The role of RNA decay during adaptation of Methicillin-resistant Staphylococcus aureus to the human bloodstream

Abstract
Methicillin-Resistant *Staphylococcus aureus* (MRSA) is a bacterial pathogen that counteracts harsh environments by rapidly remodelling its transcriptome.

Ribonucleases (RNases) are vital in altering MRSA gene expression, making them attractive targets for antimicrobial development. However, precisely how their RNase activities contribute to host infection is poorly understood.

The project aims to develop machine learning methods to analyze genome-wide time series of kinetic CRAC data, which is a novel technology for RNase-RNA UV-crosslinking. The project will build on our recent work using Gaussian process clustering, which already gave evidence that RNases differentially degrade RNAs in a temporally coordinated manner. Here, we will generalize the methodology to move from pairwise comparison of RNase binding profiles to the concerted response by all major RNases of MRSA.

Introduction
The success of Methicillin-Resistant *Staphylococcus aureus* (MRSA) as a bacterial pathogen is attributable to its ability to efficiently counteract harsh environments by rapidly remodelling its transcriptome. In addition to transcription factors, post-transcriptional regulation by RNA-binding proteins significantly contributes to pathogenicity. In particular, ribonucleases (RNases) are vital in altering MRSA gene expression, making them attractive targets for antimicrobial development. However, precisely how their RNase activities contribute to host infection is poorly understood.

By integrating time-resolved UV-crosslinking analyses with machine learning, we recently discovered that while many RNases share the same RNA substrates, they degrade these at different times when adapting to host environments. We hypothesise that these waves of RNA decay activities enable the rapid adaptive responses crucial for MRSA pathogenicity.

Research Challenge
Our goal is to understand how temporal regulation of RNA decay influences MRSA host survival and to uncover the corresponding regulatory mechanisms. We will address this by developing robust machine learning methodology to analyse RNase-RNA UV-crosslinking time series data. A main challenge will be to integrate data from various sets of experiments to simultaneously analyse the roles of all RNases present in MRSA.

Data & Methodology RRI/Ethical Considerations Expected Outcome
The Granneman lab has developed kinetic CRAC as a technology to quantify protein-RNA binding at genome scale and with high temporal resolution. They have a large body of existing data, and in particular, high-resolution time series data of the 4 major RNases of MRSA upon change to an environment that resembles the human blood stream.

References

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