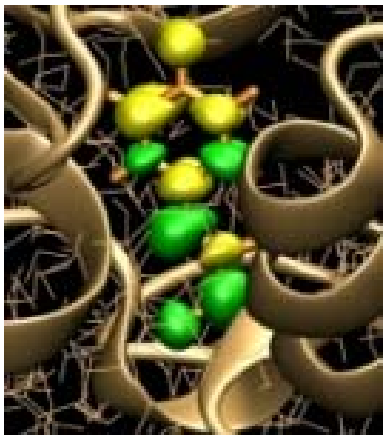
Scientific report of the workshop
Progress in ab initio modelling of biomolecules : towards computational spectroscopy



Department of Physics, University of Roma "La Sapienza", 2-4 April 2007

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ESF (Simbioma and Psi-k networks), COST-MOLSIMU, University of Rome "La Sapienza", IBM, Cooperative Lazio, and INFN (Italian National Institute for Nuclear Physics).

Summary

The workshop focused on first principle electronic structure calculations as an emerging theoretical and computational tool to unravel mechanistic details of biological systems. As a matter of facts, its rapid development is opening the avenue to the study of increasingly complex systems and, at the same time, to the possibility to perform affordable and accurate calculations of structural, dynamical and spectroscopic properties of biomolecules. The workshop aimed at giving to researchers active in this field the opportunity to exchange and integrate their expertise with the specific target of merging together different techniques, which might help bring the calculations closer to the experiments.

The presence of theoreticians with profoundly different backgrounds (chemists, physicists, and biophysicists) considerably helped to create a genuine multidisciplinary environment, which encouraged everyone to face a given problem following others' perspective and not only his. We believe that this kind of spirit for the workshops can be remarkably useful in the field of simulation of biological systems. This opportunity can allow different scientific communities (like the SimBioMa, the Psi-K and COST-MOLSIMU) to face each other and to integrate around a common scientific target.

The participation of four experimental talks was also an added value to the wokshop success. Their talks indeed guided many discussions on the way of bringing the theoretical community closer to experimental biophysics to envisage common strategies for the development of a “quantitative computational molecular biology”.

Critical assessment of the current methodological limitations and future directions were drown during discussions.

The workshop was held at the University of Rome “La Sapienza” and was funded by ESF (Simbioma and Psi-k networks), COST-MOLSIMU, University of Rome "La Sapienza", IBM, Cooperative Lazio, and INFN (Italian National Institute for Nuclear Physics).

Scientific Content and discussion at event

In the last few decades biology has been undergoing a revolution that is leading it closer to the microscopic atomic scale. Experimentally determined 3D structures of biological molecules refined with atomic resolution are indeed becoming available and they represent nowadays a fundamental starting point to understand the molecular interactions in living matter. At the same time, many other experimental techniques are expanding their predictive capabilities to the point that it is now feasible the study of single molecules properties, such as structural, optical, magnetic, and dynamical properties with increasing resolution.

In order to go beyond speculative conjectures or qualitative interpretations of this exponentially increasing amount of data, it is constantly necessary to develop new computational tools to properly simulate these systems and correctly describe their molecular properties and dynamics at the atomistic level. In this respect, in the last ten years, first principles calculations have opened a venue in both the study of increasingly complex systems and the possibility of a direct quantitative comparison between the calculated molecular properties and the biochemical experiments.

We succeeded in bringing together more than 100 scientists with different backgrounds, giving rise to a constructive and stimulating debate. Very important was the participation of very young researchers, from diploma and PhD students, to postdoctoral fellows and tenure track level scientists. Central to this workshop was the discussion on methodological developments within computer simulations and recent efforts to broaden the range of applications to more and more complex systems. A very large variety of methodologies and spectroscopic techniques were taken into account. The debate developed around four main biophysical topics:

1. Excited states and electron transfer. A variety of biological processes, such as vision and photosynthesis, are guided and regulated by electronic excitations of light-sensitive protein chromophores. Absorption and emission spectra as well as time-resolved optical properties of these molecules can be monitored accurately by experiments directly in both their complex biological environment and in the gas phase. Although a large quantity of spectroscopic data is nowadays available for a large number

of photosensitive systems, such as rhodopsin, fluorescent proteins and photosystems complexes, a quantitative treatment of the electronic structure of large molecules in their excited states is still a big challenge in first principles methods.

2. Computational spectroscopy. Beside optical spectroscopy, a plethora of other spectroscopic techniques, including NMR, IR, Raman, Mossbauer, electronic spectroscopy, EXAFS etc. is crucial to experimentally characterize structure, dynamics and function of biomolecules. The calculation of several of these quantities for large macromolecules remains however a major challenge for theoreticians, especially because these quantities often depend on the environment in a quite intricate way.

3. Computational Biophysics beyond DFT. DFT-based methods, which have the advantage of being rather computationally-cheap, often fail when dealing with excited states and charge transfer. On the other hand, higher level calculations become extremely expensive for large systems, and are applicable, up to now, only to a limited number of systems, like solids (e.g., GW corrections) or small molecules in vacuo (e.g., quantum chemistry methods, like CAS-SCF or CAS-PT2 and, more recently, QMC). The development of novel techniques and the integration and improvements of the ones currently available is therefore a crucial step for the theoretical biophysics community to extend current ab intio approaches to more complex and realistic biological systems.

4. Protein stability and free energy landscapes. One of the main goal of biological modelling is indeed to bridge the ab initio description of a small part of the system with the longer time and space scales that can be modelled by molecular mechanics. In this respect it was important to link the (local) spectroscopical quantities with the (global and long term) dynamics of biomolecules.

A number of computational techniques were critically analyzed. Among these we mention post-Hartree-Fock quantum chemical methodolgies (among the others CASSCF and CASPT2), Density Functional Theory (DFT) and time dependent-DFT approaches,

Quantum Monte Carlo (QMC), Molecular Mechanics (MM) and Quantum Mechanics/Molecular Mechanics (QM/MM) schemes.

Assessment of the results and impact of the event on the future direction of the field

The results emerged by the discussions and their impact on the future developments of ab initio modeling techniques can be divided in the following items:

1. Standard quantum chemical methodologies are mature enough to study excited states and related spectroscopies within an acceptable degree of accuracy. In this regard, novel approaches such as quantum Monte Carlo or GW methods are emerging. Indeed, thanks to the progresses done both on the theory and on the computer architectures, they are a competitive tool on small-medium size problem, giving results of excellent accuracy. We therefore expect that in the next future many body approaches will be a crucial ingredient in the first principles study of biological systems.
2. DFT based approaches, were critically reviewed and their limitations for the study of excited states, charge transfer, and transition metal complexes were clearly pointed out and extensively discussed. In spite of these drawbacks, it was shown that they can be still applied with proficiency to wide range of relevant problems.
3. The presence of theoreticians with profoundly different backgrounds (chemists, physicists, and biophysicists) considerably helped to create a genuine multidisciplinary environment, which encouraged everyone to face a given problem following others' perspective and not only his. We believe that this kind of spirit for the workshops can be remarkably useful in the field of simulation of biological systems. This opportunity can allow different scientific communities (like the SimBioMa, the Psi-K and COST-MOLSIMU) to face each other and to integrate around a common scientific target.
4. A successful ingredient of the meeting was the participation of four experimental lecturers (out of 28), which was determinant to bring the theoretical physicist community present at the meeting closer to experiments. These experimental biophysicists lighted a proficuous debate on points of strength and deficiencies on various computational methodologies applied to vibrational, optical, and EPR spectroscopies.

5. The workshop witnessed a massive participation, which was beyond our expectation (over 100 registered participants from 12 European and from 2 American countries). This is a clear indication that the community active in the field of ab-inito molecular modelling of bio-molecule is rapidly expanding in Europe. For this reason we believe that ESF should continue supporting these kind of activities in the forthcoming years.

WORKSHOP PROGRAM
Monday, April 2nd

8:30 – 9:00 REGISTRATION
9:00 – 9:30 WELCOME / INTRODUCTION
E.Longo (on behalf of the Director of the *Physics Dep.* Univ. La Sapienza)
P. Carloni (head of the *ESF Psi-K* Working group "Ab initio simulations for biology")
G.Ciccotti (member of the *ESF SimBioMa* steering committee)

ULTRAFAST SPECTROSCOPY (Chair: **L. Guidoni**)

9:30 – 10:20 **S. Haacke** (France) – EXPERIMENTAL TALK
"How much femtosecond spectroscopy can tell about excited state potential surfaces of biomolecules: the retinal-cation example"
10:20 – 11:00 **I. Tavernelli** (Switzerland)
"Ab initio excited states dynamics of organic molecules in gas-phase and solution"

Coffee break

INFRARED AND RAMAN SPECTROSCOPY (Chair: **M. Cascella**)

11:20 – 12:10 **MS. Helfand** (U.S.A) – EXPERIMENTAL TALK
"***Raman crystallographic studies of β–lactamases***"
12:10 – 12:50 **R. Vuilleumier** (France)
"Vibrational spectroscopy of small molecules of biological interest in liquid water by Car-Parrinello simulations"
12:50 – 13:30 **G. Mathias** (Germany)
"Vibrational spectroscopy within QM/MM: dynamics of protonated water networks in bacteriorhodopsin"

Lunch

FREE ENERGY / PROTEIN STABILITY (I) (Chair: **A. Rubio**)

15:00 – 15:40 **G. Ciccotti** (Italy)
"Minimum free energy paths and isocommittor surfaces"
15:40 – 16:20 **V. Blum** (Germany)
"***Hydrogen bonds, cooperativity, and the stability of helical polypeptides: towards a spectroscopic fingerprint***

Coffee break

FREE ENERGY / PROTEIN STABILITY (II) (Chair: **P. Carloni**)
16:40 – 17:20 **G. Bussi** (Switzerland)
"Beta-hairpin folding with parallel tempering and metadynamics"

17:20 – 18:00 **S. Morante** (Italy)
"Metal's role on misfolding processes: X-ray spettroscopy and numerical simulations"

Tuesday, April 3rd

PHOTOPHYSICS (Chair: **U. Röthlisberger**)

9:00 – 9:50 **SB. Nielsen** (Denmark) – EXPERIMENTAL TALK
"Photophysics of DNA building blocks"
9:50 – 10:30 **AL. Sobolewski** (Poland)
"Theoretical studies of the mechanisms of photostability of selected building blocks of life"
10:30 – 11:10 **O. Pulci** (Italy)
"Ab-initio study of the excited state properties of liquid water"

Coffee break

PHOTORECEPTORS (I) (Chair: **G. Ciccotti**)

11:40 – 12:20 **A. Rubio** (Spain)
"Excited state properties of biomolecules"
12:20 – 13:00 **C. Filippi** (The Netherlands)
"Electronic excitations of photoactive molecules by Quantum Monte Carlo"
13:00 – 13:40 **M. Olivucci** (Italy)
"Ab initio multiconfigurational quantum chemistry in photobiology"

Lunch

PHOTORECEPTORS (II) (Chair: **M. Olivucci**)

15:00 – 15:40 **F. Buda** (The Netherlands)
"***Flower color variation: a TDDFT investigation***"
15:40 – 16:20 **C. Molteni** (United Kingdom)
"Modelling excitations in the photoactive yellow protein from first principles"
16:20 – 17:00 **R.Nifosì** (Italy)
"A TD-DFT approach to the intrinsically fluorescent proteins family"

Coffee break

17:00 – 18:30 Poster session

20:00 Social Dinner

Wednesday, April 4th

ELECTRON TRANSFER SYSTEMS (Chair: **G. Mathias**)

9:00 – 9:40 **M. Sulpizi** (United Kingdom)
"Simulations of redox reactions: understanding short and long range effects "

9:40 – 10:20 **U. Roethlisberger** (Switzerland)
"Influence of the 3D- structure and solvent on the electronic properties of prototypic electron transfer azurin protein"

10:20 – 11:00 **J. Blumberger** (United Kingdom)
"Free energy computation for long-range electron transfer in ruthenium modified cytochrome c"

Coffee break

EXTENDED SYSTEM / INTERFACES (Chair: **G.B. Bachelet**)

11:30 – 12:10 **J. Vandevondele** (Switzerland)
"CP2K: accurate and large scale DFT simulations"

12:10 – 12:50 **M. Iannuzzi** (Switzerland)
"Core electron spectroscopy in condensed matter"

12:50 – 13:30 **L. Colombi-Ciacchi** (Germany)
"Atomistic modelling of biomolecules on materials surfaces"

Lunch

EPR SPECTROSCOPY (Chair: **S. Raugei**)

15:00 – 15:50 **S. Chakrapani** (U.S.A.) – EXPERIMENTAL TALK
"Structural dynamics of voltage-gated ion channels in lipid bilayer: a spectroscopic approach"

15:50 – 16:30 **M. Kaupp** (Germany)
"Density functional calculation of EPR parameters of bioradicals and metalloenzyme sites to elucidate structure and function"

Coffee Break

NMR SPECTROSCOPY (Chair: **M. Aschi**)

16:50 – 17:30 **D. Sebastiani** (Germany)
"Towards realistic QM/MM calculations of nuclear magnetic resonance parameters: improving the QM/MM interface interactions"

17:30 – 18:10 **P. Carloni** (Italy)
"Applications of NMR chemical shift calculations to biomolecules"