BAST: Development of a Bayesian adaptive sampling time strategy for PK studies.

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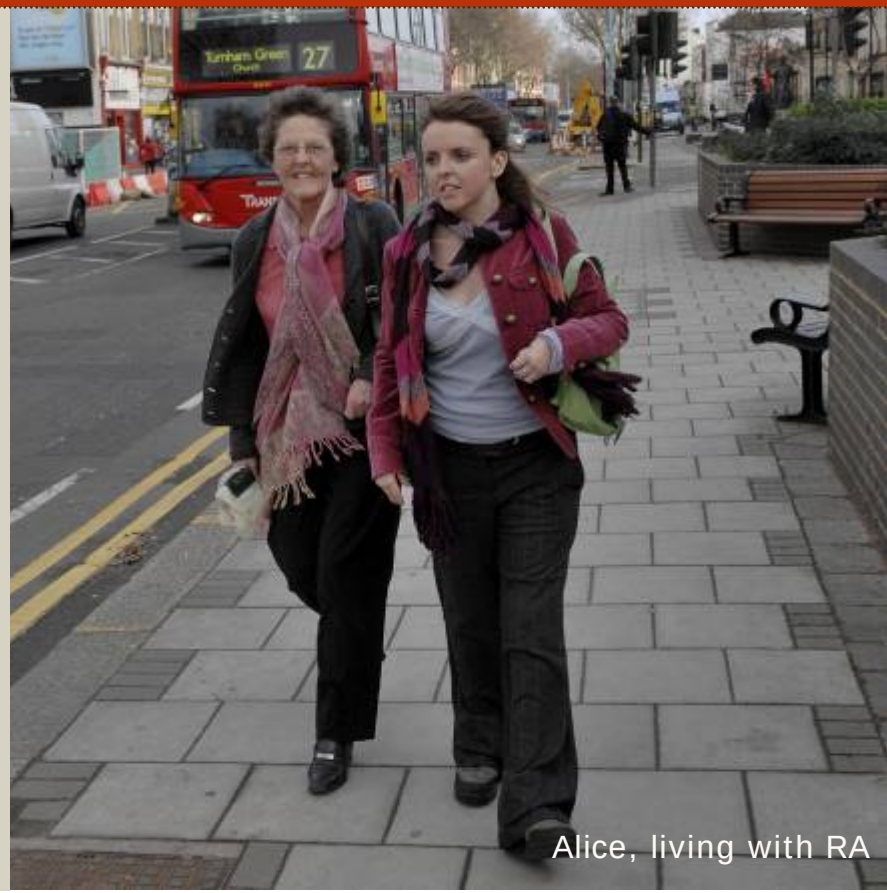


Alice, living with RA

PODE 2008

Paris, 23 June 2008

Agenda

1. Design in learning
2. Typical trial
3. Bayesian Adaptive Sampling Times – BAST
4. Structure of an adaptive design
5. Examples of results
6. Comparisons adaaptive vs fixed design
7. Conclusions

Adaptive designs in Learning Phases

Goal

- Learning about safety, efficacy, PK/PD, DR profile, i.e. benefit/risk profile
- Emphasis on modeling/estimation ←→ hypothesis testing
- Use model to predict later phases
- Accurate and faster prediction-based decision and dose selection
- Optimal trade-off between need for additional information and increased cost, timelines
  - pay the right price for the right learning objective

- PK/PD modeling is “pivotal” in learning phases.

➔ Adaptive Designs thinking can facilitate PK/PD modeling

➔ PK/PD modeling can permit appropriate use of adaptive designs

Typical challenging scenario: Pediatric PK trial

- Phase I Single Dose study in young children
  - 1 month -> 4 years
- Focus is on PK parameter accuracy of estimates
  - to be used for predictions
  - dose/regimen optimization
- A priori rather informative
  - numerous data in adults (16y -> 70y)
  - experience in allometric scaling.
- Under 1/2 year, the kinetic can drift « non-linearly »
  - ➔ need to be robust against this potential issue
- Ethics: maximum 3/4 samples per kid.

BAST: Bayesian Adaptive Sampling-Time design

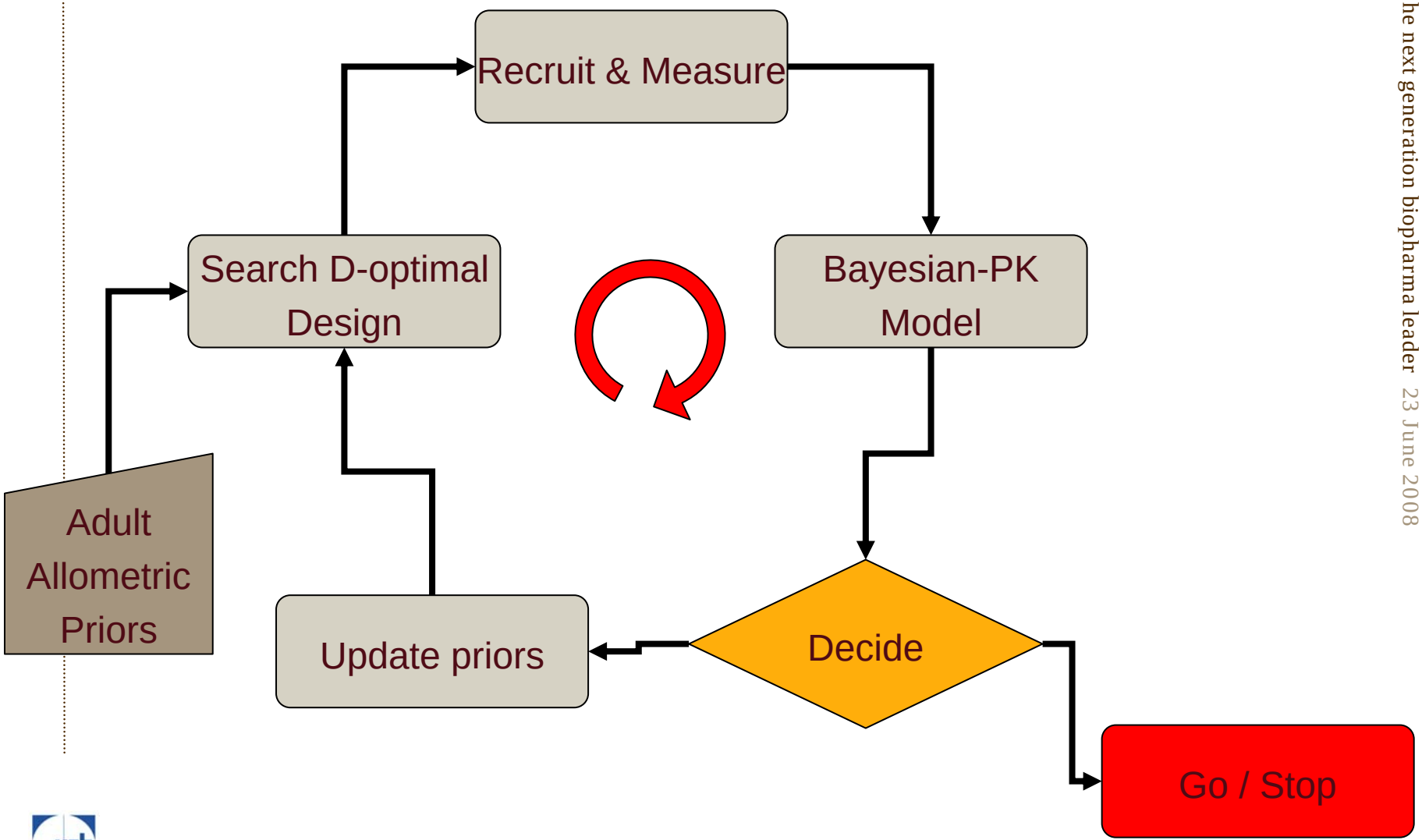
The Strategy

- An Adaptive Sampling-Time Design trial is investigated
  - ➔ guide the sampling-times in single-dose study
- Given an updated posterior information on parameters, a D-optimal design for non-linear mixed effect model is found at each interim.
  - NB: not a Bayesian D-optimal design, too computer intensive
- A Bayesian hierarchical PK model has been applied to cumulated data.
- The trial stops when estimates are sufficiently accurate.

The typical Design

1. 2-3 patients per cohort, maximum of 6-10 cohorts
2. 3-4 sampling times D-optimal given prior information
3. Bayesian Hierarchical PK model (1-cmpt, oral) with informative prior from adults and allometric scaling
4. Posteriors on parameters is used to find the D-optimal design for the next cohort.
5. Data are cumulated
6. Trial could stop when accuracy on parameters satisfactory.
7. What is the sample size?

PK Sampling-Times Adaptive Design



Bayesian (hierarchical) PK model

$$Y \sim Lognorm(C, \tau)$$

$$C = \ln\left(\frac{D}{e^{\theta 1}} \frac{e^{\theta 2}}{e^{\theta 2} - e^{\theta 3}} \left(e^{-e^{\theta 3} * t} - e^{-e^{\theta 2} * t}\right)\right)$$

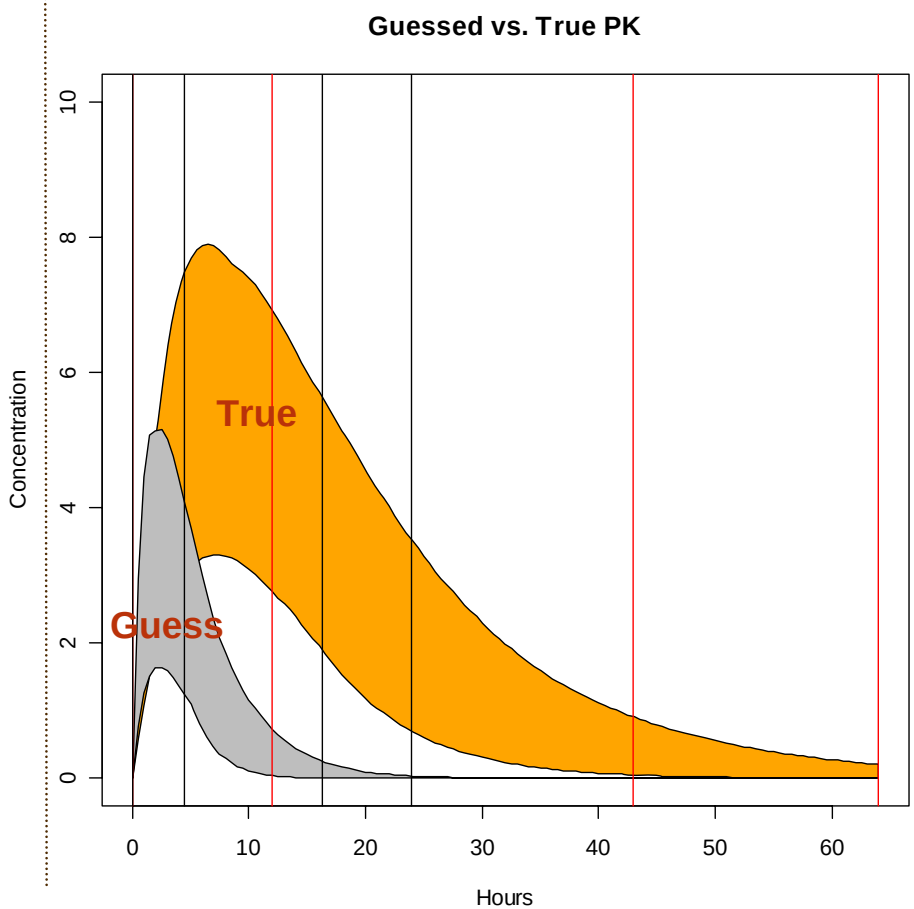
$$\Theta \sim Mnorm(M, R)$$

$$M \sim Mnorn(mu, prec)$$

$$R \sim Diag(Wish(\Omega, 3))$$

$$\tau \sim Gamma(a, b)$$

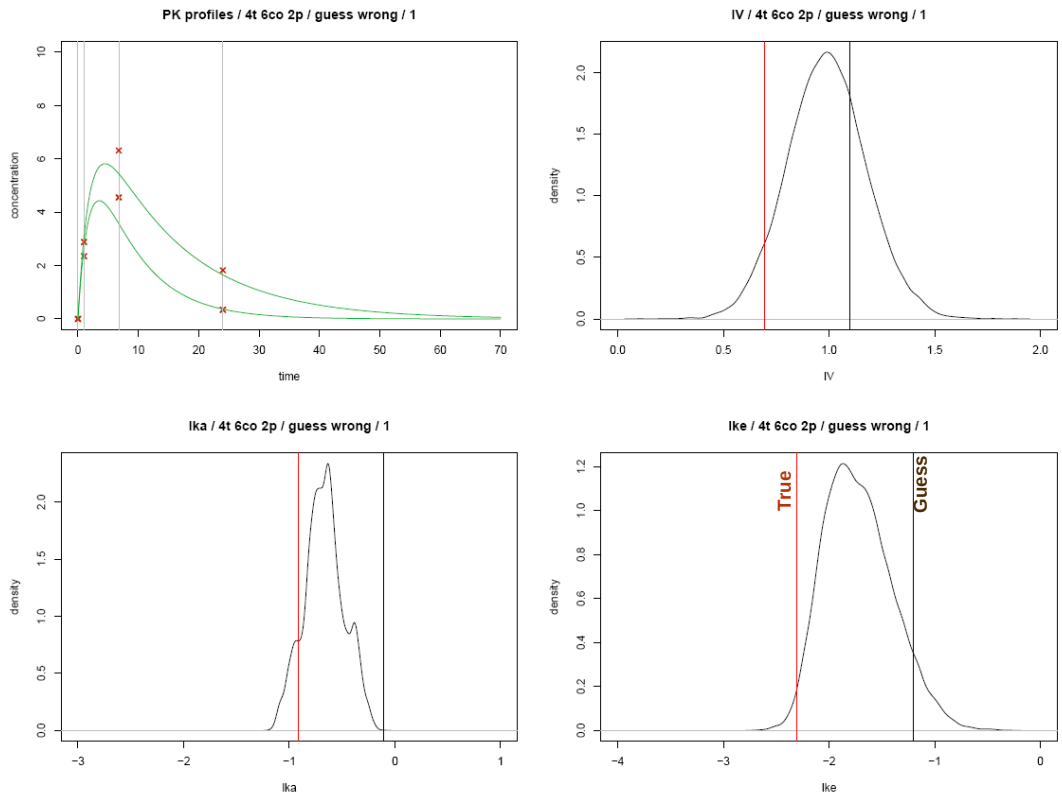
Assumptions



- The functional form of PK will remain identical, i.e. a 1-cmpt oral
- Allometric scaling given adult data give the “grey” profile and it’s corresponding optimal design
- The issue is:
  What if the “true” profile is different from the “guess” one given the a priori information?

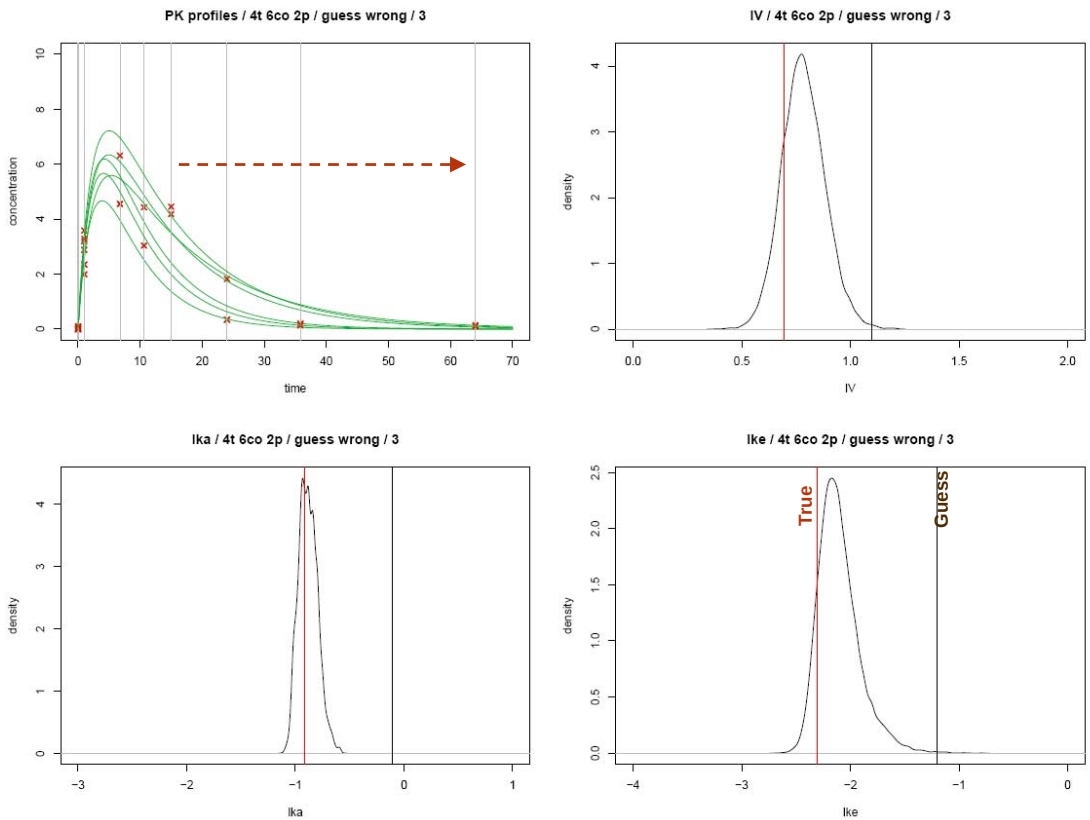
Example of Results after Cohort 1
Adaptive : 2 patients, 4 sampling times

- Sampling times are not appropriate given the observed values
- Posterior distribution on parameters rather spread between the guess (black lines) and the true values (red lines)



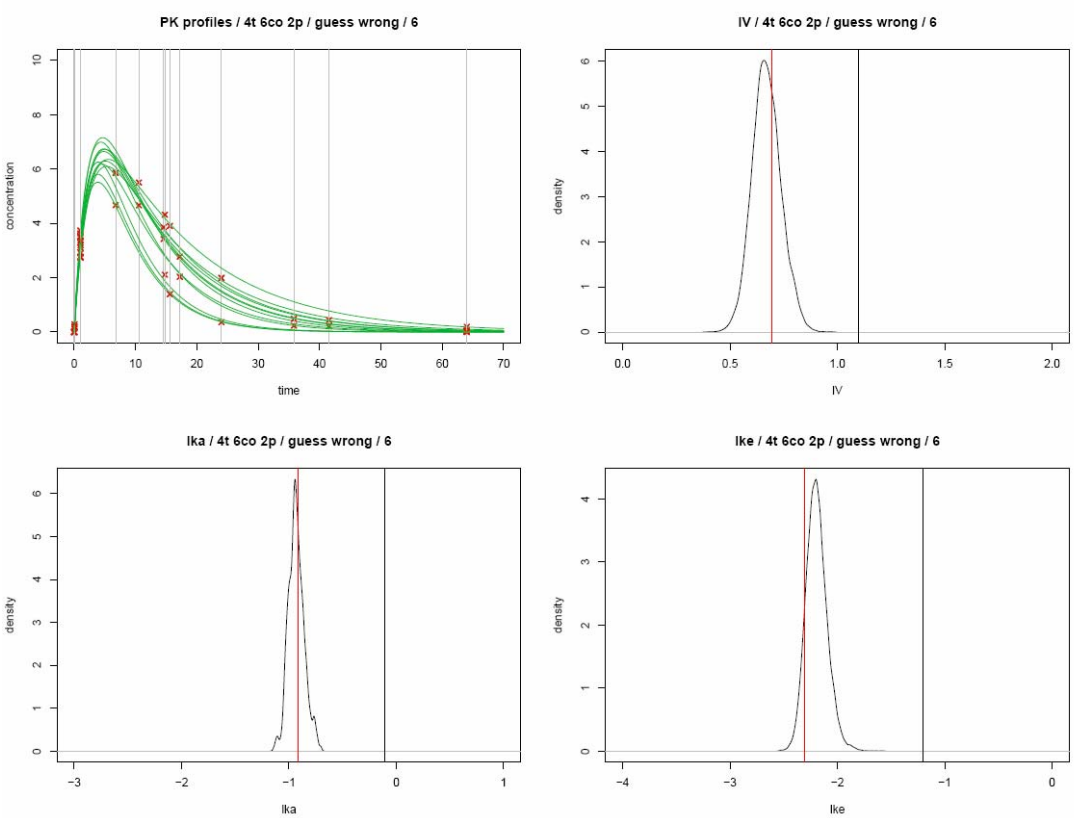
Example of Results after Cohort 3
Adaptive : 6 patients

- Sampling times are now adapted to the observed data.
- Posterior distribution still spread but migrates around the true values (red lines)



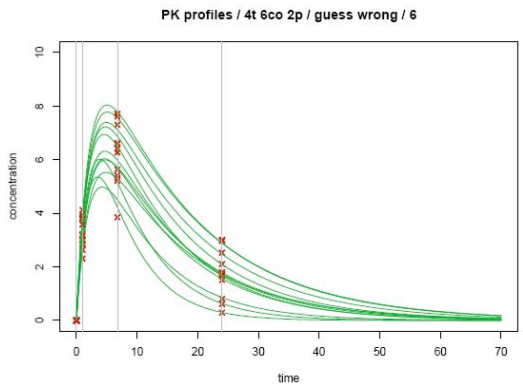
Example of Results after Cohort 6
Adaptive: 12 patients

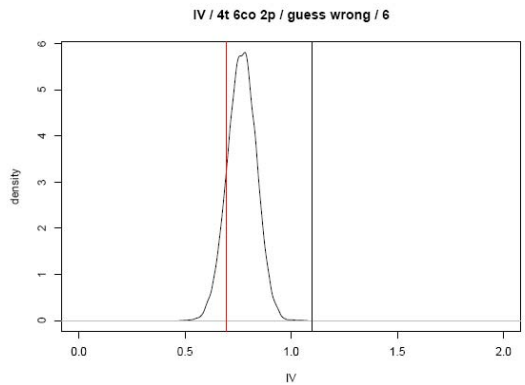
- Posterior distributions for population parameters migrates into areas of interest, i.e. with [-20%,+20%] of true value, our target.
- Results to be compared to fixed designs with Right guess and Wrong guess.

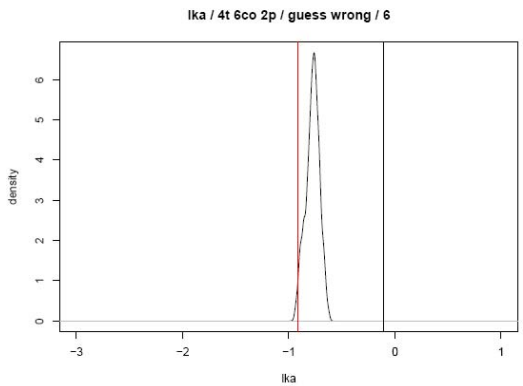


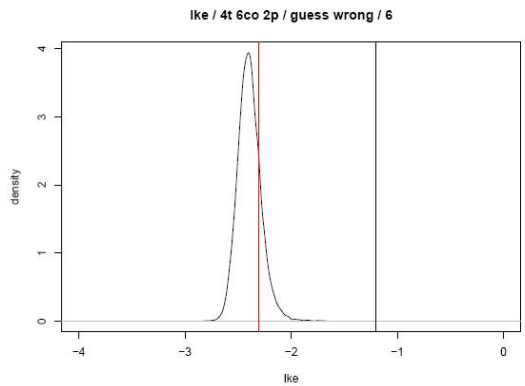
Example of Results **Wrong** guess **FIXED**: 12 patients

- Estimates are less accurate
- Bias caused by the sub-optimal sampling-times design
- Possibly Inappropriate estimates for prediction.



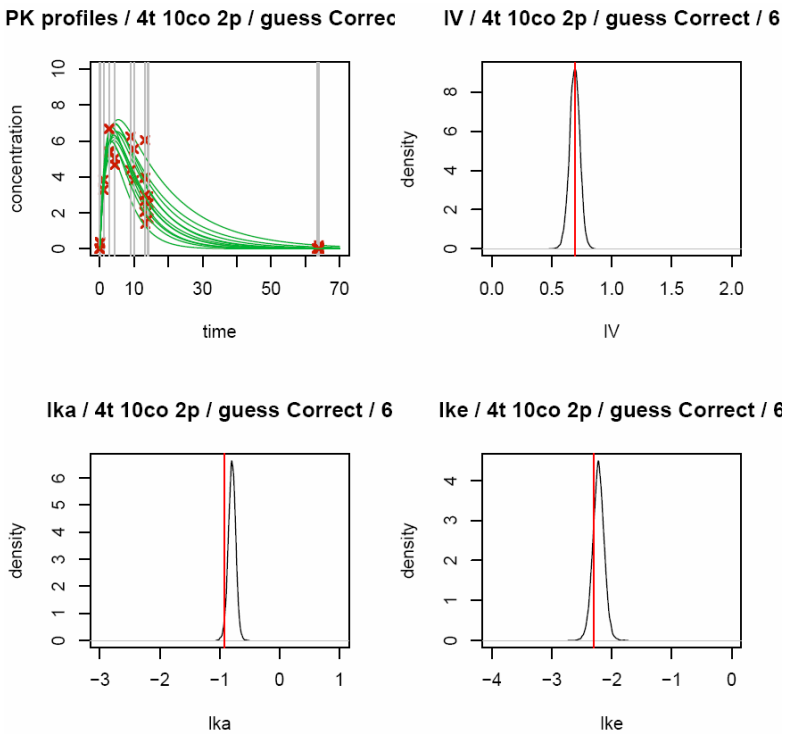


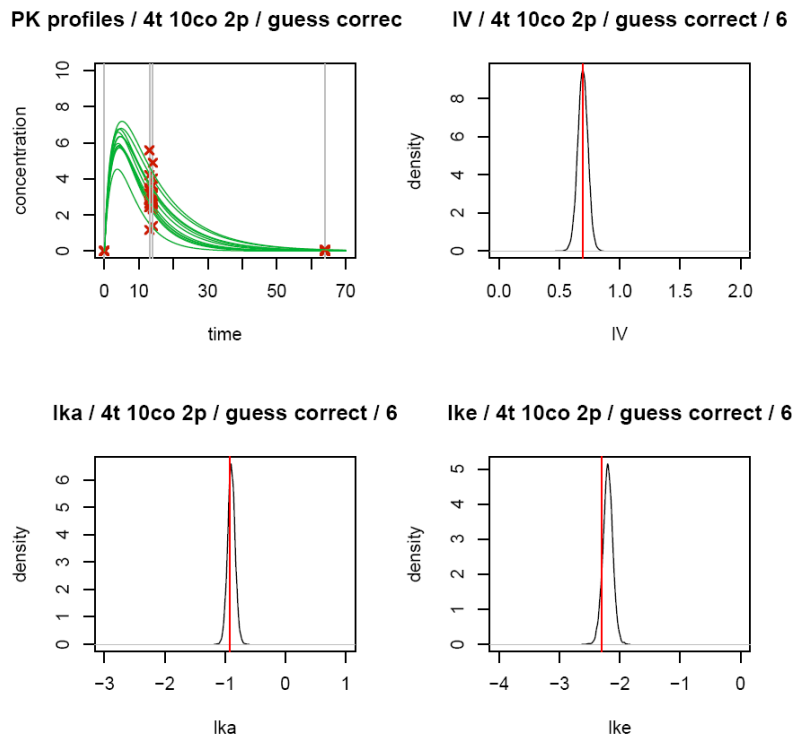




Example of Results **Correct** guess **Adaptive and fixed**: 12 patients

- With or without adaptation on sampling times results are the same.

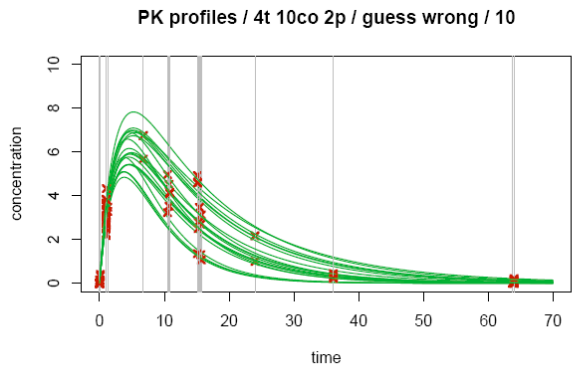


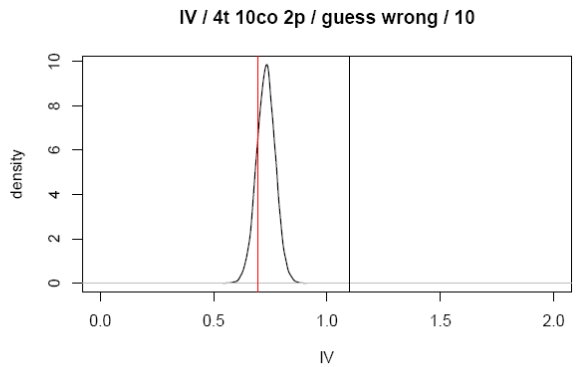


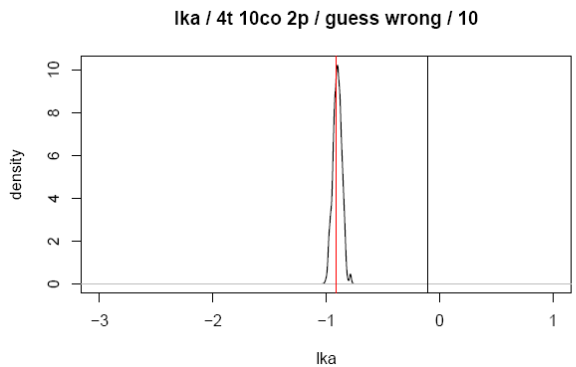
Adaptive **Fixed**

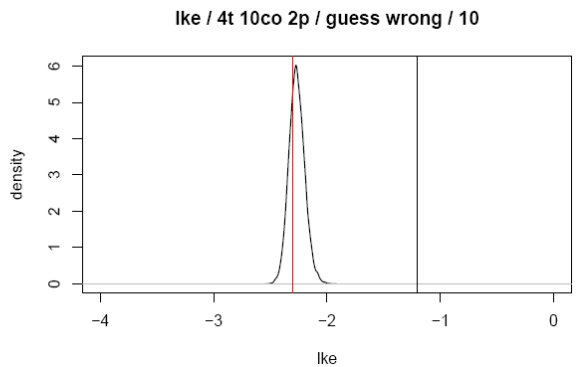
Example of Results at Cohort 10
BAST: 20 patients on total

- Just to see how the process “converge”
- Accuracy continues to improve.



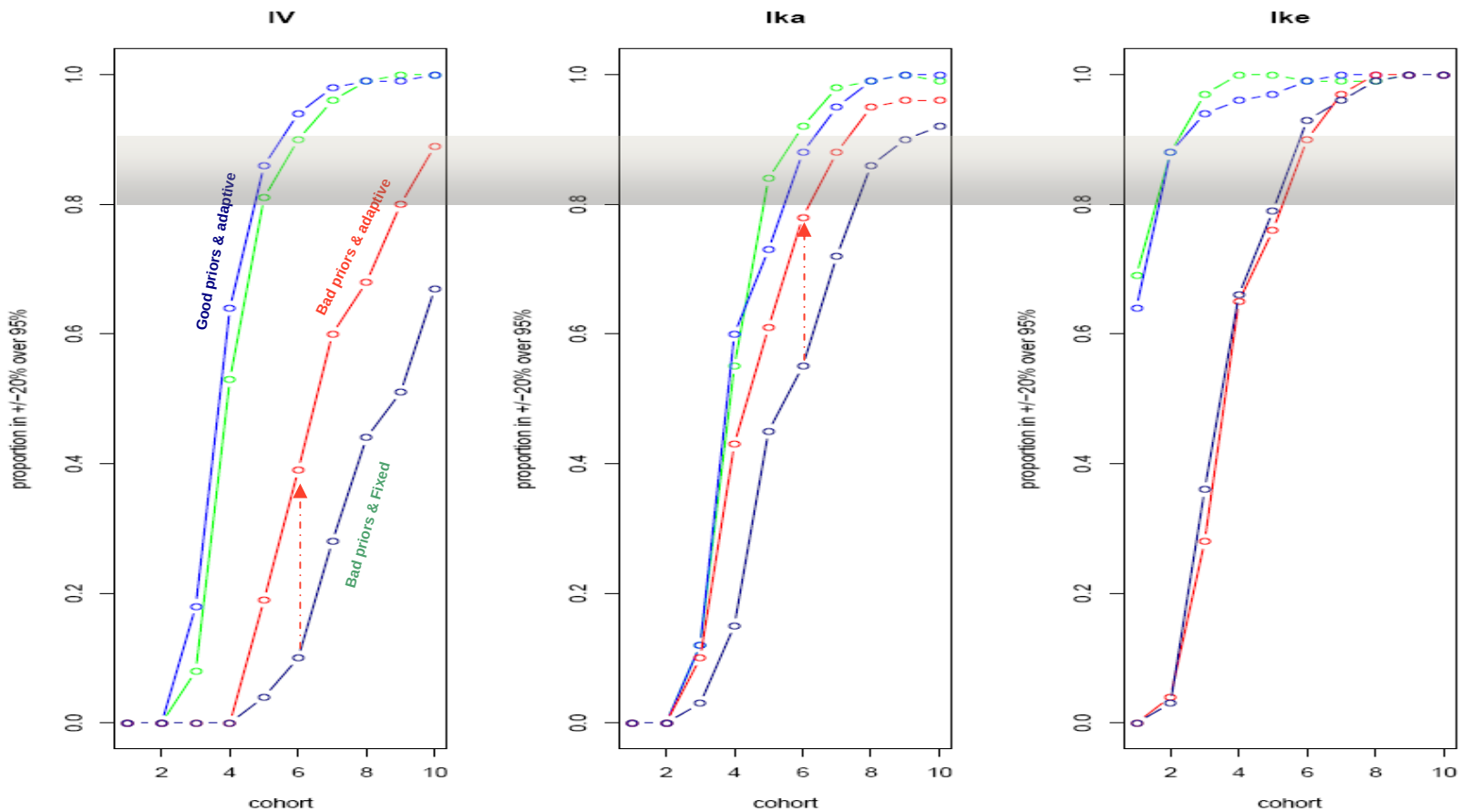






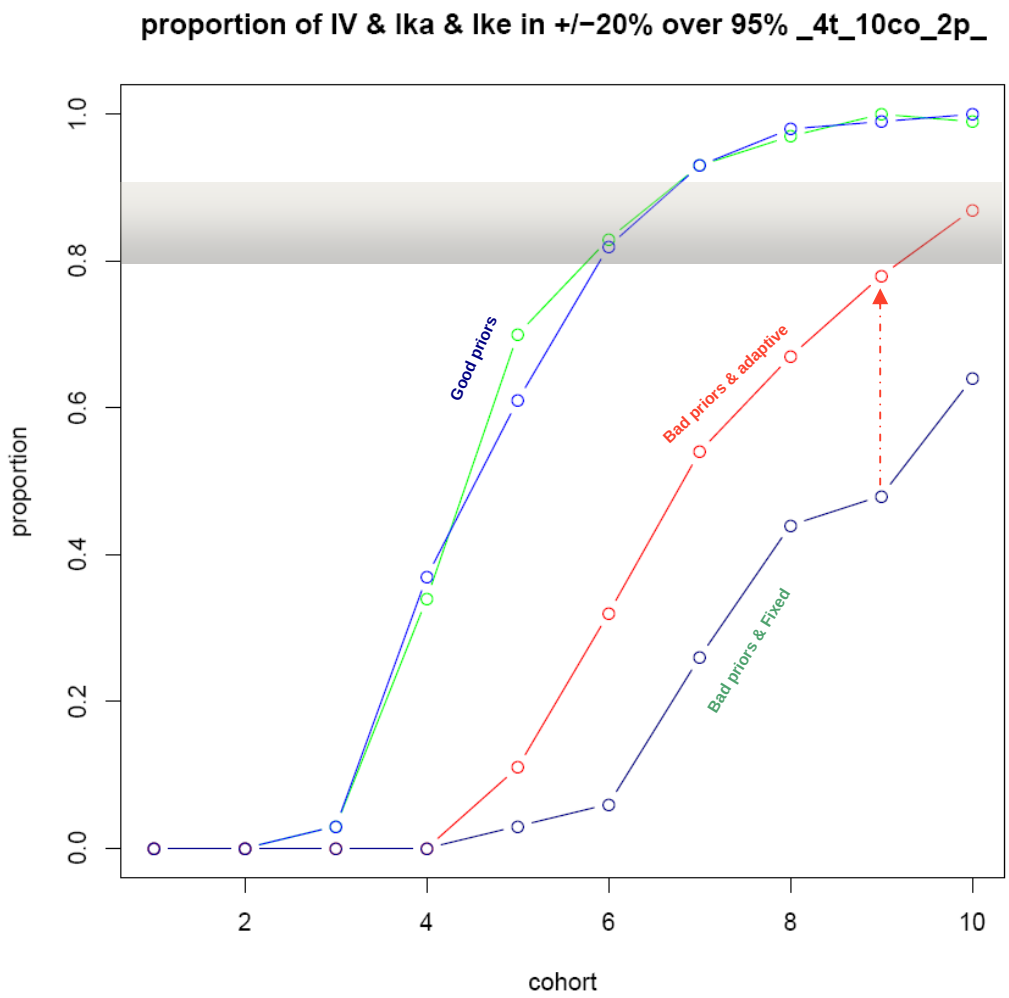
Comparative analyses: 4 sampling times/ 2pts/cohort Adaptive vs Fixed Optimal Designs

- Prob(95% posterior in [-20%,+20%] true value)



Comparative analyses: 4 sampling times/ 2pts/cohort Adaptive vs Fixed Optimal Designs

- Prob(95% posteriors ALL estimates in [-20%,+20%] true value)



Conclusions I
Adaptive sampling-times design

When guesses are **wrong**

an adaptive sampling-times design provides more accurate (less bias, more precision) parameter estimates than a fixed design with 12 patients.

When guesses are **right**

an adaptive sampling-times design provides parameter estimates as accurate than a fixed design with 12 patients.

- How are you sure about your guesses?
- Sampling times are as easy as an email to be adapted
- Require bio-analytical lab to work in “real-time”, possible with new technologies.

Potential use and development of Adaptive Sampling-times

- Use in TK studies where dose-proportionality is always challenged, to obtain better estimates for PBPK and allometric scaling
- FIM (SD&MD) based on animal priors from PBPK or allometric models
- PK studies in special population or diseases.
- Next
  - Sensitivity to #sampling times and #patients/cohort
  - Extend to ODE to allow advanced PK/PD
  - Staggered designs

Conclusions

- Adaptive Design, in particular “sampling-times” adaptive design provide PK/PD models with accurate “fit-for-purpose” estimates
- Accurate estimates permit accurate dose and regimen optimization
- Adaptive Designs and Model Based Drug Development are natural partners in learning.