Modelling within-host evolutionary dynamics of antimicrobial resistance

Antimicrobial resistance (AMR) arises due to two main reasons: pathogens are either intrinsically resistant to the antimicrobials, or they can develop new resistance mechanisms in a continuous fashion over time and space. The latter has been referred to as within-host evolution of antimicrobial resistance and studied in infectious disease settings such as Tuberculosis [1]. During antibiotic treatment for example within-host evolutionary AMR dynamics also plays an important role [2].

Given its importance as a major public health concern with enormous societal consequences around the world, the evolution of drug resistance in the context of various pathogens has been extensively studied using population genetics approaches [3]. This problem has been also addressed using mathematical modelling approaches including Ordinary Differential Equations (ODE)-based [4. 5] and more recently Stochastic Differential Equations (SDE)-based models [6].

The approach proposed by [7] utilizes integro-differential equations to mathematically capture continuity in the space of the bacterial resistance levels. The authors develop and study a model of within-host AMR evolution in the absence and presence of drug treatment. In the proposed model AMR is represented as a continuous quantitative trait, describing the level of resistance of the bacterial population. In accord with recent experimental evidence [2] the use of integro-differential equations allows to account for both, the dynamics of the bacterial population density, referred to as “bottleneck size” in [2] as well as the evolution of its level of resistance due to drug-induced selection. The model has been extensively analysed to address various scenarios including the significance of host immune response in drug efficiency, treatment failure and preventive strategies. The drug treatment chosen to be investigated in this study, namely chemotherapy, has been characterised in terms of the level of evolved resistance by the bacterial population in presence of antimicrobial pressure at equilibrium. Finally, the minimal duration of drug administration on bacterial growth and the emergence of AMR has been probed in the model by changing the initial population size and average resistance levels.

References

[1] Castro, R. A., Borrell, S., & Gagneux, S. (2021). The within-host evolution of antimicrobial resistance in Mycobacterium tuberculosis. *FEMS Microbiology Reviews*, *45*(4), fuaa071.

[2] Mahrt, N., Tietze, A., Künzel, S., Franzenburg, S., Barbosa, C., Jansen, G., & Schulenburg, H. (2021). Bottleneck size and selection level reproducibly impact evolution of antibiotic resistance. *Nature ecology & evolution*, *5*(9), 1233-1242.

[3] Wilson, B. A., Garud, N. R., Feder, A. F., Assaf, Z. J., & Pennings, P. S. (2016). The population genetics of drug resistance evolution in natural populations of viral, bacterial and eukaryotic pathogens. *Molecular ecology*, *25*(1), 42-66.

[4] Blanquart F, Lehtinen S, Lipsitch M, Fraser C. (2018) The evolution of antibiotic resistance in a structured host population. J. R. Soc. Interface 15: 20180040. <http://dx.doi.org/10.1098/rsif.2018.0040>

[5] Jacopin E, Lehtinen S, Débarre F, Blanquart F. (2020) Factors favouring the evolution of multidrug resistance in bacteria. J. R. Soc. Interface 17: 20200105. http://dx.doi.org/10.1098/rsif.2020.0105

[6] Igler, C., Rolff, J., & Regoes, R. (2021). Multi-step vs. single-step resistance evolution under different drugs, pharmacokinetics, and treatment regimens. *Elife*, *10*, e64116.

[7] Djidjou-Demasse R, Sofonea MT, Choisy M, Alizon S (2021) Within-host evolutionary dynamics of antimicrobial quantitative resistance. HAL, hal-03194023, ver. 4 peer-reviewed and recommended by Peer Community in Mathematical and Computational Biology. <https://hal.archives-ouvertes.fr/hal-03194023>