Position B

Understanding colonization resistance from a single-cell prospective: theories and stochastic simulations

Curriculum DASMEN Standard at Humanitas University

Abstract:

Since the '60s we know that disturbing the gut microbiome with antibiotics leads to an increased susceptibility to inflammation caused by pathogens [1, 2, 3]. This observation led the scientific community to discover one of the major contributions of bacteria to human health: the ability of the resident community to protect us from pathogen colonization, named *colonization resistance* [4, 5]. Over the last two decades, the combination of large-scale "omics" screenings with in vitro and in vivo models has been successful in identifying associations between specific bacterial strains and *colonization resistance* of a healthy host [2, 6]. However, the precise mechanisms that prevent pathogenic invasion are still poorly understood [2, 3, 6].

One of the reasons for the lack of knowledge of why *colonization resistance* varies across bacterial communities is that research has often neglected the role of individual cell behaviors, i.e., the ability of genetically identical bacterial cells to behave in distinct ways due to a combination of deterministic and stochastic factors [7, 8, 9]. In particular, to determine whether pathogen will invade a resident bacterial community we need to understand how pathogenic cells respond to environmental changes, how they interact with each other and with cells of the resident community, and what role is played by the intrinsic heterogeneity that makes each individual cell different [10, 11]. A difficulty arises because to understand those aspects we need to understand the spatio-temporal scales over which interactions and behaviors persist [12]. In other words, we need to understand how the cells of the community influence the pathogenic cells over space and time, and how, in turn, the pathogenic cells are able to alter the behaviors of the cells in the community.

The proposed work aims to address three questions that are central in understanding *colonization resistance* and that can only be addressed by bringing a single-cell perspective to the study of microbial invasions: How do collective properties of the resident community influence pathogen behavior and therefore *colonization resistance*? How do pathogenic cell behaviors influence the resident community and therefore *colonization resistance*? What is the role of spatial structure in *colonization resistance*?

Supervisor: Gabriele Micali - gabriele.micali@eawag.ch

Main technical approaches:

Mathematical modeling and theories applied to bacterial cell physiology and ecology. Stochastic simulations and image analysis of large images. Data interpretation. The successful candidate is expected to learn some experimental techniques: culturing cells, performing microfluidics experiments and microscopy that allow for single-cell data.

Candidates with a background in physics, mathematics, engineering, informatics or other quantitative sciences who are willing to approach biology and medicine are encouraged to apply. Good computational programming skills (e.g., in C, R, Matlab, Python) are required. Experience with microbiology or biology at any level is welcome but not strictly necessary to start. Willingness to work in an interdisciplinary environment, to learn lab techniques and to work on biological questions are requirements. Curiosity, critical thinking and motivation are desirable qualities. A Master's degree or comparable qualification is required. We believe in an interactive and inclusive environment, we are committed to promoting diversity and we encourage applications from underrepresented groups.

What we offer:

We offer a highly interdisciplinary and stimulating environment with many opportunities for personal and professional development. We are part of an emerging community of scientists that have interests in microbes and their effects on human health. We are connected with the Computational Biology department of the Human Technopole. We offer access to facilities both at Humanitas and at the Human Technopole. We have great national and international collaborators with diverse expertise that will make you feel part of a vibrant scientific community. We offer competitive salaries and the possibility to travel to international conferences. Milan is a city full of art and culture, strategically located to bridge Italy and the rest of Europe.

How to apply:

The first step is to write us by email and include a cover letter explaining why you want to join the team, your CV, and the contact information of two referees.

Scientific references:

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[4] Bohnhoff, M. & Miller, C. P. Enhanced susceptibility to salmonella infection in streptomycin-treated mice. J. Infect. Dis. **111**, 117–127 (1962)

[5] Fehervari, Z. Mechanisms of colonization resistance. Nat. Milestones S17–S18 (2019)

[6] Stern, C. D. The 'Omics' Revolution: How an obsession with compiling lists is threatening the ancient art of experimental design. BioEssays **41**, 1900168 (2019)

[7] Ackermann, M. A functional perspective on phenotypic heterogeneity in microorganisms. Nat. Rev. Microbiol. **13**, 497–508 (2015)

[8] Elowitz M.B., Levine A.J., Siggia E.D., Swain P.S. Stochastic gene expression in single cell. Science **297** 5584: 1183-6 (2002)

[9] Dal Co, A., van Vliet, S. & Ackermann, M. Emergent microscale gradients give rise to metabolic cross-feeding and antibiotic tolerance in clonal bacterial populations. Philos. Trans. R. Soc. B Biol. Sci. **374**, 20190080 (2019)

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[11] Hockenberry, A. M., Micali G., Tak'acs G., Weng J., Hardt W.-D., Ackermann M. Microbiota-derived metabolites inhibit Salmonella virulent subpopulation development by acting on single-cell behaviors. PNAS **118**, 31:e2103027118 (2021)

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