3rd Adriatic Meeting on Computational Solutions in the Life Sciences

Summary

The '3rd Adriatic Meeting on Computational Solutions in the Life Sciences' was held in Primošten, Croatia, 1-5 September, 2009. Financial supports were provided through the Sixth Framework Program, by the ESF foundation, and by Croatian Ministry of Science, Education and Sports. The programme and details are available at the workshop's website: http://dkslip.irb.hr/primosten2009.

The main aims of the event were education of young scientists in South Eastern Europe and establishment of dialogue among scientists in the region, as well as with scientists from Europe. The scientific programme was designed to enable scientists from the region to present their work on Computational Solutions in the Life Sciences, but also to provide an introduction to the new computational solutions in molecular biology, as well to include presentations on top quality work in topics ranging from bioinformatics to molecular simulation and quantum chemistry.

The meeting consisted of lectures, tutorials and a poster session with discussion. The scientific conference consisted of 22 invited lectures, 5 contributed (selected) lectures, four tutorials and a poster session. The lectures were divided thematically into five sections: Large scale molecular simulations, Molecular simulations: developments and applications, Quantum chemical study of biomolecules, Quantum dynamical study of biomolecules and Bioinformatics.

Altogether 72 scientists participated in the meeting, of that 30 women. The most numerous were scientists from Croatia (43), followed by Germany (4), Serbia, Slovenia, Bosnia and Herzegovina and Switzerland (3 scientists from each), Macedonia, Austria, Italy, Sweden and Australia (2 scientists from each), United Kingdom, Spain and Netherlands (1 scientists from each). Two participants from Albania registered, but were unable to attend. The participants covered the range from diploma students (3), doctoral students and, postdoctoral fellows (almost forty altogether) to senior scientist.

From the discussions of the Programme Committee as well as the participants, the meeting was considered to be very successful from both scientific and social aspects.

About the scientific content

One of the main problems in computational biology and medicine is how to identify interacting proteins, the protein-protein (P-P) interactions sites and protein binding properties. Apparently P-P interactions are the central pillar supporting most of biological functional activity on the molecular level. In the first section '**Large scale molecular simulations'** Rebecca C. Wade from EML Research, Heidelberg talked about new method to study protein binding. The method is based on combination of Brownian dynamics and molecular dynamics (MD) simulations. Also she spoke about their research on enzyme dehalogenase in which they used random molecular dynamic simulations (RAMD) to elucidate the water channels and on the basis of the computational results redesigned the enzyme access tunnels and prepared mutants with significantly improved activity towards a toxic, antrophogenic compounds. Another two interesting talks about P-P interactions were those of Dušanka Janežić from National Institute of Chemistry, Ljubljana, and Bojan Žagrović from MEDLIS, Split. Dušanka and her coo-workers have developed a new approach to find the protein areas that are functionally important based on the graph theory. She claimed that their method is faster and less biased than the other similar approaches. In The Bojan's group, the non-specific component of P-P interactions (size, charge, isoelectric point, hydrophilicity) have being studied. These interactions affect protein localization and their diffusional search for one another. They suggested that the non-specific component of P-P interaction determines in part the co-localization and clustering of the binding partners, which then directly in a non-specific fashion influences their interactions.

Alan E. Mark from University of Queensland spoke about their research on simulations used to understand cooperative phenomena in biomolecular systems. He pointed to the problem of lack of the available methods for this purpose. The most interesting was study of the mechanism by which antimicrobial peptides induce the formation of trans-membrane pores.

The problem of the conventional molecular simulation methods when dealing with complex biomolecular systems is their inefficiency in sampling. of the free energy surface. Fabrio Pietrucci from Lausanne (CECAM) presented a recently developed

technique BIAS EXCHANGE METADYNAMICS which enables efficient (occurs on the fs/ps scale)reconstruction of the free energy surface. The main idea of metadynamics is to enhance sampling of the free energy surface by 'filling the deep gaps on potential surface' by Gaussian functions. However this is often not a straightforward procedure, but requires lot of sampling and experience. The main problem in metadynamics is choice of the reaction coordinates, there should not be too many coordinates (computational times increase exponentially) but those selected should be sufficient to enable proper description of the transition we are considering. In combination with a weighting-histogram approach, metadynamics allows construction of a kinetic model of the studied system and comparison with the experimental data. As an example he described their research on peptide binding to HIV-1 protease.

The most provocative was the first talk of the second section **'Molecular simulations: developments and applications'** given by Wilfred F. van Gunsteren from ETH, Zurich. He indicated limitations of the available experimental methods and how non-biasing simulations can help in interpretation of measured data. On the example of NMR study of peptides he showed how their computational simulations enabled to reveal the unambiguous 3D structure of the peptides.

Protein molecules are involved in very wide time scale processes, however molecular dynamic simulations can be successfully used to study both fast (fs -ps) and slow ones (100 ns - μs). Lennart Nilsson from Karolinska Institute, Stockholm, demonstrated how this can be done using the program CHARMM. He has used MD simulations to interpret 10-100 fold slower Fluorescence Stokes Shift (FSS) relaxation (occurs on the fs/ps scale) measured in proteins in comparison to that of chromophore in solution. According to fluctuation-dissipation/LRA approximation autocorrelation of fluctuations in interaction energy does not depend on the chromophore (Trp) state considered (excited/ground).

Substantial number of talks was devoted to study of enzymes ranging from simulation of the large scale molecular motions of enzymes to quantum mechanical studies of electron and proton transfers. Karl Hult from School of Biotechnology, Stockholm, pointed to the importance of the water molecules in the lipase catalysed reactions, and presented their simulations on water entrance to the lipase active site.

In the section on '**The Quantum Chemical Study of Biomolecules'** Leo Radom, from University of Sidney, Milan Hodošček from the National Institute, Ljubljana and Miguel Gonzalez from Barcelona Universuty spoke on their research on modelling enzymatic reactions using quantum mechanical as well as hybrid quantum mechanical/molecular mechanics methods. As a conclusion we can say that importance of the DFT method, at different levels of complexity, for studying enzymatic reactions is increasing. Apparently there are number of DFT approaches available for treatment of the quantum mechanical systems with different performances and caution to choose the most appropriate one for the particular problem is needed.

Nowdays it is recognized that quantum effects such a hydrogen/deuterium tunnelling and zero point energy play an important role in numerous reactions of biological interest. '**The Quantum Dynamics'** section of this workshop focused on some of the most important quantum issues occurring in biomolecules. In the talk of Vlasta Bonacic-Koutecky a computational methodology capable of performing molecular dynamics simulations in both ground and electronically excited states was presented.

The approach allows to investigates the relaxation dynamic and conformational changes occurring in biomolecules upon UV excitation. Moreover, she presented the latest results of her group on computer simulation of bio-inspired devices that couple intrinsic properties of small metal clusters and aromatic amino-acids. The dynamics of the hydrogen bonds in DNA that are responsible for the photostability of the molecule was discussed in the talk of Oliver Kuehn. Here in particular the results of femtosecond laser experiments on DNA base pairs have been analyzed and understood in terms of *ab initio* molecular dynamics simulations. In addition Kuehn presented the first computer simulations of 2D IR spectroscopy experiments on DNA base pairs.

The relaxation of biomolecules upon femtosecond UV excitation was the subject of the presentation of Graham Worth. He first introduced the multiconfigurational time dependent Hartree approach (MCTDH), a well known computational technique for treating coupled ground and excited state dynamics, to focus subsequently on the latest developments including the Gaussian wave packed approach. Compared to MCTDH the Gaussian based approach is computationally more efficient and allows treating larger

molecular systems such as those of biological interest. Janez Mavri from National Institute of Chemistry, Ljubljana, presented a simulation of tunnelling in enzyme catalysis. By combining a biased propagation approach and the quantum classical path method he was capable to understand the unusually large H/D isotope effect in the lipoxygenase.

In the last section, '**Bioinformatics'**, Anna Tramontano from Sapienza University, Rome, spoke about the protein data base CASP and on their research on revealing varieties in folds among similar sequences and their connection with the protein structure and localisation. Jack A. M. Leunissen from Wageningen University, spoke about problems considering different approaches in protein classification. Together with his collaborators he developed ProGMap (Protein Group Mappings), an integrated protein database in which over 14 million proteins and 240,000 group descriptions are collected from different collection of databases and consistently mapped onto each other, thus creating a unique network of mappings among these collections. The purpose of the ProGMap database is threefold: i) to provide a direct insight into the relationships among the various data sets through a single entry point, ii) to refine and improve upon existing protein classification methodologies, and ultimately, iii) to gain better understanding of the concepts used for grouping proteins.

Assessments

From the discussions of the Programme Committee as well as the participants, the meeting is considered to be very successful both from scientific and social aspects. The main idea of the meeting was to increase the uptake of computational methodologies in this region of the Europe and to disseminate the knowledge on the most advanced computational methodologies in the life sciences. It may come as a surprise that the impact of the conference on further scientific work of the young participants exceeded our expectations considering the number of Computational Life Science techniques they plan to use in their research.

The main aims of the event included: a) education of young scientists in South Eastern Europe, especially those from Croatia and neighbouring countries and b) establishment of dialogue among scientists in the region, as well as with scientists from Europe. The

scientific programme was designed to enable scientists from the region to present their work on Computational Solutions in the Life Sciences, but also to provide an introduction to the new computational solutions in molecular biology, as well to include presentations on top quality work in topics ranging from bioinformatics to molecular dynamic simulation and quantum mechanics and dynamics calculations. Almost all of the lectures were of high quality and many of them provoked extensive discussion. The participants' posters were on display for three days with the main discussion being at the poster session on Tuesday evening.

An integral and very well-received module of the conference was the *Tutorial* component held to enhance the participation of the younger conference attendees. In total we organized four *Tutorial* sessions: 'Basic of Quantum Dynamics', 'Combined Quantum Dynamics/ Molecular Mechanics approaches', an overview of the empirical molecular simulation methods entitled 'From the Protein sequence to the new biologically active compounds' and 'Introduction to Bioinformatics'. They were held by the organizers, Nađa Došlić, David Smith, Sanja Tomić and Kristian Vlahoviček, respectively at afternoon September 2nd. Many of the students in attendance were, as anticipated, from Croatia and the feedback concerning these sessions was very positive.

In terms of a significant dissemination event, we couldn't have hoped for more. We also used the opportunity to reinforce our links with out partner scientists and forge new ones with eminent European scientists. We expect to reap the benefits of this event for some time to come and we anticipate the next instalment, planned for September 2011.

After the successful organization of the 3rd Adriatic Meeting on Computational Solutions in the Life Sciences, we have begun in earnest to make arrangements for its successor meeting. Main organizers of the 4th Adriatic Meeting on Computational Solutions in the Life Sciences will be our colleagues from Slovenia, Dušanka Janežić and Milan Hodošček. This meeting is scheduled to take place in September 2011 in Portorož.

Also we are aware of the new contact established not only between the senior scientists but also between students and eminent scientist from the Europe, and which resulted with arrangements for the pre-doc and post-doc studies.

The 3rd Adriatic Meeting on Computational Solutions in the Life Sciences

September 1-5, 2009

Primošten, Croatia

Program of the Conference

Tuesday, 1. September 2009

12:00 - 15:00 **Registration (in the hotel *Zora*)**

15:00 - 16:00 ***Welcome snack and introductory remarks*** (Sanja Tomić, David Smith)

Large scale molecular simulations (Chair: Sanja Tomić)

16:00 - 16:50 **Rebecca Wade**, EML Research, Heidelberg

Protein dynamics and binding: From single protein to multi-protein systems

16:50 - 17:40 **Alan Mark**, The University of Queensland, Brisbane

Simulating self-organization in biomolecular systems

17:40 - 18:30 **Fabio Pietrucci**, EPFL, Lausanne

Exploring the thermodynamics and kinetics of biomolecules with bias-exchange metadynamics

18:30 - 18:50 **Poster placement & Student meeting**

18:50 - 20:30 Dinner break

20:30 - 22:00 **Get together – Poster session**

Wednesday, 2. September 2009

Molecular simulations: developments and applications
(Chair: Darko Babić)

09:00 - 09:50 **Wilfred van Gunsteren**, ETH, Zürich

On interpreting experimental data on biomolecular systems using molecular simulation

09:50 - 10:40 **Lennart Nilsson**, Karolinska Institute, Stockholm

Protein dynamics from femtoseconds to microseconds

10:40 - 11:00 *Coffee discussion*

11:00 - 11:50 **Dušanka Janežič**, National Institute of Chemistry, Ljubljana

Mathematical modeling of biological macromolecules

11:50 - 12:40 **Karl Hult**, AlbaNova University Center, Stockholm

Interactions between substrates and the active site of lipase B from *Candida antarctica* studied by modeling and kinetics

12:40 - 15:00 *Lunch break*

15:00 - 15:50 **Matej Praprotnik**, National Institute of Chemistry, Ljubljana

Adaptive resolution simulation

15:50 - 16:40 **Bojan Žagrović**, MEDILS, Split

Studying protein-protein interactions using computer simulations: from specific effects to protein ecology

16:40 - 17:10 *Coffee discussion*

17:10 - 18:10 **Tutorial - Part I** (Nađa Došlić and David Smith)

18:10 - 19:00 **Tutorial - Part II** (Sanja Tomić and Kristian Vlahoviček)

Thursday, 3. September 2009

Quantum chemical study of biomolecules (Chair: David Smith)

09:00 - 09:50 **Leo Radom**, University of Sydney, Sydney

The mechanism of action of coenzyme B12: A computational approach

09:50 - 10:40 **Valerije Vrček**, University of Zagreb, Zagreb

Rearrangements in chlorinated piperidines relevant to environmental fate of pharmaceuticals

10:40 - 11:00 *Coffee discussion*

11:00 - 11:50 **Snežana Zarić**, University of Belgrade, Belgrade

A reexamination of the propensities of amino acids towards a particular secondary structure: classification of amino acids based on their chemical structure

11:50 - 12:40 **Milan Hodošček**, National Institute of Chemistry, Ljubljana

Exploring conformational and reaction pathways in biomolecular systems by computer simulations

12:40 - 15:00 *Lunch break*

15:00 - 15:50 **Miguel Gonzalez**, University of Barcelona, Barcelona

QM/MM study of the reaction mechanism of the HCV NS3 protease with its main natural substrates

15:50 - 16:40 **Vlasta Bonačić-Koutecký**, Humboldt-Universität, Berlin

Absorption and emission enhancement of biomolecules

16:40 - 17:10 *Coffee discussion*

Contributed talks (Chair: Borislav Kovačević)

17:10 - 17:30 **Milena Petković**, University of Belgrade, Belgrade

Infrared spectrum of the acetic acid dimer in the O-H stretching region: Presence of multiple conformers and role of Raman active modes

17:30 - 17:50 **Danijela Barić**, Ruđer Bošković Institute, Zagreb

Computational investigation of enzymatic dehydration of glycerol

17:50 - 18:10 **Zrinka Gattin**, MPI for Biophysical Chemistry, Göttingen

Molecular dynamics studies of ß-peptides: Using computer simulation to correct and interpret experimental data

18:10 - 18:30 **Larisa Zoranić**, University of Split, Split

Water-like structure with repulsive double-core interactions

18:30 - 18:50 **Michael Ramek**, Graz University of Technology, Graz

Colour perception and computer-based presentations

19:30 - ***Conference dinner***

Friday, 4. September 2009

Quantum dynamical study of biomolecules (Chair: Nađa Došlić)

08:30 - 09:20 **Oliver Kühn**, University of Rostock, Rostock

Correlated dynamics of the adenine-uracil hydrogen bonds in solution

09:20 - 10:10 **Graham Worth**, Birmingham University, Birmingham

Quantum dynamics simulations suitable for biomolecules:
the DD-vMCG method

10:10 - 10:30 *Coffee discussion*

10:30 - 11:20 **Janez Mavri**, National Institute of Chemistry, Ljubljana

Studies of proton transfer in biological systems

11:20 - 12:10 **Denis Bucher**, EPFL, Lausanne

Challenges for potential functions used in molecular dynamics simulations of ion channels

12:40 - 19:30 ***Excursion*** (*to National Park "Krka"*)

Saturday, 5. September 2009

Bioinformatics (Chair: Kristian Vlahoviček)

09:00 - 09:50 **Anna Tramontano**, Sapienza University, Rome

From genomes to proteomes and back

09:50 - 10:40 **Davor Juretić**, University of Split, Split

Selectivity prediction for frog-type peptide antibiotics against Gram-negative bacteria

10:40 - 11:00 *Coffee discussion*

11:00 - 11:50 **Jack Leunissen**, Wageningen University, Wageningen

ProGMap: integrated large-scale mapping of protein orthology classification schemes

11:50 - 12:20 ***Wrap up***