Molecular Dynamics Simulation

Why simulation?

- replace expt.
- provoke expt.
- explain expt.
- aid in establishing intellectual property.

Molecular Modeling?

descrip^n of the atomic & molecular inter^n that govern microscopic & macroscopic behavior of physical systems.

↓

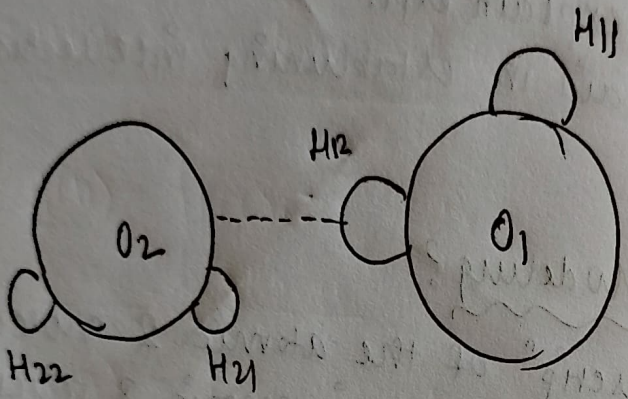
relation / connection b/w the macroscopic world and the microscopic world provided by the theory of statistical mechanics.

Computational Tools

Quantum Mechanics (QM)	Classical Molecular Mechanics (MM)	Mixed Quantum/ Classical (QM/MM)
Electronic Structure (Schrödinger)	Emperical forces (Newton)	point mass, no electrons
• accurate • expensive 10-100 atoms 10-100 ps small system	• less accurate • fast $10^4 - 10^5$ atoms 10-100 ns	$10^4 - 10^5$ atoms 10-100 ps

Proteins → performs functions in the order of milisec.

23/8/23



$(x_{O_1}, y_{O_1}, z_{O_1})$
$(x_{O_2}, y_{O_2}, z_{O_2})$
$(x_{H_{11}}, y_{H_{11}}, z_{H_{11}})$
⋮
$(x_{H_{22}}, y_{H_{22}}, z_{H_{22}})$

3N variables

Monte Carlo → 3N−6 variables

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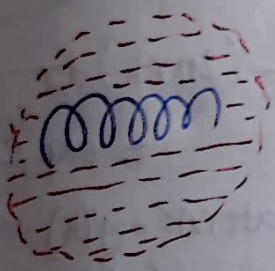
solvation → water

Stochastic boundary cond°

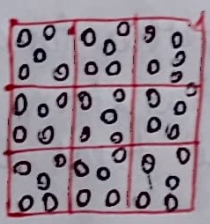
region of interest is solvated in a water sphere at 1 atm

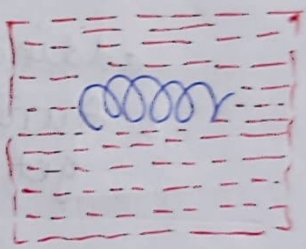
Periodic Boundary conditions

fully solvated central cell is simulated, in the environment produced by the repitition of the cell in all dim.



← Explicit Solvent Model





Periodic Repeats of System of Interest →

each box has uniform no of atoms → the algorithm takes care of that

otherwise applic° of laws of physics becomes impossible

Electrostatic Energy of Crystal

$a, b, c = [0, \infty]$.

$$V = \sum_i \sum_j \frac{332 q_i q_j}{|\vec{r_{ij}} + a\vec{l_a} + b\vec{l_b} + c\vec{l_c}|}$$

$a=0, b=0, c=0$ → original box

$a=1, b=0, c=0$ → 1st box in x dim.

Periodic repeats of coordn.

$(x_i + La, y_i, z_i), (x_i + 2La, y_i, z_i) + \ldots + (x_i + NLa, y_i$

$(x_i + La, y_i + La, z_i), x_i +$

Fourier Transform of Gaussian Charge Distrib°

$$g(h) = \int_{-\infty}^{\infty} \rho(x) e^{-2\pi i x h} dx$$

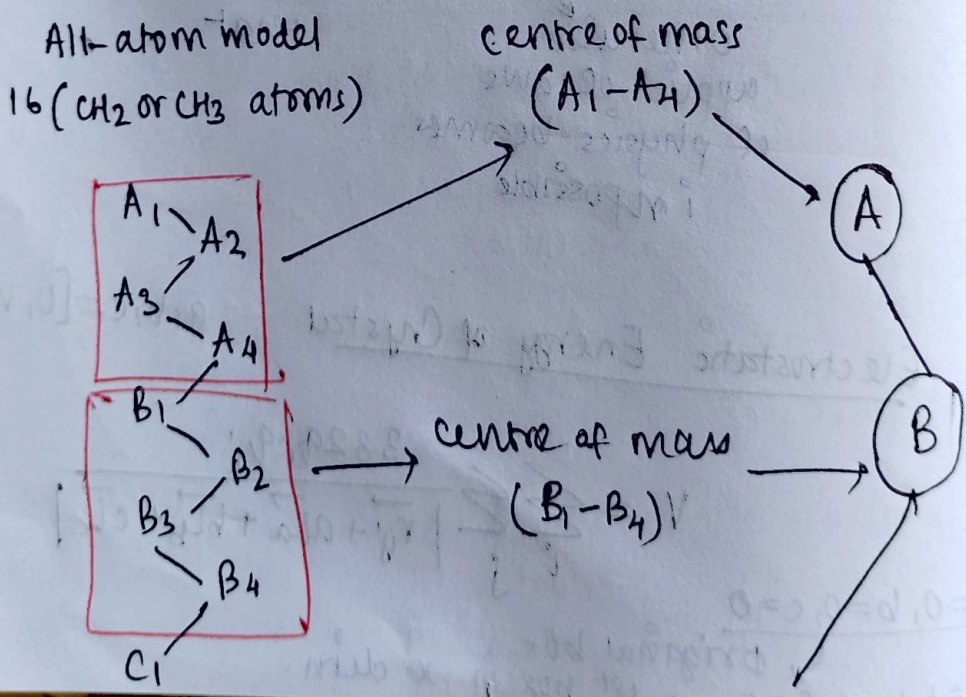
for each atomic charge:

$$g'(h) = \int_{-\infty}^{\infty} \exp(-kx^2) \exp(-i 2\pi x h)\, dx$$

$$= \exp(-ah^2)$$

adding together for all atoms $= g'(h)$
& fourier transform again to get the total energy.

Coarse Grain Models:

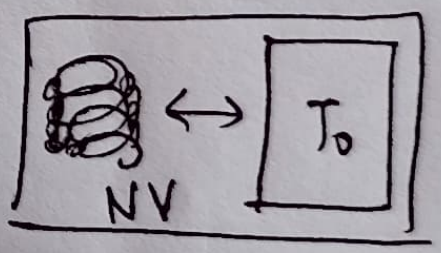


VMD - Visualization.

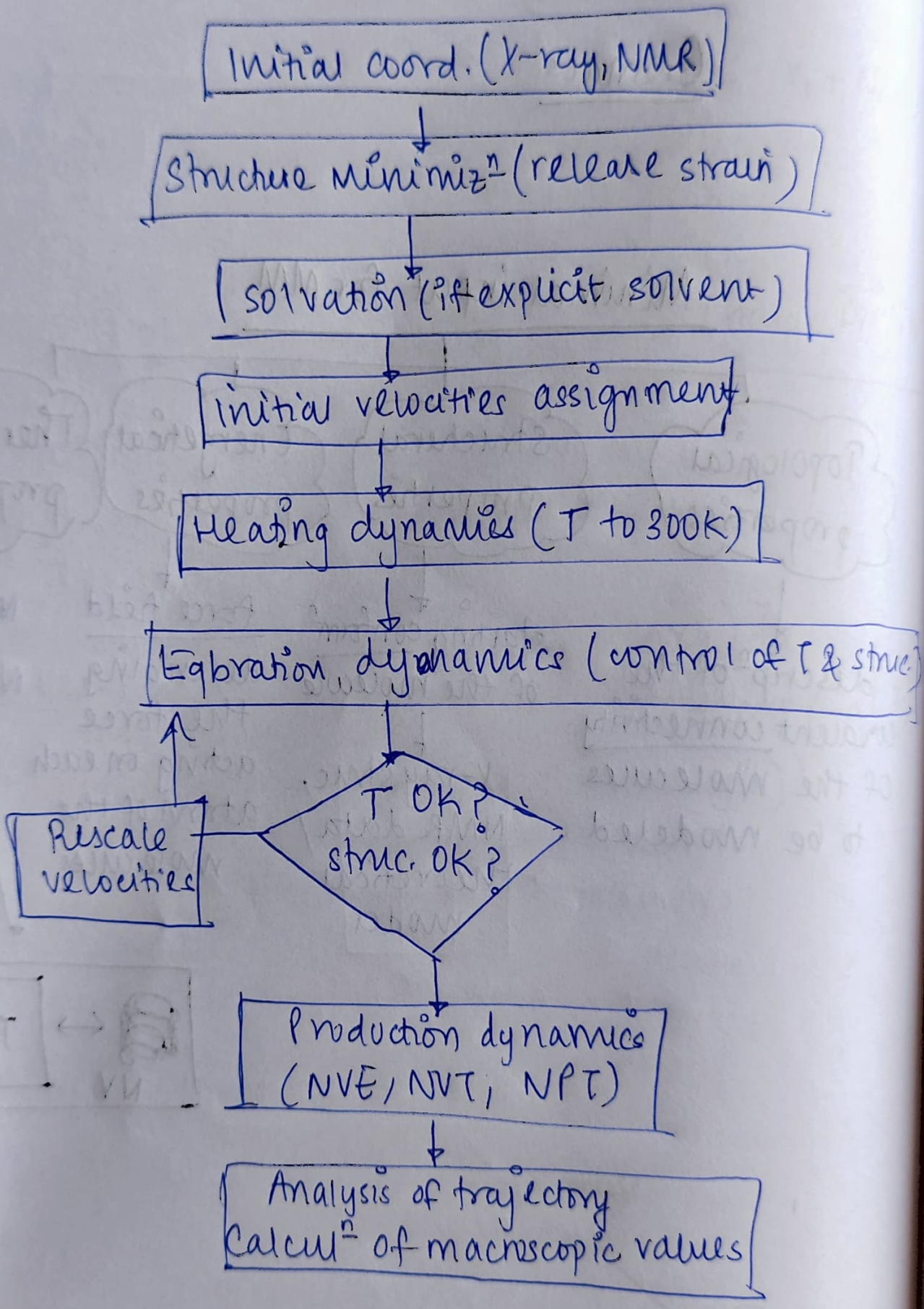
Gromacs

Minimal input for MM

- Topological properties
  - descrip^{n} of the covalent connectivity of the molecules to be modeled
- Structural properties
  - starting conform^{n} of the molecule
    - X-ray struc, NMR data / theoretical model
- Energetical properties
  - force field describing the force acting on each atom of the molecules
- Thermod properties
  - N, V, T,
  - N, P, T
  - matchin



MD Flowchart



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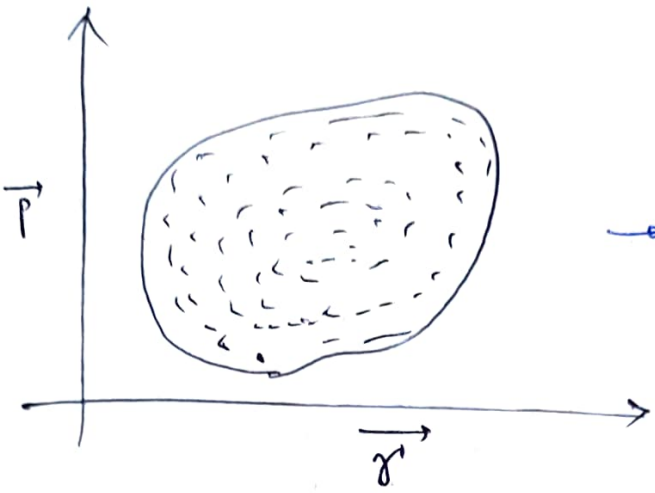


→ depends on the MD simul^n

↓

so we do replicates

↓

atleast 3

↓

if two are identical ← statistically significant

if not ← rare event

Autodock →

whichever interaction has ↓ energy → good structure

Structure minimiz^n

↳ reach a global minimum → energy.

when we minimize → we have to define a force field.

⇒ Accelerⁿ = 0 ⟹ const. velocity

⇒ Atoms are under const. force

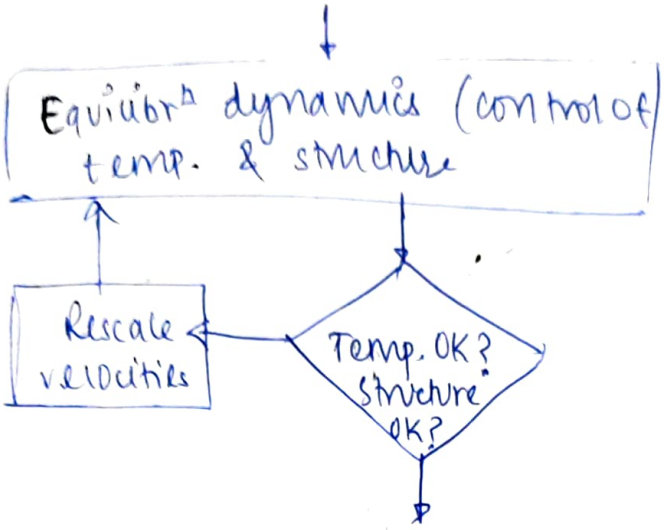
⇒ Accelerate & velocity ↑

⇒ at one point, can burst

$$T \propto (v)^2$$

Most proteins : T = room temp.

Thermostat



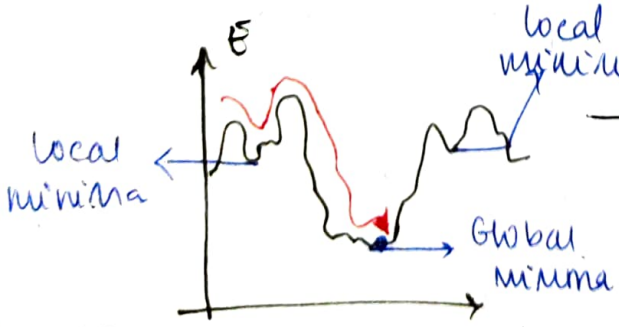
The Protein Structure file (PSF),

generated by CHARMM → from seq. of proteins, ligands, H_2O mol., etc.

Residue topology file (RTF)

6 energy components — 4 bonded terms, 2 unbonded term

Energy landscape



Complex Landscape for a protein

ϕ/ψ angle

↓

Combination in which the energy is minimum

↓

Global minima

crystal structure we get → not minimum energy

* How do we go to the minimum E:
  - iterations of small-small steps
  - small-small variations in ϕ/ψ angle
  - calculate energy at each step & check whether minimum

Minimization

- by differentiating the P.E. function

$$\frac{\partial E}{\partial x_i} = 0 \Rightarrow \frac{\partial^2 E}{\partial x_i^2} > 0$$

~~Epot~~

Taylor series expansion

$$f(x+h) = f(x) + h\frac{d}{dx}f(x) + \frac{h^2}{2!}\frac{d^2}{dx^2}f(x) + \frac{h^3}{3!}\frac{d^3}{dx^3}f(x) + \dots$$

Locating Minimum Energy near a given point:

$E(x)$ → should be differentiable at x

$$E(x+h) = E(x) + h E'(x) + \frac{h^2}{2!} E''(x) + \dots$$

h → a small step in 1 dim.

✓ Energy is minimum at a nearby point:

$$\frac{dE(x+h)}{dx} = 0$$

$$\frac{dE}{dx}(x) + \frac{h}{1!}\frac{d^2E(x)}{dx^2} + \frac{h^2}{2!}\frac{d^3E(x)}{dx^3} + \dots = 0$$

we can neglect this as h is small

$$\frac{dE(x)}{dx} = -h\frac{d^2E(x)}{dx^2}$$

$$\boxed{h = -\frac{(dE/dx)}{(d^2E/dx^2)}}$$ → Step size

✓ Modified Newton Rhapson

✓ Steepest Descent:

$$\boxed{h = -\lambda\frac{dE}{dx}}$$

λ → learning parameter