Projects for EPSRC PhD Studentships
(full funding available)
Magnetohydrodynamics

Fast energy conversion by magnetic reconnection in three-dimensional plasmas
(Dr D Pontin, Prof G. Hornig)

Plasmas – electrically conducting fluids – account for more than 99% of the matter in the Universe. Magnetic fields play a crucial role in the dynamics of the plasma on all scales, from galaxies to the Sun, the Earth's magnetosphere and laboratory nuclear fusion devices. A fundamental question in these plasmas (in which the dissipation is typically very small) is how stored energy can be liberated from the magnetic field on a dynamic timescale. The release of this magnetic energy is observed to occur explosively, as in for example flares in the Sun's atmosphere or sawtooth crashes in tokamak fusion plasmas. The process at the heart of this explosive energy release is *magnetic reconnection*. Historically, the concepts of reconnection are based on the original two- dimensional, steady-state models. In recent years a major advance in our understanding of magnetic reconnection has been the realisation that the rate at which it occurs can be substantially enhanced when the reconnection site becomes fragmented. However, there remain many fundamental, unanswered questions concerning reconnection in three dimensions for a fragmented reconnection site, such as; How should the *reconnection rate* be measured and how should it be interpreted? What is the relation to the rate of energy conversion? Into which forms is the energy converted?

This project involves the development and use of a combination of theoretical and computational modelling techniques to study the structure and dynamics of energy release in three-dimensional plasmas. A student undertaking the project will gain skills and expertise in modelling and high-performance computing. The results will enhance our understanding of energetic events in plasmas on a range of scales, from the laboratory to galaxies.

Refinements of Magnetic Helicity **(Prof G. Hornig, Dr D. Pontin)**

Magnetic Helicity is an integral, which measures the pairwise linkage of field lines in a magnetic field. It is widely used to understand the dynamics of magnetic fields in plasmas as for instance the magnetic field of the Sun. The generation, transport and evolution of this quantity is of particular importance for the dynamo in the interior of the Sun, which generates magnetic fields from the convective motions of the plasma.

With magnetic helicity mathematicians and physicist have a concept to measure the linkage of flux in a magnetic field. This quantity can be viewed as the generalisation of the linking integral of two closed curves, introduced by Gauss in the 19th century, to a continuous vector field. The concept has been successfully used to explain the turbulent relaxation of laboratory plasmas (J.B. Taylor, 1974) as well as more recently the properties of the solar wind and the magnetic dynamo.

However, magnetic helicity only measures the average linkage of magnetic flux in a volume and hence does not recognise many details of the field. Recently Yeates and Hornig (Physics of Plasmas, 2013) suggested a method to assign a contribution of magnetic helicity to individual magnetic field lines and were therefore able to extract much more information from this new quantity about the evolution and dynamics of the plasma. This project exploits these findings and develops them further. Over the last two decades over four thousand publications referring to magnetic helicity have been published. This shows how important this concept is for the scientific community. The recently published refinement of this notion is ready to be exploited and any results will certainly get significant attention from the plasma and astrophysics community.

This is a project which requires mathematical and numerical skills. It will use mathematical techniques (analysis, geometry, topology) and numerical computations to construct examples and derive new results.

Mathematical Biology and Numerical Analysis

Modelling Cell Differentiation in Bacterial Biofilms

(Prof F.A. Davidson, Prof N. Stanley-Wall)

Biofilms are social communities of microbial cells that underpin diverse processes including sewage bioremediation, plant growth promotion and plant protection, chronic infections and industrial biofouling. They are hallmarked by the production of an extracellular polymeric matrix. One of the phenotypic consequences of biofilm formation is that resident microbes are highly resistant to physical stresses and antimicrobial agents. Accordingly, biofilm disruption and stabilisation has become a popular concept for both the development of novel antimicrobial strategies and the utilisation of biofilms for productive purposes. A critical target for altering structural integrity is the biofilm matrix. Nonetheless, while studies to date have provided a biofilm matrix 'parts lists' (lipids, proteins, extracellular DNA, and exopolysaccharides), and details on the regulation of their production, surprisingly little is understood about the primary and three dimensional structures of the key component parts, how they co-assemble, and the emergent biophysical and mechanical properties of such biofilm molecular composites.

Our aim is to comprehensively define and quantify the physical and mechanical properties of the developing and mature B. subtilis biofilm. It is clear that removal of the individual matrix components has a profound macro-scale effect on the dynamic architecture of the biofilm. To test how changes to the constituent parts of the matrix scale up to affect large-scale phenomena we aim to form novel models that capture the structure of the biofilm at the micro-scale. Cell division, differentiation and production of matrix components will be modelled using a simple PDE approach to obtain a locally averaged description of matrix composition and how it changes in space and on maturation that is consistent with the experimental data acquired ion the NSW lab. At a finer scale, an individual-based approach will be taken. To make rapid progress we will utilise the freely available iDynoMics package. This individual-based-model (IMB) will detail (multiple) individual cells and will be capable of testing hypotheses regarding local heterogeneity in cell-type and matrix production and composition. As details emerge, we can increase the flexibility of the modelling approach by utilising either grid-based site and bond models or indeed grid-free models. The signalling fields can then be linked to the matrix model using a discrete-continuum hybrid approach. Simpler, averaged (lumped) models will provide a route to parameterisation.

Understanding altruism in populations of bacterial pathogens

(Prof F.A. Davidson, Prof F. Sargent)

Many species of bacteria display what is called bimoidal behaviour – different subpopulations exhibit different characteristics. This division of labour plays a key role in determining bacterial infections. This project will take a cross-disciplinary approach with multi-scale mathematical modelling at its core to better understanding the underlying mechanism of this bimodal expression.

The aim of this project is to build and analyse mathematical models with which to make significant progress towards understanding the structure of bacterial populations and how they regulate protein secretion events in a sub-population-selective manner.

This project will take a cross-disciplinary approach to understanding the underlying mechanism of this bimodal expression. Mathematical modelling will be used to bridge information across scales: models will be constructed with which to elucidate the control mechanism responsible for bistability in the gene regulation pathway for chitinase expression. These models will then be "up-scaled" to the population level. These models will be supported by biological approaches where possible that will combine live cell imaging and cell-sorting with molecular genetics to understand whether a small subpopulation are predisposed to chitinase secretion. Phenotypic behaviour at the individual cell level will be placed in the context of the (sub-) population to reveal a deeper understanding of how, why and under what conditions this altruistic behaviour occurs. The link between wet and dry approaches will be assisted by use of state-of-the-art quantitative live cell image analysis software.

Stochastic control and nonlinear feedback in models for protein synthesis

(Prof F.A. Davidson, Dr C. M. Romano)

In this project we plan to investigate stochastic control and feedback in Totally Asymmetric Exclusion Processes (TASEP) - a statistical physics modelling tool use to represent the uni-directional movement of particles along a one-dimensional lattice. There is a well established theory of standard TASEP models. However, when TASEP are linked to the production of a pool of products that provides either positive or negative feedback control and links multiple TASEPs together, then a far richer solution behaviour results, much of which is yet to be explored. We intend to investigate key aspects of this feedback process including coupling of multiple TASEPS, negative feedback control via the product pool, positive feedback via particles and combinations of these effects.

Nonlinear feedback loops are ubiquitous in natural and artificial systems. They play a central role in the theory of complex systems, responsible for fundamental effects such as memory formation and self-sustained oscillations. One crucial aspect that remains largely unexplored, however, is the effect of stochasticity on dynamical systems containing nonlinear feedback loops. One key area where this effect is pivotal is the regulation of protein production through the process of translation. This process will form the focus of applications of the theoretical work detailed above

The proposed project is in line with current activities in the Davidson and Romano groups and proposes to build on a successful jointly supervised PhD project. The proposed work will involve co-workers with both groups, in particular Dr N. Stanley-Wall UoD, Prof. C. Kuttler, Munich (biofilms) and Prof. M. Lefranc, Lille and DYCOEC - DYnamique et COntrôle des Ensembles Complexes) (complex dynamics and control)

Modelling the somitogenesis clock

(Dr P. Murray, Dr K. Dale)

Somitogenesis, one of the earliest instances of segmentation in the developing embryo, is the process by which pairs of somites form sequentially along the vertebrate axis from the presomitic mesoderm. Somite formation is preceded by spatio-temporal waves of gene expression that are thought to regulate the location, in both space and time, at which the next somite pair form. Despite the identification of numerous genes involved in the process, the mechanisms underlying the spatio-temporal patterns remain unproven. However, recent studies using high-resolution datasets, notably generated by multidisciplinary research teams, have identified intriguing phenomena that motivate the revisit of previous models.

The cornerstone of this project is a novel, recently-curated, unpublished dataset that allows the characterisation of spatio-temporal dynamics of up to 16 components of the Delta-Notch signalling in 3D mouse PSM tissue. After further processing these data, we will develop novel mathematical models of Delta-Notch signalling in PSM tissue that describe recently observed spatio-temporal oscillations and travelling wave behaviours. Furthermore, having developed a model in one spatial dimension that describes tissue-scale wave behaviours, we will develop computational algorithms that search for non-trivial patterns of local transcription in 3D and use the results to develop novel cellular-scale models that take account of the new observations. The models will be tested experimentally using the real-time imaging system that our shared PhD student is currently developing. By systematically combining observations of multiple components of the pathway with real-time images, this work will make a significant contribution to what is an exciting and evolving field of research.

Modelling the reverse transcription of the HIV virus

(Dr P. Murray)

Correct disassembly of the HIV-1 capsid shell, called uncoating, is increasingly recognised as central for multiple steps during retroviral replication. However, the timing, localisation and mechanism of uncoating are poorly understood. Previous work has suggested that uncoating occurs soon after entry of the viral core into the cell, but recent studies report later uncoating, at or in the nucleus.

Furthermore, inhibiting reverse transcription delays uncoating, providing evidence that these processes are coupled.
We have recently combined mathematical modelling and experimental interrogation of viral mutants to investigate the timing of uncoating with respect to reverse transcription. After fitting a minimal, testable, model to viral kinetics in the presence of different pharmacological inhibitors, the model predicted an uncoating threshold about 1000 base pairs along the viral genome. This result was verified using viral mutants. Hence we found that uncoating is not concomitant with the initiation of reverse transcription but instead triggered once reverse transcription reaches an intermediate stage.
In the proposed project we will build upon the existing work by developing an explicit model of virus uncoating. We will consider physical models of the virus capsid that describe its decay within the cell as reverse transcription occurs. The model will be tested using a upcoming set of experimental data that allow uncoating to be perturbed and reverse transcription to be monitored. The end goal of the PhD project will be to have accurately coupled mechanistic models of both reverse transcription and uncoating.

DNA damage repair and cancer treatment

(Dr P. Murray, Dr B. Cornelissen)

When a cell suffers DNA damage, the histone H2AX becomes phosphorylated,forming γH2AX. By raising antibodies to several of the proteins involved in DNA damage repair, such as γH2AX, and radiolabelling them, BC has demonstrated a method for detecting tumours before they are palpable and detectable by other imaging methods. Moreover, by radiolabelling the antibodies with Indium, which is a gamma ray and Auger electron emitter, he can deliver therapeutic doses of short path-length radiation to treat tumours while they are still quite small.
We develop a mathematical model that describes spatially-averaged aspects of the above experiments. The goal of the PhD project is to build on this recent work by: (i) using new foci kinetics data to model additional pathway components; (ii) model the action of DNA damage inducing drugs; and (iii) develop spatial models of DSB induction by Indium within single cells.
In particular, an intriguing observation made by BC is that after irradiation, γH2AX foci are randomly distributed throughout the genome. However, when co-treated with the indium labeled anti-γH2AX antibody, γH2AX foci form aggregates. Hence spatial location in the genome plays a critical role in the probability of a particular DNA site undergoing further DSB.
Whilst the current model uses cell population scale measurements to infer the rates of processes occurring at individual DNA DSB sites, in the next stage of the study we will consider a spatial model of DNA within a single cell. The structure of regions of DNA within a cell will be approximated in order to define a spatial domain on which DSBs can occur and the rate parameters inferred from the previous study [3] will provide us with an initial parameterized model of kinetics at individual DNA sites. The model will be used to predict the spread of DNA damage from other Auger electron emitters and identify candidates that provide optimal cancer cell death.

Modelling cell polarity in neural stem cells

(Dr. P. Murray, Dr. J. Janushke)

As stem cell activity in a tissue is positively correlated with cancer risk understanding the mechanisms that control stem cell division is of immediate biomedical relevance. Much of our knowledge on the molecular logic sustaining stem cell division is derived from model systems, such as Drosophila. Stem cells of the developing nervous system of the fly are particularly relevant since faulty stem cell division has been shown to cause malignant overgrowth. Like most cells, stem cells need to establish cell polarity in order to function correctly and loss of polarity leads to tumors. Using CrispR/Cas9 and BAC recombineering, we have engineered transgenic flies that carry functional, fluorescently-labeled probes allowing us to follow the dynamics of key polarity proteins operating during neural stem cell division.
Using advanced digital imaging in combination with primary cell culture, we can trace single stem cells over several cell cycles and quantify cell polarization events that precede each cell division.

Using this assay, our goal is to establish the temporal ordering of events preceding division and decipher sub cellular stem cell pattering that regulates polarity.
In this project we will develop computational algorithms that extract quantitative information from the experimental movies. Improved codes will be developed that track cell motion and characterize the spatiotemporal kinetics of the different fluorescently-labelled molecules. For example, preliminary observations suggest that travelling waves of protein levels along the cell membrane precede cell division. By quantifying such behaviours in large numbers of cells we will generate robust measurements that will be used to motivate modeling assumptions.
We will then develop a mathematical model that links observations of spatio-temporal kinetics to the emergence of polarity at the single cell scale. Moreover, we will simulate the model of cell polarity defined at the single cell scale in tissue-scale models of cell motion and investigate in silico conditions under which the observations of cell polarity are sufficient to give rise to the malignant overgrowth phenotype.

Biomechanics of cardiac muscles and plant tissues: multiscale modelling, analysis and numerical simulations of biological materials comprising fibrous microstructures

(Dr M. Ptashnyk, Dr I Kyza)

Interactions between biochemical processes, fluid flow, complex microstructures and mechanical properties play an essential role in the development and functionality of plant and human body tissues. The microscopic structure of heart muscles and plant cell walls is characterised by fibrous and plywood structures, given as the superposition of gradually rotated planes of parallel aligned fibres. The main objective of this project is to derive and analyse novel mathematical models for heart muscles and plant tissues biomechanics, especially to consider the impact of fibrous microstructures on mechanical properties of biological tissues and the interplay between mechanics, flow and chemistry. In the proposed research we shall combine the design of new models, mathematical analysis and numerical simulations of the model equations. Microscopic modelling approach will allow us to consider non-homogeneous distributions of structural elements of biological tissues and interactions between microstructure, chemistry and mechanics. Systems of nonlinear partial differential equations will be considered for continuous description of the biomechanics of plant and heart tissues. Mathematical analysis will involve extension of homogenization techniques for non-periodic microstructures, and rigorous derivation of macroscopic equations from microscopic description of chemical processes and mechanics of biological tissues. Numerical analysis will comprise selection and design of suitable numerical schemes for multiscale numerical simulations of mathematical models and derivation of error estimates for numerical approximations of solutions of corresponding partial differential equations.
Mathematical modelling and numerical simulations will allow us to examine how cellular changes affect stress and strain distributions within heart muscles, and, hence, support a better understanding of biomechanical changes in the heart tissue caused by diseases. Multiscale modelling and simulation of plant tissues is important to better understand the influence of microscopic interactions on macroscopic properties and mechanisms controlling plant growth.

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