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# PK/PD modelling of the CAMHB nutrients concentrations effect on polymyxin B antimicrobial activity against *Acinetobacter baumannii*

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## Background

Artificial culture media used for *in vitro* PK/PD experiments are intended to promote bacterial growth, not to mimic *in vivo* conditions, which complicates *in vitro* / *in vivo* extrapolations.

The aim of this study was to assess the effect of Cation Adjusted Mueller-Hinton Broth (CAMHB) dilutions on polymyxin B (PMB) activity against *Acinetobacter baumannii* *in vitro*, using a PK/PD modelling approach.

## Materials and methods

Time-kill experiments (TK) were performed using cation adjusted CAMHB at 100% or diluted at 50%, 25% and 10%, with 3 *A.baumannii* strains: ATCC 19606 (MIC<sub>PMB</sub>=1mg/L), and two clinical isolates<sup>1</sup> AB121 (MIC<sub>PMB</sub>=0.5-1mg/L), and AB122 (MIC<sub>PMB</sub>=32-64mg/L). The starting inoculum for TK was 10<sup>6</sup> CFU/mL. PMB concentrations were ranging between 0.125 and 256mg/L. Bacterial counts were determined (3 replicates) at various times up to 30h, and data were used to develop a PK/PD model with NONMEM®. Data for each strain were analysed separately.

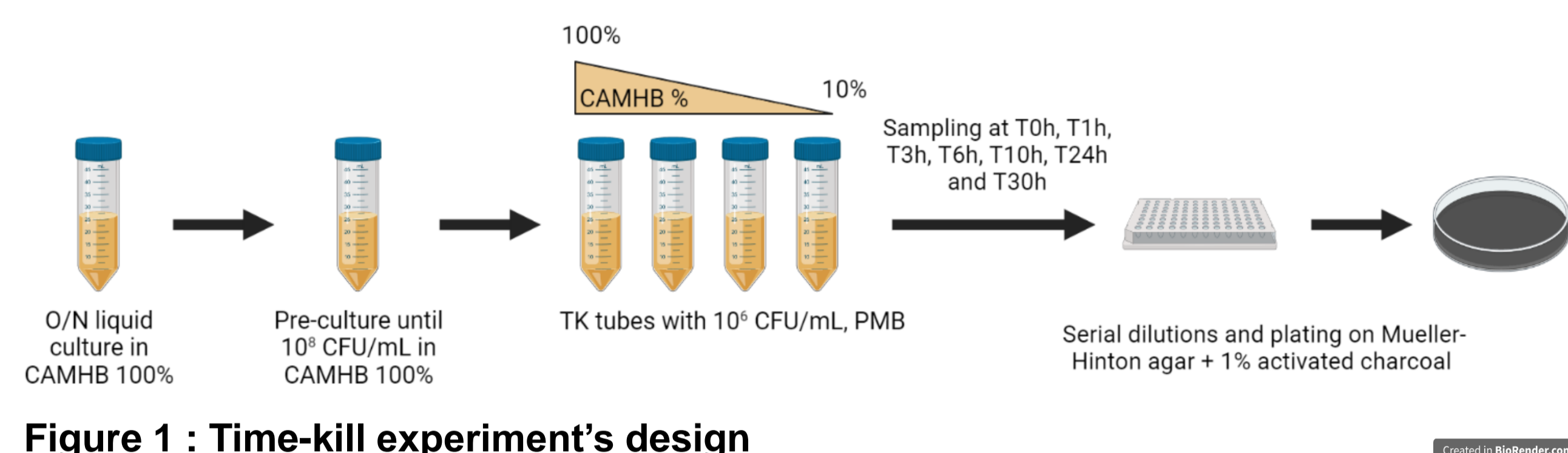


Figure 1 : Time-kill experiment's design

## Results

CAMHB dilution had no effect on bacterial growth (controls: Figure 3, 1st column for each strain), nor on the initial rapid CFU decay in the presence of PMB. However the regrowth observed for concentrations up to 8xMIC at CAMHB 100%, was progressively reduced with dilutions (Figure 3).

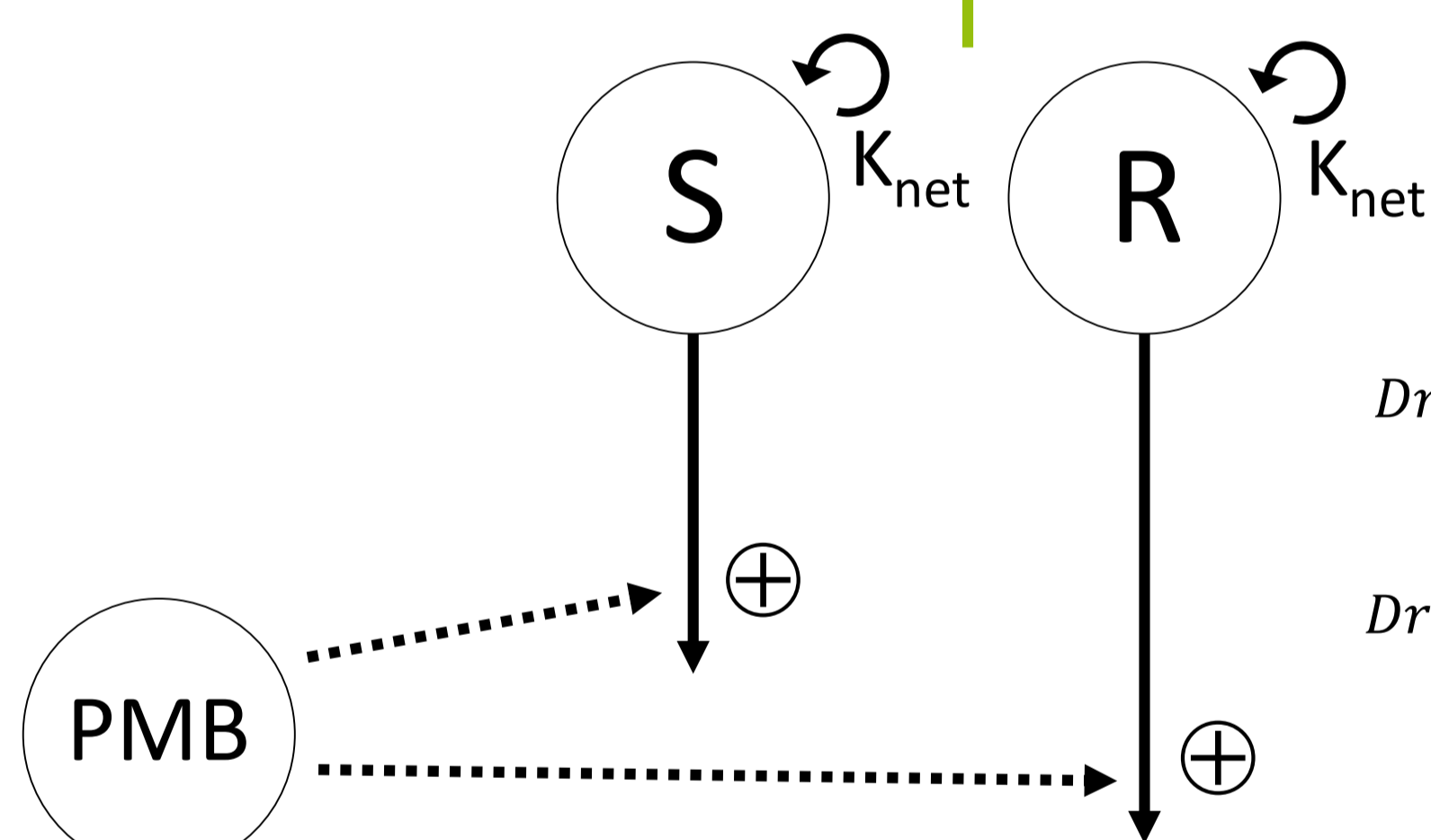
A PK/PD model including two bacterial subpopulations with different susceptibilities (S/R)<sup>2</sup> was used to describe TK data (Figure 2). The medium effect was characterized by an increase of PMB bactericidal effect with nutrients depletion, modeled by an increase of the Emax<sub>R</sub> and EC<sub>50</sub><sub>R</sub> for ATCC 19606 and AB121 but by a decrease of EC<sub>50</sub> (common to both S/R subpopulations) for AB122 (Figure 4).

Because cations interfere with PMB activity<sup>3</sup> complementary experiments with adjusted Ca<sup>2+</sup> and Mg<sup>2+</sup> concentrations were conducted and showed that cations depletion was not responsible for the observed medium effect (data not shown).

### ATCC 19606 & AB121

$$\text{Drug effect}_S = \frac{Emax_S \times PMB^y}{EC_{50}^y + PMB^y}$$

$$\text{Drug effect}_R = \frac{Emax_R \times PMB^y}{EC_{50}^y + PMB^y}$$



### AB122

$$\text{Drug effect}_S = \frac{Emax_S \times PMB^y}{EC_{50}^y + PMB^y}$$

$$\text{Drug effect}_R = \frac{Emax_R \times PMB^y}{EC_{50}^y + PMB^y}$$

$$Emax_R = A \times [CAMHB\%]^B$$

$$EC_{50R} = \frac{A \times [CAMHB\%]^{20}}{B^{20} + [CAMHB\%]^{20}}$$

$$EC_{50} = A \times [CAMHB\%]^2 - B \times [CAMHB\%] + C$$

### Figure 2 : PK/PD model representation

*K<sub>net</sub>*: apparent growth rate constant (h<sup>-1</sup>)

*S*: susceptible bacterial subpopulation

*R*: resistant bacterial subpopulation

*PMB*: polymyxin B concentration (mg/L)

*Emax*: maximum rate of PMB effect (h<sup>-1</sup>)

*EC<sub>50</sub>*: PMB concentration needed to reach 50% of *Emax* (mg/L)

*y*: Hill coefficient

### ATCC 19606

### AB121

### AB122

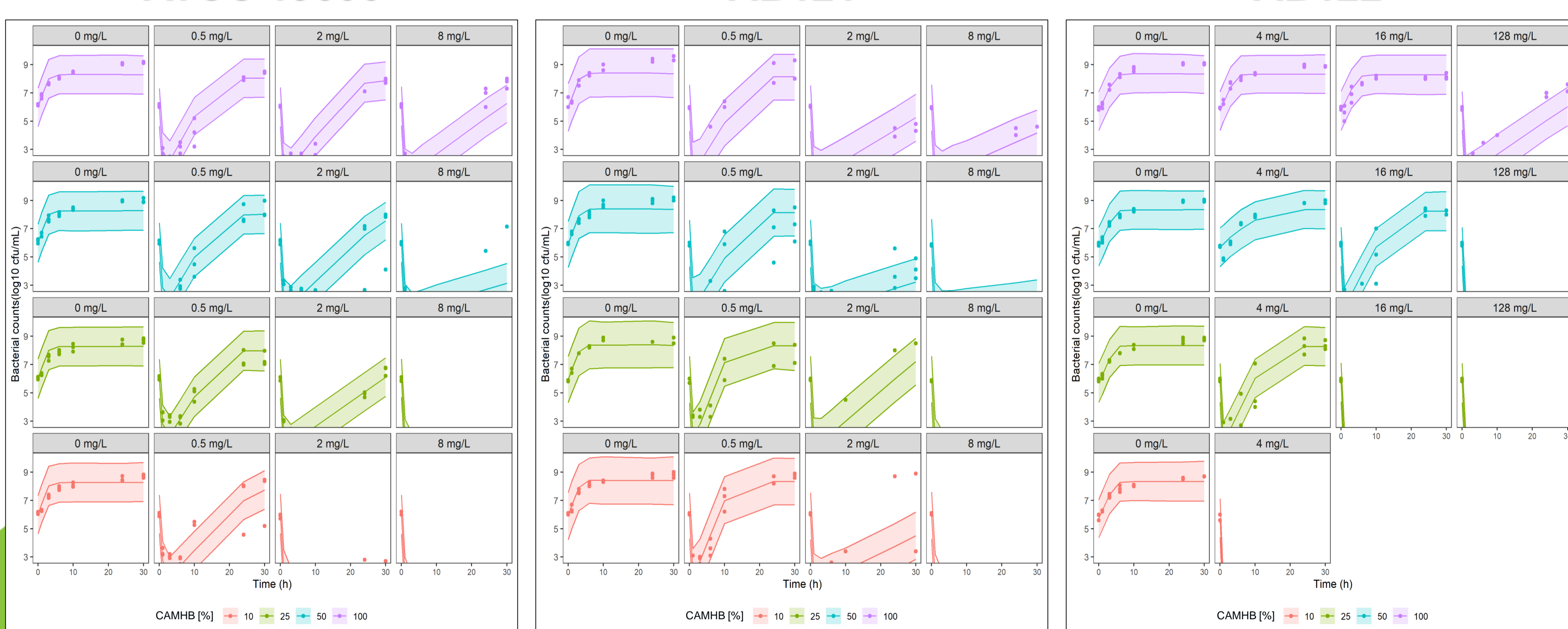
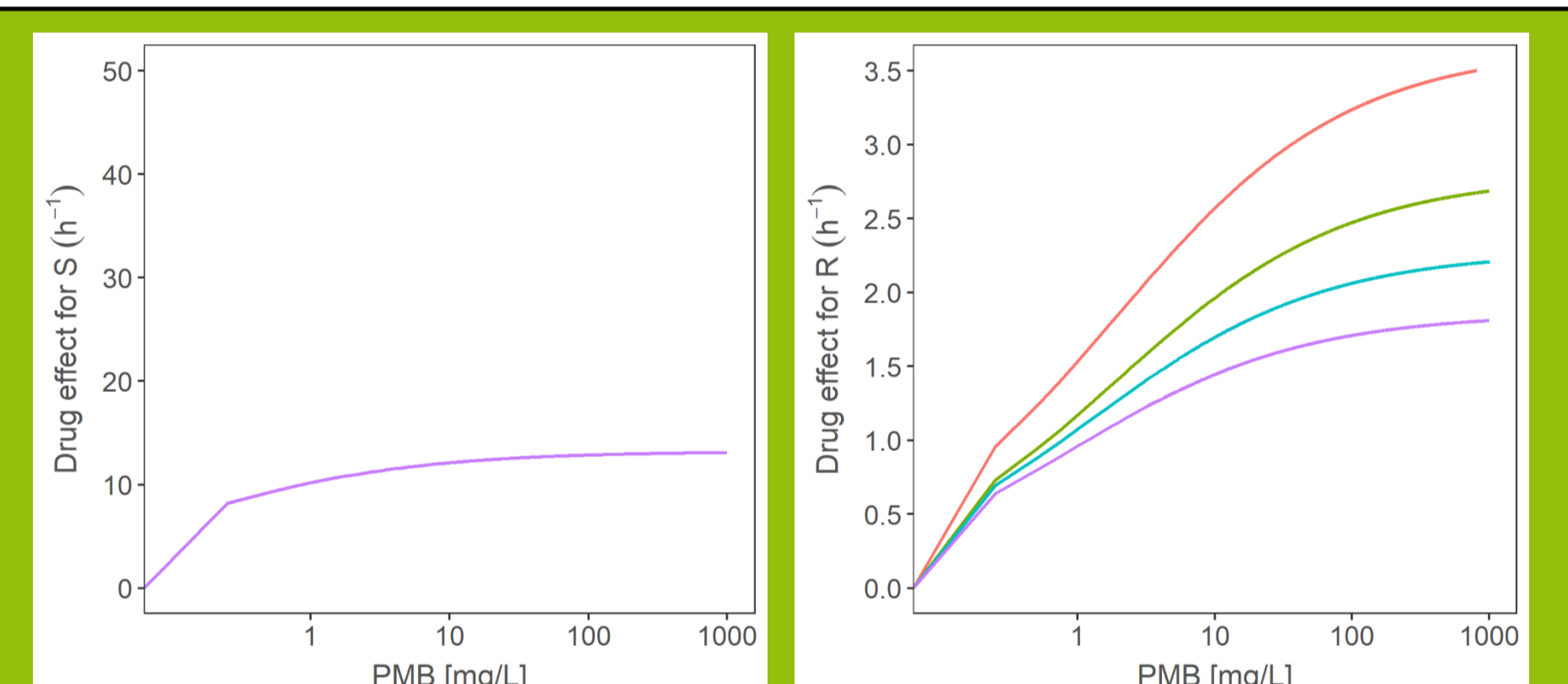
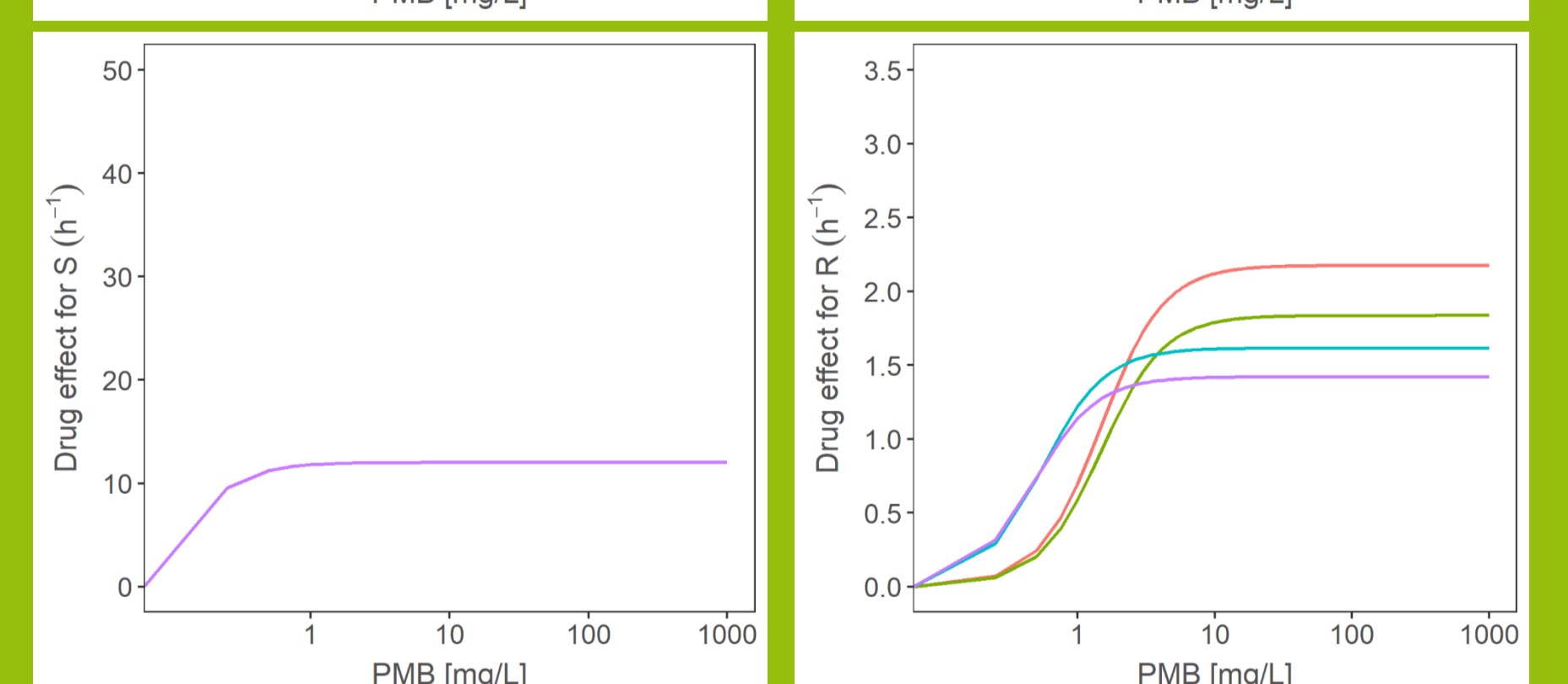


Figure 3 : Visual predictive checks (VPC) for the final model. Circles represent experimental data, solid lines depict the mean of simulated data and colored areas depict the 90% prediction interval for 1,000 simulated profiles.

### ATCC 19606



### AB121



### AB122

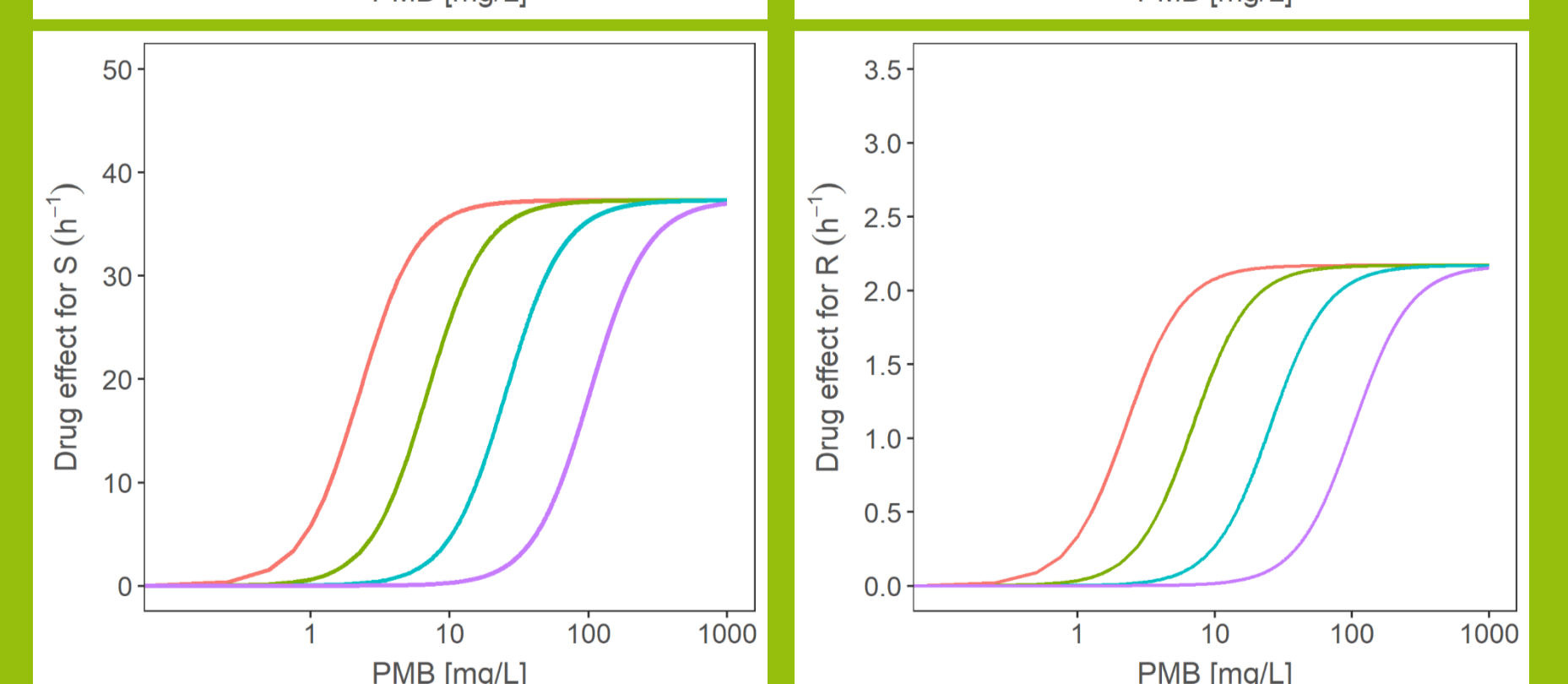


Figure 4 : Drug effect (bacterial killing rate) as a function of PMB concentration and CAMHB dilution for susceptible and resistant bacterial subpopulations.

## Conclusion

PK/PD modelling demonstrated an impaired apparent regrowth of *A.baumannii* with nutrients depletion, presumably due to an increased PMB bactericidal effect.

Further experiments would be necessary to understand this effect which might change the mutation frequency or impact the triggering of adaptation mechanism(s) responsible of the apparent bacterial regrowth.

### References:

- Jaidane et al., 2018 International Journal of Antimicrobial Agents
- Mouton JW et al., 1997 Antimicrob Agents Chemotherapy
- Bulitta et al., 2010 Antimicrob Agents Chemotherapy

