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# A GENERAL PHARMACODYNAMIC INTERACTION MODELLING APPROACH TO ASSESS SEMI-MECHANISTIC SYNERGY OF CEFTAZIDIME/AVIBACTAM AND FOSFOMYCIN IN TIME KILL EXPERIMENTS

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## Introduction

Detailed understanding of *in vitro* pharmacodynamic (PD) drug interactions is essential to derive rational clinical antibiotic combination dosing regimens [1]. Modelling approaches as subpopulation synergy or different types of semi-mechanistic synergy can provide insights into PD drug interactions, but none is universally able to distinguish different interaction types and mechanisms [1]–[3] (Fig. 1). The general pharmacodynamic interaction model (GPDI) model can offer additional benefits in understanding PD drug interactions [1][4]. Therefore, the GPDI model was utilized as a novel semi-mechanistic modelling approach to describe *in vitro* time kill data of ceftazidime (CAZ)/avibactam and fosfomycin (FOS).

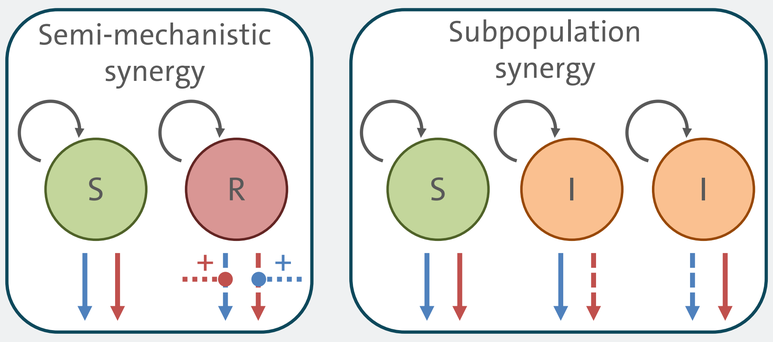



*Figure 1: PD interaction modelling approaches. Semi-mechanistic synergy describing PD interactions (left) compared to subpopulation synergy with independent killing rates for each drug and bacterial subpopulation (right). Bold arrows represent regular and dashed arrows reduced effects of two drugs (red and blue) affecting susceptible (S), resistant (R) or heteroresistant bacteria (I). A semi-mechanistic drug interaction is represented by a dotted line.*

## Methods

### *In vitro* time kill experiments

Experiments were conducted with a clinical *E. coli* strain expressing genes coding for CTX-M-15 and OXA-48 against CAZ and FOS over 30 h. Avibactam was kept at a constant concentration of 4 µg/mL.

### PD model development

The PD model was developed in NONMEM 7.5.0. Mono drug effects were described by maximum effect (Eq. 1) or power models (Eq. 2). Bliss Independence was used as additivity criterion [5]. Drug interactions were described by the GPDI model, identifying perpetrator and victim drugs in PD interactions. Different implementations of the GPDI term (Eq. 3) on the drug potency (EC50) or maximum drug effect (Emax) of the (S) and (R) subpopulation were evaluated. Inter-experimental variability was tested exponentially as variability on the different inocula. Models were selected based on model stability, condition number and the Akaike information criterion (AIC)[6].

$$E = \frac{Emax + C^{Hill}}{EC50^{Hill} \times C^{Hill}}$$

*Equation 1: sigmoidal Emax model*

$$E = Slope \times C^{Hill}$$

*Equation 2: Power model*

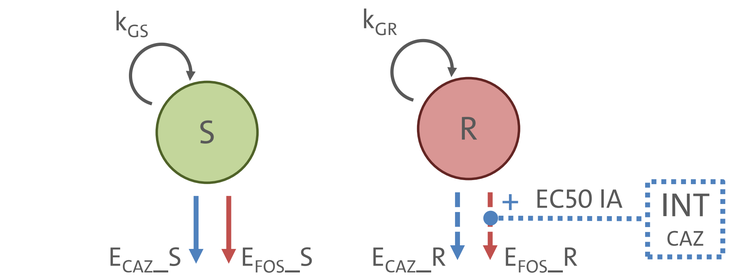
$$\theta_{GPDI} = \theta \times \left(1 + \frac{INT + C^{Hill_{INT}}}{EC50_{INT}^{Hill_{INT}} \times C^{Hill_{INT}}}\right)$$

*Equation 3: GPDI-term*

*Emax: maximum effect*
*C: drug concentration*
*Hill: sigmoidicity parameter*
*EC50: concentration of half maximal effect*
*Slope: linear drug effect*
$\theta_{GPDI}$: shifted *PD parameter (i.e. Emax, EC50) as a result of the GPDI model*
$\theta$: *PD parameter (i.e. Emax, EC50)*
*INT: fractional change of PD parameter*
$H_{INT}$: *sigmoidicity of interaction*
$EC50_{INT}$: *interaction potency*

## Results

The PD model included two bacterial sub-populations (Fig. 2): an (S) population susceptible to both drugs and a corresponding (R) population with reduced susceptibility to both antibiotics. Drug effects of CAZ and FOS on (S) and (R) were implemented as sigmoidal Emax models, the effect of FOS on (S) was supported by a power model. A directional interaction with CAZ as perpetrator altering the potency of FOS on the (R) population was identified. The model parameters are presented in Table 1. The model fit was evaluated by visual predictive checks (VPC) (Fig. 3). Parameter uncertainty was assessed by the SIR routine implemented in PsN 5.0.




| | | | | | |
|---|---|---|---|---|---|
| → | = drug effect on (S) | | $k_{GR}$ | = growth rate (R) |
| ⇢ | = drug effect on (R) | | $E_{CAZ\_S}$ | = drug effect of CAZ on (S) |
| ⋯• | = drug interaction | | $E_{CAZ\_R}$ | = drug effect of CAZ on (R) |
| S | = susceptible bacteria | | $E_{FOS\_S}$ | = drug effect of FOS on (S) |
| R | = resistant bacteria | | $E_{FOS\_R}$ | = drug effect of FOS on (R) |
| CAZ | = ceftazidime | | EC50 IA | = drug interaction affecting the EC50 |
| FOS | = fosfomycin | | INT | = drug interaction |
| $k_{GS}$ | = growth rate (S) | | | |

*Figure 2: Model structure of the semi-mechanistic GPDI-PD model*

*Table 1: Model estimates of the GPDI-PD model with their 95% confidence intervals (CI)*

| Parameter | Value | 95% CI |
|---|---|---|
| Inoculum susceptible bacteria (S) [$log_{10}$(CFU/mL)] | 6.81 | 6.68-6.95 |
| Inoculum resistant bacteria (R) [$log_{10}$(CFU/mL)] | 2.83 | 2.51-3.15 |
| Maximum bacterial capacity [$log_{10}$(CFU/mL)] | 8.84 | 8.64-9.07 |
| Growth rate (S) [$h^{-1}$] | 1.47 | 1.11-1.94 |
| Growth rate (R) [$h^{-1}$] | 0.54 | 0.43-0.67 |
| Emax of CAZ on (S) [$h^{-1}$] | 3.37 | 2.72-4.23 |
| EC50 of CAZ on (S) [mg/L] | 0.05 | 0.04-0.07 |
| Hill factor of CAZ on (S) | 1.48 | 0.90-2.41 |
| Emax of CAZ on (R) [$h^{-1}$] | 0.74 | 0.63-0.88 |
| EC50 of CAZ on (R) [mg/L] | 0.08 | 0.07-0.10 |
| Hill factor of CAZ on (R) | 3.45 | 2.26-5.18 |
| Slope effect of FOS on (S) [L/mg x $h^{-1}$] | 2.51 | 2.17-2.93 |
| Hill factor of FOS on (S) | 0.32 | 0.28-0.37 |
| Emax of FOS on (R) [$h^{-1}$] | 0.71 | 0.60-0.86 |
| EC50 of FOS on (R) [mg/L] | 5.07 | 4.13-6.18 |
| Hill factor of FOS on (R) | 2.57 | 1.76-3.96 |
| Maximum interaction shift | -0.89 | -0.91- -0.86 |
| EC50 of the interaction | 0.0011 | 0.0004-0.0015 |
| Hill factor of the interaction | 5.28 | 2.23-14.75 |
| Inter-experimental variability [%CV]: Inoculum resistant bacteria (R) | 36 | 31-44 |
| Additive residual variability [log(CFU/mL)] | 1.63 | 1.55-1.77 |

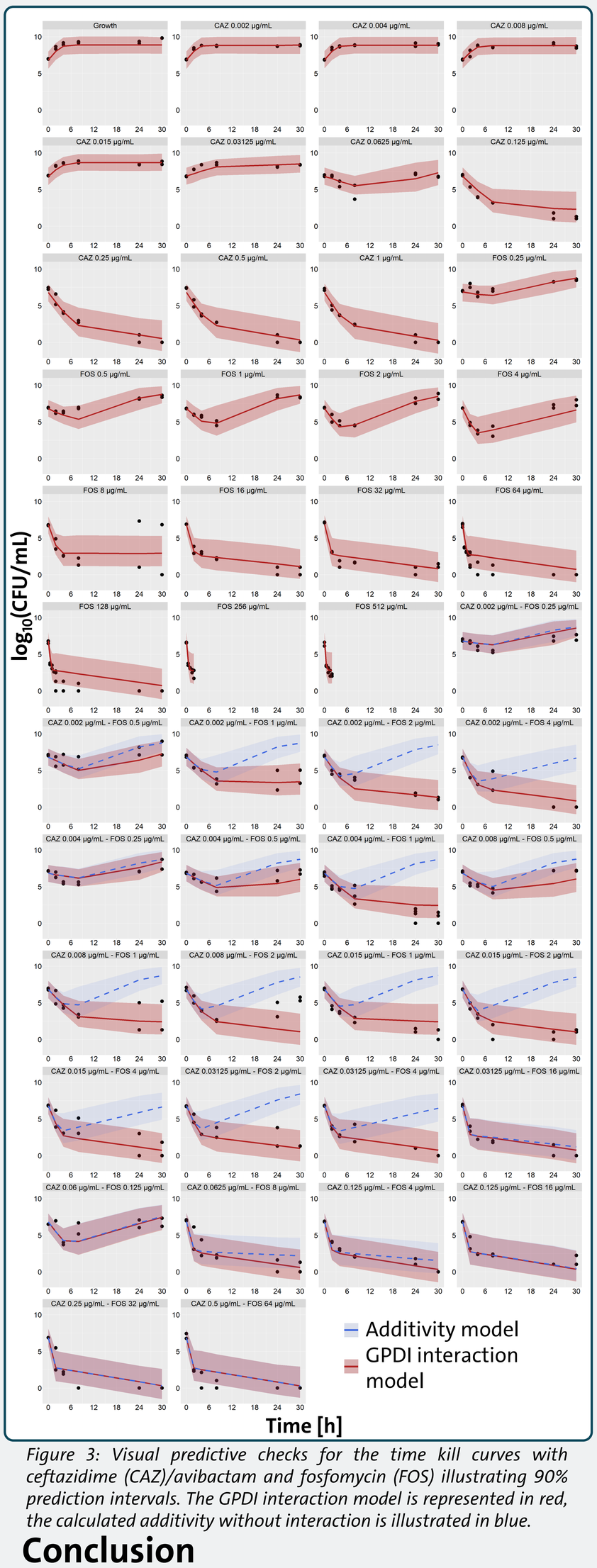



*Figure 3: Visual predictive checks for the time kill curves with ceftazidime (CAZ)/avibactam and fosfomycin (FOS) illustrating 90% prediction intervals. The GPDI interaction model is represented in red, the calculated additivity without interaction is illustrated in blue.*

## Conclusion

The GPDI model was successfully integrated as semi-mechanistic component for time kill data and:

I) described the interaction with CAZ altering the FOS effect directionally
II) quantified the interaction strength.

The model will be supplemented with a semi-mechanistic avibactam interaction model on CAZ to transfer the insights into the interaction from static into dynamic time kill experiments to ultimately derive highly efficacious clinical dosing regimens.

### References

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