PK-PD analysis and modelling

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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

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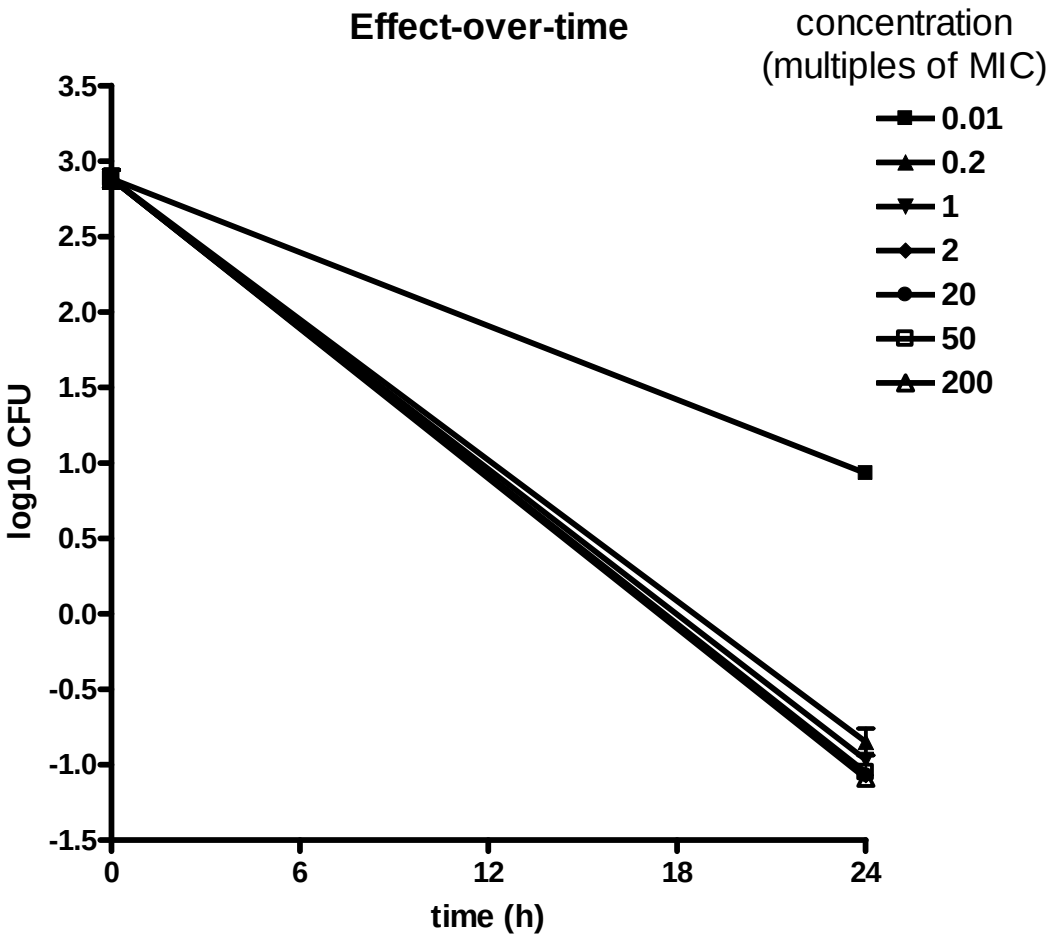
Why modelling ?

- to move from mere description to underlying phenomena…
  - nature can often be better explained in terms of equations than mere description
  - this has been essential in physics (think about gravity law, radioactive decay, study of electromagnetic field and optics, … up to the equivalence of mass and energy…)
- to allow predictions over and beyond what is immediately accessible by the experience…
- to generate rules that can be applied widely…

In vitro studies

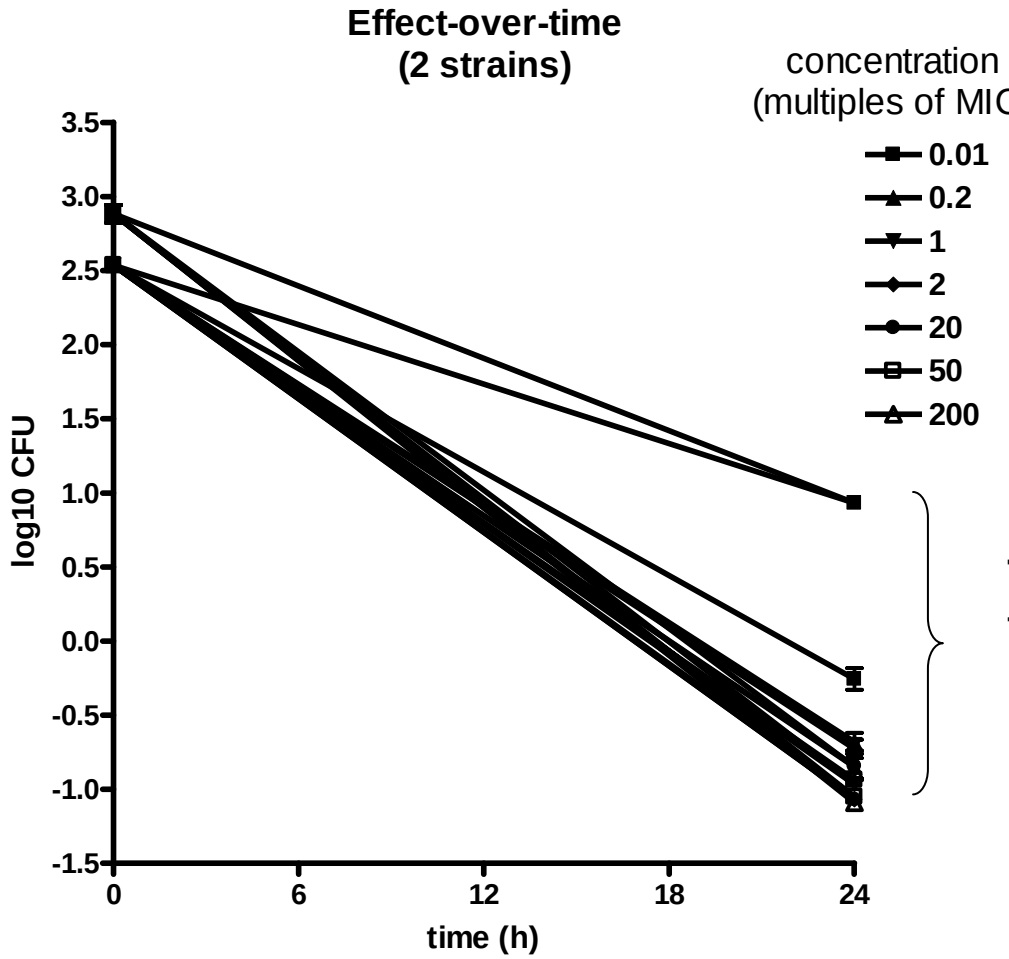
Response to an antimicrobial

an example with ceftobiprole and *S. aureus* (one strain)



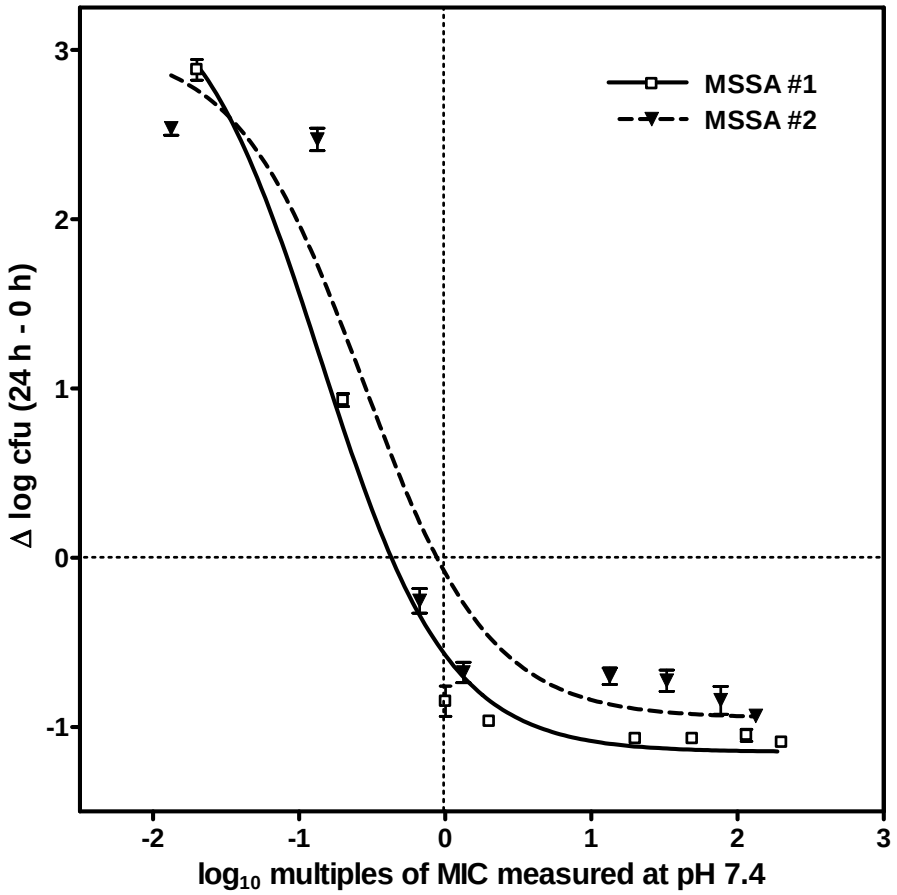
Response to an antimicrobial

an example with ceftobiprole and *S. aureus* (2 strains)



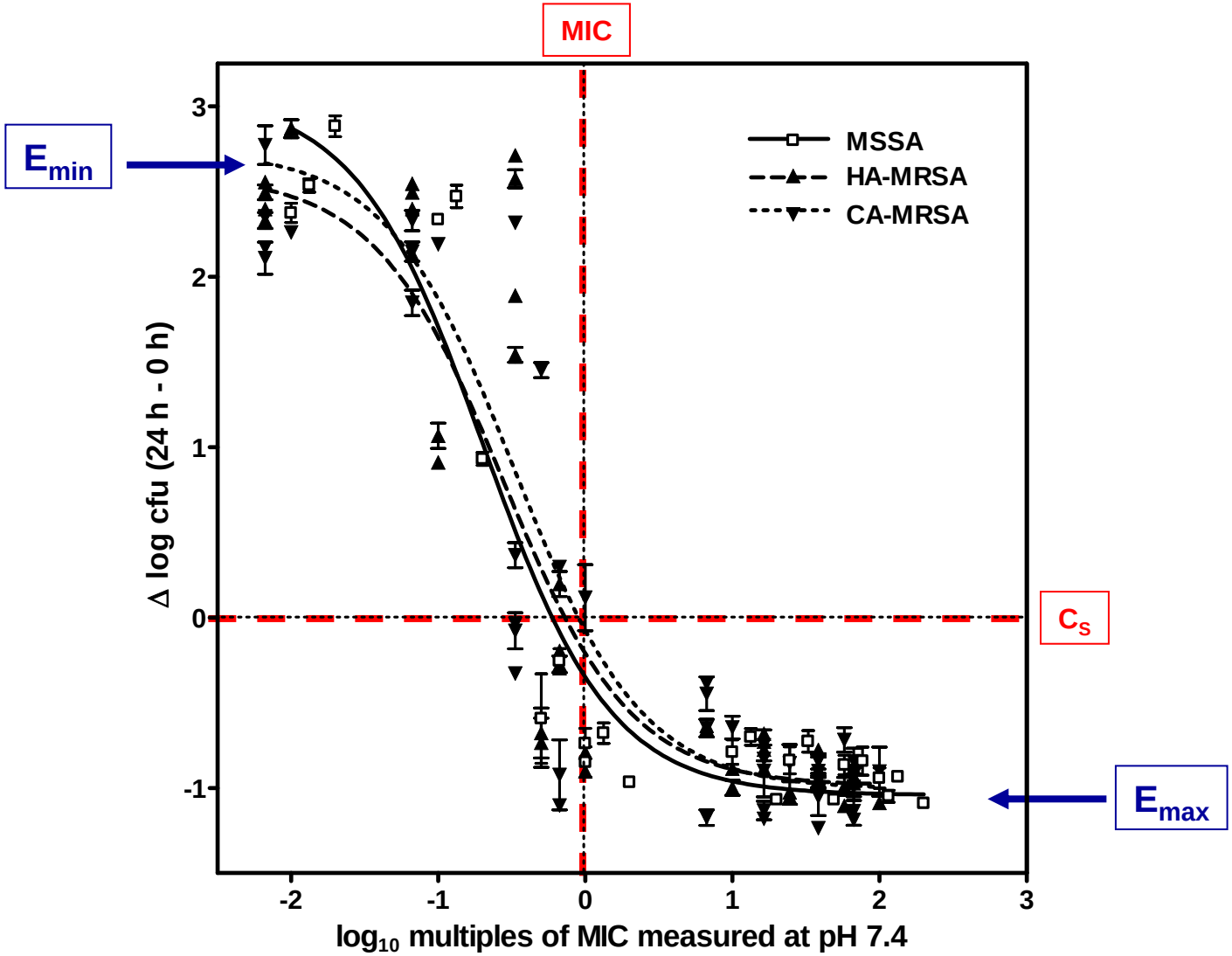
Response to an antimicrobial: the model

an example with ceftobiprole and *S. aureus* (2 strains)



Response to an antimicrobial: the model

an example with ceftobiprole and *S. aureus* (multiple strains)



Analyses

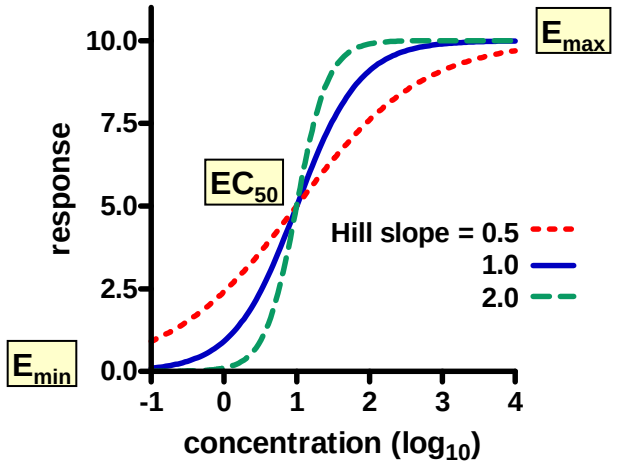
Sigmoidal dose-response:

$$Y=\text{Bottom}+\frac{\text{Top-Bottom}}{1+\left(\frac{10^{\text{LogEC}_{50}}}{10^{X}}\right)^{\text{HillSlope}}}$$

also called "4-parameters logistic equation", i.e.

- **bottom (E_{min})**
- **Top (Emax)**
- **EC_{50}**
- **Hill slope**

Sigmoid dose-response



Equation for Prism

Equation:Sigmoidal dose-response
Y=Bottom + (Top-Bottom)/(1+10^((LogEC$_{50}$-X)))

;X is the logarithm of concentration. Y is the response
;Y starts at Bottom and goes to Top with a sigmoid shape

Analyses

Equation

Equation:Sigmoidal dose-
Y=Bottom + (Top-Bottom)/

;X is the logarithm of conc
response
;Y starts at Bottom and go
shape

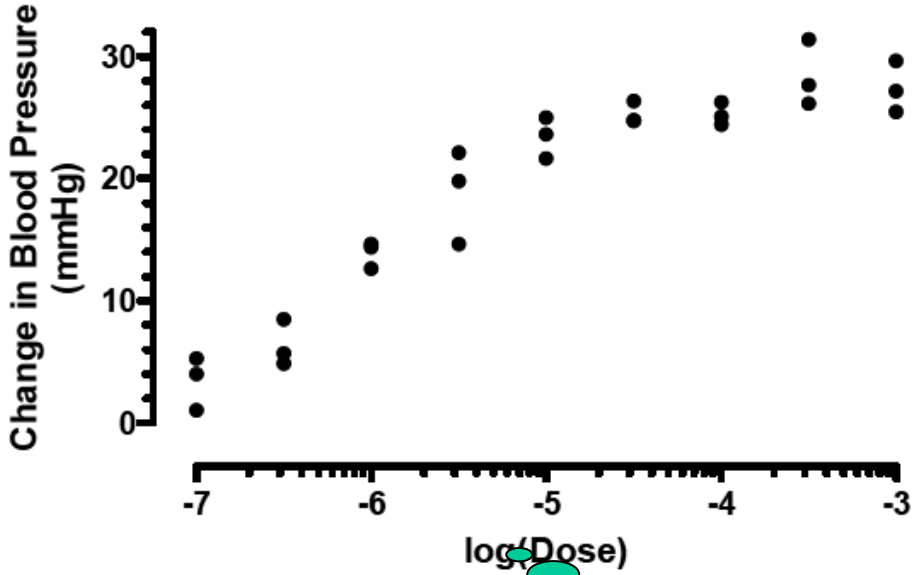
	MSSA	HA-MRSA	CA-MRSA
	Y	Y	Y
Sigmoidal dose-response			
Best-fit values			
BOTTOM	-1.042	-0.9878	-1.006
TOP	3.063	2.596	2.741
LOGEC50	-0.6931	-0.5582	-0.4805
EC50	0.2027	0.2766	0.3307
Std. Error			
BOTTOM	0.1109	0.1087	0.1346
TOP	0.2756	0.2025	0.2325
LOGEC50	0.1134	0.1069	0.1148
95% Confidence Intervals			
BOTTOM	-1.273 to -0.8117	-1.207 to -0.7684	-1.278 to -0.7347
TOP	2.490 to 3.637	2.187 to 3.005	2.271 to 3.210
LOGEC50	-0.9291 to -0.4572	-0.7739 to -0.3425	-0.7122 to -0.2489
EC50	0.1177 to 0.3490	0.1683 to 0.4544	0.1940 to 0.5637
Goodness of Fit			
Degrees of Freedom	21	43	43
R^2	0.9296	0.8795	0.8499
Absolute Sum of Squares	3.232	10.99	15.35
Sy.x	0.3923	0.5056	0.5974
Data			
Number of X values	32	98	164
Number of Y replicates	1	1	1
Total number of values	24	46	46
Number of missing values	8	52	118

Type of functions

Fitting Models to Biological Data using Linear and Nonlinear Regression

A practical guide to curve fitting

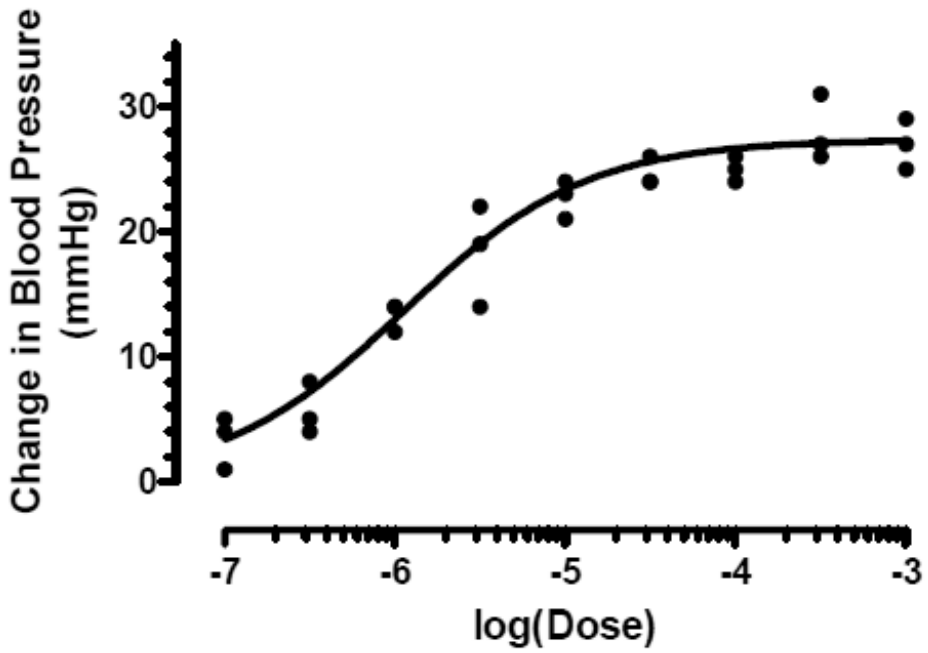
Harvey Motulsky & Arthur Christopoulos



how would you fit those data

Do not forget to use the appropriate axes !

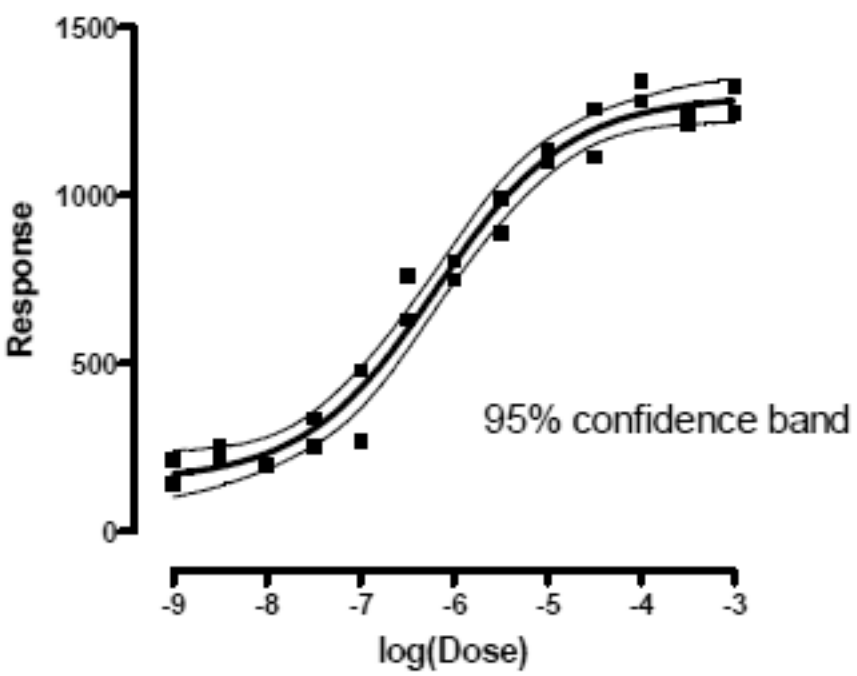
Type of functions

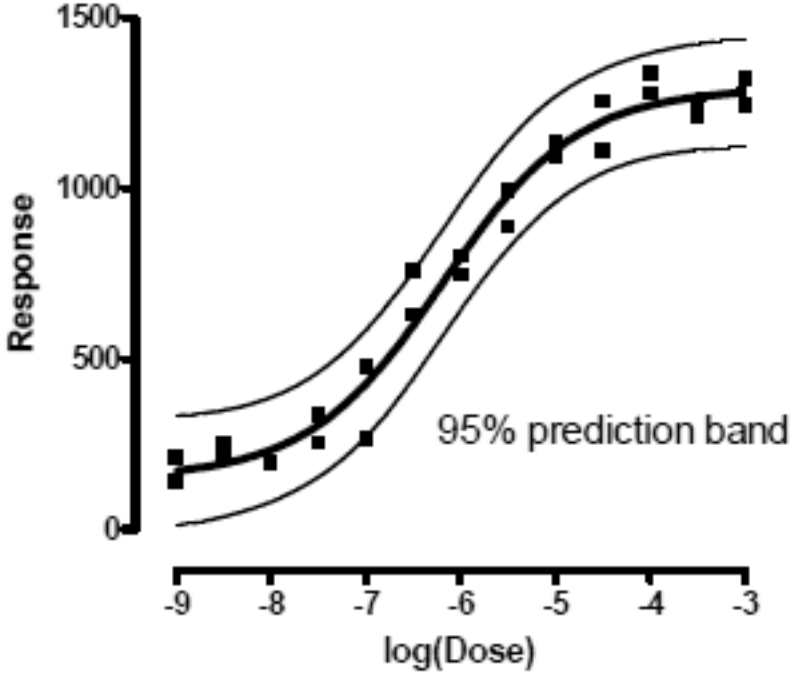


Best-fit values	
BOTTOM	0.0
TOP	27.36
LOGEC50	-5.946
HILLSLOPE	0.8078
EC50	1.1323e-006
Std. Error	
TOP	0.7377
LOGEC50	0.06859
HILLSLOPE	0.09351
95% Confidence Intervals	
TOP	25.83 to 28.88
LOGEC50	-6.088 to -5.804
HILLSLOPE	0.6148 to 1.001
EC50	8.1733e-007 to 1.5688e-006
Goodness of Fit	
Degrees of Freedom	24
R^2	0.9547
Absolute Sum of Squares	96.71
Sy.x	2.007

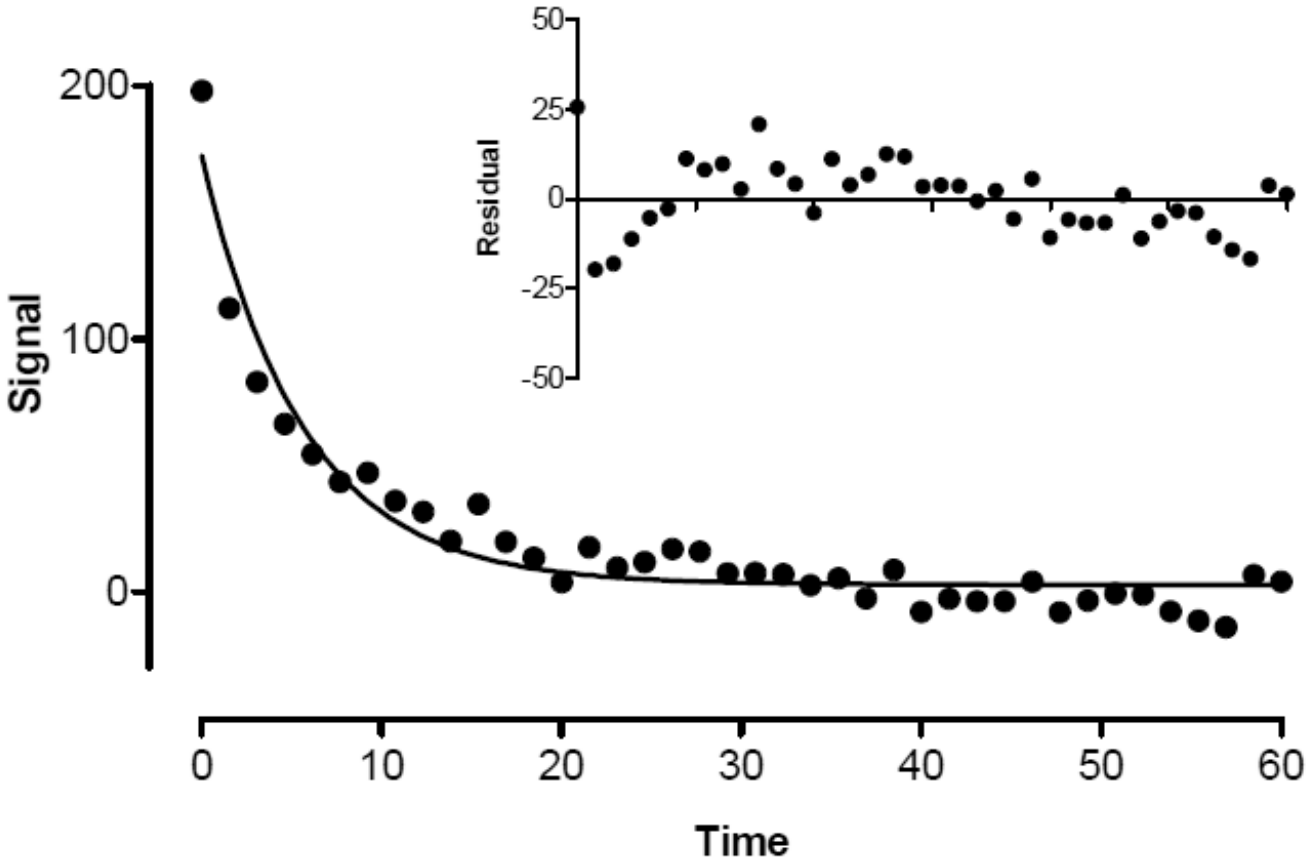
This would be a good model

Run statistics



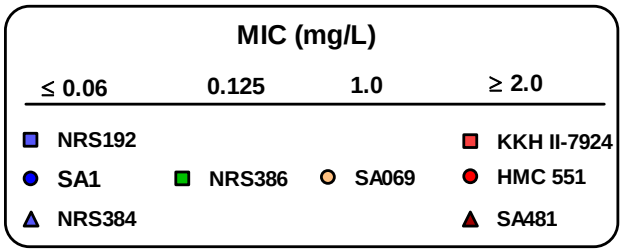


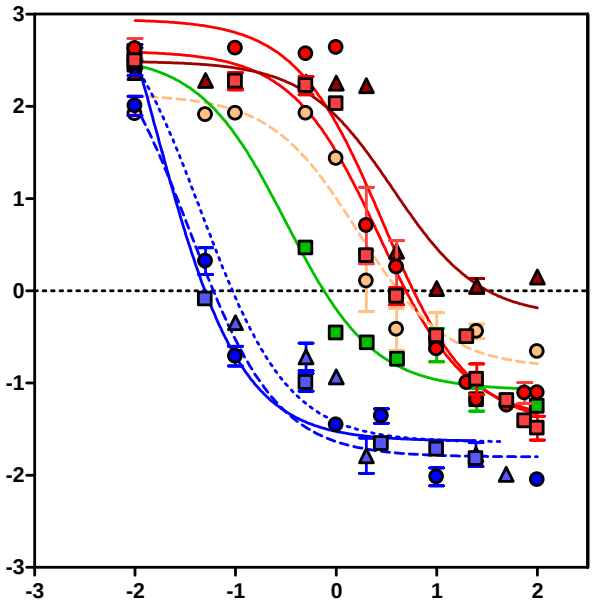
Run tests



Two examples

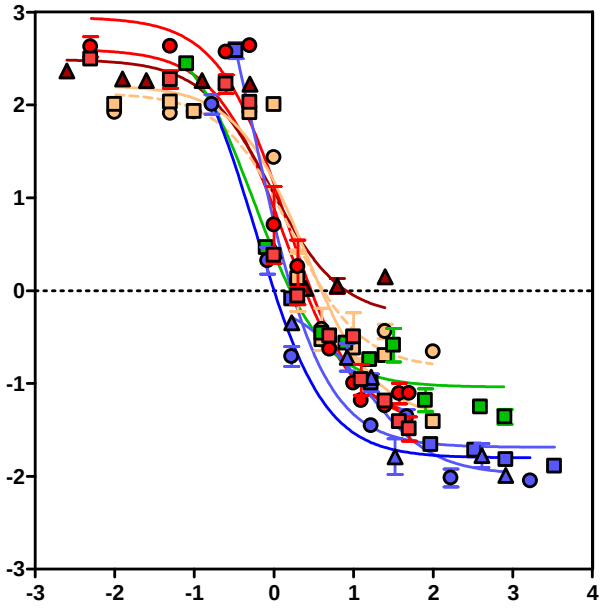
Impact of MIC on the response of intracellular bacteria to moxifloxacin





$\log_{10}$ extracellular concentration (mg/L)

after normalization for MIC



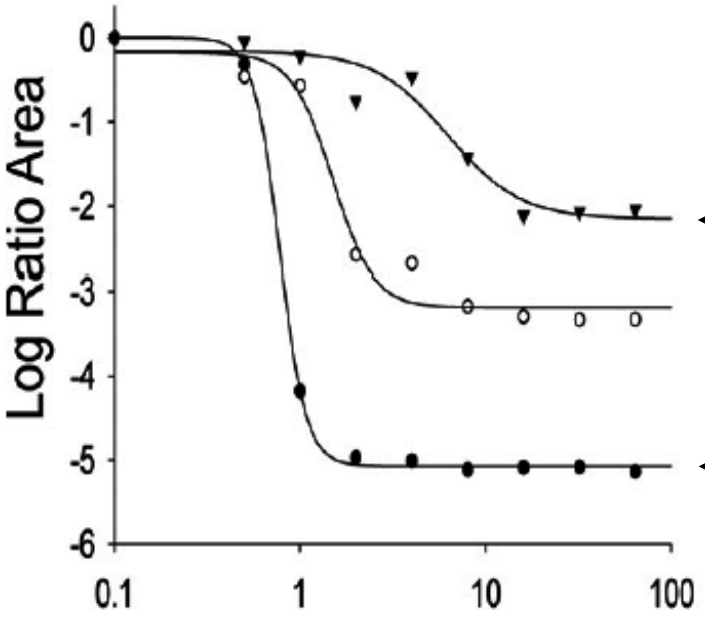
$\log_{10}$ extracellular concentration (x MIC)

Lemaire *et al*. Journal of Antimicrobial Chemotherapy (2011) 66:596-607

Colistin and inoculum effect

A)

Inoculum	E_0	Emax	EC_{50}	H
10^6 CFU/mL	-0.003	5.07	0.777	6.10
10^8 CFU/mL	-0.173	3.01	1.49	3.95
10^9 CFU/mL	-0.156	1.99	6.22	2.20

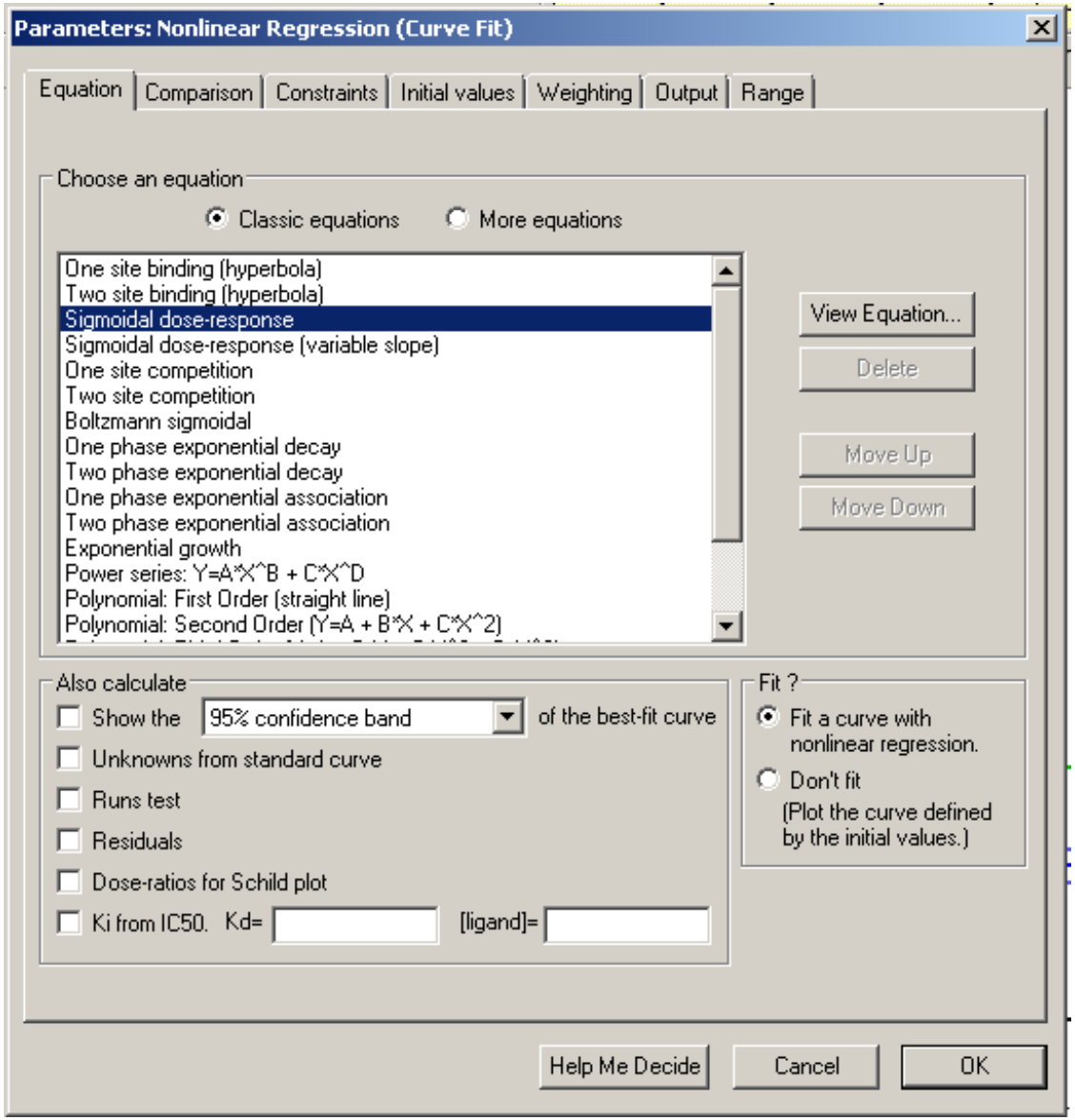


high inoculum (~ *in vivo*

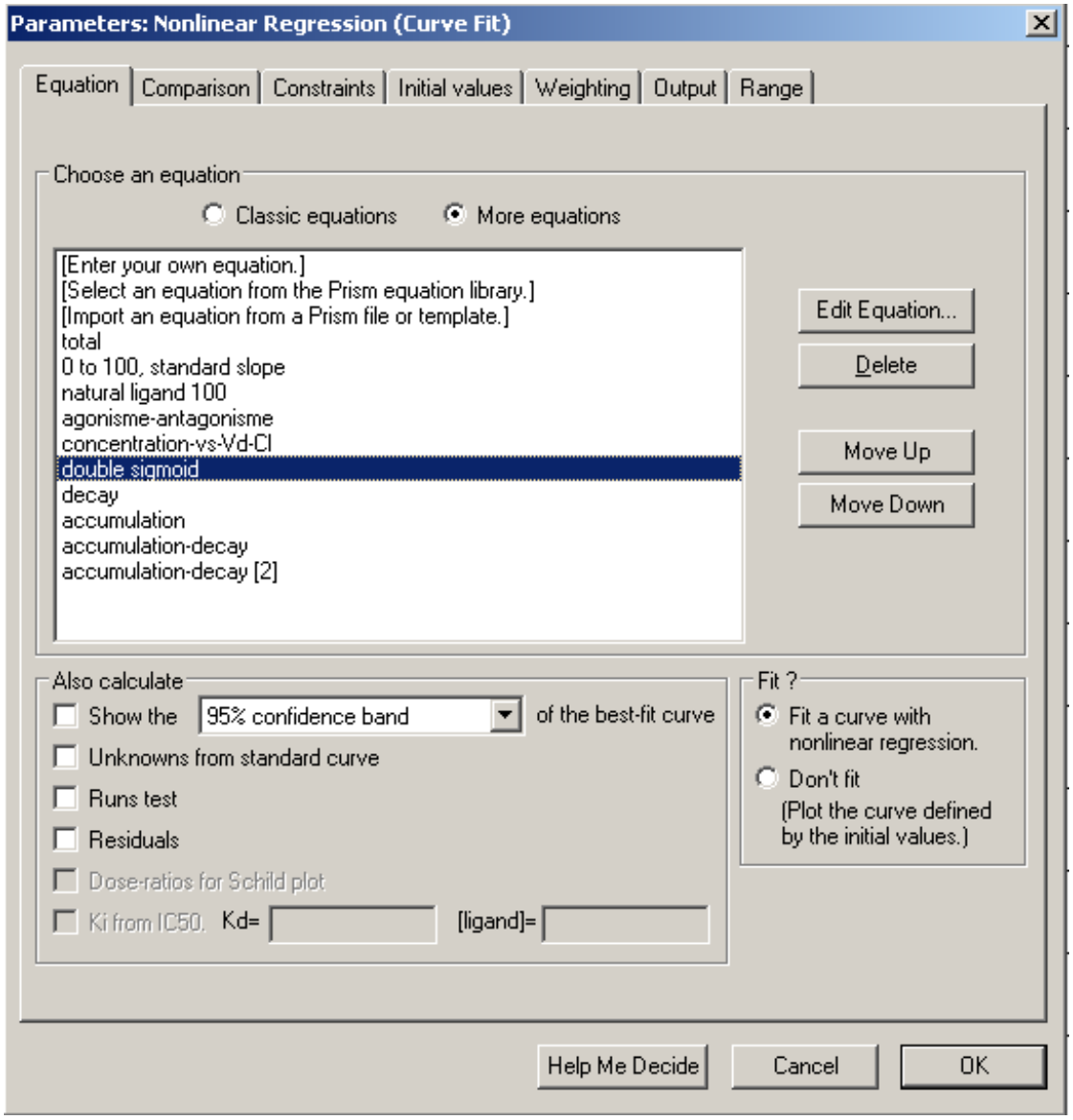
low inoculum (~ *in vitro* testing)

The extent and rate of killing of *P. aeruginosa* by colistin were markedly decreased at high CFUo compared to those at low CFUo.
Bulita et al. Antimicrob. Agents Chemother. (2010) 54:2051-2062

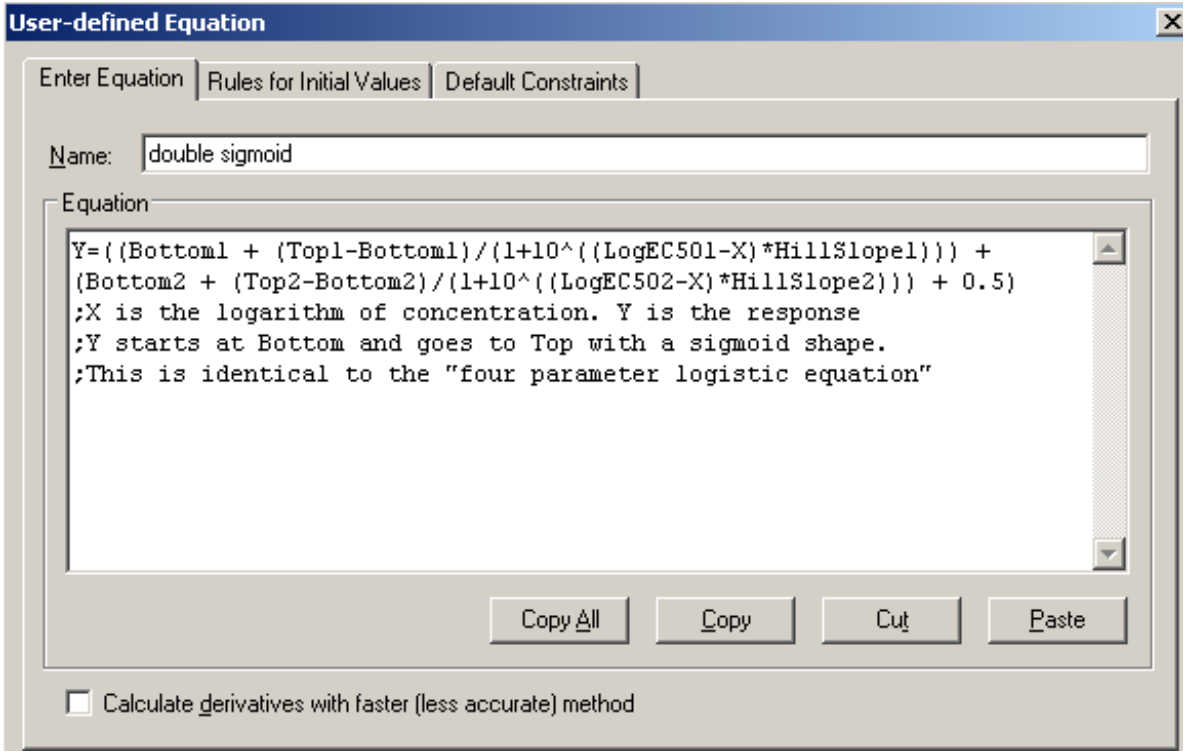
In search of models with Prism



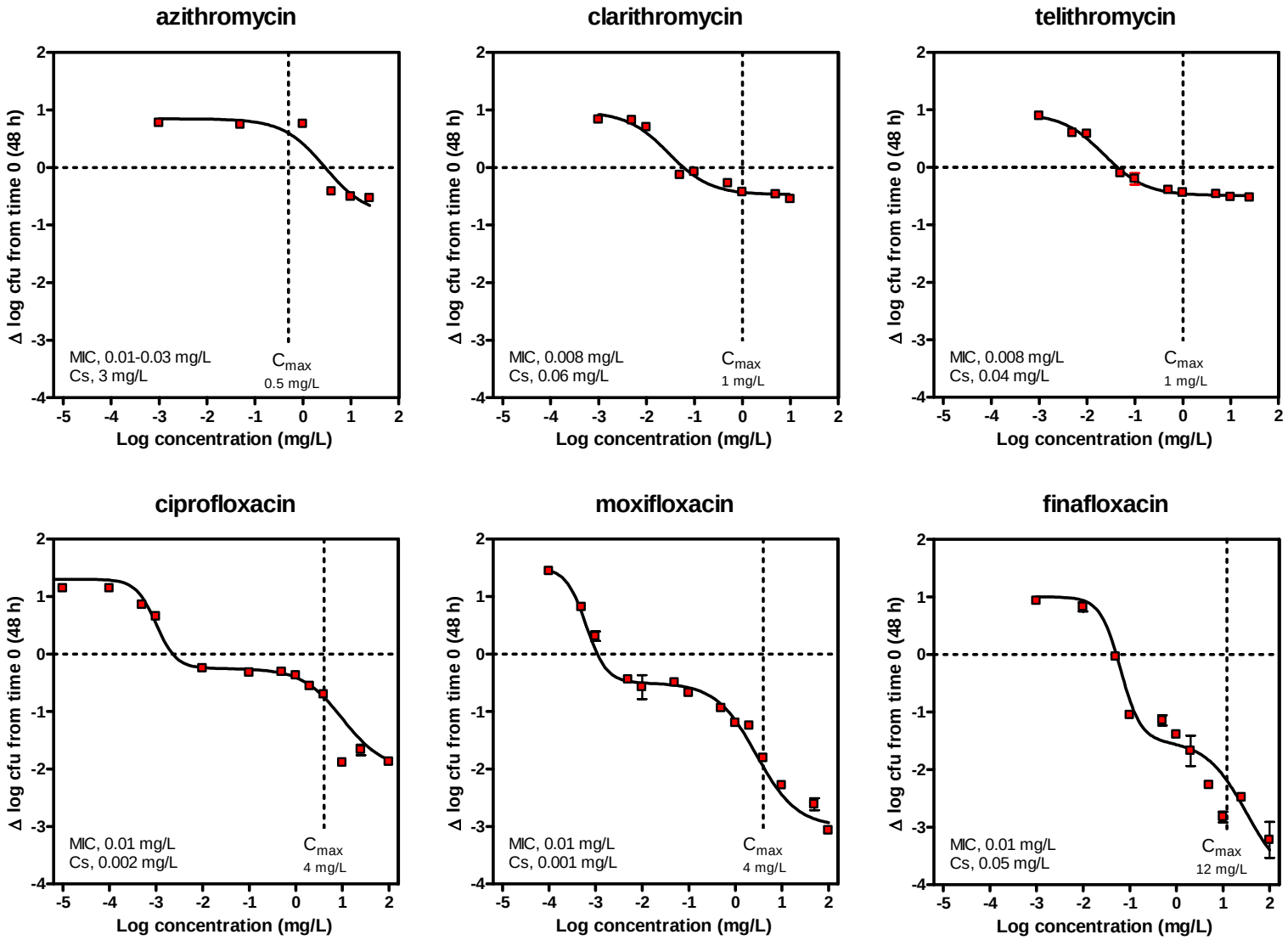
In search of models (including your own)



In search of models (including your own)



And here you are …



In vivo pharmacokinetics

What is PK analysis and modeling ?

- **Noncompartmental analysis**
  Noncompartmental PK analysis examines total drug exposure and looks for function(s) fitting the change of concentration over time without reference to where the drug may distribute.

Analysis is simple and does not imply anything concerning the actual fate of the drug.

The results are purely descriptive and non-predictive unless the function selected is linked to physical phenomena (e.g. 1st order kinetics).

What is PK analysis and modeling ?

- **Compartmental analysis**
  Describes and predicts the concentration-time curve based on the movements of the drug between compartments (kinetic or physiological model)

Once the model is indentified, it can be used to predict the concentration at any time.

The model may be (very) difficult to develop

The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and first-order elimination.

The most complex PK models rely on the use of physiological information to ease development and validation.

What is PK analysis and modeling ?

- **Compartmental analysis**

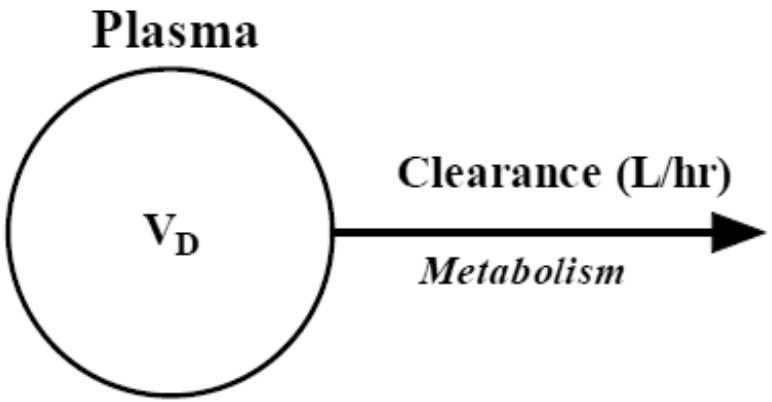
  The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and first-order kinetic elimination

  This can be developed with simple software accessible to lay users such as Prism (with some sophistication sometimes)

  More complex PK models rely on the use of physiological information to ease development and validation.

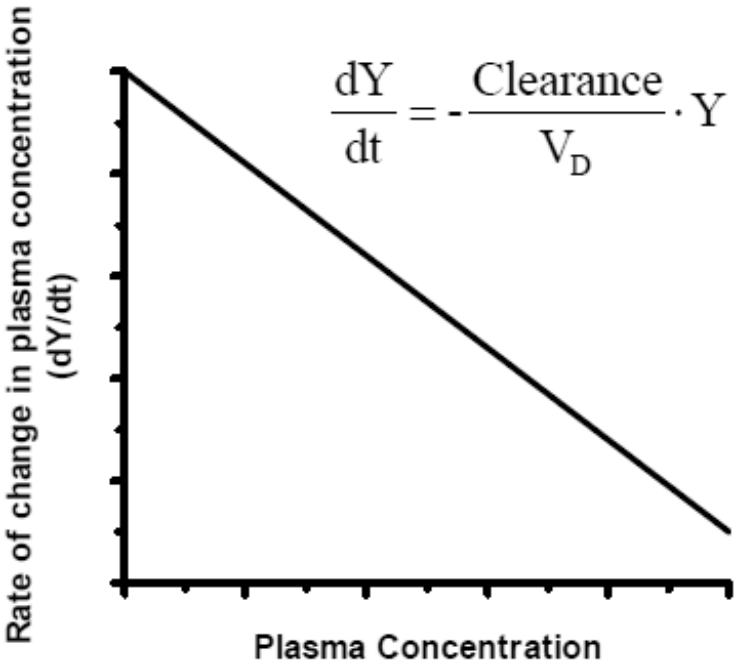
  This requires "high capacity" software that is often impossible to use without serious introduction

Simple compartmental models



$$\frac{dC_{plasma}}{dt} = -\frac{Clearance}{V_D} \cdot C_{plasma}$$

$$\frac{dY}{dt} = -\frac{Clearance}{V_D} \cdot Y$$



Integrating … (calculus)

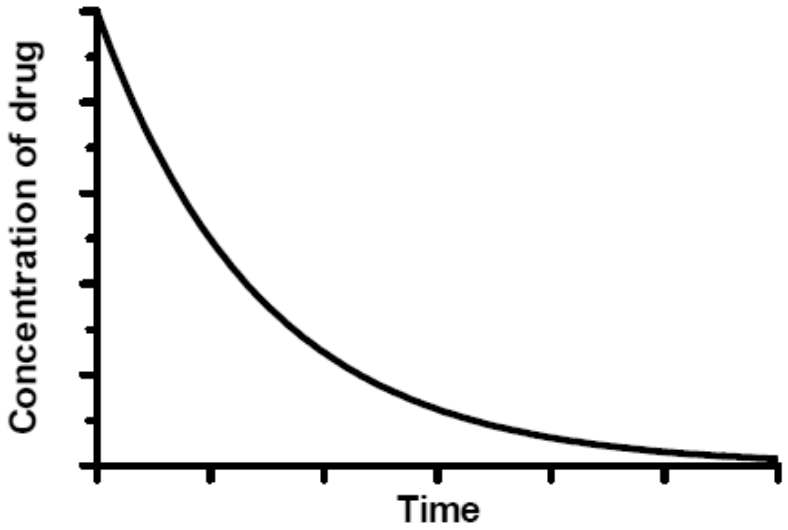
Integrating a differential equation

Using calculus, you (or someone you delegate this job to) can integrate the equation to form a standard model that defines Y as a function of t:

$$Y_t = Y_0 \cdot e^{-\frac{\text{Clearance}}{V_D} \cdot t} = Y_0 \cdot \exp(-\text{Clearance} \cdot t / V_D)$$

At time zero, the concentration of drug (Y_o) equals the dose you injected (D in mg) divided by the volume of distribution (V_o in mL). So the equation can be rewritten like this:

$$Y_t = \frac{D}{V_D} \cdot e^{\frac{C}{V_D} \times t}$$

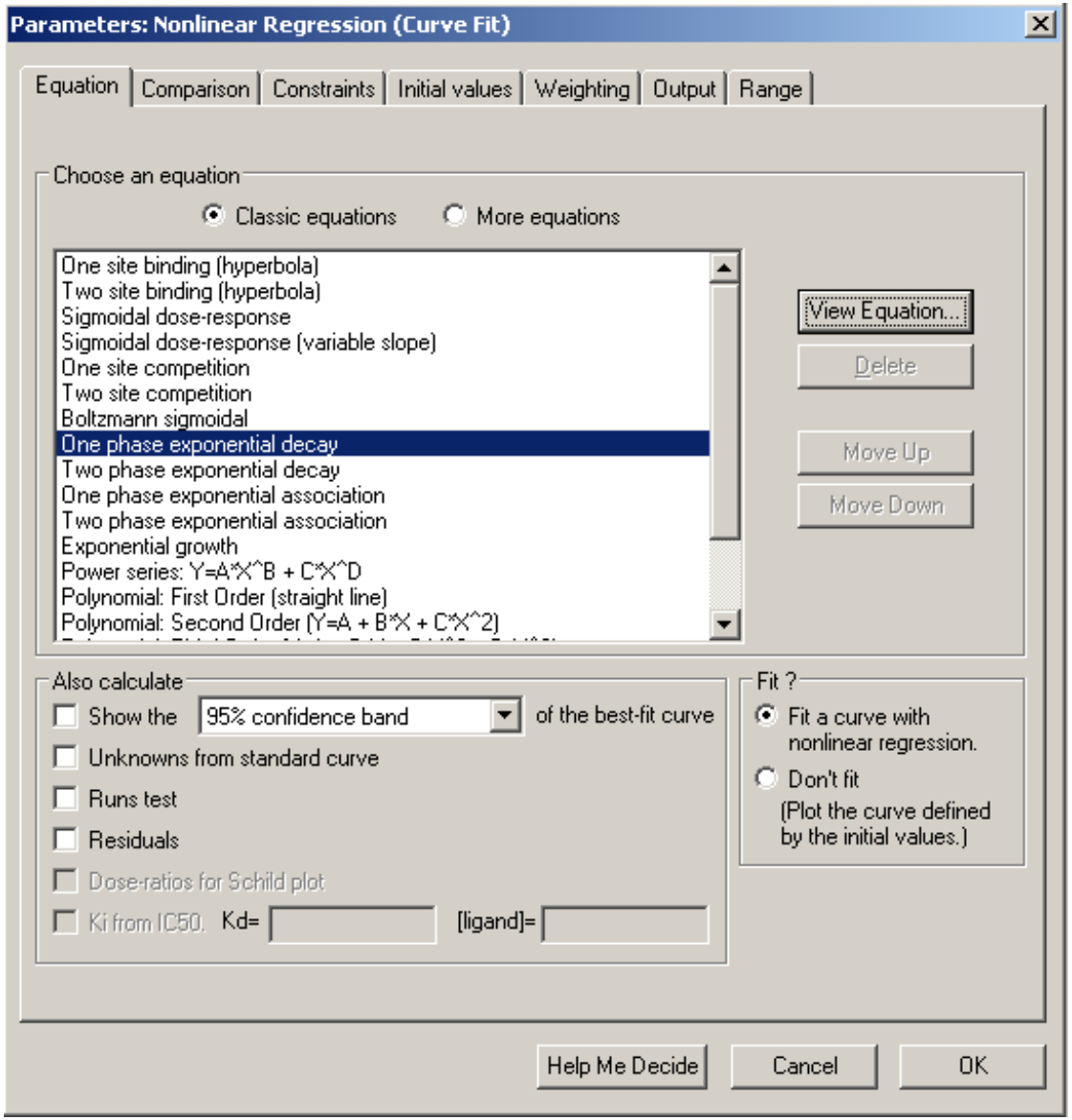


From model to data and finding "best parameters" with a computer (curve fitting)

- choose (or enter) your equation
- enter your data
- enter initial parameter values
  (best estimate; optional but useful)
- the computer will then
  - compare equation-based curve to actual data
  - modify parameters by successive iterations until a "best" fit is obtained …
  - the limit is the number of iterations

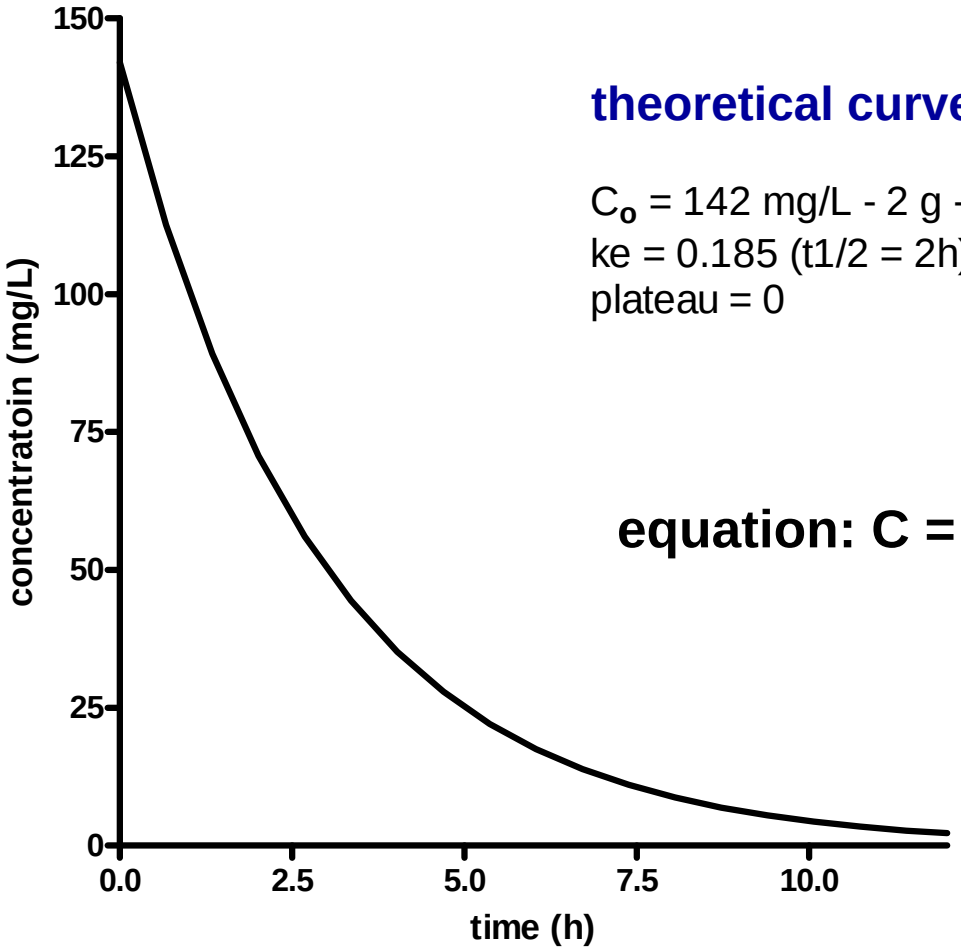
} **numerical integration**

From data to model with a computer (no calculus)



Example of monocopartmental analysis … (*)

Exponential-decay (1 compartment)



theoretical curve

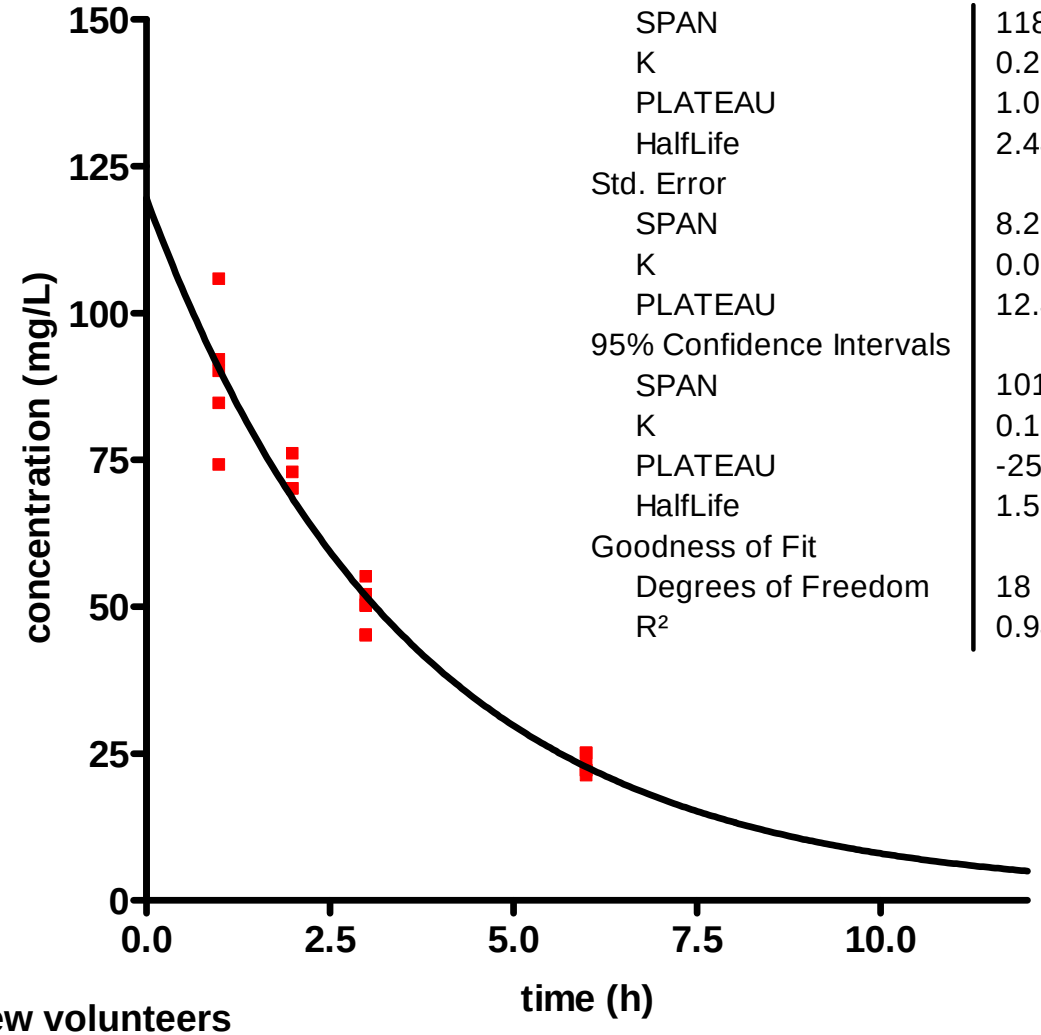
C_o = 142 mg/L - 2 g - 70 kg - V_d = 0.2 L/kg
ke = 0.185 (t1/2 = 2h)
plateau = 0

equation: $C = C_0.e^{-kt}$

*** this analysis and the following ones concern ceftazidime IV**

Fitting to ideal population data (*)

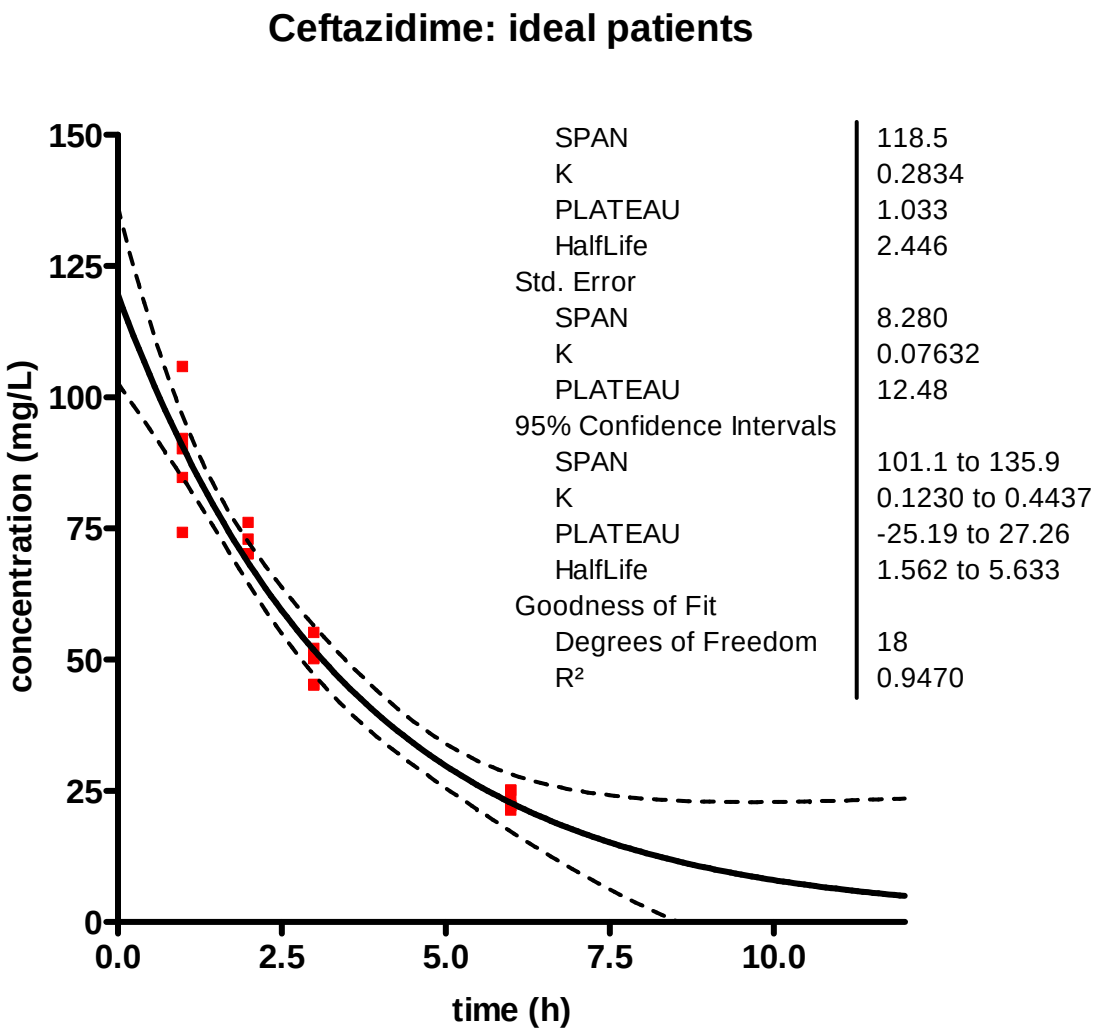
Ceftazidime: ideal patients



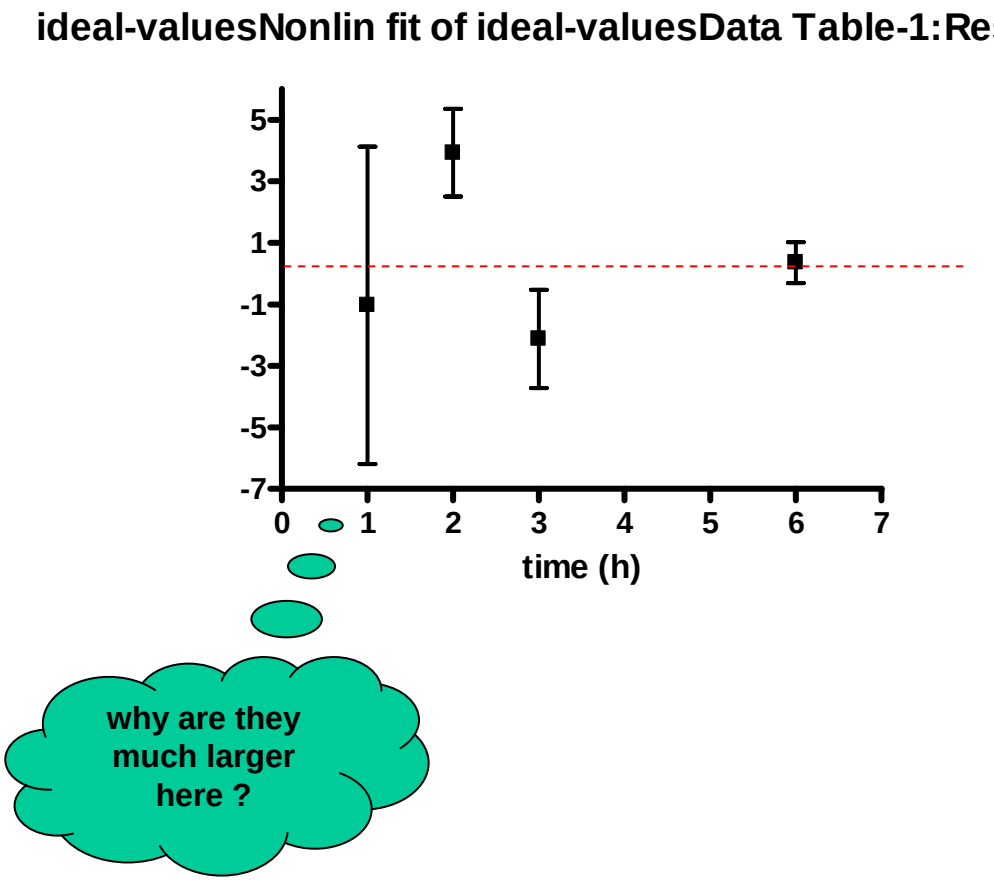
SPAN	118.5
K	0.2834
PLATEAU	1.033
HalfLife	2.446
Std. Error	
SPAN	8.280
K	0.07632
PLATEAU	12.48
95% Confidence Intervals	
SPAN	101.1 to 135.9
K	0.1230 to 0.4437
PLATEAU	-25.19 to 27.26
HalfLife	1.562 to 5.633
Goodness of Fit	
Degrees of Freedom	18
R^2	0.9470

*** data from a few volunteers**

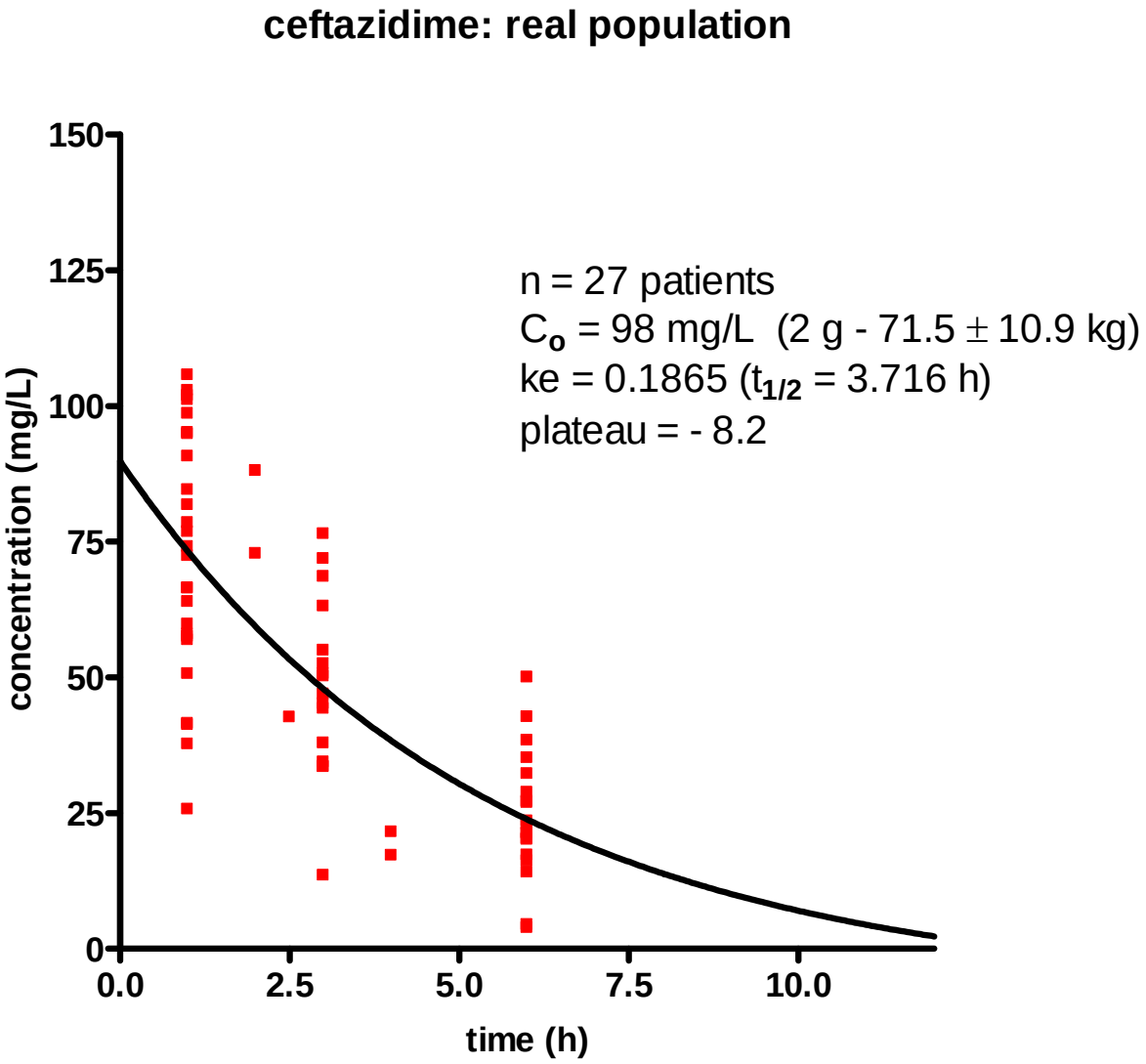
Ideal population: tests for 95 % CI



Ideal population: residuals

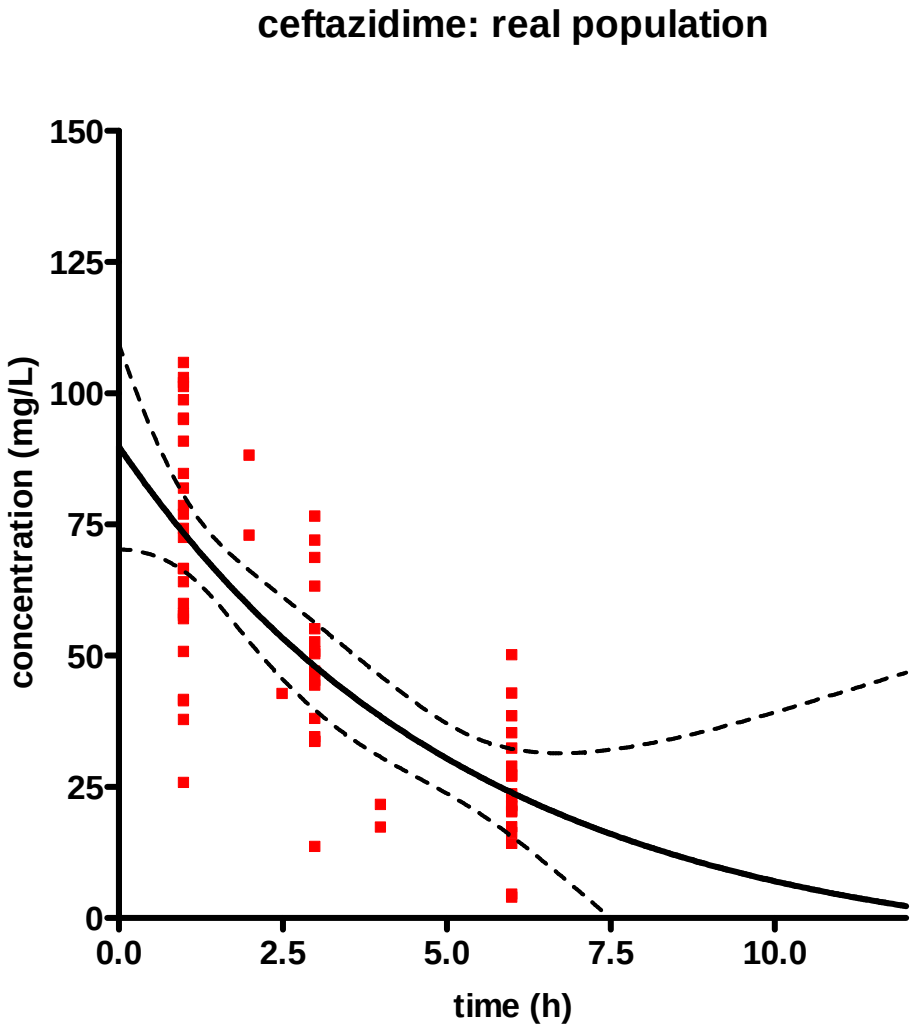


Real population (*)



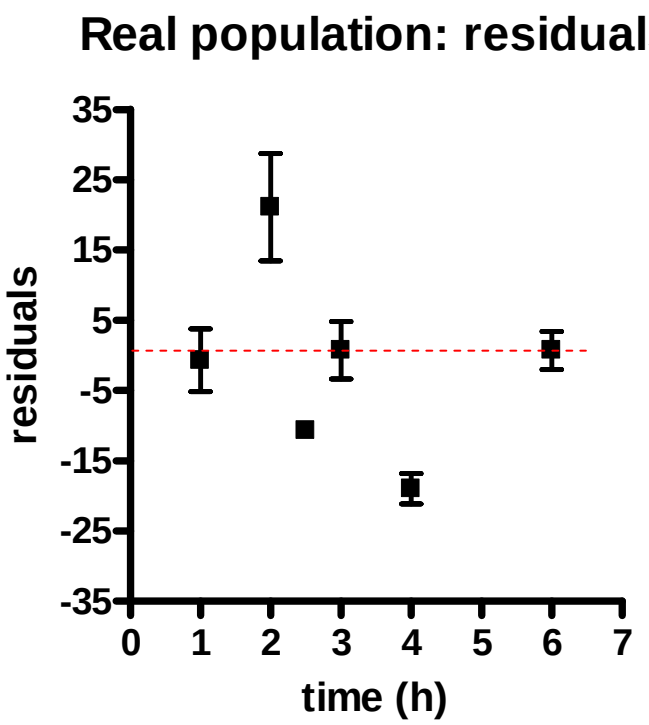
*** data from several patients**

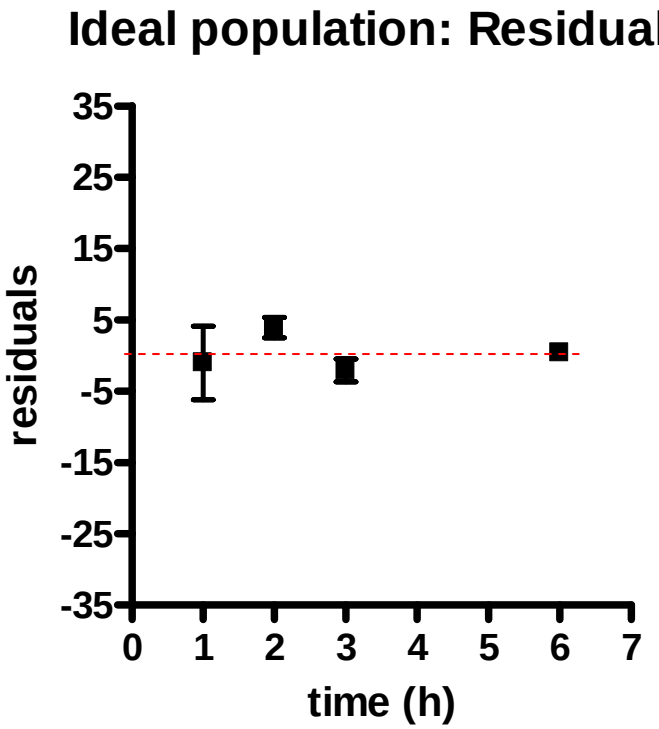
Real population: 95 % CI



One phase exponential decay	
Best-fit values	
SPAN	98.05
K	0.1865
PLATEAU	-8.174
HalfLife	3.716
Std. Error	
SPAN	39.69
K	0.1688
PLATEAU	47.23
95% Confidence Intervals	
SPAN	18.70 to 177.4
K	0.0 to 0.5240
PLATEAU	-102.6 to 86.23
HalfLife	
Goodness of Fit	
Degrees of Freedom	63
R^2	0.5638
Absolute Sum of Squares	21231
Sy.x	18.36

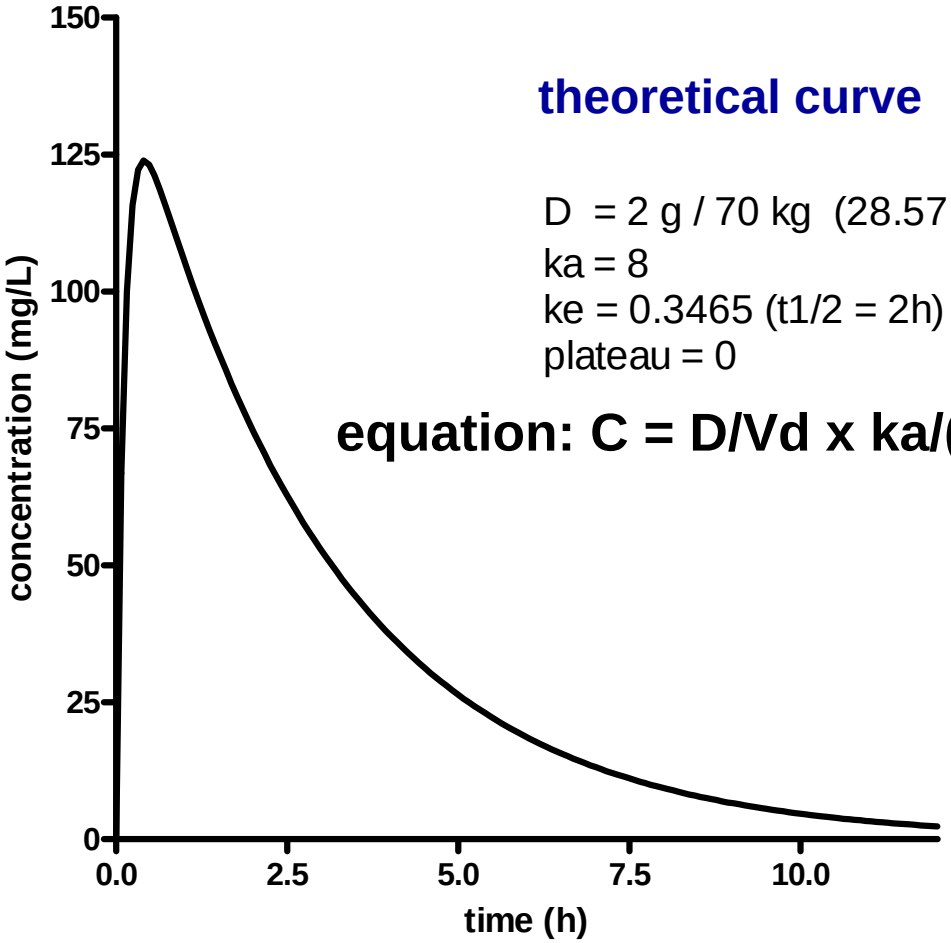
Real population: residuals





More complex models: accumulation / decay

Bateman function
(applied to ceftazidime)

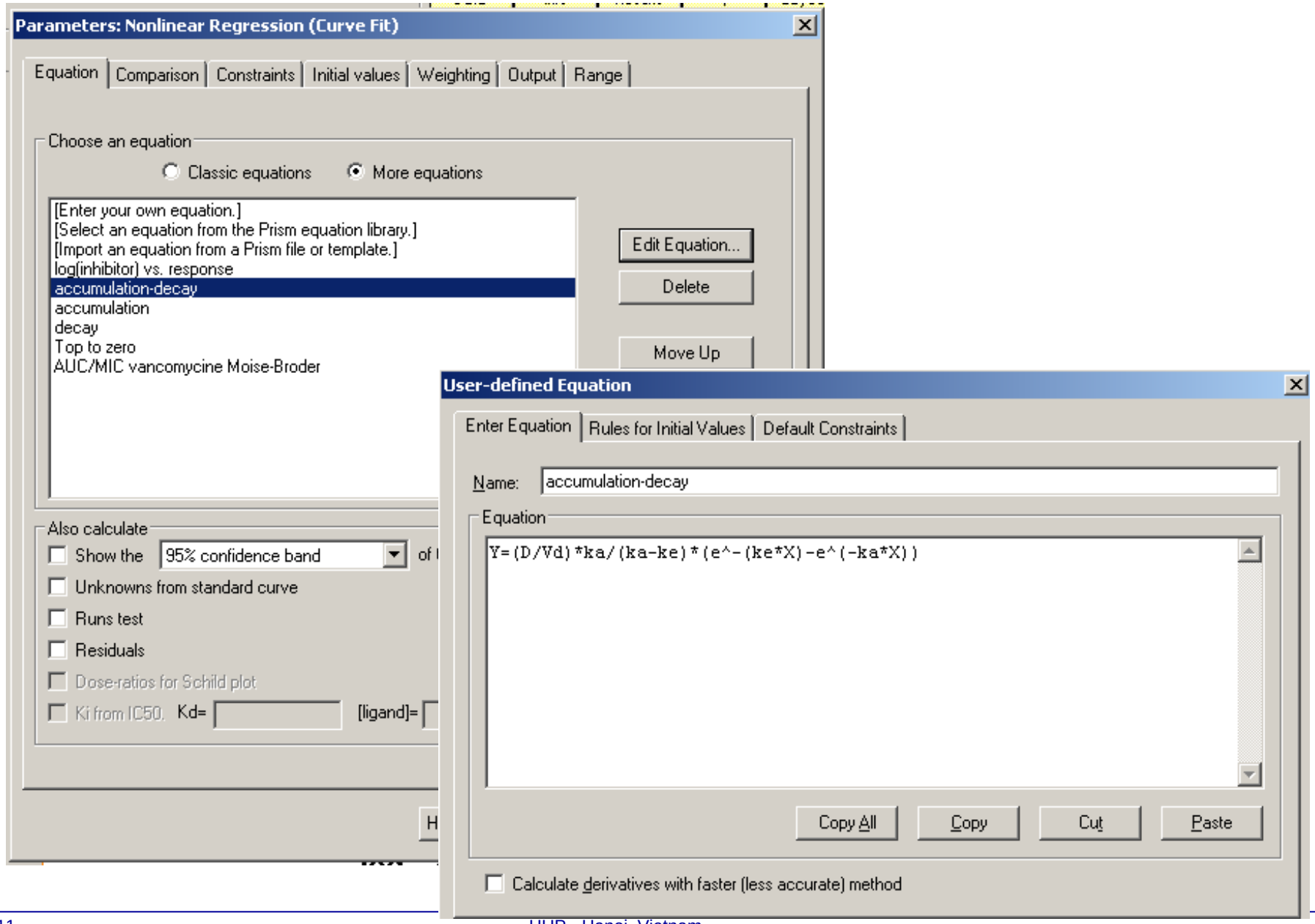


theoretical curve

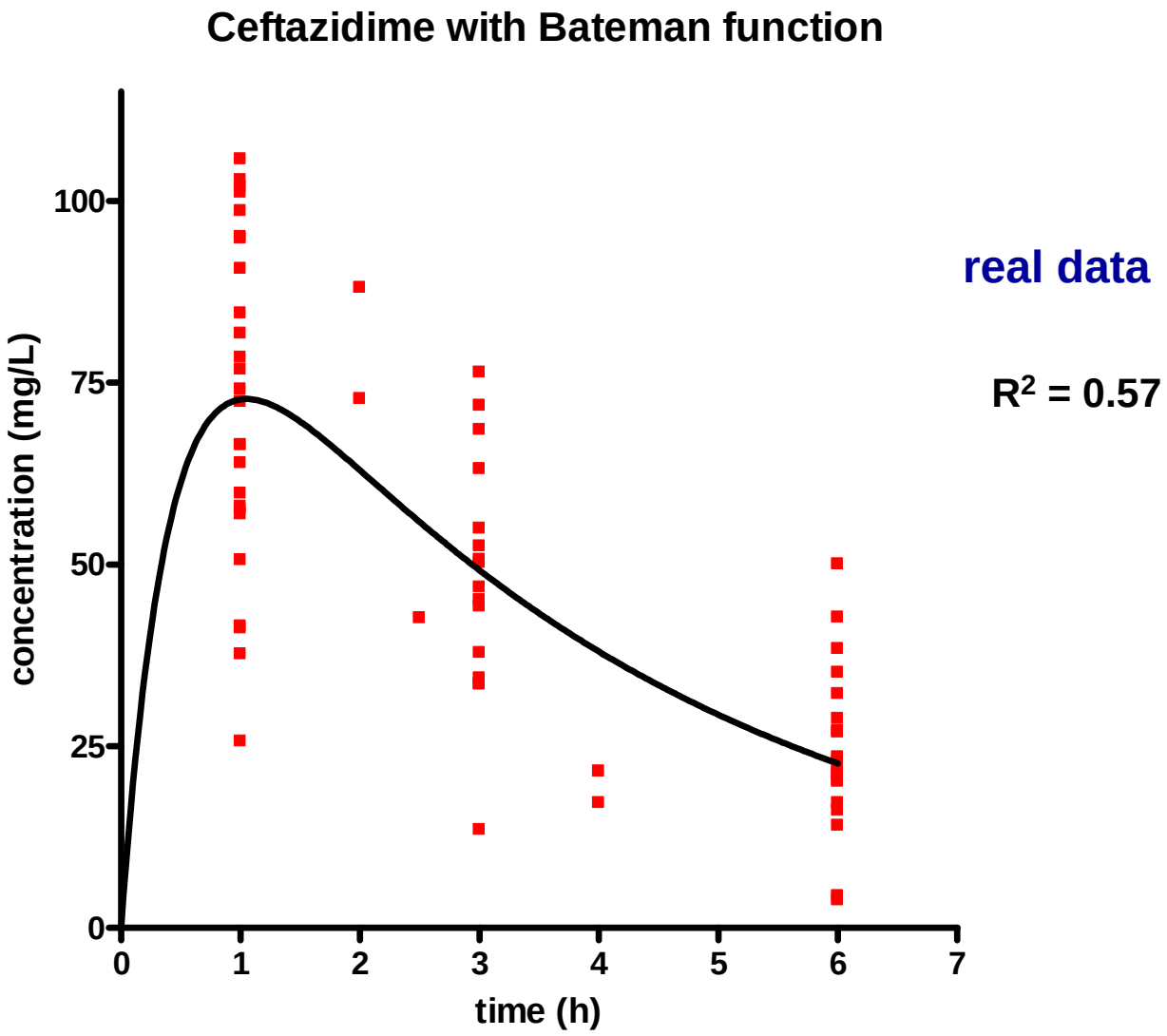
D = 2 g / 70 kg (28.57 mg/kg) - V_d = 0.2 L/kg
ka = 8
ke = 0.3465 (t1/2 = 2h)
plateau = 0

equation: $C = D/Vd \times ka/(ka-ke) [e^{-ket} - e^{-kat}]$

In search of more complex models with Prism

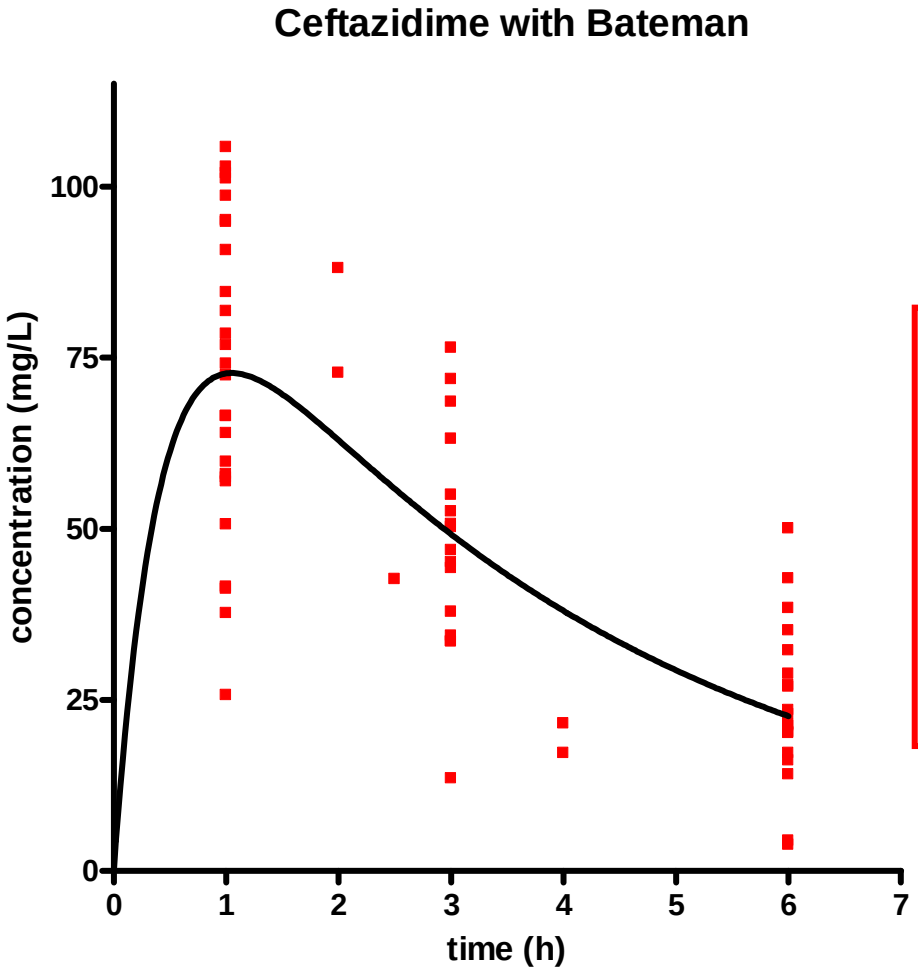


Accumulation / decay with Prism … (*)



equation: C = D/Vd x ka/(ka-ke) [e^{-ket} – e^{-kat}]

Examples d'analyse monocompartimentale … (*)



accumulation-decay	
Best-fit values	
D	28.94
VD	0.3028
KA	0.9826
KE	0.1081
E	11.04
Std. Error	
D	3.545e+007
VD	370653
KA	2.123e+006
KE	235107
E	5.761e+007
95% Confidence Intervals	
D	-70890000 to 7.089e+007
VD	-741200 to 741184
KA	-4245000 to 4.245e+006
KE	-470100 to 470135
E	-115200000 to 1.152e+008
Goodness of Fit	
Degrees of Freedom	61
R^2	0.5678

Prism has a problem here !

equation: $C = D/Vd \times ka/(ka-ke) [e^{-ket} – e^{-kat}]$

When the data become really too complex…

The Mixed non-lin approaches

Different softwares, but alll working by numerical integration based on pre-defined models

Noncompartmental

- Freeware: bear for R
- Commercial: EquivTest, Kinetica, Phoenix/WinNonlin, PK Solutions.

Compartment based

- Freeware: ADAPT, Boomer (GUI), SBPKPD.org (Systems Biology Driven Pharmacokinetics and Pharmacodynamics), WinSAAM, PKfit for R.
- Commercial: Kinetica, Phoenix/WinNonlin, PK Solutions, PottersWheel, SAAM II.

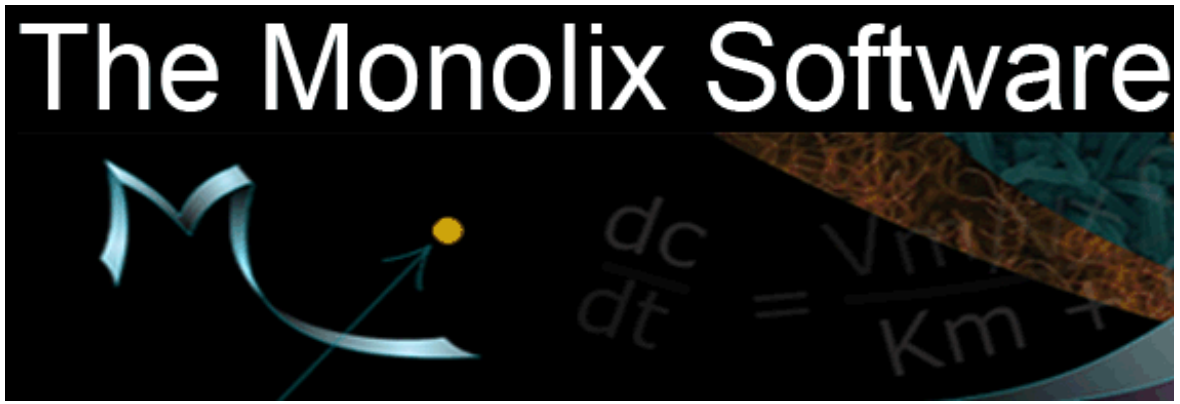
Physiologically based

- Freeware: MCSim
- Commercial: GastroPlus, PK-Sim, Simcyp.

Population PK

- Freeware: ADAPT, Boomer, Monolix, PKBugs.
- Commercial: Kinetica, NONMEM, Phoenix/NLME, PopKinetics for SAAM II, USC*PACK.

The Monlolix project



http://www.monolix.org

MONOLIX 3.2 is a free software developed by Inria and dedicated to the analysis of non linear mixed effects models. The objective of this software is to perform:

1) Parameter estimation

- computing the maximum likelihood estimator of the parameters, without any approximation of the model
- computing standard errors for the maximum likelihood estimator,

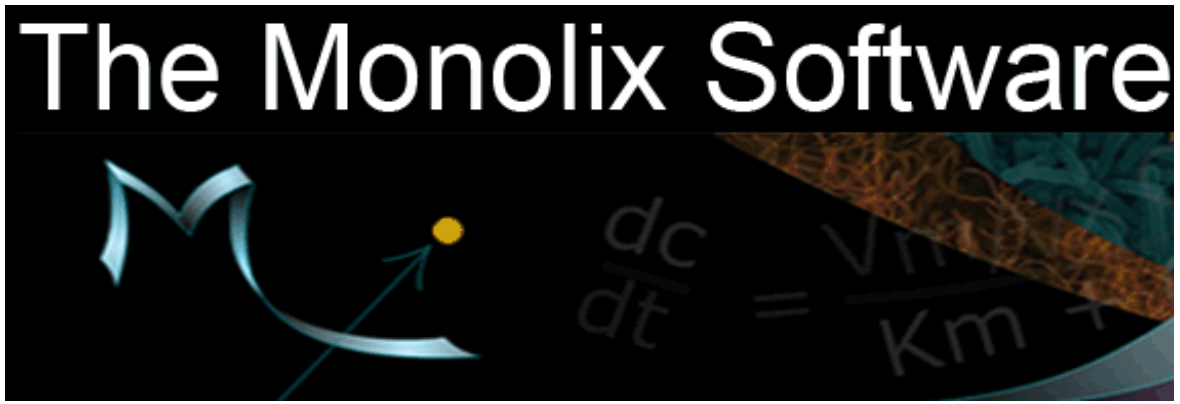
2) Model selection

- comparing several models using some information criteria (AIC, BIC),
- testing hypotheses using the Likelihood Ratio Test,
- testing parameters using the Wald Test.

3) Goodness of fit plots

4) Data simulation

The Monlolix project



MONOLIX

Version 3.2

NOVEMBER 2010

A free software for the analysis of nonlinear mixed effects models

Maximum likelihood estimation

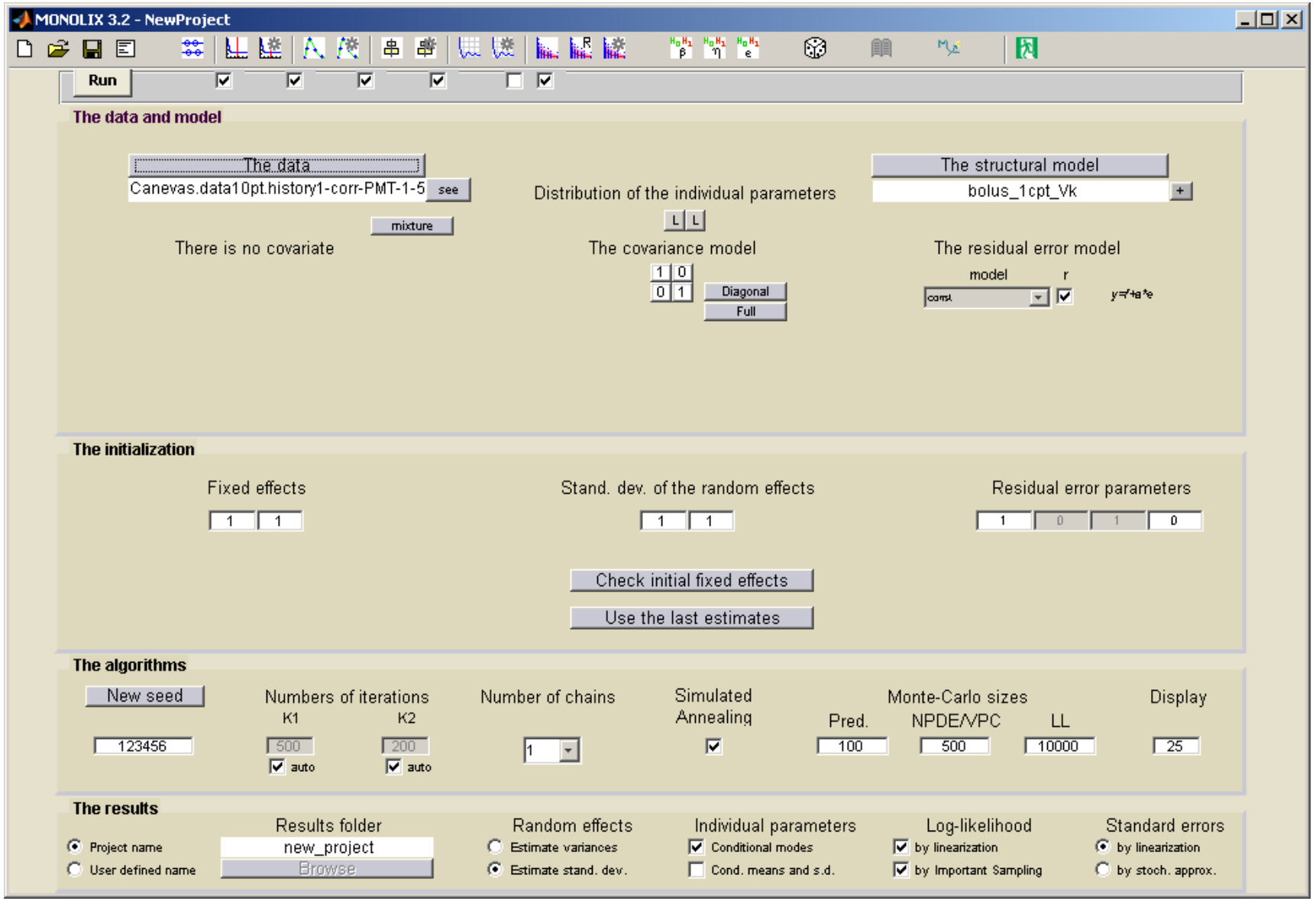
Model selection

Hypothesis testing

Graphical analysis

Data simulation

The Monlolix software



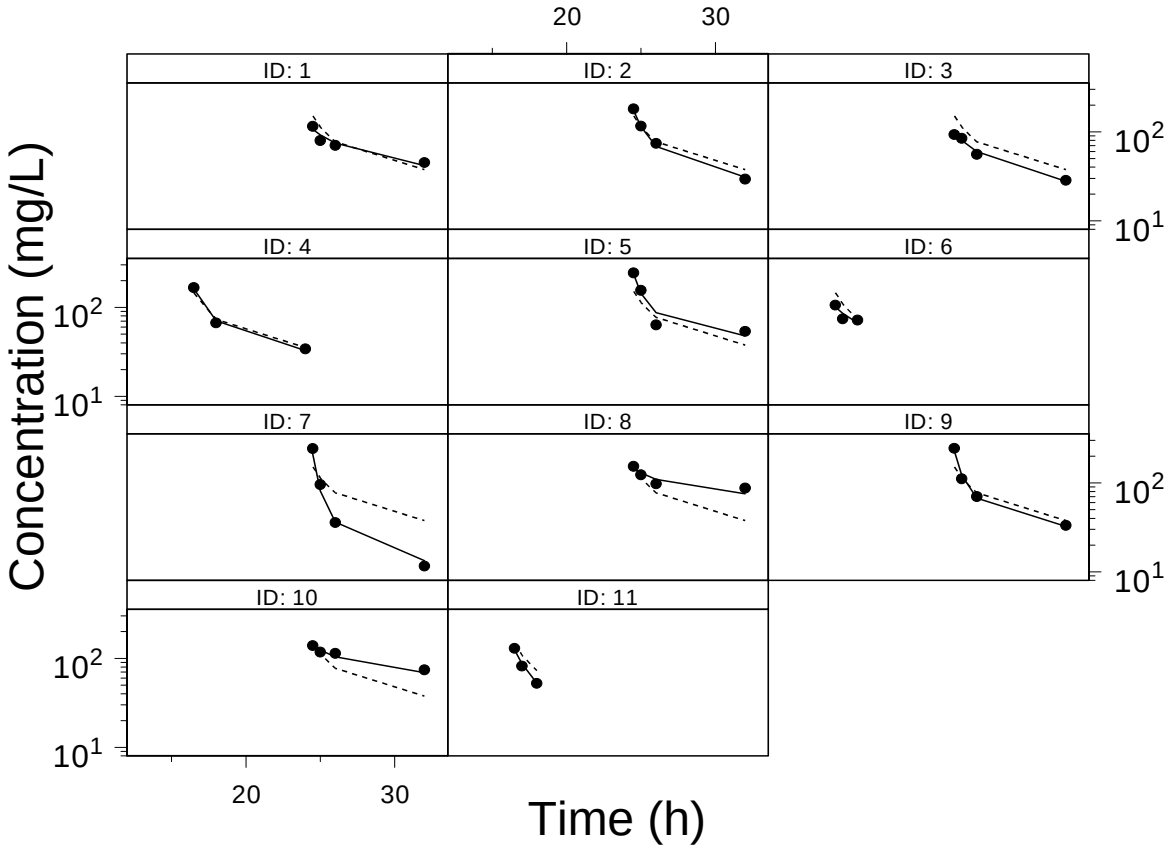
Temocillin project (full)

P-807

Population Pharmacokinetics of Temocillin in ICU patients and Monte Carlo Simulations to Evaluate Resistance Breakpoints

A.E. Muller[1], P.F. Laterre[3], T. Dugernier[3], X. Wittebole[3], N. Couwenbergh[3], P.M. Tulkens[3], S. Carryn[3], J.W.Mouton[2,4]

[1]Erasmus Medical Centre Rotterdam, [2]Radboud University Nijmegen Medical Centre, [3]Carolus Wilhelmina Hospital, Nijmegen, The Netherlands, [4]Université Catholique de Louvain, Brussels, Belgium



Projet temocillin (simplified)

P-807

Population Pharmacokinetics of Temocillin in ICU patients and Monte Carlo Simulations to Evaluate Resistance Breakpoints

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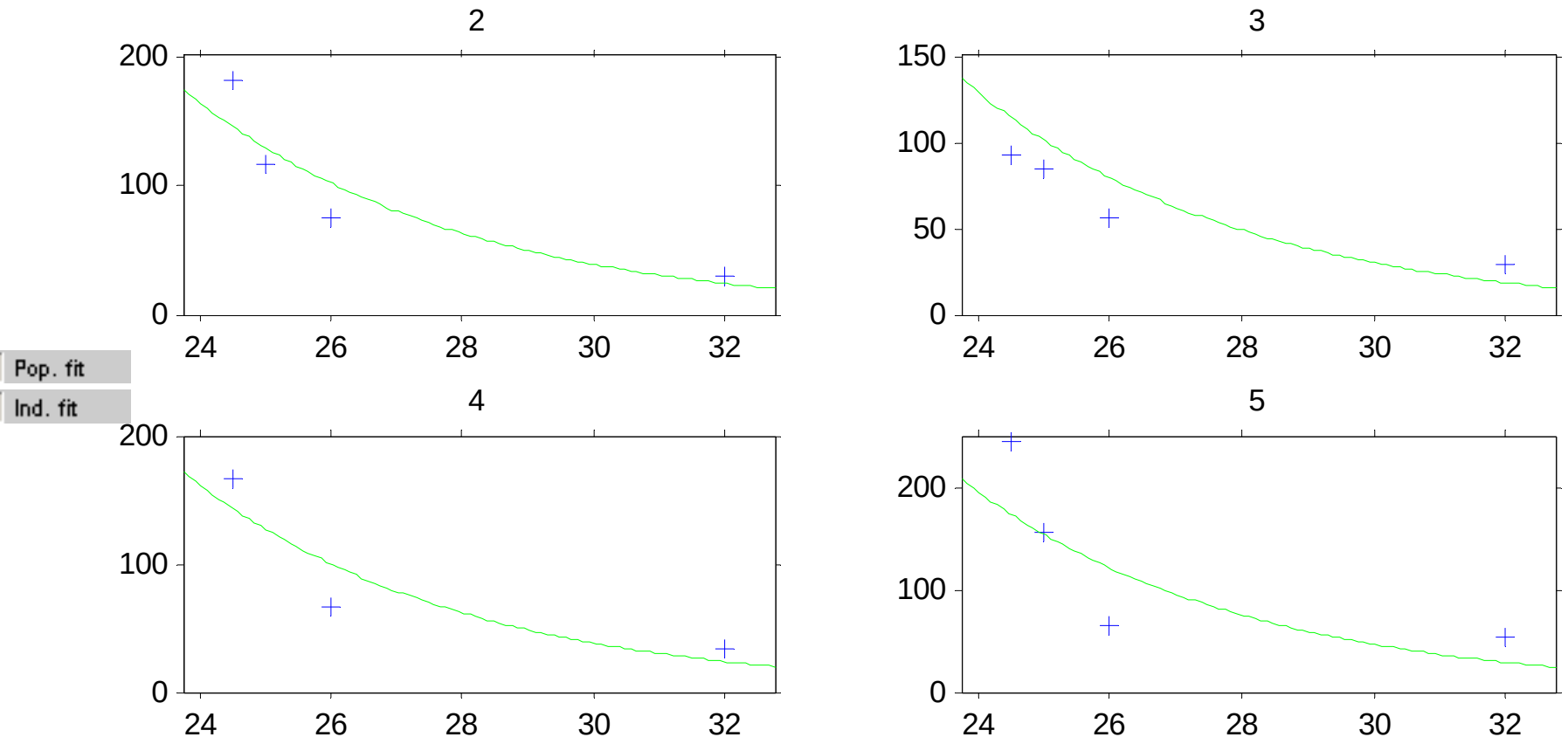
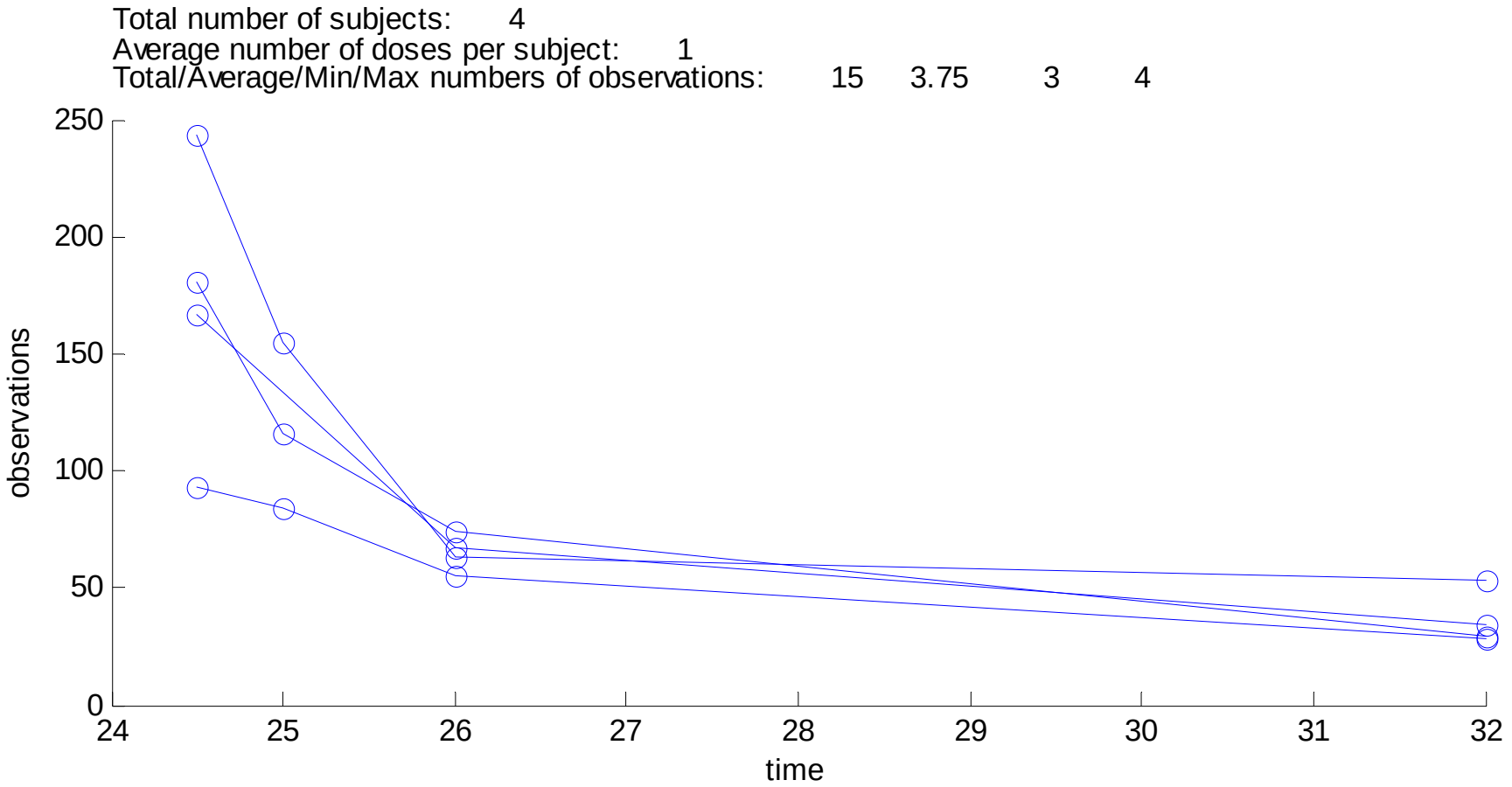
ID	TIME	DV	AMT	RATE
2	0	.	2000	4000
2	8	.	.	.
2	16	.	.	.
2	24	.	.	.
2	24.5	180.9931	.	.
2	25	116.2348	.	.
2	26	74.32156	.	.
2	32	29.47129	.	.
3	0	.	2000	4000
3	8	.	.	.
3	16	.	.	.
3	24	.	.	.
3	24.5	93.14254	.	.
3	25	84.20551	.	.
3	26	55.63816	.	.
3	32	28.52648	.	.
4	0	.	2000	4000
4	8	.	.	.
4	16	.	.	.
4	24	.	.	.
4	24.5	166.6043	.	.
4	26	66.90455	.	.
4	32	34.18707	.	.
5	0	.	2000	4000
5	8	.	.	.
5	16	.	.	.
5	24	.	.	.
5	24.5	244.0112	.	.
5	25	155.3705	.	.
5	26	63.73172	.	.
5	32	53.71434	.	.

Outputs: individual curves

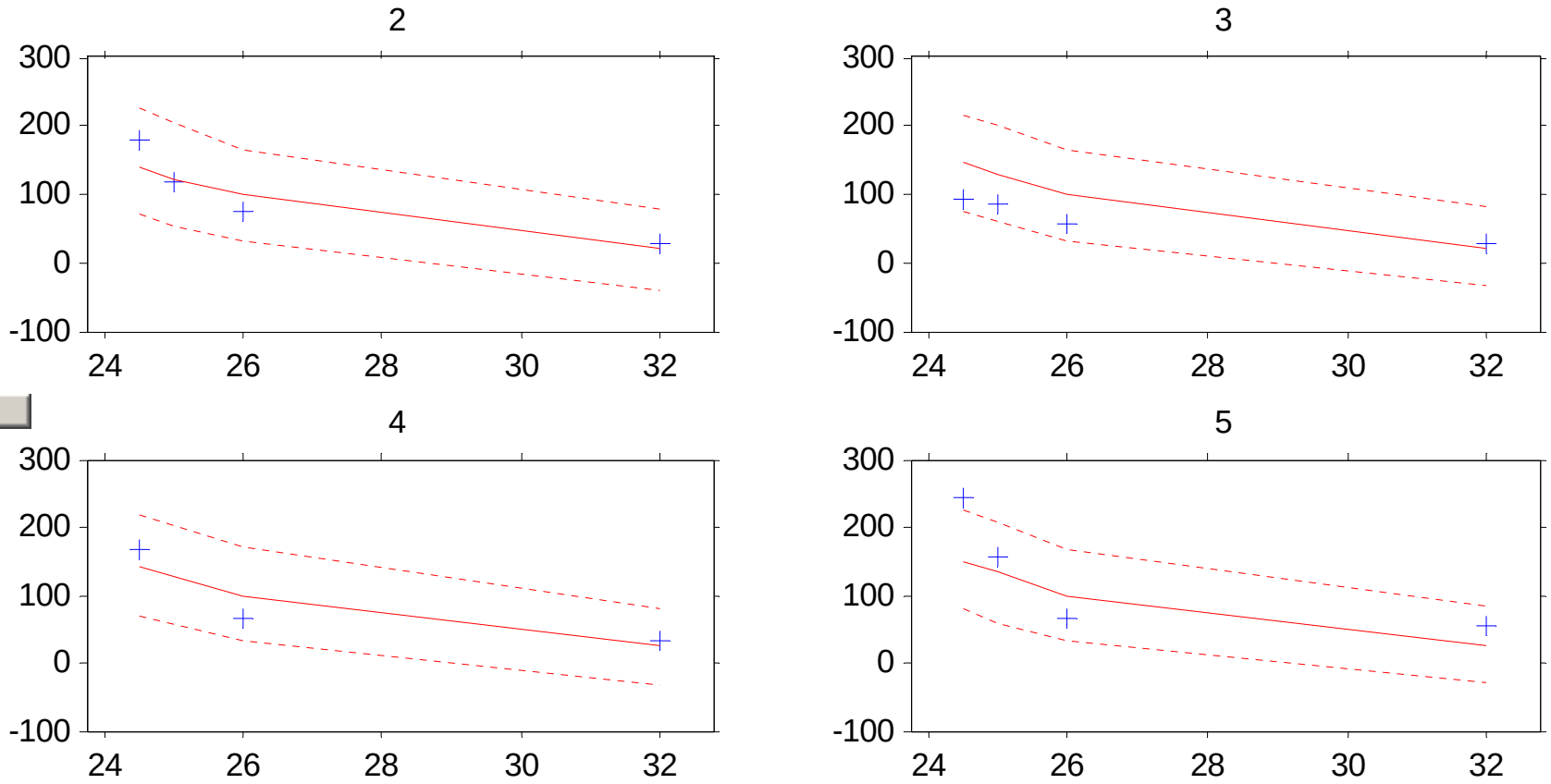


Outputs: spaghetti plot (*)

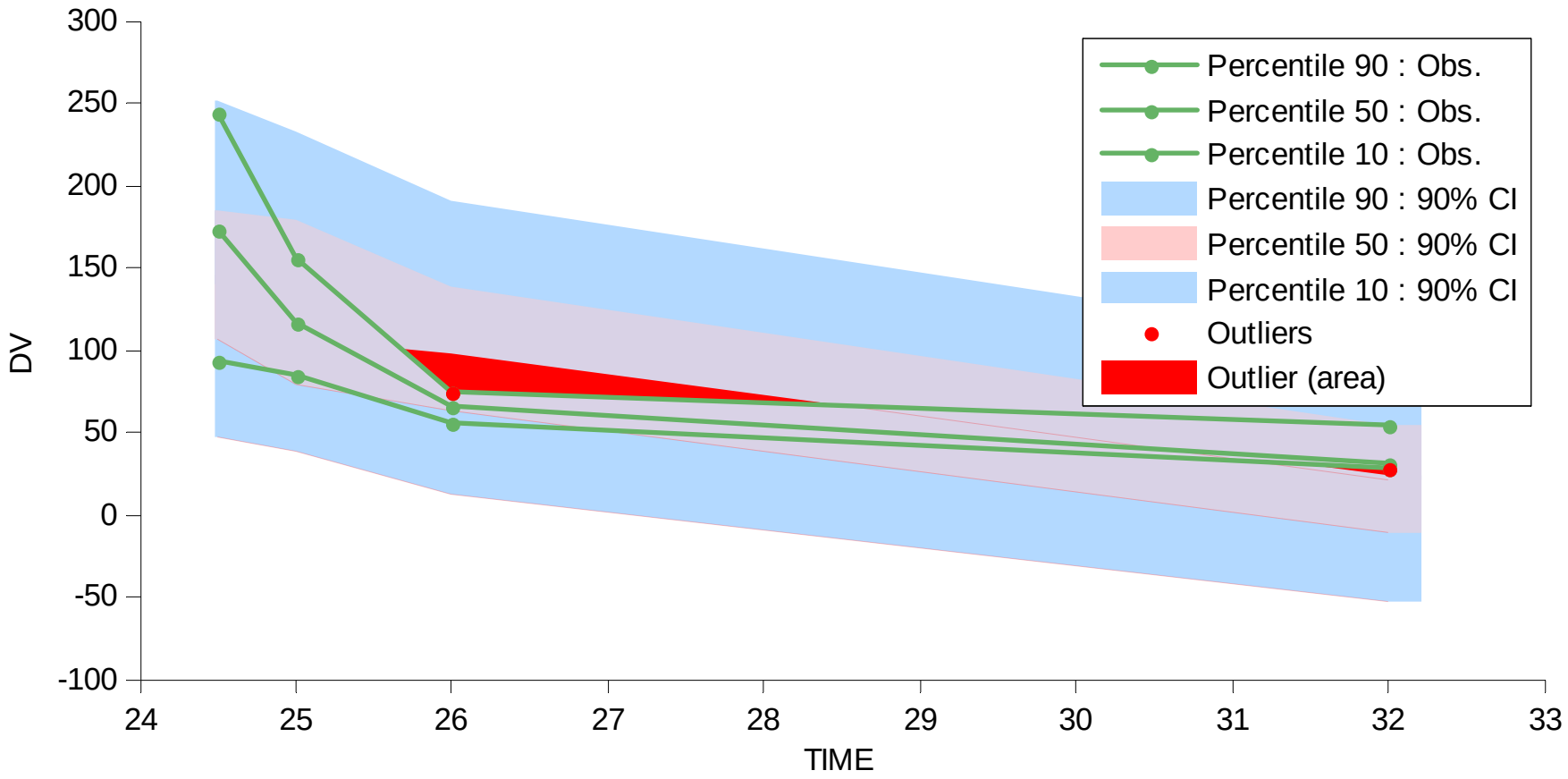


* not noodles !

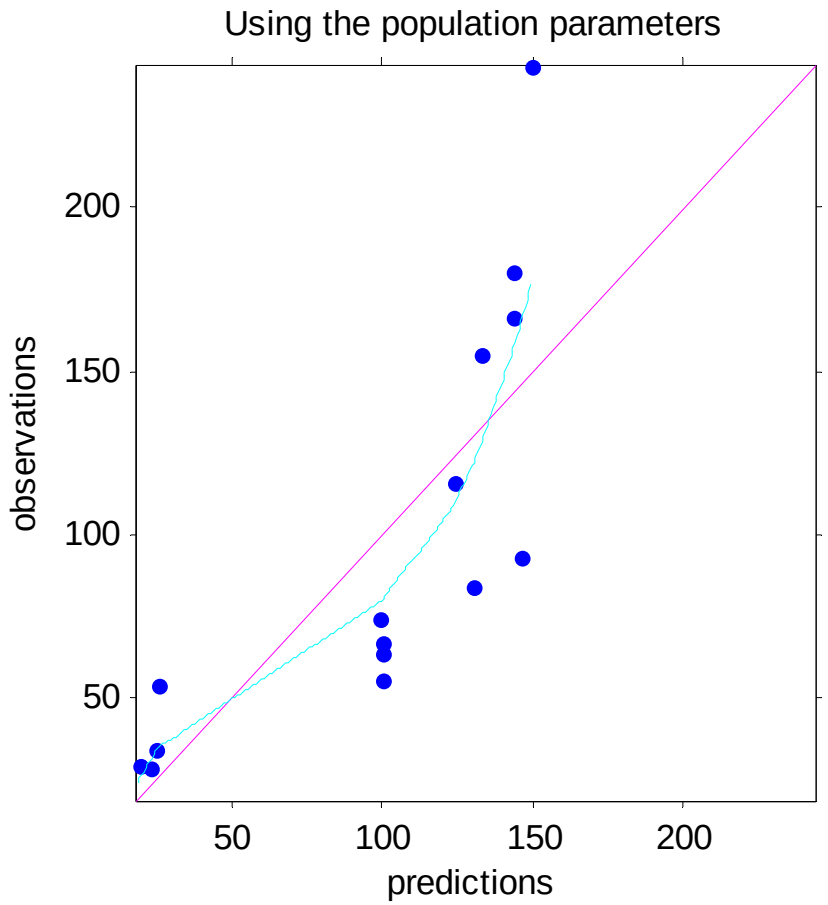
Outputs: population curves

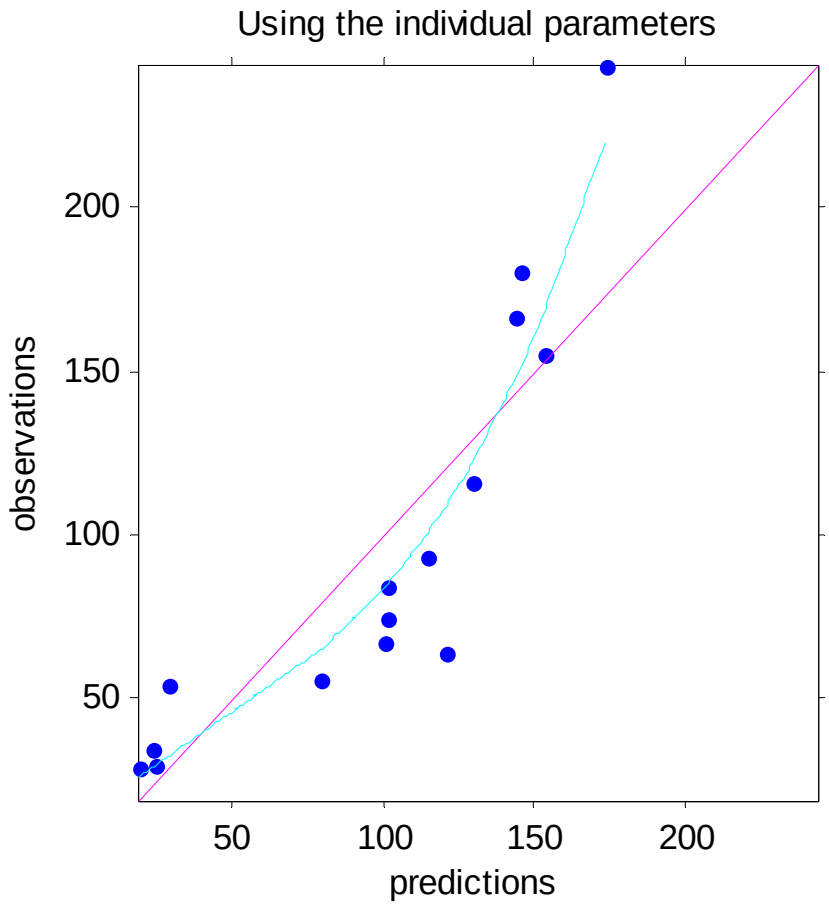


Outputs: population



Outputs: observations vs. predictions





Outputs: residuals