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Progresses Towards the Advanced Computational Chemistry of Increasingly Complex Systems

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Abstract: At the dawn of a new millennium, the perspectives offered by computational chemistry are reviewed with a strong emphasis placed on methodological developments and prospective applications of quantum chemistry. In particular, current progress in both density functional theory and linear scaling algorithms is such that accurate and realistic modeling of increasingly complex systems comprising, *e.g.* 10^3–10^4 atoms and up to 10^5 basis functions will be within the reach of standard computers in a couple of years.

Keywords: Computational chemistry · COST · Density functional theory

As stated in the memorandum of understanding of the European COST Action D9, with the title *Advanced Computational Chemistry (CC) of Increasingly Complex Systems*, CC has become a mature discipline which plays a major role in the modeling of complex systems, with applications such as rational drug design, prediction of the properties of new materials and proposals for their synthesis, design of new catalysts, and modeling of physical and chemical processes in the environment [1]. In this short paper summarizing the major aspects of the presentation delivered at the 2nd Swiss COST Chemistry Symposium, special attention is given to the progress recently achieved in computational quantum chemistry and the perspective it offers today in pushing forward the limits of large scale calculations.

There is no doubt that quantum chemistry is the method of choice for modeling or simulating complex systems when information related to electronic structure is needed or, more generally, when parameters of classical methods are not available. In particular, methods based on density functional theory (DFT) have made a remarkable breakthrough in computational quantum chemistry [2] to the point that they now offer a better performance/price (of the calculations) ratio compared with most wavefunction-based methods. This is particularly true since the advent of linear scaling DFT methods, *i.e.* of efficient techniques that involve a computational effort t scaling linearly as a function of the molecular size N, leading ultimately to a typical computer time of 2 h on a workstation for an SCF calculation on an RNA fragment containing 1026 atoms and 6767 basis functions [3]!

In any case, for both wavefunction-based and DFT methods, the cues for the treatment of increasingly complex systems (comprising, typically, 10^4–10^5 atoms) are as follows:

- A reduction in the prefactor p in the linear scaling $t \equiv p.N$, *i.e.* development of algorithms leading to p values that are as small as possible;
- Breaking the system up into several parts (subsystems);
- Using several techniques for the subsystems, *e.g.* treating the active site of a protein by means of a quantum mechanical method and a molecular mechanics model for the remaining system;
- Making the techniques work together.

As for DFT itself, the perspectives offered and challenges to be faced in advanced computational chemistry studies may be summarized as follows:

- Development of new algorithms (*e.g.* multipole methods), methodologies (*e.g.* the near-sightedness concept), and subsystem partitioning (*e.g.* divide and conquer) to improve the efficiency of linear scaling;
- Improvement of existing functionals for exchange-correlation energy and the generation of new ones;
- Improvement of time-dependent DFT algorithms for a better treatment of excited states;
- Development of further first-principles, DFT-based, molecular dynamics methods;
- Further development of the calculation of molecular properties: NMR, EPR, hyperpolarizabilities, magnetizabilities, response properties, *etc.*;
- Further developments in conceptual DFT: hardness, softness, chemical potential, *etc.*

Clearly the tremendous efforts witnessed today in computational chemistry, in particular in the areas outlined above, lead us to an optimistic conclusion: what if computing resources in ten or twenty years from now are faster than existing ones by, *e.g.* a factor of 10^3? That would mean that, using linear scaling methods, systems larger than the existing ones by a factor of 10^3 could be calculated by means of the same computational effort. Systems consisting of 10^5–10^6 atoms could thus be modeled or simulated, *i.e.* proteins in solution, large aggregates, condensed phase materials, *etc.* Even though these statements are provocative and somewhat speculative, they vividly illustrate the potentialities of state-of-the-art computational quantum chemistry in the 2000s.

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