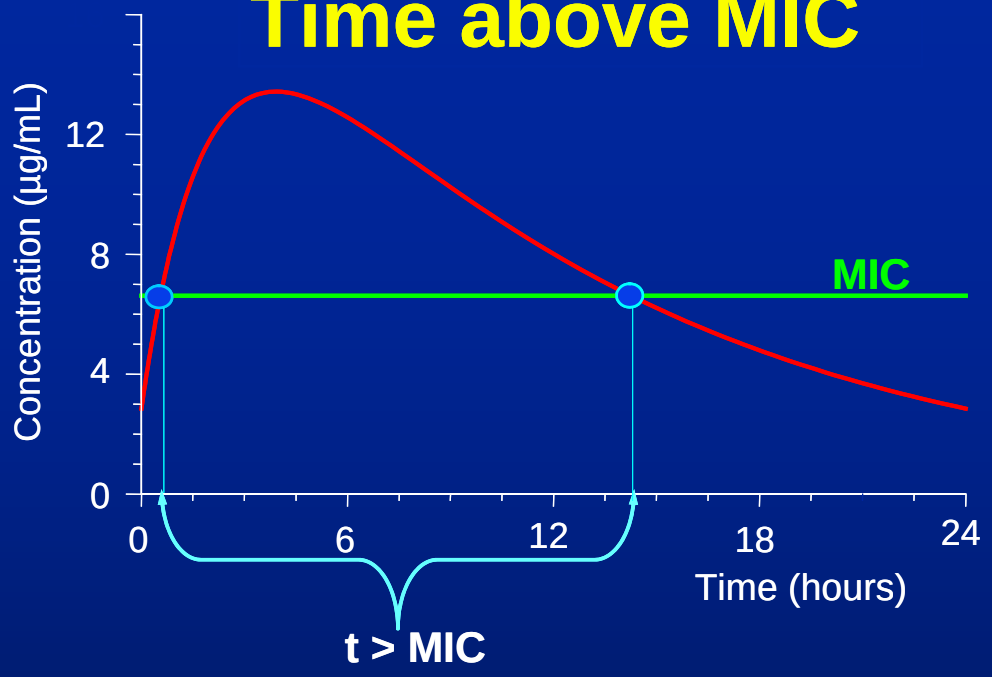
Why MIC is Poison for the Mind

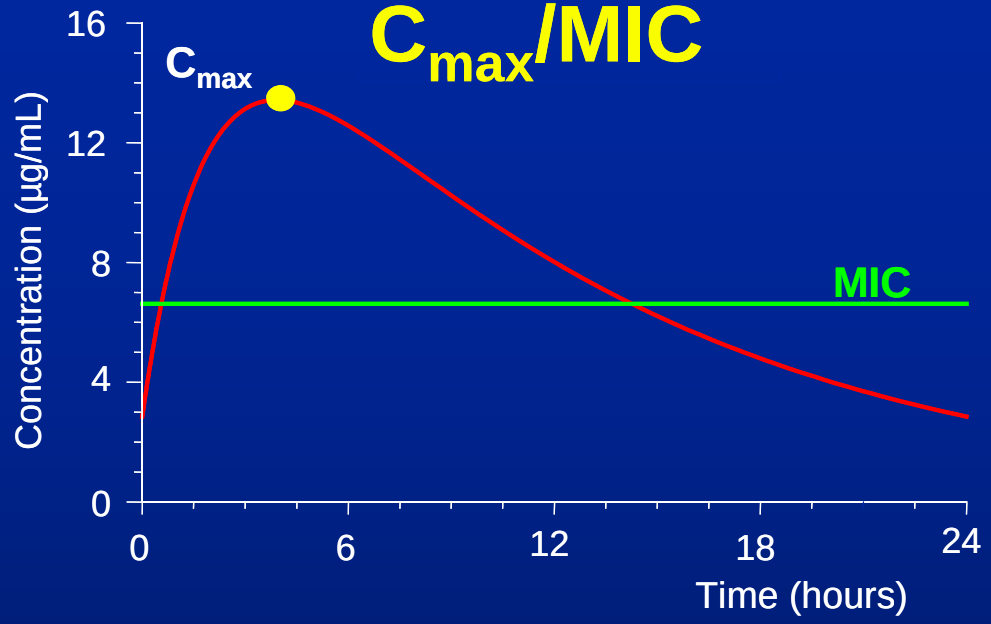
Prof. Hartmut Derendorf

University of Florida

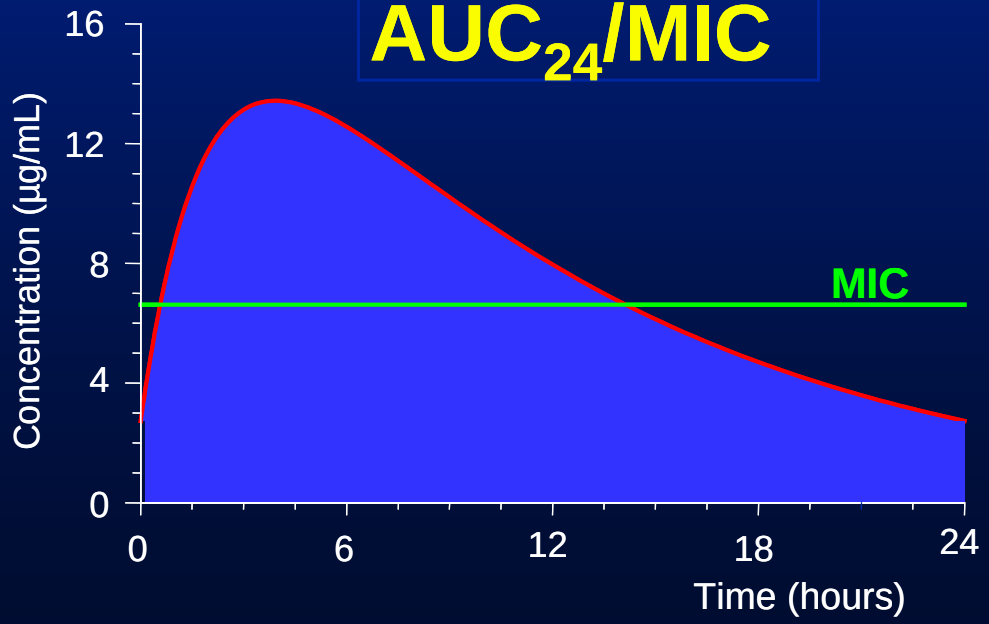
Time above MIC



C_{max}/MIC



AUC_{24}/MIC



PK

PD

Serum

MIC

Protein Binding

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3067–3074 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01433-10

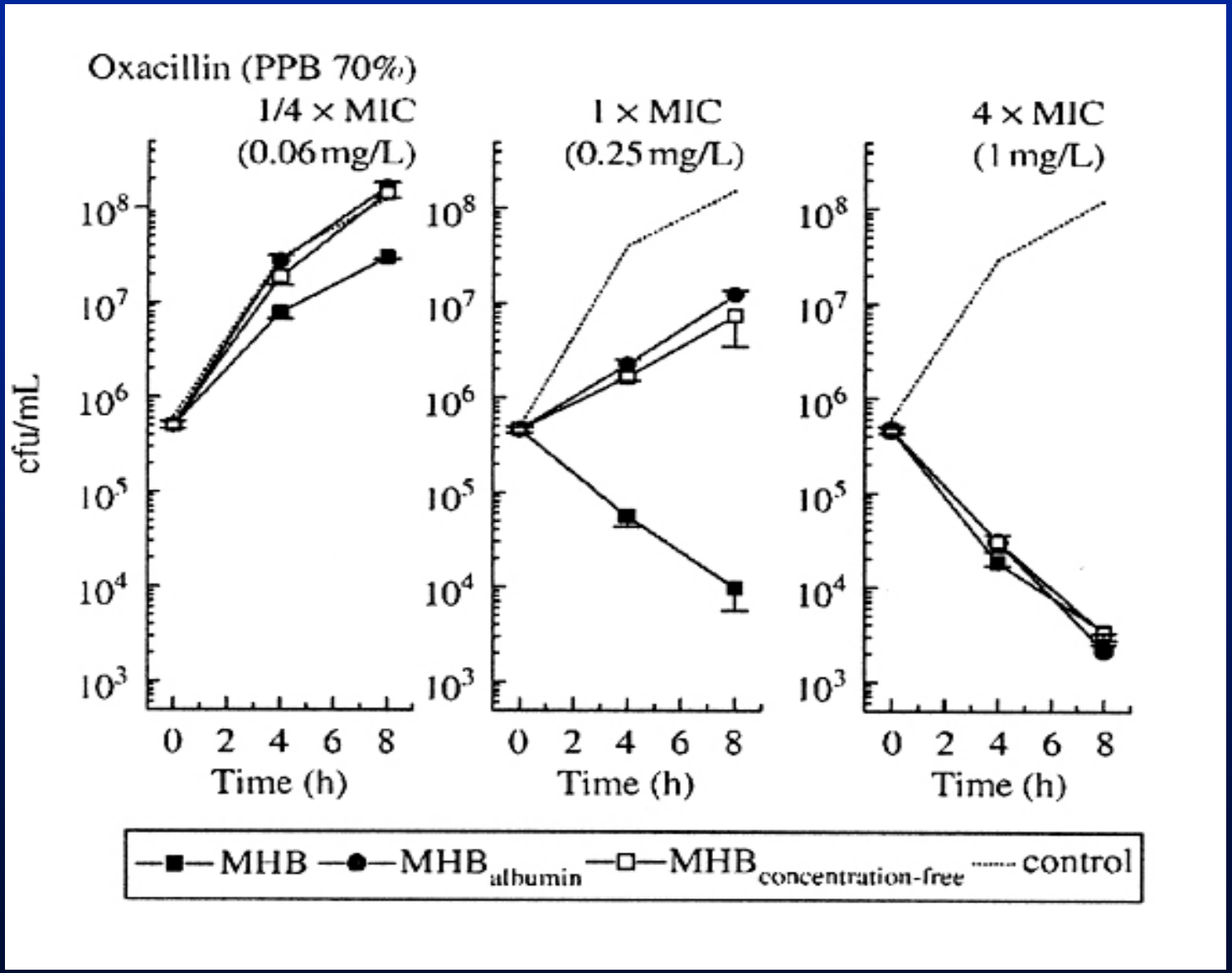
MINIREVIEW

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]*

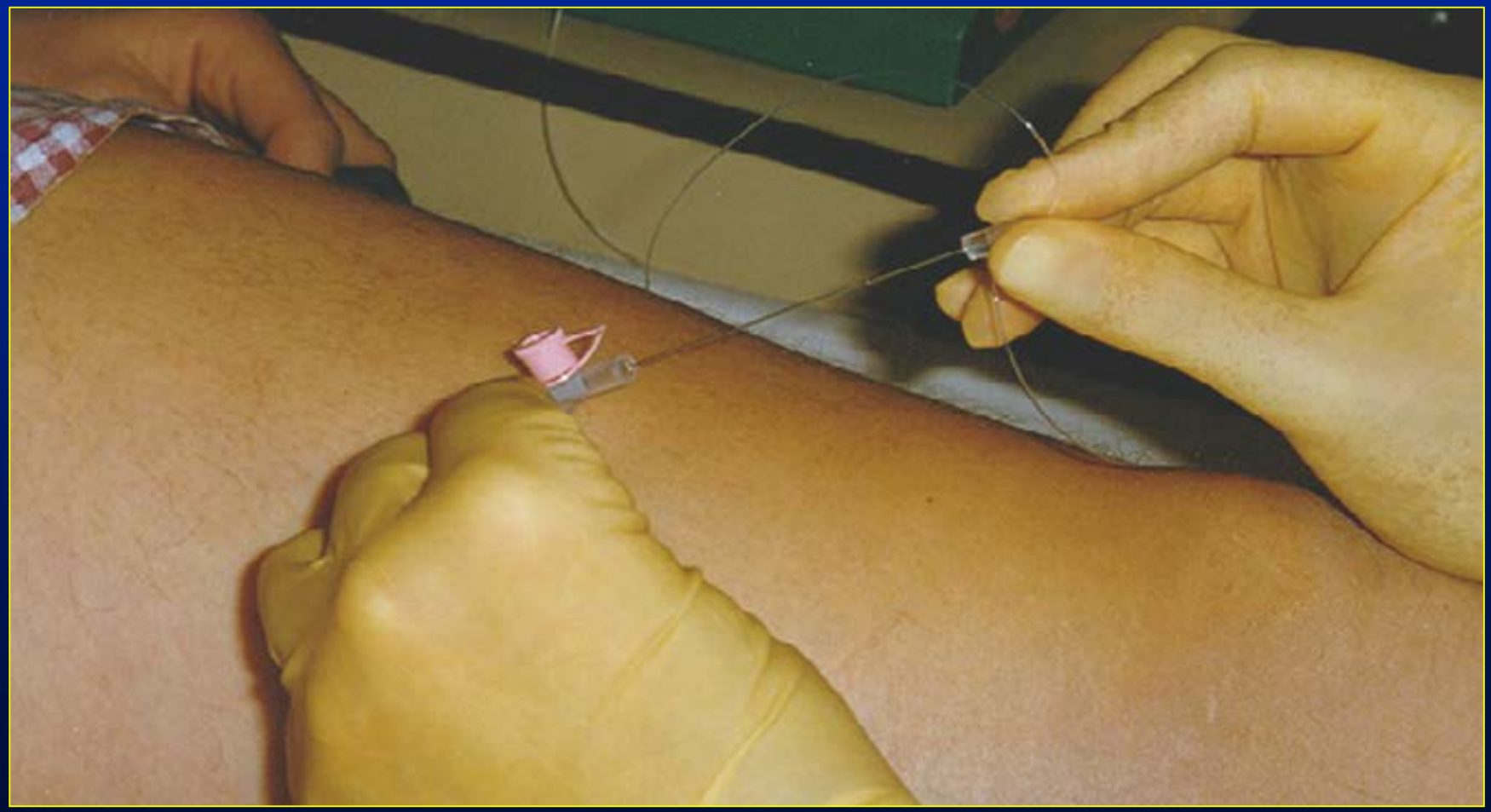
Department of Clinical Pharmacology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria[1]; Department of Pharmaceutics, University of Florida, Gainesville, Florida 32610[2]; Department of Medical Microbiology, Radboud University, Nijmegen Medical Center, Nijmegen, Netherlands[3]; 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]

Protein Binding

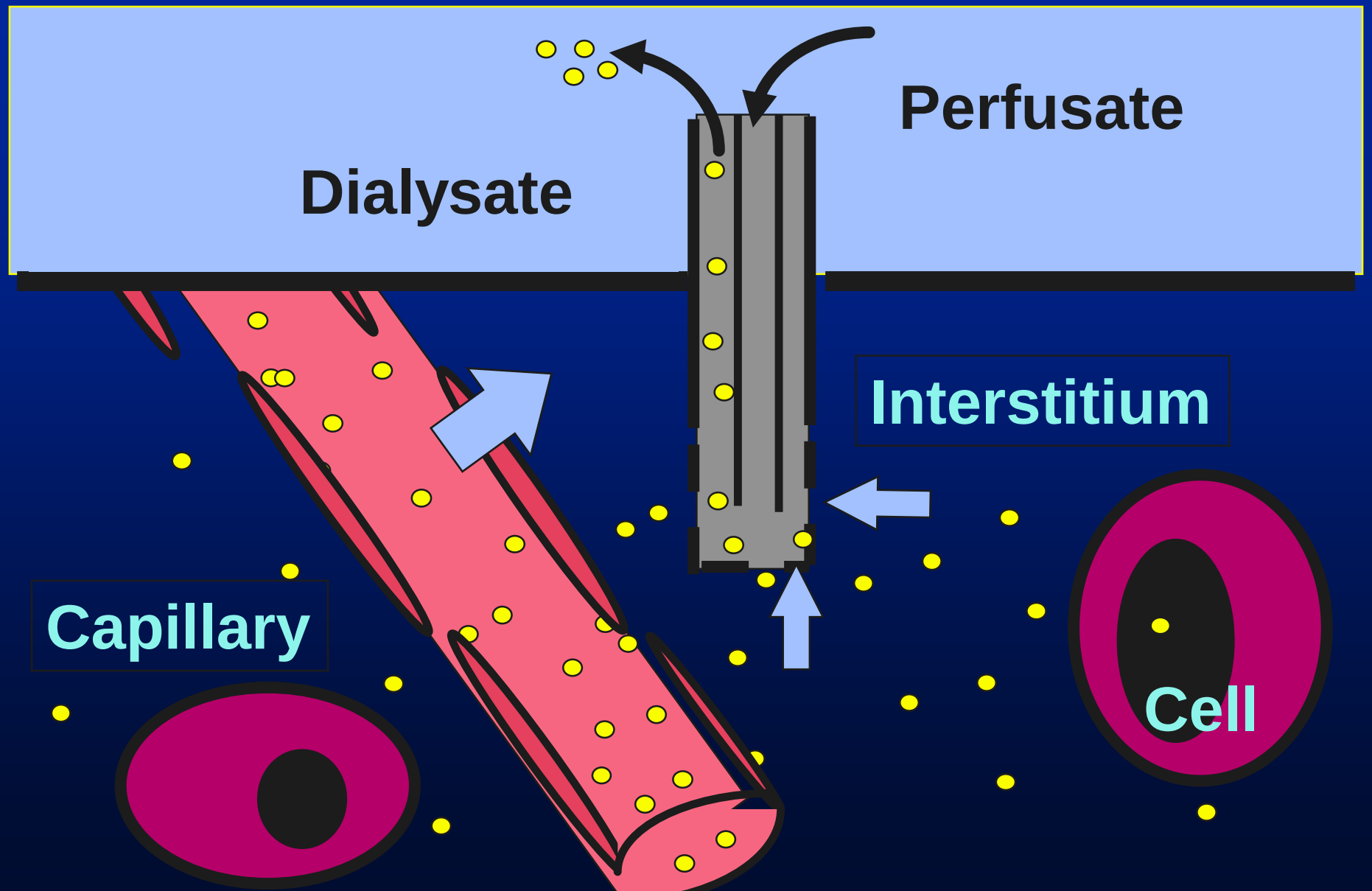


1 Zeitlinger MA, Sauermann R, Traunmuller F, Georgopoulos A, Muller M, Joukhadar C., 2004 Oct 7

Microdialysis



Microdialysis



1939-2015

AAC
Journals.ASM.org

In Memoriam: William A. Craig

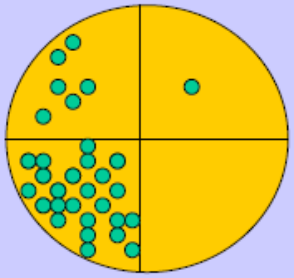
Ursula Theuretzbacher,[a] Paul G. Ambrose,[b] Alasdair P. MacGowan,[c] David R. Andes,[d] Fritz Sörgel,[e] Hartmut Derendorf,[f] Johan W. Mouton,[g] George L. Drusano,[h] Paul M. Tulkens,[i] Michael N. Dudley,[j] Otto Cars,[k] Roger L. Nation[l]

Neutropenic Mouse Thigh-Infection Model

1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1

2. Bacteria injected into thighs on day 0 (10^{4-7})

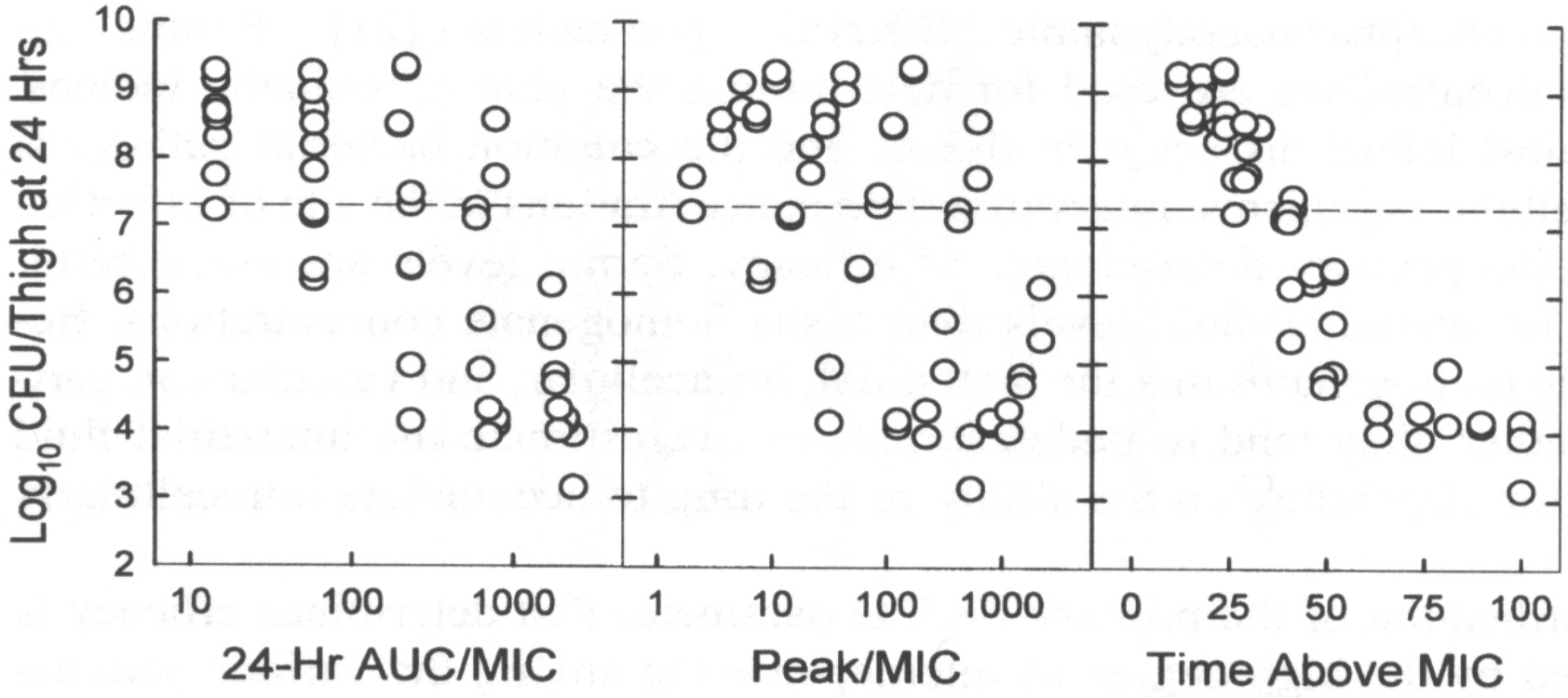
3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days



4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

Ceftazidime

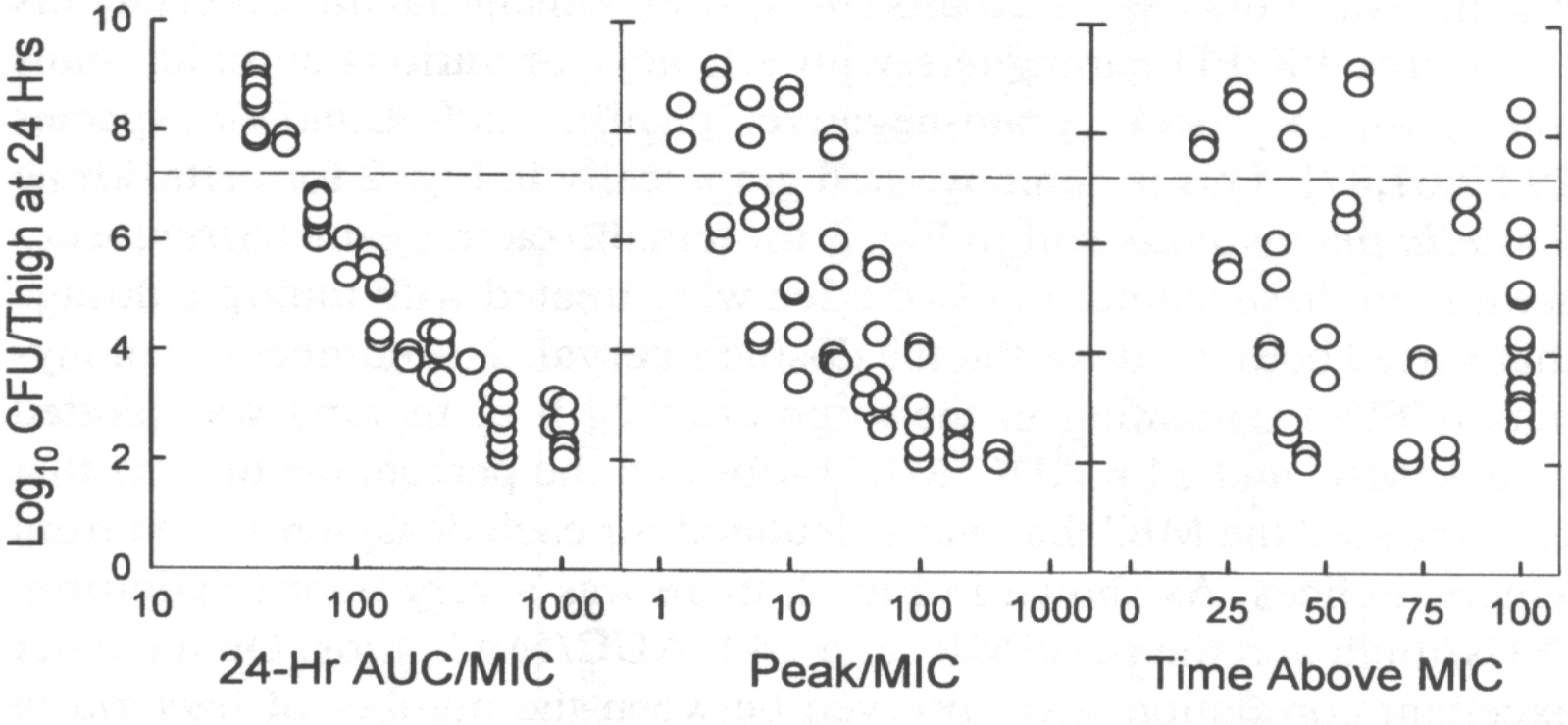
K. pneumoniae in neutropenic mice



Craig 2002

Temafloxacin

S. pneumoniae in neutropenic mice



Craig 2002

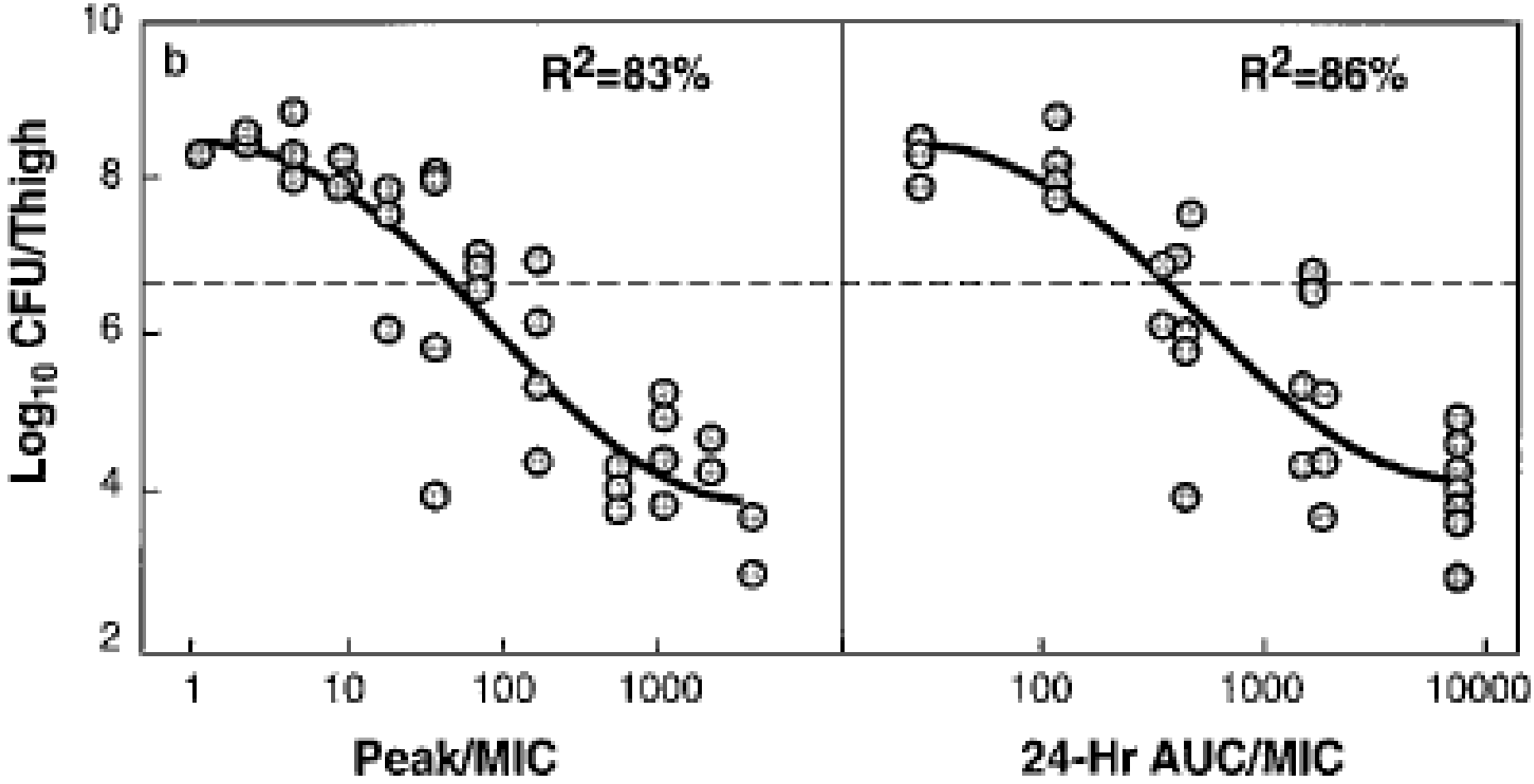
Antibiotics can be classified into concentration- and time dependent agents

The activity of antibiotics may be concentration-dependent and their characteristic antimicrobial activity increases with progressively higher antibiotic concentrations. They may also be time-dependent, where their antimicrobial activity does not increase with increasing antibiotic concentrations; however, it is critical that a minimum inhibitory serum concentration is maintained for a certain length of time. A laboratory evaluation of the killing kinetics of the antibiotic using kill curves is useful to determine the time- or concentration-dependence.

Wikipedia 2010

PK/PD of Daptomycin

S. aureus



Safdar, Andes, Craig, AAC (2004)

Tigecycline

S. pneumoniae

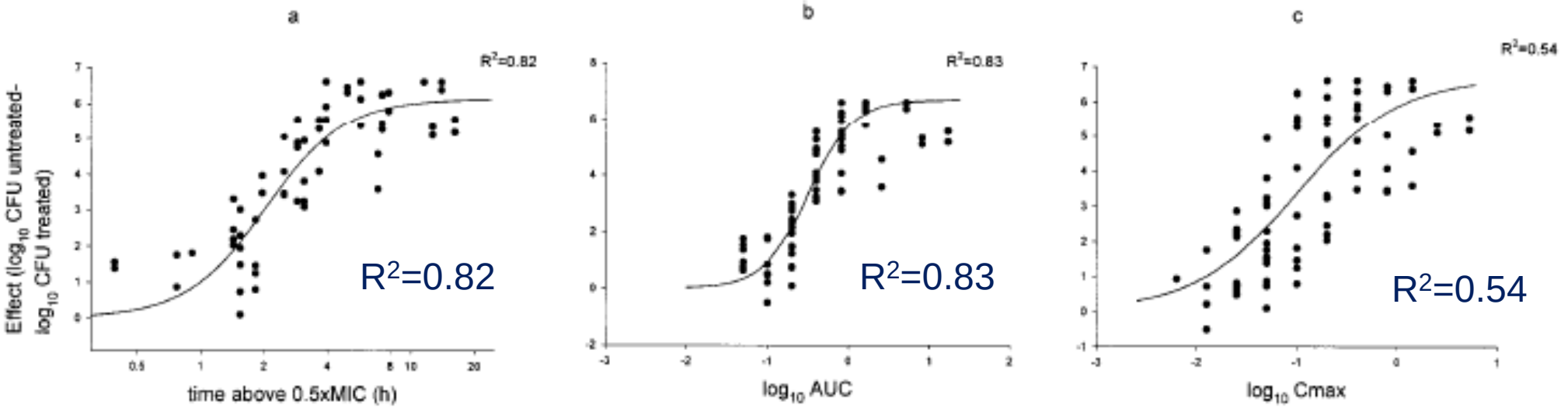
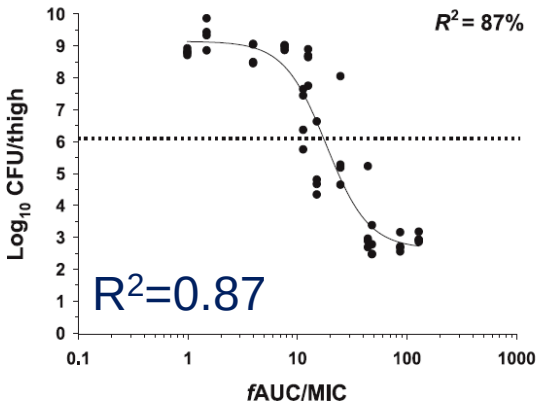
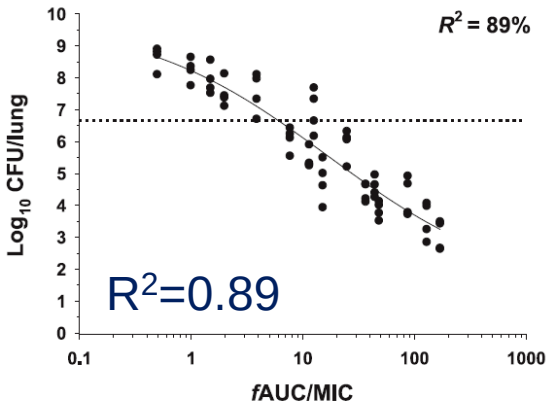
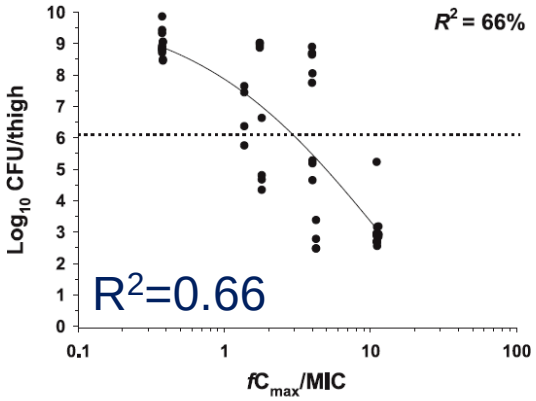
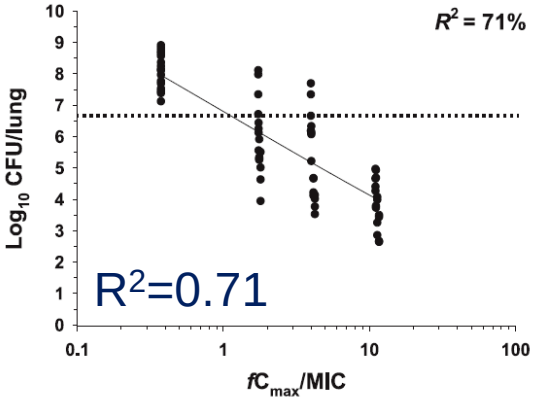
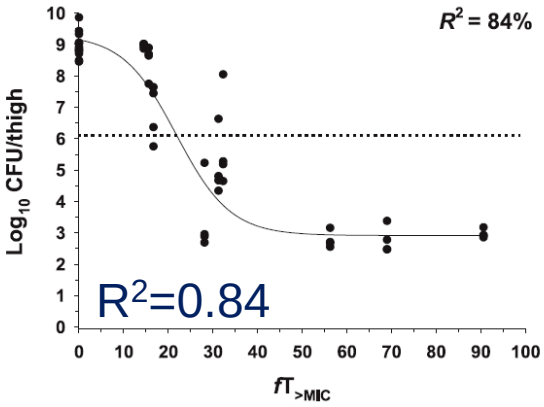
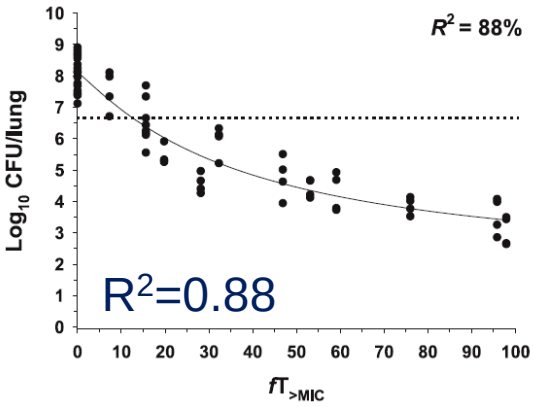


FIG. 4. Relationship between pharmacokinetic-pharmacodynamic parameters and therapeutic efficacy of GAR-936 (free drug) against *S. pneumoniae* 1199 in the neutropenic mouse thigh muscle infection model (R^2 = 0.82, 0.83, and 0.54 for panels a, b, and c, respectively). (a) time above the 0.5 × MIC versus effect. (b) Log AUC versus effect. (c) Log C_{max} versus effect.

Van Ogtrop et al., AAC 2000: 44:943-9.

Colistin

P. aeruginosa

	Thigh	Lung
fAUC/MIC		
fC_{max}/MIC		
T>MIC (%)		

Dudhani et al. 2010

Pharmacodynamics

Problems:

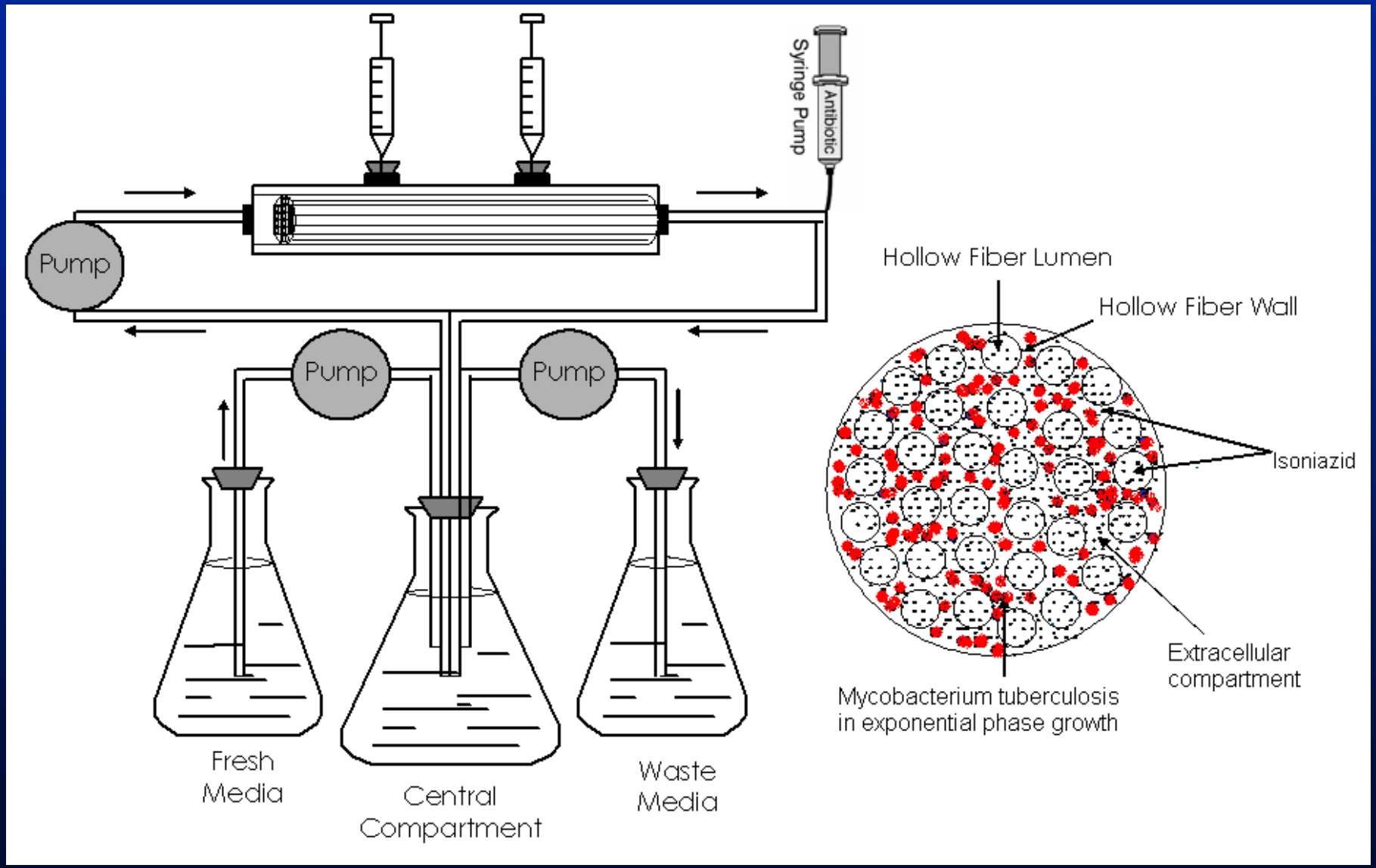
- **MIC is imprecise**
- **MIC is monodimensional**
- **MIC is used as a threshold**
- **When MIC does not explain the data, patches are used (post-antibiotic effect, sub-MIC effect)**

Eng’s Principle

The easier it is to do, the harder it is to change

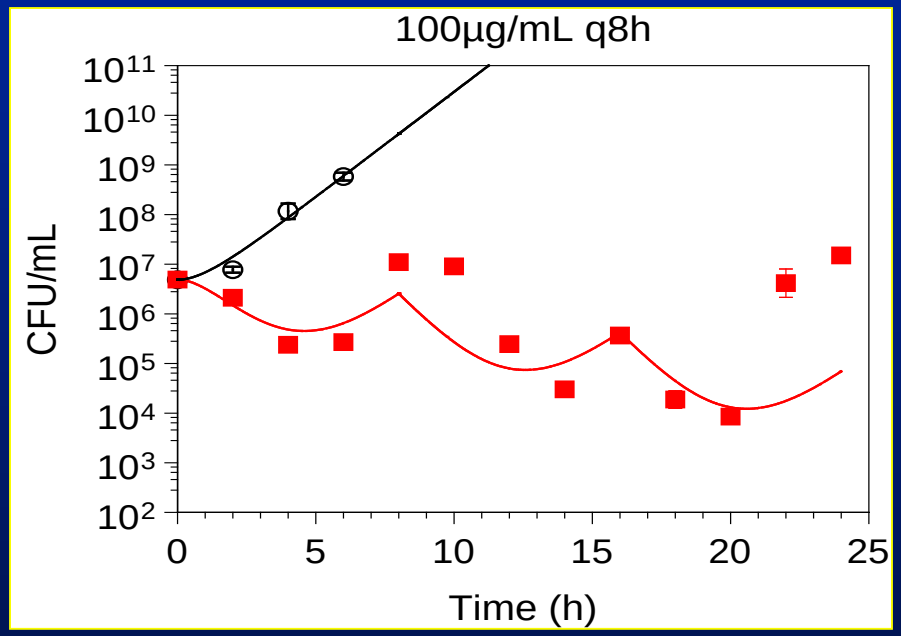
Kill Curves

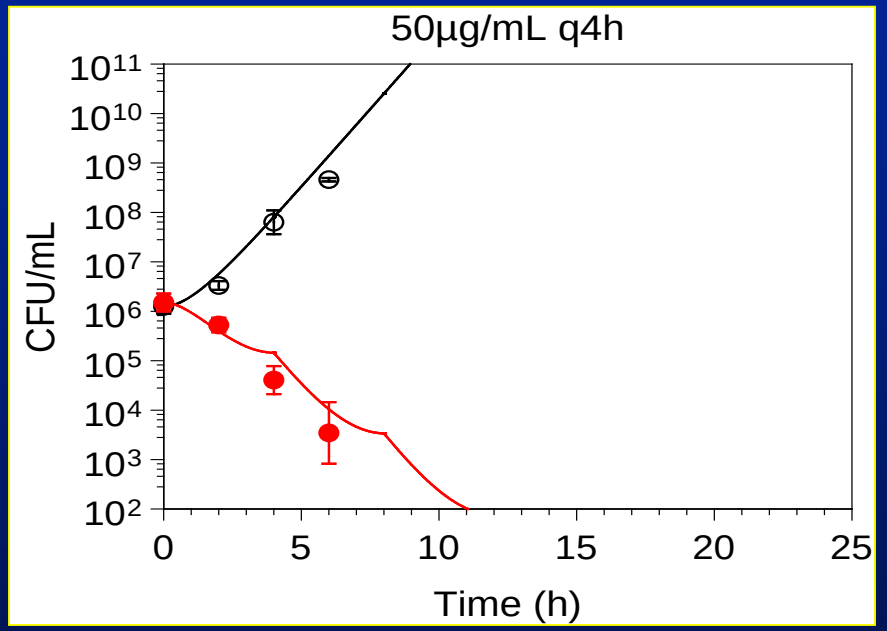
Hollow Fiber Model



Betalactam antibiotics kill time-dependent

Piperacillin vs. E. coli





4g q8h

2g q4h

PK-PD Model

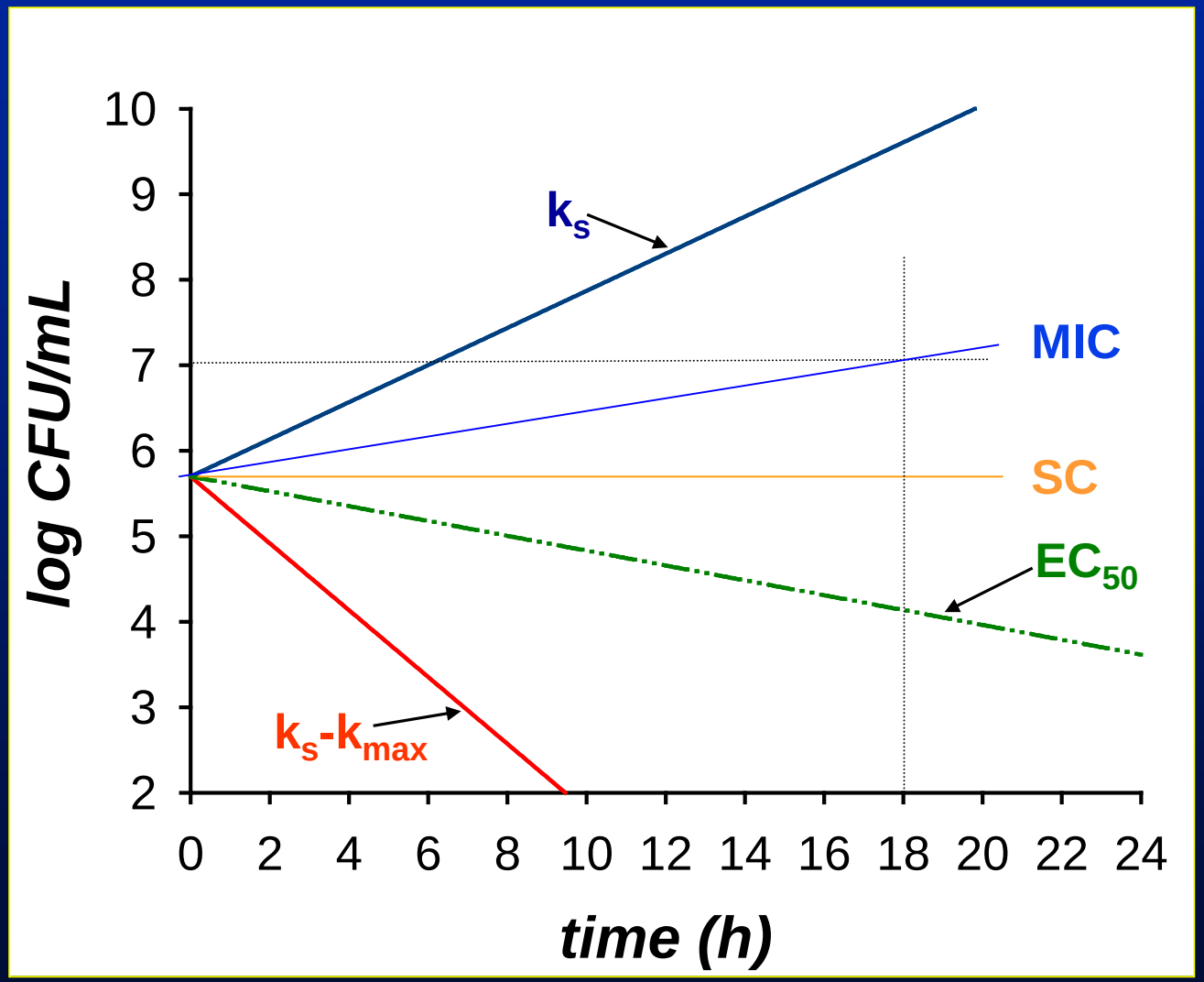
$$\frac{dN}{dt} = \left(k_s - \frac{k_{\max} \cdot C_f}{EC_{50} + C_f} \right) \cdot N$$

Maximum Growth Rate Constant k_s

Maximum Killing Rate Constant k_s-k_{max}

Initially, bacteria are in log growth phase

MIC vs. EC_{50}


10
9
8
7
6
5
4
3
2
log CFU/mL
0
2
4
6
8
10
12
14
16
18
20
22
24
time (h)
ks
MIC
SC
EC50
ks-kmax

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2004, p. 369–377 Vol. 48, No. 2
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.2.369–377.2004

MINIREVIEW

Issues in Pharmacokinetics and Pharmacodynamics of Anti-Infective Agents: Kill Curves versus MIC

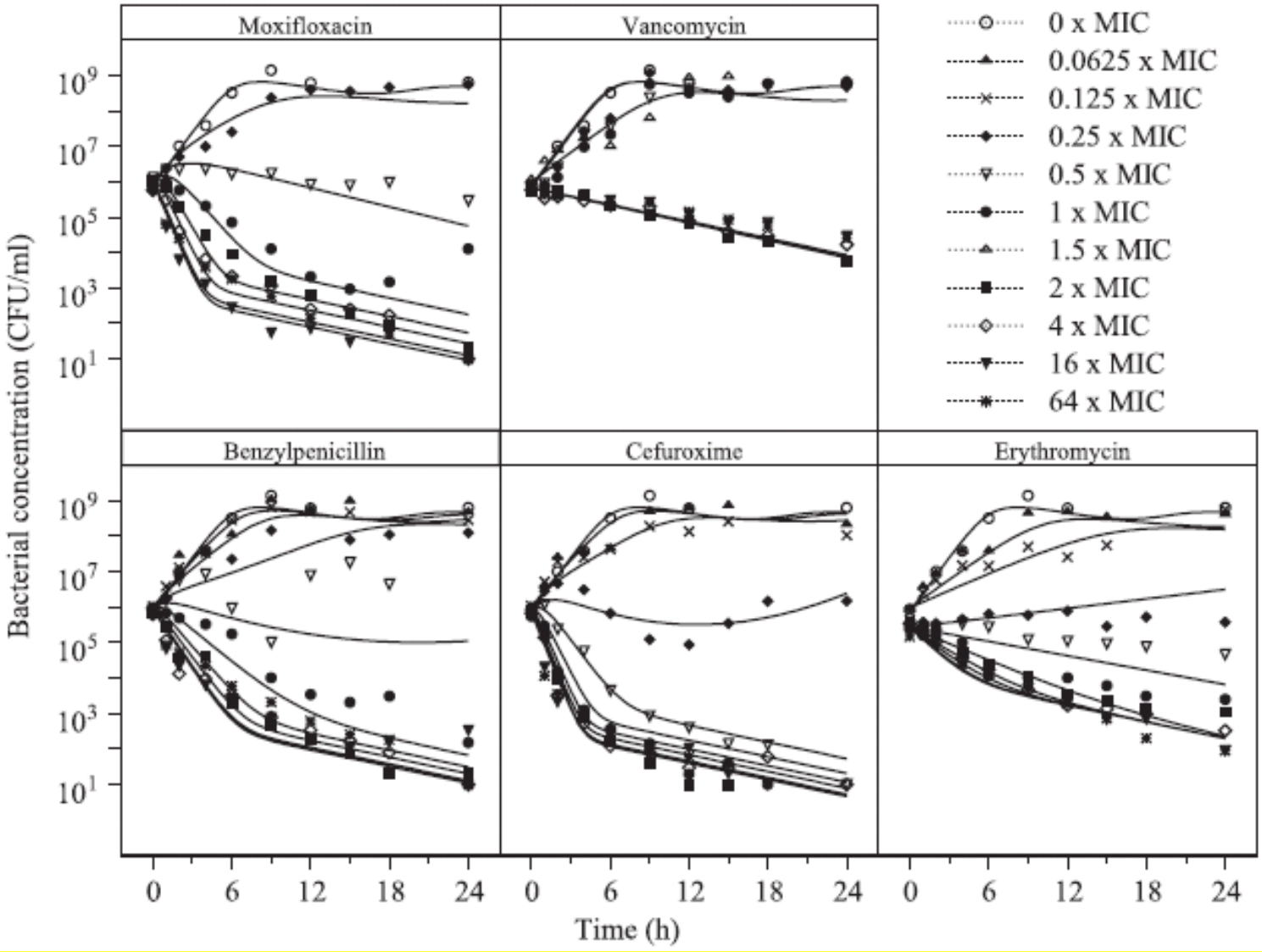
Markus Mueller,[1,2] Amparo de la Peña,[1] and Hartmut Derendorf[1]*

Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, Florida,[1] and Department of Clinical Pharmacology, Vienna University Medical School, Vienna, Austria[2]

$$\frac{k_{max} \cdot C}{EC_{50} + C} = k_0 - \frac{\ln N_t - \ln N_0}{t} \quad (8)$$

where the right-hand term is a constant defined as d. Substituting the right-hand term with d and rearranging gives: equation 9

$$C = \frac{d}{k_{max} - d} \cdot EC_{50} = \text{MIC} \quad (9)$$



Nielsen et al. 2007

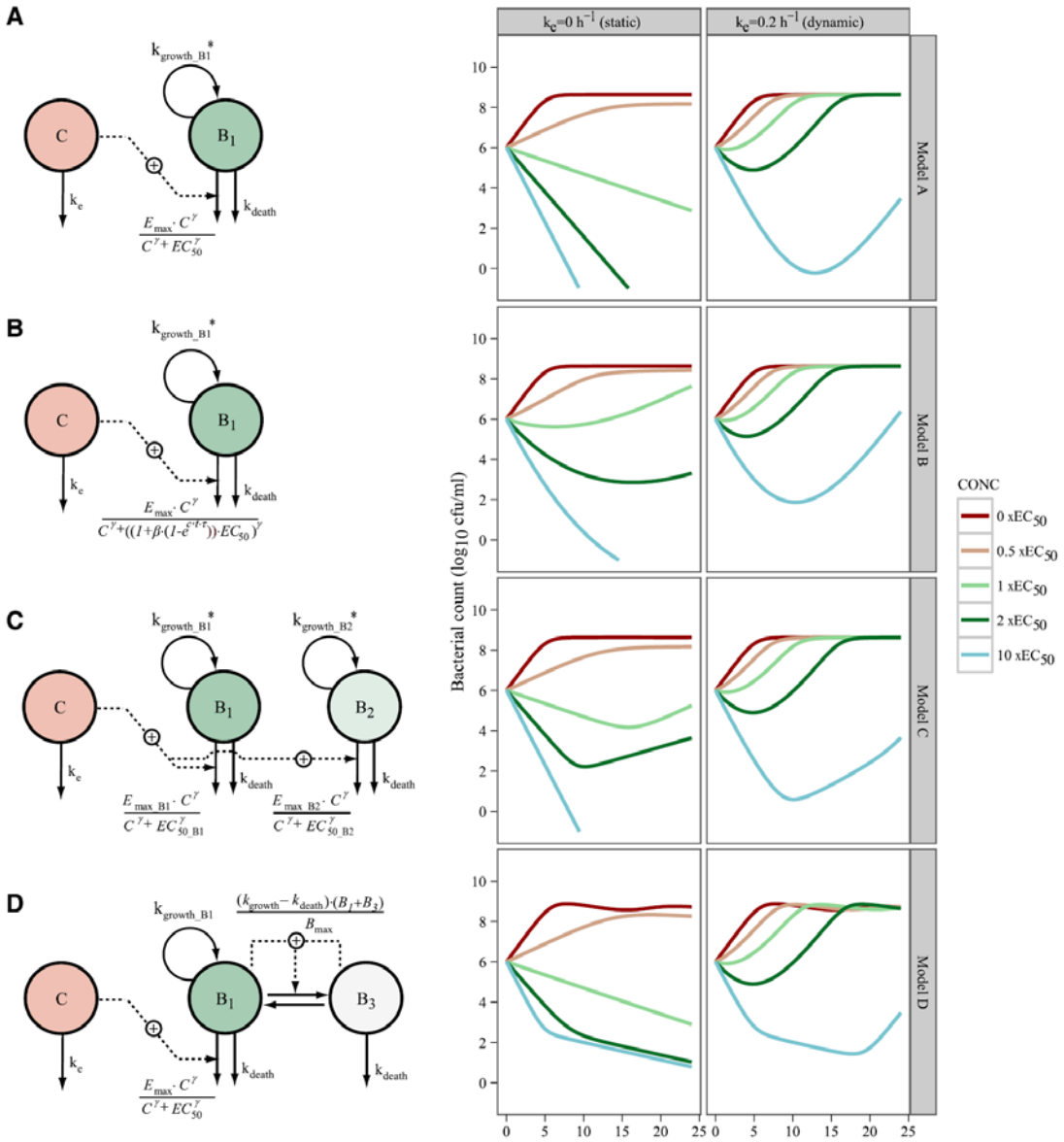
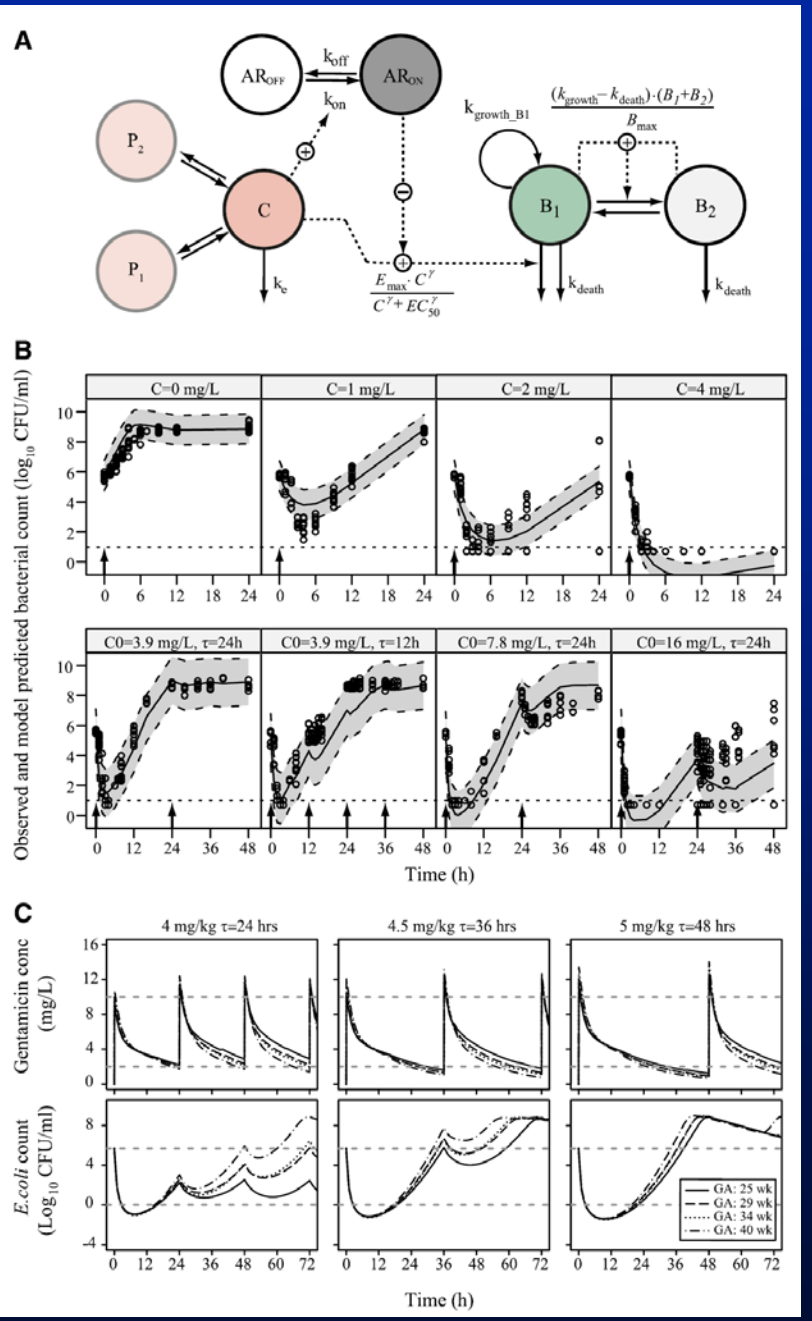


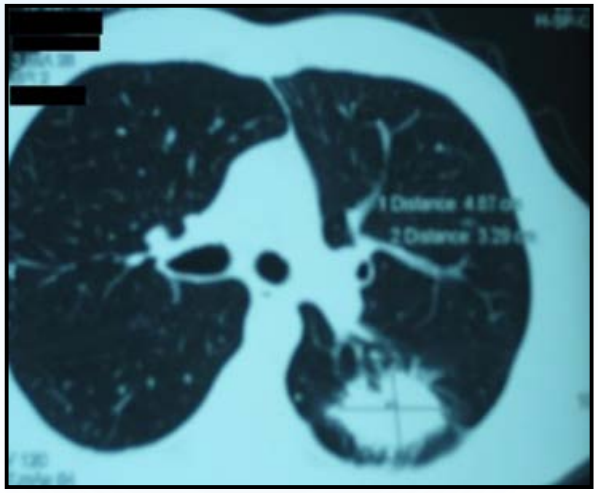
Fig. 5. Schematic illustrations of four different PKPD model structures (left panel) with typical predicted bacterial time-kill curves following a static (middle panel) or dynamic (right panel) drug exposure. *The logistic growth was applied according to $k_{growth} \times (1-(B_1+B_2)/B_{max})$. C, drug compartment; B_1, compartment with drug-sensitive bacteria; B_2, compartment with less drug-sensitive bacteria; B_3, compartment with nongrowing, drug-insensitive bacteria; k_e, first order drug elimination rate constant; k_{growth}, rate constants for multiplication of bacteria; k_{death}, rate constant for natural death of bacteria; E_{max}, maximum achievable effect; EC_{50}, drug concentration producing 50% of E_{max}; γ, sigmoidicity factor. Initial conditions used for predictions; C = 0, 0.5, 1, 2, and 10× EC_{50}, respectively; B_1 = 1,000,000 CFU/ml; B_2 = 10 CFU/ml; B_3 = 0 CFU/ml. Parameters used for the predictions: k_e = 0 and 0.2 hour $^{-1}$ for static (middle) and dynamic (right) drug exposure, respectively; k_{growth} = 1.4 hour $^{-1}$; k_{death} = 0.2 hour $^{-1}$; E_{max} = 3 hour $^{-1}$ (B_1 and B_2); EC_{50} = 10 and 100 for B_1 and B_2, respectively; γ = 1.5; B_{max} = 500,000,000 CFU/ml; β = 100; τ = 0.00005.

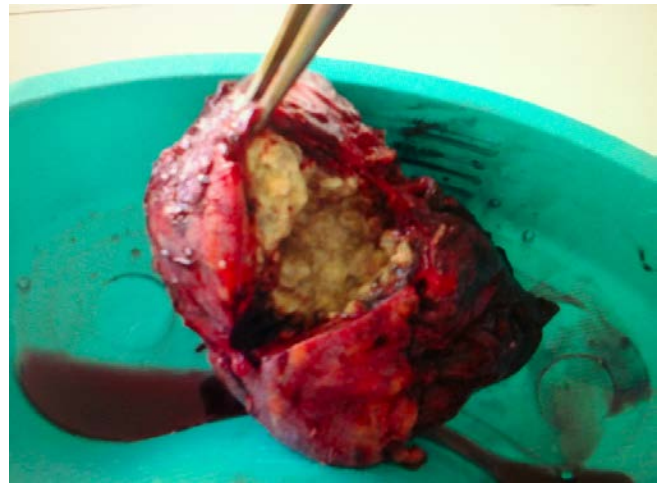


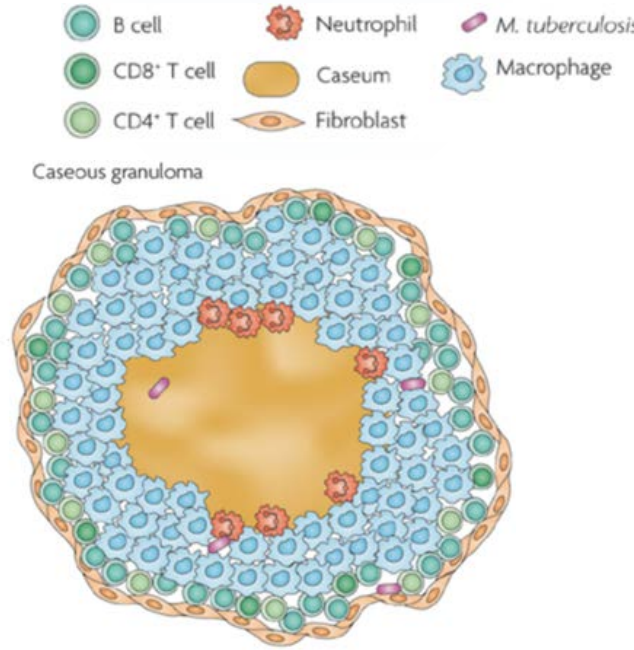
Nielsen & Friberg, Pharmacol. Rev. 2013

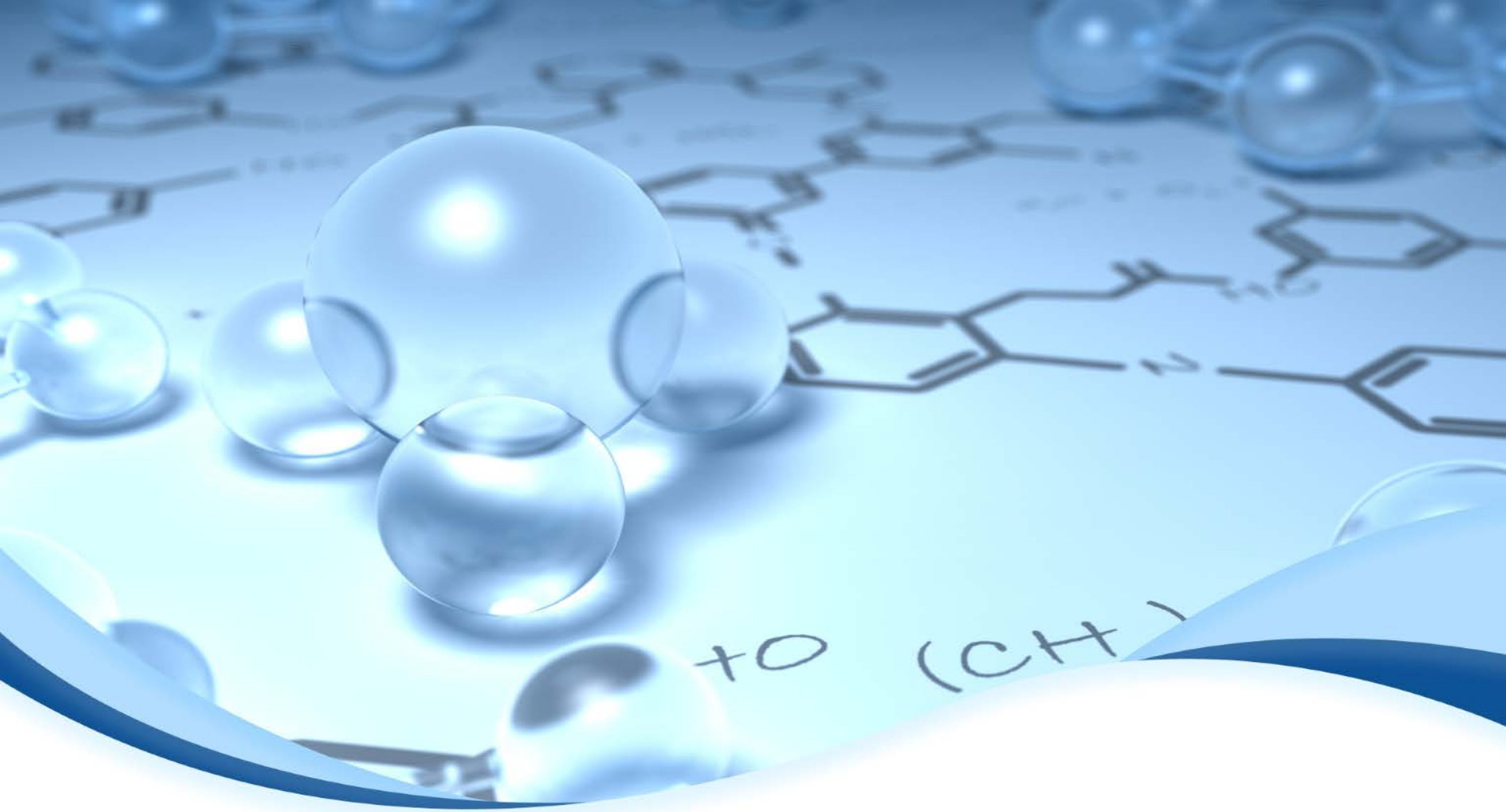
TB Microdialysis

- To determine the tissue pharmacokinetics of MOXI, PZA and LNZ in tuberculous cavitary lung among patients with MDR/XDR TB undergoing adjunctive surgical therapy
- Hypothesis: MOXI, PZA and LNZ cavitary concentrations will differ from serum concentrations









Pharmacometrics of Antibiotic Combinations

S. K. Sy, M-E. Beaudoin, W. W. Nichols, V. J. Schuck, H. Derendorf

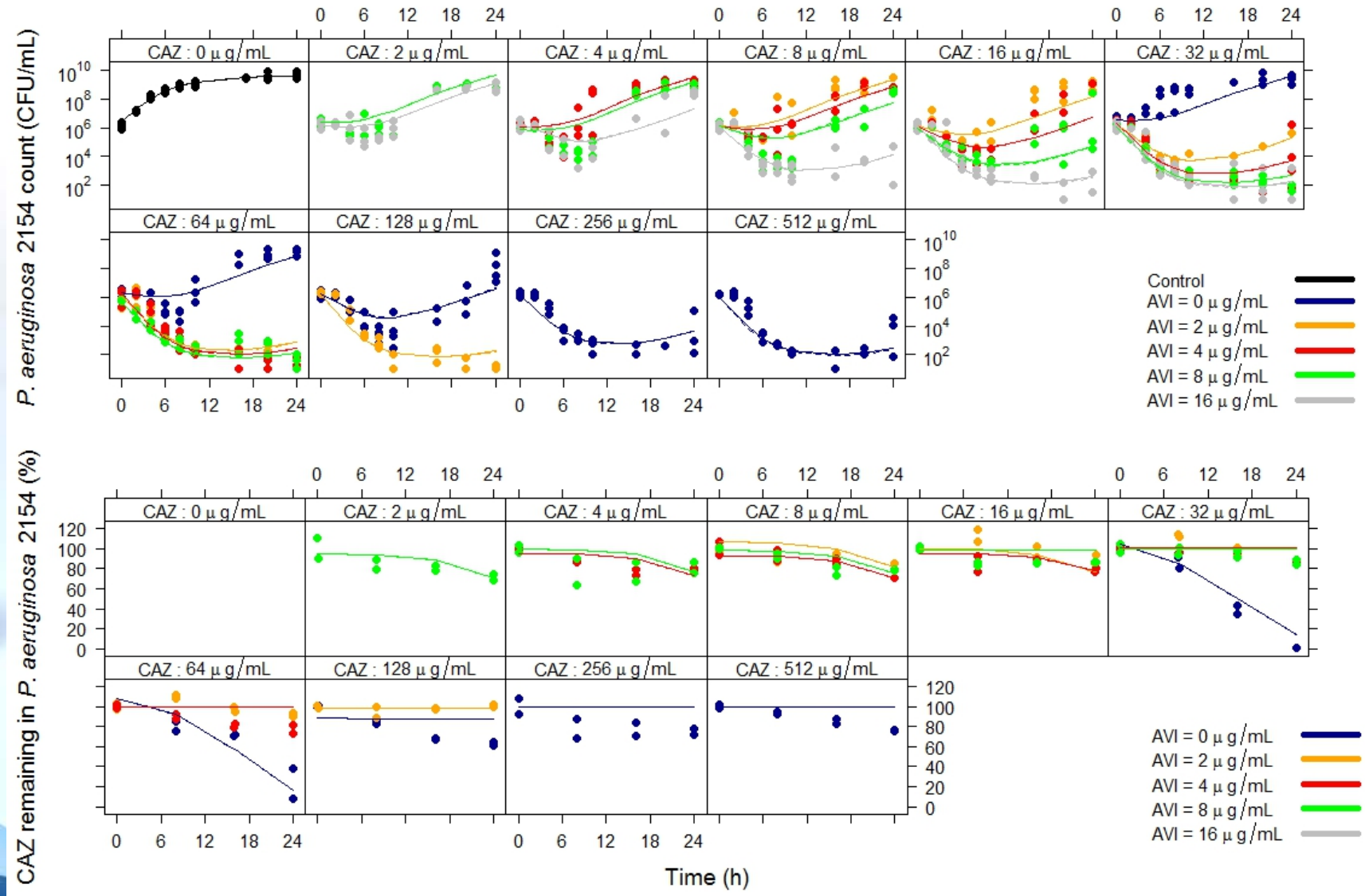
CAZ MIC with AVI

Susceptibility test

	Avibactam (NXL-104) concentration (µg/mL)					
***P. aeruginosa* isolate**	*0*	*1*	*2*	*4*	*8*	*16*
244	256	*256*	64	16	16	8
2154*	64	64	32	4	4	4
5241	64	*64*	32	8	8	8
12432	64	*64*	8	8	8	8
9750*	256	256	128	32	16	8
1493	128	*128*	32	16	16	16
465	128	*128*	32	16	16	8
10783*	128	128	64	16	16	8

*Isolates selected to run time-kill experiments

Time-kill *P ae* 2154 (MIC: 64 mg/L)



MIC
The Current Paradigm

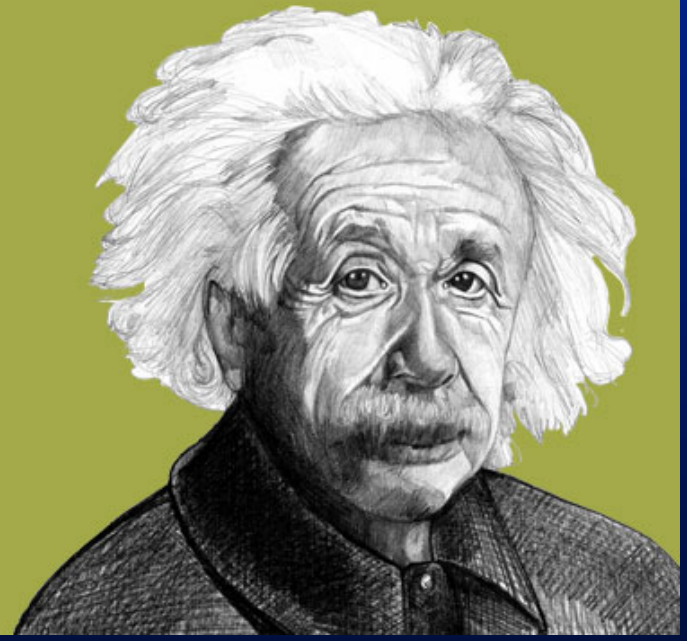
MIC is poison for the mind.

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

Why MIC is poison for the mind

- Our brains are not able to quantitatively integrate multiple simultaneous events and relationships
- That's why we have computers
- Simple answers have a lot of appeal (Eng's Law)
- A line in the sand (threshold) is an easy to understand concept (How much do I need?) but frequently too simple
- Target attainment calculations are useless if the target is not appropriate

Everything should be made as simple as possible, but not simpler.



Albert Einstein

Advantages of Kill Curves

- Kill curves give a complete time course of drug effect which allows for modeling
- Kill curves can account for changes in sensitivity
- Kill curves can be linked to steady state and non-steady state drug concentrations
- Kill curves can be linked to single dose or multiple dose situations
- Kill curves capture more completely the concentration/effect relationship

PK/PD Today

Serum Concentration vs. MIC

(AUC/MIC, C_{max}/MIC, t>MIC)

PK/PD Tomorrow

Target Site Concentration vs. Kill Curve

(Integrated modeling and simulation with appropriate user-friendly software)

Acknowledgements

Sherwin Sy

Amelia Deitchman

Tobias Heinrichs

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Russell Kempker

Charles Peloquin

Edgar Schuck

Johannes Kast

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Nivea Voelkner

Sebastian Schröpf

Qi Liu

Ping Liu

Teresa Dalla Costa

Amparo de la Peña

Arno Nolting

Stephan Schmidt

Martina Sahre

Virna Schuck

April Barbour

Kenneth Rand

Christoph Seubert

Olaf Burkhardt

Benjamin Wu

Daniel Gonzalez

Oliver Ghobrial

Rajendra P. Singh

Luning Zhuang

Ravi Singh

Markus Müller

Kazuro Ikawa