The University of Edinburgh

Population Dynamics Virtual Seminar

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12.03.21 - 9:00 am GMT

Breaking antimicrobial resistance with top-down and bottom-up approaches

Antimicrobial resistance is one of the biggest threats to global health, requiring immediate and concerted action across multiple disciplines. In this talk, I will present our work and visions to break antimicrobial resistance with interdisciplinary approaches from systems and synthetic biology. In a first, top-down approach we aim at deriving a systems-level understanding of antimicrobial resistance networks in Gram-positive bacteria. To this end we combine experiments and mathematical modelling to develop systems level descriptions of key metabolic processes in the cell, and study the interplay between antibiotic perturbations and the compensatory regulation of resistance mechanisms. Our key long-term goals are the identification of novel targets for therapeutic intervention and the prediction of synergistic drug-drug interactions. Complementing these top-down efforts of understanding natural resistance networks, in a second, bottom-up approach we focus on the rational design and experimental implementation of orthogonal synthetic gene regulatory circuits in bacteria. Our current prototypes use alternative σ factors as orthogonal building blocks and function akin to 'genetic timers' expressing a series of target genes with precise temporal control. One highly relevant application for these circuits is the heterologous expression of 'silent' antibiotic biosynthesis pathways that are present in many bacterial genomes but not expressed naturally.

Suggested Readings:

- Piepenbreier H., Diehl A., and Fritz G. (2019), Minimal exposure of lipid II cycle intermediates triggers cell wall antibiotic resistance. Nat. Comm., 10, 2733 https://www.nature.com/articles/s41467-019-10673-4

- Pinto D., Vecchione S., Wu H., Mauri M., Mascher T., and Fritz G. (2018), Engineering orthogonal synthetic timer circuits based on extracytoplasmic function σ factors. Nucl. Acids Res. 46, 7450–7464 https://academic.oup.com/nar/article/46/14/7450/5050643

- Piepenbreier H., Sim A., Kobras C.M., Radeck J., Mascher T., Gebhard S. and Fritz G. (2020) From modules to networks: A systems-level analysis of the bacitracin stress response in Bacillus subtilis. mSystems, 5, e00687-19 https://msystems.asm.org/content/5/1/e00687-19

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