Model-informed design of antibiotic therapy against antimicrobial resistance

Tandar, S.T.

Propositions

1. A semi-mechanistic pharmacodynamic model can be a useful tool for integrating various sources of information and can serve as a platform for hypothesis generation (this thesis).

2. Effective dose optimization requires the integration of clinical expertise to ensure that optimized regimens reflect real-world feasibility and clinical priorities (this thesis).

3. Large-scale antibiotic surveillance data may reveal rare collateral sensitivity pairs that are conserved across one or multiple pathogen species (this thesis).

4. The integration of knowledge on pathogen resistance evolution and pharmacodynamics, together with clinical insights into antibiotic pharmacokinetics, is essential for identifying, characterizing, and evaluating collateral sensitivity–based antibiotic combination strategies (this thesis).

5. Dissecting the role of different resistance mechanisms is key to identifying pharmacological strategies to counter antibiotic resistance (Clegg and Mac Gabhann, 2015).

6. Antibiotic sensitivity is a dynamic characteristic that can be influenced not only by resistance development, but also by the biological environment surrounding the pathogen, including its interactions with the bacterial community in polymicrobial infections (Reece, Bettio, and Renwick, 2021).

7. Dosing regimen optimization is inherently a multi-objective problem that requires balancing efficacy, toxicity, resistance prevention, and cost (Janssen *et al*, 2023).

8. The therapeutic value of an antibiotic combination associated with collateral sensitivity depends on the consistent emergence of the collateral sensitivity phenotype during treatment (adapted from Mahmud and Wakeman, 2024).

9. Learning begins when one is willing to be lost for a while.