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The case against MIC

-

**Better decisions with
pharmacometrics and systems
approaches**

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Approaches for PKPD assessment



WIKIPEDIA
The Free Encyclopedia

“A PKPD model describes the **time course** of the effect in response to administration of a drug dose”

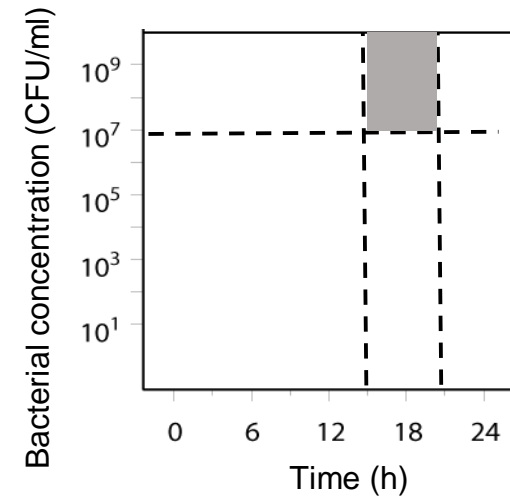
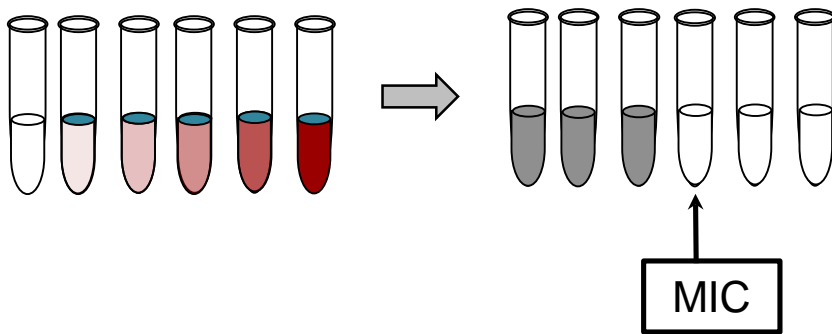
Pharmacometrics and systems approaches

- Characterize
 - the time course of Pharmacokinetics
 - the time course of Pharmacodynamics
- Use the models to perform predictions and to support decisions
 - bacterial killing and selection of resistance to support dosing decisions
- Make use of all available data and accumulate knowledge



Minimum Inhibitory Concentration (MIC)

- Start inocula (5×10^5 CFU/ml)
- Static antibiotic concentrations
- Incubate 37°C , 16-20 hrs
- MIC defined as the lowest static drug concentration that inhibits visible growth



**Translation
to dosing
decisions
unclear!**

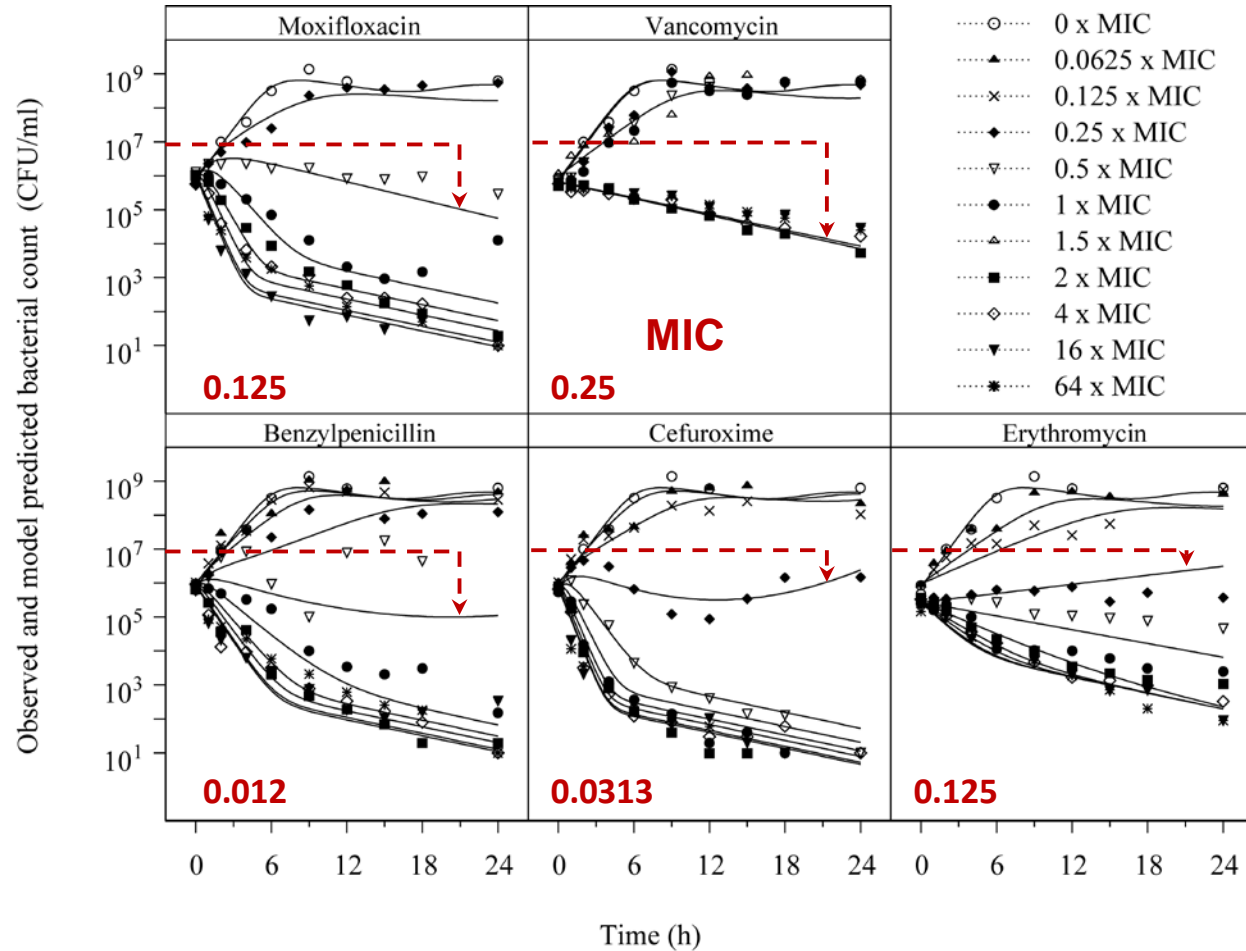
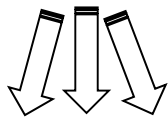
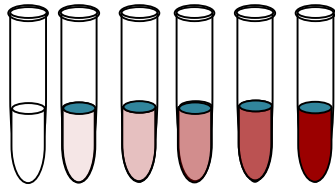




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Pharmacometric approach vs MIC

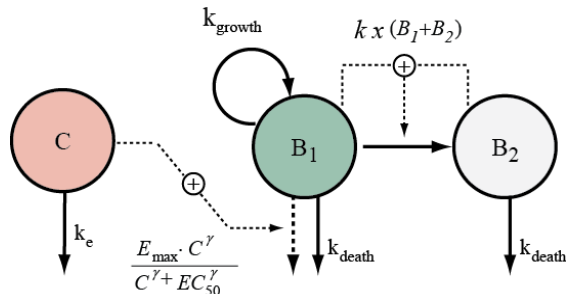
Time-kill experiments





Pharmacometric approach vs MIC

Pharmacometric approach

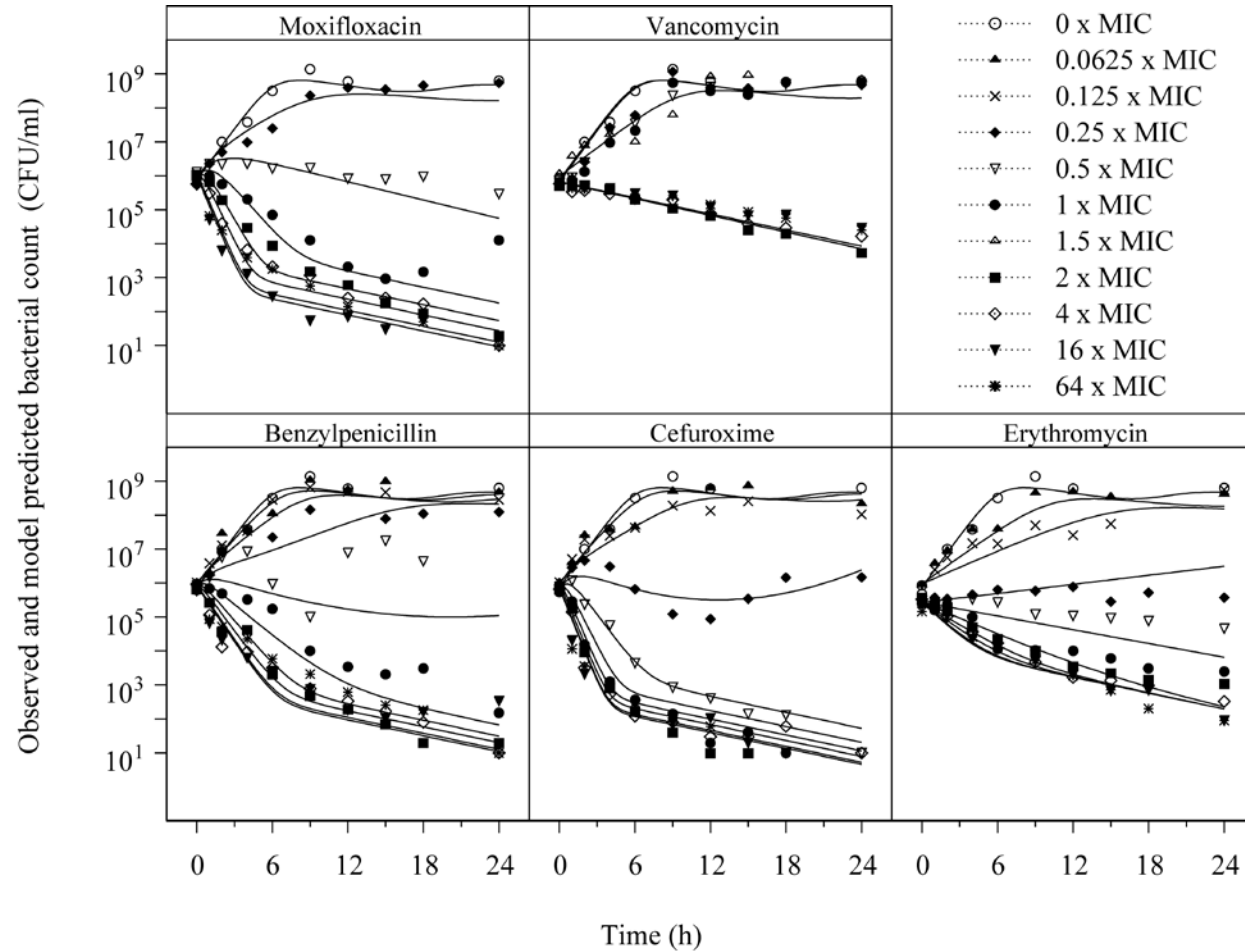


Bacterial specific params

$k_{growth}, k_{death}, B_{max}$

Drug specific params

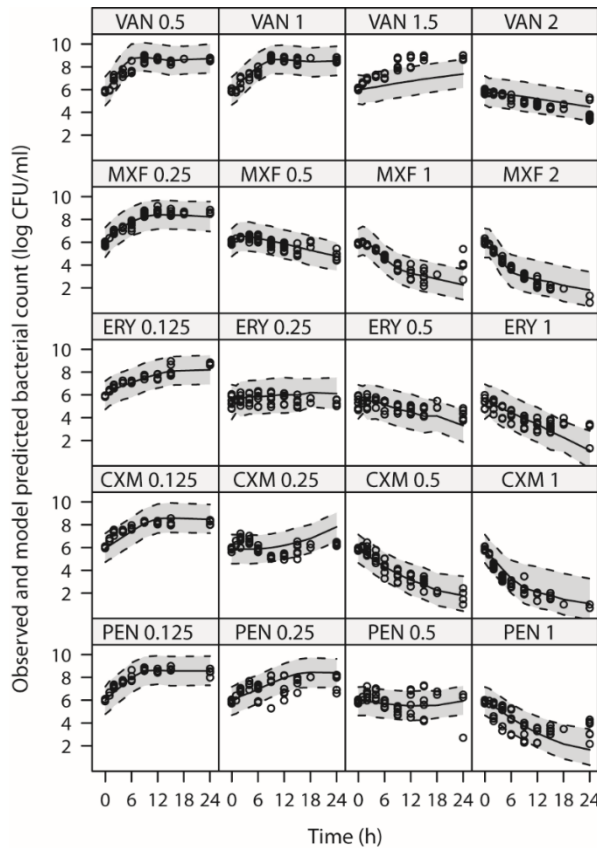
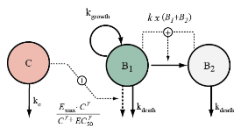
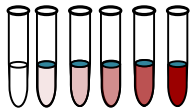
E_{max}, EC_{50}, γ



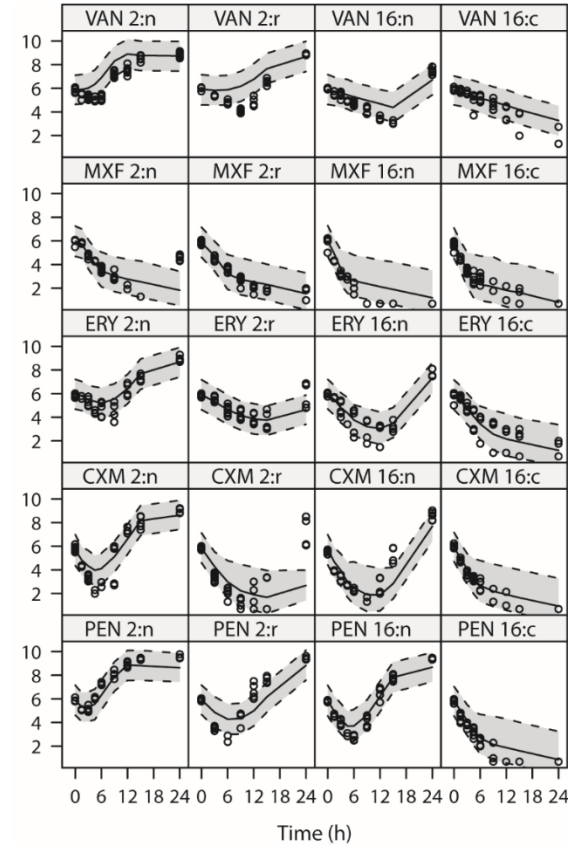
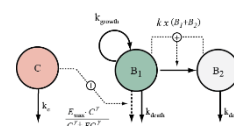
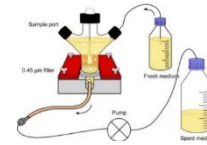


Pharmacometric approach vs MIC

Static drug concentration



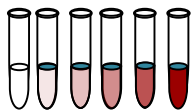
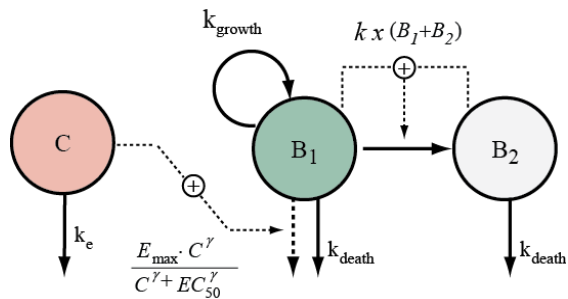
Dynamic drug concentration



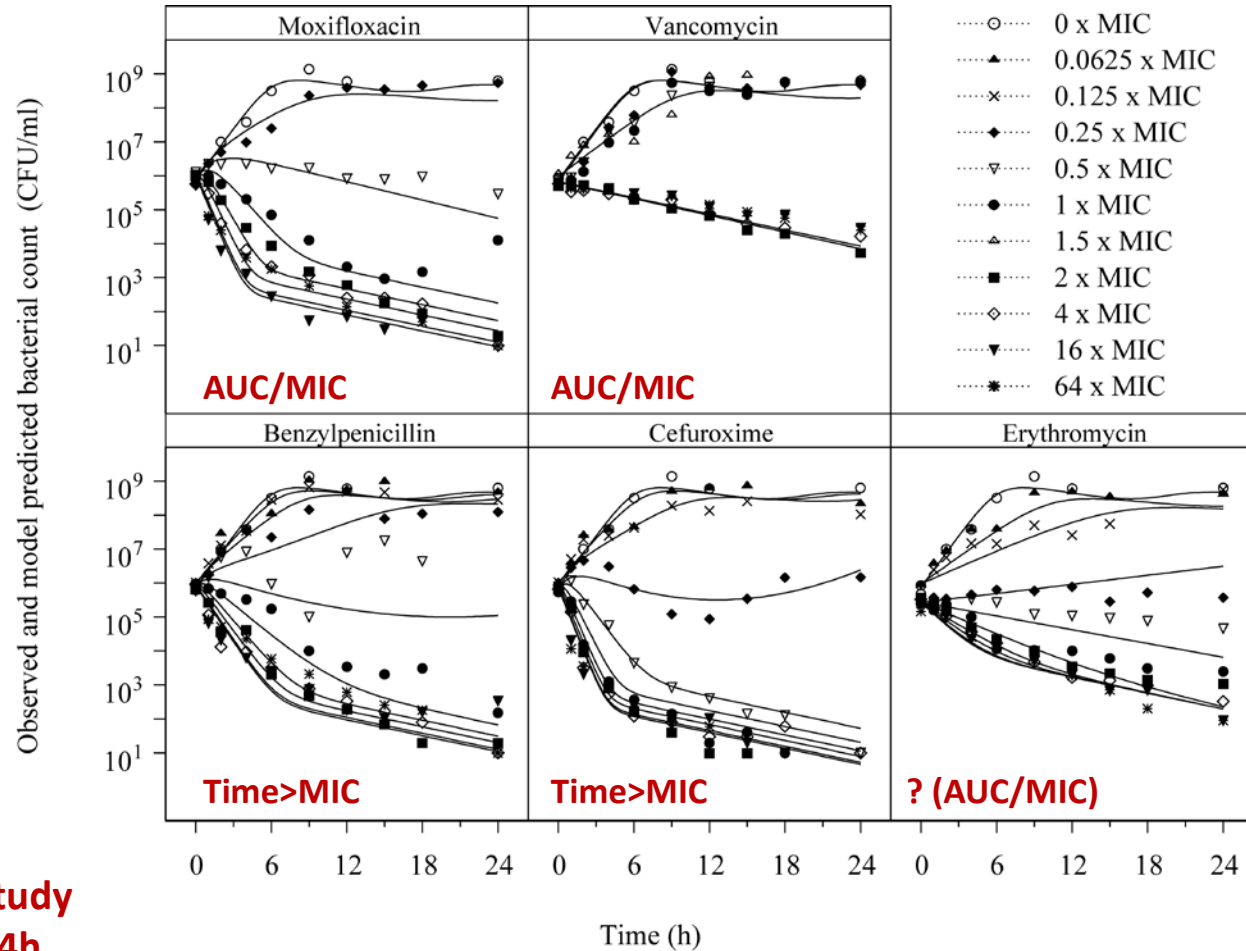


Pharmacometric approach vs PK/PD index

Pharmacometric approach



- Patient PK and PKPD model
- Simulate dose fractionation study
- Predicted bacterial count at 24h

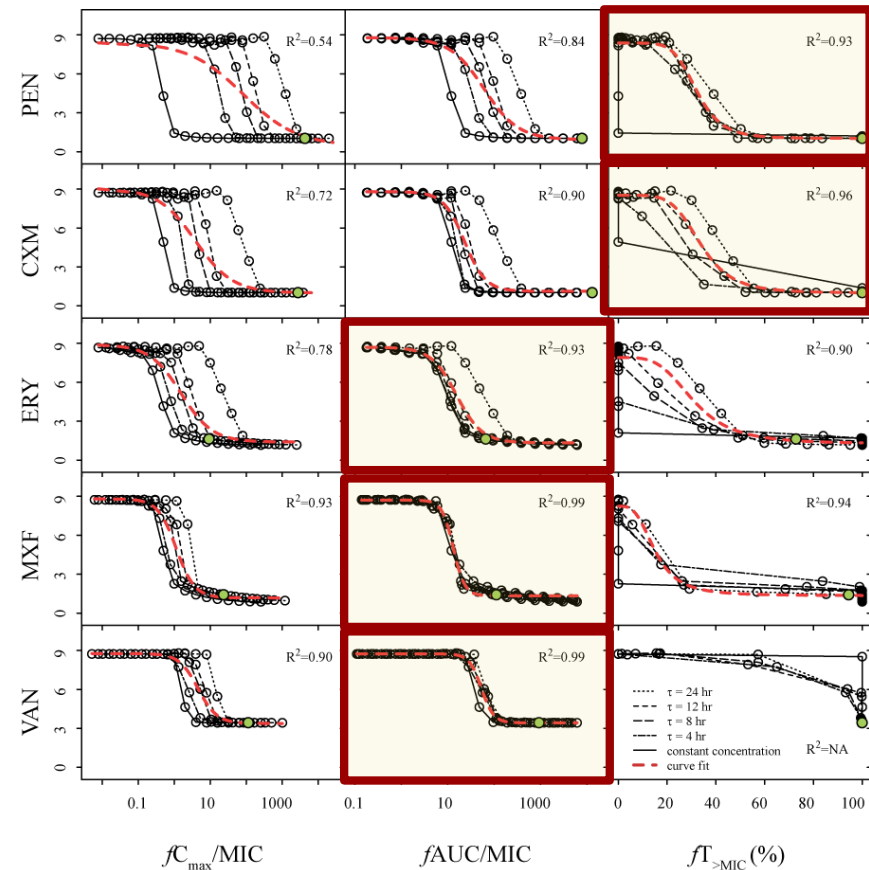
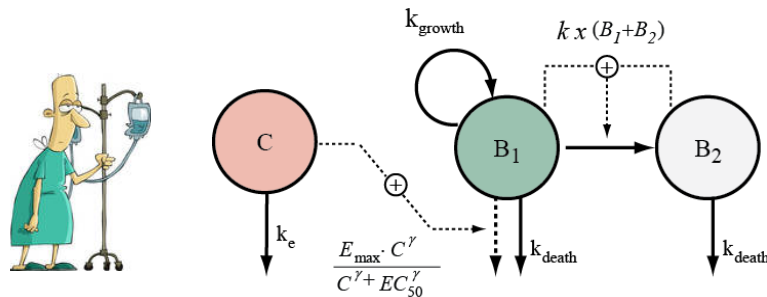




Pharmacometric approach vs PK/PD index

Simulated dose fractionation study

Antibiotic	Class	PK/PD index
Benzylpenicillin	β -lactam	$T_{>MIC}$
Cefuroxime	β -lactam	$T_{>MIC}$
Erythromycin	Macrolide	AUC/MIC ($T_{>MIC}$)
Moxifloxacin	Fluoroquinolone	AUC/MIC
Vancomycin	Glycopeptide	AUC/MIC



PKPD models – predictive of PK/PD indices

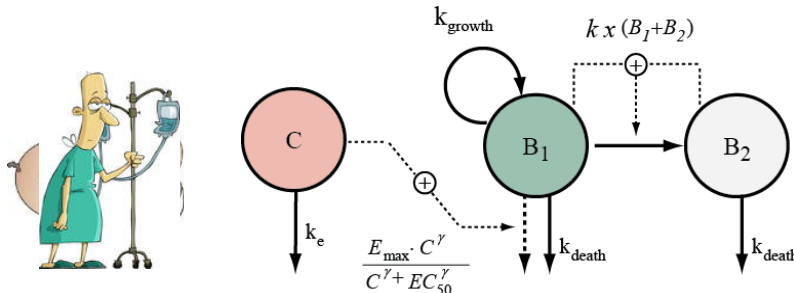
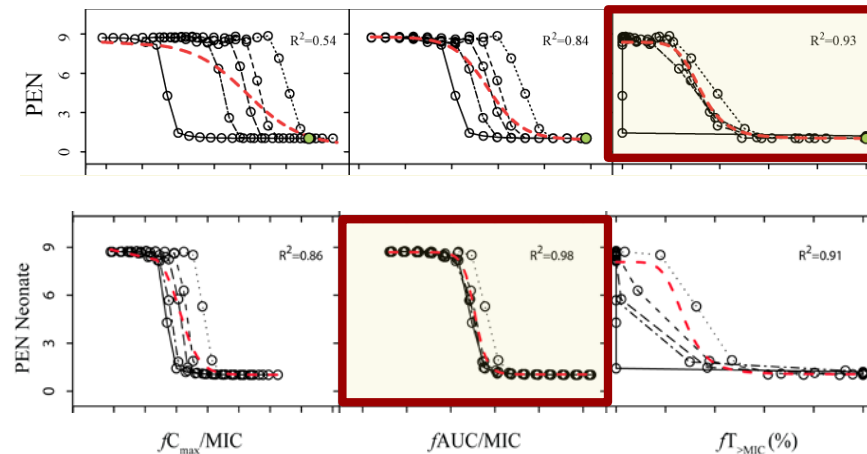
Is the PK/PD index sensitive to the PK profile?



Pharmacometric approach vs PK/PD index

Simulated dose fractionation study

Antibiotic	Class	PK/PD index
Benzylpenicillin	β -lactam	$T_{>MIC}$
Cefuroxime	β -lactam	$T_{>MIC}$
Erythromycin	Macrolide	AUC/MIC ($T_{>MIC}$)
Moxifloxacin	Fluoroquinolone	AUC/MIC
Vancomycin	Glycopeptide	AUC/MIC (or $T_{>MIC}$)



Benzylpenicillin

PK Adults – $T_{>MIC}$

PK Neonate – AUC/MIC

The selection & target PK/PD index might change due to PK differences

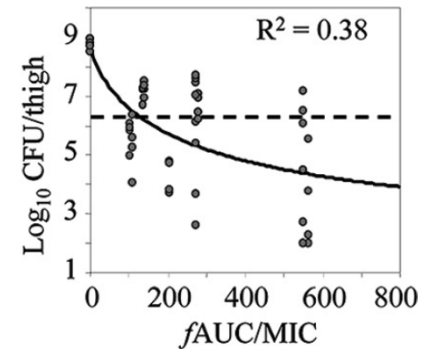
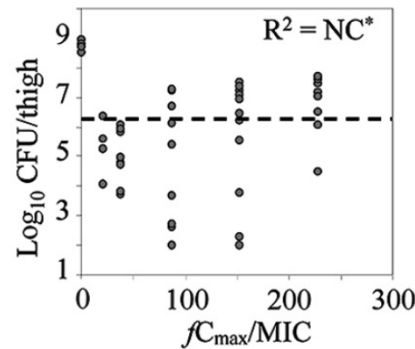
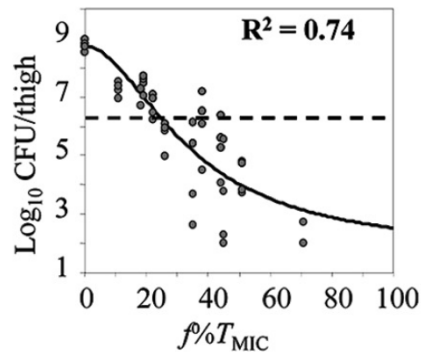


Pharmacometric approach vs PK/PD index

In Vivo Pharmacodynamic Activity of Tomopenem (formerly CS-023) against *Pseudomonas aeruginosa* and Methicillin-Resistant

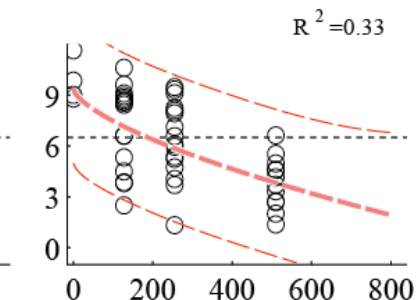
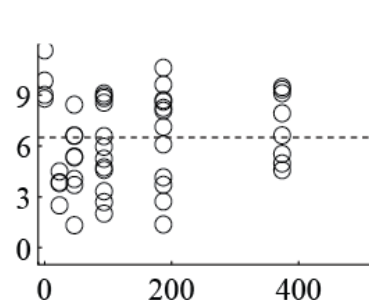
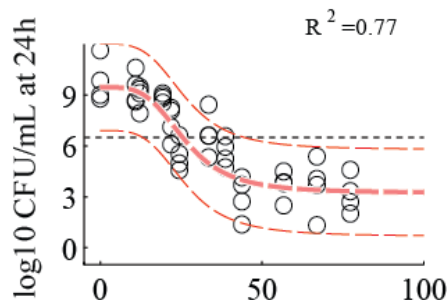
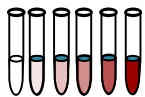
In vivo

Dose fractionation study
Meropenem
P. aeruginosa 12467



In silico replication

P. aeruginosa ATCC27853
Kristoffersson et al.





Pharmacometric approach vs PK/PD index

Meropenem



Typical:

Adult, CrCL=100 ml/min
2-comp PK, $t_{1/2,\beta} \sim 1.4$ h
(Li *et al*, J Clin Pharmacol 2006)

Augmented CL:

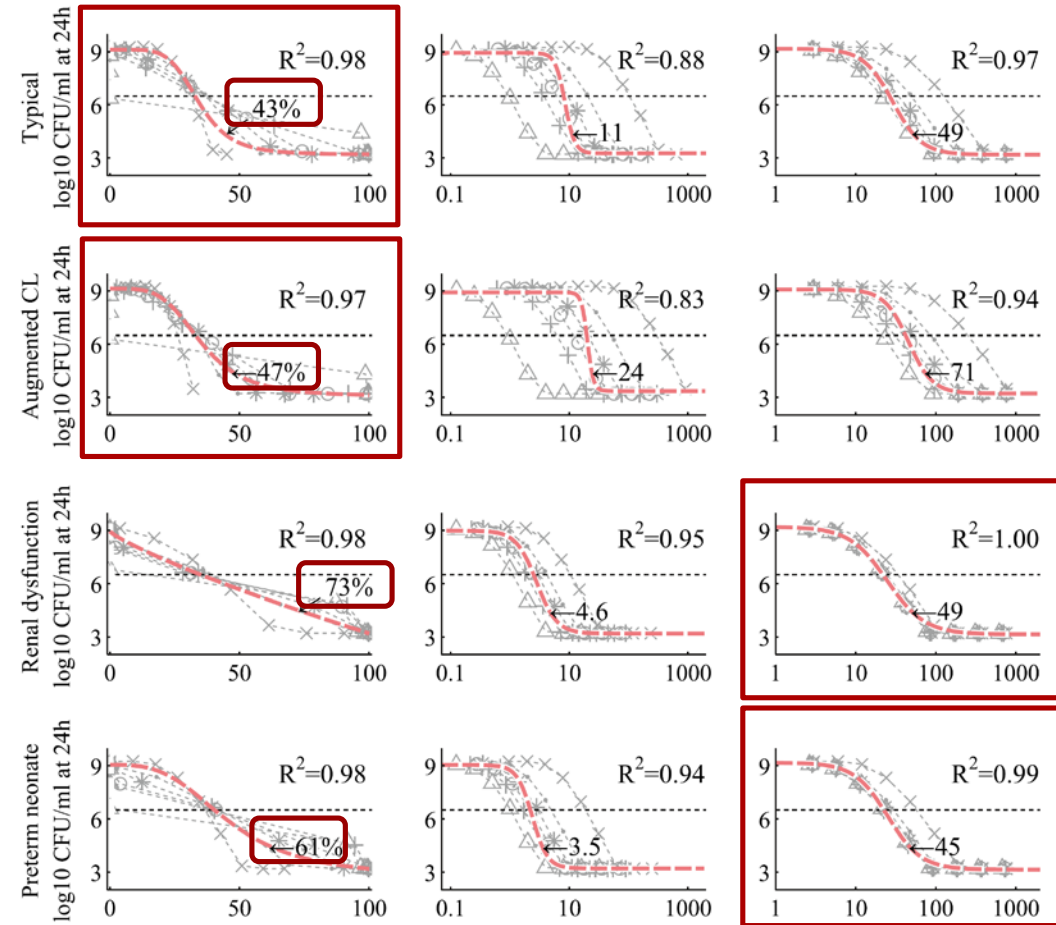
Adult, CrCL=250 ml/min
2-comp PK, $t_{1/2,\beta} \sim 0.9$ h
(Li *et al*, J Clin Pharmacol 2006)

Renal dysfunction:

Adult, CrCL=15 ml/min
2-comp PK, $t_{1/2,\beta} \sim 3.5$ h
(Li *et al*, J Clin Pharmacol 2006)

Preterm neonate:

GA 31w
2-comp PK, $t_{1/2,\beta} \sim 2.0$ h
(van den Anker *et al*, AAC 2009)



$fT > MIC$

fC_{max} / MIC

$fAUC / MIC$



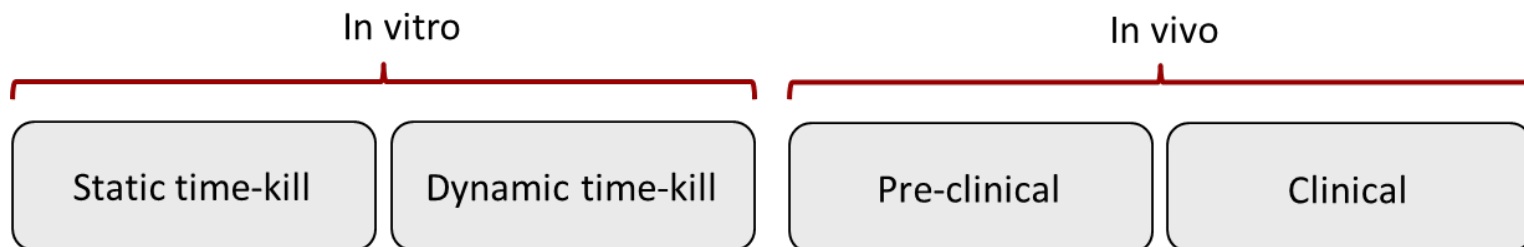
Pharmacometric approach vs PK/PD index

- Pharmacometric models are predictive of PK/PD indices
 - when replicating the same PK profile
- The selection & target PK/PD index might not be consistent across PK profiles
 - indicates that the indices might not translate well between populations
- Advantage of a pharmacometric approach
 - PK model is kept as an independent part in the overall model
 - No need to select (one or more) PK/PD indices



Benefits of pharmacometrics and systems approaches

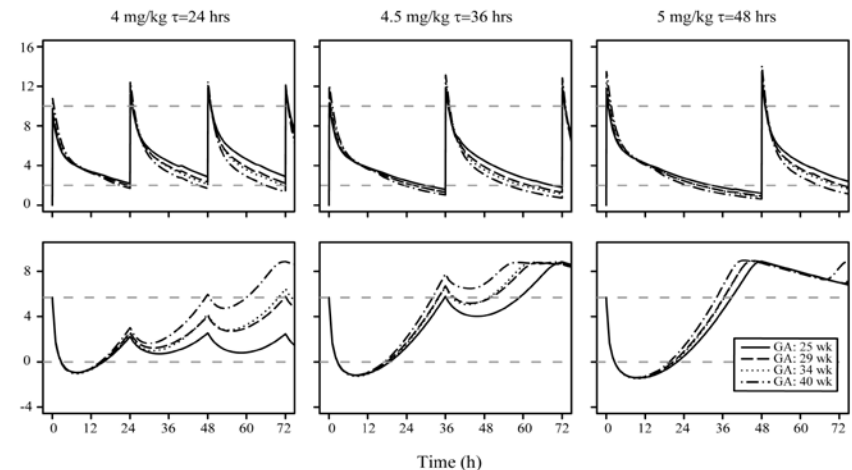
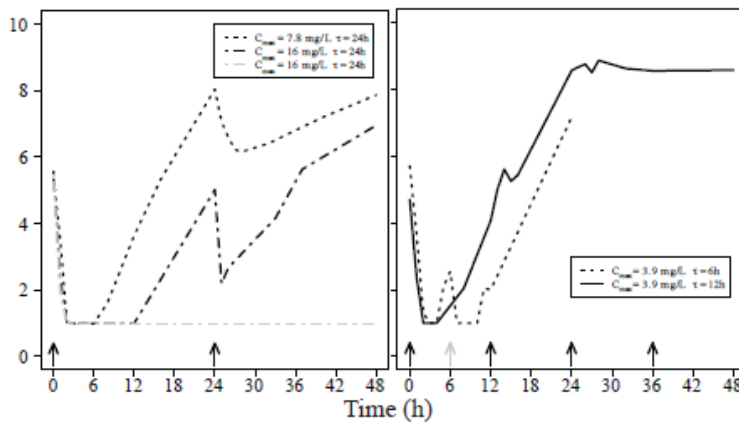
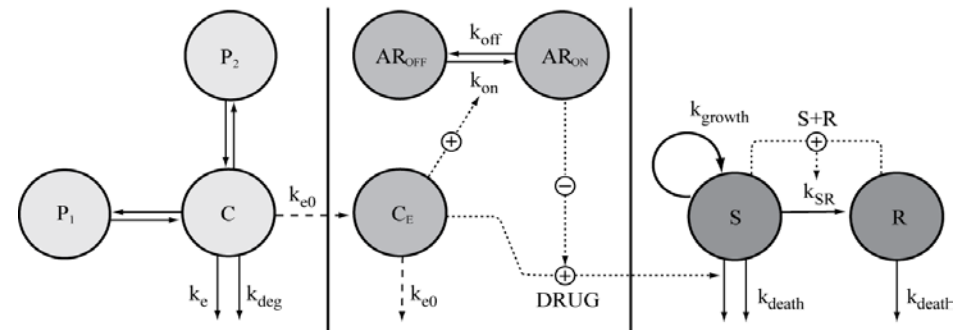
- Characterize the full time-course of the Pharmacodynamics
 - Efficacy assessments at different time points (not only 24h)
 - Efficacy for susceptible bacteria
 - Efficacy for less-susceptible bacteria (heteroresistance)
 - Changes in susceptibility (adaptive resistance)
 - Effect of drug combinations (additive, synergy or antagonism)
- Make use of all available data and accumulate knowledge
 - of special importance for efficacy assessments for antimicrobials, where clinical data is generally poor in information content (cure/no cure)





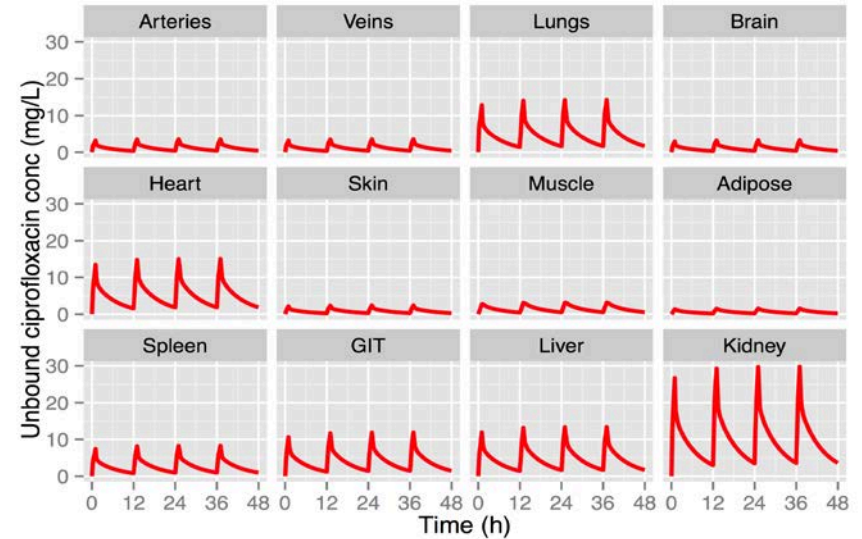
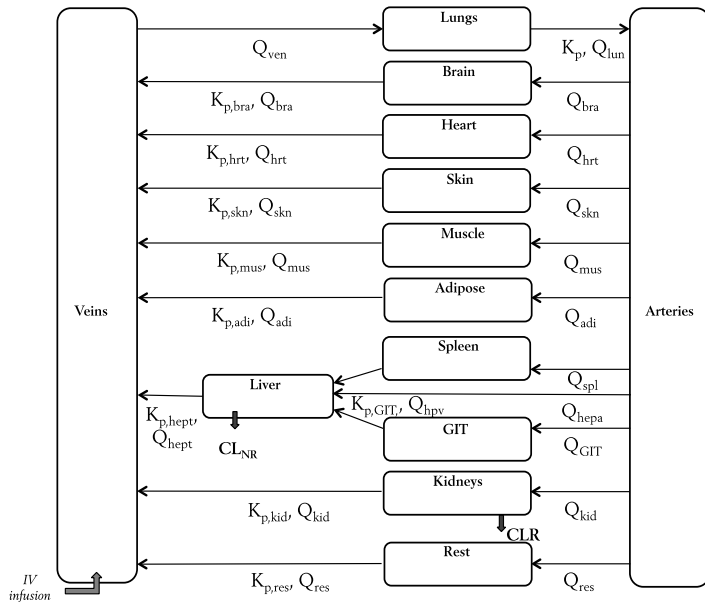
Benefits of pharmacometrics and systems approaches

- Clinical gentamicin PK study
 - 894 samples, 61 neonates
 - Population PK model
- In vitro PD data
 - Static time-kill exp.
 - Dynamic time-kill exp.
 - Single and repeated dosing



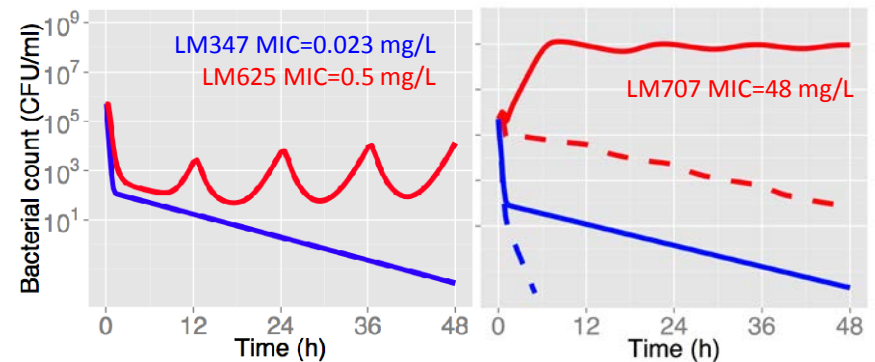
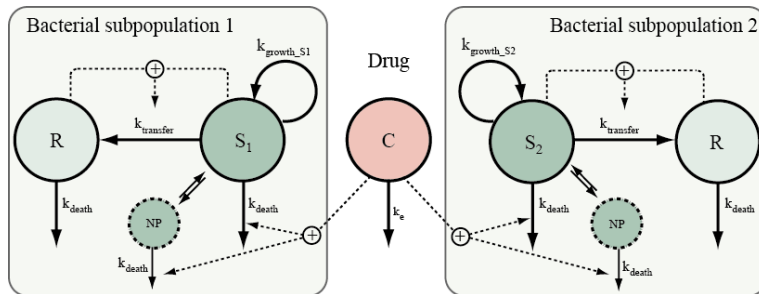


Benefits of pharmacometrics and systems approaches



Adipose

Kidney





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Acknowledgements

Pharmacometrics group, Uppsala University, Sweden

Roche Pharma Research and Early Development, Innovation Center Basel

Stiftelsen för Strategisk Forskning (SFF)

Thanks to:

- Lena Friberg
- Mats Karlsson
- Otto Cars
- Dan Andersson
- Diarmaid Hughes
- Ami Mohamed
- Anders Kristoffersson
- David Khan
- Waqas Sadiq

