MIXED EFFECTS MODELS & THE POPULATION APPROACH

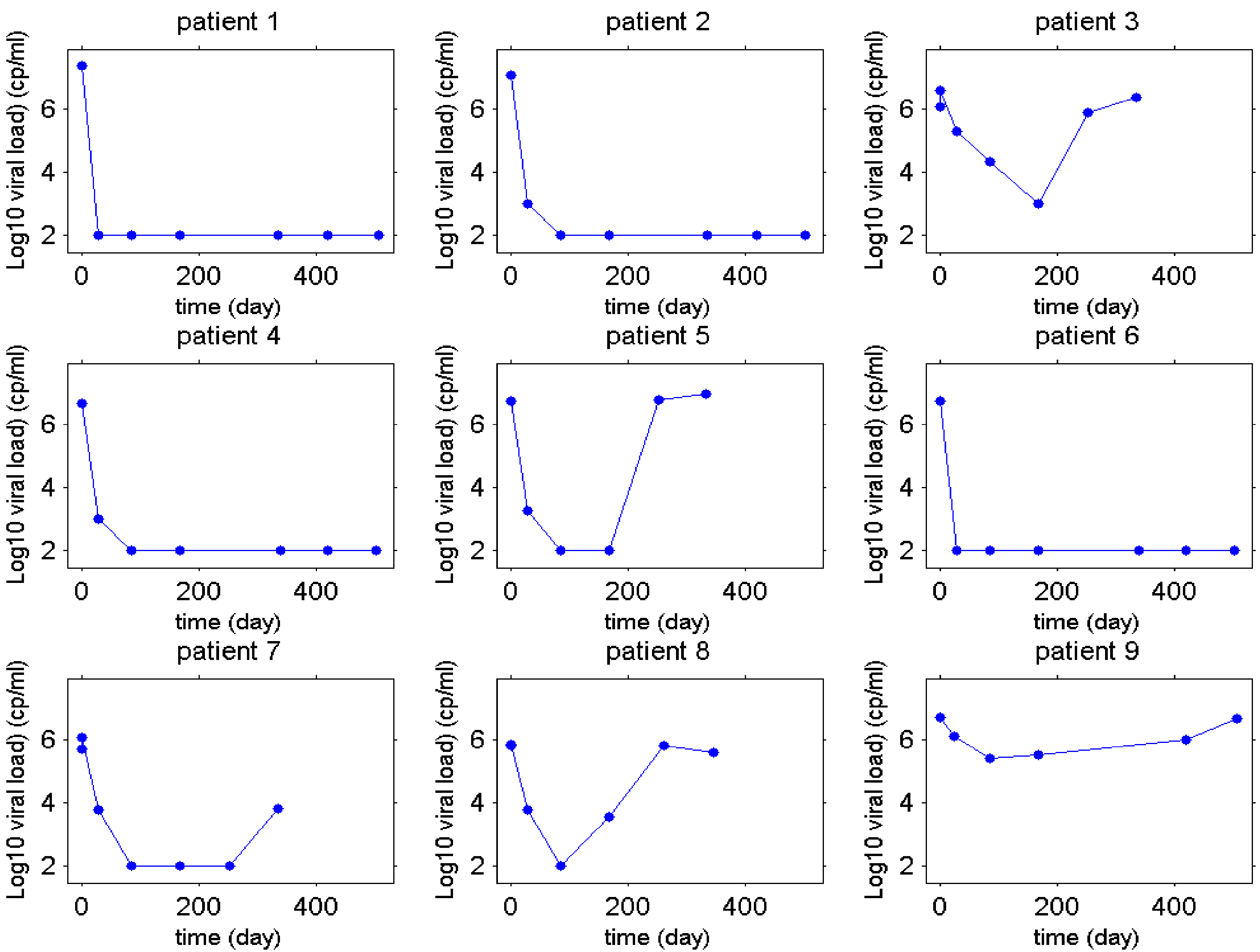
MODELS, METHODS & TOOLS

MARC LAVIELLE

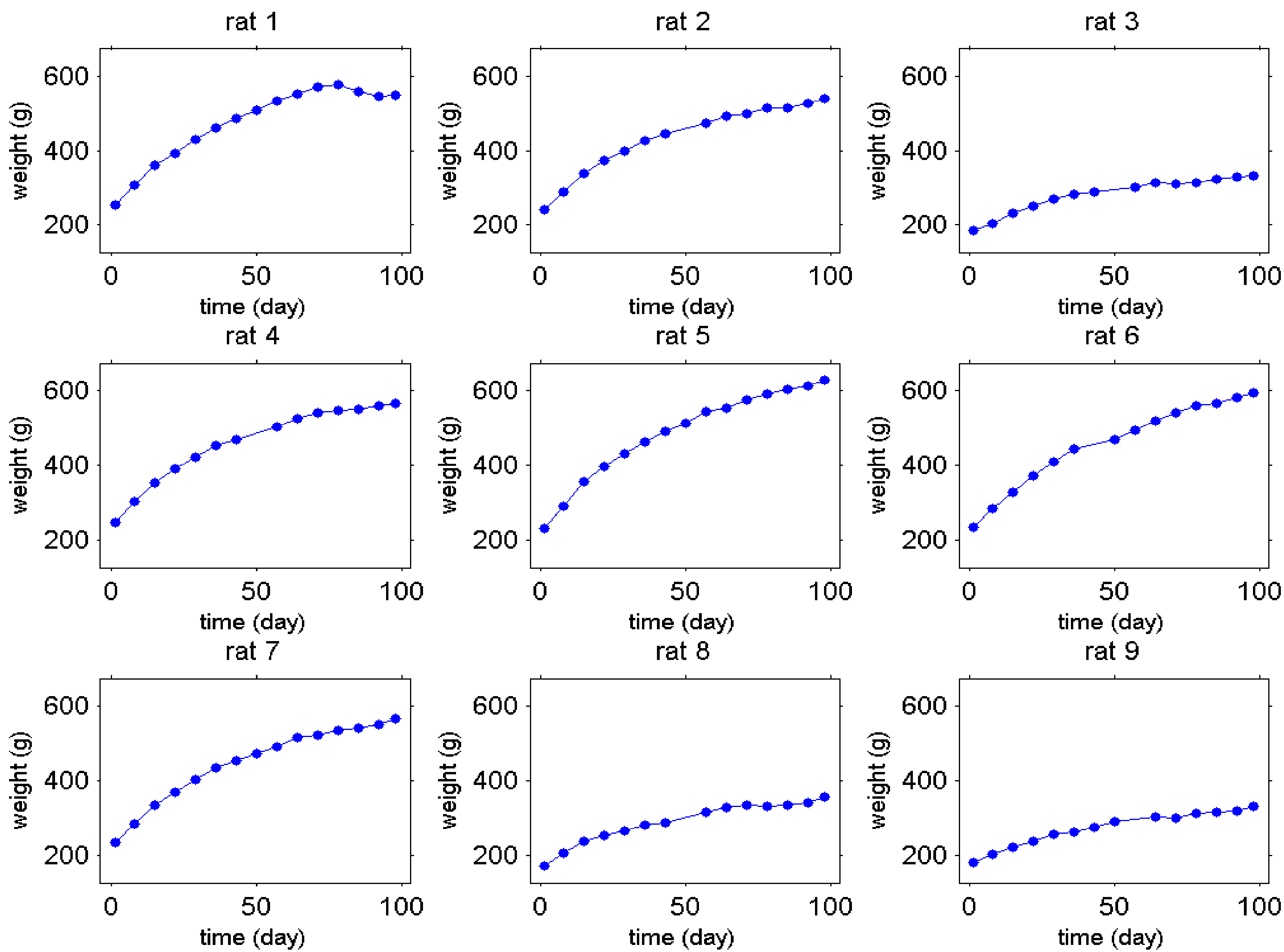
INRIA SACLAY, POPIX

Introduction: some data

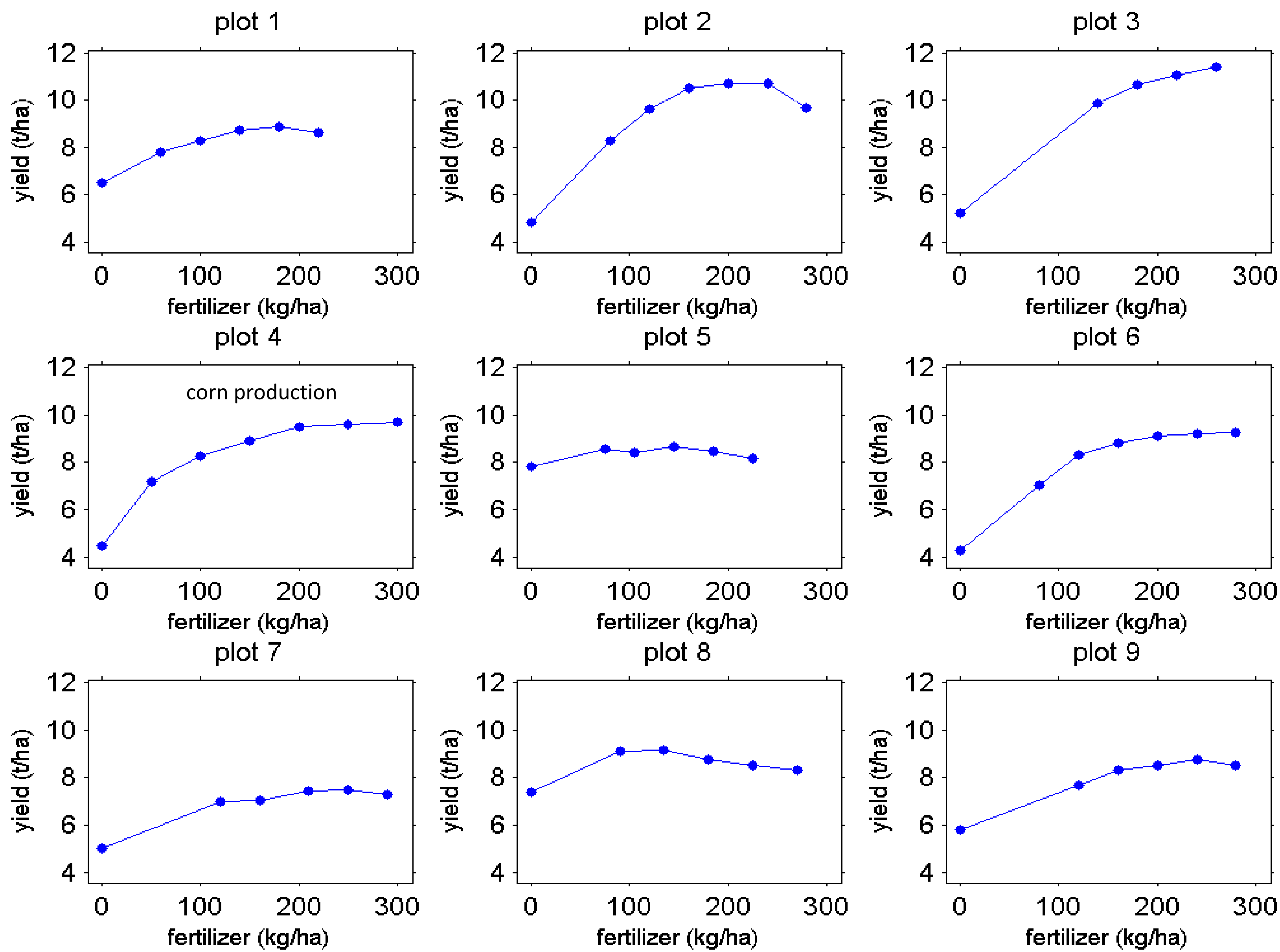
Example 1: viral loads (HIV study)

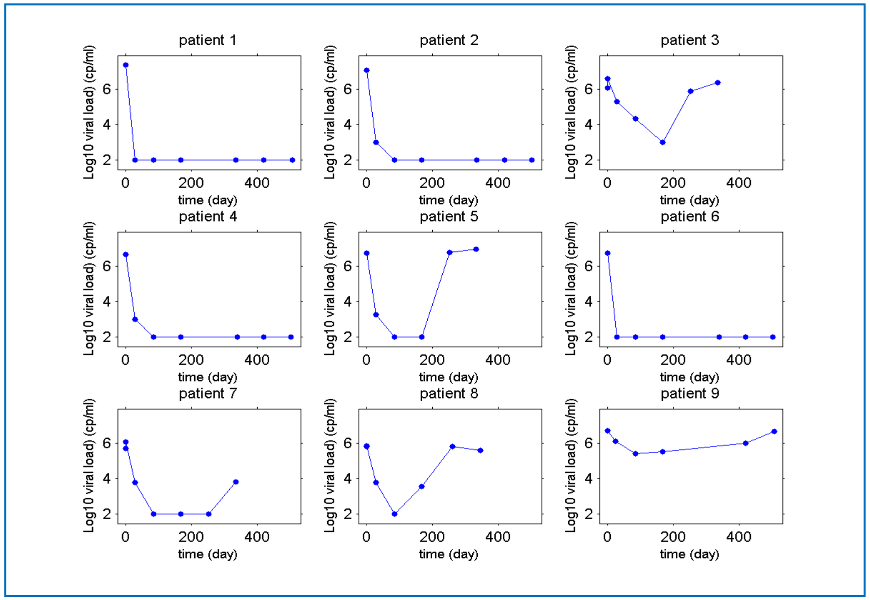


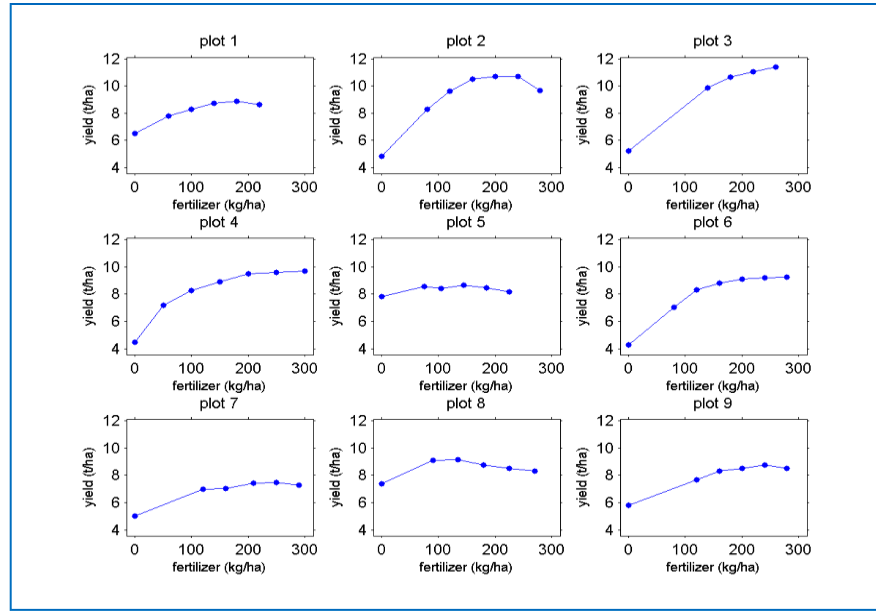
Example 2: weight data of rats (GMO experiment)

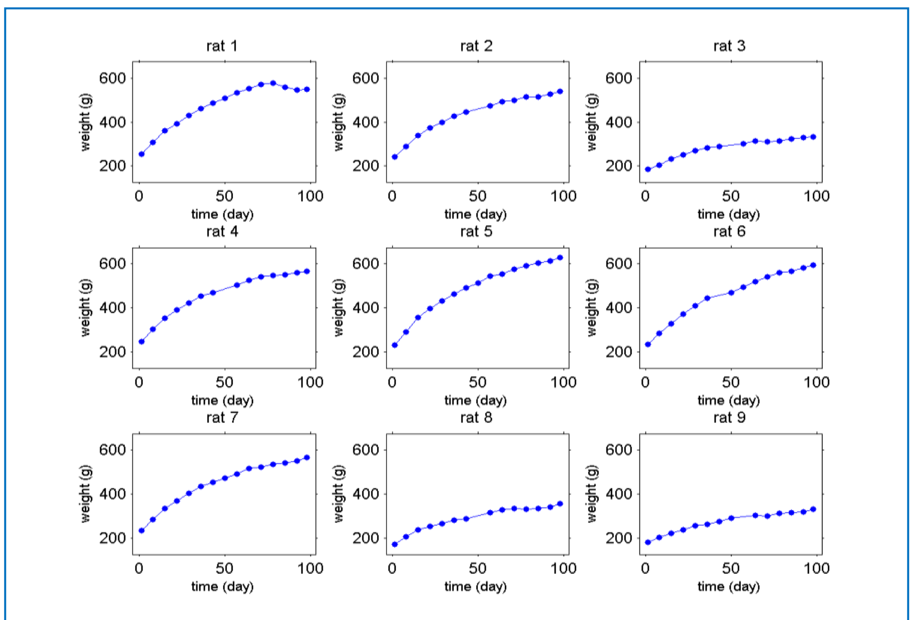


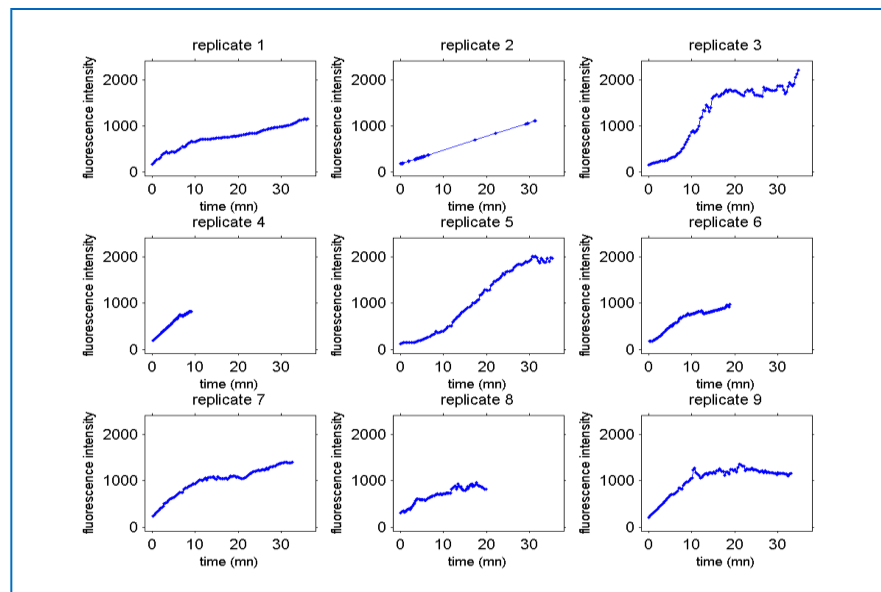
Example 3: corn production (agriculture experiment)

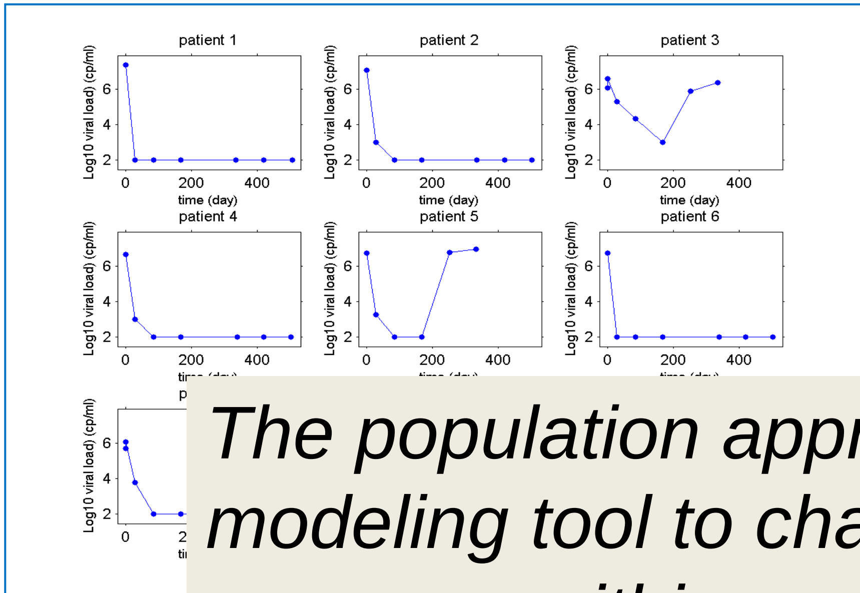


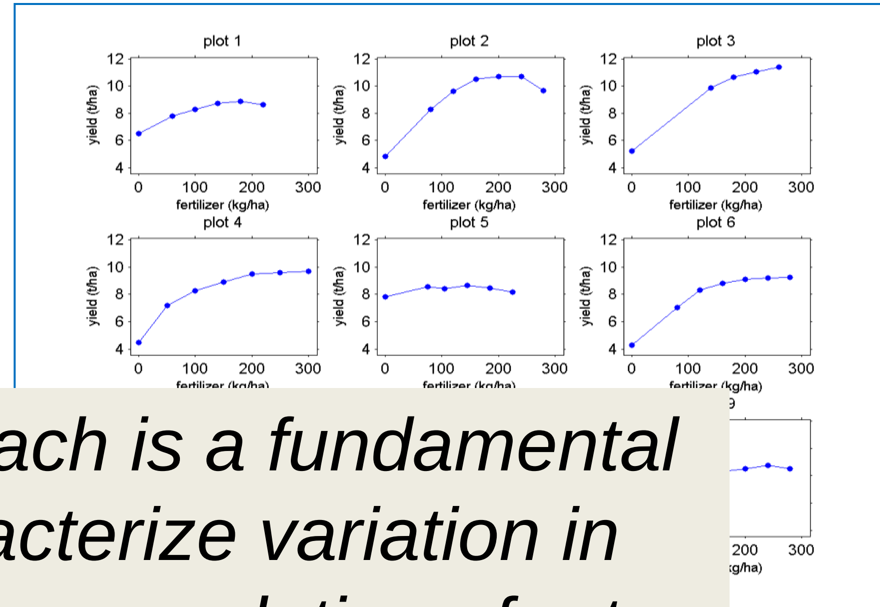

patient 1
patient 2
patient 3
patient 4
patient 5
patient 6
patient 7
patient 8
patient 9
Log10 viral load) (cp/ml)
time (day)


plot 1
plot 2
plot 3
plot 4
plot 5
plot 6
plot 7
plot 8
plot 9
yield (t/ha)
fertilizer (kg/ha)

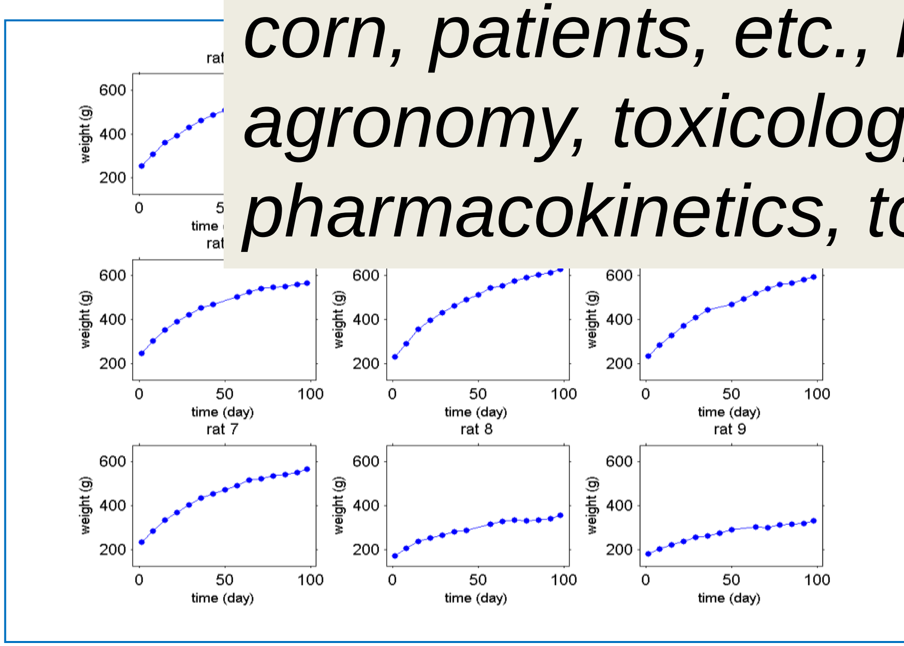

rat 1
rat 2
rat 3
rat 4
rat 5
rat 6
rat 7
rat 8
rat 9
weight (g)
time (day)

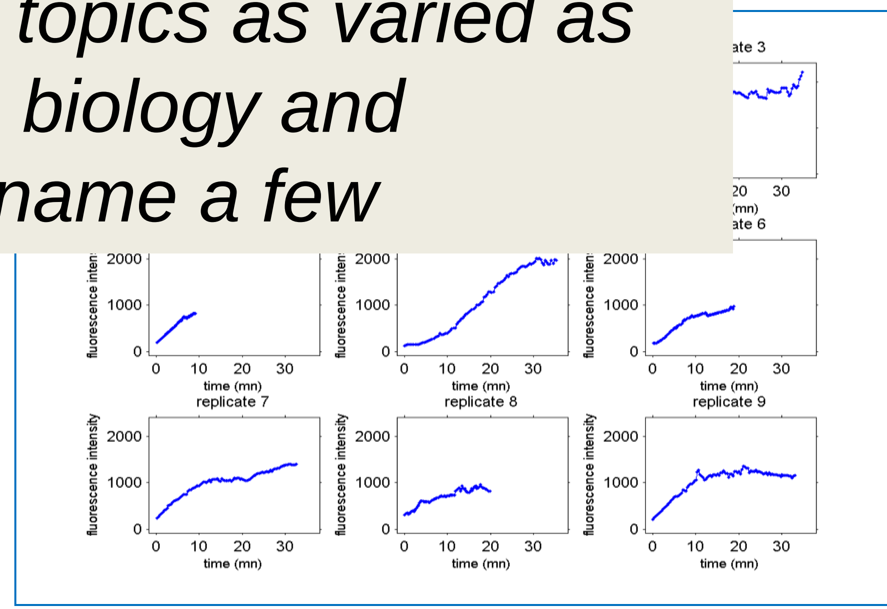

replicate 1
replicate 2
replicate 3
replicate 4
replicate 5
replicate 6
replicate 7
replicate 8
replicate 9
fluorescence intensity
time (mn)





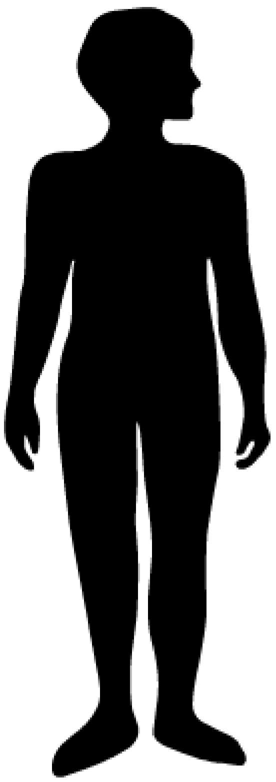
The population approach is a fundamental modeling tool to characterize variation in response within a given population of rats, corn, patients, etc., in topics as varied as agronomy, toxicology, biology and pharmacokinetics, to name a few



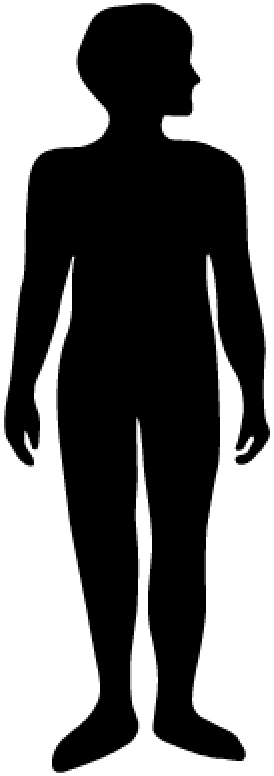


Introduction:
A pharmacokinetics example

Introduction to PKPD modeling



Introduction to PKPD modeling



warfarin

anticoagulant used in the prevention of thrombosis

Introduction to PKPD modeling

Pharmacokinetics:

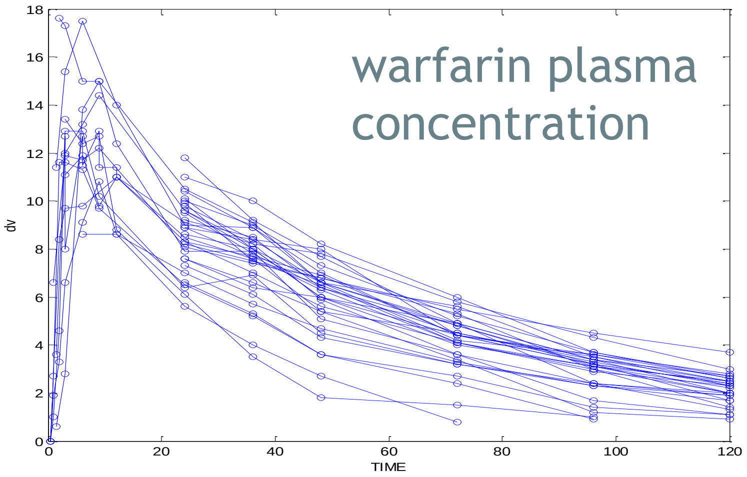
what the body does to the drug

Absorption

Distribution

Metabolism

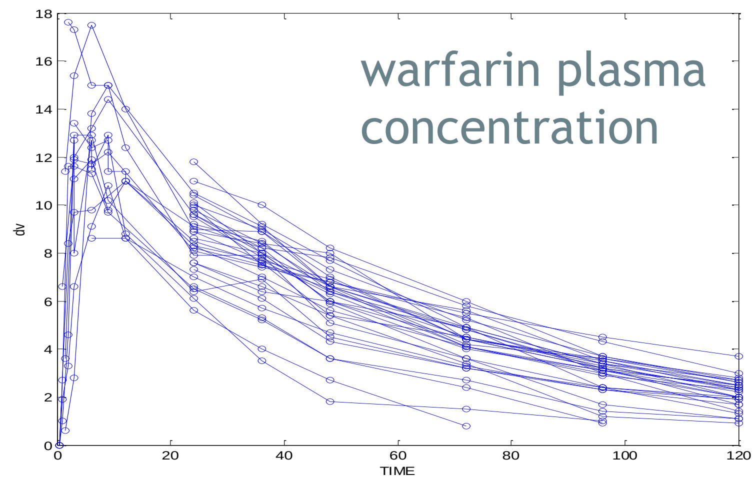
Excretion



Introduction to PKPD modeling

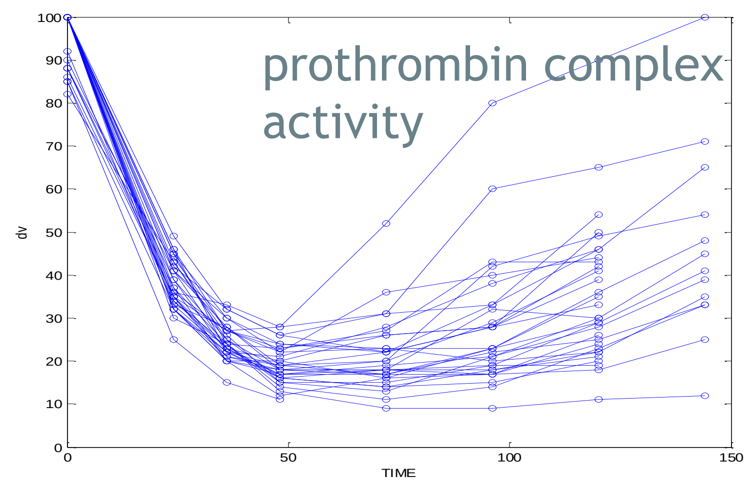
Pharmacokinetics:

what the body does to the drug

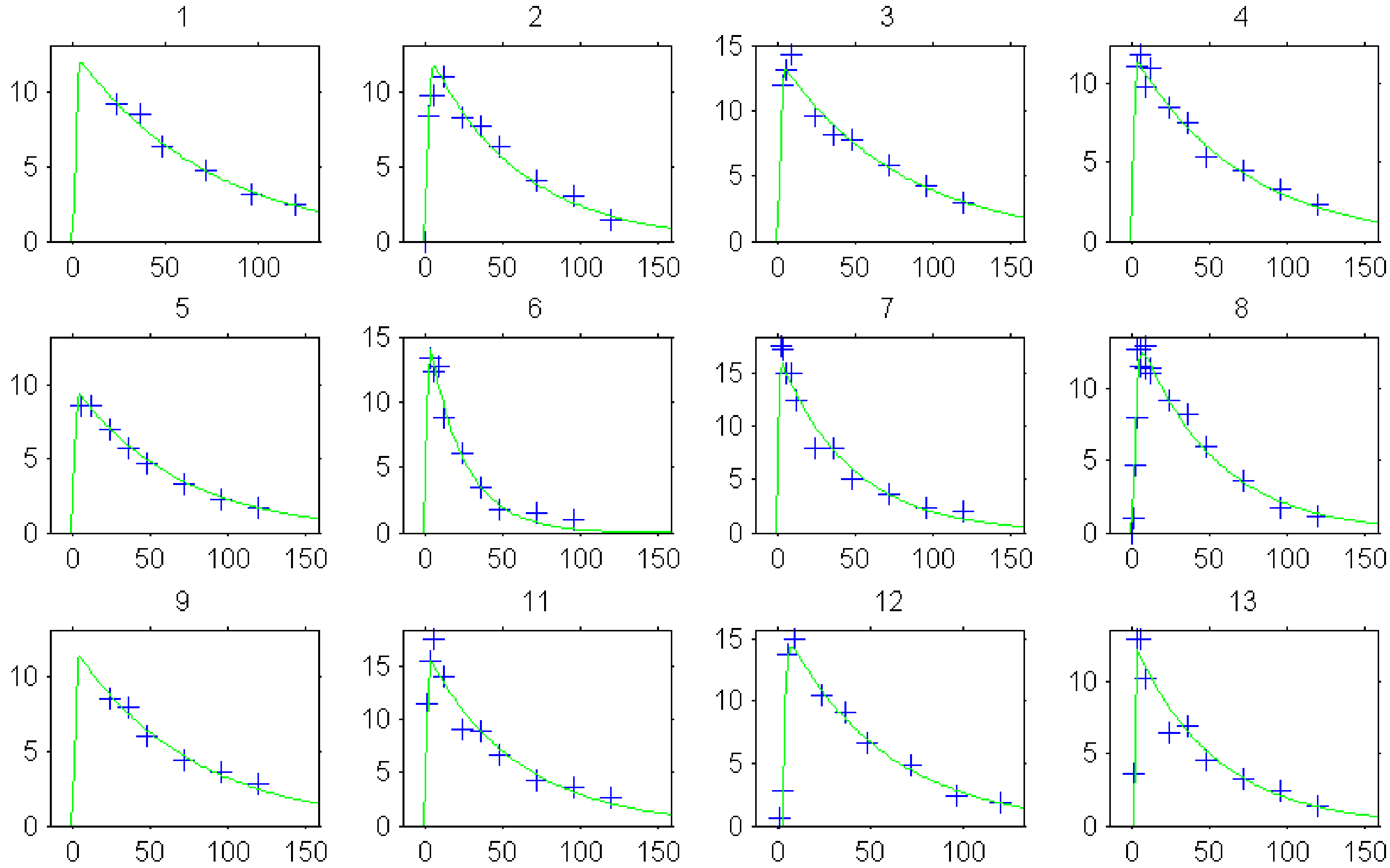


Pharmacodynamics:

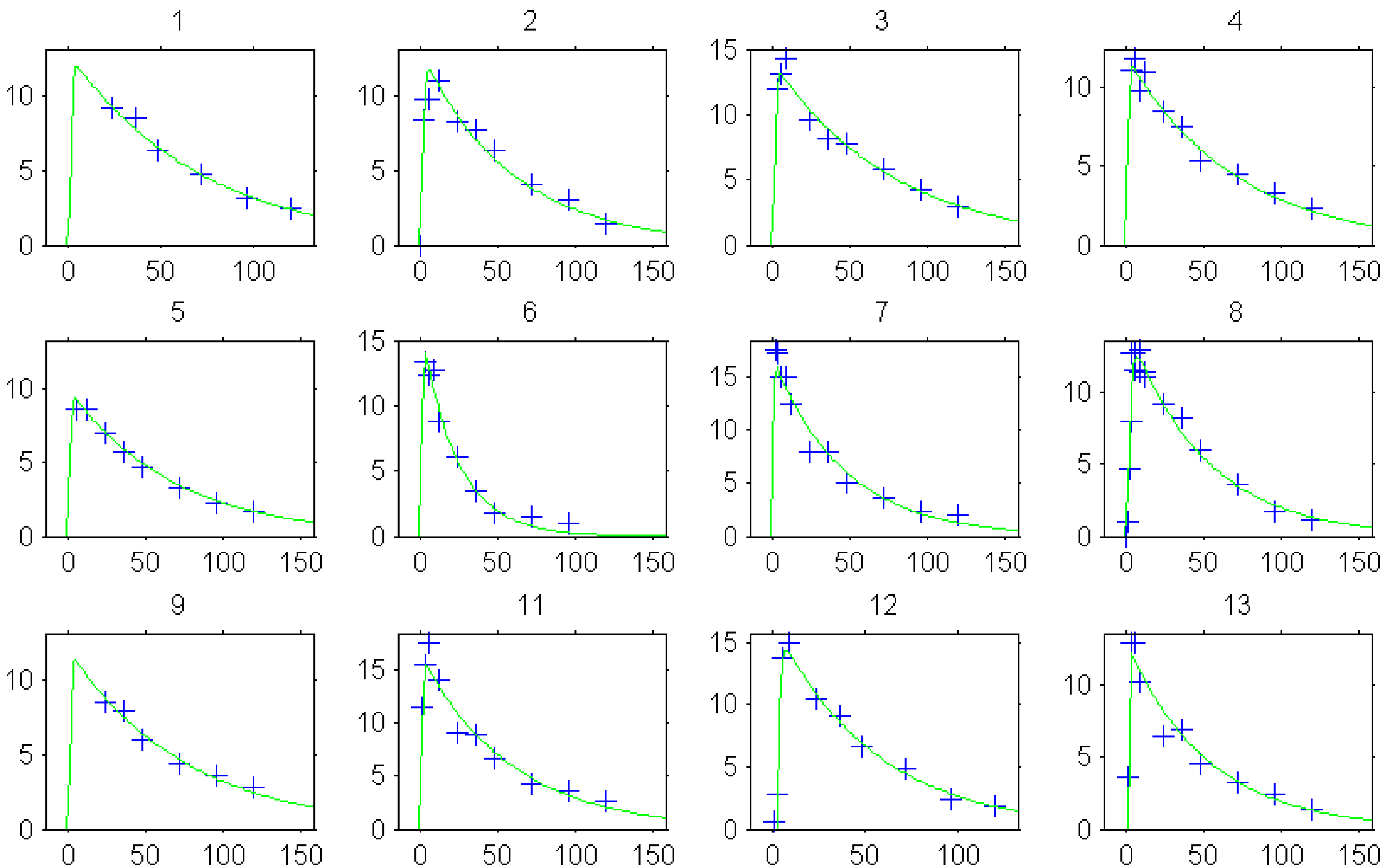
what the drug does to the body



Introduction to the population approach

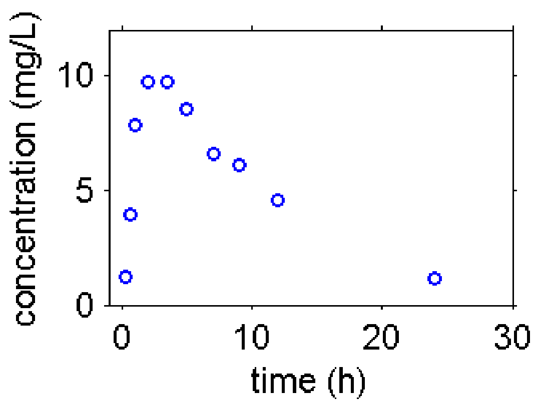


Introduction to the population approach



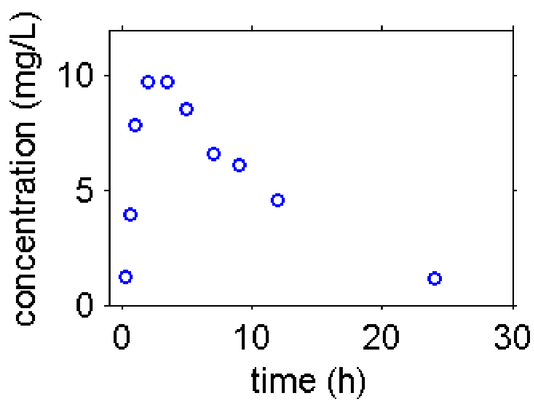
Model = pharmacological model + statistical model

The individual approach



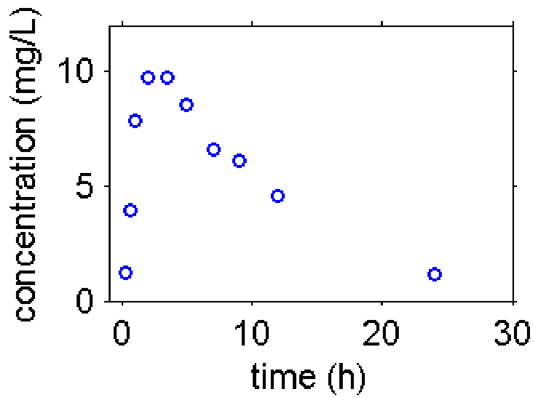
concentration (mg/L)
10
5
0
0
10
20
30
time (h)

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



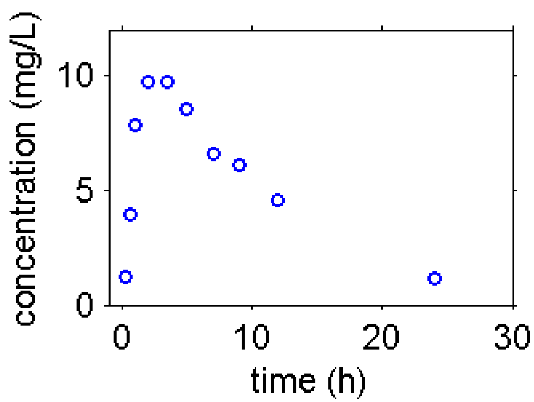
Observations: $y_1, y_2, \ldots, y_n$ at times $t_1, t_2, \ldots, t_n$

Model: $$y_j = f\left(t_j\ ;\ \varphi\right) + e_j$$

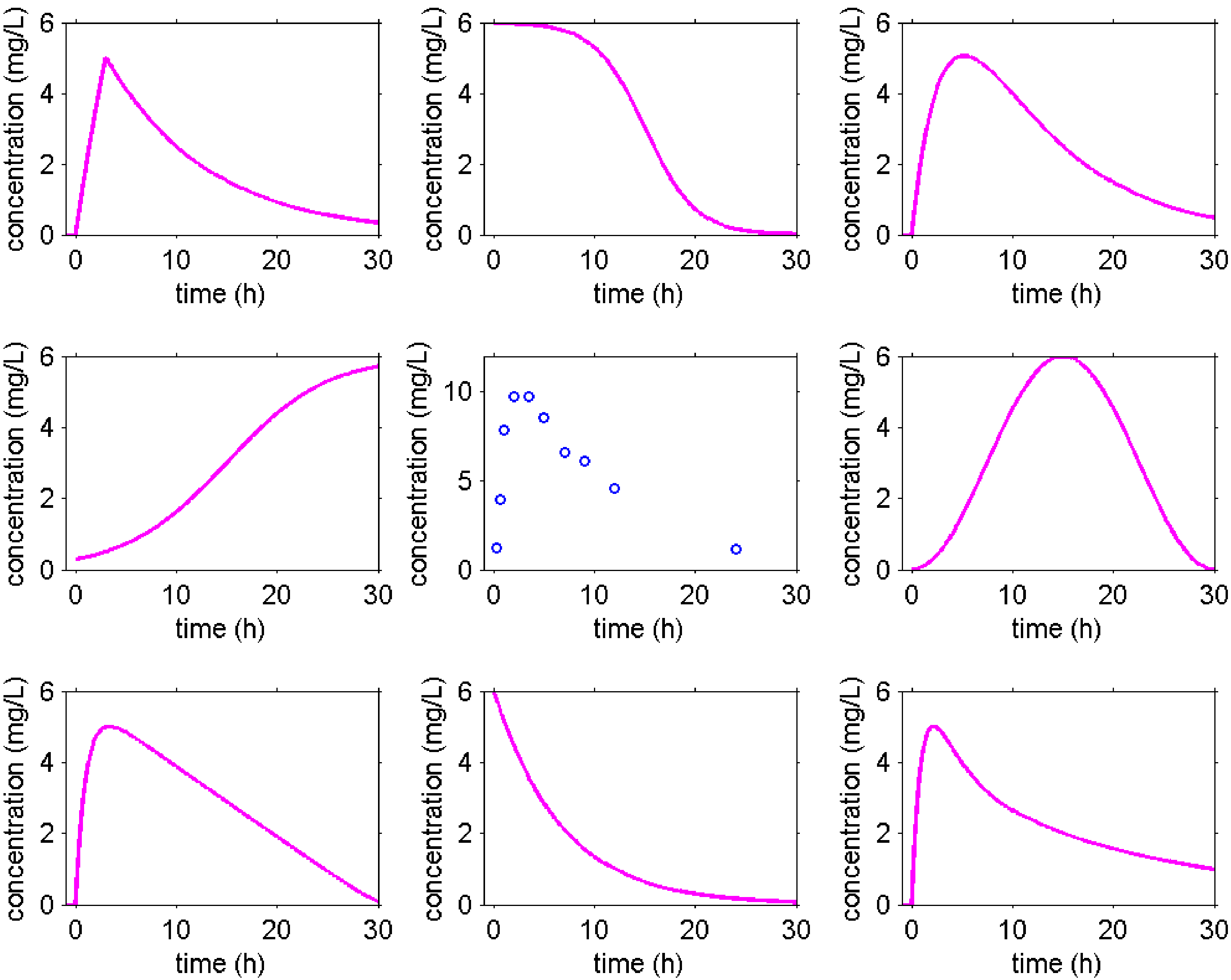


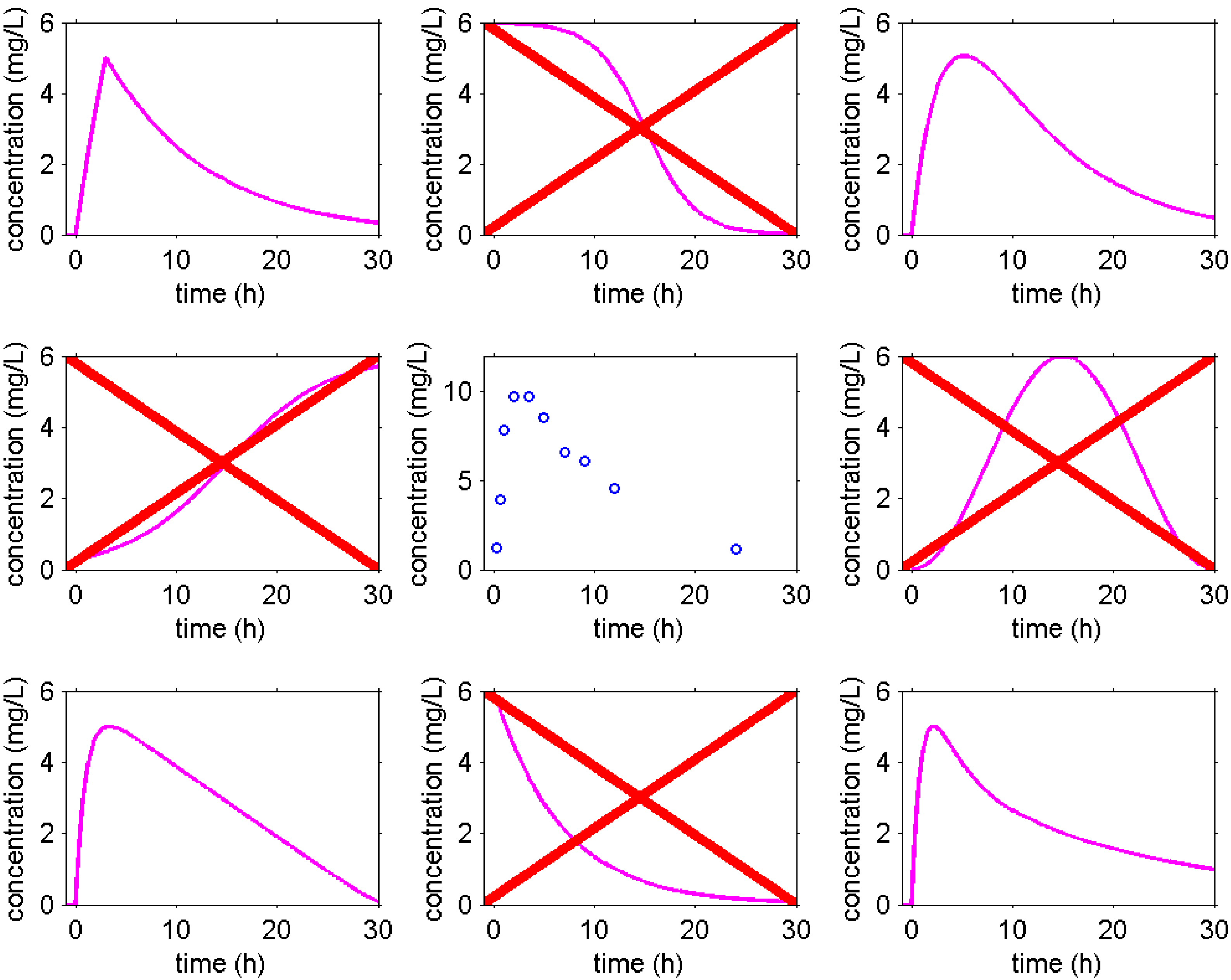
Observations: $y_1, y_2, \ldots, y_n$ at times $t_1, t_2, \ldots, t_n$

Model: $$y_j = f\left(t_j\ ;\ \varphi\right) + e_j$$

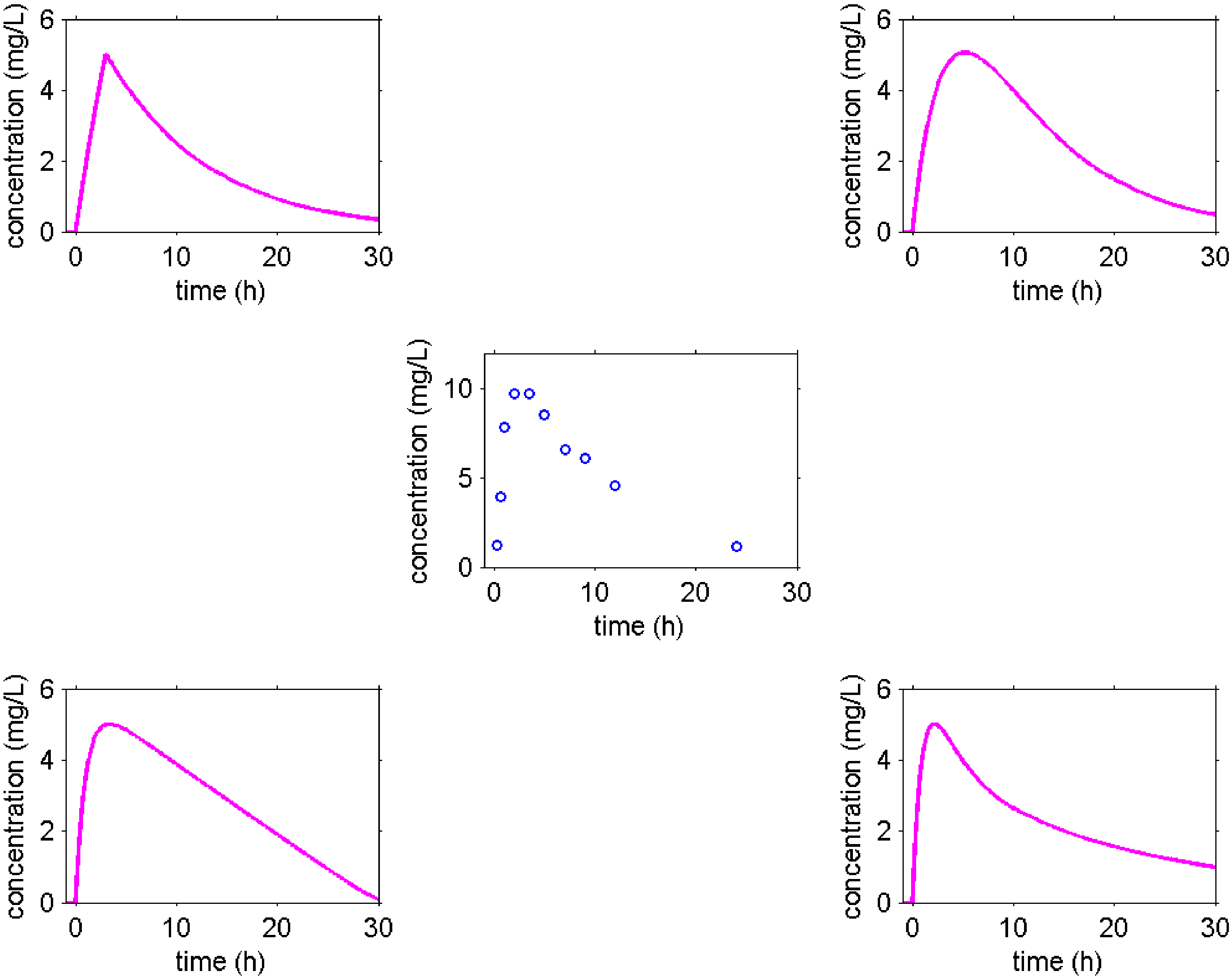


Model:
- structural model f
- residual error model (distribution of (e_j)

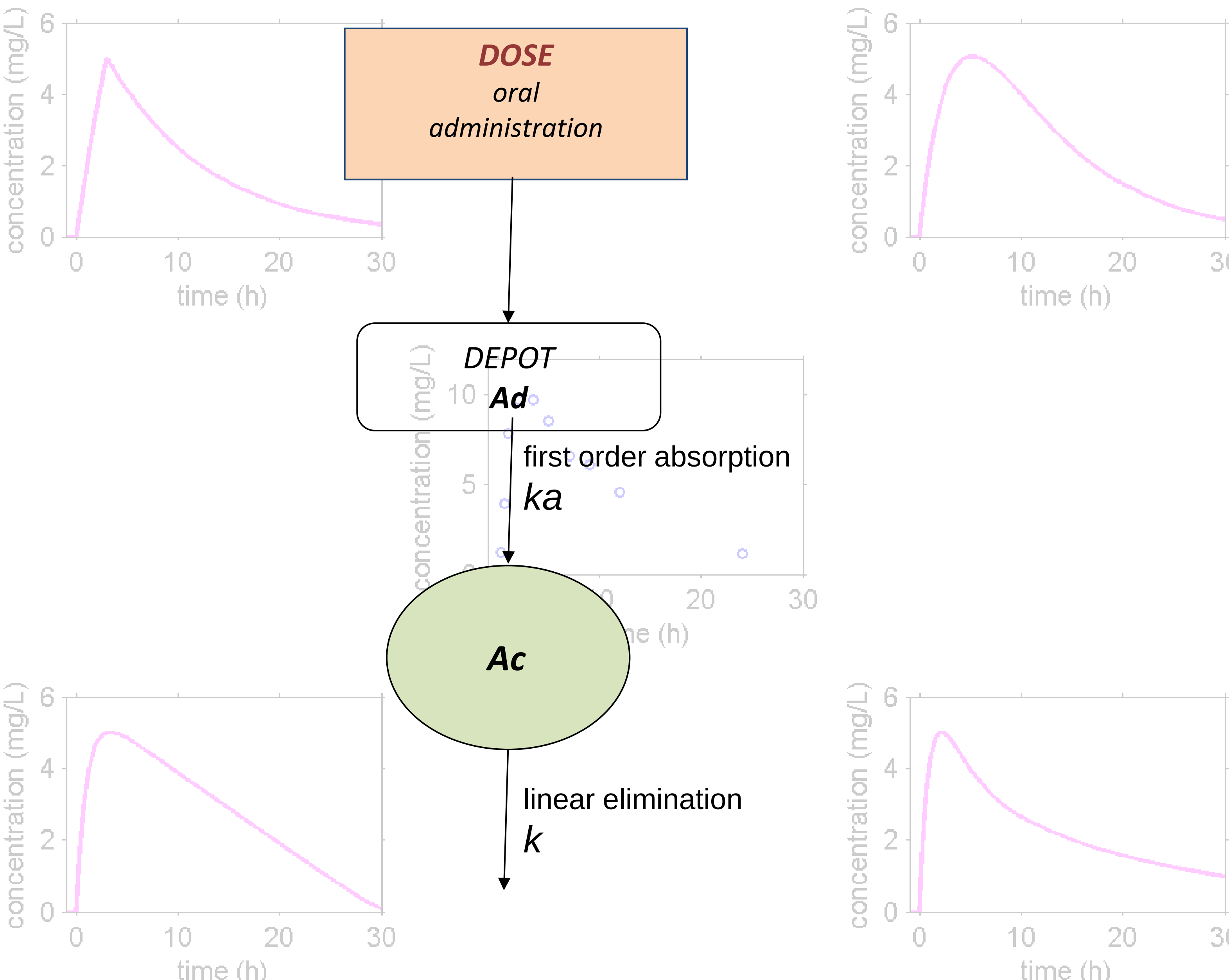

concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
5
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30
concentration (mg/L)
time (h)
0
2
4
6
10
20
30

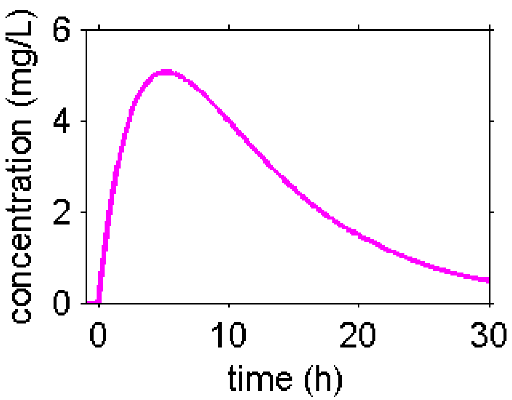


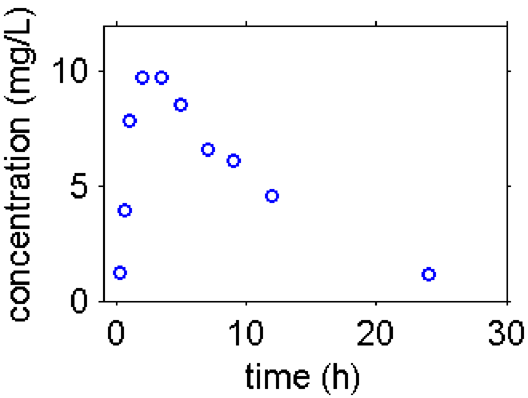
concentration (mg/L)
time (h)



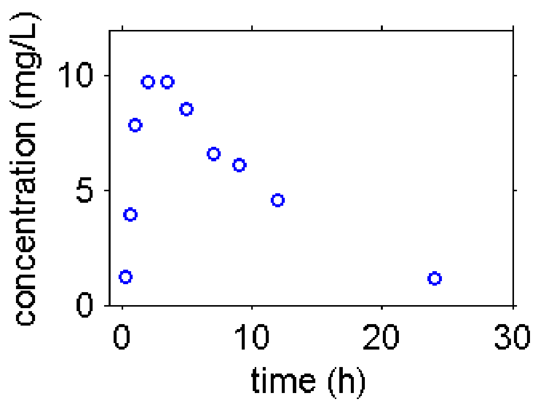
concentration (mg/L)
6
4
2
0
0
10
20
30
time (h)
concentration (mg/L)
6
4
2
0
0
10
20
30
time (h)
concentration (mg/L)
10
5
0
0
10
20
30
time (h)
concentration (mg/L)
6
4
2
0
0
10
20
30
time (h)
concentration (mg/L)
6
4
2
0
0
10
20
30
time (h)

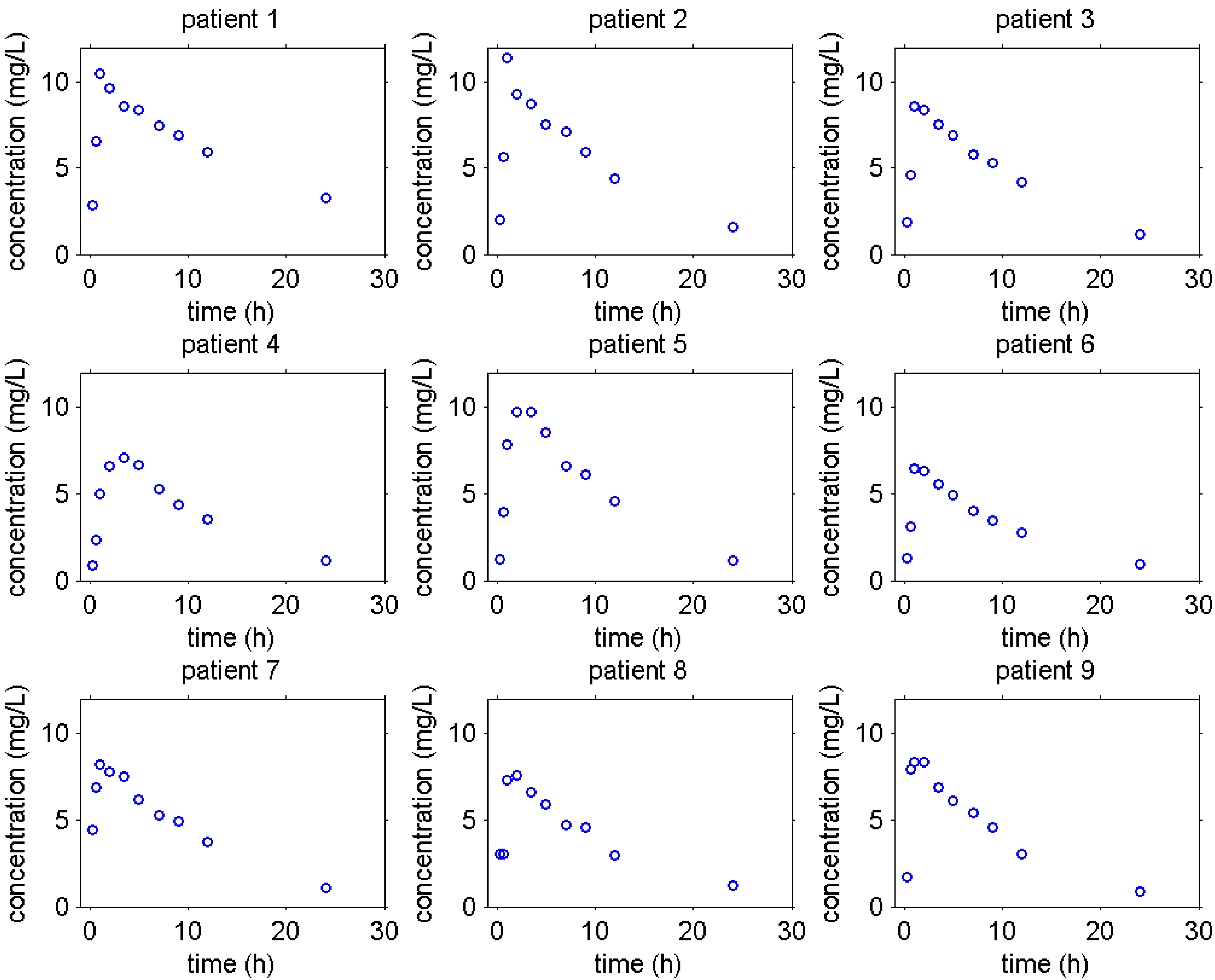

DOSE
oral
administration
DEPOT
Ad
first order absorption
ka
Ac
linear elimination
k
concentration (mg/L)
time (h)

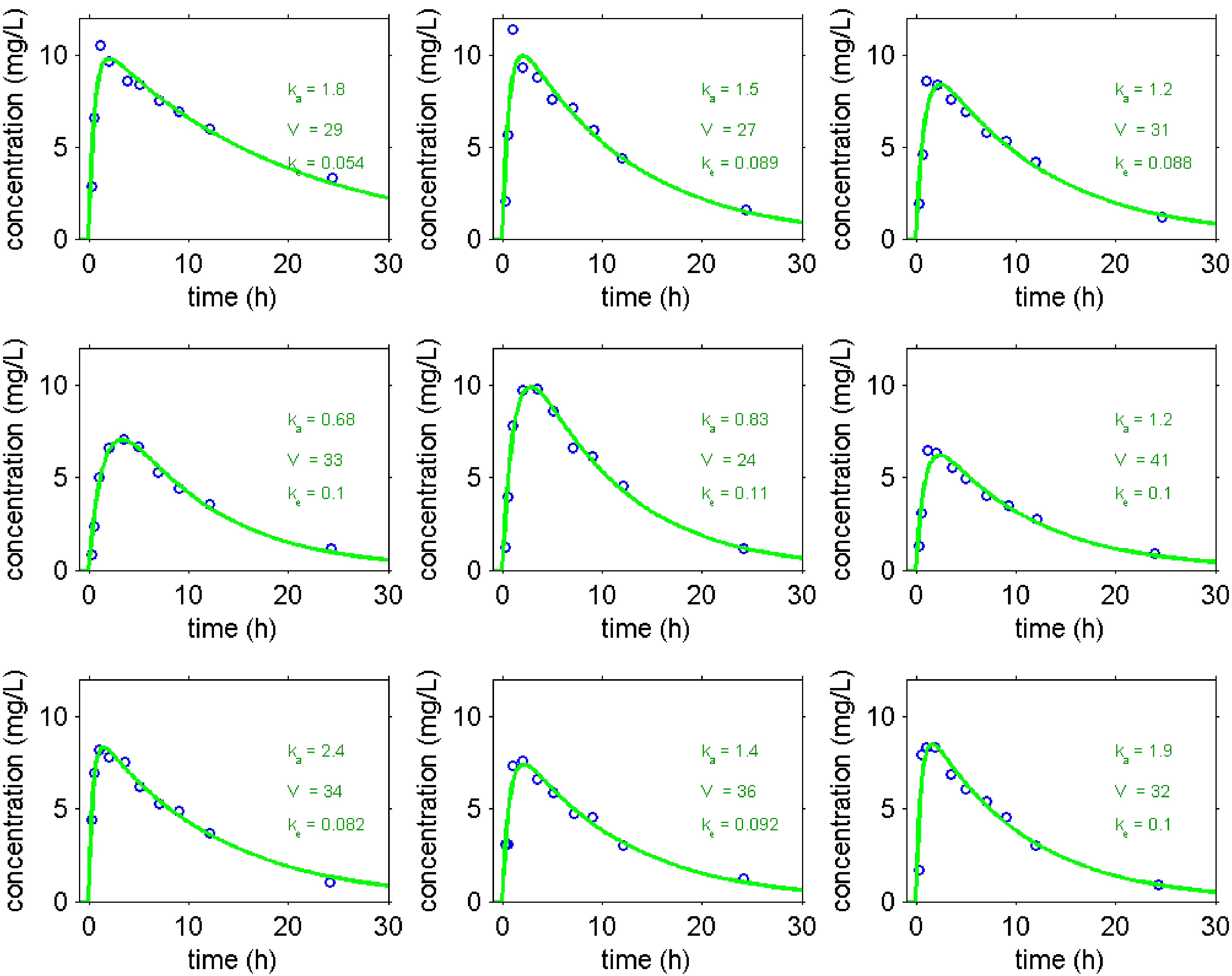

concentration (mg/L)
6
4
2
0
0
10
20
30
time (h)


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

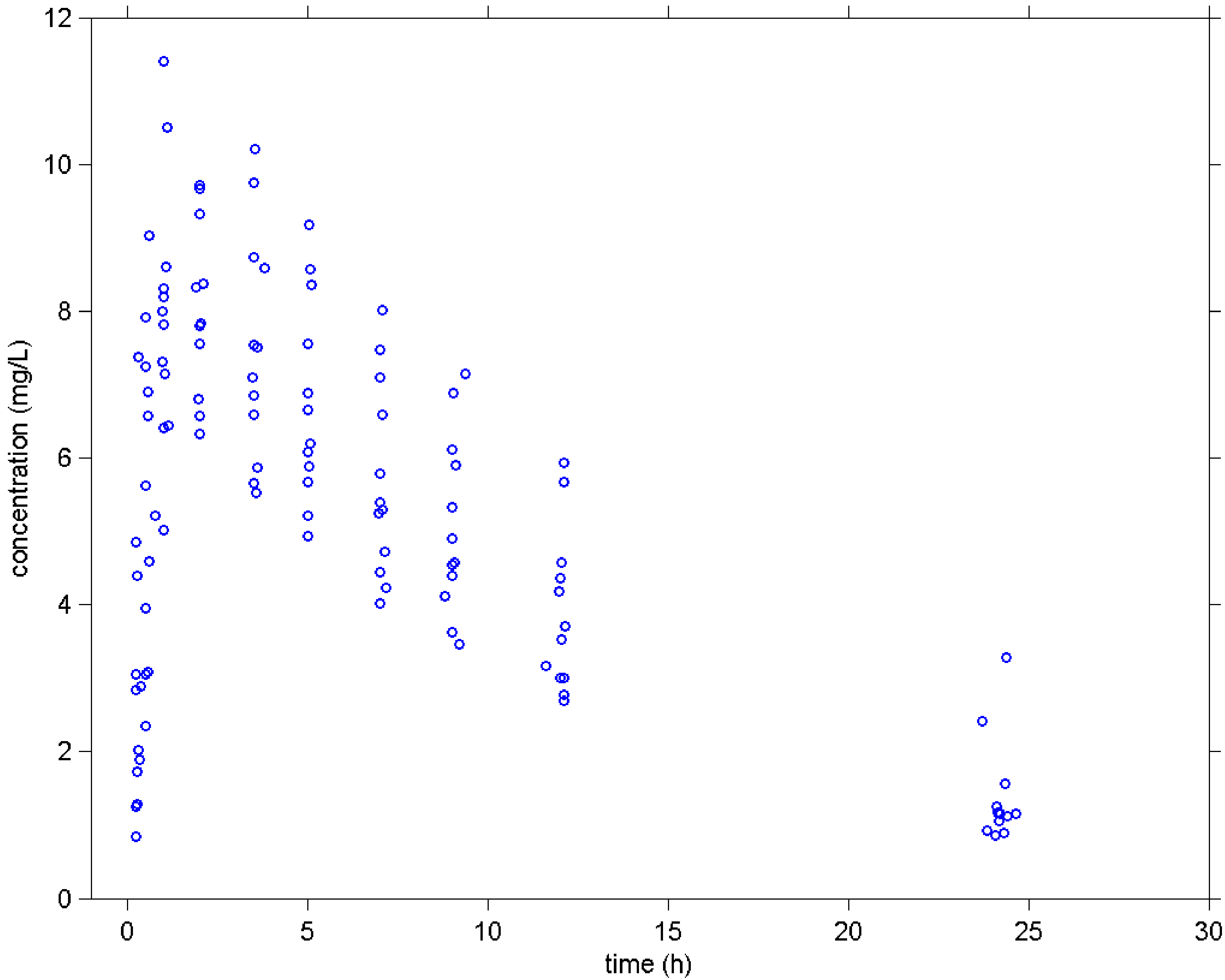
The population approach


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

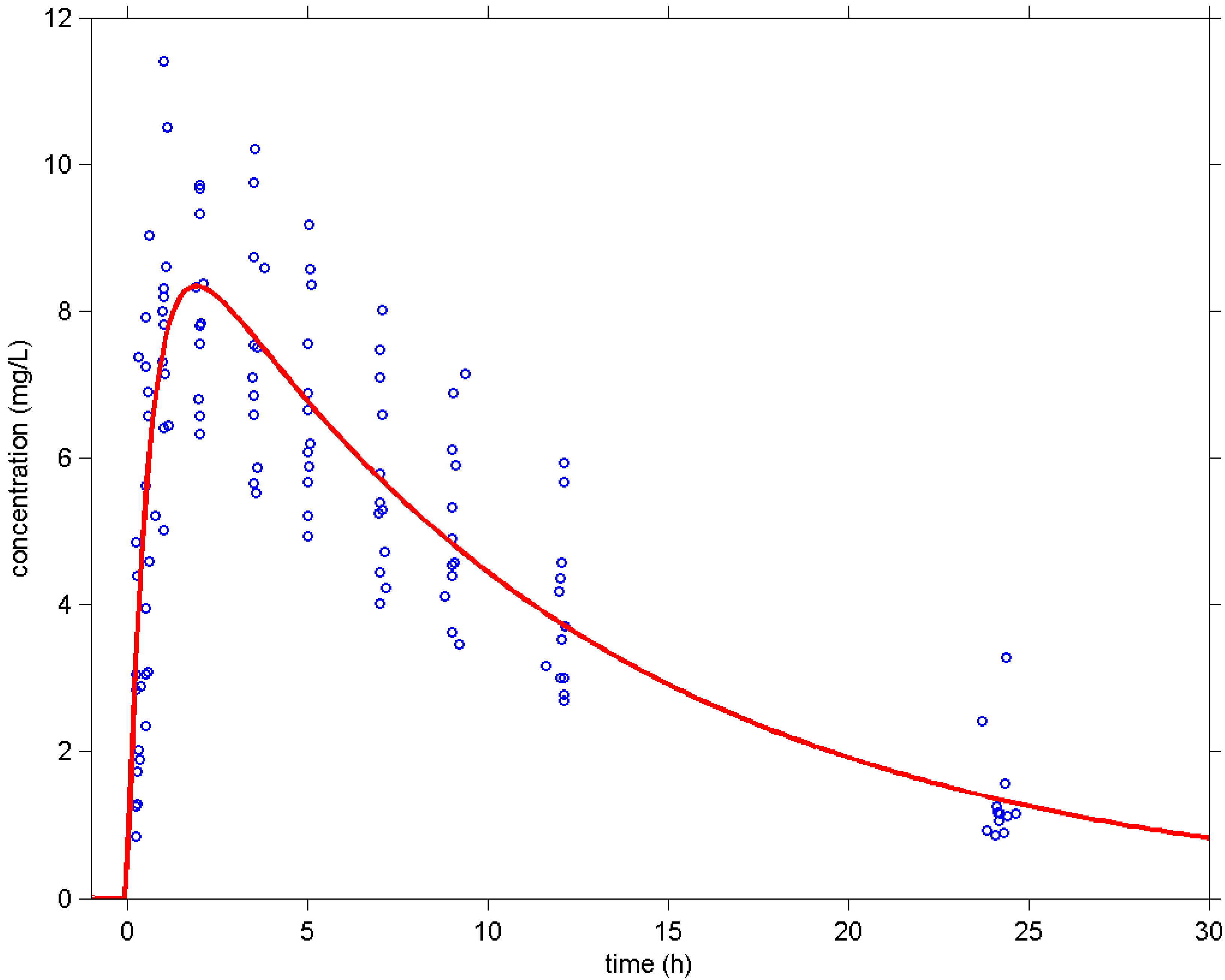

patient 1
patient 2
patient 3
patient 4
patient 5
patient 6
patient 7
patient 8
patient 9
concentration (mg/L)
time (h)



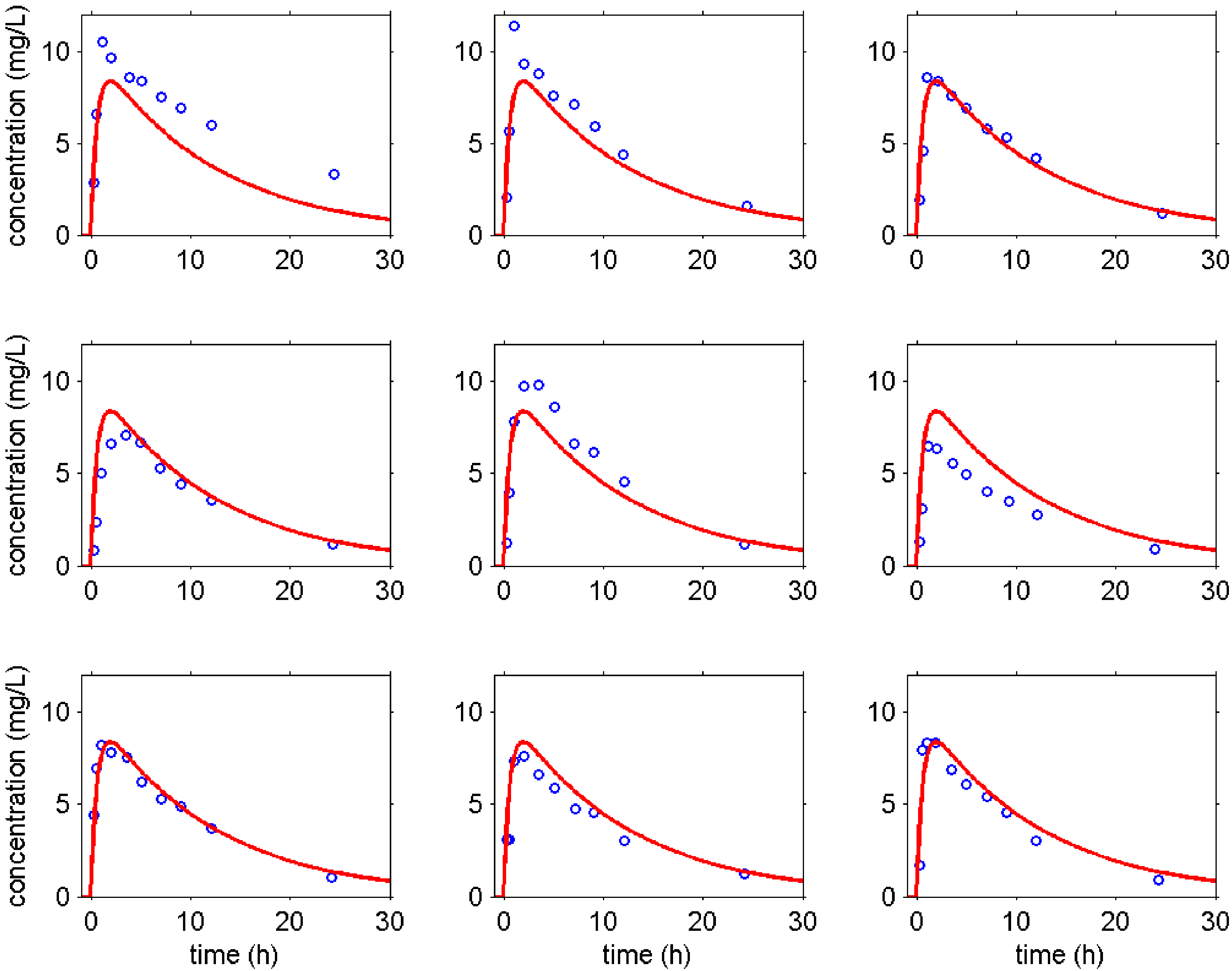
concentration (mg/L)
time (h)
k_a = 1.8
V = 29
k_e = 0.054
k_a = 1.5
V = 27
k_e = 0.089
k_a = 1.2
V = 31
k_e = 0.088
k_a = 0.68
V = 33
k_e = 0.1
k_a = 0.83
V = 24
k_e = 0.11
k_a = 1.2
V = 41
k_e = 0.1
k_a = 2.4
V = 34
k_e = 0.082
k_a = 1.4
V = 36
k_e = 0.092
k_a = 1.9
V = 32
k_e = 0.1

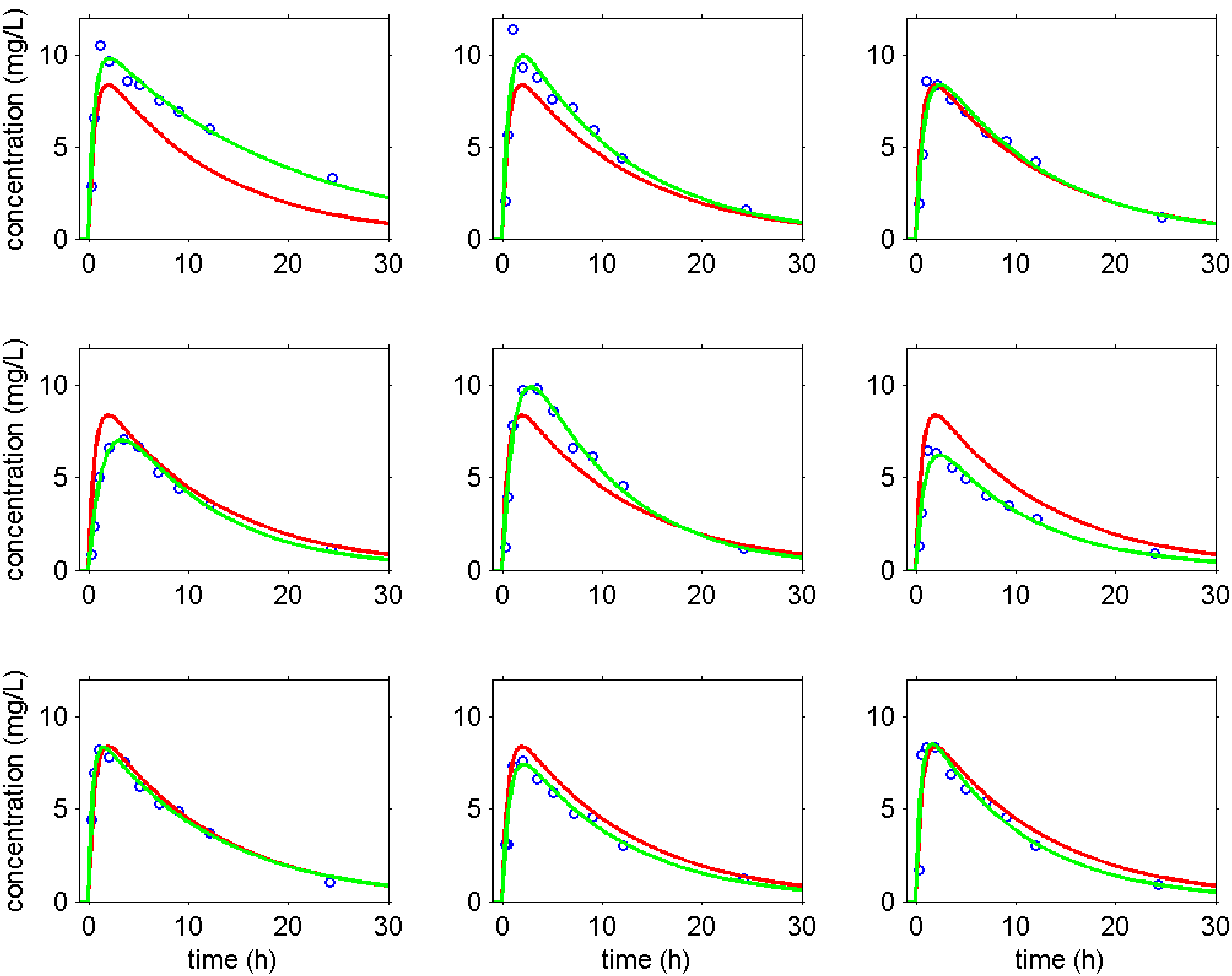


12
10
8
6
4
2
0
concentration (mg/L)
0
5
10
15
20
25
30
time (h)



12
10
8
6
4
2
0
concentration (mg/L)
0
5
10
15
20
25
30
time (h)


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



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

Introduction to the population approach

- N subjects
- $y_i = (y_{ij}, 1 \leq j \leq n_i)$: measurements for subject i (observed)

$$y_i \sim h(\,\cdot\,; \psi_i)$$

- ψ_i : individual parameters for subject i (not observed)

$$\psi_i \sim \pi(\,\cdot\,; \theta)$$

- θ : population parameters of the model (unknown)

Some tasks to perform

$$\begin{aligned} y_i &\sim h(\cdot, \psi_i) \\ \psi_i &\sim \pi(\cdot; \theta) \end{aligned}$$

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,
   - model selection,
4. **Simulation**
   - clinical trial simulation

Some Methods
& Algorithms

Some Methods and Algorithms for Mixed Effects Models

Marc Lavielle[1]

[1]Inria Saclay

Ifcam Summer School
Bengalore, July 2015

Tasks

Population approach:

$$y_i \sim h(\,\cdot\,; \psi_i)$$

$$\psi_i \sim \pi(\,\cdot\,; \theta)$$

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,
   - model selection,
4. **Simulation**
   - clinical trial simulation

Outline

1. Estimation of the population parameters (SAEM)
2. Estimation of the conditional distributions (MCMC)
3. Estimation of the observed likelihood (Importance Sampling)

Preliminary remark

If ψ was observed, maximum likelihood estimation of θ would be "easy":

$$p(y, \psi; \theta) = p(y|\psi)\pi(\psi; \theta)$$

Then,

$$\hat{\theta} = \mathrm{Arg}\max_{\theta} \pi(\psi; \theta)$$

Example:

$$\psi_i = \psi_{pop} + \eta_i \quad , \quad \eta_i \sim N(0, \Omega)$$

Then,

$$\begin{aligned} \hat{\psi}_{pop} &= \bar{\psi} \\ \hat{\Omega} &= \frac{1}{N}\sum_{i=1}^{N}(\psi - \hat{\psi}_{pop})(\psi - \hat{\psi}_{pop})' \end{aligned}$$

SAEM1: A first version of SAEM

Unfortunately, ψ is not observed... then, simulate it!

Iteration k of the algorithm:

- *Simulation:* draw the non observed individual parameters $\psi^{(k)}$ with the conditional distribution $p(\psi \,|y;\theta_{k-1})$

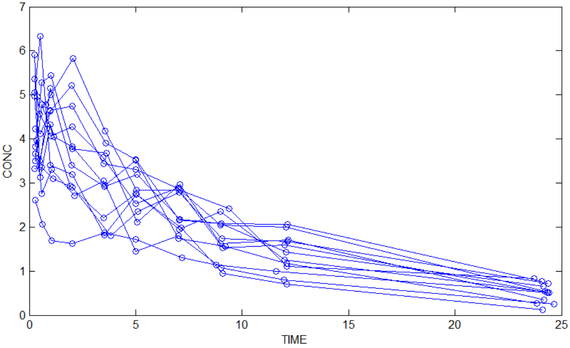
- *Estimation:* update the estimation of θ

$$\boxed{\theta_k = Argmax \;\; p(y, \psi^{(k)}; \theta)}$$

SAEM1: A first version of SAEM

A PK example:

$$
\begin{aligned}
y_{ij} &= \frac{4}{V_i} e^{-\frac{Cl_i}{V_i} t_{ij}} + \varepsilon_{ij} \quad ; \quad \sigma_\varepsilon = 0.2 \\
\log(V_i) &\sim N(\log(V_{pop}), \omega_V) \quad ; \quad V_{pop} = 1 \ , \ \omega_V = 0.2 \\
\log(Cl_i) &\sim N(\log(Cl_{pop}), \omega_{Cl}) \quad ; \quad Cl_{pop} = 0.1 \ , \ \omega_{Cl} = 0.2
\end{aligned}
$$

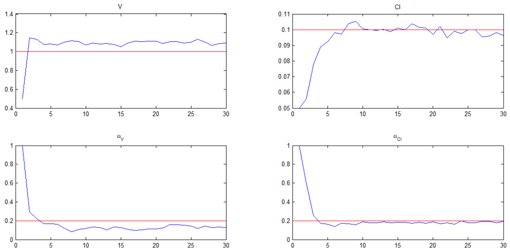


SAEM1: A first version of SAEM

$$\begin{aligned} \psi^{(k)} &\sim p(\psi|y;\theta_{k-1}) \\ \theta_k &= \mathrm{Arg}\max_{\theta} \ \log p(y,\psi^{(k)};\theta) \end{aligned}$$

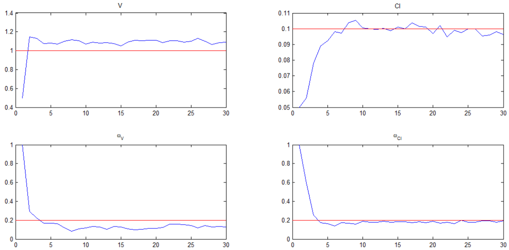
SAEM1: A first version of SAEM

$$\begin{aligned} \psi^{(k)} &\sim p(\psi|y;\theta_{k-1}) \\ \theta_k &= \operatorname*{Arg\,max}_{\theta} \log p(y,\psi^{(k)};\theta) \end{aligned}$$



SAEM1: A first version of SAEM

$$
\begin{aligned}
\psi^{(k)} &\sim p(\psi | y; \theta_{k-1}) \\
\theta_k &= \operatorname*{Arg\,max}_{\theta} \ \log p(y, \psi^{(k)}; \theta)
\end{aligned}
$$



- The sequence (θ_k) converges very quickly to a neighborhood of the "solution",
- The sequence (θ_k) is a homogeneous Markov Chain that does not converge to some $\hat{\theta}$.

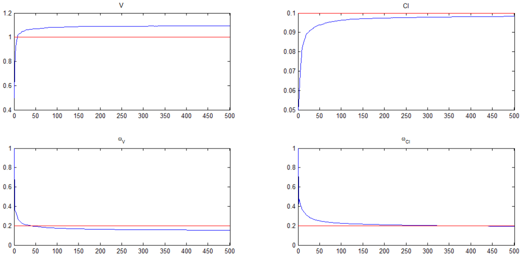
SAEM2: A second version of SAEM

$$\begin{aligned}
\psi^{(k)} &\sim p(\psi|y;\theta_{k-1}) \\
\theta_k &= \mathrm{Arg}\max_{\theta} \ \frac{1}{k}\sum_{m=1}^{k} \log p(y,\psi^{(m)};\theta)
\end{aligned}$$

SAEM2: A second version of SAEM

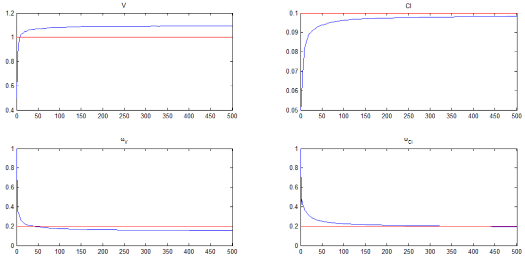
$$\psi^{(k)} \sim p(\psi|y;\theta_{k-1})$$

$$\theta_k = \operatorname{Arg}\max_{\theta} \frac{1}{k}\sum_{m=1}^{k} \log p(y,\psi^{(m)};\theta)$$



SAEM2: A second version of SAEM

$$
\begin{aligned}
\psi^{(k)} &\sim p(\psi | y; \theta_{k-1}) \\
\theta_k &= \operatorname{Arg}\max_{\theta} \frac{1}{k} \sum_{m=1}^{k} \log p(y, \psi^{(m)}; \theta)
\end{aligned}
$$



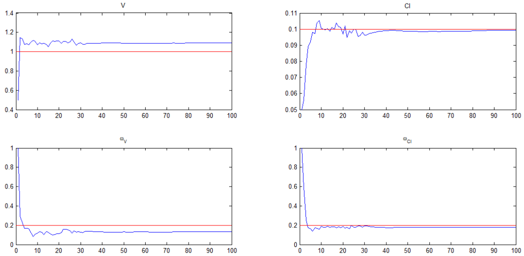
- The sequence (θ_k) converges to the Maximum Likelihood Estimate $\hat{\theta}$,
- Convergence is very slow.

An improved version combining SAEM1 and SAEM2

$$\begin{aligned}
\psi^{(k)} &\sim p(\psi|y;\theta_{k-1}) \\
\theta_k &= \mathrm{Arg}\max_{\theta} \ \log p(y,\psi^{(k)};\theta) \ \mathrm{if}\, k \leq K_1 \\
&= \mathrm{Arg}\max_{\theta} \ \sum_{m=K_1+1}^{k} \log p(y,\psi^{(m)};\theta) \ \mathrm{if}\, k > K_1
\end{aligned}$$

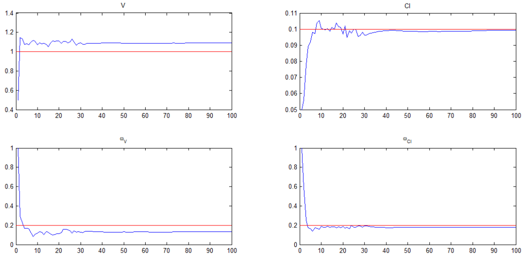
An improved version combining SAEM1 and SAEM2

$$
\begin{aligned}
\psi^{(k)} &\sim p(\psi | y; \theta_{k-1}) \\
\theta_k &= \operatorname*{Arg\,max}_{\theta} \; \log p(y, \psi^{(k)}; \theta) \text{ if } k \leq K_1 \\
&= \operatorname*{Arg\,max}_{\theta} \sum_{m=K_1+1}^{k} \log p(y, \psi^{(m)}; \theta) \text{ if } k > K_1
\end{aligned}
$$



An improved version combining SAEM1 and SAEM2

$$
\begin{aligned}
\psi^{(k)} &\sim p(\psi | y; \theta_{k-1}) \\
\theta_k &= \operatorname*{Arg\,max}_{\theta} \log p(y, \psi^{(k)}; \theta) \text{ if } k \leq K_1 \\
&= \operatorname*{Arg\,max}_{\theta} \sum_{m=K_1+1}^{k} \log p(y, \psi^{(m)}; \theta) \text{ if } k > K_1
\end{aligned}
$$



- The sequence (θ_k) converges **very quickly** to the Maximum Likelihood Estimate $\hat{\theta}$, 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

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

- step M : update the estimation of θ:

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

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

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

The expectation cannot be computed in a closed form: it can be approximated using simulations.

EM v.s. SAEM

E-step:

EM	SAEM
$Q_k(\theta) = E(\log p(y, \psi; \theta) \mid \theta_{k-1})$	during K_1 iterations: $Q_k(\theta) = \log p(y, \psi^{(k)}; \theta)$ during K_2 iterations: $Q_k(\theta) = \frac{1}{k - K_1} \sum_{k=K1+1}^{k} \log p(y, \psi^{(k)}; \theta)$ $= Q_{k-1}(\theta) + \frac{1}{k - K_1}(\log p(y, \psi^{(k)}; \theta) - Q_{k-1}(\theta))$

M-step:

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

Convergence of SAEM

Theorem

Under very general technical conditions, the SAEM sequence (θ_k) converges a.s. to some (local) maximum of the observed likelihood $p(y;\theta)$.

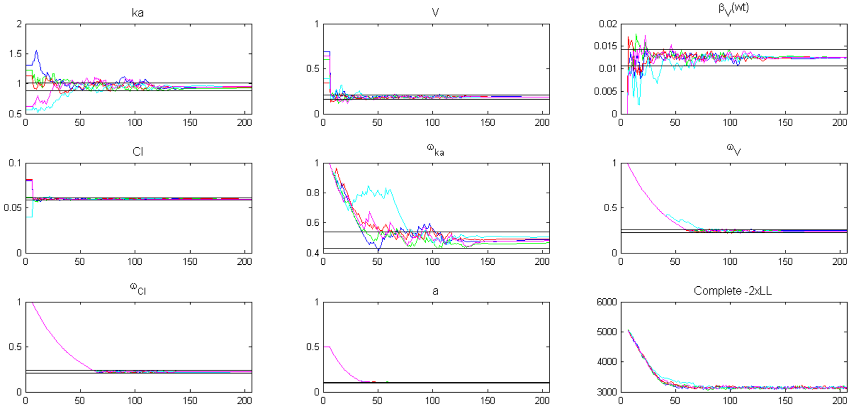
Proof.

1. Delyon, Lavielle & Moulines *The Annals of Statistics* (1999)
   Exact simulation assumed, compactness of $(\psi_i^{(k)})$ not required
2. Kuhn & Lavielle *ESAIM P&S* (2004)
   Markovian perturbation allowed, compactness of $(\psi_i^{(k)})$ required
3. Allassonnière, Kuhn & Trouvé *Bernoulli* (2010)
   Markovian perturbation allowed, compactness of $(\psi_i^{(k)})$ not required

□

Convergence assessment of SAEM

5 runs of SAEM with different initial values

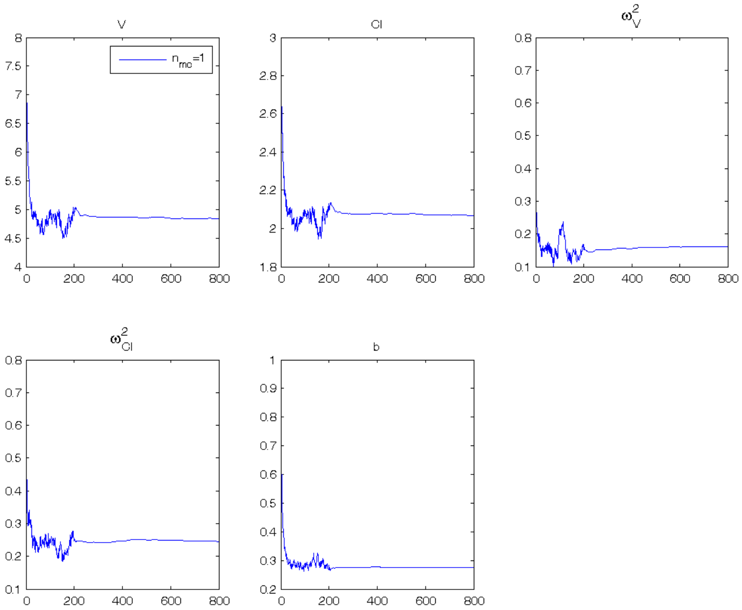


horizontal lines: confidence interval ($\pm$ 1 standard error)

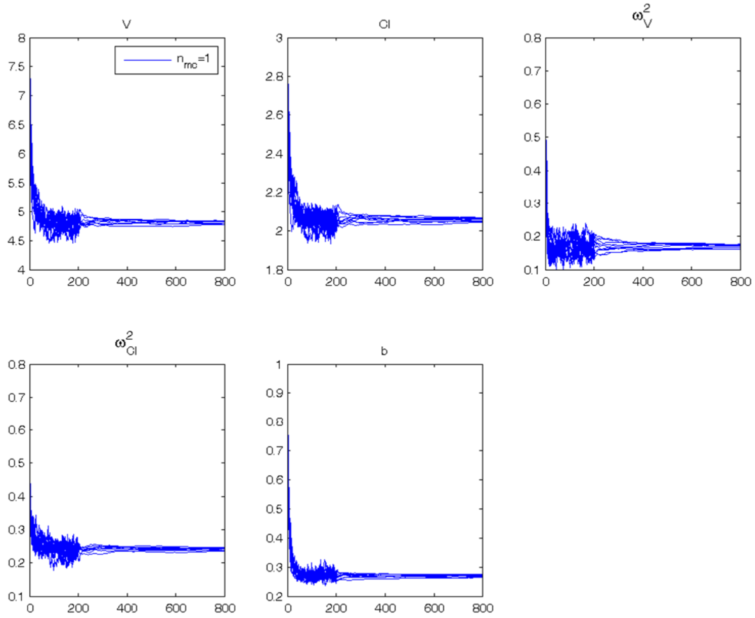
Running several Markov chains

$$
\begin{aligned}
\psi^{(k,\ell)} &\sim p(\psi|y;\theta_{k-1}) \quad , \quad 1 \leq \ell \leq L \\
\theta_k &= \operatorname{Arg}\max_{\theta} \sum_{\ell=1}^{L} \log p(y,\psi^{(k,\ell)};\theta) \text{ if } k \leq K_1 \\
&= \operatorname{Arg}\max_{\theta} \sum_{m=K_1+1}^{k} \sum_{\ell=1}^{L} \log p(y,\psi^{(m,\ell)};\theta) \text{ if } k > K_1
\end{aligned}
$$

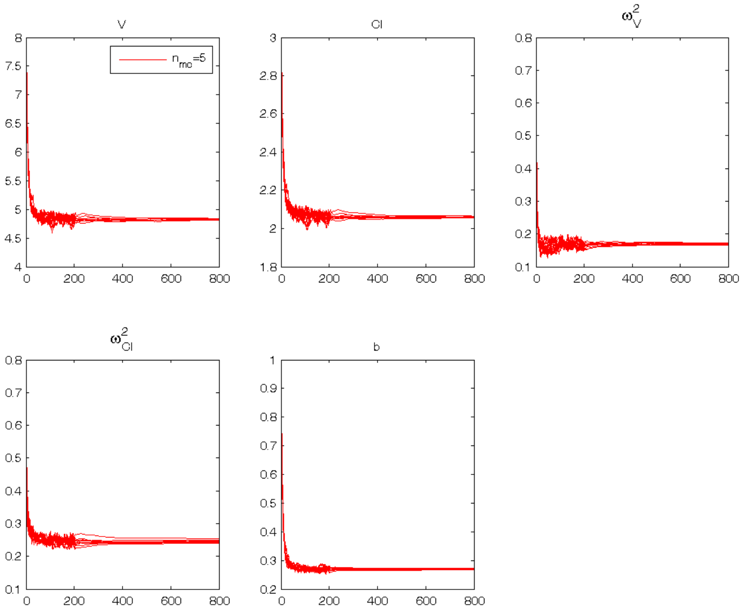
Running several Markov chains



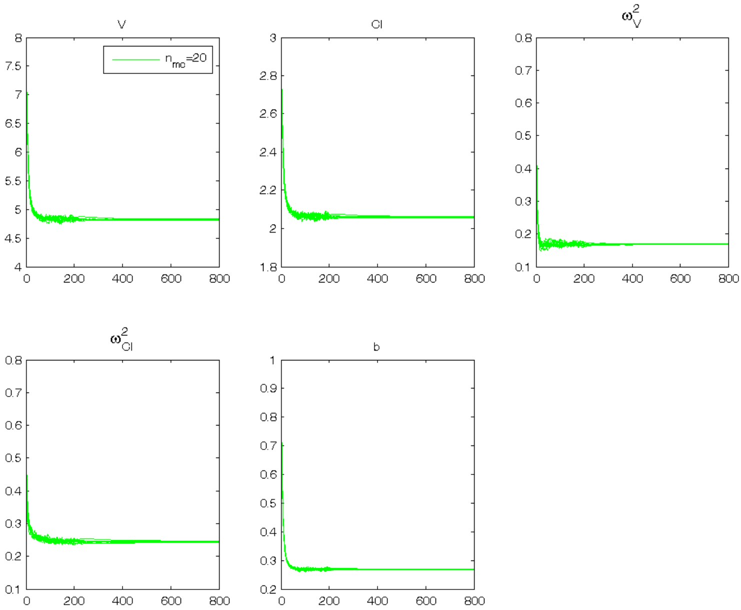
Running several Markov chains



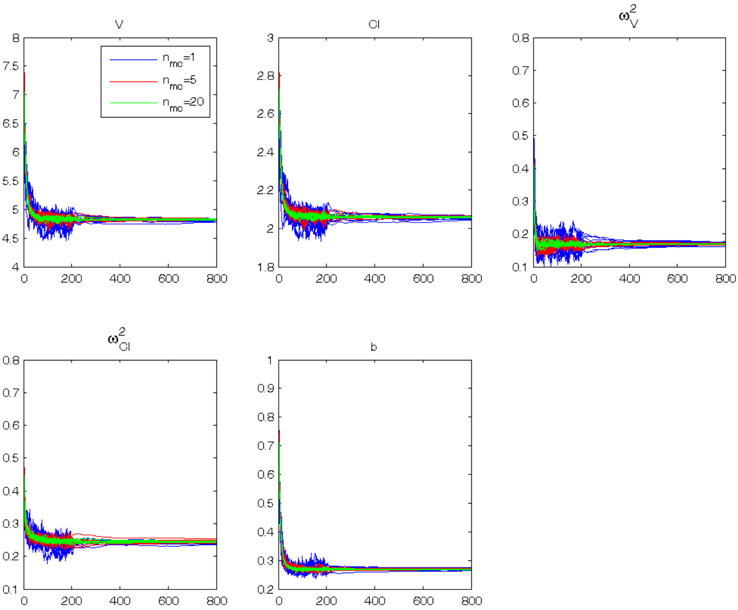
Running several Markov chains



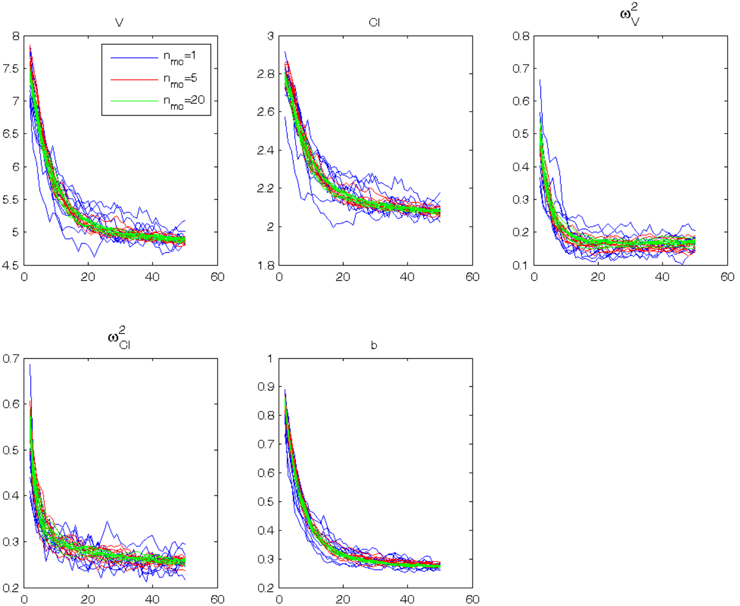
Running several Markov chains



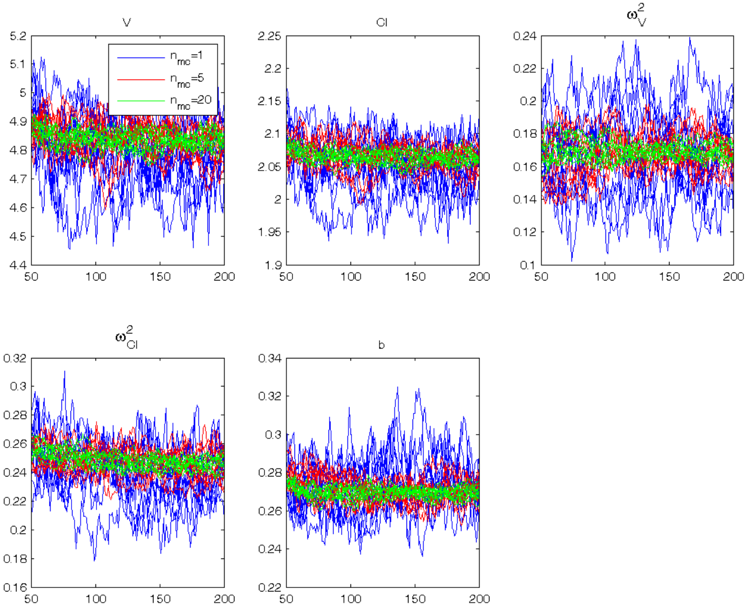
Running several Markov chains



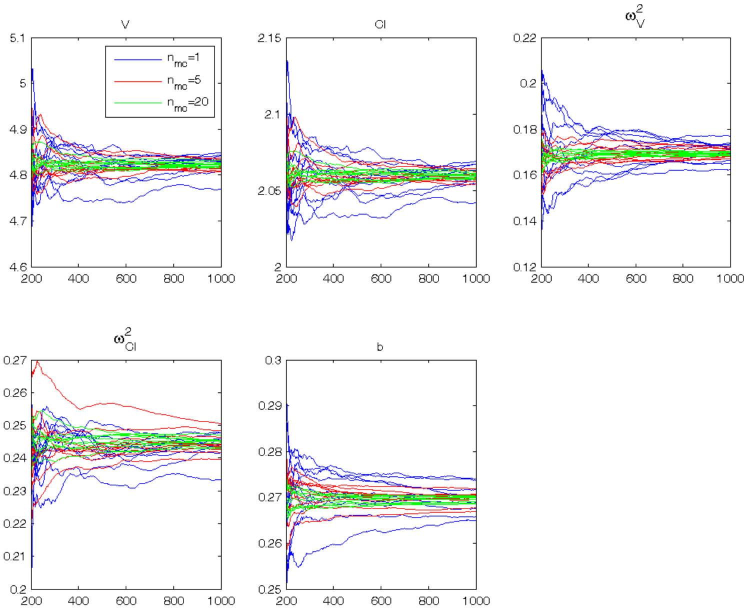
Running several Markov chains



Running several Markov chains



Running several Markov chains



A Simulated Annealing version of SAEM

Conditional distribution of ψ:

$$p(\ \psi \ |y;\theta) = C(y;\theta)e^{-U(\psi,y;\theta)}$$

Temperature parameter T:

$$p_T(\ \psi \ |y;\theta) = C_T(y;\theta)e^{-\frac{U(\psi,y;\theta)}{T}}$$

Choose a decreasing Temperature sequence (T_k) converging to 1.
Then, at iteration k of SAEM,

- E-step: draw the non observed data $\psi^{(k)}$ running some iterations of the Metropolis-Hastings with the conditional distribution $p_{T_k}(\ \cdot\ |y;\theta_{k-1})$
- M-step remains unchanged

Outline

1 Estimation of the population parameters (SAEM)

2 Estimation of the conditional distributions (MCMC)

3 Estimation of the observed likelihood (Importance Sampling)

Let h be a transformation such that $\phi = h(\psi)$ is normally distributed. The Metropolis-Hastings (MH) is used for simulating ϕ with the conditional distribution $p(\phi|y;\theta)$. Then, ψ is obtained by setting $\psi = h^{-1}(\phi)$.

Iteration ℓ of the MH algorithm for simulating $p(\phi|y;\theta)$:

1. draw a new value ϕ^c with a *proposal distribution* $q(\cdot\,;\phi^{(\ell-1)})$,
2. accept this new value, that is set $\phi^{(\ell)} = \phi^c$ with probability

$$\alpha(\phi^c;\phi^{(\ell-1)}) = \frac{q(\phi^{(\ell-1)};\phi^c)p(\phi^c|y;\theta)}{q(\phi^c;\phi^{(\ell-1)})p(\phi^{(\ell-1)}|y;\theta)}$$

In the model $y = f(x;\psi)+g(x;\psi)\varepsilon$, computing $\alpha(\phi^c;\phi^{(\ell-1)})$ only requires to compute $\psi^c = h^{-1}(\phi_c)$, $f(x,\psi^c)$ and $g(x,\psi^c)$ but not the derivatives of f and g.

The three following proposal kernels are used for simulating $p(\phi_i|y_i;\theta)$, for $i = 1, 2, \ldots, N$:

1. $q^{(1)}_{\theta,i}$ is the marginal distribution of ϕ_i, that is the Gaussian distribution $\mathcal{N}(\mathbb{E}_\theta\left(\phi_i\right), \Omega)$
2. $q^{(2)}_{\theta,i}$ is the multidimensional random walk $\mathcal{N}(\phi_i^{(\ell-1)}, \tau\Omega)$ where τ is adjusted in order to reach an acceptation rate $\rho^\star \approx 0.3$
3. $q^{(3)}_{\theta,i}$ is a succession of d unidimensional Gaussian random walks: each component of ϕ_i are successively updated with a acceptation rate $\rho^\star \approx 0.3$.

Then, the simulation-step at iteration k of SAEM consists in running for $i = 1, 2, \ldots N$:

1. m_1 iterations of the Metropolis-Hastings with proposal $q^{(1)}_{\theta_k,i}$,
2. m_2 iterations with proposal $q^{(2)}_{\theta_k,i}$
3. m_3 iterations with proposal $q^{(3)}_{\theta_k,i}$.

The size τ of the Gaussian random walks is updated at each iteration of SAEM in order to reach the acceptation rate $\rho^\star$:

$$\tau_k = \tau_{k-1}(1 + a(\overline{\rho}_{k-1} - \rho^\star)) \quad 0 < a < 1$$

where $\overline{\rho}_{k-1}$ is the empirical acceptation rate at iteration $k-1$.

Outline

1. Estimation of the population parameters (SAEM)
2. Estimation of the conditional distributions (MCMC)
3. Estimation of the observed likelihood (Importance Sampling)

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

Then, $\mathbb{E}_{\pi_\theta}\left(h(y|\psi)\right)$ can be estimated by Monte-Carlo:

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

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

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

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

1. Draw $\psi^{(1)}, \psi^{(2)}, \ldots, \psi^{(M)}$ with the marginal distribution $\mathbb{E}_{\tilde{\pi}_\theta}\left(p(y|\psi)\right)_\theta$,
2. Let

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

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

Assume that the sampling distribution $\tilde{\pi}$ is the conditional distribution $p(\psi|y;\theta)$. Then, for any j,

$$p(y|\psi^{(j)})\frac{\pi_\theta(\psi^{(j)})}{\tilde{\pi}_\theta(\psi^{(j)})} = p(y;\psi)$$

which means that only one simulation would be required since $\mathrm{Var}\left(\hat{\ell}_M(\theta;y)\right) = 0$.

In general, the conditional distribution $p(\psi|y;\theta)$ cannot be used "exactly", but it be can be estimated and approximated:

1. For $i = 1, 2, \ldots, N$, estimate the conditional mean and variance of $\phi_i = h(\psi_i)$ using MCMC
2. Use for $\tilde{\pi}$ a decentered t-distribution with ν d.f.

$$\begin{aligned}
\phi_i^{(j)} &= \mathbb{E}\left(\phi_i|y_i;\theta\right) + \mathrm{std}\left(\phi_i|y_i;\theta\right) \times T(\nu) \\
\psi_i^{(j)} &= h^{-1}(\phi_i^{(j)})
\end{aligned}$$

Estimation of the observed likelihood

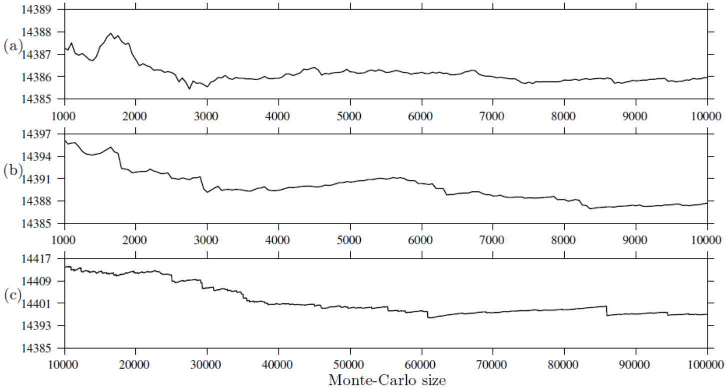


FIGURE 9.11: Estimation of the deviance as a function of the Monte Carlo size. The conditional distributions $p(\psi_i|y_i;\widehat{\theta})$ are estimated using the MH algorithm in (a) and (b) and the last 30 SAEM iterations in (c); non-central t distributions with 5 d.f. are used as proposal distributions in (a) and (c), normal distributions in (b).

Some tools for PKPD modeling

MLXTran: a new modeling language

```
[LONGITUDINAL]
input = {ka, V, k}

EQUATION:
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc = Ac/V
```

MLXTran: a new modeling language

```
[LONGITUDINAL]
input = {ka, V, k, a}

EQUATION:
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc = Ac/V

DEFINITION:
Cobs = {distribution = normal,  prediction = Cc,  sd = a}
```

MLXTran: a new modeling language

```
[LONGITUDINAL]
input = {ka, V, k}

EQUATION:
ddt_Ad = -ka*Ad
ddt_Ac = ka*Ad - k*Ac
Cc = Ac/V
;-----------------------------------------------------------------------
[INDIVIDUAL]
input = {ka_pop, V_pop, k_pop, omega_ka, omega_V, omega_k}

DEFINITION:
ka = {distribution=lognormal, reference=ka_pop, sd=omega_ka}
V = {distribution=lognormal, reference=V_pop, sd=omega_V}
k = {distribution=lognormal, reference=k_pop, sd=omega_k}
```

Glucose insulin model

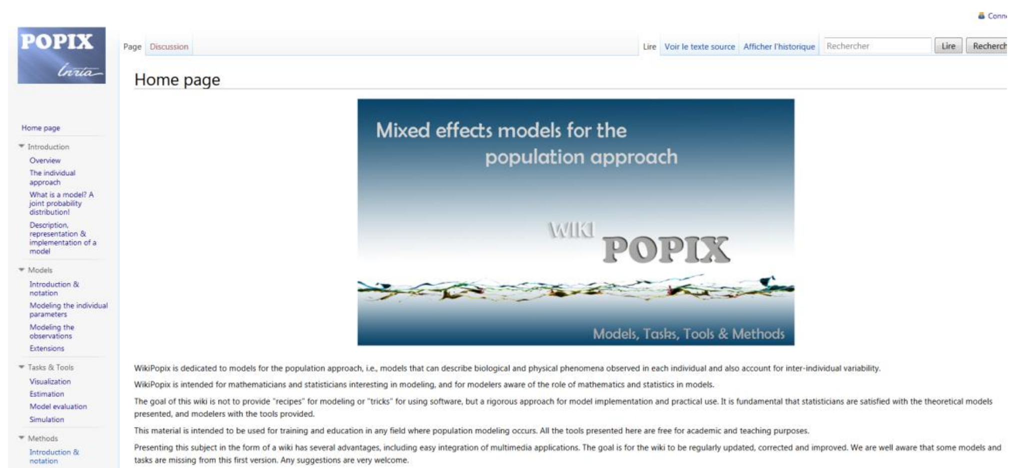
```
[[LONGITUDINAL]]
input={ta,tge2,tge3,GPV0,IPV0,VGPI}

EQUATION:
t0=0
ddt_Gs2=-Gs2/tge2
ddt_rOGA2=-(rOGA2/ta)+Gs2/(ta*tge2)
ddt_Gs3=-Gs3/tge3
ddt_rOGA3=-(rOGA3/ta)+Gs3/(ta*tge3)
VIB=0.265
VIL=1.07
VIG=0.945
VIK=0.505
VIH=0.985
VIPV=0.735
VIPI=6.3
VIPN=0.07
QIB=0.45
QIH=3.12
QIA=0.18
QIL=0.9
QIG=0.684
QIK=0.72
QIP=1.05
QIPN=0.036
TIP=20
FPIC=0.15
FLIC=0.40
FKIC=0.30
M1=0.007968
M2=0.136495
alpha=0.048229
beta=0.93141
K=0.0079378
phi1=0.003
phi2=0.0001
gam=0.57493
lmb0=6.3294
VGBV=3.5
VGBI=4.5
VGH=13.8
VGL=23.5
VGG=11.2
VGK=6.6
VGPV=10.4
VGPN=1.6
QGB=5.9
QGH=43.7
QGA=2.5
QGL=12.6
QGG=9.6
QGK=10.1
QGP=15.1
QGPN=0.5
TB=2.1
TGP=5.0
TauI=25
TauGamma=65
rBGU=70
rRBCU=10
rGGU=20
rBPGU=35
rBHGP=155
rBHGU=20
GPI=AGPI/VGPI
MIHGP_0=1
MIHGU_0=1
f_0=0
VGamma=9930
rMGammaC=910
VInc=9.930
rMIncC=0.14
TauInc=25
IncG_0=0
AInc_0=0
IB0=IPV0/(1-FPIC)
IH0=IB0
IL0=(IH0/QIL)*(QIH-QIP*(1-FPIC)-QIK*(1-FKIC)-QIB)
IPN0=(IH0/QIPN)*(QIH/(1-FLIC)-QIA-QIG-(1-FPIC)/(1-
FLIC)*QIP-QIB/(1-FLIC)-QIK*(1-FKIC)/(1-FLIC))
IK0=IH0*(1-FKIC)
IPI0=(1-(TIP*FPIC*QIP)/(VIPI*(1-FPIC)))*IPV0
IG0=IH0
IH=AIH/VIH
IB=AIB/VIB
IL=AIL/VIL
IG=AIG/VIG
IK=AIK/VIK
IPV=AIPV/VIPV
IPI=AIPI/VIPI
IPN=AIPN/VIPN
rLIC=FLIC*(QIA*IH+QIG*IG+QIPN*IPN)
rKIC=FKIC*QIK*IH
rPIC=IPI/((1-FPIC)/(FPIC*QIP)-TIP/VIPI)
AIH_0=IH0*VIH
ddt_AIH=QIB*IB+QIL*IL+QIK*IK+QIP*IPV-QIH*IH
INH=IH/IH0
AIB_0=IB0*VIB
ddt_AIB=QIB*(IH-IB)
AIL_0=IL0*VIL
ddt_AIL=QIA*IH+QIG*IG-QIL*IL+QIPN*IPN-rLIC
INL=IL/IL0
AIG_0=IG0*VIG
ddt_AIG=QIG*(IH-IG)
AIK_0=IK0*VIK
ddt_AIK=QIK*(IH-IK)-rKIC
AIPV_0=IPV0*VIPV
ddt_AIPV=QIP*(IH-IPV)+(VIPI/TIP)*(IPI-IPV)
AIPI_0=IPI0*VIPI
ddt_AIPI=(VIPI/TIP)*(IPV-IPI)-rPIC
rBPIR=IH0*(QIH/(1-FLIC)-QIA-QIG-(1-
FPIC)/(1-FLIC)*QIP-QIB/(1-FLIC)-QIPN-
QIK*(1-FKIC)/(1-FLIC))
AIPN_0=IPN0*VIPN
lIPV=log(IPV)
lIH=log(IH)
GH0=GPV0+rBPGU/QGP
GBV0=GH0-rBGU/QGB
GBI0=GBV0-rBGU*TB/VGBI
GPI0=GPV0-rBPGU*TGP/VGPI
GK0=GH0
GG0=(GH0-rGGU/QGG)
GPN0=GH0
GL0=(1/QGL)*(QGA*GH0+QGG*GG0+QGPN
*GPN0+rBHGP-rBHGU)
x0=GH0^(3.267)/(131.87^(3.267)+5.932*(GH0
^(3.024)))
y0=x0^(1.1141)
GH=AGH/VGH
GBV=AGBV/VGBV
GBI=AGBI/VGBI
GG=AGG/VGG
GPN=AGPN/VGPN
GL=AGL/VGL
GK=AGK/VGK
GPV=AGPV/VGPV
MIinfHGP=1.2088-1.138*tanh(1.669*(INL-
0.8885))
MIinfHGU=2.0*tanh(0.549*INL)
MGHGP=1.425-1.406*tanh(0.6199*(GL/GL0-
0.4969))
MGHGU=5.6648+5.6589*tanh(2.4375*((GL/G
L0)-1.48))
MGPGU=GPI/GPI0
MIPGU=7.035+6.51623*tanh(0.33827*((IPI/IP
I0)-5.82113))
ddt_MIHGP=(MIinfHGP-MIHGP)/TauI
ddt_MIHGU=(MIinfHGU-MIHGU)/TauI
rHGU=MGHGU*MIHGU*rBHGU
rPGU=MGPGU*rBPGU*MIPGU
AGH_0=GH0*VGH
ddt_AGH=QGB*GBV+QGL*GL+QGK*GK+Q
GP*GPV-QGH*GH-rRBCU
GNH=GH/GH0
AGBV_0=GBV0*VGBV
AGBI_0=GBI0*VGBI
ddt_AGBV=QGB*(GH-GBV)-
(VGBI/TB)*(GBV-GBI)
ddt_AGG=rOGA3 + rOGA2 +
QGG*(GH-GG)-rGGU
AGPN_0=GPN0*VGPN
ddt_AGPN=QGPN*(GH-GPN)
AGL_0=GL0*VGL
AGK_0=GK0*VGK
if GK<0
rKGE=0
elseif GK<460
rKGE=71+71*tanh(0.011*(GK-460))
else
rKGE=-330+0.872*GK
end
ddt_AGK=QGK*(GH-GK)-rKGE
AGPV_0=GPV0*VGPV
ddt_AGPV=QGP*(GH-GPV)-
(VGPI/TGP)*(GPV-GPI)
AGPI_0=GPI0*VGPI
ddt_AGPI=(VGPI/TGP)*(GPV-GPI)-
rPGU
lGPV=log(GPV)
lGH=log(GH)
MG=2.93-2.10*tanh(4.18*(GNH-
0.61))
MI=1.31-0.61*tanh(1.06*(INH-0.47))
AGammaN_0=VGamma
GammaN=AGammaN/VGamma
ddt_AGammaN=rMGammaC*(MG*
MI-GammaN)
Inc=AInc/VInc
ddt_IncG=-IncG/TauInc
ddt_AInc=IncG/TauInc-rMIncC*Inc
X=GH^(3.267)/(131.87^(3.267)+5.9
32*(GH^(3.024)))
Y=X^(1.1141)+phi1*Inc
I_0=x0
PP_0=y0
ddt_PP=alpha*(Y-PP)
ddt_I=beta*(X-I)
Qi=(K*lmb0+gam*y0)/(M1*y0+K)
lmb_0=Qi
ddt_lmb=K*(lmb0-lmb)+gam*PP-
(M1*Y+M2*max(0,X-
I)+phi2*Inc)*lmb
S=(M1*Y+M2*max(0,X-
I)+phi2*Inc)*lmb
SBGH=(M1*y0)*Qi
rPIR=(S/SBGH)*rBPIR
ddt_AIPN=QIPN*(IH-IPN)+rPIR
MGamma0HGP=2.7*tanh(0.388*Ga
mmaN)
MGammaHGP=MGamma0HGP-f
ddt_f=((MGamma0HGP-1)/2-
f)/TauGamma
rHGP=MGHGP*MIHGP*MGammaH
GP*rBHGP
```

Some links

Get Monolix & MLXPlore on the LIXOFT website

http://lixoft.net

WikiPopix: a wiki about the mixed effects models for the population approach

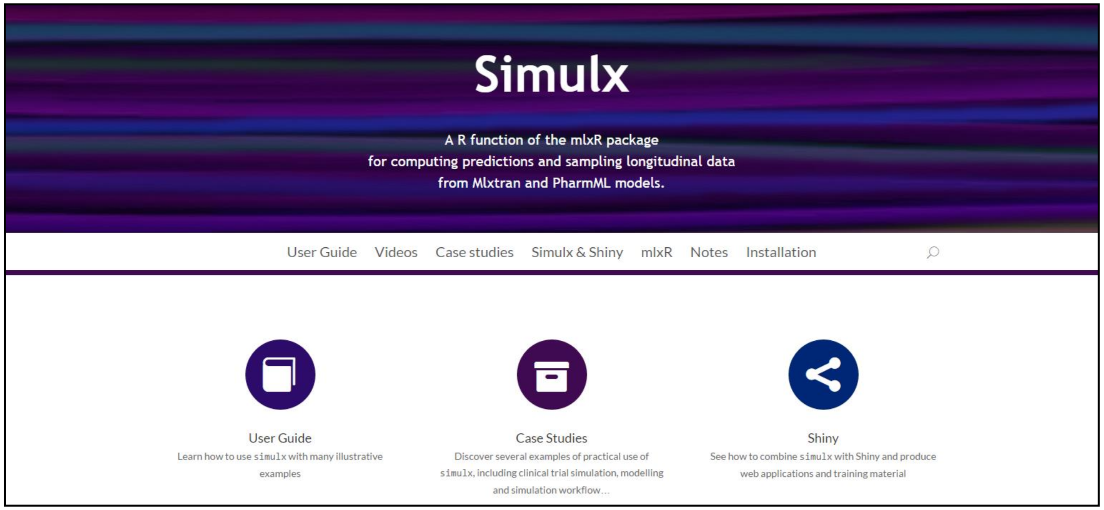


https://wiki.inria.fr/popix

Some links

Get mlxR

simulx.webpopix.org



educational platform
(under development)

model.webpopix.org