BBSRC Research Experience Placements Summer 2025

Supervisors and Projects

- **Damon Griffiths -** Developing a time-resolved hydrogen/deuterium exchange-mass spectrometry method for the conformational analysis of membrane proteins**.**
- **Dongda Zhang -** Advancing Sustainable Fermentation through Digital Twin Modelling
- **Filipa Cox -** Investigating the relationship between soil fungal communities and the drought resistance of *Pinus pinaster* saplings.
- **Giles N. Johnson** - Engineering chloroplast PTOX to understand plants acclimation mechanisms
- **Holly Shiels** - Microplastics in sea turtles
- **Joshua Lynn -** The influence of nutrient addition and plant functional diversity on ecosystem responses to drought
- **Martin Baron -** Live imaging of Notch signal responses to gain and loss of function Notch mutants in Drosophila wing development.
- **Martin Lowe** - Identifying drugs that alter the secretory pathway**.**
- **Mato Lagator -** Using molecular and synthetic biology to study bacterial evolution
- **Rasmus Petersen -** Investigation of animal behaviour using Artificial Intelligence
- **Robert Sansom** - Reproducibility in morphological phylogenetics
- **Robin Curtis -** Impact of adenosine tri-phosphate (ATP) on assembly of unfolded proteins
- **Rok Krasovec -** Density-associated mutation rate plasticity in microbial communities
- **Sam de Visser -** Mechanism of Natural Product Synthesis by Fungal Nonheme Iron Dioxygenases

Developing a time-resolved hydrogen/deuterium exchange-mass spectrometry method for the conformational analysis of membrane proteins.

Name of Supervisor: Damon Griffiths

Email: damon.griffiths@manchester.ac.uk

Integral membrane proteins (IMPs) are vital components of cellular membranes, playing essential roles in processes such as signal transduction and transmembrane transport. As the largest class of drug targets, understanding their molecular mechanisms is crucial for the development of novel therapeutics. However, their amphipathic nature and dependence on lipid membranes make them particularly challenging to study within the context of structural biology.

Hydrogen/deuterium exchange-mass spectrometry (HDX-MS) is a powerful emerging technique in the structural biology toolkit. Its capable of providing complementary information on challenging targets, such as IMPs, that are often unamenable to traditional atomistic-resolution structural approaches. By measuring the rate of amide hydrogen exchange along the polypeptide backbone –which is dependent on the protein higher-order structure – HDX-MS can report on protein conformational dynamics across different states (e.g., ligand/substrate-bound vs apo).

Using the classical HDX-MS workflow, proteins are first locked in each state under equilibrium conditions. HDX measurements are then taken to see how a specific condition (i.e., ATP-binding) alters the rate of HDX relative to a reference state (i.e., apo). A feature of this approach is that readout is averaged across the protein conformational ensemble of each state, which can potentially obscure transient conformations adopted when proteins transition between states.

Using the ATP binding cassette transporter MsbA as a model system, this project focuses on developing a time-resolved HDX-MS method capable of generating conformational reporters of transient states not observed under classical equilibrium binding conditions. The student will work closely alongside a postdoc (Damon Griffiths) to achieve the following:

1. Express MsbA protein and purify it into DDM detergent
2. Write a method on HDX-MS robotics system for time-resolved measurements
3. Perform time-resolved HDX-MS on ATP-bound MsbA in DDM

The student will, therefore, have an opportunity to gain hands-on experience in IMP sample preparation and structural mass spectrometry.

https://politislab.uk/

Advancing Sustainable Fermentation through Digital Twin Modelling

Name of Supervisor: Dongda Zhang

Email: dongda.zhang@manchester.ac.uk

Improving the economic competitiveness of industrial bioprocesses for sustainable commodity chemicals production is one of the grand research themes of the 4th Industrial Revolution. Currently, industrial bio-manufacturing systems primarily rely on the use of fermentation technology, with global market demand of their produced compounds estimated to reach £70 billion by 2025. Despite their huge success and impact, however, the conversation efficiency from organic carbon sources to final product is still very low in most of industrial fermentation processes (ranging from <1% to 20% depending on the complexity of metabolic pathways and operating conditions). Moreover, these bioprocesses contravene the concept of circular economy due to substantial CO_2 emissions and undesirable waste products generated.

In order to resolve this challenge, developing predictive digital twins to maximise bioprocess efficiency and minimise waste generation has become one of the most critical steps. Given the rapid development of advanced mathematical modelling tools and their potential in future process automation and bioreactor design, this summer placement project aims to construct an accurate kinetic model to analyse industrial bioprocess data and guide optimal design of experiments for the underlying process. Specifically, this project will focus on a fermentation process for high-value biorenewables production. Experimental data has been available at this moment. During the summer internship project, we will build and compare different kinetic model structures to simulate the dynamics of the complex bioprocess and estimate its variability. We will also provide a range of supervisions to support the student, including:

- Assigning a senior PhD student to co-supervise the student;
- Having weekly meetings with the supervisor and the PhD student to update progress;
- Providing valuable resources (e.g. specific code and teaching materials developed within the group) to help improve the student's programming skills;
- Possibility to bring the student to a research workshop/seminar to develop their interest in biotechnology.

https://research.manchester.ac.uk/en/persons/dongda.zhang

Investigating the relationship between soil fungal communities and the drought resistance of *Pinus pinaster* saplings.

Name of Supervisor: Filipa Cox

Email: Filipa.cox@manchester.ac.uk

Under anthropogenic climate change, the frequency, intensity, and duration of droughts are predicted to increase, particularly in southern parts of Europe. Drought can cause large scale forest dieback and shifts to alternative ecosystem states, resulting in substantial carbon and economic losses. Informed management is essential for the maintenance and establishment of drought tolerant forests yet the factors that determine forest responses to drought are poorly understood.

In the Soil Ecosystem and Ecology Laboratory, research centres on interactions between soil and plant microbial communities and how they regulate the structure and function of terrestrial ecosystems. This creates an understanding of how these ecosystems respond to changing land-use and climate. This project asks whether growing trees in soils conditioned to low water availability can improve their drought resistance, and whether this is related to the soil fungal community present. Saplings have been grown specifically for this project on soils collected from droughted and irrigated *Pinus pinaster* monoculture plots in South France (TreeDivNet - ORPHEE (France)).

Initially working at the Firs Environmental Research Station (The Firs environmental research station - Department of Earth and Environmental Sciences - The University of Manchester) the student will drought saplings and collect real time data on gas exchange and photosynthesis using a LI-6800. The student will then harvest the plants, collecting tissue samples to assess the effects of drought on the plants as well as soil and root samples to assess changes in the soil fungal communities. Samples will then be analysed in our state-of-the-art laboratory.

The collected data will be analysed, and the results of the work used to inform the planting and management of drought resistant forests, contributing to sustainability in forestry. The student will have a great degree of flexibility but can expect to gain skills in experimental design, laboratory work, and bioinformatics.

Soil ecosystem ecology lab: Soil and Ecosystem Ecology Lab - The University of Manchester

Filipa Cox Research: Filipa Cox - Research Explorer The University of Manchester

Engineering chloroplast PTOX to understand plants acclimation mechanisms

Name of Supervisor: Giles N. Johnson

Climate change is leading to a need for research into acclimation strategies in crop plants, so that these can be bred to withstand disrupted environments. Since plant resilience depends on crop capacity to activate physiological mechanism that improve tolerance to stressful environments, one strategy is to boost plants mechanisms protecting against excess light. The aim of this project is to study crop plants we have generated intended to have enhanced protection by introducing a protein called plastid terminal oxidase (PTOX) to release pressure on the chloroplast electron transport chain thereby improving photosynthesis.

To achieve the objectives, we have introduced PTOX into crop plants. During this summer placement, you will characterise some of these plants using plant physiology and biochemistry techniques. Expression of PTOX in crop plants will be determined using PCR and western blot analyses. Plants will be grown under different stress conditions to assess if PTOX activity is increased and whether these plants show higher tolerance of stress by measurements of chlorophyll fluorescence and CO_2 assimilation. Biochemical parameters such as chlorophyll, antioxidant and lipid hydroperoxide content will be assessed to determine potential physiological adjustments.

https://gnjohnsonlab.wordpress.com

https://research.manchester.ac.uk/en/persons/giles.johnson

https://research.manchester.ac.uk/en/persons/paula-munoz-roldan

Microplastics in sea turtles

Name of Supervisor: Holly Shiels

Email: Holly.shiels@manchester.ac.uk

Please outline the aims and objectives of the project with a brief description of the work (300 words max)

Microplastics (MPs) are a pervasive marine environmental pollutant, posing serious threats to marine ecosystems and organisms at all trophic levels. Sea turtles have been identified as promising plastic indicator species to monitor MP pollution globally; these long lived, wide-ranging species are particularly susceptible to marine MP pollution.

This project will assess the prevalence and scale of microplastic bioaccumulation in nonviable sea turtle eggs and failed hatchlings from two beaches in Panama; investigating the mechanisms of particle transfer and the associated impacts on embryonic development and offspring fitness. This project aims to provide the first information on the ability of microplastics to cross biological barriers in sea turtles either due to vertical transfer in the maternal environment prior to laying, or through penetration across the porous eggshell from the nesting environment. Microplastics will be quantified by size, colour, shape and polymer type using microscopy and FTIR spectroscopy.

The internship student would work with a PhD and MSc student processing these samples and investigating the amount and type of microplastic present in the tissues/shells.

REFERENCES

Biamis C, O'Driscoll K, Hardiman G. Microplastic toxicity: a review of the role of marine sentinel species in assessing the environmental and public health impacts. Case Studies in Chemical and Environmental Engineering. 2021 Jun 1;3:100073.

Sulaiman B, Woodward JC, Shiels HA. Riverine microplastics and their interaction with freshwater fish. Water Biology and Security. 2023 Oct 1;2(4):100192.

https://research.manchester.ac.uk/en/persons/holly.shiels

The influence of nutrient addition and plant functional diversity on ecosystem responses to drought

Name of Supervisor: Joshua Lynn

Email: Joshua.lynn@manchester.ac.uk

Droughts are becoming more severe, posing a threat to terrestrial ecosystems worldwide. Droughts directly alter plant functioning whilst hindering the activity of soil microbes and the nutrient cycles they control. As such, key agricultural ecosystem services provided by grasslands, such as forage production and nutritional content, can be degraded by the effects of droughts on plant and microbial physiology. Yet, we have a limited understanding of the coupled responses of plant and microbial functioning in response to drought, and how these systems may be managed to mitigate the consequences of drought.

This research placement will investigate plant physiological and functional responses to drought along a pronounced gradient of precipitation, and how these differ between grasslands of contrasting nutrient regimes and vegetation composition. The plant functional characterization of this placement will complement the "SoilResist" project (ERC Advanced Grant – PI Bardgett), which is investigating the roles of nitrogen addition, plant composition, and their interactions in shaping soil microbial resistance to and recovery from drought. The placement has the following objectives:

i) Characterize plant species stress–physiological responses to drought and management over time.
ii) Assess plant functional trait variation across treatments and how it relates to ecosystem functioning.

The placement student will gain valuable skills in plant physiological, functional, and ecosystem ecology. The student will work collaboratively with a team on the SoilResist mesocosm experiment hosted at the Firs Environmental Research Station, University of Manchester. For objective one, the student will use a LiCor LI-600 porometer/fluorometer to take chlorophyll florescence and stomatal conductance measurements weekly to assess plant stress responses to drought. For objective two, the student will measure and link plant functional diversity and trait measurements to ecosystem functioning. This project will generate new knowledge on how plant functional responses to global change alters ecosystem services of agricultural significance.

https://research.manchester.ac.uk/en/persons/joshua.lynn

https://research.manchester.ac.uk/en/persons/richard.bardgett

https://www.ees.manchester.ac.uk/soil-ecosystem-ecology-lab/

Live imaging of Notch signal responses to gain and loss of function Notch mutants in Drosophila wing development.

Name of Supervisor: Martin Baron

Email: martin.baron@manchester.ac.uk

Notch is a signalling receptor, highly conserved in evolution, that has widespread roles in development and in adult tissue homeostasis, through regulation of cell fate choices, cell proliferation and cell survival and its mis-regulation is linked to numerous diseases including cancer, and developmental disorders. Notch is deployed in a variety of contexts to regulate cell fate during lateral inhibition, asymmetric cell fate determination and boundary formation. These diverse roles are revealed by the many mutations of Notch that have been uncovered through genetic screens in Drosophila. Notch has a large extracellular domain (ECD), only a small part of which is involved in binding and activation by ligands. Biological function of other regions of the ECD are revealed by mutations altering single amino acids which produce phenotypes in different tissues of the fly. One particularly interesting region is known as the Abruptex (Ax) domain, and mutations in this part of the Notch protein affect cell fate during boundary formation to determine the width of the wing veins of the fly. Currently the mechanism of Notch gain of function of the Ax mutations is not known. Our preliminary cell culture work has indicated that Ax mutants do not simply alter the actual level of ligand-induced signalling. Instead, we hypothesise that Ax mutations suppress basal ligand-independent activation of Notch that arises following endocytic uptake of the receptor thus increasing the fold increase of Notch activity. Our research will now test our cell culture findings *in vivo*, in the wing disc tissues that phenotypically affected by the mutation by examining and comparing Notch signalling in WT and Ax mutants using a GFP reporter that responds to Notch activation in real time in live cells in live dissected wing discs and compare with the consequence of removing notch function completely with a temperature sensitive mutation.

https://research.manchester.ac.uk/en/persons/martin.baron

Identifying drugs that alter the secretory pathway.

Name of Supervisor: Martin Lowe

Email: martin.p.lowe@manchester.ac.uk

The secretory pathway plays a fundamental role within our cells, essential to produce all cellular membrane proteins and proteins secreted to the extracellular space, including the extracellular matrix, digestive enzymes, antibodies and numerous hormones and growth factors. The pathway is critical to human health, and many diseases are caused by defects in secretory trafficking, and it is also exploited by pathogenic viruses and bacteria during infection.

How the diverse array of secretory cargo proteins transits the secretory pathway, in terms of itineraries followed, rates of transport through the pathway, as well as sensitivity to chemical perturbation, remains poorly understood. To address these gaps in knowledge we have performed a drug screen in human liver cells and identified 28 novel chemical modulators of secretion. These drugs affect different cargo proteins to varying extents suggesting diversity in trafficking routes and machinery used by different cargoes.

The project will build on these observations to determine where in the secretory pathway the newly identified drugs operate and to explore more fully their cargo selectivity. A combination of biochemical and imaging-based approaches will be used for these purposes, using human liver cells.

The results will provide new insight into how the secretory pathway functions at the molecular level and identify potential drugs that can be repurposed for the treatment of conditions where modulation of secretory pathway may provide therapeutic benefit.

https://research.manchester.ac.uk/en/persons/martin.p.lowe

Using molecular and synthetic biology to study bacterial evolution

Name of Supervisor: Mato Lagator

Email: Mato.lagator@manchester.ac.uk

The aim of this project is to introduce an enthusiastic and passionate student to the wonders of interdisciplinary work using microbes as a model system. We use a range of molecular and synthetic biology techniques in order to study the basic rules that govern how evolution works. In particular, we are interested in improving the predictability of evolution by understanding how the existing molecular mechanisms in the cell determine the ways in which an organism or a biological system can evolve. We genetically modify and experimentally evolve bacteria to unravel the relationship between mechanisms and evolution.

There is a range of possible projects that would be suitable for a summer student, all aligned with the existing work in the lab. These ongoing projects in the lab include: predicting evolution of multidrug resistance; relationship between the number of tRNA genes and translation efficiency; how multi-drug efflux pumps are regulated; how is bacterial transcription terminated and how do those mechanisms evolve; how does resistance to one antibiotic alter the evolution of resistance to another antibiotic, the relationship between promoter architecture and its evolution, etc. However, I think the best projects are those that closely match the interests of the student, and hence would develop the specific project with student's input rather than pre-define it myself.

No matter what the project, the student can expect to gain experience in at least a few of the techniques commonly used in the lab: molecular cloning, plasmid and chromosome manipulation, flow cytometry, generation of random mutant libraries, experimental evolution, and bacterial fitness assays. We also employ a range of computational and modelling approaches and would welcome a student who prefers dry over lab work as well.

https://www.research.manchester.ac.uk/portal/mato.lagator.html

Investigation of animal behaviour using Artificial Intelligence

Name of Supervisor: Rasmus Petersen

Email: r.petersen@manchester.ac.uk

Advances in Artificial Intelligence (Machine Learning) mean that it is now possible to measure and quantify the behaviour of animals much more precisely and quickly than was previously possible. This is creating exciting new research opportunities.

An important advance is DeepLabCut (Mathis et al, 2018). This involves training a Machine Learning algorithm to automatically detect keypoints (snout, ears etc) on an animal's body. Once the algorithm is trained, it can automatically track these landmarks from video. The tracking data can then be further analysed in order to get insight into the animal's behaviour.

The Petersen lab is using these methods to study mouse tactile behaviour, and there are opportunities for Placements along these lines. This placement will give a motivated student the opportunity to learn how to apply these Artificial Intelligence techniques and to use them to get insight into how animals behave. The placement will suit a student who is motivated to learn about Artificial intelligence and computer programming approaches to neuroscience.

Reference:

Mathis et al (2018) DeepLabCut: markerless pose estimation of user-defined body parts with deep learning. PMID: 30127430

Reproducibility in morphological phylogenetics

Name of Supervisor: Robert Sansom

Email: Robert.sansom@manchester.ac.uk

Evolutionary trees are an essential tool for testing evolutionary hypotheses and building the history of life on earth. Whilst the science of building trees (phylogenetics) is mature, the principles of "open data" have rarely been applied consistently. The reproducibility of phylogenies generated from genomic data has been investigated, but the same is not true of trees generated from morphological data. This represents a challenge to morphological phylogenetics as a discipline, especially considering that there is anecdotal evidence that the results of numerous studies are not reproducible. How confident can we be in the evolutionary inferences we make from anatomical and fossil data? This placement will address this question by systematically gathering and analysing published morphological data used to construct phylogenies considering open data and reproducibility principles. The student will gain skills in data handling, bioinformatics, phylogenetics, and help us address big questions. Ultimately, we aim to test the "fitness" of the field of phylogenetics and put in place recommendations and guidelines for the future of the discipline.

https://research.manchester.ac.uk/en/persons/robert.sansom

Impact of adenosine tri-phosphate (ATP) on assembly of unfolded proteins

Name of Supervisor: Robin Curtis

Email: r.curtis@manchester.ac.uk

Recent findings suggest that adenosine triphosphate (ATP), beyond its traditional role as an energy metabolite, may contribute to maintaining proteostasis by acting as a molecular co-chaperone. ATP's potential function in stabilizing proteins during folding, particularly when hydrophobic interior regions are transiently exposed, remains underexplored. This project aims to investigate ATP's ability to prevent protein aggregation in partially folded or unfolded states.

A significant challenge in achieving this goal is designing an assay that effectively mimics the delicate balance between protein folding and aggregation. Traditional aggregation studies often rely on extreme conditions, such as elevated temperatures or chemical denaturants, which may not accurately reflect physiological processes.

This study will focus on developing a novel assay to examine folding and aggregation dynamics using dithiothreitol (DTT) as an inducer of aggregation. The approach involves real-time monitoring of aggregation immediately following the introduction of DTT into protein solutions. To achieve this, the assay will integrate two syringe pumps, a mixer, and a cuvette-based dynamic light scattering (DLS) system for precise aggregation tracking.

Initial experiments will test this methodology on commercially available proteins, including lysozyme, albumin, and alpha-chymotrypsinogen, under varying solution conditions. Complementary measurements using fluorescence spectroscopy and light scattering will provide additional insights into how ATP influences protein behavior as a function of temperature and chemical denaturant concentrations, such as urea.

By establishing this assay, the project aims to shed light on ATP’s potential role as a co-chaperone in cellular environments, while also paving the way for broader applications in protein stabilization.

https://research.manchester.ac.uk/en/persons/r.curtis

Density-associated mutation rate plasticity in microbial communities

Name of Supervisor: Rok Krasovec

Email: Rok.krasovec@manchester.ac.uk

Mutations are fundamental for adaptation, evolution and antimicrobial resistance. Rok's previous work shows that high-density microbial populations have lower mutation rates, a phenomenon dubbed density-associated mutation rate plasticity (DAMP)[1,2]. Recently we discovered that DAMP arises from the collective ability of microbes to control concentrations of hydrogen peroxide[3]. Intriguingly, in mixed populations, the reduction in mutation rate in denser populations is restored in peroxide degradation-deficient cells by the presence of wild-type cells.

DAMP suggests that the mutation rate is a dynamic trait shaped by bacterial community composition. However, we know close to nothing about mutation rates in mixed communities and microbiomes.

Project can be a wet lab study of mutations and antibiotic persistence in microbial communities containing clonal cells or a mix of genetically different strains or species.

Our approach is inter-disciplinary. We combine microbiology techniques (high-throughput fluctuation assays) with live fluorescence (super-resolution) microscopy, microfluidics and statistical modelling.

Our work is important for the fundamental understanding of mutations and evolution. We are pioneering mutation rates in bacterial communities and trying to identify mechanisms that hamper emergence of antimicrobial resistance.

Rok's group is part of a wider collective of evolutionary microbiology labs forming the Microbial Evolution Research Manchester (MERMan) grouping (https://sites.manchester.ac.uk/merman/). MERMan is one of the largest groups of evolutionary microbiologists in the world, comprising 10 group leaders and >60 research staff. Student will be based in the state-of the-art microbiology lab facility with access to a range of cutting-edge analytical instruments, bioimaging facility and robotic automation.

[1]Krašovec, R., *et al*. (2014). Nat Commun 5: 3742.

[2]Krašovec, R., *et al*. (2017). PLoS Biol 15(8): e2002731.

[3]Green R. *et al*…and Krašovec R. and Knight, C G (2024). PLoS Biol, 22, e3002711.

https://research.manchester.ac.uk/en/persons/rok.krasovec

Mechanism of Natural Product Synthesis by Fungal Nonheme Iron Dioxygenases

Name of Supervisor: Sam de Visser

Email: Sam.devisser@manchester.ac.uk

Natural product synthesis by enzymes often gives highly selective reaction patterns with high yield and turnover. These unusual compounds in nature have functions in biotechnology for the synthesis of insecticides and fungicides but also are relevant in pharmaceutics for the synthesis of drug molecules. Understanding the mechanisms of the biosynthesis of these compounds will help with the biotechnological applications of these enzymes as they will provide high-value compounds in good yield with limited amount of by-products. Recently, nonribosomal peptide synthetases from several fungi were reported that incorporate arginine and hydroxyproline in the substrate scaffold.[1] Little is known on the details of the mechanism, but if this is resolved these enzymes may have wider applications in biotechnology. The aims of the Summer placement work would be to set up computational models and run exploratory quantum chemical calculations on the mechanism of substrate activation by the enzyme.

The student will get access to the Computational Shared Facilities to run supercomputing calculations using available software packages of the de Visser group. An enzyme/protein structure of the nonribosomal peptide synthetase will be selected from the Protein Databank or generated with Alphafold. Thereafter, co-factors, substrate and co-substrate will be added and the system will be solvated. Molecular dynamics simulations will be done on the model to determine substrate binding, substrate positioning and find protein and substrate movements. Thereafter, quantum chemical calculations on the reaction mechanism for activation of substrate activation will be explored. Geometries of possible intermediates will be optimized and a prediction of the mechanism and the role of the protein will be made using known protocols.[2]

References:

1. K. W. Rothchild et al. *J. Am. Chem. Soc*. **2024**, *146*, 10263-10267.
2. S. P. de Visser et al. *Chem. Eur. J*. **2024**, *30*, e202402468.
3. **https://research.manchester.ac.uk/en/persons/sam.devisser**