Scientific Report on the Workshop
"Progress in *ab initio* modelling of biomolecules: methods and applications"

Lorentz Center, Leiden University, Leiden, NL, July 3-7, 2006

Organisers
Francesco Buda, Leiden Institute of Chemistry, Leiden University, NL
Paolo Carloni, International School for Advanced Studies, Trieste, Italy
Ursula Roethlisberger, EPFL, Lausanne, Switzerland

Summary

The workshop focused on the recent developments in the computational study of structure, dynamics and function of biomolecules. Particular attention was devoted to Density Functional Theory based methods providing an effective and accurate inclusion of the electronic structure in the simulation. The main goal of the workshop was to bring together researchers active in this field for exchanging expertise and ideas on how to deal with the multi-scale problems encountered in the simulation of macromolecules and bio-systems. The workshop has been a stimulating event for all the participants and an opportunity for young researchers to show their results in an international setting. One of the strategies for the next future which were underlined during this workshop was the need to further develop hybrid methods combining approaches with different degree of accuracy from quantum mechanics to coarse grain simulations. The workshop was held at the Lorentz Center of the Leiden University and it has been funded by the Lorentz Center and by the Psi-k ESF Programme.

Scientific content and discussion

Computer simulation methods based on first principles calculations are increasingly being used to study the structure, dynamics and function of biomolecules. Specifically, the explicit inclusion of the evolving electronic structure (for example by means of Density Functional Theory) in the simulation allows for a proper description of e.g. enzymatic reactions and drugs activity. The primary aim of the workshop was to bring together several researchers active in this field with the double purpose of (i) exchanging the expertise and the progress done in the last few years, and (ii) to envisage strategies for the next future which can increase the effectiveness and scientific impact of this field of research.

While a considerable effort in computational life science is focused on gene sequence and on a mesoscopic description of protein-protein interaction, a detailed microscopic understanding of the activity of biomolecules plays an important role and represents a major scientific and computational challenge. The *ab initio* simulations constitute a crucial tool, complementary to experiments, to elucidate at the atomic level the interplay between microscopic structure and function of a biological system. Such detailed understanding can be a useful ingredient in e.g. drug design, and can have also an impact on optoelectronic, enabling for instance the design of biomolecules with properly tuned optical properties by selective mutations.

In this workshop we discussed methodological developments within *ab initio* simulations and recent efforts to broaden the range of applications to more complex systems. There are a number of technical problems in *ab initio* simulations which are not unique to biological applications but are particularly severe and unavoidable there. (i) A serious limitation is the number of atoms in a simulation, which can only cover the central active region of a protein though longer ranged electrostatic and elastic forces are also important. Therefore a large effort has been devoted recently in the development of hybrid methods which include the protein environment around the active site by using a classical force field approach (QM/MM). Linear scaling methods are also being developed to increase the size of the system treated with *ab initio* methods (ii) The correct calculation of hydrogen bonds and Van der Waals interactions, as well as the correct description of spin states in transition metal complexes present throughout biological systems, are particularly sensitive to the precise choice of correlation and exchange functional in the Density Functional Theory method. We have thus also discussed progress done in improved functionals and the comparison with other *ab initio* many body calculations. (iii) Another issue is the time scale of biological processes that are often very slow compared to the atomic motion so that one has to invoke and compute activated processes through complex pathways. Moreover, biological processes take place at room temperature and therefore it is crucial to calculate efficiently free energy barrier and the lowest free energy reaction path. (iv) A final issue discussed during the workshop is the current state-of-the-art in the calculation of excitation energies and in excited-state molecular dynamics simulations.

Here is a list of the main topics that were discussed during the workshop:

Drug-DNA interaction
Photo-activated biological processes
Structure/functionality changes induced by mutation
Hybrid methods
Linear scaling methods
Excitation energies and excited-state dynamics

Improved exchange-correlation functionals
Metadynamics and Free energy calculation
Transition path sampling
Simulation and interpretation of spectroscopic probes (e.g. NMR chemical shift)

Assessment of the workshop

The workshop has been successful in creating an opportunity to discuss several outstanding issues in *ab initio* simulations for biomolecules. The program has been organized in such a way to give ample time to discussions which played a key role. There were a total of 33 participants from Finland, Germany, Italy, The Netherlands, Spain, Switzerland, UK, and USA, all of them playing an active role during the workshop. The workshop has been a stimulating event for all the participants and many young scientists had been given the opportunity to present their research in this international setting either as an oral presentation or in the form of a poster. Poster sessions constituted a useful occasion for informal and fruitful discussions. One of the strategies for the next future which were underlined during this workshop was the need to further develop hybrid methods combining approaches with different degree of accuracy from quantum mechanics to coarse grain simulations. The participants clearly enjoyed the workshop both for the scientific aspects as well as for the excellent facilities provided by the Lorentz Center.

This workshop would not have been possible without the financial support of the Lorentz Center and the ESF Psi-k program. The organizers are particularly grateful to Martje Kruk and Wies Groeneboer at the Lorentz Center for their help and assistance.

Program

Monday 3 July

9.30-10.00	Registration
10.00-10.10	Opening
10.10-11.00	**M. Swart**, Computational Study on the Structure of DNA
11.00-11.30	Coffee & Tea
11.30-12.20	**U. Landman**, Microscopic simulations of macroscopic consequences: fixing the continuum and hybrid methods
12.30-13.30	Lunch
14.00-15.00	Poster session
15.00-15.50	**A. Magistrato**, Understanding Anticancer Drug-DNA Interactions via Molecular Dynamics Simulations
15.50-16.10	Coffee & Tea
16.10-16.40	**C. Gossens**, DNA-Binding of Ruthenium-arene anticancer drugs
16.40-17.10	**A. Karawajczyk**, The Mechanism of the Bleomycin Activity
17.10-18.30	Wine & cheese party

Tuesday 4 July

9.00-9.50	**B. Ensing**, Metadynamics as a Tool for Exploring Free Energy Landscapes of Chemical Reactions
9.50-10.40	**G. Bussi**, Free energy landscapes from combined metadynamics and parallel tempering
10.40-11.10	Coffee & Tea
11.10-12.00	**U. Roehrig**, Amyloid Fibril Formation Studied by Molecular Dynamics and Metadynamics Simulations
12.30-13.30	Lunch
14.00-14.50	**S. Raugei**, A Quantum chemistry study of the redox potential and electronic properties of Rubredoxin
14.50-15.40	**E.J. Meijer,** Structure, dynamics and proton transfer in aqueous ion solutions
15:40 – 16:10	Coffee & Tea
16:10 – 17:00	**C. Rovira,** Substrate distortion in the Michaelis complexes of glycoside hydrolases

Wednesday 5 July

9.00-9.50	**C. Filippi**, Excitations in (bio)molecules from quantum Monte Carlo
9.50-10.40	**V. Tozzini**, Variation of color and photodynamics within the family of intrinsically fluorescent proteins
10.40-11.10	Coffee & Tea
11.10-11.40	**M. Guglielmi**, Microsolvation effects on protonated tryptophan
11.40-12.20	**E. Lenders**, Protonation of the chromophore in the photoactive yellow protein
12.30-13.30	Lunch
15.00-15.30	**L. Guidoni**, Absorption Spectra in Solution by Quantum Monte Carlo/ Molecular Mechanics (QMC/MM)

15.30-16.00	**M. Zaccheddu**, Green Flourescent Protein: Shedding Light with Quantum Monte Carlo
16.00-16.20	Coffee & Tea
16.30	Departure to Conference Dinner (BBQ at the beach starting at 18.00)

Thursday 6 July

9.00-9.50	**J. Ireta**, Why helices are right-handed and beta-sheets left-handed? : Insight from first-principles calculations.
9.50-10.40	**L. Colombi Ciacchi**, Selective inhibition of CDK proteins by small ligands: the roles of hydrogen bonding, solvation, and dispersion forces
10.40-11.00	Coffee & Tea
11.00-11.50	**C. Molteni**, Mutagenesis computer experiments on ligand gated ion channels
11.50-12.30	**P. Bolhuis**, Transition path sampling of biomolecular processes using ab initio and classical molecular dynamics
12.30-13.30	Lunch
14.30-15.20	**D. Sebastiani**, Ab-initio modeling of environmental packing effects of biomolecules in their environment: solvation and crystal NMR chemical shift
15.20-16.00	**J. Neugebauer**, Environmental Effects on Molecular Properties Modeled by Frozen-Density Embedding
16.00-16.30	Coffee & Tea
16.30-17.00	**I-Chun Lin,**
17.00-17.30	**P. Wawrzyniak,** A DFT study of the special pair in Bacterial Reaction Center: Effect of histidine protonation state on the chemical shift

Friday 7 July

9.00-9.50	**F. Krajewski**, A new stochastic linear scaling electronic structure method and accurate sampling with noisy forces
9.50-10.30	**G. Canters**, Theoretical analysis of structure and function of Cu containing redox proteins: azurin and quercetinase
10.30-11.00	Coffee & Tea
11.00-11.50	**J. VandeVondele**, A combination of linear scaling and QM/MM techniques for the study of electron transfer reactions in biological systems and solar cells.
11.50-12.30	Concluding remarks