



**CBC/MOAC Life Sciences
Conference**
26th January 2006
At Imperial College, Dept. of Chemistry



Chemical Biology Centre

THE UNIVERSITY OF
WARWICK

Imperial College
London

Modern medicine and biology present many exciting challenges that require input from mathematicians, physicists, chemists and engineers. To supply appropriately trained people, the Life Sciences Interface programme has established seven Doctoral Training Centres that offer an exciting new multidisciplinary approach to postgraduate training.

Doctoral Centre Students from Imperial College (Chemical Biology Centre) and from University of Warwick (Molecular Organisation and Assembly in Cells) will be presenting their work during the course of a day long seminar. This aims to encourage interactions and co-operation between researchers and develop a network of multi-disciplinary scientists. We hope that these interactions will continue throughout the year until next year's similar event...

*Xavier and Adair
26th January 2006*

Schedule

Coffee Room

10.30-11.00	Set up Posters
11.00	Welcome and introduction
11:10-13:00	Poster session and lunch

Tutorial Room

13:00	First set of talks (6)
14:30	Coffee
14:45	Second set of talks (5)
16:15	Coffee
16:30	Third set of talks (6)
18:00	End of conference/Dinner

<http://www.chemicalbiology.ac.uk/>
<http://www.warwick.ac.uk/go/moac/>

Both Doctoral Training Centres are funded by the EPSRC Life Sciences Interface



Presentation Schedule

Session 1 - Six Presentations from 13.00 to 14.30:

Development and applications of a tip position modulation scanning electrochemical microscope. *By Martin Edwards*

Studies towards a New Foot-and-Mouth Disease Antiviral Agent. *By Núria Roqué-Rosell*

TBC. *By Hiroko Kamei*

Eluding the thermodynamic hypothesis; the native state of actin is a metastable ensemble.
By Gabriel Altschuler

New discoveries on Fts Z. *By Raul Pacheco Gomez*

Taking the Fight to the Superbugs – Interactions of Metallo-Supramolecular Nanocylinders with Biological Systems at the Subcellular Level. *By Adair Richards*

Session 2 - Five Presentations from 14.45 to 16.00:

Phase behaviour of model membranes composed of cholesterol and diacylglycerophospholipid derivatives. *By Deborah Gater*

Bending membranes and their regulation of phosphatidylinositol phosphatases. *By Xavier Mulet*

Evidence that Drug Molecules Eat Their Way Through Membranes. *By Sarra Sebai*

Introduction to molecular modelling. *By John Grime*

Modelling Lipid Biosynthesis in the Plasma Membrane of *Acholeplasma laidlawii*. *By Stephen Alley*

Session 3 - Five Presentations from 16.30 to 17.45:

Analysing the growth/death potential of the c-Myc oncoprotein using high density microarray analysis *By Sam Robson*

Radiotherapy using the Variable Aperture Collimator. *By James Anderson*

TBC. *By Angeliki Harrisiou*

Two component signalling systems in bacteria – a bioinformatics approach. *By Peter Cock*

2D Infrared spectroscopy of Proteins. Towards a high information content and high sensitivity technique for Bioanalysis. *By Paul M. Donaldson*

Concluding Remarks

Poster Session

Membrane protein biogenesis in cyanobacteria.

Gemma Warren

MOAC, Warwick University

Characterisation of a novel photosystem in the cyanobacterium

***Acaryochloris marina*.**

Yi Chan

MOAC, Warwick University

Using Ligand Field Molecular Mechanics to model Fe(III) - Siderophore complexes.

Prakash Patel

MOAC, Warwick University

Modelling microtubule active transport.

Richard Wilson

MOAC, Warwick University

Linear dichroism of restriction enzymes.

Martyn Rittman

MOAC, Warwick University

Building a Brain: Some Biological Ideas.

James Sinfield

MOAC, Warwick University

Modelling aspects of Myxobacteria motility using a spatial simulation framework.

Antony Holmes

MOAC, Warwick University

Quantitative Analysis of Chloroplast Protein Targeting Pathways.

Mike Li

MOAC, Warwick University

Analysis of Genetic Networks.

Ulrich Janus

MOAC, Warwick University

Signal Transduction and Noise in a Fission Yeast.

Ben Smith

MOAC, Warwick University

Geometrical Reconstruction and Characterisation of the Plant Endoplasmic Reticulum.

Nacer Bouchekhima

MOAC, Warwick University

Molecular and Fluid Dynamics in a Linear Dichroism Cell.

Lahari De-Alwis

MOAC, Warwick University

Central neural control of energy balance.

Ratchade Pattaranit

MOAC, Warwick University

Maximum Solubility of cholesterol within PC lipids

Alexandra Trevenen

CBC, Imperial College

Ligand-receptor engineering: inositol phosphate analogues and mutant protein kinase B-Pleckstrin Homology domain.

Sam Cooper

CBC, Imperial College

A diverse range of cellular functions are controlled by the vital signalling enzyme protein kinase B (PKB). These include physiological pathways and pathological conditions arising from perturbations of these pathways.

PKB's activation mechanism is not fully understood, as the phosphatidylinositol poly-phosphates known to be involved are recognised by many other proteins. These include 3-phosphoinositide-dependent protein kinase-1 (PDK1), which is involved in the same pathway. This makes the PKB activation mechanism very hard to dissect.

By mutating PKB to accept an unnatural lipid, it will be possible to break this interdependence and study the individual components of the activation mechanism. Both bump-hole and ion-pair exchange strategies will be used to establish an orthogonal receptor-ligand pair.

Research has focused on the synthesis of analogues of the head group of PtdIns(3,4,5)P₃, with unnatural substituents attached to the carbons on the ring (bump-hole) and the 2-O (ion-pair exchange).

Once these molecules have been synthesised their interactions with a range of PKB α PH-domain mutants will be investigated. It is hoped that this will supply insight for rationally designing a second generation of protein/lipid pairs for eventual in vivo studies.

Synthesis and Application of a Lipid Membrane Probe.

Emma Clay

CBC, Imperial College

Lipids do not just form a passive biological bilayer, they have been shown to play a role in protein folding and function. To be able to investigate the effect of changes in the lipid composition on the lateral pressure profile a tethered lipid pressure probe can be used. A lipid probe is favourable as it causes less disruption to the membrane than a protein tether probe. The di-functionalised probe used can form excited state dimers with a frequency proportional to the collisional rate of the probe molecules, which can be correlated to the pressure in that region of the membrane. The full characterisation of the pressure characteristics of the probe in model bilayer systems will then allow the effect of biological reactions on a membrane to be investigated. This work started with the total synthesis of the lipid probe which offered flexibility of the chain length and head group selected. The probes characteristics in model bilayer systems were then investigated and the probe was then introduced into B cells.

SNARE-mediated membrane fusion; in vitro model development. *Christina*

Turner

CBC, Imperial College

SNARE (Soluble NSF Attachment Protein Receptor) proteins have been implicated in the membrane fusion mechanism between vesicles and organelles. This process is of fundamental importance to intracellular communication within eukaryotes. Research into this area is growing and the majority of research currently conducted uses *in vivo* models. Often results from these models are difficult to interpret due to the multitude of regulatory pathways and other cellular processes that occur. It is the aim of this research to establish a workable *in vitro* model. Such a model is based around the formation of GUVs (Giant Unilamellar Vesicles) into which purified protein solution can be incorporated. Fluorescence will be used to track proteins and lipids and will allow the principle aspects of membrane fusion to be studied in a simplified system.

Understanding the Role of Cubic Phases in Membrane Protein Crystallization.

Chandrashekhhar Kulkarni[‡], Oscar Ces[‡], So Iwata[§], Richard Temple[‡]

[‡] *Membrane Biophysics Group, Dept. of Chemistry,*

[§] *Membrane Protein Crystallography, Dept. of Biochemistry, Imperial College, London.*

Membranes may contain hundreds of different proteins and are asymmetrically distributed according to their structure and function. The amphiphilic nature of such proteins creates difficulty in crystallizing and hence studying them. Surfactant-detergent based methods and *In cubo crystallization* (lipid phases) are the methods which have been found successful up till now. 3-D Lipid Cubic phase provides more native environment to the membrane proteins detached from bilayer. The Cubic phase method is a relatively new technique as compared to the others.

We focus on understanding the process of membrane protein crystallization *in cubo*.

Investigation of Diacylglycerol role in Nuclear Envelope assembly using synthetic fluorescent phosphoinositol probes

Trung Huynh

CBC, Imperial College

In a cell free model system, nuclear envelope (NE) assembly proceeds by the binding of highly enriched phosphatidylinositol (PtdIns) membrane vesicles (MV) to chromatin in an ATP-dependant manner. This is followed by their fusion via a GTP or bacterial PtdIns- specific PLC induced step to form the NE double membrane. The putative liberation of diacylglycerol (DAG) from the hydrolysis of PtdIns by PLC in the MVs is thought to be required for fusion, however this association is difficult to probe. We plan to synthesise a range of PtdIns analogues covalently attached to fluorophores and study these interactions by fluorescence microscopy.

Presentation Abstracts

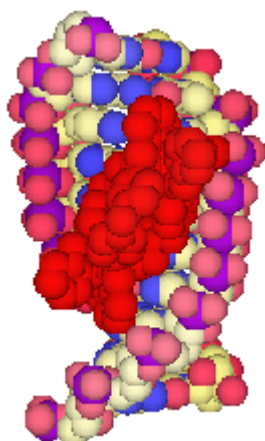
Taking the Fight to the Superbugs – Interactions of Mettalo-Supramolecular Nanocylinders with Biological Systems at the Subcellular Level.

Adair Richards,

MOAC University of Warwick

www.warwick.ac.uk/go/adairrichards

Drug-resistant bacterial diseases are increasingly becoming one of the major headaches of modern medicine. Conventional bacteriacides are no longer sufficient to treat previously easily curable infections and there is a strong need for new classes of antibiotics. We have been developing a novel type of drug which avoids all current common pathways of antibiotic resistance. It relies on supramolecular synthetic chemistry to create molecules of the exact charge and stericity to bind in the major groove of DNA and promote supercoiling, leading eventually to cell death. Various techniques from the fields of microbiology, synthetic chemistry, dichroism spectroscopy and solid-state NMR have been used to develop and characterise these molecules and their interactions with biological systems. This talk charts the recent developments and potential future progress in this exciting field of research.



NMR structure of the helicate binding in the major groove of DNA

Development and applications of a tip position modulation scanning electrochemical microscope.

M.A. Edwards, M. Vatish, P.R. Unwin, A.L. Whitworth
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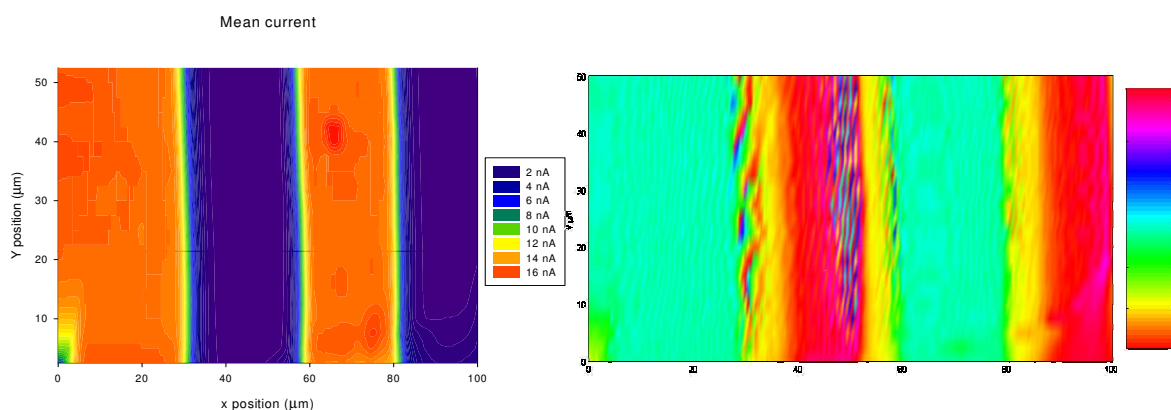
Scanning electrochemical microscopy (SECM) is a well-established technique for imaging topography, permeability and reactivity of surfaces.¹ In a typical SECM imaging experiment a mobile ultramicroelectrode (UME) with diameter 1-25 μm is scanned in a raster pattern near to a surface bathed in a solution containing a redox-active mediator. The corresponding steady-state current measured at the UME can be related to the topography and reactivity of the surface; however for conventional fixed height scanning it can be difficult to deconvolute the topographical and activity information, especially for rough (micron scale) surfaces with sites of varying activity. To overcome this problem SECM tip position modulation (TPM) has been developed in which a small sinusoidal perturbation is applied to the vertical position of the electrode.²

We have developed a new fully integrated SECM TPM setup in which the UME is mounted on a 3 axis piezoelectric actuator; electrochemical and motion control is achieved through a data acquisition card coupled to a PC using custom written software. This setup allows both distance modulation of the UME and lock-in detection of the tip current to be performed by the PC. One advantage of this setup is that it allows one to perform and adapt to “on the fly” processing of the current signal. In addition to this the exceptionally narrow band pass filtering afforded by lock-in detection allows us to surpass the noise limits offered by traditional setups.

Initial results will be presented which demonstrate the versatility of the new setup for improving spatial resolution and detection limits in SECM imaging. Furthermore we show how it can be used to provide a measure of sample permeability.

[1] *Scanning Electrochemical Microscopy* eds. A.J. Bard, M.V. Mirkin, 2001, Marcel Dekker, New York

[2] D.O. Wipf, A.J. Bard, *Anal. Chem.* 1992, 64, 1362-1367



Current (right) and phase (left) images taken using TPM over a gold band structure. Change in phase dictates that current change is due to surface activity and not topographical changes

Studies towards a New Foot-and-Mouth Disease Antiviral Agent.

Núria Roqué-Rosell
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Foot-and-mouth disease virus (FMDV) causes a highly infectious disease of cloven-hoofed livestock with economically devastating consequences. The political and technical problems associated with the use of FMDV vaccines make drug-based disease control an attractive alternative. The FMDV genome is translated as a single polypeptide precursor that must be cleaved into functional proteins by virally-encoded proteases. Ten of the thirteen cleavages are performed by the highly conserved 3C protease (3C^{pro}), making the enzyme an attractive target for anti-viral drugs.

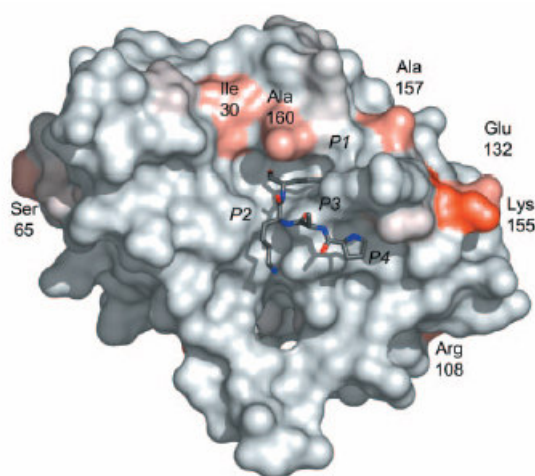
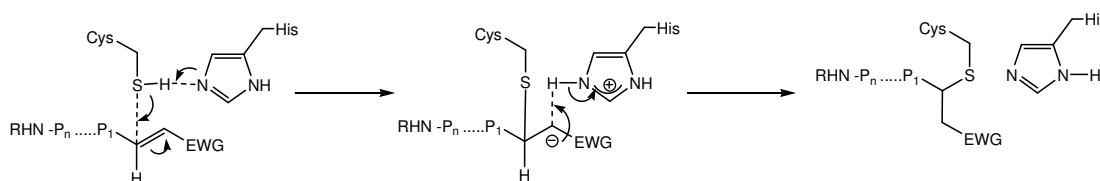


Figure 1: A surface representation of FMDV 3C^{pro}. Regions colored orange represent sites of amino acid variation among 41 strains of FMDV 3C^{pro}; darker orange shading indicates higher degrees of variation. Model substrate is included to indicate P1–P4 positions (Birtley *et al.*, 2005).

FMDV 3C^{pro} inhibitors have been designed on the basis of enzyme substrate-specificity (Birtley *et al.*, 2005). An amino acid sequence is attached to a Michael-acceptor moiety, which irreversibly interacts with the active site of the cysteine protease.



Scheme 1: Mechanism of inhibition of cysteine proteases by α,β -unsaturated ester derivatives (EWG=CO₂R') and vinyl sulfones (EWG=SO₂R').

An inhibition assay has been developed in order to test the activity of the potential synthetic inhibitors. The use of a fluorescence quenched FMDV 3C^{pro} substrate allows continuous measurement of the hydrolysis rate, which is proportional to the free enzyme

Modelling Lipid Biosynthesis in the Plasma Membrane of *Acholeplasma laidlawii*.

Stephen H. Alley, * Mauricio Barahona, * Oscar Ces, † and Richard H. Templer †

*Department of Bioengineering, Imperial College London, London, United Kingdom and †Department of Chemistry, Imperial College London, London, United Kingdom

Stephen.alley@imperial.ac.uk

The lipids in the plasma membrane of all organisms form lamellar phases at physiological conditions. We present a model of the lipid biosynthetic network of *Acholeplasma laidlawii* which controls the spontaneous curvature of the plasma membrane lipids and their phase behaviour. This control is mediated by the membrane binding of a lipid biosynthetic enzyme with an amphipathic α -helix. In the model, an exponentially-growing monolayer represents the plasma membrane. The enzymes have reversible, Michaelis-Menten kinetics which are functions of the lipid molar fractions on the membrane surface, while the membrane binding of the amphipathic α -helix is modelled by the energy of lipid bending around the α -helix. The spontaneous curvatures of the individual membrane lipids are used to model the binding of the amphipathic α -helix. In this study, the curvature of the *A. laidlawii* lipid dioleoylphosphatidylglycerol (DOPG) is measured by X-ray diffraction. A numerical integration of the model evolves to a steady-state lipid composition from all observed initial conditions. Parameters derived from an optimisation algorithm are able to reproduce the experimentally-observed steady state. Using these parameters the role of the amphipathic α -helix in ensuring the robustness of the membrane curvature is investigated.

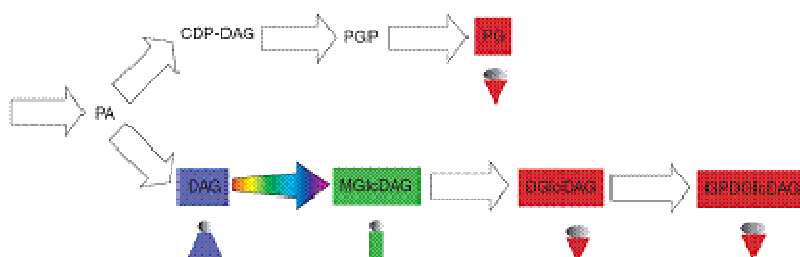


FIGURE The chemical complexity of the lipid biosynthetic network of *A. laidlawii* is simplified by the modelling the lipid spontaneous curvatures. The curvature-sensitive enzyme, MGLcDAG synthase, is depicted with a coloured arrow.

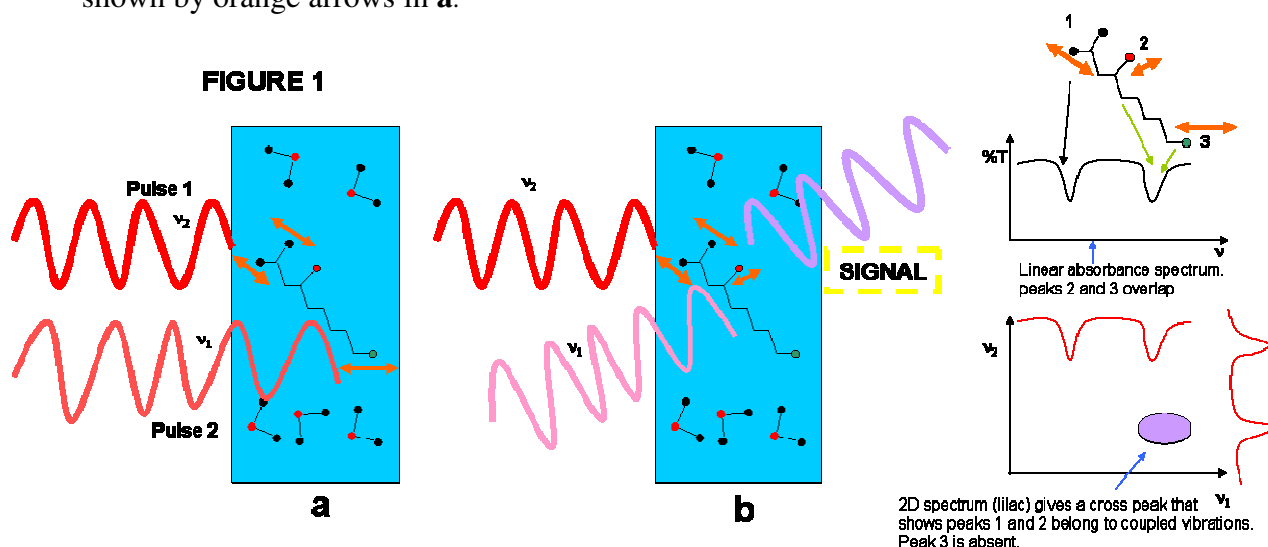
2D Infrared spectroscopy of Proteins. Towards a high information content and high sensitivity technique for Bioanalysis.

Paul M. Donaldson, Laura M.C. Barter and David R. Klug,
CBC, Imperial College

The aim of our research is to develop a totally new kind of instrument for detecting and characterising proteins. We are investigating optical spectroscopies that are theoretically capable of detecting both small amounts of protein *and* providing more structural information than existing high sensitivity techniques. Our experiments measure a molecule's *vibrational spectrum*. This gives information about molecular structure, environment and chemistry.

Vibrational spectroscopy can be very sensitive. Measurements on vibrations of *single molecules* are routine. Unfortunately the vibrations of large molecules such as proteins are very difficult to analyse – there are so many that they obscure one another. Our work seeks to minimise this problem by using a new generation of lasers which produce very short pulses of infrared light. These pulses are as short as molecular vibration periods and can be manipulated to give information about specific vibrations, even in a large molecule.

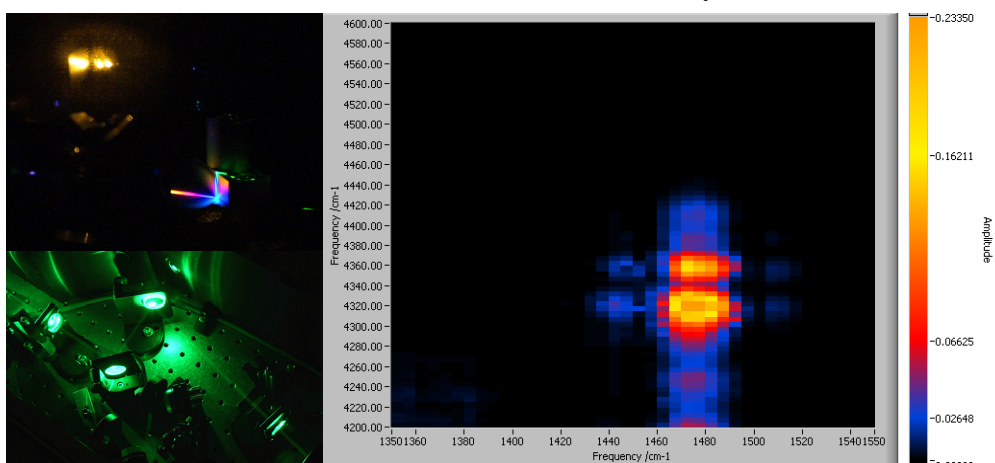
The way we select vibrations is by irradiating our sample with short laser pulses containing two different frequencies of infrared light. Look at Figure 1. By varying the frequencies of the two pulses we can make the light interact with different vibrations, as shown by orange arrows in **a**.



By using a special laser pulse sequence we can arrange for the molecules probed to give out a new signal *if* we are exciting vibrations which are *coupled* to one another – see **b**. The spectra in Figure 1 shows how measuring this signal and making a map of it can reduce an absorbance spectrum of three peaks (two of which are unresolvable in the absorbance spectrum) into a ‘2D’ spectrum consisting of only one cross peak – a major simplification. Thus 2D-IR works according to the same principles of the highly successful 2D-NMR.

Our work is currently exploratory in nature - constructing a reliable 2D spectrometer and understanding the signals it gives. This is pioneering work as internationally there are only a few 2D-IR experiments. However, if successful 2D-IR could revolutionise

the way we do vibrational spectroscopy, allowing a more simplified analysis of IR spectra and a more detailed look at chemical structure and dynamics.

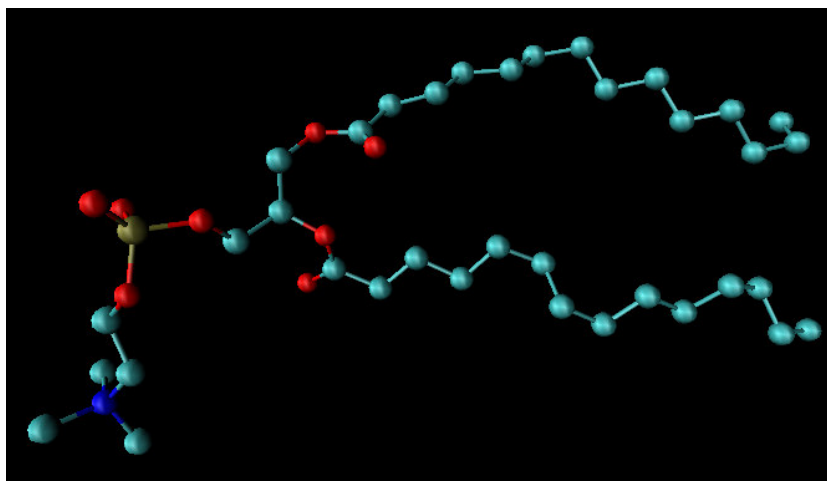


Introduction to molecular modelling

John Grime

MOAC, Warwick University

There are a large and varied number of techniques and software packages available for computer simulation of molecular systems. This talk will give a brief introduction into some major areas of this field, with motivation and examples.



DMPC

Evidence that Drug Molecules Eat Their Way Through Membranes.

Sarra C. Sebai¹, Magdalena Baciu¹, Xavier Mulet¹, Gemma Shearman¹, Oscar Ces¹, James A. Clarke¹, Robert V. Law¹, Richard H. Templer¹, Christophe Plisson², Antony Gee², Christine A. Parker²

¹ *The Chemical Biology Centre, Department of Chemistry, Imperial College London, South Kensington Campus, Exhibition Road, London, SW7 2AZ, U.K.*

² *PET Imaging Department, GlaxoSmithKline, ACCI, Addenbrookes Hospital, Cambridge, CB2 2GG, UK*

Although drug molecules are designed to bind specifically to targets such as receptors that are embedded within biological membranes it is becoming increasingly evident that a large fraction of these compounds interact non-specifically with the membrane and / or other proteins.

To address this issue we are studying the binding of D₂-dopamine receptor agonists/antagonists to model membrane assemblies in order to increase our understanding of their binding properties.

Compound binding studies were performed using specific D₂-dopamine receptor ligands such as Haloperidol and Spiperone on membrane model systems made of DOPC, DLPC and Ether linked PC. Quantification of ligand interacting with the membrane was performed using spectroscopic techniques such as SAXS and SS-NMR, and fluorescence microscopy for a direct visualization of the binding using giant vesicles.

Both ligands are shown to interact with the membrane environment, as they affect the bilayer spacing. In addition, it is also demonstrated that Haloperidol and Spiperone have a significant effect on the DOPC bilayer as they catalytically hydrolyze it into MOPC and oleic acid in rates that are comparable with in vivo drug diffusion rates. Here we present, for the first time, evidence that drugs can chemically degrade the phospholipids in bilayers and that the resulting membranous fragments carry the drug across and away from the membrane barrier.

Abbreviations:

DOPC: Dioleoylphosphatidylcholine, DLPC: Dilaurylphosphatidylcholine, SAXS: Small Angle X-ray Scattering, SS-NMR: Solid State Nuclear Magnetic Resonance, MOPC: Monooleoylphosphatidylcholine

Analysing the growth/death potential of the c-Myc oncoprotein using high density microarray analysis

Sam Robson

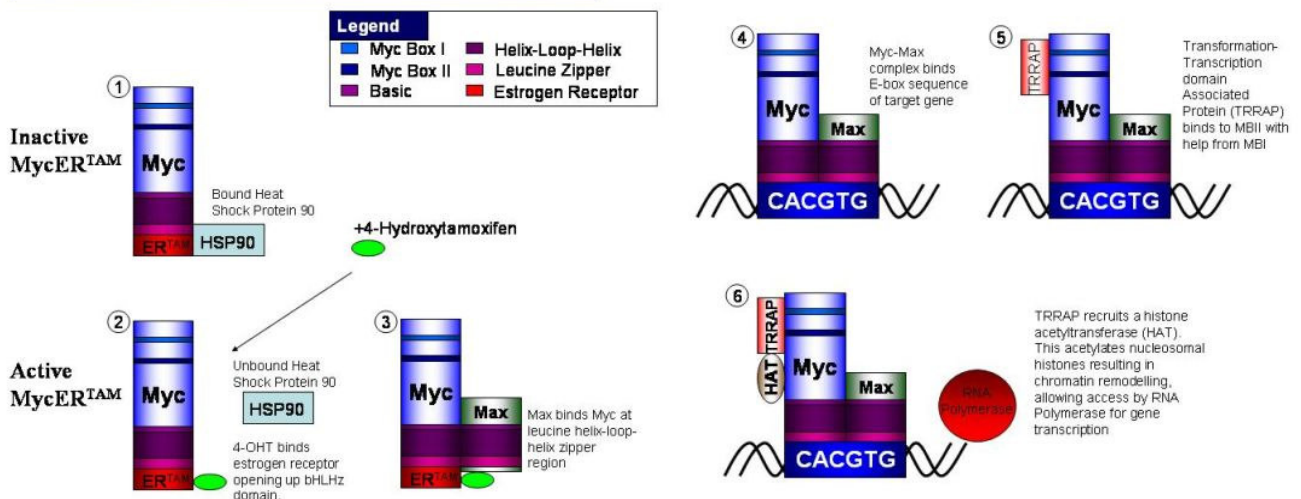
MOAC, Warwick University

Cancer is a collection of diseases with the common feature of unregulated cell growth. It is the second largest cause of death in the world, behind heart disease. Cancer treatment is hampered by the sheer number of cellular changes that occur during onset of the disease.

Understanding the sequence of cellular events that result in malignant tumour growth will allow for more direct acting cancer therapies and improved detection methods for an earlier prognosis. Earlier detection of malignant growth can greatly improve the chances of successful treatment. A model for cancer progression in vivo has been created that allows controlled activation of the proto-oncoprotein c-Myc, known to be involved in a large number of human cancers. Of great interest is the tissue specificity seen in c-Myc functionality between skin, where c-Myc activation results in synchronous entry of cells into the cell cycle and unchecked proliferation, and the pancreas, where c-Myc activation results in a massive apoptotic response.

Post-transcriptional analysis using high density oligonucleotide microarrays, able to measure mRNA expression levels across the entire genome in parallel, allows in vivo analysis of changes in gene expression during tumourogenesis. Laser capture microscopy, a novel dissection method allowing isolation of specific cells from a tissue section for RNA extraction, was utilised to ensure RNA homology. Statistical and mathematical techniques can be applied to produce functional gene networks, allowing modelling of c-Myc mediated changes in cancer onset, and analysis of direct c-Myc target genes. It is hoped that this will afford a better understanding of the cellular machinery directly controlled by the c-Myc protein.

ACTIVATION OF MYCER^{TAM} PROTEIN



Bending membranes and their regulation of phosphatidylinositol phosphatases.

*Xavier Mulet, Richard H. Templer, Rudiger Woscholski
CBC, Imperial College
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Phosphatidylinositol (PI) lipids are involved in many cellular processes which are vital in many regulatory mechanisms. These range from cytoskeletal attachments to signal transduction. The different phosphorylated forms of PI are present in different cellular compartments at different levels. Phosphorylation is carried out by kinases and the dephosphorylation occurs with phosphatases.

Protein-lipid interactions have been found to regulate the rates of several enzymes, for example the CCT system. It has been suggested (Schmid et al., 2004) that membrane lipid composition (both headgroup and chain length effects) may have an influence on the rates of reaction of PI type II phosphatases.

Initial studies of PI systems, using small angle x-ray scattering, have suggested the formation of curved, type II, lipid interfaces. A bio-mechanical microscope has been constructed to enable the study of changes in membrane properties as a function of enzymatic reaction using giant unilamellar vesicles (GUVs) combined with fluorescence, micro-manipulation and micro-aspiration techniques. It is also possible to study the effect of membrane properties on the rates of enzyme reaction. Using variations in levels of curvature and stored curvature elastic energy present within biomimetic membrane systems, the role of PI lipids in enzyme regulation can be determined.

Schmid, A. C., H. M. Wise, et al. (2004). "Type II phosphoinositide 5-phosphatases have unique sensitivities towards fatty acid composition and head group phosphorylation." *FEBS Lett* **576**(1-2): 9-13.

Eluding the thermodynamic hypothesis; the native state of actin is a metastable ensemble.

Gabriel Altschuler

CBC, Imperial College

Gabriel.Altshuler@icr.ac.uk

Nascent actin requires interactions with the highly conserved and essential eukaryotic chaperonin-containing TCP-1 (CCT) for correct folding to the native state in vivo. We have investigated the energetics and kinetics of the underlying actin folding/unfolding process using stopped flow fluorescence and biochemical techniques. This has allowed determination of the relative free energies and activation energies between some of the actin folding intermediates. It has been found that the native state of actin represents a metastable ensemble of nucleotide and cation bound conformations and that the actual thermodynamic 'Anfinsen' native state is an aggregation-prone, non-native intermediate characteristic of a partially folded, molten globule. We have shown that CCT mediates the folding of this intermediate to the native state which defines both a kinetic and a thermodynamic role for the chaperone. We hypothesise that hydrolysis of chaperone bound ATP is coupled to substrate folding in order to overcome the large activation energy and ascend the thermodynamic substrate folding landscape to reach the 'native plateau'.

Phase behaviour of model membranes composed of cholesterol and diacylglycerophospholipid derivatives.

Deborah Gater

CBC, Imperial College

Deborah.Gater@imperial.ac.uk

Solid-State NMR and x-ray diffraction techniques have been used to investigate the phase behaviour of model membranes composed of cholesterol (Chol) and the diacylglycerophospholipid derivatives. These include both lyso-phosphatidylcholine (LPC) and diacylglycerol (DAG) in excess water. Chol appears to drive the formation of a lamellar phase in the LPC system. X-ray scattering and ^2H and ^{31}P NMR results indicate that this is a liquid ordered lamellar phase (L_o) which is in equilibrium with a micellar phase at concentrations of Chol between ~20 and 70mol%. For the DAG: Chol system, initial x-ray results indicate that this also forms a L_o phase under some conditions.

Development and application of QM/MM MD to excited state processes in biological systems.

Mark Williamson

CBC, Imperial College

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The realm of biological systems is inherently dynamic; information from x-ray crystal structures paints a useful, but static picture of the situation. Fluctuations of these systems can be examined indirectly using femtosecond spectroscopy. This method consists of using radiation to interact with a specific region of the system called a fluorophore on a timescale resolution that is chemically relevant. This method is essentially a probe of the time ordered energy gap fluctuations of an electronic excited state.

Over the past year my work has involved a hybrid quantum mechanical / molecular mechanical modelling (QMMM) method to **model** such energy gap fluctuations in proteins and other biologically relevant structures. The nuclear motion is propagated in time using a classical force field, thus capturing the dynamics, whilst a computationally cheap QM method is applied to a fluorophore region to calculate the excited state electronic gap size.

The time ordered nature of calculated energy gap fluctuations opens it to a toolbox of mathematical methods that can produce empirically comparable results. Its autocorrelation function can be used to generate other properties such as the time scale of the fluorophore's interaction with its surrounding bath, and from this, the system's associated Stoke's Shift. In addition, the series can transform into the Fourier domain to yield information about key modes involved in the relaxation route from an excited to ground state.

Future work entails novel application of these methods to generate a Free Energy surface for a chemical reaction and from this the nature of the transition state. A quadratic Free Energy function for a state can be related to the state's **average** energy within the linear response limit. By extrapolating two such functions representing a product and a reactant state, a transition state may be located.

Radiotherapy using the Variable Aperture Collimator.

James Anderson

CBC, Institute of Cancer Research

James.anderson@icr.ac.uk

Radiotherapy is one of the most efficient and reliable methods of modern cancer treatment. It consists of sending beams of high-energy radiation into the patient in such a way that they overlap at the tumour site. This allows treatments to apply a high radiation dose to the tumour while sparing the surrounding healthy tissues.

In order to sculpt the high-dose region tightly around the tumour, each radiation beam must be “shaped” before it enters the patient: portions of the beam that are not required are blocked by thick pieces of tungsten or lead. In modern radiotherapy, this beam shaping is performed automatically using a multi-leaf collimator (MLC). The MLC consists of two banks of thick vertical tungsten plates that can be automatically moved into and out of the radiation beam.

The main drawback of the MLC is its expense. The electronic complexity of individually controlling as many as 40 high-precision motors in a very small space means that only the most well-funded treatment centres can afford the technology. A simpler, less expensive collimator would therefore be of great benefit to many treatment centres worldwide.

This work has considered one such collimator. Named the variable aperture collimator (VAC), it finds its simplicity in having a much smaller maximum beam size than the MLC (5x5cm compared to 40x40cm). Additionally, the tungsten plates of the MLC are replaced with rectangular tungsten “pencils” to make up for the precision lost in the smaller beam size.

The work so far has used computer simulation to evaluate the effectiveness of the VAC for radiotherapy. This evaluation was done by comparing the VAC to an MLC with the same restriction on maximum beam size. Results have shown that the VAC does not outperform a reduced MLC, indicating that further investigation of simple collimators should focus on a small maximum beam size MLC.

Two component signalling systems in bacteria – a bioinformatics approach.

Peter Cock

MOAC, Warwick University

New discoveries on Fts Z.

Raul Pacheco Gomez

MOAC, Warwick University

TBC.

Hiroko Kamei

MOAC, Warwick University

TBC.

Angeliki Harrisiou

MOAC, Warwick University