Computational Biophysics: Force Fields

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1 The Energy Landscape

The central goal of Molecular Dynamics (MD) is to calculate how proteins and complexes of atoms move. To do this, we need to know the **Potential Energy** (U) of the system based on the positions of its atoms.

$$\vec{F} = -\nabla U(\vec{r}) \tag{1}$$

> **Takeaway:** Force is the negative derivative (slope) of the energy landscape. Atoms "roll down" the energy hills.
> - **Constraint:** Your energy function $U(\vec{r})$ must be **differentiable** everywhere. If the derivative is undefined, the simulation can't proceed.

2 Force Field Equation

Calculating interactions between every pair of atoms is expensive ($O(N^2)$). To make simulations feasible, we use a Force Field, a simplified set of equations that approximates the quantum mechanical reality.

$$E_{total} = \underbrace{E_{bond} + E_{angle} + E_{dih}}_{\text{Bonded Terms}} + \underbrace{E_{vdw} + E_{coulomb}}_{\text{Non-Bonded Terms}} \tag{2}$$

3 Part 1: Bonded Interactions (Hard Degrees of Freedom)

These terms describe atoms that are directly connected. They are stiff degrees of freedom.

3.1 1. Bond Stretching (E_{bond})

Modeled as a **Harmonic Potential** (Hooke's Law/a spring).

$$E_{bond} = \sum_{\text{bonds}} k_b (r - r_0)^2 \tag{3}$$

- k_b: Stiffness of the bond.
- r_0: Equilibrium bond length.

3.2 2. Angle Bending (E_{angle})

The angle θ between 3 atoms is also treated as a spring.

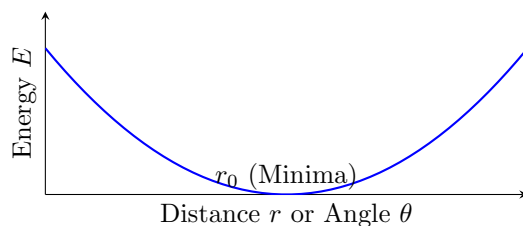$$E_{angle} = \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 \tag{4}$$

Figure 1: **The Harmonic Approximation.** We treat bonds like springs because near the bottom of the well (r_0), almost any energy curve looks like a parabola.

3.3   3. Dihedrals / Torsion (E_{dih})

This describes rotation around a central bond (4 atoms: A-B-C-D).

- **Why not a spring?** A bond can vibrate, but a dihedral can rotate a full 360°. A spring $k(\phi)^2$ would go to infinity at 360°. We need a repeating function.

- **The Equation:** We use a Cosine series.

$$E_{dih} = \sum_{\text{dihedrals}} k_\psi [1 + \cos(n\Psi - \delta)] \tag{5}$$

- Ψ (Psi): Represents the angle.

- n: Multiplicity (e.g., $n = 3$ means 3 energy barriers in one full rotation, like ethane).

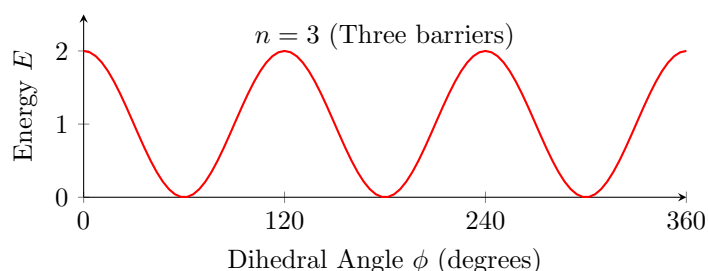- δ: Phase shift (shifts the location of the minima).

Figure 2: **Torsional Potential.** This captures conformational states like *gauche* vs *trans*.

4   Part 2: Non-Bonded Interactions (Soft Degrees of Freedom)

These are interactions between atoms that are not bonded but are in the same box. They are pairwise and expensive (N^2).

4.1   1. Van der Waals (E_{vdw})

Modeled using the **Lennard-Jones (12-6) Potential**.

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

- $(\sigma/r)^{12}$ **(Repulsion):** Describes the "hard core" of the atom. If atoms overlap, energy skyrockets (Pauli exclusion).

- $(\sigma/r)^6$ **(Attraction):** Describes London Dispersion Forces (induced dipoles).

4.2   2. Electrostatics ($E_{coulomb}$)

Modeled using Coulomb's Law for point charges.

$$E_{coul} = \frac{q_i q_j}{4\pi\epsilon_0\epsilon_r r_{ij}} \tag{7}$$

- This assumes atoms are simple spheres with a fixed charge. This fails for **Transition Metals** where electron orbitals (d-orbitals) have complex shapes and orientations.

5   Polarizability

Standard force fields (CHARMM, AMBER) use fixed charges (q). Real electron clouds can shift shape (polarize) when another charge comes near.

1. **Drude Oscillators:** We attach a fake, charged particle to the atom via a spring. As an external charge approaches, the spring stretches, moving the charge center. This simulates the electron cloud shifting.

2. **AMOEBA Model:** Uses multipoles (dipoles, quadrupoles) instead of just point charges. Much more accurate for small molecules, but very computationally expensive.

6   Molecular Dynamics Integration

We don't make random moves (like Monte Carlo). We solve Newton's $F = ma$ to be able to simulate the system through time.

6.1   Time Step (Δt)

- We must chop time into discrete steps.
- The step must be faster than the fastest vibration in the system (H-bond vibration ≈ 10 fs).
- Standard Δt: 1 to 2 femtoseconds.

6.2   Velocity Verlet

This is the "Integrator" that updates positions r and velocities v.

$$r(t + \Delta t) = r(t) + v(t)\Delta t + \frac{1}{2}\frac{F(t)}{m}\Delta t^2 \tag{8}$$

$$v(t + \Delta t) = v(t) + \frac{F(t) + F(t + \Delta t)}{2m}\Delta t \tag{9}$$

> **Takeaway: Why Velocity Verlet?** It is time reversible (symplectic). If you run the simulation forward and then reverse all velocities, the math guarantees you trace your path exactly back to the start. This ensures better conservation of energy (stability) than simpler methods.

7   Parameterization: Atom Types

We can't treat all Carbons the same.

- Carbon in ethane (sp^3) $\neq$ Carbon in benzene (sp^2).
- **Atom Types:** Force fields define specific parameters for every chemical context.
- **Data Sources:**
  - Crystal Structures (PDB) for equilibrium lengths, Quantum Mechanics for bond stiffness.
  - Spectroscopy for experimental validation.