Project Details	
Project Code	MRCIIAR26Ba Reis
Title	Novel digital diagnostics for antimicrobial resistance based on ion-channel communication
Research Theme	IIAR
Project Type	Dry lab
Summary	Bacterial infections affect millions of people worldwide. Current methodologies for bacterial identification and antibiotic susceptibility testing (AST) are time consuming or unable to inform about antimicrobial resistance (AMR). Critically, most patients lack access to sophisticated and near-the-patient microbiological laboratories, which means being not properly treated or prescribed unnecessary antibiotics, key drivers of global AMR. This project will pioneer optical and electrical signal detection of bacteria communication through ion channels with microfluidic devices and machine learning for developing a transformative approach to AST in pathogen bacteria in human samples . This will pave a new way to personalised and effective medicine.
Description	Bacterial urine or blood infections affect millions of people worldwide. Established methodologies for bacterial identification and antibiotic susceptibility testing (AST) such as broth microdilution are time consuming (36-72 hours) or, in the case of lateral flow strips, unable to inform about antibiotic resistance. Emerging AST techniques mostly based on microfluidic devices and motility or redox probes are limited to Gram+/Gram- or motile bacteria strains. Critically, most people lack access to sophisticated and near-the-patient microbiological laboratories, which means patients are empirically treated and potentially prescribed unnecessary antibiotics, a key driver of increasing incidence of antimicrobial resistance (AMR). In certain medical scenarios, for example when blood infection develops into Sepsis, morbidity correlates with the inability to provide early diagnosis, particularly in the first 36hrs of infection. Consequently, there is an urgent need to identify alternative approaches to rapid AST. This project will test the hypothesis that ion-channel cell communication can be used as a cellular platform for studying and identifying antibiotic susceptibility in bacterial populations. In brief, ion channels are transmembrane proteins that allow transport of ions in and out of the cell, with recent literature suggesting ion channels play a key role in response of bacteria populations to external stressors. Rocha, Reis et al. (Chemical Engineering Journal, 2023, 473:144985) recently proposed a model for chemical communication between individual cells of microalgae, centred around the concept of ‘handover distance’ and driven by molecular diffusion of ions. Other studies have suggested the existence of chemical communication between bacteria cells through ion channels, with a particular focus on biofilms. This electrical communication is very distinct and complementary to quorum sensing established in literature. Bacteria cope with changing external environments and must therefore sense and respond to their local conditions. Bruni et al. (PNAS, 2017, 114(35):9445–9450) demonstrated some bacteria can sense the local mechanical environment through voltage-induced calcium flux. Yeranddy et al. (Nature Communications, 2017; 8(1)) suggested that ion channels play a key role as 'first

	responders' to bacterial infection. In a recent unpublished work, Reis and Rocha delivered a miniaturised methodology for detecting growth of bacteria using electrical impedance spectroscopy with large gold electrodes. We believe miniaturisation of electrical signalling would enable using digital, ion-channel cell communication to inform about antibiotic susceptibility of bacteria inoculum which could open the opportunity for modern AMR diagnostics and wider fundamental and applied AMR innovations. To advance that vision, this project will explore the following objectives: 1) Observe electrical ion channel communication in populations of gram-positive and gram-negative bacteria using miniaturised electrical signalling benchmarked against optical time lapse imaging of single cells. 2) Generate electrical impedance signatures and optical profiles of response of bacteria to antibiotics to a range of pathogen bacteria from clinical isolates. 3) Apply machine learning approaches to unravel identification of bacteria and speeding up antibiotic susceptibility testing from digital, electrical signalling fingerprints. 4) Design microfluidic devices suitable for making the new technique compatible with clinical microbiology or point-of-care testing. To deliver on those objectives, we will use a range of state-of-the-art techniques, from electrophysiology, microfluidics, bioelectronics, machine learning and cell biology/microbiology. By being multidisciplinary in nature, this project provides plenty of opportunities to suit own interest of the candidate, for example by allowing to focus more on fundamental aspect of cell biology in understanding the role of ion channels in communication in bacteria populations; or the bioelectronics required for capturing electrical signalling in bacteria populations in the presence and absence of antibiotics; or the micro- and nano-fabrication of microfluidic devices for AST and AMR. There is no expectation the student will master all these techniques and substantial support will be in place on daily basis as the appointed candidate will work as part of wider teams of researchers exploring complementary problems, from animal cells to microalgae, at Cardiff or Bath. Visits to Rosalind Franklin Institute at Oxford (Paschoal) or a world-class bioelectronics lab led by Rocha (Coimbra) are also possible, which could include the 3-month Broadening Horizons placement during year 3 of the project, where the student will have the opportunity to expand international network and be exposed to state-of-the-art techniques complementary or overlapping with the scope of the project. The team of supervisors (Reis, Petrik, Rocha, Paschoal) has extensive track record in providing excellence in research supervision of students from a wide range of backgrounds, from biology, microbiology, chemical engineering, and bioinformatics, so we would welcome applicants from a range of backgrounds. Microbiology work with bacterial inoculum will be central to this project, so previous experience in microbiological techniques would be advantageous.

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