Parallel computing and molecular dynamics of biological membranes

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In this talk I discuss the general question of the portability of Molecular Dynamics codes for diffusive systems on parallel computers of the APE family. The intrinsic single precision arithmetics of the today available APE platforms does not seem to affect the numerical accuracy of the simulations, while the absence of integer addressing from CPU to individual nodes puts strong constraints on the possible programming strategies. Liquids can be very satisfactorily simulated using the “systolic” method. For more complex systems, like the biological ones at which we are ultimately interested in, the “domain decomposition” approach is best suited to beat the quadratic growth of the inter-molecular computational time with the number of elementary components of the system. The promising perspectives of using this strategy for extensive simulations of lipid bilayers are briefly reviewed.

1. Introduction

In simulating the behaviour of microscopic systems Molecular Dynamics (MD) faces two major problems. One is the intrinsic limitation coming from the use of classical mechanics to describe the dynamics of the “elementary” components of the system [1]. The second, not less important, is of practical nature and it has to do with the finiteness of computer resources available at any time. In recent investigations [2] [3] we addressed the second of these questions, showing that parallel computers, particularly of the APE family [4], can be successfully employed to speed up in a substantial way MD simulations of diffusive systems, i.e. of systems in which the “list” of atoms that have a non-negligible interaction with a given atom of the system changes with time. In a solid (or in Lattice Quantum Chromo-Dynamics - LQCD) the “list” is blocked and is assigned once for all at the beginning of the simulation.

Static and dynamic properties of liquids can be adequately studied [2], using the “systolic” method [3]. For the more complex case of lipid bilayers we have developed new approaches, adapting to these systems the general “domain decomposition” strategy. The latter has the virtue of leading to CPU times for the computation of the inter-molecular potential that (at constant density) grow only linearly with the number of atoms.

2. Liquid Butane

As a first significant test case, we have studied in great detail liquid butane (C₄H₁₀) [3], using a standard Multiple Time Step (MTS) integration algorithm [1] (with a “long” integration time step Δtₐ = 4 fs and a partition number Pₜ = 8). The results of the simulation of the time evolution of a system of M = 512 molecules confirm that for a homogeneous diffusive system the “systolic” method [3] is well suited for massive parallel production. The method consists in computing the inter-molecular (Lennard-Jones) interactions between atoms belonging to different molecules, by first democraticaly distributing in bunches among the N nodes of the machine the molecules of the system. Coordinates and momenta of the N bunches of molecules are copied in transitory arrays and circulated through nodes. By bringing them successively in contact with the node-residing molecules, the crossed interaction terms are all computed in N − 1 moves. The method does not beat the M² growth of the inter-molecular computational time, but decreases it by a factor equal to the number of nodes.

On the 512-nodes APE configuration (Torre) it took in all 450 hours of CPU time to collect the
whole statistics of 10 ns presented in [2]. Computer times of this size are certainly within the current standards of MD and LQCD simulations. For comparison, a system of 256 molecules has been simulated, in double precision, on a DIGITAL 200 4/233 α-station. To give an approximate reference figure we may quote a factor of 50, as a gain in speed in going from the α-station to the Torre.

Our code was written in TAO, the APE highest level language. However APE simulation times can be substantially reduced (by a factor from 3 to 4), if the APE-assembler micro-code of the most time-consuming part of the program, where the inter-molecular forces are computed, is properly optimized.

3. Towards simulating realistic membranes

Simulating realistic cell membranes and studying their interaction with small peptides (mimicking pharmaceuticals of possible therapeutic interest) is of the utmost importance, if not for immediate medical use, certainly for the development of new conceptual and practical tools in MD applications to biological systems. A lot of work has gone in this direction (see e.g. [10] and references therein), but we are still far from having a viable tool-kit for immediate practical use.

Schematically a cell membrane is constituted by an almost spherical bilayer of phospholipidic molecules, separating the interior of the cell from the external world. Various kinds of peptides and proteins, responsible for the biochemical processes necessary for the life and the functionality of the cell, are plugged into the membrane.

Phospholipids are large Y-shaped molecules (with more than 30 atoms, not counting carbon bound hydrogens) with a hydrophilic head and two hydrophobic tails. This hydrophobicity configuration leads to a well defined bilayer 3-D structure: the hydrophilic heads are in contact with water, present both outside and inside the cell, while the hydrophobic tails are more or less back-to-back pair-wise aligned.

An important parameter governing the reaction rate of many biological processes taking place in the membrane is its "permeability". In this respect a membrane can be regarded as a liquid crystal, with a permeability which depends "critically" on the temperature, on the detailed chemical composition of the constituent phospholipids and on the concentration of chemicals dispersed in the membrane itself or in the solvent.

Even from this very crude picture, it is clear that a detailed simulation of the dynamics of the membrane of a living cell is just impossible and we have to resort to a number of simplifications. As it appears experimentally that the nature and the location of the phase transitions, which control the physico-chemical properties of the membrane, are related to the bulk ordering properties of the hydrophobic tails, a first step in the direction of simulating a realistic system is to take...
a sufficiently large bilayer in a aqueous medium and begin to study 1) the behaviour of the relevant order parameters as functions of the temperature, 2) the dependence of the position of critical points upon the concentration of small intramembrane peptides.

We have started our investigation with a system of $2 \times 256$ Dimyristoyl-phosphatidylcholine (DMPC) molecules (each molecule is composed by 37 atoms) in vacuum, neglecting in these first trial simulations Coulomb interactions. We have run the dynamics of the system at various temperatures on the Torre. In each run the history of the system was followed for several hundreds ps (plus equilibration). At very low temperatures ($T < 200$ K) the system appears to be stable, although we know that, lacking Coulomb interactions and in absence of solvent, it is actually unstable and expected to “explode” at higher $T$.

Already in this oversimplified test case CPU simulation times are exceedingly large, as the computation of the inter-molecular forces require the evaluation of a daring $(2 \times 256 \times 37)^2/2$ terms! Since the vast majority of them gives a negligibly small contribution to the forces (the Lennard-Jones potential decreases very fast with the distance), the obvious way to cope with this problem is to avoid computing the very many effectively irrelevant terms. To this end the physical space in which the system lives is first decomposed into $N$ domains, each one attributed to one of the nodes of the machine. The domains are in turn subdivided in cells. The number of cells in each domain and, hence, the spatial extension of each cell, is chosen so that the interaction between atoms residing in non-nearest-neighboring cells is negligibly small. Then inter-molecular interactions are computed only between the atoms of a cell and those of the 26/2 nearest neighboring ones. Every $N_{\text{remap}}$ integration steps, the coordinates of all the molecules are cross-checked node by node and, if necessary, molecules that have wandered away from the original cell are reassigned to the cell to which they came up to belong. The remapping of the system costs a time which only growth linearly with the number of particles.

A problem with this approach on APE platforms is the lack of integer addressing to individual nodes, which makes impossible to assign locally to each node the set of indices representing the number of interaction terms to be computed between pairs of cells. This difficulty has been overcome by assigning to all nodes the same set of indices, namely the set of the largest values taken by them throughout the machine. Nodes with fewer than the maximal number of terms to be computed will wait until other nodes have finished their job.

We have fully implemented these ideas on APE computers in the case of butane, obtaining the expected linear behaviour with the number, $n$, of interacting particles and a perfect scalability with the number of nodes in going from the Cubetto ($N = 2^3$) to the Torre ($N = 2^9$). CPU times for simulating the dynamics of a system of 2048 molecules of butane for 1 ns with our standard MTS algorithm were measured on the Digital 200 4/233 $\alpha$-station, the Cubetto and the Torre, obtaining

\[
T_{\alpha-CPU} = 2.3 \cdot 10^{-4}[2.3n + \frac{6 \cdot 10^{-3}}{N_{\text{update}}}]^2 \text{ days}
\]

\[
T_{\text{Cubetto}} = 2.3 \cdot 10^{-4}[3.4n + \frac{0.72}{N_{\text{remap}}}] \text{ days}
\]

\[
T_{\text{Torre}} = 2.3 \cdot 10^{-5}[5.4n + \frac{1.4}{N_{\text{remap}}}] \text{ days}
\]

Eqs. are plotted in Fig. 2 as functions of $n$. Notice that in the case of the $\alpha$-station we have used the “list” method.
to speed up the simulation. As the list updating time grows quadratically with $n$, for a sufficiently large number of atoms the “list” method curve will always cross the “domain decomposition” straight line.

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