Bayesian Knowledge Integration for an *in Vitro-in Vivo* Correlation Model

Elvira Erhardt[1], Moreno Ursino[2], Tom Jacobs[3], Jeike Biewenga[3], Mauro Gasparini[1]

[1]Politecnico di Torino, IT [2]INSERM Paris, FR
[3]Janssen Pharmaceutica, BE

IDEAS Summer School III, 23-27 September 2018
Basel, Switzerland

Outline

Outline

$$v \times y = z$$

$$v \times y = z$$

$$v = 14r + 10$$
$$y = 3n - 2$$

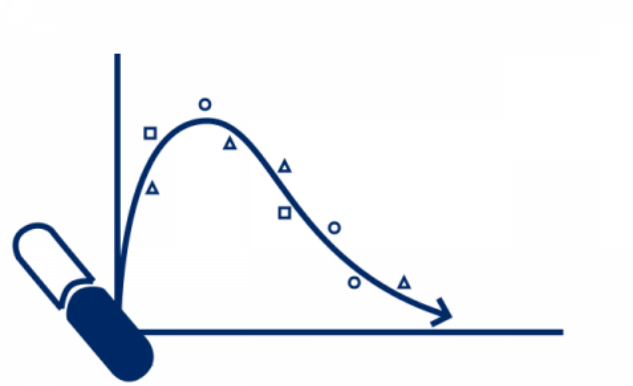
$\Rightarrow v \times y$ is a **convolution**.

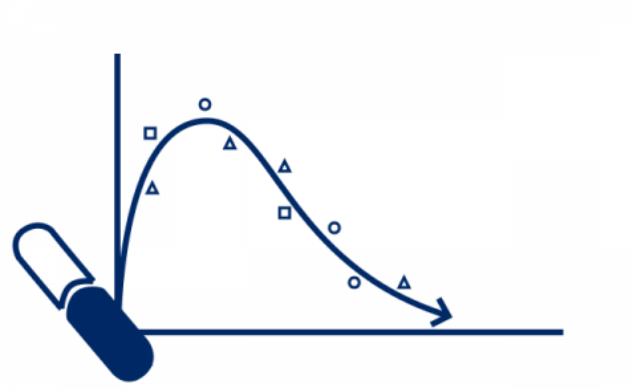
$$v \times y = z$$

$$v = 14r + 10$$
$$y = 3n - 2$$

$\Rightarrow v \times y$ is a **convolution**.

$\Rightarrow$ Knowing z and y, a **de**convolution can be performed to find v.

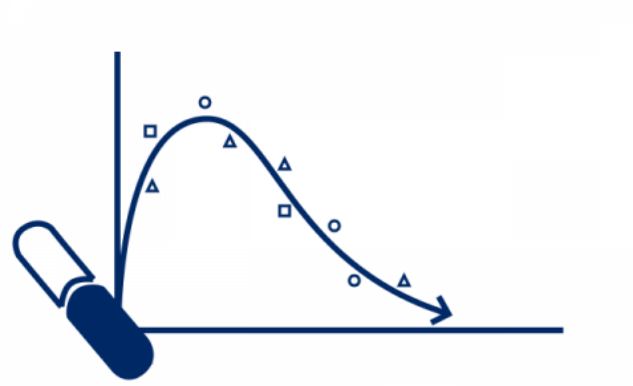




$$v \times y = z$$

[absorption function] $\times$ [disposition function]

$$= \text{[blood concentration-time curve]}$$



$$v \times y = z$$

[absorption function] $\times$ [disposition function]

$$= \text{[blood concentration-time curve]}$$

Convolution and **deconvolution** methods are frequently used to establish an...

Background

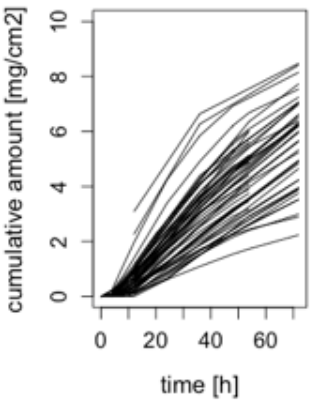
In Vitro-In Vivo Correlation (IVIVC)

Defined by the U.S. Food and Drug Administration (FDA) as "predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and an *in vivo* response".

Tool to predict entire *in vivo* drug concentration–time course based on *in vitro* drug release profiles
$\rightarrow$ supports **biowaivers** $\rightarrow$ **saves resources**.

Aim:
Establish a new method of IVIVC modelling, overcoming the disadvantages of current IVIVC methodology (averaged data, artificial certainty, deconvolution).
Case study: **transdermal patch**.

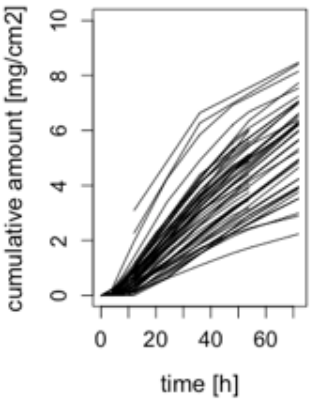
Data sets and general idea



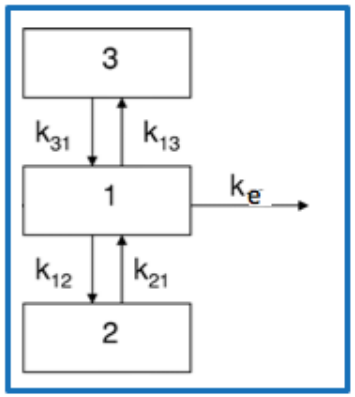
Input
function
"I_n"

Data sets and general idea

in vitro release (patch on skin portions)

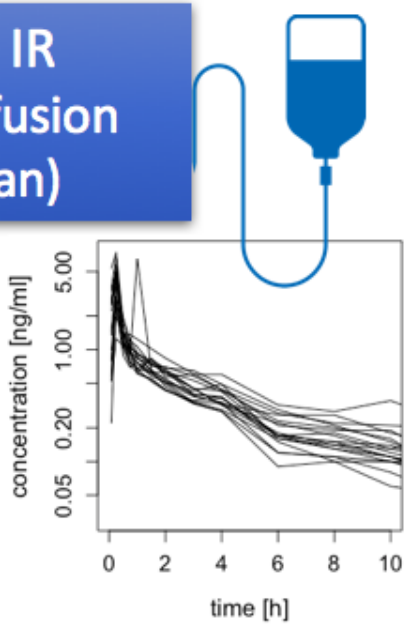


Input function "I_n"



three-compart-ment model

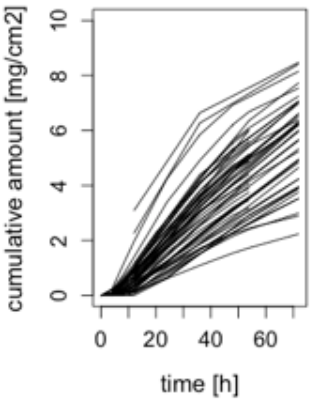
in vivo IR (intrav. infusion in human)



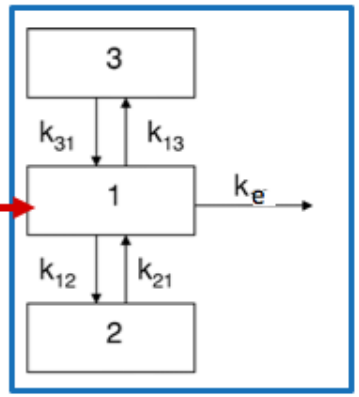
Data sets and general idea

in vitro release (patch on skin portions)

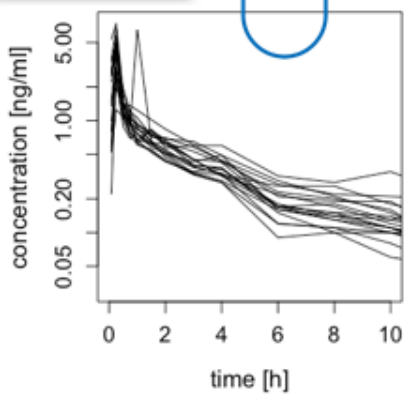
in vivo IR (intrav. infusion in human)

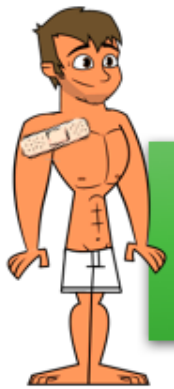


Input function "I_n"



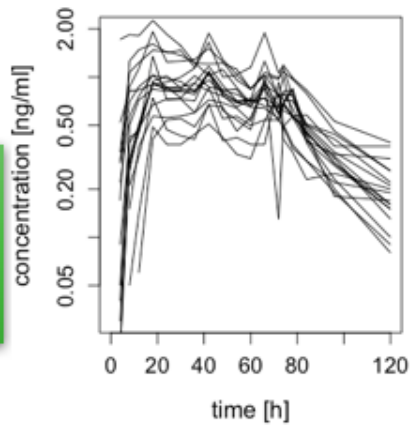
three-compart-ment model





II ?

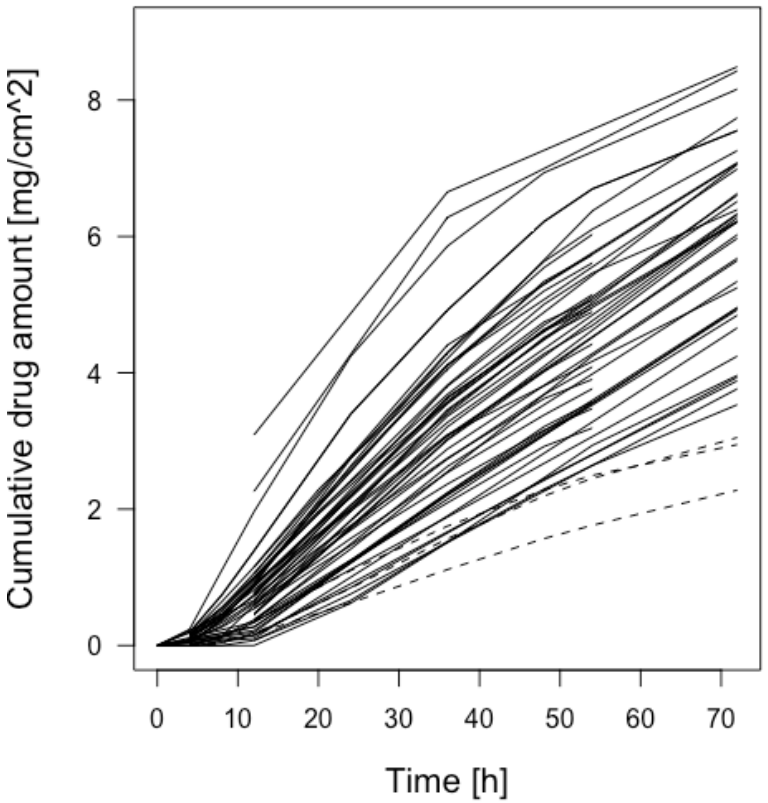
in vivo CR (patch on human)



Outline

Model 1: *in vitro* absorption/permeation

Cumulative amount of drug passed through the skin



$$\text{PDF}_W(t; h, s) = \frac{h}{s}\left(\frac{t}{s}\right)^{h-1} \exp\left\{-\left(\frac{t}{s}\right)^{h}\right\}$$

$$\text{CDF}_W(t; h, s) = 1 - \exp\left\{-\left(\frac{t}{s}\right)^{h}\right\}.$$

CDF_W Weibull distribution with time $t \geq 0$, shape $h > 0$, scale $s > 0$.

$$y_{ijp} = D_p \cdot f_{ip} \cdot \text{CDF}_W(t_{ijp}; h_{ip}, s_{ip}) + \epsilon_{ijp}$$

$$\epsilon_{ijp} \sim \mathcal{N}(0, \sigma^2_\epsilon)$$

D Dose ($p = 1, 2$); f fraction of dose delivered.

$\Rightarrow$ To estimate: h_{ip}, s_{ip}, f_{ip} ($i = 1, \ldots, N$ skin portions).

$\Rightarrow$ Frequentist nonlinear mixed effects model

Model 2: *in vivo* immediate release

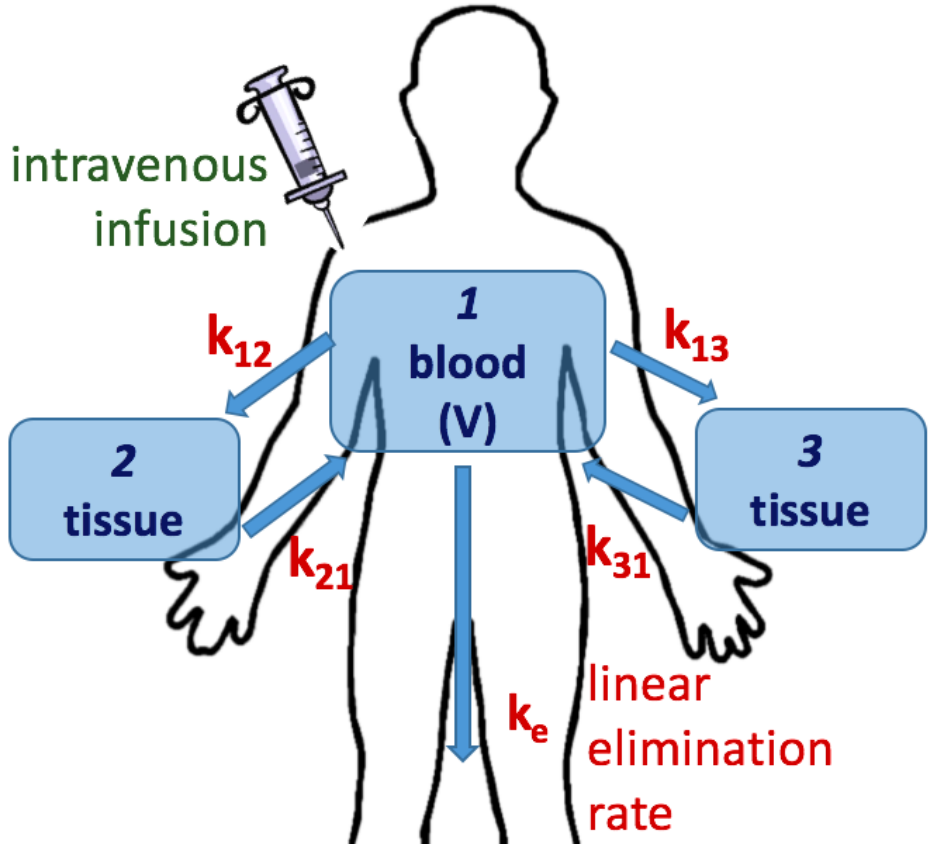
Three-compartment-model with intravenous infusion

$$\frac{da_1(t_{ijp})}{dt} = k_{21}a_2(t_{ijp}) + k_{31}a_3(t_{ijp}) - \left[k_{12}a_1(t_{ijp}) + k_{13}a_1(t_{ijp}) + k_e a_1(t_{ijp})\right],$$

$$\frac{da_2(t_{ijp})}{dt} = k_{12}a_1(t_{ijp}) - \left[k_{21}a_2(t_{ijp})\right],$$

$$\frac{da_3(t_{ijp})}{dt} = k_{13}a_1(t_{ijp}) - \left[k_{31}a_3(t_{ijp})\right],$$

$$C_1(t_{ijp}) = \frac{a_1(t_{ijp})}{V_{1,i}}.$$



$\Rightarrow$ To estimate:

$V_{1,i}, k_e, k_{12}, k_{21}, k_{13}, k_{31}$

($i = 1, \ldots, N$ individuals).

$\Rightarrow$ Frequentist nonlinear mixed effects model

Model 3: combining to *in vivo* controlled release

$$\mathrm{I}_n(t_{ijp}) = D_p \cdot F_{ip} \cdot B_i \cdot \frac{h_{ip}}{s_{ip}} \cdot \left(\frac{t_{ijp}}{s_{ip}}\right)^{h_{ip}-1} \cdot \exp\left\{\left(-\frac{t_{ijp}}{s_{ip}}\right)^{h_{ip}}\right\}$$

$$\frac{da_1(t_{ijp})}{dt} = \mathrm{I}_n(t_{ijp}) + k_{21}a_2(t_{ijp}) + k_{31}a_3(t_{ijp}) - [k_{12}a_1(t_{ijp}) + k_{13}a_1(t_{ijp}) + k_e a_1(t_{ijp})]$$

$$\frac{da_2(t_{ijp})}{dt} = k_{12}a_1(t_{ijp})) - [k_{21}a_2(t_{ijp}))]$$

$$\frac{da_3(t_{ijp})}{dt} = k_{13}a_1(t_{ijp})) - [k_{31}a_3(t_{ijp}))]$$

$$C_1(t_{ijp}) = \frac{a_1(t_{ijp})}{V_{1,i}}.$$

$\mathrm{I}_n(t_{ijp})$: input function, a_c: amount of drug in compartment c.

At time $t = 0$: $a_1(0) = a_2(0) = a_3(0) = 0$.

D: Dose; F: fraction of dose delivered; B: fraction of dose delivered which is actually absorbed into the systemic circulation.

$\Rightarrow$ Bayesian hierarchical 2-stage model

$\Rightarrow$ natural integration and transfer of parameter knowledge, incl. corresponding uncertainty, from submodels to CR model.

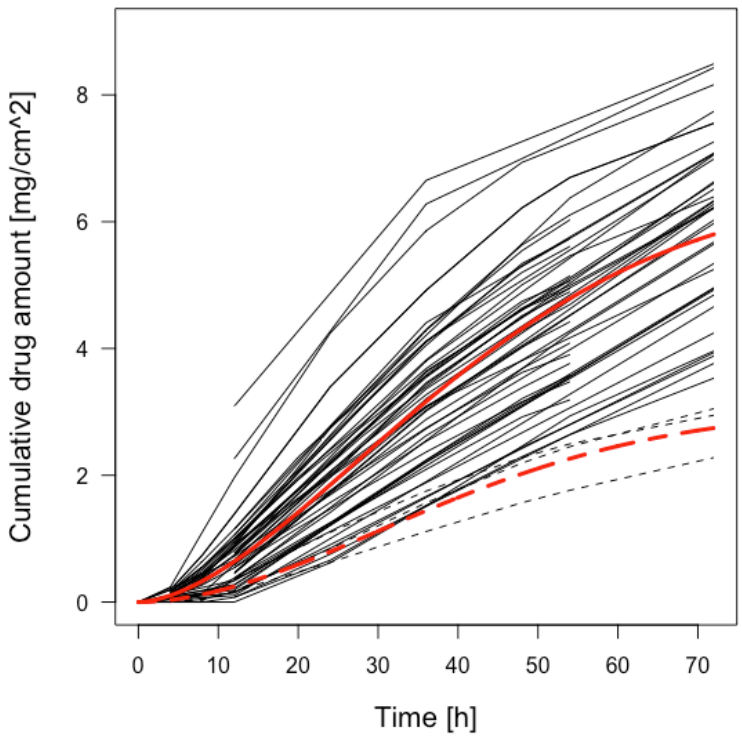
Outline

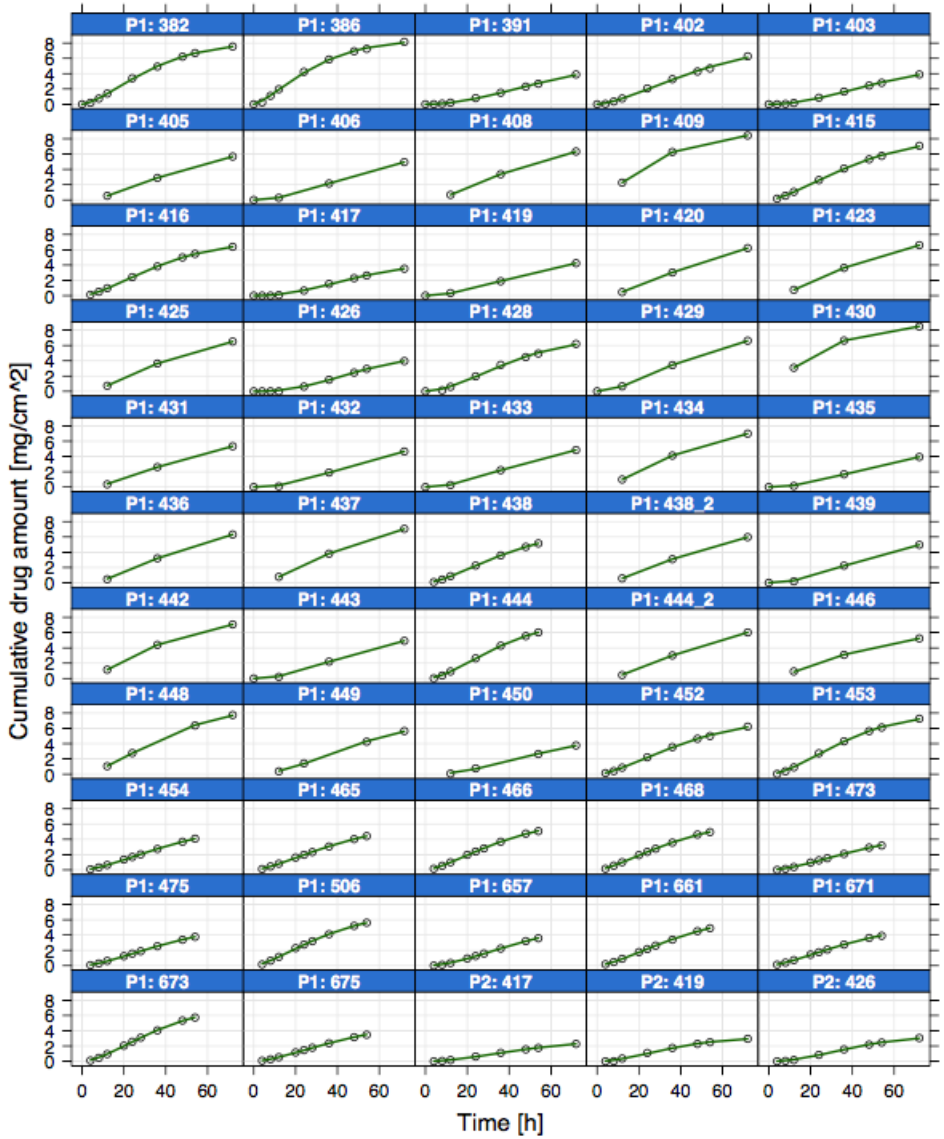
Estimates of all model parameters

Parameter	mean (SD)					
	Frequentist		**Bayesian**			
	fixed	random	fixed	$\hat{R}$	random	$\hat{R}$
	permeation		*controlled release*			
B	-	-	0.34 (0.09)	1.01	0.26 (0.15)	1.03
f_1	0.83 (0.02)	(0.16)	-	-	-	-
f_2	0.91 (0.05)	(0.07)	-	-	-	-
$\log(h_1)$	0.52 (0.02)	(0.15)	0.52 (0.02)	1.00	0.08 (0.02)	1.00
$\log(h_2)$	0.61 (0.05)	(0.05)	0.66 (0.03)	1.00		
$\log(s_1)$	3.84 (0.03)	(0.16)	3.34 (0.13)	1.00	0.42 (0.06)	1.00
$\log(s_2)$	3.82 (0.07)	(0.11)	2.72 (0.12)	1.01		
	immediate release					
$\log(V)$	10.47 (0.11)	(0.38)	10.50 (0.11)	1.00	0.17 (0.09)	1.00
$\log(k_e)$	0.39 (0.28)	-	-1.00 (0.19)	1.01	-	-
$\log(k_{12})$	0.15 (0.45)	-	0.32 (0.42)	1.00	-	-
$\log(k_{21})$	-2.16 (1.05)	-	-2.12 (0.28)	1.00	-	-
$\log(k_{13})$	1.82 (0.15)	-	2.13 (0.15)	1.00	-	-
$\log(k_{31})$	0.61 (0.20)	-	0.35 (0.17)	1.00	-	-
σ	-	-	0.18 (0.01)	1.00	-	-

Model 1: *in vitro* absorption/permeation

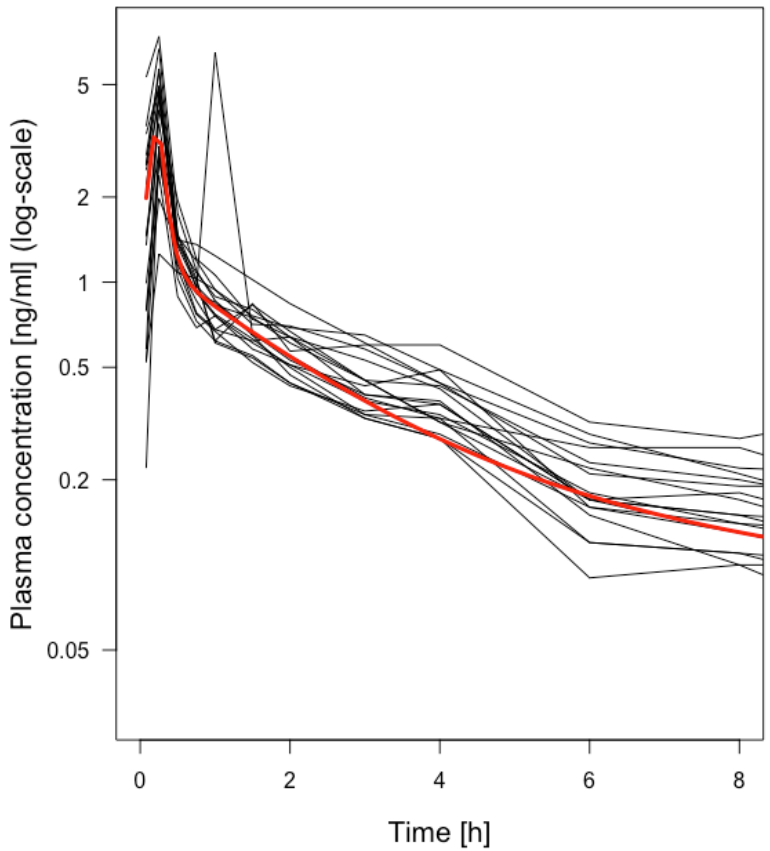
Estimation using nonlinear mixed effects models:

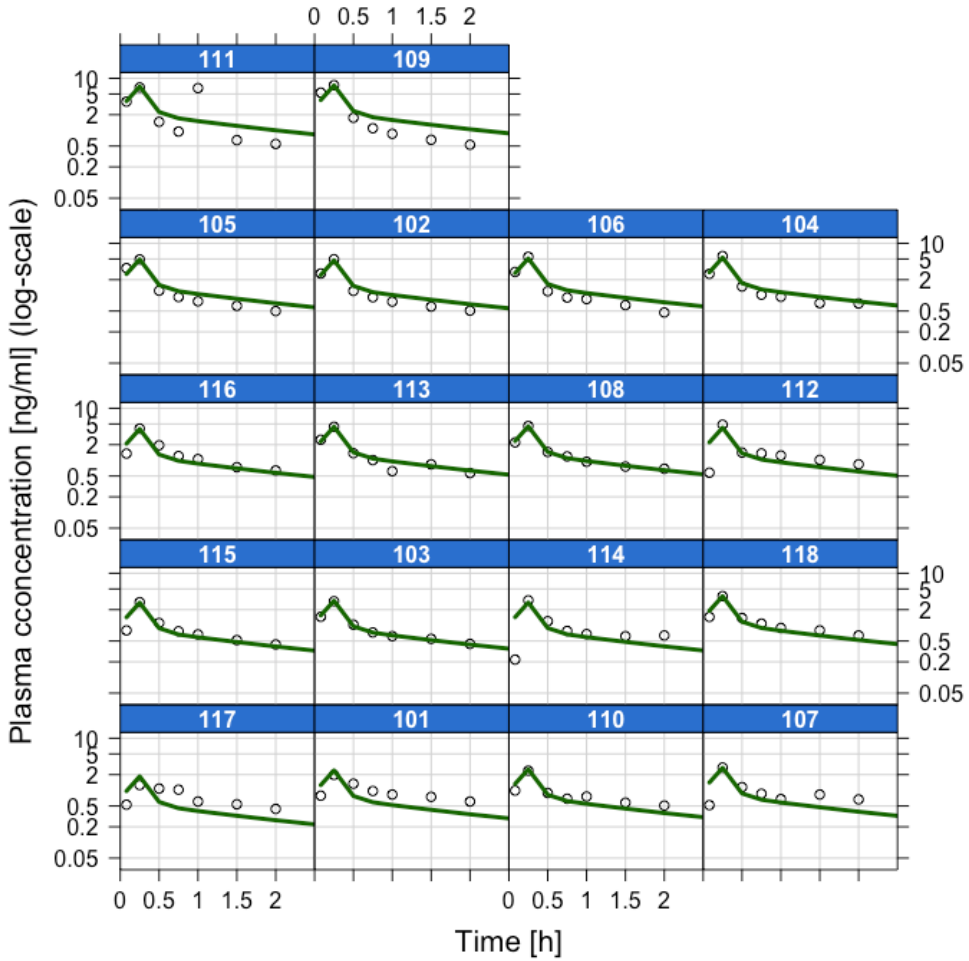




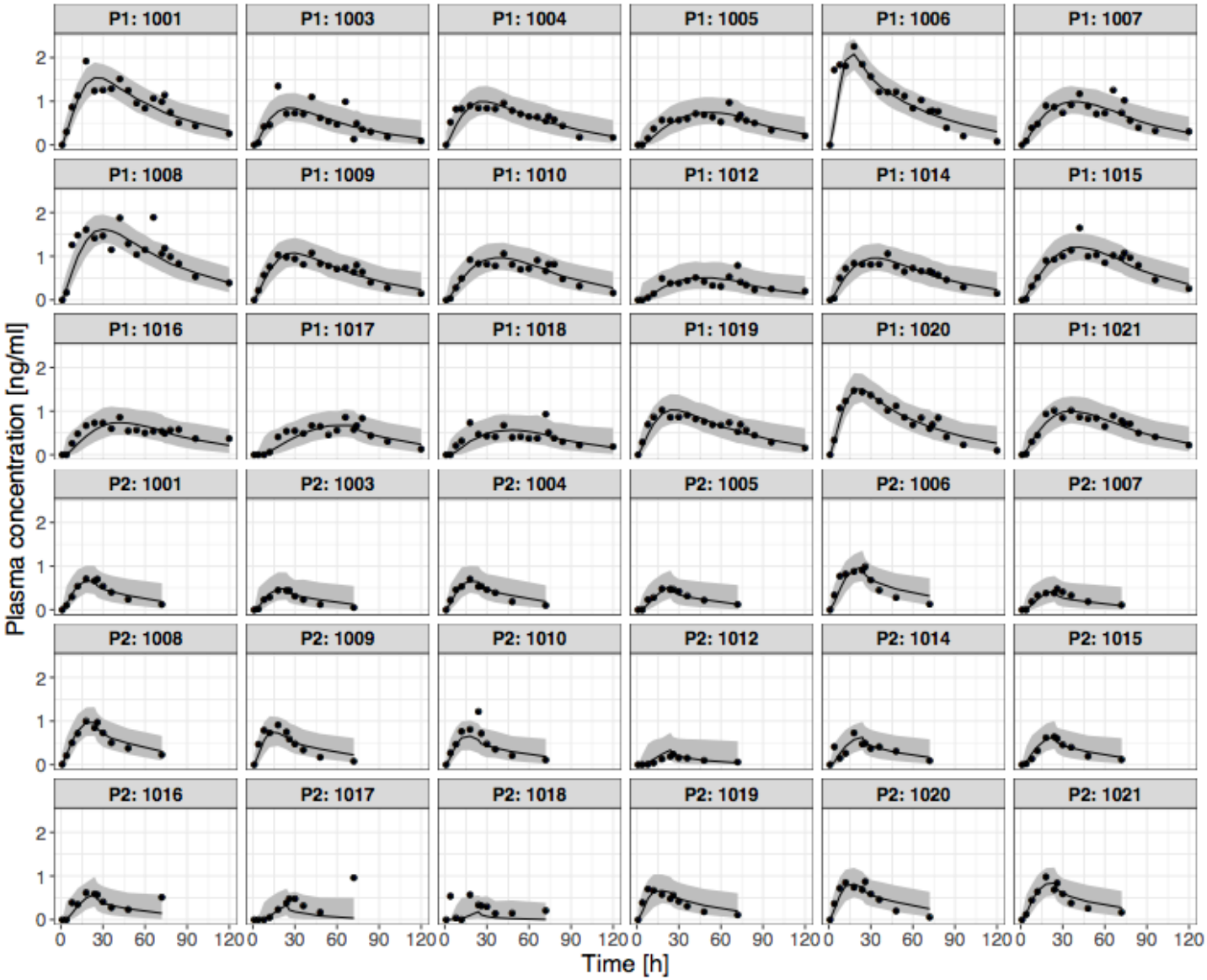
Model 2: *in vivo* immediate release

Estimation using nonlinear mixed effects models:

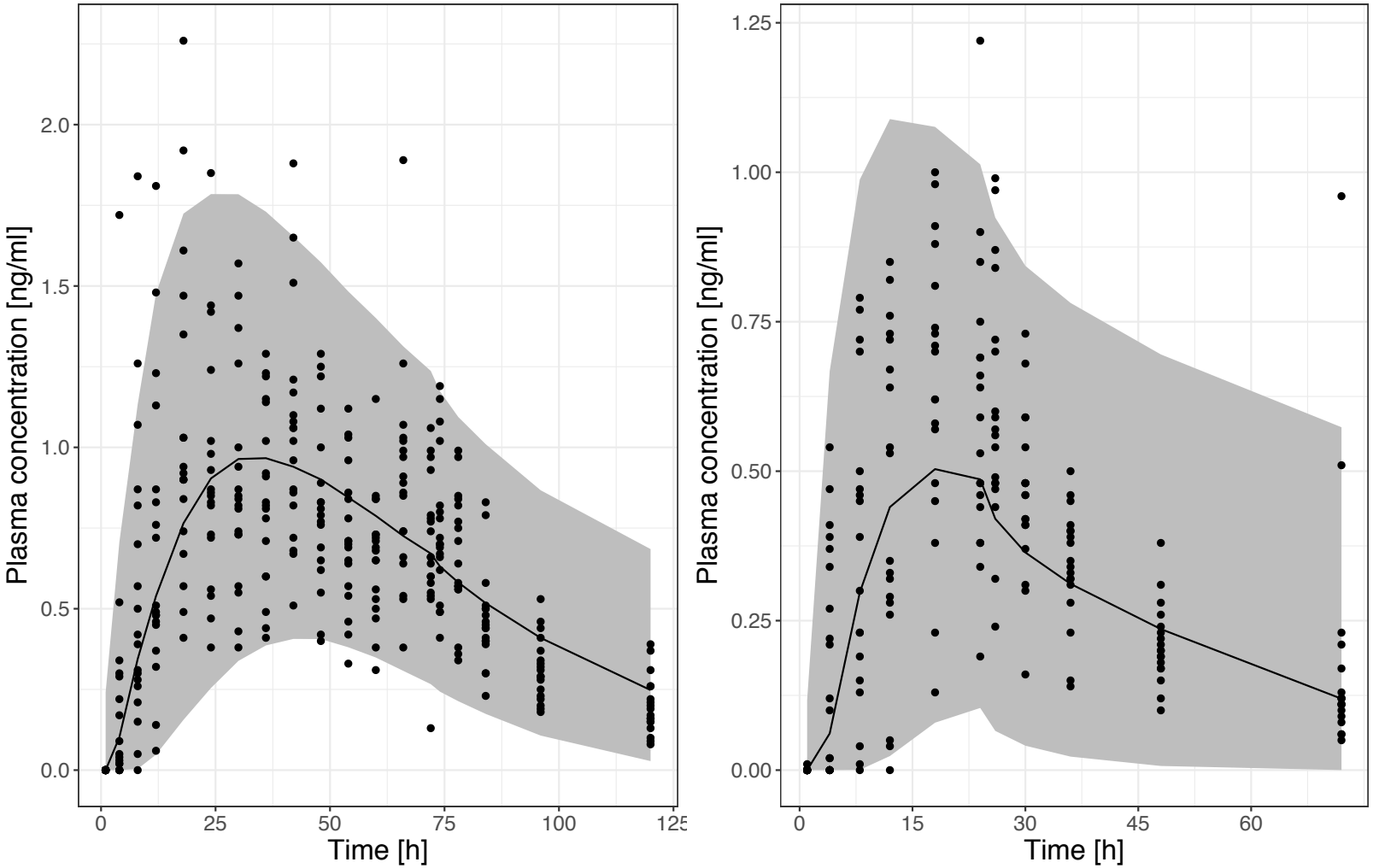




Model 3: individual predictions

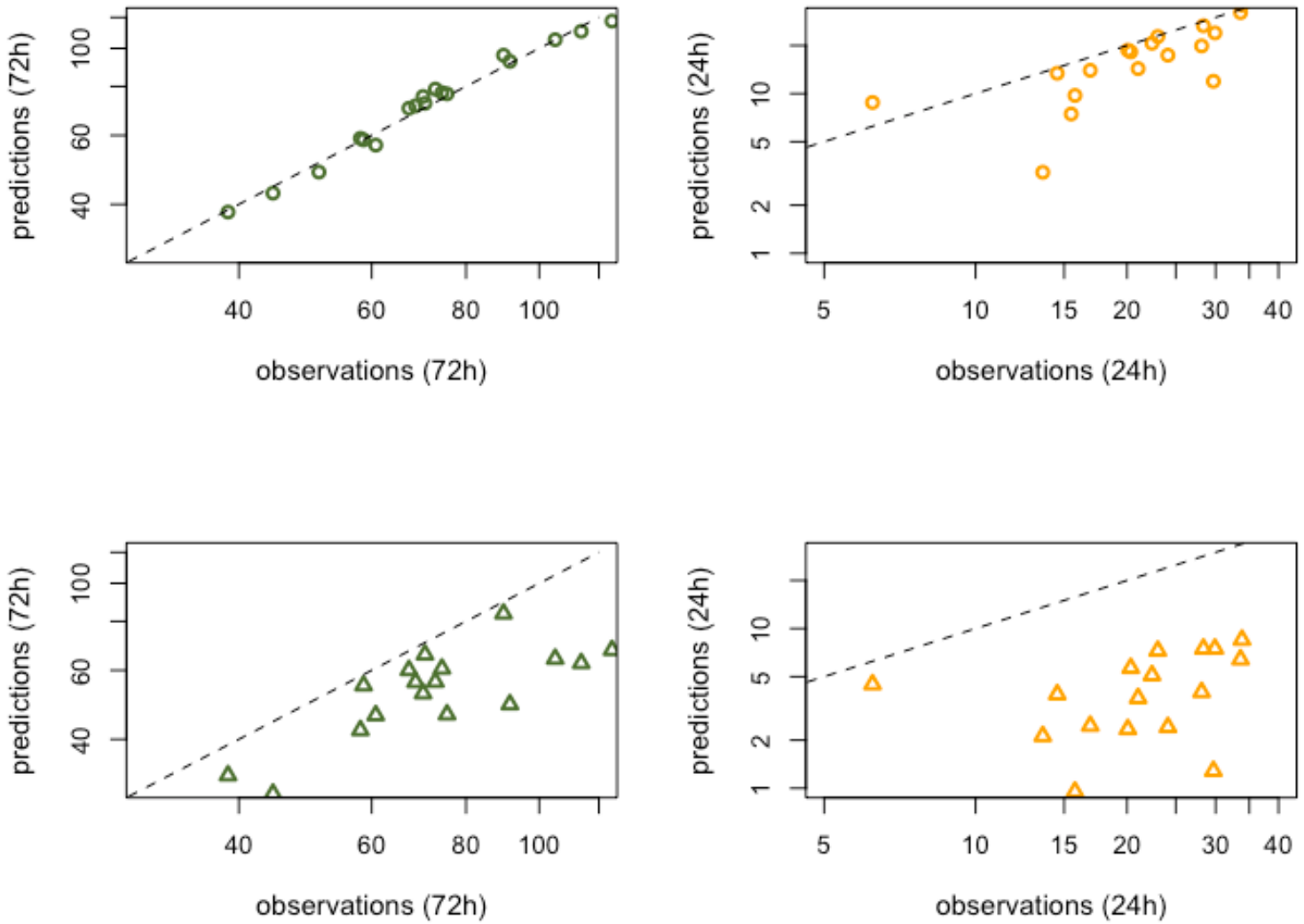


Model 3: Population predictions



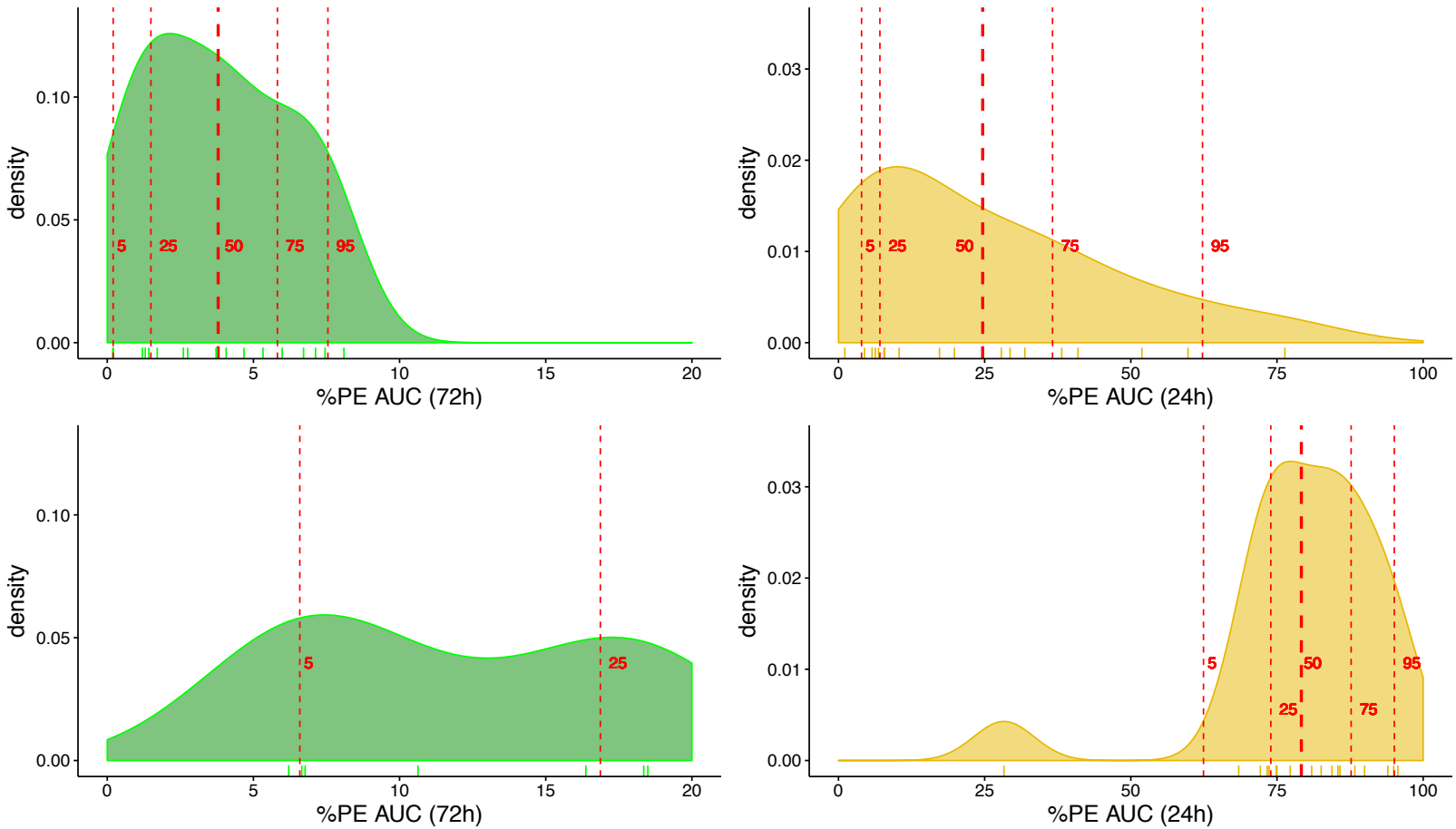
Model 3: Area under the curve (AUC)

Comparing our model *(top row)* **to the model without uncertainty propagation** *(bottom row)*.



Model 3: Density of the AUC percent prediction errors

$$\%PE = 100 * \frac{|AUC_{\text{observations}} - AUC_{\text{predictions}}|}{AUC_{\text{observations}}}$$



Conclusions

- Developed combined *in vitro-in vivo* model provides **satisfactory estimation** of the transdermal patch's PK population data.
- **Innovation** consists of shared parameter space merging the two frequentist submodels into a system of ODEs, estimated in Bayesian way.
- Bayesian framework allows natural **integration and transfer** of knowledge between different sources of information, while **accounting for parameter uncertainty**.

$\Rightarrow$ **Flexible** approach yielding results for broad range of data situations.
$\Rightarrow$ **Extension** of current IVIVC methodology where frequentist one-stage or two-stage approaches are the standard.

Bibliography

Gelman, A., J. Carlin, H. Stern, D. Dunson, A. Vehtari, and D. Rubin (2013). "Bayesian Data Analysis, Third Edition". *Taylor & Francis.*

Jacobs, T., S. Rossenu, A. Dunne, G. Molenberghs, R. Straetemans, and L. Bijnens (2008). "Combined Models for Data from In Vitro–In Vivo Correlation Experiments". *Journal of Biopharmaceutical Statistics 18.6., pages 1197-1211.*

O'Hara, T., S. Hayes, J. Davis, J. Devane, T. Smart, and A. Dunne (2001). "In Vivo–In Vitro Correlation (IVIVC) Modeling Incorporating a Convolution Step". *Journal of Pharmacokinetics and Pharmacodynamics 28.3, pages 277-298*

Davidian, M. and D.M. Giltinan (1995). "Nonlinear Models for Repeated Measurement Data". *Taylor & Francis.*

Pinheiro J., Bates D. (2000). "Mixed-Effects Models in S and S-PLUS." *Statistics and Computing. Springer New York.*

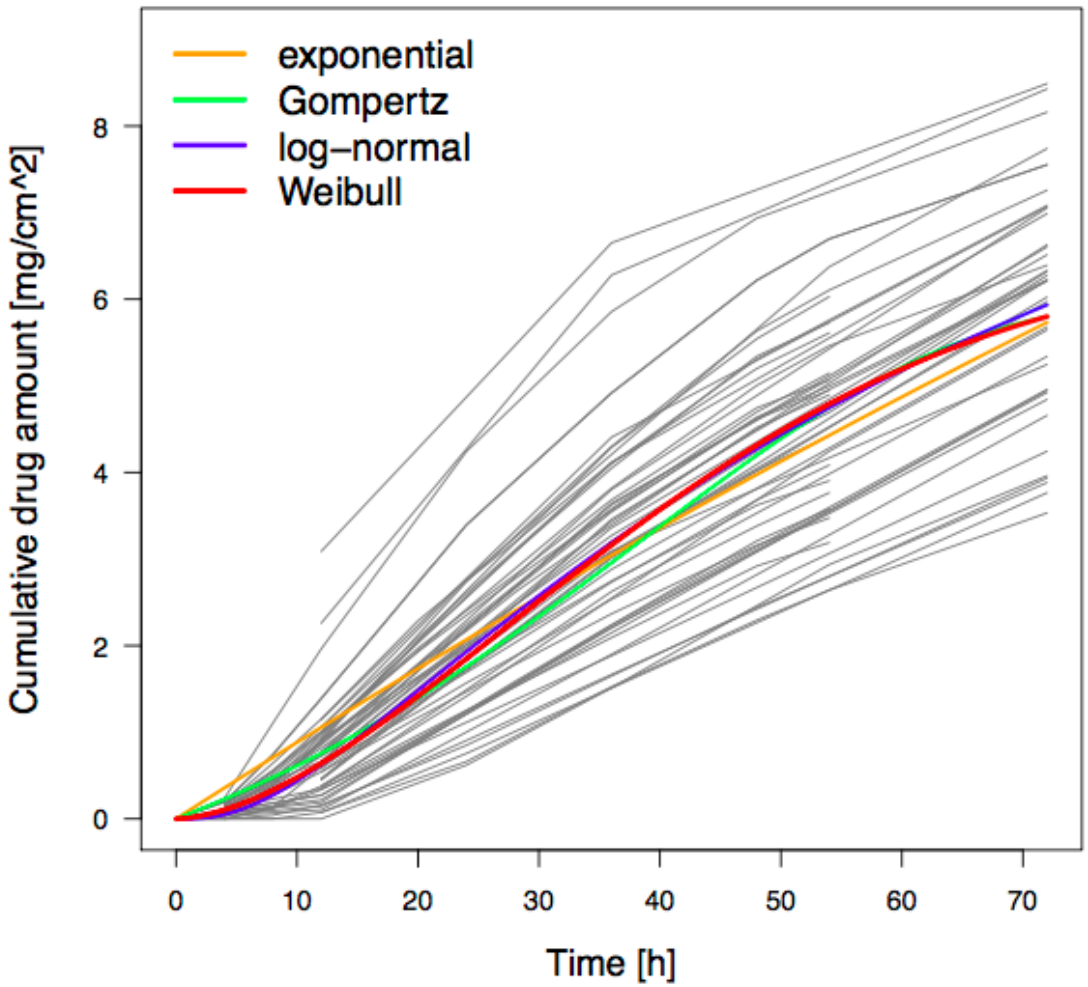
Piotrovskii, V.K. (1987). "The use of Weibull distribution to describe the in vivo absorption kinetics". *J Pharm Biopharm; 15, pages 681-686.*

Rosenbaum, S.E. (2011). "Basic Pharmacokinetics and Pharmacodynamics: An Integrated Textbook and Computer Simulations". *Wiley.*

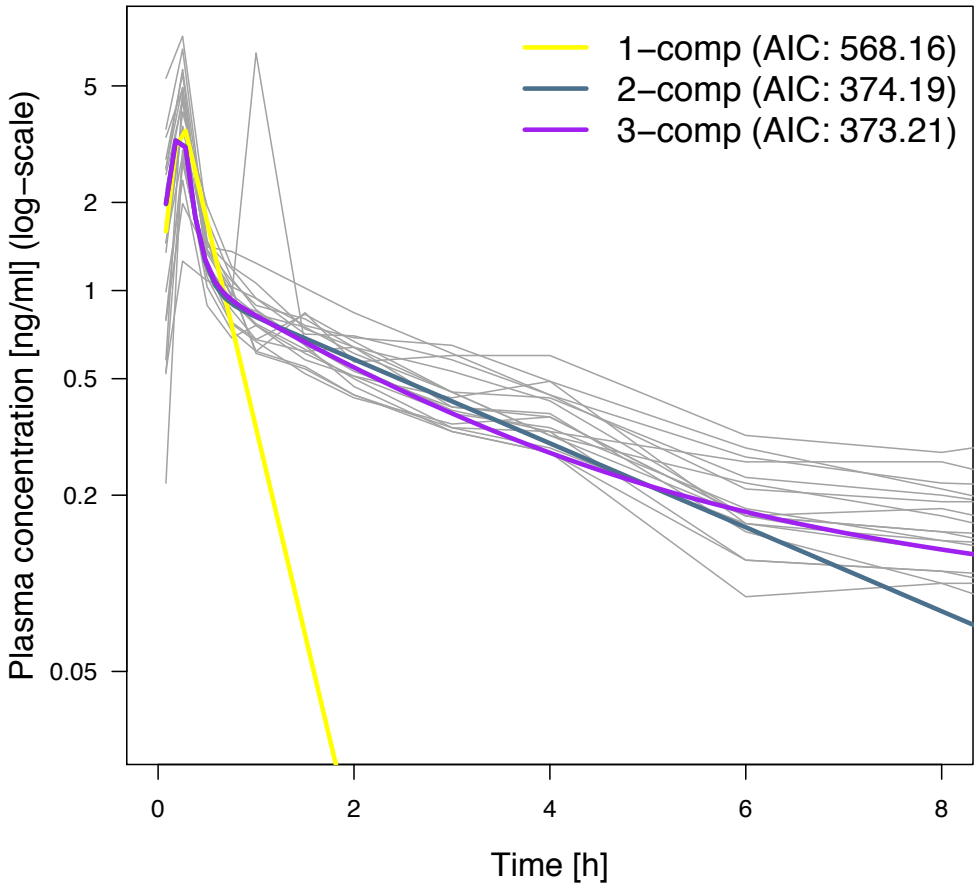
Thank you for your attention!

This project has received funding from the European Unions Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.

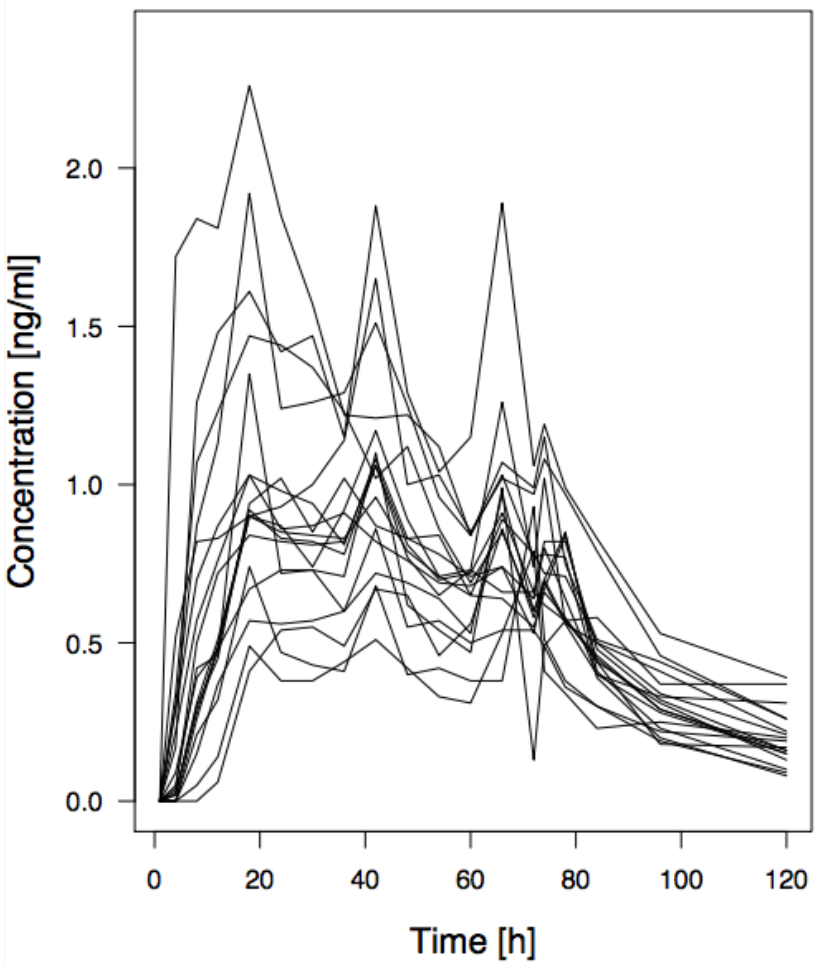
Backup I

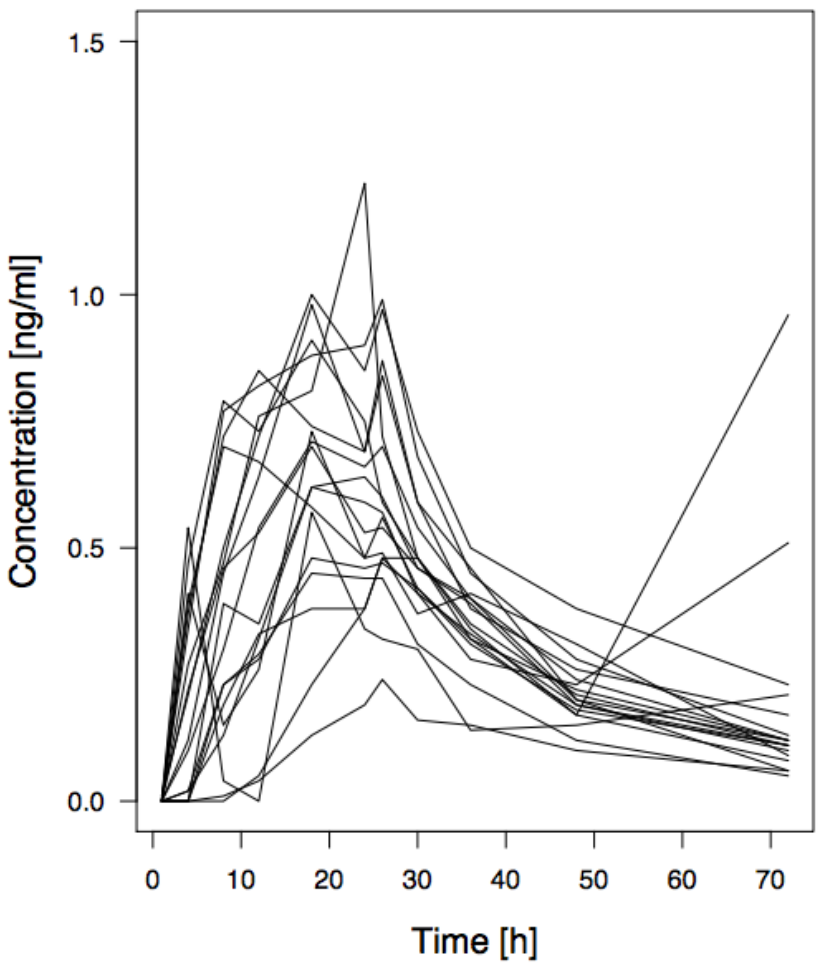

exponential
Gompertz
log−normal
Weibull
Cumulative drug amount [mg/cm^2]
0
2
4
6
8
0
10
20
30
40
50
60
70
Time [h]

Backup II

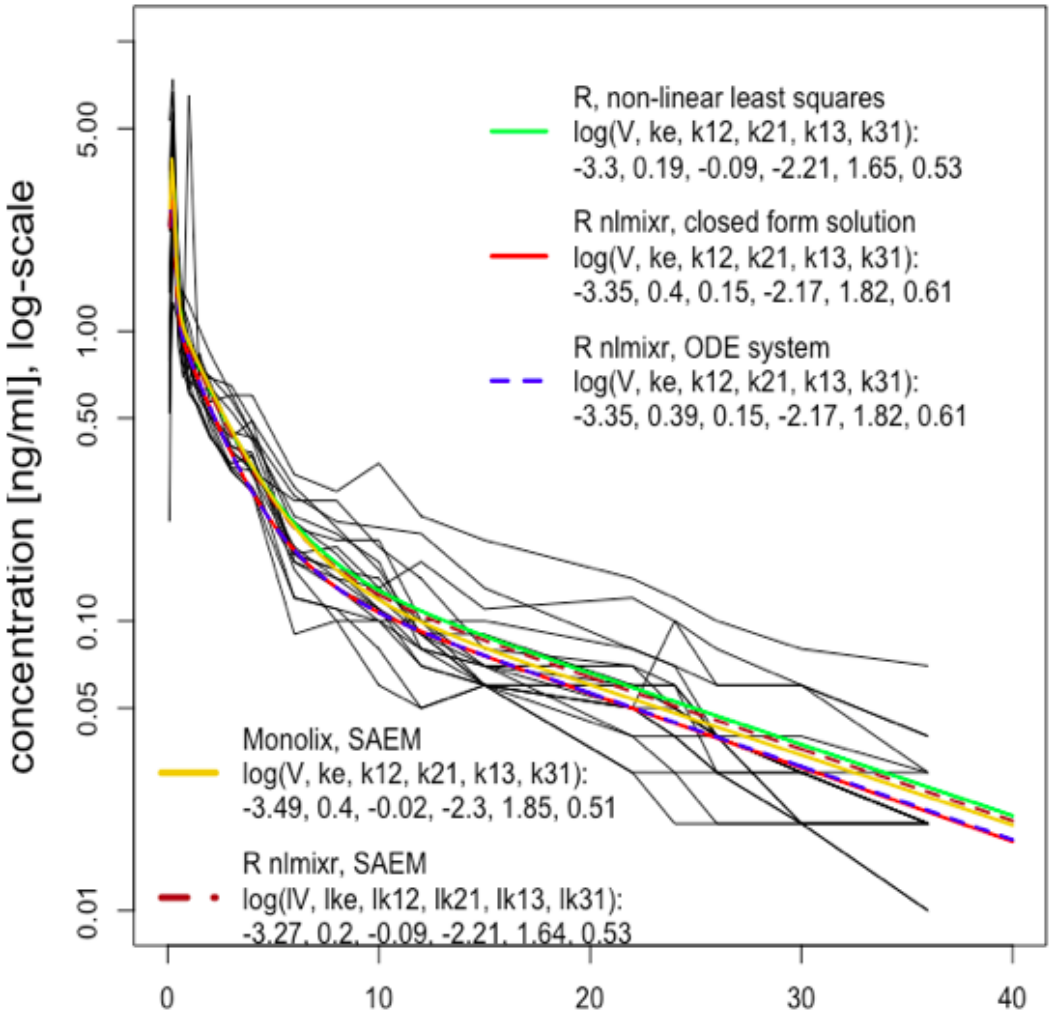

1−comp (AIC: 568.16)
2−comp (AIC: 374.19)
3−comp (AIC: 373.21)
Plasma concentration [ng/ml] (log−scale)
5
2
1
0.5
0.2
0.05
0
2
4
6
8
Time [h]

CR data

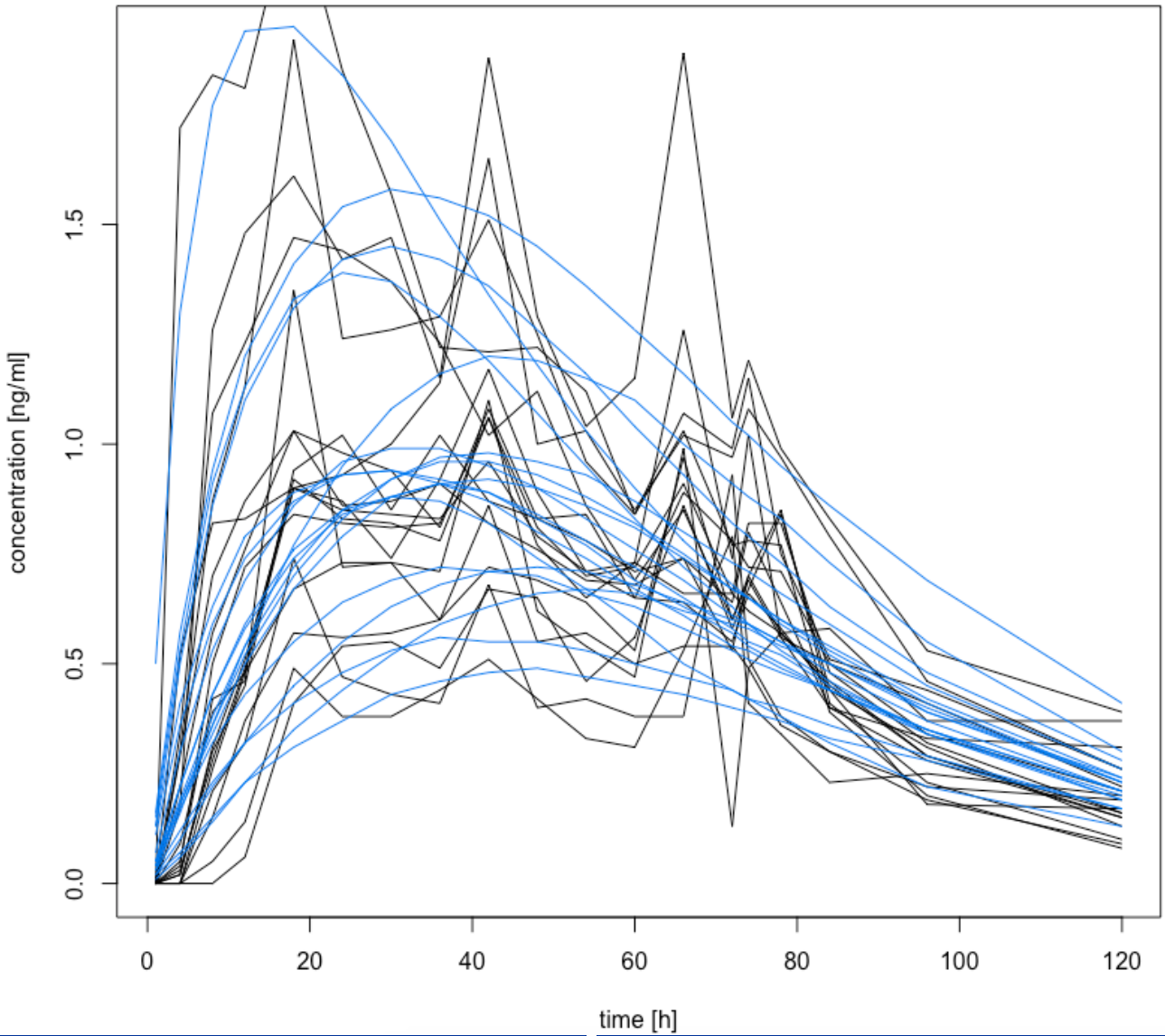

Concentration [ng/ml]
0.0
0.5
1.0
1.5
2.0
0
20
40
60
80
100
120
Time [h]


Concentration [ng/ml]
0.0
0.5
1.0
1.5
0
10
20
30
40
50
60
70
Time [h]

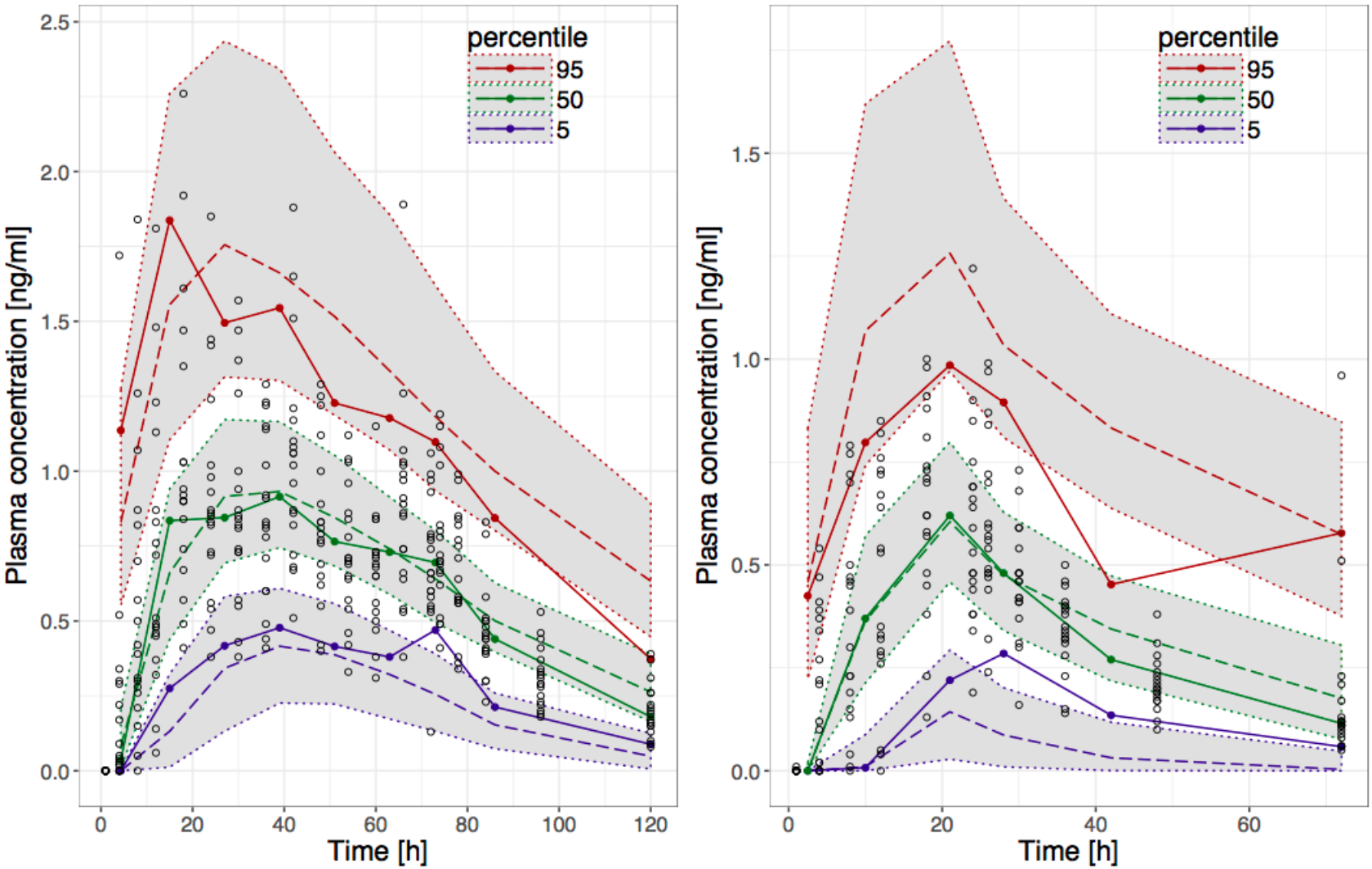
Backup IV


concentration [ng/ml], log-scale
5.00
1.00
0.50
0.10
0.05
0.01
0
10
20
30
40
R, non-linear least squares
log(V, ke, k12, k21, k13, k31):
-3.3, 0.19, -0.09, -2.21, 1.65, 0.53
R nlmixr, closed form solution
log(V, ke, k12, k21, k13, k31):
-3.35, 0.4, 0.15, -2.17, 1.82, 0.61
R nlmixr, ODE system
log(V, ke, k12, k21, k13, k31):
-3.35, 0.39, 0.15, -2.17, 1.82, 0.61
Monolix, SAEM
log(V, ke, k12, k21, k13, k31):
-3.49, 0.4, -0.02, -2.3, 1.85, 0.51
R nlmixr, SAEM
log(lV, lke, lk12, lk21, lk13, lk31):
-3.27, 0.2, -0.09, -2.21, 1.64, 0.53

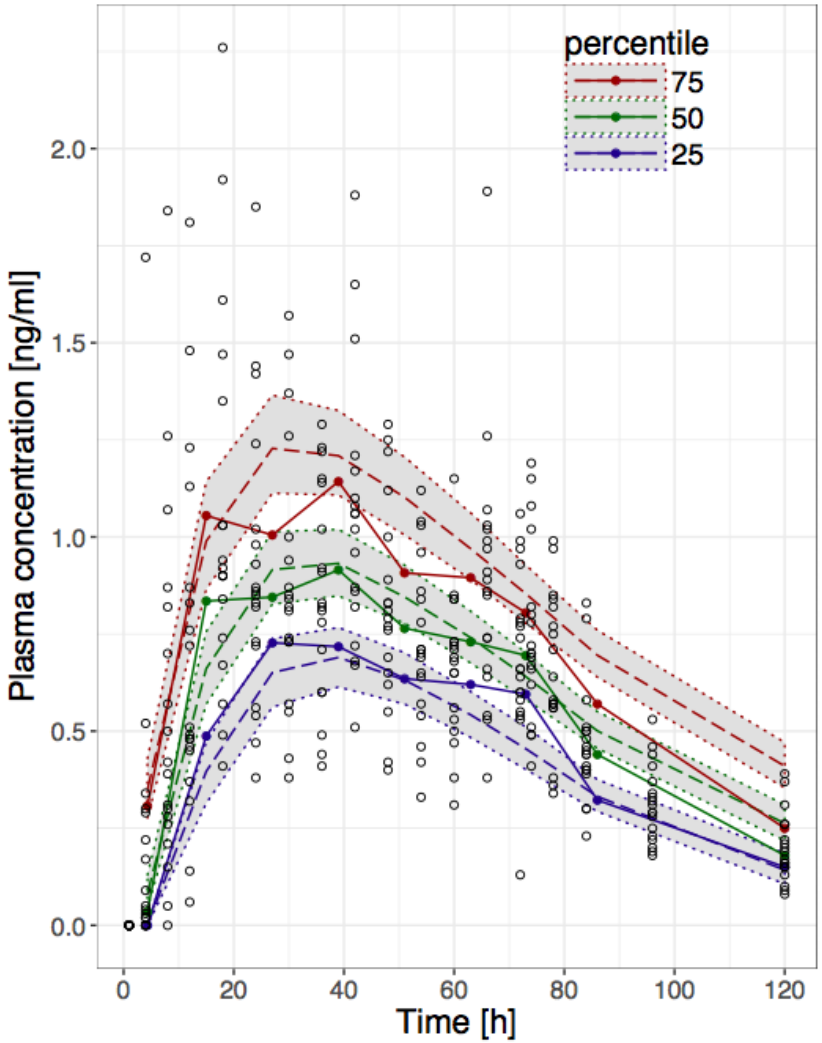
Individual predictions

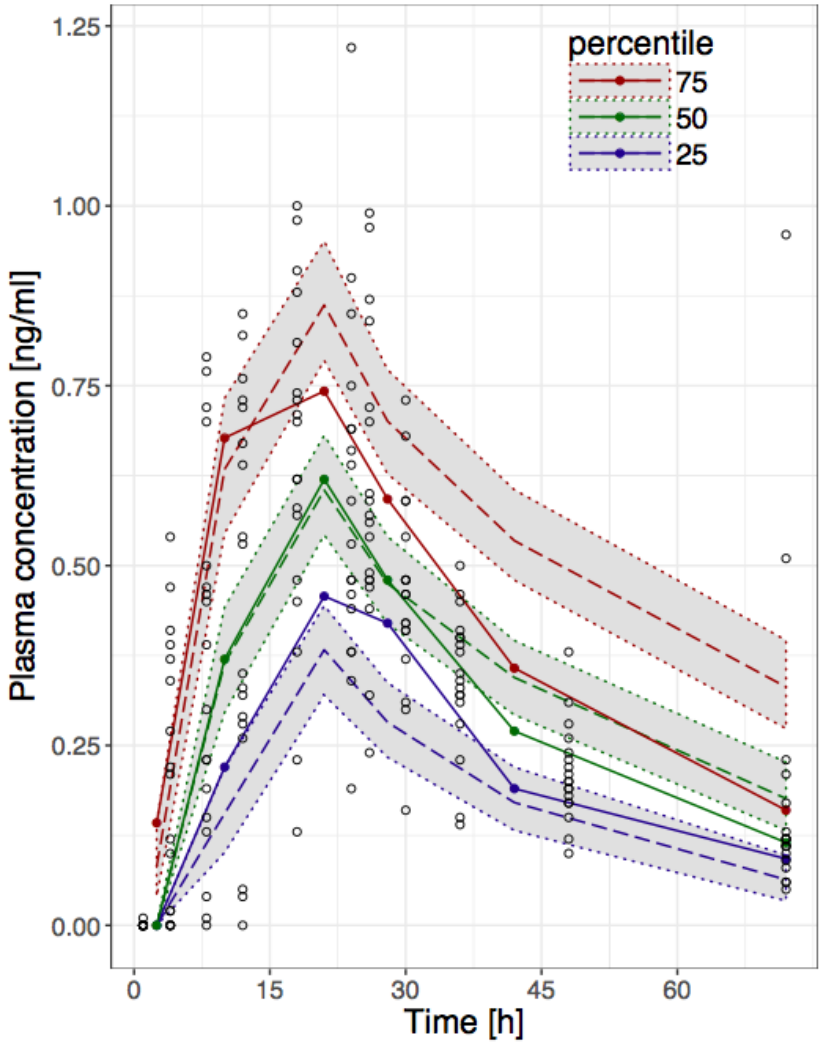


Visual predictive check population predictions - 95th

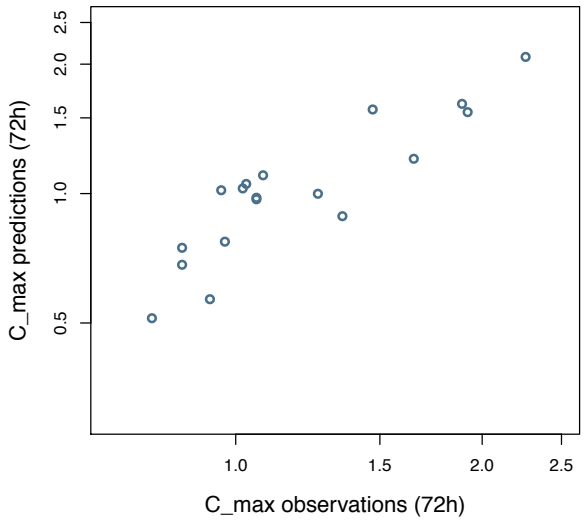


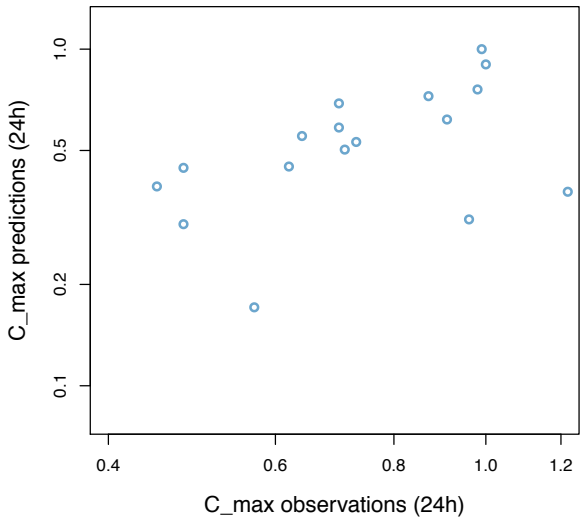
Visual predictive check population predictions - 75th

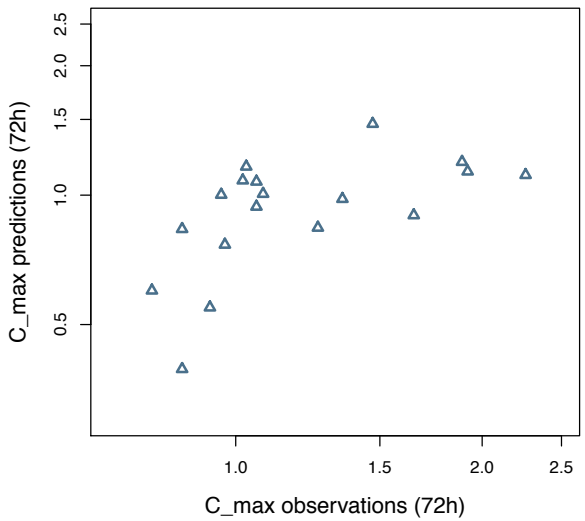


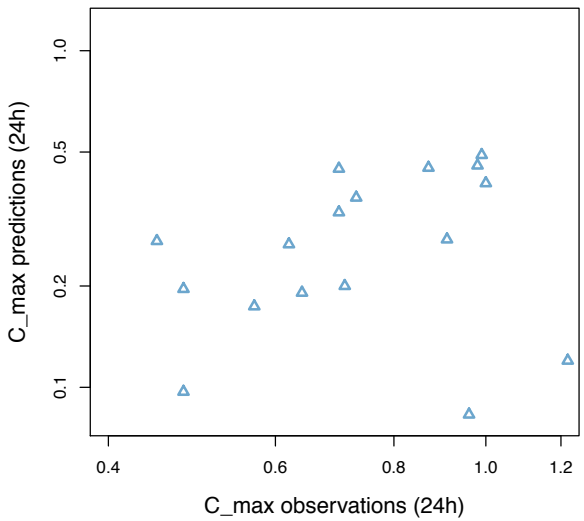


Backup VIII

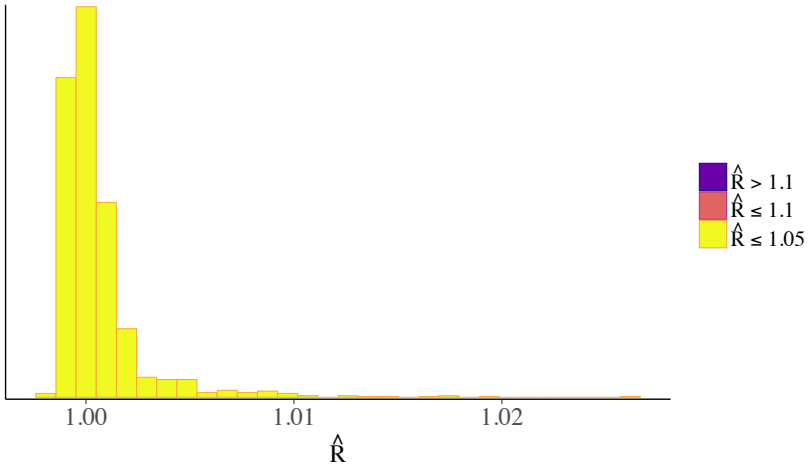

C_max predictions (72h)
C_max observations (72h)
0.5
1.0
1.5
2.0
2.5

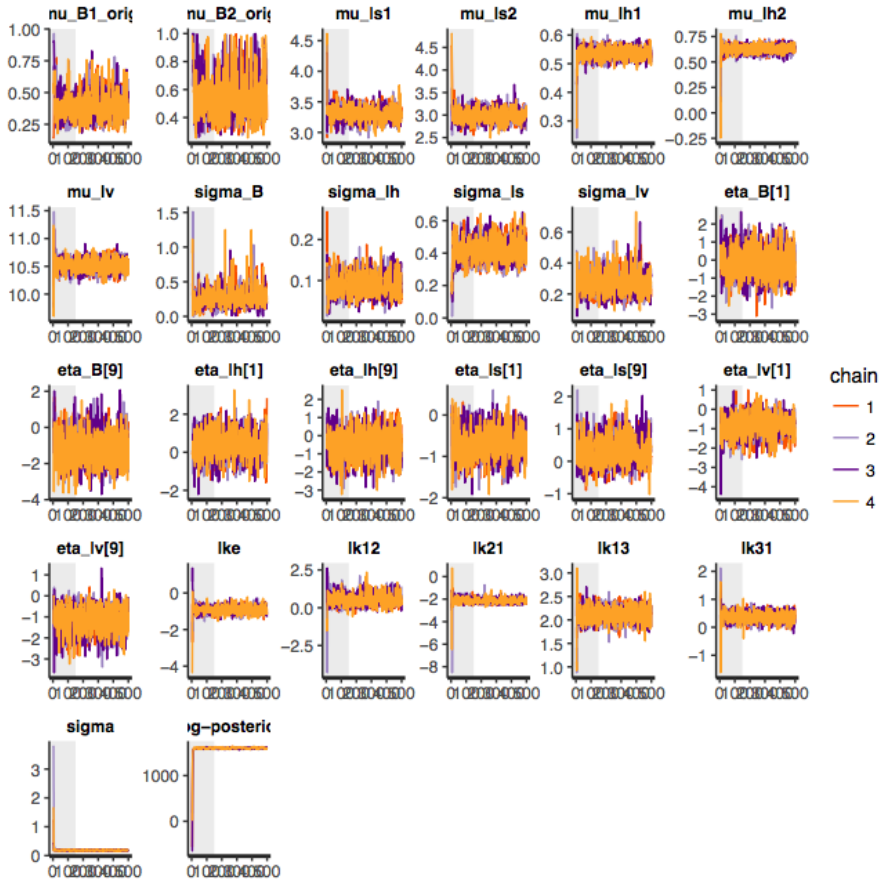

C_max predictions (24h)
C_max observations (24h)
0.1
0.2
0.5
1.0
0.4
0.6
0.8
1.0
1.2


C_max predictions (72h)
C_max observations (72h)
0.5
1.0
1.5
2.0
2.5

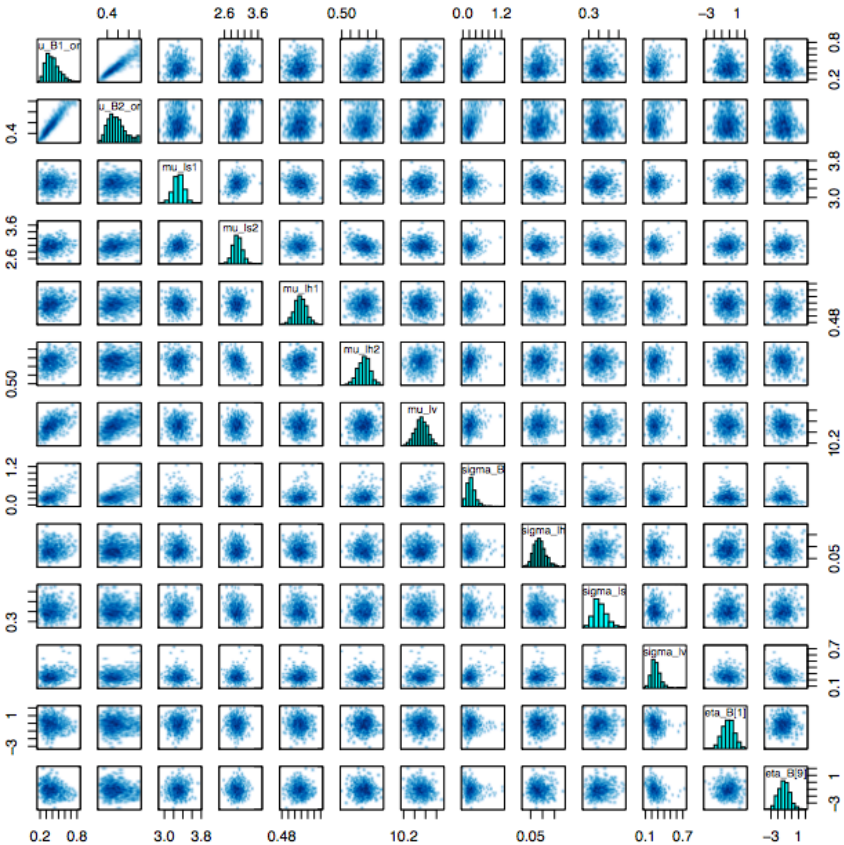

C_max predictions (24h)
C_max observations (24h)
0.1
0.2
0.5
1.0
0.4
0.6
0.8
1.0
1.2

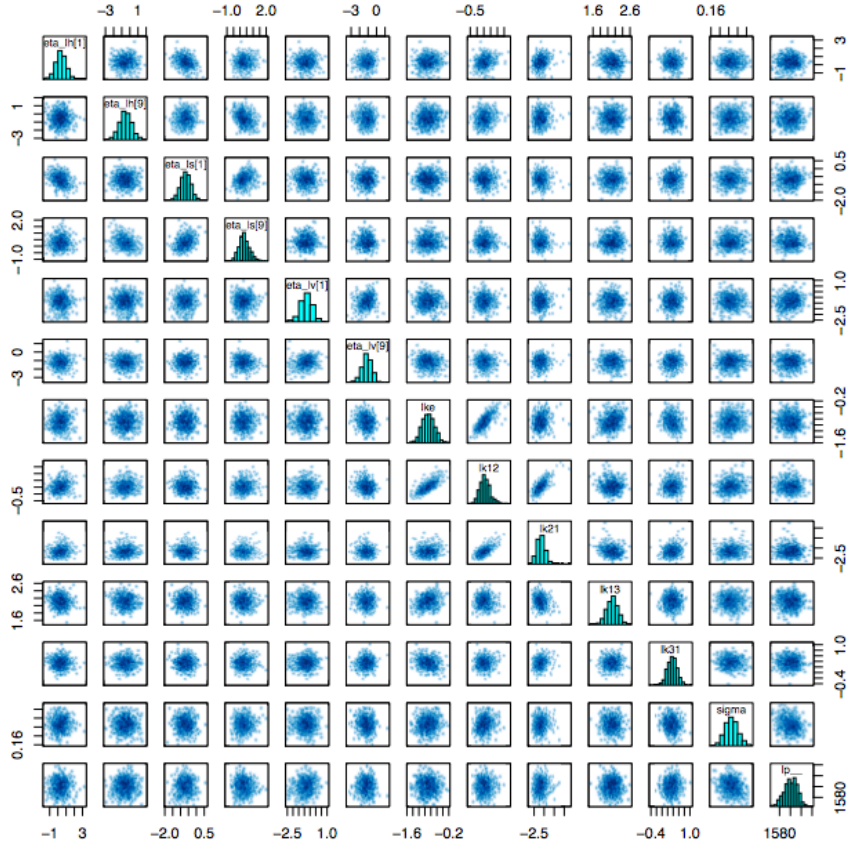
Gelman-Rubin statistic ($\hat{R}$) and trace plot





Pairs plot


mu_ls1
mu_ls2
mu_lh1
mu_lh2
mu_lv
sigma_B
sigma_lh
sigma_ls
sigma_lv
eta_B[1]
eta_B[9]


eta_lh[1]
eta_lh[9]
eta_ls[1]
eta_ls[9]
eta_lv[1]
eta_lv[9]
lke
lk12
lk21
lk13
lk31
sigma
lp__

Posterior densities overlaid