Molecular Dynamics

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Introduction

- Accurate three-dimensional structures of biochemically and biologically active proteins.
- Structural data provides the essential framework for characterizing mechanisms, analyzing evolutionary relationships and understanding of function.
- Flexibility in proteins is a major component in creating their specificity and catalytic power.
- Molmovdb: Database of Macromolecular Movements

Molecular Dynamics

- MD calculates the time dependent behavior of a molecular system.
- MD simulations have provided detailed information on the fluctuations and conformational changes of proteins.
- Routinely used to investigate the structure, dynamics and thermodynamics of molecules and complexes
- Used in determination of structures from X-ray crystallography and from NMR experiments.

History

1957: introduced by Alder and Wainwright to study interactions of hard spheres.

1964: first simulation using a realistic potential for liquid argon carried out by Rahman.

1974: first molecular dynamics simulation of a realistic system by Rahman and Stillinger in their simulation of liquid water.

1977: first protein simulations (BPTI) by J. Andrew McCammon and Bruce Gelin

Time Scales

Local Motions (0.01 to 5 Å, 10^{-15} to 10^{-1} s, fs - ms)

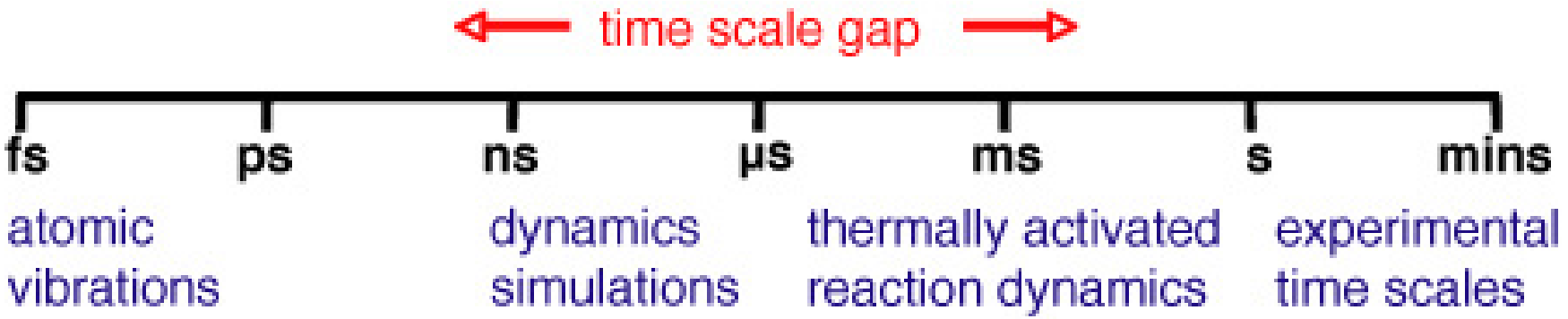
Atomic fluctuations, Sidechain Motions, Loop Motions

Rigid Body Motions (1 to 10Å, 10^{-9} to 1s, ns - s)

Helix Motions , Domain Motions, Subunit motions

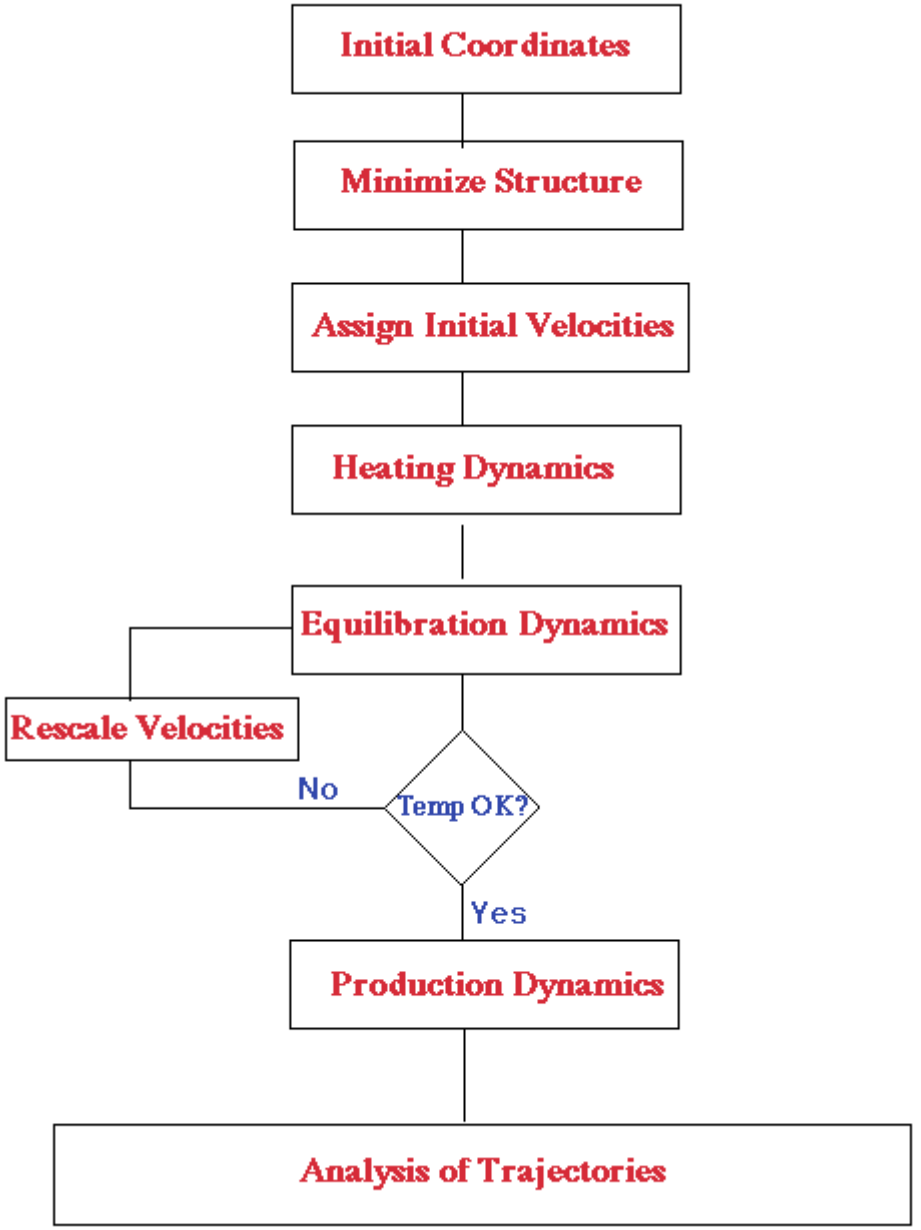
Large-Scale Motions (> 5Å, 10^{-7} to 10^{4} s, μs - m)

Helix coil transitions, Dissociation/ Association, Folding and Unfolding



Source: http://theory.cm.utexas.edu/henkelman/research/ltd/timescale.jpg

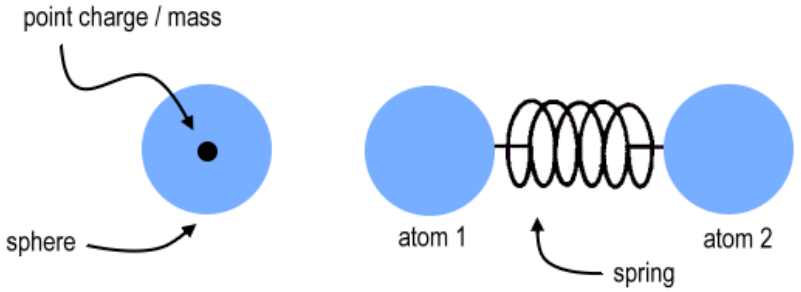
Molecular Dynamic Simulation



Source: http://www.ch.embnet.org/MD_tutorial/pages/MD.Part3.html

Molecular Mechanics

- Biomolecules are approximated as a physical network of spheres that have point charges at their centers and are connected by springs.



- Born-Oppenheimer Approximation

  electrons are not explicitly examined

- Uses Newtonian (classical) mechanics

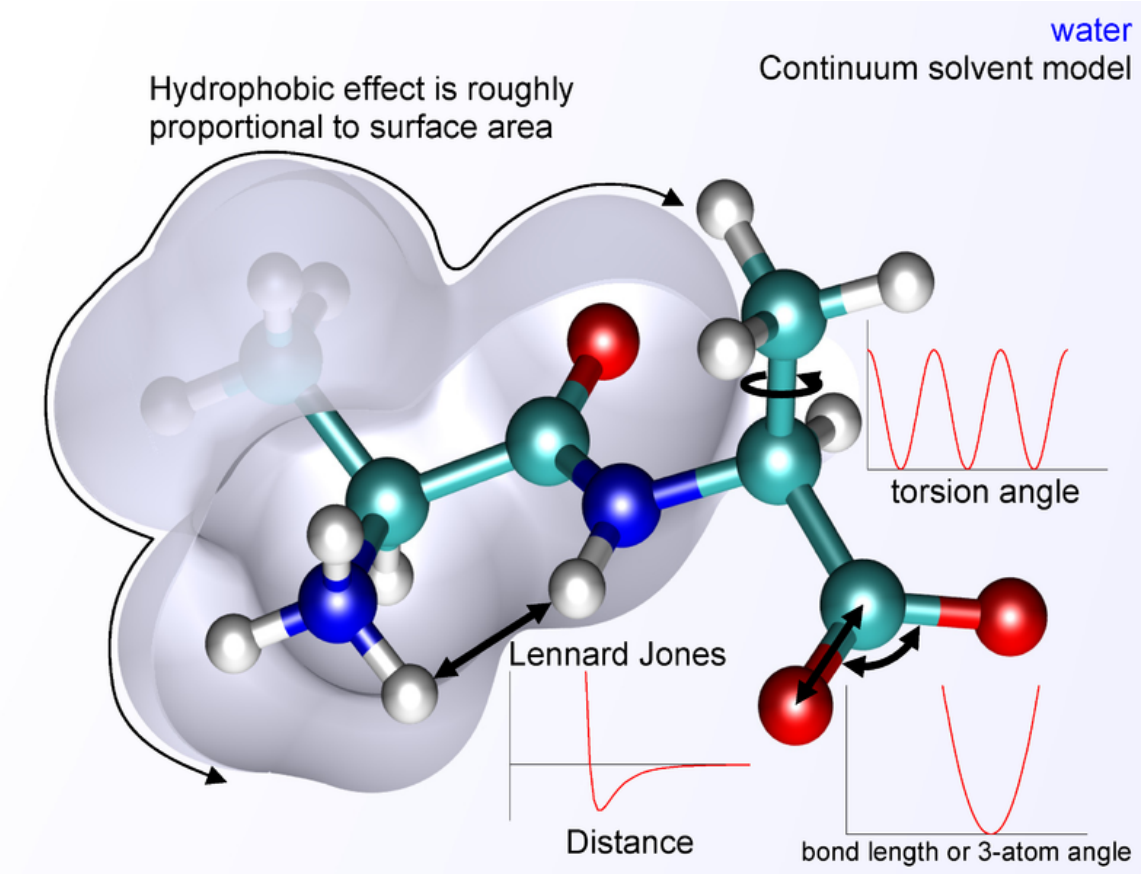
  Newtons Second Law of Motion: ***F = ma***

- Potential Energy calculated using force fields

Some theory about the energy

The Force Field

- = the potential energy of the system
- sum of bonded and non-bonded interactions
- $E_{total} = E_{bonded} + E_{nonbonded}$
- $E_{bonded} = E_{bond} + E_{angle} + E_{dihedral}$
- $E_{nonbonded} = E_{electrostatic} + E_{vanderWaals}$

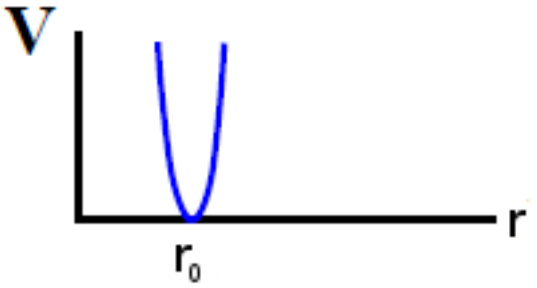


Source: http://en.wikipedia.org

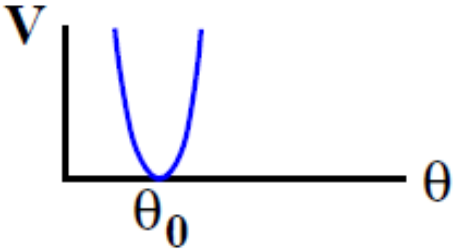
Bonded interactions

- approximated by Harmonic potential
- bond stretch
- angle bend
- dihedral torsions

$$\sum_{bonds} k_b (r - r_0)^2$$



$$\sum_{angles} k_a (\theta - \theta_0)^2$$

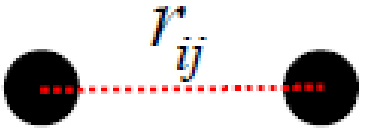


$$\sum_{dihedrals} k_d [1 + \cos(n\varphi - \delta)]$$

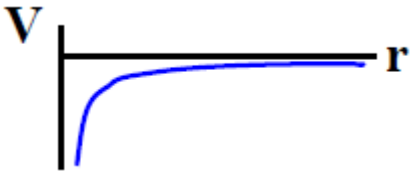
Sources: http://www.ch.embnet.org/CoursEMBnet/Basel05/Day1_Intro.pdf
http://cmm.cit.nih.gov/intro_simulation/intro_simulation.pdf

Nonbonded interactions

- Electrostatic interactions: Coulomb interactions:

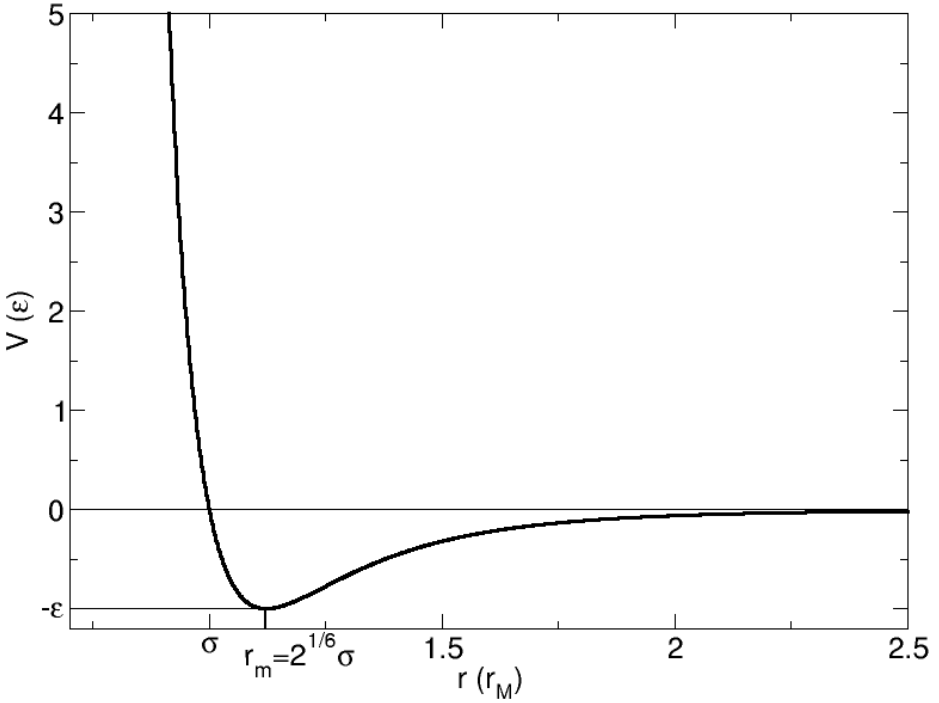


$$V(r) = \frac{1}{4\pi\varepsilon_o}\frac{q_1 q_2}{r}$$



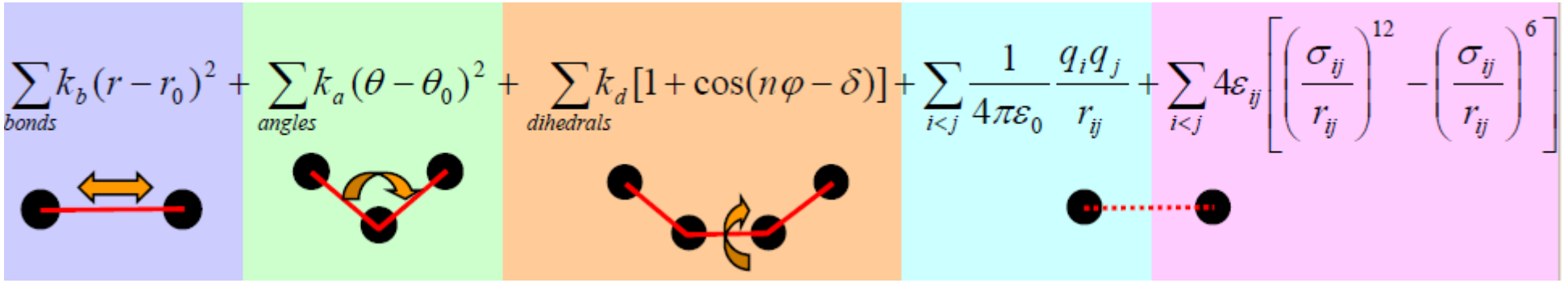
- van der Waals interactions described by Lennard Jones Potential:

$$V(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$



Sources: http://www.ch.embnet.org/CoursEMBnet/Basel05/Day1_Intro.pdf
http://cmm.cit.nih.gov/intro_simulation/intro_simulation.pdf
Wikipedia

All together



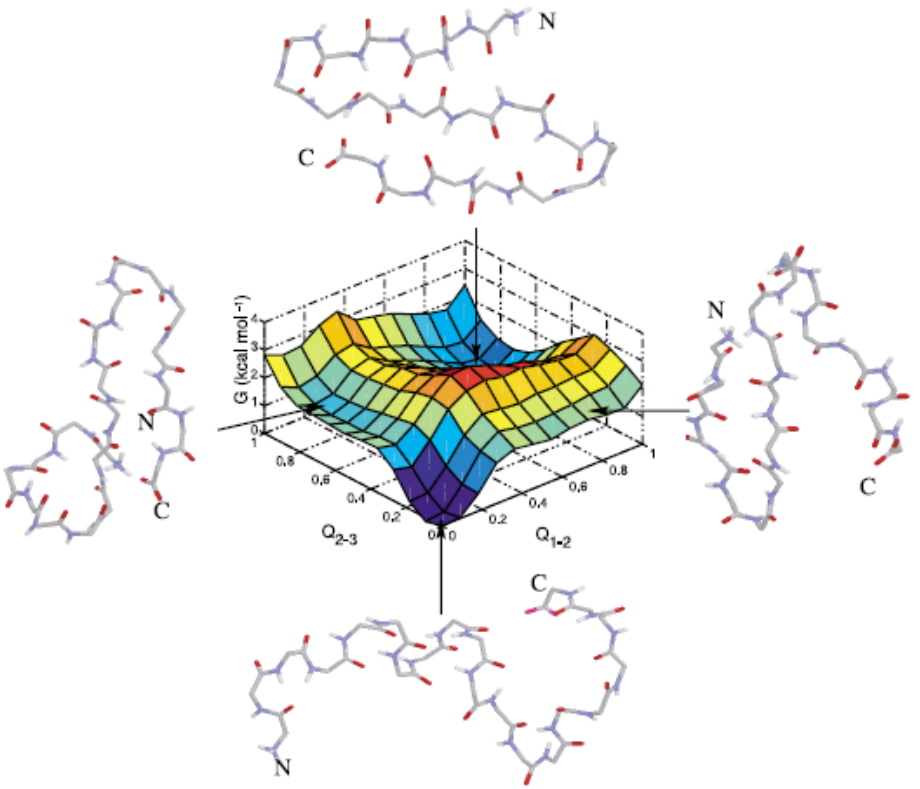
Source: http://www.ch.embnet.org/CoursEMBnet/Basel05/Day1_Intro.pdf

= general description of the classical potential energy landscape of molecules.

Find the minimum...

Minimise the energy...

- the goal is to minimise the potential energy of the system
  → the **Force Field**
- steepest descent algorithm
- better:
  - conjugate gradient
  - simulated annealing



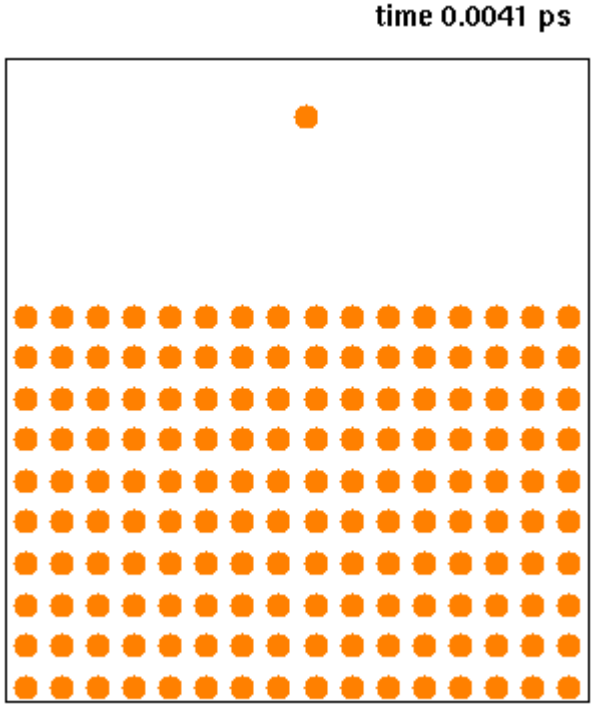
Source: Karplus, McCammon

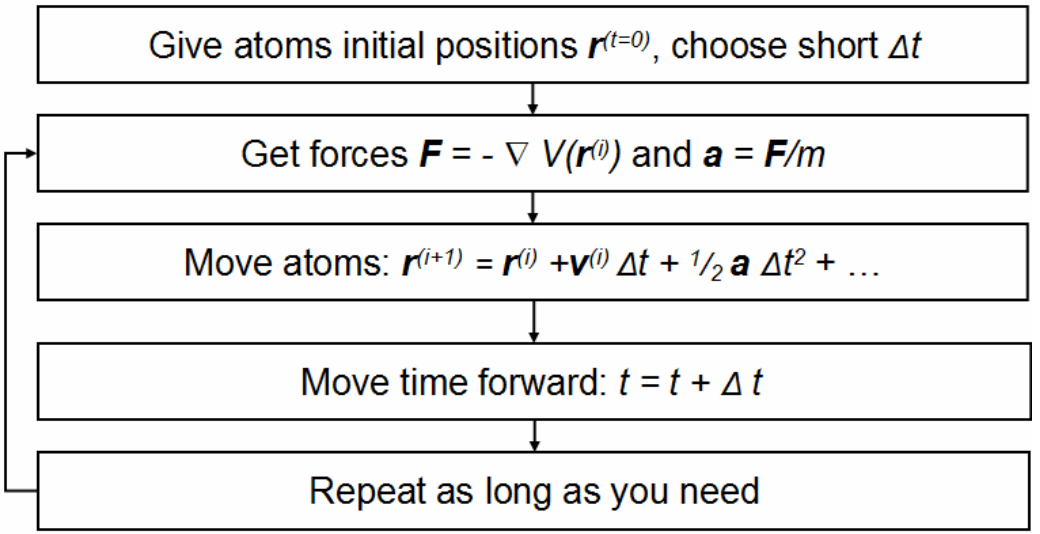
Molecular Dynamics

- potential energy function
- equation of motion: Newton etc.
- initial conditions: temperature, pressure, velocity etc.
- boundary conditions
- a lot of time

$\longrightarrow$ calculate the trajectory

Molecular Dynamics





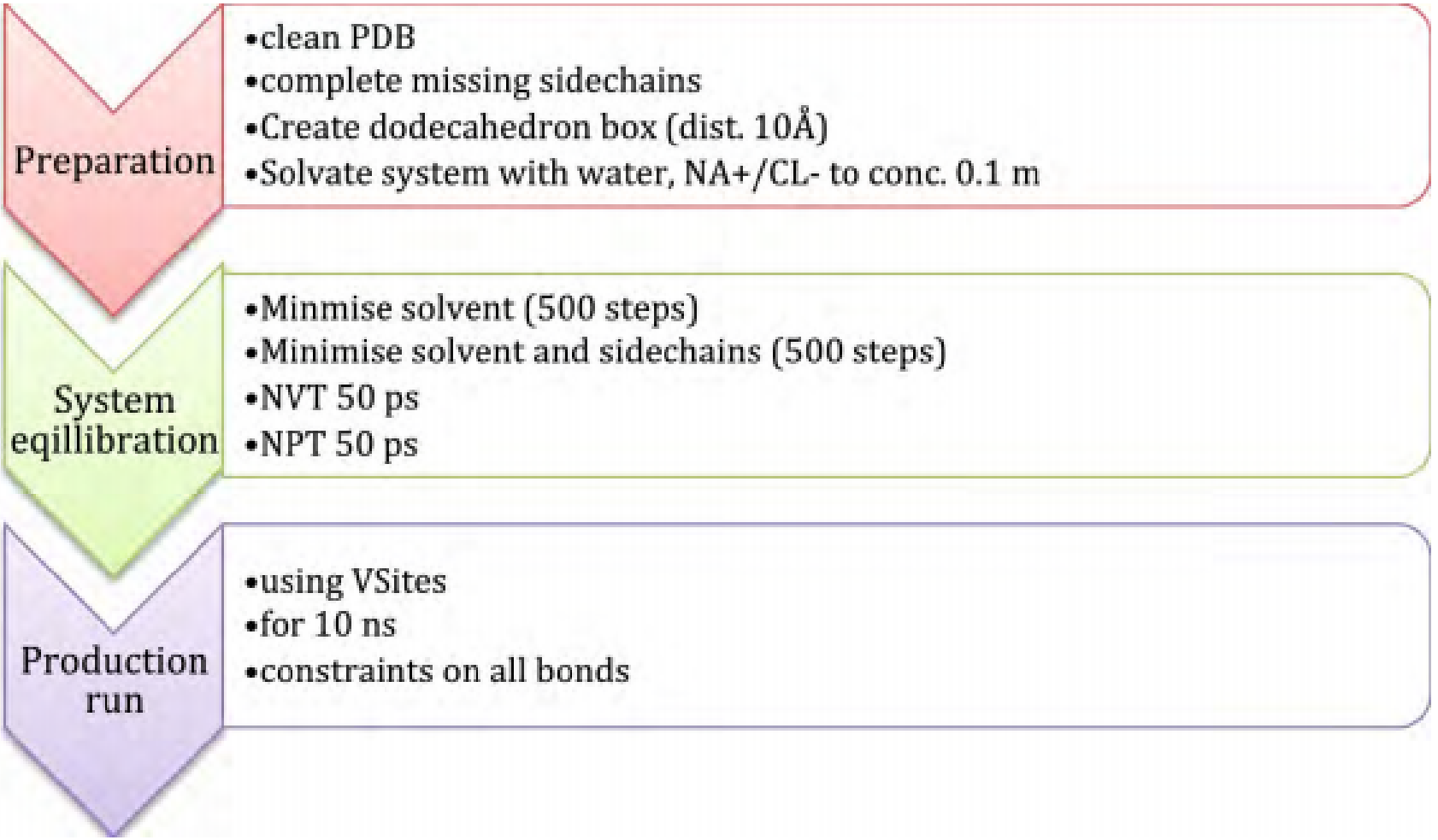
Source: Wikipedia

Tasks/Gromacs

Popular MD Packages

- Charmm – Chemistry at Harvard Macromolecular Mechanics
- Gromacs – Groningen Machine for Chemical Simulations
- Amber – Assisted Model Building with Energy Refinement
- NAMD – Not Another Molecular Dynamics Program

Task



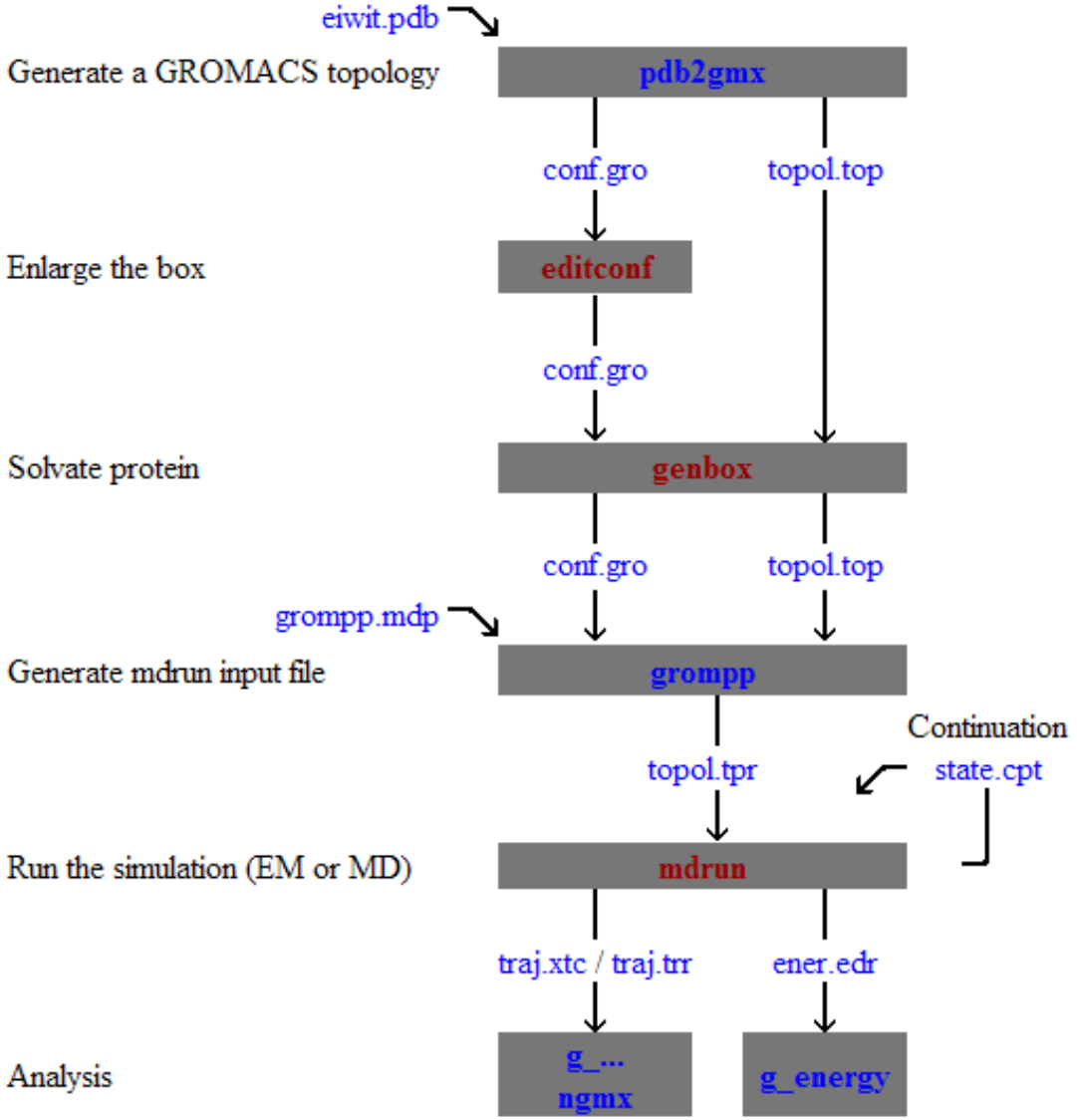
Tutorial: http://md.chem.rug.nl/~mdcourse/md.html

GROMACS FAST. FLEXIBLE. FREE.

- Molecular Dynamics Simulation package
- Primarily designed for biochemical molecules
- Developed by Berendsen et al. at the University of Groningen
- Free software

Tutorial: http://md.chem.rug.nl/~mdcourse/md.html

GROMACS FAST. FLEXIBLE. FREE.



Source: http:// manual.gromacs.org/current/online/flow.html

Some examples:

Look here: http://www.ks.uiuc.edu/Highlights

Sources

- http://en.wikipedia.org/wiki/Force_field_%28chemistry%29
- http://www.ch.embnet.org/CoursEMBnet/Basel05/Day1_Intro.pdf
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- Thanks to Marc for the talk about Molecular Dynamics :)