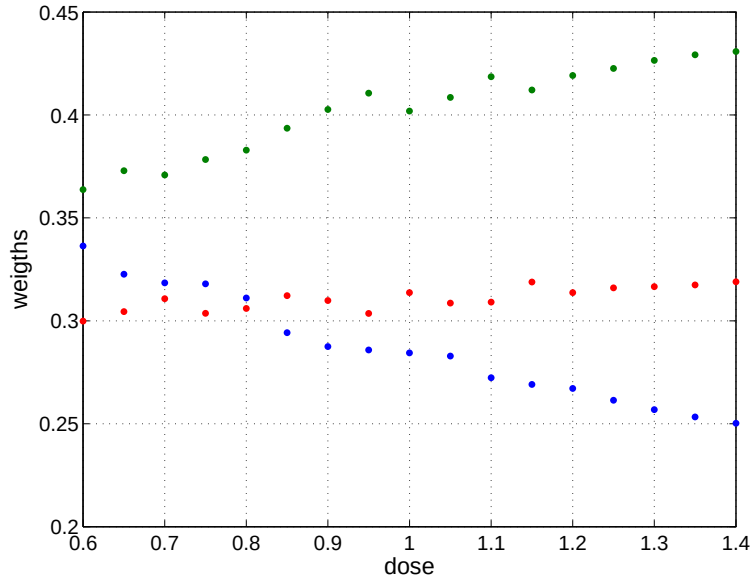
Dashed lines comes from the E_D constraint.

The dot-dashed line comes from the upper threshold for non-admissible toxicity probability.

Optimum ξ



support points $t^\star$



weights $w^\star$

Design support points and weights for different doses, for point prior $\vartheta_2^0 = (k_a^0, k_e^0, E_{\max}^0, EC_{50}^0) = (0.8, 0.3, 1.0, 0.8)$

PK/PD design depends on the dose.

Estimation: results of a few simulations

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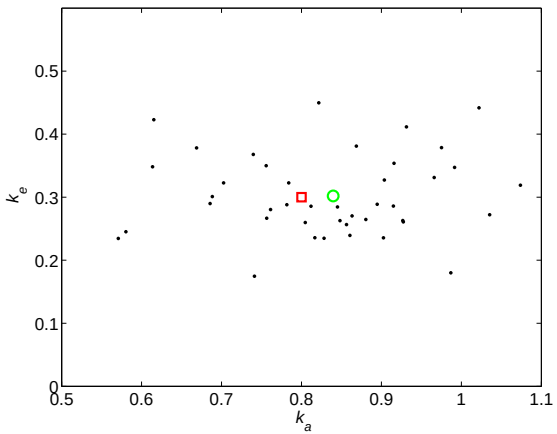

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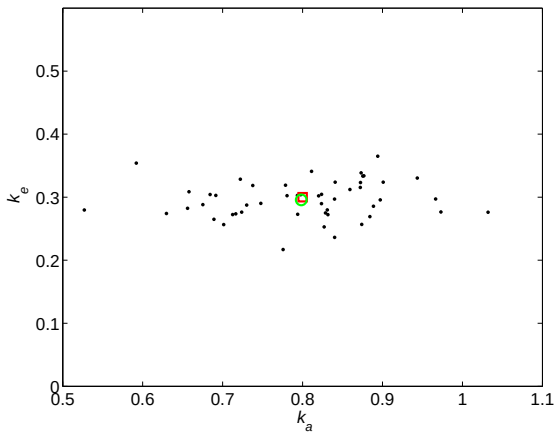

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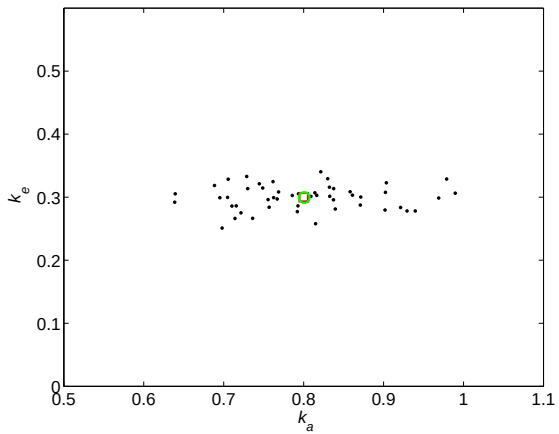

Final estimates of PK parameters

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

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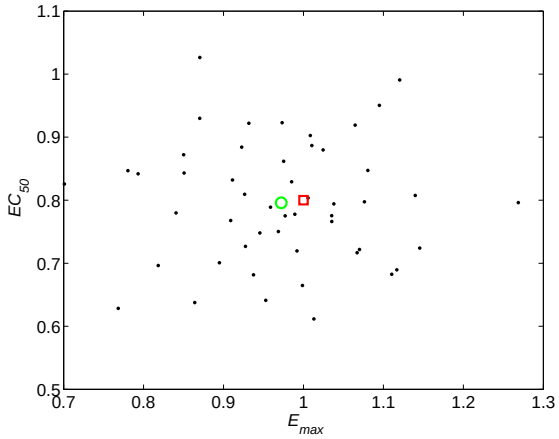

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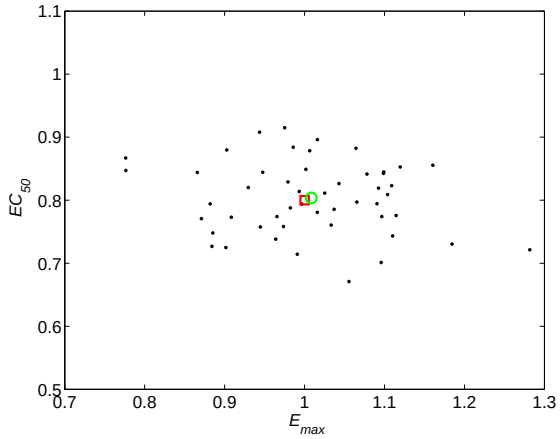

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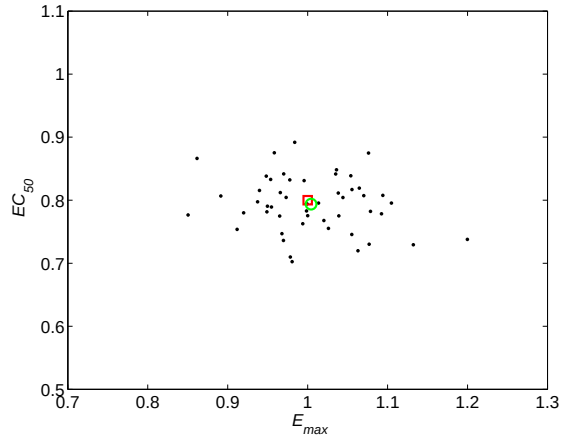

Final estimates of PD parameters

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Dose selection: results of a few simulations

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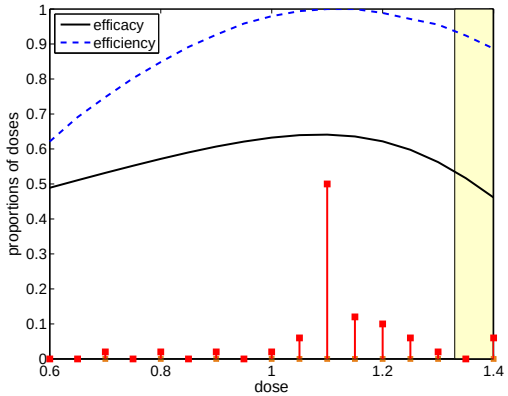

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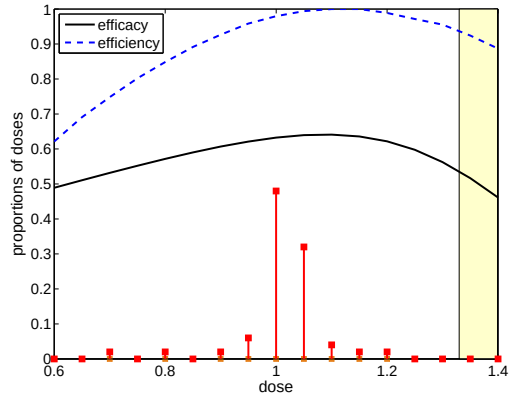

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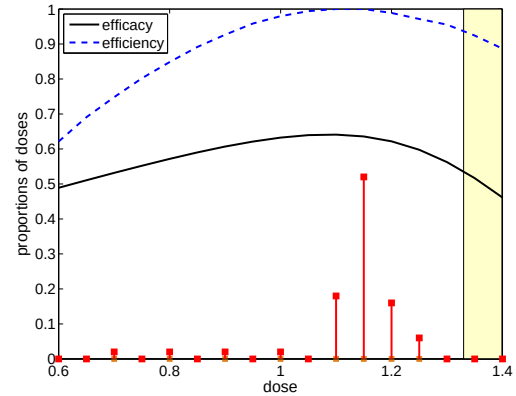
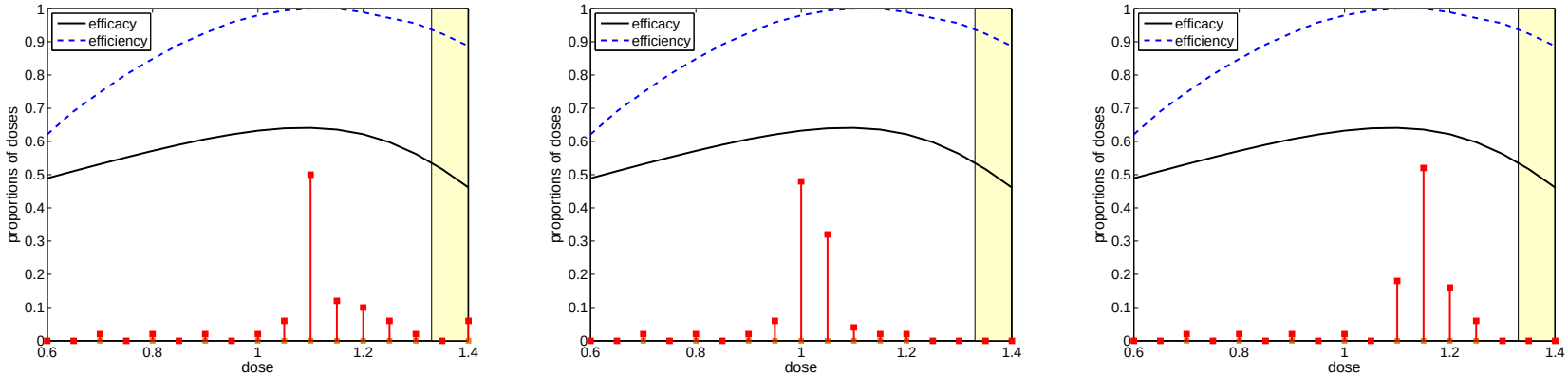


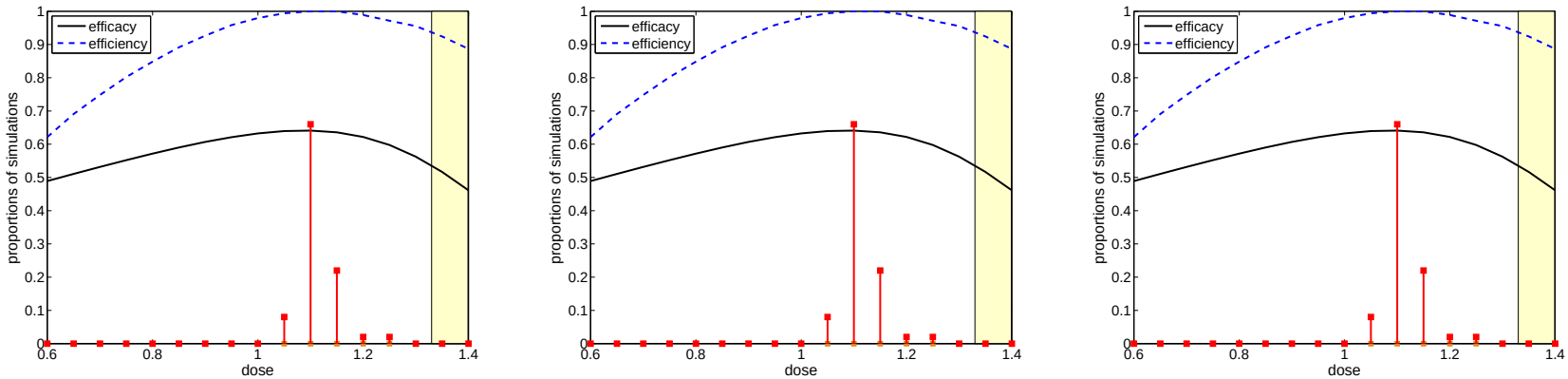
Dose frequencies averaged over total number of cohorts in all simulations.

Dose selection: results of a few simulations

(a) $E_D \geq 60\%$ (b) $E_D \geq 80\%$ (c) $E_D \geq 95\%$



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



Frequencies of the final BOD in all simulations.

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- Incorporating the constraint on the efficiency of PK/PD estimation into the dose optimization may seriously affect the dose selection.
- A reasonable E_D constraint may give high quality estimates of PK/PD parameters as well as a good dose determined as BOD.

THANK YOU