Simu — Challenges in Molecular Simulations

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NEWSLETTER

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The SIMU programme aims at building cooperation across Europe in the field of computationl physics and chemistry of condensed matter, with particular emphasis on the development of novel computational techniques to perform multiscale molecular simulations.

URL: http://simu.ulb.ac.be/

A word from the chairman

The *SIMU* steering committee met on November 18th and decided to fund various proposals submitted for 2001. More details are included over leaf, and later in this issue: *SIMU* members are encouraged to contact the organizers if they wish to participate in a given activity. It is the responsibility of the organizer to decide how this can be done.

An important stage of the programme will be the conference organized at the University of Konstanz from September 9th till 14th, 2001: "Bridging the Time-Scale Gap". We have planned sessions dedicated to specific problems, ranging from biological physics to quantum descriptions of reactions in solution, where reaching larger time-scales is a critical issue necessary for further progress. Invited speakers (*SIMU* and non-*SIMU*) will be asked to review the subjects selected and to present the issues faced. Sessions will be organized to allow all *SIMU* laboratories to contribute to the conference with oral and poster presentations of their work, showing how it fits into the programme objectives. The discussions at Konstanz will play a determining role in building future *SIMU* collaborations and networking facilities. **This is why we insist on an active participation of all teams wishing to form the *SIMU* community.**

It was with great pleasure that we heard that Daan Frenkel had been awarded the *SPINOZA* prize: this prize, described as the Dutch Nobel, is given every year to three scientists selected by the Dutch Academy of Sciences. It includes an impressive amount of money to be spent in research. To honour Daan in our own way, we have asked Henk Lekkerkerker to tell us more about Daan's work, and their collaboration.

Michel Mareschal,

Chairman of the SIMU steering committee

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SIMU 2001

FIRST SIMU CONFERENCE

BRIDGING THE TIME SCALE GAP

Konstanz, 9-14 September, see p. 82.

SIMU SUPPORTED SCHOOLS AND TUTORIALS

Understanding Molecular Simulations, *school organized by Berend Smit and Daan Frenkel, Amsterdam, January. For more information about the course, see http://molsim.chem.uva.nl/*

Methods in Molecular Simulations, *school organized by Mike Allen, and Julian Clarke, Manchester, July 1-10. For information about last years course see http://molsim.ch.umist.ac.uk/*

New algorithms of Molecular Dynamics Sampling, *tutorial organized by Glenn Martyna and Mark Tuckerman, CECAM, 5-8 June.*

Quantum Monte Carlo, *tutorial organized by David Ceperley, CECAM, 22-26 October (tentative).*

SIMU WORKSHOPS

Computational Kinetic Theory: Mesoscale Applications, *CECAM, May 28-31, organized by A.L. Garcia and M. M. Mansour, see p. 84*

Statistical Mechanics and Molecular Simulation of Nucleation and Growth, *Kings College London, 2-4 July, organized by J. Anwar and D. M. Heyes, see p. 91.*

Multiscale Modelling of Materials: Methods, Algorithms and Unsolved Problems *Crete, 2-5 July 2001, organized by E. Kaxiras, V. Pontikis, and D. Theodorou, see p. 94.*

Phase Transitions in Complex Confined Systems, *CECAM, 22-24 August, organized by M. Schoen, P. A. Monson, A. H. Fuchs, M. Rosinberg, see p. 98.*

Simulation and Theory of Solid Fraction: From Atomic Shear forces to Macroscopic Tribology, *CECAM, August 27-30, organized by M. Müser and L. Bocquet, see p. 105*

These dates are provisional, and two more workshops are being considered for approval for 2001, see http://simu.ulb.ac.be for up-to-date information.

Preface

Bridging the gap in time and spatial scales between what can be done computationally, and what is relevant in experiment or biology or even industry is the goal of *SIMU*. Coarse graining in its various guises, from the study of complex fluids to density functional theory and beyond is the indispensable tool with which we hope to build our bridge, and is present in all of the contributions, to this, the second issue of the *SIMU* newsletter. It may then come as a surprise to many of us that a similar gap also occurs in experiment, in for example, protein design, where analogs to techniques in statistical mechanics, such as coarse graining and in particular Monte Carlo simulation abound. This theme is explored by Michael Deem in a review article on combinatorial chemistry. But we should return to the beginning, where the programme chairman outlines the activities for 2001. Henk Lekkerkerker then comments on the seminal work of Daan Frenkel, and the award of the *Spinoza* prize. This is followed by a feature interview with Michael Parrinello, where he tells us about Anesur Rahman, the genesis of CPMD, recent successes in response theory, and future projects. Simone Melchionna and Jean-Pierre Hansen in a beautiful review explain how classical density functional theory can be combined with Molecular dynamics or Monte Carlo simulations, or with standard optimization techniques, like steepest descent, to simulate complex fluids involving widely different length and time scales. The reactivity of water, and the problems this poses to theories of solvation, and in particular deviations from continuum theories, is the subject of an article by Ruth Lynden Bell where she tells us of work on this in Belfast. The activities of the condensed matter theory group of Kurt Binder at Johannes-Gutenberg University of Mainz is the subject of section VI. The 2001 activities of *SIMU* are described in detail in section VII. Several external conferences, some of which will receive *SIMU* support are listed in section VIII. The newsletter is completed by section IX entitled "Did you see ?" which is a commented list of interesting/useful web-sites, books, programmes and articles (of this year), and is a collective effort of a number of us. This newsletter together with issue one is down-loadable at the *SIMU* web site. Hard copy versions are available on request. Feel free to contact us for positive or critical comments, ideas or suggestions: they will all be welcome.

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I

Daan Frenkel and the Spinoza Prize

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received 20 November 2000

It may seem surprising that someone like Daan Frenkel[2], who makes his living out of simulations, agrees with the statement that Michael Fisher[3] delights in making "A good simulation is a dead simulation". For Daan the goal of simulations is to give "microscopic" insight in natural phenomena. To him simulations are never an end in themselves. Once the insight is secured the computer programmes can be cast aside, in accordance with Daan's dictum, "A good simulation makes itself superfluous".

I have interacted closely with Daan Frenkel since the early 1980's. At that time Daan had just started his simulation work on what is now known as entropy driven phase transitions. Together with his students Bela Mulder and Rob Eppenga he worked on the isotropic-nematic phase[4] transition in systems of hard ellipsoids and infinitely thin platelets. We then discussed whether in a system of rods hard-body interactions alone could give rise to the more highly ordered smectic liquid crystal phase. Strange as this may seem, the general opinion then was that for thermodynamically stable smectic phase[5] , attractive interactions were required. The situation was reminiscent of celebrated "hard sphere crystallization" which also took a long time to become

[1] Henk N.W. Lekkerkerker is the recipient of the 1999 Norwegian Onsager Medal.

[2] Daan Frenkel (http://www.amolf.nl/research/computational/) has been awarded this years Spinoza prize, which is akin to a "Dutch Nobel prize", both in prestige and generosity, and is given by Netherlands Organization for the Advancement of Research http://www.nwo.nl/nwo/nieuws/persberichten/00pers30/contentset.html

[3] Michael Fisher, received the 1995 APS Onsager prize, for "his numerous and seminal contributions to statistical mechanics ..." http://www.ipst.umd.edu/Faculty/fisher.htm

[4] The nematic liquid crystal phase is characterized by molecules that have no positional order but tend to point in the same direction.

[5] In the smectic state, the molecules maintain the general orientational order of nematics, but also tend to align themselves in layers or planes (see fig. I.1).

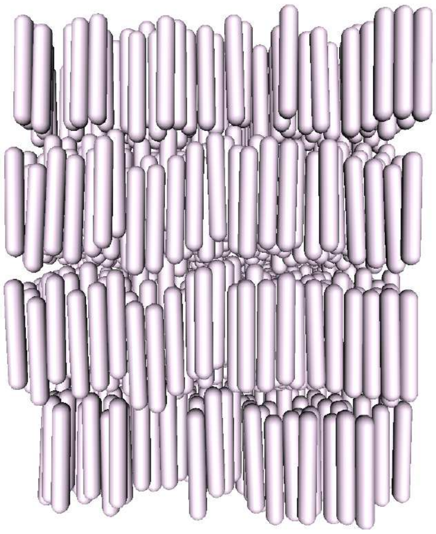

Figure I.1: Smectic Liquid Crystal Phase

generally accepted after the seminal simulation work of Alder and Wainwright[6] in the 1950's. In fact, the smectic phase was also already observed in concentrated solutions of virus particles (rod-like Tobacco Mosaic Virus particles). Together with a joint student, Alain Stroobants Daan then produced by computer-simulation convincing evidence that the smectic phase indeed occurs as a stable thermodynamic phase in a system of hard rods. Later, with his student Jan Veerman, Daan showed that in suspension of hard platelets in addition to the nematic phase also a columnar phase[7] appears (see fig. I.2.) In the meanwhile I had moved to the Van 't Hoff Laboratory for

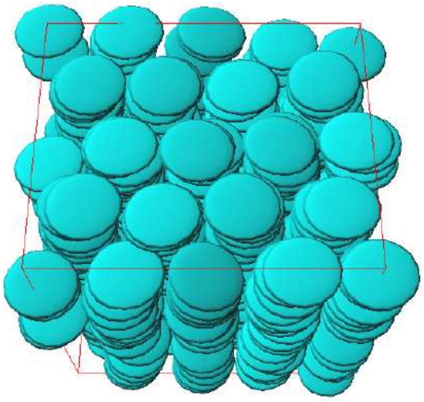

Figure I.2: Columnar Liquid Crystal Phase

Physical and Colloid Chemistry at Utrecht University. Here the preparation and study

[6]There was also clear experimental evidence that repulsive virus particles with the shape of a regular icosahedron (Tipula Iridescent Virus) arranged themselves spontaneously in a face centered cubic crystal structure.

[7]Columnar liquid crystals are different from the previous types because they are shaped like disks instead of long rods.

of phase behavior of suspensions of rod-like and plate-like colloidal particles became a major component of my work. Throughout, the collaboration with Daan and his co-workers was extremely stimulating and one of the highlights of this interaction was the discovery this year of the columnar phase in a system of sterically stabilized colloidal Gibbsite platelets.

Another area where Daan and I had a very strong interaction was the role of the range of attractive forces on the domain of existence of a distinct liquid phase. Particularly as Dutchmen we are living under the spell of Van der Waals and tended to believe its presence whenever the intermolecular interaction has an attractive component. This belief was challenged by theoretical work of Gast, Russel and Hall of Princeton University in the mid 1980's. They showed for the case of colloid polymer mixtures where the polymer gives rise to an attractive interaction with a range roughly equal to the diameter of the polymer coil, the colloidal liquid phase becomes meta- stable when the ratio of polymer diameter and colloid diameter becomes smaller than 0.3. We then realized that the appropriate way to deal with this problem is to use the semi-grand ensemble using the polymer component at a fixed chemical potential. Together with his student Evert Jan Meijer, Daan developed this notion in a highly elegant and efficient computer simulation. These simulations have served as a bench-mark for subsequent thermodynamic and experimental work. Together with his student Pieter Rein ten Wolde Daan also showed that the critical fluctuations of the submerged gas-liquid critical point may have a very significant influence on the nucleation barrier for the fluid-solid transition. This may have important consequences for protein crystallization, where in a few cases a meta-stable liquid-liquid phase transition has been reported, but apparently has been observed in many other cases (as evidenced by the appearance of 'oily droplets').

I hope these examples give you an idea of the great strength of Daan Frenkel. Not only is he a truly creative computer-simulator and a lucid writer. But, he also is able to interact with experimentalists, to understand through them what is relevant, and at the same time provoke them with his simulation work. Moreover, Daan always grasps the wider significance of developments which he initiates with his computer-simulations. He moved rapidly from colloid-polymer mixtures to protein crystallization. He also showed how his work on polymer chains could be applied to the ab-initio dynamics of electron systems and the sound-velocity of dense hydrogen. The latter in turn has implications for current models of Jupiter.

Daan Frenkel is not only an outstanding researcher, he is also a fantastic teacher. I have had the pleasure to hear him lecture many times. His expositions are always masterly and illustrated by appealing and revealing cartoons. Above all, Daan Frenkel is a warm and generous person, invariably willing to share his ideas and insights. I congratulate him heartily on the award of the Spinoza Prize and look forward to the advances it will help him bring forth.

II

Interview of Michele Parrinello

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This interview took place in Stuttgart on 3 August 2000

Introduction

In the last twenty years we have witnessed a great cross fertilization between ab-initio or electronic structure calculations, and the theory and practice of statistical mechanics and in particular molecular dynamics. This is helping to provide a bridge between condensed matter physics and chemistry to biology, enhancing the relevance of each to both. Density functional theory, and perhaps its most successful implementations, Car-Parrinello ab-initio molecular dynamics, is both a product of this union, and an increasingly important part of the bridge. It was therefore a great pleasure to interview one of its principal architects and masons. Michele Parrinello is director of one of the theoretical physics departments at the Max Planck Institute for Solid State Research, Stuttgart, having served previously as manager at the Zurich IBM research laboratory, and prior to that, been a professor of the condensed matter group at SISSA, Trieste. His work has been cited more than nine thousand times, so I expected him to have many things to say.

Dónal Mac Kernan

There are still many in the physics community who do not take molecular simulation seriously. Why ?

Well, the first observation is that the number of people who take this view is declining rapidly with time. It has to do with the way in which people in my generation, and the previous one, were educated. It reflects, in my view, a prejudice. Some people believe that there is a hierarchy of disciplines, that some things are more pure than others.

I remember clearly as a student the more abstract a theory was, like field theory for instance, the more worthwhile it was considered. And so when you go from doing things with pen and pencil, to doing applied things with a computer, then of course the purity or the degree of abstraction declines.

Another reason for this attitude is, I believe, due to a myopic view of what computer simulation does, and can do. There is an idea that computer simulation is just about pressing a button and waiting for a result. But this is not the case. Computing is not a substitute for thinking. For example, there have been a lot of debates in the literature between the defenders and opponents of computer simulations. The opponents claim that there are problems that cannot be done by computer simulation. Take a problem, such as diagonalisation. They argue that in many problems the scales or dimensions you are interested in are very different from what can be calculated. But this is a myopic view of what can be done. Certainly if you take this approach, then a given problem, say the Kondo problem, cannot be solved. So if you take a certain number of electrons, and then increase it, you will never converge to a solution.

You have to apply to this kind of problem a different strategy. The Kondo problem was first solved by Wilson numerically by using a renormalisation approach, then people came and got the analytic solution. This was a case where an intelligent application of computer simulation proved able to solve a problem.

Another instance is in critical phenomena when you want to calculate the critical indices. If you do it the hard way, you never get it because of fluctuations and critical slowing down. But then people like Binder and others showed that if you do finite size scaling, and look at the right properties, these indices can be calculated. So that's a field in which it was shown that it's not computer simulation per se that is inappropriate, but rather it's the blind and stupid application.

It should also be said that computer simulators are partly responsible for this attitude, because some have performed simulations without taking into account its limitations. There has also been a bit of machoism, trying to solve larger and larger problems in an unintelligent way, not asking the right questions.

My perception is that when I started doing computer simulation in the eighties, this negative attitude towards computer simulation was prevalent, and now it's a minority point of view. Computer simulation has so many applications, is so useful, and can give so much insight, that the evidence is overwhelmingly in favour of using this approach to many problems. There is no field of physics in which computer simulation is not applied.

Is it fair to say that a symbiosis of engineering, physico-chemical and biological sciences is beginning?

I would say so. The trend is very clearly there. Of course it is just a beginning. There are difficulties of language, the problems are different and so on. We still of course have a long way to go, but we have started. In a sense it is a bit paradoxical: on the one hand science is becoming more and more specialised, and on the other there is this inter-disciplinary drive, and the fact is that some of the methods being used are very common to many fields, ideas can be brought from one to another. This is happening, and I am very confident that it will intensify in the future. In a sense, computer simulation is ideal for doing this, because in principle it is not too difficult to jump from a calculation in solid state to one in liquids or biology, because the tool is universal, and if you have a code which you buy, or build yourself, then you can apply it to all these things. Computer simulation is really a means for bridging very different parts of science.

How is it important to combine electronic structure/ab-initio type calculations with statistical mechanics so as to handle many-body problems?

Well that's the basis of what we have been doing over the last 15 years. The motivation is out there, it depends on what kind of phenomena interest you. There is a class of problems where introducing the electronic degrees of freedom is important, but not essential. If you want to simulate a system with simple chemistry, argon or whatever, then in my view it's an overkill to introduce explicitly the electronic degrees of freedom if you want to calculate the pair potential function. But things become less easy if you look at more complicated systems. Take liquid silicon, or a system having some covalency. In the case of liquid silicon, you want to introduce the electronic degrees of freedom because it gives a better representation of the potential of interaction. In other words, one has to do this when the potential of interaction is not known, or is difficult to simulate, so that you can get the interaction right.

You also need to treat the ionic and electronic degrees of freedom on the same footing when you have chemical reactions in complex environments. Take a reaction in solution or on a surface. There it is essential to bring the two together because otherwise you simply cannot describe the formation or breaking of a chemical bond. But ab-initio calculations are expensive and should not be used where they are not needed. Nonetheless, there is a very large class of problems where indeed it is the only way to proceed.

History

Could you tell us about your early career. Your move from Messina to Trieste. Your work with physicists such as Tosi, and your continuing work, albeit now occasional, with Tosatti

I was born in Messina, but I finished my degree laurea at the University of Bologna in relativistic quantum field theory applied to particle physics. All the best people were working in that field at the time, and as I was a good student I also worked on it.

Then I met Tosi, who had been in the United States and had been working a great deal on the electron gas. He got a position in Messina, and it was natural for me to take the opportunity to return there. Tosi was my teacher, and I am indebted to him for this change of subject, which was in the end very fortunate.

Tosatti is a very good friend with whom I did a lot of enjoyable work. Now we are further apart geographically, and inevitably we work less often together. All three of us were in Trieste together. I was the first to go there, and the others followed shortly afterwards.

In 1980 you went to Argonne national laboratory to work with Rahman, developing Parrinello-Rahman constant pressure molecular dynamics. Could you tell us about your time there, and whether it was a catalyst to your increasing involvement in molecular simulation?

Well, with Tosi I had already done a lot of work on molten salts, and Anesur Rahman was interested at the time in the closely-related subject of superionic conductors. He was a remarkably fast programmer. We wanted to simulate the superionic behaviour of silver sulphate and similar compounds. For these compounds the potential of interaction was not known. My suggestion was that we could fit it to the different crystal phases. Anees remarked that this could not have been possible because of the fixed boundary conditions.

Luckily at that time the work of Hans Andersen on constant pressure molecular dynamics had just appeared. We thought we could extend his method to introduce more flexible boundary conditions. We wrote down the equations and since at the time Anees was simulating rubidium, we applied it to this case and it worked immediately. That was fortunate - had we started with Lennard-Jones we would have had a lot more trouble, since during the transition many stacking faults can be found, which confuses the picture. As a result of this success, my visit, which was intended to last three months, turned into almost two years.

Do you remember any funny stories from that time, that would give us an idea of what it was like to work with him?

Well, I don't recall anything particularly amusing. I was without a family there, and so I was up late every night, always very excited about my work. I was preparing a programme for long-range forces, for the extension of the variable box method, working, working, and I had this big pack of cards where you put your changes to the programme. It was late, and I was very tired, and at a certain point I was putting it into the card reader, and the entire pack of cards fell on the floor. I must say it was a moment of great depression, I felt like giving up and said that the computer was not for me. In the end I managed to put the cards back in the right order. That is one episode that I remember from those times.

Of Anesur, I remember his charm, his human touch. He was a fantastic person, and it's very unfortunate that he died a few years later, early in life, of cancer. I learned everything I know about molecular dynamics from him. He had a leading role in the MD community, not only because he was the founder of the method, but also for his style, his integrity, human and scientific. He was extremely meticulous, checking all that he did. I have never seen anybody so pernickety about what he did, it's beyond belief how careful he was. His scientific standards were enormously high - you should always be able to reproduce your results, you should know exactly what is there.

I remember we had a programme that had been tested and tested and tested. Every time we had to write a paper, he would become very nervous, and the first thing he did was to control each output, checking the code line by line. Of course in those days computer codes for MD were not very big. Lennard-Jones was 300 to 400 lines, and long-range forces must have been a few thousand lines. These days you simply cannot do it. The codes we use are tens of thousands, or a hundred thousand lines long. The early eighties is when the terminals that we know now began to appear. He didn't like it, because he couldn't trace what he was doing, step by step. He much preferred to have a teletype machine, so that he could have a written record of what he did. A real example of scientific rigour. I have never met anybody like him, I must say.

So from what you said, it wasn't only this scientific rigour but also his human side that was exceptional.

Yes, he was very concerned about social issues, about the young people starting in science, about justice within the department. He cared that things were done properly. Yes, his standards were very high, and I think that the community of molecular dynamics has been very lucky to have had a person like him to set the standard, making something which could have been rather sloppy into a scientifically sound discipline. He was very sharp, he could ask questions which would really expose the weak point of people. Yes, a great loss.

When did you first meet Roberto Car? Could you tell us about your interaction with him?

After Argonne, I came back to Trieste with a big pack of cards, and started to do some work with Tosatti, including molecular dynamics. Tosatti was very open, he understood the power of MD although he never personally did any such thing. I was working on surface problems. I had as a student Furio Ercolessi, and we tried to construct a potential for metals. Part of the binding comes from the electron cloud, and a two-body potential is not very good. So we invented what is called the glue potential, on which Ercolessi wrote his thesis. He was drafted for military service, and the work was stopped for a year and a half. During that time other people had similar ideas, and applied them in metals. So due to the draft we lost time, and bit of priority on this problem, but that's life.

So I was in Trieste, Roberto had been a post-doc at IBM with Pantelides and came to Trieste. We started talking about the possibility of doing things together. He had ideas on how to improve the electronic structure, I had a background in electrons and ions, statistical mechanics and molecular dynamics. It was interesting to combine these things. At the time the problem of silicon was very hot, liquid silicon in particular. Silicon changes from a semi-conductor to a metallic phase when you melt it. People had tried various potentials to describe it but none was very satisfactory. We thought that combining electronic structure and MD would be the way. We played with the idea for a while.

How long ?

We started working on it, if I recall correctly, in December 1984. We did the programming, it was a frantic thing. We had this idea of combining the two worlds. First we didn't have the correct Lagrangian, and things didn't work. Then we added the multipliers as a constraint for orthogonality, and it worked. We had this eight-atom silicon. I never worked like this and neither Roberto nor I had ever been so excited in our lives. It was a very cold winter. It even snowed in Trieste several times. We would go there at night, to make use of the fact that the computers were empty, taking coffee at a bar and working in a laboratory that was deserted.

So it went very fast and in a few months we had the programme running, and wrote a paper in the spring. It was sent to Physical Review Letters. The referees were positive, but they made some good suggestions to improve the presentation. Between one thing and another, we got the answer in the early summer. We were in the States, because Roberto was spending the summer at IBM, and I joined him, and we did lots of work together, extending the programme which was for local pseudopotentials. We then did the non-local part, and other improvements.

It was an extraordinary time, and I think we had this complementary background, also the courage to go beyond one's own field. I learned a lot of electronic structure from Roberto, and I think he learned a lot about statistical mechanics and MD from me. I also had a bit of a background in electronic structure from my days with Tosi, I had done a little of this and that, also on the electron gas, so many of the concepts were familiar to me. I think fortune and luck are important: to be in the right place at the right time.

Maybe I can take the time to make a remark. The scientific atmosphere at SISSA in Trieste was great. There was a lot of freedom, a lot of free exchange of ideas. There was a group of very gifted people, Baroni, Tosatti, Selloni, and so on. There was no jealousy. We could talk freely. Everyone knew what the others were doing. I think this spirit still survives at SISSA, but of course things change. The other part of it was that we could do this work because we didn't have to look for a grant. I think if we had had to make a proposal, it would never have been approved as we didn't have clear ideas about what we wanted to do. So I am lucky that I met all these good people, and also lucky that it was in this special place. I must say that a lot of credit for SISSA being such a friendly place is due to Tosatti. He was the heart and soul of the condensed matter group there.

After the initial success we had to go to more realistic applications, and show that we could go beyond 8 atoms, and do the real thing. At this time the first supercomputer came to Italy, it was a Cray and was put in Bologna, at Cineca. We had a very generous allocation of computer time and many able collaborators.

Later we had offers, both Roberto and myself, to go elsewhere, and with a broken heart we went. I was the first to leave in '89, and went first to IBM, where I had a lot of support, and now here where I have resources that would have been very difficult to get anywhere else. SISSA could not have provided me with this level of support. So I look back on those years with great nostalgia, and I believe that Roberto does too, it was quite a special time. We really could work very well together.

So the main reason why you moved from SISSA to IBM and then Stuttgart was for technical resources?

Well, it was actually a combination of factors. It's good to change from time to time, that's one thing, and the level of resources was declining. There were signs that we wouldn't get the same level of support necessary for a large group, both computer-wise and in manpower. So I went to IBM Zurich to build up a numeric intensive computation group. Wanda Andreoni was already there, but a bit isolated. So, over a few years a very nice group of people was brought together. Many of these people are now professors. Michiel Sprik came to join my group, as well as Peter Bloechl. Other people came as postdocs: Andrew Fisher who is now in London, Giulia Galli, Francois Gygi and Dominik Marx, people who are now making strong careers. So that was a good time. But later, there were signs that things were not going to be as steady. There was a lot of pressure in IBM to be useful for the company, to be customer-oriented, which is legitimate as it's a private company. So when the offer from the Max Planck Society came, I took it, and I have been here for six years now.

Current activities

Would you tell us about your recent interests in chemical and biological molecular systems, and finite temperature DFT

At the moment our interest is focused on complicated chemical reactions, be it on a surface, or in a solution, or in an enzyme. And to this effect, we are making simulations of real problems like industrial catalysis. But also we are improving the methodology in various ways. One way is to try to combine quantum mechanics and molecular mechanics in a controlled way, that is you take the centre where the reaction takes place, and treat it quantum mechanically, which means ab-initio, and the rest is treated with normal molecular dynamics, so the environment is treated classically. The other thing is the problem of rare events, and finite time scales, relevant for a lot of chemical reactions. In this area we use path integral sampling methods, for instance that of David Chandler, but we are also developing our own ideas on how to go about it.

Of course when we talk about solutions in biology, water is important, and so a part of our work is devoted to understanding in detail the properties of water. We try to use our ab-initio simulations to better understand ideas and concepts such as dipole moment and polarizability, which are normally used empirically in the construction of potentials. This allows us also to construct new potentials, and learn of course about water, how water changes in different environments and under different thermodynamic conditions.

The other thing we have been doing is improving as far as possible contact with experiment, that is including in our calculations the evaluation of properties which can be measured experimentally. Here, I have in mind things like the infra-red spectrum, Raman spectrum, NMR chemical shift. These are important tools for understanding the dynamics and the chemistry. When you do the molecular dynamics without electrons, you really have to model all of these things, you have to add an extra layer of approximation because the infrared, Raman, and NMR chemical shift depend on the electrons. So we develop methods to deal with that in an efficient way, so as to bridge the gap between simulation and experiment.

Do you mean that you try to use experimental results to determine some properties of the model that you want to construct?

No, the purpose is twofold. One is to check the validity of our calculations, how good our approximations are. By increasing the range of properties that can be compared with experiment, we can validate what we do in a more systematic way. The second purpose is for complex systems. Let's take the example of infrared and Raman scattering. The standard approach is to make use of the harmonic approximation. Say you have a solid, and you want to calculate the infrared spectrum. You calculate how the dipole changes when the atoms are moved within the harmonic approximation. Now if you go to a liquid, you can apply the harmonic approximation to the intra-molecular vibrations, but not to the intermolecular modes, which are anything but harmonic.

So in the literature there are lots of spectra that are simply uninterpreted, because there is no tool for doing so. For instance, we looked at the infrared spectrum of liquid water, and by interpreting it we could get insight into the physics. Similar things are true for Raman spectra and NMR chemical shifts. If you are in a finite temperature system, the NMR signal would be an average over various configurations. We can now calculate this average. This is another example where the combination of electronic structure and molecular dynamics is important. Otherwise the calculation of the NMR shift would have required a separate approximation. In our way of doing things, all these properties come out of a unified, self-consistent and self-contained procedure. That is something we have done recently that I believe is important. It opens new avenues.

I would like to ask you a question which is not directly related to your present work, but I think is worth your comment. Can you tell us about recent successes in excited states and time-dependent density functional theory, how promising it is and so on?

For excited states there are various theories. There is an approach which seems to be very accurate, the so-called GW approximation, which several people are doing: Steven Louie in Berkeley; also in Europe, Lucia Reining is also working in this field.

What does GW stand for?

It comes from many-body theory. It describes a Feynman diagram. G stands for Green function, and W for screened interaction.

In fact, these calculations can be accurate, but they are expensive, and it's difficult to calculate the forces on the ions. There are other approaches which have been undertaken, one of them is time-dependent density functional theory. However, in its present formulation it is limited to isolated systems, so if you want to work on bulk systems, you have to extend time-dependent density functional theory to periodic systems. I believe it is possible, and I know people like Sprik are working it, but it is non-trivial. Time-dependent density functional theory is quite nice because it is not too computationally expensive, but at the same time it gives reasonably good electronic spectra.

There are also other methods from quantum chemistry, but they are really too complicated and expensive to consider. We did some excited state density functional theory, actually it was the work of a former post-doc of mine, Irmgard Frank. She tried to do a density functional-like formulation for the first excited singlet state. Typically in a molecule the ground state is a singlet. When you excite it optically, it goes into the first excited singlet state. Density functional theory is a theory for the ground state, so she formulated an approximation which is in the spirit of density functional theory, but for the first excited singlet state. These I would say are the three most promising directions.

What are the problems? One is of course the accuracy with which you can determine the potential energy surface of the electrons in the excited state. Another problem, which you are probably very familiar with, occurs if you want to do ab-initio molecular dynamics with non-Born-Oppenheimer effects, where you have to face the problem of treating a non-adiabatic mixed quantum mechanical-classical system. Many theories have been proposed for this, we will see which one is going to be appropriate. So these are two problems. Several people are working in the area. I am hopeful that in a few years these problems will be worked out.

Would you tell us about your role in the development of codes such as CPMD and quickstep, from theory to algorithm to computer code?

CPMD is based on what we did with Roberto Car. We did it together, we programmed everything, and it was a very bad programme, as it was difficult to work with. When I was at IBM, I had the good fortune to hire in my group Juerg Hutter, who is a very good programmer. The idea was that he would parallelise the code, which he did very quickly and efficiently, and we also put the code into much better shape.

Until seven or eight years ago I was able to write pieces of code myself, but now I simply don't have the time. When you write a code you need continuity to find the mistakes and so on. I have to go to meetings, talk to many people. I simply cannot do it. I know what the programme does, I contribute to the development of the algorithm and the ideas that are there, and the general structure. But I don't write the code any longer, which is sad, but that's a fact of life.

That's one of the crosses you have to bear being a director of a large institute.

I wouldn't call it a cross, but it has disadvantages, this is one of its negative sides. In the last years at IBM I didn't have the time to write code, either.

So you actually enjoyed writing code?

I like doing research, and I believe writing code is an integral part of it. Also I like to be very involved with what goes on in my group. I got a lot of pleasure doing hands-on research, and that I cannot do here, I have no time. I talk with people when there are jobs running, I try to be as interactive as I can. Maybe some of my people say I interact too much, but that's the way I am. I like to take part in all of these things.

I have heard a new code, CP2K,is about to replace CPMD. What advantages should it have?

As you will have gathered from my answer to the previous question, CPMD, which is our flagship code, has developed incrementally. It used Fortran 70 and then Fortran 77, which is not the best way to produce modern, easy to maintain, transparent code.

It is very efficient, I believe. But if you have a large group, and you want everyone to be able to put their hands on the code and make modifications, it becomes very difficult. The code is very intricate, to get familiar with it requires a major effort.

There are two obvious ways out of this problem. Either you commercialise the code or you get one person to maintain it, but then you have the disadvantage that you have to channel everything through him. We decided to follow another model that has been inspired by Linux. The idea is to first rewrite the code from scratch, which we can now do as we have complete control. We will try to write in a very modular way. Ideally we would rewrite it in an object-oriented language, but there are two problems. One is that for us efficiency is an important issue. The other is that we are not very familiar with object-oriented languages and would have to learn one.

So we decided to take a compromise route and use Fortran 90, which is not an object-oriented language, but has many modern constructs, and to rewrite everything in as modular a way as possible. We have just started. We had a meeting one month ago with the people who work most closely with us and are interested in developing this code. We set down the principle, so some of the people you met are working very hard to get the first nucleus of the code running. This should happen pretty soon. Then we will put it on a web-site for a close group of collaborators, and after this, I hope it will fly. It's a new model. It will be public domain, so everybody can access and modify it. If you make a major modification, you are requested to send it back to us, and we will incorporate it into the new release or not, depending on whether or not it is good. It's really the Linux model. It has been very successful, and I know that other people are trying to do the same, evidently the time is ripe for this.

In the old days, the idea was that you had to write your own code, the hard way. Each one has his own little secret set of tricks. Even in each group there was often major confusion about which version of the code was working. We hope that this new model will be successful, that through the synergy of a very large number of users the code will be developed very quickly. Once it flies, an important aspect is that the user can easily understand the structure and make modifications without having to go through the whole code. Probably, it will not be as efficient as CPMD, but this is the price that we are prepared to pay to have the advantages of transparency and the ability to manage it and work with it.

General questions and conclusion

How can SIMU help, given its objective of bridging the length and time scale gap?

SIMU can help, for example, by getting groups to agree about the specifications of codes at different length and time scales, permitting one to go in a seamless way from the quantum mechanical level, to the classical, to the continuum. At the moment much time is lost in the porting of data from one code to another. An agreement about standards would allow one to go easily from one code to the other, and would be invaluable.

What do you believe are the main challenges and will be the likely advances in molecular dynamics over the next twenty years?

This is of course a difficult question to answer, to predict the possible advances in theory and technology. I expect that there will be an abundance of very cheap and powerful computers, so one issue will be how to develop theories and MD techniques for working on vast numbers of highly distributed computers. One possibility may be to borrow ideas from combinatorial chemistry.

You mean in the spirit of neural networks?

No, more in an evolutionary way.

But with such distributed techniques, wouldn't it be more difficult to control sources of error?

No, not necessarily. If the methods are developed carefully, the distributed nature of the problem-solving could lead to less error.

A while ago IBM announced its intention of developing a machine with Tera flop capabilities. What impact do you expect this to have on the simulation community?

Well, the machine is being designed specifically for molecular dynamics, for the protein folding problem. It could be excellent, but in the past it has happened that special-purpose machines posed great portability problems for existing codes. I believe that the machine which IBM is developing should be more general than this, but we will have to see.

III

Classical density functional methods for the simulation of complex fluid

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Abstract

It is shown how classical density functional theory can be combined with standard optimization methods (steepest descent, conjugate gradient) or Molecular Dynamics or Monte Carlo to explore complex fluids with large size asymmetry of the particles.

Introduction

Bridging widely different length and time scales is a major challenge in the simulation of complex fluids, which generally involve mesoscale entities, like colloidal particles of various shapes, flexible polymer coils, rigid polyelectrolytes rods or fluctuating membranes, as well as microscopic molecules or ions. Clearly, an efficient statistical description or simulation of such highly asymmetric multi-component systems requires an efficient coarse-graining procedure, which allows the microscopic degrees of freedom to be "traced out" in a consistent and controlled way. If one is mainly interested in static properties, like the mesostructure and the phase behaviour of the large particles, then classical density functional theory (DFT) provides a convenient and powerful tool. If one is interested in large-scale rheological properties, e.g. of suspensions, then the more phenomenological "dissipative particle dynamics" may prove more appropriate

[1]. If, on the other hand, one wishes to consider the fast internal motions of large particles, like the vibration of individual monomers of a long polymeric chain, then multiple time-scale algorithms will help to bridge the gap between fast and slow modes [2, 3].

In this article we consider the combination of classical DFT and molecular dynamics (MD) or Monte Carlo (MC) to simulate highly asymmetric "soft matter" systems, including charged colloidal dispersions and polyelectrolytes, or macromolecules in solution. The methodology which will be described is closely related to the recently revived interest in effective interactions between mesoparticles, which are of mainly entropic origin, like depletion forces [4, 5], or forces between electric double-layers [6]. Since classical DFT is the fundamental tool, we first summarize its basic principles [7].

Classical density functional theory: a reminder

While in homogeneous (translationally invariant) fluids, the Helmholtz free energy is a function of the number densities $n_\nu = N_\nu/V$ (and of the temperature) of the various chemical species, it must be considered as a functional of the local densities:

$$\rho_\nu(\mathbf{r}) = \langle \sum_{i=1}^{N_\nu} \delta(\mathbf{r} - \mathbf{r}_{i\nu}) \rangle \tag{III.1}$$

when the fluid is inhomogeneous.

The inhomogeneity may be due to a phase boundary, or to external potentials, $\phi_\nu(\mathbf{r})$ acting on particles of species ν. It is customary to introduce an intrinsic free energy functional, which is the sum of ideal and excess contributions:

$$\mathcal{F}_{[\{\rho_\nu\}]} = \sum_\nu \mathcal{F}^{id}_{[\{\rho_\nu\}]} + \mathcal{F}^{ex}_{[\{\rho_\nu\}]} \tag{III.2}$$

where

$$\mathcal{F}^{id}_{[\{\rho_\nu\}]} = k_B T \int_V d\mathbf{r} \rho_\nu(\mathbf{r}) \left[\log(\Lambda_\nu^3 \rho_\nu(\mathbf{r})) - 1\right] \tag{III.3}$$

The corresponding grand potential functional is:

$$\Omega_{[\{\rho_\nu\}]} = \mathcal{F}_{[\{\rho_\nu\}]} - \sum_\nu \int_V d\mathbf{r} \rho_\nu(\mathbf{r}) \phi_\nu(\mathbf{r}) \tag{III.4}$$

where $\phi_\nu(\mathbf{r})$ is the "local" chemical potential, $\phi_\nu(\mathbf{r}) = \mu_\nu - \phi(\mathbf{r})$.

$\mathcal{F}$ and Ω obey the two fundamental Hohenberg-Kohn-Mermin theorems [8, 9]

- Theorem 1: For any given system, characterized by a Hamiltonian H in the absence of external potentials, the intrinsic free energy $\mathcal{F}$ is a unique functional of the equilibrium densities $\rho_\nu(\mathbf{r})$. In other words, the functional form of $\mathcal{F}$ is independent of the external potentials $\phi_\nu(\mathbf{r})$.

- Theorem 2 (variational principle): Let $\{\rho^*_\nu(\mathbf{r})\}$ be a set of properly normalized trial density profiles. The grand functional (III.4) reaches its minimum when the $\rho^*_\nu(\mathbf{r})$ coincide with the equilibrium densities $\rho_\nu(\mathbf{r})$, i.e.:

$$\left.\frac{\delta\Omega_{[\{\rho^*_\nu(\mathbf{r})\}]}}{\delta\rho^*_\nu(\mathbf{r})}\right|_{\rho^*_\nu=\rho_\nu} = 0; \qquad 1 \le \nu \le \nu_{MAX} \tag{III.5}$$

  and moreover, $\Omega_{[\{\rho_\nu\}]}$ is equal to the equilibrium grand potential Ω.

The variational principle (III.5) is the basis of all practical DFT calculations. In practice, the trial local densities $\rho^*_\nu(\mathbf{r})$ are parameterized in some suitable fashion, or defines on a 3d grid spanning the whole volume V, and the coupled Euler-Lagrange equations associated with eq. (III.5) are solved by an adequate numerical optimization procedure.

Coupling classical DFT with MD

Consider a highly asymmetric system containing "large" (mesoscopic) and "small" (mesoscopic or microscopic) particles, of widely different diameters σ. Let N_1 and N_2 be the numbers of large and small particles. Due to the size asymmetry ($\sigma_1 >> \sigma_2$), $N_1 >> N_2$, so that the gap in length scales suggests to treat the large particles as individual, discrete objects, while the small particles are only represented by their local density $\rho(\mathbf{r}) \equiv \rho_2(\mathbf{r})$. This local density can then be, in principle, determined from the Euler-Lagrange equations derived from the variational principle (III.5), given adequate boundary conditions at the surfaces of the large particles, which act as the sources of a multi-centre external potential felt by the small particles.

This is precisely the method used to determine effective interactions between large particles, by tracing out the microscopic degrees of freedom of the small particles. Such a DFT strategy has been successfully applied to depletion interactions [4, 5], effective interactions between electric double-layers [6], and hydrophobicity [10].

The next, more ambitious step is to determine effective interactions between large particles, "on the fly", by combining DFT optimization with MD or MC simulations, very much in the spirit of the Car-Parrinello method for classical ions and degenerate valence electrons [11]. The density $\rho(\mathbf{r})$ is considered to be a dynamical variable which adjusts quasi-instantaneously to the more slowly varying positions $\{\mathbf{R}_i\}$ of the large particles (Born-Oppenheimer approximation). The time-dependent density profile $\rho(\mathbf{r}, t)$ of the small particles may be expanded in plane waves:

$$\rho(\mathbf{r}, t) = \sum_{\mathbf{k}} \rho_{\mathbf{k}}(t) e^{i\mathbf{k}\cdot\mathbf{r}} \tag{III.6}$$

or a real space grid representation may be preferable; we shall return to this later representation in section 5. If the Fourier representation (III.6) is adopted, one may introduce the following Lagrangian [12, 13]

$$\mathcal{L} = \frac{1}{2}\sum_{i=1}^{N_1} \dot{\mathbf{R}}_i^2 + \frac{1}{2}\sum_{\mathbf{k}} m_{\mathbf{k}}\dot{\rho}_{\mathbf{k}}^2 - V_{11}(\{\mathbf{R}_i\}) - \mathcal{F}_{[\rho(\mathbf{r},t);\{\mathbf{R}_i\}]} \tag{III.7}$$

where M is the mass of the large particles and V_{11} is the interaction energy between large particles. The "fictitious" masses $m_{\mathbf{k}}$ associated with the Fourier components $\rho_{\mathbf{k}}$ are "preconditioned", so as to ensure optimal adiabaticity [14, 13]. Note that the free energy functional $\mathcal{F}$ depends parametrically on the positions of the large particles. The resulting equations of motion couple the physical time evolution of the $\{\mathbf{R}_i\}$, and the fictitious dynamics of the $\rho_{\mathbf{k}}$:

$$\begin{aligned} M\ddot{\mathbf{R}}_i &= -\nabla_i V_{11}(\{\mathbf{R}_j\}) - \nabla_i \mathcal{F}_{[\rho;\{\mathbf{R}_j\}]} \\ m_{\mathbf{k}}\ddot{\rho}_{\mathbf{k}} &= -\frac{\delta \mathcal{F}_{[\rho;\{\mathbf{R}_j\}]}}{\delta \rho_{\mathbf{k}}} + \mu \int_V d\mathbf{r}\,[\rho(\mathbf{r}) - n] \end{aligned} \tag{III.8}$$

where the last term in eq. (III.8) implements the constraint that the total number of small particles is conserved, i.e. $\rho_{\mathbf{k}=\mathbf{0}} = n$.

Application to charged colloids

The above strategy was first successfully applied to charge-stabilized colloidal dispersions, which are extremely asymmetric "mixtures" of highly charged, spherical colloidal particles and microscopic counterions, immersed in a dielectric continuum (of dielectric constant ϵ) representing the aqueous solvent ("primitive model") [12]. The excess part of the intrinsic free energy functional was taken to be the sum of the mean field Coulomb part:

$$\mathcal{F}_c = \frac{z^2e^2}{2\epsilon}\int d\mathbf{r}\int d\mathbf{r}'\frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|\mathbf{r}-\mathbf{r}'|} \tag{III.9}$$

(where z is the valence of the counterions, and $\rho(\mathbf{r})$ their local density), and of a correlation part, which was approximated within the local density approximation (LDA), from a knowledge of the free energy density of a uniform fluid of point counterions in a uniform compensating background of opposite charge (the so-called one-component plasma [15]). Since the counterions are excluded from the volumes of the colloidal polyions, a technical difficulty arises from the discontinuity of the counterion density profile $\rho(\mathbf{r})$ near the surfaces of the latter. This would require a very large number of Fourier components to be included in the representation (III.6). The difficulty may be overcome by the introduction of a continuous polyion-counterion pseudopotential, which allows the counterions to penetrate inside the polyion cores [12]. The procedure is "norm-conserving" in that it results in a local counterion density which is smooth inside the cores, but coincides with the physical density outside the cores.

The most important conclusion to be drawn from these classical "ab initio" simulations of charge-stabilized colloidal dispersion is that the effective (counterion-averaged) forces between polyions are reasonably well represented by the standard DLVO theory, based on a linearized version of the DFT, even at high packing fraction and for relatively high polyion charges.

The method was extended to colloidal dispersion containing both counterions and coions (from added salt), requiring two local densities $\rho_+(\mathbf{r})$ and $\rho_-(\mathbf{r})$ to be considered simultaneously [16], and to suspensions of charged colloidal rods [17]. A Monte Carlo version of these classical "ab initio" ideas has been developed to simulate linear polyelectrolyte chains [13, 18]. A combination of DFT with MC is more efficient than the corresponding DFT-MD scheme, because MC can sample the polyelectrolyte configuration space more efficiently, using a range of "unphysical" moves (e.g. the "reptation" algorithm [19]) which lead to larger conformational changes. The DFT-MD scheme has also been successfully applied to a problem of solvent-induced phase separation in colloidal fluids [20].

The challenges of excluded volume

The density profiles $\rho(\mathbf{r})$ considered so far are relatively smooth, so that the Fourier representation (III.6) is adequate. This is because the solvent has not yet been considered explicitly, so that the bulk density of small particles (co and counterions in the case of charged colloids of polyelectrolytes) is relatively low. This means that there is no significant layering of the small particles near the surface of the large ones. This changes with increasing density or packing fraction. In particular, when granularity of the molecular solvent (e.g. water) is explicitly taken into account, the total packing fraction of small particles is large, and the density profiles near confining surfaces become oscillatory [21] due to excluded volume effects.

A striking consequence of excluded volume is the presence of effective interactions acting between two or more particles embedded in a fluid composed of smaller hard spheres. The so-called depletion forces are mediated by the latter and of entropic origin; they exhibit a non-trivial shape and play a central role in the structural and dynamic behaviour of colloids and macromolecules in solution, e.g. the interaction between proteins in water can be mainly due to solvent-induced depletion forces. Numerically, the problem can be tackled by taking into account the excluded volume nature of a fluid via DFT, whereas the large solid particles are treated at microscopic level.

A proper treatment of excluded volume is therefore necessary for most systems of interest and, furthermore, other types of interactions, such as electrostatics, can be included as additional terms in the free energy functional.

To date, Rosenfeld's "fundamental measure theory" provides the most successful free energy functional to study hard spheres, and more generally convex hard bodies, to high accuracy. The excess free energy functional has the form

$$\beta\mathcal{F}^{ex} = \int d\mathbf{r}\phi(\{n^{\alpha}[\rho](\mathbf{r})\}) \tag{III.10}$$

where ϕ is a function of $\{n^{\alpha}[\rho](\mathbf{r})\}$, a restricted set of weighted densities written as

$$n^{\alpha}[\rho](\mathbf{r}) = \int d\mathbf{r}'\omega_{\alpha}(|\mathbf{r}-\mathbf{r}'|)\rho(\mathbf{r}') \tag{III.11}$$

and ω_{α} are singular and short range weight functions, such as Dirac and Heaviside step functions. Details of the several forms of the Rosenfeld's functional can be found in the literature [22, 23].

The rapid oscillations of the fluid density, together with the non-local, short range and singular nature of the functional, pose severe problems to the numerical implementation. The following factors need to be considered:

1. if the hard spheres composing the fluid have radii much smaller than the typical length scales of the external field, such as for highly asymmetric systems, an accurate representation of the density must be included;

2. if no further interaction takes place in the fluid, the presence of large discontinuities for the density at contact with walls is expected;

3. surface integrals need often to be considered, as for the computation of the forces acting on the large hard spheres. These forces need to be estimated with care in order to obtain high accuracy in the MD trajectory.

When dealing with the minimization of the free energy functional, the first question to be addressed is which basis set to use to represent the local free energy and corresponding density field. The use of a plane waves basis set is not helpful in the presence of excluded volume. In fact, a Fourier representation, which could help in computing the convolutions embedded in the functional, suffers from the short-range nature of the weight functions, and it would require an exceedingly large number of plane waves to represent the density discontinuities.

Therefore a real-space representation is the natural choice. To this aim, one could use either a localized basis set (e.g. gaussians) or a computational grid, the two choices being equivalent. A grid is convenient when computing the several surface and volume integrals present in the weight densities since simple finite difference formulae can be employed. The density is written as the square of a real function $\psi(\mathbf{r})$, which is represented on grid points $\mathbf{g}$ by

$$\psi(\mathbf{r}) = \sum_{\mathrm{g}} \psi_{\mathrm{g}} w_{\mathrm{g}}(\mathbf{r}) \tag{III.12}$$

where $w_{\mathrm{g}}(\mathbf{r})$ is the characteristic function associated with the volume corresponding to grid point $\mathbf{g}$. It must be noted that within this representation, the fictitious dynamics in a Car-Parrinello type of propagation, is not given by the Fourier coefficients anymore but by the corresponding coefficients ψ_{g}.

If an evenly spaced computational grid is used, the scheme is not sufficiently efficient with respect to conventional MD or MC schemes. The reason is that for highly asymmetric mixtures one would prefer to avoid the accurate calculation of the density in those regions where the density is close to its bulk value, i.e. sufficiently far away from the external field. A possible solution is to use an adaptive grid that has high local resolution in the regions where strong oscillations are expected.

In a recent study we have used the adaptive grid method advocated by Gygi [24] in the context of electronic structure calculations, to compute depletion forces of pairs and triplets of hard spheres in a bath of much smaller hard spheres [25]. An adaptive grid is described by an analytic formulation of the free-energy in terms of a Jacobian that takes into account the local grid resolution. The excess free energy and weighted densities are rewritten in the representation of the curvilinear grid configuration $\{\mathbf{x}_{\mathrm{g}}\}$, which is a given function of the flat grid configuration $\{\mathbf{r}_{\mathrm{g}}\}$, reading

$$\begin{aligned} \beta\mathcal{F}^{ex} &= \int d\mathbf{x} J(\mathbf{x}) \phi(\{n^{\alpha}_{[\rho]}(\mathbf{x})\}) \\ n^{\alpha}_{[\rho]}(\mathbf{x}) &= \int d\mathbf{x}' J(\mathbf{x}') \omega_{\alpha}(|\mathbf{x}-\mathbf{x}'|) \rho(\mathbf{x}') \end{aligned} \tag{III.13}$$

In figure 1 the typical grid deformation induced by two hard spheres on a grid composed of 64^3 points is shown. The grid deformation is larger close to the hard sphere

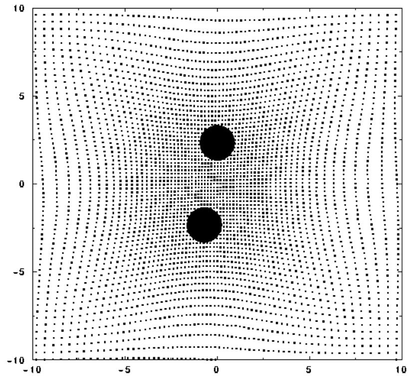

Figure III.1: Example of adaptive grid with 64^3 grid points induced by two hard spheres

boundaries, where the density is expected to vary more rapidly, by defining a suitable deformation function.

By considering two hard spheres surrounded by a fluid of small hard spheres, the two species having a size ratio of 5, we report in figure 2 the depletion forces computed with the adaptive grid method. In the figure we compare the results obtained with a different numerical scheme, that makes use of the cylindrical symmetry of the system to reduce the computational load and an evenly spaced grid to represent the density. Note however that the latter procedure is restricted to two large particles only, while the adaptive grid method can, in principle, handle larger systems.

Figure 2 shows that the adaptive grid method produces a good estimate of forces, in particular when the two large hard spheres come to contact. On the other hand, at high packing fraction the first peak is underestimated and the subsequent oscillations are damped out, probably because at large distances the grid deformation is unable to take into account the rapid variations of the density. The data show that the adaptive grid is partially capable of estimating depletion forces in an arbitrary configuration of large hard spheres, and a more accurate scheme is needed in order to improve upon the present computational capabilities.

Before concluding this section, we note that other schemes could be used for the problem at hand to reduce the computational load. A promising basis set could be composed of spherical characteristic functions that tile the available space. This choice would allow to compute the volume and surface integrals embedded in the weighted densities analytically, while the calculation of the local free energy and related functional derivatives could be achieved by quadratures. A different approach would be to employ the weighted densities, rather than the density, as the natural functions to be optimized. For this choice the free energy is represented in terms of a "local density approximation" and the variational principle is rewritten accordingly. So far, these suggested approaches have not been investigated at length, but could find application in solving efficiently the excluded volume problem for generic geometries.

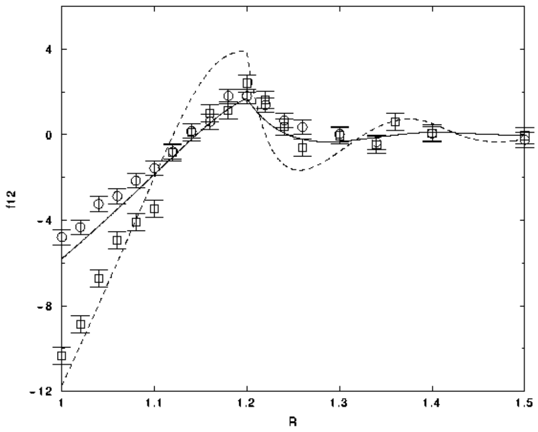

Figure III.2: Pair depletion forces (in units $\sigma k_B T$, where σ is the large hard sphere diameter) versus the distance between two large hard spheres (in σ units), computed with the adaptive grid method and with a high level calculation that makes use of the cylindrical symmetry of the configuration. The data refer to two different values of the packing fraction η. Circles : $\eta = 0.2$, adaptive grid; squares : $\eta = 0.3$, adaptive grid; solid line : $\eta = 0.2$, cylindrical symmetry; dashed line : $\eta = 0.3$, cylindrical symmetry.

Conclusion

We have shown how classical DFT can be combined with MD or MC simulations, or with standard optimization techniques, like steepest descent, to simulate complex fluids involving widely different length and time scales. The method may also be applied to the quantum regime of ion-electron systems, where the so-called "orbital-free" version of DFT [14] proved an alternative to the Kohn-Sham orbital version at the basis of the Car-Parrinello method; this alternative "ab initio" method is particularly well adapted to metallic systems [26, 27] and plasmas [28, 29, 30]. The advantages of the method is that it bypasses the time-consuming orthogonalization constraints of Kohn-Sham DFT, but the main problem lies in developing an accurate kinetic energy functional based of the local energy density alone. The simple Thomas-Fermi approximation, akin to LDA, is not nearly accurate enough, and various improvements, involving square gradient corrections, or the incorporation of exact linear and non-linear response [31, 32] have been used, with good results, particularly for alkali metals.

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IV

A Statistical Mechanical Approach to Protein Molecular Evolution

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Introduction

The goal of combinatorial chemistry is to find compositions of matter that maximize a specific material property. When combinatorial chemistry is applied to materials discovery, the desired property may be superconductivity, magnetoresistance, luminescence, ligand specificity, sensor response, or catalytic activity. When combinatorial chemistry is applied to proteins, the desired property may be enzymatic activity, fluorescence, antibiotic resistance, or substrate binding specificity. In any case, the property to be optimized, the figure of merit, is generally an unknown function of the variables and can be measured only experimentally.

Combinatorial chemistry is, then, a search over a multi-dimensional space of composition and non-composition variables for regions of high figure of merit. A traditional synthetic chemist would carry out this search by using chemical intuition to synthesize a few initial molecules. Of these molecules, those that have a favorable figure of merit would be identified. A homologous series of compounds similar to those best starting points would then be synthesized. Finally, of the compounds in these homologous series, that with the best figure of merit would be identified as the optimal material.

If the space of composition and non-composition variables is sufficiently large, novel, or unfamiliar, the traditional synthetic approach may lead to the identification of materials that are not truly the best. It is in this case that combinatorial chemistry becomes useful. In combinatorial chemistry, trial libraries of molecules are synthesized instead of trial molecules. By synthesizing and screening for figure of merit an entire library of $10^2 - 10^5$ molecules instead of a single molecule, the variable space can be searched much more thoroughly. In this sense, combinatorial chemistry is a natural extension of traditional chemical synthesis. Intuitive determination of the individual molecules to synthesize is replaced by methods for design of the molecular libraries. Likewise, synthesis of homologous compounds is replaced by redesign of the libraries for multiple rounds of parallel screening experiments.

While the combinatorial approach attempts to search composition space broadly, an exhaustive search is usually not possible. It would take, for example, a library of $20^{100} \approx 10^{130}$ proteins to search exhaustively the space of all 100 amino-acid protein domains, since there are 20 naturally occurring amino acids. Clearly, a significant aspect to the design of a combinatorial chemistry experiment is the design of the library. The library members should be chosen so as to search the space of variables as effectively as possible, given the experimental constraints on the library size.

The task of searching composition space in combinatorial chemistry for regions of high figure of merit is very similar to the task of searching configuration space by Monte Carlo computer simulation for regions of low free energy. The space searched by Monte Carlo computer simulation is often extremely large, with 10^4 or more continuous dimensions. Yet, one is able to locate reliably the regions of low free energy even for fairly complicated molecular systems.

This article pursues the analogy between combinatorial chemistry and Monte Carlo computer simulation [1]. Examples of how to design libraries for protein molecular evolution, or combinatorial chemistry of proteins, will be given. In particular, examples of how to use "biased" Monte Carlo to search the protein sequence space will be given. Chemical information, whether intuition, theoretical calculations, or database statistics, can be naturally incorporated as an *a priori* bias in the Monte Carlo approach to library design in combinatorial chemistry. In this sense, combinatorial chemistry can be viewed as an extension of traditional chemical synthesis, one ideally suited for theoretical contributions.

Protein Molecular Evolution

The space to be searched in protein combinatorial chemistry experiments is extremely large. Consider, for example, that a relatively short 100 amino acid protein domain were to be evolved. The number of possible amino acid sequences of this length is $20^{100} \approx 10^{130}$, since there are 20 naturally occurring amino acid residues. Clearly, all of these sequences cannot be synthesized and then screened for figure of merit in the laboratory. Some means must be found for searching this space with the 10^4 or so proteins than can be screened per day experimentally.

A hierarchical decomposition of the protein space can provide an effective searching procedure. It is known from protein structural biology that proteins are encoded by DNA sequences, DNA sequences code for amino acids, amino acids arrange into secondary structures, secondary structures arrange into domains, domains group to form protein monomers, and protein monomers aggregate to form multi-protein complexes. By sampling on each level of this hierarchy, one is able to search the sequence space much more effectively. In this chapter, search strategies making use of the DNA, amino acid, and secondary structure hierarchy will be described. With this approach, functional protein space has a large, yet manageable, number of dimensions. That is, in a 100 amino acid protein domain there are approximate 10 secondary structures of 5 types (helices, loops, strands, turns, and others) roughly yielding the potential for $\approx 10^7$ basic protein folds. Organization into secondary structural classes represents a dramatic reduction in the complexity of sequence space, since there are $\approx 10^{170}$ different DNA sequences and $\approx 10^{130}$ different amino acid sequences in this space.

Sampling on the different levels of protein structure is analogous to combination of different move types in a Monte Carlo simulation. A variety of moves, from small, local moves to large, global moves, are often incorporated in the most successful Monte Carlo simulations. While protein molecular evolution is carried out in the laboratory, and Monte Carlo simulations are carried out *in silico*, the parallels are striking. One of the most powerful new concepts in Monte Carlo is the idea that moves should be "biased" [2]. That is, small moves, such as the Metropolis method, sample configuration space rather slowly. Larger moves are preferred, since they sample the space more rapidly. Large moves are usually rejected, however, since they often lead the system into a region of high energy. So that the large moves will be more successful, a bias towards regions that look promising is included. Such biased Monte Carlo simulations have been a factor of 10^5 to 10^{10} times more efficient than previous methods, and they have allowed the examination of systems previously uncharacterizable by molecular simulation techniques [3, 4, 5, 6].

In this section, the possibility of evolving protein molecules by strategies similar to biased Monte Carlo will be explored. The large moves of Monte Carlo are implemented by changing an evolving protein at the secondary structure level. These evolutionary events will be biased, in that the amino acid sequences inserted will be chosen so that they code for viable secondary structures. The concept of bias also applies at the amino acid level, where different DNA sequences coding for the same amino acids can lead to different propensities for future evolution.

What is Protein Molecular Evolution

Protein molecular evolution can be viewed as combinatorial chemistry of proteins. Since protein sequence space is so large, most experiments to date have sought to search only small regions. A typical experiment seeks to optimize the figure of merit of an existing protein. For example, an improvement in the selectivity or activity of an enzyme might be sought. Alternatively, an expansion in the operating range of an enzyme might be sought to higher temperatures or pressures. This improvement would be achieved by changing, or evolving, the amino acid sequence of the enzyme.

A more ambitious goal would be the *ab initio* evolution of a protein with a specific function. That is, nothing would be known about the desired molecule, except that it should be a protein and that an experimental screen for the desired figure of merit is available. One might want, for example, an enzyme that catalyses an unusual reaction. Or one might want a protein that binds a specific substrate. Or one might want a protein with an unusual fluorescence spectrum. The *ab initio* evolution of a protein has never been accomplished before. Such a feat would be remarkable. Natural biological diversity has evolved despite the essentially infinite complexity of protein sequence. Replication of this feat in the laboratory would represent substantial progress, and mimicking this feat of Nature is a current goal in the molecular evolution field. Indeed, the protocols described in this section are crafted with just this task in mind.

A still more ambitious goal would be the evolution of a multi-protein complex. This is a rather challenging task, due to the increased complexity of the space to be searched. The task can be made manageable by asking a rather general evolutionary question. One can seek to evolve, for example, a multi-protein complex that can serve as the coat protein complex for a virus. Since there are many proteins that may accomplish this task, this evolutionary task may not be as specific and difficult as it might seem at first.

The most ambitious goal for laboratory evolution that has been imagined is the evolution of new life forms. Evolution on this scale requires changes not only at the secondary structure scale, but also at the domain, protein, and protein pathway scale. Due to their simplicity, viruses or phage would be the most likely targets of such large-scale evolution attempts. It is unclear how new life forms would be distributed in terms of pathogenicity, and so such experiments should be approached with caution.

The hierarchical decomposition of sequence space will allow effective molecular evolution if there are many proteins with a high value of any particular figure of merit. That is, if only one out of 10^{130} small protein domains exhibits a high score on a particular figure of merit, this protein is unlikely to be identified. On the other hand, if many proteins score highly on the figure of merit, only a subset of these molecules need be sampled. This same issue arises in conventional Monte Carlo simulations. Sampling all of configuration space is never possible in a simulation, yet ensemble averages and experimental behavior can be reproduced by sampling representative configurations. That life on our planet has evolved suggests that there is a great redundancy in protein space [7], and so one may hope to search this space experimentally with sufficiently powerful moves.

Background on Experimental Molecular Evolution

There are some constraints on molecular evolution as it is carried out in the laboratory. There are constraints arising from limitations of molecular biology, *i.e.* only certain types of moves are possible on the DNA that codes for the protein. There are also constraints arising from technical limitations, *i.e.* only a certain number of proteins can be screened for figure of merit in a day.

Existing approaches to the evolution of general proteins are essentially limited to changes at the single base level. Somewhat more sophisticated methods are available for evolution of antibodies, but this is a special case that will not be considered here. The first type of evolutionary change that is possible in the laboratory is a base substitution. Base substitutions are naturally made as DNA is copied or amplified by PCR. The rate at which base substitutions, or mistakes in the copying of the template DNA, are made can be adjusted by varying experimental conditions, such as the manganese and magnesium ion concentrations. It is important to note that these base substitutions are made without knowledge of the DNA sequences of the evolving proteins. Equally important is that these base substitutions are made without the use of a chemical synthesizer. These changes are made naturally within the context of efficient molecular biology methods. Another means of modifying an existing protein is to use random or directed mutagenesis to change specific DNA bases so that they code for random or specified amino acids. The approach requires both that the DNA sequence be known and that it subsequently be synthesized by chemical means. Such a laborious approach is not practical in high-throughput evolution experiments, where typically 10^4 proteins are simultaneously modified and evolved per day.

Since the average length of a human gene is roughly 1800 bases, base-by-base point mutation will achieve significant evolution only very slowly. More significantly, the figure-of-merit landscape for protein function is typically quite rugged. Base mutation, therefore, invariably ceases evolution at a local optima of the figure of merit. Base mutation can be viewed as an experimental method for local optimization of protein figures of merit.

Much of the current enthusiasm for protein molecular evolution is due to the discovery of DNA shuffling by Pim Stemmer in 1994 [8]. DNA shuffling is a method for evolving an existing protein to achieve a higher figure of merit. The great genius of Stemmer was to develop a method for combining beneficial base mutations that is naturally accomplished with the tools of molecular biology and that does not require DNA sequencing or chemical synthesis. The method is successful because combination of base mutations that were individually beneficial is likely to lead to an even higher figure of merit than is achieved by either mutation alone. Of course, this will not always be true, but the extent to which it is true is the extent to which DNA shuffling will be an effective technique. DNA shuffling, combined with base mutation, is the current state of the art experimental technique for protein molecular evolution.

Table IV.1 lists a few of the protein systems that have been evolved by the Stemmer group. Evidently, DNA shuffling is highly effective at improving the function of an existing protein, much more effective than is simple base mutation. The specificity of an enzyme can even be altered, as in the conversion of a β-galactosidase into a fucosidase. A rough median of the improvement factors is about 100. Most important, however, is that all of these improvements were achieved with a relatively small number of amino acid changes. On average, only 6 amino acids were altered out of roughly 400 total residues in the protein. As with base mutation, then, DNA shuffling is able to search sequence space only locally. After a small number of amino acid changes, DNA shuffling produces a protein with a locally rather than globally optimal figure of merit.

The current state of the art experimental techniques for protein molecular evolution can be viewed as local optimization procedures in protein sequence space. Alternatively, they can be viewed as experimental implementations of simple, or Metropolis, Monte Carlo procedure. By using our intuition regarding the design of powerful, biased Monte Carlo algorithms, we can develop more powerful experimental protocols for molecular evolution.

Interestingly, theoretical treatments of evolution, whether in Nature or in the laboratory, tend to consider only the effects of point mutation [7, 11]. Indeed, interesting theories regarding the evolutionary potential of point mutations have been developed. As shown experimentally, however, point mutation is incapable of significantly evolving proteins at substantial rate. Even the more powerful technique of DNA shuffling searches protein space merely locally. Only with the inclusion of more dramatic moves, such as changes at the level of secondary structures, can protein space be searched more thoroughly.

Table IV.1: Genes and operons evolved by DNA shuffling, from [9].

System	Improvement	Size	Mutations
TEM-1 β-lactamase	Enzyme activity 32000-fold	333 aa	6 aa
β-galactosidase	Fucosidase activity 66-fold	1333 aa	6 aa
Green fluorescence protein	Protein folding 45-fold	266 aa	3 aa
Antibody	Avidity > 400-fold	233 aa	34 aa[1]
Antibody	Expression level 100-fold	233 aa	5 aa
Arsenate operon	Arsenate resistance 40-fold	766 aa	3 aa
Alkyl transferase	DNA repair 10-fold	166 aa	7 aa
Benzyl esterase	Antibiotic deprotection 150-fold	500 aa	8 aa
tRNA synthetase	Charging of engineered tRNA 180-fold	666	not determined

[1]This was a case of family shuffling [10], so most of these changes were between homologous amino acids.

The Generalized NK Model

In order to validate the molecular evolution protocols to be presented, a model that relates amino acid sequence to protein function is needed. Of course, the real test of these protocols should be experimental, and I hope that these experiments will be forthcoming. In order to stimulate interest in the proposed protocols, their effectiveness will be simulated on a model of protein function. Such a model would seem to be difficult to construct. It is extremely difficult to determine the three-dimensional structure of a protein given the amino acid sequence. Moreover, it is extremely difficult to calculate any of the typical figures of merit given the three-dimensional structure of a protein.

It is fortunate that a model that relates figure of merit to amino acid sequence for a specific protein is not needed. The requirement is simply a model that produces figure-of-merit landscapes in sequence space that are analogous to those that would be measured in the laboratory on an ensemble of proteins. This type of model is easier to construct, and a random energy model can be used to accomplish the task.

The generalized NK model is just such a random energy model. The NK model was first introduced in order to model combinatorial chemistry experiments on peptides [12, 7, 13]. It was subsequently generalized to account for secondary structure in real proteins [14]. The model was further generalized to account for interactions between the secondary structures and for the presence of a binding pocket [15].

This generalized NK model assigns a unique figure of merit to each evolving protein sequence. This model, while a simplified description of real proteins, captures much of the thermodynamics of protein folding and ligand binding. The model takes into account the formation of secondary structures via the interactions of amino acid side chains as well as the interactions between secondary structures within proteins. In addition, for specificity, the figure of merit is assumed to be a binding constant, and so the model includes a contribution representing binding to a substrate. The combined ability to fold and bind substrate is what will be optimized or evolved. That is, the direction of the protein evolution will be based upon the figure of merit returned by this generalized NK model. This generalized NK model contains several parameters, and a reasonable determination of these parameters is what allows the model to compare successfully with experiment.

The specific energy function used as the selection criterion in the molecular simulations is

$$U = \sum_{\alpha=1}^{M} U_{\alpha}^{sd} + \sum_{\alpha>\gamma=1}^{M} U_{\alpha\gamma}^{sd-sd} + \sum_{i=1}^{P} U_i^c. \tag{IV.1}$$

This energy function is composed of three parts: secondary structural subdomain energies (U^{sd}), subdomain-subdomain interaction energies (U^{sd-sd}), and chemical binding energies (U^c). Each of these three energy terms is weighted equally, and each has a magnitude near unity for a random sequence of amino acids. In this NK based simulation, each different type of amino acid behaves as a completely different chemical entity; therefore, only $Q = 5$ five chemically distinct amino classes are considered (*e.g.*, negative, positive, polar, hydrophobic, and other). Interestingly, restricted alphabets of amino acids not only are capable of producing functional proteins [16, 17] but also may have been used in the primitive genetic code [18, 19]. The evolving protein will be a relatively short 100 amino acid protein domain. Within this domain will be roughly $M = 10$ secondary structural subdomains, each $N = 10$ amino acids in length. The subdomains belong to one of $L = 5$ different types (*e.g.*, helices, strands, loops, turns, and others). This gives L different (U^{sd}) energy functions of the NK form[12, 7, 13, 14].

$$U_{\alpha}^{sd} = \frac{1}{[M(N-K)]^{1/2}} \sum_{j=1}^{N-K+1} \sigma_{\alpha}\left(a_j, a_{j+1}, \ldots, a_{j+K-1}\right) \ . \tag{IV.2}$$

The degree of complexity in the interactions between the amino acids is parameterized by the value of K. Low values of K lead to figure-of-merit landscapes upon which evolution is easy, and high values of K lead to extremely rugged landscapes upon which evolution is difficult. Combinatorial chemistry experiments on peptides have suggested the value of $K = 4$ as a reasonable one [13]. Note that the definition of K here is one greater than the convention in [12, 7, 13]. The quenched, unit-normal random number σ_{α} in Eq. IV.2 is different for each value of its argument for each of the L classes. This random form mimics the complicated amino acid side chain interactions within a given secondary structure. The energy of interaction between secondary structures is given by

$$\begin{aligned} U_{\alpha\gamma}^{sd-sd} &= \left[\frac{2}{DM(M-1)}\right]^{1/2} \\ &\times \sum_{i=1}^{D} \sigma_{\alpha\gamma}^{(i)} \left(a_{j_1}^{\alpha}, \ldots, a_{j_{K/2}}^{\alpha}; a_{j_{K/2+1}}^{\gamma}, \ldots a_{j_K}^{\gamma}\right) \ . \end{aligned} \tag{IV.3}$$

The number of interactions between secondary structures is set at $D = 6$. Here the unit-normal weight, $\sigma_{\alpha\gamma}^{(i)}$, and the interacting amino acids, $\{j_1, \ldots, j_K\}$, are selected at random for each interaction (i, α, γ). The chemical binding energy of each amino acid is given by

$$U_i^c = \frac{1}{\sqrt{P}} \sigma_i\left(a_i\right) \ .$$

The contributing amino acid, i, and the unit-normal weight of the binding, σ_i, are chosen at random. A typical binding pocket is composed of five amino acids, and so the choice of $P = 5$ is made.

Experimental Conditions and Constraints

A typical protein evolution experiment starts with an initial protein sequence. This sequence is then copied to a large number of identical sequences. All of these sequences are evolved, or mutated, in parallel. After one round of mutation events, the proteins are screened for figure of merit. This screening step is typically the rate limiting step, and so the efficiency of this step determines how many proteins can be evolved in parallel. For typical figures of merit, 10000 proteins can be screened in a day. If selection, that is use of a screen based upon whether an organism lives or dies, were performed instead, $10^9 - 10^{15}$ proteins could be screened in a day. Selection is a special case, however, and so the more conservative case of screening 10000 proteins per day is considered.

After the screen, the proteins are ranked according to their measured value of the figure of merit. Typically, the top x percent of the sequences are kept for the next round of mutation. The parameter x is to be adjusted experimentally. In the simulated evolutions, the value of $x = 10\%$ was always found to be optimal. Other methods for selecting the proteins to keep for the next round have been considered. For example, keeping proteins proportional to $\exp(-\beta U)$ has been considered. This strategy seems to work less well than the top x percent method. The main reason seems to be that in the top x percent method, the criterion for selecting which sequences to keep adjusts naturally with the range of figures of merit found in the evolving sequences. After the top x percent sequences are selected, they are copied back up to a total of 10000 sequences. These sequences are the input for the next round of mutation and selection.

In the simulated molecular evolutions, the experiment is continued for 100 rounds. This is a relatively large number of rounds to carry out experimentally. With the most powerful protocols, however, it is possible to evolve proteins *ab initio*. This feat has not been achieved to date in the laboratory. In order to mimic this feat of Nature, one should be willing to do some number of rounds.

Several Hierarchical Evolution Protocols

Amino acid substitution

To obtain a base line for searching fold space, molecular evolution is first simulated via simple mutagenesis (see Figure IV.1a). Simulated evolutions by amino acid substitution lead to significantly improved protein energies, as shown in Table IV.2. These evolutions always terminated at local energy minima, however. This trapping is due to the difficulty of combining the large number of correlated substitutions necessary to generate new protein folds. Increasing the screening stringency in later rounds did not improve the binding constants of simulated proteins, most likely due to the lack of additional selection criteria such as growth rates. Although only non-conservative mutations were directly simulated, conservative and synonymous neutral mutations are not excluded and can be taken into account in a more detailed treatment. Indeed, the optimized average mutation rate of 1 amino acid substitution/sequence/round is equivalent to roughly 1-6 random base substitutions/round.

DNA shuffling

DNA shuffling improves the search of local fold space via a random yet correlated combination of homologous coding fragments that contain limited numbers of beneficial amino acid substitutions. As in experimental evolutions [8, 10, 20, 21], the simulated shuffling improved protein function significantly better than did point mutation alone (see Table IV.2 and Figure IV.1b). However, local barriers in the energy function also limit molecular evolution via DNA shuffling. For example, when the screen size was increased from 10000 to 20000 proteins per round, no further improvement in the final evolved energies was seen. Interestingly, the optimal simulated DNA shuffling length of 20 amino acids (60 bases) is nearly identical to fragment lengths used in experimental protocols [10].

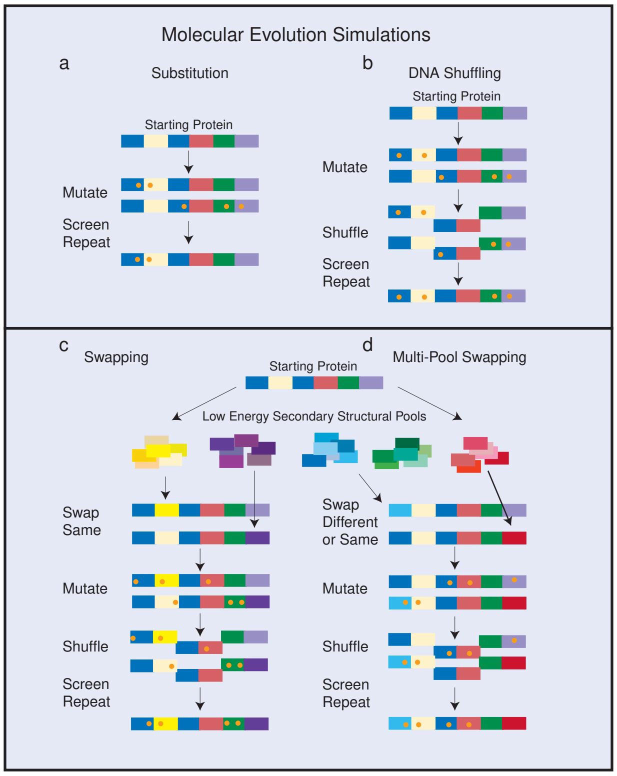

Figure IV.1: Schematic diagram of the simulated molecular evolution protocols, from [15]. a) Simulation of molecular evolution via base substitution (substitutions are represented by orange dots). b) Simulated DNA shuffling showing the optimal fragmentation length of 2 subdomains. c) The hierarchical optimization of local space searching: The 250 different sequences in each of the 5 pools (*e.g.*, helices, strands, turns, loops, and others) are schematically represented by different shades of the same color. d) The multi-pool swapping model for searching vast regions of tertiary fold space is essentially the same as in the Figure IV.1c except that now sequences from all 5 different structural pools can be swapped into any subdomain. Multi-pool swapping allows for the formation of new tertiary structures by changing the type of secondary structure at any position along the protein.

Table IV.2: Results of Monte Carlo simulation of the evolution protocols, from [15].[1]

Evolution Method	U_{start}	U_{evolved}	k_{binding}
Amino Acid Substitution	-17.00	-23.18	1
DNA Shuffling	-17.00	-23.83	100
Swapping	0	-24.52	1.47×10^4
Mixing	0	-24.88	1.81×10^5
Multi-Pool Swapping[2]	0	-25.40	8.80×10^6

[1]The starting polypeptide energy of -17.00 comes from a protein-like sequence (minimized U^{sd}), and 0 comes from a random initial sequence of amino acids. The evolved energies and binding constants are median values. The binding constants are calculated from $k_{\mathrm{binding}} = ae^{-bU}$, where a and b are constants determined by normalizing the binding constants achieved by point mutation and shuffling to 1 and 100, respectively.
[2]Note that the energies and binding constants achieved via multi-pool swapping represents typical best evolved protein folds.

Single-pool swapping

In Nature, local protein space can be rapidly searched by the directed recombination of encoded domains from multi-gene pools. A prominent example is the creation of the primary antibody repertoire in an adaptive immune system. These events are generalized by simulating the swapping of amino acid fragments from 5 different structural pools representing helices, strands, loops, turns, and others (see Figure IV.1c). During the swapping step, subdomains were randomly replaced with members of the same secondary structural pools with an optimal probability of 0.01/subdomain/round. The simulated evolution of the primary fold is limited by maintaining the linear order of swapped secondary structure types. The addition of the swapping move was so powerful that it was possible to achieve binding constants 2 orders of magnitude higher than in shuffling simulations (see Table IV.2). Significantly, these improved binding constants were achieved starting with 10-20 times less minimized structural subdomain material.

Mixing

Parallel tempering is a powerful statistical method that often allows a system to escape local energy minima [22]. This method simultaneously simulates several systems at different temperatures, allowing systems at adjacent temperatures to swap configurations. The swapping between high- and low-temperature systems allows for an effective searching of configuration space. This method achieves rigorously correct canonical sampling, and it significantly reduces the equilibration time in a simulation. Instead of a single system, a larger ensemble with n systems is considered in parallel tempering, and each system is equilibrated at a distinct temperature T_i, $i = 1, \ldots, n$. The procedure in parallel tempering is illustrated in Figure IV.2

The system with the lowest temperature is the one of our interest; the higher temperature systems are added to aid in the equilibration of the system of interest. In

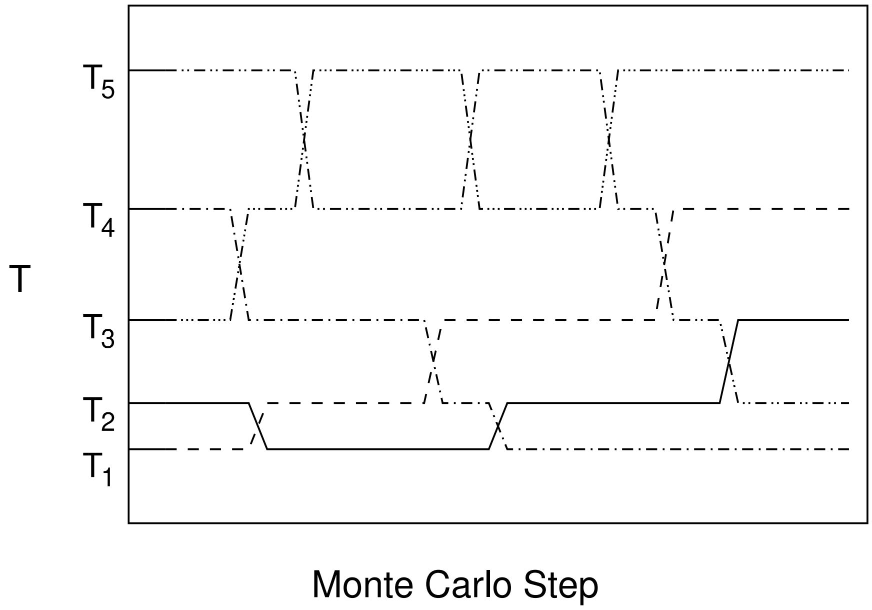

Figure IV.2: A schematic drawing of the swapping taking place during a parallel tempering simulation.

addition to the normal Monte Carlo moves performed in each system, swapping moves are proposed that exchange the configurations between two systems i and $j = i + 1$, $1 \leq i < n$. The higher temperature systems are included solely to help the lowest temperature system to escape from local energy minima via the swapping moves. To achieve efficient sampling, the highest temperature should be such that no significant free energy barriers are observed. So that the swapping moves are accepted with a reasonable probability, the energy histograms of systems adjacent in the temperature ladder should overlap.

In Nature, as well, it is known that genes, gene fragments, and gene operons are transfered between species of different evolutionary complexity (*i.e.*, at different "temperatures"). By analogy, limited population mixing is performed among several parallel swapping experiments by randomly exchanging evolving proteins at an optimal probability of 0.001/protein/round. These mixing simulations optimized local space searching and achieved binding constants $\approx 10^5$ higher than did base substitution alone (see Table IV.2). Improved function is due, in part, to the increased number of events in parallel experiments. Indeed, mixing may occur in Nature when the evolutionary target function changes with time. That is, in a dynamic environment with multiple selective pressures, mixing would be especially effective when the rate of evolution of an isolated population is slower than the rate of environmental change. It has also been argued that spatial heterogeneity in drug concentration, a form of "spatial parallel tempering," facilitates the evolution of drug resistance [23].

Multipool swapping

The effective navigation of protein space requires the discovery and selection of tertiary structures. To model the large scale search of this space, a random polypeptide sequences was used as a starting point, and the swapping protocol was repeated. Now,

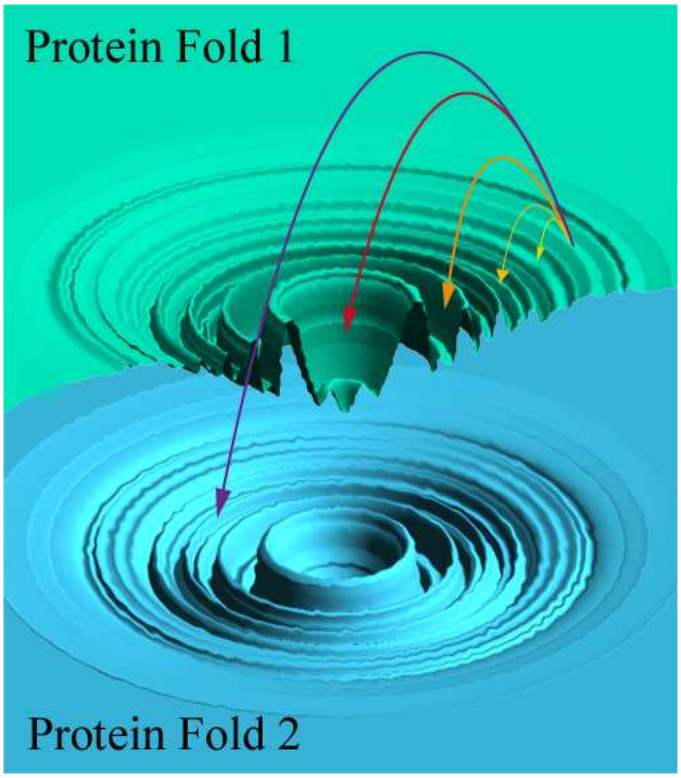

Figure IV.3: Schematic diagram representing a portion of the high-dimensional protein composition space, from [15]. The three-dimensional energy landscape of Protein Fold 1 is shown in cut away. The arcs with arrowheads represent the ability of a given molecular evolution process to change the composition and so to traverse the increasingly large barriers in the energy function. The smallest arc represents the ability to evolve improved fold function via point mutation. Then in increasing order: DNA shuffling, swapping, and mixing. Finally, the multi-pool swapping protocol allows an evolving system to move to a different energy landscape representing a new tertiary fold (bottom).

however, secondary structures from all 5 different pools were permitted to swap in at every subdomain (see Figure IV.1d). This multi-pool swapping approach evolved proteins with binding constants $\approx 10^7$ better than did amino acid substitution of a protein-like starting sequence (see Table IV.2). This evolution was accomplished by the random yet correlated juxtaposition of different types of low energy secondary structures. This approach dramatically improved specific ligand binding while efficiently discovering new tertiary structures (see Figure IV.3). Optimization of the rate of these hierarchical molecular evolutionary moves, including relaxation of the selection criteria, enabled the protein to evolve despite the high rate of failure for these dramatic swapping moves. Interestingly, of all the molecular evolutionary processes modeled, only multi-pool swapping demonstrated chaotic behavior in repetitive simulations. This chaotic behavior was likely due to the discovery of different model folds that varied in their inherent ability to serve as scaffolds for ligand specific binding.

Possible Experimental Implementations

An important motivation of this work was that the proposed protocols must be experimentally feasible. Indeed, the ultimate test of the effectiveness of these protocols will be experimental. It is hoped that the search of large regions of protein space apparently possible with these methods will identify new protein folds and functions of great value to basic, industrial, and medical research.

The main technical challenge posed by the swapping protocols is the non-homologous recombination necessary to swap the DNA that codes for different secondary structures into the evolving proteins. One approach would be to generate multiple libraries of synthetic oligonucleotide pools [24, 25] encoding the different secondary subdomain structures. Asymmetric, complementary encoded linkers with embedded restriction sites would make the assembly, shuffling, and swapping steps possible.

Alternatively, the techniques of ITCHY [26] and SCRATCHY [27] may be used to accomplish the non-homologous swapping of secondary structures required within our protocol.

Finally, exon shuffling may be used to perform the non-homologous swapping events. In this case, the pools of secondary structures would be encoded with exons of a living organism, such as *E. coli.* There is precedent for such use of exon shuffling, both at the DNA [28] and RNA [29] level.

Life has Evolved to Evolve

Although the focus has been on the higher levels of the evolution hierarchy, because that is where the biggest theoretical and experimental gap lies, all levels are important. In particular, the details of how point mutation assists protein evolution is important.

DNA base mutation leads only indirectly to changes in protein expression. How mutations occur in the bases and how these mutations lead to codon changes, and so amino acid changes, is not purely random. The inherent properties of the genetic code and biases in the mechanisms of DNA base substitution are perfectly suited for the "neutral" search of local space. Previously, the genetic code has been presented as a nodal or hypercubic structure to illustrate these relationships [30, 31]. It seems preferable to view the standard genetic code quantitatively as a 64×64 two-dimensional matrix. Seeds of this approach can be found in Kepler's work regarding evolvability in immunoglobulin genes [32, 33, 34]. The values in this matrix are the probabilities of a specific codon mutating to another by a single base change under error-prone conditions, *e.g.* mutator strains of bacteria, error prone PCR, or somatic hypermutation. Assuming each base mutates independently in the codon, this matrix can be calculated from a simpler 4×4 matrix of base mutation probabilities. The base mutation matrix can be extracted from available experimental data [35]. A synonymous transition probability can be defined for each codon, which is the probability per replication of a base change that leads to a codon that codes for the same amino acid. A conservative transition probability can further be defined, which is the probability per replication that a base change leads to a conservative mutation. Finally, a non-conservative transition probability can be defined, which is the probability per replication that a base change leads to a non-conservative mutation. The conservative and non-conservative mutation probabilities can be viewed as defining the evolutionary potential of each codon: codons with high conservative and non-conservative mutation rates can be said to exhibit a high evolutionary potential. These mutation tendencies are shown in Figure IV.4. In general, amino acids that exhibit a dramatic functional property, such as the charged residues, the ringed residues, cysteine, and tryptophan, tend to mutate at higher non-conservative rates that allows for the possible deletion of the property. Amino acids that are more generic, such as the polar neutral residues and the non-polar non-ringed residues, tend to mutate at higher conservative rates that allows sequence space to be searched for similar favorable contacts.

There is a connection between condon usage and DNA shuffling. In the most successful DNA shuffling experiments by the Stemmer group, codon assignments of the initial coding sequences are optimized for expression. This assignment typically increases the non-synonymous mutation rates described above. In particular, this assignment tends to increase the conservative mutation rate for the generic amino acids and the non-conservative mutation rate for the dramatically-functional amino acids. Codon usage, then, has already implicitly been used to manipulate mutation rates. Explicit consideration of the importance of codon assignment would be an interesting amino-acid level refinement of existing molecular evolution protocols. Optimized protocol parameters can be identified, taking into account the detailed codon usage information. Similarly, the codon potential matrix can be used in the design of the pools of secondary structures in the swapping-type molecular evolution protocols. That is, DNA can be chosen that codes for the secondary structures that i) tends not to mutate, ii) tends to mutate to synonymous sequences, iii) tends to mutate to conservative sequences, or iv) tends to mutate to non-conservative sequences.

In Nature there are numerous examples of exploiting codon potentials in ongoing evolutionary processes [34]. In the V regions of encoded antibodies, high-potential serine codons such as AGC are found predominately in the encoded CDR loops while the encoded frameworks contain low-potential serine codons such as TCT. Unfortunately, antibodies and drugs are often no match for the hydrophilic, high-potential codons of "error-prone" pathogens. The dramatic mutability of the HIV gp120 coat protein is one such example. One can envision a scheme for using codon potentials to target disease epitopes that mutate rarely (*i.e.*, low-potential) and unproductively (*i.e.*, become stop, low-potential, or structure-breaking codons). Such a therapeutic scheme is quite simple, and so could be quite generally useful against diseases that otherwise tend to become drug resistant.

Natural Analogs of these Protocols

During the course of any evolutionary process, proteins become trapped in local energy minima. Dramatic moves, such as swaps and juxtaposition, are needed to break out of these regions. Dramatic moves are usually deleterious, however. The evolutionary success of these events depends on population size, generation time, mutation rate, population mixing, selective pressure or freedom, such as successful genome duplications or the establishment of set-aside cells [36], and the mechanisms that transfer low energy, encoded structural domains.

By using the analogy with Monte Carlo to design "biased" moves for molecular evolution, a swapping-type move has been derived that is similar to several mechanisms of natural evolution. Viruses and transposons, for example, have evolved large-scale

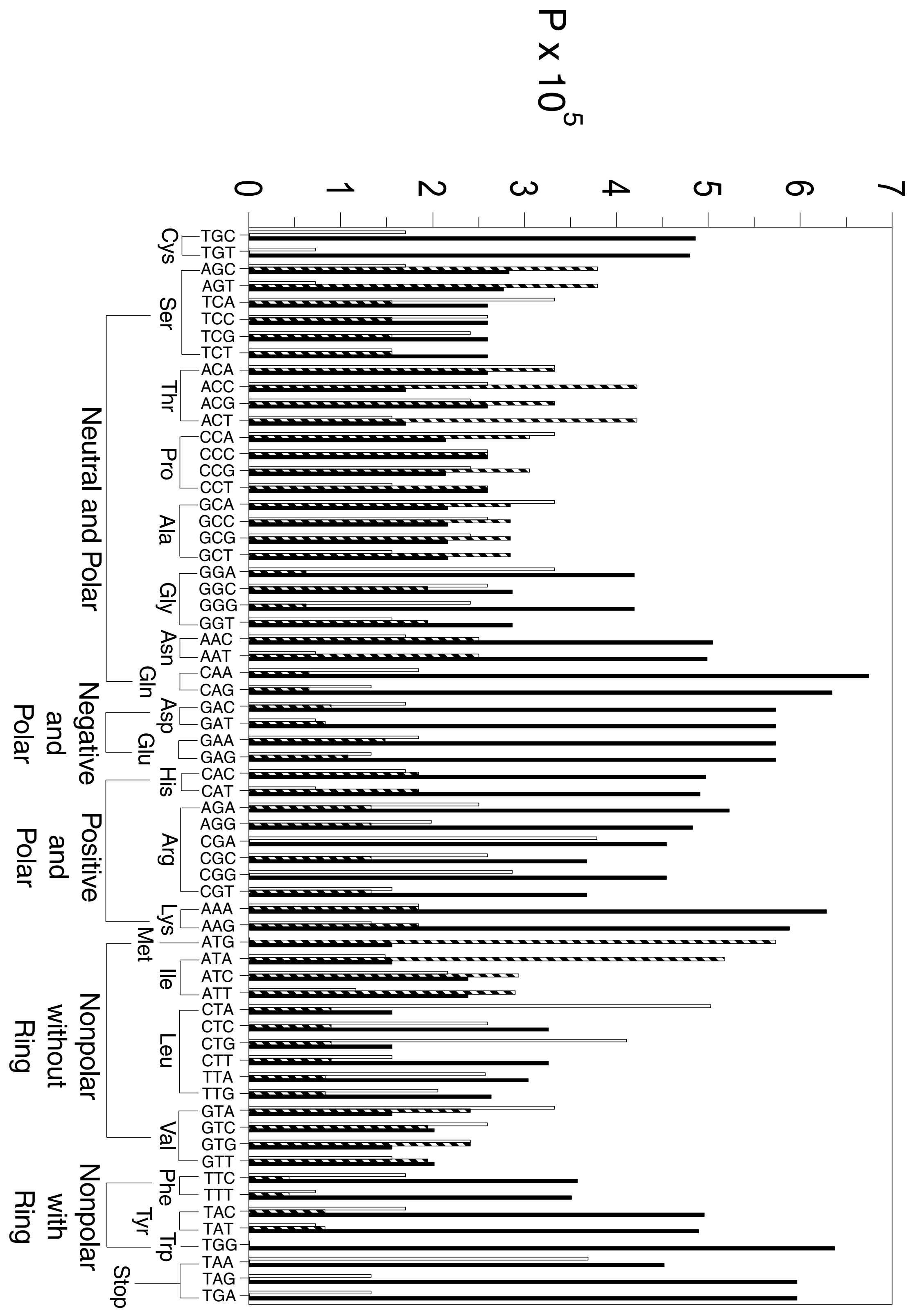

Figure IV.4: Shown are the probabilities of a given codon mutating in a synonymous (unfilled), conservative (hatched), and non-conservative (filled) way in one round of replication under error prone conditions. The codons are grouped by the amino acid encoded, and the amino acids are group by category.

integration mechanisms [37]. Exon shuffling is also a generator of diversity, and a possible scenario is that exon shuffling generated the primordial fold diversity [38, 39, 40]. Alternatively, random swapping by horizontal transfer [41], rearrangement, recombination, deletion, and insertion can lead to high in-frame success rates in genomes with high densities of coding domains and reading frames, as in certain prokaryotes and mitochondria.

While inter- and intra-species exchange of DNA is often thought to occur primarily on the scale of genes and operons, shorter exchange often occurs. Indeed, the most prevalent exchange length within *E. coli* is on the order of several hundred to a thousand base pairs [42]. Similarly, analysis of the evolution of vertebrate cytochrome-c suggests that transfer of segments significantly smaller than a single gene must have occurred [42].

Indeed, swapping mutations leading to significant diversity are not rare in Nature. *Neisseria meningitidis* is a frequent cause of meningitis in sub-Saharan Africa [43]. The Opa proteins are a family of proteins that make up part of the outer coat of this bacteria. These proteins undergo some of the same class switching and hypervariable mutations as antibody domains. A significant source of diversity also appears to have come from interspecies transfer with *Neisseria gonorrhoeae* [43]. Both the surface coat proteins and pilon proteins of *N. gonorrhoeae* undergo significant homologous recombination to produce additional diversity. It appears generally true that the intra- and interspecies transfer of short segments of genes is common in *E. coli*, *Streptococci*, and *Neisseria*. Rapid evolution of diversity such as this obviously poses a significant challenge for therapeutic protocols.

Three dramatic examples of use of swapping by Nature are particularly notable. The first is the development of antibiotic resistance. It was originally thought that no bacteria would become resistant to penicillin due to the many point mutations required for resistance. Resistance occurred, however, within several years. It is now known that this resistance occurred through the swapping of pieces of DNA between evolving bacteria [44, 45]. One mechanism of antibiotic resistance was incorporation of genes coding for β-lactamases. These genes, which directly degrade β-lactam antibiotics, appear to be relatively ancient, and their incorporation is a relatively simple example of a swapping-type event. These β-lactamases have continued to evolve, however, in the presence of antibiotic pressure, both by point mutation and by shuffling of protein domains via exon shuffling [46, 47]. The bacterial targets of penicillin, the penicillin-binding proteins, are modular proteins that have undergone significant structural evolution since the introduction of penicillin [48, 49]. This evolution was of a domain-shuffling form, and it is a more sophisticated example of a Natural swapping-type move. Multi-drug resistance is, of course, now a major, current health care problem. The creation of the primary antibody repertoire in vertebrates is another example of DNA swapping (of genes, gene segments, or pseudo-genes). Indeed, the entire immune system mostly likely evolved from a single transposon insertion some 450 million years ago [50, 51]. This insertion, combined with duplication and subsequent mutation of a single membrane spanning protein, mostly likely lead to the class switching apparatus of the primary repertoire. Finally, the evolution of *E. coli* from *Salmonella* occurred exclusively by DNA swapping [41]. None of the phenotypic differences between these two species is due to point mutation. Moreover, even the observed rate of evolution due to DNA swapping, 31000 bases/million years, is higher than that due to point mutation, 22000 bases/million years. Even though a DNA swapping event is less likely to be tolerated than is a point mutation, the more dramatic nature of the swapping event leads to a higher overall rate of evolution. This is exactly the behavior observed in the simulated molecular evolutions.

Concluding Remarks on Molecular Evolution

DNA base substitution, in the context of the genetic code, is ideally suited for the generation, diversification, and optimization of local protein space [18, 30]. However, the difficulty of making the transition from one productive tertiary fold to another limits evolution via base substitution and homologous recombination alone. Non-homologous DNA recombination, rearrangement, and insertion allow for the combinatorial creation of productive tertiary folds via the novel combination of suitable structures. Indeed, efficient search of the high-dimensional fold space requires a hierarchical range of mutation events.

This section has addressed from a theoretical point of view the question of how protein space can be searched efficiently and thoroughly, either in the laboratory or in Nature. It was shown that point mutation alone is incapable of evolving systems with substantially new protein folds. It was further demonstrated that even the DNA shuffling approach is incapable of evolving substantially new protein folds. The Monte Carlo simulations demonstrated that non-homologous DNA "swapping" of low energy structures is a key step in searching protein space.

More generally, the simulations demonstrated that the efficient search of large regions of protein space requires a hierarchy of genetic events, each encoding higher order structural substitutions. It was shown how the complex protein function landscape can be navigated with these moves. It was concluded that analogous moves have driven the evolution of protein diversity found in Nature. The proposed moves, which appear to be experimentally feasible, would make an interesting addition to the techniques of molecular biology. An especially important application of the theoretical approach to molecular evolution is modeling the molecular evolution of disease.

There are many experimental applications of the technology for molecular evolution [9]. Perhaps some of the most significant are in the field of human therapeutics. Molecular evolution can be used directly to improve the performance of protein pharmaceuticals. Molecular evolution can be used indirectly to evolve small molecule pharmaceuticals by evolving the pathways that code for small molecule synthesis in *E. coli*. Molecular evolution can be used for gene therapy and DNA vaccines. Molecular evolution can be used to produce recombinant protein vaccines or viral vaccines. Finally, molecular evolution can be used to create modified enzymatic assays in drug screening efforts. The ability to develop new assays that do not infringe on competitors' techniques is an important ability for large pharmaceutical companies, given the current complex state of patent claims. There is a similar range of applications of molecular evolution in the field of biotechnology. As shown in Table IV.1, many of the tools of molecular biology can be improved or modified through the use of molecular evolution.

A wide variety of pest organisms and parasites, including fungi, weeds, insects, protozoans, macroparasites, and bacteria, have used evolutionary processes to evade chemical control. The range of evolutionary events exhibited by these organisms is similar in spirit to the hierarchy of moves present in the molecular evolution protocol (see Figure IV.1). Bacteria provide one of the most pressing examples of the problems posed by an evolving disease (a "moving target"). Although there undoubtedly have been many selective pressures upon bacteria, the novel pressure with the largest impact in the last half century has been the worldwide use of antibiotics. This background presence of antibiotics has lead to the development of antibiotic resistance in many species of bacteria. Indeed, multi-drug resistance is now a major health care issue, with some strains resistant to all but one, or even all, known antibiotics.

Interestingly, there is another strong pressure on evolving bacteria, that of the vertebrate immune system. This pressure is thought to be responsible for mosaic, or modular as a result of swapping-type events, genes found in species of bacteria not naturally genetically competent, such as *E. coli* and *S. pyogenes* [52]. In these cases, the long-standing, strong selective pressure due to the interaction with the immune system likely led to genetic exchange.

Kepler and Perelson have noted that a spatial heterogeneity in the concentration of a drug can facilitate evolved resistance in the disease organism [23]. This occurs because regions of low drug concentration provide a "safe harbor" for the disease, where replication and mutation can occur. The regions of high disease concentration provide the selective pressure for the evolution. Explicit examples of this mode of evolution include the role of spatial heterogeneity in the spread of insecticide resistance, noncompliance to antibiotic regimes in the rise of resistance in the tuberculosis bacterium, and heterogeneity within the body of the protease inhibitor indinavir in the rise of resistant HIV-1 strains [23]. As noted above, this type of evolution is a spatial example of parallel tempering, a technique that has proven to be very powerful at sampling difficult molecular systems with many and large energy barriers. This analogy with parallel tempering suggests that heterogeneities must be of great and intrinsic importance in natural evolution.

Qualitative changes in protein space such as those modeled here allow viruses, parasites, bacteria, and cancers to evade the immune system, vaccines, antibiotics, and therapeutics. All of these pathogens evolve, to a greater or lesser degree, by large, swapping-type mutations. The successful design of vaccines and drugs must anticipate the evolutionary potential of both local and large space searching by pathogens in response to therapeutic and immune selection. The addition of disease specific constraints to simulations such as these should be a promising approach for predicting pathogen plasticity. Indeed, infectious agents will continue to evolve unless we can force them down the road to extinction.

Summary

Significant opportunities exist for the application of ideas from statistical mechanics to the burgeoning area of protein molecular evolution. While combinatorial chemistry was not invented by researchers in the field of statistical mechanics, it is fair to say that perhaps it should have been! The design of effective experimental methods for searching sequence or composition space is similar in concept to the design of effective Monte Carlo methods for searching configuration space. Optimization of the parameters in molecular evolution protocols is analogous to the integration of various types of moves in Monte Carlo simulation. Applications of protein molecular evolution abound in the fields of catalysis, sensors, coatings, biotechnology, and human therapeutics. Hopefully, statistical mechanics will have a significant role to play in shaping these new methods of protein design.

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V

Studies of Solvation in the Atomistic Simulation Group at Queen's University, Belfast

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The effects of solvation on chemical and physical processes is often very important, for example many chemical reactions only occur because the reactants are dissolved rather than in the solid state. The solvent may effect the position of chemical equilibria and the rates of chemical reaction. Water is arguably the most important solvent and we have been using simulation to study its properties.

One question which particularly interests us is how important is the fact that the solvent consists of discrete molecules rather than being a continuum fluid with a dielectric constant. There are a variety of continuum solvent models which have been moderately successful. In these models the free energy of solvation is calculated by considering first the free energy of formation of a cavity of the correct size and shape to contain the solute molecule and then adding the free energy of interaction of the solute with the solvent including a contribution from the free energy of changes in the solvent. A major contribution to the interaction energy arises from the polarisation of the medium by the electric field of the solute. For example in the Born model the free energy of solvation of an ion is given by

$$A_{solv} = -\frac{q^2}{8\pi\epsilon_0 r_{cav}}(1-\epsilon^{-1}) \tag{V.1}$$

where r_{cav} is the radius of the cavity, q is the charge on the ion and ϵ is the dielectric constant of the solvent. While this is a good approximation at large distances (and electrostatic interactions are long ranged) one might expect the molecular nature of the solvent to be important in the immediate vicinity of the solute. We have been examining this for a number of systems, particularly in aqueous solutions.

Water is a polar liquid with a high dielectric constant. This is, however, only half the story. The other important factor is its ability to form hydrogen bonds both as an acceptor and as a donor. Not only does it hydrogen bond to itself forming a network structure in the liquid, but it may hydrogen bond to the solute if the latter has acceptor or donor sites (or both). A simple example is the asymmetry of solvation between positive and negative ions of the same size. In a continuum model these would have the same free energy, but simulations show that negative ions (which are hydrogen bond acceptors) have a more negative solvation energy by about 300kJ/mol for ions the size of Na^+ or 200kJ/mol for ions the size of Cs^+ [1]. It has been known for many years [2] that the molecular orientations of water in the first shell of positive and negative ions is quite different. Around negative ions one of the two OH groups points towards the ion forming a hydrogen bond while around positive ions the two OH bonds are, on average, symmetrically placed so that the dipole moment points away from the ion. Thus the substantial difference in the solvation free energy of positive and negative ions can be attributed to the lack or presence of hydrogen bond formation by the solvent, and one might expect similar differences to be found in the solvation of polar organic molecules.

Stuart Murdock in our group has been looking at solvation of organic molecules in collaboration with Graham Sexton of AstroZeneca. The molecules they have investigated are triazoles, which are five-membered aromatic rings with three nitrogen atoms. There are four isomers which differ in the positions of the two pyridine-type nitrogen atoms and the one pyrrole type NH group in the ring. Stuart Murdock has measured the relative solvation energies of these isomers using both explicit molecular water and the rather sophisticated continuum model contained in the package AMSOL. The results [3] show quite large differences between the two types of solvent models. He has then looked at the three dimensional probability distribution functions of the water atoms relative to the triazole rings in the explicit water models to investigate where there are strong interactions between water molecules and the solute. It is not unexpected that the principal interaction is the formation of a hydrogen bond from the pyrrole-like NH group to a water oxygen. Less expected was the clear indication of what one might call hydrogen bond formation from water molecules above and below the plane of the triazole to its aromatic ring. The formation of donor hydrogen bonds from water molecules to the two pyridine-like nitrogen atoms in the ring was less important except for the isomers where these nitrogen atoms were adjacent. In the latter case the solvation free energy was lowered by 9-17kJ/mol more than was predicted by the continuum models.

The role of the water-water hydrogen bonds in solvation thermodynamics is shown in changes in the entropy of solvation. Some ions have been classed as structure-breaking and others as structure-making of the basis of comparative entropies of solution. Simulation has two advantages in studying this type of phenomenon. First one can change the ion sizes and charges independently and secondly one can measure solvation thermodynamics of individual ions. Rasaiah and I [1] have demonstrated structure making and breaking effects by studying the entropy of solvation of ions as a function of charge for ions of various fixed sizes. Figure V.1 shows a typical result.

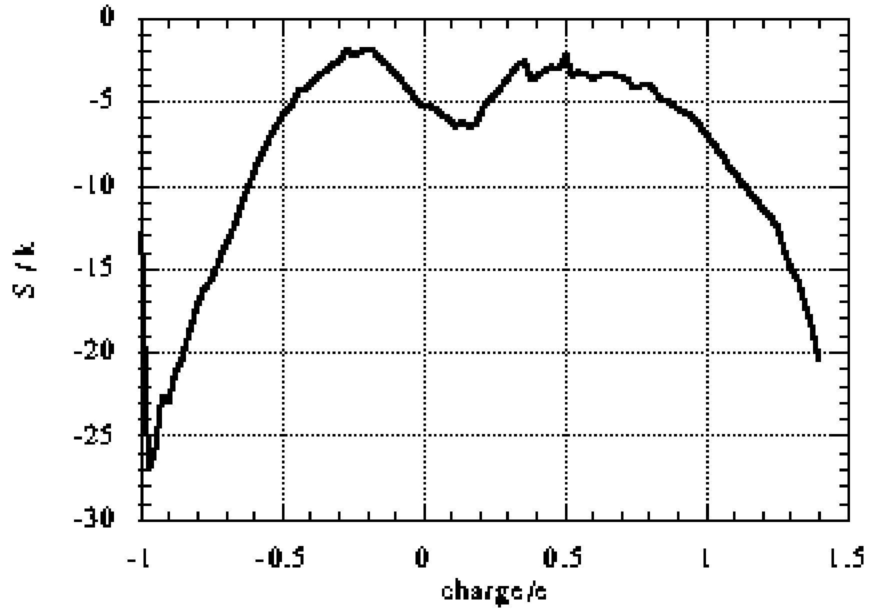

Figure V.1: Solvation entropy of an ion the size of Na^+ as a function of its charge. The double maximum is due to structure breaking

If the charge is near zero the entropy is a local minimum, and as the magnitude of the charge q is increased the ion disturbs the water structure (structure-breaking) and the solvation entropy increases. Further increases in $|q|$, however, lead to a decrease in the solvation entropy as the water molecules are aligned by the field of the ion. This is structure making. At constant charge structure breaking occurs for small ions and is succeeded by structure making as the ions increase in size. Structure breaking does not occur in a continuum solvent where the solvation entropy is a quadratic function of ion charge

$$S_{solv} = -\frac{q^2}{8\pi\epsilon_0\epsilon^2 r_{cav}}\frac{d\epsilon}{dT}. \tag{V.2}$$

The appearance of a double maximum is a sign of specific molecular effects in solvation and only occurs if the solvent has structure to be broken. It seems to depend on the strength of the intermolecular interactions rather than on the existence of a three dimensional network as is shown by our recent results on various distorted water models (Bergmann and Lynden-Bell, in preparation). In some of these models the dipole moment is kept constant so that the long range effects are similar, but the local effects varied by changing the bond angle from tetrahedral to 90° or 60°. In these models structure breaking is still seen. However, if the hydrogen bond strengths are reduced by decreasing the partial charges on the atoms the double maximum disappears. More recently (Lynden-Bell, Noworyta and Rasaiah, unpublished) we have found that if the temperature is raised above the critical point the double maximum again disappears, showing that in this respect, as in others, the supercritical water behaves more like an organic liquid than like normal water. The presence of a double maximum in the solvation entropy versus ion charge graphs can be correlated with the hydrophobic effect as the central minimum in the entropy corresponds to hydrophobic ordering.

Another example where the molecular nature of water and its ability to donate hydrogen bonds with atoms bearing partial negative charges is important is solvation-induced symmetry breaking in the triiodide ion. An isolated triiodide ion is linear and symmetrical. It is highly polarisable along the molecular axis and this allows solvation to induce symmetry-breaking if the gain of solvation free energy when the charge is unsymmetrically distributed is greater than the cost of distorting the ion. Experimentally this seems to happen in solutes which hydrogen-bond such as water and alcohols but not with acetonitrile. This is another example of the way in which the formation of hydrogen bonds from water to sites with negative charges stabilises such structures. Some years ago we showed from simulation that symmetry breaking does occur in water [4] and more recently in a collaboration with Margules and Coker from the University of Boston we have determined the extent of the distortion in water [5] and acetonitrile [6]. Figure 2 shows contours of the probability distribution function of the symmetric and antisymmetric normal coordinates of triiodide in water. The

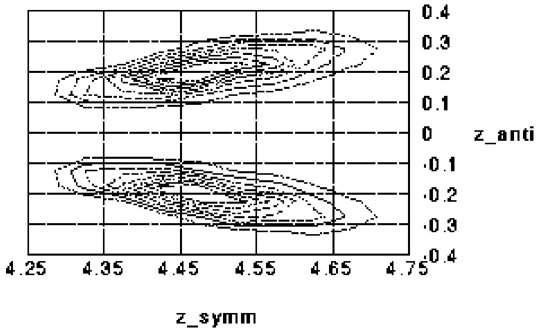

Figure V.2: Contours of the distribution function of distortions in the triiodide ion. The double minima correspond to two symmetry-related distorted forms.

pair of minima correspond to the two equivalent distorted forms. From this the most probable bond lengths are found to be 2.95Åand 3.38Åand the barrier to inversion is about 40kJ/mol. In acetonitrile our model also shows distortion but with a much lower barrier to inversion (about 2kJ/mol).

These studies show that atomistic simulation is a useful tool for studying the molecular aspects of solvation. It is particularly interesting to see old concepts such as structure-breaking and structure-making come to life when one exploits the ability one has in a simulation of changing parameters such as ion size and charge in a controlled way.

I should like to thank my colleagues and collaborators in this work (Stuart Murdock and Christof Hanke (QUB), Jay Rasaiah and Peter Noworyta (University of Maine), David Coker and Claudio Margules (Boston University) and Dan Bergmann (Stockholm). I acknowledge support from EPSRC, the SIMU network and the IFI fund for Ireland.

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VI

Mainz Group Report

Condensed Matter Theory Group Report
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Summary

The Condensed Matter Theory Group deals with research projects in the field of statistical thermodynamics of liquids and solids. Starting from an atomistic, i. e. microscopic description, cooperative phenomena are investigated and macroscopic properties of materials observable in experiment are calculated. In particular, static and dynamic properties of systems undergoing phase transitions are investigated. This is done for both equilibrium and nonequilibrium situations, with an emphasis on soft condensed matter .

A main subject of our research is the glass transition of macromolecular materials as well as of simpler systems like quartz glass, diatomic molecules, dipolar hard spheres and of orientational glasses. On these problems, we closely interact with experimental groups in the framework of the Sonderforschungsbereich (collaborative research program) of the German National Science Foundation (DFG) on Glassy state and glass transition of non-metallic amorphous materials . The studies on silica glasses are done in close collaboration with the SCHOTT Glaswerke Mainz (who sponsor this research).

Another strong focus of our research are phase transitions of soft materials , especially macromolecular materials, such as polymer solutions and polymer mixtures, block copolymers, lipid monolayers, etc., with an emphasis on systems in confined geometry and the related interfacial and wetting phenomena. Part of this research is done in the framework of a graduate study college of the Physics and Chemistry of Supramolecular Systems , another part belongs to the DFG focus program on Wetting and structure formation at interfaces . The dynamics of polymer melts (such as polyethylene, polybutadiene, etc.) is also studied and detailed comparisons with experiment are performed.

We also investigate the phase transitions of more traditional systems like fluids, fluid mixtures, adsorbed layers of small molecules where atomistic detail is carefully considered, as well as generic lattice models like Ising, Potts or ANNNI models. While most of this research belongs to the field of classical statistical mechanics, quantum-mechanical effects are sometimes studied with the help of path integral Monte Carlo methods, in order to describe low temperature properties of crystals such as Si, SiO2, N2 or orthorhombic polyethylene. These problems are treated both by numerical methods, using mostly large scale Monte Carlo and molecular dynamics simulations (WA331, Prof. K. Binder), and the self-consistent field approach for polymers. Analytical techniques are developed and applied in the group as well (WA332, Prof. R. Schilling), e. g. the mode coupling approach to describe an ideal glass transition of molecular fluids. With respect to the computer simulations, a particular effort is made towards the further development of the methodology (e. g. development of techniques to sample slowly relaxing systems more efficiently, techniques to estimate interfacial tensions between coexisting phases and to analyze their interfacial width, refinement of finite-size-scaling techniques to study crossover scaling functions, etc.)

In this context we undertake substantial efforts to efficiently use powerful computers, both in Mainz (where the group runs a local network of powerful RISC workstations and LINUX-based PCs and is a heavy user of the computers provided by the central computing facilities of the University of Mainz (ZDV, Zentrum fr Datenverarbeitung) and of national massively parallel supercomputers, such as the CRAY-T3E of the Research Center NIC/HLRZ at Jlich and of the HLRS (Stuttgart).

In addition to these computational approaches and the analytical treatment of the glass transition, the group of Prof. R. Schilling also investigates by means of analytical methods a variety of other topics, such as excitations in anharmonic crystals, tunneling in magnetic systems, microscopic investigation of transport coefficients, and some aspects of the theory of superconductivity. In the following, more details about all these research projects are given.

Tests of the molecular mode coupling theory

Investigators A. Latz, R. Schilling, C. Theis, A. Winkler
In collaboration with: L. Fabbian, F. Sciortino, P. Tartaglia (Universita di Roma “La sapienza)
Funding: German National Science Foundation (DFG) Sonderforschungsbereich 262

The molecular mode coupling theory (MMCT) for the ideal glass transition of supercooled molecular liquids has been tested for two model systems: diatomic molecules and water. For these systems the various time-dependent correlators were deduced on one side from large scale MD-simulations and on the other from MMCT. MMCT allows to study the glassy translational and orientational dynamics, as well as their interplay.

The test for water has been performed in two steps. In a first step we have treated the water molecule as a linear molecule. From MMCT for linear molecules we found a glass transition at almost the same critical temperature as found from the MD-simulation. Comparison of the glass order parameters (nonergodicity parameters) from

MMCT and simulation exhibits reasonably good agreement (Fabbian 1999a). In a second step we have analysed the validity of the various scaling laws predicted from MMCT. Consistency of the MD-results with these predictions has been found.

In a first attempt for the system of diatomic molecules we have studied the center of mass motion, only. Mode coupling theory did not yield an ideal glass-transition in a reasonable temperature range (Fabbian 1998).

Taking the molecular nature serious, we have found a critical temperature from MMCT which exceeds the numerical value by about 50parameters from MMCT and simulation agree fairly well, which, however, is not quite true for the critical amplitudes (Winkler, Diplomarbeit 1998).

In a general treatment we have shown how information on the orientational degrees of freedom can be deduced from the neutron scattering cross section in distinct intervals of momentum transfer. Particularly, this allowed us to interpret the prepeak in the static structure factor for the diatomic molecules as an antiparallel alignment of the molecular axis over a certain length scale (Theis 1999). A review of part of the several tests of MMCT is given in (Schilling 2000).

Mode coupling approach to hard ellipsoids

Investigators: A. Latz, M. Letz, R. Schilling, T. Theenhaus
Funding: German National Science Foundation (DFG) Sonderforschungsbereich 262

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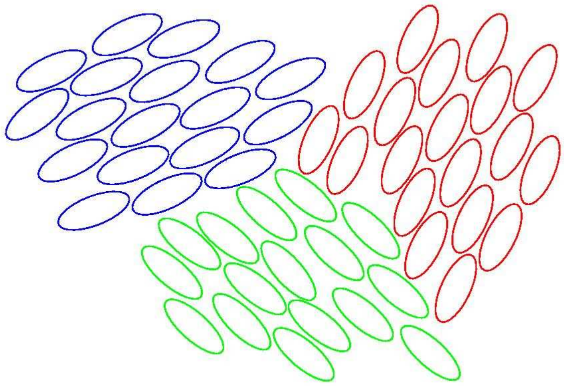

Figure VI.1:

Mode coupling approach to hard ellipsoids

Investigators: A. Latz, M. Letz, R. Schilling, T. Theenhaus
Funding: German National Science Foundation (DFG) Sonderforschungsbereich 262

In this project we have applied the molecular mode coupling theory (MMCT) to a liquid of hard ellipsoids with aspect ratio X0 and packing fraction . The Percus-Yevick solution for the static structure factors exhibits an equilibrium phase transition at a critical line (X0) from an isotropic liquid to a nematic phase (Letz 1999a). These static correlators were used to study the ideal glass transition within MMCT. These investigations have revealed a new type of glass transition which is driven by a precursor of the nematic ordering. In addition we find a new glassy phase (see Fig. 1) where the center of mass positions form an amorphous structure. The ellipsoids arrange in domains with nematic order whereas the domains themselves build an orientational glass. The domain size strongly increases with X0 for X0 2 (Letz 1999b). In a further study we have shown that the static correlators and the nonergodicity parameters of the liquid of diatomic molecules can be described very well by those of the hard ellipsoids if one chooses X0=1.5 which is also consistent with the Lennard Jones parameters for the diatomic MD-simulations for extended anharmonic systems like a -model have shown the existence of localized vibrational excitations. For a chain of particles with harmonic nearest neighbor interactions and a double-quadratic on-site potential the equation of motion can be solved almost exactly. We have found conditions on the potential parameters such that localized single-particle oscillations exist where particles oscillate between both local wells of the on-site potential. The main attention has been devoted to the existence and properties of multi-particle oscillations. Besides in-phase motion where a group of atoms performs cooperative oscillatory behavior also out-of-phase dynamics has been found where internal degrees of freedom are excited (Neus 1999).

Tunneling in magnetic systems

Investigator: A. Latz
In collaboration with: Bongsoo Kim (Changwon National University, Korea)
Funding : German National Science Foundation (DFG) Sonderforschungsbereich 262

If a liquid is quenched below the glass transition temperature, it falls out of equilibrium. In recent years this problem was studied intensively within mean field models for a certain class of spin glasses (the so-called p-spin models). It was found that this model exhibits in the equilibrium state a very similar dynamics as simple models for the glass transition in structural liquids. Below the glass transition temperature of the spin glass models the dynamical behavior changes qualitatively. Contrary to the ergodic state the time translational invariance is broken and new scaling regimes emerge, which were not known before for structural liquids. The most dramatic phenomenon is the violation of the fluctuation-dissipation theorem (FDT). The susceptibility is not anymore just the time derivative of the correlation function divided by the temperature. Instead it seems to be possible to replace the temperature by some fictitious temperature Tf. Although these properties were at least qualitatively confirmed in simulations of binary Lennard-Jones liquids by Parisi and independently by J. L. Barrat and W. Kob, the theory of this nonequilibrium relaxations for structural liquids does not yet exist. Several important problems are still unsolved. It is not clear at all whether the similarity between certain spin glass models and structural liquids holds also in the non-ergodic state. To answer this question it is important to generalize the mode coupling theory for structural liquids to treat the situation, where time translation invariance is broken. The formal theory for treating structural liquids was derived in [Latz 2000]. Also it is not clear in which sense FDT is broken and whether the fictitious temperature is independent of the quantity which is measured, e. g. whether the fictitious temperature is the same for specific heat measurements and stress relaxation measurements. To answer these questions it is crucial to develop not only the theoretical tools but also the numerical tools to solve complicated sets of integro-differential equations, which have solutions spanning more than 10 decades in time. An algorithm which can also be applied to the FDT broken state was worked out in collaboration with Prof. Bongsoo Kim [Kim and Latz 2000]. First results show that even in the simple spherical p-spin models new scaling regimes especially close to the transition temperature exist, which are of major importance for the interpretation of results e. g. obtained in MD simulations for real liquids.

Microscopic investigation of transport coefficients

Investigator: A. Latz
In collaboration with: J. R. Dorfman (University of Maryland, College Park, USA) H. van Beijeren (University of Utrecht, Utrecht, The Netherlands)

Formal theories based on the assumption, that microscopically fluids can be considered to be hyperbolic dynamical systems with non-zero Lyapunov exponents have led to very interesting connections between transport coefficients and dynamical quantities such as Lyapunov exponents and Kolmogorov Sinai entropies. One important approach, the so-called escape rate formalism, was initiated by work of Gaspard and

Nicolis. These authors consider large but finite Hamiltonian systems with escape, i. e. particles can leave the system through the boundary. In the simple example of the Lorentz gas, the escape rate is proportional to the diffusion constant times the inverse square of the linear dimension of the system. This transport quantity can be identified with the difference between the sum of the positive Lyapunov exponents, which measure the rate of separation between the two trajectories, and the Kolmogorov Sinai entropy, which measures the rate of accumulation of data necessary to follow unambiguously a trajectory on the repellor. The repellor is the set of trajectories, which never leave the system. Our main goal is to find analytic methods to calculate Lyapunov exponents of simple systems like the disordered Lorentz gas or, as a next step of complication, a system of moving hard spheres. In [van Beijeren et al. 1998] we formulate the general theory for calculating the sum of the positive Lyapunov exponents in a disordered Lorentz gas under equilibrium conditions. Also the general formulas for calculating analytically positive and negative Lyapunov exponents are derived. The basic idea is to apply kinetic theory to exact expressions of dynamical systems theory for the sum of positive Lyapunov exponents. In addition, the kinetic approach is combined with ideas from random matrix theory to obtain results for single Lyapunov exponents. In [van Beijeren et al 2000] we extend the kinetic approach to the nonequilibrium situation of an open system, i. e. system with absorbing boundary condition. Since the dynamics is now determined by the fractal repellor, the main problem is to calculate ensemble and time averages on a set with an information dimension less than the embedding dimension. This highly non-trivial problem is solved by introducing a weighted average, where the standard Boltzmann distribution is multiplied by the so-called survival probability. This guarantees, that only those trajectories are counted, which stay in the system forever. By combining the results for the Lyapunov exponents with the escape rate formalism also the Kolmogorov Sinai entropy of open 2- and 3- dimensional disordered Lorentz gases are calculated.

In [Dorfman et al. 1998] a theory of the KS entropy of a system of N- moving hard sphere system is derived. Contrary to the Lorentz gas, the hard sphere gas is a semidispersing system, i. e. there are locally a macroscopic number of directions in phase space, where the trajectories do not separate more than linearly in time. This property is a major complication for setting up an analytical theory for Lyapunov exponents. As for the Lorentz gas, we show that despite this difficulty standard methods of kinetic theory can be applied for the calculation of the sum of the positive Lyapunov exponents. We are able to formulate a BBGKY hierarchy for the distribution function of the matrix of curvature of the so-called horosphere. The horosphere is the local sphere, which is tangent to a front of trajectories accompanying a reference trajectory. Preliminary results of simple approximation schemes provide already a major improvement in the agreement with simulations compared to earlier ansatzes for low density expansions of the sum of Lyapunov exponents.

From weak coupling BCS theory towards the stronger coupling limit

Investigator : M. Letz
In collaboration with: M. Himmerich, Prof. Dr. F. Marsiglio (Univ. of Alberta,

Edmonton, Canada), Prof. Dr. R. J. Gooding, (Queens Univ., Kingston, Canada)
Funding: BMBF KAN028/98 MPT (German Canadian research collaboration)

Several superconducting materials including the high-Tc-cuprates and some heavy Fermion superconductors show unusual short coherence length of their cooper pairs. The understanding of this short coherence length pair formation remains one of the main goals for a theoretical understanding of these systems.

Only in very limited circumstances the electron gas with an attractive interaction is well understood. The first is the weak coupling three dimensional case, where the system shows at the chemical potential an instability for pairs with zero total momentum, the superconducting instability. The physics of the transition follows BCS theory, and consists of simultaneous pair formation and phase coherence. A second limit is the two electron problem, where a bound state exists in one and two dimensions for any attractive coupling strength, but only for strengths exceeding a critical value in three dimensions. Very little progress has been made beyond two electrons, however.

This leaves most of parameter space yet to be fully understood. In the last several years, a great deal of progress has been made towards increasing our understanding of the possible instabilities of a two dimensional electron gas, particularly in the dilute limit, and spanning the full range of weak to strong coupling.

We investigate the attractive Hubbard model in two dimensions at low densities starting from the T-matrix approximation. In the non-selfconsistent formulation of the T-matrix approach the system always shows an instability towards Bose condensation of pairs into an infinite lifetime two-particle bound state. This solution, however, is only exact in the zero density limit. We investigate possibilities (e. g. selfconsistency (Letz and Gooding 1998a) or the inclusion of further higher order corrections) to formulate a theory which is valid at finite densities, too. One of the main results of an inclusion of further terms which cause pair-pair interaction is that the pairs get infinite lifetime and loose their Bosonic properties (Letz 1999b). In order to obtain reliable results of spectral quantities (Letz and Gooding 1998b) which are of importance in connection with the discussion of the so-called pseudo-gap (Letz 1999b) a method has been developed which allows to calculate dynamical properties and spectral functions directly along the real axis (Letz and Marsiglio 1999).

Statistical Thermodynamics of Polymers

Investigators : J. Baschnagel, Ch. Bennemann, K. Binder, O. V. Borisov, H. L. Frisch, V. Ivanow, L. Gonzalez-Mc Dowell, T. Kreer, S. Krouchev, H. Lange, E. Luijten, S. Metzger, A. Milchev, C. Mischler, M. Müller, I. Neelov, W. Paul, E. Reister, F. Schmid, G. D. Smith, F. Varnik, A. Werner
In collaboration with: B. Farago (ILL, Grenoble), M. Fuchs (Physik-Depart., TU München), D. Johannsmann (MPI f. Polymerforschung), J. A. Johner (Inst. Charles Sadron, Strasbourg), J.-F. Joanny (Inst. Charles Sadron, Strasbourg), T. Kerle (Weizmann Institute, Rehovot), J. Klein (Weizmann Institute, Rehovot), D. Lacks (Chemi. Eng., Tulane Univ, New Orleans), R. Martonak (MPI für Festkrperforschung, Stuttgart), S. Rathgeber (IFF, FZ Jülich), D. Richter (IFF, FZ Jülich), G. C. Rutledge (MIT, Cambridge), L. Schäfer (Univ. Essen), F. Sundholm (Univ. Helsinki), V. Vasilevskaya (Russ. Acad. Sci., Moscow), C. Vega (Univ. Complutense, Madrid), L. Willner (IFF,

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Funding : German National Science Foundation (DFG) projects 436BUL 113/92; 436 RUS 113/233; SFB 262/D2; BA 1154/2-1; PA 473-1; Schm 985/3-1; Graduate Study College Physics and Chemistry of Supramolecular systems ; Federal Ministry for Education, Science, Research and Technology (BMBF) No 03N8008C; Max Planck Gesellschaft (MPI-P fellowship); Guggenheim foundation; European Science Foundation (ESF), Program SUPERNET; DFG focus program Wetting and structure formation at interfaces .

This project is concerned with polymers in solution, in the melt, and in the crystalline state; both bulk properties and polymers adsorbed at walls or fluid interfaces are studied. Homopolymers, polymer mixtures, and block copolymers are treated.

As an example for the fact that even the statistical mechanics of single polymer chains (as they occur in dilute solution) still poses challenging problems, we mention the escape transition of a polymer mushroom that is compressed by a disk of radius R that may model the tip of an atomic force microscope (Figs. 2 - 4).

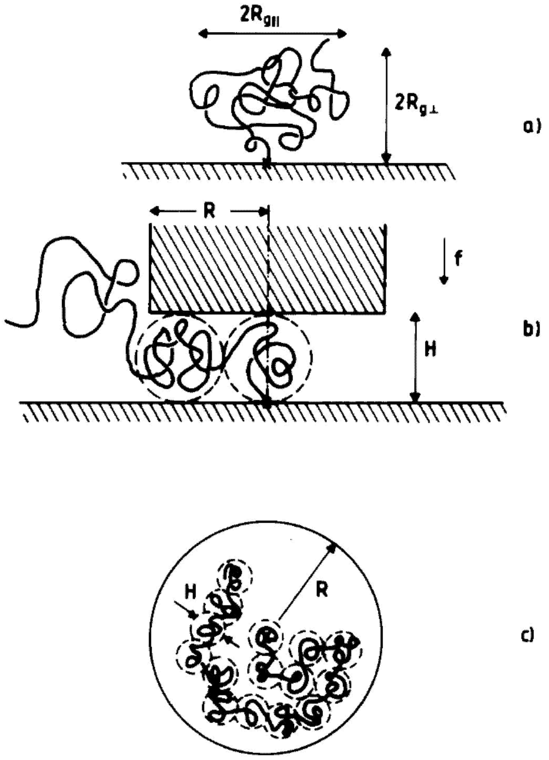

Figure VI.2:

Diplayed in Fig.VI.2 is a "polymer mushroom", which is a flexible polymer chain (formed by N segments of length b grafted by one chain-end (x) at a repulsive wall). Under good solvent conditions, both linear dimensions $R_{g||}, R_{g\perp}$ of the mushroom scale as , $R_{g||} \propto bN^{v_3}$, $R_{g\perp} \propto bN^{v_3}$ with $v_3 = 0.59$.
b) A cylinder of radius R compresses the mushroom with a force f down to a height H. If R is not too large, part of the chain escapes outside of the region of the cylinder.
c) For very large cylinder radius, the chain stays imprisoned underneath the cylinder, forming a quasi-twodimensional configuration, namely a self-avoiding chain of blobs of diameter H. From MILCHEV et al. (1999).

If this radius R is very large, the linear dimension Rg—— of the chain parallel of the grafting surface changes from a law characterized by a three-dimensional exponent (with, Fig. 2a) to a law characterized to by a two-dimensional exponent (with, Fig. 2c). However, for not too large R one experiences for some special value ft of the force a (rounded) first-order transition, where part of the chain escapes from its prison , i. e. the slit-like region of height H underneath the piston. This is illustrated in Fig. 3, where the radial density distribution of the monomers of a bead-spring model of a polymer chain is plotted for various values of the height H. For large H there is a peak in this distribution at a distance rmax with 10 rmax 20, much less than R = 60. When f increases (or H decreases, respectively), this peak first moves slowly to larger values rmax, but then (see curve for Hc=7 in Fig. 3) a second peak at values r¿R appears: this represents the escaped part of the chain. For large forces f (and correspondingly small heights H) the distribution is completely flat until r=R, and then a very pronounced peak occurs. Fig. 4 shows a snapshot picture of such a strongly compressed chain. This escape transition was first predicted theoretically by Subramanian, Williams and

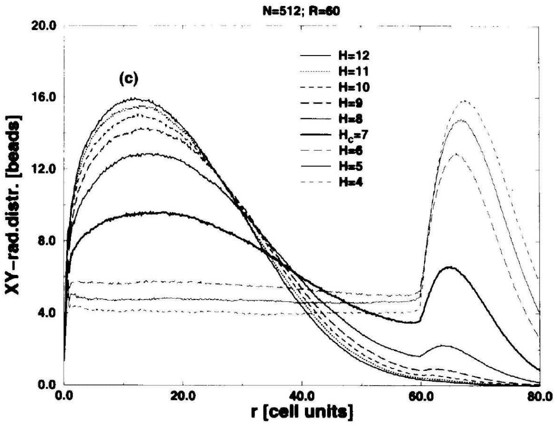

Figure VI.3: Radial density distribution of a bead-spring off-lattice model of a polymer chain of chainlength N=512 underneath a piston of radius R=60 (Note that all lengths are measured in units of the maximum extension of a spring between neighboring beads of the chain.) From MILCHEV et al. (1999).

Pincus by rather crude arguments (neglecting statistical fluctuations completely), and its existence has been doubted. Fig. 3 was the first simulation evidence in favor of the actual existence of this transition.

When one considers not a single chain grafted to a wall, but many of them, the grafted chains start to interact with each other, and depending on the character of this interaction one may get the formation of surface micelles (MILCHEV and BINDER 1999) or polymer brushes (NEELOV et al. 1998). Surface micelles form if the grafted (or adsorbed, respectively) monomers of different chains attract each other, while the non-adsorbed monomers (which have a different chemical character, e. g. choosing asymmetric block copolymers) repel each other.

Although bulk properties of semidilute and concentrated polymer solutions and melts have been studied by many groups for a long time, some aspects of their static and dynamic properties are still insufficiently understood: such problems are intramolecular structure factors of macromolecules in solution, where progress could be achieved by a combination of Monte Carlo work with P-RISM integral equation results (FUCHS and MÜLLER 1999), or the question to what extent the dynamics of short polyethylene chains in the melt is compatible with the Rouse model (PAUL 1998). A comparison between molecular dynamics simulations of an united atom-model of polyethylene with neutron spin echo data (Fig. 5) reveals excellent agreement between experiment and simulation for a wide range of scattering wavenumber q. However, the simulations cover a somewhat larger range of times t and scattering wavenumbers than the experiment, and furthermore yield various mean square displacements (of monomers, of the center of mass of chain, etc.) straightforwardly, while corresponding information can be deduced from the experiments only in an indirect way. Therefore the simulations were able to pin down the deviations from the simplistic Rouse model (where all interchain interactions are simply described as friction plus random forces, considering just the Brownian motion of a single chain in a heat bath) more clearly than the experiment.

Polyethylene has been used as our standard model for several other questions: e. g., a comparison between a path integral quantum Monte Carlo study of orthorhombic crys-

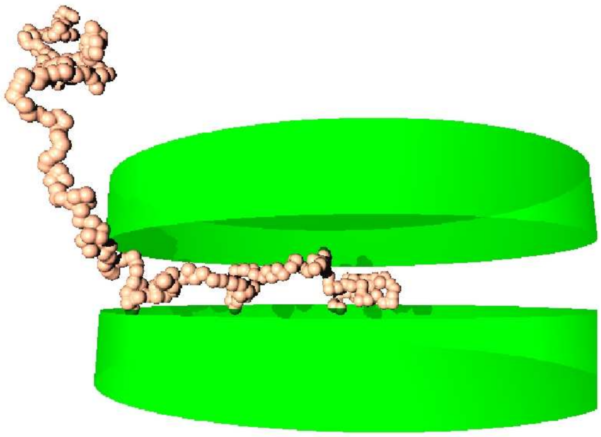

Figure VI.4: Snapshot picture of a strongly compressed polymer chain in a partially escaped configuration. From MILCHEV et al. (1999).

talline polyethylene and lattice-dynamical calculations of the selfconsistent phonon-theory-type (RUTLEDGE et al. 1998) revealed that the latter theory works well from T=0K to T=200 K but becomes increasingly inaccurate near room temperature; and the power of the mapping procedure to construct a coarse-grained-bond-fluctuation model on the simple cubic lattice with intrachain potentials constructed such that properties of real polyethylene are mimicked has been demonstrated for a bidisperse polymer melt (BASCHNAGEL et al. 1998), as a first step to deal with the important problem of chainlength distribution of polymers (polydispersity). The bond-fluctuation model on the lattice with suitable potentials for bond lengths (and bond angles) is also well-suited to study the isotropic to nematic transition of liquid crystalline polymers (WEBER et al. 1999), as well as for clarifying the glass transition of supercooled polymer melts (BINDER et al. 1998, BASCHNAGEL 1998), see also Sec. 10 of the present report. A very useful alternative to a lattice model as a coarse-grained model for polymers is a bead-spring model where beads interact with a Lennard-Jones interaction with an energy minimum at a distance () that is incompatible with the distance between monomers which are neighbors along the chain (maintained by the spring), in all common crystal structures. This model also shows glassy freezing at low temperatures and high densities (BENNEMANN et al. 1998, 1999), but is also suited to study surface and interface properties of polymer solutions (choosing lower densities and somewhat higher temperatures), as is currently under investigation (MÜLLER and GONZLEZ MAC-DOWELL 2000).

Further studies concern block copolymers in thin film geometry (BINDER 1999, GEISIN -GER et al. 1999) and adsorbed on homopolymer blend interfaces (WERNER, SCHMID and MÜLLER 1999), the interplay between polymer conformation and thermodynamic state in polymer blends (MÜLLER 1998, 1999) and the problem of capillary waves at interfaces between unmixed phases of polymer mixtures, both in the bulk and in thin film geometry (WERNER et al. 1999, MÜLLER and SCHMID 1999). Fig. 6. shows a snapshot picture of a coarse-grained interface (WERNER 1998) that illustrates that indeed long wavelength fluctuations of the local interfacial position occur. These fluctuations can explain (qualitatively, but not quantitatively!) why in experiments on interfaces in thin film geometry (KERLE et al. 1999), where one takes a lateral average over macroscopic linear dimensions, an apparent interfacial width is measured that increases strongly with increasing thickness of the film.

Finally we emphasize that polymer mixtures are very nice model systems to study wetting phenomena, capillary condensation -type distortions of phase diagrams in thin films, and

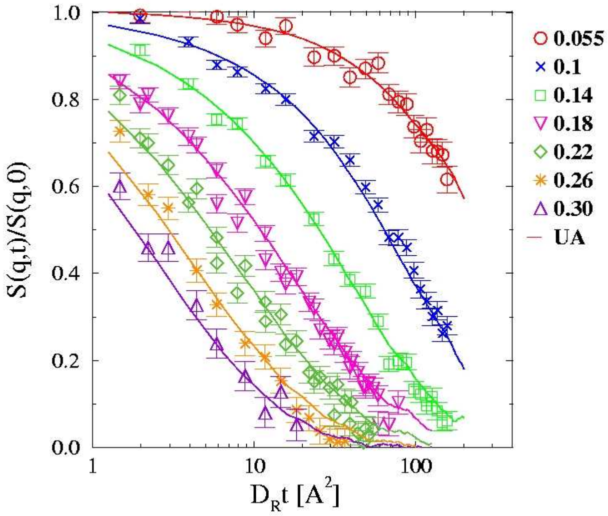

Figure VI.5: Comparison of the experimental neutron spin echo data (symbols) for the normalized intermediate coherent dynamic structure factor of polyethylene,$S(q,t)§(q,0)$, with corresponding molecular dynamics results (curves). Different symbols refer to different values of scattering wave number q, as shown by the legend in the figure (q is measured in units of $\AA^{-1}$). Note that the time-axis is normalized by the selfdiffusion constant DR of the chains, in units $\AA^2$, and displayed on a logarithmic scale. From (Paul 1999).

related phenomena (MÜLLER and BINDER 1998). These studies complement related work for simple Ising models (FERRENBERG et al. 1998) and numerical calculations based on time-dependent Ginzburg-Landau approaches (BINDER, PURI and FRISCH 1999, FRISCH et al. 1999). A very important aspect of the work on both polymer mixtures and blockcopolymer melts are the detailed comparisons with a numerical version of the self-consistent field theory in polymers which has been developed here (for reviews see MÜLLER 1999, SCHMID 1999).

Theory of disordered solids: structural glasses, orientational glasses, and other random systems.

Investigators: J. Baschnagel, Chr.Bennemann, P. E. Berch, K. Binder, C. Brangian, O. Dillmann, T. Gleim, R. Hilfer, J. Horbach, W. Janke, W. Kob, D. Lding, M. Müser, P. Nielaba, W. Paul, M. Presber, A. Roder, P. Scheidler, T. Stühn, F. Varnik, A. Winkler
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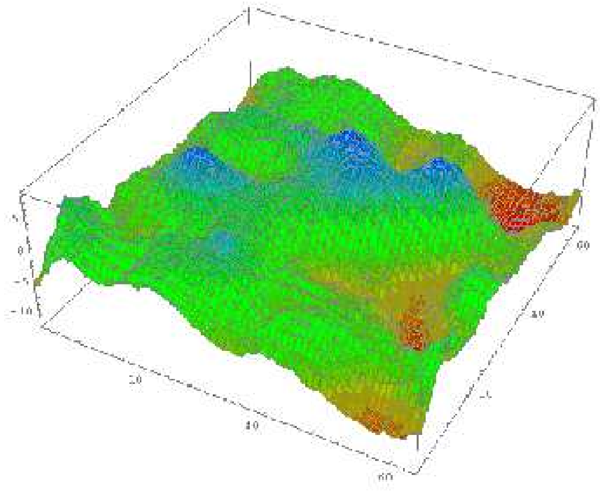

Figure VI.6: Snapshot picture of the (coarse-grained) contour separating the A-rich phase (top) from the B-rich phase (bottom) of a strongly segregated binary polymer mixture (temperature was chosen to be 48 % of the critical temperature, chainlength $N_A = N_B = 32$). Coarse-graining was done via a lateral averaging using a $B \times B$ grid with $B = 8$ lattice spacings, employing the bond fluctuation model on the simple cubic lattice. From (WERNER 1998).

Ontario, Canada), F. Sciortino (Univ. di Roma La Sapienza , Italy), P. Tartaglia (Univ. di Roma La Sapienza , Italy), R. Villanova (Univ. Autonoma de Barcelona, Spain), J. Widjajakusuma (Univ. Stuttgart),

Funding: German National Science Foundation (DFG), Sonderforschungsbereich 262/D1, D2; Federal Ministry for Education, Science, Research and Technology (BMBF) No03N8008C; SCHOTT Glaswerke Fonds; GIF I-0438-14507/95; EU. No ERB

One central theme of this project is one of the grand challenge -problems of condensed matter physics - namely the question how one can understand glass formation when fluids are supercooled until they vitrify, The second theme are more idealized models of solids with quenched disorder, such as Ising spin glasses (BERG and JANKE 1998), quadrupolar spin glasses (BINDER 1998, MÜSER et al. 1998), Potts glasses (REUHL et al. 1998, LOBE et al. 1999, DILLMANN et al. 1998, 1999), Ising- and Potts ferromagnets with quenched disorder (BERCH et al. 1998), CHATELAIN et al. 1998, JANKE and VILLANOVA 1999, RODER et al. 1999). A third line of research (now being transferred from Mainz practically completely to the University of Stuttgart) concerns structure and transport properties of random media (BISWAL et al. 1998, 1999, HILFER 1998, 1999, HILFER and BESSERER 1999, MANWART and HILFER 1999, WIDJAJAKUSUMA et al. 1999). However, in this report we shall focus on research on the glass transition of structural glasses exclusively.

Perhaps the most widely studied and most successful model of the glass transition deals with a binary (A,B) Lennard-Jones mixture (80scale of molecular dynamics simulation also no phase separation between A and B can occur (KOB 1999). This model has been used to provide the most thorough investigation of the validity of the famous mode coupling theory of the glass transition (KOB, GLEIM and BINDER 1999, KOB 1999). While the evidence for the accuracy of many features of this mode coupling description in general is compelling, there are nevertheless certain clear limitations of the theory. One aspect is the breakdown of the theory on the time-scale of the microscopic dynamics . This problem has been particularly addressed by GLEIM et al. (1998), who compare dynamical properties for two versions to the model with different dynamics but the same statics (one version uses the Newton s equations of classical mechanics, while the other version uses a Langevin equation without inertial term.) Another aspect is the occurrence of string-like clusters and cooperative motion near the glass transition (DONATI et al. 1998, 1999): these phenomena simply are out of scope of the mode coupling description; and while the simulation evidence for them is very clear, it is not so clear whether these features need to be explicitly described or whether these are just accompanying phenomena anyhow expected for any glassforming fluid.

A direction where the simulations are clearly ahead of the theory is the analysis of aging phenomena (KOB and BARRAT 1999) and the related violation of fluctuation-dissipation relations (BARRAT and KOB 1999).

As mentioned already in the previous section, both the bond fluctuation model of polymer melts on the simple cubic lattice and the bead-spring model of polymer chains in the continuum have been investigated in order to shed light on the glass transition (BENNEMANN, BASCHNAGEL and PAUL 1999; BENNEMANN et al. 1998, 1999; BINDER et al. 1999). For these models, mode coupling theory is also useful, but the range of times (and monomer displacements) where it is accurately applicable is only a small window from a much more complex behavior. In particular, for displacements clearly larger than the linear dimension of the cages (in which monomers are confined, for the regime of times for which mode coupling theory is applicable) the dynamics is still compatible with a (slightly modified) Rouse model description. In particular, all Rouse modes have the same temperature dependence (i. e., critical divergence at the mode coupling critical temperature or Vogel-Fulcher type divergence at a much lower temperature, respectively).

While the models described above attempt to elucidate the generic aspects of the glass transition, it also is of interest to try to understand particular materials, such as molten quartz (SiO2) or sodium-silicate glasses , i. e. protoype materials for window glass . Based on a pair potential derived from quantum chemistry by van Beest, Kramer and van Santen (BKS potential), in fact a very satisfactory description of molten SiO2 can be achieved (HORBACH et al. 1998, BINDER and KOB 1999, HORBACH and KOB 1999, HORBACH et al. 1999, KOB and BINDER 1999, SCHEIDLER et al. 1999). Fig. 7 shows, as an example, a comparison between the simulated static structure factor of glassy SiO2 at T=300K and corresponding neutron scattering experiments. These simulations have also yielded a very detailed insight into the diffusion mechanism (via the breaking of covalent Si-O-bonds) in supercooled silica melts. It turns out that some of the simulation data are compatible with the mode coupling theory as well - but the critical temperature would be Tc 3330 K, outside any experimentally accessible range (HORBACH and KOB 1999).

Phase transitions in model systems (in bulk and at surfaces

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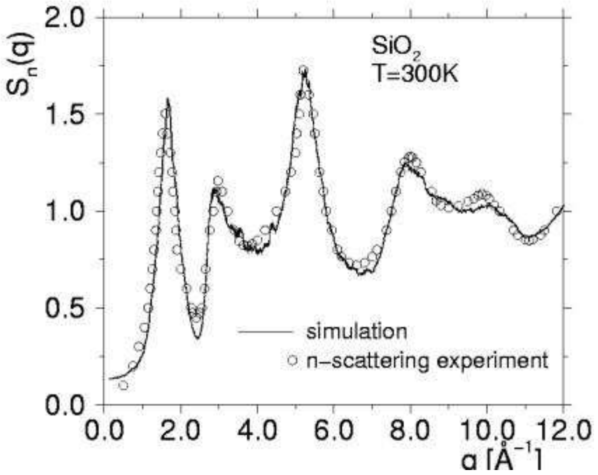

Figure VI.7: Static structure factor S(q) of amorphous SiO2 plotted versus wavenumber q. Full curve are molecular dynamics results of HORBACH and KOB (1999), broken curve shows neutron scattering data of Price et al. (1987).

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The critical behavior of Ising models with variable range of interaction R (LUIJTEN and BINDER 1998, LUIJTEN 1999, LUIJTEN and BINDER 1999) has been carefully analyzed with finite size scaling methods, in an attempt to obtain an explicit description of crossover scaling from the mean field limit to the limit of (universal) Ising critical behavior. Such crossover functions are of practical interest for the analysis of polymer mixtures, for instance, since the variation of R can be mapped on a variation of the chainlength N in symmetrical polymer mixtures. It also has been shown that the crossover scaling is compatible with a recent phenomenological two-parameter description of the crossover (ANISIMOV et al. 1999). In this context, also the finite size scaling behavior of systems with long range interactions (LUIJTEN 1999) and of systems above the upper critical dimension, such as the five-dimensional Ising model (LUIJTEN et al. 1999) have been analyzed and compared with pertinent theoretical predictions, due to the renormalization group or from perturbation theory. Surprisingly, the range of applicability of these analytic methods seems to be very restricted.

An interesting issue are also universal amplitudes that one can obtain from conformal invariance for certain three-dimensional spin models. A Monte Carlo test of these predictions yielded very satisfactory results (WEIGEL and JANKE 1999).

Hitherto unknown critical exponents have been predicted by BINDER and FRISCH (1999) who considered the free surface of an ANNNI (axial next nearest neighbor Ising) model at its Lifshitz point, but only within mean field approximation. The axis where nearest and next nearest neighbor interactions compete was oriented perpendicular to the free surface (for parallel orientation different exponents apply, see FRISCH et al. 2000).

The critical behavior of the XY model in d=2 dimensions was reanalyzed by W. JANKE (1998), while BITTNER et al. (1998), studied the critical behavior for lattice models of quantum gravity.

More complex phase transitions were studied by WILDING et al. (1998), who considered the liquid vapour phase behavior of a symmetrical binary fluid mixture, and by FERRENBERG et al. (1998) who showed that in an Ising film with competing walls variation of film thickness may lead to a tricritical interface localization-delocalization transition.

Particularly interesting phase behavior can also be found in various models for lipid layers and Langmuir monolayers (SCHMID et al. 1998, 1999, STADLER and SCHMID 1999, STADLER et al. 1999, MÜLLER and SCHICK 1998) and for off-lattice models of adsorbates on substrates where the order in the adsorbate layer may be in conflict with the periodicity of the corrugation potential (PRESBER et al. 1998, PATRYKIEJEW et al. 1999, REBER et al. 1999). Fig. 8 shows an example of the domain structures that may arise as a result of such a competition when several layers can adsorb on top of each other.

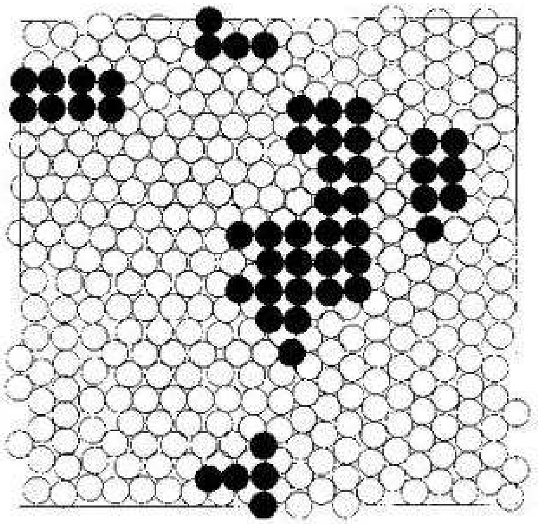

Figure VI.8: Snapshot configuration for an adsorbed film of Lennard-Jones particles of size $sigma^* = 8$ (length being measured in units of the lattice spacing of the square lattice at the (100) surface of a fcc crystal that forms the substrate). Corrugation parameter $V_b = 0.9$, reduced temperature $T_* = 0.02$, total coverage 1.5625. Particles located in the first layer are shown by open circles, in the second layer by filled circles. From PATRYKIEJEW et al. (1999).

Another interesting case of competition between different types of interactions are models for alloys with lattice misfit, where elastic interactions lead to anisotropic domain shapes (NIELABA et al. 1999).

Methodological developments in the computer simulation of many-body systems: finite size effects, cluster algorithms, reweighting techniques, quantum Monte Carlo methods

Investigators: K. Binder, M. S. Carroll, O. Dillmann, W. Janke, M. Müller, M. Müser, P. Nielaba, M. Presber, M. Reber, Chr. Rickwardt N. B. Wilding
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Funding: Alexander von Humboldt Foundation

This project is concerned with the further technical improvement of computer simulation methods, in order to either improve the way in which system configurations are generated, or to devise improved methods to their analysis. Of course, these developments are closely linked to various applications, that have already been described in the previous sections.

One such line of research concerns cluster algorithms for Ising and Potts-type lattice models. CARROLL et al. (1998) have investigated the dynamical behavior of the multibonding and multicanonical algorithms for Potts models in three dimensions. DILLMANN et al. (2000) extended the cluster algorithm for the Ising model to include surface magnetic fields in thin film geometry. JANKE (1998) reviewed both nonlocal Monte Carlo algorithms and the reweighting methods for sampling rare event states. In this context, we draw attention to an interesting extension of the standard multicanonical Monte Carlo method for spin glasses, namely the multi-overlap method (JANKE et al. 1998, 1999). An interesting question concerns also the proper choice of ensemble: for first order phase transitions, it is sometimes claimed that the microcanonical ensemble converges much better, but this claim does not hold in general (JANKE 1998).

Reweighting and multicanonical methods are also very useful for the study of surface and interface excess free energies. This idea was exploited by MÜLLER and BINDER (1998), for a model of a symmetrical polymer mixture confined by walls that preferentially attracted one component, who obtained all the various surface free energies, that occur in the well-known Young equation that controls whether or not wetting behavior at the walls is present. In this way for the first time in a simulation, wetting transitions could be located by the direct application of the Young equation.

For polymers, there is clearly a great need for more efficient algorithms. One attempt to extend the configurational bias algorithm is the recoil growth algorithm (CONSTA et al. 1999); this algorithm is currently used to study phase diagrams with critical endpoints in ternary systems polymer A+ polymer B+ solvent.

Particularly great efforts have been devoted to further develop path integral quantum Monte Carlo methods, both for rotational degrees of molecules (MÜSER 1998), and resulting applications to study phase transitions in solid N2 (PRESBER et al. 1998) and for translational degrees of freedom in systems at constant pressure rather than constant volume. In this way, the lattice expansion of systems such as silicon or crystobalite and quartz can be studied (RICKWARDT et al. 1999). Particularly interesting consequences of quantum effects occur in adsorbed monolayers of H2 and D2 on graphite, as analyzed further by REBER et al. (1999).

But not only Monte Carlo methods profit from technical improvements: Molecular Dynamics methods profit as well. Examples are extensions of the technique to study frequency-dependent specific heats (SCHEIDLER et al. 1999), and the combination with parallel tempering (KOB et al. 2000).

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VII

2001 activities

FIRST SIMU CONFERENCE

BRIDGING THE TIME SCALE GAP

Konstanz, 9-14 September, *see p. 82*

SIMU SUPPORTED SCHOOLS AND TUTORIALS

Understanding Molecular Simulations,*school organized by Berend Smit and Daan Frenkel, Amsterdam, January. For more information about the course, see http://molsim.chem.uva.nl/*

Methods in Molecular Simulations, *school organized by Mike Allen, and Julian Clarke, Manchester, July 1-10. For information about last years course see http://molsim.ch.umist.ac.uk/*

New algorithms of Molecular Dynamics Sampling, *tutorial organized by Glenn Martyna and Mark Tuckerman, CECAM, 5-8 June.*

Quantum Monte Carlo, *tutorial organized by David Ceperley, CECAM 22-26 October (tentative).*

SIMU WORKSHOPS

Computational Kinetic Theory: Mesoscale Applications, *CECAM, May 28-31, organized by A.L. Garcia and M. M. Mansour,* *see p. 84*

Statistical Mechanics and Molecular Simulation of Nucleation and Growth, *Kings College London, 2-4 July, organized by J. Anwar and D. M. Heyes,* *see p. 91*

Multi-scale Modeling of Materials: Methods, Algorithms and Unsolved Problems *Crete, 2-5 July, organized by E. Kaxiras, V. Pontikis, and D. Theodorou,* *see p. 94*

Phase Transitions in Complex Confined Systems,*CECAM, 22-24 August, organized by M. Schoen, P. A. Monson, A. H. Fuchs, M. Rosinberg,* *see p. 98*

Simulation and Theory of Solid Fraction: From Atomic Shear forces to Macroscopic Tribology, *CECAM, August 27-30, organized by M. Müser and L. Bocquet,* *see p. 105.*

These dates are provisional, and two more workshops are being considered for approval, see http://simu.ulb.ac.be for up-to-date information.

SIMU Conference in 2001

BRIDGING THE TIME-SCALE GAP

Dates: KONSTANZ, September 9-14, 2001

Contact email: konstanz@cecam.fr

Conference web site: http://KONSTANZ.CECAM.FR

Deadlines

- End of January: Second announcement giving lisit of invited speakers and submission information for contributers.
- July 15: Closing date for registration.

General Presentation

This conference is the first of two where we would like to gather computational scientists involved in the challenges that are faced in the fundamental modeling of matter on time and spatial scales which are relevant for materials. The focus of this conference will be on new techniques as well as current applications for bridging the time-scale gap between ab-initio and meso and macroscopic levels.

The conference will aim at enhancing cooperation among the groups participating in SIMU to achieve the goals of the programme. It will also be open to non-members of the programme. People wishing to get support from the programme in the future are advised to come and contribute to the conference by presenting their activities, and participating in the discussions.

Topics

The conference will be organized to increase the level of activities linked to the programme theme. We list below the themes where the development of techniques is needed for the corresponding physical applications.

For each theme, there will be a session, typically organized as follows:

- a general review (45 minutes);
- three contributing talks (20 minutes);
- a short presentation of related posters, and a poster session;
- a general discussion (with a discussion leader) which should address both the scientific issues as well as future SIMU activities (workshops, visits, tutorials, more specialized conferences, etc.

The following sessions will be organized:

1. The Protein Folding Modeling
2. Applications of Statistical Mechanics to Biological Systems

3. Polymer Structure and Dynamics
4. Complex Fluids
5. Equilibrium and Non-equilibrium Mesoscopic Fluids
6. Slow Dynamics
7. Lattice Models
8. Multi-scale Modeling in Materials
9. Perspectives in Ab-initio MD
10. Quantum Dynamics in Classical Solvents
11. Quantum Simulations

The conference will start on Sunday, 9 September, and last until Thursday evening. It will take place in the university of Konstanz, where four well equipped conference rooms will be provided, as well as internet access.

ORGANIZING PROGRAMME COMMITTEE

Daan Frenkel (Amsterdam)
Michel Mareschal (CECAM, Lyon and Brussels)
Peter Nielaba (Konstanz)

ADVISORY COMMITTEE

J. L. Barrat (Lyon); D. Borgis (Evry); D. Frenkel (Amsterdam, chairman); P. Nielaba (Konstanz); M. Mareschal (CECAM, vice-chairman); G. Ciccotti (Rome); M. Sprik (Cambridge); D. Coker (Boston); J. P. Hansen (Cambridge); S. Succi (Rome); D Chandler (Berkeley); K Binder (Mainz); M. Klein (Philadelphia); D. Theodorou (Athens); K. Kremer (Mainz); D. P. Landau (Georgia); M. Parrinello (Stuttgart); W. Andreoni (IBM Zürich)

Expected number of participants: From around 150 .

Note that the conference is taking place right after the CCP 2001 Conference in Aachen (September 5-8) where the second Berni J. Alder CECAM prize will be awarded.

COMPUTATIONAL KINETIC THEORY: MESO-SCALE APPLICATIONS

Provisional dates: Lyon, 28-31 May, 2001

SIMU-CECAM workshop

Organizers

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Scientific background

Introduced over a century ago, the Boltzmann equation remains the cornerstone of kinetic theory. To first order in Knudsen number (mean free path divided by hydrodynamic length scale), the Chapman–Enskog expansion leads to the Navier–Stokes equations [1]. Higher order expansions (i.e., Burnett and super Burnett) however, have had limited success, particularly with regard to convergence and boundary conditions [2]. The moment method, introduced by Maxwell, modified and extended by Grad [3] and by Waldmann [4], proves to be more successful in theoretical work but is not yet widely used as the basis for numerical calculations. While theoretical advances continue to be made, a general approach to solving the Boltzmann equation has not been established.

In this regard, numerical experiments have played an important role in modern kinetic theory. Historically, computational simulations of dilute systems have been done by two groups. The first is the statistical physics community [5], which has focused primarily on molecular dynamics simulations of gases and lattice-based schemes with simplified collision dynamics. The second branch is in the engineering community. Stochastic particle methods such as direct simulation Monte Carlo (DSMC) [6] and its variants were introduced by aerospace engineers during the 1960's and 70's, when space exploration was the primary application for rarefied flows.

The two branches developed separate numerical approaches since they focused on different problems. In statistical physics the work was primarily in equilibrium and simple non-equilibrium states, such as Couette and Poiseuille flow. The engineering community was interested in complex scenarios such as hypersonic flight and extreme non-equilibrium flows (e.g. plasma etching). In recent years, the two communities have discovered the utility of the algorithms developed by each, especially as their interests turn to meso-scale applications. Some of the new directions in computational kinetic theory include:

Microscopic flows: Nanometer-scale flows play an increasingly important role in fluid dynamics, thanks to advances in miniaturization technology [7]. For example, in a computer hard disk the aerodynamic design of the read-write head elevates it to only 10 nm above the spinning platter [8]. When the characteristic length scale of a flow is comparable to the mean free path of the constituent molecules (about 60 nm in air at standard conditions), the traditional macroscopic description breaks down. Particle simulations, primarily molecular dynamics [9] and direct simulation Monte Carlo [10], are at present the main computational tools in the study of these transitional flows. In some cases the conventional hydrodynamic equations can be corrected by modifications, determined by kinetic theory, to the boundary conditions or transport properties. An example is the simple Poiseuille flow where these modifications have yielded the correct temperature and pressure profiles [11]. A related problem is that of sound propagation when the acoustic wavelength is comparable to the mean free path [12].

Fluctuations and instabilities: Numerical simulations of dilute systems were the first to measure directly the long-ranged static correlations of non-equilibrium hydrodynamic fluctuations [13]. Dilute systems remain extremely useful in the study of hydrodynamic fluctuations and their influence on the onset of hydrodynamic instabilities. For instance, comparison with the numerical integration of stochastic hydrodynamic equations [14] will help to clarify the role of key parameters, such as the compressibility [15], the spatial dimension, and the influence of boundary conditions in the emergence of instabilities leading to vortex formations and to other complex behavior observed in laboratory experiments.

Dense gases: The Boltzmann equation can be extended to dense hard sphere gases by Enskog's modification in which the separation of the particles at collision is explicitly included in the distributions [16]. Recently, this idea was incorporated into the direct simulation Monte Carlo algorithm by Frezotti [17] and by Montanero and Santos [18]. The Consistent Boltzmann Algorithm (CBA) is a related approach that evaluates the displacement between particles due to collisions [19]. This latter technique can be extended to arbitrary equations of state; one application has been the simulation of a van der Waals fluid in the gas-liquid coexistence region [20].

Granular flows: Granular flows are ubiquitous in both nature and industry. In nature, rock and snow avalanches, the formation of sand dunes, and soil liquefaction during earthquakes are examples of flows involving assemblies of grains. Industrial applications include packing, segregation, mixing and drying, of granular materials, such as seeds, rocks, pellets, pills, etc. Granular fluids are composed of a large number of macroscopic elements, the grains, which undergo collisions very much like the molecules in a fluid. In contrast to regular fluids, at each collision a fraction of the grains' kinetic energy is dissipated due to a coupling with their internal energy. Granular media with can thus be reasonably modeled as an ensemble of inelastic particles and numerical simulations, primarily molecular dynamics, have been widely used in the study of granular flows [21]. For dilute and semi-dense systems, stochastic particle algorithms, such as DSMC, CBA, and other dense gas variants, are promising alternatives.

Multi component systems: Instabilities occurring in reactive fluids and coagulation processes observed in colloidal systems are two examples where traditional molecular dynamic simulations become quite inefficient. For instance, the validity of the macroscopic rate equations describing the time evolution of the composition variables implies that one needs to have a large number elastic collisions between successive reactive collisions in order to ensure mechanical and thermal equilibrium. As a consequence, only a fraction of the computation time will contribute effectively to the evolution of the chemical reactions. This results in much wasted bookkeeping with a corresponding waste of CPU time [22]. Similar difficulties arise in colloidal systems due to the vastly different time scales for collisions and coagulation. In this regard, stochastic particle simulations have proved useful in the study of reactive systems [23] and colloidal coagulation [24]. Mesoscopic algorithms, such as lattice Boltzmann [25], dissipative particle dynamics [26], or the highly efficient DSMC variant proposed recently by Malevanets and Kapral [27], are promising alternatives to model the dynamics of these dilute systems.

Plasma physics: Molecular dynamic simulations of charged fluids are extremely time consuming, mainly because of the long-ranged Coulomb iterations. The question then arises as to the possibility of setting up alternative mesoscopic methods. Today, there are some engineering plasma problems that have been analyzed by stochastic particle simulations. For example, the exhaust plume from pulsed plasma thrusters has been computed by a combination of direct simulation Monte Carlo (DSMC) and Particle-In-Cell techniques [28]. In this workshop, we intend to discuss another possibility related to the DSMC simulation of dilute charged fluids, as described by the Landau-Vlassov equations. In fact, the Landau collision operator is nothing but a modified Boltzmann collision operator that can be handled by an appropriate modification of DSMC algorithm.

Particle/Continuum hybrids: Many interesting flows that require the use of a microscopic simulation have not been studied due to their computational expense, which is several orders of magnitude greater than that of continuum hydrodynamic methods. Yet often one needs to simulate the fluid at the particle level in only a small fraction of the physical volume, for example at a shock or combustion interface. Hybrid schemes, which combine a microscopic algorithm with a continuum, hydrodynamic calculation, have proved useful is such scenarios. For example, the Adaptive Mesh and Algorithm Refinement (AMAR) scheme uses direct simulation Monte Carlo at the finest grid scale in an adaptive mesh refinement hierarchy and a Navier–Stokes solver at other scales [29]. An AMAR program adjusts grids, adding or removing finer levels, as the flow solution evolves, adaptively deciding where and when the calculation should switch from a continuum algorithm to a particle algorithm. Molecular dynamics-based hybrids have also been developed [30].

Motivation and objectives

At this workshop we want to bring together scientists and engineers who have a common interest in the numerical simulation of dilute systems and whose recent work has included the topics outlined in the previous section. Despite the diversity, the organizers anticipate significant interactions among the participants since they are the innovators in this community. As such, most of them have worked on several of these topics (the organizers have worked on nearly all of them), in many cases doing the pioneering studies.

There are several objectives that the organizers hope to achieve at this workshop. We want to discuss how simulation work can lead to the development of new hydrodynamic-like theories (with corresponding numerical methods) for large Knudsen number flows, especially for engineering design studies of microscopic flows. We hope to review the progress being made in the study of fluctuations near and past instabilities and debate whether some recent improvement of mesoscopic techniques (such as CBA for DSMC) can be used in order to achieve particle simulation of relatively high Reynolds number flows in the next years. By bringing together scientists studying dilute and semi-dense systems of reacting, granular, colloidal, and charged gases, we anticipate triggering a "gestalt" experience as these researchers realize the similarities in their problems and, hopefully, discover useful numerical methods that can be adopted from the various disciplines. Finally, the general question of how different algorithms can be effectively combined into hybrids will be the theme of one of the workshop's round-table discussions.

Since most of the participants are experts in a variety of numerical methods (DSMC, molecular dynamics, lattice-based methods, etc.), the organizers hope to stimulate round-table debates on the relative merits and deficiencies of competing algorithms. These discussion will promote a better understanding of the different range of validity, usefulness or potential of development of these methods, which is a goal of the European Science Foundation's SIMU program.

Tentative list of Participants

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STATISTICAL MECHANICS AND MOLECULAR SIMULATION OF NUCLEATION AND GROWTH

Provisional dates: London, 2-4 July 2001

SIMU workshop

Organizers

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Scientific background

Nucleation and growth associated with a phase change are central to many processes occurring in the natural world and in manufacturing. These encompass, for example, aerosols (liquid droplets in gas) and solids crystallization from a solution. For pharmaceuticals an appropriate choice of crystal form, for example, can enhance the bio-availability of the drug (S.R. Byrn (1982) Solid state chemistry of drugs, Academic Press:New York). Notable biological examples of interest include bio-mineralization of bone, teeth and shells (S. Mann and G.A. Ozin (1996) Nature, 382, 313-318), a better understanding of which would be useful for interfacing bio-minerals with inorganic orthopaedic implants, deposition of uric acid crystals in the clinical condition of gout, and the mechanism of action of antifreeze proteins. On the physical side, nucleation and growth is a major issue in the growth of quantum dots on substrates (e.g. Ge on Si). The processes are equally important in the classical area of metallurgy/materials science where nucleation of second phases occurs heterogeneously at defects such as grain boundaries and dislocations, which forms the basis of the heat treatment of steels. Another area of technological interest is the transport of fluids, where the precipitation of all manner of things e.g. scale, waxes and hydrates, can give rise to problems. Pertinent processes/industries here include oil and gas extraction, motor engine function and the wine industry. Finally, a greater understanding of crystal nucleation and growth processes should pave the way for a new class of functional solids based on self-assembly of 'designer' molecules (Ball (1996), Nature, 381, 648-650). Cavitation in liquids is another area with many practical consequences, where the nucleation physics is clearly the important stage.

Despite all this clear interest coming from many disciplines, nucleation and growth processes still remain an important fundamental problem. The essential difficulty is that the initial processes take place at the atomic scale and are therefore barely or not at all accessible to current experimental methods. Consequently it has been necessary to resort to models, both physical and theoretical. Of the 'model' experimental systems, the hard sphere colloids have given some very useful insights owing to their more readily accessible length and timescales by experiment (Zhu et al. (1997) Nature, 387, 883-885).

At the outset we note that nucleation from a metastable phase is a non-equilibrium phenomenon, and therefore elements of thermodynamics and kinetics are required in its description, without any formally exact solution. The 'classical theories of nucleation', CNT, developed over the past 60 or so years have been widely used, and are popular in no small part because of their analytic simplicity. The essential features of CNT are that there are at least two conflicting factors that characterise nucleation. These are, the surface tension, which is generally unfavorable, and acts between the nucleus and the host phase, and the favorable volume term associated with the preferential formation of the new phase. It must be recognised, however, that the CNT are semi-empirical syntheses, with significant uncertainties in the precise thermodynamic and kinetic ingredients. Also the CNT are of reduced validity on the nanoscale, in the early stages of homogeneous nucleation, as they omit such molecular detail as the distinctiveness of the structure of the incipient nuclei and the molecular-scale diffuseness of, say, the crystal-liquid interface. Recent modifications of CNT based on density functional theory and more sophisticated thermodynamic treatments have contributed to an improved understanding of both nucleation and growth, and phase separation in general (this is a vast literature, but see for example D.W. Oxtoby (1992) Nucleation in 'Fundamentals of Inhomogeneous Fluids', ed. D. Henderson (Marcel Dekker, NY), and K. Koga and X.C. Zeng (1999) J. Chem. Phys., 110, 3466).

Numerical computer simulation based on the atom-atom potential method provides an appealing analytic tool in this context. Computer simulations have contributed considerably to our understanding of phase transitions and the location of phase boundaries. This is a necessary precursor to understanding and pursuing simulations on nucleation]and growth. Computer simulations have been used to follow both nucleation and growth phenomena (e.g., P.R. ten Wolde and D. Frenkel (1998) J. Chem. Phys. 109 9901, and J. Anwar and P.K. Boateng (1998) J. Amer. Chem. Soc. 120, 9600-9604). Until recently, progress has been limited by small system sizes and short simulation timescales. These are serious restrictions in following nucleation as it is characterized by both a probability density per unit volume and per unit time. A small system size coupled with limited observation time both reduce the total probability of observing a nucleation event. In the case of solid-solid state phase transitions, an additional complicating factor is that to model macroscopic observations in the growing solid state it is also necessary to pay attention to the long-range elastic interactions (elastic stresses build up on phase transformation) as well as processes at the atomic scale, thus making the issue a truly 'multi-scale' problem, fitting naturally within the remit of SIMU.

Rather than carry out a molecular dynamics simulation and wait to observe the event, newer approaches to confront this challenge have been devised. The free energy barrier has been calculated using umbrella sampling Monte Carlo (J.S. van Duijneveldt and D. Frenkel (1992) J. Chem. Phys. 96, 4655.), wherein one forces the system to pass through the barrier using reaction coordinates based on a structural parameter. Parallel tempering has been employed to enhance the efficiency. The rate of passing the barrier has been studied using a rare-event technique of Bennett-Chandler. More recently, molecular simulation has started to be applied in a substantive way in the phase separation kinetics and growth morphology in crystal nucleation from the liquid (P.R. ten Wolde and D. Frenkel (1997) Science 109, 277, 1975.), droplet nucleation for the vapour (a few papers can be found dating back to the 1970s).

Motivation and objectives

The principle aim of the workshop is to bring together a representative selection of leading theorists, simulators and experimentalists from the different disciplines where nucleation and growth are issues of importance. They will review progress made in their fields. There will be an exchange of ideas on theoretical models and computer simulation techniques. The discussion will help identify the ranges of validity, usefulness and potential in the various approaches. By bringing together these researchers we seek to improve our understanding of the underlying physics of nucleation and identify the distinguishing features of the microscopic, mesoscopic and macroscopic stages of growth, and the factors (both chemical and physical) that affect them. The workshop will help to focus attention on areas of contention and hopefully provide the groundwork of a rational strategy for advancing theoretical developments underpinning nucleation and growth.

The topics and issues to be highlighted in the Workshop will be as follows. Generic systems including colloidal crystals, hard spheres and Lennard-Jones particles. Simple liquids (diatomics such as nitrogen and oxygen, and noble gas liquids) which are routinely amenable to molecular simulation and Density Functional Theory (DFT). Inorganic solids precipitation from aqueous solution (e.g. calcium carbonate and barium sulphate). Scaling. The role of morphology changes and growth inhibitors. Organic molecules, with special reference to the polymorphism and pharmaceutical concerns. Complex liquids, such as liquid crystals, colloids, and polymer melts and polymers in solution. The influence of the particle interactions will be discussed. Design of additives to retard/promote nucleation or growth, or to selectively promote the crystallisation of particular polymorphic phases. Solid state materials, such as ceramics and polymer composites. Nanoparticles. Inorganic/organic hybrids.

The techniques to be covered in the Workshop will be include, for example, Molecular Dynamics simulation including accelerated dynamics. Advanced Monte Carlo techniques: Barrier height calculations; Parallel tempering and variations. Static lattice methods (inorganics and inorganic/organic hybrids) Classical Nucleation Theory (and extensions) and Density Functional Theory.

There is an increasing body of experimental data in the following areas: droplet formation from the vapour phase, nucleation and growth of inorganic and organic crystals from solution, colloidal crystals, and cavitation in liquid. The experiments provide structural, thermodynamic and kinetics data that can be used to compare with theoretical predictions based on CNT (and modifications thereof) and molecular simulations. An important aspect of the workshop is to bring together some experimentalists, theorists and molecular simulators in this important area. We anticipate that the product of these discussions will lead to advances in theory and physical insights.

MULTISCALE MODELLING OF MATERIALS: METHODS, ALGORITHMS AND UNSOLVED PROBLEMS

Provisional date: Crete, Greece July 2-5, 2001

SIMU-CECAM workshop

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Scientific background

Physical properties of materials rely on phenomena operating at various space and time scales ranging respectively from nanometers to meters and from femtoseconds to seconds. At the thermodynamical equilibrium, values for quantities of interest (free energy and its derivatives) are computed analytically or numerically, as space and/or time averages of the appropriate microscopic observables within the framework of statistical thermodynamics. Under conditions not far from equilibrium, studying physical properties is still possible a task by using the linear response theory and mean field approaches. Examples are the calculation of transport coefficients via the Green-Kubo formulas, the mean field prediction of phase transformations and of microstructural changes. However, processing and employment of materials occur often under strong gradients of pressure and temperature, i.e. very far from equilibrium. As a consequence, material properties become "history" dependent (because an equation of state does not exist) and highly non-linear. It is worth mentioning, that the non-linearity is often observed to stem from the collective behavior of structural equilibrium (point defects) and metastable (dislocations, grain boundaries) defects. Numerical simulation provides a mean for studying the properties of materials under such non-equilibrium conditions. Starting from physically founded cohesion models or from an ab-initio description of atomic bonding, atomic scale simulation techniques (Molecular Dynamics and Monte Carlo) give insight to the behavior of the materials studied. This can help improving the quality of materials for technological applications and possibly to the development of new materials and/or fabrication processes. Unfortunately, the scales of most properties relevant for applications are fundamentally different from these of atomistic simulations. The challenge therefore consists for numerical simulations in bridging the gaps of space and time scales that separate atomic and macroscopic material properties.

Motivation and objectives

This SIMU-CECAM workshop proposal, aims at bringing together researchers with expertise in different areas of condensed matter and material physics. It is thereby expected to meet the following twofold objective:

- To address issues related to methods for bridging space and time scales in specific sub-fields and to identify the most promising directions of development of appropriate theoretical and numerical tools.
- To offer participants an overview of methods used in specific sub-fields they may not be aware or familiar with and thereby promote new ideas and collaborations.

Desiring to keep the meeting reasonable in size, so that to maximize chances of interaction and exchanges between participants, the following specific sub-fields will be considered:

1. Phase transformations and structural evolution of alloys
2. Mechanical properties of traditional structural materials including phenomena like fracture and corrosion.
3. Mechanical, Rheological, Transport and Interfacial Properties of Polymers
4. Friction and lubrication including associated phenomena like mixing of species, plasticity and crack propagation.

   Particular attention will be given to the following technical issues:
5. Boundary conditions
6. Coupling atomistic to the mesoscopic and mesoscopic to the macroscopic space scales
7. Coupling different time scales in simulations of flow, grain growth, crack propagation and nucleation.
8. Phase field methods

VII.0.1 Tentative list of participants

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PHASE TRANSITIONS IN COMPLEX CONFINED SYSTEMS

Provisional dates: Lyon, 22-24 August 2001

SIMU-CECAM workshop

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Scientific background

If a fluid is confined to spaces of dimensions comparable to the range of intermolecular interactions, its phase behavior is altered markedly compared with the corresponding bulk behavior under identical thermodynamic conditions. For example, the liquid–gas critical point of a confined fluid is shifted to higher densities and the critical temperature is depressed (with respect to the bulk) [1,2]. In addition, the two-phase region is narrower, indicating that the densities of the coexisting phases are closer than in the bulk. Similar results have been reported for binary liquid mixtures [3]. For a quantum fluid like ^{4}He, anomalous properties of the superfluid transition have been observed in Vycor and silica aerogels [4]. Confinement can also influence freezing and the phase behavior of liquid crystals. Depending on the nature of the solid matrix the freezing point of the confined material can be depressed or enhanced [5]. In the latter case, formation of solid-like structures in the confined phase can be induced by a template effect on account of the crystal structure of the substrate [6]. A comprehensive review of the current knowledge and understanding of phase transitions in (classical) confined systems can be found in the review article by Gelb *et al.* [7].

However, the overwhelming number of theoretical studies is concerned with rather idealized models of confined systems. For example, porous materials are often described as a collection of independent cylindrical or slit–shaped pores and the substrate is made of a single chemical species. Sorption experiments, on the other hand, are frequently done in solids like Vycor, controlled–pore glasses or silica gels consisting of disordered, interconnected networks of mesopores of various shapes and sizes (see, e.g. Fig. 2 in [7]). Interconnectivity can have profound consequences for the mechanism of ad– versus desorption [8,9]. Moreover, because of the disordered character of the pore structure, dynamical effects play a major rôle and may forbid the setting up of thermodynamic equilibrium. At present, only first attempts have been made to understand the phase behavior of fluids in random porous matrices [10,11].

Another unique feature caused by the presence of a solid substrate is wetting. Wetting phenomena have been investigated in the last decade and it is by now well–established that they should be perceived as surface–induced phase transitions which can be continuous or discontinuous depending on the nature of the substrate and the path along which the bulk liquid–gas coexistence curve is approached in thermodynamic state space [12]. Wetting characteristics are affected significantly by nonplanarity of the substrate [13] or if the substrate is decorated with a second chemical species [14–16]. Experimentally, novel techniques now permit to prepare these substrates in a controlled manner on a nanoscopic length scale by, say microcontact printing [17], lithographic techniques [18], or wet chemical etching [19]. Wetting of such substrates can be modified to the extent that a fluid can be transported across a substrate and along chemical "lanes" without spilling. In the future these techniques may be used to manufacture chemical chips or even set up minute chemical factories [20]. However, our understanding of wetting phenomena at complex structured substrates, both theoretical and experimental, is still in its infancy [21].

These examples clearly indicate that in general properties of confined phases are a consequence of processes and phenomena operating on different length and time scales. As far as relevant length scales are concerned these are set by the range of intermolecular potentials on one hand and the interaction of individual molecules with much larger mesoscopic (chemical or geometrical) structures characterizing the confining solid matrices. As far as time scales are concerned, these may range from the lifetime of typical molecular correlations, usually decaying within a few picoseconds, to hysteretic effects on account of highly cooperative dynamic processes. In many cases these hysteretic effects decay only within hours. Thus, a comprehensive understanding of confined phases will eventually emerge only if one identifies these rather disparate (length and time) scales and takes into account the consequences of their interplay.

Motivation and objectives

Experimental and theoretical efforts during the past decade have led to the observation of many new effects and phenomena uniquely caused by confinement of many–particle systems. It now seems to be the right time to ask for underlying concepts and try to systematize our present knowledge about complex confined systems by gathering leading theoreticians and experimentalists. This is not only necessary to preserve this field as an intellectually appealing branch of the natural sciences but also to foster and prolong its rapid and flourishing future development.

Therefore, the major topics for discussion at the proposed workshop will be

1. *Taxonomy of phenomena in complex confined systems.* The following issues should be

discussed in depth:

• *The nature of phase transitions.* When fluids are confined by geometrically or chemically complex substrates one may observe phase transitions. However, because of the importance of dynamical effects it is unclear if these transitions are equilibrium or out–of–equilibrium phenomena. A distinction between equilibrium and out–of–equilibrium phenomena must be based upon identifying the relevant time scales. It is very important to discriminate the different situations experimentally, if possible. Moreover, theoretical calculations predict complex (equilibrium) phase diagrams with several phases which may coexist seperately and become indistinguishable at several independent critical points. Accordingly, several questions should be addressed:

– What experiments need to be carried out to discriminate equilibrium, quasi-equilibrium, and out–of–equilibrium situations and to verify theoretically predicted phase diagrams? It may be necessary to set up several different experiments to bridge the gap between all the relevant scales governing a specific confined phase.

– Is there a way to describe these phase transitions within a general theoretical framework?

– Is there a way to link the phase diagram to the degree of randomness of the solid matrix? More generally, what are the respective rôle of confinement, disorder, and wetting phenomena?

• *Hysteresis.* In sorption experiments one frequently observes hysteresis, that is existence of a chemical–potential interval $\Delta\mu \neq 0$ (or a pressure range $\Delta P/P^{\mathrm{sat}}$, P^{sat} pressure of a bulk gas at saturation) such that the excess coverage Γ^{ex} is a double–valued function of μ along a sorption isotherm. Hysteresis is observed for fluids confined to highly–idealized, single pores and to an interconnected network represented by a random solid matrix. Experimentally, hysteresis is also observed for temperatures T below some so–called "hysteresis critical temperature" T_{ch} and vanishes for $T \geq T_{\mathrm{ch}}$. This has prompted the notion of hysteresis phase diagrams. Hysteresis is intimately linked to existence and lifetime of metastable thermodynamic states on rather different scales. Hence it should be treated dynamically. The following points should be discussed:

– What is the dynamics of states below T_{ch}?

– Can hysteresis in experimental systems be interpreted in terms of hysteresis in models and what kind of models are suitable to achieve this goal?

• *Critical phenomena.* Confined systems can be perceived as being somewhere in between $d = 2$ and $d = 3$ dimensions. It is well–known that critical phenomena depend on the dimensionality of the system (see, for example, critical exponents for Ising–class systems in $d = 2, 3$ dimensions). The purpose of this discussion point is to clarify the current experimental and theoretical situation as far as our understanding of critical phenomena is concerned.

– Are there generic critical phenomena caused solely by confinement?

• *Wetting of complex structured substrates.* Wetting is associated with the divergence of the thickness of a liquid film adsorbed on a solid substrate when the bulk coexistence line $\mu(T)$ is approached from the one–phase gas region. As pointed out in the preceding section, wetting should be perceived as a substrate–induced phase transition which can be continuous or discontinuous. If the substrate is composed of more than one chemical species or if it is nonplanar, several interesting questions arise:

– How does the wetting temperature T_{w} depend on the degree of nonplanarity of a substrate (i.e., the depth D of a wedge)?

– If a substrate consists of several parts differing by their wettability, what is the morphology of the entire film as one approaches a wetting transition and how does it depend on the nature of the wetting transition (i.e., its continuous or discontinuous character)?

– What is the relation between flow of matter under confinement and wetting characteristics of a chemically decorated or nonplanar substrate?

2. *Experimental approaches.* Here discussions should help to clarify the current situation of experiments in a variety of contexts. Among these are wetting phenomena, layering transitions, capillary condensation, freezing/melting etc. Particularly important are experiments that allow one to determine morphologies of fluid phases in complex confined systems. Specifically, the discussion should focus on:
- Thermodynamic measurements (i.e., heat capacity, mass adsorption)
- Scattering methods (neutron and x–ray)
- Nuclear magnetic resonance
- Measurements of dielectric constants
- Ellipsometry
- Ultrasound and positron annihilation
- Ageing studies

3. *Theoretical approaches.*
- *Molecular modeling and density–functional theory.* There is a tradition in the field of molecular modeling of adsorption that both computer simulations and approximate theories should be used as complementary tools in developing an understanding at the microscopic level. An excellent example has been the interplay between computer simulations and density functional theory in modeling sorption on surfaces and in single pores [12]. In the case of geometrically and/or chemically heterogeneous materials an important problem consists in choosing the appropriate degree of sophistication for these models. For instance, a sensible model of Vycor glass or silica aerogels should encompass the characteristic features of these solids without requiring a detailed description at the microscopic level. In this respect the usefulness of lattice versus continuum models should be discussed during the workshop. This is especially important for the development of density–functional methods which are reasonably tractable for lattice models of pore fluids but represent a major computational challenge when a full three–dimensional representation of the molecular density distribution is used [22].
- *Replica Ornstein–Zernike method.* Particular models of disordered porous materials can be addressed using techniques derived from liquid state theory and the replica trick from condensed matter physics [10]. In principle, these approaches reduce the problem of adsorption of fluids in porous materials to a level of difficulty comparable to that of the theory of liquid solutions. Important insights have emerged from this work although important questions are unresolved such as the choice of a good closure approximation for the corresponding integral equations.
- *Out–of–equilibrium phenomena, hysteresis, and percolation.* The origin of hysteresis in capillary condensation of fluids in porous materials is controversial. It seems that the shape of the hysteresis loop and of the so–called scanning curves cannot be explained by independent–pore models [9], and that collective phenomena spanning length scales beyond that of a single pore must be taken into account. One approach to addressing these effects has involved the application of percolation concepts [8]. In this approach a porous material is treated as a network of interconnected pores of different sizes. Sorption phenomena depend on the accessibility of the pores to mass transfer to and from the external surface of the porous material, which, in turn, will be determined by the topology of the network. Hysteresis is associated with the inability of liquid in larger pores to evaporate due to blockage by smaller pores where evaporation does not occur until lower values of the chemical potential are reached. However, hysteresis loops quite similar to the real ones are also observed in grand canonical ensemble simulations and analytical calculations where pore–blocking effects play no rôle. This can be related to the more general behavior of disordered systems driven by an external field.

4. *Computer simulation techniques.* Most of the numerical studies of confined systems to date are based upon simulations in the grand canonical ensemble (as far as equilibrium

situations are concerned). Dynamical aspects like transport and flow have received much less attention so far. A key feature of the algorithm, on which the equilibrium simulations are based, is creation and destruction of molecules controlled by the (fixed) chemical potential. These insertion/destruction processes become difficult for "simple" fluids at higher densities and for complex fluids because of the internal degrees of freedom. Moreover, because of disorder the systems may have a complex free–energy landscape with many metastable states separated by large energy barriers. This can lead to extremely slow relaxation towards the equilibrium state (which may, as a matter of fact, never be reached). Thus, a key issue for discussion should be to identify or design computational techniques suitable for an investigation of processes operating on very different length and time scales. These methods may range from equilibrium molecule–based approaches like Monte Carlo or (equilibrium and non-equilibrium) molecular dynamics simulations to Brownian dynamics or even smooth particle applied dynamics [23] where one deliberately ignores the motion of individual molecules in favor of the dynamics of larger assemblies of these molecules. It should be discussed under what circumstances combinations of molecular and macroscopic simulation techniques may be suitable to bridge the gap in length and time scales characteristic of complex confined phases to enhance our understanding of their behavior under realistic circumstances. Therefore the workshop should consider the following questions:
– What techniques should be used to overcome free–energy barriers for fluids in pores in order to reach thermodynamic equilibrium?
– Are metastable states in computer simulations related to metastable states in experiments and/or analytical treatments?
– What are the best techniques to study phase equilibria in complex confined systems? This should include both pure fluids and solids as well as fluid binary mixtures where one encounters liquid–liquid equilibria.
– What techniques are available to simulate complex molecular fluids in confinement? These complex fluids may have rotational and translational degrees of freedom. As described above, grand canonical simulations are very difficult for these systems. For reasons of direct comparison with relevant experiments one would still like to have a simulation technique which allows control of the chemical potential even if the value of the chemical potential cannot easily be calculated.
– In nonequilibrium simulations of flow, a key problem consists of removing heat from the system. What would be the most efficient and physical way to achieve this? There are several options like rescaling velocities or cooling upon collision with the substrate surface.

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SIMULATION AND THEORY OF SOLID FRICTION: FROM ATOMIC SHEAR FORCES TO MACROSCOPIC TRIBOLOGY

Provisional dates: Lyon, 27-30 August 2001

SIMU-CECAM workshop

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Scientific background

Tribology, the science of friction, lubrication and wear, is to certain extent a baffling domain. It is one of the oldest applied technologies, e.g., the use of firerods by the neanderthals dates back to 200,000 B.C and the laws of solid friction have been formalized by Amontons and Coulomb already 300 years ago [1]. It can nevertheless be considered a "young" field in view of the important progress made recently. In the last decades, novel experiments have been performed both at the macroscopic and the microscopic level on the macro and the micro scale using the latest developed techniques to probe the foundations of solid friction. Behind the seeming simplicity and "universality" of the Amontons-Coulomb's friction laws, it appears that solid friction results from the interplay of very different processes such as geometric locking of two surfaces, elastic and plastic deformations, wear, lubrication, and adhesion, to name a few [2]. All these processes occur at very different length scales: On the nanometer scale, atomic and molecular interactions take place, the micrometer is the typical length scale for real contact radii (the real contact area between two solids is usually orders of magnitudes smaller than the apparent contact area and it is distributed over many individual asperity contacts), and the largest tribological length scales are related to the stick slip motion of tectonic plates resulting in earthquakes. It is the main challenge of modern tribology to develop a fundamental understanding of solid friction, which allows us to bridge the different length scales and properly relate the atomistic processes with the macroscopically observed phenomena.

The development of new experimental techniques such as the surface force apparatus (SFA) [3] or the atomic and friction force microscopes (AFM/FFM) [4] has made it possible to probe friction from the micrometer to the nanometer scale. These experiments often show strong deviations from Amontons' laws of (macroscopic) solid friction. SFA and AFM frequently observe a sublinear dependence of the friction force F on the (excess) load L

in single asperity contacts. The dependence $F \propto L^{2/3}$ [5,6] is often suggested for the so-called elastic regime, where normal pressures do not yet exceed the yield stress. Classical theories explain this dependence by assuming the validity of Hertzian contact mechanics (or refined contact models such as the JKR model) as well as a constant shear stress in the contact - independent of the local normal stress [7]. The latter ad-hoc assumption lacks any atomistic, theoretical foundation, in particular in the absence of plastic deformation. In the recent literature, several completely different arguments have been proposed to explain the deviation of the behavior observed in SFA and AFM experiments from the linear relation, $F \propto L$, which is one of Amontons' laws. One argument which applies to AFM experiments stresses geometric considerations. The misfit or the incommensurability between an AFM tip and a crystalline substrate increases with increasing contact area or load. Thus, while for flat contacts with constant contact area $F \propto L$ is obtained, sublinear behavior is expected for curved contacts [8]. Another theory stresses the importance of dislocations. Depending on the density of contact induced dislocations, two different regimes can be found in which the shear stress is constant [9]. Yet, another argument applies to SFA experiments and relates the discrepancy between Amontons' macro law and single asperity contact friction to adhesive effects [10]. We are thus still far from a full understanding of AFM and SFA experiments of single asperity contacts, even though these experiments are conducted in relatively well defined conditions.

It is important to stress that the microscopic origin of solid friction is in fact less obvious than it first seems: many simulations predict that perfectly flat, crystalline surfaces in vacuum should be supralubric [11], i.e., the frictional forces between the two solids is a drag force that vanishes in the limit of small velocities. Moreover, the origin of finite (static) friction forces between two dry crystals due to elastic multistability such as suggested by Frenkel-Kontorova-Tomlinson models has never been seen in simulations relying on atom-atom potentials and three-dimensional solids [12]. One may hope that the predicted phenomenon of supralubricity will be used by the computer industry in order to eliminate the lubricant between reader and hard disk and therewith increase the data access rates.

One of the many complications in developing a theoretical foundation of tribology is the complexity due to ambient conditions. Real surfaces are always contaminated by airborn molecules such as adsorbed nitrogen, water, or adsorbed hydrocarbon molecules - not to mention oxygen between two metal surfaces.

These components including various forms of friction, indentation, or otherwise produced wear and debris are usually denominated all together as "third bodies". The influence of such third bodies on solid friction is not just anecdotal. Even a tiny amount of small adsorbed molecules might in fact automatically lead to non-vanishing (static) friction forces - even if the bare surfaces are perfectly supralubric [13,14]. Another example is condensated water in sliding contacts. The formation of liquid bridges may yield aging at macroscopic scales resulting in strongly increased friction coefficients [15], while in well-controlled SFA experiments, a decrease of friction is often observed with increasing relative humidity [16]. More general, the wetting properties of the solid surfaces in contact certainly influence the tribological properties significantly [17]. The understanding of this influence is still in its infancy, in particular if the number of contaminating or lubricating layers, which separate the two solids, is small. Such a situation is sometimes obtained in a controlled way by squeezing individual layers of lubricant out of a single asperity or SFA contact [18]. Finite (static) shear forces are frequently observed when only five or six layers remain in the contact [17]. The interpretation of a confinement induced solidification of the lubricant [19] is by no means the only possibility to explain the finite shear stresses. It has been shown by computer simulations that fluids consisting of particle with considerable mobility are still able to withstand finite shear stresses [20] which is a highly counterintuitive observation.

This discussion shows that even at the atomic scale many different mechanisms may come into play to construct friction forces and that it is not established what mechanism is predominant at what length scale. Another important issue concerning length-scales is the correlation of the dynamics of individual contacts which interact via long-range elasticity [21]. The macroscopic laws of friction certainly result from the physics of individual contacts and the interaction between contacting asperities [22]. Of course, atomistic simulations will not be able to address long-range elasticity directly. Instead, less detailed descriptions are required such as those used in continuum mechanics and finite element methods.

Despite the complexity of tribological processes on the atomic scale, Frenkel-Kontorova -Tomlinson (FKT) models are very successful in reproducing the dynamics of sliding solids [23]. In particular, the transition from smooth sliding to stick slip motion can be analyzed well in terms of such models. From these simple, sometimes analytically solvable models, we may well learn how it is possible to control friction, e.g., how a time-dependent normal force suppresses stick-slip motion [24]. One of the main remaining challenges is to connect the phenomenological parameters used in FKT models with interatomic potentials or vice versa.

This discussion left out many strongly irreversible solid friction mechanisms such as high sliding velocity induced material mixing [25], friction induced chemical reactions [26], nano-scraping [27], abrasive wear [28], effects of "macroscopic" debris leading to the generation of even more debris, etc, etc. These are all important effects that need to be understood in such a way that one can predict macroscopic tribological behavior from atomistic interactions. The first step in doing this, however, is to study and to understand the normal forces and the maximum shear forces that individual atoms, molecules, and larger compounds experience on surfaces. Unlike in real experiments, it is possible to probe single atom or molecule friction under perfectly controlled conditions in computer simulations.

Motivation and objectives

From the previous discussion, it becomes clear that the generic term "solid friction" refers to many different phenomena occurring in a broad range of length scales. The community working on the subject is scattered accordingly in different fields, each bearing a different point of view on the problem. With this workshop we therefore aim to encourage connections between these different communities working on each aspect of solid friction. The informality of CECAM meetings offers the possibility to share and discuss controversially different points of view. Moreover one may note that even after a decade or more of intensive computer simulations in the field of nano and micro tribology, there has not yet been such a platform allowing theoreticians (doing simulations and/or analytic work) to exchange extensively amongst themselves. The presence of a multidisciplinary panel of scientists will make it possible to discuss important issues such as

(i) the possibility to agree on a unique interpretation of SFA and AFM experiments with the help of computer simulations - at least in the wear free regime.

(ii) the relevance of long-range elasticity and plasticity, and algorithms that allow to take them into account efficiently, e.g., without having to simulate explicitly millions of atoms.

(iii) the influence of third bodies on solid friction and ways to model atmospheric conditions, when the presence of airborn molecules between sliding surfaces is important.

(iv) the link of physical phenomena occurring on the microscopic scales with macroscopic scale properties, e.g., what microsopic ingredients are responsible for the macroscopically measured state variables.

(v) the connection of atomistic simulations with FKT models and the possibility to include the effect of airborn particles in FKT models.

(vi) importance of realistic modeling building way mechanisms.

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VIII

External Conferences

The *SIMU* steering committee has decided to provide support to *SIMU* members wishing to attend the following non-*SIMU* conferences:

1. "Discrete Simulation of fluid dynamics, new trends, new perspectives ", Corsica, 2 - 7 July 2001, organized by Jean Pierre Boone,
   email: jpboon@ulb.ac.be

2. "Multiscale materials modelling", London, October/Novermber 2001, Contact Peter Coveney,
   email: p.v.coveney@qmw.ac.uk

3. "From White dwarfs to colloids: Thirty years of liquid state theory", and international conference in honour of Jean-Pierre Hansen, Lyon, April 2002, organized by J. L. Barrat,
   email: jean-louis.barrat@dpm.univ-lyon1.fr
   and G. Zérah,
   email: gilles.zerah@cea.fr

Other conferences relevant to *SIMU* are

1. A "Mini Statistical Mechanics meeting", Berkeley, January 5-7 2001, organized by David Chandler
   Conference URL: http://statmech2001.berkeley.edu/

2. CCP5 Workshop on: "Multiscale Algorithms for Simulation of Materials and Fluids", Imperial College, London, 2-3 April 2001, Organised by Sebastian Reich (Department of Mathematics, Imperial College),
   email: s.reich@ic.ac.uk
   and David Heyes (Department of Chemistry, University of Surrey),
   email: d.heyes@surrey.ac.uk
   Topics covered will include, for example,
   Multiple timestep amd extended Hamiltonian MD,
   Dissipative Particle dynamics, DPD,
   Smooth Particle Hydrodynamics, SPH,
   Brownian Dynamics, BD,
   Stokesian Dynamics, SD,
   Granular Dynamics, GD,
   and various hybrid methods.

3. Quantum Simulations of Complex Many-Body Systems: From Theory to Algorithms, Rolduc Conference Centre, Kerkrade, The Netherlands, 25 February - 1 March 2002, conference URL: http://www.fz-juelich.de/wsqs/

IX

Did you see ?

This section is an attempt by a few of us to assemble a set of links, and other information (books, and a few recent down-loadable papers) which with respect to *SIMU* are noteworthy. As there are far too many links for us to check individually, we decided to use as a selection criteria, sites belonging to contributers of the *SIMU* newsletters, or organizers of *SIMU* tutorials, provided that the links contain useful information, such as down-loadable articles etc. Certainly, many things have been missed, so feel free to email me (Dónal MacKernan) at dmack@cecam.fr and I will do an update. This section will also appear as an html text on the *SIMU* website (http://simu.ulb.ac.be/)

List of themes

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IX.11 Dissipative Particle Dynamics

IX.12 Polymers

IX.13 Protein models and molecular evolution

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IX.1 Physics

1. The XXX-LANL article depository. French mirror
   http://xxx.lpthe.jussieu.fr/

2. The SISSA (Trieste) information web site for condensed matter, a treasure trove
   http://www.sissa.it/~furio/cminfo.html

3. The NIST Physics Laboratory, is one of the major operating units of the National Institute of Standards and Technology (NIST), and is an excellent source for physical reference data constants, units and uncertainty
   http://physics.nist.gov/

IX.2 Chemistry

1. A URL for departments of chemistry is
   http://www.ch.cam.ac.uk/ChemSitesIndex.html

2. Modern Methods and Algorithms of Quantum Chemistry Proceedings, John Von Neumann Institüt für computing (2000)
   http://www.fz-juelich.de/wsqc/proceedings.html

IX.3 Computer clusters and parallel computing

1. The Portland Group, cluster software for linux systems
   http://www.pgroup.com/index.htm

2. The Message Passing Interface (MPI) standard. Description of the MPI parallel library, manuals and examples
   http://www-unix.mcs.anl.gov/mpi/index.html

3. "An Introduction to MPI for Computational Mechanics", very nice article aimed at people with little or no previous experience of using MPI but who would wish to get off to a quick start in parallel programming, by P.K. Jimack and N. Touheed, //
   http://www.scs.leeds.ac.uk/pkj/publications.html

4. "SC' 97 Tutorial MPI-2" a fine and not daunting tutorial by William Saphir, Lawerence Berkley National Laboratory
   http://www.nersc.gov/research/FTG/wcs/talks/SC97/sc97_mpi2.html

IX.4 European Super Computer Centres and Organizations

European Commission research initiatives, networks and fellowships
http://www.cordis.lu/improving/home.html

The webserver of the European Science Foundation, our sponsor is
http://www.esf.org/

Several super computer centres give free access to simulators, provided that project satisfies various scientific and computational criteria. A list of European centres is given at the URL
http://www.cesca.es/ang/PROJECTS/hoise-map.html

A good source of current news on high-performance computing and networking in Europe is provided by *Primeur*, an initiative which was supported by the European Commision under the Esprit IV RTD in the Information Technologies work programme
http://www.hoise.com/primeur/00/articles/index.html

One notable initiative is run under the auspices of the European commision through the fifth framework programme, "Access to Research Infrastructures"
http://improving-ari-fp5.sti.jrc.it/access/
For Supercomputers, 4 centres are currently part of the programme:

1. Consorzio Interuniversitario per la gestione del centro di calcolo elettronico dell' Italia nord-orientale (CINECA) (Italy)
   http://improving-ari-fp5.sti.jrc.it/access/show.gx?Object.object_id=ARI-FP5-0000000000000221
2. EPCC (Edinburgh Parallel Computing Centre), the University of Edinburgh (UK)
   http://improving-ari-fp5.sti.jrc.it/access/show.gx?Object.object_id=ARI-FP5-00000000000001D9
3. Centre Europeu de Paral.lelisme de Barcelona (CEPBA) and Centre de Supercomputaci de Catalunya (CESCA) (Spain
   http://improving-ari-fp5.sti.jrc.it/access/show.gx?Object.object_id=ARI-FP5-000000000000026F
4. Bergen Computational Physics Laboratory (Norway)
   http://improving-ari-fp5.sti.jrc.it/access/show.gx?Object.object_id=ARI-FP5-00000000000002BA

IX.5 Scientific software

1. FFTW: An efficient FFT library for sequential and parallel computers
   http://www.fftw.org/
2. Numerical Recipes on Line. PostScript and PDF files of the NR C/Fortran books
   http://www.ulib.org/webRoot/Books/Numerical_Recipes/
3. For a library of software on molecular dynamics, Monte Carlo, Lattice statistics and Lattice dynamics containing the programmes of the book, see the web site of the UK CCP5 group,
   http://www.daresbury.ac.uk/CCP/CCP5/librar.html
4. Quantum Simulations of Condensed Matter Systems, the NCSA Condensed Matter Physics home page of David Ceperley containing lots of free software,
   http://www.ncsa.uiuc.edu/Apps/CMP/cmp-homepage.html
5. LASSP Tools: A great variety of scientific visualization programmes
   http://www.lassp.cornell.edu/LASSPTools/LASSPTools.html
6. Free Ab-initio density functional Car-Parrinello algorithms: for information about CPMD, its successor CP2K, and a new verson based on Gaussian wave functions (rather than plane waves) QUICKSTEP, see the Parrinello web site
   http://www.mpi-stuttgart.mpg.de/PARRINELLO/
7. A web site dedicated to CP2K is at
   http://www.rzg.mpg.de/~abs/cp2k/index.html
8. The approach implemented in VAMP/VASP is based on a finite-temperature local-density approximation (with the free energy as variational quantity) and an exact evaluation of the instantaneous electronic ground state at each MD-step using efficient matrix diagonalization schemes and an efficient Pulay mixing. These techniques avoid all problems occurring in the original Car-Parrinello method which is based on the simultaneous integration of electronic and ionic equations of motion."
   http://cms.mpi.univie.ac.at/vasp
9. ABINIT, a gnu freeware DFT ab-initio package based on plane waves
   http://www.mapr.ucl.ac.be/ABINIT/

IX.6 Books and associated sites on molecular simulation

Books or review articles that appear here are either down-loadable, or have much associated down-loadable software.

1. Understanding Molecular Simulation: From Algorithms to Applications Daan Frenkel and Berend Smit, Academic Press (1996). For new additions, exercises, programmes and associated courses see
   http://molsim.chem.uva.nl/frenkel_smit/

2. Computer Simulation of liquids, M.P. Allen and D.J. Tildesley, Oxford Science Publications, 1997, one of the bibles of simulators. The programmes of the book, are available on the CCP5 group web site,
   http://www.daresbury.ac.uk/CCP/CCP5/librar.html
   The web site of an associated summer school is
   http://molsim.ch.umist.ac.uk/CCP5SS/

3. Classical and Quantum Dynamics in Condensed Phase Systems, Editors: Bruce J. Berne, Giovanni Ciccotti and David F. Coker.
   For associated material, check out the web site of Giovanni Ciccotti
   http://mefisto.phys.uniroma1.it/cgi-bin/wrap/ciccotti/Public/LERICI/

4. "Microscopic simulations in physics", D. M. Ceperley, Rev. Mod. Physics **71**, pp 5438 (1999)

IX.7 Statistical Physics and Monte Carlo simulations

1. For downloadable articles, lecture notes and computer programmes on computational kinetic Theory,and computational stochastic methods, see the web page of Alec Garcia
   http://www.gst.net/~algarcia/

2. For information regarding transition path sampling, solvation, reaction rate theory,proton transfer and much more, a good web site for downloadable papers is David Chandlers
   http://gold.cchem.berkeley.edu:8080/index.html

3. The Molecular Monte Carlo, a web page full of information: links, books, papers, programmes and tutorials on Molecular Monte Carlo,
   http://www.cooper.edu/engineering/chemechem/monte.html

IX.8 Multiple time scale algorithms

1. "Understanding modern molecular dynamics," G. Martyna and M. E. Tuckerman. J. Phys. Chem. B, **104**, 159 (2000).

2. See Mark Tuckerman web page for more information and references
   http://homepages.nyu.edu/~mt33/pubs.html

3. For uptodate information about Tuckerman's and Martyna's 2001 Multiple time scale algorithms SIMU-CECAM tutorial see
   http://simu.ulb.ac.be/activities/activities.html

IX.9 Simulations in quantum mechanics

1. Mixed quantum classical descriptions, downloadable papers are available on the web page of Raymond Kapral
http://www.chem.utoronto.ca/~rkapral/Research.html

2. For information on Influence functional theory, in particular for the SPin Boson problem, see Nancy Makri's web page
http://www.scs.uiuc.edu/~makri/publications.html

3. National Center for Supercomputing Applications, web page on Quantum Simulation Methods, http://www.ncsa.uiuc.edu/Apps/CMP/method.html

4. Mixed quantum-classical and semiclassical simulation approaches for condensed phase systems from the Rosskly group, including work on solvation, ee Peter Rossky's web page
http://www.cm.utexas.edu/rossky/

IX.10 Quantum and Classical Density Functional Theory

1. Classical desnity functional methods for the simulation of complex fluids, Review article by S. Melchionna and J. P. Hansen, *SIMU* newsletter **2** (2000), down-loadble from the SUMU website
http://simu.ulb.ac.be/newsletters/newsletter.html

2. Jean Pierre Hansens web page
http://www.ch.cam.ac.uk/CUCL/staff/jph.html

3. Ab initio molecular dynamics: Theory and Implementation by Dominik Marx and Jürg Hutter, in Modern Methods and Algorithms of Quantum Chemistry Proceedings, a series of books and reviews from The John Von Neumann Institut für Computing.
http://www.fz-juelich.de/nic-series/Volume1/marx.ps
http://www.fz-juelich.de/nic-series/Volume1/marx.pdf

4. See the Parrinello web page for their recent CPMD publications
http://www.mpi-stuttgart.mpg.de/PARRINELLO/

IX.11 Dissipative Particle Dynamics

1. P.V.Coveney *et al.*, SIMU Newsletter, **1**, 73.
http://simu.ulb.ac.be/newsletters/newsletter.html

2. Pep Espagnol has many other papers on DPD, all of which are down-loadable from his web-site
http://www.fisfun.uned.es/~pep/pep.html

IX.12 Polymers

1. Hierarchical Modelling of Polymers, Review article by D. N. Theodorou, *SIMU* newsletter **1**
http://simu.ulb.ac.be/newsletters/newsletter.html

2. See Doros Teodorou's web-page for more information
http://tahoe.chemeng.upatras.gr/

3. Downloadable publications and theses of the theory group (led by Kurt Kremer) of the Max Planc Institute for Polymer Research are available at http://www.mpip-mainz.mpg.de/theory.html

IX.13 Protein models and molecular evolution

1. A statistical mechanical approach to protein molecular evolution, M. Deem, *SIMU* newsletter **2**
   http://simu.ulb.ac.be/newsletters/newsletter.html
2. Michael Deems web-site
   http://www.mwdeem.chemeng.ucla.edu
3. A surprising simplcity to protein folding', D. Baker, Nature, **405**, pp 39 (2000)
4. Heteropolymer freezing and design: Towards physical models of protein folding", V. S. Pande, A. Yu. Grosberg and T. Tanaka, Rev. Mod. Physics **72**, pp 259 (2000).

IX.14 Miscellany

1. Wavelets and multiscale methods in numerical analysis and simulation, a European Commision TMR programme specialising PDE's and integral equations
   http://dragon.ian.pv.cnr.it/~wavelet/
2. Dictionary of scientific quotations
   http://naturalscience.com/dsqhome.html
3. The Ψ_k newsletter, Ab-initio (from electronic structure) calculation of complex processes in materials, which is supported by the European Science Foundation,
   http://psi-k.dl.ac.uk/
4. The CCP3 Surface Science newsletter, see
   http://www.cse.clrc.ac.uk/Activity/CCP3