Scuola Superiore Meridionale

MERC PhD Project Proposal 2023/2024

Title of the research project:

Spatiotemporal control of complex microbial communities

Keywords (up to five)

Complex networks; Synthetic biology; Control Theory; Spatial control

Supervisors (at least two from two different areas):

Supervisor 1*: Mario di Bernardo (mario.dibernardo@unina.it)*
Department of Electrical Engineering and Information Technology, University of Naples Federico II and Scuola Superiore Meridionale
https://sites.google.com/site/dibernardogroup/home
Complex Systems, Learning, Nonlinear Dynamics

Supervisor 2*: Giovanni Russo (giovarusso@unisa.it)*
Dept. of Information and Electrical Engineering & Applied Mathematics (DIEM) at University of Salerno
www.sites.google.com/view/giovanni-russo
Sequential Decision-Making, Data-Driven Systems, Control Theory, Complex Cyber-Physical Network Systems, Learning

Supervisor 3*: Davide Salzano (d.salzano@ssmeridionale.it)*
Modeling and Engineering Risk and Complexity Area at Scuola Superiore Meridionale
https://sites.google.com/site/dibernardogroup/group/davide-salzano
Complex Systems and control, System and Synthetic Biology

Project description (max 5000 characters)

Introduction and state of the art

Microorganisms play a key role in our lives, contributing to the maintenance of our physiological functions, such as in the gut microbiota, and the production of more sustainable chemicals, pharmaceuticals, and fuels [1]. In nature, these organisms frequently organize in consortia to enhance their chances of survival and robustness against environmental stress. Furthermore, the division of labor, along with the information exchange among cells via cellular signaling within synthetic microbial communities, makes them an ideal platform for generating complex biomaterials. However, the production of functional biomaterials requires an accurate regulation of the microorganisms' distribution in space to control shape, pattern, texture and physical properties [2].

To control the spatial arrangement of microbes it is necessary to identify stimuli that can change their motion. Among the available inputs, light offers a precise, fast and flexible actuation, which can change the linear speed or angular velocity in microbes such as bacteria, unicellular eukaryotic organisms and microscopic algae [3]. Complementing the ability to shed light with an experimental platform able to image, detect and track the position of each organism in real time, it is possible to design controllers that can steer the populations within the consortium in defined spatiotemporal patterns. Different experimental platforms with the ability to image microorganisms and use precise spatiotemporal light inputs have been developed in the last decade. Using those platforms, open loop and closed loop control algorithms have been developed to control microbial colonies in space [4-6]. However, most of these strategies are designed heuristically and are specific to work with a single species. The aim of this project is to develop a generalized framework for the control the spatial configuration of microbial communities, which requires the development of a suitable mathematical framework to describe the movement and light response of a class of microorganisms, as well as a macroscopic description where the spatial patterns can be described.

<u>Project objectives and methodologies</u>

The objectives of the project can be summarized as follows:

<u>Microscopic and macroscopic models for the movement of microbes:</u> The first objective of the research project is to develop a framework to describe the movement and response to external stimuli of microorganisms, both at a microscopic and at a macroscopic level. Specifically, using the knowledge coming from real experimental data available and the available phenomenological models present in literature, e.g. [7], the most suitable mathematical framework able to capture and reproduce accurately both the movement of the microorganisms in time and the effects of light inputs on their motion speed and direction will be identified. In addition, starting from the microscopic model of the movement of the microbes, a macroscopic spatial model describing how the density of each population evolves in space and time will be developed using continuification [8,9]. Finally, these models will be validated by assessing their ability in capturing the key dynamical features observed in experimental data. The realization of this objective will require modelling tools such as Stochastic differential equations (SDEs) and Partial differential equations (PDEs), as well as the ability to gather, process and analyse image data coming from experiments. In addition, tools from system identifications will be needed to parametrize a model from data, see for example [10].

<u>Development of control strategies:</u> Using the mathematical model derived to describe the movement of microorganisms both at a microscopic and at a macroscopic level closed loop feedback controllers will be devised to shape the spatial arrangement of the microorganisms. Specifically, given the description of the desired spatial pattern in term of a spatial density function, we plan to develop data-driven and learning-based controllers that are inspired by Optimal Transport [11]. These controllers will be designed to guarantee not only the fulfillment of steady-state performance (as typical in Optimal Transport) but also transient performance typical for closed-loop control. In addition, the control algorithms will be numerically validated both at the macroscopic and at the microscopic scale and appropriate metrics will be used to compare the advantages and limitations of the different approaches. The realization of this objective will require the use of tools coming from the analysis and control theory for PDEs, possibly also using reinforcement learning and tools from Optimal Transport.

<u>*In vivo* control:</u> The last objective of the research project aims at validating the strategies that have been developed experimentally using *ad hoc* set-ups (e.g. the DOME [12]). Specifically, the a suitable subset of controllers will be implemented and deployed within the experimental platform chosen, and then an exhaustive experimental data will be collected to support the analytical and numerical findings. To fulfil this objective it is necessary to acquire some basic knowledge on the protocols necessary to grow, maintain and set up experiments with the reference organisms, as well as

acquiring familiarity with the experimental set-up that will be used for the experimental validation. To this aim, the project specifically foresees a period abroad at a leading lab in this experimental field with top notch, state-of-the-art, equipment.

Relevance to the MERC PhD Program (max 2000 characters)

This project fully fit within the interdisciplinarity of the MERC PhD program. The realisation of the objectives described of the project require the use of tools coming from different scientific areas, ranging from computer science for the data analysis, to complex multi-agent dynamical systems and control for the design of the controllers, and biology for the experimental validation. The main output of this research project will be the development of a general framework that allows the modelling, analysis and control of the motion of microorganisms within microbial communities.

The successful realization of such framework will enable fast, cost-effective realization of strategies for the control of the spatial configuration of microorganisms, with potential applications in industrial and biomedical applications.

Key references

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Joint supervision arrangements

Meetings will be scheduled on an as-needed basis, in order to ensure the effective development of the project. As a minimum, supervisor(s) will meet students at least once a week.

Location and length of the study period abroad (min 12 months)

The candidate will be able to spend a research period abroad at the University of Bristol, United Kingdom. Specifically, the student will visit the Biocompute lab under the supervision of prof. Thomas Gorochowski where it will be possible to utilize the experimental platforms available and conduct the *in vivo* experiments proposed in this research project.

Any other useful information