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

Vincent Aranzana-Climent, Julien Buyck, Younes Smani, Jerónimo Pachón-Diaz, Sandrine Marchand, William Couet, Nicolas Grégoire

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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

Authors and affiliations:

BiYin Liu, XiaoXuan Chen, Jun Cao,Yong Lu

Department of Oral and Maxillofacial Surgery, Affiliated Stomatology Hospital, Medical School of Nanjing University,

No. 30 Zhong Yang's Road, Xuan Wu, Nanjing 210008, Jiangsu Province, China

Corresponding Author：

Yong Lu, PhD, Nanjing Stomatology Hospital, Medical School of Nanjing University

Permanent address:

No. 30 Zhong Yang's Road, Xuan Wu, Nanjing 210008, Jiangsu Province, China

E-mail address: cleft_surgery@sina.com

Office phone: +8602583620341

Mobile Phone: +8613815418598

Tax: +8602583620100

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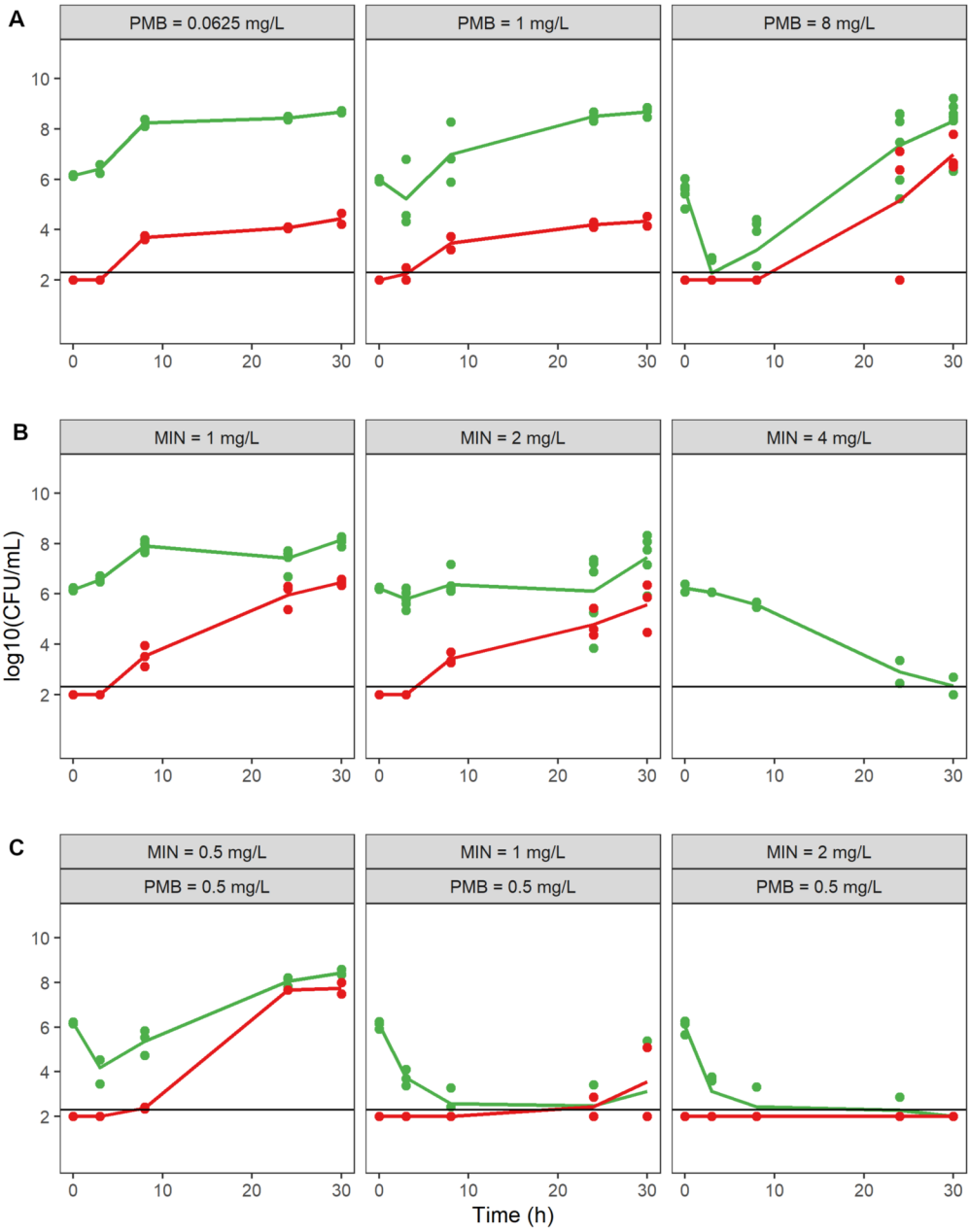
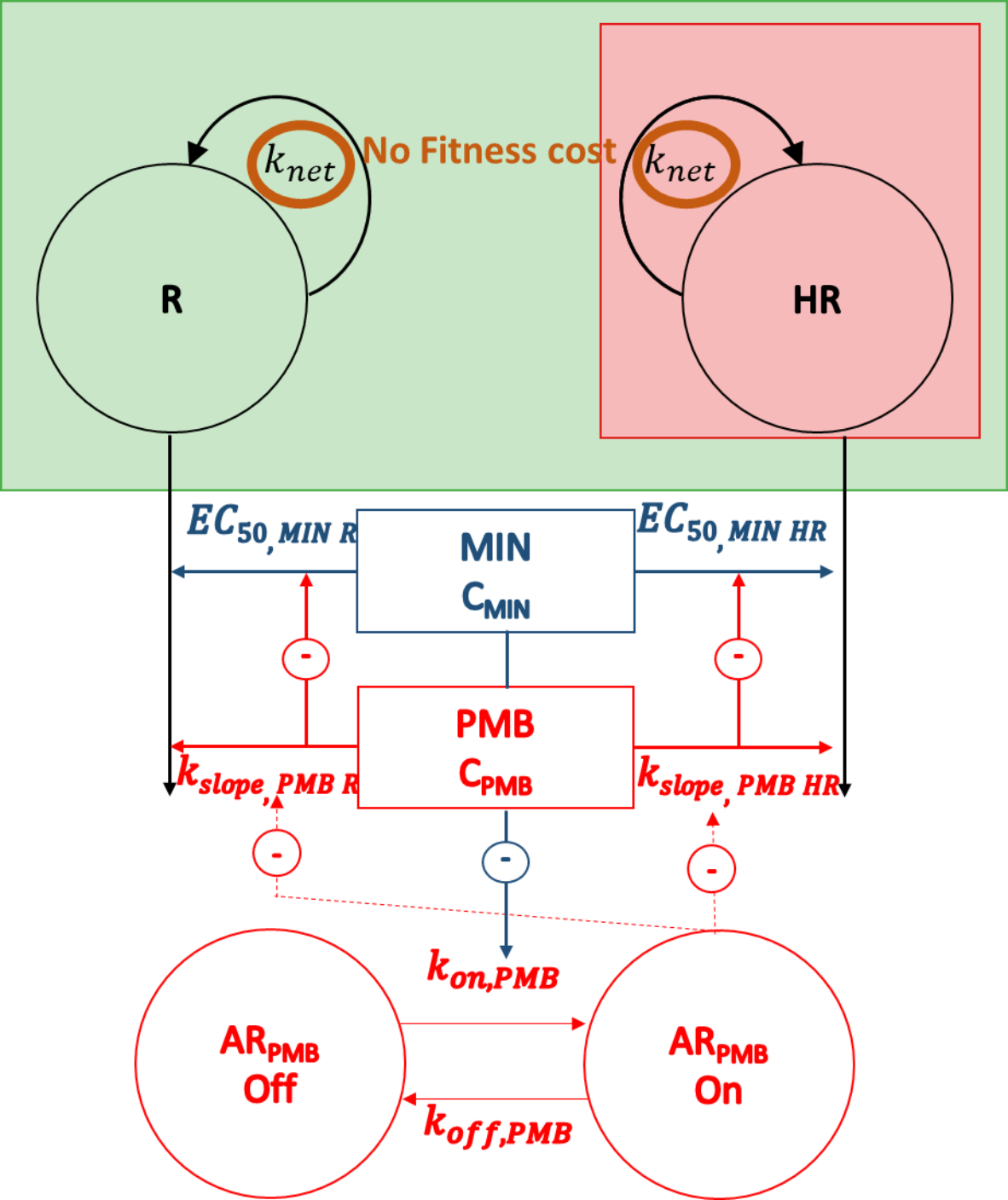
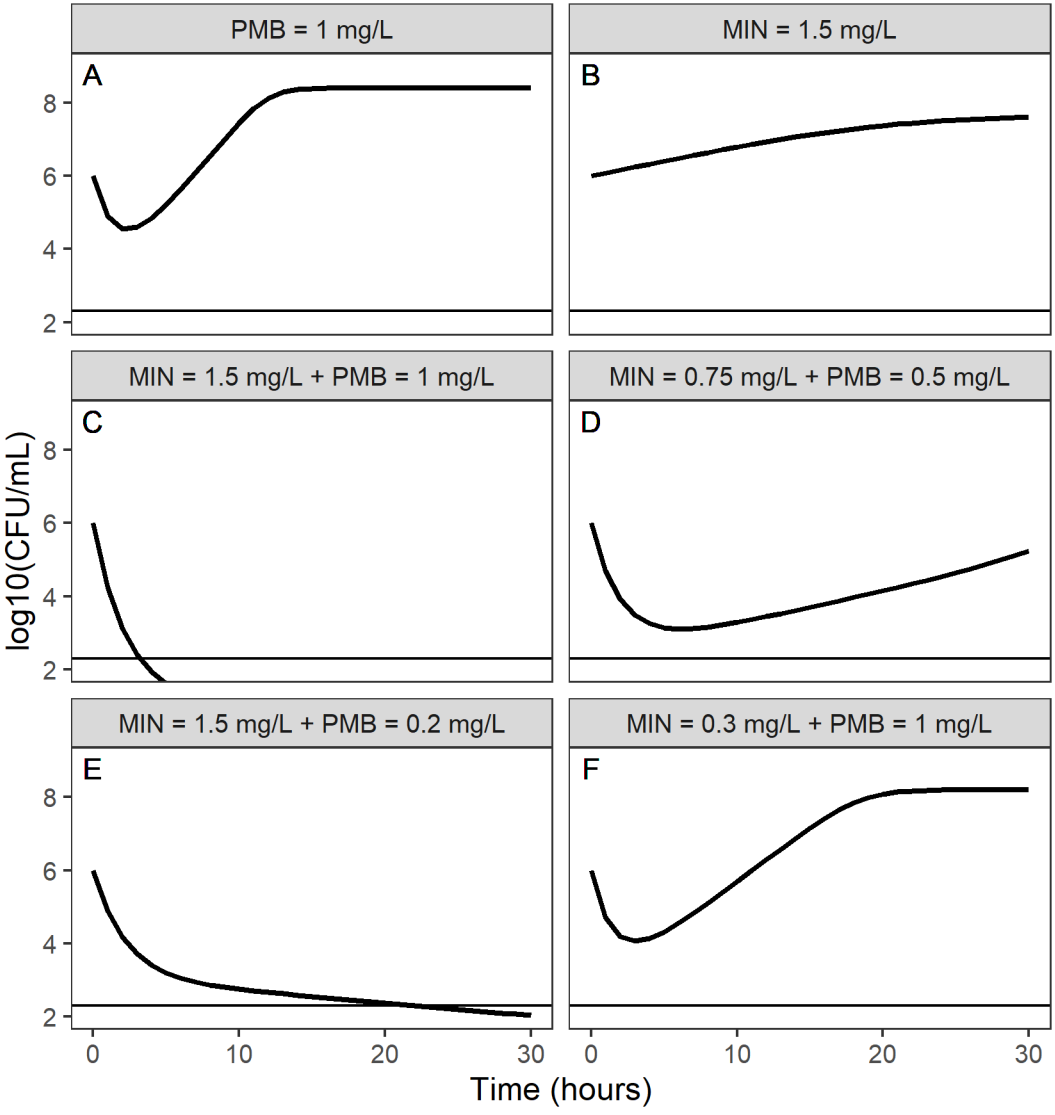

A
PMB = 0.0625 mg/L
PMB = 1 mg/L
PMB = 8 mg/L
B
MIN = 1 mg/L
MIN = 2 mg/L
MIN = 4 mg/L
log10(CFU/mL)
C
MIN = 0.5 mg/L
PMB = 0.5 mg/L
MIN = 1 mg/L
PMB = 0.5 mg/L
MIN = 2 mg/L
PMB = 0.5 mg/L
Time (h)


k_{net}
No Fitness cost
k_{net}
R
HR
$EC_{50,MIN\ R}$
MIN
C_{MIN}
$EC_{50,MIN\ HR}$
-
-
PMB
C_{PMB}
$k_{slope,PMB\ R}$
$k_{slope,PMB\ HR}$
-
-
-
$k_{on,PMB}$
AR_{PMB} Off
AR_{PMB} On
$k_{off,PMB}$


PMB = 1 mg/L
A
MIN = 1.5 mg/L
B
MIN = 1.5 mg/L + PMB = 1 mg/L
C
MIN = 0.75 mg/L + PMB = 0.5 mg/L
D
MIN = 1.5 mg/L + PMB = 0.2 mg/L
E
MIN = 0.3 mg/L + PMB = 1 mg/L
F
log10(CFU/mL)
2
4
6
8
0
10
20
30
Time (hours)

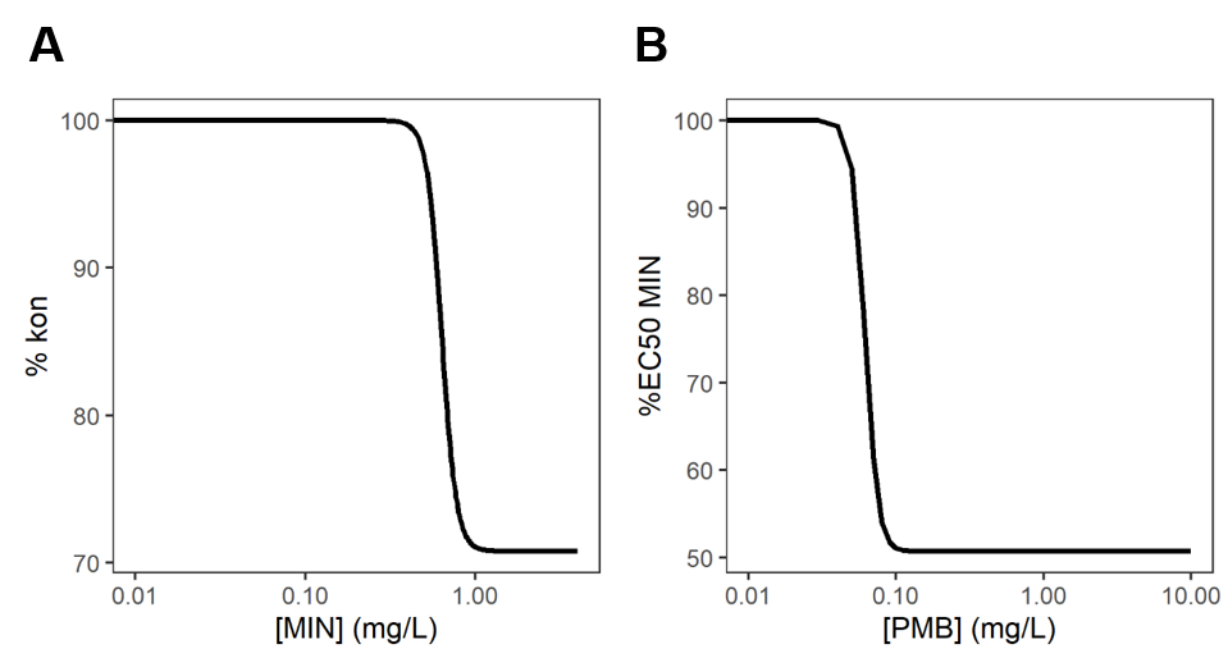

A
100
90
80
70
% kon
0.01
0.10
1.00
[MIN] (mg/L)
B
100
90
80
70
60
50
%EC50 MIN
0.01
0.10
1.00
10.00
[PMB] (mg/L)

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]

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

*CI obtained by SIR