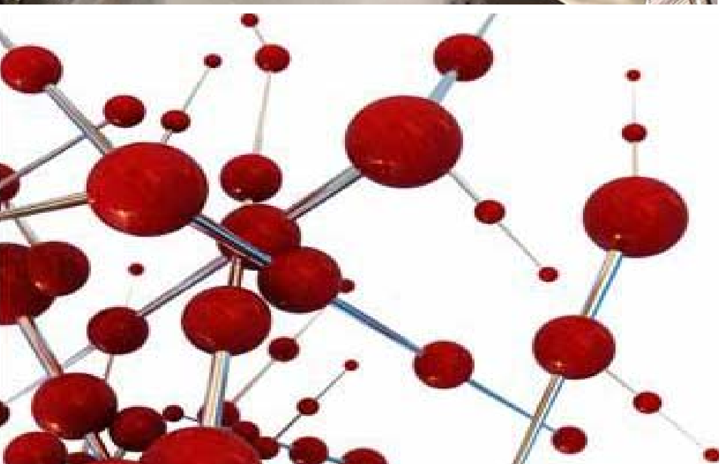
The University of Manchester
MIB

MANCHESTER 1824

Manchester Interdisciplinary Biocentre

Research Brochure



wellcome trust

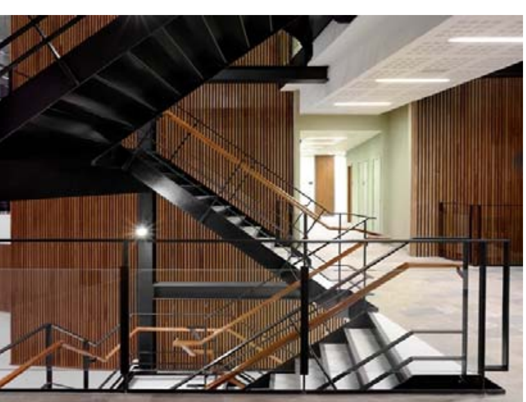
www.manchester.ac.uk/mib

The University of Manchester

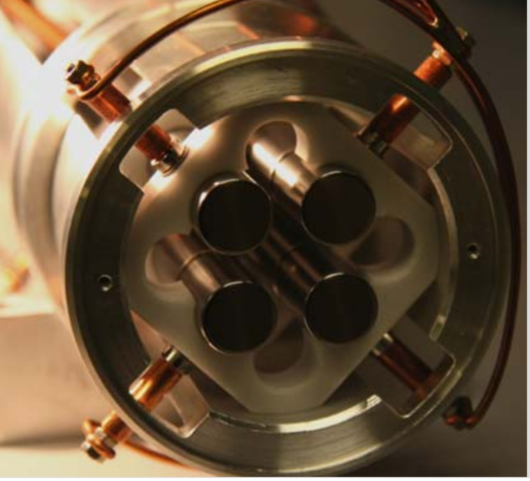
The University of Manchester is the UK's largest single-site university with more than 35,400 undergraduate and postgraduate students and 5,800 academic and research staff. The University has an annual income of more than £680 million and an annual research expenditure of over £375 million. According to the results of the 2008 Research Assessment Exercise, the University of Manchester is now one of the country's major research institutions, rated third in the UK in terms of 'research power'. The University attracts world-renowned researchers and teachers and boasts no fewer than 23 Nobel Prize winners among its current and former staff and students. The University of Manchester has 22 academic schools and a number of research institutes undertaking pioneering multi-disciplinary teaching and research of worldwide significance. The University remains the UK's most popular higher education institution, receiving more applications for undergraduate study than any other British university.

Manchester Interdisciplinary Biocentre

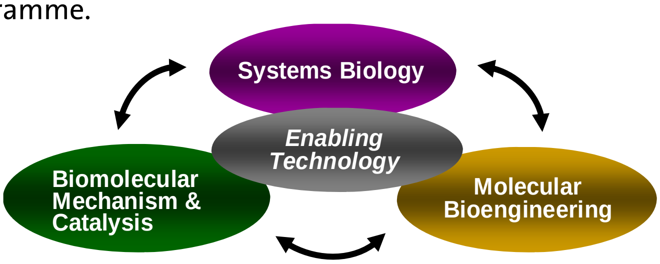
The MIB grew out of a commitment to develop a globally recognised focus of interdisciplinary research at the interfaces to biology. With the support of funding from the Wellcome Trust and the Wolfson Foundation, we were able to construct a building (completed in 2006) designed to host an outward-looking research community. With currently 60 research groups, housed in a purpose-built building, the MIB provides a unique infra-structure, research environment and culture, all specifically designed to remove the barriers between disciplines and to promote innovative science. The MIB houses scientists and engineers from across the University: the Faculties of Engineering and Physical Sciences, Life Sciences and Medical and Human Sciences.



Researchers in the MIB use advanced quantitative methods to explore the relationship between the macro behaviour of biological systems and the properties of their nanoscale components. They see this understanding as a basis for developing new Biotechnologies with applications in areas such as human health, the energy economy, food security, and the environment.



A defining feature of the MIB's mission is the incorporation of rigorous, cutting-edge principles and technologies derived from the physical sciences, engineering, mathematics and computation into novel approaches to elucidate the molecular mechanisms that underpin living processes and systems. The research focuses around three fully complementary and synergistic research themes, with an extensive programme of technology development at the heart of our research programme.



Economic impact. The MIB themes all have strong potential in terms of commercial application. We are actively engaged with more than 25 companies in the biotechnology and pharmaceutical sectors, and have established a number of spin-outs. We are keen to expand this portfolio of industrial collaborators.

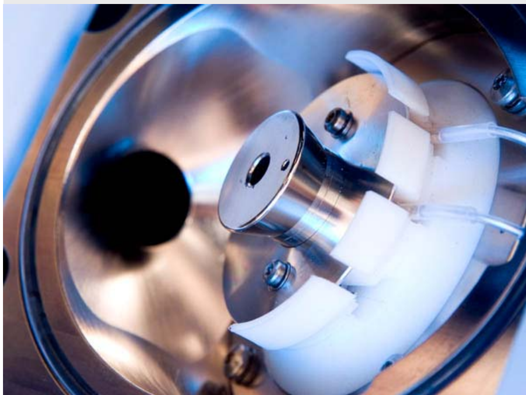
Training. The MIB is committed to providing advanced interdisciplinary training to graduate students and on a wider scale through CPD courses.

Collaborative programme. The MIB acts as a partner for many research activities across the University of Manchester campus and beyond. Capitalizing on the critical mass of expertise in our interface research areas, we can drive the expansion of novel strategies and methodologies from these cutting-edge activities into the wider community.

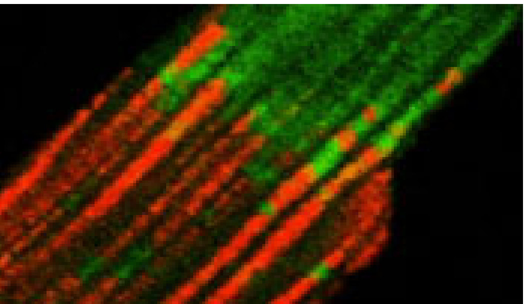
Core Facilities. The MIB has an impressive range of facilities that provide a strong foundation for research excellence. These include: Biomolecular Analysis (SPR, ITC, CD), Metabolomics, Proteomics, High Resolution Imaging, Robotics, Rheology, Microarray analysis, Microfluidics, Mechanochemistry (including AFM and Laser Tweezers), NMR, EPR, X-Ray Crystallography, Electron Microscopy, Fast Reaction Spectroscopy (aerobic, anaerobic), Mass Spectrometry (including Secondary Ion Mass Spectrometry and Fourier Transform Ion Cyclotron Resonance), Infrared, Raman and Fluorescence Spectroscopy.

This brochure features only a selection of MIB activities. For more information, please see: http://www.mib.ac.uk

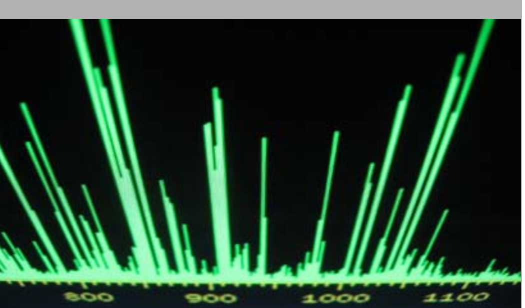


Systems Biology



Sophia Ananiadou
Ardeshir Bayat
Gerold Baier
Philip Day
Claire Eyers
Peter Gardner
Roy Goodacre
John Hyde
Dean Jackson
John Keane
Doug Kell
Joshua Knowles
Josip Lovric
John McCarthy
John McNaught
Pedro Mendes
Goran Nenadic
Paul Sims
Jacob Snoep
Jun'ichi Tsujii
Hans Westerhoff



Systems biology uses information obtained through experimental analysis and models this in the complex environment of the living cell. It takes full account of the functional properties that arise in the dynamic interactions between molecules and accordingly depends on the integrated implementation of a wide variety of scientific disciplines, ranging from molecular/cell biology and analytical chemistry to mathematics, informatics and text mining. Drawing on the rigorously defined physicochemical properties of biomolecular components, Systems Biology generates models of life that account for the "emergent properties" of complex biomolecular systems.

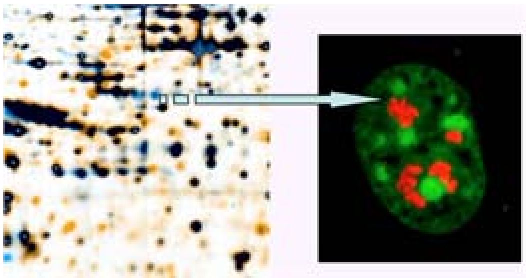
The **Manchester Centre for Integrative Systems Biology (MCISB)** was funded by the BBSRC and EPSRC to pioneer the development and application of new experimental and computational technologies in Systems Biology. The MCISB provides a hub for cutting-edge quantitative systems biology research that spans across the University campus. The approaches used encompass a wide range of experimental (Molecular Biology / Biochemistry / Biophysics), mathematical and computational (Modelling / Data Integration / Text Mining etc.) activities and lead ultimately to computer models of parts of living cells. Some of the models are already available for *in silico* experimentation through the Biomodels and JWS databases. MCISB pursues a large-scale core research programme using the baker's yeast *S. cerevisiae* as a 'model' organism. Here, we apply an iterative "bottom up" process by which quantitative experimental data from enzyme kinetic and "omics" studies are used to refine and improve models of reaction pathways developed by data from text mining. These models are then integrated to develop a systems biology understanding of processes at the cellular level. Tools developed in this research are then used in other research projects, some of which are described below. The MCISB is an international hub for Systems Biology, with a partner institute in Amsterdam and with leading roles in international systems biology consortia that focus on yeast, *E. coli* and receptor tyrosine kinases.
http://www.mcisb.org

Associated with the MCISB is a **Doctoral Training Centre** in **Integrated Systems Biology** funded by the EPSRC and BBSRC research councils
http://www.mcisb.org/dtc/

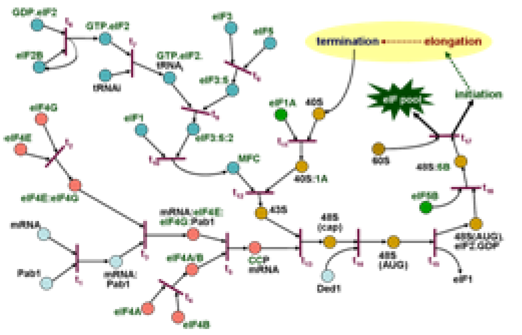
Systems Biology

Further Systems Biology projects include:

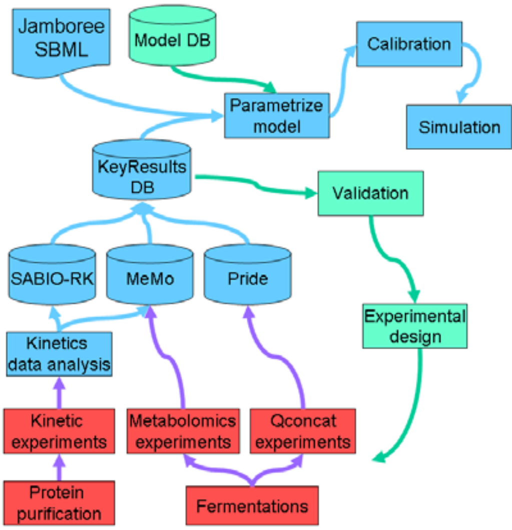
A broad combination of **advanced analytical technologies**, ranging from metabolomics and proteomics through Raman spectroscopy, mass spectrometry and chemometrics to evolutionary computational methods, are being developed and applied for the purpose of rapid and accurate characterisation of biological systems.



Computational systems biology is used to understand biological systems through the use of computer models. Interests include the development of modelling and simulation software and construction of biochemical models of the yeast pentophosphate pathways, and the oxidative stress response in yeast and breast cancer cells. Researchers pioneered the application of **numerical global optimization** in biochemical kinetic modelling and are working on **reverse engineering biological networks** to construct models directly from large-scale genomics, proteomics and metabolomics data sets.



COPASI is a leading software for modelling and simulation of biochemical networks which is used in labs worldwide. COPASI is written under a collaboration with the university of Heidelberg and Virginia Tech. MIB researchers are now expanding its functionality with web services and data standards. The group has also developed the **DOME** database system designed to manage and integrate data from projects using transciptomics, proteomics and metabolomic approaches.

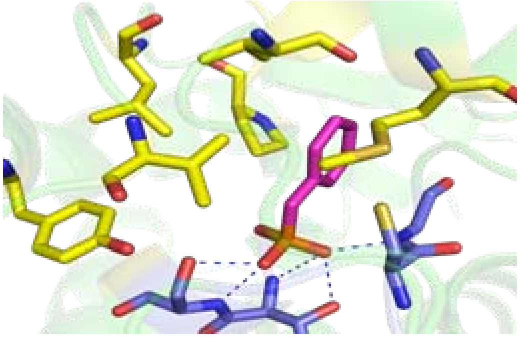


Pre-eclampsia, which affects some 5% of births, is accompanied by high blood pressure and confers considerable risks for mother and child. New pre-symptomatic metabolic biomarkers are being identified that should improve diagnosis and thus timely treatment of the disease.

Many laboratories have the Boehringer wall charts showing metabolic networks based on decades of biochemistry. A new comprehensive map of **genome-wide metabolism** in yeast has now been prepared. The equivalent human map is also close to completion, to be followed by maps for specific organs and perhaps diseases. As a consequence, finding where SNPs impact human metabolism should become a lot easier.

A Molecular Systems Biology approach has generated the first comprehensive map of **rate control** in the **eukaryotic translation machinery**. The experimental and computational tools developed here will find broad application to diverse biological pathways.

Biomolecular Mechanism and Catalysis



Andrew Almond
Johanna Avis
David Berrisford
Ewan Blanch
Samuel De visser
Andrew Doig
Sabine Flitsch
Bob Ford
John Gardiner
Peter Gardner
Sasha Golovanov
Finbarr Hayes
Richard Henchman
David Leys
John McCarthy
Jason Micklefield
Andrew Munro
Paul Popelier
Steve Prince
Vasudevan Ramesh
Stephen Rigby
Nigel Scrutton
Gill Stephens
Mike Sutcliffe
Nick Turner
Jon Waltho
Simon Webb

The BMC theme examines the properties and mechanistic details of biomolecular and biotechnological processes ranging from complex multi-component pathways and complexes to single proteins (enzymes). It generates data about biomolecular components and pathways that feed into Systems Analysis at higher levels of biomolecular organisation. It also creates novel components, devices and pathways that are utilised in Molecular Bioengineering.

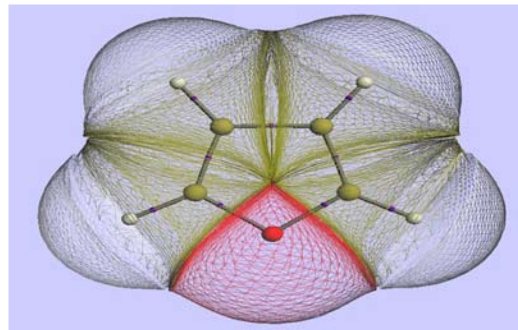
Researchers from the **Molecular Enzymology** group take a multi-disciplinary approach using fast reaction kinetic and spectroscopic methods, X-ray crystallography, NMR, computational chemistry, protein engineering and chemistry to seek a detailed understanding at the atomic level of how enzymes 'work'. With this knowledge, enzymes can be developed as drug targets, manipulated for use in biotechnology/biocatalysis or used to further our general understanding of various processes in biology and chemistry. The work is interdisciplinary and is set at the interfaces between biomolecular sciences, chemical physics and chemical biology. Computational modelling and simulation underpins and complements the experimental "wet-lab" research.

Research at the **chemistry-biology interface** has elucidated the biosynthetic origins of clinically important lipopeptide antibiotics, has developed methods for the engineered biosynthesis of non ribosomal peptide variants and for site-selective covalent protein immobilization, and has employed directed evolution in the development of new enzymes for the synthesis of homochiral building blocks. Extensive work continues on **nucleic acid** redesign, recognition and template-directed synthesis.

Another focus relates to glycosylations (glycosyltransferases) and biohydroxylations (P450 enzymes), and the development of **glycoarrays** to study **protein/glycan interactions**. A novel array platform has been developed based on self-assembled monolayers on gold which can be interrogated by mass spectrometry, surface plasmon resonance and fluorescence spectroscopy. These arrays are ideal tools for studying enzyme specificity and carbohydrate-binding proteins at the same time. In synergy with glycosylations we also focus on biopolymer synthesis and in particular **heparin-related oligosaccharides** and their biological evaluation, with an emphasis on development of anti-cancer therapeutics.

A diversity of structural, spectroscopic and computational techniques are developed and used to study **biomolecular**

Biomolecular Mechanism and Catalysis



complexes and machines (e.g. viral structures and the ribosome) and pathways (such as RNA processing).

Researchers aim at predicting the properties of large molecules by using **quantum chemical information** on small molecules. They are working on a more rigorous force field model, on **bio-isosterism**, useful in drug design, and on **self-assembling systems**.

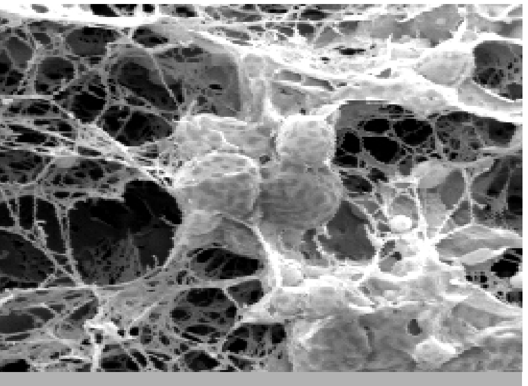
Microbial cells and **enzymes** are employed in novel ways for the purpose of **chemicals manufacturing**, with emphasis on environmentally friendly methodology. Research on the production of chemicals from **renewable feedstocks** focuses on enzyme-catalysed production of chemicals from lignin and integrated processes to produce high value chemicals directly from renewables using bio- and chemo-catalytic cascade reactions.

The Centre of Excellence for Biocatalysis, Biotransformations and Biocatalytic Manufacture (CoEBio3), set up in 2005, has rapidly become established as one of the leading biocatalysis organisations in the world. CoEBio3 has its headquarters in MIB with strategic partners at the Universities of York, Strathclyde and Heriot-Watt and the Centre for Process Innovation at Wilton in Teeside (pilot scale fermentation facility). This multi-centre consortium allows CoEBio3 PIs to undertake fundamental and applied research in the white biotechnology area to develop novel processes for production of chemicals and pharmaceuticals by embracing a "genes to kilos" philosophy. A key feature of CoEBio3 is its strong links with industry, particularly companies in the pharmaceutical, fine chemical, speciality chemical and energy sectors. These collaborations take place either through formation of a research consortium, involving a number of different companies who co-fund the research and share the arising benefits, or through 1:1 collaborations in which specific target problems are addressed by a team of scientists within CoEBio3. CoEBio3 has recently formed a trans-European network of like-minded Centres of Excellence by establishing a Marie Curie Training Network in Biocatalysis (BIOTRAINS) to train PhD's and postdoctoral fellows in modern methods and techniques of biocatalysis. CoEBio3 PIs within MIB are tackling a diverse range of challenging problems, including the synthesis of chiral building blocks for pharmaceuticals, pathway engineering of antibiotic production, new strategies for enzymatic glycosylation, biomass conversion and the development of new technologies for biofuel production.

http://www.coebio3.manchester.ac.uk/

CoEBio3

Molecular Bioengineering



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Peter Fielden
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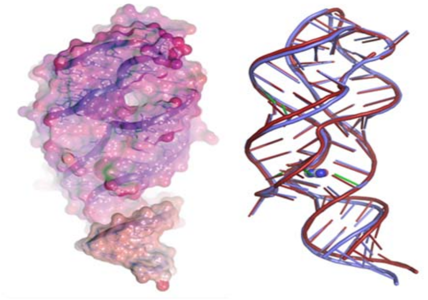


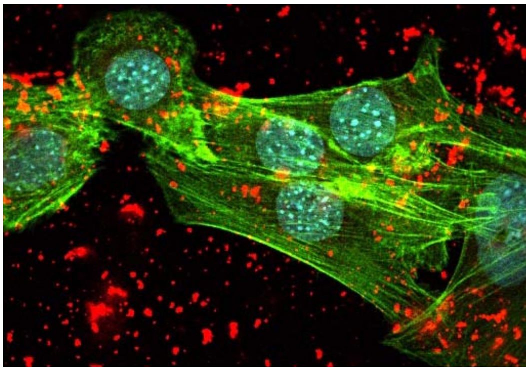
Molecular Bioengineering encapsulates a spectrum of research whose primary focus is the design, creation and application of biomolecular systems utilising natural or modified biological components and/or non-biological components in novel combinations. It combines design of new genetic circuitry in synthetic biology, new methods of interfacing man-made devices with biology, and nanoscale assembly of structures, materials and devices based on biomolecules.

Biomolecular Systems Engineering, or **Synthetic biology**, describes a burgeoning field in which biomolecular components (natural or synthetic) are newly combined or reorganised in order to create novel genetic and biochemical circuitry, pathways, and ultimately organisms. Some are already categorising it as a hybrid discipline between science and engineering. As with many developing fields, there are a number of different opinions as to what technologies and objectives are most important. For example, a number of groups have focused on the creation and use of "toolboxes" of genetic components that can be combined to build synthetic circuitry or networks. Different types of synthetic gene circuitry are built to *engineer* new properties into living cells, including oscillators, toggle switches, logic gates, positive and negative feedback loops, and cell-cell communication networks. Construction of such circuitry is usually preceded by modelling and simulation, so that theoretical predictions of systems behaviour can be rigorously tested through experimentation. Of course, novel circuitry can also be built in order to generate new devices with practical applications, such as sensors. Another approach is to construct regulatory circuitry that can be used to select for new properties of specific components (protein, DNA, RNA or small ligand) via *in vivo* evolution and selection.

Nanoscale bioengineering relates to the interface of bioscience and nanotechnology in bottom-up fabrication of precisely defined functional structures, materials and devices based on biomolecules such as peptides, saccharides and lipids. The main challenges that currently limit the complexity that can be achieved in these systems relate to a poor understanding of the 'design rules and to limited control over the self-assembly processes (nucleation and growth of structures).

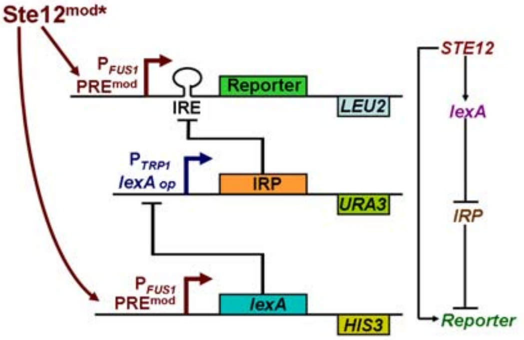
Molecular Bioengineering

These challenges are addressed by researchers in the MIB using a combination of computation, rational design and in-depth analysis based on a wide range of state-of-the-art spectroscopic and nano/microscopic techniques. In addition, new approaches that direct the self-assembling systems towards desired minima in the free energy landscape include templating using organic and inorganic nanoparticles and enzyme-assisted self-assembly. Applications of these designed biomolecule-based nanomaterials are explored in biology (3D cell culture, biosensing) and nanotechnology (nanoelectronics, templating).

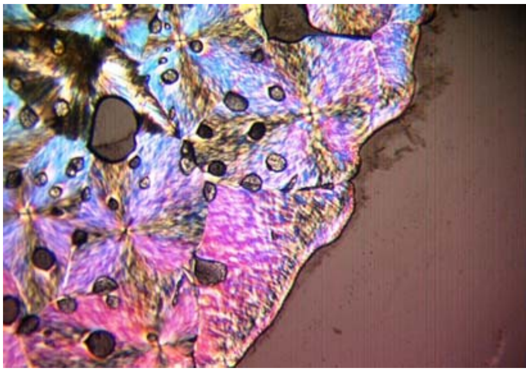


Specific areas of research and development include:

One focus in the MIB is the design, construction, testing and application of **novel components** that can be **engineered** into (partially orthogonal) **circuitry** in bacteria, yeast and mammalian cells. These components comprise a range of novel actuator:target pairs, including the types: protein:DNA, protein:RNA, small ligand:RNA (**riboswitches**) and peptide:membrane receptor. The circuitry built using these components will be applied in diverse fields, including functional genomics, pharmaceutical target validation, biosensors and fundamental bioscience research.



Physical principles are applied to mimic, manipulate and improve **biomolecular self-assembly**. The physics of self-assembly elucidated is subsequently related to functional, micro-structural and mechanical properties to gain both process and product control.



Molecular self-assembly is also used to create systems that mimic biological membranes and improve our understanding of important biological processes. For example, such work examines the role of 'cooperativity' during the binding of multivalent ligands to surfaces, elucidates the role of 'lipid rafts' in cellular recognition, creates synthetic ion channels and tissue-mimetic structures, and uses liquid crystal displays to screen enzyme specificity.

The development of new therapeutics by **aptameric evolution** enables selective binding to both immunogenic and non-immunogenic targets for use in applications including drug discovery.

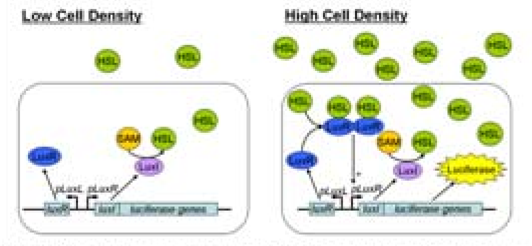
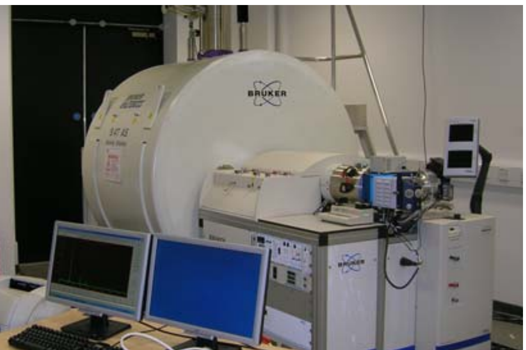


Figure 1 – The *Lux* quorum sensing system of *Vibrio fischeri* at low and high cell density.

Enabling Technologies



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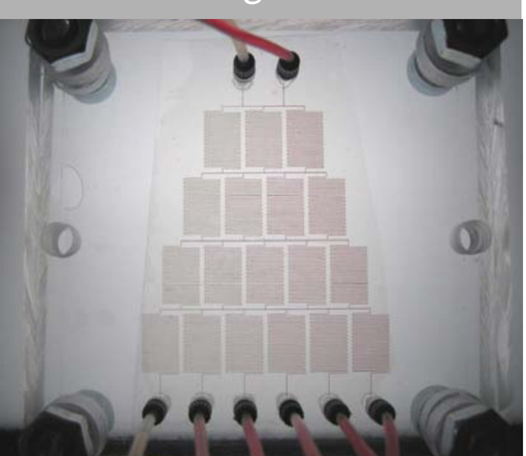
Xue-Feng Yuan



All three MIB research themes are coupled to an extensive programme of technology development driven by expertise from the physical sciences, engineering and maths/computation, allowing us to continuously accelerate progress through the implementation of state-of-the-art enabling technologies.

Examples of this technology development include:

Gas-phase ion chemistry research in the **Michael Barber Centre for Mass Spectrometry** provides an enhanced understanding of the analytical techniques that underpin proteomics, metabolomics and the investigation of other molecules of biological significance. New developments in quantitative mass spectrometry provide much needed information for modeling of biological networks, while techniques are being developed for the analysis and quantification of a variety of post-translational modifications. http://www.mbc.manchester.ac.uk/

Secondary ion mass spectrometry (**SIMS**) is being developed and used for the analysis and imaging of chemical and biological systems, including advanced materials, single cells and biological tissue. The aims include novel insights into the chemical and spatial organisation and function of these systems at the molecular level.

Specialists in quantitative analytical measurements, lab-on-a-chip, and **microfluidic experimentation platforms** have developed a range of unique high throughput platforms that may be used to study single cells and small cellular assemblies. Facilities within the MIB include a complete polymer microfabrication and rapid prototyping suite.

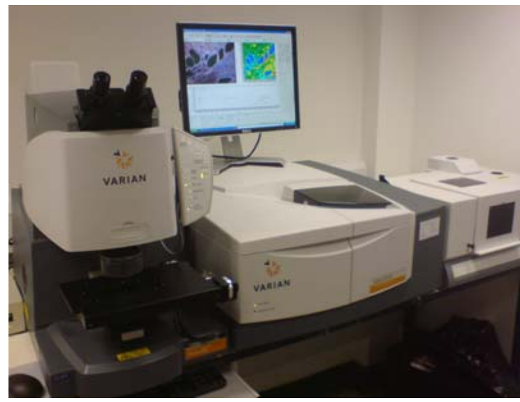
Rheology research is applied in various ways, providing a novel platform for a wide range of biological applications such as ink-jet printing and electrospinning of biomaterials, on-chip cell separation and control of physical and biological cues, development of point-of-care diagnostic kits, tissue regeneration, and the microfluidic production of artificial biomolecular compartments.

Electron magnetic resonance (**EMR**) is used to study unpaired electrons in biological systems, providing information on electron transfer, biomolecular structure, and molecular dynamics. Target systems include redox enzymes, metalloenzymes, and metal ion transport proteins.

Researchers are also utilizing specialist techniques in the analysis of **degraded DNA**, as in forensic and archaeological samples.

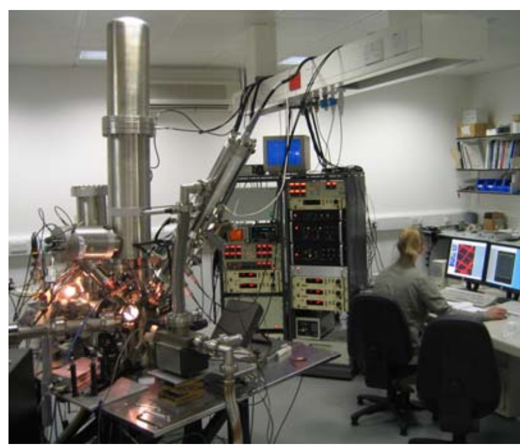
Enabling Technologies

Developments are also being made in the field of **infrared imaging** of single cells and tissue, specifically data analysis algorithms that correct for scattering.



Advanced data curation, archiving, and searching technologies are being developed and used across the MIB. The £1.1m **HUSERMET** project, will deliver a public, searchable knowledge-base of human metabolic data, meta-data and experimental results. In optimization and machine learning, we are developing fully **closed-loop experimentation**, where robotic and computational systems may select, carry out and analyse a series of experiments without human intervention.

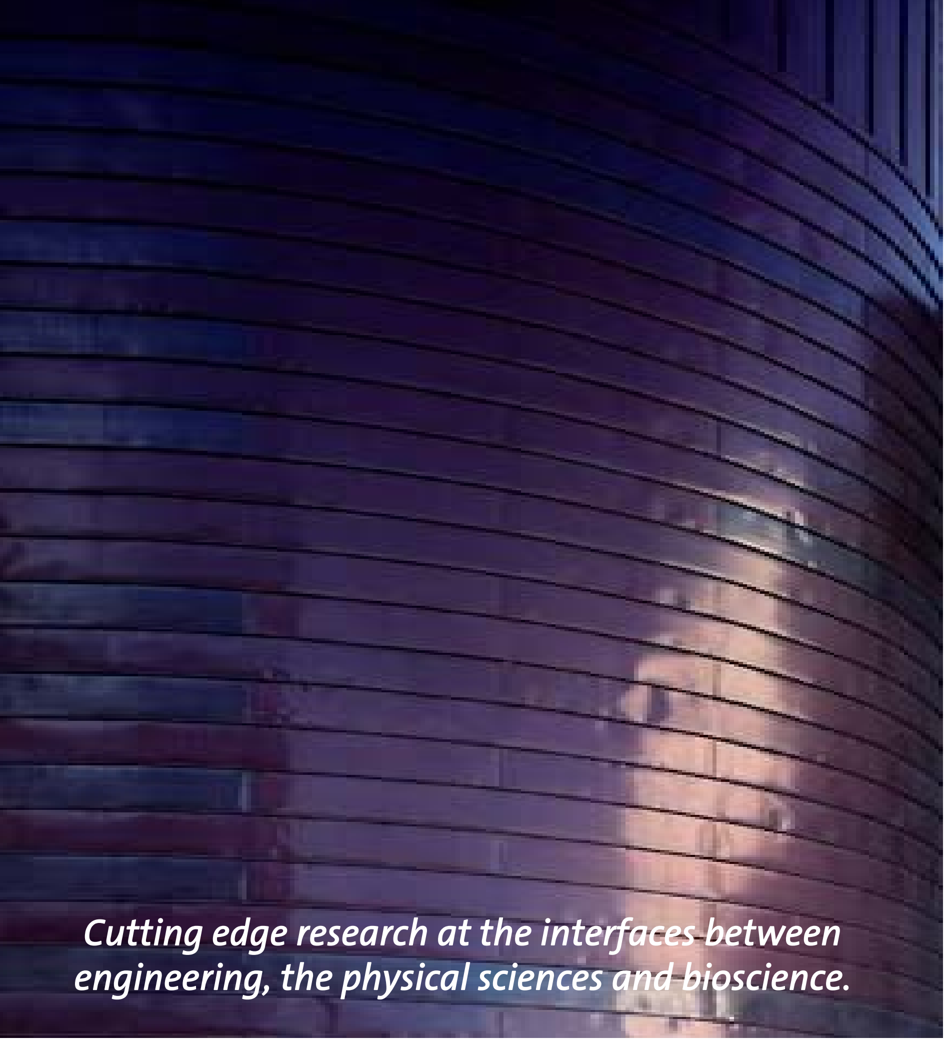
The UK National Centre for Text Mining (NaCTeM) applies innovations in text mining to large-scale bioscience and biomedical resources. NaCTeM is the largest text mining centre in the UK and is funded by JISC, EPSRC and BBSRC. NaCTeM collaborates closely with the world leading group at the University of Tokyo in developing and exploiting text mining applications. The primary goal of text mining is to extract new knowledge hidden in text and to enable scientists to collect, maintain, interpret, curate and discover knowledge for research, efficiently and systematically. NaCTeM applies text mining innovations to large-scale bioscience and biomedical resources, developing automated methods for information retrieval. http://www.nactem.ac.uk

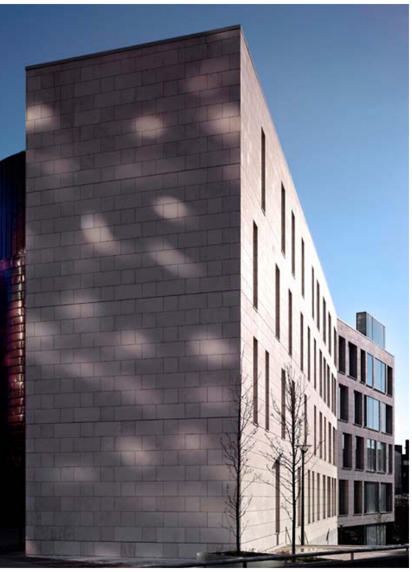


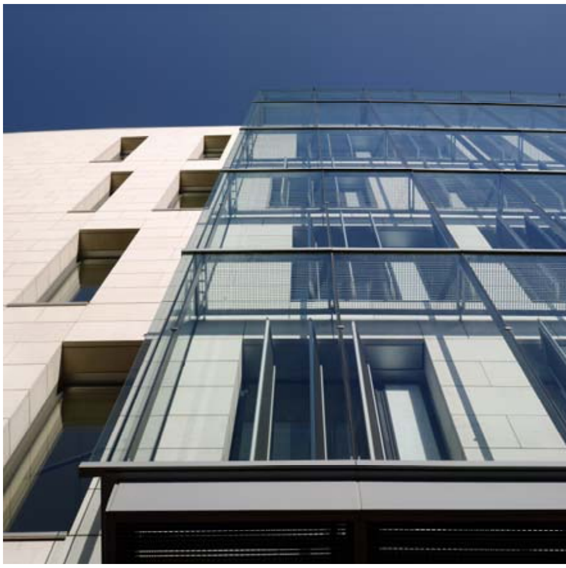
Manchester: Integrating Medicine and Innovative Technology (MIMIT) is the first international affiliate of CIMIT®, a collaborative initiative of world renowned academic and healthcare delivery organisations in Boston, US. The primary aim of MIMIT is to improve patient care by bringing scientists, engineers and clinicians together to catalyze development of innovative healthcare technologies through scoping and validation of unmet clinical need. MIMIT™ comprises a community of senior representatives throughout its partner organizations, to identity both clinical need and innovation exploitation potential. The MIMIT Industry Liaison Programme is designed to provide the most efficient route to forming collaborative relationships to design and develop innovative technology. Our approach supports a targeted scoping programme commissioned by industry and the creation of dedicated project teams to address pre-validated unmet clinical needs. The strength of MIMIT is its provision of pump priming investment, ability to tap into a comprehensive clinical network to validate unmet clinical needs, project manage at every stage of the innovation cycle (working closely with the intellectual property offices UMIP and TrusTECH) and facilitate longer term investment. http://www.mimit.org.uk

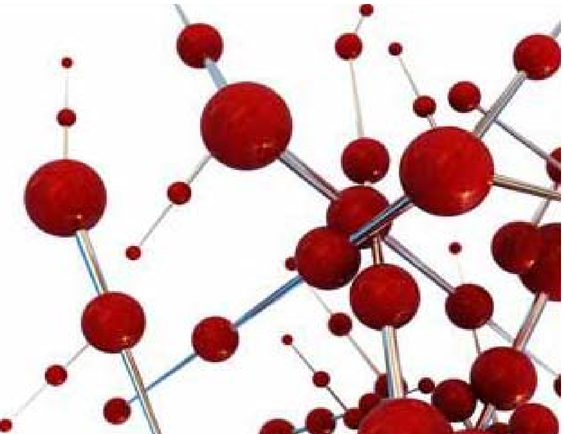
NaCTeM
The National Centre for Text Mining

mimit
MANCHESTER
INTEGRATING MEDICINE & INNOVATIVE TECHNOLOGY









Manchester Interdisciplinary Biocentre
University of Manchester
131 Princess Street
Manchester M13 9PT
Tel: +44(0)161 3065200 / 8916

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