Mechanism-based PKPD-models for Selection of Dosing Regimens for Antibiotics

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Selection of dosing regimens for antibiotics

Traditional way

1. Determine Type and Target magnitude of PK/PD index
   - *f*AUC/MIC, *f*T>MIC or fC_{max}/MIC typically identified in mice (bacterial kill at 24h)
2. Find regimen that results in acceptable Probability of Target Attainment (PTA)
   - Simulations from a Population PK model, MIC (distribution) and the defined Target magnitude

Assumptions: Same target independent of patient population

Ex. Meropenem dosed according to 40% *f*T>MIC (Drusano et al. Clin Infect Dis, 2003)

Difficulties: Summary variables cannot handle complexities such as

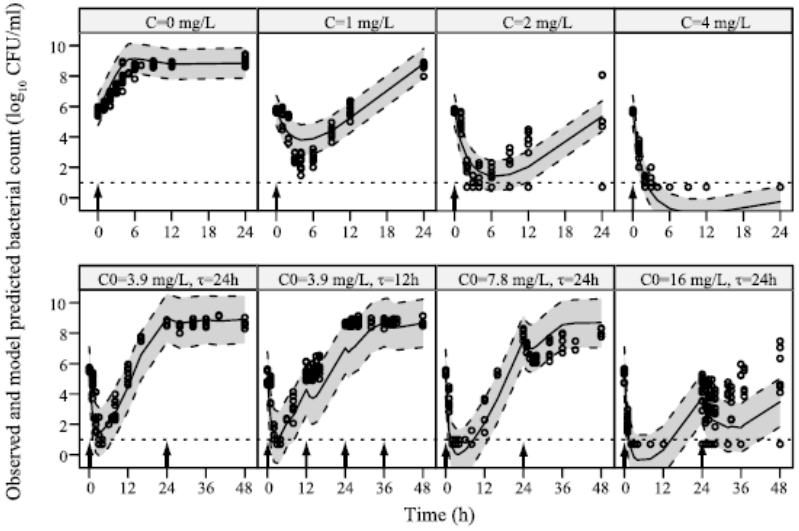
- Drug combinations
- Resistance development

Evolving way

PKPD-modelling of data from *in vitro* time-kill experiments and *in vivo* data
→ Time-courses

Mechanism-based PKPD-models for Antibiotics

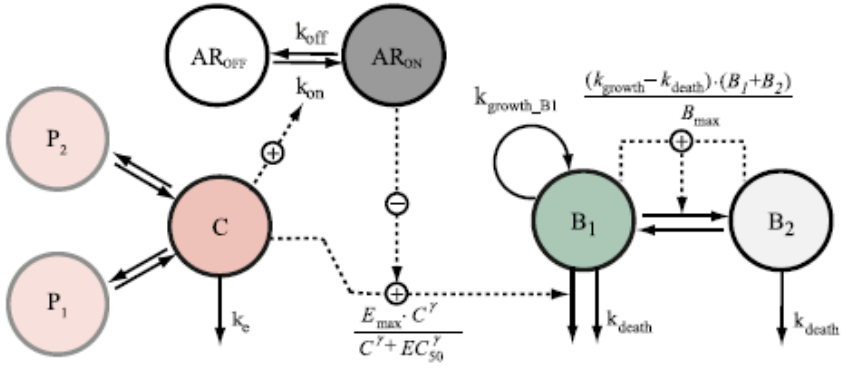
- *In vitro* time-kill curve data



Static concentrations

Dynamic concentrations

- Model structure includes
  - Natural bacterial growth
  - Drug effect
  - Resistance mechanism



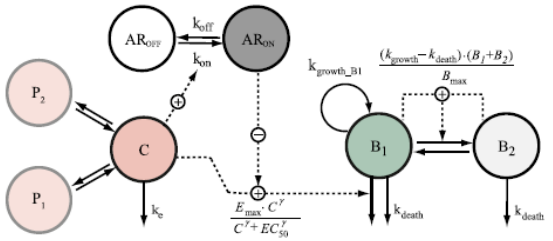
Ex. Model structure for gentamicin and colistin

Mohamed et al., AAC 2012, Mohamed et al., JAC 2014

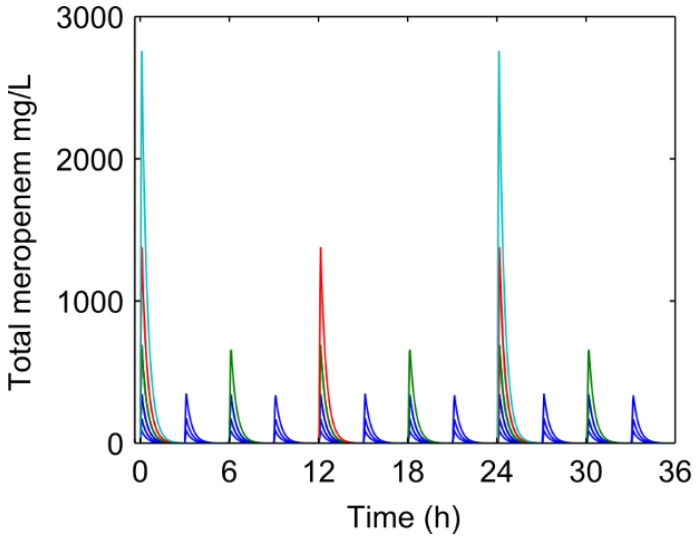
Prediction of PK/PD indices
Simulate mouse study on meropenem
(Katsube *et al.*, J Pharm Sci, 2008)

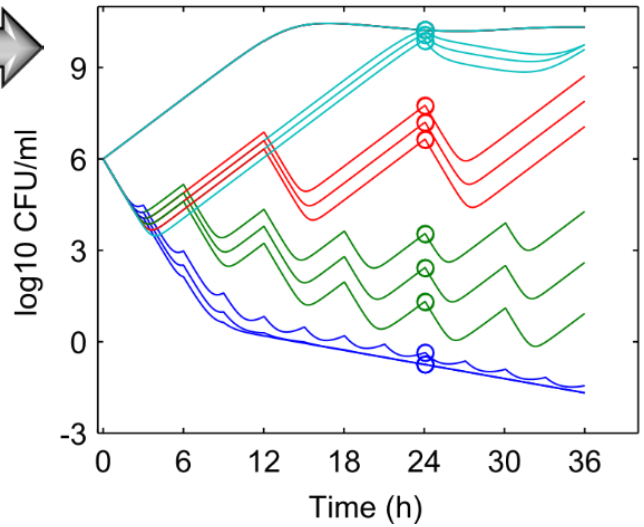
3 x 4 dosing regimens
(4 dosing intervals,
3 dose levels)

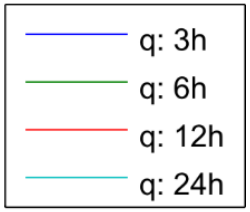
PK: $t_{1/2}$ ~ 0.3 h



Model based on
in vitro data





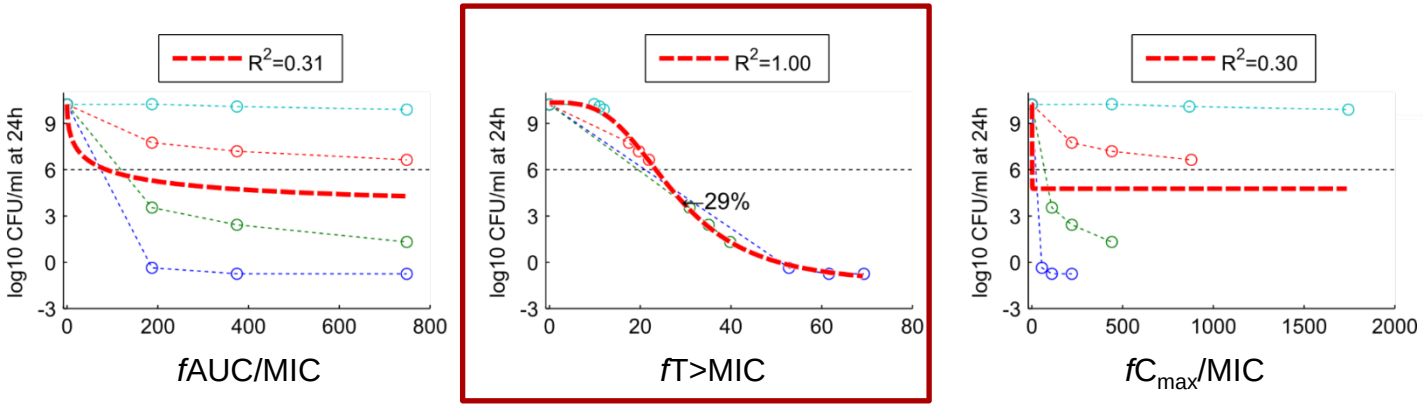


fC_{max}/MIC, *f*AUC/MIC and *f*T>MIC

Log_{10} CFU/ml at 24h

Simulation PK/PD indices - Meropenem *Mouse PK*

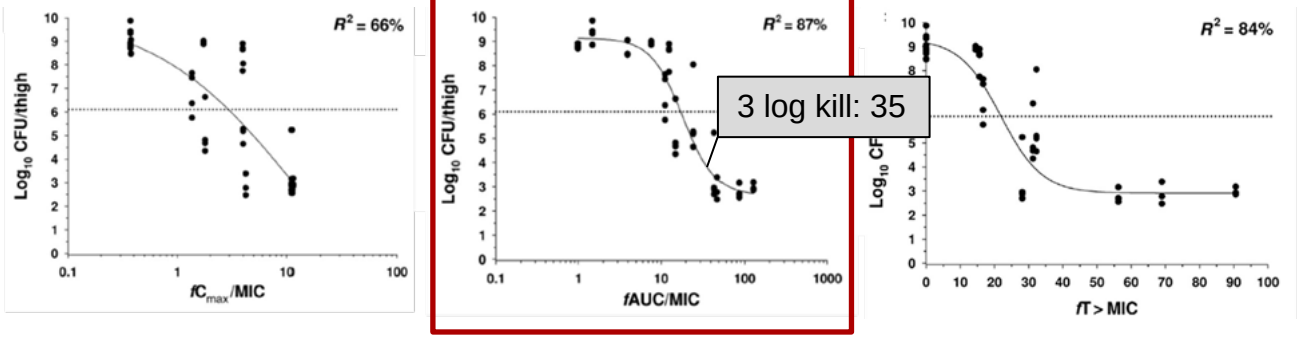
Mouse:
$t_{1/2}$ ~ 0.3 h
(Katsube *et al.,* J Pharm Sci, 2008)

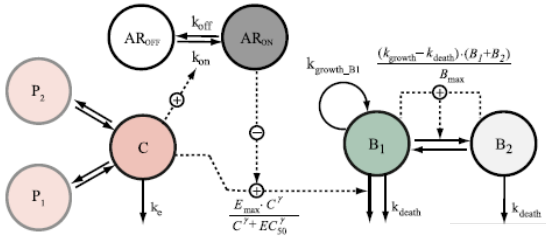


- *f*T>MIC best PK/PD index as typically reported for carbapenems (and other β-lactams)
- Target of 40% *f*T>MIC recommended for meropenem
  (Drusano et al., Clin Infect Dis, 2003)

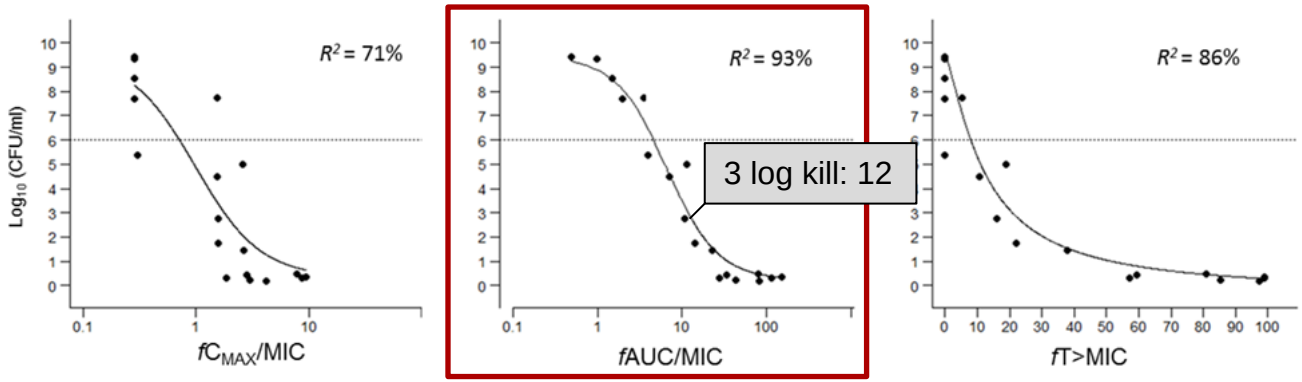
Prediction of PK/PD indices
Colistin in mice

Observed data in mice
(Dudhani et al., AAC 2010)





Predictions from same PK and a mechanism-based PKPD-model for colistin (Mohamed et al., JAC, 2014)



Khan et al., *In manuscript*

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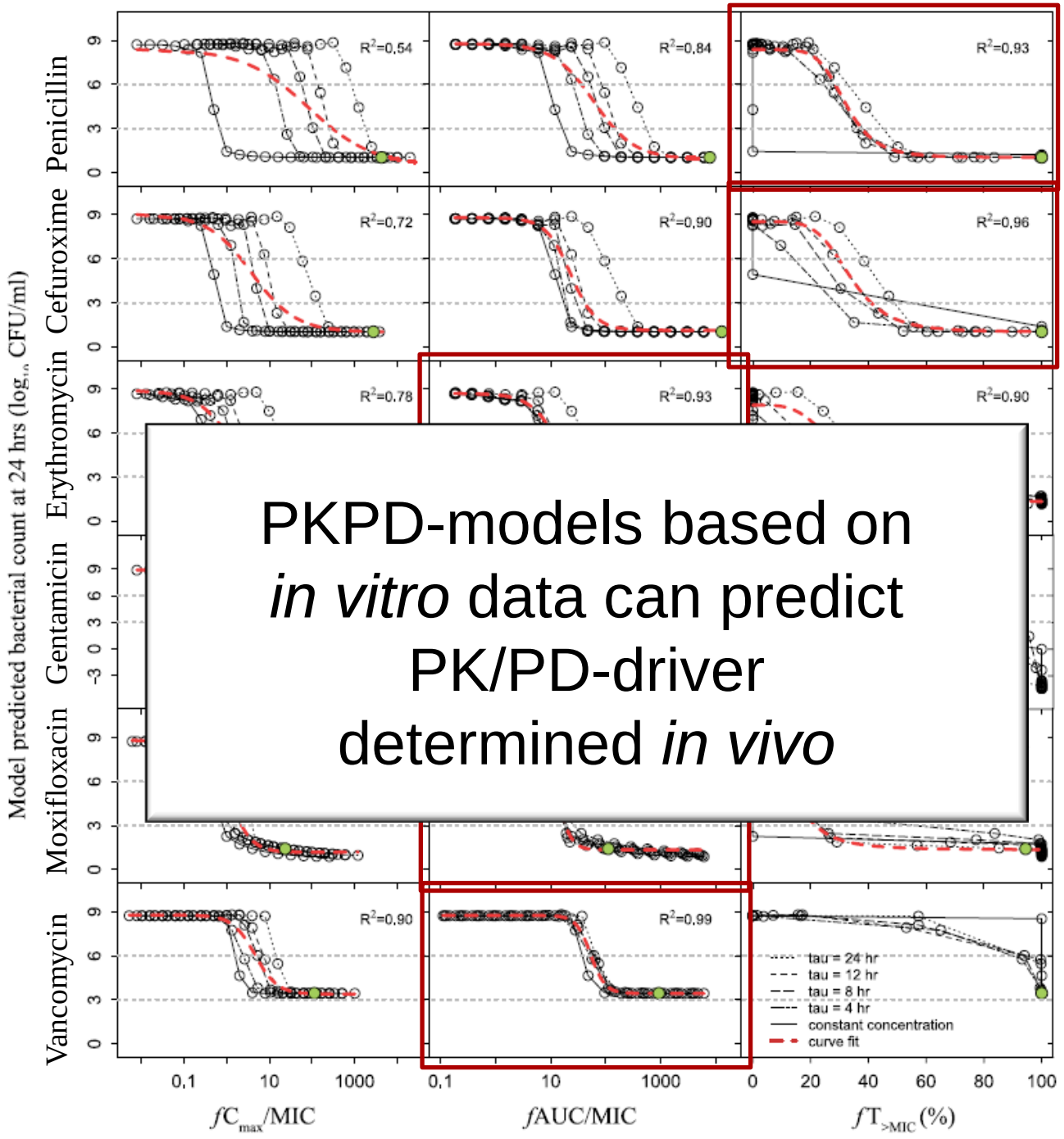
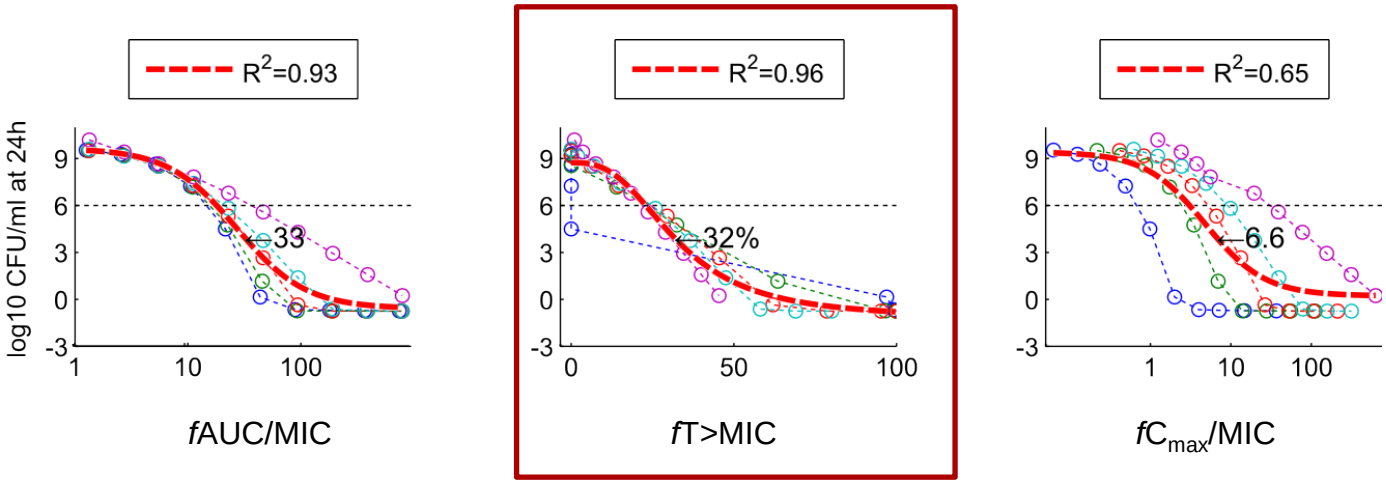


PKPD-models based on *in vitro* data can predict PK/PD-driver determined *in vivo*

Nielsen et al., AAC 2011

Simulation PK/PD indices - Meropenem
Typical adult patient PK

Typical:
Adult, CrCL=83 ml/min
2-comp PK, $t_{1/2,\beta}$ ~ 1 h
(Li *et al.*, J Clin Pharmacol, 2006)



- 32% *f*T>MIC for 2-log kill is close to the commonly cited value of 40%
  (Drusano et al., Clin Infect Dis, 2003)
- *f*AUC/MIC is nearly as good predictor as *f*T>MIC

Simulation PK/PD indices - Meropenem

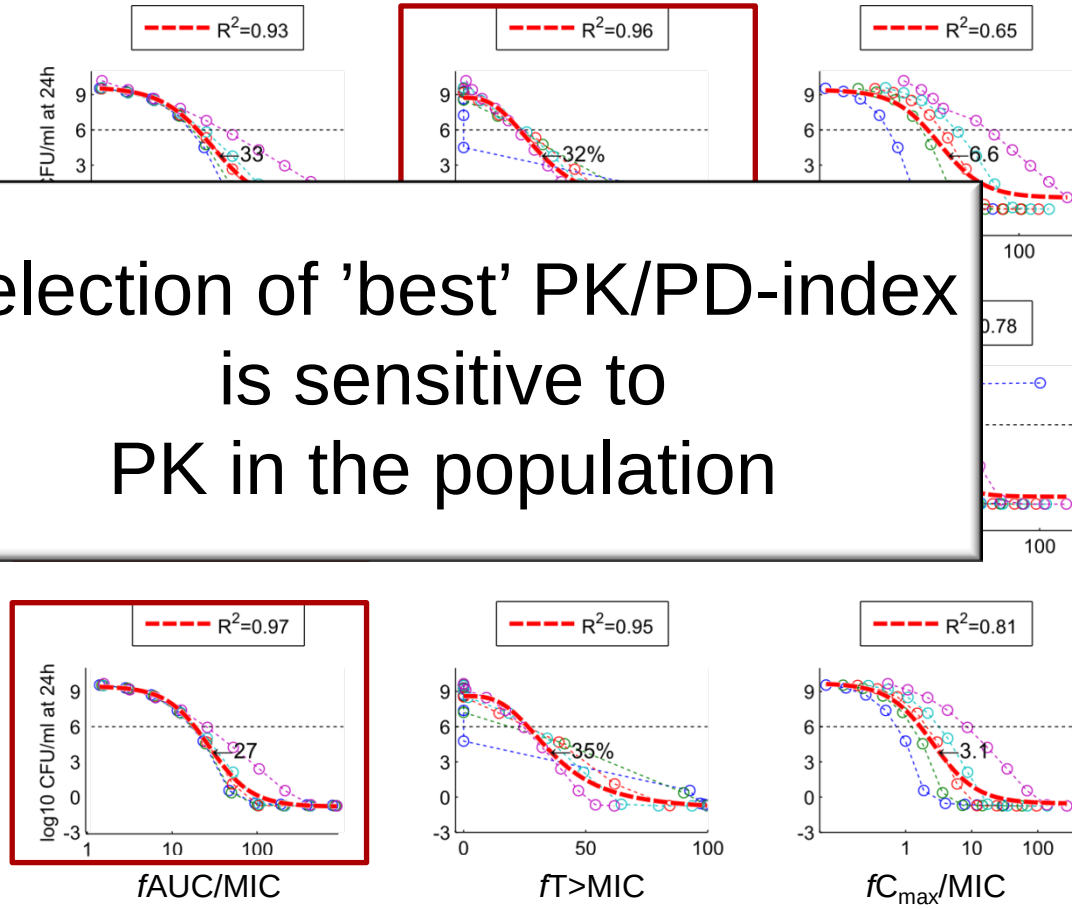
Different patient populations

Typical:
Adult, CrCL=83 ml/min
2-comp PK, $t_{1/2,\beta}$ ~ **1 h**
(Li *et al*, J Clin Pharmacol 200

Renal dysfunction:
Adult, CrCL=15 ml/min
2-comp PK, $t_{1/2,\beta}$ ~ **1.5 h**
(Li *et al*, J Clin Pharmacol 200

Preterm neonate:
GA 31w
2-comp PK, $t_{1/2,\beta}$ ~ **1.5 h**
(van den Anker *et al*, AAC 2009)

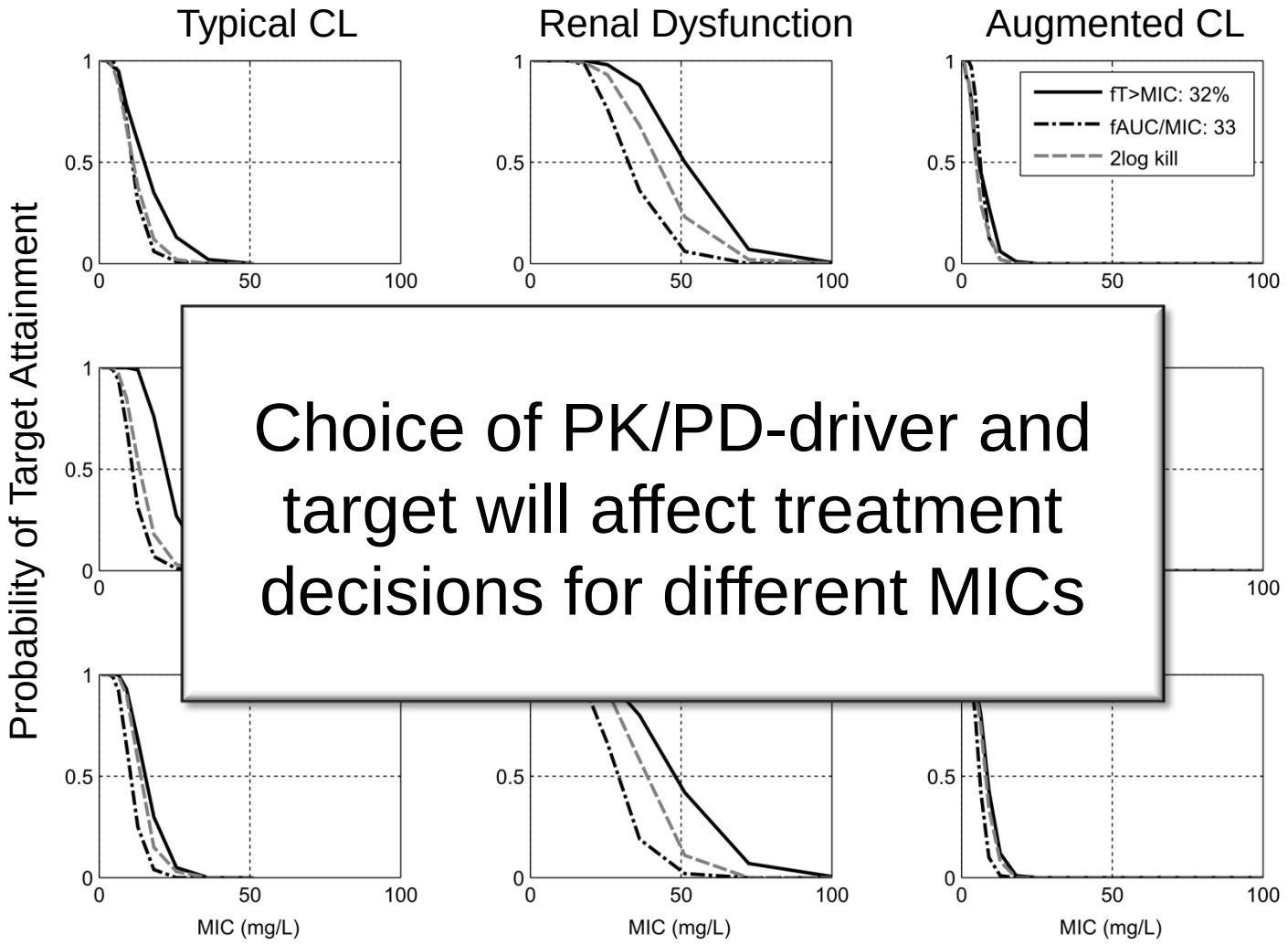
Selection of 'best' PK/PD-index
is sensitive to
PK in the population



- Best predictor moves towards *f*AUC/MIC for increased half-lives
  - *f*T>MIC indicates a higher target (exposure should be *increased*)
  - *f*AUC/MIC indicates a lower target (exposure can be *decreased*)

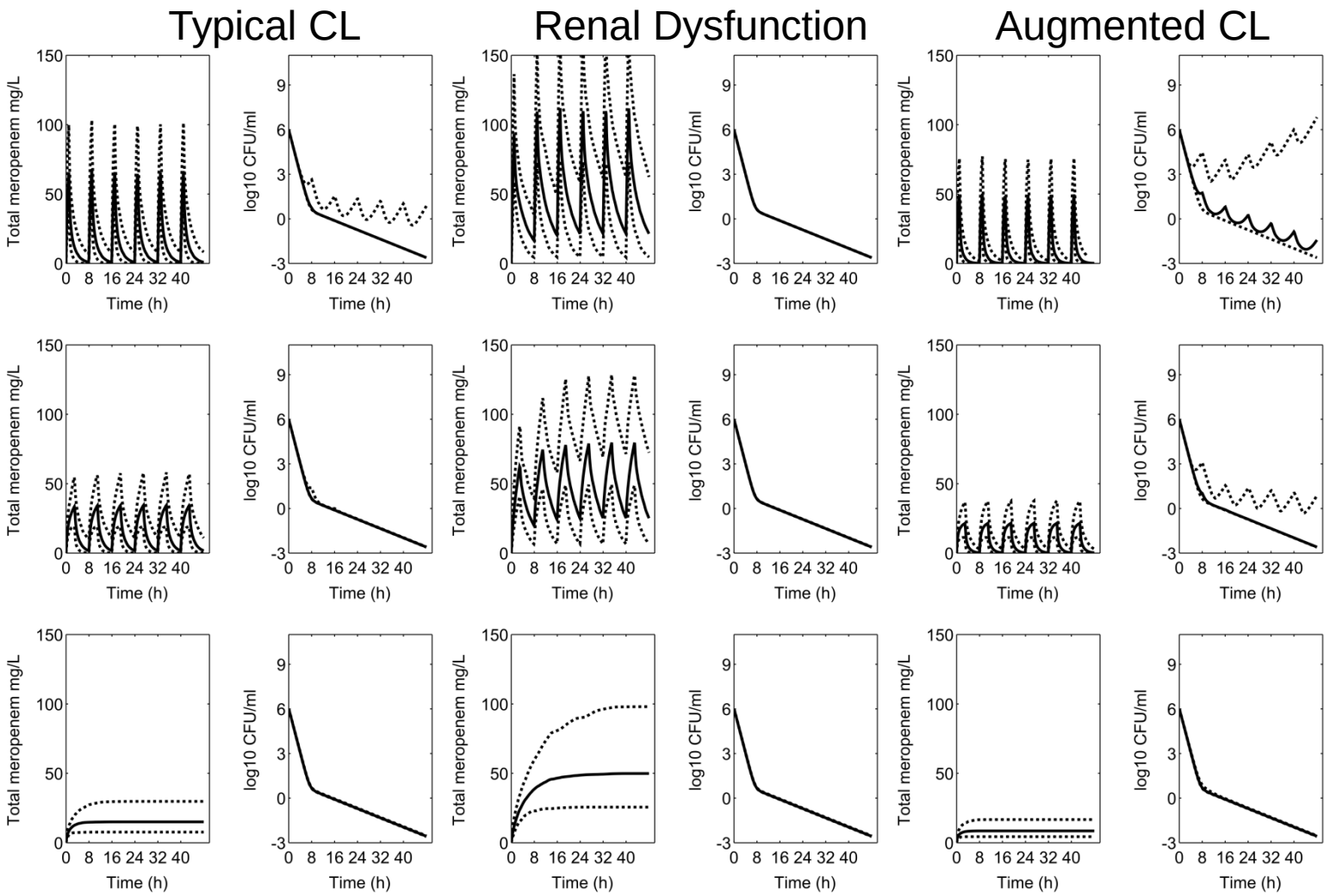
Probability of Target Attainment (PTA)

Different dosing regimens of meropenem



- *f*T/MIC predicts higher PTA at a specific MIC level

Value of continuous meropenem infusion in different patient populations?



Conclusions

- Mechanism-based PKPD-models based on *in vitro data* can predict *in vivo* PKPD results
- Typically assumed to be one ´true´ PK/PD index and target magnitude, but they are sensitive to
  - PK in the population
  - MIC value
  - Resistance development
  - Design

Potential uses of a mechanism-based PKPD-model based on *in vitro* data

- Improved designs of animal experiments
  - Ethical and financial benefits
- An understanding of the time-course of drug effects
  - Influence of resistance development
  - Predictions beyond experimental time?
- A range of dosing scenarios can be explored
  - Dosing regimens
  - Loading dose
  - Drug combinations
- Correlations between MIC and EC_{50}
  - Limited data needed to explore time-courses for new mutants (Khan et al., *Submitted*)

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Thank you!