PK-PD analysis and modelling

Why modelling ? (*)

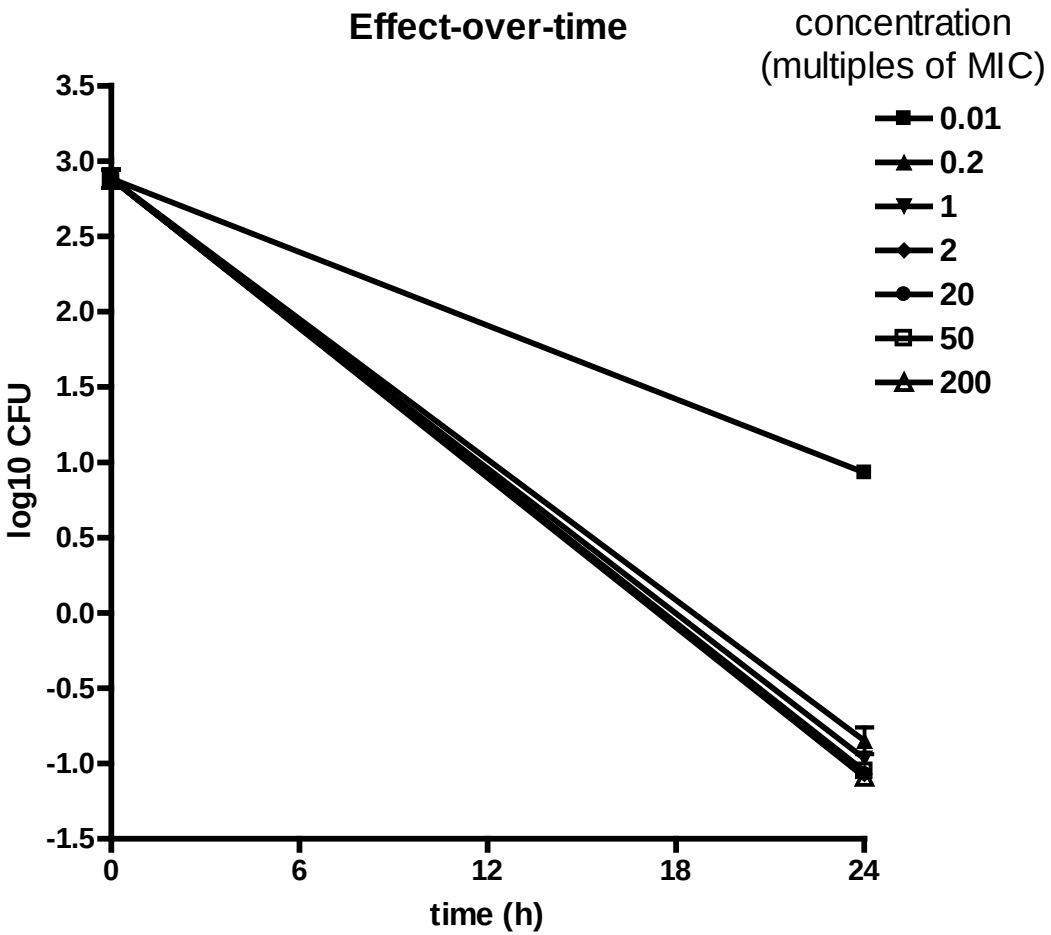
- to move from mere description to underlying phenomena…
  - nature can often be better explained in terms of equations than mere description
  - this has been essential in physics (think about gravity law, radioactive decay, study of electromagnetic field and optics, … up to the equivalence of mass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

*** CAUTION: modelling in UK English but modeling in US English …**

In vitro studies

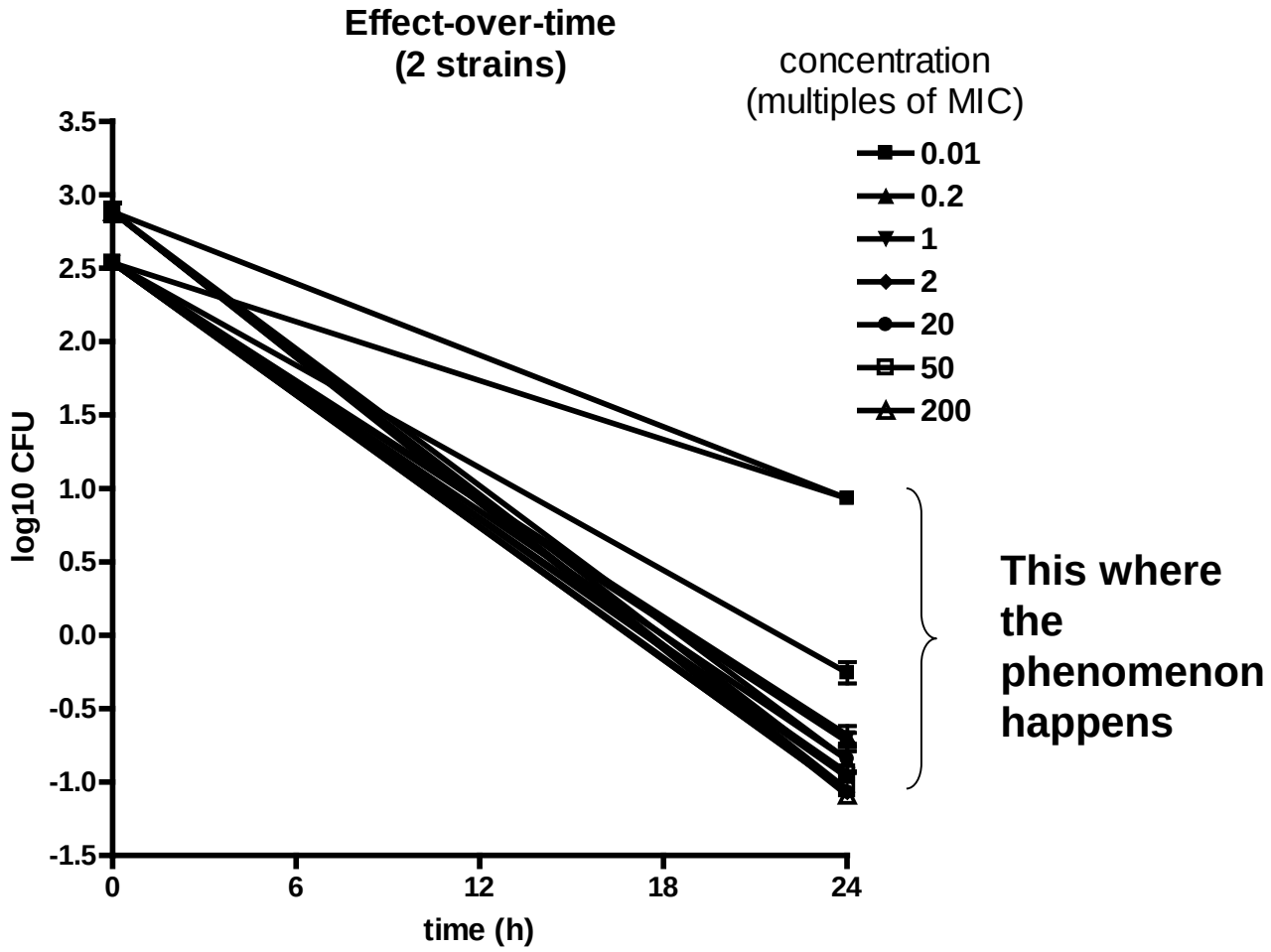
Response to an antimicrobial

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



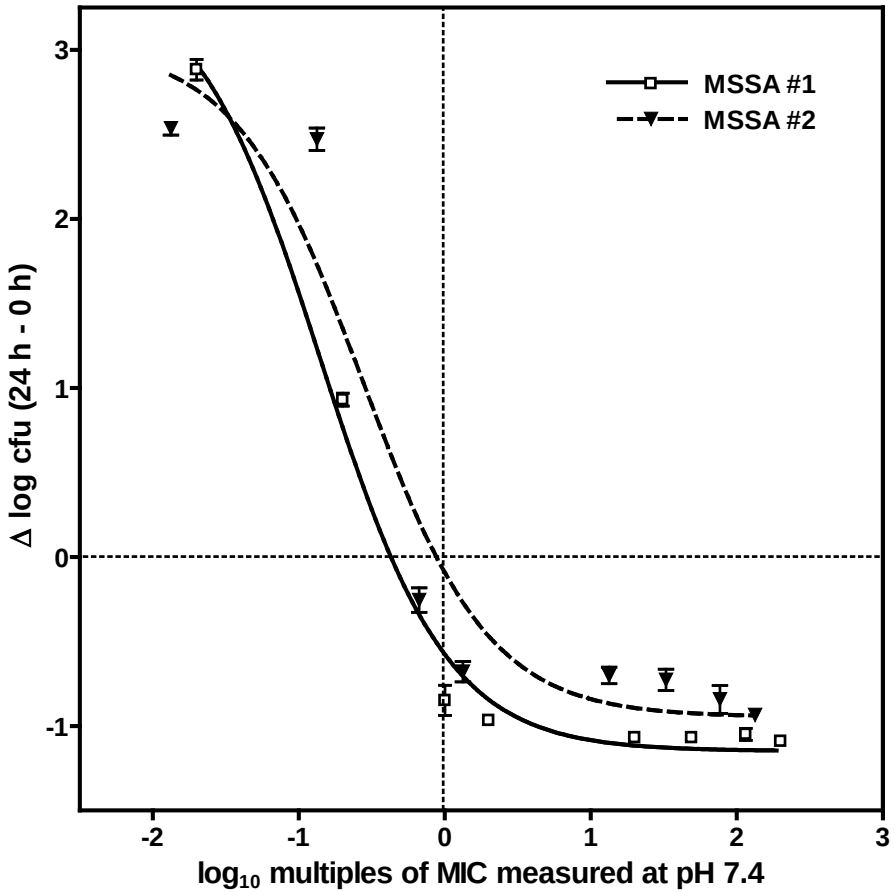
Response to an antimicrobial

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



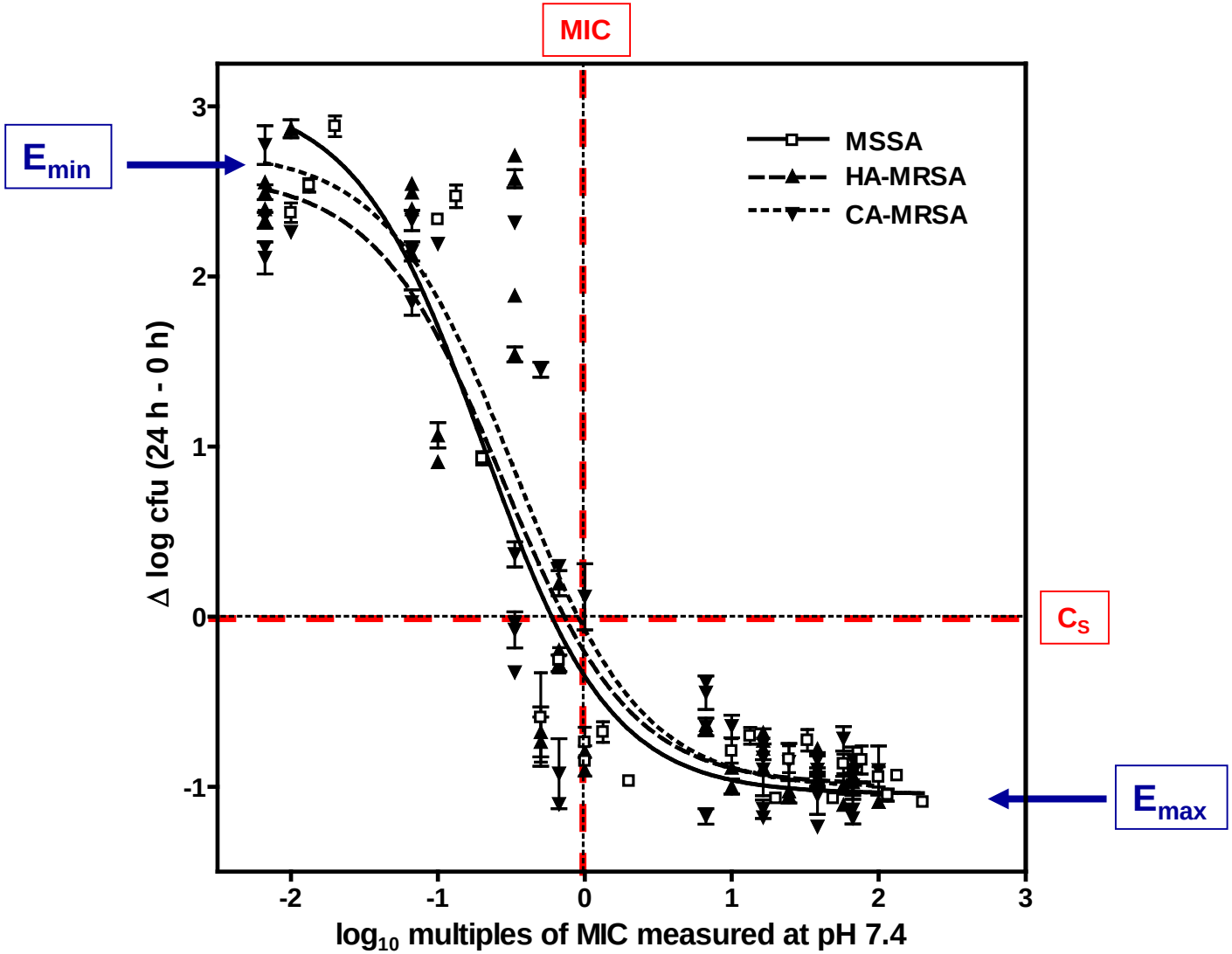
Response to an antimicrobial: the model

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

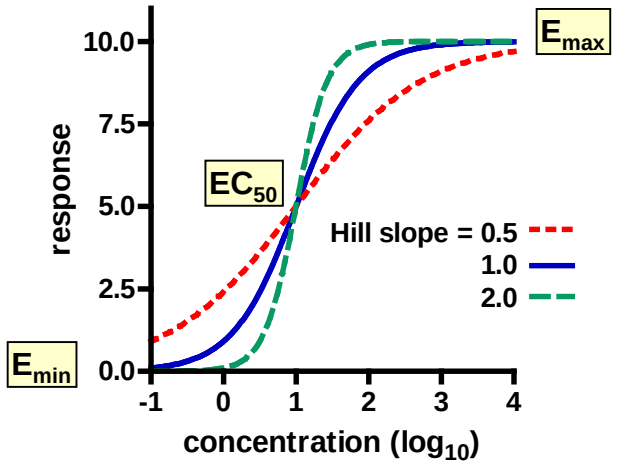
Sigmoidal dose-response:

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

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

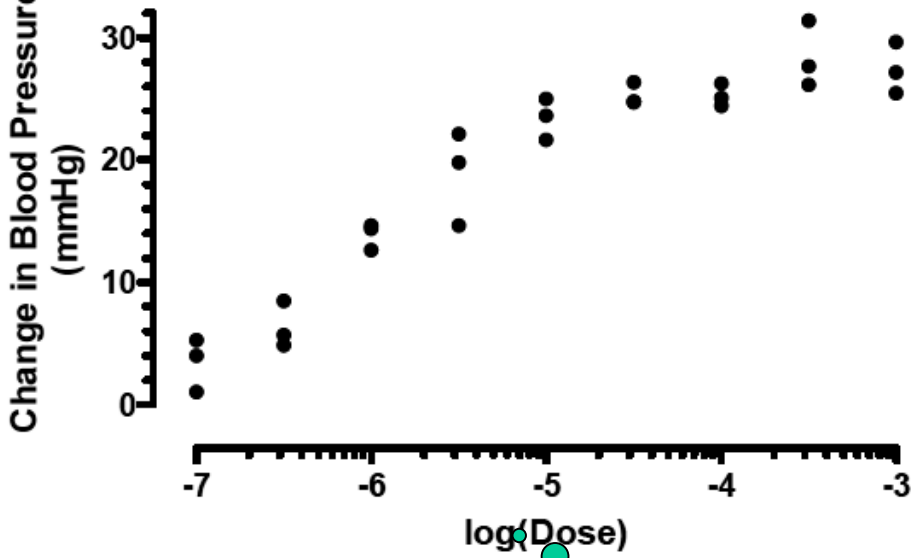
	MSSA	HA-MRSA	CA-MRSA
	Y	Y	Y
Sigmoidal dose-response			
Best-fit values			
BOTTOM	-1.042	-0.9878	-1.006
TOP	3.063	2.596	2.741
LOGEC50	-0.6931	-0.5582	-0.4805
EC50	0.2027	0.2766	0.3307
Std. Error			
BOTTOM	0.1109	0.1087	0.1346
TOP	0.2756	0.2025	0.2325
LOGEC50	0.1134	0.1069	0.1148
95% Confidence Intervals			
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

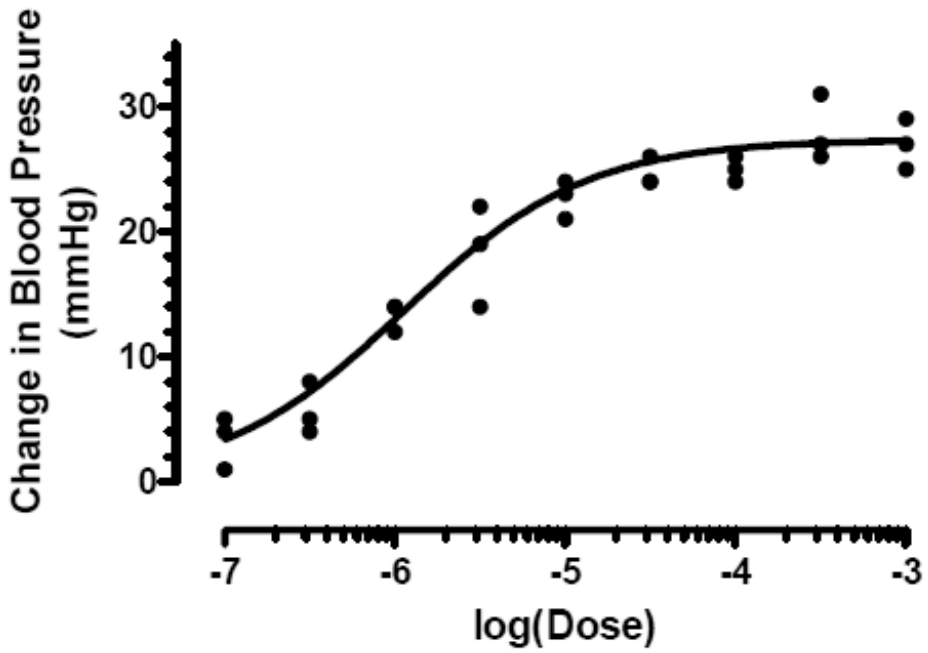
Harvey Motulsky & Arthur Christopoulos



how would you fit those data

Do not forget to use the appropriate axes !

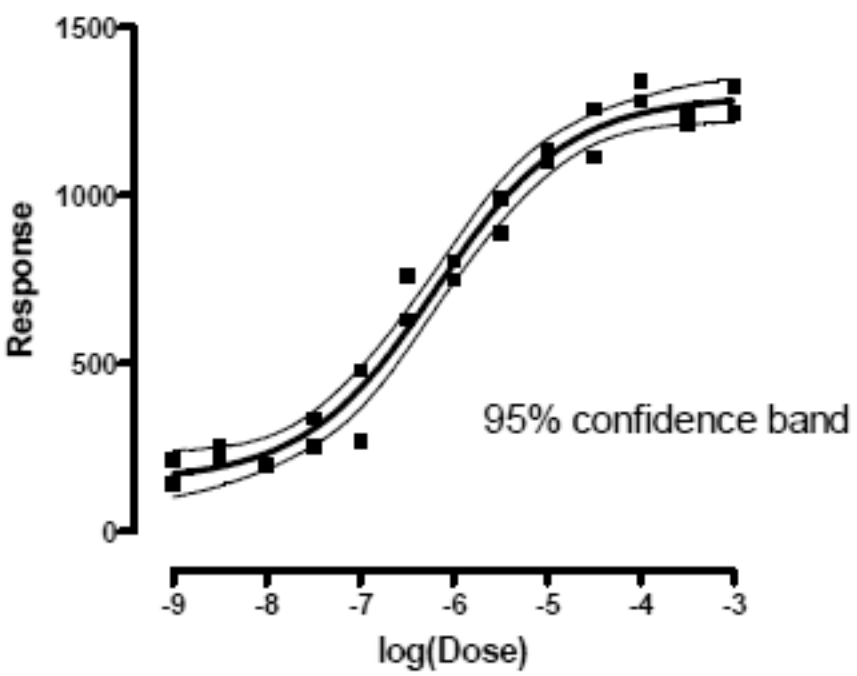
Type of functions

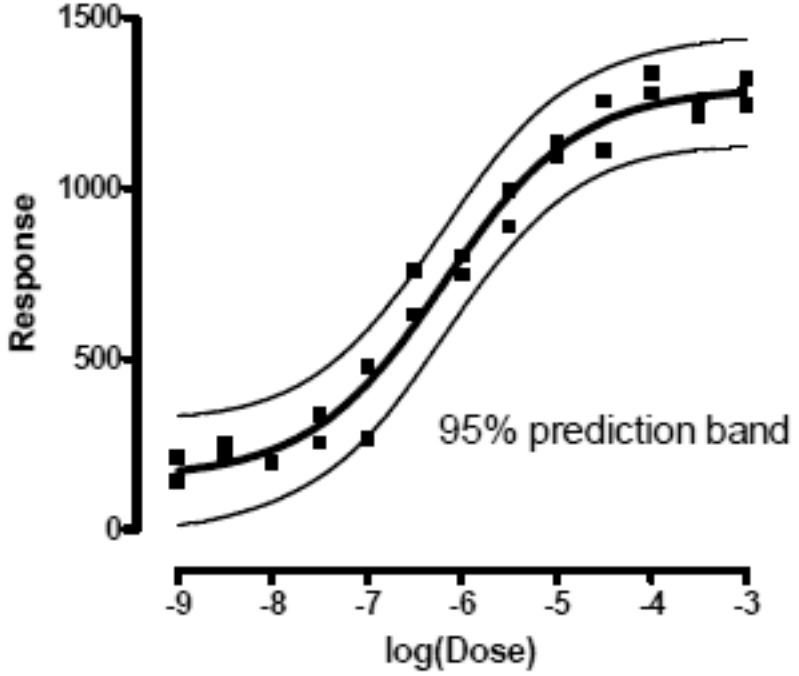


Best-fit values	
BOTTOM	0.0
TOP	27.36
LOGEC50	-5.946
HILLSLOPE	0.8078
EC50	1.1323e-006
Std. Error	
TOP	0.7377
LOGEC50	0.06859
HILLSLOPE	0.09351
95% Confidence Intervals	
TOP	25.83 to 28.88
LOGEC50	-6.088 to -5.804
HILLSLOPE	0.6148 to 1.001
EC50	8.1733e-007 to 1.5688e-006
Goodness of Fit	
Degrees of Freedom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

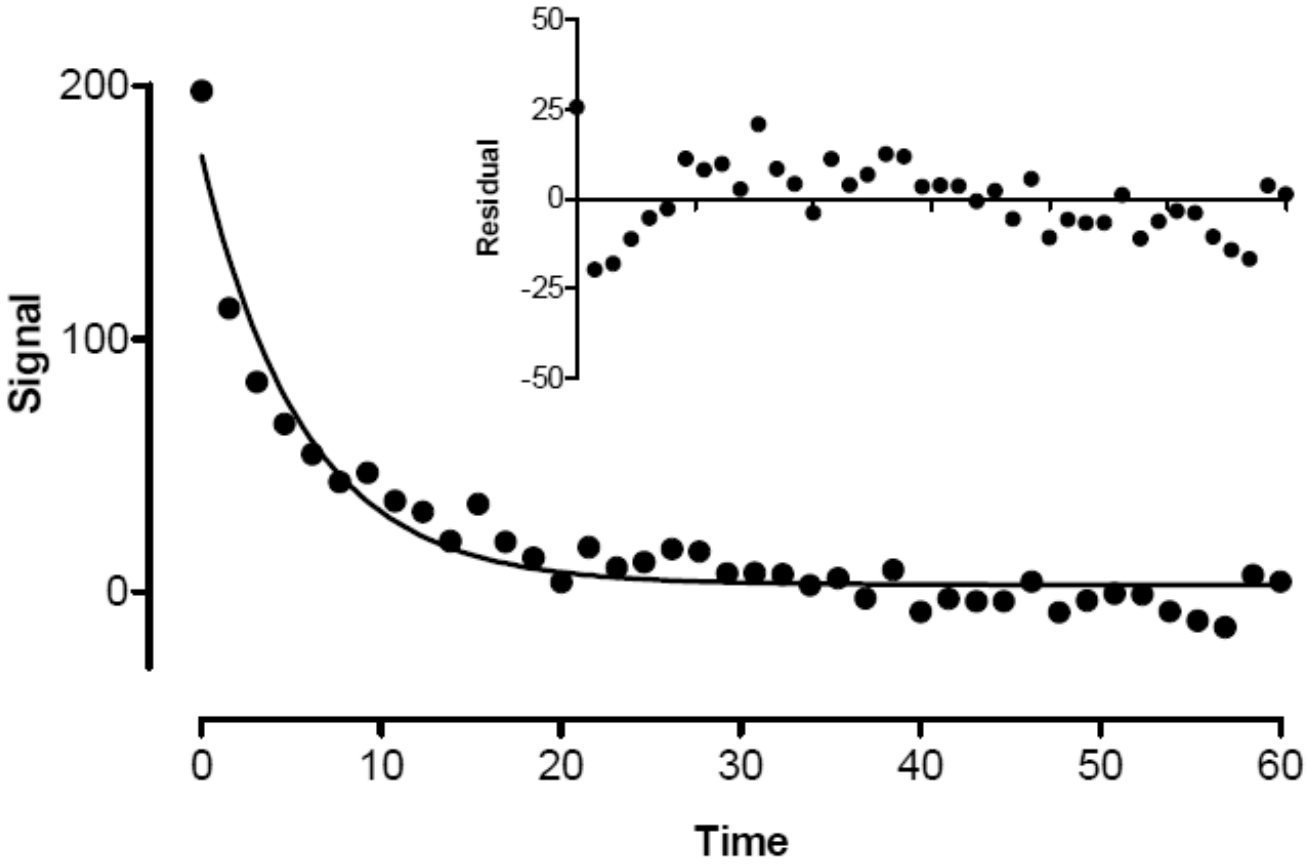
This would be a good model

Run statistics



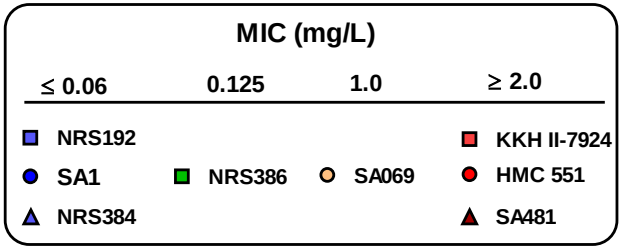


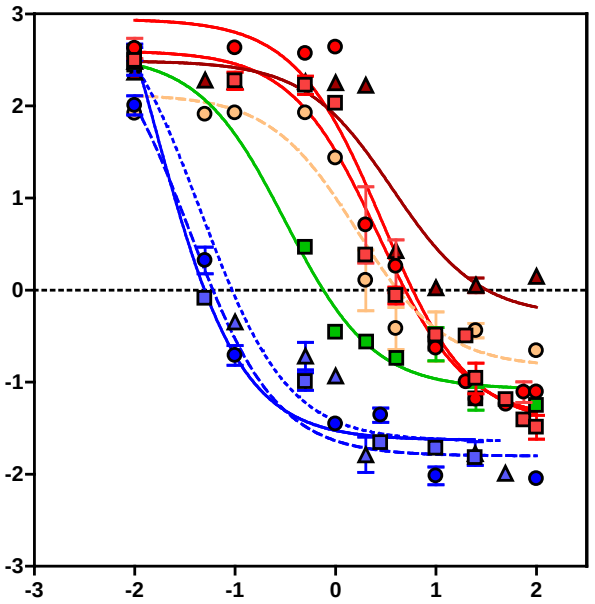
Run tests



Two examples

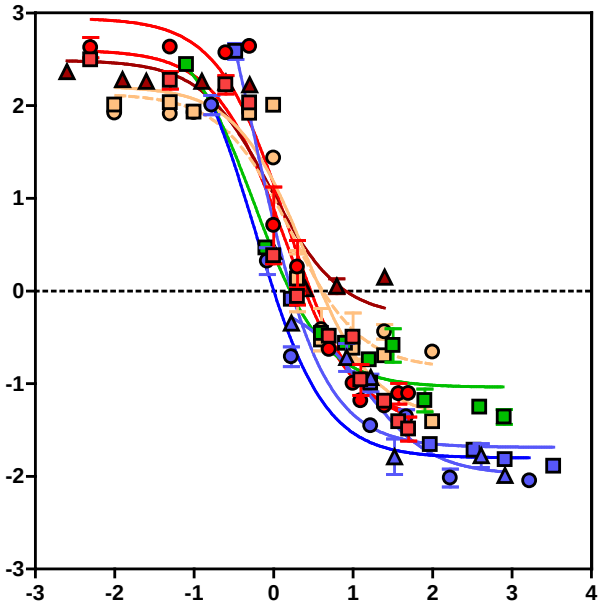
Impact of MIC on the response of intracellular bacteria to moxifloxacin





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

after normalization for MIC



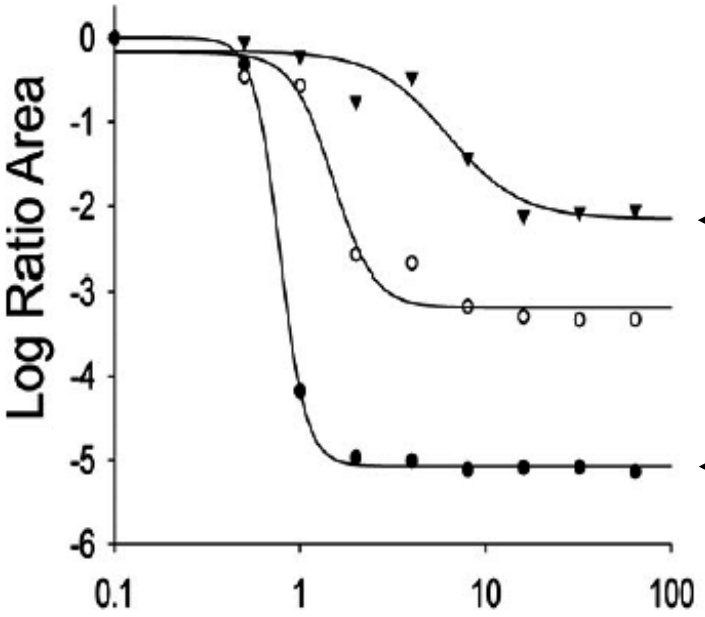
$\log_{10}$ extracellular concentration (x MIC)

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

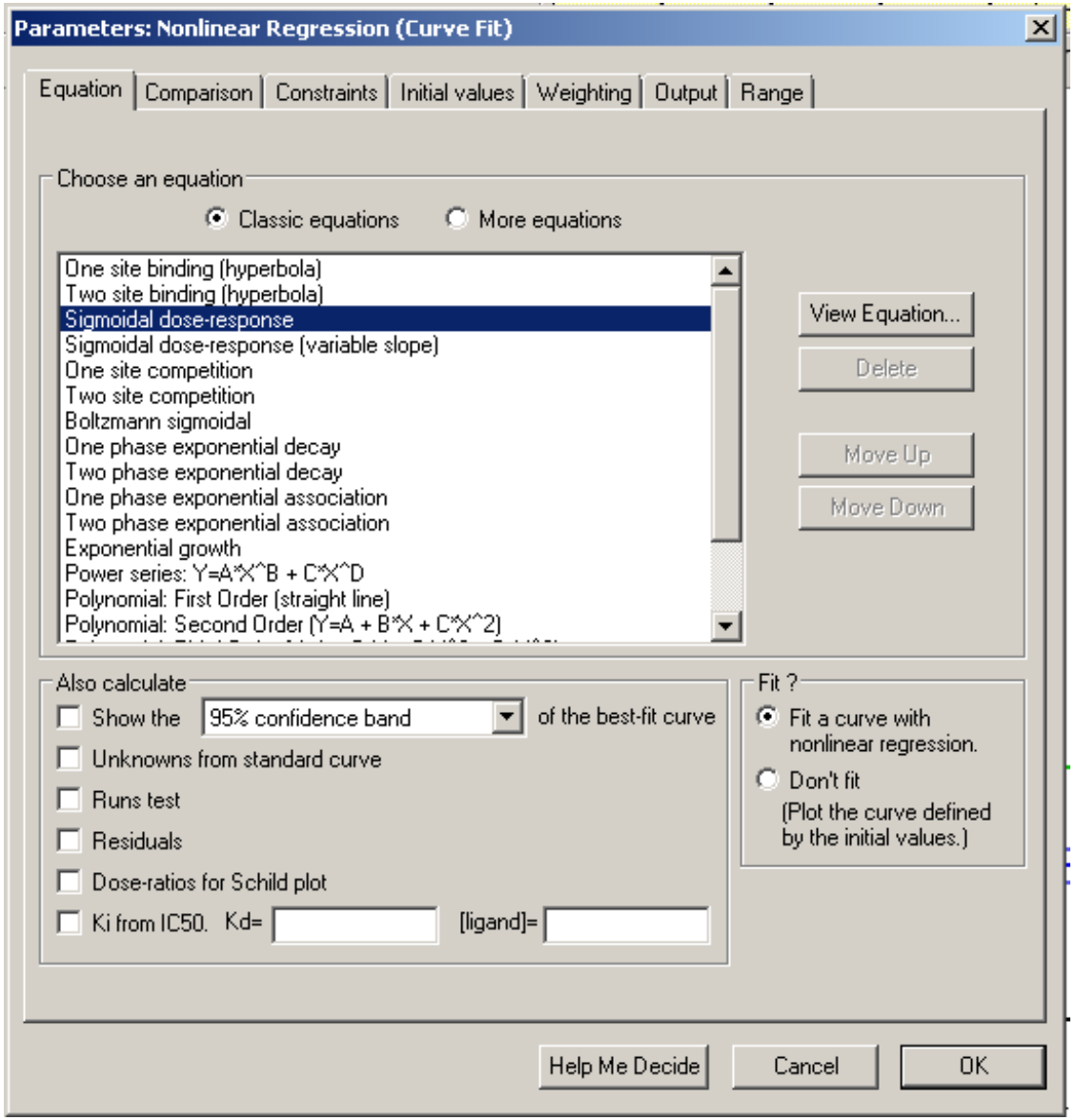


high inoculum (~ *in vivo*

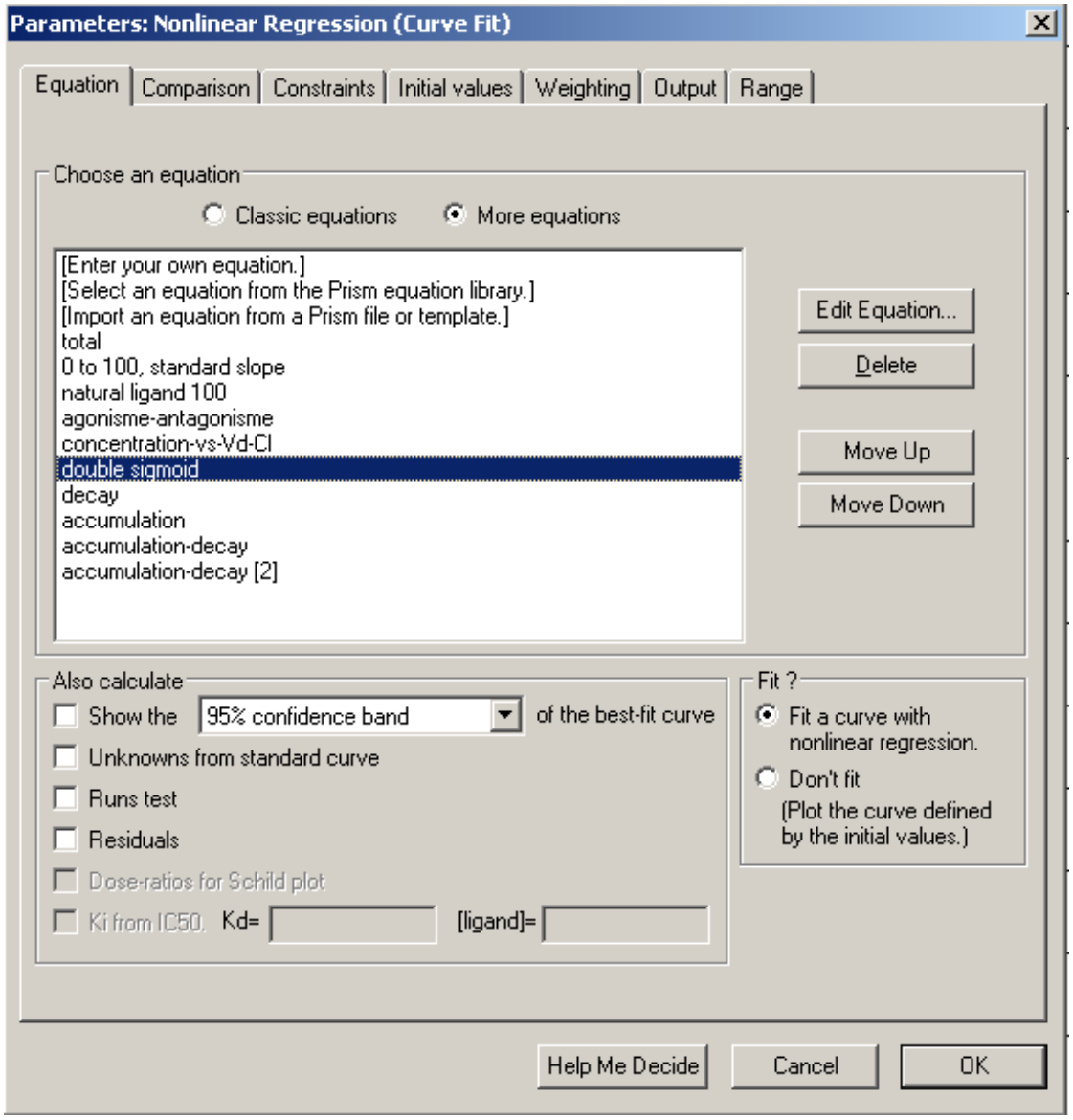
low inoculum (~ *in vitro* testing)

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

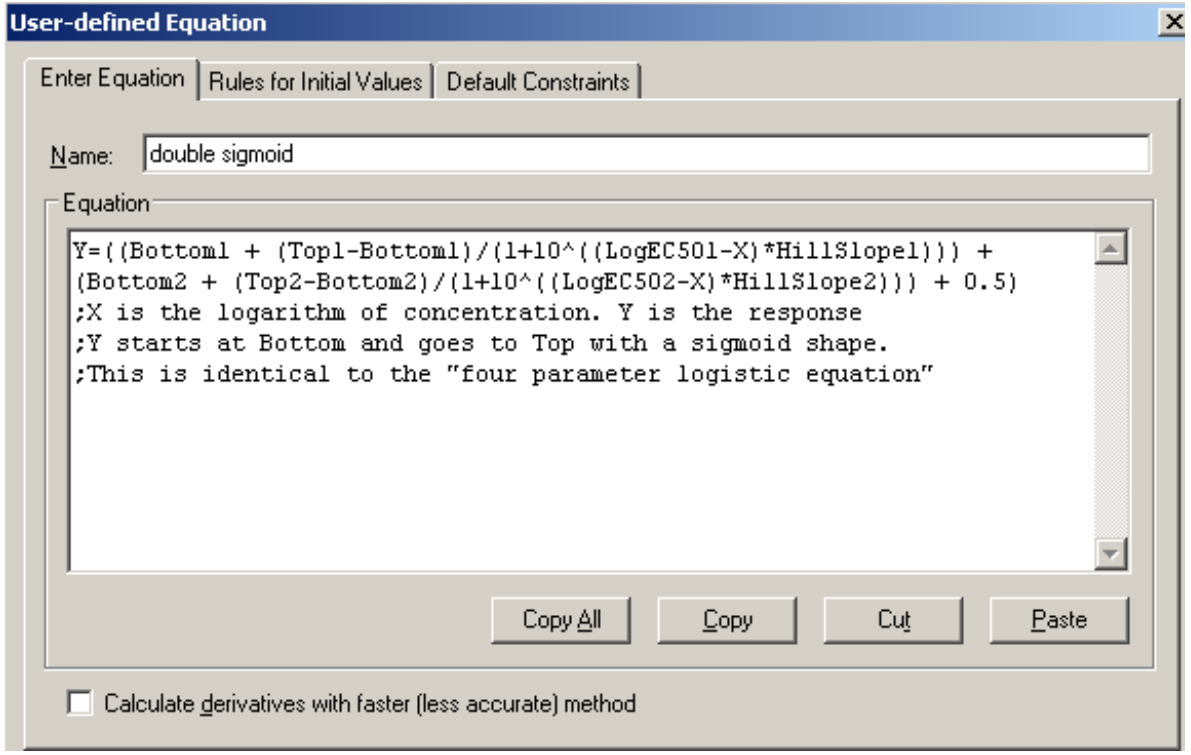
In search of models with Prism



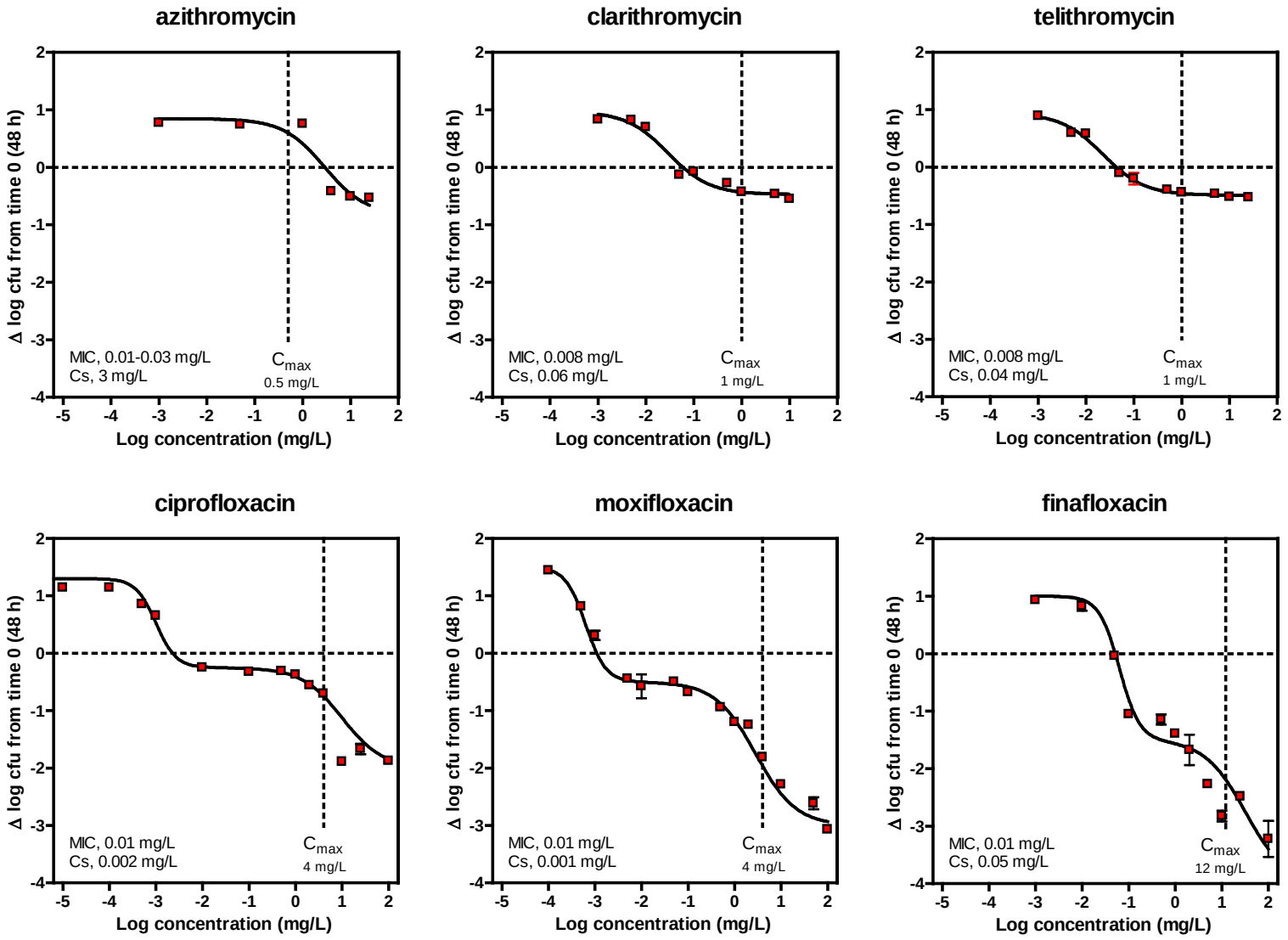
In search of models (including your own)



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**

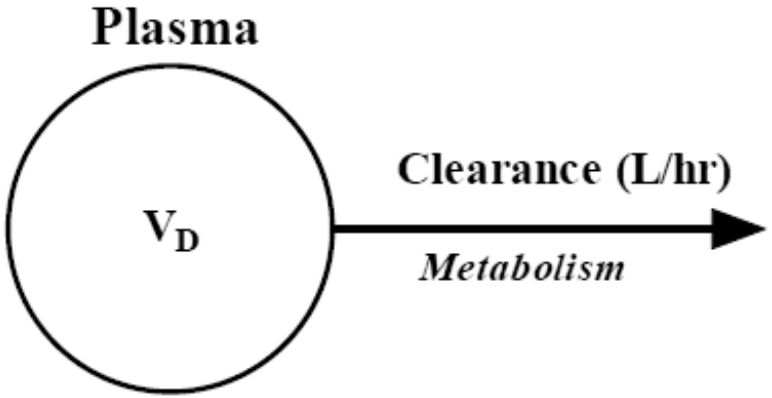
  The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and first-order kinetic elimination

  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.

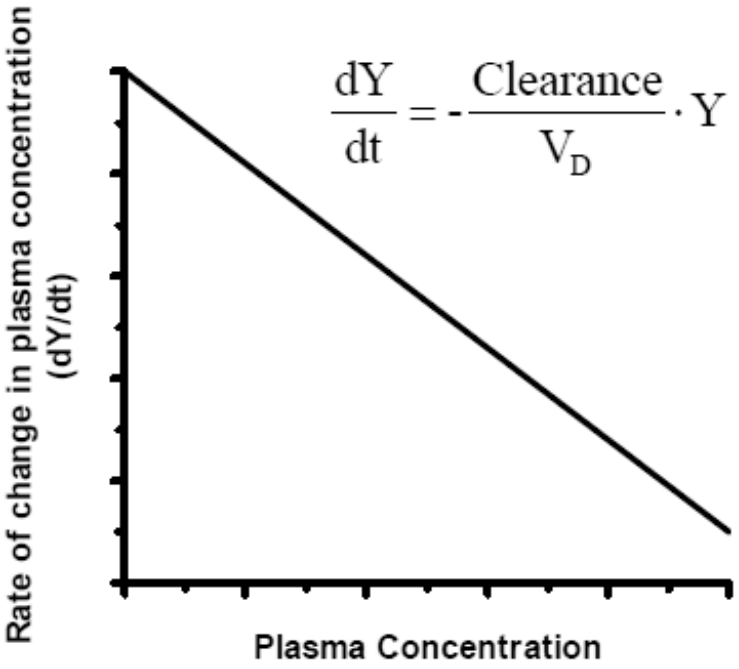
  This requires "high capacity" software that is often impossible to use without serious introduction

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)

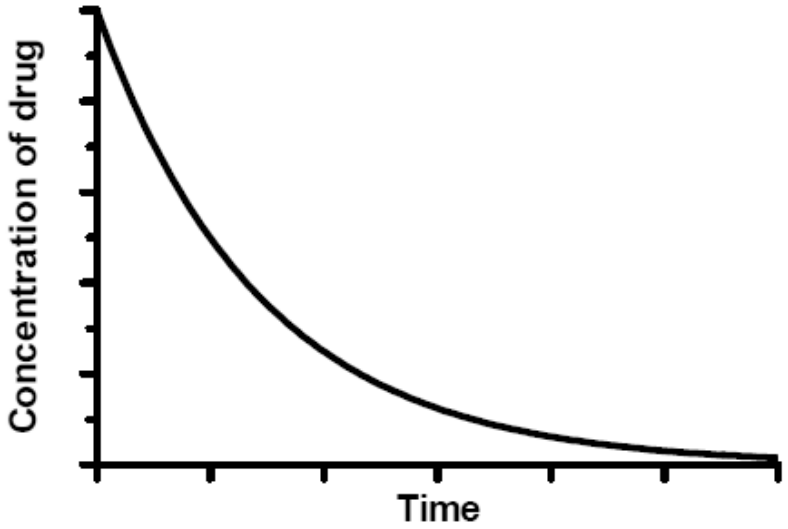
Integrating a differential equation

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:

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

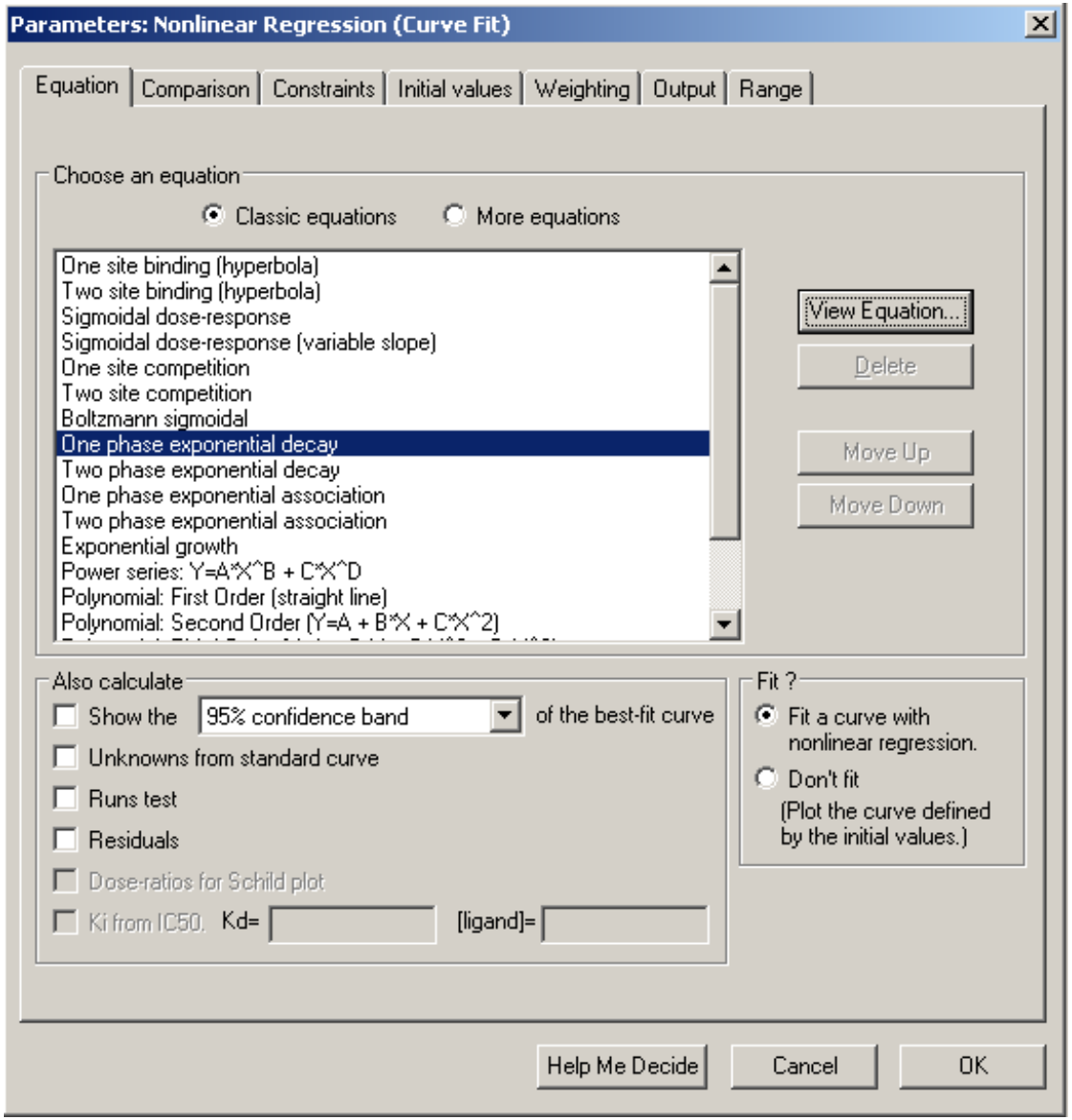


From model to data and finding "best parameters" with a computer (curve fitting)

- 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

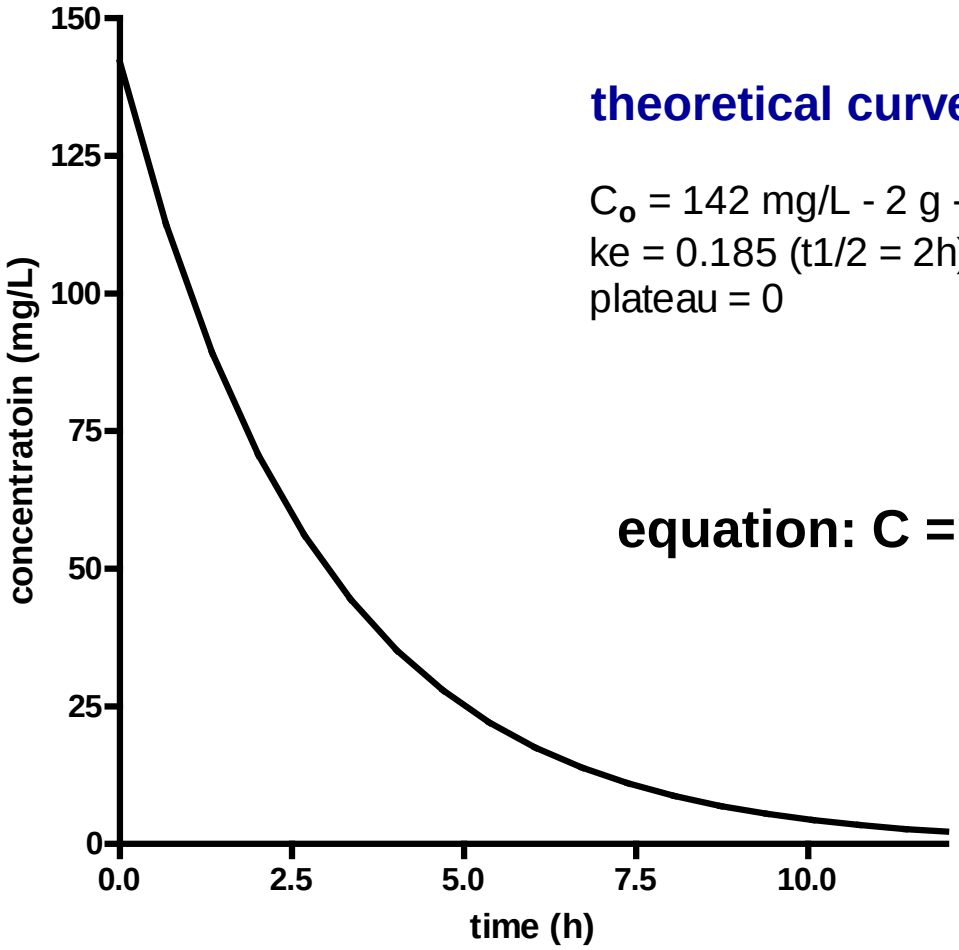
} **numerical integration**

From data to model with a computer (no calculus)



Example of monocopartmental analysis … (*)

Exponential-decay (1 compartment)



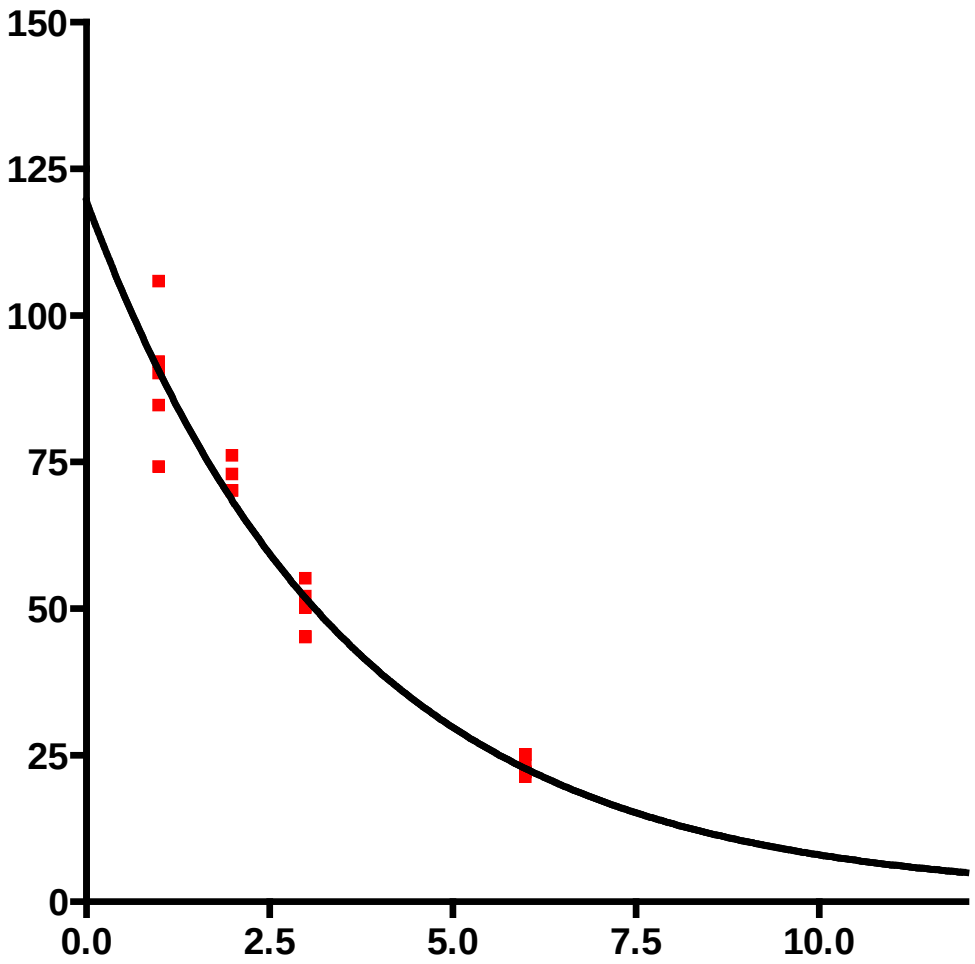
theoretical curve

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

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

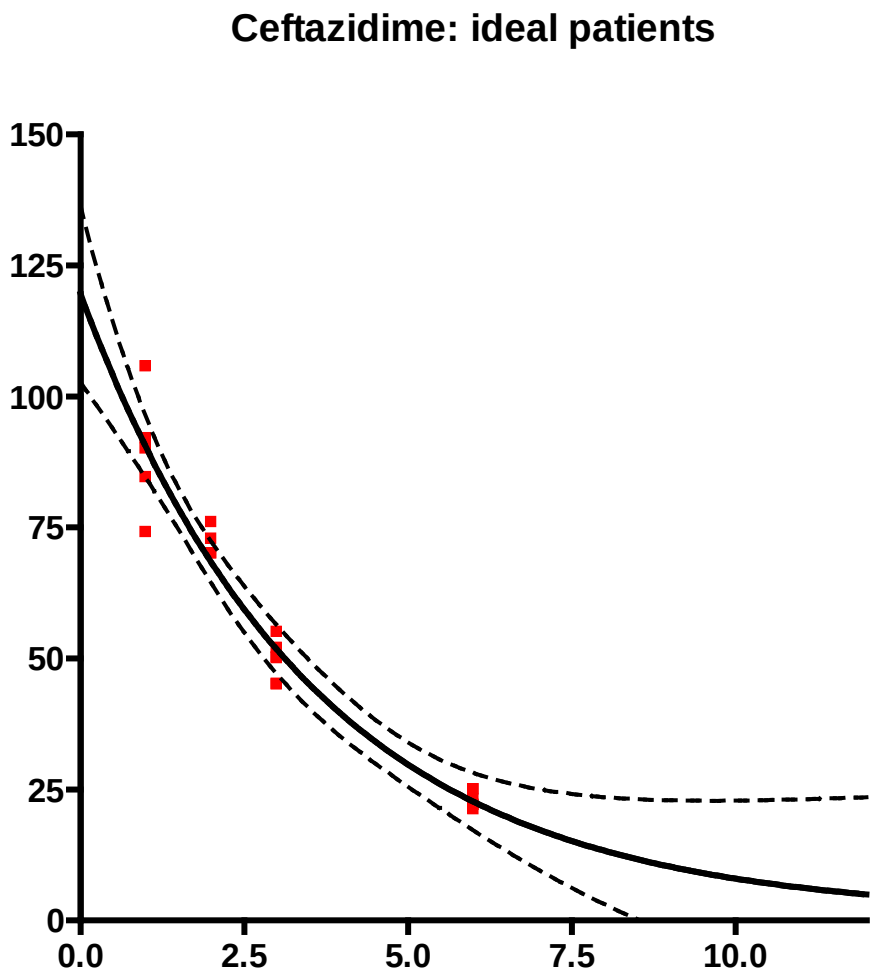
*** this analysis and the following ones concern ceftazidime IV**

Fitting to ideal population data (*)

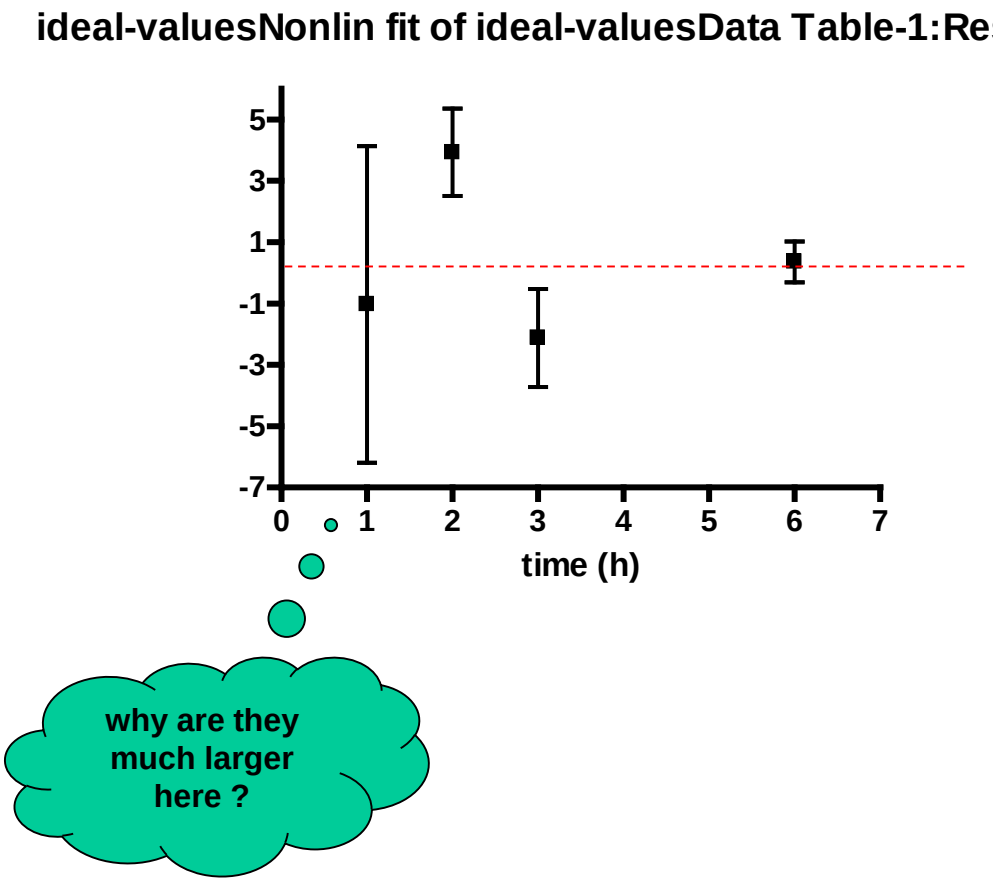


* data from a few volunteers

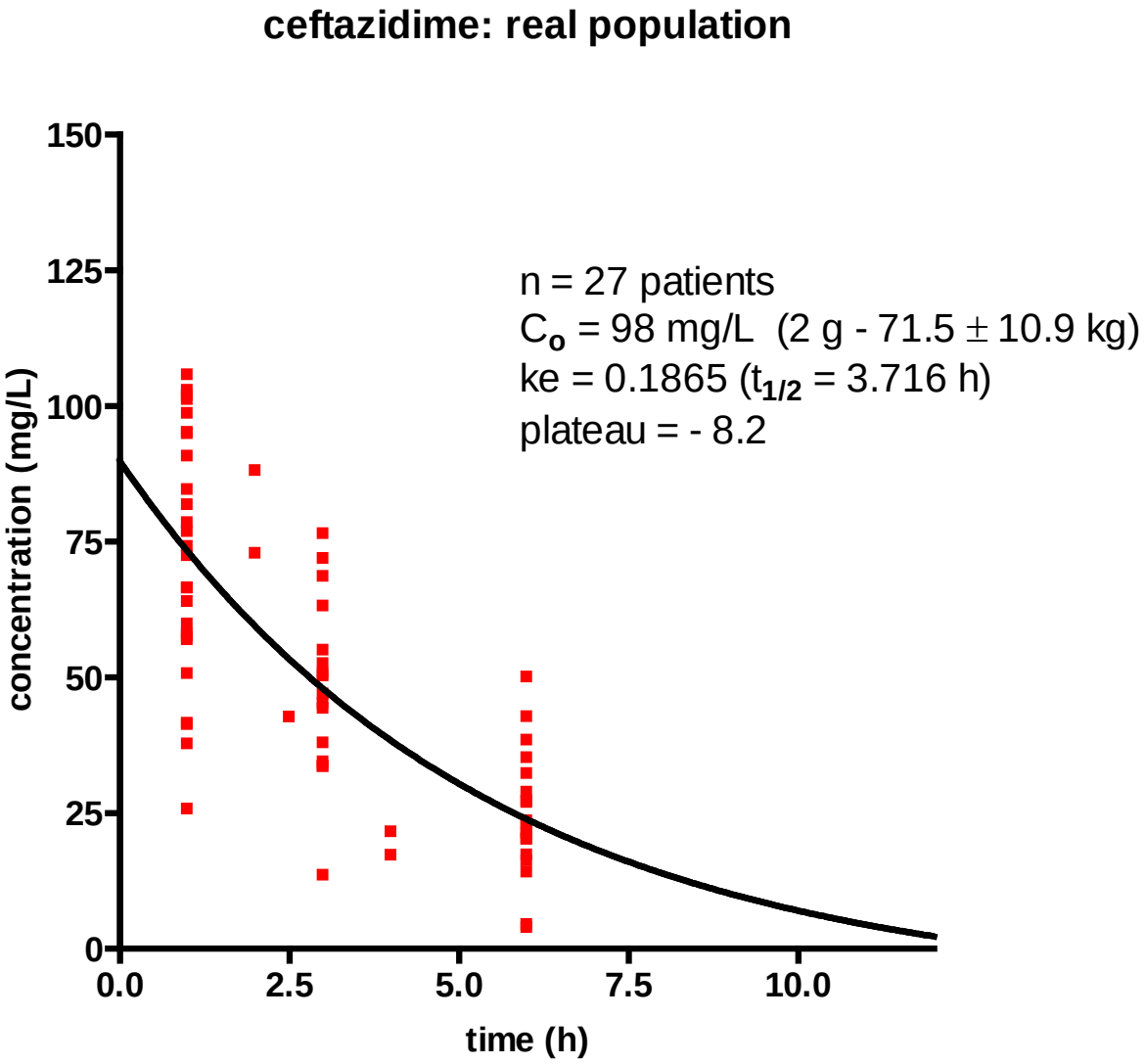
Ideal population: tests for 95 % CI



Ideal population: residuals

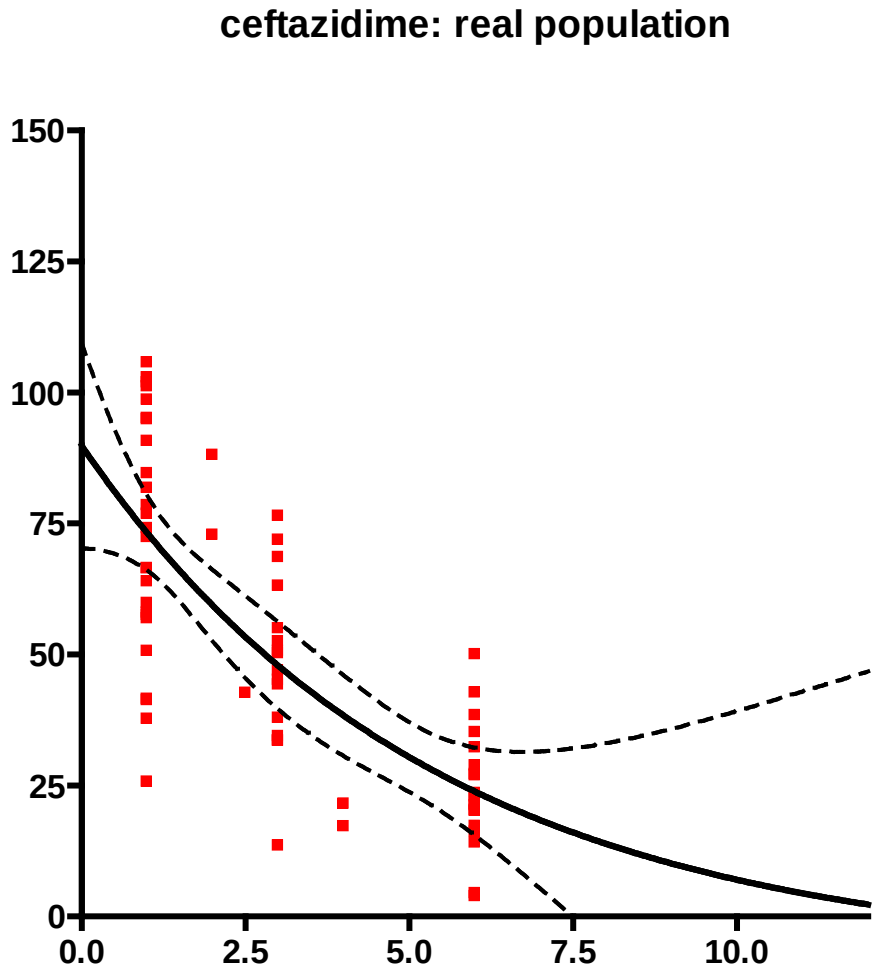


Real population (*)

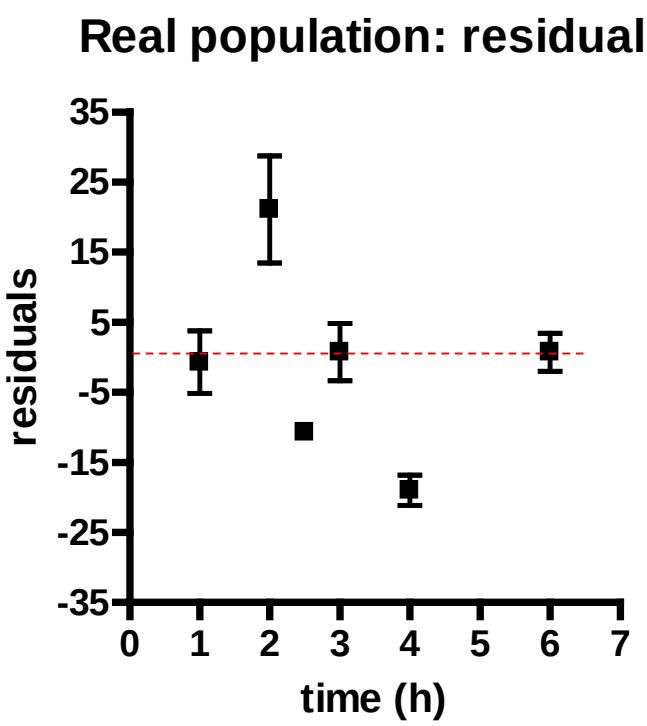


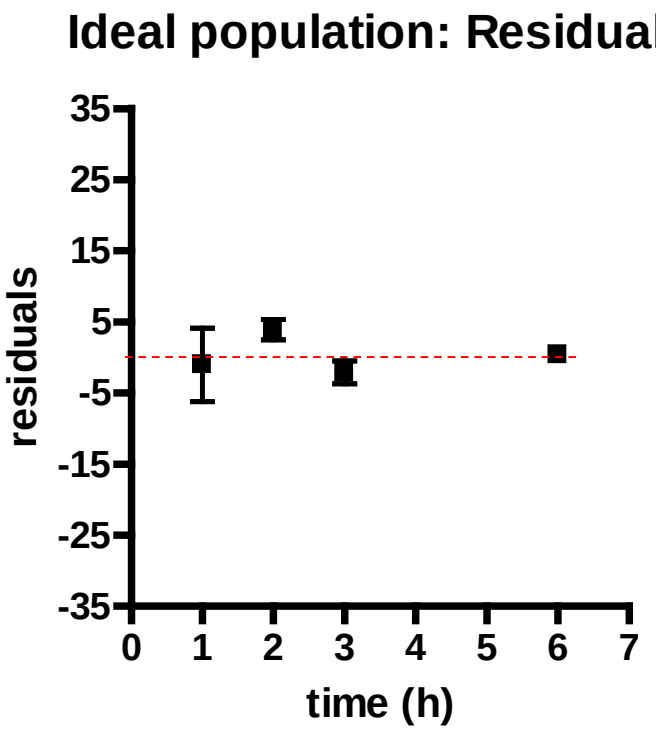
*** data from several patients**

Real population: 95 % CI



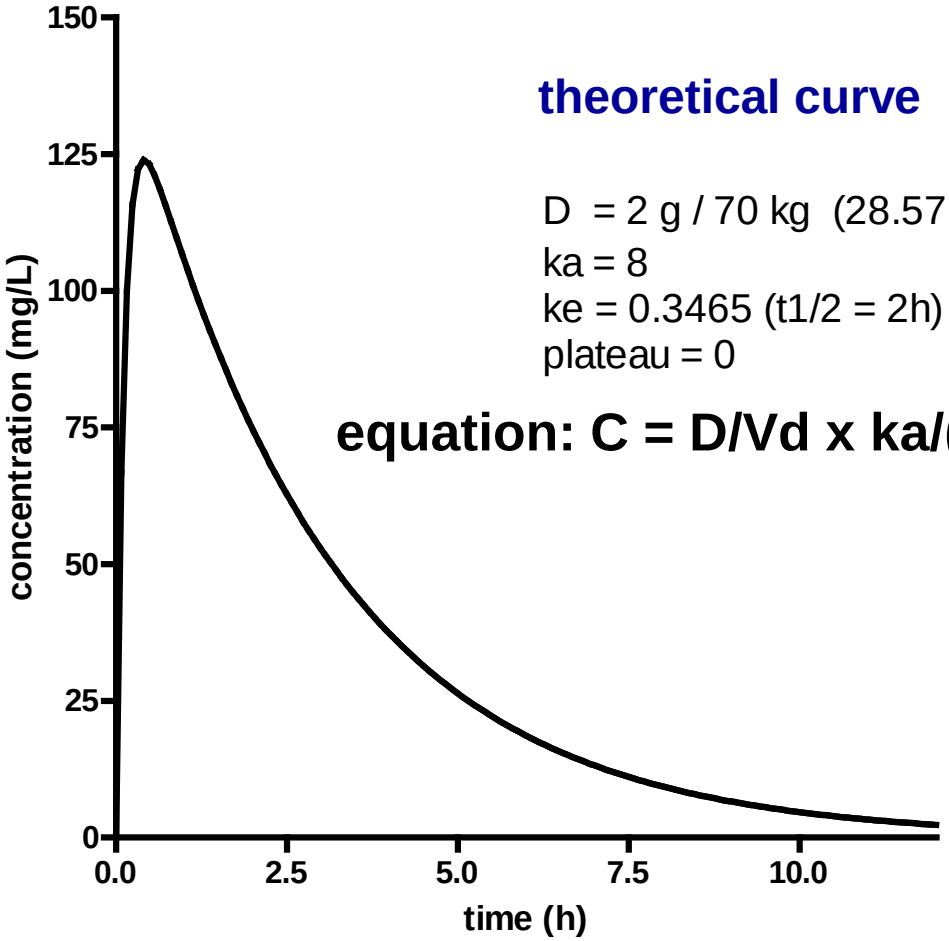
Real population: residuals





More complex models: accumulation / decay

Bateman function
(applied to ceftazidime)

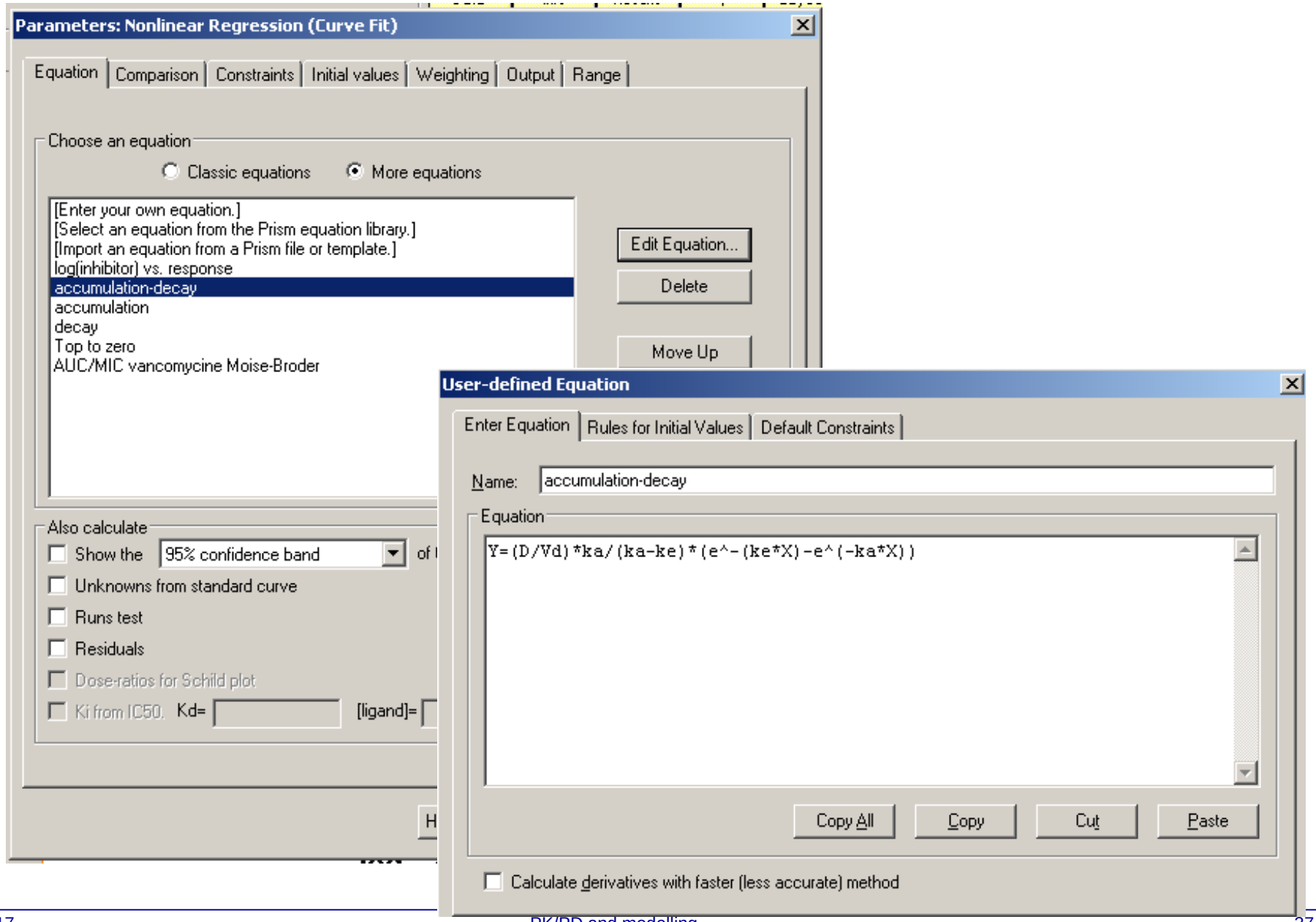


theoretical curve

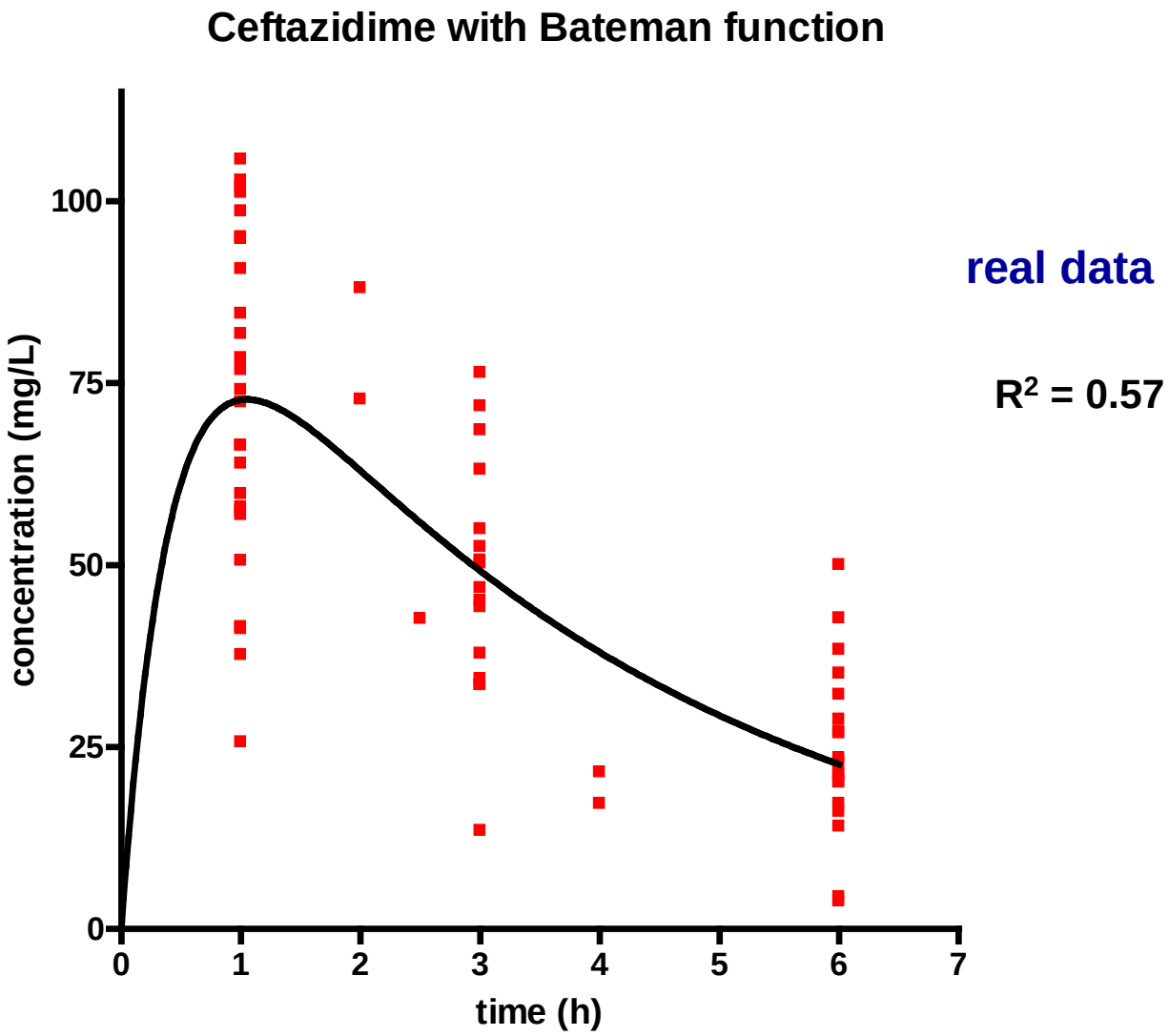
D = 2 g / 70 kg (28.57 mg/kg) - V_d = 0.2 L/kg
ka = 8
ke = 0.3465 (t1/2 = 2h)
plateau = 0

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

In search of more complex models with Prism

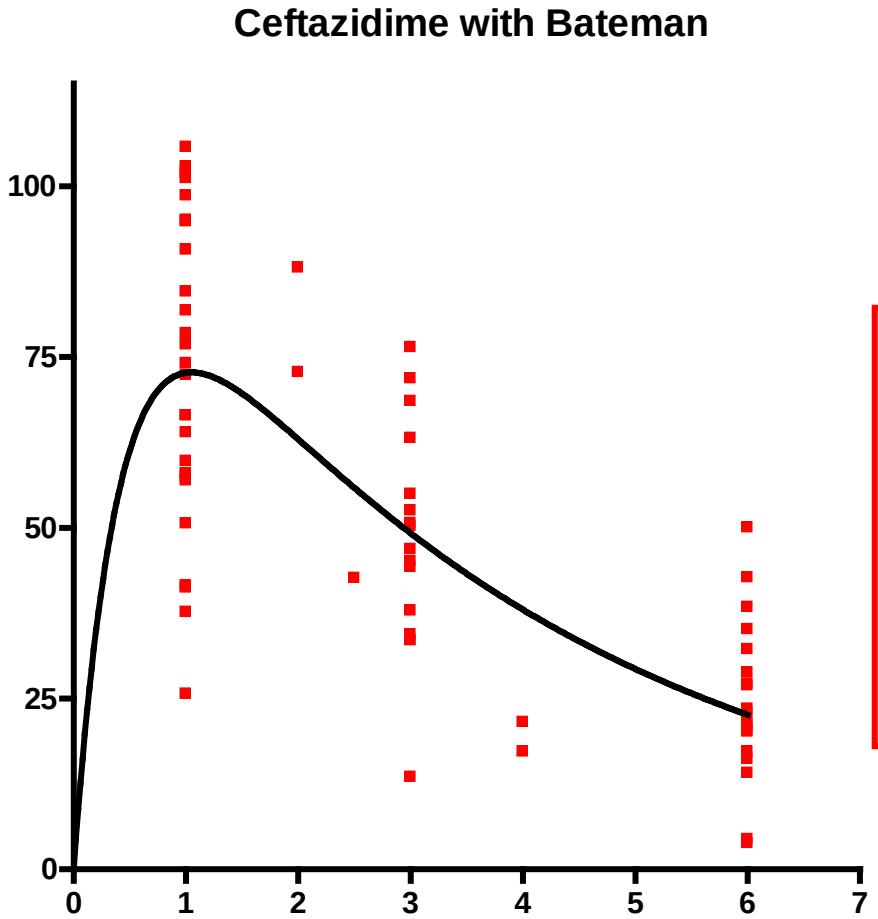


Accumulation / decay with Prism … (*)



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

Examples d'analyse monocompartimentale … (*)



Prism has a problem here !

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

When the data become really too complex…

The Mixed non-lin approaches

- A **mixed model** is a statistical model containing both fixed effects and random effects.
- These models are useful in a wide variety of disciplines in the physical, biological and social sciences.
- They are particularly useful in settings where repeated measurements are made on the same statistical units (longitudinal study), or where measurements are made on clusters of related statistical units.
- Because of their advantage in dealing with missing values, mixed effects models are often preferred over more traditional approaches such as repeated measures ANOVA.

The Mixed non-lin approaches

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

Noncompartmental

- Freeware: bear and PK for R
- Commercial: MLAB, EquivTest, Kinetica, MATLAB/SimBiology, Phoenix/WinNonlin, PK Solutions, RapidNCA.

Compartment based

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

Physiologically based

- Freeware: MCSim
- Commercial: acslX, Cloe PK, GastroPlus, MATLAB/SimBiology, PK-Sim, ProcessDB, Simcyp, Entelos PhysioLab Phoenix/WinNonlin, ADME Workbench.

Population PK

- Freeware: WinBUGS, ADAPT, S-ADAPT / SADAPT-TRAN, Boomer, PKBugs, Pmetrics for R.
- Commercial: Kinetica, MATLAB/SimBiology, Monolix[*permanent dead link*], NONMEM, Phoenix/NLME, PopKinetics for SAAM II, USC*PACK, Navigator Workbench.

Simulation

All model based software above.

- Freeware: COPASI, Berkeley Madonna, MEGen.

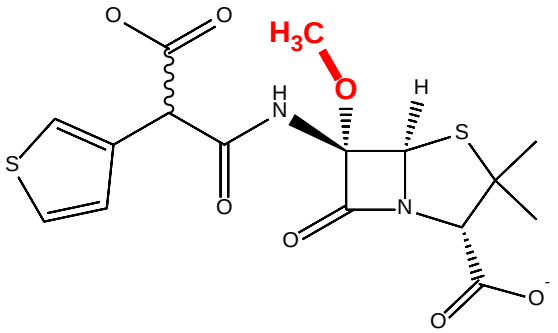
Educational centres [edit]

Global centres with the highest profiles for providing in-depth training include the Universities of Buffalo, Florida, Gothenburg, Leiden, Otago, San Francisco, Beijing, Tokyo, Uppsala, Washington, Manchester, Monash University, and University of Sheffield.[1]

Exemples avec la témocilline

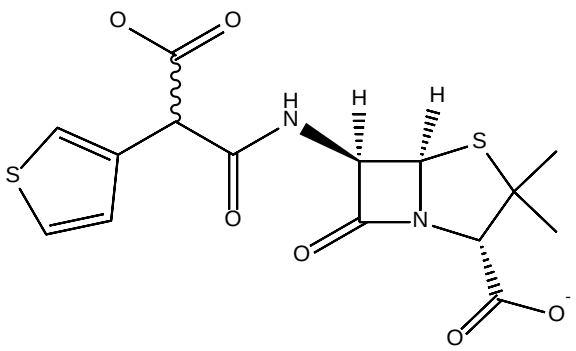
Temocillin in a nutshell

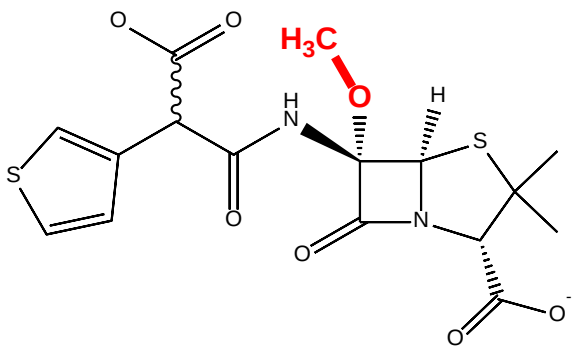
- Temocillin or 6-α-methoxy-ticarcillin
- Registered in 1984 for the first time (Beecham)
- Maintained on the market since 1998 (Eumedica)
  - BE, LU, UK and now FR



- Narrow-spectrum antibiotic (Gram-negative oriented)
  - Enterobacteriaceae
  - *B. cepacia*
  - *Neisseria, Haemophilus, Pasteurella, Legionella*
  - Inactive against most strains of *P. aeruginosa*, *Acinetobacter*, *Stenotrophomonas*,
  - no useful activity against Gram-positive and anaerobes
- Stable to most β-lactamases
  - Class A (including ESBL, KPC), class C (AmpC), class D (OXA-1)
  - Hydrolysed by OXA-48-like (class D) and class B enzymes (metallo-enzymes)

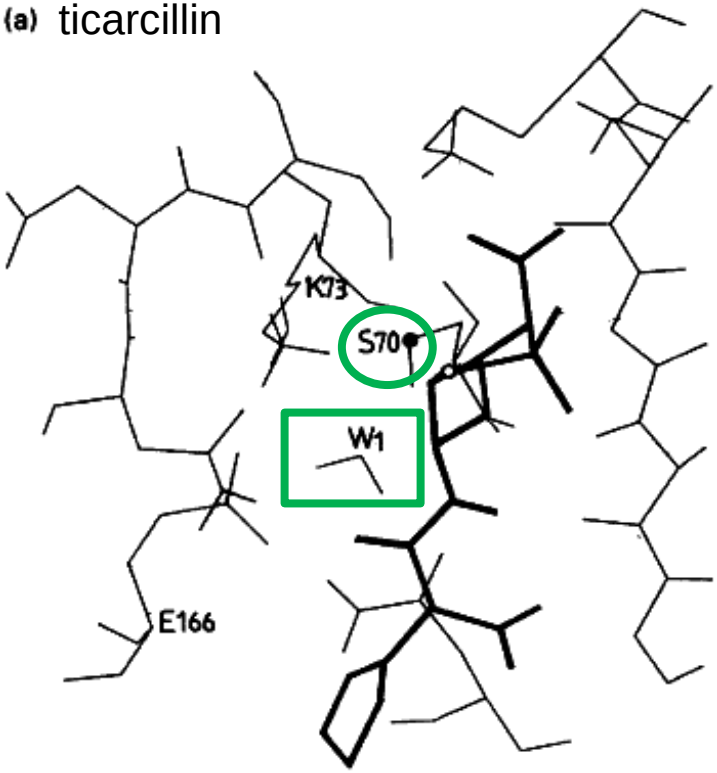
But what if you place the bulky group on the β-lactam ring ?

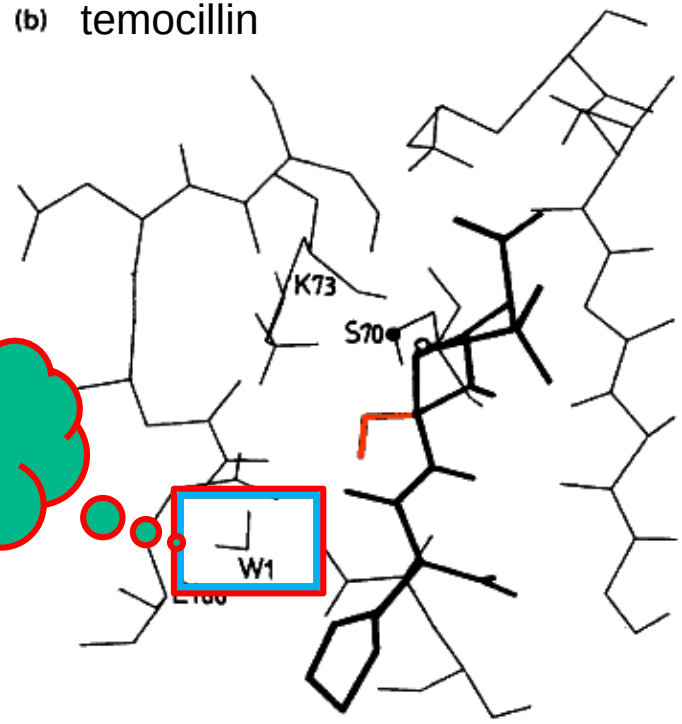




(a) ticarcillin

(b) temocillin

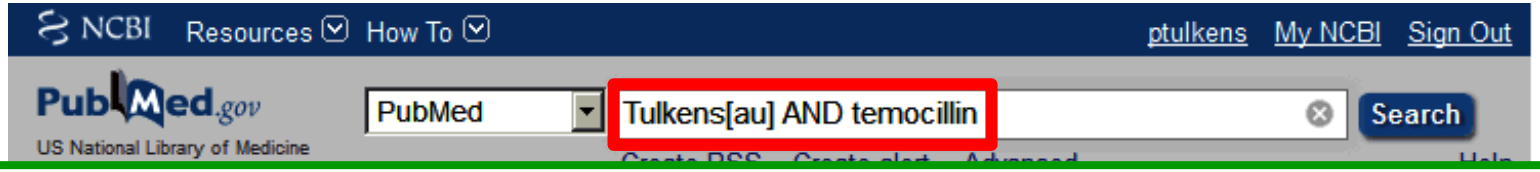




water cannot access…

Matagne et al. Biochem. J. (1993) 293, 607-411

Why me and temocillin ?



Journal of Antimicrobial Chemotherapy (2009) **63**, 243–245
doi:10.1093/jac/dkn511
Advance Access publication 18 December 2008

JAC

Temocillin revived

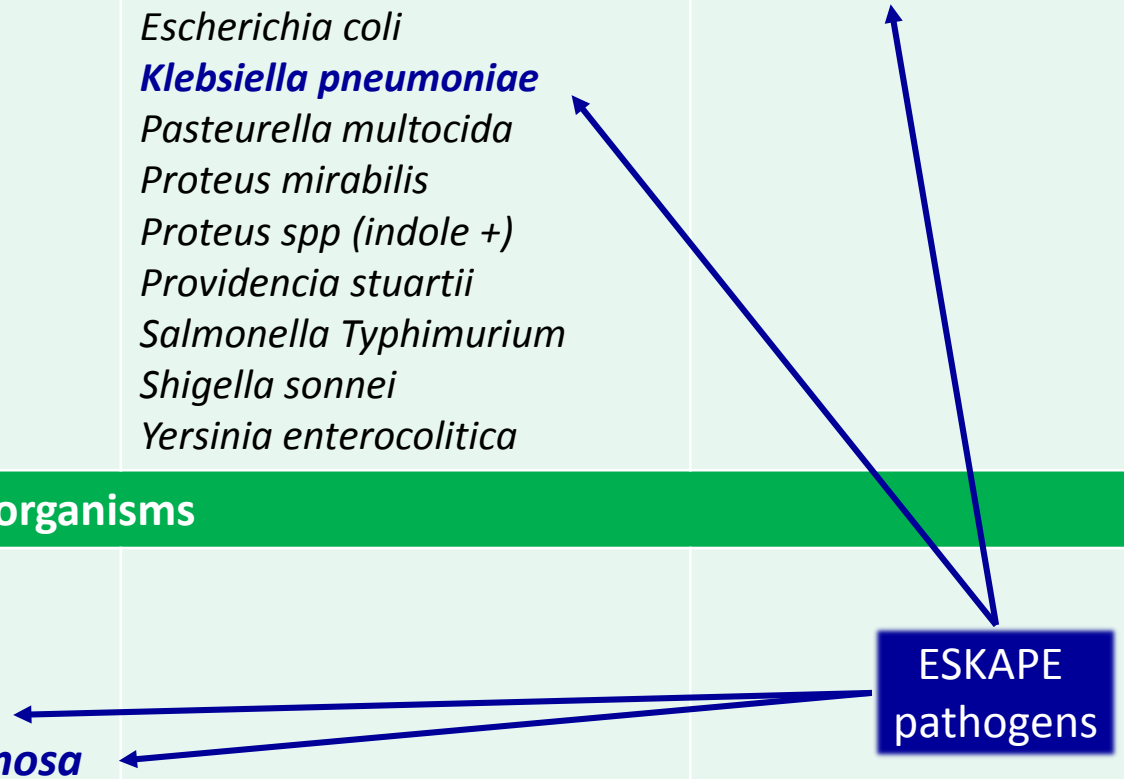
David M. Livermore[1]* and Paul M. Tulkens[2]

[1]*Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK;* [2]*Unité de Pharmacologie Cellulaire et Moléculaire & Centre de Pharmacie Clinique, Université Catholique de Louvain, Bruxelles, Belgium*

Resistance in Gram-negative pathogens is an increasing concern, with carbapenems often appearing as the only acceptable treatment option in serious infections. Reviving older compounds that have fallen into disuse may help to alleviate this burden. Temocillin (6-α-methoxy-ticarcillin) is resistant to most if not all classical and extended-spectrum β-lactamases and to AmpC enzymes. It is also chemically stable, allowing administration by continuous infusion. Pharmacokinetic/pharmacodynamic analysis, aided by Monte-Carlo simulations, suggests a breakpoint of 8 mg/L for the registered maximum dosage of 4 g daily. Temocillin's weaknesses, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas*. In settings where these are unlikely or are covered by other agents, temocillin may be useful, potentially 'sparing' carbapenems and having little apparent potential to select for *Clostridium difficile*.

As a result …

Susceptible organisms		
MIC < 1 mg/L	1 mg/L < MIC < 10 mg/L	10 mg/L < MIC < 100 mg/L
Moraxella catarrhalis *Haemophilus influenzae* *Legionella pneumophila* *Neisseria gonorrhoeae* *Neisseria meningitidis*	*Brucella abortus* *Citrobacter spp.* *Escherichia coli* ***Klebsiella pneumoniae*** *Pasteurella multocida* *Proteus mirabilis* *Proteus spp (indole +)* *Providencia stuartii* *Salmonella Typhimurium* *Shigella sonnei* *Yersinia enterocolitica*	*Serratia marcescens* ***Enterobacter spp***
Intrinsically resistant organisms		
anaerobes Gram(+) bacteria ***Acinetobacter spp*** ***Pseudomonas aeruginosa***		



Belgian SmPC, last revision 2012; Van Landuyt et al, AAC 1982; 22:535-40

Chemical stability of temocillin in concentrated solutions

Table S1. Stability of temocillin in concentrated aqueous solution (8.34% w/v; corresponding to a daily dose of 4 g in a 48 mL infusion syringe) at increasing temperatures maintained for 24 h.

Temperature (°C)	Total (% of original amount)	R/S epimer ratio
20	102.8 ± 1.1^{A}	1.908 ± 0.015^{A}
25	101.5 ± 0.7^{A}	1.792 ± 0.011^{B}
30	101.5 ± 2.6^{A}	1.729 ± 0.024^{C}
37	98.1 ± 0.3^{B}	1.660 ± 0.002^{D}

Samples were analysed by HPLC with differential detection of the *R* and *S* epimers

Data are means±SD (n=3).

Note that a drug loss upon storage ≤10% fulfills the requirements of the European Pharmacopeia [see Note for guidance on Manufacture of the Finished Dosage Form (CPMP/QWP/486/95), pp 1-6. The European Agency for the Evaluation of Medicinal Products (EMEA), London, UK].

De Jongh *et al.* Journal of Antimicrobial Chemotherapy (2008) 61:382-388 – Supplementary Material

Comparative chemical stabilities of β-lactams upon storage of concentrated solutions at 25 and/or 37° C

Conclusion	Molecule	Stability limit [1]	reference
good	temocillin	> 24 h at 37° C [2]	De Jongh *et al.* JAC 2008
	aztreonam	> 30 h at 37° C	Chanteux *et al.* (abstract)
	piperacillin	24 h at 37° C	Viaene *et al.* AAC 2002
weak	ceftazidime	24 h at 25° C / 8 h at 37° C	Servais *et al.* AAC 2001
problematic	cefepime	color appearance within 6 h	Baririan *et al.* JAC 2003
insufficient	imipenem	< 5 h	Viaene *et al.* AAC 2002
	meropenem	< 5 h	Viaene *et al.* AAC 2002
	doripenem	~ 6-10 h	Berthoin *et al.* JAC 2010

JAC: J Antimicrob Chemother
AAC: Antimcrob Agents Chemother

[1] > 90 % of original compound (European Pharmacopoiea)

[2] stable for 3 weeks at 4° C (for home medication) (Carryn *et al.*, J Antimicrob Chemother 2010;65:2045-2046)

Temocillin pharmacodynamics: the lessons of β-lactams

- For β-lactams,
  - **only the free fraction is (probably) active…**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3067–3074
0066-4804/11/$12.00 doi:10.1128/AAC.01433-10

MINIREVIEW

Vol. 55, No.

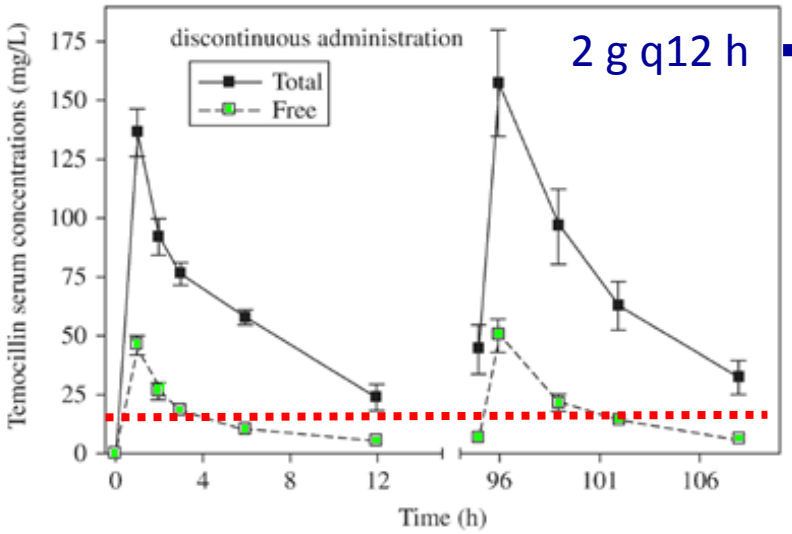
Protein Binding: Do We Ever Learn?∇

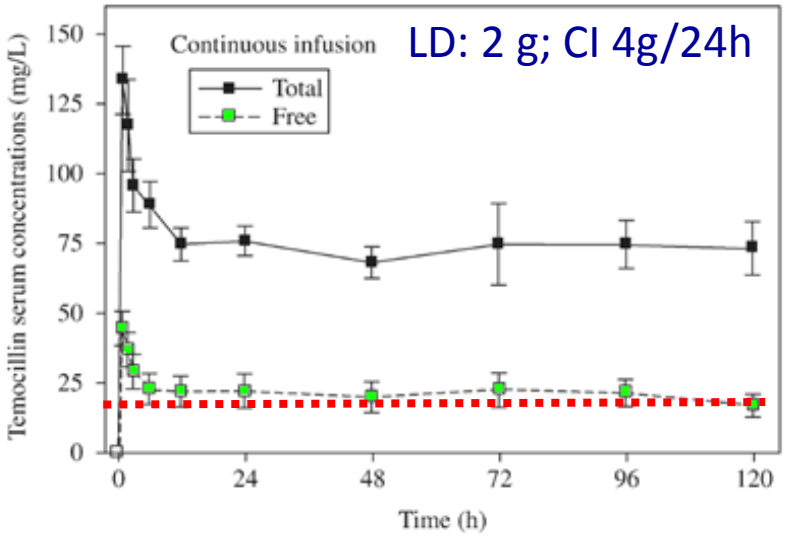
Markus A. Zeitlinger,[1] Hartmut Derendorf,[2] Johan W. Mouton,[3] Otto Cars,[4] William A. Craig,[5] David Andes,[5] and Ursula Theuretzbacher[6]*

Department of Clinical Pharmacology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria[1]; Department of Pharmaceutics, University of Florida, Gainesville, Florida 32610[2]; Department of Medical Microbiology, Radboud University, Nijmegen Medical Center, Nijmegen, Netherlands[3]; Department of Medical Sciences, Uppsala University, Box 256, 751 05 Uppsala, Sweden[4]; Department of Medicine, Section of Infectious Diseases, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin[5]; and Center for Anti-Infective Agents, Vienna, Austria[6]

Exemple #1 (très court): bolus et infusion continue

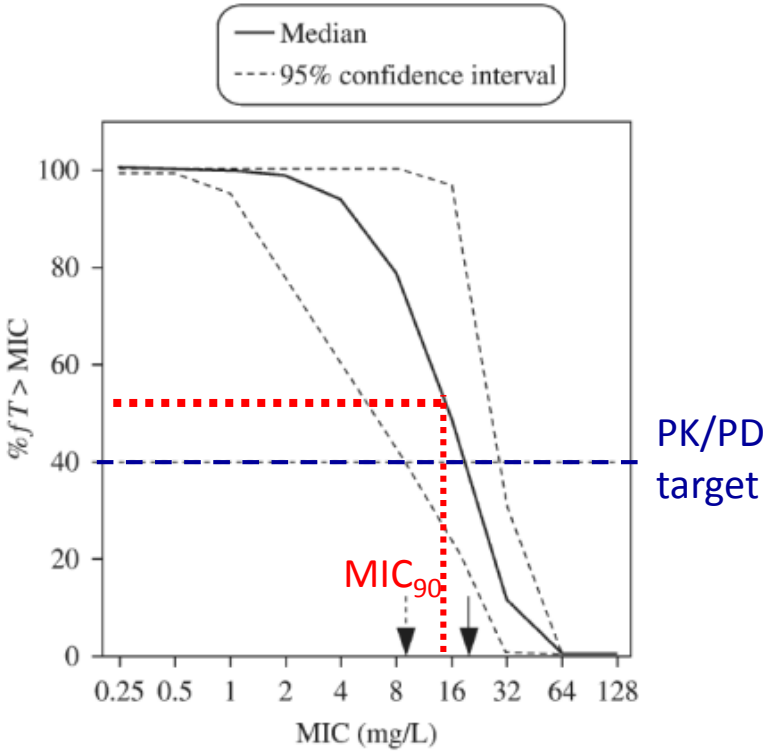
Application to clinical trials (ICU patients)





De Jongh *et al,* JAC 2008; 61:382-8

Monte Carlo simulation



PK/PD Bkpt 8-16 mg/L

Exemple #2 (plus long): patients de soins intensifs avec données manquantes

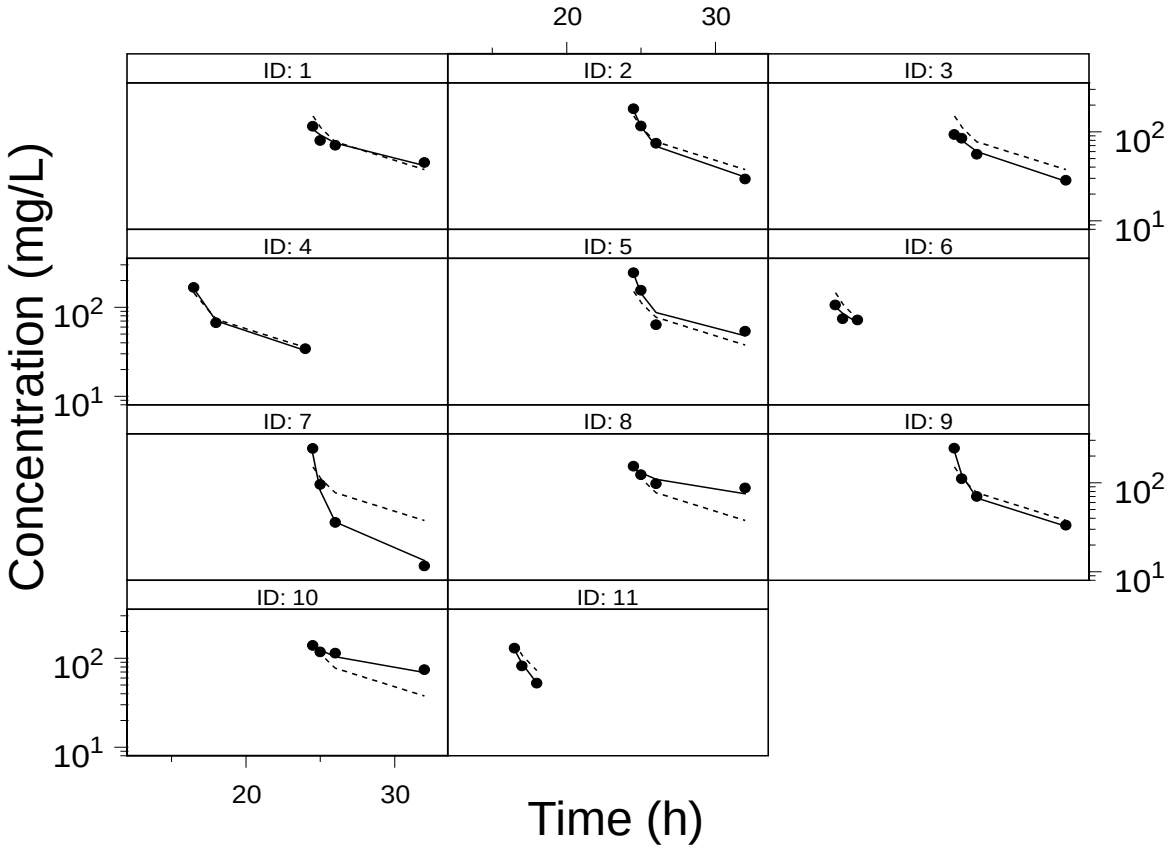
Temocillin project (full)

P-807

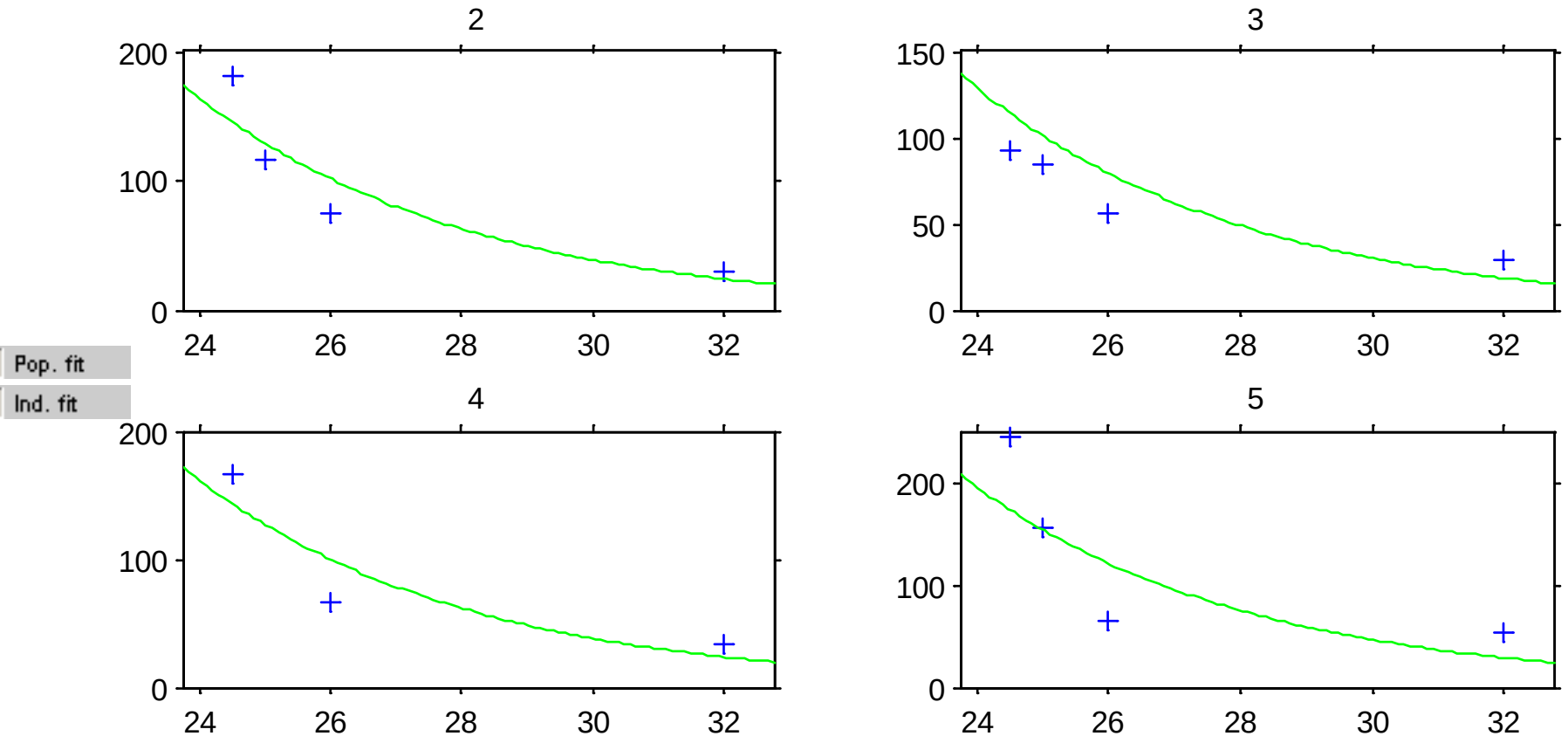
Population Pharmacokinetics of Temocillin in ICU patients and Monte Carlo Simulations to Evaluate Resistance Breakpoints

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]

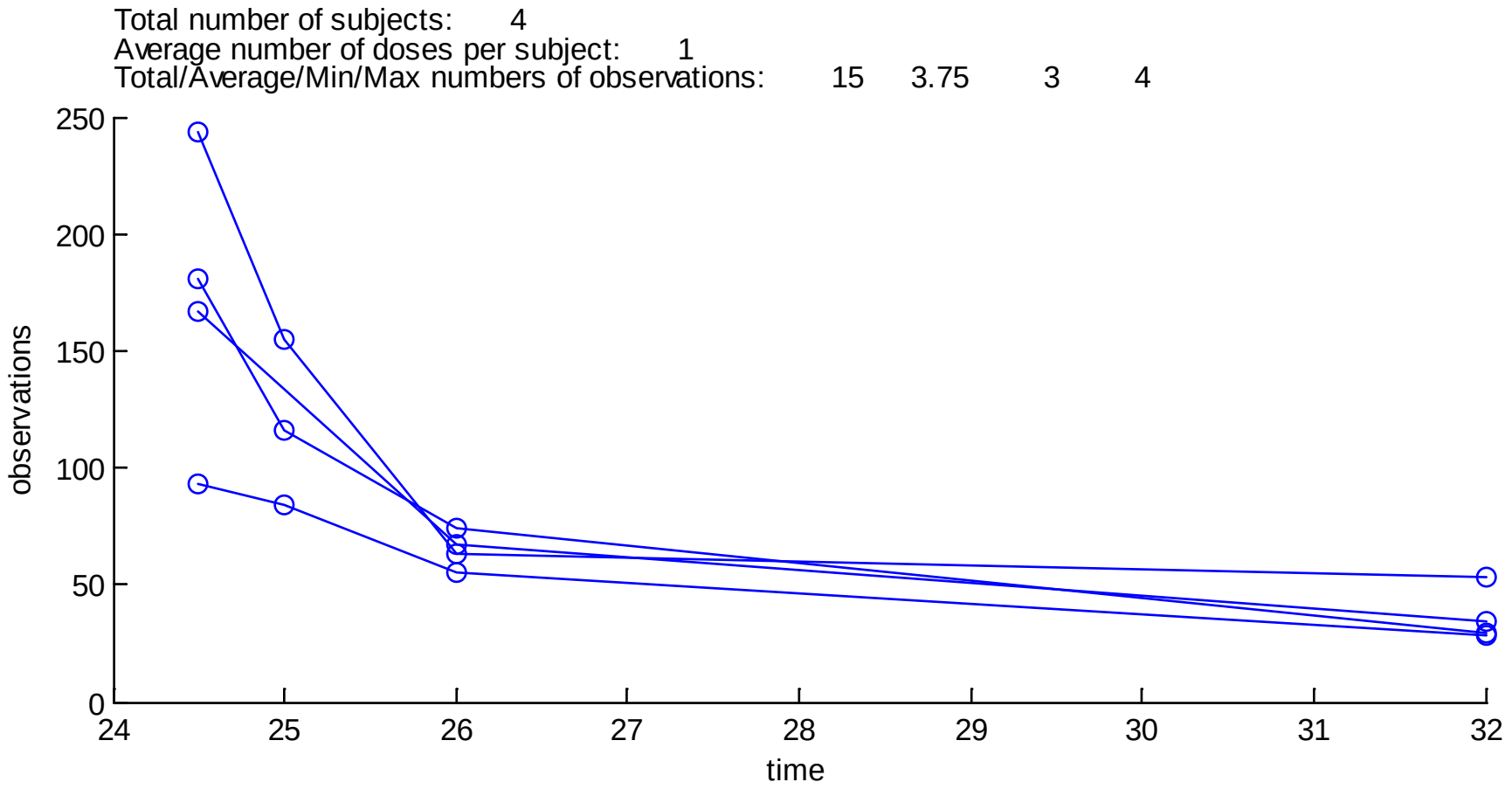
[1]Erasmus Medical Centre Rotterdam, [2]Radboud University Nijmegen Medical Centre, [3]Carolus Wilhelmina Hospital, Nijmegen, The Netherlands, [4]Université Catholique de Louvain, Brussels, Belgium



Outputs: individual curves

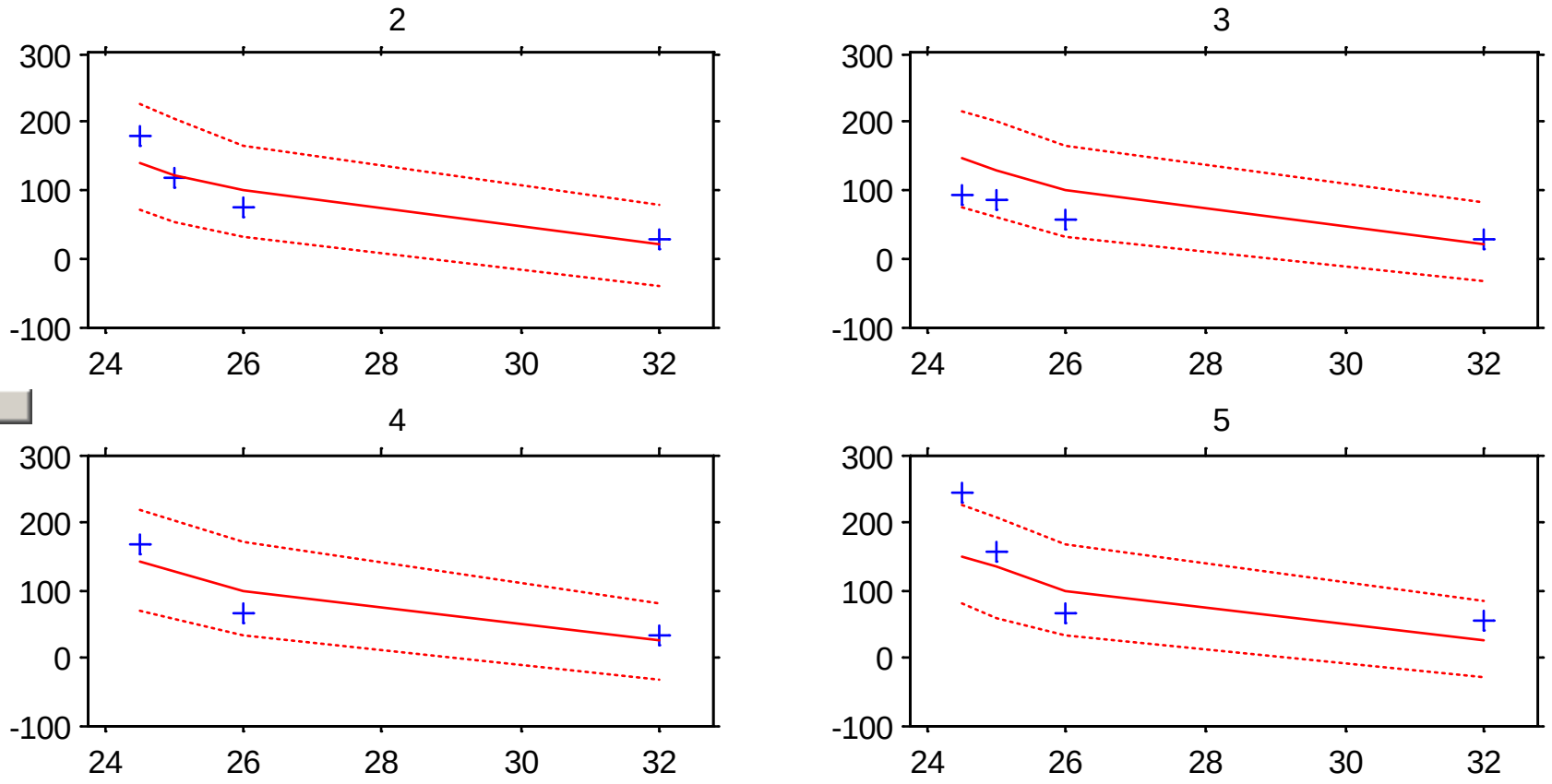


Outputs: spaghetti plot (*)

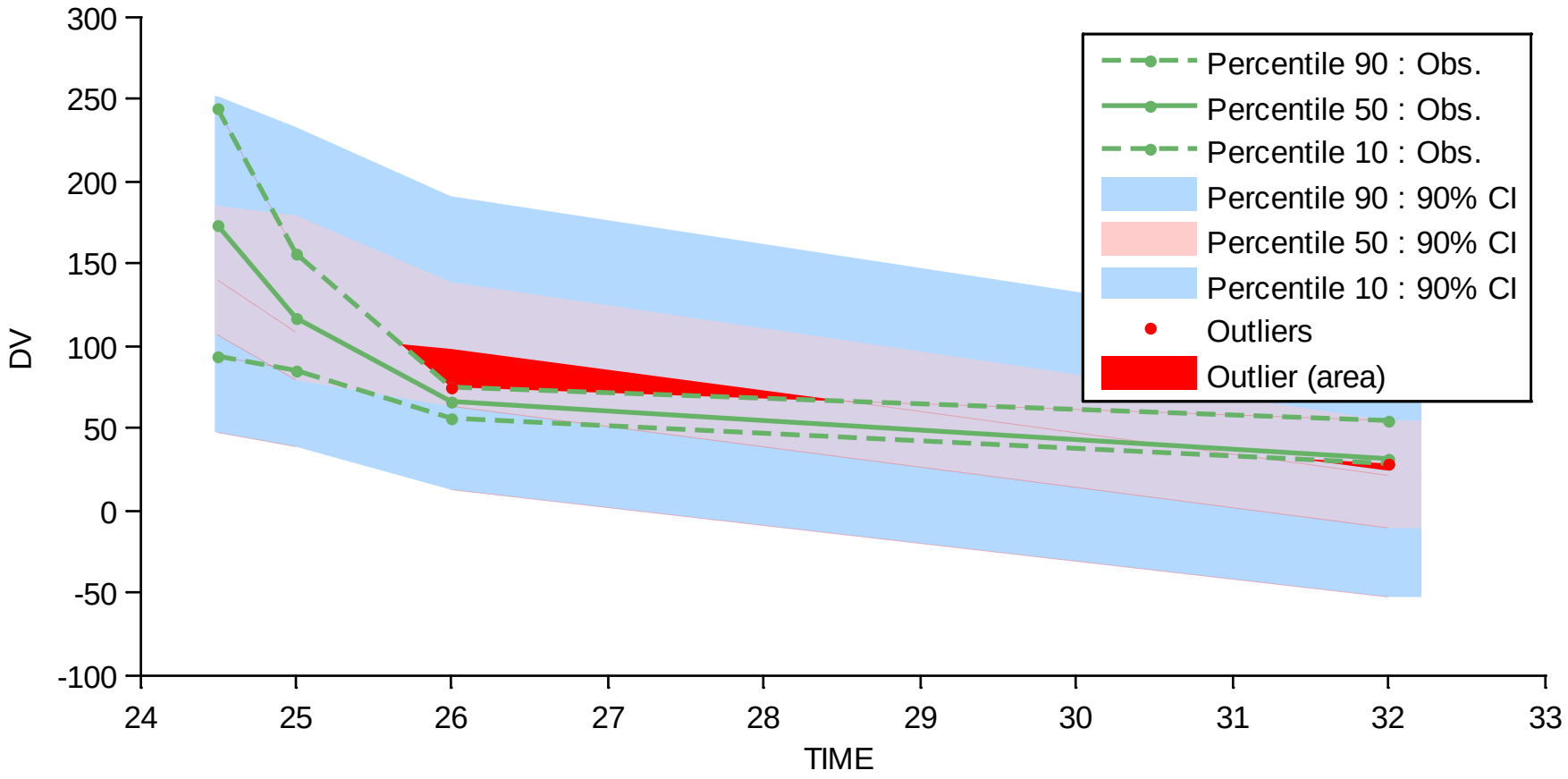


* not noodles !

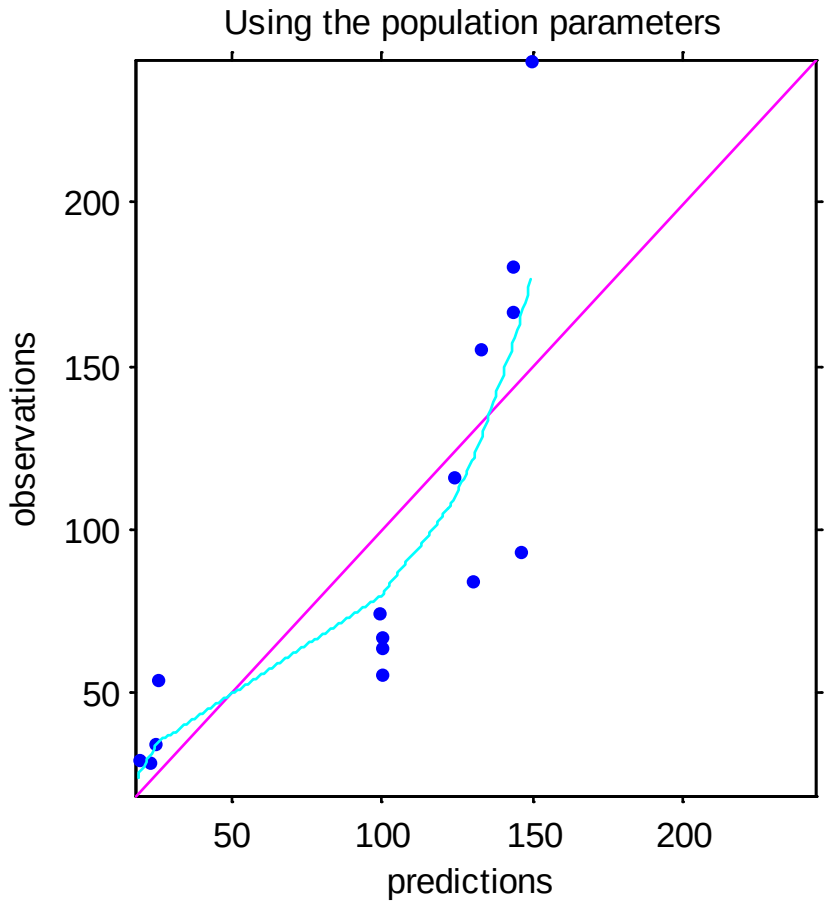
Outputs: population curves

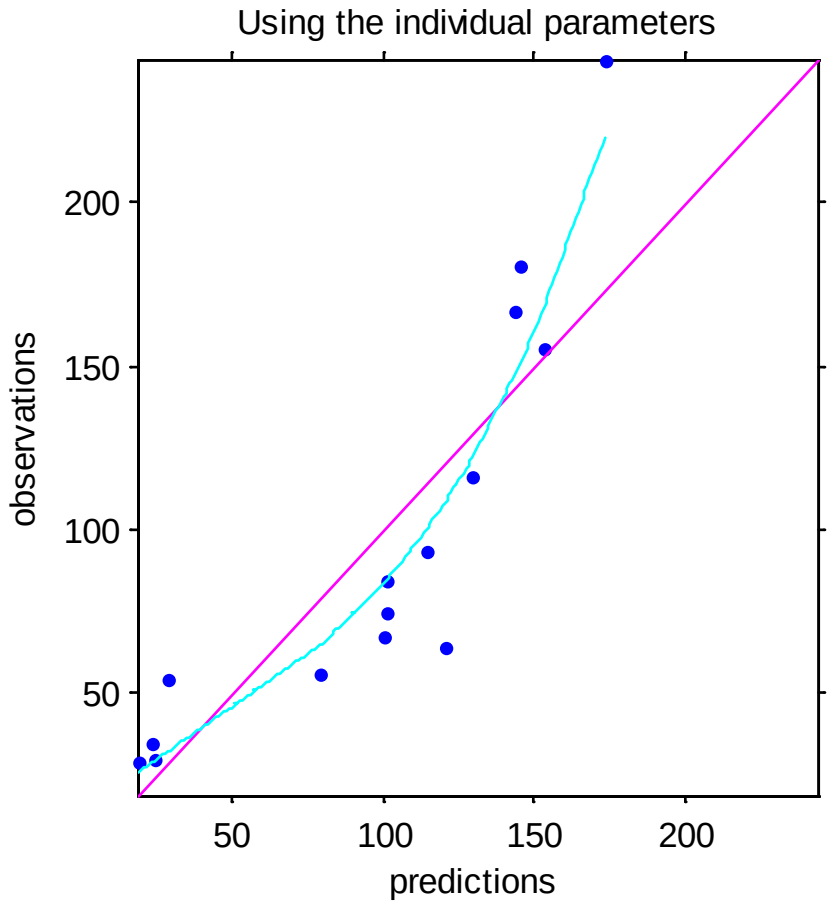


Outputs: population

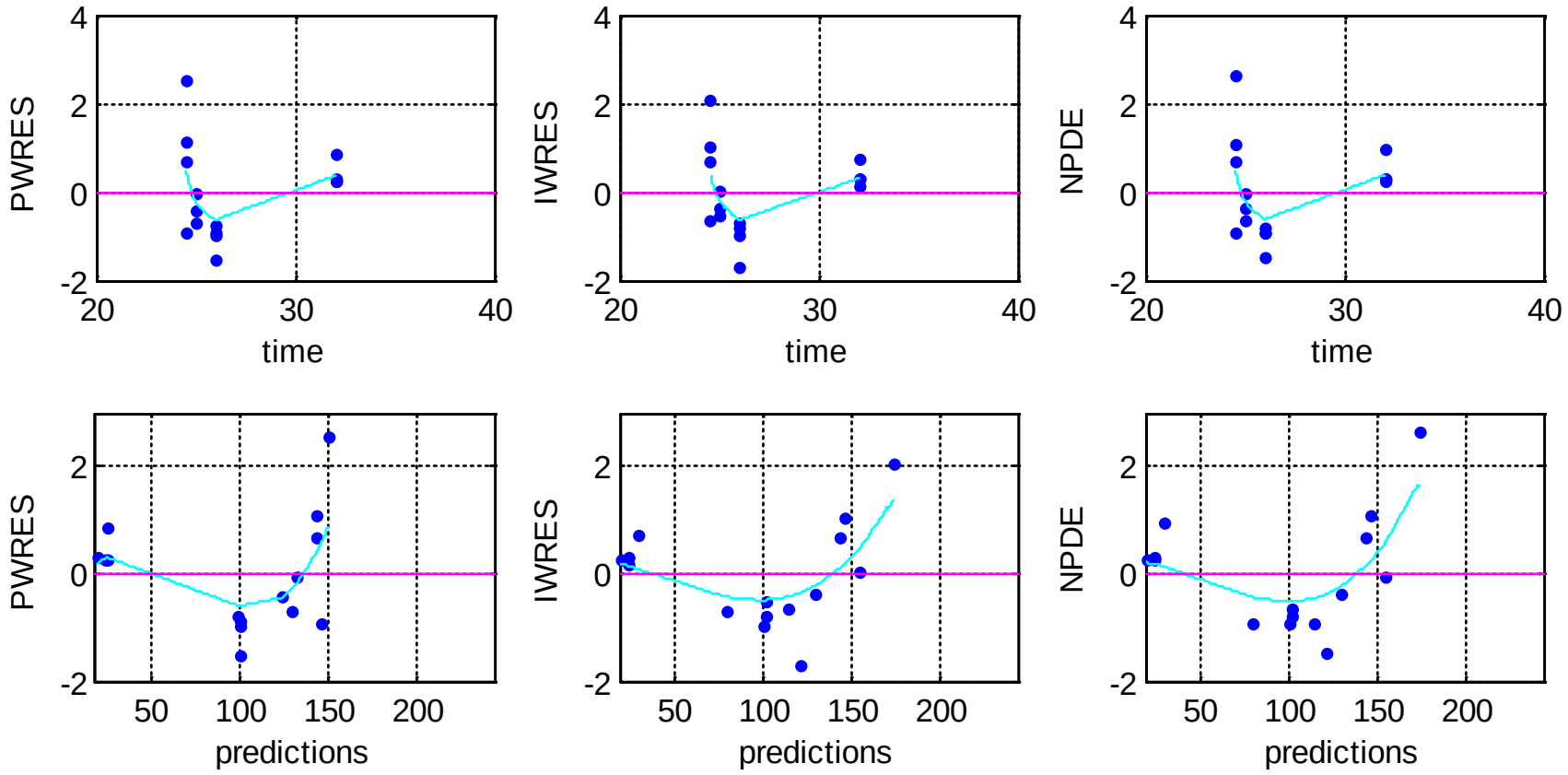


Outputs: observations vs. predictions





Outputs: residuals



Exemple #3 (long): volontaires vs soins intensifs et impact de la fraction libre

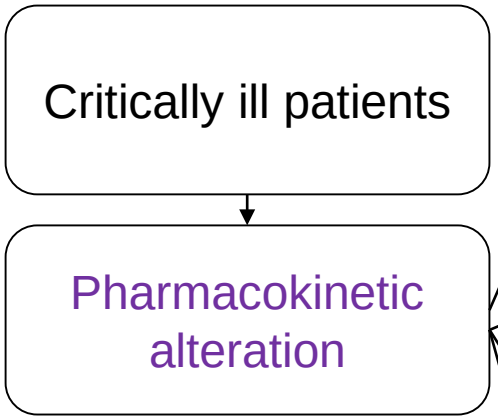
Cette partie est reprise du travail de Thèse en cours de Mr Perrin Ngougni-Pokkem

- There is growing evidence that standard antibiotic regimens may not provide adequate drug concentrations …

J.W. Mouton et al: Int J Antimicrob Agents. 2002 Apr;19(4):323-31.

Roberts *et al*, Br J Clin Pharmacol. 2012;73:27-36.

Critically-ill patients



Hyperdynamic states
Increased cardiac out, and clearance
Decreased plasma concentrations

Altered fluid balance / Altered protein binding
Increased volume of distribution
Decreased plasma concentrations

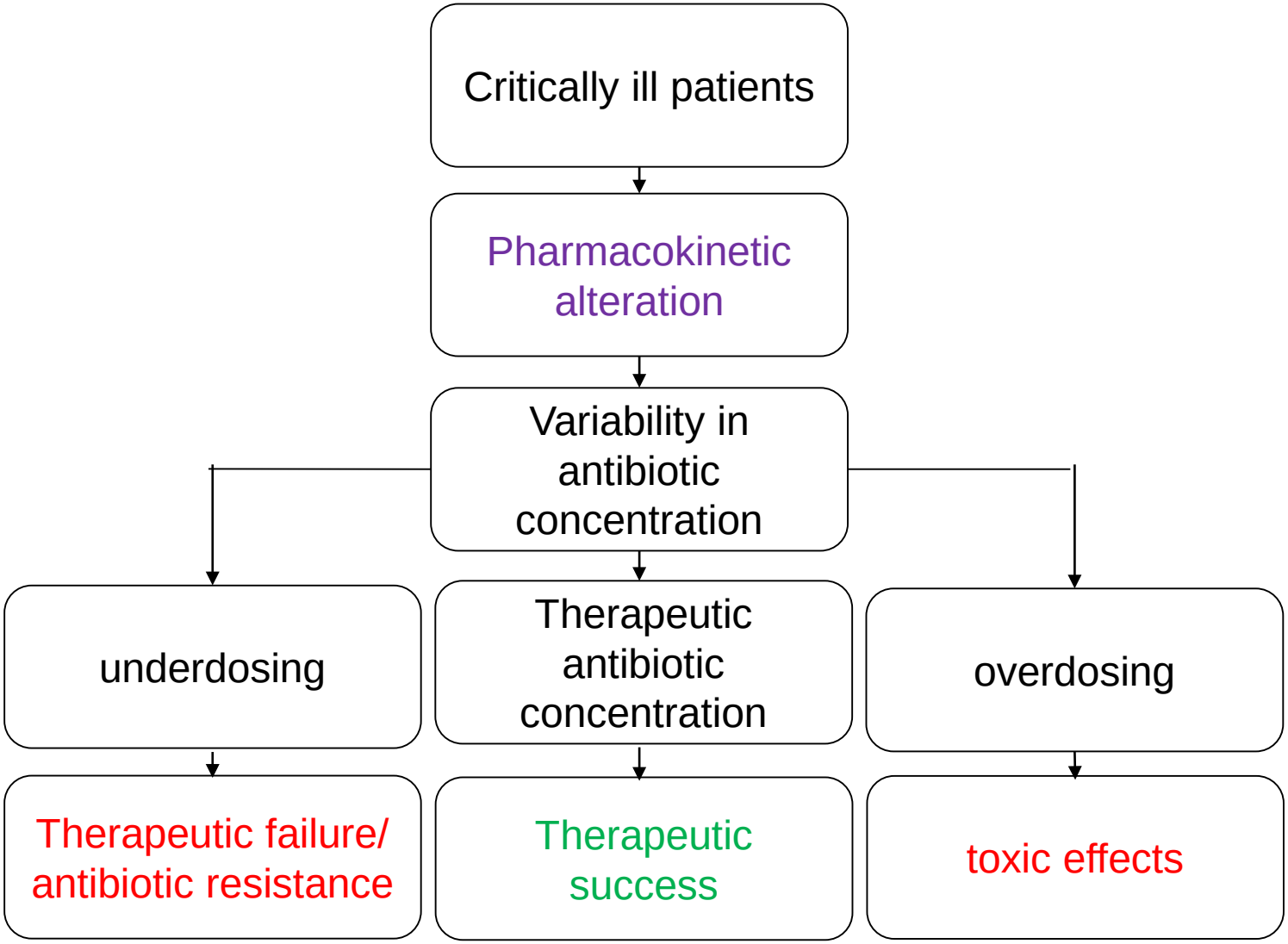
Renal and hepatic impairment
Decreased clearance
Increased plasma concentrations

Organ support (RRT/ECMO)
Increased volume of distribution / clearance
Increased/decreased plasma concentrations

Roberts JA, Lipman J. Clin Pharmacokinetic 2006; 45 (8): 755-73
Hosthoff et al, Swiss Med Wkly. 2016;146:w14368
A. Abdulla et al: University Medical Center Rotterdam; eposter 069; ECCMID 2017

RRT: renal replacement therapy
ECMO: extra corporeal membrane oxygenation

Consequences of PK alteration



Roberts JA, Lipman J. Clin Pharmacokinetic 2006; 45 (8): 755-73

Hosthoff et al, Swiss Med Wkly. 2016;146:w14368

A. Abdulla et al: University Medical Center Rotterdam; eposter 069; ECCMID 2017

The main objectives

- **Current literature data are based mainly on TOTAL temocillin concentrations**

  - **Only the free concentration is active !**
  - **Concentration in the infected tissue is important !**

Part 1 Pilot study

Population Pharmacokinetic Analysis and Protein Binding Characteristics of Free and total Temocillin concentrations in Plasma of Healthy Volunteers and patients

Design of the in vitro study

- **Comparing protein binding in spiked plasma of healthy donors (n=4) vs. plasma from patient donors hospitalized in intensive care unit (n=5) for temocillin concentrations ranging from 8 to 250mg/L**

- ***Free fraction of temocillin (%)*** $= \frac{free\ concentration \times 100}{total\ concentration}$

- ***Bound concentration of temocillin (mg/L)***
  = total concentration – free concentration

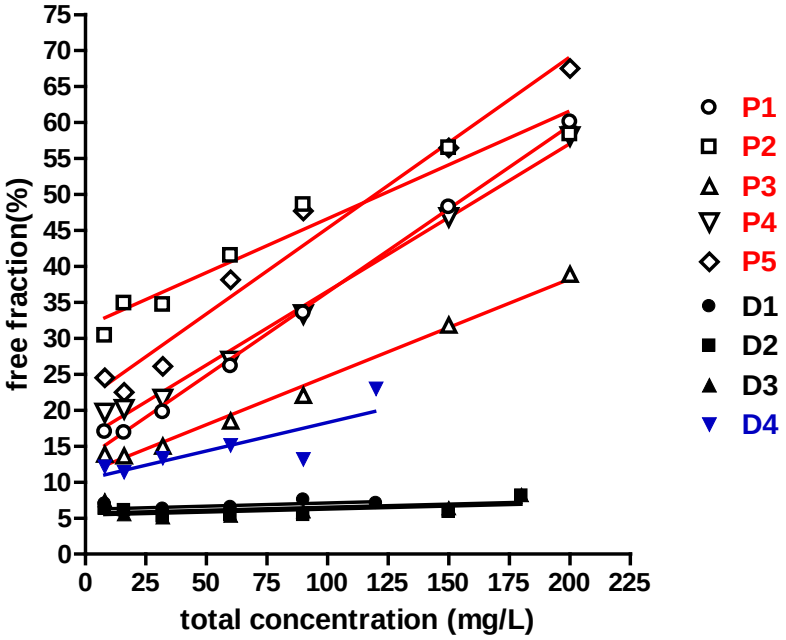
- **Study of the relationships between the free fraction of temocillin vs its total concentration.**

- **Bound concentration vs free concentration of temocillin in plasma**

- **Free Fraction at a given total concentration vs protein concentrations**

Temocillin plasma protein binding In vitro study

Free fraction *vs* total concentration of temocillin in plasma for 4 healthy donors (D) compared with 5 patients donors (P) in vitro study



Plasma total protein level (mg/L)

Reference range : 65-85g/L

P1: 52.89 g/L
P2: 48.34 g/L
P3: 61.17 g/L
P4: 55.31 g/L
P5: 55.53 g/L

D4: 57.03 g/L
D1: 71.75 g/L
D2: 84.91 g/L
D3: 70.55 g/L

For the patient donors

- ✓ High free fraction up to 65%
- ✓ Free fraction which increases with the total concentration
- ✓ High variability between the patient donors.

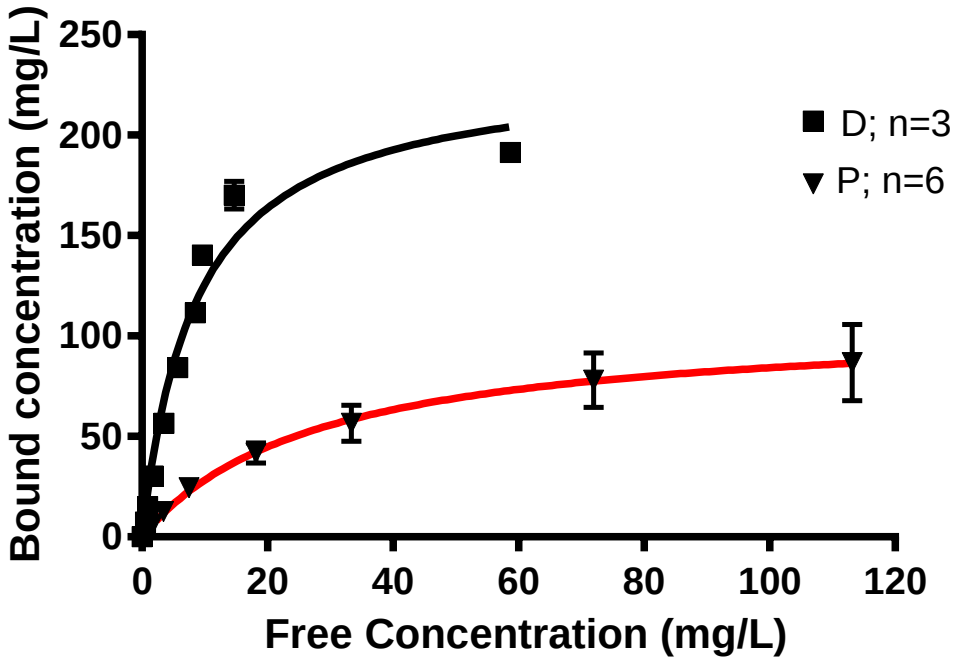
For the healthy donors, except D4

- ✓ Low free fraction between 5 to 8%
- ✓ Free fraction which is not influenced by the total concentration
- ✓ Low variability between the healthy donors

Michaelis-Menten fitting of temocillin protein binding

$$B = \frac{B_{max} \times C_{free}}{Kd + C_{free}}$$

Bound concentration vs free concentration of temocillin in plasma
In vitro study



- ✓ **Plasma protein binding of temocillin is saturable**
- ✓ **Maximum binding is lower in patients**

Design of the clinical study: « Phase1 »

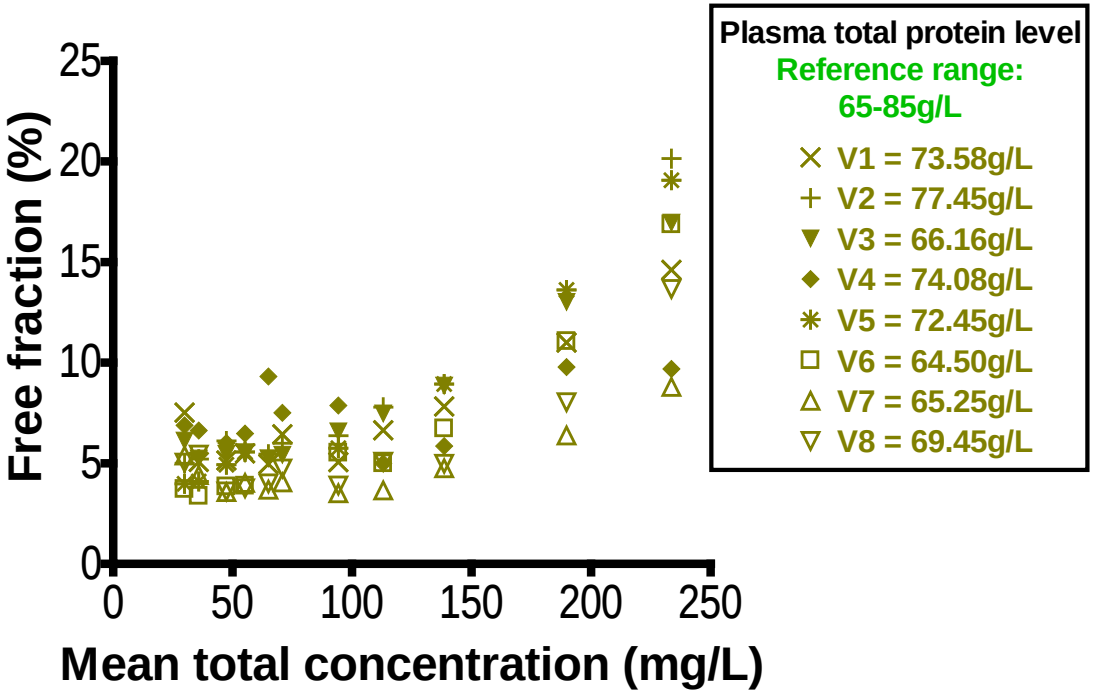
- **8 healthy volunteers.**
- **Single dose of 2g TMO in 40 min infusion; IV administration.**
- **Blood sampling: 40min, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12h.**
- **Study of the relationship between free fraction of temocillin vs its total concentration.**
- **Study of the relationship between bound concentration of temocillin vs free concentration.**

Principal Investigator according to Austrian drug law
Markus Zeitlinger,MD
Department of clinical Pharmacology,
Medical University of Vienna

Graph Pad 4 software

Temocillin plasma protein binding

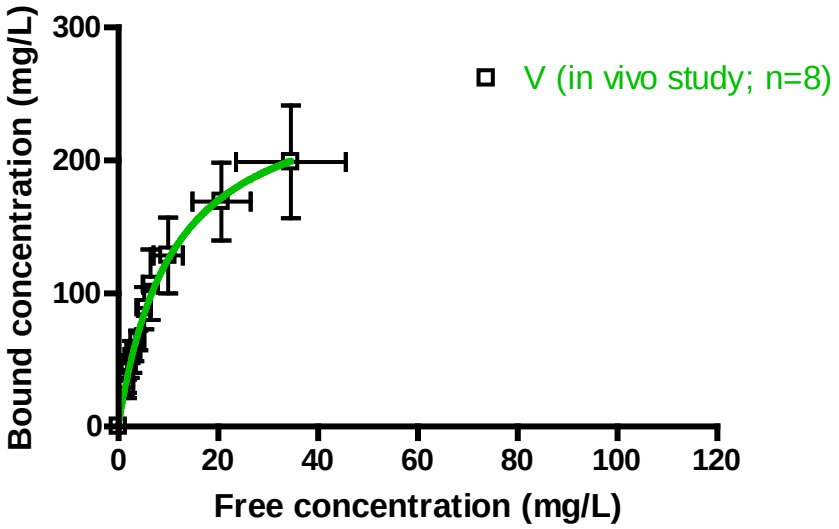
Free fraction vs total concentration of TMO in plasma for 8 healthy volunteers (V) in vivo study compared with healthy donors (D)
in vitro study



✓ **Low free fraction (3-8%) for total concentrations below 150 mg/L, and increase in free fraction up to 20% for higher total concentrations**

Michaelis-Menten fitting of temocillin protein binding

Bound concentration *vs* free concentration of temocillin in plasma

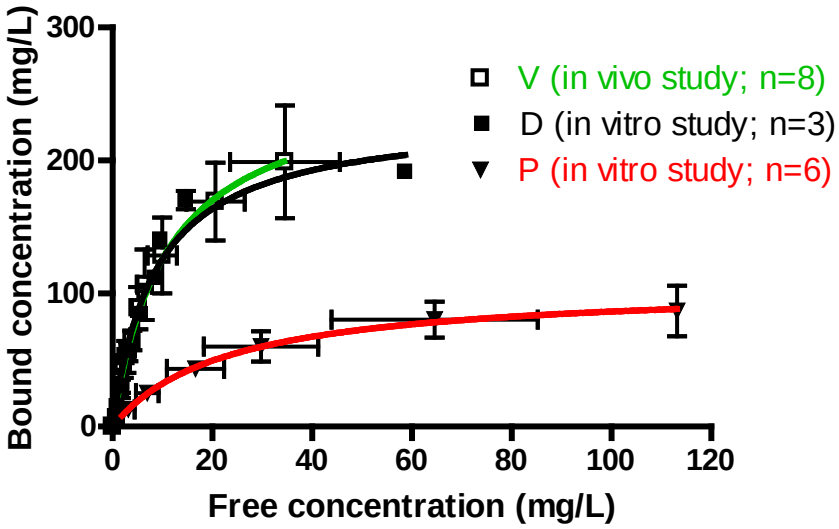


✓ **Protein binding saturation observed**

Michaelis-Menten fitting of temocillin protein binding

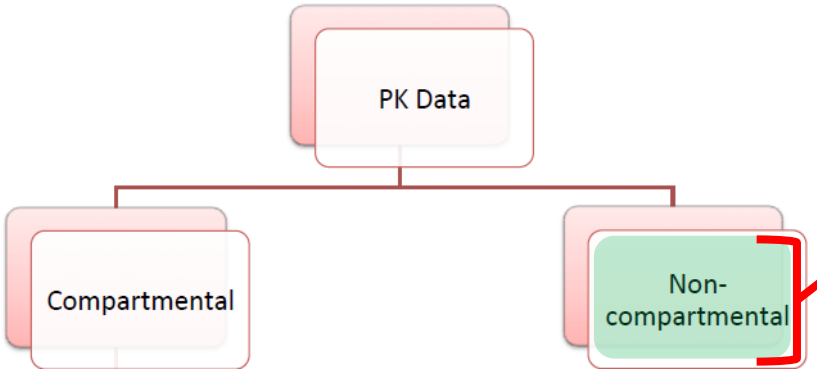
Comparison of plasma protein binding in healthy volunteers (V), healthy donors (D) and patient donors (P)

Bound concentration *vs* free concentration of temocillin in plasma



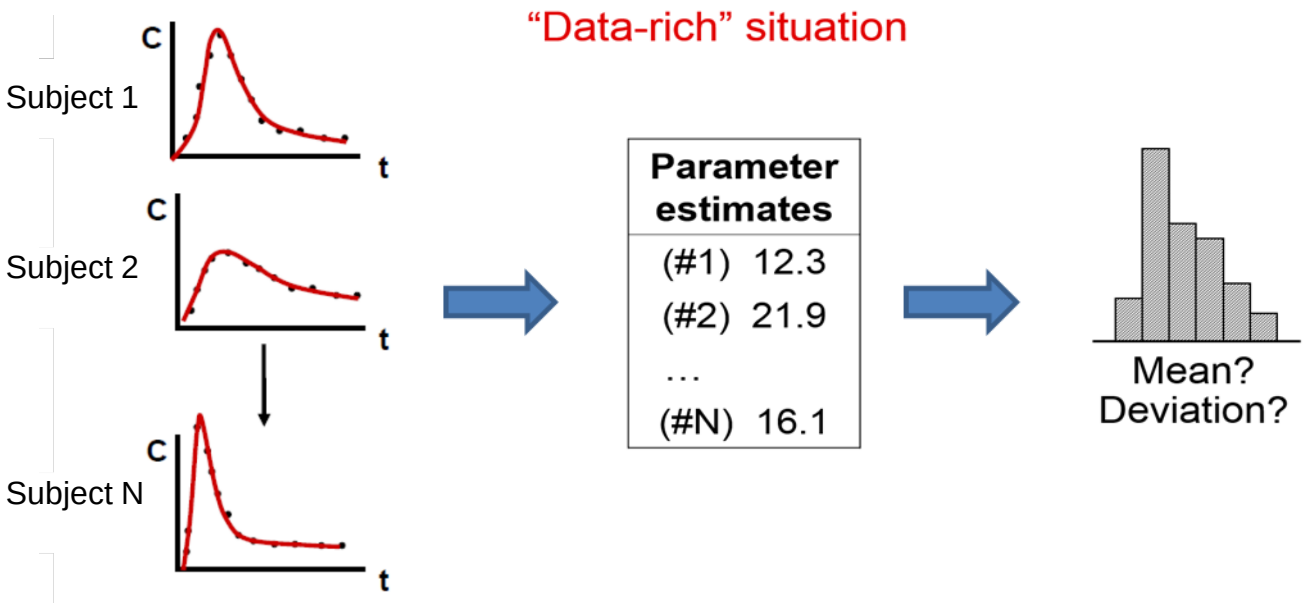
- ✓ **Similar protein binding saturation observed**
- ✓ **Lower Bmax for patients !**

PK modeling approaches



- ❑ **"Data-rich" situation**
- ❑ **Simple to implement**

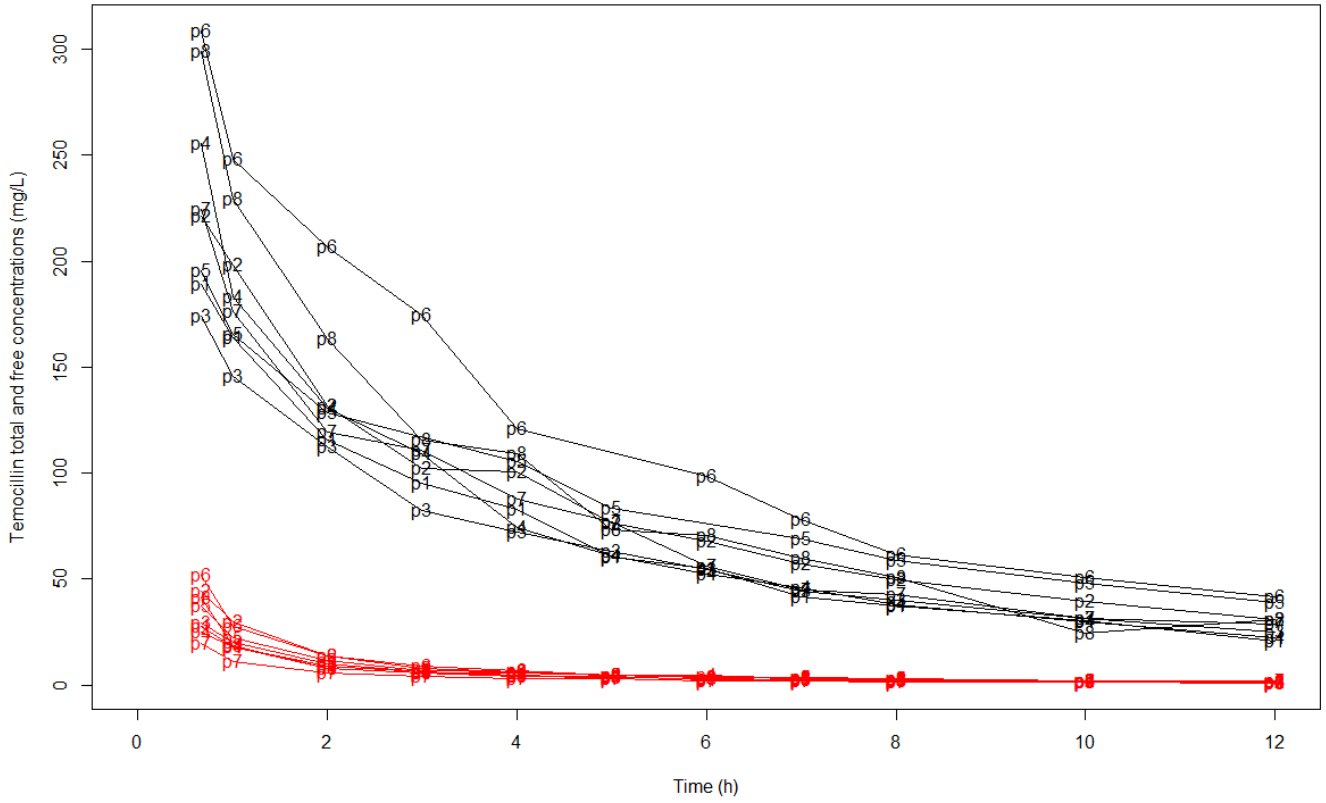
Individual analyzes in descriptive statistics



Adapted from I.Delattre. 2012

Plasma total and free concentration versus time

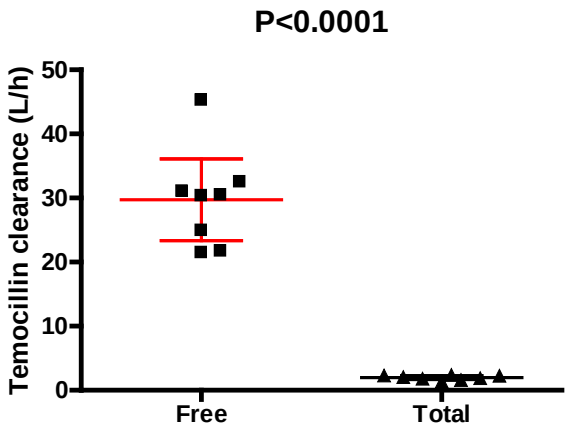
Pharmacokinetic profile of free and total concentration : individual data



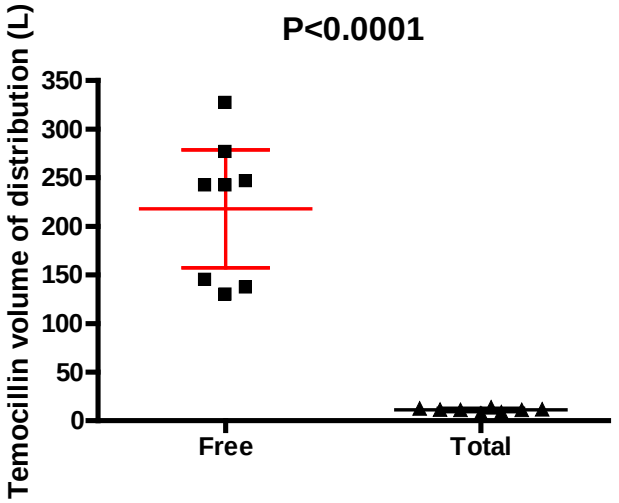
- ✓ Free concentration decreases with the total concentration
- ✓ Important variability in the pharmacokinetic profiles between the volunteers

Comparison of pharmacokinetic parameters (free vs total)

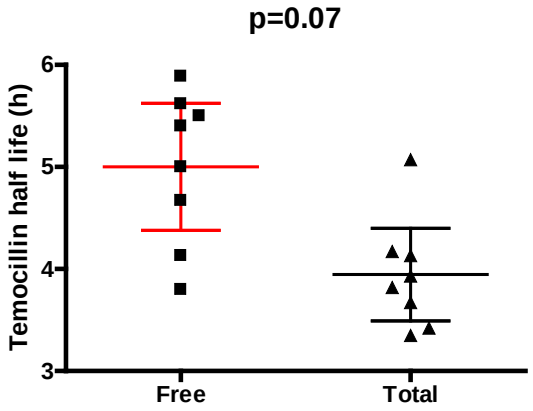
Mean and IC95% of pharmacokinetic parameters of free and total TMO



✓ **The clearance of the free temocillin is very high compared to the total**



✓ **The volume of distribution of the free temocillin is very high compared to the total**

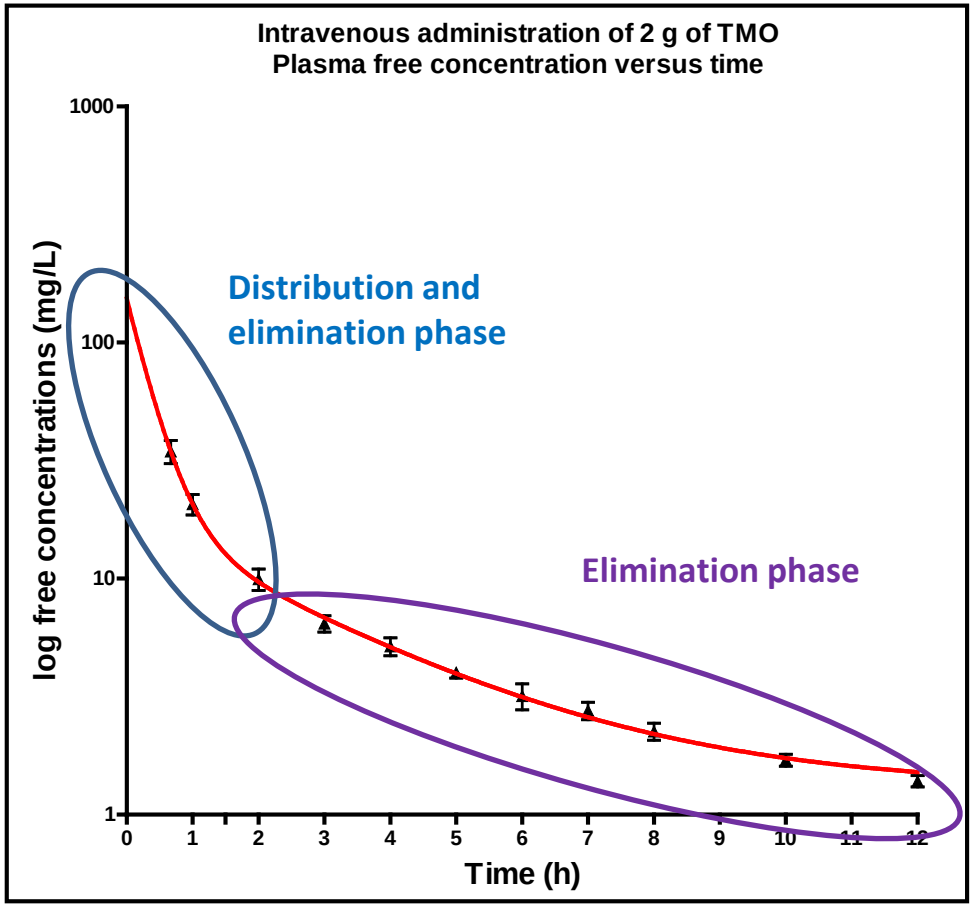


✓ **The half-life of the free temocillin has an important numerical effect; But not significant**

$$t_{1/2} = 0.693\ V_d\ /\ Cl$$

1. Structural pharmacokinetic model

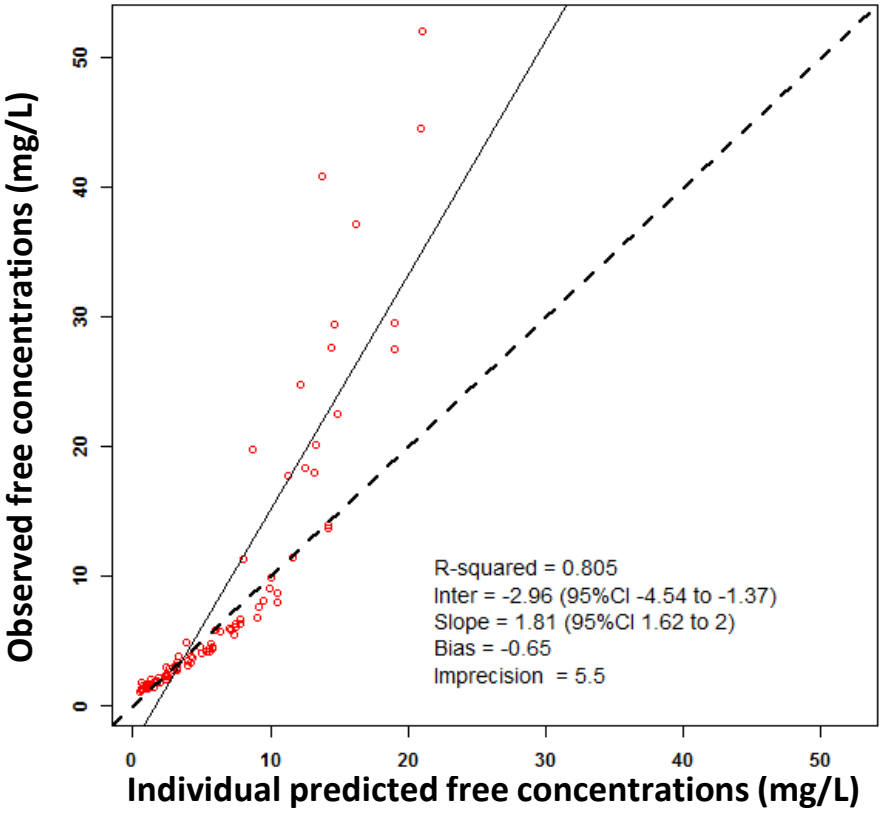
Visual evaluation of pharmacokinetic profile



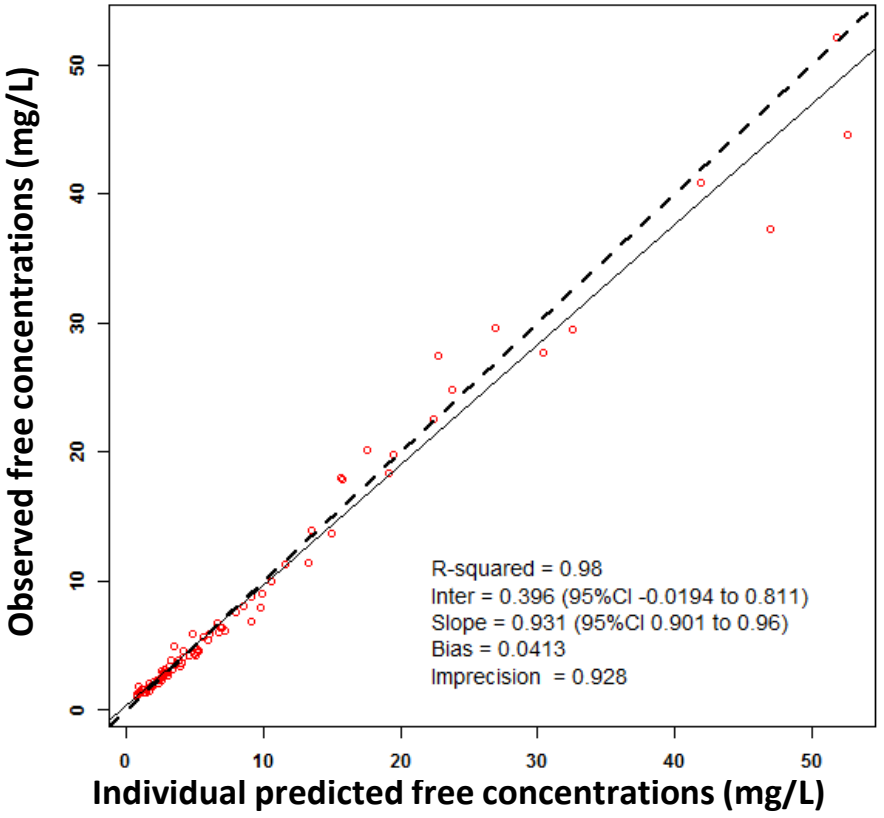
→This PK profile suggests that the kinetics of the TMO is Bi-compartmental

1. Goodness-of-fit plot

❑ **Mono compartmental model tested without covariate**



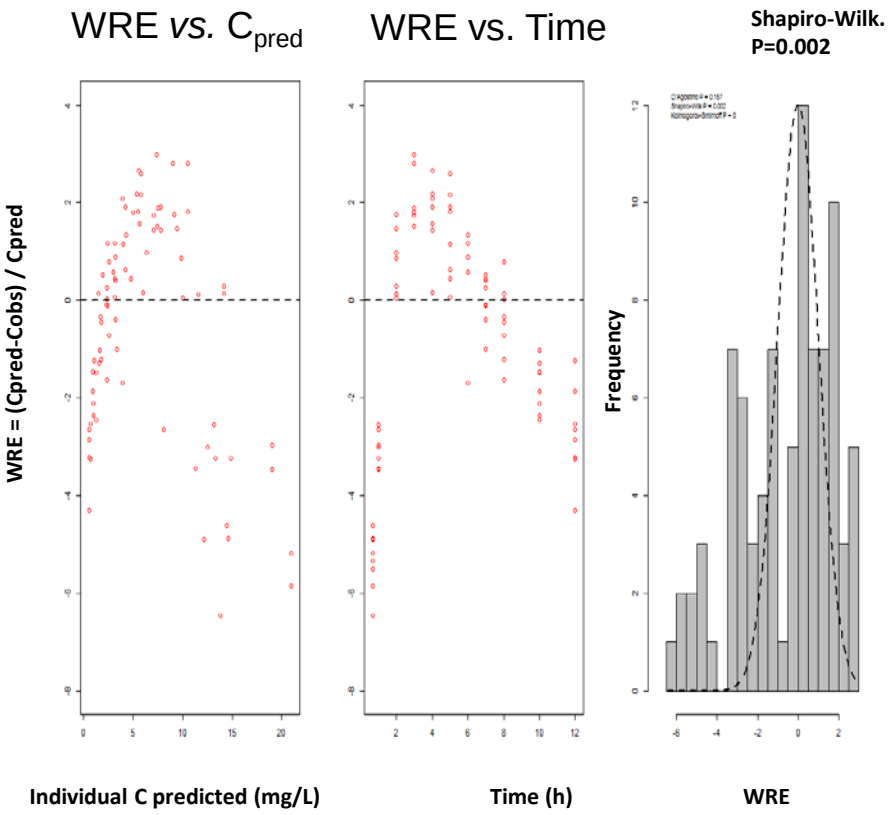
❑ **Bi-compartmental model tested without covariate**



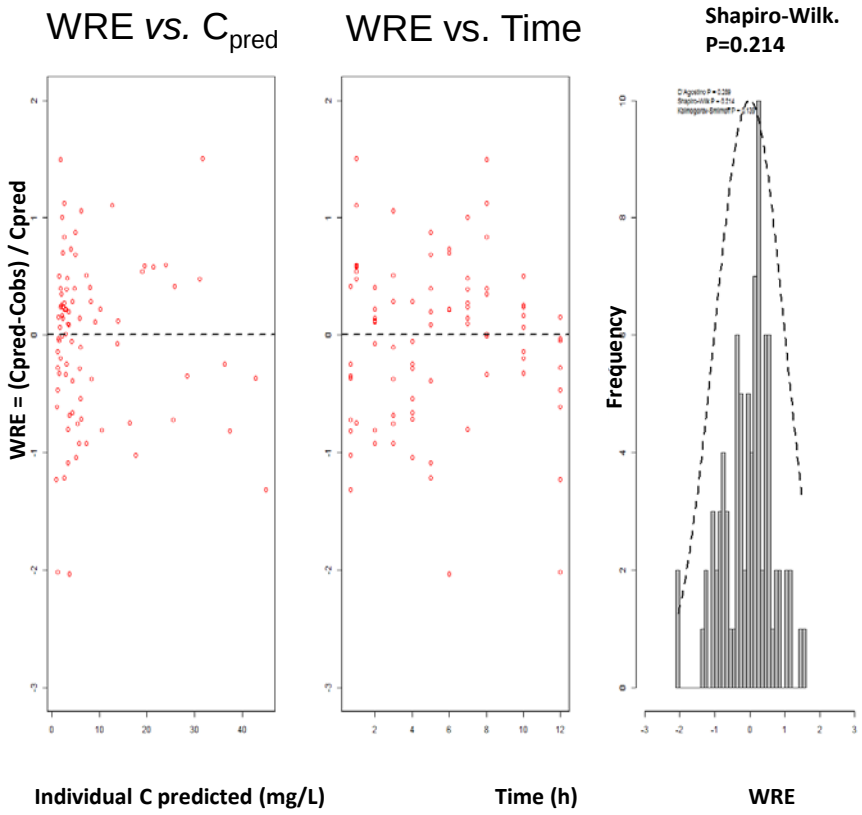
✓ **The correlation is better in this case and with less variability**

1. Goodness-of-fit plot

❑ **Mono compartmental model tested without covariate**



❑ **Bi-compartmental model tested without covariate**



- ✓ Residues should be centered on 0
- ✓ 95% of the population residues should be between approximately -2 and 2
- ✓ Residue distribution should be normal

→**Bi-compartmental model + Proportional residual error model**

2. Covariate model

- Relevant physiological, biological and demographic parameters that could change the pharmacokinetic parameters

- Make it possible to explain the inter and / or intra-individual variability

Parameter	Mean (sd)	Range
Age (yr)	32.9 (12.1)	23.0-53.0
Weight (kg)	81.9 (10.9)	70.2-105.6
Height (m)	1.8 (0.1)	1.7-1.9
BMI (kg/m2)	24.4 (2.9)	20.7-28.9
GFR (mL/min) (Cockcroft-Gault)	135.7 (16.1)	108.2-153.4
ASAT (U/L)	23.8 (4.5)	14.0-30.0
ALAT(U/L)	30.1 (9.2)	18.0-45.0
LDH(U/L)	158.8 (28.4)	143.0-195.0
Albumin (g/L)	Not analyzed	
Total protein (g/L)	70.4 (4.4)	64.5-77.5

Influence volume of distribution and clearance

Renal excretion (80% found in the urine in 24h)

Variable protein binding (-->93 %)

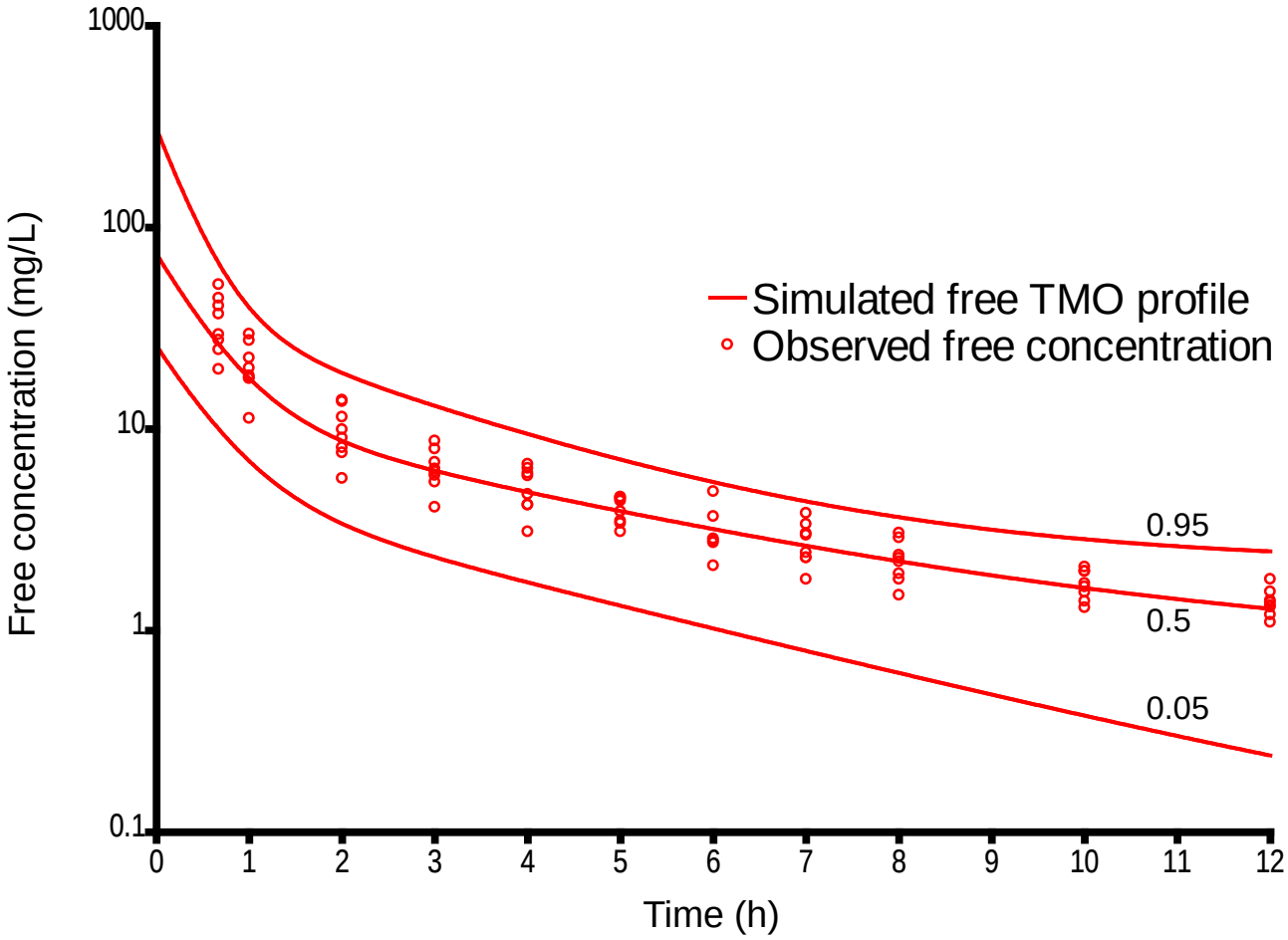
Validation population pharmacokinetic final model

❑ **Internal Validation:** Monte Carlo simulations

- Simulated profiles (n=1000) compared to observed data.
- The observed concentrations should be distributed homogeneously around the median of the simulated concentrations
- Less than 5% of observed concentrations must be outside the 5th and 95th percentiles of the simulated concentrations

❑ **External Validation**

Internal Validation: Visual Predictive Checks (VPC).



Temocillin pharmacodynamic targets

As every β-lactam, temocillin is

- bactericidal
- time-dependent
  (activity is driven by the time during which the drug plasma **free concentration** remains above the minimum inhibitory concentrations (MIC))

❑ **40% of time > MIC is enough for bacteriostatic activity**
→ **acceptable for non-immunocompromised patients**

❑ **70% of time > MIC is recommended**
→ **for immunocompromised patients**

❑ **100% of time > MIC is suggested**
→ **For critically-ill patients**
this could not only maximize efficacy but also minimize emergence of resistance

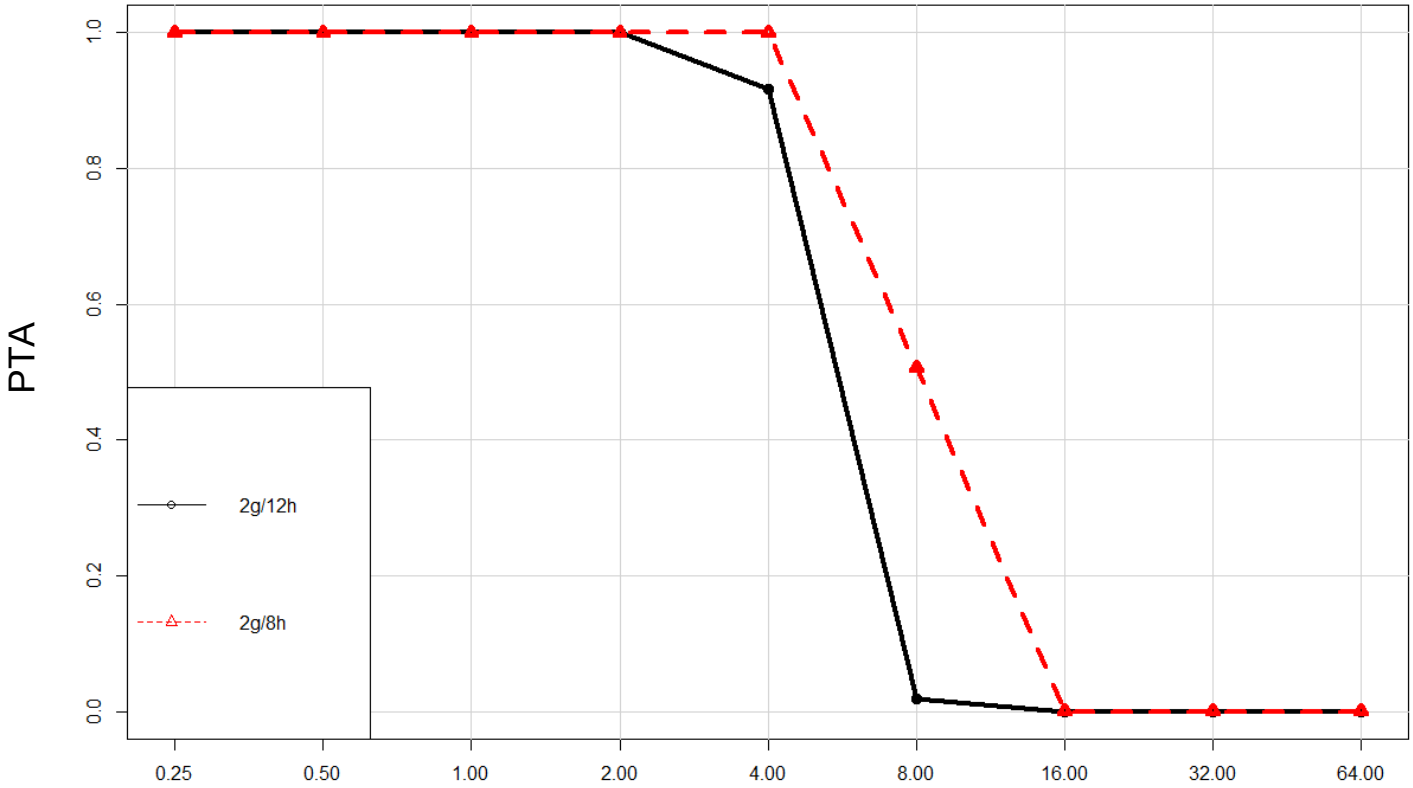
Craig WA Diagn Microbiol Infect Dis. 1995;22:89-96. PMID: 7587056.

Delattre IK et al For submission to Expert Review on Antiinfective Therapy as Special Report

Probability of Target Attainment (PTA) of plasma free temocillin concentrations

For non-immunocompromised patients

Target: *f*T > BSAC breakpoint = 8 mg/L of 40% of the time, based on a mean free fraction of 6.0 ± 1.4% (mean of values observed for total concentration < 150mg/L),



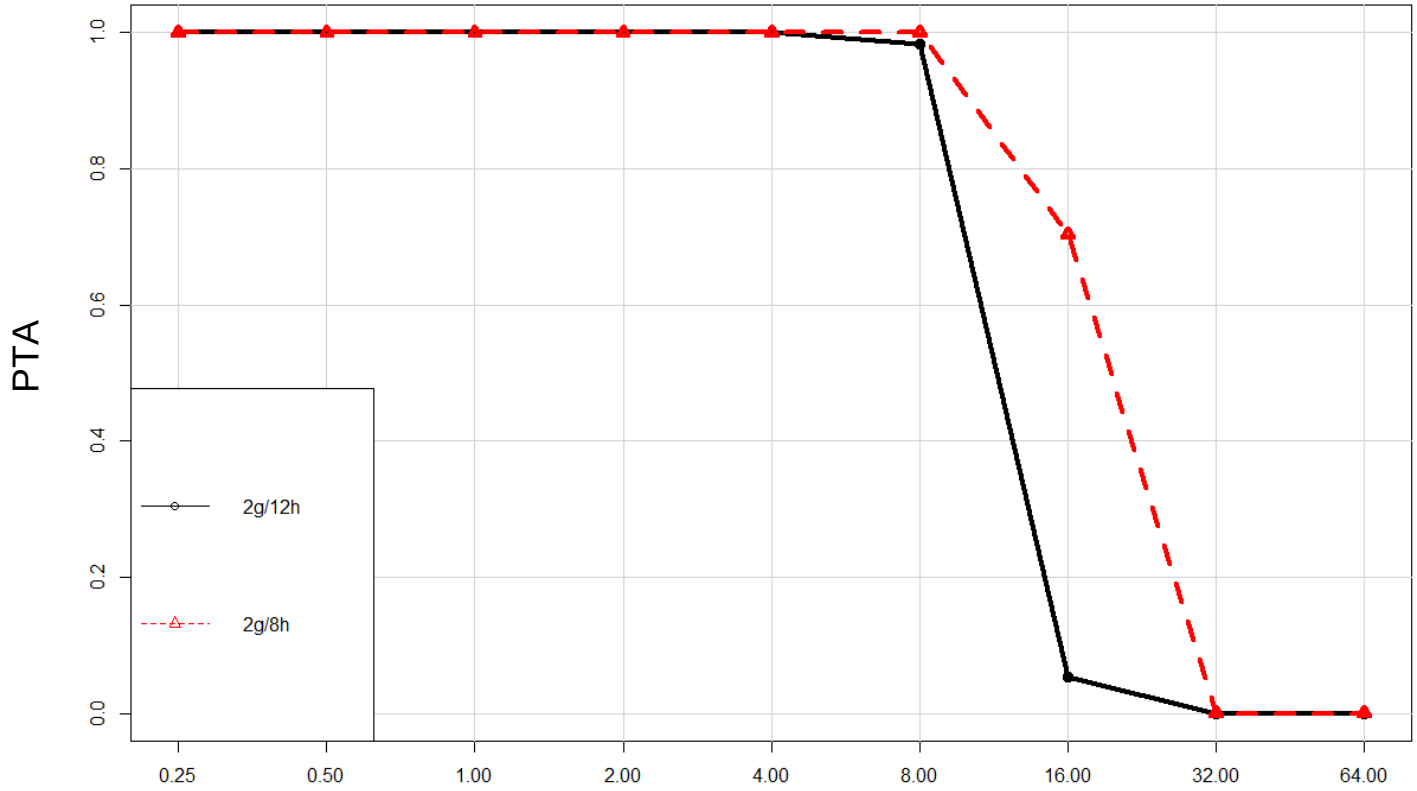
Standard dosing (2g/12h) PTA = 0

newly proposed dosing (2g/8h) PTA = 0.5

Probability of Target Attainment (PTA) of plasma free temocillin concentrations

For non-immunocompromised patients

Target: *f*T > BSAC breakpoint = 8 mg/L of 40% of the time, based on a mean free fraction of 13.0 ± 4.0% (mean of values observed for total concentration > 150mg/L),



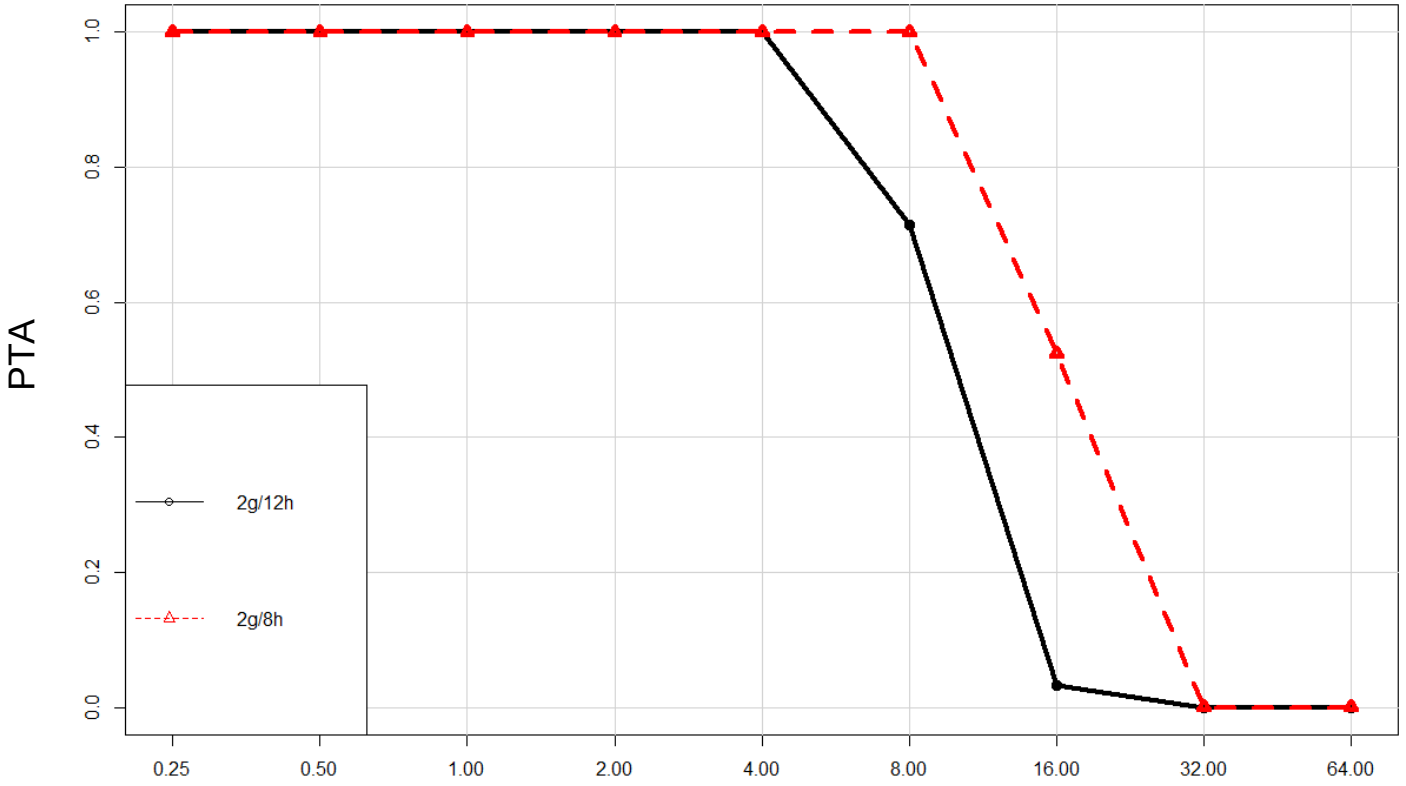
Standard dosing (2g/12h) PTA = 0.99

newly proposed dosing (2g/8h) PTA = 1

Probability of Target Attainment (PTA) of plasma free temocillin concentrations

For critically-ill patients

Target: *f*T > BSAC breakpoint = 8 mg/L of 100% of the time, based on a mean free fraction of 35.0 ± 12.3% (mean of values observed for patient),

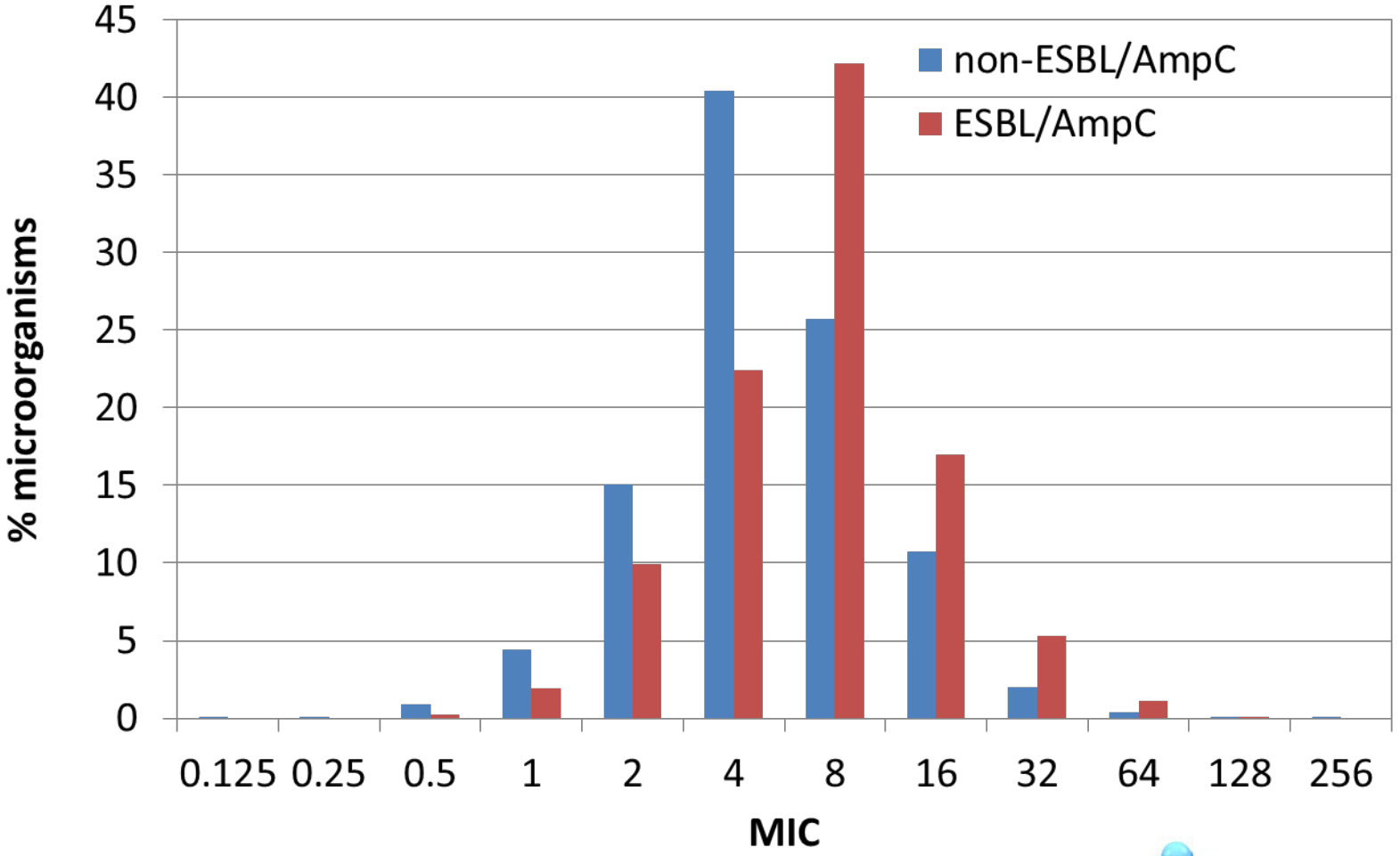


Standard dosing (2g/12h) PTA = 0.7

newly proposed dosing (2g/8h) PTA = 1

Which are the actual (and recent) observations ?

MIC distributions of *E. coli* : ESBL/AmpC (n=1155) vs non-ESBL/AmpC (n=1473)



Source: Eumedica (data on file)