Eur. Phys. J. Special Topics **224**, 2173–2176 (2015)

DOI: 10.1140/epjst/e2015-02406-y

THE EUROPEAN PHYSICAL JOURNAL SPECIAL TOPICS

Editorial

Scale bridging in molecular simulation

Recurrent problems and current options

Carsten Hartmann[a] and Luigi Delle Site[b]

Institut für Mathematik, Freie Universität Berlin, Arnimallee 6, 14195 Berlin, Germany

Received 25 June 2015 / Received in final form 15 July 2015
Published online 21 September 2015

Abstract. Multiscale and multiphysics approaches have become an integral part of the molecular modeling and simulation toolbox and are used to attack various real-world problems that would be out of reach without these techniques. This special topics issue is devoted to a critical appraisal of some of the most popular scale bridging techniques for molecular simulation. It features regular articles and a "Discussion and Debate" section, in which experts in the field discuss specific articles and general aspects of scale bridging techniques.

Recent years have seen a growing interest in multiscale and multiphysics approaches for molecular simulation that have become a part of many molecular dynamics simulation packages. On the one hand, the advent of such *scale-bridging* techniques has enabled to apply molecular dynamics simulation to real world problems that would have been out of reach otherwise [1]. On the other hand, the growing relevance of scale-bridging for computations has raised issues regarding the theoretical (mathematical and/or physical) foundation of the methods, the accuracy of the results, and the robustness of the algorithms, which play a key role for the predictive power of molecular simulations. For example, molecular drug design uses multiscale molecular dynamics simulations to study the flexibility of a protein and its interaction with a target molecule of interest; typical time scales range from femtoseconds (molecular vibrations) up to micro- or milliseconds (conformational changes) and length scales range from the size of an atom (a few angstroms) up to the size of a molecular complex with millions of atoms. As the interactions between ligand protein and target molecule are typically local, it is natural to resort to a coarse-grained description of the parts of the system that are far away from the interaction site. Coarse-grained models may use, e.g. beads to represent groups of atoms, and thus to reduce the number of unknowns in the simulation, which not only results in a speed up of the simulation, but also in a reduction of the amount of data that need to be analyzed (see Fig. 1). It is not always clear, however, whether the local dynamical interactions between protein and target molecule will lead to an overall (non-local) change in the protein backbone structure or just an unimportant side-chain rotation. Either way, the prediction of protein structures, binding free energies, or ligand association-dissociation rates require both model and algorithm to be reasonably accurate. For an efficient *in silico*

[a] e-mail: chartman@mi.fu-berlin.de
[b] e-mail: luigi.dellesite@fu-berlin.de

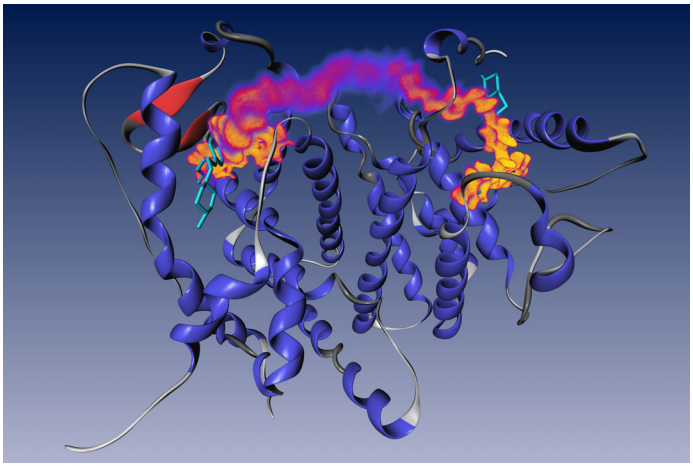

Fig. 1. Binding to an oestrogen receptor: The figure shows the coarse-grained protein backbone of the receptor molecule and a fully resolved ligand molecule in stick representation; the cloud represents the flexibility of the ligand inside the binding pocket of the receptor. Note that the ends of the ligand molecule are tightly bound to the receptor whereas it is shows different degrees of flexibility–and hence time scales–in the middle. This figure is courtesy of Marcus Weber, Zuse Institute Berlin.

drug design, understanding how local properties can influence the global behaviour of a molecule is crucial, so as to allow for a systematic search for specific molecules with properties on demand [2].

It is clear that devising accurate and efficient scale-bridging techniques requires both physical understanding of the processes involved and mathematical rigor in the construction of a model or an algorithm, without ruling out the possibility of employing data-driven approaches or parametrizations at some stage. This implies that physical accuracy or empirical adequacy is intimately linked with (a) the mathematically sound formulation of a model and (b) the robustness and consistency of the underlying algorithms, where the latter should be well distinguished from the former.

Having said this, it does not come as a surprise that this issue of EPJ ST comprises contributions from physicists, chemists, material scientists, engineers and mathematicians. The idea for this topical issue came up during the CECAM workshop *Scale-Bridging Techniques in Molecular Simulation: A Critical Appraisal* that took place at Freie Universität Berlin in 25–27 August 2014. It became manifest during the workshop that an open and critical inventory taking was due–despite of the undoubtedly existing various success stories related to multiscale molecular simulation. The articles in this issue examine some of the most prominent currently used scale-bridging methods that involve either multiple scales in space or time, or the heterogeneous coupling between different physical realms such as discrete and continuum models. The backbone of each paper is a systematic account of either existing or new methods, taking into account possible shortcomings or computational limitations, and is complemented by a discussion of open problems, desiderata and future directions. It should be stressed that mathematical analysis plays a key role here, in that it is crucial to assess the properties of computational algorithms, e.g., to analyze convergence or stability. The contributions in this issue clearly show this.

The articles of this issue roughly fall into two main categories: Part A includes papers dealing with techniques of molecular coarse-graining and the coupling of different molecular resolutions [3–11]:

- *Thermodynamic consistency and other challenges in coarse-graining models*, by Marina Guenza.
- *A Generalized–Yvon–Born–Green Method for a Coarse-Grained Modeling*, by Joseph F. Rudzinski and William G. Noid.
- *Multiscale Molecular Dynamics/Hydrodynamics implementation of two dimensional "Mercedes Benz" water model*, by Arturs Scukins, Dmitry Nerukh, Evgen Pavlov, Sergey Karabasov, and Anton Markesteijn.
- *Coarse-graining polymer solutions: a critical appraisal of single- and multi-site models*, by Giuseppe D'Adamo, Roberto Menichetti, Andrea Pelissetto, and Carlo Pierleoni.
- *Adaptive Resolution Simulation in Equilibrium and Beyond*, by Han Wang and Animesh Agarwal.
- *Advantages and challenges in coupling an ideal gas to atomistic models in adaptive resolution simulations*, by Karsten Kreis, Aoife C. Fogarty, Kurt Kremer, and Raffaello Potestio.
- *An Introduction to the problem of bridging quantum and classical dynamics*, by Sara Bonella and Giovanni Ciccotti.
- *Continuum simulations of water past fullerenes*, by Aleksandar Popadić, Matej Praprotnik, Petros Koumoutsakos, and Jens H. Walther.
- *Open Boundary Molecular Dynamics*, by Rafael Delgado-Buscalioni, Jurij Sablić, and Matej Praprotnik.

Papers in this group are concerned with scale-bridging techniques in space and time and involve methods that combine different molecular resolutions or different physical models. Typical representatives of the aforementioned techniques are atomistic-continuum methods or quantum-classical molecular dynamics (QCMD). Both modeling and numerical aspects are covered in these papers.

Part B include techniques which aim at bridging time scales by accelerated dynamics or tailored approaches for rare events [12–18]:

- *Effective interactions and large deviations in stochastic processes*, by Robert L. Jack and Peter Sollich.
- *Reactive Flows and unproductive cycles in irreversible Markov chains*, by Ralf Banisch, Nataša Djurdjevac-Conrad, and Christof Schütte.
- *Free Energies for Rare Events: Temperature Accelerated MD and MC*, by Simone Meloni and Giovanni Ciccotti.
- *Practical and conceptual path sampling issues*, by Peter Bolhuis and Christoph Dellago.
- *Accelerated dynamics: Mathematical foundations and algorithmic improvements*, by Tony Lelièvre.
- *On the full power and Essential Limitations of Markov State Models*, by Marco Sarich and Christof Schütte.
- *Pseudo generators for under-resolved molecular dynamics*, by Andreas Bittracher, Carsten Hartmann, Oliver Junge, and Péter Koltai.

This second group of papers is concerned with computational methods for the analysis of molecular time scales and the simulation of rare events. A typical scenario that is considered is a reactive event on a macroscopic (e.g. conformational) time scale that involves a hierarchy of interwoven shorter time scales, and a typical instance of a

numerical scheme would be a Monte Carlo method that aims at resolving the reactive event by generating many short scale simulations.

Clearly, the above classification, that has been made according to the tenor of the articles, is not sharp, but is meant to provide some orientation to the reader. Of course, there are strong links between the two main categories, such as the connection between free energy as a spatially coarse-grained representation of a molecule and free energy as is appears in path sampling methods, and, should the reader wish to have a finer categorization, there are several sub-categories which are relevant and which should be named, such as averaging and coarse-graining, hydrodynamics, QCMD, accelerated MD, mathematical foundations, systematic error estimates, etc.

The articles listed above are framed by a "Discussion and Debate" section that contains short commentaries. In order to represent the various scientific fields involved in Parts A and B of the issue, we have asked experienced scholars from chemistry, physics, and mathematics to provide their thoughts about, e.g., future directions that they believe to be relevant for the field of multiscale molecular simulation, or on specific aspects that are brought up in one or several of the papers. The comments should be taken as what they are: comments. May they set off further debates or research, whose continuation is left in the hands of the readers of this topical issue.

The realization of this project has been made possible through the support of the Deutsche Forschungsgemeinschaft (DFG) through grant CRC 1114.

References

1. The Nobel Prize in Chemistry 2013 – Press Release, Nobel Media AB 2014 (2015) http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2013/press.html
2. P. Tuffery, P. Derreumaux. J. R. Soc. Interface **9**, 20 (2012)
3. M. Guenza, Eur. Phys. J. Special Topics **224**(12), 2177 (2015)
4. J.F. Rudzinski, W.G. Noid, Eur. Phys. J. Special Topics **224**(12), 2193 (2015)
5. A. Scukins, D. Nerukh, E. Pavlov, S. Karabasov, A. Markesteijn, Eur. Phys. J. Special Topics **224**(12), 2217 (2015)
6. G. D'Adamo, R. Menichetti, A. Pelissetto, C. Pierleoni, Eur. Phys. J. Special Topics **224**(12), 2239 (2015)
7. H. Wang, A. Agarwal, Eur. Phys. J. Special Topics **224**(12), 2269 (2015)
8. K. Kreis, A.C. Fogarty, K. Kremer, R. Potestio, Eur. Phys. J. Special Topics **224**(12), 2289 (2015)
9. S. Bonella, G. Ciccotti, Eur. Phys. J. Special Topics **224**(12), 2305 (2015)
10. A. Popadić, M. Praprotnik, P. Koumoutsakos, J.H. Walther, Eur. Phys. J. Special Topics **224**(12), 2321 (2015)
11. R. Delgado-Buscalioni, J. Sablić, M. Praprotnik, Eur. Phys. J. Special Topics **224**(12), 2331 (2015)
12. R.L. Jack, P. Sollich, Eur. Phys. J. Special Topics **224**(12), 2351 (2015)
13. R. Banisch, N. Djurdjevac-Conrad, C. Schütte, Eur. Phys. J. Special Topics **224**(12), 2369 (2015)
14. S. Meloni, G. Ciccotti, Eur. Phys. J. Special Topics **224**(12), 2389 (2015)
15. P. Bolhuis, C. Dellago, Eur. Phys. J. Special Topics **224**(12), 2409 (2015)
16. T. Lelièvre, Eur. Phys. J. Special Topics **224**(12), 2429 (2015)
17. C. Schütte, M. Sarich, Eur. Phys. J. Special Topics **224**(12), 2445 (2015)
18. A. Bittracher, C. Hartmann, O. Junge, P. Koltai, Eur. Phys. J. Special Topics **224**(12), 2463 (2015)