Phd Position: Measuring and understanding single-cell responses to antibiotics.

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Start date: no later than December 15th 2020. Duration: 4 years.

Background and motivation

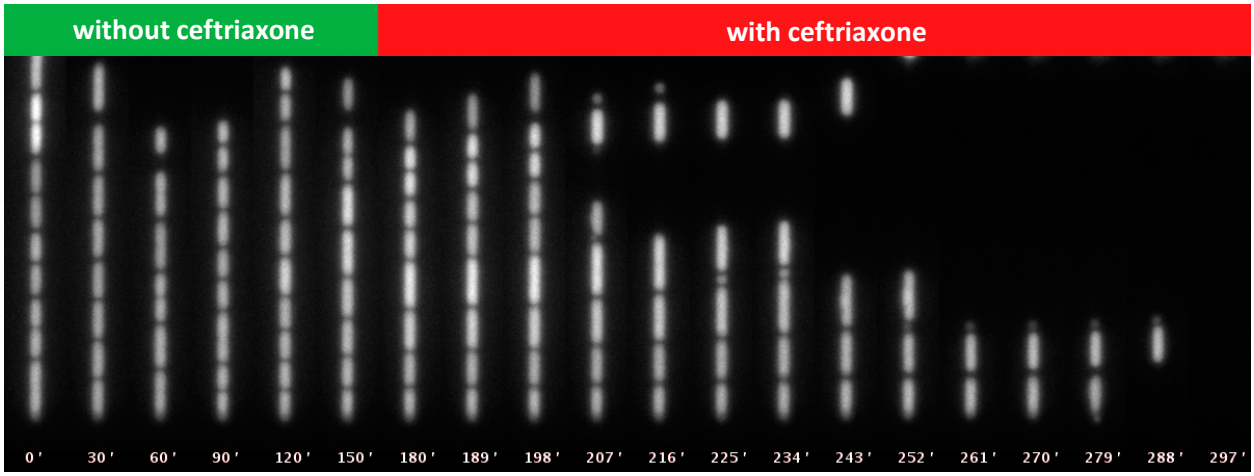
One of the key current challenges in the treatment of bacterial infections is that even genetically identical cells can take on highly heterogeneous physiological states, and current antibiotics have particular difficulty in clearing subpopulations of cells that are in slow or non-growing states. Unfortunately, methods for discovery of antibiotic compounds almost all rely on bulk population assays that inherently only assess the effects on the fastest growing cells, making it difficult to identify compounds that specifically target cells in slow or non-growing states.

In recent years, powerful methods have been developed to quantitatively measure behavior and responses in single bacterial cells. For example, by combining microfluidics with time-lapse microscopy it is possible to quantitatively track growth, gene expression, division, and death within lineages of single cells. In addition, by dynamically changing growth conditions, single-cell responses to changing environments can be characterized. Such methods have already been used to gain fundamental new insights into cell size control, gene regulation, and mutation dynamics, as well as for rapid testing of antibiotic susceptibility (e.g. Baltekin, *et al.* 2017). In this project we will develop a combined microfluidic, time-lapse microscopy, and image-analysis setup that allows high-throughput quantification of the effects of antimicrobial compounds on individual cells, as a function of their physiological state.

Project outline

The project is a collaboration between the van Nimwegen research group at the Biozentrum and the Laboratory for Micro- and Nanotechnology at the PSI. The wet lab of the van Nimwegen group, led by Dr. Thomas Julou, is at the forefront of quantitative study of bacteria at the single-cell level in dynamically controlled environmental conditions (Kaiser, *et al.* 2018, Witz, *et al.* 2019), whereas the PSI group is a leading expert on microfabrication and prototyping.

In this project, the graduate student will combine experiments and modeling to study quantitatively the effects of antimicrobial compounds on single cells, with the aim of understanding how the physiological and gene expression state of a cell determines its response to different antibiotics. In addition to microfluidic devices readily available in our lab, one aspect of the project is to develop new microfluidic designs that enable the study of multiple antibiotics and strains in parallel. These designs will involve



fabrication of channels with sub-micrometer dimensions and will employ electron beam lithography. The fabrication will be carried out at the PSI where, besides optical UV lithography, high resolution e-beam direct writing tools are available for defining high aspect ratio micro- and nanometer structures of arbitrary shape (Vila-Comamala, *et al.* 2011).

The main part of the project will be to acquire large-scale experimental data and to develop a quantitative modeling framework for understanding the sensitivity to antibiotics in individual bacteria cells (as an example, the figure shows the response of a lineage of single *E. coli* cells to a sudden exposure to ceftriaxone). A strong emphasis will be put on characterizing the response to antibiotics of slow and non-growing cells, in order to identify compounds that specifically target these subpopulations of cells, potentially complementing existing treatment strategies.

Working environment

The van Nimwegen group is a highly interdisciplinary group of researchers with backgrounds ranging from theoretical physics to molecular biology that study the structure, function, and evolution of gene regulatory networks that control gene expression. The group consists of a theoretical section that focuses on the development of novel methods for analysis of high-throughput biological data, and an experimental section that focuses on single-cell gene regulation within bacteria. The two sections are tightly integrated with most research projects involving group members from both sections, offering PhD students the unusual chance to integrate state-of-the-art theoretical and experimental approaches in their work.

The research at the Laboratory for Micro- and Nanotechnology at Paul Scherrer Institute focuses on fabricating nano- and micro-structures using different lithographic techniques and transferring them onto semiconductor, metal or polymer surfaces. Their cleanroom is equipped with optical and electron beam lithography systems, and evaporation and plasma etching tools for thin film processing. Through the collaboration, the student will collect in-depth experience in the field of nanofabrication, in particular with e-beam lithography.

Application

We expect candidates for the position to have a relevant experimental background, e.g. in biophysics, soft matter physics, or in a comparable quantitative biology field, and to have a particular interest in pursuing the topics described above using quantitative experimental approaches in combination with advanced computational and theoretical analysis. The position must start latest December 15th 2020. The selected PhD candidate will become a junior member of the SNI and benefit from personal support, a strongly interdisciplinary social environment, training in soft skills offered by the PhD program and many internal SNI events.

Applications should be made by sending a CV, application letter and contacts of two references to Prof. E. van Nimwegen at: erik.vannimwegen@unibas.ch

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M. Kaiser, F. Jug, T. Julou, *et al.*, *Nat Commun*. **9**, 212 (2018).
J. Vila-Comamala *et al.*, Optics Express 19 (1), 175-184 (2011).
G. Witz, *et al.*, eLife **8**, e48063 (2019).