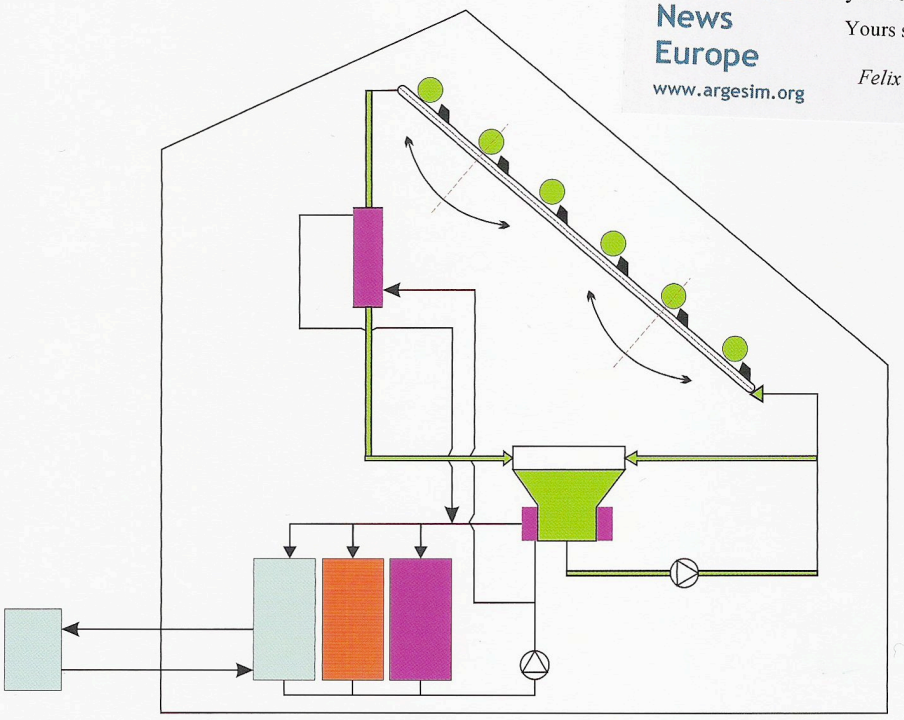
SNE SIMULATION NEWS EUROPE



Volume 17 Number 3/4 December 2007, ISSN 0929-2268

Journal on Developments and Trends in Modelling and Simulation

Membership Journal for Simulation Societies in EUROSIM

ARGESIM

SNE 17/3-4, December 2007

SHORT NOTES

Particle Dynamics Simulation at Atomic Scale: Molecular Dynamics

Lukas D. Schuler, xirrus GmbH, Switzerland, *lukas.schuler@xirrus.ch*

In this introduction we recognize Molecular Dynamics (MD) simulation as an established method. To bridge the gap between the atomic world of substances and their measurable physical properties in the visible world, MD has been developed since 50 years [1, 2]. The main challenges of MD simulations are to calculate – through the means of statistical mechanics – thermodynamic properties of (or within) liquids [3] and give us insight and explanation of the dynamics. We provide some examples for explanation.

Introduction

In nowadays' practice, we are able to use Molecular Dynamics (MD) simulation to

- examine the dynamics of individual atoms, simple molecules, or larger structures in interaction,
- perform structural refinement of experimentally measured data,
- investigate changes in structure, e.g. protein folding.

Most often, we apply MD to molecules in solution. Some experimental data has been measured, but this did not explain all the details. MD provides then insight into the invisible, i.e. not measurable situations and processes.

1 Molecular model

A molecular model is based on the choice of

- atomic particles,
- interactions between particles,
- propagation dynamics,
- boundary conditions.

1.1 Atomic Particles

The elementary particles defined in classical Molecular Dynamics are atoms. An MD atom corresponds to a chemical element of the periodic table, consisting of its mass, a partial charge (if any), its current position and its velocity in 3D-space.

1.2 Interactions between particles

Non-bonded terms

Figure 1 shows that atoms interact strongly repulsive if they overlap. At intermediate separation, the interaction is attractive, and at larger separation, atoms lose contact and cannot notice each other. The parameter σ can be thought of as the size of an atom, and ε as the fluffiness of the electron cloud. These parameters are not determined a priori by some physical facts and have to be derived and optimized specifically for the simulation model.

For charged particles, an electrostatic potential is added to the potential energy function. They sum up to the non-bonded potential V as a function of the distance r_{ij} between particle i and j, the respective parameters for σ_{ij} and ε_{ij} and their individual partial charges q_i and q_j (eq. 1). ε_0 is the electric field constant.

$$V = \underbrace{4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]}_{\text{Lennard-Jones Potential (Figure 1)}} + \underbrace{\frac{q_i q_j}{4\pi\varepsilon_0}\left[\frac{1}{r_{ij}}\right]}_{\text{Electrostatic Potential}} \qquad (1)$$

Bonded terms

If atoms are connected by chemical bonds, the non-bonded interaction is replaced by bonded interactions. Dynamics of chemical bonds (vibrations), however, are usually not of interest. So bonded atoms are constrained at a fixed bond length.

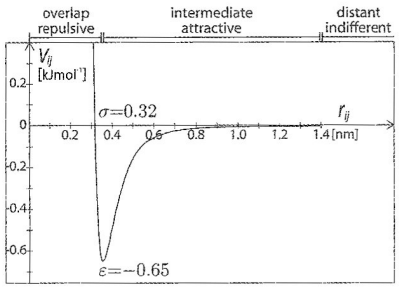


Figure 1. Example of a potential energy function for oxygen atoms of water molecules [4].

In analogy to the chemical bonds, additional interactions are introduced, that keep molecules in geometrical shape, e.g. for bond angles or torsions. These potentials are chosen to fulfill basic chemical characteristics, and convenient numerical properties instead of creating perfect physical representations of molecular situations.

The underlying parameter set determines how well experimental properties are reproduced.

1.3 Propagation dynamics

To advance the system for simulation, its particles are propagated in discrete time steps. For each time step in the range of femtoseconds (10^{-15}s) we apply the integration scheme:

- From the interaction functions, we derive the forces acting on individual particles according to their current positions.
- The forces provide us with the changes in velocities according to Newton's equation of motion.
- We derive new positions of the particles from their velocities.

This scheme is looped over the total simulation period.

1.4 Boundary conditions

During the simulation some global constraints are enforced. These are called boundary conditions.

Thermodynamic constraints. To obtain correct thermodynamic properties of the system, the propagation scheme must obey some restrictions: it shall be energy-conservative and time-reversible.

Spatial constraints. MD systems are confined in a small volume (of nanometer scale). Simulation in vacuum shows finite size effects – think of surface tension in a droplet, an effect we usually do not want to investigate.

To eliminate surface effects at all, we apply periodic boundary conditions. For example, a cubic box is virtually replicated in every dimension, so that the total system size is virtually infinite and boundaryless. For this to work properly, the box shall be large enough to separate any particle from its own effects in another replication.

Experimental restraints. Experimental methods such as *X-Ray crystallography* or *nuclear magnetic resonance (NMR)* are a means of obtaining structural data such as interatomic distances. Often, these data are not sufficient to derive full molecular structures. However, such data can be introduced into simulation as non-physical forces that drive simulated molecules to obey the experimental data.

Virtual restraints. We may also introduce any virtual potential that drives our molecule into a position or conformation we like to investigate. Virtual restraints can be subtracted after the simulation without affecting the results. This is a main advantage over experiment.

1.5 Time saving approximations

The expense to represent a system in simulation increases with the number of particles in it. Although increasing, computational power is the limiting factor for system size and simulated time. To make MD simulation more computationally efficient, we employ some tricks without negatively affecting the results, e.g.

Cut-off. The potential energy function is calculated below a certain distance only (i.e. 1.4 nm in Figure 1) without loosing much accuracy. This saves the need to calculate many interactions of negligible energy contribution.

Longer time steps advance the system further at the same computational expense. Still, the parts of interest moving fastest must be sampled smoothly.

United atoms are ball-shaped parts of molecules like hydrocarbons, e.g. CH_3 and CH_2 that are modeled as one atom instead of several [5]. This reduces the number of particles in the system.

2 Determination and validation of parameters

2.1 Parametrisation

Parameters like ε, σ and q in (1) need to be determined to yield simulation results in agreement with experiment. To do so, we used many linear, cyclic and branched hydrocarbon molecules to yield experimental densities. Think again of σ as the size of a particle. If we grow the particles confined in a box at constant volume, the pressure will rise. By adjusting the σ parameter of equation (1) for the corresponding united atoms [5], we are able to set the correct experimental density.

2.2 Validation

The obtained parameters were validated against the heat of vaporization, the energy necessary to evapo-

rate the pure liquid (H_{vap}, eq. (2)), and the free energy of hydration, the free energy it takes to solve the substance in water (F_{hyd}, eq. (3)). Let me explain how we can calculate these macroscopic properties by microscopic simulation.

Heat of vaporization

$$H_{vap} = V_{(g)} - V_{(l)} + RT \quad (2)$$

In equation 2, the average total potential molecular energy of the liquid phase $V_{(l)}$ is subtracted from the average total potential molecular energy in the gas phase $V_{(g)}$. $V_{(g)}$ basically lacks the intermolecular contacts, whose energy is extracted by the subtraction. RT, where R is the gas constant and T is the temperature, accounts for the volume expansion at evaporation according to the ideal gas equation.

We simulated a box of liquid molecules and calculated their potential energy. After that we expanded the coordinates of every individual molecule into a box of 100 times the size to avoid intermolecular contacts. We obtained the potential energy for the gas.

Free energy of hydration

$$F_{hyd} = \int_0^1 d\lambda \langle \partial E / \partial \lambda \rangle_\lambda \quad (3)$$

Let us say a molecule that interacts with surrounding water is in state A ($\lambda = 1$). When its interactions with the water molecules are switched off, it is in state B ($\lambda = 0$). The thermodynamic coupling parameter λ is used to change state A into state B in small steps. Individual MD simulations are carried out at a number of different λ values and the average of the derivative of the total energy E with respect to λ is calculated. The free energy of hydration is then obtained by numerically integrating from $\lambda = 0$ to 1.

Units in [kJ/mol]	Heat of vaporization		Free energy of hydration	
	exp	sim	exp	sim
Pentane	26.4	26.2	9.8	10.2
Cyclopentane	28.5	27.7	5.0	5.1
Isopentane	24.9	25.0	10.0	11.4

Table 1. Example results for hydrocarbon chains of 5 connected united-atoms. Taken from [5].

Table 1 shows that obtained results are in excellent agreement with experiment (within the accuracy reachable by MD simulation) and promising for the use of this parameter set for mixed hydrocarbons, and in water solution.

Experimentalists have collected data of similar branched molecules. The two molecules in Figure 2 differ by one united atom (CH_3). In simulation, the molecule to the left crystallizes, whereas the one to the right stays liquid at room temperature. This finding is again in agreement with experiment.

So far, we looked at *uncharged* atoms.

2.3 Polar molecules

Most biological or chemical molecules are built of additional atoms like oxygen, nitrogen, sulfur or phosphor. They carry partial charges what makes these molecules polar. E.g. oxygen atoms (O) are modeled with partial negative charge, such as in acetic acid (Figure 3).

Note that hydrogens that carry partial charges are treated explicitly and excluded from united atoms.

3 Lipid aggregate simulation

We performed the parametrisation in [5] with regard to lipid simulations. Lipids consist of a polar head group and a non-polar tail. The head group contains partial charges similar to Figure 3 and is attractive to water molecules, that do have partial charges as well. The tail consists of long hydrocarbon chains, similar to pentane in Table 1, and is uncharged. Fatty acids and soap are some examples of lipids.

When dissolved in water, lipids tend to aggregate, as the non-polar tails do not like being exposed to water. In experiment, lipid aggregation depends on the concentration of lipids and salt in aqueous solution, and on their size. In solution, nearly spherical aggregates of lipids are known as *micelles*. We simulated several lipid aggregates [7] under different conditions.

One micelle consisted of 90 lipids with a tail length of 12 carbons. Another one consisted of 64 of the

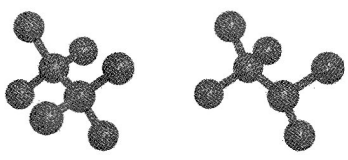


Figure 2. The molecules to the left are solid, the ones to the right liquid at room temperature.

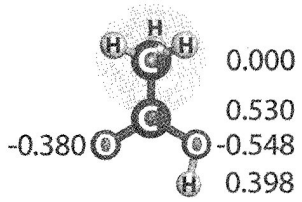


Figure 3. Acetic acid. The partial charges sum up to the total charge of the molecule, which is neutral (zero) here. The charge numbers shown are taken from glutamic acid in [6]. CH_3 is indicated as united atom.

same lipids. The aggregate containing more lipids was more stable in simulation. This is not the case if the lipid tail is shorter, containing only 8 carbon atoms. With 90 molecules in the micelle, its structure is not maintained. Some lipids start to diffuse completely into solution.

This finding was supported by experiment, which assumes an ideal aggregation for the shorter tails containing 43+/-5 lipids, way below 90.

Structural dynamics

We have analyzed whether the tail ends prefer to reside near the center or not, for the stable micelles. The lipid tail end (united atom type CH_3) appears up to close to the head group (oxygen atoms). This finding illustrates that lipids within these structures are able to expose their tails to the surface. This is not the case in simulations of the same lipids in lipid membranes – a more crystalline lipid aggregate structure.

The diffusion coefficient for the lipids was calculated from our simulation to be $2 \cdot 10^{-6} cm^2 s^{-1}$. It is in the expected range for other lipids measured experimentally. For comparison, this is about ten times slower than self-diffusion of water.

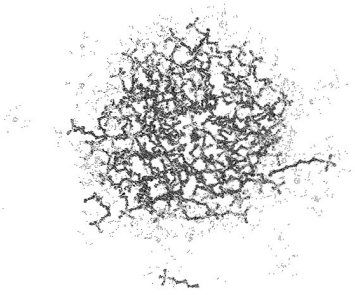


Figure 4: An aggregate of 90 lipid molecules and sodium ions with surrounding water molecules after 3 ns. Initially, all 90 lipids have been placed within the aggregate structure. Three lipids (to the lower left, right and at the bottom) have visibly left the micelle.

4 Conclusion

We use Molecular Dynamics simulation (MD) to investigate a vast variety of molecules on atomic resolution. With the appropriate choice of interaction parameters, we are able to

- reproduce experimental findings while providing atomic detail,
- explain phenomena not accessible by experiments,
- better understand the chemical and biological mechanisms that build our world.

Acknowledgements

We would like to acknowledge Philippe Hünenberger for his inspiring talk and Wilfred van Gunsteren inviting us to his 60th birthday symposium.

References

[1] B. J. Alder, T. E. Wainwright: *Phase transitions for hard sphere system.* Journal of Chemical Physics, 27, pp 1208-1209, 1957.

[2] B. J. Alder, T. E. Wainwright: *Phase transitions for hard sphere system.* In (I. Prigogine, ed.) Proc. International Symposium on Statistical Mechanical Theory of Transport Processes (Brussels, 1956), Interscience, New York, 1958.

[3] M. P. Allen, D. Tildesley: *Computer simulation of Liquids.* Clarendon Press, Oxford, 1987.

[4] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, J. Hermans: *Interaction models for water in relation to protein hydration.* In (B. Pullmann, Reidel eds.) Dordrecht, 1981.

[5] L. D. Schuler, X. Daura, W. F. van Gunsteren: *An Improved GROMOS96 Force Field for Aliphatic Hydrocarbons in the Condensed Phase.* Journal of Computational Chemistry, 22, pp 1205-1218, 2001.

[6] W.F. van Gunsteren, S.R. Billeter, A.A. Eising, P.H. Hünenberger, P. Krüger, A.E. Mark, W.R.P. Scott, I.G. Tironi: *Biomolecular Simulation: The GROMOS96 Manual and User Guide.* Vdf Hochschulverlag AG, Zürich, 1996

[7] L.D. Schuler, P. Walde, P.L. Luisi, W.F. van Gunsteren: *Molecular dynamics simulation of n-dodecyl phosphate aggregate structures.* European Biophysics Journal, 30, 330-343, 2001.

Corresponding author: Lukas D. Schuller
xirrus Simulation GmbH
Buchzelgstrasse 36, CH-8053 Zürich, Switzerland
lukas.schuler@xirrus.ch

Received: September 5, 2007
Revised: October 8, 2007
Accepted: October 15, 2007