FACULTY OF
PHARMACEUTICAL SCIENCES

DEPARTMENT OF BIOANALYSIS
LABORATORY OF MEDICAL BIOCHEMISTRY AND CLINICAL ANALYSIS

PKPD: PAST, PRESENT AND FUTURE

Applied to antibiotics - Prof. Dr. An Vermeulen - 23 Nov 2017

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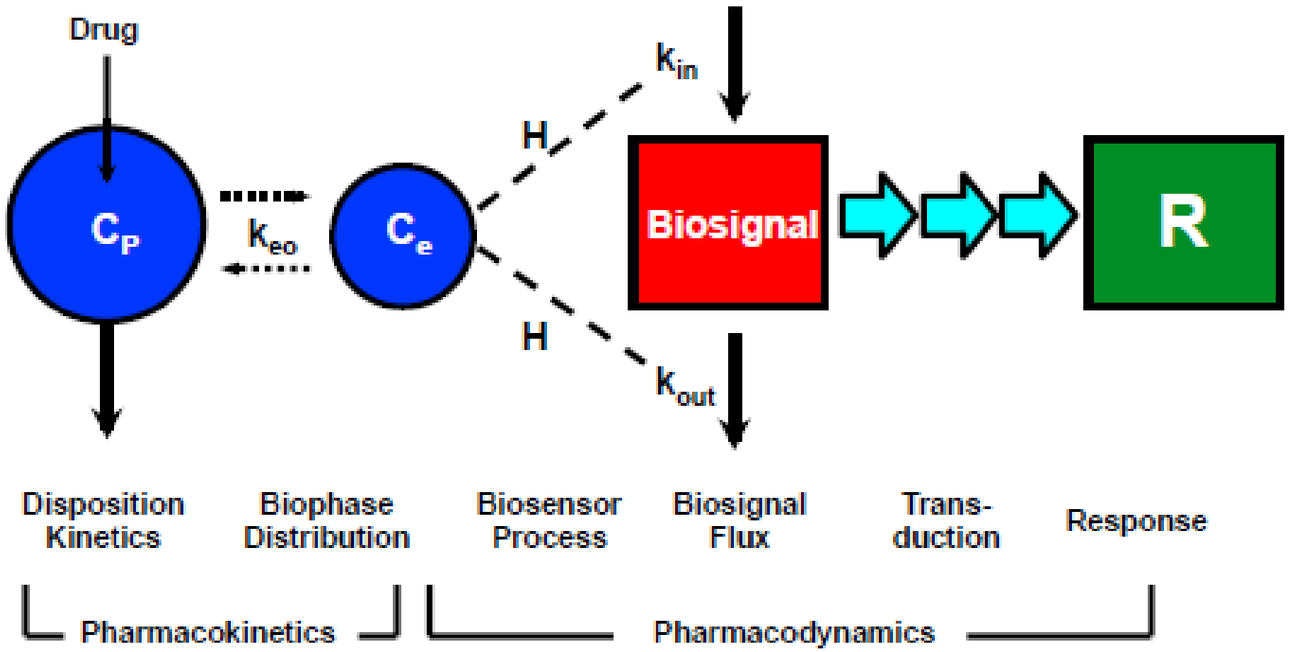
Components of Pharmacokinetic and Pharmacodynamic Systems



Adapted from Jusko et al., J Pharmacokinet Biopharm 23:5 (1995)
Mini-review: Mager et al., Drug Metab Disp 31:510 (2003)

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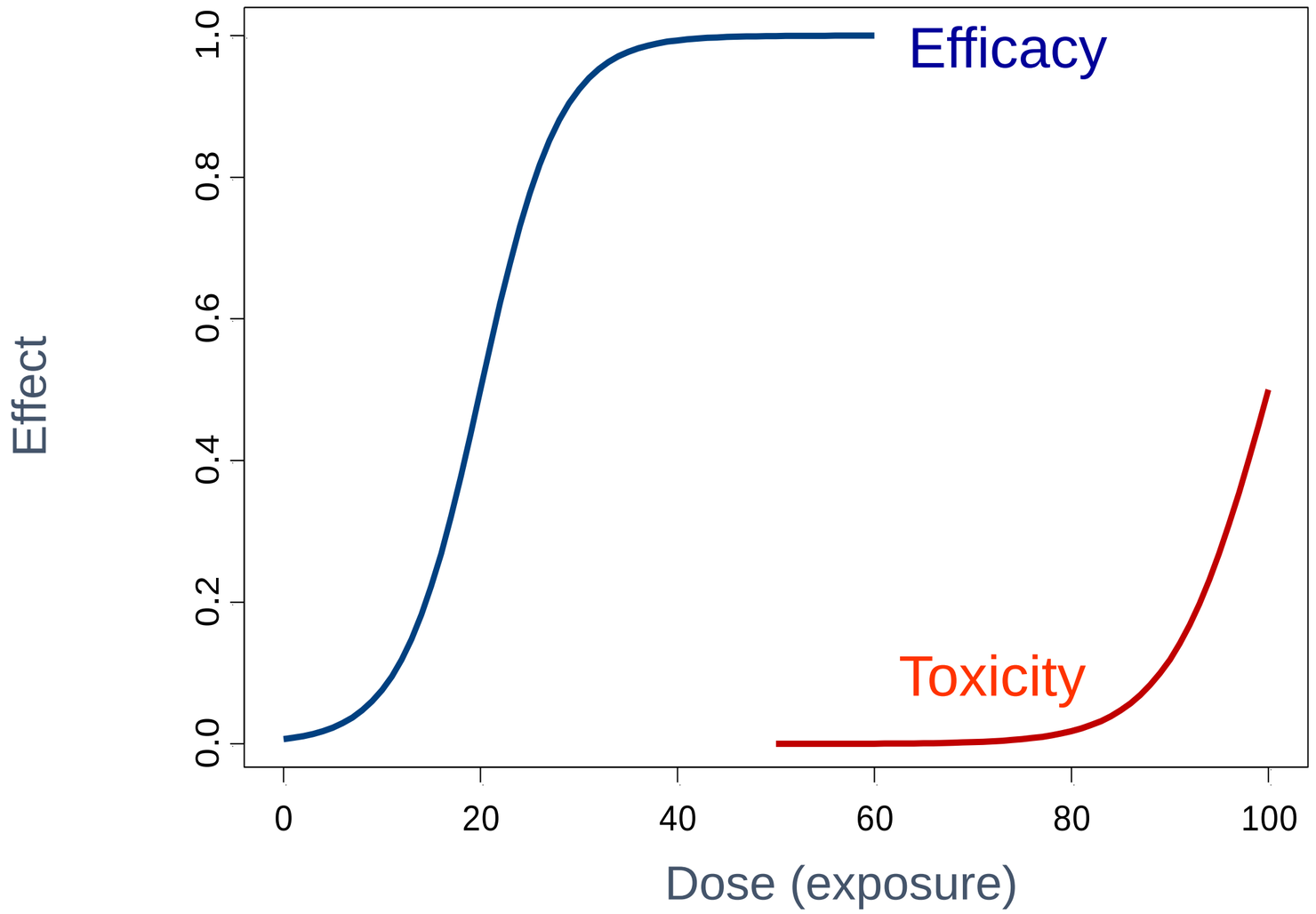
DOSE SELECTION MADE EASY



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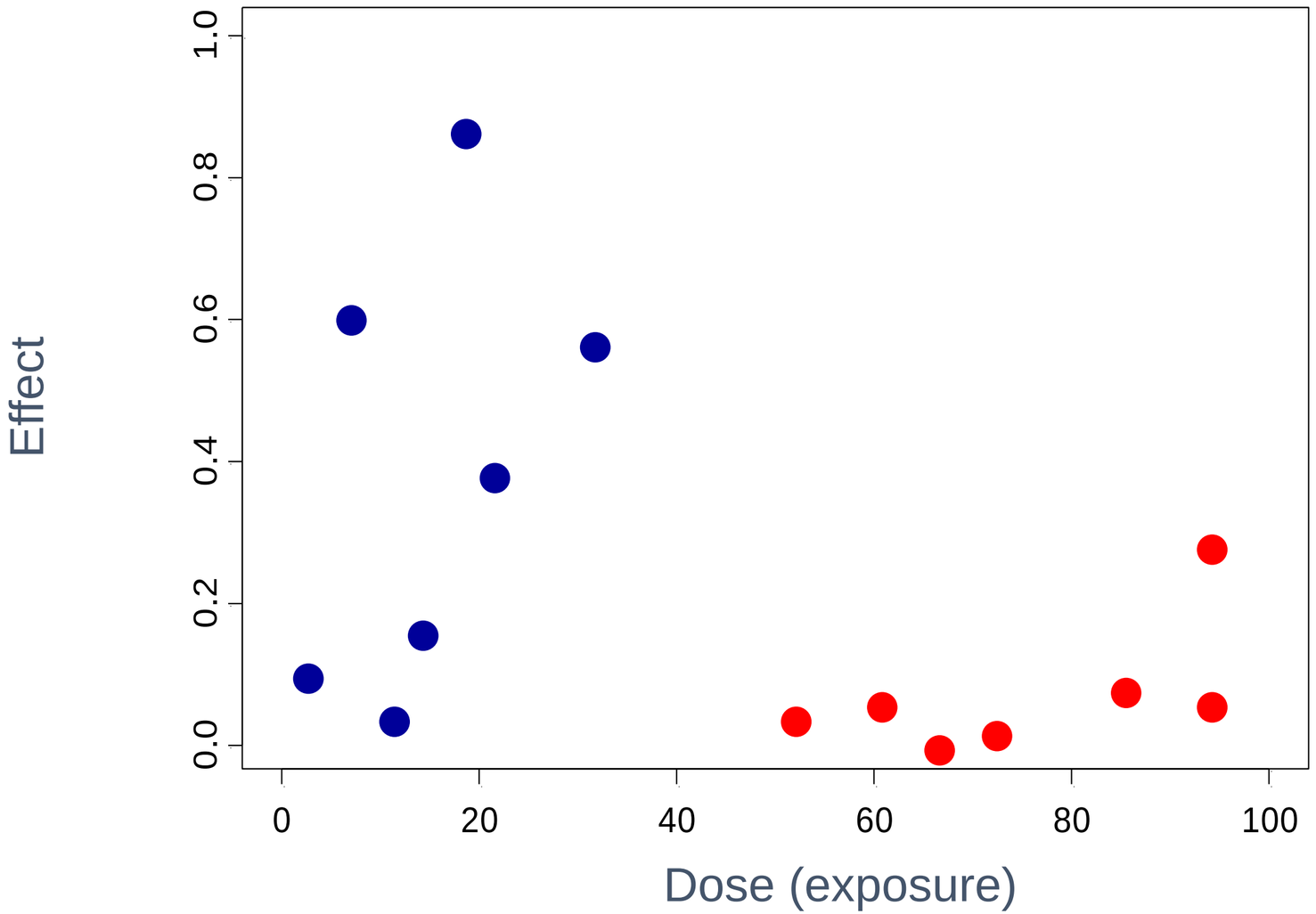
IN REALITY …



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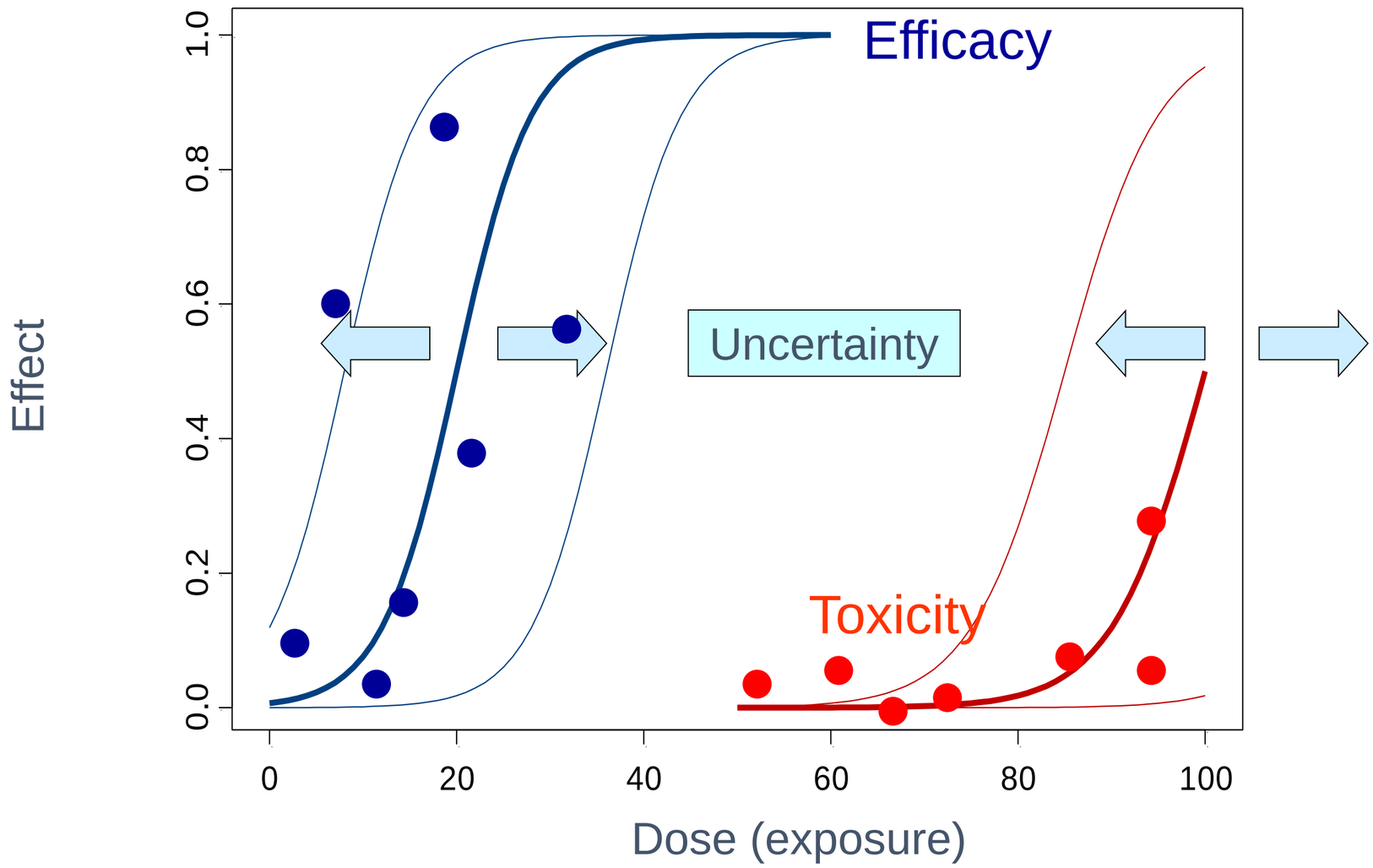
… KNOWLEDGE IS IMPRECISE



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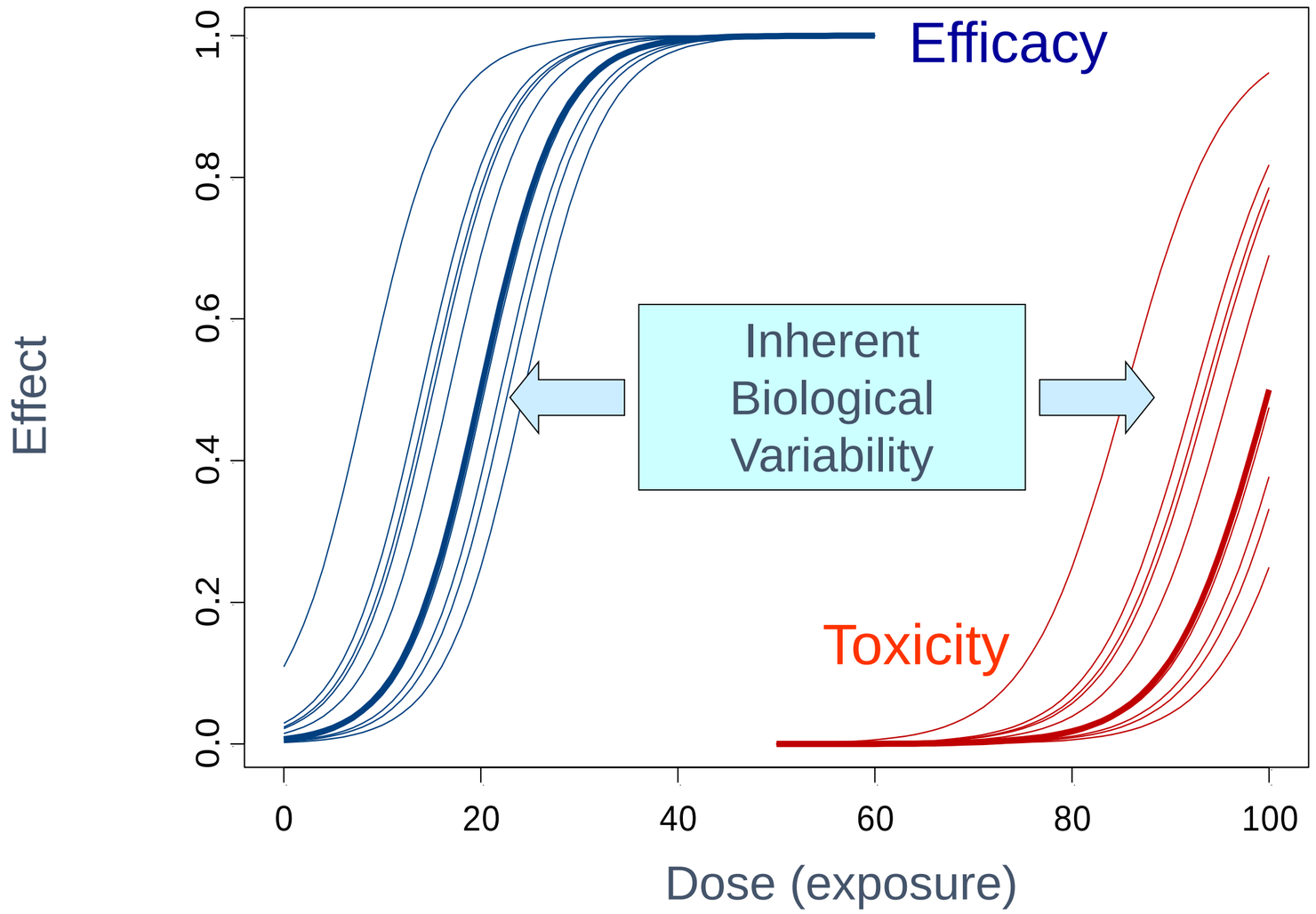
ALSO, ALL PATIENTS ARE DIFFERENT



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PKPD MODELING

- We try to establish relationships between exposure (mostly plasma concentrations) and effects
  - In a way, if we focus on PK, it is because we believe it is a biomarker for effects, and that understanding the PK profile helps to understand the PD (effects) profile
  - Most of the times, we can not measure the concentrations at the effect site, and we sample plasma concentrations instead (easy matrix to sample and to measure concentrations in)
  - The relationship between plasma and effect site concentrations is then again linked mathematically
- Once a model is developed, it allows simulations of scenarios we have not studied/for which we do not have information
  - Time points w/o sampling
  - Additional doses/dose regimen
  - Repeated dosing (using single dose data)
  - At population & individual level
  - For different covariate subgroups (pediatrics, CrCL, BWT, ..)

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PKPD MODEL APPLICATIONS

- **Conceptualization and quantification**
- **In vitro → In vivo extrapolation**
- **Species scaling**
- **Clinical trial design**
- **Design of new dosage forms**
- **Comparative efficacy/toxicity**
- **Patent enhancement**
- **Labeling advice**

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PHARMACOKINETICS

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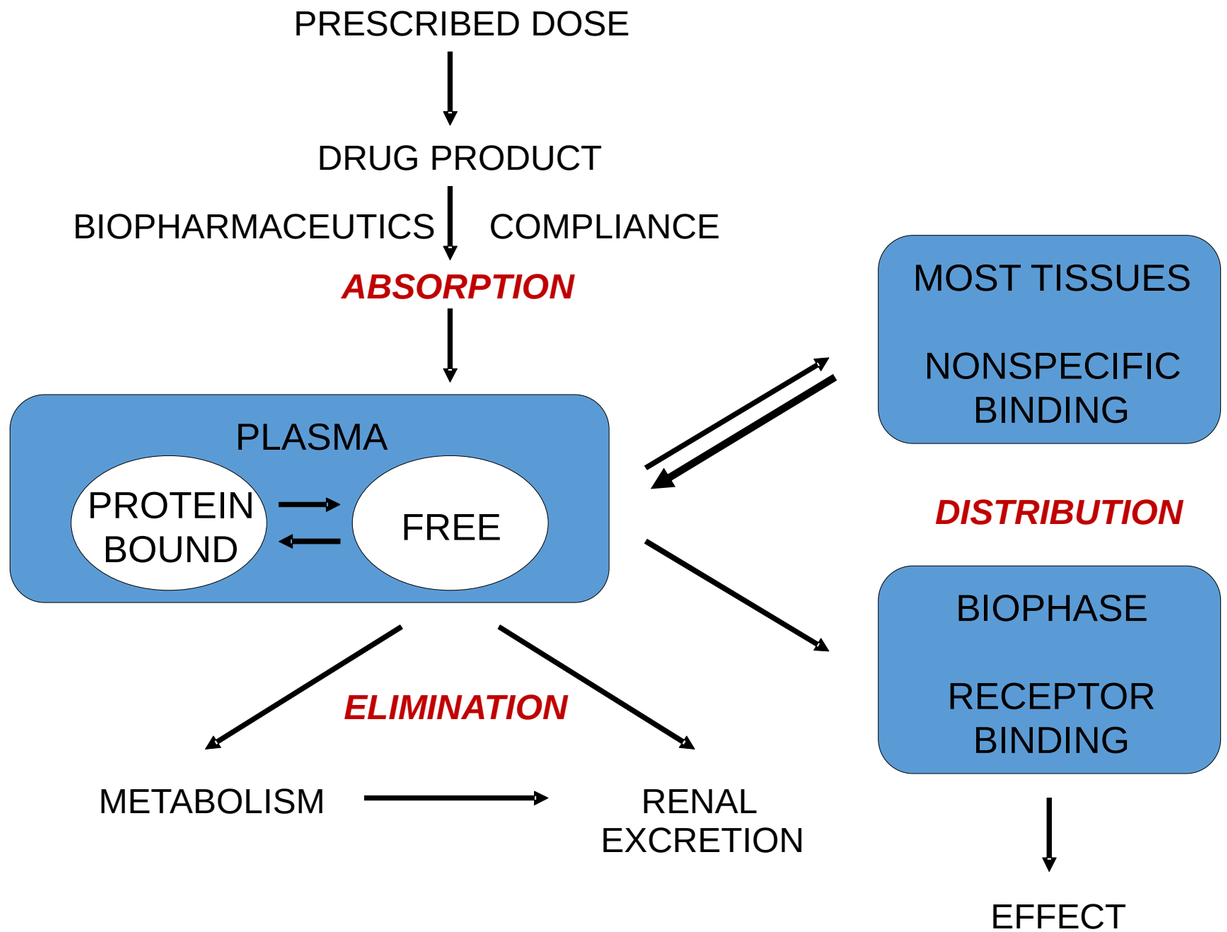
PHARMACOKINETICS

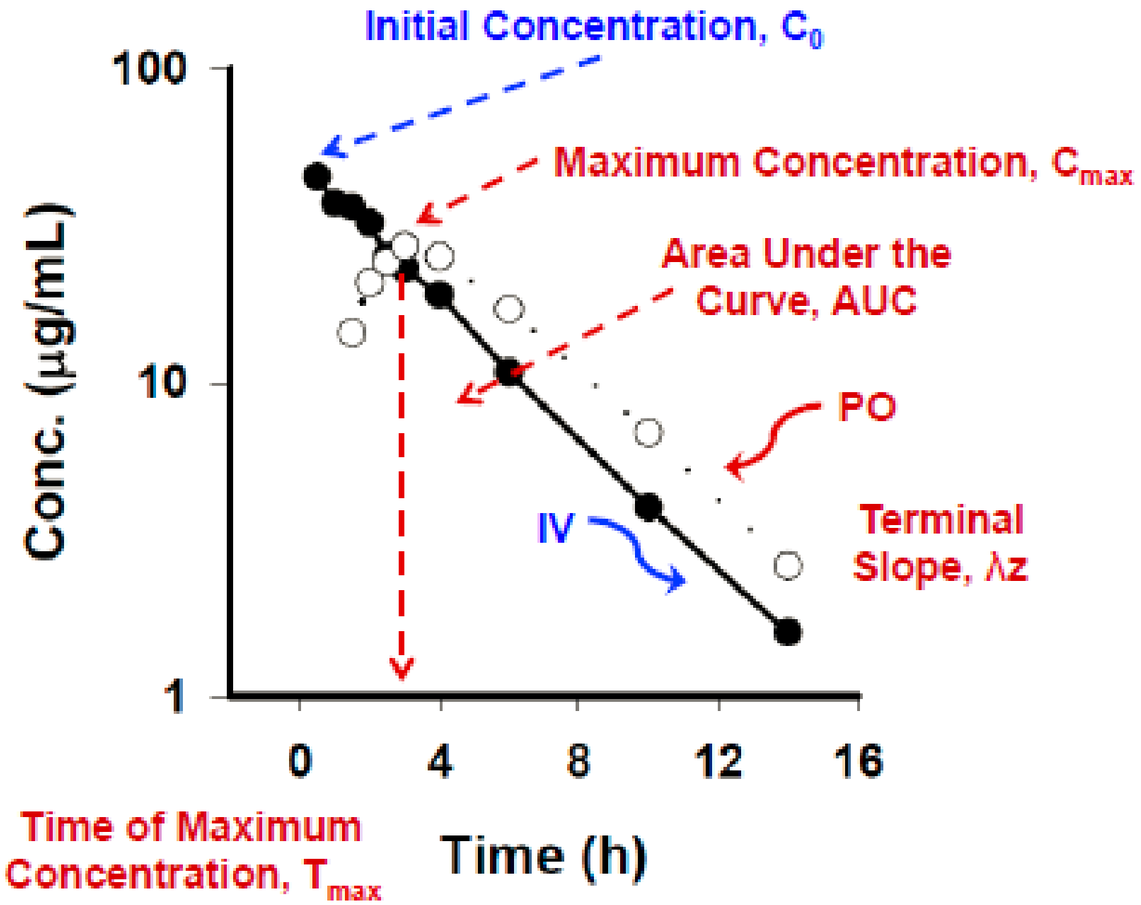
Pharmacokinetics is the study and mathematical characterization of the time course of drug absorption, distribution, metabolism, and excretion (**ADME**) processes that determine the time-course of drug action.



Adapted from Atkinson, Principles of Clinical Pharmacology (2001)

NONCOMPARTMENTAL ANALYSIS

Time-Course of Drug Exposure



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NONCOMPARTMENTAL ANALYSIS

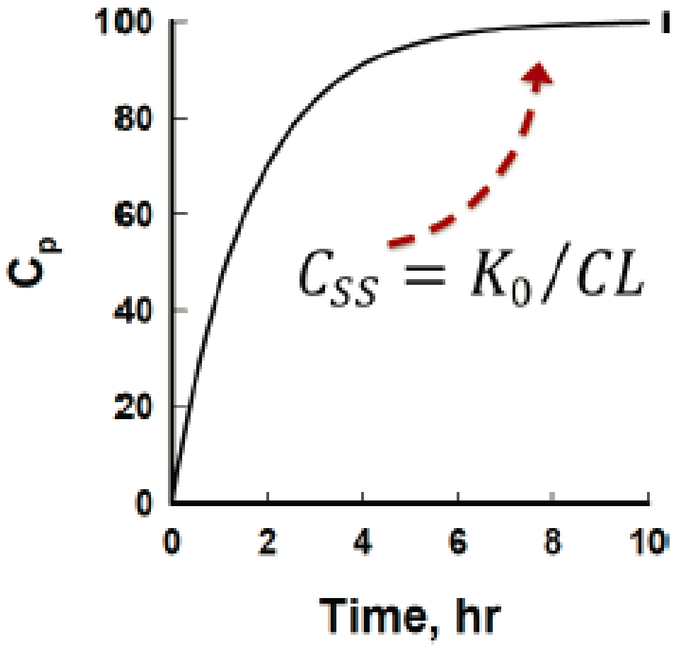
$$CL = \frac{F \times Dose}{AUC}$$

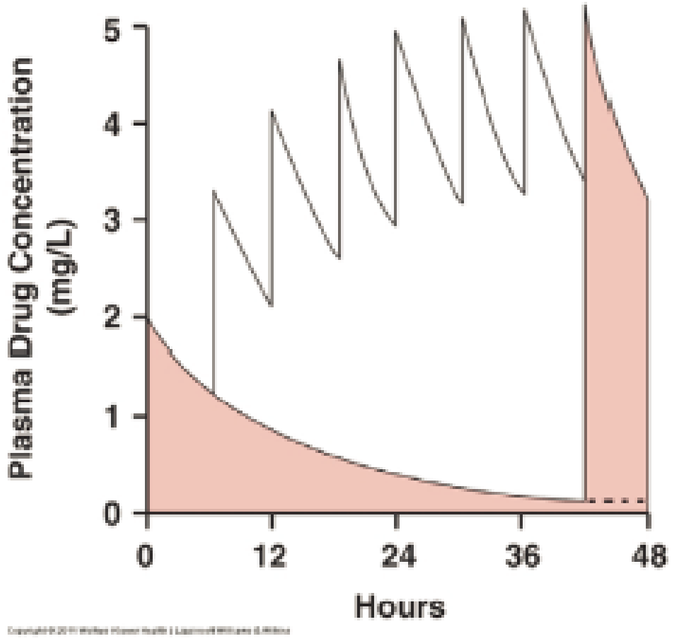
Clearance (CL)

Multiple-Dosing Regimen

$$\overline{C}_{p,ss} = \frac{F \cdot Dose}{CL \cdot \tau}$$

Constant-Rate Regimen





From Rowland and Tozer. 4th Ed. (2010)

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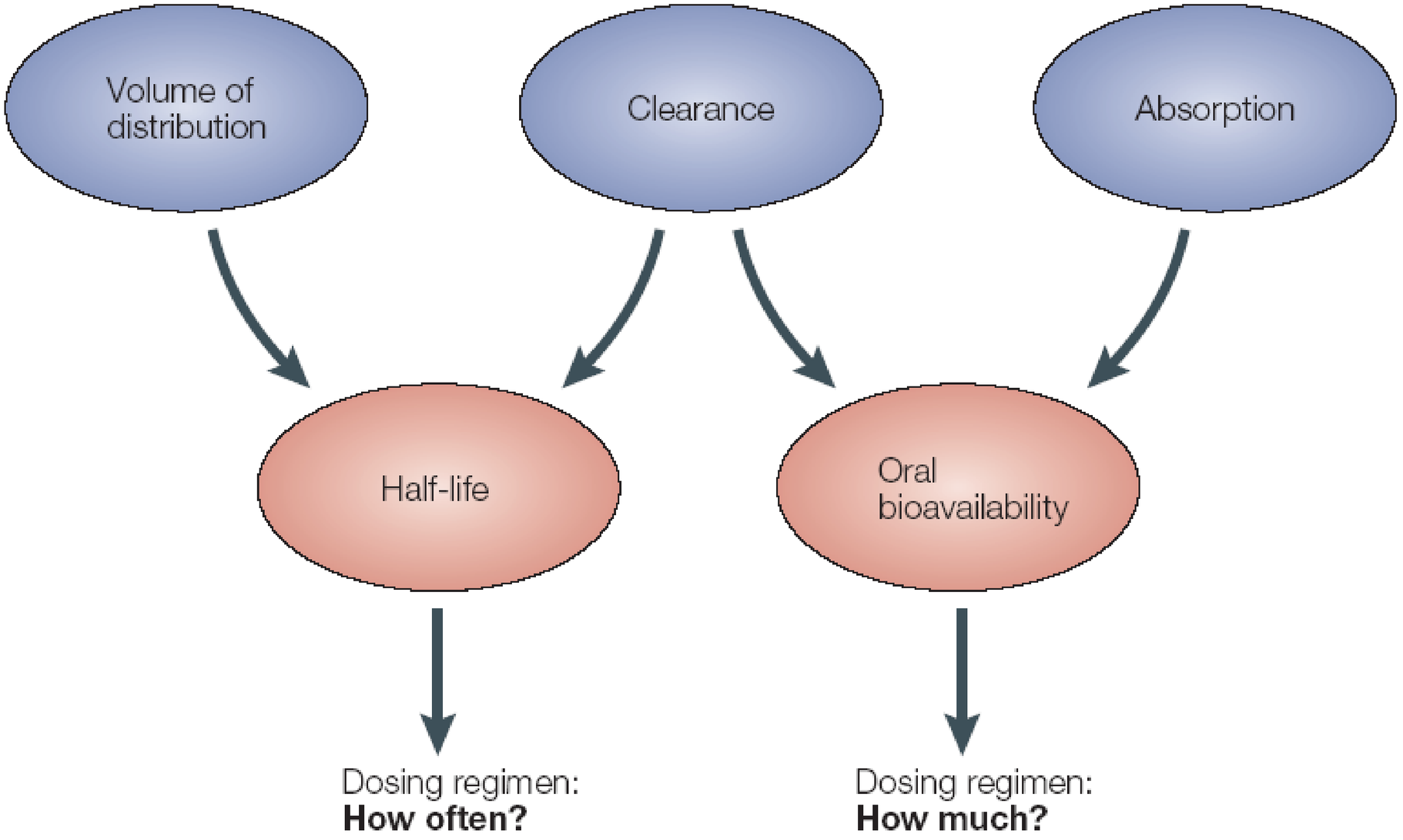
PRIMARY PHARMACOKINETIC PROPERTIES



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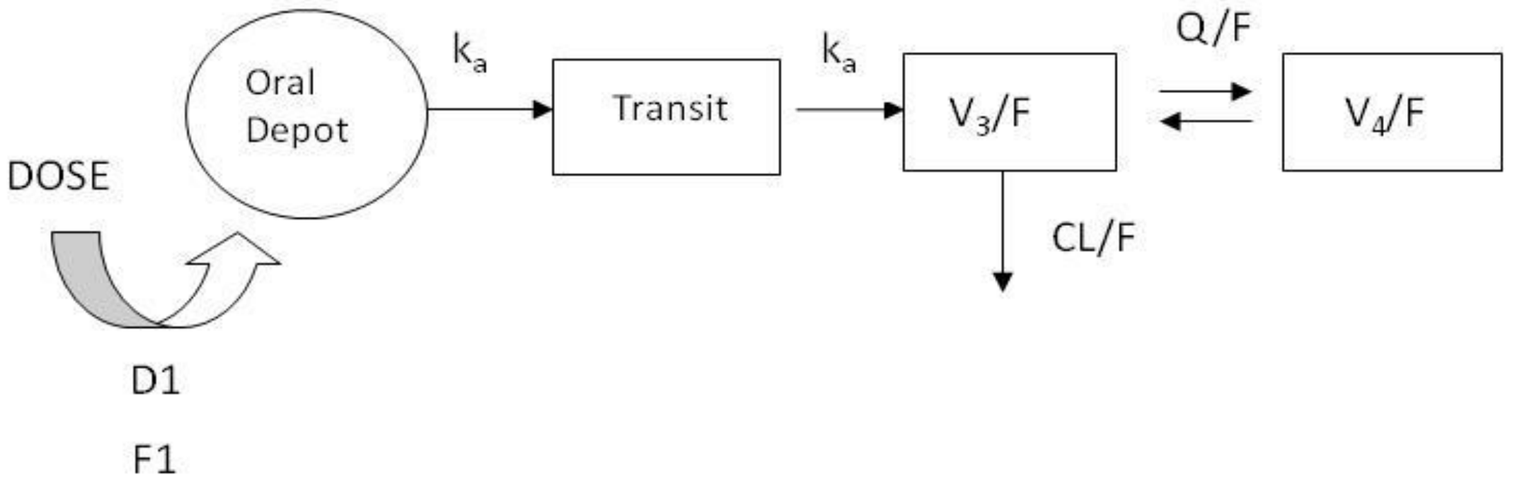
van de Waterbeemd and Gifford. *Nature Rev Drug Disc*. 2:192-204 (2003)

COMPARTMENTAL ANALYSIS



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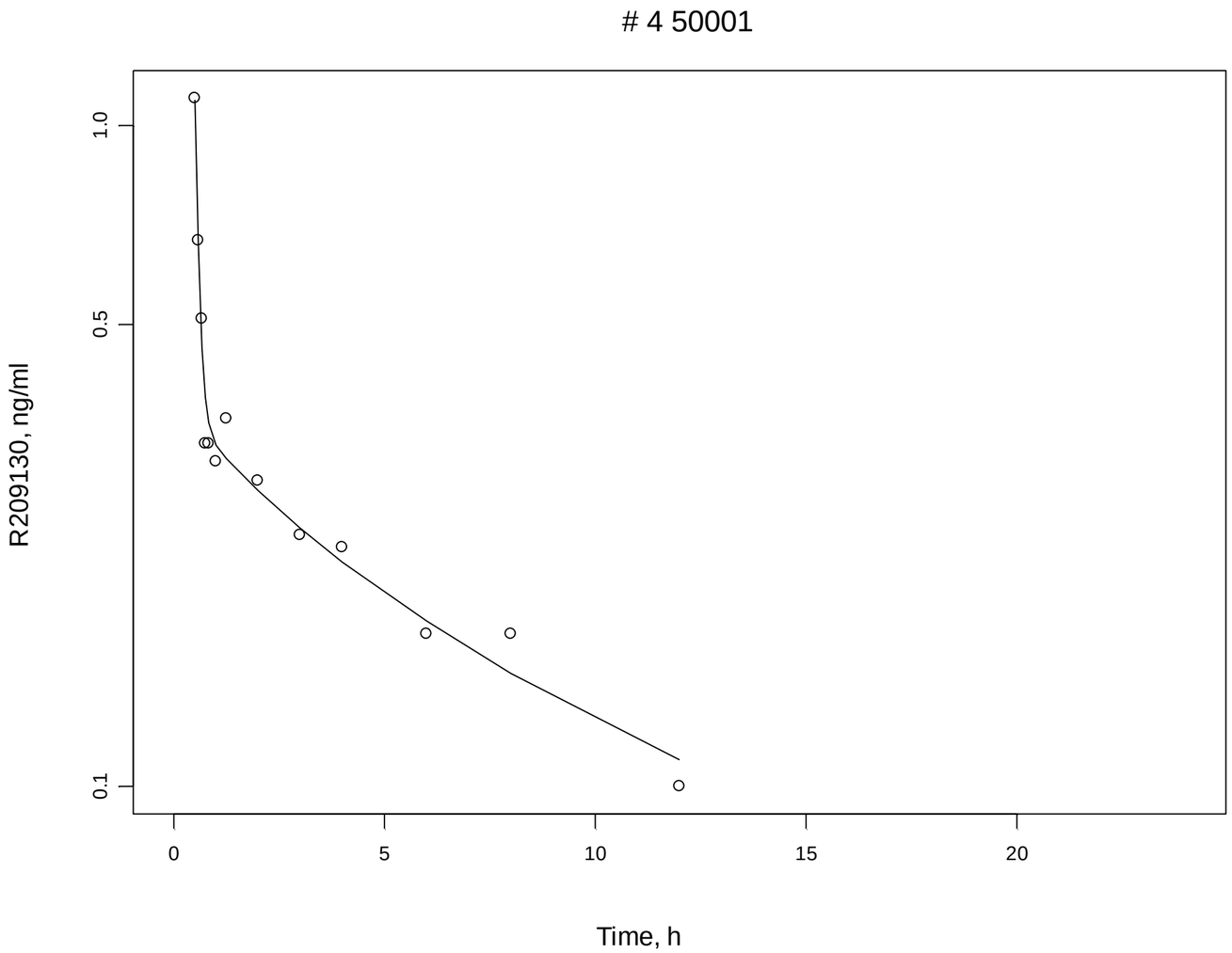
COMPARTMENTAL ANALYSIS



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THE ASPECT VARIABILITY

- Modelling is essentially similar at the population level !
- But ..
  - At the population level, the aspect *variability* comes into play
  - In a population analysis, the focus is on
    - estimating the magnitude of this variability
    - trying to identify patient characteristics that can explain (part of) this variability
    - dose-adjustments in subsets? LABELLING impact !
    - dose-individualisation in individuals? (avoid TDM - therapeutic drug monitoring)
- So ..
  - Three levels of variability have to be considered:
    - IIV or BSV: inter-individual or between-subject variability
    - IOV: inter- or between-occasion variability
    - Intra-subject, within-subject or residual (unexplained) variability

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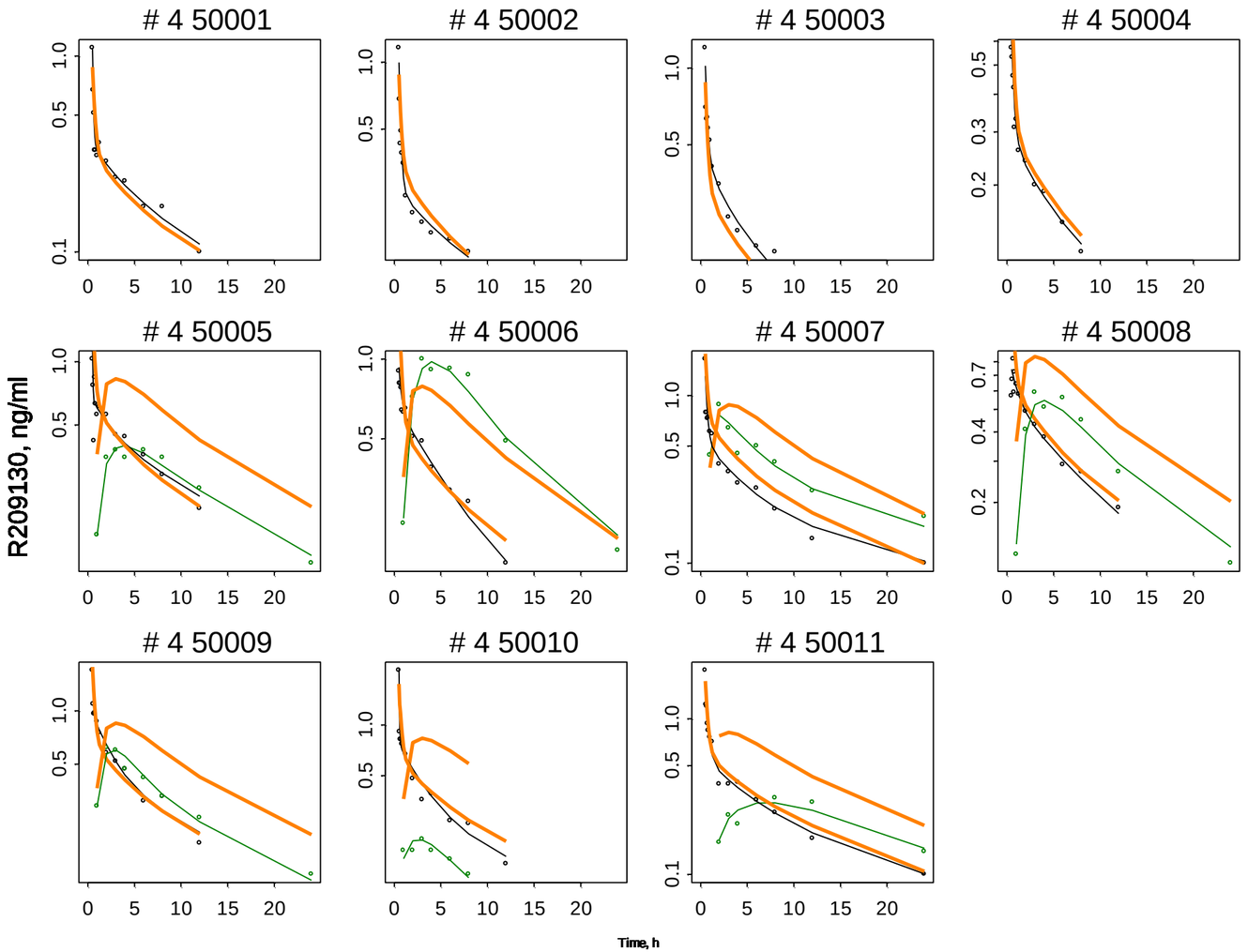
16

THE ASPECT VARIABILITY



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POPULATION PK PRINCIPLES

- Nonlinear Mixed Effects Modelling (NONMEM)
- Mixed effects
  - Fixed effects (θ)
  - Random effects (η, ε)

- Fixed effects
  - Estimate mean PK(PD) parameters in the population (= typical values, central tendency, population average, ..)
  - Identify factors that influence the PK (PD) parameters (demographics, lab values, PGx, smoking habits etc…)

- Random effects
  - Estimate unexplained variability
    => IIV, IOV and residual variability

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PHARMACODYNAMICS

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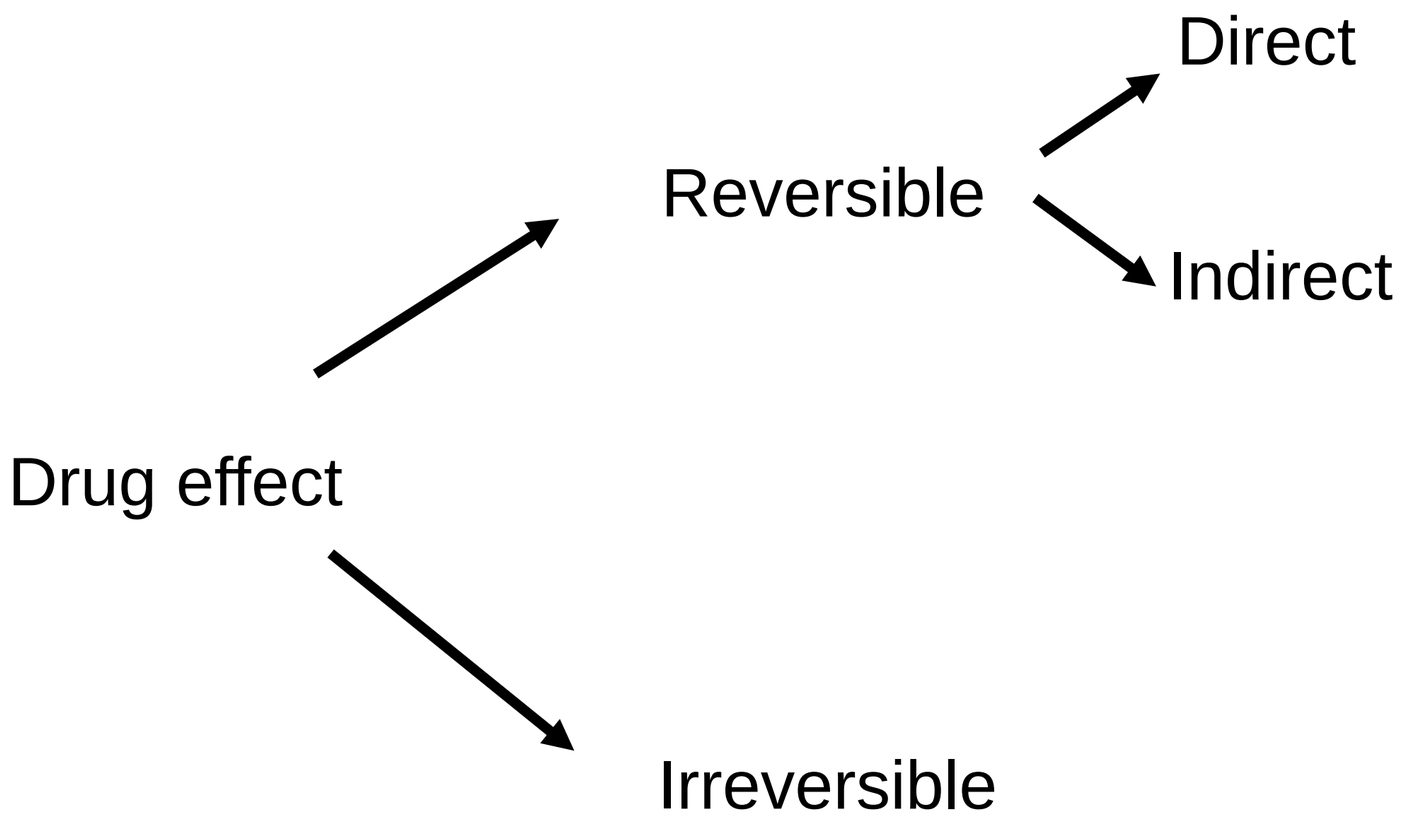
PK-PD RELATIONSHIPS: TYPE OF EFFECTS



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REVERSIBLE EFFECTS – DIRECT

CONCENTRATION-EFFECT MODELS

Linear $$Effect = \alpha \cdot C_p$$

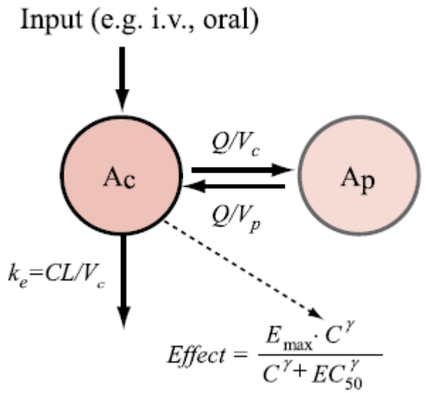
Log-linear $$Effect = \ln(C_p)$$

Power $$Effect = \alpha \cdot C_p^{\gamma}$$

E_{max} $$Effect = \frac{E_{max} \cdot C_p}{EC_{50} + C_p}$$

Effect directly related to plasma concentration

Sigmoid E_{max} $$Effect = \frac{E_{max} \cdot C_p^{\gamma}}{(EC_{50} + C_p)^{\gamma}}$$



EC_{50}/IC_{50} values: the potency of the drug
E_{max}/I_{max} values: the efficacy of the drug
γ : sigmoidicity factor

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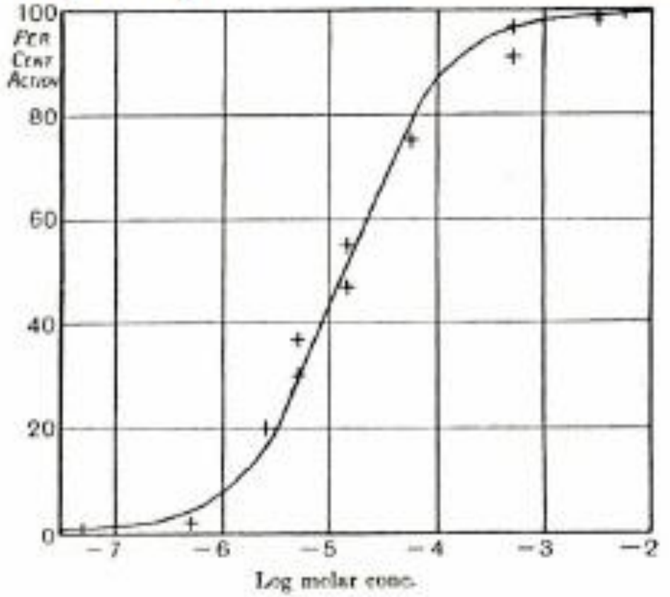
Occupancy Theory

- **A. V. Hill**
  - Law of mass action for occupancy
- **A. J. Clark**
  - Assumed response ∝ receptor occupancy

$$\frac{E}{E_{\max}} = \frac{AR}{R_{TOT}} = \frac{A}{K_D + A}$$

- **Hill Equation**

$$E = \frac{E_{\max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$



ACh induced contraction of frog rectus abdominis muscle. Clark, *J Physiol.* (1926)

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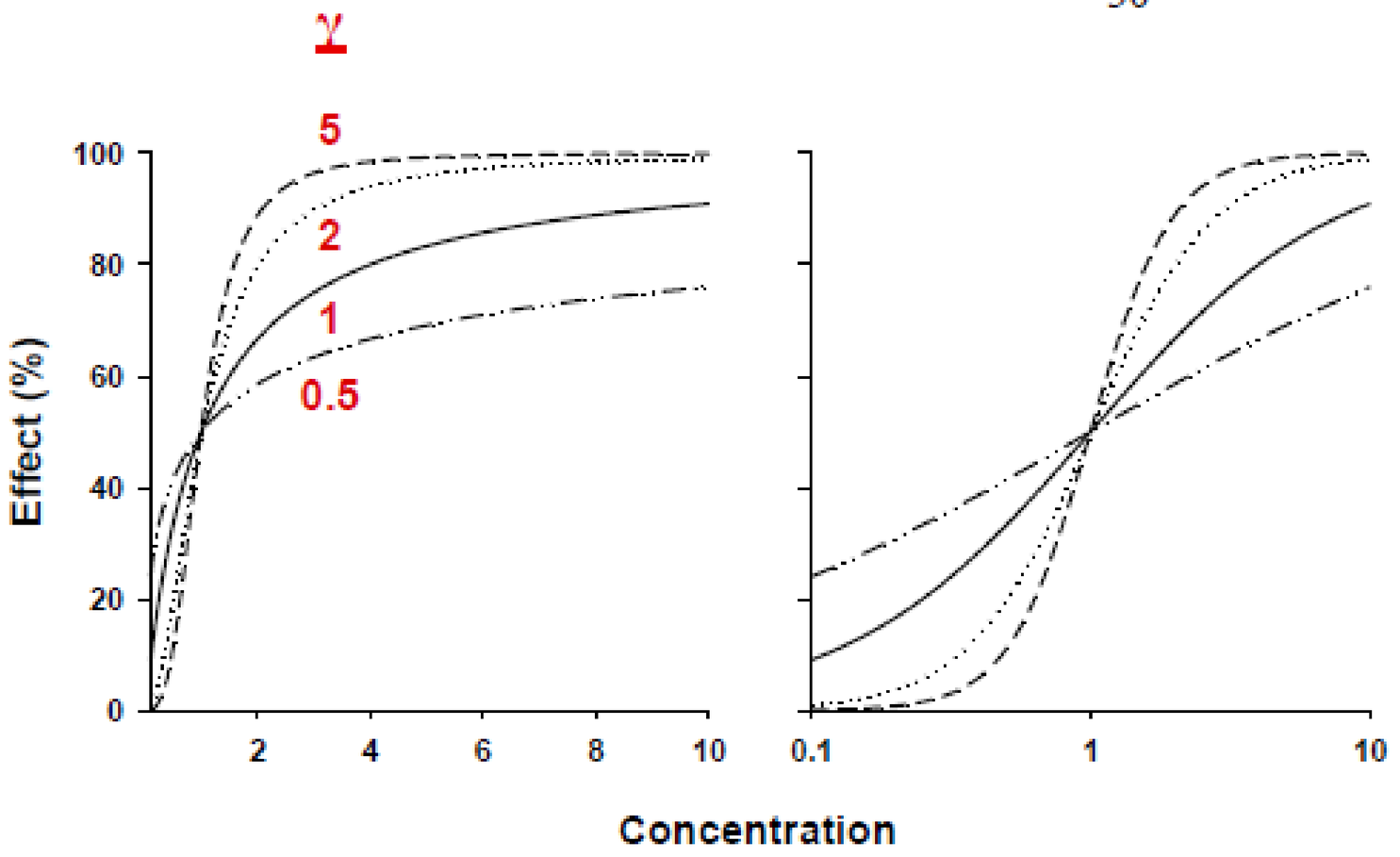
Concentration-Effect Relationship

$$E = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$



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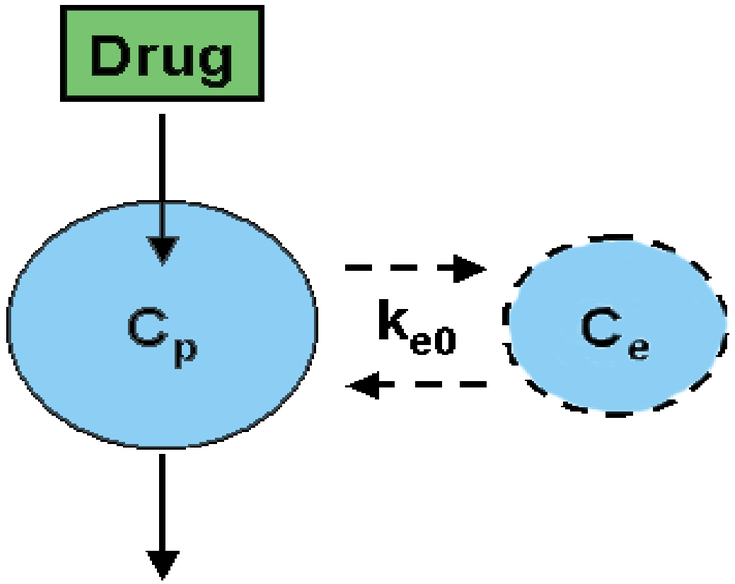
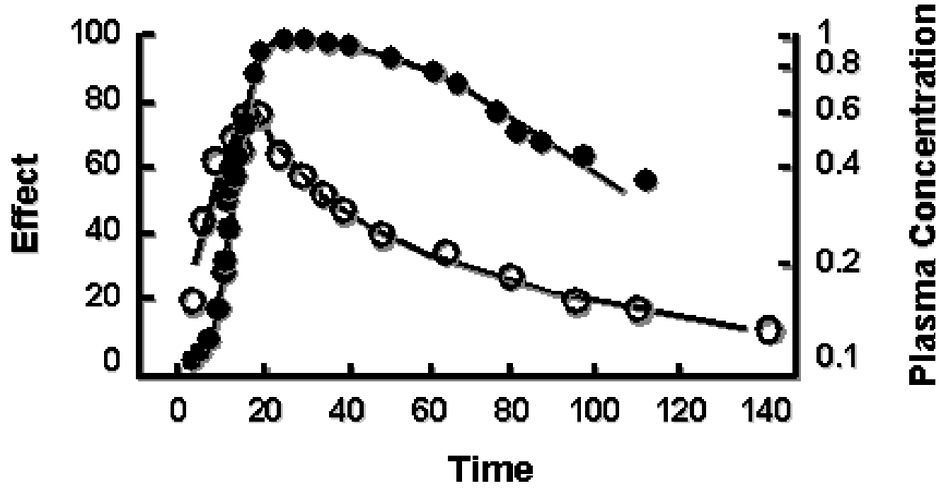
REVERSIBLE EFFECTS – INDIRECT

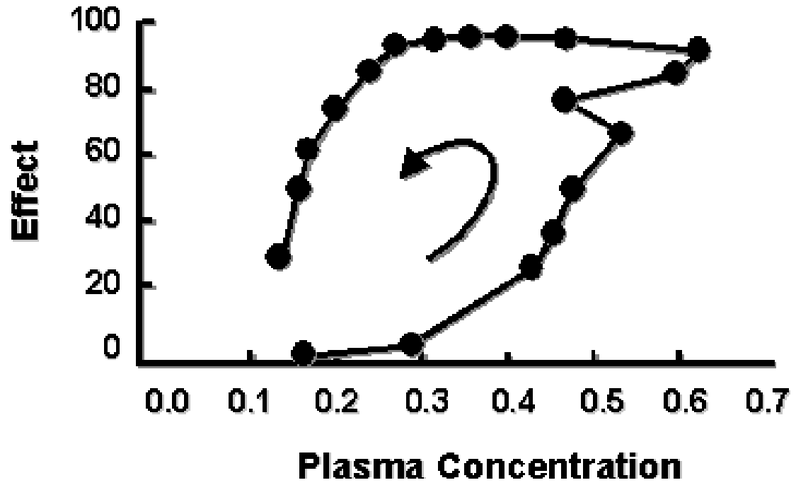
MODELING A BIOPHASE



$$\frac{dC_e}{dt} = k_{eo}\left(C_p - C_e\right)$$

$$E = \frac{E_{max} \cdot C_e}{EC_{50} + C_e}$$





Segre, Il Pharmaco (1968)
Sheiner et al., CPT (1979)

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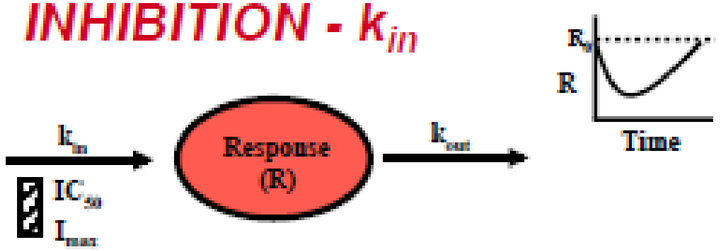
REVERSIBLE EFFECTS – INDIRECT

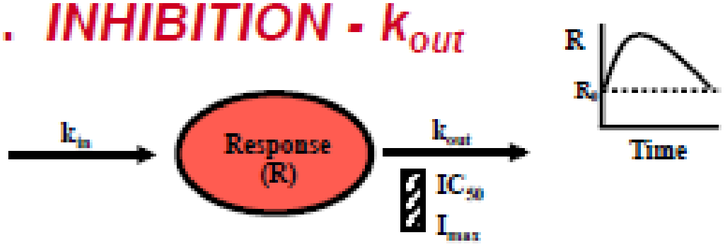
Family of Indirect Response Models

I. *INHIBITION - k_{in}*



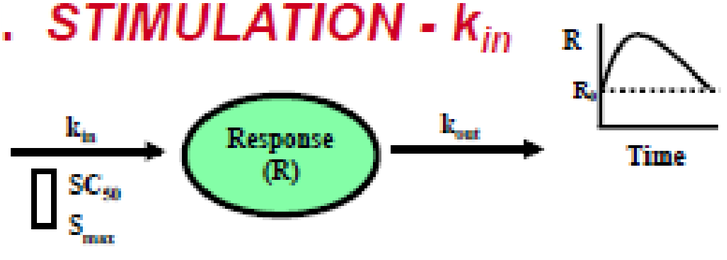
$$\frac{dR}{dt} = k_{in} \cdot \left(1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right) - k_{out} \cdot R$$

II. *INHIBITION - k_{out}*



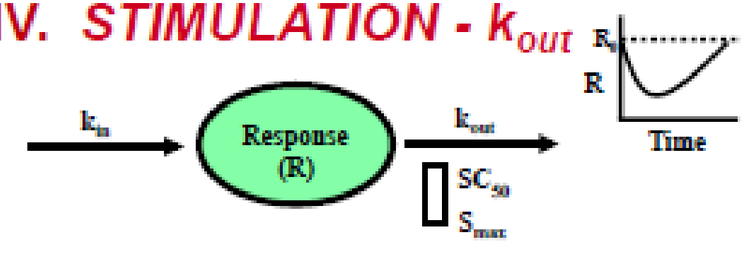
$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right) \cdot R$$

III. *STIMULATION - k_{in}*



$$\frac{dR}{dt} = k_{in}\left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) - k_{out} \cdot R$$

IV. *STIMULATION - k_{out}*



$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) \cdot R$$

Dayneka et al., *JPB* 21:457 (1993); Sharma and Jusko. *BJCP.* 45: 229 (1998)

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IRREVERSIBLE EFFECTS

- Chemotherapeutic effects
  - Simple cell killing
  - Killing and regrowth
  - Cell cycle effects
  - Clinical therapy
- Irreversible enzyme inhibition
- Reactive drug metabolites
- Simple drug toxicity
- Carcinogenicity models

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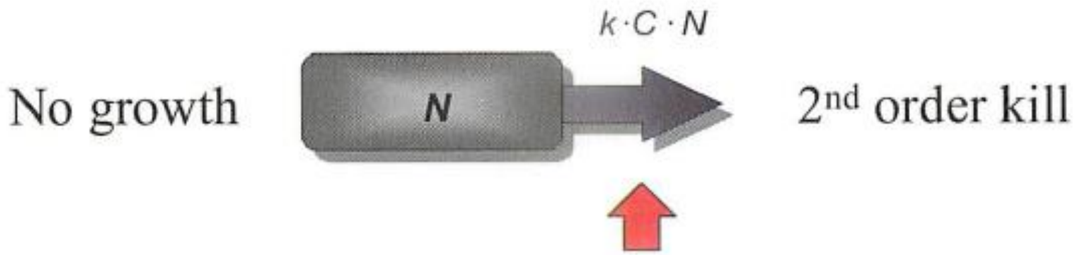
SIMPLE CELL KILLING



N = R

$$\frac{dR}{dt} = -K \cdot C \cdot R$$

Drecker function

$$R = R_0 \cdot e^{-k \cdot AUC_0^t}$$

$$S_F = \frac{R}{R_0} = e^{-k \cdot AUC_0^t}$$

$$ln\ S_F = -k * D_0/CL$$

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J. Pharm. Sci. 60:892 (1971)

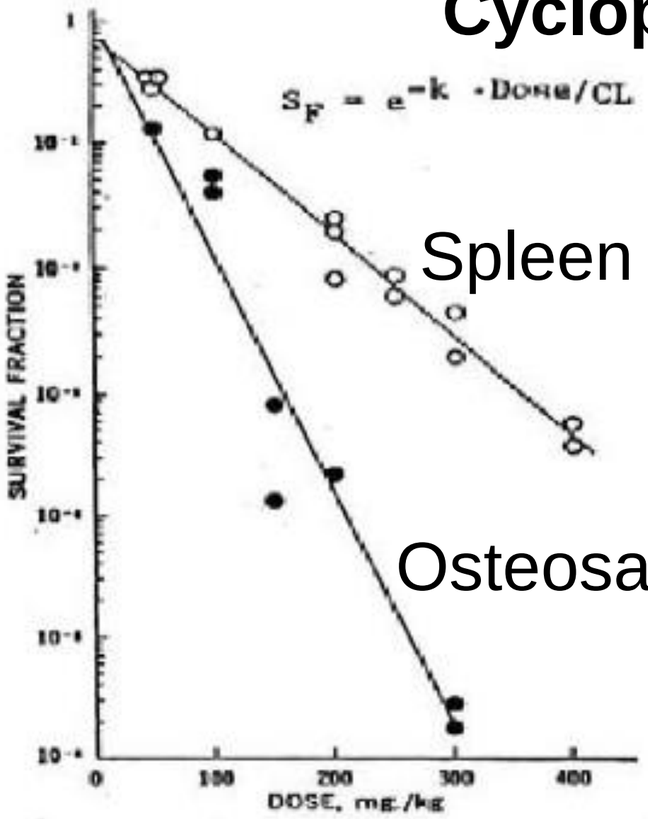
SIMPLE CELL KILLING

- Simple irreversible bimolecular interactions produce log S_F/linear dose cell survival curves.

- The $\dot{R} = -k \cdot C \cdot R$ function predicts AUC to be the major PK determinant of total response.

"DRECKER"

Cyclophosphamide - mice



Spleen cells

Osteosarcoma cells

Pharmacodynamics of Chemotherapeutic Effects: Dose–Time–Response Relationships for Phase-Nonspecific Agents

WILLIAM J. JUSKO *J. Pharm. Sci.* (1971)

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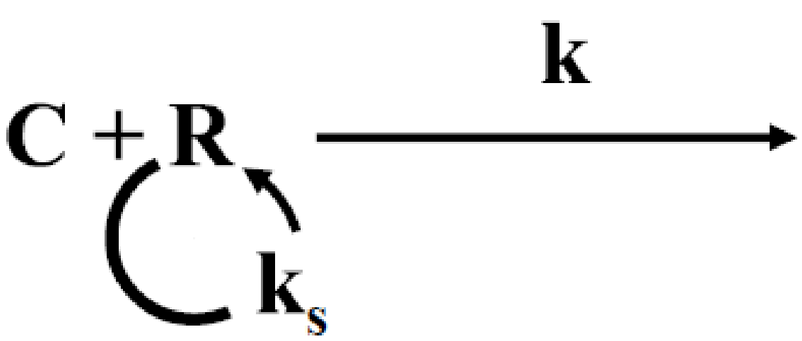
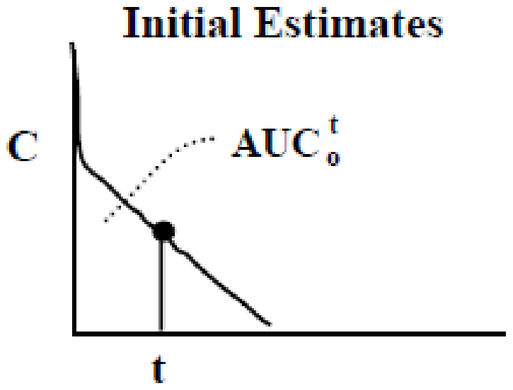
CELL KILLING – CELL GROWTH

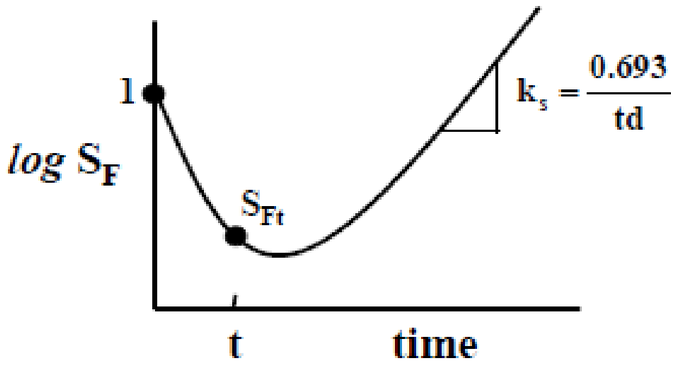


$$\frac{dR}{dt} = k_s \cdot R - k \cdot C \cdot R$$

$$R = R_o \cdot e^{k_s \cdot t} \cdot e^{-k \cdot AUC_o^t}$$

Jusko, *J. Pharm. Sci.* 60:892 (1971)





$$k = -\ln S_{Ft} / AUC_o^t$$

td = Doubling Time

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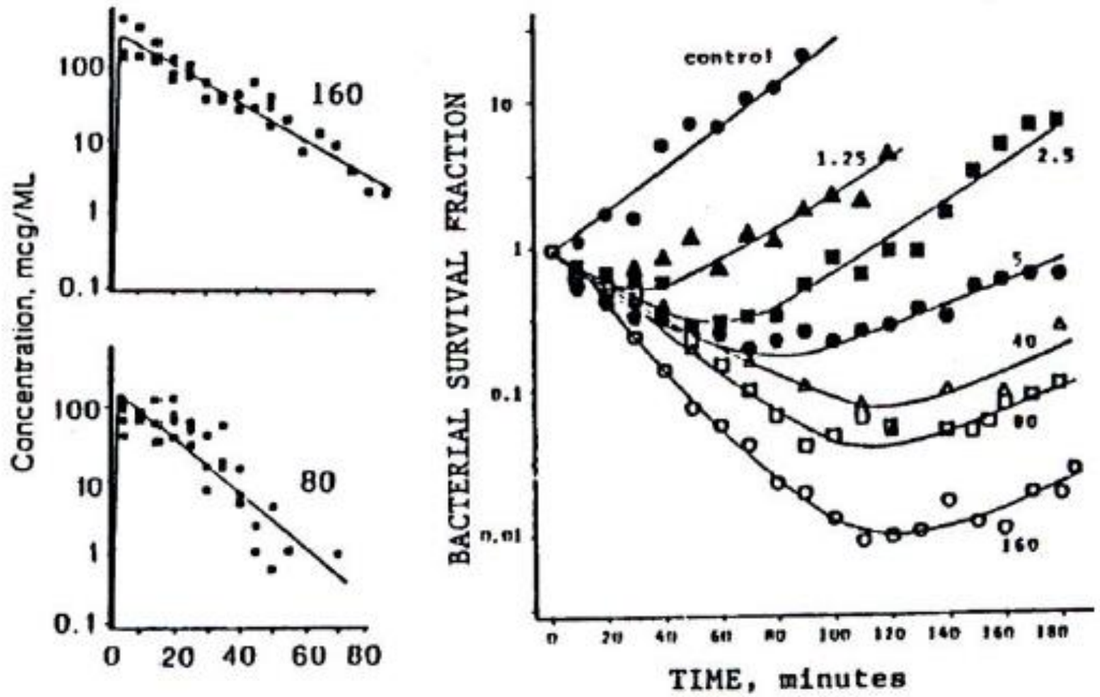
CELL KILLING – CELL GROWTH

Effects of Various Intraperitoneal Doses of Piperacillin on Killing and Growth Kinetics of Pseudomonas Aeruginosa in Neutropenic Mice. (Zhi Et Al, JPB 16:1988)



The joint effect of bimolecular drug/cell interaction and the ability of cell to grow produces biphasic survival curves with an initial phase of cell killing and a later phase of regrowth when all of the chemotherapeutic agent has been eliminated.

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ANTIBACTERIAL EFFECTS

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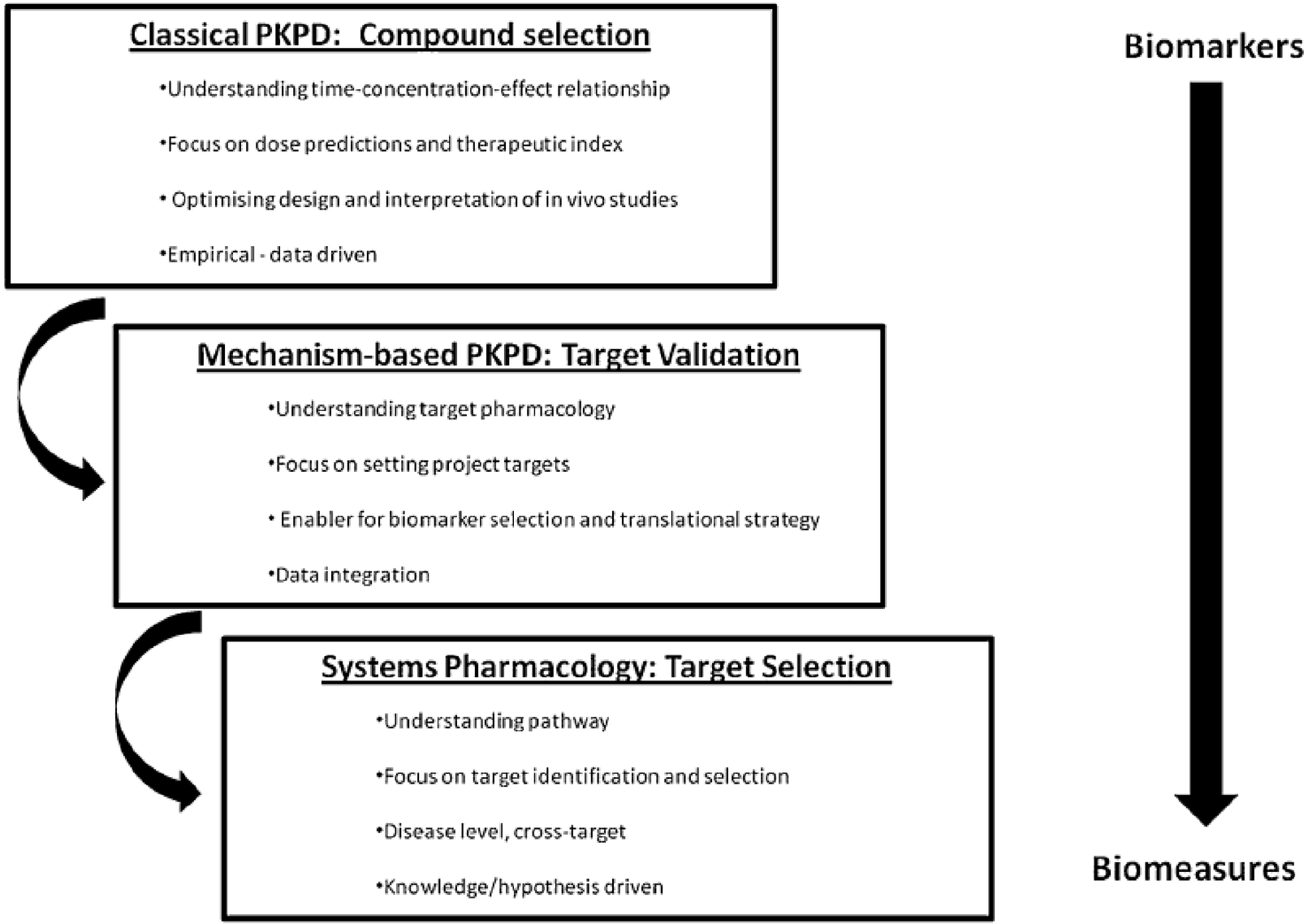
PKPD: PAST, PRESENT AND FUTURE …



Pharm Res (2011) 28:1460–1464

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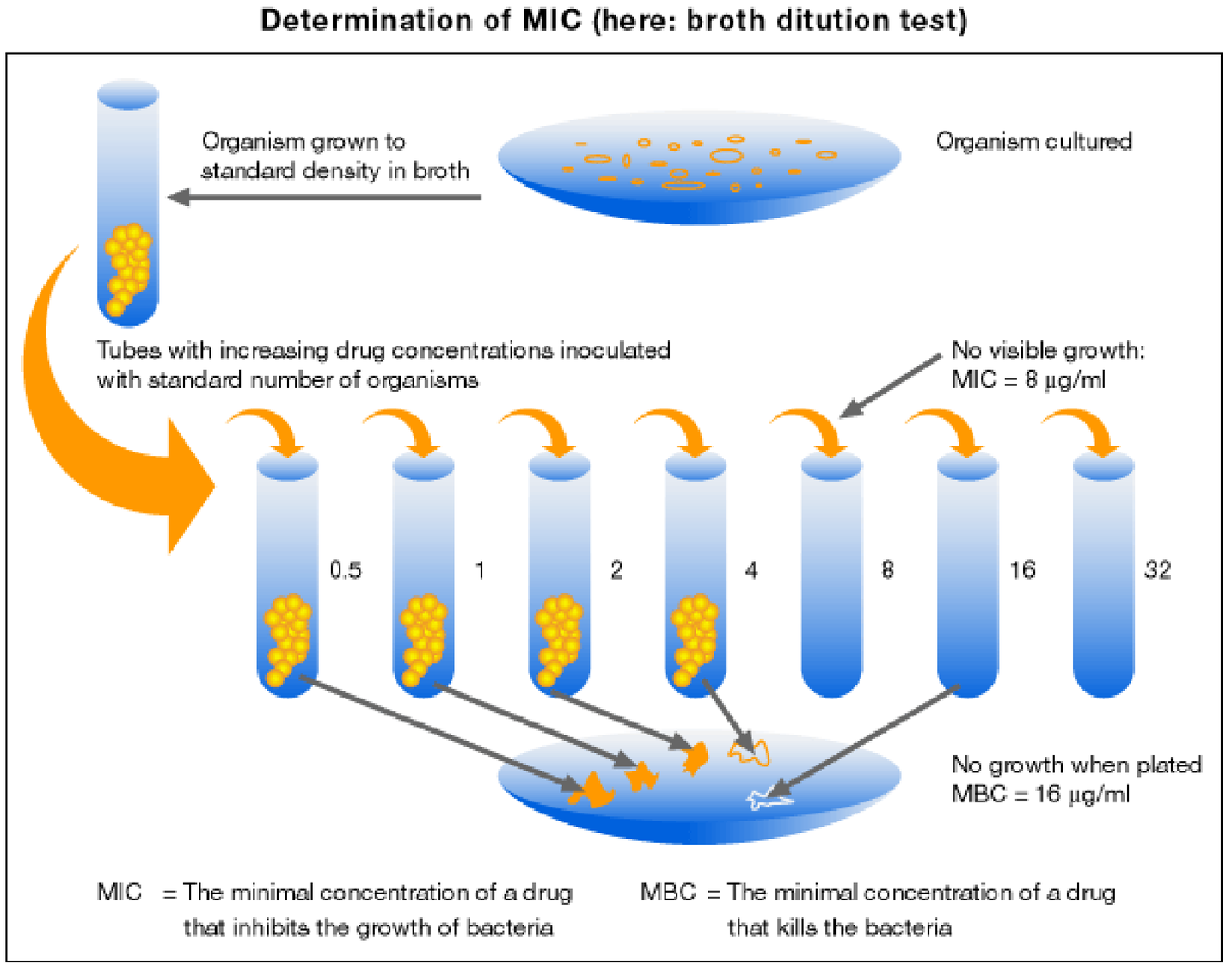
MIC



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MIC

MIC: Minimum Inhibitory Concentration

No cell growth:

$$\frac{dR}{dt} = k_g \cdot R - k \cdot C \cdot R = 0$$

$k_g = k_s$

$$k_g = k \cdot C = k \cdot MIC$$

$$MIC = k_g / k$$

Cautions:

MIC is a dependent variable fraught with experimental uncertainties.

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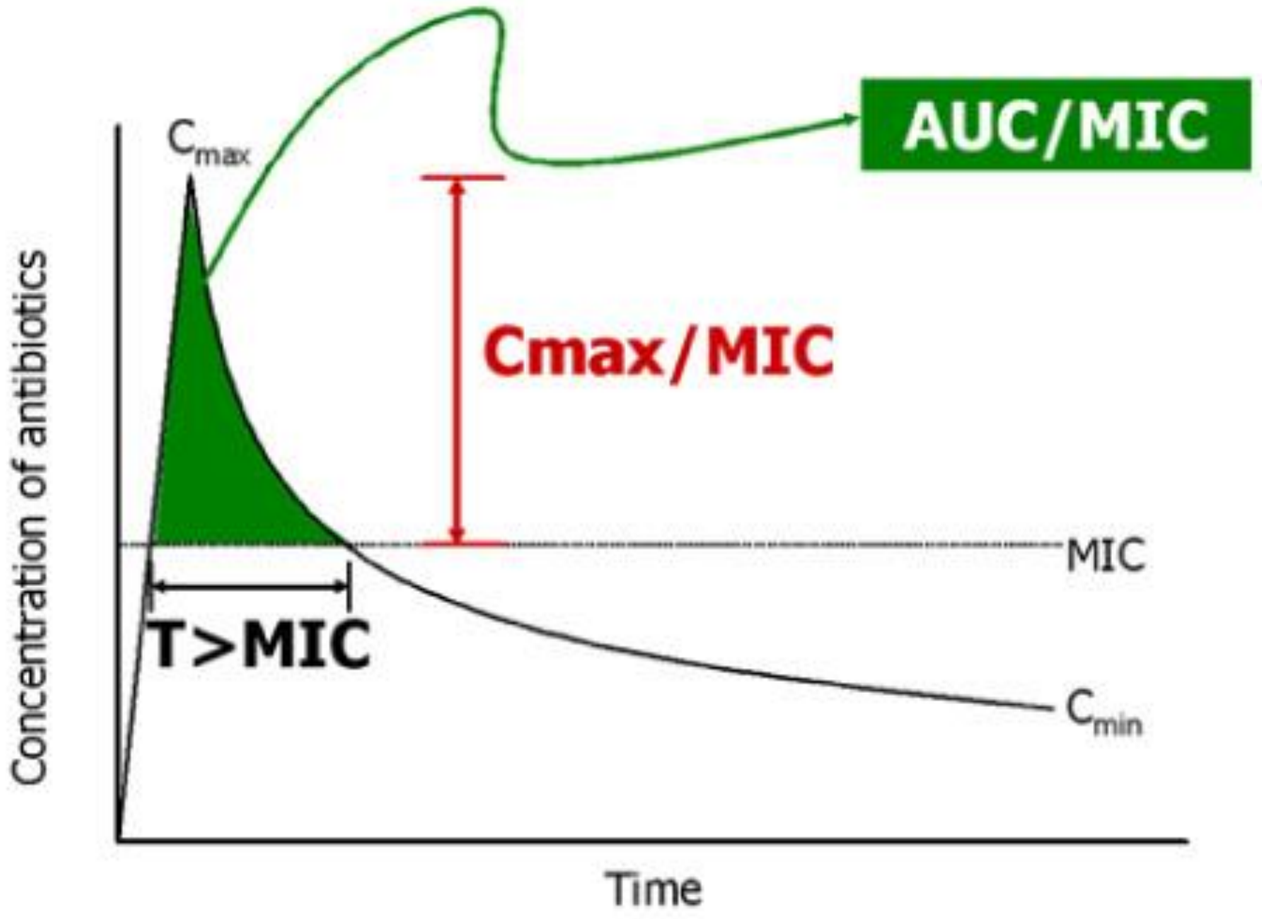
SUMMARY PK MEASURES



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ANTIBACTERIAL EFFECTS

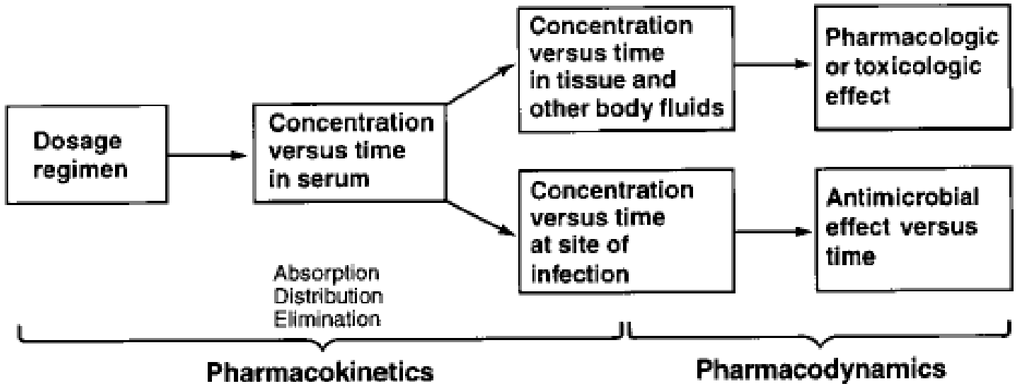

Figure 1. Overview of pharmacokinetics and pharmacodynamics in antimicrobial chemotherapy.

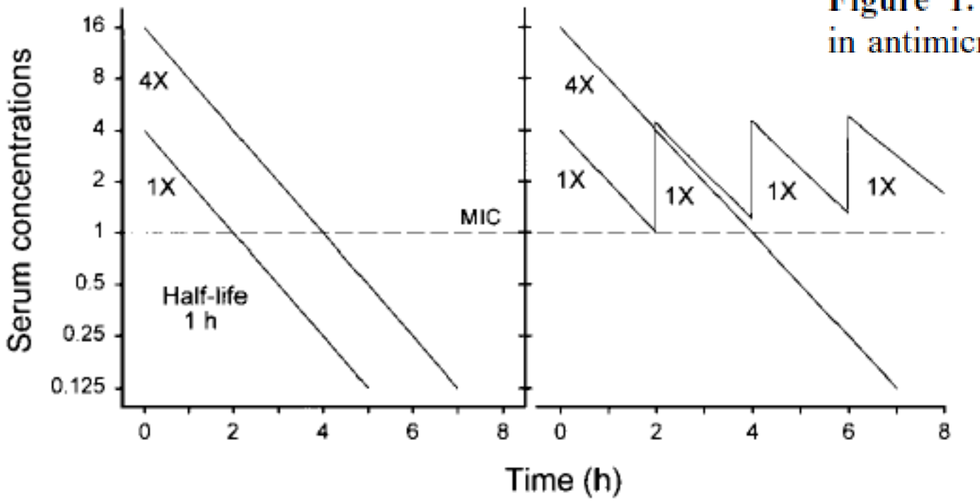

Figure 3. Effect of increasing the dose or changing the dosing regimen of a hypothetical drug on peak/MIC ratio, AUC (area under the concentration-vs.-time curve)/MIC ratio, and duration of time that serum levels exceed the MIC. Reprinted with permission from *Diagnostic Microbiology and Infectious Diseases* [25].

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Clinical Infectious Diseases 1998; 26:1–12

ANTIBACTERIAL EFFECTS

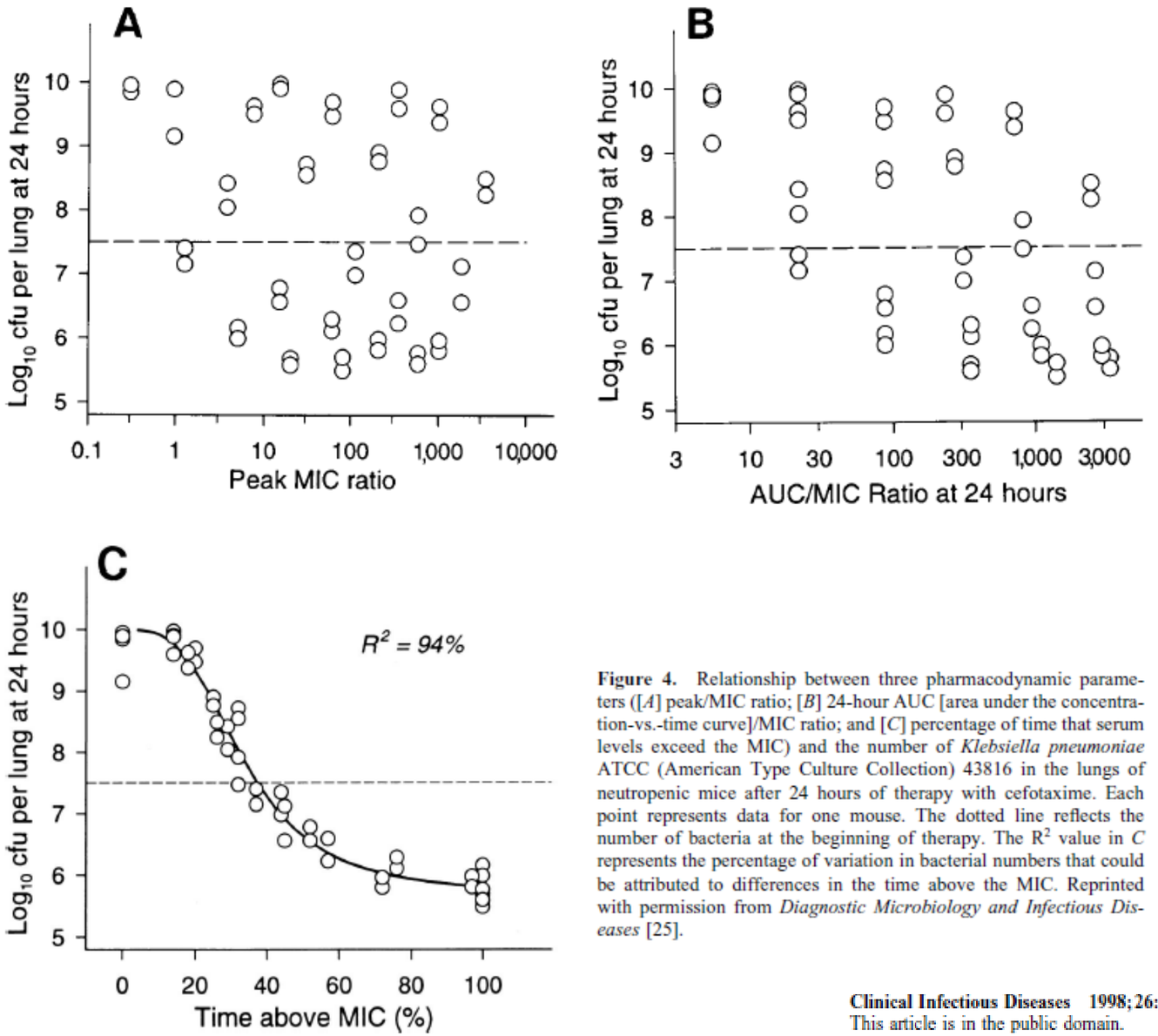

Figure 4. Relationship between three pharmacodynamic parameters ([*A*] peak/MIC ratio; [*B*] 24-hour AUC [area under the concentration-vs.-time curve]/MIC ratio; and [*C*] percentage of time that serum levels exceed the MIC) and the number of *Klebsiella pneumoniae* ATCC (American Type Culture Collection) 43816 in the lungs of neutropenic mice after 24 hours of therapy with cefotaxime. Each point represents data for one mouse. The dotted line reflects the number of bacteria at the beginning of therapy. The R^2 value in *C* represents the percentage of variation in bacterial numbers that could be attributed to differences in the time above the MIC. Reprinted with permission from *Diagnostic Microbiology and Infectious Diseases* [25].

Clinical Infectious Diseases 1998; 26:1–12

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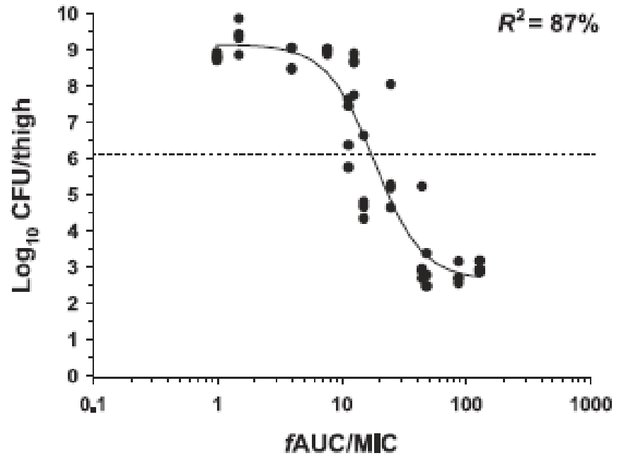
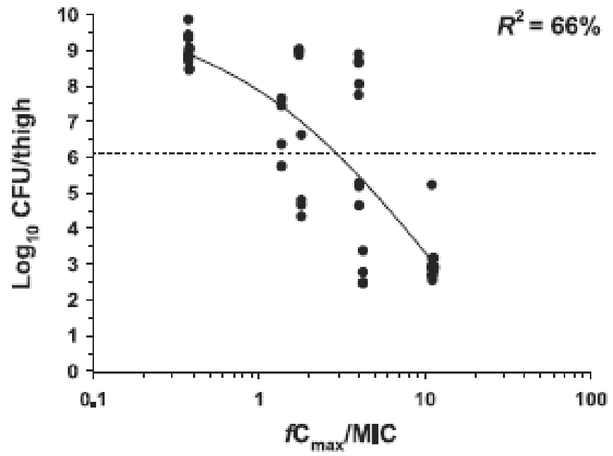
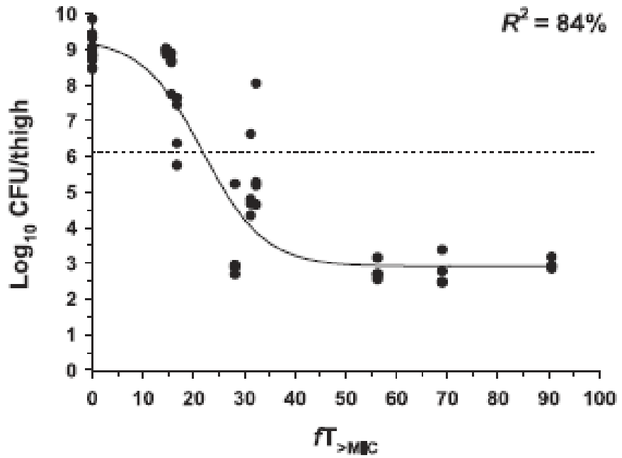
Antibiotics

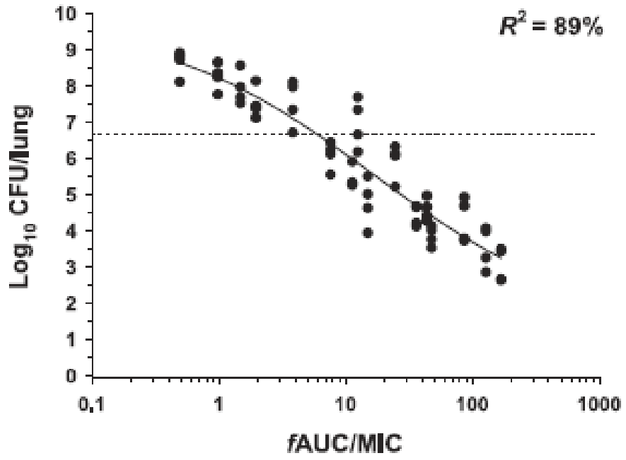
Thigh

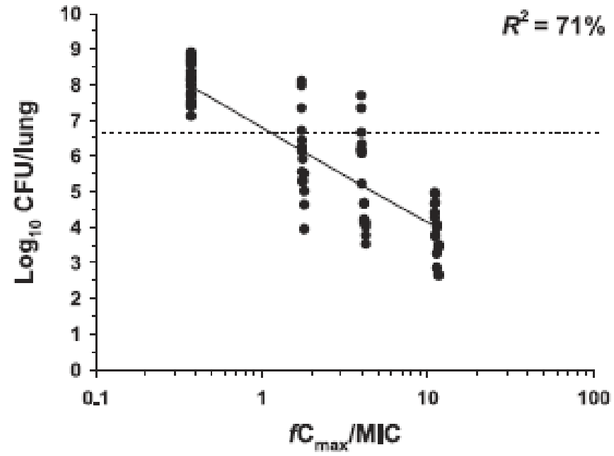


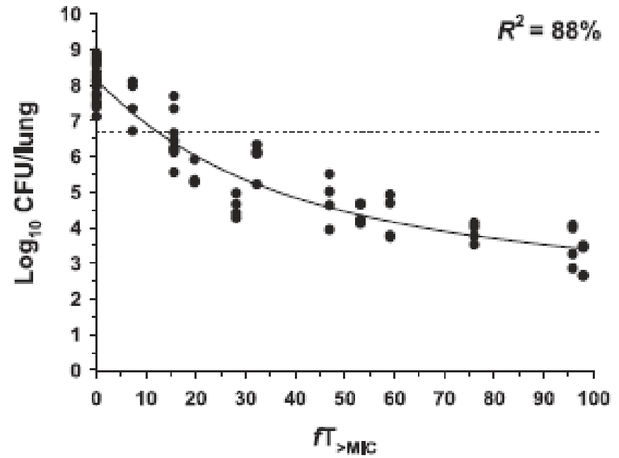




Lung







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MIC DISTRIBUTION

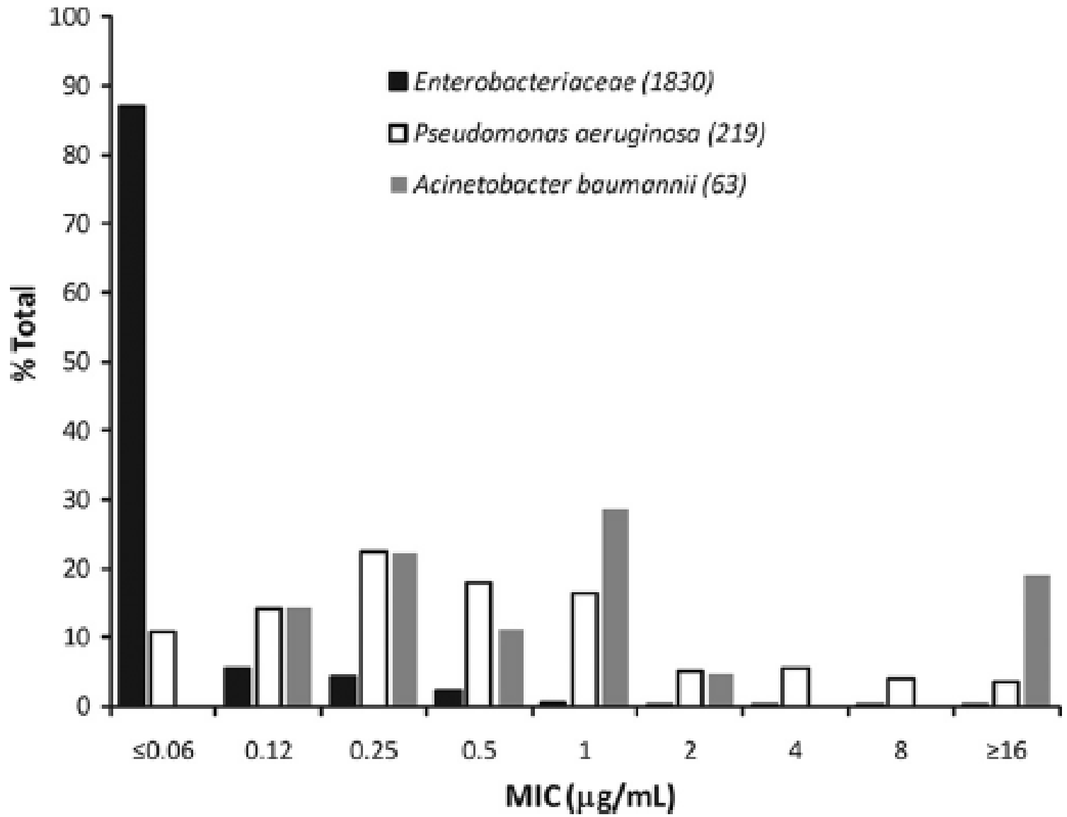

FIG. 1. Doripenem MIC distribution for selected Gram-negative pathogens from phase 3 clinical studies.

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2010, p. 2360–2364

TARGET ATTAINMENT

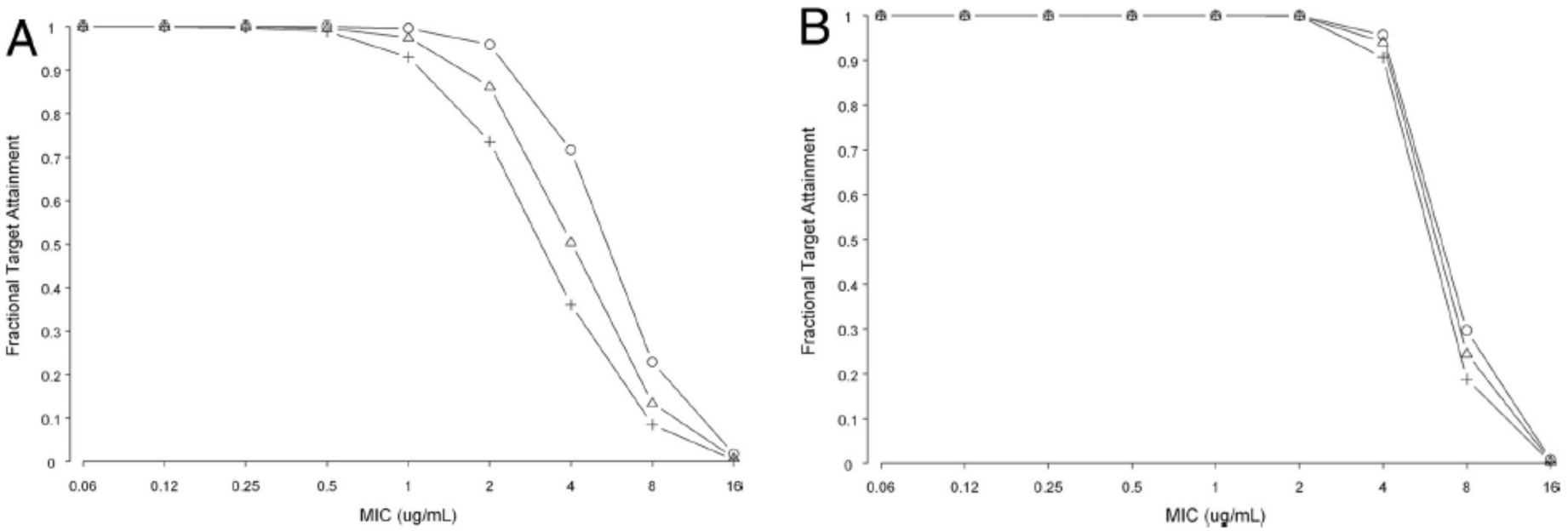

FIG. 2. Target attainment results for doripenem at 500 mg every 8 h infused over 1 h and 4 h over a wide range of creatinine clearances observed in phase 1, 2, and 3 studies (○, 25% T>MIC; △, 30% T>MIC; +, 35% T>MIC). (A) One-hour infusion; (B) 4-hour infusion.

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TARGET ATTAINMENT

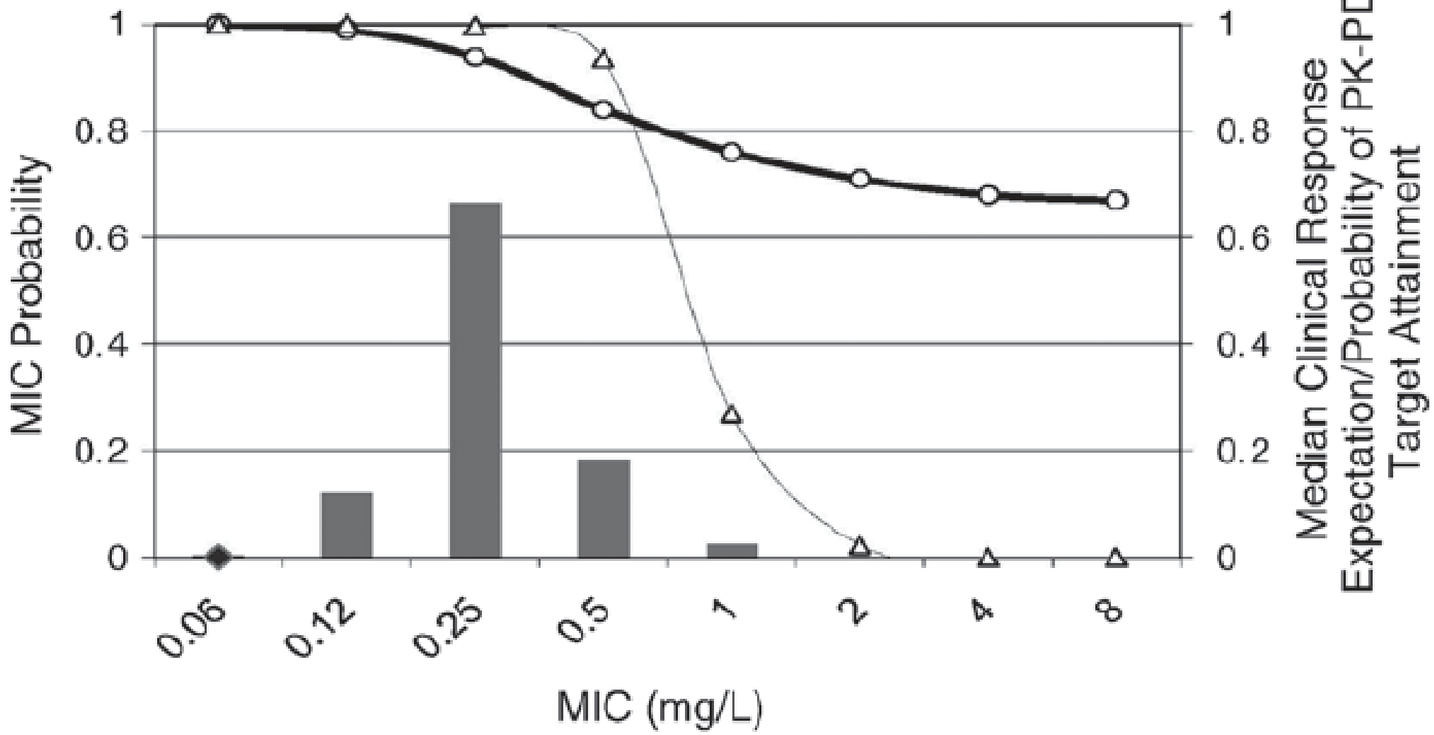

Fig. 8.1 Probability of target attainment (PTA, *open triangles*) based on $AUC_{ss,24h}$/MIC ratio, clinical response expectation (*open circles*), and tigecycline MIC distribution (*bars*), showing a trend of decreasing PTA and median clinical response expectation in increasing MIC. (Image from Ambrose et al. 2009; used with permission)

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CLINICAL AND MICROBIOLOGICAL CURE

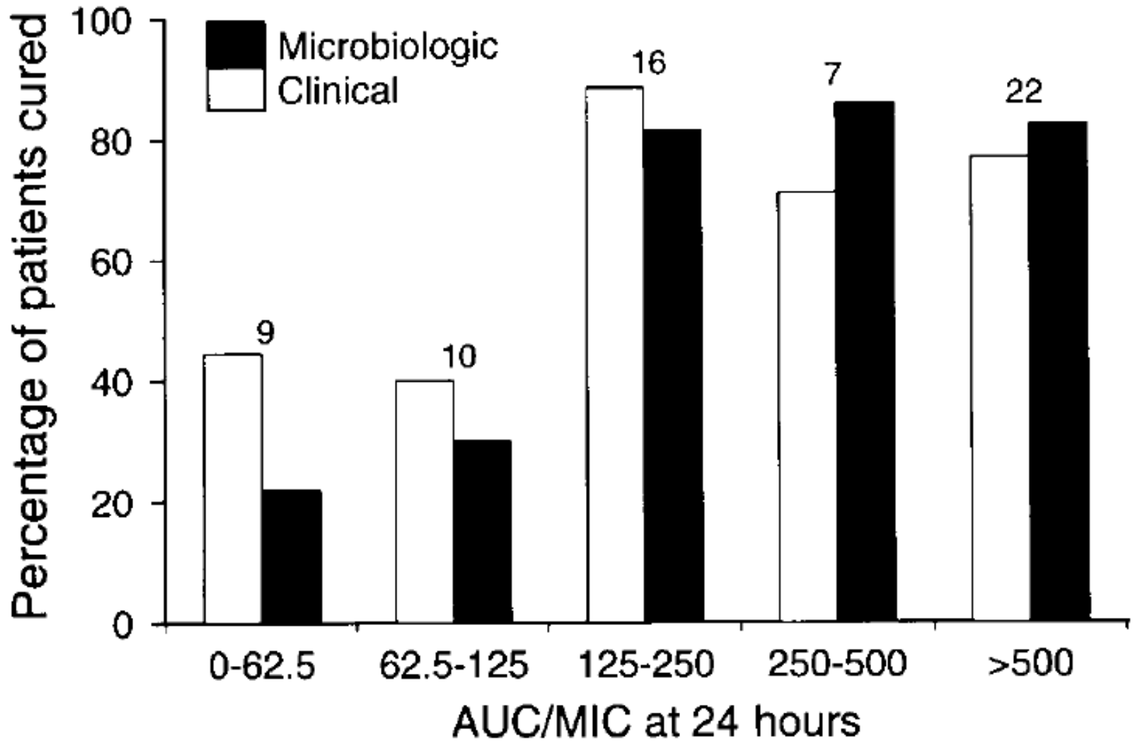

Figure 8. Relationship between the 24-hour AUC (area under the concentration-vs.-time curve)/MIC ratio and the microbiological and clinical efficacy of ciprofloxacin in 64 patients with serious bacterial infections. The 24-hour AUC/MIC is the sum of the AUCs for all doses administered every 24 hours divided by the MIC. Data are from [52].

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Clinical Infectious Diseases 1998; 26:1–12

CLINICAL CURE

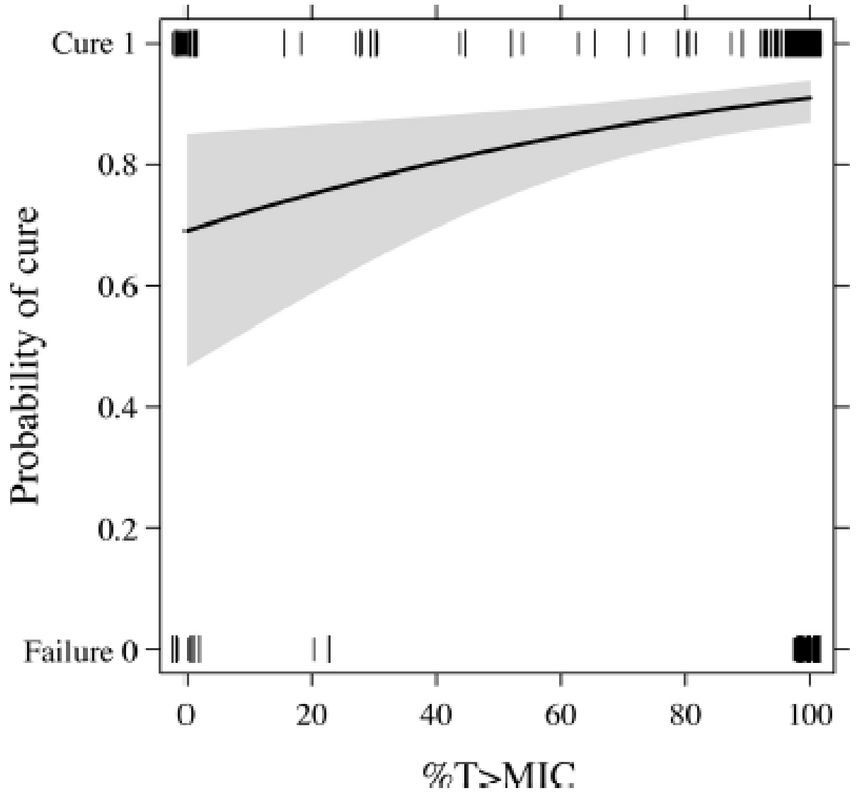

FIG. 2. Probability of therapeutic success by percent T>MIC (the shaded area indicates the 95% confidence interval) in patients receiving ceftobiprole at 500 mg every 8 h administered as a 2-h infusion. The tick marks aligned with the cure and failure categories represent the subjects' percent T>MICs and clinical outcomes.

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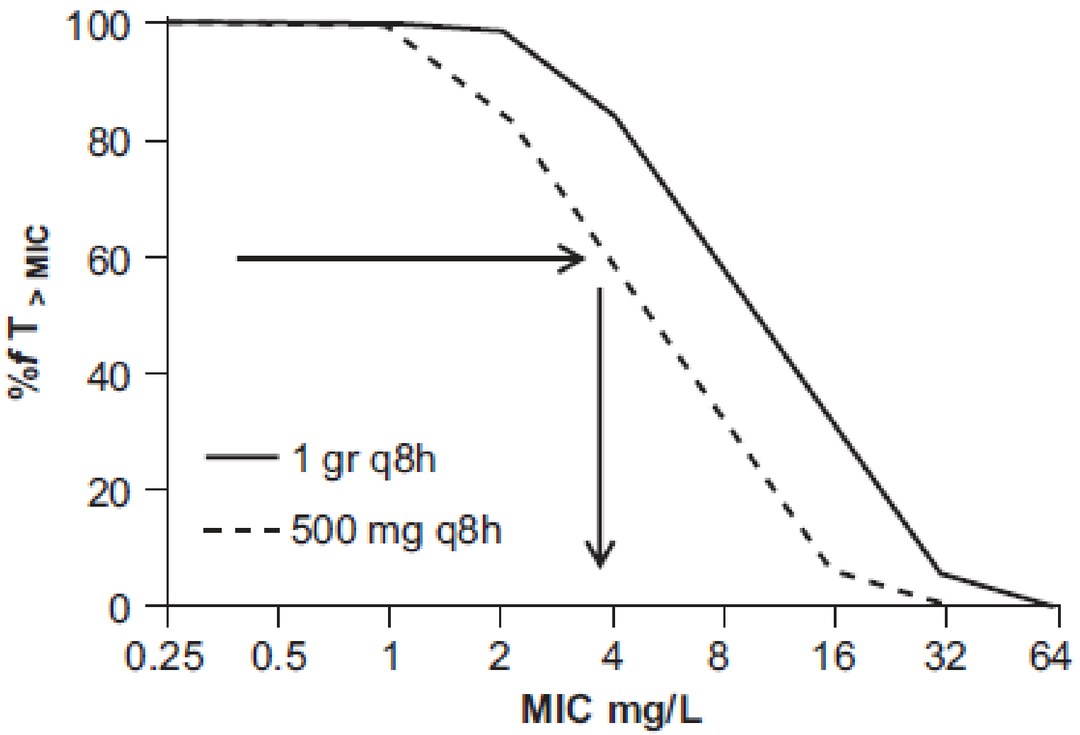
CLINICAL BREAKPOINT

PKPD BREAKPOINT

Fig. 8.2 The percent of time that the free ceftazidime concentration is above MIC (%*fT*>MIC) for two dosing regimens of ceftazidime (1 g q8h vs. 500 mg q8h) against MIC to illustrate that clinical breakpoint is dependent on the dosing regimen. *Arrows* indicate that the pharmacodynamics target corresponding to 60 % *f*T>MIC is 4 and 8 mg/L for 500 mg q8h and 1 g q8h, respectively. (Image from Mouton et al. 2012; used with permission)



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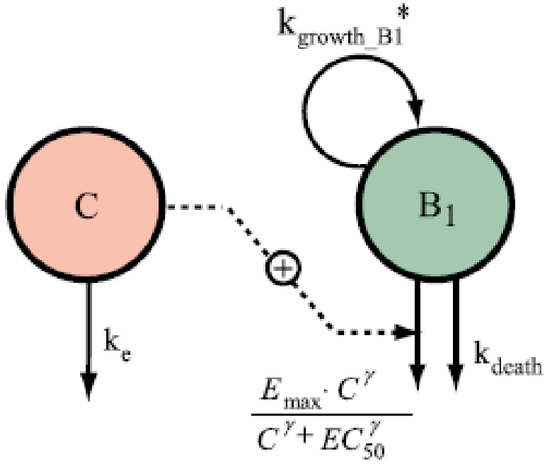
MODELING *TIME COURSE* OF ANTIBIOTIC EFFECT

- **Better to model time course of bacterial growth & killing**
- **Differentiate between the system (bacteria) and drug effects**



- **Can address resistance development**
- **.. and the effects of the host's immune system**

=> Use all available data: *in vitro*, animal, clinical

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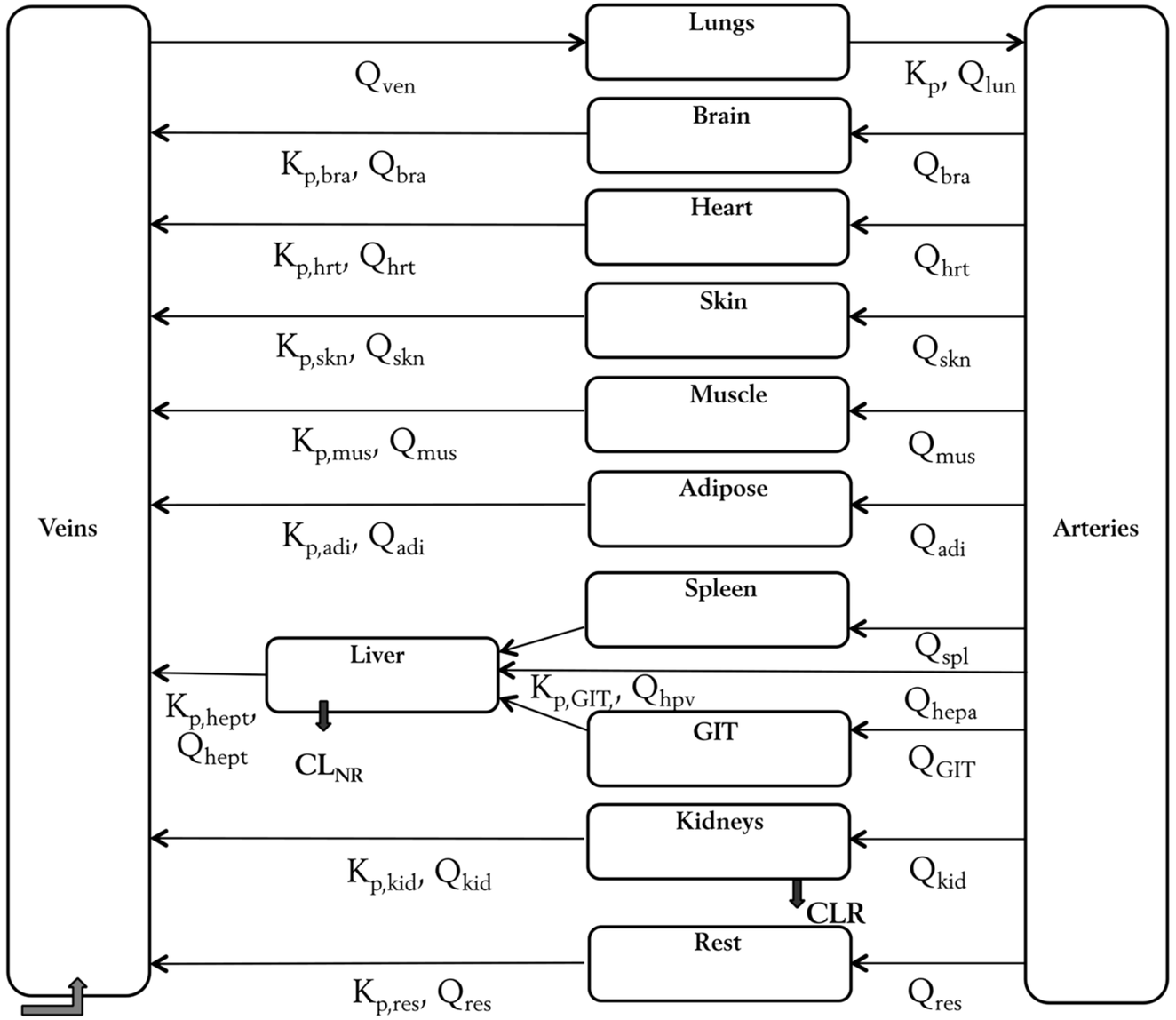
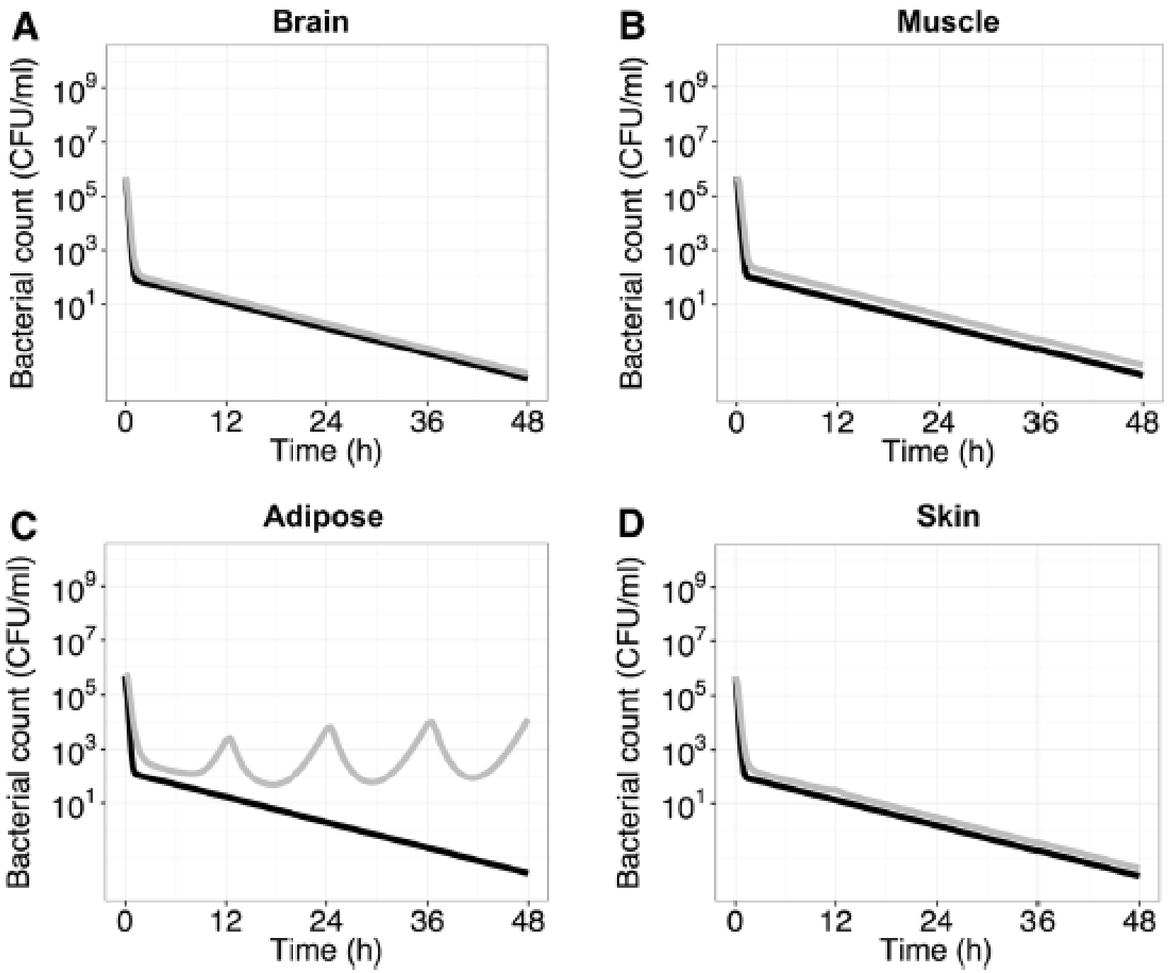
SYSTEMS PHARMACOLOGY: PBPK



J Pharmacokinet Pharmacodyn (2017) 44:69–79

… COMBINED WITH PD MODEL AT INFECTION SITE

Fig. 5 Predictions of the time course of bacterial killing of *E. coli* strains LM347 (*black*) and LM625 (*grey*) in the extracellular compartment of different tissues (brain, muscle, adipose and skin) following a ciprofloxacin dose of 400 mg b.i.d



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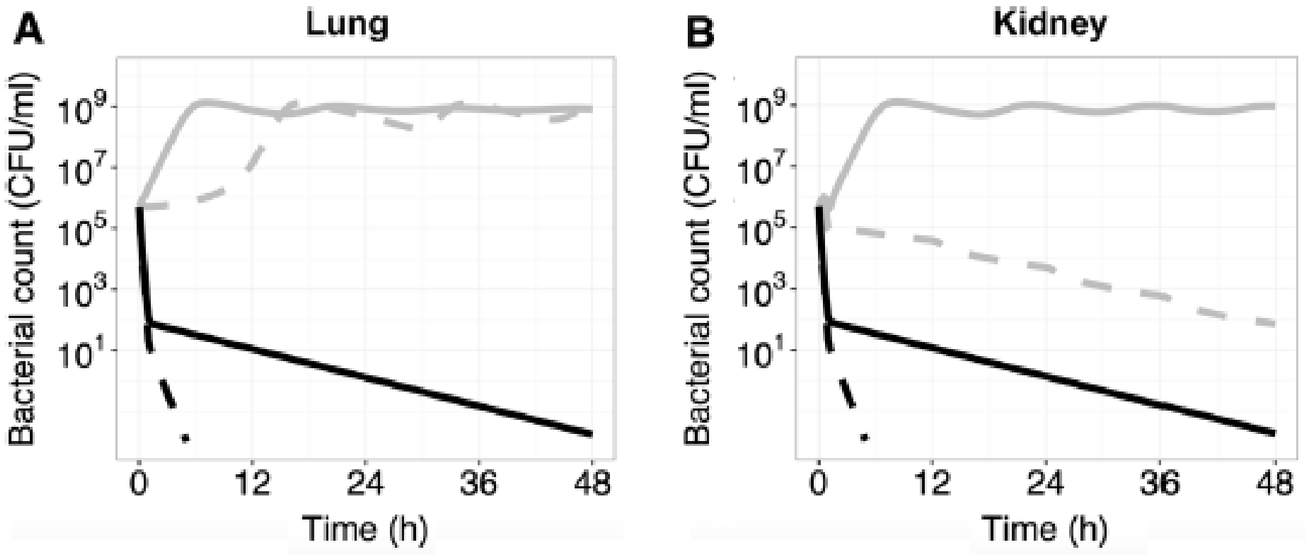
… ALLOWS TO DERIVE THE TISSUES WITH HIGHEST EFFECT

Fig. 6 Predictions of the time course of bacterial killing of *E. coli* strains LM347 (*black*) and LM707 (*grey*) in lung and kidney following administration of ciprofloxacin 400 mg b.i.d. with (*dashed lines*) and without (*solid lines*) addition of function for immune response



$$\frac{dB}{dt} = k_{growth} \times B - k_{death} \times B - \left(\frac{E_{\max} \times C_{(t)}^{\gamma}}{EC_{50}^{\gamma} + C_{(t)}^{\gamma}}\right) \times B$$

$$\mathrm{dB/dt} = \ldots - \mathrm{Kkill\_ANC} \cdot (\mathrm{ANC}/(\mathrm{ANC} + \mathrm{ANC50})) \cdot (1 - \mathrm{B}/(\mathrm{B} + \mathrm{B50})) \cdot \mathrm{B}.$$

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