Engineering Science for Health CDT – Project Descriptions

Computational Method and Modelling 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 Computational Methods and Modelling research theme.

Summary of Projects - Computational Method and Modelling Research Theme

Ref Num:	Project Name	Primary suitability for applicants from these disciplines:					
		Physics	Chemistry	Bioscience	Maths	Computing	Engineering
2.1	Drug resistance through rewiring of gene regulatory networks	**X**		**X**	**X**	**X**	**X**
2.2	Modelling cell mechanical feedbacks in organoid development	**x**			**X**	**X**	**x**
2.3	Computational inference, modelling and simulation of gene regulatory networks during neural development	**X**			**X**	**X**	
2.4	Modelling the spatial heterogeneity of gene regulatory networks in cancer leading to drug resistance			**X**	**X**	**X**	**X**
2.5	Detection of peripheral artery disease using machine learning				**X**	**X**	
2.6	Optimising shock wave therapy using modelling investigations of high-amplitude pressure waves on cells				**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

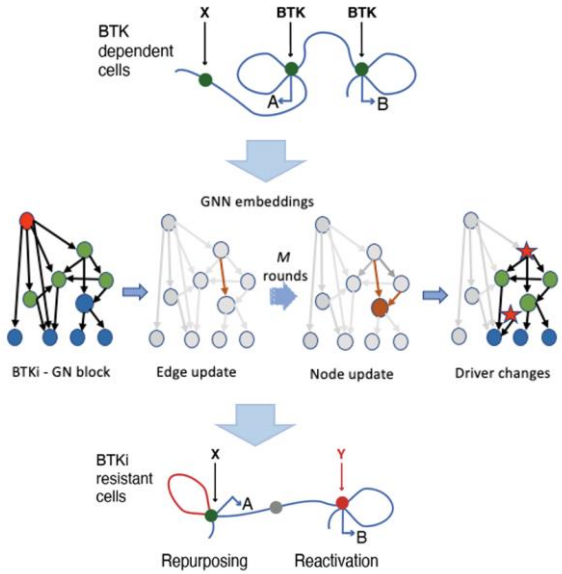
The importance of modelling and simulation in advancing new solutions to healthcare challenges is now widely recognised. Recent developments in systems biology and network science allow us to envisage a future where digital twins reach their potential to suggest new treatments and interventions. Equally systems modelling and analysis are rapidly progressing the fields of disease diagnosis across applications. Progressing these fields will require advances in computational modelling, optimisation techniques, high performance computing, and an expanding repertoire of observational data across multiple scales and modalities. Collectively the projects in this theme will produce novel techniques to integrate and fuse data across multiple scales, analyse the resulting models, and lead to increased precision medicine and treatment. Applications include cancer modelling, dementia research and heart disease. The theme focus will be on innovation through predictive equation-based modelling and simulation.

Project Descriptions:

Ref Number:	2.1	**Project Title:**	Understanding how drug resistance develops through rewiring of gene regulatory networks
Project Supervisor(s):			Sotiris Moschoyiannis, Roman Bauer, Tom Thorne Collaborative supervisor: Mikhail Spivakov, MRC London Institute of Medical Sciences and Imperial College London

Project Description:

Targeted anticancer drugs can produce striking outcomes, but in most cases resistance develops eventually. The emerging view is that acquisition of drug resistance by cancer cells frequently involves molecular changes that extend beyond coding-region mutations and potentially beyond mutagenesis per se. The proposed research capitalises on the UK's leading position in genomic healthcare and genetics research and fuses it with systematic techniques that build on AI / Machine Learning and Network Science that apply to sequential decision-making in incompletely known environments. This project aims to develop novel algorithmic techniques and advanced software to delineate key changes in the regulatory wiring upon acquisition of drug resistance and predict actionable vulnerabilities in the drug-resistant network, using network analysis including graph neural networks and deep reinforcement learning. The predictions will be validated experimentally on real gene data (gene expression profiling but also proteomics and signalling).



The successful applicant will have the opportunity to collaborate with genomics researchers from Dr Spivakov's lab at the MRC London Institute of Medical Sciences and Imperial College Faculty of Medicine. They will also collaborate with other members of the Nature Inspired Computer Engineering (NICE) group and Biosciences and Maths, and utilise the methods, models and software, including deep reinforcement learning and logical network components, developed as part of this line of research towards own research objectives.

Ref Number:	2.2	Project Title:	Modelling cell mechanical feedbacks in organoid development
Project Supervisor(s):			Carina Dunlop

Project Description: Mechanical forces play a critical role in directing cellular behaviours, in combination with biochemical signalling. However, scaling up from single-cell behaviour to multicellular tissues is challenging due to the inherent complexity generated by cell-cell and cell-tissue interactions operating over widely differing time and length scales. Indeed, it is now very clear that in three-dimensions tissues and cells respond very differently to tissues in two-dimensional culture. Mechanically these observed experimental differences may be caused by how changes in the mechanical microenvironment are transmitted into three-dimensional structures, changes in the internal force generating mechanism of the tissues and the influence of geometrical constraint.

This project will specifically develop digital twins for organoids. The aim is to use these models to better understand mechanical feedbacks in these crucial tissues, currently being widely used in a range of experimental systems ranging from pharmaceutical drug development to cell molecular biology research. The project will be used to inform experimental investigation into the role of mechanical sensing in three-dimensional tissues, drawing on currently ongoing research collaborations. The models will be based on developing continuum descriptions of two key cell-derived force-generating mechanisms: contractility and growth. Importantly the project will develop new models coupling mechanical signalling with crucial biochemical signals investigating how these may be integrated into developing tissues. The student would ideally have a strong background in applied mathematics, theoretical physics or bioengineering. No prior experience of biological modelling is required but a willingness to engage deeply with biological detail is essential.

Ref Number:	2.3	Project Title:	Computational inference, modelling and simulation of gene regulatory networks during neural development
Project Supervisor(s):			Roman Bauer, Sotiris Moschoyiannis

Project Description:

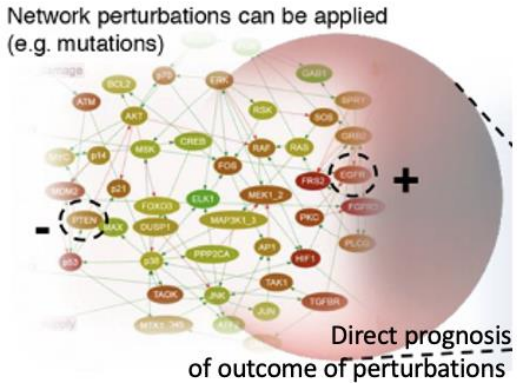
The mammalian brain is a highly complex system that develops from a single precursor cell. A better understanding of this developmental process could improve our understanding of the brain, and also give rise to new AI methods. The proposed project brings together neuroscience, computer science and engineering with the aim to develop novel AI techniques that can systematically explain and analyse brain function. The student will analyse biological gene expression data available from public databases and from experimental colleagues. Based on this analysis, the student will infer plausible models of gene regulatory networks for neural network development, and simulate these using innovative computational tools. Finally, it will be demonstrated using agent-based modelling how realistic brain tissue develops in its physical 3D environment, and how this process can go wrong in neurodevelopmental diseases.

The successful applicant will have the opportunity to collaborate with other members of the Nature Inspired Computer Engineering (NICE) group, and to utilise the models and software, including the BioDynaMo software (biodynamo.org). In addition, they will have access to existing collaborators with CERN (Switzerland) and other BioDynaMo institutions (CERN, University of Cyprus, University of Geneva, GSI Helmholtz Centre, Newcastle University, SCImPULSE Foundation) which offer the opportunity for the student recruited to be hosted at these institutions as well as benefit from the organisation of workshops / schools on agent-based modelling, and high-performance scientific computing.

Ref Number:	2.4	Project Title:	Modelling the spatial heterogeneity of gene regulatory networks in cancer leading to targeted therapeutics
Project Supervisor(s):			Spencer Thomas, Kuize Zhang, Sotiris Moschoyiannis Collaborative supervisor: Prof Francesca M. Buffa, Bocconi University, Italy, and University of Oxford, UK

Project Description:

Molecular systems involve complex interactions among various components. Gene behaviour in the cell can be studied in silico using discrete dynamical models, such as Boolean Networks, where genes are in one of two states, i.e., ON (1) / OFF (0). The behaviour of the underlying *gene regulatory network* (GRN) over time translates into the long-term expectation of health and disease, or the cell's response to stimuli such as drug treatments. Perturbations on genes, e.g., activation/over-expression (1) or silencing/loss-of-function (0) disrupt regular cell functions. However, complex interactions between genes, which pertain to specific cancer types, make predicting the effect of such perturbations on long-term expectation of health and disease rather challenging. The proposed project aims to develop novel algorithmic techniques and advanced software to aid in the prognosis of the outcome of a series of perturbations on GRNs and signalling networks. This will involve graph networks and/or reinforcement learning to learn the function that best approximates the dynamics of the gene network. The approach will be used to validate corresponding novel hypotheses on perturbation outcomes for coherence with additional cancer-related facts in oncology.



The successful applicant will have the opportunity to collaborate with integrative genomics researchers from Professor Francesca Buffa's lab who is the Head of Computational Biology and Integrative Genomics group at the Department of Oncology, University of Oxford. Francesca recently also holds an ERC Award at Bocconi University, Italy. They will also collaborate with other members of the Nature Inspired Computer Engineering (NICE) group and Biosciences and Maths, and utilise the methods, models and software, including deep reinforcement learning and logical network components, developed as part of this line of research towards own research objectives.

Ref Number:	2.5	Project Title:	Detection of peripheral artery disease using machine learning
Project Supervisor(s):			Prof. Philip Aston and Prof Christian Heiss

Project Description: This multidisciplinary project is concerned with detecting peripheral artery disease (PAD) from a photoplethysmography (PPG) signal collected from a sensor on the foot. PAD is characterised by narrowing of the arteries that results in reduced blood flow to the limbs. It is common in people with diabetes and increases the risk of ulcers, amputation, and mortality. The mortality risk exceeds 70% within 5 years which is similar to many cancers. Costs of diabetic foot care in the UK are estimated to be ~£950m annually (~0.9% of NHS expenditure). However, 9/10 people with PAD are undetected. A simple method for earlier detection of PAD would enable life changing early treatment for many patients.

The project will use the novel Symmetric Projection Attractor Reconstruction (SPAR) method to represent the signal as a two-dimensional bounded attractor that encapsulates the morphology and variability of the signal. Attractor features will be derived as input to machine learning and attractor images used as input to deep learning to address two fundamental questions: (i) does the patient have PAD? and (ii) if they do, what is the degree of severity of the disease? Interpretability methods will be used to explain the aspects of the features and the images and of the signal that are important for the predictions in order to give confidence in the results. Generalisability of the model will also be explored by testing it on other datasets collected at different hospitals and with different devices.

Ref Number:	2.6	Project Title:	Optimising shock wave therapy using modelling investigations of high-amplitude pressure waves on cells
		Project Supervisor(s):	Dr Serge Cirovic

Project Description:

Therapeutic use of high-pressure waves (shock wave therapy or SWT) has been in use since early 1980s when the first systems were developed to perform lithotripsy (non-invasive treatment of kidney stones). The physical principle of operation is based on generating high-pressure waves outside of the body and transmitting them through the tissues all the way to the treatment area. The waves can be either of very high amplitude (up to 100 MPa), short duration, and focussed narrowly on the treatment area (focussed SWT), or they can be of a lower amplitude (up to 10 MPa), longer duration, and spreading in all directions (radially) from the application area on the surface of the skin (radial SWT). The range of application for both modalities of SWT soon spread to involve the treatment of many medical conditions other than kidney stones, such as the inflammation of connective tissue (plantar fasciitis, Achilles tendonitis), bone malunion, skin ulcers, and others. The list of applications is constantly growing, and although there is still some debate on the effectiveness of SWT beyond lithotripsy, there is a consensus that the method is effective. While the physics of breaking kidney stones is well understood, the mechanical and biological effects through which pressure waves enhance the healing process in, e.g., tendonitis is still not clear. For example, in treating musculoskeletal conditions focussed and radial SWT often produce similar therapeutic effects despite the vast difference in amplitudes of the pressures applied. This lack of understanding of the mechanism behind the healing process results in a largely empirical approach when designing treatment protocols. This includes the configuration of the SWT source, frequency and number of shock pulses delivered per session, energy density, and total energy of waves delivered. We have constructed finite element models of the SWT source and human foot and conducted ex-vivo experiments to investigate the physical effect of therapeutic pressure waves on a macroscopic level (e.g., cavitation in tissue due to a negative phase of the waveform). For most researchers, though, the focus is now shifting to the effect that pressure waves have on the physiology of cells leading to a positive outcome in terms of tissue healing. The most commonly investigated cells are chondrocytes and platelets. For example, it has been shown that platelets can be activated by being exposed to radial shock waves.

In this project, the successful candidate will develop computational models of cells (chondrocytes and platelets) to simulate the mechanical stimulus generated through SWT and to predict the biological response of the cell. Although this study is intended to be mainly computational, experiments will be conducted on cell cultures to quantify the effect of exposure to the shock waves in terms of biological response. The results of these experiments will be used both to validate the models and to facilitate their development in an interactive way. The working models will be used to explore the effectiveness of different scenarios of SWT clinical protocols to optimise their design. Potentially, the study can also contribute to new SWT source designs.