Colloque du club SMAC – Cancéropôle GSO
« Statistiques et mathématiques appliquées au cancer »
Modélisation et simulation d'essais cliniques

AN INTRODUCTION TO MODELS AND METHODS IN PK-PD

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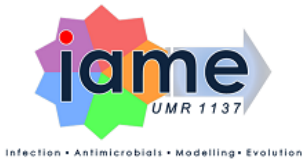
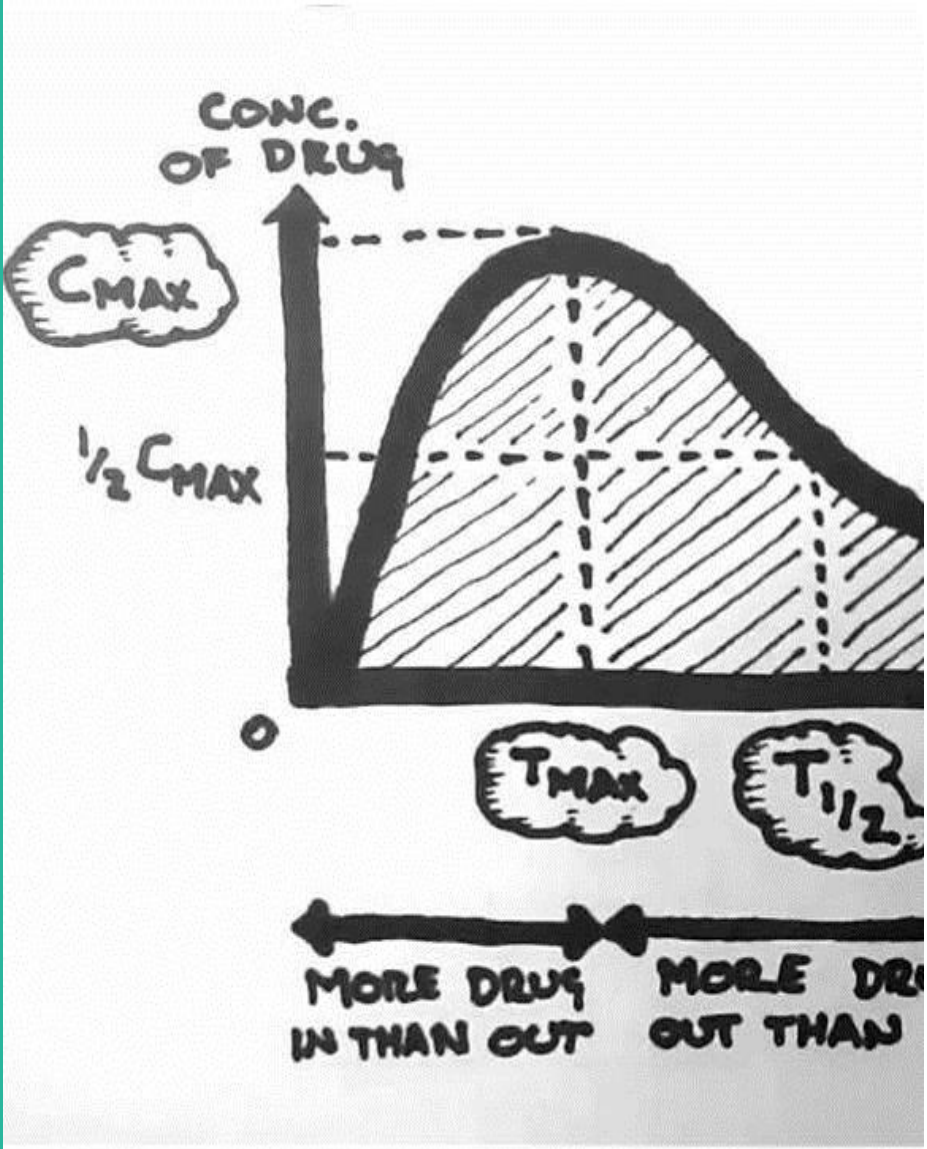


April 2015 - Toulouse, Institut de Mathématiques

OUTLINE

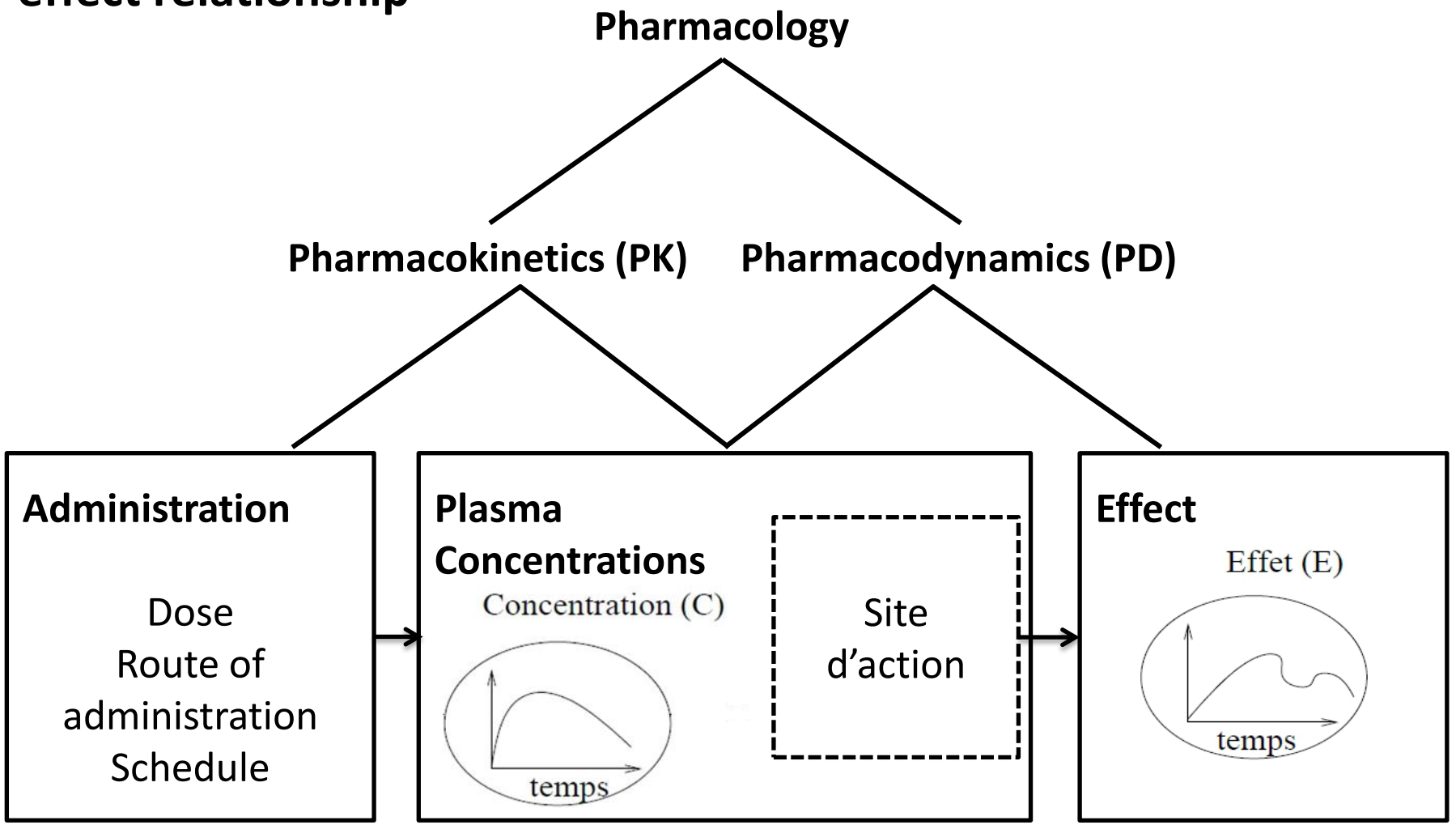
1. **Models in pharmacokinetics and pharmacodynamics**
2. **Statistical methods**
   - **Pharmacometrics**
3. **Treatment individualization**
4. **Design optimization**
5. **Conclusion**

MODELS IN PHARMACOKINETICS AND PHARMACODYNAMICS



PHARMACOKINETICS & PHARMACODYNAMICS

Dose - effect relationship



PHARMACOKINETICS & PHARMACODYNAMICS

Pharmacokinetics (PK) : « What the body does to the drug»

- Descriptive and quantitative study of the fate of substances in the body
  - drug concentrations over time

Pharmacodynamics (PD) : « What the drug does to the body or the pathogen»

- relationship between drug concentration and effect of the drug
- the effect of the drug depends on its concentration on the site of action
- generally the blood is considered as a reflect of the drug concentration on the site of action
- this is why it is critical to know what drives this concentration

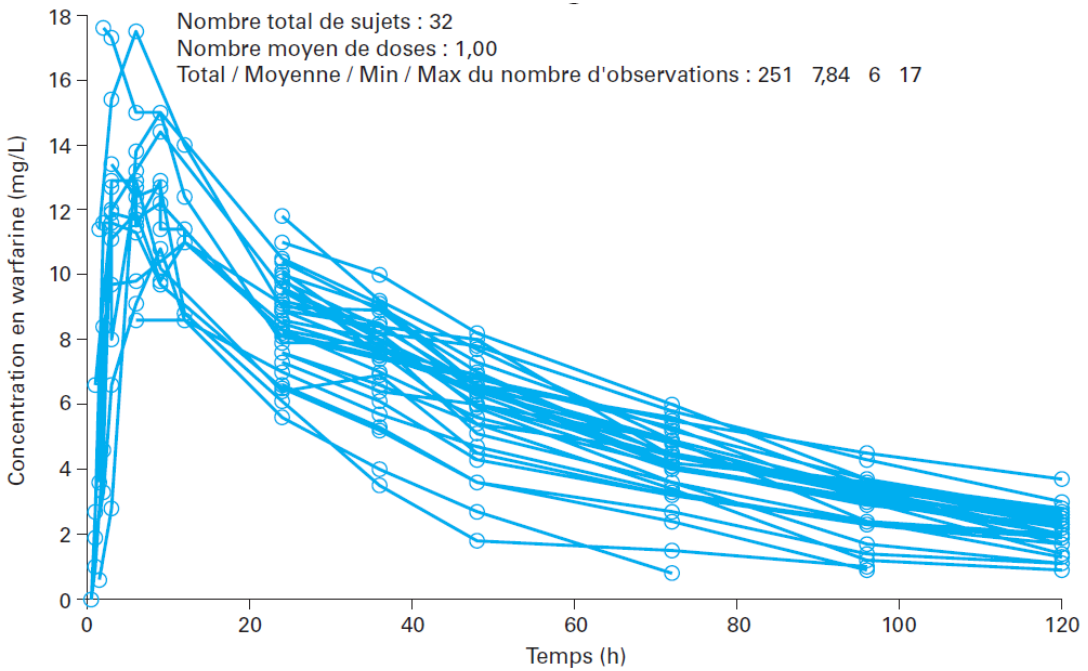
- Variety of markers depending on the context
  - biological markers, pathogen concentration (viral load)
  - clinical markers (pain)
  - continuous, discrete, categorical

TYPICAL DATA IN PHARMACOKINETICS

Warfarin: anticoagulant

32 healthy volunteers

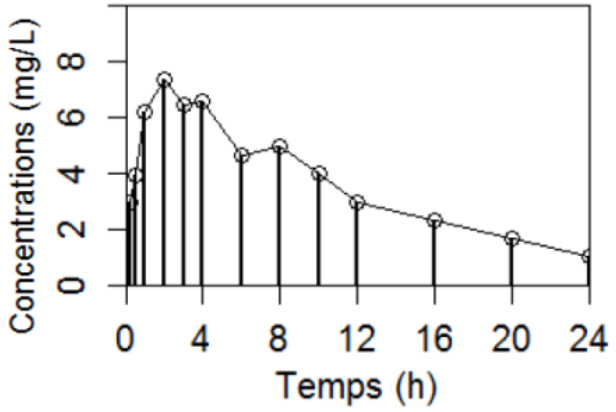
- PK data : plasma concentration after a unique oral administration
- objective: characterization of a median profile and the **between-subjects variability**



Holford, N. H. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin. Pharmacokinet.* **11,** 483–504 (1986).

ANALYSIS OF PHARMACOKINETIC DATA

Non-compartimental analysis



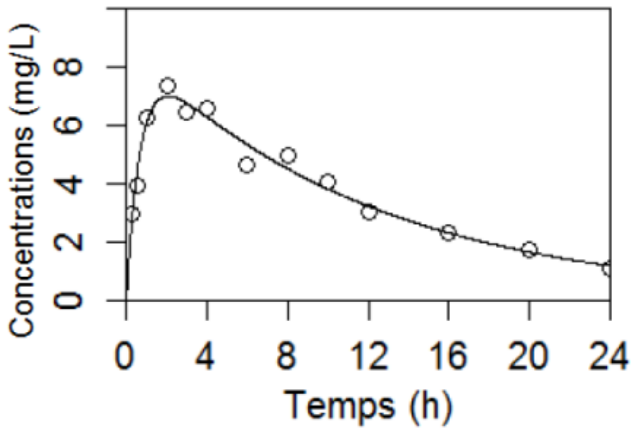
Estimate parameters summarizing the PK profile:

- area under the curve (AUC)
- maximum Concentration (C_{max})
- terminal half-life ($t_{1/2}$)

Directly on the observed concentrations:

- few assumptions
- > 10 concentrations per subject
- calculation using trapezoidal method (linear or log-linear)

Modeling



Model the **whole course** of drug concentrations

The body is considered as a set of compartments

- homogeneous kinetics in a compartment
- transfers between the compartments
- requires to understand the main determinants of the drug PK

The transfers between the compartments are modeled using **differential equations**:

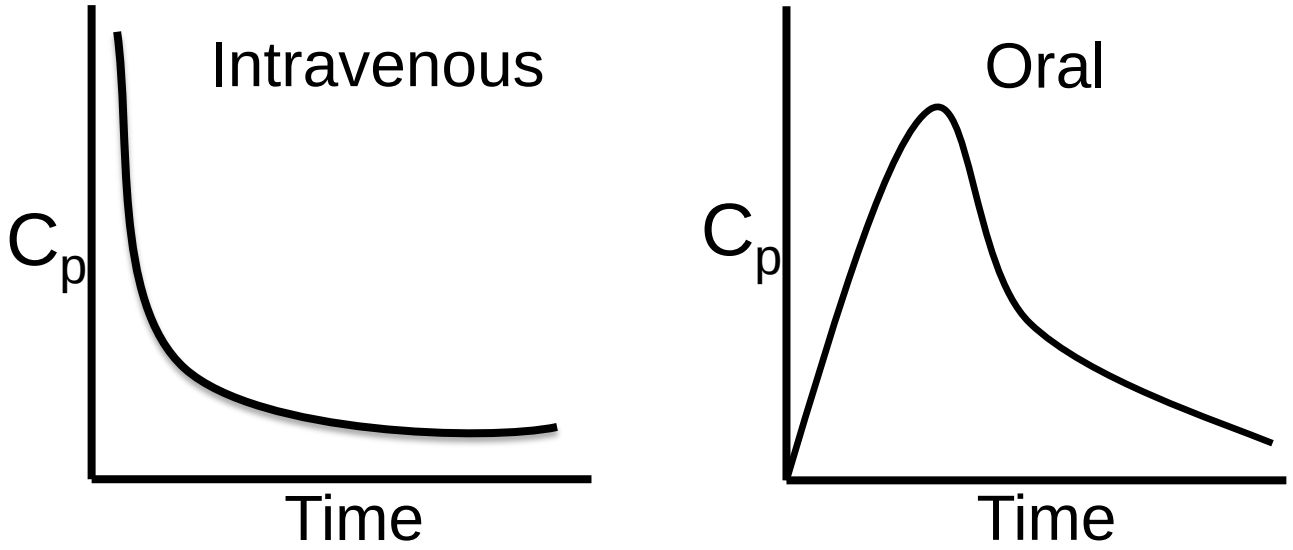
- parameters have a biological meaning
- models are **non-linear**

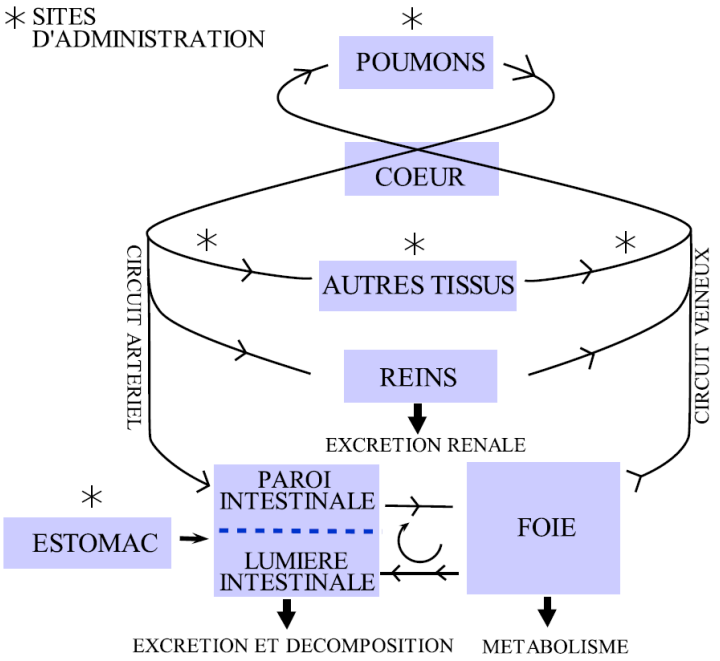
PK DETERMINANTS: ADME PROCESS

Absorption

Transfer of the drug from the site of administration to the blood

The route of administration will impact on:





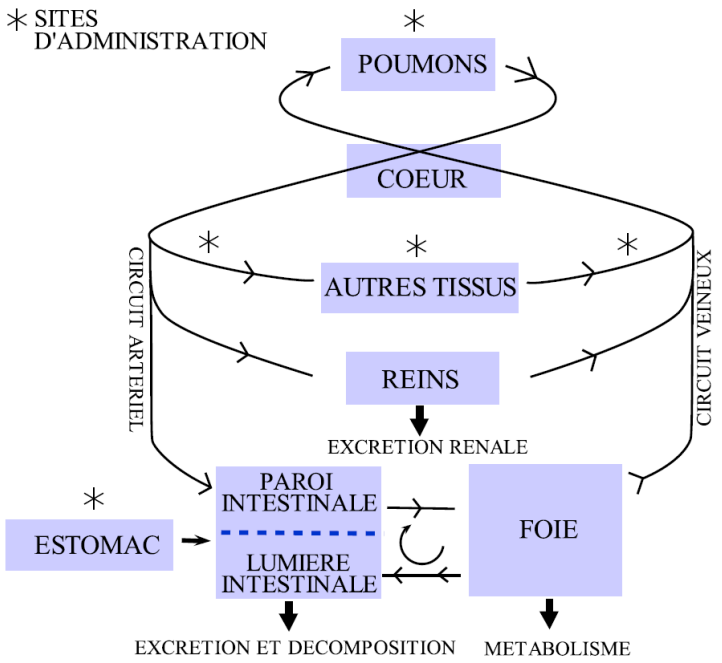
- The fraction of the dose reaching in the circulation (F = bioavailability)
- The time to reach the circulation (absorption)

PK DETERMINANTS: ADME PROCESS

Distribution

Diffusion of the drug through the blood in the different organs and tissues

Volume of distribution (V): theoretical volume that a drug would have to occupy to provide the same concentration as it currently is in blood plasma



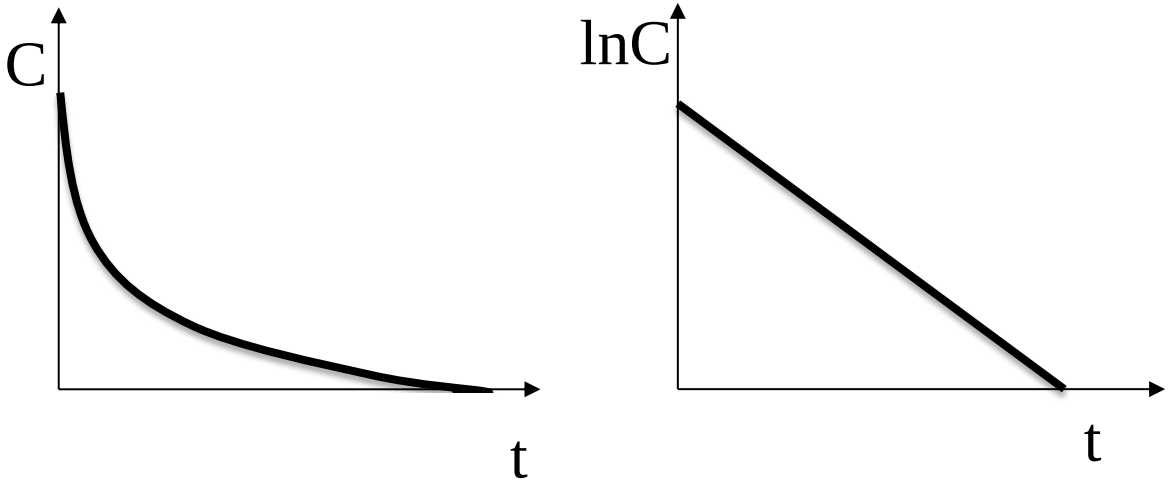
$$V = \frac{\text{Total amount of drug reaching the circulation}}{\text{Plasma concentration}} = \frac{A}{C}$$

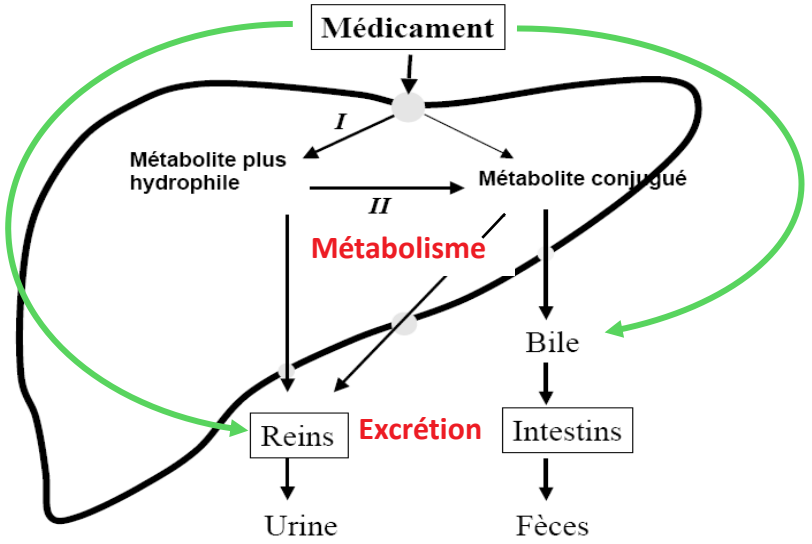
PK DETERMINANTS: ADME PROCESS

Elimination

Metabolism (transformation of the drug)

Excretion (elimination of the drug)





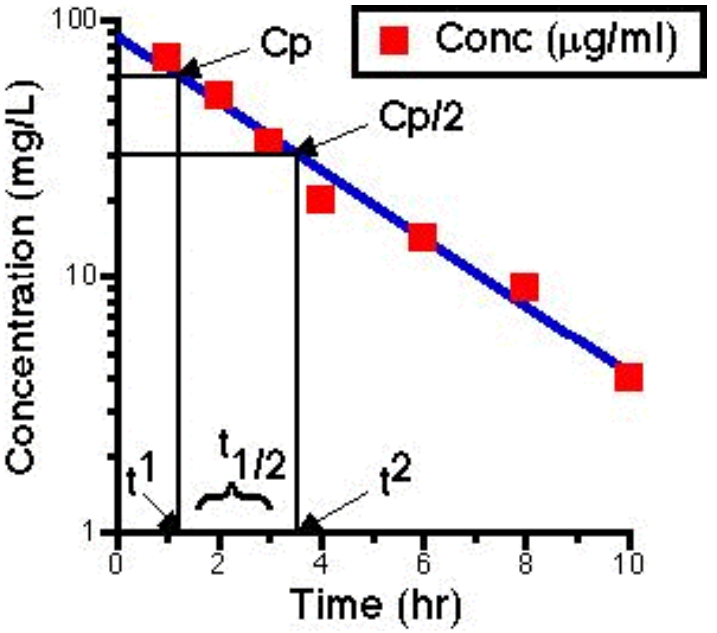
- Generally the elimination is a first-order process
  - $C(t) = C(0)e^{-kt}$

PK DETERMINANTS: ADME PROCESS

Elimination

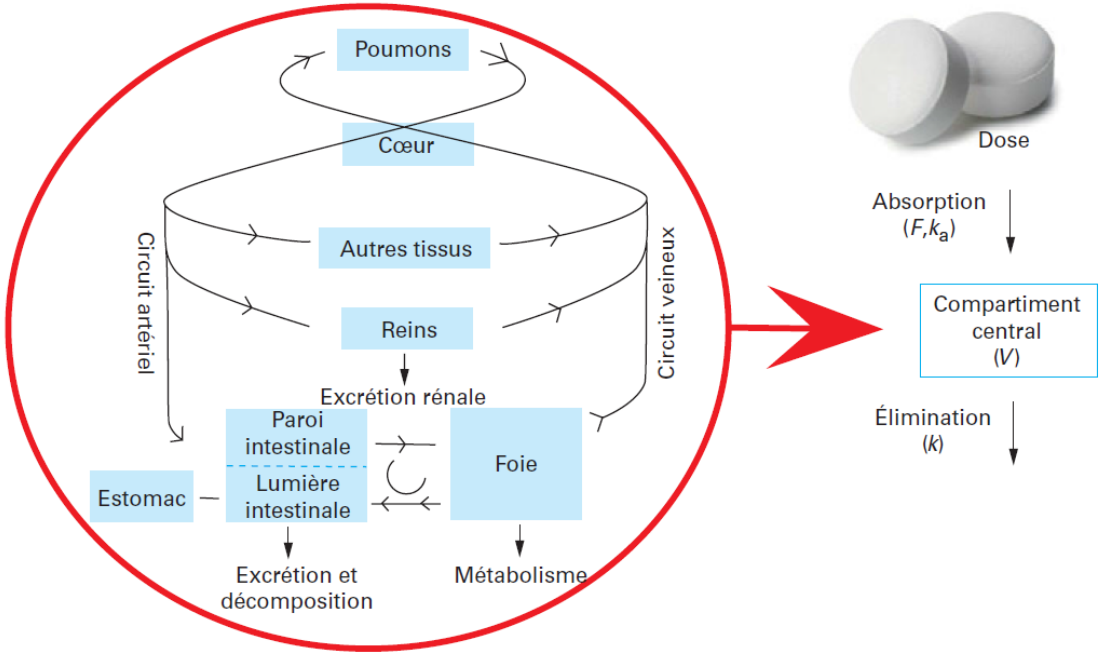
Metabolism (transformation of the drug)

Excretion (elimination of the drug)



- Generally the elimination is a first-order process
  - $\frac{dC}{dt} = -k \cdot C$
  - $t_{1/2} = \frac{ln(2)}{k}$ the half life : time to reduce the amount of drug by 50%
  - $Cl = k.V$ the drug clearance : the volume of blood cleared per unit of time

PHARMACOKINETIC MODEL



Differential equations = mass balance

$$\frac{dA(1)}{dt} = -ka \times A(1)$$

$A(1)_{t=0}$ = F x Dose

$$\frac{dA(2)}{dt} = ka \times A(1) - k \times A(2)$$

$A(2)_{t=0} = 0$

$$k = {}^{CL}/_{V}$$

A(1): drug quantity in depot compartment (gut)

A(2): drug quantity in central compartment (measure compartment)

- observed concentration $C(t) = {}^{A(2)}/_{V}$

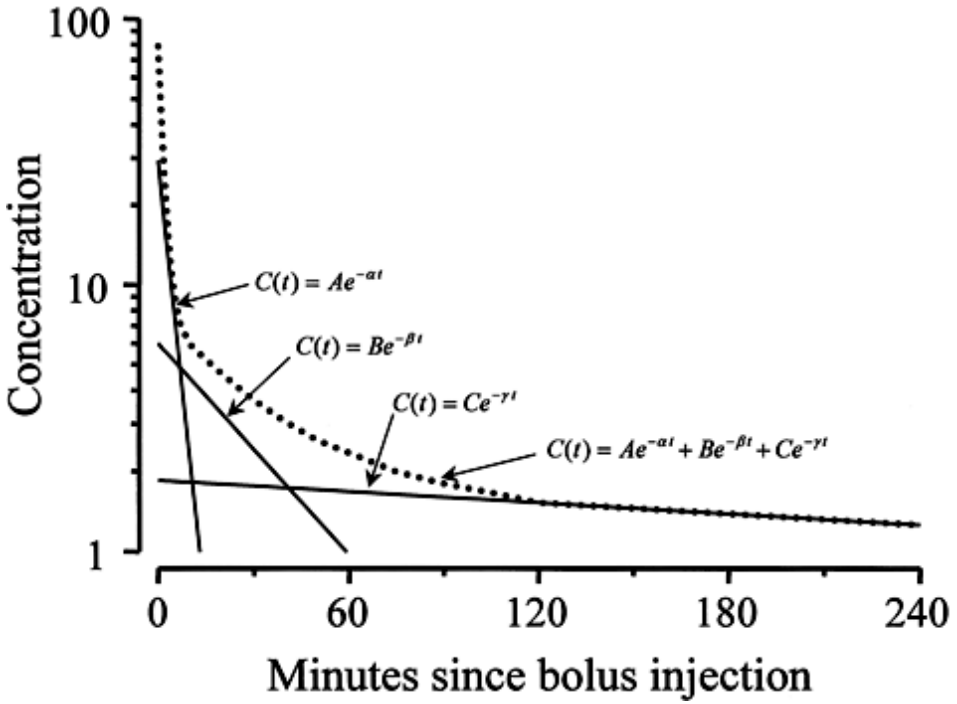
Analytical solution (Laplace transformation) :

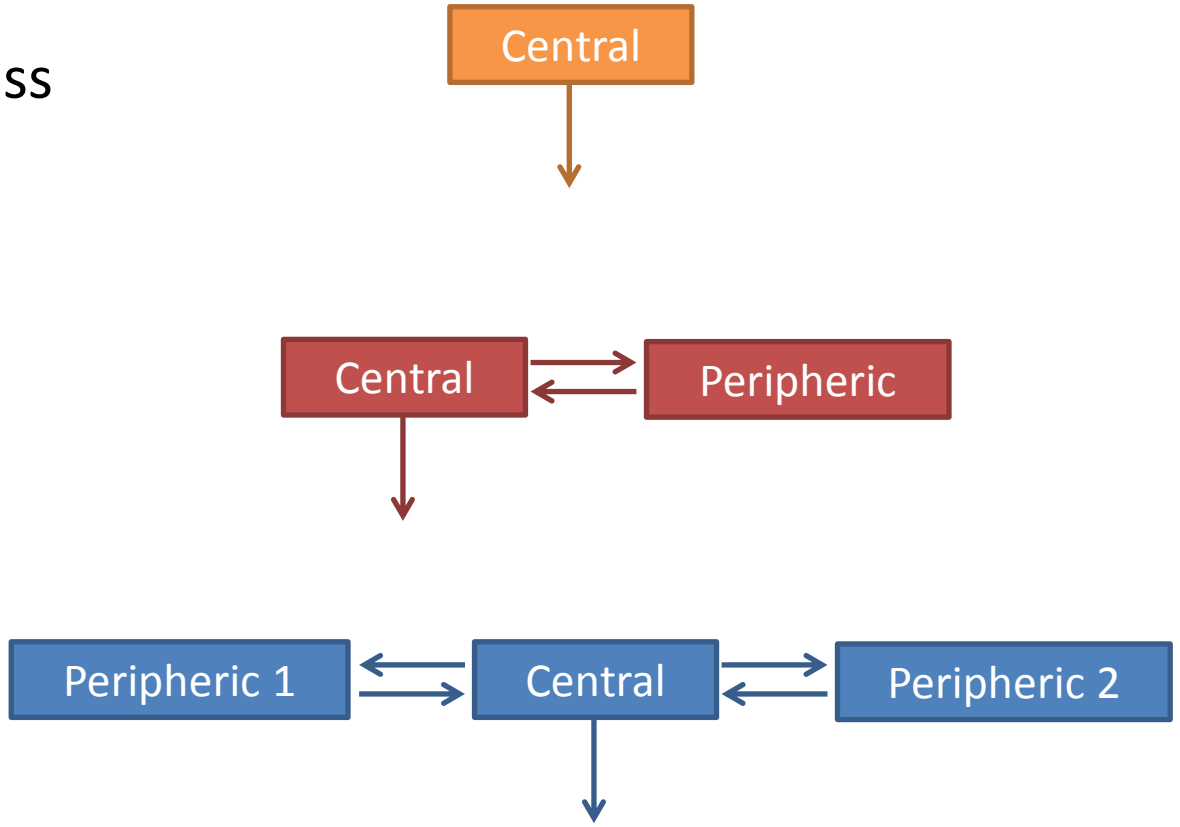
$$C(t) = \frac{F \times Dose}{V} \frac{ka}{(ka - \frac{CL}{V})} \left(e^{-\frac{CL}{V}t} - e^{-ka\,t}\right)$$

PHARMACOKINETIC MODEL

Empirical models

- Simplification of the ADME process
  - 1 to 3 compartments





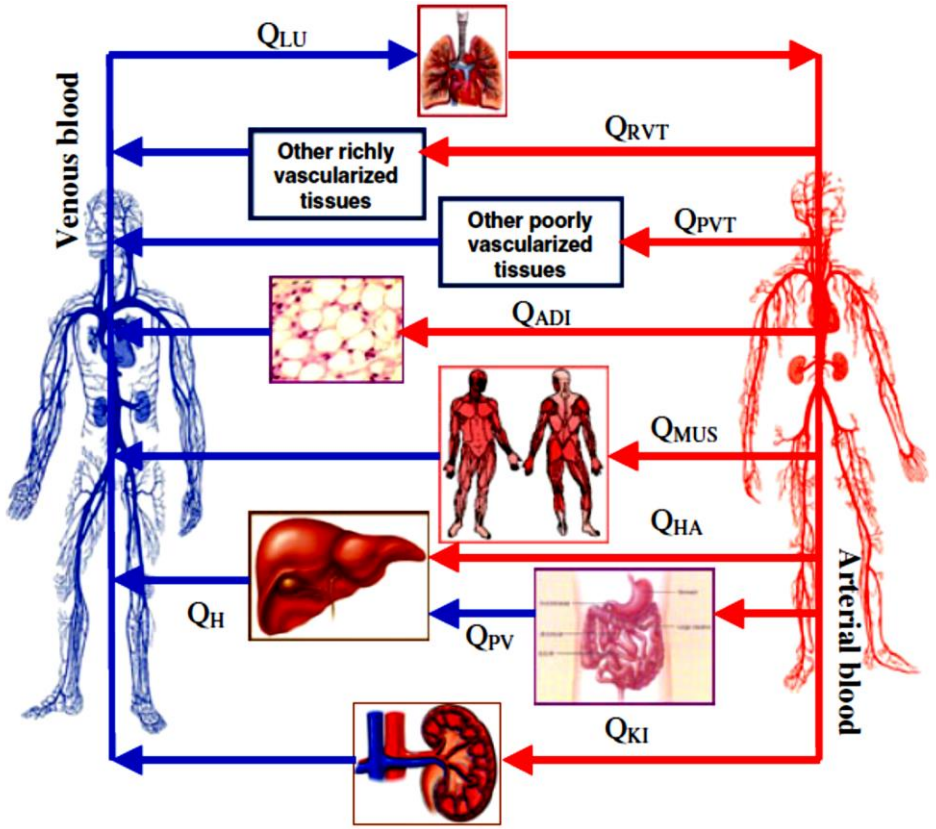
PK profile represented on log-scale

- Number of decreasing slopes = number of compartments

PHARMACOKINETIC MODEL

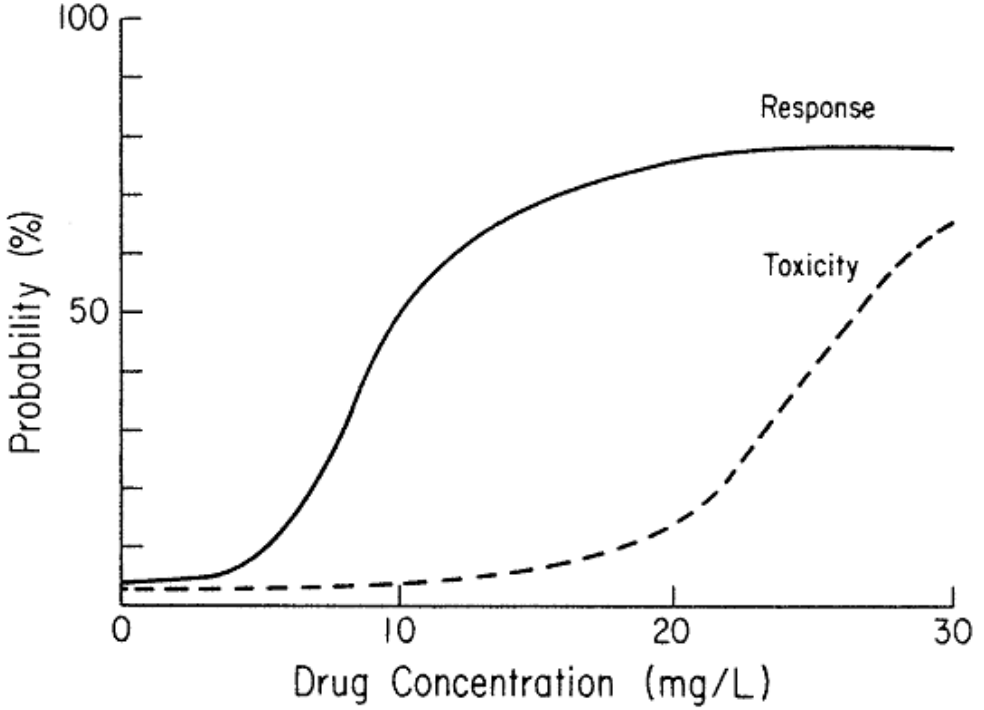
Physiological models

- PBPK : Physiologically Based PharmacoKinetics
  - ➢ using biologic and *in vitro* data



PHARMACODYNAMIC MODEL

- Direct or indirect relationship between drug concentrations and effect
- A too high drug exposure increases the risk of toxicity
- Purpose : find the best therapeutic window, *i.e.* a balance between drug efficacy and toxicity



PHARMACODYNAMIC MODEL

Direct response model

Direct relationship between drug concentrations and effect

$$E(t) = E_0\left(1 + E_{max}\frac{C}{C + C_{50}}\right)$$

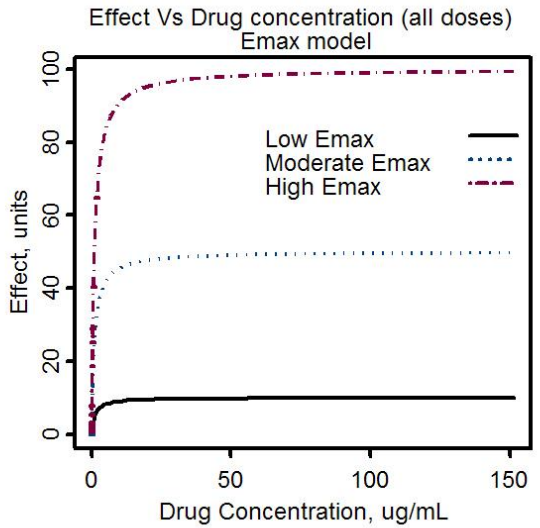
$E(t)$: observed effect

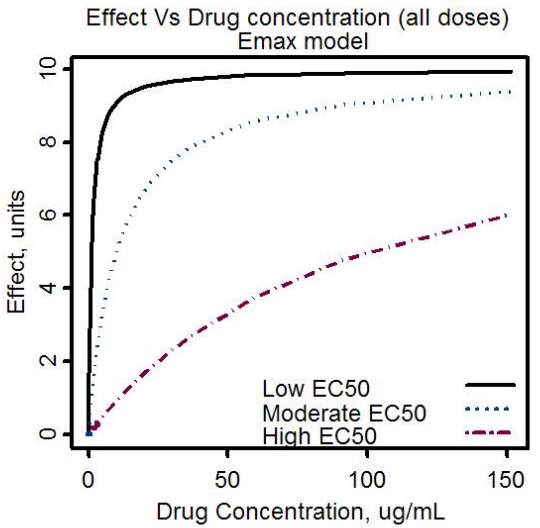
E_0 : response without treatment (baseline)

E_{max} : maximal effect

C_{50} : concentration to reach $E_{max}/2$

C : drug concentrations





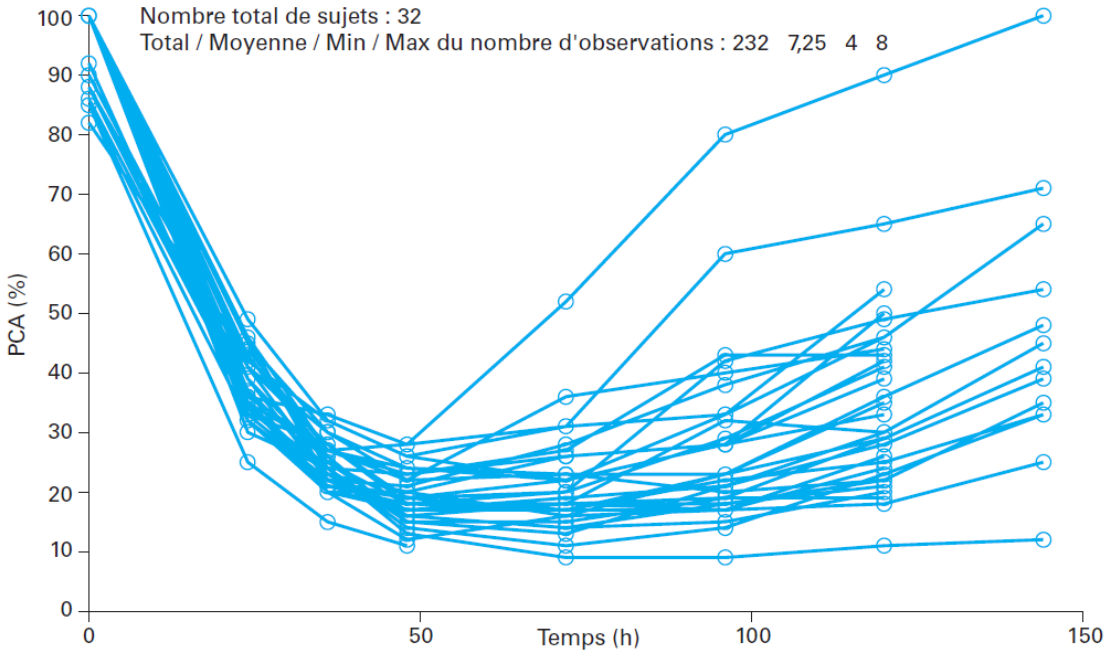
PHARMACODYNAMIC MODEL

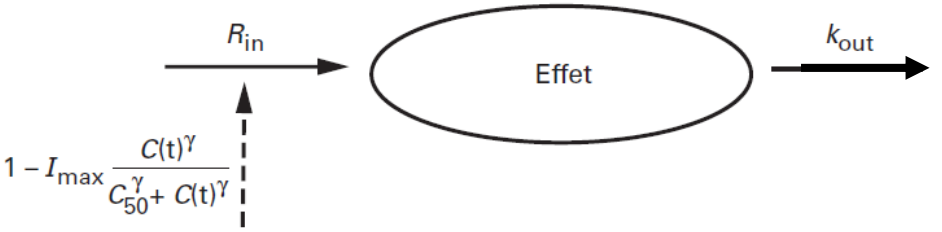
Indirect response model

Lag between the drug action and the effect observed on the marker

Warfarin : inhibition of vitamin K recycling

- prevents formation of coagulation factors
- decrease of PCA (Prothrombin Complex Activity)





$$\frac{dE}{dt} = R_{in}\left(1 - \frac{C(t)^{\gamma}}{{C_{50}}^{\gamma} + C(t)^{\gamma}}\right) - k_{out}\,E$$

$$E(t=0) = {R_{in}}/{k_{out}}$$

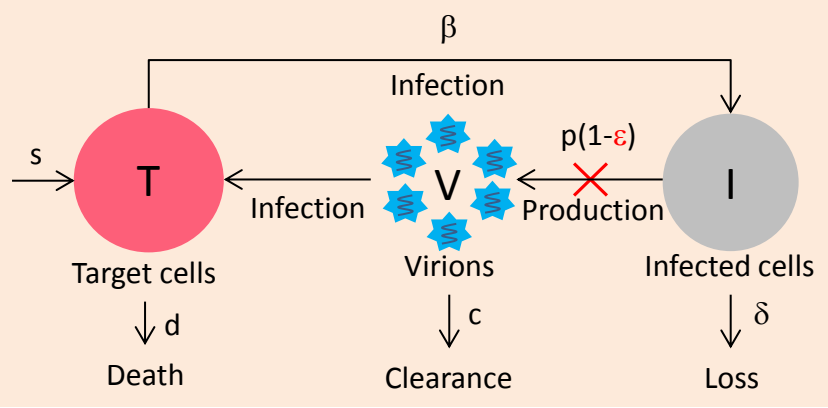
R_{in} : Input (production of coagulation factors)

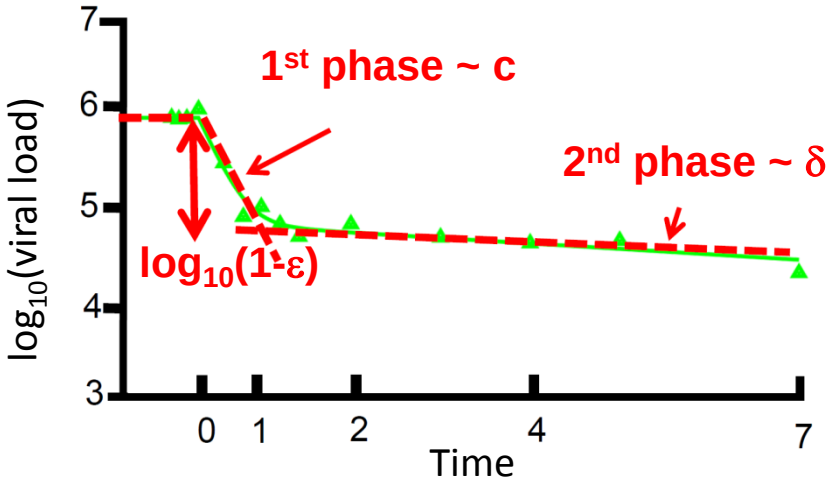
k_{out} : Loss (degradation of coagulation factors)

PHARMACODYNAMIC MODEL

Viral kinetic model

- A basic model (Neumann et al, Science. 1998)





$$\frac{dT}{dt} = s - dT - \beta VT$$

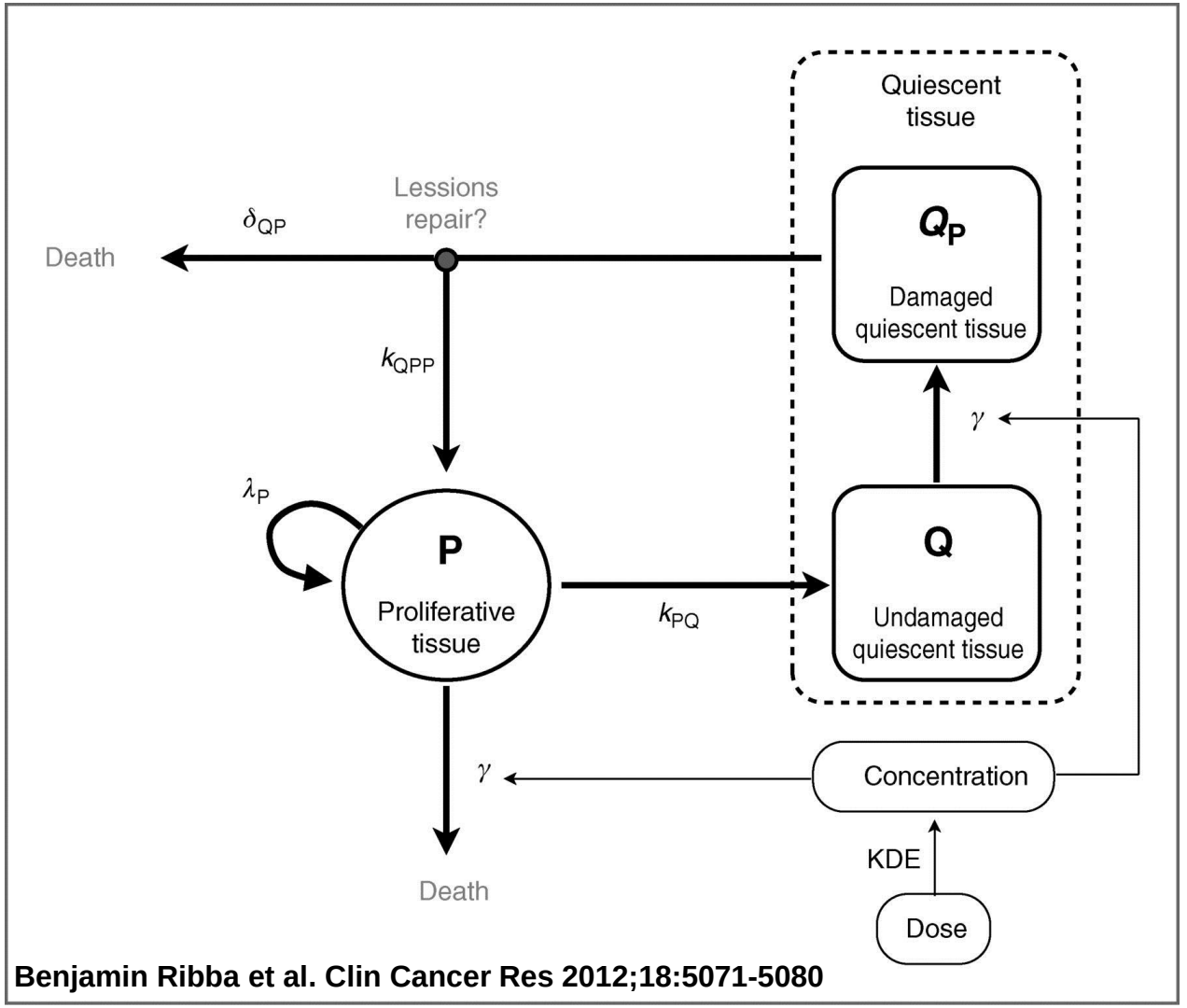
$$\frac{dI}{dt} = \beta VT - \delta I$$

$$\frac{dV}{dt} = (1-\varepsilon)pI - cV$$

s: production rate of target cells
d: death rate of target cells
β: infection rate
p: production rate per infected cell
c: clearance rate of free virus
δ: loss rate of infected cells
ε: treatment effectiveness

PHARMACODYNAMIC MODEL

Tumor growth inhibition model



Benjamin Ribba et al. Clin Cancer Res 2012;18:5071-5080

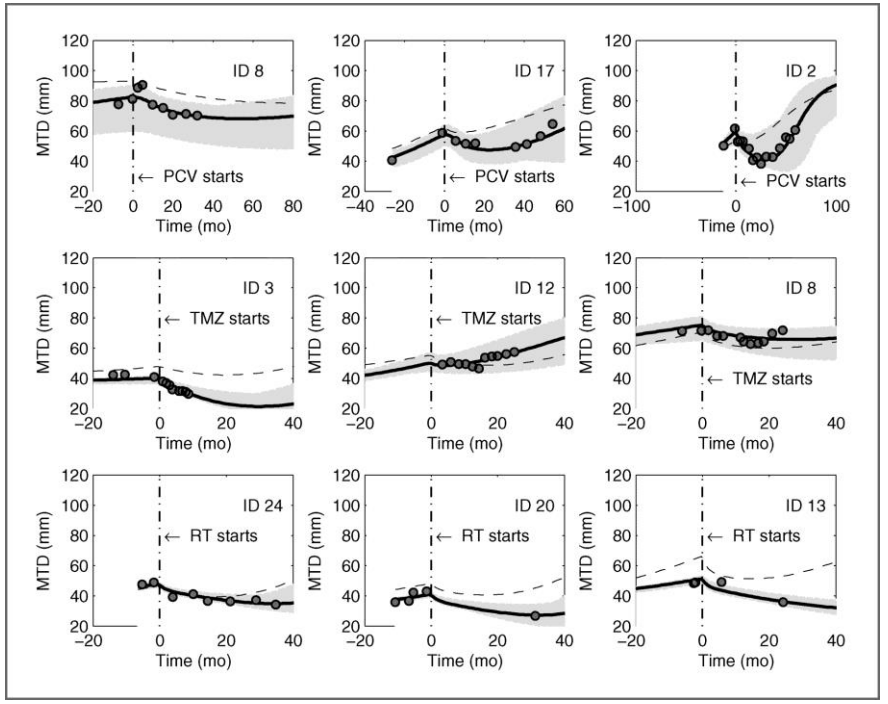
$$\frac{dC}{dt} = -\text{KDE} \times C$$

$$\frac{dP}{dt} = \lambda_p \times P\left(1 - \frac{P^*}{K}\right) + k_{Q_P P} \times Q_P - k_{PQ} \times P - \gamma_P \times C \times \text{KDE} \times P$$

$$\frac{dQ}{dt} = k_{PQ}P - \gamma_Q \times C \times \text{KDE} \times Q$$

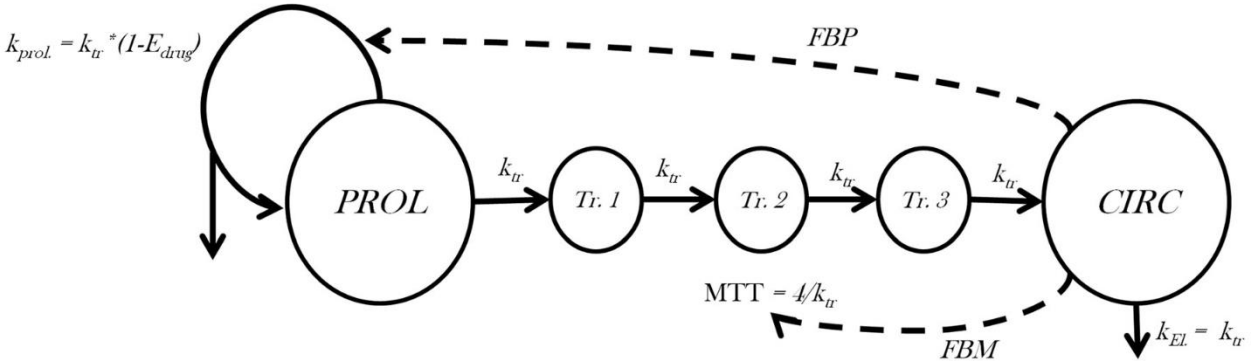
$$\frac{dQ_P}{dt} = \gamma_Q \times C \times \text{KDE} \times Q - k_{Q_P P}Q_P - \delta_{QP} \times Q_P$$

$$P^* = P + Q + Q_P$$



PHARMACODYNAMIC MODEL

Drug-induced thrombocytopenia model



$$\frac{dPROL}{dt} = k_{prol} \cdot \left(1 - E_{drug}\right) \cdot FBP \cdot PROL - k_{tr} \cdot FBM \cdot Pl$$

$$\frac{dTr\ 1}{dt} = k_{tr} \cdot FBM \cdot PROL - k_{tr} \cdot FBM \cdot Tr\ 1$$

$$\frac{dTr\ 2}{dt} = k_{tr} \cdot FBM \cdot Tr\ 1 - k_{tr} \cdot FBM \cdot Tr\ 2$$

$$\frac{dTr\ 3}{dt} = k_{tr} \cdot FBM \cdot Tr\ 2 - k_{tr} \cdot FBM \cdot Tr\ 3$$

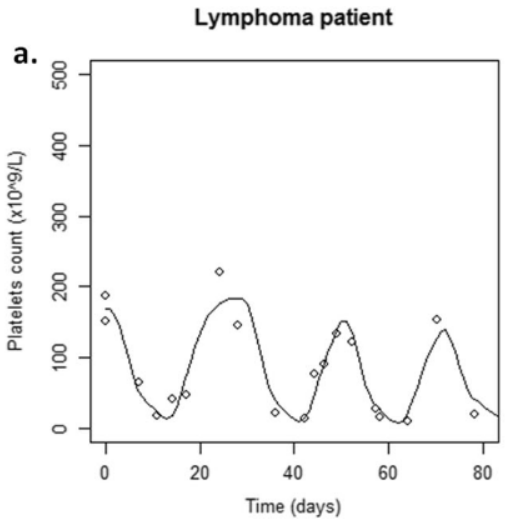
$$\frac{dCIRC}{dt} = k_{tr} \cdot FBM \cdot Tr\ 3 - k_{El.} \cdot CIRC$$

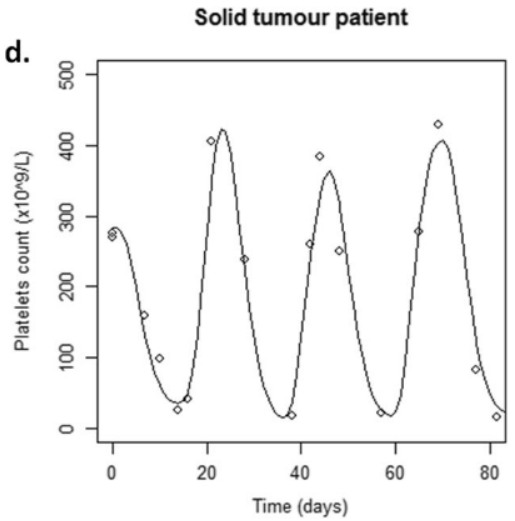
$$E_{drug} = \frac{IMAX \cdot Conc}{IC_{50} + Conc}$$

$$FBP = \left(\frac{BASE}{CIRC}\right)^{\gamma} \quad FBM = \left(\frac{BASE}{CIRC}\right)^{\delta}$$

$$If\ solid\ tumour\ patients : BASE = BASE_{0\,ST}$$

$$If\ lymphoma\ patients : BASE = BASE_{0\,LY} - \frac{IMAT \cdot t}{IT_{50} + t}$$





Chalret du Rieu et al. Invest New Drugs (2014) 32:985–994

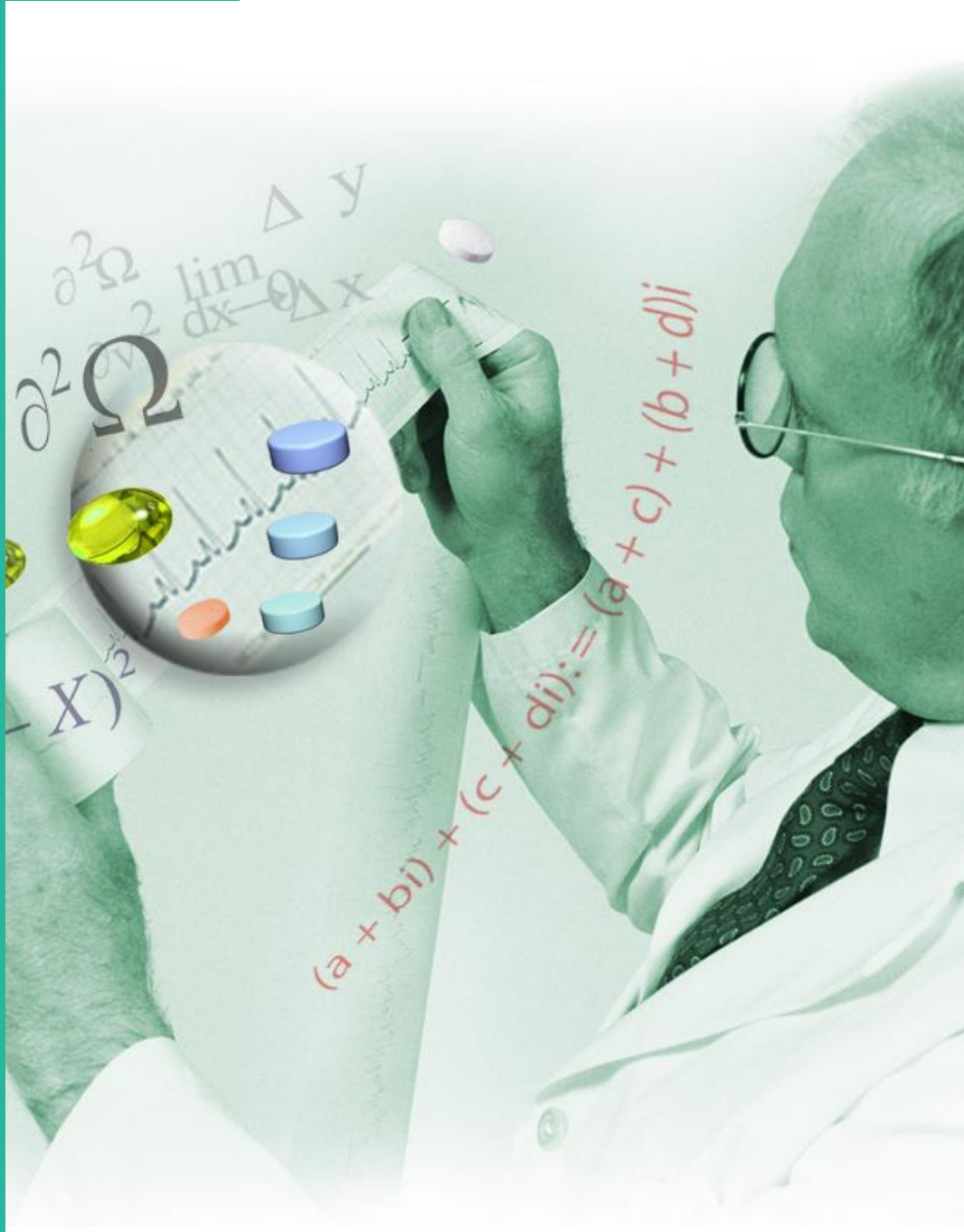
INTERESTS FOR MODELING

- Quantitative summary of the evolution of profile across time through physiological parameters
- Better predictive / simulation ability for other doses, special populations…
- Analysis of all longitudinal data in clinical trials (not only the endpoint) : more powerful to detect drug effect and less bias through the inclusion of dropouts
- Test of hypothesis on effect mechanism of drugs
- Comparison of groups of patients through statistical comparison of parameters
- Statistical issues : nonlinear models, high interindividual variability

→ Nonlinear mixed effects models for parameters estimation

STATICAL METHODS

PHARMACOMETRICS

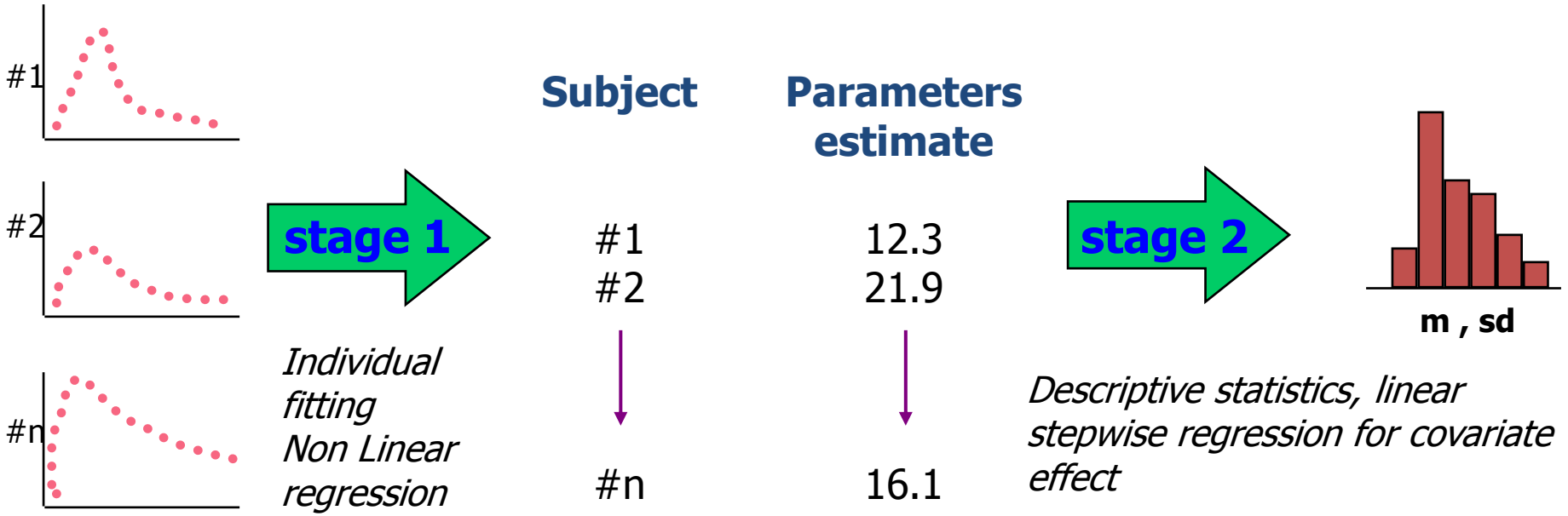


PHARMACOMETRICS

Science of quantitative pharmacology

- Quantify the pharmacologic activity of a drug and its variability between subjects and/or between occasions
  - two-stage method
  - population approach
    - main tool : nonlinear mixed effects models

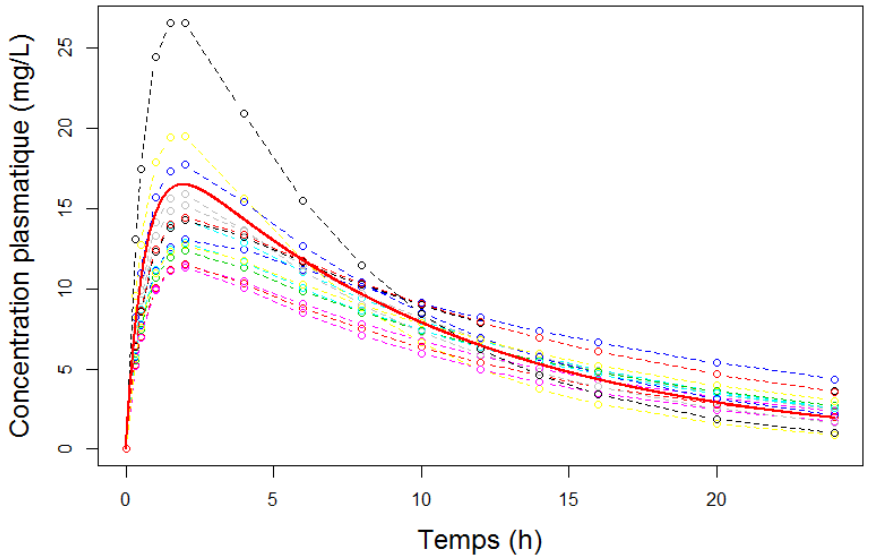
TWO - STAGES METHOD



From Steimer (1992): « Population models and methods, with emphasis on pharmacokinetics », in M. Rowland and L. Aarons (eds), *New strategies in drug development and clinical evaluation, the population approach*

1. Individual nonlinear regression
   - Estimation of individual parameters: require a large number of samples per subject
2. Statistical summary (mean, variance)
   - Overestimate the variability (do not distinguish the variability between individuals of the residual error)
3. Relations with covariates (gender, weight…)

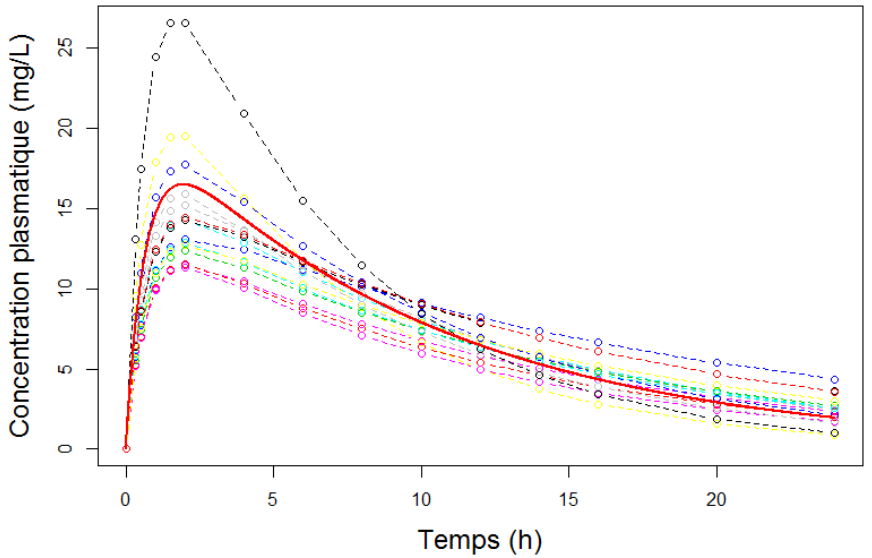
POPULATION APPROACH



Nonlinear mixed effects models

- Simultaneous analysis of all observations
  - reduce number of samples per subject
- Estimation of mean parameters and their variabilities (without bias)
- Identification of covariates influencing the variability
  - determination of relationships between covariates and model parameters

POPULATION APPROACH



Nonlinear mixed effects models

- Based on several statistical and mechanistic hypotheses
  - structural model (nonlinear function)
  - variability model
  - residual error model

NONLINEAR MIXED EFFECTS MODELS

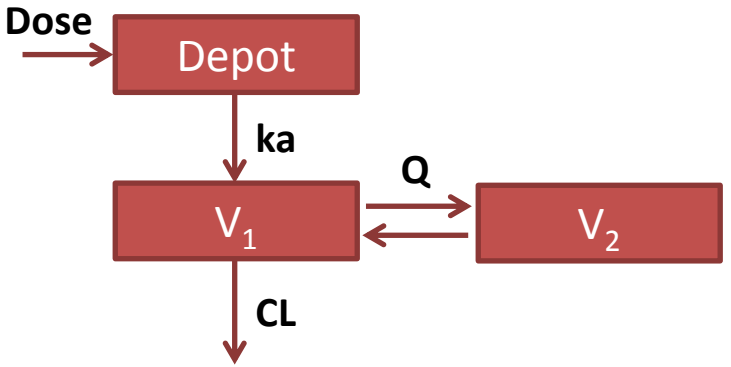
Notations

Concentration y_{ij} for subject *i* observed at time t_{ij} :

$$\boldsymbol{y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij}}$$

f : structural model

- The same for all subjects
  - ➢ One equations system for all subjects
- a specific vector of parameters $\theta_i = \{ka, V_1, Q, V_2, CL\}$ for subject *i*
  - ➢ θ_i : individual parameters



ε_{ij} : residual error

NONLINEAR MIXED EFFECTS MODELS

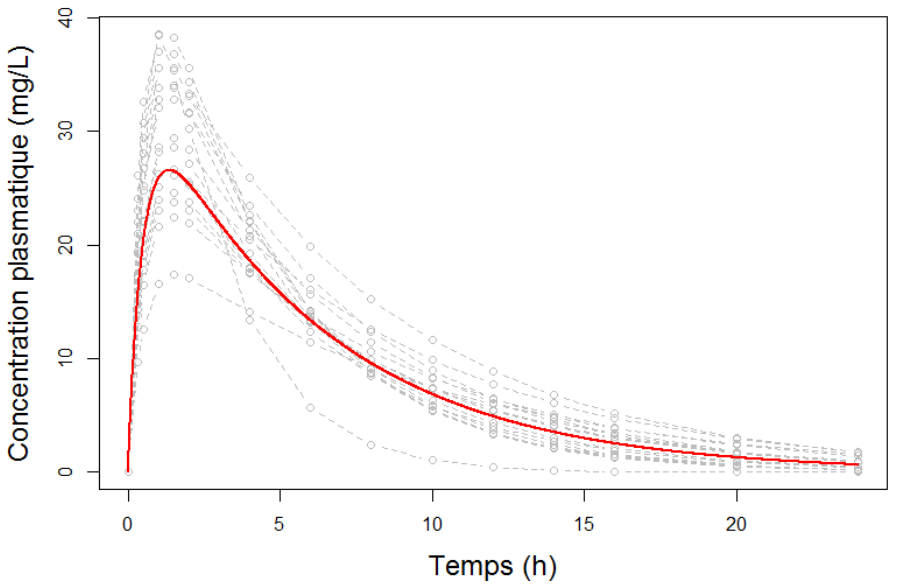
Notations

θ_i : individual parameters

$$\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i}}$$

μ : fixed effect (mean parameter)

- Estimated from observations of all subjects
- Mean profile predicted by integrating the mean values of parameters in the model ($\{ka, V_1, Q, V_2, CL\}$)



NONLINEAR MIXED EFFECTS MODELS

Notations

θ_i : individual parameters

$$\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i}}$$

μ : fixed effect (mean parameter)

η_i : random effects

- **hypothesis :** we assume the distribution of random effects is known

$$\eta_i \sim N(0, \omega^2)$$

  - $\theta_i = \mu + \eta_i$, θ_i follow a normal distribution
  - $\theta_i = \mu\, e^{\eta_i}$, θ_i follow a log-normal distribution ($\theta_i > 0$)

NONLINEAR MIXED EFFECTS MODELS

Notations

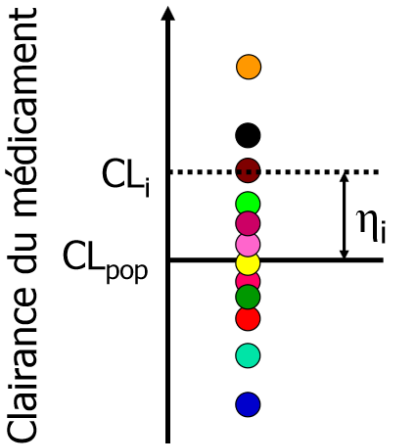
θ_i : individual parameters

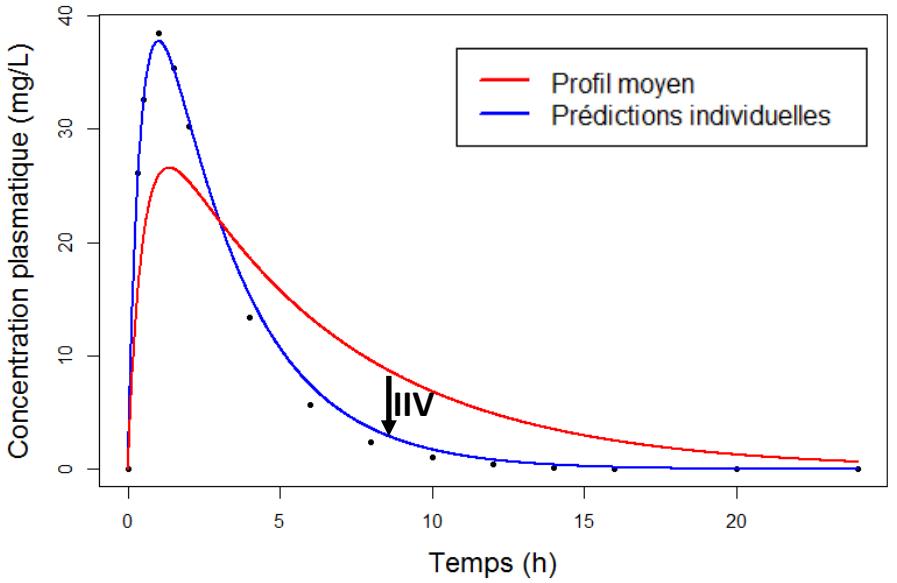
$$\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i}}$$

μ : fixed effect (mean parameter)

η_i : random effects

- interindividual variability





NONLINEAR MIXED EFFECTS MODELS

Notations

$$y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij}$$

θ_i : individual parameters

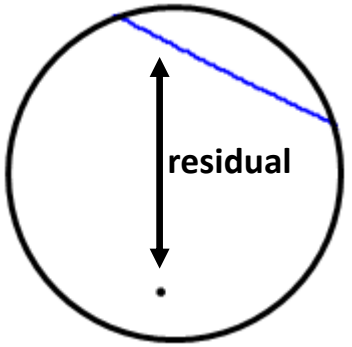
$$\theta_i = \mu\, e^{\eta_i}$$

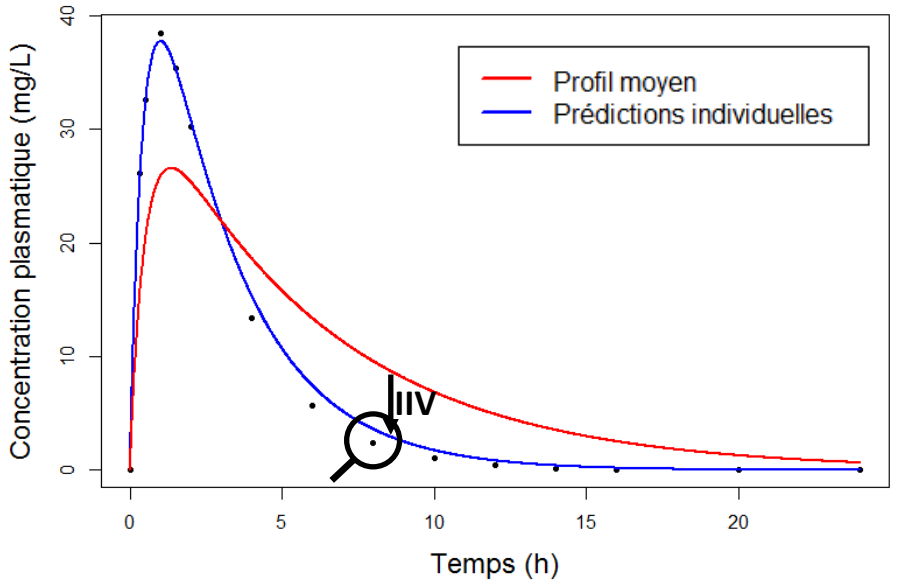
μ : fixed effect (mean parameter)

η_i : random effects

ε_{ij} : residual error

- hypothesis : $\varepsilon_{ij} \sim N(0, \sigma^2)$





NONLINEAR MIXED EFFECTS MODELS

Notations

θ_i : individual parameters

$$\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i}}$$

μ : fixed effect (mean parameter)

η_i : random effects, $\eta_i \sim N(0, \omega^2)$

ε_{ij} : residual error, $\varepsilon_{ij} \sim N(0, \sigma^2)$

- Distinction between interindividual variability and residual error

Parameters to estimate :

$$\{\mu, \boldsymbol{\omega^2}, \boldsymbol{\sigma^2}\}$$

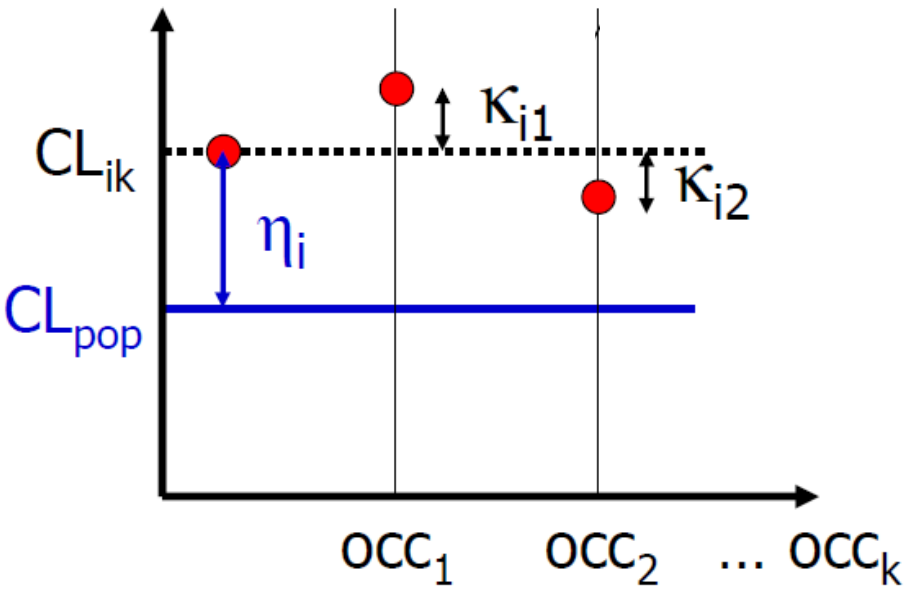
NONLINEAR MIXED EFFECTS MODELS

Intraindividual variability

κ_i : interoccasion variability

- data collected at different periods
  - Different visits
  - Changing in treatment schedule, trial arm

$$\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i + \kappa_i}}$$



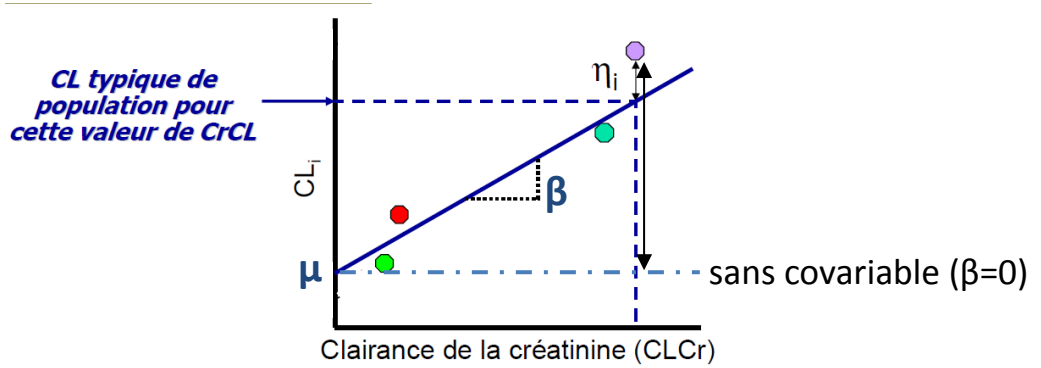
NONLINEAR MIXED EFFECTS MODELS

Covariates

- Physiological, biological, pharmacological specificities…
- Explain the sources of parameters variability

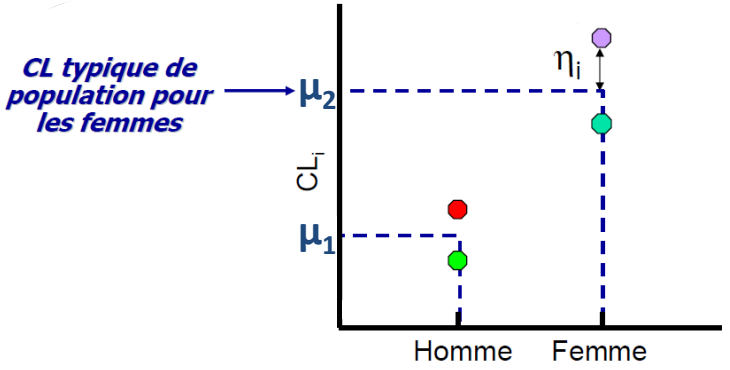
- Continuous covariates

$$CL_i = \mu + \beta \times CLCr_i + \eta_i$$



- Binary covariates

$$CL_{i,homme} = \mu_1 + \eta_i$$
$$CL_{i,femme} = \mu_2 + \eta_i$$



NONLINEAR MIXED EFFECTS MODELS

Estimation

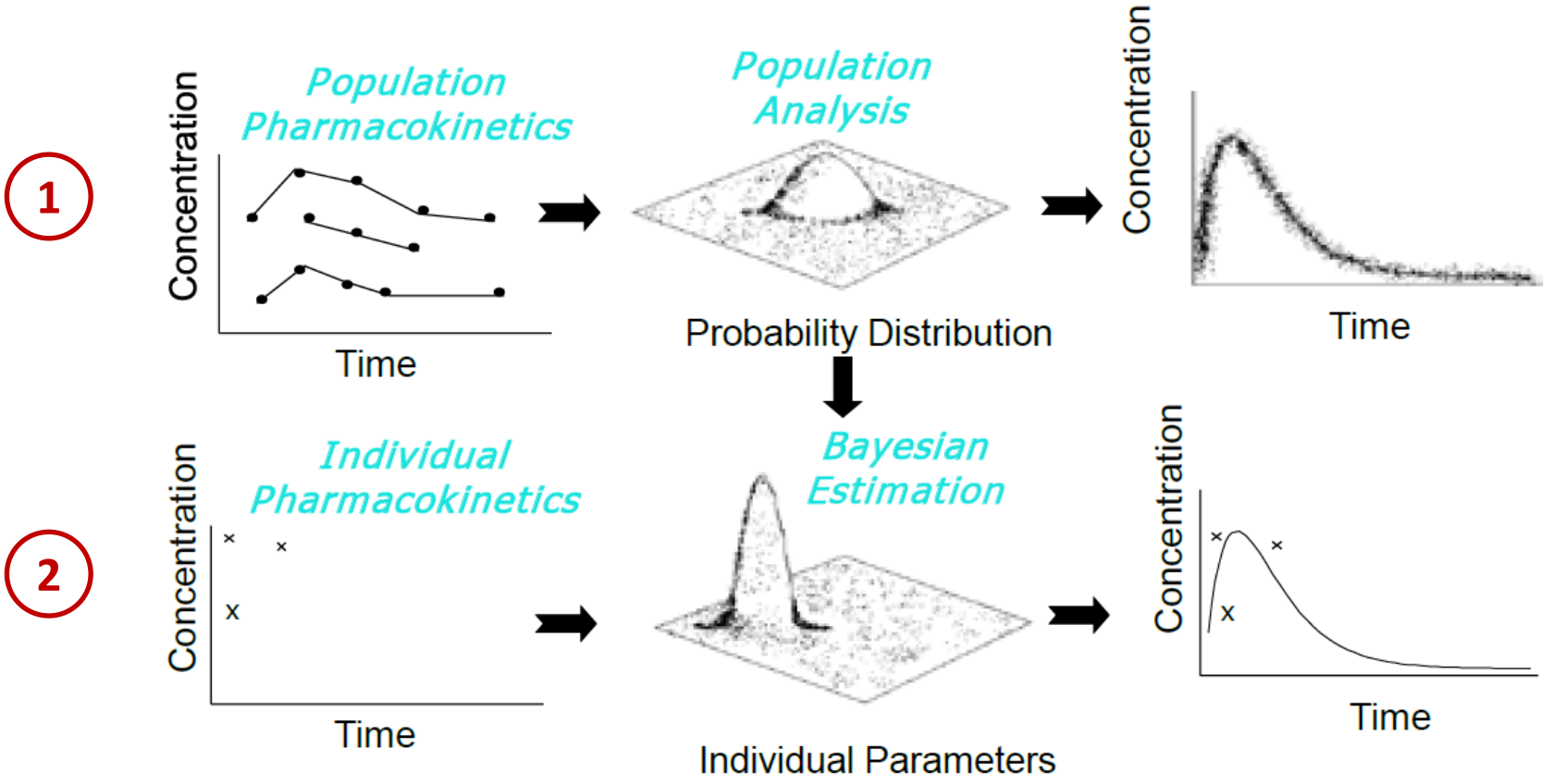
$$C(t) = \frac{F \times Dose}{V} \frac{ka}{(ka - \frac{CL}{V})} \left(e^{-\frac{CL}{V}t} - e^{-ka\,t}\right)$$

$$\theta_F = \mu_F e^{\eta_{F_i}}, \eta_{F_i} \sim N(0, \omega^2{}_F)$$
$$\theta_{ka} = \mu_{ka} e^{\eta_{ka_i}}, \eta_{ka_i} \sim N(0, \omega^2{}_{ka})$$
$$\theta_V = \mu_V e^{\eta_{V_i}}, \eta_{V_i} \sim N(0, \omega^2{}_V)$$
$$\theta_{CL} = \mu_{CL} e^{\eta_{CL_i}}, \eta_{CL_i} \sim N(0, \omega^2{}_{CL})$$

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

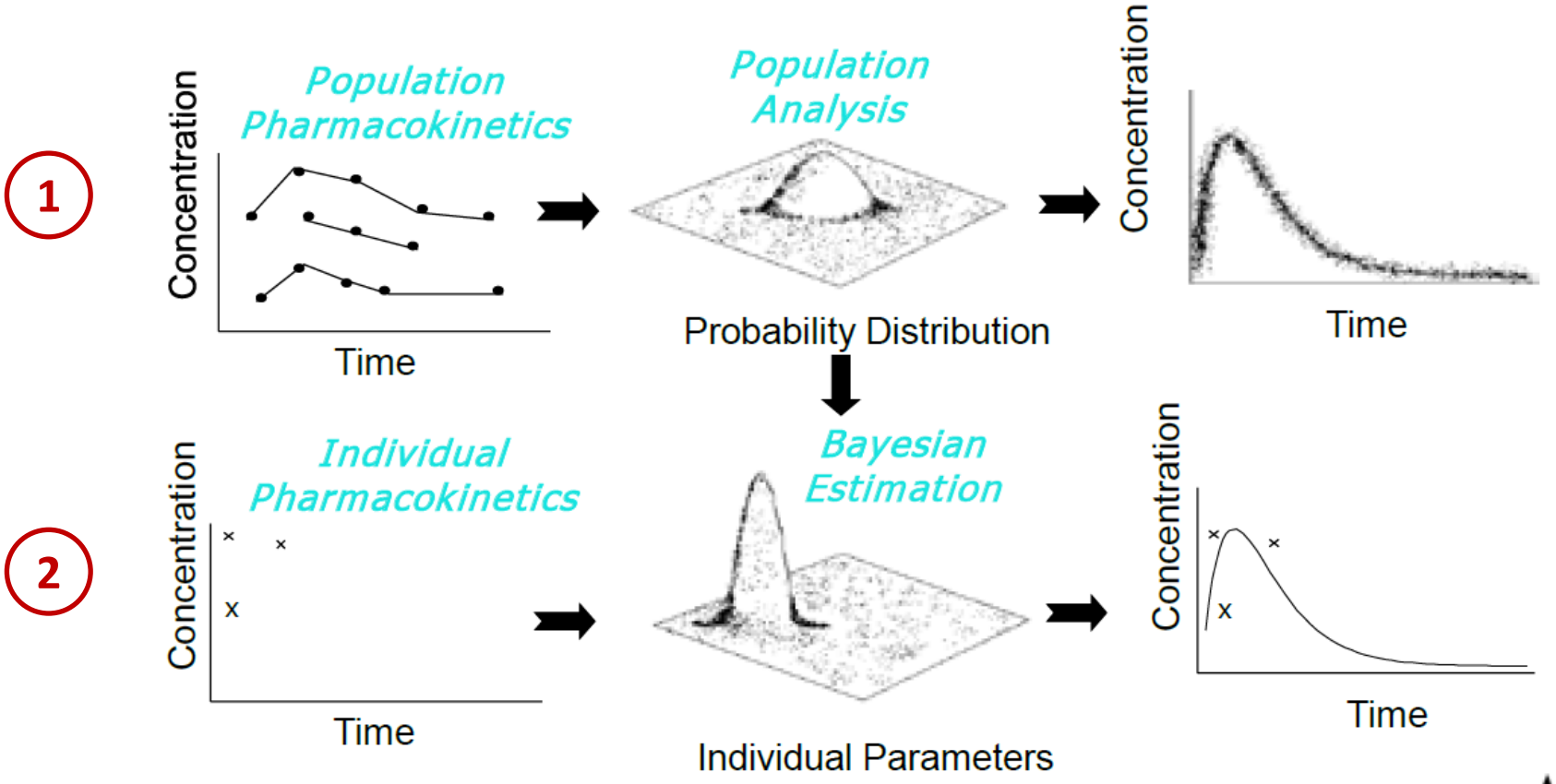
- Estimation of fixed and random effects?

NONLINEAR MIXED EFFECTS MODELS

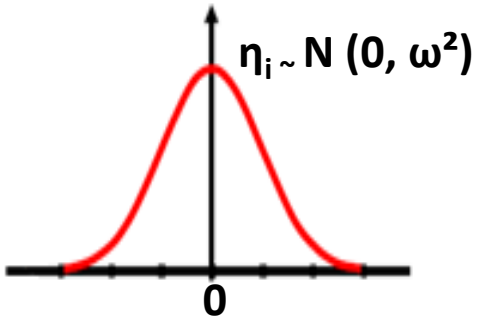


Steimer JL, Vozeh S, Racine Poon A, Holford N, O'Neil R: The population approach: rationale, methods and applications in clinical pharmacology and drug development. *In P.G. Welling & L. Balant (eds), Handbook of experimental pharmacology (vol 110 : Pharmacokinetics of drugs, Berlin : SpringVerlag, 1994, 405-451)*

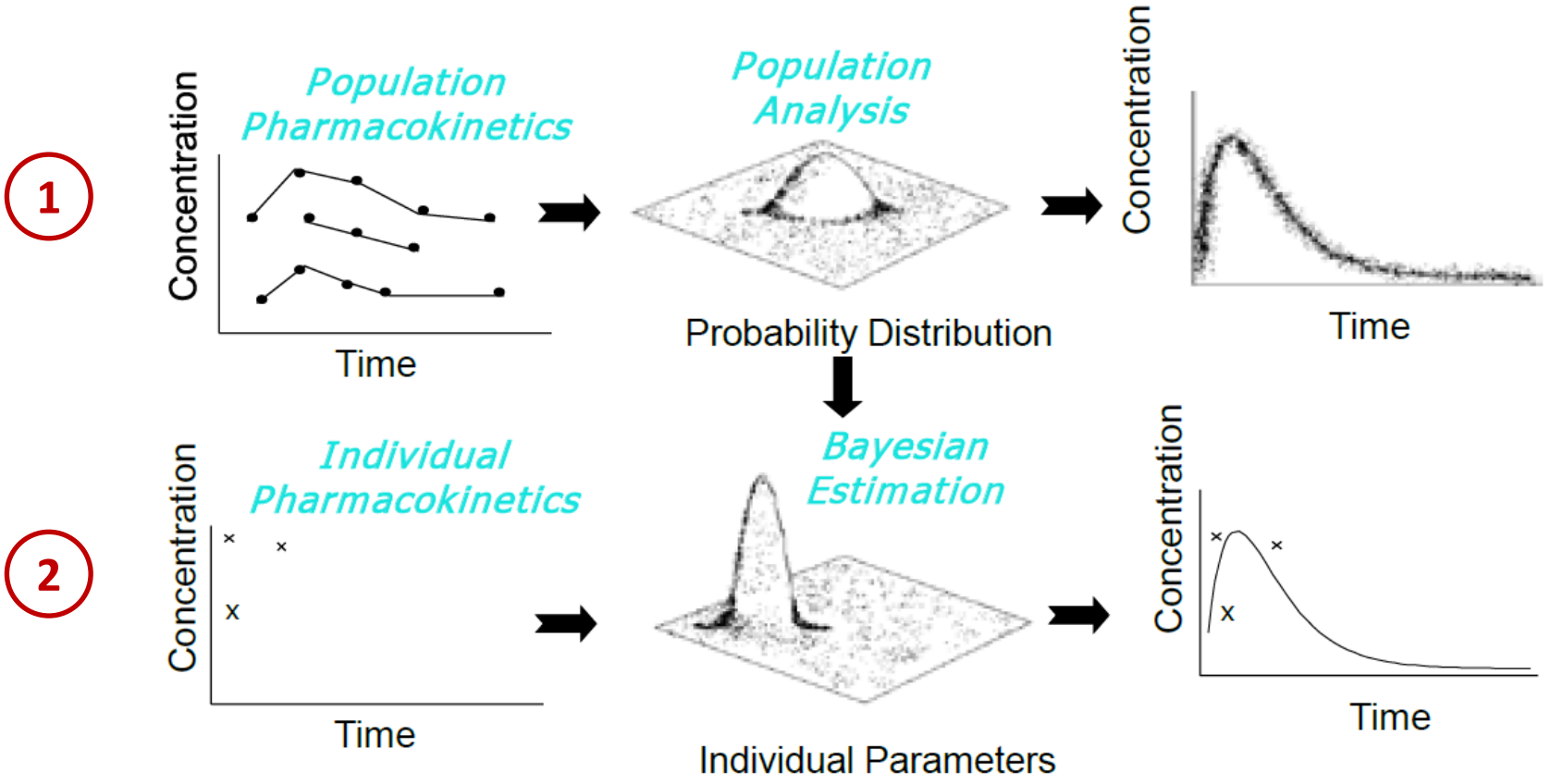
NONLINEAR MIXED EFFECTS MODELS



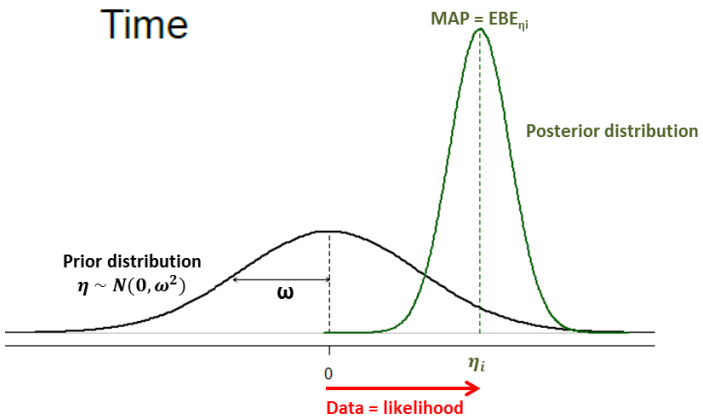
1. Analysis of all observations
   - Estimation of population parameters (μ, ω^2, σ^2)
     - maximum likelihood
     - prior distribution



NONLINEAR MIXED EFFECTS MODELS



2. Estimation of individual parameters
   - Bayesian method
     - maximum a posteriori = individual parameters
     - $\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i}}$



NONLINEAR MIXED EFFECTS MODELS

Likelihood

$$\boldsymbol{L}(\theta, \boldsymbol{y}) = \boldsymbol{p}(\boldsymbol{y}/\theta)$$

- Probability to observe y knowing θ
- Maximum likelihood : estimate the parameters θ for model predictions are as close as possible to the observed data

Issue

- f is nonlinear in its parameters
  - no analitycal expression of the likelihood
  - required to approximate the likelihood
    - estimation algorithms

NONLINEAR MIXED EFFECTS MODELS

First estimation method

NON linear Mixed Effects Model

L. Sheiner & S. Beal, UCSF

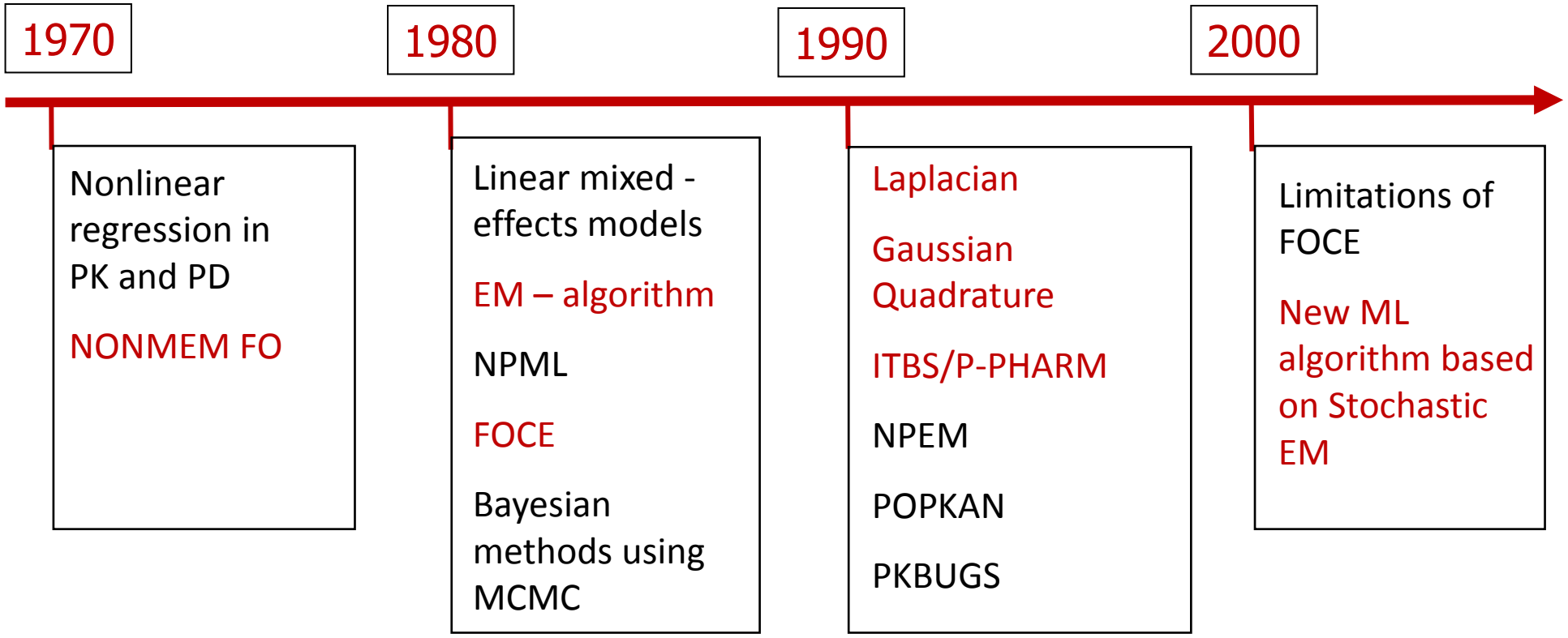
- **1972: Concept and FO method**
  Sheiner, L. B., Rosenberg, B. & Melmon, K. L. Modelling of individual pharmacokinetics for computer-aided drug dosage. *Comput. Biomed. Res. Int. J.* **5,** 411–459 (1972).

- **1977: First publication**
  Sheiner, L. B., Rosenberg, B. & Marathe, V. V. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J. Pharmacokinet. Biopharm.* **5,** 445–479 (1977).

- **1980: NONMEM - first software**
  Beal, S. L. & Sheiner, L. B. The NONMEM system. *Am Stat.* **34,**118-119 (1980).
  Beal, S. L. & Sheiner, L. B. Estimating population kinetics. *Crit. Rev. Biomed. Eng.* **8,** 195–222 (1982).

NONLINEAR MIXED EFFECTS MODELS

Development of estimation methods



Pillai, G. C., Mentré, F. & Steimer, J.-L. Non-linear mixed effects modeling - from methodology and software development to driving implementation in drug development science. *J. Pharmacokinet. Pharmacodyn.* **32,** 161–183 (2005).

NONLINEAR MIXED EFFECTS MODELS

Estimation softwares for nonlinear mixed effects models

Tableau 2 – Logiciels de population les plus utilisés

Logiciel	Algorithmes disponibles	Type	Interface
Monolix	SAEM	Mixte (1)	Oui
NONMEM	FO, FOCE, Laplace, SAEM, Bayes	Payant	Non
Phoenix	FOCE	Payant	Oui
R (librairies)	nlme, lme4 (FOCE, Laplace), saemix (SAEM)	Gratuit	Non (2)
SAS	NLMIXED (FO, FOCE, AGQ)	Payant	Oui
WinBugs	Bayes	Gratuit	Non

(1) Licence gratuite pour les universitaires et étudiants.
(2) R n'a pas d'interface graphique spécifique mais des outils comme Rstudio peuvent être utilisés pour le faire tourner.

NONLINEAR MIXED EFFECTS MODELS

Model development

Find the model which describes adequately the data, by determining :

- Structural model
- Variability model (inter and intraindividual)
- Residual error model
- Covariates

No consensus on building method

- Development of a basic model without covariates
- Analysis and integration of significant covariates in model

NONLINEAR MIXED EFFECTS MODELS

Model selection

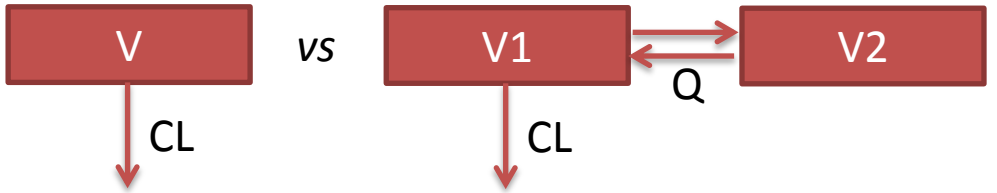
Parsimony : the model which best describe the data with the lower number of parameters

Statistical criteria:

- $-2LL = -2\log(likelihood)$
  - approximate of likelihood to minimize
- Other criteria: AIC, BIC

Likelihood Ratio Test (LRT)

- Reduced model (p parameters) : $-2LL_{reduced}$
- Full model ($p+q$ parameters) : $-2LL_{full}$
- Under H_0 : $-2LL_{reduced} - -2LL_{full} \sim \chi^2\ (ddl = q)$



NONLINEAR MIXED EFFECTS MODELS

Model evaluation

Estimation precision

$$RSE\ (\%) = \frac{Standard\ Error}{Parameter\ estimate}$$

Graphical evaluation

- Comparison of model predictions to observed data
- Residuals evaluation
- Simulations based evaluation
  - VPC (Visual Predictive Check)
  - NPDE (Normalized prediction distribution errors)

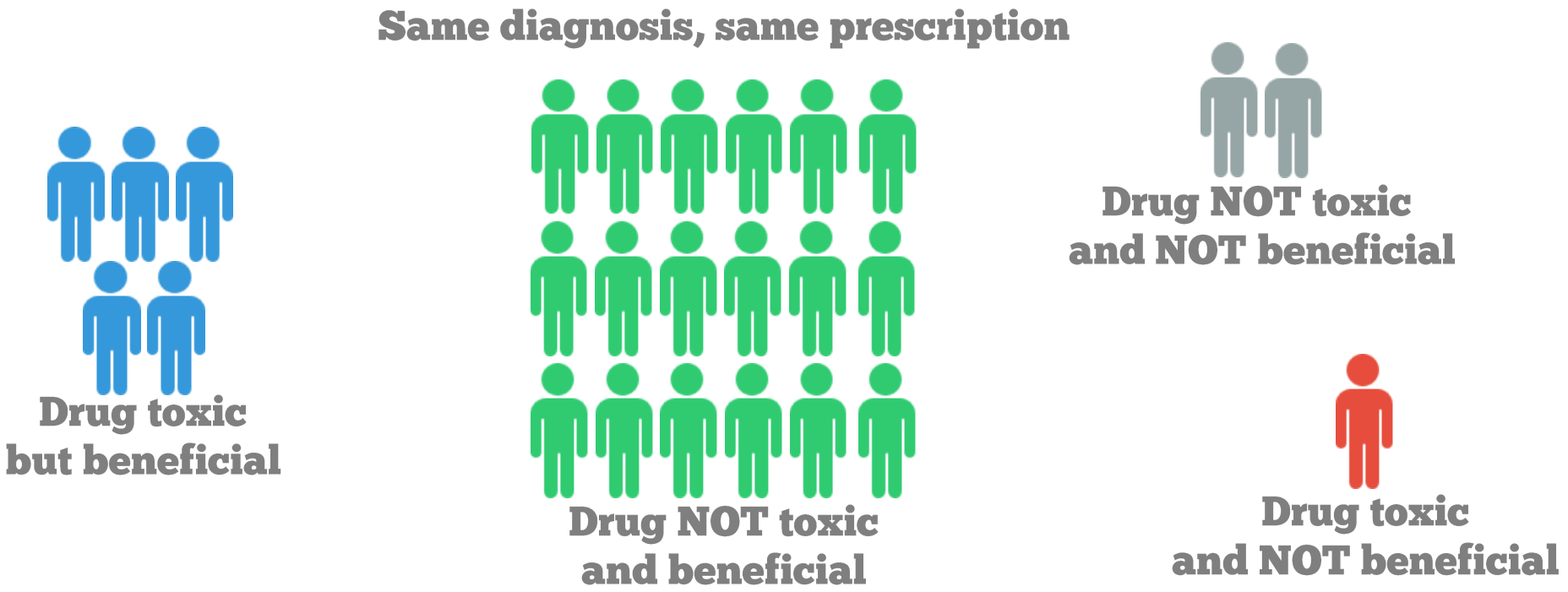
Numerical evaluation

- data splitting
- bootstrap
- Jack-knife

TREATMENT INDIVIDUALIZATION

PHOTOGRAPH BY ADAM VOORHES

THERAPEUTIC INTERESTS



- Administer the right dose for each patient depending on its features and characteristics of the drug (therapeutic range)

Methods

- *a priori* adaptation
- *a posteriori* adaptation through Bayesian method

A PRIORI ADAPTATION

Model : structure, variability, covariates

Patient : no PK data, only subject characteristics (age, weight, biology…)

- Predict the patient PK parameters using model and covariates values
  - Predict concentrations for this subject
  - Limited when variability is high or with a limited number of covariates in model

Prediction of carboplatin clearance :

- 4 covariates associated to carboplatin clearance

$$CL = 0.134 \times weight + \frac{218 \times weight \times (1 - 0.00457 \times age) \times (1 - 0.314 \times sex)}{serum\ creatinine}$$

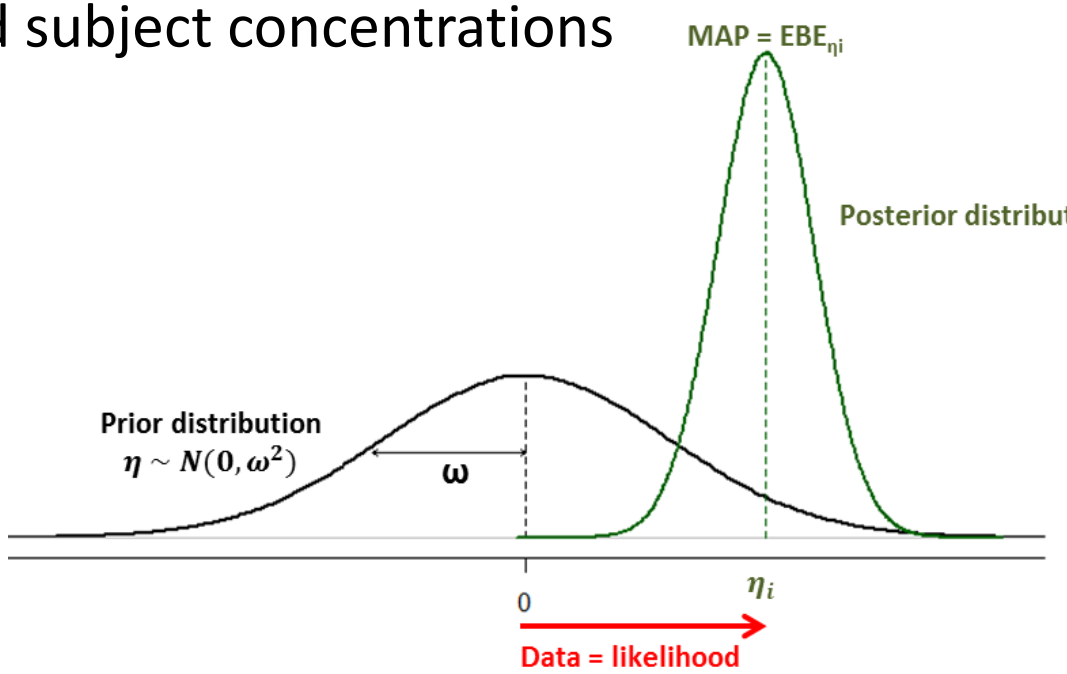
$AUC = Dose/CL$: determine the dose to reach the targeted l'AUC?

Chatelut, E. *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J. Natl. Cancer Inst.* **87,** 573–580 (1995).

A POSTERIORI ADAPTATION : BAYESIAN APPROACH

$$prior \propto data = posterior\ distribution$$

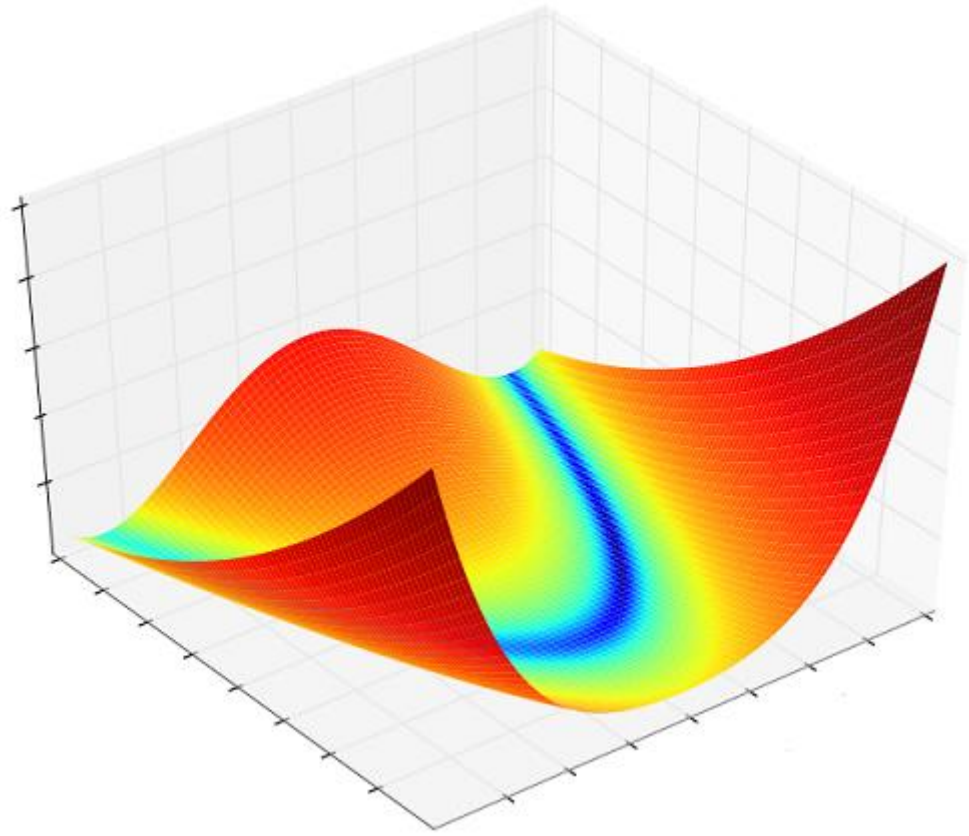
- Prior : population model parameters (mean μ and variance ω^2)
- Data : measured subject concentrations



$$\boldsymbol{\theta_i} = \mu\, \boldsymbol{e^{\eta_i}}$$

- Posterior distribution : individual PK parameters
  - Prediction of next concentrations
    - determine the next dose
    - periodic evaluation to optimize dose on intraindividual variability

DESIGN OPTIMIZATION



DESIGN FOR POPULATION PK-PD ANALYSIS

Importance of the choice

- Influence the precision of parameters estimation
- Poor design can lead to unreliable studies
- All the more important in pediatric studies
  - severe limitations on the number of samples to be taken
  - ethical and physiological reasons

Problem : choice of population design

- number of patients?
- number of sampling times?
- sampling times?

Recommendations on design in the FDA guidance

EVALUATION OF POPULATION DESIGN

Two approaches

- simulation studies: cumbersome!
- methodology based on the Fisher Information matrix (FIM) in NLMEM

Expression of MF for population PK

- complex
- based on a linearisation of the model around the fixed effects
  (Mentré, Mallet & Baccar. Biometrika,1997) (Retout, Mentré & Bruno. Stat Med, 2002)

Principle

- to compute M_F and its inverse for each population design to be evaluated
  - from the population model
  - from a priori value of the population parameters
- expected standard errors on the parameters = root mean square of the diagonal of M_F^{-1}

OPTIMIZATION OF POPULATION DESIGN

Design comparisons

- objective : to have the “smallest” M_F^{-1} or the “largest” M_F
- criteria for matrix comparison
  - D-optimality, the most usual one: det (M_F)

Optimization of exact or statistical designs

- Maximization of det(M_F)
  - Find the best design for a given value of the population parameters

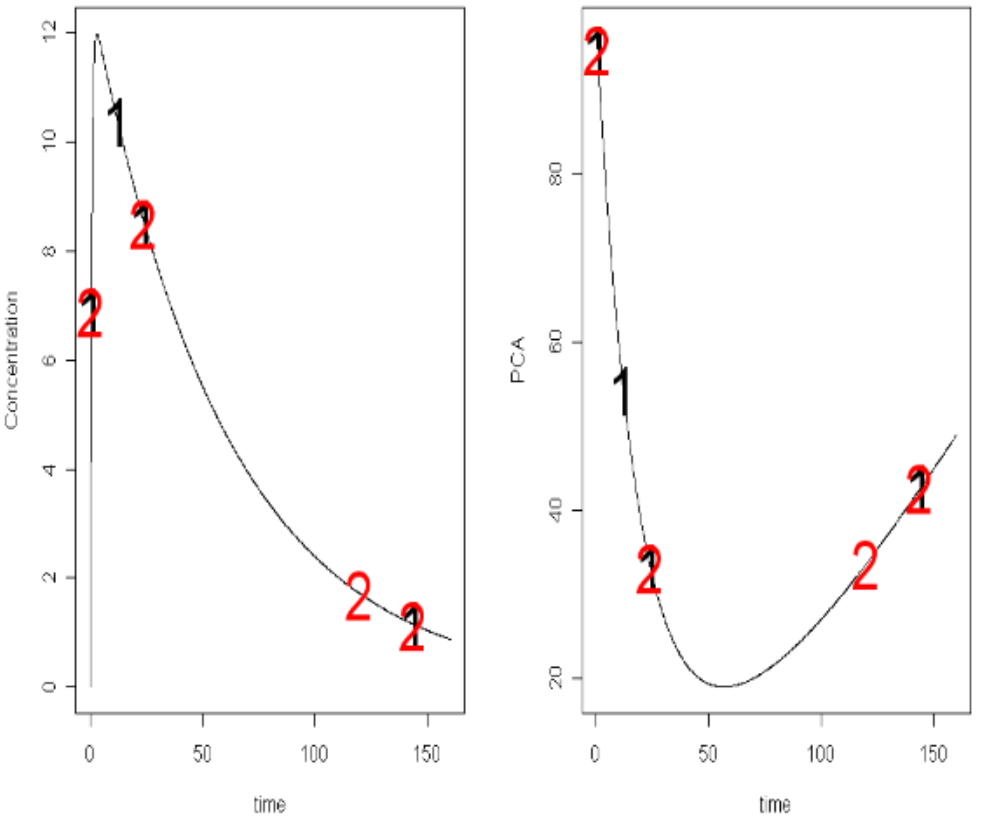
- Optimization of both the sampling times and the group structure
  - Fedorov-Wynn (specific algorithm), Simplex algorithm..

OPTIMIZATION OF POPULATION DESIGN

PFIM software

www.pfim.biostat.fr

```
*************************** OPTIMISED DESIGN ************:
Optimised population design:
Sample times for response: A
             prot.opti subjects.opti Subjects
1  c(0.5, 12, 24, 144)      0.6768466 21.65909
2 c(0.5, 24, 120, 144)      0.3231534 10.34091


Sample times for response: B
             prot.opti subjects.opti Subjects
1  c(0.5, 12, 24, 144)      0.6768466 21.65909
2 c(0.5, 24, 120, 144)      0.3231534 10.34091

Associated optimised criterion: 580.1989

************************* EXPECTED STANDARD ERRORS *********

------------------------ Fixed Effects Parameters -----------

      Beta     StdError         CV .
Ka   1.600 0.263353095 16.459568 %
CL   0.133 0.006533504  4.912409 %
V    7.950 0.322403263  4.055387 %
Rin  5.410 0.437881955  8.093936 %
C50  1.200 0.052867047  4.405587 %
Kout 0.056 0.001737771  3.103163 %


------------------------- Variance of Random Effects --------

      Omega     StdError         CV .
Ka   0.7010 0.206505767  29.45874 %
CL   0.0634 0.017561742  27.69991 %
V    0.0206 0.012226360  59.35126 %
Rin  0.1900 0.050298864  26.47309 %
C50  0.0129 0.016460059 127.59736 %
Kout 0.0167 0.007665362  45.90037 %


------------------------ Variance of residual error ---------

            SIG  StdError        CV .
sig.slopeA 0.20 0.0216894 10.84470 %
sig.interB 3.88 0.4677695 12.05591 %
```



→ **Two groups with 22 and 10 subjects**
→ **Total of 256 sampling times**

CONCLUSION

PHOTOGRAPH BY ADAM VOORHES

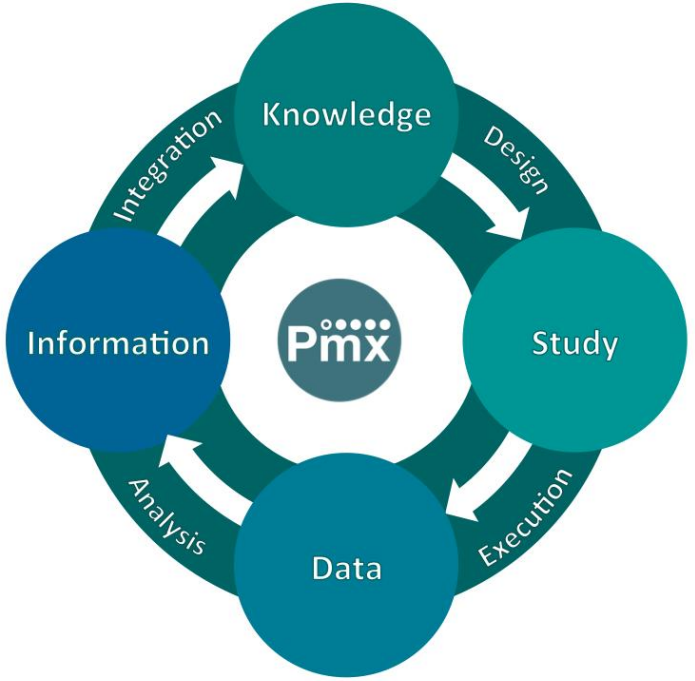
INTERESTS FOR PHARMACOMETRICS

- Empirical or mechanistic description of data and PK-PD relationships
  - Now common method in the drug authorization application files
- Analysis of pharmacodynamic data (E_{max}, EC_{50})
- Analysis of sparse data (phase II and phase III)
- Estimation of variability and sources of variability (covariates)
- Prediction : other dosage schemes (schedule, dose, administration route…), sub-population (children, renal impairments…)
- Planning of next studies (clinical trial simulations, optimal design)
- Treatment individualization

INTERESTS FOR PHARMACOMETRICS

Model-Based Drug Development

- Guiding the drugs development through the use of pharmacometrics



CONCLUSION
FINALLY

- Increasing role of quantitative analysis of data through models in drugs evaluation

- Cooperative work
  - biologists, pharmacologists, clinicians
  - engineers, mathematicians, statisticians

  } Pharmacometricians

- Many open methodological problems…

Thank you for your attention