

Pharmacokinetic-pharmacodynamic modelling to characterize the time-course of meropenem effect *in vivo* on bacteria with high MIC

Raphaël Saporta¹, Elisabet I. Nielsen¹, Jon U. Hansen²,
Edgars Liepinsh³, Iris K. Minichmayr¹, Lena E. Friberg¹

¹ Department of Pharmacy, Uppsala University, Uppsala, Sweden ² Bacteria, Parasites & Fungi, Statens Serum Institut, Copenhagen, Denmark
³ Latvian Institute of Organic Synthesis, Riga, Latvia

Background

- Carbapenem-resistance → multiple critical priority pathogens according to the WHO [1]
- Published meropenem PKPD models based on *in vivo* data have not characterized the time course of meropenem effects against high Minimum Inhibitory Concentration (MIC) strains [2-3]

Aims

- Develop a PKPD model describing meropenem effect over time *in vivo* on high MIC bacteria
- Predict PK/PD indices in mouse dose fractionation studies
- Predict PK/PD indices and expected efficacy of high-dose meropenem in patients

Methods

Data

- Neutropenic mouse thigh infection model
- 6 meropenem resistant *Escherichia coli* & *Klebsiella pneumoniae* with MIC of 32 to 128 mg/L
- Meropenem subcutaneous administration 1 to 512 mg/kg single dose or every 8 to 1 hour
- Colony Forming Units (CFU) measured once per animal between start of treatment and 24 hours after start of treatment

Model development

- PK and PKPD model development using NONMEM 7.5
- MIC investigated to describe differences in meropenem effect between strains

Simulations

- Simulations of 24 h mouse dose fractionation studies
- Derivation of PK/PD indices:
 - $fAUC/MIC$
 - fC_{max}/MIC
 - $\%fT>MIC$
- PKPD model used jointly with a PK model for meropenem in humans [4]
- Simulation of 24 h outcome after different infusion durations of high-dose meropenem in two patient populations:
 - 2g q8h for normal kidney function
 - 2g q12h for reduced kidney function
- Derivation of PK/PD indices

Results

PKPD model

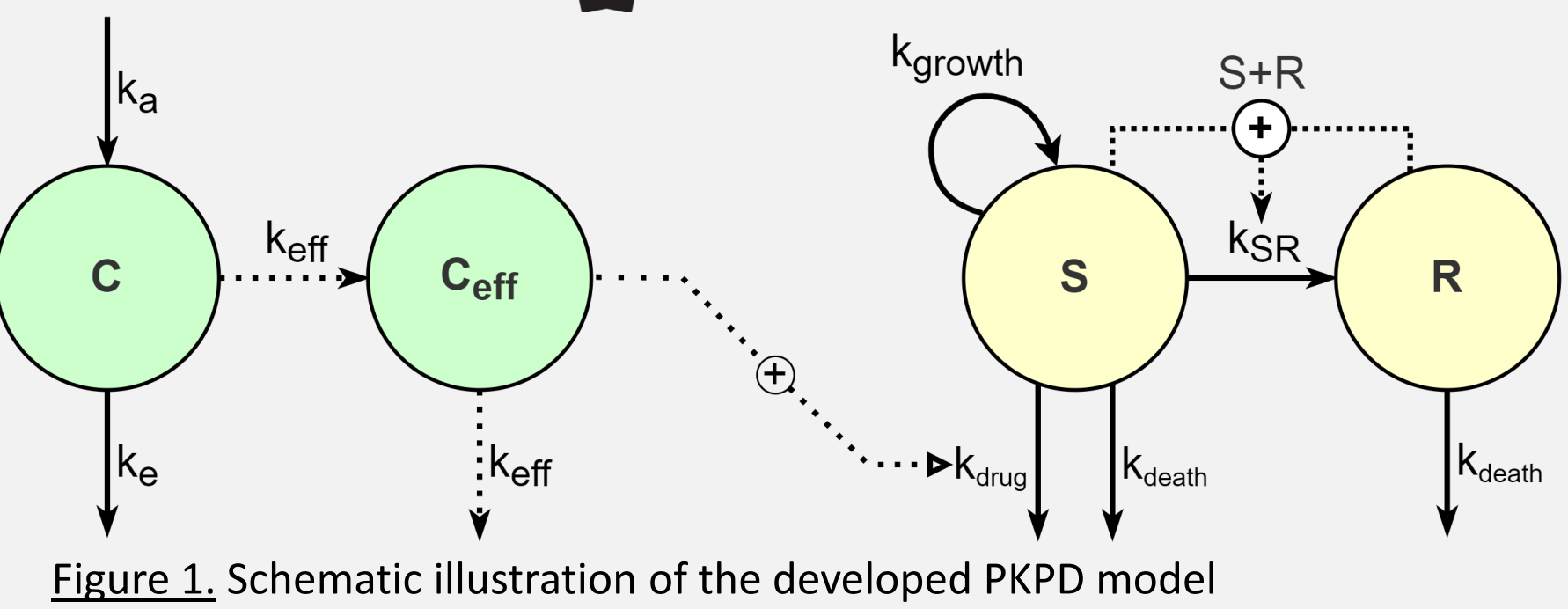


Figure 1. Schematic illustration of the developed PKPD model

- The developed PKPD model described bacterial susceptible (S) and resting (R) states [5]
- Meropenem effects were described through 2 E_{max} models:
$$k_{drug} = \frac{E_{max,1} \cdot C}{C + EC_{50}} + \frac{E_{max,2} \cdot C^{hill}}{C^{hill} + EC_{50,2}^{hill}}$$
- Differences in MIC were not associated with differences in effect between strains
→ Same effect predicted for strains of different MICs

Table 1. Parameter estimates and relative standard error (RSE) of the estimates from the final model

Parameter	Unit	Description	Estimate	RSE (%)
CL/F	L/(h·kg)	Clearance	1.72	8.3 ^a
V/F	L/kg	Volume of distribution	0.994	9.5 ^a
k_a	h^{-1}	Absorption rate constant	10.2	Fixed
$k_{growth,max}$	h^{-1}	Post-delay bacterial growth rate constant	0.733	4.6 ^b
T_{delay}	h	Growth delay	1.35	15.2 ^b
β	—	Sigmoidicity factor for growth delay	5	Fixed
k_{death}	h^{-1}	Bacterial natural death rate constant	0.179	Fixed
B_{max}	log_{10} CFU/thigh	Maximum bacterial count	8.73	0.8 ^b
k_{eff}	h^{-1}	Effect compartment rate constant	1.58	14.6
E_{max}	h^{-1}	Maximum meropenem effect (killing rate constant)	0.672	2.7
EC_{50}	mg/L	Concentration needed to achieve 50% of E_{max}	1.01	16.8
$E_{max,2}$	h^{-1}	Maximum meropenem second effect (killing rate constant)	2.04	29.3
$EC_{50,2}$	mg/L	Concentration needed to achieve 50% of $E_{max,2}$	88.8	10.9
$hill$	—	Sigmoidicity factor for the second effect	10	Fixed
RES	log_{10} CFU/thigh	Residual error (variance; additive on log_{10} scale)	0.408	7

^a Parameters fixed based on estimates from the PK model.

^b Parameters fixed based on estimates from a PKPD model with growth control data only.

Simulations: mice

- The predictive ability of $fT>MIC$ was dependent on evaluated concentrations, with EC_{50} leading to the highest correlation

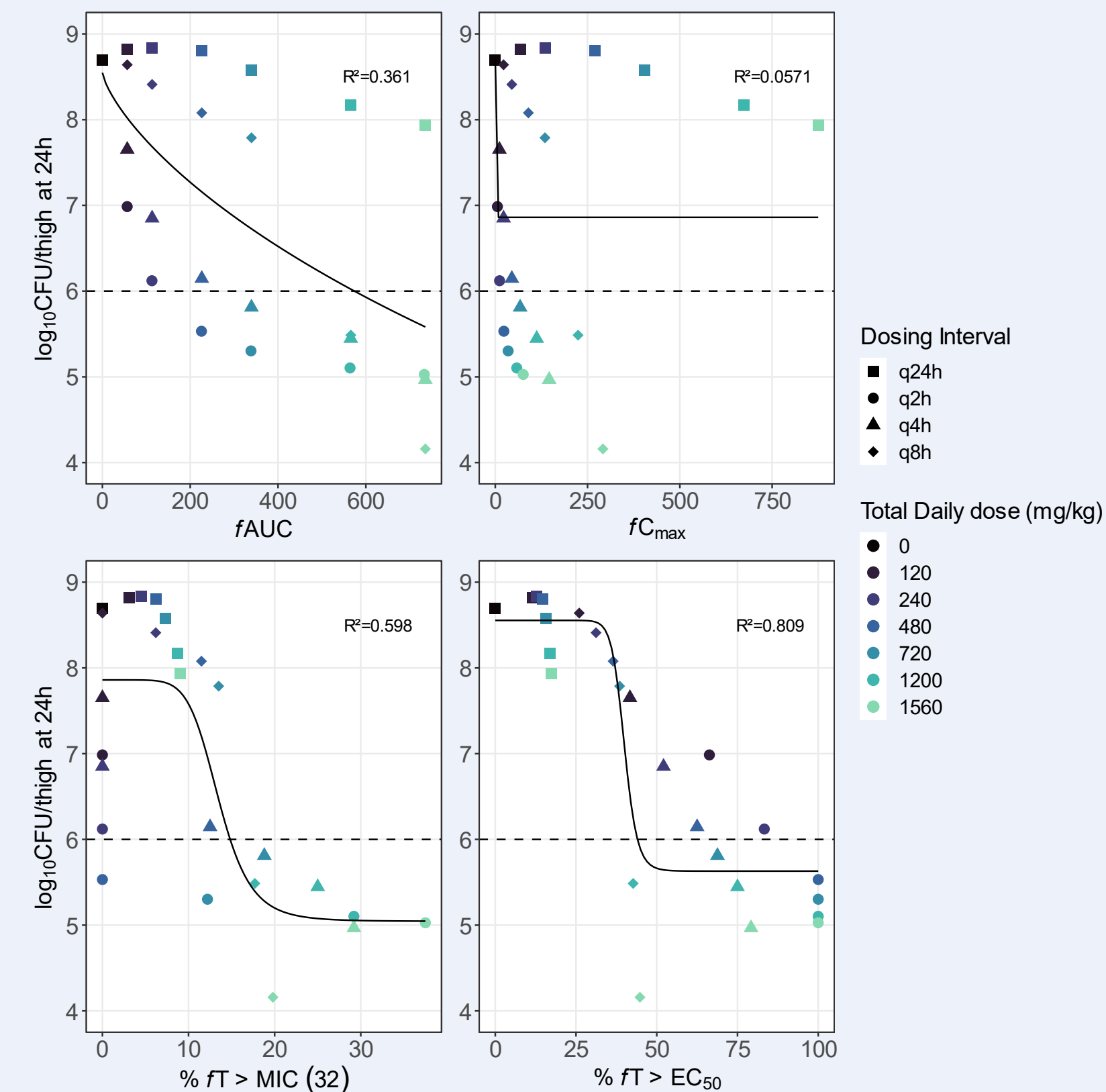


Figure 2. Relationship between PK/PD indices and the 24 h bacterial counts from simulated dose-fractionation studies in mice

Simulations: patients

- $fAUC$ predictive ability was improved in simulated patients receiving high-dose meropenem treatment
- Simulations predicted bacterial stasis or killing in >85% patients in each scenario, with a trend towards fewer predictions of growth with prolonged infusion durations

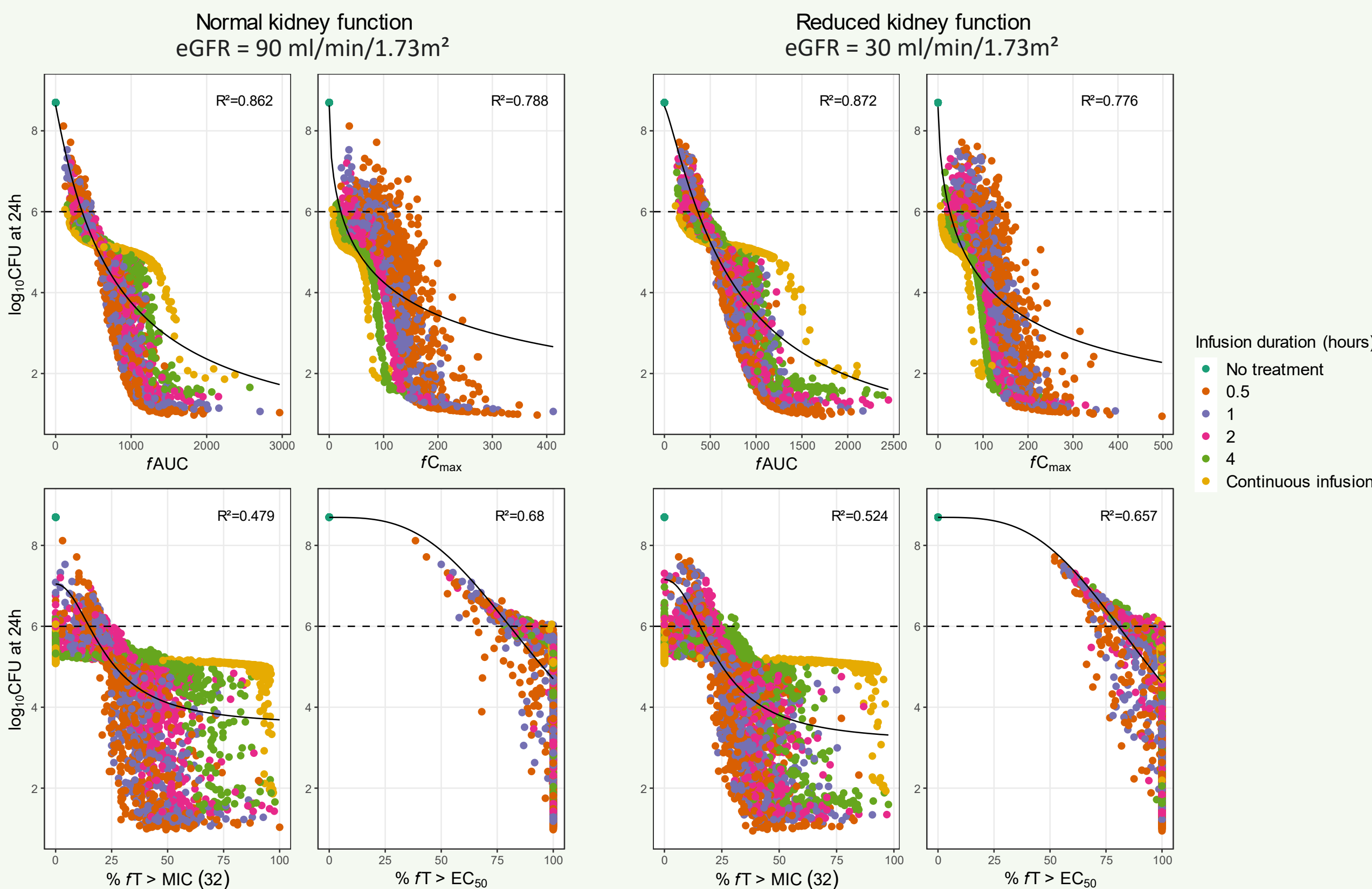


Figure 3. Relationship between PK/PD indices and the simulated 24 h bacterial counts following high-dose meropenem treatment with different infusion durations in patients with normal and reduced kidney functions

References:

- Tacconelli E et al. Lancet Infect Dis 2018; 18: 318–27.
- Katsube T et al. J Pharm Sci 2008; 97: 1606–14.
- Louie A et al. J Infect Dis 2015; 211: 1326–33.
- Trang M et al. Antimicrob Agents Chemother 2021; 65: e0260620.
- Nielsen, EI et al. Antimicrobial agents and chemotherapy vol. 51,1 (2007): 128-36.

Acknowledgment:

This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 861323.

