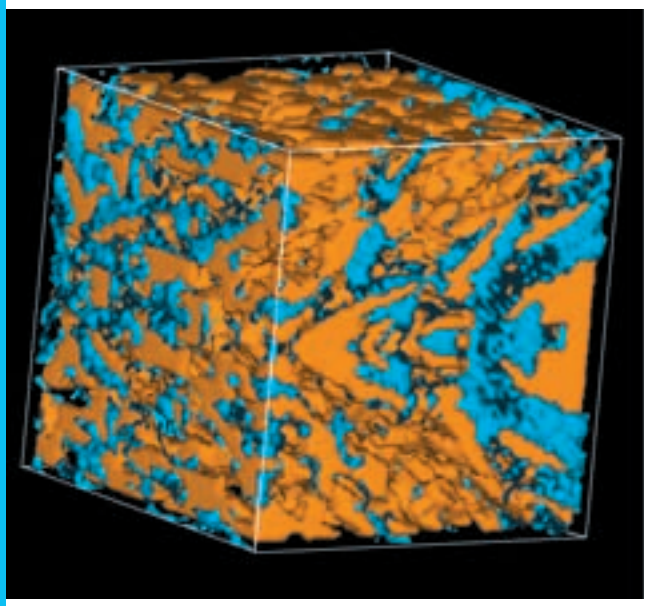
Challenges in Molecular Simulations: bridging the length and time-scale gap (SIMU)

An ESF scientific programme



The ESF programme on Challenges in Molecular Simulations: bridging the length and time-scale gap (SIMU) *aims at building cooperation across Europe in the field of computational physics and chemistry of condensed matter, with emphasis on the development of tools to perform multiscale molecular simulations.*

The challenge undertaken by the programme is to develop new computational techniques to bridge the gap that exists between the length and time scales studied in molecular simulations and those relevant for most industrial and biological processes. By pooling European expertise in over 140 laboratories from various sub-fields it intends to solve the physical problems arising when atomistic simulations, classical or quantum, are embedded in coarsed-grained mesoscopic models.

The European Science Foundation acts as a catalyst for the development of science by bringing together leading scientists and funding agencies to debate, plan and implement pan-European initiatives.

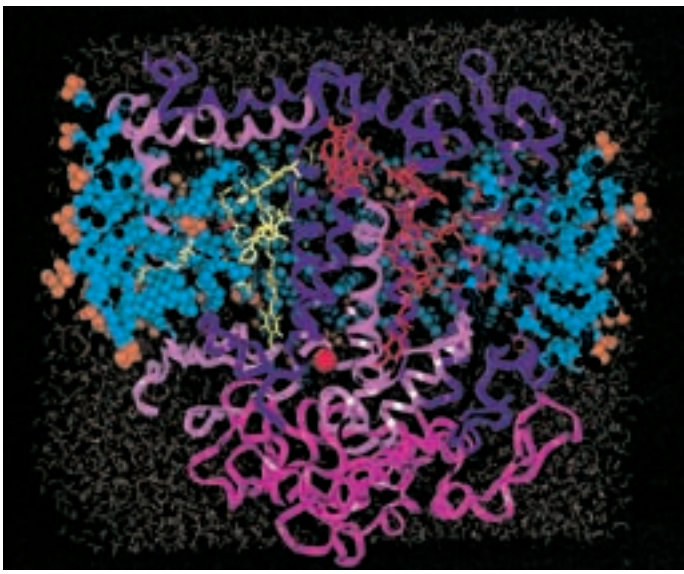


Figure 1:
A snapshot of the photosynthetic reaction centre (PRC) of the bacteria *Rhodobacter sphaeroides* in a water solvent. The orange and blue atoms are the micelle membrane forming a channel containing: the three proteins sub-units (depicted as ribbons), the eight chromophores (shown in red and yellow), and an iron atom (the large red atom close to the centre). Light excites the upper two red chromphores, releasing electrons which travel along the red chromophores until they reach the lower yellow chromophore (close to the iron). When two electrons are present there, they bind together with two protons and exit the PRC at the lower left side of the membrane (© Matteo Ceccarelli, CECAM).

Introduction

Many dreamed but few believed that a symbiosis of the biological, physico-chemical and engineering sciences could happen for generations, if ever. It has begun. Advances in measurement devices, such as atomic force microscopes, optical tweezers, and femto-second spectroscopy, now allow one to measure physical and biological phenomena occurring at atomic scales. This connects naturally to molecular simulation, which is the vocation of 140 or so laboratories participating in the SIMU programme. The molecular simulation of a system can conceptually be broken into three components:

- obtaining a knowledge of its microscopic structure typically in terms of atoms, molecules, and the forces or potential energies of interaction
- the numerical solution of the equations which govern their evolution, be they classical or quantum mechanical and
- the application of statistical mechanics to relate the behaviour of a few individual atoms/molecules to the collective behaviour of the very many (of the order of 10^{23} particles), this level, the macroscopic, being the one of which we are primarily conscious. Molecular simulation can be regarded as a theoretical workshop: allowing theories to be checked for internal and external consistency; and as an experimental laboratory, capable of yielding information at a level of detail not possible experimentally.

Two examples

The collection of sunlight by plants and bacteria to drive metabolic reactions such as the reduction of carbon dioxide to sugar is crucial to life. An essential part of photosynthesis takes place at the photosynthetic

reaction centres, which are proteins that store a photon's energy via a series of electron-transfer reactions. The absorption of light by one molecule at one end of the protein with the emission of an electron, and its subsequent transfer down the protein is known to take place in a series of steps involving time scales from picoseconds to hundreds of microseconds, and distances from two to about twenty angstroms. The typical number of atoms involved is at least fifteen thousand, neglecting the approximations of the cellular membrane and water solvating the cell. Given this complexity and the fact that photon absorption and electron transfer are fundamentally quantum mechanical effects, it is not surprising that many questions remain unresolved. For a molecular approach to give an understanding of the fundamental mechanisms in such processes, an integration of different levels of description is needed.

Polymers at their simplest are molecules consisting of one or a few distinct and simple sub-units bound end to end, and repeated periodically like the links of a chain so as to attain length from hundreds to tens of thousands of units. When assembled together they can form, for example, silks, oils, plastics, membranes and gels, and have great industrial importance and, given their partial similarity to proteins, are also relevant for understanding certain physico-biological mechanisms. Polymer problems exhibit a great variation of time and length scales, as sketched in Figure 2. The typical times range from 10^{-13}s for local oscillations, requiring molecular simulation time steps of 10^{-14}s, up to seconds or hours for the diffusion time of a chain, and to much longer times for collective phenomena or relaxation in glassy regimes. The spatial scales range from a few angstroms (the size of an atom), to hundreds of atoms for a complete polymer chain, and to millimetres for collective phenomena taking place in a solution of polymer chains. In some cases, the appropriate force fields at the atomic level have to be calculated, through *ab initio* quantum mechanical calculations. Moreover, the polymers themselves may be in a solvent, such as water, so that the solute-solvent interaction must be determined or at least approximated.

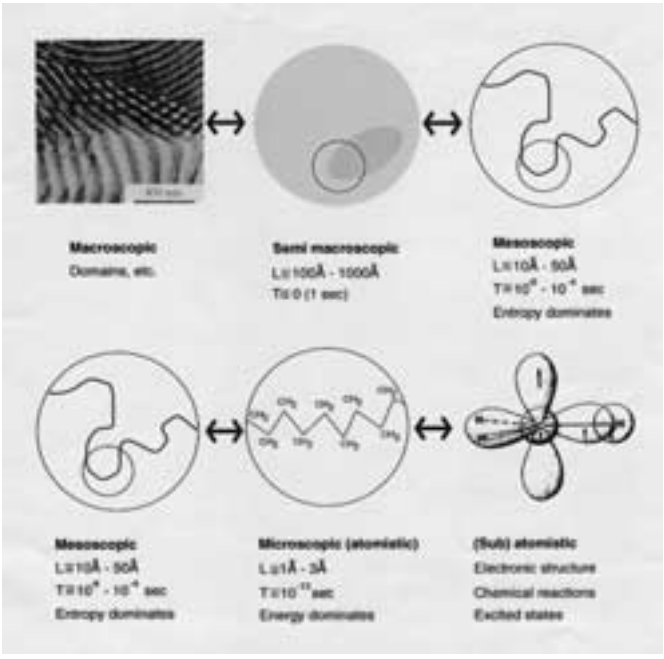


Figure 2:
The many length and time scales of polymers: from the macroscopic bulk where large scale structures such as domains are visible, via the mesoscopic where entropic effects are dominant, to the classical atomistic level, and down to sub-atomic scales and quantum mechanical descriptions (© Kurt Kremer, MPI Mainz).

The time and spatial gap

Three features common to the above examples are the wide range of time and spatial scales, and the crucial importance in some cases of quantum mechanical effects. Molecular simulations at either a classical or quantum level are generally required to arch at a time step smaller than the smallest time scales of a system, which is typically often of the order of 10^{-15} seconds. As the system grows larger, the computational time taken in solving the calculations for the simulation can increase enormously, particularly for quantum mechanical problems. But time scales corresponding to changes in a large systems overall morphology, such as the folding of a protein, or the length of time necessary to obtain good statistics can be of the order of milliseconds, seconds, or even years for very glassy materials. Thus, there is a huge spatial and time gap between what can be solved through molecular simulation, and the time scales that are often important. This gap is the major problem confronting material and biological molecular simulations. Bridging it is the objective of the SIMU programme. The difficulties that need to be addressed are physical in nature, which no conceivable improvement in computer hardware or architecture can even come close to solving.

But, macroscopic equations do not always require detailed microscopic descriptions to be derived, just as one does not need a microscopic knowledge of the constituents of a cup to be able to pick one up. More generally, for some features of a system a microscopic description may be crucial, and for others a much more coarse scale, both in time and space may be perfectly adequate.

Similarly for quantum mechanical calculations, certain aspects of a system may sometimes be treated completely quantum mechanically (for example electrons), others approximated classically (for example nuclei), and the surrounding environment may be even characterised according to a macroscopic theory (such as continuum dielectric theory). Such multiscale perspectives, suggest the notion of modelling a system over a hierarchy of spatial and time scales, where information from lower level, having a relatively fine spatial scale, is used to construct a coarser scale model a level above, having fewer variables. For this to work, the time scales at the coarser level must be slower than that occurring a level below. A complete hierarchy has at its lowest level a quantum mechanical description, its highest being macroscopic, but this is not always necessary. Precisely these types of approaches are being pursued by a number laboratories within SIMU.

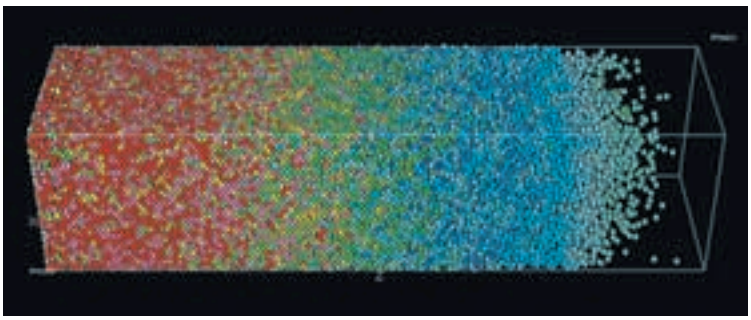


Figure 3: Large-scale classical molecular dynamics simulating the emergence of a shock-wave at the end of a solid material: the fragments produced are compared to continuum predictions. More than 200 000 particles are used in this simulation and the color code goes as the potential energy per particle (from blue to red while increasing the energy). Simulation done at CECAM by J. B. Maillet.

Classical molecular simulations

How can one determine the structure and function of a protein given its sequence of aminoacids? How are ions such as potassium and sodium, and protons transported through or selectively refused entry to conduits in cellular membranes known as ion channels? How can one design the crystalline structure of a material such as an opal, evaluate the response of a system under stress, or even model a traffic flow problem? These are a few examples of the problems that can be considered through classical molecular simulation. But while it spans subjects from drug design to complex fluids and catalysis, its scope is still severely limited by the time and spatial gap. As we saw for polymers, hierarchal modelling is one of the most likely bridges across this gap. In fact, a number of so-called mesoscopic models have been developed recently, which focus on length scales from 100 angstroms to a tenth of a micrometre, and time scales ranging from a tenth of a microsecond to seconds.

Another extremely important approach to the time and spatial gap problem are Monte Carlo simulations. As mentioned before, when we wish to relate microscopic properties to the macroscopic ones which concern us in our daily lives, one almost always has to use statistical mechanics. But statistical mechanics is also confronted by the time scale problem, in that it can take an enormously large number of calculations to have a statistically representative sample. Monte Carlo techniques, constructed to obtain such samples, are typically much faster than a classical molecular dynamics simulation based on Newton's laws. It is also possible to mix molecular dynamics, and Monte Carlo simulations.

Yet another theory which should help bridge the gap is the theory and techniques of rare events. The idea is very simple, although the detail can be otherwise. Most of the time a system is evolving, nothing remarkable happens. These periods of torpor are interrupted by events where great changes take place almost instantly. Rare-event theory tries to focus on these events. It is applicable not only to classical simulations, but also quantum ones.

Quantum molecular simulations

Quantum mechanical descriptions of molecular systems consisting of large numbers of electrons have undergone a theoretical and practical revolution over the last twenty years, mainly due to the development of efficient approximation techniques in the application of density functional theory (DFT) such as that due to Car and Parrinello. The theory itself, designed primarily for the ground state, is capable of obtaining most of the structural information about a molecule using the systems charge density which is defined in a three dimensional configuration space, rather than the many-body wave function, and due to this computational simplicity has been applied to molecules consisting of hundreds of atoms. It is playing a very important role in determining model force fields for biological molecules, such as occur in photosynthetic reaction centres, and may have yet much to say for protein folding. It has also had significant success in the prediction of nanoscale structures such as carbon nanotubes, and is already an important tool in the design of nanodevices which should lead in the future to practical nano-electronics and nanomotors. Two other theories which have undergone great advances are quantum Monte Carlo, and path-integral molecular dynamics, and deal essentially with static equilibrium properties. In practice DFT is limited to describing the dynamic properties associated with single electronic surfaces, using adiabatic approximations, and is ill-suited to dynamic situations where jumps between surfaces occur, that is where the energy surface gap is of the order of kT or smaller, which are relevant for example, for some charge transfer mechanisms.

For such non-adiabatic cases, mixed quantum-classical molecular simulations (theories) are being developed.

These are remarkable times in the biological, physico-chemical and engineering sciences, and the 140 or so laboratories across Europe participating in the SIMU programme are poised through molecular simulation to play a significant role in this symbiosis. The spatial and time gap that we have to cross to play an even deeper role in this revolution is great. But the means to make this bridge are already partly discernible, in the forms of new techniques in quantum mechanics, Monte Carlo sampling, hierarchal and mesoscopic modelling, and the theory of rare events.

Activities

The SIMU programme supports individual short visits up to one week (mainly for senior researchers) and fellowships for younger researchers to spend up to three months in a research group involved in the SIMU programme in a different European country. Either the Institute of origin or the receiving Institute should be in a country in which a funding agency contributes to the SIMU programme.

Short visits and fellowships

Requests for supports for visits of up to one week and fellowships for younger researchers should be sent to the programme chairman, using a template which can be found on the SIMU web page *(http://simu.ulb.ac.be)*.

To be considered for a fellowship, a candidate has to:

- apply for a stay in a laboratory in a European country other than the country of origin;
- return to the Institute of origin upon termination Ranking of proposals by the committee will be done according to the relevance of the project to the bridging-the-gap theme of the programme.

Grants

Grants for partial coverage of expenses linked to attending summer schools and tutorials approved by the programme committee can also be awarded to young researchers. More details can be obtained from the SIMU web page.

Workshops

The SIMU steering committee approves at its yearly meeting in November the workshops programme for the following year. In order to attend workshops, participants should contact the organisers.

Conferences

Two large conferences will also be organised within the programme. The first one, *Bridging the Time-scale Gap* will be held from 11-15 September 2001 in Konstanz (Germany).

Further details on the web sites:

- **simu.ulb.ac.be**
- **www.esf.org/simu**

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Cover picture:
a mesoscopic lattice-gas model of a binary immiscible mixture is used to simulate a flow (in blue) in a porous medium (yellow). Simulation done by P. Coveney and P. Love in London.

For the latest information on this programme consult the SIMU home pages: *http://www.esf.org/simu* or *http://simu.ulb.ac.be*

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