

C. PETIT<sup>1</sup>, V. JULLIEN<sup>2</sup>, A. SAMSON<sup>3</sup>, J. GUEJ<sup>4</sup>, J-R KIECHEL<sup>5</sup>, S. ZOHAR<sup>1</sup>, E. COMETS<sup>4,6</sup>

<sup>1</sup>INSERM, UMRS 1138, CRC, Team 22, Univ. Paris Descartes, Univ. Pierre et Marie Curie, Paris, France; <sup>2</sup>Pharmacology Dept., Univ. Paris Descartes, Sorbonne Paris Cité, Inserm U1129, HEGP, Paris, France; <sup>3</sup>Lab. Jean Kuntzmann, UMR CNRS 5224, Univ. J. Fourier, Grenoble, France; <sup>4</sup>INSERM, IAME, UMR 1137, Univ. Paris Diderot, Sorbonne Paris Cité, Paris, France; <sup>5</sup>Drugs For Neglected Diseases Initiative, 15 chemin Louis-Dunant, 1202 Geneva, Switzerland <sup>6</sup>INSERM, CIC 1414, Univ. Rennes 1, Rennes, France;

## CONTEXT

Designing studies in paediatrics is often a challenge. Poor choices of sampling time (design) can jeopardize the estimation of pharmacokinetics (PK) parameters and later, the estimation of the appropriate dose. In the paediatric population, where samples are often sparse, finding the appropriate design is essential to complete a trial successfully. In this work, **we design a pharmacokinetic (PK) study using adult prior information and evaluate the robustness of the recommended design.**

## CASE-STUDY

Mefloquine (MQ) is a drug used in treatment of malaria. The case-study included PK data for MQ from two clinical trials in patients treated with combination of mefloquine and artesunate.

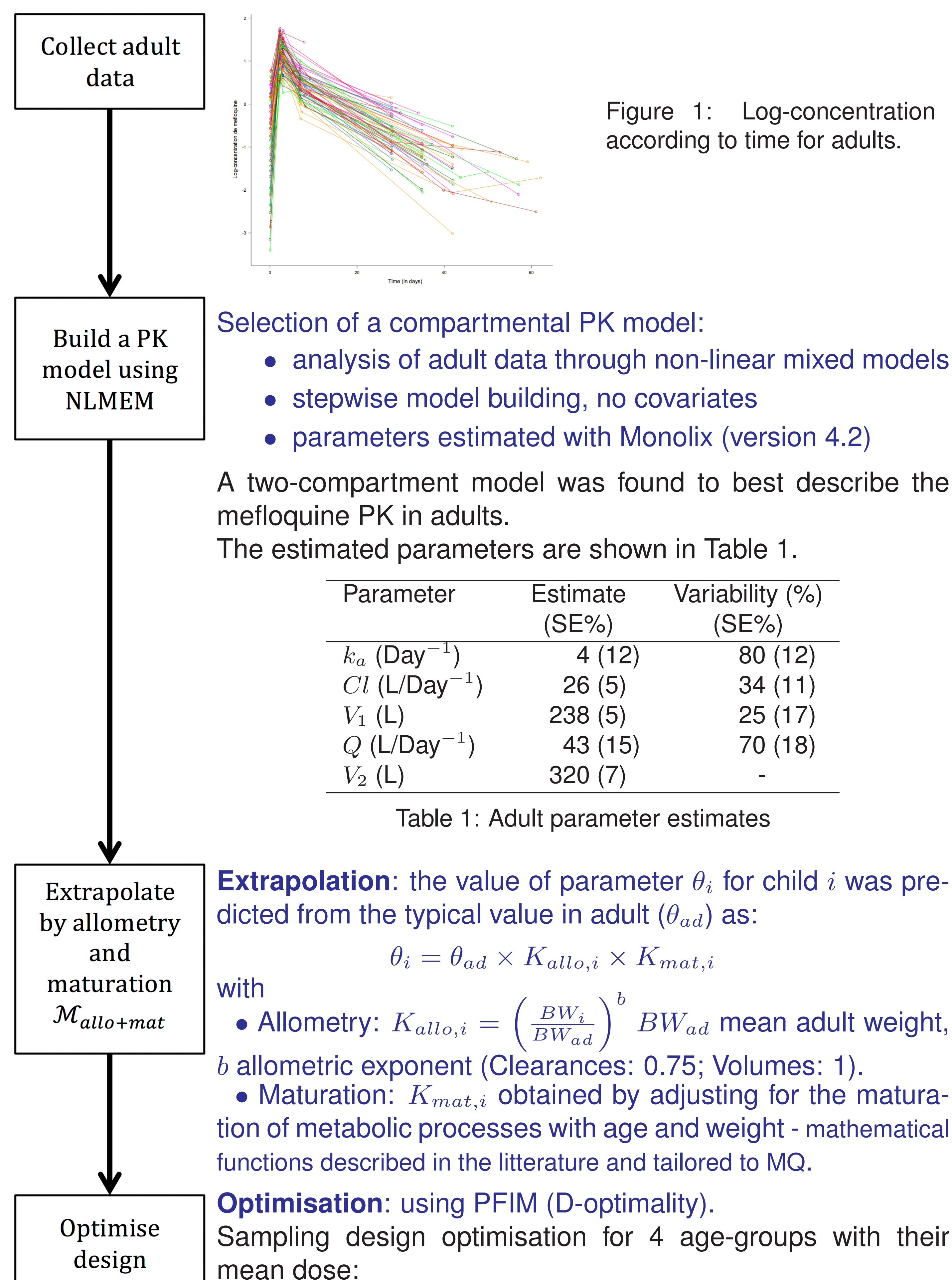
### Adults

- India
- 77 patients
- Fixed-dose(200 mg of MQ and 100 mg Artesunate per day for 3 days)
- 4 to 5 concentrations

### Children

- Thailand
- 101 patients
- Adjusted on weight (25 mg/kg of MQ split over 2 to 3 days + 4 mg/kg/day of Artesunate during 3 days)
- 2 to 3 concentrations

## FRAMEWORK FOR DESIGN OPTIMISATION IN PAEDIATRICS



⇒ Optimal Design for the paediatric study: 0.1, 1, 5, 14, 57

## EVALUATION OF THE DESIGNS

Comparison of the optimal design with the empirical design from the actual paediatric study.

Simulations under 4 different models to assess the robustness (Figure 2):

- 100 simulated datasets under both designs (empirical and optimal design).
- Comparison of estimated population parameters with simulated values.

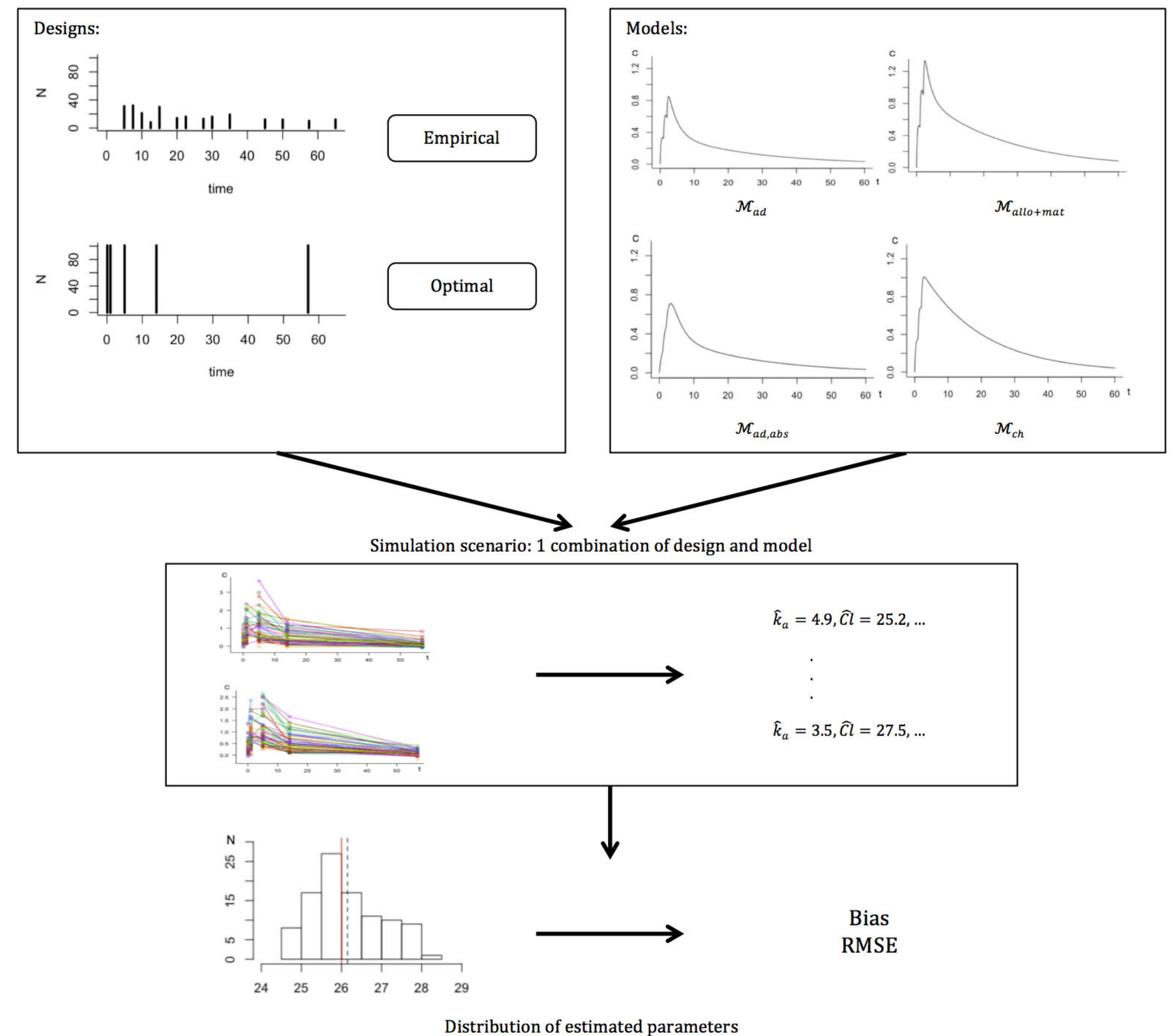


Figure 2: Schema of simulation study. Models:  $\mathcal{M}_{ad}$  (adult model),  $\mathcal{M}_{allo+mat}$  (model with allometry and maturation),  $\mathcal{M}_{ad,abs}$  (adult model with a modified absorption  $k_a = 1 \text{ day}^{-1}$ ),  $\mathcal{M}_{ch}$  (model built from adult data alone).

The optimal design yielded very low bias and empirical RSE (Table 2). Absorption was poorly estimated with the empirical design. The optimal design was more robust across all 4 models tested (not shown).

| Model                    | Parameters                  | Values | Optimal design (RSE) | Initial design (RSE) |
|--------------------------|-----------------------------|--------|----------------------|----------------------|
| $\mathcal{M}_{allo+mat}$ | $k_a$ (Day <sup>-1</sup> )  | 4.16   | 7.90                 | 486.60               |
|                          | $Cl$ (L/Day <sup>-1</sup> ) | 26.00  | 2.67                 | 3.72                 |
|                          | $V_1$ (L)                   | 248.00 | 4.39                 | 10.82                |
|                          | $Q$ (L/Day <sup>-1</sup> )  | 41.60  | 9.86                 | 21.78                |
|                          | $V_2$ (L)                   | 282.00 | 4.98                 | 7.13                 |
|                          | $\omega_{k_a}$ (sd)         | 0.81   | 8.10                 | 34.97                |
|                          | $\omega_{Cl}$ (sd)          | 0.34   | 5.66                 | 8.11                 |
|                          | $\omega_{V_1}$ (sd)         | 0.25   | 11.45                | 29.94                |
|                          | $\omega_Q$ (sd)             | 0.70   | 15.37                | 20.71                |
|                          | $k_a$ (Day <sup>-1</sup> )  | 4.16   | 10.23                | 50.28                |
|                          | $Cl$ (L/Day <sup>-1</sup> ) | 14.30  | 5.54                 | 7.32                 |
|                          | $V$ (L)                     | 263.00 | 5.43                 | 7.81                 |
| $\mathcal{M}_{ch}$       | $\omega_{k_a}$              | 0.81   | 14.36                | 53.87                |
|                          | $\omega_{Cl}$               | 0.63   | 8.69                 | 8.80                 |
|                          | $\omega_V$                  | 0.66   | 6.93                 | 10.43                |
|                          |                             |        |                      |                      |

Table 2: Validation of optimal design, results for  $\mathcal{M}_{allo+mat}$  and  $\mathcal{M}_{ch}$ .

## CONCLUSION

- The present work supports using adult prior information to design studies in paediatrics. Optimal design methodology combined with allometry and maturation allowed determination of sampling schedules appropriate for children.
- Extrapolation could be improved with alternative methods such a model combining both PBPK models and maturation functions. - C. Knibbe *et al.* [1]
- Different design optimisation methods might be suggested to improve robustness (e.g. ED-optimality) - M. Dodds, A. Hooker and P. Vicini [2]

**Acknowledgment:** we thank the University Sorbonne Paris Cité for supporting this project through a grant IDEX (2013, project 24).

[1] De Cock R., Allegaert K., Sherwin C., Nielsen E., de Hoog M., van den Anker J., Danhof M., and Knibbe C. A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm. Res.*, 31:754-767, 2014.

[2] Dodds M., Hooker A., and Vicini P. Robust population pharmacokinetic experiment design. *J. Pharmacokinet. Pharmacodyn.*, 32:33-63, 2005.

[3] Anderson B.J. and Holford N.H.G. Mechanistic basis of using body size and maturation to predict clearance in humans. *Drug. Metab. Pharmacokinet.*, 24:25-36, 2009.