

Proposal for a Psi-k workshop (cosponsored by Lorentz Center)

Title: Progress in *ab initio* modelling of biomolecules: methods and applications

Location: Lorentz Center, Leiden University, Leiden, NL

Dates: 3-7 July 2006

Organisers:

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Scientific content and motivation

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. This workshop aims 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. We know for example that a single mutation changing one amino acid in a protein can have dramatic effects on a given organism. To understand such effects, molecular biologists study the interaction of a protein with other molecules, which may be small ligands or other proteins. In the laboratory they can identify a region of tens or a hundred amino acids which are responsible for some specific action. *Ab initio* simulation can then pinpoint more precisely where and how the interaction actually works and what effect the mutation has. Such detailed understanding can be a useful ingredient in drug design, for example knowing whether the mutation makes the binding to the other molecule too weak or too strong. These studies 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 will discuss 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. 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 will thus also discuss 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.

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

- Drug-DNA interaction
- Photo-activated biological processes
- Structure/functionality changes induced by mutation
- Hybrid methods
- Linear scaling methods
- Excited state dynamics
- Improved exchange-correlation functionals
- Metadynamics and Free energy calculation
- Simulation and interpretation of spectroscopic probes (e.g. NMR chemical shift)

Participants

We expect about 45 participants, including the invited speakers and organizers. Among the participants we expect of the order of 15-20 students/postdocs.

Outline of the program:

We plan to have a combination of invited speakers and invited discussion leaders. The number of talks will be limited to 4-5 per day (long and short talks) and ample time will be given to discussions which will play a key role and will focus on tackling several outstanding issues in *ab initio* simulations for biomolecules.

We will invite young scientists to present their research also in the form of a poster (the Lorentz Center has enough boards to accommodate up to about 30 posters)

Tentative list of speakers

M. Klein	University of Pennsylvania, USA
M. Parrinello	ETH Zurich, Switzerland

S. Rauei	SISSA, Italy
A. Magistrato	SISSA, Italy
E.J. Meijer	UVA, Amsterdam, NL
D. Sebastiani	MPI Mainz, Germany
B. Ensing	University of Pennsylvania, USA
F. Gervasio	Swiss Federal Institute of Technology, Lugano, Switzerland
A. Karawajczyk	LIC, Netherlands
A. Laio	ETH Zurich, Switzerland
C. Rovira	University of Barcelona, Spain
M. Swart	VU Amsterdam, Netherlands
V. Tozzini	SNS Pisa, Italy
J. Ireta	Fritz-Haber Institute, Berlin, Germany
L. Colombi Ciacchi	University of Cambridge, UK

Budget

We would like to pay for lodging expenses of all participants. We want also to contribute to some extent to the travel expenses for younger researchers.

If we assume 45 participants for 5 nights, the total expenses are:

Lodging	$45 * 5 * 70 =$	15750 Euro
Travel contributions	=	8000 Euro
Wine & Cheese party:	$7 * 45 =$	315 Euro.
Workshop Dinner:	$40 * 45 =$	1800 Euro
Coffee/tea/drinks:	$3 * 5 * 45 =$	675 Euro
TOTAL		26540 Euro

The organizers are members of the Biophysics working group within the ESF Psi-k program. We would ask Psi-k to provide a total financial support of 8.000 Euro. Please, note that this is the first time we ask Psi-k for financial support for a conference in this important topic.

Cosponsors:

The workshop will be held at the Lorentz Center of the Leiden University. The Lorentz Center has already agreed to cosponsor the workshop with a total contribution of 10.000 Euro that includes the cost of the workshop dinner. Moreover, the Lorentz Center covers the costs for organisation, secretarial support, computer assistance and administration costs. For more information on the facilities available at the Lorentz Center, see <http://www.lc.leidenuniv.nl/>