A Short Introduction to

Molecular Dynamics

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Master practical course (summer term 2013)

Overview

- What is molecular dynamics (MD)?
- Biological roles of MD
- How to model MD?
  - CHARMM & AMBER force fields
- How to perform MD simulation?
  - GROMACS

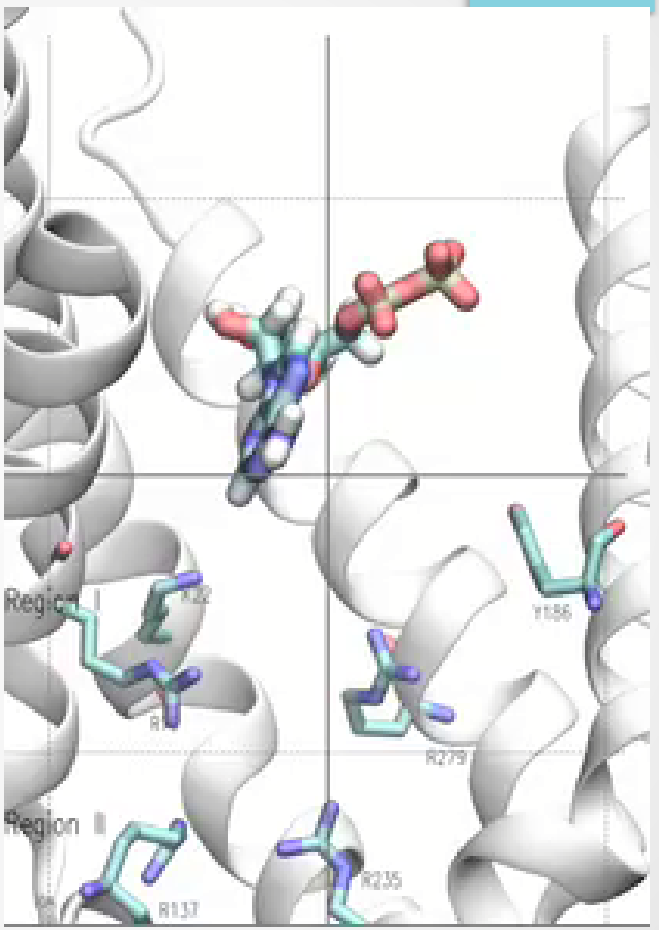
What is molecular dynamics?

- "… **computational** method calculates the **time dependent behaviour** of a **molecular system**. …" --- http://www.ch.embnet.org/MD_tutorial/

- **Molecular dynamics (simulation)**

What is molecular dynamics?

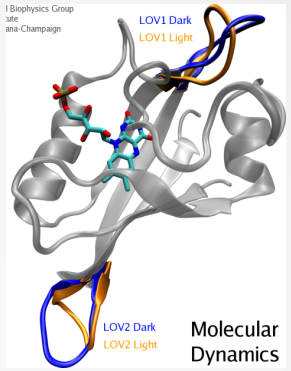
- Simulate molecular movements
- Conformations in time series
- Computing energy, trajectories



Ligand binding process: anchoring of ADP
http://www.ks.uiuc.edu

Time scales of biological processes

- Local motion (1fs to 0.1s)
  - atomic, side-chain, loops motions
- Rigid body motion (1ns to 1s)
  - helix, domain, subunit motions
- Large-scale motion (0.1ms to 10^4s)
  - Folding / unfolding
  - Dissociation / association



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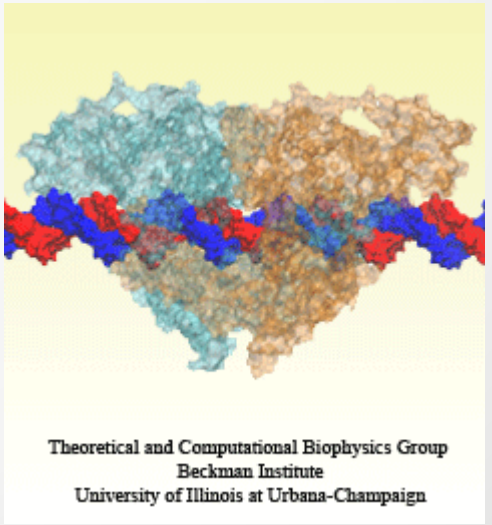


Biological role of MD

- Dynamic structural changes during:
  - Folding process
  - Molecular recognizing / binding
  - Membrane transport, etc.

- Applications
  - Drug design
  - Folding / unfolding simulation

How to model molecular dynamics?

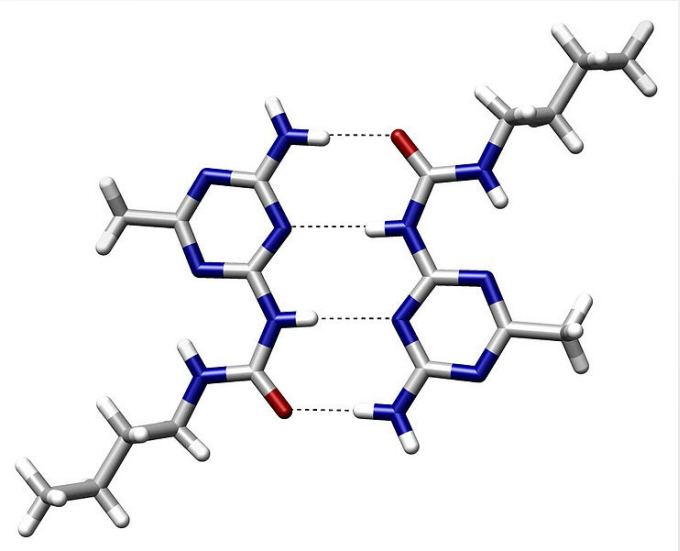
- Experimental measurements
  - molecular dynamics, thermodynamics
- Quantum mechanics (QM)
  - model all electrons in system
- **Potential energy functions**
  - empirical potential energy functions
  - knowledge from exp. measurements
- Mixing QM and MD

Potential energy functions

- **Limitation**:
  - no bond formation or bond breaking
    - Solution: quantum mechanics (very slow)
- Good tradeoff: accuracy & efficiency
- Force fields
  - CHARMM, AMBER, etc.

CHARMM force field

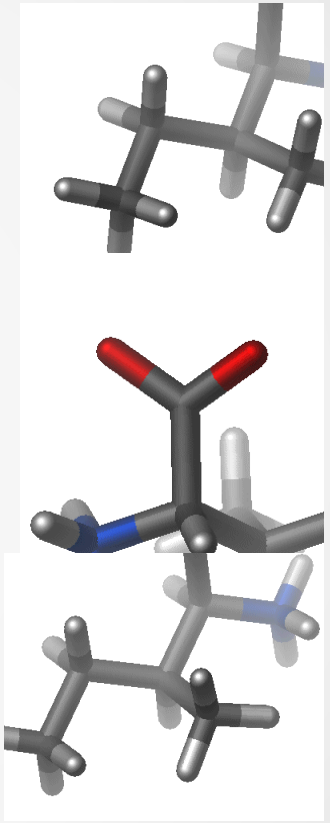
- Chemistry at HARvard Macromolecular Mechanics
- Two parts of total energy
  - Bonded and non-bonded energy terms
  - **$E_{total} = E_{bonded} + E_{non\text{-}bonded}$**



Wikipedia

Bonded energy terms

- 3 different movements
  - stretch, bend & rotation
- **$E_{bond} = E_{stretch} + E_{bend} + E_{rotation}$**



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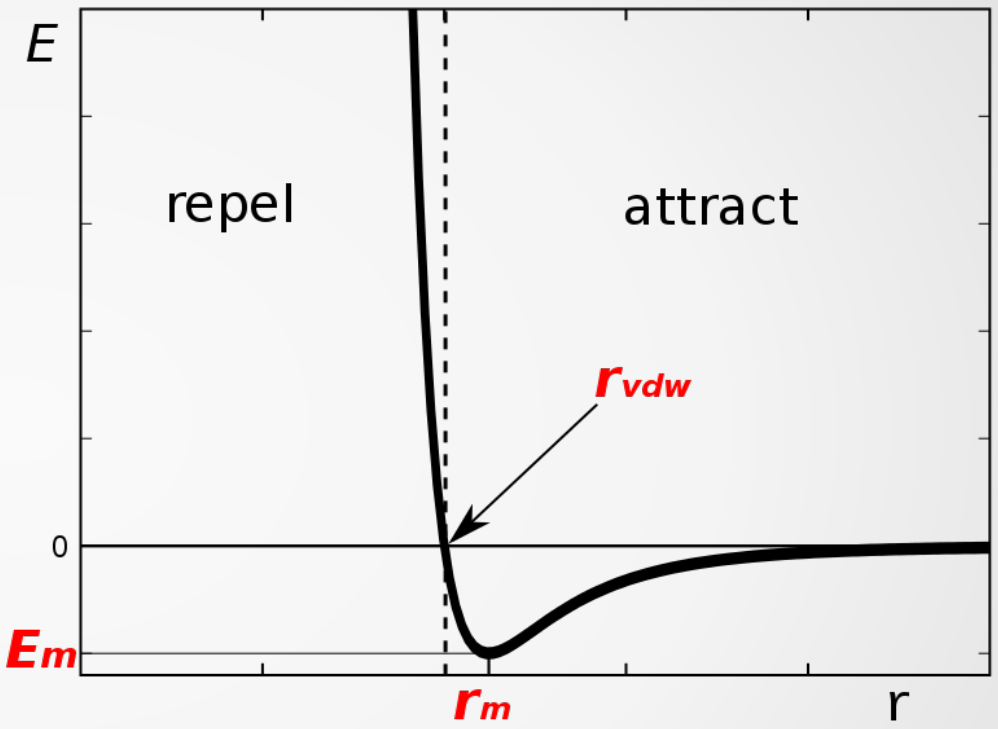
Non-bonded energy terms

- Van der Waals force
  - Lennard-Jones potential
- Electrostatic force
  - Coulomb potential



Lennard-Jones Potential

- **$E_{non\text{-}bonded} = E_{vdw} + E_{electrostatic}$**

Parameter database

- Constants parametrized from observation
  - $E_{bond-stretch} = \sum_{1,2\,pairs} K_b (b - b_0)^2$
  - $E_{bond-bend} = \sum_{angles} K_\theta (\theta - \theta_0)^2$
  - $E_{rotate-along-bond} = \sum_{1,4\,pairs} K_\phi (1 - \cos(n\phi))$
- Additional parameters
  - unable to infer from CHARMM force field
  - e.g. SwissSidechain

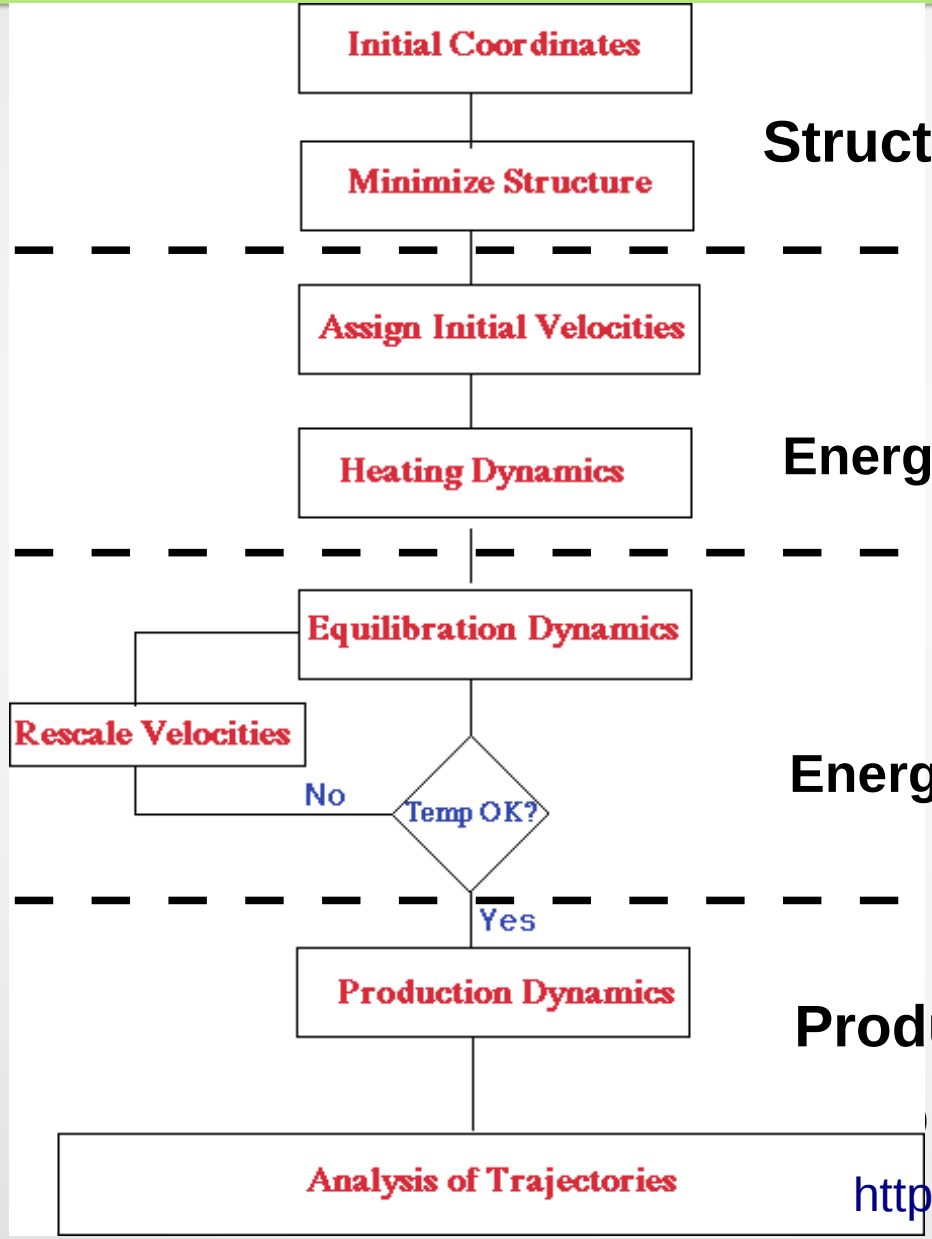
CHARMM

- **$E_{total} = E_{bonded} + E_{non\text{-}bonded} = (E_{stretch}+E_{bend}+E_{rotation}) + (E_{vdw} + E_{electrostatic})$**
- **+ additional energy terms (parameter databases)**

AMBER force field

- Assisted Model Building with Energy Refinement
- Similar but more “case specific” than CHARMM
- Collection of different parameter databases
  - Glycam force field for carbohydrates
  - parameters for RNA
  - Zinc parameters
  - REDDB (small molecules)
  - ff99SBildn & ff99SBnmr (AA side-chains)
  - ...

How to perform MD simulation?



Structure cleanup, initialization

Energy stimulation

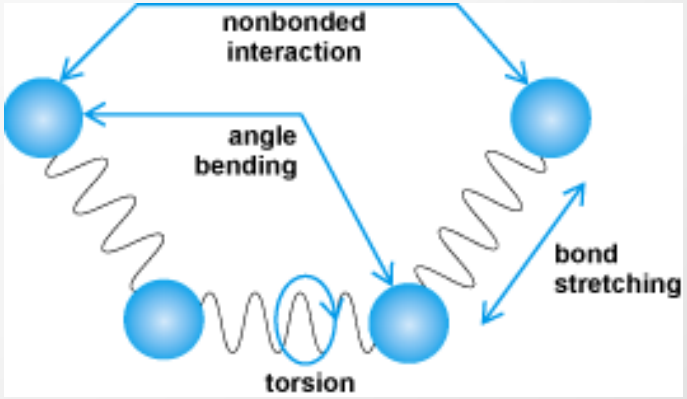
Energy optimization, equilibrium

Produce results (trajectories)

http://www.ch.embnet.org/MD_tutorial/

Structure model

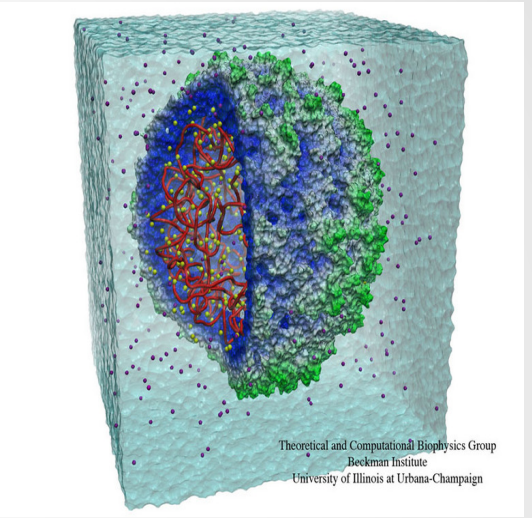
- Graph structure (bonds & atoms)
  - Ball and spring model
- Atom
  - Element type, charge, mass, van der Waals radius
- Bond
  - Initial length & energy



AccessScience: Molecular mechanics

Preprocessing

- Remove strong Vdw interactions
  - stable simulation
- Solvent environment
  - In vacuum:
    - computational efficient, inaccurate
  - In solvent (most cases: water)
    - structure, dynamics, thermodynamics
    - more CPU time, accurate



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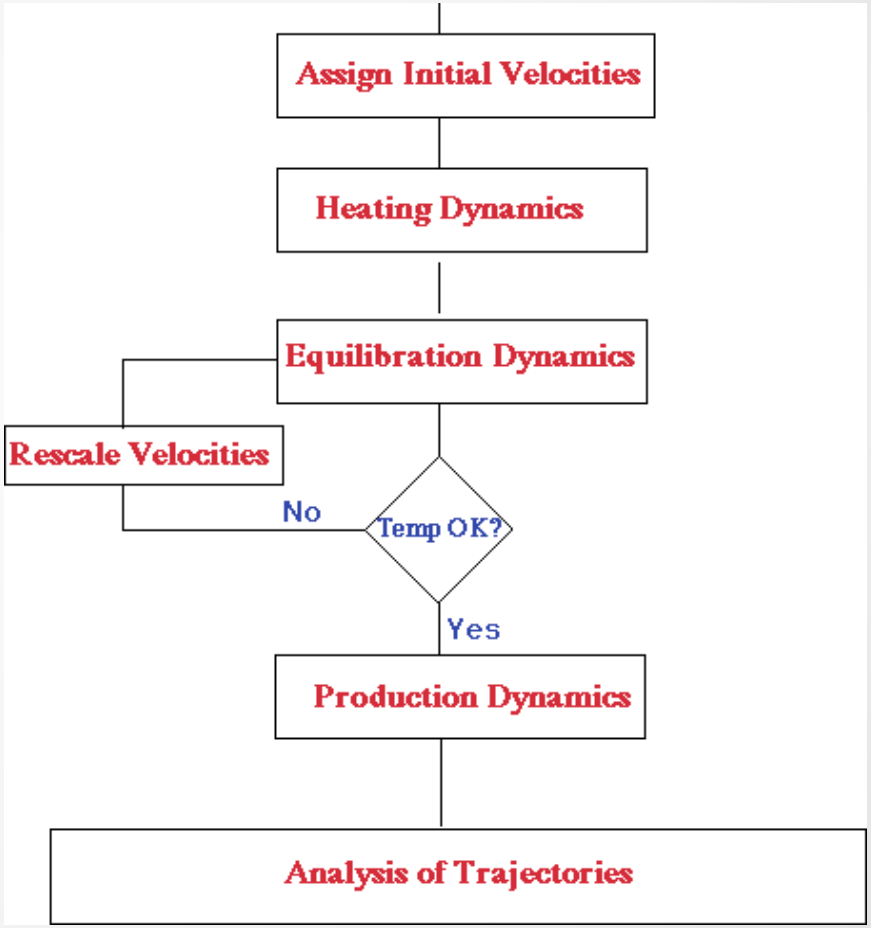
Run the simulation

- Assign initial velocities to each atom
- Rise temperature
- Monitor position, angels, energy etc.



GROMACS

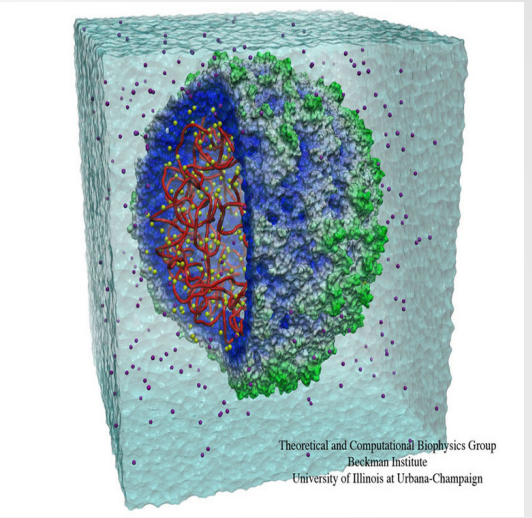
- A versatile package for MD
  - Designed for **biological macromolecules**
  - **Fast computing of non-bonded interactions**
  - Great algorithm support
  - **GPU** computing
- Estimated project cost: ~ 2.6M $
- Funding:

GROMACS in a nutshell
Lysozyme in water

- Generate topology
  - remove **crystal solvent** (water)
  - check and repair missing residues
  - pdb2gmx -f 1AKI.pdb -o 1AKI_processed.gro -water spce

```
[ atoms ]
;   nr  type  resnr residue  atom   cgnr     charge       mass  typeB    chargeB  massB
; residue   1 LYS rtp LYSH q +2.0
1   opls_287     1   LYS      N      1      -0.3    14.0067   ; qtot    -0.3
2   opls_290     1   LYS      H1     1       0.33     1.008   ; qtot    0.03
3   opls_290     1   LYS      H2     1       0.33     1.008   ; qtot    0.36
4   opls_290     1   LYS      H3     1       0.33     1.008   ; qtot    0.69
```

GROMACS in a nutshell
Lysozyme in water



http://www.ks.uiuc.edu

- Solvent box
  - put topology model into solvent
  - define box size
  - fill with water molecule
- Define box
  - editconf -f 1AKI_processed.gro -o 1AKI_newbox.gro -c -d 1.0 -bt cubic
- Fill box
  - genbox -cp 1AKI_newbox.gro -cs spc216.gro -o 1AKI_solv.gro -p topol.top

GROMACS in a nutshell
Lysozyme in water

- Add ions
  - structure model total net charge (+8p)
  - balance net charge of solution
  - replace water with ion
- Energy minimization
  - correct clashing atoms
- Run simulation and wait for equilibrium
- Produce results and analysis

Conclusion

- Dynamic structure of bio. macromolecules
  - Protein binding, folding
- Molecular dynamics simulation
  - Potential energy functions
  - Parameter databases
- Run MD
  - Structure cleanup, energy minimization
  - Solvent environment
  - Heating & Equilibrium

Thank you for listening to my presentation!

Any questions?

References

- Tutorial of Molecular Dynamics Simulation by CHARMM
  - http://www.ch.embnet.org/MD_tutorial/
- Amber Home Page
  - http://ambermd.org/
- GROMACS
  - http://www.gromacs.org/
- GROMACS Tutorial: Lysozyme in Water
  - http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/lysozyme/index.html