Louvain Drug Research Institute

Séminaire de pathologie infectieuse

Integration of Target Site Pharmacokinetics and *in-vitro Pharmacodynamics in the Assessment of Existing and New Anti-Infective Agents*

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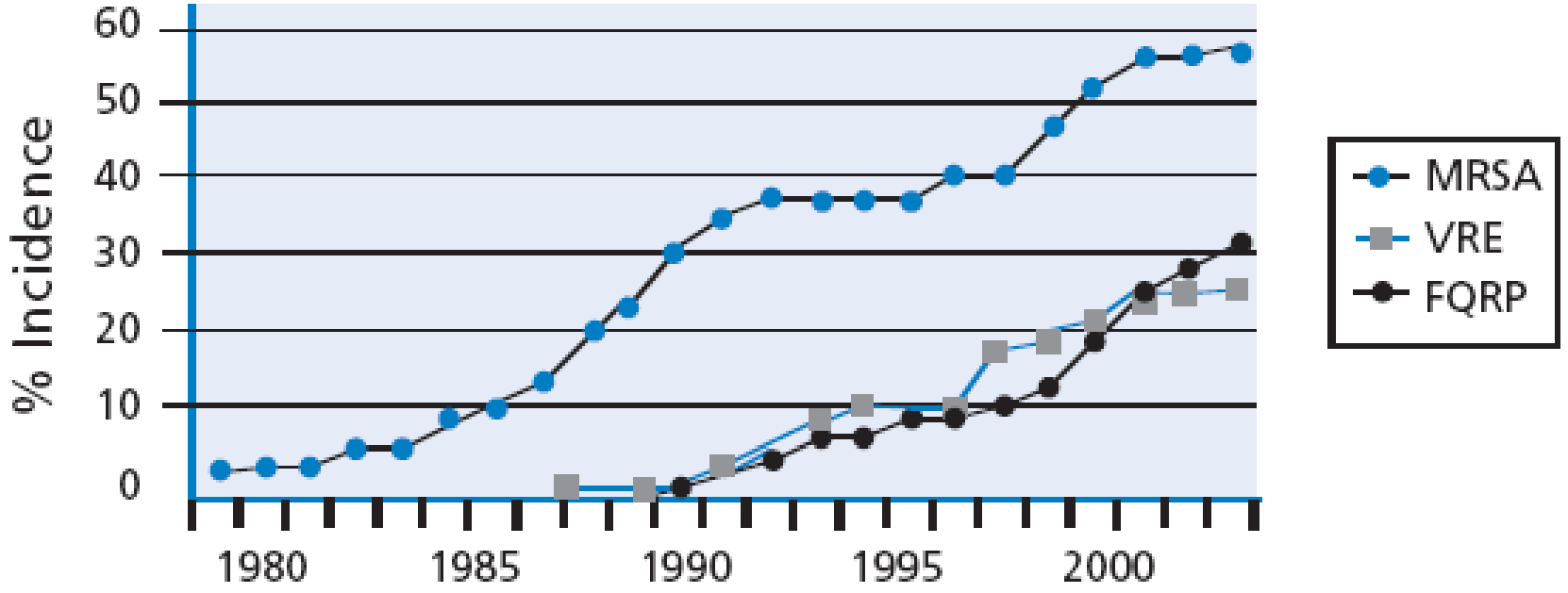
University of Florida

Resistance Development

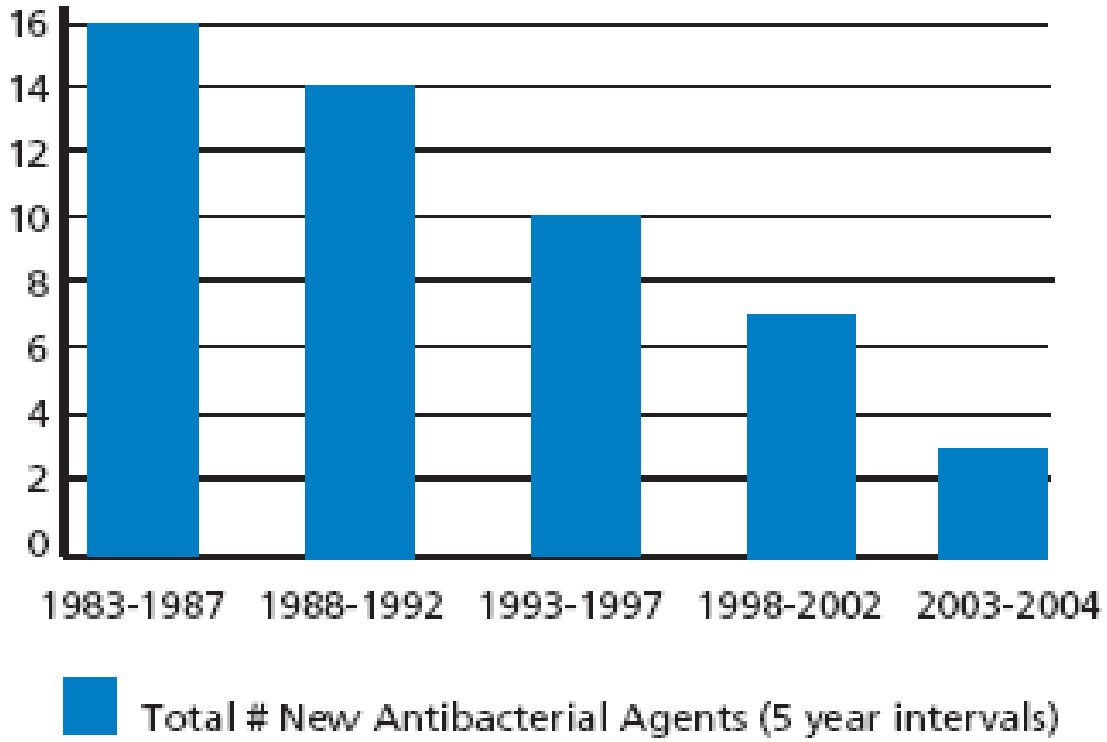


Source: Centers for Disease Control and Prevention

This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

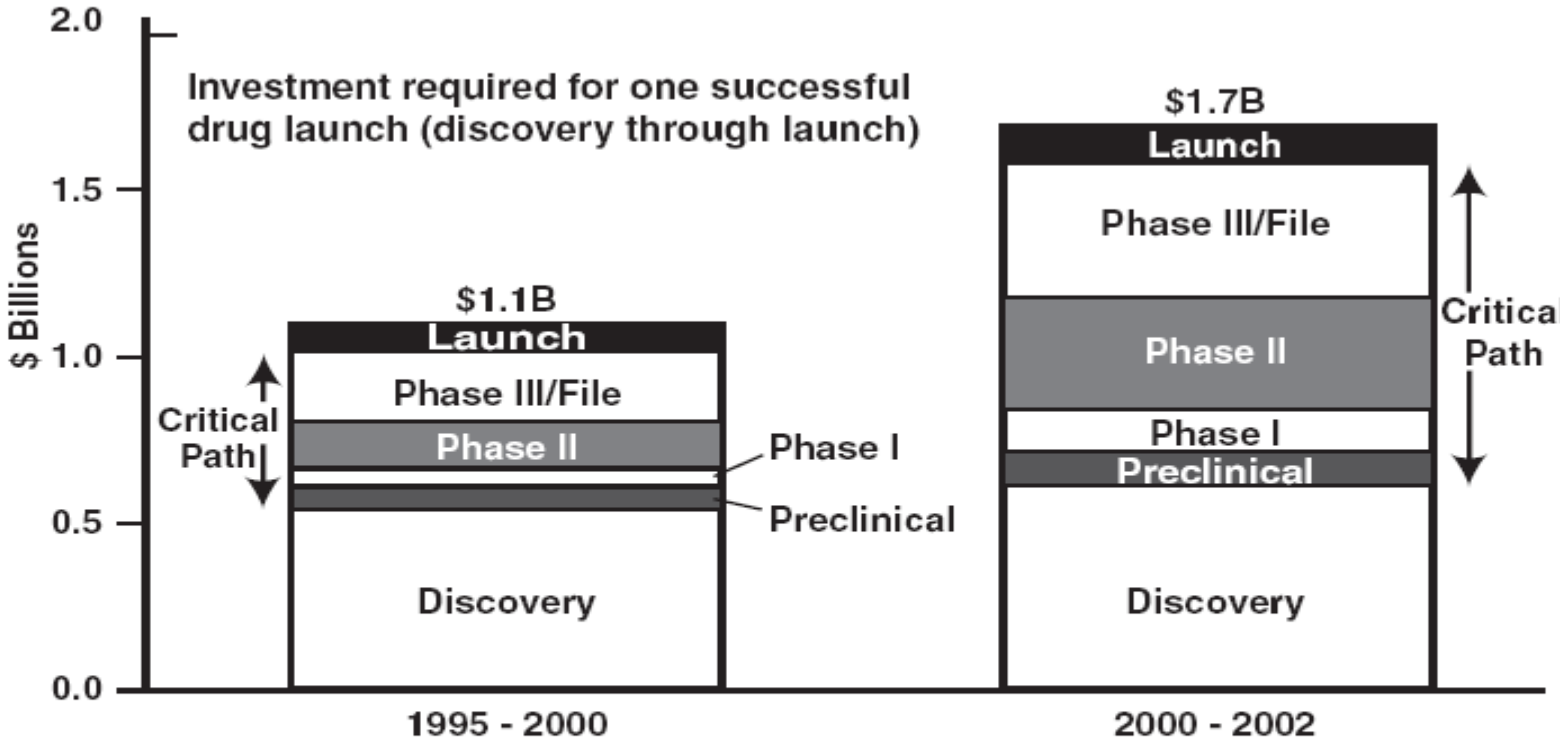
Approved Antibacterial Agents

1983-2004



Source: Spellberg et al., *Clinical Infectious Diseases*, May 1, 2004 (modified)

Figure 3: Investment Escalation per Successful Compound

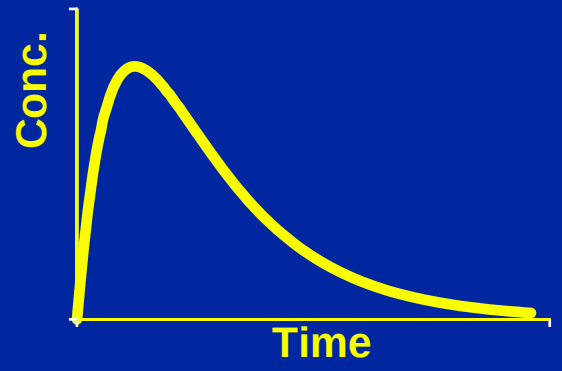


SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

The figure shows one estimate of the total investment required to "launch" (i.e., market) a successful drug in two time periods. Most of the recent cost increases are within the "critical path" development phase, between discovery and launch.

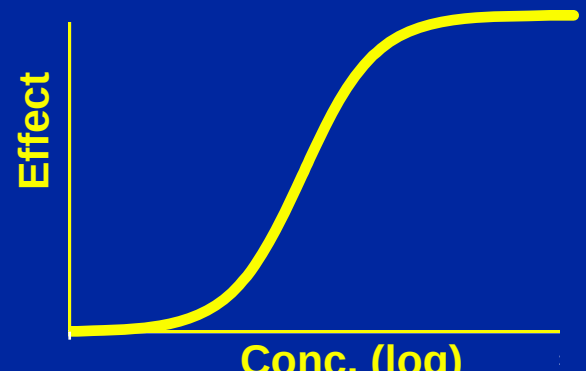
Pharmacokinetics

conc. vs time



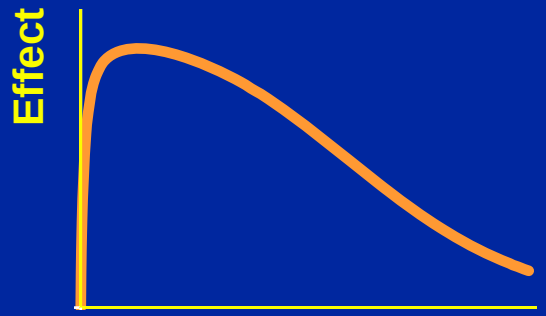
Pharmacodynamics

conc. vs effect

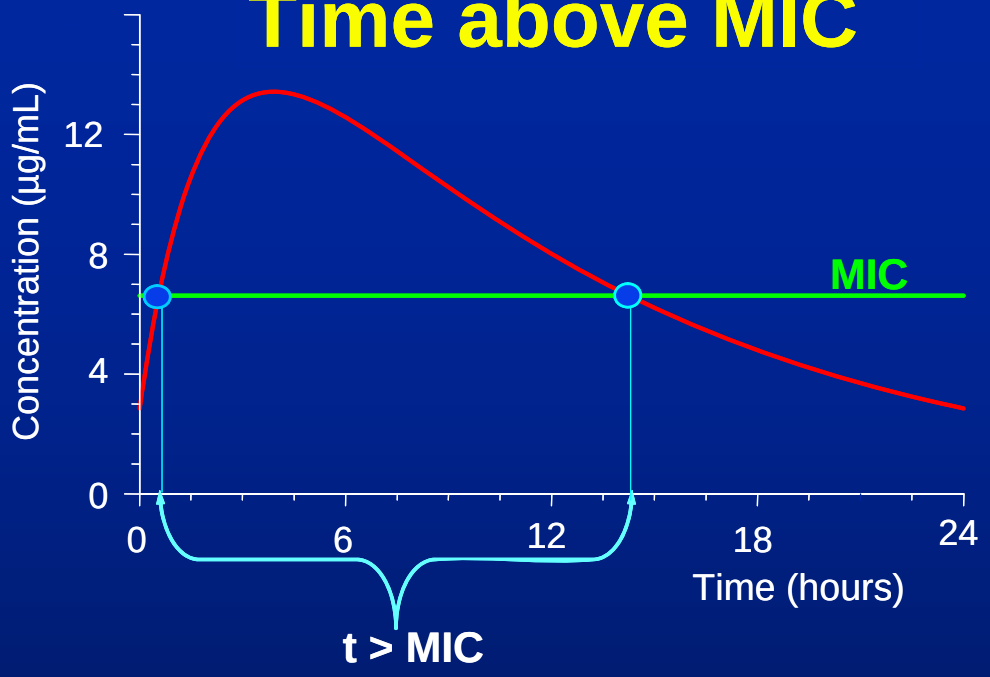


PK/PD

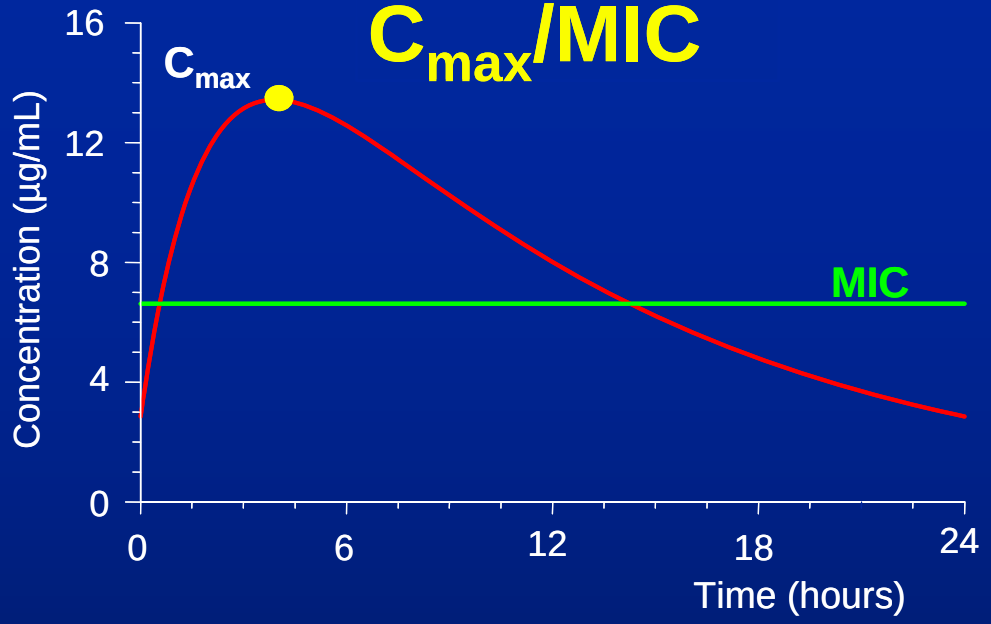
effect vs time



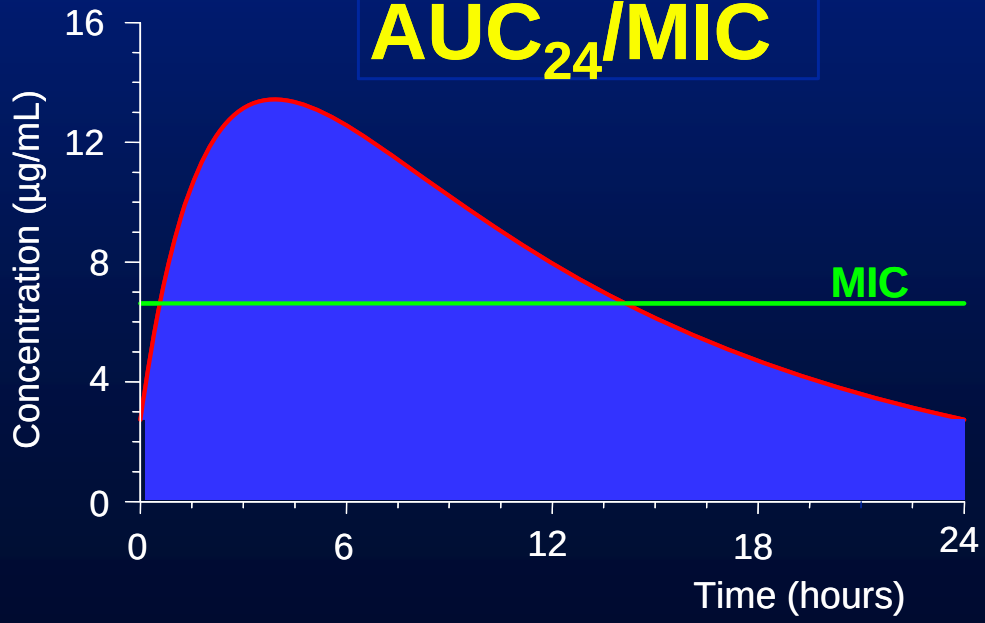
Time above MIC



C_{max}/MIC



AUC_{24}/MIC



PK

PD

Serum

MIC

Pharmacokinetics

Problems:

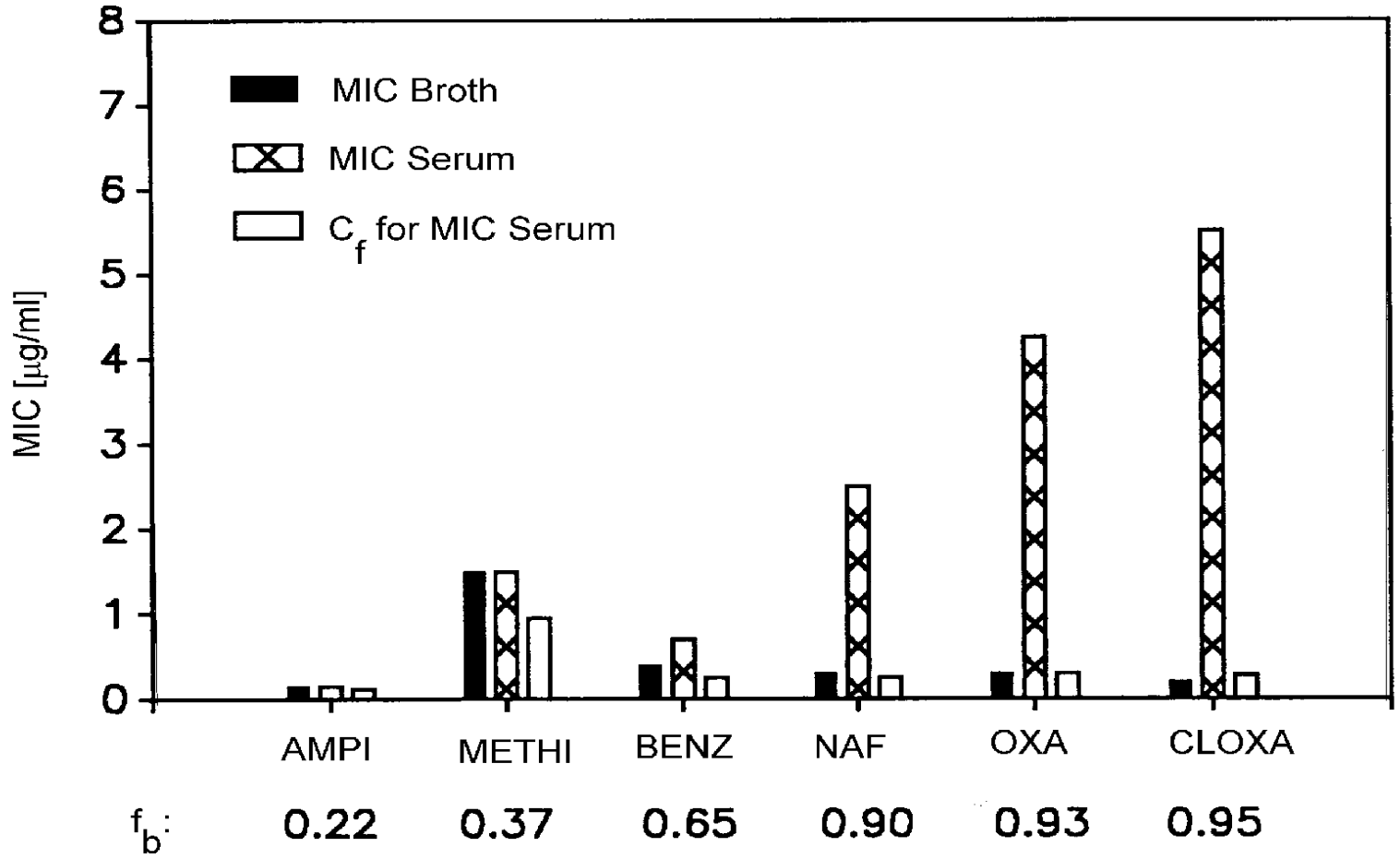
- **Protein Binding**
- **Tissue Distribution**

Protein Binding of Cephalosporines

Cefonicid	98
Ceftriaxone	90-95
Cefoperazone	89-93
Cefazolin	89
Cefotetan	85
Ceforanide	80-82
Cefamandole	74
Cefoxitin	73
Cephalothin	71
Cefmetazole	70
Cefixime	65
Cephapirin	62
Moxalactam	53-67
Cefprozil	40
Cefotaxime	36
Cefpodoxime	25

Effect of Protein Binding on Antimicrobial Activity

MICs of Staphylococcus aureus (Data from Kunin et al. (1973))

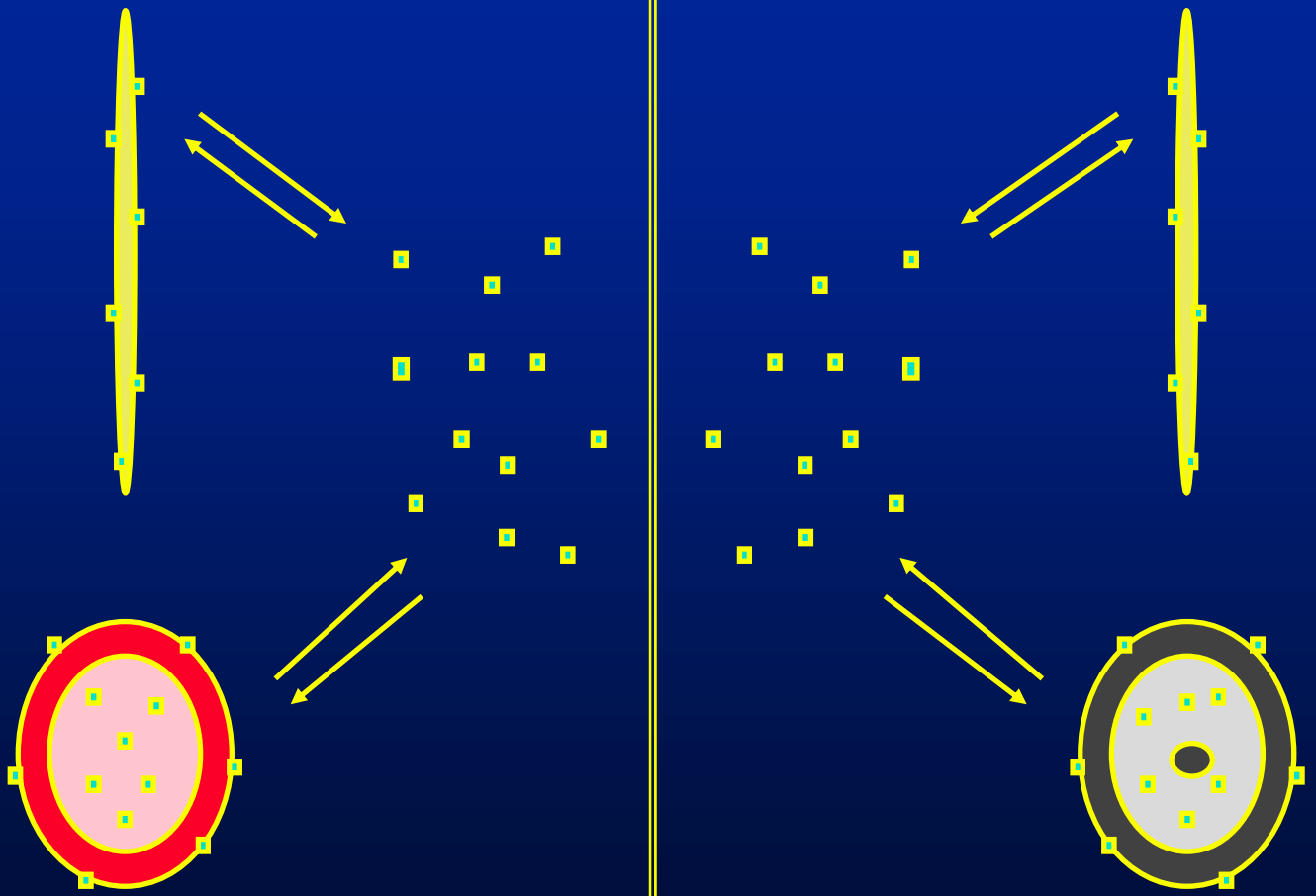


vascular space

extravascular space

plasma protein binding

binding to extracellular biological material



blood cell binding,

diffusion into blood cells,

binding to intracellular biological material

tissue cell binding,

diffusion into tissue cells,

binding to intracellular biological material

Tissue Concentrations

Tissue can be looked at as an aqueous dispersed system of biological material. It is the concentration in the water of the tissue that is responsible for pharmacological activity.

Total tissue concentrations need to be interpreted with great care since they reflect hybrid values of total amount of drug (free + bound) in a given tissue

‘Tissue-partition-coefficients’ are not appropriate since they imply homogenous tissue distribution

FDA Critical Path White Paper

2003 CDER Report to the Nation

We continue ... to extend our long-standing interest in the application of dose-response principles *by viewing drugs and their actions directly at the level of the drug target*, rather than indirectly via plasma concentrations

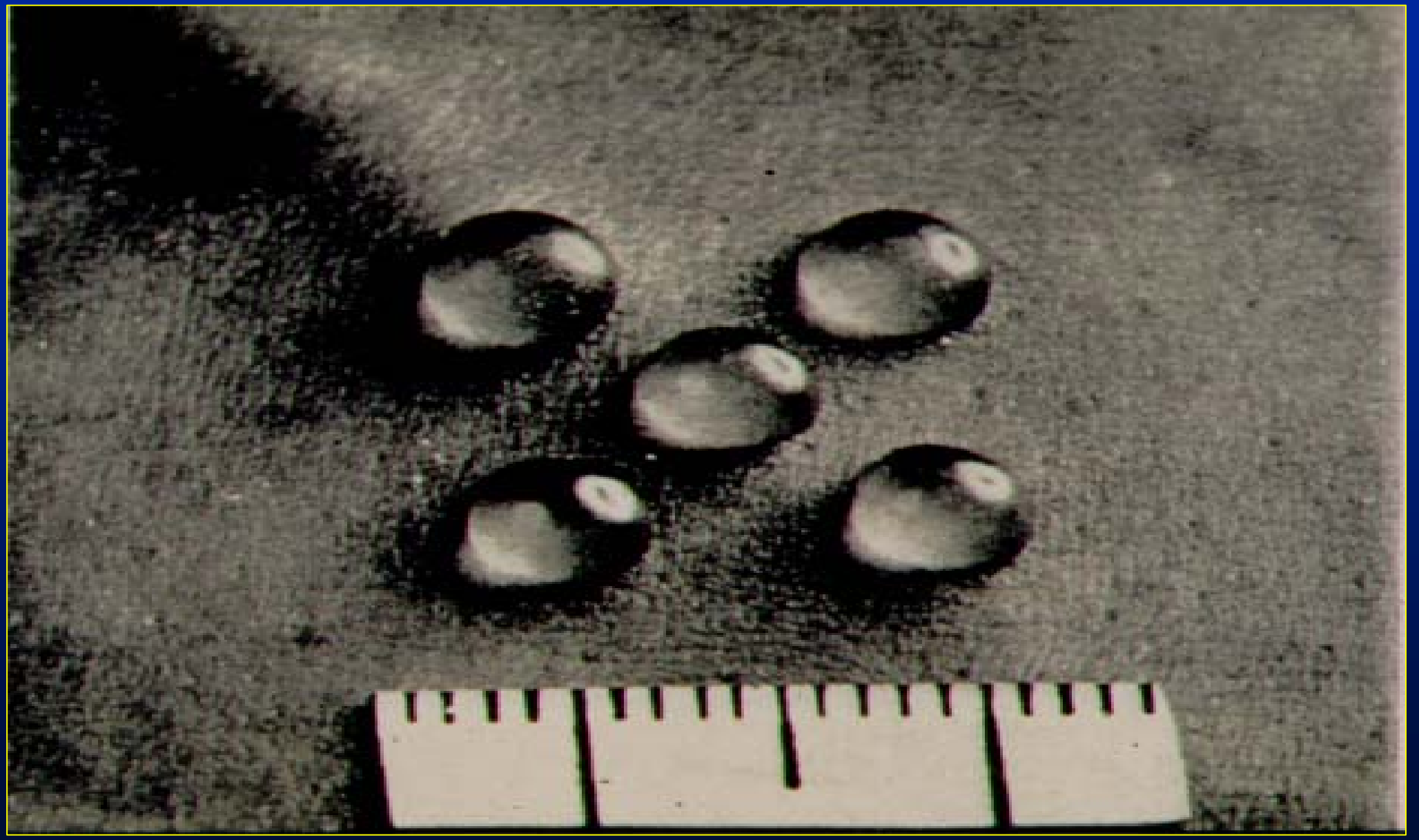
Lazy

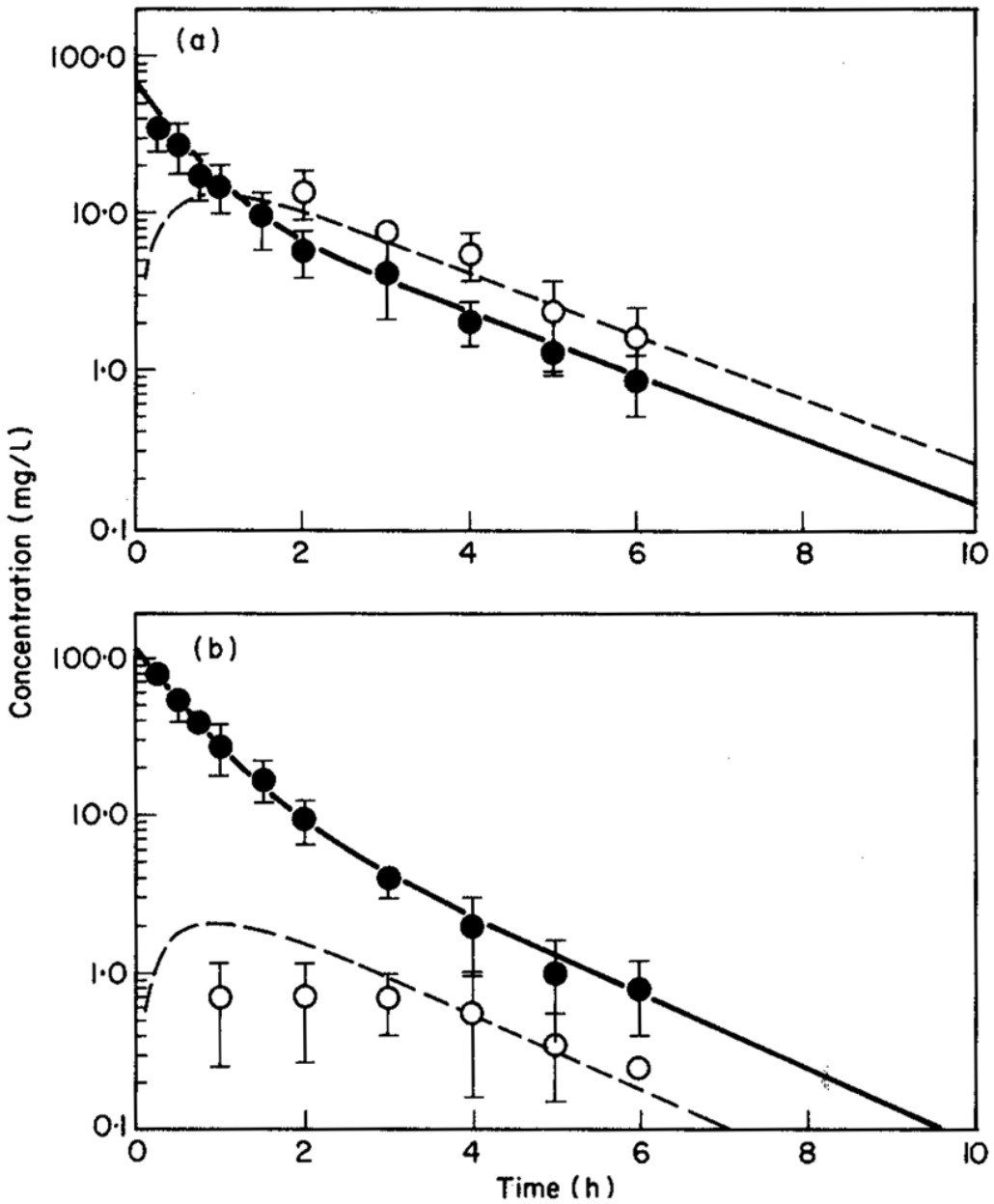
Lazy

The free (unbound) concentration of the drug at the receptor site should be used in PK/PD correlations to make prediction for pharmacological activity

Blister Fluid

- Blister fluid is a ‘homogenous tissue fluid’
- Protein binding in blister fluid needs to be considered





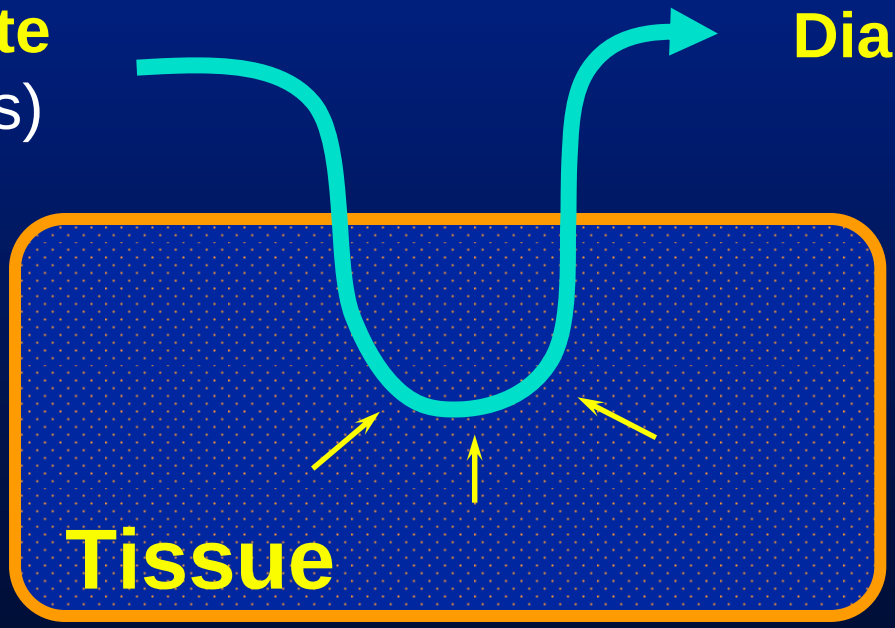
Ampicillin

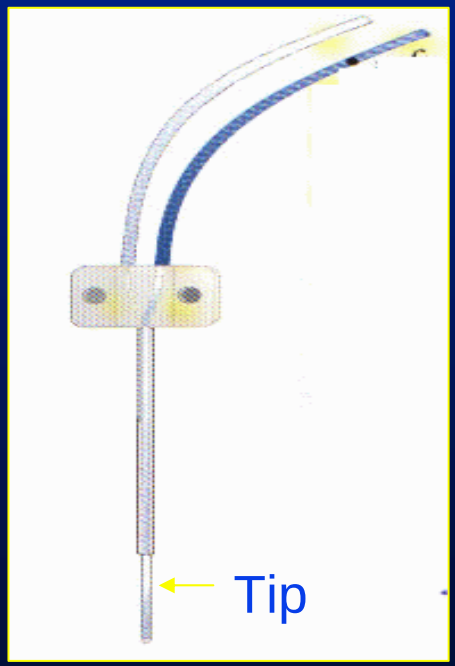
Cloxacillin

- ● Serum
- ○ Free blister fluid

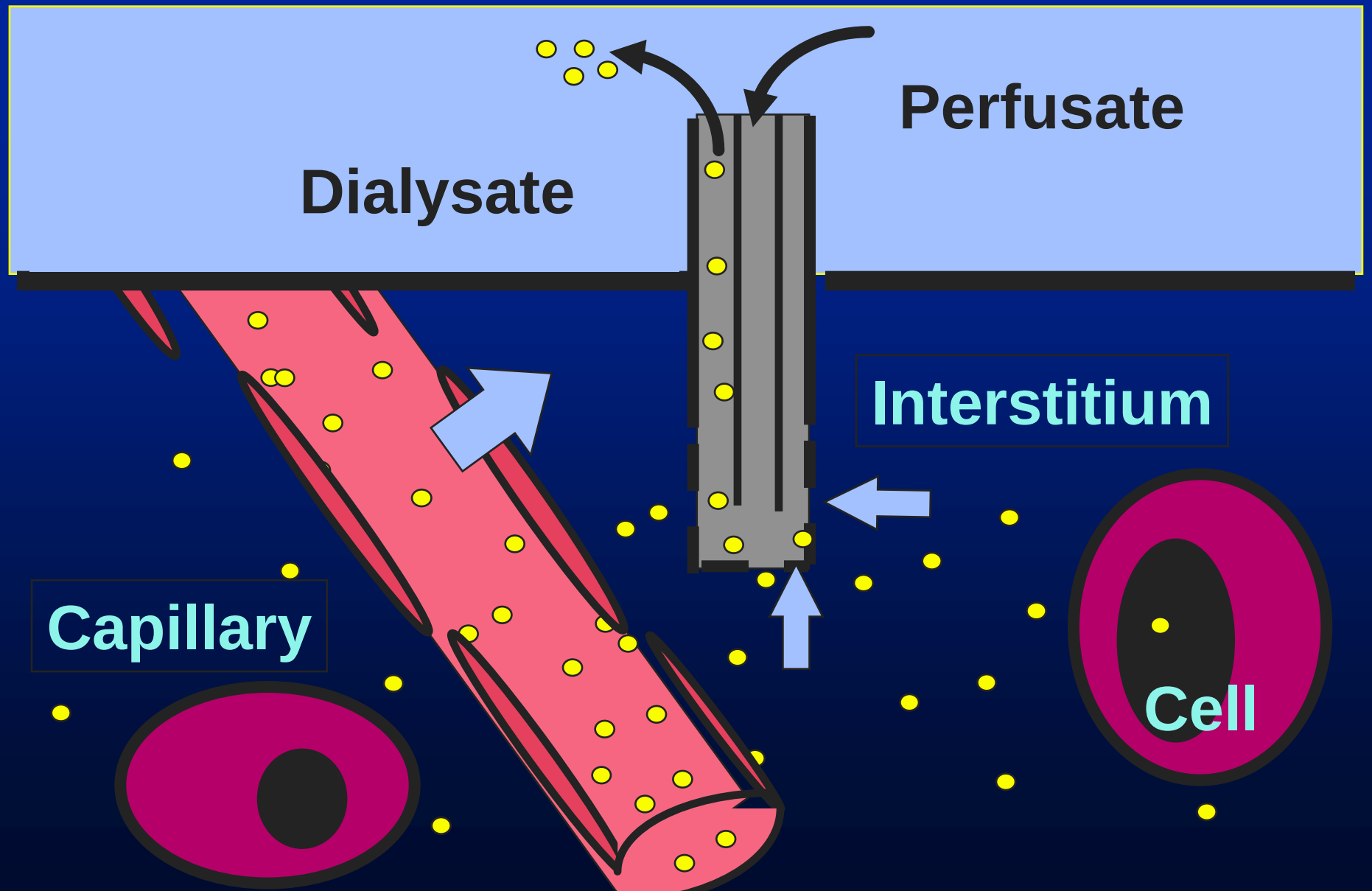
Microdialysis

- Microdialysis allows to monitor the free tissue concentrations.

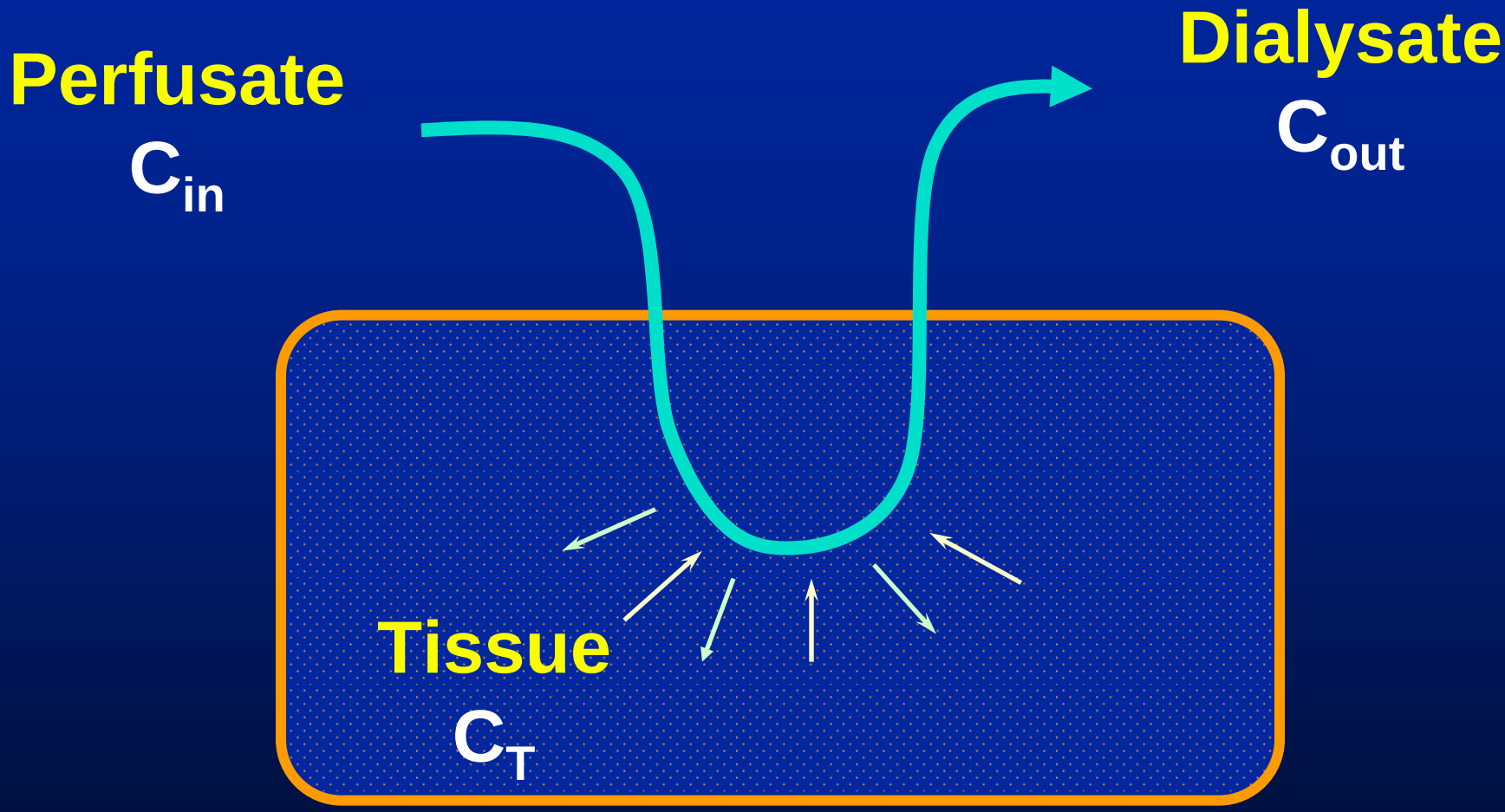




Microdialysis

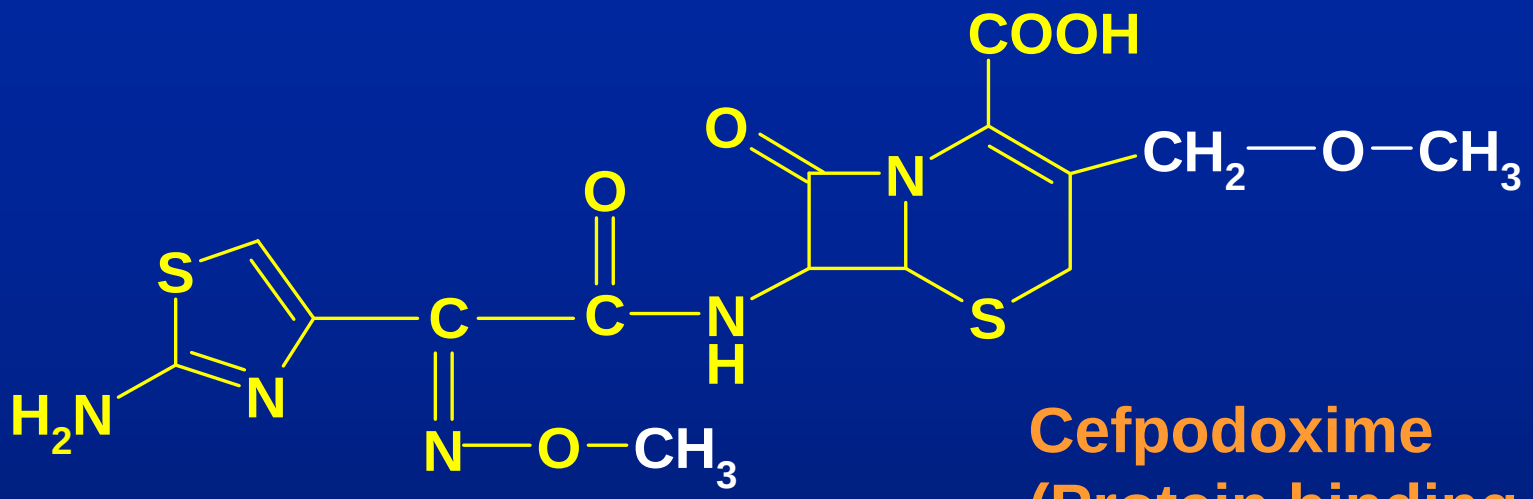


No net flux method



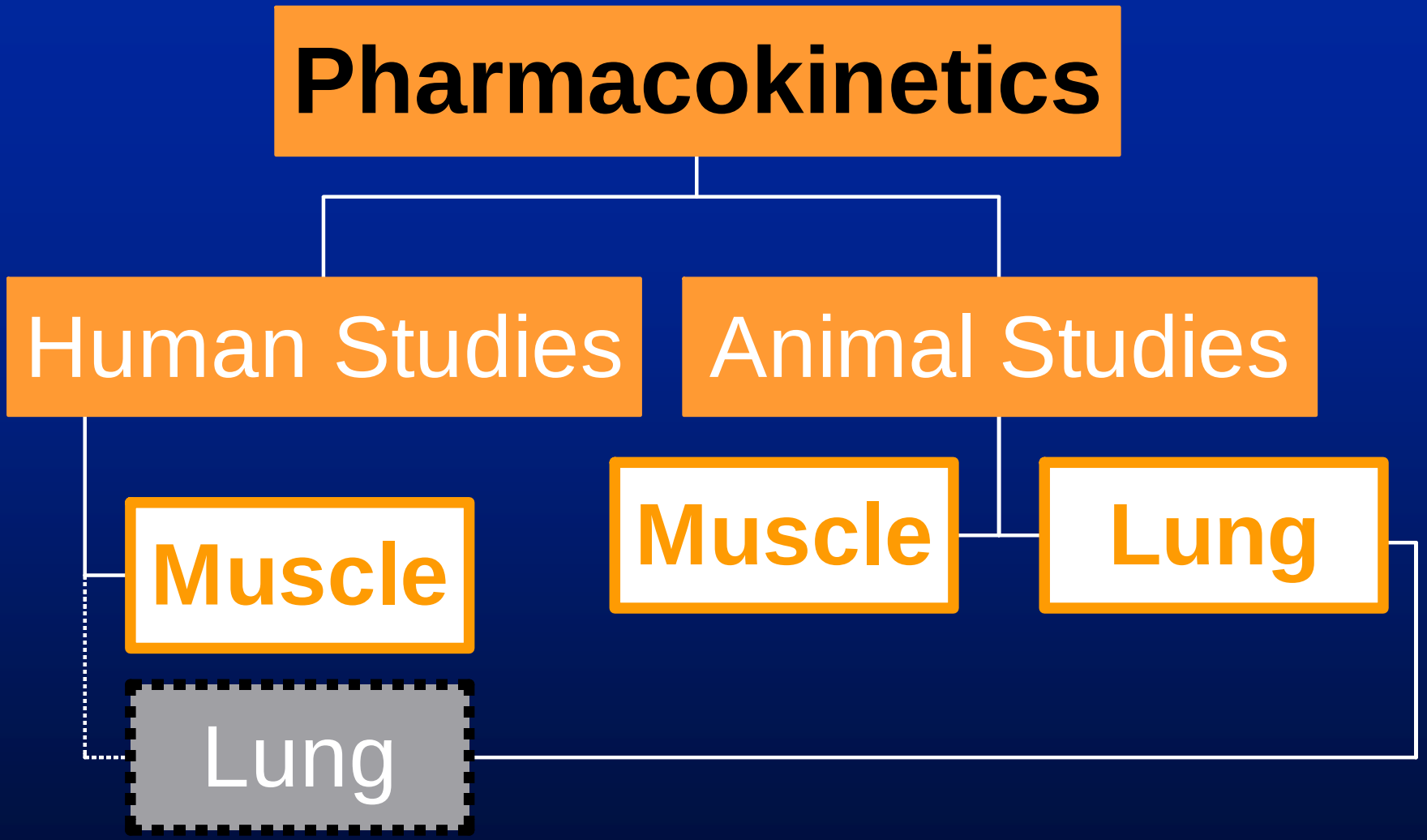
If $C_{in} > C_T$, then $C_{out} < C_{in}$

If $C_{in} < C_T$, then $C_{out} > C_{in}$

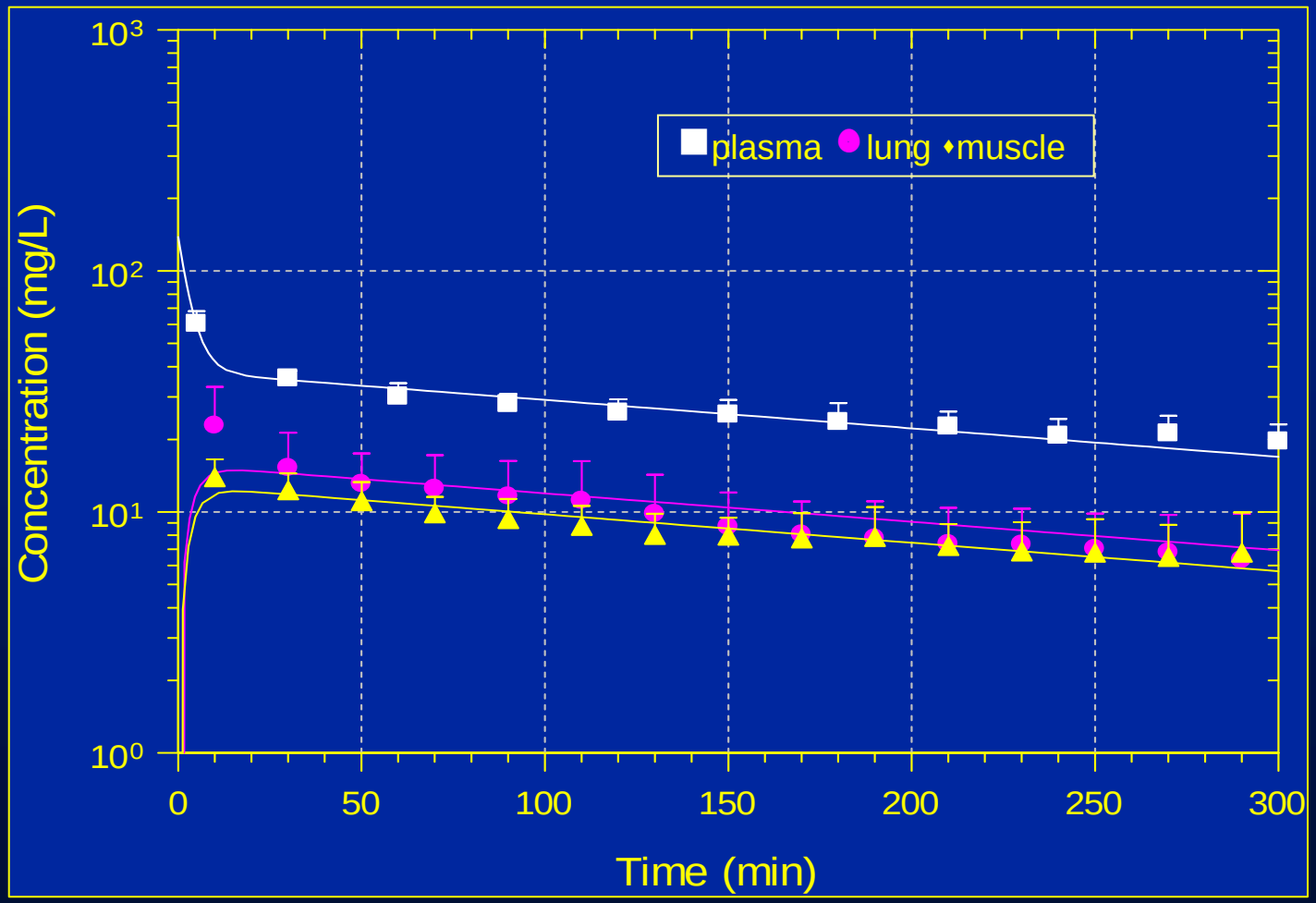


Cefpodoxime
(Protein binding 17-30%)

Cefixime
(Protein binding 65%)


Pharmacokinetics
Human Studies
Animal Studies
Muscle
Muscle
Lung
Lung

iv dose of 10 mg/kg cefpodoxime (n=6)



Summary

Animal Studies

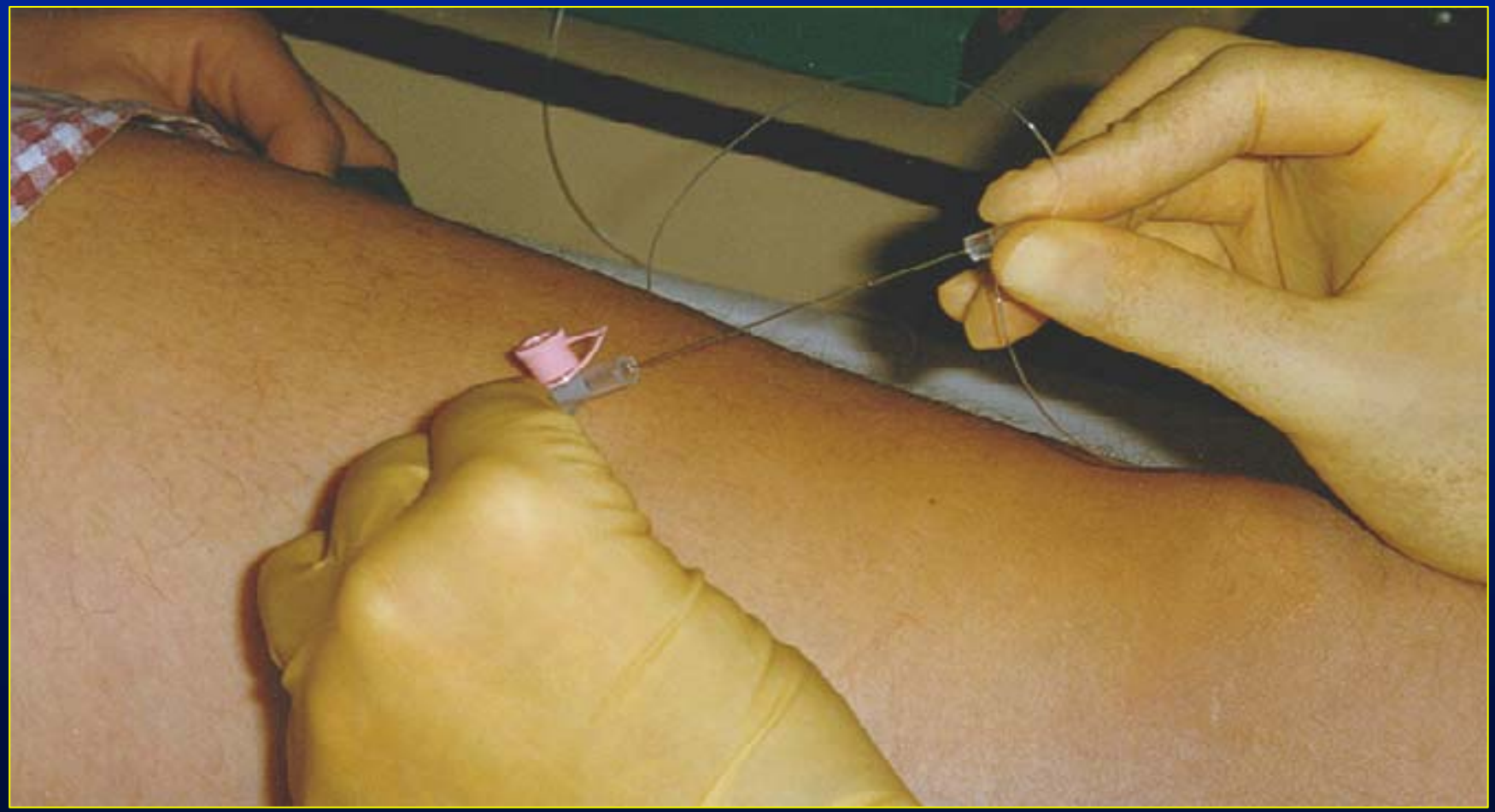
- Free concentrations in muscle and lung are almost identical and much lower than the total plasma concentrations.
- It suggests that free concentrations measured in human muscle maybe reasonable predictors for free concentrations in human lung.

Clinical study
Cefpodoxime and Cefixime

- To compare the soft tissue distribution of these two antibiotics after 400mg oral dose in healthy male volunteers by microdialysis

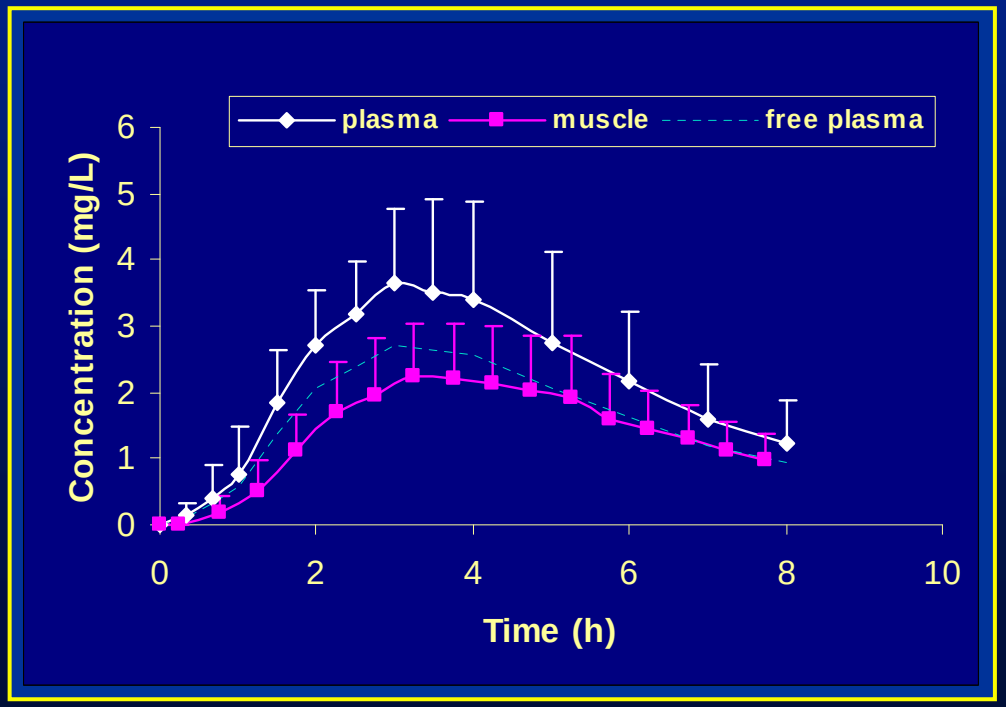
- Two way cross-over, single oral dose study

Microdialysis

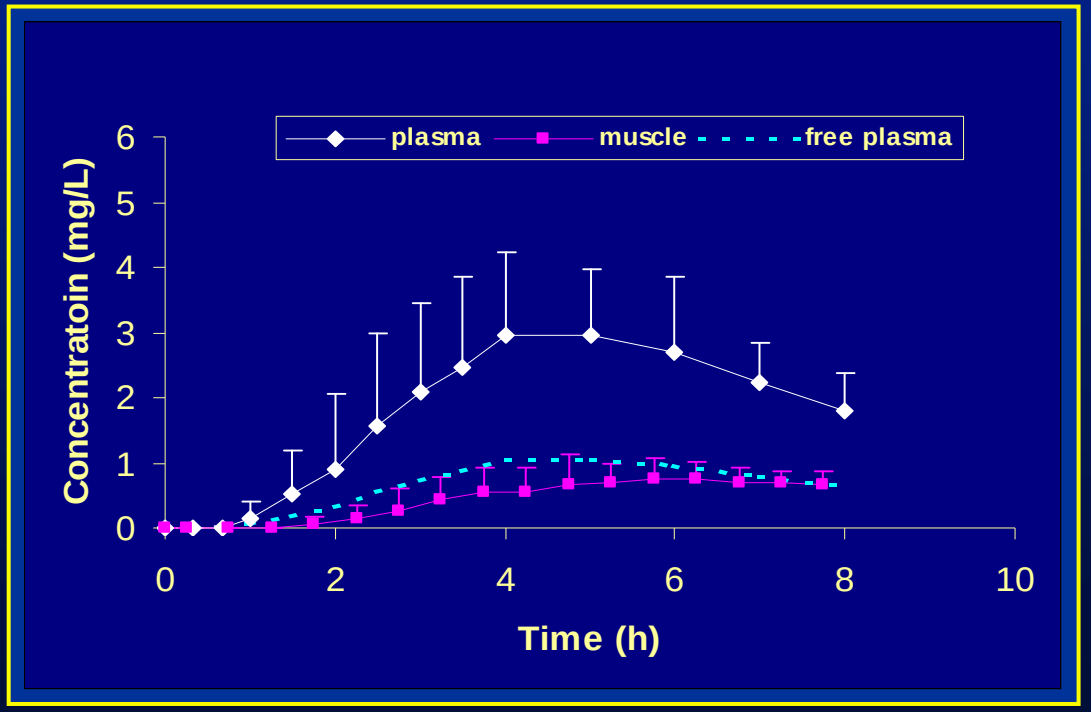


Clinical Microdialysis

Cefpodoxime
400 mg po



Cefixime
400 mg po



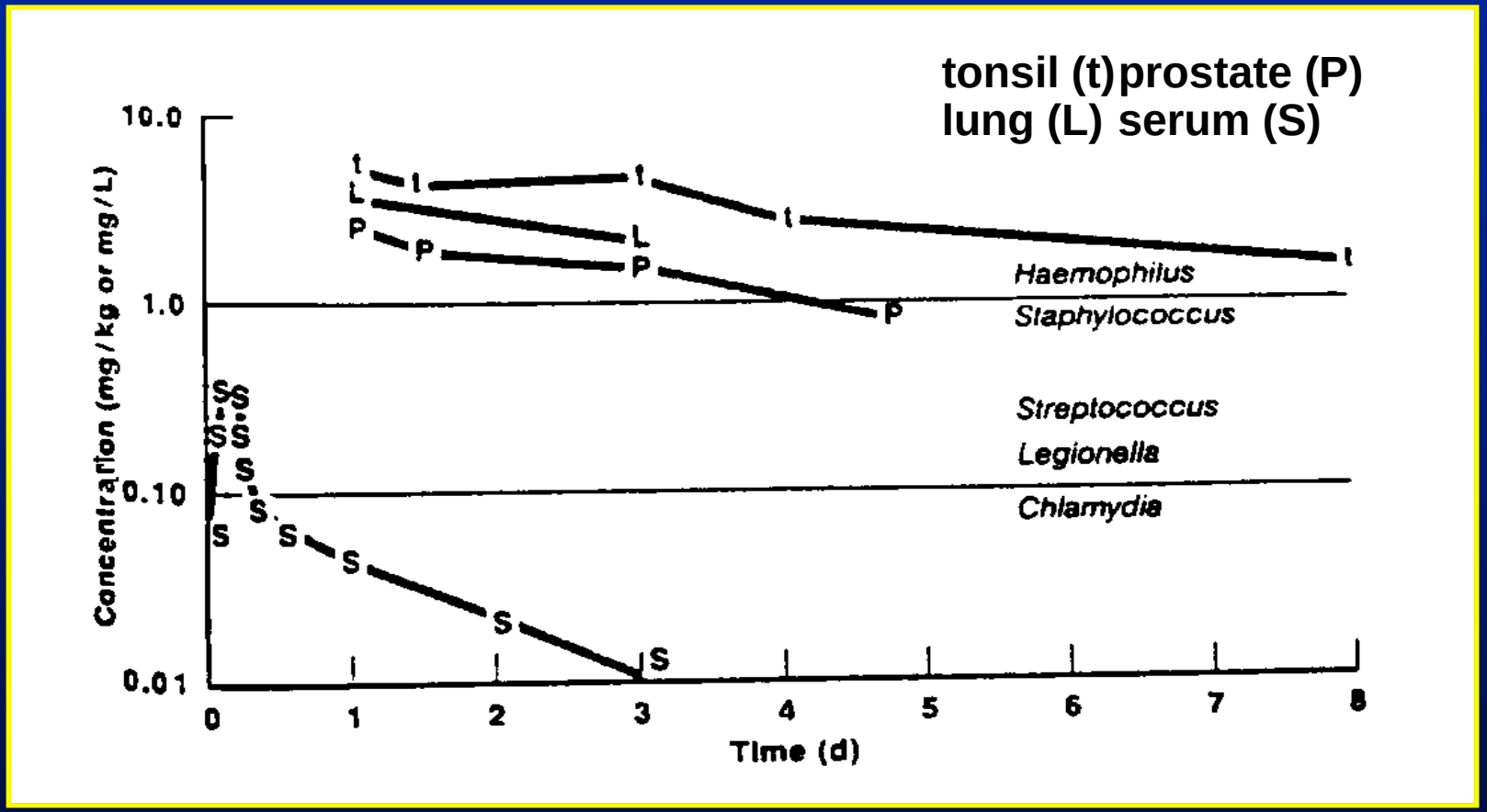
Liu & Derendorf, JAC 50, 19 (2002)

Pharmacokinetics

	Cefpodoxime	Cefixime
AUC_P [mg*h/L]	22.4 (8.7)	25.7 (8.4)
AUC_T [mg*h/L]	15.4 (5.2)	7.4 (2.1)
$C_{max,\,P}$ [mg/L]	3.9 (1.2)	3.4 (1.1)
$C_{max,T}$ [mg/L]	2.1 (1.0)	0.9 (0.3)

Azithromycin

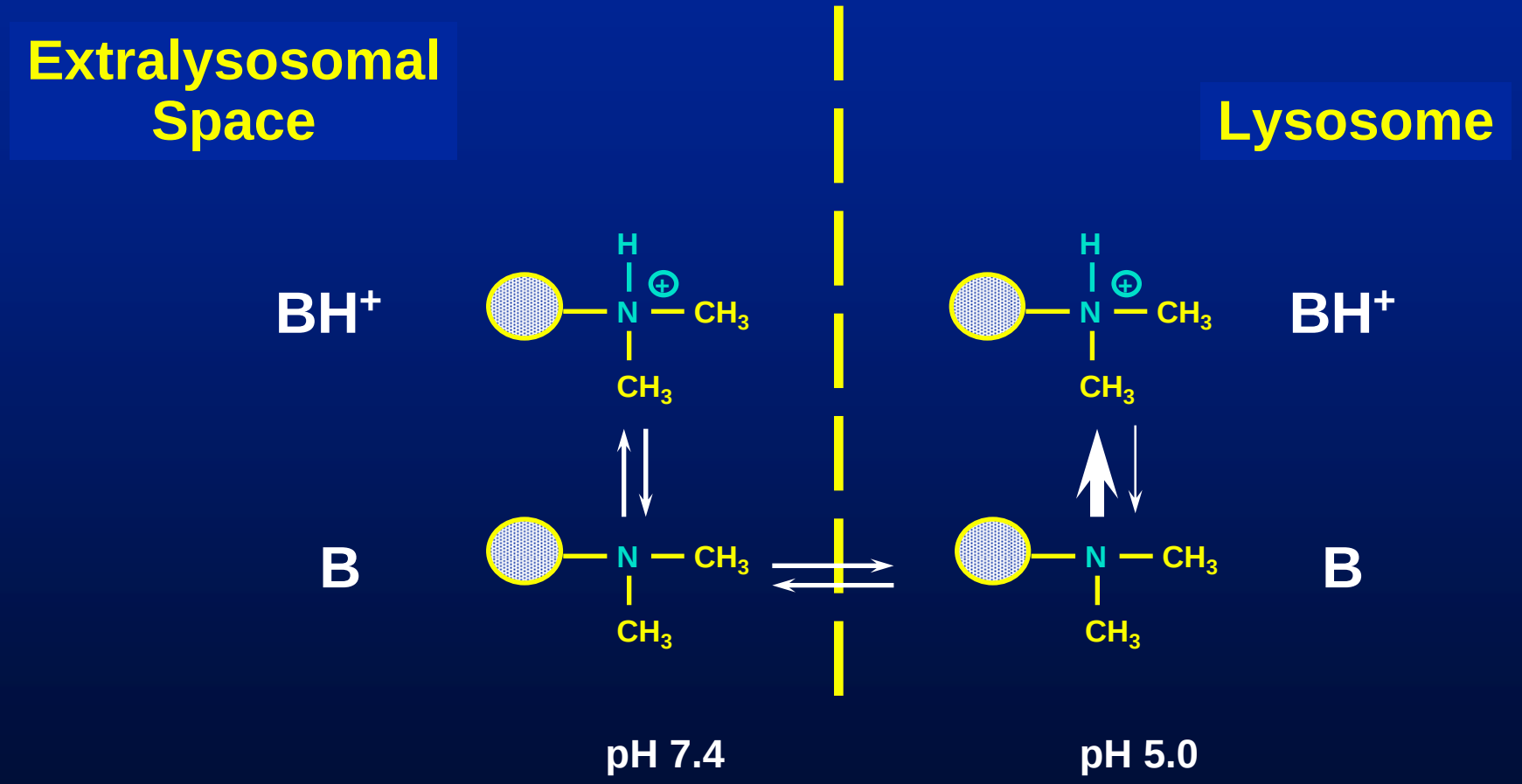
Tissue Concentrations



500 mg p.o.

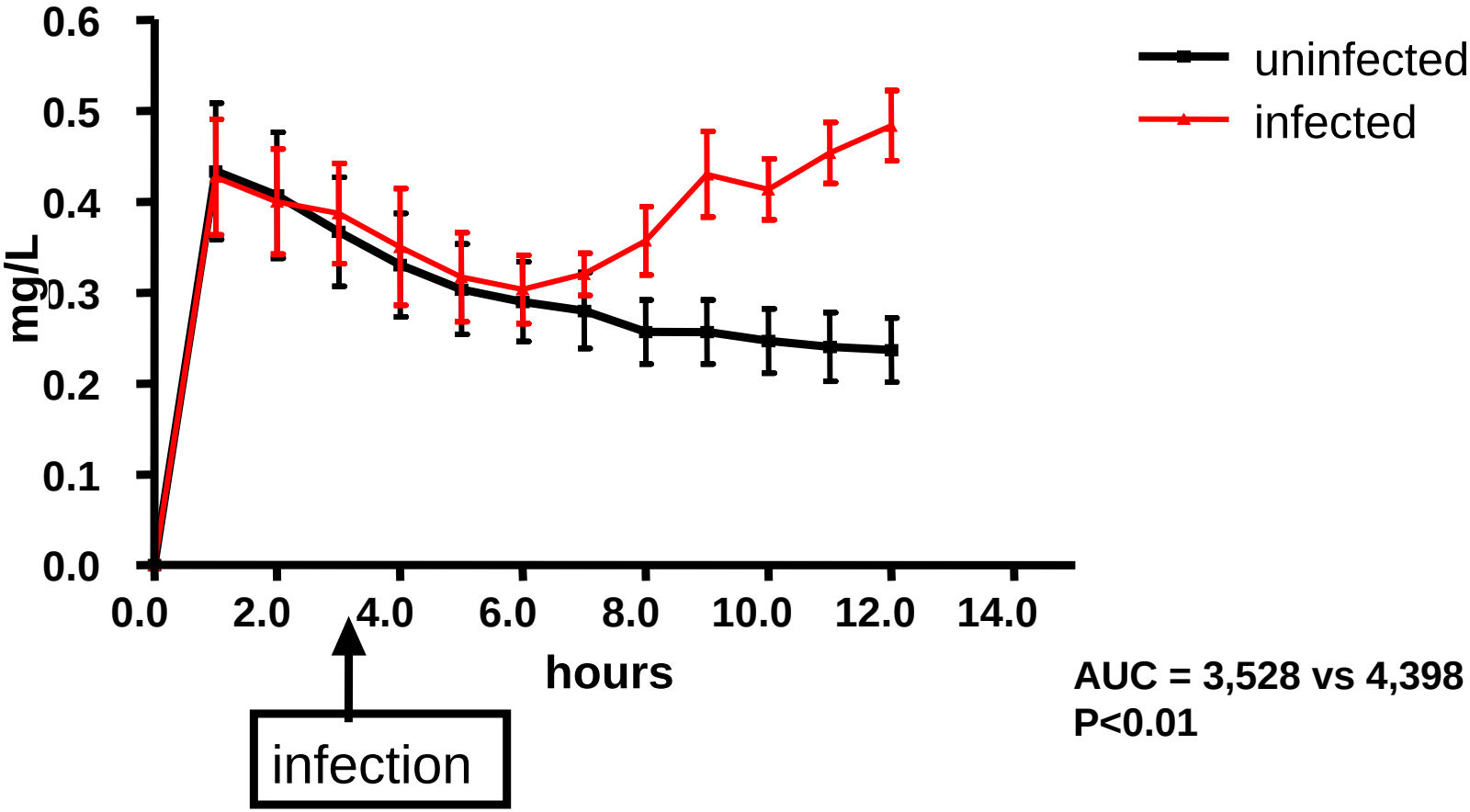
from Foulds et al. (1990)

Intracellular Ion-Trapping by Lysosomes



Azithromycin

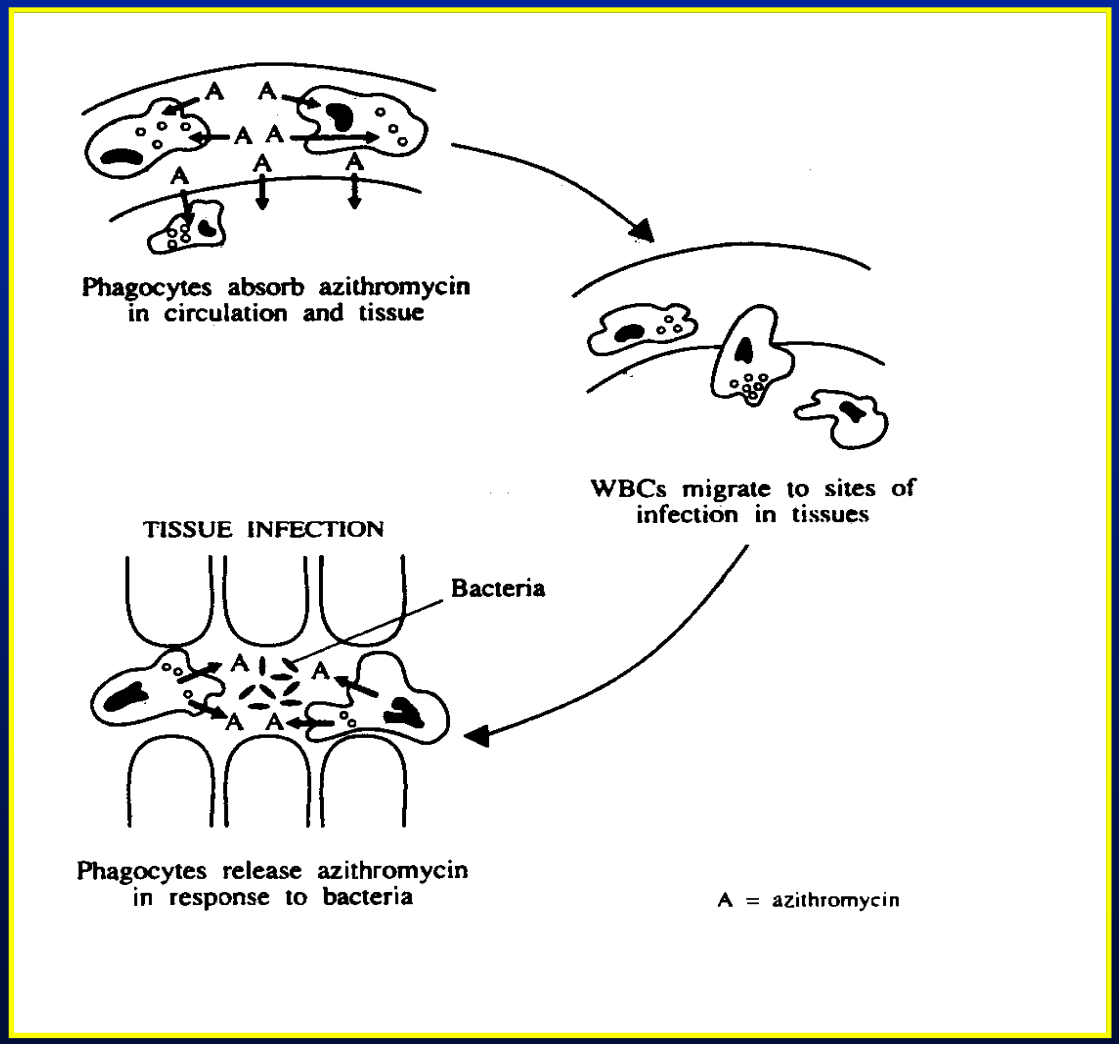
Tissue concentration (IF) of azithromycin (50 mg/kg sc) in infected (S. aureus) and uninfected rat thigh (same animal)



AUC = 3,528 vs 4,398
P<0.01

Scaglione et al. , ICAAC 2006

Phagocyte Delivery of Azithromycin



from Schentag et al. (1991)

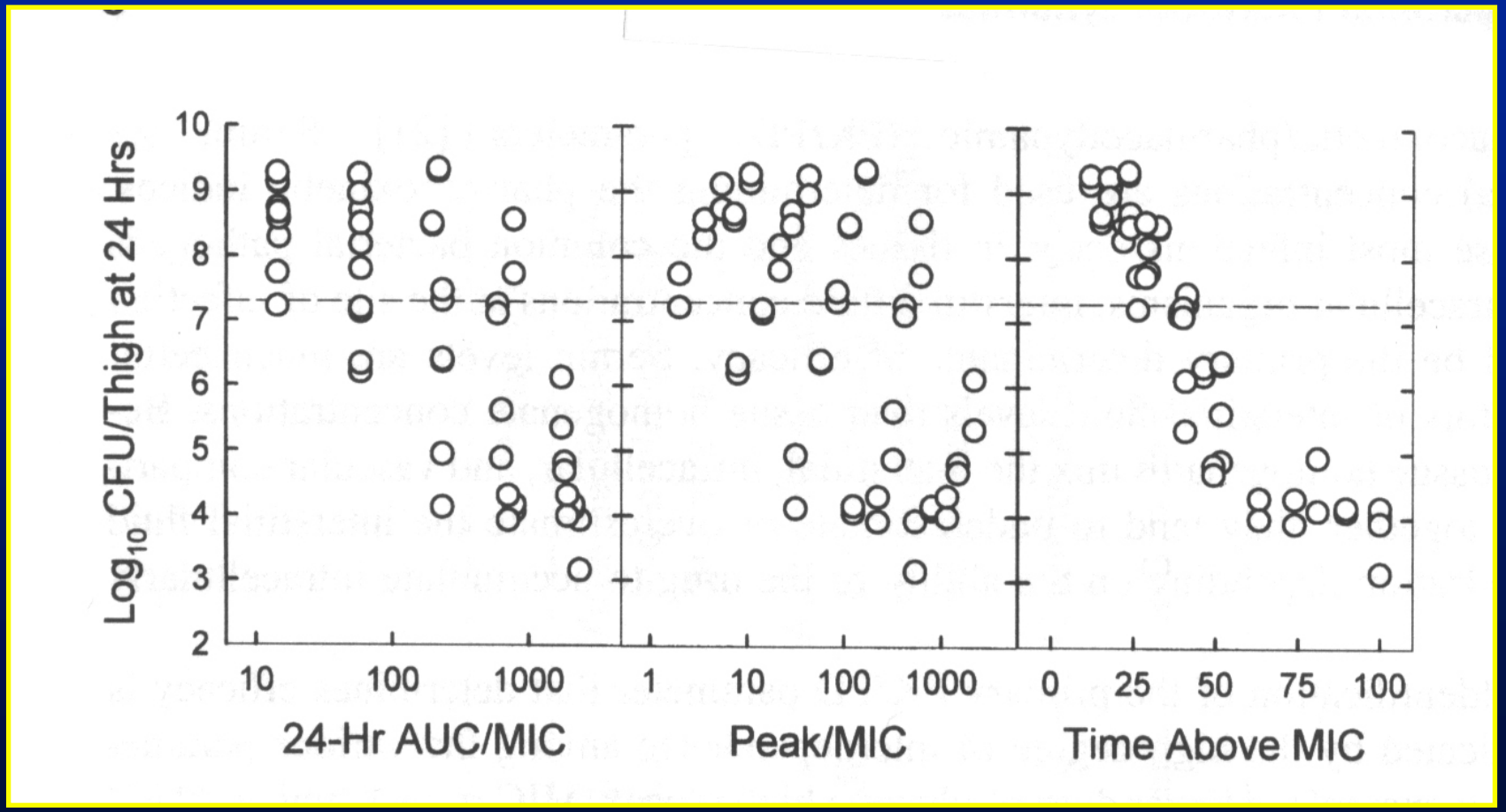
Conclusion

Microdialysis has opened the door to get better information about the drug concentrations at the site of action.

This, in combination with appropriate PK/PD-models, will allow for better dosing decisions than traditional approaches based on blood concentrations and MIC.

Ceftazidime

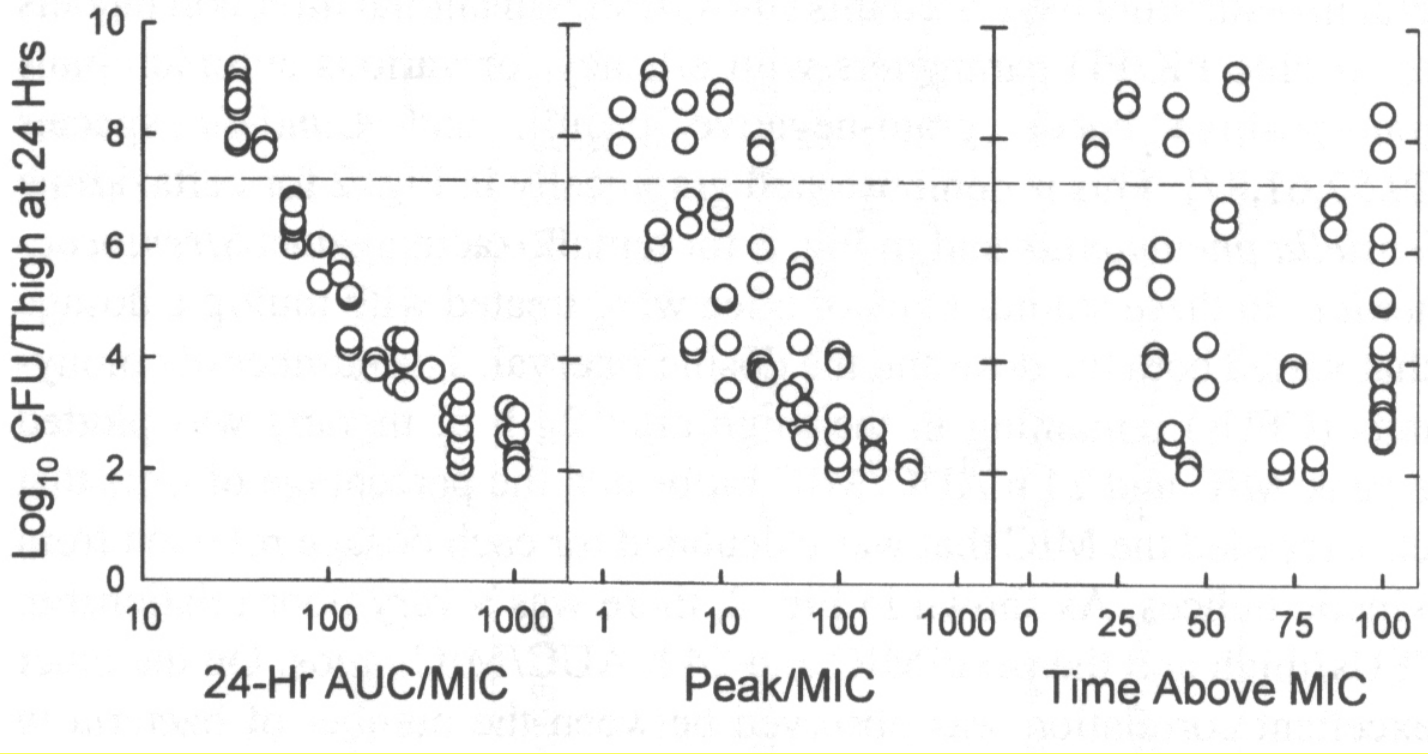
K. pneumoniae in neutropenic mice



Craig 2002

Temafloxacin

S. pneumoniae in neutropenic mice



Craig 2002

Pharmacodynamics

Problems:

- **MIC is imprecise**
- **MIC is monodimensional**
- **MIC is used as a threshold**
- **When MIC does not explain the data, patches are used (post-antibiotic effect, sub-MIC effect)**

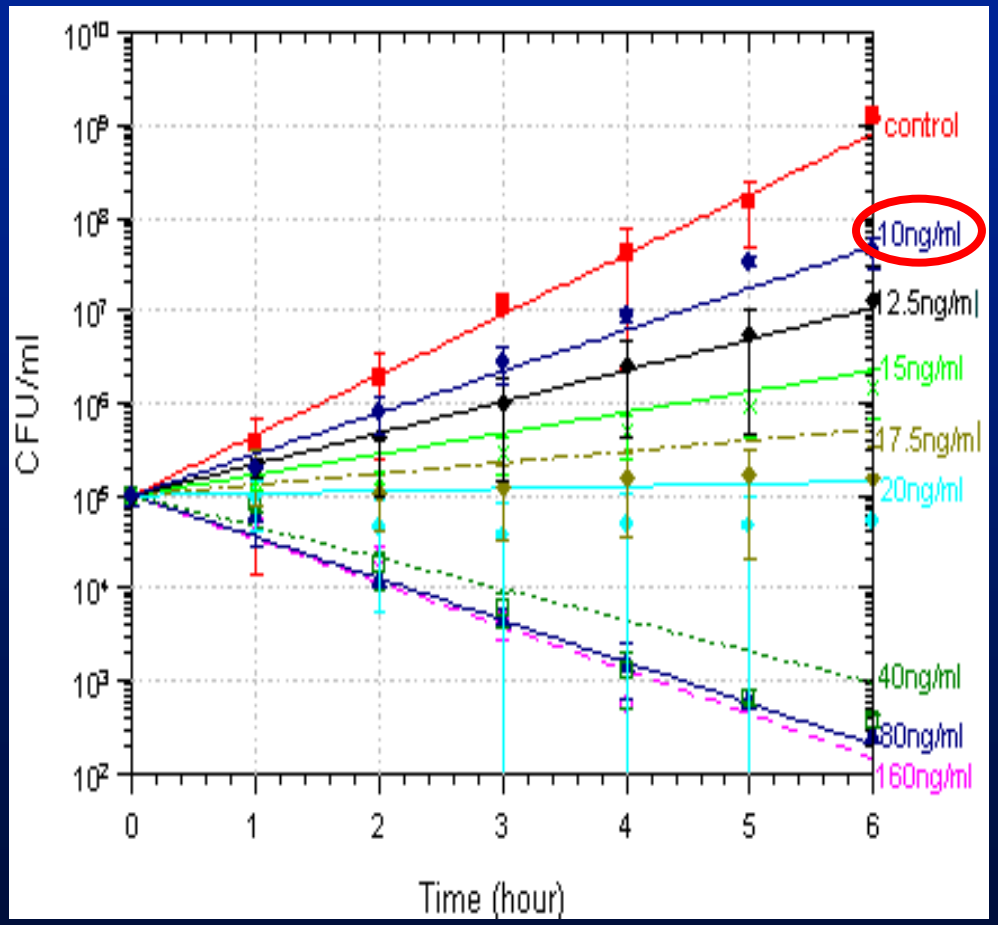
MIC
The Current Paradigm

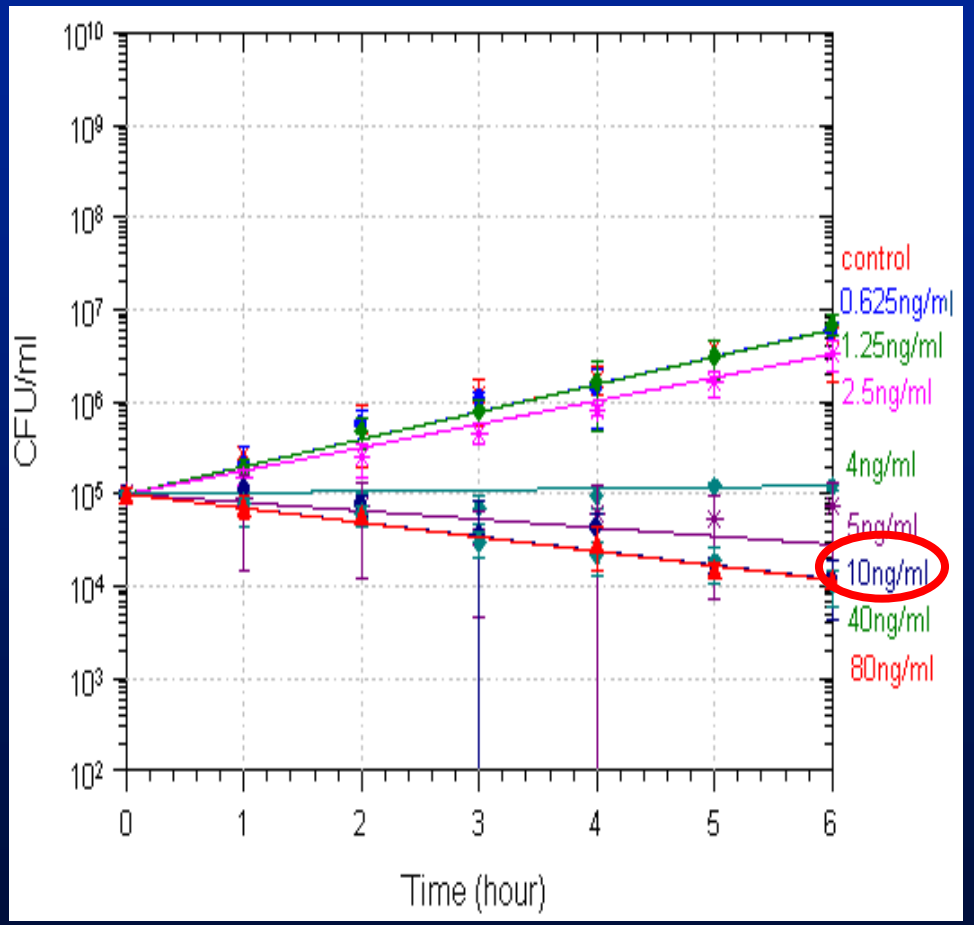
MIC is poison for the mind.

H. Mattie (1994), after a long after-dinner discussion

Kill Curves

Kill Curves of Ceftriaxone

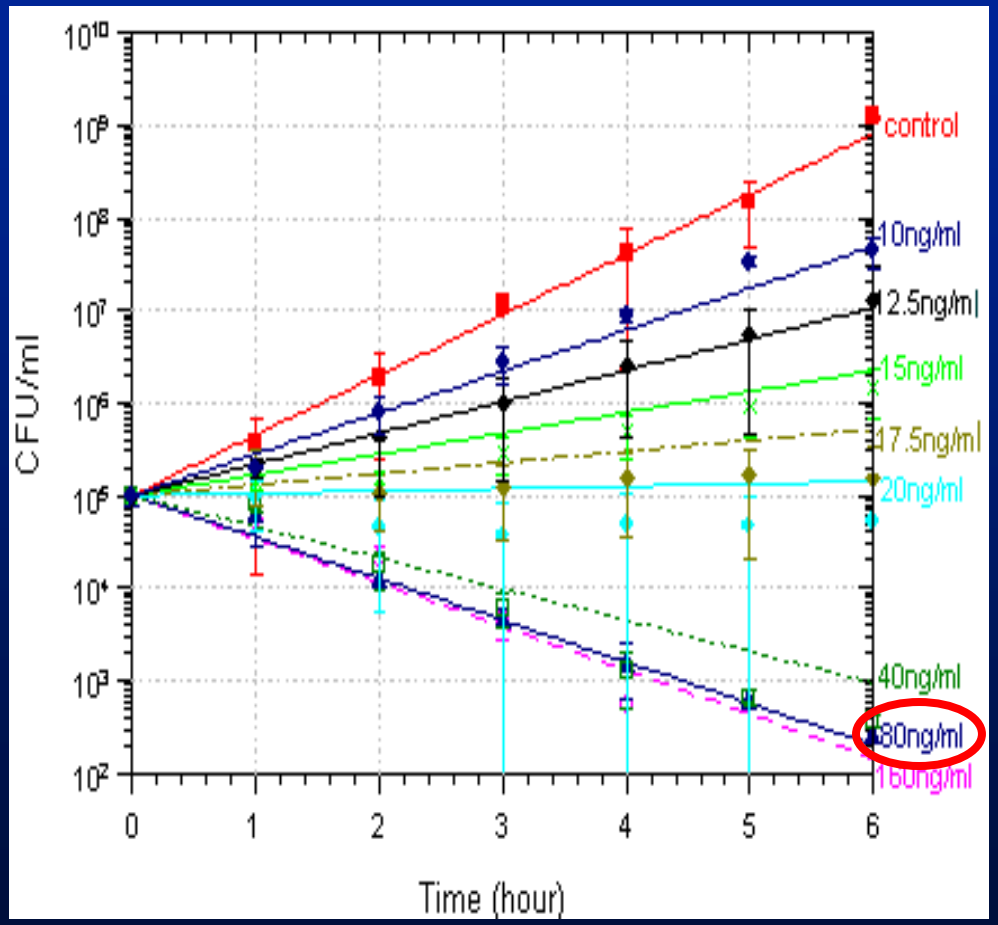


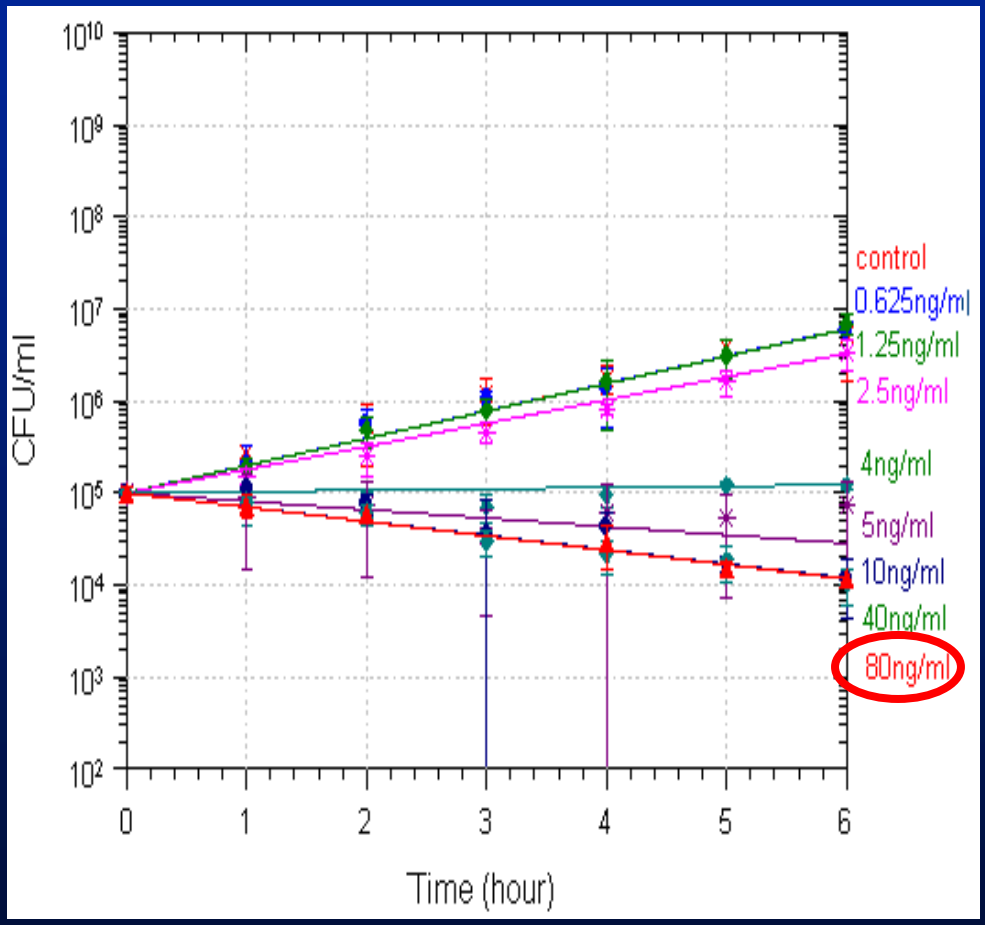


***S. pneumoniae* ATCC6303**
MIC: 20 ng/mL

***H. influenzae* ATCC10211**
MIC: 5 ng/mL

Kill Curves of Ceftriaxone





***S. pneumoniae* ATCC6303**
MIC: 20 ng/mL

***H. influenzae* ATCC10211**
MIC: 5 ng/mL

PK-PD Model

$$\frac{dN}{dt} = \left(k - \frac{k_{\max} \cdot C_f}{EC_{50} + C_f} \right) \cdot N$$

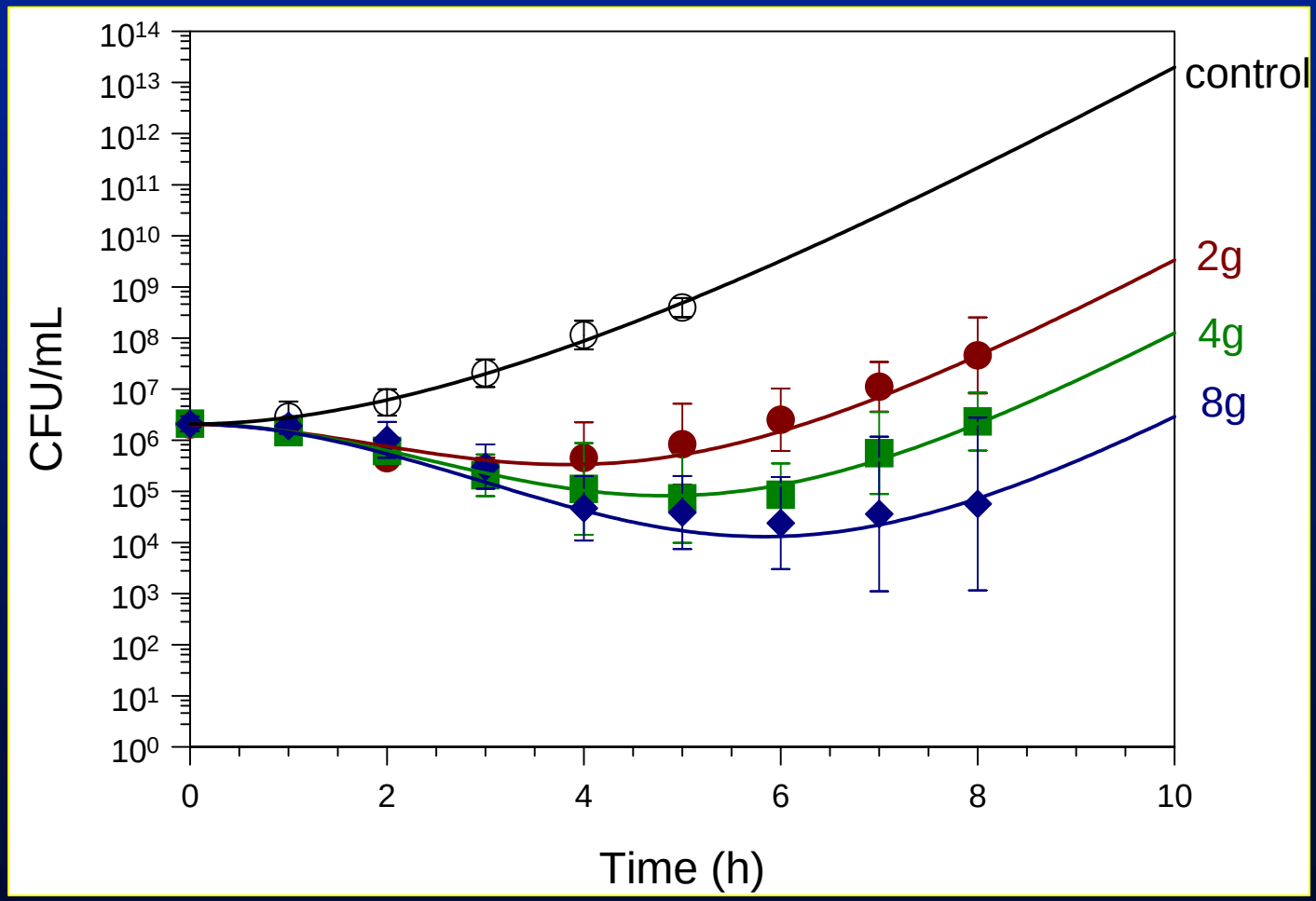
Maximum Growth Rate Constant **k**

Maximum Killing Rate Constant **$k\text{-}k_{max}$**

Initially, bacteria are in log growth phase

Single Dose

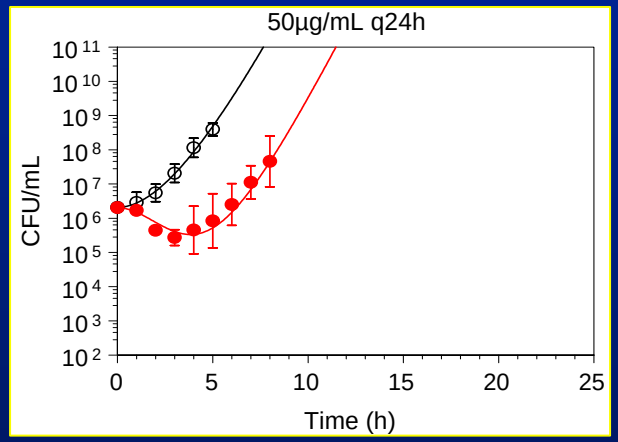
Piperacillin vs. E. coli

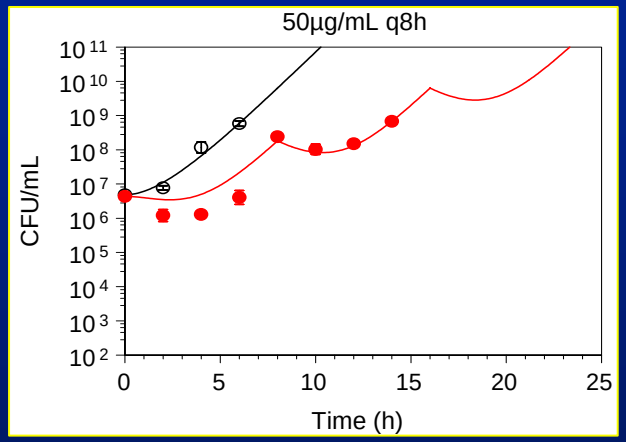


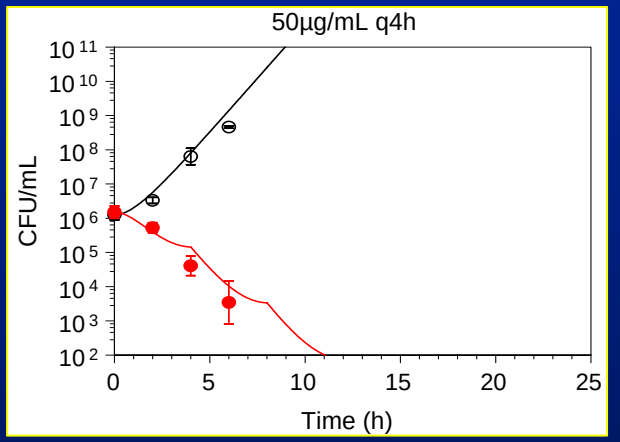
Dosing Interval

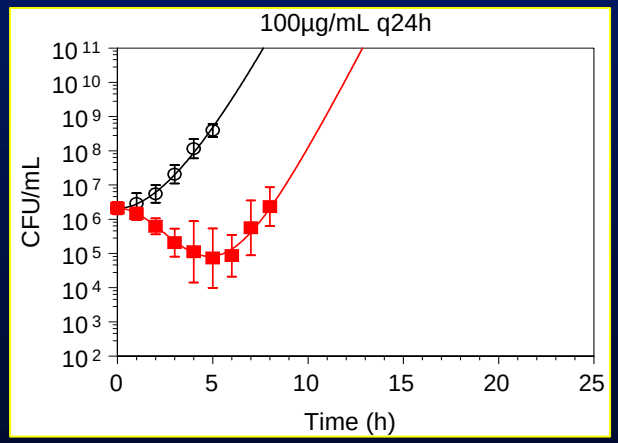
Piperacillin (2g and 4g) vs. E. coli

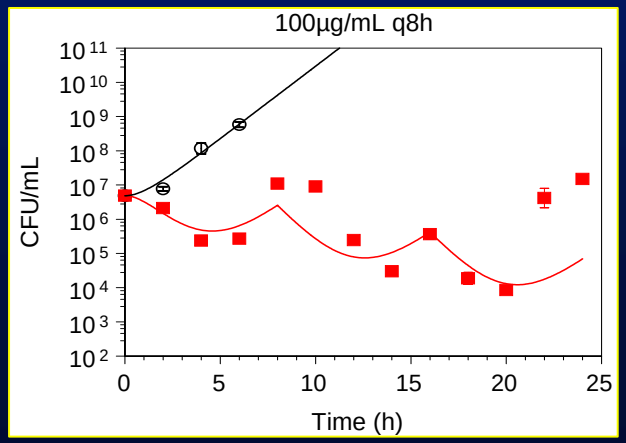
q24h	q8h	q4h

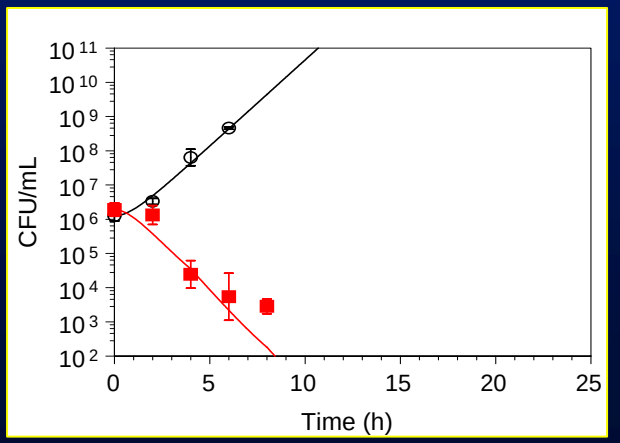




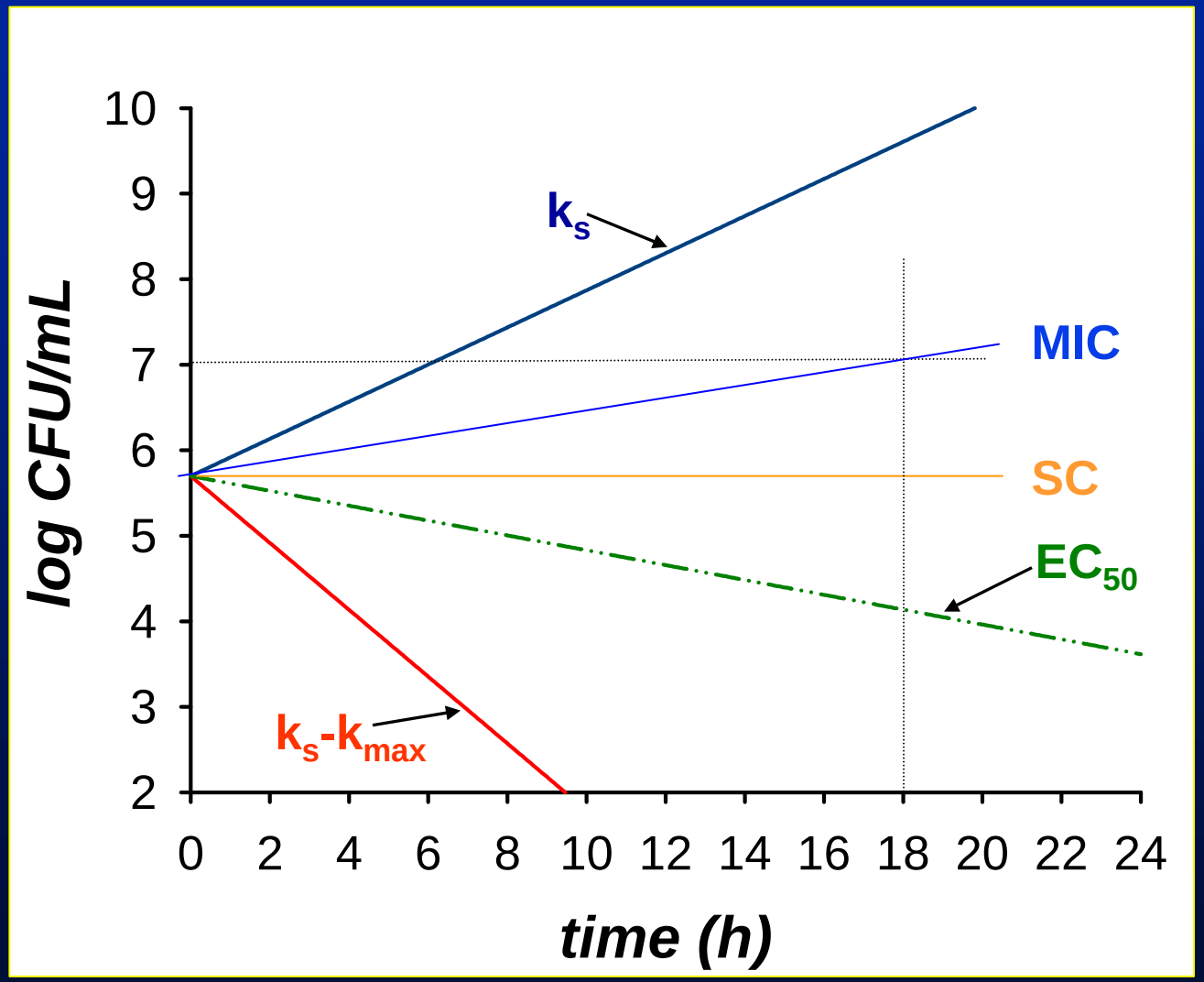




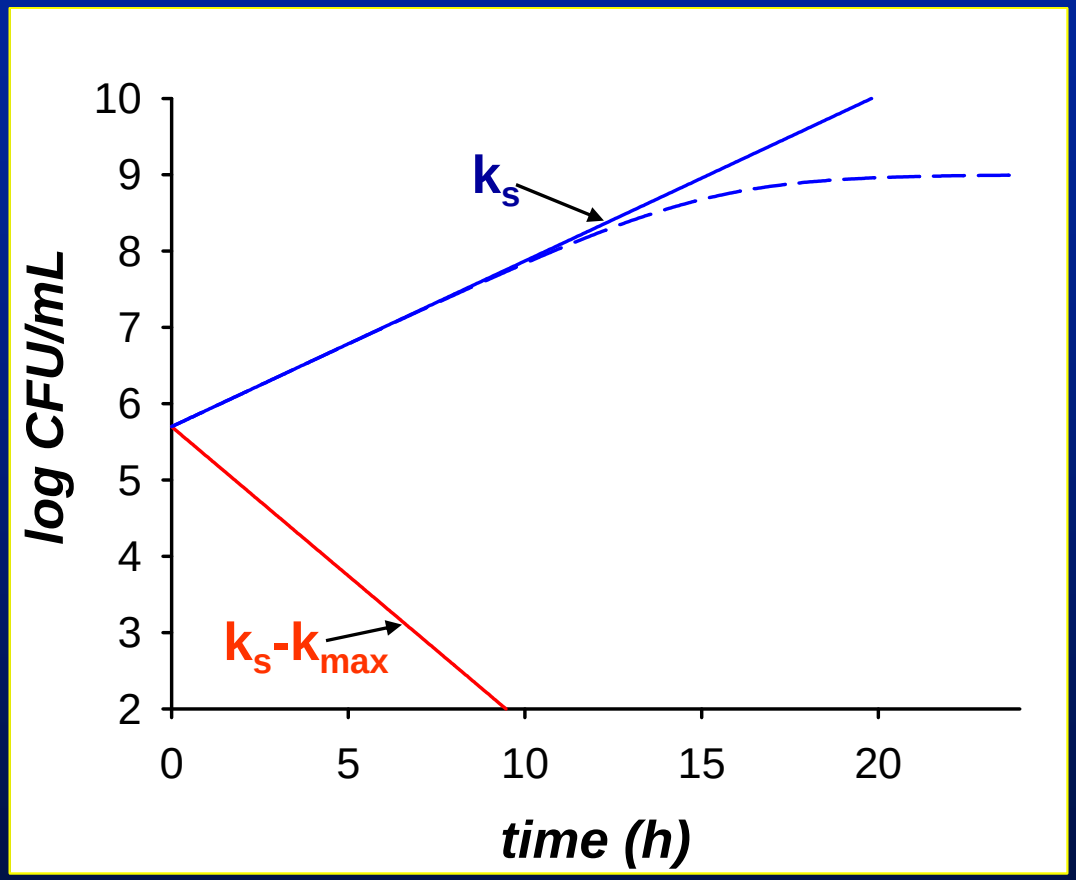




Sigmoidal E_{max}-Models

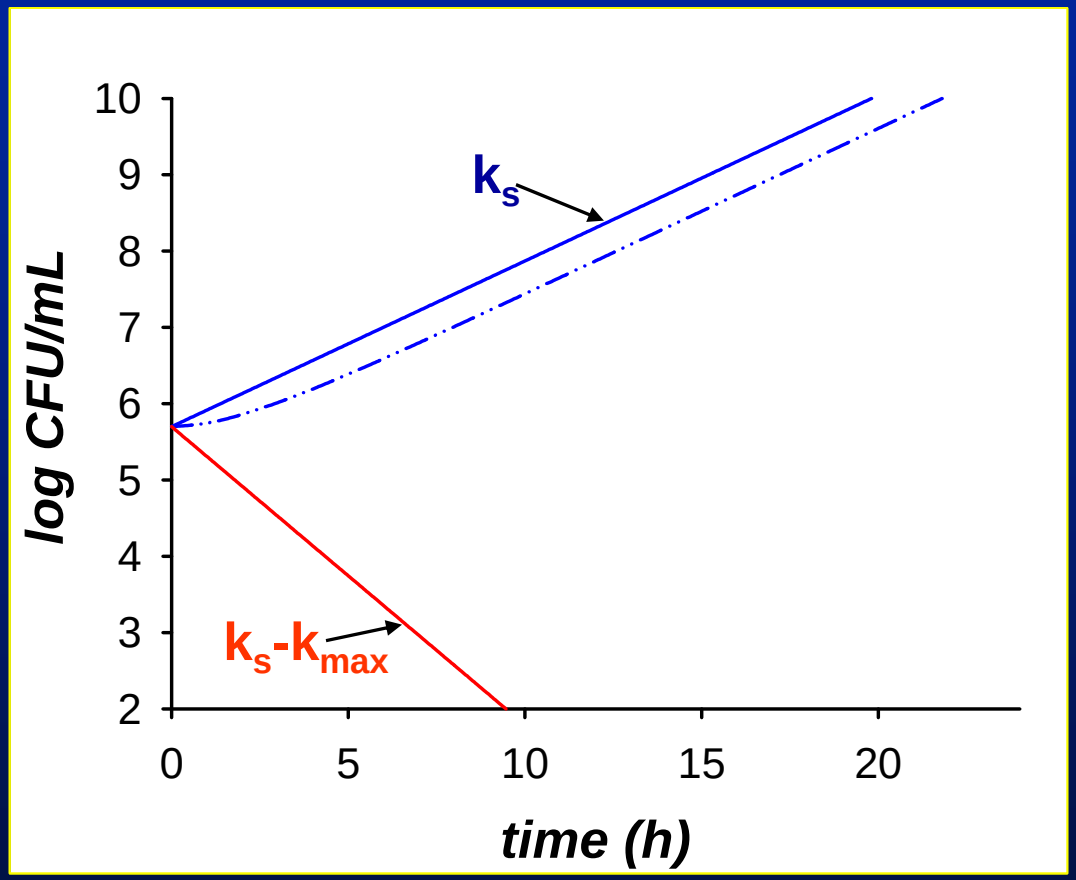


Saturation in Growth



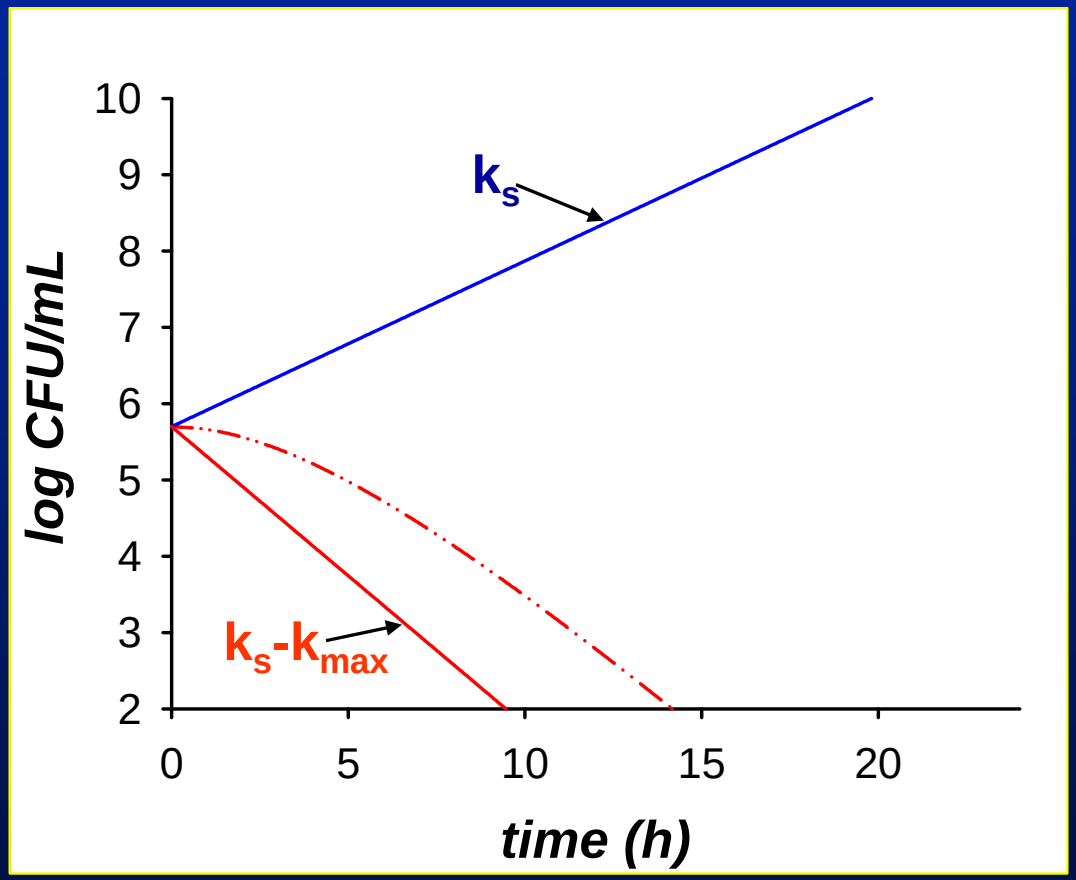
$$\frac{dN}{dt} = k_s \cdot \left(1 - \frac{N}{N_{max}}\right) \cdot N$$

Delay in the Onset of Growth



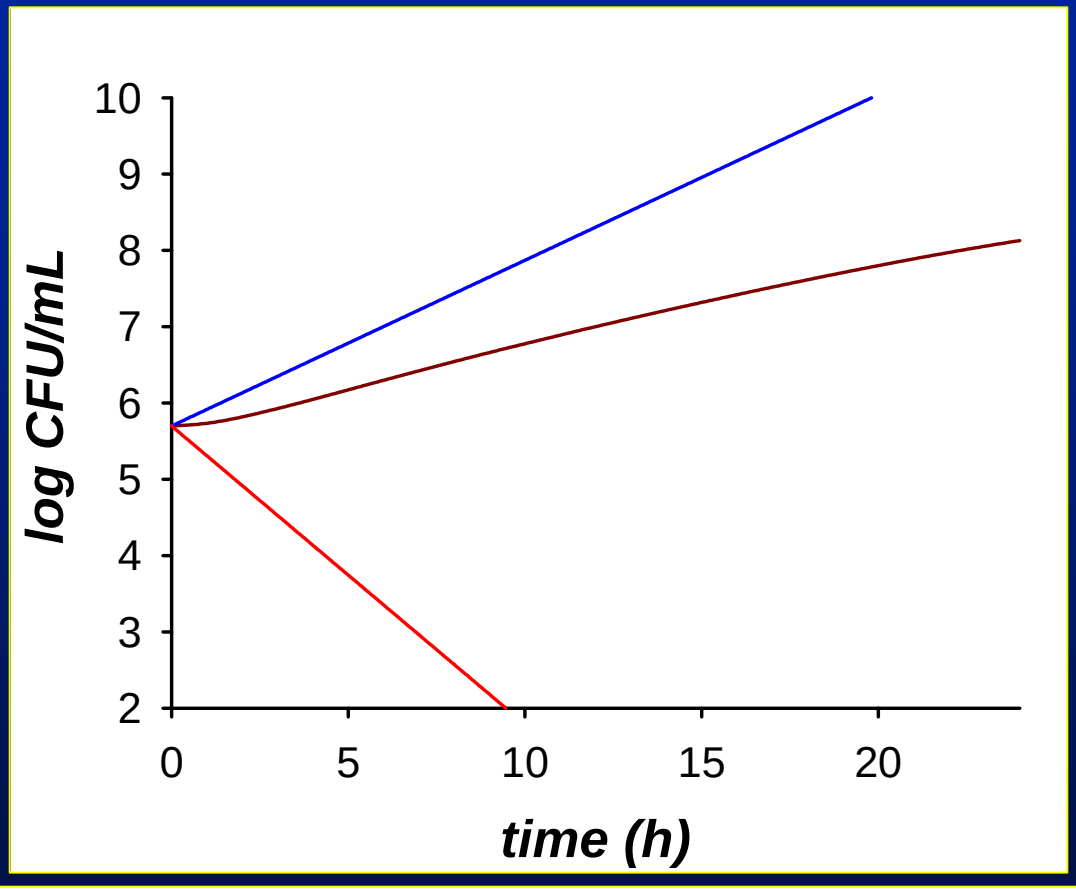
$$\frac{dN}{dt} = k_S \cdot \left(1 - e^{-dg \cdot t}\right) \cdot N$$

Delay in the Onset of Kill



$$\frac{dN}{dt} = \left(k_s - \frac{k_{\max} \cdot C^h}{EC_{50}^h + C^h} \cdot \left(1 - e^{-dk \cdot t}\right) \right) \cdot N$$

Modified Sigmoidal E_{max}-Model



$$\frac{dN}{dt} = \left(k_S \cdot \left(1 - \frac{N}{N_{max}} \right) \cdot \left(1 - e^{-dg \cdot t} \right) - \frac{k_{max} \cdot C^h}{EC_{50}^h + C^h} \cdot \left(1 - e^{-dk \cdot t} \right) \right) \cdot N$$

Treyaprasert W, Schmidt S, Rand KH, et al.: Pharmacokinetic/pharmacodynamic modeling of in vitro activity of azithromycin against four different bacterial strains. *Int J Antimicrob Agents* 2007;29(3):263-70

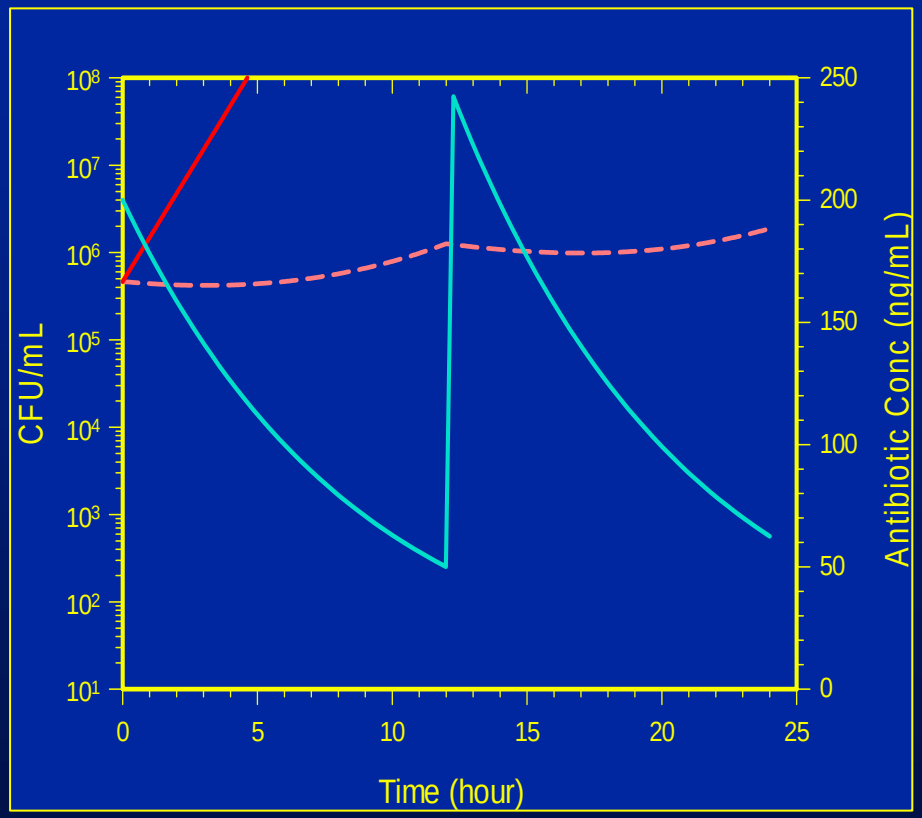
Example 1

- Same PK
- Same MIC
- Same t>MIC
- Same AUC/MIC
- Same C_{max}/MIC
- Same k (Growth Rate)

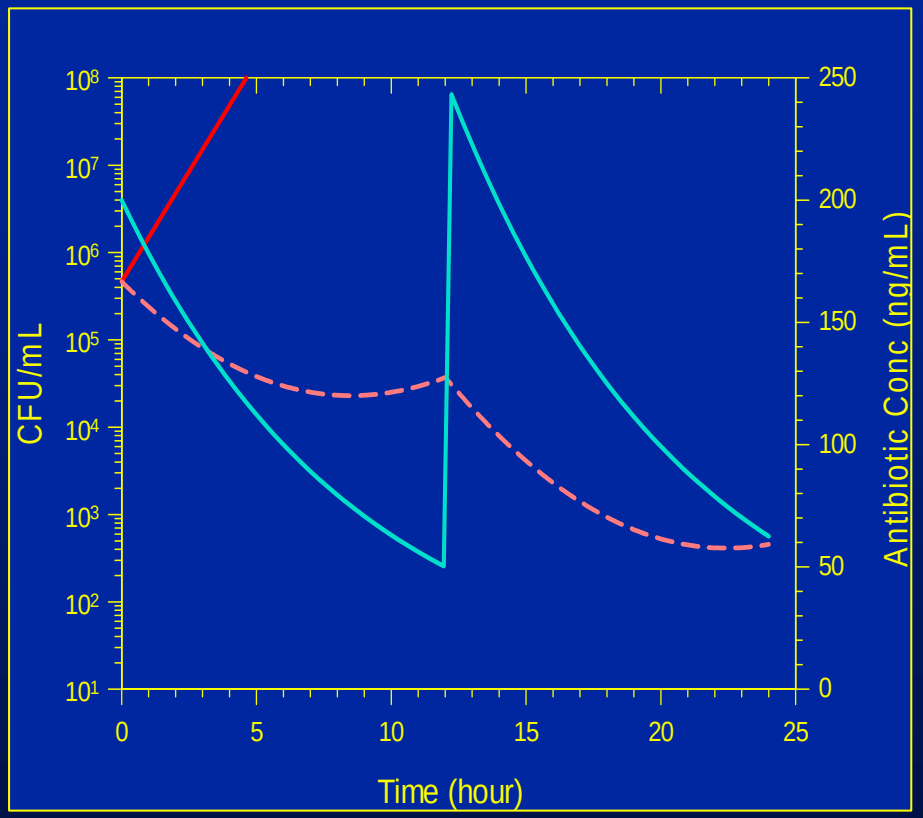
- Different EC_{50} (Sensitivity)
- Different k_{max} (Maximum Kill Rate)

PK-PD modeling based on Kill Curves

Condition 1

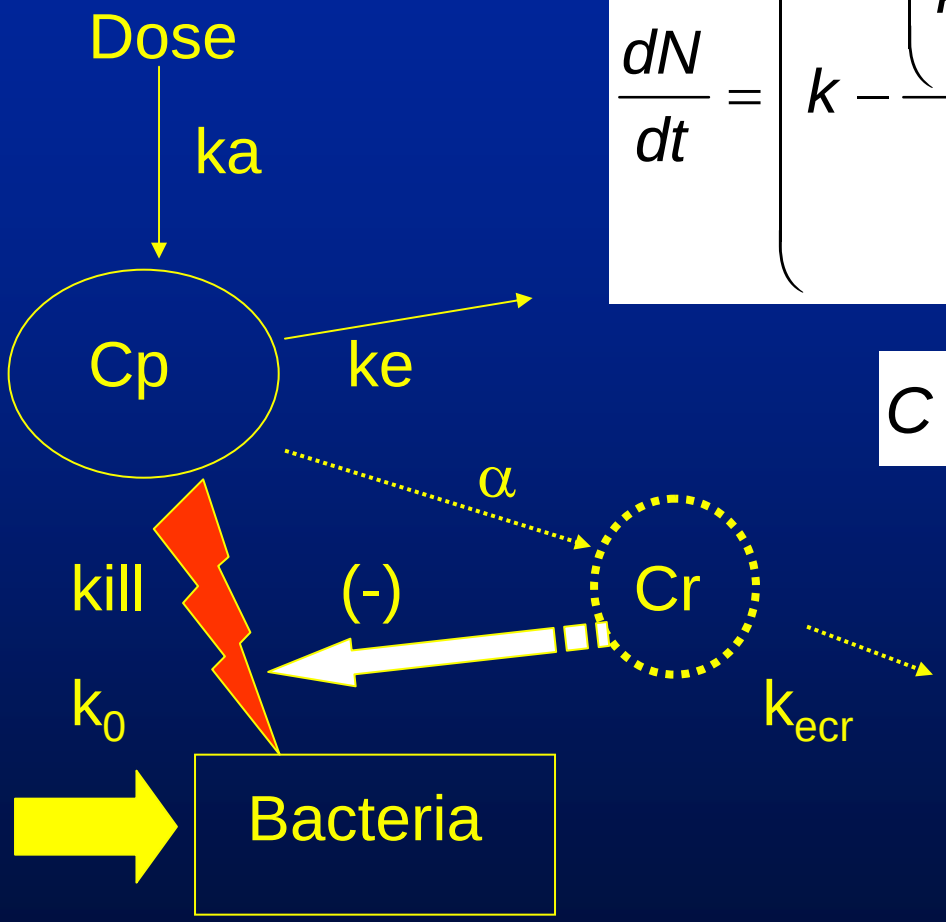


Condition 2



Control (CFU/mL)
Treated (CFU/mL)
Antibiotic concentration

Modified E_{max} Model:



$$\frac{dN}{dt} = \left(k - \frac{\left(k_1 \cdot \left(1 - \frac{C_r}{IC_{50} + C_r} \right) + k_2 \right) \cdot C}{EC_{50} + C} \right) \cdot N \cdot \left(1 - e^{-z \cdot t} \right)$$

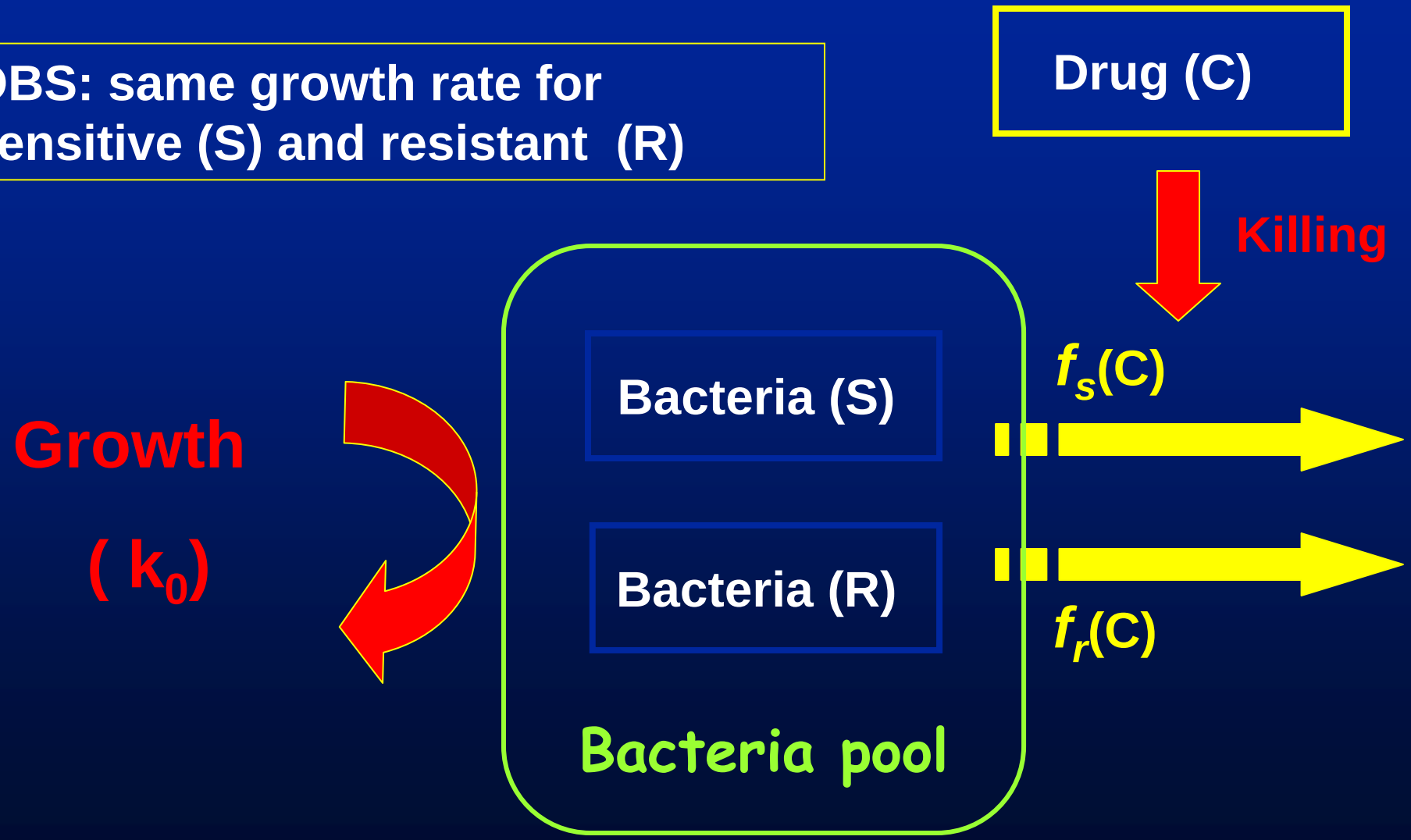
$$C_r = C_0 \cdot \left(e^{-k_e \cdot (t - t_{lag})} - e^{-\alpha \cdot (t - t_{lag})} \right)$$

Comparing to E_{max} model:

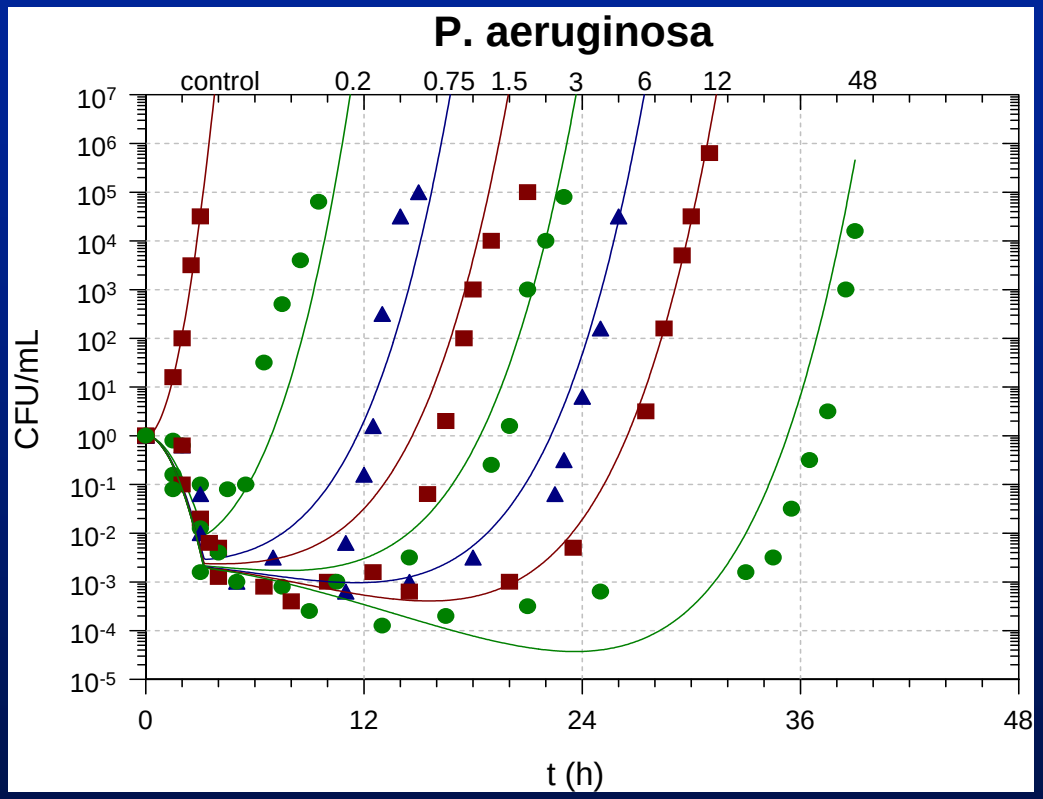
$$K_{\max} = k_1 \left(1 - \frac{Cr}{IC_{50} + Cr} \right) + k_2$$

Two sub-population model

OBS: same growth rate for sensitive (S) and resistant (R)

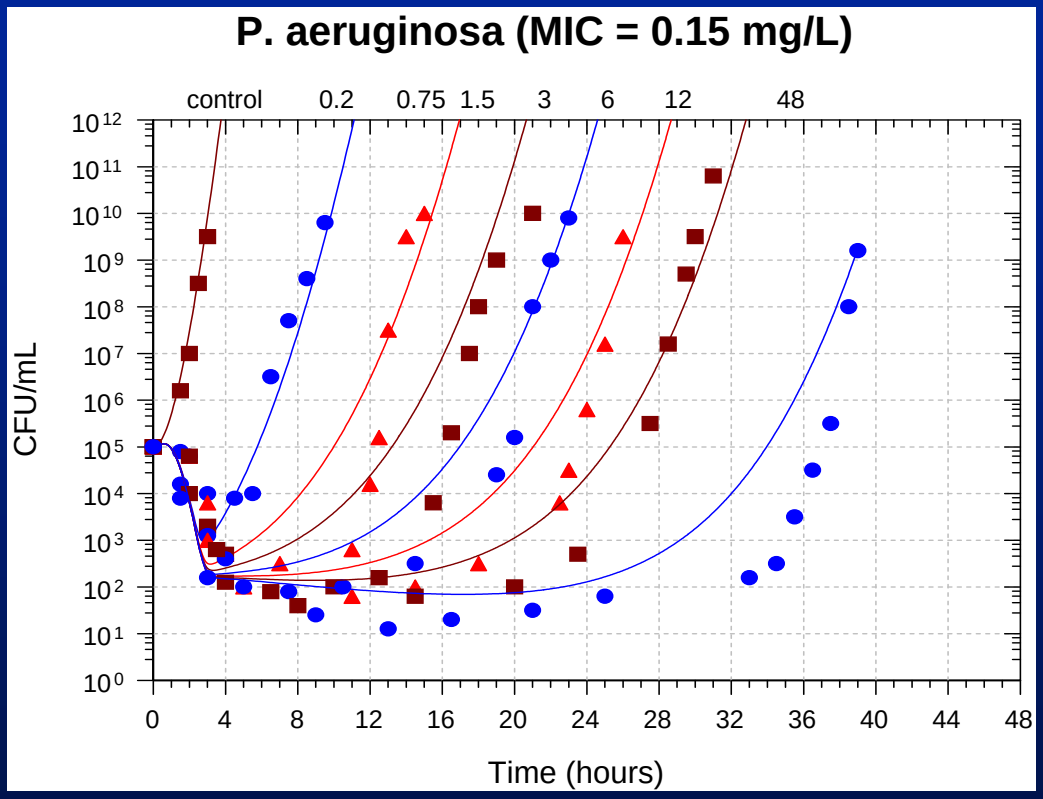


Model Comparison – *P. aeruginosa*



Modified E_{max} model

(simultaneous fit)



Two sub-population model

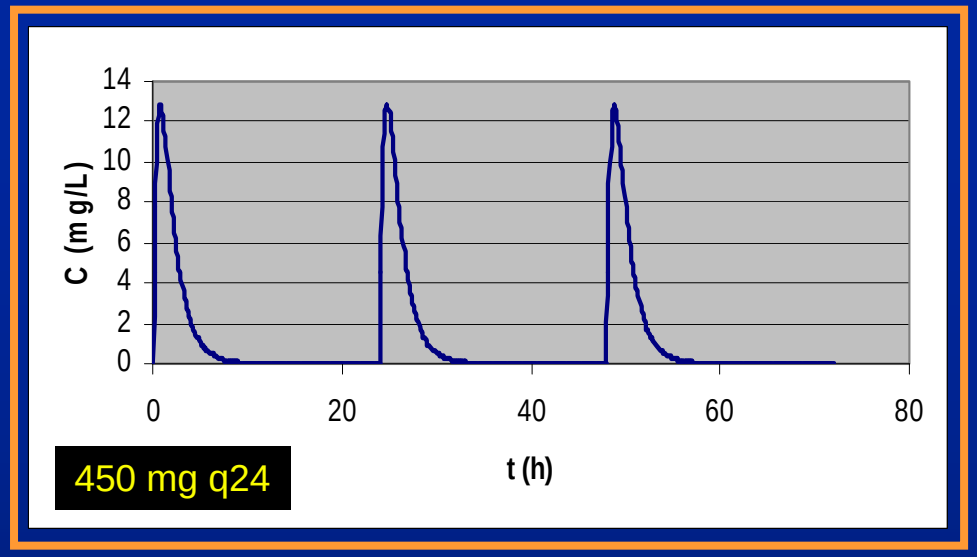
(simultaneous fit)

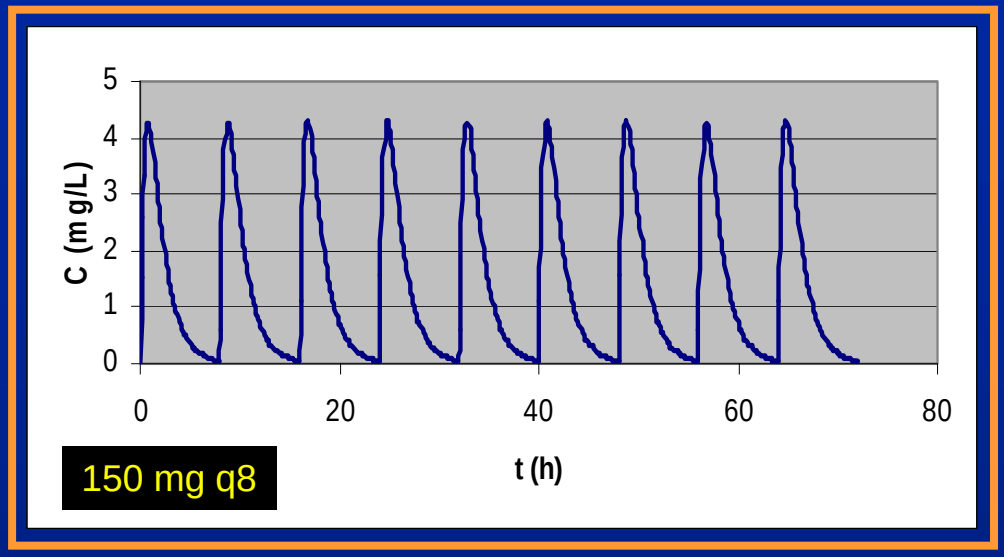
Faropenem Daloxate

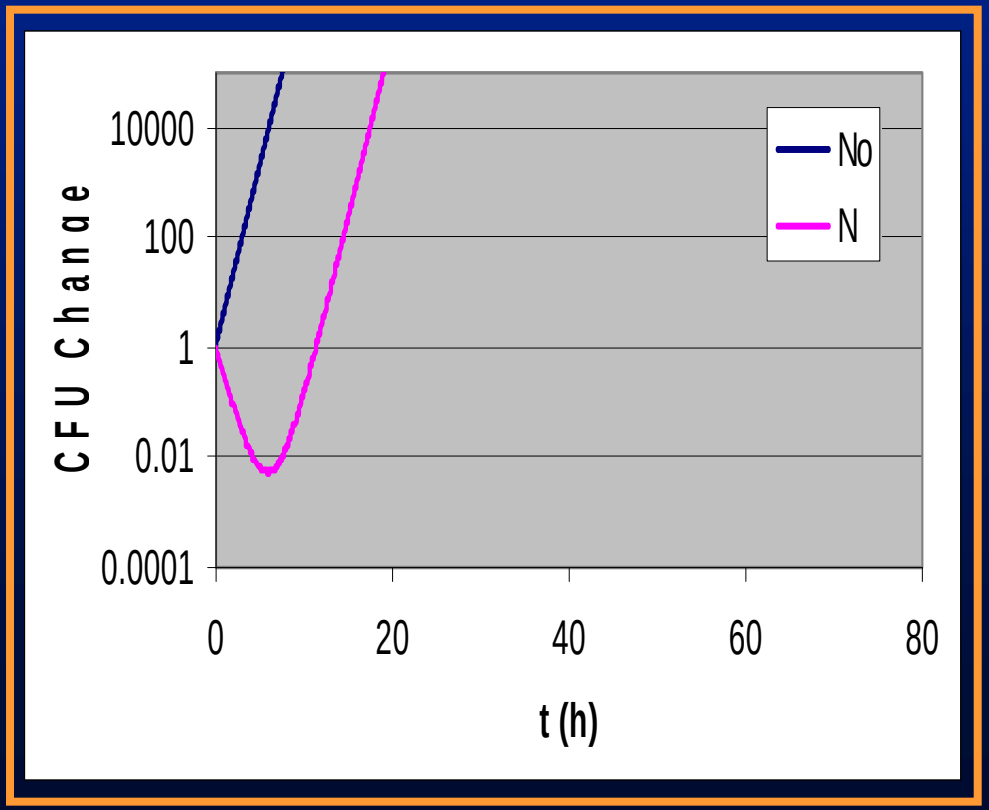
After oral administration, faropenem daloxate is rapidly absorbed and immediately converted in plasma to its active moiety faropenem

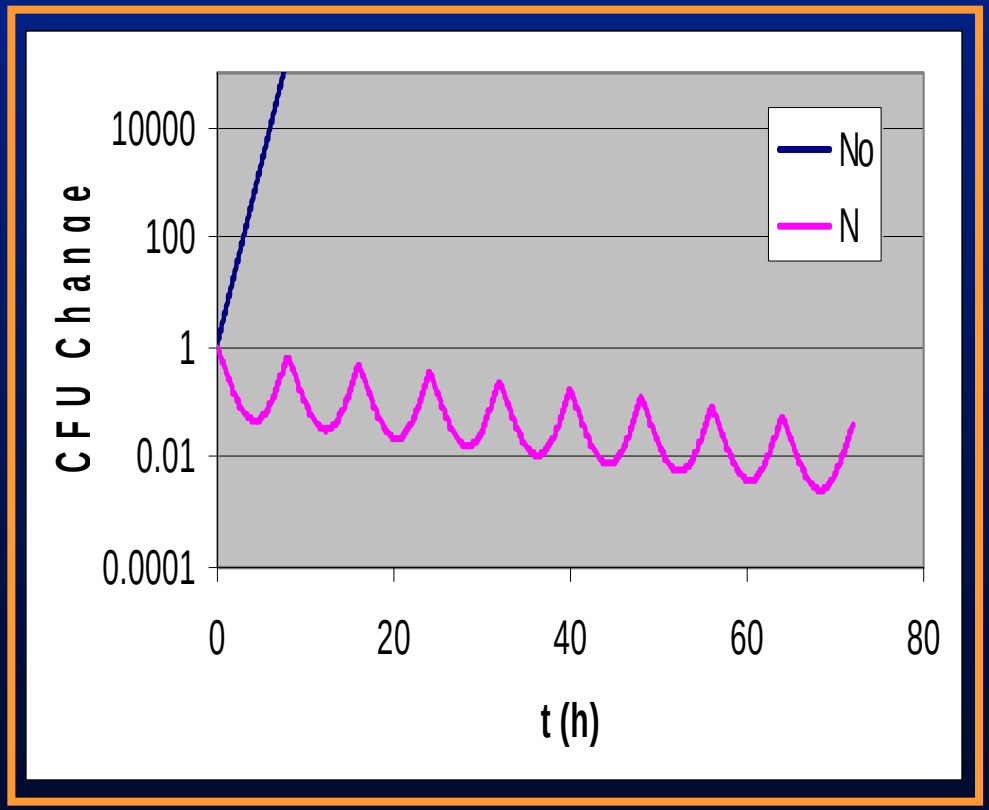
Advantages of using the pro-drug instead of faropenem sodium:

- higher oral bioavailability (70-80%)
- less gastrointestinal side effects


C (mg/L)
14
12
10
8
6
4
2
0
0
20
40
60
80
t (h)
450 mg q24

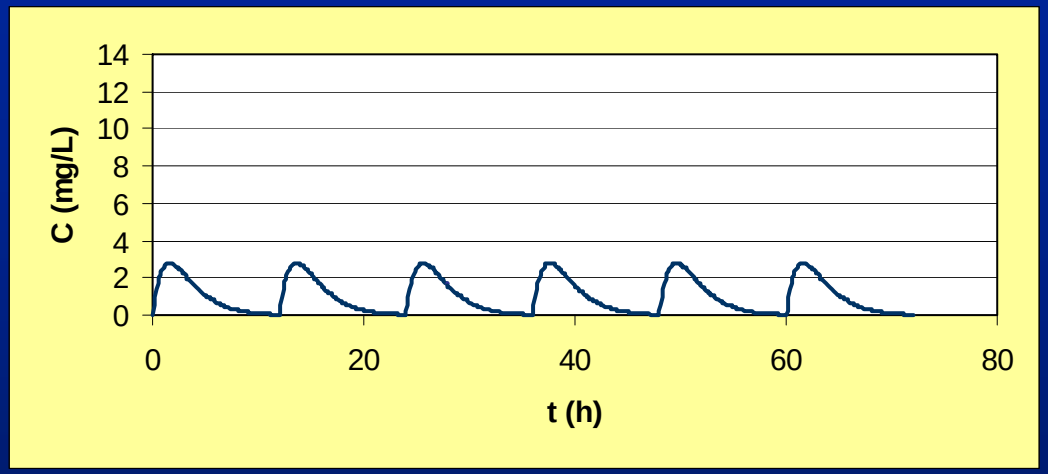

C (mg/L)
5
4
3
2
1
0
0
20
40
60
80
t (h)
150 mg q8


CFU Change
10000
100
1
0.01
0.0001
0
20
40
60
80
t (h)
No
N


CFU Change
10000
100
1
0.01
0.0001
0
20
40
60
80
t (h)
No
N

Faropenem daloxate 300 mg q12h

Fed



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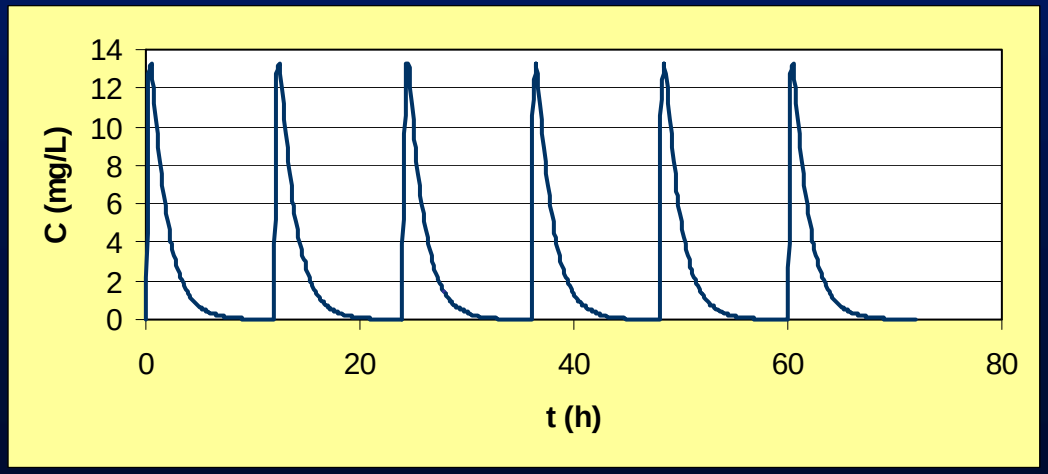
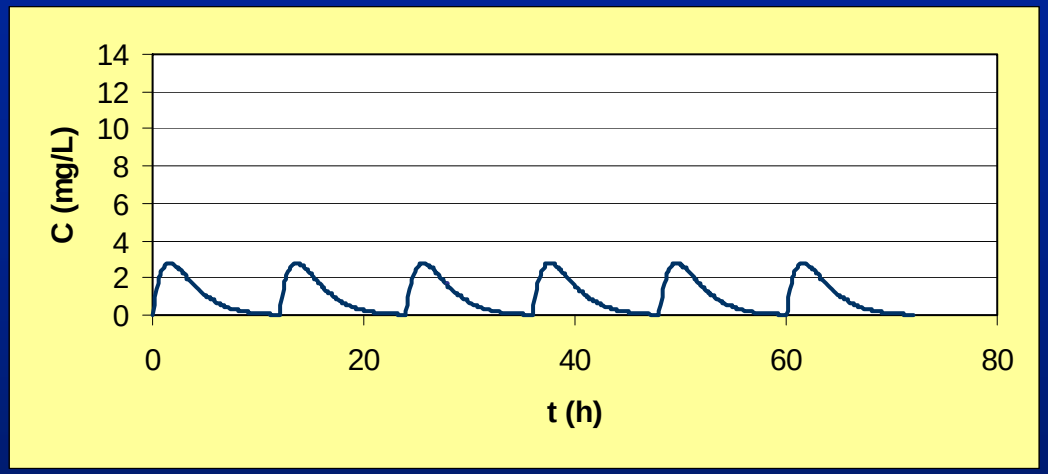


Faropenem daloxate 300 mg q12h

Fed



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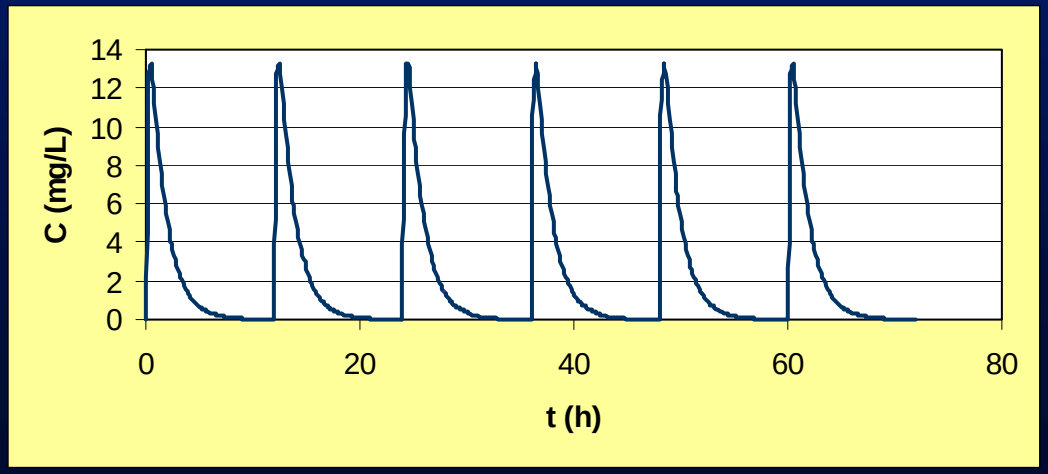
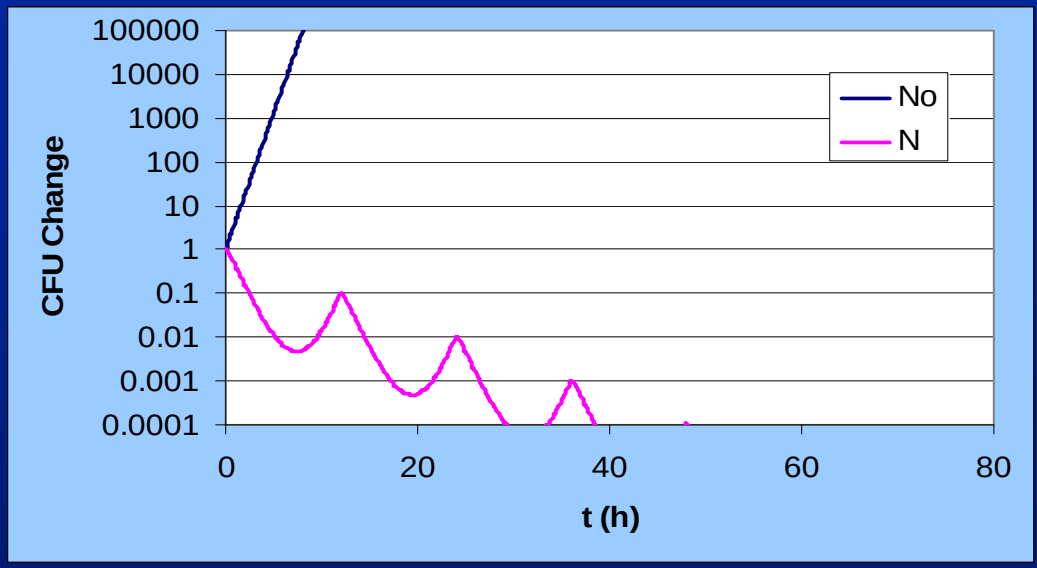
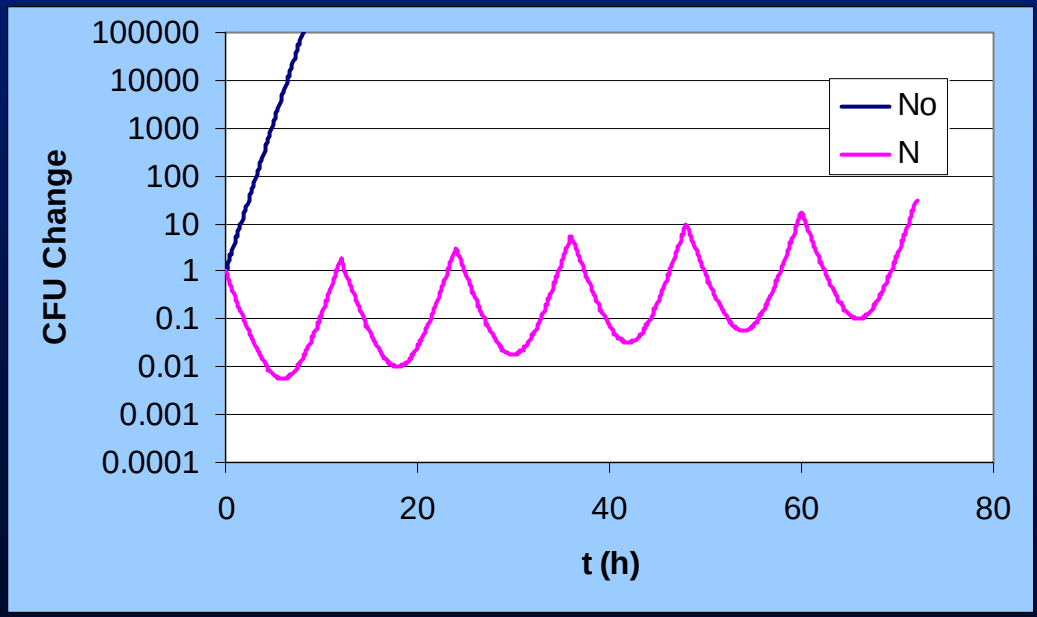
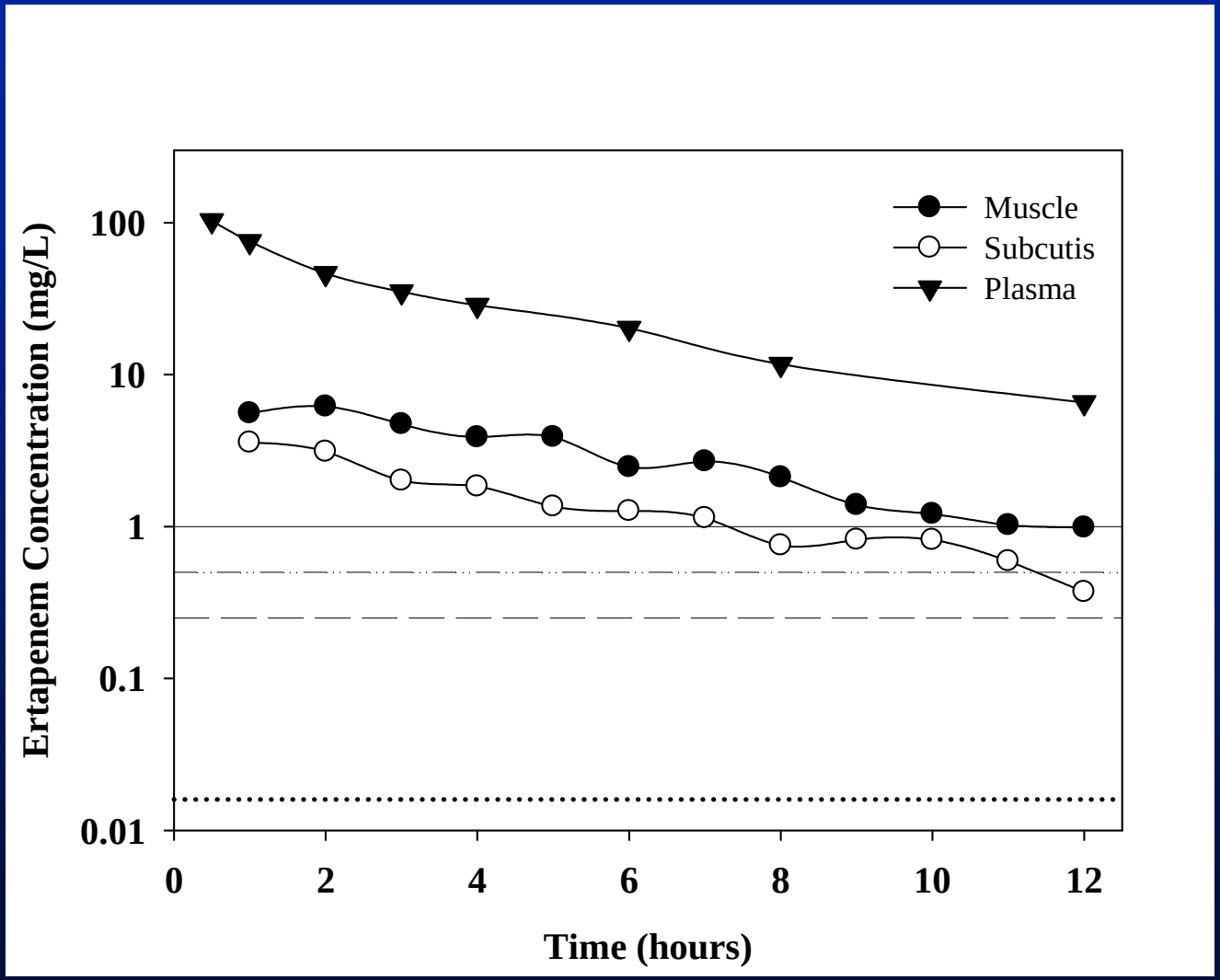


S. pneumo. #49619





Ertapenem



MIC_{90} values for Bacteroides fragilis (——), Streptococcus spp. (-···-··), methicillin-susceptible Staphylococcus aureus (----), and ESBL-producing Enterobacteriaceae (·····).

Burkhardt & Derendorf, JAC (2006)

Summary

- A simple comparison of serum concentration and MIC is usually not sufficient to evaluate the PK/PD-relationships af anti-infective agents.
- Protein binding and tissue distribution are important pharmacokinetic parameters that need to be considered. Microdialysis can provide information on local exposure.
- PK-PD analysis based on MIC alone can be misleading.
- Microbiological kill curves provide more detailed information about the PK/PD-relationships than simple MIC values.

Proposal

Wild Card Patent Extension

A company that receives approval for a new antibiotic, or a new indication for an existing antibiotic, that treats a targeted pathogen would be permitted to extend the market exclusivity period for another of the company's FDA-approved drugs.

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