Potential energy surface and molecular dynamics simulations

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Potential Energy Surface

• A potential energy surface is a mathematical function that gives the energy of a molecule as a function of its geometry.
  • Does not change if it translated or rotated in space
  • Depends on a molecule’s internal coordinates
  • Internal coordinates may be represented by simple stretch, bend, torsion, or normal model, etc.

• Quantum Mechanics provides an energy function which can be exact in principle and works for any molecule. In practice, approximate quantum methods are used due to computational expense.

• Molecular Mechanics provides this energy as a function of stretches, bends, torsions, etc. This is an approximate model that breaks down in some situations (e.g., breaking bonds). Only works when parameters are available.
Potential Energy Surface & Quantum Mechanics

3N (or 3N-6 or 3N-5) Dimension PES for N-atom system

How do we obtain the potential energy $E$?
- MM: Evaluate analytic functions (FF)
- QM: Solve Schrödinger equation

For geometry optimization, evaluate $E$, $E'$ (& $E''$) at the input structure $\mathbf{X}$ ($x_1, y_1, z_1, \ldots, x_i, y_i, z_i, \ldots, x_N, y_N, z_N$) or $\{l_i, \theta_i, \omega_i\}$. 
Molecular Mechanics

- Simplest type of calculation
  - Used when systems are very large and approaches that are more accurate become too costly (in time and memory)

- Molecular Mechanics is a method to calculate the structure and energy of molecules based on nuclear motions.
  - Electrons are not considered explicitly
  - Will find optimum distribution once position of nuclei are known
  - Born-Oppenheimer approximation of Shrödinger equation
    - Nuclei are heavier and move slower than electrons
    - Nuclear motions (vibrations, rotations) can be studied separately
    - Electrons move fast enough to adjust to any nuclei movement

- Basic assumptions:
  - Each atom is represented by a particle \((m, R)\)
  - Chemical bond represented by a spring
  - Potential energy function described intramolecular phenomena and rely on empirically derived parameters
Classical description of interatomic potential

• Electrons are not present explicitly, they are introduced through the potential energy surface that is a function of atomic positions only (Born-Oppenheimer approximation).

• The potential energy surface, in turn, is approximated by an analytic function that gives the potential energy $U$ as a function of coordinates. Forces are obtained as the gradient of a potential energy function.

• The choice of a potential function that approximates the actual (unknown) solution of the Schrödinger equation is a difficult task.

• Design of the potential function and choice of the parameters is often based on fitting to available experimental data (e.g. equilibrium geometry of stable phases, cohesive energy, elastic moduli, vibrational frequencies, temperatures of the phase transitions, etc.).
Molecular Mechanics

- Interactions between atoms (Potential Energy Function) are represented by functions of distance, angle or dihedral.
- Collection of empirical parameters and potential functions is known as a force field.

\[ U = \text{Bond} + \text{Angle} + \text{Dihedral} + \text{van der Waals} + \text{Electrostatic} \]
Molecular Dynamics

- Potential function for MD$^{1,2}$

$$U = \text{Bond} + \text{Angle} + \text{Dihedral} + \text{van der Waals} + \text{Electrostatic}$$

Molecular Dynamics

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\[ U = \text{Bond} + \text{Angle} + \text{Dihedral} + \text{van der Waals} + \text{Electrostatic} \]

Molecular Dynamics

- Potential function for MD\textsuperscript{1,2}

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Molecular Dynamics

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Molecular Dynamics

- Potential function for MD\textsuperscript{1,2}

\[ U = \text{Bond} + \text{Angle} + \text{Dihedral} + \text{van der Waals} + \text{Electrostatic} \]

Molecular Dynamics

- Non-bonded components of potential function

\[ U_{nb} = \text{van der Waals} + \text{Electrostatic} \]

\[ \sum_{pairs \ i,j} \left[ c_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2c_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^6 \right] \]

\[ \sum_{pairs \ i,j} \left( \frac{q_i q_j}{r_{ij}} \right) \]

To a large degree, soft materials structure is dependent on non-bonded atomic interactions.
Molecular Dynamics

• Non-bonded components of potential function

\[ U_{nb} = \text{van der Waals} + \text{Electrostatic} \]

\[ \sum_{\text{pairs } i,j} \left[ e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^6 \right] \]

van der Waals

Electrostatic

\[ 332 \sum_{\text{pairs } i,j} \left( \frac{q_i q_j}{r_{ij}} \right) \]
Molecular Dynamics

• Non-bonded components of potential function

\[ U_{nb} = \text{van der Waals} + \text{Electrostatic} \]

\[ \sum_{\text{pairs } i,j} \left[ \epsilon_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2\epsilon_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{6} \right] \]

van der Waals

Electrostatic

\[ 332 \sum_{\text{pairs } i,j} \left( \frac{q_i q_j}{r_{ij}} \right) \]
Molecular Dynamics

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van der Waals:
\[ \sum_{\text{pairs } i,j} \left[ e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^6 \right] \]

Electrostatic:
\[ 332 \sum_{\text{pairs } i,j} \left( \frac{q_i q_j}{r_{ij}} \right) \]
Molecular Dynamics

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van der Waals

\[
\sum_{\text{pairs } i,j} \left[ e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^6 \right]
\]

Electrostatic

\[
332 \sum_{\text{pairs } i,j} \left( \frac{q_i q_j}{r_{ij}} \right)
\]
Partial Charges

\[ E_{total} = \sum_{bonds} k_b (r - r_0)^2 + \sum_{angles} k_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} V_n [1 + \cos (n\phi - \gamma)] + \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left( \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}} \right) \]

Static Partial Charges \((q_i, q_j)\) are typically parameterized for each molecule prior to simulation.

As a result, MD practitioners use \textit{ab initio} or semi-empirical quantum mechanical calculations to estimate partial charges:

- **RESP**: Restrained ElectroStatic Potential mapping
  - Uses \textit{ab initio} calculations to construct electrostatic potential map (MEP)
  - Least squares algorithm derives atom centered charges that best reproduces MEP
  - Charges then assigned to reduce error between \textit{ab initio} electrostatic potential map and that constructed from charge assignment – “buried” atoms restrained to minimize charge
  - Results depend on \textit{ab initio} QM method used to construct ESP
- **Semi-Emperical (AM1-BCC, CM1, CM2, Mulliken)**:
  - Semi-empirical partial charges assigned based on Core Repulsion Function (CRF) and orbital structures
  - Bond Charge Correction (BCC) attempts to distribute charge based on bonds to adjacent atoms
Test Case: Acetonitrile (ACN)

- Polar aprotic solvent – commonly used in organic synthesis
- Polarity affects solvent properties
- 4 Symmetrically unique atoms
  - 3 DoF for partial charge
  - 1 buried atom (C2)
- Subject of many previous simulation studies in which partial charges were calculated dating back to 1983

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<thead>
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<tbody>
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<td>-0.475</td>
<td>-0.56</td>
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<td>H</td>
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<td>0.117</td>
<td>0.190</td>
<td>0.1185</td>
<td>0.0707</td>
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</tbody>
</table>
Importance of partial charges

- Partial Charges \((q_i, q_j)\) are parameterized for each molecule prior to simulation
- Do not change during simulation – Born-Oppenheimer approximation
- We use \textit{ab initio} or semi-empirical calculations to estimate partial charges

Example: polyvinyl chloride (PVC):
- 2\textsuperscript{nd}/3\textsuperscript{rd} most common plastic worldwide
- Applications:
  - Automotive (dashboard & underbody coating)
  - Construction (flooring & window blinds)
  - Electronics (cable & wire insulation)
  - Medical (IV bags, gloves, & tubing)...

\[
\begin{align*}
\delta &= \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \\
\delta_{ele} &= \sqrt{\delta_p^2 + \delta_h^2} \\
\delta_{vdw} &= \delta_d \\

\text{Ref.} &= \frac{E_{ele} + E_{vdw}}{V} \\
\text{Simulation} &= \sqrt{\frac{E_{ele}}{V}} \sqrt{\frac{E_{vdw}}{V}}
\end{align*}
\]

<table>
<thead>
<tr>
<th>HSP (MPa(1/2))</th>
<th>Ref.</th>
<th>AM1-BCC</th>
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<td>10.2</td>
<td>15.9</td>
<td>16.3</td>
<td>15.9</td>
</tr>
<tr>
<td>20.4</td>
<td>16.3</td>
<td>25.8</td>
<td>16.3</td>
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</table>

Molecular Dynamics

• Non-bonded components of potential function

\[ U_{nb} = \text{van der Waals} + \text{Electrostatic} \]

**van der Waals**

\[ \sum_{\text{pairs } i,j} \left[ e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^{12} - 2e_{ij} \left( \frac{r_{0,ij}}{r_{ij}} \right)^6 \right] \]

**Electrostatic**

\[ 332 \sum_{\text{pairs } i,j} \left( \frac{q_i q_j}{r_{ij}} \right) \]

**NOTE:**

Sum over all pairs of \( N \) atoms

\[ \frac{N \times N - 1}{2} \]

\( N \) is often between \( 5 \times 10^5 \) to \( 5 \times 10^6 \)

For \( 5 \times 10^5 \) that is \( 1.25 \times 10^{11} \) pairs

THAT IS A LOT OF POSSIBLE PAIRS!
**Force Field**

*Force Field* used to calculate the energy and geometry of a molecule.

\[
E = \sum_{bonds} k_b (b_0 - b)^2 + \sum_{angles} k_\theta (\theta_0 - \theta)^2 + \sum_{planes} k_\omega (\omega_0 - \omega)^2 + \sum_{dihedrals} k_\phi (1 - \cos(n\phi - \delta)) + \sum_{pairs} \left( \frac{A}{r_{ij}^{12}} + \frac{B}{r_{ij}^6} + \frac{Q_i Q_j}{r_{ij}} \right)
\]

- Collection of atom types (to define the atoms in a molecule), parameters (for bond lengths, bond angles, etc.) and equations (to calculate the energy of a molecule)
- In a force field, a given element may have several atom types.
  - For example, phenylalanine contains both *sp*³-hybridized carbons and aromatic carbons.
    - *sp*³-Hybridized carbons have a tetrahedral bonding geometry
    - aromatic carbons have a trigonal bonding geometry.
    - C-C bond in the ethyl group differs from a C-C bond in the phenyl ring
    - C-C bond between the phenyl ring and the ethyl group differs from all other C-C bonds in ethylbenzene. The force field contains parameters for these different types of bonds.
## Force field parametrization

\[
E = \sum_{\text{bonds}} K_b (r - r_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\phi [1 + \cos (n\phi - \delta)] + \sum_{\text{impropers}} K_\psi (\psi - \psi_0)^2 + \sum_{i<j} 4\varepsilon \left( \frac{\sigma}{r_{ij}} \right)^{12} - \left( \frac{\sigma}{r_{ij}} \right)^6 + \sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon r_{ij}}
\]

<table>
<thead>
<tr>
<th>Type of data</th>
<th>Type of system</th>
<th>Phase</th>
<th>Type of properties</th>
<th>Force field parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>structural data (exp.)</td>
<td>small molecules</td>
<td>crystalline solid phase</td>
<td>molecular geometry, bond lengths, angles</td>
<td>( r_0, \theta_0, \psi_0 )</td>
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<tr>
<td>spectroscopic data (exp.)</td>
<td>small molecules</td>
<td>gas phase</td>
<td>intra-molecular vibrations, force constants</td>
<td>( K_b, K_\theta, K_\phi )</td>
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<tr>
<td>quantum-chemical calculations: energy profiles (theor.)</td>
<td>small molecules</td>
<td>gas phase</td>
<td>torsional-angle rotational profiles</td>
<td>( K_\psi, \delta, \eta )</td>
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<tr>
<td>quantum-chemical calculations: electron densities (theor.)</td>
<td>small molecules</td>
<td>gas phase</td>
<td>atom charges</td>
<td>charges ( q_i ) (initial)</td>
</tr>
<tr>
<td>thermodynamic data (exp.)</td>
<td>molecules in solution, mixtures</td>
<td>condensed phase</td>
<td>heat of vaporisation, density, free energy of solvation</td>
<td>v. d. Waals : ( \sigma_i, \varepsilon_i ), charges ( q_i ) (final)</td>
</tr>
<tr>
<td>dielectric data (exp.)</td>
<td>small molecules</td>
<td>condensed phase</td>
<td>dielectric permittivity, relaxation</td>
<td>charges ( q_i )</td>
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<tr>
<td>transport data (exp.)</td>
<td>small molecules</td>
<td>condensed phase</td>
<td>transport coefficients: diffusion, viscosity</td>
<td>v. d. Waals : ( \sigma_i, \varepsilon_i ), charges ( q_i )</td>
</tr>
</tbody>
</table>
• **Molecular Mechanics** or force-field methods use classical type models to predict the energy of a molecule as a function of its conformation. This allows predictions of
  • Equilibrium geometries and transition states
  • Relative energies between conformers or between different molecules
  • Molecular mechanics can be used to supply the potential energy for molecular dynamics computations on large molecules.
Local versus Global minimum problem

- Structural landscape is filled with peaks and valleys.
- Minimization protocol always moves “down hill”.
- No means to “see” the overall structural landscape
- No means to pass through higher intermediate structures to get to a lower minima.

The initial structure determines the results of the minimization!
The molecular potential $U$ depends on two types of variables:

Potential energy gradient $g(Q)$, a vector with $3N$ components:

The necessary condition for a minimum is that the function gradient is zero:

Where $x_i$ denote atomic Cartesian coordinates and $N$ is the number of atoms.

The sufficient condition for a minimum is that the second derivative matrix is positive definite, i.e. for any $3N$-dimensional vector $u$:

A simpler operational definition of this property is that all eigenvalues of $F$ are positive at a minimum. The second derivative matrix is denoted by $F$ in molecular mechanics and $H$ in mathematics, and is defined as:

One measure of the distance from a stationary point is the rms gradient:
Molecular Minimization: First-order derivative methods

Steepest Descent Method

1.) Evaluate the sum of all forces on the system (first derivative of potential energy functions)
2.) Move in the direction of the force until potential energy stops decreasing
3.) Turn 90° and return to step 2
- not efficient, but good for initial distorted structures
- may be very slow near a solution

Conjugate Gradient (Powell)

1.) Evaluate the sum of all forces on the system (first derivative of potential energy functions)
2.) Move in the direction of the force until potential energy stops decreasing
3.) Return to step 1

When to stop:
- After a predefined energy minimum has been reached
  - For example, < 1.0 kJ / mol
- After a predefined number of steps
  - For example, after 1000 orthogonal steps

<table>
<thead>
<tr>
<th></th>
<th>Initial Refinement &lt; 1 kcal Å²</th>
<th>Stringent Minimization &lt; 0.1 kcal Å²</th>
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</thead>
<tbody>
<tr>
<td>Method</td>
<td>CPU time (s)</td>
<td># of iterations</td>
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<tr>
<td>Steepest descents</td>
<td>67</td>
<td>98</td>
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<tr>
<td>Conjugate gradients</td>
<td>149</td>
<td>213</td>
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</table>
Inherent Problem of Energy Minimization

- Only finds local minima
- No method available can find the global minimum from any starting point

Extracting information from the Potential Energy Surface (PES)

Optimizations and Phonons:
- We move on the PES
- Local vs global minima
- PES is harmonic close to min.

MD
- We move over the PES (KE)
- Good Sampling is required!!
Instead of using Quantum mechanics, we can use classical Newtonian mechanics to model our system.

Classical mechanics is the study of the motion of bodies in accordance with the general principles first enunciated by Sir Isaac Newton in his *Philosophiae Naturalis Principia Mathematica* (1687).

Classical mechanics is concerned with the set of physical laws describing the motion of bodies under the action of a system of forces.

Classical mechanics is the foundation upon which all other branches of Physics are built. It has many important applications in many areas of science:

- Astronomy (motion of stars and planets)
- Molecular and nuclear physics (collisions of atomic and subatomic particles)
- Geology (e.g., the propagation of seismic waves)
- Engineering (e.g., structures of bridges and buildings)

**Techniques:**
- *Molecular Mechanics*
- *Molecular Dynamics*
- *Dissipative Particle Dynamics*
Molecular Dynamics simulations

• MD is the solution of the classical equations of motion for atoms and molecules to obtain the time evolution of the system.

• Applied to many-particle systems - a general analytical solution not possible. Must resort to numerical methods and computers

• Maxwell-Boltzmann averaging process for thermodynamic properties (time averaging).
MD simulations provide a molecular level picture of structure function relationships.

To simulate, we:
- **Set initial particle positions and force field types**
- **Set Conditions**: Temperature, pressure, initial atom velocities
- **Evolve System**: \( \vec{F} = d(m \vec{v})/dt \)
- **Calculate new positions, velocities**
- **Calculate total energy, other properties**

### Energy Formulas

**Bond Energies**:

\[
E_{\text{bond}} = \sum_{i,j} K_i (r_{ij} - r_{eq})^2 + \sum_{i,j} K_{ij} (\theta_{ij} - \theta_{eq})^2 + \sum_{i,j} \frac{V_z}{2} [1 + \cos(n \phi - \gamma)] + \sum_{i,j} \frac{A_{ij}}{R_{ij}^2} - \frac{B_{ij}}{R_{ij}^6} + q_i q_j \]

**Angle Energies**:

\[
E_{\text{angle}} = \sum_{i,j,k} \frac{1}{2} q_i q_j q_k \]

**Dihedral Energies**:

\[
E_{\text{dihedral}} \approx \frac{1}{2} \sum_{i,j,k} q_i q_j q_k - \frac{1}{2} (1 - \frac{1}{\varepsilon_w}) \sum_{i,j} q_i q_j f_{ij}^{GB}
\]

**GB Potential**:

\[
f^{GB} = \left[ r_{ij}^2 + R_i R_j \exp\left(-r_{ij}^2 / 4R_i R_j\right) \right]^{1/2}
\]

### Solvation models

- **Explicit solvent (any solvent)**
- **Implicit or continuum solvation**
Minimal input

1) Topological properties:
   description of the covalent connectivity of the molecules to be modeled

2) Structural properties:
   the starting conformation of the molecule, provided by an X-ray structure, NMR data or a theoretical model

3) Energetical properties:
   a force field describing the force acting on each atom of the molecules

4) Thermodynamical properties:
   a sampling algorithm that generates the thermodynamical ensemble that matches the experimental conditions for the system, e.g. $N,V,T$, $N,P,T$, ...
Different Ensembles

- Vary the independent variables
- Useful for describing open and closed physical systems
- Variants:
  - NVE: microcanonical
  - NVT: canonical
  - NPT: isobaric-isothermal
  - NoσT: constant stress
  - μVT: grand canonical
  - NPH: isenthalpic-isothermal

<table>
<thead>
<tr>
<th>Name</th>
<th>All states of:</th>
<th>Probability distribution</th>
<th>Schematic</th>
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</thead>
<tbody>
<tr>
<td>Microcanonical (EVN)</td>
<td>given EVN</td>
<td>$\pi_i = \frac{1}{\Omega}$</td>
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</tr>
<tr>
<td>Canonical (TVN)</td>
<td>all energies</td>
<td>$\pi(E_i) = \frac{1}{\Omega} e^{-\beta E_i}$</td>
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<tr>
<td>Isothermal-isobaric (TPN)</td>
<td>all energies and volumes</td>
<td>$\pi(E_i, V_i) = \frac{1}{\Omega} e^{-\beta (E_i + P V_i)}$</td>
<td></td>
</tr>
<tr>
<td>Grand-canonical (TVμ)</td>
<td>all energies and molecule numbers</td>
<td>$\pi(E_i, N_i) = \frac{1}{\Omega} e^{-\beta (E_i - \mu N_i)}$</td>
<td>Note: $\beta \equiv 1/kT$</td>
</tr>
</tbody>
</table>

NVE  
\downarrow
NVT  \hspace{1cm} \mu VE
\downarrow
NoσT  \hspace{1cm} NPT  \hspace{1cm} \mu VT
\downarrow
NPH
The HIV capsid is large, containing about 1,300 proteins with altogether 4 million atoms.

Simulations of 64 million atoms for over 1 microsecond allow to conduct a comprehensive study of the physical properties of the entire HIV capsid including electrostatic potential, all atom normal modes, as well as the effects of the solvent (ions and water) on the capsid. The results from the simulations reveal critical details of the capsid protein with important implications for assembly, uncoating and nuclear import.
It took two years on a supercomputer to simulate 1.2 microseconds in the life of the HIV capsid, a protein cage that shuttles the HIV virus to the nucleus of a human cell. The 64-million-atom simulation offers new insights into how the virus senses its environment and completes its infective cycle.
• MD is a **deterministic technique**: given initial positions and velocities, the evolution of the system in time is, *in principle*, completely determined (in practice, accumulation of integration and computational errors would introduce some uncertainty into the MD output).

• MD can be also used as a **statistical mechanics method**: it generates a set of configurations that are distributed according to statistical distribution functions. In many cases we are not interested in trajectories of individual atoms, we are interested in macroscopic properties of the material. In these cases MD information can be averaged over all the atoms in the system and over time of the simulation to obtain thermodynamic parameters.
Atomistic MD simulations

Advantages:
• Excellent for studies of processes and properties of soft or/and hard materials
• Observe time evolution of the system
• Formation of non-bonded interactions
• Allowing the derivation of kinetic and thermodynamic properties

Limitations:
• No quantum effects: changes in chemical bonding, catalytic cleavage, presence of intermediates, light induced charge transfer, tunnelling of protons and electrons
  • Workaround: ab initio (first principles) MD – not practical for large systems, base on ground state DFT
  • Reactive force fields
• Quality of the force field - The results of simulations will be realistic only if the potential energy function mimics the forces experienced by the ‘real’ atoms.
• Time and size limitations - The desired length of simulations also places limits on increasing the size of the problem
## Commonly used software

<table>
<thead>
<tr>
<th>Software</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMBER</td>
<td>General Molecular Simulation Package</td>
</tr>
<tr>
<td>BOSS</td>
<td>OPLS</td>
</tr>
<tr>
<td>CHARMM</td>
<td>General Molecular Simulation Package</td>
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<tr>
<td>GROMACS</td>
<td>High performance MD</td>
</tr>
<tr>
<td>GROMOS</td>
<td>Geared towards biomolecules</td>
</tr>
<tr>
<td>LAMMPS</td>
<td>Has potentials for soft and solid-state materials and coarse-grain systems</td>
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<tr>
<td>MacroModel</td>
<td>OPLS-AA, GBSA solvent model, conformational sampling, minimization, MD</td>
</tr>
<tr>
<td>Materials Studio</td>
<td>Materials Studio is a software environment that brings the materials simulation technology to desktop computing, solving key problems throughout the R&amp;D process.</td>
</tr>
<tr>
<td>Towhee</td>
<td>Originally designed for the prediction of fluid phase equilibria</td>
</tr>
<tr>
<td>MOE</td>
<td>Molecular Operating Environment</td>
</tr>
<tr>
<td>Prime</td>
<td>Homology modeling, loop and side chain optimization, minimization, OPLS-AA, SGB solvent model, parallelized</td>
</tr>
<tr>
<td>TINKER</td>
<td>Software Tools for Molecular Design</td>
</tr>
<tr>
<td>VMD + NAMD</td>
<td>Fast, parallel MD</td>
</tr>
</tbody>
</table>
Group Members

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