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Bayesian Adaptive Sampling Time Design for Constrained PK Studies

BAYES 2010 – UCB – Braine-L'alleud

May 20th 2010

Pediatric PK trial: objectives & constraints

Phase I Single Dose study in young children:

- 1 month to 4 years

Focus is on accuracy of PK parameter estimates:

- to be used for predictions
- dose/regimen optimization

A priori rather informative:

- numerous data in adults (16y to 70y)
- experience in allometric scaling.

Ethics:

- kids are not small adults, need to be robust against this potential issue
- maximum 3 or 4 samples per kid.

To go round in a circle…

Accuracy on parameter estimates is linked on sampling time choice.

D-optimality criteria is not independent of the parameters in nonlinear (hierarchical) model:

- design is only locally optimal around preliminary estimates or guesses
- if guesses about parameters are wrong, then the design is not optimal with respect to the true value of the parameter

How to overcome these difficulties?

A **Bayesian adaptive framework** based on **D-optimality** and **prior information** on parameters.

I. **BAST: How it works?**

II. Practical case: pediatric population PK study

III. Conclusion & further work

Goal:

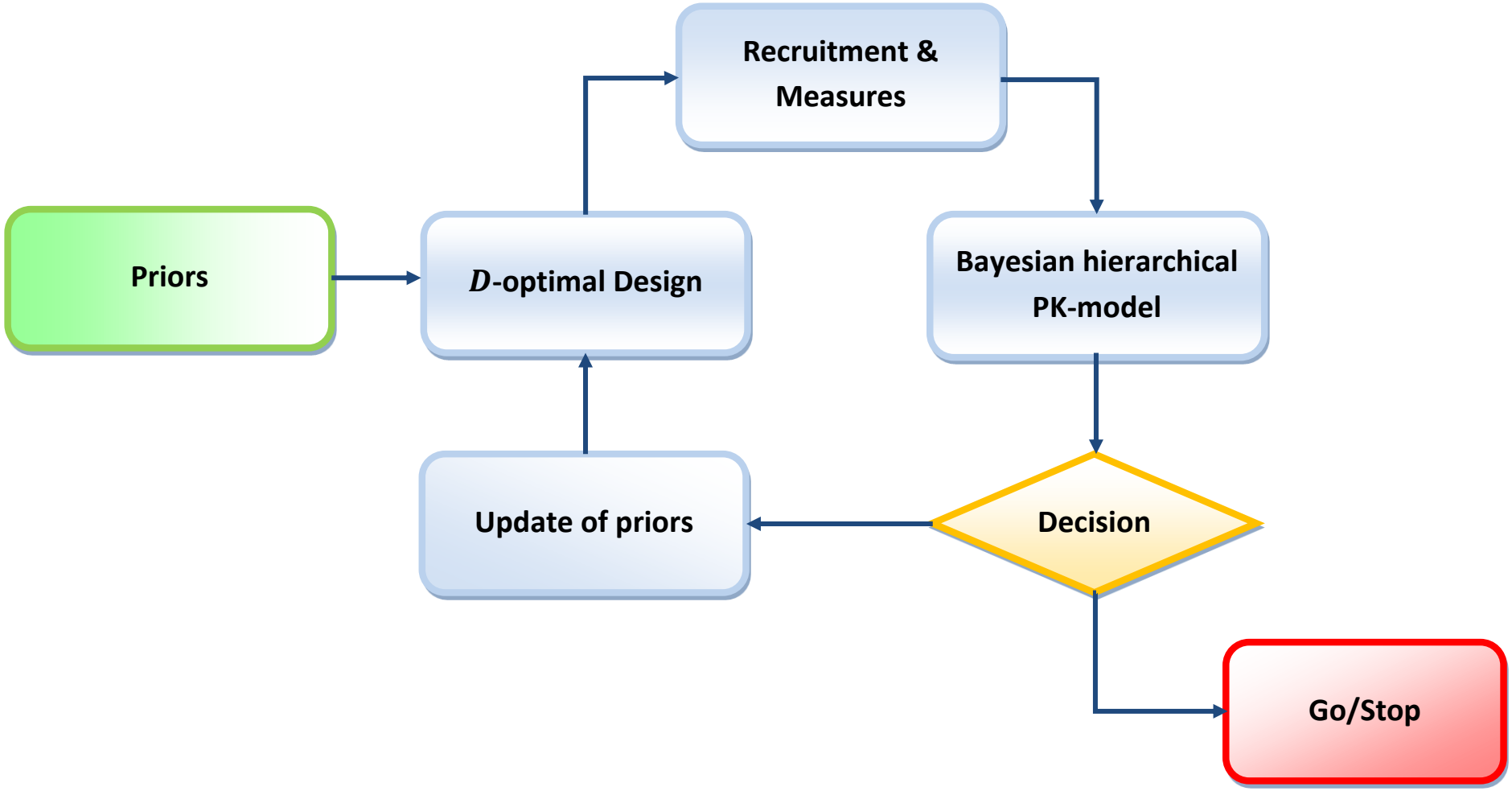
An Adaptive Sampling-Time Design trial is investigated to guide the sampling times in single-dose and multiple-dose studies

Main ideas:

- Given (updated) a priori information on parameters, a D-optimal design for non-linear mixed effect model is derived at each interim.
  NB: not a Bayesian D-optimal design, too computer intensive
- A Bayesian hierarchical PK model has been applied to update information on the parameters

The Design:

1. 2/3/4 patients per cohort, maximum of 6 cohorts
2. 3/4/5 sampling times obtain using the D-optimality criterion given prior information
3. Bayesian Hierarchical PK model with informative prior from adults and allometric scaling
4. Posteriors on parameters are used to find the D-optimal design for the next cohort.
5. Posteriors are used as priors for the Bayesian model at the next interim
6. Trial could stop when accuracy on parameters satisfactory, but 12 patients is the stopping rule.


Recruitment & Measures
Priors
D-optimal Design
Bayesian hierarchical PK-model
Update of priors
Decision
Go/Stop

Non-linear mixed effects model

For $q = 1, \dots, Q$,

$$y^q = f(\theta, \gamma^q, \xi^q) + \varepsilon^q \circ \left(\sigma_{inter} + \sigma_{slope} f(\theta, \gamma^q, \xi^q)\right)$$

The assumptions:

- $\gamma^q \sim \mathcal{N}_p(0, \Omega)$,
- $\varepsilon^q \sim \mathcal{N}_{n_q}\left(0, I_{n_q}\right)$,
- Independence between γ^q and ε^q.

The parameter to estimate is the vector $\boldsymbol{\Psi = \left(\theta^T, \omega^T, \sigma^T\right)^T}$, with:

- $\theta = \left(\theta_1, \dots, \theta_p\right)^T$ the vector of fixed effects,
- $\omega = \left(\omega_1, \dots, \omega_p\right)^T$ the variance of random effects,
- $\sigma = \left(\sigma_{inter}, \sigma_{slope}\right)^T$ for the structure of the variance of residual error.

Definition

An experimental plan is defined by:

$$\Xi = \begin{Bmatrix} \xi^1 & \dots & \xi^Q \\ N_1 & \dots & N_Q \end{Bmatrix}$$

Fisher Information Matrix

$$M_F(\Psi, \Xi) = E\left(-\frac{\partial^2 l(\Psi, y)}{\partial \Psi \partial \Psi^T}\right)$$

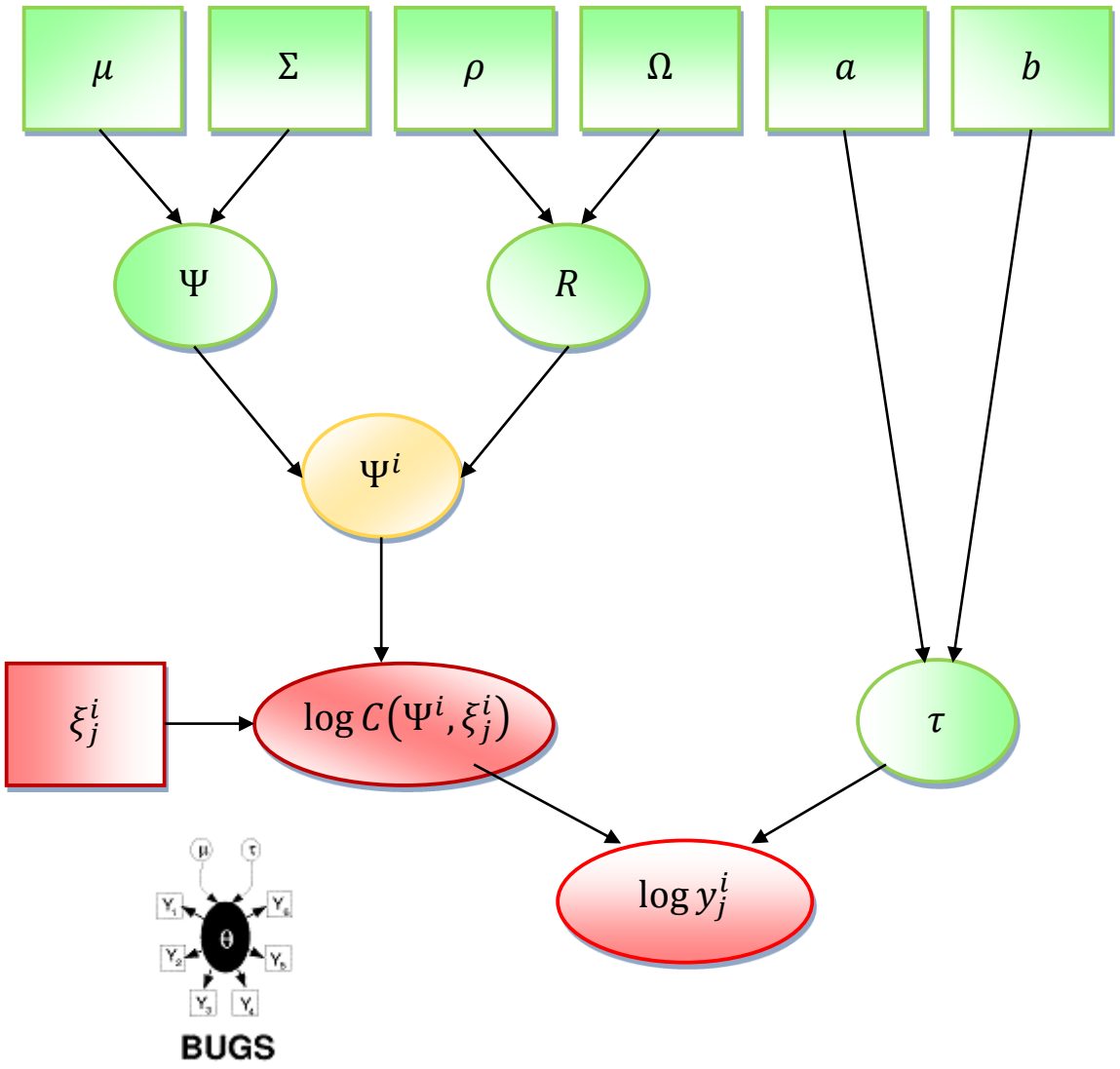
The D-optimality criterion:

$$\Phi(\Xi) = |M_F(\Psi, \Xi)|^{1/l_\Psi}$$

Goal: find Ξ that maximize the criterion Φ

Software & functions:

- software **R**,
- functions **PFIM** & **PFIMOPT** (Sylvie Retout & France Mentré)



Model for the data:

$$\log\left(y_j^i\right) = \log\left(C\left(\Psi^i, \xi_j^i\right)\right) + \varepsilon_j^i$$
$$\varepsilon_j^i \sim \mathcal{N}(0, \tau^{-1})$$

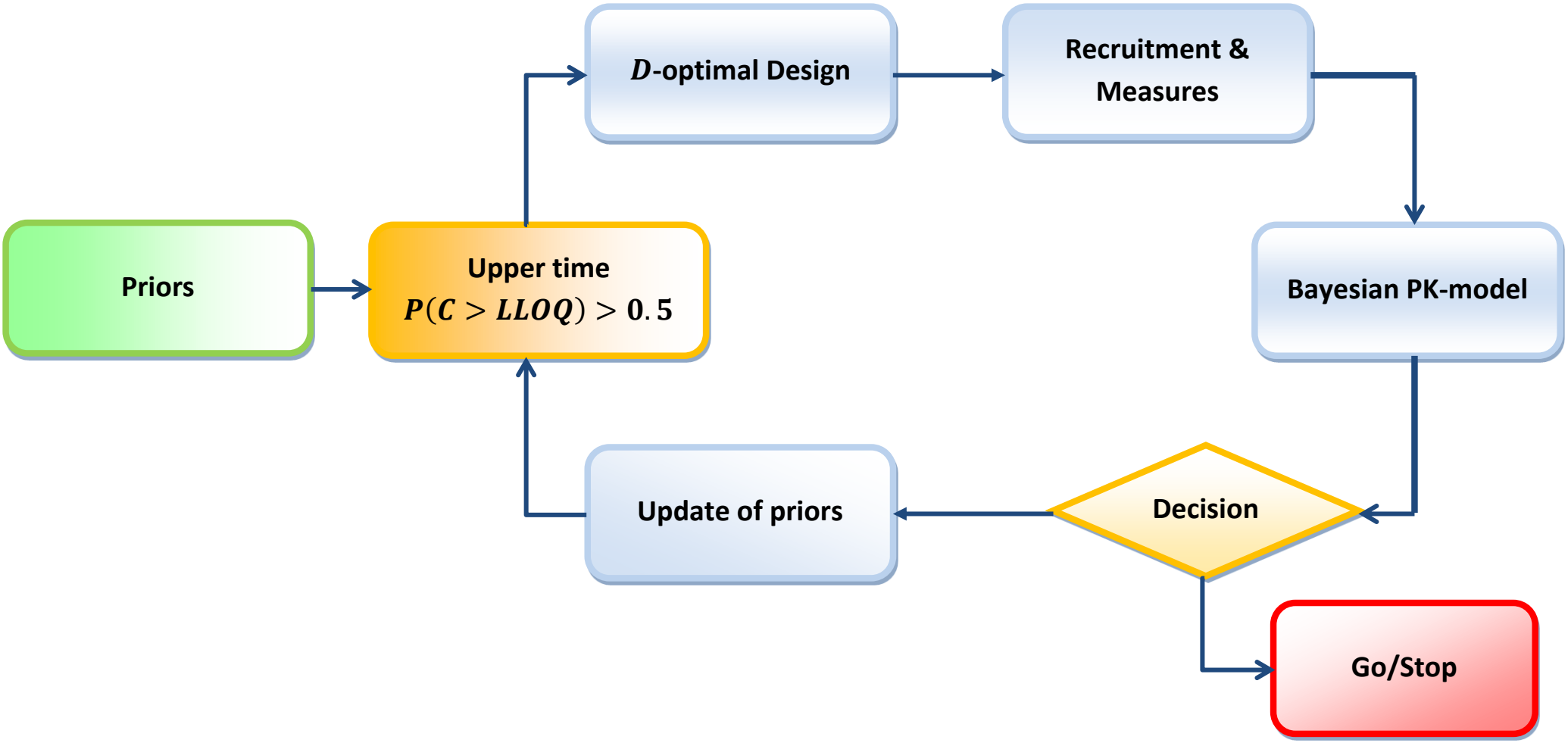
Model for the inter-individual variability :

$$\Psi^i \sim \mathcal{N}_p(\Psi, R^{-1})$$

Priors:

$$\tau \sim \mathcal{G}a(a, b)$$
$$\Psi \sim \mathcal{N}_p(\mu, \Sigma^{-1})$$
$$R \sim \mathcal{W}i_p((\rho\Omega)^{-1}, \rho)$$

	Priors	Updates
τ	$\tau \sim \mathcal{G}a(a,b)$	$a = \frac{E^2(\tau_{post})}{Var(\tau_{post})}$ $b = \frac{E(\tau_{post})}{Var(\tau_{post})}$
Ψ	$\Psi \sim \mathcal{N}_p(\mu, \Sigma^{-1})$	$\mu = E(\Psi_{post})$ $\Sigma = \left(Var(\Psi_{post})\right)^{-1}$
R	$R \sim \mathcal{W}i_p((\rho\Omega)^{-1}, \rho)$	$\Omega = \left(E(R_{post})\right)^{-1}$ $\rho = \frac{2\left(E^2(R_{post})\right)_{kk}}{\left(Var(R_{post})\right)_{kk}}$


Priors
Upper time
$P(C > LLOQ) > 0.5$
D-optimal Design
Recruitment & Measures
Bayesian PK-model
Decision
Update of priors
Go/Stop

I. BAST: How it works?

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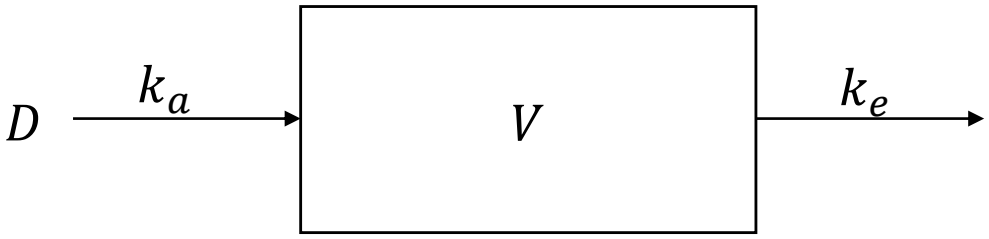
Concentration for a one compartment model:

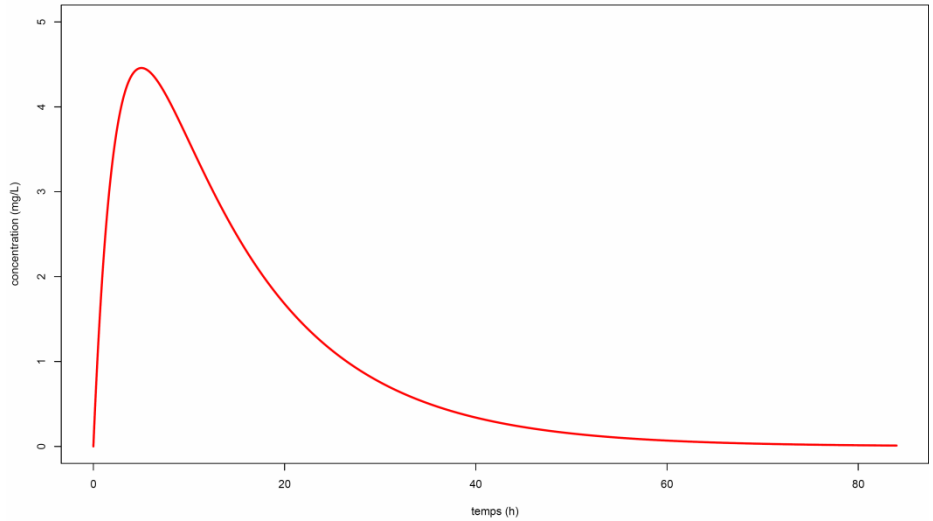
$$C(V, k_a, k_e, \xi) = \frac{D}{V} * \frac{k_a}{k_a - k_e} * \left(e^{-k_e * \xi} - e^{-k_a * \xi}\right)$$

With:

- D the oral dose,
- k_a and k_e the absorption & elimination constant,
- V the volume of the compartment.

Parameterization with $\log(V)$, $\log(k_a)$ and $\log(k_e)$.





WinBUGS code

```
model {
   for(i in 1:M){
      for(j in 1:N){
         log.y[i,j] ~ dnorm(log.C[i,j],tau)
         log.C[i,j] <- log(D/
                           exp(psi[i,1])*
                           exp(psi[i,2])/
                           (exp(psi[i,2])-exp(psi[i,3]))*
                           (exp(-exp(psi[i,3])*xi[i,j])-
                            exp(-exp(psi[i,2])*xi[i,j])))
      }
      psi[i,1:3] ~ dmnorm(mean_psi[],R[,])
   }
   mean_psi[1:3] ~ dmnorm(mu[],prec[,])
   R[1:3,1:3] ~ dwish(rho_omega[,], rho)
   tau ~ dgamma(a,b)
}
```

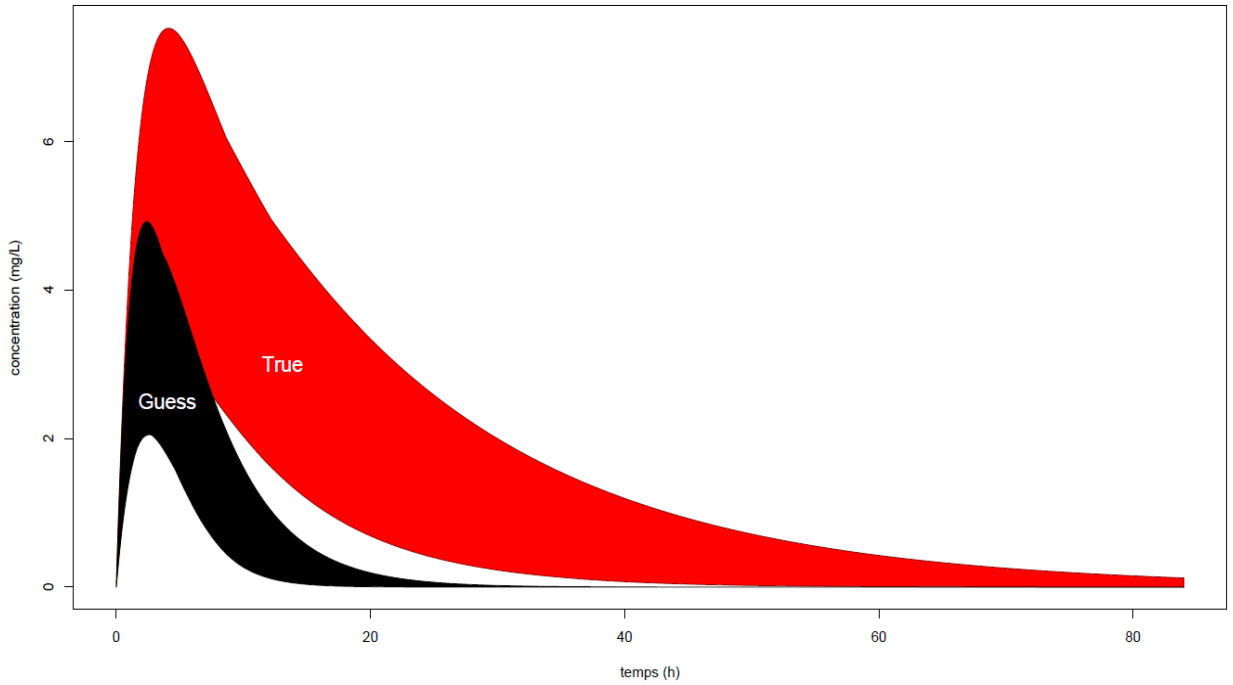
Different sizes for cohorts 2, 3, 4 & 12 patients per cohort

Different number of sampling times 3, 4 & 5 sampling times

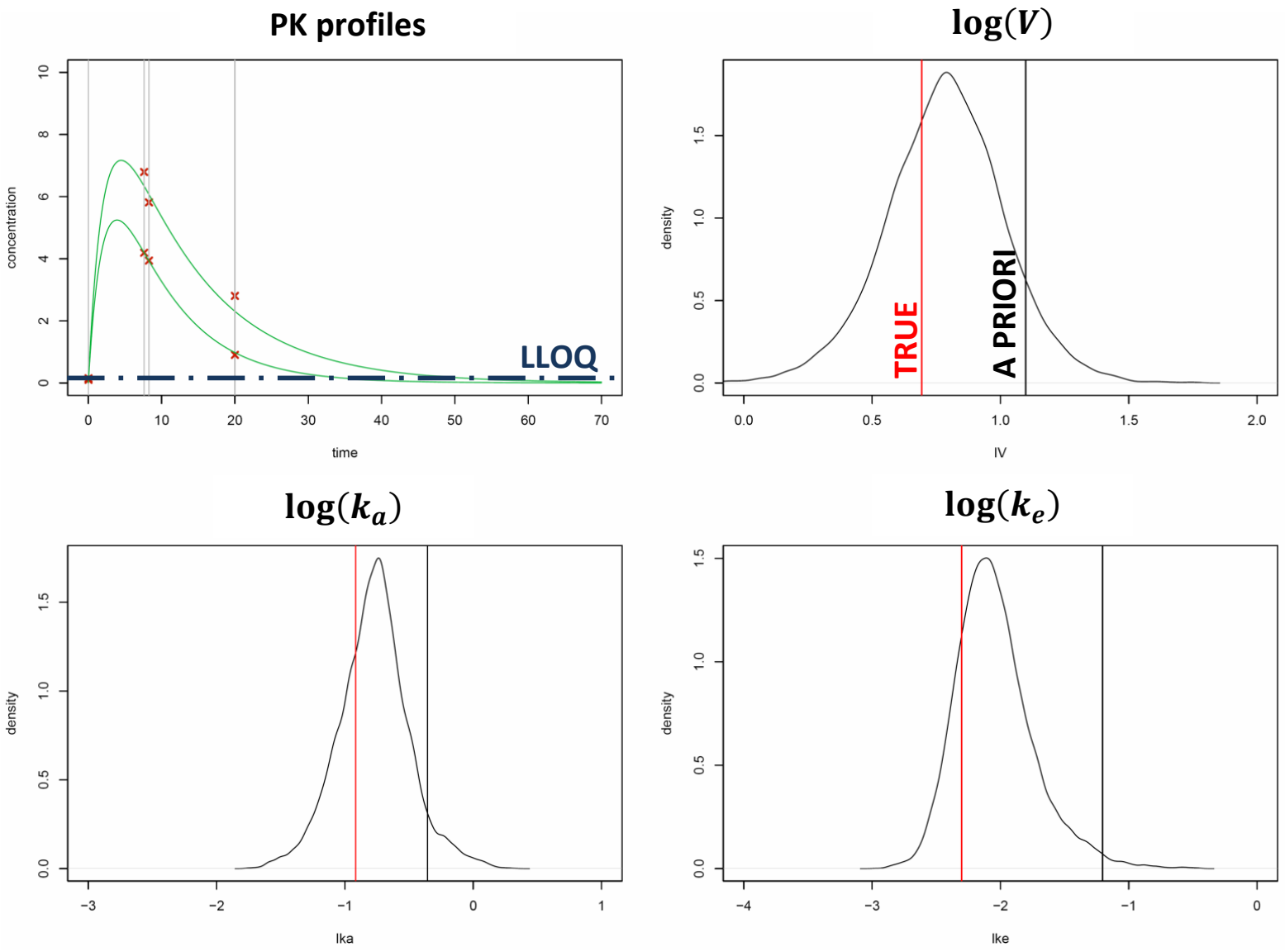
Prior values for the first cohort good guess or wrong guess

Interest for the configuration:

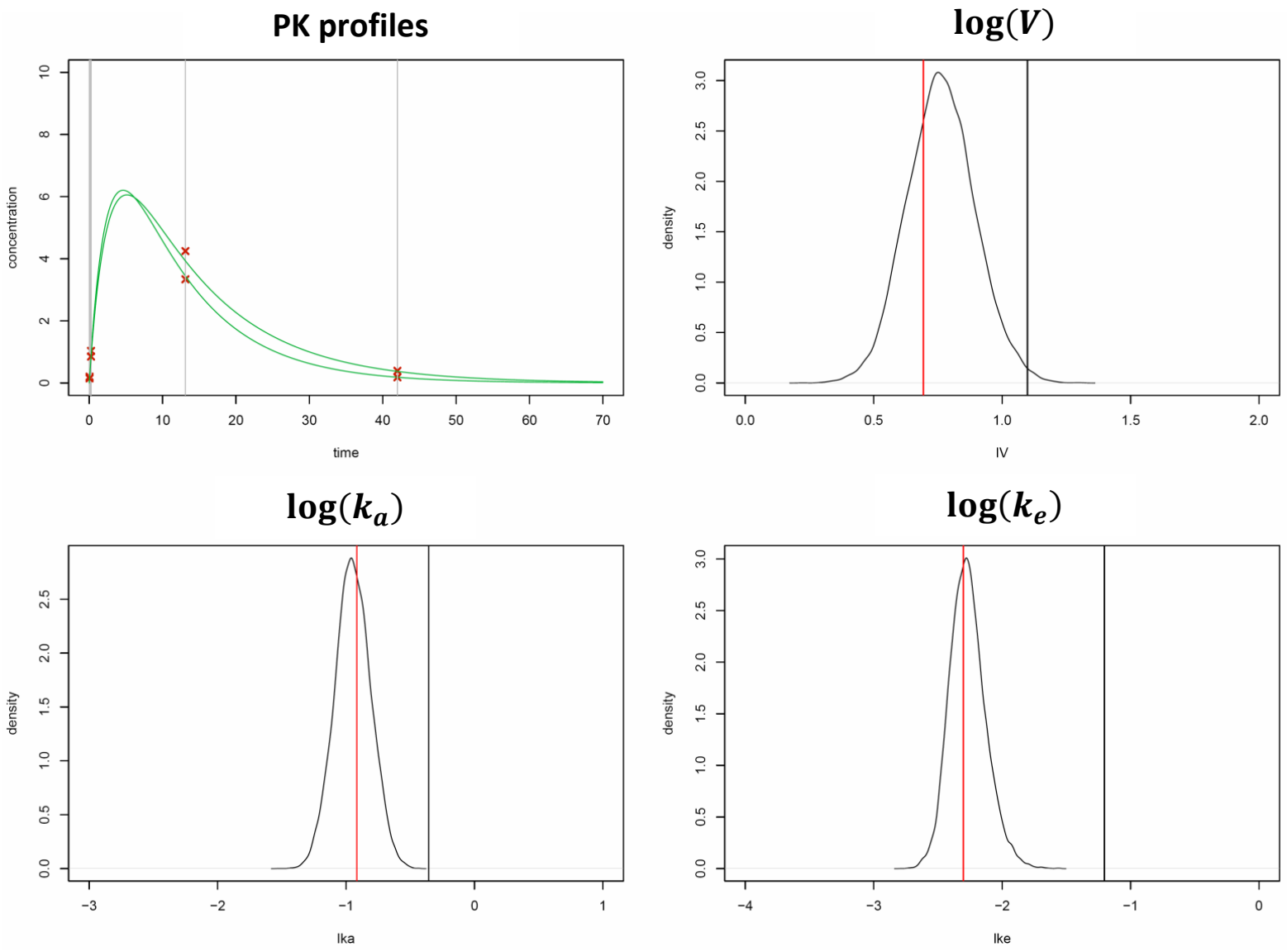
- 6 cohorts of 2 patients
- 4 sampling times per subject



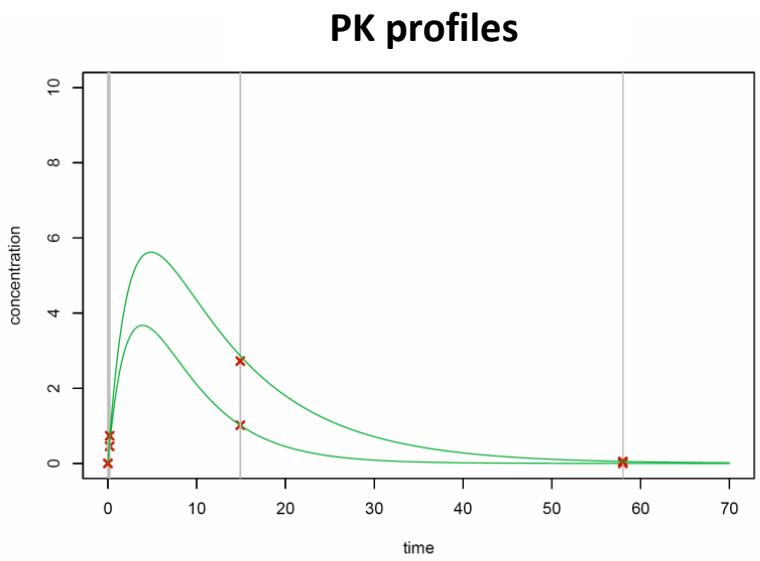
After the 1st cohort

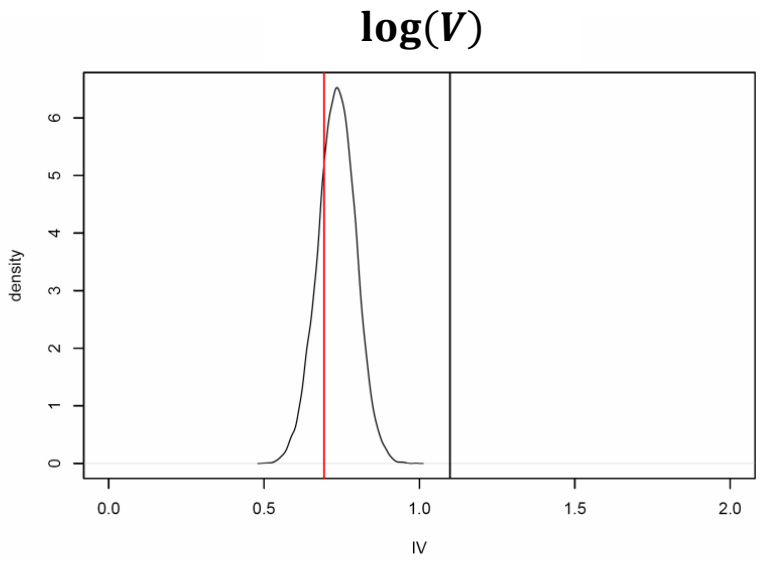


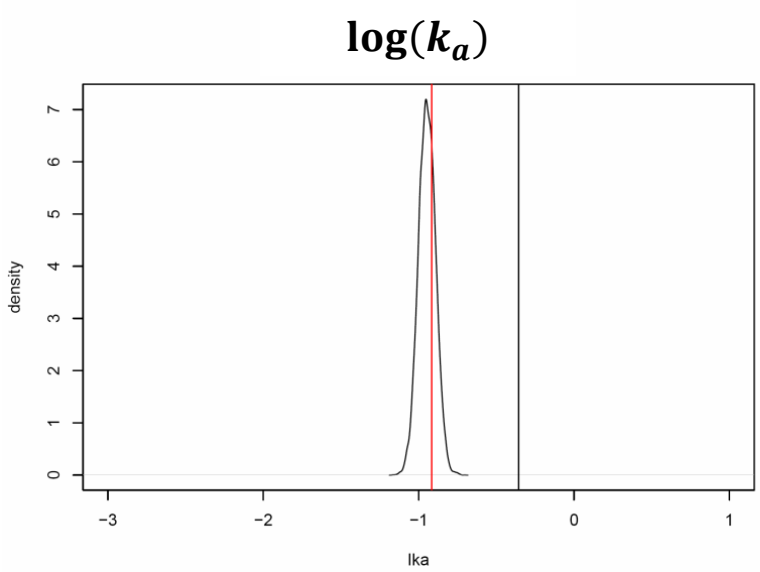
After the 2nd cohort

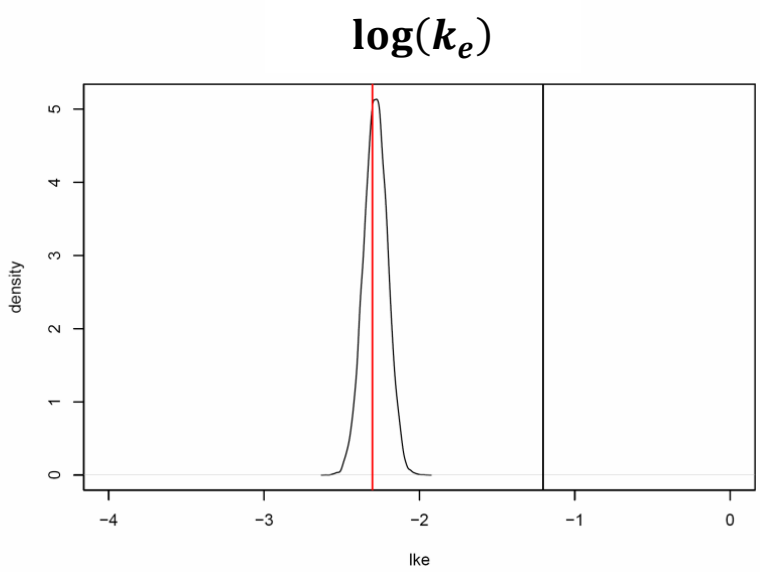


After the 6th cohort

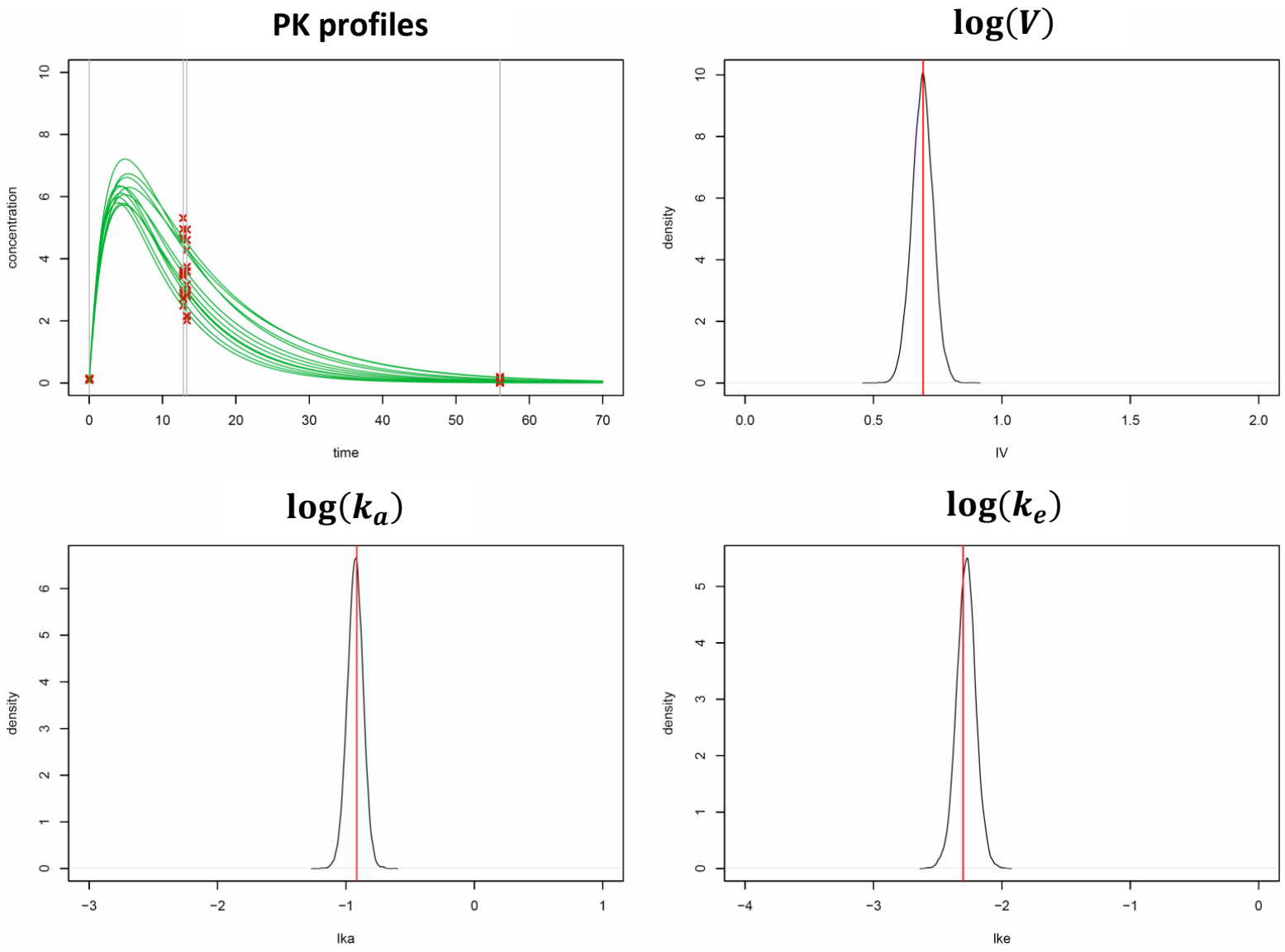






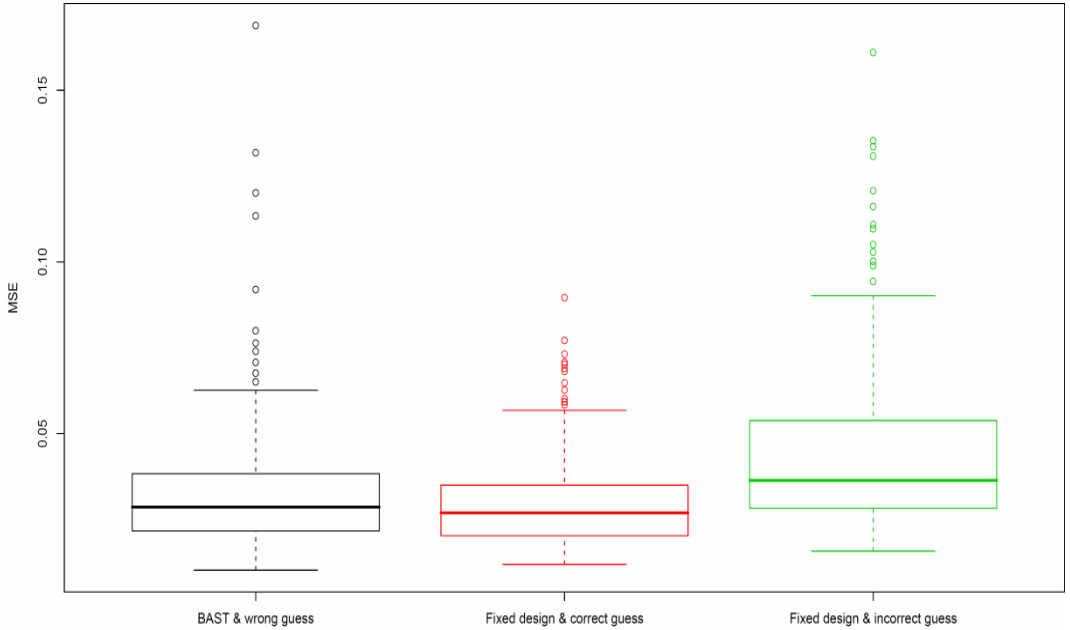


After 12 patients, fixed design & correct a priori



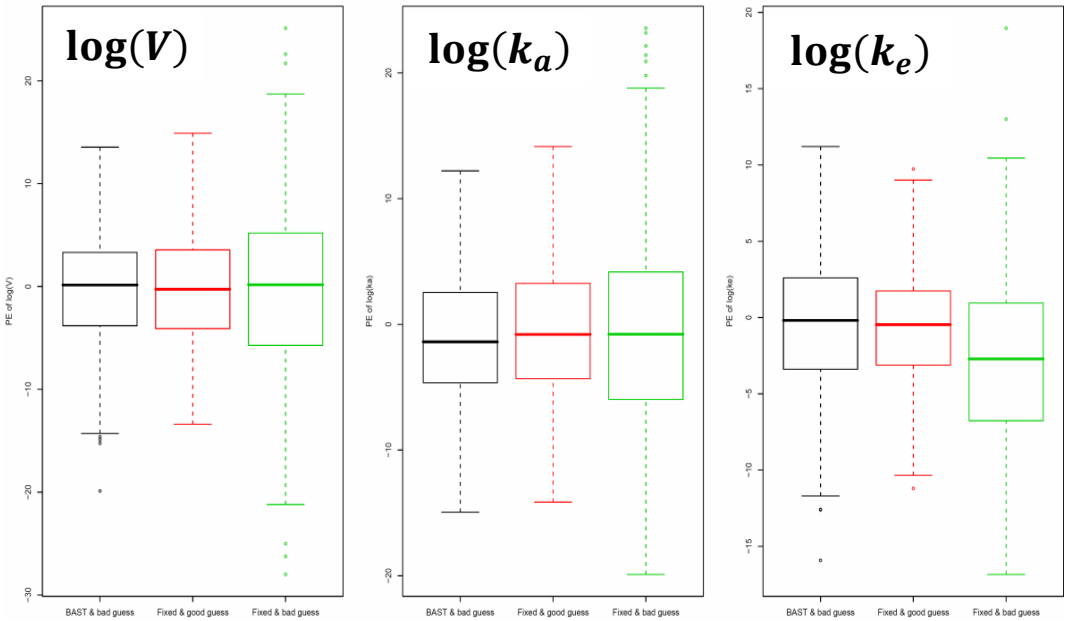
BAST vs. Fixed design & wrong guess :

- **reduction** of MSE,
- dispersion of relative bias **less important**,
- **reduction** of bias for $\log(k_e)$.



BAST vs. Fixed design & good guess :

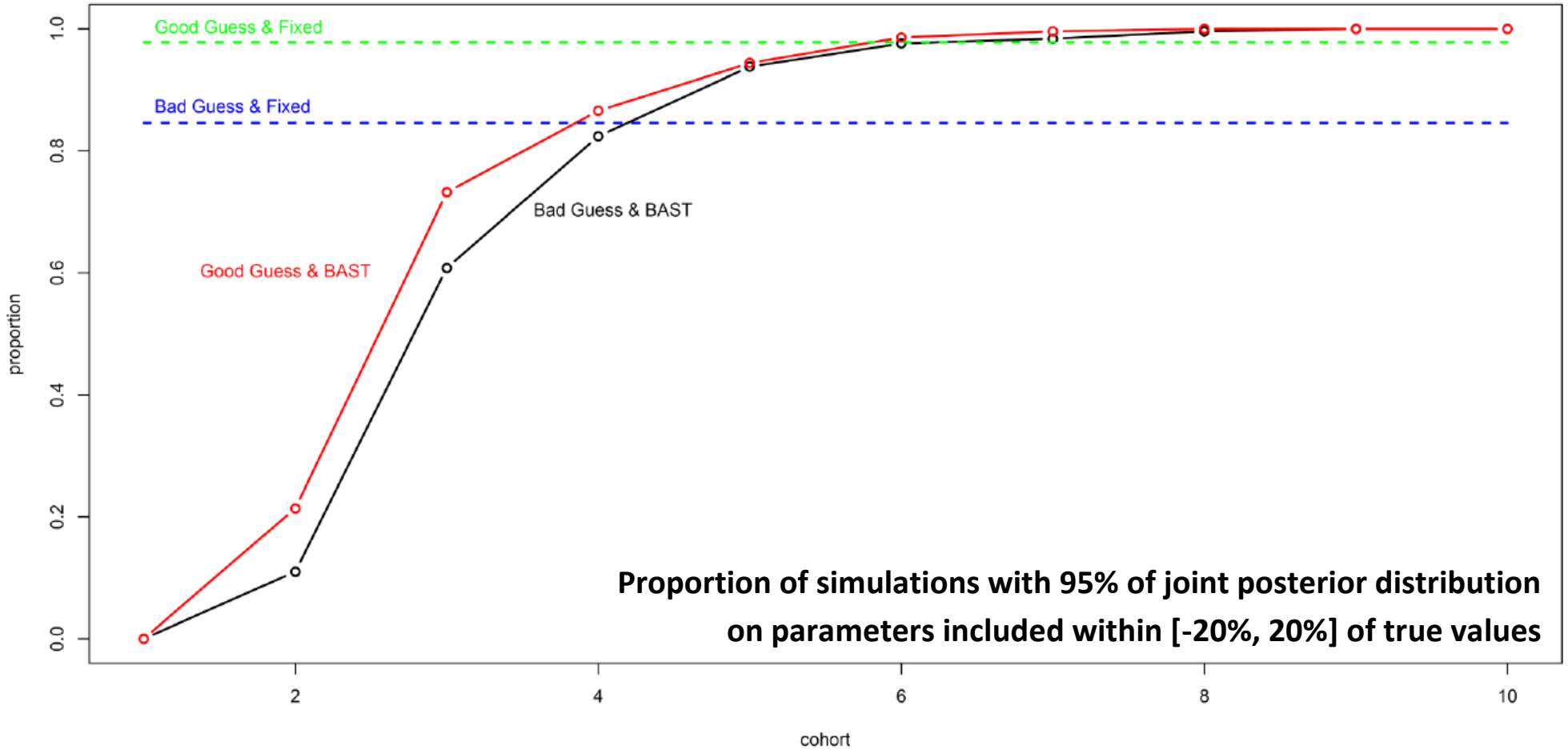
- similar results,
- MSE slightly lower,
- relative bias similar,
- **reduction** of the dispersion for $\log(k_e)$



BAST & wrong guess
Fixed Design & correct guess
Fixed Design & incorrect guess

BAST vs. Fixed designs (3 sampling times)

- BAST rapidly converges to the Fixed Design with correct a priori
- After 12 patients, both BAST and Fixed Design with correct a priori provide similar quality.
- BAST convergence is, within limits, robust against a prioris, correct or incorrect.



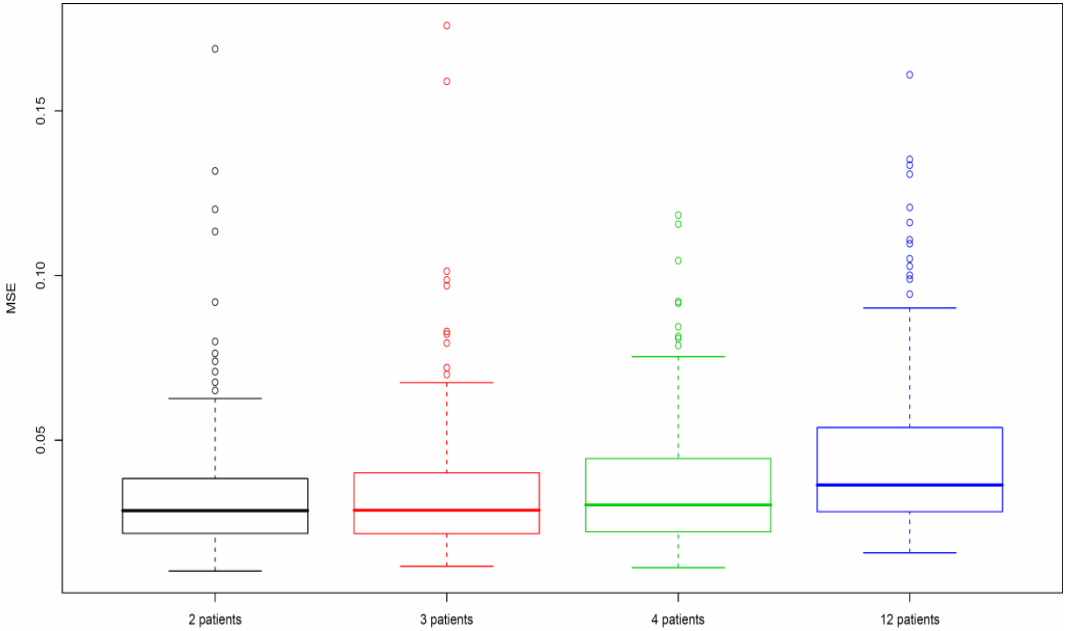
Influence of the number of patients per cohort

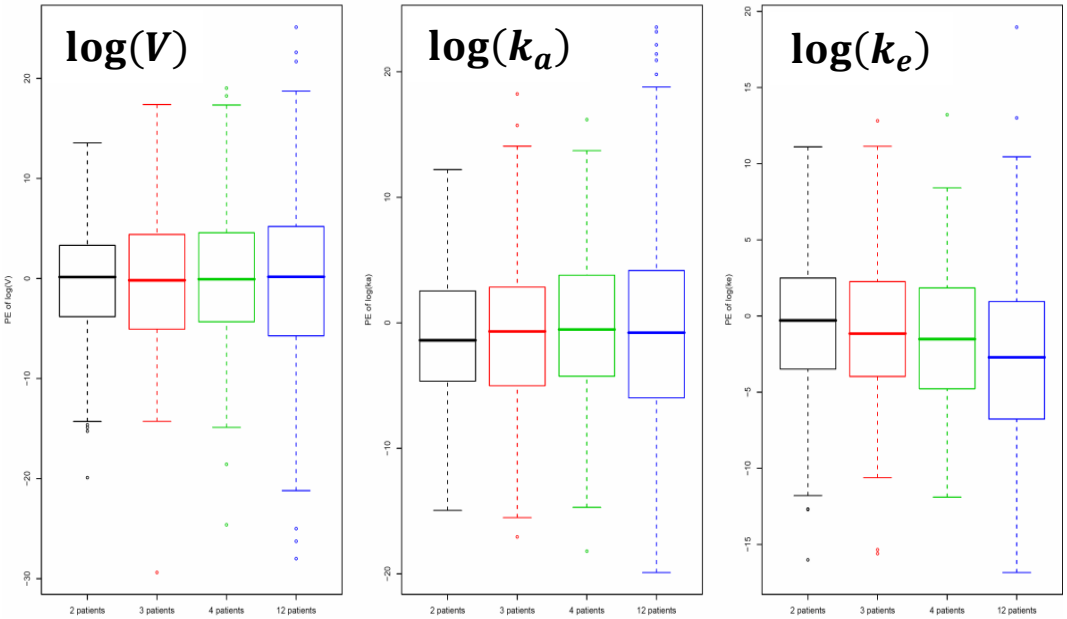
Configuration:

- 2, 3, 4 & 12 patients per cohort,
- A total of 12 patients,
- 4 sampling times.

Results:

- **Reduction** of the relative bias for $\log(k_e)$,
- **Reduction** of the dispersion of relative bias,
- **Limited gain** to the passage of **3 to 2 patients**,
- The **less** patients by cohort**,** the **faster** the **adaptation.**





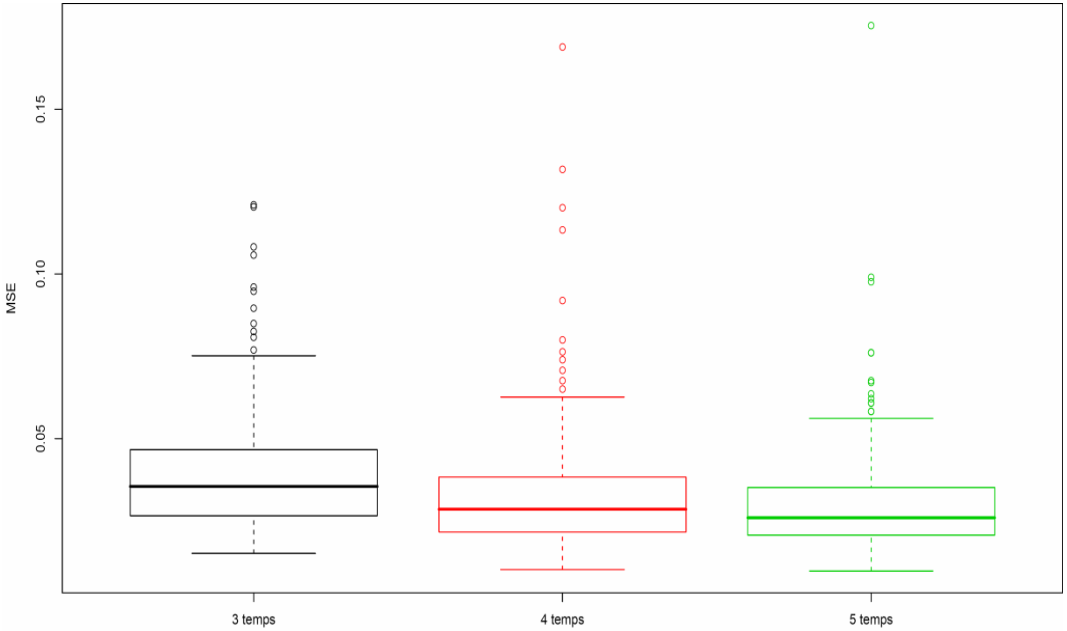
Influence of the number of sampling time:

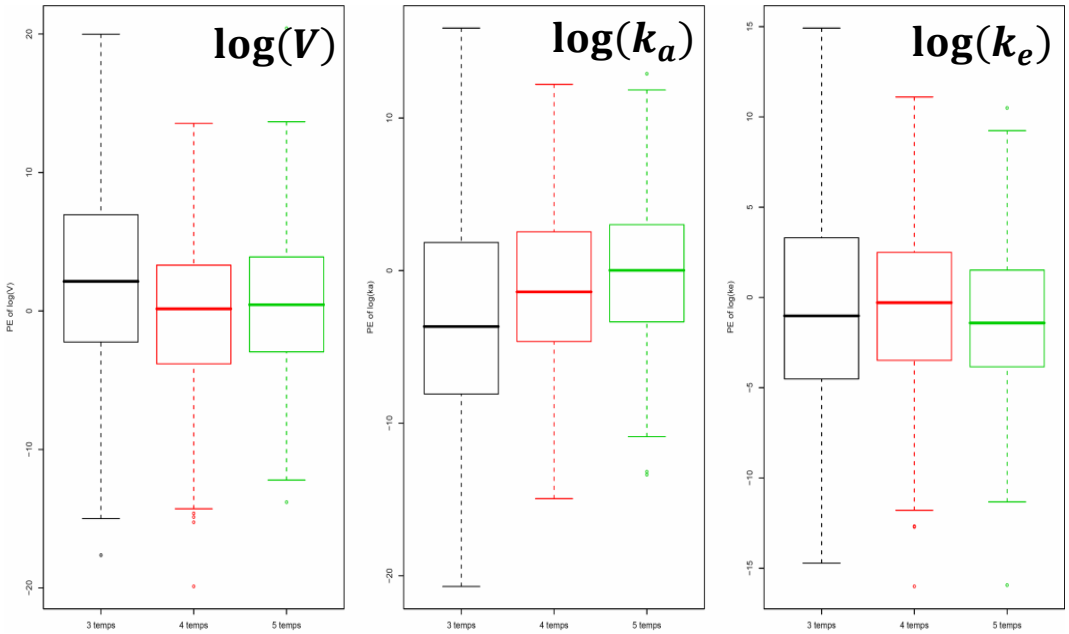
Configuration:

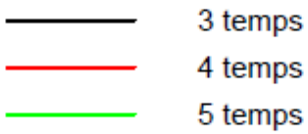
- 2 patients per cohort,
- 6 cohorts,
- 3, 4 & 5 sampling time.

Results:

- **Reduction** of the relative bias for $\log(k_a)$,
- Reduction of the dispersion of the bias,
- **Gain** for the passage of **4 to 5 times**.







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When a priori are wrong

BAST design with 12 patients provides parameter estimates more accurate (less bias, more precision) than a fixed design with 12 patients.

When a priori are right

BAST design with 12 patients provides parameter estimates as accurate than a fixed design with 12 patients.

How are you sure about a priori information?

Adaptive Design, in particular "sampling-times" adaptive design provides PK/PD models with **accurate "fit-for-purpose" estimates**.
Accurate estimates permit **better predictions** and therefore **more accurate dose and regimen optimization**.

[1] Sylvie Retout and France Mentré, Optimization of Individual and Population Designs using Splus, Journal of Pharmacokinetics and Pharmacodynamics, **30**:417-443 (2003)

[2] Sylvie Retout, Emmanuelle Comets, Adeline Samson and France Mentré, Design in nonlinear effects models: Optimization using the Fedorov-Wynn algorithm and power of the Wald test for binary covariates, Statistics in Medicine, **26**:5162-5179 (2007)

[3] Aristides Dokoumetzidis and Leon Aarons, Propagation of population pharmacokinetic information using a bayesian approach: comparison with meta-analysis, Journal of Pharmacokinetics and Pharmacodynamics, **32**:401-418 (2005)