

Applying PKPD modelling to evaluate the impact of plasma proteins in time-kill experiments; Does the protein binding matter?

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Background

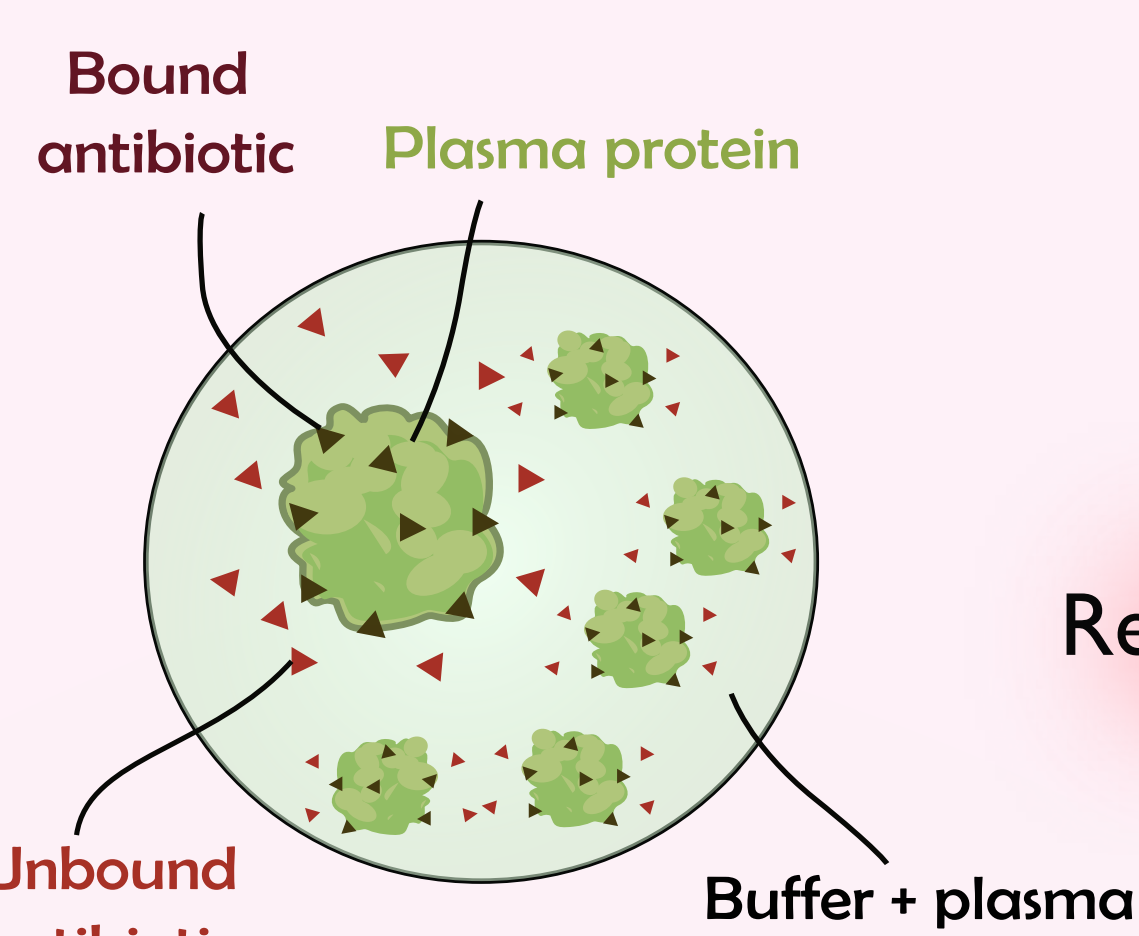
- In vitro* time-kill models offer a platform for studying antibiotic PKPD, potentially translatable to *in vivo* effects via PKPD modelling [1,2].
- Mueller–Hinton broth (MHB) is commonly used in these models, but has a limited resemblance to the *in vivo* environment [3].
- In plasma, factors such as plasma proteins may affect the antibiotic PKPD through plasma protein binding (PPB).

Aim

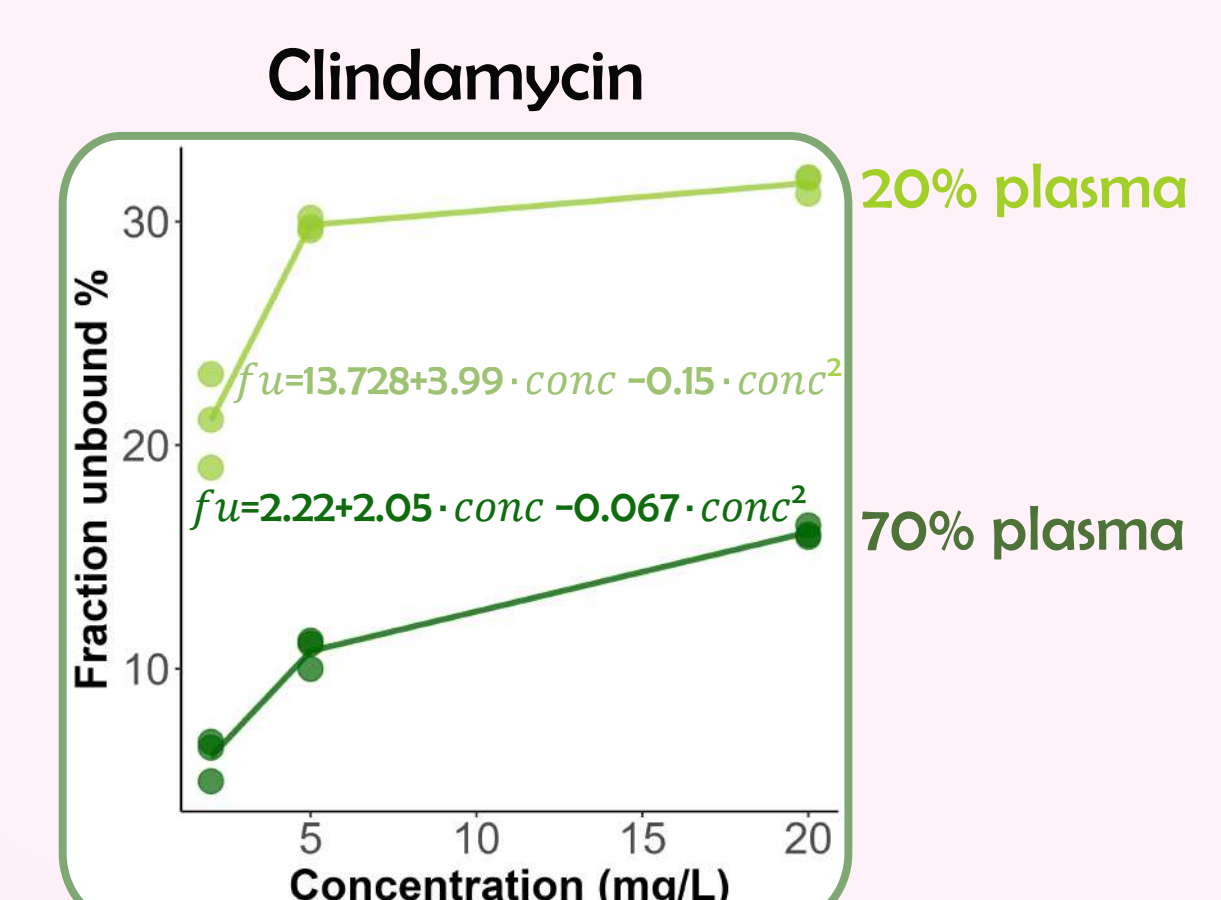
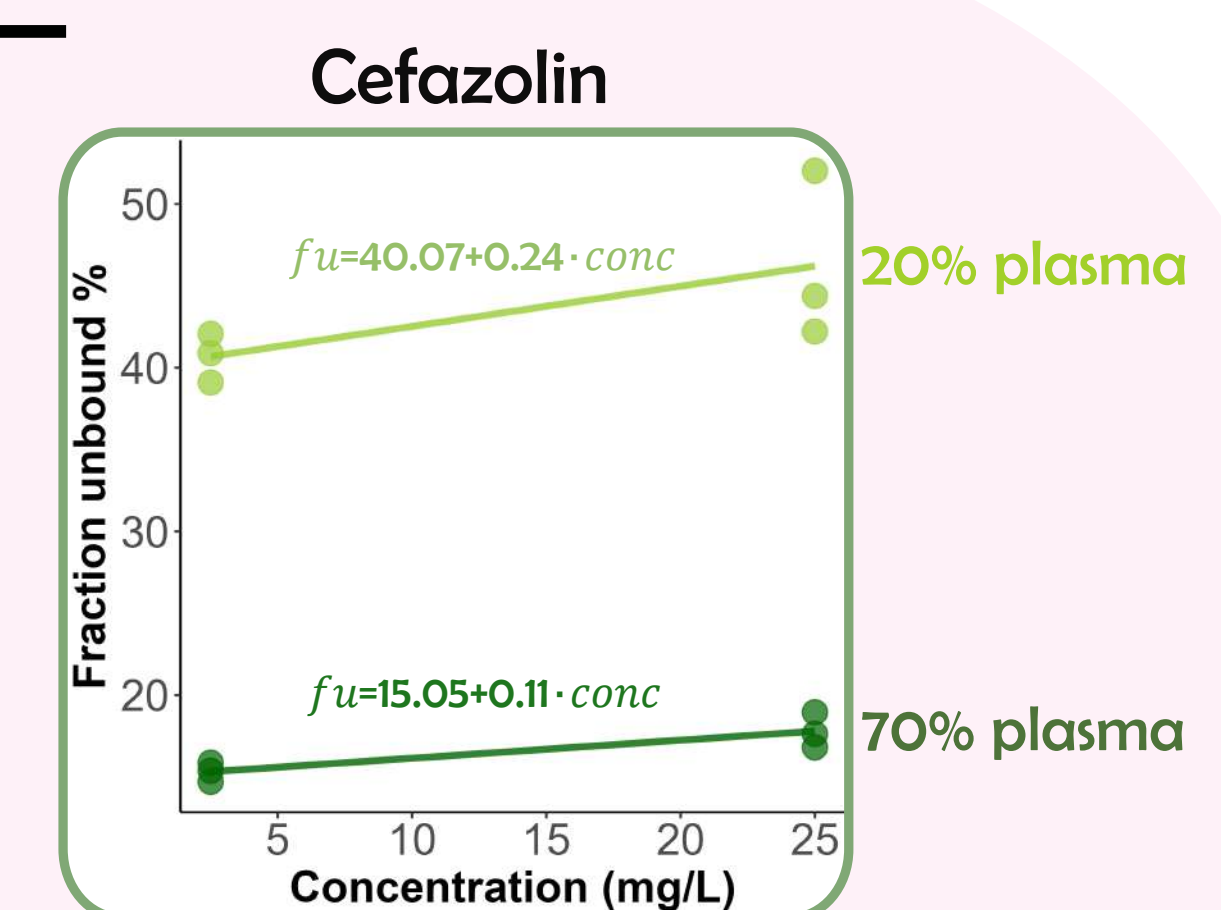
To evaluate the bacterial dynamics and PKPD of cefazolin and clindamycin in time-kill experiments across *in vitro* media spiked with varying content of human plasma.

Methods and results

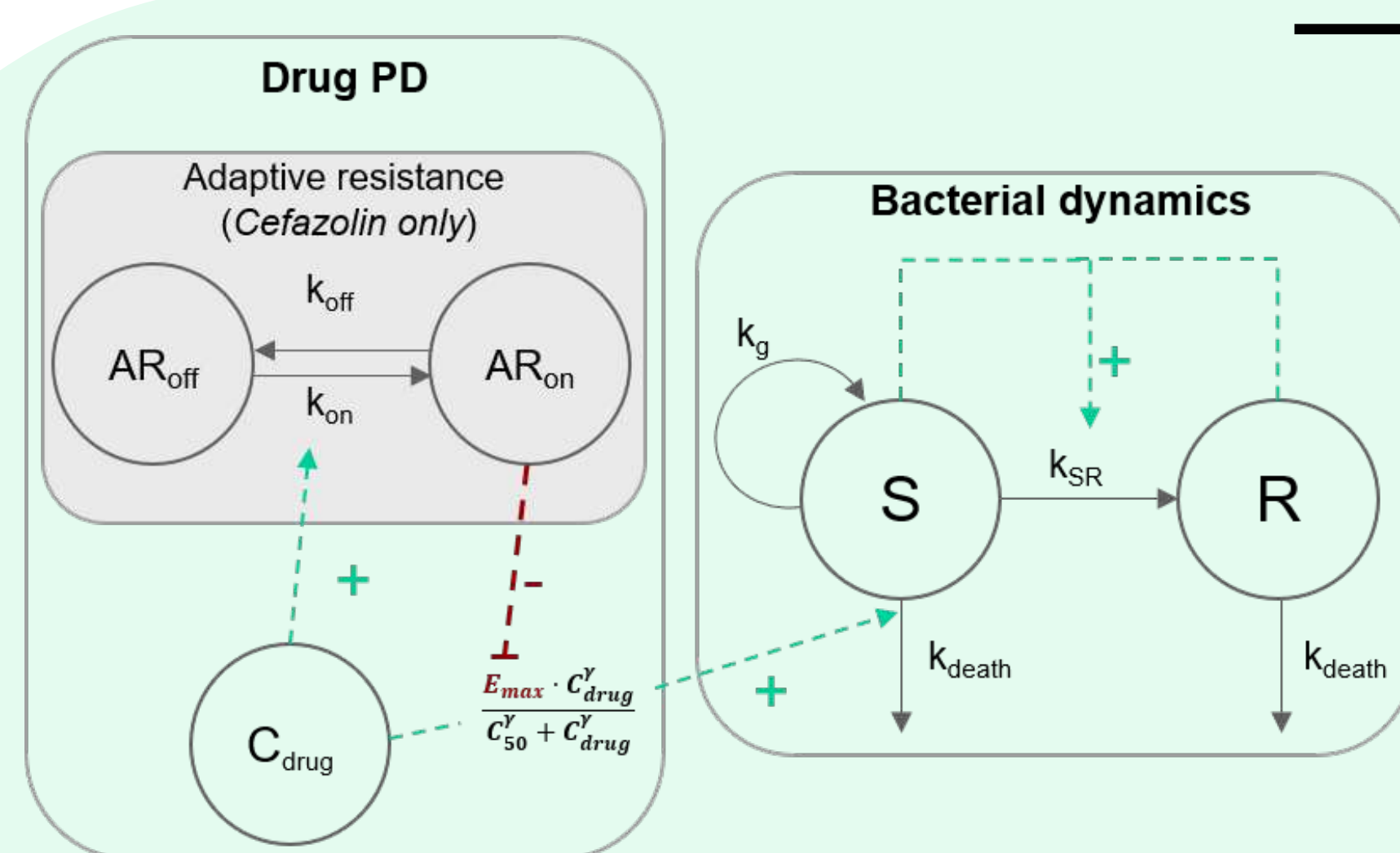
1. Plasma protein binding data



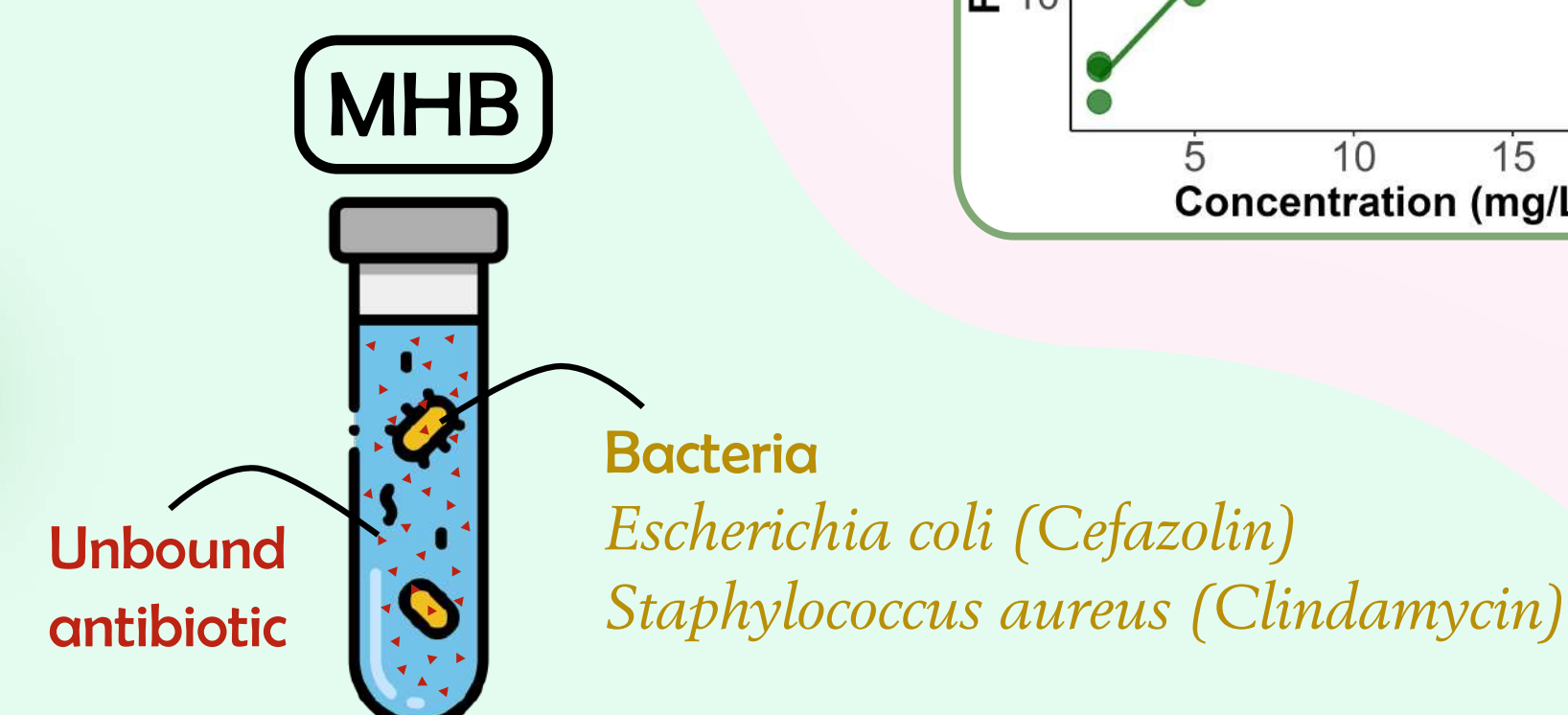
Regression model



2. Static time-kill curve (TKC)

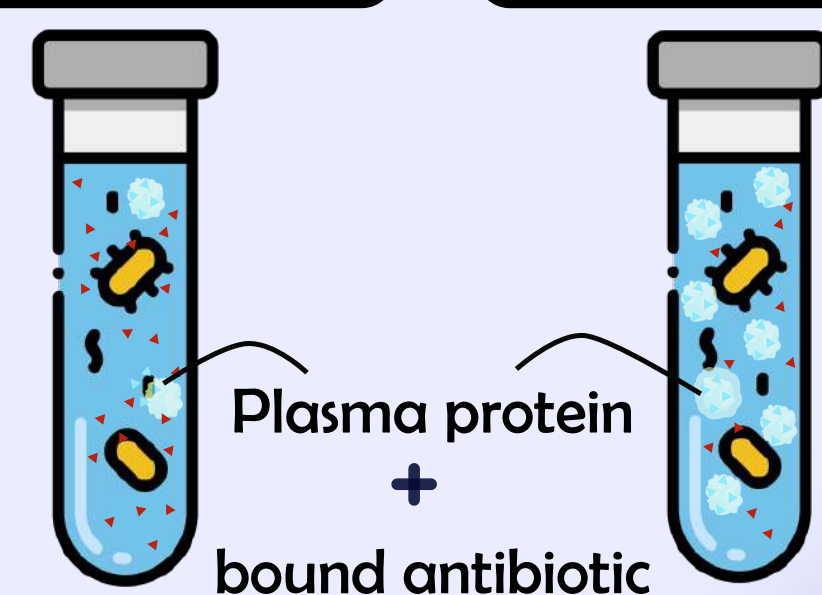


Develop PKPD model



3. Apply models to plasma-spiked TKC data

20% plasma 70% plasma



Does it predict bacterial killing in plasma?

☐ Yes

☒ No

Test scaling PD parameters

$$\text{Parameter}_{x\% \text{ plasma}} = \text{Parameter}_{\text{MHB}} \times \text{Scaling factor (SF)}$$

Cefazolin

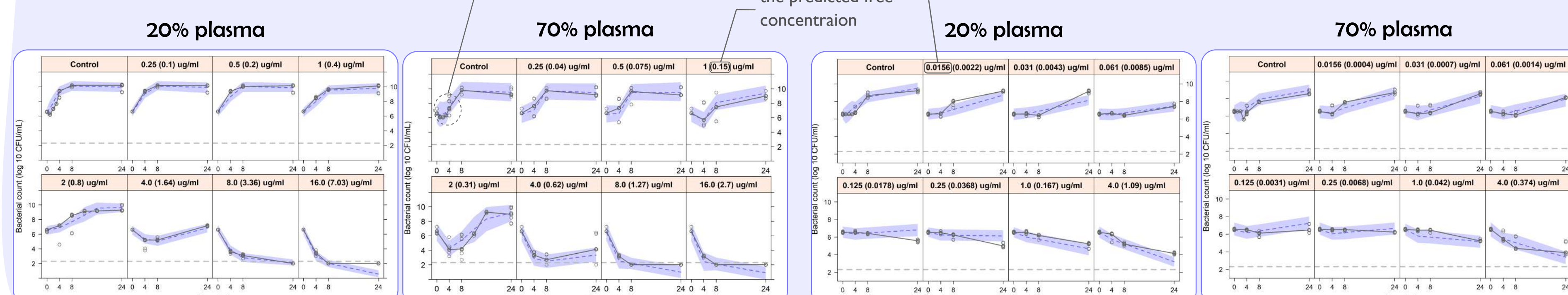
Parameter (unit)	MHB	20% Plasma	70% plasma
Lag _{growth} (h)	-	0.31	2.75
C ₅₀ SF (-)	-	0.723	0.211

Clindamycin

Parameter (unit)	MHB	20% Plasma	70% plasma
Lag _{growth} (h)	-	0.636	1.48
γ SF (-)	-	0.244	0.216

the total drug concentration

the predicted free concentration



Conclusions

- The developed PKPD models characterised a bacterial **growth delay** and **changes in the antibiotic PKPD** in time-kill experiments with plasma-spiked MHB compared to pure MHB.
- The need for scaling PD parameters in the presence of plasma could indicate **unobserved underlying mechanisms** such as bacterial phenotypic changes, or complement system activation.
- The translation of *in vitro* time-kill experiment data to *in vivo* conditions may **require considerations beyond** measuring unbound drug concentrations.
- Further experimental research using spiked media could enhance the understanding and prediction of drug activity *in vivo*.

Funded by



In collaboration with



References

- [1] van Os W and Zeitlinger M. Antibiotics 2021;10:1485.
- [2] Nielsen EI and Friberg LE. Pharmacol Rev 2013;65:1053–90.
- [3] Nussbaumer-Pröll A and Zeitlinger M. Pharmaceutics 2020;12:773.



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