## Research project and supervisory team

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| **Supervisory Team** | Enrico Marsili<br>Kim Hardie<br>Miguel Camara |
| **Short introduction & description of research project** | **Project title:**<br>**Identification of signaling and regulatory compounds involved in the early formation of polymicrobial biofilms**<br><br>**Biofilms, micro-structured microbial communities that thrive at interfaces, are among the most complex microbiological forms of life to be investigated**. They are the most common mode of life for microorganisms, in environmental and clinical settings. Biofilms are comprised of microorganisms encased in self-produced extracellular matrix, made of proteins, carbohydrates, and extracellular DNA. Biofilms are formed when free-swimming microorganisms, termed planktonic, are in close proximity of a surface or interface (e.g., liquid/solid surface). **Through a complex set of regulation and signalling mechanisms, planktonic cells attach to the surface and start producing their extracellular matrix**. Currently, the production and distribution of metabolites and signalling compounds in biofilms is poorly understood. This is particularly relevant for polymicrobial biofilms, in which different bacterial species interact with each other to define the overall biofilm properties. **The switch from planktonic to attached lifestyle is crucial in the development of the infection and should be identified precisely to allow effective treatment.** While planktonic cells can be easily removed, once the extracellular matrix starts forming, it confers high mechanical and chemical resistance to biofilms, including resistance to antimicrobial and antibiotics.<br><br>**Biofilms are responsible of 80% chronic and 65% total infection in health settings**. Recent research has focused on non-lethal drugs for biofilm control, such as biofilm dispersal agents. However, a sound understanding of biofilm microstructure, species composition and dynamics is needed to develop and test effective antibiofilm agents. Biofilms are open systems, so they are naturally exposed to influx and contamination from the surrounding environment. Consequently, most biofilms are mixed microbial communities, comprising bacteria, fungi and higher organisms. Clinical biofilms factor in also the interaction with the host, in which the host immune system alters the biofilm composition and structure and microorganisms compete with the host cells for nutrients and physical space. **The complexity of mixed microbial biofilms is mostly overlooked in current research**. In fact, most research |

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| | have focused on single biofilm-forming strains and the molecular mechanism of biofilm formation. In polymicrobial biofilms, different species interact with each other, thus modulating biofilm mechanical and chemical properties, including microstructure and antimicrobial resistance. **While modern microscopy and spectroscopy methods allow spatial resolution of complex microbial consortia at an unprecedented level of details, technologies to study the interactions between microbial species in polymicrobial biofilms at molecular level are still lacking**.<br><br>Detecting early formation of polymicrobial biofilms is a daunting task that requires the combination of several technologies at small spatial (i.e., 5-10 µm) and time resolution (i.e., minute to hours). As biofilm forms on surfaces, surface-based technologies like electrochemistry on microelectrode arrays [1], scanning electrochemical microscopy and Raman analysis [2, 3] are useful to detect the pattern of initial biofilm formation and the main chemical species involved in the process, through molecular recognition biosensors. Mass spectrometry methods provide a wealth of information about the biochemical interaction between different species, which can be interpreted with bioinformatic toolkits [4]. **In this project, the two candidates will focus on the analysis of known signalling molecules that drive interactions between different species in the formation of early polymicrobial biofilms** [5]. They will then correlate the structural and electrochemical information on biofilm with the concentration of signalling molecules at different stage of early biofilm formation (e.g., planktonic, initial attachment, appearance of microcolonies). Specific mutants lacking or overexpressing signalling compounds will be used to determine the role of these compounds in the species-species interaction and the early formation of polymicrobial biofilms.<br><br>**The ultimate goal of this project is to shed light on the mechanism of early polymicrobial biofilm formation.** Knowing the molecular network of signaling and regulatory compounds involved in biofilm formation will allow **identifying targets for novel therapeutic agents that can delay, reduce or impede altogether biofilm formation**, thus improving diagnosis and treatment of polymicrobial biofilm infections.<br><br>**PhD student 1** will focus on the electrochemical and Raman characterization of polymicrobial biofilms. S/he should have a background in Chemical/Biochemical Engineering or Physical Chemistry, with a strong interest in Microbiology. This part of the project will involve the collaboration of two external scientists, Xiaoming Zhang and Elia Marin (see supervising team section). They will contribute to the |

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| | development of electroanalytical and Raman spectroscopy protocols, respectively. The supervising team will include **Enrico Marsili, Sze Shin Low, Kim Hardie and Miguel Camara.**<br><br>**PhD student 2** will focus on the metabolomics of polymicrobial biofilms. S/he should have a background In Chemistry or Microbiology, with a strong interest in modelling and computational methods. The candidate will develop a machine learning-based data analysis pipeline, in collaboration with Weihua Meng (UNNC) to characterise polymicrobial biofilms under laboratory conditions The supervising team will include **Enrico Marsili, Weihua Meng, Kim Hardie and Miguel Camara.** |
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