# The impact of bacterial growth kinetics on predicted antibiotic efficacy under different pharmacodynamic model assumptions: An *in vivo* case example

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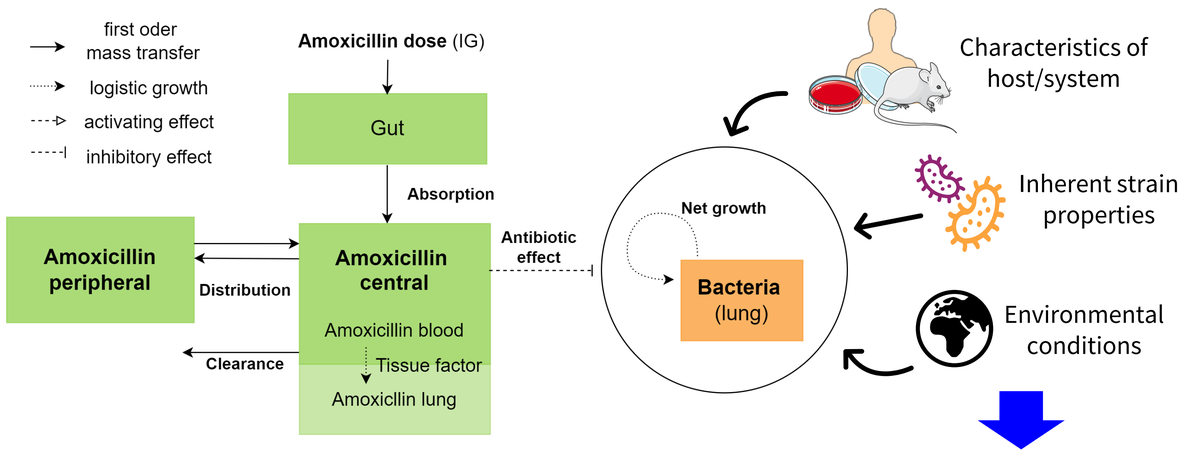
## Background and Objectives




**Semi-mechanistic antibiotic PKPD models have…**

…high potential in simultaneous analysis and translation across experimental setups and bacterial strains [1,2,3]

…allow for investigation of combination therapy and drug-drug interaction

**How are changes in bacterial growth dynamics impacting antibiotic efficacy measures?**

**What impact do model assumptions have on translatability?**

## Methods

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$$\frac{dB}{dt} = k_{net} \times \left(1 - \frac{B}{B_{max}}\right) \times B - \boldsymbol{k_{kill}} \times \boldsymbol{B}$$

**Implementations of antibiotic effect on growth**

**A** $k_{kill} = \frac{E_{max} \times C}{EC_{50} + C}$ AIC:151.7

**B** $k_{kill} = k_{net} \times \left(1 - \frac{B}{B_{max}}\right) \times \frac{E_{max} \times C}{EC_{50} + C}$ AIC:150.9

**C** $k_{kill} = \left(1 - \frac{B}{B_{max}}\right) \times \frac{E_{max} \times C}{EC_{50} + C}$ AIC:150.9

**Simulation study scenarios**

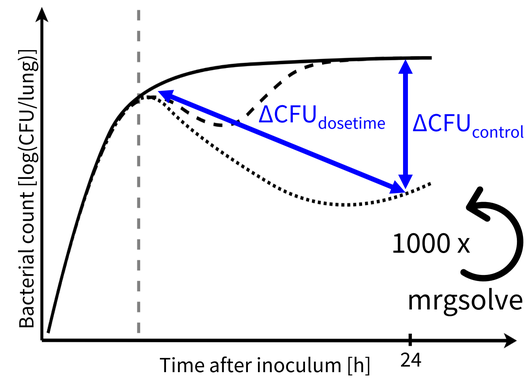
$k_{net}$: 0.163 – 2.77 $h^{-1}$ # ($\tau_d \pm 2$ h)

$B_{max}$: $10^5$ – $10^9$ CFU/lung ($\pm 2$ $\log_{10}$)

***S. Pneumoniae D39* superinfection mice**

— control
- - 5 µg AMX IG
····· 150 µg AMX IG

#Candidate model B only simulated for $k_{net}$ <0.924 due to structure related instability with ODE solver




## Results

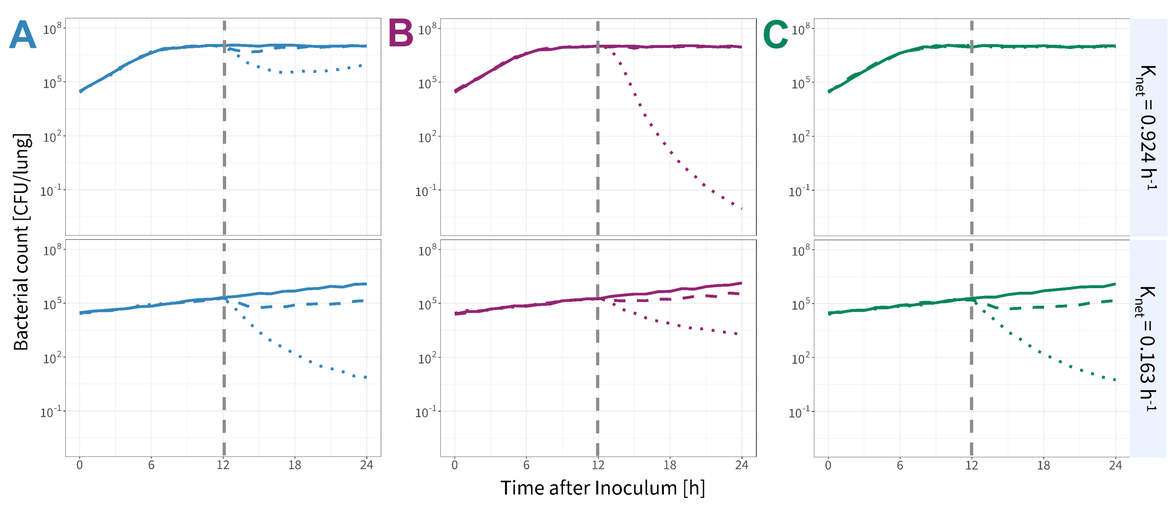



**Figure 1:** Predicted median bacterial count in lung of murine superinfection model over 24 hours after inoculum with administration of 0 (solid), 5 µg (dashed) or 150 µg (dotted) AMX IG at 12 h (grey, dashed) for candidate models A (blue), B /purple) and C (green). Simulations were performed with a fixed maximum carrying capacity of $10^7$ CFU/lung. *Abbrev. see below

**Table 1:** Predicted bacterial log10-reduction in murine superinfection lung at 24 h after inoculum following administration of 150 µg AMX IG at 12 h, given as median and 90% CI, based on 1000 simulations of models A, B and C for different growth conditions. *Abbrev. see below

| | | **Predicted $\log_{10}$-reduction of bacterial count compared to control group ($\Delta CFU_{control}$):** median (90% CI) | | |
|---|---|---|---|---|
| **Parameter [unit]** | Value | Model A | Model B | Model C |
| **Net growth rate constant $k_{net}$ [$h^{-1}$]*** | 0.163 | 5.25 (3.13 – 7.49 ) | 2.83 (0.740 – 4.91) | 5.31 (3.21 – 7.55) |
| | 0.924 | 0.99 (-1.27 – 3.14) | 8.98 (6.82 – 11.0) | -0.0134 (-2.09 – 2.30) |
| **Maximum carrying capacity $B_{max}$ [CFU/lung]#** | $10^5$ | 3.76 (1.39 – 5.90) | 2.56 (0.346 – 4.72) | 2.52 (0.46 – 4.75) |
| | $10^9$ | 5.25 (3.08 – 7.36) | 5.30 (3.21 – 7.59) | 5.44 (3.31 – 7.48) |

*predictions for $B_{max}$ = $10^7$ CFU/lung; #predictions for $k_{net}$ = 0.308 $h^{-1}$

Model A and C predicted smaller antibiotic effect (less reduction in bacterial count) with increasing net growth rate constant ($k_{net}$), model B showed opposite trends (see Figure 1,2).

Increasing maximum carrying capacity ($B_{max}$) caused an increase in $\log_{10}$-reduction of bacterial count for all models implying higher antibiotic efficacy, but the observed impact was lower in model A compared to models B and C.

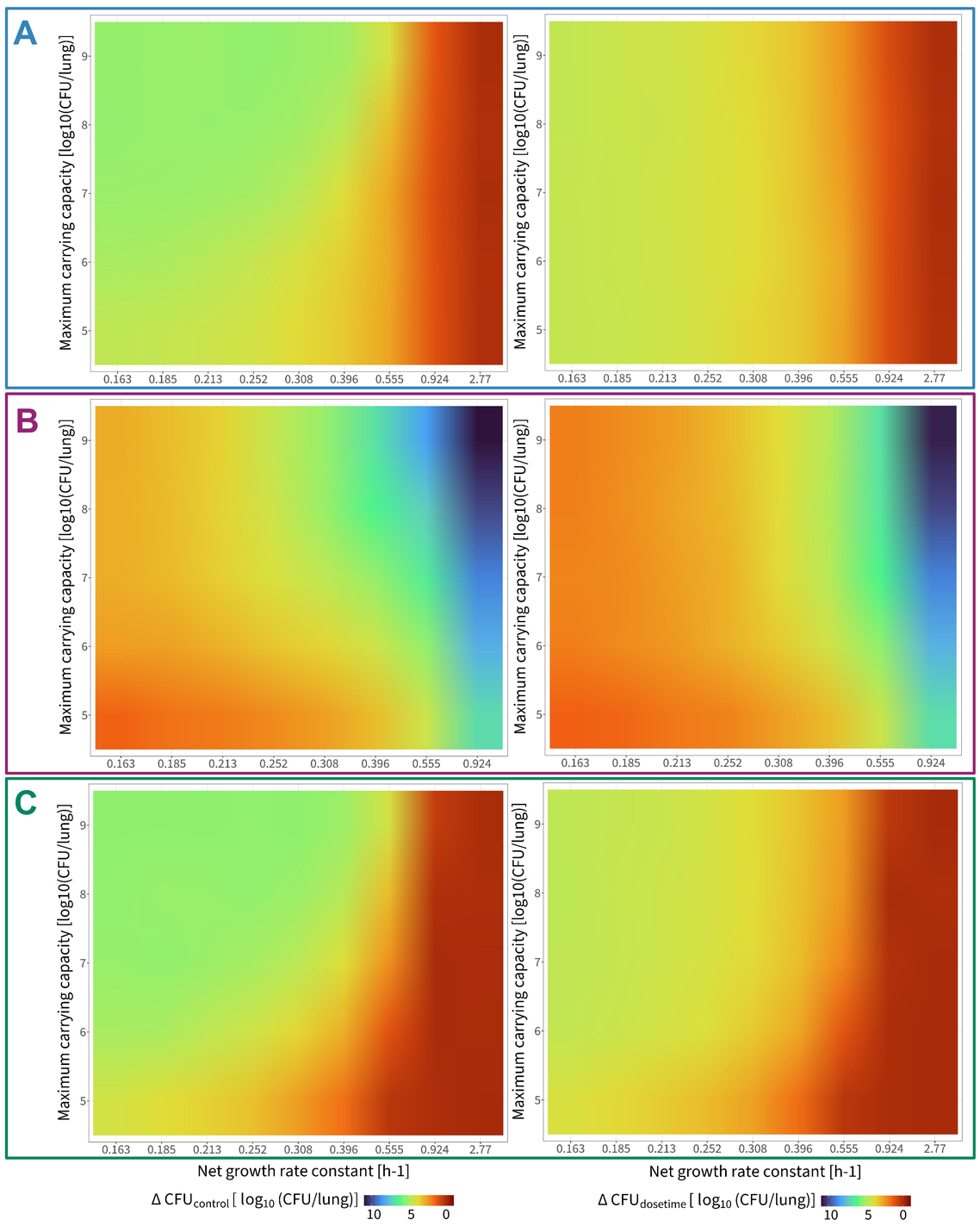



**Figure 2:** Median predicted log10-reduction of bacterial count in lung of murine superinfection model 24 hours after inoculum (0 h) with single administration of 150 µg amoxicillin IG at 12 h compared to untreated control group (left, $\Delta CFU_{control}$) and bacterial count at time of dosing (right, $\Delta CFU_{dosetime}$) dependent on net growth rate constant and maximum carrying capacity for candidate models A, B and C. *Abbrev. see below

## Discussion and Conclusions

Changes in **bacterial growth kinetics are a key factor to consider in antibiotic PKPD model extrapolation** as they relevantly impact predictions of antibiotic efficacy measures.

True relations of antibiotic PD and bacterial growth are **only visible when investigated under varying growth conditions** (e.g. Lee et al. [4]).

Different assumptions of PD effect implementation showed **opposing results when extrapolated** to unobserved bacterial growth dynamic scenarios

To ensure model translatability, **robust predictivity should be validated across varying bacterial growth dynamic scenarios**

References

[1] Frieberg, Clin Pharmacol Ther (2021)
[2] Minichmayr et al., Int J Antimicrob Agents (2022)
[3] Sou et al., Clin Pharmacol Ther (2021)
[4] Lee et al., PNAS (2018)

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Abbreviations

AMX: Amoxicillin
B: Bacterial count
$B_{max}$: Maximum carrying capacity in lung
CFU: Colony forming units
IG: Intragastrically
$K_{kill}$: Antibiotic kill rate constant
$K_{net}$: Net growth rate constant
PD: pharmacodynamic
PK: pharmacokinetic
$\tau_d$: maximum doubling time

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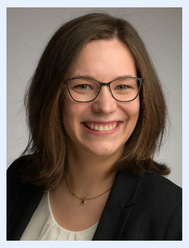

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