Controlling chromosome conformation and content as a step towards synthetic cellular differentiation

Supervisory team:
Main supervisor: Dr Thomas Gorochowski (University of Bristol)
Second supervisor: Dr Hans-Wilhelm Nuetzmann (University of Bath)
Dr Fabio Parmeggiani (University of Bristol), Dr Jill Harrison (University of Bristol)

Host institution: University of Bristol

Project description:
Synthetic biology aims to apply engineering principles to biology to allow us to create novel living systems with our own desired behaviours. In this project, the student will explore the engineering of a fundamental component of all living cells – their genome. Rather than considering it as a constant stable entity, the student will make use of molecular machines able to recognise specific sequences in DNA and carry out structural rearrangements of its content. This will allow for the programmable removal and/or restructuring of genetic information with the goal of drastically altering cellular behaviour. Such cells could then be used to many different contexts, for example, differentiating into many specialised forms to optimise the production of value chemicals in bioreactors through a division of labour.

To archive this, the project consists of two main parts. The first will involve the development of synthetic genetic circuits to control the expression of enzymes able to cut, flip and excise DNA, and the modification of a bacterial genome to include necessary recognition sites for these machines to work. As the 3D structure of the genome may hinder the ability for some modifications to occur as well as affect subsequent gene expression, the second part of the project will attempt to use biophysical modelling to understand how the cell’s genome is packed into the cell and employ an experimental technique called Hi-C to enable us to measure the conformation of bacterial chromosomes in vivo before and after differentiation. Such data will help elucidate the role that spatial organisation has on the function of DNA manipulating enzymes and the subsequent effects on gene expression and cellular function.

This project offers a new perspective on the emerging field of synthetic genomics by exploiting existing molecular machines to carry out the dynamic rearrangement and modification genetic material in living cells. It brings together a broad range of cutting-edge bioengineering methodologies and techniques and will provide insight into the role of chromosome conformation in gene regulation and overall cellular function.