FROM COMPUTATIONAL BIOPHYSICS TO SYSTEMS BIOLOGY

MAY 23-25, 2016 Beytepe – Ankara/ TURKEY

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CONFERENCE PROGRAM

Monday May 23, 2016

8:30 – 9:00	Register at Mehmet Akif Ersoy Hall

Morning Session:

9:00 – 9:30	Alexander Schug (Invited Talk) Protein and RNA structure prediction by integration of co-evolutionary information into molecular simulation
9:30 – 10:00	Sebastian Kmiecik (Invited Talk) CABS-dock web server for protein-peptide docking with significant structural flexibility
10:00 – 10:30	Break
10:30 – 11:00	Turgut Başтuğ (Invited Talk) Recent developments in calculation of free energies in biological systems
11:00 – 11:30	Maciej Blaszczyk (CBSB2016 Outstanding Young Researcher) Modeling of protein–peptide interactions using the CABS-dock web server for binding site search and flexible docking
11:30 – 12:00	Panel Discussion
12:00 – 13:30	Lunch

Afternoon Session:

13:30 – 14:00	Wolfhard Janke (Invited Talk) Knots as Stable Order Parameter for Semiflexible Polymers
14:00 – 14:30	Giovanni La Penna (Invited Talk) Probing copper catalysis in biology with multiple simulations
14:30 – 15:00	Break

15:00 – 15:30	Şahin Büyükdağlı (Invited Talk)
	Electrostatic interactions in polymer translocation through nanopores
15:30 – 16:00	Bogdan Lesyng (Invited Talk)
	Simulations and analysis of fret processes in (bio)molecular systems using a QM-MD approach
16:00 – 16:20	Murat Çavuş (Contributed Talk)
	Free energy calculation for navab channel with no equilibrium requirement
16:20 – 16:50	Panel Discussion
16:50 – 18:00	Poster Session

Tuesday May 24, 2016

Morning Session:

9:00 – 9:30	Canan Atılgan (Invited Talk)
	Molecular level strategies for the assesment of drug resistance in bacteria
9:30 – 10:00	Adam Sieradzan (Invited Talk)
	What make tellomers unique?
10:00 – 10:30	Break
10:30 – 11:00	Haleh Abdizadeh (CBSB2016 Outstanding Young Researcher)
	Multiple computational approaches disclose principles underlying human serum transferrin functioning
11:00 – 11:30	Sofia Piepoli (CBSB2016 Outstanding Young Researcher)
	Analysis on target specific transcription activator-like effectors by perturbation-response scanning and free energy calculations
11:30 – 12:00	Panel Discussion
12:00 – 13:30	Lunch

Afternoon Session:

13:30 – 14:00	Franklin Hays (Invited Talk)
	Imatinib binding to human c-Src is coupled to inter-domain allostery and suggests a novel kinase inhibition strategy
14:00 –14:30	M. Wiśniewska (CBSB2016 Outstanding Young Researcher)
	Hydration effects in protein kinanes
14:30 – 15:00	Break
15:00 – 15:30	Caroline Ross (CBSB2016 Outstanding Young Researcher)
	Structural-based prediction of novel linear b-cell epitopes in picornaviruses
15:30 – 15:50	Tandaç F. Güçlü (Contributed Talk)
	Centrality of residues and redundancies in their communication explain the distruptive mutations in DHFR
15:50 – 16:10	Gökşin Liu (Contributed Talk)
	Iron and synergistic anion binding specificity of haemophilus influenzea ferric binding protein
16:10 – 16:40	Panel Discussion
19:00 – 21:00	Conference dinner at Beyaz Ev

Wednesday May 25, 2016

Morning Session:

9:00 – 9:30	Ulrich H.E. Hansmann (Invited Talk) Generalized-Ensemble Sampling and Modeling of Protein Aggregation
9:30 – 10:00	Emre Taşcı (Invited Talk) Going from bottom to top and relating the intermediates: Applications of computational group theory
10:00 – 10:30	Break
10:30 – 10:50	Emine Deniz Tekin (Contributed Talk) Self-assembled peptide amphiphiles with molecular dynamics simulations
10:50 – 11:10	Meral Eryürek (Contributed Talk) Microcanonical molecular dynamics study of melting of small Pt clusters
11:10 – 11:30	Parting Words

Conference ends

INVITED TALKS

MOLECULAR LEVEL STRATEGIES FOR THE ASSESSMENT OF DRUG RESISTANCE IN BACTERIA

H. ABDIZADEH, O. ACAR, T.F. GUCLU, Y.T. TAMER, T. ALTINUSAK BATUR, E. TOPRAK,* A.R. ATILGAN, C. ATILGAN*

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**University of Texas Southwestern Medical Center, Green Center for Systems Biology, Dallas, USA*

We investigate structural features of mutants of a protein that allow survival at organism level under evolutionary pressure, using dihydrofolatereductase (DHFR) exposed to the antibiotic trimethoprim (TMP), as case study. The effects of dynamics and thermodynamics are assessed through a combination of computational approaches and experimental measurements. Binding constants and catalytic activities of different mutants provide conflicting results, implying alternative routes towards conferring drug resistance. We resolve the dilemma by executing extensive molecular dynamics simulations for mutants in their folate or TMP bound forms. To understand if molecules displaying competitive binding are discriminated by binding probabilities, we further perform alchemical free energy perturbation calculations. We relate $\Delta\Delta G$ values to the changes in K_m/K_i ratios. A trade-off between stability and enzymatic efficiency is revealed: Mutants having increased relative affinity for TMP compensate for the additional inhibition via increased catalytic rates. We scrutinize mutant conformations and disclose structural features of survivor DHFRs.

RECENT DEVELOPMENTS IN CALCULATION OF FREE ENERGIES IN BIOLOGICAL SYSTEMS

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In recent years, impressive advances have been made in the *calculation* of *free energies* in chemical and *biological systems, and the ultimate goal of chemical accuracy have been realized in many cases.* Examples include ion channels and transporters in membranes which we have studied extensively over the years. Almost all the free energy calculations we have carried out so far involve simulation methods tailored specifically for systems at equilibrium. I will present some methodologies used in such equilibrium free energy calculations, and will also discuss how well the calculations were able to reproduce experimental free energies. I will also present non-equilibrium free energy methods such as Jarzynski equality and Crooks theorem. The Jarzynski equality was devised for free energy calculations in non-equilibrium systems. We showed previously that it did not work well for complex biological systems. On the other hand, there are other non-equilibrium free energy calculation schemes for non-equilibrium systems such as the Crooks method. These theoretical schemes have not yet been applied to biological systems. In this presentation, I will show free energy results for biological systems obtained from molecular dynamics simulations using Crooks theorem. In contrast to Jarzynski equality, the Crooks method appears to work well for biomolecular systems. Similar results are obtained for free energies as in the case of equilibrium methods, which establishes its accuracy in complex biological systems. Compared to the equilibrium methods, the Crooks method is both simpler to use and converges faster. Thus the Crooks method has the potential to replace the traditional free energy methods such as the free energy perturbation and thermodynamic integration.

ELECTROSTATIC INTERACTIONS IN POLYMER TRANSLOCATION THROUGH NANOPORES

SAHIN BUYUKDAGLI

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Electrostatic interactions between charged macromolecules and ions are omnipresent in various nanoscale systems. From the charge and polymer selectivity of biological and artificial membrane nanopores to the functioning of nanofluidic devices, charge interactions are at the heart of many biological and industrial processes. In the first part of the talk, I will present a beyond-mean-field transport theory that aims at characterizing ionic and polymer transport properties of membrane nanopores in physical conditions where mean-field electrostatics breaks down. By comparison with ion transport experiments, I will first show that the low ionic conductivity of open a-Hemolysin pores can be quantitatively explained by the presence of surface polarization effects. Upon the penetration of a DNA molecule into the pore, these polarization forces combined with the electroneutrality of DNA sets a lower boundary for the ionic current, explaining the weak salt dependence of blocked pore conductivities observed at dilute ion concentrations. The addition of multivalent counterions into the solution will be shown to result in the reversal of the DNA charge and the direction of the electroosmotic flow. With trivalent spermidine or quadrivalent spermine molecules, the charge inversion is strong enough to stop the translocation of the DNA molecule and to reverse its motion. This mechanism can be used efficiently to improve the accuracy of translocation-based sequencing methods by maximizing the duration of DNA translocation events. Next, I will consider hydrodynamically driven polymer translocation through nanopores. It will be shown that due to electrostatic fluctuation effects, DNA translocation events are accompanied with the inversion of the sign of the ionic current through the nanopore, an effect previously observed in nanofluidic experiments.. I will conclude by presenting a brief summary of open questions in the theoretical modeling of confined liquids.

GENERALIZED-ENSEMBLE SAMPLING AND MODELING OF PROTEIN AGGREGATION

U.H.E. Hansmann

The University of Oklahoma, Department of Chemistry and Biochemistry,

Folding, association and aggregation of proteins are key processes in the biochemistry of cells but often difficult to probe in experiments or computer simulations. The later suffer from the problem that these processes happen on time scales that in general are not accessible in atomistic simulations, and the required computational resources even increase exponentially with size of the molecules. In this talk, I will describe variants of replica exchange sampling designed to overcome this sampling-problem in studies of amyloid oligomers and fibrils that are associated with various diseases. I will present some of our recent results investigating the stability of such aggregates.

Selected Publications:

- U.H.E. Hansmann, *Parallel Tempering Algorithm for Conformational Studies of Biological Molecules*, Chem. Phys. Lett. **281** (1997) 140.
- S. Mohanty, J.H. Meinke, O. Zimmermann and U.H.E. Hansmann, *Simulation of Top7-CFr: a transient helix extension guides folding*, Proc. Natl. Acad. Sci. USA, **105** (2008) 8004.
- W.M. Berhanu, F. Yasar and U.H.E. Hansmann, *In Silico cross seeding of Aβ and amylin fibril-like oligomers*, ACS Chem. Neurosci., **4** (2013) 1488.
- E.J. Alred, M. Phillips, W.M. Berhanu and U.H.E. Hansmann, *On the lack of polymorphism in Aβ-peptide aggregates derived from patient brains*, Protein Science, **2**4 (2015) 923.
- W.M. Berhanu, E.J. Alred and U.H.E. Hansmann, *Stability of Osaka mutant and wild-type fibril models*, J. Phys. Chem. B, **119** (2015) 13063.
- F. Yasar, N.A. Bernhardt and U.H.E. Hansmann, *Replica-Exchange-with-Tunneling for fast Exploration of Protein Landscapes*, J. Chem. Phys., accepted for publication.

IMATİNİB BİNDİNG TO HUMAN C-SRC İS COUPLED TO İNTER-DOMAİN ALLOSTERY AND SUGGESTS A NOVEL KİNASE İNHİBİTİON STRATEGY

Yuko Tsutsui[1], Daniel Deredge[2], Patrick L. Wintrode[2], and Franklin A. Hays[1,3,4,]*

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[2]Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, Maryland 21201, USA.

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[4]Harold Hamm Diabetes Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, 73104, USA.

Imatinib (Gleevec), a non-receptor tyrosine kinase inhibitor (nRTKI), is one of the most successful anti-neoplastic drugs in clinical use. However, imatinib-resistant mutations are increasingly prevalent in patient tissues and driving development of novel imatinib analogs. We present a detailed study of the conformational dynamics, in the presence and absence of bound imatinib, for full-length human c-Src using hydrogen-deuterium exchange and mass spectrometry. Our results demonstrate that imatinib binding to the kinase domain effects dynamics of proline-rich or phosphorylated peptide ligand binding sites in distal c-Src SH3 and SH2 domains. These dynamic changes in functional regulatory sites, distal to the imatinib binding pocket, show similarities to structural transitions involved in kinase activation. These data also identify imatinib-sensitive, and imatinib-resistant, mutation sites. Thus, the current study identifies novel c-Src allosteric sites associated with imatinib binding and kinase activation and provide a framework for follow-on development of TKI binding modulators.

KNOTS AS STABLE ORDER PARAMETER FOR SEMIFLEXIBLE POLYMERS

WOLFHARD JANKE

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Universitat Leipzig,
Germany

We investigate the influence of bending stiffness on the conformational phases of a bead-stick homopolym**er** model and present the pseudo-phase diagram for the complete range of semiflexible polymers, from flexibleto stiff. By varying the internal bending stiffness, the model exhibits different pseudo phases like bent, hairpin and toroidal. In particular, we find thermodynamically stable knots and unusual transitions into these "knotted" phase with a clear phase coexistence, but almost no change in the mean total energy and hence no latent heat. It will be explained how we arrive at these intriguing results by computer simulations based on a combination of replica exchange Monte Carlo algorithms and multicanonical method and discussed how one can understand these effects by basic statistical physics properties.

M. Marenz and W. Janke, Phys. Rev. Lett. 116, 128301 (2016).

CABS-DOCK WEB SERVER FOR PROTEİN-PEPTİDE DOCKİNG WİTH SİGNİFİCANT STRUCTURAL FLEXİBİLİTY

M. KURCİNSKİ, M. BLASZCZYK, M. CİEMNY, A. KOLİNSKİ ve S. KMİECİK

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Protein–peptide interactions play a key role in cell functions. Their structural characterization, though challenging, is important for the discovery of new drugs. The CABS-dock web server provides an interface for modeling protein–peptide interactions using a highly efficient protocol for the flexible docking of peptides to proteins. While other docking algorithms require pre-defined localization of the binding site, CABS-dock does not require such knowledge. Given a protein receptor structure and a peptide sequence (and starting from random conformations and positions of the peptide), CABS-dock performs simulation search for the binding site allowing for full flexibility of the peptide and from small- to large-scale fluctuations of the receptor backbone. This protocol was extensively tested over the largest dataset of non-redundant protein–peptide interactions available to date (including bound and unbound docking cases). For over 80% of bound and unbound dataset cases, we obtained models with high or medium accuracy (sufficient for practical applications). Additionally, as optional features, CABS-dock can exclude user-selected binding modes from docking search or to increase the level of flexibility for chosen receptor fragments. CABS-dock is freely available at: http://biocomp.chem.uw.edu.pl/CABSdock.

SIMULATIONS AND ANALYSIS OF FRET PROCESSES IN (BIO)MOLECULAR SYSTEMS USING A QM-MD APPROACH

B. LESYNG

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Förster resonance energy transfer (FRET) is popular in biomolecular studies. A novel and relatively simple FRET methodology has recently been developed by us and applied to purine nucleoside phosphorylase (PNP) complexed with a fluorescent ligand – formycin (*A*) – see: M. Sobieraj *et al.*, J. Mol. Modeling, 2015, 21(4):75. FRET occurs between an excited Tyr residue (*D**) and *A*. Interactions of *D** with its molecular environment were accounted by including changes of the ESP charges in S_1, compared to S_0, and computed at the SCF-CI level. FRET probability W_F depends on the inverse six-power of the *D**-*A* distance, R_{da}. The orientational factor $0<\square^{\square}<4$ between *D** and *A* is computed and included in the analysis. W_F is time-averaged over the MD trajectories. Deactivation mechanisms are analyzed. Excited state properties of tyrosine in molecular evolution processes of proteins are indicated.

Acknowledgements: Studies were supported by IMDiK PAS, computations by POIG.02.03.00-00-0030/09 and POIG.02.01.00-14-122/09.

PROBING COPPER CATALYSIS IN BIOLOGY WITH MULTIPLE SIMULATIONS

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Copper is required by living cells for moving electrons between reducing and oxidizing agents. Copper reactivity is kept under control by well ordered macromolecules that bind copper. When this control is lacking, ions are found in abnormal amount in cellular and extracellular compartments, a process known as disohomeostasis. When the compartment is populated by disordered proteins, these latter can interact with ions producing new catalysts. This occurs, for instance, in the synapse of degenerating neurons: disordered amyloid-□ (A□) peptides interact with copper; oligomeric and aggregated forms of Cu[A□] develop different functions. When dioxygen is present together with organic reducing agents, electron transfer to dioxygen is observed and dioxygen activation to superoxide is explained by interactions with carboxylate *anti* to Cu(I)-O_2 binding position.

Starting with this example, we discuss how to use computational models to understand and eventually control the catalytic properties of complexes formed by metal ions and disordered proteins.

PROTEIN AND RNA STRUCTURE PREDICTION BY INTEGRATION OF CO-EVOLUTIONARY INFORMATION INTO MOLECULAR SIMULATION

Alexander Schug[1],

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Exploring the interrelationship of structure and function is crucial for the understanding of molecular life. Despite significant progress of experimental methods, the structural characterization of important structures for both proteins and RNA – typically preceding any detailed mechanistic exploration of their function – remains challenging. In recent years, increasingly ubiquitous availability of sequential information and novel statistical analysis has allowed to trace the co-evolution of residues and predict contact maps. These contact maps can be exploited in structure prediction tools. One maximum entropy based approach is called Direct Coupling Analysis (DCA)[1] and, e.g., was found to be sufficient for the blind prediction of a protein complex[2] and its active conformation[3] later confirmed by experiment. Similarly, DCA can infer mutational landscapes and capture epistatic couplings [4]. For RNA it is comparably simple to predict secondary structure through analyzing possible Watson-Crick base pairings. Predicting tertiary contacts, however, has remained an elusive task met with limited success. In contrast, our novel rnaDCA is able to extract tertiary contacts from genomic data which are sufficient to systematically improve tertiary RNA prediction [5]. Considering the large gap of known sequences to experimentally resolved tertiary structures, this progress goes far beyond basic research: Given the importance of such interactions for pathogenesis, we also expect significant impact on pharmacological and medical research and applications.

References

[1] Weigt M et al., Proc Nat Acad Sci USA (2009) 106, 67-72; F. Morcos et al., Proc Nat Acad Sci (2011) 108, E1293-E1301
[2] Schug A et al., Proc Nat Acad Sci USA (2009) 106, 22124-22129
[3] Dago A et al., Proc Nat Acad Sci USA (2012), 109: E1733-42
[4] M. Figliuzzi, et al., Mol Bio Evol (2015), msv211.
[5] E. De Leonardis et al., Nucleic acids research (2015), gkv932

[1] Steinbuch Centre for Computing & Faculty of Physics, Karlsruhe Institute of Technology, Karlsruhe, Germany

WHAT MAKES TELLOMERS UNIQUE?

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Since the discovery of telomeres and their loop structures scientist wonder why such repeating sequence has been chosen by nature. What is common feature of different telomer sequences among different classes or kingdoms? Why their sequences are so similar, despite the tremendous differences in their genetic codes and evolution? We studied human-like (TTAGGG), plant (TTTAGG) and insect (TTAGG) telomeric sequences. In this study we present how mechanical properties of telomer sequences differ from other non-telomeric sequences and what makes them unique. We used steered molecular dynamics with all-atom AMBER14 force field and Nucleic Acid united RESidue (NARES) coarse-grained force field. Our results reveal distinct features of all telomeric sequences, show their exceptional high mechanical resistance and stability to untangling and stretching.

This work was supported by National Science Center (Poland) Sonata UMO-2015/17/D/ST4/00509.

GOING FROM BOTTOM TO TOP AND RELATING THE INTERMEDIATES: APPLICATIONS OF COMPUTATIONAL GROUP THEORY

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Simple, yet powerful, group theory imposes heavy constraints on the possibilities of phase transitions and allowed symmetries. The fact that representations are mostly projected through matrices have hindered the practicality of the theory and the existence of alternative ways shied away the already reluctant researchers and for decades. Thankfully, the advance of the computational power and especially the focus on matrix algebra have allowed fast and very practical applications of the group theory in solid state.

A number of computational tools have been devised by the Bilbao Crystallographic Server (http://www.cryst.ehu.es) group and one can easily determine possible low and high symmetry structures related to an observed phase by considering the available options, in addition to quantitatively evaluating the similarities by direct comparison of given structures.

The applications of group theory via these tools will be demonstrated on a different range of structures and the algorithms behind the processes will be presented.

ACCEPTED ORAL PRESENTATION

CBSB2016 Outstanding Young Researcher

MULTIPLE COMPUTATIONAL APPROACHES DISCLOSE PRINCIPLES UNDERLYING HUMAN SERUM TRANSFERRIN FUNCTIONING

HALEH ABDIZADEH, ALI RANA ATILGAN, CANAN ATILGAN***

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We aim to understand distal communication and dynamics for transferrin(Tf), a bilobal transport protein which circulates iron in the blood and delivers it to tissues. Tf displays pH dependent cooperativity between the two lobes. We aim to capture the local motions of Tf that affect its subdomains and trigger the global conformational change. Molecular dynamics simulations(MD) of various conformational states of hTf delineate large conformational changes occurring before and after iron release. We address the molecular basis for the differences between N/C-lobe dynamics operational in the iron release mechanism. In a total of 2μs MD simulations, residue fluctuations elucidate the cross-talk between the lobes at serum pH, while their communication is lost under endosomal conditions. To explore the binding/dissociation of iron, steered MD simulations are performed on the lobes of Tf. Iron escape pathways from binding cavities are disclosed and potentials of mean force along the reaction coordinate are resolved.

CBSB2016 Outstanding Young Researcher

MODELING OF PROTEIN–PEPTIDE INTERACTIONS USING THE CABS-DOCK WEB SERVER FOR BINDING SITE SEARCH AND FLEXIBLE DOCKING

M. BLASZCZYK, M. KURCINSKI, M. KOUZA, L. WIETESKA, A. DEBINSKI, A. KOLINSKI, S. KMIECIK

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Protein-peptide interactions play essential functional roles in living organisms and their structural characterization is a hot subject of current experimental and theoretical research. Computational modeling of the structure of protein-peptide interactions is usually divided into two stages: prediction of the binding site at a protein receptor surface, and then docking (and modeling) the peptide structure into the known binding site. In contrast, CABS-dock method is designed for the simultaneous search of binding sites and flexible protein-peptide docking. We present example CABS-dock results obtained in the default CABS-dock mode and using its advanced options that enable the user to increase the range of flexibility for chosen receptor fragments or to exclude user-selected binding modes from docking search. Furthermore, we demonstrate a strategy to improve CABS-dock performance by assessing the quality of models with classical molecular dynamics.The CABS-dock web server is freely available at http://biocomp.chem.uw.edu.pl/CABSdock/.

Contributed Talk

FREE ENERGY CALCULATION FOR NAVAB CHANNEL WITH NO EQUILIBRIUM REQUIREMENT

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In recent years, the most important reason of the work with molecular dynamics simulation method of biomolecular systems is to ensure understanding physical mechanism and dynamic properties that is not readily accessible to experimental methods. The crystal structure of the voltage-gated bacterial Nav channel obtained in 2011 by Payandeh et al. Voltage-gated sodium channels is very important due to the onset of action potentials. Molecular dynamics modeling has been conducted to understand the structure-function relationship for this channel. NavAb channels (Figure 1) are bacterial channels with radius of approximately 8 Å. In addition, theoretical calculations of free energy that called Crooks fluctuation theorem for non-equilibrium systems are available at literature. In this study, primarily, free energy calculation methods that do not require equilibrium state were developed for complex systems and compared with the free energy simulation work in equilibrium condition. Finally the validity of the method was tested for the NavAb channels.

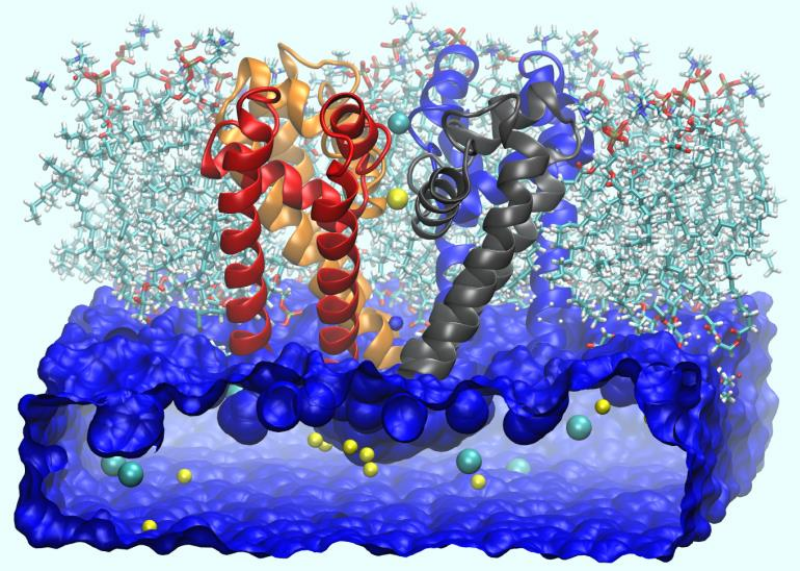

Figure 1: NavAb simulation system from a side view

Contributed Talk

MICROCANONICAL MOLECULAR DYNAMICS STUDY OF MELTING OF SMALL PT CLUSTERS

M. ERYUREK

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The melting of geometrical magic number Pt clusters in the size range $13 \leq N \leq 55$ has been studied by microcanonical molecular dynamics simulation. The model interatomic potentials are used: a Gupta potential which favor icosahedral structures. The microcanonical thermodynamics quantities of melting are calculated by using multiple histogram methods. Melting temperature T_m and latent heat are determined by heat capacity curves and caloric curves respectively and they are plotted as a function of cluster size and were compared. The characteristics of melting behaviors of Pt magic clusters are determined by heat capacity curves that are indicative of first-order-like transition and potential energy distribution curves that are indicative of Gaussien or bimodal distrubitions.

Contributed Talk

CENTRALITY OF RESIDUES AND REDUNDANCIES IN THEIR COMMUNICATION EXPLAIN THE DISTRUPTIVE MUTATIONS IN DHFR

T.F. GÜÇLÜ, C. ATILGAN, and A. R. ATILGAN

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Antibiotic resistance is a challenge that threats humanity by rendering infections incurable. Bacterial dihydrofolate reductase(DHFR) is a model system used to explain the origins of this problem. To investigate the effect of point mutations on the communication within its residue network, we have performed computational alanine scanning. The scheme is based on mutating each amino acid to alanine, and minimizing in water at physiological ionic strength at the all-atom resolution. We then assign a node to each residue and links between directly coordinating node-pairs, treating the protein as a graph. We focus on changes in shortest path length of residues(ΔL) and betweenness centrality(ΔBC) of mutated nodes with respect to the wild-type, averaged over all mutations. We relate these measures to conservation scores for DHFRs within the bacterial families and all known DHFRs. We explain the origins of resistance invoking point mutations, particularly at positions P21, D26, L28, W30, I94 and F153.

Contributed Talk

IRON AND SYNERGISTIC ANION BINDING SPECIFICITY OF HAEMOPHILUS INFLUENZEA FERRIC BINDING PROTEIN

G. LİU, T. F. GÜÇLÜ, I. KARMOUS, Z. S. SAYERS, C. ATILGAN

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Iron is s a fundamental metabolite for all organisms, transported by proteins due to its toxicity in free form. Bacteria have developed elaborate mechanisms to sequester iron from the environment. Haemophilus Influenzae Ferric Binding Protein(hFBP) is part of this mechanism evolved to hijack iron. We have expressed and purified hFBP by recombinant DNA technology. Its specificity to metals other than iron was experimentally investigated in an attempt to use it in nanosensor applications for detecting iron levels in individual cells. Computationally, binding affinity of different iron coordinating synergistic anions was assessed by potential of mean force calculations. The order of affinity was found as PO_4 > P_2O_7 > $C_6H_8O_7$ > SO_4, in conformity with experiments. This approach paves the way for fast and reliable relative affinity prediction under different conditions for a protein such as FBP that survives in environments that span a range of pH and ionic strength values.

CBSB2016 Outstanding Young Researcher

ANALYSIS ON TARGET SPECIFIC TRANSCRIPTION ACTIVATOR-LIKE EFFECTORS BY PERTURBATION-RESPONSE SCANNING AND FREE ENERGY CALCULATIONS

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TALE(transcription activator-like effector) proteins are considered among the principal tools for targeted genome editing. Crystal structure of *PthXo1* TALE protein bound to its DNA target reveals specificity of interactions between the two. TALE is coiled around DNA in a super-helix conformation, consisting of 33-34 conserved amino acids repeated at each turn. Amino acids at positions 12-13 specifically bind to DNA bases according to the code: HD→C, NG→T, NI→A, NN→G in most cases. To quantify specific binding stability, we apply Perturbation-Response Scanning method that classifies four regions of intrinsic stability. We further analyze point mutations introduced into select positions by free energy perturbation calculations. Based on these findings, we make a model for DNA recognition by TALEs that also explains the lower and upper bounds on the number of base-pairs recognized. We therefore expand on current methods for computational design of TALEs for experimental tests of binding affinity and off-target specificity.

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STRUCTURAL-BASED PREDİCTİON OF NOVEL LİNEAR B-CELL EPİTOPES İN PİCORNAVİRUSES

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The *Picornaviridae* family includes pathogens of clinical and economic importance. There are no antivirals against these infections and vaccines have only been successful for certain viruses. Understanding virus antigenicity and the identification of epitopes present in multiple serotypes is fundamental to the development of improved vaccines. Picornavirus capsids comprise of 60 copies of proteins VP1-VP4. External proteins include VP1-VP3. This study investigates the conservation of motifs which match predicted and experimentally determined epitopes across the family. Motif discovery was performed across all available VP1-VP3 sequences. *In- silico* epitope prediction was performed using crystal structures of 22 picornavirus species. We identified 29, 13 and 23 motifs in the VP1, VP2 and VP3 proteins that matched experimental epitopes and characterise 17 VP1, 6 VP2 and 8 VP3 motifs corresponding to novel epitope predictions. Surface exposure was determined through structural mapping, with normal mode analysis to examine exposure during capsid breathing.

Contributed Talk

SELF-ASSEMBLED PEPTIDE AMPHIPHILES WITH MOLECULAR DYNAMICS SIMULATIONS

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Understanding the self-assembly mechanism of the Peptide Amphiphile molecules and the related noncovalent interactions are important in structural biochemistry to design new Peptide Amphiphiles and Peptide Amphiphile-based materials for biomedical applications, such as drug delivery, regenerative medicine and tissue engineering.

In this work, using the Gromacs program, a detailed Molecular Dynamics simulation of cylindrical nanofibers, formed by self-assembling peptide amphiphiles, is carried out to study the stability of the fibers and forces (interactions) which bring/hold them together.

CBSB2016 Outstanding Young Researcher

HYDRATION EFFECTS IN PROTEIN KINASES

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Water plays important role in most biological aspects of life. Isolated water molecules are frequently found inside protein structures. Their presence at specific locations is important for protein dynamics. The analysis of protein kinases, which in spite of little sequence homology share the high level of structures conservation, reveals several buried water molecules. Interestingly, hydration sites are localized within the functionally important motifs. A question arises wheter the bound waters play functional role?

We are investigating the role of selected, universally preserved water molecules for kinase function by compuatational approaches. We focus on answering for the following questions:
1. Where are conserved hydration sites in kinases structure dependening on different states (active/inactive)?
2. How tightly are the localized water molecules bound?
3. What is the influence of the considered hydration sites on conformational mobility of kinase catalytic subunits?

ACCEPTED POSTER PRESENTATION

Poster

INVESTIGATION OF THE CONFORMATIONAL STABILITY OF DESIGNED HOMO TETRAMERIC STRUCTURE

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In recent years, impressive applications with computer-designed structures have been observed in biotechnology and drug discovery. The conformational stability of computer-designed structures is one of the main design principles. In order to determine the conformational stability of antisymmetric homo tetrameric structure designed by using the de novo dimer unit, HexCoil-Ala (PDB Code 3S0R), we have performed MD simulation with all atom Amber99SB force field and explicit SPC water model at 300 K. Our results show that designed tetrameric structure has high conformational stability characteristics.

Poster

REPLICA-EXCHANGE TUNNELING SIMULATION OF THE TRP-CAGE MINIPROTEIN IN EXPLICIT SOLVENT

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From the point of simulations, traditional Monte Carlo (MC) or Molecular Dynamics methods are not well suited for obteining a true sample of the complete conformational space of realistic protein and peptides. The main factor that create this difficulty is the very rugged shape of potential energy surface of protein and peptides which usually causes conventional simulation methods to be come trapped in the valley of a particular energy minimum at relatively low temperature. This problem can be overcome by a novel technique. In present work, the Replica-Exchange-with-Tunneling method is tested by simulating the Trp-cage protein in explicit solvent.

Poster

CONFORMATIONAL PREFERENCES AND VIBRATIONAL SPECTRA OF ARACHIDONIC ACID

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Arachidonic Acid [(5Z,8Z,11Z,14Z)-eicosa-5,8,11,14-tetraenoic acid, C20:4] is a polyunsaturated acid with a 20-carbon chain and four *cis*-double bonds; the first double bond is located at the sixth carbon from the omega end. It is present in the phospholipids of cellular membranes in the body and is abundant in the brain, muscles and liver.

Arachidonic Acid (AA) can be used to make prostaglandins which they can have a broad spectrum of biological activities. AA has great torsional mobility about the C-C bonds situated adjacent to double bonds in the acyl chain. The investigation of structures of stable conformers and also their active sites may lead to a better understanding of its metabolism and possibly to the development of more specific drugs.

In this study, we aimed to investigate the conformational behavior and structural stability of AA by using density functional theory (DFT) with B3LYP method using 6-311++G(d,p) basis set. The extended angle-iron (tts´CssCs´s´CssCs´ttt) conformation of AA is found to be more stable.

The optimal geometries and harmonic vibrational frequencies of the minimum energy conformers of AA were calculated at the same level of theory. Fourier Transform Infrared (FTIR) spectrum of liquid AA was recorded in the region 4000–450 cm^{-1}. The DFT/B3LYP/6-311++G(d,p) method was also used to study for dimer form of AA. The observed FTIR vibrational wavenumbers were analyzed and compared with the theoretically predicted vibrational spectra of monomer and dimer forms.

Poster

THE INVESTIGATION OF PEPTİDE ABETA(11-40) BY REPLICA-EXCHANGE-WITH TUNNELING METHOD

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Although Replica Exchange Molecular Dynamics (REMD) is used for efficient sampling of the phase space of large biomolecular systems, in practise, it has many application difficulties. To overcome these difficulties, Replica-Exchange-with Tunneling (RET) method has been developed by integrating ideas of hybrid MC/MD into the replica exchange protocol. We performed the simulation of peptide Abeta (11-40) by using RET method. The deposition of β-amyloid peptide (Abeta) is thought to be the cause of Alzheimer's Disease (AD). Alzheimer's diseased brains show significant levels of Abeta(11-40).

Poster

THE QUANTUM CHEMICAL CALCULATIONS OF SALMON CALCITONIN PEPTIDE

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Salmon calcitonin was used in clinical utilities as treatment of metabolic bone diseases as osteoarthritis, osteoporosis and Paget's disease for decades of years. In this work the quantum chemical calculation of model 1 of Salmon Calcitonin Peptide (2GLH), obtained from protein databank, was investigated by using Density Functional Theory with the hybrid functional B3LYP (Becke, 3-parameter, Lee-Yang-Parr). The 6-311G(d,p) Gaussian type basis set is used for all atoms except for S atom for which LanL2DZ (Los Alamos National Laboratory 2-double-z) basis set is used.

Poster

SEMI-EMPIRICAL &RHF GEOMETRY OPTIMIZATION AND MINIMIZATION ANALYSIS OF TAMOXIFEN MOLECULE

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Tamoxifen (Figure-1) is a medication that is used to prevent breast cancer in women and treat breast cancer. It is also studied for other types of cancer. Besides, tamoxifen is used to treat infertility in women and improve fertility in males. Our purpose is to minimize the structure of tamoxifen and analyze the results. For this purpose, we firstly optimized the structure of tamoxifen with AM1, MNDO, PM3, PM7 and RHF methods using Mopac and Gamess (us) programs. Then we found the missing parameters by Antechamber and Parmchk programs. Finally, we made minimize tamoxifen by sander.

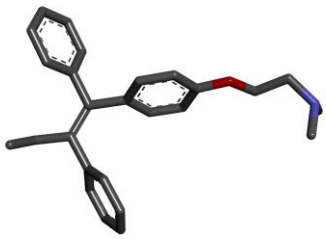

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Figure-1 Ball-and-stick model of tamoxifen molecule (1).

Reference:

1) X-ray diffraction data from G. Precigoux, C. Courseille, S. Geoffre et M. Hospital (1979). "[p-(Diméthylamino-2 éthoxy)phényl]-1 trans-diphényl-1,2 butène-1 (tamoxfène) (ICI-46474)". *Acta Crystallographica Section B* **35**: 3070-3072. DOI:10.1107/S0567740879011407.

Poster

STRUCTURAL ANALYSIS of THE FORMATIONS BY AROMATIC AMINO ACIDS

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We investigate the self-assembly of amino acids (phenylalanine, tyrosine and trptophan). The amino acids are with charged end-groups. In this work, we focus on the structural similarities and differencies of the formations by these amino acids. The structures are obtained from individual solutions of the amino acids and also various mixtures of these amino acids. We investigate the stability and mechanism of the structures too.

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