

CHAPTER 2

THEORY

2.1 Molecular Dynamics

Molecular dynamics (MD) simulations has become one of the important tools in the research areas of biology, chemistry and physics. It combines the principles of statistical mechanics and classical physics for the examination of molecular systems at atomic detail. MD is the time dependent integration of the classical equations of motion. The equations of motion are of sufficient complexity that the integration must be done numerically over a large number of very small discrete time-steps rather than analytically in a continuous fashion.²⁶ The most common MD algorithm is relied on the numerical solution of Newton's equation of motion, which allows both equilibrium thermodynamic and dynamical properties of a system at finite temperature to be computed.²⁷

An important issue of simulation studies is the accessible time and length-scale covered by microscopic simulations. Figure 2.1,²⁸ shows a schematic representation for different types of simulations in a length-time-diagram. It is clear that the more detailed a simulation technique operates, the smaller is the accessibility of long times and large length scales. Therefore quantum simulations, where fast motions of electrons are taken into account, are located in the lower left corner of the diagram and typical length and time.



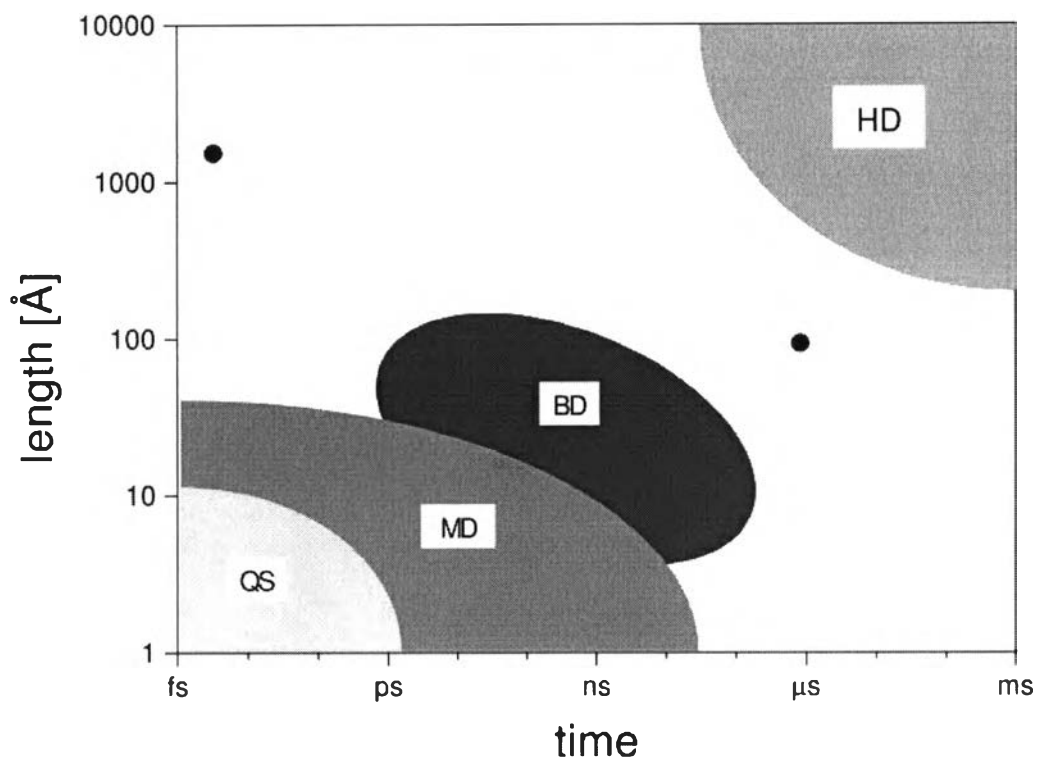


FIGURE 2.1 Schematic comparison of time- and length-scales, accessible to different types of simulation techniques (quantum simulations (QM), molecular dynamics (MD), Brownian dynamics (BD) and hydrodynamics/fluid dynamics (HD)). The black dots mark the longest ($\approx 1 \mu\text{s}$) and the biggest ($N > 5 \times 10^9$, $L \approx 0.4 \mu\text{m}$) molecular dynamics simulations).



In the MD simulation, the initial coordinates and velocities of each atom in the system are needed. In order to calculate force acting on each particle, the classical equation of motion consisting of N particles (Eq.2.1) needs to be solved. The second law of the classical Newton's equation²⁶ is given by

$$m_i \frac{d^2 r_i}{dt^2} = f_i = -\nabla_{r_i} U(r_1, r_2, \dots, r_N) \quad (2.1)$$

Where $U(r_1, r_2, \dots, r_N)$ is the interatomic potential energy function of coordinate of N particles which consist of energy and non-bonded energy. f_i is the force acting on i^{th} atoms. m_i is the particle mass. To compute U , it is known as the N -body problem which cannot be solved exactly. In practice, the interatomic potential energy in Eq. 2.1 is commonly computed based on the two-body approximation. Particularly for large biomolecular systems, molecular mechanical (MM) force field method is employed rather than quantum mechanical (QM) approach.²⁹

2.2 Molecular mechanics force fields

A force field is a mathematical expression describing the dependence of the energy of a system on the coordinates of its particles.³⁰ Widely used mathematical model for the potential energy of a molecular system consists of six types of interactions.³¹

$$U = \underbrace{V_{LJ} + V_{EL}}_{U_{non-bonded}} + \underbrace{V_{BS} + V_{AB} + V_{PT} + V_{IT}}_{U_{bonded}} \quad (2.2)$$

The non-bonded interaction represents the sum of pair-wise interaction energies of all possible interacting non-bonded between atom two atoms.³² The first represent V_{LJ} that the Lennard-Jones potential that has an attractive part representing the van der Waals energy and a repulsive part representing the Pauli repulsion

$$V_{LJ} = \frac{1}{2} \sum_{i,j,i \neq j} 4\epsilon \left[\left(\frac{\sigma_{ij}}{R_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{R_{ij}} \right)^6 \right] \quad (2.3)$$

where, R_{ij} is the distance between the atom i and atom j , ϵ_{ij} is the van der Waals dissociation energy, and σ_{ij} is the collision diameter between atom i and atom j . Dissociation energy is equal to the amount of energy needed to pull a pair of atoms in the strongest van der Waals in the binding state. The power of the negative term that sometimes also called the London dispersion force. The collision diameter is approximately the distance at which a pair of atoms bounces off from each other in anormal, non-reacting condensed state.

V_{EL} , is the electrostatic potential energy that describes the force resulting from the interaction between two partial charge particles q_i and q_j . The energy between atoms i and j is expressed according to Coulomb's Law

$$V_{EL} = \frac{1}{2} \sum_{i,j,i \neq j} \frac{q_i q_j}{R_{ij}} \quad (2.4)$$

Where q_i is the charge of the atom i . Compared with the van der Waals potential, the electrostatic potential is a stronger, more long-rang interaction.

The bonded interactions,³² which maintain the bond lengths, the bond angles and the dihedral angles so that chemical groups will remain sterically stable in an MD simulation.³² Which V_{BS} , V_{AB} , V_{PT} and V_{IT} are the bond stretching energy, angle-bending energy, torsion energy, respectively. V_{BS} is the bond-stretching energy standing for the elastic interaction between a pair of atoms connected by a covalent bond followed in Eq2.5.



$$V_{BS} = \frac{1}{2} \sum_{m \in \text{bonds}} k_m^l (l_m - l_m^0)^2 \quad (2.5)$$

Where, l_m is the distance between the two atoms of the m^{th} bond, l_m^0 is the equilibrium bond length, and k_m^l is the bond strength.

V_{AB} is the angle-bending energy standing for the interaction among three covalently bonded atoms that form a stable angle

$$V_{AB} = \frac{1}{2} \sum_{m \in \text{angles}} k_m^\theta (\theta_m - \theta_m^0)^2 \quad (2.6)$$

Where θ_m is the m^{th} angle between the two adjacent bonds that share a common atom, θ_m^0 is the equilibrium bond angle, and k_m^θ is the strength of bond angle bending.

V_{PT} and V_{IT} the proper and improper torsional energies standing for the interactions among four covalently-bonded atoms that form a stable proper and improper dihedral angle.

$$V_{PT} = \frac{1}{2} \sum_{m \in \text{torsions}} V_m [1 + \cos(n_m \omega_m - \gamma_m)] \quad (2.7)$$

$$V_{IT} = \frac{1}{2} \sum_{m \in \text{torsions}} k_m^\xi (\xi_m - \xi_m^0)^2 \quad (2.8)$$

Where, ω_m is m dihedral angle between the two adjacent angles that share a common bond, n_m is the periodicity factor which determines the number of equilibrium dihedral angles in a 360° rotation, γ_m is the phase shift, V_m is the amplitude, ξ_m is the m improper dihedral angle among four atoms that are not bonded successively to one another, ξ_m^0 is the equilibrium improper dihedral angle, and k_m^ξ is the strength. Show in Figure 2.2³¹



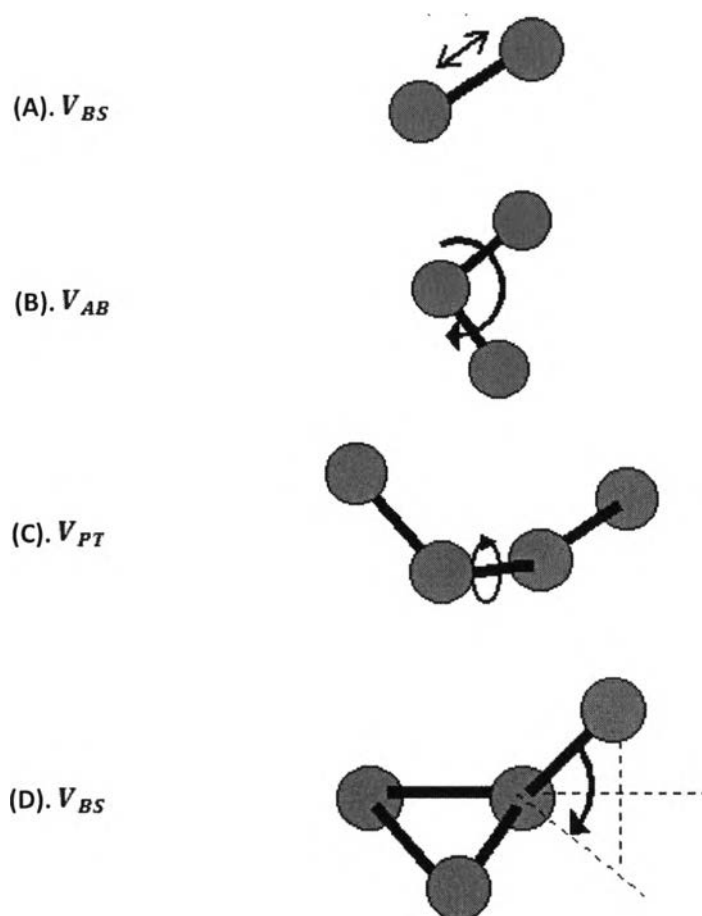


FIGURE 2.2 Schematic representation of (A) Bond-stretching force, (B) Angle-bending force, (C) Proper torsional force and (D) Improper torsional force.



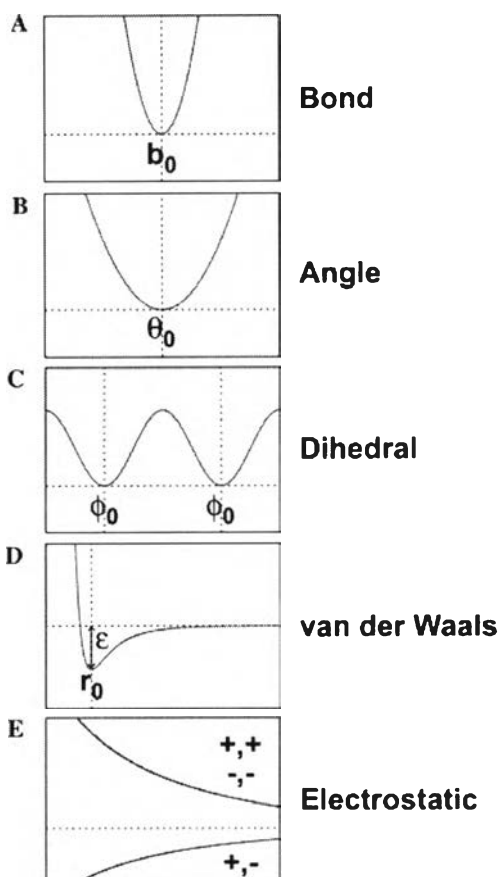


FIGURE 2.3 The potential energy function, U , that potential energy of each term is the y -axis. (A) The interaction energy of two bonded atoms as a function of the distance of their atomic centers with ideal distance b_0 as harmonic term. (B) The harmonic term, similar in form to (A), but of lower energy, that describes the interaction of two atoms bonded to a third atom as a function of the angle between them with the ideal angle θ_0 . (C) A typical periodic ($n=2$) cosine term with a minimum ϕ_0 at 0 used to describe both in- and out-of-plane dihedral angle energies. Plots (A–C) share the same range for energy. (D) The van der Waals interaction energy of two atoms with ϵ and r_0 the geometric mean of their respective ϵ and r_0 . (E) Three typical electrostatic interactions. The top line idealizes the interaction of charges with like signs while the bottom line idealizes the interaction of two charges with different signs. The sum of (D–E) constitutes the non-bonded interaction energy of two atomic centers.³²

2.3 Expansion based integration algorithm

A number of integration algorithms using finite difference techniques are available to solve the Newton's equation for MD simulation in Equation 2.1. Basically, MD trajectory is divided into several small stages and small enough time step δt . The simple class of integrators is called Verlet-Störmer integrator that expands the positions and velocities in a Taylor series as follows.³³

$$v(t + \delta t) = v(t) + a(t)\delta t + \frac{1}{2}b(t)\delta t^2 + \frac{1}{6}c(t)\delta t^3 + \dots \quad (2.9)$$

$$r(t + \delta t) = r(t) + v(t)\delta t + \frac{1}{2}a(t)\delta t^2 + \frac{1}{6}b(t)\delta t^3 + \dots \quad (2.10)$$

Where a, b, c are the 2nd, 3rd and 4th time derivative of the coordinates. In the same way, the expansion may be performed for $\delta t \rightarrow -\delta t$, which gives

$$r(t - \delta t) = r(t) - v(t)\delta t + \frac{1}{2}a(t)\delta t^2 - \frac{1}{6}b(t)\delta t^3 \pm \dots \quad (2.11)$$

$$v(t - \delta t) = v(t) - a(t)\delta t + \frac{1}{2}b(t)\delta t^2 - \frac{1}{6}c(t)\delta t^3 \pm \dots \quad (2.12)$$



Eqs 2.8 and 2.10 as well as Eqs 2.9 and 2.11, give for the new positions and velocities.

$$r(t + \delta t) = 2r(t) - r(t - \delta t) + a(t)\delta t^2 + O(\delta t^4) \quad (2.13)$$

$$v(t + \delta t) = 2v(t) - v(t - \delta t) + b(t)\delta t^2 + O(\delta t^4) \quad (2.14)$$

δt^{n+1} , n -th order method are truncation errors. Eq.2.12 and 2.13 are therefore of 3rd order. The drawback of Eq.13 is, however, that it requires the 3rd derivative of the coordinates with respect to time which is not routinely calculated in MD simulations and thus introduces some additional computational and storage overhead. To overcome this drawback one can simply subtract Eq.2.10 from Eq.2.8, giving the central difference scheme for the velocity

$$v(t) = \frac{1}{2\delta t} (r(t + \delta t) - r(t - \delta t) + O(\delta t^3)) \quad (2.15)$$

Eq.2.12 and 2.14 are not optimal, since information is required from positions not only at time t but also at time $t - \delta t$. Thus an equivalent algorithm, which stores only information from one time-step is the so called *velocity verlet algorithm*:

$$r(t + \delta t) = r(t) + v(t)\delta t + \frac{1}{2}a(t)\delta t^2 \quad (2.16)$$

$$v(t + \delta t) = v(t) + \frac{1}{2}\delta t(a(t) + a(t + \delta t)) \quad (2.17)$$



At the timestep $t + \delta t$. Eq16. can be divided into two steps, First calculate

$$v\left(t + \frac{\delta t}{2}\right) = v(t) + \frac{1}{2}\delta t a(t) \quad (2.18)$$

And then computed the actual forces on the particles at time $t + \delta t$ and finish the velocity calculation with

$$v(t + \delta t) = v\left(t + \frac{\delta t}{2}\right) + \frac{1}{2}a(t + \delta t) \quad (2.19)$$

2.4 The Periodic boundary conditions (PBC)

Periodic boundary is a computational technique that introduces repeating unit cells into a simulation system. With PBC, the system which consists of only a few hundred atoms behave as if it was infinite in size. Due to the effect of the surface that any finite sample of matter must have, and which ensure that the internal structure of the sample is dominated by surface rather than bulk forces, Thus necessaries to remove this effect. Primary cell is paticle are generate in Volume V . All atoms in primary cell are replicated in all direction to form an infinite lattice of image cell (Figure 2.4). Image cells have the same size and shape of the primary cell. In open boundaries, particles can freely enter or leave any cell. When a particle moves out of the cell, its image particle will enter the cell at the opposite site. The number of image cells needed depends on the range of intermolecular forces.³⁴



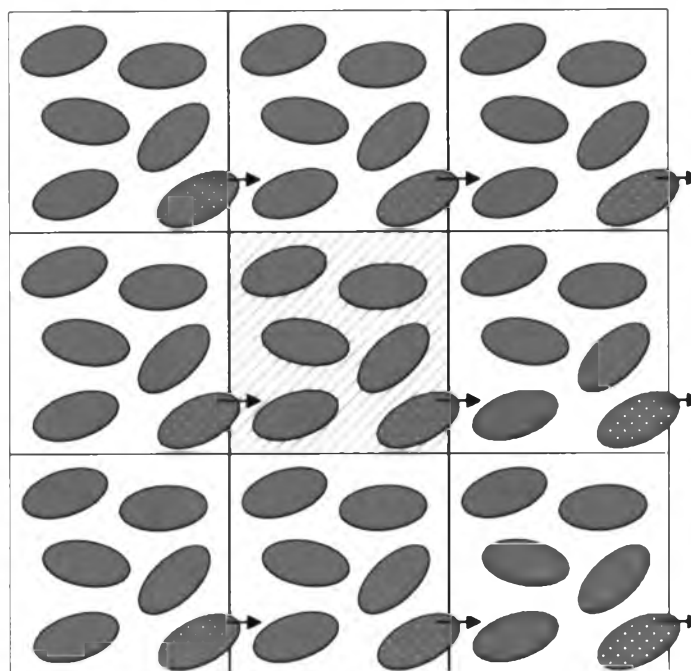


FIGURE 2.4 Periodic boundary condition in two dimensions with the primary cell surrounded by its image cells. Molecules that leave the cell will be replaced by their images entering the cell from the opposite side.³⁴

2.5 The Particle Mesh Ewald (PME)

Particle-mesh Ewald (PME)³⁵ method is often employed to correct the long-range interactions in the simulation with PBC as well as to reduce the computational cost required in the calculation. The Particle Mesh Ewald method calculate direct-space interactions involve electrostatic interactions of macromolecules system using a modification of Coulomb's Law in periordic broundary condition and to build a "mesh" of charges, interpolated onto a grid using Fourier transform in reciprocal space. It is from this charge interpolation that long-range forces can be calculated and incorporated into the non-bonded interactions in a simulation system. PME concept that Poisson equation can be solved much more efficiently distribution of the charges in a mesh. Thus, the three dimension grid of particle mesh is created in the system over the distribution of the system charge. After that, the forces and potentials of atoms are determined from this charge. It's note that the grid size should be not too small in order to reproduce accurately charge distribution. The basic idea of particle mesh Ewald summation is to replace the direct summation of interaction energies between point particles.

The PME method is best suited of systems, when physical systems require the imposition of periodic symmetry that can be simulated as infinite in spatial extent.

