MGMS and RSC MMG Young Modellers' Forum 2015 PROGRAMME & ABSTRACTS

Programme of Oral Presentations

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10.00 – 10.20	**Estimating hydration free energy of charged compounds by molecular theory and simulation** Maksim Mišin, University of Strathclyde
10.20 – 10.40	**The Secret Life of the Methyl Cation** Philippe Wilson, University of Bath
10.40 – 11.00	**The role of cation-π interactions for ligand-bromodomain binding** Wilian Cortopassi, University of Oxford
11.00 – 11.30	**Poster Presenters "Lightning Talks"**
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11.50 – 12.10	**Modelling Electron Transport in Organic Semiconductors** Hui Yang, University College London
12.10 – 12.30	**Use of MBAR in Monte Carlo simulations** Yuanwei Xu, University of Warwick
12.30 – 12.50	**Protein-Ligand Interaction Preferences: An Evaluation of Actual vs. Possible Hydrogen Bonds** Eva Nittinger, University of Hamburg
12.50 – 14.10	**Lunch and Poster Session**
14.10 – 14.30	**Accurate calculation of the absolute free energy of binding for drug molecules** Matteo Aldeghi, University of Oxford
14.30 – 14.50	**The Development and Assesment of Computational Approaches to the Thermodynamics and Kinetics of Binding** Iva Lukac, Liverpool John Moores University
14.50 – 15.10	**Energy decomposition analysis for linear-scaling DFT calculations in drug design** Max Phipps, University of Southampton
15.10 – 15.30	**JAFS: Free Energy, binding and competition in fragment based drug discovery** Ana Cabedo Martinez, University of Southampton
15.30 – 15.30	**Tea/Coffee break**
15.50 – 16.10	**Atomistic simulations of small molecule permeation through lamellar/nonlamellar lipid membranes.** Michail Palaiokostas, Queen Mary University of London
16.10 – 16.30	**A Three-Site Mechanism for Agonist/Antagonist Action on the Vasopressin Receptors** Noureldin Saleh, Friedrich-Alexander-Universität Erlangen-Nürnberg
16.30 – 17.00	**Deliberations and Prizes**
17.00	**End**

Talk 1

Estimating hydration free energy of charged compounds by molecular theory and simulation.

Maksim Mišin[a], *David Palmer*[b], *Maxim Fedorov*[a]

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Calculation of hydration free energy of charged compounds has been associated with a lot of conceptual difficulties. Despite theoretically being similar to the prediction of solvation free energy for neutral compounds, for a long time there has been no agreement on the exact methodology of such calculations, with results being significantly affected by the levels of theory, solvent models, and even the size of the system. While a number of issues have been resolved for molecular dynamics in terms of computing hydration free energy for monoatomic compounds, there is still no reliable benchmark of hydration free energies predicted using molecular dynamics for polyatomic ions [1]. Additionally, the possible effects of the computation haven't been considered for integral equation based models such as 3D-RISM.

Recently we have proposed a pressure based correction to 3D-RISM model that allowed us to accurately predict hydration free energies of neutral compounds for a wide range of temperatures. In this work we further extend and test this approach, by showing that it also works for charged compounds, provided that the Galvani potential of solute is taken into account. Similar approach also works for molecular dynamics calculations. Overall, accuracy of the predictions is comparable across molecular dynamics simulations, corrected 3D-RISM, and continuum solvation models.

References:
[1] Hunenberger, P., Reif, M., 2011. Single-Ion Solvation: Experimental and Theoretical Approaches to Elusive Thermodynamic Quantities. Royal Society of Chemistry, Cambridge.
[2] Misin, M., Fedorov, M.V., Palmer, D.S., 2015. Communication: Accurate hydration free energies at a wide range of temperatures from 3D-RISM. The Journal of Chemical Physics 142, 091105.

Talk 2

The Secret Life of the Methyl Cation

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The methyl cation is ubiquitous in chemistry and biology, being the key feature of notable biochemical processes and an important facet of organic stereochemistry.

Our interest in the methyl cation stems from its involvement in the inactivation of dopamine, and the factors affecting the catalysis of this methyl transfer within the active site of the enzyme *catechol-o-methyltransferase*. Using quantum methods, as well as a hybrid QM/MM approach, we use isotope effects to characterise the structure and mechanistic behaviour of the methyl cation in a series of environments.

Beginning with a test of the solvation methods employed in Gaussian09, we discovered an anomaly in the cavity models employed within the polarised continuum model. Comparing our calculated isotope effects to those output from QM/MM simulations, we concluded that the Universal Force Field model predicted the qualitatively correct trend as predicted by our QM/MM calculations [1].

Building upon this work, we used the anharmonic correction function within Gaussian09 to carry out a critical evaluation of the combination of anharmonicity with various electronic structure methods. We calculated scaling factors for each functional and basis set, recommending a scaled harmonic approach with the B3LYP functional as the most reasonable compromise between method accuracy and computational efficiency for the vibrational frequencies of the methyl cation isotopologues [2].

We are now considering the effect of applying a cutoff procedure on the reliability of calculated isotope effects. In QM/MM simulations, enormous amounts of data are output for each MD step, all of which must be treated. One way of reducing the cost of such calculations is reducing the number of atoms in the simulation. The QM region of QM/MM simulations consists of by far the most computationally expensive part of the calculation, so how big must the QM region be in order to still obtain reasonable isotope effects? Additionally, how many atoms or elements of the Hessian matrix need to be considered to still accurately describe the simulated system?

References:

1. P. B. Wilson, P. J. Weaver, I. R. Greig and I. H. Williams, *The journal of physical chemistry. B*, 2015, **119**, 802-809.
2. P. B. Wilson and I. H. Williams, *Molecular Physics*, 2015, **113**, 1704-1711.

Talk 3

The role of cation-π interactions for ligand-bromodomain binding

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Chromatin remodelling and histone modifications regulate several biological processes, e.g. DNA replication and repair, and their understanding is crucial for the design of more effective anti-cancer medicines.[1] CREBBP bromodomains are epigenetic "reader" proteins that recognize acetylated histone lysine residues and their inhibition is currently implicated in gene expression. Recently, we have discovered that a series of dihydroquinoxalinone (DHQ) derivatives binds selectively to the CREBBP receptor[2] and these interactions are strongly influenced by the potential to form a cation-π interaction with an arginine residue. Other important non-covalent interactions have also been analysed by us through a combination of molecular dynamics (MD) and quantum mechanical (QM) approaches. To understand the importance of the cation-π interaction for the design of other CREBBP inhibitors, we investigated the potential of a series of 5-isoxazolyl-benzimidazoles to interact with the same arginine residue and we built a quantitative structure-activity relationship (QSAR) based on the electrostatic potential of each π-system. Experimental binding affinities are described (R^2 = 0.88, n=15) using two quantum chemical descriptors for fifteen 5-isoxazolyl-benzimidazoles; for a test set of novel DHQ derivatives the model is capable of good predictive accuracy. The resulting model provides insight into the nature of CREBBP inhibition and demonstrates the utility of molecular descriptors based on quantum chemistry.

References:

[1] W. A. Cortopassi, R. Simion, C. E. Hornsby, T. C. C. Franca and R. S. Paton. *Chem. Eur. J.* In press.
[2] T. P. C. Rooney, P. Filippakopoulos, O. Fedorov, S. Picaud, W. A. Cortopassi, D. A. Hay, S. Martin, A. Tumber, C. M. Rogers, M. Philpott, M. Wang, A. L. Thompson, T. D. Heightman, D. C. Pryde, A. Cook, R. S. Paton, S. Müller, S. Knapp, P. E. Brennan and S. J. Conway, *Angew. Chem. Int. Ed*. **2014**, *126*, 6240.

Talk 4

Modelling Electron Transport in Organic Semiconductors

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Organic semiconducting materials have advantages of easy fabrication, mechanical flexibility, and low cost with a wide range of applications, like OLED, organic field effect transistors and photovoltaic cells. However, the search is hampered by the lack of an adequate theory to explain the exact mechanism of electron transport (ET) in organic systems. The standard theories such as band theory or activated electron hopping in many cases are inadequate since these organic materials preferm strong, anharmonic thermal fluctuations and small energy barriers for charge transport [1].

An ultrafast method of estimation of electronic coupling for ET between π-conjugated organic molecules has been developed in our group [2]. Benzene, pentacene and rubrene crystals are investigated using an efficient mixed quantum-classical non-adiabatic simulation method.

In the talk, we will discuss the calculation methods and some fresh results of electronic couplings, site energies, rates of ET and mobilities of electrons, which is breaking the limitation of our fundamental understanding of CT in organic semiconductors.

References:
[1] F. Gajdos. H. Oberhofer et al. *J. Phys. Chem. Lett.*, (2013), **4** (6), 1012-1017
[2] F. Gajdos, S. Valner et al. *J. Chem. Theory Comput.,* (2014), **10** (10), 4653–4660

Talk 5

Use of MBAR in Monte Carlo simulations

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Monte Carlo (MC) methods have been used as an alternative simulation tool in biomolecular modelling, although perhaps not as widely adopted as Molecular Dynamics (MD). In contrast to MD simulations, MC methods have the flexibility of choosing proposal moves that are not governed by physical laws, thereby enabling exploration of molecular processes (e.g. aggregate assembly in protein aggregation) with timescales way beyond those can be probed by MD.

Whereas MD has been used in the study of protein aggregation, these studies focus only on the stability of aggregate. In order to look into the actual assembly process, one often has to resort to low-resolution (e.g. lattice) models and, in such cases, MC may come in handy. In this talk, I will show a new method to calculate the density of states using the multistate Bennett acceptance ratio (MBAR) estimator [1]. The estimated density of states can then be used to guide subsequent MC simulations. The MBAR estimator, proven to be statistically optimal, was originally developed for final estimation of thermodynamic properties. We show that using the MBAR estimator as an intrinsic part of MC sampling, rather than its more normal use for post-simulation analysis, can improve simulation efficiency. To demonstrate this method in practice, we apply it (i) to a well-defined statistical model to show its validity, and (ii) to a lattice model for the aggregation of membrane proteins. The latter model is motivated by the aggregation of TatA proteins in the Twin-Arginine Translocation pathway as a mechanism for protein transport across bacteria cytoplasmic membrane.

This talk is based on our recently published work. [2]

References:
[1] M.R. Shirts and J.D. Chodera, *J. Chem. Phys.,* (2008) **129**, 124105
[2] Y. Xu and P.M. Rodger, *J. Chem. Theory Comput.,* (2015) DOI: 10.1021/acs.jctc.5b00189

Talk 6

Protein-Ligand Interaction Preferences: An Evaluation of Actual vs. Possible Hydrogen Bonds

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Hydrogen bond networks are among the most relevant features for molecular modelling approaches, but how many hydrogen bonds are actually build by different functional groups? Do we see distinct features for acceptor and donor functions? The number of available X-ray crystallographic structures has tremendously increased within the last years. Additionally, tools for hydrogen bond network optimization are nowadays also at hand. Now, both aspects provide the basis for the performance of large scale analysis of hydrogen bond network properties.

Based on a high-resolution PDB subset[1], containing 5484 PDB structures with less than 1.5 Å resolution and available electron density, we have analysed diverse hydrogen bond characteristics. Herein, we have used the program Protoss[2] to optimize the hydrogen bond network of every biological complex by respecting freely rotatable hydrogens, tautomers, as well as protonation states. The optimized network allows the analysis of hydrogen bond preferences, from the raw number and quality of hydrogen bonds, to preferred interaction partners. Further, it enables us to distinguish acceptor and donor properties of different functional groups.

In order to correctly distinguish accessible from inaccessible hydrogen bond functions, we have developed a new method for the identification of free space. Based on an intuitive approach by sampling the interaction surface of a hydrogen bond function, we are able to correctly locate almost 97 % of crystallographically determined water molecules within the protein structures. Using our previously developed estimate of electron density for individual atoms[1], we validate the biological structure with its available experimental evidence. Additionally, we compare the hydrogen bonding preferences within proteins, of proteins with ligands or water molecules to detect similarities as well as differences. These results allow the validation of existing modelling approaches and support the design of new methods.

References:
[1] E. Nittinger, N. Schneider, G. Lange and M. Rarey, *J. Chem. Inf. Model.,* 2015, **55**, 771– 83.
[2] S. Bietz, S. Urbaczek, B. Schulz and M. Rarey, *J. Cheminform.,* 2014, **6**, 12.

Talk 7

Accurate calculation of the absolute free energy of binding for drug molecules

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Accurate prediction of binding affinities has been a central goal of computational chemistry for decades, yet remains elusive. Despite good progress, the required accuracy for use in a drug-discovery context has not been consistently achieved for drug-like molecules. However, thanks to recent advances in theory and computing, predictions of binding affinities using physics-based simulations are gaining popularity. In particular, binding free energy estimates based on molecular dynamics and alchemical pathways have been shown to be a rigorous approach for the affinity prediction problem and hold the promise to be able to guide lead optimisation. Whilst relative calculations have started being employed in a drug-discovery context, absolute calculations have been mostly applied to model systems and still lack validation against drug-like molecules and real therapeutic targets.

We performed absolute free energy calculations based on an alchemical thermodynamic cycle for a set of diverse inhibitors binding to bromodomain-containing protein 4 (BRD4) and demonstrate that accurate results can be obtained, either starting from x-ray structures or docked ligand poses. Bromodomains are epigenetic mark readers that recognize acetylation motifs and regulate gene transcription, and are currently being investigated as therapeutic targets for cancer and inflammation. The accuracy achieved by the estimates based on molecular dynamics offers the exciting prospect that the binding free energy of drug-like compounds can be predicted for pharmacologically relevant targets.

References:
[1] C. Chipot, *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, 2014, **4**, 71–89.
[2] M. Aldeghi, A. Heifetz, M.J. Bodkin, S. Knapp and P.C. Biggin, *Chem. Sci.*, 2015, DOI: 10.1039/C5SC02678D

Talk 8

The Development and Assesment of Computational Approaches to the Thermodynamics and Kinetics of Binding

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Over recent decades there have been many improvements in the techniques available for predicting the pharmaceutically relevant properties of a compound. However, predicting the binding strength between a compound and a protein target remains an unsolved problem. The challenge of predicting this binding strength has been complicated in recent years by the insights provided from the measurements of thermodynamics and kinetics. Those attempting to design drugs now have more parameters, rather than less to worry about! [1,2]

At John Moores University, we are undertaking a program of work to design and evaluate computational tools to predict the thermodynamics and kinetics of binding. These tools will help drug designers to navigate this complex array of interdependent properties.

The project presents a novel approach in which QM (quantum mechanics) is used to calculate binding energies: by constructing 'theoceptors'- theoretical receptors constructed by computing the optimal geometry. QM calculations on LDHA (Lactate Dehydrogenase A) have been performed: previous work has shown that for iNOS (inducible nitric oxide synthases) a QM model system was able to provide binding energies that correlate well with LLE (ligand lipophilic efficiency) [3]. LLE as a property resembles enthalpy of binding; hydrophobic binding is associated with entropic forces.

The aim of this work, besides explaining the link between the structure and thermodynamic/kinetic signatures, is to address some of the issues and uncertainties associated with two biophysical techniques: Surface Plasmon Resonance (SPR) and Isothermal Titration Calorimetry (ITC). In this presentation, we will disclose the insights available for a congeneric series of ligands that has been studied using ITC and SPR and the observations rationalized with experimental structures and computational modeling.

These findings contribute beneficially to the development of computational methods for interpreting potency in terms of thermodynamic or kinetic parameters. This will reduce the time and cost of making and testing compounds that are unlikely to become drugs.

References:

1. Ladbury, J.E., Klebe, G. & Freire, E., 2010. Adding calorimetric data to decision making in lead discovery: a hot tip. *Nat. Rev. Drug discovery*, **9**(1), 23–27.
2. Tummino, P.J. & Copeland, R. a, 2008. Residence time of receptor-ligand complexes and its effect on biological function. *Biochemistry*, **47**(20), 5481–92.
3. Leach, A.G., Olsson, L.-L. & Warner, D.J., 2013. A monomeric form of iNOS can rationalise observed SAR for inhibitors of dimerisation: quantum mechanics and docking compared. *MedChemComm*, **4**(1), 180.

Talk 9

Energy decomposition analysis for linear-scaling DFT calculations in drug design

Max Phipps[a], Thomas Fox[b], Christofer S. Tautermann[b], *Chris-Kriton Skylaris*[a]

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In quantum chemistry calculations, energy decomposition analysis (EDA) approaches enable the partitioning of the interaction energy of a complex (such as a protein-ligand complex) into energy components of chemical interest, such as electrostatic, exchange, charge transfer and polarisation terms. In biomolecular association events in particular, the insights that EDA can produce can be invaluable for the fine-tuning of interactions as is necessary for applications such as drug optimisation. No unique definition exists for the components of EDA, and for this reason a large number of methods have been proposed.

A prototypical EDA approach is the popular Kitaura-Morokuma (KM) scheme in which intermediate wave functions that express specific chemical properties are used to partition the supermolecular interaction energy. From this scheme, many other EDA methods have evolved. We have recently assessed these methods in terms of their chemical relevance on protein-drug interaction patterns[1]. From our investigation, the absolutely localised molecular orbital (ALMO) EDA was found to be particularly well suited for such interactions.

So far, EDA calculations have generally been limited to molecules with no more than a few tens of atoms[1]. We have implemented an EDA scheme in the ONETEP linear-scaling DFT package[2] based upon the ALMO scheme and the localised molecular orbital (LMO) scheme. Our method provides a detailed decomposition of the interaction energy in terms of electrostatic, exchange, correlation, Pauli-repulsion, polarisation and charge transfer components. We have applied our approach to a test set of small interacting molecular complexes which display interactions typically encountered in protein-ligand systems. Future directions will include applications on entire biomolecules with thousands of atoms.

References:
[1] M. J. S. Phipps, T. Fox, C. S. Tautermann, C.-K. Skylaris, *Chem. Soc. Rev.,* (2015), **44***,* 3177-3211.
[2] C. K. Skylaris, P. D. Haynes, A. A. Mostofi, and M. C. Payne. *J. Chem. Phys.*, (2005), **122***,* 084119.

Talk 10

JAFS: Free Energy, binding and competition in fragment based drug discovery

Ana I. Cabedo Martinez[a], Gregory A. Ross[a], Samuel Genheden[a], Marcel Verdonk[b], Paul Mortenson[b], Michelle L. Lamb[c], Richard A. Ward[d], Jonathan W. Essex[a]

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Computational chemistry, within drug discovery, is generally considered as a tool to increase efficiency of the drug development process. In particular, strategies which focus on rational drug development can benefit considerably from the insight that computational methods provide. Among those, Fragment Based Drug Discovery (FBDD), within the structure-based approaches, stands out for its potential and interest within pharmaceutical industries.

FBDD is based on studying small chemical moieties (fragments), selecting those with the most promising qualities to add further chemical components until reaching the desired drug-sized molecule. While providing many advantages ranging from better optimized properties of the final drug candidate to more efficient screening of the chemical space, the small size of the fragments proves a challenge. Even within computational methods, fast and easy techniques such as docking and scoring may find problems estimating affinities of these small molecules which inherently present few interaction points with the target.

We will be presenting the JAFS method to estimate binding geometries and affinities of fragments to protein targets. Based on free energy techniques, it provides the opportunity to rank fragments by estimated affinity to a target without previous knowledge of the binding geometry as well as to capture water mediating interactions when estimating binding poses. The method, based on JAWS[1] and related to λ-dynamics[2], extends standard molecular mechanics simulations to sample an extra degree of freedom: the interaction potential of the fragments (θ). Here θ accounts for the scaling of the interaction energies of each fragment. These are sampled as a continuum from θ=0, where interactions are off, to θ=1, where the fragment fully interacts with the environment.

Using the JAFS methodology, binders with the highest affinity, as well as non-binders (decoys), have been identified from a pool of fragments in our preliminary studies. The crystallographic pose has been successfully found when several key interactions between fragment and target were mediated by water molecules. While requiring considerably higher computational resources than faster methods like docking and scoring, JAFS has proven successful in challenging circumstances where simpler methodologies are known to perform poorly.

References:
[1] J. Michel, J. Tirado-Rives and W.L. Jorgensen, *J. Phys. Chem,* (2009) **113**, 13337-13346.
[2] X. Kong and C.L. Brooks III, *J. Phys. Chem,* (1996) **105**, 2414.

Talk 11

Atomistic simulations of small molecule permeation through lamellar/nonlamellar lipid membranes

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Passive permeation through biological membranes is an important mechanism for transporting molecules and regulating the cell's content. Studying and understanding passive permeation is also extremely relevant to many industrial applications, including drug design and nanotechnology. *In vivo* membranes typically consist of mixtures of lamellar and nonlamellar lipids. Lamellar lipids are characterized by their tendency to form lamellar bilayer phases, which are predominant in biology. Nonlamellar lipids, when isolated, instead form non-bilayer structures such as inverse hexagonal phases. While mixed lamellar/nonlamellar lipid membranes tend to adopt the ubiquitous bilayer structure, the presence of nonlamellar lipids is known to have profound effects on key membrane properties, such as internal distributions of stress and electrostatic potential.

In this study, we examine the effect of changing the lamellar vs. nonlamellar lipid composition on the transmembrane passive permeation process. Our hypothesis is that different lipids induce changes in membrane permeation and that such changes can be related to a small number of fundamental physical properties. In particular, we investigate a series of small molecules including water, carbon dioxide, ammonia, and fluoromethane. Permeation through membranes is difficult to study experimentally, because of the small scale and complexity of lipid bilayer systems. Therefore, we utilize atomistic molecular dynamics simulations and the z-constraint method, to obtain transfer free energy profiles, as well as the diffusion and permeation coefficients. Our preliminary results indicate that the addition of nonlamellar lipids enhances the transfer of permeants through the interfacial lipid head region, while it hinders it in the hydrocarbon tails core. This work represents an advancement towards the development of more realistic *in silico* permeability assays, which may have a substantial future impact in the area of rational drug design.

Talk 12

A Three-Site Mechanism for Agonist/Antagonist Action on the Vasopressin Receptors

Noureldin Saleh,[1] Giorgio Saladino,[2] Francesco L. Gervasio,[2] Elke Haensele,[3] Lee Banting,[3] David C. Whitley,[3] Jana Sopkova-de Oliveira Santos,[4] Ronan Bureau,[4] Timothy Clark[1,3]

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Extensive classical molecular-dynamics simulations including metadynamics enhanced sampling reveal three distinct binding sites for arginine vasopressin (AVP) at its V_2-receptor (V_2R). Two of these, the vestibule and intermediate sites, block (antagonize) the receptor and the third is the orthosteric activation (agonist) site. The contacts found for the orthosteric site satisfy all the requirements deduced from mutagenesis experiments, including the involvement of residues near the extracellular N-terminus of the receptor. The biologically active conformation of AVP has been determined for each binding site. Metadynamics simulations on V_2R and its $V_{1a}R$-analog give an excellent correlation with experimental binding free energies by assuming that the most stable binding site in the simulations corresponds to the experimentally determined binding free energy in each case. We extended our results to the β_2-adrenergic receptor to study the co-operative mechanism of the ligand and G-protein on GPCR activation. The resulting three-site mechanism for both β_2 and V_2-activity is compatible with the ternary complex model.

Programme of Poster Presentations

Poster 1	**Development of a fragment-based in silico method for the prediction of chemical reactivity** David J. Ebbrell, Liverpool John Moores University
Poster 2	**Mapping the structural proteome: what does 'biologically relevant binding-site space' look like?** Joshua Meyers, The Institute of Cancer Research
Poster 3	**Shrinking immortality characteristics of cancer by targeting key protein-protein interaction in telomere stabilization complex** Khaled Tumbi, University of Nottingham
Poster 4	**The Analysis and Validation of Shape Fingerprints** Joanna Zarnecka, Liverpool John Moores University
Poster 5	**Network of pharmacological assays: ChEMBL as a graph** Magdalena Zwierzyna, University College London
Poster 6	**Development of Functional Computational Workflow Methods for Quality Automated Molecular Modelling-based Drug Design** Fiona McMahon, Sunderland University
Poster 7	**From the Computer to the Bench: Novel Selective Glycomimetics Take Life** Alessandra Lacetera, Centro de Investigaciones Biológicas, Madrid
Poster 8	**Computer Simulations of Borosilicate Glass** Abdul Rashidi, University College London
Poster 9	**Internal allosteric sodium in the δ-opioid receptor responds to transmembrane voltage** Owen Vickery, University of Dundee
Poster 10	**Computational investigation into the formation of inclusion complexes of hydrophobic drug molecules with cyclodextrins** Sandhya Rani Tattala, University of Greenwich
Poster 11	**Conformational sampling of intrinsically disordered peptides by Replica Exchange Molecular Dynamics** Marija Miljak, University of Southampton
Poster 12	**Water dynamics and proton translocation in cytochrome *cbb3* oxidase; insights from large scale MD simulations** Catarina Carvalheda, University of Dundee

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

Development of a fragment-based *in silico* method for the prediction of chemical reactivity

David J. Ebbrell, *Judith C. Madden, Mark T.D. Cronin, Steven J. Enoch*

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The Adverse Outcome Pathway (AOP) paradigm details the existing knowledge that links the initial interaction between a chemical and a biological system, termed the molecular initiating event (MIE), through a series of intermediate events, to an adverse effect[1]. An important example of a well-defined MIE is the formation of a covalent bond between a biological nucleophile and electrophilic compounds[2]. This particular MIE has been associated with various toxicological endpoints such as acute aquatic toxicity, skin sensitisation and respiratory sensitisation. This study has investigated the calculated parameters that are required to predict the rate of chemical bond formation (reactivity) of a dataset 64 α-β-unsaturated aliphatic carbonyls (linear Michael acceptors) (15 ketones, 14 aldehydes and 35 esters). Reactivity of these compounds towards glutathione was predicted using a combination of a calculated activation energy value (Eact, calculated using Density Functional Theory calculation at the B3YLP/6-31G+(d) level of theory (DFT-DZ)), and indicator variables for the presences or absences of substitutes at the alpha and beta positions. The analysis produced excellent models for the aldehydes and ketones (R^2 = 0.95 and 0.97 respectively) and good models for the esters and the entire dataset as a whole (R^2 = 0.61 and 0.72 respectively). Based on the results, a fragment-based algorithm was developed enabling the reactivity to be predicted for linear Michael acceptors without the need to perform the time-consuming DFT calculations. This poster will outline the development of the fragment-based algorithm for predicting chemical reactivity and discuss its application for the prediction of toxicity within the AOP approach.

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Poster 2

Mapping the structural proteome: what does 'biologically relevant binding-site space' look like?

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Protein binding-site comparison is principally used to elucidate the function of orphan proteins and to predict polypharmacology.[1] The availability of data and new methods means that analysis of protein binding-sites can now be more powerful than ever before. By creating a dissimilarity map of available protein crystal structures, we can visualise biologically-relevant binding-site space, which can then be used to inform medicinal chemistry design efforts. Data retrieved from the Protein Data Bank (PDB) has been curated and guided using both supervised and unsupervised machine learning techniques to develop and validate a means of clustering the potential pockets of the known structural proteome.

To consider potential binding-sites that as yet do not have ligands known to bind, two freely available pocket detection software programs have been evaluated for their ability to identify and rank binding-sites capable of binding medicinal chemistry relevant small molecules. It is frequently stated that 'The largest cleft often corresponds to the ligand-binding pocket',[2] this assertion is investigated and compared to relevant druggability scoring metrics. The ability of binding-site comparison techniques to differentiate between similar and dissimilar protein binding-sites was then evaluated on a manually curated dataset of seven protein families. The same dataset was used to identify an optimum unsupervised learning technique to generate well-defined clusters of similar protein binding-sites. This workflow was then applied to a larger dataset of protein crystal structures, representative of the currently known structural proteome. Here, the method is presented along with a number of pitfalls associated with the methodologies employed therein.

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Poster 3

Shrinking immortality characteristics of cancer by targeting key protein-protein interaction in telomere stabilization complex.

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Telomeres are the specialised DNA–protein complexes found at the tips of linear eukaryotic chromosomes which serves as a buffer of non-coding DNA that in normal cells is gradually eroded over the cycles of cell division due to the end replication problem. This gradual erosion works as biological clock for cells and let them know when to trigger apoptosis. But, in cancer cells, enzyme telomerase (enzyme which synthesizes telomeres) is overexpressed and eventually making cancer cells theoretically immortal. The telomere-associated protein complex ('Shelterin') or 'telosome' masks the chromosome terminus, preventing it from being mistaken for a double-strand break and eventually inhibiting cell death and senescence.

In this project we aim to design, synthesize and evaluate novel peptide-like molecules which can disrupt interaction between crucial Shelterin components TRF1-TIN2 based on knowledge gained from previous work in our lab. Here we performed in-depth analysis of MD simulation, MMGBSA and biological assay data for 13 TRF1-peptide complexes from our lab. Each MD simulation and MMGBSA calculations were repeated 50 times with different initial velocities to cover maximum conformational space and to attained significant statistical significance. In addition to this, per-residue energy decomposition for all 50 replicas of each complex were performed to ascertain contribution of each residue in binding process.

Here we will discuss how we able to establish a key pocket opening event in binding site of TRF1. Furthermore, with the help of per-residue decomposition data, we designed series of novel linear/cyclic peptides. Large scale molecular docking, MD simulations, and MMGBSA calculations predict these molecules to have increased binding affinity towards TRF1 compared to already know linear/cyclic peptides and may act as lead molecules for TRF1-TIN2 interaction inhibitors. Additionally, a python programme (mmgbsa_analyser.py) to efficiently analyse large scale MMGBSA and per-residue decomposition data will be introduced.

Poster 4

The Analysis and Validation of Shape Fingerprints

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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 uses this concept in virtual screening to improve potential drugs.

Molecular fingerprints are binary bit strings that encode the structure or 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.

We aimed to design a set of reference shapes that generate fingerprints, which will be useful in drug discovery. A public-domain ligand dataset was filtered and an algorithm described by Haigh J. *et al.* [1] identified various sets of reference shapes.

A test set described by Taylor R. *et al.* [2] was used (both crystal structures and conformations generated from SMILES) to evaluate the performance of the sets of reference shapes. The molecules in the test set were compared with each other. The distance matrices that were created were analyzed by performing student t-test and Cohen's d, as well as compared by analyzing the Tanimoto similarity distribution plots, to determine whether it is possible to correctly group the sets of compounds.

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Poster 5

Network of pharmacological assays: ChEMBL as a graph.

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ChEMBL is a large-scale chemogenomics database hosted by the European Bioinformatics Institute of the European Molecular Biology Laboratory (EMBL-EBI). It is comprised primarily of data extracted manually from the primary literature. By linking chemical structures to biological targets and pharmacological activities, it provides a comprehensive overview of historical drug discovery.
To facilitate the exploration of relationships between assays in ChEMBL, we have built a graph database using Neo4j technology. This allows us to easily navigate the screening space and formulate queries that would be infeasible using the original relational schema.

We use various algorithms derived from graph theory to explore the resulting complex network and increase the functionality of our database. For instance, we use transitive closure algorithms to reduce the number of connections and facilitate fast traversals. Betweenness centrality scores helped highlight drug-drug interaction and antitarget modelling studies, whilst community detection revealed some interesting features of the dataset. For example, assays involving biologically related targets tend to cluster together, and, likewise, the position of approved drugs in the network reflects similar mode of action or therapeutic indication.
Finally, we are building tools to aid in the interactive visualization of our data; these use browser-based technologies and web services to, for example, allow inspection of the structures of compounds tested in the assays of interest.

Poster 6

Development of Functional Computational Workflow Methods for Quality Automated Molecular Modelling-based Drug Design

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Introduction: We are developing an automated *ab initio* high throughput workflow which will be used to investigate the potential of novel drug candidates. This employs different computer program packages that will calculate the binding energies of the drug candidates in complexes with drug targets, any transition states that may occur in covalent bonding, and the geometries of both drug candidates and drug target-drug candidate complexes. This will be used to find the most likely candidate in a library in order to accelerate drug discovery.

Method: The workflow utilizes Python scripts, allowing the software packages to communicate with each other, as well as leaving room for the expansion in capabilities of the workflow. Gaussian09 is used to calculate energies and optimized structures of drug candidates, which are then docked into their drug target using AutoDock 4.0, giving a drug candidate-drug target complex conformation. Using QM/MM calculations, the workflow then calculates the energy of this complex. In comparing other drug candidates within a drug library, it is then possible to determine which drug candidate will have likely success in further investigations. This is made automated by the use of a passport system we have developed which will delegate calculations to different computer nodes available within a cluster computer, using the scripts as decision makers for the next step of the workflow. [1]

Discussions: A "live" drug discovery project is also carried out alongside development of the workflow to validate the material. Cyclooxygenase enzymes and their inhibitors are being investigated, as this is a much researched area. This allows for comparisons between calculated values and published experimental results.

Conclusions: We have demonstrated the ability to write scripts which will analyse output files, create new job files, and submit jobs to Gaussian for calculations. We have also been successful in utilizing a python/C# interface, allowing us to take full advantage of a popular scientific computer language (python), and the more robust C# environment preferred by traditional programmers. This allows us to both have structure and rigidity in the automation process, and the flexibility of analysing different data from large output files.

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Poster 7

From the Computer to the Bench: Novel Selective Glycomimetics Take Life

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Carbohydrates are a family of molecules involved in physiological and pathological processes. The sugars represent a very big challenge for the chemists, due to their characteristics: on the one side, the wide variety and possible final combinations they may lead to, and, on the other side, the complexity of their synthesis. Galectins are a family of lectins which recognize selectively β-galactoside moiety. They are involved in cancer, HIV, inflammatory disease, rheumatoid arthritis [1]. To date, 14 members of the galectins have been identified in mammals. All galectins share a carbohydrate recognition domain (CRD) which makes difficult to aim selective binding [2]. Among the family, we have focused on galectin-1, -3 and -7 due to their biological/pathological roles.

A fragment-based virtual screening (FLAP and Glide protocols) into the adjacent pocket to the principal binding site has been undertaken. Four generations of different compounds (around 500) were designed by using different scaffolds, and were submitted to docking calculations (AutoDock and Glide) in the three galectins (gal-1, -3 and -7). Results were compared with the docking of reported compounds (CHEMBL database). Based on the predicted selectivity and affinity, we chose the best compounds for each galectin and we performed molecular dynamics (Amber) in order to evaluate the stability of the complexes. Once designed the new glycomimetics, the synthesis has been undertaken.

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Poster 8

Computer Simulations of Borosilicate Glass

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Borosilicate glasses display a number of interesting properties including low thermal expansion, unique chemical resistance and high surface strength. All of these properties make these glasses very desirable for use in a wide range of sectors such as optical lenses/photonics, in the pharma industry, to chemically resistant glassware in the chemical industry.[1] A component in borosilicate glass is Boron Trioxide (B_2O_3), one of the three oxides of Boron. B_2O_3 is primarily found in two forms; a glassy, hygroscopic, white solid and the second being a more commonly found amorphous, vitreous form. In fact it is commonly known as one of the hardest known compounds to crystallise.[2] The structure of glassy B_2O_3 is debated amongst researchers. The fundamental building block has been recognised as an interconnected network of $BO_{3/2}$ group, a trigonal planar molecule. The connectivity between these $BO_{3/2}$ groups is not fully understood but several models have been proposed. A widely accepted understanding is that glassy boron trioxide (g-B_2O_3) is constructed with boroxol rings, a 6 membered ring with alternating coordination on the boron and oxygen atoms. It is thought that the boron and oxygen alternate from 3 to 2 coordination numbers, respectively. It is thought that these rings play a vital part in creating difficulties when attempting crystallisation.

This study aims to investigate the relationship between structure, dynamics and properties of borosilicate glasses through computational molecular dynamics (MD) techniques. Subsequently developing a model that incorporates these particular features. Our initial work has focussed on Boron Trioxide. A structural model of B_2O_3 was constructed based on previous research carried out by the Takada research group[3] using the DL POLY programme. This research involved the use of the low-pressure crystalline phase of B_2O_3-I under standard operating conditions.

Through MD studies, we have successfully modelled the crystal to glass transition of Boron trioxide. The system size has also been expanded and has now been tested with both two and three body potentials with melt and quenches steps separated for further analysis. Modelling B_2O_3 ,using both a two and three body potential, has outlined the importance of both the B-O-B and O-B-O terms, which is seen to be essential for the quench stage. In the absence of these bond bending terms we have seen inadequate quenching of the system and complete system recorder using the two body potential.

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Poster 9

Internal allosteric sodium in the δ-opioid receptor responds to transmembrane voltage

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G-protein-coupled receptors (GPCRs) are the largest superfamily of membrane proteins within the human genome. They participate in numerous physiological functions, including neuronal excitability and pain signalling. Owing to their functional and structural characteristics, they are excellent drug targets. In spite of their diversity, it is thought that GPCRs share a conserved pathway of signal transduction via conformational changes in their transmembrane (TM) domain. The full range of movements leading to activation, and their interaction with external factors, are however still incompletely understood. Many GPCRs are for instance modulated by sodium. The recent high-resolution crystal structure of the delta-opioid receptor (DOR) provides detailed insight into the sodium binding site in the core of the TM domain. In this work, we looked at the effect of sodium ions and transmembrane voltage on the flexibility and conformational changes of DORs. We investigated the structure of DOR in double-bilayer, atomistic simulation systems under physiological and supra-physiological transmembrane electric fields applied by CompEL, to characterise the role of sodium in DOR. Our results implicate sodium and voltage as key players in controlling the conformation and function of the δ-OR.

Poster 10

Computational investigation into the formation of inclusion complexes of hydrophobic drug molecules with cyclodextrins

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Many drug molecules have poor aqueous solubility, and thus the bioavailability is limited. Routes to enhancement of aqueous solubility are advantageous as this will lead to an increase in uptake and therefore efficacy of the drug molecule. There are a number of ways to achieve this and the formation of inclusions complexes of the drug molecules with cyclodextrins. The mechanism of action is often superficially described as having the hydrophobic drug taken up by the comparatively hydrophobic cyclodextrin core. However, the details at the atomic level may be somewhat more complex. For example, stability constants based on data extracted from phase solubility studies using a Higuchi-Connors model are often used to propose 1:1 binding ratios. This may overlook the errors associated to low intrinsic solubility and values derived from phase solubility plots.[1] To unlock the drivers associated with inclusion complex formation, and thereby attempt to understand solubility enhancement, the complexation of a series of poorly soluble drugs have been studied with β-cyclodextrin.

Here, the phase solubility behaviour of ibuprofen, Ketoprofen and flurbiprofen with β-cyclodextrin has been studied at a range of temperatures and association constants determined along with attendant changes in enthalpy and entropy. These have been linked to calorimetric data[2]. Thermodynamic constants derived from the phase solubility studies and published calorimetric data have been used to validate a study using molecular dynamics simulations of the inclusion complexes. Here, the GAFF forcefield was used along with a TIP3P solvent box as implemented in AMBER. Production NPT simulations were commenced following NVT then NPT equilibration steps. The resulting binding energies were calculated from comparison of simulations from the cyclodextrin, drug, solvent box and cyclodextrin-drug complex and then compared to experimental data for validation.

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Poster 11

Conformational sampling of intrinsically disordered peptides by Replica Exchange Molecular Dynamics

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Molecular dynamics simulations have been widely used to provide atomistic details of conformational changes in peptides. However, their accuracy is limited by the long time scale required to see many conformational motions. To address this problem, different enhanced sampling methods have been introduced which use a wide range of approaches to improve the efficiency of conformational sampling. One of the most widely used enhanced sampling methods is Replica Exchange Molecular Dynamics (REMD) where a system is simulated across a range of different temperatures and swaps are initiated between replicas at different temperatures using a Metropolis criterion. To overcome high energy barriers, a wide range of temperatures need to be applied to facilitate conformational changes.

In this work, the REMD method was applied to the natural neuropeptides Urotensin II (UII) and Urotensin-related peptide (URP) characterised by a conserved six amino acid ring and a short tail, to test the rate of convergence in conformational sampling. Since these peptides are involved in important biological functions, like vasoconstriction, and are part of the G protein coupled receptor signalling pathway, understanding their conformational dynamics may help in rationalising their functional diversity.

The peptides, each with three different starting geometries, were simulated and analysed in terms of structure stability over 400 ns of REMD. We have not only identified the same conformations as already reported in the NMR experiments and other conventional MD simulations, but new conformations have emerged. From the conformer populations, the relative free energies of the different conformations have been estimated. Surprisingly, the simulations show that the rate of convergence, in our case in terms of sampling efficiency, is slow even with a small peptide and using an enhanced sampling method.

Poster 12

Water dynamics and proton translocation in cytochrome *cbb3* oxidase; insights from large scale MD simulations

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Cytochrome c oxidases (CcOs) are large membrane protein complexes found in bacteria and the mitochondria of eukaryotes. They catalyse the final step of aerobic respiration, namely the reduction of oxygen to water, and couple the redox energy to proton pumping across the membrane, thus contributing to the establishment of an electrochemical gradient that is used for ATP synthesis. Our work focuses on distinctive C-type CcOs, which are mostly present in Bacteria and exhibit a number of unique features such as high catalytic activities at low oxygen concentrations and nitric oxide reduction activity under anaerobic conditions. It has been shown that such characteristics are essential for the colonization of anoxic tissues by some human pathogens (e.g. *Campylobacter jejuni* and *Helicobacter pylori*). At the moment, the functioning mechanism of type-C CcOs is still poorly understood.

In this work we used large-scale all-atom molecular dynamics simulations and continuum electrostatic calculations to obtain atomic-level insights into the hydration and dynamics of a C-type CcO (cbb_3 from *Pseudomonas stutzeri*). We have provided a detailed analysis of the water dynamics and proton transfer pathways for both the “chemical” and “pumped” protons, and modelled the effect of mutations experimentally shown to affect the enzymatic activity. Our results contribute to a better understanding of cbb_3 mechanism and provide basis for future experimental and computational studies.