Correlation of imaging and impedimetric data to predict cell state and changes in bioreactors

Supervisory team:
Lead supervisors: Prof Paul Verkade (University of Bristol), Prof Richard Luxton (University of the West of England; UWE)
Prof Alin Achim (University of Bristol), Prof Janice Kiely (University of the West of England; UWE)

Host institutions: University of Bristol, University of the West of England (UWE)

Submit applications for this project to the University of Bristol

Project description:

The ability to monitor and influence the physiological state of a cell (population) is of critical importance not just for reproducible results in academia but especially in the pharmaceutical industry. Here, the cell physiological state is directly correlated with the production of biologicals and consequently profitability and quality.

There are multiple ways to measure the cell state but most look at a single parameter. It is much more informative to integrate and correlate different types of data. Correlative Light Electron Microscopy (CLEM) is one of the most powerful imaging technologies combining the advantages of (live) light microscopy (LM) with the nanometer spatial resolution of electron microscopy (EM) into one experiment. Using this technology, key biological questions have been answered [1].

Cell structures and metabolic activity affect the electrical properties of the cell and by employing a broadband approach to impedance spectroscopy multiple cell properties can be investigated. In general terms, high-frequencies are associated with changes in the cell cytoplasm/internal structures (10-60Mz), middle-frequencies with the cell membrane (2–10MHz) and lower-frequencies with cell size (0.1–2 MHz). We have shown that dose-dependent characteristics of the impedance spectra of cell culture when exposed to a toxic challenge are related to the toxin's mode of action [2].

There is a need and drive to extract more than just LM and EM data from a single experiment and to include other types of information, expanding the CLEM field to an approach called Correlative Multimodal Imaging (CMI). In principle the CMI approach would extract any type of information from a single event and correlate and integrate the data.

This project enables, for the first time, to understand and correlate morphological and anatomical changes in the cell structure, detected microscopically, to changes in characteristics of an impedance spectrum. Impedance spectroscopy can be employed to monitor cells growing in a bioreactor and by understanding the changes in the impedance spectra related to cell stress will enable the early detection and mitigation of cell stress.

We propose to develop a CMI approach that combines live imaging with impedance measurements in control and stressed (e.g. toxins) conditions in order to better understand the different responses to stressors. We will use live calcium and / or ATP imaging in combination with impedance measurements. Subsequently we will also aim to introduce stress receptor-GFP imaging and EM morphology into this correlative approach to increase the power of the technology.

[1] DOI: 10.1038/nature14503. [2] DOI: 10.1016/j.sbsr.2019.100269