Comparison of different tools for the optimization of a pediatric clinical trial

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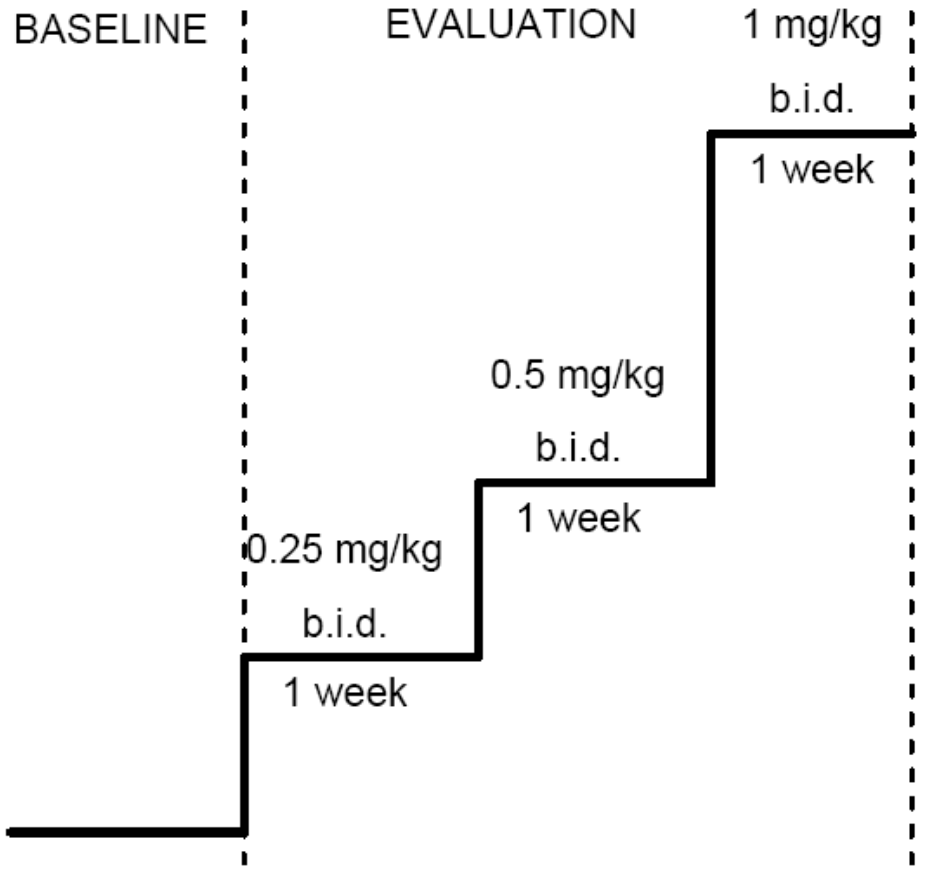
The pediatric clinical trial

- Objective of the trial:

  Characterize the steady-state pharmacokinetics (PK) of a drug under development in children aged 1 month to 16 years old

- Design
  - a fixed 3-step dose up-titration study
  - B.i.d. doses
  - 48 patients:
    - 1 month-2 years: 12
    - 2 – 4 years: 12
    - 4 – 8 years: 6
    - 8 – 12 years: 6
    - 12 – 16 years: 6



The pediatric clinical trial

- Initial dose dependent on weight category

- PK samples constraints:
  - One visit per dose at the end of the treatment week;
  - No more than 2 PK samples per visit

Optimisation of the pediatric clinical trial

- Objective: optimise the times of the limited number of samples to reduce the compromise for the pediatric parameter estimation

- Optimal design tools employed:
  - PFIM version 3.0
  - POPT version 3.0
  - PopED version 2.08

Rapid overview of the optimisation tools

	PFIM3.0	POPT3.0	PopED2.08
Optimisation	D-optimal	D-optimal ED-optimal	D-optimal ED-optimal
Algorithm	Simplex (continuous time) Federov-Wynn (discrete time)	Exchange & Simulated annealing (continuous & discrete times)	Random search & Stochastic gradient & Line search (continuous) Modified Fedorov Exchange Algorithm (discrete)
Interface	Yes	Yes (limited)	Yes (limited)
Language	R (freeware)	Matlab or Stand-Alone version (limited)	Matlab
Developers	INSERM, University Paris 7 (S.Retout & F.Mentré)	University of Otago, University of Queensland, J&J (S.Duffull)	Uppsala University (A. Hooker, J. Nyberg)

Common major assumption

- The PK is assumed to follow a population PK model built with **adult** data, in particular:

$$\mathrm{Ka}\left[\mathrm{h}^{-1}\right] = \theta_{Ka} \times \exp\left(\eta_{\mathrm{Ka}}\right) \quad \text{where } \theta_{\mathrm{Ka}} = 0.902$$

$$\mathrm{CL/F}\left[\mathrm{L/h}\right] = \theta_{\mathrm{CL}} \left(\frac{\mathrm{WT}}{69}\right)^{0.75} \times \exp\left(\eta_{\mathrm{CL}}\right) \quad \text{where } \theta_{\mathrm{CL}} = 3.63$$

$$\mathrm{V/F}\left[\mathrm{L}\right] = \theta_{\mathrm{V}} \left(\frac{\mathrm{WT}}{69}\right) \times \exp\left(\eta_{\mathrm{V}}\right) \quad \text{where } \theta_{\mathrm{V}} = 35.9$$

Variances of $\eta_{\mathrm{Ka,CL,V}} = 0.611;\ 0.0575$ and 0.0150

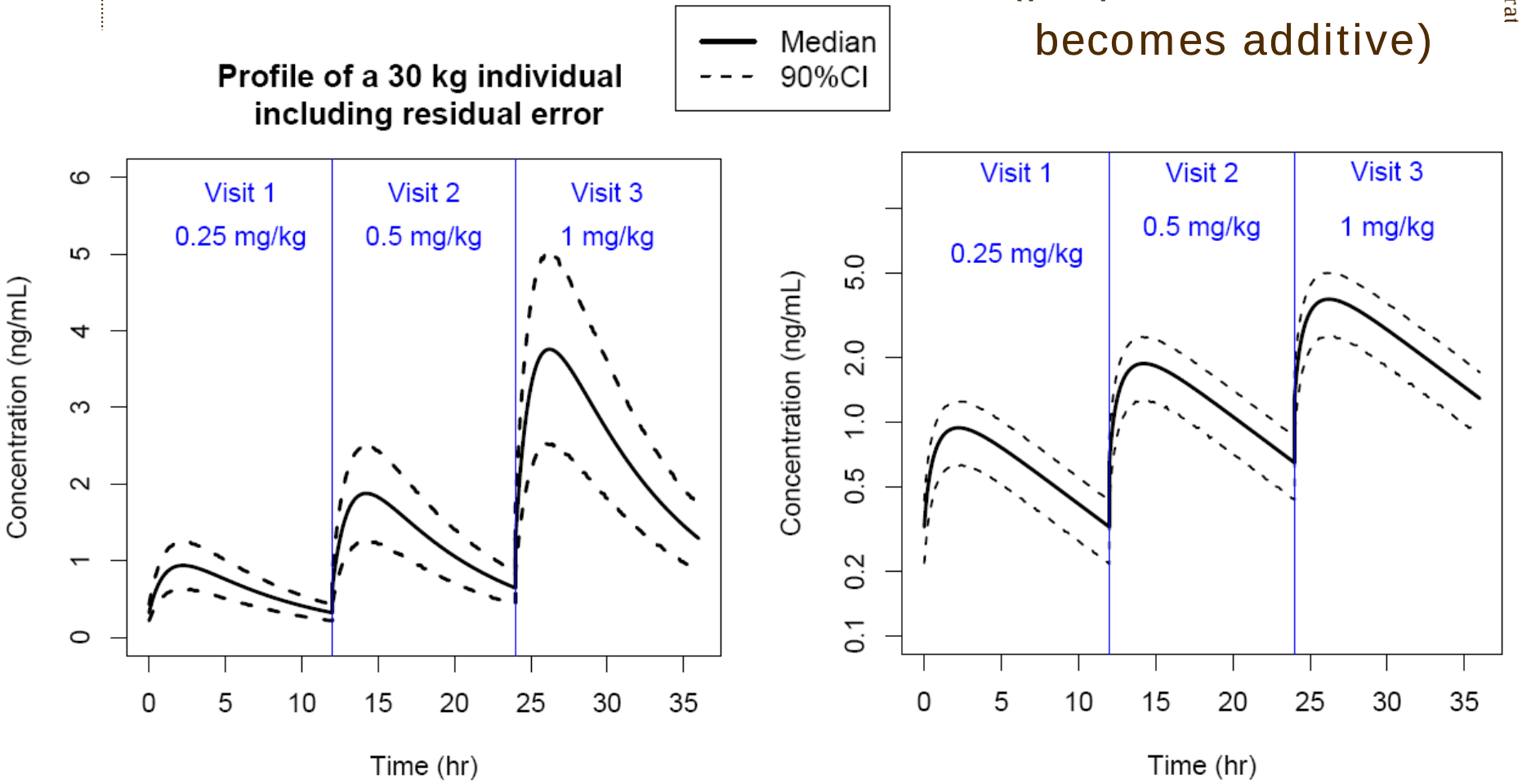
Proportional error with variance 0.0402

Time-Concentration equations

Linear scale

Logarithmic scale

(proportional error becomes additive)

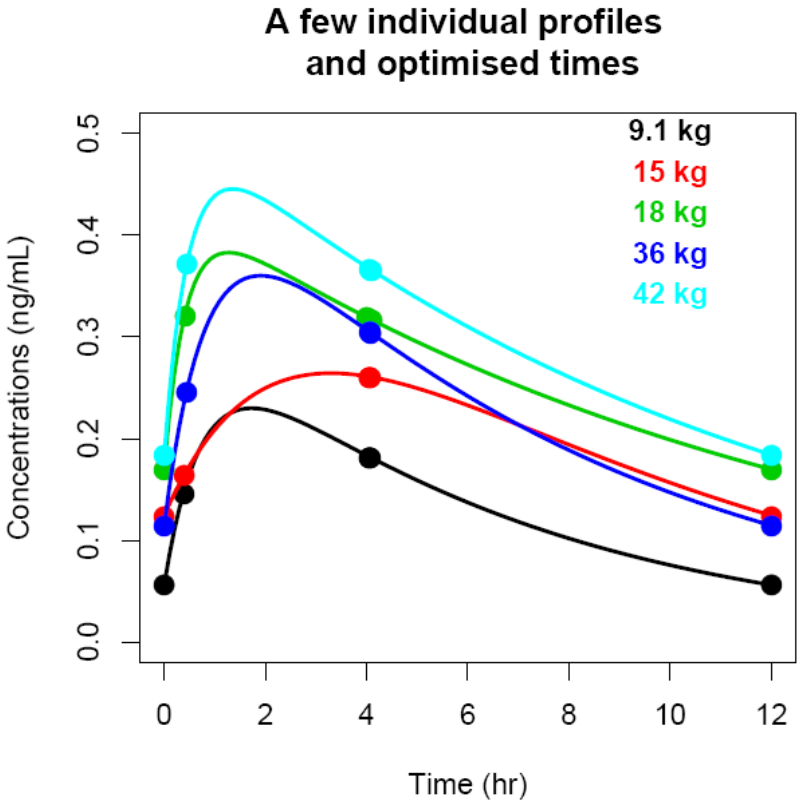


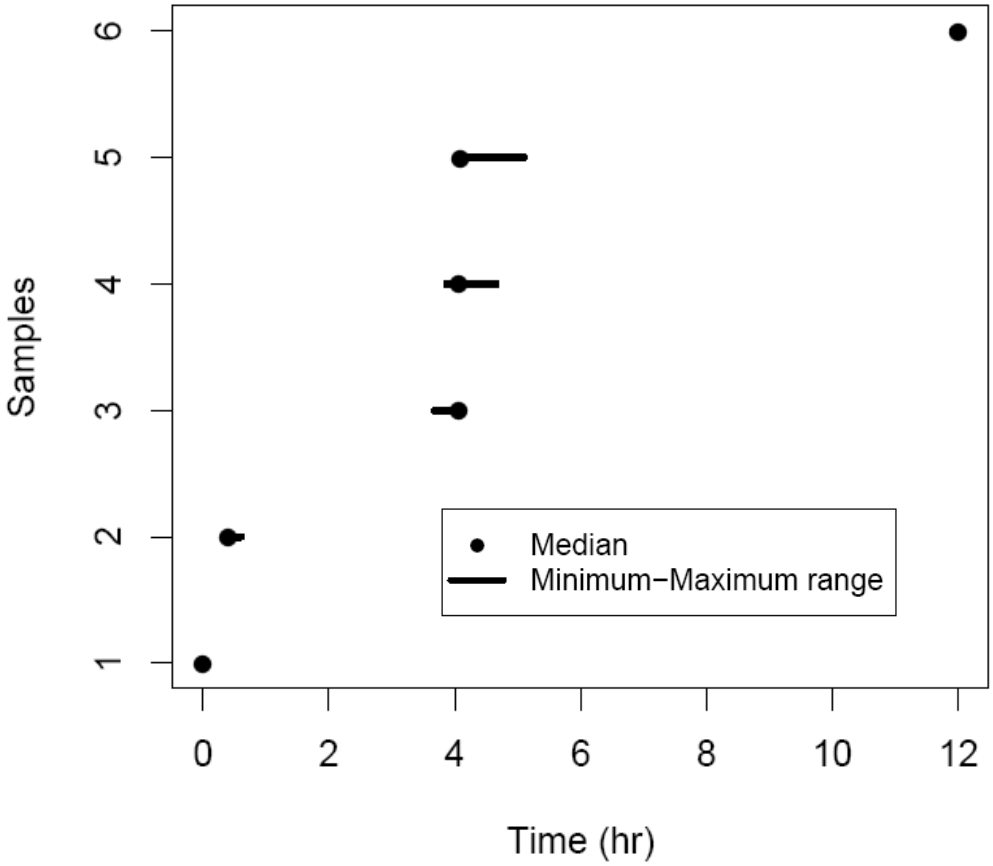
Comparison of problem implementation and output

	PFIM	POPT	POPED
Up-titration	Log-transformation	Fix dose for each sampling time	Log-transformation
Weight-dependent PK	Optimise individual sampling times	5 age groups with 3 competing models – each corresponding to 5th,50th and 95th quantile weights	5 age groups with a uniform weight distribution between minimum and maximum weights
Outcome	Intervals of optimised times over a large population	• Optimised times; • Expected parameter precision for the « median » and extreme populations	• Optimised times; • Expected parameter precision of the clinical trial

Outcome in PFIM

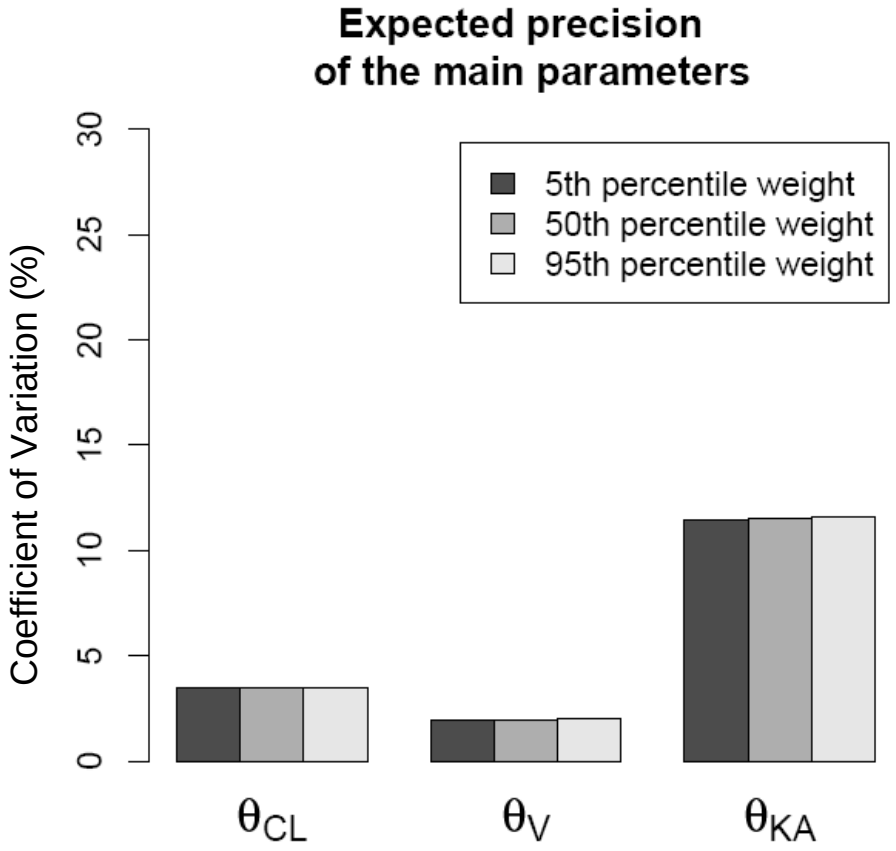
- Outcome
  - Intervals of optimised sampling times over a large population… but no information on expected parameter precision

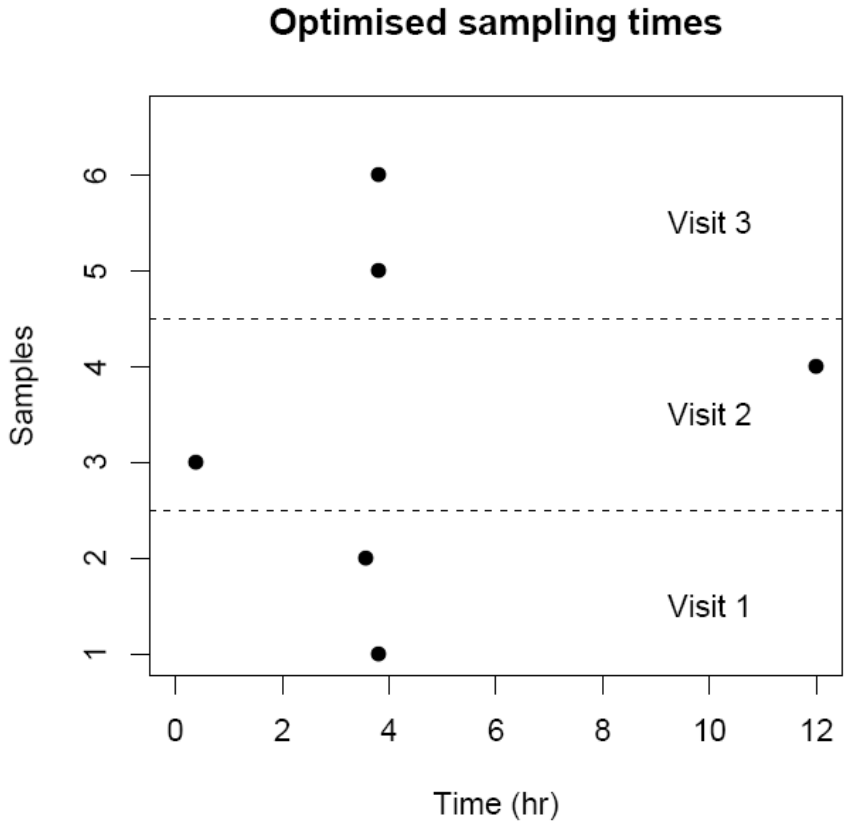




Outcome in POPT

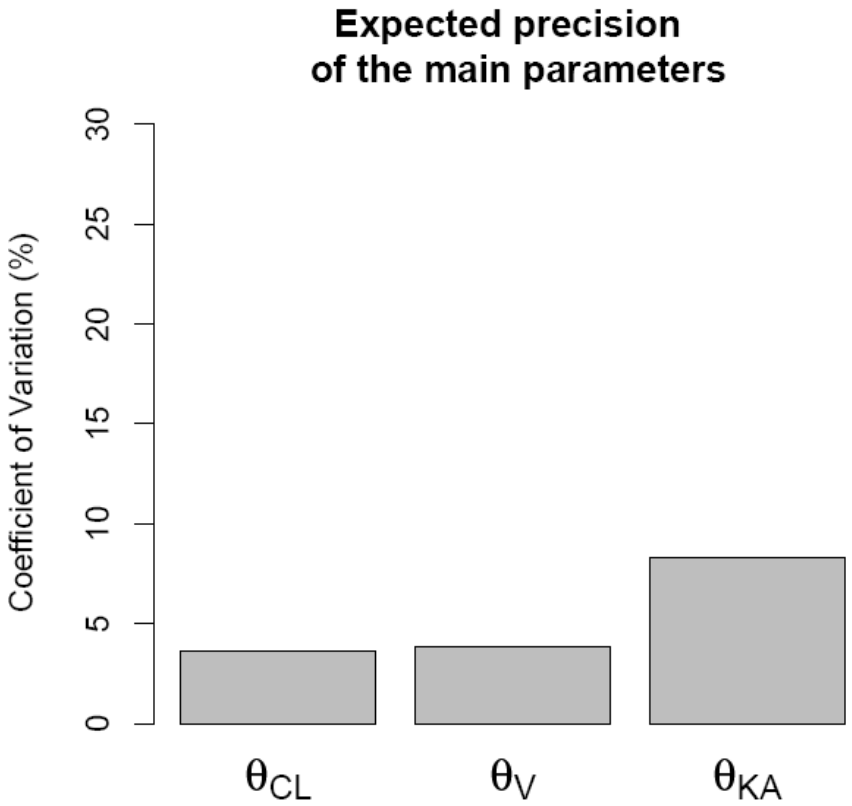
- Outcome
  - Overall 6 sampling times;
  - Expected precision of the parameters for each model

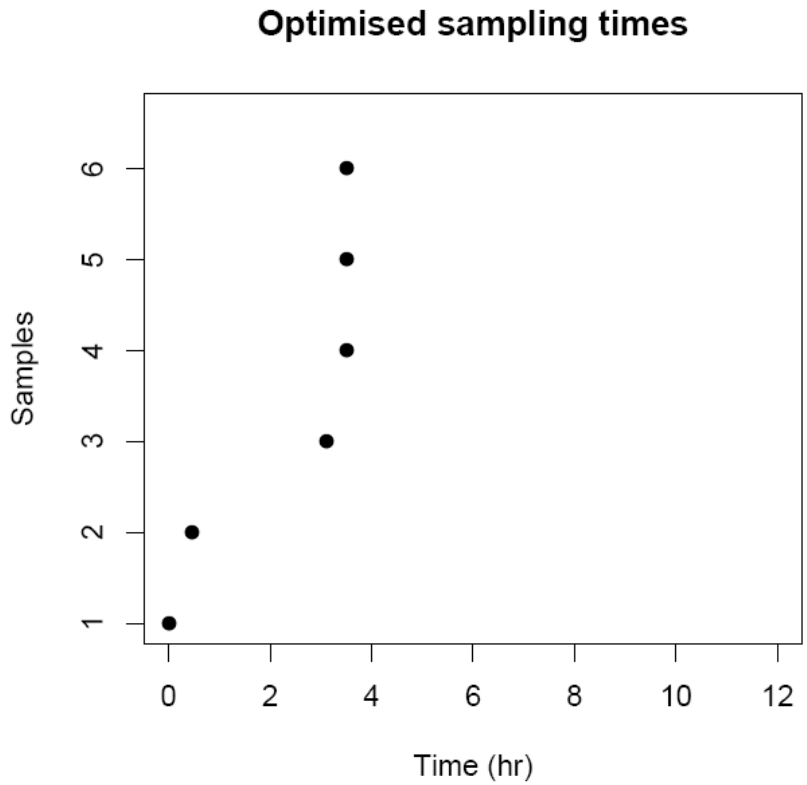




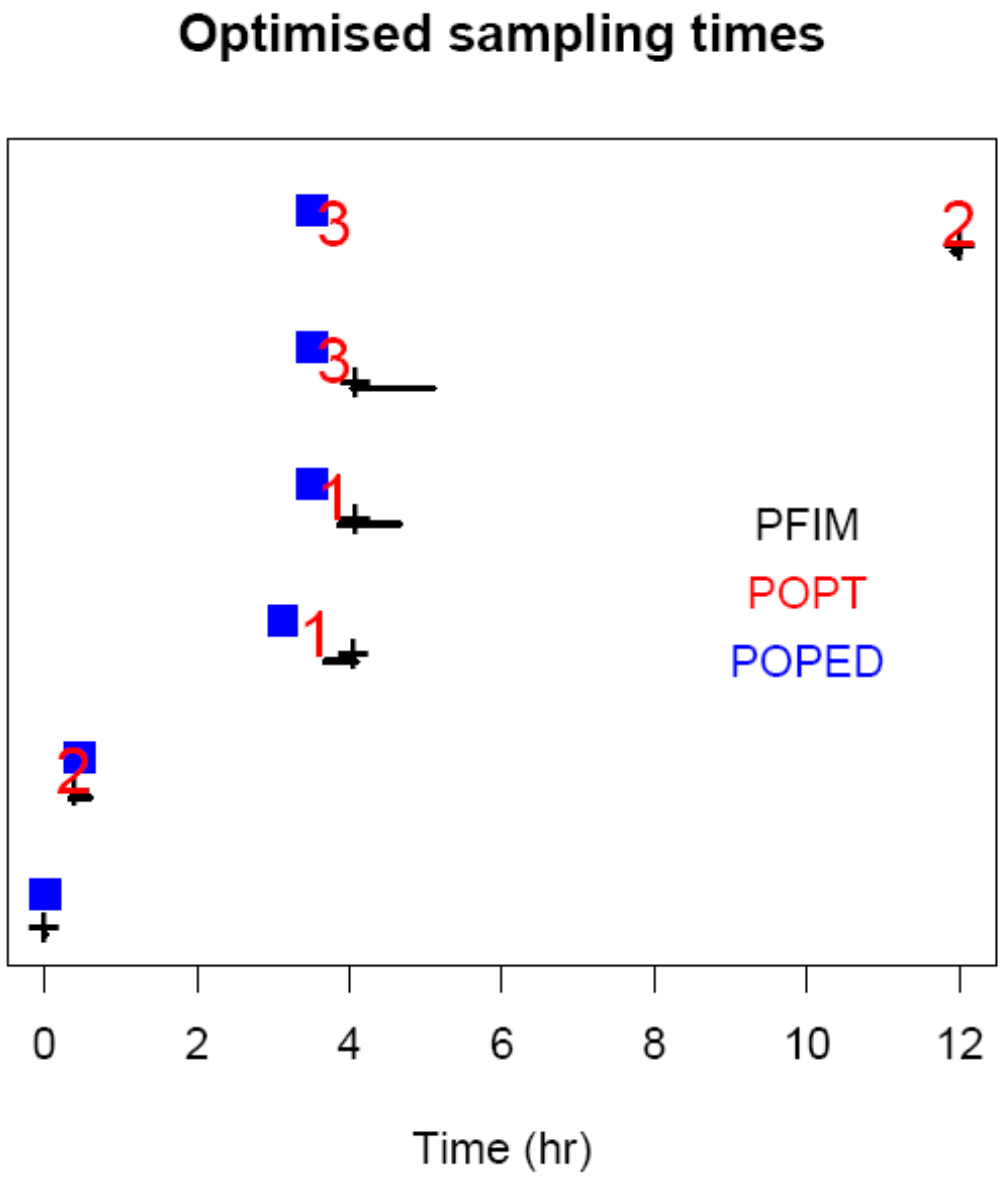
Outcome in POPED

- Outcome
  - Overall 6 sampling times;
  - Expected precision of the parameters of the trial

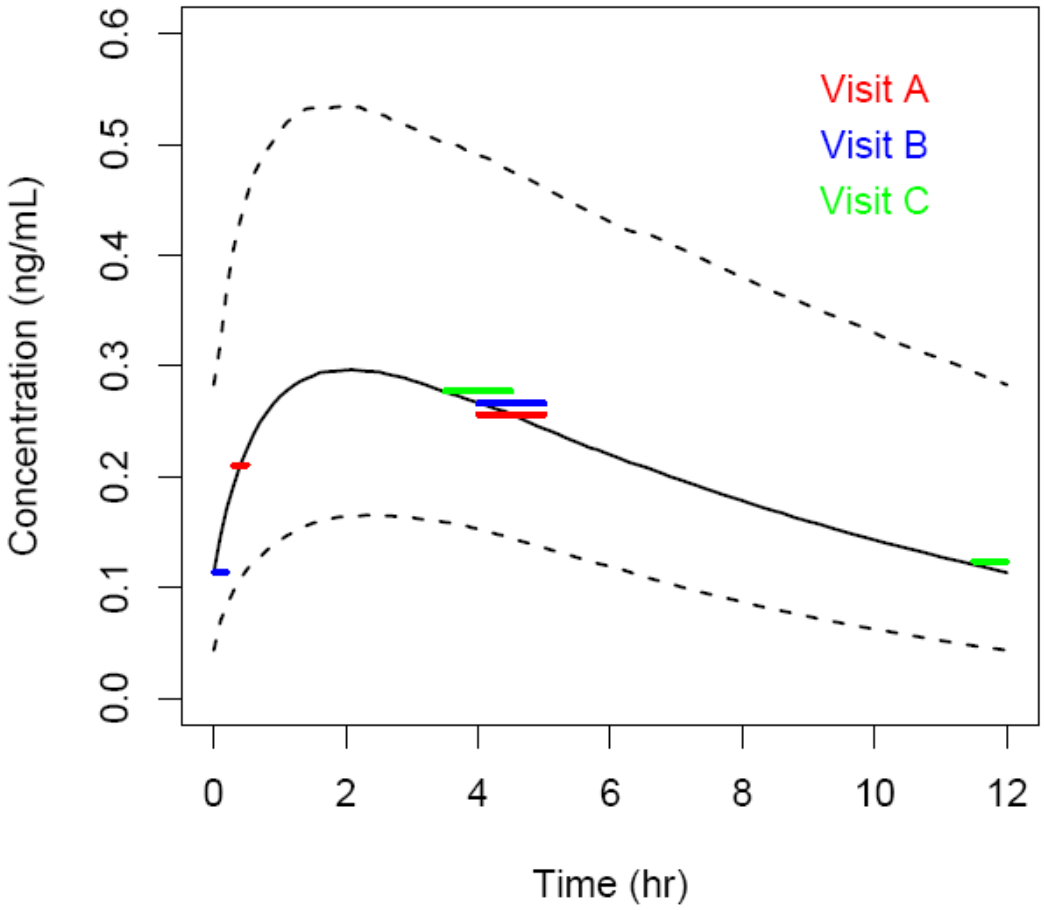




Comparison of the results



Design retained



Visit	Sampling times
A	0.3-0.5hr 4-5 hr
B	Postdose (0-0.2 hr) 4-5 hr
C	Predose (11.5-12hr) 3.5-4.5 hr

Times for visits 1, 2, 3:

A-B-C for 1/6th of the patients
A-C-B for another 1/6th patients
B-A-C for another 1/6th patients
B-C-A for another 1/6th patients
C-A-B for another 1/6th patients
C-B-A for another 1/6th patients

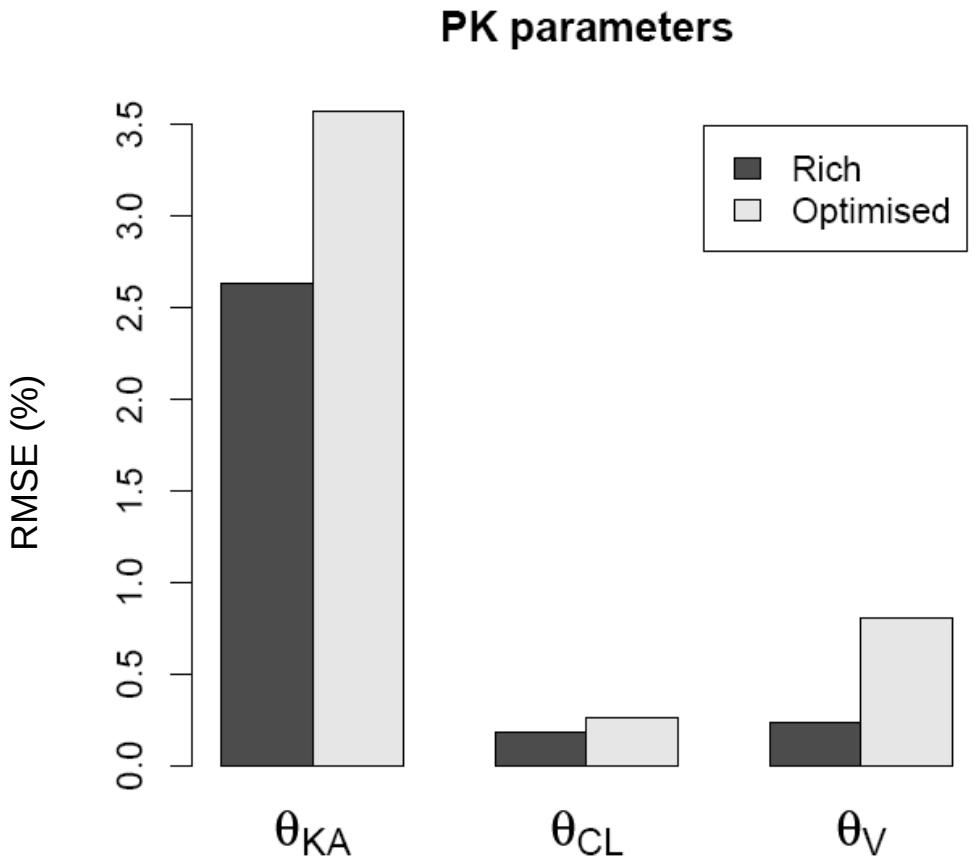
Evaluation of the design

- Methodology
  - Simulated a large number of trials;
  - Evaluated the parameters with NONMEM;
  - Compared the estimated parameters with the « true » parameters used for the simulation;
  - Calculated RMSE values (see Hooker et al, 2003)

$$\mathrm{RMSE} = \frac{1}{\theta_k^{\mathrm{TRUE}}} \sqrt{\left[\frac{1}{N} \sum_{i=1}^{N} \left(\theta_{k,i} - \theta_k^{\mathrm{TRUE}} \right)^2 \right]} \times 100\ (\%)$$

Evaluation of the design

- Rich sampling profile: 7 samples per visit (0,0.25,0.5,1,3,6,12), i.e. 21 samples per subject



Conclusions

- The main differences between the 3 optimising tools are:
  - the implementation of the problem
  - the outputs
- The sampling times optimised by the 3 different tools were similar for this case;
- However, the optimised design is very much dependent on the assumed PK profile….

Acknowledgement

- Steve Duffull
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