MODELING AND SIMULATION IN PHARMACOMETRICS:
SOME METHODS, TOOLS AND OPEN PROBLEMS

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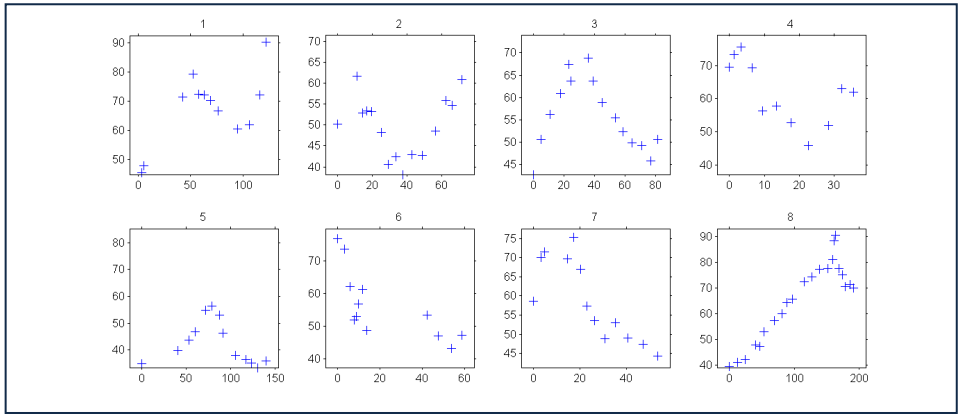
Inria Saclay & Ecole Polytechnique

April 5th 2023

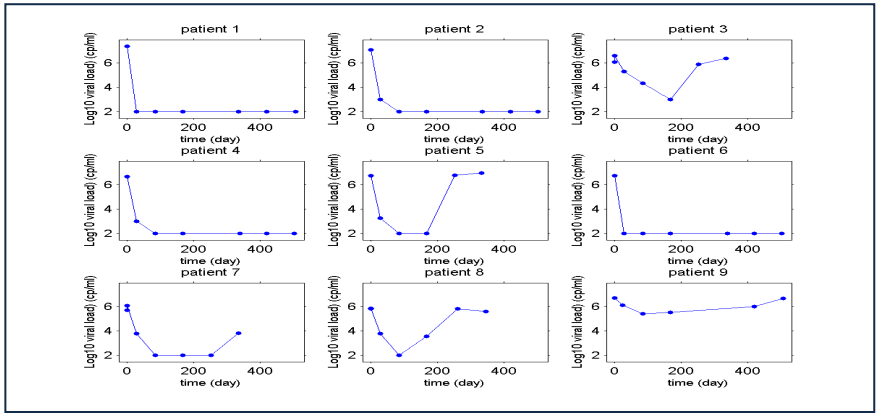
MASCOT-NUM 2023

SOME CLINICAL DATA

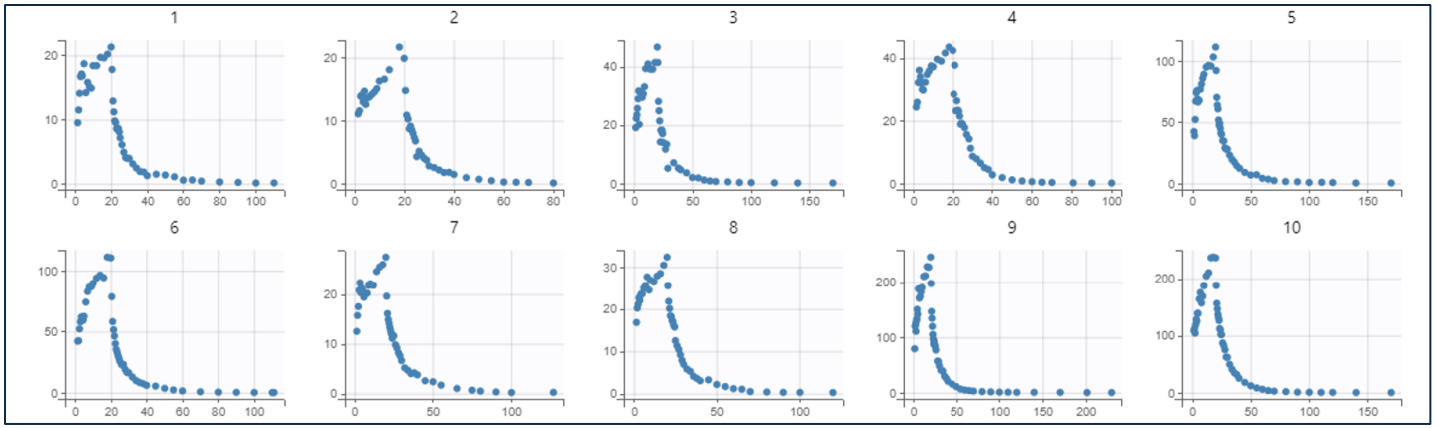
tumor sizes



viral loads (HIV)



drug concentration



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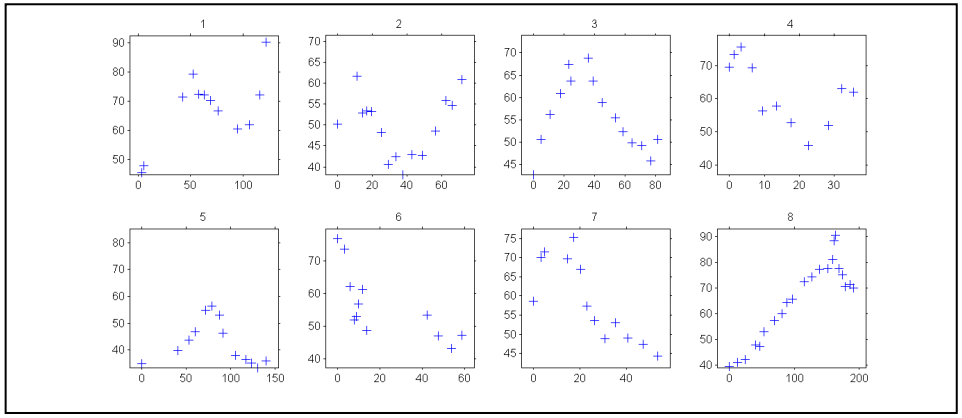

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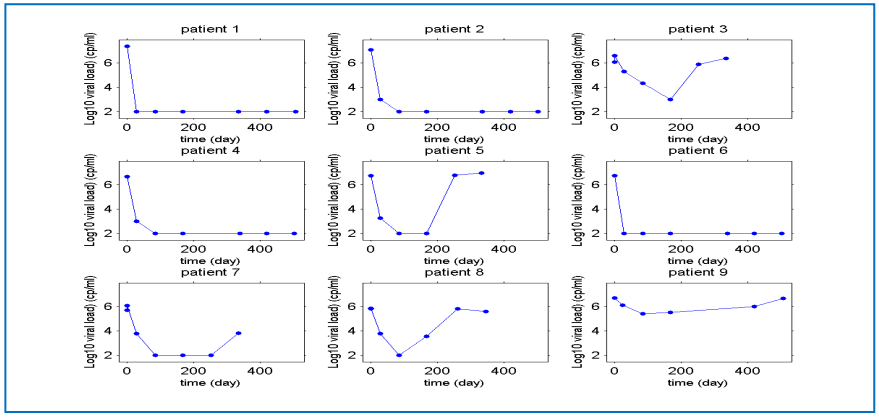

Objective : build

- *A mecanistic model* that describes the dynamics of the phenomena under study

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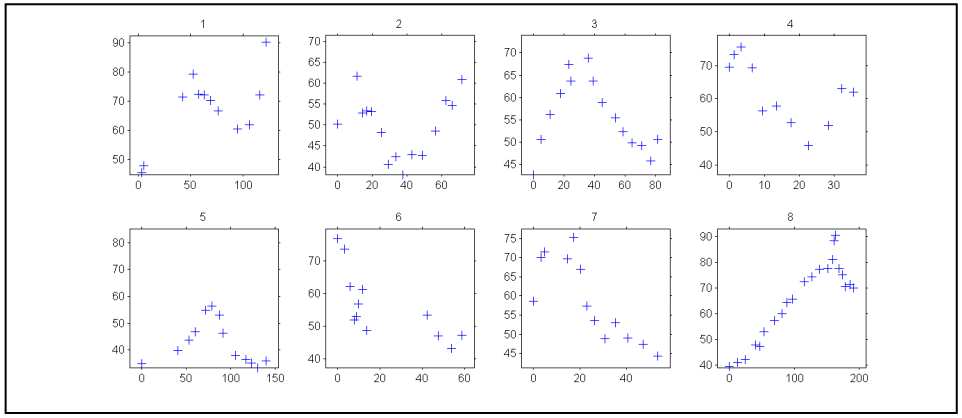

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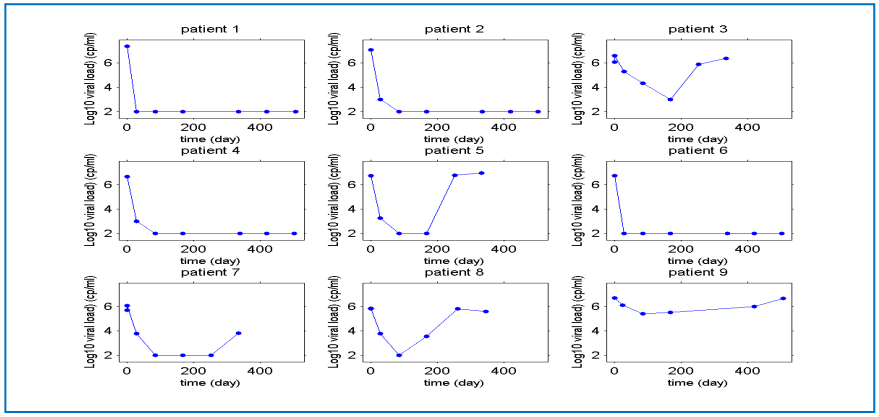

Objective : build

- *A mecanistic model* that describes the dynamics of the phenomena under study
- *A statistical model* that describes the variability of the observed data

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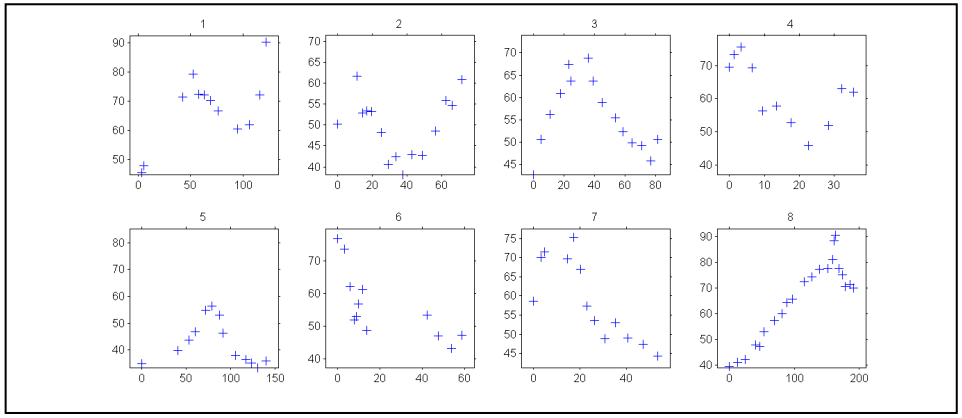
tumor sizes



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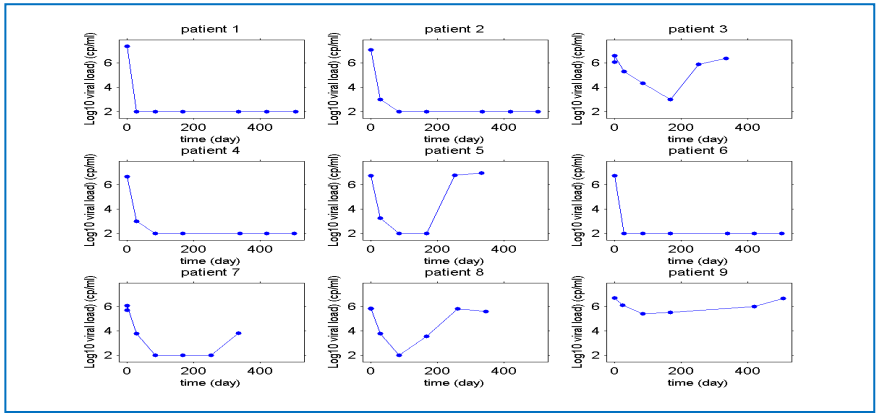

Method for model building

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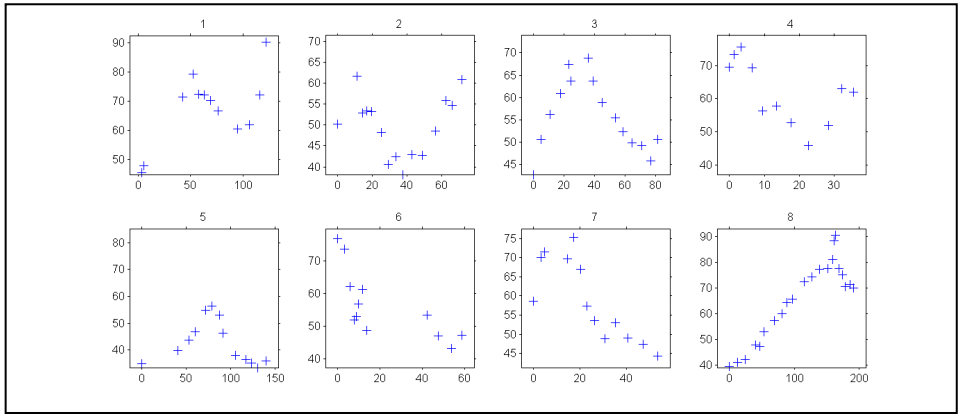

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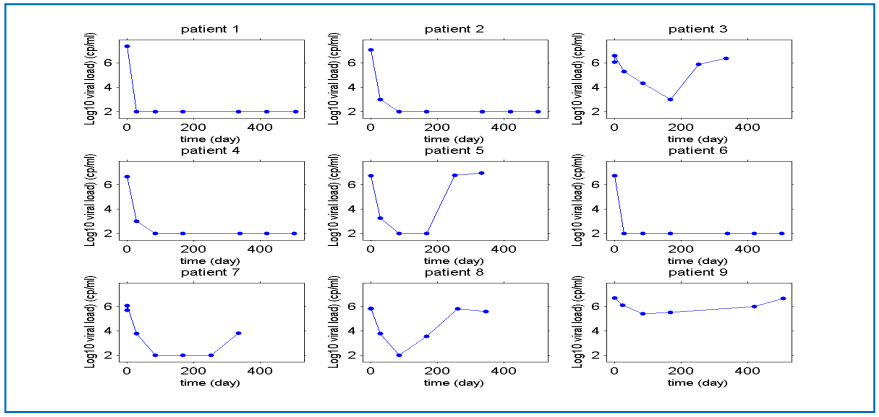

Method for model building

1. Make some hypothesis about the model

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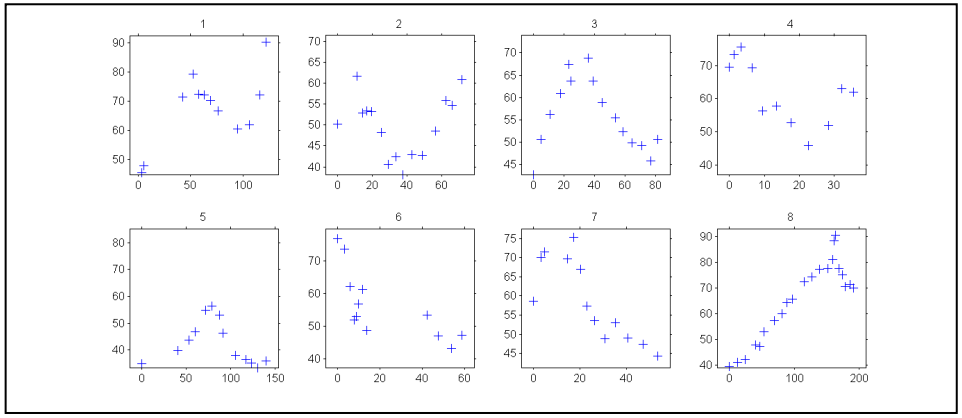

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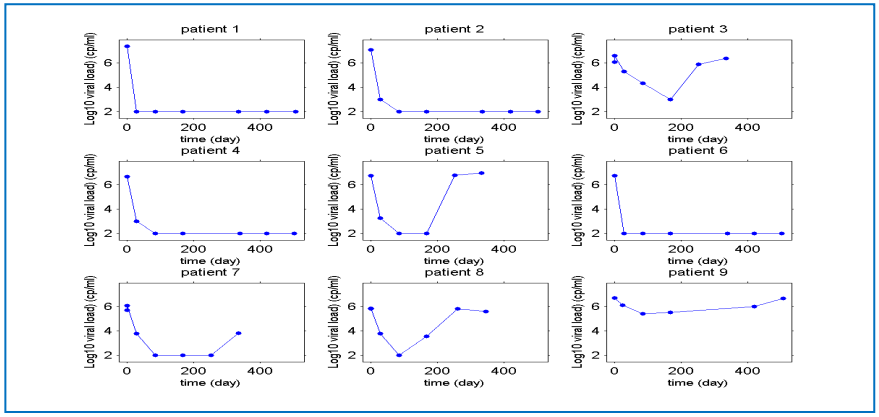

Method for model building

1. Make some hypothesis about the model
2. Implement and fit this model to the data

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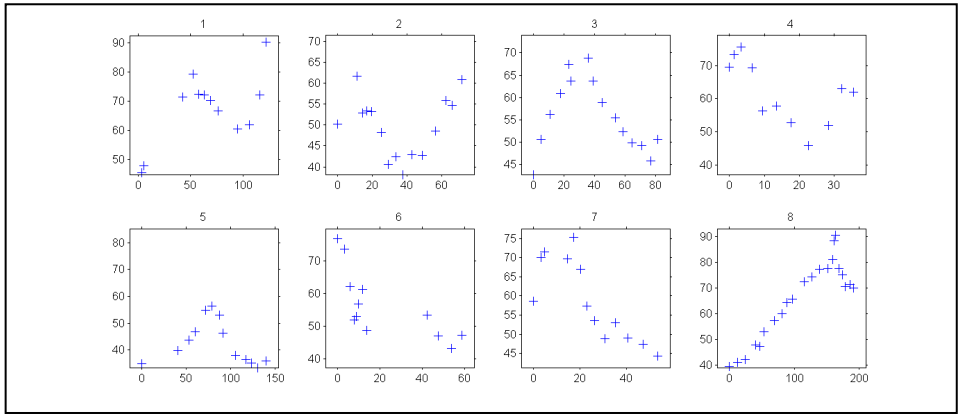

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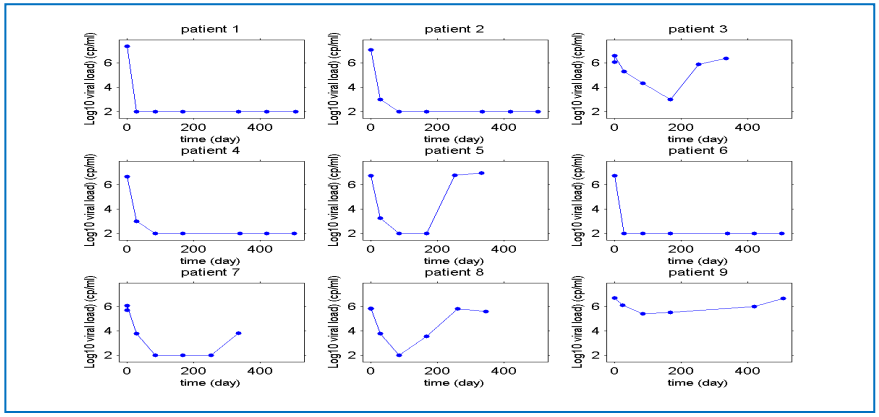

Method for model building

1. Make some hypothesis about the model
2. Implement and fit this model to the data
3. Detect possible misspecifications in the model

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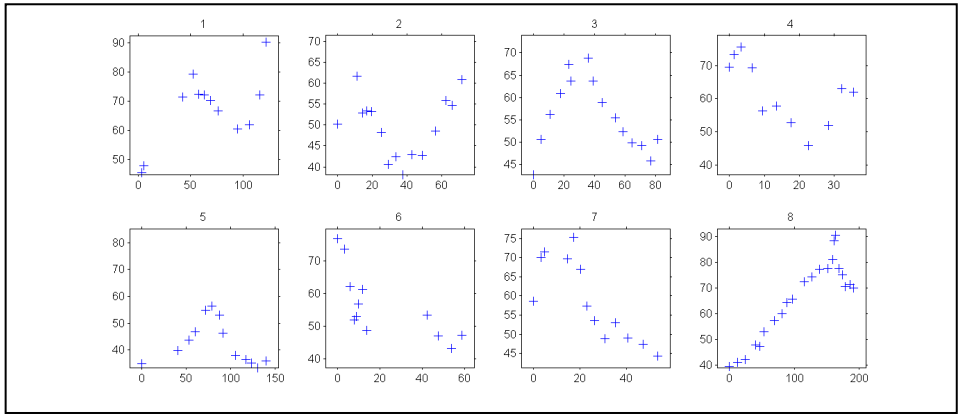

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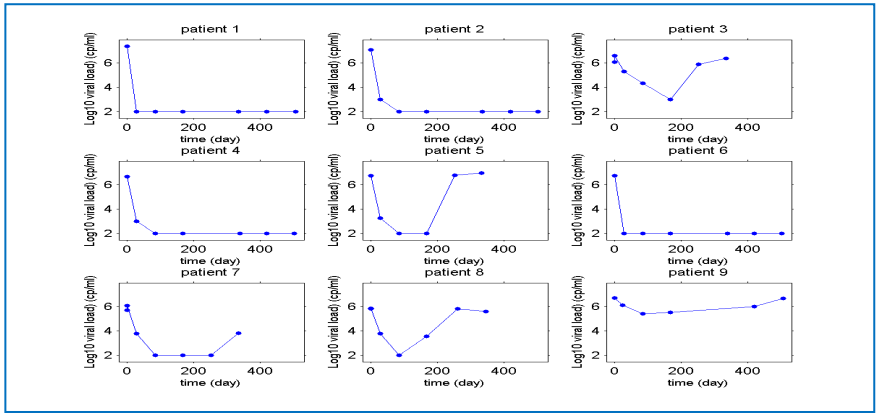
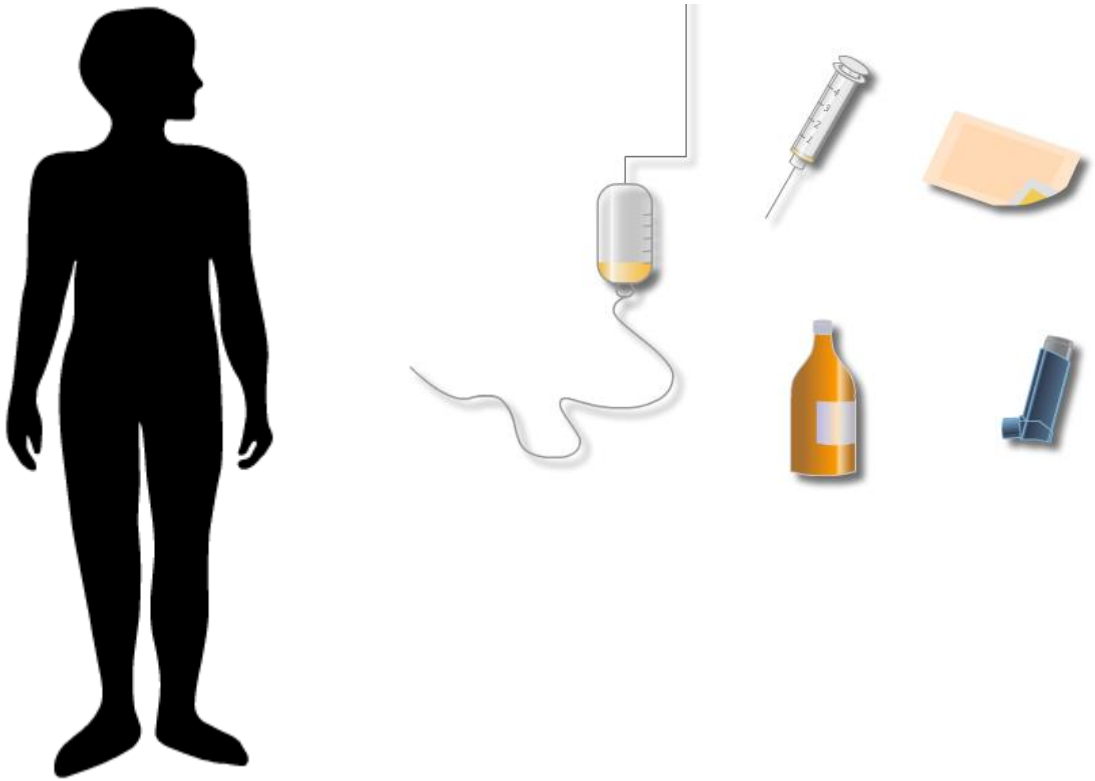


Method for model building

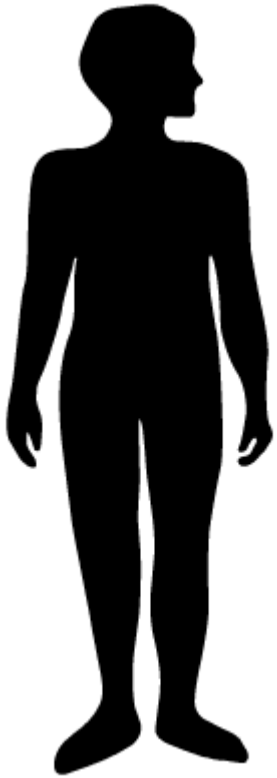
1. Make some hypothesis about the model
2. Implement and fit this model to the data
3. Detect possible misspecifications in the model
4. Define a new model and go to step 2.

Introduction to PKPD modelling

Introduction to PKPD modeling



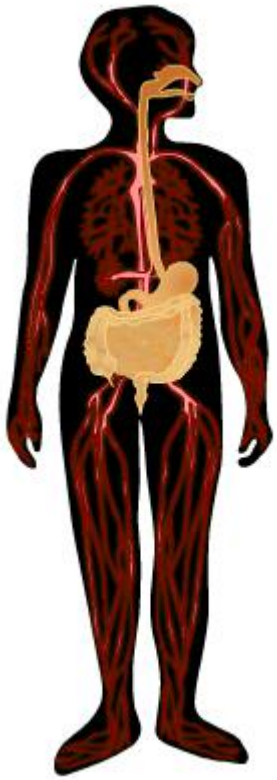
Introduction to PKPD modeling



warfarin

anticoagulant used in the prevention of thrombosis

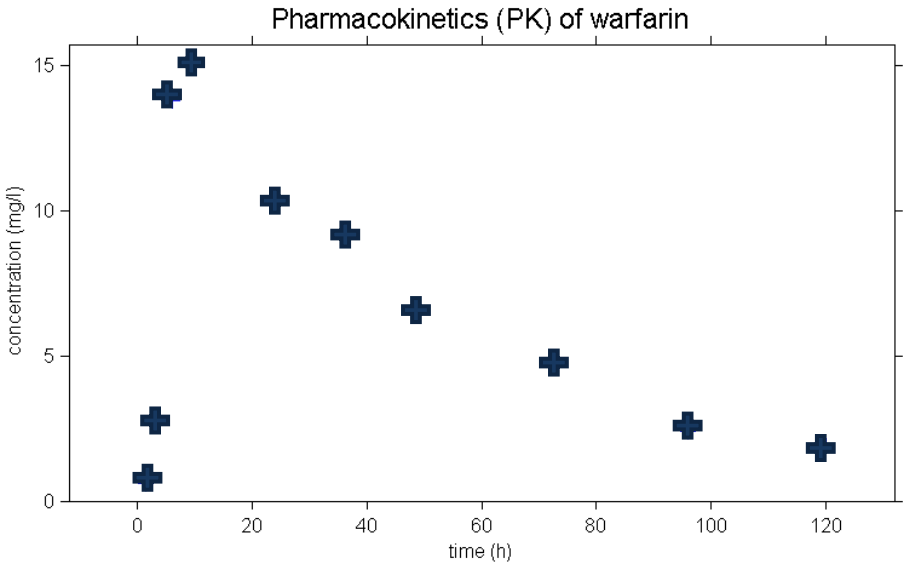
Introduction to PKPD modeling



Pharmacokinetics:

what the body does to the drug

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion



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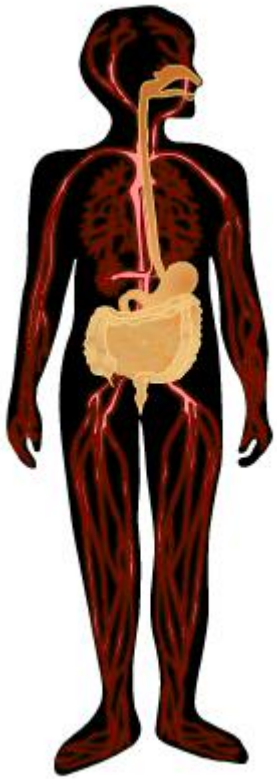

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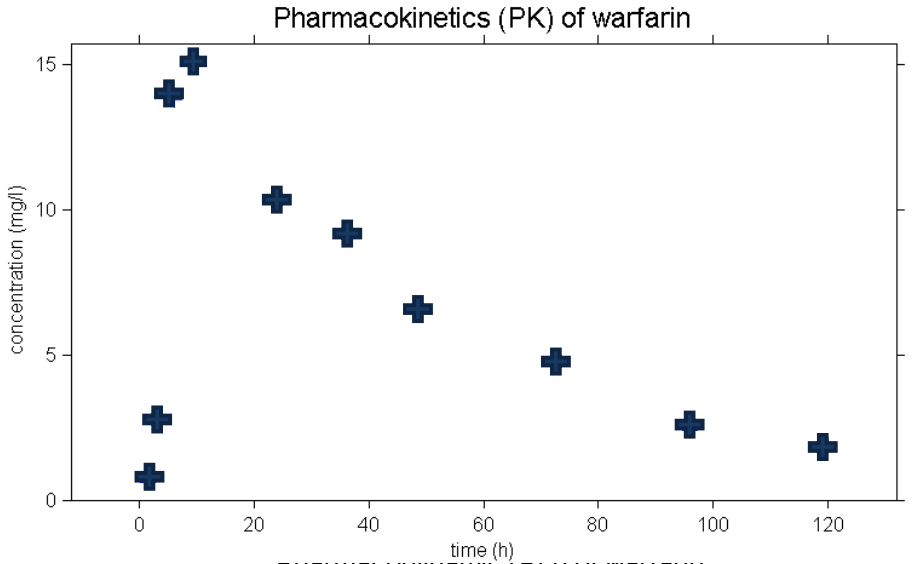
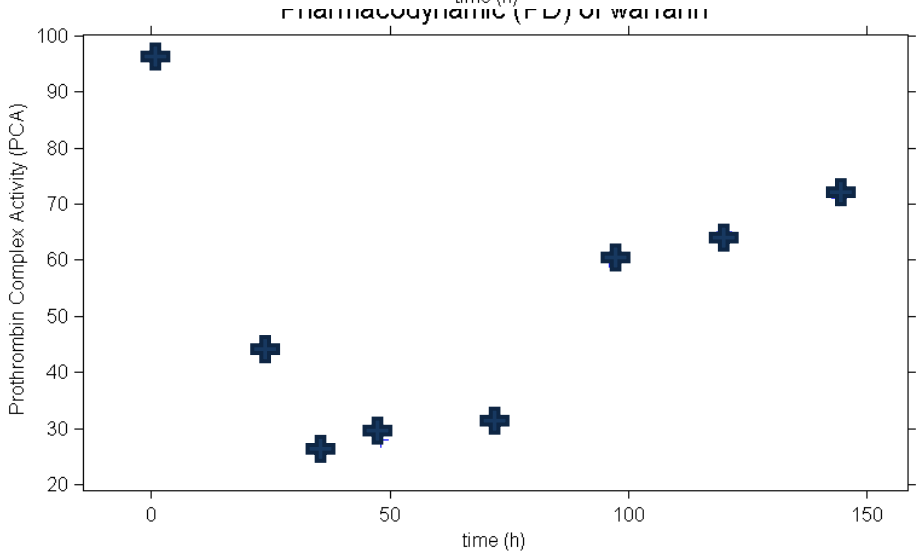
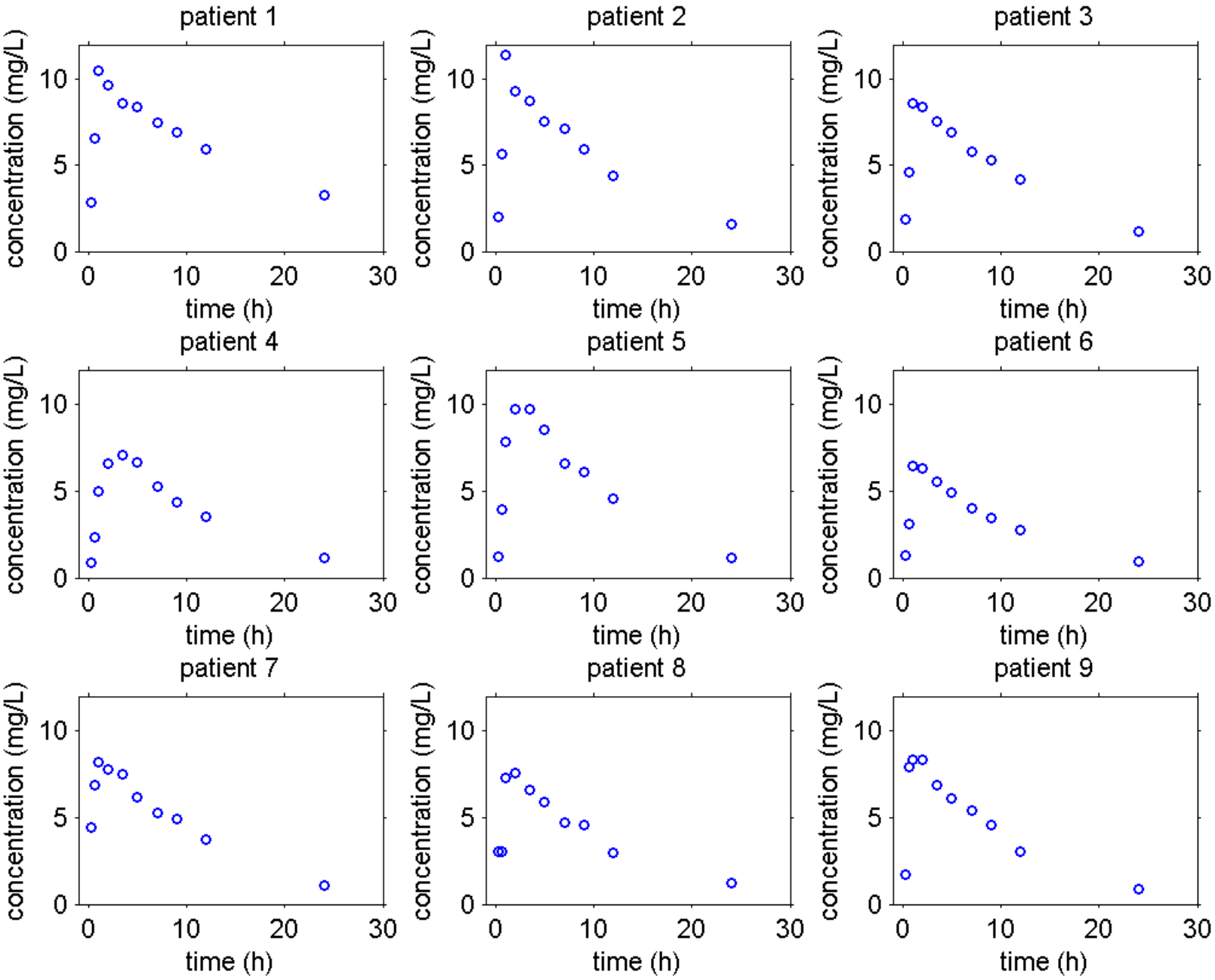


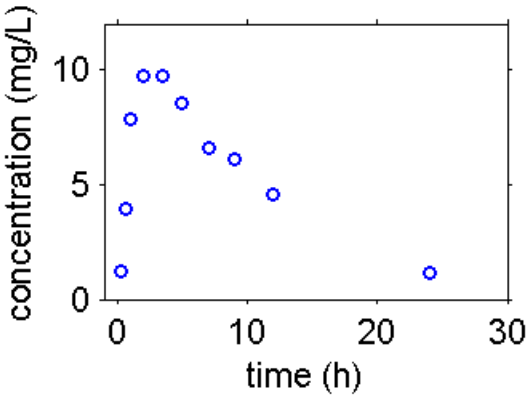
Pharmacodynamics:

what the drug does to the body



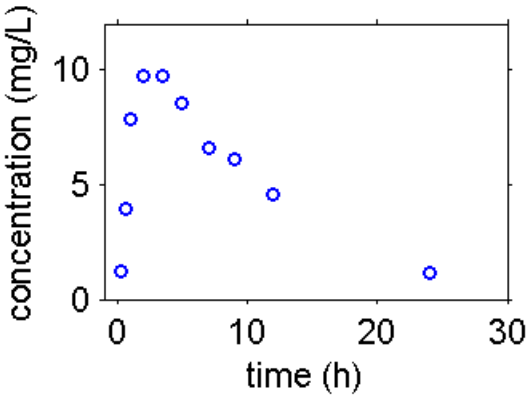

patient 1
patient 2
patient 3
patient 4
patient 5
patient 6
patient 7
patient 8
patient 9
concentration (mg/L)
time (h)
0
5
10
0
10
20
30

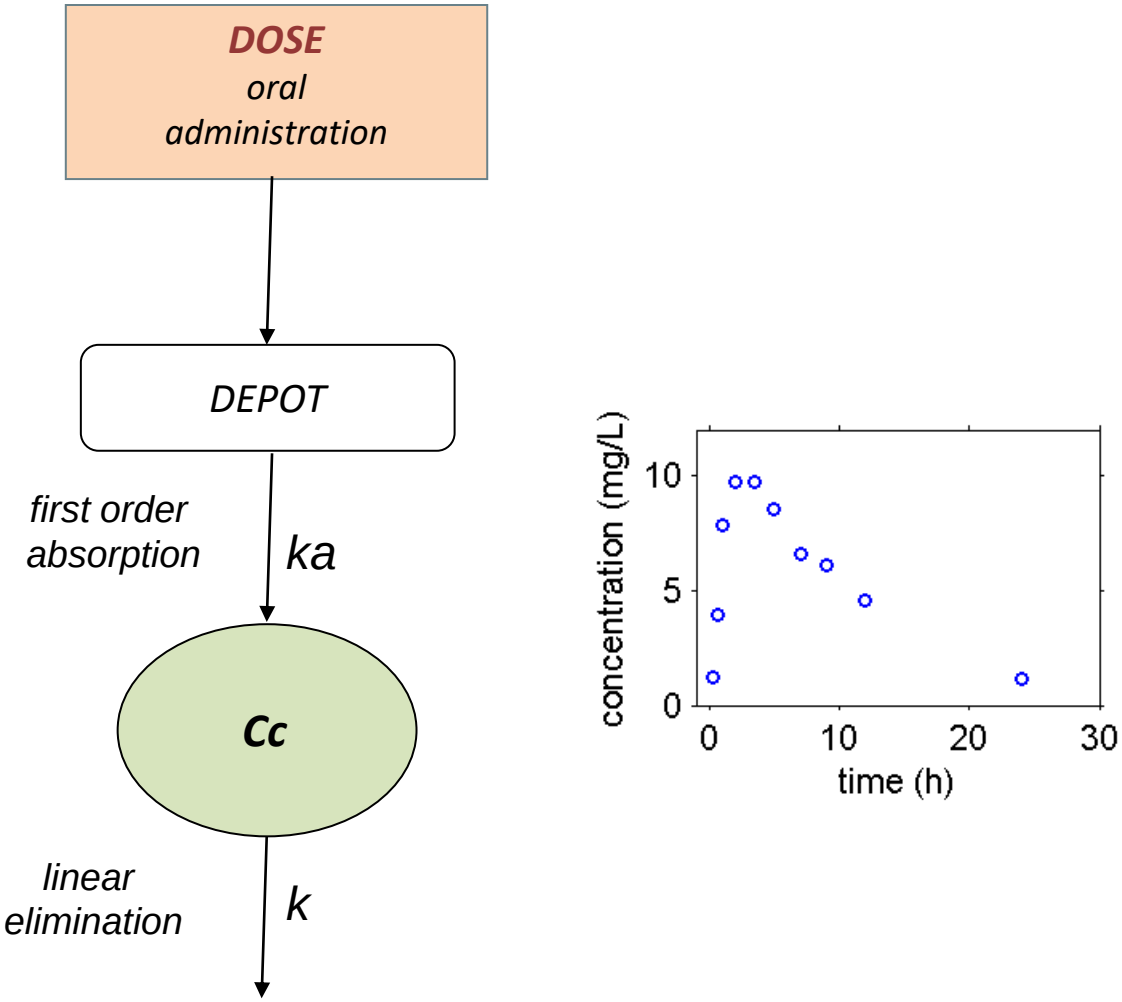
The individual approach

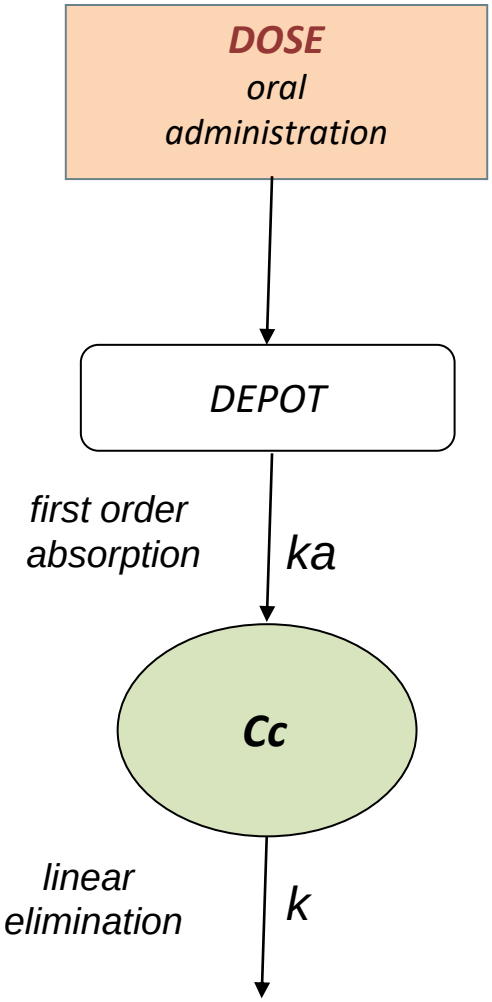

concentration (mg/L)
10
5
0
0
10
20
30
time (h)

Observations: $y_1, y_2, \ldots, y_n$ at times $t_1, t_2, \ldots, t_n$

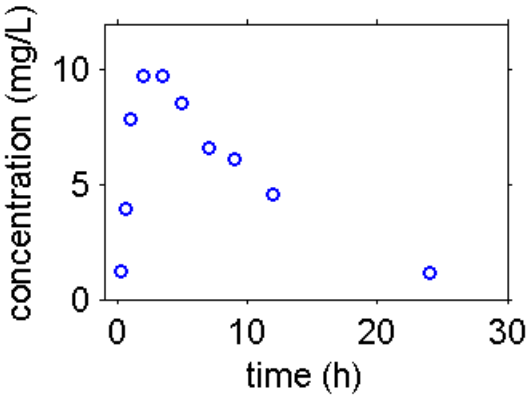
Model: $y_j = f(t_j, \psi) + e_j \quad , \quad 1 \leq j \leq n$

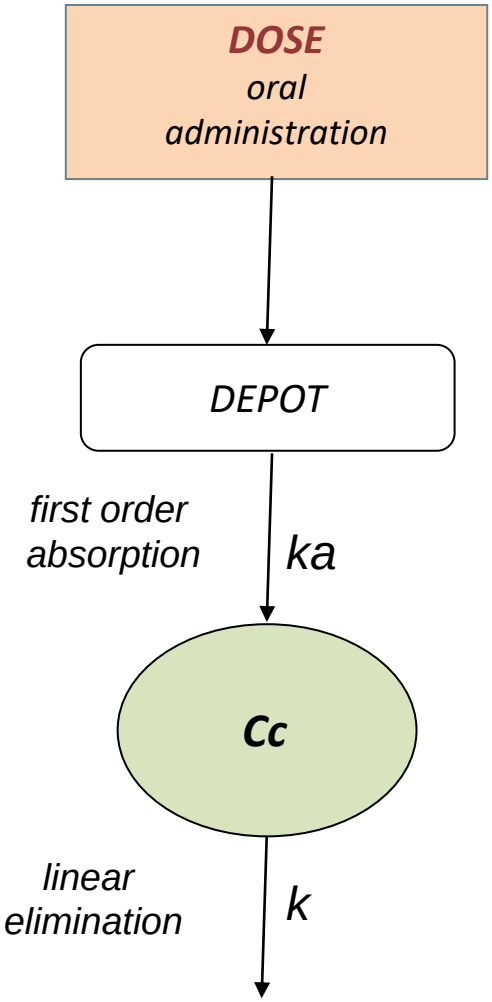



DOSE
oral
administration
DEPOT
first order
absorption
ka
Cc
linear
elimination
k
concentration (mg/L)
10
5
0
0
10
20
30
time (h)



$$\begin{aligned} \frac{d}{dt} A_d(t) &= -k_a\, A_d(t) \\ \frac{d}{dt} A_c(t) &= k_a\, A_d(t) - k\, A_c(t) \\ Cc(t) &= Ac(t)/V \end{aligned}$$





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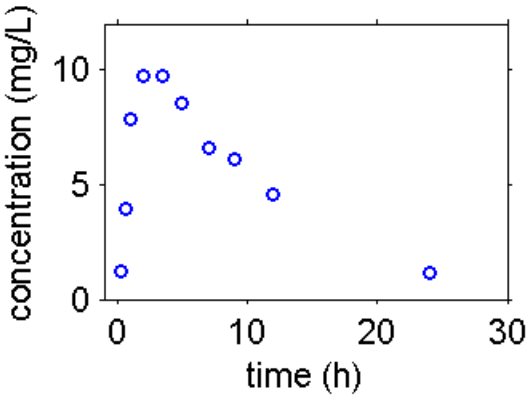
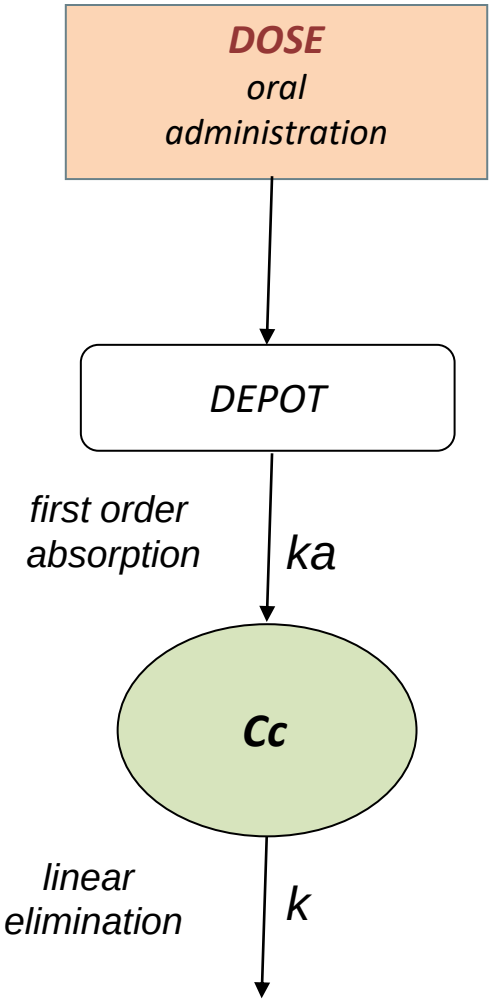


$$y_j = Cc(t_j, \psi) + e_j \quad , \quad e_j \underset{\text{i.i.d.}}{\sim} \mathcal{N}(0, \sigma^2)$$

$$\psi = (k_a, V, k)$$



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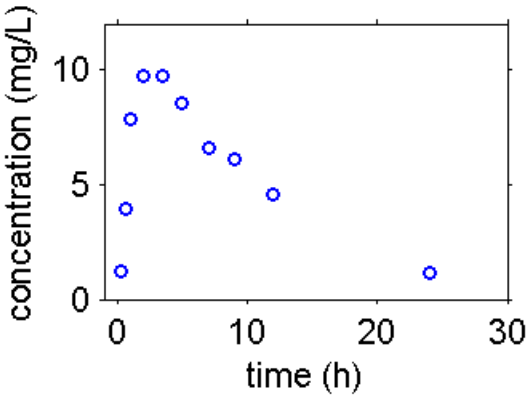

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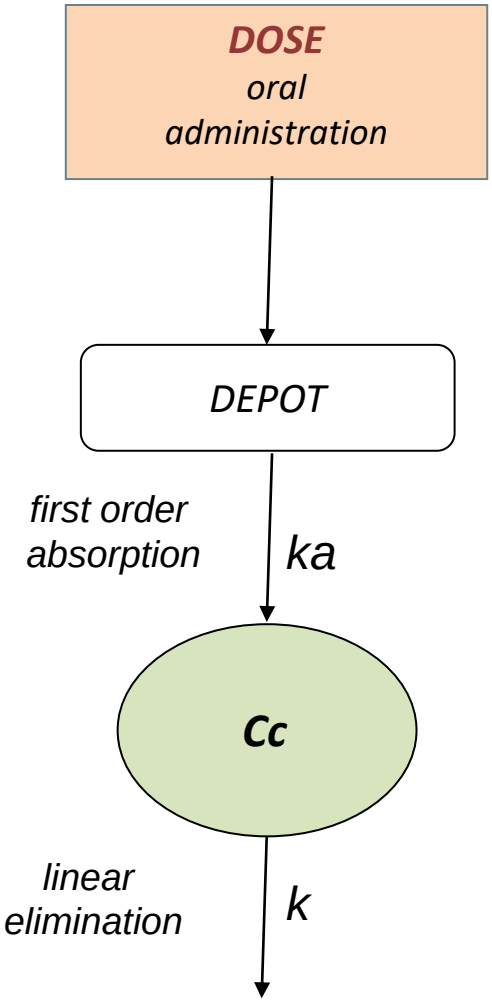
$$\hat{\psi} = \arg\max_{\psi} \mathbf{p}(y; \psi) = \arg\min_{\psi} \sum_{j=1}^{n} (y_j - Cc(t_j, \psi))^2$$



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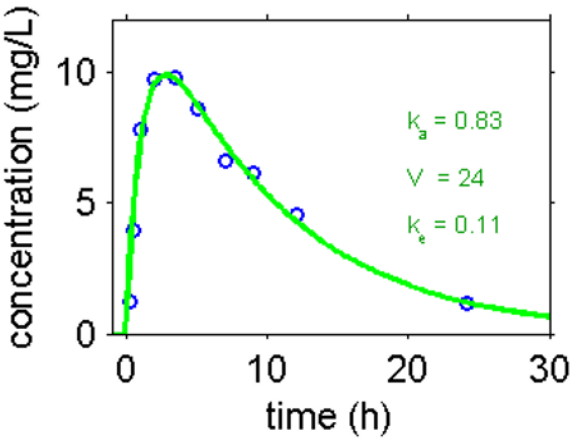

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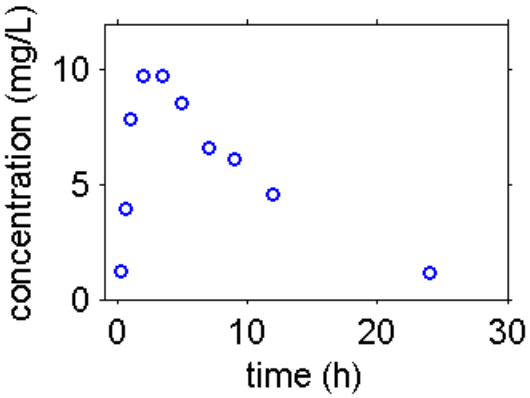
The population approach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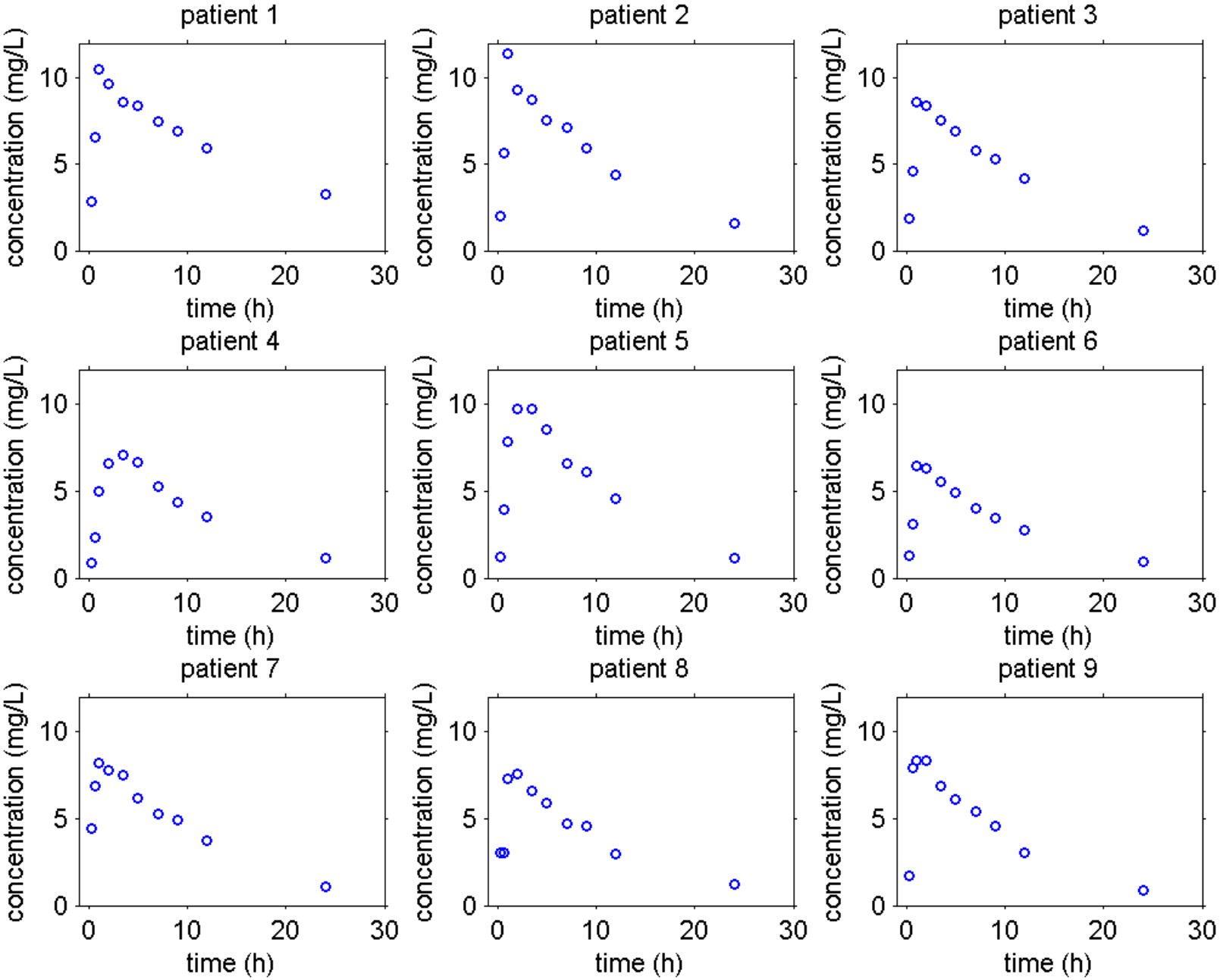
time (h)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$$
\begin{aligned}
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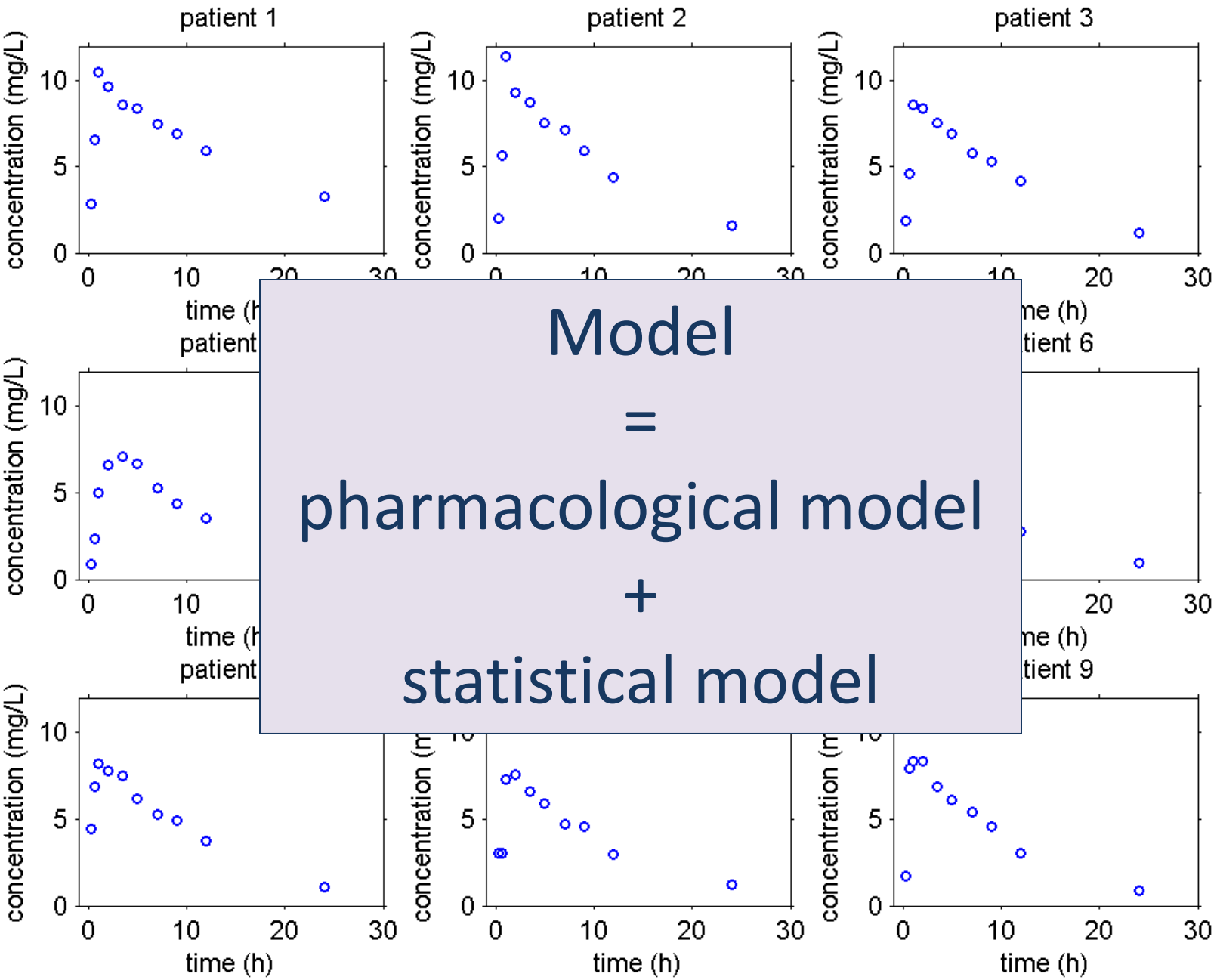
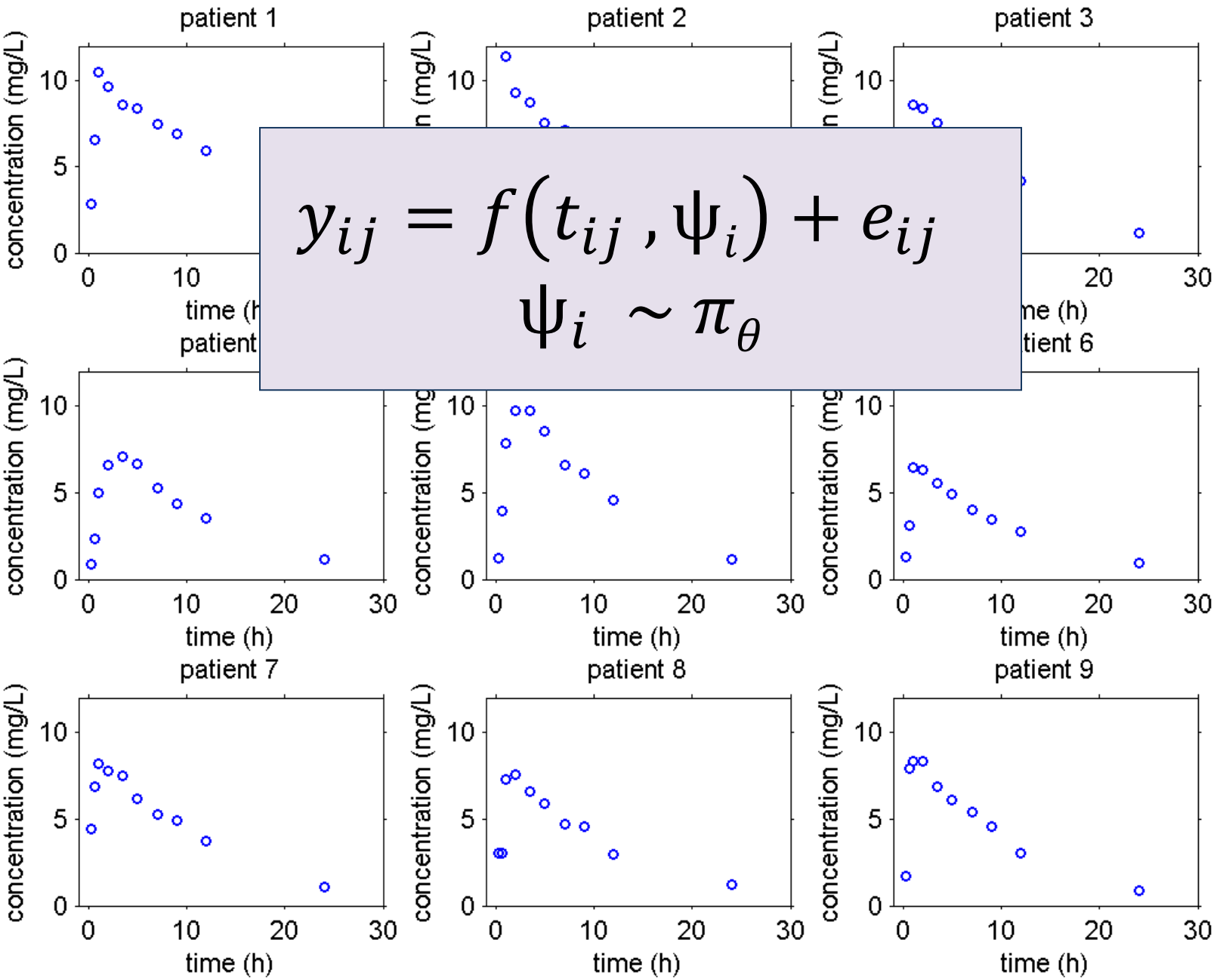
\end{aligned}
$$

$$y_{ij} = Cc(t_{ij}, \psi_i) + e_{ij} \quad , \quad 1 \leq i \leq N \, , \, 1 \leq j \leq n_i$$

$\psi_i = (ka_i, V_i, k_i)$: vector of individual parameter randomly distributed around some *typical value* ψ_{pop}

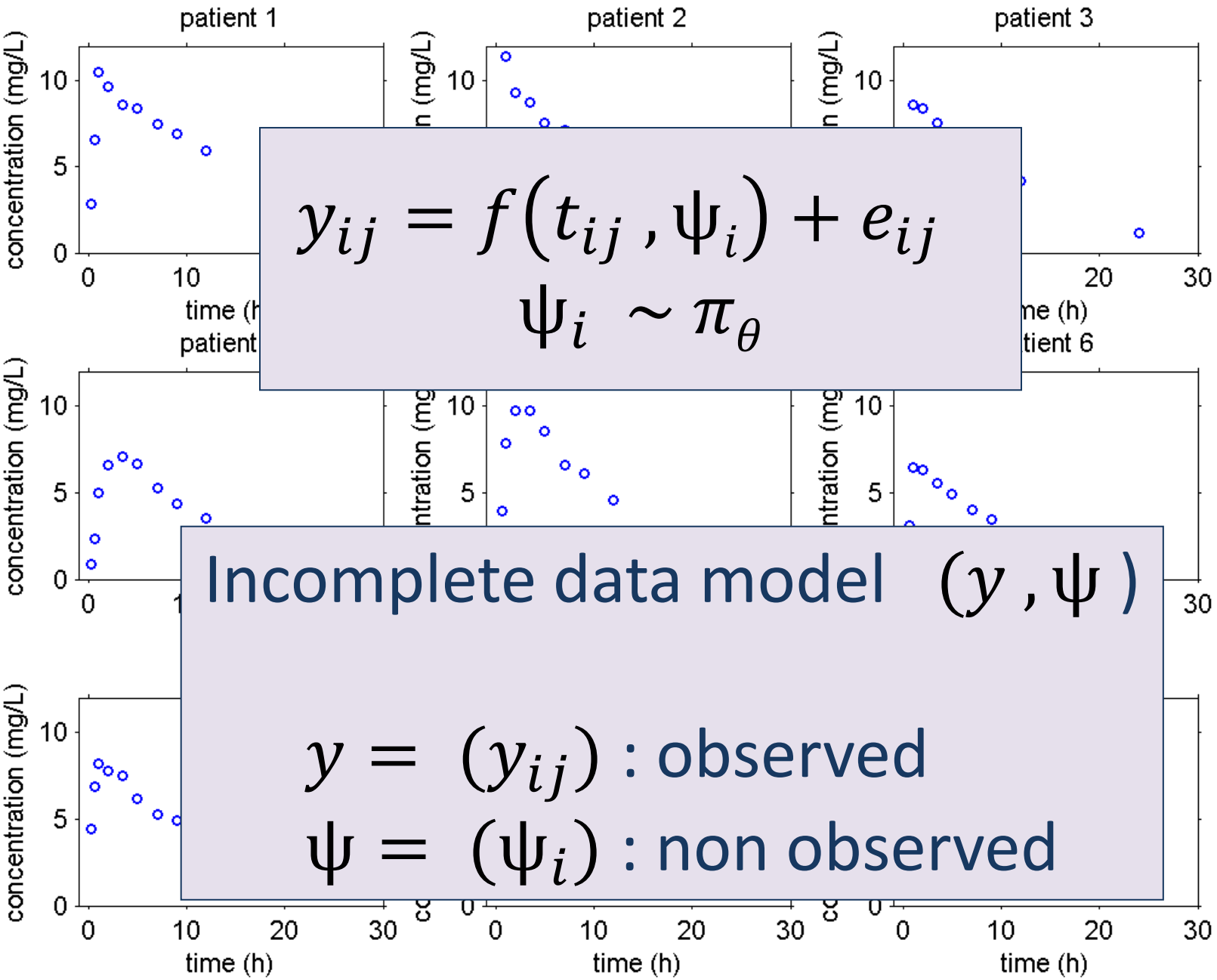


Model
=
pharmacological model
+
statistical model



$$y_{ij} = f(t_{ij}, \psi_i) + e_{ij}$$

$$\psi_i \sim \pi_\theta$$



$$y_{ij} = f(t_{ij}, \psi_i) + e_{ij}$$

$$\psi_i \sim \pi_\theta$$

Incomplete data model (y, ψ)

$y = (y_{ij})$: observed

$\psi = (\psi_i)$: non observed

$$y_{ij} = f\left(t_{ij}, \psi_i\right) + e_{ij}$$
$$\psi_i \sim \pi(\cdot, \theta)$$

Some tasks to perform with this model...

1. **Model exploration**
   - sensitivity analysis,
   - visual exploration,
2. **Parameter estimation**
   - population parameters θ,
   - Fisher Information matrix,
   - individual parameters (ψ_i),
3. **Model evaluation**
   - model diagnostic,
   - statistical tests
4. **Simulation**
   - clinical trial simulation

The EM algorithm (Expectation-Maximization)

(Dempster, Laird et Rubin, JRSSB, 1977)

Since ψ is not observed, $\log p(y, \psi; \theta)$ cannot be used for estimating θ. Then

Iteration k of the algorithm:

- step E : evaluate the quantity

$$Q_k(\theta) = \mathbb{E}[\log p(y, \psi; \theta) | y; \theta_{k-1}]$$

- step M : update the estimation of θ:

$$\theta_k = Argmax \;\; Q_k(\theta)$$

The SAEM algorithm (Stochastic Approximation of EM)

Delyon, Lavielle and Moulines (the Annals of Statistics, 1999)

Iteration k of the algorithm:

- step E :
  - *Simulation:* draw the non observed data $\psi^{(k)}$ with the conditional distribution $p(\psi \,|y; \theta_{k-1})$
  - *Stochastic approximation:*

$$\boxed{Q_k(\theta) = Q_{k-1}(\theta) + \gamma_k \left[\log p(y, \psi^{(k)}; \theta) - Q_{k-1}(\theta)\right]}$$

    (γ_k) is a decreasing sequence: $\sum \gamma_k = +\infty$, $\sum \gamma_k^2 < +\infty$.

- step M:
  - *Maximisation:* update the estimation of θ

$$\boxed{\theta_k = \mathit{Argmax}\ \ Q_k(\theta)}$$

Running several Markov chains

Convergence is improved by running several Markov chains for each individual

$$Q_k = Q_{k-1}(\theta) + \gamma_k \left(\frac{1}{L} \sum_{\ell=1}^{L} \log p(y, \psi^{(k,\ell)}; \theta) - Q_{k-1}(\theta) \right)$$

- $\gamma_k = 1$ and L "large": MCEM algorithm
- when L is large, SAEM looks more and more like EM

Estimation of the observed likelihood

An Importance Sampling method

$$\begin{aligned}\ell(\theta; y) &= p(y; \theta) \\ &= \int \left(p(y|\psi) \frac{\pi_\theta(\psi)}{\tilde{\pi}_\theta(\psi)} \right) \tilde{\pi}_\theta(\psi) d\psi \\ &= \mathbb{E}_{\tilde{\pi}_\theta} \left(p(y|\psi) \frac{\pi_\theta(\psi)}{\tilde{\pi}_\theta(\psi)} \right)\end{aligned}$$

Then, $\mathbb{E}_{\tilde{\pi}_\theta}(p(y|\psi))$ can be estimated by Monte-Carlo:

1. Draw $\psi^{(1)}, \psi^{(2)}, \ldots, \psi^{(M)}$ with the marginal distribution $\tilde{\pi}_\theta$
2. Let

$$\hat{\ell}_M(\theta; y) = \frac{1}{M} \sum_{j=1}^{M} p(y|\psi^{(j)}) \frac{\pi_\theta(\psi^{(j)})}{\tilde{\pi}_\theta(\psi^{(j)})}$$

$$\mathbb{E}\left(\hat{\ell}_M(\theta; y)\right) = \ell(\theta; y) \text{ and } \text{Var}\left(\hat{\ell}_M(\theta; y)\right) = \mathcal{O}(1/M)$$

Hypothesis testing in incomplete data models

A procedure for hypothesis testing in incomplete data model

Model to test: $\mathcal{M}_o$

1) Fit model $\mathcal{M}_o$ to the data (*e.g.* by estimating the parameters of the model by maximum likelihood estimation)

2) Draw individual parameters with the conditional distributions

$$p(\psi_i \mid y_i \,;\, \widehat{\mathcal{M}_0})$$

3) Use the "completed" data $(\psi^{(s)}, y)$ to test the components of model $\mathcal{M}_o$

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$$\begin{aligned} \mathrm{p}(\psi_i) &= \int \mathrm{p}(\psi_i|y_i)\mathrm{p}(y_i)d\, y_i \\ &= \mathbb{E}_{y_i}\left(\mathrm{p}(\psi_i|y_i)\right). \end{aligned}$$

Mixed-effects model

$$y_{ij} = f(t_{ij}, \psi_i) + g(t_{ij}, \psi_i, \xi)\varepsilon_{ij} \quad , \quad \varepsilon_{ij} \sim \mathcal{N}(0, 1)$$

$$h(\psi_i) = h(\psi_{\text{pop}}) + \beta\, c_i + \eta_i \quad , \; 1 \leq i \leq N \quad , \quad \eta_i \sim \mathcal{N}(0, \Omega)$$

Components of the model to be tested

- the structural model f,
- the form of the residual error model g,
- the transformation of the individual parameters h,
- the list of the covariates c_i for each individual parameter,
- the structure of the variance-covariance matrix Ω.

Mixed-effects model

Testing the covariate model

$$h(\psi_i) = h(\psi_{\text{pop}}) + \beta c_i + \eta_i$$

We aim to test H_0: " $\beta = 0$" v.s. H_1: "$\beta \neq 0$"

Let $\psi_i^{(1)}, \psi_i^{(2)}, \ldots \psi_i^{(M)}$ be M (possibly conditionally dependent) samples of $\mathrm{p}(\psi_i|y_i)$.

Let

$$\overline{h(\psi_i)} = \frac{1}{M} \sum_{m=1}^{M} h(\psi_i^{(m)})$$

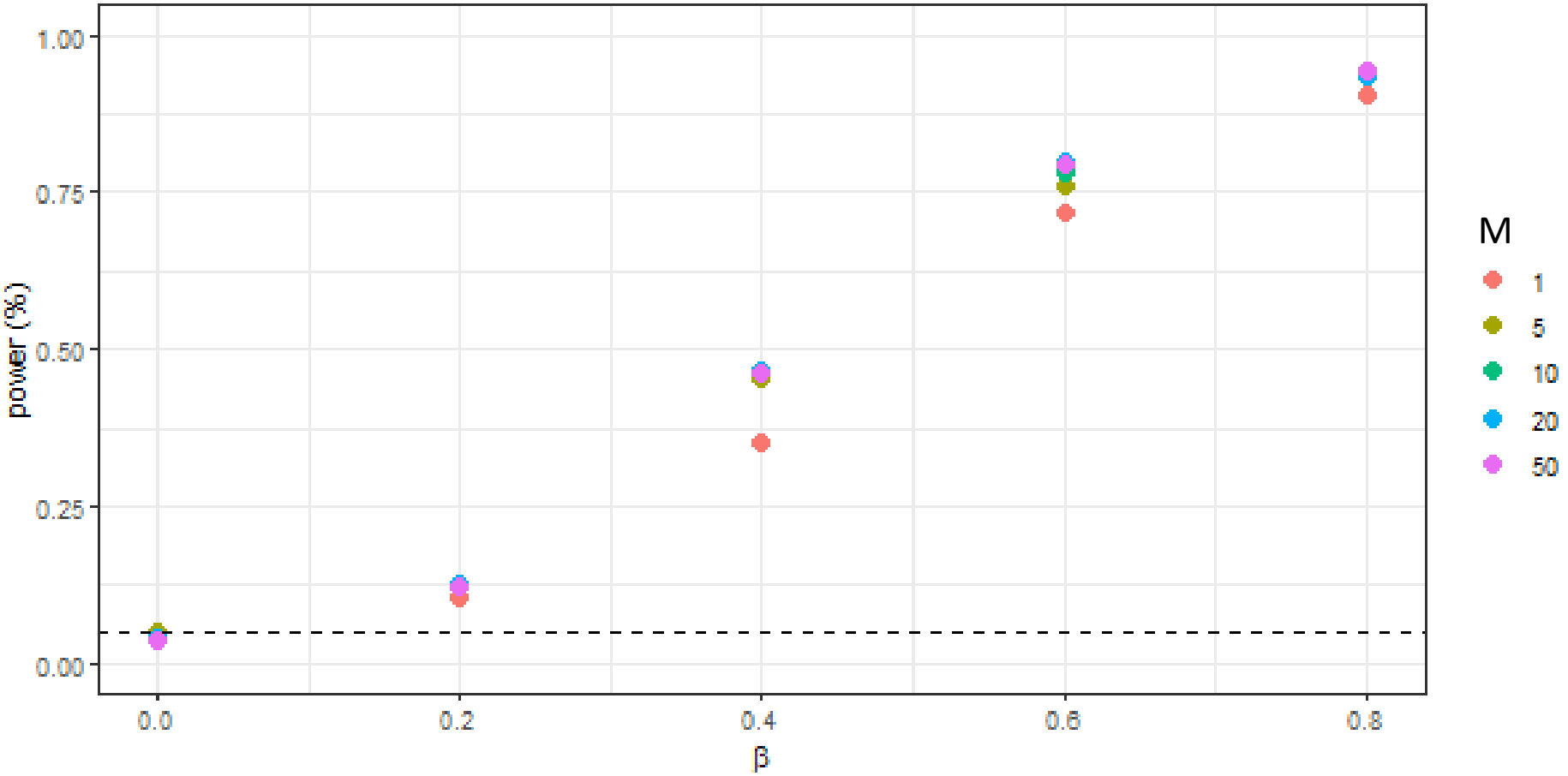
Then,

$$\overline{h(\psi_i)} = h(\psi_{\text{pop}}) + \beta c_i + \overline{\eta_i}$$

We can then use $(\overline{h(\psi_i)}, 1 \leq i \leq N)$ for testing H_0 (t test, F test, Pearson correlation test,...)

Mixed-effects model

Testing the covariate model - Monte Carlo experiment



Mixed-effects model

Testing the correlation model

$$\eta_i = (\eta_{k,i}, 1 \leq k \leq p)$$

We aim to test H_0: " $\mathbb{E}(\eta_{k,i}\eta_{\ell,i}) = 0$" v.s. H_1: "$\mathbb{E}(\eta_{k,i}\eta_{\ell,i}) \neq 0$"

Let $(\eta_i^{(1)}, \ldots, \eta_i^{(M)})$ be M (possibly conditionally dependent) samples of $\mathrm{p}(\eta_i \mid y_i)$.

Let

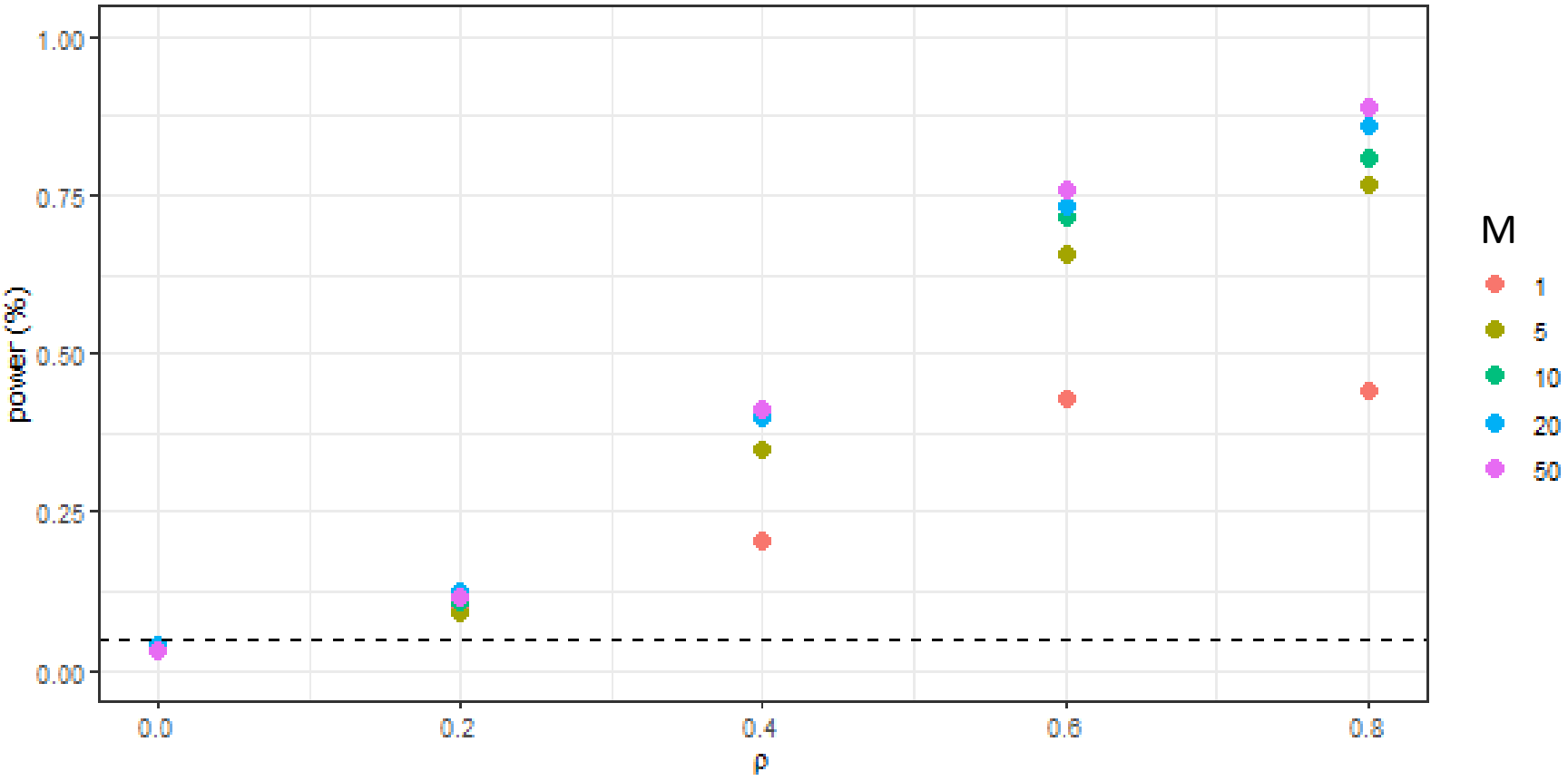
$$\overline{\eta_{kl,i}} = \frac{1}{M}\sum_{m=1}^{M} \eta_{k,i}^{(m)}\eta_{\ell,i}^{(m)}$$

Then, under H_0, the $\overline{\eta_{kl,i}}$ are i.i.d with $\mathbb{E}(\overline{\eta_{kl,i}}) = 0$.

We can then use $(\overline{\eta_{kl,i}}, 1 \leq i \leq M)$ for testing H_0 (e.g. t-test)

Mixed-effects model

Testing the correlation model - Monte Carlo experiment



Incomplete data model building

A procedure for model building in incomplete data model

Initial model: $\mathcal{M}_0$

1) Fit model $\mathcal{M}_0$ to the data (*e.g.* by estimating the parameters of the model by maximum likelihood estimation)

2) Draw individual parameters with the conditional distributions $p(\psi_i \mid y_i ; \widehat{\mathcal{M}}_0)$

A procedure for model building in incomplete data model

Initial model: $\mathcal{M}_0$

1) Fit model $\mathcal{M}_0$ to the data (*e.g.* by estimating the parameters of the model by maximum likelihood estimation)

2) Draw individual parameters with the conditional distributions $p(\psi_i \mid y_i ; \widehat{\mathcal{M}_0})$

3) Use the "completed" data $(\psi^{(s)}, y)$ to build a new model $\mathcal{M}_1$

Repeat this procedure until convergence, i.e. $\mathcal{M}_{k+1}$ "=" $\mathcal{M}_k$

Method for (incomplete data) model selection

Objective: select a particular model $\widehat{\mathcal{M}}$ in a (possibly very large) set of models $\mathbb{M}$.

Penalized likelihood approach:

$$U(\mathcal{M}, y) = -2 \log \left(\mathrm{p}(y; \mathcal{M}) \right) + \mathrm{pen}(\mathcal{M})$$

$$\widehat{\mathcal{M}} = \arg \min_{\mathcal{M} \in \mathbb{M}} U(\mathcal{M}, y)$$

$\mathrm{p}(y; \mathcal{M})$: pdf of the observations
$\mathrm{pen}(\mathcal{M})$: penalty term

EM for (incomplete data) model building

Penalized version of the *complete log-likelihood*:

$$V(\mathcal{M}, y, \psi) = -2 \log \left(\mathrm{p}(y, \psi; \mathcal{M}) \right) + \mathrm{pen}(\mathcal{M}).$$

We can then define the following *Expectation-Maximization* (EM) algorithm:

- An initial model $\mathcal{M}_0$ is chosen
- At iteration k
  - E-step: compute

$$Q(\mathcal{M}, \mathcal{M}_{k-1}) = \mathbb{E} \left(V(\mathcal{M}, y, \psi) \,|\, y, \mathcal{M}_{k-1} \right)$$

  - M-step: compute

$$\mathcal{M}_k = \arg \min_{\mathcal{M} \in \mathbb{M}} Q(\mathcal{M}, \mathcal{M}_{k-1})$$

Proposition *Under very general conditions,* $(U(\mathcal{M}_k), k \geq 0)$ *is a decreasing sequence.*

SAMBA:
Stochastic Approximation for Model Building Algorithm

Stochastic Approximation version of EM (SAEM):

At iteration k,

- **Simulation step**: a single realization $\psi^{(k)}$ is drawn with the conditional distribution $\mathtt{p}(\psi|y;\mathcal{M}_{k-1})$.
- **Expectation step**: $Q(\mathcal{M},\mathcal{M}_{k-1})$ is approximated by

$$Q^{(k)}(\mathcal{M}) = Q^{(k-1)}(\mathcal{M}) + \gamma_k \left(V(\mathcal{M}, y, \psi^{(k)}) - Q^{(k-1)}(\mathcal{M}) \right).$$

- **Maximization step**:

$$\mathcal{M}_k = \arg\min_{\mathcal{M}\in\mathbb{M}} Q^{(k)}(\mathcal{M})$$

(γ_k) is a decreasing sequence s.t. $\sum \gamma_k = \infty$ and $\sum \gamma_k^2 = \infty$.

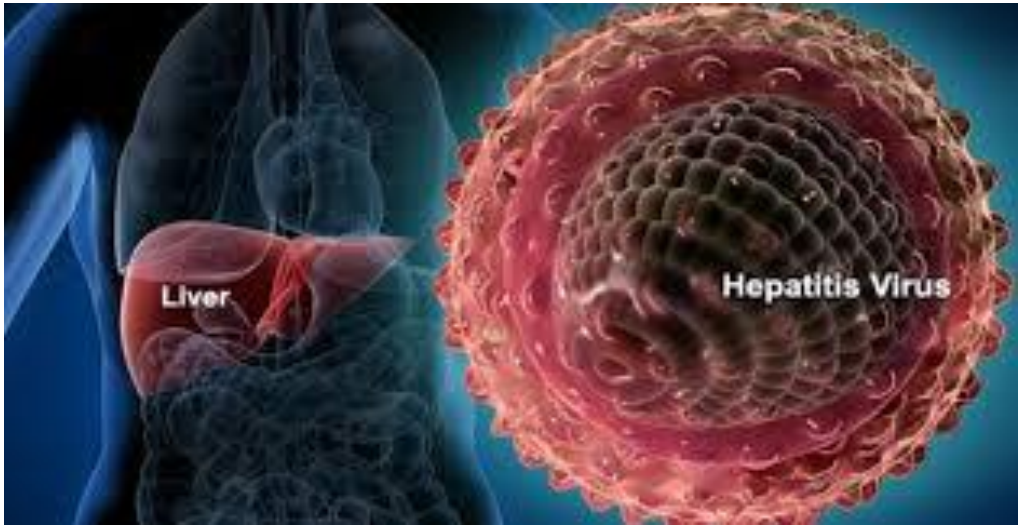
Comparison of SCM, COSSAC and SAMBA

	SCM		COSSAC		SAMBA	
WarfarinPK	**678.3**	44	**678.3**	4	**678.3**	**2**
RemifentanilPK	**6986.4**	295	**6986.7**	13	6987.2	**4**
TheophyllinePK	**371.2**	12	**371.2**	4	**371.2**	**2**
QuinidineSparsePK	**1241.8**	22	**1241.8**	11	**1241.8**	**1**
TobramycinSparsePK	**593.4**	22	**593.4**	6	597.6	**2**
TheophyllineExtRelPK	485.9	98	501.2	8	**474.2**	**6**
WarfarinPKPD	2169.6	92	2169.6	10	**2168.2**	**2**
Cholesterol	**9898.7**	12	**9898.7**	5	9912.2	**2**
Alzheimer	**16989.5**	73	16994	8	16995.5	**2**
Tranexamic	**5753.2**	298	**5753.2**	12	**5753.2**	**2**

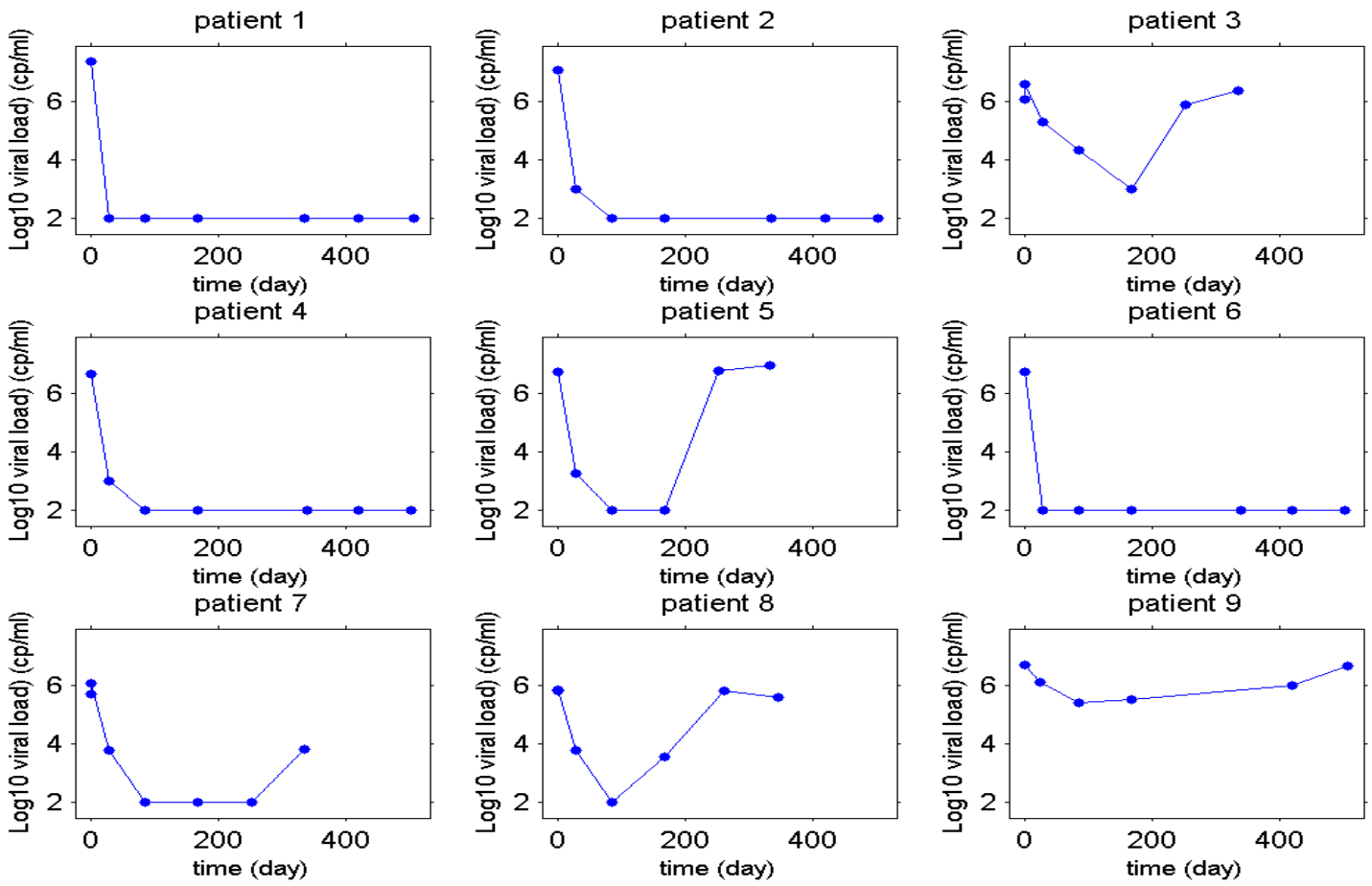
(BIC of the selected model, Number of runs)

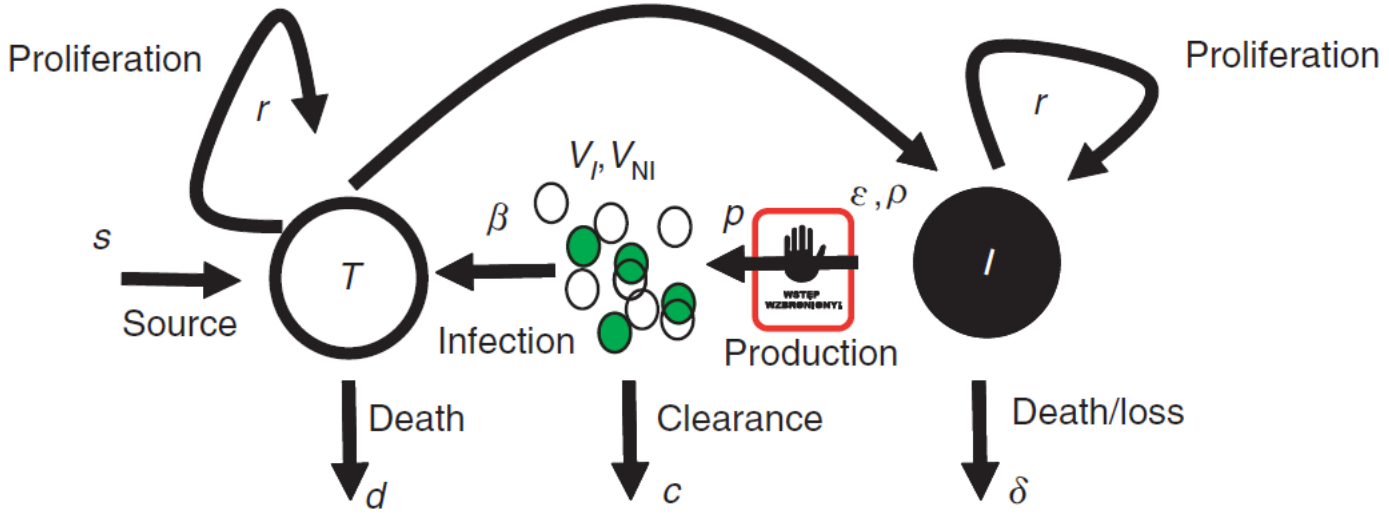
Viral load modelling

Hepatitis C



Some hepatitis C viral loads

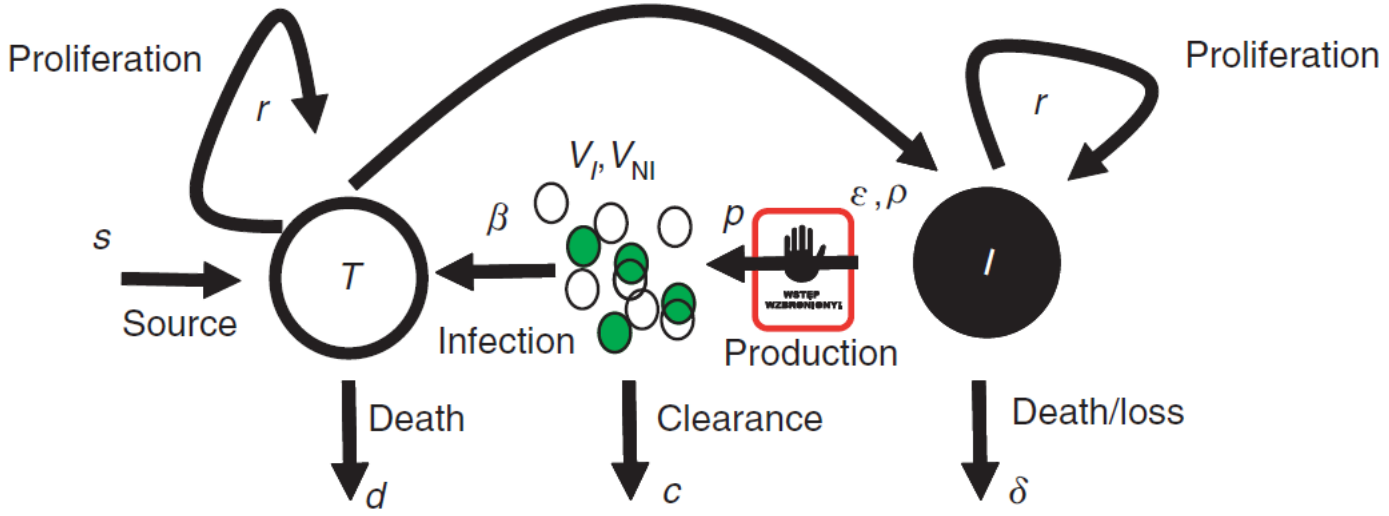




Clin Pharmacol Ther. 2010 Jun;87(6):706-13. doi: 10.1038/clpt.2010.35. Epub 2010 May 12.

A comprehensive hepatitis C viral kinetic model explaining cure.

Snoeck E[1], Chanu P, Lavielle M, Jacqmin P, Jonsson EN, Jorga K, Goggin T, Grippo J, Jumbe NL, Frey N.

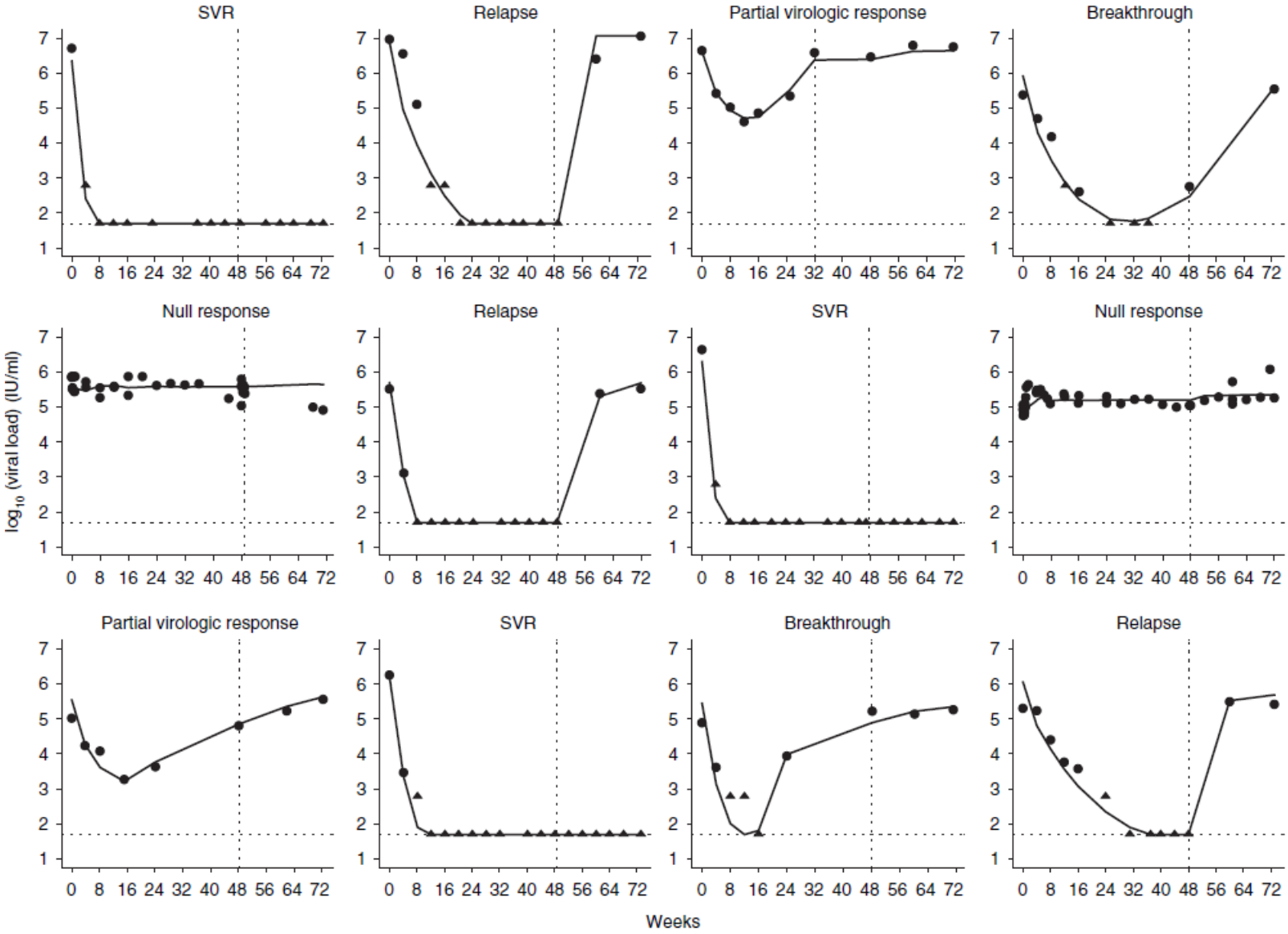


$$\frac{dT}{dt} = s + r \cdot T \cdot \left(1 - \frac{T+I}{T_{max}}\right) - d \cdot T - \beta \cdot V_I \cdot T$$

$$\frac{dI}{dt} = \beta \cdot V_I \cdot T + r \cdot I \cdot \left(1 - \frac{T+I}{T_{max}}\right) - \delta \cdot I$$

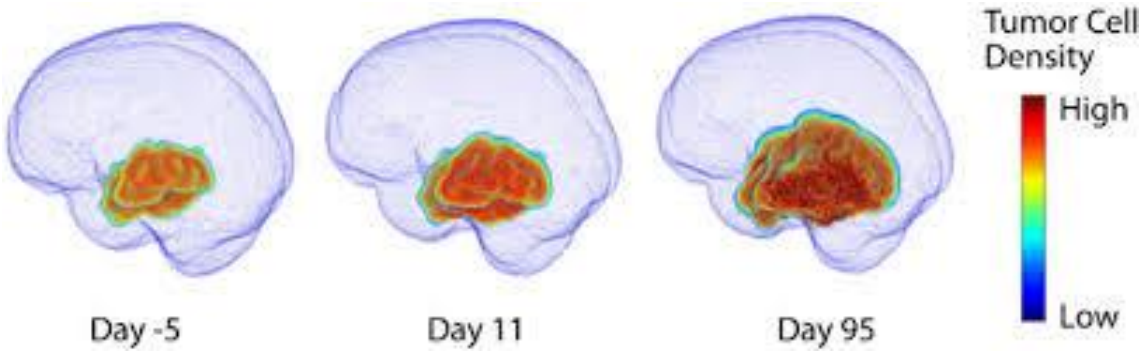
$$\frac{dV_I}{dt} = (1-\rho) \cdot (1-\varepsilon) \cdot p \cdot I - c \cdot V_I$$

$$\frac{dV_{NI}}{dt} = \rho \cdot (1-\varepsilon) \cdot p \cdot I - c \cdot V_{NI}$$


SVR
Relapse
Partial virologic response
Breakthrough
Null response
Relapse
SVR
Null response
Partial virologic response
SVR
Breakthrough
Relapse
log10 (viral load) (IU/ml)
Weeks

Tumor growth modelling

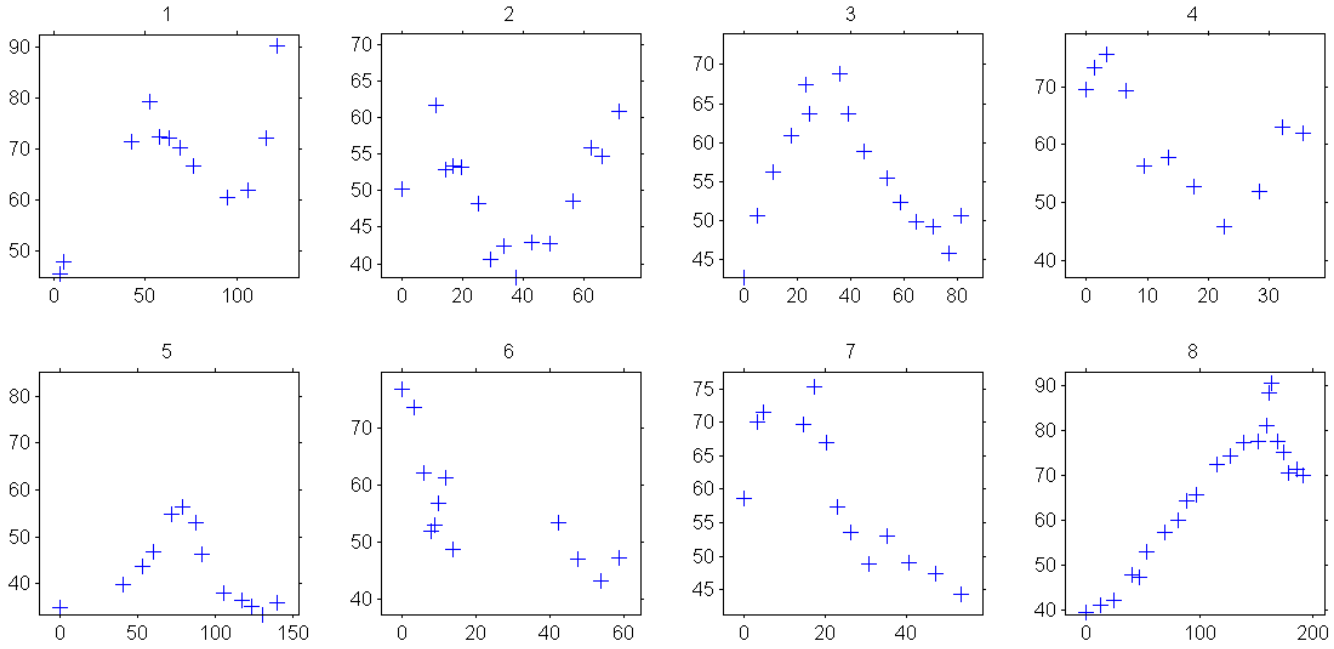
Low-grade glioma



Tumor sizes of 8 patients under treatment

Same observed pattern for the tumor sizes of different patients:

- tumor size increases before treatment starts,
- decreases during treatment period,
- increases when treatment stops



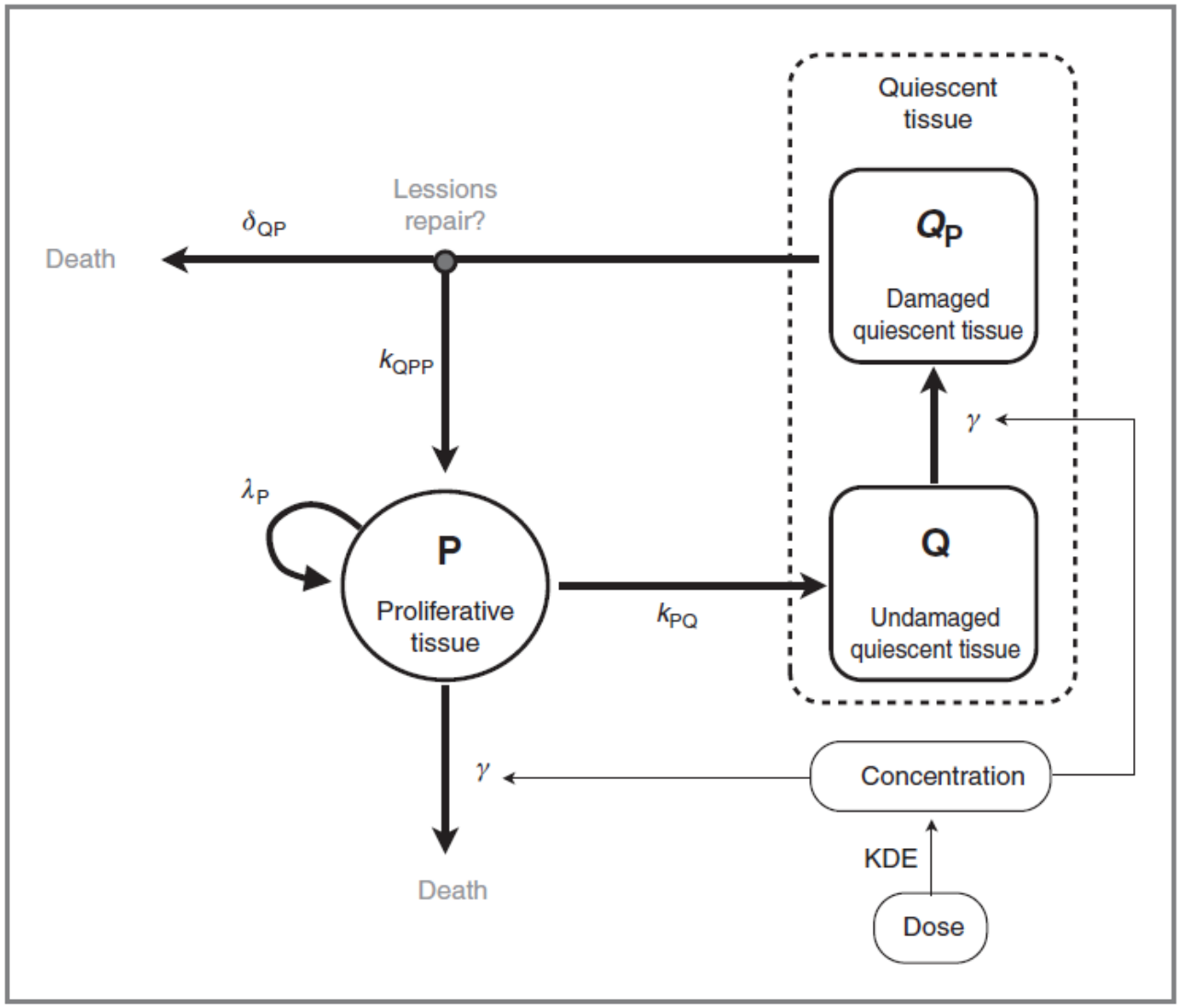


Figure 2. Schematic view of the model. *P* denotes the proliferative tissue and *Q* the nonproliferative or quiescent tissue. Proliferative tissue is assumed to transition to quiescence at a rate constant k_{PQ}. The treatment concentration, calculated from the individual dose through an exponential decay with the rate constant KDE, affects both proliferative and quiescent tissue. The tissue composed of cells in proliferation (*P*) is directly eliminated because of lethal DNA damages induced by the treatment. Nonproliferative tissue (*Q*) is also subject to DNA damages due to the treatment. When re-entering the cell cycle, the DNA-damaged quiescent cells (Q_P) can either repair their DNA damages and return to a proliferative state (*P*) or die because of unrepaired damages.

The structural model:

$$\frac{dC}{dt} = -\text{KDE} \times C \qquad \textit{+ dose input}$$

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

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

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

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

The statistical model:

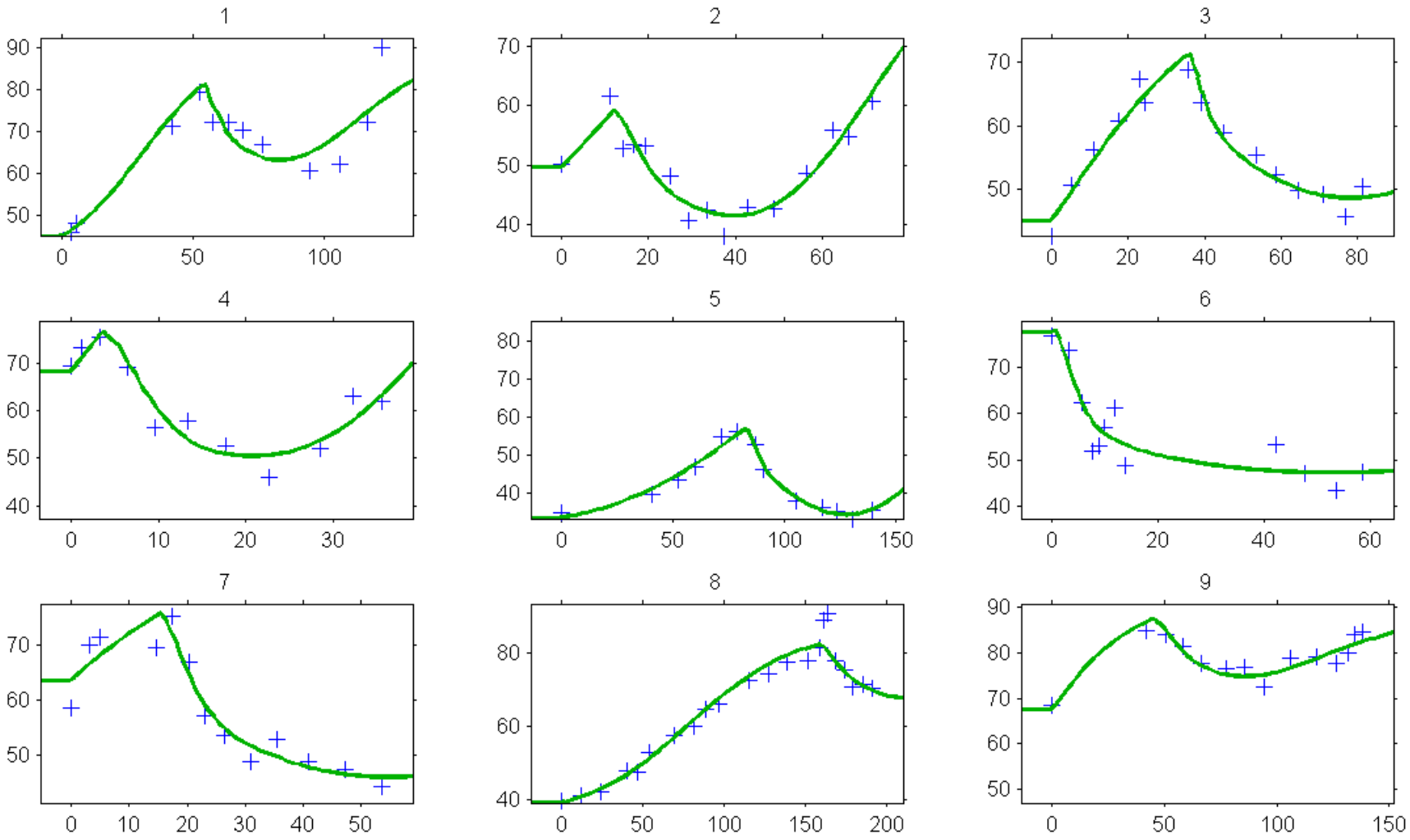
$$y_{ij} = P^*\left(t_{ij}, \psi_i\right) + e_{ij}$$
$$\psi_i \sim \pi(\cdot, \theta)$$

IMPLEMENTATION DU MODELE

```
[LONGITUDINAL]
input = {K, KDE, KPQ, KQPP, LAMBDAP, GAMMA, DELTAQP, PT0, Q0, a}
PK:
depot(target = C)
EQUATION:
t0 = 0
PT_0 = PT0
Q_0 = Q0
PSTAR = PT+Q+QP
ddt_C = -KDE*C
ddt_PT = LAMBDAP*PT*(1-PSTAR/K) + KQPP*QP - KPQ*PT - GAMMA*KDE*PT*C
ddt_Q = KPQ*PT - GAMMA*KDE*Q*C
ddt_QP = GAMMA*KDE*Q*C - KQPP*QP - DELTAQP*QP
DEFINITION:
y ={distribution=normal, prediction=PSTAR, sd=a}

;-------------------------------------------------------------------
[INDIVIDUAL]
input={PT0_pop,omega_PT0,Q0_pop,omega_Q0, KPQ_pop,omega_KPQ,KQPP_pop, omega_KQPP,
LAMBDAP_pop,omega_LAMBDAP,GAMMA_pop,omega_GAMMA,DELTAQP_pop,omega_DELTAQP}
DEFINITION:
KPQ     = {distribution=lognormal, prediction=KPQ_pop,     sd=omega_KPQ}
KQPP    = {distribution=lognormal, prediction=KQPP_pop,    sd=omega_KQPP}
LAMBDAP = {distribution=lognormal, prediction=LAMBDAP_pop, sd=omega_LAMBDAP}
GAMMA   = {distribution=lognormal, prediction=GAMMA_pop,   sd=omega_GAMMA}
```

Some individual fits



PBPK modelling
(Phisiologically based Pharmacokinetics