



A simulation-based evaluation of the pharmacokinetic-pharmacodynamic (PK/PD) index approach for avibactam

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Background

- β-lactamase inhibitors (BLI) are an increasingly important group of drugs, used to restore the activity of β-lactam (BL) antibiotics against β-lactamase-producing bacteria. Ceftazidime (CAZ) - a BL - and avibactam (AVI) - a BLI - is one example of such a drug combination.
- The traditional PK/PD index approach is not directly applicable for dose finding on drug combinations, particularly if both compounds have an antibacterial effect of its own. Moreover, the limitations of using summary-indices for inter-species translation has earlier been demonstrated [1]. Free drug concentration remaining above a threshold concentration for a defined portion of the dosing interval (%fT > C_T) has been previously suggested as the best predictor of efficacy for avibactam [2,3].
- Aim:** use a mechanism-based PKPD model developed from *in vitro* static time-kill kinetics data to simulate the bacterial response following different exposures of ceftazidime-avibactam in mice and humans and compare with traditional PK/PD indices.

Discussion & conclusion

- Both in mice and in humans, a same PK/PD index (fAUC/MIC) was found for AVI in combination with CAZ against β-lactamase-producing Gram-negative bacteria
- Conflicting result with %fT > C_T previously identified by Sy et al. as the most predictive PK/PD index for *P. aeruginosa* [3]
- Highlights the limitations of the PK/PD index approach to characterize antibacterial response:
 - Despite wide spread of bacterial responses, (relatively) good fits for all PK/PD indices (and small differences in r² values)
 - none of them are good enough?
 - Dependency on study design (chosen dose of CAZ given)
- Further supports the use of a model-based approach that consider the full-time course of bacterial growth and killing in the selection of antibiotic dosing regimens, especially for drugs in combination

Simulated CAZ-AVI dosing regimens in mice

Dose rationale allowing comparison on frequency of administration and mode of infusion

- CAZ: one dosing regimen (1230mg/kg q24h)
- AVI: total daily dose increments, various frequencies (from q2h to q24h), various modes of infusion (0.5h-, 2h-, 4h- or continuous-infusion)
- Population: infected mice

Simulations performed using the R package mrgsolve [4]

CAZ-AVI PK model in mice [3]

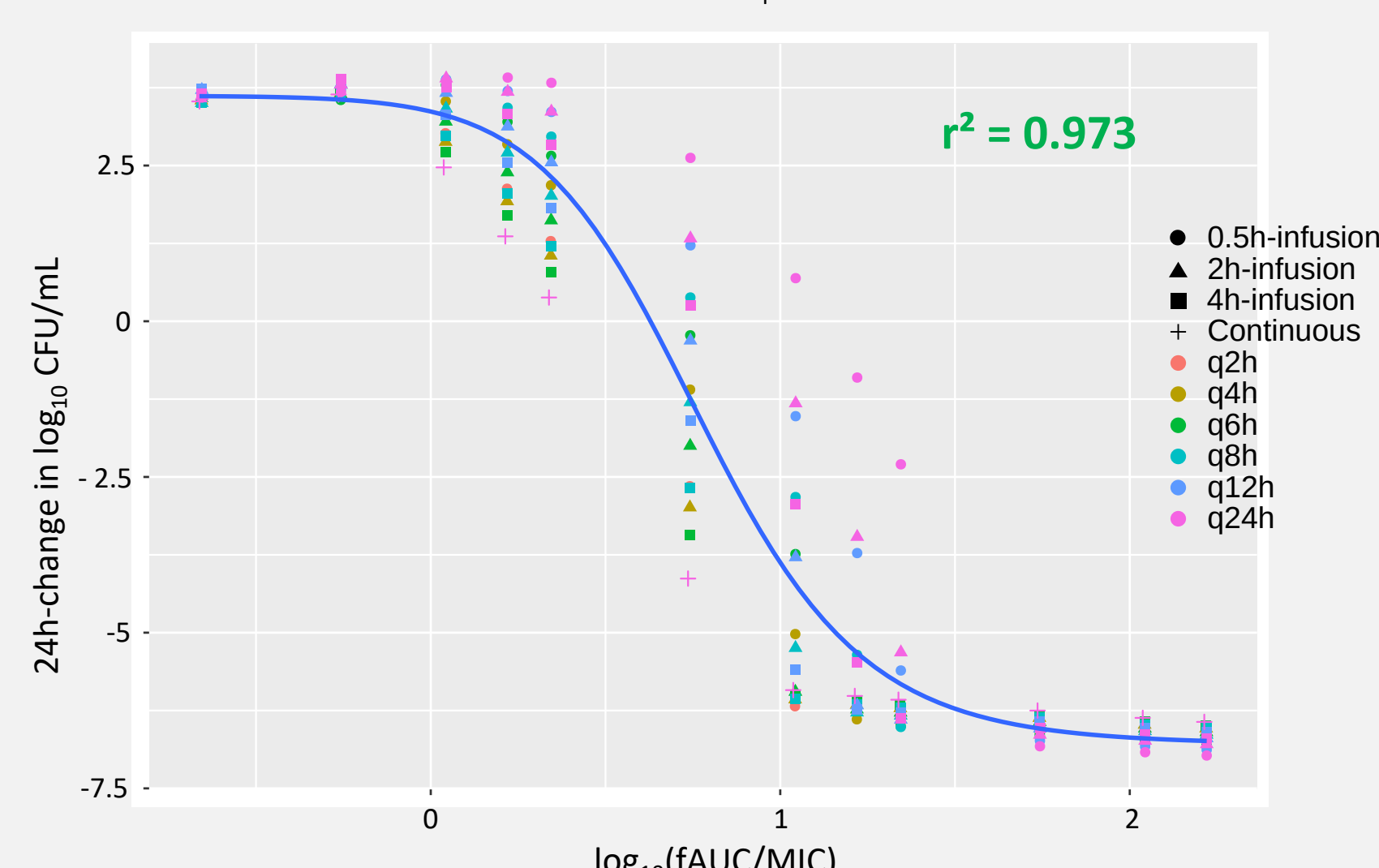
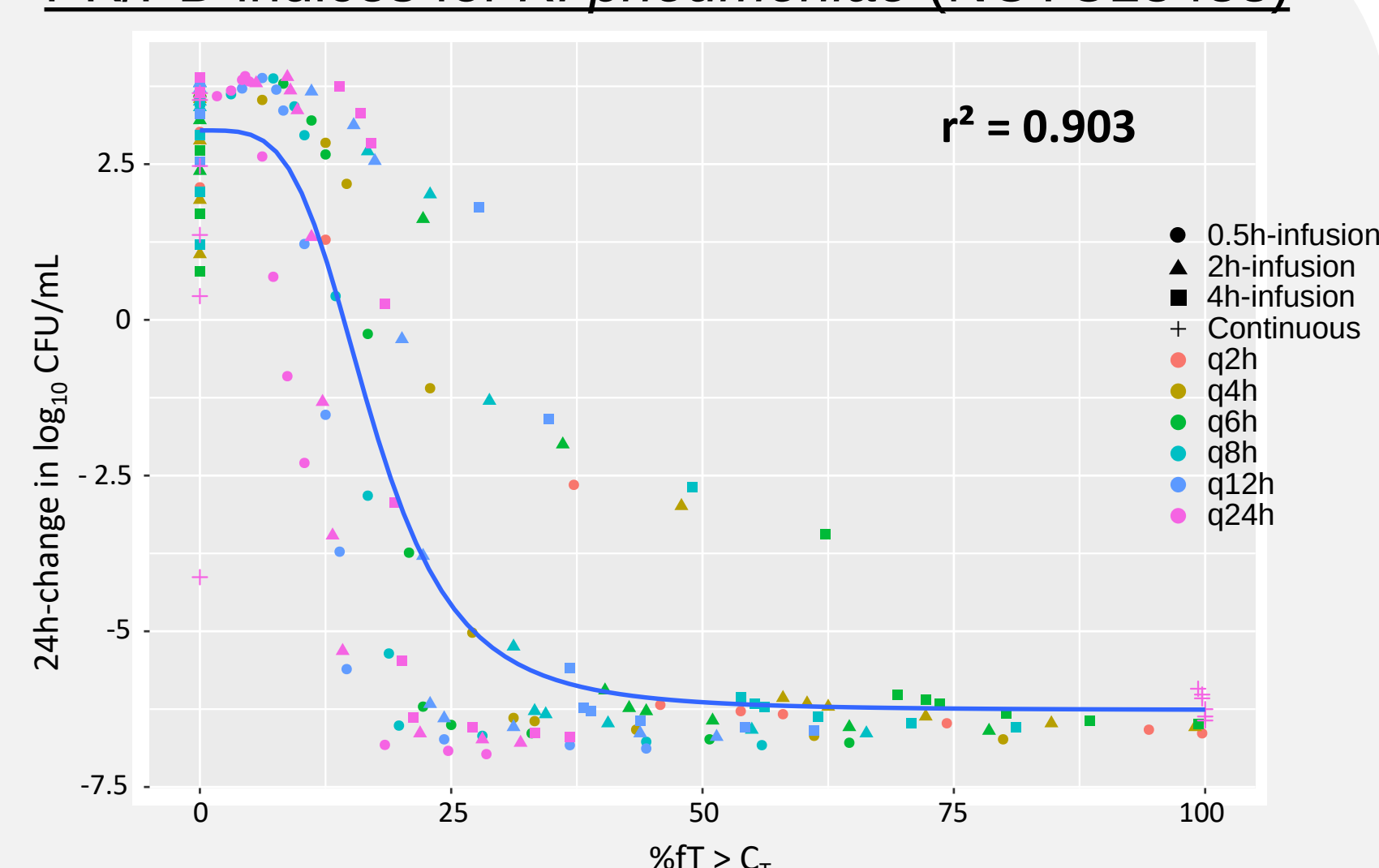
CAZ-AVI PopPK model in humans [5]

Simulated CAZ-AVI dosing regimens in humans

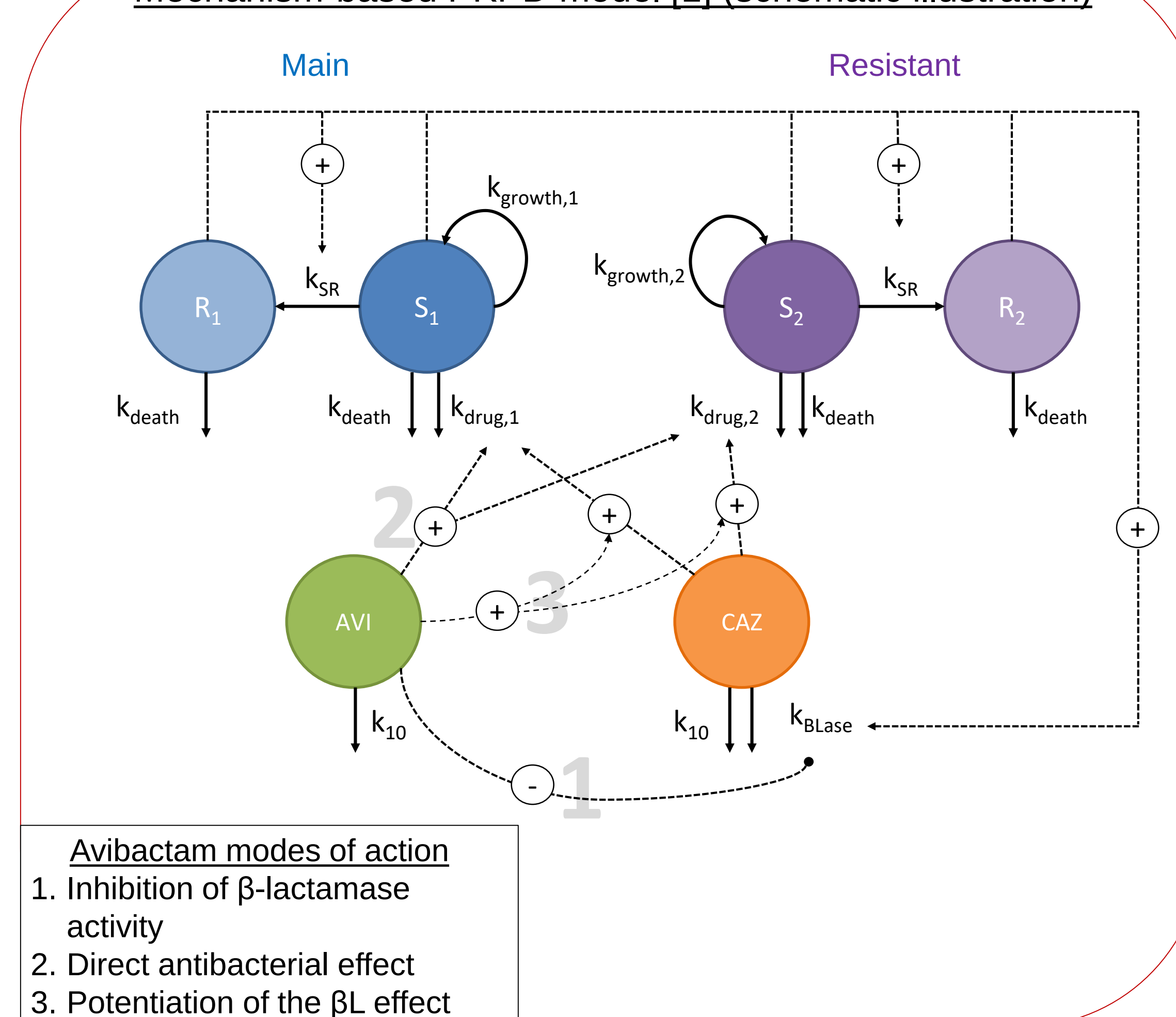
Dose rationale allowing comparison on disease population

- CAZ: one dosing regimen (2000mg q8h)
- AVI: total daily dose increments, one frequency (q8h), one mode of infusion (2h-infusion)
- Population: different diseases (prostatitis, cIAI, HAP/VAP, sepsis) generated through the PopPK model

PK/PD indices for *K. pneumoniae* (NCTC13438)



Mechanism-based PKPD model [1] (schematic illustration)



Avibactam modes of action
1. Inhibition of β-lactamase activity
2. Direct antibacterial effect
3. Potentiation of the βL effect

Magnitude of avibactam exposures associated with stasis and bacterial killing of 3 strains of β-lactamase-producing Gram-negative bacteria in mice:

Species	Strain	MIC _{CAZ/AVI}	Target	Stasis	1-log kill	2-log kill
<i>K. pneumoniae</i>	NCTC13438	4	fAUC/MIC	4.253	5.254	6.462
			%fT > C _T	14.32	16.05	17.88
<i>K. pneumoniae</i>	KP981690	1	fAUC/MIC	3.647	4.623	5.809
			%fT > C _T	2.94	6.97	8.72
<i>E. cloacae</i>	EL871203	8	fAUC/MIC	4.207	5.210	6.430
			%fT > C _T	19.12	21.39	23.91

MIC_{CAZ/AVI} (mg/L): MIC of ceftazidime in the presence of 4mg/L of avibactam

Relationships between the effect and the 3 PK/PD indices were evaluated according to a sigmoidal Emax type function:

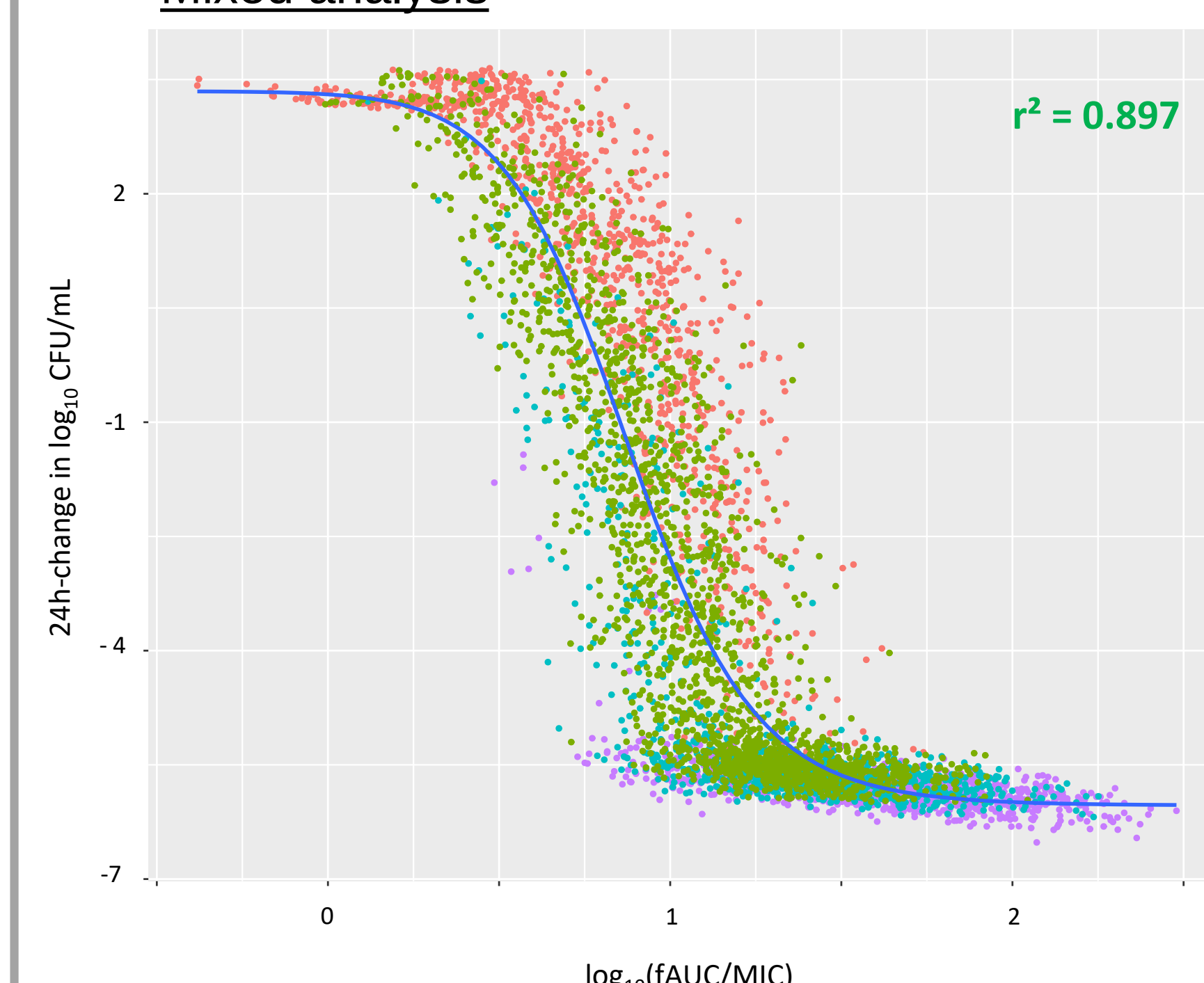
$$E = E_0 - \frac{PD_{max} \times X^{hill}}{X^{hill} + EX50^{hill}}$$

Tested PK/PD indices:
- %fT > C_T
- fAUC/MIC
- fCmax/MIC

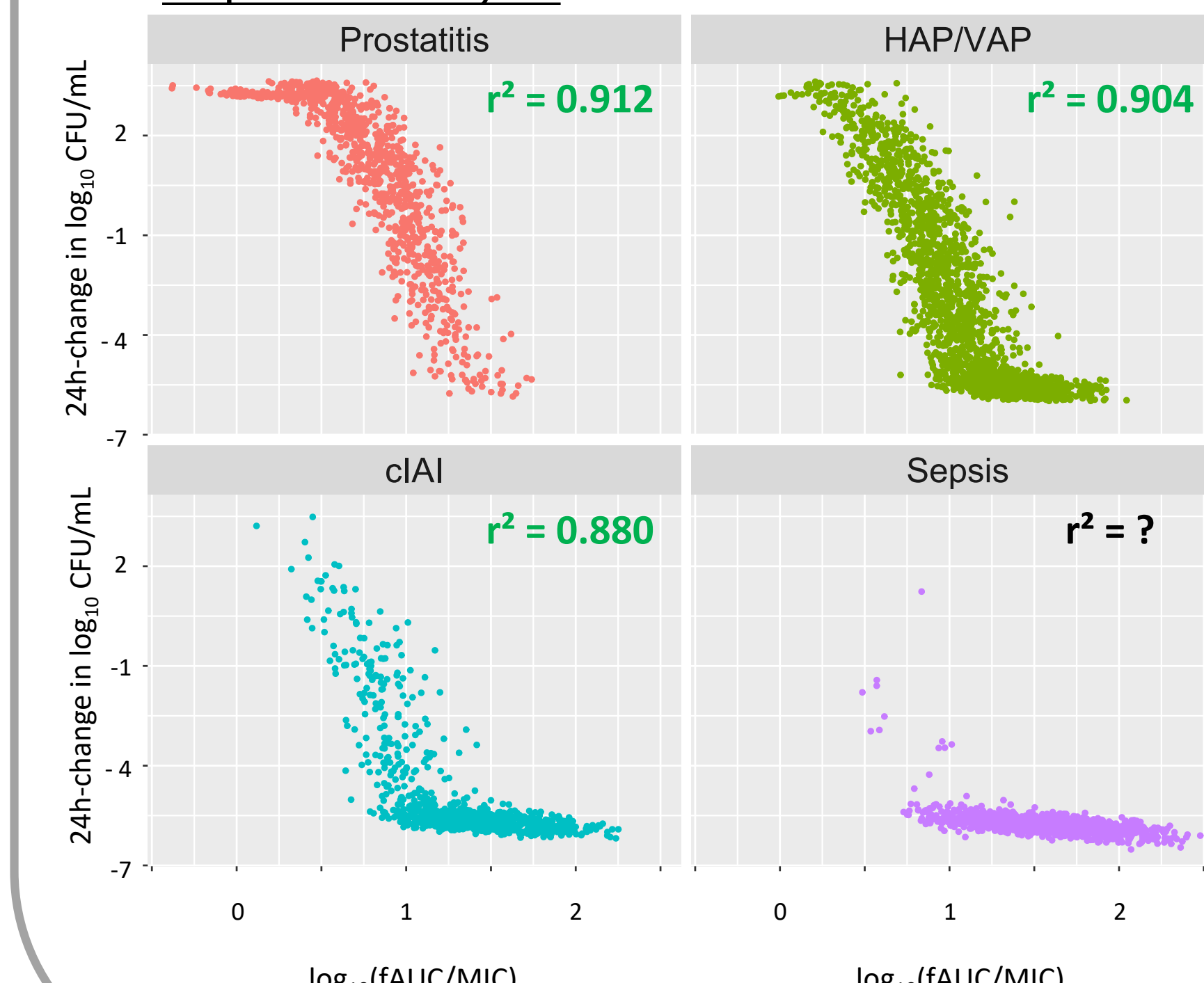
Baseline effect
Maximum effect
Sigmoidicity factor
Magnitude of X that is needed to achieve 50% of the Emax

PK/PD index in humans: fAUC/MIC *K. pneumoniae* (NCTC13438)

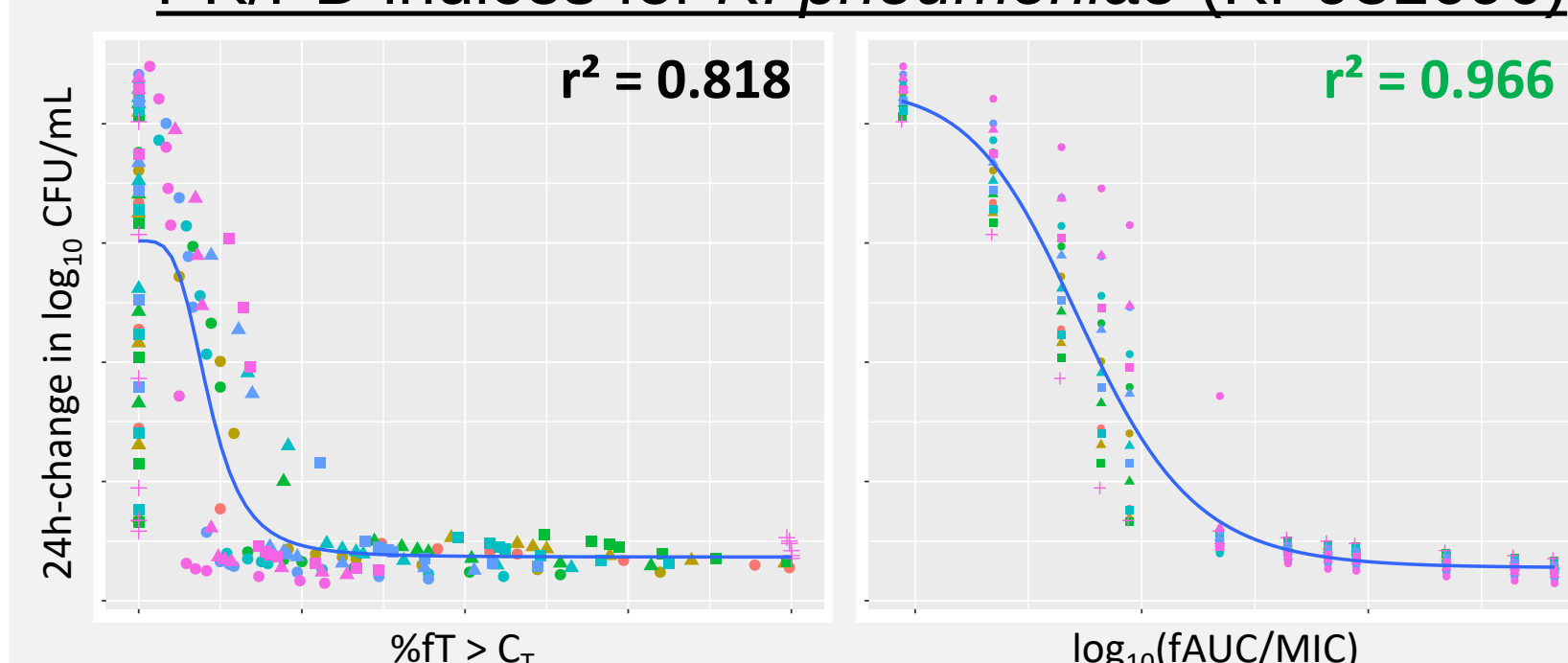
Mixed analysis



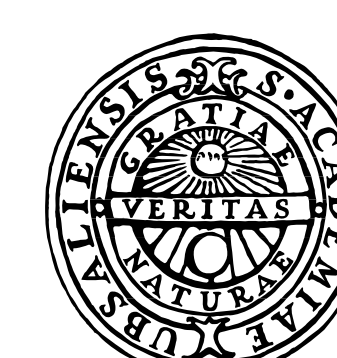
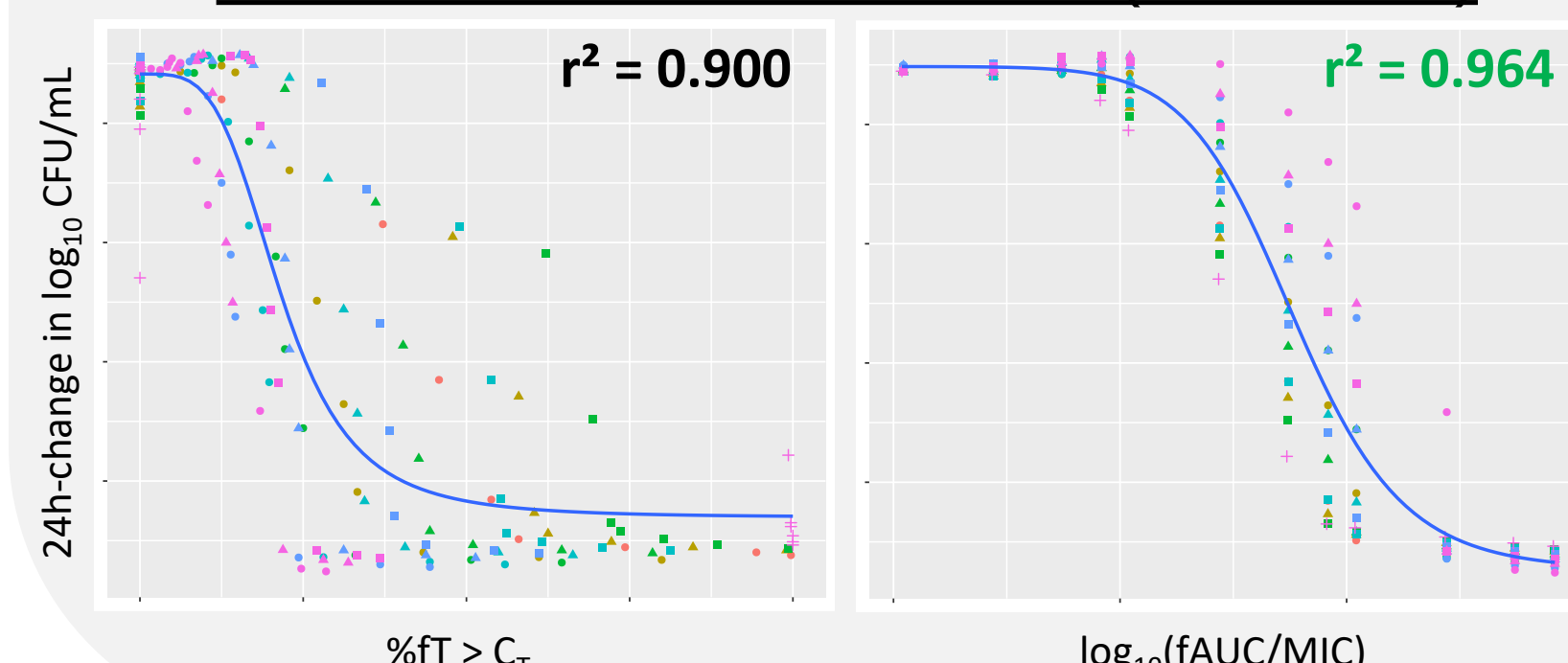
Separate analysis



PK/PD indices for *K. pneumoniae* (KP981690)



PK/PD indices for *E. cloacae* (EL871203)



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