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Semi-mechanistic PK-PD modelling of combined polymyxin B and minocycline against a polymyxin-resistant strain of *Acinetobacter baumannii*

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**Analysis of Velopharyngeal Function and Speech outcomes of
Sommerlad Palatoplasty Combined with Sphincter Pharyngoplasty
in Surgical Repair of Older Patients with Cleft Palate: experience
from a major craniofacial surgery center in eastern China**

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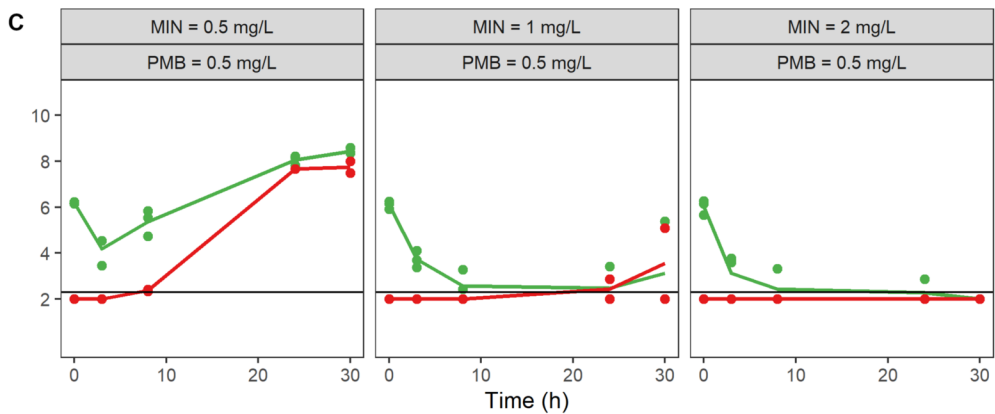
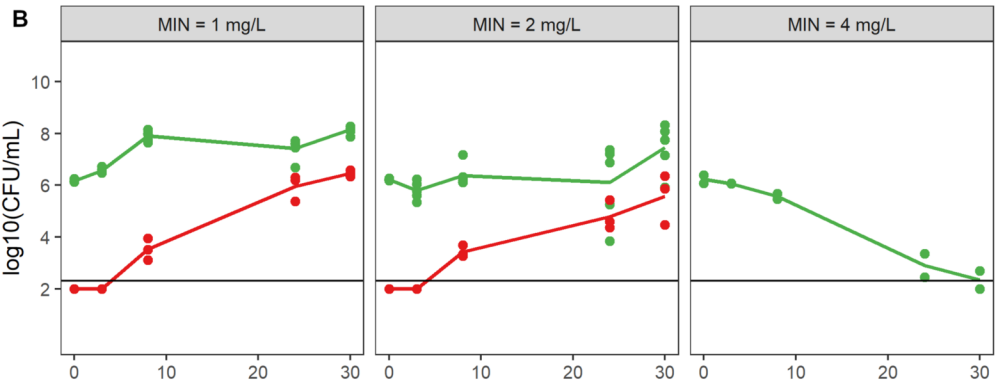
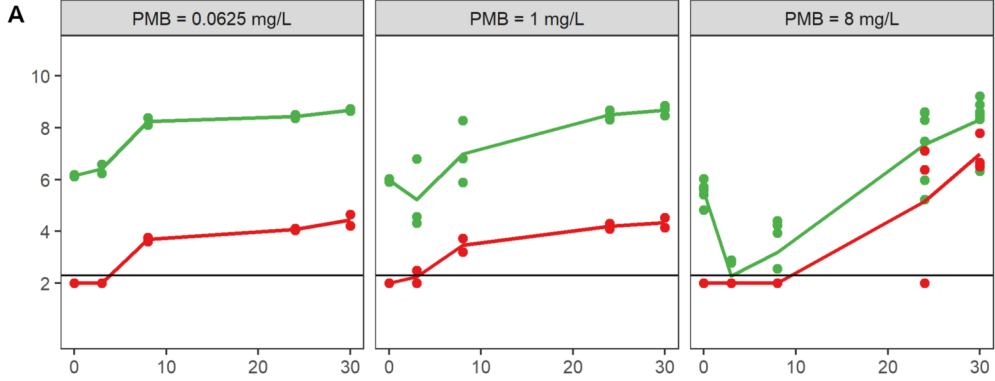
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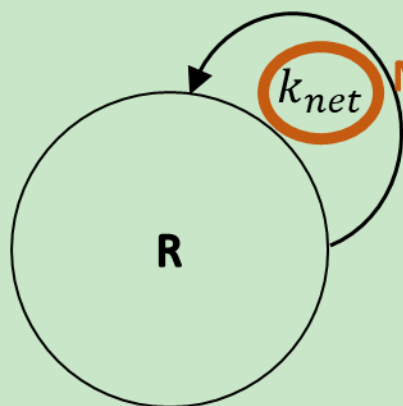
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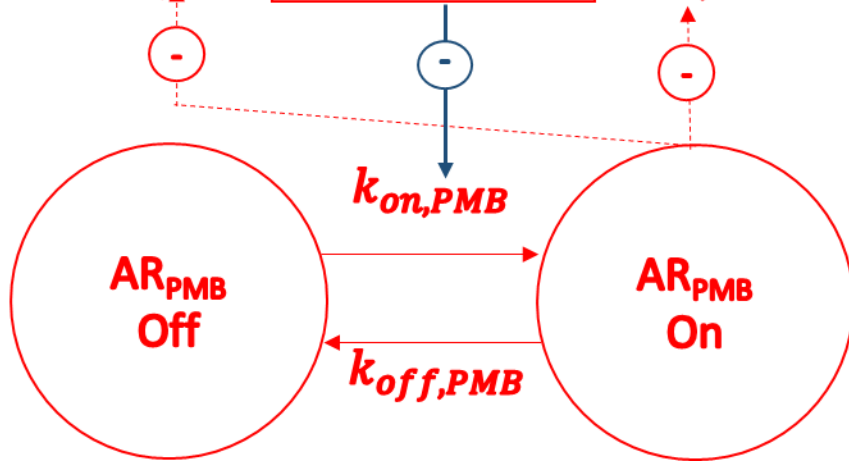
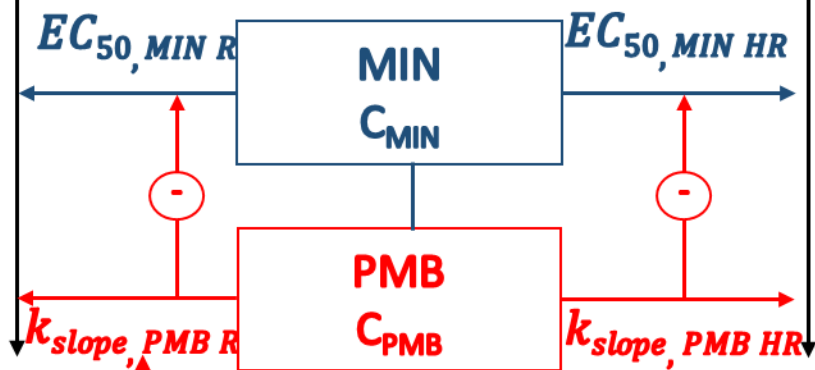
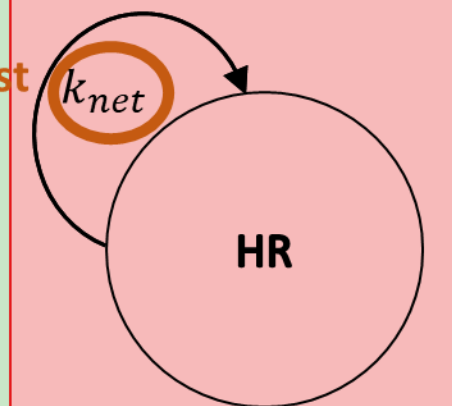
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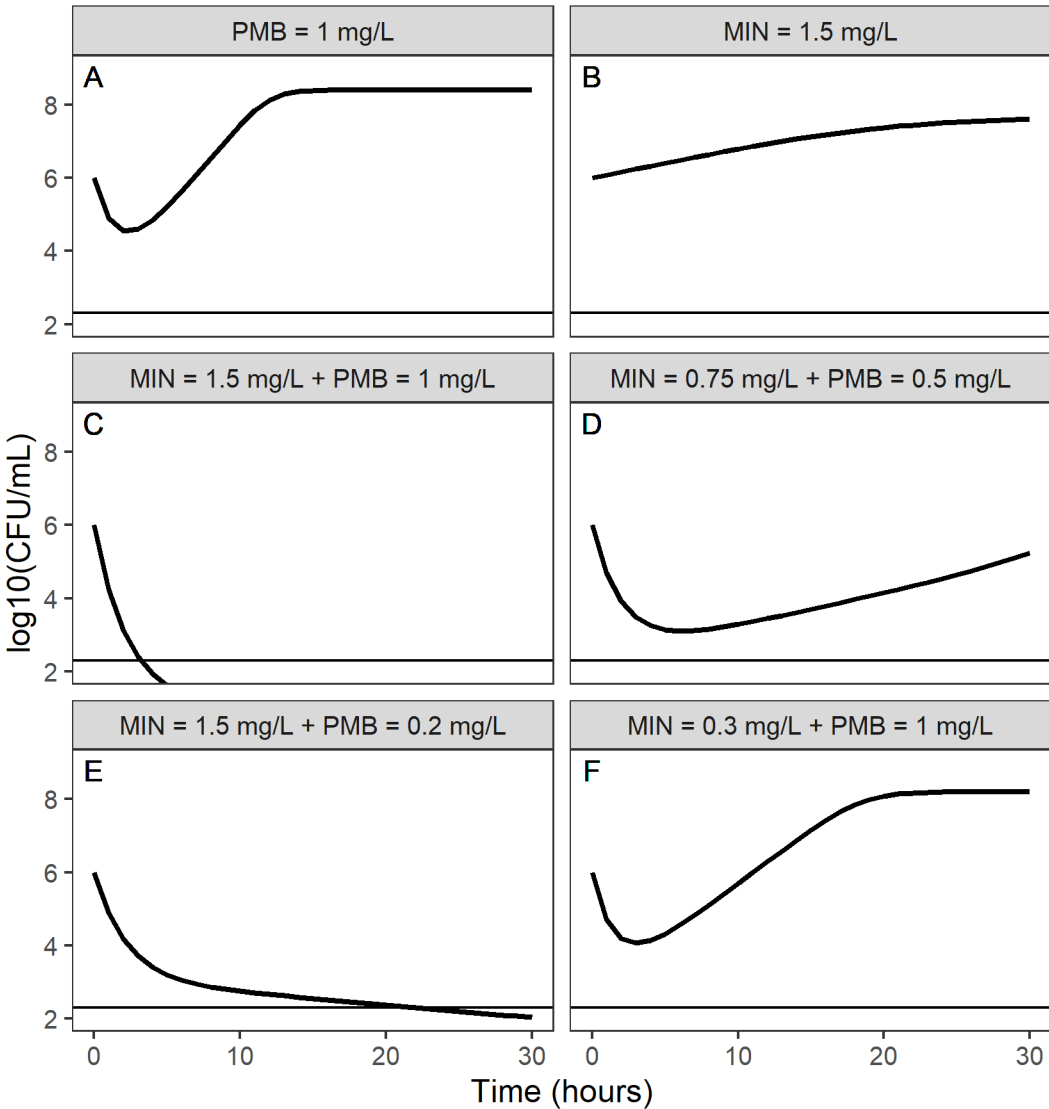
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No Fitness cost





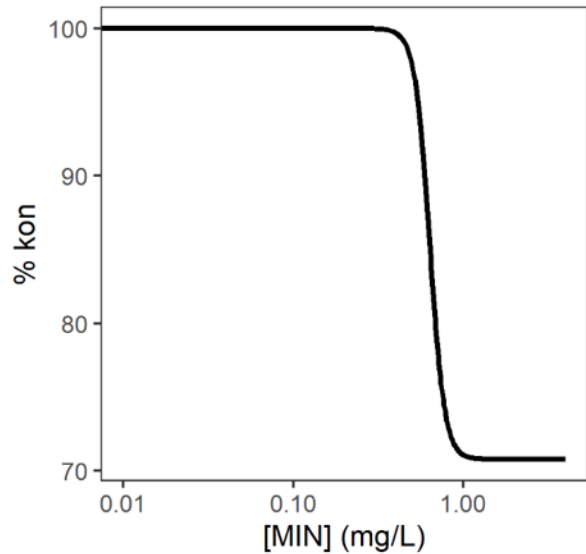
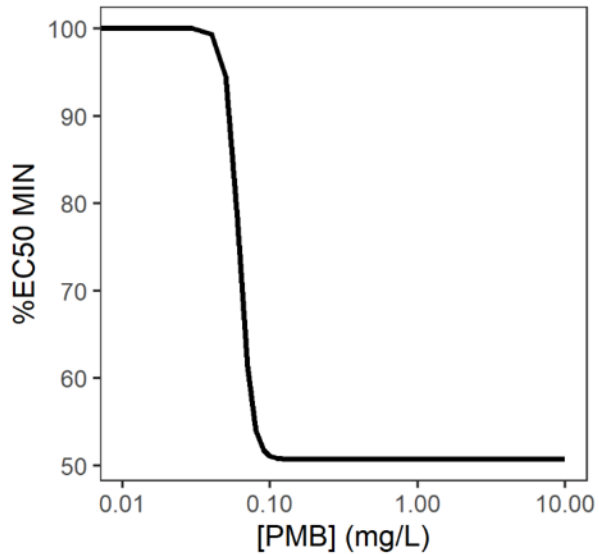
A**B**

Table 1. Final model parameters

Parameter	Description	Value [CI95%]*
k_{net} (h^{-1})	Apparent growth rate constant	1.11 [1.03 -1.20]
B_{max} (CFU/mL)	Maximum capacity of the in vitro system	$10^{8.41}$ [$10^{8.34}$ - $10^{8.48}$]
mutf	Fraction of resistant bacteria at time = 0	$10^{-5.10}$ [$10^{-5.28}$ - $10^{-4.92}$]
Polymyxin B		
$k_{slope,PMB-R}$ (L/mg·h)	Kill rate constant due to polymyxin B on resistant subpopulation	4.94 [4.32 -5.59]
$k_{slope,PMB-HR}$ (L/mg·h)	Kill rate constant due to polymyxin B on highly resistant subpopulation	3.00 [2.57-3.51]
γ_{PMB}	Power parameter for polymyxin B effect on both subpopulations	0.292 [0.265-0.321]
$k_{on0,PMB}$ (h^{-1})	Rate constant for development of adaptive resistance to polymyxin B in absence of minocycline	0.646 [0.538 -0.760]
$k_{off,PMB}$ (h^{-1})	Rate constant for reversal of adaptive resistant to polymyxin B	0 (fixed)
Minocycline		
$E_{max,MIN}$ (h^{-1})	Maximum rate constant for minocycline effect on both subpopulations	1.41 [1.31 -1.51]
$EC_{50,MIN-R}$ (mg/L)	Minocycline concentration for which the effect is 50% on the resistant subpopulation	1.02 [0.90-1.13]
$EC_{50,MIN-HR}$ (mg/L)	Minocycline concentration for which the effect is 50% on the highly resistant subpopulation	1.67 [1.46-1.86]
γ_{MIN}	Power parameter for minocycline effect on both subpopulations	1.59 [1.40-1.79]
INTERACTION		
INT_{PMB} (%)	Maximal reduction of $EC_{50,MIN-S}$ and $EC_{50,MIN-R}$ due to potentiation by polymyxin B	-49.3 [-55.0- -42.6]
$EC_{50,INT-PMB}$ (mg/L)	Polymyxin B concentration needed to achieve 50% of INT_{PMB}	0.0615 [0.0.570 – 0.0673]
$H_{INT-PMB}$	Power parameter for polymyxin B potentiation of minocycline effect	10 (fixed)
INT_{ADA} (%)	Maximal reduction of k_{on} due to inhibition by minocycline	-29.2 [-39.7 - -19.8]
$EC_{50,INT-ADA}$ (mg/L)	Minocycline concentration needed to reach 50% of INT_{ADA}	0.634 [0.547-0.801]
$H_{INT-ADA}$	Power parameter for minocycline inhibition of k_{on}	10 (fixed)
RESIDUALS		
$\sigma_{total\ bacteria}$ ($\log_{10}CFU/mL$)	Additive residual error on \log_{10} scale for total bacteria count	0.474 [0.420 – 0.546]

σ highly resistant bacteria (log ₁₀ CFU/mL)	Additive residual error on log ₁₀ scale for highly resistant bacteria count	1.28 [1.07– 1.56]
Correlation	Correlation between σ _{total bacteria} and σ highly resistant bacteria	0.426 [0.317 - 0.537]

*CI obtained by SIR