Does the presence of noradrenaline influence the acquisition of antimicrobial resistance in *Escherichia coli?*

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Introduction

- Antimicrobial resistance in critical care settings is a pressing concern[1].
- Patients admitted to critical care units often:
  - develop healthcare-acquired infections, often due to Gram negative organisms such as *E. coli*
  - require antimicrobial therapies
  - have altered physiology; such as increased levels of stress hormones including noradrenaline.
  - require noradrenaline to be administered therapeutically.
- *E. coli* growth and pathogenic behaviours may change in response to altered patient physiology[2].
- Previous work has shown that mutation rates in *E. coli* vary in response to environmental conditions[3].

Aims

1. Investigate the effect of noradrenaline on growth in clinical strains of *E. coli*
2. Investigate the effect of noradrenaline on mutation rate and acquisition of antimicrobial resistance in clinical strains of *E. coli*

Methods

- Experiments used a panel of 89 clinical isolates of *E. coli,* possessing a range of antibiotic resistances.
- Experiments were conducted in a minimal media using four concentrations of noradrenaline (0, 5, 50 and 100mM).
- Growth was assessed by measuring optical density every 30 minutes for eighteen hours.
- Mutation rates in three clinical strains and the lab strain MG1655 were assessed using a fluctuation assay[4] in the presence of rifampicin.
- Linear mixed effects models (using R package nlme) were used to model the effect of noradrenaline on growth and mutation rate.

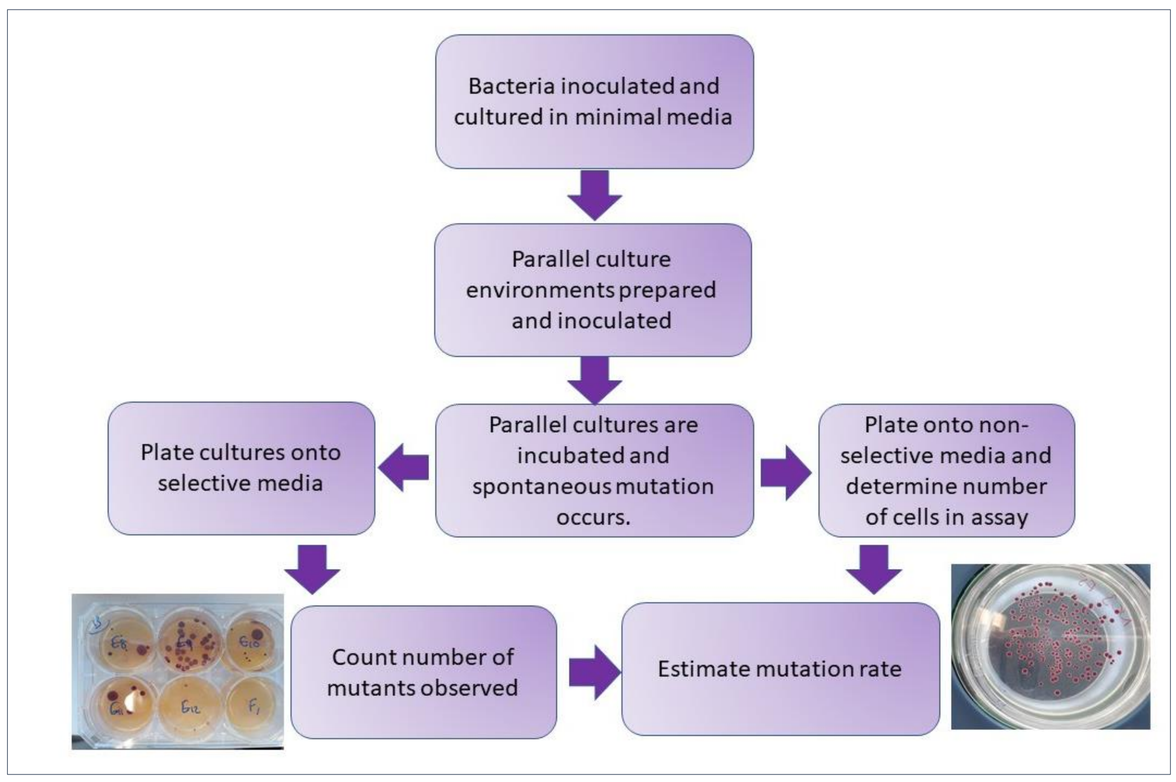

Figure 1: Schematic of fluctuation assay.

Results

The presence of noradrenaline in the growth media had small positive effects on growth across the 89 clinical strains. With 50mM of noradrenaline area under the optical density growth curve increased by 15% (SE ± 3.32%, $p = 1.5 \times 10^{-8}$).

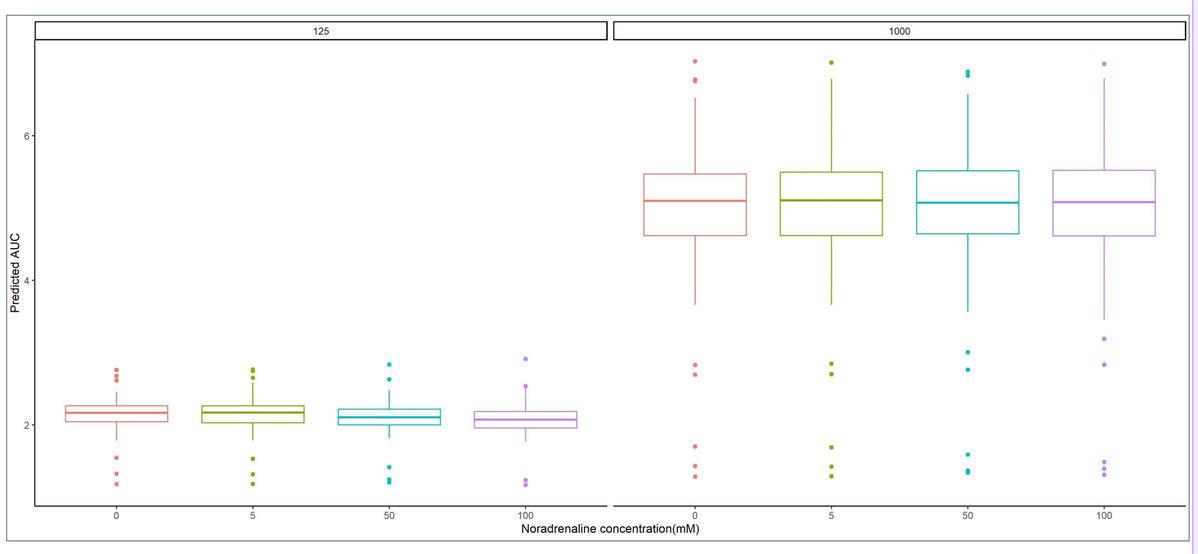

Figure 2. Growth data modelling for all strains in Noradrenaline and 125mmol or 1000mmol of glucose. Box plots indicate the predicted growth using the best fitted model.

In a subset of three clinical strains and MG1665 the addition of noradrenaline to the growth media was found to result in a 0.6% (SE ± 0.01%, $p = 1.49 \times 10^{-10}$) increase in mutation rate for every 1mM of noradrenaline added. Equivalent to a 30% (SE ± 5.6%) increase in mutation rate in 50mM of noradrenaline.

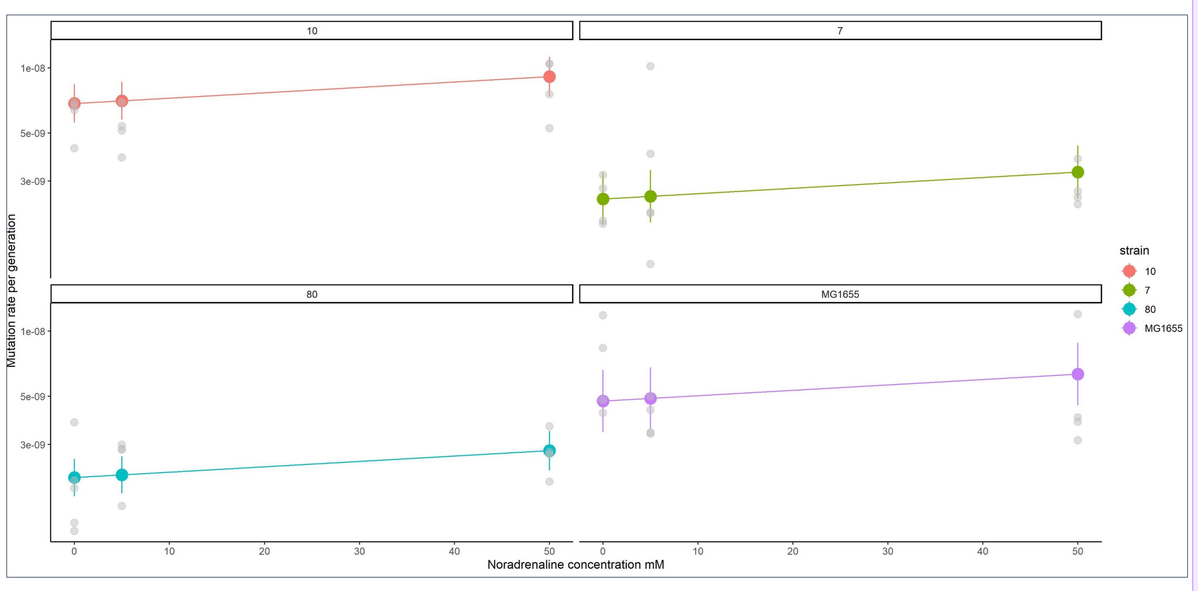

Figure 3. Mutation rates for each strain tested. Grey dots indicate the data collected. Colored dots are the predicted mutation rates for each strain (with 95% CI) using the best fitted model

Conclusion

- The presence of noradrenaline in an *in vitro* environment was associated with a small increase in growth clinical strains of *E. coli*.
- The presence of noradrenaline in the growth media resulted in a statistically significant increase in mutation rates in *E. coli*.
- Further examining the influence of environmental factors on mutation rate could provide insights into the development of antimicrobial resistance in the clinical setting.

References

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