An industry perspective on PODE

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Overview

Optimal design reality and wish list

- Introduction
- PODE knowledge & software use
  - P”O”DE
  - Limited resources and thus uptake of tools
- Examples
  - Various slightly modified examples
- Wish list
  - …

Novartis

Basel, CH

PODE in Pharma Industry

- Study design essential for study success, but…
- When to use PODE in Pharma Industry?
  - In research and early development phases rather rich sampling
  - In late phases in clinics shift to clinical endpoints (e.g., only troughs)
  - … so, of little use?
- How much flexibility is there for sampling time points?
- Valuable in specialized trials where modeling is used as primary analysis
  - E.g., bridging to special population (pediatrics, genetics,…)

PODE versus P”R”DE or P”G”DE

What is the biggest need for Pharma?

- PODE: Optimal design?
  - Restrictions in possible sampling times (in clinics)
  - Primary analysis is not model based
  - Too many uncertainties (model structure and parameter estimates)
- “R” for robust or “G” for good-enough
  - Given a design – how good would be my parameter estimates?
  - Which part of the study informs which part of the model?
  - Design should be good enough to extract the information
- Often we “evaluate” designs but do not “optimize”

PODE knowledge

Theory is known, practice is often simulation-estimation

- Academic interactions/trainings provide basic knowledge
  - Basic knowledge is present
  - Theory not fully understood
- Mostly: Design evaluation - Nonmem simulation-estimation
- Why?
  - Need for “optimal” design not that apparent
  - Learning curve for “new tools and methods”
  - Run-times (ODEs) and stability of tools (PFIM)
  - Using scripts for batch jobs not straight forward
    - Testing sensitivity to parameter choices using batch scripts

My PODE knowledge

Little, mainly self-taught

- Experience with sensitivities and generalized sensitivities
- Coming from the non-stats world

- Got stuck in “R” and thus with PFIM
- No hands-on training – thus self-taught
- To understand PODE and PFIM
  I started re-programming bits and pieces

Examples

Anonymized

- Innovative study design
- Model identifiability (PK/PD binding model)
- Sample size for estimating PK/PD model paramters
- Sample time “optimization”
- Complex example “downsized” for PFIM
- PK/PD example for training purposes

Evaluation of innovative study design

New study design

Only a sketch…

- Development of innovative study design
  - Most interesting and most exciting example
- Batch script for testing different models and parameters
- Running various different scenarios
- Still, all done on “evaluation” not “optimization” due to restrictions on possible sampling time points

Model identifiability of PK binding model

Estimability of peripheral volume?

Objectives

- Primary: **Improve PK Binding Models**
- Secondary: **Estimate Interstitial Volume**

Two Compartment PK Binding Model
Comparatively Complex

- PK binding models are comparatively complex, e.g.:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} TD_C \\ TD_P \\ TL_C \\ TL_P \end{pmatrix} = \begin{pmatrix} CL_D/V_C & PS_D/V_P & 0 & 0 \\ (1-\alpha_D)PS_D/V_C & 0 & 0 & 0 \\ 0 & 0 & \frac{CL_L}{V_C} & \frac{PS_L}{V_P} \\ 0 & 0 & \frac{(1-\alpha_L)PS_L}{V_C} & 0 \end{pmatrix} \begin{pmatrix} TD_C \\ TD_P \\ TL_C \\ TL_P \end{pmatrix} + \begin{pmatrix} P_D \\ 0 \\ 0 \\ P_L \end{pmatrix}$$

No binding

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} TD_C \\ TD_P \\ TL_C \\ TL_P \end{pmatrix} = \begin{pmatrix} CL_D/V_C & PS_D/V_P & 0 & 0 \\ (1-\alpha_D)PS_D/V_C & 0 & 0 & 0 \\ 0 & 0 & \frac{\mathrm{f_C}(.)CL_D + (1-\mathrm{f_C}(.))CL_L}{V_C} & \frac{\mathrm{f_P}(.)PS_D + (1-\mathrm{f_P}(.))PS_L}{V_P} \\ 0 & 0 & \frac{\mathrm{f_C}(.)(1-\alpha_D)PS_D + (1-\mathrm{f_C}(.))(1-\alpha_L)PS_L}{V_C} & 0 \end{pmatrix} \begin{pmatrix} TD_C \\ TD_P \\ TL_C \\ TL_P \end{pmatrix} + \begin{pmatrix} P_D \\ 0 \\ 0 \\ P_L \end{pmatrix}$$

Binding

$$\mathrm{f_C}(.) = \mathrm{f}(TD_C, TL_C, V_C, K_D)$$
$$\mathrm{f_P}(.) = \mathrm{f}(TD_P, TL_P, V_P, K_D)$$

$$\mathrm{f}(TD, TL, V, K_D) = \tfrac{1}{2}\left((K_D V + TD + TL) - \sqrt{(K_D V + TD + TL)^2 - 4\,TD\,TL}\right)$$

- Closed form solutions of the integrals are at least difficult to obtain.
- What can/should be estimated?

PFIM to assess PK binding models

Setting up the trial

- PK study with 2 hours infusion, study arms at different concentrations and comparatively rich sampling:
  - # Rich sampling: sampling times (days) for each elementary design
    obs <- c(c(0,0.5,2,4,12)/24,1,2,4,7,14,21,28,35,42,56,70,84)
  - # 6 different doses in mg/kg times 70kg
  - doses<-c(0,0.1,0.3,1,3,10)*70
  - # 5 subjects for each elementary design
  - subjects<-rep(6,5)

PFIM to assess PK binding models

Good estimates of fixed effects and most random effects

- Results: Expected Standard Errors:

```
------------------------ Fixed Effects Parameters -------------------------
      Beta    StdError        CV .
CLD  0.161 0.009792566  6.082339 %
VD   3.130 0.147423975  4.710031 %
CLL 18.500 2.419213480 13.076830 %
RLI  7.090 0.820998986 11.579675 %
VP  20.000 2.709554573 13.547773 %
PSD  0.434 0.046964660 10.821350 %
PSL  0.408 0.038539732  9.446013 %
KD   0.635 0.087186612 13.730175 %
ALD  0.100 0.010556939 10.556939 %
ALL  0.700 0.080323249 11.474750 %

------------------------ Variance of Random Effects ----------------------
     Omega   StdError        CV .
CLD 0.1010 0.02722802  26.95843 %
VD  0.0599 0.01711995  28.58089 %
CLL 0.4350 0.12717323  29.23522 %
RLI 0.3610 0.10027314  27.77649 %
VP  0.0663 0.10358684 156.23958 %
PSD 0.1140 0.06187876  54.27962 %
PSL 0.1140 0.05469142  47.97493 %
KD  0.4720 0.14240457  30.17046 %
ALD 0.1000 0.05979315  59.79315 %
ALL 0.1000 0.05951293  59.51293 %
```

Assessment successful

- Conclusions:
  - It might be possible to fit peripheral volume and reflection coefficients for the drug and the ligand in two compartment PK binding models.
  - In favorable cases, the fitted peripheral volumes might provide estimates of the interstitial volumes.
  - PFIM may be used to assess over-parametrization.

Sample size for dose-range studies

Dose-range studies for PK/PD model

Goal: choose sample size such that %CV < 20%

- Using PK/PD model with indirect response (ODE)
- Question to answer:
  - Sample size per group to obtain parameter estimates for popPK/PD model with %CV < 20% for population parameters
- The general design was fixed
  - 5 dose groups
  - Sampling time points given

Good results for n=10 – except for SC_{50}

The approach worked, but with very long runtimes

- For n=10 per group
- 24 min for EVAL
- To optimize > 3 days
  - Run was stopped
- PFIM sample size changes with sqrt(n) as for linear model…

	Beta	StdError	RSE
ka	0.20	0.03169188	15.845939 %
Cl	15.00	0.88000480	5.866699 %
V1	900.00	117.04749065	13.005277 %
Q	45.00	4.69713995	10.438089 %
V2	2200.00	198.71992989	9.032724 %
Rin	1.60	0.24227734	15.142334 %
kout	0.90	0.16013657	17.792953 %
Imax	0.87	0.07598339	8.733723 %
C50	0.35	0.09720602	27.773147 %

	Omega	StdError	RSE
ka	0.15	0.04234990	28.23326 %
Cl	0.14	0.03172233	22.65881 %
V1	0.06	0.01987237	33.12062 %
V2	0.11	0.05619632	51.08756 %
Rin	0.06	0.05889112	98.15186 %
kout	0.14	0.07201611	51.44008 %
C50	0.34	0.19101526	56.18096 %

Sample time optimization in PKPD model

Indirect response model

Monkey PK/PD study of monoclonal antibody

- Support design of PK/PD study in monkeys
  - Dose was selected from previous experience
  - Sample size was calculated for AUEC (based on Nonmem simulations)
  - Optimal sampling time points...?
- But, no BLQ implemented in PFIM
  - Additive error included to mimic BLQ
- Too many possible time points to select
  - Fedorov-Wynn algorithm crashed (memory issue)
  - Simplex algorithm too slow

Indirect response model

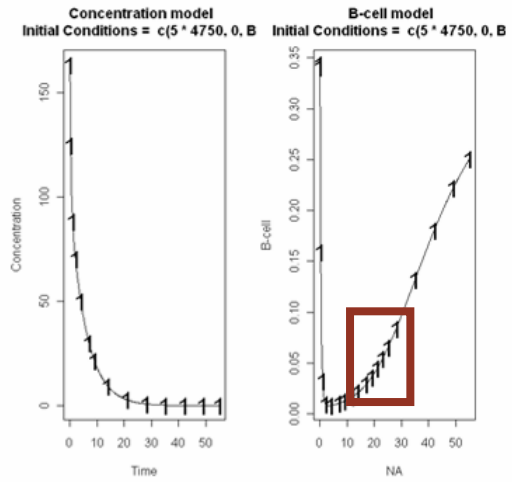
Monkey PK/PD study of monoclonal antibody

- Rather “qualitative” optimization
  - Investigated sampling time points in different intervals
  - Partial derivatives would have been beneficial
- Only one dose
  - Difficult for turnover model
  - Main info not at 50% recovery!
  - Start of recovery is most informative

Table 5-5 **Expected relative standard errors for model parameters using different sampling schemes**

	Proposed design	+5 samples	Dense
Sampling schedule PD	0,0.0035,0.29,1,2,4,7,9 ,14,21,28,35,42,49,55	+12,17,19,23,25	0.0035,0.29,1,2,3,...,20 ,22,24,26,..,56
Smax r.s.e	32.9%	29.6%	24.1%
SC50 r.s.e	56.9%	48.7%	41.1%
N_{group} for BE of Smax	24.1	24.1	24.1

Figure 5-9 **Sampling scheme with 5 more samples in the recovery than proposed**



Sample time optimization in PK model

PK sampling schedule for PhIII

Limited samples, mainly around first dose

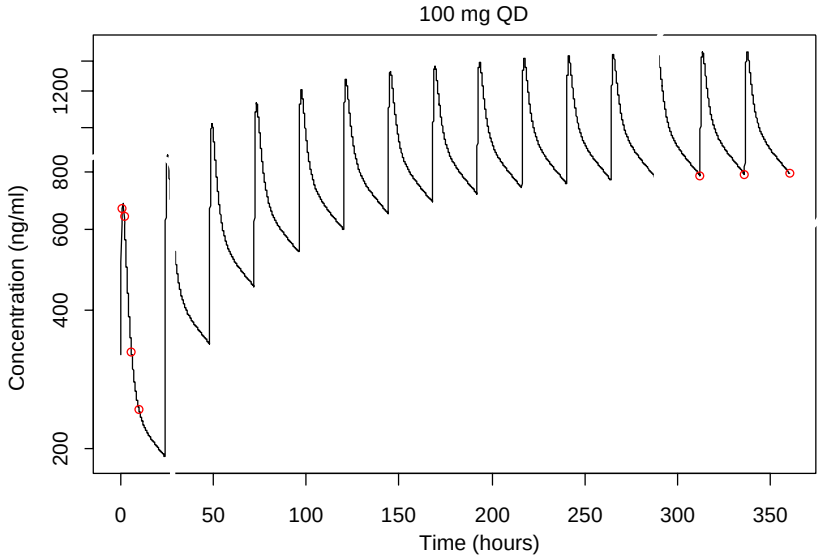
- Oral formulation
  - High inter-occasion variability on bioavailability
- Multiple doses
  - Team only wanted rich sampling after first dose
  - 3 trough samples planned at steady state
- What precision could we expect to get on the parameters for our model developed for healthy volunteers?
- Not out-of-the-box
  to combine first dose with steady-state solution

An optimal design approach (PFIM) was used to assess alternative designs for PK sampling

- A rich design was used as a benchmark
  - 15 samples on D1 + 3 trough samples at steady state
    (C1D1: 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 4, 5, 6, 8, 10, 12, 16, 24 hours post dose + 3 trough at steady state)
  - Several sparser designs were compared to this
- Limitations
  - Simplified version of population model developed based on previous data was used
    - 2 compartment model with 1st order absorption
    - Due to software limitation the original model needed to be simplified
    - IOV on F was removed
    - Lag-time was set to 0
    - Higher residual error for early time points post dose was removed
    - IIV parameters, ka and proportional error component were re-estimated to compensate for the above simplifications. The model fits with the simplified model were over all similar to the original model.

Suggested design: Repeated sampling on D1 followed by trough samples at steady state

- Suggested sampling for PK
  - 4 samples on D1 (e.g. 1, 2, 6, 10 hours post dose)
    - The later the 4th sample on D1 the better
  - 3 trough samples at steady state (must not be on subsequent days)



- Predicted parameter precision is expected to be reasonable with a relatively sparse sampling schedule
- Repeated trough samples will give some information about IOV although this was not in the model used for optimization

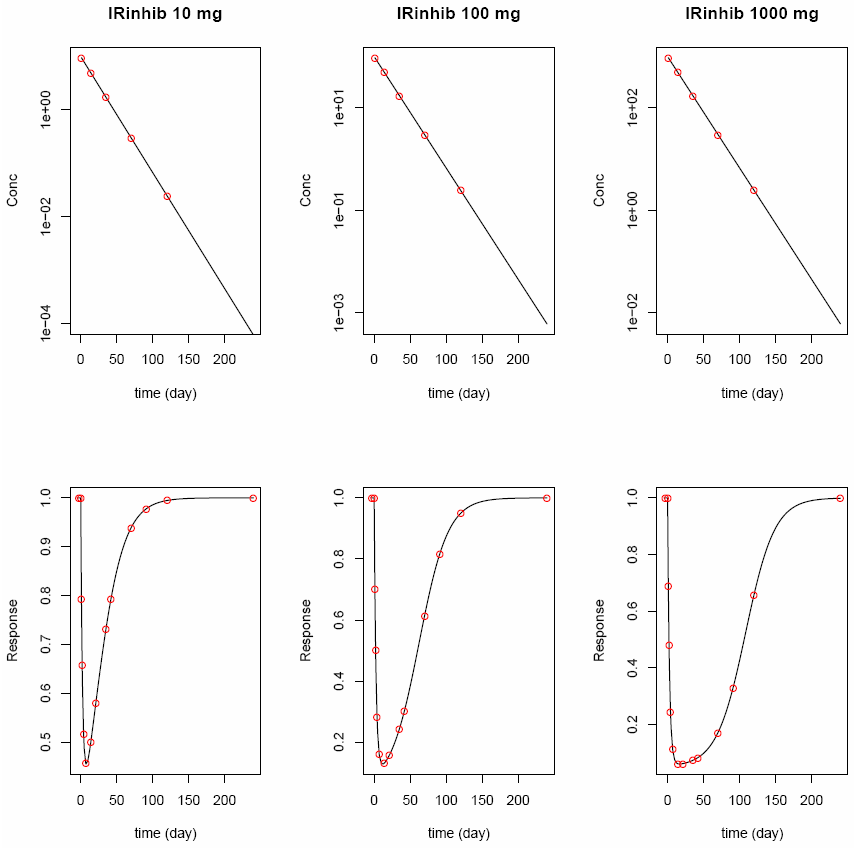
Teaching indirect response models

Indirect response models

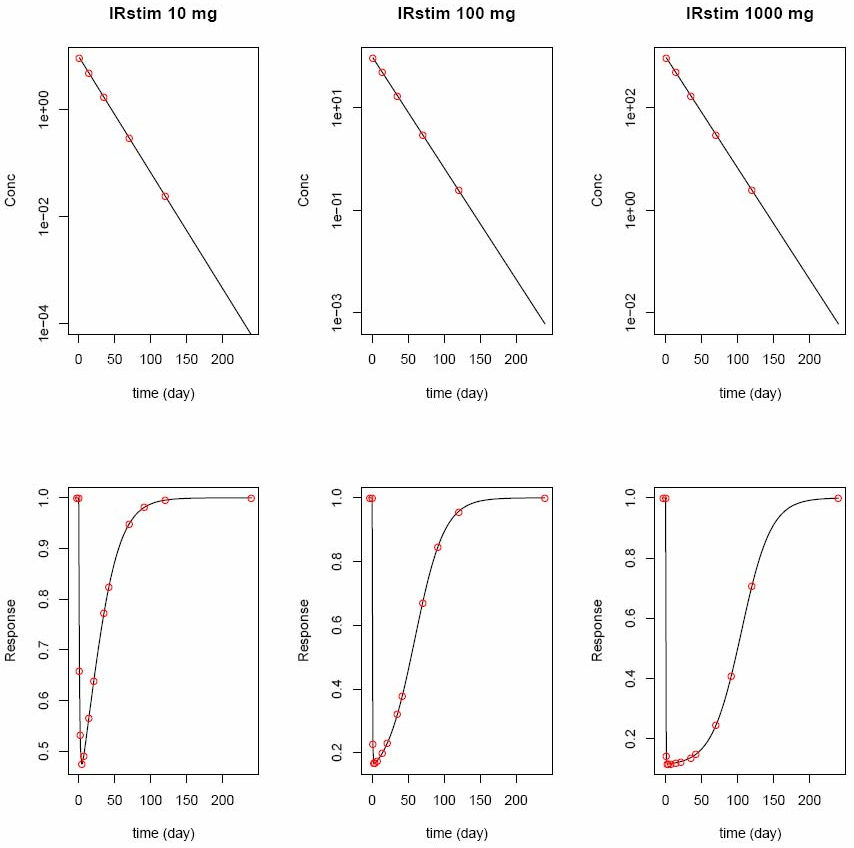
Two PK/PD examples for comparison: inhibiting kin & stimulating kout

- 2 models with similar dynamics

Inhibition of kin



Stimulation of kout



Indirect response models

Expected standard errors from myPFIM

Inhibition of kin

```
Fixed effect parameters
= = = = = = = = = = = = =
      Value  StdErr RSE(%)
   ke  0.05 0.00252   5.03
 Base  1.00 0.10237  10.24
 kout  0.40 0.04575  11.44
 Emax  0.95 0.06656   7.01
 EC50  5.00 0.76943  15.39

Random effect parameters (IIV/BSV)
= = = = = = = = = = = = = = = = = = =
      Value StdErr RSE(%)
   ke  0.25 0.0356   14.3
 Base  1.00 0.1463   14.6
 kout  0.60 0.1600   26.7
 Emax  0.35 0.0581   16.6
 EC50  0.20 0.2674  133.7

Residual error
= = = = = = = = =
               Value StdErr RSE(%)
    Conc prop    0.2 0.0071   3.55
  Response add   0.2 0.0106   5.28
 Response prop   0.2 0.0189   9.47

Subjects per arm
= = = = = = = = = =
 33 subjects per arm
```

Mimic LOQ

Stimulation of kout

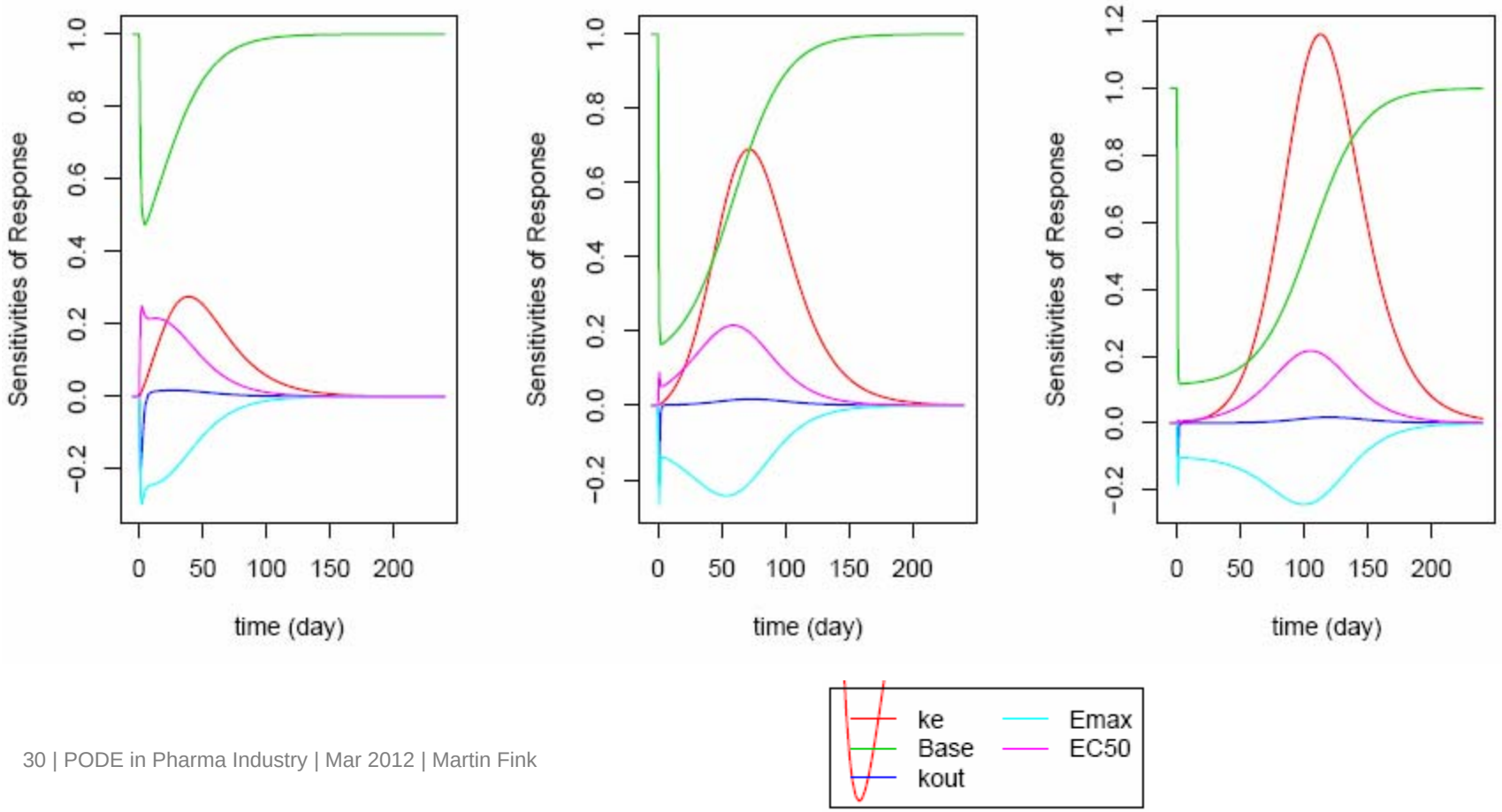
```
Fixed effect parameters
= = = = = = = = = = = = =
      Value   StdErr RSE(%)
   ke  0.05  0.00252   5.03
 Base  1.00  0.10241  10.24
 kout  0.40  0.08057  20.14
 Emax  8.00  1.17654  14.71
 EC50 50.00 10.07166  20.14

Random effect parameters (IIV/BSV)
= = = = = = = = = = = = = = = = = = =
      Value StdErr RSE(%)
   ke  0.25 0.0356   14.3
 Base  1.00 0.1464   14.6
 kout  0.60 0.4438   74.0
 Emax  0.25 0.1211   48.4
 EC50  0.10 0.2465  246.5

Residual error
= = = = = = = = =
               Value  StdErr RSE(%)
    Conc prop    0.2 0.00711   3.55
  Response add   0.2 0.00956   4.78
 Response prop   0.2 0.01867   9.34

Subjects per arm
= = = = = = = = = =
 33 subjects per arm
```

Indirect response models

Sensitivities of the PD with respect to changes in parameters

- 2 models with similar dynamics

Stimulation of kout

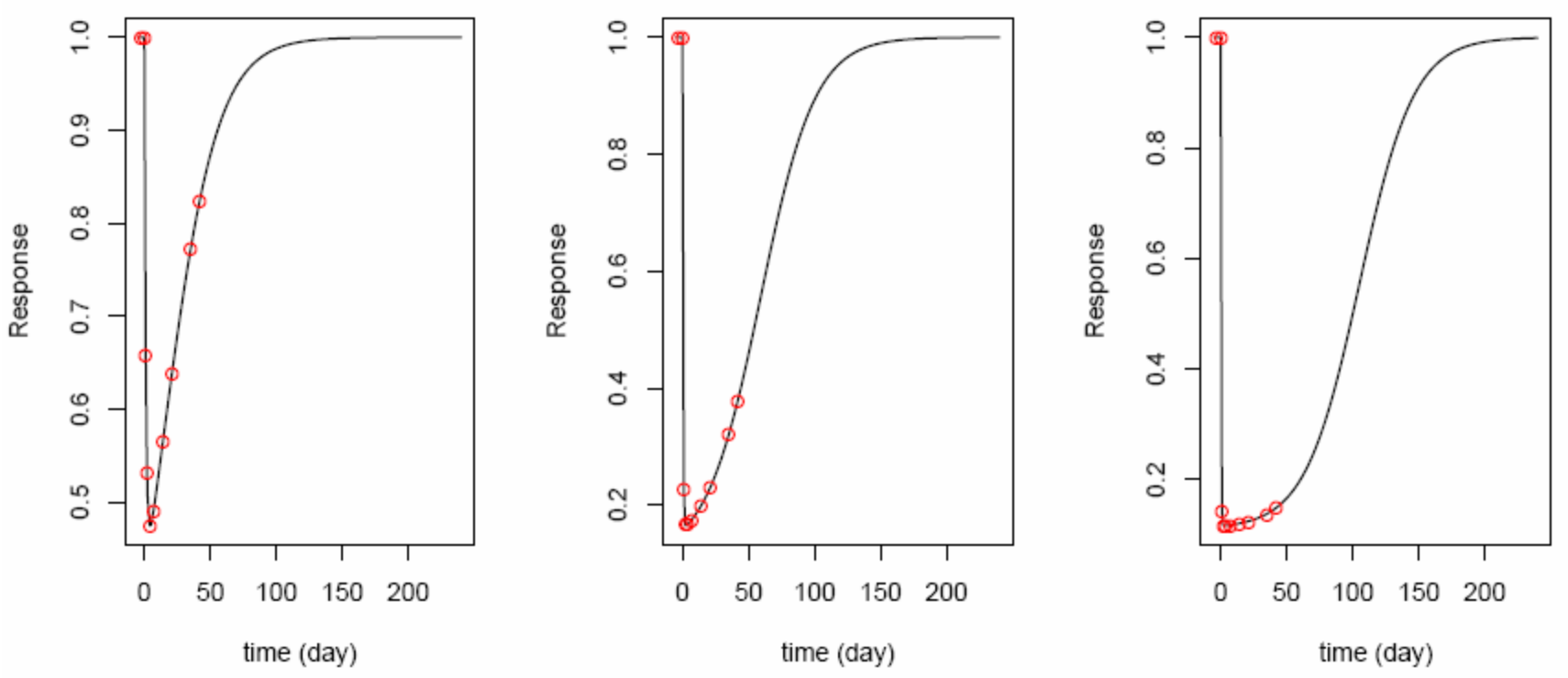


Indirect response models

Samples taken only for the initial 42 days – incomplete recovery

- Not enough time to wait for recovery (or turnover wrongly estimated)

Stimulation of kout



Indirect response models – Only initial samples

Remove time points or set additive error for BLQ – always biased

- Samples taken only for the initial 42 days
  - All doses (33 subjects/dose)

```
Fixed effect parameters
= = = = = = = = = = = =
      Value   StdErr RSE(%)
 Base  1.00  0.10418  10.42
 kout  0.40  0.08112  20.28
 Emax  8.00  1.27929  15.99
 EC50 50.00 12.79278  25.59

 Response add   0.2 0.0105   5.27
```

  - High dose (99 subjects)

```
Fixed effect parameters
= = = = = = = = = = = =
      Value   StdErr RSE(%)
 Base  1.00  0.10445  10.44
 kout  0.40  0.13338  33.34
 Emax  8.00  1.26683  15.84
 EC50 50.00 44.34800  88.70

 Response add   0.2 0.00854   4.27
```

  - Medium dose (99 subjects)

```
Fixed effect parameters
= = = = = = = = = = = =
      Value  StdErr RSE(%)
 Base  1.00  0.10444  10.44
 kout  0.40  0.09375  23.44
 Emax  8.00  1.74145  21.77
 EC50 50.00 17.58582  35.17

 Response add   0.2 0.0115   5.76
```

Indirect response models

Summary

- Substantial differences between inhibition of kin and stimulation of kout
  - Inhibition has information on kout at initial depletion phase
  - Emax could be fixed to 1 (if reasonable) => no estimate needed

- Essential to include recovery phase
  - Important to cover where the response recovers
  - Important to cover return to steady state
    (but more for understanding disease progression / change of system)

- Difficulty to include values of BLQ in optimal design (currently)

Wish list

To increase the uptake in Pharma Industry

- Scriptable examples
- Short runtimes with ODEs
- Clear and flexible interface
  - Inter-occasion-variabilities
  - Fixing some parameters while still estimating their variabilities
  - Plot of solution & sensitivities
  - Clear output structure to be able to plot additional graphs or do additional analyses
- Hands-on training
- Do we need the “optimization”?