# Design evaluation and optimisation in multi-response nonlinear mixed effect models with cost functions:

## Application to the pharmacokinetics of zidovudine and its active metabolite

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# Design in nonlinear mixed effects models (NLMEM)

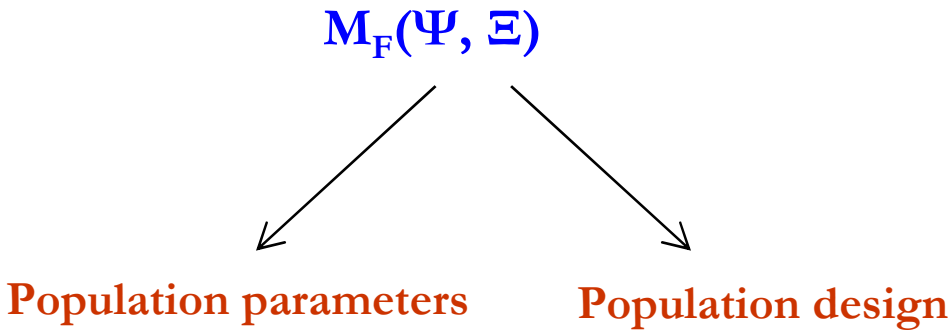
- Importance of the choice of the design
  - **Influence the precision of parameter estimation**
  - **Few samples per patient → informative samples**

- Balance
  - **Number of patients / number of samples per patient**
  - **Allocation in time**

- Important task for pharmacologists
  - **To evaluate and compare different designs**
  - **And /or to optimise a design**
    - Clinical constraints
    - Total number of sampling times
    - …

# Approach for design evaluation and optimisation (1)

- Fisher information matrix :




- No analytical expression of $M_F$ for NLMEM
  - **Single response model**
    - Linearisation of the model using a first order Taylor expansion around the expectation of the random effects[1]
    - Good properties of this approach shown by simulation[2]


1. Mentré F, Mallet A, Baccar D. *Biometrika*, 1997
2. Retout S, Mentré F, Bruno R. *Statistics in Medicine*, 2002

# Approach for design evaluation and optimisation (2)

- Extension of $M_F$ for multiple response model[1, 2]
  - **Same method as for a single response model**
  - **Complete matrix :**

$$M_F(\Psi,\Xi) \cong \begin{bmatrix} M_F(\beta,\Xi) & C \\ C & M_F(\Omega,\sigma,\Xi) \end{bmatrix}$$

– $\beta$ fixed effects, $\Omega$ variance of random effects, $\sigma$ parameters of error model

- Implementation in different softwares[3]
  - **Only one in R: PFIM**[4]


1. Hooker A, ViciniP, *The American Association of Pharmaceutical Scientists Journal*, 2005
2. GueorguievaI I et al. Journal of Pharmacokinetics and Pharmacodynamics, 2006
3. Mentré F et al. 16th Population Approach Group in Europe, 2007 (Abstr 1179)
4. www.pfim.biostat.fr

# Approach for design evaluation and optimisation (2)

- Extension of $M_F$ for multiple responses[1, 2]
  - **Same method as for a single response model**
  - **Block diagonal matrix :**
    - Assumption of independence between the variance of the observations and the fixed effects

$$M_F(\Psi,\Xi) \cong \begin{bmatrix} M_F(\beta,\Xi) & 0 \\ 0 & M_F(\Omega,\sigma,\Xi) \end{bmatrix}$$

    - $\beta$ fixed effects, $\Omega$ variance of random effects, $\sigma$ parameters of error model

- Implementation in different softwares[3]
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# Objectives

1. Evaluation of the expression of the Fisher information matrix for multiple response models
2. Design optimisation with cost functions
3. PFIM extensions
4. Application to the joint pharmacokinetic modelling of zidovudine and its active metabolite

# I. Evaluation of the Fisher information matrix for multiple response models

# Evaluation by simulation (1)

- PK model

$$f_{PK}(\theta_{PK},\xi_{PK}) = \frac{Dose}{V} \times \exp(-\frac{Cl}{V} \times \xi_{PK})$$

  - $\theta_{PK}$ : Cl et V
  - **Proportional error model**

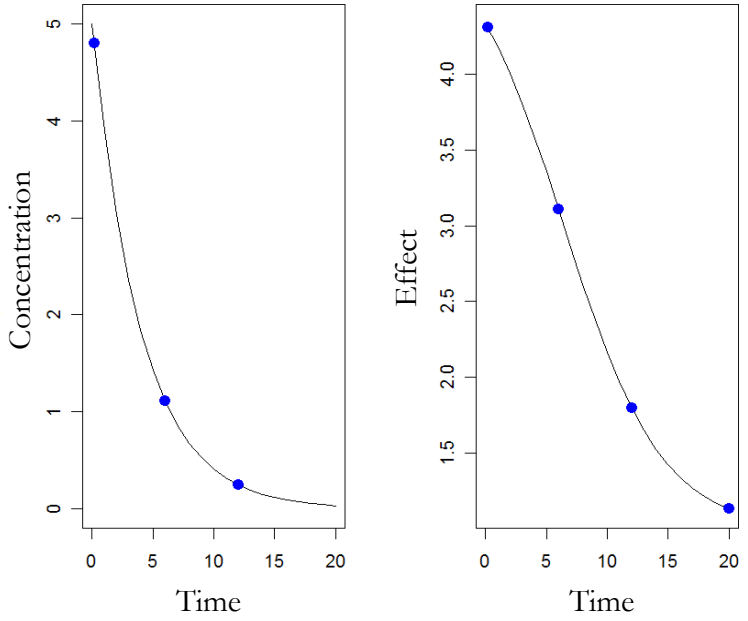
- PD model

$$f_{PD}(\theta_{PK},\theta_{PD},\xi_{PD}) = E_0 + \frac{E_{\max} \times f_{PK}(\theta_{PK},\xi_{PD})}{C_{50} + f_{PK}(\theta_{PK},\xi_{PD})}$$

  - $\theta_{PD}$ : $E_0$ , $E_{max}$ et $C_{50}$
  - **Additive error model**

- Population design
  - $\xi_{PK} = \{0.166, 6, 12\}$
  - $\xi_{PD} = \{0.166, 6, 12, 20\}$
  - N= 100

$$\Xi = \{[(\xi_{PK},\xi_{PD}), N]\}$$

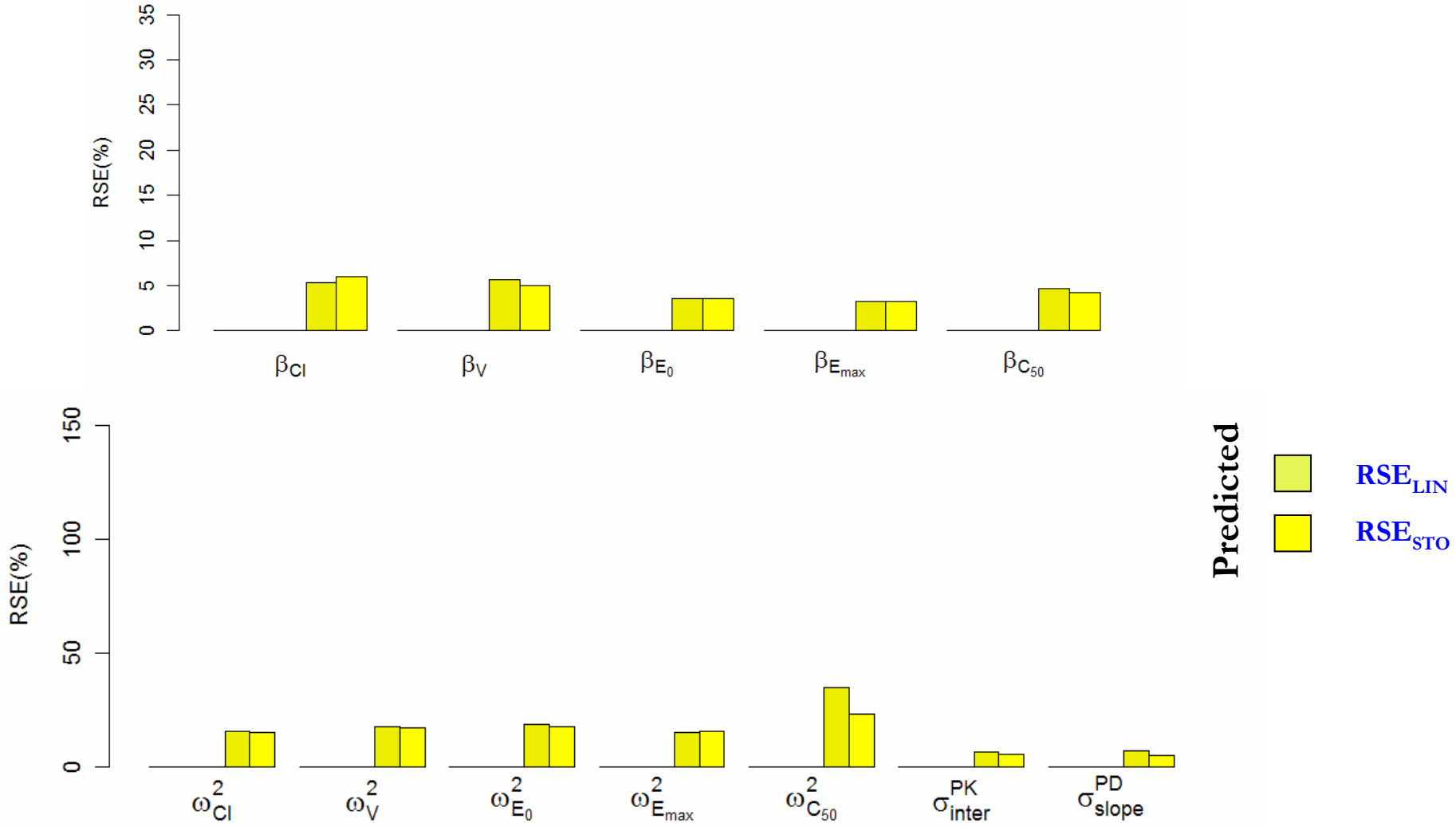


# Evaluation by simulation (2)

- Evaluation of the standard errors (SE) predicted by linearisation
  - **Computation of the relative SE : $RSE_{LIN}$**
- SE predicted by a stochastic approach[1, 2] → without linearisation
  - **Simulation of one data set with 10000 individuals**
  - **Estimation with the SAEM algorithm (MONOLIX)[3, 4]**
    - $M_F$ observed on the data set of 10000 individuals → Louis method[5]
  - **Rescale of the RSE for 100 individuals : $RSE_{STO}$**


1. Retout S, Comets E, Samson A, Mentré F, *Statistics in Medicine,* 2007
2. Samson A, Lavielle M, Mentré F. *Statistics in Medicine*, 200
3. Khun E, Lavielle M. Computational *Statistics and Data Analysis*, 2005
4. http://www.monolix.org
5. Louis TA. *Journal of the Royal Statistical Société*, 1982

# Results - Predicted RSE (%)



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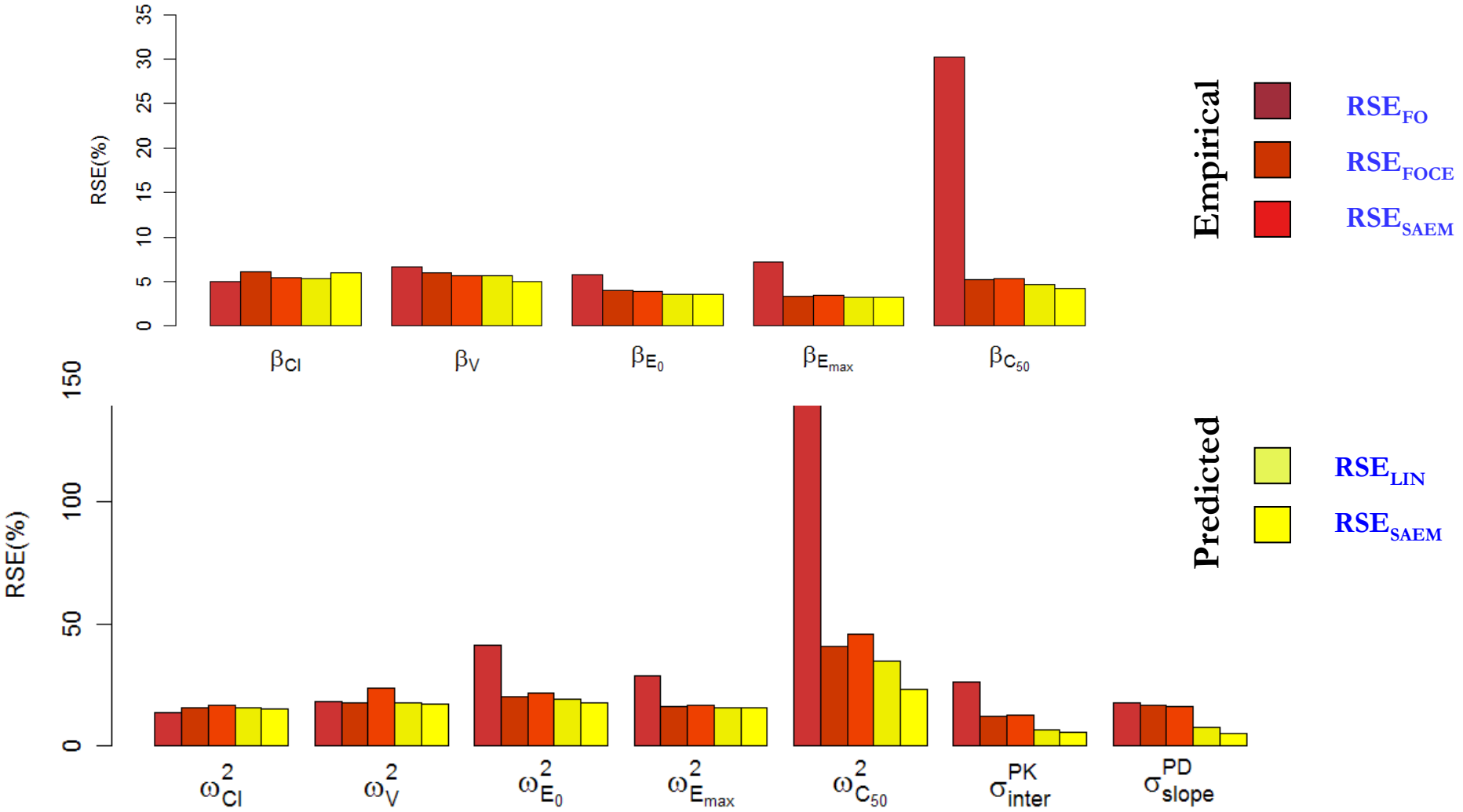
  - **Rescale of the RSE for 100 individuals : $RSE_{STO}$**

- Empirical RSE by an extensive simulation
  - **Simulation of 1000 data sets of 100 individuals**
  - **Estimation of the population parameters**
    - FO and FOCE (NONMEM V) → **$RSE_{FO}$ and $RSE_{FOCE}$**
    - SAEM (MONOLIX V2.1)[3,4] → **$RSE_{SAEM}$**
  - **Standard deviation of the parameter estimates**


1. Retout S, Comets E, Samson A, Mentré F, *Statistics in Medicine,* 2007
2. Samson A, Lavielle M, Mentré F. *Statistics in Medicine*, 200
3. Khun E, Lavielle M. Computational *Statistics and Data Analysis*, 2005
4. http://www.monolix.org
5. Louis TA. *Journal of the Royal Statistical Société*, 1982

# Results –Predicted and empirical RSE (%)




→ Bazzoli C, Retout S, Mentré F. ***Statistics in Medicine***. 2009

# II. Design optimisation with cost functions

# Design optimisation

- Maximisation of $M_F$
  - **D-optimality : maximisation of det($M_F$)**

- Population design $\Xi$
  - $N$ **individuals**
  - $Q$ **groups with** $N_Q$ **patients with a same elementary design** $\xi_q$

$$\Xi = \left\{ [\xi_1, N_1]; [\xi_2, N_2]; \ldots; [\xi_Q, N_Q] \right\}$$

- Optimisation based on the design theory
  - **Optimisation of the structure (statistical designs)**
    - $\alpha_q = \frac{N_q}{N}$
    - $\xi_q$

  → **Determination of** $Q$, $\alpha_q$, $\xi_q$

# Cost function

- Elementary design $\xi_q$ associated to the cost $C(\xi_q)$[1,2]
- Usual "cost function"
  - **Number of sampling times**

$$C\left(\xi_q\right) = n_q$$

- Other more complex cost functions
  - **Cost of an intracellular concentration assay**
  - **Cost of the addition of a new patient in the study**

1. Mentré F, Mallet A, Baccar D. *Biometrika*. 1997
2. Gagnon S, Leonov S. *Journal of Biopharmaceutical Statistics*. 2005

# Optimisation algorithm

- Constraint
  - **Total cost : $C_{tot}$**
  - **Possible sampling times**

$$C_{tot} = N\sum_{i=1}^{Q}\alpha_q C\left(\xi_q\right)$$

$$M_F\left(\Psi,\Xi\right) = N\sum_{q=1}^{Q}\alpha_q M_F\left(\Psi,\xi_q\right) = C_{tot}\sum_{q=1}^{Q} w_q \frac{M_F\left(\Psi,\xi_q\right)}{C\left(\xi_q\right)}$$

    - $w_q$ proportion of total cost attributed to the elementary design $\xi_q$

- Fedorov-Wynn algorithm [1, 2, 3]
  - **Specific to the optimisation of statistical designs**
    - Optimisation of both proportions $w_q$ and elementary designs $\boldsymbol{\xi_q}$
    - Deduction of the number of subject with $N_q = w_q \frac{C_{tot}}{C(\xi_q)}$ and $Q$
  - **Convergence to D-optimal design**

→ Retout S, Comets E, Bazzoli C, Mentré F. ***Communications in Statistics***. 2009


1. Fedorov V.V. *Theory of optimal experiments*. 1972
2. Wynn H.P. *Results in construction of D-optimum experimental designs*. 1972
3. Mentré F, Mallet A, Baccar D. *Biometrika*. 1997

# III. PFIM extensions

Single response model
**Multiple response models**

Analytical form
**Library of PK models**
**Differential equation system**

Simplex algorithm
**Fedorov-Wynn algorithm**
**($C(\xi_q)=n_q$)**

**PFIM 3.0**

Inter-subject variability

- April 2008, **Copyright © PFIM3.0 - *Caroline Bazzoli, Sylvie Retout, Emmanuelle Comets, France Mentré* - Université Paris Diderot- INSERM**

→ Bazzoli C, Retout S, Mentré F. ***Computer Methods and Programs in Biomedicine***. 2009

Single response model
Multiple response models

Analytical form
Library of PK models
Differential equation system
**Library of PD models**

Simplex algorithm
Fedorov-Wynn algorithm
($C(\xi_q)=n_q$)

**PFIM 3.2**

Inter-subject variability
**Inter-occasion variability[1]**

**Discrete covariates[1]**
**Power of the Wald test[1,2]**
**Number of subjects needed**
Comparison / equivalence tests

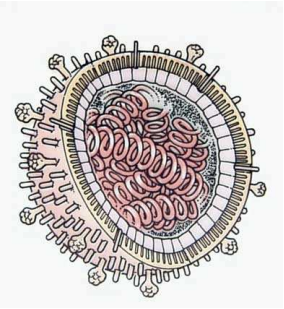
⇒ **Availability of both versions**

- January 2010. **Copyright © PFIM3.2 - *Caroline Bazzoli, Thu Thuy Nguyen, Anne Dubois, Sylvie Retout, Emmanuelle Comets, France Mentré* - Université Paris Diderot- INSERM**
  - **User guides (*examples*)**
  - **www.pfim.biostat.fr**

1. Retout S, Comets E, Samson A, Mentré F. *Statistics in Medicine*, 2007
2. Nguyen TT, Bazzoli C, Mentré F. *American Conference on Pharmacometrics*. 2009

# IV. Application to the joint pharmacokinetic modelling of zidovudine and its active metabolite

# AZT & AZT-TP



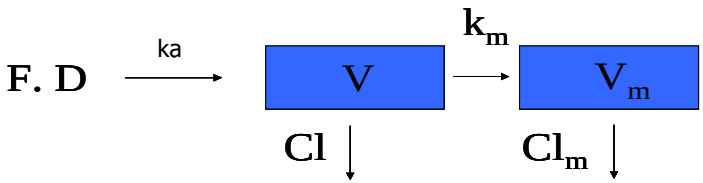
- Zidovudine or azidothymidine (ZDV or AZT)
  - **Antiretroviral drug**
  - **Nucleoside analog**
- Recommended by WHO as part of the treatment of HIV infection[1]
- Metabolism AZT in AZT-TP in the cell[2]
  - **Active metabolite AZT-TP**
    - Determinant of the toxicity and the efficacy of AZT
    - Complex and costly assay performed in few laboratories[3-4]


1. WHO Guidelines, http://www.who.int/hiv/pub/arv/advice/en/, 2009
2. Bazzoli et al. *Clinical Pharmacokinetics*, 2010
3. Becher F. et al. *Journal of Mass Spectrometry*, 2001
4. Pruvost A. et al. *Journal of Mass Spectrometry*, 2002

# Joint PK model of AZT and AZT-TP

- Data : clinical trial COPHAR2-ANRS 111[1]
  - **73 patients with AZT concentrations after 2 weeks of treatment**
    - Dose of 300 mg twice daily
    - Sampling times at 1, 3, 6 and 12 h after administration
  - **62 patients with AZT-TP intracellular concentrations**
    - Sampling times at 1, 3, 6 and 12 h after administration : 11 patients
    - Sampling times at 3 and 12 h after administration : 51 patients

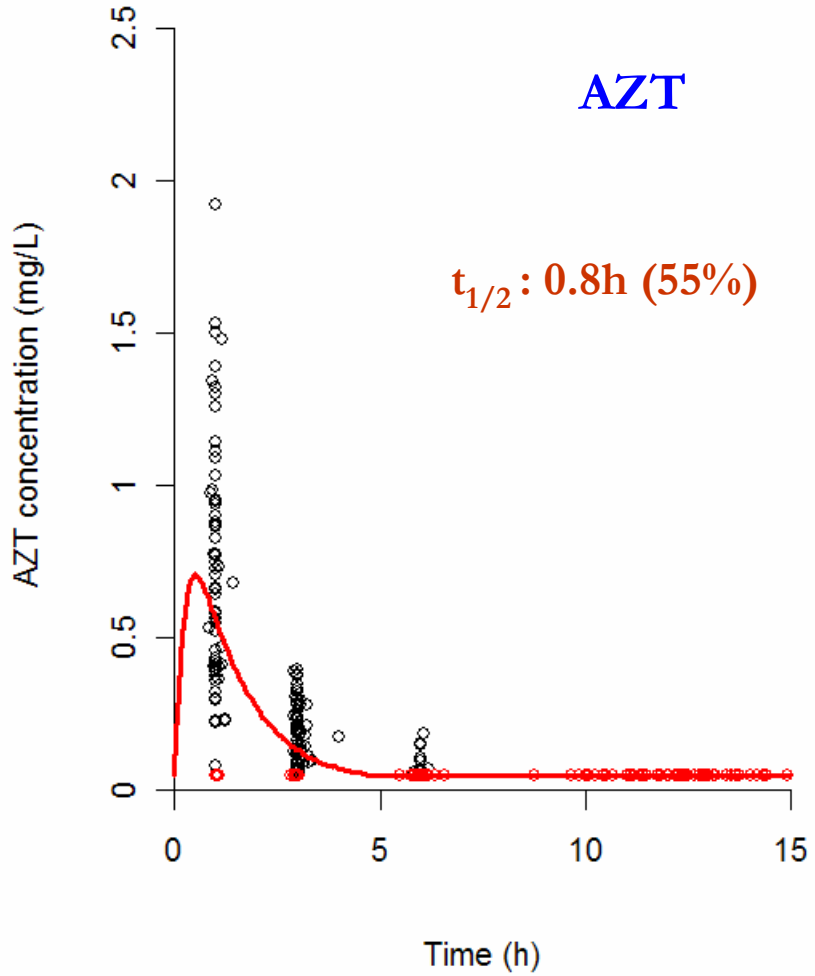
- Model

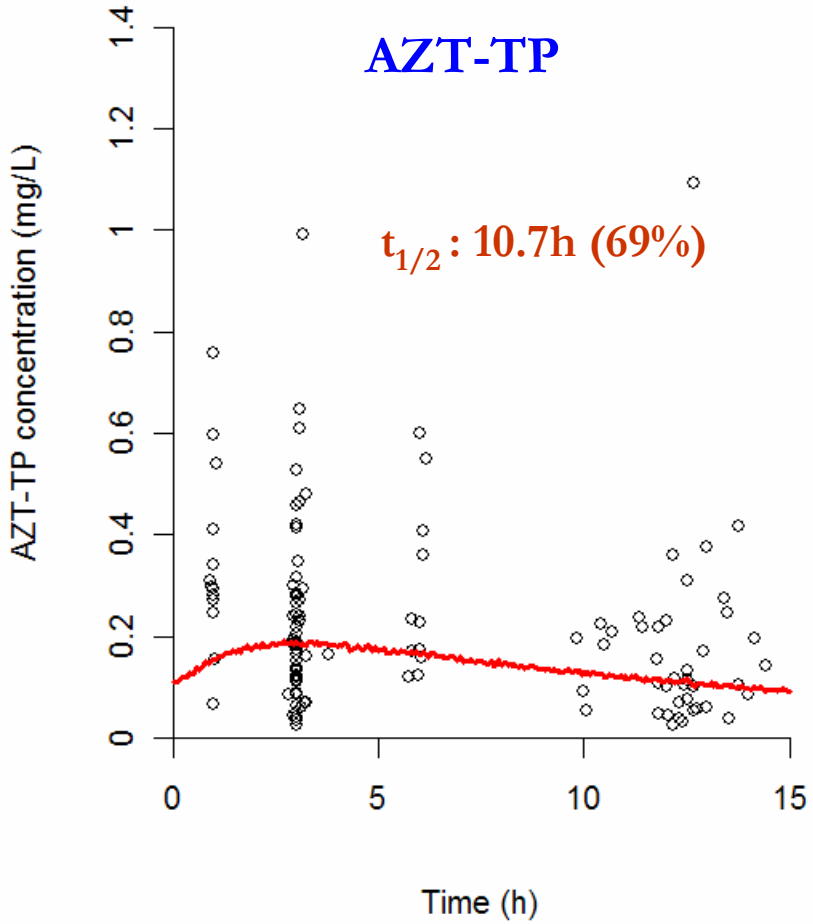



  - **Identifiable population parameters**
    - AZT : ka, Cl/F et V/F
    - AZT-TP : $Cl_m/(Fk_m)$ et $V_m/(Fk_m)$
  - **Estimation with the SAEM algorithm (MONOLIX V2.4[2])**

1. Duval X, Mentré F, Rey E et al. *Fundamental and Clinical Pharmacology*, 2009
2. www.monolix.org

# Observed data - Population curve[1]




° *Data under LOQ taken into account in the estimation step*

1. Bazzoli C et al.. *10th International Workshop on Clinical Pharmacology of HIV Therapy*, April 15-17, 2009, Amsterdam, The Netherlands. (Poster)

# Design optimisation : AZT / AZT-TP

- Use of the previous joint PK model
- Initial design
  - **50 patients with sampling times at 1, 3, 6 et 12 h for AZT et AZT-TP**
- Design optimisation for both responses with PFIM
  - **Total cost = 400**
  - **Usual « cost function » (= number of samples)**
    - Identical sampling times $\Rightarrow$ **$Opt_{iden}$**
    - Different sampling times $\Rightarrow$ **$Opt_{diff}$**

# Results – Number of samples

| | Sampling times | | Proportion of subjects by group (%) | Total number of subjects | Total number of samples | | Criterion ($det(M_F)^{1/dim(\Psi)}$) |
|---|---|---|---|---|---|---|---|
| | AZT | AZT-TP | | | AZT | AZT-TP | |
| Initial | 1, 3, 6, 12 | 1, 3, 6, 12 | 100 | 50 | 200 | 200 | 1.17 |
| $Opt_{iden}$ | 0.5, 1, 3, 12 | 0.5, 1, 3, 12 | 100 | 50 | 200 | 200 | 1.96 |
| $Opt_{diff}$ | 0.5, 1, 3 | 3, 12 | 100 | 80 | 240 | 160 | 2.52 |

# Design optimisation : AZT / AZT-TP

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  - **Total cost = 400**
  - **Usual « cost function » (= number of samples)**
    - Identical sampling times $\Rightarrow$ **$Opt_{iden}$**
    - Different sampling times $\Rightarrow$ **$Opt_{diff}$**
  - **Other cost functions (different sampling times)**
    - Cost of an intracellular concentration analysis $\Rightarrow$ **$Opt_{diff\_intra}$**
      - $C_{diff\_intra}(\xi_q) = n_q^{AZT} + n_q^{AZT\text{-}TP} \times 10$
    - Cost of the addition of a new patient in the study $\Rightarrow$ **$Opt_{diff\_patient}$**
      - $C_{diff\_patient}(\xi_q) = n_q^{AZT} + n_q^{AZT\text{-}TP} + 8$

# Results – Cost functions

| | Sampling times | | Proportion of subjects by group (%) | Total number of subject | Total number of samples | |
|---|---|---|---|---|---|---|
| | **AZT** | **AZT-TP** | | | **AZT** | **AZT-TP** |
| $Opt_{diff}$ | 0.5, 1, 3 | 3, 12 | 100 | 80 | 240 | 160 |
| $Opt_{diff\_intra}$ | 0.5, 1, 3, 4 | 12 | 45.8 | 24 | 96 | 31 |
| | 0.5, 1, 1.5, 3 | 3, 12 | 29.2 | | | |
| | 0.5, 1, 1.5, 3 | 3 | 20.8 | | | |
| | 0.5, 1, 3, 4 | 3 | 4.2 | | | |
| $Opt_{diff\_patient}$ | 0.5, 1, 3, 4 | 2, 3, 12 | 57.6 | 26 | 104 | 89 |
| | 0.5, 1, 1.5, 3 | 2, 3, 4, 12 | 42.4 | | | |

⇒ Design structure → reflection of the imposed penalities

⇒ Difficulty to compare designs → different cost functions

# Conclusion

- Relevance of the extension of the Fisher information matrix for NLMEM with multiple responses
  - **First order linearisation of the model**
- Development of a powerful tool to determine informative population designs
  - **Extension of the Fedorov-Wynn algorithm**
    - Multiple response models
    - Introduction of cost functions
- Implementation in new extensions of PFIM
  - **www.pfim.biostat.fr**
  - **Complex cost functions → working version**
- Illustration on plasma and intracellular pharmacokinetics of an antiretroviral drug
  - **First joint population analysis of zidovudine and its active metabolite**
  - **Derivation of efficient designs according to clinical and technical constraints**

# Thank you for your attention