

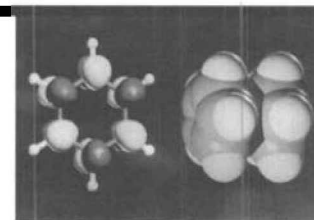
COMPUTATIONAL CHEMISTRY COLUMN

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Presentation of the New COST Chemistry Action D9: Advanced Computational Chemistry of Increasingly Complex Systems

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1. Introduction

As reported in a previous column [1], computational chemistry was not absent from the first seven COST (European co-operation in the field of science and technology) Chemistry Actions D1-D7 launched in 1991. Indeed, the D3 Action was dedicated to this field under the title *Theory and Modelling of Chemical Systems and Processes*. However, the D3 Action came to an end on September 9, 1997, and the vast majority of the research groups involved considered it as a success. This has prompted some members of the Management Committee of D3 to launch a new Action devoted to Computational Chemistry, and the purpose of this column is to present it to our readers. Known as D9, its title is *Advanced Computational Chemistry of Increasingly Complex Systems* and it actually started already on June 19, 1997, for a duration of five years.

It has become clear during the course of the D3 action that computational chemistry has become a mature discipline playing an increasing role in the modelling of complex systems, with applications such as rational drug design, prediction of properties of new materials and proposals for their synthesis, design of new catalysts, and modelling of physical and chemical

processes in the environment. However, for computational chemistry to be even more successfully involved in such research issues, new methodological developments and synergistic combinations of different theoretical methods have to be introduced. This will allow an extension of theoretical investigations to the realistic modelling of many-particle phases in which chemistry takes place, such as solute-solvent, liquids, solid materials and biological macromolecules. To summarize, theoretical chemistry should be able to treat nonideal heterogeneous systems with a large number of particles and components.

Both scientific and economical implications of such a development are important for European industries. To take an obvious example from pharmaceutical research, *de novo* drug design, *i.e.*, the computer generation of possible biologically active structures, has recently come on so strong to compete with the experimental screening. This advance leads to a reduction of time and cost of new products development as well as to an improvement in productivity and safety of research and development.

The new action should therefore differ from the previous one in promoting European collaboration along the following lines:

- Tackle the frontiers of theoretical and mathematical chemistry.
- Develop new computational schemes especially designed to exploit the innovative features of parallel computers.

- Establish better contacts with contiguous disciplines (such as physics, mathematics, biology, and computer science) to promote interdisciplinary collaboration.

2. Purpose and Strategy of the New Action

Chemistry is a science with beneficial impacts of utmost importance for mankind. Accordingly, both basic and applied research in chemistry should be of significant help in important issues such as world population, new energy sources, environment protection, *etc.* Needless to say, the role of chemical industries is crucial in this context, and European chemical companies have a long-standing tradition of high-level products and competitiveness. As the application of computers has become central in the doing of chemistry, and as computer-aided molecular design is an important component of computational chemistry, the European chemical industry needs to be able to benefit from the latest developments in this field. To this end, chemical research in Europe should involve a direction devoted to advanced computational chemistry, namely global accurate molecular modelling of increasingly complex systems.

The present concept of advanced computational chemistry is different from the standard molecular modelling tools based on molecular mechanics/dynamics and quantum chemistry. Indeed, most of these tools have reached today a stage where

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they can be used more or less as black boxes in routine applications, and there would be little point to initiate a European action aimed at developing new tools of the same kind. Most of the corresponding program packages are commercially available and many man-years have already been invested in their development, so that new initiatives aiming at similar purposes would be wasteful today. Even though they are deeply needed in some areas of chemistry and biochemistry, the same is true for the development of better parameters for force field methods, since the advance taken by US-based groups or consortia is enormous. It is the opinion of the proponents of the new action that computational chemistry should decidedly turn to advanced techniques along the following lines:

- Combine different approaches in order to obtain the synergistic effect of the individual methods.
- Generalize the treatment of molecular processes by improving molecular dynamics algorithms.
- Design more effective methods to treat electron correlation and relativistic effects in order to improve the quality of electronic energy calculations (coupled-clusters, perturbation theory, and density functional approaches).
- Develop techniques to deal with the interaction of electronic and nuclear motion, *i.e.*, going beyond the *Born-Oppenheimer* approximation which is generally necessary in treating excited states of molecules and transition states in photochemical and thermal reactions.
- Develop methods to make use of new computer architectures, in particular efficient algorithms for parallel computers.

All these advances should obviously be in-line with the most recent hardware and software technologies.

By *increasingly complex systems*, it is meant that both the systems investigated and the models used should reflect chemical conditions in a realistic way. This requires the proper and simultaneous treatment of different species and phases involved as well as the adequate control of relevant parameters such as time, temperature, *etc.* Such simulations will then be applicable to problems of paramount importance in chemistry. The purpose of the new action is therefore to accurately model systems and processes such as:

- Reactions of complex chemical systems such as those of environmental and biological relevance.
- Molecular systems and aggregates with

special optical, electric, and magnetic properties.

- Structural and electronic phenomena such as those occurring at surfaces and interfaces.
- Condensed phase materials simulated under nonequilibrium conditions over the nanosecond timescale with inclusion of polarizabilities.
- Potential drugs *de novo* designed with the aid of molecular quantum similarity, 3D-QSAR (Quantitative Structure-Activity Relationships), and artificial intelligence techniques.

These are selected applications of advanced computational chemistry techniques. The technology could also be applied to other fields like materials science, catalysis, and supramolecular chemistry.

A characteristic feature of the new action is its large interdisciplinarity since the contribution of physicists, mathematicians, computer scientists, and biologists is implied to a large extent. This is especially true for the methodological developments which most often lie at the borderline of these disciplines. That will constitute a marked difference with the previous action. The fundamental know-how in Europe for these theoretical and mathematical developments is high, as, for instance, several countries have a long tradition of high-level research in theoretical physics and mathematics.

Undoubtedly, a COST action oriented towards advanced computational chemistry of increasingly complex systems will strongly help European research and development in keeping its competitiveness and creativity. To this end, it seems realistic to strive for a representative sampling of the various communities involved and to identify likely prospects for interdisciplinary synergy.

3. General Background

3.1. Why a COST Project for this Topic?

The term Advanced Computational Chemistry is used in the following in order to describe a technology, wherein computational methods are used for the prediction of structural, dynamical, and thermodynamical properties of chemical systems. Examples for increasingly complex systems are molecules in interaction with their environment (solvent, surface, catalyst, *etc.*) or with radiation, reactive systems with several degrees of freedom, guest-host interactions in solution, energy surfaces with many local minima, liquid crystals, polymers and clusters, *etc.*

Traditionally, computational chemistry is considered as a natural outgrowth of theoretical chemistry, the role of which should involve the creation and dissemination of penetrating conceptual infrastructure for the chemical sciences. As far as atomic and molecular levels are concerned, this infrastructure could be well established: there are numerous methodologies (at all levels of complexity) available for the treatment of quantum chemical problems as well as for molecular dynamics and Monte Carlo-type simulations. The applications of these methods in computational chemistry have led to the solution of many problems in real chemical systems, especially when these systems are of limited complexity. At present, for systems of larger complexity, the traditional tools can be applied only to very special cases because of the dramatical increase in the computational effort with the size of the molecules (or number of electrons). Therefore, the main goal of the action will be an extension of these methods to a rational design of drugs, to the prediction of properties of new compounds and proposals for their synthesis, to the support of catalysts design, and simulation of physical and chemical processes in the environment. In this case, significant progress can be made by taking advantage of the innovative features of modern computers. Furthermore, new concepts and new tools are needed in this field. For example, there are only a few attempts to extend the set of computational chemistry toolkits which root back to mathematical statistics, databases analysis, fuzzy logic, artificial intelligence, and theoretical biology. In this case, efforts have to be directed to make them applicable to real systems in an effective manner.

The aim of the new COST Action is to bring under a common umbrella European researchers, who either work on the extension of standard methods or have already started to develop (and apply) nonstandard strategies, and to bring them together with colleagues from other fields (mathematics, computer science, database handling, bioinformatics, *etc.*) and boost future developments.

3.2. Status of Research in the Field

At present, the main emphasis of computational chemistry has been on solving the many-body electronic structure problem and on using the resulting potential-energy surfaces to investigate nuclear motion. This has led to a collection of programs based on classical, semiclassical, and quantum techniques. Since 1980, the use of these programs has become a key

tool for modelling molecules and gas-phase chemical reactions of relatively small molecules. The list of achievements is long and only typical ones are reported below. Structural determination can be performed with so-called chemical accuracy (± 0.01 Å on bond lengths, $\pm 1^\circ$ on angles) using computational methods, not only for gas-phase systems but also for crystalline materials. The fingerprint of most molecules provided by the vibrational spectra (IR and Raman spectroscopy) can be reproduced rapidly and reliably with computational techniques. Molecular dynamics is easily providing accurate prediction on the density of states at different temperatures. Scattering experiments from electrons or neutrons can be simulated with notable accuracy from trajectories analyses in primary output from molecular dynamics. The availability of molecular trajectories coupled with computer graphics and visualization allows to represent important aspects of molecular aggregation, which were previously totally inaccessible. Virtual reality is expected to bring these techniques to higher and higher resolution. Thermodynamic data and dissociation energies, once a most difficult prediction for theoretical and computational chemistry, are now accessible with an error no longer measured in a few eV but in a few kcal/mol or even better. Relativistic effects very important for heavy-atom molecules can now be computationally predicted. For large molecules, simple methods have been used by chemists for a long time to estimate the energy near their equilibrium geometry. In the molecular mechanics approach the total energy of a chemical system is approximated by a sum of simple terms involving distances between atoms, bond angles, and dihedral angles. These terms involve parameters estimated by assuming that they have the same value as those fitted to properties of simpler molecules (chemists have since long known that many structural and energetic features of molecules are nearly transferable among similar subfragments of molecules). This representation of the energy has made it possible the modelling of biological systems and a rational design of drugs.

The application of molecular dynamics and Monte Carlo methods to proteins and other biomolecules in the 1970s has led to their widespread use by the theoretical and experimental chemical community. The need for efficiency in designing molecular dynamics algorithms and Monte Carlo simulations to address relevant questions like those about protein folding is also prompting a renewed contact of

computational chemists with the applied mathematics and physics community.

Molecular quantum mechanics was extended to the treatment of chemical reaction rates of large molecules by modelling the reactive event as a passage over the barriers to reaction of a multidimensional potential-energy surface. In its simplest form, the model corresponds to splitting the reactive process into a first step of reactants moving towards transition states (the critical configurations), and a second step of transition states evolving towards reaction products.

Search for new drugs or pesticides typically involves the investigation of thousands of compounds, whose biological properties can be correctly forecast using computational methods. Intelligent database retrievals play also an important role within the strategy for searches for new drugs or pesticides. There are well-documented cases of the use of computer methods, particularly quantitative structure-activity relationship methods, as an integral part of the design of compounds presently marketed as drugs or agrochemicals. Usually in QSAR methods, the relationships are examined using multiple linear or nonlinear regression, classical multivariate statistical techniques. However, discriminant analysis, principal components regression, factor analysis, and neural networks have also been applied to these problems. In the last ten years, molecular quantum similarity techniques have emerged as a comprehensive tool for drug design.

A need for a merge of fluid dynamics with either classical microdynamics or cellular automata as well as the use of computed process rates constitute the scientific base to develop chemistry jointly with chemical engineering, with a great effect on chemistry and industry productivity.

Topology and artificial intelligence techniques are coupled to describe molecular transformations such as reactions and conformation changes.

3.3. Relationship with other European Programs

There is, presently, no organization in Europe with the mission of coordinating the design and the methodological development of 'new and pioneering' software for European computational chemistry; this contrasts the trend whereby the USA Science Foundation and the USA Department of Energy (and other agencies as well) are supporting computational chemistry in American Universities. The Esprit III program, with EUROPORT, likely has

been the most direct and comprehensive program for computational chemistry, but it is now in its last phase. Therefore, despite the widespread research work in this field, there is no official involvement from Europe in developing collaborative efforts. The relevance of the topic has been recognized by the CERC3 (Chairmen of the European Research Council Chemistry Committees), who organized a 'European Young Chemists Workshop' on 'Advanced computational studies of increasingly complex chemical systems' (Wien, March 17–21, 1996). Therefore, a coordination of this research is needed through the COST Action.

4. Objectives of the Action and Scientific Content

The main objective of the new COST Action is to enlarge the scope of computational chemistry techniques so as to perform a realistic modelling of chemical systems. This means that computational chemistry tools should be considerably improved to gain efficiency and friendliness. Efficiency improvement will be gained by extensive design of algorithms for innovative parallel architectures. It will also be improved by using alternative non-directive approaches typical of artificial intelligence and data-mining techniques. On the other hand, friendliness will be improved by boosting graphical tools and interactive approaches.

This means also that both the systems investigated and the models used should reflect chemical conditions in a realistic way. This requires the proper and simultaneous treatment of different species and phases involved as well as the adequate control of relevant parameters such as time, temperature, *etc.* Such simulations will then be applicable to problems of paramount importance in chemistry such as rational drug design, prediction of properties of new materials and proposals for their synthesis, design of new catalysts, and modelling of physical and chemical processes in the environment. New methodological developments and synergistic combinations of different theoretical methods have to be introduced.

The objective of the new Action is therefore to efficiently and accurately model systems and processes such as:

- Reactions of complex chemical systems such as those of environmental and biological relevance.
- Molecular systems and aggregates exhibiting special optical, electric, and magnetic properties.

- Structural and electronic phenomena such as those occurring at surfaces and interfaces.
- Condensed phase materials simulated under nonequilibrium conditions over the nanosecond timescale with inclusion of polarizabilities.
- Potential drugs *de novo* designed with the aid of Molecular Quantum Similarity, 3D-QSAR, and artificial intelligence techniques.
- These are selected applications of advanced computational chemistry techniques. The technology could also be applied to other fields like materials science, catalysis, and supramolecular chemistry.

4.1. Subtopics

The new Action should focus on methodological developments for increasingly complex systems, in particular by taking into account the needs of advanced experiments, along the following lines:

- 1) Combine different approaches in order to obtain the synergistic effect of the individual methods. A relevant example of this is the embedding of quantum mechanics techniques into molecular mechanics approaches. Another example of interest for this action is the coupling of fluid dynamics codes with scattering and molecular dynamics methods.
- 2) Generalize the description of molecular processes by improving the algorithms treating dynamical aspects. This is the case of techniques based on cell-multipole and multiple time-step methods. Other relevant examples are the use of symplectic integrators and N-scaling methods for quantum molecular dynamics.
- 3) Develop efficient techniques and algorithms *de novo* designed for parallel architectures to boost the performance of computational chemistry codes when considering large systems. Interesting developments are expected in fields like adaptive multigrids techniques for treating electrostatic problems, domain decomposition for integrating dynamical differential equations, multilevel farm organization for approaches consisting of computational grains of different size, *etc.*
- 4) Design efficient methods to treat electron correlation and relativistic effects. This may occur by adopting new exchange-correlation functionals in density functional theory by designing procedures to account for localized correlation, by improving coupled-cluster and perturbation theory methods, by

taking into account correlation in semi-empirical schemes or by compact configuration interaction schemes.

- 5) Develop techniques to deal with the interaction of electronic and nuclear motions (going beyond the 'Born-Oppenheimer Approximation'). This is important for transition states in reactions, in photochemical processes, and in the spectroscopy of electronically excited states. It could be very useful as well in modelling atmospheric and environmental processes, and materials with unusual properties.

5. Conclusions

The response of the European Chemical Community to the new COST D9 Action has been very encouraging so far. No less than ten countries, including Switzerland, have signed the Memorandum of Understanding by which they accept to participate in the Action. In addition, several research projects have already been submitted to the European Management Committee, and other ones are in preparation. Undoubtedly, this Action is going to be the proper successor of D3. Readers interested in preparing a D9 research project or in taking part in an existing one should consult the web sites <http://www2.cordis.lu/cost/home.html> or <http://www.unil.ch/cost/chem> which contain all the information. If their project is accepted by Brussels, Swiss participants may possibly get some partial support from the Swiss Federal Office for Education and Science by submitting a proposal for their own sake. If needed, further information about the COST Action D9 may be obtained from the author of this article.

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[1] J. Weber, *Chimia* 1996, 50, 285