Practical Course on Molecular Dynamics and Trajectory Analysis

Episode 1: Introduction (environment and data)

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MD Course and Trajectory Analysis
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Contents

Episode objectives

- Link thermodynamics, statistical mechanics, and simulation.
- Define variables, state functions, and observables.
- Establish the data flow and working environment.

Time and length scales

$$\begin{aligned}
\Delta t_{\text{vibrations}} &\sim 10^{-15}\,\mathrm{s},\\
\Delta t_{\text{conformations}} &\sim 10^{-9}\,\mathrm{s} \text{ to } 10^{-3}\,\mathrm{s},\\
L_{\text{atoms}} &\sim 10^{-10}\,\mathrm{m}, \quad L_{\text{proteins}} \sim 10^{-8}\,\mathrm{m}.
\end{aligned}$$

- Atomic simulation resolves ultra-fast scales.
- Statistics link microstates to macroscopic averages.

Microscopic model

$$\begin{aligned} \text{State} &= (\mathbf{r}_1, \ldots, \mathbf{r}_N, \mathbf{p}_1, \ldots, \mathbf{p}_N), \\ \mathbf{p}_i &= m_i \dot{\mathbf{r}}_i. \end{aligned}$$

- The system is defined by $6N$ phase-space coordinates.
- Potential energy captures the interactions between particles.

From micro to macro

$$\langle A \rangle = \int A(\mathbf{r},\mathbf{p})\,\rho(\mathbf{r},\mathbf{p})\,d\mathbf{r}\,d\mathbf{p},$$

$$\bar{A} = \lim_{T\to\infty} \frac{1}{T}\int_0^T A(t)\,dt.$$

- Ergodicity links time averages with ensemble averages.

Simulation pipeline

1. System preparation (topology, coordinates, parameters).
2. Define the Hamiltonian and boundary conditions.
3. Time integration and trajectory generation.
4. Statistical analysis of observables.

State variables

$$P,\ V,\ T,\ U,\ H = U + PV,\ G = H - TS,\ A = U - TS.$$

- State functions depend only on the macroscopic state.
- Path functions include work W and heat Q.

First law and work

$$
\begin{aligned}
dU &= \delta Q + \delta W, \\
\delta W &= -P\, dV + \sum_i f_i\, dx_i .
\end{aligned}
$$

- Internal energy changes through heat or work exchange.
- In simulation, δW arises from forces on particles.

Second law and entropy

$$\begin{aligned} dS &\geq \frac{\delta Q}{T}, \\ S &= k_{\mathrm{B}} \ln \Omega. \end{aligned}$$

- Ω is the number of microstates compatible with the macrostate.

Thermodynamic potentials

$$G = U + PV - TS,$$
$$A = U - TS.$$

- G minimizes at constant T, P; A minimizes at constant T, V.

Differential relations

$$dG = -S\,dT + V\,dP + \sum_i \mu_i\,dN_i,$$

$$dA = -S\,dT - P\,dV + \sum_i \mu_i\,dN_i.$$

- Partial derivatives give measurable observables.

Microstates and macrostates

$$S = k_{\mathrm{B}} \ln \Omega, \quad \Omega = \sum_{\text{micro}} 1.$$

- Entropy increases favor states with more configurations.

Free energy and equilibrium

$$\Delta G = \Delta H - T\Delta S,$$
$$\Delta A = \Delta U - T\Delta S.$$

- At equilibrium, $\Delta G = 0$ for processes at fixed T, P.

Chemical potential

$$\mu_i = \left(\frac{\partial G}{\partial N_i}\right)_{T,P,N_{j\neq i}}.$$

- Controls matter exchange and phase equilibrium.

Relation to probabilities

$$P(\text{estado}) \propto e^{-\beta G}, \quad \beta = 1/(k_{\mathrm{B}} T).$$

- Free energy governs the statistical weight of macrostates.

Example: equilibrium A $\rightleftharpoons$ B

$$K = e^{-\beta \Delta G},$$
$$\Delta G = -k_{\mathrm{B}} T \ln K.$$

- Relative stability is expressed in terms of ΔG.

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Classical ensembles

- Microcanonical (NVE): N, V, E fixed.
- Canonical (NVT): N, V, T fixed.
- Isothermal-isobaric (NPT): N, P, T fixed.

Canonical partition function

$$Z = \frac{1}{h^{3N} N!} \int e^{-\beta H(\mathbf{r},\mathbf{p})} \, d\mathbf{r} \, d\mathbf{p}.$$

- Central to deriving free energies and averages.

Observables in NVT

$$\langle A \rangle = \frac{1}{Z} \int A\, e^{-\beta H}\, d\mathbf{r}\, d\mathbf{p}.$$

- In simulation, they are estimated via time averages.

NPT ensemble

$$\Delta = \int dV\, e^{-\beta PV}\, Z(N, V, T),$$
$$G = -k_{\mathrm{B}} T \ln \Delta.$$

- Includes volume fluctuations controlled by the barostat.

Thermodynamic fluctuations

$$C_V = \frac{\langle E^2 \rangle - \langle E \rangle^2}{k_\mathrm{B} T^2},$$

$$\kappa_T = \frac{\langle V^2 \rangle - \langle V \rangle^2}{k_\mathrm{B} T \langle V \rangle}.$$

- Fluctuations connect statistics with macroscopic response.

Classical Hamiltonian

$$H(\mathbf{r}, \mathbf{p}) = \sum_{i=1}^{N} \frac{\mathbf{p}_i^2}{2m_i} + U(\mathbf{r}).$$

- Split into kinetic and potential energy.

Hamilton's equations

$$\dot{\mathbf{r}}_i = \frac{\partial H}{\partial \mathbf{p}_i},$$
$$\dot{\mathbf{p}}_i = -\frac{\partial H}{\partial \mathbf{r}_i}.$$

- Equivalent to Newton's second law.

Newton's equations

$$m_i \ddot{\mathbf{r}}_i = -\nabla_i U(\mathbf{r}).$$

- Force equals the negative gradient of the potential.

Energy conservation

$$\frac{dH}{dt} = 0 \quad \text{(ideal NVE).}$$

- Numerical integration introduces controllable errors.

Phase-space flow

$$\frac{d\rho}{dt} = \{\rho, H\} = 0 \quad \text{(Liouville equation).}$$

- Probability density is conserved by the Hamiltonian flow.

Forces from the potential

$$\mathbf{F}_i = -\nabla_i U(\mathbf{r}).$$

- In MD, the dominant cost is evaluating U and $\mathbf{F}_i$.

Pair potentials

$$U = \sum_{i<j} u(r_{ij}), \quad r_{ij} = \|\mathbf{r}_i - \mathbf{r}_j\|.$$

- Simplify the total energy using pairwise interactions.

Example: Lennard-Jones

$$u_{\mathrm{LJ}}(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right].$$

- Short-range repulsion, medium-range attraction.

Electrostatic energy

$$u_C(r) = \frac{1}{4\pi\epsilon_0}\frac{q_i q_j}{r_{ij}}.$$

- Dominant in biomolecular systems.

Gradients and Hessian

$$\nabla U \equiv \left(\frac{\partial U}{\partial r_1}, \ldots, \frac{\partial U}{\partial r_{3N}}\right),$$
$$\text{Hess} = \nabla\nabla U.$$

- The Hessian describes local curvatures (normal modes).

Kinetic/potential separation

$$Z = Z_{\text{kin}}\, Z_{\text{conf}},$$

$$Z_{\text{kin}} = \prod_i \left(\frac{2\pi m_i}{\beta h^2} \right)^{3/2}.$$

- Z_{conf} depends only on $U(\mathbf{r})$.

Configuration distribution

$$P(\mathbf{r}) = \frac{e^{-\beta U(\mathbf{r})}}{Z_{\text{conf}}}.$$

- Basis for Monte Carlo and thermostatted MD sampling.

Configurational free energy

$$A = -k_{\mathrm{B}} T \ln Z_{\mathrm{conf}} + \mathrm{const.}$$

- Links sampling to ΔA between states.

Velocity distribution

$$P(\mathbf{v}) \propto e^{-\beta \sum_i \frac{1}{2} m_i v_i^2}.$$

- Allows initializing velocities at temperature T.

Equipartition theorem

$$\langle K \rangle = \frac{3N}{2} k_{\mathrm{B}} T.$$

- Each quadratic degree of freedom contributes $\frac{1}{2} k_{\mathrm{B}} T$.

General form

$$P(E) = \frac{1}{Z} e^{-\beta E}.$$

- The exponential weight penalizes high-energy states.

Maxwell-Boltzmann distribution

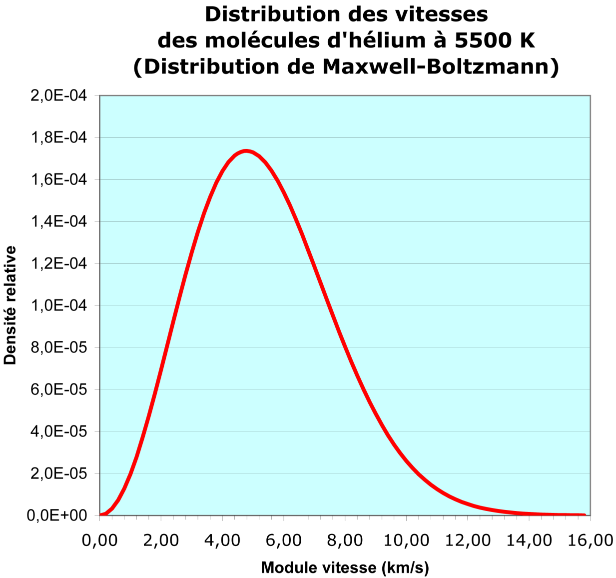
$$f(v) = 4\pi \left(\frac{m}{2\pi k_{\mathrm{B}} T} \right)^{3/2} v^2 e^{-\frac{mv^2}{2k_{\mathrm{B}} T}}.$$

- Characterizes the equilibrium velocity distribution.

Statistical interpretation

- Most particles cluster around v_{m}.
- The width grows with T.

Graphic example



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Simulation application

- Initializing velocities according to $f(v)$ prevents thermal bias.
- Lets us check that the thermostat reproduces equilibrium.

Phase space

$$\Gamma = (\mathbf{r}, \mathbf{p}) \in \mathbb{R}^{6N}.$$

- Each point represents a full microstate.

Liouville equation

$$\frac{\partial \rho}{\partial t} + \{\rho, H\} = 0.$$

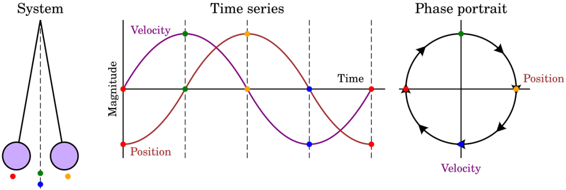
- Volume in Γ is conserved (Liouville theorem).

Ergodicity

$$\lim_{T\to\infty} \frac{1}{T} \int_0^T A(t)\, dt = \langle A \rangle_{\text{ensemble}}.$$

- Key assumption for replacing ensemble averages with time averages.

Trajectories in Γ



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Physical interpretation

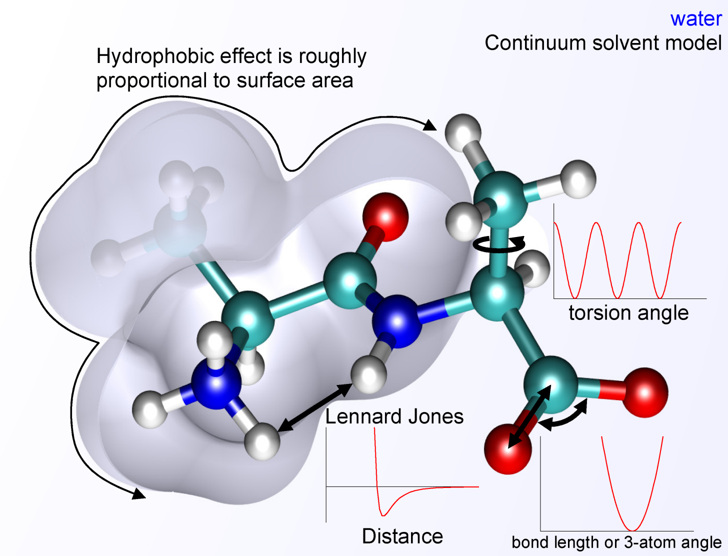
- Closed orbits: periodic motion.
- Open orbits: diffusion in high-energy regions.

Definition

$$U(\mathbf{r}) : \mathbb{R}^{3N} \to \mathbb{R}.$$

- Describes the energy landscape where the system evolves.

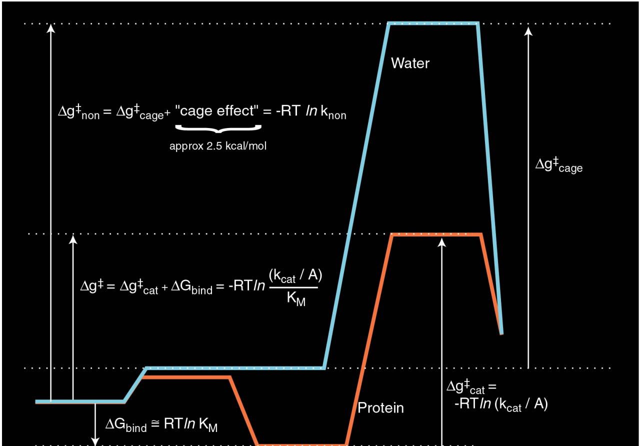
Molecular mechanics potential



Visualizing the typical multi-basined MM surface for a small system.

Enzymes and reactive Hamiltonians

- Enzymatic catalysis reshuffles bonds, so the Hamiltonian must describe bond breaking/forming events beyond fixed-topology potentials.
- Reactive force fields or QM/MM fragments introduce extra terms that depend on electronic reorganization.



Reaction coordinates

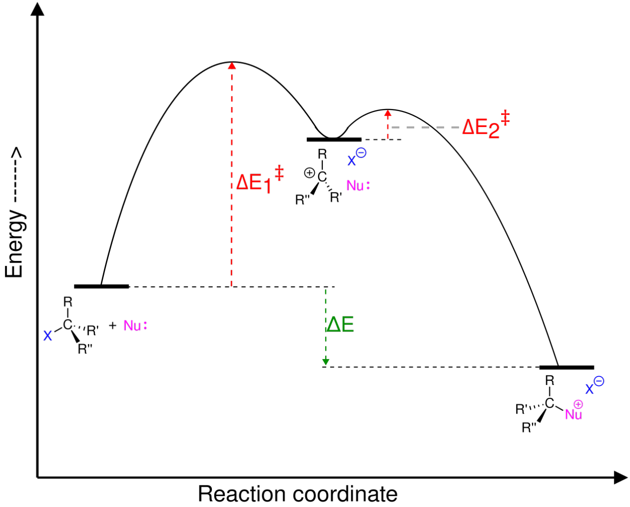
$$\xi = \xi(\mathbf{r}), \quad F(\xi) = -k_\mathrm{B} T \ln P(\xi).$$

- Projection that summarizes the dynamics in a key coordinate.

Barriers and metastable states

- Local minima: metastable conformations.
- Barriers control transition scales.

Surface example



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Dynamics on the surface

- Classical integration produces trajectories on $U(\mathbf{r})$.
- Thermostats ensure canonical sampling.

Potential decomposition

$$U = U_{\text{bond}} + U_{\text{angle}} + U_{\text{dihedral}} + U_{\text{nonbond}}.$$

- Separation between bonded and non-bonded terms.

Bonded terms

$$U_{\text{bond}} = \sum_b k_b (r_b - r_b^0)^2,$$
$$U_{\text{angle}} = \sum_a k_a (\theta_a - \theta_a^0)^2.$$

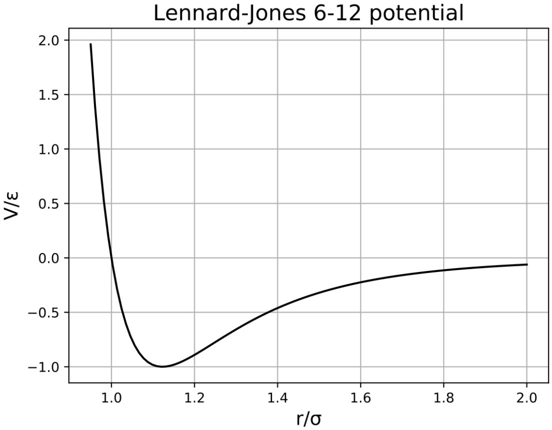
- Harmonic approximation around equilibrium geometries.

Dihedrals and rotation

$$U_{\text{dihedral}} = \sum_{d} \frac{V_d}{2} \left[1 + \cos(n_d \phi_d - \gamma_d)\right].$$

- Control rotational barriers and conformational preferences.

LJ example



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Parameters and validation

- Force fields are fitted to quantum and experimental data.
- Validation includes densities, energies, and conformations.

Working directory

- Environment variable `COURSE_DIR`.
- Structure: `data/` (inputs) and `results/` (outputs).

Course systems

- Simple system: alanine.
- Complex system: protein + ligand.

Data flow

1. Download base data.
2. Prepare topologies and coordinates.
3. Validate the computing environment.

Reproducibility

- Track library versions and random seeds.
- Save input files and scripts.

OpenMM general workflow

- Load PDB/GROMACS/AMBER/CHARMM/TINKER structures with the official scripts (e.g., `simulatePdb.py`, `simulateGromacs.py`, `simulateAmber.py`, and `simulateCharmm.py`).
- Create the `Topology`, `System`, and `Integrator` objects and wire `StateReporter`/`TrajectoryReporter` to capture energies, forces, and coordinates.
- Execute integration steps defined by the application layer and save checkpoints with the OpenMM-Setup routines (User Guide §3.5–3.15).
- `simulateAmber.py` accepts '.prmtop' + '.inpcrd', while `simulateCharmm.py` and `simulateGromacs.py` respect their native formats.
- `simulatePdb.py` is the traditional starting point for alanine dipeptide or unparameterized protein–ligand systems.
- All scripts expose hooks to tweak `reporters` and shape output formats that we then process with Python analysis scripts.

Episode summary

- The thermodynamic groundwork connects to statistical sampling.
- The potential defines forces and probabilities.
- The working environment ensures reproducibility.

References I

[1] AdiPhysics. *Lennard Jones potential graph*. CC BY-SA 4.0. URL: https://commons.wikimedia.org/wiki/File:Lennard_Jones_potential_graph.svg (visited on 01/12/2026).

[2] Krishnavedala. *Pendulum phase portrait illustration*. CC BY-SA 4.0. URL: https://commons.wikimedia.org/wiki/File:Pendulum_phase_portrait_illustration.svg (visited on 01/12/2026).

[3] Gilles MAIRET. *Distribution de Maxwell-Boltzmann. Distribution des vitesses de l'helium a 5500 K*. CC BY-SA 3.0. URL: https://commons.wikimedia.org/wiki/File:Distribution_de_Maxwell-Boltzmann._Distribution_des_vitesses_de_l%27h%C3%A9lium_%C3%A0_5500_K.png (visited on 01/12/2026).

References II

[4] Unknown author. *Potential Energy Surface for a generic SN1 reaction.* CC BY-SA 4.0. Source: LibreTexts (Organic Chemistry, Morsch et al.) URL: `https://commons.wikimedia.org/wiki/File:Potential_Energy_Surface_for_a_generic_SN1_reaction.svg` (visited on 01/12/2026).