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Author(s):	Junghans, Christoph
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GROMACS Tutorial

Christoph Junghans

Los Alamos National Laboratory
NM, USA

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Plan for the Course

- Installing GROMACS
- From PDB to MD
- HPC Tips & Tricks
- Question & Answer Session
- Advanced Simulations
  - Spectral clustering (MDSCTK)
  - Coarse-graining (www.votca.org)
  - Martini
- What is next ?

Installing GROMACS

Dependencies

GROMACS is a GPL code and free of charge.

Hard Dependencies

- C++ compiler
- cmake
- GNU make (or MSVS or Google Ninja)

Soft Dependencies

- fftw (can be built-in, legal implications)
- Intel MKL
- Nvidia Cuda

Installing GROMACS

Considerations

Single vs. Double precision

- Why do you want double?
- Can you afford a factor two in speed?
- Do you do NVE or normal mode analysis?

MPI vs. Threads

- Are you going to use more than one node (shared memory)?
- Communication overhead vs. performance gain

Intel vs. GNU

- Are you an Intel fan boy?
- Are you using the latest gcc/icc/MKL/fftw ?

Installing GROMACS

Preparations

- Download GROMACS: wget↩

  ```
  ftp://ftp.gromacs.org/pub/gromacs/gromacs-5.0.tar.gz
  ```

- Unpack tarball:

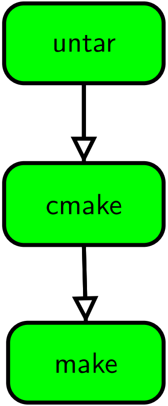
  ```
  tar -xzvf gromacs-5.0.tar.gz
  ```

- Make a build directory:

  ```
  cd gromacs-5.0
  mkdir build
  cd build
  ```

- Run cmake:

  `cmake ..` (or `ccmake` or `cmake-gui`)



Installing GROMACS

Cmake Options

Add options to `cmake -DSOME=THING -DSOMETHING=ELSE ..`

Useful options

- Enable/Disable MPI: `-DGMX_MPI=<ON|OFF>`
  if disabled make sure to use: `-DGMX_THREAD_MPI=ON`
- Enable/Disable GPU: `-DGMX_GPU=<ON|OFF>`
- Install prefix: `-DCMAKE_INSTALL_PREFIX=<PATH>`
- Single or Double: `-DGMX_DOUBLE=<ON|OFF>`
- Enable minimal viewer: `-DGMX_X11=<ON|OFF>`
- Enable built-in fftw: `-DGMX_BUILD_OWN_FFTW=ON`

In short: `cmake ..  -DGMX_X11=ON`↩
`-DCMAKE_INSTALL_PREFIX=$HOME/gromacs`

Installing GROMACS

Build & Install

- Get number of cores:
  - Linux: `grep -c processor /proc/cpuinfo`
  - MacOs: `sysctl -n hw.ncpu`
- Build: `make -j<number of cores>` (add VERBOSE=1 for verbose output)
- Install: `make -j<number of cores> install`
- Setup paths: `source↩ $HOME/gromacs/bin/GMXRC.bash`
- Run: `gmx`

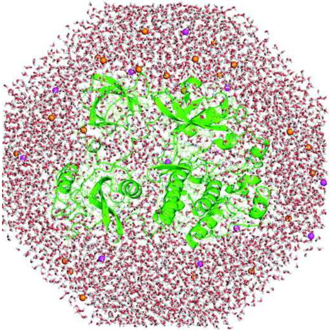
"Move about like a Scientist, lay down, get kissed"
(Red Hot Chili Peppers)

From PDB to MD

Introduction

PDB is a standard format for protein structures, which contains:

- Atom positions
- Atom types
- Residue name & number
- *No* topological information (bonds, angle)
- *No* force field information
- *No* solvent



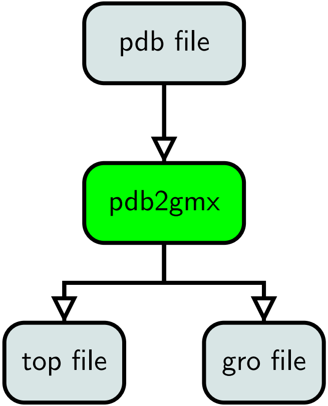
Src kinase protein, from: M. Karplus and J. Kuriyan, PNAS **102**),6679-6685 (2005).

From PDB to MD

Considerations

pdb2gmx Inputs

- Force field: interactive or `-ff` option
- GROMACS supports multiple force fields!
- Water model: interactive or `-water` option
- Interactive termini selection or `-ter`
- Hydrogen removal: `-ignh` option
- Hydrogen to virtual site: `-vsite hydrogens` option



From PDB to MD

Force Fields in a Nutshell

- Force fields describe the interactions between the atoms
- Incl. their functional form
- Bonded and non-bonded interactions

Non-bonded interactions

$$U(r) = 4\epsilon\left[(\sigma/r)^{12} - (\sigma/r)^{6}\right]$$

or

$$U(r) = C_{12}/r^{12} - C_6/r^6$$

or Buckingham or tabulated

Bonded interactions

- Bonds
- Angle
- Dihedrals

Supported Force Fields

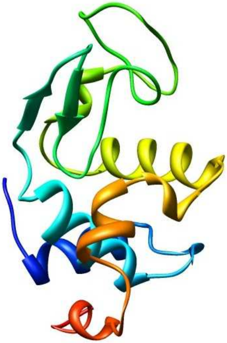
- CHARMM
- Amber
- GROMOS
- OPLS
- Martini

From PDB to MD

1AKI Conversion

This tutorial is modeled after Justin Lemkul's 1AKI tutorial[1]

- Goto `http://www.rcsb.org/`
- Get 1AKI as PDB (text)
- `gmx pdb2gmx -f 1AKI.pdb`
- Select OPLS-AA force field and SPC/E water
- Look at topol.top

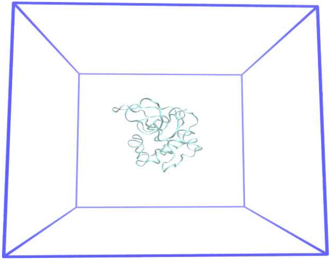


[1] Justin's tutorial(link)

From PDB to MD

1AKI Solvating

- Put 1AKI into a cubic box with distance 1 nm from the boundary
  ```
  gmx editconf -f conf.gro↩
  -o conf2.gro -c -d 1.0↩
  -bt cubic
  ```
- Solvate in spce water
  ```
  gmx solvate -cp conf2.gro↩
  -cs spc216.gro -o↩
  conf3.gro -p topol.top
  ```
- Compare `topol.top` with `#topol.top.1#` (backup file)
- Create runtime setting file



From PDB to MD

Runtime Settings

Create grompp.mdp:

```
integrator      = steep
emtol           = 1000.0
emstep          = 0.01
nsteps          = 50000
nstlist         = 1
rlist           = 1.0
coulombtype     = PME
rcoulomb        = 1.0
rvdw            = 1.0
pbc             = xyz
```

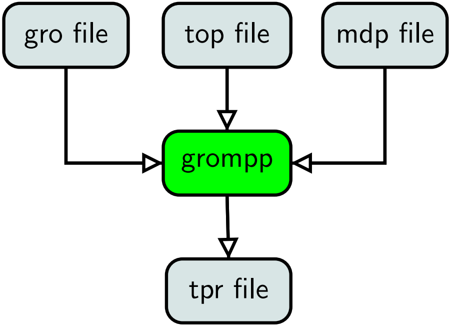
- Use steepest descent (not really an integrator)
- Initial step size 0.01nm
- Minimize until max force is 1000.0 kJ/mol/nm
- All cutoffs = 1nm
- Use smooth PME for electrostatic
- Use periodic boundary conditions in xyz
- Need more details? See the gromacs manual!

From PDB to MD

GROMACS Preprocessor

- Compile a tpr file: `gmx↩ grompp -c conf3.gro`
- Uh, a charged system
- To check defaults look at mdout.mdp
- Add counter ions: `gmx↩ genion -o conf4.gro↩ -p topol.top -pname↩ NA -nname CL -nn 8`
- Select SOL to replace Water molecules
- Compare `topol.top` with `#topol.top.2#` (backup file)

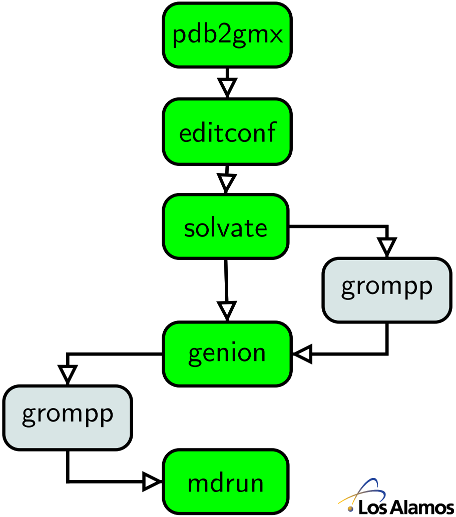
Note: tpr is actually the only file needed for the simulation (except tables)



From PDB to MD

1AKI Minimization

- Recompile tpr: `gmx↩ grompp -c conf4.gro`
- Minimize `gmx mdrun -v`
- Look at `md.log`
- Calculate energy (not actually calculated, but just converted) `gmx energy`
- Select potential energy
- Look at `energy.xvg` using `xmgrace`



MD in a Nutshell

GROMACS stands for "GROningen Mixture of Alchemy and Childrens' Stories"[2] and is a molecular dynamics code optimized for bio-simulations.

$$m_i \ddot{\vec{r}}_i = \sum_j F_{ij}(r_{ij}) = \dot{\vec{p}}_i$$

Molecular dynamics is the “art” of integrating Newton's equation of motion.

[2] Or: "GROningen MAchine for Chemical Simulation"

MD in a Nutshell

Integrators

Simple idea: Taylor expansion

Velocity Verlet Algorithm

$$\vec{r}_i(t+\Delta t) = \vec{r}_i(t) + \frac{\Delta t}{m_i}\vec{p}_i(t) + \frac{\Delta t^2}{2m_i}\vec{F}_i(t) + \mathcal{O}(\Delta t^3) \ ,$$

$$\vec{p}_i(t+\Delta t) = \vec{p}_i(t) + \frac{\Delta t}{2}\left(\vec{F}_i(t) + \vec{F}_i(t+\Delta t)\right) + \mathcal{O}(\Delta t^3)$$

- Only correct up to 2nd order
- One force call per time step
- Higher order will need more force calculations per time step

MD in a Nutshell

Integrators

Alternative Formulation:

Leap-Frog Algorithm

$$\vec{p}_i(t+\Delta t/2) = \vec{p}_i(t-\Delta t/2) + \Delta t \vec{F}_i(t) + \mathcal{O}(\Delta t^2)$$

$$\vec{r}_i(t+\Delta t) = \vec{r}_i(t) + \frac{\Delta t}{m_i}\vec{p}_i(t+\Delta t/2) + \mathcal{O}(\Delta t^3) \ ,$$

- Leap-Frog and Velocity Verlet differ when combined with Thermostats and Barostats
- What is a good integrator? A symplectic integrator![3]

[3] See the gromacs manual!

MD in a Nutshell

Ensembles

- Newton's equation conserved energy → NVE
  `integrator=md`
- Thermostat → NVT
  `tcoupl=...`
- Barostat → NPT
  `pcoupl=...`

Ensemble should correspond to experimental conditions!

MD in a Nutshell

Thermostats

Thermostats are additions to equations of motion to go from NVE to NVT.

4 Groups:

- Local thermostats couple to every particle
- Global thermostats couple to the total kinetic energy
- Stochastic thermostats have random variables
- Deterministic thermostats have no random variables

MD in a Nutshell

Rescaling Thermostats

- Simple rescaling thermostat (Global, deterministic)
  - Rescales total kinetic energy $K' = \lambda K$ with $\lambda = \sqrt{T/T_0}$
  - Iso-kinetic ensemble
- Berendsen thermostat (Global, deterministic)[4] `tcouple=Berendsen`
  - Rescales with a finite rate:

$$\frac{\mathrm{d}K}{\mathrm{d}t} = \frac{K(T) - K(T_0)}{\tau}$$

- "flying ice cube" problem
- No canonical ensemble!

[4] Berendsen et al., JCP **81**,3684 (1984)

MD in a Nutshell

Rescaling Thermostats

- Stochastic velocity rescaling thermostat (global)[5]
  `tcouple=v-rescale`
  - Chooses kinetic energy from the canonical distribution:

$$\frac{\mathrm{d}K}{\mathrm{d}t} = \frac{K(T) - K(T_0)}{\tau} + 2\sqrt{\frac{K(T)K(T_0)}{\tau}}\eta$$

  - Canonical ensemble!
  - equivalent to Langevin thermostat in K
- "flying ice cube" problem
- Localization: acts on kinetic energy of separate groups indepently

[5] Bussi, Donadio, Parrinello JCP **126**, 014101 (2007)

MD in a Nutshell

Stochastic Dynamics

- Add a stochastic and damping force to each particle:

$$m_i\ddot{\vec{r}}_i = \vec{F}_i - \xi_i\vec{v}_i + \sigma_i\vec{\eta}_i \ ,$$

with $\xi_i k_\mathrm{B} T = \sigma_i^2$ (Fluctuation-Dissipation theorem)

- Every particle is coupled to its own distribution
- Changes the dynamics
- Stabilizes dynamics → bigger time step
- Also known as Langevin thermostat
- No momentum conservation
- Can be used as implicit solvent
- `integrator=sd`

MD in a Nutshell

Andersen Thermostats

- Choose velocities randomly from a Maxwell distribution[6]
- Used to generate starting velocities
  `gen_vel=yes`

[6] Andersen, JCP **72**,2384 (1980)

MD in a Nutshell

Nosé-Hoover Thermostats

- Add an extra degree of freedom to the Hamiltonian

$$H = \sum_{i=1}^{N} \frac{\vec{p}_i}{2m_i} + U\left(\vec{r}_1, \vec{r}_2, \ldots, \vec{r}_N\right) + \frac{p_\xi^2}{2Q} + N_f kT\xi$$

- Deterministic
- Virtual mass Q needs to be chosen
- Extension: Nosé-Hoover chain - thermostat the thermostat[7]. `nh-chain-length=X`

$$H = \sum_{i=1}^{N} \frac{\vec{p}_i}{2m_i} + U\left(\vec{r}_1, \vec{r}_2, \ldots, \vec{r}_N\right) + \sum_{k=1}^{M} \frac{p_{\xi_k}^2}{2Q'_k} + N_f kT\xi_1 + kT\sum_{k=2}^{M} \xi_k$$

- `tcouple=nose-hoover`

[7] Martyna, Klein and Tuckerman, JCP**97**, 2635 (1992)

MD in a Nutshell

Barostats

Barostats are extensions to the equations of motion to go from NVT to NPT.

- Berendsen barostat
  `pcoupl=Berendsen`
  - Rescales simulation box to the right pressure with a constant rate

$$\frac{\partial \mathbf{P}}{\partial t} = \frac{\mathbf{P}_0 - \mathbf{P}}{\tau_p}.$$

- Parrinello-Rahman barostat[8]
  `pcoupl=Parrinello-Rahman`
  - Adds degree of freedom for the box vectors

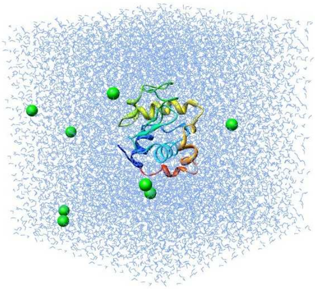
$$\frac{\partial \vec{b}^2}{\partial t^2} = V\mathbf{W}^{-1}\vec{b}'^{-1}\left(\mathbf{P} - \mathbf{P}_{ref}\right).$$

[8] Parrinello and Rahman, J Appl Phys **52**, 7182 (1981)

MD Simulations

1AKI constrained NVT equilibration

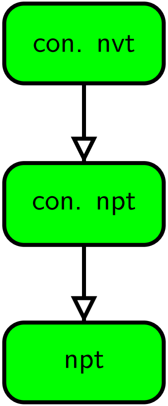
- Use new directory:
  `mkdir nvt; cd nvt`
- Copy over `confout.gro`
  `cp ../confout.gro conf.gro`
- Copy over `topol.top` and `posre.itp`
- Get Christoph's mdp file
- Let's discuss it.
- Compile a tpr file: `gmx grompp`
- Run `gmx mdrun -v`
- Use `gmx energy` to look at the pressure



MD Simulations

1AKI constrained NPT Equilibration

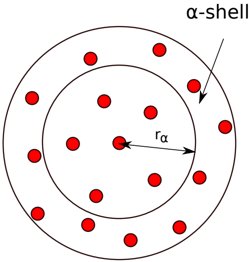
- Use new directory:
  `mkdir npt; cd npt`
- Copy over `confout.gro`
  `cp ../nvt/confout.gro conf.gro`
- Copy over `topol.top` and `posre.itp`
- Get Christoph's mdp file
- Let's discuss the input
- Compile a tpr file: `gmx grompp`
- Run `gmx mdrun -v`
- Use `gmx energy` to look at the box size



MD Simulations

1AKI MD Production

- Use new directory:
  `mkdir md; cd md`
- Copy over `confout.gro`
  `cp ../npt/confout.gro conf.gro`
- Copy over `topol.top`
- Get Christoph's mdp file
- Let's discuss the input
- Compile a tpr file: `gmx grompp`
- Run `gmx mdrun -v`
- Use `gmx energy` to look at the energies
- Use `gmx rdf` to calculate the radial dist. function

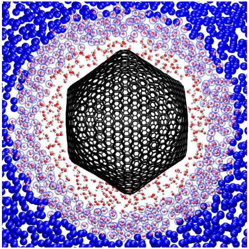


MD Simulations

Outlook

Things we have not discussed:[9]

- Free energy and PMF calculations
- Replica exchange (mpi version only)
- Coarse-grained simulations
- GROMACS supports multiple force fields
- Shell molecular dynamics simulations
- Adaptive resolution simulations
- Essential dynamics
- Implicit solvent simulations
- many, many more analysis features (try `gmx help commands`)
- . . .



[9] See the gromacs manual!

GROMACS on HPC

Introduction

"GROMACS Runs One Microsecond At Cannonball Speeds" using:

- Optimized neighbor list for water
- Vectorized force kernels
- Parallelization:
  - Domain Decomposition
  - Threaded particle blocks (Verlet only)
  - Threaded PME calculations
  - Offload to GPUs (Verlet only)
- Separated nodes for PME calculations (use `gmx tune_pme`)

Don't panic in case of a doubt let `gmx mdrun` decide!

GROMACS on HPC

Test System

- Create topol.top:

  ```
  #include "gromos43a1.ff/forcefield.itp"
  #include "gromos43a1.ff/spce.itp"
  [ system ]
  Water
  [ molecules ]
  ```

- Create a box of water

  ```
  gmx solvate -cs spc216.gro -p topol.top↩
  -box 5 5 5 -o conf.gro
  ```

- Get Christoph's mdp file
- Build different system sizes using:

  ```
  gmx genconf -nbox X X X
  ```

GROMACS on HPC

Considerations

Options of `gmx mdrun` to play

- `-nb`
- `-nt`
- `-ntomp`
- `-ntmpi`
- `-dd`
- `-dlb`
- `-npme`

Other tweaks

- MPI vs threads
- Group scheme (`cutoff-scheme=Group`)
- Verlet scheme (`cutoff-scheme=Verlet`)

GROMACS on HPC

GROMACS in the Queue

- to wall clock time use: `gmx mdrun -maxh xxx`
- `gmx mdrun` creates checkpoint every 15min (-cpt option)
- to start from a checkpoint use -cpi option (smart option)
- chain jobs[10]

```
...script header
gmx mdrun -maxh 36 -cpi state.cpt -append
[ $? -eq 0 ] && [ ! -f confout.gro ] && msub $0
```

[10] moab: `msub -l depend=jobid xxx.log`

Conclusion

- GROMACS is great!
- GROMACS is fast!
- GROMACS is free!
- There is a manual out there! (RTFM)
- Join gmx-users mailing list and ask questions!

The End

Thank you for your attention !

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