Project Description

*Abstract

The project investigates a recent model of cellular mechanisms in bacteria that underpin antibiotic resistance and uses experimental design to improve our ability to predict potential treatment interventions. The project will demonstrate the effectiveness of ML-based experimental design within the biomedical field and extend the methods to ensure their robustness against potential model inaccuracies.

*Introduction

Bacteria constantly evolve to adapt to their surroundings, potentially becoming unresponsive to previously effective medicines. This adaptation complicates the treatment of infections and increases the risk of disease transmission. Indeed, antimicrobial resistance are recognized as among the top global public health threats facing humanity (AMR2023).

As bacteria evolve to resist the effects of antibiotics, the need to better understand the associated biological mechanisms and pathways becomes urgent.

Here, we will investigate a cellular repair system which upon expression enables cells to rescue their growth amid antibiotic assault. The system affords cells with an intrinsic antibiotic resistance present only in cells that express the repair system as a regulated stress response upon damage caused by antibiotics. We recently developed a mathematical model [Hindley2024] that incorporates the current body of knowledge around the mechanisms underpinning the expression and repair action of the gene system.

The project will use model-guided experimental design to infer experiments that are maximally informative about model parameters and to assess model limitations. It will be an opportunity to improve research workflows by accelerating the scientific learning cycle and thus to accelerate scientific discovery in a biomedical field that urgently needs speedy innovation.

*Research Challenge

Recent work in machine learning has developed Bayesian methods to design experiments that maximise their information gain [Kleinegesse2020, Ivanova2021]. The developed methods are in principle applicable to the mathematical model considered here, but they have not yet been tested on models of comparable complexity. While the methods aim at experimental designs that are optimal for the assumed model, it is unclear how they perform when the model is not a fully accurate reflection of reality, that is, when the model is misspecified. On the methodological side, the research objectives thus are twofold:

(1) Assess the effectiveness of the ML-based experimental design methods by Kleinegesse et al (2020) and Ivanova et al (2021) for the considered model of antibiotic resistance and assess the impact of model misspecification.

(2) Improve the experimental design methods to ensure their robustness against potential model misspecification.

On the biomedical side, the goal will be to:

(3) Design practically feasible experiments that maximise model predictivity and thus the potential to deliver model-guided discoveries.

(4) Identify potential model limitations that would inform about mechanisms essential to the resistance response, thereby generating new and testable biological hypotheses.

∗Data & Methodology

The project will build on a recently developed mathematical model and preliminary data, which includes qPCR data for absolute quantification of expression of the repair system [Hindley2024].

For research objective (1), we will first map out the information gain as a function of the number of experiments performed if the model is well-specified. This will provide the reference we need to quantify the impact of model misspecification. We then incorporate plausible misspecifications into the model and assess their impact on the information gained and the inferred values of the parameters.

For research objective (2), we will first investigate whether techniques developed for inference of mis-specified models [Ward2022, Huang2023] can be extended to the case of experimental design. An orthogonal direction is to combine the existing mechanistic model with a machine learning model to compensate for potential model misspecification. This may involve adding neural interaction terms inspired by work by [Rackauckas2021]. The resulting model will be of hybrid nature, exploiting the synergy between mechanistic and data-driven modelling.

To address objectives (3) and (4), we will work in close collaboration with our partner labs at Imperial College London and Queen Mary University of London, providing ample opportunity for the development of effective interdisciplinary research skills.

∗RRI/Ethical Considerations

The project has overall positive effects on society and environment. First, model-based experimental design increases the transparency of the research process as it forces scientists to fully specify the assumptions made. This openness increases the trust from the public and the scientific community. Moreover, it increases reproducibility of experiments. Second, model-based experimental design enables in-

silico research which reduces the need for animal experiments. Finally, a better understanding of antibiotic resistance contributes positively to the sustainability goals of the World Health Organisation.

*Expected Outcome & Impact

The project will increase our understanding of biological mechanisms underpinning antibiotic resistance and improve our ability to predict potential treatment interventions. The project will demonstrate the effectiveness of recent ML-based experimental design methods within the biomedical field and extend these methods to ensure their robustness against potential model inaccuracies.

*References

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