MGMS
Young Modellers' Forum 2017
24th November 2017
PROGRAMME & ABSTRACTS

Programme of Oral Presentations

9.15 – 9.50	Coffee and Registration
9.50 – 10.00	Welcome and Introduction
10.00 – 10.20	**Carl Mensch, Universities of Antwerp and Ghent** Towards a standardized characterization of solution phase protein structure using Raman optical activity
10.20 – 10.40	**Luca Iuzzolino, University College London** Use of crystal structure informatics for defining the conformational space needed for predicting crystal structures of pharmaceutical molecules
10.40 – 11.00	**Can Simon Pervane, University of Southampton** Enhancing conformational sampling by modifying the underlying velocity distribution: Digitally filtered hybrid Monte Carlo
11.00 – 11.30	Poster Presenters "Lightning Talks"
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11.50 – 12.10	**Heider A. Hussein, University of Birmingham** Structural Investigations and Stabilities of Au-Pd Sub-nanometre Clusters
12.10 – 12.30	**Adam Baskerville, University of Sussex** Going beyond standard approximations in quantum chemistry
12.30 – 12.50	**Hannah Bruce Macdonald, University of Southampton** Water networks in protein-ligand complexes using Grand Canonical ensemble methods
12.50 – 14.10	Lunch and Poster Session
14.10 – 14.30	**Christian Jorgensen, King's College London** Energetics of Ion Permeation in an Open-Activated TRPV1 Channel
14.30 – 14.50	**Juan Eiros Zamora, Imperial College** Markov State Models of cardiac Troponin dynamics
14.50 – 15.10	**Xiuyun Jiang, University College London** Simulation of Pump-Probe Experiment in Small Tetraheme Cytochrome
15.10 – 15.30	**Pattama Wapeesittipan, University of Edinburgh** Allosteric effects in a catalytically impaired variant of Cyclophilin A are unrelated to millisecond time scale motions
15.30 – 15.30	Tea/Coffee break
15.50 – 16.10	**Nick Fowler, University of Manchester** Prediction of reduction potentials of copper proteins with continuum electrostatics and density functional theory
16.10 – 16.30	**Olivia Lynes, University of Lancaster** Ab initio Molecular Dynamics Simulations of Hydrated Hydroxide Systems
16.30 – 17.00	Deliberations and Prizes
17.00	End

Talk 1

Towards a standardized characterization of solution phase protein structure using Raman optical activity

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Over the past 20 years, Raman optical activity (ROA) has shown much promise as a strong technique to elucidate the structure and dynamics of proteins in solution. ROA is measured as the small difference in the right and left circularly polarised components in the Raman scattered light by chiral molecules. This technique is uniquely sensitive to local conformational propensities of peptides and proteins. While the ROA spectrum of a protein gives rich information on the secondary structure of a protein, the biggest and most urgent challenge is to understand the relation between the ROA patterns and the protein structure in detail. Because of important advances in computational chemistry and computer power, it is now possible to use quantum chemical calculations to simulate ROA spectra of peptides.

Here, we present the first large scale study on the relation between the ROA patters and protein conformation.[1] By creating a large library of peptide models with systematically varying conformations and calculating the ROA signatures quantum mechanically, we are developing an approach to characterise the solution structure of peptides and proteins with unprecedented detail. By using similarity indices, experimental Raman and ROA spectra can be compared to the simulated spectra in the database, which allows an objective and detailed assignment of the experimental spectra.

Using this approach, the experimental spectra of different peptides with diverse but known conformational preferences were studied. The newly developed database correctly assigns the solution structure of these peptides. Furthermore, the results demonstrate the strong conformational sensitivity of ROA, as very slight changes in protein structure result in specific changes in the ROA patterns. The database assigns these differences in the spectra to structural differences of the peptides.

While structural biology relies on the powerful techniques of NMR and crystallography, complementary methods are necessary to provide additional information on protein structure and dynamics where the former techniques fall short. ROA has a unique structural sensitivity to protein structure and the database developed in this work is a strong tool to assign preferential conformations and changes of proteins based on the ROA spectrum.

[1] C. Mensch, L. D. Barron and C. Johannessen, *Phys. Chem. Chem. Phys.*, 2016, **18**, 31757–31768.

Talk 2

Use of crystal structure informatics for defining the conformational space needed for predicting crystal structures of pharmaceutical molecules.

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Crystal Structure Prediction (CSP) studies aim to predict all the thermodynamically plausible crystal structures of a molecule from the chemical diagram, and so can act as a complement to the solid form screening work carried out in drug development.[1] The key to successful CSP studies is performing an effective crystal structure search, i.e. to generate a comprehensive set of putative crystal structures, each belonging to a separate minimum on the lattice energy surface. The most promising generated structures can then be further refined and re-ranked in terms of energy using more accurate methods. Molecular flexibility complicates the crystal structure search, since it drastically increases the size of the energy surface. Hence, determining the range of conformations that a flexible pharmaceutical could plausibly adopt in a crystal structure is essential for successful and time-efficient CSP studies. This is particularly important for pharmaceuticals, which tend to have several bulky molecular fragments linked by flexible torsion angles.

In this talk, a workflow developed for this purpose[2] is presented. It is based on using conformational information retrieved from the Cambridge Structural Database (CSD), which contains more than 850,000 experimentally-determined crystal structures. The conformations produced by the CSD Conformer Generator are reduced by considering the underlying rotamer distributions, an analysis of changes in molecular shape, and a minimal number of molecular *ab initio* calculations. This workflow was tested for five pharmaceutical-like molecules, where an extensive CSP study had already been performed, namely molecules XXIII and XXVI from the 6th Blind Test, molecule XX from the 5th Blind Test, GSK269984B and mebendazole. The CSD informatics-derived set of crystal structure searches generated almost all the low-energy crystal structures previously found, including all experimental structures, with a reduction in the overall computational cost. The issues involved in comparing solid-state and isolated-molecule conformations are discussed.

References:
[1] A.M.Reilly, *et al.*, *Acta Cryst.*, (2016) **B72**, 439-459
[2] L.Iuzzolino, *et al*., *J. Chem. Theory Comput*., (2017), **13(10)**, 5163-5171

Talk 3

Enhancing conformational sampling by modifying the underlying velocity distribution: Digitally filtered hybrid Monte Carlo

Can S. Pervane, *Jonathan W. Essex*

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The rugged energy landscape of proteins often leads conventional molecular dynamics simulations to get stuck in local minima leading to inefficient sampling and slow convergence. There are two main methods to improve sampling. First, by smoothing the underlying energy surface thereby encouraging barrier crossing, and second, by modifying the simulation velocities. There are many examples in the literature of the former, but velocity modification is a comparatively less well exploited approach.

In a method previously developed in our group called Reversible Digitally Filtered Molecular Dynamics (RDFMD), we have been able to induce conformational changes in proteins by amplifying low-frequency molecular vibrations via application of a Digital Filter to the velocity set [1]. However, by applying the digital filter to the molecules, the system is no longer in equilibrium, leading to incorrect ensemble averages. To sample a statistical ensemble and still benefit from the application of the digital filter a novel method called Digitally Filtered Hybrid Monte Carlo (DFHMC) is proposed. This method builds on the work of Momentum Enhanced Hybrid Monte Carlo (MEHMC) [2]. Low frequency motions are selectively enhanced via application of a specifically designed Digital Filter (as in RDFMD), but equilibrium is maintained using a Hybrid Monte Carlo approach.

In this presentation, the theory behind the DFHMC method is explained. The capability of sampling from the canonical ensemble and the enhancement in energy barrier crossing, and hence convergence, is demonstrated on a simple 2D system. As a model for the dihedral motions in proteins, the application of the DFHMC method to a single alanine dipeptide molecule is discussed. We show that DFHMC is able to yield enhanced conformational sampling and convergence of thermodynamic properties over conventional simulation approaches.

References:

[1] S. C. Phillips, M. T. Swain, A. P. Wiley and J. W. Essex, *J. Phys. Chem. B.,* (2003), **107(9)**, 2098-2110.
[2] I. Andricioaei, A. Dinner and M. Karplus, *J. Chem. Phys,* (2003) **118**, 1074-1084.

Talk 4

Structural Investigations and Stabilities of Au-Pd Sub-nanometre Clusters

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Sub-nanometre clusters can be defined as groups or aggregates of a few to tens of metal atoms which are below 1.0 nm in size. These clusters may contain the same atoms, giving pure clusters, or two or more different atoms presenting hetero-clusters. These clusters are attracting significant interest, e.g. in catalysis, where they offer the advantages of size-selection and tuning of selectivity or reactivity.

I will present the BPGA-DFT approach, with applications to: the study of the segregation and 2D-3D transition in (4-18) atom mono- and bi-metallic clusters of Au and Pd. We performed global optimization calculations on gas-phase and MgO(100)-supported sub-nanometre AuPd alloys. The energetics, structures, and tendency of segregation have been evaluated by different stability criteria such as binding energy, excess energy, second difference in energy, and adsorption energy. The role of cluster size, presence of Pd doping, and effect of MgO(100)-surface were found to be significant, and non-monotonic in altering cluster stability and structural behaviour. The ability of the approach in searching for putative global minimum has been assessed against a systematic homotop search method, which shows a high degree of success. I will also mention recent calculations on the direct DFT global optimisation of sub-nanometre mono-cationic Au-Pd clusters.

References

1- H. A. Hussein, J. B. A. Davis, and R. L. Johnston, *Phys. Chem. Chem. Phys.*, (2016), **18**, 26133.
2- H. A. Hussein, I. Demiroglu, and R. L. Johnston, *Eur. Phys. J. B*, (2017), accepted. *DOI: 10.1140/epjb/e2017-80314-2*

Talk 5

Going beyond standard approximations in quantum chemistry

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Mainstream quantum chemistry is built upon two key approximations, the Born-Oppenheimer approximation and Hartree Fock theory. In the Born-Oppenheimer approximation, a molecular structure is assumed and the equilibrium structure corresponds to a local minimum structure on a potential energy surface. Computational quantum chemistry is built on the one-electron operators arising in the Hartree-Fock (HF) method for solving the many-electron Schrödinger equation, and HF theory treats the electron-electron repulsion using a mean-field approach and thus the Coulomb correlation is missing.

In the present work no such assumptions are made and atoms and molecules are treated on an equal footing as few-particle quantum systems. High accuracy, non-relativistic, calculations are used to study the electronic and nuclear motion in the ground state of three-particle atomic and molecular systems using a series solution method with a triple orthogonal Laguerre-based wavefunction[1].

Results will be presented demonstrating that nuclear motion in diatomic ions is strongly correlated; which is evaluated using the particle density at the centre of mass. It is shown that the spatial distribution of the like-charged particles depends on the relative masses of the nuclei rather than just their absolute mass[2].

A new Hartree-Fock implementation using a Laguerre basis set is used to evaluate electron correlation and results will show the presence of a primary Coulomb hole for low nuclear charge systems. For helium and the lithium cation a secondary Coulomb hole is present which indicates that electron correlation can act to bring distant electrons closer together, counter-intuitively.

References:
[1] A. King, F. Longford and H.Cox, *J. Chem. Phys,* (2013), **139**, 224306-1-224306-7.
[2] A. Baskerville, A. King and H.Cox, *Phys. Rev. A,* (2016), **94**, 042512-1-042512-9.

Talk 6

Water networks in protein-ligand complexes using Grand Canonical ensemble methods

Hannah E. Bruce Macdonald[a,b], Chris Cave-Ayland[a], Marley Samways[a], *Richard D. Taylor[b], Jonathan W. Essex[a]*

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Understanding the location and energetics of water molecules is helpful for rational drug design. We present our grand canonical Monte Carlo[1] (GCMC) method for predicting water locations and binding free energies in proteins.

The energetics of an active site water molecule can be vital to drug binding, through either stabilising the bound complex, or releasing entropy upon water displacement. Rationalising how water molecules should be treated is difficult – whether a water molecule should be retained in a bound structure, or if it should be displaced to recover entropy and allow for direct protein-ligand interactions, is unclear. GCMC is able to calculate the free energy of multiple water networks in a single simulation, and as the water location is predicted automatically as part of the simulation, no experimental knowledge of hydration site location is required. The binding free energies determined are rigorous and have been shown to be consistent with other gold-standard methods.

In this presentation, the GCMC method will be described and demonstrated on targets of significant pharmaceutical interest. The water locations calculated will be compared to good quality crystallographic data. The method has been optimised, both through reducing the number of chemical potentials needed to be simulated, as well as introducing replica exchange moves between neighbouring chemical potentials. The implications of the water networks observed in terms of ligand optimisation and binding will be discussed.

References:

[1] G. A. Ross, M. S. Bodnarchuk, J. W. Essex, *JACS,* (2015), **137**, 14930–14943

Talk 7

Energetics of Ion Permeation in an Open-Activated TRPV1 Channel

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Ion channels regulate the diffusion of ions down physiological electrochemical gradients in cells. The modulation of ion permeation is crucial for the physiological functioning of cells, and misregulation of ion channels is linked to a myriad of channelopathies.

A novel set of ion channels, the transient receptor potential (TRP) ion channel family, has attracted great interest as druggable targets in *de novo* drug design. TRP channel ion conduction is currently not understood at an atomistic level. In this work, we employed a simulation strategy for ion permeation (molecular-dynamics simulations with bias-exchange metadynamics) to study and compare monovalent (Na^+, K^+) ion permeation in the open-activated TRP vanniloid-1 (TRPV1) ion channel. Using ~3.6 μs of simulation trajectories, we obtained atomistic evidence for the nonselective nature of TRPV1. Our analysis shows that solvated monovalent ions permeate through the selectivity filter with comparable energetic barriers via a two-site mechanism.

[1] C. Jorgensen, S. Furini, C. Domene, *Biophys. J, (2016)* **111**, 1214-1222.

Talk 8

Markov State Models of cardiac Troponin dynamics

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The Troponin complex is comprised of three proteins: troponin C, troponin I, and troponin T. Together they constitute a single functional unit with the two other proteins that form the thin filament, fibrous actin and tropomyosin. Through its interactions with them, Troponin is the molecular switch that mediates muscle contraction as dictated by the myocyte's cytosolic levels of Ca^{2+}. It is of particular interest to study the cardiac-specific isoform of Troponin for two reasons: (i) it has a unique Ca^{2+} sensitivity regulation system mediated by phosphorylation that allows the heart to perform under highly demanding conditions (ii) hereditary mutations disrupt this mechanism and are linked to possibly fatal cardiomyopathies. It is of therapeutic interest to understand the molecular mechanism of Ca^{2+} sensitivity regulation, as this can be altered through phosphorylation, point mutations and small molecules. Cardiac Troponin has some labile regions, which have made it challenging for experimentalists to gain a complete understanding of this system's dynamics. Therefore, it is a good candidate for computational studies to circumvent this problematic.

Building on our published computational model of cardiac Troponin[1], we revisit the effect of cardiac Troponin I Ser23 and Ser24 phosphorylation on its dynamics. We have analysed multiple multi μs-long Molecular Dynamics simulations with time-independent component analysis in conjunction with Markov State Models. This analytical framework has gained popularity in recent years thanks to its simplification of chaotic and multidimensional molecular dynamics datasets. In particular, it is able to extract long timescales information out of multiple short-lived simulations by 'stitching' them together.

In this talk, I will present the successes and shortcomings of this analysis technique as applied to the cardiac Troponin system, as well as the on-going efforts to apply it to the study of ligand binding process for promising therapeutic molecules.

References:

[1] Zamora, J.E. et al., *Phys. Chem. Chem. Phys.*, (2016), **18(30)**, pp.20691–20707.

Talk 9

Simulation of Pump-Probe Experiment in Small Tetraheme Cytochrome

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Bacteria like Shewanella and Geobacter are species that express multi-heme proteins which enable them to transfer electrons from the inside of the cell to extracellular solid substrates [1]. Studying long-range electron transfer (ET) events in multi-heme proteins is important for the understanding of geochemical cycling of different metals and the design of promising biological nano-materials. The protein we are focusing on, small tetraheme cytochrome (STC)[2], is one of the smallest multi-heme proteins isolated to-date in bacteria Shewanella Oneidensis, which has only 4 heme cofactors embedded in one protein domain and is a good model for fundamental studies. In order to obtain a molecular-level insight into the ET process, our experimental collaborators docked a [Ru]-ligand (tris(bipyridine)ruthenium) to the STC protein. A laser flash triggers an ET from the label to the protein and transient absorption spectroscopy is used to monitor time-resolved redox states of the hemes. In our presentation I will report on the simulation of this experiment in the framework of semi-classical Marcus theory: Classical Molecular Dynamics (MD) simulation together with Density Functional Theory methods are used to calculate the charge recombination rates from the protein to the ruthenium ligand. Together with previously-calculated inter-heme ET rates we solve for the kinetics of charge transport through the protein using a simple master equation. Our results are compared to and discussed in light of the kinetic traces obtained from pump-probe experiments.

References:

[1] M. Breuer, et. al, *J. R. Soc. Interface*, (2015) vol. 12, no. 102, p. 20141117.

[2] D. Leys et al., *J. Biol. Chem.,* (2002) **277**, 35703–35711.

Talk 10

Allosteric effects in a catalytically impaired variant of Cyclophilin A are unrelated to millisecond time scale motions

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There is much debate about the role of molecular motions in enzyme catalysis. Previous NMR studies have shown that introduction of a distal Serine to Threonine (S99T) mutation in the proly-isomerase Cyclophilin A (CypA) cause a slowdown in a millisecond time scale confomational change that correlates with a decrease in microscopic catalytic rate constants. X-ray crystallography studies suggested that the conformational change implicates a network of coupled side-chain rotations that link Serine99 to active side residues.[1] Because it remains unclear how millisecond timescale motion couple to catalysis, the present work used extensive equilibrium molecular dynamics (MD), umbrella sampling and Markov State (MSM) modeling simulation methodologies to investigate the link between protein motions and function in CypA WT and S99T forms.

Comparative analysis of MSMs constructed for the apo CypA WT and S99T forms show that the X-ray crystallography-derived minor state is well reproduced by the simulations. However coupled rotations of the network of side-chains occur at a rate that is at least 3 orders of magnitude faster than suggested by NMR. Further, simulations of substrate-bound WT and S99T show that no coupled side-chain rotations occur during the isomerization reaction. Yet, the simulations yield computed activation free energies for the cis/trans isomerization reaction supporting the experimental findings that the mutant is catalytically less active than wild-type.
Trajectory analyses suggest that the increased activation free energies in the S99T-catalyzed reaction are due to weakened hydrogen bonding interactions between key residues and the transition state. Decreased hydrogen bonding interactions are shown to be a consequence of a global increase in binding site flexibility due to poorer sidechains packing in the S99T mutant.

Therefore we conclude that the allosteric effects caused by the S99T mutation are due to decreased electrostatic preorganization of the transition state ensemble, and that the NMR measured changes in millisecond timescale motions are not causally linked to catalysis.

References:
[1] J. Fraser, M. Clarkson and S. Degnan, *Nature,* (2009), **462**, 669-673 end.

Talk 11

Prediction of reduction potentials of copper proteins with continuum electrostatics and density functional theory

Nicholas J. Fowler[α], *Christopher F. Blanford*[β], *Jim Warwicker*[α] & *Samuel de Visser*[γ]
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Blue copper proteins, such as azurin, show dramatic changes in Cu2+/Cu+ reduction potential upon mutation over the full physiological range. Hence, they have important functions in electron transfer and oxidation chemistry and may have potential in biotechnology. The details of what determines these reduction potential changes upon mutation are still unclear. Moreover, it has been difficult to model and predict the reduction potential of azurin mutants and currently no unique procedure or workflow pattern exists. Furthermore, high-level computational methods can be accurate but are too time consuming for practical use. In this work a novel approach for calculating reduction potentials of azurin mutants is shown, based on a combination of continuum electrostatics, density functional theory and empirical hydrophobicity factors [1]. Our method accurately reproduces experimental reduction potential changes of 30 mutants with respect to wildtype within experimental error and highlights the factors contributing to the reduction potential change. Finally, reduction potentials are predicted for a series of 124 new mutants that have not been investigated experimentally yet. Several mutants are identified that are located well over 10Å from the copper center that change the reduction potential by more than 85mV. The work shows that secondary coordination sphere mutations mostly lead to long-range electrostatic changes and hence can be modelled accurately with continuum electrostatics.

[1] Fowler, N. J., Blanford, C. F., Warwicker, J. and de Visser, S. P. (2017), Prediction of Reduction Potentials of Copper Proteins with Continuum Electrostatics and Density Functional Theory. *Chem. Eur. J.*. doi:10.1002/chem.201702901

Talk 12

Ab initio Molecular Dynamics Simulations of Hydrated Hydroxide Systems

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An important problem in the nuclear power industry in the UK is the reprocessing of the legacy waste storage ponds at Sellafield in Cumbria. Understanding the solvation structure of the radionuclides present in these ponds, as well as the stability of their hydroxide and carbonate complexes is vital for effective reprocessing. [1] Our work improves on our current theoretical understanding of these complexes, previously obtained by phase or implicitly solvated density functional theory (DFT), through the use of *ab initio* molecular dynamics simulations(AIMD), thereby aiding the characterisation, and potential reprocessing of the waste present in the storage ponds.

To establish an accurate solvation model, this study uses AIMD to investigate the interactions of Mg^{2+}, Ca^{2+} and Sr^{2+} ions with water. The properties of the first solvation shell have been categorised, including average metal oxygen bond length, total coordination number and the accompanying residence times. When compared to current experimental and computational literature our results are in excellent agreement, justifying the solvation model developed.

We investigate the alkaline properties of the storage ponds and its effect on the radionuclides by introducing two hydroxide ions. Previous DFT simulations found little energetic difference between mono and di-hydroxide systems, with only a small (~3 kJ/mol) barrier between the two.[2] Our results indicate a preference for a mono-hydroxide structure for magnesium, while the hydroxide ions prefer to be outside of the first coordination shell for calcium and strontium. The dynamics of hydroxide movement via proton transfer has also been investigated, finding that proton transfer occurs frequently (~ every 1 ps) and is more likely to occur outside of the first coordination shell.

References:

[1] S. A. Parry, L. O'Brien, A. S. Fellerman, C. J. Eaves, N. B. Milestone, N. D. Bryan and F. R. Livens, *Energy Environ. Sci.*, 2011, **4**, 1457.

[2] E. Makkos, A. Kerridge and N. Kaltsoyannis, *Dalt. Trans.*, 2015, 11572–11581.

Programme of Poster Presentations

Poster 1	**Leanna Smith, University of Leicester** Architectural insights into CHFR structure through homology modelling of the central RING domain
Poster 2	**Marc Daemgen, University of Oxford** Alternative Binding Mode of Full and Partial Agonists in the Glycine Receptor Stabilises Loop C in an Open Conformation
Poster 3	**Angus Voice, University of Bristol** Investigating reactivity of covalent drugs by QM/MM modelling
Poster 4	**Jacqueline Tan, University of Oxford** Understanding regioselectivity in radical cation Diels-Alder reactions using quantum and molecular dynamics
Poster 5	**Maeve Kavanagh, Imperial College** Excited States of the Photosystem II Reaction Centre
Poster 6	**Matthew Dwyer, University of Sheffield** The Role of Hydrocarbon Composition on the Thermal Stability of Aviation Fuel
Poster 7	**Lee Steinberg, University of Southampton** Understanding the Structure of Water Networks through Topological Data Analysis
Poster 8	**Sowmya Indrakumar, Technical University of Denmark** Characterization of protein-excipient interactions for designing formulation
Poster 9	**Ganesh Shahane, Queen Mary University of London** Depth-dependent physical properties of model biological lipid bilayers
Poster 10	**Joan Clark-Nicholas, University of Edinburgh** Exploring the druggability of hPNMT with the JEDI collective variable
Poster 11	**Mateusz Bieniek, King's College London and the Francis Crick Institute** Fibronectin III 9-10 Adhesion and Material-Driven Fibrillogenesis
Poster 12	**Ricardo Parra-Cruz, University of Nottingham** Engineering thermostable biocatalysts for CO2 capture and utilization purposes

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

Architectural insights into CHFR structure through homology modelling of the central RING domain

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Within eukaryotic cells, the antephase checkpoint plays an incredibly important role in delaying mitotic cell division in the presence of intracellular stress, DNA damage or microtubule targeting reagents. **CH**eckpoint with **F**ork-head associated and **R**ING domain (CHFR) is a key component of the antephase checkpoint, with down regulation exhibited in numerous cell lines and tumours via promoter hypermethylation or mutation. The N-terminal FHA and C-terminal cysteine rich domain (CRD) are well characterized, binding phosphopeptides [1] and poly(ADP-ribose) [2] , respectively. Biochemical assays have also demonstrated the importance of the central RING domain in mediating CHFR's E3 ubiquitin ligase activity both *in vitro* and *in vivo*. However, and in contrast to the N-terminal FHA and C-terminal CRD, no high-resolution structure of the RING domain is available and details underpinning substrate recognition are unknown.

Here we have undertaken a detailed bioinformatical approach to gain structural insights into the RING domain and investigate CHFR's interaction with E2 ubiquitin-conjugating enzymes and ubiquitin. Analysis of amino acid sequences of full-length CHFR proteins as well as FHA and RING domain-containing homologues from numerous species were used to create a comparative model of the central RING domain in human CHFR. Molecular Dynamic (MD) simulations were then used to explore the properties of the model in more detail. MD simulations reveal a well-folded CHFR RING homology model with considerable flexibility and movement within both the N-terminal and C-terminal loops.

Furthermore, we hypothesise possible binding modes of known CHFR substrates (such as the Ubc13 E2 enzyme and ubiquitin), with interactions verified *in vitro* using site-directed (recombinant) mutant proteins within autoubiquitination assays.

This study provides the first detailed insight into the molecular mechanisms underpinning CHFR's interactions with Ubc13 and ubiquitin, essential in mediating the antephase checkpoint during mitotic cell division. Our results could form the basis for future biochemical and cell-based studies investigating the structural basis of CHFR substrate recognition.

[1] Stavridi, E. S., Huyen, Y., Loreto, I. R., Scolnick, D. M., Halazonetis, T. D., Pavletich, N. P., Jeffery, P. D. (2002) *Structure* **10**, 891-899.
[2] Oberoi, J., Richards, M. W., Crumpler, S., Brown, N., Blagg, J., Bayliss, R. (2010) *J Biol Chem* **285**, 39348-39358.

Poster 2

Alternative Binding Mode of Full and Partial Agonists in the Glycine Receptor Stabilises Loop C in an Open Conformation

Marc A. Dämgen[a], Timo Greiner[b], Remigijus Lape[b], *Lucia G. Sivilotti[b], and Philip C. Biggin*[a].

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Cys-loop receptors are ligand-gated ion channels that mediate fast synaptic transmission and are important drug targets for a variety of neurological conditions. Agonist binding opens the transmembrane pore, allowing ions to flow into (or out of) the cell.

In the case of the glycine receptor, the channel is selective for chloride ions. Previous research has identified agonists with varying ability to open the ion channel, yet an explanation of partial agonism at atomistic resolution remains elusive. An understanding would be crucial for drug design, since depending on the clinical situation, the ideal therapeutic drug should elicit a fine-tuned channel response somewhere in between that of a full agonist and a silent antagonist.

We have performed molecular dynamics simulations of the glycine receptor with full and partial agonists in the orthosteric binding site. The observed glycine binding mode is in excellent agreement with a recent crystal structure where density of glycine with a stable water molecule in the binding pocket is discernible. We find that a stable water molecule in the binding pocket plays a crucial role for all examined ligands. Here, we report an alternative binding mode, located slightly further away from the transmembrane domain, at the subunit interface that stabilises loop C in an open conformation. The stability of this alternative pose differs for full and partial agonists. Moreover, we reveal the detailed atomistic mechanism of the transition of loop C between the closed and the open conformation. Insight into this conformational change is important, as loop C closure is thought to be the first step in the signal-transduction mechanism from ligand binding to pore opening.

Our findings are consistent with the view that agonist efficacy is linked to the ability of stabilising loop C in a closed conformation.

Poster 3

Investigating reactivity of covalent drugs by QM/MM modelling

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Targeted covalent inhibitors (TCIs) are of increasing interest for the treatment of numerous indications including cancers, cardiovascular disease and infectious disorders. One example is ibrutinib, a Bruton's Tyrosine Kinase (BTK) inhibitor used to treat B cell cancers. [1] TCIs possess several advantages over their conventional reversible counterparts including high potency, low dose and extended duration of action. However, safety concerns arising from a covalent inhibitor's intrinsic reactivity have so far limited their development as therapeutic agents. Reactive electrophilic 'warheads' can potentially react indiscriminately with off-target proteins, causing serious side effects and toxicity issues. Careful optimisation of covalent reactivity is therefore required to mitigate these concerns and for the development of safe and selective covalent drugs. This requires an understanding of intrinsic reactivity, and of the effects that activate TCIs for reaction in proteins.
Combined quantum mechanics/molecular mechanics (QM/MM) methods have the potential to contribute to the design and development of TCIs, e.g. analysing the determinants of reactivity, and could be used to help 'tune' the reactivity of covalent drugs in the design process. We have investigated the reactivity of covalent inhibitors from both a ligand and protein based perspective. Previous work has indicated that proton affinity calculations performed at the B3LYP/6-31G(d) level provide a useful ligand-only bioactivity metric for small, fragment type compounds. [2] However, we find that this approach is not sufficient to model reactivity trends for larger 'drug-like' molecules, suggesting that additional factors contribute to reactivity. We therefore invoke QM/MM methods to assess the reactivity of the BTK inhibitor ibrutinib in a protein environment. We have also used constant pH molecular dynamics simulations to investigate the pK_as of potentially reactive cysteine residues in enzyme targets. The results show how modelling can contribute to the development of specific TCIs.

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Poster 4

Understanding regioselectivity in radical cation Diels-Alder reactions using quantum and molecular dynamics

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The Diels-Alder (DA) reaction is among the most important and versatile methods in creating ring molecules, and factors governing stereoselectivity and rate have been widely studied[1]. However, the chemoselectivity in products are often restricted, as electronic natures of the reactants (typically electron-rich diene and electron-poor dienophile) have to be matched.

On the other hand, in radical chemistry, the removal of a free election helps promote an entirely different chemical environment within the reactants.
This is experimentally shown to be imperative in forming a different set of products not predicted in neutral DA reactions using photochemistry or redox chemistry[2]. However, since the 1990s, there had been contentions about the concerted/stepwise mechanistic pathways in explaining the stereospecificity observed in product formation.

With density functional theory (DFT) calculations and an emerging quantum mechanic (QM) time-dependent technique known as quantum dynamics (QD) we investigated the radical cation DA reactions of a model system consisting of ethylene with cyclopentadiene (Cp) to provide quantitative understanding to this observed phenomena. This has never been applied to the study of radical cycloadditions before. We also aim to demonstrate the applicability of this understanding in reactions where minor products are actually desired.

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Poster 5

Excited States of the Photosystem II Reaction Centre

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During photosynthesis the Photosystem II reaction centre must generate an oxidising potential of >1.1V, the highest achieved in any natural system, in order to oxidise water. The key to its oxidising power is a highly charge separated radical pair state, which follows from excitation of a multimer of six reaction centre pigments. Study of the excited states of the multimer can provide a better understanding of charge transfer mechanisms within the reaction centre and potentially aid the design of new artificial photosynthetic devices.

Time Dependent Density Functional Theory was used to probe the excited states of the Photosystem II Reaction Centre. Long-range corrected functionals wB97X-D and CAM-b3LYP were employed as charge transfer states were expected. Models were based on the frozen crystal structure of *T. Vulcanus*[1] and all calculations included the six core pigments In order to study the effects of the protein environment; two, 22 and 60 of the nearest amino acid residues were also included in three models. It is worth noting that the largest purely QM model evaluated is over 2,600 atoms in size.

A delocalised excited state involving three reaction centre chlorophylls is detected for all models and its configuration is found to be in keeping with experimental Stark spectroscopy and low temperature absorption spectroscopy findings.[2] This state increases in oscillator strength as the number of surrounding amino acids included in the QM region is increased from two to 60. Only for the largest model was charge transfer directed towards the primary electron acceptor, whereas the two smaller models predict charge transfer in the opposite direction.

This work confirms the importance of including the protein environment when studying the reaction centre of Photosystem II, and provides a benchmark for lower-cost hybrid calculations on the largest model.

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Poster 6

The Role of Hydrocarbon Composition on the Thermal Stability of Aviation Fuel

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Aviation fuel is used to remove the excess heat from the jet engine, causing it to undergo oxidation reactions which lead to insoluble gums being formed. Advances in jet engine efficiencies and environmental concerns have lead to increased demands being placed on aviation fuel. This has driven interest in the use of alternative fuels, such as those derived from synthetic processes, in the aviation sector. This development however requires a greater understanding of the dependence of a fuels chemical composition on its thermal stability. Previous work on the oxidation mechanisms of hydrocarbons has been restricted to treating them as a general class of species. With the increased control of fuel composition that alternative fuels can achieve, it is necessary to research the role that chemical composition has on the oxidation process, allowing for the development of fuels with increased thermal stability, for use in more efficient engines. This work investigates the oxidation mechanisms for three classes of hydrocarbon commonly found in fuel with quantum chemistry techniques, using methods established for use in mechanistic organic chemistry studies. A straight chain alkane, dodecane, a cyclic alkane, decalin, and an aromatic hydrocarbon, toluene, were used to model the three classes of hydrocarbons. Our calculations indicate that aromatic and aliphatic hydrocarbons oxidise through different routes. Aromatic hydrocarbons act as antioxidants in the fuel, donating hydrogen to other hydrocarbons, thus stabilising radicals formed during the oxidation process. However this increases their susceptibility to oxidation, and as a consequence they undergo aromatic substitution reactions to form deposits, while aliphatic alkanes oxidise through different mechanisms. The theoretical modelling work has been supported by experiments carried out on small-scale thermal stability test devices.

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Poster 7

Understanding the Structure of Water Networks through Topological Data Analysis

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The nature of water networks is of fundamental importance to the field of drug discovery. For example, understanding how the presence of a solute affects the native water structure enables us to build better models for the prediction of free energy changes of solvation. Previous investigations in this problem include the use of radial and spatial distribution functions, or a graph theoretical approach. However, such methods suffer from difficulties in understanding behavior beyond nearest neighbor interactions, and the requirement for some chemical heuristic determining correlation respectively.

Topological data analysis, a development in the field of data science, seeks to understand the "shape" of data. In particular, persistent homology is an effort to determine the underlying structure of a data set, by searching it for n-dimensional "holes". Such techniques have found uses in chemical fields – in particular materials science. Examples include the determination of similarity in nanoporous materials through pore recognition[1], and the understanding of various motifs in amorphous structures[2].

Here, we use a persistent homology approach to understand the structure of water networks, developed in simulation. We improve pre-existing techniques to construct an "average" persistence, and use these techniques to build a persistent homology model for a fluid system. Furthermore, we show that a persistent homology formalism can provide unique insights towards understanding periodic boundary conditions. We also apply this new method of understanding intermolecular structure to three commonly used water models (TIP3P, TIP4P, SPC/E), and demonstrate how this information relates to that gathered from commonly used techniques, such as radial distribution functions. We finally present a perspective as to how these techniques can directly aid in the field of solubility prediction.

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Poster 8

Characterization of protein-excipient interactions for designing formulation

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Protein therapeutics have numerous advantages over small molecule drugs, as these are often characterized by high specificity and potency with low toxicity, and thus have interested many pharmaceutical industries. A major potentiality resides in their intrinsic compatibility with living systems as compared to small molecule drugs [1]. However, several challenges confront pharmaceutical scientists involved in the development of protein therapeutics. For instance, the proper stabilization of biologics is one of the major concerns. To overcome this issue, excipients play a major role in stabilizing biologics to prevent protein-protein interactions and hence aggregation. Currently, a detailed molecular understanding of the effect of different physicochemical formulation conditions on the stability of proteins are sparse as molecular interactions are difficult to investigate experimentally at the molecular level. Thus, computational approaches as applied in the current study can provide insight on the single-molecule level.

In this study, we focus on the use of molecular docking and simulations methods to develop a computational approach that will enable to predict hotspots for protein-excipient interactions and to determine preferential interaction coefficients of excipients on the protein surface. Additionally, using free energy approaches such as molecular mechanics (MM-PBSA) and linear interaction energy (LIE) methods, relative binding affinities of excipients to the proteins can be determined in order to rank excipients and to determine the effect of excipients on protein dynamics and flexibility. The identification of binding modes of excipients to the target structure is carried without any prior knowledge using the 3-D structure.

Our study has shown that certain residues are crucial for protein-excipients and protein-protein interactions. These results will be further supported by NMR studies.

In conclusion, this rational approach is an attempt to identify protein-excipient interaction sites, if the predicted sites are also plausible sites for protein-protein interactions, such excipient are potential good candidates for inclusion in the formulation.

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Poster 9

Depth-dependent physical properties of model biological lipid bilayers

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Lipid bilayers are thin, polar structures made up of two layers of lipid molecules. They are one of the constituents of the cellular plasma membrane, which forms a curved and continuous barrier around the cells and are responsible for exchange of molecules in and out of the cell1. The type and composition of lipids that make up the many different types of bilayers can alter its various physical properties that change significantly with depth, such as the highly fluctuating lateral pressure profile. Studying the various depth-dependent properties can give important insights into membrane functionality and the way they modulate membrane proteins2, which could be hard to investigate by experimental means. In this study, we use atomistic molecular dynamics simulations to quantify a number of bilayer properties in model bacterial, mammalian and cancer membranes that have heterogeneous lipid compositions. We first reproduce and validate some basic properties of individual lipids that make up these bilayers and then calculate the transmembrane lateral pressure profile. This facilitates us to simulate and analyse these properties for the aforementioned complex systems. Our results show how individual lipids modulate the physical properties of these model biological lipid bilayers, with potential implications on membrane function.

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Poster 10

Exploring the druggability of hPNMT with the JEDI collective variable

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Although proteins represent the vast majority of targets of pharmaceutical interest, only a small portion of the human proteome is known to be able to bind drug-like molecules. Proteins, however, are flexible and they often undergo conformational rearrangements that may reveal pockets that could potentially be druggable (*i.e.* able to bind a drug-like molecule). The study of these pockets, known as cryptic pockets, could potentially lead to the development of new drugs that target proteins that *a priori* would be considered undruggable.

Cryptic pockets exist for very short times and they usually cannot be detected at experimental time scales, which makes the use of computational methods such as molecular dynamics necessary to characterise them. However, their transient nature implies that very long simulation times would be necessary in order to detect them in an equilibrium dynamics simulation, a difficulty that can be overcome by using enhanced sampling methods such as those based in collective variables. In the present work, the JEDI[1] druggability function has been used as a collective variable to bias molecular dynamics simulations of human Phenylethanolamine N-Methyl Transferase (hPNMT), the enzyme that catalyses the terminal step of adrenaline synthesis and which is known to be involved in a wide range of diseases.

Different hPNMT inhibitors bind different conformations of the flexible noradrenaline binding site with binding affinities that differ in the order of magnitude[2] and which JEDI is able to distinguish in single point calculations. JEDI has been used to restrict the conformational sampling to conformations with a druggability score equal or higher than that of a structure that binds an inhibitor at low micromolar concentrations, which was used as a starting point.

In order to further enhance the sampling of the conformations of interest and to prevent the system from getting trapped in an energy minimum, an iterative taboo-search protocol based on the torsions of the residues in the binding site has been used. This protocol consists in clustering the snapshots obtained from each iteration, selecting representative structures and generating a bias based on the torsions of the binding site residues so that different regions of the torsional space of the binding site are explored during the next iteration. The obtained representative structures have been subsequently compared to a structure of the protein in which a cryptic pocket binds a different inhibitor at low nanomolar concentrations.

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Poster 11

Fibronectin III 9-10 Adhesion and Material-Driven Fibrillogenesis

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Fibronectin (FN) is a large extracellular matrix glycoprotein that affects many cell processes including differentiation, migration and proliferation. FN's function requires its quaternary structure to transition from a compact to an extended form, a process that is integrin dependant and which leads to FN fibrillogenesis. Recently a significant amount of research was carried out on an alternative to this integrin dependant process - a material driven approach, with the significant portion of the work carried out on poly (methyl/ethyl) acrylates by Prof. Manuel Salmeron-Sanchez's group in Glasgow [1]. FN on poly(ethyl acrylate) assumes the extended form, leading to network assembly, whereas the chemically similar surface poly(methyl acrylate) shows FN aggregation and no network formation [1]. To understand how such a small difference in the surface chemistry has such drastic consequences in FN's structure, we used molecular dynamics to simulate the crucial domains 9-10 FNIII on self-assembled monolayers (SAMs) that were functionalised using the previously mentioned polymer's side chains. We observe adhesion on ethyl acrylate SAMs, surface on which fibrillogenesis takes place, and diffusion of fibronectin on methyl acrylate SAMs, surface which does not lead to fibrillogenesis. Our simulations indicate that a) the strong water hydration around the functional groups of methyl acrylate SAMs impedes the adhesion of the domains, and b) the residues that are particularly important in the FN-integrin binding, the RGD motif and the PHSRN synergy region, are not the major drivers in the adhesion on ethyl acrylate SAMs. These results are consistent with the latest atomic-force microscopy experiments (unpublished).

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Poster 12

Engineering thermostable biocatalysts for CO_2 capture and utilization purposes

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The concentration of CO_2 in the atmosphere is increasing proportionately with the human population growth (0.075 ppm/year recorded in 1960 to 3.05 ppm/year reported in 2015), depicting a pessimistic scenario in the fight of climate change. The CO_2 burden has gained considerable public awareness prompting a world quest for the most feasible and globally scalable carbon capture technology. However, several aspects of carbon capture technologies remain as hurdles for their industrial application, such as: carbon capture efficiency, operational cost and eco-friendliness[1].

Carbon capture strategies like amine scrubbing or membranes are currently very costly, inefficient and unsustainable. Developing an approach that is potentially able to fix $CO_{2\,(g)}$ for the conversion of valuable carbonates with carbonic anhydrase (CA) has been proven effective at a bench scale level[2]. However, protein-based approaches have not yet been integrated to smokestacks, due to harsh conditions (elevated temperatures and alkaline pH values). The aim of this study was to use *in silico* methods to design a new biocatalyst that is able to thrive in industrial-like conditions (>100°C & pH>9). We have used molecular dynamics (MD) simulations to evaluate the thermal stability of three different thermophilic α-CAs (4C3T, 4X5S and 4G7A) at three different temperatures (343K, 353K and 363K), to provide some insight into the flexibility and free energy landscapes within these proteins. We investigated the most flexible regions in the aforementioned proteins by root mean square flexibility (RMSF) and principal component analysis (PCA), and we discovered six amino acids within *Themovibrio ammonificans* (4C3T) that are more susceptible to extreme temperatures (Figure 1). In future studies, these residues (THR175, PHE 231, ALA242, ASN138, GLY30 and CYS67) will be mutated into charged and small non polar residues in order to increase thermal stability.

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