Use of a semi-mechanistic PK-PD model to quantify the combination effect of polymyxin B and minocycline against polymyxin-resistant *Acinetobacter baumannii*

Vincent ARANZANA-CLIMENT

U1070 – Pharmacology of Antimicrobial Agents– Poitiers, France

ISAP Young Investigator Meeting– 12 April 2019

Goal of the study

Investigate the *in vitro* determinants of polymyxin B + minocycline efficacy against a polymyxin resistant *A. baumannii* strain

Strain

1 *Acinetobacter baumannii* clinical isolate

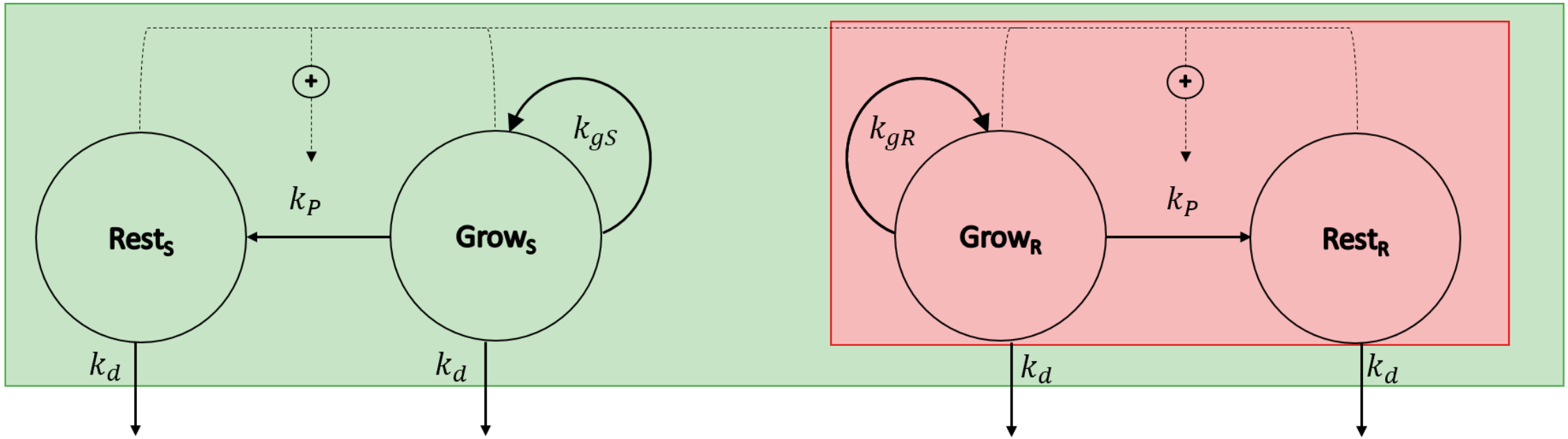
Strain	MIC PMB (mg/L)	Breakpoint (mg/L)	MIC MIN (mg/L)	Breakpoint (mg/L)
CR17	**8**	>4	**4**	>4

López-Rojas et al., JID, 2011

Time kill experiments

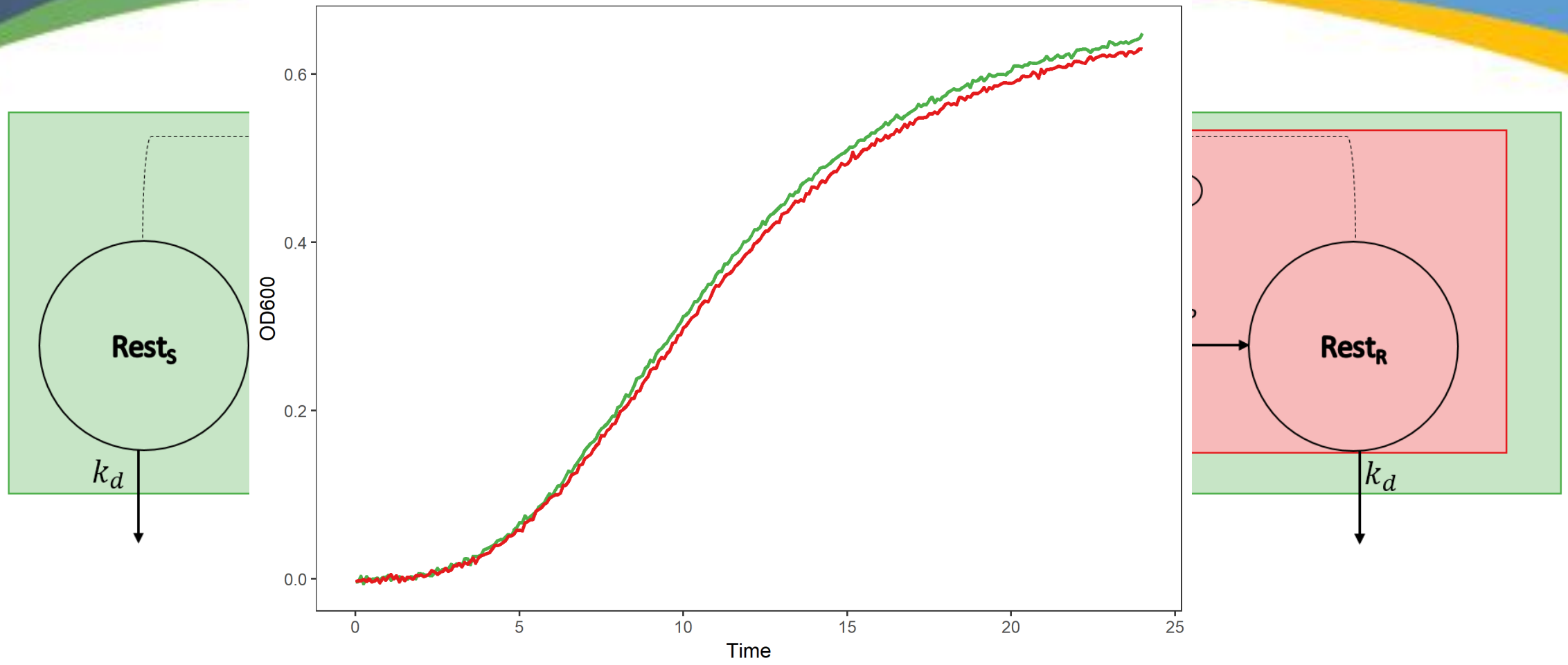
- Antibiotic concentrations
  - Polymyxin B : 0.0625 mg/L to 8 mg/L (1/128 to 1*MIC)
  - Minocycline : 0.25 mg/L to 16 mg/L (1/16 to 4*MIC)
- Antibiotics alone and in combination
- N≥2 for each condition
- 5 timepoints : 0, 3, 8, 24 and 30h
- 2 platings by timepoint :
  - Drug free plate
  - Plate containing 64 mg/L of PMB (8*MIC)

Mathematical modelling

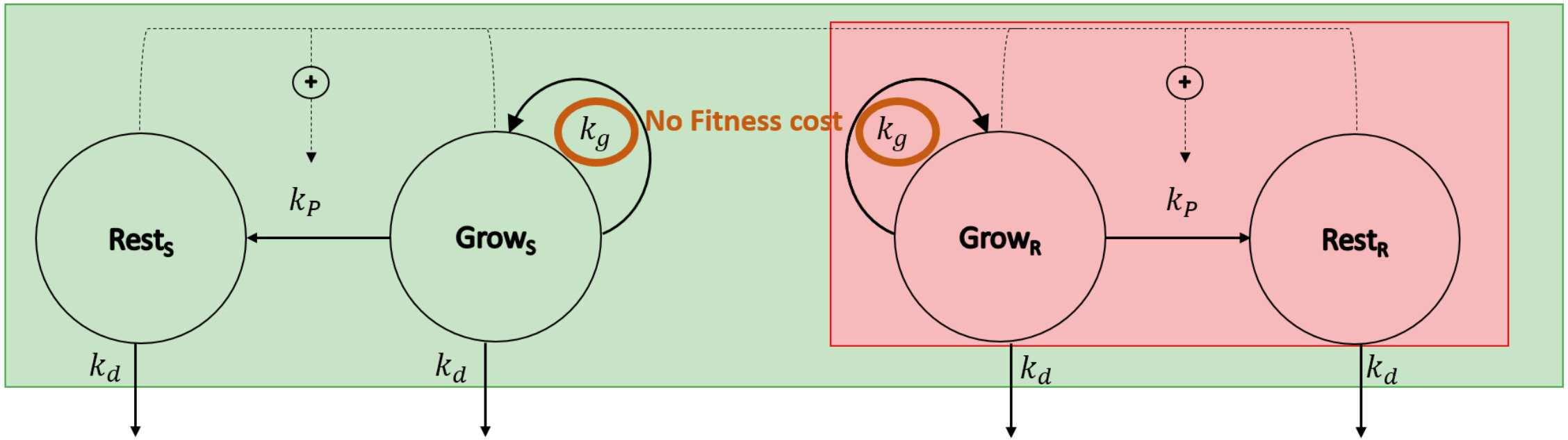


Nielsen and Friberg., Phar. Rev., 2013

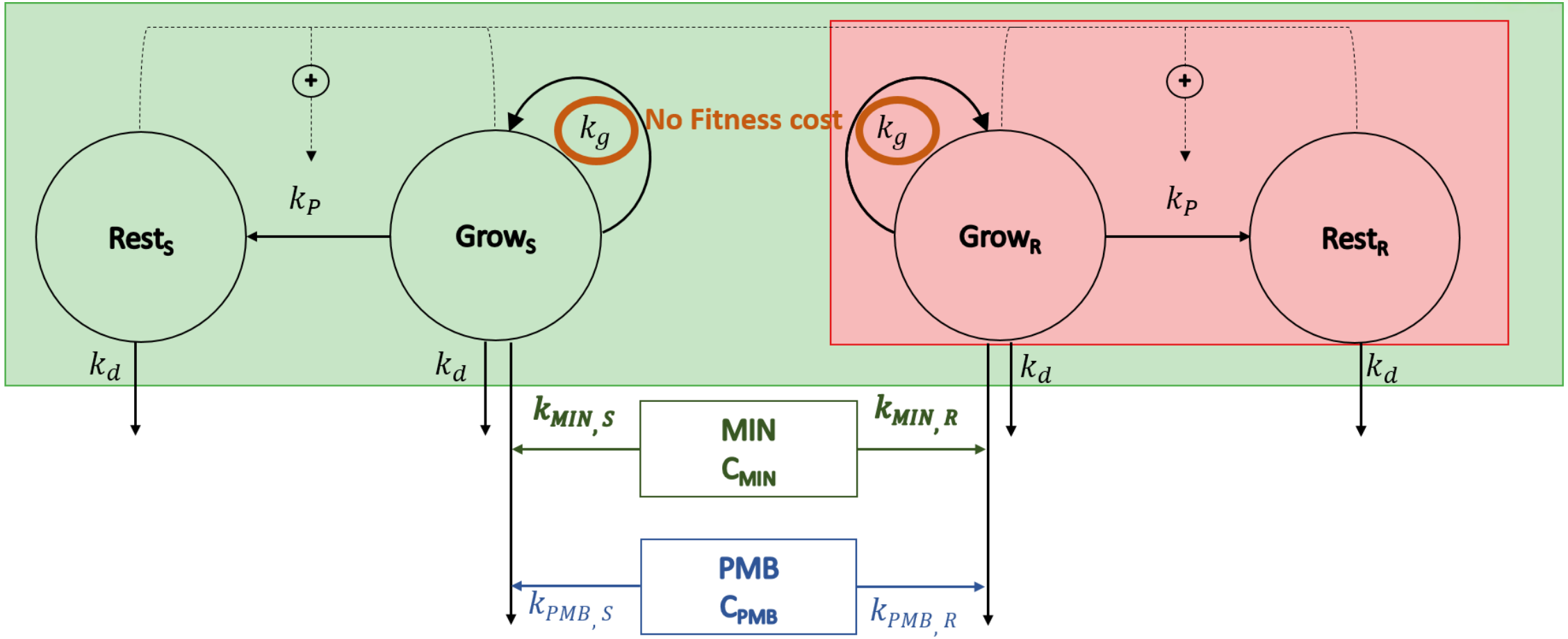
Mathematical modelling



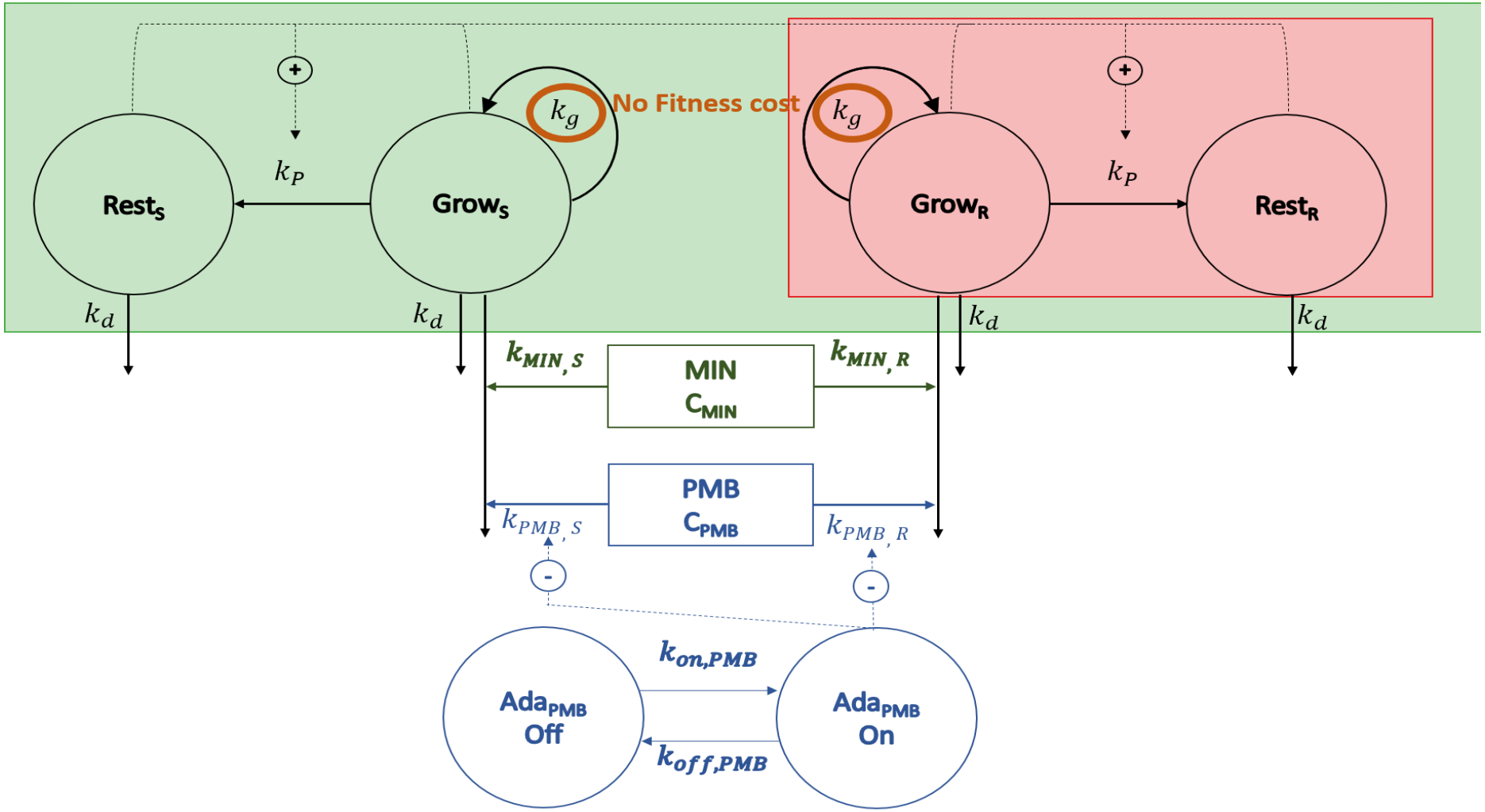
Mathematical modelling



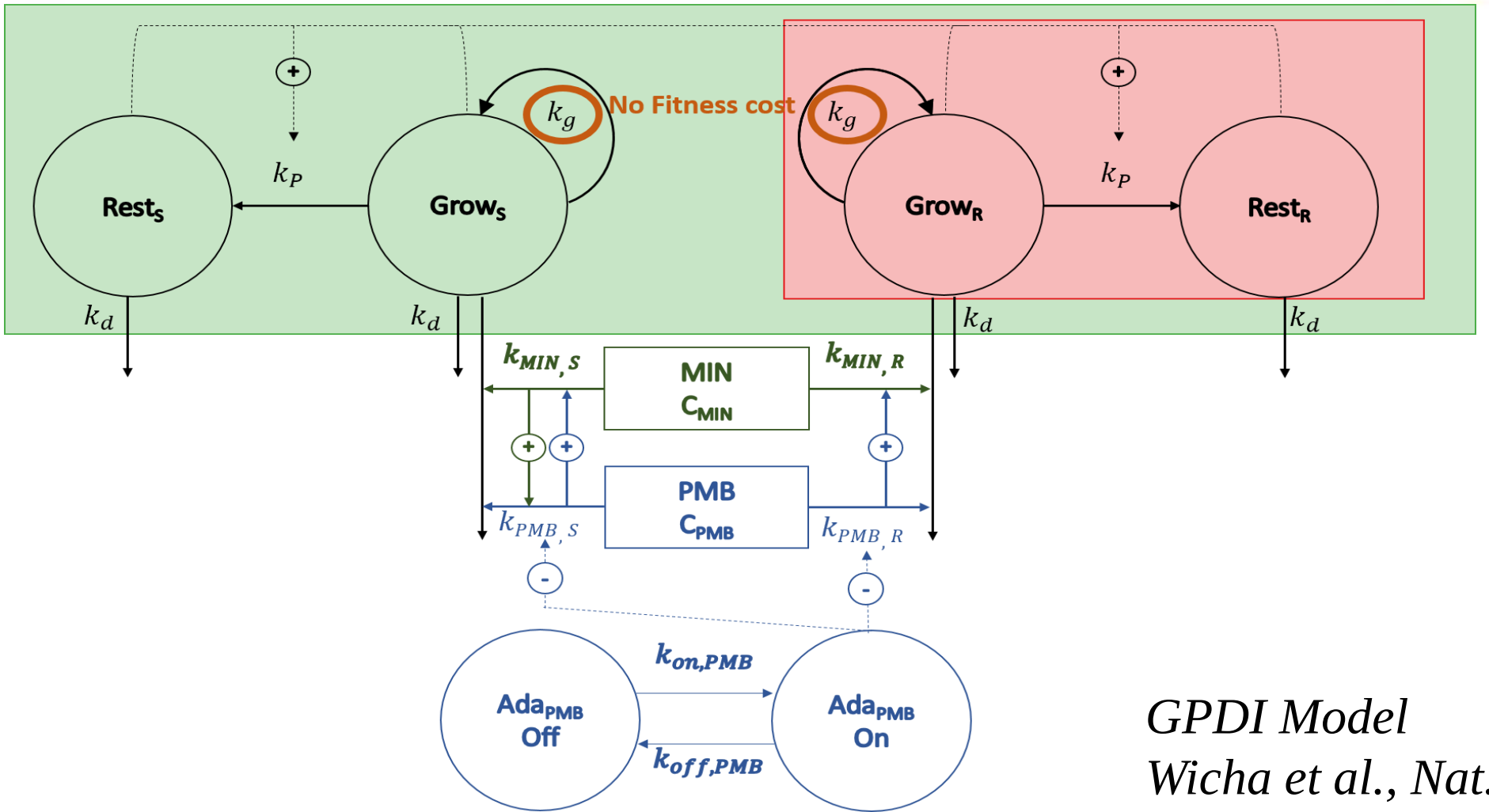
Mathematical modelling



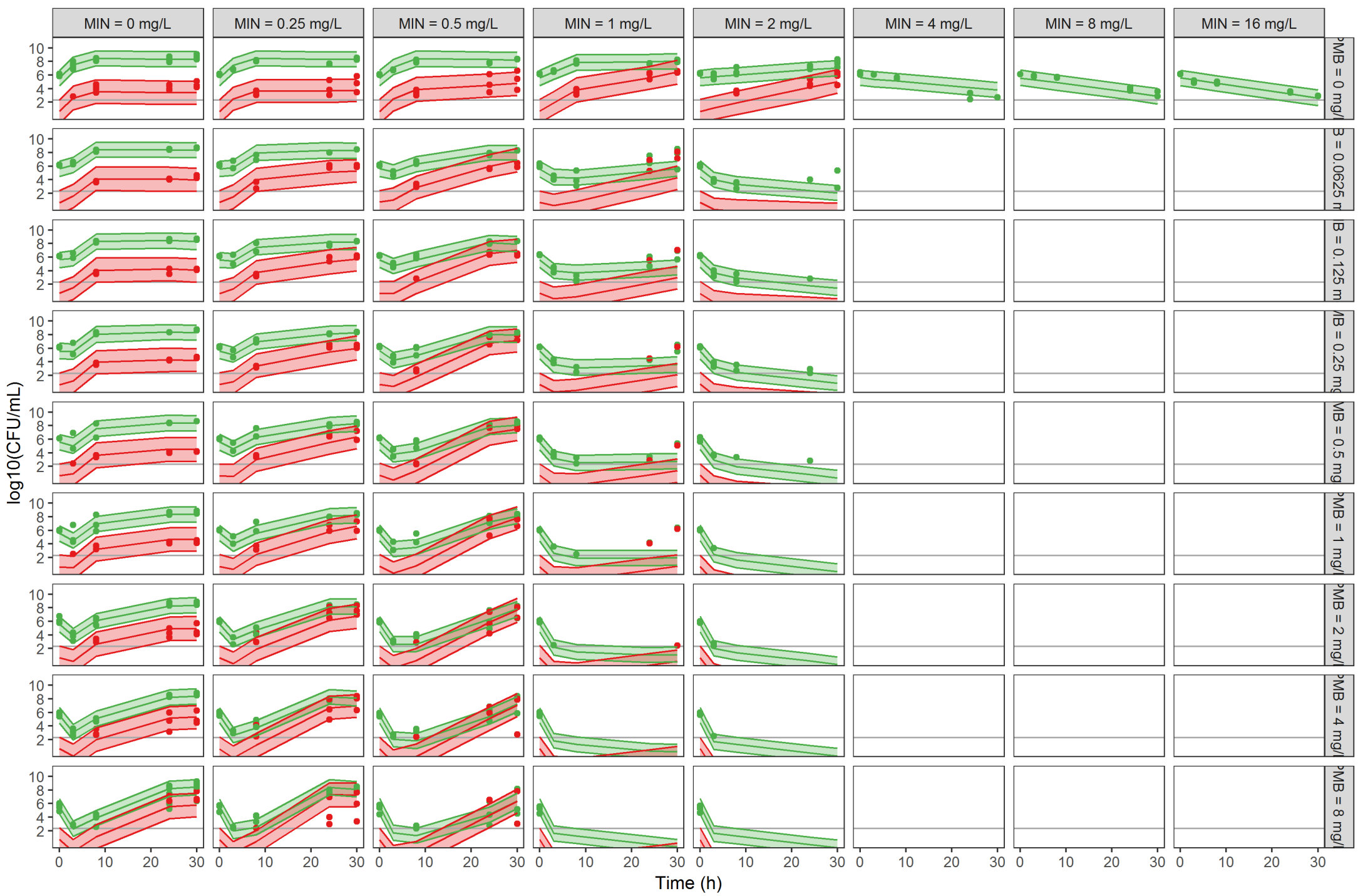
Mathematical modelling



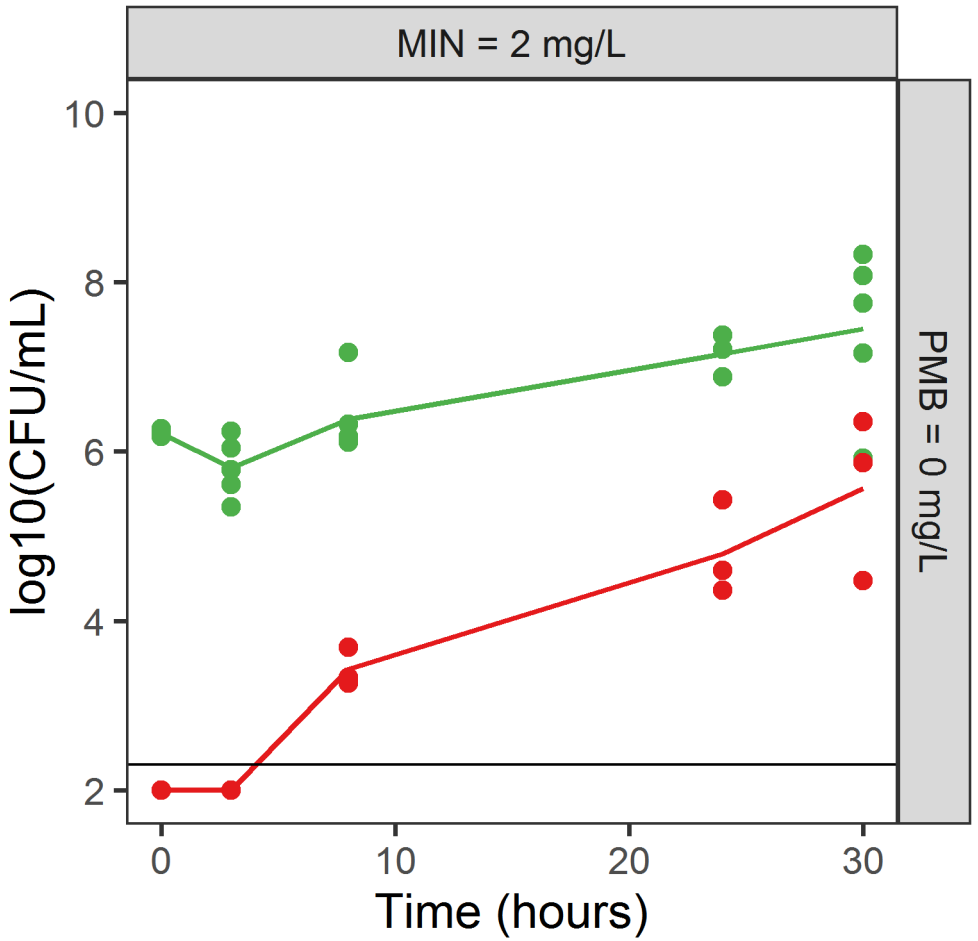
Mathematical modelling



GPDI Model
Wicha et al., Nat. Com., 2017

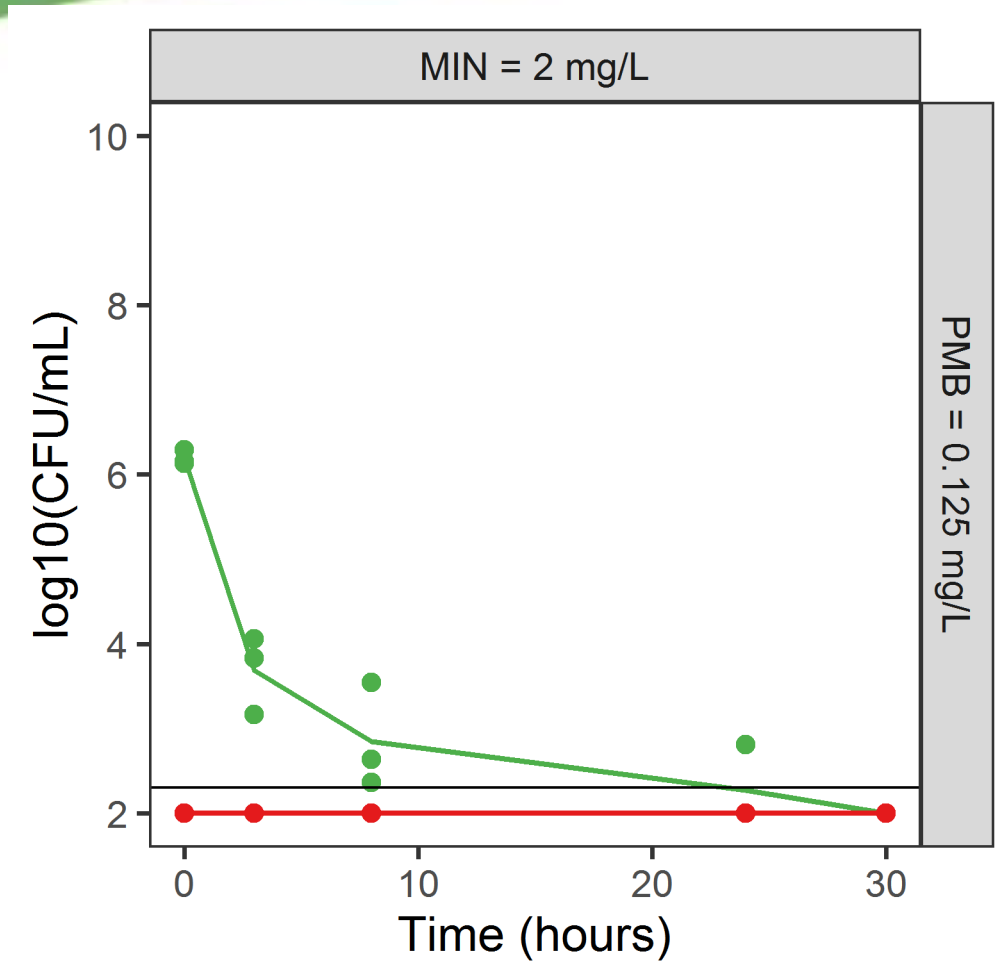

MIN = 0 mg/L
MIN = 0.25 mg/L
MIN = 0.5 mg/L
MIN = 1 mg/L
MIN = 2 mg/L
MIN = 4 mg/L
MIN = 8 mg/L
MIN = 16 mg/L
PMB = 0 mg/L
PMB = 0.0625 mg/L
PMB = 0.125 mg/L
PMB = 0.25 mg/L
PMB = 0.5 mg/L
PMB = 1 mg/L
PMB = 2 mg/L
PMB = 4 mg/L
PMB = 8 mg/L
log10(CFU/mL)
Time (h)

Monotherapy is not effective



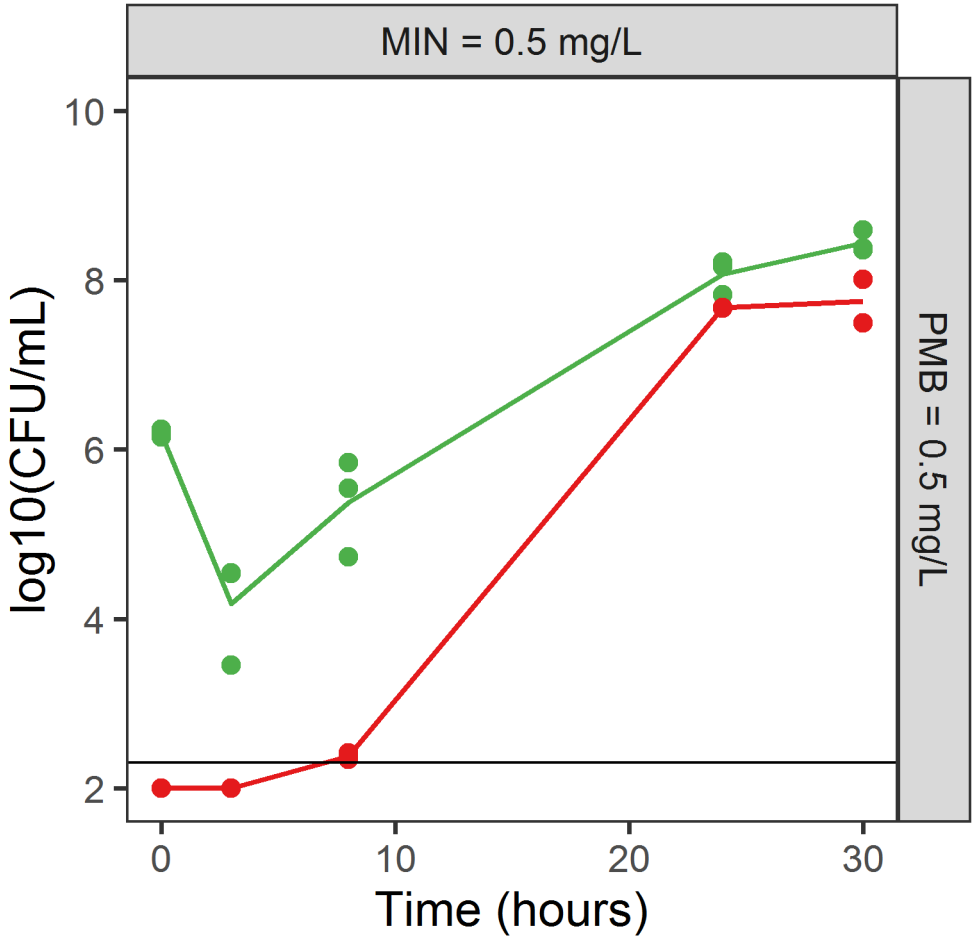
- 0.5 * MIC of MIN
- No killing
- Selection of resistant subpopulation

Combination is effective



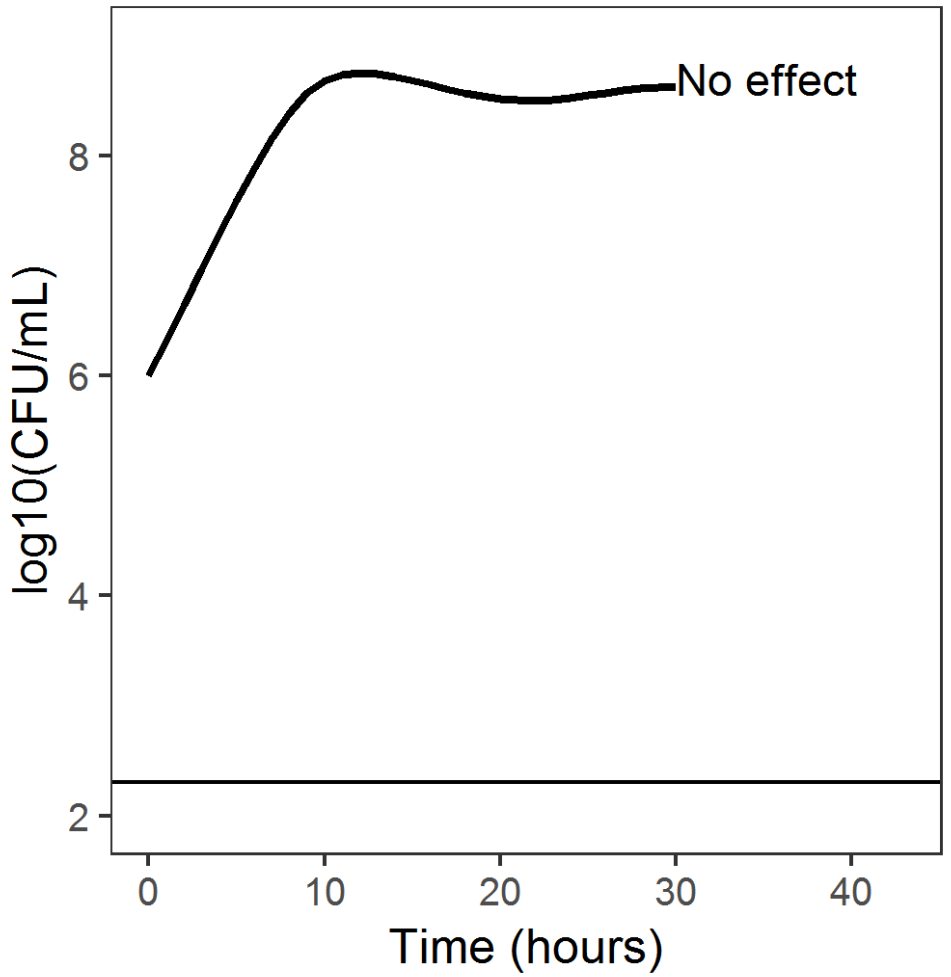
- 0.5 * MIC of MIN + 1/64 * MIC of PMB
- Total killing at 30 h

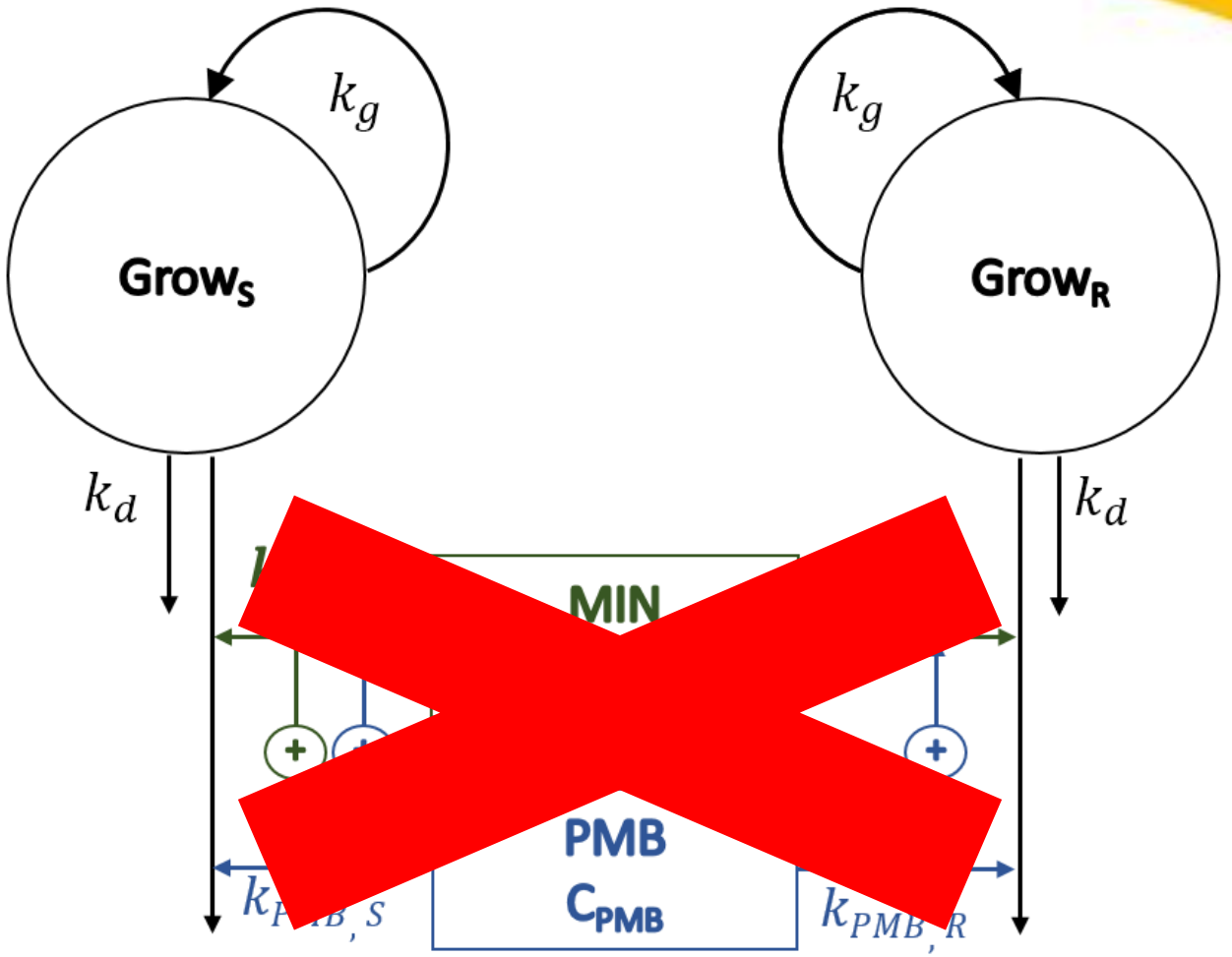
Resistance selection



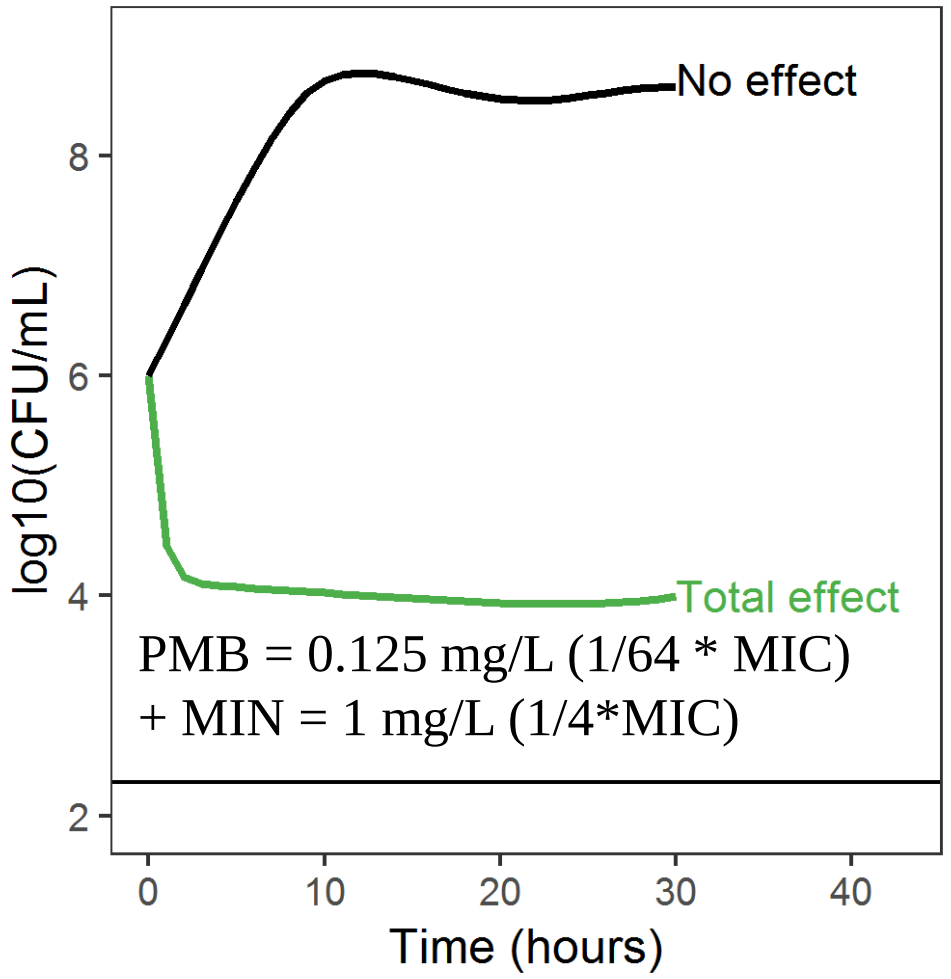
- 1/8 * MIC of MIN + 1/16 * MIC of PMB
- Initial killing but regrowth
- Selection of resistant bacteria

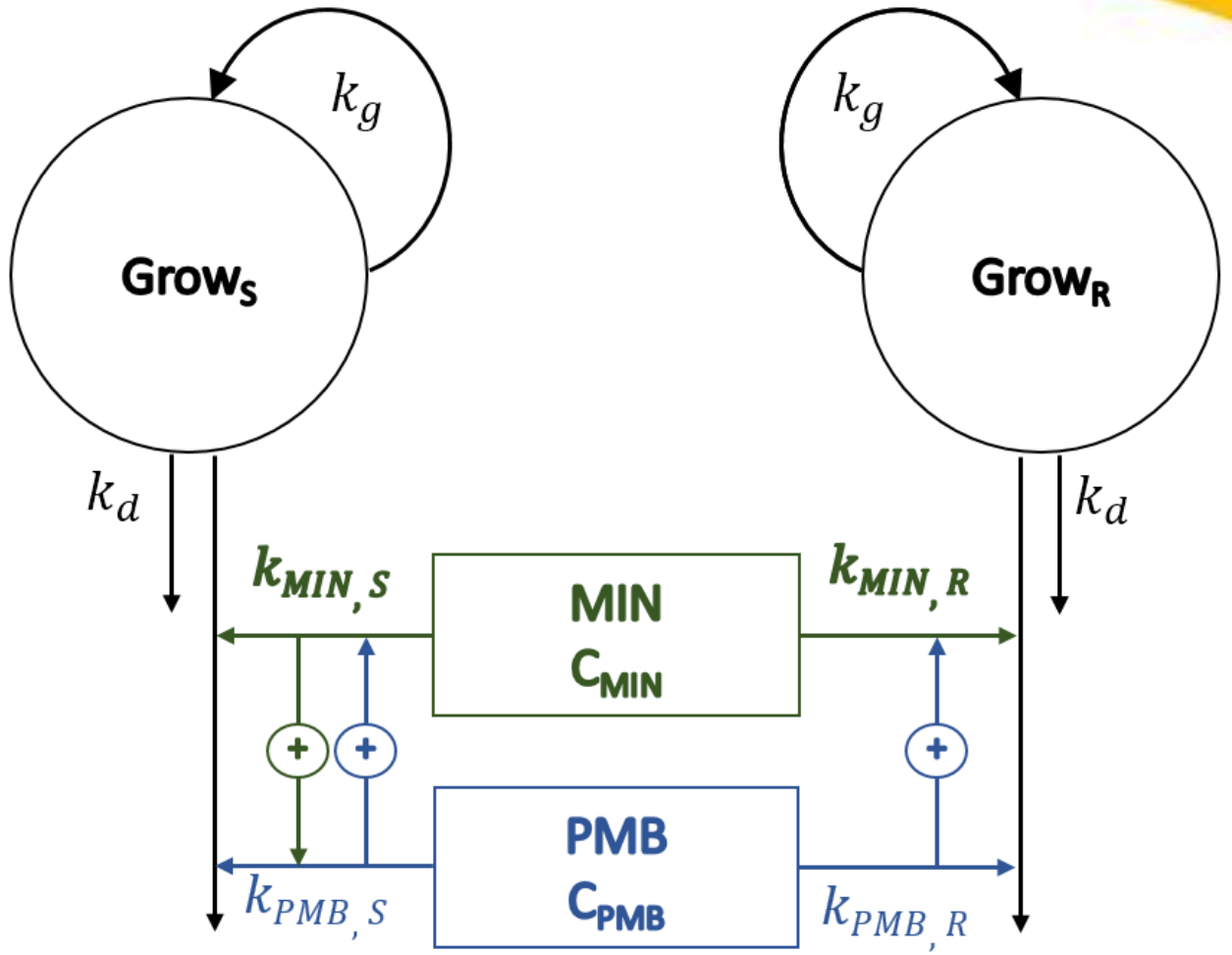
Contribution to total effect



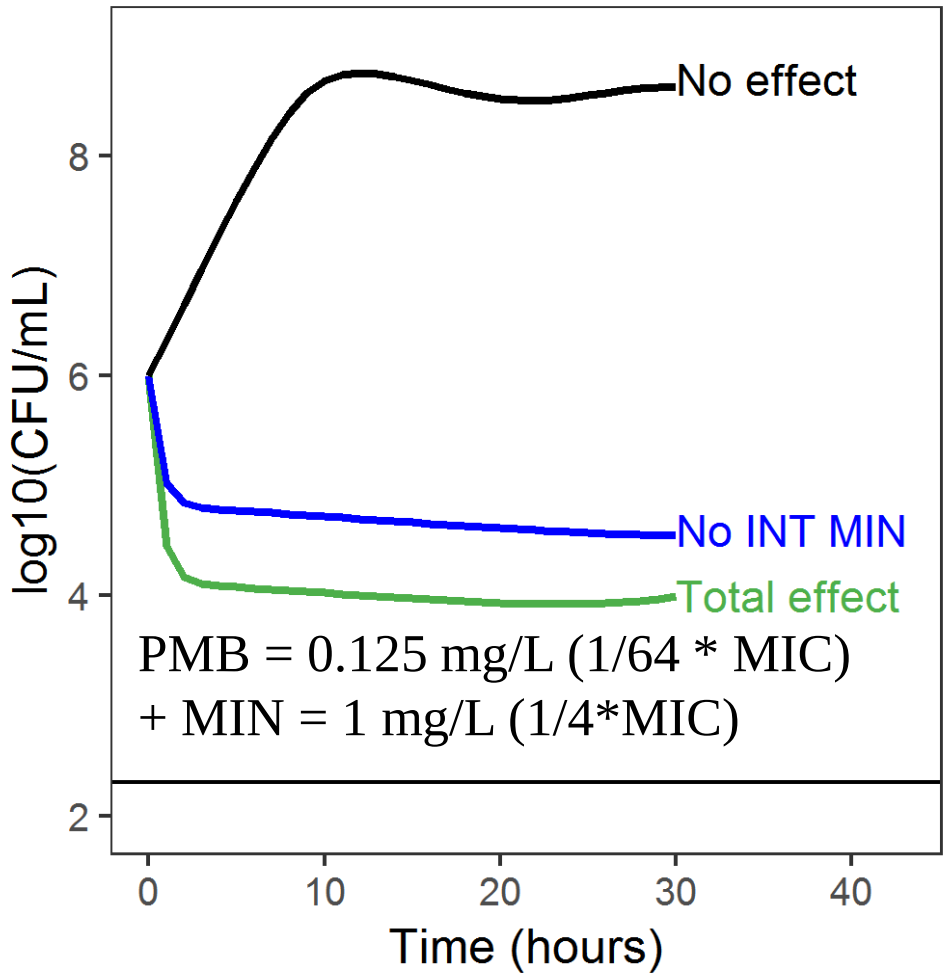


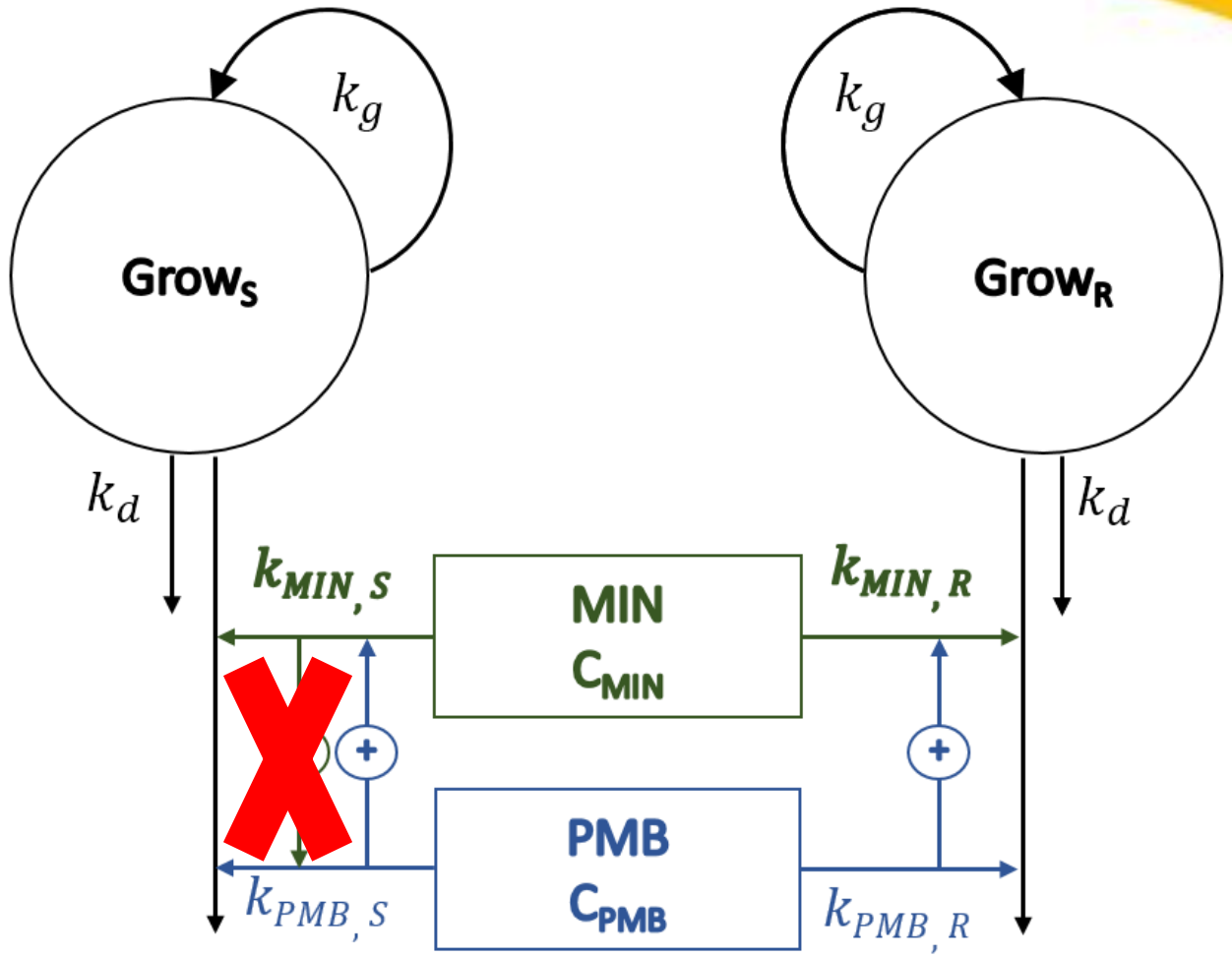
Contribution to total effect



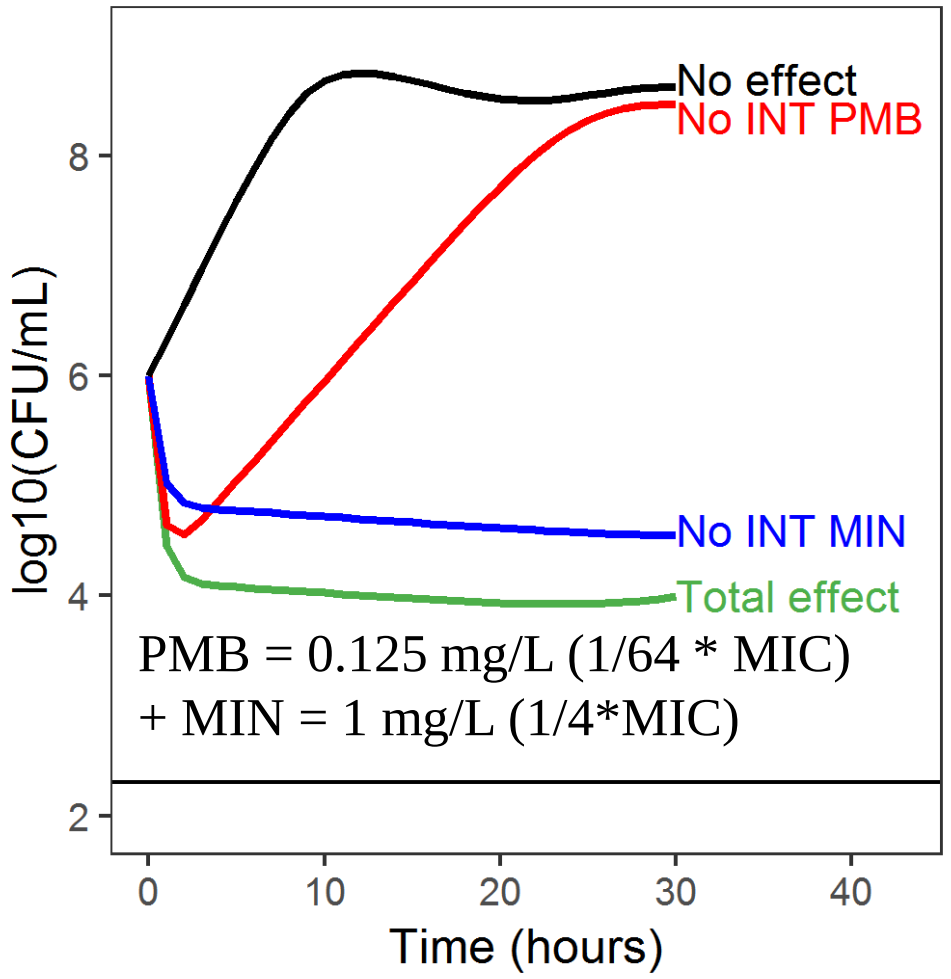


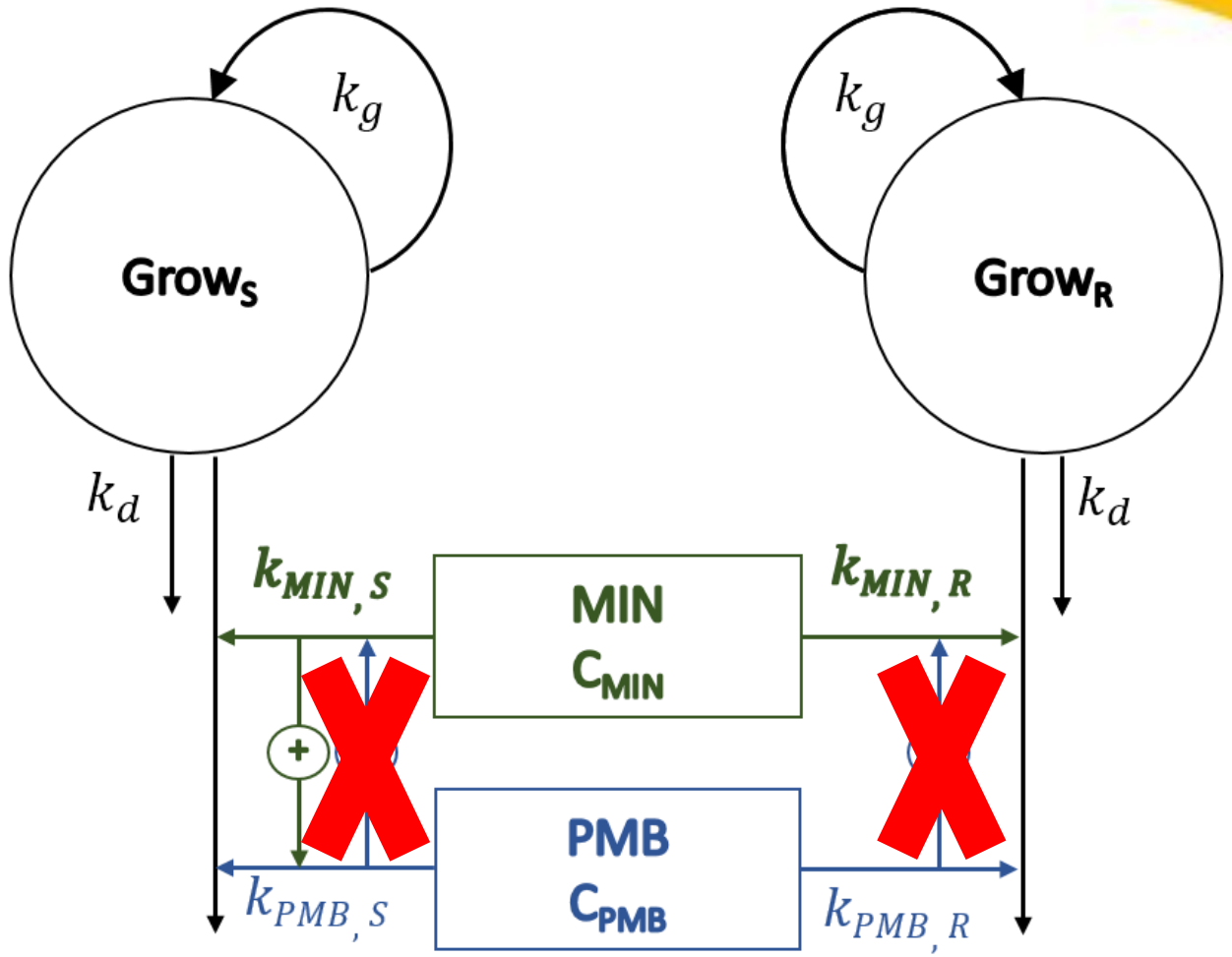
Contribution to total effect





Contribution to total effect





Conclusion

A methodology enabling the qualitative and quantitative study of antibiotic combinations was developed.

Heteroresistance to polymyxin B without fitness cost was observed.

The combination was shown to be synergistic in in vitro time-kill curves but too low concentrations of minocycline contributed to resistant selection.

By performing semi-mechanistic PK/PD modelling, polymyxin B was shown to be a good helper molecule for minocycline even at low concentrations.

Acknowledgments

U1070 Poitiers

Participants of the study :

Emma Marquizeau
Sandrine Marchand
Julien Buyck
Nicolas Grégoire
William Couet

JPIAMR : CO-ACTION

Team Leaders :

Johan Mouton
Françoise Van Bambeke
Lena Friberg
Thomas Tängden
Alain Bousquet-Mélou

Thank you very much !