**T1: Simulating DNA from the electron to the chromosome**

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**T2: DNA confined: Advantages of Non-linear behavior**

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The nonlinear elastic properties of DNA molecules are sensitive to environment. DNA is double stranded and occasionally knotted but must open to for replication, repair, transcription and recombination. On opening the elastic persistence length changes by over two orders of magnitude. The size of many virus or phage capsids is the same as the persistence length making packing of perfect helices unreasonable. The interface between hard surfaces or proteins and nucleic acids changes the properties of DNA.. Interfaces offer large electrostatic fields and density gradients changing the local free energy surface and therefore form a challenging set of problems in current design issues. We show simple analytic models for melting temperature shifts in reasonable agreement with experiment for both DNA. Our coarse grained models describe aspects of sequence and target length dependence. Our description of phage packing includes atomic and coarse grained simulations.

**T3: The role of Protein-DNA interactions in the DNA binding specificity of hormone receptors**

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-Horrmone receptors such as the Androgen (AR) and Glococorticoid (GR) receptor bind to genomic response elements and regulate gene transcription within the cell. Both receptors bind as a homo-dimer on the same inverted repeat elements 5–AGAACA–3. However, GR fails to bind to direct repeats whereas AR forms stable enough protein-(DR)DNA complexes to allow crystallization. This different behavior, which can be regarded as a crucial key in specific regulation upon hormone binding, has been discussed to originate in differences in the protein dimer stability or dimer formation rather than in protein-DNA interaction. In the light of the large similarity of the two hormone receptor proteins and their subtle differences in specificity we are exploring which factors in protein-DNA interaction or in the protein subunit-subunit interaction allow the receptor proteins to recognize their specific site among an overwhelming number of non-specific DNA sequences. Also, neighboring effect on the DNA have been studied to show how flanking sites are essential in protein-DNA interaction. We have performed molecular dynamics (MD) simulations of direct and inverted response elements with and without presence of proteins as well as Glococorticoid receptor-DNA systems with different flanking bases. Changing the flanking site bases appears to result in a different relative positioning of the dimer-halves. Moreover, hydrogen-bond and correlation analyses show that the two receptors (Ar and GR) interact differently with the two half-sites.

**T4: Triplex forming oligonucleotides and gene therapy**

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An ever increasing number of pathological conditions have been found to have genetic components. Sometimes a single defective gene (e.g. Huntingtons’s), other times more complex multigene causes are implicated. If the cause is a non-functional gene (i.e., the protein product does not work) it might help to supply the cell with a good copy of the gene in question – gene therapy. The replacement gene construct can be contained in a plasmid, which has to be delivered to the nucleus. By decorating the plasmid in a modular way with functional groups, the machinery already present in the cell may be 'hi-jacked' to perform this delivery.

We use simulations to optimize the composition (including the use of modified nucleotides, e.g. LNA or novel bases) and sequence of triplex forming oligonucleotides (TFOs) to bind with high affinity and specificity to double stranded DNA and function as an anchor for functional groups decorating a plasmid carrying genetic material to be introduced in the nucleus. Systematic free energy calculations are applied to sets of systems with the modified nucleotides in different positions and different sequence contexts in the TFO.

**T5: From decoding dynamics to tailoring cooperativity in protein-DNA interactions**

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Protein-DNA interactions are at the core of transcriptional regulatory networks defining cellular identities. I will focus on our efforts to describe the dynamics underlying protein-DNA interactions using atomistic simulations. In particular, I will present our recent progress in deciphering dynamic mechanisms of cooperative DNA binding by transcription factors and how these may impact on cell fate decisions. Engineered transitions between different cell types have a great potential to influence future regenerative therapy approaches and are usually induced by cocktails of very few transcription factors. To design optimization strategies for such cellular processes, it is crucial to understand the mechanisms by which the transcription factors recognize DNA from both a genomic and an atomistic perspective. I will reflect on how our data and molecular simulations in general may contribute to this important biological and medical problem.

**T6: It's not all broken: Challenges and successes in modeling RNA structure, dynamics and interactions with ions.**

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RNA force fields continue to improve and provide an accurate understanding of ion-dependent conformational changes or folding, yet at the same time there are still serious limitations. We can expose these limitations by overcoming sampling problems through very large scale ensemble simulations. Exposing the limitations provides hints as to how to adapt or improve the force field as we move towards methods to more systematically test and evolve the nucleic acid force fields.

**T7: Interactions of aminoglycoside antibiotics with RNA**

*J. Trylska [1]\*,*

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Many antibiotics target bacterial ribosomal RNA by binding to its functionally important sites. One crucial site is the decoding site, which is also the binding site for aminoglycoside antibiotics. Aminoglycoside binding decreases the accuracy of decoding by affecting the mobility of two adenines taking part in the recognition of cognate tRNAs.

I would like to describe our efforts to understand (thermo)dynamics of aminoglycoside recognition by ribosomal RNA. Aminoglycoside binding site forms a flexible RNA bulge and even single point mutations change aminoglycoside affinities. We apply molecular dynamics simulations to investigate the reasons for different selectivities of aminoglycosides toward their RNA binding sites of various organisms. We also compare the binding modes of different aminoglycosides to propose aminoglycoside modifications that would enhance their affinities and reduce bacterial resistance.

**T8: Modelling allosteric effects in DNA**

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It has been increasingly appreciated that allosteric effects take place not only in proteins but also in DNA. In the recent years, several experimental works investigated DNA allostery involving small molecules, some of them prospective drugs (1,2) as well as proteins (3), but a plausible theoretical model was missing. We have proposed a theoretical framework to describe DNA allostery (4,5). Our model represents the DNA as a linear elastic system including intra-basepair and inter-basepair coordinates, and groove widths. The shape and stiffness parameters are inferred from large-scale, atomic-resolution unrestrained molecular dynamics simulations of DNA oligomers. The resulting elastic energy function then undergoes constrained minimization, with allosteric effector binding mimicked by the constraints. The assumption of quadratic (harmonic) deformation energy allows us to find an analytic solution for the minimum. The model has been used to nearly quantitatively predict various allosteric effects in DNA involving small molecules and proteins (4,5). We will briefly present the model, discuss its advantages and limitations, and show some of its applications.

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2. Tevis, D.S., ..., Wilson, W. D. (2009): Large, sequence-dependent effects on DNA conformation by minor groove binding compounds. Nucleic Acids Res. 37, 5550-5558

3. Kim, S. et al. (2013): Probing allostery through DNA. Science 339, 816-819

4. Drsata, T., ..., Lankas, F. (2014). Mechanical model of DNA allostery. J. Phys. Chem. Lett. 5, 3831-3835

5. Drsata, T., ..., Lankas, F. (2016). On the use of molecular dynamics simulations for probing allostery through DNA. Biophys. J. 110, 874-876

**T9: Computational approaches to the molecular thermometers of the human body**

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Transient receptor potential (TRP) ion channels constitute a notable family of cation channels involved in the ability of organisms to detect noxious mechanical, thermal and chemical stimuli that gives rise to the perception of pain. One of the most experimentally studied agonist of TRP channels is capsaicin, which is responsible for the burning sensation produced when chili pepper is in contact with organic tissues. Understanding how TRP channels are regulated by capsaicin and other natural products is essential to high impact pharmacological applications, particularly those related to pain treatment. By selected examples from the work we have carried out, I will provide an overview of the current knowledge we have about activation, permeation and selectivity of one of the human molecular thermometers.

**T10: Molecular simulations that put the chemical complexity into model bacterial membranes**

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All cells, whether prokaryotic or eukaryotic, are separated from the external environment by at least one membrane. These membranes provide a physical barrier to the entry of unwanted or toxic substances including drugs, into the interior of the cell. To enter the cell, drugs must either permeate through the lipid component of the bilayers, or through the proteins that are embedded within the membranes. The native membrane proteins are estimated to be the targets of > 50% of drugs.

Some drugs, including many antibiotics work by causing cell lysis through direct disruption of the cell membrane, rather than entry into the cell. Thus it is clear, that understanding the cell membranes of bacteria are imperative for the future, rational design of novel drugs, in particular antibiotics. I will present results of our recent efforts to simulate the interaction of antimicrobial peptides and other molecules such as fullerenes with the membranes of Gram-negative bacteria. I will first describe how we have constructed realistic, complex models of the membranes at two different levels of resolution, followed by a discussion of how the models are being used to understand the action of membrane-active chemical species. I will conclude with a discussion of future directions and possibilities for collaboration with experimental colleagues.

**T11: Taking advantage of membrane diversity in intracellular trafficking pathways**

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Biological membranes play an essential role in many cellular signaling pathways. Yet, because of difficulties in performing structural studies on lipid membranes, several of their molecular properties remain elusive, thus preventing to establish clear structure-function relationships.

To overcome these limitations and to elucidate the role of membrane properties in different trafficking pathways, we developed a multidisciplinary approach that combines molecular dynamics simulations with experimental measurements in vitro and in vivo.

In this talk, I will present our recent efforts to develop new experimental and computational approaches to further push forward our understanding of cellular membranes in molecular terms.

**T12: Explaining the recognition process of ice binding proteins**

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Pure water freezes at -37 °C, because the formation of ice is kinetically hindered at higher temperatures.[1] The common known property of water, freezing at 0 °C, results only from impurities in the water acting as ice nuclei. Ice nuclei are substances catalyzing the formation of ice. This phenomenon is especially significant, when water is found in small droplets, as it is in the artificial snow production and the formation of clouds in the atmosphere, where it has a huge impact on the earth’s climate.[3]

Experimental studies showed that the most efficient class of known ice nuclei are proteins. These proteins are termed ice nucleation proteins [2] and catalyze freezing of water already at higher temperatures (0 to -5 °C).

The mechanism of ice nucleation itself is poorly understood, when seen in relation to its relevance. In our studies we investigated the ice nucleation process by molecular dynamics simulations to gain insight in the underlying principle. The focus in this study was to describe the hydration properties of water molecules in the surrounding of the protein. Our study revealed that ice nucleation is facilitated, if the enthalpic interaction between water and the protein is low, and in contrast, the entropy of the surrounding water molecules is medium or high. Based on these results, we proposed a new improved mechanism for the ice nucleation process of ice nucleation proteins.

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[2] Pummer, B. G.et al. J. Atmos. Chem. Phys. 2015, 15, 4077-4091.

[3] Morris, C. E. et a. lPhys. IV France 2004, 121, 87–103.

**T13: In silico prediction of biomolecular recognition**

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I will describe recent applications of molecular modelling and Brownian [1,2] and molecular dynamics simulation methods to studying how proteins recognise and bind to their diverse binding partners. I will discuss the prediction of both specific and non-specific interactions between proteins while focusing on the effects of macromolecular crowding [3], transient interactions of chaperone proteins [4], and allosteric regulation of glycolytic enzymes [5].

[1] Martinez et al. J. Comput. Chem., (2015) 36:1631-1645

[2] Yu et al. Nucl. Acids Res., (2015) 43:W220-W22

[3] Balbo et al, Biophys. J., (2013) 104:1576-84.

[4] Nillegoda et al. Nature, (2015) 524:247–251

[5] Gdynia et al, Nat. Commun. (2016) 7: 10764

**T14: New Challenges and Opportunities in G Protein-Coupled Receptor Drug Discovery**

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G Protein-Coupled Receptors (GPCRs) remain one of the most pursued targets for drug development, and the subject of focused studies. However, much has changed in the GPCR field since I joined Dr. Gilda Loew’s Molecular Research Institute fifteen years ago. For instance, high-resolution crystal structures of GPCRs have improved our perception of receptor binding and activation, and have established new directions for understanding the molecular mechanisms underlying the diverse physiological functions mediated by these receptors. High performance computational capabilities, combined with efficiently parallelized molecular dynamics codes and/or multiscale system representations, have also improved dramatically, allowing us to reach time scales in molecular simulations that were once considered inaccessible. While these advancements have created new opportunities for rational drug discovery, they have also revealed new challenges. Taking full advantage of both high-resolution crystallographic information and powerful computational resources, my lab has most recently focused on testing enhanced, molecular dynamics-based strategies in an attempt to overcome these challenges and to contribute mechanistic details of GPCR function that are impossible or difficult to retrieve experimentally. I will provide a few examples of these approaches and their results.

**T15: Design and Discovery of Potent Enzyme Inhibitors**

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Drug discovery is being pursued through computer-aided design, synthesis, biological assaying, and crystallography. Lead identification features de novo design with the ligand growing program BOMB or docking of commercial compound libraries. The focus of this lecture will be optimization of the resultant leads to yield potent inhibitors. Specifically, Monte Carlo/free-energy perturbation (FEP) simulations are executed to identify the most promising choices for substituents on rings, heterocycles, and linking groups. The illustrated applications center on the design of inhibitors targeting HIV-1 reverse transcriptase and macrophage migration inhibitory factor. Micromolar leads have been rapidly advanced to low nanomolar or picomolar inhibitors, and numerous crystal structures for the protein-inhibitor complexes have been obtained. Development of a fluorescence polarization assay for MIF binding will also be presented. Key issues for success are considered including confidence in the structure of protein-ligand complexes, biological assays, force fields, atomic charge models, and conformational sampling.

Discovery and crystallography of bicyclic arylaminoazines as potent inhibitors of HIV 1 reverse transcriptase. Lee, W.-G.; Frey,K. M.; Gallardo-Macias, R.; Spasov, K. A.; Chan, A. H.; Anderson, K. S.; Jorgensen, W. L. Bioorg. Med. Chem. Lett. 2015, 25, 4824-4827.

Design, Synthesis, and Protein Crystallography of Biaryltriazoles as Potent Tautomerase Inhibitors of Macrophage Migration Inhibitory Factor.Dziedzic, P.; Cisneros, J. A.; Robertson, M. J.; Hare, A. A.; Danford, N. E.; Baxter, R. H. G.; Jorgensen, W. L. J. Am. Chem. Soc. 2015, 137, 2996-3003.

**T16: Rigorous Free Energy Calculations Applied to Protein Homology Models**

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One of the most prominent challenges in computer-aided drug design is the reliable and accurate prediction of protein-ligand binding affinities. Molecular dynamics based free energy perturbation (FEP) calculations are among the most suitable methods to reach this goal. Recent advancements in sampling methods and force fields coupled with modern computational resources make FEP practical in a drug design context.[1-3] However, previous FEP validation works have relied on accurate crystal structures, which are often not available in drug discovery projects. As such, the ability to apply FEP on homology models would greatly expand the domain of applicability and value of FEP in drug discovery. In this work we apply the FEP+ procedure[2] on congeneric ligand series binding to four diverse targets (Tyk2 kinase, an epigenetic bromodomain target BRD4, a transmembrane GPCR A2A, and BCL-2 family protein MCL-1) using crystal structures and homology models. Surprisingly, the performance using homology models is good, and generally on a par with the crystal structures. This can be attributed to the dynamics simulations, which allow the modeled receptor to adapt to the “real” conformation.

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[2] L. Wang, Y. Wu, Y. Deng, B. Kim, L. Pierce, G. Krilov, D. Lupyan, S. Robinson, M. K. Dahlgren, J. Greenwood, D. L. Romero, C. Masse, J. L. Knight, T. Steinbrecher, T. Beuming, W. Damm, E. Harder, W. Sherman, M. Brewer, R. Wester, M. Murcko, L. Frye, R. Farid, T. Lin, D. L. Mobley, W. L. Jorgensen, B. J. Berne, R. A. Friesner, R. Abel, J Am Chem Soc 2015, 137, 2695-2703.

[3] T. B. Steinbrecher, M. Dahlgren, D. Cappel, T. Lin, L. Wang, G. Krilov, R. Abel, R. Friesner, W. Sherman, Journal of Chemical Information and Modeling 2015, 55, 2411-2420

**T17: Supramolecular Ligands as Regulators of Biomolecular Interactions**

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The interactions of proteins with small molecules can significantly influence the functionality of systems of diverse structural complexity. Our aim is to understand these associations in order to design molecules that can modulate protein – protein interactions, among others. The combination of Molecular Dynamics simulations with Free Energy calculations and QM/MM methods allows us to predict ligand binding sites in a protein and to propose improved ligands able to reach specific protein regions of biological relevance.

Molecular tweezers (MT) act as potent hosts for positively charged residues. Experimental studies have shown that MT are promising candidates for the regulation of protein interactions.(1) In this context, we investigated the bishydrogenphosphate molecular tweezer CLR01, with amyloidogenic peptides to propose mechanisms for the inhibition of toxic aggregation by molecular tweezers.(2-3) As a key step toward the design of improved ligands we also investigated the effect of the substituents in the ability of MTs to interact with amino acids and small peptides.(4) The study of MTs with protein hosts like 14-3-3 adapter proteins, allowed us to establish general rules for predicting the relative strength and type of interaction of the tweezers with specific residues in proteins featuring several tentative binding sites.(5) Last but not least, by investigating the effect of molecular tweezers on lipid bilayers, we were able to propose a novel mechanism for viral membrane disruption by a supramolecular ligand.

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2. ACS Chem. Biol. 2015, 10, 1555–1569.

3. elife, 2015, 4:e05397

4. J. Org. Chem. 2013, 78, 6721-6734.

5. Nat. Chem. 2013, 5, 234-239.

**T18: Using an old drug to target a new drug site**

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In viral proteins, labile Zn-sites, where Zn2+ is crucial for maintaining the native protein structure but the Zn-bound cysteines are reactive, are promising drug targets. Here, we aim to (i) identify labile Zn-sites in viral proteins using guidelines established from our previous work and (ii) assess if clinically safe Zn-ejecting agents could eject Zn2+ from the predicted target site and thus inhibit viral replication. As proof-of-concept, we identified a labile Zn-site in the hepatitis C virus (HCV) NS5A protein and showed that the anti-alcoholism drug, disulfiram, could inhibit HCV replication to a similar extent as the clinically used antiviral agent, ribavirin. The discovery of a novel viral target and a new role for disulfiram in inhibiting HCV replication will enhance the therapeutic armamentarium against HCV. The strategy presented can also be applied to identify labile sites in other bacterial or viral proteins that can be targeted by disulfiram or other clinically safe Zn-ejectors.

**T19: Multi-level strategy for analysis of bioactive drug conformations**

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Computer-aided drug design (CADD) is one of the powerful tools which can be used to increase the efficiency of the drug discovery. Estimating the relative free energy of a ligand in its target-bound state (bioactive conformation) is necessary to optimize the potency of bioactive molecules and to improve the accuracy of SDBB methods. Our aim is to develop an efficient framework for finding the bioactive conformation of the flexible ligands. Since the bioactive conformation of the ligand may differ from the global minimum of the free ligand in the physiological environment, one has to evaluate the energetic cost required for adopting the bioactive conformation. A set of 100 crystal structures of pharmaceutically relevant drug-like molecules was tested using multi-level approach. We combined low-level method (LL) for sampling the conformational minima and high-level (HL) ab-initio calculations for estimating their relative stability in order to examine the conformational space of flexible ligands and to obtain the relative free energy of the conformational wells. The method was automated and tested on various ligands with different numbers of atoms, charge and rotatable bonds. The preliminary results show that it is necessary to perform Hamiltonian Replica Exchange simulations for LL method in order to explore all possible states of energy landscape of given dihedrals. Our findings suggest that the method is an effective way to improve analysis of the bioactive conformations of drug-like molecules. It is worth noting that present framework for multilevel strategy is a complex and long-term task, which requires a lot of rehearsals and implementations. Taking into account the flexible nature of molecules, protonation state and tautomeric forms, makes our task even more challenging. The proposed strategy may represent an efficient tool for predicting the conformational landscape of drugs while keeping a reasonable balance between chemical accuracy and computational cost.

**T20: Stapled diets: tackling resistance**

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A major problem with current molecular therapies is toxicity and resistance and overcoming these has proven to be largely difficult. Recent developments in understanding, technology and applications of peptides as modulators of protein-protein interactions, combining computational and experimental methods has begun to open new windows into tackling this problem and provide cause for cautious optimism.

**T21: Overview of the Classical Drude Oscillator Polarizable Force Field for Biomolecules.**

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Explicit treatment of electronic polarizability in empirical force fields offers the potential to significantly improve the accuracy of molecular simulations of macromolecules in condensed phases. Towards achieving this we have developed a polarizable force field based on the classical Drude oscillator model. Importantly the model is computationally accessible allowing for microsecond simulations of macromolecules as well as the application of enhanced sampling and free energy perturbation methodologies. Improvements in the model over the additive CHARMM36 force field on the treatment of the cooperativity of helix formation of the (AAQAA)3 peptide, on base flipping in DNA and on the interactions of ions with DNA indicates the utility of explicit treatment of electronic polarizability in a force field. An overview of the model will be presented along with ongoing developments in the force field including in the areas of nucleic acids, proteins and carbohydrates.

**T22: High-throughput, free energy based ligand discovery and optimization using multi-site λ-dynamics**

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*[2] Department of Biophysics, University of Michigan, USA*

Evaluating protein-ligand binding affinities is a central problem in computational statistical mechanics of biological molecules. While free energy simulations are well established, they are also highly computationally intensive, and limit the range and scope of systems that can be studied. Over the past decade we have developed an extended Lagrangian approach to free energy simulations called λ-dynamics, and more recently a multi-site version we term multi-site λ-dynamics. In this rigorous statistical mechanical framework the system of interest “evolves” dynamically in the space of chemical substituents of interest and thus significantly enhances the efficiency of the search problem and convergence of the overall free energy calculations. Moreover, within this formalism, we introduce biases that represent the solvation component of the relevant thermodynamic cycle, and thereby directly simulate ligand binding competition experiments, from which we directly evaluate relative binding affinity for large families of ligands. I will describe the extended Lagrangian methodology and illustrate it in the context of large-scale ligand screening calculations. Generalizations to permit both sequence-based resistant mutations and ligand affinities will be described.

**T23: Hybrid Particle-Field Approach with Electrostatics for Mesoscale Biomolecular Simulations**

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Recent developments on hybrid particle-field approach where Molecular Dynamics is combined with Self Consistent Field theory (MD-SCF)[1] have proven to be efficient in exploring large spatial and temporal scales for systems in the condensed phase at molecular resolution. Unlike typical coarse grain (CG) Hamiltonians, which are based on pairwise interaction potentials, MD-SCF computes the energy of the system of interest as a functional of the particle density. Implementation of grid computation methods allows quasi-linear scaling and minimal use of node-communication, making MD-SCF simulations intrinsically faster than particle-based conventional approaches[2].

The extension of the MD-SCF method with explicit treatment of electrostatic interactions has been introduced very recently[3]. Like in density field, the charged molecules are interacting with the external charge field that depends on the distribution of charge densities. This method has been successfully implemented in both serial and parallel versions of the OCCAM code[4]. This approach is currently being extended to the field treatment of electrostatic multipole densities. The accuracy of the method is tested for a set of prototypic polyelectrolyte multiphase systems, monitoring both bulk and interface properties. An advantage for biomolecular systems is the integration of MD-SCF approaches to CG models for biopolymers where electrostatic features are mapped by topological multipolar reconstruction [5]. This proposed approach is general and can be used to simulate diverse complex multiphase systems (i.e. polymers, membranes, proteins, nucleic acids) beyond the time- and length-scales affordable today.

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[2] A. De Nicola et al., J Chem Theory Comput, 10, 5651 (2014).

[3] You-Liang Zhu et al., (submitted)

[4] http://www.smms.unisa.it/occam

[5] M. Cascella et al., J Chem Theory Comput, 4, 1378 (2008); D. Alemani et al., J Chem Theory Comput, 6, 315 (2010).

**T24: Molecular Integration Simulation Toolkit - interfacing novel integrators with Molecular Dynamics codes.**

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Modern production Molecular Dynamics codes represent a significant investment of effort by the community to develop highly optimised force evaluation routines able to take advantage of state-of-the art hardware such as GPUs and multi-core CPUs. However, this comes at a cost of code complexity which makes it hard for new integration algorithms to be implemented in these packages. This creates a catch-22 for algorithm developement - if new algorithms cannot be implemented and tested in production codes it may be impossible to demonstrate their benefits over existing schemes; conversely, if the community cannot see the benefit of new algorithms, code developers will not spent time implementing them!

The Molecular Integration Simulation Toolkit (MIST) library is a solution to this problem by providing plug-ins to existing optimised MD codes, coupled with a simple interface for the development of new integration methods. MIST currently provides interfaces to GROMACS, Amber and NAMD-Lite, allowing it to benefit from OpenMP and GPU acceleration for force-evaluation. Several standard (Verlet, Leapfrog) and new (Langevin Dynamics based on a BAOAB splitting) integrators have been implemented to date. The MIST library interface results in significant ease-of-development, at negligible loss of performance. New integration algorithms are implemented once, in a code-agnostic manner, and can then be immediately deployed in all the MD codes supported by MIST.

As well as algorithms for sampling the canonical and micro-canonical ensembles, MIST is also a platform for building more advanced schemes. For example, we have implemented an extended-system method for 'Continuous Tempering', which enables computation of free energy maps in systems with large energy barriers.

Several new features are under development in MIST - new constraint solvers for extremely long timesteps and multi-timestep splittings, MPI parallelisation, and support for more MD codes. We welcome the community's input on direction for future development.

**T25: Computational Protein Design with an MMGBSA Energy Function**

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Protein design aims at conceiving new proteins or modifying existing ones to obtain a given function. Computational approaches are a valuable help for protein design, to rationalize the predictions and guide the experimental tests. Computational protein design (CPD) has sparked important methodological efforts and obtained spectacular successes such as the creation of a protein with a new fold or enzyme active site engineering. The main difficulty of CPD lies in the astronomical number of possible sequences and conformations, of the order of (20x10)^100 for a protein with 100 amino acids. Another key element for CPD success is the energy function used to evaluate and select the sequences and conformations.

Our approach of CPD is based on an atomic model of the protein structure and a molecular mechanics energy function. An important aspect is the solvent treatment, represented as a dielectric continuum with a Generalized-Born term, supplemented by a term proportional to the solvent accessible surface area. The key elements of our implementation are: 1) the protein backbone is maintained fixed, 2) the side-chain conformational space is reduced to a discrete library of rotamers, 3) the energy function is decomposed into interaction pairs. The first step consists in calculating a matrix of interactions between each pair of rotamers. In the next step, the sequence-conformation space is explored with an optimization algorithm. Energy evaluations in this second step are fast thanks to the pre-calculation of the energy matrix. The implementation of our CPD procedure will first be discussed. Then, applications to the prediction of side-chain conformations and to the design of protein sequences will be presented.

**T26: Development and acceleration of multiscale QM/MM methods for simulations of complex biomolecular systems**

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The quantum mechanical and molecular mechanical (QM/MM) methods have been an important tool in theoretical studies of enzymatic reactions in solvated environments. However, because of complexity of underlying QM algorithms, development of efficient and parallel QM/MM methods has lagged behind the development of parallel MM simulation algorithms. This resulted in the length of typical QM/MM molecular dynamics (MD) simulations to be a few hundreds of picoseconds or less, which is relatively too short for accurate determination of free energies and reaction rates. This also limited severely their use in performing long-time MD simulations, utilizing high performance supercomputers based on multi-core CPU architectures. To enable long time scale QM/MM molecular dynamics simulations, my lab has been developing novel multiscale QM/MM methods that are equipped with efficient and scalable QM/MM methods and integrated with advanced free energy simulation methods, such as the string method. The developed methods include the stable and parallel semiempirical QM/MM methods, which are based on MPI and hybrid OpenMP/MPI parallelizations and robust SCF convergence accelerators, and the QM/MM-PME method for efficient determination of long-range QM-MM electrostatic interactions under periodic boundary conditions. Further, these methods are combined with ab initio/DFT QM/MM methods and multiple time step algorithm for enhanced accuracy and efficiency of the AI-QM/MM potentials. With these methods, we are able to achieve about one order of speed-up relative to the speed of conventional QM/MM methods. In this presentation, the current status of each method is presented, and their application to protein kinase systems is briefly discussed, together with future direction to improve their efficiency.

**T27: Aluminum and Bioligand interactions with phosphate containing groups.**

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The increased availability of aluminum in biological environments, due to human intervention in the last century, raises concerns on the effects that this so far "excluded from biology" metal might have on living organisms. Consequently, the bioinorganic chemistry of aluminum has emerged as a very active field of research. However, the experimental determination of structure and affinities of Aluminum-Bioligand complexes is not without difficulties and theoretical methods have emerged as a fundamental tool to unveil aluminum biochemistry. In the present talk I will review some of the recent advances made by our group on this field. In particular we will focus on Aluminum interactions with phosphate-containing biomolecules using a variety of methods, DFT, QM/MM and classical molecular dynamic simulations.

**T28: Structural dynamics and signalling mechanisms in nuclear retinoid receptors**

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Nuclear Retinoic Acid receptors (RARs) are ligand-dependent transcriptional regulators that form heterodimers with Retinoid X receptors (RXRs). They mediate the effects of retinoic acid (RA), the active metabolite of Vitamin A, and regulate essential physiological processes such as embryonic development, organogenesis, homeostasis, vision, immune functions and reproduction. The regulation of RARs occurs through the binding of retinoic acid (RA) to the ligand binding domain (LBD), which triggers conformational changes in the receptor that lead to the formation of interfaces for the binding of co-activator proteins. Aside from this classical mechanism of ligand-triggered nuclear receptor activation, recent studies showed that RARs and RXRs are complex allosteric modulators and that their activity can be fine-tuned by different post-translational modifications, in particular, by phosphorylation.

Structural information concerning the molecular mechanism underlying RAR’s response to RA has been collected largely by studies of the LBD. Although structural snapshots of essential structures along the regulation pathway of NRs have been obtained largely by crystallographic studies of the LBD, regulation is also linked to changes in the receptor dynamics, as well as to subtle changes in conformer populations. The characterization of these structural dynamical effects is crucial to our understanding of the allosteric mechanisms occurring in these receptors.

Here we use molecular dynamics simulations to study the changes in receptor structure and dynamics that occur upon phosphorylation and how these changes may affect the binding affinity for different co-regulatory proteins. In particular, we studied two phosphorylation events that occur in RAR as a consequence of the action of RA. The first concerns the phosphorylation of the RAR LBD and the second that of the receptor’s N-terminal domain (NTD). The molecular details afforded by these simulations allow us to not only understand the structural changes that occur upon phosphorylation and how these changes may affect the binding affinity for different co-regulatory proteins, but also to understand allosteric communication related to phosphorylation of nuclear receptors and to identify key residues involved in this process.

**T29: An unusual allosteric mechanism for regulating protein interactions of Syk tyrosine kinase**

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The phosphorylation of a linker region between two tandem SH2 domains of Syk tyrosine kinase regulates the binding affinity for Syk association with membrane receptors; affinity for receptor mediated by the Syk SH2 domains decreases 100-fold upon phosphorylation of the remote tyrosine site on linker A. The mechanism of this allosteric regulation has been suggested to be a switch from a high affinity bifunctional binding, mediated through both SH2 domains binding two phosphotyrosine residues, to a substantially lower affinity binding of only one SH2 domain. Nonetheless, this postulated switch to a single-SH2-domain binding mode was refuted by NMR experiments. With the residue-level power of NMR, we determined that phosphorylation affects an isomerization step of bifunctional binding. Molecular dynamics simulations were exploited to explore the conformational effects associated with linker A phosphorylation and thus gain physical insight into the isomerization process. The results were indeed illuminating. The domain structure of the tandem SH2 domains is strongly perturbed by phosphorylation. Moreover, numerous electrostatic interactions between domains, previously unknown to be involved in regulation, are perturbed upon phosphorylation and predicted to be the basis for regulation.

**T30: Understanding Charge Transfer in Cryptochromes and Photolyases via QM/MM Simulations: Application to PhrB Protein**

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Cryptochrome and Photolyase represent a ubiquitous family of flavoprotein photoreceptors. While the former is involved in plant growth, animal circadian rythm or perception of the Earth’s magnetic field, the latter participates to DNA repair by oxidizing CPD (cyclobutane pyrimidine dimers) or 6-4 photoproducts. After excitation of a FAD (flavin adenine dinucleotide) cofactor, an electron transfer (ET) occurs between the protein surface and the flavin through a chain of several aromatic residues. A widely conserved tryptophan triad has been identified but tyrosine or a fourth residue can be sometimes involved in the ET.

Recently, many QM/MM simulations were performed to understand the mechanism of this long range electron transfer. A common issue consists of the localization of the electron along the pathway and the definition of the different redox states. Cailliez et al propose protocols based on classical MDs coupled to constrained DFT calculations. In our group, we follow another strategy based on the electronic propagation between the different molecules, efficient for the fast ETs observed in these proteins. Both strategies provide elegant conclusions and highlight the mechanism nature of the ET, the role of different residues, the existence of alternative pathways or the importance of the solvent.

We currently focus on a prokaryotic (6-4) photolyase, the PhrB protein. It presents some particularities such as a Fe-S cluster or a tyrosine as the first residue of the triad. Directed mutagenesis experiments have shown that mutation of this tyrosine to phenylalanine does not affect flavin reduction while mutations of others residues from the triad or not modify the ET and the DNA repair activity. We studied this system using a coupling between long classical and short electronic simulations at DFTB level. Our results give a molecular insight of the effects of these different mutations.

**T31: Norovirus Capsid Assembly**

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Noroviruses are small non-enveloped viruses with single-stranded positive sense RNA. They are the leading cause of acute viral gastroenteritis in humans and animals and are of world significance for health. The Capsid is composed of 180 copies of a single structural protein VP1 consists of two main domains: the shell domain (S) and the protruding domain (P) which contains two subdomains (P1 and P2). The P domain is the part exposed to the biological environment, it allows in particular to stabilize and adjust the size of the capsid. The S domain is, meanwhile, the assembly module of viral capsid.

Our lab and others have shown experimentally that Norovirus capsids can be disassembled and reassembled in vitro according to the pH of the medium (high pH = disassembled, low pH = reassembled). The assembly process begins with VP1 dimers which quickly produce intermediates of 10~11 dimers which then slowly assemble themselves to capsids.

Using computational approaches such as homology modelling, simulated annealing, molecular dynamics simulations in all atom and coarse grain systems, we are looking to extend theses kinetic studies on human norovirus and thus to determine the molecular basis of norovirus capsid assembly.

Our first results extend previous studies already achieved in the team. Theses results show that the deprotonated form of the N-terminal arm establishes many salt bridges and allow its stabilization on the S domain. Our new SAXS experiments show that at high pH the dimer is in a quite extended form and very different from the crystallographic structure. Thanks to modelisation and molecular dynamics tools we have developed a model that fits the experimental SAXS data. Our results indicate that pH and protonation state have a major role in the first step of assembly : Dimer to intermediate.