SCIENTIFIC REPORT FOR THE WORKSHOP

BIOMOLECULAR SIMULATIONS:

ADVANCED METHODS AND APPLICATIONS

LÅNGHOLMEN, STOCKHOLM, SWEDEN, 28-30 JUNE 2009

ORGANIZERS
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SUMMARY

In the post-genomic era interest shifts from the properties of individual components of living cells (*e.g.* proteins) to their many interacting complexes, of various size, composition and duration, that are at the heart of what makes the cell a living entity. Cellular components that do not communicate or interact would not contribute to the sustained organization characteristic of life. The intricate interplay between macromolecules confined in a cell thus forms the biological motivation of the present proposal.

Studies of such systems have now reached a point where computational models often have an important role in the design and interpretation of experiments. Of particular interest is the possibility of employing molecular simulations to obtain information that is difficult to determine experimentally. Typical studies range from those concerned with the structures, energies, and vibrational frequencies of small molecules, through those dealing with Monte Carlo and molecular dynamics simulations of pure liquids and solutions, to the analysis of the conformational energies and fluctuations of large molecules and molecular complexes in solution and in a crystal environment. A recurring concern is the need for convergent sampling of thermally available conformations, which is necessary for a quantitative and statistically meaningful analysis.

The 31 lectures in the workshop were divided in 8 sessions and dealt both with state-of-the-art methodologies and pertinent problems in biochemistry/molecular biology.

SCIENTIFIC CONTENT

The workshop started at lunchtime, Sunday 28 June 2009, and ended with lunch on Tuesday 30 June 2009. The venue is a conference site on an island in central Stockholm, Långholmen. The island is mainly a park, with an excellent conference facility (previously a prison) that also offers affordable accommodations (www.langholmen.com). The rooms ("cells") are small but comfortable and quite adequate according to reports from the participants; all participants from other cities than Stockholm stayed at the conference site. Monday evening was devoted to a common dinner during a 4-hour boat trip in the inner Archipelago of Stockholm – both the weather and the food were very much appreciated!

Three "plenary" 45-minute lectures were given by Profs. Martin Karplus, Michael Levitt and Wilfred van Gunsteren, pioneers of MD-simulations of biological systems. All other lectures were 30 minutes each.

The first lecture of the workshop, by Prof. Martin Karplus, summarized results from MD simulations on proteins as molecular machines. Prof. Karplus illustrated how deep insights into the inner workings of proteins can be obtained from the simulations, in particular how the conversion of chemical energy to mechanical motions occurs through asymmetric conformational changes.

Electrostatics and pKa calculations were covered in the next session, with lectures describing experimental data on a large number of titratable sites in proteins (Garcia-Moreno), an empirical computational method to predict protein pKa (Jensen) and a method using an implicit solvent representation where the pH is kept constant and the protonation state of titratable sites is allowed to vary during an MD simulation (Brooks). These issues were also brought up in lectures on QM/MM methods (York) with applications to catalytic RNAs ("ribozymes"), and in the protein session where the use of multiple configurations was demonstrated to yield improved results in protein pKa calculations (Simonson).

The session on sampling covered methods from materials science to study rare nucleation pathways (Dellago), ideas that in principle would be applicable to biosystems as well. In dynamic importance sampling (Woolf) the transition between two (experimental) states or conformations is followed without the need for an *a priori* defined reaction coordinate.

The first day ended with a session on multiscale methods, commonly used to treat problems concerning chemical reactions, *eg* using hybrid MM/QM (York, Brooks), but also with a classical approach were the system is allowed to switch between reactant and product energy surfaces (Meuwly). One interesting strategy was to optimize metabolic pathways, and also to identify possible new reaction paths that may be of interest in biotech applications (Röthlisberger).

In the session on membranes and membrane proteins the focus was very much on the utility of coarse grained models and multiscale models, which do seem to have great potential for long-time simulations of these systems where many important structural and dynamic features cover long time- and length-scales. Application to proteins (Sansom, Grubmüller) as well small molecules/drugs (Essex, Pastor) were presented.

Two sessions on proteins dealt with recognition/selectivity (Roux) and properties of hydrogen bonds (of importance for recognition) (van der Spoel), structural/dynamic adaptations in low-temperature active proteins (Brandsdal), a comparison of three methods for generating transition paths: Targeted, steered, and biased molecular dynamics (Post). Furthermore the importance of dynamics was described for the assembly of bacterial pili (Paci), and for information transfer in protein complexes (van der Vaart).

Efficient methods to assess host-guest interactions, of crucial importance in drug discovery and lead optimization, were discussed with examples illustrating successful fragment-based docking (Caflisch) and a method to find binding sites by allowing small functional units to compete for the sites in MD simulations (MacKerell). In addition to conformational flexibility of the ligand (and of the receptor binding site) it was argued that tautomeric states and protonation states also may make difference and should be accounted for in the

docking/scoring algorithm (Duan). Initial stages of the diffusional encounter process were also presented (Wade).

In the final session two lectures showed that simulations of DNA (Orozco) and RNA (Sponer), originally more difficult than protein simulations due to the highly charged nature of the nucleic acids, today can be performed quite reliably, although a word of caution was given – as ever longer simulation times are reached there is a possibility that some hitherto unseen, kinetically difficult to reach, artifact may show up. The last lecture (van Gunsteren) showed the utility and great value of using simulations to interpret experimental data, and stressed the importance of targeting the primary data as far as possible, not derived quantities.

RESULTS AND IMPACT ON FUTURE DIRECTIONS

The workshop gathered 19 speakers and 16 participants from 14 ESF countries, 13 speakers and 7 participants from USA, and ca 20 Swedish observers (mainly PhD students from Stockholm/Uppsala), who all enjoyed high level lectures and stimulating discussions in conjunction with (sometimes also during) the lectures.

In spite of the maturity of the field, as evidenced by the many lectures dealing with biological function and interpretation of experimental data, there was also a clear drive towards further developments, in particular regarding ways to achieve the necessary enhancements in sampling. Advanced biasing algorithms will be further explored together with various parallel enhancement methods (multiple simulations, replica exchange). Coarse graining is clearly in a very strong development phase, with a variety of approaches being tested in different systems. At the same time the detailed information available in atomistic simulations, either on their own or as part of even more detailed multi-scale (MM/QM) approaches, will continue to be important to explain a large number of process in cellular signaling and energy transduction/conversion. Here a need for improvements in force fields was seen, with polarizability as the next level of sophistication. The big challenges for the future lie in coming to terms with the

multifaceted complexity that is evident in biological processes already at the molecular level.

LIST OF SPEAKERS AND PARTICIPANTS

Organizers

Prof. Lennart Nilsson Stockholm (SE)

Prof. Johan Åqvist Uppsala (SE)

Speakers

Dr. Björn Olav Brandsdal	**Tromsö, (NO)**
Dr. Bernard R. Brooks	**Bethesda, (US)**
Professor Charles L. Brooks III	**Ann Arbor, (US)**
Professor Amedeo Caflisch	**Zürich, (CH)**
Professor Christoph Dellago	**Wien, (AT)**
Dr. Jianxin Duan	**Mannheim, (DE)**
Dr. Jonathan Essex	**Southampton, (UK)**
Professor Bertrand Garcia-Moreno	**Baltimore, (US)**
Professor Helmut Grubmüller	**Göttingen, (DE)**
Professor Jan Jensen	**Copenhagen, (DK)**
Professor Martin Karplus	**Cambridge, (US)**
Professor Michael Levitt	**Stanford, (US)**
Professor Jianpeng Ma	**Houston, (US)**
Professor Alexander MacKerell	**Baltimore, (US)**
Professor Markus Meuwly	**Basel, (CH)**
Professor Modesto Orozco	**Barcelona, (ES)**

Dr. Emanuele Paci	**Leeds, (UK)**
Dr. Rich Pastor	**Bethesda, (US)**
Professor Carol Post Post	**West Lafayette, (US)**
Professor Ursula Röthlisberger	**Lausanne, (CH)**
Professor Benoit Roux	**Chicago, (US)**
Professor Mark Sansom	**Oxford, (UK)**
Professor Thomas Simonson	**Palaiseau, (FR)**
Dr. Jiri Sponer	**Brno, (CZ)**
Professor David van der Spoel	**Uppsala, (SE)**
Professor Arjan van der Vaart	**Tempe, (US)**
Professor Wilfred F. van Gunsteren	**Zürich, (CH)**
Dr. Jordi Villa	**Barcelona, (ES)**
Dr. Rebecca Wade	**Heidelberg, (DE)**
Professor Tom Woolf	**Baltimore, (US)**
Professor Darrin York	**Minneapolis, (US)**

Participants

Dr. Georgios Archontis	**Nicosia, (CY)**
Dr. Arnaud Blondel	**Paris, (FR)**
Dr. Michael Crowley	**Golden, (US)**
Professor Michael Feig	**East Lansing, (US)**
Dr. Stefan Fischer	**Heidelberg, (DE)**
Dr. Nicolas Foloppe	**Winnersh, (UK)**
Professor Jiali Gao	**Minneapolis, (US)**
Dr. Berk Hess	**Stockholm, (SE)**
Dr. Milan Hodoscek	**Ljubljana, (SI)**

Dr. Andrey Karshikoff	**Huddinge, (SE)**
Mr. Gerhard Koenig	**Wien, (AT)**
Dr. Katarzyna Kulinska	**Poznan, (PL)**
Dr. Tadeusz Kulinski	**Poznan, (PL)**
Professor Themis Lazaridis	**New York, (US)**
Dr. Erik Lindahl	**Stockholm, (SE)**
Dr. Francois Marchand	**Zürich, (CH)**
Dr. Robert Petrella	**Cambridge, (US)**
Dr. Joanna Sarzynska	**Poznan, (PL)**
Dr. Roland Stote	**Strasbourg, (FR)**
Ms. Arzu Uyar	**Istanbul, (TR)**
Dr. Lee Woodcock	**Bethesda, (US)**
Dr. Xiongwu Wu	**Bethesda, (US)**