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FACULTY OF SCIENCES

Symposium in Honor of Tim Clark's 70th Birthday

April 11th, 2019
University of Erlangen-Nuremberg
Chemikum, Nikolaus-Fiebiger-Strasse 10,
91058 Erlangen

ZISC Zentralinstitut SCIENTIFIC COMPUTING

MGMS molecular graphics modelling society

SYMPOSIUM IN HONOR OF TIM CLARK'S 70TH BIRTHDAY

Thursday, April 11th 2019

08:50-09:00	**Welcome**
09:00-09:45	**K1: Francesco Gervasio (London, UK)** Modelling ligand binding and allostery in kinases and GPCRs with enhanced-sampling algorithms
09:45-10:05	**L1: Christof Jäger (Nottingham, UK)** Reaction control in radical SAM enzymes: how nature plays with radical and redox reactivity
10:05-10:50	**K2: Stefan Kast (Dortmund, Germany)** From macroscopic to local molecular thermodynamics
10:50-11:20	**Coffee Break**
11:20-11:40	**L2: Hakan Kayı (Ankara, Turkey)** Design of the tellurium-containing semiconducting polymers
11:40-12:25	**K3: Peter Hildebrand (Leipzig, Germany)** Role of structural dynamics for GPCR signaling
12:25-13:30	**Lunch**
13:30-14:15	**K4: Holger Gohlke (Düsseldorf, Germany)** What to gain from protein statics
14:15-14:35	**L3: Johannes Margraf (München, Germany)** Correlation energy densities from coupled cluster theory
14:35-14:55	**L4: Pavlo Dral (Mülheim, Germany)** The ODMx methods: new consistent semiempirical methods
14:55-15:30	**Coffee Break**
15:30-16:15	**K5: Jon Essex (Southampton, UK)** The role of water in mediating biomolecular binding: from water locations to their impact on binding affinity
16:15-17:00	**Surprise, Surprise!**
17:00	**Closing remarks**

Modelling ligand binding and allostery in kinases and GPCRs with enhanced-sampling algorithms

Francesco L. Gervasio

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Allosteric regulation plays a fundamental role in biology. In signalling proteins such as protein kinases and G protein-coupled receptors (GPCRs), ligand binding to allosteric sites are able to up- or down-regulate the catalytic activity and activate downstream signalling cascades. Understanding the molecular mechanisms underlying the observed allosteric effects is of great importance for the rational design of novel biologically active allosteric regulators. One major challenge and opportunity in computational chemistry is the accurate description of the conformational landscape prior to and upon the binding of the allosteric regulator. To this aim we have developed, tested and successfully applied various enhanced sampling algorithms (based on Metadynamics and/or Hamiltonian replica exchange) together with atomistic simulations. Here we show how these methods were successfully used to compute complex conformational landscapes associated with kinase and GPCR activation and predict how they change in response to ligand binding and post-translational modifications.[1-8] We also show how atomistic simulations were used to reveal a previously unknown catalytic activity of glutamine synthetase.[9]

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Reaction control in radical SAM enzymes: How nature plays with radical and redox reactivity

Christian Suess[1], Floriane L. Martins[1], Samuel Gaughan[1,2], Jonathan Hirst[1,2], Anna K. Croft[1] and Christof M. Jäger[1]

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How enzymes have developed to catalyse and control specific reactions is one of the most complex questions necessary to understand in order to be able to rationally influence enzyme activity and selectivity for medicinal and biotechnological applications. Intriguingly interesting in this concept are enzymes that need to control highly reactive intermediates that tend to undergo rapid stabilising side reactions, like radicals.

Radical *S*-adenosylmethionine (SAM) dependent enzymes [1] share the communality to initiate radical intermediates vie hydrogen abstraction reactions controlled by SAM and the redox chemistry associated with central iron sulfur clusters. They are perfectly designed to control these highly reactive intermediates in order to facilitate and drive the desired reaction involved in number of biosynthetic pathways towards anti-viral, anti-cancer and antibiotic products. [2]

Complex radical ring rearrangements like in the example of 7-carboxy-7-deazaguanine (CDG) synthase (QueE) [3] are a particular speciality of rSAM enzymes and we recently demonstrated how these rearrangements need to be fine-tuned by controlling the thermodynamics of the central radical clock reaction. [4] Here, we show how the enzymes control the reactivity of the radical rearrangement and how efficient computational assessment of thermodynamic reaction profiles through calculating radical stabilization energies (RSEs) [5] of key intermediates from simulation ensembles can be used for screening for alternative substrates and designing radical enzymes with improved substrate range and turnover.

A second key influencing parameter for many examples in enzyme catalysis is the internal electrostatic field in the enzyme active site, often referred to as electrostatic preorganization. [6] Recently Shaik *et al.* [7] and others demonstrated how externally orientated electric fields can influence biocatalytic reaction rates by orders of magnitude. Hydrogen abstraction reactions and effects on the reactivity of metal clusters in enzymes, both important in radical SAM enzyme catalysis, are prone to be highly influenced by changes in the surrounding electrostatic field. Along similar lines to the example of QueE, we will discuss very recent investigations on the role of orientated electric fields at different stages of rSAM enzyme catalysis.

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From macroscopic to local molecular thermodynamics

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Molecular thermodynamics reflects the driving forces governing chemical processes, accounting for direct and solvent-mediated interactions and entropic contributions, where the latter originates from both structural flexibility and solvent degrees of freedom. By definition, thermodynamics is a macroscopic approach to molecular energetics as a large number of atomic degrees of freedom or energy states leads to a small number of thermodynamic quantities that can be measured experimentally; this is the domain of statistical thermodynamics. From a predictive perspective, two approaches are available to tackle the problem, molecular simulations (molecular dynamics or Monte-Carlo) and, with special emphasis on solvation features, liquid state theory. Both depend on knowledge of intra-solute and –solvent and solute-solvent interactions which can be determined from force fields or quantum-chemical calculations. In this context, the question arises whether these macroscopic thermodynamic features can be mapped to *local*, i.e. atom or group based components that would allow for an analysis of the impact of local changes on macroscopic data, a key feature of molecular design.

In this talk, the perspective of liquid state theory, more specifically the integral equation approach known as 3D RISM (reference interaction site model) theory is outlined for the prediction of thermodynamic quantities and their localization. Starting with the basic elements and practically useful approximations, it will be demonstrated that predictive models can be developed by combining 3D RISM with quantum chemistry in the form of the embedded cluster (EC-)RISM method [1-3]. Following-up on these benchmarks, physically sound localization methods are outlined and discussed. In particular, a local picture of hydration thermodynamics is developed which can be utilized for drug discovery [4], the energetic and entropic components of solvation thermodynamics are analyzed [5], and preliminary results are presented for the localization of binding free energies in host-guest complexes [6]. The talk concludes with a perspective on exploiting local thermodynamics in the context of machine learning for addressing the molecular design challenge.

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Design of the tellurium-containing semiconducting polymers

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A series of donor-acceptor-donor (D-A-D) type semiconducting polymers containing tellurium atom in their acceptor units were designed and their structural and electronic properties were investigated by using density functional theory (DFT). Energy levels for highest occupied molecular orbitals and lowest unoccupied molecular orbitals were calculated, and then the electronic band gap values, which directly affects the electronic properties of the semiconducting polymers, were obtained for all the systems being investigated. The results of our investigations implied that the use of tellurium atoms in the acceptor units significantly decreases the electronic band gap which results with providing superior conducting properties to these polymers. Due to their superior electronic properties, these polymers may find important applications, such as in photovoltaic and electrochromic devices. During the study, we performed all DFT calculations by using Becke three-parameter hybrid exchange-correlation functional combined with Lee-Yang-Parr correlation functional and the LANL2DZ basis set.

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Role of structural dynamics for GPCR signaling

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G Protein coupled receptors (GPCRs) are one of the most heavily investigated drug targets in the pharmaceutical industry covering different pathological areas including cancer, cardiovascular disorders, diabetes, central nervous system disorders, obesity, inflammation, and pain. A present key interest of the pharmaceutical industry is to design GPCR-targeted drugs with improved specificity and reduced side effects. This is challenging as one and the same receptor can activate different intracellular downstream signalling proteins such as heterotrimeric G proteins ($G\alpha\beta\gamma$, α-families Gi, Gs, Gq, G12/13) or arrestins (arrestin 1–4), resulting in different (either wanted or unwanted) cellular and physiological responses. Understanding the molecular mechanism of this coupling promiscuity is thus a major question in current receptor research.

I will summarize our attempts to elucidate coupling specificity in G protein coupled receptor signalling using molecular dynamics simulations referencing related experimental work. According to our knowledge based concept, structural flexibility plays a key role in specific recognition and binding of G proteins to active receptors. Our concept of receptor G protein coupling specificity may pave the way for novel concepts and approaches to develop drugs with limited side effects. Computer simulations are available through web-services developed in my laboratory using innovative approaches for interactive visualisation of even huge amounts of data.

What to gain from protein statics

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G-protein coupled receptors (GPCR) serve as relays for recognizing signals outside the cell, which are transmitted through the membrane to initiate cellular signaling cascades. Their diverse physiological responses in living cells established GPCRs as important drug targets. Binding of extracellular modulators either induce, inhibit, or alter the activation of GPCRs by stimulating different signaling pathways. However, despite increasing structural information of GPCRs, complemented by intensive computational studies, a detailed knowledge of the signaling mechanisms in GPCRs has remained elusive.

Recently, we introduced a rigorous approximation of vibrational entropy changes upon ligand binding based on analyzing constraint network representations (1) of biomolecular complexes.(2) We also formulated an ensemble- and rigidity theory-based free energy perturbation approach to analyze dynamic allostery.(3) In this work, we apply these methodologies, first, to analyze how different extracellular modulators affect signaling of the GPCRs β_2 adrenoreceptor (β2AR) and μ-opioid receptor (MOR). Based on altered stability characteristics of the GPCRs, our approaches allow discriminating between agonist, antagonist, and inverse agonist binding and reveal different pathways of connected residues in both β2AR and MOR depending on the type of extracellular modulator. Second, we investigate why the human histamine H_4 receptor (hH_4R) shows a high degree of constitutive activity in contrast to mouse H_4R (mH_4R). By sequence comparison, molecular dynamics simulations, and rigidity analyses, we identify, and experimentally validate, residues in the extracellular loop 2 region of hH_4R that apparently mimic agonist binding and, thus, lead to basal activity.

Overall, our results shed new light on signaling mechanisms in GPCRs at an atomistic level and demonstrate that the rigidity theory-based analysis of dynamic allostery provides a computationally cheap, yet information-rich, way to scrutinize the role of ligands and sequence variations for GPCR signaling.

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Correlation Energy Densities from Coupled Cluster Theory

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(Semi-)local density functional approximations (DFAs) are the workhorse electronic structure methods in condensed matter theory and surface science. Central to defining such DFAs is the exchange-correlation energy density e_{xc}, a spatial function that yields the exchange-correlation energy E_{xc} upon integration.

Unlike E_{xc}, e_{xc} is not uniquely defined. Indeed, there are infinitely many functions that integrate to the correct E_{xc} for a given electron density ρ. The challenge for constructing a useful DFA is to find a systematic connection between ρ and ε_{xc}. While several empirical and rigorous approaches to this problem are known, there has been little innovation with respect to the fundamental functional forms of DFAs in recent years.

Herein, we discuss a less explored route to constructing DFAs. Specifically, a recipe for deriving e_{xc} directly from many-body wavefunctions is presented. The corresponding energy densities are analyzed and (semi-)local approximations are presented. The extension to non-local DFAs will be discussed.

The ODM*x* Methods: New Consistent Semiempirical Methods

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Recently we have introduced two new NDDO-based semiempirical quantum-chemical (SQC) methods ODM2 and ODM3 (ODM*x*), which include orthogonalization and dispersion corrections along with penetration integrals and core–valence interactions as integral parts.[1] These corrections are important for improving the underlying NDDO model[2] and for obtaining more accurate SQC methods.[3-4] The ODM*x* methods build upon the NDDO-based SQC methods OM*x*[3] with D3-dispersion corrections including three-body terms for Axilrod–Teller–Muto dispersion interactions (D3T). In the new methods, the historical convention of assuming that the SCF atomization energy is equal to the atomization enthalpy at 298 K is abandoned. In addition, the ODM*x* methods are parametrized not only with regard to ground-state properties, but also vertical excitation energies, because of the frequent use of general-purpose SQC methods for excited-state calculations and dynamics simulations.

Mean Absolute Errors

		MNDO	OM2	OM2-D3T	ODM2
Heats of formation (CHNO set)	kcal/mol	6.36	3.05	5.10	2.64
Noncovalent interaction energies (S66x8 set)	kcal/mol	9.48	1.93	0.79	0.75
Vertical excitation energies (Thiel's set)	eV	1.11	0.46	0.46	0.35
Atomization energies w/o ZPVE at 0 K (TAE140 set)	kcal/mol	20.13	14.93	14.27	4.89
corrected		11.90	4.81	4.64	

The ODMx methods perform consistently better than other SQC methods for a broad range of properties ranging from ground-state to excited-state properties and noncovalent interactions. They manifest the successes in SQC method improvement since 1977, when the first successful general-purpose SQC method MNDO was introduced.

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The role of water in mediating biomolecular binding: from water locations to their impact on binding affinity

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Water plays an intimate role in protein-ligand binding, not only through solvation/desolvation effects, but more subtly through the formation of direct interactions between the protein and ligand in the binding site. The targeting of bound water molecules for displacement as part of ligand optimization is a long invoked paradigm based around the release of configurational entropy, but there are many examples where displacing water leads to a loss in ligand binding affinity. Quantitatively accurate approaches to address this problem are arguable inadequate – water displacement and ligand interactions are intimately related and difficult to disentangle both experimentally and, hitherto, computationally.

We have a long-standing interest in developing and using Grand Canonical Monte Carlo (GCMC) simulation approaches to explore water binding in protein-ligand systems. Through GCMC we are able to locate water molecules with good accuracy when compared against crystal structures. More significantly, the simulations clearly demonstrate the important role of water cooperativity; the mutual stabilization of water molecules means that individual water molecules cannot always be considered in isolation, but rather as part of a network.

GCMC allows water binding sites and network binding free energies to be simultaneously calculated. In addition, by combining GCMC with alchemical perturbations of the ligand, networks of bound water molecules are able to adapt and maintain equilibrium with bulk water as the perturbation proceeds. Furthermore, the ability to extract active-site hydration free energies allows the deconvolution of protein-ligand binding free energies into separate protein- and water-mediated components, thereby providing rich, additional detail to the structure-activity relationship (SAR).

In this presentation, our underlying methodology GCMC methodology will be described, together with examples of its application to water placement, binding free energy calculations, and protein-ligand affinity prediction.

Surprise, Surprise!

NOTES

Congratulations!

1995

1996

1997

1970-1980?

2012

2006