University of Basel
Swiss Nanoscience Institute

BIOZENTRUM
Universität Basel
The Center for
Molecular Life Sciences

PAUL SCHERRER INSTITUT
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EINE INITIATIVE DER UNIVERSITÄT BASEL UND DES KANTONS AARGAU

High-throughput multiplexed microfluidics for antimicrobial drug discovery

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Background and motivation

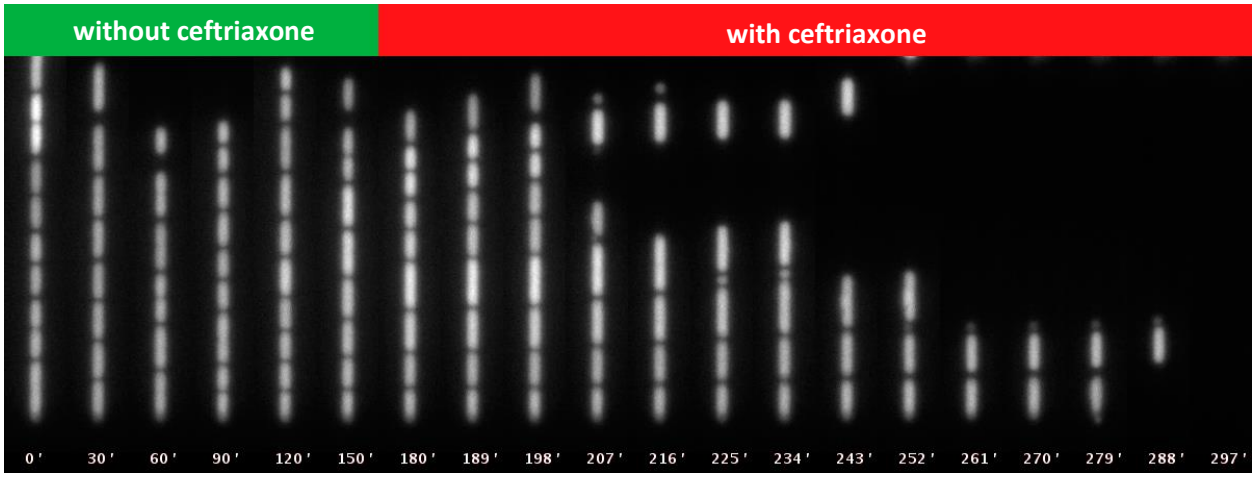
One of the key current challenges in the treatment of bacterial infections is that even genetically identical cells can take on highly heterogeneous physiological states, and current antibiotics have particular difficulty in clearing subpopulations of cells that are in slow or non-growing states. Unfortunately, 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 that combine microfluidics with time-lapse microscopy to quantitatively track growth, gene expression, division, and death within lineages of single cells, and in dynamically controlled growth conditions. 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 (Baltekin, *et al.* 2017). Here we propose to 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 method development for quantitatively tracking bacteria at the single-cell level in dynamically controlled environmental conditions (Kaiser, *et al.* 2018), whereas the PSI group focuses on microfabrication and prototyping.

The main goal of the project is to develop a new method for high-throughput quantification of the effects of antimicrobial compounds on single cells as a function of their physiological state. In the first phase of the project the student will develop new microfluic designs that allow arrays of strains and treatments to be assayed in parallel, building on existing prototypes that have already been developed in the van Nimwegen lab (e.g. the figure shows the response of a lineage of single E. coli cells to a sudden exposure to ceftriaxone). These designs will involve fabrication of channels with sub-micrometer dimensions and thus the use of 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).

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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 Institut 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. Preference will be given to candidates willing to start early. 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 online at: phd.nanoscience.ch.

For further information, contact Prof. E. van Nimwegen at: erik.vannimwegen@unibas.ch

Ö. Baltekin, *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **114**, 9170–9175 (2017).
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)