Engineering Science for Health CDT – Project Descriptions

Biological and Molecular Systems Research Theme

The Engineering Science for Health (ESH) CDT explores research in engineering, mathematics and the physical sciences with applications to Healthcare technologies. The CDT is highly multidisciplinary and includes PGR students with backgrounds in Chemistry, Physics, Biosciences, Engineering, Computer Science and Mathematics. Our research is divided into 4 main research themes which are all focussed on Healthcare applications:

(1) Sensors and Imaging

(2) Biological and Molecular Systems

(3) Computational Methods and Modelling

(4) Patient Focussed Technologies.

A range of PhD research projects will be offered across all 4 themes, with students supported by a multi-disciplinary supervisory team.

This document gives more information about the projects offered within the Biological and Molecular Systems research theme.

Summary of Projects - Biological and Molecular Systems Research Theme

Ref Num:	Project Name	Primary suitability for applicants from these disciplines:					
		Physics	Chemistry	Bioscience	Maths	Computing	Engineering
1.1	Quantification of radiation-induced DNA damages using DNA nanotechnology	**X**	**X**	**X**			**X**
1.2	Studying noise-induced gene transitions using DNA computing	**X**			**X**		
1.3	A Synthetic Biology Approach to Studying the Survival of Airborne Viruses	**X**	**X**	**X**			**X**
1.4	Development of spatial single cell proteomics and application to probe bystander effects from proton beam irradiation in single cells	**X**	**X**	**X**			
1.5	Development of ZenoToF mass spectrometry for single cell “omics”	**X**	**X**	**X**			
1.6	Derivatisation at the one cell level to enhance analyte coverage	**X**	**X**	**X**			

For general information about any of the ESH projects, or the application process, please contact eshcdt@surrey.ac.uk

Research Theme Overview

One focus of this theme is frontier research on matter that is derived from living things or that is still living. Living matter is distinct from inert condensed matter by being active, capable of self-assembly and response to stimuli. It is often composed of molecules of biological origin, such as nucleic acids. PhD students in this theme will draw upon knowledge in soft matter physics, analytical chemistry and engineering to study the fundamental principles of how living matter self-organises. Objectives include controlling and engineering living matter to achieve functions such smart drug delivery via controlled response to external stimuli, and understanding the soft matter physics of virus survival in the environment. In addition to this, the students will develop new ways to observe cellular materials at unprecedented levels of detail. The centre will prepare scientists for careers in this rapidly growing interdisciplinary area, an area revolutionising our understanding of how living organisms from viruses to us function, as well as allowing unprecedented control over matter.

Project Descriptions:

Ref Number:	1.1	**Project Title:**	Quantification of radiation-induced DNA damages using DNA nanotechnology
		Project Supervisor(s):	Wooli Bae, Giuseppe Schettino

Project Description: Ionising radiation has two opposite natures. On one hand, it is an important tool in radiotherapy, X-ray imaging, manufacturing and engineering. On the other hand, it can cause heavy damage to our DNA and thus we need to protect ourselves from exposure to ionising radiations. Therefore, various techniques have been developed to quantify the damage done to DNA by ionising radiation. However, most of currently available methods do not give a direct, quantitative result for DNA damage and take a long time.

In this project, the student will first develop a fluorescence-based method to directly quantify the amount of damaged DNA within 15 minutes. This is done by extending the damaged double-stranded DNA using fluorescein-modified DNA base (Figure 1). After optimising the annealing temperatures and annealing time to maximise the signal-to-noise value of our fluorescence signal, the student will test the effect of different types of radiations and environmental conditions on the amount of damage done to DNA. Then the student will use DNA nanoarray and nanostructures to identify spatial patterns of DNA damage done by alpha particles and their secondary radiations. The spatial patterns will be imaged with atomic force microscopy.

Throughout the project, the student will have access to the soft matter physics laboratory and radiation laboratory space for experiments. In addition, the student will have a chance to join the PostGraduate Institute for Measurement Science, receive support from staffs and access to facilities at the National Physical Laboratory. The project is supervised by Dr Wooli Bae (w.bae@surrey.ac.uk) and Professor Giuseppe Schettino (giuseppe.schettino@surrey.ac.uk). Dr Wooli Bae is a lecturer in experimental soft matter physics, specialised in experimental biophysics including DNA/RNA nanotechnology and synthetic biology. Professor

Giuseppe Schettino is a professor of Medical Physics at the University of Surrey and a Principal Research Scientist in the Medical Radiation Science Group at the National Physical Laboratory.

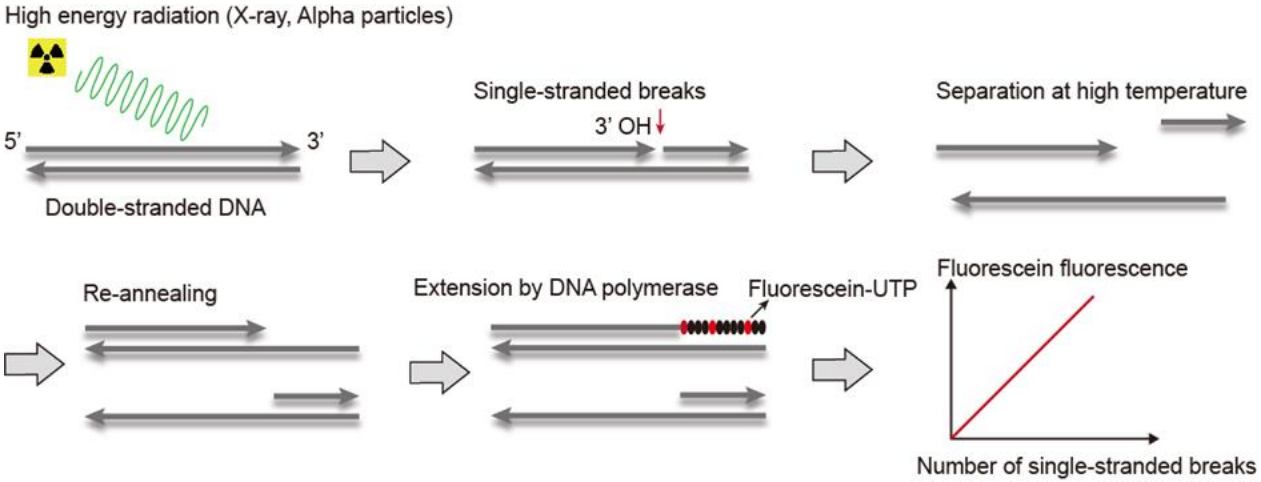


Figure 1. Proposed procedure to quantify DNA single strand breaks. DNA double strand breaks can be quantified by same mechanism simultaneously.

Ref Number:	1.2	Project Title:	Studying noise-induced gene transitions using DNA computing
Project Supervisor(s):			Andrea Rocco, Wooli Bae

Project Description:

Stochastic fluctuations (or noise) affect chemical, physical, and biological systems at different spatial and temporal scales. In biology, although noise can challenge the survival of living systems, it can also play important 'active' roles, such producing heterogeneous phenotypes in genetically identical cell populations.

One example of noise as an active dynamical player is provided by the phenomenon of noise-induced transitions. These may occur for instance when the system is under the influence of a fluctuating environment, undergoing thereby so-called ‘extrinsic noise’. Extrinsic noise can produce highly non-trivial effects, such as the ‘creation’ of stable states, which in turn leads to the emergence of multistability or oscillatory behaviours in systems deterministically monostable.

We have recently formulated a description of extrinsic noise at the level of gene expression that applies when the noise is nonlinear, non-Gaussian, and slower than typical protein synthesis and degradation processes [see for instance G. Aquino & A. Rocco, *Bimodality in gene expression without feedback: from Gaussian white noise to log-normal coloured noise*, Math. Biosci. Eng. **17** (6), 6993 (2020)]. The aim of this project is to extend this formalism further, investigate theoretically noise propagation and transitions in different gene networks, and validate the theoretical predictions in dedicated experiments.

The student will use mathematical analysis to describe noise in specific gene networks by adopting stochastic differential equations models and by performing direct stochastic simulations. A previous background in statistical mechanics or stochastic physics is an advantage. The project also involves an experimental component, aiming for an experimental realisation of the theory on a cell mimic using dynamic RNA nanotechnology.

This project will constitute an important step forward in addressing the role of noise in our understanding of the principles of life and of evolutionary processes.

The project is supervised by Dr Andrea Rocco and Dr Wooli Bae. Dr Andrea Rocco is Associate Professor in Physics and Mathematical Biology, with extensive experience in the analysis of stochastic processes in physical, chemical, and biological systems. Dr Wooli Bae is a lecturer in experimental soft matter physics, specialised in experimental biophysics including DNA/RNA nanotechnology and synthetic biology.

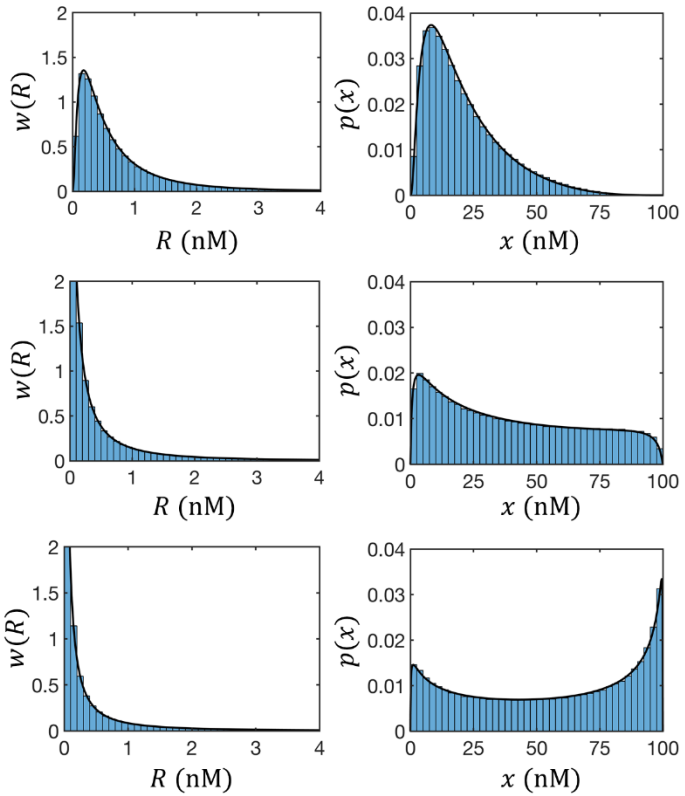
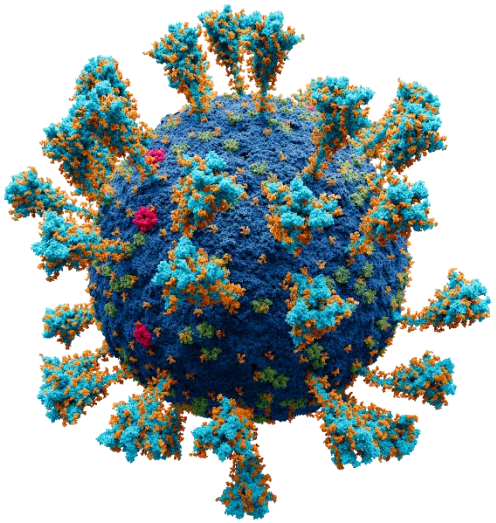


Fig.1. Example of noise-induced transition in the repressed gene in presence of a fluctuating repressing transcription factor. Left column: input noise on repressor; Right column: output noise on gene expression. Noise intensity increasing from top to bottom. The deterministic system is always monostable, but the stochastic system becomes bimodal for high enough noise intensity [From G. Aquino & A. Rocco, Math. Biosci. Eng. **17** (6), 6993 (2020)].

Ref Number:	1.3	Project Title:	A Synthetic Biology Approach to Studying the Survival of Airborne Viruses
Project Supervisor(s):			Richard Sear, Wooli Bae

Project Description:



SARS-CoV-2 particle (Wikimedia). Lipids are shown in dark blue, spike proteins in pale blue and yellow in image, RNA is inside lipid shell.

COVID-19 is estimated to have killed over 10 million people. It also caused a huge worldwide disruption to both people's lives and to economies. Transmission of the virus is known to be over the air, which means it is spread via infected people breathing out tiny respiratory droplets containing viruses. The virus – a hundred-nanometre nanoparticle of lipids, proteins and RNA can survive the rapid (< 1 s) drying process that occurs when small respiratory droplets mix with room air. We don't know how this delicate nanoparticle survives the large stresses drying produces. In this project, we will develop a model virus system and try and answer questions such as: Which part of the virus is the weak link? What are the forces that are most dangerous to a virus? How can we change the environment to destroy more viruses?

The PhD project is flexible in how we will try and answer these questions. One possibility is to make a model virus system and test its survival during rapid drying process. The model viral particle (MVP) will be a small vesicle - i.e., a microscopic spherical shell of lipid-molecules encapsulating synthetic RNA molecules. A solution containing MVPs will be sprayed inside an environment-controlled chamber to mimic the drying process of viruses at different relative humidity and temperature. If the MVP is destroyed during the process, so will the RNA molecules. You will quantify the survival rate of the MVPs using quantitative reverse transcription PCR. We could also take a computational approach and build minimal computational MVPs, and model how both the dramatically increasing osmotic pressure on drying, and the air/water surface tension affects the MVPs integrity.

Ref Number:	1.4	Project Title:	Development of spatial single cell proteomics and application to probe bystander effects from proton beam irradiation in single cells
Project Supervisor(s):			Geoff Grime, Melanie Bailey, Roger Webb, Sneha Pinto, Tony Whetton

Project Description:

Proton beam therapy has gained increasing utility in cancer treatment in recent years. Obtaining a deep understanding of how proton beam impacts affect cell chemistry is important in delivering clinical impact, and yet our knowledge is incomplete. This is because the technology to study the chemistry of living cells following proton beam irradiation does not yet exist. The University of Surrey has recently installed an exciting new system for single and sub-cellular analysis (SEISMIC), which should enable the analysis of proteins, lipids and metabolites from single living cells (Figure 1). We also house the UK's national ion beam centre, where the proton beam therapy will be performed.

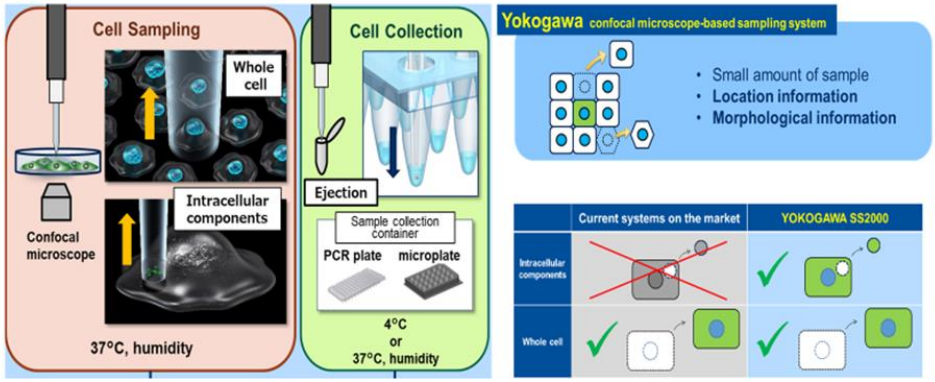


Figure 1: The SEISMIC facility for Cell Sampling at Surrey

In this project, the student will be trained at the BBSRC SEISMIC facility to extract single living cells and their neighbours from 2D culture. They will then work with our collaborators e.g. University of Liverpool to develop methods for transferring single cells into the wells used for single cell proteomics. They will visit the University of Singapore to train in recent developments in microbeam cell irradiation, and will bring their knowledge to Surrey's National Ion Beam Centre. They will combine the developed methodologies to explore proteomics changes in cells and their neighbours following proton beam irradiation.

Ref Number:	1.5	Project Title:	Development of ZenoToF mass spectrometry for single cell “omics”
Project Supervisor(s):			Senha Pinto, Melanie Bailey, Tony Whetton, Olivier Cexus

Project Description:

This project makes use of some exciting, state of the art new instrumentation that has recently been installed in the University of Surrey’s ion beam centre and will apply it to make measurements of biomolecules in living cells at an unprecedented scale.

Time of flight mass spectrometers are widely used for the analysis of lipids, metabolites and proteins, but suffer from low absolute sensitivity due to the duty cycle of the ToF, which falls in the range of 5-25%. A new innovation in mass spectrometry is the ZenoTrap. This is where ions in a selected mass range are trapped in a linear ion trap and released in time with the ToF pulse, enabling a duty cycle of 90% and much higher sensitivity. We have recently installed a ZenoToF mass spectrometer. In this project we will evaluate its potential for the analysis of single, living cells.

The student will be trained at Surrey’s BBSRC National SEISMIC facility to isolate single cells and their organelles under microscope observation. This uses a newly commerialised instrument from the Yokogawa Corporation, which allows cells and their sub-cellular compartments to be aspirated into capillaries under a microscope. The student will work with Sciex to develop optimised methodology for untargeted “omics” analysis of single living cells. Finally, the student will work with collaborators of the SEISMIC facility to demonstrate biological and medical application of this new approach – for example to study bacteria, viruses and circulating tumour cells.

Ref Number:	1.6	Project Title:	Development of Live Cell Metabolomics
		Project Supervisor(s):	Melanie Bailey, Dany Beste, Debra Skene

Project Description:

Consideration of the healthy organism and its development absolutely demands we consider individual cells. The ability to carry out "omics" analysis at the single cell level is already significantly enhancing our understanding of cellular properties and interactions. Commercial solutions for high throughput single cell transcriptomics have recently made important contributions to our understanding of development, infectious diseases, immunology, and ageing. Simultaneously, technologies for high throughput single cell proteomics are evolving. However, these approaches are limited in that they **do not allow spatial resolution**, which is critical for understanding important biology that happens at the sub-cellular level, or spatial phenomena that govern cell survival, proliferation, development, or death. **The aim of this project is to develop a new capability for the UK's first facility for spatially resolved single cell "omics",** to improve animal and human health**.**

In this project, the student will develop live single cell metabolomics. This will be done by adapting derivatisation methods for bulk cells and scaling them down to the single cell level. The student will be trained at the BBSRC SEISMIC facility to extract single living cells and their sub cellular compartments from 2D culture. This uses a newly commercialised instrument from the Yokogawa Corporation, which allows cells and their sub-cellular compartments to be aspirated into capillaries under a microscope (see Figure 1).

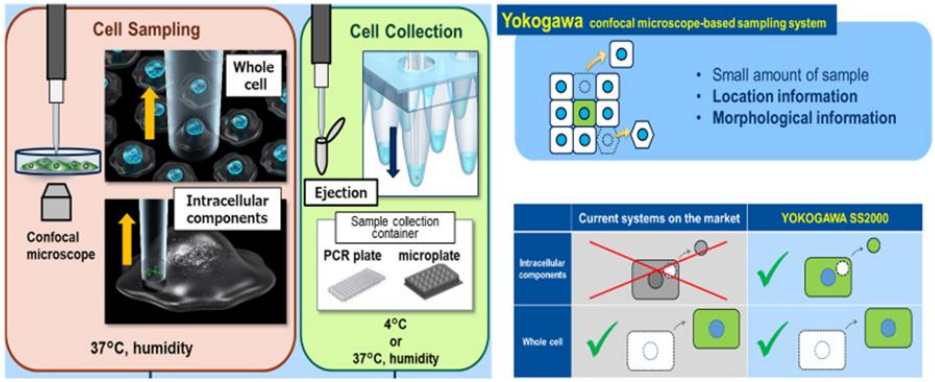


Figure 1: Cell Sampling Instrumentation at University of Surrey