NERC GW4+ DTP Projects 2020

PROJECT TITLE: Engineering *de novo* microscopic ecologies to monitor and dissect disease spread

DTP Research Theme(s): Dynamic Earth, Living World

Lead Institution: University of Bristol

Lead Supervisor: Dr Thomas Gorochowski, University of Bristol, School of Biological Sciences

Co-Supervisor: Dr Chris Clements, University of Bristol, School of Biological Sciences

Co-Supervisor: Dr Sinead English, University of Bristol, School of Biological Sciences

Co-Supervisor: Dr Jeremy Metz, University of Exeter, College of Life and Environmental Sciences

Co-Supervisor: Dr Oliver Kaltz, University of Montpellier, Institute of the Science of Evolution

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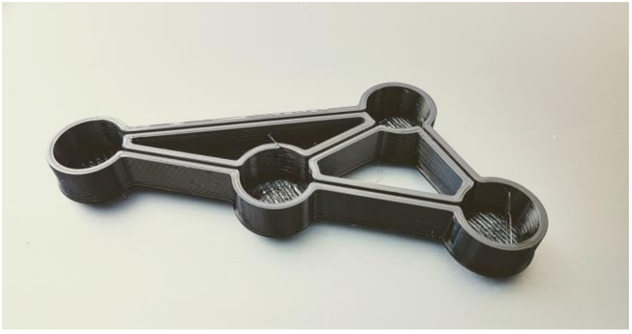
Project keywords: spatial ecology, epidemiology, synthetic biology, microscopy, machine learning

Paramesium caudatum will be one the key organisms studied and modified. Image courtesy of Wikipedia.



Cells will be grown in complex and highly structured environments that are 3D printed to constrain movement and interactions between spatially explicit populations. Image courtesy of Chris Clements.

Project Background

Understanding what regulates the spread of diseases in space and time is critical if we are to combat them effectively. However, identifying the determinants of disease spread in natural populations – be they human or animal – is challenging due to the difficulties of establishing whether an individual is infected or not, lack of replication, and non-control conditions. Furthermore, the complex spatial ecology of connected populations is known to be key for predicting disease spread, but often difficult to quantify and monitor under natural conditions. A solution to these issues is to use model systems – small-scale experiments where the movement of individuals can be tracked over time, their infection status determined, and treatments such as environmental warming implemented. One such model system is the ciliate protist *Paramecium caudatum* which is infected by the bacteria *Holospora undulata*. However, at present identifying whether an individual is infected requires it to be killed, fixed, and stained. Were it possible to non-invasively identify whether individual *P. caudatum* are infected or not, this model system could be used to generate valuable high-dimensional high-resolution data on the dynamics of disease spread at a landscape scale.

Project Aims and Methods

The aim of this project is to develop a new experimental system and supporting computational tools to enable the creation of engineered ecologies in which the spread of *H. undulata* infections of *P. caudatum* can be easily tracked over time. To control the structure of the ecologies produced, spatial organisation will be constrained using 3D printed arenas (see image above), and monitoring will be carried out using automated microscopy. The focus of this project will be on developing two complementary ways to infer the infection state of individual *P. caudatum* cells from these microscopy images. The first approach will use bio-engineering tools to directly modify *P. caudatum* cells such that infection by *H. undulata* leads to the expression of a pigment which changes the colour of a cell. This will be achieved by using transcriptomics data of healthy and infected cells, and then developing synthetic genetic circuitry to redirect the native infection response to the production of a desired pigment. The second approach will attempt to use machine learning techniques to see whether subtle changes in cell behaviour, morphology and appearance might alone provide sufficient information to determine infection state. This will involve the training of deep artificial neural networks (e.g. U-Net) with large numbers of healthy and infected cell images, validating the accuracy of the predictions, and then integrating this system into the monitoring software of the arenas.

Candidate Requirements
Applicants must have an excellent undergraduate or Masters degree (2:1 or first) in an area related to the project (e.g. Biology, Biochemistry, Biological Engineering). They must also be willing to work as part of a highly inter-disciplinary team and have a passion for learning the diverse skills needed to make this project a success (e.g. microbiology, synthetic biology, microscopy and machine learning).

Training
The student will be given training in cutting-edge molecular and synthetic biology methods, 3D printing, robotics and microscopy at the University of Bristol, machine learning techniques for image analysis during regular visits to co-supervisor Dr Metz at the University of Exeter, and essential hands-on microbiology knowledge for working with *P. caudatum* and *H. undulata* through a placement with co-supervisor Dr Kaltz at Montpellier. More broadly, there will be opportunities to gain public engagement experience as part of the "Become a Biological Engineer" project run within the Biocompute Lab [Link], and the Bristol Doctoral College (BDC) will provide extensive opportunities for training in transferable skills and personal development, including productivity, teaching and communication [Link].

References / Background reading list

- Benton *et al.* (2007) Microcosm experiments can inform global ecological problems. *Trends in Ecology and Evolution* **22**, 516-521. [Link]
- Lunn *et al.* (2013) Modelling the Dynamics of an Experimental Host-Pathogen Microcosm within a Hierarchical Bayesian Framework. *PLoS One* **8**, e69775. [Link]
- Greco *et al.* (2019) Living computers powered by biochemistry. *The Biochemist* **41**, 14–18. [Link]
- Falk et al. (2019) U-Net: deep learning for cell counting, detection, and morphometry. *Nature Methods* **16**, 67–70. [Link]

Useful links
School of Biological Sciences – http://www.bristol.ac.uk/biology/courses/postgraduate/
Biocompute Lab – http://www.biocomputelab.org/
Experimental Ecology & Conservation Group – https://www.experimentalconservation.com/
Evolution & Vector Ecology Lab – https://evelab.github.io/

NERC GW4+ DTP Website:
For more information about the NERC GW4+ DTP, please visit: http://nercgw4plus.ac.uk/

Bristol NERC GW4+ DTP Prospectus:
http://www.bristol.ac.uk/study/postgraduate/2020/doctoral/phd-great-western-four-dtp/

How to apply to the University of Bristol: http://www.bristol.ac.uk/study/postgraduate/apply/

The application deadline is 16:00 hours GMT Monday 6 January 2020 and interviews will take place between 10 and 21 February 2020

General Enquiries: Bristol NERC GW4+ DTP Administrator - Email: bristol-nercgw4plusdtp-admin@bristol.ac.uk