

Vietnam National University Ho Chi Minh City

IWCBP-1

The First International Workshop
on Computational Biophysics



Ho Chi Minh City, February 01-05, 2010

About IWCBP-1

Molecular computational biophysics is at its infancy in Vietnam. This conference will help to develop a basic knowledge in this emerging field to VN scientists and students of various backgrounds. It will allow establishing connections between the experimental work in molecular medicine and computational physics at universities and research institutes in Vietnam.

The meeting consists of the three-day school and two-day workshop.

The school will be focused on state-of-the-art of molecular simulation methods for studying biomolecules. Emphasis will be given to the investigation of human diseases, like the Alzheimer's, AIDS, bird- and swine-origin influenza diseases. The choice of specific topics is dictated by needs for promotion of research in these areas in several laboratories in Vietnam.

The workshop will cover aspects of protein folding and misfolding, computer-aided drug design, coarse-grain modeling, quantum simulation, free energy calculations, computational spectroscopy and other topics. Most lecturers will give 2 hours lectures at the school and 40 min talk at the workshop. Some of the lecturers will be asked to do four hours of lectures/hands-on exercises (they also will give 40 min lectures at the workshop).

Topics

The topics will include (but they will not be limited to):

Diseases like the Alzheimer's and Parkinson diseases, which affect a large portion of senior population, are associated with amyloid protein aggregates. Understanding of mechanisms of fibril formation is extremely important for the development of drugs to treat these diseases. Molecular simulation can serve as a useful tool to study easily observable effects such as effects of mutations and more importantly to uncover general principles behind molecular aggregation processes.

Influenza viruses cause annual epidemics and occasional pandemics that have claimed the lives of millions. The emergence of new strains will continue to pose challenges to public health and the scientific communities. A prime example is the recent emergence of swine-origin H1N1 viruses that have transmitted to and spread among humans, resulting in outbreaks internationally. Currently, there is increasing evidence that H5N1 virus is highly resistant to commercial drugs Tamiflu and Relenza. The swine A/H1N1 have been found to resist to Tamiflu in some cases. Therefore, the development of new vaccines and antiviral drugs should be of high priority. In addition to other techniques such as protein-ligand docking, the molecular dynamics (MD) simulations can be used for searching new inhibitors.

Students will have the opportunity to learn a variety of simulation methods, including Car-Parrinello MD (Prof. Carloni) and effective potentials- based MD (Prof. J-H. Lin and Prof. M. S. Li).

Invited speakers will also give talks on progress of computational study of various diseases such as conformational diseases, avian and swine flu. The participants are encouraged to present their results on relevant problems.

Committees

Chairmen

Paolo Carloni, International School for Advanced Studies, Italy (SISSA) and German Research School for Simulation Sciences GmbH, Julich, Germany

Mai Suan Li, Institute of Computational Science and Technology, Ho Chi Minh City (ICST), Vietnam and Institute of Physics, Polish Academy of Sciences (IF PAN), Poland

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Invited Speakers

Michele Parrinello, ETH, Zurich, Switzerland

Paolo Carloni, SISSA, Italy and German Research School for Simulation Sciences
GmbH, Germany

C. K. Hu, Academia Sinica, Taiwan

Russell Devane, University of Pennsylvania, Philadelphia (UPP), USA

Trinh Xuan Hoang, Institute of Physics, VAST, Vietnam

Hisashi Okumura, Institute for Molecular Science, Okazaki, Japan

Giovanni Bussi, SISSA, Italy

Mai Suan Li, ICST and IF PAN

Jung-Hsin Lin, National Taiwan University (NTU), Taiwan

Thai Khac Minh, Faculty of Pharmacy, University of Medicine & Pharmacy HCMC,
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SCHOOL PROGRAM

Monday, February, 1st, 2010	
Start from 8:30	Introduction to biomolecules and MD (Paolo Carloni): 5 hours Visualization of biomolecules (Paolo Carloni, Nguyen Ha Hung Chuong): 1 hour Introduction to Gromacs (Mai Suan Li and Giovanni Bussi): 2 hours
Tuesday, February, 2nd, 2010	
Start from 8:30	Practical use of Gromacs (Mai Suan Li): 4 hours Introduction to Amber (Jung-Hsin Lin): 2 hours Practical use of Amber (Jung-Hsin Lin): 2 hours
Wednesday, February, 3rd, 2010	
Start from 8:30	Practical use of Amber (continue, Jung-Hsin Lin): 2 hours Introduction to DFT calculations (Giovanni Bussi and Paolo Carloni): 2 hours Practical use of DFT (Giovanni Bussi): 4 hours

WORKSHOP PROGRAM

Thursday, February, 4th, 2010	
8:30 - 9:30	Registration
<i>Chairman: Paolo Carloni</i>	
9:30 - 10:00	Opening Section: - Introduction (Hoang Zung, Paolo Carloni) - Welcome message from VNUHCM (Huynh Thanh Dat, Vice President of VNUHCM)
10:00 - 11:30	Special Session in honor of Prof. Michele Parrinello (ETH Zurich, Switzerland)
10:00 - 10:30	- Scientific achievements of Prof. Michele Parrinello (Paolo Carloni)
10:30 - 11:30	- <i>Advanced sampling methods</i> (Keynote lecture by Prof. Michele Parrinello)
11:30 - 13:00	Lunch of Prof. Parrinello with students
<i>Chairman: Hisashi Okumura</i>	
13:00 - 13:50	<i>Simple models for relaxation and aggregation of biopolymers</i> * Chin Kun Hu (Academica Sinica, Taipei, Taiwan)
13:50 - 14:30	<i>Self assembly of large aggregates using coarse grain molecular dynamics</i> * Russell Devane (Temple University, USA)
14:30 - 15:10	<i>How one might design a nanomachine: learning from Nature</i> * Trinh Xuan Hoang (Institute of Physics, Hanoi, Vietnam)
15:10 - 15:30	Tea break
<i>Chairman: Trinh Xuan Hoang</i>	
15:30 - 16:10	<i>Generalized-ensemble molecular dynamics simulations of alanine dipeptide</i> * Hisashi Okumura (Institute for Molecular Science, Okazaki, Japan)
16:10 - 16:50	<i>Stochastic thermostats in classical and ab initio molecular dynamics</i> * Giovanni Bussi (SISSA, Trieste, Italy)
16:50 - 17:10	<i>Temperature dependence of the rate constants of charge recombination from the P+AQ- states in Bacteria Reaction Centres from Rhodospirillum rubrum</i> Tran Thanh Thuy (Institute of Physics, VAST, Vietnam)
19:00 - 21:00	Welcome Party in honor of Prof. Michele Parrinello given by VNU

The First International Workshop on Computational Biophysics
IWCBP-1

Friday, February, 5th, 2010	
<i>Chairman: Rusell Devane</i>	
8:30 - 9:20	<i>Molecular simulation of proteins involved in neurodegenerative diseases: when theory meets experiment *</i> Paolo Carloni (German Research School for Simulation Sciences GmbH, Jülich, Germany)
9:20 - 10:00	<i>Fibril formation of polypeptide chains and related conformational diseases *</i> Mai Tuan Li (Institute of Physics, Polish Academy of Sciences and ICST, Ho Chi Minh City, Vietnam)
10:00 - 10:15	Tea break
<i>Chairman: Chin Kun Hu</i>	
10:15 - 10:55	<i>Applying an extended relaxed complex scheme for discovery of new neuraminidase inhibitors *</i> Jung-Hsin Lin (National Taiwan University, Taipei, Taiwan)
10:55 - 11:15	<i>Top-hits for A/H1N1 Identified by Virtual Screening Using Ensemble-based Docking</i> Hung Tien Nguyen (Institute for Computational Science and Technology, Ho Chi Minh City, Vietnam)
11:15 - 11:35	<i>Top-leads for A/H1N1 revealed by steered molecular dynamics approach</i> Binh Khanh Mai (Institute for Computational Science and Technology, Ho Chi Minh City, Vietnam)
11:35 - 13:00	Lunch break
<i>Chairman: Jung-Hsin Lin</i>	
13:00 - 14:00	Poster Section
14:00 - 14:40	<i>Computational toxicology for drug design: hERG activity and drug trapping *</i> Thai Khac Minh (University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam)
14:40 - 15:00	<i>Molecular simulation studies of the structure, interaction and diffusion of drug in chitosan matrix</i> Visit Vao-soongnern (Suranaree University of Technology, Nakhon Ratchasima, Thailand)
15:00 - 15:15	Tea break

The First International Workshop on Computational Biophysics
IWCBP-1

<i>Chairman: Giovanni Bussi</i>	
15:15 - 15:35	<i>Application of homology modeling and hybrid molecular simulation to study ligand binding to G-protein coupled receptors</i> Nguyen Ha Hung Chuong (German Research School for Simulation Sciences GmbH, Julich, Germany)
15:35 - 15:55	<i>Molecular studies of HIV-1 TAR and its complex with a cyclic peptide inhibitor.</i> Do Nhu Trang (SISSA, Trieste, Italy)
15:55 - 16:15	<i>Relationship between population of the fibril-prone state in the monomeric state and fibril formation times of peptides: Insights from all-atom simulations</i> Hoang Bao Nam (Institute for Computational Science and Technology, Ho Chi Minh City, Vietnam)
16:15 - 16:35	<i>Computational docking of oligosaccharides to cellulases</i> Thu V. Vuong (Cornell University, USA)
Saturday, February, 6th, 2010	
Tour	

Abstracts

Invited Talks

Advances in Biomolecular Simulations

Michele Parrinello

*Computational Science, Department of Chemistry and Applied Biosciences, ETH Zurich, USI Campus, Via
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We introduce the well-tempered ensemble (WTE) which is the biased ensemble sampled by well-tempered metadynamics when the energy is used as collective variable. WTE can be designed so as to have approximately the same average energy as the canonical ensemble but much larger fluctuations. These two properties lead to an extremely fast exploration of phase space. An even greater efficiency is obtained when WTE is combined with parallel tempering. Unbiased Boltzmann averages are computed on the fly by a recently developed reweighting method [M. Bonomi et al. J. Comput. Chem. 30, 1615 (2009)]. We apply WTE and its parallel tempering variant to the 2D Ising model and to Gō-model of HIV protease, demonstrating in these two representative cases that convergence is accelerated by orders of magnitude.

**Molecular simulation of proteins involved in neurodegenerative
diseases: when theory meets experiment**

Paolo Carloni

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Simple models for relaxation and aggregation of biopolymers

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Relaxation and aggregation of biopolymers are related to function or malfunction of biological systems. Here we consider simple models for such problems. We have used molecular dynamics to simulate various systems of polymer chains and Lennard-Jones molecules; the neighboring monomers along a polymer chain are connected by rigid bonds^[1] or spring of strength k_{spring} ^[2]. We find that the velocity distributions of monomers in a wide range of simulation time can be well described by Tsallis q -statistics^[3] with $q \geq 1$ and a single scaling function; the value of q is related to the conformation constraining potential, the interactions with background fluid, the destruction of chain homogeneity^[1] or the value of k_{spring} ^[2]; when q approaches 1, the velocity distribution of monomers becomes Maxwell-Boltzmann distribution. We also find that the polymer chains tend to aggregate as neighboring monomers of a polymer chain having small or zero bending-angle and torsion-angle dependent potentials^[4]. The implication of our results for the aggregation of proteins is discussed.

[1] W.-J. Ma, and C.-K. Hu. *Generalized statistical mechanics and scaling behavior for non-equilibrium polymer chains I: monomers connected by rigid bonds*, J. Phys. Soc. Jpn., in press (2010).

[2] W.-J. Ma, and C.-K. Hu. *Generalized statistical mechanics and scaling behavior for nonequilibrium polymer chains II: monomers connected by springs*, J. Phys. Soc. Jpn., in press (2010).

[3] C. Tsallis, J. Stat. Phys. **52**, 479 (1988).

[4] C.-K. Hu and W.-J. Ma. *Molecular dynamics approach to relaxation and aggregation of polymer chains*, Prog. Theo. Phys. Supp., to be published.

Coarse grained modeling of large macromolecular aggregates

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Computational resources continue to rapidly increase allowing theoretical investigation of larger systems on longer timescales. Indeed the capacity of all-atom (AA) molecular dynamics (MD) has reached a level that permits somewhat routine exploration of systems containing on the order of hundreds of thousands of atoms for timescales approaching hundreds of nanoseconds. Nonetheless, with these spatial and temporal scales, many soft matter and biological systems of interest still extend far beyond this capability. In order to overcome this issue, techniques such as enhanced sampling methods or reduced description models can be used, just to name a couple. Models using a reduced description of the system are typically referred to as coarse grain (CG) models. Recently there has been a renewed interest in CG techniques with numerous models now appearing in the literature. As well, there are numerous methods for deriving parameters for CG models. However, each method has its limitations, which has limited greater adoption of these methods. One rather consistent characteristic of CG models is their dependence on AA MD simulations. This has the negative consequence of including any undesirable characteristics of the AA model into the CG model. We have recently developed a novel parametrization approach that relies heavily on experimental data including surface tension, density and free energy and reduces the dependence on atomistic molecular dynamics simulations. The resulting CG potential is based upon rather standard, functional forms facilitating implementation in conventional MD codes. This approach has been applied to non-ionic and anionic surfactants, biologically relevant lipid molecules and amino acids. The results demonstrate the ability to make modular transferable CG sites that are capable of accurately predicting the phase and surface behavior specific to a system.

Coarse grained modeling of large macromolecular aggregates

Giovanni Bussi

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A new molecular-dynamics algorithm for sampling the canonical distribution will be presented^[1]. In this approach the velocities of all the particles are rescaled by a properly chosen random factor. Its properties will be illustrated for Lennard-Jones and water in the solid and liquid phases. Moreover, a new scheme based on colored noise Langevin equation will be presented, together with applications to Car-Parrinello molecular dynamics^[2] and to the description of nuclear quantum effects^[3].

[1] Bussi, Donadio and Parrinello, *Canonical sampling through velocity-rescaling*, J. Chem. Phys. 126, 014101 (2007)

[2] Ceriotti, Bussi and Parrinello, *Langevin equation with colored noise for constant-temperature molecular dynamics simulations*, Phys. Rev. Lett. 102, 020601 (2009)

[3] Ceriotti, Bussi and Parrinello, *Nuclear quantum effects in solids using a colored-noise thermostat*, Phys. Rev. Lett. 103, 030603 (2009)

Applying an extended relaxed complex scheme for discovery of new neuraminidase inhibitors

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There are two important glycoproteins on the membrane of influenza virus, haemagglutinin and neuraminidase, and both are recognized as drug design targets for this infectious disease. HA mediates cell-surface sialic acid receptor binding to initiate virus infection, while NA removes sialic acid from virus to facilitate virus release and spread. There have been two well-known drugs targeting to neuraminidase, relenza (zanamivir) and tamiflu (oseltamivir). In 2006, Russell et al. crystallized neuraminidase structures with oseltamivir binding, and they found that there is a large cavity adjacent to oseltamivir binding site, which was near to the 150-loop. In 2007, we reported molecular dynamics simulations on this structure and found that the loop flexibility in N1 is even more pronounced than anticipated. Besides, it was found that there is another cavity near the 430 loop. The transition between the more wide-open and nearly closed structures in these cavities was also investigated. According to this finding, it should be possible to design new inhibitors for neuraminidases that are for the open 150-loop or the open 430-loop conformations, which would have the potential to bind more strongly than oseltamivir or zanamivir. We developed and applied an extended relax complex scheme to discovery new neuraminidase inhibitors. In addition, the explicit MD simulation of the neuraminidase N1 was compared with the simulation with the implicit solvent generalized born approach. In particular, we compared the dynamics and correlated motions of three important pockets in neuraminidase. Subsequently, several clustering methods were utilized to reduce the number of the docking calculations of relaxed complex scheme. The rank of binding affinities of previously identified neuraminidase inhibitors can be reproduced correctly via the binding free energy spectrum analysis of the relaxed complex scheme.

Fibril formation of polypeptide chains and related conformational diseases

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Fibril formation of peptides and proteins are associated with a number of conformational diseases such as Alzheimer's, mad cow etc. Using all-atom and coarse-grained models we have shown that the kinetics of fibril elongation obeys the two-step dock-lock mechanism. In accord with experiments, our simulation results reveal that sequences, hydrophobicity, charges and the population the fibril-prone conformation in the monomeric state are main factors that govern the aggregation process of polypeptide chains.

Computational toxicology for drug design: hERG activity and drug trapping

Thai Khac Minh, Pham C. Huy, and T. Nguyen Dung

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Inhibition of human ether-a-go-go-related-gene (hERG) channels prolongs the ventricular action potential with the risk of torsade de pointes arrhythmia that may result in sudden cardiac death. Therefore, computational approaches for classification and prediction of hERG affinity in an early phase of the drug discovery and development process are of increasing interest. Both structure-based and ligand-based approaches have been undertaken to shed more light on the molecular basis of drug-channel interaction as well as to predict hERG affinity and to classify hERG inhibitors. In this study, an in silico system for classification and prediction hERG blockers is reported which combines computational models from ligand-based (binary QSAR and counter-propagation neural networks) and structure-based approaches. This system might provide possible strategies for improving the performance of separation of clear no-go compounds from safe compounds and also should guide the design of new hERG channel blockers. Finally, it provides a predictive tool for early detection of possible undesired hERG activity.

How one might design a nanomachine: learning from Nature

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Learning from nature's amazing molecular machines, globular proteins, we present a framework for the predictive design of nano-machines. We show that the crucial ingredients for a chain molecule to behave as a machine are its inherent anisotropy and the coupling between the local Frenet coordinate reference frames of nearby monomers. We demonstrate that, even in the absence of heterogeneity, protein-like behavior is obtained for a simple chain molecule made up of just thirty hard spheres. This chain spontaneously switches between two distinct geometries, a single helix and a dual helix, merely due to thermal fluctuations.

Generalized-ensemble molecular dynamics simulations of alanine dipeptide

Hisashi Okumura

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Molecular Science, the Graduate University for Advanced Studies, Okazaki, Japan*

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Biomolecules such as proteins have complicated free energy surfaces with many local minima. Conventional molecular dynamics (MD) and Monte Carlo (MC) simulations in physical ensembles. One of the powerful techniques to avoid this difficulty is generalized-ensemble algorithms such as the multicanonical algorithm. However, because the multicanonical simulation is performed in a fixed volume, neither the pressure dependence nor temperature dependence at certain pressure can be investigated as in experiments. In order to overcome this difficulty, I have recently proposed multibaric-multithermal MC [1-3] and MD [4-6] algorithms. In this ensemble, two-dimensional random walks not only in the potential-energy space but also in the volume space are realized. I applied the multibaric-multithermal MD algorithm to an alanine dipeptide in explicit water [7]. The multibaric-multithermal MD simulation covered a wide range of conformational space and sampled all of the states. On the other hand, the conventional isobaric-isothermal simulation was trapped in local-minimum free-energy states and sampled only a few of them. I calculated the partial molar enthalpy difference and partial molar volume difference among these states. This is the first simulational work to calculate these quantities. Another problem of the multicanonical algorithm is that the determination of the multicanonical weight factor to give a flat distribution becomes difficult in a large system. In order to alleviate this difficulty, I have proposed the partial multicanonical algorithm [8]. The partial multicanonical simulation samples a wide range of a part of the potential energy terms which is necessary to sample the conformational space widely. Thus, one can concentrate the effort to determine a multicanonical weight factor only on the important energy terms. I applied the partial multicanonical, multicanonical, and canonical molecular dynamics algorithms to an alanine dipeptide in explicit water again. The results mean that the partial multicanonical algorithm has higher sampling efficiency than the multicanonical and canonical algorithms.

Contributed Talks

Temperature dependence of the rate constants of charge recombination from the P+AQ- states in Bacteria Reaction Centres from Rhodobacter sphaeroides

Tran Thanh Thuy, Phan Duc Anh, Vu Thuy Huong, Ngo Van Thanh, Nguyen Ai Viet

Institute of Physics, VAST, Hanoi, Vietnam

Bacterial reaction centres (RCs) convert light excitation energy into chemical free energy. This is accomplished inside the intracytoplasmic phospholipid membranes of photosynthetic bacteria in which these proteins are embedded. Photosynthesis is the process of energy conversion of sunlight into chemical energy in the form of organic compounds. Electron transfer effect of light is one of the bright phase nature of process of photosynthesis. A constant most important when charge transfer is the rate constant, scientists have been studying. In this work, we have investigated the dependence on the temperature of the rate constant of charge recombination from the P+AQ- states. By using a quantum expression for the rate introduced by Marcus, we obtained a good result which is not only agree with previous studies [Biochimica et Biophysica Acta (2009), 46261; No of pages: 11; 4c: 3,9] on the rate at high temperature, but also could be applied for the case of low temperature.

Top-hits for A/H1N1 Identified by Virtual Screening Using Ensemble-based Docking

Hung T. Nguyen¹, Ly Le², Thanh N. Truong^{1,2}

¹*Institute for Computational Science & Technology, HCM City, Vietnam*

²*Department of Chemistry, University of Utah, United States*

A list of 27 promising antiviral drugs is proposed for use against the A/H1N1 strain. Since the binding site of the A/H1N1 neuraminidase is similar to that of the bird flu H5N1, an effective means to quickly identify top candidates for use against A/H1N1 is to use known bird-flu drugs and the 27 compounds from the NCI diversity set which bind best to H5N1 neuraminidase. These compounds serve as viable candidates for docking against the A/H1N1 neuraminidase, using ensembles extracted from molecular dynamics simulations of the A/H1N1 system. The ranking order of these top candidates was found to be different from the previously published results for H5N1. The results indicated that the Oseltamivir (Tamiflu) and Peramivir drugs have higher ranking than Zanamivir (Relenza). However, six drug candidates were found to bind more effectively to A/H1N1 neuraminidase than Tamiflu. Detailed hydrogen bond network analysis for these six candidates is also provided.

Top-leads for A/H1N1 revealed by steered molecular dynamics approach

Binh Khanh Mai¹, Man Hoang Viet², Mai Suan Li²

¹ *Institute for Computational Science and Technology, Ho Chi Minh City, Vietnam*

² *Institute of Physics, Polish Academy of Science, Warsaw, Poland*

Since March 2009, a new strain of influenza A virus (swine 2009 A/H1N1) has spread rapidly and evolved into global pandemic. Currently two antiviral drugs, oseltamivir (Tamiflu) and zanamivir (Relenza), are available for the treatment of influenza, and were reported effective for 2009 A/H1N1 influenza. However, as the virus is evolving fast, some drug resistance strains are emerging. Therefore, it is critical to seek potential alternative treatments, and identify the roots of the drug resistance. In previous studies, in order to search for leads which are potentially better than existing drugs, many methods like MM-PBSA, LIE etc have been employed to estimate the binding free energy of ligands to the glycoprotein neuraminidase. But the drawback of this method is very time consuming. In this report we use the steered molecular dynamics approach to estimate binding ability of 32 ligands to glycoprotein neuraminidase from A/H1N1. It is shown that peramivir, tamiflu and relenza are ranked 8, 15 and 20. Ligand 141562 from NSC set was found to be the most promising candidate for combating with A/H1N1.

Molecular simulation studies of the structure, interaction and diffusion of drug in chitosan matrix

Natthida Rakkapao and Visit Vao-soongnern

School of Chemistry and Laboratory of Computational and Applied Polymer Science (LCAPS), Institute of Science, Suranaree University of Technology, Nakhon Ratchasima, Thailand

Molecular modeling has been performed at atomistic level of chitosan and its complex with aspirin *i.e.* a model of drug control-release system. Deacetylation of chitin acetylamine groups by chemical reaction has a significant effect on the conformational properties of the glycosidic bonds linking two repeat units. Both the location and the relative energies of the low energy areas of the potential energy surfaces slightly differ. The amorphous bulk model was then constructed to model the solid state of these polysaccharides. The results reported, including energetics, chain dimension, torsional distribution, pair distribution function and X-Ray structure factor, provide a detailed description of the disordered state of the polysaccharide chains as well as an interaction with a model drug. The amine groups in chitosan were found to interact strongly with the carbonyl groups in Aspirin. This interaction, however, existed only when the amine groups was in its protonated form. The diffusion coefficient of a drug model in chitosan matrix was also calculated.

Application of homology modeling and hybrid molecular simulation to study ligand binding to G-protein coupled receptors

Nguyen Ha Hung Chuong¹, Xevi Biarnés², Veronica Mattioli³, Alejandro Giorgetti³ and Paolo Carloni^{1,2}

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G-Protein-Coupled Receptors (GPCRs) are the largest class of human receptors responsible for the majority of signal transduction across the cell membrane. Almost 30% of all marketed drugs act on GPCRs. Despite their importance as drug targets, few experimental structural information is available since the difficulties in obtaining their X-ray structures. Therefore, homology modeling and molecular dynamics are key approaches in probing the 3D structural information of GPCRs. Here we propose the combination of homology modeling (HM) with molecular mechanics/coarse-grained (MM/CG) model to build the 3D structure of GPCRs. In this approach, the model obtained by HM is used as initial structure for MM/CG simulation. MM/CG allows a fast and efficient description of the mechanical coupling between the active site with the enzymatic substrate. Therefore, this method could help to improve the quality of GPCR models for studying ligand binding. Our approach is being tested with human beta2-adrenergic receptor (PDB code: 2RH1).

Molecular studies of HIV-1 TAR and its complex with a cyclic peptide inhibitor

Do Nhu Trang¹, Emiliano Ippoliti², Gabriele Varani³, Michele Parrinello⁴, Paolo Carloni^{1,2}

¹ *International School for Advanced Studies (SISSA), Trieste, Italy*

² *German Research School for Simulation Sciences GmbH, Jülich, Germany*

³ *Department of Chemistry & Department of Biochemistry, University of Washington, Seattle, USA*

⁴ *Computational Science, Department of Chemistry and Applied Biosciences, ETH Zurich, Lugano, Switzerland*

Dynamical behavior of HIV-1 TAR RNA and its complex with a cyclic peptidic inhibitor in aqueous solution are simulated by means of molecular dynamics. Starting structures are taken from NMR experiments. During the simulations, water is included explicitly, periodic boundary conditions are applied, and Particle Mesh Ewald method is used for treating long-range electrostatic interaction. AMBER force field ff03 with Orozco correction is utilized. Structural and free energy analyses are performed to understand the dynamical behavior of free TAR and TAR in complex with the inhibitor. Contribution of van der Waals and electrostatic interaction to the formation of the complex is evaluated, and conformational rearrangement from free to bound state of TAR is analyzed. Comparison with NMR results shows the agreement between simulation and experiment.

Relationship between population of the fibril-prone state in the monomeric state and fibril formation times of peptides: Insights from all-atom simulations

Hoang Bao Nam¹, Maksim Kouza², Hoang Zung³ and Suan Li^{1,2}

¹ *Saigon Institute for Computational Science and Technology, 6 Quarter, Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam*

² *Institute of Physics, Polish Academy of Sciences, Al. Lotnikow 32/46, 02-668 Warsaw, Poland*

³ *Vietnam National University Ho Chi Minh City, 6 Quarter, Linh Trung Ward, Thu Duc District, Ho Chi Minh City, Vietnam*

Despite much progress in understanding the aggregation processes of biomolecules, the factors that govern their rates have not been fully understood. This problem is of particular importance since many conformational diseases such as Alzheimer's, Parkinson's and type-II diabetes are associated with protein oligomerization. Using all-atom models with explicit water for two short peptides KFFE and NNQQ, we show that their fibril formation times are strongly correlated with the population of the fibril-prone conformation in the monomeric state. The larger the population the faster is the fibril growth process. Our result not only suggests that this quantity plays a key role in the fibril elongation but also opens a new way to understand the fibrillogenesis of biomolecules at the monomeric level. The nature of oligomer ordering of NNQQ is studied in detail.

Computational docking of oligosaccharides to cellulases

Thu V. Vuong and David B. Wilson

Cornell University

There is a strong interest in studying and engineering cellulases as these enzymes are important for the development of biofuels. Second generation biofuel technologies have been developed to effectively break down cellulosic biomass. One of potential issues with cellulases acting on biomass is non-specific binding. Plant cell walls consist of different polysaccharides integrated with each other; non-specific binding of cellulases to other polysaccharides instead of cellulose might reduce hydrolysis efficiency. Computational docking of different types of oligosaccharides including xylo- and laminari-oligosaccharides into the active sites of *Thermobifida fusca* cellulases suggested that their active sites can bind these oligosaccharides. Experimental binding assays showed that *T. fusca* cellulases bind other polysaccharides besides cellulose. However, their activity on these substrates is very low or undetectable; therefore, the binding is mainly non-productive.

Posters

Combined studies of cell response to electric pulses: A simple approach

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Research indicates that ultrashort and high-intensity electric pulses can cause effects on the cellular organelles, in some cases, larger than on the plasma membranes. These effects are the consequence of the voltages induced on the membranes. Kotnik et al investigate this phenomenon by an analytical method for the interaction between trapezoidal pulses and biological membranes. However, they ignore the electroporation which can decrease the voltages induced by a few volts. Joshi et al, on the other hand, use a complex numerical approach including the dynamic conductivities of cell membranes and substructures, and achieve better results. In this paper, we base on the Kotnik's analytical method, but consider the electroporation effect by using an approximate theory of pore and achieve very good results, in agreement with the Joshi's one.

Modelling the effect of structural QSAR parameters on skin penetration using Genetic Programming

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In order to model relationships between chemical structures and biological effect in quantitative structure-activity relationship (QSAR) data, an alternative technique of artificial intelligence computing – genetic programming (GP) – was investigated and compared to the traditional methods – statistics. GP, with the primary advantage of generating mathematical equation, was employed to model QSAR data and to define the most important molecular descriptions in QSAR data. The models predicted by GP agreed with the statistical results, and the most predictive models of GP were significantly improved when compared to the statistical models using ANOVA analysis. Recently, artificial intelligence techniques have been applied widely to analyse QSAR data. With the capability to generate mathematical equations, GP can be considered as an effective and efficient method for modelling QSAR data. KEYWORDS: genetic programming; genetic algorithms; statistical method; quantitative structure-activity relationship (QSAR), skin penetration.

Understanding the recognition mechanism of O6-methylguanine:thymine and the O4-thymine:guanine DNA damage from quantum chemistry calculation

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Ab initio calculations were carried out to study the O6-methylguanine:thymine (O6-meG:T) and the O4-methylthymine:guanine (O4-meT:G) mispairs as an attempt to understand the mechanism of their recognition and repair by O6-alkylguanine-DNA-alkyltransferase (AGT) protein. Pairing energies and local geometries of these mispairs were obtained and compared with those of intact Adenine:Thymine (A:T) and Guanine:Cytosine (G:C) basepairs at the HF, B3LYP and MP2 levels of theory with the 6-31+G(d) basis set. Pairing energy profile suggests that O4-meT:G is more stable than intact A:T, suggesting that the lesions might not be recognized by schemes based on the weakness of the mispairs. O6-meG:T is less stable than A:T and O4-meT:G, which is consistent with experimental observation that O6-meG was repaired by AGT with an efficiency significantly higher than that of O4-meT. Our results provide some hints in understanding the recognition mechanism of these two mispairs by AGT.

**Synthesize and research Fe₃O₄@Au core – shell nanostructure,
potentially applications in biomedicine**

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Fe₃O₄@Au core – shell nanostructure is potentially candidate for applications in biomedicine. Super-paramagnetic Fe₃O₄ core can be isolated by external magnetic. Au thin shell with surface plasmonic resonant (SPR) is useful in optical diagnostics. In this article, we synthesized and researched its properties. The first, Fe₃O₄ nanoparticles are prepared by co-precipitation method. Then, Au thin shell is coated on Fe₃O₄ nanoparticles by ultrasound assisted reducing HAuCl₄.3H₂O on Fe₃O₄ seeds. UV – Vis, XRD, TEM and VSM were used to research its properties. UV – Vis showed Au thin coating with SPR peaks range in 525 – 535 nm varied with shell and core size. TEM showed core – shell nanostructures with 16 – 18 nm core size and 22-24 nm core – shell. XRD showed all peaks of face – centered cubic Fe₃O₄ of uncoated Fe₃O₄ nanoparticles and also few peaks of Au crystal. VSM showed saturation magnetization is 57 emu/g for bare Fe₃O₄ and 20 emu/g for Fe₃O₄@Au nanoparticles. Prepared Fe₃O₄@Au core – shell nanostructure has high stable, potentially applications in biomedicine.

Factors governing fibrillogenesis of polypeptide chains

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Despite much progress in understanding the aggregation processes of biomolecules, the rules defining their rates have yet to be fully defined. This problem is of particular importance since many conformational diseases are associated with protein misfolding. Using lattice models, we show that fibril formation times of polypeptide chains are strongly correlated with hydrophobicity, Coulomb interaction and the population of the fibril-prone conformation in the monomeric state. The higher the population the faster is the fibril growth process and this dependence may be described by a single exponential function. Our result opens a new way to understand the fibrillogenesis of bio-molecules at the monomeric level.

Molecular dynamics study of mutation effect on A/H1N1 influenza virus resistance to Oseltamivir

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Current swine flu (A/H1N1) and avian flu (H5N1) were reported to share similar sequence in subtype 1 neuraminidase (N1), a glycoprotein on a virus' surface, which facilitates to widespread infection, since they both react positively to Oseltamivir (Tamiflu), known as neuraminidase (NA) inhibitor. Previous study that specific mutants in H5N1 virus caused resistant to Tamiflu has raised a concern to a potential outbreak of swine flu throughout the world as drug's effectiveness can be reduced by H1N1 mutation. Therefore, these mutants at H274Y, N294S, E119G on NA was examined in this study to predict potential drug-resistant mutations of A/H1N1 virus. Molecular dynamics (MD) simulations for 15ns with explicit solvent were applied to three complexes of Tamiflu and variants of NA- A/H1N1 virus. Then, the binding free energies of these complexes were ranked by Molecular Mechanics/Poisson-Boltzmann Surface Area (MM-BPSA) calculation. As a result, the highly unfavorable contribution of electrostatics from solute and solvent mainly causes stronger drug resistance in H274Y, E119G mutants, compared with N294S, although its binding site with Tamiflu was observed to be dislocated mostly during simulation process.

Atomistic Molecular Dynamics Simulation of the Structures and Properties of Poly (L-lactic acid)

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The structure and thermodynamic properties of poly (L-lactic acid) (PLA) are investigated via computer simulations. The initial chain conformations were generated using atomistic molecular dynamic (MD) simulations technique including periodic boundary conditions, were relaxed by potential energy minimization. Dihedral angle population density distributions for PLA chains show that *trans* conformation is favored for C-O bonds while the more compact *gauche* conformation is favored for C-C bonds. Atomic-level packing in the simulated polymer bulk is examined through the calculation of neutron/x-ray structure factor. Hildebrand solubility parameter is in good agreement with the experimental value. Diffusion coefficient for both O₂ and H₂O were estimated from the mean-square displacement. O₂ was found to diffuse slightly slower than H₂O in PLA.

Computer Modelling of Phospholipid Micelle and Liposome

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Biological micelles and liposomes are important biochemical structures in the bio-surfactant, for example, and drug delivery industries, respectively. In this study, in-house constructed FORMula TRANslation (FORTRAN) programs, version g77 on Scientific Linux 4.5 platform were used to model the atomistic phospholipid micelle and liposome models. A single phospholipid dipalmitoylphosphatidylcholine (DPPC) was used to build the initial micellar and liposomal structures. The FORTRAN programs can also be used to model other phospholipids such as the palmitoyloleoylphosphatidylcholine (POPC) and dimyristoylphosphatidylcholine (DMPC) by changing the rotational angles, scaling factors and orientation parameters in the program. We have successfully constructed the DPPC micelle and liposome structures starting from a single lipid in Protein Data Bank (PDB) format and output as the PDB format. The DPPC micelle built is the normal micelle of head-out-tail-in type. It is also possible to build the reverse micelle of head-in-tail-out type. In building the liposome structure, the micelle builder was modified to build a layer of smaller head-in-tail-out micelle and this structure is covered with the bigger head-out-tail-in micelle. Our in-house program is automated to be able to also specify the number of lipids required to build the micellar or liposomal structures. The Packmol software could also be used to build micellar and liposomal models but it is not as direct as our FORTRAN program. In the mean time, we are also in the process of writing another FORTRAN program to analyze the local density profiles (LDP) of the micellar and liposomal structures especially after the simulations using molecular dynamics (MD). The structure of micelles built can be used to study the stereochemistry and chemical interactions of the hydrophilic headgroups with solvent water, normally. On the other hand, the liposome structure built can be used to study the mechanism of membrane fusion, exocytosis, endocytosis and drug delivery system. Simulations of atomistic micellar and liposomal models can be achieved by the MD software such as GROMACS and AMBER.