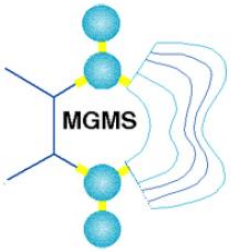

MGMS and RSC MMG
Young Modellers' Forum 2016
PROGRAMME & ABSTRACTS

Programme of Oral Presentations

9.15 – 9.50	Coffee and Registration
9.50 – 10.00	Welcome and Introduction
10.00 – 10.20	Qi Yuan, Imperial College A density functional theory study on triplet intermolecular hydrogen transfer between Cycloxydim and Chlorothalonil
10.20 – 10.40	Amy Barber, Surrey Development of a dynamic multi-scale, computational model of breast cancer
10.40 – 11.00	Christina Roggatz, Hull How quantum chemical methods help to unravel the effects of pH on marine communication
11.00 – 11.30	Poster Presenters "Lightning Talks"
11.30 – 11.50	Tea/Coffee break
11.50 – 12.10	George Hedger, Oxford Lipid-Protein Interactions: Insights from Molecular Simulation
12.10 – 12.30	Stefano Bosisio, Edinburgh Towards high-throughput alchemical free energy calculations
12.30 – 12.50	Matthew Turner, Cardiff Prediction of Ligand Effects in Platinum-Amyloid-β Coordination
12.50 – 14.10	Lunch and Poster Session
14.10 – 14.30	Joanna Zarnecka, Liverpool John Moores Optimization of shape fingerprints for protein-ligand systems
14.30 – 14.50	Vladimiras Oleinikovas, UCL Understanding cryptic pocket formation in protein targets by enhanced sampling simulations
14.50 – 15.10	Joshua Meyers, ICR Mapping the 3D Structures of Small Molecule Binding Sites
15.10 – 15.30	Richard Lewis, Cambridge A Deep Learning Approach to Modelling Diverse Chemical Data
15.30 – 15.30	Tea/Coffee break
15.50 – 16.10	Valentina Santolini, Imperial College Topological design of porous organic cages
16.10 – 16.30	Maxwell Fulford, King's College Plates and Needles: A Computational Study of the Growth of Hexagonal Ice
16.30 – 17.00	Deliberations and Prizes
17.00	End

Talk 1

A density functional theory study on triplet intermolecular hydrogen transfer between Cycloxydim and Chlorothalonil

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Application of adjuvants in combination with active ingredients, as well as mixtures of agrochemical compounds, is becoming a dominant trait in modern agriculture. It should be noted, however, that mixtures of agrochemicals might influence their photochemical fate. Several experimental studies on the influence of photostability of agrochemicals upon mixing have been performed, but there is no theoretical validation of the altered photostability upon mixture of agrochemicals and thus the understanding of the underlying mechanism is quite limited.

We have performed computational studies on the photochemical fate of a mixture of two commonly applied agrochemical compounds Cycloxydim (CD) and Chlorothalonil (CT). It is suggested by experiment that photodegradation of CD is accelerated in the presence of CT via triplet intermolecular hydrogen transfer [1], however, the detailed mechanism has not been identified from the experimental data. We identified the possible reaction pathways by locating the local minimum structures of CD/CT dimers at both the ground state and the first triplet state. Potential energy profiles along possible pathways were explored and compared to determine the preferential reaction pathway. To understand the underlying reason for the differences in the energy profiles for the possible pathways, natural population and surface charge analysis were performed, resulting in an explanation of the possible reaction mechanism. Computational studies investigating the effect of mixing herbicides and fungicides upon their photochemical processes have not previously been performed, therefore, this study provides the first computational study of the CD/CT system and evaluates the methodology to determine if it would be suitable to apply to future studies of interacting molecules with altered photochemical properties.

References:
[1] S. Monadjemi, A. ter Halle and C. Richard, *J. Agric. Food Chem.*, 2014, **62**, 4846-4851.

Talk 2

Development of a dynamic multi-scale, computational model of breast cancer

A. Barber[1], M. Ajaz[1], A.M. Kierzek[1, 2] and N.J. Plant[1]

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[2]Simcyp Limited (a Certara Company), Sheffield

The multifactorial nature of breast cancer is a major barrier to the development of effective treatment. Despite recent and on-going advancements, breast cancer remains the most common cause of cancer deaths globally. Inter- and intra-tumoral heterogeneity contributes to differences in aggressiveness, prognosis and therapeutic response, complicating treatment. In particular, the development of targeted therapeutics against triple-negative breast cancers has had limited success. This provides motivation for the development of novel methodologies for breast cancer drug discovery.

Here we show the development of a dynamic model, integrating genome-scale metabolism, a gene and signalling regulatory network centred on the estrogen and progesterone receptors, and a kinetic model of the cell cycle. We have constrained both parts of the network using microarray data, producing reconstructions for several breast cancer cell lines. In addition, we further constrain the model using in vitro metabolomics flux data. We demonstrate that this model can reproduce behaviours of in vitro cell lines: consumption of glucose and lactate; response to metabolic drugs; response to cancer chemotherapeutics.

The cell- and tumour- specific models provide novel opportunities for in silico testing of cancer cell responsiveness to different experimental conditions, in particular identifying metabolic vulnerabilities as potential drug targets. We anticipate this will be invaluable to researchers studying the network biology of breast cancer. Furthermore, utilisation of this model will aid development of effective combinatorial treatments and begin to remove barriers to the reduction of mortality from breast cancer.

Talk 3

How quantum chemical methods help to unravel the effects of pH on marine communication

Christina C. Roggatz, *Mark Lorch* and *David M. Benoit*

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Marine organisms use a large variety of small chemical compounds to communicate. These signalling molecules are used, for example, to detect predators, find mating partners, locate the best place to settle or the next meal[1]. Increasing amounts of atmospheric CO_2 that dissolve into the oceans cause a drop of ocean pH. This process called ocean acidification is known to affect the physiology and fitness of organisms. Lately it has also been reported to affect numerous animal behaviours that are mediated by chemical signalling cues[2]. However, little is known about the underlying mechanisms, especially in invertebrates.

We investigate the molecular effects of decreasing ocean pH on the structure and function of peptide signalling cues as one potential mechanism to explain altered animal behaviour in high CO_2 conditions[3]. This requires a multi-disciplinary approach including NMR spectroscopy to determine the peptide cues' susceptibility to protonation and quantum chemical calculations to explore the differences in conformation and charge distribution of the relevant protonation states. Here we present the results of our structural molecular investigation and highlight the quantum chemical methods required to successfully model molecular conformation and molecular electrostatic potential in solution.

References:
[1] M. E. Hay, Annu. Rev. Mar. Sci., 2009, 1, 193–212.
[2] M. Briffa, K. de la Haye and P. L. Munday, Mar. Pollut. Bull., 2012, 64, 1519–1528.
[3] C. C. Roggatz, M. Lorch, J. D. Hardege and D. M. Benoit, Glob. Change Biol., 2016; doi: 10.1111/gcb.13354.

Talk 4

Lipid-Protein Interactions: Insights from Molecular Simulation

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Lipid molecules can bind selectively to specific sites on integral membrane proteins modulating their structure, stability, and function. Molecular dynamics simulations provide a powerful tool for identifying lipid interaction sites, characterising the energetics and dynamics of these interactions, and ultimately gaining mechanistic insight into the molecular details of lipid modulation of membrane protein function [1]. In this talk I will describe work from my PhD in applying molecular simulations to characterize the interactions of a range of lipid species with biomedically important membrane proteins. In particular I will focus on the human receptor tyrosine kinase (RTK) family of cell surface receptors. These receptors play essential roles in diverse cellular processes and their activity is regulated by lipids in the surrounding membrane, including PIP_2 in the inner leaflet, and GM3 in the outer leaflet. Using a multiscale molecular dynamics approach, we have characterized anionic lipid interactions with the juxtamembrane regions of all 58 known human RTKs. Our simulations reveal the ability of all 58 receptors to induce nanoscale clustering of anionic lipids, and in particular PIP_2, into ordered ring-like patterns or 'shells' around the receptor. Characterization of the underlying free energy landscape reveals the strength and selectivity of these interactions, and enables us to make predictions on the effects of protein mutation, confirmed by experiment. We are now moving towards assembly of full-length receptor models *in silico* from component structural data, to enable further exploration of the effects of these lipid interactions on signaling events at the cell membrane.

These methods have also shown utility in exploring the energetics of cardiolipin interactions with the ADP/ATP carrier, and are now being applied to probe interactions of cholesterol and PIP lipids with G-protein coupled receptors (GPCRs) in collaboration with experimentalist partners. The approaches described in these studies may provide generalizable tools for characterizing the interactions of lipids which bind to specific sites on integral membrane proteins.

References:

[1] G. Hedger and M. S. P Sansom, *Biochim. Biophys. Acta Biomemb.*, (2016) **1858**, 2390-2400.

Talk 5

Towards high-throughput alchemical free energy calculations

Stefano Bosisio, Antonia S. J. S. Mey, *Julien Michel*

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There is strong interest in use of free energy calculation methods to support early-stage drug discovery in academia and the pharmaceutical industry. However significant efforts are still needed to translate the 'free energy science' into a robust engineering tool that may be used routinely. A key challenge is the definition of a robust simulation protocol that may be used prospectively with minimal user intervention.

Thus, to assess the state-of-the art of free energy techniques we took part in the SAMPL5 competition (Statistical Assessment of the Modelling of Proteins and Ligands) and submitted blinded predictions. We used our in-house free energy code SOMD to predict binding free energies of 22 host-guest systems, and distribution coefficients of 53 drug-like molecules. Multiple protocols featuring cutoffs and/or standard state correction terms were compared. We achieved significant correlation with experimental data for host-guest binding energies, but encountered major difficulties in estimating log D values of ionisable species.

Comparison of our results with those from other groups indicates that molecules parameterised with the same force-field but simulated with different simulation packages sometimes lead to significantly different results. To clarify the reasons we have pursued a collaborative effort to systematically compare computed hydration free energies between the SOMD, GROMACS (with the Mobley lab, University of California Irvine) and AMBER (with Hannes Loeffler, STFC) codes. This work has shown that reasonable reproducibility can be achieved for small organic molecules, but code-specific details in the implementation of the free energy algorithms currently prevent the use of a generic simulation protocol. This work suggests steps the field could take to facilitate wider use of free energy methods for molecular design.

References:

[1] S. Bosisio, A. S. J. S. Mey and J. Michel, *J. Comput. Aided Mol. Des.,* (2016), DOI: 10.1007/s10822-016-9933-0

[2] S. Bosisio, A. S. J. S. Mey and J. Michel, *J. Comput. Aided Mol. Des.,* (2016), DOI: 10.1007/s10822-016-9969-1

Talk 6

Prediction of Ligand Effects in Platinum-Amyloid-β Coordination

Matthew Turner [a], Robert J. Deeth [b] and *James A. Platts* [a*]

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Alzheimer's disease (AD) is a neurodegenerative condition associated with progressive cognitive decline in patients. The causes and development of AD are poorly understood, but one hallmark of AD is the presence of amyloid plaques. The early stages of the Aβ aggregation process have therefore become a target for the development of AD-therapeutics. The N-terminal domain of Aβ contains His-rich high-affinity metal binding sites, responsible for physiological coordination of Cu^{II}/Zn. One route to AD-therapeutics involves disrupting coordination by using compounds that occupy these binding sites, hindering the Aβ aggregation process. Recently, Barnham *et al.* showed that Pt^{II}(phenanthroline) complexes inhibit Aβ aggregation and limit its neurotoxicity *in vitro*.

In this work, Ligand Field Molecular Mechanics (LFMM), DFT and semi empirical methods are applied to a series of six Pt^{II}-Ligand systems binding to the N-terminal domain of the Aβ peptide. Molecular dynamics (LFMM/AMBER) is used to explore the conformational freedom of the peptide fragment, and identifies favourable Pt^{II}-binding modes and peptide conformations. Pt^{II} coordination depends on the nature of the ligand, providing evidence that binding mode may be controlled by ligand design. Structural analysis of the sampled Pt^{II}-Aβ conformations shows that platinum coordination disrupts existing secondary structure in Aβ and promotes formation of ligand-specific turn-type secondary structure.

References:
[1] M. Turner, J. A. Platts and R. J. Deeth, *J. Chem. Theory Comput.*, 2016, **12**, 1385–1392.
[2] M. Turner, R. J. Deeth and J. A. Platts, *In preparation.*

Talk 7

Optimization of shape fingerprints for protein-ligand systems

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One of the most important properties that dictate whether a molecule is likely to be an effective drug is its shape. Molecules similar in shape are more likely to show similar activity towards the same target protein. The pharmaceutical industry relies on this concept widely but lacks effective tools to apply it in detail.

Molecular shape fingerprints are binary bit strings that encode the shape of compounds. They involve fast calculations and low storage needs. Shape is measured indirectly by alignment to a database of standard molecular shapes – the reference shapes.

The aim of the investigation was to design a set of reference shapes that generate fingerprints, which will be useful in drug discovery. The shapes of all molecules that have ever been reported in complex with a protein were downloaded and filtered using an algorithm described by Haigh *et al.*[1]; this identified several alternative sets of reference shapes. A test set described by Taylor *et al.*[2] was used to evaluate the performance of the sets of reference shapes. We have demonstrated that molecules can be grouped according to shared biological activity. This is remarkable considering that none of the usual features of molecules (such as hydrogen bonds or other interactions) have been included, the analysis relies exclusively on their shape.

References:

[1] J. A. Haigh, B.T. Pickup, J. A. Grant, A. Nicholls, *J. Chem. Inf. Model.* (2005) **45**, 673–684.

[2] R. Taylor, J. C. Cole, D. A. Cosgrove, E. J. Gardiner, V. J. Gillet, O. Korb, *J. Comput. Aided Mol. Des.* (2012) **26**, 451–472.

Talk 8

Understanding cryptic pocket formation in protein targets by enhanced sampling simulations

Vladimiras Oleinikovas[a], Giorgio Saladino[a], Benjamin P. Cossins[b], *Francesco L. Gervasio*[a,c]

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[b] UCB Pharma, Slough, United Kingdom
[c] Institute of Structural and Molecular Biology, University College London, London WC1E 6BT, United Kingdom

Over 75% of disease-involved proteins cannot be readily targeted by conventional chemical biology approaches. Cryptic binding pockets, i.e. pockets that transiently form in a folded protein, but are not apparent in the crystal structure of the unliganded apo-form, offer outstanding opportunities to target proteins otherwise deemed 'undruggable' and are thus of considerable interest in academia and the pharmaceutical industry. Unfortunately, not only they are notoriously difficult to identify, but also the molecular mechanisms by which they open is still widely debated. Indeed, most of the known cryptic pockets have been found serendipitously, and neither experimental nor computational approaches are very effective in their localization. The aim of the present work, is to fill the knowledge gaps by clarifying the molecular mechanisms underlying the cryptic site formation and then to devise an effective computational approach to systematically detect known and unknown cryptic pockets. To this aim1 we performed a computational tour-de-force on three systems of pharmaceutical interest with experimentally-validated cryptic pockets: TEM1 β-lactamase, interleukin-2 (IL2) and Polo-like kinase-1 (PLK1). We ran several μs-long fully solvated atomistic molecular dynamics simulations (MD), massive parallel tempering simulations and a number of parallel-tempering-Metadynamics runs as well as developed and used an Hamiltonian replica exchange-based approach in combination with fragmentbased simulations.

References:
[1] V. Oleinikovas, G. Saladino, B. P. Cossins and F. L. Gervasio, *JACS*, Just accepted manuscript, doi: 10.1021/jacs.6b05425

Talk 9

Mapping the 3D Structures of Small Molecule Binding Sites

Joshua Meyers, *Nathan Brown*, *Julian Blagg*

Cancer Research UK Cancer Therapeutics Unit, Division of Cancer Therapeutics, The Institute of Cancer Research, London, SM2 5NG, United Kingdom

Effective sampling of chemical space is crucial to the future of small molecule drug discovery. Compound library design has historically focused on chemical structure analysis. However, the increasing availability of structural data, together with new protein binding site analysis tools, has enabled more analysis of protein binding sites than ever before. A shift in the way we navigate chemical space towards a more binding site centric approach will enable us to find small molecule hits for a wider range of targets in future screening campaigns [1].

The utilisation of the geometric pocket detection tool, fpocket, enables consideration of known binding sites and also potential binding sites that have not, as yet, been shown to bind small molecule ligands. A new binding site comparison tool, SiteHopper, calculates the degree of 3D similarity between a pair of binding sites. The comparison of small molecule binding sites is primarily employed to elucidate the function of orphan proteins or to predict polypharmacology. These analyses permit the generation of a similarity 'map' of available protein crystal structures and the subsequent visualisation of biologically-relevant binding site space.

Here, we present a map of the 3D structures of potential binding sites derived from a dataset of well-studied medicinal chemistry-relevant protein targets curated from the PDB – The BS-MedChem dataset [2]. We analysed the resultant map of small molecule binding sites along with associated experimental ligand-binding data. We propose that such protein binding site maps, coupled with ligand binding data will be useful for hit discovery, medicinal chemistry design and further building our understanding of ligand polypharmacology. Furthermore, this analysis highlights regions of protein binding site space that are not satisfied by current compound screening libraries and will provide a direction for future library optimization and chemical diversity projects.

References:
[1] S. Pérot, O. Sperandio, M. A. Miteva, A. C. Camproux and B. O. Villoutreix, *Drug Discov. Today*, (2010), **15** (15), 656-667.
[2] J. Meyers, N. Brown and J. Blagg, *J. Cheminf.*, (2016), accepted.

Talk 10

A Deep Learning Approach to Modelling Diverse Chemical Data

Richard Lewis and *Andreas Bender*

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Deep learning is a popular machine learning technique that has recently set the state of the art in many diverse fields from computer vision to machine translation[1]. The ability of deep neural networks to automatically learn a hierarchy of increasingly complex representations suggests potential in the chemical data domain, in which natural feature hierarchies (e.g. low level atoms, mid-level functional groups and high level pharmacophores) are commonly considered. Indeed, Deep Learning has been recently proved successful in several Cheminformatics challenges, including the recent Tox21 Data Challenge[2]: Cheminformatics is rapidly becoming an area of interest for the machine learning community.

This work aims to demonstrate the use of deep neural networks in modelling diverse chemical data domains, including protein affinity (QSAR), physical properties (QSPR), and even ^{13}C NMR shifts. To this end, neural networks were trained using the CHEMBL_22, PhysProp and NMRShiftDB2 respectively. Notably, a Graph Convolutional Neural Network using atom-based descriptors was used for physical properties and ^{13}C NMR, in addition to the more conventional fully connected multitask variant trained on circular fingerprints for the QSAR. Efforts were made to visualise the higher level features learned by the networks, in an attempt to shed light inside a model traditionally thought of as a black box. The performance of these models on held out test sets were compared to those built using other techniques.

The deep neural networks were in general found to outperform other traditional machine learning approaches such as Random Forests and linear models, although notably, some protein targets were found to still be better modelled my Random Forests. Some of the higher level features learned the model were visualized, and were cautiously assigned as detectors for selected chemical motifs. The ^{13}C NMR model achieved a mean absolute error of 2.2ppm in 5 fold nested cross validation, much lower than the 3.4ppm achieved by our benchmark HOSE (Hierarchically Organised Spherical Environments)[3] implementation.

References:

[1] Y. LeCun, Y. Bengio and G. Hinton, *Nature,* 2015, **521**, 436-444.
[2] A. Mayr, G. Klambauer, T. Unterthiner, and S. Hochreiter, *Frontiers in Environmental Science*, 2016, **3**, 80.
[3] W. Bremser, *Analytica Chimica Acta*, 1978, **103**, 355–365.

Talk 11

Topological design of porous organic cages

Valentina Santolini, Enrico Berardo, *Kim E. Jelfs*

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Porous organic molecules are a class of materials that, by contrast with framework materials, are constructed by the intermolecular packing of discrete organic molecules that contain void space in an internal cavity[1] and are typically solution processable. Many experimental and computational studies have been conducted on porous cages, however design and prediction of new molecular structures still represents a great theoretical challenge.

In this context, we developed a computational strategy to generate new porous organic molecules and test their experimental feasibility. Building blocks with different number of reactive ends (from 2 to 4) were assembled according to the topology of Platonic and Archimedean polyhedra. The cages we obtained were divided into four different families, each family including cages made up by the same pair of building blocks, but with different topologies.

An initial force field evaluation was applied to the structures in order to test the shape persistency of their cavity, and any collapsed cages were "inflated" with a technique based on Molecular Dynamics developed in the group to simulate scaffolding solvent effects.[2] Following this, the structures were refined with DFT methods and the cages were ranked by their relative energy, assuming that the cage with the lowest relative energy would be the most experimentally feasible outcome. The technique was applied to different kinds of cages and our prediction successfully matched experimental results.

The project naturally evolved into an experimental-computational collaboration with our co-workers from Cooper's Group (University of Liverpool). A high-throughput experimental screening of a large collection of cages is under current investigation, and computational prediction on the most feasible outcomes has been carried out in parallel. Our procedure is so far successful in predicting possible candidates for the synthesis as preliminary results show that experiments and simulations are in good agreement.

References:
[1] G. Zhang, M. Mastalerz, *Chem. Soc. Rev.,* (2014), **43**, 1934-1947.
[2] V. Santolini, G. A. Tribello and K. E. Jelfs, *Chem Commun,* (2015), **51**, 15542-15545.

Talk 12

Plates and Needles: A Computational Study of the Growth of Hexagonal Ice

Maxwell Fulford[a], Matteo Salvalaglio[b], Michele Parrinello[c,d], *Carla Molteni*[a]

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[c]Department of Chemistry and Applied Biosciences, ETH, Zurich, Switzerland
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Hexagonal Ice (Ih) plays a number of essential roles in controlling and maintaining the natural environment on Earth. It is the predominant crystalline form of ice and permanently coats at least 10% of all land. It occurs in cirrus clouds which cover ~20-40% of the Earth's surface and provides the environment for atmospheric chemical reactions to proceed. In spite of its ubiquity, a detailed understanding of the mechanism of ice growth at the atomic level remains incomplete.

Depending on the conditions of growth, Ih can form a broad range of crystal shapes, each with hexagonal symmetry. At high humidity, complex fern-like snow crystals grow, whilst at low humidity simple prisms form. In this project we focus on growth at low humidity, where the shape of Ih depends on the relative rate of growth of its two crystallographic surfaces – the basal and the prism surface. The competing action of the two rates results in thin hexagonal plates at very low temperatures and elongated prisms at higher temperatures. Curiously, as temperature is increased further, thin plates form once again.

To understand the mechanisms of growth at the molecular level and ultimately predict the shape of Ih crystals, we use a combination of molecular dynamics (MD) and metadynamics calculations in a range of temperatures. Metadynamics is an enhanced sampling technique that enables efficient sampling of rare events and yields an estimate of the free energy as a function of collective variables.

Our simulations show the formation of a quasi-liquid layer (QLL) on the surfaces. The QLL mediates crystal growth and has a thickness which varies with temperature. We investigate how the ice/QLL and QLL/vapour interface influences the water adsorption potential, surface diffusion properties and growth shape.

Programme of Poster Presentations

Poster 1	Raquel Romero, UCL Computational studies of Glucocerebrosidase in complex with its activator protein Saposin-C.
Poster 2	Dezső Módos, Cambridge/Semmelweis University, Hungary Neighbours of cancer-related proteins have key influence on pathogenesis and increase the drug target space for anti-cancer therapies
Poster 3	Samiul Ansari, Strathclyde Allosteric-Activation Mechanism of Bovine Chymosin Revealed by Bias-Exchange Metadynamics and Molecular Dynamics Simulations
Poster 4	Julain Gaberle, UCL Adsorption of Organic Molecules at Insulating Surfaces: Role of Molecular Flexibility
Poster 5	Noor Asidah Mohamed, Southampton Using the AMOEBA polarisable force field in biomolecular simulation
Poster 6	Srdan Jovanovic, UCL Rapid, Reliable and Precise Binding Affinity Prediction for Application in the Pharmaceutical Setting
Poster 7	Katy Sutcliffe, Bristol Molecular dynamics simulations of the μ-opioid receptor reveal distinct binding poses of structurally similar ligands
Poster 8	Kiran Kumar, Oxford Molecular Dynamics and DFT analysis of electrostatic dominated interactions in CREBBP
Poster 9	Victoria Oakes, King's College Exploring the Dynamics of the TWIK-1 Channel
Poster 10	Hershna Patel, Hertfordshire Discovery of inhibitors targeting evolutionary conserved influenza A virus proteins
Poster 11	Charis Georgiou, Edinburgh Computational and experimental approaches for the rational design of isoform-specific cyclophilins ligands
Poster 12	Fiona Naughton, Oxford Interaction of PH domains with phosphatidylinositol phosphates: Structures and Energetics by Simulation

Poster presenters will give their 2 minute "Lightning Talks" in the above order starting at 11:00.

Posters will be on display during the breaks and at lunchtime.

Poster 1

Computational studies of Glucocerebrosidase in complex with its activator protein Saposin-C

Romero Raquel, *Haider Shozeb*

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Gaucher's Disease (GD) is a rare recessive disorder produced by the dysfunction of the lysosomal enzyme Glucocerebrosidase (GCase).[1] GCase catalyses the cleavage of the glycolipid Glucosylceramide. The lack of functional GCase leads to the accumulation of its lipid substrate in lysosomes causing GD. GD presents a great phenotypic variation, symptoms ranging from asymptomatic adults to early childhood death due to neurological damage. More than 250 mutations in the protein GCase have been discovered that result in GD. Being able to link structural modifications of each mutation to the phenotypic variation of GD would enhance the understanding of the disease. The aim of this work is to provide a structural explanation to the phenotypic manifestation of GD using computational techniques.

A model of the complex of the enzyme GCase with its facilitator protein, Saposin-C (Sap-C) was generated using Protein-Protein docking (PPD). In this work, a knowledge-based docking protocol that takes into account experimental data of the protein- protein binding has been carried out to find the correct interaction mode between the two proteins.[2] Here, a reliable model of the enzyme GCase with its activator protein is presented. This model is in agreement with the experimental data of the binding mode of the proteins.

To understand the structural mechanism of function of the enzyme GCase, it was imperative to study its structural dynamics and conformational changes promoted by the interaction with other components including lipid bilayer, facilitator protein or substrate. Coarse-Grained MD (CG-MD) is a simplified method that gives the opportunity to study the lipid self-assembly and hence, the protein anchoring to the membrane. The protein with and without its substrate, and in presence and absence of the facilitator protein was simulated in order to study protein-membrane interactions. Atomistic MD (AT-MD) allows us to study in the detail of the dynamics of the interactions between different components of the simulation. All CG-MD simulations were converted to atomistic detail and simulated as AT-MD. Active and inactive GCase as well as the most extended mutated GCase were used in the transformation.[1]

In this work, we have analysed the results of ten different AT-MD simulations. We propose an activation method of GCase by Sap-C, analyse the difference in substrate binding in active and inactive GCase and the differences in membrane binding. We highlight the change of conformation of GCase when its facilitator protein is present, through the stabilization of the loops at the entrance of the binding site. We also emphasise the protein-protein binding differences when GCase is mutated. Prinicipal Component Analysis has served us to discriminate harmonic motions and focus in the essential dynamics of the protein. Clustering methods such us Markow State Modelling or Metadynamics will be used to analyse the results in a kinetically relevant manner.

References:

[1] Lieberman, R. L. Enzyme Research. Vol 2011, Article ID 973231, 15 pages (2011).
[2] Weiler, S., Kishimoto, Y., O'Brien, J. S., Barranger, J. A. & Tomich, J. M. Protein Sci. 4, 756–64 (1995).

Poster 2

Neighbours of cancer-related proteins have key influence on pathogenesis and increase the drug target space for anti-cancer therapies

Dezső Módos[1,2,3,4], Dávid Fazekas[2,4], Krishna C. Bulusu[5], János Kubisch[2], Johanne Brooks[4,6,7], István Marczell[8], Péter M. Szabó[8,9], Tibor Vellai[2], Péter Csermely[10], *Katalin Lenti*[1], *Andreas Bender*[5], *Tamás Korcsmáros*[2,3,4]

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[2] Department of Genetics, Eötvös Loránd University, Budapest, Hungary
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[4] Gut Health and Food Safety Programme; Institute of Food Research; Norwich Research Park; Norwich, UK
[5] Centre for Molecular Informatics, University of Cambridge, Cambridge, UK
[6] Faculty of Medicine and Health, University of East Anglia, Norwich, UK
[7] Department of Gastroenterology, Norfolk and Norwich University Hospitals, Norwich, UK
[8] 2nd Department of Internal Medicine, Semmelweis University, Budapest, Hungary
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Even targeted chemotherapies against solid cancers show a moderate success increasing the need to novel targeting strategies.

To address this problem, we designed a systems-level approach investigating the neighbourhood of mutated or differentially expressed cancer-related proteins in four major solid cancers (colon, breast, liver and lung). Using signalling and protein-protein interaction network resources integrated with mutational and expression datasets, we analysed the properties of the direct and indirect interactors (first and second neighbours) of cancer-related proteins, not found previously related to the given cancer type.

We found that first neighbours have at least as high degree, betweenness centrality and clustering coefficient as cancer-related proteins themselves, indicating a previously unknown central network position. We identified a complementary strategy for mutated and differentially expressed proteins, where the effect of differentially expressed proteins having smaller network centrality is compensated with high centrality first neighbours. These observations strikingly suggest targeting first neighbours as a novel strategy for disrupting cancer-specific networks. Remarkably, our survey revealed 223 marketed drugs already targeting first neighbour proteins but applied mostly outside oncology, providing a potential list for drug repurposing against solid cancers. For the very central first neighbours, whose direct targeting would cause several side-effects, we suggest a cancer-mimicking strategy by targeting their interactors (second neighbours of cancer-related proteins, having a central protein affecting position, similarly to the cancer-related proteins).
Hence, we propose to include first-neighbours to network medicine based approaches for (but not limited to) anti-cancer therapies.

Poster 3

Allosteric-Activation Mechanism of Bovine Chymosin Revealed by Bias-Exchange Metadynamics and Molecular Dynamics Simulations

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The aspartic protease, bovine chymosin, catalyzes the proteolysis of κ-casein proteins in milk. The bovine chymosin−κ-casein complex is of industrial interest as the enzyme is used extensively in the manufacturing of processed dairy products. The apo form of the enzyme adopts a self-inhibited conformation in which the side chain of Tyr77 occludes the binding site. On the basis of kinetic, mutagenesis, and crystallographic data, it has been widely reported that a HPHPH sequence in the P8−P4 residues of the natural substrate κ-casein acts as the allosteric activator, but the mechanism by which this occurs has not previously been elucidated due to the challenges associated with studying this process by experimental methods. Here we have employed two computational techniques, molecular dynamics and bias-exchange metadynamics simulations, to study the mechanism of allosteric activation and to compute the free energy surface for the process. The simulations reveal that allosteric activation is initiated by interactions between the HPHPH sequence of κ-casein and a small α-helical region of chymosin (residues 112−116). A small conformational change in the α-helix causes the side chain of Phe114 to vacate a pocket that may then be occupied by the side chain of Tyr77. The free energy surface for the self-inhibited to open transition is significantly altered by the presence of the HPHPH sequence of κ-casein.

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Poster 4

Adsorption of Organic Molecules at Insulating Surfaces: Role of Molecular Flexibility

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We present the results of computational modelling of adsorption and diffusion of large organic molecules on terraces and step edges on the KCl (001) surface, focussing on the effects that molecular flexibility has on their dynamic behaviour. Two functionalised organic molecules: a rigid 1,3,5-tri- (4-cyano-4,4biphenyl)-benzene (TCB) and flexible 1,4-bis(cyanophenyl)-2,5-bis(decyloxy)benzene (CDB), were studied on the KCl (001) surface using density functional theory (DFT) and classical molecular dynamics (MD) simulations. MP2 calculations within CP2K code were used to benchmark the performance of van der Waals corrected DFT-D3 calculations of adsorption energies and geometries and a classical force field was parameterised for the interaction of each of the molecules with KCl(001) using a genetic algorithm.[1] These force fields allowed us to perform long time-scale simulations to study the motion of molecules on the surface.

In order to better understand adsorption of TCB and CDB molecules at elevated temperatures, potential of mean force calculations were employed. It was found that the entropy change on adsorption constitutes almost half of the adsorption free energy. Diffusion coefficients for molecular diffusion on terraces were calculated using molecular dynamics at different temperatures and the activation energies evaluated as 0.52 eV for TCB and 0.36 eV for CDB. Furthermore, adhesion to step edges was investigated along with the associated changes in entropy. While the flexible CDB molecule can readily adapt to step edges, the rigid TCB molecule is unable to and exhibits a significant entropy loss upon step adhesion. We show that the simple rigid rotor model can accurately estimate entropy loss upon step adhesion for TCB but fails for CDB. The results highlight how molecular flexibility directly influences surface dynamics, which can lead to different self-assembly growth modes.

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Poster 5

Using the AMOEBA polarisable force field in biomolecular simulation

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Electronic polarisation is one of the components that plays an important role in many biomolecular systems. The effects of polarisation will act differently depending on the local environment of the system, such as in DNA, proteins and membranes. Traditionally, molecular mechanics force fields describe electrostatics as the interactions of fixed, atom-centred, point charges, and the past decade has seen many additions and improvements to existing force fields to better correlate dynamics with experimental observations. A more physically realistic description of electrostatics is, however, through the explicit inclusion of electronic polarisation. The Amoeba force field is one of many possible models designed to be capable of capturing this effect. The AMOEBA polarisable force field, developed by Ponder and co-workers,[1] directly treats this polarisation effect by introducing mutually polarising induced atomic dipoles at every atomic site, as well as a multipolar representation of fixed electrostatics.

To investigate the performance of AMOEBA and where its successes over existing fixed-charge methods may lie, we first apply the AMOEBA polarisable force field to simple systems based on the evaluation of solvation free energies for small molecules in a range of common organics solvents.[2] We identify several challenges and limitations of AMOEBA in this study, when making comparisons to the results obtained with simple fixed charge models. We extend our investigation to more complex systems involving protein-ligand interactions. Initially, clear cases of failure in fixed-point-charge force fields, as applied to binding free energies of cytochrome c peroxidase ligands,[3] were identified. The sensitivity of the calculated free energies to parameter sets and simulation protocols were explored. Finally, we use these results to inform binding free energy calculations in which the AMOEBA force field is being tested. We discuss the implications of these results in relation to the use of AMOEBA in biological applications.

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Poster 6

Rapid, Reliable and Precise Binding Affinity Prediction for Application in the Pharmaceutical Setting

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In recent times, good progress has been made in accurately predicting binding affinities for drug candidates [1]. Advances in high-performance computation (HPC), mean it is now possible to run a larger number of calculations in parallel, paving the way for multiple replica simulations from which binding affinities are obtained. This, then, allows for a tighter control of errors and in turn, a higher confidence in the binding affinity predictions.

Here, we present ESMACS [2] (Enhanced Sampling of Molecular dynamics with Approximation of Continuum Solvent); a new framework from which binding affinities are calculated. ESMACS performs 25 replica simulations of the same ligand-receptor system with the only difference being the initial momentum of each atom. From this ensemble of trajectories, an extended MMPBSA (Molecular Mechanics Poisson-Boltzmann Surface Area) free energy method is employed. This is all tied together using the BAC (Binding Affinity Calculator) which automates the ESMACS workflow.

ESMACS, given suitable access to HPC resources, can compute binding affinities in a matter of hours on a supercomputer; the size of such machines therefore means that we can reach the industrial scale of demand necessary to impact drug discovery programmes because we can compute many binding affinities concurrently.

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Poster 7

Molecular dynamics simulations of the μ-opioid receptor reveal distinct binding poses of structurally similar ligands

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G protein coupled receptors (GPCRs) comprise the largest portion of cell-surface receptors in the genome and the greatest class of drug targets. Opioid analgesics bind to the μ-opioid receptor (MOPr); a GPCR which couples to the G_i G protein and arrestins. Currently, there is limited knowledge of the receptor conformational changes which occur on agonist binding, and the differences between full and partial agonists on a molecular level. A greater understanding of the activation mechanism of this clinically important GPCR will aid the drug development process. This study has therefore employed molecular dynamics (MD) simulations to investigate the binding mode of two structurally similar MOPr ligands, the full agonist norbuprenorphine and partial agonist buprenorphine, in order to explore the underlying molecular mechanism of MOPr activation.

Ligand-induced activation of two signalling pathways downstream of MOPr, G_i protein activation and recruitment of arrestin-3, was determined by a bioluminescence resonance energy transfer (BRET) assay in HEK293 cells expressing MOPr-HA, G_i-RlucII and Gβγ-GFP, or MOPr-YFP and arrestin3-Rluc. For the MD simulations, the antagonist-bound crystal structure of MOPr[1] was used as the starting point and ligands were docked using the crystallised ligand β-FNA as a template. Receptors were embedded in a native-like POPC:POPE:cholesterol bilayer and solvated in TIP3P water and 0.15 M NaCl using the CHARMM-GUI membrane builder. Accelerated MD simulations[2] were run in 125 ns parallel steps with the Amber ff14SB forcefield[3] for a total of 1 μs for each ligand.

The BRET assay confirms norbuprenorphine is a full agonist for both signalling outputs, whereas buprenorphine is a partial agonist for G_i activation and unable to significantly recruit arrestin-3. From the MD simulations, we find that despite sharing a common morphinan scaffold, buprenorphine and norbuprenorphine adopt distinct binding poses in the ligand binding pocket. Whilst sharing a series of common ligand-receptor interactions (e.g. D147, H297), they also interact with distinct subsets of residues. Notably, the ligands differ in their interaction with the sodium-coordinating residue, W293, a conserved rotomer toggle switch for GPCR activation. Principal component analysis on the movements of the transmembrane helices show the buprenorphine-bound receptor exploring a distinct array of conformations from that of the norbuprenorphine-bound receptor. The differences described here may underlie the differing efficacies observed for cellular signalling outputs for these two ligands.

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Poster 8

Molecular Dynamics and DFT analysis of electrostatic dominated interactions in CREBBP

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CREBBP bromodomain containing proteins are epigenetic readers that have received increasing attention in recent years as promising cancer drug targets. To aid in inhibitor design, we utilized computational chemistry techniques such as classical molecular dynamics (MD) and quantum mechanics (QM) to analyse key interactions that drive selectivity for CREBBP by a series of fifteen 5-isoxazolyl-benzimidazole inhibitors (IBIs). In this study we explore the formation of a key cation-π interaction between fifteen known IBIs and a conserved arginine residue unique to CREBBP.

100 ns MD simulations with explicit solvation were performed with an initial inhibitor template bound to a CREBBP protein. Cation-π interactions were critical for binding and present for more than 70% of simulation time, although not initially observed in crystal structures. Given the importance of this interaction for the stability of the inhibitor, we performed additional binding free energy calculations on 15 IBIs using molecular mechanics/Poisson-Boltzmann (PB) and generalized Born (GB) surface area (MM-PBSA, MM-GBSA) scoring functions. We also performed QM-complexation energies for an accurate prediction of cation-π interactions. A third technique analysing the Electrostatic Potential Surface Area (ESPs) of the substituted benzenes demonstrated that consideration of only the surface above the π system is enough for a quantitative ($R^2 = 0.84$, $n=15$) and qualitative prediction of these interactions.

Results from our three methodologies correlated well with experimental binding affinities for prediction of cation-π interactions with CREBBP inhibitors. However, ESP is significantly faster without compromising accuracy. Applications of these MM, QM, and ESP calculations can be easily extended to other small molecule protein complexes in which cation-π interactions are necessary for driving selectivity.

Poster 9

Exploring the Dynamics of the TWIK-1 Channel

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Potassium channels in the two-pore domain family (K2P) have various structural attributes that differ from those of other K^+ channels, including a dimeric assembly constituted of non-identical domains and an expansive extracellular cap. Crystallization of the prototypical K2P channel, TWIK-1, finally revealed the structure of these characteristics in atomic detail. TWIK-1 has emerged as a putative drug target for antiarrhythmic drugs; therefore, in-depth exploration of the molecular determinants of conduction, selectivity, and gating in TWIK-1 will likely contribute to the development of targeted therapies. Here, we have performed extensive molecular-dynamics simulations discern the mechanism of ion transport in TWIK-1. Despite the overall topological similarity of the x-ray structure of the selectivity filter to other K^+ channels, the structure diverges significantly as a consequence of non-conserved residues in both pore domains contributing to the selectivity filter.

Poster 10

Discovery of inhibitors targeting evolutionary conserved influenza A virus proteins

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Influenza A is a prevalent infectious virus capable of causing significant respiratory illness worldwide. The virus genome encodes several proteins and upon infection, antiviral drugs targeting the neuraminidase surface protein and M2 transmembrane protein are the only treatment options available. However, emergence of antiviral resistance due to mutations highlights the requirement of investigating other proteins as targets for antivirals. Therefore, this research aims to identify inhibitors that may bind to conserved regions of internal influenza A proteins through the application of molecular modelling methods.

Sequences of the influenza A non-structural 1 protein (NS1), nuclear export protein (NEP) and basic polymerase 2 (PB2) were aligned and the degree of amino acid conservation was calculated for each protein. Missing parts of the experimental structures were predicted using a state-of-the art protein structure prediction method, and molecular dynamics (MD) simulations to improve the accuracy of the protein models. Potential binding hot spots were identified with computational solvent mapping based on the FTMap algorithm. Selected binding sites were subjected to virtual screening against a library of ~50,000 chemical compounds from the ZINC database using a combination of two docking algorithms, namely AutoDock Vina and AutoDock 4.

Several highly conserved areas that overlap with ligand binding sites were located and mapped onto the protein structures. MD simulations revealed conformationally flexible regions of the NS1 and NEP models, and virtual screening and docking results revealed drug-like molecules with predicted binding affinities of up to -10.0 kcal/mol. Molecules targeting evolutionary conserved regions are less likely to undergo mutations that could render antiviral drugs ineffective. The findings from this work may lead to the discovery of a novel influenza A inhibitor that remains viable long term.

Poster 11

Computational and experimental approaches for the rational design of isoform-specific cyclophilins ligands

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Cyclophilins (Cyp) are proteins able to catalyze the interconversion of *trans*/*cis* isomers of proline and belong to the peptidyl-prolyl isomerases family (PPIase).[1] In addition to their PPIase activity, Cyps have diverse biological roles and have been implicated in a number of different diseases such as HIV-1 and HCV. Although several Cyp inhibitors have been reported in the literature, none are able to inhibit with high specificity Cyp isoforms. To facilitate the development of isoform-specific Cyp ligands, we are pursuing detailed studies of Cyp dynamics and binding thermodynamics using molecular simulations, biophysical assays and protein X-ray crystallography.

Research efforts were focussed on the identification of novel Cyp inhibitors using X-ray crystallographic studies and Surface Plasmon Resonance (SPR) experiments on fragments from an in-house bespoke library of small compounds. These biophysical studies revealed a number of fragments that are able to bind to diverse Cyp isoforms with high micromolar – low milimolar activity.

To further examine the binding of these fragments to Cyps, identify interactions with the proteins and explain specificity trends from SPR and X-ray results, molecular dynamics (MD) simulations and free energy calculations were pursued. Models of *apo* and *holo* Cyps in complex with fragments that we had experimentally tested were set up using the Amber, AmberTools and FESetup software. Free energy calculations were performed using the thermodynamic integration (TI) technique with the Sire/OpenMM software.[2] Results were analysed with custom scripts. Correlations between computed and measured binding energies were pursued to produce fresh insights into the basis for binding affinity and selectivity of compounds in the fragment library.

Comparison between the outcomes of these experimental and computational techniques will be reported, and emphasis will be given on opportunities for synergies to facilitate the identification of new cyclophilin inhibitors.

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Poster 12

Interaction of PH domains with phosphatidylinositol phosphates: Structures and Energetics by Simulation

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Pleckstrin Homology (PH) domains are among the most prevalent domains in the human proteome. Many have been shown to associate with phosphatidylinositol phosphate (PIP) lipids, mediating interactions between peripheral proteins and cell membranes in a range of vital cellular processes. These PH domains bind to different PIP species with a range of specificities and affinities, but the exact molecular and energetic details behind these interactions are not always clear, partly because of the complexity of these interactions.

Through use of coarse-grained molecular dynamics simulations combined with an umbrella sampling methodology to generate a potential of mean force profile, the binding of PH domains to PIP-containing model membranes may be quantified and investigated on a molecular scale. This approach has previously been applied to the PH domain of GRP1 [1]. In this study, we expand this analysis to compare 12 PH domains known to associate with PIPs, obtaining free energy profiles for binding of each to PIP_3 and PIP_2. Favourable binding was observed in all cases. PH-PIP interactions formed while bound at the membrane were consistent with structural data. The presence of an additional 'atypical' PIP binding site (which may be involved in coincidence detection) adjacent to the 'canonical' site was demonstrated, including identification of later-stage atypical-site interactions in domains for which previously only canonical binding had been reported. Domains exhibiting initial atypical-site interactions show in general less favourable binding. This work demonstrates how coarse-grained umbrella-sampling simulations may be used to investigate and compare the energy landscape and molecular details of protein-lipid interactions within a family of molecular recognition proteins.

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